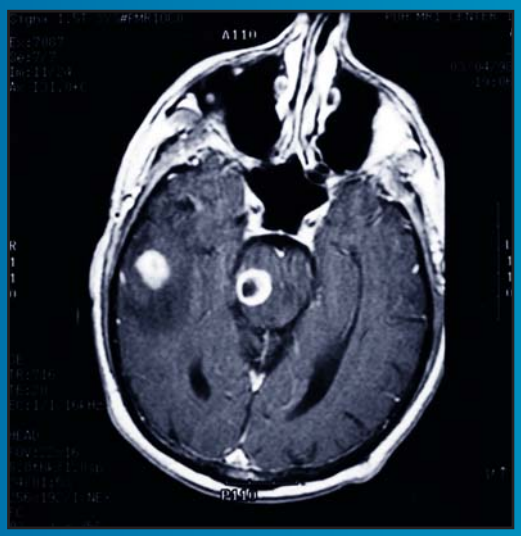
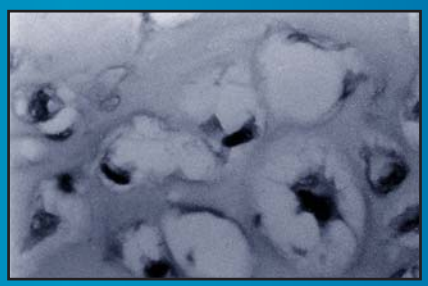
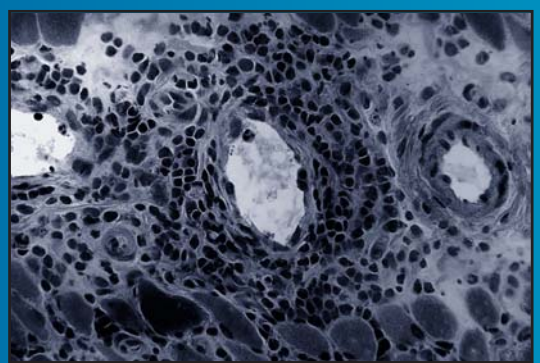
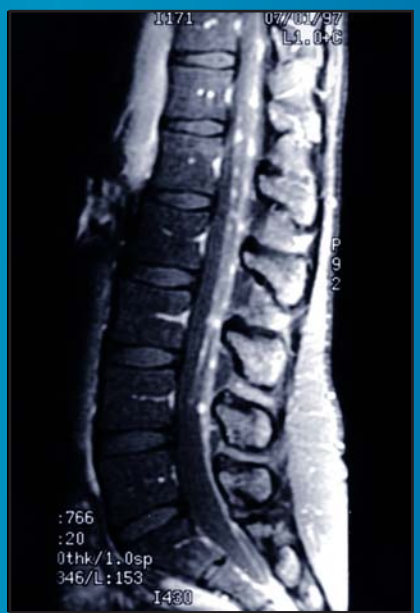
# Cancer Neurology in Clinical Practice

EDITED BY
David Schiff, MD AND Patrick Y. Wen, MD

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Cover Illustration: The top left (brain) MRI is a post-contrast T1 scan demonstrating multiple cerebral metastases in a patient with renal cell carcinoma. The bottom right spine MRI reveals multiple enhancing leptomeningeal nodules reflecting metastatic spread of melanoma. Both of these photos are courtesy of Dr. Schiff from personal archives. Upper right photo is Fig. 1A in Chapter 29, "Neuro-Oncologic Complications of Sarcomas" by Lara Kunscher. Lower left photo is Fig. 10 in Chapter 11, "Neuromuscular Disease and Its Complications" by Magdy Selim, David A. Chad, and Lawrence D. Recht.

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# FOREWORD

I last wrote a Foreword for a book on neuro-oncology in 1995. At that time, I suggested that neuro-oncology was an important and emerging subspecialty involving neurologists, neurosurgeons, radiation oncologists, neuroradiologists, and medical oncologists. In the ensuing seven years, interest in neuro-oncology has increased. A new American organization, the Society for Neuro-Oncology, has joined the European Association for Neuro-Oncology as a multidisciplinary organization devoted to the study of neuro-oncology in all of its aspects. In addition, a number of books have appeared encompassing neuro-oncologic material and a second journal, *Neuro-Oncology*, has joined the *Journal of Neuro-Oncology* as a specialty journal related to the subject.

With so much written literature, one might ask why this book? There are several answers: First, many books emphasize primary brain tumors rather than the more common neurologic complications of systemic cancer. *Cancer Neurology in Clinical Practice* gives a comprehensive analysis of how cancer affects the nervous system. A book such as this one allows the reader interested, but not working, in neuro-oncology an opportunity to peruse the entire field of cancer neurology in one reference. Second, the field is evolving. Although neuro-oncologists are discouraged by our slow progress, there have been substantial advances in our understanding of the biology that underlies the clinical subspecialty of neuro-oncology and, in addition, there have been some areas in which treatment has changed, e.g., radiosurgery for single or multiple metastatic lesions and chemotherapy for some metastases. Thirdly, the editors of this book, David Schiff and Patrick Wen, have pulled together a group of experts who are currently active in the clinical management of the problems they are writing about.

It is with pride, I note, that 24 of the 50 authors received their neuro-oncological training at Memorial Sloan-Kettering, and that several others were trained by those who received their training here. Nonetheless, this is not a provincial book. It encompasses the experience of senior physicians actively engaged in neuro-oncology at centers throughout the world. I also note that most of the authors are clinical neurologists. It is important and appropriate that neurologists play a leadership role in neuro-oncology. Neurologists are in a better position than their colleagues in radiation oncology and medical oncology to understand nervous system function and how tumors affecting it differ from tumors affecting other organs of the body. They are also better able than the neurosurgeons to manage the chronic neurologic disability seen in these patients. Because of this unique perspective, clinical neurologists can serve as coordinators in the diagnosis and management of all neuro-oncological problems.

The broad scope of this book will appeal to physicians who are not specialists, but who want an up-to-date reference on all aspects of neuro-oncology. And it will appeal to practicing neuro-oncologists who want to get the viewpoint of an expert on a particular problem. I hope it will also serve as an inducement for young physicians and scientists to become interested in this most important discipline. As I have indicated before, one role of highly specialized institutions such as Memorial Sloan-Kettering Cancer Center is to train physicians who can then disseminate their knowledge to less specialized institutions. This book indicates that we are fulfilling that role.

***Jerome B. Posner, MD***

# PREFACE

Neuro-oncology has evolved substantially as a clinical and research discipline over the past few decades. Initially the province of isolated devotees, it has become a well-recognized subspecialty of neurology, oncology, and neurosurgery. The Society for Neuro-Oncology, founded just five years ago, now has almost 1000 members. Most tertiary care hospitals have staff physicians who consider themselves neuro-oncologists. These physicians typically are involved in the evaluation and management of neurologic complications of systemic cancer and its treatment, as well as of primary brain tumors. Neurologic complications occur in a substantial proportion of cancer patients, often present complex diagnostic and management problems, and commonly have a major impact on quality of life.

Simultaneously, improvements in and the widespread availability of such diagnostic studies as magnetic resonance scanning, as well as market forces, have resulted in most patients with neurologic complications of cancer receiving treatment outside of the tertiary care setting. Many medical and radiation oncologists have little formal training in the evaluation of neurologic symptoms. Conversely, most neurologists see relatively few cancer patients and do not have time to keep abreast of technological and pharmacological advances in cancer management. These circumstances contribute to the risk that some patients may not have access to a desirable level of expertise.

The principal aim of this work is to provide clinicians from various backgrounds and levels of training with a reference to help focus the differential diagnosis, diagnostic strategy, and treatment plan for the cancer patient with neurologic symptoms and findings. The volume begins with an overview of the field of neuro-oncology. Several chapters on interpretation and management of common neuro-oncologic symptoms follow. Subsequent sections contain chapters on the direct and indirect neurologic complications of cancer as well as complications of therapy. After a chapter reviewing the role of neuroimaging in the diagnosis of neuro-oncologic disease, the final section focuses on the spectrum and management of neurologic disease in patients with cancer of specific organs. Although there is necessarily some overlap between these chapters and the earlier, more general chapters, this structure allows the reader the flexibility of approaching a clinical problem either from the symptoms or in the context of the patient's known diagnosis of malignancy.

Our great hope is that in broadening and deepening the familiarity of clinicians with the range and management of neuro-oncologic diagnoses we may improve the quality of care for cancer patients. The increased confidence and competence of the treating physicians in securing a diagnosis, selecting a treatment plan, and communicating prognosis should translate into increased peace of mind and quality of life for patients and their loved ones.

***David Schiff,*** *MD*

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Patrick Wen, Jerry Posner, Lisa DeAngelis, Kathy Foley, and Brian O'Neill have served as role models of consummate clinical and academic neuro-oncologists and have provided support, encouragement, and enthusiasm. I am also indebted to the individual chapter authors for their skilled efforts in providing fresh topical reviews. Agnes Zachoszcz provided requisite organizational and secretarial assistance with unflagging good cheer and competence. The editors at Humana Press have been patient and helpful at every turn. Most of all, I would like to thank my patients, my family, and Tanya Nezzer, MD, for all they have taught me and for allowing me to do what I love.

***David Schiff, MD***

I would also like to thank all the authors for their willingness to contribute to this book, despite their busy schedules, the editors for their support and encouragement, and Suzanne Markloff for administrative and secretarial assistance. I am especially grateful for all the work that David Schiff did to make this book possible and for his friendship over the years. I would like to dedicate this book to my parents Hsiang-Lai Wen, MD and Grace Wen and to my family, May, Katherine, and Jessica.

***Patrick Wen, MD***

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# Part I Overview

# 1 The Prevalence and Impact of Neurologic Disease in Cancer

CHARLES J. VECHT, MD, PHD

## INTRODUCTION

Interest in neuro-oncology has increased rapidly over the last 30 years, and subspecialties have emerged within the fields of neurology, neurosurgery, radiotherapy, and medical oncology. Each of these specialties deals with different aspects and has made important contributions to this new branch of oncology. The principal practitioners of medical neuro-oncology, in contrast to surgical neuro-oncology, are neurologists and occasionally medical oncologists. Medical neuro-oncologists focus their attention on diagnosis, nonsurgical therapy (including symptomatic treatments and chemotherapy), and follow-up of neuro-oncological disorders. By training, neurologists have the asset of being well-equipped to localize and interpret neurological signs and symptoms and are familiar with diagnosing and treating disorders of the nervous system. Among the oncological subspecialties, neuro-oncology has become a recognized area. Thus, the field of neuro-oncology can be viewed from two different angles, either as a subspecialty of one of the mother specialties, be it neurology, neurosurgery, radiotherapy, or medical oncology or, alternatively, as a subspecialty of oncology.

Multidisciplinary care is one of the hallmarks of neuro-oncology, reflecting the involvement and contributions of professionals from several disciplines. Neuro-oncology patients often need surgery, radiotherapy, systemic chemotherapy, and symptomatic care necessitating the judicious use of anticonvulsants, glucocorticoids, and opioid or nonopioid analgesics. One attribute of the medical neuro-oncologist is the capability to oversee the potential advantages and disadvantages of the various therapeutic options. This enables the creation of a comprehensive treatment plan consisting of one or more oncological modalities. Unfortunately, most neuro-oncological diorders cannot currently be cured. Therefore, maintenance or improvement of the quality of life of the patient is of utmost importance. This mandates careful follow-up and, particularly for clinical research, application of scales for measuring quality of life. Separate scoring systems have been developed to measure cognitive function, physical independence, and general well-being for patients with primary brain tumors or with brain metastasis *(1–3)*.

Medical neuro-oncology can grossly be distinguished in the areas of:

1. Primary brain tumors;
2. Neurological complications of cancer; and
3. Pain.

Each of these domains represents a large field, making it a daunting task for the practicing neuro-oncologist to master the entire discipline with confidence.

The relevance of neuro-oncology extends to general neurologists. Neurologists working in general practice are frequently confronted with neuro-oncological consultations. Approximately 200 patients die from cancer each year per 100,000 inhabitants, of whom 15% or more develop brain metastasis. One may thus expect that the average neurologist serving a population of 50,000 people will see 15 patients with brain metastasis. Apart from metastatic disease, neurologists working in general hospitals are also confronted with other complications of cancer, including metabolic or toxic encephalopathies, pain syndromes caused by radiculopathies or plexopathies secondary to tumor infiltration, and primary brain tumors.

From a primarily diagnostic field, general neurology has evolved into a specialty that is more and more oriented to applying new and proven therapies. Neuro-oncology is no exception to this. Tremendous progress in diagnostic capabilities with modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) have paralleled advances in molecular biology and innovations in neurosurgery and radiotherapy. The field of medical therapy is blossoming. Huge research efforts are directed at systemic or local delivery of chemotherapy, new modalities of immune therapy, and the nascent discipline of gene therapy

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*(4,5)*. Research-oriented neuro-oncologists have contributed greatly to the field with studies focused on understanding underlying mechanisms of abnormal cell growth, improving diagnostic tools, and evaluating new therapeutic modalities.

## NEURO-ONCOLOGY OFFERS TRAINING POSSIBILITIES FOR NEUROLOGISTS

Overall, neuro-oncology is a bewildering field with many facets. Diagnostically, it offers a wide array of acute, subacute, and chronic disorders of each part of the nervous system. These circumstances provide great opportunities for fellowship training for future neuro-oncologists in addition to improving training in general neurology. Because the range and severity of neurological signs and symptoms in neuro-oncology are on the whole more diverse and often more severe than in general neurology, rotations in neuro-oncology provide excellent teaching and training opportunities for residents in adult or child neurology *(6)*. Frequently, because of the presence of single tumor deposits within the central nervous system (CNS), the patient manifests specific signs enabling the clinician to localize the lesion accurately within the nervous system, which subsequently can be confirmed by neuro-imaging studies. These circumstances provide a perfect setting for clinical training in neuroanatomy *(7)*. Furthermore, the acute or subacute complications that many neuro-oncology patients experience create a need for rapid and accurate diagnosis followed by expeditious although considered decision-making regarding therapeutic intervention. This circumstance offers a valuable opportunity for the trainee to learn neurologic decision-making skills.

Historically, the first neurology department with a strong fellowship program completely directed at neuro-oncology arose at Memorial Sloan-Kettering Cancer Center in New York under the direction of Jerome Posner. Dr. Posner has trained many second generation neuro-oncologists, who in turn have set up neuro-oncology clinics in university hospitals, in cancer clinics, or in general hospitals and have provided training opportunities in neuro-oncology *(8)*. That a majority of the authors in this volume did fellowship training at "Memorial" reflects one important aspect of his many contributions to the field.

## PRIMARY BRAIN TUMORS

Traditionally, the care of brain tumors has been in the hands of neurosurgeons. However, the interest of medical neuro-oncologists in primary brain tumors has grown substantially over the last 15–20 yr. Improved diagnostic capabilities with neuroimaging, neuropathology, and molecular characterization of tumors as well as improved treatment options have helped foster this interest. We now have substantial insight into the genetic make-up of gliomas.

Substantial recent refinements in neurosurgical technique include the use of stereotactic biopsy and improved resections with the application of cortical mapping and image guidance with MRI, including real-time MRI. Improvements in radiotherapy include stereotactic radiosurgery, fractionated stereotactic radiotherapy, and the use of three-dimensional conformal techniques. Systemic chemotherapy has been extensively tested in a multitude of clinical trials, albeit with modest results. Although progress improving the outcome of glioblastoma with chemotherapy has been painfully slow, benefits for anaplastic astrocytomas are more clear-cut *(9)*. Options for systemic chemotherapy have expanded with the recent approval of temozolomide, a new alkylating agent tested in recurrent anaplastic astrocytoma and glioblastoma multiforme *(10)*. Another major breakthrough in the treatment of gliomas has been the recognition of the remarkable sensitivity of anaplastic oligodendrogliomas to systemic chemotherapy *(11)*. Contributions from medical neuro-oncologists were also seminal in demonstrating efficacy of combined radiotherapy and systemic chemotherapy for primary CNS lymphomas and in improving the diagnosis and treatment of leptomeningeal carcinomatosis *(12–14)*.

Pediatric neuro-oncology is a field in itself, primarily devoted to the treatment of primary brain tumors, which represent the second most common cancer in childhood. Interestingly, the spectrum of primary brain tumors in childhood demonstrates—apart from the gliomas—a much larger variety of histologies including medulloblastomas and other primitive neuro-ectodermal tumors, germ cell tumors, craniopharyngiomas, which all occur relatively rarely in adults.

Neurological complications of cancer are common and include metastatic and nonmetastatic complications of cancer. In one study examining neuro-oncology consults at Memorial Sloan-Kettering Cancer Center, fewer than half of the patients undergoing consultation had metastatic involvement of the nervous system. The most common reasons for consultation were back pain (18.2%), altered mental status (17.1%), and headache (15.4%). The most common neurological diagnosis was brain metastasis (15.9%), followed by metabolic encephalopathy (10.2%), pain associated with bone metastases only (9.9%), and epidural extension or metastasis of tumor (8.4%). In undiagnosed headache, 61% had a nonstructural cause, including migraine, tension headache, or headache related to systemic illness (e.g., fever, sepsis) *(15)*. In the realm of neurological complications of cancer, the rationale of whether and when to apply whole brain radiation therapy for brain metastasis has been tested prospectively *(16,17)*. Likewise, the optimum dose of glucocorticoids to control vasogenic brain edema has been determined *(18)*.

Finally, neuro-oncology includes the subject of paraneoplastic disease of the nervous system, which represents a rare, though most intriguing part of neuro-oncology. At the time of presentation with these syndromes, two-third of patients are not known to have cancer, and therefore the general neurologist is usually the first to make the diagnosis. Paraneoplastic disorders of the nervous system are characterized by a host of neurological signs and symptoms, often severely incapacitating the patient. Clinical diagnosis without the aid of specific auto-antibodies or the presence of cancer can be difficult. The challenge of making a timely diagnosis of paraneoplastic disease before damage to the CNS has become irreversible is formidable. New insights in cross-reacting antibodies with antigens expressed both by tumor cells and neurons provide possibilities for exploring new therapies by either vaccination of modified antigens or modulating the immune system *(19)*.

## NEUROTOXICITY

Neurotoxicity or iatrogenic disease of the nervous system is an emerging area of neuro-oncology. The persistent nature of cancer often necessitates application of therapies at the upper dose range of tolerability. This often implies a calculated risk regarding toxicity. Nevertheless, the application of oncological therapy is frequently restricted in efficacy by toxicity. Neurotoxicity may manifest with dementia or with focal or diffuse signs of neurological damage and is one of the major concerns in applying treatment *(20–23)*. Radiation therapy to the brain or spinal cord is delivered in doses with a complication rate of a few percent, which is considered acceptable *(24)*. The short median life expectancy of patients with brain metastasis or malignant glioma ensures that late toxicity of radiation therapy does not often become manifest. However, in long-term survivors the incidence of dementia secondary to whole brain radiation therapy may be ≥ 5% *(25)*. Similarly, prophylactic radiation therapy of the brain to prevent metastatic complications in leukemia and small cell lung cancer carries serious drawbacks *(26)*.

These delayed complications emphasize the fact that only through carefully designed studies and close follow-up can improvements be achieved. In radiation oncology such clinical trials have resulted over the years in well-founded choices on appropriate target volume and fractionation schedules in order to achieve optimal results both in terms of efficacy of tumor control and minimal early and late damage to the brain or spinal cord. Some forms of neurotoxicity can be reversible. Most of the reversible neurotoxicities have to do with acute or subacute organ failure secondary to the direct effects of cancer or the immediate effects of therapy. Moreover, chemotherapy and immunotherapy may lead to early and often reversible or late and often irreversible damage to the brain, spinal cord, or peripheral nerves. Examples of reversible neurotoxicity include metabolic and toxic encephalopathies. Sensory neuropathies constitute another example of neurotoxicity dealt with by neuro-oncologists. Because these syndromes can be studied prospectively, they may also function as a model for testing nerve growth factors in preventing or treating neuropathies *(27,28)*.

## PAIN

About 80% of cancer patients suffer from pain, mainly in late stages of disease. With the exception of headache, facial pain, and to a lesser extent peripheral neuropathy, most neurologists have not focused their clinical research efforts on pain. Neuro-oncology serves as an exception; major advances in the field of cancer pain have come from neuro-oncologists, many of whom served in the Neurology department at Memorial Sloan-Kettering Cancer Center *(29,30)*. Among cancer patients referred to neurologists or neuro-oncologists are those with suspected metastatic spinal cord compression and radiculopathies or plexopathies secondary to tumor involvement. In cancer patients suffering from pain, about 40% have pain that includes a neuropathic component, and in almost 25% the pain syndrome is directly related to tumor involvement of nervous tissue mainly of nerve roots or plexus *(31)*.

## PALLIATIVE CARE

Neuro-oncological complications of cancer often occur in the late stages of cancer. Apart from direct involvement of the nervous system as in brain metastasis, spinal cord compression, or leptomeningeal disease, patients may suffer from metabolic encephalopathies related to organ failure or from toxic encephalopathies secondary to administration of chemotherapy, opioids, or other sedative agents. Frequently, these complications occur concurrently, and at a time that administration of further anti-tumor therapy would be futile. For proper management of these symptoms, recognition of concurrent neurological and medical disorders is crucial. Because of his or her acquaintance with both cancer and disorders of the nervous system, the medical neuro-oncologist is well-equipped to recognize and manage pain and other distressing symptoms in the setting of impaired consciousness or other signs and symptoms of the nervous system. Thus, the neuro-oncologist is in a position to assist in palliative care, improving patient management in the late and complicated stages of cancer *(32)*.

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# Part II Neurologic Symptoms

# 2 The Epidemiology and Management of Seizures in Patients with Cancer

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## INTRODUCTION

Despite the increasing incidence of brain tumors and a corresponding increase in basic and clinical research, the overall survival of patients with primary or metastatic central nervous system cancer has not changed substantially over the last 20 years *(1,2)*. In these diseases, where cures are rare and symptom management is often the most valuable service the physician can provide, treatment of seizures assumes major importance. Seizures are common in patients with brain tumors, and a single seizure, or even the fear of a seizure, can profoundly impair quality of life. In addition to the potential for injury from seizures, seizures can lead to the forfeiture of driving privileges and employment. Seizures and their sequellae can mimic tumor progression and prompt unwarranted diagnostic interventions. Anticonvulsant therapy and the monitoring which therapy necessitates can be inconvenient and uncomfortable, can produce side effects that mimic or exacerbate disease-related symptoms, and can interfere with therapy for the underlying tumor. For all of these reasons, an understanding of the epidemiology, clinical manifestations, and available treatments for patients with brain tumors and seizures is essential.

## EPIDEMIOLOGY OF SEIZURES IN PATIENTS WITH BRAIN TUMORS

More than 34,000 patients in the United States were diagnosed with primary brain tumors, and more than 170,000 developed brain metastases in 1998 *(1–5)*. Overall, 20–40% of adults with primary brain tumors experience at least one seizure prior to the diagnosis of their tumor, and another 20–45% will develop seizures at some point following diagnosis. Both numbers vary appreciably, however, depending on the histology of the underlying tumor (Table 1) *(2,6,20)*. In general, slow-growing, histologically low-grade primary brain tumors are associated with the highest incidence of seizures, and seizure incidence falls with increasing grade *(20–29)*. Fifty to eighty percent of children with supratentorial tumors ultimately develop seizures, reflecting the frequent low-grade histology of pediatric hemispheric tumors *(30,31)*. Tumors are discovered in roughly one third of patients undergoing temporal lobe surgery for medically intractable seizures *(32–36)* and in 28% of those undergoing surgery for seizures with extratemporal foci; such tumors are virtually always low-grade *(37)*. Approximately 20% of patients with brain metastases present with seizures, and an additional 20% develop seizures later in their course. Multiple metastases and hemorrhagic metastases may be associated with a higher incidence of seizures. Patients with neoplastic meningitis alone present with seizures in 15% of cases, and patients with both parenchymal brain metastases and neoplastic meningitis may be especially likely to experience seizures *(38–40)*.

Regardless of tumor or patient characteristics, seizures are much more common with supratentorial than with infratentorial tumors, and among supratentorial tumors, much more common with superficial and cortical lesions (63% of cases) than with tumors located within the basal ganglia or entirely within the white matter (29% of cases) *(7,20,23,29,41)*. For cortical tumors, seizure frequency increases with increasing proximity to the Rolandic fissure, and early-onset seizures are more frequent with increasing proximity to the central sulcus *(42,43)*. In contrast, tumors located in the occipital lobes are less likely to be associated with seizures.

From a diagnostic standpoint, tumors are an increasingly common cause of seizures with increasing age (Fig. 1) and often provide the first indication of an underlying tumor (Table 1). The type of tumor most likely to underlie new onset seizures varies according to patient age (Table 2). The likelihood of a tumor etiology for new onset seizures also increases when the seizures are complex-partial and when abnormalities on the neurologic examination are present *(43–45)*. Thus neuroimaging studies are rarely abnormal and in many centers are not routinely performed in children with clinically typical primary generalized or febrile seizures *(46)*. While still relatively

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**Table 1**
**Frequency of Seizures by Tumor Histology**

| | *Incidence of seizures* | |
|---|---|---|
| *Tumor histology* | *At presentation* | *Overall* |
| Glioblastoma multiforme | 30–40% | 40–60% |
| Anaplastic astrocytoma | 40–50% | 60–70% |
| Astrocytoma | 60–95% | |
| Oligodendroglioma | 75% | 85% |
| Meningioma | 30–40% | 50–60% |
| Medulloblastoma | 1–2% | 2–3% |
| Brain metastasis | 20% | 25–40% |
| Neoplastic meningitis | 14% | 19% |

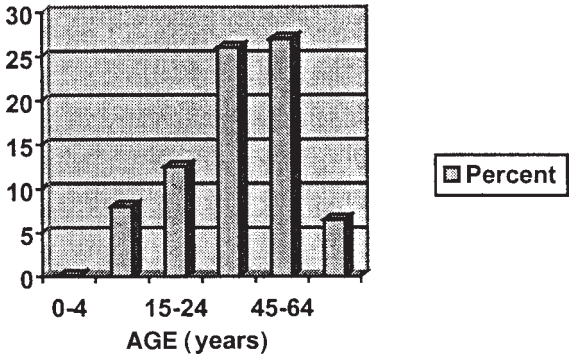


**Fig. 1.** Frequency of tumor as the etiology of first seizures (by age).

**Table 2**
**Frequency of Different Tumor Histologies as the Cause of First Seizures**

| *0–24 yr* | *25–44 yr* | *> 65 yr* |
|---|---|---|
| Astrocytoma | Malignant glioma | Metastasis |
| Oligodendroglioma | Metastasis | Malignant glioma |
| Malignant glioma | Meningioma | Meningioma |
| Ganglioglioma | Astrocytoma | CNS lymphoma |
| Dysembryoplastic Neuroepithelial tumor *(22,24)* | Oligodendroglioma | |

uncommon, new onset seizures in adults are more frequently associated with intracranial tumors (1.3–16% of cases) and always necessitate a brain imaging study, especially when the seizure itself or the post-ictal examination suggests a focal onset or when the inter-ictal neurologic examination is abnormal *(47–52)*. The inclusion of fluid attenuated inversion recovery (FLAIR) sequences, gadolinium enhancement, and coronal cuts through the temporal lobes may significantly enhance the diagnostic yield *(53–55)*. Even in patients with normal neurologic examinations and very longstanding epilepsy, low-grade gliomas are being identified with increasing frequency as the routine use of magnetic resonance imaging (MRI) scanning becomes more widespread *(56,57)*.

## CLINICAL FEATURES OF TUMOR-ASSOCIATED SEIZURES

As with other symptomatic seizures, the ictal and post-ictal characteristics of tumor-associated seizures depend on the location of the seizure focus and are rarely "false localizing." Several authors have emphasized the frequent association of olfactory or gustatory hallucinations with tumor, perhaps reflecting the propensity of malignant gliomas to involve the temporal lobes *(59,60)*. Increasing seizure frequency and variability in seizure phenotype may also be more characteristic of tumor-related seizures than of other seizure types. When focal seizures occur in the setting of an underlying brain tumor, associated focal neurologic findings are also usually present *(9,47–52)*. Conversely, prolonged or permanent focal deficits can occur in patients with brain tumors following seizures of focal onset *(20,61)*. Similarly, prolonged or irreversible cognitive decline may occur following generalized seizures in brain tumor patients. Seizure-induced increases in intracranial pressure, disruption of the blood-brain barrier (BBB), and elevations in excitotoxic neurotransmitter levels in patients with pre-existing abnormalities in intracranial pressure, blood-brain barrier integrity, and excitotoxic neurotransmitter levels may provide a physiologic explanation for these observations *(62,63)*.

## EVALUATION OF SEIZURES IN PATIENTS WITH KNOWN CANCER

The differential diagnosis of seizures occurring in patients with known cancer is considerably different in many respects than that of patients without an underlying malignancy (Table 3). Although seizures can assume a natural history independent of the underlying tumor, new seizures or a change in the frequency or phenotype of seizures in patients with known central nervous system (CNS) cancer often heralds tumor progression or recurrence. Therefore, a neuro-imaging study of the brain, preferably an enhanced MRI scan with FLAIR sequences, is mandatory. If the MRI provides insufficient explanation for the new seizure pattern, a lumbar puncture with a large volume cytologic examination is appropriate *(64)*. First or recurrent seizures in patients with cancer but without known CNS involvement require an identical evaluation: enhanced MRI of the brain and cerebrospinal fluid (CSF) evaluation. Even when an apparent neuroradiographic or cytologic explanation for the seizure is identified, a more extensive evaluation is still required for both groups of patients, as suggested by Table 3. Screening for metabolic derangements, infection, and potentially offending drugs (including missed or inadequate doses of prescribed anticonvulsants) is particularly important.

## TREATMENT OF TUMOR-ASSOCIATED SEIZURES: DRUG THERAPY

The potentially irreversible neurologic decline sometimes seen in patients with brain tumors and seizures, in addition to the impairment in quality of life that seizures can produce in any patient, constitute strong rationale for the aggressive treatment of seizures when they occur. The basic principles of seizure therapy, including optimum monotherapy, meticulous monitoring for toxicity, and detailed questioning to detect the

**Table 3**
**Differential Diagnosis of Seizures in Patients with Cancer**

| *Etiology* | | *Comment* |
|---|---|---|
| **Infection** | Meningitis | Listeria is common; ventricular reservoirs or shunts predispose |
| | Brain abscess | |
| | Sepsis | Usually in the setting of high fever, hypoxia, or hypotension |
| **Metabolic** | Hypomagnesemia | Common with cisplatin use, often 3–8 d after therapy; pamidronate |
| | Hyponatremia | Common following neurosurgery; also vincristine, carbamazepine, SIADH, or chemotherapy requiring co-administration of large fluid volumes |
| | Hypocalcemia | Following cisplatin or pamidronate |
| **Drug-induced** | Cisplatin | Related to electrolyte disturbances |
| | Vincristine, Etoposide | Uncommon |
| | IL-2 | |
| | Ifosfamide | Particularly in patients with renal failure or hypoalbuminemia |
| | Imipenem | |
| **Radiation-related** | Radiation necrosis *(62)* | MRI may be indistinguishable from recurrent tumor |
| **Intracranial hemorrhage** | Thrombocytopenia | Disease, chemotherapy, or drug (e.g., heparin) related hemorrhage |
| | Coagulopathy | Disseminated intravascular coagulation |
| **Tumor-related** | New or progressive disease | Including neoplastic meningitis |
| **Paraneoplastic** | Limbic encephalitis *(63)* | Rare, but most common with small cell lung cancer |

occurrence of subtle seizures, are the same for patients with brain tumors as for those with idiopathic or other seizure types. Although there is no compelling evidence suggesting the superiority of any particular anticonvulsant in the setting of tumor-associated seizures, some reasonable guidelines are possible.

Anticonvulsant side effects, including sedation, cognitive impairment, psychomotor slowing, hepatic toxicity, and bone marrow suppression, are more common in patients with brain tumors than in those without and occur at lower drug doses *(13,67–72)*. Symptoms severe enough to warrant discontinuation of medication occur in nearly one quarter of cancer patients (range: 5–38%) *(6,7,9,10,12,18)*. In addition, the drug-specific side effects of certain anticonvulsants may make those agents less optimum choices for seizure control in patients with cancer. For example, the language dysfunction seen in 10% of patients receiving topiramate *(73)*; "shoulder-hand syndrome," which occurs in nearly 20% of brain tumor patients receiving phenobarbital *(71)*; and the encephalopathy and parkinsonian symptoms which develop rarely in patients receiving valproic acid *(75–76)* may mimic the signs and symptoms of tumor progression or exacerbate tumor-related neurologic deficits. Rashes (occasionally progressing to Stevens-Johnson syndrome) occur in 14–25% of patients. Most cases have been reported with the use of carbamazepine, phenytoin, and phenobarbital, although this may in part reflect longer experience with these agents. Cranial irradiation may be implicated, although the precise mechanism is uncertain, and patients are frequently receiving decreasing doses of corticosteroids at the time the rash develops. The additional risks of immunosuppression with phenytoin and carbamazepine *(77–80)*. leukopenia with carbamazepine, and thrombocytopenia with valproic acid are considerations whose clinical importance is uncertain.

Perhaps the most concerning problem with the use of anticonvulsants in patients with cancer is the interaction of anticonvulsants metabolized by the cytochrome P-450 system ("enzyme inducing anti-epileptic drugs" or EIAEDs) with corticosteroids *(81–85)* and with many common antineoplastic agents, including cisplatinum, paclitaxel, irinotecan, topotecan, cyclophosphamide, methotrexate, adriamycin, and the nitrosoureas *(86–98)*. Induction of hepatic microsomal enzymes by EIAEDs increases the catabolism of corticosteroids and chemotherapeutic agents. Consequently, the biological effect of a given dose of dexamethasone may be less powerful in a patient receiving an EIAED, and the exposure of a patient's tumor to an antineoplastic agent ("area under the curve") may be dramatically reduced *(99)*. Conversely, these interactions may result in subtherapeutic anticonvulsant levels despite seemingly adequate doses *(100–109)*. As a result, more frequent and higher drug doses and more frequent monitoring of drug levels are often necessary, and problems with under and overdosing and consequent seizures or toxicity are more common. EIAEDs are listed in Table 4. To further complicate patient management, both the cognitive side effects of overdosing and seizures resulting from underdosing may be interpreted as evidence of tumor progression, leading to unnecessary diagnostic or therapeutic interventions. For all of these reasons, some of the newer, nonenzyme-inducing anticonvulsants (e.g., gabapentin, tiagabine, levetiracetam) *(110)* may prove to be the most attractive agents for patients with cancer, although limited experience to date precludes firm recommendations.

## TREATMENT OF TUMOR-ASSOCIATED SEIZURES: RADIATION AND SURGERY

While no formal studies have been conducted, elimination of seizures or reduction in seizure frequency has been reported following cranial irradiation *(111)* and occasionally in patients whose tumors have responded completely or partially to chemotherapy. Similar benefits have been reported following stereotactic radiosurgery and interstitial radiation implants *(112–113)*.

Randomized, controlled trials are also lacking in the area of tumor surgery, but numerous case series suggest that gross total

**Table 4**
**Currently Available Enzyme-Inducing and Nonenzyme-Inducing Anticonvulsants**

| |
|---|
| *Enzyme-inducing anti-epileptic drugs* |
| Carbamazapine |
| Oxcarbazepine[a] |
| Phenytoin |
| Fosphenytoin |
| Phenobarbital |
| Primidone |
| Felbamate |
| *Nonenzyme-inducing anti-epileptic drugs* |
| Valproic acid |
| Gabapentin |
| Lamotrigine[c] |
| Levetiracetam |
| Tiagabine[c] |
| Topiramate[b] |
| Zonisamide[c] |
| Klonopin |
| Vigabatrin |

[a]Enzyme induction limited and less potent than carbamazapine.
[b]Induces catabolism of ethinyl estradiol but inhibits metabolism of phenytoin.
[c]Metabolized by the P-450 system, low enzyme-inducing potential, but experience is limited to date.

resection of tumors can lead to improved seizure control or elimination of seizures. Benefits are more common and more durable in patients with histologically low-grade tumors, in whom 65–80% become seizure-free; one-third of all patients can be weaned off anticonvulsant medication entirely *(31, 115–121)*. According to some (but not all *[120]*) authors, this number increases to more than 90% of all patients if an extensive resection including lobectomy and removal of medial temporal and frontal lobe structures is performed *(115,116,122)*. The duration of pre-operative seizures, epileptiform activity on the postoperative electroencephalogram, and the absence of a focal lesion identified on the pre-operative MRI scan may be predictors of poorer postoperative seizure outcome *(114, 117,120)*. Even patients with high-grade gliomas become seizure-free in 30–60% of cases following surgery; however, the significance of this is less clear since such patients are almost always maintained on anticonvulsant medications *(11,31, 121,123)*. Similarly, in modern series more than 60% of patients with meningiomas are seizure-free postoperatively *(124,125)*.

There are several explanations for the failure of surgery to eliminate seizures in all patients. Incomplete tumor resection is the most obvious reason. Tumor recurrence and the development of postsurgical seizure foci related to reactive changes and scarring represent additional common explanations. Another possibility is that the offending epileptogenic focus or foci are frequently located at considerable distance from the tumor, in completely tumor-free areas of brain *(126)*. In such patients, these tumor-free epileptogenic foci have been found to contain significantly lower concentrations of GABA and somatostatin neurons than in adjacent normal brain *(127–129)*. This apparent tumor-induced deafferentiation and loss of inhibitory neurotransmitters in areas of brain remote from the tumor may account for many of the apparent failures to control seizures in patients undergoing gross total tumor resections. These observations have led some to advocate performing both a tumor resection and additional resections of seizure foci identified by intraoperative electrocorticography *(33,130–133)*.

## OUTCOME IN TUMOR-ASSOCIATED EPILEPSY

The prognosis for seizure control in patients with tumor-associated seizures has not been examined rigorously. The necessity of incomplete tumor resection in many patients, the presence of seizure foci remote from the identified tumor, difficulties in achieving and maintaining therapeutic anticonvulsant levels in patients with cancer due to multiple drug interactions and increased sensitivity to anticonvulsant side effects, and the multiple alternative causes of seizures in the cancer population all conspire against optimum seizure control. Consequently, one-half of patients with gliomas experience recurrent seizures during the course of their disease, while 11% of patients with brain metastases and 19% of patients with neoplastic meningitis suffer recurrent seizures during their substantially shorter lifetimes *(20)*. Seizures that develop late in the clinical course are typically more responsive to treatment than those that occur early *(9)*. Seizures that are initially controlled but return at the time of tumor recurrence are also relatively refractory to treatment *(134)*.

In some studies, presentation with a seizure constitutes a favorable prognostic sign for survival in patients with gliomas *(135–137)*. In part this observation reflects the overrepresentation of patients with lower-grade tumors in the population of glioma patients presenting with seizures. Nevertheless, even among patients with malignant gliomas, presentation with a seizure may constitute a favorable prognostic sign. One explanation is that seizures typically result in more expeditious detection and treatment of the underlying tumor; alternatively, tumors presenting with seizures are more commonly cortically based and potentially more amenable to resection than deep-seated lesions.

## ANTICONVULSANT PROPHYLAXIS IN PATIENTS WITH BRAIN TUMORS

Although adequate studies are lacking, anticonvulsant therapy in patients with tumor-associated epilepsy does appear to reduce frequency of recurrent seizures. Anticonvulsant prophylaxis (the use of anticonvulsants to prevent seizures in patients who have never had a seizure) constitutes an important special issue about which there has been much debate and substantial variation in practice both between and within the subspecialties of neurology, neurosurgery, oncology, and radiation oncology *(2,7)*. Because seizures are common in patients with brain tumors, because seizures add to the fear and limitations with which cancer patients already contend, and because of the risk of permanent neurologic injury following a seizure in patients with brain tumors, prevention of seizures is a desirable goal. If drugs effectively prevented first seizures and were associated with a modest risk of side effects, the prophylactic use of anticonvulsants would be very attractive. Unfortunately, the potential side effects of anticonvulsants in cancer patients are neither uncommon nor insubstantial. Moreover, the consistent evidence from four randomized, controlled clinical trials

and eight retrospective studies demonstrates that anticonvulsant prophylaxis is not effective in preventing first seizures *(138)*. The explanation for this finding is uncertain. Therapeutic anticonvulsant levels are difficult to achieve in many patients, but even when therapeutic levels were documented at the time of initial seizures, anticonvulsant prophylaxis was not effective *(7)*. Alternatively, the mechanisms that initiate first seizures may differ from those that sustain recurrent seizures in patients with epilepsy (and for which anticonvulsant therapy is beneficial). This conclusion is the same whether the underlying tumor is primary or metastatic, and regardless of tumor histology. Pretreatment patient characteristics such as age, performance status, number of brain metastases, brain surgery for the tumor, tumor location, or EEG features have no influence on the success of prophylactic therapy. A number of issues remain unresolved, including the possibility of a very small prophylactic effect in certain subsets of patients, and the potential benefit of newer anticonvulsants. Nevertheless, the currently available evidence is sufficient to support a clear recommendation against the routine use of prophylactic anticonvulsants in patients with brain tumors.

## SPECIAL ISSUES IN PATIENTS WITH TUMOR-ASSOCIATED SEIZURES

The issue of anticonvulsant withdrawal arises frequently in patients with brain tumors who have been placed on an anticonvulsant at the time of diagnosis or prior to craniotomy, but who have never experienced a seizure. Once again, there have been no formal studies to guide clinical practice. Despite compelling evidence against the use of anticonvulsants in this setting, many clinicians are reluctant to withdraw anticonvulsants from stable patients. While this reluctance is understandable, our own practice has been to carefully taper and ultimately discontinue anticonvulsants in any patient who is receiving truly prophylactic anticonvulsant therapy and who has had drug-related side effects. We define "side effects" broadly, and include subtle cognitive deficits, anorexia or other gastrointestinal symptoms, and the risk of interactions with chemotherapeutic agents when enzyme-inducing anticonvulsants are being used in patients also receiving cytotoxic therapy. This approach requires an exhaustive clinical evaluation to exclude the possibility of subtle seizures, which are frequently unreported by patients and unrecognized by their physicians. When even a single, very brief, partial seizure has occurred, we believe that prolonged if not life-long anticonvulsant therapy is necessary except in the exceptional circumstances of tumor cure or, possibly, complete resection of a low-grade tumor and associated epileptogenic foci. This approach also requires a careful review of the potential risks and benefits of anticonvulsant withdrawal with the patient and patient's caregivers in light of current knowledge.

A second common concern in patients with tumor-associated epilepsy is whether driving is permissible. Frequently the greatest barrier to driving in patients with CNS cancer is not the potential for seizures, but the neurologic and non-neurologic deficits associated with their disease and its treatment. When seizures are the sole barrier to operating a motor vehicle, decisions must be guided by state-specific legal statutes. In patients who have never had a seizure, anticonvulsant prophylaxis does not reduce the risk of first seizures and should not be a requirement for driving.

## SUMMARY

Seizures are common in patients with CNS cancer, although the exact frequency of seizures depends considerably on the location, growth rate, and histology of the tumor. The occurrence of a first seizure in an adult mandates a neuro-imaging study of the brain, preferably a gadolinium-enhanced MRI scan with FLAIR sequences. Focal seizures in children, particularly in the presence of post-ictal or inter-ictal deficits, may merit a similar evaluation. In patients with known cancer, an MRI scan with FLAIR images and contrast enhancement is the optimum neuro-imaging test. Extensive studies to evaluate infectious, metabolic, and drug-related etiologies are also critical, and in many cases a CSF examination is indicated. While surgical therapy of tumor-associated seizures holds promise, particularly for patients with low-grade primary brain tumors, intraoperative electrocorticography may be required for optimum seizure control, and postoperative anticonvulsant medication is usually necessary. Anticonvulsant medications are associated with more frequent and often more severe side effects in patients with cancer than in patients with other causes for their seizures. These side effects include important interactions with corticosteroids and chemotherapeutic agents, and should influence the choice of anticonvulsant agents, and the monitoring schedule of patients under treatment. Prophylactic anticonvulsants are not effective, and should not be used routinely.

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# 3 Corticosteroids in Neuro-Oncology

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## INTRODUCTION

This chapter has two distinct parts. The first will deal with the clinical aspects of the use of corticosteroids in neuro-oncology. The second will review what is known of the biological basis of the remarkable effects of this class of drugs upon peritumoral brain edema. Unfortunately, despite decades of work, we still know all too little. Most of what we do clinically with corticosteroids is empirical. The absence of a full understanding of their mechanism of action has blocked the search for drugs with similar benefit but that lack their troublesome side effects. Nonetheless, this deficiency in our understanding of how steroids work does not detract from the tremendous impact that this class of drugs has had upon the care of patients with brain tumors since they were introduced for control of tumor-induced edema nearly 40 years ago.

The original paper is worth reading. The now-retired neurosurgeon Joseph Galicich did the work with Lyle French and J.C. Melby and published it in 1961 *(1)*. While there were fragmentary ideas about the use of steroids for brain edema, perhaps as early as 1933 *(2)*, it was not until this article appeared that there was any real awareness of the importance of steroids for brain tumor patients. A virtual revolution in brain tumor care, now remembered by only a few, occurred immediately. Most neuro-oncologists know of this 1961 article, but we suspect few have actually read it. It was published in an obscure journal called *The Journal Lancet*, not *Lancet* of international fame. The latter is usually given the credit in bibliographies for publishing this seminal article, surely because of the importance of the observations. (*The Journal Lancet* was an earlier name of the journal of the Minnesota State Medical Society, which is not readily available in many medical libraries.) It is of some historical interest to note that the rationale for Galicich's work was not to control cerebral edema in brain tumor patients. Instead, he and his colleagues were after chemotherapeutic response. They had some laboratory evidence that large doses of corticosteroids would inhibit the growth of experimental brain tumors. They gave high doses of corticosteroids to 14 brain tumor patients in conjunction with angiography and promptly observed that within 24 h the patients were remarkably improved in a way that could not be explained by any chemotherapeutic effect. They used dexamethasone, which had first been synthesized in 1958, because it had a low index of sodium and water retention compared to the other corticosteroids then available. It has since been the favored drug in neuro-oncological practice, and it is with this drug that this chapter will primarily deal.

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## CLINICAL NEURO-ONCOLOGIC USAGE OF STEROIDS

Prednisone, prednisolone, dexamethasone, and methylprednisolone are active antineoplastic agents chiefly against hematologic malignancies. In addition to the usage of dexamethasone for peritumoral edema in primary and secondary brain tumors, glucocorticoids are also used to control pain, edema, nausea and vomiting, as well as to improve appetite. They also may be effective in controlling pain in patients with carcinomatous meningitis and are effective antineoplastic agents in primary central nervous system (CNS) lymphoma. Dexamethasone has become the drug of choice in neuro-oncology, probably more because of its long half-life (Table 1) than the original rationale of Galicich et al. *(1)*.

There has been only one small prospective clinical trial to determine dexamethasone's best dosage in neuro-oncology *(3)*, but four decades of experience has led to fairly standardized usage. Several important points deserve emphasis. Large doses of dexamethasone must be given intravenously when a patient presents with acute neurological symptoms or signs suggestive of the presence of a brain or spinal cord tumor. If the signs and symptoms are severe with potentially dangerous increased intracranial pressure, 50–100 mg intravenously (IV) is required before starting maintenance dosage. In situations when the tempo of evolution or degree of symptoms is less critical, there

**Table 1**
**Steroid Comparision**

| *Glucocorticoid* | *Approximate equivalent dose (mg)* | *Biologic half-life (h)* | *Relative mineralo-corticoid activity* |
|---|---|---|---|
| Cortisone | 25 | 8–12 | ++ |
| Hydrocortisone | 20 | 8–12 | ++ |
| Prednisolone | 5 | 18–36 | + |
| Prednisone | 5 | 18–36 | + |
| Methylprednisolone | 4 | 18–36 | 0 |
| Dexamethasone | 0.75 | 36–54 | 0 |

is no need for intravenous administration. Oral dexamethasone at a dosage of 4–12 mg orally twice a day is usually adequate after an oral loading dose of 24 mg. The clinical effects usually begin within hours, with most patients improving symptomatically within 24–72 h. Dexamethasone is well-absorbed orally and has a remarkably long biological half-life (Table 1). It is therefore unnecessary to dose patients more than twice daily. Because it is conventional neurosurgical practice to use an every 4- or 6-h IV dosing schedule, many of these patients are discharged on the same schedule for oral medication. This is very difficult for patients to comply with at home and is not necessary given what is known about dexamethasone's long biological half-life.

Neuroimaging studies may show a dramatic improvement in peritumoral edema and mass effect (Fig. 1), although it may lag behind clinical improvement and not show a decrease in edema for at least 1 wk *(4)*. Nonfocal deficits such as headache and lethargy tend to respond better than focal deficits. Dexamethasone can always be tapered down or even discontinued in a few days if the initial vigorous treatment proves unnecessary. In patients who have evidence of spinal cord compression we usually use high doses of dexamethasone at 50–100 mg initially. While no controlled study in tumor patients documents that 50–100 mg is better than smaller doses, high-dose steroids have been shown in traumatic cord injury to be of benefit, and moreover no clear additional patient risk occurs from using larger doses as compared to smaller doses in the acute setting. There is little to lose and much to be gained by treating patients with known cancer who complain of sensory loss or weakness in the legs before definitive diagnosis. If myelopathy due to cord compression is excluded with appropriate neuroimaging, then dexamethasone can be discontinued.

If primary CNS lymphoma is a diagnostic consideration, dexamethasone should be withheld unless cerebral edema and mass effect is clinically significant. The reason for this is the prompt antineoplastic effect of dexamethasone. In some cases the response can be so dramatic as to impact on the ability to biopsy the tumor. In only a few days the enhancing tumor can improve to a degree that it may not appear on the localizing scan done prior to biopsy.

In patients with brain tumors who have had gross total resections or large subtotal resections, dexamethasone can usually be tapered down and discontinued within a week or two after surgery. In that patient population there is usually no need for dexamethasone through radiotherapy. In patients who are not able to undergo surgical resection, or who have significant residual tumor, dexamethasone can be useful in controlling edema during radiation therapy. Dexamethasone should be maintained throughout radiation therapy in patients being treated for spinal cord compression. The dose can then usually be tapered over the following 2–3 wk depending on stability or improvement in neurological function.

## TOXICITY

The side effects and complications that can occur with all of the glucocorticoids may be bothersome and reversible or cause significant disability. While a detailed review of the many side effects of steroids (Table 2) is beyond the scope of this chapter, a few merit discussion.

Most patients receiving corticosteroids are routinely treated with medications (usually histamine H2 antagonists) to reduce the risk of gastric ulcer and hemorrhage, but an association between steroid usage and peptic ulceration has not been clearly shown. No prospective trials have been done. In retrospective analyses of clinical trials evaluating corticosteroid usage in a number of diseases, no significant association between steroid usage and gastrointestinal bleeding could be found *(6–8)*. If an association between corticosteroids and peptic ulceration and bleeding does exist, the incidence must be very low. We believe that the use of H2 antagonists is not justified in all patients, unless new clinical data become available. The usage of H2 antagonists should probably be restricted to patients with a history of, or who are at risk for, peptic ulceration or gastrointestinal bleeding. This includes those who are in the immediate postoperative period and perhaps those patients receiving unusually high doses of corticosteroids. In most patients, twice daily corticosteroid dosing with meals may reduce the risk of possible stomach irritation and may spare patients the added side effects and expense of H2 antagonists. In a personal series of 100 brain tumor patients on that schedule, with dosages varying depending on neurologic need, none developed gastrointestinal bleeding *(9)*. Only three of those patients were on H2 antagonists, only because they had a prior history of stomach or duodenal ulcer disease.

Steroid myopathy is troublesome at times, impacting significantly on the quality of function and life of patients with cancer. It is the most common side effect of dexamethasone in patients with primary brain tumors and occurs in as many as 10.6% of those patients *(9,10)*. The majority of patients develop weakness between the ninth and twelfth weeks of treatment *(10)*. Individual susceptibility varies dramatically. Some patients develop significant weakness after taking a low dose of steroids for only a few weeks while other patients receive large doses for months to years and never develop symptoms. Those who do not develop myopathy also seem to be patients who do not become cushingoid.

It is thought that fluorinated glucocorticoids, such as dexamethasone, are more likely to produce muscle weakness and atrophy than nonfluorinated glucocorticoids such as hydrocortisone or prednisone *(11–14)*. While there may be improvement in steroid myopathy with substitution of a nonfluorinated glucocorticoids such as prednisone for dexamethasone, prednisone

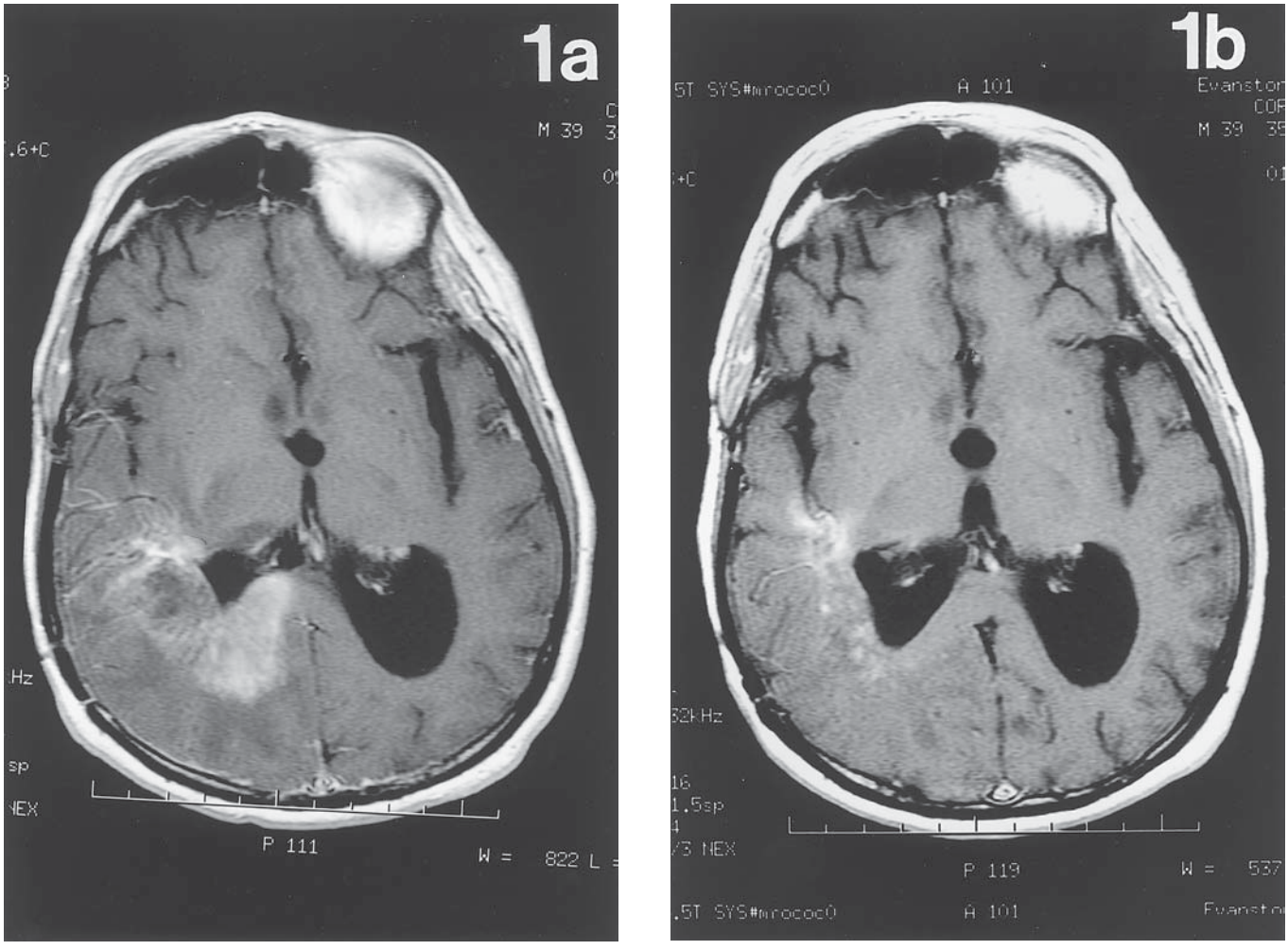


**Fig. 1.** **(A)** MRI (T1 postgadolinium) of a patient with recurrent glioblastoma, on a low-dose (4 mg twice a day) of dexamethasone, whose symptoms were worsening. **(B)** MRI (T1 postgadolinium) of the same patient 8 d after increasing the dexamethasone to 20 mg twice a day. There were no other changes in management.

may not be as effective in controlling brain edema. One of us (N. V.) attempted to use high-dose alternate day prednisone in place of daily dexamethasone in six patients. Only in one of those was alternate day prednisone as effective as the previous equivalent dosage of dexamethasone. One of the six did so poorly that the switch may have contributed to his decline and death.

Steroid myopathy may improve if the drug can be withdrawn or the dose reduced *(15)*. Recovery may take a few months after discontinuation of the steroid. In animal models, muscle activity may reduce steroid-induced muscle wasting, suggesting the possibility that exercise or a physical therapy program may help reduce the severity of myopathy in patients receiving steroids chronically *(16)*.

## DRUG INTERACTION

Phenytoin increases the metabolic clearance rate of cortisol and dexamethasone and reduces the plasma half-life of dexamethasone by up to 50% *(17–19)*. It has been postulated that this may be a mechanism for a protective effect of phenytoin in reducing the risk of development of steroid myopathy *(10)*. Carbamazepine and phenobarbital may also induce the hepatic metabolism of dexamethasone *(20)*. Patients with brain tumors on anticonvulsants may therefore need a higher dose of dexamethasone to control brain edema.

## MECHANISMS OF ACTION

In 1967, in a paper entitled "Neuropathological Aspects of Brain Edema" *(21)*; Klatzo proposed that his topic should be divided conceptually into two major and usually distinct types, *vasogenic* and *cytotoxic*. This article, like the original description of the use of dexamethasone in brain tumor patients by Galicich et al. *(1)*, is still worth reading. The earlier literature on the subject was very confusing; this classic article proved to be extremely important for future thinking about the subject. Earlier in the electron microscopic era, it was thought that edema around brain tumors was confined to the intracellular space and specifically to glial processes.

However, it soon became known that artifacts caused by hypertonic fixatives delayed full recognition of an even more important space in which fluid accumulates adjacent to brain tumors, the *inter*cellular space. Intercellular edema is obvious in white matter. In lightly myelinated gray matter structures, such as the thalamus, intercellular swelling is very inconspicuous.

**Table 2**
**Complications of Corticosteroid Therapy**

| *Type* | *Common* | *Uncommon* |
|---|---|---|
| Neurologic | Behavioral change | Psychosis, seizures |
| | Insomnia | Dependence |
| | Myopathy | Paraparesis due to epidural lipmatosis |
| | Tremor | |
| | Reduced taste and smell | |
| Dermatologic | Thin, fragile skin | Kaposi's sarcoma |
| | Purpura | |
| | Ecchymoses | |
| | Striae, acne | |
| | Inhibition of wound healing | |
| | Hirsutsm | |
| Gastrointestinal | Increased appetite | Gastrointestinal bleeding |
| | Bloating | Pancreatitis |
| | Liver hypertrophy | |
| | Perforation | |
| Rheumatologic | Osteoporosis | Avascular necrosis |
| | Fracture | Tendinous rupture |
| | Growth retardation in children | |
| Ophthalmologic | Visual blurring | Glaucoma, uveitis |
| | Cataract | Exopthalmos |
| | Arrhythmia (with IV push) | |
| Endocrine/metabolic | Hyperglycemia | |
| | Hypokalemia | |
| | Hypernatremia | |
| | Hyperlipidemia | |
| | Redistribution of body fat | |
| | Amenorrhea | |
| Urogenial | Polyuria | Genital burning (with IV push) |
| Hematologic | Neutrophilia | |
| | Lymphopenia | |
| Miscellaneous | Night sweats | Some opportunistic infections (PCP, aspergillosis etc.) |
| | Candidiasis | |
| | Infection | |

Adapted in part from ref. *5*.

This correlates quite well with what is seen clinically as revealed by contrast enhanced computed tomography (CT) and magnetic resonance imaging (MRI): generally, it is tumors involving white matter that have consequential mass effect due to edema. Such instances provide as good an example of the clinical reality of vasogenic edema as one can see. In Klatzo's words, vasogenic edema is the type "in which the starting point of the edema is related to the injury of the walls of cerebral vessels leading to the escape of water and plasma constituents into the surrounding parenchyma." Cytotoxic edema, on the other hand, is the type "in which a noxious factor directly effects the structural elements of the parenchyma producing intracellular swelling, vascular permeability remaining relatively undisturbed."

Cytotoxic edema, such as occurs in ischemia and infarction, has been repeatedly shown to be resistant to the effects of corticosteroids. Many studies have shown no benefit of corticosteroids for patients with strokes; Fishman stated authoritatively as far back as 1982 that "in ischemic cerebral edema, whether it is cardiogenic or thromboembolic in origin or secondary to asphyxia or cerebral malaria, steroid therapy has been found wanting and even deleterious" *(22)*. The recognition of the extraordinary difference between the brain swelling due to tumors and that due to strokes is part of our daily working knowledge. What needs to be understood, then, is what is special about vasogenic edema and the pathophysiology of peritumoral brain edema. Simply stated, what biological mechanisms underlay the remarkable response of brain tumor edema to corticosteroids?

The structural background underlying the problem was worked out in the 1960s and 1970s, and little has been added since *(23–26)*. In the normal mammalian brain, except for some small special regions mentioned below, the endothelium is continuous. It is held together by continuous belts of tight or pentalaminar junctions, and has few microvesicles in the cytoplasm. Gaps or fenestrations are conspicuously lacking. This specialized endothelium is the anatomic locus for the blood-brain-barrier (BBB) as defined almost a century ago with the use of cationic dyes and in the 1970s by various electron dense tracers suitable for ultrastructural investigation. Regions of the brain that have been known for years to "lay outside the blood-brain-barrier," such as choroid plexus and area postrema, are

freely permeable to cationic dyes and tracers in current usage because in these regions the capillaries are fenestrated. In these brain regions, there is complete access to the plasma and its constituents, such as the contrast agents in use for CT and MRI. While such contrast agents and other test substances are normally excluded from the brain by its specialized continuous endothelium, the endothelium in brain tumors is altered structurally and resembles fenestrated endothelium. The mechanism by which tumors cause such abnormal endothelium is unknown. We do know that leakage of contrast is quite variable from one tumor type to another, and even within the same tumor. This variability is the basis for many diagnostic neuroradiological criteria; without contrast agents, CT or MRI for brain tumors is very limiting and, by current standards, simply not acceptable.

Solute transport across normal brain capillaries is confined to two mechanisms. Solutes may either dissolve in and diffuse through the endothelial membranes or be transported to the cytoplasm of the endothelial cell. Blood-to-brain transfer of substances depends directly upon the substance's membrane (lipid) solubility and, inversely, on molecular size. Transport through the cytoplasm of endothelial cells is by carrier-mediated transfer processes, which are highly stereo-specific, saturable, and often competitive. This mechanism, unlike diffusion, is relatively independent of lipid solubility and molecular size. Bulk flow of water is very slow in the normal brain due to the low hydraulic conductivity of normal brain vessels. The osmotic pressure of plasma proteins at the endothelial cell membrane of normal brain capillaries balances the hydrostatic pressure gradient between intravascular and extravascular tissue compartments. In addition, since normal brain capillaries are relatively impermeable to the main ionic constituents of plasma, such as sodium and chloride, there is an additional osmotic buffering capacity that slows passage of water into the brain. The small, narrow channels that comprise the extracellular space of the brain also restrict the flow of extracellular fluid. They are, in effect, high resistance pathways. These phenomena that regulate the normal BBB are overwhelmed in brain tumors by an increase in the hydraulic conductivity of the endothelium due to the presence of fenestrations and gaps of the endothelial wall. These defects permit bulk flow of fluid from the vascular compartment into the brain tumor and adjacent brain. The rate and extent of the development of edema depends upon hydrostatic pressure gradients in the tissue, the hydraulic conductivity of fluid flow through the tissue through the extracellular space and the rate at which the edema fluid is removed. The flow of plasma derived fluid into tumor and adjacent edematous brain is, in fact, exactly what Klatzo described as vasogenic edema.

It has not been easy to measure the factors that govern the flow of edema fluid across endothelium and through brain tumor and adjacent edematous tissue. The most important study was done by Nakagawa and his colleagues *(25)* who treated rats with experimental brain tumors with dexamethasone to see its quantitative effect on albumin distribution. They measured local tissue concentrations of radiolabeled serum albumin with quantitative audoradiography using a two compartment model and provided quantitative data on blood-to-tissue influx, extracellular volume, and plasma vascular volume. Their results showed that treatment with dexamethasone consistently and dramatically reduced the albumin distribution space in the brain of the tumor-bearing rats as compared to normal brain. All evidence suggested that the defects across the wall of the capillaries of these experimental brain tumors were large and did not restrict the free flow of the radiolabeled albumin. The investigators actually were able to calculate the total pore space and correlated this with the known morphological abnormalities of the vessels of this particular experimental brain tumor. Dexamethasone markedly reduced or even eliminated the filtration of plasma-derived fluid across tumor capillaries. It also reduced movement of albumin through the extracellular space, which they thought was due to a reduction in the size of the extracellular space. This study permits the conclusion that dexamethasone reduces the extracellular space of brain tumors and adjacent brain by reducing the water flow across the capillaries and the influx of albumin across them by a factor of at least 100%. Subsequent studies in both rats *(28)* and dogs *(29)*, with different types of experimental brain tumors, have supported these observations.

Taken as a whole, we have some explanations for the striking effects of dexamethasone on peritumoral brain edema. Lacking, however, are the details required to develop new drugs that have benefits similar to dexamethasone without its side effects. In addition to the intellectual challenge of understanding the biological basis for vasogenic edema, it is for this obvious reason that the matter is in need of additional investigative efforts.

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# 4 Headache Associated with Intracranial Neoplasms

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## INTRODUCTION

In general practice, headaches are one of the most common presenting symptoms, resulting in 10–15% of office visits with approx 11 million people in the United States having migraine headaches *(1)*. Often the cause is benign but there is nothing more worrisome than "missing" that rare patient with a brain tumor. The most common cause of headache in both adults and children remains as tension or muscle contraction type headaches. This accounts for 75% of headaches in adults and also 60–75% of headaches in children. Other causes include migraine, which occurs in 10–15% of cases. The other 10% are related to other causes and it is within this 10% that brain tumors present. In approx 60% of supratentorial based primary tumors, and 50% of metastatic brain tumors, headache is one of the main presenting symptoms *(2–4)*. Although it is a relatively rare cause of headaches, it is the one that physicians fear the worst, and is often the main reason for multiple investigations. Unfortunately there are no typical presenting characteristics as the headache is usually described as a dull ache, steady in nature, and is "located" deep in the head *(2,5,6)*. Certain aspects of the history, however, may be suggestive of this diagnosis *(7–12)*. Factors such as: (1) a sudden onset of headaches in someone not prone to headaches; (2) a gradually worsening headache that seems to increase over a number of days to weeks; (3) early morning headaches, which often awaken the patient or are present on awakening; (4) improvement during the day as the patient tends to be upright; (5) worsening of the headache with any maneuver that causes an increase in intracranial pressure, such as bending, coughing, or sneezing; and (6) an association of the headache with other neurological symptoms tend to suggest the possibility of a pathological cause for headache *(2,5,6)*. If the patient has a history of previous headaches, this headache usually has the same description, but may appear to be more intense with time *(2,6)*. The rate of increase in size and the location of the tumor affect the headache more so than its size. Typically the headache is located over the area of the tumor on the ipsilateral side. The main cause of headache in brain tumors is related to a mass effect of the tumor, resulting in a traction effect on brain tissue and the surrounding structures. This is often seen in patients with: (1) an increase in intracranial pressure, and (2) a large enhancing tumor mass associated with a midline shift.

Since headache is a very common symptom in otherwise healthy people, the physician's role is to identify those few patients in whom the headache is caused by a brain tumor and to reassure the rest. The purpose of this chapter is to elucidate the cause of headache in brain tumors, to describe the characteristics of headaches in patients with brain tumors (primary or metastatic), to identify the factors that cause these headaches, and to provide a diagnostic and management approach. Some of the pathological and clinical features of headaches in patients with brain tumors will be presented to aid the clinician in differentiating benign headaches from those requiring further investigation.

## HEADACHE INCIDENCE IN BRAIN TUMORS

The incidence of headache in patients with brain tumors is variable. It ranges from 36–80% (Table 1) and to some degree depends on tumor type (Table 2), location of the tumor, and age of the patient. Some of these estimates may be inaccurate as most of the older studies were retrospective, lacked pathologic confirmation, and were performed prior to the era of modern imaging. A prospective study by Forsyth and Posner *(2)* found headaches were present in 48% of patients with brain tumors and occurred equally in primary and metastatic brain tumors. Other studies have reported headaches at presentation in 33–72% of patients with primary brain tumors and 31–67% of patients with metastatic brain tumors *(6,13–16)*. Headaches appear to be somewhat more common with infratentorial tumors than with supratentorial ones (Table 1). A retrospective review *(17)* found headache to be the presenting symptom of brain tumor in 56% of patients diagnosed through the

From: *Cancer Neurology in Clinical Practice* (D. Schiff and P. Y. Wen, eds.), © Humana Press Inc., Totowa, NJ.

**Table 1**
**Frequency of Headaches in Brain Tumor Patients by Location**

| Location | *Kunkle et al. (13)* | *Northfield (1938) (14)* | *Rushton and Rooke (1962) (15)* | *Honig and Charney (1982) (19)* | *CBTC (1991) (102)* | *Forsyth and Posner (1993) (54)* | *Suwanwela et al. (1994) (6)* | *Pfund et al. (1999) (5)* |
|---|---|---|---|---|---|---|---|---|
| Overall | 90 | 36 | 60 | 69 | 62 | 48 | 67 | 58 |
| Supratentorial | – | 34 | 58 | – | 58 | 40 | 59 | 55 |
| Infratentorial | – | 48 | 64 | – | 70 | 82 | 84 | 75 |

emergency department of a major US hospital. The duration of the symptoms were less than 1 wk in 23% of patients, less than 1 mo in another 38%, and less than 6 mo in an additional 29%. Pfund *(5)* found headache in 49% of brain tumor patients, with the headache being progressive in 80%. The progressive nature of the headache showed a close relationship with the amount of cerebral edema, but not with the size of the tumor.

A review *(18)* in the pediatric population found vomiting to be the most common symptom (65%) and headache the second most common symptom (64%) in children with brain tumors. Thirty-four percent of these headaches were associated with vomiting, and 28% occurred in the early morning hours. The increased incidence of headache in pediatric brain tumors may relate to the higher percentage of posterior fossa tumors in this age group *(19)*.

Headache is also a common complaint in systemic cancer; in one study up to 15.4% of patients with systemic cancer reported headaches as a symptom *(20)*. Headache in cancer patients arises from both structural and nonstructural factors. In the structural group, the common causes were related to metastases and accounted for 39% of headaches *(20)*. Causes included: parenchymal and leptomeningeal metastasis (21%), skull base metastasis (9%), intracranial bleed (6%), upper cervical metastasis (2%), and primary brain tumor (1%). Thus, nonstructural causes were responsible for 61% and included: fever (38%), migraines (13%), tension-type headache (4%), side effects of therapy (3%), and postlumbar-puncture headache (2%).

The reported incidence of headache in central nervous system (CNS) metastasis is approx 50% *(4,21–25)* but this is probably an overestimate as many metastases are asymptomatic and discovered only at autopsy *(26)*. Metastases to the leptomeninges *(4,27)* cause headache in 30–75% of patients *(28–33)*. Approximately one-third of patients with rare primary meningeal tumors have headaches *(34–38)*. Headaches are common in patients with both primary and metastatic skull base tumors, presumably relating to dural irritation. For example, 83% of patients with nasopharyngeal carcinoma have headache *(39)*; 27% of patients with skull base chordomas have headache *(40)*; and skull base metastases from breast, lung, and prostate cancer commonly (44%) present with headache *(41)*.

Headache from brain tumors is related to traction and displacement of intracranial pain-sensitive structures located in the blood vessels, cranial nerves, and dura. As a result, the development of headache is related to duration of disease, rate of tumor growth, compensatory mechanisms of the brain, and location of the tumor. Melzack et al. *(42)* and Pfund et al. *(5)* noted that in patients with tumors of similar locations and histology the headache was described in differening terms, possibly related to individual compensatory mechanisms mediated through both opioid and non-opioid mechanisms. Slow-growing low-grade supratentorial tumors are much more likely to cause seizures than headaches *(43–48)* presumably related to continuous adaptation of the pain-sensitive structures as the tumor grows. The faster growing malignant gliomas cause headaches in approx half of patients, and this may in part be due to the relatively short time the brain has to adapt *(42)*. Tumors that obstruct cerebrospinal fluid (CSF) pathways, such as infratentorial tumors, are commonly associated with headache *(2,6)*; headaches are present in 90–100% of patients with medulloblastoma *(6)*. Brain tumors presenting as isolated headache are most common with posterior fossa tumors causing hydrocephalus *(16)*; even subependymomas, (usually asymptomatic), may cause headaches if CSF flow obstruction occurs *(49)*. Meningioma and acoustic neuroma have a lower incidence of headache *(49)*. Acoustic neuromas cause headache in about a third of patients *(50–52)*, but headache is rare in tumors smaller than 2 cm. Headache in these tumors is likely due to obstructive hydrocephalus from compression of the brainstem and fourth ventricle.

## PATHOPHYSIOLOGY

Brain parenchyma does not contain pain fibers and therefore does not participate in pain sensation. Consequently, most brain tumors cause headaches by directly or indirectly stimulating one or ore of the pain-sensitive intracranial structures. These pain-sensitive structures include: (1) cerebral arteries at the base of the brain; (2) dural arteries; (3) great venous sinuses and their tributaries; (4) dura at the base of the brain; and (5) intracranial portions of the trigeminal, glossopharyngeal, vagus, and upper cervical nerves. It has been proposed that as the tumor grows it exerts pressure on these structures, resulting in the sensation of pain *(13)*. In slow-growing brain tumors, headache tends to be a late symptom, as pain-sensitive structures adapt themselves to the increased pressure. In rapidly growing tumors or tumors that experience rapid increase in size due to other factors such as hemorrhage or edema, headache tends to occur more suddenly and as a presenting symptom. The exact role of pain-inhibitory structures and their role through opioid- and non-opioid-mediated mechanisms is not fully understood but likely plays an important role.

**Table 2**
**Incidence of Headache by Tumor Type in Supratentorial Tumors**

| *Tumor type* | *Pfund et al. (1999) (5)* | *Suwanwela et al. (1994) (6)* | *Forsyth and Posner (1993) (54)* | *Vasquez-Barquerro et al. (1994) (16)* | *CBTC (1991) (102) Pediatrics* |
|---|---|---|---|---|---|
| Astrocytoma/oligodendroglioma | 55.6% | – | – | – | 54.6% |
| Craniopharyngioma | – | – | – | – | 72.6 |
| Meningioma | 58.7% | 57.6% | – | 13.3% | – |
| Glioblastoma | 46% | 100% | – | 26.7% | – |
| Anaplastic astrocytoma | 65% | 89.6% | – | – | 61% |
| Metastatis | 77.4% | 66.6% | 66% | 40% | – |

The high incidence of headache from extracerebral tumors located near the skull base, which is the center of the aforementioned pain-sensitive structures, appears to support the traction concept. Traction or stretching can occur by one of two mechanisms: direct or indirect. Direct involvement occurs from local traction or invasion of pain-sensitive structures by the tumor mass itself. Indirect mechanisms occur either through: (1) distant traction or (2) stretching of one or more of these structures by tumor effects such as: (a) hydrocephalus, which results in compression of normal brain parenchyma and other structures, or (b) associated edema from the brain tumor resulting in compression of structures that may be far removed from the tumor mass itself. Unilateral and ipsilateral headaches would therefore be more likely related to local traction or invasion effects *(53)*, whereas bilateral headaches would occur more commonly from distant traction effects caused by an increase in intracranial pressure *(54)*.

Increased intracranial pressure alone may not be reliably associated with headache. Artificially raising intracranial pressure in normal individuals above 800 mm $H_2O$ does not cause headache *(55)*, and many brain tumor patients normally have intracranial pressures that are much lower than this. Plateau waves may account for headache in these patients. A significant number of patients with increased intracranial pressure did not have headache *(13–15)*, including 14% of patients in one prospective study *(2)*. Seven percent of patients in one series with hydrocephalus did not have headaches. On the other hand, patients with pseudotumor cerebri commonly have headache that is relieved by lowering intracranial pressure. The cause of headache in pseudotumor is unknown but does not appear to be traction on pain-sensitive structures.

The location of the headache may provide some clues as to where the tumor may be found. Ray and Wolff *(56)* reported that stimulation of the superior surface of the tentorium referred pain to the ipsilateral forehead and eye while stimulation of pain-sensitive structures in the posterior fossa referred pain to the ipsilateral ear (via the recurrent meningeal branch of the vagus nerve) and the lower occipital and upper cervical region (via the upper three cervical roots). Wirth and Van Buren *(25)* reported a much less consistent pattern of referral and concluded that the pain of dural origin had poor localizing value. Raskin et al. *(57)* showed that traction occurring from supratentorial tumors resulted in pain transmission by the fifth cranial nerve to the anterior part of the head, and from infratentorial tumors resulted in pain over the posterior part of the head. These patterns, however, can easily be modified and confounded by other factors such as increased intracranial pressure, midline shift, and hydrocephalus. Fronto-temporal headaches occurred more commonly regardless of the site of the tumor *(2,6)*.

## CLINICAL PRESENTATION

The IHS (International Headache Society) includes three diagnostic criteria for headache associated with intracranial neoplasm (Headache Classification Committee, 1988):

A. Symptoms and/or signs and intracranial neoplasm.
B. Confirmation by appropriate investigation.
C. Headache as a new symptom or of a new type temporally related to intracranial neoplasm.

There are few studies of the clinical features of headache in patients with brain tumors. In this section we will review some of these features as well as the value of modern imaging and how the clinical context influences the likelihood that a brain tumor will be found. For example, it is rare for a family physician or neurologist to diagnose a brain tumor in a patient with an acute headache in an outpatient clinic, as these cases are more likely to be seen and diagnosed in an emergency room. We have divided this section into a number of clinical settings to help understand the various presentations of a headache in brain tumor patients.

### CLINICAL FEATURES OF HEADACHE IN BRAIN TUMORS

1) Type of headache (description) and relationship to previous headache history.
2) Timing and duration of the headache.
3) Location of the headache.
4) Quality and intensity.
5) Other associated clinical symptoms and signs.

### TYPE OF HEADACHE (DESCRIPTION)

No specific classical description for a brain tumor headache exists. The number of patterns described by patients is variable but some consistencies exist. The most common type of brain

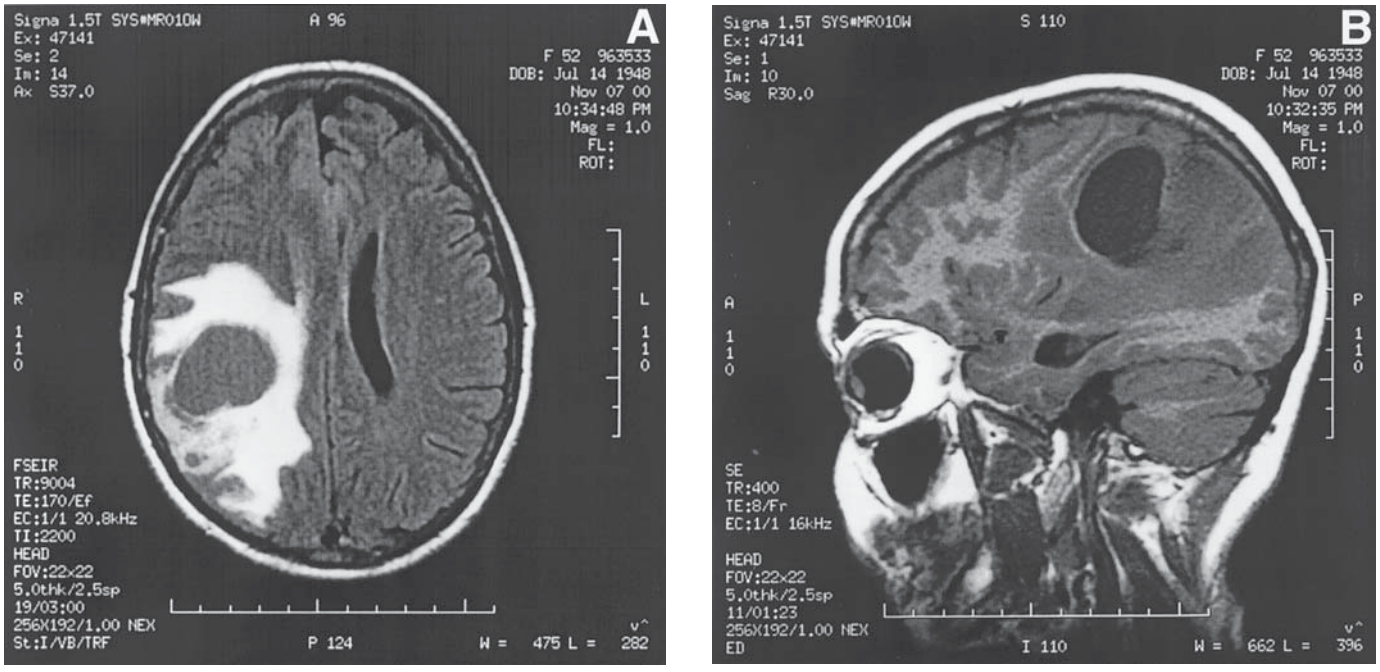


**Fig. 1(A)(B).** This 52-yr-old woman with a history of migraine headaches for 35 yr that were well-controlled noticed a change in their quality, intensity, duration, and frequency recurrence pattern over a 6-mo period prior to diagnosis. The headaches were mostly unilateral but did occur bilaterally. The frequency increased from a previous average rate of one per month to weekly and then almost daily. She suffered from photophobia and nausea but no vomiting. NSAIDs and anti-migraine medications such as Zomig, which previously controlled the headaches, were no longer effective. MRI showed a large cystic necrotic mass in the right parietal lobe associated with peritumoral edema. At surgery a glioblastoma was resected.

tumor headache is a "tension type" headache seen in 77% of patients and is usually described as a "dull ache," "pressure," or "like a sinus headache" *(2)*. In one series 78% of patients were found to have intermittent headaches whereas continuous headaches occurred in 22% *(6)*. Seventy-four percent described the headache as "dull" and aching and 26% described the headache as a "throbbing" sensation. The "pain intensity" was severe in 37%, moderate in 46%, and mild in 17%. Fifty-eight percent of patients described relief to some degree after the use of "over-the-counter" medications such as acetylsalicylic acid and or acetaminophen.

In the report by Forsyth et al. *(2)*, 78% of patients with previous headaches described headache as a symptom of their brain tumor, whereas 33% of those patients who had no previous history of headaches had headaches with their brain tumor. In 36% of patients the headache was described as being similar to their prior headache. In all instances, however, the headache was more severe or frequent than the patient's prior headache and was associated with other symptoms such as seizure, confusion, prolonged nausea, hemiparesis, or other abnormal signs. The physician confronted with this constellation of symptoms needs to maintain a high index of suspicion to prevent a delay in diagnosis. A change in quality of the headache, new symptoms or signs must therefore be considered a justifiable cause for further investigation in the absence of any other relevant clinical history.

## INTRACRANIAL MASS AND MIGRAINE ASSOCIATION

After tension-type headaches, the second most common type of headache seen in patients with brain tumors is a migraine-like headache. These have been reported to occur in 9–26% of patients *(2,6)*. These headaches were throbbing in nature, developed gradually over several minutes to a half an hour and were accompanied by nausea but no other signs or symptoms. Nausea and vomiting occurred in up to 36% of the patients in one series *(6)*. No tumor type, location, or other pathology such as increased intracranial pressure consistently identified patients with migraine-like tumor headache in either group. In one report *(58)*, migraine-like headache appeared to be more common in patients with intraventricular tumors. Several patients with brain tumors and migraine-like headaches have been noted to improve with anti-migraine medication, suggesting that a response to therapy should not mislead the clinician into assuming that there is no underlying etiology. One potentially reassuring clinical factor may be the length of time the headache has been present. Eighty-five percent of brain tumors are diagnosed within 18 mo of the onset of headache. A headache that has been present for more than 2 yr was rarely associated with intracranial neoplasm.

"Classic migraine" headaches have also been reported to occur in brain tumor patients. In one report *(59)*, a patient was described who presented with a 5-mo history of a "classic" migraine associated with a visual prodrome of "colored stars." A parietal lobe metastasis was found to be the cause. Reports from other authors *(60–62)* also described patients with "classic" migraines presenting with brain tumors. One patient had a classic history of migraine with teichopsia for 2 yr and was found to have a glioblastoma multiforme; another had a migraine headache associated with "auras" and was found to

**Table 3**
**Headache Characteristics in Brain Tumors (Including Low and High-Grade Tumors)**

| | |
|---|---|
| Description | "Tension type," "dull ache," "pressure-like," and "sinus-like headache" in 77% of patients<br>"Migrainous" in 9–26% of cases |
| Timing | Intermittent, develops and resolves over several hours<br>Worse with cough, valsalva maneuver, and bending in 23%<br>Interferes with sleep in 32% |
| Duration | Less than 1 mo: 29%<br>1–6 mo: 26%<br>Greater than 6 mo: 45% |
| Location | 72% bilateral and 25% unilateral<br>Frontal in 68% |
| Intensity | May be mild, moderate, or severe. Mean intensity of 8.5/10 when associated with increased intracranial pressure and 6.5/10 if no evidence of increased intracranial pressure |
| Associated symptoms | Nausea and vomiting (38%)<br>Visual disturbance (40%)<br>Seizures (50%) |

have an occipital lobe tumor. One of our patients (Fig. 1A,B) had a history of migraine headaches since childhood. Her symptoms changed with an increase in frequency and duration of the headaches, but the description remained similar to her classic migraine headaches with nausea, photophobia, and visual auras. The headaches gradually became more unilateral, and her usual anti-migraine medications became ineffective. Ultimately, a computed tomography (CT) and magnetic resonance imaging (MRI) of the brain revealed a mass in the right temporoparietal area, which on excision was found to be a glioblastoma multiforme. Migraines presenting in a cluster headache temporal pattern have also been reported as a symptom of brain metastases *(63)* and of primary CNS lymphoma *(64)*.

## TIMING AND DURATION OF THE HEADACHE

Brain tumor headaches are usually intermittent and tend to develop and resolve over several hours *(2,5,6)*. In a review by Forsyth and Posner, brain tumor headache was found to be worse in the morning in only 36% of patients; 32% complained the headache was worse with bending; and in 23% the headache was worse with Valsalva maneuver. The headache roused patients from sleep or interfered with sleep in 32%. The classic description of a "brain tumor headache," i.e., severe, worse in the morning, and accompanied by nausea and vomiting, occurred in only 17% of their patients. Another study found nocturnal headache was present in 71% of patients and 18% had early morning headache severe enough to awake from sleep *(6)*. Headache was also precipitated by change in body position (particularly rising from bed) in 20%, while straining and movement also worsened the headache in 18.0% and 7.4%, respectively *(6)*.

We found it useful to classify headaches into four different patterns based on the duration of the headache and the likelihood that a brain tumor is the cause. Eighty percent of brain tumors are diagnosed within 6 mo of headache onset, and another 15% within another 18 mo. It is only in slow-growing, relatively benign lesions that the headache will be present for more than 18 mo prior to diagnosis. In most reports the onset of headache as a symptom of brain tumors has been reported to occur within 1 mo, 6 mo, 12 mo, and 18 mo of diagnosis. We therefore felt a classification based on this time frame would help in differentiating a brain tumor headache from a more benign cause.

**The Acute Headache (Less than 1 mo)** This headache is usually severe and occurs without a previous history of headache. The pathophysiology relates to acute traction on various brain supportive structures from rapid tumor growth, peritumoral edema, intratumoral hemorrhage, or increased intracranial pressure. Neurological signs may be absent in up to 30% of such patients. Up to 40% of brain tumors present with this type of headache and are diagnosed within 1 mo of onset.

**Acute Recurrent Headache (1–6 mo)** This we classified as headaches that have been present on and off for approx a 6 mo-time period, as most brain tumors (85%) are diagnosed within that time frame. The headache is usually described as being "vague" and may improve to some degree with the use of nonsteroidal over-the-counter medications. Patients tend to seek the advice of a physician not because the headache is severe but because it is persistent. There are many causes of acute recurrent headaches, with benign causes predominating. Some of the factors that may predict a brain tumor are: (1) frequency of the headache, (2) type of headache, (3) location of the headache, (4) timing and duration of the headache, (5) severity of the headache, (6) associated neurological signs and symptoms, and (7) no other history of concurrent problems, such as stress, family problems, or depression (Table 3).

For example, one of our patients, a 29-yr-old male, had a 3-mo history of headaches that were vague, intermittent, gradually progressive in nature, and were "distributed all over the head." The headache started early one morning and then recurred every morning. Headache was most intense around 9:00 am and then diminished. No other neurological symptoms or signs occurred, and the only treatment that helped the headache was rest. On the day of diagnosis the headache became very severe, and the patient developed problems with his gait. It was the severity of the headache that prompted him to go to the emergency department. An urgent MRI scan (Fig. 2A,B)

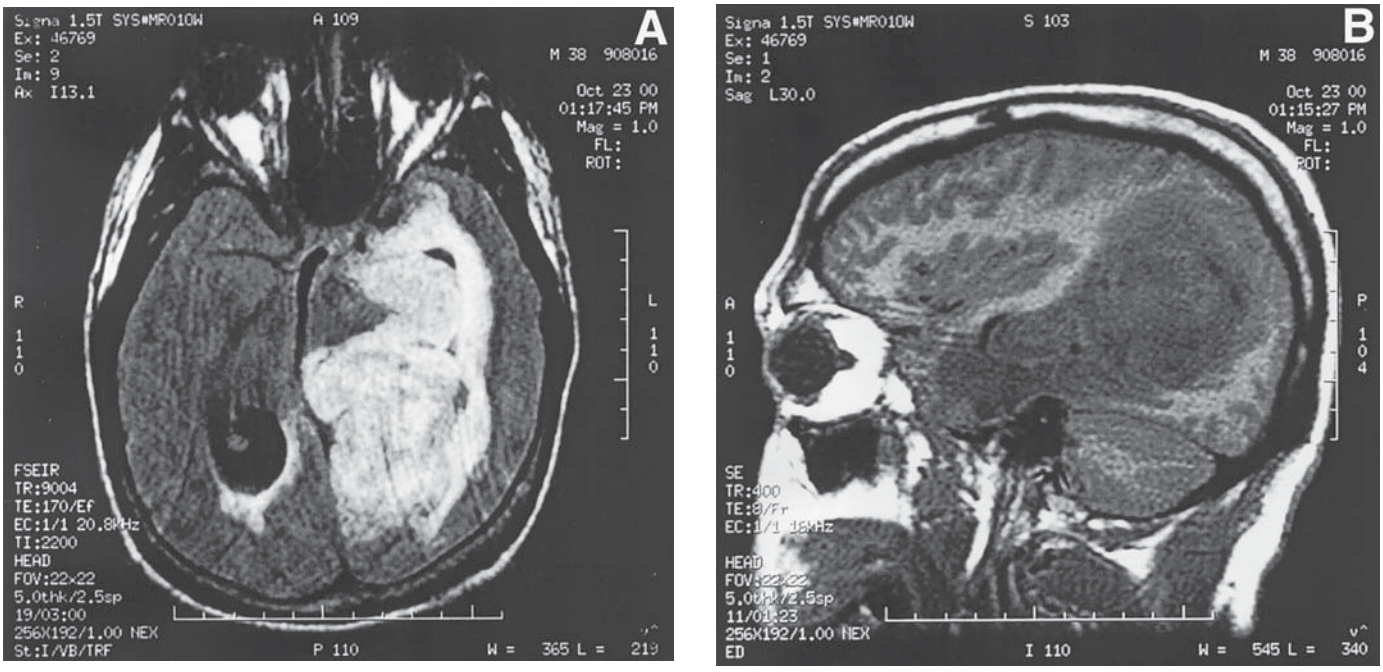


**Fig. 2(A)(B).** This 29-yr-old man had a 6-mo history of increasing headaches, worse in the morning and at night. Memory loss and cognitive problems began 1 mo prior to diagnosis. As the headache progressed and became very severe he presented to the emergency department. MRI revealed a large intracranial tumor with edema, midline shift, and a "trapped" posterior horn of the lateral ventricle consistent with obstruction of CSF flow. Surgery demonstrated a grade 3 oligodendroglioma. He received postoperative radiotherapy and chemotherapy with improvement of his headache.

showed a large mass, some midline shift, and a trapped ventricle. The clinical features of the headache presented in Table 3 may help to predict that a headache is related to a brain tumor, and many of the features that apply to this case emphasize the need for imaging in an otherwise neurologically intact person.

**Chronic Progressive Headache** This headache is commonly described by patients as one which consistently worsens or changes in character, intensity, and location over time. In one series of brain tumor patients *(5)*, 76% of patients had progressive headaches whereas only 17% had nonprogressive headaches. Twenty-three percent (23%) of patients with progressive headaches had their tumor diagnosed within 1 mo of the onset of headache and another 67% within 6 mo. Another series reported headache to be present for more than a year in 15.4% of brain tumor patients with progressive headache *(6)*. Headache progression was associated with cerebral edema, midline shift, as well as hydrocephalus. Patients with prior existing headaches also had a progression or worsening of symptoms in all cases, substantiating the need for further evaluation.

In the pediatric brain tumor population, headache is variable and less frequently associated with the classical triad of headache, vomiting, and papilledema. Overall, headaches occurred in 64–69% of patients; however, early morning headaches occurred in only 27–31% of patients *(18,19)*. Vomiting unassociated with headache occurred in 65–78% of cases but was associated with the headache in only 21–34% of cases. Migraine was the initial diagnosis in 19%. The mean interval to diagnosis was 31.5 wk although 92% of patients had increase in frequency, severity, and progression to nocturnal awakening *(18)*. Severe, recurrent, or chronic progressive headaches that do not meet the IHS criteria require careful monitoring or further evaluation to rule out the presence of an underlying pathological etiology.

**Chronic Nonprogressive Headache** In this type of headache no increase in symptoms relating to timing, duration, and quality occur. It is unusual for brain tumor patients to present as such except in the case of very slow-growing tumors such as meningiomas. Fewer than 10% of patients with metastatic brain tumors, astrocytomas, or glioblastomas have chronic nonprogressive headaches.

**LOCATION OF THE HEADACHE** Brain tumor headache is usually be described as being located "all over the head." The headache is usually bifrontal but worse ipsilateral to the tumor. Seventy-two percent of patients in one series *(2)* had bilateral headache, and 25% reported unilateral headaches. Frontal headaches predominated, occurring in 68% of patients, and were associated with supratentorial tumors or increased intracranial pressure. In another series *(63)*, only 22% of patients were found to have unilateral headaches. Of the patients with supratentorial tumors, 52% had frontal headaches, 6% had occipital headaches, 20% had diffuse headaches, and 20% had unilateral headaches. Infratentorial tumors caused frontal headaches in 36%, occipital headache in 17%, were diffuse in 23%, and occurred unilaterally in 23%.

Even though the majority of patients have bilateral headaches, increased intracranial pressure is present in only 18–34%, and bilateral or midline tumors occur in only 11–21% of these cases. Neck pain was also reported to occur equally in

patients with increased or normal intracranial pressure. However, neck pain without increased intracranial pressure was only reported to occur with supratentorial tumors.

When associated with increased intracranial pressure, a unilateral headache correctly predicted tumor laterality in 80% of supratentorial tumors and 62.5% of infratentorial tumors *(2)*. Without any clinical evidence of increased intracranial pressure, the tumor was found to be ipsilateral in 100% of patients with supratentorial tumors and 80% of patients with infratentorial-based tumors. Unsurprisingly, few patients had a unilateral headache contralateral to the site of the tumor.

**HEADACHE QUALITY AND INTENSITY** In the acute setting, brain tumor headache is usually described as being severe, excruciating, and unrelieved by most medications. However, in the acute recurrent or chronic setting, the headaches can be mild, moderate, or severe in intensity (median of 7 on a scale of 1–10) *(2)*. The headache was found to be severe in 37%, moderate in 46%, and mild in 17%. Oral medications such as acetylsalicylic acid relieved the headache in 58% of patients in one series and 42% of patients in another series *(6)*. The headache was described as the worst symptom in 45% of patients, and 57% of these patients had imaging done because of this symptom. When associated with increased intracranial pressure, the headache had a mean intensity of 8.5 and when unassociated with increased intracranial pressure (ICP) the mean intensity was 6.5 on a scale of 1–10.

An acute or very severe headache in a cancer patient is most likely due to obstructive or communicating hydrocephalus producing ICP. Other causes such as hemorrhage into or around the tumor occur infrequently. The headache caused by ICP is associated with nausea and vomiting in 36% of patients and is frequently resistant to over-the-counter analgesics. Eighty-six percent of patients with increased intracranial pressure due to communicating or obstructive hydrocephalus had evidence of headache in the series by Forsyth *(2)* In another series, when papilledema was present 95% of patients had headache *(6)*. The increased ICP headache is usually severe and described as "the worst pain I have had" or "like my head is blowing off." The headache is usually constant (61%), not relieved by common analgesics (72%), worse in the morning (37%), and worse with Valsalva maneuver (33%). Headache location is frontal in 44%, in the neck and bifrontal region or neck and vertex in 33%, and solely at the vertex in 6% of patients.

In the absence of increased ICP, brain tumor headache was commonly described as being less severe, more likely to be intermittent, less likely to interfere with sleep or to be associated with nausea, vomiting, ataxia, or papilledema, and more likely to be relieved by common over-the-counter analgesics. With supratentorial tumors the headache was similar to tension-type headache in 80% of these patients and was migrainous (without aura) in 8%. In this group the pain was usually an "ache" or "pressure" or "sinus headache" and lasted several hours. In only 12% was the headache "the worst pain" of their life. Forty-one percent of patients with supratentorial tumors not associated with increased intracranial pressure had no headache. The "classic" brain tumor headache occurring only in the morning and progressive in nature occurred only in 17–18% of patients. The headaches caused by cerebral metastasis more commonly have subacute progressive headache *(2,18)*. The "benign" character of many brain tumor headaches often leads to a delay in diagnosis as they are commonly mistaken for tension headaches or other nonintracranial causes. The quality and intensity of the headache must therefore be correlated with the other clinical features described to establish a high index of suspicion for an underlying pathological cause such as a brain tumor.

**OTHER ASSOCIATED CLINICAL SYMPTOMS AND SIGNS** Isolated headache as the presenting symptom of a brain tumor is uncommon. In one prospective study *(16)* of 183 intracranial tumors, including 97 primary brain tumors and 86 metastatic tumors, only 8.2% of patients had headache as their first and isolated symptom. Headache associated with focal symptoms or seizures accounted for another 19.6%. These figures were similar for both primary and metastatic brain tumors. At the time of diagnosis, 33% of patients with a primary brain tumor and 31% of patients with metastasis had headache. Only one patient had headache as the only symptom at time of diagnosis. In this study, isolated headache remained the sole symptom for a maximum of 77 d. When isolated headache was present for more than 10 wk the incidence of a brain tumor was low.

In the report from Duarte et al. *(65)*, symptoms such as nausea and vomiting (38%), worsening of headache with the valsalva maneuver (38%), bending or coughing, and awakening from sleep (29%), occurred more commonly in patients with an organic cause of their headache as compared to nonorganic causes. Papilledema was present in 40% of brain tumor headache patients in one study *(6)*. Nausea and vomiting occurred most commonly with headache in this and other series, and was present in half the patients with brain tumors. Transient visual obscuration are commonly (68%) reported in benign intracranial hypertension ("pseudotumor cerebri") *(66)*; however, their incidence in brain tumor headache is not known.

The single most important clinical feature of brain tumors is the progressive nature of their underlying symptoms. Since the rate of tumor progression is variable, the symptoms and their progression also are highly variable and are related to the method of tumor growth (infiltrative vs compression due to encapsulation), tumor location, and the degree of associated edema and or mass effect. Mass effect causes poorly localizing symptoms such as headache, nausea, and vomiting, seizures, cognitive or personality changes, alteration of consciousness, and diplopia. Focal symptoms such as focal seizures, motor or sensory changes, speech disturbances, visual-field abnormalities, and gait disturbances may also occur. These symptoms may occur in any combination or in isolation. Focal symptoms alone occurred in 57% of patients presenting with brain tumors with or without headache. Patients with brain tumors and headache have a longer duration of symptoms prior to diagnosis because patients presenting with seizures, rapidly progressive hemiparesis, or other neurological signs tended to be imaged more quickly than patients with headaches alone *(2)*.

## FACTORS ASSOCIATED WITH AN INCREASED INCIDENCE OF BRAIN TUMOR HEADACHE

We identified *(2)* four factors associated with an increased incidence of headache in patients with primary or metastatic

**Table 4**
**Factors Associated with an Increased Incidence of Headache in Brain Tumors**

| | |
|---|---|
| Increased intracranial pressure | 86–93% have increased ICP |
| Location | Infratentorial: 82–83%<br>Leptomeningeal: 75%<br>Midline tumors: 95%<br>Skull base lesions: 70% |
| Size | Mean size of tumors with headache = 18.3 $cm^2$, without headache 9.3 $cm^2$ |
| Midline shift | With headache mean midline shift of 6.1 mm vs 2.7 mm with no headache |
| Edema | Edema area 33.9 $cm^2$ noted with headache vs 26.1 $cm^2$ with no headache |
| Previous history of headache | 78% of patients with previous headache have headache as a presenting symptom of brain tumor. Increase in frequency, duration, and intensity of headache common |

**Table 5**
**Frequency of Headache from Intracerebral and Extracerebral Causes**

| *Tumor type* | *Frequency of headache (%)* |
|---|---|
| Primary brain tumor (adults) | 50–72 |
| Primary brain tumor (children) | 64 |
| CNS parenchymal metastasis | 50–67 |
| Leptomeningeal metastasis | 33–76 |
| Skull base metastasis | 44 |
| Primary meningeal tumors | 33 |
| Nasopharyngeal carcinoma | 83 |
| Skull base chordoma | 27 |

brain tumors (Table 4). These factors appear to have been confirmed by other authors in their individual reports. These are: (1) Increased intracranial pressure: 18 of 21 (86%) patients with increased ICP had headache. Another series also found hydrocephalus to be present in 28 of 30 (93%), of patients with headache. (2) The location of the brain tumor: 82% of infratentorial tumors and 75% of leptomeningeal tumors caused headache, which was due to obstruction of the CSF pathways. Suwanwela also reported an incidence of 83.8% for headache in infratentorial lesions, 95% for midline tumors and 70% for skull base tumors. (3) The size of the enhancing lesion, degree of midline shift, and amount of edema; larger tumors with more midline shift and edema tended to cause headaches. The mean size of brain tumors without headache was 9.3 $cm^2$ compared to 18.3 $cm^2$ in patients with headache. The midline shift was 2.7 mm in patients without headache but 6.1 mm in patients with headache. The amount of edema without headache was 26.1 $cm^2$ but with headache was 33.9 $cm^2$. (4) Patients with a previous history of headache were more prone to headache associated with brain tumor; 78% of patients with prior headaches had headaches with their brain tumor. Several patients had headaches of similar character to the patient's prior headaches. However in every case the headache was more severe, more frequent, or associated with other symptoms (seizures, confusion, prolonged nausea, or abnormal signs). Others have reported a change in severity or frequency of headache or abnormal signs may signal the presence of brain tumor in patients with chronic headache even if the quality of the headache is unchanged *(9,60,67)*.

## HEADACHE CAUSED BY TUMOR INVOLVING INTRACRANIAL, MENINGEAL, EXTRACRANIAL, AND DURAL STRUCTURES

In patients with systemic cancer, metastases to other intracranial structures (Table 5) such as the skull, dura, and venous structures may cause headache. Unfortunately, these have not been carefully studied. Primary tumors also may arise from these areas and produce headache. Some of the characteristics of these headaches have been discussed by various authors *(2,5,6)*. Headaches may also occur as referred pain from tumors affecting extracranial structures situated around the base of the brain. Some of these issues will be discussed below.

**CLASSICAL PITUITARY APOPLEXY** Randeva et al. *(68)* described 35 patients who presented with this syndrome characterized by sudden headache, vomiting, visual impairment, and meningismus. It is thought to occur secondary to rapid enlargement of a pituitary tumor, usually due to hemorrhagic infarction of the tumor. Headache was the most common symptom (97%); nausea (80%) and a visual field abnormality occurred in (71%). MRI identified hemorrhage in 88%, whereas CT identified hemorrhage in only 21%. Transsphenoidal surgery within 8 d of onset of symptoms resulted in improvement of symptoms in 86% of cases.

**HEADACHE IN PITUITARY ADENOMAS AND INCREASED INTRASELLAR PRESSURE** Arafah et al. *(69)* described headache in a group of patients with large pituitary macroadenomas and occasionally in microadenomas. Patients who presented with headache had a higher mean intrasellar pressure ($p = 5.44 \times 10^{-7}$) than those who did not have headache regardless of their pituitary function or tumor size. These data suggest that intrasellar pressure contributes to the development of hyperprolactinemia, hypopituitarism, and headache. Since the walls of the sella turcica cannot expand, increased pressure would result in compression of the pituitary stalk and the portal vessels, causing an obstruction to the delivery of hypothalamic hormones to the anterior pituitary. Headache has also been described in other suprasellar and intrasellar masses such as craniopharyngioma and Rathke's cleft cysts.

**SKULL BASE METASTASES** Greenberg et al. *(41)* characterized five distinctive syndromes due to skull base metastases, which commonly cause headache; their recognition helps to localize the metastasis and direct further therapy: (1) The orbital syndrome is caused by metastases to the orbit (usually from

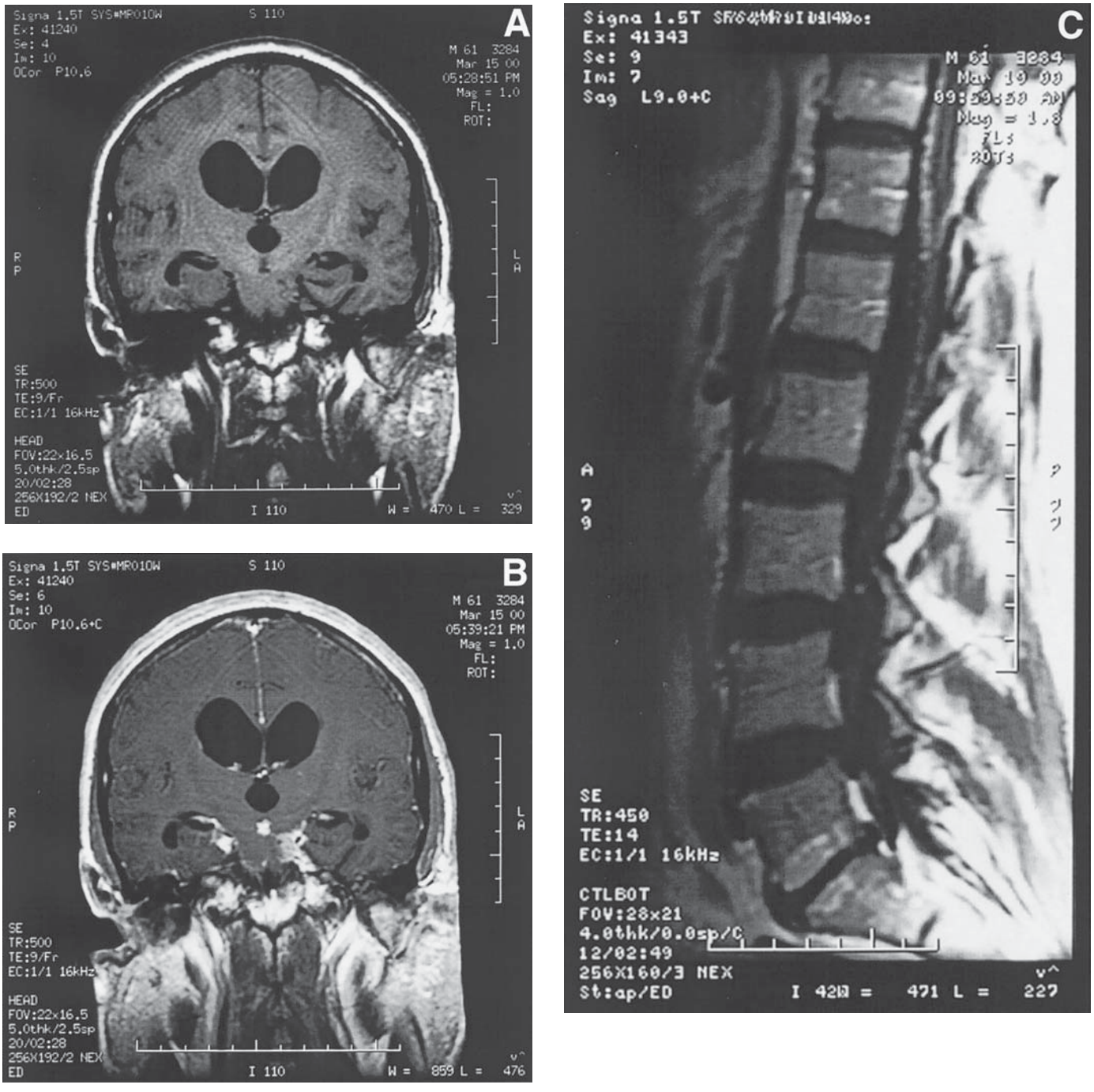


**Fig. 3.** This man was diagnosed with a cerebellar hemangioblastoma 8 yr previously and was treated with surgery but no other therapy. He had a 6 mo history of severe headaches and lethargy. He felt nauseated and the headaches were described as being all over the head. **(A)** and **(B)** show unenhanced and enhanced coronal MRI images indicating diffuse meningeal enhancement and communicating hydrocephalus. **(C)** shows patchy enhancement around the cauda equina consistent with leptomeningeal metastases. Biopsy and pathology review confirmed a recurrence of his hemangioblastoma with leptomeningeal spread of disease, which caused his severe headaches. Radiotherapy (4500 cGy in 25 fractions) was administered to the whole brain for palliation and his headaches improved.

breast, lung, prostate, lymphoma, or neuroblastoma) and consists of dull supraorbital ache that is followed by diplopia, proptosis, $V_1$ sensory loss, and decreased visual acuity. (2) The parasellar syndrome is caused by metastases to the sella that erodes into the cavernous sinus (usually from carcinoma of breast, lung, or prostate) and produces unilateral frontal headache, ocular paresis, and $V_1$ sensory loss. Striking periorbital edema may occur related to compression of veins draining into the cavernous sinus. (3) The gasserian ganglion syndrome consists of trigeminal nerve distribution pain and numbness (usu-

ally seen with breast, lung, or head and neck cancer invading the gasserian ganglion). The pain is a dull ache in the cheek, jaw, or forehead. Trigeminal neuralgia-like pain can occur. Sensory changes usually begin close to the midline in the chin or lip and spread laterally. Motor involvement is usually late. (4) The jugular foramen syndrome from metastases to the jugular foramen (usually from breast, lung, prostate, or head and neck cancer) is associated with dull, unilateral, aching retroauricular pain, hoarseness, and dysphagia. Weakness of vocal cords, palate and spinal accessory muscles may develop. Papilledema from jugular vein compression may occur. (5) The occipital condyle syndrome is caused by metastasis to the occipital condyle (usually from breast, lung, or prostate cancer) and consists of severe unilateral occipital headache, often worse with neck flexion. About half the patients complain of dysarthria and dysphagia. Ipsilateral tongue atrophy is common *(5,41)*.

**LEPTOMENINGEAL METASTASES** These produce headaches in about one-third to one-half of patients *(31–33)* that are usually nonspecific in location and timing. Headaches can be progressive and accompanied by nausea, vomiting, and changes in mental status, which reflect raised intracranial pressure or meningeal irritation. Cranial nerve involvement and spinal nerve root dysfunction are common. Figure 3A–C demonstrates a recurrent hemangioblastoma associated with leptomeningeal metastases; the patient manifested increasing headache over 6 mo.

**HEAD AND NECK TUMORS** Pain is experienced by 40–80% of patients with head and neck cancers *(70)*. Tumors in this location are located in close proximity to many pain-sensitive structures (mucosa, bone, nerves, etc.) Head pain associated with head and neck tumors can be quite severe. Nociceptive pain caused by A-delta and C-fiber stimulation is the most common type of pain. Often this pain is the result of tumor, tumor recurrence, or inflammation. Neuropathic pain is also common, usually as a result of nerve damage from neck dissection *(71)* or other therapies. Patients with advanced head and neck cancer often have more than one cause for pain *(72)*.

**VENOUS SINUS THROMBOSIS** This is a rare but serious cause of headache in the cancer patient. Patients develop sagittal sinus thrombosis either from external compression (from an adjacent metastases) or a hypercoagulable state (e.g., induced by l-asparaginase) *(73–76)*. Headache is almost universal, may be mild, and may not be accompanied by other symptoms or signs *(77)*. Papilledema commonly occurs *(78)*.

## UNCOMMON HEADACHE SYNDROMES IN PATIENTS WITH BRAIN TUMORS

Several uncommon headache syndromes have been described in patients with a variety of brain tumors. These include pressure wave headaches (also known as "paroxysmal headache"), benign exertional headaches, cluster headaches, trigeminal neuralgia, and atypical facial pain.

**PAROXYSMAL HEADACHE (PRESSURE WAVE HEADACHE)** Raskin and Appenzeller *(57)* summarized features related to this type of headache. It is a distinctive headache associated with colloid cysts of the third ventricle or other pedunculated tumors that can block the flow of CSF *(79–81)*. These headaches are usually severe, occur suddenly, peak in intensity in seconds, are of brief duration (minutes to a few hours), and often terminate quickly. The pain is often bifrontal or generalized, and may be precipitated by changes in posture. It may be associated with loss of consciousness, sudden weakness in the legs ("drop attacks"), vertigo, nausea, vomiting, and sudden death. Occasionally the headache is relieved by resuming the previous position. Patients often have gait imbalance between episodes. One author reported these headaches to occur more commonly in adult patients with large frontal or temporal malignant astrocytomas that had evidence of significant edema and mass effect *(69)*. They appeared to occur more commonly in patients who had only biopsies as opposed to surgical debulking, during steroid tapering phases, when starting a course of radiotherapy, and at the terminal phase of their illness.

These paroxysmal headaches were originally thought to result from intermittent obstruction of the foramen of Monro by a "ball valve" action of the tumor. A more recent explanation is that the symptoms are those of plateau waves caused by the sudden rises in intracranial pressure superimposed on chronic increased intracranial pressure *(82)*. The plateau waves probably result from sudden dilatation of intracranial small vessels, resulting in increased cerebral blood flow and volume *(83)*.

**BENIGN COUGH OR BENIGN EXERTIONAL HEADACHE** This consists of transient severe headache precipitated by coughing, sneezing, straining at stool, laughing, stooping, lifting, or running. Headache is brief in duration of headache and without a characteristic location. Symonds *(84)* found intracranial masses in 11% of his patients with "cough headaches," and Rooke *(85)* found brain tumors in 2% of 303 patients with "exertional headaches."

**ATYPICAL CLUSTER HEADACHE** DeAngelis and Payne *(64)* described a patient with atypical cluster headache as a presentation of leptomeningeal lymphoma. The atypical features were that the patient was a female; she had no nocturnal attacks, the pain was moderate to severe but not excruciating; the first attack was at age 50; and the only autonomic symptom was lacrimation. Headaches fulfilling diagnostic criteria for episodic or chronic cluster headache have also been reported in acoustic neuroma *(86,87)*, sphenoid ridge *(88)*, cavernous sinus *(89)* and foramen magnum meningiomas *(90)*, and metastases *(63)*. Taub et al. *(91)* describe a patient with chronic cluster headache for 20 yr. After a trochlear nerve palsy developed, neuroimaging revealed a meningioma of the tentorium cerebelli. Surgical removal of the meningioma led to resolution of headaches.

**TRIGEMINAL NEURALGIA** Two percent of all patients with trigeminal neuralgia are found to have brain tumors as the underlying cause *(92)*. An overwhelming majority of these tumors are meningiomas or schwannomas, most commonly located in the posterior fossa and occasionally in Meckel's cave in the middle cranial fossa. Approximately half of these patients eventually develop trigeminal sensory deficits, sometimes associated with trigeminal motor deficits or deficits of nearby cranial nerves. Tumor removal is the most effective means of controlling the pain, but medications like carbamazepine are often helpful. Nearly three-quarters of patients are women, reflecting the predominance of meningiomas and their gender

**Table 6**
**Predictors for Brain Tumor in Headache Presenting to the Emergency Department**

| |
|---|
| New headache (less than 1 mo in duration) |
| Occipitonuchal location |
| Age > 55 yr |
| Headache associated with early morning awakening, or sleep |
| Progressive severity |
| Headache associated with vomiting |
| Headache associated with other neurological symptoms or signs (seizure, gait disturbance, mental changes, visual deficits, weakness, etc.) |

predilection as well as female overrepresentation among sufferers of trigeminal neuralgia. The finding of trigeminal sensory deficit or other cranial neuropathy in patients with pain typical for trigeminal neuralgia should prompt a contrast-enhanced brain MR scan.

**Atypical Facial Pain** Atypical facial pain has been reported in patients with nonmetastatic lung cancer *(93–97)*. These authors describe an often debilitating, unilateral facial pain located mainly around the ear, but also involving the temple, jaw, cheek, or eye. The character of this pain is a constant aching, unlike the sharp jabbing pain of trigeminal or glossopharyngeal neuralgia occasionally reported by metastatic infiltration of these nerves. In all instances the facial pain is ipsilateral to the lung cancer. No evidence of metastasis to brain, leptomeninges, or skull base has been found. Many patients also have weight loss and digital clubbing. The most plausible explanation is local invasion or compression of the vagus nerve within the thorax; the vagus nerve contains somatic and visceral afferents necessary for referred pain. The right-sided predominance is likely attributable to the close anatomic relationship of the right vagus nerve to the trachea and mediastinal lymph nodes. Radiation or local tumor resection improved facial pain in most cases (sometimes dramatically). A chest radiograph in all smokers with unexplained facial pain is recommended.

## BRAIN TUMOR HEADACHE: PRESENTATION IN THE EMERGENCY DEPARTMENT

Patients who present to emergency departments with acute severe headaches need careful evaluation and may require neuroimaging studies to determine the cause. To avoid failing to diagnose the patient with an intracranial mass, all emergency department physicians need to maintain a high index of suspicion *(98)*. There are no absolute indications that a headache is related to a brain tumor. We will review factors predictive for an intracranial mass in this setting (Table 6). Since pediatric and adult patients may have different causes for their headache, we will address these separately.

The onset of a severe headache related to an intracranial mass is most commonly related to rapid growth of a tumor mass, obstruction of CSF flow, acute cerebral edema, or intratumoral hemorrhage. Headache occurred in 95% of patients with papilledema and 86% of patients with increased intracranial pressure *(2,6)*. Concomitant symptoms are common. Nausea and vomiting are also common, but in some series have been absent in up to 30% of patients.

**PEDIATRIC AND ADOLESCENT PATIENTS** In one series (*99*), the most common cause of acute headaches seen in the pediatric emergency department was infectious diseases (upper respiratory infection and sinusitis), accounting for 39% of the causes. Brain tumors accounted for only 2.6% of the cases. Occipital location and the inability to describe the headache were the only two clinical features that were statistically significant in predicting the cause of headaches as being related to an intracranial tumor. Other series have reported sleep-related headaches and headache duration of less than 1 mo as being associated with brain tumors *(100–106)*.

**ADULTS** A retrospective review for presenting signs and symptoms of brain tumors to the emergency department indicated headache as the initial presenting problem in 56% of patients *(17)*. Another study at St. Paul-Ramsey Medical Center *(107)* reviewed a consecutive group of patients who presented with headache to the emergency department for clinical characteristics predictive of intracranial pathology. Eighteen of 468 patients (4%) were found to have intracranial pathology. The factors that predicted for intracranial lesions were acute onset and occipitonuchal location. Presence of associated symptoms and patient age 55 yr or older were also significantly associated with a positive finding. The study concluded that the best clinical parameter to predict a structural abnormality was an abnormal neurologic examination (39%). However, age ≥ 55 with an acute onset of a headache (especially if located in the occipitonuchal area) also appeared to predict for an intracranial abnormality.

Another issue is the utility of neuroimaging for headache in the emergency department *(108–112)*. In one prospective series, the overall yield for a scan indicating a brain tumor was 10% even if the physical examination was normal *(65)*. Thus, the possibility of finding a brain tumor is not insignificant even in patients with no localizing signs. Neuroimaging of headache patients to diagnose brain tumor should be undertaken if the above clinical parameters are fulfilled.

## APPROACH TO HEADACHE IN A PATIENT WITH SYSTEMIC CANCER

Intracranial metastases are common and occur in approx 25% of cancer patients *(4,113,114)*. Therefore, brain imaging with a MR or CT with contrast is usually warranted in a cancer patient with a new or different headache. MR or CT may also help identify other frequent causes of headache such as hemorrhage, arterial infarction, or venous thrombosis. A history and physical examination are indispensable in determining which other laboratory investigations are needed to differentiate between the many possible causes of headache in cancer patients (Table 7).

A headache history determines which patients require imaging, how quickly it needs to be done, and which structures should be visualized. As discussed previously in this chapter, there is no single feature pathognomonic for brain tumor headache. However, in general, cancer patients who experience any of the worrisome features listed in Table 8 should be imaged. Careful questioning may be required, and interviewing the fam-

**Table 7**
**Causes of Headache in Cancer Patients**

| | |
|---|---|
| *Tumor-related causes* | |
| Acute | Intratumoral hemorrhage |
| | Acute venous sinus thrombosis |
| | CSF obstruction with resulting increase in intracranial pressure |
| | Pressure wave headache |
| Chronic | Persistent or new tumor growth |
| | New metastatic lesion involving skull, meninges, brain, skull base, sinuses, orbits, etc. |
| | Invasion of tumor into calvarium, skull base, meninges, leptomeninges. |
| | Increased intracranial pressure with midline shift causing traction on veins, arteries, nerves, etc. |
| *Nontumor-related causes* | |
| Treatment-related causes | |
| Chemotherapy | Hormones (e.g., Tamoxifen) |
| | Differentiation agents (retinoic acids) |
| | Antibiotics |
| | Reverse transcriptase inhibitors (e.g., AZT, DDI) |
| | Conventional agents (e.g., l-asparaginase, procarbazine, PCNU, fludarabine, fazarabine, caracemide, gallium nitrate) |
| | Cytokines (e.g., tumor necrosis factor, $OKT_3$, interferons, interleukins, levamisole, GM-CSF) |
| | Intrathecal therapy (e.g., methotrexate, Ara-C) |
| Radiotherapy | Acute cerebral edema (early onset during radiotherapy) |
| | Radionecrosis (late onset commonly months to years after radiotherapy) |
| | Radiation induced neoplasm (late: years after radiotherapy) |
| | Radiation induced atherosclerosis causing stroke |
| Supportive therapies | Corticosteroids, cimetidine, ondansetron, narcotics (withdrawal), metoclopramide, anticoagulants (intratumoral hemorrhage), dipyridamole, ibuprofen (aseptic meningitis) |
| Surgery | Hemorrhage, vascular injury, perioperative stroke, cerebrospinal fluid leak |
| Other causes of headache | |
| Acute | Cerebral infarcts |
| | Fever |
| | Infection (abscess, meningitis) |
| | Metabolic (hypoxemia, hypercarbia, and hypoglycemia) |
| Chronic | Referred pain from extracranial structures (cervical metastases, lung tumors, etc.) |
| | Postlumbar-puncture headache |

ily may be particularly useful. In some cases a history alone may render the diagnosis, as is the case when there is a close temporal relationship between the use of an agent such as ondansetron or retinoic acid, which commonly cause headache and the onset of the headache. A physical examination is similarly important in determining the cause of the headache.

An MR scan is the best diagnostic test for brain metastasis. If a carefully done MR scan with contrast is negative, it effectively rules out brain metastasis. MR scan with gadolinium is preferable to a CT scan because it is more sensitive; it can reveal smaller lesions not detected by CT; does not suffer from bony artifact in the brainstem or cerebellum; may show enhancement from leptomeningeal disease; or may show involvement of cranial nerves or blood vessels or thrombosis of the venous sinuses. It may also help with therapy if a resection of a single brain metastasis is planned or if focal radiotherapy is contemplated.

Other laboratory tests should be used as clinically indicated from the history and physical examination. CT scan with bone windows and fine cuts through the region of interest, or a bone scan may be superior to MRI in a patient with metastasis to the calvarium or skull base. Epidural or subdural metastases are best imaged with MR scans. MR scan may demonstrate meningeal enhancement or communicating hydrocephalus suggestive of leptomeningeal tumor dissemination; a spinal fluid examination is critical to establish the diagnosis, but the lumbar puncture should follow, not precede the scan because the lumbar puncture may produce meningeal enhancement *(115)*. All patients with suspected meningeal metastases should be considered for a lumbar puncture done with an opening pressure, cell count, protein and glucose concentrations, and a cytologic examination. Other special spinal-fluid studies may include biochemical and cellular markers, flow cytometry, or cell-surface markers.

Headache may also be a side effect of cancer treatment, such as the acute edema seen early in the course of radiotherapy, or from surgical complications such as hemorrhage, vascular injury, or CSF leaks. Certain chemotherapy or supportive therapies such as retinoic acids and 5-HT3 receptor antagonists also commonly cause headaches; headache occurs in up to 14% of patients taking the anti-emetic ondansetron *(116)*. Cytokines and biological modifiers also may commonly cause headache (Table 7).

**Table 8**
**Headache Features in a Cancer Patient that Suggest a Structural Cause**

| |
|---|
| Any change in prior headache pattern |
| Headaches unresponsive to previous therapy |
| Any focal motor, sensory, or visual symptoms or signs |
| Change in memory, personality, or mentation |
| Vomiting |
| Worse with bending over, cough, sneeze, or valsalva maneuver |

## INVESTIGATIONS: THE VALUE OF IMAGING IN HEADACHES AND BRAIN TUMORS

**PEDIATRICS AND ADOLESCENTS** Headache is a common symptom among adults and children, accounting for 18 million outpatient visits per year in the United States. In a recent study, the prevalence of headache in adolescent boys and girls was found to be 56 and 74%, respectively. Migraine prevalence was 3.8 and 6.6%, respectively. In children, brain tumors account for the largest group of solid neoplasms; however, the annual incidence is only 3 per 100,000. The value of neuroimaging in the evaluation of headache is therefore controversial *(117–119)*. Two retrospective studies *(101,120)* concluded that there was a very limited role for neuroimaging in the evaluation of headache in children; however, a sample size that did not yield any brain tumors may have influenced these results. Evans *(121)* reviewed the literature on imaging of 1282 patients with chronic headaches and a normal neurologic exam; only 1 had a brain tumor. Elderly patients with a new headache are more likely to harbor a brain tumor *(122,123)*. Burton et al. *(99)* reviewed 696 children who visited an emergency department for headache; one meningeal tumor and no parenchymal brain tumors were found. No large prospective study has been performed to evaluate this problem, and may never be done due to the low incidence.

In a recent review from Boston *(101)* a four-year retrospective analysis was done to identify clinical predictors of an underlying brain tumor in children with headache and to determine the indications for brain imaging in this group. Three hundred fifty-five patients who underwent imaging for headaches were evaluated, 9% of whom were found to have space-occupying lesions. The factors that appeared statistically to predict for a space-occupying lesion were headache less than 1 mo in duration, sleep-related headaches, vomiting, confusion, and absent family history of migraines. Sleep-related headaches and the absence of family history of brain tumors were the strongest predictors for an intracranial mass. Other factors were headache less than 6 mo in duration, absence of visual symptoms, and vomiting. Univariate predictors included headache of less than 1 mo duration and an abnormal neurologic exam. An increase in the number of predictors correlated with a higher risk of a brain tumor. All the patients who were found to have an abnormality in this series had at least three of the above predictors.

**ADULTS** The causes of headache in adults mirror those in children; however, predictors of brain tumors may be slightly different. In a review of 3026 scans done at the University of Texas for the symptoms of headache *(121)*, brain tumors were found in 0.8% of patients. In this study, 15% of patients over 65 yr of age who had been referred to a neurologist with the recent onset of a new headache had either a stroke or brain tumor. In general, age greater than 55 yr and a headache duration less than 1 mo seem to be the most useful clinical predictors for an intracranial mass in adults.

## MANAGEMENT OF HEADACHES IN CANCER PATIENTS

The management of headache in cancer is straightforward. If the headache is not severe, analgesics such as acetaminophen should be tried first. The dose of acetaminophen should not exceed 4–6 g per day to prevent liver damage. Aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided if surgical intervention is likely because of the increased risk of bleeding. If an NSAID is used, the patient must be monitored closely for gastropathy, renal failure, and hepatic dysfunction *(124)*. Misoprostol at a dose of 200 μg twice a day is very effective in preventing NSAID-induced gastric ulceration *(125)*. NSAIDs are particularly effective in pain associated with bone metastasis, soft-tissue infiltration, and recent surgery *(126)*.

If headache persists despite nonopioid treatment, an opioid drug should be added. Codeine is the best option, as it is prepared in fixed combinations with nonopioid analgesics. An increased incidence of side effects occurs at doses above 1.5 mg per kg body weight *(126)*. Patients with a deficiency of CYP2D6 enzyme or patients taking inhibitors of CYP2D6 such as quinidine, cimetidine, or fluoxetine may not be able to convert codeine to morphine and therefore derive no analgesic effect *(127,128)*.

Strong opioids such as morphine, hydromorphone, or fentanyl may be useful adjuvants in the treatment of severe headache that does not respond to nonopioid and codeine therapy.

Opioids may theoretically induce increased ICP by precipitating hypercapnia and subsequent vasodilation *(129)*. This is an acceptable risk when considering the morbidity associated with undertreatment of severe headache. Morphine is the most commonly used opioid. The controlled-release formulations allow oral administration once every 12 h. Hydromorphone (Dilaudid) may also be used; its increased solubility and potency allow for smaller injections or infusion volumes when parental opioids are required. Transdermal Fentanyl patches can control pain for up to 72 h and are particularly useful in patients who cannot take pain medications orally. Meperidine should not be prescribed because of short half-life and toxic metabolites. Mixed-opioid agonists-antagonists such as pentazocine and butorphanol should also not be prescribed because of the potential for reverse analgesia and lack of efficacy *(124)*. Methadone offers some advantages over other opioids as it is well-absorbed enterally but has a long half-life.

If a significant amount of edema is seen on neuroimaging studies and is thought to be causing the headache or other symptoms and signs, then dexamethasone 4 mg twice to four times daily is usually effective. Higher doses of dexamethasone (40–100 mg daily in two doses) can also be administered safely if necessary. Corticosteroids are useful for pain associated with

acute nerve compression, soft-tissue infiltration, and leptomeningeal metastasis *(124,130)*. If CNS lymphoma is a consideration, then dexamethasone should be avoided prior to biopsy. Lymphoma is exquisitively sensitive to corticosteroids, and a biopsy could yield normal, necrotic, or nondiagnostic tissue and delay definitive diagnosis and treatment *(131)*.

Tricyclic antidepressant drugs should be considered in neuropathic pain. Desipramine and nortriptyline cause fewer side effects and facilitate upward titration. Anticonvulsants such as carbamazepine, clonazepam, and gabapentin are also useful in neuropathic pain *(124)*, particularly if a stabbing or lancinating quality is present *(70)*.

Management of headache associated with head and neck tumors can be especially difficult. Dysphagia and a history of substance abuse are common in this population. Therapy directed against the tumor may be beneficial. Neurolytic or neurosurgical procedures for headache management are not preferred, as severe side effects are common and pain relief is of limited duration. Pharmacotherapy is again the mainstay of treatment. Usually several attempts at treatment are required before relief is achieved. Diagnosing the cause of pain (nociceptive or neuropathic) will lead to appropriate and effective treatment *(70)*. Enteral or transdermal routes of administration are preferred even if nasogastric or gastrostomy is required, as this route allows for prolonged analgesia, avoids toxicity, and causes less restriction in patients' activities. Multiple drug regimens are often required. A four-drug regimen of methadone, acetaminophen or NSAID, tricyclic antidepressant, and hydroxyzine was very effective in one study *(72)*.

Brain tumor headaches from primary brain tumors usually resolve with surgical or radiotherapeutic treatment. In our experience these are usually not difficult to control once definitive treatment of the tumor has begun. Resolution of headache is especially dramatic in patients who undergo surgical procedures that decrease raised ICP. Patients with acoustic neuromas seem especially prone to postoperative headaches. One study found that 82% of patients had continuous headaches postoperatively, including 40% of patients without headaches preoperatively *(52)*. Headache may be more frequent and severe after retrosigmoid surgery than after translabyrinthine surgery *(132,133)*. Cranioplasty with methylmethacrylate performed at the end of retrosigmoid surgery resulted in reduction of postoperative headache *(134)*. Radiotherapy may induce headache initially, presumably by increased edema, but this is usually transient and well-controlled with corticosteroids. Maintenance of appropriate corticosteroid dose for the first 2 wk of radiotherapy is advised *(130)*.

## SUMMARY

A brain tumor presenting solely as headache is rare and occurs in only 8% of cases. More commonly, headache accompanies other neurological symptoms and signs such as nausea, vomiting, seizures, and motor deficits. Several clinical features do increase the chances of predicting a brain tumor. These are its description, timing, location, quality, and intensity. The factors that predict for a brain tumor in adults with an acute headache are: (1) age greater than 55, (2) new onset of headaches with a duration of less than 1 mo, and (3) occipitonuchal location. In the pediatric and adolescent group with an acute headache, the significant clinical factors are: (1) sleep-related headaches, and (2) occipital location. CT imaging detects a brain tumor in acute headaches with no neurological symptoms or signs in approx 6% of cases, and 72% of the time if neurological symptoms or signs are present in the emergency room. However in the nonacute setting (such as patients with acute-recurrent headaches or chronic progressive and nonprogressive headache) neuroimaging is positive for a brain tumor in only 0.8% of cases. This yield may increase if clinical parameters as discussed in this chapter are applied. Not all headaches in cancer patients are attributable to parenchymal brain masses. Headaches may be related to medications as well as invasion or compression from intracranial, extracranial, meningeal, and dural-based lesions. One must not forget that even in the cancer patient headache may still occur from benign causes such as stress, depression, and migraines.

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# 5 Confusion and Delirium

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## INTRODUCTION

Delirium is one of the most frequent neurological complications occurring in patients with cancer, ranking second after pain among the reasons for requesting a neurological consult at a tertiary cancer center *(1)*. Inappropriate behavior, cognitive disturbance, and lack of judgment can be distressing for patients and families and impact upon attempts to deliver optimal medical care. In addition, delirium is usually a sign of the presence of significant medical complications and is associated with increased mortality. The signs and symptoms of this disorder are diverse and may be mistaken for other psychiatric disorders including mood and anxiety disorders. Different terms have been used to denote delirium over the years, including confusion, acute confusional states, acute brain failure, acute dementia, acute organic syndrome, cerebral insufficiency, metabolic encephalopathy, organic brain syndrome, reversible toxic psychosis, and intensive care unit psychosis *(2)*. This inconsistent terminology has contributed to the insufficient understanding of delirium in clinical and research settings *(2)*. This chapter will describe the terminology used for delirium, the symptoms that characterize the condition and its diagnosis, etiologic factors, treatment, and prognosis.

## HISTORY AND TERMINOLOGY

Delirium has recently been defined as a transient organic brain syndrome characterized by acute disturbances in attention, cognition, psychomotor behavior, and perception *(2)*. The term "delirium" is derived etymologically from the Latin: *de* meaning "down" or "away from" and *lira* meaning a "furrow or track in the fields;" it thus means to be "off the track" *(2)*. Historically, the term "delirium" was first used by Celso in the first century as a synonym of phrenitis—a term previously used by Hippocrates (who is known to have well-described the syndrome of an agitated state with compromised cognition occurring in course of fevers) *(2,3)*. This state was opposed to "lethargus," a term used to describe a state that today may be described as "somnolent hypoactive delirium." While the history of the concept developed over the centuries *(2)*, it was only in the 19th century that the difference between symptoms due to altered perception and cognition in course of fevers (and other organic conditions including surgical interventions, poisoning, and alcohol withdrawal) was clearly distinguished from similar symptoms due to other psychiatric conditions. This development produced the present use of the word "delirium" as a separate term from "delusion" in the anglophone world. The contribution of the French literature to the evolution in the psychiatric and neurologic classifications was fundamental in that it highlighted the concepts of "acute confusional state," introduced by Chaslin, and "oneiric consciousness," used by Regis *(4)*. This led to the distinction of symptoms of acute confusion and agitation occurring in the context of acute medical illness and those symptoms occurring in the psychopathological state—"*delire*"—the latter translating into the English "delusion" *(4)*.

During this same period, Hughling Jackson proposed a model to explain confusional states based on a hierarchical structure of the CNS *(5)*. Mental confusion in his model was seen as a separate syndrome from other psychiatric conditions. In this model the occurrence of confusion was attributed to the loss of voluntary control and intellectual functioning with the associated clinical findings deriving from psychological automatisms of lower brain functions "released" as a consequence of lack of control of higher brain functions.

Recent views have generally considered the global failure of cognitive processes to be at the core of the etiology of delirium, occurring in an "acute" form opposed to the chronic progressive form of cognitive dysfunction that is found in dementia. Two other recent theories to explain the pathophysiology of delirium persist. Some authors, rather than adhering to the theory of a "global failure of cognition" have considered delirium be the consequence of a selective failure of attention *(6)*.

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Others, given the compromise that occurs in delirium in vigilance and level of consciousness, have described it as an abnormality in the level of consciousness that occurs on the continuum between normal wakefulness and coma *(7)*.

It is known that acutely altered mental states, despite an array of different etiologic triggers, can be characterized by a common "spectrum" of fluctuating clinical phenomena. In addition, symptoms can fluctuate and the whole "range" of symptoms may or may not be present in one individual. As a consequence of this clinical observation *and* the history described previously, there has been persistence in the literature of two terms or categories—"delirium" and "acute confusional state (or encephalopathy)." Some authoritative neurologists have preferred to keep these states separate, with "delirium" being used to describe acute mental status changes characterized by agitated hallucinated phenomena—delirium tremens (DT) being the prototype—and "acute mental confusion or encephalopathy" to describe those states characterized by confusion but not characterized by agitated phenomena *(8)*.

Although the terms "delirium" and "acute confusional state or encephalopathy" persist, Engel and Romano have demonstrated that the electroencephalographic (EEG) correlates of most acute confusional states and deliria are very similar (although of note the EEG findings specific to DT are somewhat different with unique and characterizing features) *(9)*. Their work has set the scientific basis for a unified concept of delirium, a concept that Lipowski has further developed *(2)*. This work has evolved and now underlies the definitions of delirium found within the Diagnostic Statistical Manual of Mental Disorders *(10,11)*. The latter is a document produced by the American Psychiatric Association to provide a "standard" classification for psychiatric conditions. In addition, the International Classification of Diseases (ICD-10) also now provides a definition of delirium *(12)*. Both definitions recognize the spectrum of phenomena that occur among and within cases of this condition and both recognize that it is a transient syndrome characterized by acute disturbances in attention, cognition, psychomotor behavior, and perception (*see* detail below for each definition). Although the terminology utilized to describe states characterized by acute confusion continues to be inconsistent in the medical literature, the developments to date have set the stage for the adoption of a unitary concept of delirium—a condition characterized nonetheless by a spectrum of clinical phenomena.

## PATHOPHYSIOLOGY

The pathophysiology of delirium is not fully clarified, but an understanding of several anatomical functions and neurotransmitter substrate disturbances is important if an attempt is to be made to interpret the clinical findings. Numerous areas of neurological dysfunction have been identified in this condition, and it is difficult to attribute this finding to the abnormal functioning of any one discrete cerebral structure. One debated interpretation is that the syndrome is caused by the ability of different etiological factors to impact on a final common pathway producing stereotyped clinical consequences *(13,14)*.

One fundamental neurologic concept must be recognized if the pathophysiology of delirium is to be understood: the functional distinction, on both clinical and neuroanatomical grounds, of arousal and alertness from cognition and awareness. (Arousal and alertness are generally considered to be synonyms reflective of level of consciousness or wakefulness, and therefore the term arousal will be utilized from hereon.) In simplistic terms arousal may be considered to reflect a general activation of the brain cortical functions by the action of subcortical structures linked also with the regulation of the sleep-wake cycle. Arousal can be present despite cognitive failure, but arousal is a prerequisite for clear cognition. For example, both arousal and the sleep-wakefulness cycle may be preserved in patients with profound cognitive failure triggered by dementia and even more dramatically in patients without any sign of active cognition or awareness, such as those in a vegetative state.

Another compelling clinical observation that must be acknowledged in considering the potential pathophysiologic explanations for delirium is that cases of delirium in which the cause cannot be removed commonly evolve to stupor and coma. This further supports the interpretation of delirium pathophysiology that considers the cerebral structures involved in the modulation of arousal to be dysfunctional in delirious states *(14)*.

It has been speculated that selective altered arousal may be the trigger of all or most of the other disordered brain functions in delirious states. This concept requires that it be possible to distinguish brain structures (or functions of specific structures), that are responsible for a basic form of brain arousal (synonyms: activation, level of consciousness, alertness, wakefulness) from those structures responsible for clear cognition manifest by the "higher" cognitive processes such as emotion, memory, and the ability to accurately interpret sensory phenomena. As mentioned earlier, arousal is considered to be a prerequisite for such clear cognition. The pioneering work by Moruzzi and Magoun has described a primary role of brainstem structures in regulating arousal and sleep-wake cycle and indeed provides an anatomical basis upon which the theory of delirium being based on a disturbance of these structures can be put forward *(15,16)*. Recently three cases of patients with Machado-Joseph disease were reported who had delirium in the course of their illness. Two necropsies showed degeneration of the reticular formation, raphe nuclei, and locus ceruleus in the brain-stem tegmentum *(17)*.

On the other hand, it is also known that *any* type of lesion diffusely affecting the brain will impact on the level of consciousness, and it has been shown that integrative brain functions are lost proportionally to the amount of brain matter lost but also in relation to the rapidity of the onset of the pathological insult *(7)*. The selective deficits in neurologic function that may occur during the onset of delirium, in the absence of arousal disturbance, suggest the presence of a more diffuse, multifocal process affecting structures other than the brain stem. A failure of selective attention, which is the ability to select in the environment significant stimuli and to focus attention for a protracted time, is found in all cases of delirium and it has indeed been suggested that this be considered to be an essential feature of the syndrome. Selective lesions of cortical association areas in the right, nondominant, cerebral hemisphere can produce

acute confusional states *(18)*. Other symptoms typical of delirium such as language and memory alterations, disruption of the wakefulness-sleep cycle, or hallucinations can be early findings in the course of the syndrome and also isolated findings of partial syndromes. These presentations suggest focal origins for a diffuse global syndrome triggered by metabolic derangements that first affect the most sensitive cerebral structures, causing focal symptoms that subsequently combine with other symptoms and signs to manifest as the full delirium syndrome. In this latter situation arousal and consciousness also become impaired *(14)*.

Many neurotransmitters have been implicated in the pathogenesis of delirium. Abnormalities in cholinergic neurotransmission, overstimulation or understimulation of the γ-aminobutyric acid (GABA) system, N-Methyl-D-aspartate (NMDA) receptor blockade, serotonin antagonism, and overstimulation of dopaminergic pathways have all been described in association with etiologically diverse forms of delirium *(14)*. Currently, the neurotransmitter system that is most commonly cited in relation to its involvement in delirium pathophysiology is the cholinergic system *(16)*. The cholinergic projection pathways from the brainstem to the thalamus, cortex, and hypothalamus are implicated in the sedative properties of many drugs and their dysfunction is demonstrated in dementing illnesses such as Alzheimer and Lewy body dementia *(16)*. Further, the use of cholinesterase inhibitors seems to improve some of the symptoms of dementia that are also found in delirium *(19)*. It has been known for some time that anticholinergic drugs can cause delirium while many other drugs that are associated with delirium also have anticholinergic activity. In addition, hypoglycemia, hypoxia, ischemia, and other toxic metabolic and nutritionally induced insults impact on the function of neurotransmitters in the cholinergic system, primarily on acetylcholine *(20)*.

The cellular link between neurotransmitter abnormalities, altered brain metabolism, and the clinical manifestations of delirium is most likely based on alterations of the second-messenger system involving calcium, cyclic GMP, and/or the phosphatidylinositol cascade *(20,21)*. One other proposed explanation for the cerebral effect of infective states or of altered immune reactions is that neurotransmitter synthesis and neurotransmission are directly or indirectly influenced by the effect of cytokines. Although the association between cytokine release and delirium remains to be fully determined *(22)*, this hypothesis could provide an explanation for why immunomodulation therapy with interferon-α (IFN-α) and interleukin-2 (IL-2) has a relatively high rate of associated cognitive, emotional, and behavioral disturbances.

Although delirium may occur as a consequence of a variety of pathophysiologic processes or events, most of these processes and events interfere with oxygen-glucose metabolism at the cerebral level, which in turn affects the function of groups of neurons that are necessary for normal arousal and cognition activities. In many individuals there are not only multiple potential causes of delirium but also some predisposing factors that may compound the clinical manifestations. For example, the degeneration of the cholinergic system—typical of brain aging and Alzheimer's disease—may explain why both of these conditions are recognized risk factors for developing delirium. Other metabolic factors and impairments in oxidative metabolism can also affect cholinergic transmission. An increase in serum anticholinergic activity has been associated with the onset of delirious episodes due to many different exogenous toxic or pharmacological factors and this has also been observed in course of fevers *(23)*. Another example of a potentially concurrent causal factor is the presence of thiamine deficiency, a condition that is more common in the elderly and in medically ill institutionalized patients *(24–26)*. These observations have practical value in assessing the role of potential causal factors in precipitating delirium and support a treatment approach that focuses on the minimization of *any* potentially reversible cause of delirium (including assessing the need for each medication that is being administered to the patient with respect to its potential to precipitate anticholinergic effects or result in other neurologic dysfunction).

The presence of concurrent etiologic factors with the potential to impact on differing aspects of neural functioning may create in an individual a particular sensitivity to an insult that alone may not have been associated with particularly severe alterations in functioning *(27)*. In summary, in a particular individual, multiple potential causes of delirium may be present. Alone, each of these etiologic factors may not be sufficient to cause the syndrome, but the clinical manifestations and the individual reaction to the etiologic insult may be modulated as a consequence of host biological variables (general predisposing factors) in play together with environmental and psychological factors.

Clearly there is a need for a greater understanding of the pathophysiology of delirium, especially at the cellular and neurotransmitter level. As such an understanding evolves, it may facilitate the development of treatment strategies aimed at specific aberrations in second-messenger system, neurotransmitters, and the like *(28)*.

## CLINICAL FEATURES

**EPIDEMIOLOGICAL ASPECTS** In the last 10 yr new epidemiological data are beginning to reveal the magnitude of the problem of delirium in different settings of care. It has been estimated that the prevalence of delirium in acute general hospitals is around 10% *(2)*. The prevalence is higher in intensive care units, cardiac surgery units, and burn units, where it can reach 30% *(2,29)* . Studies are lacking in the general oncological population, but the prevalence of delirium is likely to be between 10% and 30%. The lower figure is equivalent to that found in the general population hospitalized in the acute care setting; however, prevalence is likely to vary greatly depending on a variety of factors including the severity of illness and the age of patients. For example, in the advanced phases of cancer the prevalence of delirium is around 30% and reaches 70–90% prior to death *(30–33)*.

One important factor that has facilitated a more accurate description of the epidemiology of delirium relates to the fact that the syndrome can be diagnosed through the use of specific diagnostic criteria *(34)*. Using these more accurate criteria it has become apparent that underreporting of this condition has been a problem. For example, in an emergency care unit set-

ting, only 6% of cases of delirium in the elderly were correctly identified *(35)*.

**DESCRIPTION** The clinical features of delirium include a variety of neuropsychiatric symptoms that are common in depression, dementia, and psychoses. Its onset is often preceded by subtle mood or personality changes that may go unnoticed by professional caregivers but be observed and reported by family. This prodromal phase may be characterized by fatigue, irritability, insomnia, daytime somnolence, malaise, headache, hypersensitivity to visual and auditory stimuli, illusions, vivid dreams, nightmares, lack of concentration, inattention, and mild disorientation. The patient is often aware of these changes but may discount their significance or even conceal the symptoms.

Variability in clinical findings is typical with a wide range in the severity and nature of symptoms among and within cases. It is common for symptoms to be present through the course of the day with nocturnal exacerbations. It is not uncommon for the first symptoms of delirium to occur at night. Nocturnal episodes of cognitive failure can be sensitive indicators of an incipient delirium. Anxious, aggressive, or depressive reactions are frequent at the onset of cognitive failure in addition to other less "dramatic" reactions including, among others, apathy and affective inhibition. From this early stage the patient may proceed into remission or progress to more severe symptoms.

The onset of delirium is, by definition, acute or subacute within hours to days. At times the time course is protracted, and it may be difficult to recognize an acute phase. Attention failure is always present and characterized by easy distractibility, difficulty in focusing and maintaining attention, and frequent shifts in the focus of attention. Perseveration is common, and memory deficits occur frequently. Orientation to time is usually lost before orientation to place and person. Clarity of thought is altered; incoherent, rambling, fragmented, and poorly systematized delusions may be found. Delusions are often persecutory, influenced by elements of the environment, and are commonly not recalled by the patient *(36)*. Perception is abnormal at times with illusions and hallucinations, the latter frequently being visual rather than auditory *(36)*. Erroneous identifications are common.

In the hypoactive variant of delirium the patient can be somnolent—in contrast to the hyperactive form in which the patient can appear excited or hyperalert. In the latter type of case the patient is often excessively reactive to external stimuli. Light and sound may be perceived by the patient as being unpleasant stimuli. Illusions, hallucinations, and incorrect interpretations can lead to an overall delusion. In the hypoactive form the patient is usually lethargic with little interest in external stimuli. Hallucinations and delusions may be present but the patient may not manifest or report them. Very frequently the hypo- and hyperactive forms are not distinct subtypes but indeed may coexist in an individual patient with fluctuations or evolutions in the clinical findings over time. Indeed, mixed hypo/hyperactive forms are considered to be the most frequent delirium variant *(13,37)*.

**OTHER NEUROLOGICAL SIGNS** As discussed earlier, delirium is primarily characterized by cognitive impairment, but other neurologic signs may also occur. For example, tremors and myoclonus can be associated with delirium. Asterixis is typically found in hepatic encephalopathy but may also occur in other types of delirium. (This latter sign can be seen best when the patient is asked to hold arms and hands extended for at least 30 s; another sensitive alternative maneuver in the fatigued patient consists in asking him or her to keep the index finger extended with the hand laying prone on a surface). Frontal release reflexes (palmomental, glabella, snout, forced grasping) are useful confirmatory signs of another underlying neural pathology contributing to the origin of the syndrome. These signs, in young patients, are more indicative of an acute underlying neurologic problem and, in patients who are known not to have had these signs before—in the elderly especially, these signs may have been present prior to the onset of delirium in which case they are likely to have another etiology. Multifocal myoclonus and asterixis are signs that may occur early in cases of opiate toxicity and in other metabolic conditions.

Impaired writing and design abilities are known to be very sensitive indicators of initial dysfunction of the higher integrative brain function and can be very helpful to screen early symptoms of delirium. One of the following—the classic clock drawing test, reproduction of a geometric figure as required by the Mini Mental State Examination, or writing a complete sentence—should be a standard part of the neurological examination in a confused patient *(38,39)*.

## DIAGNOSTIC CRITERIA AND CLASSIFICATIONS FOR DELIRIUM

A well-defined diagnostic system is very important to allow standardized assessment and to ensure accuracy in clinical reporting and communication. The diagnosis of delirium currently relies on the classification of the DSM-IV *(11)*. The DSM-IV includes delirium in the same chapter as dementia and amnestic disorder, based on the fact that impairment of cognitive functions is typical of each of these syndromes. There is overlap of the psychopathological features in delirium and many other conditions. Through adherence to the DSM criteria diagnostic accuracy can be facilitated and will allow the distinction to be made between this and other psychiatric conditions.

The main diagnostic systems in use, in addition to the DSM IV are the DSM III-R and the ICD 10 *(10–12)*. Although the DSM III-R is not the most recent version of the DSM, many recently published reports reflect work done using these classification criteria which differ slightly from those described in the more recent DSM IV.

- DSM III-R *(10)*: In DSM III-R, delirium is considered an organic brain syndrome and the criteria for diagnosis are listed on Table 1. The differential diagnosis from psychiatric conditions and the biological correlates of delirium are not considered specifically.
- DSM IV *(11)*: In the most recent version of the DSM, delirium is considered as a single nosological entity, the term "organic brain-syndrome" is abandoned, and the diagnostic criteria are simplified with a focus on two main areas of brain function derangement—consciousness and attention, and cognition (Table 2). Specific symptoms and secondary manifestations are not included. It is worth not-

**Table 1**
**DSM IIIR Criteria for Diagnosing Delirium[a]**

| | |
|---|---|
| A. | Reduced ability to maintain attention to external stimuli (e.g., questions must be repeated because attention wanders) and to appropriately shift attention to new external stimuli (e.g., perseverates answer to previous question). |
| B. | Disorganized thinking as indicated by rambling, irrelevant, or incoherent speech. |
| C. | At least two of the following: |
| | 1) Reduced level of consciousness, e.g., difficulty keeping awake during examination; |
| | 2) Perceptual disturbances: misinterpretations, illusions, or hallucinations; |
| | 3) Disturbances of sleep-wake cycle with insomnia or daytime somnolence; |
| | 4) Increased or decreased psychomotor activity; |
| | 5) Disorientation to time, place or person; |
| | 6) Memory impairment, e.g., inability to learn new material such as the names of several unrelated objects after 5 min, or to remember past events, such as the history of the present illness. |
| D. | Clinical features develop over a short period of time (usually hours to days) and tend to fluctuate over the course of a day. |
| E. | Either (1) or (2): |
| | 1) Evidence from the history, physical examination or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance; |
| | 2) In the absence of such evidence, an etiological organic factor can be presumed if the disturbance cannot be accounted for by any non-organic mental disorder, e.g., manic episode accounting for agitation and sleep disturbance. |

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**Table 2**
**DSM IV Criteria for Diagnosing Delirium due to a General Medical Condition[a]**

| | |
|---|---|
| A. | Disturbance of consciousness with reduced ability to focus, sustain, and shift attention. |
| B. | Change in cognition (such as memory deficit, disorientation, language disturbances) or perception disturbances not better explained by a preexisting stabilized or evolving dementia. |
| C. | The disturbance develops over a short period of time and tends to fluctuate during the course of the day. |
| D. | There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition. |

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ing that in the DSM IV the impairment of the level of consciousness (a concept that can overlap with arousal) is a primary characteristic of the syndrome.

- ICD 10 *(12)*: The International Classification of diseases classifies delirium that is not due to alcohol or other psychoactive substances, among the "organic psychic syndromes and disturbances including the symptomatic ones" (Table 3). In this classification delirium is considered to be a syndrome that is characterized by disturbances of consciousness, cognition, behavior and sleep-wakefulness cycle, rapid onset, transient course, and fluctuation of symptoms. For an ICD-10 diagnosis the etiology of the delirium does not necessarily need to be specified. If this classification is used the diagnosis requires that all areas of dysfunction described in Table 3 are present even if in a mild form *(12)*.

## DIFFERENTIAL DIAGNOSIS OF DELIRIUM

When assessing patients for delirium it is important to recognize that almost any of the symptoms that occur in delirium can occur also in other psychiatric and neurologic conditions. The differential diagnosis focuses on dementia and acute psychosis, but may encompass many other psychiatric disorders and neurological entities.

Many of the psychiatric symptoms that are common in cancer patients can occur as manifestations of delirium, including anxiety, tearfulness, nervousness, depression, and irritability. The presence of such symptoms in the medically ill cancer patient, it is always important to examine the patient's mental status; when there is evidence of impaired cognition, the potential diagnoses include delirium; dementia of various types; and acute neurologic conditions including epilepsy, amnestic disorders, and drug-induced psychoses. The features that can be helpful in distinguishing the conditions responsible for cognitive impairment include the timing of the onset of the disorder, alterations in the level of consciousness, the systematization of delusions, evidence of psychomotor disturbances, and deviations from normal speech patterns.

In contrast to delirium, which is characterized by the onset of an acute change in cognition, the dementias are characterized by progressive cognitive impairment. A history of chronic decline without alteration in the level of arousal can assist in distinguishing these syndromes from delirium. The diagnosis of delirium can be especially difficult when delirium and dementia occur concurrently. Demented patients are particularly sensitive to drug toxicity, metabolic abnormalities and physical stress, all of which have clear associations with the onset of delirium. This is especially relevant in elderly or otherwise debilitated patients. A history of the patient's baseline mental status, level of cognitive impairment, and behavioral pattern is most important in assessing mental status changes in demented patients.

The term "pseudodeliria" has been used to describe acute psychotic episodes that resemble delirium. Most of these episodes can be distinguished from delirium on the basis of a his-

**Table 3**
**ICD 10 Criteria for Diagnosing Delirium, not Induced by Alcohol and Other Psychoactive Substances[a,b]**

For a definite diagnosis, symptoms, mild or severe, should be present in the following areas:

a) Impairment of consciousness and attention (on a continuum from clouding to coma; reduced ability to direct, focus, sustain, and shift attention);
b) Global disturbance of cognition (perceptual distortions, illusions, and hallucinations—most often visual; impairment of abstract thinking and comprehension, with or without transient delusions, but typically with some degree of incoherence; impairment of immediate recall and of recent memory but with relatively intact remote memory; disorientation for time as well as, in more severe cases, for place and person);
c) Psychomotor disturbances (hypo- or hyperactivity and unpredictable shifts from one to the other; increased reaction time; increased or decreased flow of speech; enhanced startle reaction);
d) Disturbance of the sleep-wake cycle (insomnia or, in severe cases, total sleep loss or reversal of the sleep-wake cycle; daytime drowsiness; nocturnal worsening of symptoms; disturbing dreams or nightmares, which may continue as hallucinations after awakening);
e) Emotional disturbances, e.g., depression, anxiety or fear, irritability, euphoria, apathy, or wondering perplexity.

[a]Includes acute brain syndrome, acute confusional state (nonalcoholic), acute infective psychosis, acute organic reaction, acute psychoorganic syndrome.
[b]Reprinted with permission from ref. *12*.

tory of psychosis and by certain clinical signs manifest on mental status examination. In delirium, for example, vigilance is not usually preserved and there is clear impairment of arousal usually manifesting as concentration deficits and fluctuating levels of alertness. In psychotic episodes this latter feature is not present, the EEG is normal, and delusions are most frequently sustained and systematized. Nonetheless—as can occur in cases of dementia—delirium and psychosis can occur concurrently; consequently, a known history of psychiatric disease should not eliminate the need for careful screening to assess for other causes of altered mental status.

Some of the symptoms of delirium may be seen in mood disorders, which are common particularly among the elderly and among cancer patients. Depression, for example, is common in the cancer population, and depressive symptoms are often an associated feature of delirium. Because of the high prevalence of both mood disorders and delirium in the medically ill population, it is extremely important that evaluation of a seemingly depressed patient include a comprehensive assessment that incorporates neurological, psychiatric, and cognitive evaluations. It is not uncommon when a patient is clearly confused for a clinician to consider a diagnosis of delirium. In contrast, if an ill patient is anxious it is common for subtle mental status changes to go undetected and for the appropriate diagnosis—delirium—to be overlooked. This provides further support for the need for mental status examinations in all patients with psychiatric symptoms.

In summary, the diagnosis of delirium must involve careful examination of the mental state of the patient, often repeated over time in cases where symptoms may be fluctuating. An accurate diagnosis of delirium may also be facilitated by the use of an instrument or diagnostic tool (see below). The other key part of diagnosis involves the careful examination of the patient with a clinical work-up aimed at defining reversible etiologic factors. The intensity and detail of this aspect of the diagnostic process will depend on the clinical situation and goals of care.

## DIAGNOSTIC TOOLS AND INSTRUMENTS FOR ASSESSMENT OF DELIRIUM

Although the clinical psychiatric interview using the DSM criteria remains the "gold standard" for the evaluation and diagnosis of delirium, several instruments have been developed to facilitate its diagnosis. The ideal instrument to assess and diagnose delirium both in research and in clinical practice should have the following characteristics *(40,41)*:

1. Be validated specifically for diagnosing delirium according to accepted criteria (content validity).
2. Be simple and administrable by different staff members (inter-rater reliability).
3. Discriminate delirium from dementia and psychoses (discriminant validity).
4. Allow for repeated administrations and be sensitive to time fluctuations of symptoms and to therapeutic intervention (i.e., it should be sensitive to clinically relevant changes).
5. Identify all the clinically relevant aspects of the syndrome.

To date, there is no instrument that fully satisfies all of these requirements *(41)*. Nonetheless, for diagnosis in the clinical setting, we suggest that consideration be given the integration of a diagnostic system based on clinical criteria with an assessment instrument that has some utility in the quantification of severity, symptoms, and course. The diagnosis can be based on the previously mentioned criteria (DSM IV, ICD 10). Many neuropsychological assessment tools can be adapted to assess the patient with delirium (*see* Smith et al. for a very comprehensive review of instruments for use in the setting of delirium) *(41)*, but very few have been specifically designed to assess this syndrome. Instrument selection for use in research will depend on the purpose of the research but the aforementioned criteria should also be considered in this process *(41)*. Certainly the consistent use of appropriate scales will be useful in addressing the gaps that exist in the description and quantification of the clinical phenomena of delirium that, to date, have often been reported in idiosyncratic forms and are open to variable interpretations.

In this chapter we will briefly review the Confusion Assessment Method *(42,43)*, the Delirium Rating Scale *(44)*, and the Memorial Delirium Assessment Scale *(45)*. While we also recognize that other scales or method are also available *(46,47)*, we elected to review those instruments that are more recent, practical, respond to most of the criteria required for a clinically useful assessment tool, and have more data available about their validity in the field.

- *Confusion assessment method (CAM) (42,43)*: This is a useful tool for ensuring that all the criteria for the DSM III-R are met; however, it should be noted that the instrument was developed using these criteria and not those in the DSM IV. The instrument is short and assesses four areas—acute change in mental status, failure of attention observed by the interviewer, disorganization of thought, and altered state of consciousness. The CAM had 94–100% sensitivity and 90–95% specificity in the original validation study *(42)*. Similar results have been subsequently reproduced *(43)*. The instrument is designed for use by trained medical personnel *(48)*.
- *Delirium rating scale (DRS) (44):* The DRS is an instrument that contains a list of symptoms that describe typical clinical aspects of delirium and rates their relevance in the phenomenology of delirium. Ten clinical aspects or symptoms of delirium are scored. The maximum score is 32, and scores from 12–32 are found in patients with delirium. The DRS has been assessed as a diagnostic tool using different cutoffs of scores between 8 and 12, but the results obtained by using these different thresholds are not without some problems *(49,50)*. The DRS is intended to reflect a 24-h assessment period. The scores are designed to differentiate the patient with delirium from patients with dementia and psychiatric disorders but certainly areas of overlap exist *(50)*.
- *Memorial delirium assessment scale (MDAS) (45)*: The MDAS is also a 10-item instrument that quantifies the severity of symptoms found in delirium. It is based on criteria that are included in both the DSM-IIIR and the DSM-IV. Scores from the MDAS and DRS are significantly correlated and also correlate with a global clinical judgment of delirium severity *(45,50)*. The MDAS is intended for repeated administrations over a short time period; and it is hoped that this new instrument will be useful to capture short-term fluctuations in delirium.

In addition to diagnostic tools based on clinical assessment it is important to address the role of the electroencephalogram (EEG). The EEG can be a useful tool in assessing the diagnoses of delirium, psychosis, and dementia *(51,52)*. The main EEG finding in the course of delirium is a progressive slowing of the EEG-dominant frequencies with reduction of alpha rhythm, as well as the onset of an increase in delta and theta frequencies *(9)*. In metabolic encephalopathies EEG changes can also evolve into burst suppression patterns and epileptiform activity. These latter changes are found both as effect of general anesthetics and of metabolic encephalopathies, while triphasic waves are typical of metabolic encephalopathies alone. The EEG is especially important in differential diagnosis. For example, nonconvulsive status epilepticus is a condition that results in altered consciousness that can lead to a clinical state of delirium. The latter diagnosis can be confirmed by EEG. In oncology complex metabolic situations can lead to partial status and this condition is also typical of ifosfamide encephalopathy *(54)*. In such instances a "diagnosis" of delirium may still be present with its "etiology" being a seizure disorder.

**Table 4**
**Diagnostic Tests[a]**

| |
|---|
| Temperature |
| Bedside Screen of Medication profile |
| Pulse oxymetry |
| Blood glucose |
| Serum electrolytes (Na, K, CL, Mg, Ca) |
| BUN, creatinine |
| Liver function tests |
| Ammonia |
| Leukocyte count |
| Red cell count |
| Coagulation profile |
| Urinalysis |
| Blood/urine and other cultures for infection screen |
| Urine or blood drug screening |
| Blood gases and acid-base balance |
| CSF examination: blood, glucose, proteins, lymphocytes leukocytes, malignant cells, culture |
| B12 and folate levels |
| Thyroid hormone and TSH |
| Adrenal function |
| Paraneoplastic antibodies |
| Brain CT or MRI |
| EEG[b] |

[a]The clinical situation and goals of care will influence decisions regarding investigations. On occasions, proceeding with an investigation may not change the treatment strategy in an individual case and therefore it may be concluded that proceeding with such an investigation would have little role.

[b]The EEG has a special role in the investigation of delirium and its place in last position on this list should not be read to imply that it has limited usefulness. The EEG has an important role in the differentiation of different pathological conditions resulting in cognitive impairment. It should be considered when there is a specific factor in the history or clinical situation to suggest its utility.

## ETIOLOGY AND RISK FACTORS

Having established a diagnosis of delirium, defining the etiology is key to the implementation of appropriate therapy. There are innumerable causes of delirium with the etiologic categories of delirium being arbitrarily grouped into primary CNS diseases, systemic diseases with secondary CNS effects, exogenous intoxications, and alcohol or drug withdrawal. As discussed above, multiple etiologic factors can occur concurrently in an individual who may have few, or many, predisposing characteristics. All etiologic and predisposing factors should be considered in defining potential factors amenable to treatment. Table 4 provides a list from simple to more complex tests and laboratory or imaging procedure that may be useful in assessing the etiology of delirium.

**Table 5**
**Causes of Delirium in Cancer Patients**

| |
|---|
| Primary CNS tumor |
| Secondary CNS tumor |
| Brain metastases |
| Meningeal metastases |
| Nonmetastatic complications of cancer |
| Metabolic encephalopathy due to hepatic, renal, or pulmonary failure |
| Infections |
| Electrolyte abnormalities |
| Glucose abnormalities |
| Hematological abnormalities |
| Paraneoplastic neurological syndromes |
| Nutritional deficiency (including thiamine and vitamin B12 deficiency) |
| Toxicity of antineoplastic therapies |
| Chemotherapy toxicity (*see* Table 6) |
| Radiation to brain |
| Toxicity of other medications (*see* Table 6) |
| Other diseases/conditions not related to neoplasm |
| CNS diseases (including cerebrovascular disease, vasculitis, or trauma) |
| Cardiac disease |
| Lung disease |
| Endocrinopathy |
| Alcohol or drug abuse or withdrawal |
| Other |

**PRIMARY CENTRAL NERVOUS SYSTEM (CNS) DISEASES (TABLE 5)**

- *Cerebrovascular diseases*: Cerebral infarcts and transient ischemic attacks (TIAs) can present with delirium. Cases of vascular insufficiency in which small focal lesions have been found to be the cause of delirium have been described due to the involvement of the territory of the medial cerebral artery of the nondominant hemisphere *(18,55,56)*. A recent systematic prospective survey, however, showed that the most relevant factor associated with the onset of delirium after ischemic stroke is the prestroke cognitive status *(57)*. Other vascular causes such as brain hemorrhage or hypertensive encephalopathy can globally affect brain function and level of vigilance by producing brain edema or herniation.
- *Trauma*: Delirium is often the only sign of brain contusion, concussion, or hematoma.
- *Epilepsy*: Postictal states are a common cause of persistent cognitive failure. The possibility of a partial status epilepticus or of partial complex seizures is an important differential diagnosis that can be revealed by EEG. As mentioned earlier, in oncology this condition has been well recognized in association with ifosfamide toxicity *(54)*.
- *Infections*: Meningitis and encephalitis are commonly associated with altered sensorium and cognition.
- *Intracranial tumor*: Consciousness and cognition are frequently affected by intracranial tumors. Intracranial hypertension and involvement of brainstem functions are obvious causes of impaired consciousness. Frequently the presence of cerebral or meningeal metastases, in the absence of focal neurologic deficits, results in mental changes and neuropsychological symptoms that can be detected only after careful examination. Indeed with careful detection techniques, mental changes are the most frequent sign of brain dysfunction due to intracranial and meningeal metastases *(58–60)*. Case studies show that microscopic meningeal infiltration can cause mental status changes without focal signs and/or symptoms *(61)*. The mechanism of encephalopathy due to meningeal metastases is uncertain. Tumor cell seeding to the meninges can interfere with CSF formation and resorption, compete with the brain parenchyma for essential nutrients, and/or produce ischemic damage by infiltrating the Virchow-Robin spaces. Intracranial pressure changes may be present early in course of leptomeningeal disease due to altered dynamics of the CSF and present without the classic findings of papilledema, severe headaches, or meningismus *(62)*. Fluctuations of intracranial pressure (plateau waves) can be responsible for unexpected, reversible, acute changes of mental status *(59)*. In the advanced stages of cancer, brain metastases are associated with an increased risk of developing delirium. In this setting patients frequently also have other problems present, such as hypoxia, anorexia, and poor performance status, placing them at additional risk for complications of cancer (and for delirium) *(32)*.
- *Degenerative diseases*: Dementia is a well known predisposing condition for delirium. There are no studies that evaluate the degree to which other primary neurological diseases and systemic diseases with secondary CNS effects predispose to delirium, although it is clear that they do have this effect.

**SYSTEMIC DISEASES WITH CNS EFFECTS** Delirium is probably the most frequent neurological complication of non-neurological general medical illness. Many of the etiologic factors for delirium occur commonly in the patient with cancer *(59)*. Fever and infection have long been described as triggers of delirium; indeed, this was described by Hippocrates *(3)*. Liver, renal, pancreatic, or pulmonary failure can cause brain dysfunction and give rise to delirium. Brain hypoperfusion and consequent hypoxia can be due to cardiac or extra cardiac causes. Vitamin, cofactor, and glucose deficiency affect cerebral metabolism directly and may be responsible for acute confusion. Electrolyte imbalances influence brain water content and may result in osmotic neuronal damage triggering delirium, stupor, or coma. In addition, most endocrine organ dysfunction can manifest as delirium (panhypopititarism, hypoparathyroidism, hypo- or hyperthyroidism).

**EXOGENOUS INTOXICATIONS, AND ALCOHOL OR DRUG WITHDRAWAL** Drug toxicity is frequently implicated in the etiology of acute confusional states, especially in the elderly and in patients with other predisposing factors such as severe illness or organ failure. Drugs with primarily anticholinergic activity are commonly implicated in delirious states but many other drugs can also trigger delirium (although the mechanism by which they trigger brain dysfunction remains unknown). Excessive cholinergic stimulation can also cause delirium *(63)*. The elderly population is particularly at risk for delirium due to common alterations in pharmacokinetic and pharmacodynamic parameters that occur with aging. Table 6 provides a classification of the drugs that have been associated with delirium (or in some studies "encephalopathy") and in particular includes drugs that are commonly used in oncology.

In the oncology setting, the role of opioids in delirium deserves a brief summary as this group of medications are commonly used for the treatment of pain. Opioids are sedative, with at least part of this sedation resulting from their anticholinergic activity. It is well-known that opioid-related somnolence is usually dose-related. The impact of opioids on alertness can be documented by specific testing, especially after a dose increase or in healthy volunteers *(64,65)*. Most commonly, however, the cognitive impairment in patients with cancer is a complex multifactorial phenomenon that is explained by decline in general performance, severe pain, and concurrent illness, and is *not* necessarily caused by the effect of opioids alone *(66)*. Opioid toxicity can, however, certainly manifest as delirium, with idiosyncratic patient reactions occurring with *any* opioid at *any* dose *(67,68)*. This probably occurs due to the anticholinergic effects of opioids, but also in certain instances may occur as a consequence of excitatory CNS phenomena that have been reported with high doses of opioids *(69,70)*. Hallucinations, delirium, myoclonus, hyperalgesia, and seizures have each been described as part of this syndrome.

**RISK AND PRECIPITATING FACTORS** Not only is it more frequent to find multiple etiologies of delirium than to find a single identifiable cause, but it has also been suggested that the patient's underlying condition could modify his or her susceptibility to external factors that may otherwise not, in less susceptible individuals, be pathogenic *(2,7)*. Furthermore, in some instances, the rate of change of a metabolic or toxic factor may be more important than the absolute value of the factor *(2,7)*. An example of such would be a sudden, vs a slow, decrease in a metabolic parameter such as serum sodium. Several studies undertaken in the elderly have identified a number of risk factors including age, previous cognitive failure (dementia), severity of illness, infections, renal failure, use of psychotropics, and electrolytes abnormalities *(71–73)*. In the specific case of alcohol withdrawal triggering delirium tremens, risk factors have been shown to include intercurrent febrile illnesses, trauma, reduced food intake, and gastrointestinal disturbances *(74)*.

Recently a multifactorial model for the development of delirium has been proposed and validated by Inouye and colleagues *(73,75,76)*. These authors distinguish baseline vulnerability factors—factors already present at the time of hospitalization—from precipitating factors that occurred after hospitalization. Baseline vulnerability in their model was associated with age, cognitive failure, visual impairment, and gravity of disease. Precipitating factors included among others the use of psychotropics, dehydration, and polypharmacy. The "true" pathogenic role of each of these latter factors in inciting delirium was not clear within these studies, as the investigators utilized statistical methods that explored the specific events and diagnoses rather than known etiologic triggers, that were documented during hospitalization. Nonetheless, hypotheses related to potential risk factors for delirium can be made. Further, by modifying environmental and biological conditions, including for example using reorientation methods and patient counseling, the same authors were able to demonstrate a decrease in the cases of delirium in an elderly hospitalized population *(76)*.

In the oncological population many of the risk factors that have been studied in other populations are common. In addition, some other specific factors exist as previously listed in Table 5. As alluded to earlier these may be "risk" factors that increase baseline vulnerability or "precipitating" factors, which appear to initiate an episode of delirium. In a study of 140 cancer patients assessed for altered mental status (not specifically defined in this series as "delirium") in a cancer center, a single cause of the altered mental status was found in 33% of patients, whereas 67% had multiple causes *(77)*. Drugs, especially opioids, were associated with altered mental status in 64% of patients, metabolic abnormalities in 53%, infection in 46%, and recent surgery in 32%. A structural brain lesion was the sole cause of the mental status change in 15% of patients *(77)*. In another group of patients admitted to a palliative care unit for the control of difficult symptoms due to advanced cancer 71 delirium episodes were documented *(31)*. In the 71 episodes, 158 probable and 70 possible precipitating factors were identified and included psychoactive medications (mainly opioids); dehydration; nonrespiratory infections; alcohol/drug withdrawal; intracranial causes; respiratory infections; and lung cancer causing hypoxia, metabolic, and hematologic causes. In the same study about half of the delirium episodes were reversible while the rest were irreversible. In this study, reversibility of delirium was associated with opioid toxicity while irreversibility was associated with hypoxia due to lung cancer or respiratory infection *(31)*.

**COMMON CLINICAL SITUATIONS IN WHICH DELIRIUM OCCURS** Although delirium can occur in many settings, there are three specific clinical situations in which delirium is particularly frequent: delirium tremens, postoperative delirium, and delirium in the elderly patient. These deserve particular attention by the consultant neurologist or psychiatrist. A fourth common condition is "terminal" delirium, a condition that is common at the end of life and also warrants specific mention.

- *Delirium tremens*: The symptoms of acute alcohol withdrawal are usually grouped in three different syndromes: alcoholic hallucinosis, alcohol withdrawal syndrome, and delirium tremens (DT). When consideration is given to the criteria for these three conditions, it becomes apparent that DT is an uncommon complication of alcoholism (reported in only 5% of alcoholic patients admitted to a general hospital) *(74,78)*. Alcohol withdrawal syndrome is more common. This syndrome typically occurs in patients who have had 5–15 yr of excessive alcohol consumption and in subjects of 30–40 yr old. It is more common in males *(74,78)*. DT is the most severe clinical manifestation of alcohol withdrawal and usually occurs 72–96 h after the cessation of alcohol intake in those patients prone to withdrawal. This syndrome is the most classic form of hyperactive delirium. Disorientation to time and space is associated with visual and auditory hallucinations, agitation, hypervigilant state, tremors, and autonomic hyperactivity (tachycardia, sweating, arterial hypertension, at times fever). Visual hallucinations are reported by most patients and can consist of microzoopsias (visions of small animals), but are usually of a variable nature and are not

**Table 6**
**Examples of Drugs that Have Been Associated with Reports of Delirium or Confusion[a]**

| |
|---|
| Prototypical anticholinergic medications[b] |
| (Examples: Belladonna alkaloids, scopolamine, atropine, hyoscine, biperiden) |
| Medications for psychiatric conditions, including anxiolytics/hypnotics/sedatives |
| (Examples: Barbiturates, benzodiazepines, chloral hydrate, chlorpromazine[b], lithium carbonate, tricyclic antidepressants[b], SSRIs) |
| Pain medications |
| (Examples: Opioids, NSAIDs) |
| Antihistamines[b] |
| Chemotherapeutic agents |
| (Examples: More frequently cited: asparaginase, ifosfamide. Rarely reported associations, usually reported in patients in unusual circumstances or with other complications and/or medications present: cisplatin, cytosine arabinoside, etoposide [at high doses], 5-fluorouracil, methotrexate, nitrosoureas [at high doses or via arterial route], procarbazine, vincristine) |
| Immunosuppressants and immunomodulatory agents |
| (Examples: Corticosteroids, interferons and interleukins, cyclosporin, tacrolimus) |
| Antibiotics and antivirals |
| (Examples: More frequently cited: quinolones, acyclovir, gancyclovir. Numerous other antibiotics, including for example imipenem and aztreonam have reported associations, usually reported in patients with other complications and/or medications present.) |
| Medications for gastrointestinal conditions |
| (Examples: H2-antagonists including cimetidine, ranitidine, famotidine; omeprazole) |
| Medications for CNS conditions |
| (Examples: Anticonvulsants, levodopa) |
| Medications for cardiovascular conditions |
| (Examples: Beta-blockers, digitalis) |

[a]The purpose of this table is to illustrate some of the common medications used in oncology settings that have been associated (rarely in some cases) with the occurrence of confusion or delirium and to demonstrate the spectrum of medications that have been associated with this condition. Examples are not inclusive of all medications in the category that may be associated with confusion or delirium. Reports of confusion with one medication often document the occurrence of this problem in ill patients who are taking more than one medication and, consequently, the exact etiology of the confusion can be difficult to define.

[b]Medications with established anticholinergic activity.

necessarily frightening. Auditory hallucinations can include menacing voices but also neutral sounds or music.

- *Postoperative delirium*: Delirium can follow immediately after surgery but may also be delayed for 3–5 d *(79,80)*. Factors contributing to the pathogenesis of this postsurgical complication may include sleep deprivation, sensory deprivation, pain, metabolic factors, anesthetic drugs, anticholinergic medications, analgesics, hypoxia, fever, and blood loss. The incidence of this condition is particularly high after open heart surgery, and following orthopedic surgery in the elderly patient *(80–83)*. A predictive model for this condition has been validated and can be used to assess the relative risk of the individual patients *(83–85)*. This model is based on some intraoperative stress factors (i.e., type of surgery) and some preoperative predisposing factors (including age > 70 yr; preexisting cognitive impairment; history of alcohol abuse; poor functional status; marked abnormalities of serum sodium; potassium; or glucose) *(83–85)*.
- *Delirium in the elderly*: The elderly population is at particularly high risk of developing delirium when hospitalized. In this setting delirium impacts on morbidity, functional recovery, time of hospitalization, and probably also on survival *(86)*. In the elderly, delirium may be a complication of a known or subclinical pre-existing dementia. The recovery from an acute episode can be protracted and often incomplete, such that the distinction between an acute and chronic condition can be difficult or impossible *(87,88)*. In the elderly, hypoactive and depressive features of delirium are common. Depression is a common erroneous diagnosis in elderly patients who are suffering from delirium *(89)*. In elderly patients with delirium it is not uncommon to find neurological evidence of brain aging and other concomitant diseases. The presence of tremors, dysarthria, gait ataxia, and incontinence should alert the clinician to the possibility of the clinical condition having another underlying cause or predisposing factor.
- *Terminal delirium*: Delirium is frequent in terminal cancer patients and is an independent predictor of shortened life prognosis *(32,90)*. In the patient with advanced disease, delirium can be the consequence of irreversible organ or multi-organ failure leading to death. It is important to note that in many cases, despite far advanced disease, reversible etiologic factors are present. For example, a recent study demonstrated that almost 50% of the episodes of delirium occurring in patients with very advanced cancer were reversible *(31)*.

## DELIRIUM TREATMENT

The therapy of delirium is based on interventions directed both towards symptoms and towards etiologic and, if possible, predisposing factors. The patient and/or family decisions made within the context of the overall clinical condition will dictate the goals of care in each case, which will in turn impact on the diagnostic and therapeutic interventions. Approaches include the removal of etiologic triggers, environmental changes, and pharmacological interventions; each of these will be briefly reviewed.

**ETIOLOGICAL INTERVENTIONS** As mentioned previously, the identification of a single etiologic, risk, or precipitat-

ing factor is not always easy. Attention to fluid and electrolyte balance, vitamin and glucose support, oxygenation, and treatment of infections should be considered as baseline primary interventions. A review should be undertaken to consider the possible withdrawal of any drug that is not considered strictly necessary (keeping in mind that the withdrawal of certain drugs can also aggravate delirium). Consideration should be given to the role of optimal hydration. For patients requiring opioids, dose reduction or opioid substitution should be considered among early interventions *(91)*.

**ENVIRONMENTAL INTERVENTIONS** It has long been considered important to foster a tranquil environment and, if feasible, to consider the role of nonintrusive sensory and cognitive reorientation protocols (clock, calendar, familiar people and objects, audiovisual aids). Psychological support for the patient and family should be provided to enhance communication with the staff and clarify questions about causes, clinical fluctuations, reversibility, and prognosis. Family counseling is very important to impede the vicious cycle of incorrect treatments for distress; for example, requests for pain medication may be made in the setting of agitation related to delirium rather than pain *(92,93)*. Patient awareness is usually compromised in delirium but is not always lost, and the perception of cognitive failure can be an important source of suffering. For this reason re-orientation should, where possible, be approached in a manner that does not increase the patient's sense of awareness of his/her disorientation. Environmental changes and reorientation protocols have indeed been proven to be effective in reducing the incidence of delirium in the elderly at risk population *(76)*.

**PHARMACOLOGICAL INTERVENTIONS** A clear role for pharmacological interventions in delirium has been established for the treatment of symptoms and distress. At present no study has been undertaken that provides data to clarify the role for these interventions in mild, asymptomatic cases of delirium—this is an area in need of research. Nonetheless it is clear that agitated delirium is difficult for both patients and their family caregivers and can also be dangerous. In such cases a pharmacological symptomatic intervention is certainly justified. Continuous monitoring and frequent assessment are necessary and are an integral part of treatment.

The American Psychiatric Association has developed guidelines based on the available research for the assessment and treatment of delirium *(94)*. Antipsychotic medications are generally considered first-line treatment except in cases of alcohol or benzodiazepine withdrawal and in situations where there are clear contraindications to their use. Although there have been few studies to determine exact strategies for the optimal use of antipsychotic medications in the treatment of delirium, haloperidol is generally recommended as the initial drug in the majority of cases because of its limited anticholinergic, hypotensive, and sedative actions *(94)*. Acute treatment is usually initiated with oral, SC or IV medication. Of note, although there is literature to support the safe and effective use of intravenous haloperidol, its use has not been approved by the US Food and Drug Administration. Small doses of oral haloperidol are usually effective in mild cases (1–2 mg) and higher doses in more severe cases (2–5 mg). In the elderly, in frail medically ill patients, and in the patients with low performance scores, lower initial doses should be used (0.25–0.50 mg q 4 h) *(95)*. Dosing guidelines recommend that the treatment commence with a dose every 2–4 h as needed although some authors have discussed a "loading dose" with the administration of a dose of haloperidol initially every 30–60 min in cases involving significant agitation or distress *(94,96)*. The use of prn medication or, in more severe cases, the establishment of an around-the-clock regimen, should be considered thereafter.

Severely agitated patients may require parenteral medication and, sometimes, titration of antipsychotic medication to higher doses. High-dose intravenous boluses of haloperidol with total daily doses of 500–1200 mg/IV per day have been reported, but this is by far the exception with common doses being in the realm of 1–10 mg/IV per day of haloperidol *(97–99)*. Continuous IV infusion of haloperidol has been used in extremely difficult cases of delirium in the intensive care setting using fixed haloperidol concentrations and increasing infusion rates according to outcome *(97,99)*. This is considered a possible approach to minimizing the risk of hypotension that may be associated with bolus dosing. Continuous infusion of droperidol has also been utilized *(100)*. High doses of these medications have been administered in the ICU with minimal effects on heart rate, respiratory rate, blood pressure, and pulmonary artery pressure and minimal extrapyramidal side effects *(97)*. Nonetheless, the possibility of side effects must always be considered.

A significant potential side effect of haloperidol and other commonly used neuroleptic anti-psychotics is cardiac dysrythmia related to prolongation of the QT interval in the EKG *(101–105)*. EKG monitoring may be useful when using IV infusions and in patients with baseline cardiac conduction abnormalities who are, as a consequence of these abnormalities, considered to be at increased risk.

Other neuroleptics, in particular chlorpromazine and droperidol, have been used for delirium and have been, to date, selected where more profound sedation is necessary to control symptoms *(106)*. A few case reports have been published reporting the use of atypical neuroleptics with activity on dopamine, serotonin, and histamine receptors (risperidone, olanzapine, clozapine) *(94,107)*. These medications have not been widely used to date for delirium, but it will be important for their role to be explored in future studies. There have also been anecdotal reports of the combination of a neuroleptic with an antihistamine (promethazine or chlorphenamine) to treat delirium in advanced cancer patients who are experiencing pain or other symptoms and are on opioids in the terminal phases of their disease; the role of this approach is uncertain.

Benzodiazepines are generally not used as first line interventions in delirium except in cases of alcohol withdrawal *(94,108)*. Although studies are lacking, benzodiazepines can be used for sedation in cases of agitated delirium in which symptoms are not controlled with the use of neuroleptics alone. As mentioned earlier, they are the treatment of choice for delirium related to alcohol or benzodiazepine withdrawal. Benzodiazepines may also be useful when there is a need for a medication that can raise the seizure threshold (of note antipsychotics can lower the seizure threshold) or when

anticholinergic side effects or akathisia associated with antipsychotics would seriously exacerbate a patient's condition *(94)*. They also have a role in patients for whom their anxiolytic and sedative effect is desired, including for example in some cases of terminal delirium *(109–111)*.

Studies that explore the pharmacological treatments of delirium are rare, and in fact there is only one study providing insight into the comparative role of benzodiazepines and antipsychotic medications *(112)*. This study, undertaken in a HIV-infected population, prompted the recommendation to utilize benzodiazepines in the manner suggested earlier. This randomized controlled clinical trial compared the use of lorazepam, haloperidol, and chlorpromazine in treating delirium and showed that while haloperidol and chlorpromazine produced an objective improvement in symptoms, lorazepam worsened confusion *(112)*. In general it is also considered best to, where possible, avoid the use of benzodiazepines in hepatic encephalopathy and in the elderly, as in both these populations benzodiazepines are associated with frequent adverse reactions. When benzodiazepines are to be utilized, drugs with short half-life and no active metabolites are generally the preferred approach, with lorazepam meeting these criteria *(94)*. Low doses of lorazepam can be used orally or sublingually (0.5–1 mg) or doses administered IV starting with 0.5–2 mg. Midazolam has frequently been used in the palliative care of advanced patients *(111,113–115)*. It has the advantage of being well-absorbed after SC administration. It has very fast onset of action and can be of use also for short-term reversible sedation starting with doses of 0.5–1 mg for induction, with the dose being repeated as needed and, if needed, escalated sometimes 1–2 hourly. Achieving prolonged sedation with midazolam can be difficult as it often requires frequent dose adjustment. Daily doses of this medication commonly range from 40–60 mg with the occasion use of higher doses needed to achieve comfort *(111,113–115)*. The pharmacokinetics of midazolam are such that as it can be difficult to establish prolonged sedation, and once it is achieved, it can be slow to reverse. This is especially relevant in cases where the patient may be improving medically and the delirium resolving *(96)*.

Despite these broad recommendations there is often a need, especially in the terminally ill cancer population, to consider the use of drug combinations to control delirium. For example, investigators aiming to treat delirium and provide palliation of symptoms undertook a study of 39 advanced cancer patients with delirium and found that 60% were managed with haloperidol alone and, in the remaining 16 patients other psychotropic drugs had to be added (lorazepam, chlorpromazine, or methotrimeprazine) *(111)*. In 10 patients (26%) symptoms of delirium were reported to only be controllable with sedation—usually achieved in this study through the use of midazolam *(111)*.

Several other categories of medication have been used in the treatment of delirium. For example, physostigmine has been utilized in the treatment of delirium induced by anticholinergic drugs *(2,116)*. This drug should be used only if anticholinergic toxicity is proven and requires careful monitoring for the occurrence of side effects due to cholinergic hyperstimulation. Contraindications to the use of physostigmine include a history of heart disease, asthma, diabetes, peptic ulcer, and bladder or bowel obstruction; it must be administered cautiously so as to avoid seizures and cardiac arrhythmias. The recent introduction of another group of cholinesterase inhibitors for the treatment of dementia has raised suggestions about their potential usefulness to ameliorate symptoms of delirium. Some clinical observations regarding the use of donepezil in this regard are interesting and have resulted in a few case reports that provide preliminary data about reversal of hallucinations and delusions and improved alertness *(19,117)*. Finally, in cases of hypoactive delirium the use of psychostimulants has been suggested, but thus far clear guidelines for these indications are lacking and clinical experience has been very limited *(118,119)*.

## PROGNOSIS

The classic perception of delirium is that it represents a transitory state that is brief and usually resolves promptly. Providing a contrast to this perception a recent study of elderly delirious patients found the average duration of an episode to be longer than 2 wk *(120)*. In this group the most common etiologies for delirium were stroke, infections and metabolic disorders; coexistent structural brain disease was also present in a substantial majority of patients (81%). Levkoff et al. evaluated a group of acutely hospitalized elderly patients and demonstrated that among those with delirium resolution of symptoms was often incomplete with only 4% experiencing resolution of all new symptoms before hospital discharge and an additional 20.8% and 17.7% having symptom resolution by 3–6 mo, respectively *(121)*. To complicate this issue further, many patients experience delirium in the terminal phases of illness and may have no resolution of symptoms prior to death. In some cases sudden failure of cognition develops in the setting of advanced disease with no specifically definable reversible cause and this condition persists for days to weeks through the rest of the clinical course of disease until death. These data suggest that delirium may be substantially less transient than currently believed and that incomplete manifestations of the syndrome may be frequent *(121)*.

The mortality associated with delirium has been reported to be between 10 and 65% *(122)*. In a recent study of oncology inpatients by Tuma and DeAngelis, although delirium improved in 67% of patients, it was a prognostic factor for poor overall outcome—the 30-d mortality was 25%, and 44% of patients died within 6 mo, usually from progression of the underlying cancer *(77)*. Delirium is more frequent in patients with multiple medical problems and it is likely that these processes and their complications, rather than the delirium itself, contribute to the high mortality rate. Nonetheless, delirium has been shown to be an indicator of poor prognosis. For example, in a study conducted in the elderly, the presence of delirium identified those patients at risk for prolonged hospitalization, loss of independent community living, and future cognitive debility *(87)*. In this group, mortality was not significantly associated with delirium after adjusting for the severity of comorbidity *(87)*. In patients with advanced cancer the opposite is true; delirium is considered to be an independent predictor of worse prognosis and has been used in a model with other clinical and laboratory data to establish a short-term prognosis *(32,90)*. In another study in advanced cancer patients

reversibility of the delirious episode was associated with drug toxicity and irreversibility with hypoxia (due to pulmonary infection or tumor) *(31)*, but the relationship, if any, of these problems with mortality was not reported. It can be concluded that delirium may be reflective of reduced brain functional reserve in the elderly, of the severity of irreversible organic processes that may lead to death, or of the toxicity of a readily reversible cause.

## CONCLUSIONS

Delirium is a highly prevalent disorder among the medically ill. The cancer patient is at risk for developing delirium as a consequence of several general and specific factors. Delirium can be a condition responsive to interventions that address its etiologic factors, or it may be an irreversible event characterizing the final evolution of terminal illness. Neurologists involved in the assessment of oncological patients need to have an understanding of both oncology and palliative care if they are to be able to conduct a comprehensive assessment of the patient and embark upon an appropriate treatment plan. The breadth of the etiologic factors also suggests the frequent need for multidisciplinary interaction with other medical specialties and health professionals. Certainly the responsibility of the consulting neurologist must go beyond the provision of an elegant neurological diagnosis. Neurologists treating delirium must also consider the importance of care that utilizes diagnostic and therapeutic decisions within the context of the patient's goals of care, and addresses needs for treatment of physical and psychological symptoms and for patient and family support.

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# 6 Cancer Pain

JULIE E. HAMMACK, MD

## INTRODUCTION

Cancer pain is an enormous problem in the United States and worldwide. It has been estimated that over 70% of patients with advanced cancer will experience pain severe enough to require opioid medications. Applying this estimate to cancer statistics supplied by the American Cancer Society *(1)*, approx 395,360 of the 564,800 people who died of cancer in the United States in 1998, and hundreds of thousands of the 8 million surviving cancer patients experienced moderate to severe cancer-related pain. These data are even more staggering when applied to worldwide cancer statistics. Cancer related pain may affect patients at the time of the initial cancer diagnosis in as many as 20–50% of cases and has been estimated to occur in 30% of patients while receiving active cancer treatment, either as a direct result of the disease or its treatment *(2–4)*. Good to excellent pain relief can be obtained in 90% or more of patients if their physicians are skilled in the use of analgesic medications and aware of the appropriate indications for neuroanesthetic and neurosurgical procedures. In developing countries, the lack of medical care and unavailability of opioid analgesics is a tremendous barrier to cancer pain relief. However, in the United States, where medical care and opioids are readily available, it has been estimated that only 50% of patients receive adequate pain relief *(5)*.

There are many barriers to adequate pain control. Poor communication may exist between the patient and caregiver regarding the severity of the pain and the impact on his or her quality of life. Many patients are reluctant to complain of pain or may not realize that adequate analgesia is available. They may assume that pain is an expected feature of their malignant disease or that by "complaining" they may distract their physician from primary treatment of the underlying cancer. More commonly, medical professionals fail to assess the severity of cancer pain and are ill-informed regarding the proper use of analgesics in treating cancer pain. This is not a deficiency in compassion or competence in most instances, but reflects the lack of education and training in symptom management in most medical and nursing curricula. Medical training in most Westernized countries focuses on treatment of disease with less emphasis on relief of symptoms such as pain. Few medical and nursing personnel are aware of the wide variations in opioid requirements to control pain in different individuals or at different stages of disease in the same patient. Although attitudes are changing with improved education, many patients and medical professionals still harbor a unrealistic fear of addiction (psychological dependence) when opioid are used despite overwhelming data that this is a very small risk in cancer patients *(6)*.

The goals of this chapter are the following:

- *Recognize that cancer-related pain is common and has a major destructive impact on quality of life.* It is important that caregivers routinely inquire about the presence and severity of pain and take responsibility for pain treatment.
- *Establish the mechanism of pain: the "pain diagnosis."* Not only will this lead to improved cancer pain treatment, but it may also yield important information about the extent of malignant disease and better guide cancer therapy.
- *Understand the appropriate use of opioid and adjuvant analgesics.* The physician should be able to distinguish physical dependence and tolerance from psychological dependence (addiction). He or she should be able to appropriately dose and titrate opioid analgesics and know when it is appropriate to switch from one opioid to another or from one route of administration to another. The physician should be adept at anticipating and managing drug-related side effects.
- *Consider other therapeutic options when appropriate.* In the small proportion of patients who are refractory to standard medical therapies, these options may include intraspinal administration of medication, nerve blocks, or ablative procedures, and neurosurgical interventions including cordotomy and hypophysectomy.

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## CLINICAL ASSESSMENT

The first step in the control of cancer pain is recognition of its existence. Many studies have demonstrated the failure of medical professionals to identify the presence of pain and quantify it *(7,8)*. Many formal scales for quantifying pain exist *(9–11)*. The simplest bedside method is to ask the patient to quantify his or her pain on a scale from "0 to 10," in which 0 is "no pain" and 10 is "the worst pain imaginable." Patients who have difficulty with this method should be asked if their pain is mild, moderate, or severe. The severity of the pain will at least partially dictate the selection of analgesic. Discovering the underlying mechanism of the underlying pain, the "pain diagnosis," is equally important.

**CANCER PAIN MECHANISMS** Although most cancer patients experience pain as a direct result of invasion of body tissues by malignancy, pain may also arise from surgery, chemotherapy, and radiation therapy. A small percentage of cancer patients may develop a painful condition unrelated to their malignancy. Pain is the most common symptom of tumor recurrence or new metastases. Gonzales et al. *(12)* found previously unsuspected neurologic disorders (including epidural cord compression, plexopathy, and brain metastases) in 36% of patients undergoing a cancer pain evaluation. Investigating the source of pain in patients with cancer may thus have important implications in the management of not just the pain but also the underlying malignancy.

The most common cause of pain is direct tumor invasion of pain-sensitive somatic structures (bone, muscle, fascia, dura, skin, blood vessels) or viscera (pleura, peritoneum, organ capsules, obstruction of a hollow viscus). Injury to these structures is referred to as "nociceptive" pain. When injury to central or peripheral neurologic structures produces pain it is called "neuropathic" and results from aberrant nerve fiber activity in central and peripheral pain pathways. "Idiopathic" pain refers to syndromes in which an underlying cause cannot be found. It is a diagnosis of exclusion and accounts for a minority of painful conditions in patients with cancer.

**SPECIFIC CANCER PAIN SYNDROMES** In order to properly diagnose and treat patients with cancer-related pain, it is critically important to establish a "pain diagnosis." This refers to the both the specific location and mechanism of the underlying painful condition. As with any diagnostic process, making a pain diagnosis requires an accurate history and examination and may require additional diagnostic testing.

## PAIN DUE TO DIRECT TUMOR INVOLVEMENT

**BONE METASTASES** Bone metastases are the commonest cause of nociceptive somatic pain and the commonest cause overall in patients with cancer. Cortical and cancellous bone tissue is relatively lacking in pain fibers. Periosteum is richly innervated by nociceptive nerve fibers. Injury to periosteum by direct tumor invasion or pathologic fracture is the usual mechanism of bone pain in patients with cancer. Generally the pain is dull and aching in quality and localized over the involved bone. It is typically worse when the bone is stressed, as by weight bearing. Bone pain is typically worse at night.

Bone metastases are most common in the axial skeleton: vertebrae, skull, ribs, and long bones. Although the pain is usually localized over the affected bone, at some sites the pain may refer elsewhere (*see* below). Particularly in the skull and vertebrae, adjacent neurologic structures may be involved. Thus, neuropathic pain and neurologic deficits can be components of these syndromes. Any tumor may metastasize to bone. Among solid tumors, breast, lung, prostate, renal cell, and thyroid carcinomas account for most.

**SKULL METASTASES** Skull metastases are common and usually asymptomatic. They may produce localized head pain. Occasionally a parasagittal skull metastasis may occlude the superior sagittal sinus and produce headache from raised intracranial pressure. Invasion of dura adjacent to a skull metastasis may predispose the patient to subdural hematoma. At least five different syndromes of skull base involvement by tumor are commonly seen *(13)*. Cranial nerve deficits and neuropathic head and face pain are common associated features with these syndromes.

**Jugular Foramen Syndrome** Pain from metastasis to this region typically refers to the occiput or post-auricular region and is dull and aching in quality. Rarely, the pain refers to the neck or ipsilateral shoulder. Sharp lancinating neuropathic pain in the throat or ear (glossopharyngeal neuralgia) may occur with involvement of cranial nerves IX or X. The bone pain (nociceptive) typically worsens with neck flexion and the neuropathic pain often worsens with swallowing. Dysphagia, dysarthria, syncope, and weakness of the sternocleidomastoid and trapezius muscles result from involvement of cranial nerves IX. X, and XI.

**Orbital Syndrome** Nociceptive pain from metastases to the bony orbit is localized behind, above, or around the eye. It may be worse with eye movement and associated involvement of cranial nerves II, III, IV, VI, V1, and V2 may produce ipsilateral visual loss, diplopia, and facial pain and anesthesia. Proptosis is also common.

**Clivus Syndrome** Tumor invasion of the clivus produces dull aching pain that refers to the vertex that is typically worse with neck flexion. Cranial nerves VI through XII may be involved as they pierce the dura in the vicinity of the clivus.

**Cavernous Sinus Syndrome** This is also known referred to as the "parasellar syndrome." The signs and symptoms may closely resemble the orbital syndrome although proptosis is less frequent. The pain is typically periorbital. Trigeminal nerve involvement is more common and manifests itself with lancinating face pain, facial anesthesia, and weakness of mastication.

**Occipital Condyle Syndrome** The pain from this syndrome refers to the occiput and is worse with neck movement. The hypoglossal nerve (CN XII) is commonly involved and produces ipsilateral tongue wasting, fasciculations, and weakness.

Bone scan and plain X-ray of the skull may demonstrate bony lesions in the skull base. Contrasted head computed tomography (CT) with bone windows and head magnetic resonance imaging (MRI) with coronal views are more sensitive both for bony and soft tissue skull base lesions.

**VERTEBRAL METASTASES** Malignant involvement of the spine most commonly involves the vertebral body or pedicle. Although thoracic spine involvement is more common that cervical or lumbosacral, multiple levels of involvement are

typical. Pain from vertebral metastasis is generally felt directly over the involved vertebra. High cervical metastases often refer pain to the occiput and low thoracic and upper lumbar metastases typically refer pain to the iliac crest. C7 and T1 vertebral lesions often refer pain to one or both scapula. Vertebral pain is worse with percussion over the involved site and it is worse with activities that stress the spinal column (standing, walking, and bending). Most patients will note that their spine pain is worse at night. This results from elongation of the spine and stretching of injured periosteum after several hours of resting in a reclining position.

Extension of tumor into the epidural space may compress nerve roots and produce radicular (neuropathic) pain radiating into the arms (cervical), legs (lumbosacral), or around the trunk "like a tight belt"(thoracic), depending on the level of involvement. This pain is worse with Valsalva maneuver, which increases intraspinal pressure. Radicular-distribution muscle weakness, paresthesiae, and anesthesia are common.

Epidural cord compression is a serious complication of cervical and thoracic vertebral metastases, mandating immediate diagnosis and emergent treatment *(14)*. Patients who develop epidural cord compression have often had bony pain for weeks or months prior to developing neuropathic (radicular) pain and neurologic deficits. Depending on the level of cord involvement, the patient may develop spastic quadriparesis or paraparesis, a sensory level to pin and temperature at the level of the lesion, and bowel and bladder incontinence. Epidural cord compression is a neurological emergency requiring high dose corticosteroids, MRI or myelography, and emergency radiation therapy or neurosurgical decompression. Even in those patients without evidence of epidural tumor extension, neurosurgical and orthopedic consultation may be necessary to assess spine stability.

**BRAIN METASTASES** Brain metastases (intra-parenchymal, meningeal, and dural) are the most common neurologic complication of cancer, occurring in approx 15–20% of patients at some point in their clinical course *(15)*. Headache and neurologic deficit is the usual presentation. Cerebral, brainstem, and cerebellar tissue lack pain-sensitive nerve fibers. Dura mater, extra-dural blood vessels, soft tissues of the head and neck, and cranial nerves (particularly CN V, VII, IX, and X) are pain-sensitive and injury to these structures may produce head pain.

Intra-parenchymal brain metastases or primary brain tumors produce pain by increasing intra-cranial pressure (ICP) and producing dural traction *(16)*. The headache is usually poorly localized and often holocephalic. Supratentorial tumors usually produce frontal or temporal head pain and infratentorial tumors usually produce occipital head pain. Occipital head pain occurring in patient with supratentorial tumors may indicate tonsillar herniation. Headache from dural traction is usually worse at night and may awaken the patient from sleep. It worsens with Valsalva maneuvers. Focal neurologic deficits are common and their nature will depend upon the location of the tumor. Vomiting, hiccough, and somnolence suggest involvement of the brainstem either by transtentorial brain herniation or direct tumor involvement.

Meningeal spread of tumor may produce headache by raising IP (usually secondary to communicating hydrocephalus),

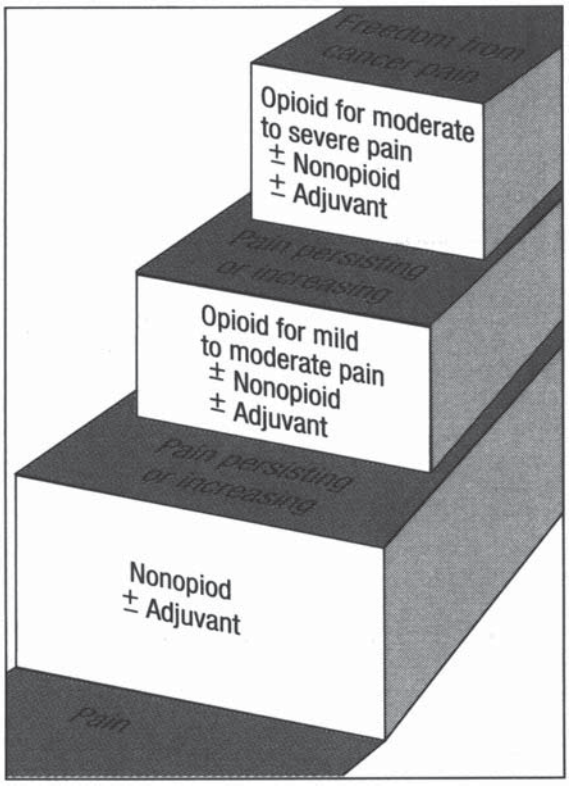


**Fig. 1.** Step approach to cancer pain. Reprinted with permission from World Health Organization. Cancer relief and palliative care: Report of a WHO expert committee (World Health Organization Technical Report Series 804). Geneva, Switzerland: WHO; 1996 *(28)*.

by direct dural invasion, or by infiltrating pain-sensitive cranial or upper cervical nerve roots. Neurologic signs and symptoms are often present at multiple levels of the neuraxis reflecting the spread along meningeal pathways. MRI with gadolinium enhancement typically shows diffuse or nodular enhancement of the meninges, although it may be negative. The cerebrospinal fluid (CSF) examination usually shows elevated protein and a pleocytosis. Repeated taps may be necessary to isolate malignant cells *(17)*.

Dural metastases are commonly seen in patients with breast, prostate, and lymphoproliferative tumors. They produce head pain by direct dural invasion or by dural traction from mass effect, particularly if a secondary subdural hematoma is present. Occasionally dural or skull metastases invade and occlude a cerebral venous sinus, producing raised ICP and venous infarction. Sepsis, dehydration, coagulopathy, and L-asparaginase administration are other factors that may predispose a patient to developing venous sinus occlusion. MRI and magnetic resonance venography of the head will demonstrate absent or slow flow in the affected sinus.

**OTHER CAUSES OF HEADACHE** Tumors involving the mediastinum may produce superior vena cava obstruction, producing reduced cerebral venous return and raised ICP with headache. These patients typically have facial, neck, and upper chest edema and plethora with visibly dilated jugular and upper chest superficial veins. Tumors invading lung and mediastinal soft tissues may also refer pain to the neck or face *(18)*.

Herpes zoster infection of CN $V_1$ presents with severe "stinging" pain and itching of the ipsilateral eye and forehead, often several days prior to eruption of the characteristic vesicular rash. Zoster infection may also involve CN VII (Ramsay Hunt Syndrome), in which case the patient presents with ipsilateral ear pain and facial weakness prior to developing vesicles in or around the ear or on the ipsilateral tongue. Five to 10% of patients may develop chronic intractable face or head neuropathic pain (postherpetic neuralgia). Patients with trigeminal involvement may suffer corneal scarring and retinitis and should be followed by an ophthalmologist.

**VISCERAL PAIN SYNDROMES** When cancer invades or stretches organ capsules (pleura, peritoneum) or obstructs hollow viscera, nociceptive fibers within these structures are activated and the patient experiences pain. Typically, organ dysfunction accompanies this pain. The most common visceral pain syndromes involve the organs contained within the abdominal cavity. The celiac plexus and spinal nerves innervate the peritoneum and retroperitoneum.

Visceral pain is usually poorly localized, dull, and constant. Patients with pleural or mediastinal tumor often experience pain in the chest, thoracic spine, or scapular region that may be worse with inspiration or cough. Those with liver, pancreatic, gastric, spleen, and upper bowel lesions typically experience pain in the epigastrium, which radiates into the upper lumber spine. Pelvic visceral pain is usually felt in the lower abdomen and may radiate to the lumbosacral region. Involvement of peritoneum abutting the diaphragm will produce ipsilateral shoulder pain. Patients with retroperitoneal involvement may note worsening of their pain when lying supine and improvement with forward flexion or lying in a fetal position. Pain from biliary, ureteral, or bowel obstruction is usually episodic, colicky, or cramping. Some pleural or retroperitoneal tumors may directly invade the vertebrae or spread through in the intervertebral foramina to involve spinal nerves, producing radicular pain and neurologic deficits.

Signs and symptoms of organ dysfunction such as nausea, vomiting, jaundice, ascites, dysuria, obstipation, and dyspnea may be present depending on the organ involved. The diagnostic studies should be tailored to the individual patient and may include plain X-rays, CT, upper and lower GI series and other studies specific to the involved viscera.

**NEUROPATHIC PAIN SYNDROMES** Tumor may involve structures at all levels of the nervous system and produce pain with unique features. Classically, neuropathic pain is "sharp and stabbing" although it may also be "dull and gnawing." Lancinating pain, "burning," and "pins and needles" paresthesia are typical as is "itching" and hypersensitivity to touch over the involved dermatome. A feeling as if the skin is stretched or swollen is also common. Neuropathic pain is usually felt distant to the site of malignant involvement reflecting the dermatomal distribution of the involved nerve or sensory tract. Other evidence of neurologic dysfunction (weakness, sensory loss, or autonomic dysfunction, including bowel or bladder incontinence, loss of sexual function, and skin color and temperature) changes may be present, depending on the site of neurologic involvement.

Neural structures of the peripheral nervous system (PNS), (i.e., roots, plexus, peripheral nerve) carry many nociceptive fibers and are exquisitely pain-sensitive. Brain and spinal cord tissue is insensitive to pain. Pain deriving from involvement of these structures usually is the result of stretching or injury to their investing dura or surrounding structures such as skull or vertebrae (see previous sections on brain and spine metastases). Rarely, lesions of the CNS and PNS may produce chronic neuropathic pain by disruption (deafferentation) and reorganization of central pain pathways. Except for postherpetic neuralgia, this type of pain is rare in patients with cancer, at least partly because cancer patients often do not often survive long enough for central neuronal reorganization to occur after a neural injury from brain and spinal cord tumors.

**BRACHIAL PLEXOPATHY** The brachial plexus is immediately adjacent to the apex of the lung and the supraclavicular lymph nodes. When the latter structures are involved by tumor (primary or metastatic), disease may spread to involve the plexus as well. The lower trunk and medial cord are most commonly affected *(19)*. Tumor invasion of the upper plexus is distinctly less common and is more characteristic of radiation-induced injury to the plexus (*see* below). The most common presenting symptom of malignant brachial plexus involvement is severe aching discomfort of the ipsilateral shoulder and scapula followed by pain and paresthesia radiating down the arm and into the hand in a C8-T1 distribution. Weakness and wasting of the intrinsic hand muscles of the hand may occur. If the lesion invades the proximal lower trunk or C8-T1 root, there usually evidence of an ipsilateral Horner's syndrome with partial ptosis and miosis.

MRI of the brachial plexus with gadolinium contrast is superior to CT and has the added advantage of visualizing the epidural space to rule out tumor spread to the cervical spine. Electromyography (EMG) is usually not required but may be useful in differentiating plexus from root involvement. The main role of EMG is in differentiating malignant plexopathy from radiation-induced plexopathy, although usually this distinction can be made clinically with the assistance of neuroimaging.

**LUMBOSACRAL PLEXOPATHY** The lumbosacral plexus is in close proximity to the colon and rectum, prostate, uterus and ovaries, and pelvic and abdominal lymph nodes. Thus, any tumor involving these structures can invade the plexus *(20)*. As with brachial plexopathy, pain is usually the first symptom, and it is present at diagnosis in 95% of patients with malignant plexopathy. The pain typically begins in the flank or buttock, and later radiates down the leg. Pain from involvement of the upper plexus radiates to the groin or anteromedial thigh, while pain from involvement of the lower plexus radiates to the posterior thigh and leg and may involve the sole or dorsum of the foot. Weakness in L2-L3-L4 innervated muscles (iliopsoas, adductor, and quadriceps) characterizes upper plexus lesions and weakness in L4-L5-S1-S2 muscles (glutei, hamstrings, tibialis anterior and posterior, peronei, and gastrocnemius) is typical for lower plexus lesions. Bowel, bladder, and sexual dysfunction will occur if there is bilateral plexus or root involvement and should raise concern about epidural cauda equina or cord involvement. Both CT and

MRI of the abdomen and pelvis with contrast are adequate to visualize the plexus and the surrounding structures. MRI is superior for visualizing the epidural space, cord, and cauda equina, if involvement of these structures is suspected. EMG is often helpful in distinguishing root lesions from plexus lesions and in distinguishing malignant plexopathy from radiation-induced lumbosacral plexopathy.

**PERIPHERAL NEUROPATHY** Peripheral neuropathy in cancer patients is usually a side effect of chemotherapy or attributable to cancer-unrelated causes such as diabetes. Tumors may infiltrate peripheral nerve, although this is less common than plexus involvement. Pleural and retroperitoneal tumors often invade spinal nerves producing radicular-type pain in the involved thoracic or upper lumbar dermatomes. Limb tumors (osteogenic sarcoma) may produce solitary or multiple mononeuropathies from direct tumor invasion. Skin cancers of the head and neck (particularly squamous cell cancer) often infiltrate cutaneous branches of the trigeminal nerve producing facial pain and paresthesia and other cranial nerve palsies *(21)*. Paraneoplastic neuropathies are distinctly rare. Paraneoplastic subacute sensory neuronopathy (Anti-Hu syndrome) is associated with small cell lung cancer and may manifest itself clinically with limb pain, paresthesia, and prominent sensory loss to all modalities *(22)*. The pathology of this subacute sensory neuronopathy involves severe inflammation of the dorsal root ganglia. Serum and CSF antibodies in these patients react with discrete nuclear proteins of central and peripheral neurons. Patients with anti-Hu syndrome may also have cerebellar degeneration, limbic encephalitis, and dysautonomia.

## PAIN SYNDROMES DUE TO CANCER THERAPY

Although pain related to cancer treatment is less common than pain due to direct involvement of tissues by tumor, this possibility needs to be considered in all cases. Appropriate therapy will depend on accurate diagnosis. Surgery, radiation, chemotherapy all may have painful sequelae. The following section will deal only with chronic pain syndromes related to cancer treatment.

**POSTSURGICAL PAIN SYNDROMES** Acute pain following surgery for malignancy is common and usually self-limited. It is generally treated in the immediate postoperative period with oral or parenteral analgesics. The treatment of this pain does not differ from that administered to patients undergoing minor or major surgical procedures for nonmalignant conditions. A small percentage of patients may experience chronic pain for months or years after surgery, due to injury to neural structures within the operative field. I will focus on four well-characterized chronic postsurgical pain syndromes

1. *Post-thoracotomy pain*. This is pain located along the thoracotomy incision with neuropathic features. It results from cutting or stretching of one or more intercostal nerves and is more common if rib resection is required during the thoracotomy. Many patients describe burning, itching, tightness, or lancinating pain. There is often sensitivity to touch and altered sensation in the dermatomes around the incision. There may be exquisite point tenderness along the scar.

   Three distinct mechanisms of pain after thoracotomy have been defined *(23)*. The first group is the largest, in which patients have their most severe pain immediately following surgery. By 2 mo the pain resolves or is minimal. In patients whose pain recurs after this point, there is a high likelihood of recurrent tumor as the cause. The second group includes patients in whom pain steadily increases in intensity from the time of surgery. Recurrent tumor and postoperative infection are the most common causes. In the third group, the chest wall pain remains stable or decreases only slightly over a protracted period of time. This is not usually associated with recurrent malignancy but most commonly reflects chronic injury to the intercostal nerve, often with neuroma formation. The conclusion is that a careful search for recurrent tumor or infection should be undertaken in any patient experiencing progressive or recurrent pain after thoracotomy.
2. *Postmastectomy pain*. This pain syndrome is considerably more common than chronic post-thoracotomy pain, affecting between 5–10% of women undergoing breast biopsy, lumpectomy, or mastectomy *(24)*. It is not associated with recurrent cancer in the vast majority of sufferers and usually develops within a few weeks or months of surgery. This pain is caused by the formation of a post-traumatic neuroma involving the intercostobrachial nerve. The latter is a cutaneous sensory nerve formed by branches of T1 and T2 sensory roots, which supplies sensation to the anterior chest wall and axilla. It is virtually impossible to incise breast tissue without sectioning a branch of this nerve. The pain is neuropathic and felt in the chest wall, along the incision and in the ipsilateral axilla. Patients describe burning, tightness, itching, and aching in this location. They may experience the so-called "phantom breast" syndrome, in which the patient experiences a feeling as if the removed breast is present, often in an abnormal or painful position. Skin sensitivity is prominent and allodynia is often present. Arm movements exacerbate the pain and may lead to a secondary shoulder capsulitis.
3. *Postamputation limb pain*. Two distinct neuropathic pain syndromes may follow amputation of a limb. " Stump pain" is located distally, along the incision. It is usually sharp and stabbing and may be associated with tender points along the incision. This pain often makes wearing a limb prosthesis uncomfortable. Stump pain is usually secondary to neuroma formation within the incisional scar. It usually begins shortly after surgery and rarely indicates recurrent cancer. If refitting of the prosthesis or medications for neuropathic pain is ineffective, then surgery to excise the neuroma or transpose the nerve under protective soft tissue may be required.

   Immediately after limb amputation surgery, most patients will experience the presence of a phantom limb in its place. There is usually only mild to moderate discomfort with this and over time the phantom will gradually shrink or telescope into the stump. "Phantom limb pain" is a painful sensory experience that the patient localizes to the absent limb. This pain is often severe and has neuropathic features. Some patients may describe the phantom limb as feeling as if it were swollen, twisted, or in an unusual position. Phantom limb pain usually does not indicate persistent or recurrent malignancy unless it suddenly reappears after initial resolution. Interestingly, phantom limb pain is much more common if the limb was painful prior to

surgery. Epidural anesthesia and aggressive pain control in the pre- and postoperative period significantly reduces the incidence of phantom limb pain *(25)*.

4. *Postradical neck dissection pain.* Injury to the cervical plexus (C2-C4) or its peripheral sensory nerve branches (greater and lesser occipital, greater auricular, transverse colli, and supraclavicular nerves) at the time of neck dissection produces neuropathic type pain in the neck and shoulder. This pain is best treated with medications specific for neuropathic pain. Mechanical, myofascial neck and shoulder pain may result from muscular weakness due to paralysis or injury to the hyoid muscles, sternocleidomastoid, trapezius, scalene, and levator scapulae muscles. A "dropped shoulder" may result with symptoms of thoracic outlet syndrome. These symptoms are often best treated with physical therapy. The neuropathic and mechanical pain syndromes typically begin soon after surgery and stabilize or gradually improve. A patient with a history of head and neck cancer who suddenly develops escalating neck or shoulder pain weeks or months after surgery should be suspected of harboring recurrent malignancy or indolent infection (often with anaerobic bacteria). Appropriate imaging studies (CT or MRI) assist in making the diagnosis.

**POSTRADIATION PAIN SYNDROMES** During and immediately after treatment, radiation may cause acute, self-limited pain secondary to mucosal, cutaneous, and subcutaneous tissue injury. Mucositis of the mouth and esophagus are common after radiation to the head and neck. Proctitis often follows radiation to the pelvis. Skin and soft tissue erythema and swelling are common within the ports of radiation therapy delivered to any part of the body. Local therapies (oral viscous lidocaine, rectal steroid, or aloe-based lotions) and nonsteroidal anti-inflammatory drugs may be all that is required for comfort. For patients with more severe involvement oral or parenteral opioids may be required depending on the severity of the pain.

Chronic, painful soft tissue injury may result from radiation. Bone necrosis with proneness to stress fractures in weight-bearing bones heals very slowly and may be extremely painful. Rarely, many years after radiation, some patients may develop radiation-induced malignancies in the radiated site. Malignant sarcomas of the peripheral nerve sheath are most common and typically present with a painful enlarging mass within the radiated field, sometimes with neuropathic pain in the distribution of the involved nerve. Patients who received radiation to the head may develop meningiomas, gliomas, or dural sarcomas years later, presenting with progressive neurologic deficit and headache.

Radiation may produce chronic damage to neural structures, including the brain, spinal cord, root, plexus, and peripheral nerve. Radiation injury to the CNS is usually painless or the pain is mild and overshadowed by the neurologic deficits. Rarely a central neuropathic pain syndrome may develop after radiation to the cord or sensory areas of the brain. In radiation injury to the PNS, pain is more common. It tends to be less severe than pain produced by tumor infiltration. Vascular endothelial cells and Schwann cells are the most affected as these have the highest rate of cell turnover. Pathologically, demyelination, vascular hyalinization, fibrosis, and necrosis are seen within the nerve tissue. The brachial and lumbosacral plexi are the structures most vulnerable to radiation injury, probably due to their proximity to commonly radiated areas.

**RADIATION BRACHIAL AND LUMBOSACRAL PLEXOPATHY** This disorder usually presents from 6 mo to 20 yr after the administration of radiation. The risk is higher if the total dose and fraction size is higher. Unlike malignant plexopathy, radiation plexopathy is associated with pain in less than 25% of patients and the pain tends to be less severe than malignant pain. Neuropathic features, including tingling, itching, and burning are common. In radiation injury to the brachial plexus, the usual site of anatomic involvement is different from malignant plexopathy. The upper trunk and lateral cord bear the brunt of injury in most patients, while the lower trunk and medial cord are relatively spared, as these structures are protected from radiation by the overlying clavicle. Most patients present with C5/C6 weakness involving the supra and infraspinatus, deltoid, and biceps and have paresthesiae radiating into thumb. The biceps and brachioradialis reflexes are reduced. A Horner's syndrome is usually absent. In malignant plexopathy, C8/T1 innervated muscles are usually involved and pain and paresthesia radiate into the little finger. A Horner's syndrome is often present in the latter.

Patients receiving pelvic radiation are at risk to develop radiation injury to the lumbosacral plexus, particularly if they received intracavitary or intra-operative radiation in addition to external beam. Radiation-induced lumbosacral plexopathies usually cannot be differentiated from malignant plexopathy on the basis on anatomic involvement. L5/S1 distribution sign and symptoms are common for both types of plexopathy. Lumbosacral radiation injury usually presents with unilateral lower extremity weakness, reduced reflexes, and paresthesiae with minimal pain.

Lymphedema of the arm or leg is a common accompaniment to radiation injury to the brachial or lumbosacral plexus but is not commonly associated with malignant plexopathy. The lymphedema itself may be a primary source of discomfort and dysfunction.

MRI or CT through the plexus is the most helpful study to differentiate radiation-induced from malignant plexopathy. Usually these images will show a circumscribed mass with malignant invasion and will be normal or show only indistinct tissue planes with radiation injury. EMG will show characteristic myokymic discharges in muscles innervated by the involved plexus in radiation injury *(26)*. This may be of limited usefulness in differentiating it from malignant plexopathy, as anyone who has received radiation to the plexus may have this feature, which does not rule out coexisting malignant involvement.

**PAIN SYNDROMES FROM CHEMOTHERAPY** Pain produced by chemotherapy agents is usually due to injury of the peripheral nerve. In most cases this is a length-dependent sensorimotor axonal polyneuropathy. Autonomic nerve fibers may also be involved. Cisplatin, vinca alkaloids, etoposide, paclitaxel, procarbazine, and misonidazole are among the most commonly utilized chemotherapy agents that are known to produce neuropathy. Patients with these neuropathies experi-

ence burning and tingling ascending from the toes. In most cases, the neuropathy is self-limited and the symptoms resolve once the drug is discontinued. Symptomatic relief of neuropathic pain is often obtained with adjuvant analgesics including tricyclic antidepressants and anticonvulsants, or opioids.

Corticosteroids are commonly used to treat a variety of symptoms in patients with cancer. They have anti-emetic properties, reduce tumor-associated swelling, and reduce bone pain. Corticosteroids are a component in many combination chemotherapies for lymphoma and leukemia. When dexamethasone is given as a high-dose bolus injection, as in treatment of epidural cord compression, over 50% of patients experience intense perineal burning *(27)*. The mechanism is unknown. Fortunately, the sensation is brief and can be avoided if the administration of the drug is slowed. No therapy is required.

Patients maintained on corticosteroids for prolonged periods of time may develop painful avascular necrosis of the femoral or humeral head. The pain is localized to the involved joint or its referral zone and is worse with stressing the joint. Bone scan and MRI of the joint usually make the diagnosis and precede X-ray abnormalities. This condition sometimes will resolve if the steroid is stopped. Often, surgical intervention is required if the joint is severely compromised.

Steroid pseudorheumatism is a painful condition caused by withdrawal from corticosteroids. The syndrome is characterized by diffuse, severe, myalgias and arthralgias that typically begin while the corticosteroid is being tapered. There appears to be no relationship to the steroid dosage, duration of therapy, or speed of withdrawal. The mechanism is unknown but may be due to sensitization of muscle and joint nociceptors. The preferred treatment is to re-institute the corticosteroid at a higher dosage and withdraw it more slowly.

Phenobarbital, an anticonvulsant used to treat seizures in patients with tumors involving the CNS, may produce a similar pain syndrome. Phenobarbital pseudorheumatism is a rare disorder, characterized by aching discomfort and immobility in one or both shoulders. The pain is worse with shoulder movement and some patients may actually go on to develop an adhesive capsulitis (frozen shoulder syndrome) and signs of a superimposed complex regional pain syndrome (reflex sympathetic dystrophy). Phenobarbital pseudorheumatism will typically resolve if the phenobarbital is discontinued. Physical therapy is helpful as well.

The preceding section dealt with the different mechanisms that may produce pain in patients with cancer. It is critically important that the clinician discovers the cause of cancer-related pain and, where possible, treats that underlying cause. This will optimize the treatment of pain and overall care of the cancer patient. The following section will deal with the appropriate use of medications and other modalities to treat cancer-related pain.

## TREATMENT OF CANCER-RELATED PAIN

Analgesic drug therapy is the cornerstone of cancer pain therapy. Most patients will be able to obtain good relief with a relatively simple regimen of oral medications. As the previous section stressed, it is important to have a good understanding of the underlying cause of the patient's pain. However, in most instances, regardless of the pain mechanism, the choice of medications will depend primarily on its severity.

Utilizing the pain evaluation scale "1 to 10" outlined in the section titled "Clinical Assessment," pain ratings of 1 to 4 generally correspond to "mild pain." A rating of 5 to 7 generally is considered "moderate" and 8 to 10 is "severe." In most patients, a pain rating over 4 will substantially interfere with day to day activities and level of function.

The World Health Organization has developed a simple three-step pharmacologic approach to managing cancer pain, depending on whether the patient's pain is mild, moderate, or severe (*see* Fig. 1) *(28)*. Adherence to this basic approach will provide adequate analgesia in 80–90% of patients experiencing cancer-related pain *(29)*. Step 1 is for patients with mild to moderate pain and involves the use of nonopioid analgesics, including acetaminophen, salicylates, and nonsteroidal anti-inflammatory drugs (NSAIDs). Step 2 analgesics include low-potency opioids including codeine, oxycodone, hydrocodone, and propoxyphene. Step 2 drugs are indicated for those patients with mild to moderate pain who do not obtain relief with nonopioid analgesics and for patient with moderate to severe pain at the onset. Step 3 drugs are high-potency opioids, including morphine, oxycodone, hydromorphone, levorphanol, methadone, and fentanyl. Step 3 is indicated for patients with severe pain or for those who fail to obtain adequate relief with a low-potency opioid. An "adjuvant" analgesic may be co-administered with drugs in Steps 1, 2, and 3. An adjuvant drug is defined as a medication that may not be considered analgesic by itself, but that may enhance the effectiveness of opioids, relieve opioid-related side effects, or act independently as an analgesic only or some specific types of pain.

It is important to select the appropriate drug, dosage, and route of administration for the individual patient as well as know how to titrate the dosage according to the analgesic response. Drug side effects should be anticipated and managed. A sequential trial of drugs may be appropriate if one medication is ineffective or the side effects unmanageable. The following sections will deal with Step 1, 2, and 3 analgesic medications and the appropriate use of adjuvants in greater detail.

**STEP 1: NONOPIOID ANALGESICS** Step 1 drugs are listed in Table 1. All are available in oral formulations. Some are available as rectal suppositories. Ketorolac is the only NSAID available in a parenteral formulation. Tolerance and physical dependence do not develop with Step 1 medications. Unlike opioid analgesics, these medications have a "ceiling effect." This means that as the dosage of medication is increased past a certain point, no additional analgesia is obtained. This limits their usefulness in treating cancer pain, as most cancer patients have pain severe enough to require opioids. The coadministration of a nonopioid with an opioid may be quite helpful, producing additive analgesia, particularly in patients with bone metastases.

Step 1 drugs include acetaminophen, which has analgesic and anti-pyretic effects similar to aspirin but only weak anti-inflammatory properties. The precise mechanism of analgesia is unknown.

Acetaminophen is a weak inhibitor of cyclooxygenase. It lacks the gastric irritant effects associated with salicylates and

**Table 1**
**Step 1: Nonopioid Analgesics**

| *Drug* | *Half-life (h)* | *Average dose (mg)* | *Maximum daily dose (mg)* | *Comments* |
|---|---|---|---|---|
| Acetaminophen | 3–4 | 500 Q4–6 h PO or PR | 4000 | Avoid in patients with hepatic disease |
| Aspirin | 2.5–9 | 325 Q4–6 h PO or PR | 4000 | Avoid in children<br>Avoid in renal disease<br>Avoid in bleeding disorders |
| Choline magnesium trisalicylate | 8–12 | 1500 BID PO tabs and liquid | 4000 | Less GI upset and platelet dysfunction than aspirin and NSAIDs |
| Ibuprofen | 1.8–2.5 | 400 Q4–6 h | 3000 | Avoid in renal disease<br>Avoid in bleeding disorders<br>GI upset common |
| Ketorolac | 2–8 | 10 Q4–6 h PO<br>30 Q6 h IM or | 40 (PO)<br>120 (IM or IV) | Avoid in renal disease |
| Celecoxib | 11 | 200 QD PO | 200 | Less GI upset |
| Rofecoxib | 17 | 50 QD | 50 | Similar to Celecoxib |

NSAIDs and will not affect platelet aggregation. The maximum recommended dose is 4000 mg/d in divided doses. Hepatotoxicity is the main dose-limiting side effect of acetaminophen. This latter effect is most common after ingestion of a large overdose (10–15 g) of acetaminophen. It may also occur in patients with chronic liver disease, heavy alcohol use, taking therapeutic dosages. Nephropathy, hypoglycemia, and accentuation of warfarin anticoagulation are other less common effects of acetaminophen.

Salicylates and NSAIDs work peripherally by blocking the enzyme cyclooxygenase and inhibiting the formation of prostaglandins *(30)*. Prostaglandins are potent mediators of inflammation that sensitize peripheral nociceptors. With the possible exception of nonacetylated salicylates (salsalate and choline magnesium trisalicylate) and the selective cyclooxygenase-2 inhibitors (Rofecoxib and Celecoxib), these drugs have a high incidence of adverse effects. These effects include GI bleeding, antiplatelet effects, and renal insufficiency. NSAIDs should not be co-administered with anticoagulants or corticosteroids, both of which enhance the risk of GI bleeding. Omeprazole, misoprostol, or an H2-histamine blocking agent lessens the risk of GI bleeding and gastric upset when given with NSAIDs.

As with the other medications on the analgesic ladder, Step 1 drugs should be given on an around-the-clock (ATC) schedule, not only "as needed" (PRN). This insures stable blood levels of drug and improves analgesia.

**STEP 2: LOW-POTENCY OPIOIDS** Step 2 opioid medications are appropriate treatment for patients with moderate pain or those with less severe pain who do not obtain adequate relief with a nonopioid analgesic. Step 2 drugs include codeine, dihydrocodeine, oxycodone, propoxyphene, hydrocodone, and tramadol. Most of the low-potency opioids are available alone or in combination with acetaminophen or aspirin. Use of the opioid/nonopioid combination limits the maximum dose that can be administered, due to adverse effects from high doses of acetaminophen or aspirin. With the exception of codeine and oxycodone, these lower-potency opioids appear to have a ceiling effect to their analgesia. Thus, patients whose pain is refractory to maximum doses of low-potency opioid will require a switch to a high-potency opioid (Step 3) in which the ceiling effect is absent. Table 2 lists the Step 2 opioids and their equianalgesic dosages.

All of the low-potency opioids are approximately equally efficacious. Individual patients may respond better to one of these drugs with fewer adverse effects than another, emphasizing the importance of individualization of drug therapy. Propoxyphene should be avoided in elderly patients or those with reduced renal function. The major metabolite of propoxyphene is norpropoxyphene. Norpropoxyphene has a 30-h half-life, and tends to accumulate in those patient with reduced renal function. It appears to be responsible for many of the opioid-related side effects of propoxyphene and also produces cardiotoxicity *(31)*. Tramadol hydrochloride is a weak agonist of mu receptors and has an adjuvant analgesic effect by inhibiting serotonin and norepinephrine reuptake within the CNS.

**GENERAL PRINCIPLES OF HIGH POTENCY OPIOID USE** Most patients with cancer-related pain will require the use of opioids for adequate pain control. These drugs produce analgesia by activation of mu, kappa, and delta opioid receptors at multiple sites within the CNS (spinal and supraspinal). There is evidence that opioids have peripheral analgesic effects as well *(32)*. Partial opioid agonists (e.g., buprenorphine) and mixed agonist/antagonists (butorphanol, pentazocine, and nalbuphine) generally should be avoided. These drugs tend to have excessive psychotomimetic effects, have a ceiling effect to analgesia, and may produce withdrawal symptoms in opioid-dependent patients.

All opioids have common adverse effects and administration of these drugs may produce tolerance, physical dependence, and psychological dependence. The clinician must understand the mechanism and management of these effects in order to use opioids safely and effectively.

**Table 2**
**Step 2: Low-Potency Opioid Analgesics**

| *Drug* | *Half-life (h)* | *Average starting dose (mg)* | *Maximum daily dose (mg)* | *Comments* |
|---|---|---|---|---|
| Codeine | 2.5–3.5 | 30–60 Q4–6 h PO or IV | Determined by titration | May be combined with non-narcotics |
| Oxycodone | 2–3 | 5–10 mg Q4–6 h PO | Determined by titration | May be combined with non-narcotics<br>Available in sustained release formulation |
| Propoxyphene | 8–24 | 65 Q4 h PO | 390 | May be combined with non-narcotics<br>Norpropoxyphene may cause seizures<br>Avoid in renal disease and elderly |
| Hydrocodone | 3–4 | 7.5 Q4–6 h PO | 45 | Available only in combination with non-narcotics |
| Tramadol | 6–8 | 50 Q4–6 h PO | 400 | Nausea common<br>Seizures reported |

**Tolerance and Dependence** Tolerance refers to the need for increasing doses of drug in order to maintain a medication effect. Sometimes tolerance is desirable, as when tolerance develops to opioid-induced respiratory depression, sedation, and nausea. It is undesirable when it develops to opioid-induced analgesia, requiring escalating dosages to maintain pain control. Human data suggests that true analgesic tolerance to opioids in cancer patients is rare *(33)*. When cancer patients require increasing dosages of opioid for analgesia, it is usually because their underlying painful disease is progressing or another exacerbating factor is present (i.e., infection or mood disorder). Similarly, patients whose underlying cancer is successfully treated with surgery, radiation, or chemotherapy will typically require less opioid medication to maintain analgesia. Most patients with progressive cancer will require excalating dosages of high-potency opioid for adequate pain control. Fortunately, the high-potency opioids do not appear to have a ceiling effect to analgesia.

Physical dependence refers to the development of a withdrawal syndrome if the opioid is discontinued of if an opioid receptor antagonist is administered. The opioid-withdrawal syndrome is characterized by anxiety, insomnia, muscle cramps, and autonomic hyperactivity, including mydriasis, sweating, piloerection, diarrhea, tachycardia, hypertension. Physical dependence is a physiologic certainty in any patient receiving regular doses of opioids on a chronic basis. The withdrawal syndrome can be avoided or treated by reinstitution of the opioid and tapering slowly over a period of days. Physical dependence is not "addiction," which refers to psychological dependence.

Psychological dependence is a behavioral pattern of drug abuse in which the patient uses an opioid for nonmedically sanctioned purposes. Patients who are psychologically dependent on opioids use the drug to obtain the psychotomimetic effects, not analgesia. Fortunately, psychological dependence or "addiction" is rare in patients with cancer *(6)*. Fear of tolerance, physical dependence, and psychological dependence should never cause the clinician to withhold the use of opioids in patients with cancer.

**Choose the Appropriate Drug and Route of Administration** The factors that govern selection include the severity of the pain, the patient's previous adverse or favorable responses to a particular opioid, available routes of administration, patient age, and patient renal and hepatic function. If a particular opioid has caused severe side effects in an individual patient in the past, that opioid should be avoided. Similarly, if a particular opioid was well-tolerated previously by a particular patient, that medication may be tried again if its potency is appropriate for the patient's current level of pain.

The oral route is the most simple and least expensive. Most opioids are available in an oral formulation and the bioavailability by this route is good. For those patients who are not able to take oral medications, opioids can be given rectally, trans-dermally, or by intravenous or subcutaneous injection. Intramuscular injection has no advantage over other routes of administration and is unnecessarily uncomfortable for the patient. Epidural or intrathecal infusion of opioids is rarely required and should be reserved for a small subset of patients who are unable to obtain relief by more conventional routes of administration (*see* below).

For patients with very severe pain, the intravenous route is the fastest way to obtain analgesia and determine the patient's opioid requirements. Once the pain is controlled, the opioid is easily converted into an equianalgesic oral dosage.

Most opioids are metabolized by the liver into active and inactive metabolites, which are then excreted by kidney. In elderly patients and those with renal dysfunction, the opioid or its metabolites can accumulate. While many of these metabolites produce analgesia they may also cause side effects. Opioids with a longer half-life (e.g., methadone and levorphanol) and opioids with long half-life metabolites (e.g., morphine and meperidine) are especially likely to produce sedation, nausea,

and myoclonus in those patients with reduced renal clearance. These drugs should be avoided as first line analgesics in these patients. Meperidine, as mentioned previously, should never be used in the treatment of cancer-related pain.

For patients with severe pain under age 65 with normal renal function, morphine is usually the first drug of choice. For those over age 65 or those with renal impairment, hydromorphone is probably best in most cases.

**Titrate the Opioid to Obtain Adequate Analgesia** In an opioid-naive patient or one who has received only low-potency opioids, it is best to start with the opioid dosages listed in Table 3. In order to obtain good, continuous pain control and few side effects, the medication should be prescribed on an scheduled, around-the-clock (ATC) not just an "as needed" (PRN) schedule. For most high-potency opioids, the dosing interval is 4–6 h for the immediate release preparations and 8–12 h for the extended release. The initial dosage is a safe starting point, but may be insufficient to adequately control the patient's pain. Therefore, provision should be made for PRN "rescue" doses of the same medication for breakthrough pain if the ATC dosage is too small. The PRN dosage should be 10–15% of the total 24-h dosage administered as needed every 2 h between the scheduled doses. This plan optimizes pain control and also allows the clinician to better determine opioid requirements during the titration process. Eventually, it should be possible to find the appropriate scheduled dosage of medication that does not require frequent rescue doses.

Initially, the clinician should assess: (1) the patient's level of analgesia, (2) the use of rescue medications, and (3) type and severity of side effects, at least every 24 h. If the patient's analgesia is adequate but he or she has used frequent rescue doses, the amount of rescue drug should be added to the total amount of scheduled drug and that amount of opioid should then be administered in divided doses the next day. Once the pain is under control the assessments do not need to be as frequent. Ideally the nurse or physician should be available to reassess the situation

Opioid dosage requirements may differ greatly between patients. The appropriate dosage of a high-potency opioid is the one which controls the pain without undue side effects. Most patients require escalating dosages as their disease progresses. Although most patients will requires dosages ranging from 60–400 mg or oral morphine equivalents per day, some will require much more. Thus, there is no "standard" dosage and therapy is highly individualized. Opioid side effects are the most frequent stumbling block in titrating the dosage upward. They will be dealt with in the following section.

**Treat Opioid Side Effects** The most common opioid side effects are constipation, sedation, delirium, nausea, respiratory depression, pruritus, convulsions, and myoclonus. Generally, the high-potency opioids (*see* below) are more likely to produce side effects than the low-potency opioids. All opioid drugs have similar side effects, although an individual patient may tolerate one opioid better than another. Opioid side effects are preventable or treatable, and with the exception of constipation, patients will develop some degree of tolerance to them. If these treatment efforts fail, however, switching the patient to an equianalgesic dose of a different opioid may remedy the situation.

Constipation is the most common and refractory opioid-related adverse effect. Opioids produce increased resting tone in smooth muscle of the small and large intestine and reduce peristalsis. Prevention is the best approach. Stool softeners should be started when opioids are first prescribed. A combination of senna and docusate works best. If constipation has already developed, stimulant laxatives or osmotic agents should be added.

Respiratory depression is the most feared opioid side effect. Fortunately, tolerance develops rapidly to this effect and it rarely limits the chronic use of opioids in patients with cancer. It most commonly occurs in opioid-naive patients who receive high initial doses of narcotic (particularly IV) or in those patients chronically receiving opioids in whom the dosage is titrated upwards too quickly. Sedation always accompanies the respiratory depression. If the patient is not comatose, physical and auditory stimulation may reverse the sedation and respiratory depression. This will alert the patient and the respiratory rate will increase as well. Subsequent opioid doses should be slightly reduced if analgesia is adequate. The dosage can be carefully titrated upwards once tolerance to the respiratory depression develops. It is best to avoid the administration of an opioid antagonist (naloxone) unless the respiratory depression and sedation are severe. If naloxone must be administered, it should be given slowly in small doses (0.4 mg in 10cc of saline given IV in 1 mL increments) so as to avoid opioid withdrawal and reversal of analgesia. Other supportive measures, including airway protection with an endotracheal tube, should be instituted to prevent aspiration.

Opioids may produce sedation, particularly when starting the medication in an opioid-naive individual or when titrating the dosage upwards. Generally the sedation is not severe and tolerance will develop within a period of days. If the tolerance is incomplete or the patient is not willing to wait, then a stimulant may be administered. Caffeinated beverages sometimes are sufficient. If something stronger is required, small doses of methylphenidate or dextroamphetamine may be administered. These latter medications should be avoided in patients with coronary artery disease, uncontrolled hypertension, cardiac dysrhythmia, or psychosis.

There are several mechanisms to opioid-induced nausea. (1) Opioids activate receptors in the chemoreceptor trigger zone of the dorsal medulla. Patients experience nausea, which is constant and not affected by eating or movement. Treatment with a phenothiazine, such as prochlorperazine, is most effective. (2) Opioids reduce gastric emptying by increase smooth muscle tone in the gastroduodenal sphincter. These patients experience early satiety and post-prandial nausea. Metoclopramide is the treatment of choice. (3) Opioids may sensitize the vestibular apparatus in the inner ear, particularly in young patients. The nausea occurs mostly with movement and transderm scopolamine or meclizine is the treatment of choice.

Any opioid may produce myoclonus, although meperidine is particularly prone to producing this adverse effect. The myoclonus is accentuated with drowsiness, and occasionally reversing the sedation with a stimulant (*see* above) will improve

**Table 3**
**Step 3: High-Potency Opioids**

| Drug | Half-life (h) | Equianalgesic dose (mg) | | Duration (h) | Comments |
|---|---|---|---|---|---|
| | | Parenteral | Oral | | |
| Morphine | 2–4 | 10 | 30–60 | 4–6 | Available in sustained release form for Q8, Q12, and Q24 h administration |
| Hyrdromorphone | 1–3 | 1.5 | 7.5 | 4–5 | May be better tolerated in elderly and those with renal dysfunction |
| Methadone | 15–29 | 10 | 20 | 6–8 | Drug accumulates after several days<br>Avoid in elderly and those with renal dysfunction |
| Fentanyl | 2–4 | 0.1 | — | 0.5–1 (IV) | Available in transdermal patch (25, 50, 75, and 100 mcg/h patch)<br>50 mcg/h patch = 90 mg/d morphine<br>Transmucosal formulation for break-through pain |
| Meperidine | 2.5–4 | 75 | 300 | 2–4 | Normeperidine has high risk of seizures<br>Avoid in patients requiring chronic use<br>Toxic interaction with MAO inhibitors |
| Oxycodone | 2–3 | — | 20 | 4–5 | Available in sustained release form |

the myoclonus as well. Clonazepam may be helpful but will accentuate opioid-induced sedation.

High doses of opioids in an opioid-naive patient may rarely produce convulsions. Meperidine, however, may produce convulsions even at relatively low dosages with chronic administration, particularly in those patients with reduced renal function. Normeperidine, a toxic metabolite of meperidine, appears to be responsible *(34)*. Consequently, meperidine has no role in the treatment of chronic cancer-related pain.

When opioids produce pruritus, it is usually from direct histamine release not a true allergic reaction. Anti-histamines may be sufficient. Switching to an alternate opioid may also be helpful. Among the high-potency opioids, fentanyl is least likely to produce pruritus.

**Converting from One Opioid to Another** Occasionally it may be necessary to switch a patient from one opioid to another or from one route of administration to another. If the patient is unable to obtain good analgesia without unmanageable side effects, converting to alternate high-potency opioid may provide the solution. Or, if the patient is no longer able to take oral medications, the clinician will need to convert the opioid into an equianalgesic parenteral form. The opioid equianalgesic conversion table is very helpful in this regard (*see* Table 3). All dosages listed are equianalgesic with 10 mg of IV morphine. When making the initial switch from one high-potency opioid to different one, the equianalgesic dosage of the new opioid should be reduced by one-third to one-half of the calculated figure, as cross tolerance between opioids in incomplete. When converting from a short half-life drug like morphine or hydromorphone to methadone, the equianalgesic dosage reduction should be as much as 80%. The patient may well require upward titration of the new opioid to obtain good analgesia.

**STEP 3: HIGH-POTENCY OPIOIDS** Patients who have severe pain or those with moderate pain who fail to obtain good analgesia with a low-potency opioids should be started on a high potency opioid. Morphine is the prototype and is the drug of choice in patients with normal renal function under age 65, unless the patient has previously experienced unacceptable side effects to this drug. It is available in multiple formulations including oral tablets, oral solution, rectal suppositories, and parenteral injection. The extended release tablet, which comes in 15 mg to 200-mg strengths, is particularly convenient with dosing intervals of 8–12 h. A newer formulation (Kadian) is newly available in 20, 50, and 100 mg capsules and has a dosing interval of 24 h. The extended release tablets should not be broken or chewed and immediate release oral morphine should be used for supplementary doses when breakthrough pain occurs.

Hydromorphone is a useful alternative to morphine in elderly patients, those with impaired renal function, and those patients experiencing unmanageable morphine side effects. It has a shorter half-life than morphine and may be less prone to accumulate and produce adverse effects. The oral formulation is approx five times more potent than morphine.

Transdermal fentanyl is useful alternative in patients who cannot tolerate oral medications. Fentanyl is approx 100 times more potent than morphine when given intravenously, but only about 20 times more potent when given trans-dermally. It is available in a transdermal patch in formulations which deliver 25, 50, 75, and 100 mcg/h. When starting the patch, it usually takes at least 12 h to obtain analgesia and 48 h to attain a steady state drug level in the blood. This may hamper drug titration. Supplementary opioids for breakthrough pain should include immediate release morphine tablets or transmucosal fentanyl. The latter should be used with caution due to its high potency and rapid onset of action. All formulations of fentanyl are considerably more expensive than other oral high-potency opioids.

**Intraspinal (Epidural and Intrathecal) Opioids** The vast majority of cancer patients will be able to obtain good analgesia with simple methods as outlined earlier. Occasionally, the pain may be refractory to sequential trials of several oral or parenteral (IV or SQ) high-potency opioids or the side effects to systemic opioids may be unmanageable. In these instances, it is appropriate to consider spinal opioid infusions. It is most effective if the patient's pain is localized to the lower

half of the body. Chronic spinal opioid treatment is feasible and safe when administered by experienced clinicians. The advantages of spinal administration are that the opioid has direct access to the opioid binding sites within the CNS and much smaller dosage is required. This can improve analgesia and reduce some opioid side effects like sedation, nausea, and constipation. Local anesthetics (bupivacaine) may be given in conjunction with opioids to enhance analgesia. The disadvantages are increased risk of respiratory depression, complications related to catheter placement (e.g., epidural hemorrhage and infection), and greatly increased cost and invasiveness. Fentanyl and morphine are the opioids most commonly administered by this route.

**Adjuvant Analgesics** An adjuvant is a medication that enhances analgesia either by enhancing opioid analgesia or counteracting an opioid side effect. Some adjuvants have specific analgesic properties only in certain clinical situations, such as neuropathic pain or bone pain. The use of an adjuvant may be appropriate for patients with mild, moderate, or severe pain.

Tricyclic antidepressants (TCAs) are probably the most frequently prescribed adjuvant analgesics. In addition to their known benefits on mood, sleep, and appetite, they produce analgesia by increasing brain and spinal cord norepinephrine and serotonin levels. Both neurotransmitters are important in pain-modulating pathways. TCAs are most useful in neuropathic pain syndromes. Amitriptyline and nortriptyline are used most frequently. Both can produce side effects including delirium, dry mouth, postural hypotension, and urinary retention, particularly in the elderly. Nortriptyline is usually better tolerated in this group of patients.

Depression and anxiety may significantly increase the subjective suffering the cancer patient experiences. This may lead to escalating pain, increased opioid requirements, and worsened opioid side effects. It is extremely important to evaluate and treat these psychological issues. Appropriate treatment of mood and anxiety disorders may in turn lessen pain and reduce opioid requirements.

Anticonvulsants including carbamazepine, phenytoin, valproic acid, clonazepam, and gabapentin are helpful adjuvants in patients with lancinating neuropathic pain. Clonazepam is helpful for the treatment of opioid-induced myoclonus.

Corticosteroids improve appetite and mood and reduce nausea. They are very good analgesics in patients with pain from bony metastases due to their effects on prostaglandin synthesis. Other adjuvant drugs useful in the treatment of bone pain include calcitonin and pamidronate. Corticosteroids reduce tumor-associated edema and can relieve pain from visceral and brain metastases as well. The primary short-term adverse effects include mania, hiccoughs, hyperglycemia, myopathy, and GI bleeding. They should not be used in conjunction with NSAIDs due to the greatly increased risk of GI bleeding.

Psychostimulants like methylphenidate and dextroamphetamine have little or no analgesic effect when used alone. They improve opioid-induced sedation and allow more rapid opioid titration and better drug tolerance. They should be avoided in patients with a history of psychosis, uncontrolled hypertension, or cardiac dysrhythmia. They may make delirium worse and can produce anxiety, anorexia, and insomnia.

Neuroleptics have been used as adjuvants in cancer pain treatment for many years with few controlled studies to support their use. Most are effective anti-emetics and sedatives, but only methotrimeprazine has clear analgesic effects. Methotrimeprazine has potent sedative effects and may produce pronounced postural hypotension. It can be quite effective in the treatment of terminal delirium or in bedridden patients who cannot tolerate opioids.

**Anesthetic Procedures for the Treatment of Cancer Pain** The placement of epidural and intrathecal catheters for opioid and local anesthetic infusion was covered previously. Other anesthetic procedures include nerve blocks and ablative procedures. With the exception of celiac plexus block, these invasive procedures should be reserved for patients who fail to achieve satisfactory analgesia with adequate trials of multiple high-potency opioids administered systemically.

Chemical neurolysis of the celiac plexus in patients with severe midline upper abdominal visceral pain from GI and retroperitoneal malignancies (pancreas, liver, stomach, and gallbladder) can be extremely effective in over 50% of patients *(35)*. This procedure may provide lasting relief for many months, although usually the patient will continue to require opioids. This procedure is so effective that celiac plexus block is often performed without the requirement for multiple trials of opioids. In experienced hands the complications from this procedure are rare and include retroperitoneal hemorrhage, pneumothorax, ileus, and peritonitis.

Other neurolytic procedures for treatment of nociceptive and neuropathic pain are not usually so successful. Most of these procedures involve the instillation of a neurolytic solution into the paraspinal, epidural, or intrathecal space to destroy nerves carrying sensory afferents from the painful area. Unfortunately, the analgesia is usually temporary, permanent neurologic deficit may result, and the patient may develop a deafferentation pain syndrome.

Temporary nerve blocks with local anesthetics are usually not helpful in the long term with the exception of patients who have developed a complex regional pain syndrome (CRPS or RSD), usually as a complication of nerve injury. In these patients, a series of sympathetic nerve blocks in the involved region may be quite helpful.

**Neurosurgical Procedures** Cordotomy is the most commonly performed neurosurgical procedure for relief of cancer pain. The procedure involves lesioning of the spinothalamic tracts within the cervical or thoracic spinal cord, thus interrupting the transmission of pain and temperature sensation from the contralateral body, beginning several segments below the level of the lesion. These invasive procedures should be reserved for patients whose pain has been refractory to intensive, repeated trials of medical therapy and whose pain is unilateral and below the C5 dermatome. Midline and upper extremity pain syndromes do not respond well to cordotomy. There are several methods of performing a cordotomy. The most common one is done percutaneously at C1-C2 under fluoroscopic control *(36)*. This procedure is performed under local anesthesia with the patient lying supine. A needle with a small electrode is introduced laterally. The cord is electrically stimulated to localize the spinothalamic tract and then a radiofrequency lesion is

made. With unilateral cordotomy the risk of paralysis, hypotension, incontinence, or apnea is low, when performed by a skilled neurosurgeon. With bilateral C1-C2 cordotomy, the risks are significantly greater. For patients who require cordotomies for bilateral lower body pain, it is generally advisable to do an open cordotomy in the thoracic region. This requires a laminectomy and hospitalization. Although cordotomy can afford excellent relief of lower body pain, the effects are temporary and these procedures probably should only be done on those whose life expectancy is less than 1 yr.

Neurosurgical procedures to interrupt the pain pathways within the brainstem, and thalamus (tractotomies and thalamotomies) are highly invasive procedures. While these procedures have been reported to produce good, temporary analgesia they are not appropriate for the vast majority of patients. These procedures are fraught with risk and skilled surgeons who can safely perform them are few. Bilateral cingulotomy can be performed stereotactically. Although it does not interrupt pain pathways, it does appear to reduce the affective response or suffering that pain causes. Although this procedure does not usually adversely affect cognitive function, it often does produce personality change.

Implanted stimulators on the peripheral nerve, plexus, spinal cord, brain stem, and thalamus have been used for the treatment of chronic nonmalignant pain. There are not sufficient data at this time to recommend their use in the treatment of cancer-related pain. All are invasive and expensive procedures.

Pituitary ablation, whether by surgical excision or stereotactic alcohol injection, has been a helpful analgesic procedure, particularly in those patients with widespread bony metastases from hormone-responsive tumors like breast and prostate *(37)*. Pituitary ablation appears to help pain even in those patients without hormone-sensitive tumors and the amount of pain relief does not correlate with tumor regression. The mechanism of analgesia is unknown but may result from alterations in central pain neurotransmitters. That analgesia usually lasts only a few months.

## CONCLUSION

Pain is a prevalent and important symptom associated with all stages of cancer. The clinician must learn to assess the presence and severity and pain and identify its cause in order to best treat both the malignant disease and manage the pain. The vast majority of patients can obtain good analgesia with relatively simple and inexpensive measures if the physician is skilled in the selection and use of opioid and adjuvant medications. The risk of psychological dependence is low when opioids are used to treat cancer pain. Most patients will require around the clock dosing of medication with allowance for supplemental doses if breakthrough pain occurs. Pain control should be frequently reassessed and the dosage of medications adjusted accordingly. The opioid usually must be increased if the painful disease progresses. The physician should understand opioid-related side effects and their management, and the advantage of switching to another opioid if unmanageable side effects occur. Newer, novel opioid-delivery systems offer promise for easier drug delivery although not lower cost. Only a small minority of patients will require invasive anesthetic or neurosurgical procedures to adequately control their pain.

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# Part III Direct Complications of Cancer

# 7 Brain Metastases

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## INTRODUCTION AND EPIDEMIOLOGY

Metastases are the most common malignant tumor affecting the brain *(1–3)*. The incidence of parenchymal brain metastases from systemic cancer has increased since 1959 and approx 70,000 new patients are diagnosed with brain metastases each year *(1,4–7)*. However, the prevalence is even higher as autopsy series have shown that the brain is involved in about 15–40% of cancer patients *(1,3,8,9)*. Up to 30% of adults and 6–10% of children with cancer will develop brain metastases *(6,7,10)*. Better treatment of systemic cancers leading to longer survival, and better detection techniques, like magnetic resonance imaging (MRI), have contributed to the increased incidence. MRI has also shown that the incidence of multiple brain metastases is much higher than previously estimated and may be as high as 75% *(11)*.

In adults, the most common primary sources of brain metastases are lung and breast cancer and melanoma (Table 1) *(1,6,12)*. Breast is the most common primary tumor in women with brain metastasis. Malignant melanoma has the greatest propensity to metastasize to brain but the higher number of breast and lung cancers in the population make these tumors more common causes of brain metastases. In up to 10% of patients with cerebral metastases no identifiable primary tumor is found at presentation *(1,13–15)*. In children, sarcomas, neuroblastoma and germ cell tumors are the most common primaries *(16,17)*.

The incidence of metastases to the cerebrum is greater than to the cerebellum and the posterior fossa (ratio 8:1 approx) *(9,18)*; both hemispheres are equally affected *(18)*, frontal and parietal lobes being more commonly involved *(9,15,19)*. This approximates the relative proportion of cerebral blood flow to the supra and infratentorial compartments; however, different primaries have variable rates of metastasizing to different regions of the brain. Primary tumors located in the pelvis and abdomen are much more likely to metastasize to the posterior fossa, specifically cerebellum *(9)*; brainstem metastases are rare *(15)*. This suggests there are factors, in addition to blood flow volume, responsible for localization of metastatic tumors in the central nervous system (CNS). Spread via Batson's venous plexus does not explain this distribution of lesions completely, as there are no spinal metastases in most patients with posterior fossa metastases.

Brain metastases tend to occur at the grey matter-white matter junction and watershed zones of the cerebral circulation *(9,20)*. This may be due to entrapment of tumor cell microemboli in the end arteries or capillaries. The vascular watershed zones account for only one-third of the total brain substance but they harbor two-thirds of metastases *(20)*.

## BIOLOGY

Tumor metastasis formation is a multi-step process and for a primary tumor to metastasize, it has to overcome a number of hurdles. Tumor has to grow efficiently at the primary site, penetrate blood and lymphatic vessels, survive in the circulation, arrest in the microvasculature of the distant organs, extravasate, migrate in the organ, and grow. From all primaries only a small number of cells entering the circulation will eventually form metastases *(21)*. In the brain tumor cells additionally have to overcome the blood brain barrier and extracellular matrix (ECM). Brain ECM is small in volume and devoid of stroma along which tumor cells might migrate *(22)*. Host factors are also critical *(23)*. Exact mechanism of organ tropism is not completely understood but data are emerging regarding the molecular mechanisms that play a significant role.

Many cancer cells have been shown to produce proteolytic enzymes. Matrix metalloproteinases (MMPs) are a group of enzymes able to digest ECM and basement membranes. Expression of different MMPs have been shown in cancers of colon, prostate, pancreas, ovary, breast, and melanoma *(24,25)*. Tumor growth and metastatic colonies of melanoma were significantly reduced in MMP-2 and MMP-9 knockout mice, respectively, suggesting a role for these enzymes in tumor pro-

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**Table 1**
**Primary Tumor Type in Brain Metastases Patients, Number of Lesions, and Time to Metastases**

| Primary tumor | Number | | | Interval[a] |
|---|---|---|---|---|
| | Total (%) | Single | Multiple | (mo) |
| Lung cancer | 288 (39) | 137 | 151 | NA |
| NSCLC | 178 | 89 | 89 | 3 |
| SCLC | 110 | 48 | 62 | 6 |
| Breast | 121(17) | 59 | 62 | 40 |
| Melanoma | 80 (11) | 39 | 41 | 31 |
| Genito-urinary | 81 (11) | 49 | 32 | NA |
| Renal cell | 45 | 25 | 20 | 28 |
| Bladder | 14 | 9 | 5 | 15 |
| Prostate | 11 | 9 | 2 | 22 |
| Testicular | 11 | 6 | 5 | 15 |
| Gynecological | 52 (7) | 28 | 24 | NA |
| Uterine/vulvar | 38 | 20 | 18 | 23 |
| Ovarian | 14 | 8 | 6 | 23 |
| Gastrointestinal | 45 (6) | 30 | 15 | 14 |
| Unknown | 33 (5) | 23 | 10 | <1 |
| Miscellaneous | 29 (4) | 19 | 10 | 16 |
| Total | 729 | 384 | 345 | 12 |

[a]From diagnosis of primary tumor to brain metastases.
NSCLC, non-small cell lung carcinoma; SCLC, small cell lung carcinoma.
Adapted from ref. *15*.

gression *(26,27)*. Upregulation of other proteases in tumors has also been shown to be a prognostic marker of increased recurrence *(28,29)*.

Once in the circulation, tumor cells or microemboli have to survive immune surveillance. There is some recent evidence that platelets may protect tumor cells from natural killer (NK) cell-induced lysis *(30)*. Tumor-derived adenosine diphosphate and thrombin cause platelet aggregation. Aggregated platelets on the surface of tumor emboli protect them from NK cell attack. Finally adhesion molecules help tumor cells attach to the endothelium of the microvasculature of the host organs. Families of adhesion molecules such as selectins, integrins, CD44, and cadherins are expressed in many tissues including endothelial cells, lymphocytes, and tumors. Selective distribution of these molecules and their receptors on different cancers and target organs may partially explain the organ tropism of different cancers. The capillary endothelial cells in organs differ considerably in their cytokine and adhesion molecule content. Similarly there is marked variation in the ECM of different organs. The extent to which the cytokines and adhesion molecules are up- or downregulated plays an important role in organ specificity *(31)*. Adhesion molecules in concert with different proteases also help in tumor cell extravasation and migration in the ECM of the host organ *(23)*. Finally tumor growth beyond a few millimeters requires angiogenesis. This is achieved by activating oncogenes leading to transcription of transforming growth factors (TGF), vascular endothelial growth factor (VEGF), tumor necrosis factor alpha (TNF-*a*) as well as others, which promote neoangiogenesis to support tumor proliferation *(32,33)*.

**Table 2**
**Presenting Signs and Symptoms of Brain Metastases[a]**

| Symptoms | Nussbaum (15) n = 729 | Posner (45) n = 160 | Le Chevalier (43) n = 120 |
|---|---|---|---|
| Headache | 24 | 53 | 64[b] |
| Altered mental status | 24 | 31 | 42 |
| Seizure | 16 | 15 | 30 |
| Paresis | 16 | 40 | 50 |
| Gait disturbance | 9 | 15 | 30 |
| Visual complaints | 6 | NA | NA |
| Nausea/vomiting | 5 | NA | NA |
| Dysphasia | 5 | 10 | 18 |
| Sensory disturbance | 2 | NA | 24 |
| None | 10 | NA | NA |

[a]More than one sign and symptom may be present in a single patient.
[b]Headache and vomiting.
NA, not available.

## PATHOLOGY

Metastatic tumors in the brain are usually well-circumscribed and tumor cells can be easily distinguished from surrounding glial cells *(34)*. Common sources for adenocarcinomas are lung, gastrointestinal tract, ovaries, breast, prostate, and uterus *(18)*. Well-differentiated adenocarcinomas usually retain architectural features of the primary tumor *(35)*. Squamous cell carcinomas are mostly from lung, esophagus, and cervix. In difficult cases, positive staining for mucin and keratin and absent staining for glial fibrillary acidic protein helps to differentiate metastatic carcinomas from primary glial tumors.

In tumors of unknown primary, microscopy may suggest the primary source but this is rarely definitive. Immunohistochemical staining may help if tumor antigen-specific antibodies are available *(36)*. Electronmicroscopy can be useful occasionally by identifying tumor- or organ-specific ultrastructural features.

About 50–70% of patients have only one or two metastatic lesions *(9,15)*. Although macroscopically compact, microscopically, metastatic lesions spread by expansion and infiltration. Small cell carcinoma, lymphoma, leukemia, and melanoma have a much higher tendency than others to infiltrate *(36)*. These tumors can penetrate the pia mater and ependyma and spread via the cerebrospinal fluid (CSF). In the white matter they can grow along the white matter fibers in irregular fashion *(34,35)*.

Angiogenic factors produced by the tumor cells cause vascular proliferation in the tumor and surrounding brain tissue. The blood-brain barrier (BBB) is poorly formed in these vessels *(37)*. There is increased transudation of fluid into the brain parenchyma leading to peritumoral edema. White matter becomes vacuolated and distended and there may be axonal degeneration. Neurons get trapped by the tumor cells and die. Around the tumor, reactive hypertrophic astrocytes appear. Macrophages may also invade the necrotic areas of the tumor. Small microscopic hemorrhages are common and symptomatic large bleeds can occur, most frequently with melanoma, choriocarcinoma, renal and thyroid carcinomas; however lung cancer is the most common primary leading to tumor hemor-

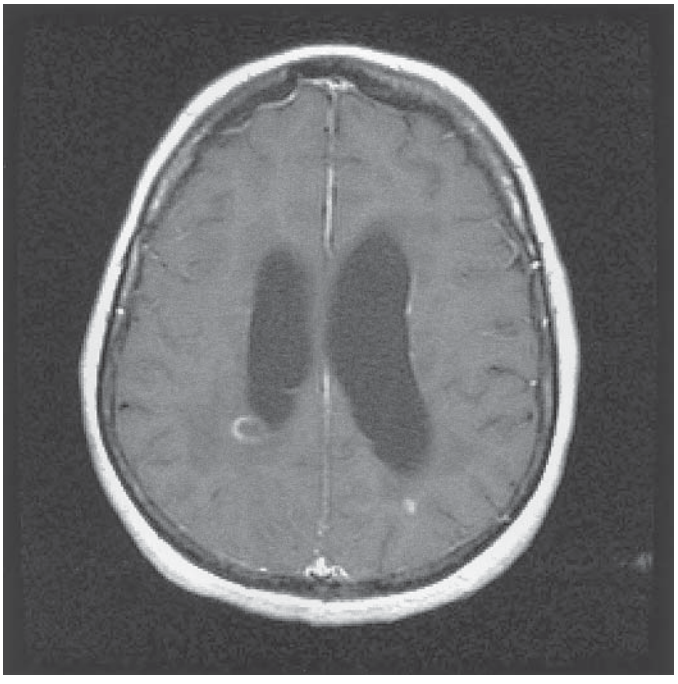

**Fig. 1.** T1 weighted, postgadolinium MRI scan shows two enhancing lesions. Note the incomplete ring enhancement of the right periventricular lesion. This patient had demyelination and not cancer.

rhage *(38,39)*. Tumor embolization to blood vessels can result in infarction of the brain.

## CLINICAL PRESENTATION

The interval between the diagnosis of the primary cancer and brain metastases varies for different cancers, being 4 mo for lung cancer and 3 yr for breast cancer (Table 1) *(15,40)*. Most patients with brain metastases have disseminated disease and about 70% will have pulmonary metastases at diagnosis of cerebral lesions *(9,41)*. Metastases from some tumors like colon and renal tend to be single while those from lung and melanoma are more often multiple (Table 1) *(9,10,15)*.

Symptoms usually start slowly and progress gradually. They are produced by tumor growth increasing the intracranial volume, compressing the surrounding brain tissue and causing increased intracranial pressure (ICP). Peritumoral edema and hydrocephalus can further increase intracranial pressure. The latter occurs more commonly with lesions in the posterior fossa. Metastases can also present acutely in the brain by causing a seizure, infarction, or hemorrhage.

Headache is the most common symptom of brain metastases in most series *(41–43)*. Headache is usually mild, and can be bifrontal or located on the side of the tumor. It usually resembles tension type headache and occasionally typical migraine *(44)*. In a retrospective study of 729 patients, common neurologic symptoms were headache, altered mental status, seizure, focal weakness, and gait disturbance *(15)*. In the same study about 10% were asymptomatic and 6% presented acutely with intratumoral hemorrhage. Others have reported similar results (Table 2). Patients can present with personality change, memory impairment, and cognitive decline. Although many do not complain, careful examination reveals cognitive deficits in as many as 75% of patients (45). Confusion and cognitive impairment may be the only symptom in patients with miliary brain metastases. Symptoms of high ICP like morning headaches, increased headache on bending and coughing, and visual obscurations can be present. Papilledema is found in less than 10% of patients at presentation *(46)*.

Symptoms and signs also depend on the site of the tumor. Frontal lesions can present with personality change and impaired executive function, and these changes are commonly attributed to depression. Dysphasia is seen with left-sided lesions. A parietal lesion may cause apraxia and the patient may neglect the opposite side. Temporal lobe lesions can cause hallucinations. Hemiparesis can occur if tumor involves the motor cortex or pathways and ataxia is seen with cerebellar lesions. Vomiting and dizziness is seen in patients with cerebellar lesions but is uncommon without associated cerebellar signs *(47)*.

## DIAGNOSIS AND INITIAL EVALUATION

Brain metastases should be suspected in all patients with cancer who present with neurological symptoms localized to the brain. Once suspected, the imaging study of choice is MRI scan, with and without contrast. MRI is clearly superior to CT scan in detecting metastatic lesions but CT is a reasonable alternative when MRI is contraindicated *(48,49)*. It is important to differentiate metastatic lesions from primary brain tumors and other CNS lesions such as demyelination and abscesses since up to 10% of intracranial lesions in cancer patients are not metastases (Fig. 1) *(50)*. MRI is again superior in this respect and in establishing the number of metastatic lesions *(49,51,52)*. The latter is important as treatment for brain metastases differs according to the number of lesions. Double or triple-dose contrast MRI studies may reveal additional metastatic lesions but also increase the false-positive results and their role is not yet established *(53)*. Other MRI techniques such as use of turbo-FLAIR and magnetization transfer need further evaluation *(54,55)*.

Once brain metastases have been identified in a patient with known cancer, workup should be done to define the extent of disease. If the primary tumor is unknown, a careful physical examination should be done including that of skin, testes, rectum, and breast. Stool should be tested for occult blood. Chest X-ray, bone scan, and a CT scan of chest, abdomen, and pelvis may detect a primary site or an accessible lesion for biopsy. Additional tests such as bone marrow examination, mammogram in women, or serum tumor markers may be helpful. When this battery of tests fails to identify a primary tumor then FDG PET scan is sometimes useful *(56)*. Biopsy or resection of the brain lesion should be considered early in evaluation and may clarify the nature of the lesion and if metastatic point to a primary source *(57)*.

## SYMPTOMATIC TREATMENT

**CORTICOSTEROIDS** Once the diagnosis is established, patients with brain metastases should be treated with corticosteroid, especially if radiation treatment is a consideration *(1)*. Corticosteroids improve symptoms by reducing capillary permeability and vasogenic edema *(58)*. They were initially used

**Table 3**
**Anticonvulsant Prophylaxis in Brain Tumor Patients**

| | | | % Patients with seizures | |
|---|---|---|---|---|
| *References* | *Number* | *AED* | *Drug group* | *Placebo group* |
| Cohen et al. *(63)* | 133 | Dilantin | 13 | 11 |
| Dent et al. *(64)* | 247 | Not recorded | 17 | 7 |
| Glantz et al. *(65)*[a] | 74 | Depakote | 35 | 24 |
| Weaver et al. *(66)*[a] | 100 | Dilantin | 13 | 10 |
| North et al. *(68)*[a] | 81 | Dilantin | 21 | 13 |

[a]Randomized trials.
AED, Anti-epileptic drug.

more than 40 yr ago *(59)* and have now become a standard treatment for all brain tumors.

Dexamethasone is the steroid of choice because of its low mineralocorticoid activity and possible lower risk of opportunistic infections *(58)*. Standard starting dose is 4 mg every 6 h. However, Vecht et al., in a randomized study, compared 4, 8, and 16 mg daily doses of dexamethasone in patients with single or multiple brain metastases *(60)*. All patients were able to take medication orally and did not display signs of impending herniation. They found no significant difference in neurological improvement among the three groups. Higher incidence of side effects, including steroid myopathy, were seen in the 8 and 16 mg groups. Consequently, a smaller daily dose of 4 or 8 mg may be used in patients who do not display symptoms or signs of increased ICP. In patients with high ICP, a bolus of 10 mg may be given at the onset of treatment and should be followed by a more conventional dexamethasone dose. Most patients will show improvement in their symptoms and focal signs within 72 h, many in the first 12 h *(1)*. In the absence of improvement the dose should be increased to achieve maximal neurologic function. In the case of impending herniation a 100 mg bolus followed by 96 mg/24 h, divided in four doses for 3 d should be used and then tapered over 10 d.

Once neurologic function is optimized, the steroid dose should be tapered to the minimum required to maintain maximum neurologic function. Patients should remain on steroids during radiation treatment, but many can start a taper while receiving radiotherapy. Although symptomatic improvement occurs in a few days, radiographic recovery of peritumoral edema lags behind and may not be apparent for a week *(46)*.

Glucocorticoids can have many adverse effects. These include psychiatric changes, proximal myopathy, insomnia, osteoporosis, weight gain, gastric irritation and perforation, cataracts, immuno-suppression, and hyperglycemia. Brain tumor patients who receive steroids are at increased risk of developing *Pneumocystis carinii* pneumonia (PCP) *(61,62)*. Prophylaxis for PCP should be considered if steroid treatment is necessary for longer than 6 wk.

Caution should be exercised in using steroids in brain lesions when there is no diagnosis of malignancy. Infection can mimic tumors and can get worse with steroid treatment. Demyelinating lesions can also resemble tumors and will improve. Primary CNS lymphoma can occur as a second primary in patients with systemic cancer and may respond dramatically due to the cytolytic effect of steroids on malignant lymphocytes. Resolution of the lesion may give a false negative result on biopsy and the opportunity for a definitive diagnosis is lost.

**SEIZURE TREATMENT AND PROPHYLAXIS** Seizures may be the presenting symptom of brain metastasis in 20% of patients *(63)*. Patients with seizures should be treated with anticonvulsants. Seizure is usually a clinical diagnosis based on history and eye witness account, if available. When the history of seizure is certain, the electroencephalogram (EEG) does not provide additional information and the patient requires anticonvulsant therapy. More importantly, the EEG rarely establishes the diagnosis of a seizure when the history is unclear or in doubt, and the decision to use anticonvulsants should not be based upon the EEG. When anticonvulsants are used, monotherapy should be the goal and the minimum dose required to control seizures should be used.

The incidence of seizures in metastases confined to the posterior fossa is very low *(63)* and prophylactic anticonvulsants are not indicated. Seizure prophylaxis in supratentorial metastatic disease is more controversial although all published data indicate a lack of efficacy for prophylactic anticonvulsants (Table 3). Retrospective studies have not shown significant difference in seizure outcome between treated and untreated patients *(63,64)*. Two prospective trials using prophylactic anticonvulsants have also shown no benefit in primary and metastatic brain tumors *(65,66)*. Therefore seizure prophylaxis in patients without a history of seizures is not indicated and this is the position taken by a recent practice parameter of the American Academy of Neurology *(67)*. Furthermore in these studies, age, KPS, tumor location, tumor histology, number of lesions, and history of brain surgery were not associated with increased risk of seizures *(63,65,66)*. Patients are often placed prophylactically on anticonvulsants following craniotomy. However, a number of studies and a meta-analysis have found no evidence that this practice reduces the incidence of epilepsy *(68–71)*.

Adverse reactions to anticonvulsant medications are frequent and may exceed the number of seizures *(71)*. There can be significant drug interactions including with dexamethasone. Glucocorticoids and many anticonvulsants can induce their metabolism, thus reducing each other's serum levels *(72,73)*. In addition, some chemotherapeutic agents can lower the plasma levels of anticonvulsants; conversely, enzyme-inducing anticonvulsants increase metabolism and clearance of chemotherapeutic agents, reducing their efficacy *(74–77)*. In cancer patients, there is an increased risk of allergic reactions including Stevens Johnson syndrome with phenytoin and carbamazepine, especially with concomitant cranial radiotherapy *(78,79)*.

Prophylactic anticonvulsants in brain metastases patients should not be used due to the significant risk of adverse reactions and lack of efficacy. Possible exceptions are patients gravely ill with suspected high ICP in whom a seizure may threaten herniation by increasing the intracranial pressure further.

**THROMBOEMBOLIC DISEASE** There is an increased incidence of thromboembolic disease in brain tumor and sys-

**Table 4**
**Randomized Studies Evaluating Surgical Resection of Single Brain Metastasis**

| | *Surgery/RT* | | | |
|---|---|---|---|---|
| *Reference* | *Number* | *Survival (mo)* | *FIS (mo)* | *1-yr (%) Local control* |
| Patchell et al. *(50)* | 25/23 | 10/4 | 9.5/2 | 80/48 |
| Vecht et al. *(86)* | 32/31 | 10/6 | 7.5/3.5 | Not recorded |
| Mintz et al. *(87)* | 41/43 | 5.6/6.3 | # | Not recorded |

FIS, functionally independent survival; RT, radiotherapy; #, no statistical difference.

temic cancer patients *(80,81)*. This increased incidence has also been reported in patients with brain metastases *(82)*. Many clinicians are wary of using anticoagulation in patients harboring intracranial tumors and choose inferior vena cava filtration devices to treat deep venous thrombosis. However Levin et al. have shown a 60% incidence of complications in brain-tumor patients treated with inferior vena cava filters *(83)*. Schiff and DeAngelis in a retrospective review of Memorial Sloan-Kettering patients found a 40% rate of pulmonary embolism in filtration device-treated patients *(82)*. Of the 42 patients who received anticoagulation, 3 (7%) had intracranial hemorrhage, 2 of whom had supra-therapeutic coagulation parameters. Other studies also suggest a low risk of complications with anticoagulant treatment if strictly monitored *(84)*.

These studies demonstrate that anticoagulation is safe in patients with brain metastases and more efficacious than inferior vena caval devices. The international normalized ratio should be kept strictly in therapeutic range.

## SPECIFIC TREATMENT

In untreated patients with brain metastases the median survival is 7.5 and 5 wk for single and multiple metastases, respectively *(85)*. The aim of treatment is to control symptoms and achieve long-term disease control. Different treatment options available include surgery, radiation including radiosurgery, chemotherapy, and hormonal treatment. There are many variables such as age, functional status, status of the systemic cancer, and number and location of the brain tumors, which guide the choice of treatment.

### SURGERY

**Single Brain Metastasis** There have been three randomized prospective trials of surgical treatment of single brain metastasis (Table 4). Patchell et al. compared surgical resection followed by whole brain radiotherapy (WBRT) to a total dose of 36 Gy with biopsy and WBRT *(50)*. There was a statistically significant difference in the median survival between the two groups, 40 wk for the surgical group and 15 wk for the WBRT only group. There was also a significant difference favoring surgery comparing local recurrence and functional independence. Younger age and absence of extracranial disease correlated with longer survival.

The study by Vecht et al. also showed survival benefit for the surgically resected group *(86)*. Diagnosis was established by CT scan and some patients with multiple metastases may have been included in the study. Improved survival was seen only in patients with stable systemic disease (12 vs 7 mo) and age > 60 was associated with poorer outcome.

Alternatively, a third prospective study by Mintz et al. did not show any benefit of surgery in patients with single cerebral metastasis *(87)*. Their results may have been influenced by the facts that the majority of their patients had uncontrolled extracranial disease and 25% of the patients in WBRT group required surgical intervention during the study period. A fourth prospective but nonrandomized trial of 80 patients also showed benefit for surgery with radiation treatment compared to radiation alone *(88)*. There was improved survival, reduced brain recurrence, and greater neurological improvement in the operated group.

Consequently, the data are strong to support resection of single brain metastasis in patients with a surgically accessible lesion, in good clinical condition and who have controlled or controllable systemic disease.

**Multiple Brain Metastases** No prospective trial has assessed the role of surgery in multiple brain metastases. Surgery is used in these patients when one of the lesions is large enough to endanger life or compromise function. Retrospective trials have produced conflicting data. Bindal et al. showed a significant survival benefit for patients with completely resected multiple metastatic tumors vs no benefit in partially resected multiple tumors *(89)*. They advocate surgical resection when there is stable extracranial disease and complete resection of multiple tumors is possible.

Hazuka et al. showed no benefit of surgery for multiple metastases *(90)*. However, in a recent study, Iwadate et al. showed that patients who have complete or near complete resection of multiple lesions do as well, or better than those who have a complete resection of a single lesion *(91)*. We do resect multiple metastases (<3) in patients with radioresistant primaries, such as renal carcinoma, since WBRT is ineffective in these patients. Furthermore, resection of a single large lesion in a patient with multiple metastases, especially if it is causing ventricular obstruction, minimizes symptoms, and facilitates administration of WBRT.

**Recurrent Brain Metastases** Three retrospective studies have shown benefit for surgery in patients with recurrent metastases *(92–94)*. Multivariate analysis revealed that survival was significantly improved for patients with stable extracranial disease, Karnofsky performance status (KPS) > 70, age < 40, primary tumor other than breast or melanoma and time to recurrence of brain metastasis > 4 mo.

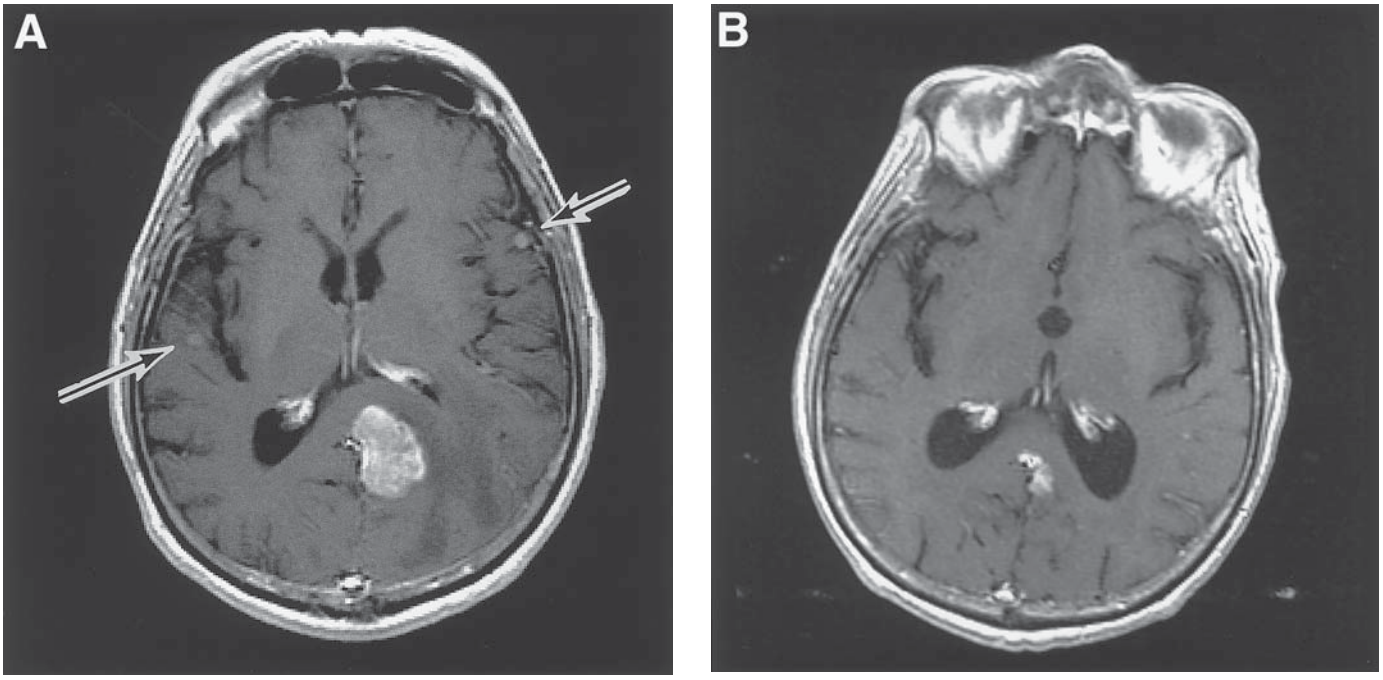


**Fig. 2. (A)** Pre-WBRT. T1 weighted, postgadolinium MRI scan of a patient with breast cancer. A large left occipital enhancing metastatic lesion and smaller tumors in perisylvian areas on either side (arrows). **(B)** Post-WBRT. T1 weighted, postgadolinium MRI scan in the same patient 6 wk after 30 Gy WBRT. The perisylvian tumors have disappeared and occipital lesion is reduced in size.

## RADIATION TREATMENT

**Whole Brain Radiotherapy (WBRT)** WBRT is palliative and only an occasional patient will have long-term control or cure *(95)*. Median survival after WBRT in patients with multiple metastases is 3–6 mo and only 10–15% are alive 1 yr after treatment *(1,41,96)*. WBRT improves neurological symptoms in 66–85% of the patients *(1,96,97)*, and those with smaller tumors respond better. Recursive partitioning analysis (RPA) is a statistical method of applying a decision tree to prognostic indicators. Application of RPA to 1200 patients with brain metastases showed that patients who have KPS > 70, controlled primary disease, age < 65 and metastases only to the brain (Group I, median survival 7.1 mo) have the best prognosis. Patients with KPS < 70 fared worst (Group III, median survival 2.3 mo), while all the others had an intermediate median survival (Group II, median survival 4.2 mo) *(98)*. Abgoola et al. applied RPA to retrospective analysis of 125 patients and found similar results, with median survivals of 14.8, 9.9, and 6.0 mo, respectively for Groups I-III *(99)*. Lack of steroid responsiveness and multiple metastases are also poor prognostic factors *(39)*.

Dose fractionation schedules have been evaluated by the Radiation Therapy Oncology Group (RTOG) in two randomized trials conducted in the 1970s *(97)*. The first trial randomized patients to 40 Gy in 4 wk, 40 Gy in 3 wk, 30 Gy in 3 wk, and 30 Gy in 2 wk. The second trial randomized patients to 40 Gy in 3 wk, 30 Gy in 2 wk, and 20 Gy in 1 wk. There was no statistically significant difference in the median and overall survival among the treatment regimens. Median survival was 18 and 15 wk in each trial. Patients receiving larger doses responded earlier but progression-free interval was similar in all treatment groups. However, large fractions were associated with a higher incidence of acute radiation toxicity.

A further trial by the RTOG in a prognostically favorable group, compared 30 Gy in 10 fractions and 50 Gy in 20 fractions, but no difference in outcome was observed *(100)*. The RTOG also conducted a randomized trial of accelerated hyperfractionation, 1.6 Gy twice daily to 54.4 Gy, compared to 30 Gy in 10 fractions *(101)*. Both groups had a median survival of 4.5 mo. Thus, balancing the palliative goal with effective treatment at minimal toxicity, most institutions use 30 Gy in 10 fractions as the standard dose for WBRT for brain metastases.

Radiosensitizers in brain metastases have been disappointing so far. Misonidazole, bromodeoxyuridine and pentoxifylline have been tried without showing any benefit *(102–104)*. Lucanthone, a topoisomerase II inhibitor has been shown to cross the BBB in animal models and in a small randomized trial (5 patients in the lucanthone group), it increased regression of brain metastases in humans receiving WBRT *(105)*. All the patients had extensive extracranial disease and no difference in survival was apparent. Texaphyrins are expanded porphyrins which localize selectively in the tumors *(106)*. Gadolinium texaphyrin increases the oxidative stress produced by radiation on tumor cells, and studies of this compound as a radiosensitizer are currently underway.

**WBRT After Surgical Resection** Several retrospective studies have shown benefit of WBRT after resection of a single brain metastasis *(107–109)*. Smalley et al. *(107)* compared WBRT after resection of a single brain metastasis to surgery alone. Relapse in the brain was 21% in the WBRT group vs 85% in the surgery alone group. Median survival was also better in the WBRT group, 21 mo vs 11.5 mo.

A prospective trial has also shown benefit for WBRT after surgery. Patchell et al. showed a reduction in neurological death and better cerebral control of the disease with postoperative WBRT; however, survival was not improved compared to sur-

**Table 5**
**Radiosurgery for Brain Metastases**

| *Study* | *Type of radiosurgery* | *Number of patients/lesions* | *Median dose (Gy)* | *Local control rate (%)* | *Median survival (mo)* | *Necrosis (%)* |
|---|---|---|---|---|---|---|
| Mehta et al. *(118)* | Linear acc | 40/58 | 18[a] | 82 | 6.5 | 0 |
| Flickinger et al. *(120)* | Gamma knife | 116/116 | 17.5[a] | 85 | 11 | 1 |
| Gerosa et al. *(121)* | Gamma knife | 225/343 | 21.1[a] | 88 | 9.3 | NA |
| Alexander et al. *(122)* | Linear acc | 248/421 | 15 | 85 | 9.4 | 3 |
| Cho et al. (123) | Linear acc | 73/136 | 17.5 | 80 | 7.8 | 8 |
| Shiau et al. *(131)* | Gamma knife | 100/219 | 18.5 | 77 | 12 | 4 |
| Auchter et al. (134) | Gamma knife and linear acc | 122/122 | 17 | 86 | 12 | 0 |

[a]Mean dose.
Gy, Gray; Linear acc, Linear accelerator.

gery alone group because patients died of their systemic disease *(110)*. Salvage WBRT in the surgery alone group was used at the discretion of the treating physician and it is not clear how many patients received it. This may have influenced the survival analysis as salvage WBRT is frequently used in relapse of brain metastases after surgical resection or stereotactic radiosurgery (RS). Current oncologic evidence favors adjuvant WBRT after resection of a single brain metastasis. However, WBRT is associated with neurotoxicity, especially in long-term survivors. More studies are required to ascertain whether there are clear subgroups in whom postoperative WBRT can be withheld.

**Reirradiation** Occasionally patients who have received WBRT are considered for reirradiation when there is progression of their CNS metastases. Most studies have shown improved symptom control in 40–70% and median survival of 2–4 mo after second radiation treatment *(111–113)*. On multivariate analysis, absence of extracranial disease was the only factor associated with improved outcome *(113)*. Some authors suggest reirradiating brain metastases in patients who had a > 6 mo response to first treatment, are not surgical candidates, and are in good general condition *(7)*.

**Toxicity of WBRT** Acutely, patients can have increased neurological symptoms and signs after onset of WBRT. This is due to increased peritumoral edema and is the reason all patients should receive dexamethasone for 24–48 h prior to starting WBRT *(1)*. Patients with multiple lesions and high ICP are particularly at risk. The risk is higher if large fractions, such as 600 cGy, are used *(114)*. Severe symptoms are rarely observed with current radiotherapy techniques, but mild symptoms, such as headache and nausea are common during radiation treatment but often must be elicited by the physician. If present, an increase in glucocorticoid dose usually ameliorates them.

Cognitive decline will develop in 10–30% of patients by 1 yr if they survive and CT and MRI will demonstrate atrophy with diffuse white matter hyperintensity on T2 weighted and FLAIR images *(115,116)* (Fig. 3). Ventriculo-peritoneal shunt may cause significant but incomplete improvement in some of these patients with leucoencephalopathy *(115)*.

**Radiosurgery** In 1951, Leksell first described stereotactic radiosurgery (RS) as a method to treat intracranial lesions *(117)*. In this technique multiple convergent beams of radiation are used to deliver a high dose to a discrete part of the brain. There is a rapid fall in the radiation dose around the target site, sparing the normal surrounding brain tissue. X-rays from linear accelerators, gamma rays from cobalt-60 source (the gamma knife), and less commonly charged protons produced by a cyclotron are the source of radiation. Most centers use 16–20 Gy as standard dose depending upon the size of the lesion with smaller lesions receiving higher dose.

RS has many potential benefits. It can treat lesions inaccessible to surgery, no hospitalization is required, multiple small lesions may be treated and radiation is focused only on tumor and not the normal brain. Potential disadvantages are the inability to treat microscopic lesions not visible on modern imaging and it may produce radiation necrosis necessitating surgical removal. The metastatic lesions must be < 3 cm in diameter and not adjacent to critical structures, such as optic nerve.

Several published retrospective studies have shown RS to be effective in the control of brain metastases (Table 5). Median survival after RS has been reported as 6–11.5 mo *(118–122)*. Patients with a single lesion, absent extracranial disease, and KPS of 70% or greater have longer survival, 17 mo in one series *(123)*. Other good prognostic markers are age < 60 yr, smaller tumor volume, female sex, and supratentorial location *(121)*. Histological type has no effect on the outcome and even radioresistant tumors such as melanoma and renal cell carcinoma respond favorably *(122,124,125)*.

Local control of tumor after RS at 1 yr is 80–90% in most series *(118–122,125)*. Local control is defined as shrinkage or no growth of the lesion (Fig. 4). Whether WBRT should be used with RS is controversial. There is a high incidence of tumor relapse within the brain after surgery or RS alone *(110,126,127)*, but overall survival is not different in RS and RS+WBRT treated patients if salvage RS is used for recurrent tumors *(126,127)*. However, Pirzkall et al. in a retrospective analysis, found significantly improved survival with RS+WBRT vs RS alone in patients with no extracranial disease (15.4 vs 8.3 mo) *(128)*. Comparable to the situation after resection of a single brain metastasis, more studies are required to define the role for WBRT in patients treated with RS.

Lesions in locations such as the brainstem are usually not treated with RS. However, Huang et al. recently reported 26

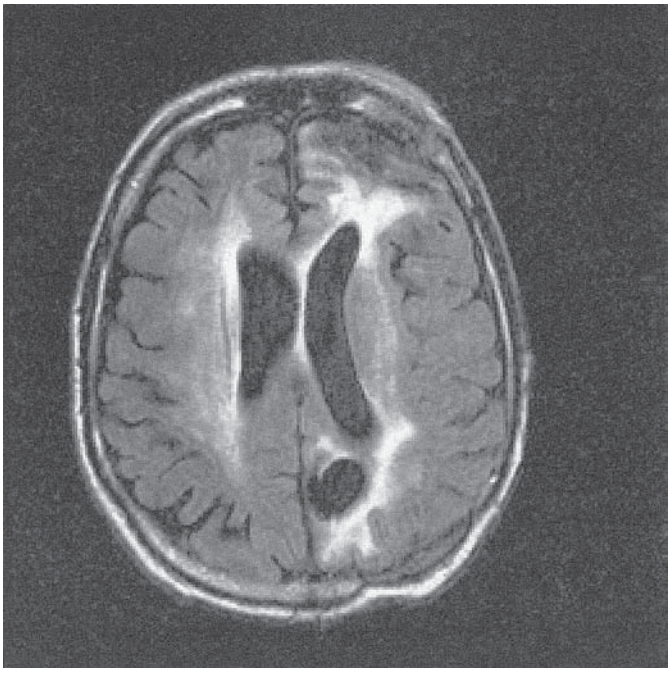

**Fig. 3.** Toxicity WBRT. MRI scan, FLAIR image, 3 yr after WBRT and resection of a single metastatic melanoma lesion (left occipital). Patient is bedridden, has no sphincter control, and is demented from severe leucoencephalopathy.

patients with brainstem metastases treated with RS *(129)*. Local control was achieved in 95%, and median survival after RS was 9 mo. 50% of patients had improved neurological function and none died from local disease recurrence or radionecrosis.

It may take up to 3 mo for tumors to shrink on MRI scan after RS and an initial increase in lesion size is seen in a minority of patients. Transient low-grade toxicity can occur and responds to steroid treatment *(128)*. The most feared complication is delayed radiation necrosis, which can occur as early as 4 mo after treatment. The incidence increases with larger tumor volume and higher radiation dose *(130)*. Patients may require long-term steroid treatment and surgery to treat and control radiation necrosis, which if untreated can cause death. The resultant steroid dependence and frequently, increased seizure incidence, may be associated with significant morbidity as well as mortality.

**Radiosurgery for Multiple Brain Metastases** Several retrospective studies have shown that freedom from progression, overall survival and freedom from neurological death are not significantly different between patients with single or multiple metastases when treated with RS *(123,126,131)*. Kondziolka et al. recently reported a prospective, randomized trial comparing WBRT with WBRT and RS in patients with 2–4 brain metastases < 25 mm in size and KPS > 70% *(132)*. The study was stopped at an interim analysis after accrual of 27 patients because the median time to local failure was 6 mo after WBRT vs 36 mo with RS and WBRT. Median survival was 7.5 and 11 mo in each group, respectively, and did not reach statistical significance. The number of patients and events were small in this study, particularly since there were only four patients with four metastases who had a median survival of 3 mo only, suggesting there may be a limit on the number of metastatic lesions which can be controlled effectively with RS. RTOG has recently released preliminary results of their trial, 95-08, at their website. They are reporting no difference in median survival of patients with 2–3 brain metastases when treated with WBRT alone or WBRT with RS. There was also no survival difference between patients with controlled and uncontrolled primary disease. A trial by ECOG (E-6397), looking at RS use in 1–3 brain metastases, is still underway.

**Radiosurgery vs Surgery** There are no randomized trials comparing RS to surgical resection in treatment of brain tumors. Only retrospective studies have been done and some authors believe RS to be as effective as surgery *(118,124,133)*.

Auchter et al. *(134)* selected 122 patients on the criteria used by Patchell et al. *(50)*. These were patients with single, surgically resectable lesions, KPS > 70, and no previous craniotomy or WBRT. Patients were treated with WBRT to a median dose of 37.5 Gy followed by RS median boost of 17 Gy. Local control was achieved in 86%, median survival after RS was 56 wk and 2-yr survival 30%. 25% of all deaths were from CNS disease. These results were comparable to those reported for surgical resection and WBRT in the literature and much better than results for WBRT alone.

Bindal et al. studied 31 consecutive patients treated with RS *(135)*. All patients had good KPS, limited systemic disease, and tumors < 3 cm. These patients were matched to 62 surgically treated patients at their center. 80.5% of RS treated patients were deemed resectable retrospectively. Sixty-six and 71% of patients in surgery and RS group received WBRT, respectively. Median survival in the surgery group was 16.4 mo compared to 7.5 mo in RS-treated patients ($p = .0009$). One explanation may be the poor local control (61%) achieved in their RS-treated group. Poor local control resulted in neurologic death in 50% of RS treated patients compared to 19% in the surgery group. Moreover 20% of RS-treated patients were deemed unresectable retrospectively and it is not clear whether it was extent of disease or tumor location rendering them unresectable. Although there was similar percentage of patients with multiple metastases (25%) in each group, separate analysis of data was not provided for patients with single and multiple lesions.

A more recent study by Muacevic et al. also compared patients treated with RS and surgery *(127)*. Patients with single metastasis, 3.5 cm or less in size and stable systemic disease were included in their retrospective analysis. Patients with previous surgery and WBRT were excluded. Fifty-two patients were identified who had surgery followed by WBRT. Fifty-six had RS alone with mean dose of 21 Gy. One-year tumor local control was 83% and 75% in RS and surgery group, respectively, and neurological death rates were 39 and 37%. There was a trend toward longer survival in surgically treated patients (median survival 68 vs 35 wk), but this was not statistically significant ($p = .19$). There was also a trend towards lower systemic death rate in the surgical group, suggesting that selection bias may have been an important feature of this retrospective study.

At this time data do not support superiority of either treatment over the other *(136)*. A randomized trial is currently underway at MD Anderson Cancer Center (NS97-199) and once reported may give an answer to this important question.

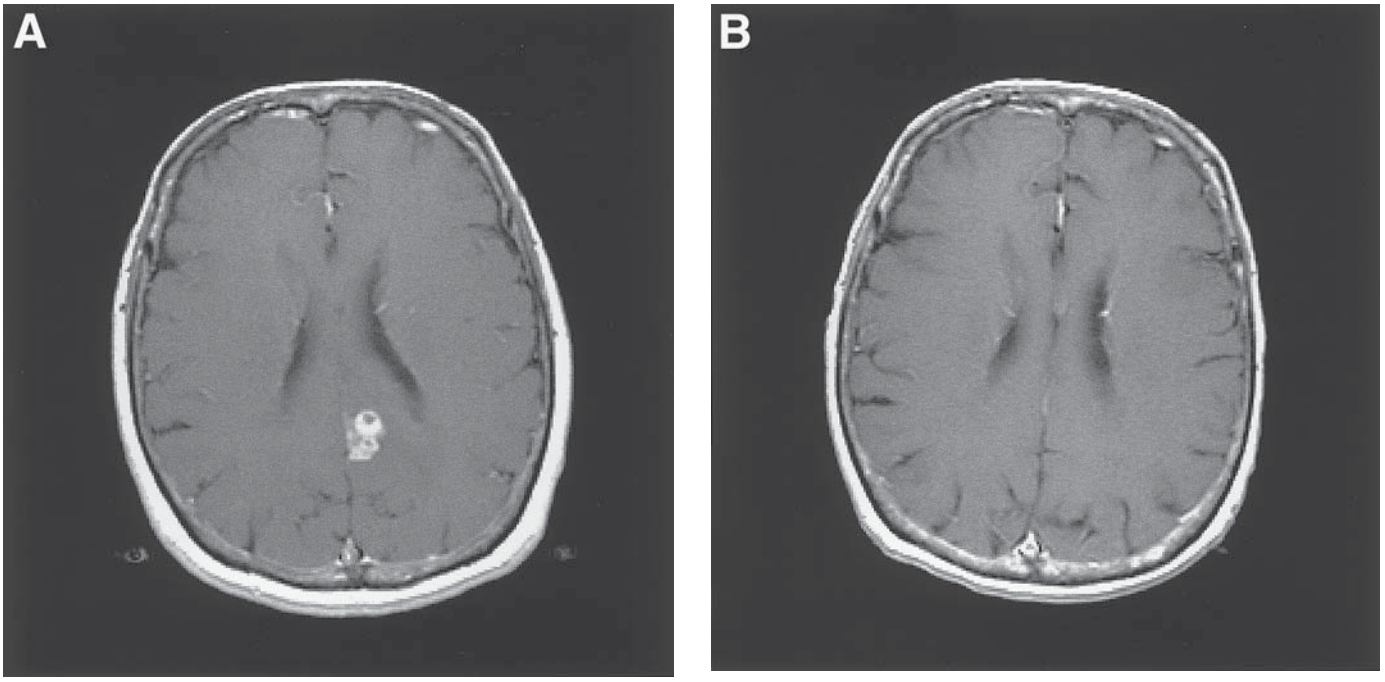


**Fig. 4. (A)** Preradiosurgery. T1 weighted, postgadolinium MRI scan of a patient with renal cell carcinoma. Single left occipital metastasis. **(B)** Postradiosurgery. T1 weighted, postgadolinium MRI scan of the same patient 12 wk after radiosurgery. There is no evidence of the tumor.

**Toxicity of Radiosurgery** There are few acute complications of RS. In one study 11% of 196 patients reported nausea, 6% had a seizure and 2% reported transient motor weakness *(137)*. Most of the patients with a seizure had had a prior seizure and had sub-therapeutic anticonvulsant levels. Other series have reported worsening of pre-existing deficits which responded to steroid treatment *(128,138,139)*. Patients on anticonvulsants should have their levels optimized prior to therapy. All patients should be on glucocorticoids prior to RS. Patients can develop increased peritumoral edema, causing increased neurological deficits usually 2 wk to 3 mo after treatment *(140)*. This usually responds to steroid treatment. The most serious complication is radionecrosis (Fig 5). It has been reported in 1–16.6% of patients from 2–22 mo post-RS *(120,122,138)*. This can present with increasing neurological deficits and a contrast-enhancing lesion on MRI, which mimics tumor recurrence. Higher radiation dose and larger tumor size increases the risk of necrosis *(130)*. Steroid treatment may control symptoms but many patients will require surgery.

**Cost-Effectiveness** A meta-analysis was conducted to calculate cost-effectiveness of RS vs surgery *(141)*. Three surgical and one RS study met eligibility criteria. The authors concluded that RS was more cost-effective in all parameters tested. Equalization will require either a 34.7% increase in RS procedure cost or 18.8% reduction in surgical procedure cost. 12.7% reduction in RS median survival or 16.8% increase in surgical resection survival will also equate the two groups. Mehta et al. also reported RS to be more cost-effective than surgical resection *(142)*. They calculated the average cost per week of survival is $310 for WBRT, $524 for surgery and WBRT, and $270 for RS and WBRT. However, these analyses are based on imperfect data regarding surgery and especially RS. Medical considerations still remain the driving force concerning the selection of therapy for patients.

**Salvage Radiosurgery** Previous Phase II and III studies have shown potential benefit for salvage RS in patients previously irradiated with WBRT or RS *(127,128,130,143)*. Chen et al. recently reported a retrospective analysis of 45 patients treated with salvage RS *(144)*. They, like others *(126–128)*, found that the addition of WBRT to upfront treatment with RS significantly reduced the need for salvage therapy. However, there was no survival benefit for RS+WBRT compared to RS alone and then treated with RS again at recurrence.

**Brachytherapy** Brachytherapy is intratumoral implantation of radioactive seeds to deliver focused radiation and limit the exposure to normal brain tissue as there is a rapid dose decay away from the source. There have been several small studies with Iodine-125 sources in patients with single metastasis upfront or at recurrence *(145–149)*. Median survival ranges from 10–18 mo in these studies. Radiation necrosis is the most serious side effect and occurs in approx 50% of patients *(146)*. Brachytherapy has largely been supplanted by RS and is rarely used any longer.

## CHEMOTHERAPY

Chemotherapy has not been a major therapeutic modality in the management of brain metastases. The BBB is often touted as the explanation for a poor response to chemotherapy by brain metastases; however there is evidence that the BBB is partially disrupted in brain metastases > 1 mm in size *(150)*. Intrinsic sensitivity of the tumor to the available agents is probably more important in obtaining a response to treatment than limited drug access to CNS. A number of retrospective and uncontrolled prospective studies have shown survival benefit for

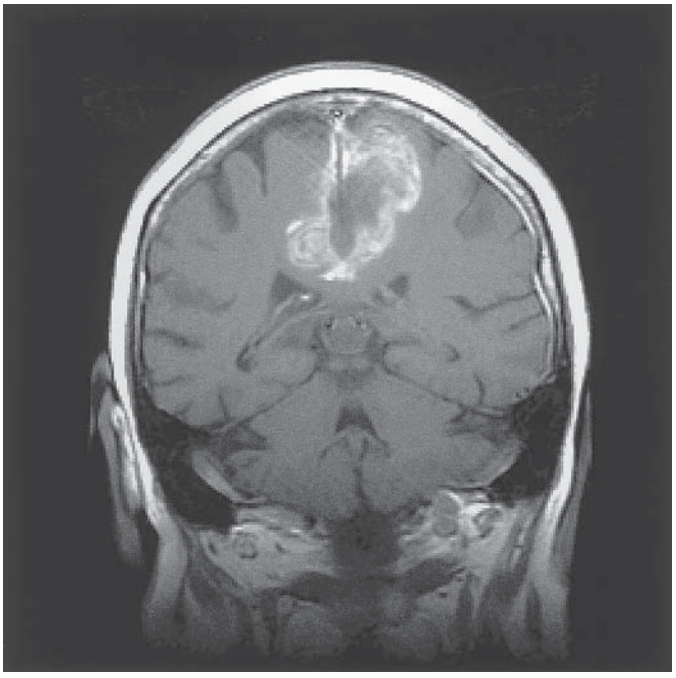

**Fig. 5.** Radionecrosis after radiosurgery. T1 weighted, post-gadolinium MRI scan. Patient with non-small cell carcinoma of the lung, had a single left parasagittal metastatic lesion treated with RS. She required multiple surgical resections of the necrotic tissue and prolonged steroid treatment.

some chemosensitive tumors such as breast, small cell lung cancer (SCLC), and choriocarcinoma.

**Lung Cancer** A meta-analysis of 12 studies of brain metastases in SCLC treated with etoposide alone or in combination with cis or carbo-platinum, showed a 76% response rate in patients whose brain metastases were diagnosed at the initial presentation of primary tumor *(151)*. Conversely, only 43% of patients previously treated with chemotherapy had a response to further chemotherapy. A median survival of 10 mo was reported by Crino et al. in their study using cisplatin with etoposide or teniposide *(152)*. In another study more than 100 patients with SCLC and brain metastases were randomized to receive either teniposide alone or WBRT+ teniposide *(153)*. The response rate in the brain was 57% for the combined treatment vs 22% for chemotherapy alone. However, there was no difference in the systemic response rate and overall median survival (3.5 vs 3.2 mo).

Nonsmall cell lung cancer (NSCLC) is less chemosensitive. A prospective study of 39 patients with progressive or recurrent brain metastases in NSCLC patients, previously treated with WBRT, used thioguanine, procarbazine, dibromodulcitol, CCNU, fluorouracil, and hydroxyurea (TPDC-FuHu). There was a 52% overall response rate (stable disease + partial and complete response) and median survival of 24 wk *(154)*. A recent prospective study treated 116 patients with NSCLC, breast cancer and melanoma with brain metastases using cisplatin and etoposide *(155)*. These patients were previously untreated with WBRT. Of 43 patients with NSCLC, 3 achieved complete response, 10 partial, and 15 had stable disease. Median survival was 32 wk. Similar results were reported by Quantin et al. using vinorelbine, ifosfamide, cisplatin, and 18 Gy WBRT (median survival 7.6 mo, objective brain response 56%) *(156)*. A recently conducted study at Memorial Sloan-Kettering Cancer Center using temozolomide in recurrent brain metastases had only 2 patients of 22 with NSCLC responding partially *(157)*.

**Breast Cancer** Rosner et al. have reported the largest series so far on the use of chemotherapy in breast cancer metastatic to the brain *(158)*. They treated 100 consecutive patients with different regimens, including cyclophosphamide, 5-fluorouracil and prednisone (CFP, 52 patients), CFP with methotrexate and vincristine (CFPMV, 35 patients) and methotrexate, vincristine and prednisone (MVP, 7 patients). 98% had extracranial metastases present and 42 patients had received prior chemotherapy. Overall 50% of the patients responded. 10% had CR, 40% PR, and 9% had stable disease. Response rate to CFP and CFPMV was 52 and 54%, respectively. Patients who received MVP had a 43% response rate. Prior chemotherapy did not affect the response rate as 50% of 14 patients with prior chemotherapy and 32% of those treated with prior chemotherapy and hormonal therapy responded. Thirty-five patients received second line drugs for progressive brain metastases. Thirteen responded and all had had a prior response to chemotherapy. Patients who did not respond to first-line drugs and those with initial stable disease had no response to second-line chemotherapy. Median remission in CR was more than 10 mo and CR+PR was 7 mo. Median survival of patients with CR and PR was 39 and 10 mo, respectively. Patients with SD had median survival of 6.5 mo. Those who progressed had a median survival of only 1.5 mo.

Several other studies using CMF, CAF, TPDC-FuHu, cisplatin, and etoposide have shown comparable results *(154,155,159,160)*. There are also single case and small clinical case series reporting remissions with hormonal treatment with tamoxifen *(161,162)* and megesterol acetate *(163)*. A recent study of temozolomide did not show any benefit in brain metastases from breast cancer *(157)*.

**Other Cancers** Positive responses have been reported with other chemosensitive tumors such as choriocarcinoma, ovarian cancer, and germ cell tumors *(150,164,165)*. There is some evidence that brain metastases from germ cell tumors respond to cisplatin when no prior chemotherapy has been used and do not when diagnosed after prior chemotherapy *(166,167)*.

## CONCLUSION

Brain metastases are the most common intracranial tumor in adults. Important advances have been made in the management of these tumors in recent years. Effective palliation can be achieved in most patients with multi-modality treatment using steroids, WBRT, surgery, or radiosurgery. Some patients will even have prolonged survival or rarely cure from their metastatic disease. Vigorous therapy can not only prolong life but will improve neurological function and prolong independence in many patients.

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# 8 Skull and Dural Metastases

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## INTRODUCTION

Skull and dural metastases are caused by hematogenous spread of malignant cells from distant tumors. Over several decades their frequency has appeared to rise, probably as a consequence of better neuroimaging tools and prolonged patient survival *(1)*. Skull or dural metastases can either be symptomatic or go unrecognized, and in some instances are found accidentally. Nevertheless, if untreated, progressive neurologic deficit and discomfort may follow. Early detection and appropriate treatment can improve or maintain quality of life, since antitumor therapy is effective in a majority of patients *(2)*. In this chapter we will discuss epidemiology, pathophysiology, clinical signs and symptoms, diagnosis and treatment of skull and dural metastases.

## SKULL METASTASES

Grossly the skull can be divided in the bony calvarium and the skull base. The flat calvarial bones (frontal, temporal, parietal, and occipital parts) fuse to form the convexity of the skull. The skull base comprises the ethmoid and sphenoid bones and the basal parts of the frontal, temporal, and occipital bones. These contain several foramina, allowing cranial nerves and vessels to enter or exit the skull. The presence of mass lesions in the skull base will therefore cause early symptoms due to cranial nerve dysfunction, whereas metastases located in the cranial vault can remain clinically silent for a longer period. Apart from an arterial route, tumor cells may travel along the vertebral venous plexus (named after Batson), bypassing the systemic circulation *(3)*. Blood shunting via this venous system is made possible by intrathoracic and intraabdominal pressure increases, causing a rostral pressure gradient. In this way the relatively high incidence of gastrointestinal and urogenital metastasis in skull bones (and dura) can be understood.

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The incidence of skull metastasis is likely to be underestimated in studies based on hospital records and death certificates, since many such metastases go clinically unrecognized. Additionally, the bony skull is not routinely sectioned at autopsy. Generally the prevalence of skull metastasis is believed to be higher than parenchymal brain metastasis, ranging between 15% and 25% of all cancer patients *(1)*. Probably half of these are asymptomatic as is illustrated by the documentation of clinically silent metastasis in the skull vault in 11% of lung carcinoma patients being staged prior to surgery *(4)*.

The most frequently detected metastatic tumors to the skull base and calvarium are breast, lung, and prostate, followed by renal, thyroid and melanoma *(5)*. Renal cell and thyroid carcinoma may produce solitary calvarial metastasis *(6)*.

As previously mentioned, metastases in the calvarium may cause no symptoms at all. Sometimes local pain over the affected part of the skull is the only complaint. In other patients a palpable mass or deviating skull contour is found. Inward extension may occur, leading to brain compression or secondary edema, focal neurologic deficits, or epileptic seizures. Calvarial metastasis may invade or compress cerebral venous sinuses, inducing venous congestion, raised intracranial pressure, papilledema, and headache. In skull base metastases, symptoms and signs will usually have more localizing value. Characteristic combinations of headaches and cranial nerve deficits point towards a specific site in the skull base that explains the clinical picture (Figs. 1 and 2). Greenberg et al. proposed a useful classification of five common clinical syndromes caused by metastasis to the base of the skull (Table 1) *(7)*. However, other malignant disorders (e.g., leptomeningeal carcinomatosis, metastasis in brainstem or cerebellum) or benign conditions (e.g., idiopathic neuritis, granulomatous, or infectious disease) cannot always be distinguished clinically. Since these conditions call for a different therapy, it is important to confirm a suspicion of skull base metastasis with radiologic or sometimes histologic proof. In patients with known cancer who develop symptoms or signs indicating skull-base

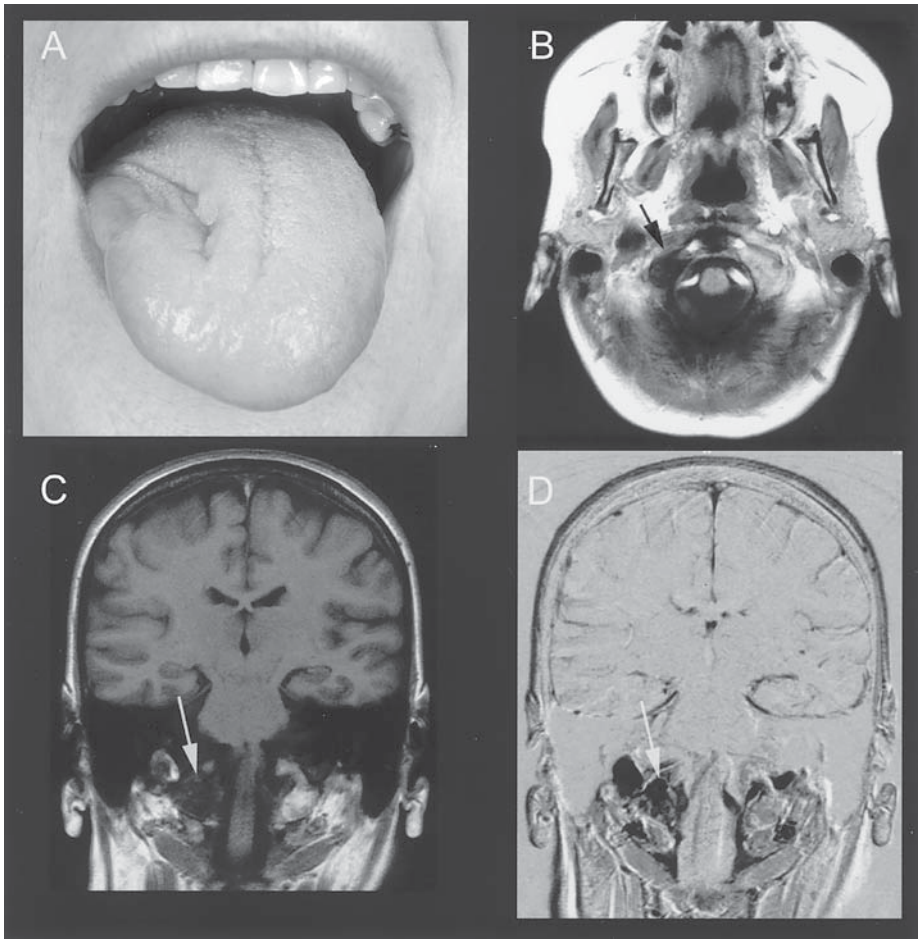


**Fig. 1.** A woman with known metastatic breast cancer presented with slurred speech and right-sided occipital headache. On examination the tongue deviated to the right and was atrophied on that side **(A)**. T1 weighted MRI images demonstrate a metastatic lesion at the right occipital condyle (arrow) compressing the XIIth cranial nerve in the hypoglossal canal **(B,C)**. MRI subraction images demonstrate enhancement of the bony lesion after gadolinium administration **(D)**.

disease, a thorough search for tumor is warranted, including radiologic and CSF studies.

Radiologic abnormalities suggestive of metastasis in the calvarium can be found relatively easily. A plain skull radiograph may show multiple irregular lucencies of similar size, and evidence of bony metastasis elsewhere can be found in 90% of cases *(5)*. CT and MRI will usually show these lesions to involve all three tables of the skull bone, and provide information as to intracranial extension and relation to venous sinuses. Gadolinium-enhanced MRI is superior to CT in visualizing small intradiploic metastases in the calvarium as well as flow void signal in the sagittal or lateral venous sinus *(8,9)*. The differential diagnosis of multiple skull defects includes normal structures such as venous lakes, Pacchionian granulations, and parietal foramina. Pathological conditions include Langerhans cell histiocytosis, hyperparathyroidism, osteomyelitis, and radiation necrosis *(5)*. In case of a single skull vault defect one should consider not only metastasis, but also meningioma, hemangioma, epidermoid cysts, leptomeningeal cysts (in children), Langerhans cell histiocytosis, Paget's disease, postsurgical defect, and osteomyelitis *(10)*. Primary intraosseus meningioma can be particularly hard to differentiate from metastatic disease *(11)*. In patients not known to have cancer, comparison with an old skull film showing an identical congenital lesion may prove its benign nature. In other cases, histological verification of a calvarial lesion must be obtained to exclude malignancy.

The radiographic detection of metastases in the skull base is generally more difficult than in the calvarium. Plain skull radiographs are of little use in this area. CT is very helpful in showing bone destruction or sclerosis, the latter occurring especially in metastases from prostate adenocarcinoma. Optimally, thin (3-mm) sections through the skull base are made, allowing reconstruction in various planes, before and after contrast administration, completed with images viewed in bone window setting. MRI of the skull base is best done in proton density, T2-weighted sequence and in T1-weighted sequence before and after intravenous gadolinium administration. Metastases typically show diminished signal intensity on T1-weighted MR images with variable enhancement after gadolinium. T2-weighted images are typically hyperintense relative to skeletal muscle *(12)*. MRI is superior to CT in disclosing comorbidity such as posterior fossa or leptomeningeal metastasis, and is therefore helpful in narrowing differential diagnostic

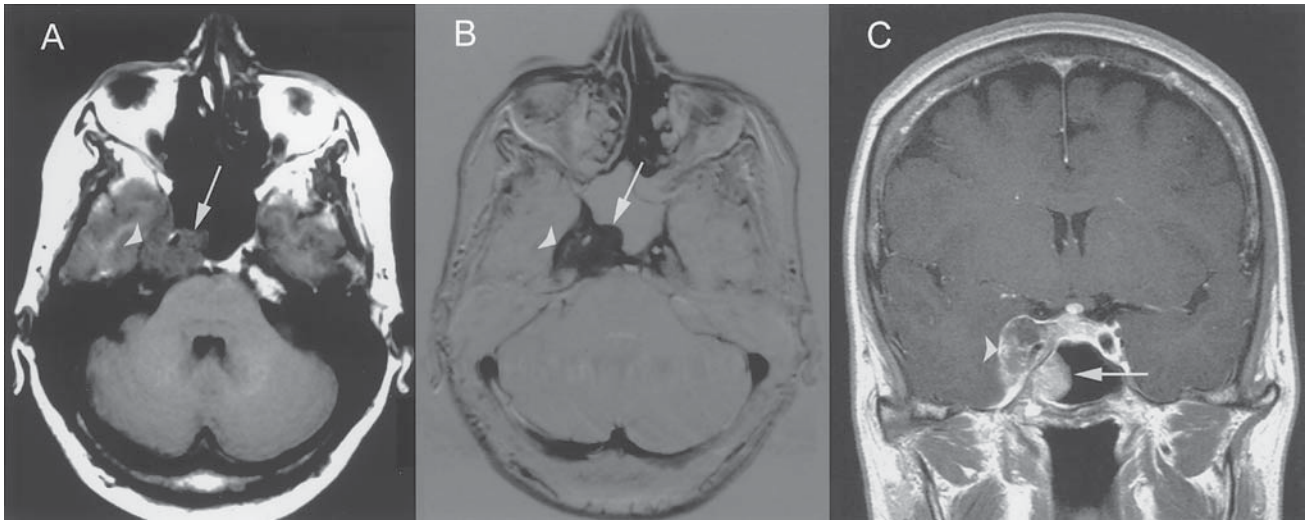


**Fig. 2.** A woman with known breast cancer presented with horizontal diplopia followed by right-sided ptosis. There was complete ptosis and ophthalmoplegia with a dilated nonreactive pupil (7 mm) on the right. Sensation was normal in particular in the distribution of the first branch of the Vth cranial nerve. T1 weighted MRI images before **(A)** and after gadolinium (**B**,**C**; B: subtraction image) demonstrate a lesion in the right sphenoid bone extending into the sphenoidal sinus (arrow), middle fossa, and cavernous sinus (arrow head).

possibilities in patients suspected of having skull-base lesions *(13,14)*. However, even CT and MRI are reported false-negative in up to a quarter of patients *(7,15)*. In these cases a role for $^{99m}$Tc-SPECT of the skull base has been established *(16)*. SPECT is additive to planar bone scintigraphy because the latter lacks sensitivity and anatomical detail to assess the skull base, although it can show relevant bone metastases elsewhere in the body (e.g., vertebral column) that may require therapy. CSF studies are often needed to rule out leptomeningeal metastases, which usually present with similar signs and symptoms. The decision to perform a lumbar puncture should be taken considering patient factors and the likelihood of finding tumor cells (e.g., less likely in prostate and more likely in breast carcinoma or lymphoma).

Treatment of cranial vault metastasis depends largely on the presence of symptoms and radiologic findings *(17)*. Asymptomatic metastases require no specific therapy. As with bone metastases in other locations, analgesics and bisphosphonates may bring pain relief. Whether symptomatic patients with skull metastases should receive corticosteroids remains unresolved, but experience shows that steroids rapidly ameliorate symptoms in some patients *(1)*. Symptomatic calvarial metastases with or without venous sinus compression are treated with fractionated radiotherapy, typically with doses of approx 30 Gy in 10 fractions *(18)*. Higher dose schedules (36 Gy or higher) are recommended are recommended for skull base metastases *(2)*. Chemotherapy can relieve symptoms in chemosensitive tumors, and has the advantage of treating other systemic metastases at the same time. Starting or altering hormonal therapy may be indicated breast and prostate cancers. In skull base metastasis with cranial nerve deficit, medical treatment alone is usually not sufficient and carries the risk of leaving the patient with irreversible dysfunction. Therefore, in these patients treatment regimens as a rule include radiation therapy. Radioactive isotopes are an attractive option if there are multiple sites of bone pain, either because they are tumor-specific (radioactive iodine for thyroid carcinoma) or bone-seeking (radioactive phosphorus and strontium) *(19)*. Stereotactic radiosurgery using linear accelerator or gamma knife offers an opportunity to deliver a high local dose at the tumor site, but experience and availability are still limited. A recent study documented tumor control and symptom relief in 12 of 18 patients with skull base metastasis or invasion using gamma knife radiosurgery *(20)*. Occasionally surgical removal is required. Advances in surgical and anesthetic technique now permit biopsy and resection of metastases previously termed inoperable. For calvarial metastases, indications for surgery include: diagnostic uncertainty, expanding bone lesions resistant to irradiation and chemotherapy, and solitary calvarial metastasis that is the only residual of systemic malignancy *(17)*. Sometimes reconstructive surgery is necessary for cosmetic reasons. Skull base surgery for metastasis is only rarely indicated and requires great navigating expertise *(21)*. Feared complications include CSF leak, meningitis and wound necrosis.

The prognosis of calvarial metastases depends on systemic tumor control as well as local factors, including invasion of venous sinus or dura, leptomeninges, and brain parenchyma. A local response rate of 60% is reported after radiotherapy *(18)*. In skull base metastases the outcome depends strongly on the interval between onset of symptoms and start of treatment: 87% of patients improved if radiotherapy was initiated within 1 mo, while only 25% responded if symptoms already existed for more than 3 mo *(2)*.

Extracranial tumors located in the proximity of the skull base may travel centrally along cranial-nerve branches and even enter the skull through foramina. Squamous cell carcinoma of the nasopharynx is well-known for this growth pattern, and patients may present with atypical facial pain or dysesthesia due to trigeminal involvement. In a well-documented series, 59 of 110 patients with nasopharyngeal carcinoma had radiologic

**Table 1**
**Classification of Clinical Syndromes Caused by Skull Base Metastasis**

| *Site of skull-base metastasis* | *Symptoms and signs* |
|---|---|
| Orbital | Local pain, proptosis, sensory loss $V_1$, diplopia, decreased vision (late) |
| Parasellar/cavernous sinus | Unilateral frontal headache, oculomotor palsies (III, IV, VI), sensory loss $V_1$ |
| Middle cranial fossa | Facial numbness or pain ($V_{2,3}$), sometimes abducens or facial nerve palsy (VI, VII) |
| Jugular foramen | Unilateral postauricular pain, hoarseness, dysphagia (IX, X), sternocleidomastoid or trapezius weakness (XI) |
| Occipital condyle | Unilateral occipital pain, stiff neck, unilateral tongue weakness (XII) |

Adapted with permission from ref. *7*.

evidence of perineural trigeminal spread, although only 26 patients had sensory symptoms *(22)*. Symptomatic trigeminal invasion was more common in patients in whom perineural tumor growth extended through the foramen ovale to involve the intracranial portion of the nerve. Adenoid cystic carcinoma, generally arising from a minor salivary gland, also tends to grow along nerve sheaths. This was noted to occur in 136 of 198 patients, 55 of these involving major nerves *(23)*. Treatment consists of surgery and radiation therapy, but perineural growth and foraminal invasion serve as unfavorable prognostic factors. Other tumors associated with perineural growth patterns include esthesioneuroblastoma, lymphoma, nerve sheath tumors and skin cancers *(24)*.

## DURAL METASTASIS

Metastases reach the dura by inward invasion from the skull or by direct hematogenous spread. Dural disease may be focal or diffuse, and either epidural or subdural space or both can be involved (Fig. 3). In autopsy studies of cancer patients, the incidence of dural metastasis is up to 20%, but it is clearly less often diagnosed during life *(1)*. Associated primary tumors are carcinomas of the lung, prostate and breast, and melanoma. Other reported primary tumors include gastric, colon, small cell lung and renal cell carcinoma, pleural mesothelioma, carcinoid tumors, and lymphoma *(17,25)*.

Dural metastases cause symptoms in several ways: either by compressing or invading the underlying brain, by obstructing blood flow in the lateral or sagittal venous sinus, or by producing subdural fluid collections and hematomas. If local expansion is the cause, symptoms resemble those of parenchymal brain metastasis, although seizures at onset may be more common due to irritation of local cerebral cortex *(1)*. Venous sinus obstruction becomes symptomatic when rising intracranial pressure ensues (producing headache, nausea, vomiting, lethargy, and papilledema) or when hemorrhagic brain infarction results in focal neurologic symptoms and signs. Dural or calvarial metastases are the leading causes of sinus thrombosis in patients with solid tumors, while in hematologic malignancies coagulation disorders prevail *(26)*. The subdural membranes contain a rich vascular bed, and subdural effusions are probably caused by exudation of plasma through pathologic neovascular vessel walls or following necrosis within a dural metastasis *(17)*. Subdural hemorrhage secondary to dural metastasis may be a consequence of obstruction of dural vessels by tumor cells, complicated by coagulopathy *(27,28)*. In the setting of metastatic cancers, coagulopathy may be the result of bone marrow replacement, diffuse intravascular coagulopathy, or chemotherapy-induced thrombocytopenia. These subdural fluid collections often cannot be distinguished radiologically from subdural hematoma or hygroma in a healthy population, and they share the same clinical presentation, with mental status changes out of proportion to focal neurologic signs *(1)*. The collection of material for cytological examination during surgical evacuation of the subdural fluid is essential for diagnosis.

MRI is the preferred imaging modality for dural metastasis. Axial CT, even contrast-enhanced, may miss smaller dural nodules and is less sensitive due to adjacent bone artifacts and partial volume effects *(29)*. Furthermore, MRI is superior in showing leptomeningeal or dural enhancement and venous flow disturbances. In practice, differentiating small dural-based tumors such as meningiomas from metastases may be difficult. The presence of calcifications in a minority of meningiomas makes this easier. In unresolved cases histologic verification will provide the answer. Linear enhancement ("dural tail" sign) of the dura around a meningioma on T1 weighted MRI images after gadolinium has been described. Although this dural tail sign is often seen with meningioma it is not pathognomonic and can also be found in craniofacial tumors with possible direct intracranial extension and in gliomas or brain metastases in close proximity to the dura *(30)*. Dural enhancement per se is no proof of malignancy and has also been reported in the presence of CSF leak or shunting, dural sinus thrombosis, and pachymeningitis. Enhancement has been noted to occur in dura underlying a skull metastasis, while biopsy only showed granulation tissue in the dura surface facing the inner skull table *(31)*. In one study, linear dural enhancement was noted in only 16% of superficial malignant intracranial tumors, compared to 60% of meningioma cases *(32)*. The authors concluded that enhancement is more likely to represent nonspecific reactive changes than tumoral invasion.

Radiation therapy is the main treatment for dural metastasis. Either whole brain irradiation or adequate focal radiation therapy directed at the lesion can be chosen. Clinical improvement is seen in 60–75% of patients, the best responders being

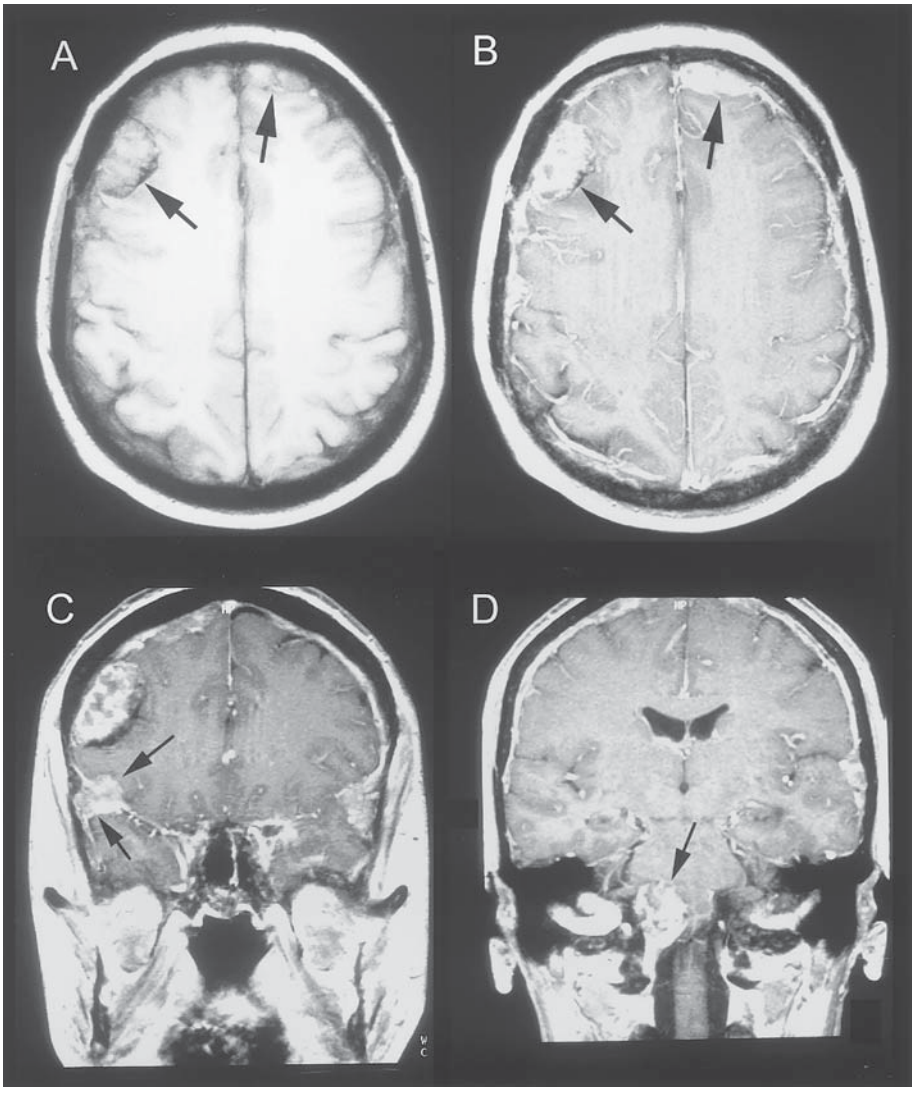


**Fig. 3.** T1 weighted brain MRI performed before **(A)** and after adminstration of gadolinium **(B–D)** on a patient with known metastatic adenocarcinoma of the prostate who presented with diplopia, dysarthria, vertigo, difficulty swallowing, and unsteady gait. Examination revealed bulbar dysarthria, bilateral partial abducens paresis, and right-sided dysfunction of cranial nerves V, VII, IX, XI, and XII with hypalgesia in the distribution of the 2nd and 3rd branch of the trigeminal nerve, diminished nasolabial fold, retraction of the uvula, diminshed gag reflex, and protrusion of the tongue to the right. Multiple dural enhancing lesions (arrows) are observed at the convexity (A,B), along the tentorium (C), and compressing the brainstem (D). The latter lesion explained most of the symptoms in the patients. With steroids and radiotherapy, the symptoms disappeared.

those with small dural lesions, the worst those with concurrent leptomeningeal disease *(33)*. Even occluded venous sinuses reopen in a majority of cases after radiation therapy. Some patients with chemosensitive tumors (e.g., lymphoma, small cell lung carcinoma, breast carcinoma, germ cell tumors) may be candidates for chemotherapy as a first line of treatment. These patients should remain under close neurological observation, because response rate cannot be predicted with certainty, and treatment failure must lead to a timely switch to radiation therapy. Patients with a single large dural metastasis should be considered for extirpative surgery prior to radiation *(1)*.

After 30 Gy focal photon beam radiation prognosis for patients with dural metastasis is somewhat better than for parenchymal metastases. Median survival for dural metastases is 24 wk vs 18 wk for brain metastases *(34,35)*. The most important variable for prognosis of dural metastasis is control of systemic tumor activity.

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# 9 Spinal Metastases

DAVID SCHIFF, MD

## INTRODUCTION

Spinal cord dysfunction is a devastating complication of systemic cancer. This chapter focuses on the two most common ways in which cancer directly affects the spinal cord: epidural spinal cord compression and intramedullary spinal cord metastasis. Less common causes of spinal cord disease are covered in detail in other chapters, including radiation myelopathy in Chapter 14, paraneoplastic disorders in Chapter 13, and leptomeningeal metastases in Chapter 10.

## EPIDURAL SPINAL CORD COMPRESSION

Neoplastic epidural spinal cord compression (ESCC) is a common complication of cancer that causes pain and sometimes irreversible loss of neurologic function. The degree of thecal sac compression required for the designation of ESCC has been variably defined; in this chapter any radiologic evidence of indentation of the thecal sac is considered evidence for ESCC *(1,2)*. In adults, the tip of the spinal cord usually lies at the L1 vertebral level; below this level, the lumbosacral nerve roots form the cauda equina. Since the pathophysiology of compression of the thecal sac at the level of the cauda equina does not differ significantly from that of more rostral compression, compression of the cauda equina is still generally referred to by the slightly inaccurate name of ESCC.

## EPIDEMIOLOGY

Many cancer patients may have asymptomatic or unrecognized ESCC or develop ESCC after the decision has been made to forgo extensive diagnostic testing or therapy. For these reasons, the incidence of this complication is not precisely known and can only be estimated. An autopsy study from the 1950s suggested that 5% of cancer patients died with ESCC *(3)*. Similar findings were noted in a Danish study based on referrals to a regional treatment center: between 1979 and 1985 the incidence of ESCC in cancer patients rose from 4.4 to 6% *(4)*. The authors argued that this was probably an underestimate of the true incidence. Based on these reports, there are likely at least 25,000–30,000 cases yearly in the United States.

Metastatic tumor from any primary site can produce ESCC, with tumors displaying a tendency to metastasize to the spinal column responsible for the bulk of cases *(4–6)*. Prostate cancer, breast cancer, and lung cancer each account for about 15–20% of cases, while renal cell carcinoma, non-Hodgkin's lymphoma, and multiple myeloma each account for 5–10% of cases. Tumors of unknown primary, colorectal carcinoma, sarcoma, and other tumors are responsible for the remaining cases. The distribution of epidural metastases is different in children. Sarcomas (especially Ewing's sarcoma) and neuroblastomas are the main causes, followed by germ-cell neoplasms and Hodgkin's disease *(7)*.

Vertebral metastases without epidural extension are much more common than ESCC. At autopsy, vertebral metastases have been reported in 90% of patients with prostate cancer, 74% with breast cancer, 45% with lung cancer, 29% with lymphoma or renal cell carcinoma, and 25% with gastrointestinal cancers *(8)*.

## ESCC AS THE INITIAL MANIFESTATION OF MALIGNANCY

Approximately 20% of cases of ESCC occur in patients not previously recognized to have cancer *(6)*. The distribution of primary tumors in this presentation differs from that seen in patients with ESCC and known cancer. In a series of 337 patients with spinal epidural metastasis, lung cancer, cancer of unknown primary site, multiple myeloma, and non-Hodgkin's lymphoma were responsible for 78% of all cases of ESCC as the initial presentation of cancer, compared to 26% of those with ESCC and known cancer *(6)*. Breast and prostate cancer, causative in 51% of ESCC arising in patients with known cancer, accounted for only 12% in patients not known to have cancer (Table 1). Among patients in this study who presented with ESCC, the diagnosis was usually established by percutaneous needle

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**Table 1**
**Distribution of Primary Tumor Types Producing Spinal Epidural Metastasis**

| | *SEM-IMM* | | *SEM-PEM* | | |
|---|---|---|---|---|---|
| *Cancer type* | *No.* | *%* | *No.* | *%* | *Total no.* |
| Solid neoplasmd | | | | | |
| Lung | 20 | 34.5 | 38 | 65.5 | 58 |
| Carcinoma of unknown primary site | 9 | 60 | 6 | 40 | 15 |
| Prostate | 7 | 8.6 | 74 | 91.4 | 81 |
| Renal cell | 4 | 26.7 | 11 | 73.3 | 15 |
| Hepatocellular | 1 | 33.3 | 2 | 66.7 | 3 |
| Sarcoma | 1 | 6.7 | 14 | 93.3 | 15 |
| Breast | 1 | 1.6 | 63 | 98.4 | 64 |
| Colorectal | 1 | 7.7 | 12 | 92.3 | 13 |
| Others | 0 | | 25 | 100 | 25 |
| Hematologic neoplasms | | | | | |
| Multiple myeloma | 12 | 52.2 | 11 | 47.8 | 23 |
| Non-Hodgkin's lymphoma | 11 | 44 | 14 | 56 | 25 |
| Total | 67 | 19.9 | 270 | 80.1 | 337 |

Abbreviations: SEM, spinal epidural metastasis; IMM, initial manifestation of malignancy; PEM, previously established malignancy.
Adapted with permission from ref. *6*.

biopsy of the vertebral lesion. Only a minority of these patients had symptoms or physical findings suggestive of the site of the primary tumor.

## LOCALIZATION WITHIN THE SPINE

ESCC has a proclivity for certain regions of the spine. Approximately 60% of cases occur in the thoracic spine, 30% in the lumbosacral spine, and 10% in the cervical spine *(8)*. These percentages are in rough proportion to the combined volumes of the vertebral bodies in each region. Some studies have suggested that certain types of tumors have a tendency to produce ESCC in specific spinal regions, such as lung cancer in the thoracic spine, and renal, prostate, and gastrointestinal cancers in the lower thoracic and lumbar spine *(8,9)*. However, others have been unable to confirm this observation *(2)* (Table 2).

## PATHOPHYSIOLOGY

The spinal cord is enclosed by a protective ring of bones comprised of the vertebral body anteriorly and the lamina, pedicles and spinous process posteriorly. The vertebral bodies, separated by intervertebral discs, increase in height and volume in a rostral caudal direction. Within this bony ring is the thecal sac, the outermost layer of which is comprised of dura mater. The dura is continuous with cranial dura and fuses with periosteum of the sacrum at S2. Between the periosteum of the vertebral bones and the dura lies the epidural space, which normally contains connective tissue, fat, and the venous plexus. The normal lordosis of the cervical and lumbar spine helps to protect these regions against retropulsion of bone fragments into the spinal canal in the event of fracture. In contrast, the natural kyphosis of the thoracic spine, in concert with the narrow anteroposterior dimension of the spinal canal at this level, predisposes this region to development of spinal cord compression.

At each spinal level, nerve roots exit lateral to the spinal cord and posterior to the vertebral body (Fig. 1). Epidural spinal cord compression occurs when tumor invades the epidural space and compresses the thecal sac. The degree of thecal sac compression can range from a minor, asymptomatic indentation on the normal thecal sac contour to complete encirclement and strangulation of the spinal cord with associated paraplegia.

Approximately 85–90% of cases of ESCC are due to metastatic tumor in the vertebral bones. The mechanism of bony metastsis is incompletely understood. One likely mechanism, particularly relevant to explaining patterns of metastasis in breast and prostate carcinoma, is Batson's venous plexus. Batson's venous plexus refers to a valveless venous system draining the vertebrae and connecting to veins draining pelvic organs, abdominal and thoracic organs, breasts, and the skull. The valsalva maneuver shunts blood from visceral organs into the low-pressure vertebral system, promoting vertebral metastases. Arterial seeding of vertebrae may also play an important role. Injection of tumor cells into the left ventricle of nude or syngeneic mice resulted in localization of tumor to hematopoietic bone marrow in vertebral bodies. These tumor cells proved capable of forming tumor nodules that grew towards and into the spinal canal, producing ESCC *(10)*. Another mechanism of ESCC, acounting for perhaps 10% of cases, is direct spread of the primary tumor or a metastatic focus (such as a lymph node in the paraspinal space) through the neural foramen into the epidural space. Such a mechanism frequently pertains to lymphoma as well as to superior sulcus pulmonary tumors. Rarely, tumor appears to emanate from the epidural space without a bony or paraspinal component. Finally, malignant tumors such as sarcomas can originate in the spinal column, producing ESCC as a direct and early consequence of the primary tumor.

**Table 2**
**Distribution of Main Site of ESCC by Primary Tumor Type**

| | *Cervical (n = 33, 10%)* | | *Thoracic (n = 206, 61%)* | | *Lumbosacral (n = 98, 29%)* | | *Total* | |
|---|---|---|---|---|---|---|---|---|
| *Tumor type* | *N* | *%* | *N* | *%* | *N* | *%* | *N* | *%* |
| Prostate | 8 | 10% | 50 | 62% | 23 | 28% | 81 | 24% |
| Breast | 5 | 8% | 40 | 62% | 19 | 30% | 64 | 19% |
| Lung | 7 | 12% | 37 | 64% | 14 | 24% | 58 | 17% |
| Lymphoma | 1 | 4% | 15 | 60% | 9 | 36% | 25 | 7% |
| Myeloma | 0 | — | 20 | 87% | 3 | 13% | 23 | 7% |
| Unknown primary | 1 | 7% | 10 | 67% | 4 | 27% | 15 | 4% |
| Renal cell | 2 | 13% | 7 | 47% | 6 | 40% | 15 | 4% |
| Sarcoma | 2 | 13% | 9 | 60% | 4 | 27% | 15 | 4% |
| Colorectal | 3 | 23% | 3 | 23% | 7 | 54% | 13 | 4% |
| Others | 4 | 14% | 15 | 54% | 9 | 32% | 28 | 8% |

Adapted with permission from ref. *2*.

When bone is the source of an epidural mass, the vertebral body is involved in over 80% of metastases, with involvement of the posterior arch less common. Thus, the bulk of tumor in most cases of ESCC is anterior or anterolateral to the thecal sac *(8,11)*. Nonetheless, co-existing involvement of both anterior and posterior bony structures is the rule, occurring in 75% of patients in a recent MR-based study *(12)*. Metastatic disease restricted to the vertebral body producing ESCC accounted for only 3% of ESCC cases. In 22% of ESCC patients tumor circumferentially compressed the spinal cord, and in another 43% there were co-existing anterior and posterior epidural soft-tissue components. These authors suggested that vertebral metastatic disease may progress along an anterior to posterior gradient, implying that the presence of posterior vertebral involvement in spinal metastases may predict imminent compression of the cord.

Precisely how epidural tumor results in spinal cord dysfunction is uncertain. As the epidural venous plexus becomes obstructed, vasogenic edema may develop in the white matter and eventually the gray matter of the spinal cord. Animal studies, as well as the beneficial actions of corticosteroids in humans and animals, support a role for vasogenic edema *(13)*. Direct pressure on the spinal cord from tumor likely contributes as well. In experimental models, elevated levels of prostoglandin E2 and serotonin metabolites are found in the compressed spinal cord, and treatment with serotonin antagonists improves outcome *(14)*. If the epidural tumor is unchecked, spinal cord infarction eventually ensues.

## CLINICAL FEATURES

Recognition and attention to the clinical features of ESCC offers more hope of improving outcome than any technological or treatment advances. Since the efficacy of therapy is most dependent on the patient's neurologic status at the time treatment is initiated, the goal must be to diagnose patients prior to the development of spinal cord damage. Unfortunately, the diagnosis is delayed in most patients. In a review of 1392 patients presenting between 1963 and 1982, only 32% were ambulatory at the onset of therapy *(15)*. Similar results were noted in a study published in 1998 in which only 33% of patients were ambulatory and 53% catheter-free at the time of therapy, indicating that little progress has been made in the early detection of ESCC *(16)*. Even recent studies find that pain has often been present for as long as 2 or 3 mo before the diagnosis is established *(17)*. In one series of 301 consecutive patients, the median delay from the onset of weakness (not just pain) to diagnosis was 14 d (10 d in patients with known cancer and 18 d in patients without known cancer). Responsibility for the delay, as assessed by extent of delay at each stage of referral, was evenly divided among the patient, general practitioner, general hospital, and in some cases hospice *(16)*. Most importantly, the majority of patients deteriorated by at least one grade in motor or bladder function during the delay. The net effect of delayed recognition is that the majority of patients with ESCC are not ambulatory at diagnosis *(4,16,18,19)*.

**PAIN** Pain is usually the first symptom of ESCC, being present in 83–95% of patients at the time of diagnosis *(4,8,20)*. On average, pain precedes other neurologic symptoms of ESCC by 7 wk. Affected patients usually notice a severe local back pain, which progressively increases in intensity. Pain is often worse with recumbency, a feature attributed to distension of the epidural venous plexus. Neck flexion and straight leg raise may also exacerbate pain.

Local pain may be due to disruption of the periosteum or dural nerves, the spinal cord, or paravertebral soft tissue. The frequent alleviation with the use of corticosteroids suggests that neural compression plays a significant role *(8)*. Over time, the pain may develop a radicular quality. It may, for example, radiate into a limb with movement of the spine or valsalva maneuver. Radicular pain is more common in lumbosacral lesions than thoracic lesions *(20)*. Thoracic radicular pain is commonly bilateral and wraps around anteriorly in a bandlike fashion. Abrupt worsening of pain may herald a pathologic compression fracture.

Unfortunately, although the presence of myelopathy or radiculopathy increases the likelihood of pain related to ESCC as opposed to isolated vertebral metastasis, the absence of these features in no way excludes the possibility. A prospective study evaluated 87 patients with cancer and back pain radiologically *(21)*. Three groups were identified: myelopathy; radicular pain;

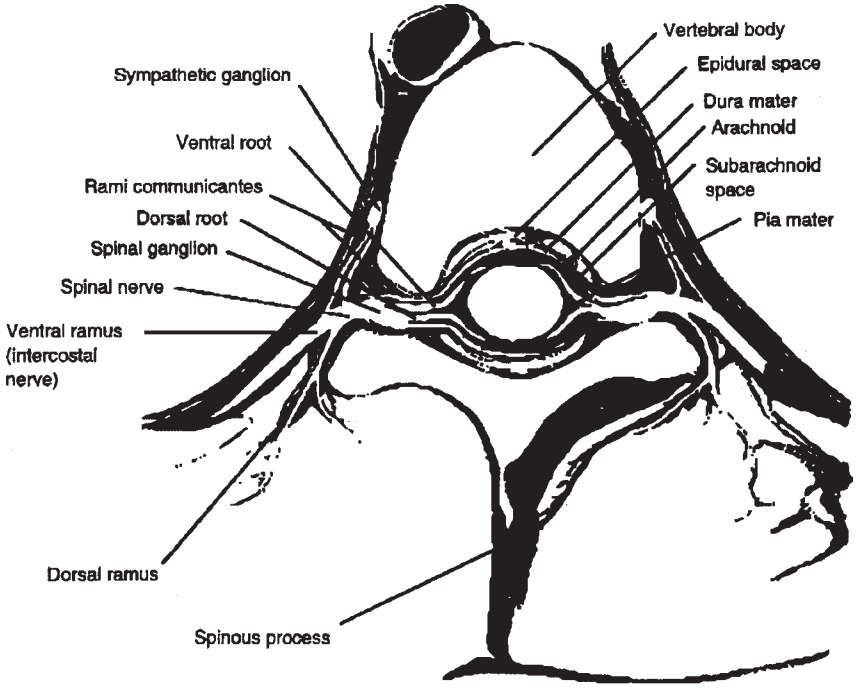


**Fig. 1.** Anatomy of the thoracic spinal canal.

and back pain with normal neurologic findings. The respective likelihood of epidural metastases in the three groups was 78%, 61%, and 36%. Similarly, a recent study of 170 patients with cancer and back pain found that no historical or plain radiograph feature differentiated patients with and without ESCC *(22)*. Thus, back pain alone must trigger a suspicion of ESCC in all patients known to have cancer.

**MOTOR FINDINGS** Weakness is present in 60–85% of patients with ESCC at the time of diagnosis *(18,20)*. Almost always it has been preceded by pain *(19)*. When the lesion is at or above the conus medullaris, weakness is from corticospinal dysfunction and has the typical pyramidal pattern, preferentially affecting the flexors in the lower extremities and (if above the thoracic spine) the extensors of the upper extremities. Hyperreflexia below the level of the compression and extensor plantar responses may be seen.

ESCC generally produces fairly symmetric lower extremity weakness. With cauda equina lesions, the weakness is associated with depressed deep tendon reflexes in the legs. A laterally situated epidural lesion may preferentially affect a nerve root exiting the neural foramen and produce a superimposed or isolated motor radiculopathy.

The progression of motor findings until diagnosis typically consists of increasing weakness followed sequentially by loss of gait function and paralysis *(20)*. In most large series, the majority of patients are not ambulatory at diagnosis *(4,16,18,19)*. This is usually secondary to weakness, although patients with ESCC are often discouraged from walking because of severe pain with movement. The severity of weakness is greatest in patients with thoracic metastases *(20)*.

**SENSORY FINDINGS** Sensory findings are a little less common than motor findings but are still present in a majority of patients at diagnosis *(20)*. They are rarely the initial complaint of ESCC *(19)*. In general there is a correlation between loss of sensation and inability to ambulate *(23)*. Patients frequently report ascending numbness and paresthesias if questioned and examined carefully. When a spinal sensory level is present, it is typically one to five levels below the actual level of cord compression *(8)*. Saddle sensory loss is commonly present in cauda equina lesions, while lesions above the cauda equina frequently result in sparing of sacral dermatomes to pinprick. Sensory loss can occur in a radicular distribution. It has been suggested that radicular pain with sensory complaints is particularly common with lumbar ESCC, whereas bilateral leg weakness with back pain is the rule with thoracic ESCC *(20)*. Lhermitte's sign, the experience of electricity down the spine with neck flexion, may be seen in multiple sclerosis, cervical spondylotic myelopathy, cisplatin-induced neurotoxicity, radiation-induced myelopathy, neck trauma, and rarely with an epidural or subdural neoplasm *(24)*.

**LOSS OF BLADDER AND BOWEL FUNCTION** Bladder and bowel dysfunction due to ESCC is generally a late finding that may be present in as many as one-half of patients *(20)*. The autonomic neuropathy most commonly presents as urinary retention and is rarely the sole symptom of ESCC *(8)*. The opiates that patients with ESCC frequently require can contribute to constipation and urinary retention.

**ATAXIA** Gait ataxia in the setting of back pain in a cancer patient should raise suspicion of ESCC *(25)*. In the absence of demonstrable sensory loss, spinocerebellar tract dysfunction has been presumed to account for the ataxia.

## RADIOLOGIC CONFIRMATION

The diagnosis of ESCC depends upon the ability to demonstrate a neoplastic mass extrinsically compressing the thecal sac. Definitive studies to image the thecal sac have always been relatively costly and, prior to the advent of magnetic resonance imaging (MRI), invasive. However, plain radiographs and clinical examination are insufficient. Specialists miss the localization of symptomatic ESCC by more than one spinal level more than 25% of the time *(26)*.

Careful imaging of the thecal sac and epidural space is mandatory for both diagnosis and for optimal treatment planning. Definitive imaging of the thecal sac by MRI or myelography may demonstrate multiple lesions that are clinically unsuspected or may reveal that a clinically mild lesion is producing high-grade spinal block (which could influence choice of treatments). As noted earlier, radiologic testing for early diagnosis should be performed in all cancer patients who develop otherwise unexplained and persistent back pain; signs of a radiculopathy or myelopathy markedly increase the likelihood of epidural metastases *(21)*.

MRI and myelography are superior to plain radiographs, bone scans, and computed tomography (CT) as diagnostic imaging methods. The importance of these imaging tests is illustrated by several observations. In one retrospective study, 59 of 130 patients (45%) had changes in the choice of therapy associated with findings on spinal MRI. As an example, the MRI results influenced the addition or modification of radiation-therapy treatment in 33% of the patients suspected of metastatic disease to the spine *(27)*. In another series of 24 patients, the initial treatment fields planned on the basis of X-ray findings and clinical data were inadequate in 69% of the patients *(28)*. Even in those with discrete bony lesions, the results of myelography affected the treatment in almost one-half of cases.

**RADIOGRAPHY** Plain spinal radiographs are the easiest study to obtain and are of value in certain situations. In a cancer patient with back pain, either major vertebral body collapse or pedicle erosion with a matching radiculopathy predicts a 75–83% chance of ESCC when a definitive study is performed *(21,29)*. However, false-negative plain spinal radiographs occur in 10–17% of patients with ESCC *(4,8)*. Three factors are primarily responsible for the false-negative results. First, at least 50% of bone must be destroyed before a plain radiograph becomes abnormal. Second, metastatic involvement of multiple vertebrae (as is the rule with multiple myeloma, prostate, and breast cancer) may obscure the clinically relevant lesion. Finally, paraspinal tumor invading through the neural foramen may produce no radiographic abnormality. For example, one-third of patients with ESCC from lymphoma have normal spine radiographs *(30)*.

**BONE SCAN** Radionuclide bone scanning is more sensitive for detecting bony metastasis than plain spinal radiograph and a single study has the advantage of visualizing the entire skeleton. However, bone scans may be negative in neoplasms without increased blood flow or new bone formation; this is frequently the case in multiple myeloma *(8)*. Other limitations in the diagnosis for ESCC are that increased radionuclide uptake may be seen in numerous conditions other than cancer, that scans may be positive at multiple levels, and that bone scanning is not informative about thecal sac compression.

One study combined plain radiography and bone scanning retrospectively in a small patient group and concluded that, if both studies were negative in a cancer patient with localized spinal pain, the risk of ESCC was only 2% *(31)*. This finding, if confirmed prospectively, would suggest that certain low-suspicion patients may safely forgo definitive spinal imaging. Nevertheless, patients with cancer and myelopathy, radiculopathy, or severe or progressive back pain need to undergo such testing.

**COMPUTED TOMOGRAPHY** The utility of CT scanning of the spine to evaluate patients for ESCC has been studied *(32,33)*. CT scan does not depict the spinal cord or epidural space clearly. However, in patients without severe osteoporosis, it depicts metastatic disruption of the bony cortex surrounding the spinal canal, a finding highly predictive of epidural tumor extension. Epidural tumor within the spinal canal may enhance following administration of intravenous contrast, facilitating its identification *(34)*. Disadvantages of CT include its reliance on ionizing radiation and the time required to obtain images, which limit the length of the spinal canal that can be screened. As epidural disease can arise from rostral caudal extension of bony metastasis, another theoretical concern is that CT scanning could miss a lesion producing ESCC within the region targeted by the scan if the associated cortical disruption occurred beyond the scan's bounds *(33)*. The availability of MR scanning has greatly diminished the role of CT scanning in the diagnosis of ESCC.

**MYELOGRAPHY AND MR SCANNING** The two definitive means of diagnosing ESCC are myelography (often combined with postmyelogram CT) and MR scanning. Each provides an image of the thecal sac and can display indentations and encircling of the sac by neoplasm.

MRI offers several potential advantages over myelography. It produces anatomically faithful images of the spinal cord and intramedullary pathology and is even more sensitive than radionuclide bone scans at identifying bony metastases *(35)*. It images the entire thecal sac regardless of whether a spinal subarachnoid block is present. Furthermore, it is not contraindicated with large brain metastases and spares the patient a lumbar puncture. Myelography may be better tolerated by patients in considerable pain, since image quality in MR scanning is very dependent on the ability to lie still. Myelography permits cerebrospinal fluid (CSF) analysis, which, although not useful for the diagnosis of ESCC, is the cornerstone of the diagnosis of leptomeningeal metastases. In ESCC, CSF examination frequently reveals an elevated protein (as would be expected with subarachnoid block) with a normal cell count and negative cytology. Postmyelogram CT scans at the level of thecal sac impingement provide additional anatomic information about the tumor (such as its rostral extent and the presence of a paraspinal component) and usually demonstrate some rostral passage of contrast at the level of high-grade subarachnoid block not appreciated on the myelogram itself *(36)*.

Rarely, patients with complete spinal subarachnoid block deteriorate neurologically when CSF pressure below the block

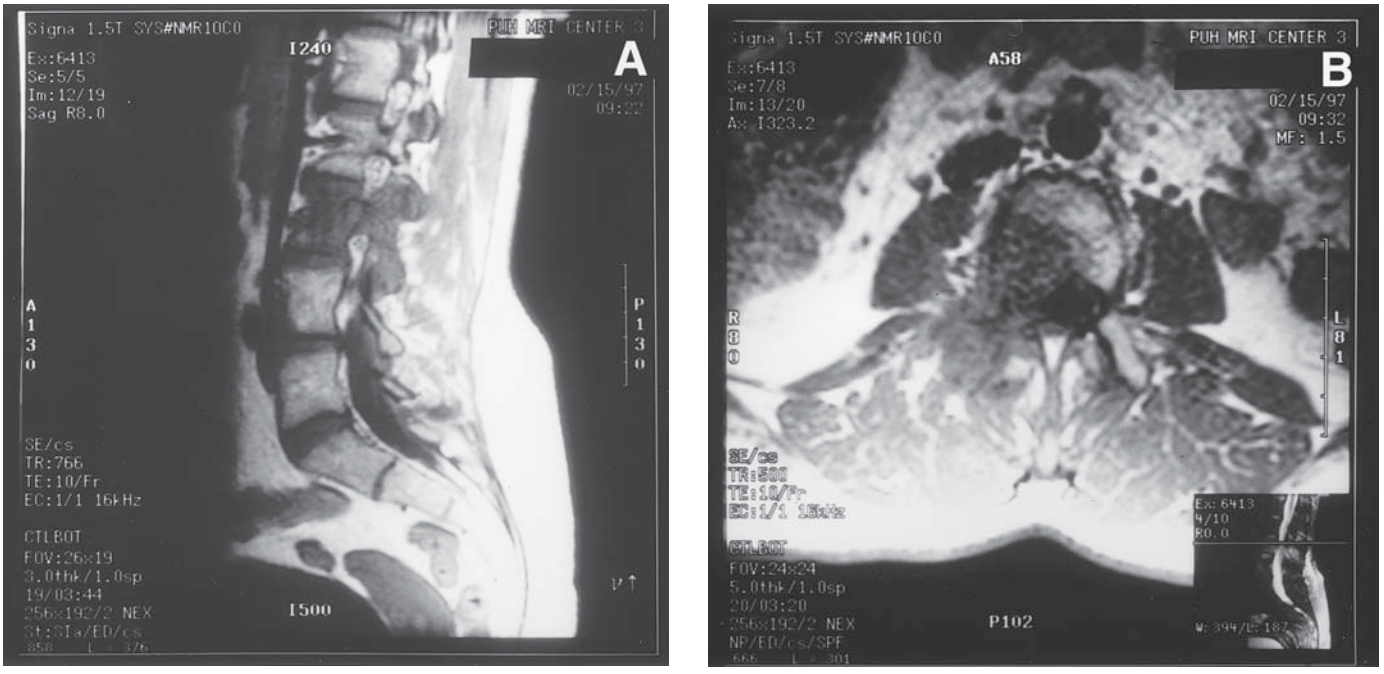


**Fig. 2.** Sagittal **(A)** and axial **(B)** postcontrast MR scans of the lumbar spine in a 37-yr-old woman with node-positive breast cancer, 4 mo chronic low back pain, and 1 d of acute localized back pain. Neurologic examination was normal apart from severe spinal tenderness and refusal to walk because of pain. The scans demonstrate abnormal signal in the L3 and L4 vertebral bodies with extension into posterior elements, partial collapse of L3, and compression of the right ventrolateral thecal sac. The right L2 and L3 neural foramina were also affected.

has been reduced by the lumbar puncture (spinal "coning"). For this reason, it is important to have neurosurgical input when a myelogram is considered for suspected ESCC. Patients known or suspected of having brain metastases should undergo brain CT or MR scan pior to myelogram given the risk of brain herniation.

Several studies dating from the early years of spinal MRI compared this procedure to CT myelogram for the diagnosis of ESCC. The two technologies were roughly equivalent in sensitivity and specificity *(37–39)*. Given the convenience and widespread availability of MRI, we may not see future comparative studies. Nevertheless, there are occasional cases, particularly with laterally located lesions, in which CT myelogram demonstrates abnormalities not visualized on MR scanning. In addition, patients with mechanical valves, pacemakers, paramagnetic implants, and shrapnel remain dependent on myelography.

Noncontrast T1 and T2 weighted MR images are generally quite satisfactory to screen for abnormalities in the bone and epidural space. The administration of gadolinium may be helpful, as most tumors enhance, in contrast to some benign lesions like disc herniation. Furthermore, the disappearance of contrast enhancement following treatment suggests a successful treatment. Typically radiologists perform scans in the sagittal plane, with selected axial images through regions of interest identified on the sagittal images (Figs. 2 and 3).

**SCREENING FOR MULTIPLE DEPOSITS** Approximately one-third of patients with ESCC have multiple epidural tumor deposits on MR scanning or myelography *(2,9,40,41)*. Although it remains debatable whether asymptomatic or incidentally detected ESCC should be treated, the presence of multiple sites of ESCC significantly affects prognosis and treatment planning *(2,9)*.

The relatively high frequency of multiple deposits has led some authorities to recommend that the entire spine be screened in all ESCC patients *(8,40–43)*. Radiologists sometimes balk at the time and expense such screening requires. A retrospective study of 337 cases found that failure to image the cervical spine in patients with symptomatic thoracic or lumbar epidural lesions would have missed secondary epidural lesions in only 1% of patients; however, this figure increased to 21% with failure to image either the thoracic or lumbosacral spine when symptomatic disease was located elsewhere *(2)*. It would therefore seem advisable to image at least the thoracic and lumbar spine routinely in addition to the clinically suspected region.

## DIFFERENTIAL DIAGNOSIS OF ESCC

Cancer patients are prone to malignant, non-ESCC causes of back pain and neurologic dysfunction, as well as common nonmalignant causes of these symptoms.

**MUSCULOSKELETAL DISEASE** Benign causes of back pain, including muscle spasm, intervertebral disk disease, and spinal stenosis, warrant consideration. One feature that is sometimes helpful in differentiating pain of ESCC from benign causes of back pain is thoracic localization; the benign causes generally occur in the lumbar or cervical spine.

**SPINAL EPIDURAL ABSCESS** Spinal epidural abscess is an uncommon condition. Predisposing factors include intravenous drug use, vertebral osteomyelitis, and hematogenous infection. The clinical manifestations may be indistinguishable

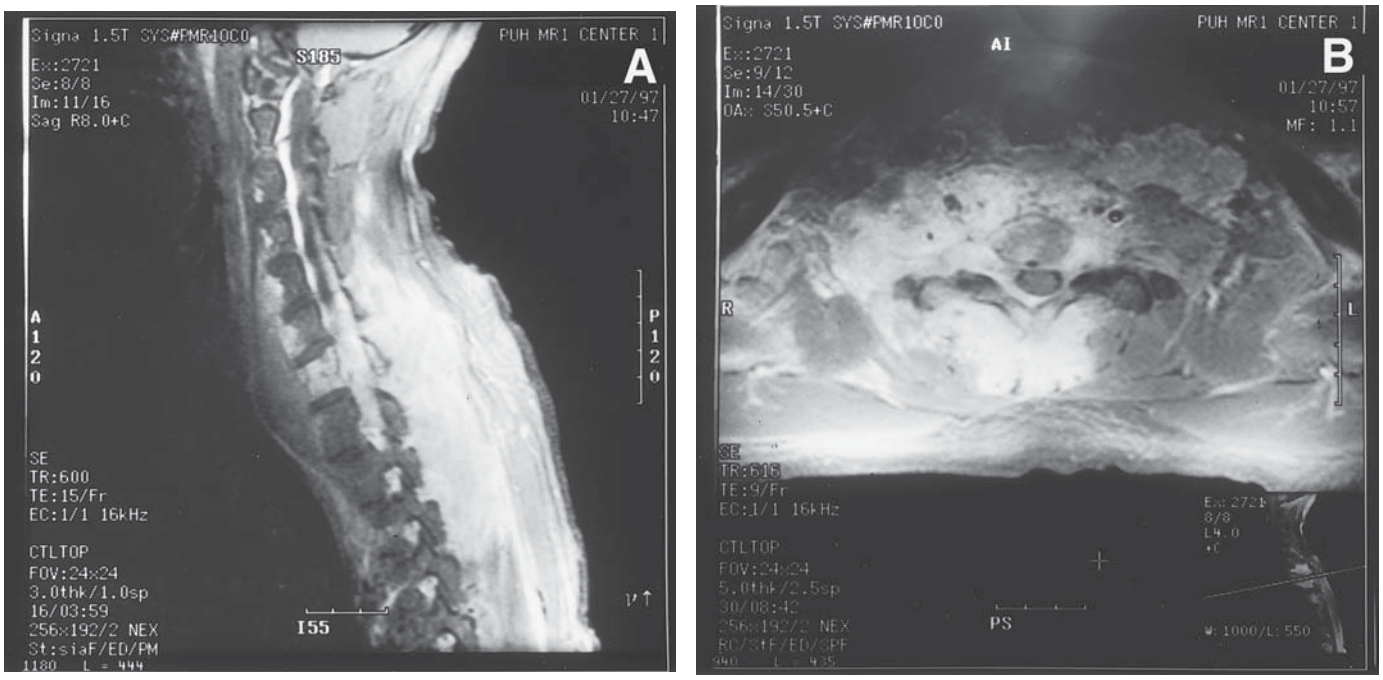


**Fig. 3.** Sagittal **(A)** and axial **(B)** postcontrast cervical MR scans of a 33-yr-old man with Hodgkin's disease, 2 mo progressive shoulder pain, bilateral hand and arm weakness, leg tingling, and gait unsteadiness. Exam was notable for severe triceps and hand weakness, a C7 sensory level to light touch, absent triceps reflex but pathologic hyperreflexia elsewhere, and an ataxic gait. The MR scan demonstrates extensive adenopathy with infiltration of the C7 vertebra extending into posterior elements and C6-7 and C7-T1 neural foramen and epidural space, displacing the cord. There was also involvement of both T1-2 neural foramen as well as a smaller epidural lesion at T10.

from rapidly progressive neoplastic ESCC. Neuroimaging may suggest infection, but in some cases biopsy will be necessary for diagnosis.

**METASTATIC DISEASE** Vertebral metastases without epidural extension frequently produce local back pain, which may be severe. The differentiation from ESCC will ultimately depend on neuroimaging studies.

**INTRAMEDULLARY SPINAL CORD METASTASES** Intramedullary metastases occur much less frequently than epidural metastases and are discussed later in this chapter. They produce pain, weakness, and numbness similar to ESCC. Unlike ESCC, they often produce a hemicord syndrome of unilateral weakness below the level of the lesion with contralateral diminution of pinprick and temperature discrimination; continued growth can lead to subsequent bilateral spinal cord dysfunction *(44,45)*.

**LEPTOMENINGEAL TUMOR** Leptomeningeal metastases commonly produce a cauda equina syndrome, which frequently co-exists with mental status changes, headache, and cranial-nerve palsies *(46,47)*. Local back pain may not be present but affected patients usually complain of radicular pain. MR scanning in patients with leptomeningeal metastases demonstrates no epidural tumor and may show pathologic meningeal enhancement; CSF examination is usually diagnostic.

**NEOPLASTIC PLEXOPATHY** Malignant plexopathy may involve any of the peripheral nerve plexuses. Brachial plexopathy most commonly occurs in carcinoma of the breast and lung; lumbosacral plexopathy is usually due to colorectal and gynecologic tumors, sarcomas, and lymphomas. In most cases, the major clinical feature of malignant plexopathy is severe unrelenting local or radicular pain. Later, weakness and focal sensory disturbances occur in the distribution of the involved plexuses *(48)*. In the absence of a palpable mass or ipsilateral extremity swelling, these symptoms can mimic ESCC; in fact, the paraspinal location of the plexus means that ESCC and malignant plexopathy can and often do coexist. MR or CT scanning can differentiate between these possibilities.

**RADIATION MYELOPATHY** Rarely, patients who have previously received radiation to the spine or nearby structures develop chronic progressive radiation myelopathy. The total previous radiation dose, fraction size, and length of spinal cord treated are important risk factors. The latency following radiotherapy is typically 9–15 mo. Affected patients usually develop ascending numbness and upper motor neuron findings that often have a hemicord localization, presumably because radiation has produced a vascular lesion *(49,50)*. MRI or myelography distinguishes this entity from ESCC. Radiation myelopathy is discussed at length in Chapter 14.

**OTHER** A number of other disorders can simulate some of the findings in ESCC.

- Spinal epidural cavernous hemangiomas can cause acute or chronic progressive spinal cord syndrome and local back pain or radiculopathy *(51)*. The diagnosis can usually be established by MRI.
- Spontaneous nontraumatic spinal epidural hematomas, occurring in the presence of anticoagulant therapy, arterial

venous malformations, or inherited or acquired bleeding disorders, are a rare cause of spinal compression *(52)*. The distinctive imaging characteristics of blood on CT and MR scan suggest this diagnosis *(53)*.

- Meningiomas and neurofibromas can compress the spinal cord and produce radicular and myelopathic syndromes. Their intradural location is usually apparent on imaging studies.
- Spinal cord compression can rarely be induced by extramedullary hematopoiesis due to thalassemia or chronic myeloproliferative or myelodysplastic disorders *(54,55)*, as well as epidural involvement by rheumatoid arthritis, sarcoidosis, or tophaceous gout *(56–58)*.

## THERAPY

The goals of therapy for ESCC include pain control, avoidance of complications, and a rational attempt to preserve or improve neurologic functioning utilizing techniques appropriate to the patient's burden of disease, life expectancy, and values. Symptomatic treatment of ESCC generally begins prior to more definitive therapy and consists of the following general principles.

**PAIN MANAGEMENT** Patients with ESCC are frequently in severe pain, often limiting the physician's ability to perform a thorough neurologic examination. Corticosteroids usually improve the pain within several hours, but most patients will require opiate analgesics to tolerate the physical examination and necessary diagnostic studies. External spinal bracing is sometimes advocated but has not been carefully studied. Bracing is often uncomfortable and is reserved for cases of spinal instability or pain refractory to other interventions. Similarly, enforced bedrest is usually unnecessary.

**ANTICOAGULATION** Patients with cancer are prone to a hypercoagulable state. Although the value of prophylaxis against venous thromboembolism has not been studied in patients with ESCC, it would seem reasonable to give prophylactic subcutaneous heparin or sequential compression devices to nonambulatory patients who are at moderate to high risk of forming deep venous thrombosis and who are not at a terminal stage of their disease.

**PREVENTION OF CONSTIPATION** Autonomic dysfunction from the spinal lesion, limited mobility, and analgesics may contribute to the development of constipation, ileus, and occasionally perforation of an abdominal viscus, the symptoms of which may be masked by corticosteroids *(59)*. Consequently, an aggressive bowel regimen is indicated.

**DEFINITIVE MANAGEMENT** Management options include the administration of corticosteroids, radiotherapy, and surgery. Most patients receive a combination of corticosteroids and radiotherapy as definitive treatment. Spinal decompression is used in selected patients, while chemotherapy may be beneficial in patients with chemosensitive tumors.

**CORTICOSTEROIDS** The beneficial actions of corticosteroids in restoring neurologic function in patients with ESCC were first reported in the late 1960s. Animal studies documenting salutary effects in various models of ESCC soon followed *(60,61)*.

High-dose corticosteroid therapy is generally considered to be part of the standard regimen for ESCC, despite limited documented evidence of benefit and a significant risk of serious side effects *(1)*. Several studies have suggested that lower doses can be effective, but they have not been assessed in randomized trials. Only one randomized clinical trial has addressed the utility of corticosteroids in ESCC *(62)*. In this study, 57 patients with carcinoma (two-thirds with breast cancer) and myelographically confirmed ESCC were randomized to receive either no dexamethasone or dexamethasone (96 mg intravenously followed by 24 mg four times daily for 3 d and then tapered over 10 d). Stratification factors included primary tumor type and the extent of neurologic dysfunction, and all patients received standardized radiation therapy. A significantly higher percentage of patients in the dexamethasone group remained ambulatory both at the conclusion of therapy (81% vs 63%) and at 6 mo (59% vs 33%). Significant side effects were seen in three patients in the corticosteroid group (11%), including one patient requiring surgery for gastric perforation.

Steroid-induced complications with this regimen were prominent in another series of 28 patients undergoing radiation therapy *(63)*. Although all patients received H2 blockers or antacids, two developed gastric perforation and two developed gastrointestinal bleeding (fatal in one case). As a result, the high-dose regimen was abandoned and the dose was lowered to 16 mg daily tapered over 2 wk. There were no serious side effects seen in 38 patients treated with this reduced dose, and the ambulatory outcome was similar to that with higher-dose therapy. This study also highlights the uncertain benefits of H2 blocker administration in patients receiving corticosteroids.

In an attempt to identify the optimal initial steroid dose, 37 patients with ESCC and complete myelographic block were randomized to an initial dexamethasone bolus of 10 mg or 100 mg intravenously, both followed by 16 mg daily orally *(64)*. Both doses were effective in rapidly improving pain. At both 1 d and 1 wk there was no difference between the two groups in terms of ambulatory status, bladder function, or pain.

It remains uncertain if patients with less severe epidural disease require steroid therapy. One small phase II trial showed that patients with back pain but no myelopathy and less than 50% narrowing of the spinal canal by epidural tumor could successfully undergo radiotherapy without receiving steroids *(65)*.

In summary, the physician has a choice between the "high" dose of dexamethasone with proven efficacy and a relatively high rate of serious side effects and a "low" dose with notably fewer side effects but no randomized controlled data to support its use. Definitive recommendations await randomized controlled trials. I reserve the high-dose regimen for patients with paraparesis or paraplegia and halve the dexamethasone dose every 3 d. Patients with pain but minimal neurologic dysfunction receive a 10 mg intravenous bolus followed by 16 mg daily in divided doses. The dose is gradually tapered once definitive treatment is well underway. Patients with small epidural lesions, a normal neurologic examination, and relative contraindications to therapy may safely forgo the use of corticosteroids *(1)*.

**RADIATION THERAPY** Radiation therapy is the treatment of choice for most patients with ESCC. The radiation portal is usually about 8 cm wide, centered on the spine, and extends one to two vertebral bodies above and below the epi-

dural metastasis *(66)*. The port is widened when the patient is known to have paraspinal extension of tumor. Radiation therapy for ESCC is generally extremely well-tolerated. When large segments of the spine are irradiated, particularly in patients heavily pretreated with chemotherapy, myelosuppression may develop. Similarly, gastrointestinal symptoms of mucositis occasionally occur. These complications are much more frequent with craniospinal irradiation.

There have been no comparative studies of different dose-fractionation schemas for ESCC, and an optimal schedule has not been identified *(67,68)*. The Radiation Therapy Oncology Group (RTOG) has conducted studies comparing different schedules for the palliation of symptomatic bone metastases in general. The initial trial did not demonstrate any advantage to various schedules ranging from 300 cGy × 5 fractions to 400 cGy × 5 fractions to 500 cGy × 5 fractions to 300 cGy × 10 fractions to 270 cGy × 15 fractions *(67)*. A subsequent reanalysis using logistic regression suggested that increasing number of fractions led to improved pain control *(69)*. Single large fractions have been successfully used (particularly in England) to palliate pain from bony metastases but have not been utilized for ESCC *(70)*. One study evaluated a regimen of two fractions of 800 cGy given 1 wk apart in 53 patients with ESCC who had radioresistant tumors or a poor prognosis (e.g., poor performance status, paresis, plegia), and/or a short life expectancy *(71)*. The outcome was comparable to more standard courses, although more gastrointestinal side effects were observed. In another report, this regimen was compared prospectively in patients with prostate cancer and ESCC to a split course regimen of 1500 cGy in three fractions, 4 d rest, and then 1500 cGy in five fractions *(72)*. The short course was used in 17 patients with a poor prognosis and the split course was used in 27 other patients. There were no differences in functional response or complications between the treatment regimens. Most commonly, radiation oncologists administer 2000–4000 cGy in 5–20 fractions, with 3000 cGy in 10 fractions being a particularly popular regimen.

Radiation therapy leads to resolution of back pain in most patients. Pretreatment neurologic function is the strongest *(4,18,36,72–78)* and in some reports the only predictor of posttreatment neurologic function *(72,78)*. In most series, 80–100% of patients treated while still ambulatory remain ambulatory at the conclusion of therapy. Approximately one-third of patients who are nonambulatory because of paraparesis regain the ability to walk with treatment, as do 2–6% of paraplegic patients. Among patients who required a urinary catheter before therapy, 20–40% become catheter-free *(4,72)*. The second strongest predictor of response in patients unable to walk is the underlying tumor type. Patients paraparetic or even paraplegic have a much better chance of recovery if they have a radiosensitive tumor such as lymphoma, multiple myeloma, breast or prostate cancer *(75,79)*. Patients with these favorable histologies also are less likely to suffer local relapse of their epidural disease *(19)*. The degree of subarachnoid block produced by the tumor is also a predictor of posttreatment neurologic function; complete block is a poor prognostic sign *(36,80)*.

Patients treated for ESCC frequently do not undergo routine follow-up spinal imaging, and thus relatively little is known about the radiographic response to treatment. In one study, the radiographic response to radiation therapy for ESCC was evaluated in a series of 64 patients who underwent repeat myelography between 20 and 170 d (median, 34 d) after the initiation of therapy *(36)*. Regression of the epidural lesion, stable disease, and progression were noted in 47%, 37%, and 16%, respectively.

Median survival following diagnosis of ESCC is approx 6 mo *(2,72,75,81)*. The outcome is better in walking patients *(75)* and approx one-half of patients surviving 1 yr are still ambulatory at that time *(78)*.

**RECURRENT ESCC** Approximately 10% of patients treated with radiotherapy for ESCC eventually develop local recurrence *(34,82)*. This figure increases with time so that roughly one-half of 2-yr survivors and nearly all 3-yr survivors will develop recurrence *(18,19)*. Chemotherapy and surgery should be considered in patients with locally recurrent ESCC. Frequently, however, these patients have exhausted good chemotherapy options and are poor surgical candidates because of widespread bony and/or visceral disease. In such patients, a second course of spinal radiation can be given reasonably safely *(83)*. Although repeat irradiation may result in a cumulative dose exceeding the reported radiation tolerance of the spinal cord (4500 cGy in 200 cGy fractions), radiation myelopathy in this setting is an apparently infrequent occurrence. This may be attributable to repair of sublethal radiation damage between courses *(84)* and/or the generally short survival of patients receiving repeat irradiation (median, 5 mo) compared to the latency of radiation myelopathy. In addition, some radiation oncologists have argued that spinal cord tolerance has been defined too conservatively and probably is closer to 6000 cGy in 200 cGy fractions *(50)*. Nine percent of patients with ESCC ultimately develop a second episode of ESCC at a remote spinal site *(34)*.

**SURGERY** For many years, posterior decompression of ESCC via laminectomy was the initial approach to the patient with neurologic compromise. However, retrospective comparison of case series of patients treated with laminectomy with or without radiotherapy vs radiotherapy alone revealed no advantage to the surgical approach *(15)*. Nor did a small randomized trial find any benefit to the addition of laminectomy to radiotherapy vs the administration of radiotherapy alone *(85)*. The failure of laminectomy to improve outcome substantially is not surprising since generally the bulk of tumor is located in the vertebral body anterior to the thecal sac. Decompressing the spine posteriorly provides little access to anterior tumor and may further destabilize the spine (Fig. 4). Posterior approaches remain appropriate for dorsal tumors without spinal instability.

Improvements in spinal instrumentation have led some surgeons to investigate more aggressive tumor resections for patients with ESCC, often consisting of vertebral corpectomy *(87–89)*. The goal of aggressive surgery is gross total tumor resection followed by spinal reconstruction if necessary. This approach fulfills the basic principles of cancer surgery, providing extensive exposure for complete resection and adequate access for anterior stabilization. After exposing the tumor, the surgeon curettes the tumor from the vertebral body and epidural space and then stabilizes the spine with either bone grafting or using methylmethacrylate and instrumentation (*see* Fig. 5).

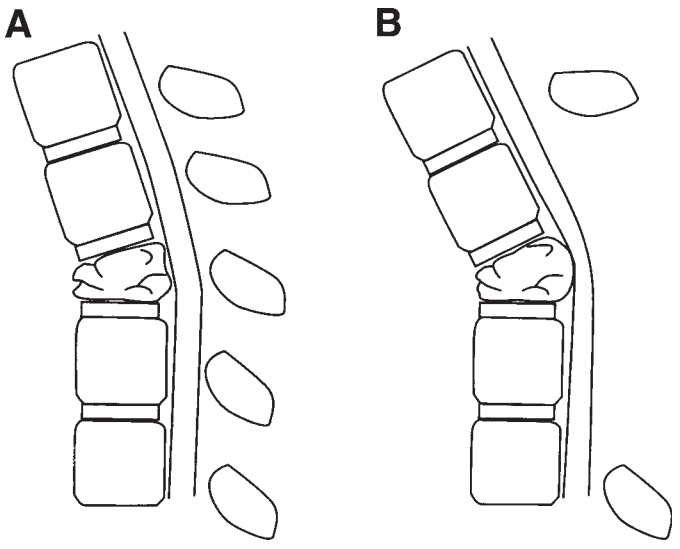


**Fig. 4.** Resection of the lamina spinous processes and intervening ligaments (all are components of the spine that function as a tension band, preventing kyphosis in a checkrein manner) via laminectomy in the face of a ventral tumor **(A)** may result in further spinal cord compression or distortion. Kyphotic spinal deformation (kyphosis) is also a possible result **(B)**. Spinal stability may, therefore, be significantly threatened as well. Reprinted with permission from ref. *86*.

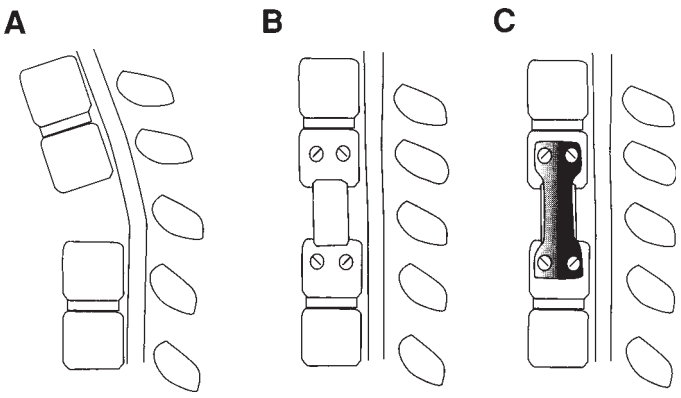


**Fig. 5.** The ventral approach to a vertebral body lesion can achieve a ventral decompression **(A)** and augment stability. Stability and deformity correction were achieved following placement of a screw (for distraction and extension) and an interbody strut **(B)**, followed by a plate **(C)**. Reprinted with permission from ref. *86*.

In view of the limited life expectancy of these patients and the frequent need for postoperative radiotherapy, methylmethacrylate has important advantages over bone grafting. Radiotherapy can begin 1 wk following methylmethacrylate but must be deferred for at least 6 wk to allow for fusion after bone grafting. Patients are mobilized within a few days of the surgery.

Published case series suggest substantial value to vertebral corpectomy. The largest series published to date reported encouraging results of aggressive surgery in 110 patients, 47 of whom had failed to respond to prior irradiation *(89)*. Before surgery, 48 patients (44%) were nonambulatory, with severe paresis present in 20. Surgery included staged anterior-posterior resections in 48 percent, anterior resection in 30%, and posterior resection in 5%. Almost all required spinal instrumentation for reconstruction. Improvement was noted in 82% in terms of both pain relief and ambulatory status. The overall median survival was 16 mo, with 46% alive at 2 yr. These excellent results were achieved despite frequent complications. The most common complications were wound breakdown (probably related to corticosteroids and in some cases prior radiotherapy), stabilization failure, infection, and hemorrhage. Postoperative complications occurred in 48%, these were related statistically to age over 65 yr, prior treatment, and presence of paraparesis. One-month mortality was about 10%.

The outcomes were not so encouraging in another report involving 109 patients with thoracic spine metastases treated with surgical decompression and radiotherapy *(90)*. The overall median survival was 10 mo. Patients who were ambulatory preoperatively survived significantly longer than those who were nonambulatory or had sphincter incontinence. Patients with renal cell carcinoma survived the longest, followed by those with breast, prostate, lung, and colon cancer. The number of vertebral bodies involved also affected survival.

Whether aggressive tumor resection of epidural metastasis followed by radiotherapy improves on the outcome from radiotherapy alone is the subject of an ongoing multi-center Phase III trial in the United States. Patients eligible for this trial must have known cancer, a single symptomatic epidural lesion that is surgically approachable, no prior radiotherapy to that spinal segment, and an estimated survival greater than 4 mo. Patients with very radiosensitive tumors (best treated with radiotherapy alone) or with complete paraplegia for greater than 48 h are excluded. The surgical approach will be customized in each case. Corticosteroids will be initiated at 40 mg of dexamethasone daily and tapered during radiotherapy. Both groups will receive 10 fractions of 300 cGy radiation to the site of ESCC. Patients will be evaluated every 8 wk following completion of treatment for assessment of neurologic status. Pending conclusion of this trial, aggressive resection should be strongly considered only in cases with the following features *(1,8)*:

- Spinal instability.
- Retropulsion of bone within the spinal canal.
- Local recurrence after spinal radiotherapy or deterioration during radiotherapy.
- Known radioresistant tumor (e.g., renal cell carcinoma) and minimal or controllable tumor elsewhere.

**CHEMOTHERAPY** There are no inherent reasons why chemotherapy cannot be used to treat ESCC. Unfortunately, the great majority of patients with ESCC have tumors that are not chemosensitive. In those patients with a sensitive tumor, chemotherapy is an attractive option because it can also treat tumor deposits elsewhere in the body.

Sensitive tumors in which ESCC has been treated successfully with chemotherapy include Hodgkin's disease *(91)*, non-Hodgkin's lymphoma *(92)*, neuroblastoma *(93)*, germ cell neoplasms *(94)*, and breast cancer *(95)*. Hormonal manipulation has occasional documented benefit in ESCC from prostate cancer and breast cancer *(95,96)*.

**NOVEL APPROACHES** Other therapies have been used in selected patients, including embolization and stereotactic

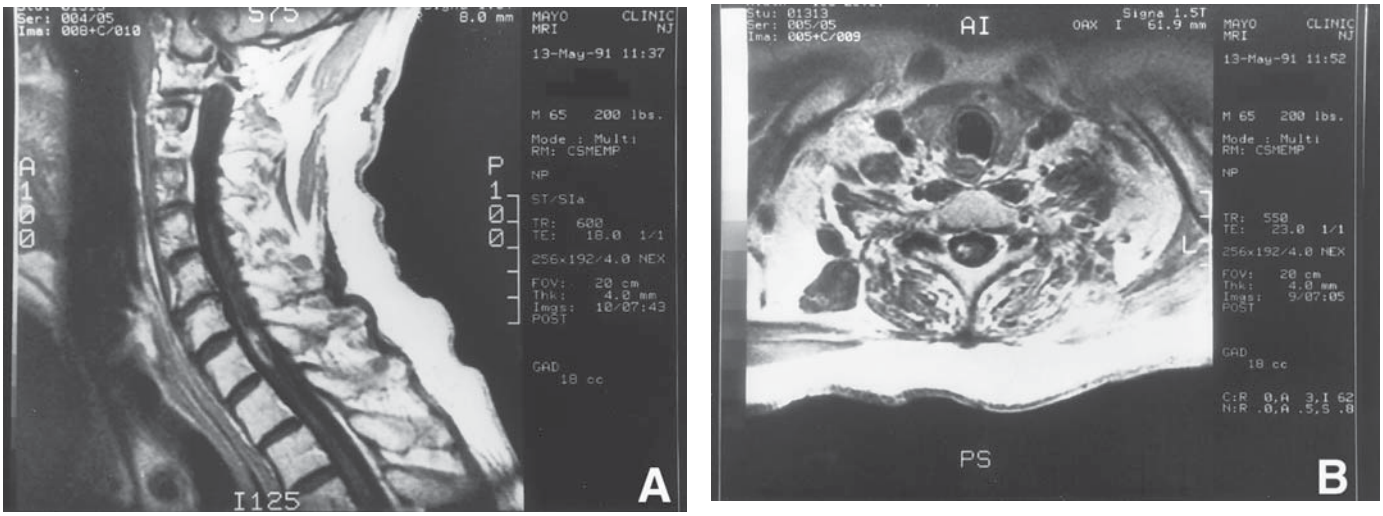


**Fig. 6.** Sagittal **(A)** and axial **(B)** postgadolinium cervical spine MR scans of a 65-yr-old man with known adenocarcinoma of the lung for 2 yr. The patient presented with right leg weakness. The scans demonstrate an enhancing intramedullary spinal cord metastasis. The patient was treated with fractionated radiotherapy and was neurologically stable on follow-up 5 mo later.

radiosurgery. Embolization of hemorrhagic neoplasms has occasionally been used as an adjunct to surgery. In one case report, a patient with renal cell carcinoma had two episodes of geographically distinct ESCC successfully treated with transarterial embolization utilizing microcoils and alcohol particles *(97)*.

Another approach has been to develop an extracranial system for delivering stereotactic radiosurgery. In one study, five patients with paravertebral metastases (including two with ESCC) that recurred after radiation were treated with stereotactic radiosurgery *(98)*. The dose to the spinal cord was calculated to be 300 cGy. Two patients died from systemic metastatic disease. In the three survivors, there was CT or MR-documented regression of the treated tumor with a decrease of thecal sac compression at a median follow-up of 6 mo. No radiation toxicity was reported. Larger patient numbers and longer follow-up are required to support these encouraging observations.

## PROGNOSIS

As noted earlier, median survival following the diagnosis of ESCC is approx 6 mo *(2,72,75,81)*. The outcome is better in walking patients *(72,75)*: the median survival for patients ambulatory prior to radiation therapy is 8–10 mo compared to 2–4 mo for those who are nonambulatory. For those who remain nonambulatory at the conclusion of radiation therapy, the median survival is only 1 mo *(75)*. The prognosis is better in breast or prostate cancer (median survival 9–10 mo) and significantly worse in lung cancer (median survival 3 mo) *(2,75)*. Similar factors are found when survival after spinal metastasis is examined (irrespective of whether the patient has ESCC) *(90,99,100)*. Patients with radiosensitive tumors and a single spinal metastasis do best, while patients with lung cancer, multiple vertebral metastases, or visceral or brain metastases fare poorly.

In addition to improved therapies for established disease, two preventive strategies in patients with known malignancy at risk for ESCC may reduce the incidence and severity of this complication The first approach is education so that ESCC can be diagnosed before neurologic function is irreversibly lost. Given that back pain is typically present for weeks before weakness and other symptoms of ESCC supervene, responsible health care providers must inform patients and their families about symptoms that warrant immediate evaluation, particularly otherwise unexplained or unrelenting back pain. By the same token, physicians must expeditiously and thoroughly evaluate such complaints. Delays in diagnostic evaluation may account for the observation that ESCC referrals to radiation oncologists are far more likely to occur on Friday than any other day *(101)*. The second strategy is to try to reduce the development of ESCC with bisphosphonates in patients with bony metastases. Bisphosphonates such as pamidronate are of proven benefit in reducing pathologic fractures and bone pain in patients with multiple myeloma or breast cancer with lytic bony lesions *(102,103)*. Although these studies were not designed to look at ESCC as an endpoint, it is plausible that reducing bony progression and pathologic fractures will impact favorably on ESCC.

## INTRAMEDULLARY SPINAL CORD METASTASES

Although systemic malignancies most commonly produce spinal cord dysfunction via epidural extension, they occasionally metastasize to the spinal cord parenchyma itself, a phenomenon termed intramedullary spinal cord metastasis. This phenomenon occurs approx one-sixteenth as often as ESCC *(45)*. In the pre-MRI era, the diagnosis could only be made by biopsy or with myelographic demonstration of a focally swollen spinal cord in the setting of known cancer *(44)*. The ability with MR scanning to demonstrate intramedullary lesions has resulted in this entity being diagnosed far more frequently. Almost half the cases are associated with lung cancer, and small cell lung cancer is a more common cause than nonsmall cell lung cancer *(44,45)*. Breast and renal cell cancer, lymphoma,

and melanoma are other less common causes. Most commonly this complication arises in patients with widespread metastatic disease; the majority of patients have brain metastases and lung metastases, and leptomeningeal metastases are seen in approx one-quarter. In 20% it occurs as the initial manifestation of malignancy. The initial symptom may be sensory alteration (43%), pain (30%), weakness (30%), gait unsteadiness (5%), or sphincter dysfunction (3%). At diagnosis, 93% have motor deficits and 63% urinary incontinence *(45)*. The Brown-Séquard syndrome of hemicord dysfunction is a common initial finding and may suggest this entity. In contrast, hemicord syndromes occur in only 1–8% of patients with ESCC *(3,19,104)*. MR scanning generally demonstrates a focally enhancing parenchymal nodule (Fig. 6) with a wider area of T2 signal abnormality presuming reflecting vasogenic edema. Eighty-seven percent of patients have a single visible lesion *(45)*. In contrast to the thoracic predilection of ESCC, 45% of spinal cord metastases occur in the conus, 34% in the cervical spinal cord, and only 21% in the thoracic cord. CT-myelogram may be undertaken in patients who cannot undergo MRI although it is less sensitive. Management generally consists of focal fractionated radiotherapy and usually enables the patient to maintain his or her pretreatment level of neurologic function. However, since only 20% of patients are capable of independent ambulation at diagnosis, the treatment outcome is often suboptiomal. As with brain metastases and epidural spinal cord compression, corticosteroids are generally also employed until radiotherapy is completed. Given the usual scenario of concomitant brain and visceral metastases, surgical extirpation of the intramedullary metastasis is rarely entertained. Median survival following diagnosis of spinal cord metastasis is 3 mo, with 15% 1-yr survival.

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# 10 Leptomeningeal Metastases

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## INTRODUCTION

Cancer cells can invade the cerebrospinal fluid (CSF) and seed the leptomeniges in a diffuse and multifocal manner, producing a complication known as leptomeningeal metastases or seeding. These cancer cells can remain confined to the meninges or penetrate the brain, spinal cord, or nerve roots, leading to a variety of symptoms and neurologic signs. The multiplicity of clinical findings associated with leptomeningeal metastases has made this diagnosis particularly challenging for the clinician. This devastating complication was first described by Eberth in 1870 *(1)*, and later named "meningitis carcinomatosa" by Siefert in 1902 *(2)*. Once considered uncommon and described usually as a finding at autopsy, leptomeningeal metastases has been diagnosed with increasing frequency in recent decades. For this reason, and because of the severe and devastating symptoms caused by this disorder, leptomeningeal metastases has become a common problem in neuro-oncology. Early diagnosis of leptomeningeal metastases is important because recent studies have suggested that intervention is most beneficial for patients who have minimal symptoms, high performance status, and low leptomeningeal tumor burden.

## INCIDENCE

The incidence of leptomeningeal metastases is difficult to know with certainty, but it appears to be increasing for most cancers *(3,4)*. An exception is childhood acute lymphocytic leukemia, where recognition of isolated central nervous system (CNS) relapse and the development of appropriate and effective prophylaxis, have reduced the incidence of this complication from as high as 66% to the present level of approx 5% *(5)*. This apparent increase in the incidence of leptomeningeal metastases is due to improved diagnostic modalities, prolonged survival of patients with systemic cancers, and increased awareness of this disorder. Although leptomeningeal metastases can be the initial presentation of an underlying cancer, most patients who develop this disorder do so late in the course of their illness *(6–8)*. Not uncommonly, patients with breast carcinoma and leukemia may develop leptomeningeal metastases many years after the initial diagnosis and treatment of their cancers. Most patients who develop leptomeningeal metastases have been heavily pretreated and have widespread metastatic and progressive systemic cancer *(9–12)*. Leptomeningeal metastases is rarely the only intracranial site of disease. Posner and Chernik found isolated leptomeningeal metastases in only 1.9% of 2088 patients with intracranial metastases and cancer excluding leukemia *(13)*. Usually parenchymal brain metastases, or dural or bony tumors accompany leptomeningeal metastases. For reasons such as these, a clinician may attribute new neurologic symptoms and signs to parenchymal CNS or systemic metastases, or nonmetastatic complications of cancer, and not search for leptomeningeal metastases. Moreover, because many patients who develop leptomeningeal metastases are terminally ill, the clinician may choose a palliative approach and not investigate for this complication. Consequently, leptomeningeal metastases is often underdiagnosed by the clinician. Recent autopsy studies have suggested that leptomeningeal metastases occurs in approx 3–8% of all cancer patients *(13,14)*. However, postmortem underdiagnosis is also suspected because leptomeningeal metastases is a multifocal and often microscopic disorder, and unless the pathologist samples many sites, the diagnosis may be overlooked. A report published by the Memorial Sloan-Kettering Cancer Center documented an 8% incidence of leptomeningeal metastases in 2375 patients with cancer and a postmortem neuropathologic evaluation *(13)*. A study conducted by the National Cancer Institute reported an antemortem diagnosis of this condition in 11% and a postmortem confirmation of 25% of patients with small cell lung cancer *(7)*. Autopsy reports from patients with breast cancer have identified leptomeningeal metastases in 3–40% of patients *(15,16)*. Other autopsy studies have revealed that as many as 19% of patients with neurologic symptoms and signs have pathologi-

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**Table 1**
**Cerebral Symptoms and Signs**

| *Symptoms* | *Signs* |
|---|---|
| Gait difficulty | Mental status change |
| Headache | Papilledema |
| Mental change | Seizures |
| Nausea and vomiting | Hemiparesis |
| Loss of consciousness | Diabetes insipidus |
| Dizziness | |
| Dysphagia | |

cal evidence of carcinomatous infiltration of the meninges at postmortem examination *(17)*.

Any cancer can potentially infiltrate the leptomeninges. Clinical reports have suggested that leptomeningeal metastases occur in 4–15% of carcinomas, 4–15% of non-Hodgkin's lymphomas, and 5–15% of acute nonlymphocytic leukemia *(3,6,10,11,18–20)*. Among solid tumors, the most common systemic cancers to spread in this way include breast cancer, small cell lung cancer and melanoma where approx 5%, 9–25%, and 23% of patients, respectively, will develop this complication *(7,8,21)*. Occasionally, uncommon tumors such as multiple myeloma, thyroid cancer, chronic lymphocytic leukemia, and Hodgkin's disease can cause leptomeningeal metastases. Gastric carcinoma, reported in the past as a tumor that commonly infiltrates the meninges, is today rarely a cause of this disorder. Carcinomas of unknown primary account for between 1–7% of leptomeningeal metastases *(6,10,11,18)*. Primary brain tumors can also disseminate throughout the leptomeninges, with recent reports suggesting that this complication occurs in as many as 10–32% of cases *(13,18,22–24)*. Occasionally, tumors can arise as primary malignancies in the leptomeninges. Melanomas, rhabdomyosarcomas and lymphomas can be confined to the leptomeninges. However, most cases of primary CNS lymphoma are parenchymal, with leptomeningeal seeding common and often asymptomatic *(25)*.

## CLINICAL FINDINGS

The clinical manifestations of leptomeningeal metastases are protean because multifocal involvement of the brain, spinal cord, or nerve root is characteristic *(6,10,26–28)*. Leptomeningeal metastases should be suspected whenever a patient presents with multiple nervous system symptoms and signs. Typically, signs are more widespread than patient symptoms, but if this diagnosis is considered early during the course of the illness, there is greater likelihood of uncovering subtle or unifocal neurologic findings. Thus, a high index of suspicion in an appropriate clinical context is required if this diagnosis is to be made during the initial stages of the illness. The most common site of involvement of the neuraxis is the spinal region, with lower motor neuron weakness the most common finding, being present in 80% of patients at diagnosis. Other common findings on examination are reflex loss or asymmetry, and dermatomal sensory loss. Signs suggestive of leptomeningeal irritation, such as nuchal rigidity or pain on straight leg raising, are detected in only 15% of patients *(10)*. Findings such as aphasia, hemiparesis, or visual field loss usually indicate advanced disease, and usually are attributed to concomitant parenchymal metastases. As the symptoms and signs of leptomeningeal metastases are pleomorphic, it is best to conceptualize the potential clinical abnormalities as being localized to the cerebral hemispheres, cranial nerves. and spinal cord and roots.

**CEREBRAL SYMPTOMS AND SIGNS** Common cerebral signs and symptoms are presented in Table 1. Headache is among the most common symptoms, but is usually nonspecific, and may be associated with nausea and vomiting. Severe episodic headache with disturbance of consciousness may be attributed to plateau waves associated with increased intracranial pressure. Gait abnormalities may be related to increased intracranial pressure as well, with the development of a gait apraxia. However, difficulties walking are often ascribed to multiple causes including cerebellar dysfunction, and lower motor neuron radicular involvement. Other common complaints related to cerebral involvement include memory and concentration disturbance, seizures, either focal or generalized, and vertigo or lightheadedness. Common signs caused by cerebral leptomeningeal involvement include papilledema, mental status changes including confusion and dementia, seizures and extensor plantar responses. Some uncommon signs attributable to cerebral dysfunction include central diabetes insipidus due to involvement of the posterior pituitary, or hemiparesis due to parenchymal dysfunction *(29)*. However, significant hemispheric signs usually suggest the coexistence of CNS metastases in addition to leptomeningeal disease.

**CRANIAL NERVE SYMPTOMS AND SIGNS** Common cranial nerve symptoms and signs are listed in Table 2. Cranial nerve abnormalities usually become more prominent as leptomeningeal metastases progress and become more severe. Common findings include abnormalities of ocular movement manifesting as diplopia, facial weakness or asymmetry, hearing loss, and abnormalities of facial sensation. Although diplopia is the most common complaint due to cranial nerve infiltration, examination of ocular motility is often normal. When palsies become apparent, involvement of the abducens nerve is more common than oculomotor or trochlear nerve dysfunction. The development of ophthalmoplegia usually indicates infiltration of the cavernous sinus by tumor. Blindness is a common finding as well, and is due to infiltration of the optic nerve, chiasm, or tracts by tumor. Other common cranial nerve findings include the development of a facial paresis mimicking Bell's palsy, or hearing loss or tinnitus. The occurrence of multiple cranial nerve palsies, particularly if they are bilateral, should suggest the diagnosis of leptomeningeal metastases rather than pathology involving the dura or skull base.

**SPINAL CORD AND ROOT SYMPTOMS AND SIGNS** Spinal symptoms and signs are the most common manifestations of leptomeningeal metastases. Symptoms are referable to either the leptomeninges or nerve roots (Table 3). Symptoms and signs related to spinal meningeal involvement include neck or back pain, sometimes associated with nuchal rigidity. Lumbar puncture with the detection of malignant cells in the CSF distinguishes leptomeningeal metastases from an infectious process. Infiltration of nerve roots frequently presents as weakness, radicular sensory dysfunction, or bowel and bladder dys-

**Table 2**
**Cranial Nerve Symptoms and Signs**

| *Symptoms* | *Signs* |
|---|---|
| Diplopia | Ocular muscle paresis |
| Visual loss | Optic neuropathy |
| Hearing loss | Facial weakness |
| Facial numbness | Hearing loss |
| Tinnitus | Trigeminal neuropathy |
| Hoarseness | Hypoglossal neuropathy |
| Dysphagia | Decreased gag reflex |

**Table 3**
**Spinal Cord and Root Symptoms and Signs**

| *Symptoms* | *Signs* |
|---|---|
| Back/neck pain | Lower motor neuron weakness |
| Radicular pain | Reflex asymmetry |
| Weakness | Dermatomal sensory loss |
| Paresthesias | Straight leg raising |
| Bowel/bladder dysfunction | Nuchal rigidity |

function. Absent deep tendon reflexes are the most common neurologic sign in patients with leptomeningeal metastases, and a cauda equina syndrome with leg weakness, foot numbness, and bowel and bladder impairment is frequently encountered in patients with this complication.

## PATHOLOGY AND PATHOPHYSIOLOGY

Malignant cells can invade the leptomeninges and gain access to the subarachnoid space by a number in mechanisms including:

1. Hematogenous dissemination, by which tumor cells circulating in the blood invade the meninges by first penetrating arachnoid vessels and choroid plexus. Furthermore, tumor cells from metastatic deposits adjacent to the nervous system can also gain access to the subrachnoid space by invading the venous plexus of Batson and by perivenous spread from bone marrow *(30,31)*. This mechanism has been best described in autopsy cases of patients with leukemia, where tumor cells have been observed in the walls of superficial arachnoid veins, the surrounding adventitia, the CSF, and the Virchow-Robin spaces *(32)*.
2. Direct invasion of the meninges and CSF by tumor cells from metastases that are in contact with the meninges (dural, subdural, bony, or intraparenchymal metastases) *(4)*. Such cancer cells can gain access to the subarachnoid space by penetrating the pia or ependyma, or by tracking along perivascular spaces.
3. Perineural migration of tumor cells from systemic metastases to the subarachnoid space. This mechanism has been described as a means by which tumors of the head and neck can produce leptomeningeal metastases.
4. Iatrogenic seeding of the meninges during surgical extirpation of CNS metastases. In particular, this complication has been frequently observed in patients undergoing posterior fossa surgery where cerebellar metastases are resected *(33)*.

The two most common mechanisms by which tumor cells seed the leptomeninges are by hematogenous dissemination or by direct extension from metastatic deposits. Most patients with leptomeningeal metastases have widely metastatic disease, and the meninges are but one site of infiltration. In fact, between 33 and 75% of patients with leptomeningeal metastases have concurrent brain metastases, and between 16–37% have dural metastases *(6,10,17)*. Once malignant cells enter the subarachnoid space, they can form distant meningeal tumor deposits by being carried to distant sites within the neuraxis by CSF flow. The most common sites of tumor deposition include the basal cisterns, the dorsal surface of the cerebral hemispheres, the dorsal surface of the spinal cord, and the cauda equina where the forces of gravity and sluggish CSF flow promote the deposition of suspended tumor cells. Once tumor cells have anchored themselves on the surface of the meninges, they grow, invade the parenchyma of the brain or spinal cord, cranial or spinal nerve roots, and form bulky subarachnoid deposits.

Leptomeningeal metastases can cause symptoms and signs by several mechanisms. CNS dysfunction secondary to the development of hydrocephalus is a common finding. Tumor cells that gain access to the subarachnoid space can cause disruption of normal CSF dynamics by causing obstruction at the fourth ventricle foramina or other sites such as the arachnoid villi. Ventricular pressure is usually elevated, but this may not occur if hydrocephalus develops slowly and causes progressive ventriculomegaly with a trivial increase of CSF pressure. Even in the absence of hydrocephalus, however, CSF flow dynamics as measured by radioisotope flow studies are abnormal in as many as 70% of patients with leptomeningeal metastases *(34)*. Additionally, tumor cells can invade the brain, spinal cord, and roots to cause neurologic symptoms such as seizures, weakness, or sensory dysfunction. The formation of tumor deposits in the spaces of Virchow-Robin can cause compression of arteries and arterioles with consequent ischemia to the underlying parenchyma *(10,35)*. This phenomenon has been observed in cerebral arteriograms of patients with leptomeningeal metastases, and probably accounts for strokes, TIAs, and diffuse encephalopathies that occur in these patients *(10,35)*. Finally, the idea that tumor cells consume vital nutrients, thereby starving surrounding neurons, has given rise to a hypothesis of metabolic competition between tumor and neuronal cells as an explanation for nervous system dysfunction *(36)*. Hypoglycorrhacia is a typical CSF finding in leptomeningeal metastases, but this may not be due entirely to consumption of CSF glucose by metastatic tumor cells and deposits. However, the phenomenon whereby infiltrating tumor cells disrupt the normal functioning of adjacent neurons by consumption of glucose explains the occurrence in hypothalamic leukemia, of patients with leukemic infiltration of the posterior pituitary gaining weight as their only manifestation of hypothalamic-pituitary dysfunction. In this unusual situation, it is believed that tumor cells deprive sugar-sensitive hypothalamic neurons of this vital nutrient, thereby setting into motion a complicated behavioral response that increases food consumption.

## LABORATORY INVESTIGATIONS

The two investigations that are useful for establishing the diagnosis of leptomeningeal metastases are CSF analysis and MR scans of the brain and spine.

**CSF ANALYSIS** CSF analysis, usually from a sample obtained by lumbar puncture, is abnormal in the vast majority of patients with leptomeningeal metastases *(3,6,10,11,17,18,27,28)*. An opening pressure should be obtained and CSF should be submitted for protein and glucose, cell count, and cytology. Opening pressure is elevated in approx 50% of patients with leptomeningeal metastases because of impaired CSF dynamics and attendant hydrocephalus. CSF protein concentrations are often elevated as well, due to disruption of the blood-brain barrier (BBB) by this disorder, and the breakdown of white blood and tumor cells extruded into the CSF. A depressed CSF glucose relative to concurrent serum levels is observed in 30–40% of patients with leptomeningeal metastases. Reasons for this relate to impaired glucose transport across the blood-CSF or BBB, and consumption of this nutrient by proliferating tumor cells, white blood cells, and reactive pial cells.

The identification of neoplastic cells in CSF is diagnostic for leptomeningeal metastases. A positive CSF cytology is found on the initial lumbar puncture in approx 50% of patients with leptomeningeal metastases. The yield of this diagnostic procedure increases to approx 90% of patients if a total of three high-volume lumbar punctures are obtained *(10)*. Diagnostic yield improves if at least 10 cc of CSF are withdrawn. Adding a fixative to the CSF is not necessary, but the specimen should be delivered to the laboratory expeditiously. The specimen should be processed immediately in the laboratory *(110)*. Patients with extensive leptomeningeal infiltration by neoplastic cells are more likely to have a positive cytologic examination than patients with scant and focal involvement of the meninges. For patients with suspected leptomeningeal metastases and an apparent negative CSF cytology, there is little benefit in performing multiple lumbar punctures after the initial three procedures. In a series of patients with leptomeningeal metastases due to systemic solid tumors reported by Wasserstrom, approx 5% of patients had a positive CSF cytology only from samples obtained from the cerebral ventricles or cisterna magna *(10)*. Hence there is a subset of patients with leptomeningeal metastases who will have persistently false-negative CSF cytologic examinations unless CSF is obtained from rostral sites of the neuraxis. Occasionally, patients with extensive infiltration of the meninges by tumor have persistent negative CSF cytologic tests. In this situation, it is believed that tumor cells are highly adherent to the membranes, and rarely exfoliate into the CSF. Glass and associates have emphasized this point in a series of patients who underwent postmortem examination. In their study, 41% of patients with autopsy proven leptomeningeal metastases had negative premortem CSF cytologic examination *(17)*. Some investigators have suggested that CSF is more likely to be positive for malignant cells when the underlying tumor is a carcinoma, but Kaplan and colleagues have reported no difference in CSF cytologic results between patients with carcinomas, leukemias, or lymphomas *(27)*.

A false-positive cytology is an uncommon finding, but can occur in rare situations. Occasionally, cerebral metastases can infiltrate focally adjacent leptomeninges. In this situation, tumor cells can be shed into the CSF, and thereby produce a positive result. In this situation, it may be prudent to treat such patients as if they have active leptomeningeal metastases. Similarly, rare patients with systemic cancers and no neurologic findings have malignant cells identified in the CSF. These patients, although asymptomatic, should probably also receive treatment directed at the leptomeninges. Finally, occasionally reactive or degenerated lymphocytes can be mistaken for neoplastic cells by the cytopathologist *(17)*.

In difficult cases, a number of ancillary diagnostic techniques available to the cytopathologist can be useful. The use of monoclonal antibodies (MAbs) has been combined with routine cytology to increase diagnostic yield *(37–39)*. The use of immunocytochemistry has been employed to improve diagnostic certainty in cases of suspected CNS lymphoma, where the identification of a monoclonal cell population by lymphocyte surface markers and yield the diagnosis of a tumor. However, the demonstration of a polyclonal population of lymphocytes in the CSF does not exclude this diagnosis, as often a malignant CNS lymphoma will stimulate the migration and proliferation of reactive polyclonal lymphocytes.

A variety of tumor markers have been studied in the CSF of patients with suspected and confirmed leptomeningeal metastases as a means of improving the yield of a CSF specimen (Table 4) *(40–42)*. Unfortunately, poor sensitivity and specificity generally limit the use of these markers in the CSF. Tumor markers can be separated into specific and nonspecific. Specific markers such as carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP), β-human chorionic gonadotrophin (βHCG) and monoclonal immunoglobulins elaborated from multiple myeloma are diagnostic of tumor invasion into the CSF compartment when they are identified in a CSF specimen. Occasionally, when serum levels of these specific markers are markedly elevated, false elevations in the CSF can be caused by passage of a tumor marker across a normal or partially disrupted BBB. In this situation, determination of a CSF-serum ratio for a specific marker will help determine whether the CSF concentration is abnormally elevated. CSF levels of specific tumor markers can be useful for determining response to therapy, as they tend to decline with successful treatment, and sometimes rebound at the time of relapse before other findings become evident.

Nonspecific tumor markers such as β-glucuronidase, $\beta_2$-microglobulin, and isoenzyme V of lactate dehydrogenase are frequently elevated in the CSF of patients with leptomeningeal metastases as well as a variety of acute and chronic meningitic processes. The tumor marker $\beta_2$-microglobulin is elevated particularly in leukemias and lymphomas as opposed to solid tumors. If other causes for elevations of these markers, such as infectious or inflammatory meningitis, can be excluded, marked elevations of nonspecific tumor markers can signify the presence of leptomeningeal metastases in an appropriate clinical context. While nonspecific tumor markers are often in the normal range in cases of definite leptomeningeal metastases, these markers can be useful clinically in situations where they are elevated, where serial determinations can be used as adjunctive measures of response to treatment.

The evaluation of DNA abnormalities by flow cytometry has the potential to identify tumor cells that may be missed by conventional cytology. Flow cytometry detects aneuploid cells, as well as estimates the proportion of cells in the S and $G_2M$ phases of the cell cycle, and thus can identify populations of malignant cells *(43)*. This technique appears to be most useful for diagnosing meningeal leukemia and lymphoma where distinguishing malignant cells from reactive ones can be challenging. More recently, investigators have explored the role of fluorescent *in situ* hybridization (FISH) and polymerase chain reaction (PCR) techniques to identify malignant cells in CSF *(44–47)*. Presently these technically challenging and resource intensive tools remain investigational and complimentary to conventional cytology, and are available at only a few research-oriented medical centers.

**CT OR MR IMAGING** Neuroradiographic techniques are assuming increasing importance in the diagnosis of leptomeningeal metastases *(48–54)*. The tools currently employed to assist in the diagnosis of leptomeningeal metastases are cranial computed tomography (CT), magnetic resonance imaging (MRI) of the brain and spine, myelography, and radionuclide CSF flow studies. Contrast-enhanced CT or MR scans of the brain should be obtained in all patients with suspected leptomeningeal metastases and an intracranial mass lesion before lumbar puncture to estimate the risk of cerebral herniation following this procedure. Moreover, scans should be preformed of regions of the neuraxis where the patient is symptomatic.

CT scans are abnormal in 25–56% of patients with leptomeningeal metastases *(51)*. Abnormalities suggestive of leptomeningeal involvement by tumor include enhancement of the meninges, ventricular ependyma, basilar cisterns, tentorium or cauda equina, hydrocephalus, and effacement of sulci or cisterns. Enhancement can appear linear or nodular. Significantly, 30–60% of patients with leptomeningeal metastases will have concurrent brain metastases. Contrast-enhanced MR scans are more sensitive and specific than contrast-enhanced CT scans in revealing abnormalities consistent with leptomeningeal metastases, and have become the diagnostic imaging modality of choice for this disease (Figs. 1 and 2). False-negatives in patients with suspected leptomeningeal metastases can be minimized by repeating MR scans with increased doses of gadolinium *(55)*. These scans require meticulous interpretation by experienced individuals, however, because some enhancement of the meninges and nerve roots is expected *(56)*.

Contrast-enhanced spinal MRI and computerized tomographic myelography are both capable of detecting abnormalities suggestive of leptomeningeal metastases such as nerve root or cord thickening, subarachnoid nodules, scalloping of the subarachnoid membranes, and spinal canal block. A study comparing these two imaging modalities for patients with leptomeningeal metastases by Chamberlain and associates revealed no striking differences in the sensitivity and specificity of these two techniques *(57)*. Consequently, MRI of the spine has become the preferred spine-imaging modality for detecting leptomeningeal metastases at this site because of its noninvasive nature, minimal morbidity, and patient preference. Moreover, the expanding familiarity with characteristic MR features of leptomeningeal metastases has led some authors to suggest that MR scans can be diagnostic in patients with known cancer, multifocal neurologic findings, and characteristic imaging abnormalities *(48)*.

**Table 4**
**CSF Tumor Markers**

| *Specific* | *Nonspecific* |
|---|---|
| Carcinoembryonic antigen | β-microglobulin |
| Human chorionic gonadotrophin (Choriocarcinoma, embryonal cell carcinoma, germ-cell tumor) | β-glucoronidase |
| Alpha-fetoprotein (Teratocarcinoma, yolk sac tumor, embryonal carcinoma, endodermal sinus tumor) | Lactate dehydrogenase |
| CA-125 (Ovarian carcinoma) | |
| CA 15-3 (Breast carcinoma) | |
| Prostate specific antigen (Prostate carcinoma) | |
| Melanin (Melanoma) | |

Recently radionuclide CSF flow studies have been used increasingly for the evaluation of patients with leptomeningeal metastases prior to the administration of regional chemotherapy *(18,34,58–62)*. Radionuclide CSF flow studies provide a reasonable radiographic assessment of CSF flow dynamics, and are abnormal in approx 30–40% of patients with leptomeningeal metastases (Fig. 3). Failure of radionuclide to migrate in a predictable manner following lumbar or ventricular administration of radioimmunoconjugate is defined as a CSF flow block. Typical sites of CSF obstruction include the cisterna magna, spinal canal, and cerebral convexities. Sites of CSF obstruction often but not always correlate with bulky leptomeningeal disease on CT or MR imaging. Chamberlain and associates, who have extensive experience using CSF flow studies in patients with leptomeningeal metastases, have suggested that a significant proportion of patients with no obvious CSF block on conventional imaging will have CSF flow abnormalities that can often be reversed by involved-field radiotherapy *(58)*. In their series, patients who did not experience flow reversal appeared to benefit minimally from intrathecal chemotherapy and had a disproportionately poor survival. While CSF flow studies do predict the distribution of intrathecally administered drug, the role of radionuclide flow studies in the management of patients with leptomeningeal metastases is unclear. It is possible that CSF flow studies are of prognostic significance by virtue of their ability to serve as a sensitive measure of disease burden for patients with leptomeningeal metastases. CSF flow studies may provide the most information for patients without evidence of bulky and extensive leptomeningeal metastases, where abnormal CSF flow studies might predict a poor response to regional chemotherapy and associated risks *(62)*.

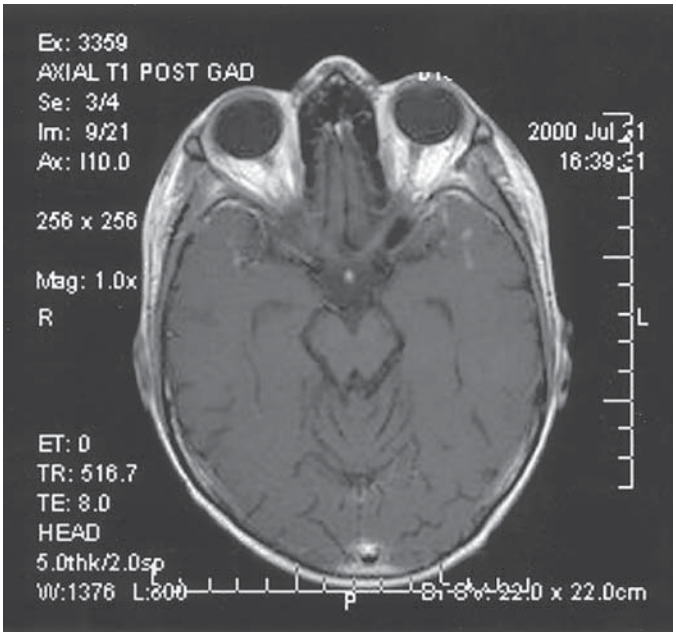


**Fig. 1.** A T1-weighted MR scan with gadolinium contrast discloses abnormal enhancement of the meninges in both anterior temporal lobes. This patient received neuraxis radiotherapy and adjuvant chemotherapy for a medulloblastoma before developing patchy leptomeningeal metastases 4 yr after initial treatment.

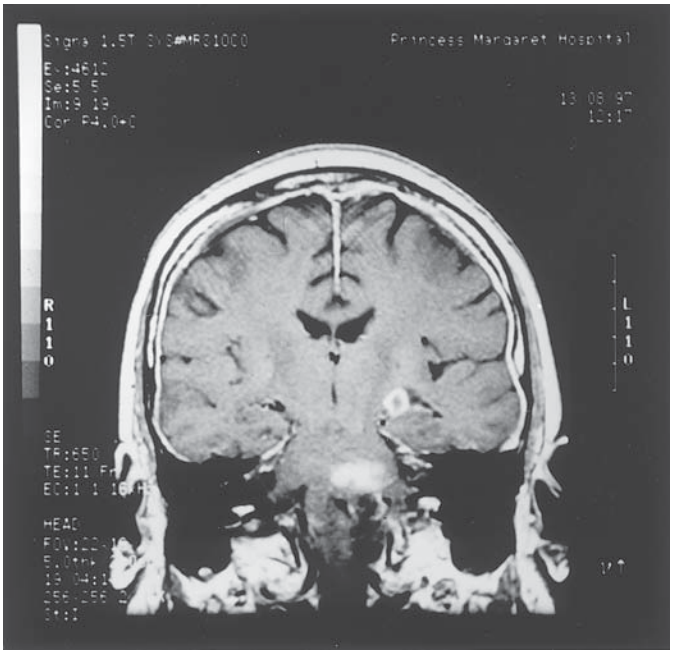


**Fig. 2.** A T1-weighted MR scan with gadolinium contrast shows two parenchymal lesions and diffuse thickening and enhancement of the cerebral leptomeninges. This man developed severe headaches 15 yr after receiving radiotherapy for a pituitary adenoma. An initial MR scan showed only abnormal meningeal enhancement. Meningeal biopsy revealed clumps of neoplastic astrocytes, and a subsequent MR scan confirmed the presence of an underlying high grade glioma, presumably radiation-induced.

## DIFFERENTIAL DIAGNOSIS

Findings suggestive of leptomeningeal metastases in cancer patients are multifocal symptoms and signs, and evidence of meningeal irritation. The differential diagnosis usually is limited to multiple parenchymal metastases of the brain or cord, extensive epidural disease, or an inflammatory or infectious meningitic process *(63)*. Metastatic bulky disease to the brain or spinal cord can be diagnosed by MR or CT scans, and a lumbar puncture with appropriate analysis of CSF including culture can help resolve the possibility of an infection. Typically patients with infections have more meningitic symptoms and signs than fixed neurologic findings. The situation is reversed for patients with leptomeningeal metastases. Occasionally a meningeal biopsy is required to make a definitive diagnosis and exclude other uncommon meningitic processes *(56)*. To maximize the yield of this invasive procedure, the biopsy site should correspond to a site of abnormal enhancement on MR scans.

## STAGING

Patients with suspected leptomeningeal metastases should undergo the following investigations:

1. MRI with gadolinium injection of the area of maximal symptomatology. If leptomeningeal metastases is suspected, and an MR scan of the brain does not reveal leptomeningeal enhancement, an MR scan with gadolinium of the spine should be performed to search for asymptomatic spinal or root involvement. Imaging of the entire neuraxis should be considered and is useful for documenting bulky leptomeningeal disease and parenchymal metastases that are often best treated by focal radiotherapy.
2. Lumbar puncture for CSF analysis. If the initial lumbar puncture is negative for malignant cells, and leptomeningeal metastases is suspected, this procedure should be repeated up to three times over subsequent days or weeks to search for malignant cells. If the CSF remains negative for malignant cells, treatment can be initiated if characteristic MR features of leptomeningeal metastases are noted and not explained by other processes such as meningeal infection, or unquestionably elevated levels of specific tumor markers are found in the CSF.
3. Radionuclide CSF flow studies to establish the presence or absence of CSF flow delays or obstruction should be considered, particularly if intrathecal chemotherapy is planned. If abnormal flow is detected, MRI of sites of CSF flow obstruction should be performed to search for bulky leptomeningeal disease, parenchymal metastases, or epidural tumor. Moreover, radionuclide imaging may be useful for determining prognosis, and to ensure that normal CSF flow dynamics are present before initiating intrathecal chemotherapy.
4. In cases where the diagnosis of leptomeningeal metastases is suspected but all investigations are negative, it may be useful to repeat imaging or CSF analysis several weeks or months later, if symptoms and signs persist. Occasionally asymptomatic patients may have malignant cells identified in a CSF specimen collected for unrelated reasons.

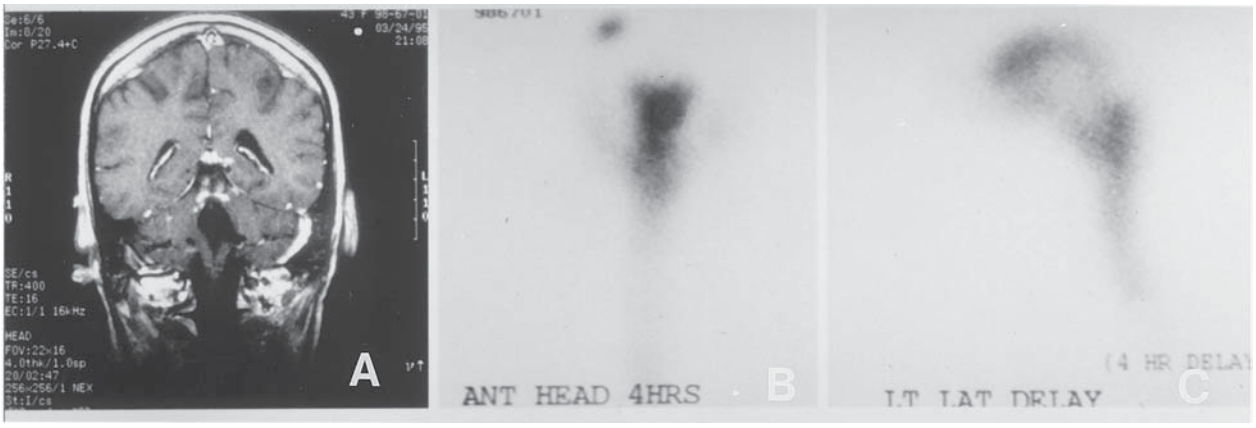


**Fig. 3. (A)** T1-weighted MR scan with gadolinium enhancement reveals abnormal enhancement surrounding a surgical cavity. This woman with breast cancer developed leptomeningeal metastases following resection of a cerebellar metastasis. **(B)** Anteroposterior and (B) lateral $^{111}$Indium-DTPA radionuclide scans performed 4 h after Ommaya reservoir injection revealed a partial CSF flow block at the level of the foramen magnum.

These patients are probably best treated with intrathecal chemotherapy alone. Rarely, patients with no known cancer are found to have focal meningeal enhancement. Such patients, and the rare patient with a known history of cancer, who is found to have an area of unexplained meningeal enhancement, should be considered for a meningeal biopsy. In this instance, the biopsy should be of a site of meningeal enhancement to increase the likelihood of establishing a firm diagnosis.

5. Serial CSF analyses are useful, and samples should be obtained prior to each intrathecal therapy and periodically after treatment is completed if remission is achieved. Serial CSF cytologic evaluations are useful for documenting response to therapy, and for detecting cytologic progression or relapse.

## TREATMENT

The treatment of leptomeningeal metastases must be directed at the entire subarachnoid space including the cerebral ventricles, basal cisterns, and spinal subarachnoid space *(3,6,10,11,27,28)*. The prognosis for patients with untreated leptomeningeal metastases is approx 4–6 wk, and death usually results from progressive neurologic dysfunction. If only areas of symptomatic involvement are treated, progression elsewhere or relapse at treated sites will develop rapidly due to continued growth and ongoing CSF dissemination of cancer cells from untreated tumor deposits. The difficulties associated with delivering treatment to the subarachnoid compartment, and the scarcity of effective chemotherapeutic agents available for treatment of this disorder, frequently results in remissions of short duration and therapeutic failures. Moreover, because patients with leptomeningeal metastases often have widespread and progressive systemic disease resistant to further treatment, the treatment of leptomeningeal metastases is generally considered palliative. Typically, fixed neurologic deficits such as cranial-nerve palsies and radicular weakness do not resolve with therapy, but encephalopathic symptoms can improve, particularly if the underlying cause is hydrocephalus that can be reversed by CSF shunting procedures. Despite the grim prognosis associated with this complication, aggressive multimodal treatment can result in effective palliation and prolonged survival for a minority of patients *(64)*. Patients who are the best candidates for intensive treatments are those with limited and chemosensitive tumors, absent or minimal fixed neurologic deficits, controlled or no systemic disease, and a high performance status *(26,65–67)*. While there are no standard approaches to the therapy of this disorder, the major modalities of cancer treatment, chemotherapy, radiotherapy, and to a lesser degree surgery, play important roles in the management of this illness.

**RADIOTHERAPY** Radiotherapy is the most effective treatment for leptomeningeal metastases, and often produces symptomatic palliation *(52)*. Pain appears to be the symptom most responsive to this modality. External-beam radiotherapy is often administered to symptomatic sites, and to areas of bulky leptomeningeal metastases, even if they are asymptomatic because intrathecal chemotherapy does not penetrate beyond two to three millimeters from the tumor-CSF interface *(68)*. Patients with leptomeningeal metastases and significant symptoms from an area without radiographic evidence of bulky disease should have these areas irradiated to relieve symptoms. Thus, patients with back pain and radicular leg weakness should receive focal radiotherapy to the lumbosacral spine, and patients with cranial neuropathies should receive radiation treatments to the base of the brain. Whole brain radiotherapy is usually reserved for patients with symptomatic hydrocephalus. While treatment schedules vary, patients receiving focal palliative radiotherapy for leptomeningeal metastases usually receive a total of 3000 cGy in 10 fractions.

Leptomeningeal metastases is a disseminated disease, and for this reason occasional patients receive entire neuraxis radiotherapy. This approach, while reasonable from a theoretic perspective, is often highly morbid, not curative, and causes profound myelosuppression to the extent where the prescribed course of radiotherapy cannot be completed, or further systemic chemotherapy for the underlying cancer cannot be contemplated. Furthermore, many patients who develop leptomeningeal metastases cannot receive neuraxis radiotherapy

because of previous treatment to various regions of the CNS for other cancer-related complications. Soluble radioconjugates have been injected into the CSF as a means of delivering neuraxis radiotherapy, but this approach is constrained by the limitations of intrathecal therapy, including impaired CSF distribution and limited parenchymal penetration *(69,70)*. For these reasons, neuraxis radiotherapy is impractical and should not be administered to most patients with leptomeningeal metastases.

Focal radiotherapy usually does not result in neurologic recovery. Exceptional patients are often those with radiosensitive cancers such as leptomeningeal leukemia or lymphoma, or less frequently patients with breast carcinoma. However, even in situations where radiotherapy is effective in eradicating circulating and adherent tumor cells, axonal injury and demyelination caused by tumor infiltration are generally irreversible and limit the extent of clinical recovery. For this reason, early diagnosis of and treatment of leptomeningeal metastases is crucial.

**REGIONAL CHEMOTHERAPY** Intrathecal chemotherapy is the principal medical therapy for patients with leptomeningeal metastases. This approach enhances exposure of leptomeningeal tumor to drug while minimizing systemic toxicity. The subarachnoid compartment can be accessed by lumbar puncture or by the placement of a subcutaneous catheter and reservoir (Ommaya reservoir) into the lateral ventricle. The insertion of an Ommaya reservoir is a minor surgical procedure associated with minimal morbidity when performed by an experienced neurosurgeon *(71,72)*. The most common complications include misplacement of the catheter tip, infections, and rarely intracranial hemorrhage. A postoperative CT scan can confirm the correct placement of a catheter, and the risk of hemorrhage can be minimized by careful attention to preoperative coagulation parameters. Infections associated with Ommaya reservoirs are usually due to skin flora and primarily *Staphylococcus epidermidis*, and can usually be managed with intravenous and intraventricular antibiotics, thereby obviating the need to remove the device. Most clinicians prefer to instill intrathecal chemotherapy via an Ommaya reservoir for a variety of reasons:

1. Repeated lumbar punctures are uncomfortable, and cannot be performed safely when thrombocytopenia or a coagulation disorder is present. Ommaya reservoirs can usually be accessed even if a bleeding tendency is present. Repeated lumbar punctures increase the risk of post-LP headache and intracranial hypotension. The latter can result in diffuse meningeal enhancement, which can be mistaken radiographically for progression of leptomeningeal disease.
2. Administration of drug into the subarachnoid space is assured when an Ommaya reservoir is used, but as many as 10–15% of lumbar punctures do not succeed in injecting drug into the lumbar subarachnoid space *(73)*. Repeated lumbar punctures often result in the formation of subdural and epidural fluid collections, which can interfere with the accurate installation of drug if continued lumbar punctures are performed *(74)*. Additionally, fluid sampled from these iatrogenic fluid collections is not representative of circulating CSF and thereby cannot be used to monitor treatment response.
3. Even when lumbar punctures succeed in the accurate injection of drug into the subarachnoid space, the common occurrence of impaired CSF flow and obstruction found in this disorder may result in incomplete distribution of drug throughout the subarachnoid compartment *(34,60,62)*. Furthermore, the use of an Ommaya reservoir ensures that the ventricular system receives adequate concentration of drug, which may not occur following lumbar injection, even if CSF dynamics are normal *(75)*. Consideration should be given to the use of radionuclide flow studies prior to the commencement of intrathecal chemotherapy because sites of impaired flow can often be corrected by focal radiotherapy.
4. There is evidence to suggest that intrathecal chemotherapy delivered by an Ommaya reservoir is more effective than by lumbar puncture *(76)*.

The agents widely available for intrathecal injection are methotrexate, cytarabine, and thioTEPA. Methotrexate and cytarabine have activity against leukemia and lymphoma, and thioTEPA and methotrexate have activity against breast carcinoma, but other common solid tumors such as melanoma and lung cancer are resistant to these agents. Consequently the limited spectrum of activity conferred by these drugs accounts in part for the modest therapeutic efficacy of intrathecal chemotherapy. A number of investigational agents such as temozolomide, topotecan, 4-hydroperoxycyclophosphamide, interferon (IFN), and interleukin-2 (IL-2) have been evaluated, but only in research settings and are thus not widely available *(77)*. Methotrexate is the most frequently used agent, and a therapeutic level of at least 1 μm can be achieved for 48–72 h in the CSF by administering a dose of 12 mg *(3,73,78,79)*. There is no need to reduce this dose for children over age 4 because the subarachnoid space reaches its adult volume by this age *(80)*. Most clinicians administer drug initially on a twice-weekly schedule for 3–4 wk, followed by a reduction in frequency over a total treatment period of 3–6 mo. The most effective duration of treatment is not established, and some patients appear to benefit from indefinite treatment. Alternative treatment schedules have been devised, most notably a "concentration times time" schedule where methotrexate is administered initially at a dosage of 2 mg for five consecutive days every 2 wk *(81–83)*. While this approach has the theoretical advantage of increasing the duration over which drug levels in the CSF are therapeutic, it is very labor-intensive, and has not been demonstrated to be superior to conventional treatment schedules. Methotrexate is absorbed into the systemic circulation by the bulk flow of CSF or by the choroid plexus. Administering folinic acid on the day following treatment for a total of 3 d can minimize common systemic toxicities such as myelosuppression and mucositis. Because folinic acid does not penetrate the BBB to a significant degree, the administration of this antidote does not interfere with the efficacy of metotrexate in the CSF.

Cytarabine is a common alternative to methotrexate, particularly for patients with hematogenous malignancies, and is used commonly following methotrexate failure *(84,85)*. This drug is administered initially at a dosage of 50 mg twice weekly and tapered in a manner similar to that of methotrexate. The

recent availability of a liposome-encapsulated cytarabine formulation (DepoCyt) that can be administered once every 2 wk may simplify treatment for patients receiving this drug *(86)*. Cytarabine is rapidly metabolized in the systemic circulation, but in the CSF its half-life is prolonged due to the absence of cytidine deaminase in the CNS. DepoCyt produced a 71% cytologic response rate in patients with leptomeningeal lymphoma, as compared to 15% for cytarabine *(111)*. Additionally, treatment with DepoCyt was associated with a statistically significant improvement in KPS. However, despite this impressive difference, improvements in time to neurologic progression and survival were less impressive and not significant statistically. A study describing the experience in solid-tumor LMD suggested DepoCyt significantly prolonged time to neurologic progression but not overall median survival *(112)*. The fewer administrations required with DepoCyt provide an advantage over convention cytarabine, but further studies of effectiveness and cost-effectiveness with clinically relevant endpoints are needed.

Some clinicians prefer to alternate methotrexate with cytarabine, but there is no evidence to support the superior efficacy of multiple agents over a single intrathecal drug *(87–89)*. ThioTEPA is rapidly cleared from the CSF after a standard dose of 10 mg, usually administered twice a week *(79,90)*. For this reason, and because this prodrug requires hepatic activation, its efficacy is questioned. Nonetheless, responses have been documented, and this drug is a common treatment, particularly for patients with meningeal metastases from breast cancer. Occasionally patients receiving intrathecal chemotherapy develop an aseptic chemical meningitis characterized by fever, headache and a neck pain, nausea, and vomiting and photophobia following treatment. This side effect can be ameliorated by the use of dexamethasone for a few days following drug administration. Late neurotoxicity manifested by the development of a leukoencepalopathy is a risk for patients receiving methotrexate and cytarabine, particularly if whole-brain irradiation is also administered *(91–93)*. It develops months after the initiation of therapy, is irreversible and manifested by a progressive dementia, ataxia, and sphincteric incontinence.

**SYSTEMIC CHEMOTHERAPY** The management of leptomeningeal metastases rarely involves systemic chemotherapy because most agents do not penetrate the BBB in sufficient concentration when administered systemically. Furthermore, the interval between systemic treatment necessary for bone marrow recovery usually results in inadequate exposure interval in the CSF. However, in patients with leptomeningeal metastases, the BBB is disrupted, and adequate drug levels within the CSF can sometimes be attained after systemic administration *(94–99)*. A potential advantage of systemic chemotherapy is the ability of this approach to reach all regions of the subarachnoid space. Furthermore, bulky leptomeningeal metastases that would not be treated effectively by intrathecal chemotherapy may respond to drugs that can penetrate the tumor via the circulation.

Agents that can be used systemically for leptomeningeal metastases include lipophilic drugs such as thioTEPA, or chemotherapies such as methotrexate and cytarabine, which can safely be administered systemically at high concentrations such that sufficient drug penetrates the subarachnoid space to create therapeutic CSF levels. Meningeal leukemia and lymphoma have been treated effectively in this way, but managing leptomeningeal metastases from solid tumors has proven more challenging, in part because of drug resistance few chemotherapeutic choices. However, Siegal and associates have had promising preliminary results substituting for intrathecal chemotherapy and thereby avoiding its complications for selected patients with leptomeningeal metastases from solid tumors, suggesting that this approach is worthy of further investigation *(100,101)*.

**SURGERY** Surgery plays a very limited role in the management of leptomeningeal metastases. The most common surgical procedure performed in this group of patients is the placement of an intraventricular catheter with a subgaleal reservoir (Ommaya reservoir) to facilitate the administration of intraventricular chemotherapy. This procedure is usually uncomplicated, and this device can usually be accessed frequently with rare complications.

Patients with symptomatic hydrocephalus are occasionally candidates for CSF diversion via a ventriculoperitoneal shunt. Symptomatic hydrocephalus includes patients with intractable headaches, papilledema with threatened visual loss, impaired mentation or consciousness, and recurrent plateau waves. Such patients can sometimes be managed with steroids and whole-brain or base of brain radiotherapy, but many eventually require shunt placement. The placement of a shunt is one of the most effective palliative treatments for patients with leptomeningeal metastases, and results in rapid resolution or improvement of symptoms due to increased intracranial pressure.

Following shunting, intrathecal chemotherapy becomes problematic, and can be administered only if a catheter with an on-off valve has been inserted. This device allows the instillation of drug into the ventricle when the valve is in the off position, thereby preventing reflux of injected drug into the catheter and eventually the peritoneal cavity. However, in patients with hydrocephalus, CSF flow is markedly disturbed, and drug injected when the valve is in the off position usually sits in the ventricle, and does not reach most of the subarachnoid space. Furthermore, drug often penetrates the ventricular ependyma, eventually causing neurotoxicity if administration is repetitive. Finally, many patients with symptomatic hydrocephalus cannot tolerate having the shunt turned off for several hours, and shunts with on-off valves are cumbersome to use and frequently malfunction. For these reasons, it may be best to avoid intrathecal chemotherapy for patients who require CSF diversion.

## PROGNOSIS

The prognosis for most patients with leptomeningeal metastases is poor. Untreated patients usually succumb to their illness within 6–8 wk from their initial diagnosis *(6,7)*. Despite an extensive literature documenting treatment approaches in usually small series of often-disparate patients with leptomeningeal metastases, there is no standard approach to management. Even with aggressive treatment, the average survival for most patients with leptomeningeal metastases from solid tumors is in the range of 4–6 mo *(102)*. Therapy is unlikely to

improve neurologic disability and symptoms other than pain. However, treatment can stabilize or improve up to 75% of patients for a period of time, and for this reason treatment is often offered *(26,58,103)*. Furthermore, treatment can often preserve quality of life for weeks to months for these patients. Treatment can also result in improvement of CSF abnormalities, with disappearance of malignant cells, reduction in tumor marker levels and normalization of CSF glucose and protein concentrations.

Selection of appropriate patients for aggressive therapy is often based on a number of prognostic factors that appear to predict survival. Favorable prognostic factors include good performance status, minimal neurologic symptoms and signs *(60)*, the absence of bulky leptomeningeal disease, parenchymal CNS metastases or epidural cord compression, limited systemic disease, and a chemosensitive tumor *(26,65,102,104)*. Recently radionuclide CSF flow studies have been used to predict response to therapy and survival, and should be considered for patients who are to receive intrathecal chemotherapy *(60,62)*.

Patients with leptomeningeal leukemia and lymphoma have the best prognosis, and should be treated aggressively *(5,76,105)*. Intrathecal methotrexate and cytarabine can eradicate these tumor cells from the CSF. The recent DepoCyt studies suggested a cytologic response rate of approx 71% compared to only 20% for LMD from solid tumors *(111,112)*. Patients with hematologic malignancies producing LMD can remain in a sustained remission for months to years following early and intensive therapy. Of solid tumors, breast cancer appears to have the best prognosis, with Ongerboer de Visser and associates reporting a 1-yr survival of 25% for patients receiving intensive intraventricular chemotherapy *(103)*. Moreover, a minority of patients with leptomeningeal metastases for breast carcinoma can have indolent disease that can be controlled with therapy for 2 yr or more. Patients with leptomeningeal metastases from small cell lung cancer sometimes respond to therapy, and also should be considered for treatment *(106,107)*. The prognosis for patients with leptomeningeal metastases from nonsmall cell lung cancer, other adenocarcniomas, and melanoma is so poor that many investigators have seen little justification for aggressive therapy *(102)*.

## FUTURE DIRECTIONS

Leptomeningeal metastases has become a well-described and increasing recognized complication of cancer. Recent advances in diagnostic radiology have increased the ability of the clinician to make this diagnosis and to make therapeutic decisions. The incidence of this disorder will continue to rise as treatments for systemic cancer become more effective. Unfortunately, the prognosis for this illness remains grim even for patients who receive aggressive multimodal therapy. Reasons for our failure to make a significant impact on the course of this disease are multiple, and include limited therapeutic choices, the challenge of having to treat the entire subarachnoid compartment, the development of drug resistance, progressive systemic and CNS parenchymal disease, the limited capacity of patients to tolerate further treatment, and toxicity of available therapies.

Although leptomeningeal metastases has been the focus of numerous clinical studies, no therapy has emerged as a standard treatment for this disorder. Indeed, the overall efficacy of common treatments such as intrathecal methotrexate has been called into question in recent years, and several investigators have suggested that intrathecal chemotherapy has no convincing role to play in this disorder *(100)*. Provocative reports suggesting that systemic chemotherapy can result in clinical outcomes no different from treatments using intrathecal chemotherapies suggest that systemic chemotherapy may have a more important role in this disorder. For consensus to be reached on several key therapeutic dilemmas, future studies will need to select carefully appropriate and homogeneous study populations, and define rigorous response criteria. Given the limited efficacy of therapeutic choices at present, future studies should focus on identifying subsets of patients who could benefit from the limited available therapies. Recent evidence suggests that patients with epidural cord compression, CNS metastases, and bulky leptomeningeal disease have poor outcomes, but more work is required to identify reliable prognostic factors. Radionuclide ventriculography appears to have promise here as a clinical tool for evaluating prognosis.

Further clinical and laboratory research is sorely needed to improve the outcome of this devastating complication of cancer. There is a desperate need for new and better therapies. Agents in development for possible intrathecal administration include temozolomide, mafosfamide, and topotecan *(77)*. It is likely that liposomal cytarabine will be of increasing use for patients with leptomeningeal leukemia and lymphoma. Furthermore, novel approaches using immunotoxins and gene therapy, although in preclinical or early clinical development, have shown encouraging results in animal models, and hold promise as emerging future *(108)*. Further research is required on the mechanisms whereby conventional therapies cause neurotoxicity. The mechanisms whereby intrathecal chemotherapy and radiotherapy cause neurologic dysfunction remain poorly understood *(109)*. A better understanding of how treatments cause nervous system damage may yield improved and less toxic therapies. Unfortunately, most patients with leptomeningeal disease die quickly of progressive leptomeningeal or systemic cancer; significant advances in the prognosis of this disorder await the development of more effective and less toxic drugs, and improved drug-delivery systems.

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# 11 Neuromuscular Disease and Its Complications

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## INTRODUCTION

A variety of neuromuscular disorders often lead to significant motor disability or even death in cancer patients. Therefore, timely recognition and aggressive management of these complications is essential not only for the patients' quality-of-life, but also for their survival.

Neuromuscular dysfunction in cancer patients occur as a result of: (1) infiltration or compression of neuromuscular elements by metastatic neoplastic cells; (2) side effects of anticancer treatment, i.e., radiation, chemotherapy, and steroids; (3) metabolic and nutritional disturbances; (4) infections; or (5) remote (paraneoplastic) effects of the systemic malignancy. By far, the most common etiology is treatment-related.

## ANATOMICAL COMPONENTS OF THE PERIPHERAL NEUROMUSCULAR SYSTEM

Patients with neuromuscular disease generally present with weakness, sensory disturbance, or autonomic dysfunction. Basic anatomical components of the neuromuscular axis include the anterior horn cell, dorsal root ganglion, dorsal and ventral nerve roots, plexus, peripheral nerve (motor and sensory), neuromuscular junction, and muscle. Accurate diagnosis of various neuromuscular disorders requires precise anatomical localization. Disorders of the anterior horn cell, neuromuscular junction, and muscle produce pure motor symptoms. Deep tendon reflexes are commonly preserved in these disorders unless the weakness is severe. Hyporeflexia or areflexia suggests neuropathy. The major anatomic subtypes and etiologies of neuromuscular disease in cancer patients are listed in Table 1.

## MOTOR NEURON DISEASE

**PARANEOPLASTIC MOTOR NEURON DISEASE** Amyotrophic lateral sclerosis (ALS) has been reported in patients with ovarian carcinoma *(1)*, lymphoma *(2,3)*, pancreatic adenocarcinoma *(4)*, thymoma *(5)*, breast *(6)*, small cell bronchogenic carcinoma *(7)*, and renal cell carcinoma *(8)*. Rarely, patients with ALS improve substantially or stabilize with treatment of the underlying cancer, and in this very small subset of the ALS population, the disease may be paraneoplastic *(9)*.

A causal relationship probably exists between Hodgkin's disease and subacute motor neuronopathy, the symptoms and signs of which may be mistaken for ALS *(2,3)*. This condition is subacute, progressive, painless, and often asymmetric with legs more involved than arms. The neurologic syndrome tends to stabilize or improve over months to years and is rarely severely debilitating *(3)*. Upon pathological examination, there is loss of neurons in the anterior horn and Clarke's column, as well as demyelination of anterior roots and posterior columns *(3)*.

A slowly progressive amyotrophy, with greater involvement of the arms than of the legs, due probably to inflammatory changes in the anterior horn cells has been described in anti-Hu seropositive patients with paraneoplastic limbic encephalitis (*see* Chapter 13) *(8,9)*. In most patients with paraneoplastic encephalomyelitis, motor neuron signs are accompanied by abnormal findings referable to other areas of the nervous system. Thus ALS per se is not generally a part of paraneoplastic encephalomyelitis, although motor weakness is occasionally the first neurologic symptom and motor neuron dysfunction is prominent in about 20% of patients with the anti-Hu antibody *(10)*.

Several anti-neural antibodies, including anti-Yo *(1)* and anti-Hu *(7)*, have been implicated in the pathogenesis of paraneoplastic motor neuron disease. Whether motor neuron-like disease in patients with cancer is the result of preferential antibody-mediated damage to the anterior horn cells alone, or in combination with other immune mechanisms, remains to be clarified. Paraproteins (11), $GM_1$ and $GD_{1b}$ gangliosides *(12)*, and cytotoxic T cells *(13)* have all been linked to motor neuron disease.

It has been suggested that the presence of paraproteinemia in a patient with motor neuron-like disease increases the likelihood of the presence of an underlying malignancy, lymphoma

From: *Cancer Neurology in Clinical Practice* (D. Schiff and P. Y. Wen, eds.), © Humana Press Inc., Totowa, NJ.

**Table 1**
**Anatomic and Etiologic Subtypes of Neuromuscular Diseases in Cancer Patients**

| *Anatomic site* | *Disease* | *Etiology* |
|---|---|---|
| Anterior horn cells | ALS-like motor neuron disease | Postirradiation |
| | Lower motor neuron (LMN) disease | Paraneoplastic |
| Dorsal root ganglia | Neuronopathy | Drug-induced (cisplatin) |
| | (Ganglionitis) | Paraneoplastic |
| Nerve roots | Radiculopathy | Neoplastic |
| | Postirradiation | |
| | Infectious (Herpes zoster) | |
| Plexi | Plexopathy | Neoplastic |
| | | Radiation-induced |
| Peripheral nerves | Neuropathy | Chemotherapy-induced |
| | | Paraneoplastic |
| | | Paraproteinemia |
| | | Neoplastic |
| Neuromuscular junctions | Myasthenia Gravis | Paraneoplastic |
| | Lambert-Eaton Syndrome | |
| Muscles | Myopathy | Drug-induced (steroids) |
| | Myositis | Paraneoplastic |

in particular *(14)*. Similarly, elevated CSF protein or the presence of oligoclonal bands or paraneoplastic antibodies in a patient with known malignancy and motor neuron-like disease suggest a paraneoplastic etiology *(8,14)*. However, it is still important to exclude other disorders, such as leptomeningeal polyradiculopathy, neoplastic plexopathy, and Guillain-Barré syndrome, before arriving at the diagnosis of paraneoplastic motor neuron disease.

**POST-IRRADIATION MOTOR NEURON DISEASE** Several authors have proposed that radiation to the spinal cord can lead to selective anterior horn cell injury *(15–17)*. A predominantly motor syndrome, characterized by slowly progressive asymmetric lower motor neuron weakness of the legs and less often of the arms, has been described 3–25 yr after irradiation of the spine *(15,16,18–22)*. However, others believe that the underlying damage predominantly involves the motor roots proximal to the dorsal root ganglia, and that the syndrome is instead a radiculopathy *(18,23)*. A more complete discussion can be found in the radiculopathy section.

## NEURONOPATHY

In addition to subacute motor neuronopathy described previously, a paraneoplastic syndrome of purely sensory polyneuropathy, subacute sensory neuronopathy, has been described in cancer patients *(24–26)* that is associated with the presence of anti-Hu antibodies *(25,27)*. In the vast majority of patients, the associated tumor is a small cell lung carcinoma, but an association with breast, gynecological, and gastrointestinal cancer also exists *(13,25–27)*.

Clinically, the syndrome is characterized by numbness or painful paresthesias that spread proximally to involve the trunk, face, and scalp. In a matter of weeks to months, areflexia and diminution of all primary sensory modalities including vibration and proprioception results in severe gait ataxia and pseudoathetoid movements of the limbs *(24,28)*. Muscle strength tends to be preserved, except for some degree of muscle wasting. Autonomic dysfunction is common and can be fatal *(29)*.

Histopathological studies are consistent with a ganglionitis *(30)*. Dalmau et al. *(10)* proposed that the paraneoplastic dorsal root ganglion disease is simply a manifestation of a more widespread inflammatory encephalomyelitis in >50% of patients. Most patients with sensory neuronopathy die within months of onset regardless of treatment modality *(10)*. However, spontaneous neurological improvement in some cases has been reported *(13,31)*.

The differential diagnosis of the subacute sensory neuronopathy syndrome includes hereditary sensory neuropathies, pyridoxine abuse, cisplatin toxicity, HIV, and Sjögren's syndrome *(25,26,32,33)*. Anti-Hu testing is useful in distinguishing carcinomatous sensory neuronopathy from these other etiologies since it is almost always associated with paraneoplastic dysfunction when present in high titers *(27,34)*.

## RADICULOPATHY

**LEPTOMENINGEAL RADICULOPATHY** Leptomeningeal carcinomatosis frequently involves multiple nerve roots (Fig. 1), resulting in a polyradicular syndrome that often mimics sensorimotor polyneuropathy. Occasionally, leptomeningeal metastasis can cause isolated single nerve root involvement, i.e., monoradiculopathy *(35)*. Signs and symptoms result from injury to the nerve roots as they traverse the subarachnoid space, invasion of nerve roots by tumor cells, and alterations in nerve blood supply and metabolism *(36,37)*.

Clinically, there is radicular pain, dermatomal sensory loss, areflexia, and weakness of the lower motor neuron type. Associated findings such as headache, nuchal rigidity, and/or cranial neuropathies are variably present, but their presence provides clues to accurate diagnosis.

The diagnosis is most commonly established by lumbar puncture. Detection of malignant cells on cytologic examination of the cerebrospinal fluid (CSF) is the diagnostic gold standard. Other diagnostic hallmarks in the CSF are low glucose and elevated protein content. However, CSF cytology can be persistently negative in 10% of patients with leptomeningeal

**Fig. 1.** Leptomeningeal carcinomatosis. Seeding of multiple nerve roots (cauda equina) by adenocarcinoma produces a nodular appearance. (Courtesy of Dr. T.W. Smith, M.D., Department of Pathology [Neuropathology], University of Massachusetts Medical Center, Worcester, MA.)

disease *(36,38,39)*. Radiological studies may provide additional supportive evidence in patients with suspected leptomeningeal disease. Contrast enhancement of the meninges or nerve roots and subarachnoid masses can be detected with magnetic resonance imaging (MRI) while myelography may reveal nodular masses on the nerve roots or a CSF blockage. Prolonged F-wave latencies or absent responses on nerve conduction studies are indicative of nerve root involvement and should raise the suspicion for leptomeningeal disease in cancer patients *(40)*.

**POST-IRRADIATION POLYRADICULOPATHY** A rare lower motor neuron-like syndrome of the lower extremities has been described following irradiation of the the para-aortic region (thoraco-lumbar spine T10-L4) and cauda equina *(17,19–21,41,42)*. It most commonly occurs when the total irradiation dose exceeds 40 Gy *(18,42)*. The latency between the completion of radiation therapy and onset of symptoms can be quite variable (6 mo–23 yr), but is often prolonged (6–10 yr) and appears to be inversely proportional to the radiation dose.

Clinically, most patients present with progressive ascending leg weakness, occasionally accompanied by mild sensory and sphincter symptoms. The weakness is often asymmetric, painless, distal, and beyond the territory of a single root or peripheral nerve. It can be monomelic initially. Amyotrophy, cramps, and fasciculations may be seen *(21)*. The sensory deficits are often subtle at presentation, but are invariably present at some point during the course of the illness. Interestingly, most patients have diminished deep tendon reflexes in the legs at presentation. Sphincter disturbances are absent at presentation, but mild dribbling and occasional incontinence may develop years after the onset of the motor symptoms.

The lack of significantly detectable sensory and sphincter dysfunction at presentation led many to believe that the underlying damage is in the anterior horn cells *(17,21,41)*, or proximal motor roots *(21,43)*. However, pathologic studies revealed fibrosis of nerve roots, compression by clusters of dilated thickened vascular channels, and prominent hyalinization of the small arterioles in the cauda equina area *(18)*. Electrophysiological studies also point to an abnormality at the level of the cauda *(18,23,44)*. The term "postirradiation lumbosacral radiculopathy" or "postirradiation cauda equina syndrome" is therefore a better descriptor of this syndrome *(18,23)*.

The differential diagnosis of postirradiation polyradiculopathy includes leptomeningeal radiculopathy and plexopathy. The presence of pain should raise the suspicion for a direct effect of cancer. CSF analysis is usually nonspecific, notable only for slight elevation of protein content with no pleocytosis and normal cytology. MRI may demonstrate linear and focal gadolinium enhancement of the affected roots. Electromyography may be particularly helpful in differentiating postirradiation lumbosacral radiculopathy from plexopathy. Preservation of sural sensory nerve action potentials, prolonged F-wave latencies, and/or paraspinal muscle fibrillations are suggestive of a radiculopathy. Myokymia, thought to be a marker of radiation-induced plexopathy, does not appear to distinguish postirradiation plexopathy from radiculopathy *(18,20,23)*.

The syndrome follows a slowly progressive course, although 1–2 yr periods of relative remission may occur. The best available treatment is preventative, i.e., substituting chemotherapy for radiotherapy in treating testicular cancer or using the lowest effective radiation dose (30–35 Gy) in more fractions if possible. Anecdotal evidence suggests that anticoagulation may be of some therapeutic benefit.

**HERPES ZOSTER RADICULOPATHY** Following a primary infection with chickenpox, varicella-zoster (VZ) virus remains dormant in the dorsal root ganglia along the entire neuroaxis *(24,45)*. Herpes zoster infection occurs as a result of subsequent reactivation of the dormant VZ virus. The biologic mechanisms underlying viral reactivation are yet to be identified. Immunosuppression and advancing age appear to play a role *(46)*. Herpes zoster virus (HZV) infection occurs in up to 10–25% of cancer patients compared to less than 5% in immunocompetent ones *(47)*. It is particularly common in those with lymphoma and who have received radiation therapy or immunosuppressive drugs.

Pathologically, HZV infection is characterized by inflammation of the cranial and/or spinal nerve dorsal root ganglia as well as adjacent nerve roots and peripheral nerve(s). Meningoradiculo-myelitis can also be present *(48)*.

Clinically, zoster infection usually causes a painful dermatomal vesicular rash. Segmental sensory loss and weakness may occasionally be present. Fever, malaise, and pain or dysesthesia along the involved dermatome often herald the eruption of HZV by 2–4 d. The pain often has a superficial tingling or lancinating quality and usually is associated with mild itching and allodynia. Occasionally, however, the pain may be sharp and deeply localized, mimicking cholecystitis, appendicitis, or pleuritis *(49)*. The rash rapidly progresses from small red macules to tense vesicles on an erythematous base to dry crusts within 5–10 d. Although the distribution of the cutaneous lesions often corresponds to sensory nerve dermatome(s), a generalized confluent rash is not uncommon in cancer patients. Almost two–thirds of all skin lesions occur along the thoracic dermatomes, particularly T5–T10. Most of the remaining one-third involves sensory branches of cranial nerves and craniocervical regions. This corresponds to the predominant localization of viral DNA in the thoracic and trigeminal ganglion cells *(45)*. Zoster meningoradiculitis can also occur in immunocompromised patients without skin involvement *(50)*.

Motor function may also be affected along the involved cervical, thoracic, or lumbar dermatomal segments, resulting in unilateral diaphragmatic paralysis, weakness of intercostal muscles, focal limb weakness, and bowel and bladder dysfunction *(4,46)*. Focal asymmetric peripheral weakness, "segmental zoster paresis," may occur in the limb affected by cutaneous zoster in 3–5% of patients *(51,52)*. Limb weakness is thought to be due to involvement of the ventral nerve root in proximity to the initiating dorsal ganglionitis.

A regional form of myelitis, characterized by asymmetrical paraparesis, sphincter disturbance, and a sensory level, has been described in association with involvement of the thoracic dermatomes in immunocompromized patients *(53)*. It often is progressive and can sometimes be fatal. Pathological features are consistent with necrotizing myelitis and vasculitis involving the dorsal horn. Long-term use of steroids may predispose patients to this rare complication of zoster infection *(54)*.

Since Herpes zoster produces a radicular distribution of pain with or without sensorimotor deficits, it should be included in the differential diagnosis of radiculopathy. Zoster-related radiculopathy usually can be easily diagnosed when rash is present. Finding multinucleated giant cells with intranuclear inclusions in Giemsa-stained scrapings or fluorescent Varicella-zoster antibody staining from the base of the vesicles confirms the diagnosis. Before the development of the rash, however, the diagnosis may be in doubt, especially if motor symptoms and signs predominate, thus mimicking other spinal disorders *(55,56)*. The CSF is often nonspecific, frequently showing mild lymphocytosis and a slight increase in protein content. The electrophysiological findings in segmental zoster paresis are nondiagnostic. MRI of the spine may reveal a T2 hyperintense cord lesion and/or enhancement of the nerve root(s) and leptomeninges, suggesting a meningoradiculitis. Polymerase chain reaction (PCR) to detect Herpes zoster DNA antigen and testing for antibodies against its membrane antigen in the CSF are useful tools to establish early diagnosis *(46)*.

Although most patients with HZV infection will recover uneventfully, the prognosis is more guarded in immunocompromised patients. Therefore, a 10 d course of intravenous acyclovir is strongly recommended to minimize zoster dissemination. In those who fail to respond to intravenous acyclovir, a trial of VZ immune globulin (VZIG) is warranted. Corticosteroids should not be used in the immunocompromised patient because of the increased risk of cutaneous and visceral dissemination.

Immunocompromised patients are also prone to develop persistent pain even after the acute infection has subsided (postherpetic neuralgia). The management of this sequela can be extremely challenging. Capsaicin ointment, tricyclic antidepressants, phenothiazines, gabapentin, phenytoin, and carbamazepine, alone or in combinations, have variable effects in ameliorating the pain and dysesthesia in individual patients.

## PLEXOPATHY

**NEOPLASTIC BRACHIAL PLEXOPATHY** Neoplastic infiltration of the brachial plexus is most often metastatic in nature. The most common implicated primary tumors are those from the lung, breast, and systemic lymphoma; sarcoma and melanoma are less common. Lymphatic spread from these tumors to the axillary lymph nodes leads to involvement of the adjacent brachial plexus. The divisions of the lower trunk, lying in close proximity to the lateral group of axillary lymph nodes, are most commonly involved (Fig. 2). The upper trunk and its divisions are remarkably free of lymph nodes *(57)*, and are seldom involved in metastatic plexopathy. This generalization, however, is not reliable since some patients have signs indicating pan-plexus involvement.

Clinically, the hallmark of neoplastic plexopathy is pain. The pain is often severe, located in the shoulder girdle with radiation to the elbow, medial forearm, and fourth and fifth digits. Neurologic examination often reveals weakness and sensory changes in the distribution of the lower trunk and its divisions. There is weakness and wasting of the small muscles of the hand, weakness of long finger flexors and extensors, claw hand deformity, and impaired sensation over the inner aspect of forearm and ulnar border of the hand. Involvement of the first thoracic root, which lies in close proximity to the inferior cervical sympathetic ganglion, may result in a Horner's syndrome in more than half of the patients. Lymphedema of the affected arm is not uncommon.

Neurological symptoms and signs of neoplastic brachial plexopathy are insidious in onset. Reflex sympathetic dystrophy of the upper limb may occur 4–6 mo before the development of neurological deficits or detection of a neoplastic process involving the axilla *(58)*. Brachial plexopathy is usually not the presenting feature of malignancy, except in Pancoast's syndrome *(59,60)*, in which an apical lung carcinoma directly invades or compresses the lower trunk. The syndrome described by Pancoast is not a plexopathy per se, but rather results from neoplastic invasion of C8 and T1–T3 spinal roots, sympathetic chain and stellate ganglion, first three ribs, and borders of the vertebral bodies (C7–T3) (Fig. 3).

Distinguishing neoplastic plexopathy from idiopathic or postirradiation plexopathy can sometimes be difficult. The presence of lymphedema and insidious onset of symptoms and signs may help differentiating malignant from idiopathic plexopathy. Neoplastic plexopathy is more likely than radia-

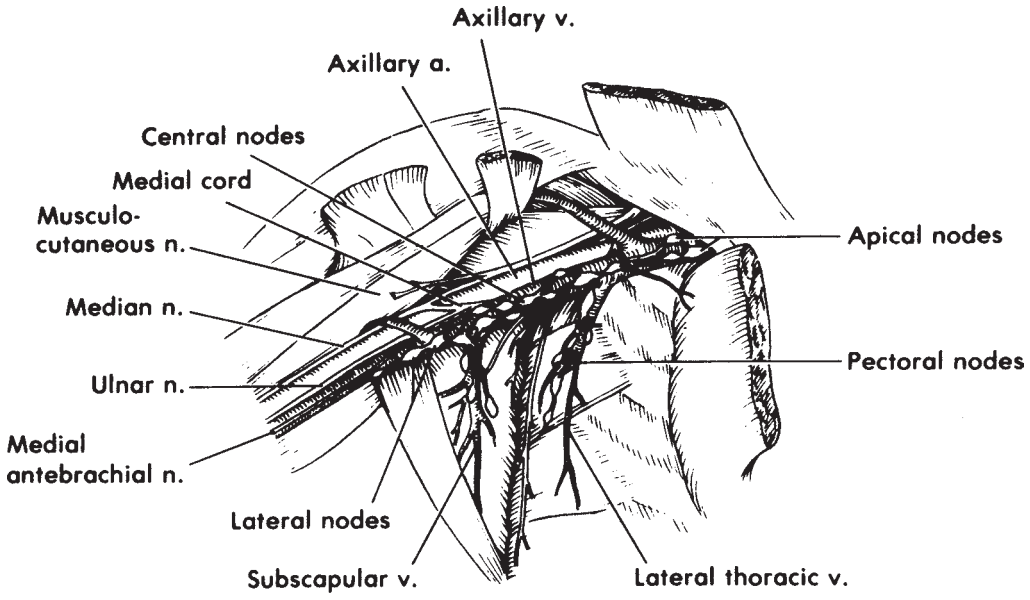


**Fig. 2.** Relation of axillary lymph nodes to the brachial plexus. Lymphatic spread of breast carcinoma tends to involve the medial cord of the plexus and the proximal portions of the ulnar and median nerves. (Reprinted with permission from Layzer RB. Neuromuscular Manifestations of Systemic Disease. FA Davis, Philadelphia ©1985, Oxford University Press.)

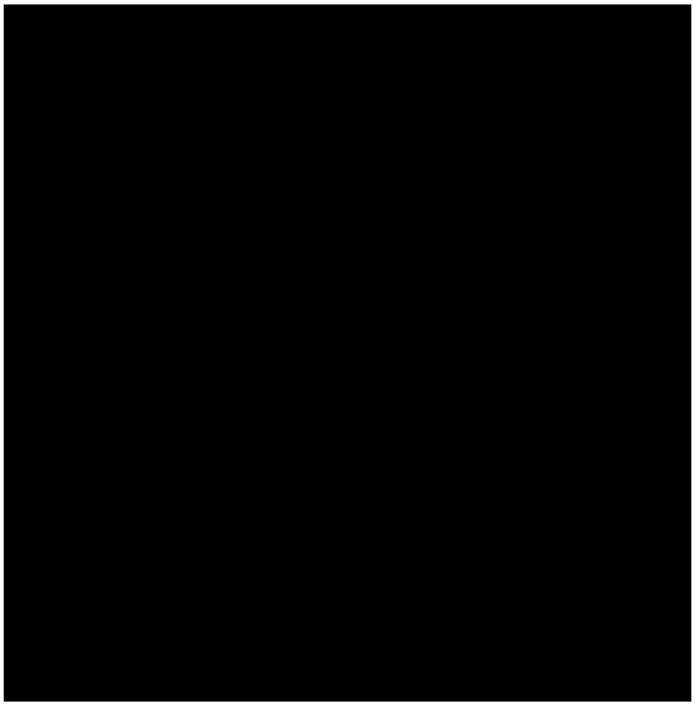

**Fig. 3**. The major nerve trunks and branches of the brachial plexus, paravertebral sympathetic chain, and stellate ganglion. The areas highlighted may be involved by superior sulcus tumors. Reprinted with permission from ref. *60*.

tion plexopathy to be painful and involve the lower trunk. However, this generalization is not always reliable. MRI with gadolinium is the best diagnostic test because it can establish the diagnosis when a mass is visualized in the vicinity of the plexus. Furthermore, changes in soft tissue signal intensity can help distinguish a tumor (low T1 and high T2 signal intensity) from radiation-induced fibrosis (low T1 and T2 signal) *(13,61)*. Recent evidence suggests that $^{18}$FDG-PET scanning may be useful in evaluation of patients with suspected neoplastic plexopathy, particularly if other imaging studies, such as CT and MRI are negative. Abnormal uptake of $^{18}$FDG in the region of the symptomatic plexus is highly suggestive of neoplastic pathology *(62)*. In difficult cases, when tumor infiltration is suspected on clinical grounds, but imaging studies are normal, invasive techniques such as myelography or even surgical exploration may be required to identify tumors in the region of the plexus.

Other diagnostic possibilities such as mononeuropathy or radiculopathy, which can present with symptoms identical to plexopathy, should be excluded. Electromyography and nerve conduction studies can be helpful in this regard and in distinguishing metastatic from radiation-induced plexopathy. Fasciculation-myokymic discharges are present in 80% of radiation-induced brachial plexus neuropathies *(63)*.

Radiation therapy is the mainstay of treatment for neoplastic plexopathy. Unfortunately, the results of treatment are often disappointing and the pain continues unabated in more than half of the patients. Surgical intervention, such as rhizotomies and sympathetic blockade, are seldom beneficial.

## POST-IRRADIATION BRACHIAL PLEXOPATHY

Radiation-induced damage to the brachial plexus most frequently follows irradiation fields involving the axilla for breast cancer. Up to 73% of patients receiving a total irradiation dose in excess of 6000 cGy develop symptoms and signs of brachial plexopathy *(57,64)*. Doses less than 6000 cGy are less likely to result in clinically significant radiation damage. The latency between the completion of radiotherapy and onset of

symptoms is quite variable (3–72 mo), with a mean of 1–3 yr *(57,64,65)*.

Postirradiation damage of the brachial plexus is thought to result from radiation-induced fibrosis with subsequent nerve entrapment and Wallerian degeneration, together with radiation-induced vasculopathy. The relative resistance of the lower trunk to radiation injury is explained by the protective effect of the clavicle and its short course through the radiation field *(57)*.

Clinically, the most common presentation of postirradiation brachial plexopathy is painless lymphedema and paresthesias of the affected arm. Radiation produces patchy involvement of the plexus. The upper plexus (C5–6) is almost always involved, with weakness of shoulder abduction, external rotation, elbow flexion and forearm supination, variable triceps weakness, and impaired sensations over the deltoid region, external aspect of the arm, and radial side of the forearm. Approximately 25% of patients with radiaion-induced brachial plexopathy will have signs and symptoms suggestive of involvement of the entire plexus *(57,66)*. The sensory symptoms in radiation plexopathy are often insidious in onset, with slowly progressive weakness predominating. Radiation plexopathy is rarely painful. Isolated involvement of the lower trunk or Horner's syndrome should raise other diagnostic considerations.

The presence of lymphedema, minor pain (if any), insidious onset of symptoms and signs, and history of radiation therapy is helpful in distinguishing postirradiation plexopathy from idiopathic brachial plexitis. A rare, but challenging, diagnostic entity is sarcoma arising in the brachial plexus as a delayed complication of radiation *(67)*. Because of its rarity, early diagnosis requires a high degree of suspicion.

The major diagnostic features between neoplastic and radiation brachial plexopathy were discussed previously. Although myokymic discharges, semi-rhythmic spontaneously occurring grouped action potentials, are characteristic of radiation damage, it should be noted that up to 20% of patients of patients with radiation-induced brachial plexopathy do not exhibit myokymia on EMG *(63)*.

There are no established guidelines for the treatment of postirradiation plexopathy. Some patients may benefit from oral anticoagulation for 3–6 mo, particularly if started soon after onset of symptoms *(13,68)*. Occupational therapy intervention helps to minimize disability and facilitate functional independence of these patients *(69)*. Recent reports suggest that hyperbaric oxygen therapy may be helpful in managing late neurological sequelae of radiotherapy *(70)*. To date, the best available treatment is prevention; substituting surgery for radiotherapy in management of axillary involvement; using the lowest effective radiation dose in more fractions; and fixed planned positioning of the arms of patients during radiation to the breast and axilla *(13)*. Up to 72% of patients with breast cancer who move during radiotherapy develop radiation-induced brachial plexopathy, compared to 24% of those who maintain a fixed position *(65)*.

**NEOPLASTIC LUMBOSACRAL PLEXOPATHY** The lumbosacral plexus is situated within the substance of the psoas muscles. It is divided into an upper part (L1–4), and a lower part (L4–S4) (Fig. 4). Neoplastic infiltration of the lumbo-sacral plexus is most often secondary to direct extension of abdomino-pelvic tumors, including cancers of the testes, colorectum and uterus, and retroperitoneal lymphoma extending along the paravertebral gutter or perineurial lymphatics *(72)*.

Neoplastic lumbosacral plexopathy is recognizable by pain and sensorimotor deficits in the lower extremities, extending outside the territory of a single root or nerve. The symptoms and signs are often unilateral. Pain, often aching or cramping in quality, is usually the earliest and most prominent manifestation. Subsequent weakness and sensory loss develops insidiously over weeks to months. Neurologic examination often reveals sensorimotor deficits referable to the lower part of the plexus in more than 50% of patients *(72)*. Table 2 provides a summary of the clinical features of lumbosacral plexopathy. If the lower sacral roots are involved, there may be some impairment of bowel, bladder, and/or sexual function. Obstruction of the lymphatic or venous drainage by the infiltrating tumor often results in swelling of the affected leg.

The differential diagnosis of lumbosacral plexopathy includes trauma, retroperitoneal hematomas, diabetic plexopathy, Herpes zoster infection, radiation-induced damage, and idiopathic plexopathy. Retroperitoneal hematomas and diabetic plexopathy often involve the upper part of the lumbosacral plexus *(73)*. Distinguishing neoplastic plexopathy from postirradiation effects can be difficult. As in the case of brachial plexopathy, early onset of prominent pain, leg swelling, and unilateral sensorimotor deficits favor a neoplastic etiology.

Although CSF analysis is often routinely performed in these patients, it is almost always unremarkable. Electrophysiological studies are of value in differentiating neoplastic plexopathy from polyneuropathies, polyradiculopathies, and radiation-induced lumbosacral plexopathy. MRI scanning of the region of the lumbosacral plexus is the best test to establish the diagnosis *(61,74)*. We also recommend MRI of the lumbosacral spine to rule out cord, polyradicular, or epidural pathology. In cases where MRI is negative, $^{18}$FDG-PET scanning may be of some value *(62)*. If noninvasive studies are negative, exploratory laparotomy may be required to establish the diagnosis.

Available treatment for malignant plexopathy comprises radiation therapy and symptomatic pain management. Early mobilization and exercise is advocated. Unfortunately, the benefits from current treatment options are often minimal.

**POST-IRRADIATION LUMBOSACRAL PLEXOPATHY**

Damage to the lumbosacral plexus can occur following local total doses exceeding 4000–6000 cGy *(18,75,76)*. The interval between radiotherapy and onset of neurological manifestations ranges from 1–31 yr; the median time from irradiation to onset of symptoms is 5 yr *(76)*.

Clinically, leg weakness is the earliest manifestation of radiation-induced lumbosacral plexopathy in more than 60% of patients. It is often painless, distal, and slowly progressive. Pain, if present, is often mild. Sensory abnormalities, such as numbness or paresthesias, may be the presenting feature in up to 30% of patients. The sensorimotor deficits can be monomelic initially, often becoming bilateral and asymmetrical later as the disease progresses. The upper part of the lower plexus (L4–S1) is most frequently involved (Table 2). Symptoms of bowel or bladder dysfunction, mostly attributed to proctitis or bladder fibrosis, occur in 20% of patients.

**Fig. 4**. (Left) The lumbar plexus is formed by anterior primary rami of lumbar spinal nerves L1, L2, L3, and L4. Note the branches that arise from the plexus. (Right) The sacral plexus is connected to the lumbar plexus by the lumbosacral trunk. Note the branches that arise from the plexus in the pelvis. Reprinted with permission from ref. *71*.

**Table 2**
**Clinical Features of Lumboscral Radiculopathy**

| | *Pain* | *Sensory loss* | *Weakness* |
|---|---|---|---|
| Upper plexus (L1-L4) | Groin, anterior/lateral thigh, hip | Anterior thigh, medial leg, medial and lateral thigh | Mostly proximal (iliopsoas, quadriceps, and adductors), ± foot dorsiflexors (tibialis anterior; the only L4-innervated muscle below the knee), diminished knee jerk. |
| Lower plexus (L4-S4) | Posterior thigh, leg and foot | Foot, lateral ankle, lateral and posterior leg | Mostly distal (evertors, (L4-S4) invertors, flexors of toes and ankle), hamstrings, diminished ankle jerk ± anal reflex. |

The pathogenesis of postirradiation plexopathy involves radiation-induced vasculopathy, nerve fibrosis, and subsequent wallerian degeneration. Differentiating radiation-induced plexopathy from postirradiation lumbosacral radiculopathy can be particularly difficult. Paraspinal muscle fibrillations, indicative of a radiculopathy, can be seen in up to 50% of patients with radiation-induced lumbosacral plexopathy, suggesting concomitant radiation damage to both nerve roots and the plexus (radiation radiculoplexopathy) *(76)*. Myokymic discharges occur in both conditions *(63,75)*. Sural nerve-action potentials, however, are absent in plexopathy but preserved in postirradiation lumbosacral radiculopathy *(75)*. MRI is more sensitive than computed tomography (CT) in detecting radiation-induced fibrosis *(61,74)*.

As in the case of postirradiation brachial plexopathy, there is no effective treatment of radiation-induced lumbosacral plexopathy.

## NEUROPATHY

**GENERAL CLASSIFICATION OF PERIPHERAL NEUROPATHIES** From an anatomical perspective, the peripheral nerve consists of the axon and the Schwann cell and its myelin sheath. Abnormalities of the axon or myelin sheath may be the pathological substrate resulting in axonopathy or demyelinating neuropathy, respectively. Axon loss polyneuropathy, in general, tends to manifest itself as a distal symmetric sensorimotor neuropathy, with slight impairment of distal deep tendon reflexes and distal atrophy in chronic cases. Demyelinating neuropathies, on the other hand, are often asymmetric, with depressed deep tendon reflexes early in the course of the disease and prominent weakness with minimal atrophy.

Neuropathies associated with cancer can be distinguished by their time course, affected modality, and underlying pathology. An acute onset is often suggestive of an inflammatory, immunologic, or vascular etiology while most of the toxic, nutritional, metabolic, and systemic diseases of the nerve develop subacutely over weeks to months. Peripheral neuropathy is present in all cancer patients by the time they have lost 15–40% of their body weight and its severity correlates with increasing percentage of weight loss *(77)*; thus, this problem can affect the quality of life of many cancer patients.

The nature of the neuropathic symptoms, whether positive (paresthesia or pain) or negative (loss of sensation, weakness), is related to the underlying pathology and pattern of fiber loss. Small fiber neuropathies show loss of pain and temperature, with preservation of light touch, joint position, and vibration sense, and presence of abnormal burning sensation. Such neuropathies are also more likely to be associated with autonomic dysfunction. It is therefore helpful to determine whether a neuropathy is sensorimotor (predominantly sensory), predominantly motor, purely sensory, purely motor, or autonomic. Most neuropathies are sensorimotor; identifying other subtypes, particularly painful neuropathy, limits the differential diagnosis considerably.

It is estimated that up to 40% of cancer patients will show clinical or electrophysiological evidence of peripheral neuropathy *(78–80)*. Nerve conduction studies and electromyography are often crucial to distinguish axonal from demyelinating neuropathy, polyneuropathy from mononeuropathy multiplex, and neuropathy from plexopathy or polyradiculopathy.

## CANCER-RELATED NEUROPATHIES

**Chemotherapy-Induced Neuropathy** By far, the most common cause of cancer-associated neuropathies is related to the administration of anti-neoplastic neurotoxic agents. A number of chemotherapeutic agents are capable of producing a distal, predominantly sensory, or sensorimotor polyneuropathy. Most chemotherapy-induced neuropathies are dose-dependent and represent a dose-limiting toxicity. The most frequently encountered neuropathies are those associated with the use of vincristine, cisplatin, and paclitaxel (Taxol). Vincristine-induced neuropathy is primarily axon loss in nature; associated autonomic neuropathy may also occur. Cisplatin- and paclitaxel-induced neuropathies are associated with degeneration of both large myelinated and small unmyelinated fibers. Both drugs are selectively concentrated in the dorsal root ganglia, thus implicating ganglionopathy as well. In general, recovery begins after drug withdrawal or dose reduction. However, it is often incomplete and may take several months. Occasionally, paclitaxel therapy can result in dose-independent painful proximal weakness and predominantly motor neuropathy secondary to a distal axonopathy *(81)*. Chemotherapy-induced neuropathy is discussed fully in Chapter 15.

**Neoplastic Neuropathy** Neoplastic neuropathies resulting from infiltration, direct or metastatic, or compression of the peripheral nerve trunk by tumor cells are extremely rare. These are mostly seen in association with head and neck tumors that tend to invade cranial and cervical nerves and lymphoproliferative diseases, particularly lymphoma. Their pathogenesis appears to involve infiltration of the nerves by malignant lymphoma cells, as in the case of neurolymphomatosis; ischemia of the nerve fibers secondary to occlusion of small blood vessels and vasa nervorum with tumor cells, as in the case of intravascular lymphoma (Fig. 5); and rarely direct compression of the nerves by metastatic lesions *(13,82–84)*. Approximately 10% of patients with intravascular lymphoma (angiocentric B-cell lymphoma)—a rare form of systemic lymphoma in which neoplastic B-lymphocytes are confined within the lumens of blood vessels—develop a peripheral neuropathy *(85)*. Neurolymphomatosis is another form of systemic lymphoma that preferentially involves nerve roots and peripheral nerves *(13)*.

Most described neoplastic neuropathies present as mononeuropathy or mononeuropathy multiplex *(82,84)*. Some argue, however, that infiltration by neoplastic cells is only a primary event, and that subsequent immunologic derangement leads to a neuropathy. Antibodies to nuclear cytoplasmic antigens (ANCA) have been detected in intravascular lymphoma, thus implicating vasculitis as a possible mechanism. Similarly, cryoglobulinemia and immunoglobulin M anti-sulfatide antibodies have been implicated in non-Hodgkin's lymphoma-associated neuropathy *(86)*.

The diagnosis is often confirmed by positive CSF cytology or demonstration of lymphomatous infiltration of the nerves by nerve biopsy. Occasionally, patients with these so-called neoplastic neuropathies may improve after treatment with steroids and plasmapheresis. Treatment of the infiltrating neuropathies is, however, usually based on treatment of the primary tumor with chemotherapy, radiotherapy, and/or surgical resection as indicated. Local treatment with nerve block may sometimes be needed for symptomatic relief.

**Paraproteinemic Neuropathy** Twenty-five to fifty percent of patients with monoclonal paraproteinemia have a peripheral neuropathy *(32,87)*. The presence of a paraprotein may be an isolated abnormality (MGUS; monoclonal gammopathy of unknown significance), or a signal of an underlying plasma-cell dyscrasia, such as multiple myeloma, osteosclerotic myeloma, lymphoma, Waldenström's macroglobulinemia, and systemic amyloidosis.

These neuropathies are predominantly symmetric sensory or sensorimotor and immunologically mediated; antibodies against components of the peripheral nerve, axon or myelin, are identified in the sera of most patients. They may clinically resemble chronic inflammatory demyelinating polyneuropathy (CIDP), which, in turn, has been associated with such tumors as systemic lymphoma *(88)*, gastrointestinal carcinoma *(89)*, and malignant melanoma *(90)*.

Available treatment options include immunosuppressive drugs, IVIG, or plasmapheresis. The response to treatment on the whole is disappointing, except in osteosclerotic myeloma, where the neuropathy usually improves with localized radiotherapy to the tumor (*see* Chapter 26).

**Anti-Hu-Associated Neuropathy** A distal, symmetrical, sensorimotor polyneuropathy is the most common presentation of paraneoplastic neuropathies, which, although well-publicized, are rarely encountered. Even less common is a subacute, painful, purely sensory, progressive neuropathy with pseudoathetosis and sensory ataxia, described originally by Denny-Brown in association with bronchogenic carcinoma. The lung is often the source of the primary tumor in most cases; however, tumors in other organs and lymphoma may rarely be involved *(87,91,92)*.

The sensorimotor neuropathy may have a varied clinical picture, from acute GBS-like to a chronic and relapsing type. Autonomic neuropathy, also felt to be paraneoplastic in nature, has been reported with several tumors including lung cancer *(92)*.

**Fig. 5**. Intravascular lymphoma. Section of muscle shows malignant lymphoid cells within small blood vessels. Immunochemistry shows most of the cells to be of B-cell origin. (Courtesy of Dr. T.W. Smith, M.D., Department of Pathology [Neuropathology], University of Massachusetts Medical Center, Worcester, MA.)

Over 90% of patients with small cell lung cancer and purely sensory neuropathy have significantly elevated titers of Anti-Hu antibodies in their sera and CSF *(10)*. The onset of these neuropathies may antedate the finding of the associated malignancy by 2–6 yr. Therefore, Anti-Hu seropositive patients should have chest CT/MRI or bronchoscopy in order to search for an associated occult lung malignancy. The term "malignant inflammatory sensory polyganglionopathy" has been introduced to describe the purely sensory variety, since it is characterized pathologically by inflammatory and destructive changes, most prominently in the sensory ganglia *(30)*. Associated inflammatory changes throughout the nervous system, including the temporal lobes with subsequent limbic encephalitis, and autonomic ganglia with subsequent autonomic neuropathy may also occur in anti-Hu seropositive patients *(10,92)*.

Despite the autoimmune basis of these neuropathies, immune-modulating therapies usually do not help. Treatment of the underlying malignancy should always be undertaken, although the results are often disappointing (Chapter 13).

**Entrapment Neuropathy (Peroneal Mononeuropathy)** Peroneal nerve compression against the fibular head has been described in patients with systemic cancer and is mostly attributed to weight loss *(93)*. However, associated factors, such as chemotherapy, cutaneous vasculitis, and discrete metastatic lesions, may also contribute. The outcome of this entrapment neuropathy is often favorable, with partial resolution in more than half of patients and complete recovery in 20% *(93)*. Poor nutritional status and associated metabolic disturbances probably causes or aggravates peripheral neuropathies in cancer patients.

## DISEASES OF THE NEUROMUSCULAR JUNCTION

**MYASTHENIA GRAVIS** Myasthenia gravis (MG) is an autoimmune disorder caused by the production of antibodies against the acetylcholine receptor (AChR) at the neuromuscular junction (NMJ) *(94)*. It is a postsynaptic disorder, where the physiologic abnormality results from reduction in AChR on the muscle endplate, simplification of the postsynaptic membrane, and blockade of AChR by these antibodies; acetylcholine is released normally. The etiology underlying the generation of AChR antibodies is unknown, but there is a clear association with other autoimmune disorders and with abnormalities of the thymus gland *(95)*.

In most patients, MG is not associated with neoplastic conditions. Only 10–15% of patients have an underlying thymoma and only 30% of patients with a thymic tumor have MG *(96,97)*.

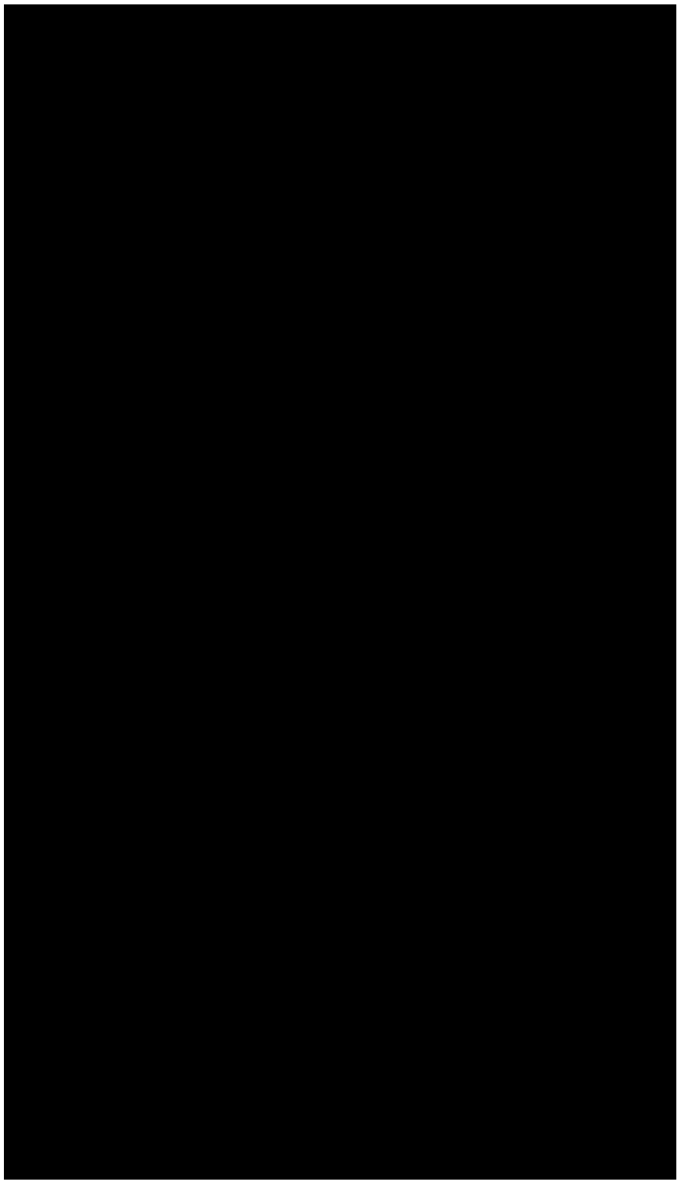

**Fig. 6**. MRI of the cervical spine showing a destructive extradural, extramedullary tumor causing spinal cord compression at C-2/C-3 levels. Microscopic section from this lesion demonstrated a spindle cell thymoma; thymectomy for a thymoma (spindle cell) had been performed in this myasthenic patient 10 yr earlier. Since that time, the patient's myasthenia gravis had been in clinical remission until after resection of the spinal metastasis. (Reprinted with permission from Selvaraj et al. Myasthenic crisis after resection of an isolated metastatic thymoma of the cervical spine. J Clin Neuromusc Disease. 1999; 1: 11–13. [Lippincott, Williams and Wilkins].)

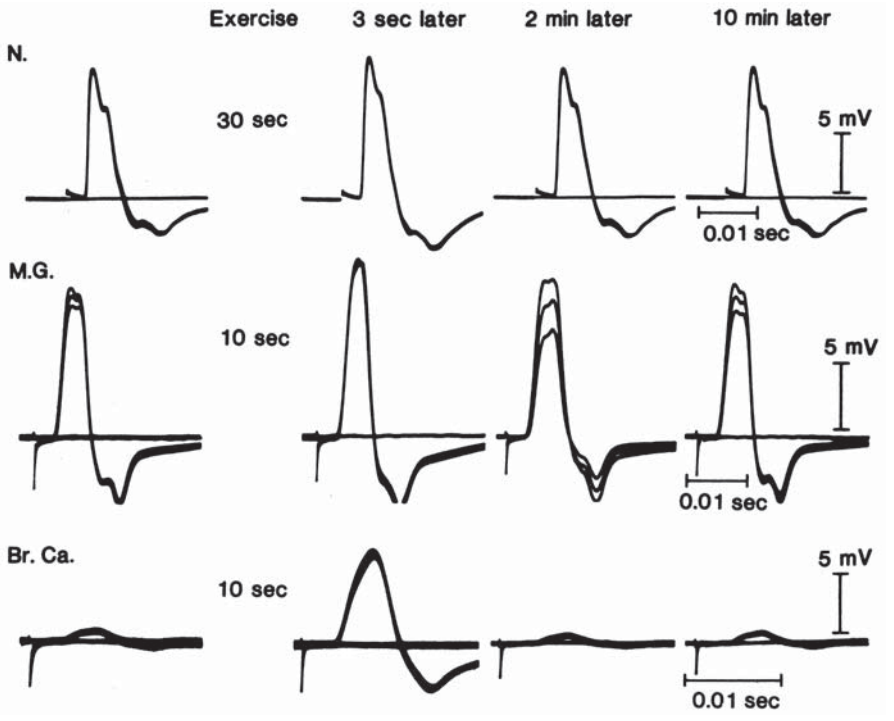


**Fig. 7.** Effect of exercise on the action potential of the hypothenar muscles evoked by maximal stimulation of the ulnar nerve at the wrist. The response of the rested muscle (far left) is compared with the responses 3 s, 2 min, and 10 min after the end of a maximal voluntary contraction of the muscle. Each record consists of three superimposed action potentials evoked at a rate of 3/s. N., responses of a normal subject; M.G., responses of a patient with generalized myasthenia gravis. In the rested muscle, a progressive decline in amplitude occurs during stimulation at a rate of 3/s. Three seconds after exercise the defect is repaired and there is some increase in the amplitude of response. Two minutes after exercise, the defect is more marked than it was initially. At 10 min, the response has returned to the baseline level. Br. Ca. (LEMS), patient with a bronchogenic carcinoma. The initial response in very small compared to normal and M.G. There is marked posttetanic facilitation 3 s after exercise, but a return to baseline is seen 2 min after exercise. (Reprinted with permission from Lambert et al. Myasthenic syndrome occasionally associated with bronchial neoplasm: Neurophys studies, in Viets, HR, ed., 1961, pp. 364–410 [Mosby].)

Most thymic tumors in patients with MG are benign and encapsulated; and can be easily removed completely surgically. It is of interest that in 2% of patients, MG can develop years after resection of a thymic tumor *(97,98)*. Rarely, thymoma may metastasize to extrathoracic locations and myasthenia gravis may recur after surgical resection of a thymic metastasis *(99)* (Fig. 6).

Twenty percent of men with MG between the ages of 30 and 60 yr have a thymoma. The frequency of thymoma is much lower when symptoms of MG begin after age sixty. The symptoms and signs of MG are similar to those that occur when it is not associated with tumor and are characterized by weakness predominantly involving ocular and oropharyngeal muscles and increased severity of the weakness as the day goes on.

The diagnosis of MG is supported by the presence of serum antibodies to AChR, electrophysiological studies and the Tensilon test. The electrophysiological hallmark of the disease is a decremental muscle response to low rates of repetitive nerve stimulation which is found in 60% of patients (Fig. 7). Single-fiber EMG is the most sensitive test of NMJ transmission; increased jitter in some muscles is present in almost all patients with MG. Virtually all patients with MG and thymoma have elevated AChR binding antibodies, and many have high concentrations of AChR modulating and antistriational muscle antibodies. Absence of these latter circulating antibodies provides evidence that thymoma is unlikely to be present.

All patients with newly diagnosed MG should undergo a chest CT to detect thymoma; routine chest X-rays are not sufficient. Detection of a thymoma is the one mandatory indication for thymectomy in MG patients; most authorities recommend a transsternal approach. Patients are often pretreated with high-dose daily prednisone, with or without plasmapheresis, until maximal improvement is achieved. Postoperatively, mediastinal irradiation is used if tumor resection is incomplete. Medical treatment thereafter is the same as for MG patients without thymoma. These patients, however, do not do as well as nonthymoma patients in terms of remission or improvement after initiation of treatment.

**LAMBERT-EATON MYASTHENIC SYNDROME** Lambert-Eaton myasthenic syndrome (LEMS) was first described in association with lung cancer *(100)*. Although initially felt to be invariably associated with neoplasia, it is now clear that it also is an autoimmune disorder caused by antibodies against the voltage-gated calcium channels (VGCC) of the motor-nerve terminals *(101)*.

The disease usually begins after age 40. The male:female ratio is 2–5:1 *(102)*. Approximately 75% of males and 25% of females have an underlying malignancy, most often small cell

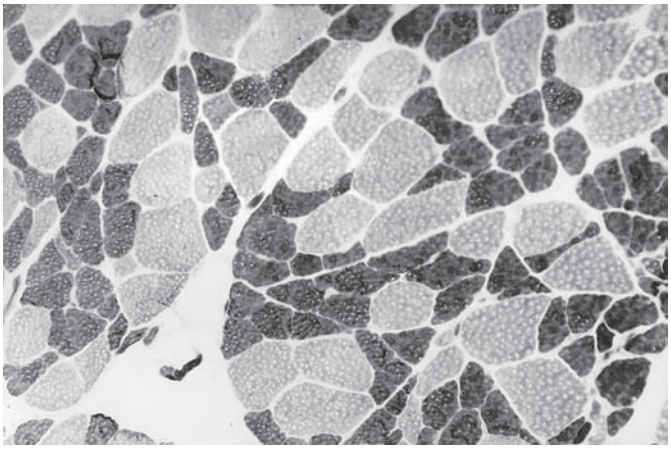

**Fig. 8**. Corticosteroid myopathy. Most of the Type II fibers (darkly staining) are mildly to moderately atrophic compared to the relatively spared Type I fibers (staining lightly) (ATPase, pH 9.4).

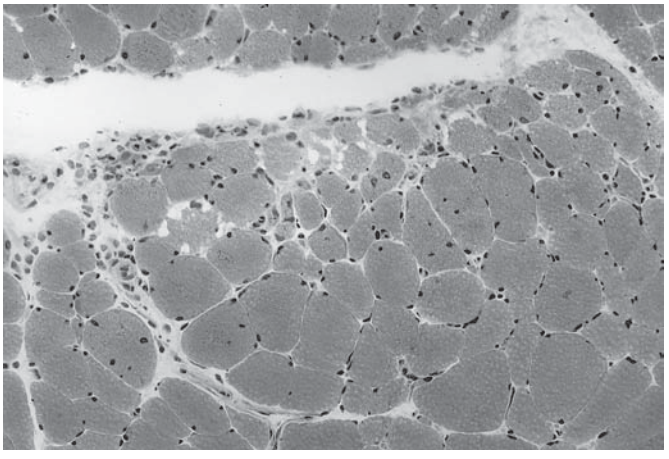

**Fig. 9**. Dermatomyositis. Cross-section of muscle showing perifascicular atrophy (hematoxylin and eosin).

carcinoma of the lung that presumably contain antigens that induce the production of calcium-channel antibodies. Other associated tumors include those of the breast, prostate, kidney, and gastrointestinal tract and lymphoma *(102,103)*. The associated malignancy may be discovered years before the disease begins, or develops within 1–2 yr after diagnosis *(98)*. Noncarcinomatous cases are usually associated with other autoimmune diseases.

Clinically, LEMS resembles myopathy more than MG. Weakness and muscle aching, most notable in the thigh muscles, is the major presentation of LEMS. Oropharyngeal and ocular muscles are usually spared or only mildly affected. Reduced or absent deep tendon reflexes and symptoms of dysautonomia, in particular dry mouth, are often present. Characteristically, muscle strength and reflex activity may improve initially after isometric muscle exercise, but then weaken with sustained activity.

The physiologic abnormality in LEMS results from decreased presynaptic release of acetylcholine at the NMJ *(104)*. The diagnosis of LEMS may be confirmed by the characteristic EMG findings of decreased size of CMAPs, with further reduction in response to repetitive (1–5 Hz) nerve stimulation. The cardinal electrodiagnostic finding in LEMS is a greater than 100% increase of CMAP size in response to repetitive stimulation at higher frequencies (20–50 Hz) and after voluntarily muscle contraction for 10–15 s *(105)* (Fig. 7). The presence of elevated concentrations of VGCC antibodies also provide clues to the accurate diagnosis.

Once the diagnosis of LEMS is established, an extensive search for underlying malignancy should be carried out. Patients who have risk factors for lung cancer, in particular, should undergo vigorous and repeated testing including chest CT and bronchoscopy if chest CT is unremarkable. Chronic smokers with symptom onset after age 50 almost certainly have an underlying lung cancer *(106)*. On the other hand, patients younger than 50 yr without a history of chronic smoking and those in whom no tumor is detected after 2 yr of symptom onset have a very low risk of associated malignancy, especially if there is evidence of coexisting autoimmune disease *(98)*.

The symptoms of LEMS improve with many of the same treatments used in MG, but rarely as completely. Specific treatment may include guanidine hydrochloride, which increases the release of acetylcholine, and 3,4-diaminopyridine. When the weakness is severe, IVIG or plasmapheresis may be used to induce rapid, albeit transient, improvement; immunosuppressants should be added to maintain sustained improvement. However, immunotherapy without effective treatment of the underlying malignancy, if present, usually produces no improvement. Treatment should therefore be directed towards the tumor if present, since the weakness often improves with effective cancer therapy; no further treatment may be necessary in some patients.

## DISEASES OF THE MUSCLE

Cancer-related causes of muscle disease include steroid myopathy, paraneoplastic or drug-induced necrotizing myopathy, and the immunologically mediated inflammatory myopathies.

**STEROID MYOPATHY** Steroid-induced myopathy *(107)* is estimated to occur in more than 60% of cancer patients *(108)*. It is often characterized by insidious onset of proximal weakness, especially in the lower extremities. Weakness of neck flexors and respiratory muscles is not uncommon. Steroid-induced weakness is more common with fluorinated (dexamethasone), than nonfluorinated (prednisone) compounds *(109)*; its development is related to the cumulative dose, rather than average daily dose or duration of treatment *(108)*. Creatine kinase is normal, the EMG is either normal or mildly myopathic *(110)* and the muscle biopsy discloses atrophy of the Type II fibers (Fig. 8). Treatment includes dose reduction to the lowest possible level, and/or alternate-day therapy, together with adequate physical therapy and diet. The myopathy is completely reversible once steroids are discontinued, although recovery may take weeks to months.

**NECROTIZING MYOPATHY** Malignancy-related necrotizing myopathy has been rarely described in association with gastrointestinal, bladder, prostate, and nonsmall cell lung cancers *(111–113)*. As the name implies, necrotizing myopathy is characterized by necrosis of striated muscle fibers, rhabdomyolysis, and myoglobinuria. Its pathogenesis was

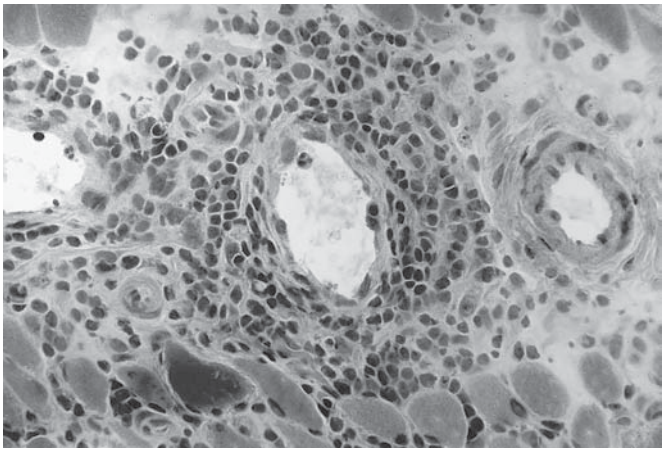

**Fig. 10**. Dermatomyositis. Cross-section of muscle showing a pronounced perivascular mononuclear cell infiltrate (hematoxylin and eosin).

initially thought to be related to polymyositis *(113,114)* but it is now recognized that most cases are paraneoplastic, where the associated malignancy may trigger secondary immunological abnormalities affecting remote muscles; use of high-dose corticosteroids may also be a contributing factor.

Clinically, necrotizing myopathy is characterized by acute/subacute onset of rapidly progressive, disabling, painful, symmetric, predominantly proximal weakness; tendon reflexes are usually preserved. Laboratory evidence of myoglobinuria is invariably present; serum CK is almost always significantly elevated. The urine may be discolored burgundy red—brown if significant myoglobinuria is present.

Muscle biopsy is essential for the diagnosis of necrotizing myopathy. Prominent necrosis with intense alkaline phosphatase staining of muscle connective tissue and little inflammation are the usual pathological findings *(111,114)*, and are helpful in distinguishing necrotizing myopathy from polymyositis. Paraneoplastic necrotizing myopathy may precede the discovery of the associated neoplasm; therefore, a thorough surveillance for occult malignancy is indicated in patients with these clinico-pathological findings.

Treatment should be aimed at the underlying malignancy. Additional treatment includes corticosteroids and immune modulating agents. Careful monitoring of renal functions and urinary output is advisable in all patients, especially in case with severe myoglobinuria.

**INFLAMMATORY MYOPATHIES** The inflammatory myopathies include dermatomyositis and polymyositis. Both of these syndromes may be associated with malignancy, but this association is more common in dermatomyositis. Reports of the incidence of underlying carcinoma vary between 6–45% for dermatomyositis and 0–28% for polymyositis *(115,116)*. This association has no sex predilection, but is more frequent in patients over the age of 40. Identification of the malignancy may precede or follow the diagnosis of either condition, although the onset of each disorder is usually within 12 mo of the other.

Clinically, both conditions are characterized by insidious onset of slowly progressive proximal weakness, often in association with muscle pain and tenderness. Dysphagia and weakness of neck flexors and respiratory muscles may follow in severe cases. Cardiac dysrhythmias, heart failure, and restrictive lung disease may develop in a minority of patients. The presence of an associated heliotrope rash in the periorbital region and over the knuckles, elbows, and knees is almost pathognomonic for dermatomyositis.

Serum CK and the ESR are usually elevated in both conditions, although not invariably so; EMG discloses myopathic motor unit potentials and increased insertional activity. Like necrotizing myopathy, muscle biopsy is essential for the diagnosis of poly- and dermatomyositis. Prominent mononuclear inflammatory cellular infiltration of muscle fibers, with scattered necrotic changes and regeneration are characteristic. In dermatomyositis, perifascicular atrophy (Fig. 9) and perivascular collections of inflammatory cells (Fig. 10) are seen.

The mainstay of treatment is immunosuppression with steroids or other immunosuppressive agents. Searching for and treatment of any underlying malignancy should be undertaken, although there is little evidence to suggest that cancer therapy per se improves the myopathic process.

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# Part IV Indirect Complications of Cancer

# 12 Cerebrovascular Complications of Cancer

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## INTRODUCTION

As cancer and stroke are the second and third leading causes of mortality in the United States respectively, it is not surprising to encounter patients with these conditions concomitantly. A wide variety of cerebrovascular disorders can occur within the oncologic population, complicating the cancer patient's overall clinical course, treatment, and long-term outcome. Unfortunately, the incidence of stroke within this population is substantial. Graus and colleagues' 1985 autopsy series of 3426 systemic cancer patients revealed that stroke was second only to metastases as the most common CNS lesion, occurring in 14.6% of patients *(1)*. Hemorrhages and ischemic lesions were present in equal numbers; however, hemorrhages were more frequently symptomatic. Of the patients with pathologically defined stroke, greater than half had significant clinical symptomatology due to their cerebrovascular injury. In addition, Posner and Chernik's earlier 1978 postmortem study suggests the incidence of stroke in the oncologic population may actually be as high as 30% *(2)*. Certainly stroke and cancer co-occur far more than would be expected by chance, and frequently enough to render knowledge of the cerebrovascular complications of malignancy essential to the care of the oncologic patient.

Detailed investigation and precise diagnosis of cerebrovascular disorders in cancer patients is critical for several reasons. Early recognition of acute stroke may allow the cancer patient access to interventional thrombolytic, surgical, and endovascular therapies, and improve overall patient outcome. Secondary stroke prevention therapies in the cancer patient are guided by the etiology of the initial cerebrovascular event. Lastly, diagnostic workup in young or cryptogenic stroke patients without overt cancer not infrequently leads to the first recognition of the underlying malignancy.

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In determining the etiology of stroke in the cancer patient, various factors must be considered. Traditional cerebrovascular risk factors seen in the general population such as age, hypertension, coronary artery disease, hypercholesterolemia, tobacco use, diabetes, and family history of stroke should be assessed, and the possibility of a stroke mechanism independent of malignancy should be considered. Cancer patients, however, frequently have stroke as a cancer-related event, in which the malignancy directly contributes to the cerebrovascular insult through vessel compression, hypercoaguable state, bleeding diathesis, or other mechanisms.

This chapter will explore the various etiologies of stroke within the oncologic population and discuss their diagnosis and management.

## STROKE DUE TO DIRECT TUMOR INVASION

### INTRATUMORAL PARENCHYMAL HEMORRHAGE

Intracranial hemorrhage into brain tumors, both metastatic and primary, is a relatively frequent occurrence, reported to account for 1.7–9.6% of all intracranial hemorrhages *(3–6)*. Metastatic tumors are more often associated with hemorrhage than are primary tumors *(7,8)*. Intracranial hemorrhage is the initial manifestation of primary or metastatic tumor in 0.54–3.4% of oncologic patients *(3,6,9–12)*.

**Primary Central Nervous System Tumors** The most common primary CNS malignancies associated with intratumoral hemorrhage are oligodendroglioma, glioblastoma, and germ cell tumors. Macroscopic, clinically significant, hemorrhage is more common in low-grade astrocytoma than glioblastoma, but bleeding with both neoplasms has been reported (*see* Fig. 1) *(5–7)*. Among astrocytoma patients, the highest hemorrhage rate has been noted in cases of mixed gliomas (oligoastrocytomas), with gross bleeding reported in up to 29.2% *(5)*. Other primary CNS malignancies have been infrequently associated with intratumoral hemorrhage. Hemorrhage into meningioma is relatively uncommon but has been reported *(5,13,14)*. Lazaro and colleagues noted that meningotheliomatous meningiomas were most likely to bleed, accounting for

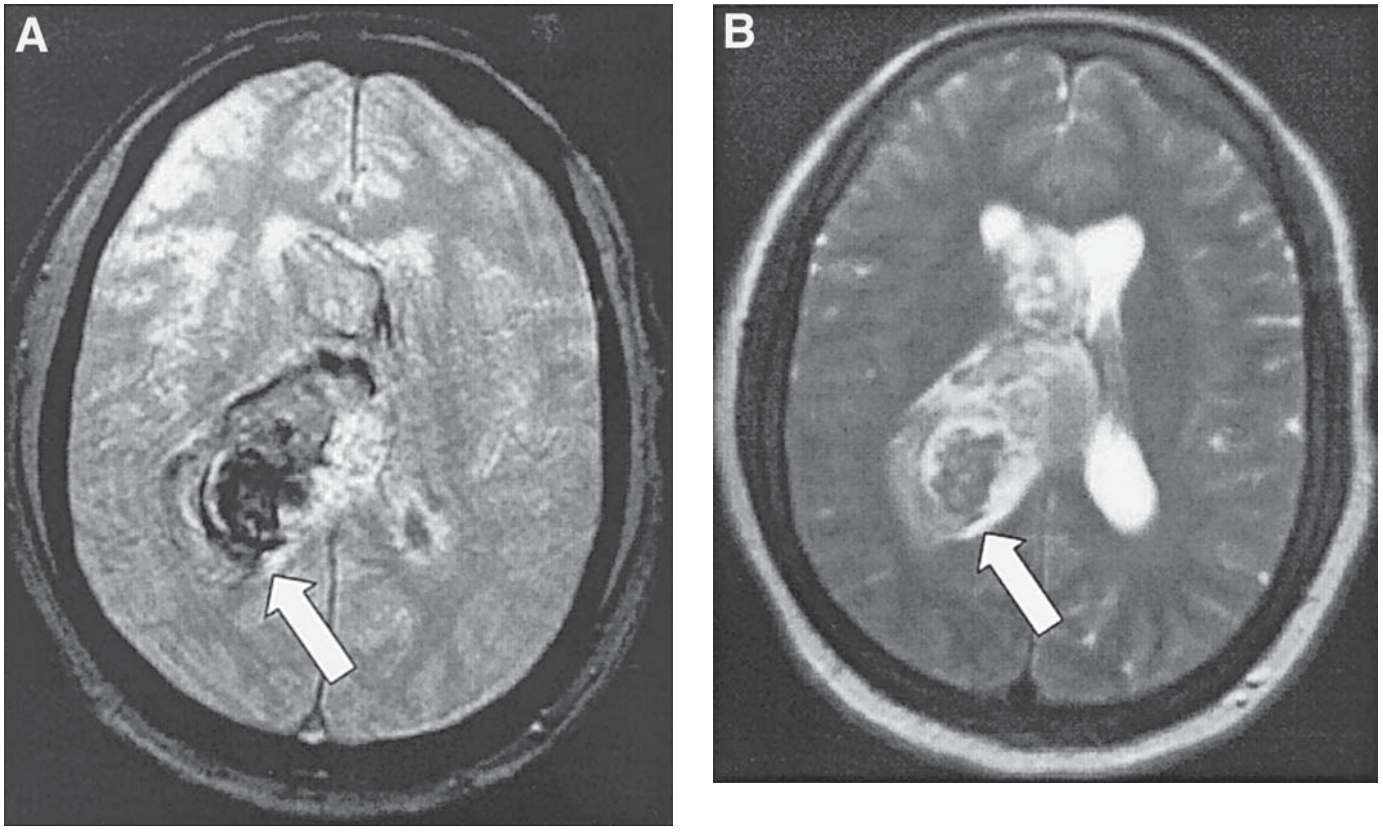


**Fig. 1.** Glioblastoma multiforme with intratumoral hemorrhage. A 51-yr-old female with left hemiparesis and global aphasia. **(A)** MRI gradient refocused echo sequence shows large areas of hypointensity reflecting intratumoral hemorrhage (white arrows); **(B)** T2-weighted MR sequence with mixed signal intensity (white arrow).

50% of meningioma-associated hemorrhages *(14)*. Cases of meningioma-associated bleeding have been reported with transitional and fibroblastic meningiomas as well *(9)*. Hemorrhages into medulloblastoma, choroid plexus papilloma, ependymoma, pineal region tumors, and primary intracranial sarcoma have also been reported.

**Metastases** Brain metastases are prevalent in the oncologic population, affecting 20–40% of all systemic cancer patients *(15)*. Among metastatic malignancies, two of the most common culprits associated with intratumoral hemorrhage are melanoma and lung cancer *(6,8)*. Bleeding into metastases has also been reported in patients diagnosed with renal cell carcinoma, sarcoma, stomach carcinoma, adrenal cancer, breast cancer, prostate cancer, choriocarcinoma, laryngeal cancer, testicular cancer, hepatocellular carcinoma, cholangiocarcinoma, neuroblastoma, rhabdomyosarcoma, acoustic neurinoma, carcinoid, and lymphoma. Bleeding with thyroid metastases has also been observed, and the diagnosis of thyroid metastases is a suggested consideration in a patient with multiple hemorrhagic masses *(7,16)*.

The most common clinical symptoms in patients with intratumoral brain hemorrhage are headache, nausea, vomiting, obtundation, and seizures *(6–8,10,17)*. Focal neurological deficits are also frequently present. Predisposing factors associated include head trauma, hypertension, coagulopathy, shunting procedures, and anticoagulation *(3,8,12,18)*. Various pathophysiologic processes likely contribute to the pathogenesis of intratumoral hemorrhage, including endothelial proliferation with vascular obliteration, vessel compression and distortion secondary to tumor growth, vessel necrosis, invasion of vessel walls by tumor, and an increase in venous pressure due to elevated intracranial pressure *(5,19–22)*. Histologic factors associated with intratumoral hemorrhage include rapid tumor growth, tumor necrosis, vessel thrombosis, the presence of multiple thin-walled vessels, and tumor invasion of adjacent cerebral vessels/vessel wall degeneration *(4–6,8,23)*.

Massive hemorrhage can develop in metastatic tumors in any location in the cerebral hemispheres, brain stem, and cerebellum. Both isolated and multiple hemorrhages have been observed. At present, computed tomography (CT) remains the imaging modality of choice in the detection of acute intracranial hemorrhage *(24)*. Magnetic resonance imaging (MRI) has also become increasingly used in the acute stroke setting, and preliminary reports suggest that susceptibility-weighted MRI sequences adequately detect acute intracerebral hemorrhage as well *(25,26)*. Hemorrhage into tumor must be differentiated from other etiologies of intracerebral hemorrhage, including cerebral aneurysm, vascular malformations, amyloid angiopathy, and hypertension. Unusual locations for hemorrhage should suggest an underlying etiology of tumor or vascular abnormality *(5,9)*. CT findings suggestive of tumoral hemorrhage include an indentation appearing on the hematoma surface on noncontrast studies and a hyperdense lesion appearing adjacent to the hematoma on postcontrast images. In one series,

CT scanning was able to differentiate the hemorrhage etiology in 61% of oncologic patients *(6)*. MR findings suggestive of tumoral hemorrhage are signal heterogeneity, evidence of nonhemorrhagic tumor mass, delayed hemorrhage evolution and hemosiderin deposition, and prolonged edema *(27)*. In one series, MR imaging revealed a tumoral etiology for intracerebral hemorrhage unrecognized by CT in 4% of patients studied with both modalities *(28)*.

Patient outcome after intratumoral hemorrhage is notably related to the specific histological malignancy of the tumor. Additionally, there appears to be a higher risk of recurrent hemorrhage if the tumor is incompletely excised or if metastases recur. Rebleeding is associated with graver prognosis *(6)*.

**SUBDURAL HEMORRHAGE** In cancer patients with cerebrovascular disease, subdural hematomas and subdural fluid collections are common, comprising 12.6% of all strokes and 25.8% of hemorrhagic lesions within this population *(1)*. Subdural hematomas have been reported in association with a wide variety of malignancies *(1,29–37)*. Typically, however, subdural hematomas tend to occur with dural tumor metastases *(1,38,39)*. Neoplastic infiltration of the dura results either from hematogenous spread of tumor via the dural vessels or from direct extension of skull metastases. Histologically, the tumors most frequently associated with subdural hematoma include gastric carcinoma, prostate carcinoma, breast cancer, leukemia, and lymphoma. Subdural hematomas have also been reported with meningioma, glioblastoma, seminoma, paranasal sinus cancer, sarcoma, and esophageal cancer.

Clinical manifestations of subdural hematoma in the oncologic population differ little from the general population. Patients may have an acute, subacute, chronic, or asymptomatic initial course. Graus and colleagues found that 26.4% of their 53 autopsied subdural hematoma patients with cancer were symptomatic *(1)*. The most common clinical symptoms are altered mental status, headache, and lethargy. Focal neurological deficits and seizures may also be present *(17,38)*.

Predisposing factors for subdural hematoma in cancer patients include trauma, anticoagulation, coagulopathy, and metastatic involvement. In Minette and Kimmel's series of 70 patients with systemic cancer and subdural hematoma, dural metastatic lesions were the most common cause of subdural hematoma in patients with no predisposing risk factors (21%) *(38)*. Of their patients with predisposing risk factors, trauma and anticoagulants appeared to be major predisposing risk factors in 68% of their patients with primary CNS tumor-associated subdural hematoma. Of their patients with hematologic malignancy-associated subdural hematoma, trauma, and anticoagulation posed a somewhat smaller risk, affecting 12%.

Three proposed potential mechanisms for the occurrence of subdural hematoma secondary to dural metastases include hemorrhage directly into the dural tumor, hemorrhage secondary to dilatation and rupture of inner dural layer capillaries/venules/veins due to outer vessel layer obstruction by tumor, and in rare cases, dural tumor production of a hemorrhagic effusion *(17,39)*.

Acute subdural hematomas, chronic subdural hematomas, and skull metastases are generally easily visualized with both CT and MRI. Isodense subdural hematomas, especially when present bilaterally, may be missed. Contrast studies are helpful in revealing dural enhancement suggestive of dural metastases. Histologic examination of the dura with biopsy or cytologic studies of the subdural fluid is necessary to confirm the tumoral origin of the subdural hematoma. Treatment of dural metastatic-associated hemorrhage is palliative and includes drainage of subdural fluid and brain radiation therapy *(17)*. If a cancer patient with subdural hematoma undergoes surgical treatment, an adequate biopsy of the dural membrane should be obtained. Radiation therapy should then be administered once the diagnosis is confirmed *(38)*.

## NEOPLASTIC INFILTRATION OF VESSELS

**Venous Infiltration** Thrombosis of cerebral veins or dural sinuses is a rare event in any patient population, including the oncologic population. In a recent series, cerebral venous thrombosis accounted for 0.3% of neurologic consultations at a large cancer center *(40)*. When obstruction of cerebral venous drainage in cancer patients occurs, a frequent culprit is invasion or compression of cortical veins or dural sinuses by tumor *(41)*. Direct dural/calvarial metastases are the most common cause of cerebral sinus thrombosis in patients with solid tumors, while procoagulable states are the most common cause in patients with hematologic malignancies *(40)*. Rarely, bulky leptomeningeal metastases can cause cerebral sinus occlusion *(42)*. The most common sinus affected by metastases is the superior sagittal sinus *(17,40)*. A variety of malignancies have been reported in association with sinus thrombosis, including leukemia, lymphoma, neuroblastoma, breast carcinoma, lung carcinoma, cervical carcinoma, gallbladder carcinoma, Ewing's sarcoma, and myeloma *(1,17,40,41,43)*. The proposed mechanism for dural sinus thrombosis due to local metastases is similar to that proposed for subdural hematoma: skull or dural metastases infiltrate or compress the sinus, producing stasis, thrombosis, and occlusion *(17)*.

The typical clinical presentation is headache, vomiting, papilledema, and seizures. Focal neurological signs and encephalopathy may also be seen, particularly in association with venous infarction due to sinus or cortical vein occlusion. The headache, often constant and severe, may be present for minutes to weeks prior to the development of focal neurological deficits *(41)*. Occasionally patients present with an isolated intracranial hypertension syndrome, with headache and papilledema as the only manifestations ("tumoral pseudotumor cerebri") *(44,45)*. Radiologic studies helpful in diagnosis include CT scanning with contrast dye to visualize the lack of a normal flow void within the sagittal sinus, a finding known as the "empty delta sign" *(46)*. Conventional MRI and MR venography are more reliable than CT, and are an excellent noninvasive method to diagnose and follow venous thrombosis. The sensitivity of MRI alone in detecting cerebral venous thrombosis is 90%; however, small case series suggest that sensitivity increases close to 100% with the concomitant use of MRA and MRV *(40,47)*. CT angiography/venography correlates well with MRV *(48)*. MRI is less sensitive than conventional catheter angiography, particularly in cases involving only the cortical veins. Conventional angiography/venography remains the gold standard. In catheter angiography/venography, the late venous phase of the injection will reveal a dural

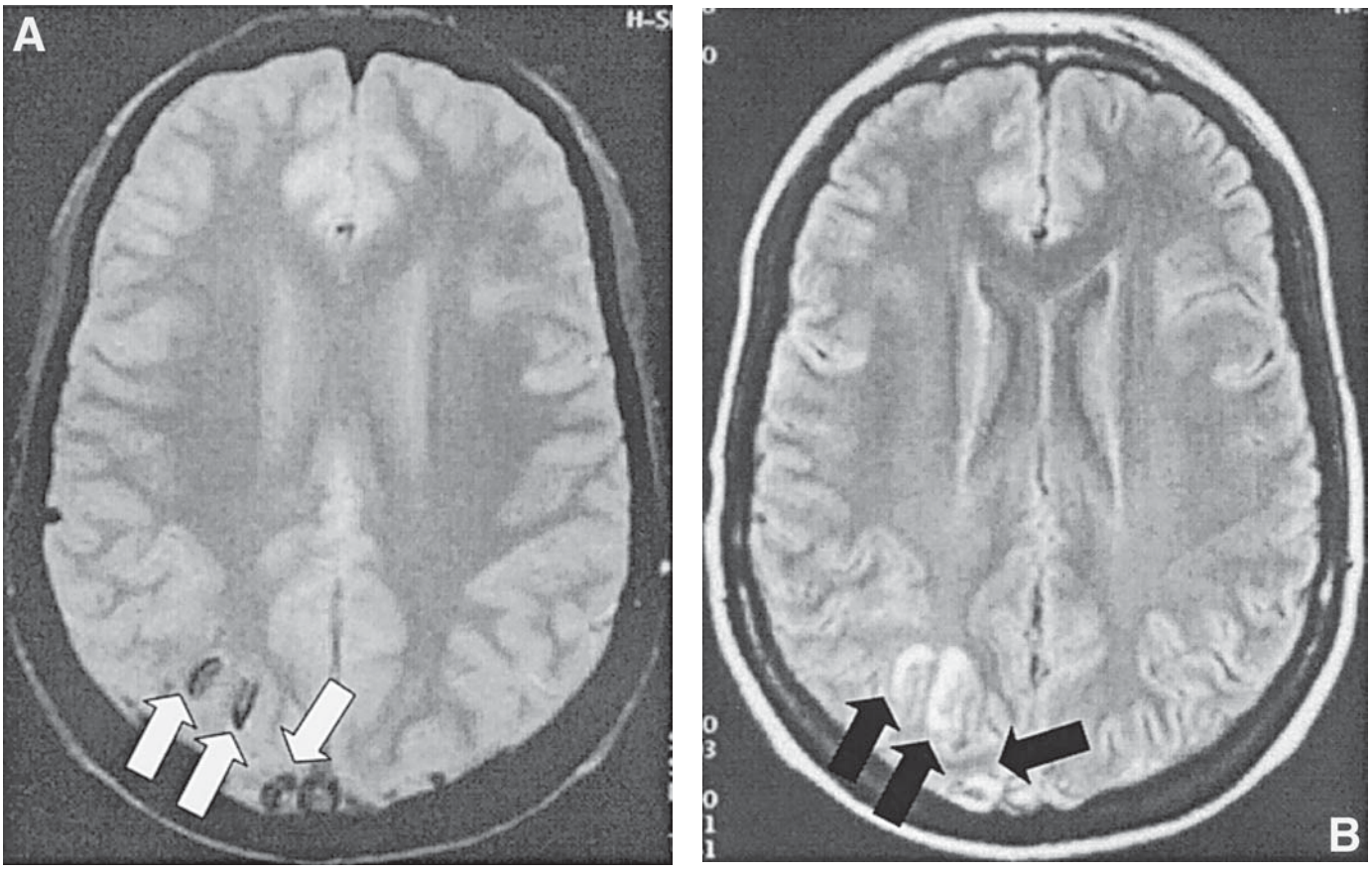


**Fig. 2.** Cerebral venous thrombosis related to leukemia. A 31-yr-old woman with acute lymphoblastic leukemia presented with generalized tonic-clonic seizures. **(A)** Gradient refocused echo imaging and **(B)** FLAIR imaging show multiple small areas of hemorrhage (arrows). **(C)** (*opposite page*) Magnetic resonance venography reveals occlusion at the anterior and posterior portions of the sagittal sinus and near occlusion of the right transverse sinus at its origin (white arrows) The occluded sinuses were reopened with catheter-administered tissue plasminogen activator and rheolytic thrombectomy with the Angiojet device.

sinus or cortical venous luminal deficit, consistent with impaired or absent venous drainage.

Two randomized clinical trials have studied the benefits and risks of anticoagulation in patients with sinus thrombosis without cancer. A small trial of intravenous, unfractionated heparin found a benefit, a larger trial of low molecular weight heparin only a nonsignificant trend to benefit *(49,50)*. Recent series in the literature have reported success in treating venous cerebral thrombosis with selective dural catheterization and local thrombolysis *(51,52)*. Endovascular mechanical rheolytic thrombectomy followed by low-dose local thrombolysis (for persistent cortical vein thrombosis) is an additional emerging treatment modality that has been reported to accelerate recanalization of occluded dural sinuses (*see* Fig. 2) *(53)*. The safety and efficacy of these treatments in the oncologic population is not established. Radiation therapy or surgical intervention should also generally be pursued in patients with cerebral sinus occlusion due to metastases *(17,44)*.

**Arterial Infiltration** Neoplastic infiltration of arterial vessels has been reported to cause both hemorrhagic and ischemic strokes. Commonly, neoplastic infiltration of arteries results first in aneurysm formation, and subsequent aneurysm rupture then produces intracerebral and/or subarachnoid hemorrhage. Less often, aggressively destructive tumoral invasion produces pseudoaneurysms–vessel breakdown and rupture without formation of a true aneurysm (*see* Fig. 3). Cardiac myxomas account for two-thirds of neoplastic aneurysms and choriocarcinoma for one-quarter, with rarer cases due to bronchogenic carcinoma, undifferentiated carcinoma, and glioma *(1,54–56)*. Neoplastic aneurysms are typically small in size and are often located in distal cerebral arterial branches, in contrast to saccular aneurysms, which typically arise in proximal cerebral arteries around the circle of Willis. One potential mechanism for the formation of neoplastic aneurysms is that a tumor embolus invades the arterial wall but does not cause a major infarct, either because the embolus is only partially occlusive or because collateral flow continues to perfuse the area. The tumor damages vessel wall integrity, and hydrostatic pressure from flow through the arterial lumen results in dilatation of the damaged arterial wall *(1,54)*. A second, perhaps less frequent potential mechanism is secondary invasion of nearby vessels by parenchymal brain metastases *(1)*.

Ischemic stroke has also been associated with tumor infiltration of arteries. Autopsy studies of cancer patients with leptomeningeal metastases have documented ischemic strokes due to neoplastic arterial wall infiltration *(57–59)*. Metastases to the leptomeninges are a relatively uncommon complication of systemic cancer *(60)*. The neoplasms most frequently associated

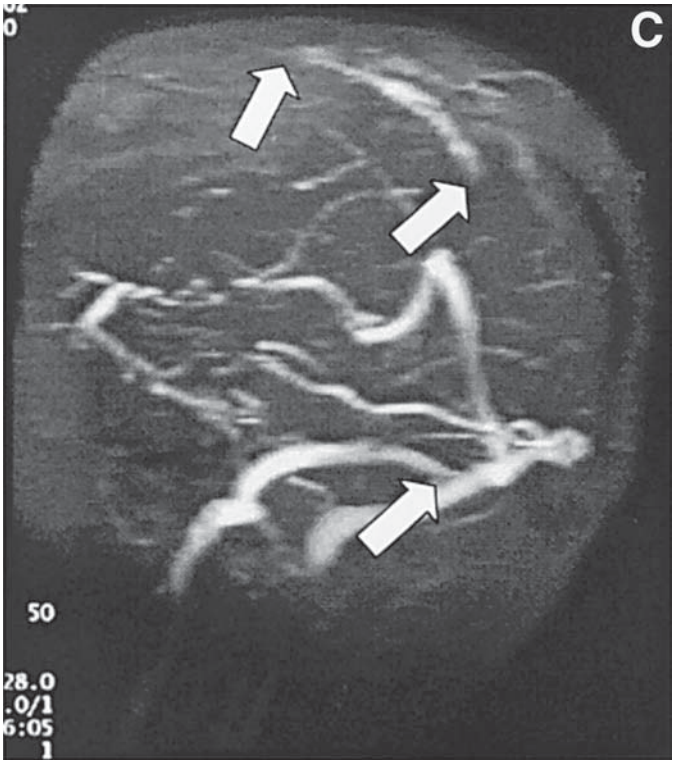


**Fig. 2C.**

with leptomeningeal metastasis include breast cancer, lung cancer, melanoma, and hematologic malignancies *(58)*. Patients suffering from stroke secondary to leptomeningeal metastases present with abrupt, focal neurological deficits in addition to the typical features of leptomeningeal metastases such as meningeal irritation and nerve root lesions *(57,58)*. There are two proposed mechanisms for cerebral infarction due to leptomeningeal metastases: infarction due to infiltration of arterial walls by tumor cells and infarction due to pial vessel vasospasm *(61)*. Focal arterial wall invasion by adjacent tumor, rather than tumor embolus, has been suggested to result in a tumor-associated vasculopathy in these cancer patients *(57,58)*. Pathologically, multifocal mural invasion by tumor cells with occlusion of the arterial vessel is accompanied by a variable perivascular inflammatory reaction and intraluminal thrombosis. Angiography may reveal focal arteriolar narrowing at the base of the brain, over the cerebral convexities, or both *(17,58,62)*.

**Hematologic Malignancies** Proliferation of blood elements can lead to ischemic stroke both by direct, hyperviscous obstruction of arterial vessels by neoplastic cells and by an induced procoagulant state. Thrombocytosis in polycythemia vera is linked to transient ischemic attacks and cerebral infarction *(17,63)*. Ischemic stroke accounted for approx 33% of 119 neurologic events reported in 443 patients with polycythemia vera followed by the Polycythemia Vera Study Group *(63,64)*. Cytoreductive treatment of blood hyperviscosity by phlebotomy or chemotherapy substantially reduces thrombotic events and improves survival. The rate of stroke in a more recent large cohort of aggressively treated patients was reported at 0.3% annually *(65)*. Patients with essential thrombocythemia have an increased risk of transient ischemic attack and ischemic stroke *(66)*. Cytoreductive therapy and low-dose aspirin appear beneficial in this population *(67)*.

Intravascular lymphomatosis is an uncommon variant of non-Hodgkin's lymphoma characterized by a proliferation of lymphoma cells within small caliber blood vessels, with a predilection for the cerebral circulation *(68,69)*. Clinical presentations are protean, but most commonly patients present with systemic manifestations of fever, anemia, and elevated sedimentation rate, subacute progressive multifocal cerebral infarcts, and/or a rapidly progressive encephalopathy. Neuroimaging frequently shows multiple infarcts and parenchymal and meningeal enhancement *(70)*. Noninvasive and catheter angiography may demonstrate a vasculitis-like appearance. Chemotherapy or radiotherapy can initially stabilize the clinical course, but average survival from symptom onset is only 4 mo.

**TUMOR EMBOLUS** Interestingly, although tumor embolus is generally thought a common cause of cerebral metastases, ischemic stroke directly secondary to tumor embolism is rare. In Graus and colleagues' review of 256 patients with known systemic cancer and stroke, only two patients had tumor emboli listed as the etiology of their infarcts *(1)*.

Most reported cases of ischemic stroke due to tumor emboli have resulted from intracardiac tumors. The incidence of primary cardiac tumors in autopsy series ranges from 0.000017% to 0.03% *(71)*. In general, half of these tumors are myxomas, with the other 50% being papillary fibroelastomas (papillomas), hamartomas, malignant neoplasms, teratomas, and other uncommon intracardiac tumors *(72)*. Myxomas are located far more commonly in the atria than in the ventricles. Neurological complications most commonly occur from myxomas in the left atrium, especially from polypoid lesions with soft, irregular shapes and a mobile surface *(73–75)*. Of nonmyxomatous benign primary cardiac tumors, papillomas are the most frequent cause of emboli to the cerebrovascular circulation *(71,76,77)* (*see* Fig. 4). Other benign cardiac tumors such as fibrolipomas, rhabdomyomas, teratomas, lipomas, and hemangiomas have been reported in the literature, yet none have been associated with cerebrovascular complications *(71)*. Among the primary malignant cardiac tumors, myxosarcomas have been associated with stroke in case reports *(78)*, while fibrosarcoma and rhabdomyosarcoma have not been reported to result in neurologic complications.

Cerebral infarction may occur from tumor emboli arising from tumors that have metastasized to the heart *(79)*. The most common malignant neoplasms metastasizing to the heart include lung carcinoma and breast carcinoma, followed by melanoma, lymphoma, leukemia, and sarcoma *(71,80,81)*.

Among nonprimary cardiac tumors, cerebral infarction due to tumor emboli has been reported most frequently with choriocarcinoma and lung carcinoma *(1,71,82)*. Ischemic stroke secondary to tumor emboli has also been reported with pulmonary myxosarcoma, adrenal cortical carcinoma, thyroid carcinoma, chondrosarcoma of the femoral head, osteogenic sarcoma, breast carcinoma, synovial cell sarcoma, colon adenocarcinoma, hypopharyngeal epidermoid carcinoma, squamous carcinoma of the mediastinum, testicular carcinoma, and bronchial

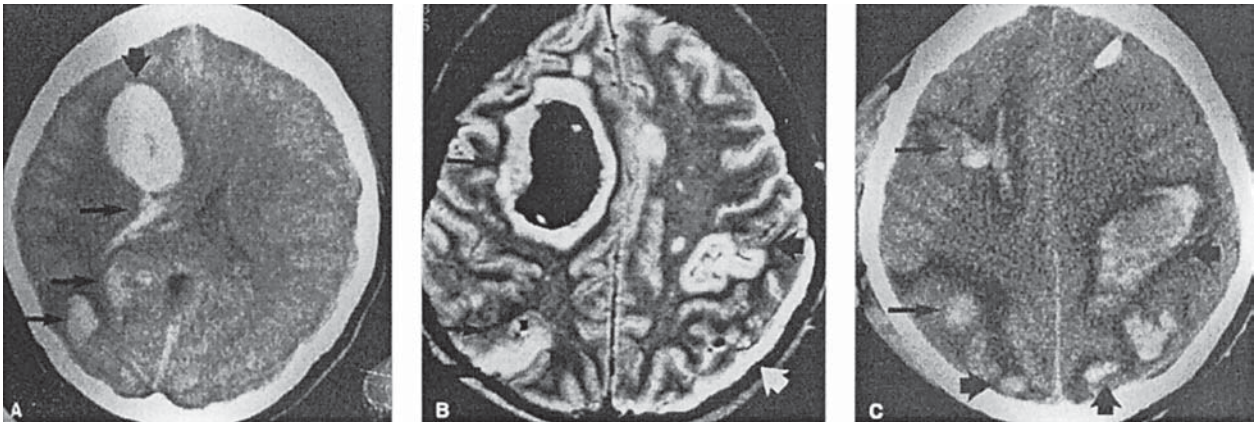


**Fig. 3.** Intracerebral hemorrhages due to metastatic choriocarcinoma with pseudoaneurysm formation. A 33-yr-old woman developed recurrent intracerebral hemorrhages 5 mo following delivery of a term infant. She died after suffering her 10th hemorrhage. Autopsy revealed intrauterine choriocarcinoma with diffuse metastases. Multiple tumor emboli and thrombosis occluded the left carotid artery. Microscopically, numerous meningeal arteries and arterioles were infiltrated with choriocarcinoma. (A) Computed tomography on hospital d 20 with new right frontal hemorrhage and old right parietal hemorrhages with extension to lateral ventricle (small arrows). (B) Magnetic resonance imaging on d 25 showing new left posterior frontal hemorrhage (large black arrow) and left parieto-occipito-temporal subdural hematoma (large white arrows) and old right frontal and parietal hemorrhages (small arrows). **(C)** Computed tomography on d 29 with new left frontal and occipital hemorrhages (large arrows) and old right temporal and parietal hemorrhages (small arrows). Adapted with permission from ref. *54*.

carcinoma *(1,83–85)*. Finally, although rare, aortic arch tumor-associated embolic stroke has also been reported *(86)*.

Ischemic stroke secondary to tumor emboli may affect either or both the anterior and posterior circulations. Transient ischemic attacks may precede the cerebral infarction *(83)*. Symptoms tend to occur suddenly, and patients frequently exhibit focal neurological deficits on examination. Multiple microscopic tumor emboli to small vessels may also clinically present as an encephalopathy *(87)*. History and physical examination evidence of cardiac dysfunction are helpful in identifying a cardiac tumor as a potential source, with dyspnea, peripheral edema, and precordial murmurs the most common cardiac clinical manifestations *(72,83)*. In many patients, death shortly follows cerebral infarction *(83)*.

When noncardiac tumor emboli produce cerebral infarcts, the most likely mechanism is an embolus originating from a primary or metastatic pulmonary tumor. The embolus accesses the pulmonary venous system, passes through the left heart chambers, and reaches and occludes the intracranial arterial circulation.

Diagnostically, echocardiography is a reliable means of noninvasively diagnosing intracardiac tumors *(73,74,88,89)*. Both transthoracic and transesophageal approaches are helpful in diagnosing the presence of an intracardiac tumor, and in suggesting tumor type by evaluating the area of tumor attachment, tumor size, and degree of mobility. Transesophageal echocardiogram is superior to transthoracic in evaluating right atrial and small and atypically situated left atrial tumors. False-negative echocardiograms have been reported in cardiac neoplasm patients. MRI and CT may also contribute to the diagnosis of intracardiac tumor, and are useful in delineating the extent of tumor involvement in the great vessels and mediastinum *(86,90,90)*. Tissue diagnosis involves obtaining a pathological specimen through endomyocardial biopsy or through surgical resection of the tumor *(75,92)*. Caution must be exercised when obtaining tissue in atrial myxoma patients, as these tumors are fragile and may embolize during resection.

The rapidity of tumor progression, cardiac complication rate, and recurrent stroke rate are unpredictable in cardiac tumors. Thus, the treatment of choice in these patients is prompt surgical resection. In addition, some authors suggest that cerebral aneurysms may improve after resection of the primary cardiac tumor *(71,93)*.

**PITUITARY APOPLEXY** Pituitary apoplexy is a distinctive clinical entity characterized by hemorrhage, infarction, or both, primarily in pituitary adenomas, occasionally in nontumorous pituitary glands *(94,95)*. The classical clinical presentation is sudden retro-orbital headache, vomiting, visual impairment, oculomotor paresis, and meningismus. Partial or complete hypopituitarism follows. In different series, the incidence of pituitary adenomas presenting with apoplexy ranges from 1.5–27%. Pathologic examination frequently demonstrates hemorrhage or hemorrhagic infarction, with bland infarction less common. Proposed mechanisms include tumor growth outstripping blood supply leading to ischemic necrosis, compression of vessels by tumor causing ischemia, tumor associated intracranial aneurysms, and an intrinsic bleeding tendency of pituitary adenomas. MRI is superior to CT for radiologic diagnosis. Transphenoidal decompression of apoplectic tumors is commonly pursued, although many cases treated with conservative medical therapy recover well.

## II. STROKE DUE TO REMOTE EFFECTS OF TUMOR: HYPER AND HYPOCOAGULOPATHIES

**HYPERCOAGULABILITY AND THROMBOSIS** Coagulation disorders resulting in thrombosis and/or hemorrhage commonly complicate the natural history of cancer and its treatment. Hypercoagulability in cancer patients was first described by Trousseau in 1865, who reported "accelerated bleeding times" and thrombophlebitis in greater than 60% of the onco-

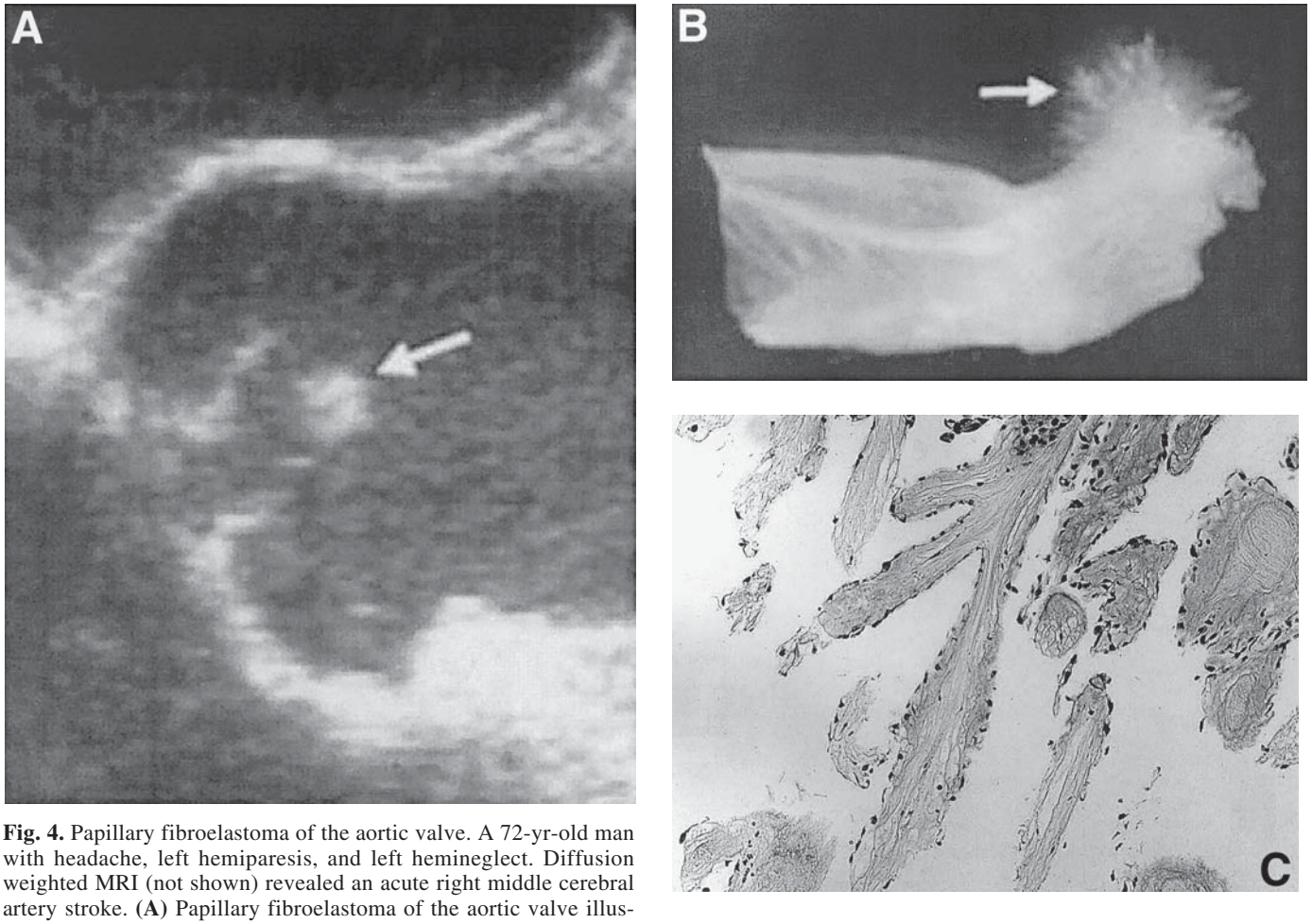


**Fig. 4.** Papillary fibroelastoma of the aortic valve. A 72-yr-old man with headache, left hemiparesis, and left hemineglect. Diffusion weighted MRI (not shown) revealed an acute right middle cerebral artery stroke. **(A)** Papillary fibroelastoma of the aortic valve illustrated with transesophageal echocardiogram (white arrow), with **(B)** "sea anemone" appearance on gross examination (white arrow), and **(C)** multiple branching fronds noted on microscopy. Adapted with permission from ref. *76*.

logic patients he observed *(96)*. Modern studies confirm that abnormalities of the coagulation system are indeed remarkably common in the cancer patient. Hemostatic abnormalities on blood tests are found in more than 90% of oncologic patients and venous thromboembolism and disseminated intravascular coagulation complicate the course of 15%. Increases of coagulation factors V, VIII, IX, and XI are often documented in malignancy. Markers of coagulation activation are frequently elevated, including prothrombin fragment 1.2, thrombin antithrombin complex, fibrin degradation products, and D-dimers. Also consistent with a consumptive coagulopathy is the frequent finding of increased fibrinogen and platelet turnover.

The pathogenesis of cancer-related thrombophilia is complex and multifactorial. The interaction of neoplastic cells with the hemostatic system includes activation of the coagulation and fibrinolytic systems directly, release of inflammatory cytokines, perturbation of the vascular endothelium, activation of monocytes and platelets, and promotion of blood stasis *(97–100)*. Tumor cells release multiple procoagulant substances, among which the best characterized are tissue factor, cancer procoagulant, and a factor V receptor. Most tumor cells express on their surface all the major proteins that regulate the fibrinolytic pathway, including urokinase- and tissue-type plasminogen activator and plasminogen activator inhibitors 1 and 2. Among the proinflammatory cytokines released by tumor cells, several can impair the normal anticoagulant activity of the vascular endothelium, including TNF-$\alpha$ and IL-1$\beta$. Tumor cells also interact with vascular endothelium through direct adherence by membrane adhesion molecules, including integrins and selectins. Malignant cells attached to vessel walls promote localized clotting activation and thrombus formation. Tumor cells activate platelets by several distinct mechanisms, including platelet adhesion to tumor cell surface and malignant cell release of proaggregratory molecules, including ADP and a cathepsin B-like cysteine proteinase. Tumor cells also activate the monocyte-macrophage system and induce their expression of tissue factor. Stasis occurs frequently in cancer patients due to general debilitation and to narrowing of vessels by local tumor growth and infiltration.

In general, venous thromboembolism is more frequent in solid tumors, while disseminated intravascular coagulation (DIC) is more common in widespread metastatic cancer and hematologic malignancies. The neoplasms most frequently associated with thrombosis include colon cancer, gallbladder cancer, gastric cancer, lung cancer, ovarian cancer, pancreatic cancer, paraprotein disorders, and myeloproliferative syndromes *(101,102)*. While venous occlusions are far more frequent, arterial occlusions also occur as a result of an oncologic-associated hypercoaguable state.

**Venous Occlusions** Cerebral venous thrombosis can occur not only from direct tumor invasion of the dural sinuses (reviewed earlier), but also from a hypercoagulable state induced by a remote neoplasm. Thrombophilia is the most common cause of cerebral venous thrombosis in patients with hematologic malignancies, with direct dural/calvarial metastases the leading etiology in patients with solid tumors *(40)*. Treatment options, as reviewed previously, include anticoagulation, local, catheter-administered thrombolysis, and emerging endovascular mechanical recanalization techniques.

In addition to the general hypercoagulable state of malignancy, several molecular abnormalities in the hemostatic system have been particularly associated with cerebral venous thrombosis in the oncologic population.

***Acquired Protein S Deficiency*** Acquired protein S deficiency has been reported in association with leukemia, multiple myeloma, and pancreatic adenocarcinoma *(103–105)*. Total protein S concentrations may be normal to high but free protein S concentrations low in patients with advanced cancer *(104,105)*. Recurrent thrombotic processes despite warfarin therapy have been noted in patients with acquired free protein S deficiency *(105)*. An increase in the C4b binding protein by the neoplasm-induced free protein S deficiency contributes to the predilection for venous thromboses. As warfarin treatment may result in an additional decrease of free protein S, unfractionated heparin and low molecular weight heparin are preferred anticoagulants if recurrent thrombosis occurs on warfarin *(105)*.

Low free protein S is not the sole cause of functional protein S deficiency in the oncologic population. One patient with chronic lymphocytic leukemia and associated recurrent venous thromboses reportedly had undetectable activity levels of protein S. Laboratory investigation revealed the concomitant presence of an inhibitor directed against protein S as well as a monoclonal protein in the patient's plasma. After treatment with prednisone and cyclophosphamide the protein S inhibitor and the monoclonal protein disappeared, suggesting that treatment of the underlying malignancy can be an important factor in addressing acquired protein S deficiency in this population *(106)*.

***Protein C Deficiency*** Venous thrombosis due to marked protein C deficiency has been reported in association with hepatocellular carcinoma, chronic lymphocytic leukemia, acute monocytic leukemia, and acute myeloid leukemia *(107,108)*. The presence of a second hypercoagulable risk factor, such as heterozygosity for the factor V Leiden mutation, may increase risk for venous thrombosis *(107)*.

***Activated Protein C Resistance*** Activated protein C resistance is most commonly due to an Arg506-Gln point mutation in the Factor V gene. The Factor V Leiden mutation may interact with malignancy-induced or chemotherapy-induced hypercoagulability to cause thrombosis. In a prospective study of 65 children with leukemia and 65 controls, three children in each group had the Factor V Leiden gene mutation *(109)*. The three children in the leukemic group all had venous thromboembolic events, whereas the three children in the control group did not.

Activated protein C resistance may occur as an acquired condition, independent of the Factor V Leiden mutation, in oncologic patients. In a prospective study of 113 adult cancer patients with and without venous thromboembolism and 110 control patients with and without thromboembolic events, cancer patients with thromboembolism had a significantly greater prevalence of acquired activated protein C resistance than cancer patients without thromboembolism or both control groups. Control patients with thromboembolism had a significantly higher prevalence of Factor V Leiden mutation than did the cancer patients *(110)*. Cohort studies of cancer patients with advanced disease have found that 13–55% of patients exhibit acquired activated protein C resistance *(111,112)*.

**Arterial Occlusions** Arterial cervicocephalic occlusions occur less frequently in the hypercoagulable states of malignancy than venous thromboembolism, but constitute a major source of morbidity. Three common culprits responsible for arterial occlusions in cancer-associated thrombophilia are: nonbacterial thrombotic endocarditis, mucin positive adenocarcinoma associated hypercoaguability, and hypercoagulability secondary to an antiphospholipid syndrome.

***Nonbacterial Thrombotic Endocarditis*** In 1938, Sproul described widespread venous thrombosis, multiple arterial infarcts, and nonbacterial thrombotic endocarditis (NBTE) in patients with pancreatic cancers *(113)*. Since that time, a variety of studies have linked NBTE with cancer and with embolic phenomena, typically to the arterial circulation. In NBTE, an underlying coagulopathy results in a predisposition for sterile platelets and fibrin to deposit on cardiac valves *(114–116)*. An autopsy series found that NBTE is significantly more common in cancer patients than in patients without malignancy, 1.25 vs 0.2% *(117)*. Vegetations are most commonly located on the aortic and mitral valves, although thrombi have also been reported on the tricuspid and pulmonic valves. Dual valve involvement occurs in roughly 12% of patients *(118)*.

NBTE is the most common cause of ischemic stroke in the oncologic population *(114,116)*. Although NBTE is associated with a variety of neoplasms, recent studies suggest that it most commonly occurs in adenocarcinoma patients *(114,116,117)*. In a large autopsy study, the frequency of NBTE in the setting of adenocarcinoma was 2.7 vs 0.5% with other malignancies. Of the adenocarcinomas themselves, NBTE was most strongly associated with pancreatic cancer in comparison with other forms of adenocarcinoma (10.3 vs 1.6% risk) *(117)*. Several other studies have found that mucin-producing adenocarcinomas, of which many are pancreatic, are strongly associated with NBTE *(17,114,119)*. MacDonald and Robbins' autopsy series in 78 cancer patients with NBTE noted that, although the sites of the primary tumors differed significantly, all the neoplasms were well-differentiated and mucinous *(120)*. Histochemical studies on the valvular vegetations and thrombi in NBTE patients with mucin-producing adenocarcinomas have revealed that histochemically stainable mucin was an integral part of the vegetation/thrombi *(119)*.

Primary tumors associated with NBTE include pancreatic adenocarcinoma, lung adenocarcinoma, colon adenocarcinoma, esophageal epidermoid adenocarcinoma, gastric adenocarcinoma, duodenal adenocarcinoma, hepatocellular

carcinoma, breast carcinoma, cervical epidermoid adenocarcinoma, poorly differentiated cervical adenocarcinoma, prostate adenocarcinoma, ovarian adenocarcinoma, endometrial adenocarcinoma, bladder epidermoid tumors, testicular germ cell tumors, malignant melanoma, tongue epidermoid tumors, larynx epidermoid tumors, malignant thymoma, malignant glioma, sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, acute leukemia, and multiple myeloma.

Systemic thromboembolism (thrombophlebitis of a limb, pulmonary embolism, myocardial infarction) may be clues to an underlying NBTE. One-third of patients, however, have only neurologic symptomatology. NBTE can result in either focal, diffuse encephalopathic, or mixed neurological deficits when there is embolization from the affected cardiac valve to the brain. Spinal cord infarction has also been reported *(121)*. Focal neurological signs in NBTE-associated embolism begin abruptly and may be preceded by transient ischemic attacks. A small to moderate proportion of patients have a concomitant disseminated intravascular coagulation (DIC) syndrome as evidenced by laboratory testing; however, the majority of patients with NBTE have only mildly abnormal coagulation parameters *(114,118,122)*. Although NBTE typically occurs in disseminated cancers, NBTE can precede the diagnosis of malignancy and may be the initial sign of occult neoplasm *(17,114,123)*.

The diagnosis of NBTE is most often rendered in vivo by echocardiographic detection of valvular vegetations *(17,115)*. Transesophageal echocardiogram may be more sensitive than transthoracic *(115, 124,125)*. Blood cultures are negative for an infectious process. Both neuroimaging and autopsy studies show cerebral infarcts that may be multiple, sometimes with a hemorrhagic component *(126,127)*. Cerebral angiography typically discloses multiple abrupt vessel branch occlusions *(114)*, but may show changes suggestive of vasculitis *(127)*.

Treatment of NBTE should focus on the underlying etiology of the coagulation disorder, such as the neoplasm itself or a sepsis/DIC picture indirectly due to the neoplasm or its treatment. There are no prospective studies of anticoagulation in these patients; however, authors of individual case reports and retrospective cases series suggest that anticoagulation with heparin appeared to reduce ischemic symptomatology in certain patients *(114,122)*. The potential benefits of anticoagulation should be weighed cautiously against the potential risks of hemorrhage in each cancer patient with NBTE-associated stroke.

***Mucin-Positive Adenocarcinoma Associated Hypercoaguabilit***y Mucin-producing adenocarcinomas have also been associated with arterial ischemic stroke, both in association with and independently of NBTE. A 1989 study by Amico and colleagues examined oncologic patients with mucinous adenocarcinoma, systemic infarcts, and cerebral infarcts, clinically and at autopsy *(101)*. Widely disseminated metastases were present in all cases. All patients had microinfarcts, which tended to be disseminated throughout the nervous system. Most patients also had large brain infarcts, and frequently patients had small to moderate sized infarcts as well. The large infarcts involved the territories supplied by the common carotid, internal carotid, middle cerebral, and the superior cerebellar arteries. Nervous system compromise was widespread, and included the cerebral hemispheres, cerebellum, brainstem, basal ganglia, spinal cord, and dorsal spinal roots. Petechial and small hemorrhages were also relatively common.

In all cases in the Amico series, intravascular mucin was noted within CNS capillaries and small arteries on pathological examination *(101)*. Mucinous material was most commonly located in areas of necrosis/brain infarct, in areas of hemorrhage, and in the microcirculation surrounding the dorsal spinal roots. The mechanism of hypercoaguability in mucin-secreting adenocarcinoma is still not clearly understood. Mucin itself may be prothrombotic, mucin-producing tumor cells may themselves be prothrombotic, or both *(101,128)*. At present the diagnosis of mucin positivity is only reliably made pathologically. Treatment of the underlying malignancy is of utmost importance to reduce further cerebrovascular events. Cautious anticoagulation has been suggested in the setting of ischemic stroke and mucin-positive neoplasm, although this therapy is unproven.

***Antiphospholipid Antibodies*** Antiphospholipid antibodies increase the risk of both arterial and venous cerebral thrombosis *(129)*. An antiphospholipid antibody may occur in up to 17% of patients with active underlying malignancies *(130)*. Antiphospholipid antibodies have also been noted in oncologic patients in clinical remission *(131)*. There are multiple subspecies of antiphospholipid antibodies, including anticardiolipin antibodies, the lupus anticoagulant, and antibeta 2-glycoprotein 1 antibodies. Non-Hodgkin's lymphoma has been associated with both positive anticardiolipin and antibeta2-glycoprotein-I antibodies *(132)*. Positive lupus anticoagulant and anticardiolipin antibodies have also been associated with thymoma, leukemia, lymphoma, ovarian cancer, and mesothelioma, often in the setting of transient ischemic attack and stroke *(133–141)*. Treatment of the underlying malignancy may result in resolution of the antiphospholipid syndrome. One report of a chronic myeloid leukemic patient with positive lupus anticoagulant antibodies noted disappearance of the antibodies after allogenic bone marrow transplant *(142)*.

***Hyperfibrinogenemia*** Hyperfibrinogenemia has been associated with transient ischemic attacks, ischemic stroke, atherosclerotic carotid plaques, and internal carotid artery occlusion *(143–145)*. Plasma fibrinogen levels have been shown to be statistically higher in ischemic stroke patients than in TIA or normal control patients *(144)*. Atherosclerotic plaques from patients with carotid disease and hyperfibrinogenemia are characterized by a high incidence of thrombosis compared with plaques of patients with low to moderate fibrinogen levels. Plaque rupture has also been associated with high fibrinogen levels, and a multivariate logistical regression analyzing 71 carotid plaques found that hyperfibrinogenemia is an independent risk factor for decreased cap thickness, macrophage foam cell cap infiltration, and thrombosis *(145)*.

Hyperfibrinogenemia is common in cancer patients. A prospective laboratory study of 108 oncologic patients demonstrated hyperfibrinogenemia in 46% *(146)*. Hyperfibrinogenemia in the setting of malignancy has been associated with internal carotid artery occlusion and ischemic stroke *(143)*.

**COMBINED HYPERCOAGUABILITY/BLEEDING DIATHESIS** Normal physiologic hemostasis involves a balance between thrombus formation and thrombolysis. Disseminated intravascular coagulation (DIC) is characterized by widespread activation of coagulation, with resulting acceleration of fibrin clot formation and thrombotic occlusion of small- and medium size vessels. Concurrently, consumption and depletion of platelets and coagulation proteins may induce severe bleeding. Patients may present with symptoms and signs of excessive hypercoaguability, uncontrolled hemorrhage, or both simultaneously *(147,148)*. DIC in cancer patients has been associated with both ischemic stroke as well as intracerebral hemorrhage *(149–153)*. The DIC course, chronic vs acute, may be an important predisposing factor for the type of stroke that occurs in oncologic patients.

The chronic, or compensated, form of DIC is typically seen in patients with solid tumors such as adenocarcinoma of gastrointestinal, lung, or breast origin. Chronic DIC more often manifests as thrombosis, rather than bleeding, although both hematologic dyscrasias are possible. Chronic DIC has been reported in the clinical settings of venous thrombosis, NBTE, and mucin-positive adenocarcinoma-associated thrombosis. Patients in chronic DIC typically present with deep venous thrombosis and pulmonary thromboembolism, although some may develop arterial ischemic stroke as well.

Acute, or uncompensated, DIC occurs most frequently with hematogenous malignancies such as acute promyelocytic leukemia and acute myelogenous leukemia, and less often with solid tumors. Acute DIC typically presents as abnormal bleeding with concomitant thrombosis. Bleeding from venipuncture sites and surgical wounds may be seen, as well as diffuse mucosal, skin, or retroperitoneal hemorrhage. CNS hemorrhage is a significant, potentially fatal complication, especially in acute promyelocytic leukemia *(149,150)*. Although the clinical picture is dominated by evidence of hemorrhage, autopsy examinations often provide striking evidence of diffuse venous and arterial thrombosis.

Routine coagulation tests, such as the prothrombin time (PT) and the partial thromboplastin time (PTT), may be normal or only mildly prolonged in DIC, especially the chronic variety. Fibrinogen levels may be low due to consumption, but often are normal because of an acute phase response. A platelet count less than 100,000, or one that is rapidly declining, is suggestive. Additional molecular markers of hemostatic system activity that frequently provide laboratory support for the diagnosis include serum levels of D-dimer, fibrinopeptide A, thrombin-antithrombin complex, plasmin-plasmin inhibitor complex, and soluble fibrin monomer *(149,154,155)*.

No prospective clinical trials exist regarding the optimal treatment for chronic or acute DIC associated with symptomatic thrombosis. Treatment of the precipitating cause, the malignancy, is fundamental to successful long-term therapy *(147,149)*. Anticoagulants, by interrupting the coagulation cascade, are of theoretical benefit. Unfractionated and low molecular weight heparins have appeared beneficial in small, uncontrolled cohorts, but have not been definitively evaluated in controlled clinical trials *(147,156)*. Even in patients with bleeding, heparin in cohort studies appears to be relatively safe. A low starting dose of heparin is often recommended, for example continuous infusion of unfractionated heparin at 5–10 U/kg/h, adjusting the dose as needed to stabilize and normalize platelet count and fibrinogen level. Direct thrombin inhibitors are promising, but also not validated in controlled trials. Administration of antithrombin III concentrate at supraphysiologic doses has shown modest benefit in controlled clinical trials *(147,157)*. In patients with severely low levels of platelets and coagulation factors, treatment with platelet transfusion and plasma is beneficial.

**BLEEDING DIATHESIS/HEMORRHAGE**

**Primary Fibrinolysis** Primary fibrinolysis is characterized by systemic activation of plasmin or direct fibrinogen degradation, and intracranial hemorrhage may result. Both DIC and systemic primary fibrinolysis may co-exist in patients with acute promyelocytic leukemia and in patients with prostate cancer. Primary fibrinolysis alone has been observed in lymphoblastic leukemia, monocytic leukemia, sarcoma, and in urothelial malignancies *(149,158)*. Neoplasms may precipitate primary fibrinolysis through several potential mechanisms, including direct tumor production of tissue plasminogen activator (t-PA), direct tumor production of urokinase plasminogen activator (u-PA), and direct tumor production of a protease that digests fibrinogen. Laboratory findings suggesting the diagnosis of primary fibrinolysis include a normal platelet count in the setting hemorrhage associated with hypofibrinogenemia, elevated fibrinogen degradation products, and negative tests of markers of activation of the coagulation system. Factors V and VIII may be diminished due to plasmin digestion. Treatment consists of administering cryoprecipitate or fresh frozen plasma. If DIC is convincingly excluded, epsilon-aminocaproic acid, or tranexamic acid may also be given *(149,159)*.

**Hyperleukocytic Syndrome** The primary neurological manifestation of the hyperleukocytic syndrome is intracranial hemorrhage *(148,160)*. The hyperleukocytic syndrome is a distinct entity that typically affects patients with acute myelogenous leukemia (AML), although it can also occur in chronic lymphocytic leukemia. The increased number of abnormal white blood cells, or myeloblasts, elevates the patient's white blood cell count. Circulating myeloblasts, especially in acute myelogenous leukemia, tend to be less deformable than normal leukocytes. These abnormal calls dramatically increase blood viscosity, which in turn can precipitate "sludging" and vessel occlusion with aggregation of white thrombi in the vasculature. Additionally, myeloblasts can be invasive and directly damage blood vessel walls. Vessels in the CNS and pulmonary circulations are most vulnerable to invasion *(148,161)*. An AML patient with a total white blood cell count greater than 100,000/$mm^3$ or a chronic lymphocytic leukemic patient with an absolute lymphocyte count greater than 250,000/$mm^3$ should be considered at risk for this event. When leukemic patients have elevated white blood cell counts, the number of circulating blasts cells must be rapidly decreased. Treatment for CNS leukostasis can include one or two high-dose fractions of radiation therapy, combined allupurinol/hydroxyurea therapy, exchange transfusions, or leukapheresis. The effectiveness of these treatments is unclear, especially in the setting of intra-

cranial hemorrhage *(148,160,162)*. Some have suggested that only by the induction of a remission can the hyperleukotic syndrome be controlled in these patients *(148)*. If intracranial hemorrhage occurs, the survival rate is extremely low.

**Thrombocytopenia** Thrombocytopenia is not uncommon in the cancer population and poses a risk for intracranial hemorrhage *(149,163–165)*. Thrombocytopenia-associated cerebral hemorrhage in oncology patients can be secondary to extensive marrow infiltration by tumor, peripheral destruction of platelets due to tumor-associated hypersplenism, underproduction of platelets due to chemotherapy-induced toxicity, thrombocytopenia due to DIC, autoimmune dysfunction, and microangiopathic hemolytic anemia *(149,163)*. Diffuse bone marrow infiltration-induced thrombocytopenia is most commonly associated with leukoerythroblastic malignancy. However, marrow metastases are also observed in breast cancer, prostate cancer, other hematologic malignancies, lung cancer, and melanoma *(149,163)*. From a diagnostic standpoint, elevation of serum alkaline phosphatase and lactate dehydrogenase may provide laboratory clues of marrow infiltration *(149)*.

Hypersplenism-associated thrombocytopenia is usually mild, with platelet counts typically in the 40,000–100,000/mm$^3$ range, and only rarely results in significant hemorrhage. Hypersplenism is typically due to lymphoma and chronic lymphocytic leukemia. It may also be occasionally noted in patients with breast cancer or melanoma that have metastasized to the spleen, with congestive splenomegaly secondary to splenic vein infiltration in pancreatic cancers, and in the rare situation of portal hypertension as a result of diffuse hepatic metastases. Splenectomy, chemotherapy, and supportive care may decrease the risk of recurrent hemorrhage *(149)*.

Immune-mediated peripheral platelet destruction may produce thrombocytopenia in oncologic patients. This condition is rarely seen with solid tumors, but has been consistently reported with the lymphoproliferative disorders such as Hodgkin's disease, chronic lymphocytic leukemia, and low-grade lymphoma *(149,166–168)*. Diagnosis is difficult, but physicians should suspect immune-mediated thrombocytopenia in patients with a lymphoproliferative disorder and rapidly worsening, severe thrombocytopenia. Diagnosis may be supported by a clinically acute onset of thrombocytopenia, large platelet size, elevated megakaryocyte count, and increased platelet-associated immunoglobulin. Treatment may include corticosteroids, IgG infusions, plasmapheresis, antineoplastic therapy directed at the specific underlying malignancy, vincristine, danazol, and immunoabsorption with staphylococcal protein A in steroid-resistant patients *(149)*.

Thrombotic thrombocytopenic purpura (TTP) is a syndrome of target organ dysfunction due to marked platelet aggregation in the microcirculation that can be induced both by cancer and by chemotherapeutic treatment. TTP is characterized by severe thrombocytopenia, a microangiopathic hemolytic anemia, and renal failure (hemolytic uremic syndrome) *(169–171)*. Recent pathophysiologic investigations suggest that endothelial cell perturbation and apoptosis caused by as yet unidentified plasma factors lead to release of an abnormal von Willebrand factor that facilitates the deposition of platelet microthrombi. Intracerebral hemorrhage and cerebral infarction are potentially disastrous events that may complicate the course of patients with TTP *(172–174)*. Platelet aggregates in TTP most commonly occlude the arterioles and capillaries in the brain, heart, kidneys, and adrenal glands. Clinically, purpuric rash, fever, and neurological and renal symptoms are common. Laboratory studies demonstrate severe hemolytic anemia, thrombocytopenia, and schistocytosis. TTP may be differentiated from DIC by the absence of a coagulopathy. PT and PTT are normal. In cancer patients, TTP is most commonly seen with gastric adenocarcinoma, followed by breast, colon, and small cell lung carcinoma. Treatment options include corticosteroids, plasma exchange, immunoabsorption with staphylococcal protein A (Prosorba), platelet inhibitor drugs, vincristine, and splenectomy. Platelet transfusions are reserved for situations of documented bleeding. Mortality in TTP without treatment is 90–100%. With appropriate treatment mortality decreases to 10%.

**Vitamin K Deficiency** The dietary source for vitamin K is green leafy vegetables, and vitamin K is also synthesized by intestinal bacteria. Deficiencies in vitamin K have been associated with intracerebral hemorrhages *(175,176)*. Although typically hereditary, vitamin K deficiency can also occur in patients with poor dietary intake of vitamin K, as well as in patients receiving antibiotic therapy, which sterilizes the gut. Both of these situations are relatively common in oncology patients, and acquired vitamin K deficiency can occur relatively rapidly, especially in debilitated patients *(111,141,177, 201)*. Coagulation factors II, VII, IX, and X, as well as protein C and protein S are dependent on vitamin K to function normally within the coagulation cascade. Abnormal prolongation of PT occurs initially, followed by prolongation of PTT 48–76 h later. Fibrinogen and thrombin time remain unaffected. Treatment is slow administration of parenteral vitamin K. The usual dose is 10–20 mg by slow IV infusion, repeated daily for 2–3 d, in addition to fresh frozen plasma if active intracranial hemorrhage is occurring. Vitamin K stores are depleted in approx 7 d time so patients may require additional treatments in following weeks *(141)*.

**Hypocholesterolemia** Large scale epidemiological studies have demonstrated that hemorrhagic stroke is inversely related to total cholesterol levels, with hypocholesterolemia increasing the odds for intracerebral hemorrhage 2.25-fold *(178)*. A 1994 review of 20 systematic cohort studies noted an association between hypocholesterolemia in men and mortality from cancer, suggesting that many individuals with low serum cholesterol levels are harboring neoplasms *(179)*. Accordingly, in cancer patients, neoplasm-induced hypocholesterolemia likely constitutes a predisposing factor to hemorrhagic stroke. Certain neoplasms are especially commonly associated with hypocholesterolemia, including lung, liver, lymphatic, and hemopoietic malignancies *(180)*.

## III. TRADITIONAL STROKE MECHANISMS APPEARING IN THE SETTING OF TUMOR

Patients with cancer frequently have risk factors for stroke independent of their neoplasm, such as hypertension, atrial fibrillation, hypercholesterolemia, diabetes, coronary artery disease, and tobacco use. Accordingly, cancer patients may

experience ischemic stroke through mechanisms entirely unrelated to oncologic factors. Ischemic stroke can result from large and small vessel atherosclerosis, cardioembolism, paradoxical embolism, arterial dissection, congenital hypercoaguable state, and migraine. In many cases, the risk of these standard mechanisms may be potentiated by neoplasm-associated thrombophilia. Determining whether and to what extent neoplasm-associated hypercoagulability contributed to an infarct in an individual patient is often difficult. Similarly, cancer patients may develop intracerebral hemorrhages due to hypertension, amyloid angiopathy, or coagulopathy irrespective of their tumor, or due to an interaction of standard risk factors and a neoplasm-associated bleeding diathesis.

## IV. SEQUELAE OF CANCER TREATMENT

Unfortunately, stroke is a not infrequent complication of management in patients with cancer. Iatrogenic ischemic or hemorrhagic stroke can result from invasive diagnostic procedures, radiation therapy, surgical therapy, endovascular treatments, or chemotherapy.

### DIAGNOSTIC PROCEDURES

**Lumbar Puncture** Spinal subdural hematoma is a rare complication of lumbar puncture in cancer patients with severe thrombocytopenia or other coagulopathies *(1,181,182)*. Back pain, myelopathic symptoms from spinal cord compression, or radiculopathy from nerve root compression typically develop 24 h after the procedure. Early surgical treatment is indicated for patients with symptoms of cord compression, and often yields good recovery of function. To prevent lumbar puncture-associated subdural hematoma, preprocedural platelet transfusions should be considered if the procedure is mandatory despite severe thrombocytopenia.

**Lymphangiography** Lymphangiography is rarely associated with ischemic stroke due to lipid embolism *(1)*. Typically, the clinical picture is an encephalopathy appearing within hours of the procedure, although mild focal deficits have also been noted. Pulmonary embolism and skin petechiae may occur as well.

**Radiation-Induced Vasculopathy** Delayed vasculopathy is a common complication of radiotherapy. Patients develop a nonatherosclerotic occlusive vasculopathy or accelerated atherosclerosis in cervicocephalic vessels falling within the radiated field. Pathologic studies demonstrate that radiotherapy produces a sequence of changes in arteries characterized by initial damage to endothelial cells, thickening of the intimal layer caused by smooth muscle cell proliferation, cellular degeneration, and hyaline transformation *(183,184)*. Postradiation vasculopathy can affect both cervical and intracranial vessels. In two series, large vessel vasculopathy developed intracranially in 19% of children treated with cranial irradiation. Risk factors for vasculopathy were increased radiation dose to the circle of Willis and major cerebral arteries and possibly younger age *(185,186)*. Intracranial vasculopathy may appear after whole brain radiation, gamma knife or other focused cranial radiation, and radiation brachytherapy *(187)*. Stenosis and occlusion of medium and large vessels leading to ischemic infarction is the most common sequelae, but lacunar infarction, primary intracerebral hemorrhage, moyamoya changes with hemorrhage or ischemia, formation of cerebral aneurysms with subarachnoid or intraparenchymal hemorrhage, and formation of vascular malformations have also been reported *(188–192)*.

The cervical internal and common carotid arteries are a particularly common site for radiation-induced accelerated atherosclerosis following radiotherapy for head and neck cancer (*see* Fig. 5). In recent large ultrasound series, the frequency of common or internal carotid artery stenosis after external irradiation for head and neck malignancy ranged from 12–60% *(193,194)*. Symptomatic clinical presentation is typically delayed by months to years following irradiation, due in part to the larger caliber of the involved cervical vessels *(195)*. Hemispheric TIAs, hemispheric strokes, amaurosis fugax, and/or seizures are the typical neurological presentation in patients with carotid/anterior circulation disease *(195)*. TIA, stroke, and vertebrobasilar insufficiency have been observed in patients with vertebral/posterior circulation stenoses *(196)*. On physical exam, affected patients may exhibit extensive postradiation skin atrophy and fibrosis of the tissues overlying the diseased vascular segment in the neck, and radiation-induced necrosis of the mandible *(1)*. Several authors have recommended routine surveillance noninvasive imaging of the carotid following head and neck radiation *(197,198)*.

For symptomatic postradiation carotid stenosis, and possibly for asymptomatic severe postradiation stenosis, revascularization procedures are indicated. Though technically more difficult than in standard cases, carotid endarterectomy is feasible in radiation-induced carotid stenosis, and long-term patency rates similar to that obtained in the absence of radiation therapy have been reported *(199,200)*. Other variations of carotid artery repair, such as external carotid endarterectomy, carotid patch angioplasty alone, aorto-carotid bypass grafting, subclavian-carotid bypass grafting, and carotid interposition grafting have also been reported to be safe in this patient population. Carotid angioplasty and stenting has been a safe and effective technique for high-risk surgical candidates, although the long-term patency after stenting is not yet fully characterized *(201,202)*.

In head and neck cancer patients, arterial injury due to radiation therapy may also present as arterial rupture. Postradiation rupture of the carotid artery typically occurs within 2–16 wk after radical neck surgery and radiation therapy *(1,203)*. Of note, in the series reported by McCready and colleagues, all patients with carotid rupture were infected, with sloughing of the skin flaps and development of orocutaneous fistulas *(203)*.

**Laser Treatment** Nd:YAG laser bronchoscopy treatment of patients with unresectable pulmonary cancer has been associated with stroke due to air embolism to the cerebral circulation *(204)*.

### SURGERY-ASSOCIATED STROKE

**Directly Related to Surgery** Bronchoscopic biopsies and pneumonectomies for pulmonary cancer have been associated with perioperative and postoperative stroke secondary to tumor emboli. Surgical manipulation of the lung promotes release of emboli, especially in the setting of tumor invasion into pulmonary vasculature. Stroke tends to occur within the first 48 h postpneumonectomy (*see* Fig. 6) *(83,84,205)*.

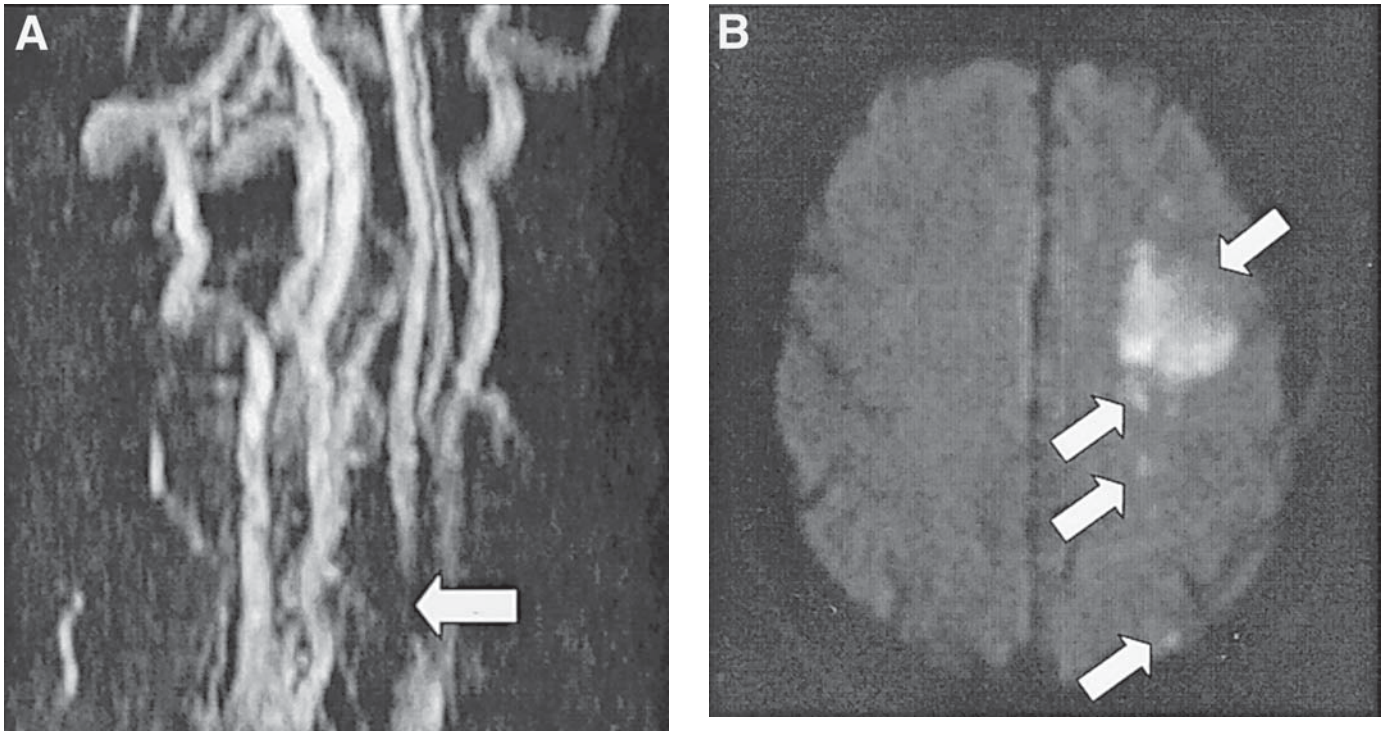


**Fig. 5.** Radiation-accelerated atherosclerosis of the internal carotid artery, intra-operative blood pressure drop, and resulting unilateral watershed stroke. A 63-yr-old man with a history of squamous cell carcinoma metastatic to the right neck lymph nodes was treated with radiation therapy. Four years later he developed destruction and pathological fracture of his left posterior mandibular body, and was admitted for left mandibular composite resection and fibular free flap reconstruction. On postoperative d 1, he developed right upper extremity weakness and aphasia. **(A)** Magnetic resonance angiography shows flow gap (white arrow) in the proximal internal carotid artery indicating severe stenosis. **(B)** Diffusion weighted MRI reveals one large and several small areas of infarction in the superficial borderzone ("string of pearls" appearance) consistent with a watershed stroke (white arrows).

Stroke is a well-known risk of resections of advanced head and neck cancer when the neoplasm encroaches upon, encases, or invades the carotid artery. Surgical options for this challenging management dilemma include carotid ligation, "shaving" the tumor from the carotid, or en bloc resection/replacement of the carotid artery by polytetrafluoroethylene, vein graft, or superficial femoral artery graft *(206–210)*. Surgical ligation of the carotid in unselected patients has been associated with stroke rates of 41–54% and mortality rates of 32–60% *(211)*. Presurgical endovascular test occlusion of the carotid artery permits identification of patients with adequate circle of Willis collaterals who will tolerate permanent carotid occlusion, and of patients with inadequate Willisian collaterals who will require extracranial-intracranial bypass surgery or resections that spare or reconstruct the carotid artery *(208,210–213)*. In patients with adequate collaterals, permanent balloon occlusion may be undertaken, and may decrease the risk of perioperative carotid rupture *(210,211)*.

With regards to oncologic neurosurgical procedures, cerebral venous thrombosis has been reported as a rare complication of craniotomies and craniectomies. Anticoagulation, lumboperitoneal shunting, or ventriculoperitoneal shunting may be appropriate treatments in this situation *(214,215)*. Symptomatic cerebral vasospasm is a complication of surgery in 2% of patients undergoing cranial base tumor resection *(216)*. Standard vasospasm treatment is indicated, including hypervolemic, hypertensive therapy, intraarterial angioplasty, and intraarterial papaverine.

**Hypercoagulability Related to Surgery** Postoperative hypercoaguability has been reported in patients both with and without cancer *(217,218)*. Protein C levels have been noted to decrease within 72 h in all patients undergoing minor and major surgeries. In cancer patients, however, the decrease in protein C occurs more rapidly, typically within the first 24 h *(217)*. One prospective study of 10 patients undergoing free flap microvascular reconstruction of cancer-related defects in the head and neck noted protein C deficiency in 70% of all patients within the first 72 postoperative hours *(218)*. In addition to protein C abnormalities, antithrombin III and plasminogen levels have been noted to decrease within the first 48–96 h postoperatively *(219)*. Lastly, DIC has been reported in several cancer patients postoperatively.

**Endovascular Treatment Associated Stroke** Selective intraarterial infusion of blood-brain barrier (BBB) disrupting and antineoplastic agents is a growing treatment approach for cerebral malignancies *(220)*. Ischemic stroke is a reported

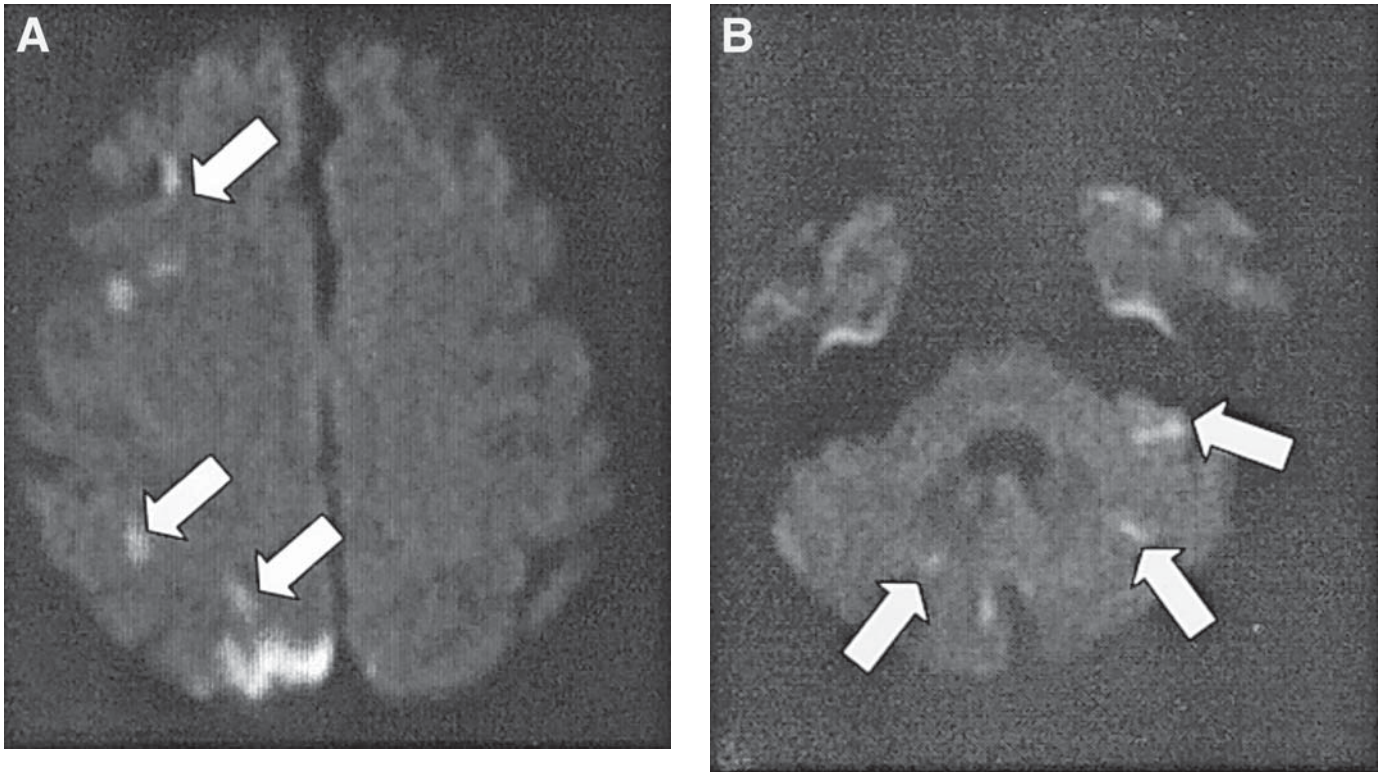


**Fig. 6.** Bronchoscopy procedure-induced tumor emboli. A 70-yr-old woman with nonsmall cell lung adenocarcinoma underwent fiberoptic bronchoscopy and mediastinoscopy with tracheobronchial lymph node biopsy. Two hours after the procedure, she developed left faciobrachial weakness. **(A)** Diffusion weighted MRI shows right frontal, right parietal, and right occipital infarcts (white arrows). **(B)** Lower slice from diffusion MR study demonstrates additional acute bilateral cerebellar infarcts (white arrows).

complication of these procedures *(221)*. Superselective catheter-administered embolization to occlude the vascular supply to meningiomas has been associated with postprocedural, peritumoral hemorrhage *(222)*.

Ischemic stroke has been reported following bone marrow transplantation infusion. A patient with a patent foramen ovale permitting right to left shunting experienced multiple cerebral emboli *(223)*. Positioning the infusion catheter tip in the main pulmonary artery and reducing the volume of marrow infused are steps that can prevent this complication.

## CHEMOTHERAPY

**Hypercoagulability and Thrombocytopenia** Antineoplastic chemotherapy, including single or multiagent chemotherapy, hormonal therapy, and hematopoietic growth factors, can produce a hypercoagulable state in cancer patients and contribute to cerebral arterial and venous thrombosis. Physiologic investigations in patients treated with chemotherapeutic agents have documented activation of the coagulation pathway, suppression of natural anticoagulants, suppression of natural fibrinolysis, and injury to vascular endothelium *(17,114,117,169,224,225)*. Thrombocytopenia, TTP, DIC, and microangiopathic hemolytic anemia have all been linked to chemotherapeutic agents *(38,149,165,226,227)*. Postulated mechanisms for antineoplastic drug-related thrombophilia include release of procoagulants and cytokines from injured tumor cells, direct drug toxicity to vascular endothelium, direct induction of monocyte or malignant cell tissue factor, and decrease in physiological anticoagulants *(97)*.

Among individual chemotherapeutic agents particularly associated with stroke, L-asparaginase is one of the most well-known culprits *(1,17,114,164,228–232)*. L-asparaginase is an enzymatic inhibitor of protein synthesis used in combination with other chemotherapeutic agents in the treatment of acute lymphoblastic leukemia and a few other lymphoid malignancies. The reduction in protein synthesis produced by L-asparaginase not only inhibits growth of leukemic neoplasms, but also decreases liver production of multiple plasma proteins involved in hemostasis. L-asparaginase-induction therapy strokes may present as cortical infarction, capsular infarction, intracerebral hemorrhage, hemorrhagic infarction, or dural sinus thrombosis. Venous thrombosis is very common. The incidence of stroke in patients treated with L-asparaginase induction therapy has ranged in different series from 0.9–2.9%. Stroke reportedly tends to occur at the end of the induction treatment *(1)*. The clinical presentation varies depending on the location and type of stroke. The exact mechanism for L-asparaginase induced stroke is unclear, although L-asparaginase has been shown to diminish antithrombin III, protein C, protein S, factor XI, factor IX, and fibrinogen, and to increase PT/PTT and platelet aggregability. Coagulation factors return to normal within 7–10 d after therapy. Therapies for L-asparaginase associated strokes vary widely and may include (depending on the particular patient's clinical situation as well as the stroke type): fresh frozen plasma, heparin, cryoprecipitate, platelet transfusion, aspirin, and surgery for hematoma drainage.

Stroke has been associated with a variety of other chemotherapeutic agents. 5-fluorouracil therapy, alone and in combination with cisplatin, methotrexate, and cyclophosphamide, has been associated with acquired protein C deficiency and stroke *(233–235)*. Acute stroke and acquired protein C deficiency has also been reported following cisplatin therapy without 5-fluorouracil *(236,237)*. Taxol, or paclitaxel, has been reported in association with acute stroke shortly after treatment (238,239,281,281). The antiestrogen tamoxifen induces a mild hypercoagulable state and increases the incidence of stroke in women over age 50 *(240)*. Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been associated with venous and arterial thrombosis, possibly by enhancing aggregation and binding of neutrophils to vascular endothelium *(229)*. A meta-analysis of 52 reported series found an incidence of venous and arterial thrombosis of 4.2% with GM-CSF and 1.2% with G-CSF *(241)*. Thrombocytopenia related to chemotherapy, particularly for solid tumors, is a predisposing factor to intracerebral hemorrhage *(242)*.

Pre-existing coagulation abnormalities can complicate cancer treatment. A prospective evaluation of 301 children with acute lymphoblastic leukemia (ALL) reported that 19% exhibited hypercoaguable risk factors before the initiation of chemotherapy *(193)*. Specific abnormalities included 20 patients with the heat-labile methyl folate reductase genotype affecting homocysteine metabolism, 11 with the Factor V G1691A mutation producing activated protein C resistance, 5 with heterozygous prothrombin G20210A mutation, 11 Factor V G1691A mutation, 9 with familial dyslipoproteinemia, 4 with familial protein C deficiency, 4 with protein S deficiency, and combined disorders in 10 patients. The prevalence of the prothrombotic dyscrasias were reportedly within the range typically diagnosed in the childhood population. However, the group of 65 leukemic children with risk factors had an increased incidence of thromboembolic events and reduced survival time compared to leukemic children without risk factors.

**Cardiomyopathy** Cardiomyopathy is a well-known complication of anthracycline chemotherapy with agents such as doxirubicin and epirubicin, occurring in up to 20% or more of patients *(243)*. Other chemotherapeutic agents less commonly associated with cardiotoxicity include cyclophosphamide, ifosfamide, cisplatin, carmustine, busulfan, and mitomycin. Severe cardiomyopathy with reduced flow in cardiac chambers permits thrombus formation and cardioembolic stroke. In patients presenting with cerebral cardioembolism, long-term secondary prevention with anticoagulation is recommended.

**Infection and Stroke** Patients with immunosuppression from antineoplastic therapy or from hematologic malignancy directly are at increased risk for infection-related stroke through several mechansims, including sepsis-induced DIC, bacterial endocarditis, and angioinvasive microorganisms *(1,244,245)*. Immunosuppressed leukemic patients may experience cerebral infarcts secondary to vessel infiltration with fungi such as Mucor, Aspergillus, and Candida. In Graus' series, of 22 patients with septic infarction, 67% were symptomatic with seizures, focal neurological deficits, and encephalopathy *(1)*.

**Anticoagulation Induced Hemorrhage in the Cancer Patient** In cancer patients who develop deep venous thrombosis, treatment options include longterm warfarin anticoagulation or placement of filters in the inferior vena cava. Patients with malignancy placed on warfarin therapy are at increased risk for major hemorrhages, with an incidence rate of 13.3 per 100 patient years *(246)*. Patients with brain metastases and deep venous thrombosis may be at particularly increased risk for intracerebral hemorrhage on warfarin therapy. Among 42 patients who received anticoagulation for a mean of 100 d, the incidence of symptomatic intracerebral hemorrhage was 7%, generally in the setting of supratherapeutic anticoagulation *(247)*. This risk must be balanced against data suggesting greater effectiveness of warfarin than filter placement in preventing recurrent deep venous thrombosis and pulmonary embolism *(247)*.

**Bone Marrow Transplantation** Thrombotic microangiopathy occurs in up to 6% of patients following bone marrow transplantation *(248,249)*. Contributing factors include cyclosporine A, graft-versus-host disease (GVHD), irradiation, intensive conditioning chemotherapy, and infection. The incidence of subdural hematoma complicating bone marrow transplantation is 2.6%, with prolonged thrombocytopenia and coagulopathy as predisposing factors *(250)*. Cases of NBTE-associated stroke and stroke secondary to an acquired protein C deficiency have also been reported following bone marrow transplantation.

## CONCLUSION

A diverse array of pathophysiologic processes increases the risk of stroke in patients with malignancies. Systematic work-up will usually disclose the type, location, and proximate cause of stroke, allowing patient classification among the specific etiologies of cerebral infarction and hemorrhage reviewed in this chapter, and guiding acute intervention and secondary prevention treatment. All physicians who encounter patients with cancer should be cognizant of the elevated risk of cerebrovascular disease within the oncologic population, and include stroke in the differential diagnosis of any alteration in CNS function.

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# 13 Paraneoplastic Syndromes of the Nervous System

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## INTRODUCTION

In patients with cancer the development of neurological symptoms usually represents metastatic involvement of the nervous system, or complications secondary to coagulopathy, infection, metabolic and nutritional deficits, and toxic effects of cancer therapy *(1)*. A neurologic disorder is defined as paraneoplastic when none of the aforementioned causes are detected or when specific cancer-related immunological mechanisms are involved. Paraneoplastic neurologic disorders are important for several reasons. First, they may affect any part of the central and peripheral nervous system (CNS/PNS) (Table 1) and mimic any other neurologic complications of cancer. Second, the paraneoplastic disorder (PND) usually develops before the presence of a cancer is known, and its prompt recognition may help to uncover the neoplasm. Third, the neurologic symptoms are often severe and can result in the patient's death. Finally, the discovery of several antineuronal antibodies associated with specific paraneoplastic syndromes and tumors has provided useful tests that facilitate the diagnosis of some of these disorders.

The frequency of paraneoplastic neurologic syndromes varies depending on the term used to define them and the diagnostic tests used. It is estimated that probably fewer than 1% of patients with cancer develop antibody-associated paraneoplastic neurologic syndromes, but many paraneoplastic disorders are not associated with antineuronal antibodies. For example, in disorders such as plasma cell dyscrasias (myeloma, Waldenström's macroglobulinemia), the development of paraneoplastic peripheral neuropathy may affect 10–30% of patients.

Immunological mechanisms appear to mediate most paraneoplastic neurologic disorders (Table 2). The occurrence of antibodies directed to proteins selectively expressed by tumor cells and the nervous system has suggested a mechanism whereby the tumor expression of neuronal proteins triggers an immunological response that results in the paraneoplastic disorder. Studies indicate that in most instances the antineuronal antibodies are not the cause of the paraneoplastic disorder, and that cytotoxic T-cell mechanisms are also involved. In these disorders the detection of antineuronal antibodies serves as a diagnostic marker of the paraneoplastic disease and associated tumor *(2)*.

In other paraneoplastic neurologic disorders, the presence of inflammatory cells or deposits of IgG or complement in involved areas of the nervous system suggest immune-mediated mechanisms, but specific antibodies or target antigens have not been identified. This chapter focuses on paraneoplastic neurologic disorders associated with immunological responses defined by the presence of specific antibodies in serum or CSF. Also included are neurologic disorders that are unassociated with specific antibodies but whose association with cancer appears to be more than coincidental and cannot be explained by other known mechanisms. Other disorders, sometimes reported as paraneoplastic but whose association with cancer is probably coincidental, are shown in Table 1 but are not discussed in this chapter. A review of these disorders has been recently published *(3)*.

## PARANEOPLASTIC SYNDROMES OF THE CENTRAL NERVOUS SYSTEM

**PARANEOPLASTIC LIMBIC ENCEPHALITIS** This disorder is characterized by depression, irritability, seizures, and short-term memory loss. Neurological symptoms usually develop in days or weeks and then stabilize, leaving the patient with severe short-term memory loss. In two thirds of the patients, the CSF shows mild pleocytosis, increased proteins, intrathecal synthesis of IgG, and oligoclonal bands. The detection of several antineuronal antibodies in serum and CSF helps to establish the diagnosis of the disorder and to identify the tumor *(4,5)*. MRI studies may show uni- or bilateral mesial temporal lobe abnormalities that are best seen on T2-weighted

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**Table 1**
**Paraneoplastic Syndromes of the Central Nervous System**

| |
|---|
| *Central nervous system* |
| Limbic encephalitis |
| Cerebellar degeneration |
| Encephalomyelitis |
| Brainstem encephalitis |
| Myelitis |
| Sensory neuronopathy |
| Opsoclonus-myoclonus |
| Stiff-man syndrome |
| Motor neuron syndrome and motor neuronopathy |
| Necrotizing myelopathy[a] |
| *Peripheral nervous system* |
| Chronic sensorimotor neuropathy |
| Acute sensorimotor neuropathy (Guillain-Barré, plexitis)[a] |
| Vasculitis of the nerve and muscle |
| Neuropathy associated with malignant monoclonal gammopathies |
| Neuromyotonia |
| Autonomic neuropathy |
| Lambert-Eaton myasthenic syndrome |
| Myasthenia gravis |
| Polymyositis/dermatomyositis |
| Acute necrotizing myopathy |
| Cachectic myopathy |
| Carcinoid myopathy[a] |
| Myotonia[a] |

[a]Reviewed by Rudnicki and Dalmau *(3)*.

images and sometimes contrast enhance. EEG studies are useful in assessing whether changes in level of consciousness or behavior are related to temporal lobe seizures.

Neurological symptoms usually precede tumor diagnosis. The tumor most frequently involved is lung cancer, usually small cell lung cancer (SCLC). Other tumors include germ cell tumors of the testis, breast cancer, Hodgkin's lymphoma, thymoma, and immature teratoma of the ovary.

Pathological findings include perivascular and interstitial inflammatory infiltrates, neuronal loss, and microglial proliferation that predominate in the limbic system (hippocampus, amygdala, hypothalamus, and insular and cingulate cortex). In addition, the majority of patients have variable involvement of other areas of the nervous system, mainly the brainstem *(6)*.

In contrast to other PNDs of the CNS, this disorder may improve with treatment of the tumor. In a recent study, 44% of the patients had neurological improvement, usually associated with tumor treatment *(4)*.

## PARANEOPLASTIC CEREBELLAR DEGENERATION

The presenting symptoms of this disorder are dizziness, nausea, blurry or double vision, oscillopsia, and gait difficulties. Concomitant with these symptoms, or after a few days, the patient develops truncal and limb ataxia, dysarthria, and dysphagia. On examination, patients usually have down-beating nystagmus *(7)*. This clinical picture is similar for most types of paraneoplastic cerebellar degeneration, irrespective of the type of cancer or antibody association, although the course of the disease may be different depending upon the associated immune response. In general, neurologic symptoms precede the tumor diagnosis. The CSF usually shows pleocytosis, increased protein, and intrathecal synthesis of IgG and oligoclonal bands. In the early stages of the disease, brain MRI is usually normal, but after several months may show global cerebellar atrophy.

There is a strong association between the development of certain antineuronal antibodies and the type of tumor associated with the paraneoplastic cerebellar disorder. These include SCLC and anti-Hu antibodies *(8)* (Fig. 1), ovarian and breast cancer and anti-Yo antibodies *(7)*, Hodgkin's lymphoma and anti-Tr antibodies *(9)* (Fig. 2), and breast cancer and anti-Ri antibodies *(10)*. Furthermore, the presence of anti-Hu antibodies is usually associated with symptoms indicating involvement of other areas of the nervous system (i.e., encephalomyelitis and sensory neuronopathy). The presence of anti-Ri antibodies is associated with opsoclonus or other abnormalities of ocular motility, including nystagmus, abnormal visual tracking, and abnormal vestibulo-ocular reflexes in 70% of patients.

Symptoms of paraneoplastic cerebellar dysfunction may occur without the presence of antineuronal antibodies. In this case, the tumors more frequently involved are non-Hodgkin's lymphoma and lung cancer (non-SCLC and SCLC) *(8)*.

Pathological studies show a diffuse loss of Purkinje cells accompanied by degeneration of the dentate and olivary nuclei, and long tracts of the spinal cord. These findings can be associated with mild or absent inflammatory infiltrates, or with prominent lymphocytic infiltrates *(11)*. When present, the inflammatory infiltrates usually involve the deep cerebellar nuclei in addition to the brainstem and other areas of the nervous system, suggesting that the cerebellum is the main target of a multifocal encephalomyelitis.

Treatment of the tumor and immune-suppressants do not usually affect the course of the cerebellar disorder. However, neurological improvement can occur in patients with anti-Ri and anti-Tr antibodies *(9,12)*.

## PARANEOPLASTIC ENCEPHALOMYELITIS (PEM)

This disorder describes patients with cancer who develop multifocal neurological deficits and signs of inflammation involving two or more areas of the nervous system, including cerebrum, cerebellum, brainstem, and spinal cord *(11)*. This gives rise to a mixture of symptoms derived from limbic encephalitis, cerebellar degeneration, brainstem encephalitis, myelitis, and autonomic dysfunction.

Symptoms of paraneoplastic brainstem encephalitis can include diplopia, dysarthria, dysphagia, internuclear or supranuclear gaze abnormalities, facial numbness, and subacute hearing loss. The spinal cord symptoms usually result from an inflammatory degeneration of the lower motor neurons *(13)*. Symptoms of autonomic dysfunction may include gastrointestinal paresis and pseudo-obstruction, orthostatic hypotension, cardiac arrhythmias, and others (*see* later).

The neurological symptoms often precede the detection of the tumor, and brain MRI is usually normal. In patients with prominent limbic dysfunction, the MRI may demonstrate the abnormalities previously described. Since the tumor most frequently involved is a SCLC, anti-Hu antibodies are frequently detected *(14)*. Patients with anti-Hu associated PEM usually develop sensory neuronopathy secondary to dorsal root ganglia involvement *(15)*. Other antineuronal antibodies identified much less frequently (sometimes in combination with anti-Hu)

**Table 2**
**Antibodies Associated with Paraneoplastic Neurologic Syndromes**

| *Antibody* | *Associated cancer* | *Syndrome* | *Immunohistochemical and Western-blot reactivity* |
|---|---|---|---|
| Anti-Hu | SCLC, other | Encephalomyelitis, sensory neuronopathy | All neuronal nuclei; 35–40 kDa |
| Anti-Yo | Gynecological, breast | Cerebellar degeneration | Cytoplasm Purkinje cells; 34, 62 kDa |
| Anti-Ri | Breast, gynecological, SCLC | Cerebellar ataxia, opsoclonus | Neuronal nuclei of the CNS; 55, 80 kDa |
| Anti-Tr | Hodgkin's lymphoma | Cerebellar degeneration | Cytoplasm neurons, Purkinje spiny dendrites |
| Anti-CV2 | SCLC, other | Encephalomyelitis Cerebellar degeneration | Glial cells (subset); 66 kDa |
| Anti-Ma proteins[a] | Testicular germ-cell tumors and other neoplasms | Limbic, brainstem encephalitis, cerebellar degeneration | Neuronal nuclei and cytoplasm; 37, 40 kDa |
| Anti-amphiphysin | Breast | Stiff-man syndrome | Synaptic vesicle protein; 128 kDa |
| Anti-VGKC[b] | Thymoma, others | Neuromyotonia | Several VGKC |
| Anti-VGCC[b] | SCLC | LEMS | Presynaptic P/Q type VGCC |
| Anti- acetylcholine receptor[b] | Thymoma | Myasthenia gravis | Postsynaptic acetylcholine receptor |

[a]Antibodies limited to Ma2 (also called anti-Ta antibodies) usually associates with limbic and brainstem encephalitis and germ-cell tumors. Antibodies directed at Ma1, Ma2, and Ma3 usually associate with brainstem encephalitis, cerebellar degeneration, and several types of cancer (lung, breast, ovary, etc.).
[b]These antibodies are also identified in the nonparaneoplastic form of the syndrome.

include anti-CV2 and anti-amphiphysin *(16,17)*. The paraneoplastic encephalitis of patients with immunity to Ma proteins is more restricted to limbic, hypothalamus, brainstem, and cerebellum than the encephalomyelitis associated with other antibodies *(18)*.

PEM rarely improves with treatment of the tumor or immunotherapy; however, prompt treatment of the tumor offers the best chance for stabilization of the neurologic symptoms *(19)*.

**PARANEOPLASTIC SENSORY NEURONOPATHY** This disorder is characterized by progressive sensory loss involving lower and upper extremities, trunk, and face. The sensory deficits are frequently accompanied by painful paresthesias and dysesthesias. This and the frequent asymmetric presentation of symptoms may lead to the diagnosis of radiculopathy or multiple mononeuropathies *(20)*. At presentation, vibration and joint position sensations may be more affected than nociceptive sensation. The sensory loss causes disorganization of movement resulting in sensory ataxia and pseudoathetoid movements. Some patients develop sensorineural hearing loss.

Nerve conduction studies demonstrate small amplitude or absent sensory nerve-action potentials. Motor nerve and F-wave studies are usually normal, with no signs of denervation unless there is involvement of the spinal motor neurons in the setting of PEM. Some patients develop motor conduction abnormalities as a result of a mixed axonal and demyelinating neuropathy that accompanies the degeneration of dorsal root ganglia neurons *(20)*.

PSN frequently develops in association with PEM and autonomic dysfunction (*see* PEM). In more than 80% of the patients, PSN precedes the diagnosis of the tumor, usually a SCLC. The specificity of detection of anti-Hu antibodies for PSN is 99.8% and the sensitivity 82% *(15)*.

Pathological studies show an inflammatory, probably immune-mediated degeneration of the neurons of the dorsal root ganglia and equivalent ganglia of cranial nerves (i.e., Gasserian ganglia). Other findings include atrophy of the posterior nerve roots, axonal degeneration, and secondary degeneration of the posterior columns of the spinal cord. Mild inflammatory infiltrates can be found in peripheral nerves and sometimes muscle *(21)*.

PSN rarely responds to immunotherapies, including plasma exchange, intravenous IgG, and immunosuppressants. In some patients the use of steroids resulted in partial improvement of symptoms *(22)*. Efforts should be directed towards prompt identification and treatment of the tumor.

**PARANEOPLASTIC OPSOCLONUS-MYOCLONUS (POM)** POM usually affects infants younger than 4 yr of age (median age, 18 mo), and is often associated with hypotonia, ataxia, and irritability *(23)*. Nearly 50% of children with POM have neuroblastoma, and about 2% of children with this tumor develop opsoclonus. Neurologic symptoms may precede or develop after the diagnosis of neuroblastoma. Symptoms usually fluctuate and may have a prolonged course. POM frequently responds to treatment of the tumor, steroids, and IVIg, but neurologic relapses are frequent, often as a result of intercurrent infections *(23,24)*. About 65% of patients are left with deficits, including psychomotor retardation and behavioral abnormalities. Patients with POM have a better tumor prognosis than patients without paraneoplastic symptoms.

In adults, POM develops in association with truncal ataxia resulting in gait difficulty and frequent falls. In more than half of the patients, POM precedes the diagnosis of the tumor, usually a SCLC *(25)*. Patients with breast cancer may harbor anti-Ri antibodies (*see* Paraneoplastic Cerebellar Degeneration) *(10)*. The clinical course of paraneoplastic opsoclonus is worse than that of idiopathic opsoclonus. Paraneoplastic opsoclonus may respond to immunotherapy or IVIg, but symptom improvement is usually partial. It is not uncommon for the disorder to progress to a severe encephalopathy resulting in the

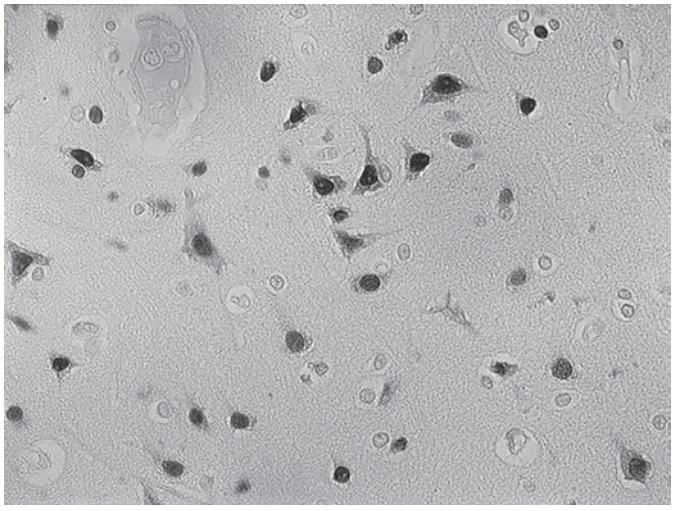

**Fig. 1.** Anti-Hu antibodies. Human cortical neurons immunolabeled with anti-Hu antibodies. The Hu antigens are predominantly expressed in the nuclei of neurons.

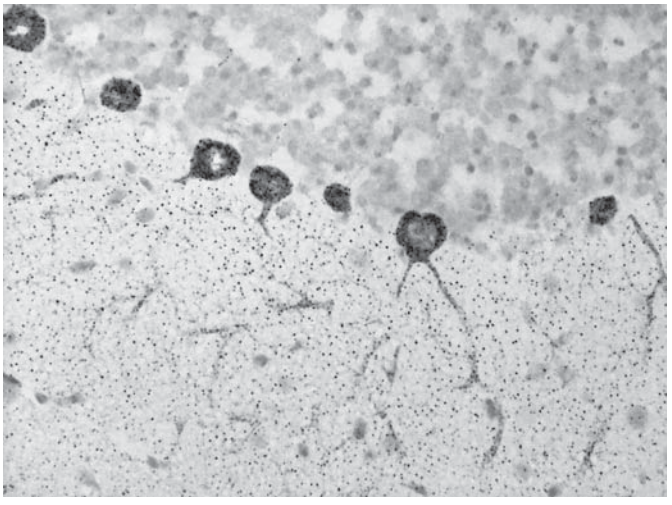

**Fig. 2.** Anti-Tr antibodies. Rat cerebellum immunolabeled with anti-Tr antibodies. Note the predominant immunoreactivity of the Purkinje cells and dot-like labeling of the molecular layer.

patients' death. One study showed that the prognosis of the neurologic disorder was better for patients whose tumor was promptly diagnosed and treated than for those whose tumor was untreated *(26)*.

In addition to treatment of the tumor and IVIg, there are reported clinical responses to depletion of serum IgG using protein-A columns, clonazepam, and thiamine *(12,27)*. Interpretation of these results is confounded by the possibility of spontaneous improvement.

**PARANEOPLASTIC STIFF-MAN SYNDROME** This disorder is characterized by fluctuating rigidity of the axial musculature and superimposed spasms. Rigidity primarily affects the lower trunk and legs, but it can extend to the shoulders, the upper limbs and neck *(28)*. Face muscles are usually spared. Spasms are precipitated by voluntary movement, emotional upset, and auditory and somesthetic stimuli. As a result of muscle stiffness and spasms, the patient develops abnormal postures, usually an exaggeration of the normal lumbar lordosis. Typically, the rigidity disappears during sleep or following local or general anesthesia, suggesting dysfunction at the spinal or supraspinal level. Sometimes, symptoms are limited to one extremity (stiff-limb syndrome) *(29)*.

Although at the onset of the disease the rigidity and spasms are sporadic, with time they become persistent and incapacitating and the muscle spasms can result in bone fractures. Electrophysiologic studies show continuous activity of motor units in the stiffened muscles, which considerably improve after treatment with diazepam.

The disorder can occur as a paraneoplastic manifestation of cancer or, more frequently, without a cancer association *(30)*. The serum and CSF of patients with paraneoplastic stiff-man syndrome may contain antibodies to amphiphysin I *(31,32)*. Another paraneoplastic antigen, called gephyrin, has recently been identified as the target of serum antibodies in a patient with a mediastinal tumor *(33)*. In patients without cancer the major autoantigen is glutamic acid decarboxylase (GAD), and 70% of these patients develop type I diabetes and other autoimmune diseases *(34)*. The current hypothesis regarding the pathogenesis of stiff-man syndrome is that the disorder is caused by autoimmunity directed to spinal cord interneurons, which control motor neuron activity and co-secrete both GABA and glycine. Interestingly, the three target antigens identified in stiff-man syndrome (GAD, amphiphysin, and gephyrin) are part of GABA/glycine inhibitory synapses. Histopathological abnormalities found in a few cases of stiff-man syndrome include mild perivascular lymphocyte infiltration and loss of motor neurons and interneurons in the anterior horn of the spinal cord *(35–37)*.

In the paraneoplastic form of stiff-man syndrome, neurological symptoms may develop before or after the diagnosis of the tumor, (usually breast or lung cancer). Diazepam, clonazepam, or baclofen may produce symptomatic improvement, but more definitive improvement is usually obtained with treatment of the tumor and steroids *(31)*. In some patients, symptoms may not respond to any of these treatments.

**MOTOR NEURON DISEASE (MND)** The occurrence of motor neuron disease as a paraneoplastic syndrome is controversial. Two systematic reviews of the literature *(38,39)* concluded that there was not an increased incidence of cancer among patients with amyotrophic lateral sclerosis (ALS). However, there is evidence to suggest that MND does rarely occur as a paraneoplastic phenomenon. This includes reports of patients with typical MND (i.e., without unusual features such as sensory loss) who have improvement following treatment of their malignancy *(40)*. There are three situations in which a PND may manifest with symptoms of MND. First, some patients with PEM and sensory neuronopathy may develop symptoms of MND due to predominant involvement of the spinal cord (myelitis). Second, patients with lymphoma may develop upper and lower motor neuron dysfunction, which progresses in a fashion typical of ALS. Some patients develop a lower motor neuron syndrome that appears to have a better prognosis that classical ALS. Third, an association between primary lateral sclerosis and breast cancer was suggested in one

study; no paraneoplastic markers were identified and the development of both disorders could have been coincidental *(13)*.

In conclusion, patients with MND and an elevation of CSF protein or detection of a serum paraprotein should undergo an investigation for lymphoma *(41,42)*. Patients who present with atypical MND, including sensory findings, autonomic instability, or ataxia may have MND as a fragment of PEM, and testing for serum anti-Hu antibodies is appropriate. Finally, women with primary lateral sclerosis should undergo mammography *(13)*.

## PARANEOPLASTIC SYNDROMES OF THE PERIPHERAL NERVOUS SYSTEM

### PARANEOPLASTIC SENSORIMOTOR NEUROPATHY

Many patients with advanced malignancy develop a peripheral neuropathy, which is usually mild, with little impact on quality of life *(43)*. The cause of these neuropathies is multifactorial, including metabolic and nutritional deficits, and cytokines produced by the tumor or the immune system. Additionally, many terminal cancer patients have toxic neuropathies due to chemotherapy; many protocols for the most common cancers include cisplatin, paclitaxel, docetaxel, and/or vinca alkaloids as well as thalidomide *(44)*.

There is a group of sensorimotor neuropathies that usually develop before or by the time the malignancy is discovered, and have major impact on quality of life. Symptoms may present in a subacute or acute fashion and are usually progressive, although some patients have relapsing and remitting symptoms *(43)*. Pathologic studies usually show axonal degeneration with frequent inflammatory infiltrates, and some patients have predominant demyelinating findings. Patients with electrophysiologic signs of demyelinating neuropathy usually improve with steroids or IVIg.

**PARANEOPLASTIC VASCULITIS OF NERVE AND MUSCLE** This disorder is a nonsystemic vasculitic neuropathy, which involves nerve, muscle, or both. Neurologic symptoms may develop before or after the tumor diagnosis. The tumors more frequently involved are SCLC and lymphoma *(45)*. The disorder usually affects older men and the neuropathy is subacute and progressive. Patients develop a painful symmetric or asymmetric sensorimotor polyneuropathy, and less frequently a multiple mononeuropathy. Electrophysiological studies show axonal degeneration equally involving motor and sensory nerves. Typically, the erythrocyte sedimentation rate is elevated and the CSF shows a high protein content. Nerve biopsy studies show intramural and perivascular inflammatory infiltrates, usually without necrotizing vasculitis. The inflammatory infiltrates are mainly composed by CD8+ T cells *(46)*. A similar microvasculitis can be identified in the muscle biopsy of some patients *(47)*.

Paraneoplastic vasculitis of nerve and muscle may respond to treatment of the tumor and immunosuppression *(48)*. The combination of steroids and cyclophosphamide may have better results than steroids alone *(45)*. Some patients with paraneoplastic vasculitis of nerve and muscle also suffer from Lambert-Eaton myasthenic syndrome (LEMS) *(47)* or PEM *(49)*.

**SENSORIMOTOR PERIPHERAL NEUROPATHY ASSOCIATED WITH MALIGNANT MONOCLONAL GAMMOPATHIES** The malignancies that are associated with monoclonal gammopathies or M proteins include multiple myeloma and sclerotic myeloma, which are typically associated with IgG or IgA M proteins, and Waldenström's macroglobulinemia, B-cell lymphoma, and chronic B-cell lymphocytic leukemia, which are associated with IgM M proteins.

**Multiple Myeloma** One-third of patients with multiple myeloma have electrophysiologic signs of peripheral neuropathy *(50)*, but only 5–10% develop clinical symptoms. Neurologic symptoms usually precede the diagnosis of myeloma. Patients may develop a mild sensorimotor axonal neuropathy, a pure sensory neuropathy, or a subacute monophasic or relapsing and remitting neuropathy with evidence of demyelination on electrophysiologic and morphologic studies *(51)*. Amyloid deposition occurs in 20–40% of myeloma patients with peripheral neuropathy *(52,53)*. In these patients, symptoms are similar to those with distal axonal sensorimotor neuropathy, but frequently include atypical features, such as carpal tunnel syndrome, a clinical picture of multiple mononeuropathy, and autonomic dysfunction. There is no specific treatment for these neuropathies. Treatment of the myeloma does not usually improve the neuropathy.

**Osteosclerotic Myeloma** This is an unusual form of myeloma characterized by single or multiple plasmacytomas that manifest as sclerotic bone lesions. These lesions involve ribs, vertebrae, pelvic bones, and proximal long bones, and usually spare skull and distal extremities *(54)*. More than 50% of patients with sclerotic myeloma develop a peripheral neuropathy, which resembles a chronic demyelinating polyradiculoneuropathy with motor predominance and high CSF protein content. All or some features of the POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* component, and *s*kin changes) can be present. Treatment of the sclerotic lesions with resection, radiation therapy, or systemic chemotherapy often results in neurologic improvement *(54–56)*.

**Waldenström's Macroglobulinemia** Peripheral neuropathy occurs in 5–10% of these patients. The neuropathy may result from antibody activity of the IgM M-protein against myelin-associated glycoprotein (MAG) or against various gangliosides *(57,58)*. The neuropathy associated with IgM anti-MAG is characterized by a progressive distal symmetric sensorimotor polyneuropathy with predominant involvement of large sensory fibers (in particular, vibration sense). Postural tremor and pseudoathetosis are common. The CSF often shows increased proteins. Electrophysiologic studies demonstrate slow conduction velocities and prolonged distal motor and sensory latencies, compatible with a demyelinating neuropathy. Pathology studies show widening between lamellae of myelin sheaths due to intercalation of anti-MAG antibodies.

Treatment should be directed at the Waldenström's macroglobulinemia. Patients with demyelinating neuropathy and IgM anti-MAG M proteins occasionally respond to therapy with plasma exchange or IVIg. However, most patients require aggressive treatment with chemotherapeutic agents such as chlorambucil, cyclophosphamide, or fludarabine.

**PARANEOPLASTIC NEUROMYOTONIA** This disorder, also called Isaac's syndrome *(59)*, is characterized by spontaneous and continuous muscle-fiber activity of peripheral nerve origin. Symptoms include muscle cramps, weakness, and

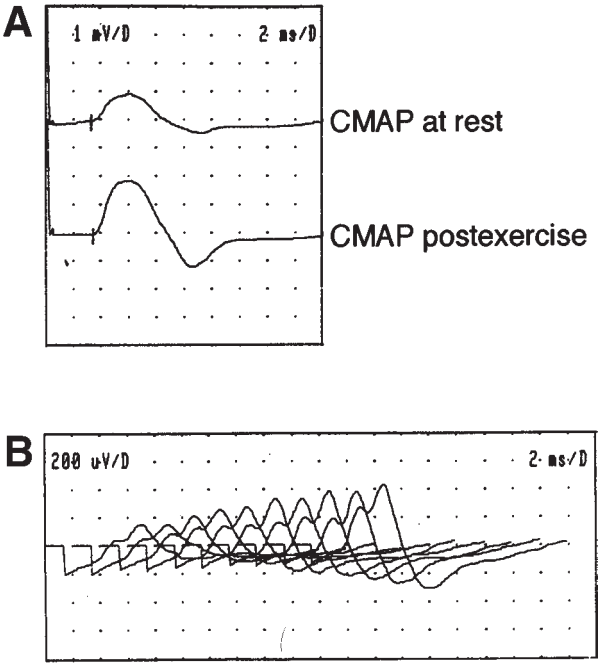


**Fig. 3.** Electrophysiologic testing in a patient with SCLC and LEMS. **(A)** The upper tracing represents the CMAP of the abductor pollicis brevis at rest, after stimulating the median nerve at the wrist. The lower tracing shows a twofold increase of the CMAP after 10 s of maximal voluntary contraction. **(B)** Repetitive nerve stimulation (20 Hz) of the ulnar nerve, recording over the abductor digiti minimi. There is a 300% increment of the amplitude of the response between the first and tenth stimuli. (Courtesy of Dr. Stacy A. Rudnicki.)

sometimes excessive sweating *(60)*. The involved muscles show undulating myokymia and may be hypertrophic *(61)*. EMG shows fibrillation, fasciculation, and doublet, triplet, or multiplet single-unit discharges that have a high intraburst frequency, the frequency of the bursts themselves being irregular. This abnormal activity continues during sleep and general anesthesia, is abolished by curare, and may be unaffected, reduced or abolished by peripheral nerve block *(59,62)*.

Neuromyotonia is associated with autoantibodies to voltage-gated potassium channels (VGKC) which increase the release of quanta of acetylcholine and prolong the action potential *(63,64)*. The tumor most frequently involved is thymoma, and these patients may also have myasthenia gravis (MG) *(65)*. Other tumors include Hodgkin's lymphoma *(66)*, bronchial carcinoma *(67)*, SCLC *(68)*, and plasmacytoma with IgM paraproteinemia *(69)*. Symptoms improve with diphenylhydantoin, carbamazepine, and plasma exchange *(62)*.

**PARANEOPLASTIC AUTONOMIC DYSFUNCTION** This disorder usually develops in association with other paraneoplastic syndromes, such as PEM or LEMS. Symptoms often precede the detection of the tumor, usually a SCLC. Other tumors include cancer of the pancreas *(70)*, testis *(71)*, Hodgkin's and non-Hodgkin's lymphoma *(72,73)*, and carcinoid tumor of the lung *(74,75)*.

The autonomic dysfunctiom may result from adrenergic or cholinergic nerve dysfunction at the preganglionic or more commonly postganglionic level *(71,76)*. There are three disorders that can be life-threatening: esophageal and gastrointestinal dysmotility with intestinal pseudoobstruction *(77,78)*, cardiac dysrhythmias *(14)*, and orthostatic hypotension *(70, 79–81)*. Other accompanying symptoms may include dry mouth, erectile dysfunction, anhidrosis, and sphincter dysfunction *(74)*. Because autonomic dysfunction can be the presentation of PEM, testing for anti-Hu antibodies should be considered in some patients *(82,83)*.

**LAMBERT-EATON MYASTHENIC SYNDROME** LEMS is a disorder of the neuromuscular junction characterized by impaired acetylcholine release from the presynaptic motor terminal *(84)*. Symptoms include fatigue, leg weakness, muscle aches, and vague paresthesias. Dry mouth and other symptoms of autonomic dysfunction are common *(85)*. Cranial nerve involvement tends to be mild and transient, usually described as transient diplopia. Neurologic examination shows proximal weakness in the legs more than the arms and depressed reflexes, sometimes accompanied by eyelid ptosis and sluggishly reactive pupils *(86)*. Brief muscle contraction may potentiate deep tendon reflexes. Similarly, strength may improve after brief exercise.

LEMS is associated with cancer in 50–70% of patients, most commonly SCLC *(84,87,88)*. Neurologic symptoms typically precede or coincide with the diagnosis of the tumor. For patients without a known tumor, a work-up for cancer including chest CT and bronchoscopy is recommended at presentation and regularly for 2–5 yr. LEMS can also occur in conjunction with other paraneoplastic syndromes, such as paraneoplastic cerebellar degeneration *(8,89)* and PEM/PSN *(90)*.

Routine nerve conduction studies show small amplitude compound muscle action potentials (CMAP) *(91)*. At slow rates of repetitive nerve stimulation (2–5 Hz), a decremental response of greater than 10% is seen. At fast rates (20 Hz or greater), facilitation occurs and there is an incremental response of at least 100% *(92)* (Fig. 3). A less painful and equally sensitive alternative test to fast repetitive nerve stimulation is to establish a baseline CMAP and then ask the patient to maximally contract the muscle for 10–15 s. In LEMS, a single shock delivered to the nerve after voluntary muscle contraction is associated with 100% or greater increase in amplitude of the CMAP *(93)*. If facilitation of >100% occurs in multiple muscles, or if a single muscle shows facilitation of 400% or greater, the diagnosis of LEMS is essentially certain *(94)*.

LEMS results from an immunological attack against the presynaptic voltage-gated calcium channels (VGCC), interfering with the release of acetylcholine vesicles. The transfer of IgG from patients with LEMS into mice reproduces the clinical and electrophysiologic features of the disease *(95,96)*. The detection of antibodies to P/Q-type VGCC is used as a serologic test for LEMS *(97)*.

Therapies for LEMS include treatment of the cancer if identified, medication to increase the release of acetylcholine, and immunomodulation *(94,98)*. The majority of patients with cancer have neurological improvement with combined treatment of their cancer and therapy specific for LEMS. If after initial improvement there is neurologic deterioration, a search for recurrent cancer should be undertaken *(99)*. 3,4-diaminopyridine produces a moderate to marked neurologic improve-

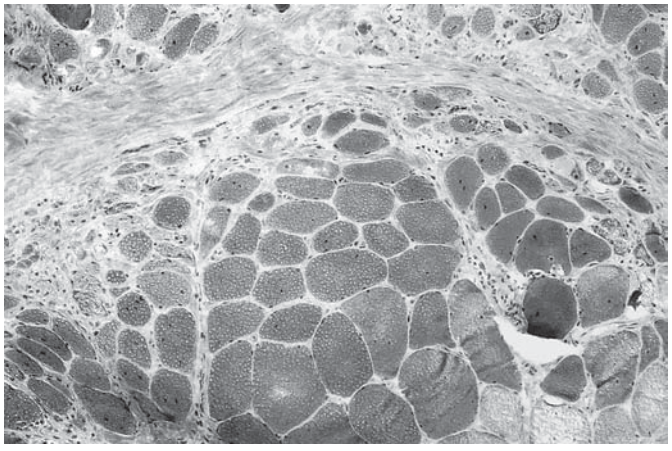

**Fig. 4.** Perifascicular atrophy in dermatomyositis. Muscle biopsy of a patient with dermatomyositis, showing characteristic perifascicular atrophy. (Courtesy of Dr. Robert E. Mrak.)

ment in 80% of patients, regardless of whether cancer is present. Pyridostigmine usually enhances the response to 3,4-diaminopyridine *(100,101)*. If 3,4-diaminopyridine is not available, a combination of pyridostigmine and guanidine may be beneficial *(102)*. IVIg may improve strength within 2–4 wk but the benefits are transient *(103,104)*. Plasma exchange is another alternative for treating patients with severe weakness, although its effects are also transient *(95)*. Long-term immunosuppression with prednisone or azathioprine should be considered in patients who remain symptomatic despite 3,4-diaminopyridine *(105)*.

**MYASTHENIA GRAVIS** Myasthenia gravis (MG) is a postsynaptic disorder of neuromuscular transmission caused by antibodies against the acetylcholine receptor *(106)*. A thymoma is found in about 10% of patients, and one-third of patients with thymoma develop MG *(107)*. Neurologic symptoms and the occurrence of acetylcholine receptor antibodies is similar in patients with and without thymoma *(108)*. Anti-titin antibodies may help predict the presence of thymoma *(109)*, but patterns of binding and blocking acetylcholine receptor antibodies do not *(110)*. The association of MG with extrathymic malignancies is controversial.

Treatment of paraneoplastic MG should be directed at removal of the thymic tumor. Additional therapeutic strategies, including symptomatic treatment (i.e., anticholinesterase drugs, plasma exchange, IVIg), immunosuppression (steroids, azathioprine, and others), or both, are similar for patients with and without thymoma.

**POLYMYOSITIS AND DERMATOMYOSITIS (PM/DM)** PM/DM are inflammatory disorders of the muscle and are likely autoimmune in nature. The association of PM/DM with cancer is rare, and the existence of paraneoplastic PM controversial. However, a number of studies support the view that patients with DM are at higher risk for cancer *(111–116)*. In women the most common tumors are ovarian and breast cancer, and in men, lung and gastrointestinal cancer. An association with cancer has not been demonstrated in childhood DM.

Patients with PM/DM typically present with proximal muscle weakness of subacute onset, elevated levels of serum creatine kinase, and electromyographic evidence of myopathy. Neck flexors and pharyngeal and respiratory muscles are commonly involved; their dysfunction may result in aspiration and hypoventilation and contribute to death. Reflexes and sensory exam are normal.

In DM the classic skin manifestations include purplish discoloration of the eyelids (heliotrope rash) with edema, and erythematous, scaly lesions over the knuckles. Necrotic skin ulcerations and pruritus are predictive factors for the development of cancer *(117,118)*. The skin symptoms usually precede the neurologic deficits.

Clinical, electromyographic, and pathological findings of PM/DM are similar in patients with and without cancer. In some patients, the serum creatine kinase levels are normal. Patients with interstitial lung disease may harbor antibodies to histidyl-tRNA synthetase (anti-Jo-1) *(119)*. Low titers of antinuclear antibodies typical of other connective tissue diseases can also be detected. There are no specific markers indicative of the paraneoplastic origin of DM.

Different immune mechanisms appear to be involved in PM and DM. While PM results from cell-mediated cytotoxic mechanisms, DM results from a humoral immune-mediated vasculopathy leading to ischemia, muscle fiber necrosis, and perifascicular atrophy (Fig. 4). Some patients develop cutaneous involvement without myopathy (amyopathic dermatomyositis) in association with cancer *(120,121)*. In these patients MRI studies may show subclinical muscle involvement *(121)*.

The course of PM/DM is independent of the malignant disease. Treatment of the tumor may or may not improve the neurological syndrome. Steroids and other immunosuppressants (azathioprine, cyclophosphamide, methotrexate) have been used successfully in paraneoplastic and nonparaneoplastic DM. IVIg is proven to be effective in DM refractory to other treatments *(128)*.

Patients with graft-versus-host disease (GVHD) may develop symptoms of PM. Some of these patients also have skin abnormalities secondary to GVHD, which are easily differentiated from DM. In these patients, treatment should be directed to the GVHD.

**ACUTE NECROTIZING MYOPATHY** Patients with this disorder develop muscle pain and proximal weakness, associated with high levels of serum creatine kinase. The disorder evolves rapidly to generalized weakness, which involves pharyngeal and respiratory muscles, often leading to death in a few weeks. Several types of tumors are involved, including SCLC, cancer of the gastrointestinal tract (stomach, colon, gall bladder, pancreas), breast, kidney, and prostate *(122)*. Muscle biopsy shows prominent necrosis with little or absent inflammation. There is alkaline phosphatase staining of connective tissue, and some muscle fibers are immunolabeled by antibodies to terminal components of the complement cascade (C5–C9). Treatment of the tumor may result in neurological improvement *(122)*. In cancer patients, the differentialdiagnosis should include chemotherapy and cytokine-induced (interleukin-2 [IL-2], interferon-α [IFN-α]) rhabdomyolysis *(123)*.

**CACHECTIC MYOPATHY** Cachexia is a state of involuntary weight loss that complicates debilitating diseases, such as cancer, and contributes significantly to mortality *(124)*. Several cytokines (tumor necrosis factor-α [TNF-α], IL-1, IL-6, IFN-γ) produced by the cancer or by the immunologic system in response to the cancer, are involved in the mechanisms of anorexia-cachexia. These cytokines appear to affect the homeostatic loop of body weight regulation, mimicking leptin, and some of them modulate a ubiquitin-proteasome proteolytic pathway in the muscle of cancer patients *(125,126)*.

The strength of patients with cachexia is often preserved until late in the course of the disease. Muscle biopsy demonstrates marked small grouped atrophy involving both types of fibers; in advanced stage of cachexia there is proliferation of nuclei and fragmentation of muscle fibers *(127)*. These findings are not associated with inflammation or nerve degeneration.

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# Part V Complications of Cancer Therapy

# 14 Neurologic Sequelae of Radiotherapy on the Nervous System

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## INTRODUCTION

Radiation therapy (RT) plays a central part in current cancer treatment modalities. However, despite advances in our knowledge of the mechanisms of radiation-induced neurotoxicity and the subsequent development of safer procedures, radiotherapy still accounts for disabling and sometimes life-threatening conditions. In addition, the range of indications of RT is spreading to nontumoral disorders such as vascular malformations or trigeminal neuralgia, a move spearheaded by the development of radiosurgery and other modern irradiation techniques.

The nervous system is widely distributed and thus often situated within a radiation portal, a situation relevant to nervous system tumors but also many other neoplasms; for instance, the brain may be injured during RT for head and neck or pituitary tumors, as may the spinal cord after RT for lung cancers. Contrary to previous opinion, the radioresistance of the nervous tissues is relative. Several parameters influence their tolerance: volume, total dose, dose per fraction (a central factor in this case), and duration of irradiation. Even if these factors are better understood, an individual sensitivity to RT, probably linked to genetic predisposition, still exposes the patient to complications even after a "safe" procedure. Furthermore, the therapeutic index is low, and in many cases the dose required for tumor control is very close to, if not higher than the toxic dose for neighboring tissues.

Radiation oncologists have devised formulas that try to equate different dose-fractionation schemes in terms of biological equivalence producing radiation damage to the nervous system. Each of these formulas takes into account the total dose of radiation (D) in centigray (cGy), the number of fractions (N), and the total days of treatment time (T). One widely used formula is *(1)*:

$$\text{Neuret} = D \times N^{-0.41} \times T^{-0.03}$$

From: *Cancer Neurology in Clinical Practice* (D. Schiff and P. Y. Wen, eds.), © Humana Press Inc., Totowa, NJ.

Doses greater than 1000 to 1100 neuret are associated with a substantially increased risk of focal radiation damage.

The effects of radiation therapy on the brain and spinal cord have been studied over the past decades, so that the main clinical, radiological, or neuropathologic features of radiation-induced syndromes are increasingly well known. However, the pathophysiology of cerebral and spinal radiation injury is not fully understood. Neurological sequelae are usually classified according to their date of onset after RT including acute, early-delayed, and late-delayed complications. The latter differ in most cases from the two former conditions because of its irreversibility. Acute complications occur days to weeks after RT and early-delayed damage about 1–6 mo after irradiation, whereas late-delayed injuries follow RT by more than 6 mo and may be delayed by many years.

## SEQUELAE OF RADIOTHERAPY ON THE BRAIN

**ACUTE ENCEPHALOPATHY** Acute encephalopathy usually appears within 2 wk after the beginning of cranial RT, often a few hours after the first fraction delivery. The patient presents with nausea and vomiting, drowsiness, headache, dysarthria, and a worsening of pre-existing neurological deficits, sometimes associated with fever. The clinical course is usually favorable, but herniation and death are a threat in patients with large tumors or who already presented with intracranial hypertension at the beginning of irradiation (for instance in multiple metastases, posterior fossa or intraventricular tumors). Large doses per fraction (usually over 3 Gy/fraction) are the main risk factor: Young et al. *(2)* reported acute disorders in 50% of patients with brain metastases treated with 15 Gy in 2 fractions, and Hindo et al. *(3)* reported 4 deaths within 48 h of a 10 Gy RT given in 1 fraction. As these large doses are no longer in use, the frequency of the severe forms of this syndrome has decreased. A minor form of this condition is seen in many patients, consisting of nausea and moderate headache occurring within hours following cranial irradiation.

Steroids may help preventing or limiting the consequences of acute encephalopathy, especially in patients with large pri-

**Table 1**
**Main Neurological Complications of Radiotherapy**

| *Site* | *Acute complications* | *Early-delayed complications* | *Late-delayed complications* |
|---|---|---|---|
| Brain | Acute encephalopathy | • Somnolence syndrome<br>• Worsening of pre-existing symptoms<br>• Transitory cognitive impairment<br>• Subacute rhombencephalitis | • Cerebral radionecrosis<br>• Cognitive dysfunction and leukoencephalopathy<br>– mild or moderate impairment<br>– dementia<br>• Radiation-induced brain tumors |
| Spinal cord | | • Lhermitte's sign | • Spinal cord radionecrosis<br>• Progressive myelopathy<br>• Spinal hemorrhage |
| Cranial nerves | | • Hearing loss<br>• Anosmia<br>• Ageusia | • Hearing loss<br>• Visual loss<br>• Lower cranial nerve paralysis |
| Other peripheral nerves | Paresthesias | • Brachial or lumbosacral reversible plexopathy | • Brachial or lumbosacral late plexopathy<br>• Motor neuron syndrome<br>• Radiation-induced tumors |

mary or secondary brain tumors or with considerable edema particularly at risk of herniation. In such patients, daily doses of steroids of at least 16 mg dexamethasone should be prescribed 48–72 h before the first fraction; a limitation of dose per fraction (2 Gy or less per fraction) is also recommended in this situation *(4,5)*.

The pathophysiology of acute complications probably implies radiation-induced alterations of the blood-brain barrier (BBB). In the brain, this disruption could lead to an increase in intracranial pressure responsible for acute encephalopathy. Animal studies have shown that a single cranial dose as low as 3 Gy can cause a significant increase of the BBB capillary permeability 2 h later; the barrier partially reformed 24 h later *(6)*.

**EARLY-DELAYED COMPLICATIONS** These reactions occur 2 wk to 6 mo after RT. A transitory demyelinating process associated with BBB lesions or selective injury to the oligodendrocytes has been proposed to explain these disorders. They may take several forms (Table 1).

**Somnolence Syndrome** This condition was first described in the late 1920s in children receiving low-dose RT for scalp ringworm. Several studies reported cases of children without brain tumor who developed somnolence syndrome 5–8 wk after prophylactic cranial RT for leukemia *(7,8)*; other reports have shown that it also occurs in adults. The incidence of somnolence syndrome greatly differs from one study to another, with figures from 8% *(9)* to 84% *(10)*; this difference is related to various factors including tumor types, radiation dose, fractionation, and diagnostic criteria.

The symptoms include drowsiness, lethargy, excessive sleep sometimes requiring hospitalization, headache, nausea, and anorexia; fever and papilledema are sometimes seen. Irritability, attention deficits, and difficulties with recent memory are possible; on the whole, the patient feels unwell and slow. Littman et al. *(8)* have elaborated somnolence syndrome criteria evaluating the severity of symptoms (*see* Table 2).

Most studies report a monophasic course of symptoms. However, in a recent detailed prospective study on 19 adult patients treated with cranial RT (45 to 55 Gy) for primary brain tumors, Faithfull and Brada *(10)* reported a biphasic pattern of the symptoms, with two critical periods from the 11th to the 21st day and from the 31st to the 35th day after RT. Furthermore, in this study, an accelerated fractionation led to significantly more severe drowsiness and fatigue than a conventional scheme.

MRI studies are not contributory. Electroencephalographic findings consist of nonspecific diffuse slow waves.

The course of somnolence syndrome is usually favorable, resolving within a few weeks. Steroids have been proposed, either prophylactically or as a therapy to alleviate the symptoms *(11)*; however, the data are sparse and contradictory and no clear prospective data exist on their use in this situation. In all cases, warning the patient of the possible occurrence of this syndrome is important and decreases anxiety linked to it.

**Worsening of Pre-Existing Symptoms** In patients under treatment for brain tumors, a worsening of pre-existing neurological focal deficits can be an alarming situation, leading to concerns of tumor progression or recurrence, especially when observed in association with features of the somnolence syndrome and with transitory cognitive impairment *(4)*. This syndrome can be a consequence of RT, usually following the treatment by about 2 mo. Neuroimaging can be normal or shows edema and contrast enhancement within the tumor bed, a situation that does not allow this syndrome to be differentiated from tumor recurrence and explains why inclusion of patients in experimental regimens for "recurrence" is not indicated during this period; it is worthwhile noting that this radiological pattern can also be associated with no clinical worsening. Improvement usually follows within a few weeks or months and a close follow-up of computed tomography (CT)-scan or magnetic resonance imaging (MRI) will show a regression of

**Table 2**
**Somnolence Syndrome Scale**

| *Grade* | | *Description of symptoms* |
|---|---|---|
| 0 | None | No evidence of change in behavior |
| 1 | Minimal | Disturbance with some tiredness but activity not curtailed |
| 2 | Mild | Decreased activity and increased tiredness; may have a low-grade pyrexia |
| 3 | Moderate | Sleeping much of the day; decreased appetite; low-grade fever; most activities curtailed |
| 4 | Severe | Inactive; sleeping 18-20 h per day; low-grade fever; markedly decreased appetite and only taking fluids |

Adapted from ref. *8*.

these signs in 4–8 wk *(12)*. As in the somnolence syndrome, the treatment lies on supportive care; steroids are usually proposed in this situation.

**Transitory Cognitive Impairment** A transitory cognitive decline can be observed within the first 6 mo after cranial RT, mainly affecting attention and recent memory, and may sometimes be associated with a somnolence syndrome. Several studies have underlined the frequency and the nature of this impairment. Armstrong et al. *(13)* prospectively studied 5 patients receiving focal fractionated cranial RT (43 to 63 Gy) for primary brain tumors and showed memory impairment in all 5 patients 1.5 mo later; the results were normalized 2.5–10.5 mo afterwards. In a prospective study comparing 17 patients treated with focal cranial RT (54 Gy) for a good prognosis glioma and 14 control patients with the same type of glioma who did not undergo RT, Vigliani et al. *(14)* found a significant alteration of the reaction test in 36% of the patients. The patients returned to normal baseline results 12 mo after RT. This test result was correlated with their occupational status: 69% of the patients could not work at 6 mo, whereas 73% had continued or resumed their job at 1 yr. In our experience, informing patients about this possible difficulty to return to a normal life (particularly work) at least during the first 6 mo following radiotherapy is useful. To our knowledge, the only contradictory report studied 5 patients with small cell lung cancer treated with prophylactic whole brain irradiation (30 Gy); no dysfunction was noted in cognitive tests performed at 1 and 5 mo *(15)*.

Early-delayed persistent and severe symptoms have rarely been reported *(16)*. In most cases, transitory cognitive impairment does not appear to predispose patients to developing long-term cognitive disorders or dementia.

***Subacute Rhombencephalitis*** Distinct from brainstem radionecrosis, which occurs later, early-delayed subacute rhombencephalitis may be observed about 1–3 mo after RT using portals involving the brainstem, as in ocular, pituitary, or head and neck tumors. The clinical picture includes ataxia, dysarthria, diplopia, and/or nystagmus as well as auditory loss. In some cases, the cerebrospinal fluid (CSF) analysis shows inflammatory signs. MRI may demonstrate white matter abnormalities appearing as grossly round or more extensive T1-weighted hypointensities and T2-weighted hyperintensities affecting the brainstem and the cerebellar peduncles; the lesions may enhance after gadolinium injection *(17)*. The condition usually improves progressively over a few weeks to a few months, either spontaneously or with steroids, but coma and death have been reported in rare cases *(18)*.

**LATE-DELAYED COMPLICATIONS** These complications follow RT by a few months to many years. Their principal forms are local radionecrosis and mild to severe cognitive impairment associated with leukoencephalopathy.

**Cerebral Radionecrosis** Focal cerebral radionecrosis constitutes a challenging complication of radiation therapy because it often mimics tumor recurrence and its functional consequences can be devastating.

Radiation necrosis has become rarer. It has been demonstrated that a total external-beam cranial radiation dose of 55–60 Gy administered to a focal field with fractions of 1.8–2 Gy per day makes up the upper limit of a "safe" dose; most of the schemes used nowadays fall within these limits. Vascular risk factors such as diabetes, old age, and associated chemotherapy may also favor the potential development of radionecrosis. An individual sensitivity to irradiation may also account for cases of radionecrosis in patients without particular risk factors *(19)*.

In cases of radiosurgery for arteriovenous malformations (AVM), the risk of brain necrosis varies greatly according to the location and volume of the lesion *(20)*. For instance, in a study on 169 patients with Linac radiosurgery (peripheral dose 25 Gy to the 60–70% isodose; volume range from 280–19,920 $mm^3$), Schlienger et al. *(21)* found a necrosis rate < 5%. Miyawaki et al., using the same technique in a group of 73 patients treated for large volume intracranial AVM, found that large treatment volumes (>14 cc) and dose > 16 Gy were associated with a 22% rate of radiation necrosis requiring resection *(22)*.

Radiation necrosis usually follows RT by 1–2 yr *(23)*, but a latency as short as 3 mo is possible, especially after interstitial brachytherapy *(24)* or radiosurgery. A very long latency has also been reported, with extremes of more than 30 yr after completion of RT.

This complication occurs in patients irradiated for brain tumors or extracerebral tumor (e.g., head and neck or pituitary tumors, osteosarcomas of the skull) when radiation portals included a portion of the normal brain. For instance, bilateral medial temporal lobe destruction may follow RT for nasopharyngeal or pituitary tumors. In about half of the patients, seizures are the first signs of radiation necrosis. In the case of an irradiated brain tumor, the patient usually presents with symptoms simulating tumor recurrence or progression; in other cases, the symptoms consist of intracranial hypertension syndrome and/or focal neurological deficits *(25–27)*.

CT scan generally shows a hypodense area within the irradiated region, responsible for mass effect on the neighboring structures. Contrast enhancement is variable. MRI is much

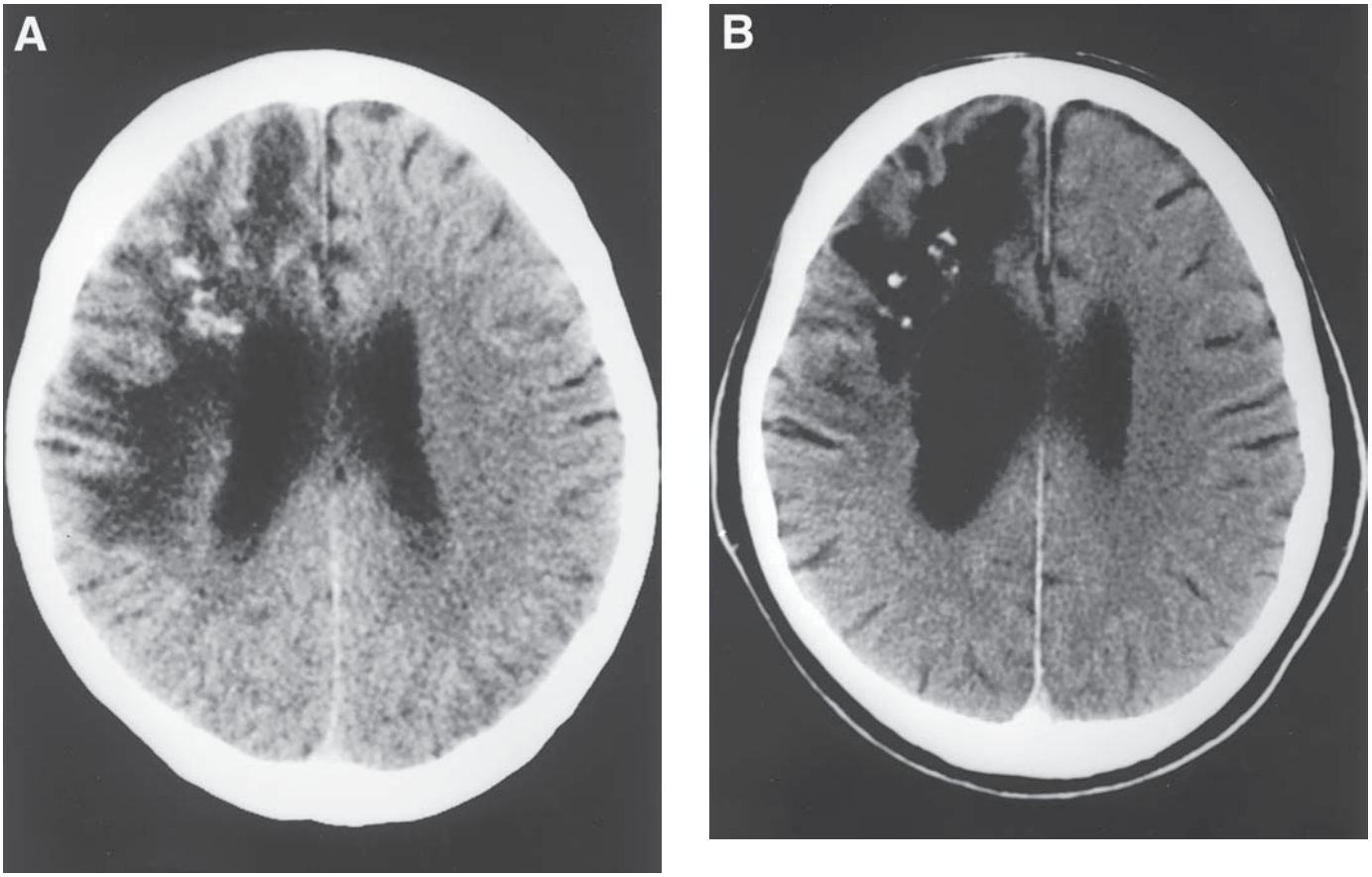


**Fig. 1.** Axial CT scan in a 42-yr-old man treated with external beam conventional RT for a right frontal anaplastic astrocytoma. **(A)** Radionecrosis focus appearing as an enhancing lesion in the tumor bed 1 yr after RT. **(B)** Isolated calcifications 4 yr later.

more sensitive, and shows predominant white matter lesions appearing as T1-weighted hypointensities and T2-weighted hyperintensities. Gadolinium enhancement is common. The overall aspect of the lesions may be impossible to differentiate from a recurrence of the primary tumor (Fig. 1) or from a new or secondary tumor location *(28)*.

Positron emission tomography (PET) with $^{18}$F-fluorodeoxyglucose *(29)* or $^{11}$C-methionine, single photon emission computed tomography (SPECT) with $^{201}$Thallium or methoxyisobutyl-isonitrile ($^{99m}$Tc-MIBI) *(30)* have been proposed to assess the nature of the lesions; in typical cases, radionecrosis is characterized by hypometabolism, and tumoral growth by hypermetabolism. The use of MR spectroscopy has also been explored. However, no current imaging modality is able to differentiate definitively between tumor and radiation necrosis, as illustrated by several reports *(31,32)*. Furthermore, results may be blurred by the fact that many patients exhibit a mixture of radiation necrosis and tumor growth *(4)*.

Angiography is sometimes performed; its interest lies in the fact that an area of necrosis appears as an avascular mass, in contrast with malignant tumors.

Histological examination, usually obtained by cerebral biopsy *(33)*, is the only means of obtaining a diagnostic certainty. Radiation lesions are characterized by coagulative necrosis predominant in the white matter (the cortex is relatively spared). Blood vessels show important alterations including wall hyalinized thickening and fibrinoid necrosis often associated with vascular hemorrhage and thrombosis; an accumulation of perivascular fibrinoid material is also noted.

The current treatment of cerebral radionecrosis includes surgical excision of the necrosis foci and steroid therapy. Surgery is the most effective whenever possible, as patients treated with steroids alone are often only transiently improved or relapse when this treatment is discontinued. However, a few reports show long-term improvement in patients on steroids, even after discontinuation *(4)*.

Anticoagulants have been studied by Glantz et al. *(34)* in 8 patients (7 with histological evidence of necrosis) treated with RT for gliomas. A course of warfarin in one patient and IV heparin followed by warfarin in 7 patients was begun after the failure of steroids and continued for 3–6 mo. This treatment led to an improvement in 5 patients. In our experience, anticoagulants have been more disappointing. Further assessment of this therapy is required to confirm those results.

Some authors have advocated the use of hyperbaric oxygen (HBO). The rationale of its use is underlain by the fact that HBO increases the tissue pO2 and enhances angiogenesis. Chuba et al. *(35)* treated 10 patients with CNS radionecrosis (proved by biopsy in 8 cases) with 100% oxygen at 2.0–2.4 atmospheres for 90–120 min/session in at least 20 sessions. All patients were stabilized or improved initially, and the 6 surviving patients showed durable improvement after 3–36 mo. How-

ever, most patients were given steroids, and the respective effect of each treatment is not clear. Leber et al. *(36)* treated 2 patients for radionecrosis following gamma-knife radiosurgery for arteriovenous malformations with 100% oxygen at 2.5 atmospheres for 60 min/d repeated 40 times in 10 session cycles without any steroid prescription; both patients were clinically improved, and one lesion disappeared on clinical imaging. More studies are necessary to assess the utility of this therapy.

The pathophysiology of white matter abnormalities potentially leading to necrosis are not fully understood, but several hypotheses have been proposed. As histological examination usually shows vascular lesions and demyelination, vessels and glial cells have often been considered as the primary target of radiation injury. However, the situation could be more complicated: recently, the interactions between radiation and other cell types have been studied more closely, as well as the recuperative abilities of the CNS *(37)*.

***Vessels as the Primary Target of Radiation Injury: The Vascular Hypothesis*** This theory has been advocated to explain radiation necrosis, and is based on the postulate that necrosis would be a consequence of ischemia secondary to blood vessel damage. Several arguments support this theory: vessel dilation and wall thickening, nuclear enlargement in endothelial cells have been described after RT, as well as a decrease in vessel density and endothelial cell loss (with correlations to time and dose) preceding white matter necrosis *(38–40)*. Furthermore, animal studies show tissue necrosis following radiation-related endothelial lesions responsible for a progressive increase in capillar permeability in a rat model *(41)*. Another argument comes from experimental studies on lesions induced by boron neutron capture therapy: using this technique, which allows a selective irradiation of the blood vessels of the spinal cord, Morris et al. produced lesions similar to those following X-radiation schemes *(42)*.

Nevertheless, necrosis without vascular damage has also been reported *(38)*, a fact that suggests a more complex pathophysiology. On the other hand, neurons are very sensitive to the lack of oxygen *(43)* and despite differences in the vascularization of gray and white matter, should be damaged in a purely ischemic model *(37)*.

Therefore, the significance of the role of vessel injury is almost certain but does not seem sufficient to explain radiation necrosis.

***Oligodendrocytes as the Primary Target of Radiation Injury: The Glial Hypothesis*** The putative role of oligodendrocytes as a target of radiation damage is underscored by the demyelinating lesions observed after RT. These differentiated cells are responsible for the production of neuron myelin sheath in the CNS and derive from progenitor clones called O-2A. It has been shown that reproductive ability was lost in O-2A progenitors in brain and spinal cord of irradiated rats *(44–46)*; this incapacity results in inability to replace mature myelin-producing oligodendrocytes.

Several facts stand in opposition to this theory: first, the kinetics of oligodendrocytes may account for relatively early-onset necrosis, but not for late damage *(47)*; second, other demyelinating conditions such as multiple sclerosis do not often lead to necrosis *(37)*; third, glial cell loss can be found in animals and humans after radiation doses that are usually not associated with necrosis *(48,49)*. Although this theory accounts for predominant white matter lesions, arguments clearly go against an exclusive explanation.

***Radiation and Other CNS Cell Types*** Trying to explain radiation damage through single cell dysfunction seems in contradiction with the complex network structure of the CNS. Many examples show the necessity of interactions and regulations between the different cell types (e.g., to maintain the BBB), and several studies over the past few years have focused on neurons, astrocytes, microglia, or neural stem cells to understand their possible implication in the development of radiation-induced lesions, either as primary targets or through alterations of their regulatory capacity.

Neuronal involvement is suggested by several animal studies. Apoptosis may also be the primary consequence of irradiation in vitro, leading to cellular death *(50,51)*. However, this observation probably has few clinical implications because of the important protective mechanisms surrounding the neuron inside the CNS, primarily involving astrocytes *(52)*.

Astrocytes, which are the most numerous cell type in the CNS (9 astrocytes for 1 neuron) *(53)*, have an essential regulatory function, including the secretion of several cytokines and other molecules *(54,55)*, but also the response to injuries, a fact well-observed in trauma and ischemia. It has been shown that the number of astrocytes increases after irradiation *(54)*. Several facts illustrate the protective role of astrocytes. Astrocytes produce growth factors (such as FGF-2, CNTF, PDGF) implicated in the activity of O-2A progenitors and survival factors (PDGF, IGF-1, CNTF) for the mature oligodendrocytes *(54,57)*. They also protect neurons from oxidative injury *(58–60)*, for example through their catalase activity *(61)*. Furthermore, they play an important part in maintaining the BBB *(62)*.

Microglia are normally implicated in inflammatory processes occuring in the brain, and a tight functional link exists between microglia and astrocytes *(63)*. Irradiation of the brain or spinal cord induces an increase of microglia and alterations *(56,64)*. The role of microglia could be important in particular because of the capacity of these cells to produce hydrolytic enzymes or oxygen radicals *(65)* that could enhance radiation injuries.

Radiation damage to the subependyma, a tissue containing glial and neural stem cells, was reported more than 25 yr ago *(66)*. Recent studies have shown that the level of neural stem cells of the subependyma was decreased after irradiation; this depletion is dose-dependent *(67)*. Their implication in radiation injury thus seems probable but remains to be specified by further studies.

As a whole, the development of radiation injury is complex, and results from an imbalance between cell lesions (implying vascular cells and oligodendrocytes, but probably other cell types such as neural stem cells) and the protective capacities of the CNS. A wide range of cell interactions mediated by cytokines and other molecules and the influence of indirect factor such as the proliferation of microglia or the production of oxidative products resulting from cell destruction may account for the wide variety of lesions observed from a patient to another.

### Cognitive Dysfunction and Leukoencephalopathy

Distinct from brain radionecrosis, this potentially devastating

condition is characterized by a progressive cognitive impairment ranging from mild dysfunction to severe dementia, associated with variable white matter abnormalities without focal radionecrosis. Otherwise described as "radiation-induced leukoencephalopathy" or "diffuse radiation injury," its importance is growing with the lengthening of survival in many irradiated patients, and it is currently the most frequent complication in long-term survivors.

Several predisposing factors have been isolated, including:

1. Old age. Several studies have demonstrated that demented patients were clearly older (55–60 yr) than nondemented patients (<45 yr-old) *(49,68,69)*.
2. Radiation scheme. The data on RT alone are limited, as chemotherapy is often utilized with this modality. Higher doses (>1000 neuret, approximately corresponding to 58 Gy delivered with 2 Gy per fraction 5 d a week) clearly increase the risk of dementia, but a safe dose has not been defined;
3. Radiation volume. The importance of mild to moderate cognitive impairment is dependent on the volume of irradiated brain. Whole brain radiotherapy (WBRT) may induce cognitive dysfunction in nearly 50% of patients with primary brain tumors *(68,70)* and in up to 100% *(71)* of recipients of prophylactic RT for small cell lung cancer. However, pre-existing cognitive deficits and concurrent treatments could also play a role. After focal-brain radiotherapy, the incidence of cognitive impairment in this situation is variable *(72)*. However, dementia hardly ever occurs in patients treated with focal conventional RT alone *(73)*.
4. Association with chemotherapy. The incidence of dementia in patients treated with combined RT and chemotherapy ranges from 4–63%. Methotrexate (MTX) is clearly implicated in combined toxicity; neurotoxic by itself *(74)*, it is responsible for frequent cognitive dysfunction when associated with RT. Overall, a 10–12% incidence of progressive severe cognitive impairment in patients treated with WBRT (40 Gy + 14 Gy boost) and a combination of intravenous and intrathecal MTX has been reported *(75)*. Here again, age apparently plays a key role: in a report on 30 patients treated with MTX-based chemotherapy followed by RT, Abrey et al. found an 83% (10 patients out of 12) late-delayed neurotoxicity rate in a group of patients over 60 yr, contrasting with only 6% (1 patient out of 18) in the younger patients group *(76)*. Other agents suspected to increase the risk of radiation-induced toxicity include nitrosoureas, cisplatin, etoposide, cytarabine, and actinomycin D. Multidrug regimens and high-dose chemotherapy associated with WBRT *(45)* could also increase the risk of late-delayed cognitive impairment.

Although there is a progressive continuum between mild to moderate cognitive impairment and severe fatal dementia, we will consider the two conditions separately.

**Radiation-Induced Mild or Moderate Cognitive Impairment** A mild to moderate cognitive dysfunction is more frequent than real dementia in long-term survivors. The features of this condition are not perfectly defined, as results greatly vary according to the studies, probably due to neuropsychological evaluation procedures, duration of follow-up, and population discrepancies *(77)*.

Cognitive impairment affects mainly attention and short-term memory in most reported cases, while intellectual functions are generally preserved on neuropsychological evaluations. Nevertheless, most patients have to decrease or even discontinue their professional activities. CT scan may be abnormal, showing periventricular hypodensities, an increase in the normal interface between white and gray matter, and ventricular enlargement. However, there seems to be no correlation between CT scan abnormalities and the degree of cognitive impairment. MRI shows variable degrees of T2-weighted hyperintensities in the white matter, with a gross correlation between neuropsychological status and white matter lesions.

The course of the disease is difficult to predict: some patients deteriorate slowly while a majority remain apparently stable. Progression to dementia is seldom reported. There is no recognized treatment for this syndrome although some authors have advocated the use of methylphenidate for symptomatic relief *(78)*.

**Radiation-Induced Dementia** The incidence of this devastating complication varies widely in the literature (from 0 to more than 60%) according to the series. In a large review of several studies comprising 748 adult patients, the incidence of severe cognitive impairment compatible with dementia was at least 12.3% *(79)*.

The clinical picture is characterized by a "subcortical dementia" pattern that probably reflects consequences of diffuse white matter injuries, occuring within 2 yr in 69% of patients developing this complication *(69)*. Patients present with progressive memory and attention deficits, intellectual loss, gait abnormalities, and fatigue. Subsequently, emotional lability and apathy enrich the symptoms. The absence of hallucinations or delirium and the very unusual occurrence of aphasia, agnosia, or apraxia (deficits suggesting cortical involvement) are important clinical features for narrowing the differential diagnosis, especially in elderly patients. Depression is frequent, probably favored by the absence of anosognosia, but cognitive functions are not improved by antidepressants. Eventually, patients may develop gait ataxia, incontinence, and sometimes a picture of akinetic mutism. Nonspecific features such as seizures, pyramidal or extrapyramidal signs, or tremor are also frequently encountered in the course of the disease.

Neuroimaging always shows diffuse white matter lesions, best seen on MRI as T2-weighted hyperintensities, associated with cortical and subcortical atrophy as well as ventricular enlargement (Fig. 2). When performed, the lumbar puncture usually shows normal to moderately elevated (<1 g/L) CSF protein levels.

There is no treatment for this condition, but detailed investigations may be necessary to exclude the other causes of dementia in cancer patients (Table 3). In particular, the possibility of an association with normal pressure hydrocephalus, a possible complication of radiation therapy, should always be considered. The outcome of ventriculoperitoneal shunting is controversial; however, a recent study showed that, although improvement is often incomplete and transitory, it could play a part in enhancing quality of life *(80)*.

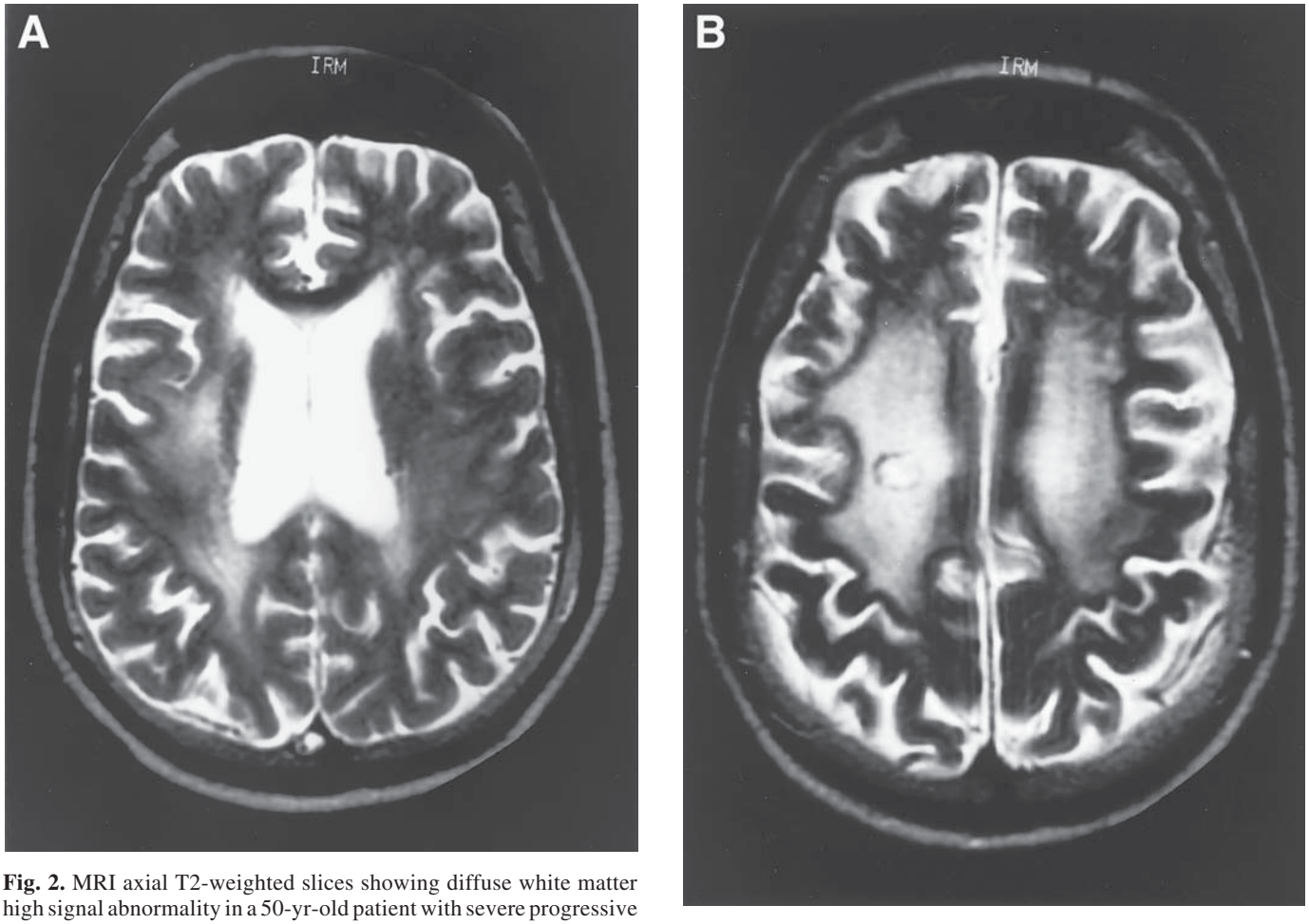


**Fig. 2.** MRI axial T2-weighted slices showing diffuse white matter high signal abnormality in a 50-yr-old patient with severe progressive cognitive impairment 4 yr after external beam conventional RT for a right frontal anaplastic astrocytoma

Deterioration occurs in about 80% of cases, leading to the death of the patient; stabilization is possible (18% of cases). Lasting improvement is exceptional *(16)*. Death generally occurs within 1–48 mo after the onset of the disorder *(73)*.

**Radiation-Induced Brain Tumors** The precise role of RT in the development of a tumor is difficult to determine and cannot be assessed with certainty, in great part because these tumors have no distinctive features in previously irradiated and unirradiated patients. However, data from animal and epidemiological studies indicate that irradiated patients or animals have a higher likelihood to develop a second brain tumor than would have been expected from the control data. An Israeli retrospective study on 10,834 patients treated with low-dose cranial and cervical RT (mean 1.5 Gy delivered to the neural tissue) for *Tinea capitis (81)* found a relative risk of 6.9 for tumors in general and 2.6 for gliomas. In another study by the British Childhood Cancer Research Group on 10,106 survivors of childhood cancers, the relative risk of developing a secondary CNS tumor (excluding patients with retinoblastoma who have a naturally increased risk) was 7 *(82)*. Most other studies have confirmed these figures *(83)*. However, the risk greatly increases in patients treated for acute lymphoblastic leukemia (ALL); for example, a large retrospective cohort study on 9720 children showed a relative risk of developing a nervous system tumor of 22 in this population *(84)*.

Imputability criteria include: (a) a long time before the occurrence of the second tumor (the mean onset delay is 12 yr, with cases ranging from 1–40 yr); (b) tumor development within the radiation portal or at its margins; (c) a different histological subtype.

Three types of tumors have been reported to be linked with cranial irradiation: meningioma in about 70% of cases, glioma in 20% and sarcoma in fewer than 10%.

More than 300 cases of radiation-induced meningiomas have been reported in the literature *(85)*. Authors often differentiate meningiomas arising from low-dose radiation schemes (<10 Gy) and from high-dose schemes (>20 Gy), a third group including doses between 10 and 20 Gy. A female predominance has been identified, although less prominent than in spontaneous meningiomas. The relative risk of developing a meningioma after low-dose RT was 9.5 in the study by Ron et al. *(81)*, and about 37 after high-dose RT *(83)*. In a review on high-dose radiation-induced meningiomas, Strojan et al. reported a mean latency period of 18.7 yr (ranging from 2–63 yr) *(86)*. Most patients (68%) had been irradiated during childhood, and the interval between RT and the onset of the tumor was shorter in younger patients; however, the radiation dose did not influence the latency. Radiation-induced meningiomas are often multiple and recurrent with malignant histological features *(87)*.

**Table 3**
**Some Possible Causes Of Diffuse Cognitive Impairment In Cancer Patients**

| *Tumor-related causes* | *Other causes* |
|---|---|
| Brain metastases | Radiation-induced endocrinopathy |
| Primary or secondary gliomatosis cerebri | Subclinical status epilepticus |
| Leptomeningeal carcinomatosis | Drug-induced toxicity (chemotherapy, anticonvulsants, steroids . . . ) |
| Paraneoplastic encephalopathy | Progressive multifocal leukoencephalopathy |
| | Other CNS infection |
| | Metabolic encephalopathy |

In a recent review *(88)*, 114 cases of radiation-induced gliomas (including 43 glioblastomas) were found in the English literature since 1960; the tumor was more often multifocal (20% of cases) in patients treated for acute leukemia than in patients irradiated for other tumors or in spontaneously occurring gliomas (<5% of cases). The interval between radiation therapy and the onset of the secondary tumor was shorter in patients treated for leukemia, with a median latency of 6–7 yr vs 9 yr in other patients. The outcome of secondary gliomas is often poorer than spontaneous forms, in particular because of intrinsic resistance or because less aggressive treatment schemes are proposed in these pretreated patients.

Fewer than 40 cases of sarcomas have been reported to date, including several histological types (gliosarcomas, meningiosarcomas, neurofibrosarcomas).

## RADIATION-INDUCED VASCULOPATHY

Distinct from radionecrosis, in which severe lesions of the arterioles and capillaries constitute a cardinal feature, radiation can induce other types of vascular damage leading to stroke or hemorrhage.

**ISOLATED LESIONS OF LARGE AND MEDIUM INTRA- AND EXTRACRANIAL ARTERIES** An arteriopathy affecting the large cervical blood vessels, especially the carotid artery, may be a complication of cervical RT, usually proposed for lymphomas or head and neck cancers *(89)*. Intracranial vessels may also be affected.

The main early-delayed vascular complication is carotid rupture *(90,91)* which usually follows an association of cervical RT and surgery for head and neck tumors by a few weeks. Associated skin lesions such as necrosis or wound infection are common. The outcome of this exceptional complication is of course very poor.

Late-delayed complications are more frequent, and generally occur many years after RT (median time about 20 yr for extra-cranial, 7 yr for intracranial artery lesions). The lesions are similar to those induced by atherosclerosis, but are often located in unusual places for common atherosclerosis and occur in an accelerated way. It has been observed that the larger the diameter of an irradiated artery, the longer the latency between RT and the onset of vasculopathy, a fact which could explain the shorter latency of RT-induced vasculopathy in children. Shorter latencies have also been reported with interstitial radiotherapy *(92)*. The dose required to induce vascular lesions usually exceeds 50 Gy, but the type of irradiation, fractionation, and portal differs greatly from one case to another. The lesions consist of one or several stenosis or occlusions on the arteries included within the radiation portal. The diagnosis, suspected when a cervical murmur is heard in the immediate vicinity of radiation-induced skin lesions, relies on magnetic resonance angiography, ultrasound examinations, and arteriography.

The treatment is similar to that of usual atherosclerotic lesions; in the event of carotid lesions, endarterectomy may be appropriate. However, surgery may be more difficult than in unirradiated patients because of vascular fibrosis and skin lesions, with higher postoperative risk of infection or healing problems. In other patients, antiplatelet agents may be prescribed if there is no contraindication. Some authors have advocated lowering serum cholesterol levels to prevent such lesions in patients at risk *(93)*.

**RADIATION-INDUCED VASCULOPATHY ASSOCIATED WITH A MOYAMOYA PATTERN** Intracranial vasculopathy leading to a progressive occlusive disease and a moyamoya pattern (characterized by abnormal anastomoses and netlike blood vessels) accounting for focal seizures, strokes, or transient ischemic attacks may follow intracranial irradiation, especially in very young children. This complication is particularly frequent in children treated for optic chiasm glioma, a condition often associated with neurofibromatosis type 1 (NF-1), which is a risk factor for vasculopathy in itself. It may also occur with other tumors such as brainstem glioma and craniopharyngioma *(94)*. In a recent series *(95)* of 69 children (11 with NF-1) treated for optic pathway glioma with RT (median dose 55 Gy), 13 (19%) developed clinical and radiological signs of vasculopathy after a median latency of 36 mo. The treatment focuses on preventing further strokes through surgical revascularization techniques *(96,97)*; calcium blockers such as flunarizine has been advocated by some authors *(95)*. No specific evidence supports the use of anti-platelet agents in this setting.

**SILENT LACUNAR LESIONS** A recent report *(98)* described a pattern of silent cerebral lacunes occurring in children treated for brain tumors. In this study reviewing 524 consecutive children, 5 of 421 treated with RT and chemotherapy had lacunes. Patients were a median of 4.5-yr-old at the time of the diagnosis and RT, and developed lacunes after a median latency of 2 yr (range 0.26–6 yr). This pattern was associated with no further clinical deficit or neuropsychological impairment when compared to patients without lacunes. This condition is probably linked with delayed radiation-induced capillary and small-vessel lesions.

**RADIATION-INDUCED CAVERNOMAS, ANGIOMATOUS MALFORMATIONS, AND ANEURYSMS** A few cases of radiation-induced cerebral vascular malformations have been reported, including cavernomas and telangiectasias. In a recent review, Amirjamshidi et al. *(85)* found 21 brain occult vascular malformations reported in the literature, following varied irradiation schemes. In addition, several cases of multiple radiation-induced cavernous angiomas have been reported *(99)*. These complications emerged 18 mo to 23 yr after RT. Their main risk is intracranial hemorrhage.

Finally, fewer than 15 cases of radiation-induced intracranial aneurysms have been described in the literature *(100)*. The median age of the patients was 37.5 yr (range from 11–65 yr) and a latency of 10 mo to 21 yr, with no correlation between the onset of aneurysms and the radiation dose. This represents a rare but severe problem, as rupture is always possible; 6 of 9 aneurysm ruptures proved fatal. A growing aneurysm can also mimic tumor recurrence. Aneurysms are sometimes detected preclinically with usual imaging procedures for tumors (CT scan and MRI), as was stressed by Azzarelli et al. *(101)*, and particular attention should be drawn to evaluating the onset of such lesions during the imaging follow-up. When an aneurysm detected on CT or MR scan, or if the clinical history strongly suggests its presence, cerebral angiography is required for delineation.

## ENDOCRINE DYSFUNCTION

Frequently underestimated *(102)*, endocrine disorders can be the consequence of direct irradiation of a gland (e.g., the thyroid gland, with about 50% of patients developing hypothyroidism within 20 yr following radiotherapy for Hodgkin's disease or certain head and neck cancers) or result from a hypothalamic-pituitary dysfunction secondary to cranial irradiation (several authors believe that the hypothalamus is more radiosensitive than the pituitary gland) *(103)*. We will focus on the second type of disorder, which can be induced by cerebral or nasopharyngeal tumor irradiation.

There is a positive correlation between radiation dose and the incidence of endocrine complications. For instance, in a prospective study on 268 patients treated with different RT schemes involving the brain, Littley et al. found 5 yr after RT a 9% incidence of TSH deficiency in patients treated with 20 Gy, 22% with 35–37 Gy and 52% with 42–45 Gy *(104)*. A hormonal deficit can appear at any time after RT, but this may arise more rapidly in patients treated with higher radiation doses *(105)*.

In children, varied endocrinologic deficits may result from cranial RT (administered for brain tumors or during prophylactic irradiation in acute lymphoblastic leukemia [ALL]). Growth hormone (GH) is usually the first and in many cases the only anterior pituitary deficit in those young patients. Bothersome because of its consequences on statural growth, this complication affects about 50% of children treated with prophylactic cranial RT for ALL *(106)*. According to a recent Danish study of 73 children treated with RT for a primary brain tumor (not involving the hypothalamo-pituitary axis directly) and with a long follow-up (median 15 yr), 80% of the patients manifested GH deficiency; the median biological effective dose (BED) in the hypothalamo-pituitary area was higher in GH deficient children than in patients who did not develop any GH deficiency *(107)*.

In adults, a recent study *(108)* evaluating 31 long-term brain tumor survivors followed 1.5–11 yr after RT with a mean total dose of $62.3 \pm 2.8$ Gy compared with 31 age- and sex-matched controls, found hypothalamic hypothyroidism in 26% of patients, hypothalamic hypogonadism in 32% of patients, hyperprolactinemia in 29% of patients and panhypopituitarism in one patient. Low adrenal hormone levels were found in most patients, but without apparent clinical consequence. In the control group, only 6% had a baseline hormonal concentration outside the normal range. None of the controls had two or more hormonal abnormalities, while 42% of the patients had multiple deficits. Only 23% of patients had normal thyroid, gonadal, and adrenal baseline levels; this result is consistent with another earlier study by Taphoorn et al. reporting hypothalamic-pituitary dysfunction in 10 of 13 (77%) long-term survivors irradiated for supratentorial low-grade glioma *(109)*. Another study of patients treated for nasopharyngeal cancer found secondary hypothyroidism in 27% of cases (of hypothalamic origin in 19% and pituitary origin in 8%) *(110)*.

The neurological consequences of severe hypothyroidism are well-known, including encephalopathy, cerebellar ataxia, pseudo-myotonia, and sometimes peripheral neuropathy. Moderate hyperproteinorachia is also usual. All these abnormalities may be misleading if the correct diagnosis is not considered.

Secondary hypogonadism is an important concern especially in male patients, responsible for a decrease in libido and sometimes impotence, impacting negatively on quality of life. Hyperprolactinemia of hypothalamic origin is a notable concern in women who develop oligo-amenorrhea and galactorrhea *(111)*; in men, it may result in gynecomastia and a decrease in libido.

Follow-up consultations are a good place for a regular clinical endocrine evaluation; the precise biological follow-up scheme is debated and is adapted according to the emerging deficits, but long-term assessment should be the rule. The treatment of hormonal deficits lies in replacement therapy, and usually leads to an improvement in the patient's condition. Bromocriptine has been utilized with success in patients with symptomatic hyperprolactinemia *(111)*.

## SEQUELAE OF RADIOTHERAPY ON THE SPINAL CORD

Damage to the spinal cord can be the consequence of RT for spinal cord tumors, Hodgkin's disease, mediastinal or head and neck cancers. The early descriptions of the 1940s *(112)* were followed by numerous descriptions of postradiation myelopathy delineating the main clinical patterns, i.e., early-delayed myelopathy and several types of late-delayed complications including progressive myelopathy, lower motor neuron disorder, and spinal hemorrhage. There is no clear clinical or experimental evidence of acute spinal cord toxicity due to RT, and a sudden worsening during irradiation should lead to the search for intratumoral hemorrhage or tumor progression *(4)*.

**EARLY-DELAYED (TRANSIENT) RADIATION MYELOPATHY** The onset of this complication occurs from 6 wk to 6 mo after RT, and improvement follows in most cases within 2–9 mo *(113)*, though persistence of the symptoms for a longer time is possible in rare cases. It usually follows radiation of the cervical or thoracic spinal cord. After mantle RT for Hodgkin's disease, early-delayed myelopathy occurred in 15% of cases *(114)*. In another study, Fein et al. found a global incidence of 3.6% (40 cases out of a group of 1112 patients receiving 30 Gy or more). The incidence was 8% in the group of patients receiveing 50 Gy or more, 3% after doses of 45–49.9 Gy, 4% for patients between 40 and 44.9 Gy and 2% between 30 and 39.9 Gy. The risk was also increased with a fraction size over 2 Gy *(115)*.

The clinical pattern, first described in 1964 by Jones on 7 patients *(116)*, is generally limited to Lhermitte's sign, characterized by brief unpleasant sensations of numbness, tingling, and/or often electric-like feelings going down from the neck to the spine and to the extremities and triggered by the flexion of the neck. There is no known MRI change associated with this condition. This sign is nonspecific, and other causes should be considered in a patient with cancer *(117)*, including chemotherapy (cisplatin or docetaxel), spinal tumor, vitamin B12 deficiency, herpes zoster, or even multiple sclerosis (which may be aggravated by irradiation) *(118)*. The presumed pathophysiology of early-delayed myelopathy is a transient demyelination, probably secondary to a loss of oligodendroglial cells following RT *(119)*. There is no known specific treatment for this condition, and none is required, as recovery occurs in most cases. Early-delayed spinal cord disorder is not predictive of a possible evolution to the much more serious progressive myelopathy.

**LATE-DELAYED RADIATION-INDUCED SPINAL CORD DISORDERS** Spinal radionecrosis (Fig. 3) with features similar to its cerebral counterpart, progressive myelopathy, and spinal hemorrhage have been described.

**Progressive Myelopathy, or Delayed Radiation Myelopathy (DRM)** This complication occurs 6 mo to 10 yr after exposure to RT. Risk factors include older age, large radiation doses and fractions, previous irradiation (medical or incidental) especially in childhood, and large portals involving thoracic or lumbar spinal cord *(113)*. Chemotherapy may increase the risk of delayed radiation myelopathy *(120)*, but data are still unclear on this point.

The generally accepted tolerance for the spinal cord is 45 Gy in 22–25 daily fractions, with a risk <1% for a dose of 50 Gy increasing to 5% for a dose of 60 Gy delivered in 1.8–2 Gy fractions *(121)*.

Delayed radiation myelopathy may begin abruptly or more often in a progressive way; the patients complain of sensory and/or motor deficits leading to para- or tetraparesis. A typical initial clinical presentation is a Brown-Sequard's syndrome, consisting of a motor deficit associated with ipsilateral sensory loss affecting tactile, vibration, and proprioception on one side, and contralateral sensory loss affecting mainly temperature and pain sensory modalities. In some patients, a transverse myelopathy develops with bilateral leg weakness and sensory loss up to the irradiated region. Some patients also experience pain.

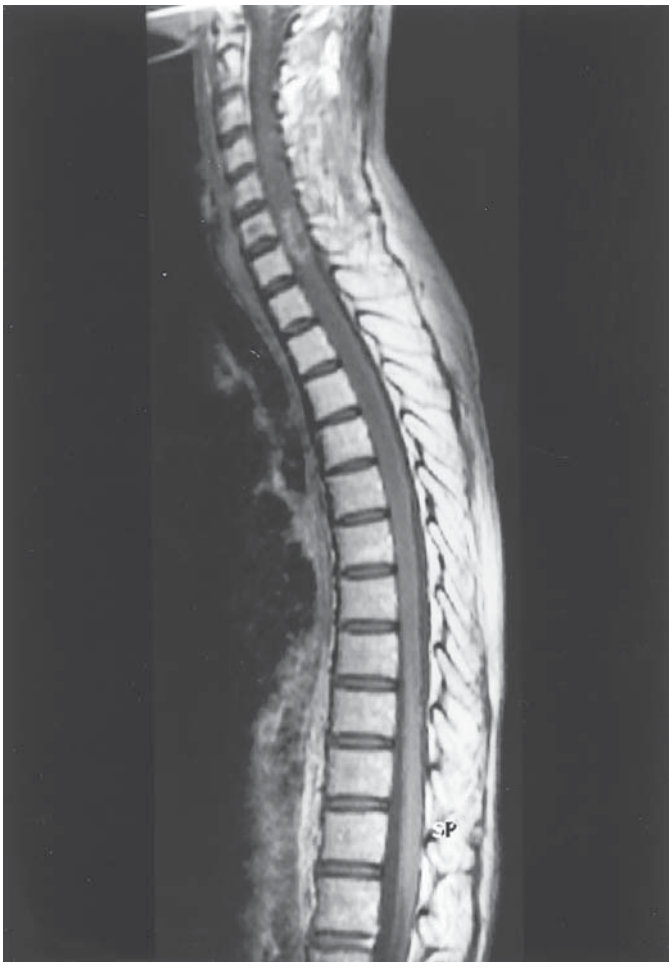

**Fig. 3.** Radionecrosis of the lower cervical spinal cord appearing as an MRI T1-weighted gadolinium enhancing lesion, occuring one year after irradiation for a cancer of the pharynx with cervical nodes in a 47-yr-old woman.

Bladder and bowel sphincter as well as diaphragmatic dysfunction (in upper cervical spinal cord lesions) are possible. The evolution of delayed radiation myelopathy varies; in some patients the symptoms stabilize, while in others they progress to a complete deficit.

The diagnosis of delayed radiation myelopathy implies, as was underlined as early as 1961 by Pallis et al. *(122)*, that the site of the main lesion is within the radiation-exposed area of the spinal cord and that all other potential causes of myelopathy have been carefully reviewed and eliminated.

Spinal cord MRI is helpful, though nonspecific. The initial description of Wang et al. on 10 patients *(123)* has been confirmed by several more recent studies *(124–127)*: the initial MRI can be normal if performed during the first weeks of the disease, but a slightly delayed examination usually reveals a swollen cord with T1-weighted hypointensity and T2-weighted hyperintensity. The lesions enhance in about 50% of cases after gadolinium injection *(128,129)*. In contrast, late examinations, performed years after the onset of the disease, may show spinal-cord atrophy without any signal abnormality; a case of cystic formation in late-delayed radiation myelopathy has also been reported *(130)*.

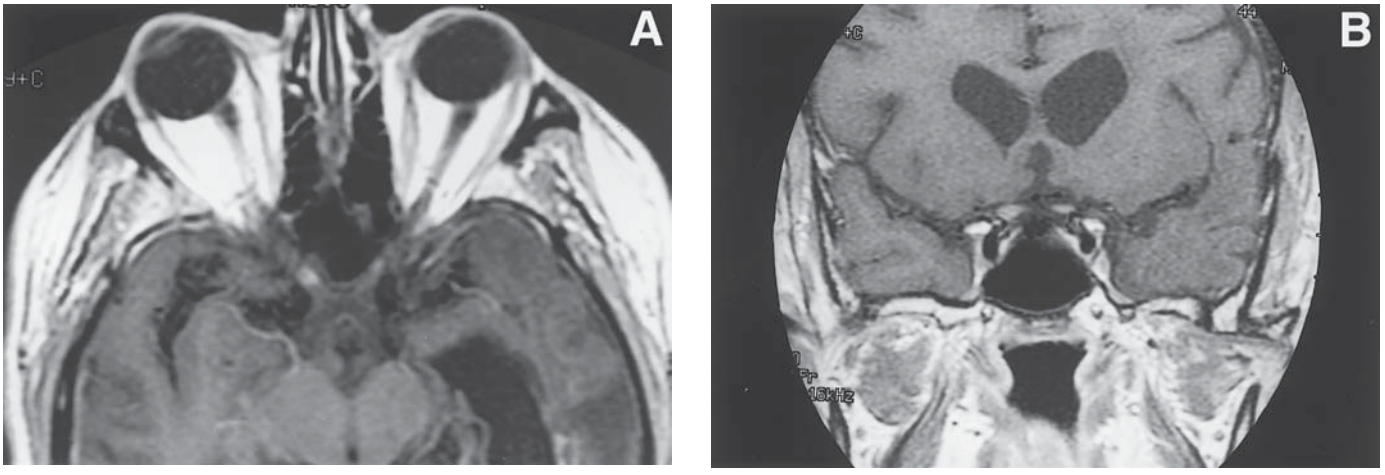


**Fig. 4.** MRI axial and coronal T1-weighted sequences showing enlargement and gadolinium enhancement of the prechiasmatic optic nerves after cranial RT in a 44-yr-old man. The patient became progressively blind, and the follow-up scan revealed chiasmatic atrophy 4 yr after RT.

Moderately elevated protein is the most common finding in the CSF but lacks any specificity. If performed, somatosensory evoked potentials show changes correlated to the extent of the lesions *(131)* whereas spinal conduction velocity is decreased *(132)*.

Demyelination, focal necrosis, and axonal loss are the principal lesions found in delayed radiation myelopathy in humans, associated with vascular abnormalities including telangiectasias, endothelial swelling with fibrin exudation, hyaline degeneration, thickening and fibrinoid necrosis of the vessel walls with perivascular fibrosis, and occasionally vasculitis *(113)*. As with cerebral radionecrosis, the pathophysiology remains unclear.

Steroids can improve some patients, probably because of their action on the inflammatory and edematous components of the disorder; however, patients often become steroid-dependent and only a few of them experience long-term improvement. There is no current proven long-term treatment for delayed radiation myelopathy. However, Angibaud et al. have reported the efficacy of hyperbaric oxygen in stabilizing or improving 6 out of 9 patients with DRM *(133)*, and Calabro et al. recently reported a similar case *(134)*. Anticoagulation has also been tried, with improvement in one patient with myelopathy treated for >3 mo with full anticoagulation *(34)* and stabilization in another treated with warfarin *(127)*.

**SPINAL HEMORRHAGE** This rare complication has only been described in a few cases, following spinal radiotherapy by 6–30 yr, and occurring within the radiation portal but outside the location of the primary tumor *(135)*; acute onset leg weakness and back pain rapidly lead to para- or tetraparesis. The diagnosis relies on MRI demonstration of hemorrhage. Spontaneous symptom resolution is possible, but new episodes may occur later. There is no proven effective treatment for this condition. Avoidance of aspirin or NSAIDs is prudent. Radiation-induced telangiectasias with secondary hemorrhage could explain this condition.

## CONSEQUENCES OF RADIOTHERAPY ON THE PERIPHERAL NERVOUS SYSTEM

Besides cranial nerve lesions, the main patterns of radiation-induced peripheral nervous system (PNS) toxicity include brachial and lumbosacral plexopathies.

**CRANIAL NERVE INJURY** Apart from acute reversible radiation toxicity, any of the cranial nerves can be involved in radiation-induced, late-delayed complications if the nerve is included in the radiation portal. These complications are rare, probably fewer than 1% of cases after conventional radiotherapy (60 Gy, 2 Gy per daily fraction), although higher when larger doses are administered in each fraction. The main complications are described below:

**Olfactory Nerves** During cranial radiation, patients can describe reversible sensations of smelling an odor *(136)*. This could be due to direct acute stimulation of the olfactory neurons. Anosmia has also been described in some patients *(137,138)*, often associated with taste disorders.

**Optic Nerves** Probably facilitated by pre-existing lesions (e.g., in diabetic patients), optic neuropathy may occur 6 mo to 14 yr after radiation therapy for a tumor of the orbital, pituitary, or suprasellar regions. In one study, the incidence of retrobulbar optic neuropathy was 3.8% after a conventional radiation scheme for head and neck cancer *(139)*. Optic neuropathy can also overshadow the prognosis of patients treated with high-energy electron-beam therapy for age-related macular degeneration in up to 19% of cases *(140)*. Proton beam irradiation, currently proposed in the treatment of several tumors including meningioma and choroidal melanoma, may also induce this complication *(141)*. The classical pattern consists of progressive or sometimes acute-onset visual loss, leading to monocular or binocular blindness with optic atrophy *(142)*. This disorder is painless. In case of anterior lesions, the ocular fundus usually shows papilledema and prepapillary and premacular hemorrhage, sometimes associated with radiation-induced retinal lesions. In contrast, fundoscopy may be normal if the lesions are posterior. In those cases, cerebral MRI can be useful, showing an enlargement of the optic nerve and chiasma, with T2-weighted hyperintensities and contrast enhancement (Fig. 4). The lesions are histologically characterized by demyelination, axonal loss, gliosis, and modifications of the vessel walls; endothelial cell loss has recently been stressed in this setting, with more significant abnormalities in patients treated with high-dose (55–70 Gy) compared with those treated with low-dose (10 Gy or less) radiation therapy *(143)*. These lesions are irreversible in many

patients. Steroids and anticoagulants have been advocated in chiasmatic lesions, but their efficacy is quite inconstant, while the use of hyperbaric oxygen in optic neuropathy remains controversial *(144,145)*. Optic nerve sheath fenestration has been attempted with some success in a few patients *(146)*.

**Ocular Motor Nerves** Rarely reported, their involvement may be associated with optic neuropathy. The most frequent of those palsies affect the abducens nerve (VI). Transient ocular motor palsies have been reported following radiation schemes focused on the pituitary tract, but permanent palsies have also been described after radiation therapy of nasopharyngeal carcinoma. Possible regression suggests that a demyelinating process could be involved, rather than progressive fibrosis *(4)*.

Neuromyotonia is a late-delayed complication following RT to the sella turcica or the cavernous sinus region by several years, and is characterized by spontaneous spasms of the eye muscles. These produce episodes of transitory painless diplopia, usually lasting a few seconds; these episodes can occur up to several times an hour *(147)*. This disorder can be improved using membrane stabilizers such as phenytoin or carbamazepine. Pathophysiology is not precisely known, but could be explained by radiation-induced hyperexcitability of the nerve fibers.

**Trigeminal Nerve** Involvement of the trigeminal nerve is quite rare. Neuromyotonia is exceptionally encountered; treatment with carbamazepine is effective in this condition *(148,149)*. After gamma knife radiosurgery for trigeminal neuralgia, the main reported complication to this day is mild facial numbness occuring in 2.7–14% of patients *(150,151)*. Trigeminal neuropathy can also result from radiosurgery for vestibular schwannoma.

**Facial Nerve** The different branches of the facial nerve are not equally affected by radiation. Taste dysfunction is usual and many patients complain of ageusia, a symptom that can be permanent in up to 50% of patients irradiated with 50–60 Gy for head and neck tumors *(152)*. However, taste disturbances are a common feature in cancer patients, and chemotherapy may play a part *(153)*.

Motor deficit is almost never the consequence of fractionated RT and should lead to looking for tumoral invasion *(4)*. In contrast, after radiosurgery for vestibular schwannoma, facial weakness has been reported in 17% *(154,155)* to 53% *(156)* of patients.

**Acoustic Nerve** Acute damage to the cochlea may be responsible for usually reversible complaints of high-frequency hearing loss and tinnitus. Otitis media can also be responsible for an early-delayed hearing loss. Following RT by a few weeks; this condition results from an obliteration of the eustachian tube by edema and mucosal vasodilatation. The diagnosis is often easy, as otoscopic examination reveals fluid behind the tympanic membrane. Usually spontaneously regressive, otitis media can require myringotomy in some cases for symptom alleviation. In most cases, relief can be obtained by prescribing nasal vasoconstriction agents. Late-delayed hearing loss could result from lesions to the organ of Corti with subsequent acoustic nerve atrophy; however, a recent report underlines the relative resistance of the organ of Corti to radiation *(157)*. The precise histological pattern of these disorders is not known; however, the labyrinth has been shown to be damaged in some previous studies *(158,159)*.

Hearing loss is possible after radiosurgery for vestibular schwannoma. In a recent report, 14% of patients with measurable hearing before treatment became deaf after radiosurgery, and 42% of patients had an elevation of their pure tone threshold of 20 dB or more. The risk factors for hearing loss in this study included neurofibromatosis type 2 (NF-2), history of prior surgical resection, and tumor size *(160)*. Several other studies showed varying complication rates *(161–164)*. However, the contribution of RT is not always easy to assess, as spontaneous growth of the tumor may also lead to deafness.

**Lower Cranial Nerves** These nerves (glossopharyngeal, vagus, spinal accessory, and hypoglossal nerves) can be damaged after head or neck radiation therapy with large doses. Complication occur earlier the larger the radiation dose and typically arise months to years after the treatment. The pathophysiology is likely radiation fibrosis. The hypoglossal nerve is the most commonly involved lower cranial nerve *(165)*; the patient may present with unilateral, often asymptomatic tongue paralysis *(166,167)*, or with bilateral and disabling paralysis. This complication may occur many years after RT *(168)*. Longstanding paralysis is responsible for tongue atrophy, with asymmetry that may be associated with fatty infiltration or edema-like changes on MRI *(169,170)*. Paralysis of the vagus nerve leads to unilateral paralysis of the vocal cord and of the palate, responsible for difficulties in swallowing *(171)*. Horner's syndrome may be associated with these disorders, resulting from injury to the sympathetic fibers *(4)*. Lesions of the spinal accessory nerve lead to shoulder drop easily diagnosed during the clinical examination. Patients may also present with multiple lower cranial nerve palsies *(172)*.

**BRACHIAL PLEXOPATHY** Brachial plexopathy results from RT to the supraclavicular, infraclavicular, or axillary regions, usually for lung or breast cancers and sometimes Hodgkin's disease. In most cases, the main problem is to differentiate this condition from neoplastic invasion of the plexus.

**Early-Delayed Brachial Plexopathy** This complication occurs a median of 4.5 mo after RT, with a range from 2–14 mo. Its incidence is about 1–2% after irradiation for breast cancer *(173,174)*. The clinical pattern includes paresthesia in the hand, and a distal motor deficit; amyotrophy and fasciculations may be present at later stages. Axillary pain is reported in about 60% of cases; always moderate, it may be spontaneous or occur when the patient moves. Although a progressive course towards paralysis of the brachial plexus is possible, a complete improvement is the rule, in most cases after 3–6 mo. Electrophysiological investigations show a decrease in nerve-conduction velocities. The pathophysiology of this condition is not fully understood; a direct radiation toxicity on the Schwann cells inducing demyelination has been invoked *(175)*.

**Late-Delayed Progressive Brachial Plexopathy** Delayed radiation-induced brachial plexopathy appears after a median time of 40 mo (up to 20 yr) *(176)*. Its incidence varies widely in the literature, with figures ranging from 14–73% *(177)*, the most important risk factors being total radiation dose (> 60 Gy) and fraction size (> 2 Gy). Overlap of radiation fields has also been incriminated as well as combined radio-chemotherapy.

For example, Olsen et al. found a definite or probable radiation plexopathy in 42% of patients treated with chemotherapy (cyclophosphamide, tamoxifen, or a combination of cyclophosphamide, methotrexate, and 5-fluorouracil) and RT vs 26% in patients treated with RT alone *(178)*.

The pathophysiology is unclear; the course of postradiation neuropathy could be biphasic: during the first phase, direct radiation damage to the nerves may cause electrophysiological and histochemical changes; later on, injury to the small vessels and fibrosis around the nerves may account for severe nerve injury *(179)*.

The disorder is usually progressive. Initial symptoms include distal paresthesias (typically, pins and needles or numbness of the thumb and first finger) and mild sensory deficit on clinical examination, often with no clear radicular topography. The other initial findings consist of some degree of amyotrophy and an early abolition of reflexes. Proximal weakness is found in about a quarter of cases *(180)*. Visible myokymia, when present, is quite suggestive of the diagnosis. The examination may also show local complications of radiotherapy, such as radiation dermatitis, painful induration of the axillary region, and/or lymphedema. During the later course of late-delayed plexopathy, a generally progressive motor deficit may be observed (in a few cases, an apoplectic onset has been reported, sometimes after a physical effort). Pain is quite uncommon at diagnosis and is usually a relatively minor feature. The severity of the condition is variable, from a simple discomfort to an almost complete paralysis of the limb.

The differential diagnosis must necessarily eliminate a neoplastic invasion of the brachial plexus. Some clinical signs may be important clues. In a large retrospective study on 100 cases of brachial plexus lesions, including 22 radiation plexopathies and 78 metastatic brachial plexopathies (34 in irradiated patients and 44 in nonirradiated patients), Kori et al. *(180)* found several factors as indicators of neoplastic invasion: 1) pain, especially when severe, is an important feature, present in 89% of irradiated patients with neoplastic infiltration of the plexus (vs 18% of patients with radiation plexopathy); 2) Horner's syndrome was present in 56% of patients with tumor infiltration (vs 14%). On the contrary, the following signs argue for a radiation-induced disorder: (1) dysesthesia, present in 55% of radiation plexopathies (vs 6% of plexopathies linked with tumor infiltration); (2) lymphedema, reported in 73% of cases (vs 15%). These results are consistent with those of other authors *(181)*.

The main aim of imaging is to differentiate between radiation plexopathy and neoplastic invasion. CT scan was the first noninvasive examination to be useful *(182,183)*; this imaging technique may show a distortion of the tissue planes and fat or may be normal. MRI is superior to CT scan in this indication *(184)*; furthermore, bone artifacts do not impair the interpretation of MRI, which also allows a study of the cervical spine in search for epidural or cervical-root secondary lesions. Radiation fibrosis is responsible for a thickening of the components of the brachial plexus, sometimes with contrast enhancement *(184)*. Tumor invasion is diagnosed when a mass lesion is visible along the roots of the branches of the brachial plexus. Nevertheless, a retrospective study at the Mayo Clinic of 71 patients with cancer and brachial plexopathy who had an MRI yielded a 21% (15 patients) discordance rate between imaging and eventual diagnosis *(181)*. A recent study of 50 breast cancer patients *(185)* using an association of body-coil and surface-coil techniques suggests a major role for MRI to assess neoplastic recurrence; this technique allowed a correct diagnosis of tumor recurrence in 26 of 27 patients, directly related to brachial plexus in 17 of them, and associated to cervical-spine degenerative lesions in 7 cases. Exclusion of a malignant disease was accurate in 20 of 21 cases. These results corresponded to a sensitivity of the MR criteria for tumor detection of 96% and a specificity of 95%, with similar positive and negative predictive values. Positron emission tomography using 18-fluoro-2-deoxyglucose ($^{18}$FDG-PET) may also be helpful to differentiate tumor infiltration from radiation-induced plexopathy *(186)*.

Motor conduction velocities are usually normal or slightly decreased in radiation plexopathies. Sensory conduction velocities are rarely altered. The F waves can be absent or delayed. Electromyography is always abnormal, with fasciculations, fibrillation, and slow denervation potentials *(187)*. The most important finding in favor of radiation-induced plexopathy is the presence of myokymic discharge, present in about two-thirds of patients; this feature is quite rare (< 5%) in patients with an infiltrating tumor. Myokymic discharges are often located on the area of the abductor pollicis brevis and pronator quadratus muscles *(188)*.

Sometimes, noninvasive investigations are inconclusive, and a biopsy may be indicated. In radiation plexopathy this reveals fibrosis and the absence of tumor infiltration.

The treatment of pain is often challenging, and includes analgesic drugs, tricyclic antidepressants, and/or anticonvulsivants. Steroids can also be helpful. Techniques such as transdermal electrical nerve stimulation and dorsal column roots stimulation have also been proposed. Neurolysis with or without omentoplasty has been performed in radiation-induced brachial plexopathy, but the benefit of this approach is questionable. Prudent physiotherapy is indicated *(189)*.

**Ischemic Late-Delayed Brachial Plexopathy** Sudden late-delayed plexopathy has exceptionally been reported following an occlusion of the subclavian artery *(190)*.

**LUMBOSACRAL PLEXOPATHY** This complication of irradiation for pelvic or lower abdominal cancer (uterus, ovary, testis, rectum, or lymphoma) is far less common than brachial plexopathy. Schiodt et al. reported 5 cases out of 99 patients (5%) treated for testicular cancer *(191)*; in this study, the most severely impaired patients had received doses of 54.5 Gy or more over 6 wk with 5 fractions/wk, but lower doses (40–45 Gy) can also be harmful.

**Early-Delayed Lumbosacral Plexopathy** As with brachial plexopathies, an early-delayed, generally transient lumbosacral plexopathy is possible. It usually begins a few months (median 4 mo) after RT, with a typical pattern of distal bilateral paresthesias of the lower limbs. Clinical examination is normal in most cases, and improvement follows within 3–6 mo.

**Late-Delayed Lumbosacral Plexopathy** This disorder shares similar features with brachial plexopathy but is much less frequently reported. The onset follows initial RT by 1–30 yr (median 5 yr). The clinical pattern is characterized by a

progressive, usually asymmetric and bilateral, motor deficit of the lower limbs associated with less marked sensory deficits. As in brachial plexopathy, pain is generally mild or absent. The course of the disease leads to a slow worsening of the motor deficit. The patient may stabilize after several months or years *(192)*.

On electromyography (EMG), motor nerve conduction velocities are normal or moderately decreased in the leg. The saphenous nerve sensory potential is absent or has a decreased amplitude in about 50% of cases. Detection shows myokymias in the proximal muscles in 60% of cases. Fibrillation potentials in the paravertebral muscles are found in 50% of patients *(187)*. Histology, when performed, may show fibrosis tightly hugging the plexus, and in some cases the cauda equina as well.

Treatment of pain is identical to that of brachial plexopathy. Two patients treated with anticoagulation remained stable with an improvement of pain *(34)*.

**LOWER MOTOR NEURON SYNDROME** A lower motor neuron syndrome can be a consequence of pelvic irradiation for testicular tumors, lumbosacral RT, or craniospinal RT for medulloblastoma, and begins 3 mo to 25 yr after RT. Maier et al. *(193)* reported 15 cases of this syndrome out of 343 patients who had undergone a lumboaortic irradiation scheme. About 30 cases have been reported since that period with various radiation schemes.

The patient presents with a progressive proximal and distal, often bilateral and more or less symmetrical weakness of the inferior limbs; muscle atrophy and fasciculations may be associated with this deficit. Flaccid motor deficit and areflexia are confirmed by clinical examination, but no sensory loss appears during the early stages. The course is quite variable: a patient reported by Posner et al. *(4)* could still walk 12 yr after abdominal RT. Sensory deficit may appear after several years, as well as sphincter disturbance characterized by lack of bladder sensation and incontinence *(194)*.

MRI may be normal, but contrast enhancement of the roots of the cauda equina has been described *(194)*. The CSF is usually acellular, frequently showing high protein levels. On electromyography, different stages of denervation are identified while sural sensory nerve action potentials are usually preserved.

It is unclear whether the lesions localize to the anterior horn cells of the spinal cord or the proximal part of the nerve roots. Some reports advocate an anterior horn cell disorder, as no sensory signs were reported and electrophysiological data were compatible with pure motor neuron syndrome *(195)*. However, the few available neuropathological data support radicular lesions affecting the nerve roots of the cauda equina *(195)*. In a study of 6 patients treated with RT (mean dose 45 Gy) for testicular cancer and including neuropathological examination of one case, Bowen et al. *(194)* found strong arguments favoring radiculopathy, including (1) the presence of late-delayed sensory and sphincter disturbances, appearing 4–8 yr after the motor symptoms; (2) MRI abnormalities showing contrast enhancement of the lumbosacral roots of the cauda equina in 2 out of 3 patients; (3) no lesion in the cord at necropsy but thickening of the roots of the cauda equina with focal areas of hemorrhagic discoloration, fibrosis and axonal loss; the roots included abnormal dilated vessels with thickened and hyalinized walls. There is no recognized treatment of this condition.

**RADIATION-INDUCED PERIPHERAL NERVE TUMORS** Fewer than 35 cases of radiation-induced nerve sheath tumors have been reported *(196)*. Patients with neurofibromatosis type 1 (NF-1) have an increased risk of developing this complication. In a retrospective study on radiation-induced peripheral nerve-sheath tumors, 3 patients out of 9 (33%) had familial and/or clinical signs of NF-1 *(197)*; in this series, the latency between RT and the onset of the secondary tumor ranged from 4–41 yr. Pain followed by the development of a sensorimotor deficit typifies the clinical presentation. The differential diagnosis of a local recurrence of the primary tumor generally requires biopsy. The treatment of these nerve-sheath tumors relies principally on aggressive surgery with tumor-free margins; amputation of a limb, when performed, does not significantly change overall survival *(198)*. Neither chemotherapy nor radiotherapy have yet shown any clear benefit in terms of survival in those tumors *(199)*.

## CONCLUSION

RT remains one of the most efficient treatments of cancer and will probably become, through the development of new irradiation techniques, a standard option for treating some nonmalignant diseases. Familiarity with its potential risks is thus essential in order to prevent complications when possible as well as to be able to inform the patients of their possible onset. As progress has been made in understanding the pathophysiology of radiation-induced injury and in determining "safe" doses, many complications have become rarer than a few years ago.

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# 15 Cancer and Cancer Treatment-Related Neuromuscular Disease

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## GENERAL CONSIDERATIONS

Peripheral neuropathies distort the normal motor, sensory, and autonomic functions. Among the numerous causes are inherited disorders, entrapments, infections, toxins, nutritional deficiency states, and inflammatory, demyelinating, or ischemic conditions. Polyneuropathy is often a complication of systemic disease, such as diabetes, connective tissue disorders, or uremia. Neuropathy may also be a direct or remote effect of malignant disease. Compression by tumor or direct infiltration of nerve by malignant cells can cause radiculopathy, plexopathy, or mononeuropathy. Nonmetastatic or paraneoplastic neuropathy, a remote effect of cancer, occurs in 1% of all patients with malignancy. In addition, neuropathy may be a side effect of a therapeutic drug. In this review, we are concerned with neuromuscular conditions associated with malignant diseases or those caused by cancer treatment.

### DIAGNOSING AND MONITORING PERIPHERAL NEUROPATHY

**The Neurological Examination** The "gold standard" for the diagnosis of clinical neuropathies is the neurological examination and a detailed history regarding symptoms of peripheral nerve injury: numbness or tingling (paresthesias), usually in glove-stocking distribution, as well as cramps and weakness. Pain may be spontaneous or elicited by light touch over the affected area ("hyperpathia"). The neurological examination emphasizes the cranial nerves, motor testing, sensory testing, reflexes, gait, and ability to perform activities of daily living. Sensory examination should include vibration and position senses (mediated by large myelinated fibers), as well as temperature and pin perception (carried by small unmyelinated fibers). Signs of neuropathy include loss of tendon reflexes, distal sensory loss, muscle wasting and weakness, cramps, or fasciculations (muscle twitches seen under the skin). Autonomic involvement may manifest as pupillary abnormalities, orthostatic hypotension, anhydrosis, and impotence or sphincter symptoms.

**EMG and NCS** Electromyography (EMG) and nerve conduction studies (NCS) are essential in evaluating possible neuropathy. For EMG, a needle electrode is placed in the muscle to detect the electrical activity. Based on the type and amount of spontaneous activity and the recorded motor units during muscle activation, it is possible to distinguish neurogenic from myopathic disorders, different types of myopathy, and neuromuscular transmission disorders such as myasthenia gravis or Lambert-Eaton syndrome. Conduction studies are performed on both motor and sensory nerves by applying an electrical stimulus over a nerve and recording the electrical response from the innervated muscle (for motor nerves) or from a more proximal portion of the nerve (for sensory nerves) to determine the conduction velocity. Low amplitude of evoked responses with normal velocity is observed in neuropathies that affect the axon (axonal neuropathies), while slow velocity is more characteristic of demyelinating neuropathy.

**The Use of Quantitative Sensory Testing** Quantitative sensory testing (QST) is another way to evaluate peripheral neuropathy. QST refers to the use of precisely measured and repeatable sensory stimuli to determine the absolute threshold of sensation to various sensory modalities including pain, temperature, and vibration. The data can be used to follow patients in clinical trials. This technique can evaluate small-caliber fibers and also evaluate paresthesias or hyperalgesia *(1)*. However, there is no agreement about the criteria for normal responses, test procedures, or stimuli *(2)*. A consensus report issued by the Peripheral Neuropathy Association gave specific recommendations on the probes needed to asses pressure, pain, temperature, and on the specific algorithms of testing. QST may be overly sensitive, showing subclinical neuropathy in

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**Table 1**
**Solid Tumor-Associated Neuropathies**

| | *Syndrome* | *Onset/course* |
|---|---|---|
| A. Compressive or infiltrative nerve lesions | a. Cranial neuropathy | Subacute/progressive |
| | b. Radiculopathy | " " |
| | c. Plexopathy | " " |
| | d. Peripheral neuropathy | " " |
| B. Paraneoplastic neuropathies | a. Sensory neuropathy (may be associated with ecephalomyelitis) | Subacute/progressive or stable |
| | b. Sensorimotor neuropathy | Acute<br>Subacute<br>Relapsing-remitting |
| | c. Autonomic neuropathy | Subacute/progressive |

25% of diabetic patients with normal nerve conduction studies *(3)*. Thus, its use has generated debate *(4)*.

The role of QST in cancer patients is not defined. In cancer patients Lipton found abnormal vibration thresholds in 31% and abnormal temperature thresholds in 43% *(5)*. In paclitaxel-induced peripheral neuropathy, QST was excellent in quantifying the neuropathy but was less sensitive than clinical examination *(6,7)*. Similarly, Hilkens and colleagues found that the threshold for perception of vibration was not reliable in monitoring patients with docetaxel-related neuropathy *(8)*.

**Ancillary Tests** Other tests, ranging from nerve biopsy to special serologic studies, are occasionally useful. When a nerve biopsy is required, the sural nerve is commonly chosen because it is accessible and the resulting loss of sensation is limited, but it is a purely sensory nerve. Nerve biopsy may be used in a cancer patient if there is no clear explanation for a neuropathy, or if an immunological disorder is possible. Nerve biopsy may show vasculitis, infiltration by malignancy, or amyloidosis *(9)*. Immunohistochemical studies may show deposition of an autoantibody or complement. Tests of cardiovascular function may help to identify an autonomic neuropathy. Antibodies described in the common paraneoplastic syndromes may also be found in some patients with neuropathy and cancer. Western blots or enzyme-linked immunosorbent assay (ELISA) may detect monoclonal or polyclonal antibodies (MAbs/PAbs) in serum or cerebrospinal fluid (CSF).

**PATHOGENESIS** There are four main mechanisms of peripheral neuropathy: (1) Neuronal degeneration (neuronopathy): nerve cell bodies are the primary site of pathology; (2) Wallerian degeneration: degeneration of distal axons and their myelin sheaths follows nerve damage; (3) Axonal degeneration (axonopathy): this is the most common pathological reaction of peripheral nerve, with distal axonal breakdown usually due to a systemic metabolic disorder or toxins. The process may extend to the myelin sheath of affected axons, starts distally, and usually progresses back to the nerve cell body, a "dying-back neuropathy." This type of neuropathy is manifested clinically as a symmetrical, distal loss of sensory and motor functions beginning in the legs *(4)*. Segmental demyelination: degeneration of peripheral nerve myelin is seen with relative sparing of axons, a pattern that occurs in immune-mediated demyelinating neuropathy.

## SOLID TUMOR-ASSOCIATED NEUROPATHIES (TABLE 1)

### COMPRESSIVE OR INFILTRATIVE NERVE LESIONS

**Cranial Nerves** Cranial nerves may be involved by nasopharyngeal *(10)*, prostate, or lung carcinoma *(11)*. The 6th, 5th, and 3rd nerves are most commonly affected. Nasopharyngeal carcinoma can involve the trigeminal nerve as discussed in Chapter 30. "Mental neuropathy" or the "numb chin" syndrome is an ominous sign of malignant disease. A metastasis to the mental foramen of the mandible compresses the inferior alveolar branches of the mandibular division of the trigeminal nerve. The most common tumors are breast, thyroid, renal, lung, prostate, or melanoma *(12)*. Mandibular metastasis may or may not be accompanied by pain. Bone scans may show increased uptake at the jaw. The numb chin syndrome may also result from carcinomatous meningitis.

**Nerve Roots** Nerve roots may be affected in meningeal infiltration from various cancers *(13)*. Radicular pain and sensory loss, lower motor neuron weakness, and areflexia may then be associated with clinical signs of meningeal irritation. CSF shows pleocytosis with high protein content and often, but not always, low sugar. The false negative cytology rate in pathologically documented leptomeningeal carcinomatosis may be as high as 55% *(13)*, making extensive sampling and sometimes repeated spinal taps imperative to establish a diagnosis *(13)*. Suspected diagnosis of neoplastic radiculopathy may be confirmed by a gadolinium-enhanced MRI of the spine *(14)*.

**Plexopathy** Neoplasms are responsible for 1.4–14.5% of all brachial plexopathies *(15)*, most often caused by carcinoma of lung or breast *(16)*, and less often sarcoma. Pain is the most frequent symptom at onset, affecting over 80% of the patients, located in the shoulder, and radiating down the medial side of the arm. The distribution of the pain depends on the site of plexus involvement. Involvement of the lateral axillary nodes usually results in a lower brachial plexus syndrome, in which the sensorimotor abnormalities have a C7–T1 root distribution. Lymphedema is rare. A Horner syndrome may result from paravertebral infiltration of the sympathetic trunk and is present in 50% of cases of metastatic plexopathy. It is an ominous sign because it suggests paraspinal and epidural extension of the tumor. The Pancoast syndrome is a characteristic result of tumor

infiltration of the brachial plexus, arising from either primary or metastatic tumors that involve the lung apex *(17)*. Pain is the first symptom in up to 95% of patients, often described as an aching at the elbow. On examination, there is usually involvement of the lower brachial plexus, with hand atrophy, sensory loss, and weakness.

The etiology of neoplastic lumbosacral plexopathy differs, unsurprisingly, from brachial plexopathies. Over two-thirds of the cases arise from direct extension from an intra-abdominal tumor, such as colorectal carcinoma or cervical cancer *(18)*. Persistent unilateral pain in the pelvic or sacral area may be the first symptom. The clinical picture may resemble that of lumbar-disc prolapse or meralgia paresthetica. Onset of pain is followed weeks or months later by paresthesias and weakness in a pattern that involves more than one nerve root. Some patients have a palpable rectal or pelvic mass. Fifty percent show lower plexus involvement (L4–S1); 33% have upper plexus lesions, and in a few the entire plexus is affected. Pelvic CT shows the abnormality in 78–96% of patients *(19)*.

Electrodiagnostic studies of patients with tumor-related plexopathy usually reveal fibrillation potentials and sharp waves in the distribution of the plexus injury. The cervical paraspinal muscles are normal, excluding involvement of the spinal roots. CT or MR scan may be particularly helpful, identifying bony erosion, soft tissue masses, and paravertebral or epidural extension of the tumor. Radiation injury to the brachial plexus should be included in the differential diagnosis of tumor-related brachial plexopathy. A full description of radiation fibrosis is detailed under Treatment-Related Neuropathies (*see* later in the chapter).

**Metastatic Infiltration** Metastatic infiltration of peripheral nerves is a rare complication of a carcinoma *(20)*. Primary or secondary tumors may also invade peripheral nerves. Direct invasion by malignant cells causes axonal degeneration and has been reported in breast and pelvic cancer as well as leukemia *(21)*.

## PARANEOPLASTIC NEUROPATHIES

**General Features of Paraneoplastic Neurologic Syndromes** That peripheral neuropathy may be paraneoplastic was recognized as far back as 1948, when Denny-Brown *(22)* and Wyburn-Mason *(23)* described a sensory neuropathy with degeneration of the dorsal root ganglia in patients with occult malignancy. This neuropathy is recognized as one component of a more widespread syndrome, as described by Henson et al. *(24)*, in patients with cancer and multisystem neurological disorders. Pathologically there are nonmalignant infiltrates and neuronal degeneration of the dorsal root ganglia, spinal cord, nerve roots, cerebrum, and brainstem. Dalmau and colleagues fully described the disorder, now termed "paraneoplastic encephalomyelitis/sensory neuronopathy" *(25)*. Clinically, most (up to 73%) of the patients develop signs and symptoms of multifocal involvement. Limbic encephalitis manifests as confusion, depression, agitation, anxiety, memory disturbance, dementia, or seizures and is the second most common presentation after neuropathy. It can be the predominant symptom in 20% of patients. Motor neuron dysfunction can cause limb weakness, fasciculations, and muscle atrophy, and is the predominant symptom in 20% of patients. Cerebellar dysfunction usually causes gait ataxia, but a pancerebellar syndrome, with dysarthria, incoordination, action tremor, and pendular reflexes, ultimately develops. Brainstem encephalitis is recognized by nystagmus, dysphagia, dysarthria, gaze abnormalities, hearing loss, and facial numbness. It may develop in 32% of patients, but it is a predominant finding in fewer than 14%. Myelitis causes weakness, wasting, fasciculation, loss of tendon jerks, and the Babinski sign. Autonomic dysfunction may be seen in up to 28% of patients, but it is not usually a predominant symptom. The specific autonomic manifestations reported in the literature are described below. Sensory neuropathy is present in about 74% of the patients and can be a predominant symptom in about 62%. The clinical characteristics are also described below.

The most commonly associated tumor is small cell lung cancer (SCLC) *(25,26)*. Some of these patients have an antibody, named anti-Hu *(27)*, in serum or CSF. This IgG antibody, also termed "anti-neuronal nuclear antibody" (ANNA-type 1), and reacts against a 35–40 kD protein in the nuclei of neurons, including the dorsal root ganglia cells, as well as SCLC cells *(28,29)*. Immunohistochemical techniques can detect anti-neuronal antibodies in paraneoplastic syndromes, Sjögren's syndrome, or idiopathic sensory neuropathy; it is therefore necessary to determine the specificity of the neuronal antigen by Western blot analysis of cortical or cerebellar neurons or Hu recombinant proteins. Autopsy studies of patients with paraneoplastic sensory neuropathy or encephalomyelitis show binding of the antibody to areas of the nervous system that correlate with the neurological symptoms, implying a pathogenic relationship *(30)*. Other immunohistochemical studies suggest that both humoral and cell-mediated damage to neurons are pathogenic *(31)*. Patients with paraneoplastic sensory neuropathy or encephalomyelitis may have autoantibodies with patterns of immunoreactivity other than anti-Hu; the antibodies may react with a synaptic vesicle-associated protein, amphiphysin *(32)*, or a 66 kD oligodendroglial protein *(33)*.

Anti-Hu sensory neuropathy can be the first manifestation of a cancer confined to the chest *(34)*. In paraneoplastic sensory neuropathy/encephalomyelitis syndrome, most patients with anti-Hu antibodies have a SCLC, but the tumor may be a carcinoma of some other organ (breast, ovary, uterus, stomach, testis), especially if no anti-Hu antibodies are detected. As the tumor may be undetectable, other causes of sensory neuropathy must be considered *(35)*. The largest series of patients with anti-Hu paraneoplastic sensory neuropathy and encephalomyelitis was that of Dalmau et al. *(25)*. The 71 patients described had anti-Hu antibody in serum and a sensory neuropathy/encephalomyelitis syndrome; in about 78% of patients the tumor was SCLC. CSF had anti-Hu antibodies in all cases, and the protein content was often elevated. Oligoclonal bands were detected in some. Rarely, the typical paraneoplastic syndrome is seen in a patient with SCLC and no anti-Hu antibodies. Absence of the antibody in a patient with sensory neuropathy/encephalomyelitis should lead to a more widespread search for malignancy, not limited to lung carcinoma.

The following are the three most common peripheral nervous system (PNS) manifestations of paraneoplastic syndromes. It must be remembered that these neuropathies rarely

occur in isolation, but rather as part of a more widespread neurological dysfunction.

1. *Sensory neuropathy*. The clinical picture includes numbness and paresthesias in the hands and feet. The neuropathy may be painful, disabling, and asymmetric. All sensory modalities may be affected; perception of position and vibration is severely impaired, giving rise to sensory ataxia and unsteady gait. Areflexia is global. Weakness and muscle wasting are not seen until late. Cranial nerve abnormalities have been described *(36)*. In most patients the symptoms of neuropathy precede discovery of the cancer by 6–15 mo *(37)*, rarely up to 7 yr *(38)*. The neuropathy develops over weeks or months and may be slowly progressive or stable *(34,39)*. Rarely, the onset is acute *(24)*. The CSF may or may not be abnormal. The protein content is frequently elevated and there may be a lymphocytic pleocytosis. Nerve conduction studies were abnormal in 20 of 23 patients, with the most common findings absent sensory potentials *(25)*. EMG signs of denervation were detected in six patients. In three patients nerve biopsies showed loss of myelinated fibers and, in one case, perivascular infiltrates.
2. *Paraneoplastic sensorimotor neuropathy*. Paraneoplastic sensorimotor neuropathy occurs more frequently than purely sensory neuropathy *(40)*. Carcinoma of the lung is most common, but the tumor may be found in stomach, breast, colon, rectum, pancreas, uterus, cervix, thyroid, kidney, prostate, or testis *(41)*. The course may be acute, subacute, chronic remitting, or relapsing. Paraneoplastic acute peripheral neuropathy resembles Guillain-Barré syndrome with an acute onset of respiratory or bulbar symptoms *(42)*. The neuropathy may be demyelinating, but axonal features are more frequent. Graus et al. *(43)* described a paraneoplastic encephalomyelitis affecting dorsal root ganglia and motor neurons, simulating acute polyneuritis. Anti-Hu antibodies may suggest the diagnosis. Subacute neuropathy is predominantly distal and may precede or follow recognition of carcinoma. A mild axonal form may occur in late stages of cancer and associated with severe weight loss *(44)*. Cachexia may be partly responsible for the neuropathy. One patient with subacute sensorimotor neuropathy also had a multiple cranial neuropathy as well as altered consciousness, seizures, and IgG anti-Hu antibodies *(45)*. Autopsy revealed SCLC with encephalo-myelo-ganglionitis.

   *Chronic relapsing and remitting sensorimotor neuropathy*, unlike other forms of paraneoplastic neuropathy, is seen less frequently with lung cancer *(46)*. CSF protein content is often increased and, if demyelinating features are present, the neuropathy may fulfill the criteria of chronic inflammatory demyelinating polyneuropathy (CIDP). In some patients steroid therapy induces remissions, and improvement may follow removal of the tumor *(46)*. Rarely, sensorimotor neuropathy is caused by vasculitis in patients with cancer of kidney, prostate, lung, stomach, or common bile duct *(47–49)*. The progressive, initially asymmetric, painful neuropathy may precede (up to 29 mo) or follow the discovery of malignancy. Proximal limb weakness may be due to a concomitant vasculitic myopathy *(47)*. Electrophysiologic studies show evidence of axonal damage. Diagnosis is made by finding vasculitis in the nerve biopsy; muscle biopsy may also disclose an underlying vasculitic process. Immunohistochemistry shows a predominance of CD8-positive T lymphocytes, suggesting T cell-mediated cytotoxicity as the primary mechanism of vessel injury *(49)*. Steroid or immunosuppressive therapy with cyclophosphamide may be beneficial *(49)*.
3. *Autonomic neuropathy*. In 1975 Ahmed and Carpenter *(50)* described a patient with autonomic instability and SCLC that had infiltrated the myenteric plexus. Later Lhermitte *(51)* suggested that myenteric plexopathy with SCLC could be paraneoplastic. Autonomic tests may implicate both the sympathetic and parasympathetic nervous systems. Anti-Hu antibodies are commonly associated with autonomic neuropathy; 28% of patients with paraneoplastic encephalomyelitis also show symptoms of autonomic dysfunction *(31)*. Lennon et al. *(52)* identified patients with myenteric plexopathy, autonomic neuropathy, and antibodies against the nuclei of neurons as well as antigens in the dorsal-root ganglia, cerebellum, and brainstem. These antibodies reacted with antigens found in SCLC and were similar to the anti-Hu antibody.

   Intestinal pseudo-obstruction can be seen as a dysautonomic neuropathy, with orthostatic hypotension, pupillary abnormalities, and impotence, sometimes with other neurologic paraneoplastic syndromes (53). Paraneoplastic pseudo-obstruction is usually of subacute onset with early satiety, anorexia, vomiting, constipation, and gastrointestinal discomfort. In the differential diagnosis is a "true" mechanical obstruction, pseudo-obstruction from connective tissue diseases (lupus, scleroderma, amyloidosis), endocrine disorders (hypoparathyroidism, hypoparathyroidism, diabetes), or other neurologic diseases that affect the autonomic nervous system (Shy-Drager syndrome). Identifying the malignancy may direct early appropriate treatment to both the paraneoplastic syndrome and the neoplasm. Treatment of the malignancy may arrest progression of the dysautonomia *(54)*, but most patients do not regain normal neurological function *(55)*.

## LYMPHOPROLIFERATIVE DISEASE-ASSOCIATED NEUROPATHIES (TABLE 2)

**LYMPHOMAS** Lymphoma may cause brachial plexopathy *(56)* or neuropathy *(57)*. Peripheral neuropathy occurs in 0.1–2.0% of patients with malignant lymphoma *(58)*; 35% show abnormal nerve conductions *(59)*.

**Sensory Neuropathy** Sensory neuropathy occurs less frequently in lymphoma than in lung carcinoma. A subacute predominantly sensory neuropathy may be associated with Hodgkin's disease *(60)*. Plante-Bordeneuve et al. *(61)* described two patients with Hodgkin's disease and a subacute, predominantly sensory neuropathy with areflexia, which improved after tumor removal. The disorder is attributed to an inflammatory demyelinating polyneuropathy rather than paraneoplastic sensory ganglionitis. Sensory neuropathy complicating non-Hodgkin's lymphoma has also been reported *(62)*.

**Sensorimotor Neuropathy** The sensorimotor neuropathy may be acute or subacute (over 4–8 wk) in onset, chronic progressive or, less often, remitting and relapsing. The clinical

**Table 2**
**Lymphoproliferative Disease-Associated Neuropathies**

| | *Syndrome* | *Onset/course* |
|---|---|---|
| A. Lymphomas | a. Sensory neuropathy | Subacacute |
| | b. Sensorimotor neuropathy | Acute |
| | | Subacacute |
| | | Relapsing/remitting |
| | | Chronic progressive |
| | c. Motor neuronopathy | Subacute/progressive acute |
| | d. Autonomic neuropathy | |
| B. Leukemias | Sensorimotor polyneuropathy | Acute/subacute-chronic |

picture of the acute polyneuritis complicating lymphoma resembles that of the Guillain-Barré syndrome *(63)*. High CSF protein content and slow nerve-conduction velocities may be features. It is not clear whether the association of lymphoma and acute inflammatory polyneuropathy is paraneoplastic or fortuitous. However, this neuropathy is more frequent in patients with Hodgkin's disease than with any other tumor, and, according to Lisak *(63)*, immunosuppression may predispose to development of the acute polyneuritis. Pathological studies have shown lymphocytic infiltration of peripheral nerves and roots with segmental demyelination, suggesting a primary demyelinating process *(63)*. Acute sensorimotor neuropathy may also be caused by direct infiltration of the nerve by lymphomatous cells as demonstrated in a nerve biopsy *(64)*. Lymphomatous infiltration of the roots and peripheral nerve may cause a peripheral neuropathy of subacute onset *(65)* or relapsing-remitting course *(66)*. Relapsing and remitting sensorimotor neuropathy is rarely associated with lymphoma, mostly non-Hodgkin's *(44)*. Pathological evidence of demyelination has been found *(67)*, and partial remissions have been observed with steroid treatment *(67)*. Chronic progressive sensorimotor neuropathy, either axonal or demyelinating, may be associated with either Hodgkin's or non-Hodgkin's lymphoma *(68,69)*. The neuropathy may precede or follow the diagnosis of lymphoma. Infiltrating malignant cells have been found in the peripheral nerves *(69)*. Sensorimotor neuropathy is rarely due to nerve vasculitis *(48)*.

**Subacute Motor Neuronopathy** Subacute motor neuronopathy or motor neuron disease may be a remote effect of Hodgkin's disease and lymphoma *(70,71)*. Patients develop a progressive painless weakness without bulbar involvement, with or without upper motor neuron signs *(72)*. The legs are usually affected more than arms. Neurophysiological studies are consistent with anterior horn cell disease. The cause of this syndrome is unknown, though viruses have been considered *(73)*.

**Acute Autonomic Neuropathy** Acute autonomic neuropathy characterized by orthostatic hypotension, urinary retention, constipation, and pupillary abnormalities have been described in Hodgkin's disease *(74)*. Subclinical autonomic dysfunction may be detected with Hodgkin's or non-Hodgkin's lymphomas *(75)*.

**LEUKEMIAS** Peripheral neuropathy is less common than cerebral and meningeal pathology in acute leukemia. Either cranial or peripheral nerves may be affected by hemorrhage or leukemic infiltration of nerves *(76)*. A peripheral polyneuropathy with acute onset and rapid progression may be seen. CSF protein content may be elevated with normal cell count. At autopsy, leukemic infiltrates have been found in the nerves *(77)*. Peripheral and autonomic nerve leukemic infiltration was seen in a patient with acute monoblastic leukemia and hematologic remission *(78)*. In chronic lymphocytic leukemia (CLL) neuropathy may be acute *(79)* or subacute and chronic *(58,67)*. CSF pleocytosis may be found. Cellular infiltration of perineurium and endoneurium has been described *(80)*. Peripheral neuropathy may occur as late complication of chronic myeloid leukemia (CML) *(58)* or other forms of leukemia *(81)*.

**OTHER LYMPHOPROLIFERATIVE DISORDERS WITH MONOCLONAL GAMMOPATHY** The lymphoproliferative B-cell disorders associated with peripheral neuropathy include the "monoclonal gammopathies of unknown significance" (MGUS) and the malignant gammopathies related to multiple myeloma, Waldenstrom macroglobulinemia, B-cell lymphoma, or CLL. Although MGUS sometimes progresses to malignancy, the term "nonmalignant monoclonal gammopathies" is still preferred. Most neuropathies arise in the setting of nonmalignant gammopathy. Approximately 50% of patients with neuropathy and monoclonal gammopathy have IgM M proteins, 30% have IgG M proteins, and 20% have IgA M proteins *(82,83)*. IgM monoclonal gammopathy may be associated with Waldenström's macroglobulinemia; the neuropathy may be sensory or sensorimotor. An intention tremor may accompany the slowly progressive distal and symmetrical neuropathy. The CSF is usually acellular with increased protein concentration. Conduction studies show demyelinating features.

The antibody responsible for the syndrome is a monoclonal IgM protein, usually with a kappa light chain, reacting against a myelin antigen (myelin-associated glycoprotein, MAG); the autoreactivity may be detected by ELISA, a convenient and quantitative method that correlates with results of the immunoblot technique *(84)*. Pathological studies show demyelination, deposits of MAbs and complement on affected myelin sheaths, and typical widening of myelin lamellae *(85–87)*. The neuropathy frequently improves with immunosuppressive therapy *(88)*. Plasmapheresis *(89)* and intravenous immunoglobulin *(90)* may also be useful. Axonal neuropathy is also seen in Waldenstrom's disease but without anti-MAG antibodies *(91)*.

Neuropathy may occur in 1–13% of all patients with multiple myeloma *(92)*. Although tumor infiltration of the nerve can occur *(93)*, in patients with typical osteolytic myeloma the neuropathy is usually caused by amyloidosis *(94)*. Numbness

or painful paresthesias affect the hands or feet. The amyloid neuropathy then progresses proximally to affect motor and autonomic fibers. Extracellular accumulation of amyloid derived from a monoclonal light-chain immunoglobulin causes the disease *(95)*. Pathological studies usually show axonal degeneration with loss of myelinated and unmyelinated fibers *(96)*. The walls of nerve vessels may be thickened by the presence of amyloid deposits *(97)* that can be detected immunohistochemically *(95)*. In some patients with myeloma, amyloid deposits may cause a carpal tunnel syndrome that precedes the diagnosis of myeloma by many months *(98)*. Amyloid neuropathy responds poorly to therapy. Often myelomatous neuropathy is not associated with either amyloidosis or tumor infiltration *(99)*.

Peripheral neuropathy is seen in half of all patients with osteosclerotic myeloma *(99)*. The neuropathy affects both sensory and motor fibers; weakness is often severe and results in inability to walk or rise from a chair. The serum M proteins are IgG or IgA, and almost always lambda. In some patients osteosclerotic myeloma is part of the Crow-Fukase or POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M protein and Skin changes) *(100)*. Association of osteosclerotic myeloma or POEMS with Castleman disease (angiofollicular lymph node hyperplasia) has also been described *(101)*. The neuropathy may improve with radiation of the solitary plasmocytoma or with chemotherapy for widespread disease *(102,103)*.

## TREATMENT-RELATED NEUROPATHIES

### CHEMOTHERAPY

**General** Peripheral neurotoxicty has been a dose-limiting effect of many chemotherapeutic agents. New dosing schedules and combinations and higher dose-intensity regimens have made it mandatory to address this toxicity. Research in animal models and tissue culture has also provided insight into the mechanism of chemotherapy-related neuropathy.

**Evaluation of Treatment-Related Neuropathy** Grading of chemotherapy-related neuropathy is complex. The grade reflects both objective and subjective parameters; the latter attempts to reflect impairment in day-to-day functioning. The different grading criteria may be ambiguous; as what constitutes "severe paresthesias" to one patient may not to another. Likewise, what is "disabling" to a driver who needs to manipulate car pedals may not be so to a typist. Many scales have been established, but no scale prevails, thus compromising the evaluation of different studies in the literature and probably the true prevalence of chemotherapy-related neuropathy *(104)*.

Postma and colleagues evaluated four different toxicity-grading scales: WHO, ECOG, and NCIC-CTC (National Cancer Institute of Canada Common Toxicity Criteria) *(104)*. In 148 comparisons, there was a 34.5% rate of disagreement about the severity of the neuropathy. Disagreement was a result of differences on grading signs and symptoms (mild vs moderate weakness, mild vs moderate paresthesias). There is also no consensus with respect to which factors are most important in determining the clinical severity of the neuropathy (the objective sensory abnormalities, the abnormalities on EMG/NCS or quantitative sensory testing, the severity of symptoms, or interference with activities of daily life). The authors also caution against interpreting results across multiple institutions.

#### The Vinca Alkaloids

1. *General*. Vincristine is an essential component of most regiments for lymphoproliferative diseases. Neurotoxicity of the vinca alkaloids is frequently dose-limiting; an arbitrary upper limit of 2 mg is often placed on single doses of vincristine.

   Lower vincristine doses have been associated with lower survival rates *(105–107)*, leading to attempts to increase either the peak level or duration of drug exposure. Both single IV and continuous infusion of vincristine have been associated with significant neuropathy. Attempts to decrease vinca alkaloid neuropathy have included liposomal encapsulation, administration by continuous infusion, and treatment with neuroprotective drugs *(108–111)*.
2. *Clinical*. Peripheral neuropathy is observed at conventional doses (1.4 mg/m$^2$). The first manifestation is loss of ankle reflexes; the most common symptom is paresthesias, often starting at the fingers. Objective sensory loss is usually infrequent or mild *(112,113)*. There are usually no abnormalities in joint position sense. Vibration is reduced at both fingers and toes, but at a greater extent at the toes. Pain sensation is affected in both hands and feet *(114)*. The aforementioned findings per se do not warrant a dose reduction. Motor weakness develops within days, may be severe *(115)*, and is the dose-limiting effect. The first evidence of motor involvement is usually cramps and hand clumsiness. Weakness is most apparent in the extensors of the hands, followed by the intrinsic hand muscles. While formal examination reveals weakness that is mild to moderate, patients' limitations may seem disproportionate to weakness determined by motor testing alone *(114)*. After a course of vincristine of 0.5 mg/m$^2$ IV bolus followed by a 3 d continuous infusion of 1.5 mg/m$^2$ every 2 wk for 12 wk, all patients required assistance in activities that required fine manipulation (jars, buttons). The authors concluded that sensory symptoms contributed to weakness in the limitation of manipulative activities *(114)*. The neuropathy usually improves after dose reduction or discontinuation. Prolonged use may result in autonomic neuropathy manifested as constipation or pseudo-obstruction in up to 15% of patients *(114)*. Rarely, the neurotoxic effects of vincristine can be enhanced by radiation if the trajectory of the peripheral nerve falls within the radiation port *(116)*.

   Involvement of the trigeminal and glosopharyngeal nerves by the vinca alkaloids has been well-documented *(117)*. Other focal neuropathies include unilateral vocal cord palsy, dysphagia, and sensorineural hearing loss *(117)*.

   The clinical symptoms of vincristine neuropathy are considered reversible to a large extent, but there are reports of long-standing motor disabilities *(119,120)*. Long-term effects have been observed as persistent fine motor and handwriting difficulties in 67% of patients treated for childhood leukemia examined > 2 yr after treatment *(120)*.
3. *Vincristine and hereditary neuropathy*. Patients with hereditary sensory motor neuropathies, particularly Hereditary Sensory Motor Neuropathy (HSMN) with chromosomal

17 duplication have increased susceptibility to develop a severe sensory and motor neuropathy with very large or even single doses of vincristine *(121–123)*. For example, an 8 yr-old boy with acute lymphocytic leukemia (ALL) developed profound motor weakness after an induction dose of vincristine (1.5 mg/m$^2$) to the point where he was unable to raise his limbs against gravity; a year later he was able to walk. EMG/NCS were suggestive of a demyelinating neuropathy. Diagnostic testing in the boy's mother also showed a demyelinating neuropathy, and DNA analysis suggested a HSMN type 1A. The authors conclude that vincristine unmasked a latent familial neuropathy and suggest that chromosome 17p11 duplication studies or NCS, even in asymptomatic patients, should be done when considering vincristine therapy.

4. *Severe fulminating neuropathy*. Several cases have been described in which patients developed a severe fulminating neuropathy consisting of quadriplegia and respiratory failure after vincristine treatment; recovery was seen in a year. EMG/NCS showed absence of motor and sensory responses and diffuse fibrillation potentials. CSF contained elevated protein, while nerve biopsy revealed complete loss of myelin with relative preservation of axons. Toxic vincristine neuropathy is included in the differential of Guillain-Barré Syndrome (GBS) *(124)*.
5. *Electrophysiological studies*.
   a. EMG/NCS. Conduction velocities are usually decreased by wk 12 of an every other week treatment, but are normal at wk 8. A reduction in amplitude is seen in all nerves and can continue to progress even after discontinuation of treatment *(114)*.
   b. Somatosensory evoked potential (SSEP). SSEP and neurological examinations were studied for 2 yr after the end of the intensive chemotherapy for ALL. The total dose of vincristine ranged from 12–22 mg/m$^2$. Mean time between the last injection of vincristine and SEP recording was 2.1 yr. The amplitudes of the median SEP at the brachial plexus and at the spinal cord were significantly lower in the 27 patients with ALL than in their matched controls (suggesting axonal loss). A significant delay in the mean conduction time (implying demyelination) was also seen for the median nerve. A longer follow-up might be required to determine whether the SEP abnormalities return to normal.
6. *Mechanism*. Vincristine exerts its antineoplastic effect by inhibiting microtubule dynamics in mitotic spindles and preventing cell division *(125)*. The effects on microtubules produce abnormalities in axonal transport, accounting for neurotoxicity *(126)*. The high affinity to both neuronal and mitotic microtubules suggests that it may be difficult to prevent neurotoxicity without reducing clinical efficacy.

   Peripheral neurons may be very sensitive to vincristine because nerve terminal function is dependent on intact axonal transport. Paresthesias and dysesthesias are mostly seen in fingers and toes, the areas innervated by the longest sensory neurons, presumably the most sensitive to disrupted axonal transport.

   The painful peripheral neuropathy in humans is thought to be related to alterations in C-fiber nociceptor function. C-fibers of vincristine-treated rats show a marked hyperresponsivenes to suprathreshold stimulation (heat and mechanical).
7. *Animal models of vincristine-induced painful neuropathy*. In animals the neuropathy appears in two stages. In the first, peripheral axons are damaged; clinically, this corresponds to symptoms of paresthesias and dysesthesias and hyperalgesia. In the later stages, occurring when large doses are given over a prolonged period of time, one observes loss of motor function *(126)*.

   Light micrographs from vincristine-treated rats do not differ from that of controls *(126)*. On electron microscopy several differences between the cytoskeletal structure in the control and the vincristine-treated axons were seen. The neurofilaments in vincristine-treated axons were abnormally clustered in the central portion of the axoplasm. The authors concluded that vincristine-induced painful neuropathy is accompanied by ultrastructural changes in unmyelinated sensory neurons.
8. *Neuropathology*. Axonal degeneration of the nerves has been the predominant finding, but secondary demyelination has also been observed *(118,127–129)*.
9. *Other vinca alkaloids*.
   a. Vinorelbine. This is a new semisynthetic vinca alkaloid that interferes with axonal transport *(130)*. A prospective study showed that breast cancer patients treated with 25 mg/wk of vinorelbine developed a mild to moderate sensorimotor neuropathy, distal, symmetrical, and axonal. Neurotoxicity is dose-dependent and partially reversible after drug discontinuation *(131)*.
   b. Liposomal vincristine. Phase I trials using a maximum dose per cycle of 2.8 mg/m$^2$ over 1 h every 21 d for two cycles led to grade 3 or 4 neuropathy in 4% of patients, constipation in 12%, and myalgias in 4%. Myalgias occurred several days after the infusion and required narcotic analgesia. Constipation became severe at the highest dose levels. In this preparation, neurotoxicity was still dose-limiting. The pattern of neuropathy with the encapsulated version was mostly characterized by constipation; peripheral neuropathy was less marked than with free vincristine *(132)*.

## The Taxanes

### *Paclitaxel*

1. *General*. The target of the antineoplastic activity of paclitaxel is the microtubule system. Because of the widespread use of hematopoietic factors mitigating this agent's myelosuppressive effects, neuromuscular toxicity is the principal dose-limiting toxicity.
2. *Clinical*. Approximately 70% of patients who receive paclitaxel develop signs or symptoms of neuropathy *(133)*. A predominantly large fiber sensory polyneuropathy invariably occurs at doses > 200 mg/m$^2$. Symptoms include paresthesias, numbness, and/or burning pain in a glove/stocking distribution. They are usually symmetrical, but unilateral involvement may occur at the beginning and can develop as early as 72 h after the initiation of therapy. Other manifestations include motor neuropathy, autonomic neuropathy and CNS toxicity, myalgias, and arthralgias *(134)*. Duration of symptoms correlates with total dose. The neuropathy is rarely dose-limiting, rarely disabling at doses < 250 mg/m$^2$, and usually improves

within months of treatment completion. Very rarely, paclitaxel neuropathy can progress even after discontinuation of the drug *(135)*.

Motor neuropathy is not well-described, but has been reported to occur at high doses affecting most commonly the toe and foot extensors *(136)*. Autonomic neuropathy is manifested as paralytic ileus and orthostatic hypotension, but is only seen with doses > 250 mg/m$^2$ or in patients with diabetes.

In animals, neuropathy depends both on dose and frequency of administration *(137)*. The most important risk factor in humans appears to be the dose, followed by prior exposure to neurotoxic agents and concurrent medical disorders (diabetes or alcoholism) *(134)*. In such patients, dose modification may be considered.

3. *Neurotoxicity of high-dose paclitaxel*. Neurotoxicity includes motor neuropathy, autonomic neuropathy, myalgias, and arthralgias. In a Phase I study of paclitaxel given a single at doses agent at doses of 500–800 mg/m$^2$ followed by stem cell support, 94.7 % of the patients developed neuropathy. By d 30 after the chemotherapy, sensory symptoms had subsided in most, but deep tendon reflexes (DTRs) remained absent. Neuropathy, including DTR loss, resolved completely at 2–8 mo in 10 out of 18 patients. Neuropathy resolved completely at a median of 3.5 mo in patients without prior chemotherapy and 6.5 mo in those with prior neurotoxic chemotherapy. There was no correlation between dose escalation and severity of neuropathy, but there was a correlation between the dose and delayed recovery. These findings have been confirmed by other investigators, who found that some patients had moderate distal weakness, particularly foot dorsiflexors and toe extensors.

   Myalgias may be severe at doses > 200 mg/m$^2$, and may require dose reduction. Proximal muscle weakness has been described in patients receiving high doses (250–350 mg/m$^2$) in combination with cisplatin and G-CSF or in those receiving multiple doses of single-agent paclitaxel (cumulative doses of 1170 mg/m$^2$ or greater). An autonomic neuropathy, usually orthostatic hypotension or paralytic ileus, has been only seen at doses > 250 mg/m$^2$ *(134)*.
4. *Electrophysiology*. At doses of 175 mg/m$^2$ either as a 3 h or 24 h infusion, nerve conduction studies show involvement of both motor and sensory fibers, with significantly decreased amplitudes and normal conduction velocities. Clinically, however, one observes mostly sensory problems. At high doses, the peroneal nerve is most commonly affected.
5. *Mechanism*. In contrast to vincristine, which leads to microtubule dissociation, paclitaxel binds to the B-subunit of tubulin, inhibits microtubule depolymerization, and induces cell-cycle arrest. As with the vinca alkaloids, taxane neuropathy is related to interference with microtubule-based axonal transport and secondary axonal degeneration *(138)*. Some speculate that the predominance of distal sensory loss simultaneously in hands and feet suggests that this may not be a dying-back neuropathy, but rather a neuronopathy affecting the dorsal root ganglia (DRG) *(139)*. Axonopathy and secondary demyelination are seen in sural nerve biopsies *(140)*. Rowinsky and colleagues showed that there was no correlation between steady-state plasma paclitaxel concentration and neurotoxicity *(141)*.

### Docetaxel

1. *Clinical*. In studies where docetaxel is given as a single agent at doses ranging from 150–1100 mg/m$^2$, about 50% of patients developed a mild sensory neuropathy *(142)*. Symptoms usually improve within weeks after discontinuation of treatment but may progress for several months after that *(143)*, a phenomenon also observed with cisplatin *(144,145)*. As Hilkens says, "recovery of taxoid neuropathy following discontinuation of treatment cannot be taken for granted" *(143)*. Proximal weakness has been reported *(146,147)*.

   When docetaxel is administered at 100 mg/m$^2$ over 1 h, every 3 wk, for a cumulative dose of 600 mg/m$^2$, a severe neuropathy may be seen in about 25% of the pts. The neuropathy consisted of paresthesias, numbness, gait unsteadiness, loss of toe joint position sense, and foot drop. Some patients have distal weakness. With continued therapy, the paresthesias become painful, suggestive of small fiber involvement *(148)*.

   The decisive factor for docetaxel neuropathy appears to be the dose, but some patients may have a particular susceptibility. Abnormal liver function may lead to reduced clearance and more toxicity. Short infusion schedules may increase neurotoxicity, as compared with 24 h dosing *(149)*.
2. *Electrophysiology*. Although most studies suggest that docetaxol neuropathy is axonal in nature, more severe cases may show also a demyelinating pattern. QST is not as useful as the clinical exam or NCS in determining neuropathy *(146)*, and was thus found to be a poorly reliable method to monitor docetaxel neuropathy *(142)*.

### Platinum Agents

#### Cisplatin (CDDP)

1. *General*. Cisplatin has been a major component of most combination regimens to treat advanced ovarian cancer. Neuropathy has become the major dose-limiting toxicity, typically developing in most patients after several courses of 75–100 mg/m$^2$ (cumulative doses > 300 mg/m$^2$ *(150,151)*. The exact incidence of cisplatin-related neuropathy is unknown, but it has been reported in 30–100% of patients.
2. *Clinical*. Features include: (a) pure sensory involvement, (b) relationship to the cumulative dose, and (c) progression for several (3–8) weeks even after discontinuation of the drug *(152)*. The neuropathy involves predominantly large diameter myelinated sensory fibers, affecting vibration and position sense.

   Symptoms: Initially, patients may complain of numbness or tingling; exam reveals decreased reflexes and vibration. Signs: As therapy is continued, proprioception becomes impaired, resulting in ataxia, which sometimes makes walking impossible. At high doses (30–40 mg/m$^2$/d × 5 d), about half the patients develop a severe sensory ataxia requiring assistive walking devices *(153)*. Vibration sense pain and touch sensitivity are decreased. Only the most severely affected patients have weakness *(131)*. Autonomic

dysfunction is rare. Otoxoxicity leads to hearing loss and tinnitus. Recovery is variable, and the quality of life of survivors may be permanently affected *(154,155)*.

3. *Mechanism*. It is suggested that CDDP kills cancer cells and neurons by the same mechanism *(156)*. Mechanistic studies are limited *(157–159)*. Animal morphometric studies suggest that the primary target is the dorsal root ganglion (DRG). The DRG satellite cells are also a target *(160)*. When rats are given CDDP, apoptosis of the sensory neurons is observed in the DRG, changes include neuronal shrinkage and nucleolar abnormalities *(161)*, inducing first sensory neuronopathy and then a peripheral neuropathy *(162)*. Variable involvement of the peripheral nerves is observed. It is speculated that CDDP leads to decreased neurotrophic support at the DRG leading to a primary neuronopathy followed by a mild axonopathy involving large myelinated fibers; other sources suggest it affects all types of peripheral nerves. The DRG is supplied by fenestrated capillaries; sensory neurons appear to be most susceptible because they are not protected by the blood-brain barrier (BBB) and are thus exposed to serum levels of the drug.

   In experimental models, reduction in the concentration of transmitter neuropeptides such as calcitonin generated peptide and substance P have been observed in the DRG of mice given CDDP. It is not clear, however, that these are of primary importance in the neurotoxicity *(156,163,164)*.

4. *Unusual clinical presentations*.

   a. Optic neuropathy. A case report describes a 52-yr-old woman with ovarian carcinoma treated with CDDP. After four cycles, the patient developed peripheral neuropathy, and treatment was changed to carboplatin. One week after carboplatin, and 13 wk after the CDDP, she developed decreased visual acuity. Exam showed papilledema, which disappeared in 3 wk *(165)*.

   Another report involves a patient receiving a cumulative dose of 640 mg/m$^2$. Clinically, there was Lhermitte's sign and a sensory neuropathy. The chemotherapy was changed to carboplatin (300–400 mg/m$^2$ every 3 wk, × 3 doses). One week after the last dose of carboplatin, she developed decreased visual acuity and bilateral papilledema. The authors speculated that the optic neuropathy was a delayed effect from CDDP. Other cranial neuropathies may follow internal carotid infusion *(166)*.

   b. Plexopathy. Intra-arterial infusion of cisplatin may cause plexopathy that is likely due to small vessel damage and nerve infarction *(167)*.

5. *Pathology*. Sural nerve biopsies show decreases in the number of large myelinated fibers, myelin thickness and in axonal diameter *(150,157)*.

6. *Electrophysiology*. Changes consist of decrease in nerve conduction velocities (affecting sensory more than motor nerve fibers), reduction of amplitude, and a decrease in sudomotor function.

7. *Other platinum agents*. Ormaplatin showed severe neurotoxicity in Phase I trials *(168)*. Oxaliplatin is a platinum derivative approved in France and under study in the United States for treatment of advanced colorectal cancer. At a dose of 130 mg/m$^2$, a grade 3–4 sensory neuropathy is seen *(169)*. Acute dysesthesias may occur within hours to minutes of drug infusion. After several cycles, there are paresthesias and proprioceptive loss. Moderate to severe paresthesias is seen in 10% of patients after six cycles *(170)*. Most symptoms disappear within 6–8 mo after drug discontinuation, which is somewhat different from the temporal profile observed with CDDP discontinuation *(171)*.

CARBOPLATIN

1. *General*. At conventional doses, carboplatin is less neurotoxic than the parent compound, cisplatin *(172,173)*. At high doses, it does produce the same type of neuropathy as cisplatin *(174,175)*. Animal studies show that the neuropathy of cisplatin and carboplatin are morphologically similar *(176)*.

2. *High-dose carboplatin (HD CBCDA)*. Carboplatin neurotoxicity has never been a limiting effect at conventional doses. Cavaletti reported on the neurotoxicity and ototoxicity of high-dose carboplatin as first-line treatment for ovarian cancer. At baseline, no patients had signs or symptoms of neuropathy. After treatment, there was high frequency (4000–8000) hearing impairment in most patients due to cochlear hair cell damage, with the complete preservation of central auditory pathway. Out of nine patients, only one had signs of peripheral neuropathy on examination and four had symptoms (distal paresthesias). On NCS, seven of nine patients had decreased amplitude of the ulnar sensory action potential, but recovery was observed. The amplitude of the motor action potential decreased more than 20% in six of nine ulnar and peroneal nerves tested *(175)*.

   Three patients were reported to develop severe neuropathy after HD CBCDA. All three patients had received prior CDDP as induction chemotherapy (450 mg/m$^2$–800 mg/m$^2$, cumulative dose). Cumulative doses of carboplatin were 1000–2750 mg/m$^2$. All patients developed signs and symptoms a few days after the high-dose treatment, and had severe sensory ataxia requiring walking devices. Light touch, vibration, and proprioception were decreased or absent in all four limbs. Temperature and pin were just slightly diminished. Motor deficits were mild and limited to hands and feet. Improvement began one or two months after the last course of chemotherapy. The authors propose that cisplatin alone could have accounted for the neuropathy or that it may have acted as a predisposing agent or had a synergistic effect *(177)*.

***Ara-C*** The incidence of peripheral neuropathy is 0.6%, occurring at both conventional and high-dose IV therapy (cumulative dose 600 mg–36 g/m$^2$). Several types of neuropathies have been described: a pure sensory neuropathy, a rapidly ascending polyneuropathy, a sensorimotor neuropathy, and bilateral brachial plexopathies. Improvement is the rule, but some patients have deficits for years. Electrophysiological studies and biopsies are consistent with both demyelination and axonal damage. The pathogenesis is not clear.

***Suramin***

1. *General*. Suramin belongs to a new class of agents, which interferes with growth factor stimulation of cancer cell growth. Severe neurotoxicity and nephrotoxicity have limited its use *(178–180)*.

2. *Clinical.* Up to 50% of patients develop a mild axonal neuropathy; in about 10% of patients a severe proximal and distal radiculopathy may occur, which may progress into respiratory failure. Paresthesias develop first, followed by proximal weakness and in severe cases bulbar weakness, respiratory weakness, and dysautonomia. Patients may improve slowly, and plasma exchanges have been used because of the similarity to acute inflammatory demyelinating polyneuropathy.

   Peak concentrations of > 300–350 mg/mL were associated with a toxic distal axonal neuropathy (55%) or a partially reversible inflammatory demyelinating neuropathy (18%) *(179)*. Electrophysiological studies show demyelination first followed by axonal damage. CSF protein is elevated.
3. *Mechanism.* Suramin induces apoptosis of sensory neurons in vitro. At low doses, suramin activates the NGF receptor *(181)* and at high doses, it inhibits the binding of NGF to the NGF receptor tyrosine kinase *(182)*. However, there is no evidence that the neurotoxicity is due to interference with NGF function. Disturbances in lipid metabolism may be primary to suramin-induced neuronal death. Suramin treatment leads to elevation of ceramide levels in both neurons and cancer cells *(183-185)*; ceramide is a key precursor in the synthetic pathway for gangliosides and also a mediator of cell death for both cancer cells and neurons *(181,183)*.

***Procarbazine*** Peripheral neuropathy has been reported in 10–20% of patients, with distal paresthesis and depressed DTRs. The symptoms resolve after drug discontinuation.

***Epipodophyllotoxins*** A mild to moderate sensorimotor neuropathy has been described with etoposide *(186)*. Risk factors include advancing age, weight loss, and prior neurotoxic chemotherapy. Electrophysiological studies show both demyelination and axonal damage.

***Ifosfamide*** Exacerbation of a preexisting neuropathy has been observed in patients receiving high-dose (14 g/m$^2$) IV ifosfamide for sarcomas *(187)*. Severe pain and paresthesias in hands or feet are seen 10–14 d after chemotherapy, lasting hours to days and improving to baseline after several weeks. Retreatment leads to neuropathy exacerbation *(187)*.

***Misonidazole*** Sensory polyneuropathy is dose limiting, occurring at cumulative doses of >18 g. Electrophysiology shows a decrease in the amplitude of the sensory more than the motor action potentials. Histopathology shows both axonal degeneration and segmental demyelination.

***Thalidomide*** Thalidomide has been noted to produce a primarily sensory polyneuropathy, with reported incidence ranging from 1–70%. A recent study of thalidomide for recurrent gliomas utilized doses ranging from 800 mg/d to 1200 mg/d. Of 39 patients, only one developed a peripheral neuropathy *(188)*.

## COMBINATION REGIMENS

1. *General.* Combination therapy has proven highly effective as first-line therapy for patients with several malignancies. A summary of the neuropathic toxicity of several combination regimens is shown in Table 3 *(189–212)*.
2. *Clinical.* Paclitaxel + cisplatin. Berger and colleagues treated patients with paclitaxel (175 mg/m$^2$ over 3 h) followed by cisplatin (50 mg/m$^2$/d d1, d2). There were no neuropathic symptoms at baseline. Cumulative doses ranged from 175–1225 mg/m$^2$ for paclitxel and from 100–700 mg/m$^2$ for CDDP. Eighty-six percent of patients developed sensory symptoms, and 50% had reduced vibration sense. Symptom severity was dependent on the cumulative dose. Severe neuropathy was seen in 43% of patients, while 57% had motor weakness, predominantly of the legs. As compared to paclitaxel monotherapy, the combination resulted in enhanced neurotoxocity *(212)*. Chaudry and colleagues reported a 95% incidence of neurotoxocity in a Phase I trial of paclitaxel (135–350 mg/m$^2$) and cisplatin (75–100 mg/m$^2$). Moderate to severe neurotoxicity occurred at cumulative doses of paclitaxel and CDDP of 525 mg/m$^2$ and 300 mg/m$^2$, respectively.

Hilkens showed that 53% of patients on a combination regimen of docetaxel and cisplatin develop a primarily sensory neuropathy; when cisplatin cumulative doses exceed 200 mg/m$^2$, 71% develop neuropathy. The authors could not conclude which of the two drugs was more a factor in the development of peripheral neuropathy but thought a synergistic effect was important.

**GROWTH FACTORS** A severe, reversible atypical neuropathy developed in 22% of patients treated with hematopoetic growth factors and vincristine for NHL *(213)*. There was weakness and severe pain of legs only, which is atypical for vincristine neuropathy. The authors speculated that G-CSF might exacerbate existing neuropathy or increase the risk of neuropathy when used in combination with neurotoxic agents. Other hypotheses are that G-CSF may interfere with growth factors involved in nerve damage repair, stimulate neurotoxic cytokines, or delay clearance of vincristine from the body *(214)*.

**RADIOTHERAPY** Radiation fibrosis is usually progressive and irreversible. Paresthesias and lymphedema of the arm are early clinical manifestations of radiation injury of the brachial plexus, while pain tends to be moderate and develop late *(215)*. Typically the distribution of weakness corresponds to a C5-6 dermatomal distribution, with proximal weakness of the arm. Radiation-induced brachial plexopathy may affect patients treated for breast or lung cancer, or lymphoma *(216)*. Postradiation lumbosacral plexopathy is usually manifest as slowly progressive leg weakness, typically 5–6 yr after irradiation of the pelvis for lymphoreticular, testicular, uterine, or ovarian tumors *(217)*. The delay may vary from 3 mo to 26 yr for brachial plexopathy *(16)* and 1–31 yr for lumbosacral plexopathy *(19)*. Electrodiagnostic studies in patients with radiation fibrosis demonstrate fibrillations, positive sharp waves, and myokymia; the latter is not found in patients with tumor infiltration of the plexus.

## TREATMENT-RELATED MYOPATHY

**THE TAXANES** Painful proximal weakness has been described in about 17% of patients receiving paclitaxel at conventional doses *(218)*. The weakness occurred at any stage

**Table 3**
**Peripheral Neuropathy of Some Currently Used Cancer Regimens**

| *Authors/ references* | *Tumor* | *Current regimen mg, × times (dose)* | *# Patients* | *Peripheral neuropathy grade, %* | *Grading* |
|---|---|---|---|---|---|
| Hainsworth et al. *(189)* | NSCLC | Paclitaxel – 200 mg/m$^2$/1 h/ 1<br>Carboplatin – 5.0 AUC/d 1<br>Gemcitabine – 1000 mg/m$^2$/d 1&8<br>Treatment q 21 d | 77 | Grade 3–4: 8% | NCI |
| Hunter et al. *(190)* | Ovarian | Cisplatin – 120 mg/m$^2$/4 cycles<br>Adramycin – 100 mg/m$^2$/4 cycles | 61 | 46% – no grade listed<br>3% – severe | NL |
| Perez et al. *(191)* | Breast | Paclitaxel – 200 mg/m$^2$/3 h<br>Carboplatin – 6 mg/mL/min AUC<br>Treatment q 3 wk | 53 | Grade 1–2: 48%<br>Grade 3: 16% | NCI |
| Ray–Coquard et al. *(192)* | Breast | CIVIC – Cisplatin – 20 mg/m$^2$ q 21 d<br>VNB – 6 mg iv bolus —><br>VNB – 6 mg/m$^2$/day q 21 d<br>Total – 210 cycles | 58 | Grade 0: 41%<br>Grade 1: 24%<br>Grade 2: 10%<br>Grade 3: 5% | WHO |
| Grigg et al. *(193)* | Ovarian – 40%<br>NSGCT – 60% | Carboplatin – 700 mg/m$^2$/3 h × 3<br>Etoposide – 1.2 g/m$^2$ as 17 h<br>Melphalan – 125 mg/m$^2$ | 5 | Mild: 20%<br>(80% were not evaluated) | WHO |
| de Witt et al. *(194)* | Urothelial | Docetaxel – 100 mg/m$^2$/h q 3 wk<br>Total – 100 cycles | 30 | Grade 2: 3%<br>Grade 3: 3% | NCI |
| Shapiro et al. *(195)* | Ovarian | Carboplatin – 600 mg/m$^2$/d 1<br>Cyclophosphamide – 250 mg/m$^2$/d 1<br>Cisplatin – 100 mg/m$^2$/d 8<br>Treatment – q 4 wk<br>+/– Amifastine – 740–1140 mg/m$^2$/d 1&8 | 26 | Grade 2–3: 26% (10 pts) | NL |
| Guastalla et al. *(196)* | Ovarian | Paclitaxel – 175 mg/m$^2$/3 h<br>Carboplatin – 5 mg/mL/min AUC<br>Treatment – q 4 k | 73 | Grade 1-2: 47%<br>Grade 3: 7.3% | WHO |
| Pagani et al. *(197)* | Breast | Starting dose:<br>Paclitaxel (P) – 135 mg/m$^2$ q 3 wk<br>Cyclophosphamide (C) – 750 mg/m$^2$ q 3 wk<br>End dose:<br>Paclitaxel (P) – 200 mg/m$^2$ q 3 wk<br>Cyclophosphamide (C) – 1000 mg/m$^2$ q 3 wk | 80 | Grade 2: 23%<br>Grade 3: 0.4% (3 pts) | WHO |
| Nardi et al. *(198)* | Ovarian | Paclitaxel:<br>1 or 2 prior chemo – 175 mg/m$^2$<br>> 3 prior chemo – 135 mg/m$^2$ | 33 | Grade 1–2: 87.8%<br>Grade 3: 12.1% | WHO |
| Salter et al. *(199)* | Head & neck | Cisplatin – 30/35 mg/m$^2$/d × 5<br>q 4 wk × 3 courses<br>5-FU – 200/300 mg/m$^2$/d q 12 wk | 22 | 36% – Paresthesias? | NL |
| Felip et al. *(200)* | NSCLC | Cisplatin – 100 mg/m$^2$ d 1<br>Vinorelbine – 30 mg/m$^2$/d 1&8<br>3 cycles | 33 | Grade 1: 42%<br>Grade 2: 6% | WHO |
| Sarris et al. *(201)* | NHL | Liposomal lincristine – 2.0 mg/m$^2$/60 min<br>q 14 d total 12 injections | 35 | Grade 3–4: 34.4% | NL |
| Soulie et al. *(202)* | Ovarian | Cisplatin – 100 mg/m$^2$/d q 3 wk<br>Oxaliplatin – 130 mg/m$^2$/d q 3 wk | 25 | Grade 1–2: 36% (9 pts) after 2 cycles<br>Grade 3: 12% (3 pts) after 4 cycles<br>Grade 3–4: 87.5% (7/8 pts) > 5 cycles | CTC |
| Haisnworth et al. *(203)* | NSCLC | Paclitaxel – 225 mg/m$^2$/1 h<br>Carboplatin – 6.0 AUC<br>q 21 d | 100 | Grade 1–2: 46%<br>Grade 3: 15% | NL |
| Simsek et al. *(204)* | Uterine sarcoma | I. VAC: vincritine – 1.5 mg/m$^2$<br>Dactinomycin – 0.5 mg/d × 5 d q 4 wk<br>Cyclophosphamide – 5–7 mg/kg/d × 5 d q 4 wk<br>II. Ifosfamide – 1.2 g/m$^2$/5 d | 13 | VAC group: 16.6% | GOG |
| Vahdot et al. *(205)* | Breast | I. Paclitaxel – 400–825 mg/m$^2$<br>II. Melphalan – 180 mg/m$^2$<br>III. Cyclophosphamide - 600 mg/m$^2$<br>Thiotepa – 50 mg/m$^2$<br>Carboplatin – 800 mg/m$^2$ | 36 | Grade 4<br>(3 mo post-treatment) | NCI |

(*continued*)

**Table 3 (*Continued*)**
**Peripheral Neuropathy of Some Currently Used Cancer Regimens**

| *Authors/ references* | *Tumor* | *Current regimen Mg, × times (dose)* | *# Patients* | *Peripheral neuropathy grade, %* | *Grading* |
|---|---|---|---|---|---|
| Pal et al. *(206)* | Lymphoma 50% NHL | Vincristine – 2–8 mg; 0.012 mg/kg/wk | 18 | 100% – Absent ankle jerk<br>75% – Sensory symptoms<br>18.7% – Motor abnormalities | NL |
| Diomopoulos et al. *(207)* | Endometrium | Paclitaxel – 175 mg/m$^2$/3h q 3 wk<br>Cisplatin – 75mg/m$^2$ w/ GCSF q 3 wk | 24 | Grade 1–2: 44%<br>Grade 3: 9% | WHO |
| Shapiro et al. *(208)* | Ovarian | I. Cyclophosphamide – 200 mg/m2/d × 5 d<br>Cisplatin – 30–40 mg/m$^2$/d × 4–5 d<br>q 28 d (2 cycles) —> 2nd surgery then<br>II. Cisplatin – ip 500–100 mg/m$^2$ q 21 d<br>4 cycles; If no CR – 3rd surgery | 40 | Grade 3: 12.5% | NCI |
| Langer et al. *(209)* | NSCLC | I. Paclitaxel – 175–280 mg/m$^2$/1 h<br>Carboplatin – 7.5 AUC q 3 wk × 6 cycles<br>II. Paclitaxel – 175–215 mg/m$^2$/1 h<br>Carboplatin – 1.5 AUC | 57 | I. Grade 3: 30%<br>II. Grade 3: 6% | NL |
| Eddy et al. *(210)* | Cervical | Cisplatin – 50 mg/m$^2$ q 10 d<br>Vincristine – 1 mg/m$^2$ q 10 d<br>Total 3 courses | 35 | Grade 0: 68.6%<br>Grade 1: 17.1%<br>Grade 3: 5.7% | NL |
| Elias et al. *(211)* | Advanced malignancies | Etanidazole – 3–22 g/m$^2$<br>Carboplatin – 1600–1800 mg/m$^2$<br>Ifosfamide – 16 g/m$^2$<br>Etoposide – 1.2 g/m$^2$ | 55 | Grade 2–3: dose depnd. | NCI |
| Berger et al. *(212)* | Different solid tumors | Paclitaxel – 175–1225 mg/m$^2$<br>Cisplatin – 100–700 mg/m$^2$<br>Total 1–7 courses | 14 | Grade 1: 21%<br>Grade 2: 29%<br>Grade 3: 43% | WHO |

NL, not listed; NSCLC, nonsmall cell lung carcinoma; NCI, National Cancer Institute; SLL, second look laporotomy; AUC, area under the curve; Q., every; WHO, World Health Organization; 5-FU, 5-fluorouracil; NHL, non-Hodgkin's lymphoma; CTC, common toxicity criteria; GOG, Gynecological Oncology Group; CR, complete response; NCIC-CTC, National Cancer Institute of Canada Common Toxicity Criteria; PNP, peripheral neuropathy; VNB, vinorelbine.

intreatment, had a variable course, and reversed upon cessation of drug administration. It is not clear whether patients had a myopathy; the authors speculated that the cause was a distal axonopathy.

A myopathy with proximal muscle weakness has been described in patients receiving high doses of paclitaxel (250–350 mg/m$^2$) in combination with cisplatin and G-CSF or in patients receiving multiple doses of paclitaxel as single agent (1170 mg/m$^2$ cumulative doses or greater). An anecdotal report suggests that the antihistamine Seldane (terfenadine) may reduce paclitaxel-related myopathy. Transient myalgias are common with doses of > 170 mg/m$^2$; these start within 2 d after treatment, and resolve within 5 or 6 d.

**INTERLEUKIN 2 (IL-2)** Immunotherapy has proven to be of benefit in some malignancies such as melanoma or renal cell carcinoma. Treatment has been associated with significant side effects, including liver and renal dysfunction, coma, and the development of autoimmune diseases. A case of necrotizing myositis was seen in a patient who received IL-2 for the renal cell carcinoma. After the sixth dose, the patient developed acute proximal muscle pain and weakness. Creatine phosphokinase (CPK) levels were 23,360 U/L. After discontinuation of therapy the CPK returned to normal. A quadriceps biopsy showed nercotizing myositis. The close temporal relationship between the onset of the myositis and IL-2 therapy and the resolution when the IL-2 was discontinued strongly implicate IL-2 in the pathogenesis of the myositis.

**POLYMYOSITIS ASSOCIATED WITH DRUG COMBINATIONS** A case report describes a patient with metastatic thymoma treated with ifosfamide, cisplatin, and etoposide. He was then treated with octreotide and prednisone, after which he developed myalgias and dyspnea. Examination revealed proximal extremity and respiratory muscle weakness. The authors speculate the myopathy was secondary to tumor cell lysis and increased tumor antigen presentation, resulting in distant organ dysfunction, or a drug-induced myopathy either related to octreotide or to steroids. Muscle biopsy was consistent with polymyositis; CPK was elevated. The patient failed corticosteroids and intravenous immunoglobulin but improved with methotrexate *(219)*.

**GROWTH FACTORS** In humans, growth factors may produce myalgias and diffuse body pain. Mice receiving large doses of GM-CSF have developed a fatal cachectic state, with multiple inflammatory foci present in both skeletal and cardiac muscle. It is theorized that elevated levels of GM-CSF may stimulate production of muscle toxins.

**TIRAPAZAMINE** This is a new cytotoxic agent, synergistic with cisplatin *(220)*. Muscle cramping, particularly in the legs, is the most common neuromuscular toxicity, observed in 5.3% of the patients within 2–3 d of drug administration *(221)*.

## CLINICAL COMMENTS: DIFFERENTIAL DIAGNOSIS, MONITORING, AND TREATMENT

**DIFFERENTIAL DIAGNOSIS** Radiculopathy, plexopathy, and neuropathy in cancer patients may sometimes be a consequence of conditions that are not tumor-related. Patients with cancer are also susceptible to other causes of peripheral nerve damage such as diabetes mellitus, chronic alcoholism, or nutritional deficiency. The diagnosis of a metabolic peripheral neuropathy, such as diabetic neuropathy, is facilitated when symptoms or signs develop in a patient with an established metabolic disease. However, a cancer-related neuropathy must always be considered. In cachectic patients with terminal cancer vitamin deficiency may play a role in neuropathy, but it is uncertain whether the malnutrition causes the neuropathy. Patients with depressed cellular immunity from malignancy (especially lymphoma) or treatment may have herpes zoster of thoracic or cranial regions. Postherpetic neuralgia seems to be two to three times more frequent in cancer patients than in general population *(222)*.

Differentiating neoplastic and radiation-induced plexopathy can be difficult. Several features have been proposed as useful clues for differentiation *(215)*; Horner syndrome and severe pain suggest neoplastic involvement of brachial plexus. Predominant paresthesias suggest a radiation-induced lesion.

Isolated peroneal nerve palsy has been reported to be higher in patients with cancer than in other people *(223)*. However, it is not clear whether peroneal neuropathy is the result of metabolic and mechanical factors or is paraneoplastic. Some neuromuscular disorders, such as muscle stiffness, neuromyotonia, and myotonia, may be paraneoplastic *(116)*. EMG also identifies other processes that occur in cancer patients and could be confused with peripheral neuropathy, such as myopathy or disorders of the neuromuscular junction *(224,225)*.

Peripheral neuropathy may be a side effect of therapy, metabolic disorder, or nutritional inadequacy. The diagnosis of a neoplasm in a patient with neuropathy does not necessarily imply a paraneoplastic disorder; other causes of neuropathy have to be excluded. On the other hand, a paraneoplastic sensory neuropathy is suspected when paresthesias and sensory loss have appeared subacutely, are asymmetric in initial distribution, and involve trunk, face, or arms rather than legs.

Detection of anti-Hu antibodies is a strong indicator that a neuropathy is paraneoplastic and mandates a search for SCLC. In anti-Hu antibody-negative patients, other types of cancers may be considered, but lung tumor is still the most common. Sensorimotor neuropathies of acute or chronic-relapsing evolution may be associated with a solid tumor, particularly lung cancer, or a lymphoma. In patients not known to have a cancer, extensive search for an occult neoplasm is not indicated unless routine clinical and laboratory examinations suggest it. In chronic neuropathies associated with lymphoproliferative diseases, demyelinating, or axonal features on EMG, respectively, suggest the presence of anti-myelin autoantibody reactivity or amyloidotic nerve deposits. In these cases, nerve biopsy is indicated for diagnosis.

**PRACTICAL RECOMMENDATIONS ON MONITORING PERIPHERAL NEUROPATHY** Every cancer patient who will be treated with potentially neurotoxic chemotherapy should have a baseline neurological examination. The treating clinicians should be attentive to the development of neuropathic symptoms, which include paresthesias, numbness, or dysesthesias. Routine follow-up examinations should monitor sensation, reflexes, strength, and gait. NCS are not used routinely in clinical practice to monitor patients. If, however, a patient with a known malignancy develops neurological symptoms that are not clearly treatment-related, EMG and NCS may be helpful in distinguishing neuropathic, myopathic, or neuromuscular disorders, and in detecting entrapment neuropathies or demyelinating neuropathies that may respond to immunological treatment. Blood studies should include glycosylated hemoglobin, B12, thyroid tests, and/or paraneoplastic antibodies.

Patients enrolled in large clinical trials where neuropathy is expected to develop from treatment or those receiving neuroprotective agents may benefit from NCS or QST. NCS or QST may be performed prior to the administration of chemotherapy to detect subclinical neuropathy, and then with each cycle of treatment, but these studies should probably be reserved for the context of clinical studies. QST is considered complementary to NCS but correlates poorly with the clinical examination *(4,6,7)*. Multicenter studies are needed to assess the role of QST in specific disease states.

## THERAPY AND PREVENTION OF TREATMENT-RELATED NEUROPATHY

**General** Apart from drug withdrawal or dose reduction, there is no established therapy for drug-related neuropathy. For the clinician, it is important to recognize that several groups of patients have a higher likelihood of development of vincristine neurotoxicity: older patients and those with Charcot-Marie-Tooth disease or lymphoma *(226)*. Concurrent medications such as isoniazid, cyclosporine, or colony-stimulating factors may potentiate the severity or duration of neurotoxicity *(227)*. Clinicians treating patients with these risk factors may need to calculate the dose of vincristine separately, rather than adhering to the conventional rule of 2 mg maximum dose of vincristine. Vincristine is often discontinued if motor dysfunction appears, but paresthesias or loss of tendon reflexes do not prohibit vincristine use. Vincristine-related autonomic neuropathy may not be related to either single or cumulative dose, and many oncologists do not discontinue the agent after one episode of autonomic neuropathy *(228)*. Cranial nerve palsies, including ptosis, laryngeal nerve paralysis, and facial palsy, usually occur after the first or second dose of vincristine, but may not recur despite repeated vincristine administration *(233)*.

**Symptomatic Treatment** Neuropathic pain may respond to tricyclic antidepressants or anticonvulsants (gabapentin, lamotrigine, carbamazepine). Opioids are commonly added to the pain regimen.

**Neuroprotectants**

***General*** Methods to alleviate chemotherapy-related neuropathy have received increasing attention because of the finding that there may be a correlation between dose intensity and outcome. For many of the drugs listed earlier, peripheral neuropathy is the dose-limiting toxicity.

There have been two main limiting factors in the development of neuroprotectants: firstly, the difficulty in developing animal or in vitro models that reflect the clinical neuropathy observed in humans *(230)*, and secondly, the possibility that some neuroprotectants may interfere with chemotherapy's cytotoxic effect *(231,232)*. It is not clear whether the mechanism of chemotherapy-induced damage is similar for neurons and for cancer cells. If the mechanisms are different, alteration of drug structure may optimize drug effect while minimizing neurotoxicity. For those drugs whose mechanism of cytotoxicity is identical to that of neurotoxicity, neuron-specific protective strategies must be sought. Many neuroprotectants are specific for certain fibers (either large or small nerve fibers). Some authors suggest that in order to treat chemotherapy-related neuropathy, where multiple neuronal populations may be affected, it may be necessary to use a "cocktail" of growth factors, or alternatively, use growth factors with a broad activity range *(233)*.

### *Glutamic Acid*

General Glutamine has been shown to reduce the severity of peripheral neuropathy in breast cancer patients receiving high dose (825 mg/m$^2$) paclitaxel *(234)*. In clinical practice, its use has been limited by the concern that it may impair cytotoxicity of the vinca alkaloids *(235)*.

Animal Studies In a rat model of vincristine-induced neuropathy, glutamate significantly decreased the incidence of neuropathy. This protection was selective, and there was no interference with cytotoxicity *(236,237)*. In a similar model, glutamate proved effective in ameliorating or delaying both sensory and motor neuropathies associated with CDDP and paclitaxel. By wk 8 after CDDP, 100% of the rats receiving CDDP alone had impaired gait vs 30% of the rats that received glutamate. When paclitaxel was given alone, significant delay in gait disturbance occurred in the glutamate-treated animals as compared with those who received chemotherapy alone *(234)*. No interference with tumor response was observed *(238)*. These findings suggest an action of glutamate on multiple neuronal cell types.

Mechanism Glutamate induces neurite growth, possibly by exerting an effect on the microtubule after interacting with a receptor in the neural cells *(239)*. The presence of glutamate receptors on DRG cells but not in malignant cells may explain the lack of interaction with cytotoxicity. Glutamate may regulate neurite growth *(240)* or interact with specific receptors on peripheral nerves *(239)*, which may explain the different effects of glutamate on nerves and malignant cells. Another speculated mechanism is that glutamate has a calcium modulating activity, which is most important in the destabilization of the microtubules.

### *ORG 2766*

General Melanocortins may exert trophic influences on nerve tissue, and analogs may reverse or block the neurotoxic effects of chemotherapeutic agents. The neurotrophic action may result from enhancement of endogenous nerve repair mechanisms *(241)*.

Animal Studies The adrenocorticotropin (ACTH) analog ORG2766 (ACTH 4–9) has been shown to prevent cisplatin-induced neuropathy in rats.

Clinical Trials Administration of ORG 2766 concurrently with cisplatin did not completely prevent cisplatin nerve damage, but the neuropathy was less severe *(243)*. Vibratory threshold, a reliable indicator of subclinical cisplatin sensory neuropathy, increased by 19% in patients treated with cisplatin and ORG 2766 and by 42% in patients treated with cisplatin and placebo, showing that ORG 2766 substantially reduces the cisplatin-induced elevation of vibratory thresholds. ORG 2766 did not ameliorate the neuropathy that developed or became worse several months after cisplatin discontinuation. A study of ORG 2766 by Roberts and colleagues failed to protect patients against CDDP-related neurotoxicity *(241)*.

***Cronassial*** Cronassial is a mixture of naturally occurring gangliosides suggested to benefit patients with diabetic neuropathy. DeAngelis reported on patients with non-Hodgkin's lymphoma treated with doxorubicin, cyclophosphamide, bleomycin, etoposide, methotrexate, and dexamethasone and vincristine. Patients were randomized to Cronassial or placebo. Cronassial had no protective effect against vincristine neuropathy *(114)*.

***Neurotrophin 3 (NT-3)*** NT-3 may protect the large DRG proprioceptive neurons where it accumulates. Large fiber neuropathy (manifested as severe proprioceptive loss) can be seen after CDDP administration. The choice of NT-3 as a neuroprotectant is based on its selective effects on large sensory neurons, the preferential retrograde axonal transport to the largest neurons of the DRG, and the localization of its receptor to the same population of neurons. Experiments conducted in rats exposed to high doses of pyridoxine (B6), which normally produce a large fiber neuropathy, showed that concomitant administration of NT-3 attenuated pyridoxine-induced impairment in proprioception *(244)*.

***Low Calcium Environment*** Calcium entry into cells is a common feature of experimental models of neurologic injury *(245)*. Wang and colleagues demonstrated that vincristine-induced neuropathy in vitro is a calcium-dependent process, and that there were partial protective effects of a low calcium environment against the axonal degeneration produced by vincristine.

The calcium receptor antagonist nimodipine may have a more fundamental mode of action beyond cerebral vasodilatation, protecting neural tissue exposed to ischemia by limiting cellular calcium overload *(246,247)*. This mechanism may account for the neuroprotective effect against cisplatin neuropathy in the rat model. The results could not be reproduced in humans.

***Recombinant Human Glial Growth Factor 2 (RHGGF-2)*** RHGGF-2, normally released by neurons, is thought to be important for peripheral nerve maintenance in adults. On one hand it acts as a Schwann cell mitogen, and on the other, it stimulates them to secrete neurotrophic factors, enhancing resistance against noxious stimuli. This has led to the speculation that RHGGF-2 may protect against chemotherapy-related neuropathy. In a rat model RHGGF-2 provided full protection against cisplatin-induced deterioration of sensory nerve conduction velocity *(248)*.

***Amifostine*** Amifostine may act as a neuroprotectant in cisplatin-induced neuropathy *(249–251)*. Its metabolite

WR1065 is taken up intracellularly, preferentially by nontumor cells, and protects also against its hematological and renal toxicity. The compound is thought to scavenge oxygen-free radicals, leading to secondary removal of DNA-platinum adducts. In vitro studies have shown that when amifostine (or WR1065) is incubated with CDDP, there is a protective effect against the CDDP-induced decrease in neurite formation *(252)*.

### *Nerve Growth Factor (NGF)*

GENERAL The neurotrophic NGF plays a crucial role in the growth and differentiation of neuronal populations of the PNS *(253,254)* and has been found to reduce neuronal damage in both humans and animal models. Some speculate that the development of chemotherapy-induced neuropathies might be secondary to impaired synthesis or release of NGF *(255)*.

ANIMAL STUDIES In both tissue culture and animal models, NGF has led to dramatic protection against neurotoxicity caused by platinum compounds, the taxanes, alkaloids, and suramin *(156,161,182,256)*.

Hayakawa examined whether various treatment schedules of NGF could prevent chemotherapy-related neurotoxicity, and how the neuroprotective effect of NGF was dependent on the underlying mechanism of neurotoxicity in rats. Three drugs were used: vincristine, paclitaxel, and cisplatin. With vincristine and paclitaxel, an increase in neurite length was observed in all cultures that received NGF, but not in the control cultures without NGF. In the cisplatin group, increase in neurite length was only observed in cultures receiving NGF before or concurrent with chemotherapy. The authors concluded that the preventive effects of NGF on drug-related neuronal damage are dependent on the type of drug rather than on the schedule of NGF treatment *(256)*. In this study vincristine and paclitaxel caused no neuronal changes, contrary to what was observed with CDDP *(257,258)*. These findings suggest that NGF can promote neurite extension and proliferation as long as neurons are kept intact, but that it fails to prevent neuronal death following cisplatin-induced toxic insults.

CLINICAL STUDIES A seminal study evaluated 23 cancer patients receiving neurotoxic agents. Neurological evaluations and serum sampling for NGF were performed before and after chemotherapy. Seventeen of 19 evaluable patients developed peripheral neuropathy. There was a significant decrease of NGF levels in patients after chemotherapy, and a significant correlation between decrease in NGF and increased neurotoxicity after chemotherapy. These observations suggest a possible link between low levels of NGF and the development of neuropathy. The authors also suggest that the decrease in circulating NGF might be one of the mechanisms via which chemotherapeutic agents induce peripheral neuropathy.

***Glutathione (GSH)*** Among the different neuroprotective agents against cisplatin-induced neuropathy, GSH seems to be most promising *(155,259)*. Sensory nerve conduction abnormalities and drug abnormalities induced by cisplatin were less severe after administration of GSH *(155)*. The authors concluded that GSH prevents, to some extent, the neurotoxic effects of CDDP in the DRG, and that it is also probably effective at the level of the peripheral nerve. There was no increased protection with higher doses of GSH, suggesting that GSH may interfere with only some of the mechanisms of CDDP-induced neurotoxicity. GSH may act directly in DRG neurons, or there may be a peripheral uptake with retrograde transport of GSH. Alternatively, GSH might accelerate cisplatin metabolism so that drug exposures are less toxic.

***Antioxidants*** There is some evidence that oxidative stress may be involved in cisplatin neuropathy. Retinoic acid has also been suggested as an antioxidant, but has not been effective in a rat model of cisplatin neurotoxicity *(260)*.

### *Insulin-Like Growth Factor*

GENERAL IGF-I is neurotrophic for a variety of peripheral and central neurons *(261)*. Immunoreactivity has been detected in motor neurons, sensory and autonomic ganglia, skeletal muscle, and brain *(261–263)*. This suggests that IGF-I may be useful to treat vincristine neurotoxicty, where the damage is thought to affect multiple types of neurons.

ANIMAL STUDIES High doses of IGF-1 prevented vincristine-induced histological changes in mice and protected against motor weakness in rats. In vivo, there was no significant effect of rhIGF-1 on the antitumor effect of vincristine *(264)*.

MECHANISM IGF-1 might increase the levels of GAP43 and tubulin mRNA, enhancing neuronal regeneration, and preventing vincristine neuropathy by enhancing the regenerative process *(233)*.

***Prosaptides*** Prosaposin is a neurotrophic factor reported to facilitate sciatic-nerve regeneration after traumatic nerve injury *(229)*. Prosaptides are peptides encompassing the neurotrophic sequences in prosaposin. Animal studies have shown that prosaposin normalized thermal withdrawal times in paclitaxel-treated rats. Prosaptides also attenuated the decrease in the area of substance P-containing neurons in the DRG after sciatic nerve transsection, suggesting that prosaptide may protect substance P neurons from death after injury. Pretreatment with prosaptide prevented paclitaxel-induced thermal hypoalgesia in rats without reducing paclitaxel cytotoxicity *(133)*.

**THERAPY FOR NEUROPATHIES ASSOCIATED WITH CIRCULATING IMMUNOGLOBULINS** Paraneoplastic sensory neuropathy has a poor prognosis. In some cases clinical stabilization may follow successful treatment of the underlying tumor, but the neuropathy ussually progresses despite therapy with steroids, immunosuppressive agents, or plasmapheresis. Cancer patients with sensorimotor neuropathy that resembles the GBS or relapsing CIDP (chronic inflammatory demyelinating polyneuropathy) may respond to immunomodulation or immunosuppression *(88)*. Plasmapheresis (used within seven days of onset, three to five exchanges every other day) or intravenous immunoglobulins (5 d course of iv infusion, 0.4 g/kg body weight/d) are considered equally effective as first-line treatment for GBS-like acute polyneuritis. Prednisone (induction dose 0.5–1 mg/kg for 4–6 wk) is the first choice for CIDP and vasculitic neuropathy. In a minority of cases the chronic neuropathy improves with removal of the neoplasm. Paraprotein-associated polyneuropathy may improve with alkylating agents (intravenous cyclophosphamide at monthly intervals) or chlorambucil (0.1 mg/kg daily), plasmapheresis, or intravenous immunoglobulins (*see* Chapter 26).

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# 16 Central Nervous System Complications of Cancer Therapy

PATRICK Y. WEN, MD

## INTRODUCTION

Recent years have witnessed the introduction of an increasing number of new chemotherapeutic agents to treat patients with cancer. These include not only traditional cytotoxic chemotherapeutic agents, but also hormonal agents, biologic agents, monoclonal antibodies (MAbs), and most recently, small-molecule signal transduction inhibitors. The increasing use of aggressive antineoplastic therapy with potential neurotoxicity, together with improved patient survival, have resulted in central nervous system (CNS) complications occurring with greater frequency in cancer patients.

Conventional cytotoxic agents generally target rapidly dividing cells. In the adult CNS there is usually no active cell turnover with the exception of glia, macrophages, and endothelial cells. In addition, the presence of the blood-brain barrier (BBB) excludes many hydrophilic agents and large molecules *(1)*. As a result the CNS is relatively spared from the neurotoxicity of many of these agents unless the BBB is disrupted, the drug is administered directly into the cerebrospinal fluid (CSF), or the drug is administered in large doses into the cerebral vasculature (e.g., intra-arterial chemotherapy for CNS tumors) *(1)*. With the exception of a few drugs, CNS complications are relatively uncommon and usually reversible when the drug is discontinued. However, some drugs like methotrexate are associated with a relatively high frequency of CNS dysfunction, which may be severe and progressive, especially if the drug is administered after radiation therapy. The development of CNS complications and their severity are dependent on many factors *(1)*. These include the dose, frequency and route of administration of the drug, the age of the patient, the presence of other therapies such as prior or concurrent radiation therapy or chemotherapies (e.g., levamisole administered with 5-FU may be associated with demyelination *[2]*); organ dysfunction, which may affect drug metabolism (e.g., patients with hepatic or renal dysfunction are at increased risk of CNS toxicity from high-dose cytosine arabinoside *[3]*); preexisting CNS lesions or dysfunction; and metabolic abnormalities. Some drugs that do not penetrate into the CNS may produce CNS complications indirectly. For example, L-asparaginase produces a coagulopathy that may result in venous sinus thrombosis *(4)*, while vincristine may cause confusion as a result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) *(5)*.

The precise pathogenesis of many CNS complications is unknown. These complications may result from the direct toxic effects of the drug on the nervous system or indirectly from metabolic abnormalities or cerebrovascular disorders induced by the drugs. Recognition of these complications is important both because they may be confused with metastatic disease, radiation neurotoxicity, paraneoplastic disorders, or opportunistic infections and because discontinuation of the drugs may prevent irreversible injury.

The CNS complications of the more commonly used antineoplastic agents in cancer patients will be discussed (*see* Table 1). This topic is reviewed in greater detail elsewhere *(1,6–14)*.

## DRUGS THAT COMMONLY CAUSE CNS NEUROTOXICITY

**IFOSFAMIDE** This is an alkylating agent that is metabolically activated in the liver to ifosfamide mustard and acrolein. The ifosfamide mustard produces crosslinking of DNA strands. It is an analog of cyclophosphamide, with similar systemic toxicities. Unlike cyclophosphamide, it produces an encephalopathy in 20–30% of patients *(15–17)*. The encephalopathy may include confusion, hallucinations, cerebellar dysfunction, seizures, cranial nerve palsies, extrapyramidal signs, and occasionally coma. The encephalopathy begins hours or days after administration of the drug and usually resolves completely after several days *(18)*. Electroencephalography initially shows mild slowing and then high-voltage rhythmic delta *(19)*. The development of encephalopathy is a relative contraindication

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**Table 1**
**CNS Complications of Cancer Therapy**

| *Acute encephalopathy* | *Seizures* | *Headaches* |
|---|---|---|
| Asparaginase | Amifostine | Asparaginase |
| 5-Azacytidine | Asparaginase | Capecitabine |
| BCNU (IA or HD) | BCNU (IA) | Cisplatin |
| Chlorambucil | Busulfan (HD) | Corticosteroids |
| Cisplatin | Chorambucil | Cytosine arabinoside |
| Corticosteroids | Cisplatin | Danazol |
| Cyclophosphamide | Corticosteroids | Estramustine |
| Cytosine arabinoside (HD) | Cyclophosphamide | Etoposide |
| Dacarbazine | Cytosine arabinoside | Fludarabine |
| Doxorubicin | Dacarbazine | Gemtuzumab (Mylotarg) |
| Etoposide | Etoposide | Hexamethylmelamine |
| Fludarabine | 5-Fluorouracil | Hydroxyurea |
| 5-Fluorouracil | Hexamethylmelamine | Interferons |
| Hexamethylmelamine | Hydroxyurea | Interleukins 1, 2, and 4 |
| Hydroxyurea | Ifosfamide | Levamisole |
| Ifosfamide | Interferon | Mechlorethamine |
| Imatinib (Gleevec) | Interleukin-2 | Methotrexate (IT) |
| Interferons | Letrozole | Octreotide |
| Interleukin-1 and -2 | Levamisole | Opralvekin (Neumega) |
| Mechloramine | Mechloramine | Plicamycin |
| Methotrexate | Methotrexate | Rituximab (Rituxan) |
| Misonidazole | Octreotide | Retinoic acid |
| Mitomycin C | Paclitaxel | SU5416 |
| Paclitaxel | Pentostatin | Tamoxifen |
| Pentostatin | Suramin | Temozolomide |
| Procarbazine | Thalidomide | Thiotepa (IT) |
| Suramin | Vinca alkaloids | Topotecan |
| Tamoxifen | Tenoposide | Tositumomab |
| Thalidomide | | Trastuzumab (Herceptin) |
| Thiotepa (HD) | | ZD1839 (Iressa) |
| Tumor necrosis factor | | |
| Vinca alkaloids | | |
| *Cerebellar syndrome* | *Dementia* | *Vasculopathy and stroke* |
| Cyrosine arabinoside (HD) | BCNU (IA and HD) | Aspaginase |
| 5-Fluorouracil | Carmofur | BCNU (IA) |
| Hexamethylmelamine | Cisplatin | Bleomycin |
| Ifosfamide | Corticosteroids | Carboplatin (IA) |
| Procarbazine | Cytosine arabinoside | Cisplatin |
| Tamoxifen | Fludarabine | Doxorubicin |
| Vinca alkaloids | 5-Fluorouracil | Estramustine |
| | Interferon alpha | 5-Fluorouracil |
| | Levamisole | Methotrexate |
| | Methotrexate | |

(*continued*)

to using the drug again, although some patients have been successfully rechallenged without recurrence of the encephalopathy *(19)*. The encephalopathy is thought to result from accumulation of chloracetaldehyde, one of the breakdown products of ifosfamide. Patients at increased risk for the encephalopathy include those with renal dysfunction, low serum albumin *(20)*, underlying brain disease *(21)*, phenobarbital use *(22)*, prior treatment with cisplatin *(17)*, and previous encephalopathy with ifosfamide *(15)*. There have been reports that methylene blue may be useful in preventing or treating ifosfamide encephalopathy by inhibiting monoamine oxidases *(23,24)*. Benzodiazepines may also produce rapid clinical and electrographic improvement *(25)*. For most patients no specific treatment is necessary, and the encephalopathy usually improves with time. Rarely, the deficits are irreversible *(18)* and deaths have been reported *(26,27)*.

**METHOTREXATE** This is a dihydrofolate reductase inhibitor, which prevents the conversion of folic acid to tetrahydrofolate, required for purine and thymidine synthesis. It inhibits DNA synthesis in the S-phase of the cell cycle and is used in the treatment of a wide range of cancers, including leukemias, lymphomas, choriocarcinoma, breast cancer, CNS lymphoma, and leptomeningeal metastases.

Methotrexate crosses the BBB relatively poorly, but significant CNS concentrations can be achieved when the drug is administered intrathecally or when high intravenous doses are

**Table 1 (continued)**

| *Extrapyramidal syndrome* | *Focal deficits* | *Aseptic meningitis* |
|---|---|---|
| 5-Fluorouracil | BCNU (IA) | Cytosine arabinoside (IT) |
| Hemamethylmelamine | Interleukin-2 | Methotrexate (IT) |
| Interferon alpha | Methotrexate | Levamisole |
| Ifosfamide | Tumor necrosis factor | Thiotepa |
| Cis-retinoic acid | | |
| Vincristine | | |
| *Visual loss* | *Cranial neuropathies* | *Myelopathy* |
| BCNU (IA) | BCNU (IA) | Cisplatin |
| Carboplatin | Cisplatin | Cladribine |
| Chlorambucil | Cytosine arabinoside | Corticosteroids (epidural lipomatosis) |
| Cisplatin (IA) | Ifosfamide | Cytosine arabinoside (IT) |
| Cis-retinoic acid | Methotrexate | Fludarabine |
| Cytosine arabinoside | Vincristine | Interferon alpha |
| Etoposide | | Methotrexate (IT) |
| Fludarabine | *Cortical blindness* | Mitoxantrone (IT) |
| 5-Fluorouracil | Carboplatin | Taxotere (Lhermitte's sign) |
| Interleukin-2 | Cisplatin | Vincristine (IT) |
| Paclitaxel | Methotrexate (HD) | |
| Pentostatin | | |
| Tamoxifen | | |
| Suramin | | |
| Vincristine | | |

HD, high-dose; IT, intrathecal; IA, intraarterial.

used *(8)*. The clinical expression of its neurotoxicity is determined by the dosage, its route of administration, and the use of other therapeutic modalities with overlapping neurotoxicities such as irradiation.

**Intrathecal Methotrexate Toxicity** Aseptic meningitis is the most common neurotoxicity associated with intrathecal methotrexate therapy *(28–30)*. This occurs in approx 10% of patients, although some series have reported incidences as high as 50% *(8,30)*. It usually begins 2–4 h after the drug is injected and may last for 12–72 h. It is characterized by headaches, nuchal rigidity, back pain, nausea, vomiting, fever, and lethargy and is indistinguishable from other types of chemical meningitis. The rapid onset after intrathecal injection argues against iatrogenic bacterial meningitis. The CSF shows a lymphocytic pleocytosis and an elevated protein. The symptoms are usually self-limited and require no specific treatment. Most patients have no sequelae, although rarely this syndrome may lead to delayed leukoencephalopathy *(31)*. Aseptic meningitis can be prevented to some extent by injecting methotrexate with hydrocortisone or using oral corticosteroids. Some patients who developed aseptic meningitis have subsequently received intrathecal methotrexate without problems.

Transverse myelopathy, a much less common complication of intrathecal methotrexate, is characterized by back or leg pain followed by paraplegia, sensory loss, and sphincter dysfunction *(8,32,33)*. The symptoms usually occur between 30 min and 48 h after treatment but may occur up to 2 wk later *(8,33)*. The majority of cases show clinical improvement, but the extent of recovery is variable *(34)*. The pathogenesis is unknown. Pathologically there is vacuolar demyelination and necrosis in the spinal cord without inflammatory or vascular changes *(35)*. This complication is more common in patients receiving concurrent radiotherapy or frequent treatments of intrathecal methotrexate. Rarely, intrathecal methotrexate produces an acute encephalopathy *(31)*, especially if CSF outflow is obstructed *(36)* or the methotrexate is injected directly into cerebral white matter as a result of a misplaced ventricular catheter *(37)*. It can also cause seizures *(38)*, subacute focal neurologic deficits *(39)*, cranial nerve palsies, radiculopathy *(40)*, neurogenic pulmonary edema, and sudden death *(1,13,29)*.

Accidental overdosage of methotrexate (> 500 mg) usually results in myelopathy, encephalopathy, and death *(41)*. The use of rapid CSF drainage, ventriculolumbar perfusion *(42,43)*, carboxypeptidase G2 *(44),* high-dose leucovorin *(45)*, and alkaline diuresis has allowed occasional patients to survive.

**Weekly Low-Dose Methotrexate Neurotoxicity** Up to 25% of patients receiving weekly low-dose methotrexate may experience headaches, dizziness and subtle cognitive impairment *(46)*. These symptoms resolve when the methotrexate is discontinued.

**High-Dose Methotrexate Neurotoxicity** High-dose methotrexate may cause acute, subacute, or chronic neurotoxicity. Acute high-dose methotrexate neurotoxicity is characterized by somnolence, confusion, and seizures within 24 h of treatment. Symptoms usually resolve spontaneously without sequelae and patients can often continue to receive this drug *(8,29,47)*. In children, administration of high-dose methotrexate can produce a reversible acute confusional state and cortical blindness associated with increased T2 signal in the parietal-occipital lobes on magnetic resonance imaging (MRI) *(48)*.

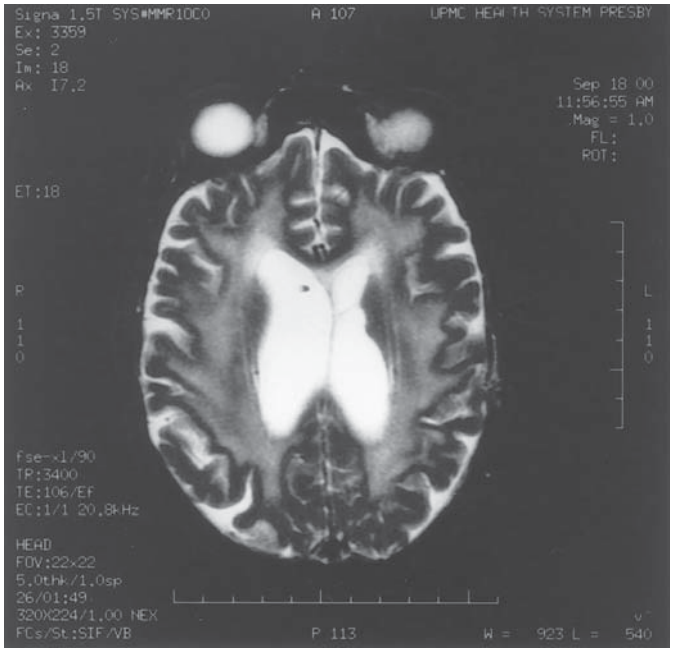


**Fig. 1.** Leukoencephalopathy: A 75-yr-old woman with primary central nervous system lymphoma was treated with CHOP, 10 doses of intraventricular methotrexate, and fractionated whole brain radiotherapy (5040 cGy in 28 fractions). Her tumor responded and never recurred. Three years later, she noted moderate short-term memory deficits and gait unsteadiness. MR scanning (T2-weighted image) demonstrated extensive periventricular white matter changes. The patient's dementia progressed, and she developed rigidity and mutism prior to her death 1 yr later.

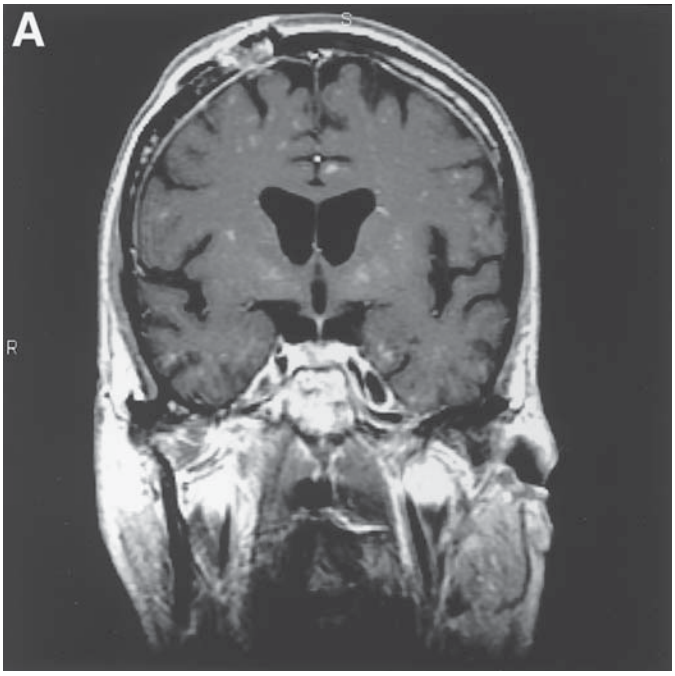


**Fig. 2.** Disseminated necrotizing leukoencephalopathy: This 44-yr-old man with Burkitt's lymphoma developed the acute onset of bihemispheric coma weeks after receiving fractionated radiotherapy to the skull base and eight doses of intraventricular methotrexate for lymphomatous involvement of the right cavernous sinus. Multiple CSF exams demonstrated no leptomeningeal lymphoma despite his neurologic deterioration. Persistent vegetative state ensued, and he died two months later from systemic relapse. MRI demonstrates multiple scattered punctate foci of abnormal signal, particularly in the deep gray nuclei, with contrast enhancement. Postmortem revealed multiple discrete, microscopic foci of demyelination, axonal loss, and necrosis distributed in a random manner throughout the white matter and gray-white interface. The foci contained a moderate to large number of CD68-immunoreactive foamy macrophages and a scant number of perivascular lymphocytes; although there was dural lymphoma, there was no leptomeningeal tumor identified.

These patients all had hypomagnesemia, raising the possibility that the electrolyte abnormality may have been a contributing factor.

Weekly intravenous treatments with moderate to high-dose methotrexate may produce a subacute "stroke-like" syndrome characterized by transient focal neurologic deficits, confusion, and occasionally seizures *(49,50)*. Typically, the disorder develops 6 d after high-dose methotrexate, lasts 15 min to 72 h, and resolves spontaneously without sequelae. Neuroimaging studies are usually normal, although non-enhancing increased T2 lesions in the white mater have been reported *(51)*. CSF is normal but the EEG shows diffuse slowing. Methotrexate may be subsequently administered without the encephalopathy recurring. The pathogenesis of this syndrome is unknown but may be related to reduced cerebral glucose metabolism *(52)* or reduced biogenic amine synthesis *(53)*.

**Chronic Leukoencephalopathy** The major delayed complication of methotrexate therapy is a leukoencephalopathy *(29,54–56)*. Although this syndrome may be produced by methotrexate alone, it is exacerbated by radiotherapy, especially if radiotherapy is administered before or during methotrexate therapy (Figs. 1 and 2). The leukoencephalopathy usually occurs following repeated administration of intrathecal methotrexate or high-dose intravenous methotrexate, but has also been described after standard-dose intravenous methotrexate *(54)*. The development of acute methotrexate neurotoxicity usually does not increase the likelihood of leukoencephalopathy. However, there has been a report of leukoencephalopathy developing in patients with methotrexate-induced aseptic meningitis *(31)*. The gradual development of cognitive impairment months or years after treatment with methotrexate characterizes the clinical picture. Deficits range from mild learning disabilities to severe progressive dementia together with somnolence, seizures, ataxia, and hemiparesis. Children with leukemia treated with intrathecal methotrexate and radiation therapy or high-dose methotrexate show a deterioration in IQ in excess of 15 points *(8,57)*. CT and MR scans show cerebral atrophy and diffuse white matter lesions. CSF may show increased myelin basic protein concentration as a result of myelin breakdown *(58)*. Pathologic lesions range from loss of oligodendrocytes and gliosis to a necrotizing leukoencephalopathy *(54)*. There is demyelination, axonal swelling, dystrophic mineralization of axonal debris, and fibrinoid necrosis of small blood vessels *(8)*. Occasionally children may have a mineralizing microangiopathy, characterized by calcification of capillaries and venules, especially in the basal ganglia *(59)*. The clinical course is variable. Many patients stabilize, but the course is progressive in some patients and may lead to death.

**Table 2**
**CNS Complications of Cisplatin**

| |
|---|
| **Common** |
| Lhermitte's sign |
| Hearing loss |
| Tinnitus |
| **Uncommon** |
| Encephalopathy |
| Seizures |
| Cerebral herniation (related to hydration) |
| Electroyte imbalance (SIADH, low calcium, magnesium, and sodium) |
| Vestibular toxicity |
| Visual loss (optic neuropathy, retinal toxicity, cortical blindness) |

No effective treatment is available. The cause of the leukoencephalopathy is unknown. Possibilities include injury to cerebral vascular endothelium increasing blood-brain barrier permeability, depletion of reduced folates in the brain, inhibition of cerebral glucose or protein metabolism, inhibition of catecholamine synthesis *(8,52)*, or disturbance of myelin metabolism *(60)*. It is possible that cranial irradiation either potentiates the toxic effects of methotrexate or disrupts the BBB, allowing higher concentrations of methotrexate to reach the brain.

**THALIDOMIDE** Thalidomide was introduced in Europe in 1954 as a sedative/hypnotic agent but was withdrawn in 1961 as a result of the high incidence of limb malformations in children of women who took the drug. In 1998, the drug was approved by the FDA for treatment of erythema nodosum leprosum. In preclinical studies, thalidomide has shown potent anti-angiogenic effects. Based on this property, it has been used in clinical trials for multiple myeloma *(61)*, gliomas *(62)*, Kaposi's sarcoma *(63)*, and breast cancer *(64)*. The most common side effect is somnolence, affecting between 43–55% of patients. Many patients develop tachyphylaxis to this side effect and report decreased somnolence after 2 or 3 wk. Seizures have occurred in a minority of patients with gliomas with a history of seizures in the past; the contribution (if any) of thalidomide is uncertain. Thalidomide can also cause neuropathies.

## DRUGS THAT OCCASIONALLY CAUSE CNS NEUROTOXICITY

**CISPLATIN (CIS-DIAMMINEDICHLOROPLATINUM (II), PLATINOL)** Cisplatin is an alkylating agent, producing its cytotoxic effects by forming DNA crosslinks and thereby impairing DNA synthesis and transcription *(65)*. It is used to treat ovarian, germ cell, cervical, bladder, lung, gastrointestinal, and head and neck cancers as well as medulloblastomas. It is detectable in high concentrations in the dorsal root ganglia and peripheral nerves, but only small amounts pass through the intact BBB *(66,67)*. However, CSF penetration may be higher in patients with brain tumors. In one study, intravenous administration of cisplatin resulted in a peak CSF concentration as high as 40% of nonprotein bound cisplatin *(68)*. Despite the poor penetration of cisplatin across the BBB, a number of CNS complications may occur *(66)* (Table 2).

The main neurologic complication of cisplatin is a neuropathy affecting predominantly large myelinated sensory fibers *(69–72)*. This results primarily from injury to the dorsal-root ganglion, although the peripheral nerve may also be affected. There is no treatment for cisplatin neurotoxicity. Ethiofos (WR-2721) *(73)*, amifostine *(74)*, and the ACTH *(4–9)* analog, Org 2766 *(75,76)*, partially protect peripheral nerves from cisplatin neurotoxicity. Arterial infusions of cisplatin in the extremities or neck may produce focal neuropathies. Autonomic neuropathies have also been rarely observed *(8)*. Peripheral neuropathy from cisplatin is discussed fully in Chapter 15.

**Cranial Neuropathies** Cisplatin commonly produces ototoxicity, leading to high-frequency sensorineural hearing loss and tinnitus. The toxicity is due to peripheral receptor (hair) loss in the organ of Corti and is related to dose *(77)*. Audiometric hearing loss is present in 74–88% of patients receiving cisplatin, and symptomatic hearing loss occurs in 16–20% of patients. Cranial irradiation probably increases the likelihood of significant hearing loss *(78)*. Other risk factors include the use of ifosfamide, furosemide, and ototoxic drugs such as aminoglycosides *(77,79)*. Hearing loss tends to be worse in children, although children have a slightly greater ability to improve after the drug has been stopped. Neurotrophin 4/5 enhances the survival of cultured spiral ganglion cells in vitro and may have therapeutic value in preventing cisplatin-induced ototoxicity *(80)*. Cisplatin may also cause a vestibulopathy, resulting in ataxia and vertigo, which may or may not be associated with hearing loss. Affected patients may complain of difficulty walking in the dark, particularly on uneven surfaces. Previous use of aminoglycosides may exacerbate the vestibulopathy *(77,81)*.

Intra-arterial infusion of cisplatin for head and neck cancer produces cranial palsies in approx 6% of patients *(82)*. Intracarotid infusion of cisplatin may also cause ocular toxicity *(83)*, although these complications may also rarely occur after intravenous administration of the drug. Ocular toxicity may include retinopathy, papilledema *(84)*, optic neuritis *(84)*, and disturbed color perception due to dysfunction of retinal cones *(85)*. Other complications of intra-arterial cisplatin include headaches, confusion, and seizures *(86)*.

**Spinal Cord Involvement (Lhermitte's Sign)** This symptom, characterized by paresthesias in the back and extremities with neck flexion, is seen in 20–40% of patients receiving cisplatin. Patients tend to develop this after several weeks or months of treatment. Neurologic exam and MR scans are usually normal. Somatosensory-evoked responses may suggest spinal cord involvement *(87)*. Lhermitte's sign usually resolves spontaneously several months after drug discontinuation *(88,89)*. It is believed to result from transient demyelination of the posterior columns *(79)*. Very rarely, a true myelopathy has been reported *(7,89)*.

**Uncommon Complications** Rarely, cisplatin produces an encephalopathy resulting in seizures and focal neurologic symptoms, including cortical blindness *(8,90–92)*. The encephalopathy is associated with reversible abnormalities in the white matter of the occipital, parietal, and frontal lobes and clinically resembles the reversible posterior leukoencephalopathy syndrome *(91)*. The encephalopathy tends to be more common after intra-arterial administration of the drug *(93)*. It must be distinguished from metabolic encephalopathy resulting

from water intoxication caused by prehydration *(94)*; renal impairment; hypomagnesemia resulting from impaired magnesium absorption in the proximal renal tubule *(95,96)*; hypocalcemia, and SIADH *(97)* that may follow treatment with cisplatin. Cisplatin can also cause late vascular toxicity, resulting in strokes *(8,98,99)*. This usually occurs when cisplatin is administered in combination with other agents. It is unclear whether this toxicity is a direct effect of the drug on endothelial cells, hypomagnesemia-induced vasospasm, coagulopathy, or is attributable to other agents given concomitantly such as bleomycin *(8)*. Another rare complication is loss of taste *(8)*. Cisplatin may also have a long-term effect on cognitive function *(100)*.

**CYTOSINE ARABINOSIDE (CYTARABINE, ARA-C)**

This is a pyrimidine analog, which is converted by deoxycytidine kinase to its active metabolite Ara-CTP. Ara-CTP inhibits DNA polymerase and incorporates itself into the DNA molecule resulting in premature chain termination. It is used in the treatment of leukemias, lymphomas, and leptomeningeal metastases. This agent has little neurotoxicity when used at conventional doses. High doses (3 g/m$^2$ every 12 h) produce an acute cerebellar syndrome in 10–25% of patients *(101–103)*. Patients above the age of 50 *(104)* with abnormal liver or renal function *(3)*, underlying neurologic dysfunction, or receiving more than 30 g of the drug are especially likely to develop cerebellar involvement. Typically, patients develop somnolence and occasionally encephalopathy 2–5 d after completing treatment. Immediately afterwards, patients develop cerebellar signs ranging from mild ataxia to inability to sit or walk unassisted. Rarely, patients experience seizures. Imaging studies may show white matter abnormalities, and later, cerebellar atrophy. CSF is usually normal. The EEG may reveal slowing. The pathologic changes are localized to the cerebellum, where there is widespread loss of Purkinje cells. No specific treatment is available but the drug should be discontinued immediately. In some patients the cerebellar syndrome resolves spontaneously, but it is permanent in others. Avoidance of very high doses of the drug, especially in patients with renal impairment, has led to a decline in the incidence of this syndrome *(105)*.

High-dose cytosine arabinoside occasionally causes encephalopathy, seizures, reversible ocular toxicity *(106)*, lateral rectus palsy, bulbar and pseudobulbar palsy, Horner's syndrome, aseptic meningitis, anosmia, and an extrapyramidal syndrome *(1,8,107,108)*.

Intrathecal administration of cytosine arabinoside produces high levels of drug in the CSF for at least 24 h and is used to treat leptomeningeal metastases. Approximately 10% of patients develop aseptic meningitis *(8)*. Rarely, intrathecal administration causes a transverse myelopathy similar to that seen with intrathecal methotrexate *(109)*. Other complications ranging from uncommon to rare include encephalopathy *(110)*, headaches, seizures *(111)*, and a locked-in syndrome *(8,112)*. The risk of neurotoxicity is increased with higher doses and increased frequency of administration of cytosine arabinoside.

**5-FLUOROURACIL** 5-Fluorouracil (5-FU) is a fluorinated pyrimidine that disrupts DNA synthesis by inhibiting thymidylate synthetase. It is used to treat many cancers, including gastrointestinal, breast, and head and neck cancers. 5-FU readily crosses the BBB, but CNS toxicity is limited primarily to patients who receive high doses of the drug (>15 mg/kg/wk) *(1)*.

An acute cerebellar syndrome occurs in approx 5% of patients *(107,113)*. This usually begins weeks or months after initiation of treatment and is characterized by the acute onset of ataxia, dysmetria, dysarthria, and nystagmus. Neuroimaging and CSF studies are usually normal. The drug should be discontinued in any patient who develops a cerebellar syndrome, and with time these symptoms usually resolve completely. Rechallenge may result in recurrence of the symptoms *(114)*. The development of a cerebellar syndrome may be partly explained by the fact that 5-FU readily crosses the BBB, with the highest concentrations found in the cerebellum. The etiology is unknown, but 5-FU appears to be toxic to Purkinje and granular cells in the cerebellum *(113)*.

5-FU can produce encephalopathies *(115,116)*. This is sometimes associated with hyperammonemia and tends to occur more commonly in patients with dehydration and infections *(117)*. 5-FU can also cause optic neuropathies *(118)*, eye movement abnormalities *(119)*, focal dystonias, cerebrovascular disorders *(120)*, parkinsonian syndromes *(7,121)*, or seizures *(122)*. Intra-carotid infusion of 5-FU may cause somnolence, ataxia, and upper motor neuron signs. Patients with decreased dihydropyrimidine dehydrogenase activity are at an increased for developing severe neurological toxicity following 5-FU chemotherapy *(123)*. The administration of 5-fluorouracil with other drugs may increase the incidence of neurotoxicity. The coadministration of 5-fluorouracil and allopurinol, N-Phosphonoacetyl-L-aspartate (PALA), thymidine, doxifluridine, carmofur, or tegafur has been reported to cause encephalopathies and cerebellar syndromes *(7,124)*.

The combination of 5-FU and levamisole used to treat colon cancer has been rarely associated with the development of an encephalopathy and ataxia resulting from multifocal demyelinating lesions in the periventricular white matter *(2,125,126)*. Biopsy of these lesions shows multifocal demyelination, relative axonal sparing, and perivascular lymphocytic infiltration. The cause of these lesions is unknown, although an immune etiology has been suggested. These lesions usually improve with corticosteroids and discontinuation of the drugs. The importance of recognizing this syndrome is that the cerebral lesions may be mistaken for brain metastases.

**L-ASPARAGINASE** This drug hydrolyses L-asparagine to aspartic acid and ammonia, depleting the extracellular supply of L-asparagine, indirectly inhibiting protein synthesis in tumor cells dependent on asparagine. It is used mainly to treat acute lymphocytic leukemia (ALL). Neurotoxicity with asparaginase is rare, as the agent does not cross the BBB. In early studies, high doses of asparaginase were used and resulted in a reversible encephalopathy in 33–60% of patients *(1,127–129)*. The encephalopathy was possibly related to hepatic toxicity *(128,129)*. L-asparaginase is currently used at much lower doses and encephalopathy is rarely seen.

L-asparaginase also interferes with coagulation, leading rarely to thrombotic or hemorrhagic cerebrovascular complications. It depletes serum levels of several hemostatic factors, including anti-thrombin III, protein C and S, fibrinogen, factors IX and XI, and fibrinolytic enzymes such as plasminogen *(1)*.

The most common cerebrovascular complication is venous sinus thrombosis with cerebral infarction *(4,130,131)*. The sagittal sinus is usually involved but other sinuses may be affected (*see* Fig. 10 in Chapter 31). These complications typically occur after several weeks of treatment. Patients usually present with headaches, seizures, and focal neurologic deficits. There may be papilledema as a result of increased intracranial pressure. MRI may show venous infarction, which is often hemorrhagic, and MR venography demonstrates decreased or absent flow in the affected sinus *(132)*. Computed tomography (CT) scan of the head may show lack of contrast enhancement in the superior sagittal sinus with enhancement of the surrounding dura, giving rise to the "empty delta sign *(133)*." Treatment is controversial but anticoagulation with heparin is generally recommended *(1)*. Others have proposed treatment with fresh frozen plasma *(4)*. Steroids and opioids may be needed to relieve the headache. The prognosis for recovery is generally good *(4)*, although recurrent episodes of venous thrombosis can occur with repeat treatment with L-asparaginase. Rarely, asparaginase can cause seizures *(134)*. The related pegasparaginase has similar neurotoxicity. This drug can also cause lethargy and somnolence.

**PENTOSTATIN (2′-DEOXYCOFORMYCIN)** This adenosine deaminase inhibitor is used for the treatment of a variety of leukemias, including hairy cell leukemia. At low doses lethargy and fatigue are common. Higher doses can cause a severe encephalopathy, seizures, and coma *(10,135)*. Optic neuritis, photophobia, and tinnitus may also occur *(136)*.

## DRUGS THAT RARELY CAUSE CNS NEUROTOXICITY

**ANTHRACYCLINE ANTIBIOTICS (DOXORUBICIN [ADRIAMYCIN], DAUNORUBICIN, EPIRUBICIN, IDARUBICIN, MITOXANTRONE)** Doxorubicin is an anthracycline antibiotic used to treat a variety of cancers including hematogenic malignancies and breast cancer. It can cause arrhythmias and cardiomyopathies, which in turn can result in cerebrovascular complications *(137)*. Doxorubicin in combination with cyclosporine can lead to coma and death *(10)*. Accidental intrathecal injection can cause myelopathy and encephalopathy *(8,138)*. Intracarotid administration of the drug can lead to necrosis and hemorrhagic infarction *(139)*. Idarubicin, epirubicin, and daunorubicin do not appear to be neurotoxic. Mitoxantrone has no neurotoxicity when given intravenously, but may produce a radiculopathy and myelopathy when given intrathecally *(140,141)*.

**AZACYTIDINE** This is used for refractory acute myelogenous leukemia (AML) and myelodysplastic syndrome. It can cause weakness and lethargy.

**BLEOMYCIN SULFATE** This binds to guanosine and cytosine portions of DNA through intercalation mechanisms, as well as cleaving DNA strands via free-radical production. It is used to treat lymphoma, Hodgkin's disease, testicular cancer, and head and neck cancer. When used in combination with cisplatin, it can produce cerebral infarction *(142,143)*.

**BUSULFAN** This is a bifunctional alkylating agent used to treat chronic myelogenous leukemia, and as part of the conditioning regimen for some bone marrow transplantation regimens. The drug has little neurotoxicity at standard doses, but high dose therapy can cause seizures *(144)*.

**CAPECITABINE (XELODA)** This oral pro-drug is metabolized to its cytotoxic form, 5-FU, by the enzyme thymidine phosphorylase and is used to treat breast cancer. Neurologic complications are uncommon, but some patients experience parasthesias, headaches, dizziness, and insomnia.

**CARBOPLATIN** Carboplatin is an alkylating agent used for ovarian, cervical, testicular, lung, and head and neck cancers. Unlike cisplatin, peripheral neuropathy and CNS toxicity occur only rarely at conventional doses. Intra-arterial carboplatin may produce stroke-like syndromes *(145)*, cortical blindness *(146)*, and retinal toxicity *(147)*.

**CHLORAMBUCIL** This is an alkylating agent used for the treatment of chronic lymphocytic leukemia and non-Hodgkin's lymphoma. It usually has little neurotoxicity but can cause encephalopathy, myoclonus *(148,149)*, and seizures when administered in very high doses *(150,151)*. Ocular toxicity, including keratitis, retinal edema, and hemorrhages have also been described following oral administration of chlorambucil *(152)*.

**CLADRIBINE (2-CHLORDEOXYADENOSINE)** This drug inhibits DNA polymerase and ligase and ribonucleotide reductase, resulting in DNA strand breakage. It is used for hairy cell leukemia, low-grade non-Hodgkin's lymphoma, chronic myelogenous leukemia (CML), and Waldenstrom's macroglobulinemia. It has little neurotoxicity at conventional doses but can produce a paraparesis at high doses *(153)*.

**CYCLOPHOSPHAMIDE (CYTOXAN)** Standard-dose cyclophosphamide has little neurotoxicity. High-dose cyclophosphamide has produced reversible visual blurring, dizziness, and confusion *(8)*. Its metabolite, 4-hydroperoxyxyclophosphamide, is used experimentally as intrathecal therapy for leptomeningeal metastases. At high doses it can cause lethargy and seizures *(154)*.

**DACARBAZINE (DTIC)** This is used to treat melanoma. Neurotoxicity is very rare but seizures, encephalopathy, and dementia have been reported *(155)*.

**ESTRAMUSTINE (ESTRACYTE, EMCYT)** This is an estradiol molecule linked to a nor-nitrogen mustard. It has estrogenic effects as well as causing dissociative effects on microtubules leading to metaphase arrest. It is used to treat advanced prostate carcinoma. It has been associated with headaches and cerebrovascular events *(153)*.

**ETOPOSIDE (VP-16)** This is a topoisomerase II inhibitor used in the treatment of lung cancer, germ cell tumors, and refractory lymphoma. It does not readily penetrate the BBB and generally has little neurotoxicity, even in high doses. Rarely it can cause a peripheral neuropathy, mild disorientation, seizures, transient cortical blindness, or optic neuritis *(7,156)*.

**FLUDARABINE (FLUDARA)** Fludarabine, an inhibitor of DNA polymerase and ribonucleotide reductase, is used to treat chronic lymphatic leukemia (CLL), macroglobulinemia, and indolent lymphomas. Neurotoxicity is uncommon and appears to be dose-related. Over one-third of patients receiving more than 96 mg/m$^2$/d of intravenous fludarabine develop severe neurotoxicity, while fewer than 0.5% of patients receiving standard doses of fludarabine (<40 mg/m$^2$/d) develop neurologic complications *(135)*. At low doses fludarabine can

produce headaches, somnolence, confusion, and paresthesias *(8,135,157,158)*. Patients with mild neurologic complications usually improve when the drug is discontinued, but some patients have permanent deficits *(1)*. At high doses, fludarabine can cause a delayed progressive encephalopathy with visual loss, tremor, ataxia, seizures, paralysis, and coma *(135,159,160)*. Some of these patients progress to a persistent vegetative state and occasionally death. Patients may also develop a severe myelopathy, leading to quadriparesis. MRI may show diffuse or multifocal areas of nonenhancing, increased T2 signal in the white matter and brain stem *(135,157)*. Pathologically there is multifocal demyelination and necrosis *(158)*.

**GEMCITABINE** This is a deoxycytidine analog used for the treatment of pancreatic cancer, but it also has activity against other tumors, including breast cancer and lung cancer. Neurotoxicity is very uncommon, and usually involves the peripheral nervous system (PNS). Administration of gemcitabine after radiation therapy for brain metastases may increase the risk of neurotoxicity (Melinda Jeter, personal communication).

**HEXAMETHYLMELAMINE (ALTRETAMINE)** This is probably an alkylating agent with activity against ovarian cancer, lymphoma, and lung cancer. It can produce headaches, encephalopathy, absence seizures, tremor, ataxia, and parkinsonism. These neurologic complications appear to be dose-related and are usually reversible *(1,8)*.

**HYDROXYUREA** This is an antimetabolite used to treat resistant CML and certain solid tumors including melanoma, ovarian carcinoma, trophoblastic neoplasms, meningiomas, and cervical, head and neck, and prostate cancers. Rarely, it causes headaches, drowsiness, hallucinations, confusion, and seizures *(8)*.

**IRINOTECAN (CAMPTOSAR, CPT-11)** This is a topoisomerase inhibitor used to treat colon cancer. Severe neurologic toxicity has not been observed, but some patients experience transient visual disturbances and symptoms suggestive of cholinergic overactivity *(10)*.

**LEVAMISOLE (ERGAMISOL)** This is an immune-enhancer, which is used in combination with 5-FU for patients with colon cancer. A metabolite, p-hydroxy-tetramisole, may enhance 5-FU activity by inhibiting tyrosine phosphatase. When used in combination with 5-FU it can cause a multifocal leukoencephalopathy *(2,125,126)*. Levamisole alone can rarely cause headache, insomnia, dizziness, seizures, and aseptic meningitis *(10)*.

**MECHLORETHAMINE (NITROGEN MUSTARD)** This alkylating agent is used to treat Hodgkin's disease and malignant pleural effusions. Rarely, it causes sleepiness, headaches, weakness, hearing loss, and encephalopathy *(8)*. At high doses used for bone marrow transplantation it has been reported to cause confusion and seizures *(161)*. Intra-carotid administration produces uveitis and cerebral necrosis *(1,8)*. Advanced age and concomitant use of cyclophosphamide or procarbazine are associated with an increased risk of neurotoxicity.

**MITOMYCIN C** This is an alkylating agent used to treat carcinomas of the gastrointestinal tract, breast cancer, and head and neck malignancies. It has been associated with an encephalopathy caused by thrombotic microangiopathy *(143)*.

**NITROSOUREAS** The nitrosoureas (BCNU, CCNU, PCNU, ACNU) are lipid-soluble alkylating agents that rapidly cross the BBB and are used to treat brain tumors, melanoma, and lymphoma. These drugs generally have little neurotoxicity when used at conventional doses. Rarely, patients may experience confusion, lethargy, and ataxia. In contrast, high-dose intravenous BCNU used in the setting of autologous bone marrow transplantation can cause an encephalomyelopathy and seizures, which develop over a period of weeks to months after the administration of the drug *(162)*.

Intra-arterial BCNU produces ocular toxicity and neurotoxicity in 30–48% of patients *(163,164)*. Patients often complain of headache and eye and facial pain; retinopathy and blindness may occur. The neurotoxicity includes confusion, seizures, and progressive focal neurologic deficits. Imaging and pathologic studies show findings similar to radiation necrosis confined to the vascular territory perfused by the BCNU *(8)*. Concurrent radiotherapy increases the neurotoxicity of intracarotid BCNU *(165)*. Injection of the drug above the origin of the ophthalmic artery reduces the incidence of ocular toxicity but increases the neurotoxicity.

Gliadel is a biodegradable polymer impregnated with BCNU, which is directly implanted into the resection cavity at the time of surgery for malignant gliomas. At standard doses it has little neurotoxicity, but at high doses, local neurotoxicity can occur.

**OXALIPLATIN** This is a third-generation platinum complex that has activity against cisplatin-resistant tumor cells in vitro *(65)*. Its main use has been in the treatment of colon cancer. A peripheral neuropathy is the dose-limiting toxicity *(166,167)*. Rarely it may cause visual disturbance.

**PLICAMYCIN (MITHRAMYCIN)** This is used to treat refractory hypercalcemia and the blast crisis of CML. It may cause headaches, lethargy, and irritability. These side effects tend to be dose-dependent.

**PROCARBAZINE (MATULANE)** This is a weak monoamine oxidase inhibitor that probably acts as an alkylating agent. It is used to treat lung carcinoma, lymphoma, and brain tumors. At normal oral doses it can cause a mild reversible encephalopathy, and rarely psychosis and stupor *(7,8,168)*. The incidence of encephalopathy may be increased in patients receiving "high-dose" procarbazine, CCNU, and vincristine (PCV) chemotherapy for malignant gliomas *(169)*. Procarbazine also potentiates the sedative effects of narcotics, phenothiazines, and barbiturates. Intravenous and intracarotid procarbazine produce a severe encephalopathy.

**PYRAZOLONACRIDINE (PZA)** This is a DNA intercalating agent with activity against a variety of solid tumor cells lines. In Phase I studies, neurotoxicity was dose-limiting. The complications seen included neuropsychiatric symptoms (restlessness, agitation, anxiety, personality changes, nightmares), motor symptoms, myoclonus, and dizziness *(170,171)*.

**RETINOIC ACID** All-trans-retinoic acid (Tretinoin [Vesanoid]) and 13-cis-retinoic acid (Isoretinoin [Accutane]) are vitamin A derivatives, which induce differentiation in some tumors. They readily cross the BBB. Headaches are a common complication with both drugs *(172)*. All-trans-retinoic acid, which is used to treat promyelocytic leukemia, can rarely cause

pseudotumor cerebri *(173)* and multiple mononeuropathies *(174)*. Cis-retinoic acid has been reported to cause oculogyric crisis in a patient *(175)*. Abnormal color vision and transient blindness may also rarely occur.

**SURAMIN** Suramin inhibits the binding of a number of growth factors to their receptors, including platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and transforming growth factor beta (TGF-β). It also inhibits DNA polymerases and glycosaminoglycan catabolism. Suramin is used mainly for the treatment of refractory prostate cancer. It causes a severe peripheral neuropathy in 10% of patients *(176,177)*. Visual changes have been reported in 7–9% of patients *(178)*. Suramin can also cause mood changes, confusion, encephalopathy, ototoxicity, and seizures.

**TAXANES: PACLITAXEL (TAXOL) AND DOCETAXEL (TAXOTERE)** These are promising agents used to treat a variety of cancers including ovary, breast, and nonsmall cell lung cancers. They contain a plant alkaloid that inhibits microtubule function, leading to mitotic arrest *(179–181)*. Paclitaxel is also a radiation sensitizer *(182)*. Its main toxicity is a dose-limiting, predominantly sensory peripheral neuropathy, which occurs in 60% of patients receiving 250 mg/m$^2$ of the drug *(183)* (*see* Chapter 15). Since paclitaxel does not cross the BBB to any significant degree *(184)*, CNS toxicities are rare. The most common CNS complications are visual disturbances, including transient scintillating scotomas during infusion of the drug and visual loss. The visual loss may be a result of involvement of the optic nerves, as visual evoked potentials are abnormal. Most patients eventually recover, although visual loss can be permanent *(185)*. Rarely, paclitaxel causes seizures or transient encephalopathies *(186–188)*, perioral numbness, or phantom limb pain in patients with prior amputation *(189)*. High-dose paclitaxel (>600 mg/m$^2$) can lead to an acute encephalopathy and death between 7 and 23 d after treatment *(190)*. Neuropathies are less common with docetaxel but some patients develop sensory and motor neuropathies similar to paclitaxel *(191,192)*. Docetaxel can occasionally produce Lhermitte's sign *(193)*.

**TEMOZOLOMIDE (TEMODAR)** This is an alkylating agent related to imidazotetrazines with activity against malignant gliomas and melanoma. Forty percent of patients receiving the drug experience headaches, although serious neurologic complications are rare *(194)*.

**TENOPOSIDE (VM-26)** This is a topoisomerase inhibitor used for ALL, Kaposi's sarcoma, and cutaneous T-cell lymphoma. It has rarely been associated with fatigue, somnolence, and seizures *(136)*.

**THIOGUANINE (6-TG)** This antimetabolite is used to treat leukemia. It does not readily cross the BBB and generally has little neurotoxicity. Rarely, it causes ataxia or an encephalopathy associated with hepatic toxicity *(8)*.

**THIOTEPA (THIOPLEX)** This is an alkylating agent occasionally used to treat leptomeningeal metastases. Intrathecal thiotepa can cause aseptic meningitis, and very rarely, a myelopathy *(195)*. Both thiotepa and its metabolite, TEPA, are lipid soluble and readily cross the BBB. High intravenous doses of thiotepa can produce an encephalopathy that can be fatal *(10)*.

**TOPOTECAN (HYCAMTIN)** This is a topoisomerase I inhibitor used in ovarian cancer, nonsmall cell lung cancer and Ewing's sarcoma. It can occasionally cause headaches and parasthesias.

**VINCA ALKALOIDS: VINCRISTINE (ONCOVIN), VINBLASTINE (VELBAN), VINDESINE AND VINORELBINE (NAVELBINE)** These agents bind to tubulin and prevent microtubule formation, thereby arresting cells in metaphase *(8)*. Vincristine is a vinca alkaloid derived from the periwinkle plant used to treat many cancers, including leukemia, lymphomas, sarcomas, and brain tumors. Its main toxicity is an axonal neuropathy resulting from disruption of the microtubules within axons and interference with axonal transport (*see* Chapter 15).

Vincristine occasionlly produces cranial neuropathies. The most common nerve to be involved is the oculomotor nerve, resulting in ptosis and ophthalmoplegia. Other nerves that may be involved include the optic nerve *(196)*, recurrent laryngeal nerve, facial nerve, and auditory nerve. Vincristine may also cause retinal damage and night blindness. Some patients may experience jaw and parotid pain.

CNS complications are rare as vincristine penetrates the BBB poorly. Accidental administration of vincristine into the CSF produces a rapidly ascending myelopathy, coma, and usually, death *(197–199)*. Rarely, vincristine may cause SIADH, resulting in hyponatremia, confusion, and seizures *(5)*. CNS complications unrelated to SIADH may also occur, including seizures *(200)*, encephalopathy, transient cortical blindness *(201)*, ataxia, athetosis, tremor, and parkinsonism *(1,7,8)*.

The related vinca alkaloids vindesine, vinblastine, and vinorelbine tend to have less neurotoxicity. This may be related to differences in lipid solubility, plasma clearance, terminal half life, and sensitivities of axoplasmic transport *(7,8)*. Vinorelbine is a semisynthetic analogue of vinblastine that is being increasingly used for patients with breast and lung cancer. Like vincristine, vinorelbine inhibits microtubule assembly but has less affinity for neural tissue and is less neurotoxic.

## HORMONAL THERAPY

**AMINOGLUTETHIMIDE** This inhibits the synthesis of steroid hormones and is used to treat breast carcinoma, adrenocortical carcinoma, and ectopic Cushing's disease. It frequently causes mild lethargy, and rarely causes vertigo and ataxia *(136)*.

**ANASTROZOLE (ARIMIDEX)** This is a selective nonsteroidal aromatase inhibitor (inhibitor of estrogen) used for postmenopausal women with hormone receptor-positive advanced breast cancer. It can cause weakness and back pain.

**CORTICOSTEROIDS** Corticosteroids are frequently used in cancer patients for a variety of reasons. They reduce peritumoral edema in patients with primary and secondary brain tumors and spinal cord edema in patients with epidural spinal cord compression. Corticosteroids have a direct cytolytic effect against neoplastic lymphocytes and are used in the treatment of leukemias and lymphomas. High-dose corticosteroids are frequently given with chemotherapy to reduce nausea and vomiting, whereas low doses are used to improve the appetite and sense of well-being in some cancer patients.

The side effects of prolonged steroid therapy are well known and are reviewed thoroughly in Chapter 3 and elsewhere

**Table 3**
**CNS Complications of Corticosteroids**

| *Common* | *Uncommon* |
|---|---|
| Visual blurring | Psychosis |
| Behavioral changes | Hallucinations |
| Tremor | Hiccups |
| Insomnia | Dementia |
| Reduced taste and olfaction | Seizures |
| Cerebral atrophy | Epidural lipomatosis |

*(12,202)*. The incidence of complications increases with higher doses and prolonged therapy, but individual susceptibility varies significantly.

One of the most common neurologic complication of corticosteroids is myopathy *(203)*, but CNS complications also occur frequently (Table 3). Corticosteroids often produce alterations in mood *(204,205)*. An improved sense of well-being, anxiety, irritability, insomnia, difficulty concentrating, and depression are all relatively common. Occasionally, patients may develop "steroid psychosis" *(206)*. This usually takes the form of acute delirium, but the manifestations may resemble mania, depression, or schizophrenia. Other common neurologic complications of corticosteroids include tremors, visual blurring, reduced sense of taste and smell, and cerebral atrophy on neuroimaging studies. Rare complications include hiccups *(207)*, dementia, seizures, and cord compression as a result of epidural lipomatosis *(12,208)*.

Steroid withdrawal can also produce a variety of symptoms, which can be quite disabling. These include headaches, lethargy, nausea, vomiting, anorexia, in addition to systemic symptoms such as myalgia, arthralgia, and postural hypotension. Rarely pseudotumor may occur.

**DANAZOL (DANOCRINE)** This suppresses the pituitary-ovarian axis. It also has weak antiandrogenic activity. It is rarely used to treat endometrial cancer. It can cause headaches, somnolence, and irritability.

**GOSERELIN (ZOLADEX)** This is an analog of luteinizing hormone-releasing hormone used to treat prostate and breast cancer. When the drug is first used it can produce a tumor flare, resulting in bone pain and potentially exacerbating cord compression.

**LETROZOLE (FEMARA)** This is a nonsteroidal aromatase inhibitor (inhibitor of estrogen synthesis) used in breast cancer. It can cause headaches, insomnia, and arthralgias.

**LEUPROLIDE ACETATE** This is a gonadotropin-releasing hormone analogue used to treat prostate cancer and refractory breast cancer. Neurologic complications are uncommon, but it can cause headaches, dizziness, and paresthesias. Bone pain and cord compression may initially worsen when the drug is first used. This flare can be prevented by concurrent use of an antiandrogen such as flutamide *(8)*.

**MITOTANE (OP'-DDD)** This drug, which suppresses adrenocorticosteroid production and is cytotoxic to adrenal cortical cells, is used to treat adrenocortical carcinoma. It produces lethargy, sedation, and dizziness in up to 40% of patients *(209)*.

**OCTREOTIDE (SANDOSTATIN)** This long-acting analogue of somatostatin is utilized for carcinoid tumors, vasoactive intestinal peptide-secreting tumors, and certain pituitary adenomas. It can cause headaches, dizziness, and rarely seizures.

**TAMOXIFEN** This is an antiestrogen used to treat breast cancer and high-grade gliomas. The most common neurotoxicity is a reversible retinopathy and keratopathy *(210–212)*. Patients experience decrease visual acuity and examination may show retinal edema. Rarely, optic neuritis may occur *(213)*. It can also produce an encephalopathy *(214)* and ataxia *(215)*, especially when used in high doses *(8)*. Mild headaches occur fairly frequently, and tamoxifen can exacerbate migraines. It can also cause depression, irritability, insomnia, poor concentration *(8)*, and a radiation recall syndrome *(216)*. Tamoxifen is associated with an increased incidence of systemic vascular thrombosis, but there is no definite evidence that it is associated with an increased risk of cerebrovascular disease *(217)*. Other antiestrogens and antiandrogens such as leuprolide and flutamide are usually not associated with neurotoxicity, although some patients may experience headaches.

**TOREMIFENE CITRATE (FARESTON)** This is an antiestrogen used to treat breast cancer. Neurologic complications are uncommon but patients may experience dizziness, depression, tremor, blurred vision, and ataxia.

## BIOLOGIC AGENTS

In recent years there has been increasing interest in the use of biologic agents for the treatment of cancers. Frequently, they are used in combination with conventional chemotherapeutic agents.

**ALPHA INTERFERON** This is a glycoprotein cytokine with antiviral, cytotoxic and immunomodulatory activities. It is used therapeutically in a number of cancers including hairy cell leukemia, Kaposi's sarcoma, CML, non-Hodgkin's lymphoma, melanoma, renal cell carcinoma, and myeloma. Systemic toxicities include flu-like symptoms and myelosuppression. The flu-like symptoms, which include lethargy and headaches, tend to be worse at the onset of therapy and usually improve with time. Neurotoxicity tends to be dose-related. It is generally mild when low doses of alpha interferon (IFN-$\alpha$) are used as adjuvant therapy in patients with malignant melanoma *(218)*. At higher doses, IFN-$\alpha$ can cause headaches, confusion, lethargy, hallucinations, and seizures *(219–221)*. These effects are more common in older patients *(222)*. Neuroimaging studies are usually normal. EEG may show diffuse slowing *(223)* and rarely, epileptiform activity *(224)*. These neurotoxicities are usually reversible, but occasionally a permanent dementia or a persistent vegetative state may result *(220,221)*. Rarely, IFN-$\alpha$ has been associated with oculomotor palsy, visual hallucinations, retinopathy *(225,226)*, parkinsonism *(1)*, and spastic diplegia *(227)*.

Recently, a high incidence of neuropsychiatric toxicity has been noted in patients treated with recombinant IFN-$\alpha$-2b. In a study of 91 patients with CML, one-quarter experienced grade 3 or 4 neuropsychiatric toxicity that affected daily functioning. All patients recovered upon withdrawal of IFN-$\alpha$-2b. Patients

with a psychiatric history were more likely to develop severe neuropsychiatric toxicity than patients without a psychiatric history *(228)*.

Intrathecal administration of IFN-α has been evaluated for the treatment of meningeal and brain tumors, multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and progressive multifocal leukoencephalopathy. An acute reaction is usually seen within hours of the first injection and consists of headache, nausea, vomiting, fever, and dizziness. The symptoms usually resolve over the next 12–24 h. A severe encephalopathy develops in a significant number of patients within several days of the onset of treatment. This is dose-dependent and tends to be worse in patients who have received cranial irradiation *(4,220)*. The mechanism of interferon neurotoxicity is unknown, but may include induction of neurotoxic cytokines and competition with naturally occurring neurotrophic hormones and opioids *(1)*.

**BETA AND GAMMA INTERFERON (IFN-β/IFN-Γ)** These have neurotoxicities similar to IFN-α, although IFN-β appears to be better tolerated *(14)*.

**INTERLEUKIN-1 (IL-1)** This can cause headache, encephalopathy, and seizures *(10)*. The headaches and encephalopathy are usually mild and dose-dependent.

**INTERLEUKIN-2 (ALDESLEUKIN, PROLEUKIN, IL-2)** This is a glycoprotein released during T-cell activation. It has been used alone or in combination with lymphokine-activated killer (LAK) cells and tumor-infiltrating lymphocytes for the treatment of a number of cancers, including renal cell carcinoma and melanoma. Neuropsychiatric complications occur in 30–50% of patients *(14,229)*. These include cognitive changes, delusions, hallucinations, and depression. Rarely, a severe encephalopathy and coma may result *(230)*. In addition there have been reports of transient focal neurologic deficits. These include monocular blindness and homonymous hemianopia *(231)*, aphasia, hemiparesis, hemisensory loss, seizures, and encephalopathy *(232)*. MRI may show multiple cortical and subcortical areas of increased T2 signal, which may improve over time *(232,233)*. CSF is usually normal *(232)*. IL-2 can also cause a fatal acute leukoencephalopathy *(234)*. Administration of IL-2 into the tumor bed for the treatment of gliomas can produce significant cerebral edema by increasing capillary permeability *(235)*. Intraventricular administration of IL-2 for leptomeningeal metastases may cause a progressive subcortical dementia due to diffuse leukoencephalopathy *(236)*. The MRI shows multiple white matter lesions.

One case of grade 5 neurotoxicity has been reported in a patient treated with IL-2 and granulocyte-macrophage-colony stimulating factor (GM-CSF). This patient experienced a fatal cerebral hemorrhage associated with thrombocytopenia, leading the authors to recommend extreme caution in using these agents together *(237)*.

The mechanism of neurotoxicty of IL-2 is unknown. It stimulates the production of a number of cytokines, including tumor-necrosis factor (TNF), which may be toxic to neurons and glia. It also stimulates the release of neuroendocrine hormones, which could also contribute to the encephalopathy *(1)*.

**INTERLEUKIN-4** This has been associated with headaches.

**TUMOR NECROSIS FACTOR** This cytokine can cause encephalopathy, transient aphasia, or other focal deficits when administered systemically *(10)*.

## GROWTH FACTORS

**COLONY-STIMULATING FACTORS (GRANULOCYTE COLONY-STIMULATING FACTOR [FILGASTRIM, NEUPOGEN], GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR [SARGRAMOSTIM, LEUKINE, PROKINES])** These are used to increase the granulocyte count and reduce the incidence of infections in patients with nonmyeloid tumors receiving chemotherapy. Rarely, they cause fatigue and headaches. GM-CSF has also been reported to cause confusion.

**ERYTHROPOIETIN (PROCRIT, EPOGEN)** This is used to stimulate red cell production. Some patients may experience fatigue, dizziness, and paresthesias, but serious neurologic complications have not been described.

**OPRELVEKIN (NEUMEGA)** This is a platelet growth factor used to prevent severe-chemotherapy induced thrombocytopenia. Neurologic complications are uncommon but some patients complain of headaches, dizziness, insomnia, and parasthesias.

## MONOCLONAL ANTIBODIES

**GEMTUZUMAB OZOGAMICIN (MYLOTARG)** Gemtuzumab ozogamicin (Mylogarg) is an antibody targeted chemotherapeutic agent used in patients with CD33+ acute myelogenous leukemia. It can cause headaches and dizziness.

**RITUXIMAB (RITUXAN)** Rituximab (Rituxan) is a genetically engineered chimeric murine/human monoclonal antibody (MAb) directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. It is used for the treatment of low-grade or follicular B-cell lymphoma. Neurologic complications are uncommon but some patients complain of headaches, myalgia, dizziness *(238,239)*, or paresthesiae *(240)*.

**IODINE-131 TOSITUMOMAB** This is a radiolabeled immunoglobulin G-2a murine MAb directed against the CD20 antigen. In addition to the cytotoxic effects induced by the antibody, the presence of iodine-131 results in focused targeting of beta radiation to the tumor and surrounding tissue. To date, it has been primarily used to treat relapsed or refractory non-Hodgkin's lymphoma. Iodine-131 tositumomab is well-tolerated. A minority of patients experience headache or myalgia and a few develop hypothyroidism *(241,242)*.

**TRASTUZUMAB (HERCEPTIN)** This is a humanized anti-p185 HER-2/MAb used alone or in combination with chemotherapeutic agents in patients with HER2–neu-overexpressing metastatic breast cancer *(243)*. Rarely, patients will experience headaches, dizziness, and insomnia after infusion of the antibody *(244)*.

## SMALL MOLECULE INHIBITORS

**IMATINIB (STI-571, GLEEVEC)** Imatinib is a protein-tyrosine kinase inhibitor that potently inhibits the Abl tyrosine kinase and the receptors for platelet-derived growth factor (PDGF) and stem cell factor, c-kit. STI-571 has been shown to

have significant activity in patients with CML *(245,246)* and c-kit expressing gastrointestinal stromal tumors *(247)*. CNS side effects are uncommon but there have been isolated reports of patients with confusion and papilledema.

**R115777 (ZARNESTRA)** This is a methyl-quinolone, which is a selective inhibitor of farnesyl transferase. It is currently being evaluated in Phase II trials in a variety of cancers. It can cause a peripheral neuropathy. CNS complications are uncommon but some patients experience lethargy.

**SU5416** This is an inhibitor of vascular endothelial growth factor (VEGF). It frequently causes migraines.

**ZD 1839 (Iressa)** This is an epidermal growth factor receptor (EGFR) inhibitor being evaluated in Phase II studies. It can cause headaches and visual loss.

## OTHER AGENTS

**AMIFOSTINE (ETHYOL)** This is a thiophosphate cytoprotectant agent, which is used to reduce renal toxicity associated with cisplatin. There is also evidence that it may also reduce the neurotoxicity of many chemotherapeutic agents, including cisplatin *(248)*. Neurologic complications are uncommon, but amifostine may cause hypotension and lead to syncope; there have been rare reports of seizures.

**DENILEUKIN DIFITOX (ONTAK)** Denileukin difitox (Ontak) is a fusion toxin used to treat cutaneous T-cell lymphoma expressing the CD25 component for the IL-2 receptor. The most common complication is a vascular leak syndrome but some patients experience myalgias, dizziness, parasthesias, nervousness, confusion, and insomnia.

**PAMIDRONATE (AREDIA)** This is a bisphosphonate used to treat hypercalcemia and bony metastases. Approximately 2% of patients experience insomnia, sleepiness, or abnormal vision *(136)*.

**ZOLEDRONIC ACID (ZOMETA)** This is a potent biphosphonate used to treat bony metastases and tumor-induced hypercalcemia. CNS complications are uncommon and similar to those of pamidronate.

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# 17 Neurologic Complications of Hematopoietic Stem Cell Transplantation

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## INTRODUCTION

Bone marrow (hematopoietic stem cell) transplantation (BMT or HSCT) can be broadly defined as infusion of bone marrow or peripheral blood cells in a properly prepared (conditioned) patient. It is estimated that annually 30,000–40,000 HSCT are performed worldwide due to better availability of suitable donors. Some of the indications are well defined and more widely accepted. HSCT is now a common procedure to treat hematologic malignant disorders thought to be largely incurable. HSCT also has potential use for a number of solid neoplasms and non-neoplastic disorders *(1)*.

Of considerable interest to the neurologist is the recent exploration of HSCT for disorders such as multiple sclerosis *(2–6)*, primary systemic amyloidosis with peripheral nerve involvement *(7,8)*, primary brain tumors *(9–11)*, Alexander's disease *(12)*, and even traumatic brain injury *(13)*. These indications are currently experimental, and without a strong basis to conclude a beneficial effect.

A detailed description of the various types of HSCT is beyond the scope of this chapter, and the reader is referred to other texts *(1,14)*. Three types of bone marrow transplants are in vogue: allogeneic bone marrow transplant (bone marrow from HLA-matched sibling or unrelated donor obtained under general anesthesia); allogeneic peripheral blood stem cell transplant (mobilizing stem cells in donor using granulocyte colony-stimulating factor); and autologous bone marrow transplant or, more popular now, peripheral blood stem cell transplant (patient's own bone marrow or peripheral blood stem cells, same procedure as allogeneic but no graft-vs-host disease prophylaxis). Graft-vs-host disease (attack of donor lymphocytes on recipient's tissue) prophylaxis often involves use of cyclosporine and methotrexate. Pertinent to the current topic is the fact that autologous HSCT generally is associated with a lower frequency of complications and therefore lower morbidity and mortality rates than allogeneic HSCT. Another advantage of autologous HSCT is that it may be carried out in elderly patients (> 65 yr). The advantages of allogeneic HSCT (marrow does not contain tumor cells; donor cells may have anti-tumor effect, so-called graft-vs-tumor effect) need to be weighed against the risk of graft-vs-host disease (GVHD). Medications used for GVHD prevention are also causes of neurological complications for the first 6–12 mo posttransplantation.

With an annual growth rate of 10–20% for HSCT procedures performed worldwide, mostly for hematologic cancer (Table 1), an increasing number of neurological complications is expected. Typically neuro-oncologists are peripheral to the decision-making process of bone marrow transplantation but sometimes have become involved when risk factors for development of neurologic complications are deemed high. However, neuro-oncologists' experience with management of cancer patients gives them an important role when neurologic complications emerge after HSCT.

## OVERVIEW OF NEUROLOGIC COMPLICATIONS IN HSCT

Table 2 provides a summary of recent series of neurological complications in HSCT patients. These data should be interpreted with caution. The current literature has tracked only a fraction of the performed transplants, and it includes experiences (and perhaps disasters) from the earlier days of transplantation.

In most clinical series, encephalopathy predominates, followed by central nervous system (CNS) infections and cerebrovascular disorders. It is telling that peripheral nervous system (PNS) disorders are less common. In neuropathological series *(21,22)*, cerebrovascular complications are most commonly found, followed by (opportunistic) infections. The discrepancy in prevalence with the clinical series is due to inclusion of encephalopathies which are less life-threatening and, if resulting in death, may leave relatively few if any neuropathological marks. More frequent use of newer diagnostic modalities may also have an effect on incidence rates. Allogeneic HSCT has generally been reported to lead to more

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**Table 1**
**Malignant Diseases Treated with Hematopoietic Stem Cell Transplantation**

- Acute myeloblastic leukemia
- Acute lymphoblastic leukemia
- Chronic myelogenous leukemia
- Chronic lymphocytic leukemia
- Myelodysplastic syndrome
- Non-Hodgkin lymphoma
- Hodgkin's disease
- Hairy cell leukemia
- Neuroblastoma
- Carcinoma of the breast
- Amyloidosis

frequent neurological complications than autologous HSCT *(15,23)*. Graus and co-authors have found more hemorrhagic CNS complications in autologous HSCT than in allogeneic HSCT patients, and more CNS infections and treatment related complications in allogeneic HSCT. Subdural hematomas were common in patients treated with autologous BMT and were attributed to platelet refractoriness *(17)*.

Neurological complications adversely affect survival *(18,22,23)*. One group found a negative impact on survival from CNS infection *(19)*. A retrospective review of 116 adult HSCT patients admitted to the intensive care unit over a 6-yr period emphasized the prognostic value of depressed level of consciousness as the principal reason for ICU admission. It was present in 10 patients (8%), with other common indications being respiratory failure (66%), sepsis with hypotension (10%), and cardiac arrest (8%). None of these 10 patients survived to hospital discharge, as opposed to 24% of those with respiratory failure and 33% of those with sepsis and hypotension. Although details about the underlying cause of the depressed level of consciousness were not provided *(24)*, these data do illustrate the seriousness of CNS dysfunction in HSCT.

In any event, change in responsiveness, seizures, and newly emerging localizing neurologic signs should trigger a neurologic consultation. The evaluation of such patients, although in clinical practice probably far more complicated than conveyed here, is the major thrust of this chapter.

## ENCEPHALOPATHY IN HSCT

Combative behavior, sundowning, and excessive sleepiness are such nonspecific findings that they are difficult to interpret. They have been categorized as encephalopathy, a term that is virtually impossible to define strictly in these circumstances. It is the most frequently used "wastebasket" diagnosis to indicate a change in the normal cognitive status of an HSCT patient. In evaluating encephalopathy it is useful to consider the effects of conditioning agents and the effects of multiorgan failure on the brain.

Diffuse encephalopathy may be a side effect of commonly used drugs in the conditioning regimens. Cytarabine (cytosine arabinoside, Ara-C, 1-B-D arabinofuranosylcytosine) is a component of chemotherapeutic regimens for acute nonlymphocytic leukemia (ANLL), acute lymphoblastic leukemia (ALL) and non-Hodgkin's lymphoma (NHL), and is also used for intrathecal administration for leukemic or lymphomatous meningitis. High-dose cytarabine (HIDAC) therapy given intravenously (>3–6 g/m$^2$/d), especially if infused within one hour, has resulted in a diffuse generalized encephalopathy. The clinical signs of somnolence, confusion, disorientation, memory loss as well as psychosis characterize this syndrome, but seizures may occur. Seizures are usually of the generalized tonic-clonic type but occasionally of a complex partial nature. More commonly seen (in ± 10% of patients treated with IV-HIDAC) is a cerebellar syndrome occurring between 3–8 d after initiation of treatment. The typical features of this syndrome include dysarthria, dysdiadochokinesia, dysmetria, nystagmus, and ataxia. Approximately 70% of patients with this cerebellar syndrome will recover, provided the administration of cytarabine is promptly discontinued. A few will have persistent cerebellar damage due to permanent loss of Purkinje cells in the cerebellar hemispheres and vermis *(25)*.

High-dose busulfan (>4 mg/kg/d for 4 d) has been reported to cause seizures in ± 10% of patients undergoing HSCT with a busulfan-based conditioning regimen. Generalized tonic-clonic seizures could be related to a direct toxic effect of busulfan on the cerebral cortex due to its rapid entry into the cerebrospinal fluid *(26)*. Prophylaxis with phenytoin commencing two days prior to busulfan therefore seems reasonable *(27)*.

Methotrexate given in low doses for GVHD prophylaxis may on occasion cause seizures. Neuroimaging studies are usually normal, but the more serious long-term and frequently fatal, chronic leukoencephalopathy resulting from combined intrathecal methotrexate and whole brain radiation therapy will yield abnormal imaging results *(28)*.

Mechlorethamine is an alkylating agent which may result in both acute and chronic encephalopathy, with a strong dose relationship (0.5–2.0 mg/kg). The acute encephalopathy usually clears but may persist and become chronic, with personality changes, dementia and confusion. CT scan has revealed ventricular dilatation in some of these patients, but no intraparenchymal abnormalities *(29)*.

Ifosfamide, an oxazaphosphorine and structural isomer of cyclophosphamide, is part of several high-dose chemotherapy regimens. It is used for NHL, Hodgkin's disease, breast cancer and other advanced malignancies followed by autologous HSCT, as well as for mobilization of peripheral blood progenitor cells, in combination with granulocyte (G-CSF) or granulocyte macrophage colony stimulating factors (GM-CSF). It is usually given in combination with Mesna to prevent hemorrhagic cystitis. It may result in a serious but reversible encephalopathy in a small number of patients (8–9%), but EEG abnormalities without clinical symptoms have been noted more frequently *(31)*. The clinical spectrum includes confusion, hallucinations, mutism and (rarely) profound coma. Extrapyramidal symptoms with opisthotonus, choreoathetosis, and myoclonus may also occur *(30)*. Predisposing factors include low serum albumin level (<3.5 g/dL), elevated serum creatinine level, and presence of pelvic neoplastic disease *(31,32)*. Metabolites of ifosfamide such as chloracetaldehyde are thought to be responsible for this syndrome.

Other drugs such as melphalan, thiotepa, BCNU, cisplatin, and paclitaxel are discussed in Chapter 16.

**Table 2**
**CNS Complications in HSCT Patients (in %)**

| *Author* | *n* | *CNS infections* | *Encephalopathy*[a] | *Cerebrovascular* | *Other*[b] |
|---|---|---|---|---|---|
| *Clinical series* | | | | | |
| Snider et al. *(15)*[c] | 168 | 0.6 | 40.5 | 1.2 | 9.5 |
| Gallardo et al. *(16)*[d] | 27 | 15 | 15 | 11 | 4 |
| Graus et al. *(17)*[e] | 425 | 2.1 | 3.0 | 4.2 | 1.6 |
| Antonini et al. *(18)*[f] | 115 | 0.8 | 13.9 | 0.8 | 34.7 |
| den Brabander et al. *(19)*[g] | 141 | 8.5 | 19.9 | 2.8 | 12.8 |
| *Autopsy series* | | | | | |
| Patchell et al. *(20)*[h] | 78 | 8 | 37 | 6 | 14 |
| Mohrmann et al. *(21)*[i] | 109 | 12.8 | ? | 26.6 | 8.3 |
| Bleggi-Torres et al. *(22)*[j] | 180 | 15.0 | 5.5 | 32.2 | – |

[a]Includes seizures if drug-induced.
[b]Includes unexplained headaches, tremor, myoclonus, myelopathy.
[c]Hodgkin's disease only; autologous HSCT only.
[d]All hematological malignancies except one; allogeneic HSCT only.
[e]Leukemia only; autologous and allogeneic HSCT.
[f]Leukemia only; allogeneic HSCT only; prospective study.
[g]Over 80% leukemia, standard and high-risk; allogeneic HSCT only.
[h]80% Leukemia or lymphoma; autologous, allogeneic, and syngeneic HSCT.
[i]70% Leukemia or lymphoma; 93% allogeneic HSCT.
[j]49% Leukemia or lymphoma; 98% allogeneic HSCT.

Encephalopathy may also be the consequence of concurrent liver, lung or kidney dysfunction. For example, veno-occlusive disease (VOD) of the liver has been reported to occur in up to 54% of HSCT recipients, is strongly associated with multi-organ failure, and is the cause of death in almost 15% of cases *(33)*. Hemolytic-uremic syndrome (HUS) and intravascular hemolysis with renal insufficiency (due to acute radiation nephritis) are well known complications in this patient population, occasionally progressing to coma and death *(34,35)*. In addition, Gordon and coworkers recently proposed that CNS dysfunction after HSCT is an early manifestation of a systemic disorder known as multiple organ dysfunction syndrome (MODS) *(23)*. The preparatory regimen is most likely the first stimulus. This unifying theory hypothesizes the gradual and sequential failure of almost any organ system in critically ill patients. MODS is thought to be the result of a complicated interaction of numerous cytokines, the complement cascade, the kinin-generating pathways, the hemostatic system, and the vascular endothelial cells (as well as hitherto unknown factors). Gordon and coworkers found in their study of 186 adult HSCT patients 21 patients (11%) who developed CNS dysfunction as their first organ dysfunction. Those who had undergone an allogeneic transplant were more likely to develop this complication, as were those who had received a total body irradiation-based preparative regimen. Of these patients, half progressed to second organ dysfunction (either pulmonary or hepatic), and only a third of these survived beyond three months. No factors predictive of progression to MODS and death were identified. These explanations for CNS dysfunction are reminiscent of septic encephalopathy and multiorgan failure in cancer patients *(36)*.

This type of encephalopathy is without distinguishing clinical features and may include delirium or drowsiness progressing to coma. Most commonly, there are neither localizing signs on examination nor myoclonus or asterixis. However, seizures may be part of the syndrome and may be the cause of focal neurologic deficits in the postictal phase (especially in partial seizures). We believe MR imaging should be part of a workup of any patient with a persistent unexplained "encephalopathy," as multifocal structural disease may produce a similar clinical picture. Institutions that afford themselves highly sophisticated care should allow expedient top-of-the-line neuroimaging to explain neurologic worsening or exclude structural damage to the brain. Cerebrospinal fluid examination or drug levels may follow if neuroimaging is unrevealing. The differential diagnosis and approach using MR as a benchmark are shown in Table 3.

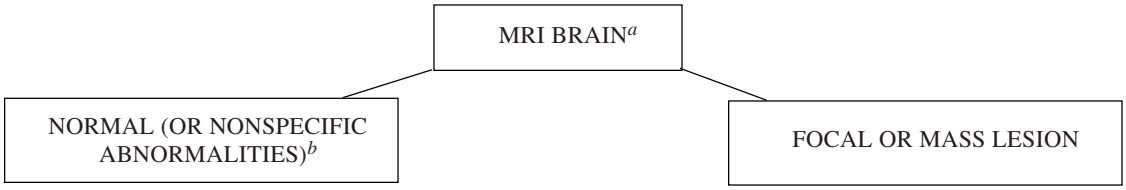
## CEREBROVASCULAR DISORDERS IN HSCT

Elsewhere in this monograph (Chapter 12) a separate section is devoted to cerebrovascular complications in cancer. These complications can occur in several clinical contexts. Some data suggest cerebral hemorrhage to be more common than arterial or venous occlusive disease. Cerebral hemorrhages were quite common in Bleggi-Torres' study of BMT complications, with subarachnoid hemorrhage more frequent than intraparenchymal hematomas *(22)*.

Subarachnoid hemorrhage (SAH) typically is localized in sulci and not basal cisterns. Mycotic aneurysms may be suspected in appropriate clinical circumstances, but more frequently SAH is observed in a patient with relapsing leukemia. Many of these patients concomitantly display epistaxis and pulmonary hemorrhages. Outcome is determined by control of blast crisis and rarely by the impact of subarachnoid hemorrhage.

Subdural hematomas in HSCT recipients have been reported and may be due to leukemic infiltration, but many are benign and do not require surgery *(17,37,38)*. Intraparenchymal hematomas may be due to infestation with aspergillus species

**Table 3**
**Approach to HSCT Patient with CNS Dysfunction**




- Encephalopathy (toxic, metabolic)
- Drug-induced neurotoxicity
- Meningoencephalitis/meningitis (viral, fungal, parasitic, bacterial)
- Rare/yet unknown syndromes

- CNS infection (bacterial, viral, fungal, parasitic)
- Cerebrovascular disorder (SAH, SDH, ICH)
- Leukoencephalopathy (immunosuppression-associated)
- Rare/yet unknown syndromes

[a]Without and with gadolinium; should include diffusion weighted imaging (DWI) sequences and fluid-attenuated inversion recovery (FLAIR) sequences.
[b]For example, microvascular abnormalities, leptomeningeal enhancement only.
SAH, Subarachnoid hemorrhage; SDH, Subdural hematoma; ICH, Intracerebral hemorrhage.

or cerebral venous sinus thrombosis *(39,40)*. Lobar hematomas have been linked to cyclosporine toxicity due to direct damage to endothelial cells *(41)*. Intracerebral hemorrhage is often a fatal event in a moribund relapsed end-stage patient. Ischemic stroke is less common, and although multiple causes should be considered (particularly in the perioperative phase) prior risk factors (e.g., atrial fibrillation or hypertension) may play a role (*see* Chapter 12). In Gordon's series, the most likely explanation was felt to be protein C deficiency. This congenital thrombophilic state as well as deficiencies of factors XII and VII, antithrombin 3, and presence of anticardiolipin antibodies, could contribute to a hypercoagulable state in HSCT patients (both autologous and allogeneic) *(42–45)*. Additional factors are endothelial cell injury and microangiopathy possibly due to cyclosporine and methylprednisolone *(46,47)*. Another well known predisposing mechanism to embolic infarction is nonbacterial thrombotic endocarditis (NBTE) *(48)*. NBTE was identified in 7.7% of HSCT patients in an autopsy series from Johns Hopkins *(49)*. Two of these seven patients had cerebral infarcts. Finally, thrombotic thrombocytopenic purpura (TTP) after allogeneic HSCT may result in fluctuating neurological deficits *(50)*.

One recent provocative study suggested the presence of cerebral angiitis in five patients with longstanding GVHD *(51)*. Cerebral angiogram was diagnostic in only one patient, and pathologic examination revealed vessel wall lymphocytic infiltration. Response to cyclophosphamide and corticosteroids was good, with resolving MRI signal abnormalities in the white matter.

## SEIZURES IN HSCT

The incidence of seizures (generalized, partial, or status epilepticus) in HSCT patients varies between 3% *(15)* and 29% *(52)*, with most HSCT series reporting an incidence of approx 10% *(16,20)*. The underlying primary disease may play a role, with the highest percentage of seizures in patients treated for sickle cell anemia *(52)*. Potential causes of seizures in HSCT patients are numerous. Since most of these will result in identifiable MRI lesions (including various CNS infections, infarction, hematoma and leukoencephalopathies), we will list here causes of seizures in patients with a normal MR scan. Whereas electrolyte disturbances and acid-base abnormalities (common in combination) may cause seizures, a number of drugs used throughout the transplant procedure may be responsible. The most commonly implicated drugs are listed in Table 4. Several of these agents are part of the conditioning regimen given prior to HSCT, whereas others are used for either the underlying malignancy or complications of HSCT.

Particularly pertinent to HSCT is a late-onset seizure as a first manifestation of recurrent primary disease in the brain in patients who underwent HSCT for leukemia or lymphoma *(53)*. Even more uncommon, but disproportionately overrepresented in HSCT patients, are *de novo* neoplasms of the CNS (lymphomas and gliomas) as a late complication of HSCT *(54–56)*. Socie found a sevenfold increase of malignant tumors of the CNS in long term survivors of HSCT, particularly in patients with leukemia transplanted at a young age *(57)*. Children who received cranial or craniospinal radiation therapy as prophylaxis as part of their transplant procedure are also at risk *(58)*.

## DRUG-INDUCED NEUROTOXICITY IN HSCT

Neurotoxicity from immunosuppressive agents may cause early neurological manifestations, usually without abnormalities on MR scans, and is seen with the commonly used agents cyclosporine, tacrolimus and, to a much lesser degree, muromonab-CD3 (OKT3). The early symptoms (within 2 wk after transplantation) include tremor (postural, usually mild), delusions and visual hallucinations, disorientation to time and place, nonsensical speech (cyclosporine) or apraxia of speech (tacrolimus). Tacrolimus may also cause perioral paraesthesias, hyperesthesias of the hands, and "restless legs." All three agents can cause headache *(59)*. Since the aforementioned symptoms

**Table 4**
**Drug-Induced Seizures in HSCT**

| |
|---|
| *Antineoplastic agents* |
| Cytarabine (Ara-C) |
| Busulfan |
| Methotrexate |
| BCNU |
| Mechlorethamine |
| Ifosfamide |
| Cisplatin |
| *Immunosuppressive agents* |
| Cyclosporine |
| Tacrolimus (FK-506) |
| Muromonab-CD3 (OKT3) |
| *Antimicrobial agents* |
| Aminoglycosides |
| Penicillins |
| Cephalosporins |
| Imipenem |
| Vancomycin |
| Isoniazid |
| Metronidazole |
| *Antiviral agents* |
| Acyclovir |
| Ganciclovir |
| Foscarnet |
| *Miscellaneous* |
| Lidocaine |
| Narcotics |
| Theophylline |
| Tricyclic antidepressants |
| Antipsychotics |
| Aqueous iodinated contrast agents |

and signs are now well known among transplant physicians, discontinuation or adjustment of the dose of a given immunosuppressive drug usually results in improvement. Thus, the more severe neurological manifestations (cortical blindness, generalized tonic-clonic seizures, mutism and coma) are now uncommon *(60,61)*.

What may be a fairly constant clinical observation is that immunosuppressive neurotoxicity occurs in most patients during intravenous loading of tacrolimus or cyclosporine and is much less common and severe after the posttransplant phase has subsided and the patient is stable. Cyclosporine neurotoxicity occurs in fewer than 5% of HSCT patients as opposed to 25% of liver transplant patients. The reason for this difference is unknown.

Both cyclosporine and tacrolimus are highly lipophilic drugs and contain many aliphatic groups. Their chemical structure is totally different but these groups reduce polar charges, making them virtually insoluble in water. Thus, these drugs need to be dissolved in oils or alcohols. The lipophilic nature of both substances does not imply that they rapidly enter brain tissue. Several barriers have to be overcome. The blood-brain barrier is actually created by an anatomical barrier and a transport system that extrudes drugs. One of the possible mechanisms of entry is at the capillary level. Injury to the brain capillary endothelial cells may inhibit the expression of a P-glycoprotein which functions as a drug efflux pump (Fig. 1) *(62)*. Cyclosporine also

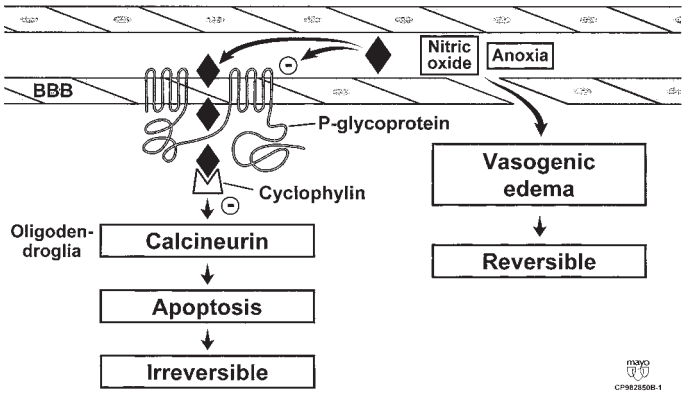



**Fig. 1.** Proposed mechanism of cyclosporine neurotoxicity. Disturbance of the blood-brain barrier (BBB) may lead to vasogenic edema but prolonged exposure may trigger apoptosis. Nitric oxide and possible anoxic injury may facilitate opening of the BBB *(63)*.

appears to enhance nitric oxide production, which may further cause dysfunction of the blood-brain barrier. It seems that the earliest abnormality in cyclosporine or tacrolimus neurotoxicity is fluid extravasation (vasogenic edema) and not cell destruction (cytotoxic edema). A recent MR study in a patient with cyclosporine neurotoxicity using diffusion mapping showed increased diffusion on the ADC map highly suggestive of vasogenic edema. Cytotoxicity and cytotoxic edema may occur after prolonged exposure *(64–69)*. When this occurs, severe vasoconstriction, due to a disturbance of the endothelial control of the vascular tone, will lead to ischemia.

Neuroimaging abnormalities with cyclosporine and tacrolimus immunosuppressive toxicity have been well described but remain uncommon *(66,70,71)*. The most characteristic feature is posterior leukoencephalopathy on CT scan or MR imaging. Cortical hyperintensity has been reported, and this unusual feature predominantly localized in the cingulate gyrus and occipital lobe has been explained by blood flow reduction in pial vessels and would support the vasoconstriction hypothesis. The true prevalence of MR abnormalities in patients with cyclosporine or tacrolimus neurotoxicity is not known. These MRI abnormalities involve white matter abnormalities but also may involve the cortex, cerebellum, and deeper structures such as the basal ganglia *(70)*. All these abnormalities are quickly reversible after discontinuation of the drug, again supporting the notion of vasogenic edema (*see* Fig. 2).

Many antibacterial and antiviral agents are used during the stage of pancytopenia following HSCT and chronic GVHD when the patient is at a high risk for systemic or neurologic infections with a multitude of organisms. Neurotoxicity from these agents is not always readily distinguishable from the effects of the underlying infection or GVHD. As alluded to earlier, metabolic factors, and in particular abnormalities of kidney function, may lead to increased serum levels of many of these drugs resulting in side effects.

Antimicrobial agents listed in Table 4 have been reported in association with encephalopathy with or without seizures, but usually without abnormalities on neuroimaging studies *(72–74)*. In addition, cranial nerve toxicity, particularly eighth nerve, with symptoms of vertigo, tinnitus and hearing loss, is

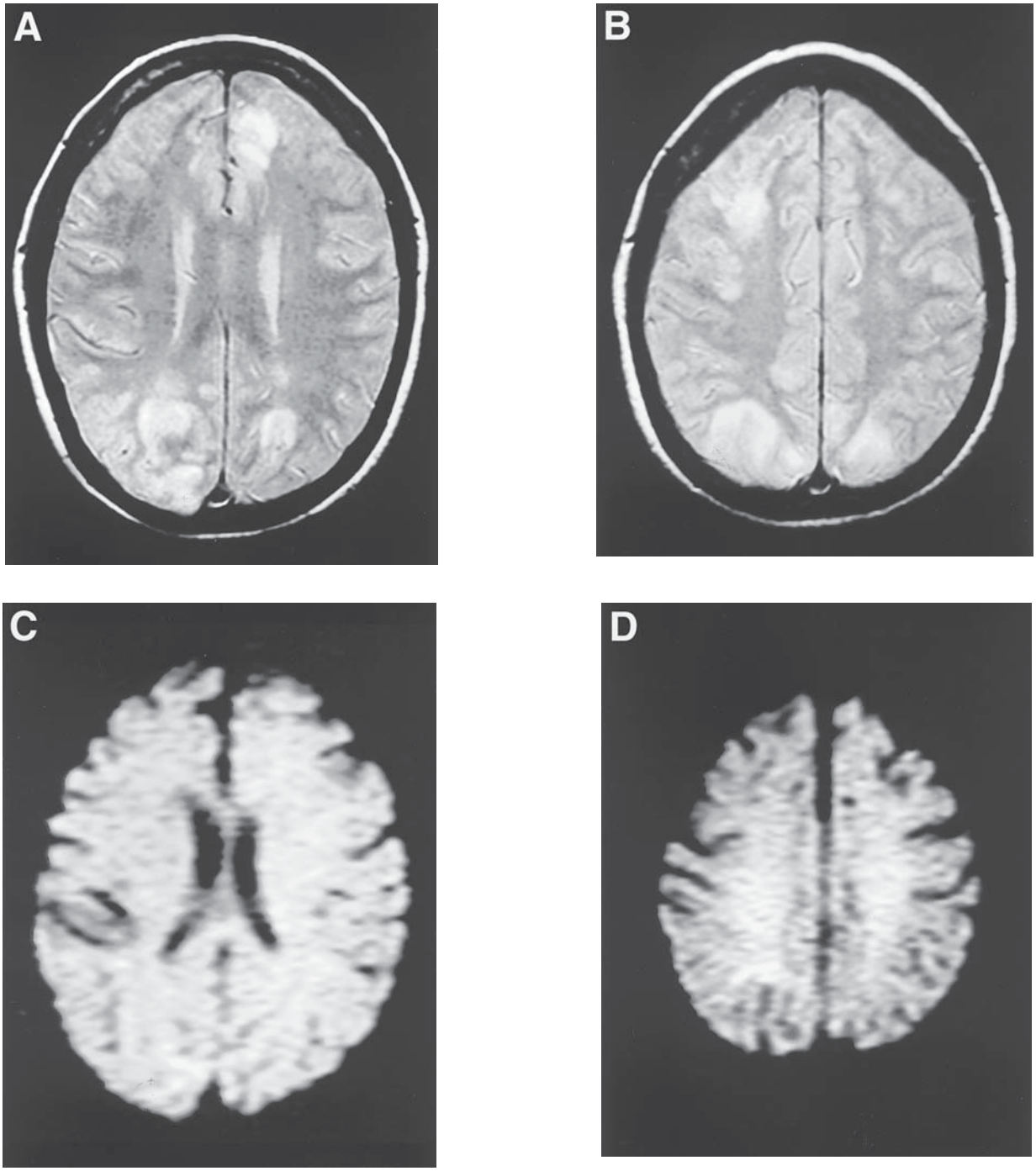



**Fig. 2.** MRI in a patient with tacrolimus neurotoxicity. Note diffuse white matter hyperintensities with no specific predilection for the posterior hemispheres (**A** and **B**). The diffusion-weighted MR (**C** and **D**) was normal (further mapping showed increased ADC levels consistent with vasogenic edema).

associated with the use of aminoglycosides, erythromycin, vancomycin, and sulfonamides. Optic neuritis has been seen with chloramphenicol and isoniazid *(72)*.

Antiviral agents such as acyclovir, ganciclovir, and foscarnet are now established agents in the preemptive management of cytomegalovirus (CMV)-positive HSCT patients, particularly in cases of allogeneic marrow recipients with GVHD. The main side effects of these drugs are neutropenia (thus creating a new risk for other infections), thrombocytopenia, and nephrotoxicity. Particularly in combination with renal dysfunction, reports of encephalopathy with seizures, tremors, headache and vertigo have been associated with the use of these agents. Exceptional cases of coma, usually reversible, have resulted from both oral and intravenous use of acyclovir *(75–77)*.

## MENINGOENCEPHALITIS IN HSCT

The phase of pancytopenia and immunosuppression in allogeneic HSCT patients increases the risk of infections of the

central nervous system. Like other immunocompromised patients (e.g., AIDS or congenital immunodeficiencies) the causative agents are generally opportunistic pathogens. The predominance of opportunistic infections is a result of impairment of cell-mediated immunity due to use of immunosuppressive drugs *(78)*. The diagnosis of these infections requires a high index of suspicion. CNS symptoms and signs may be the first manifestation of a disseminated infectious process and further evaluation of lungs, gastrointestinal or genitourinary tract is indicated. Whereas the more advanced stages of these infections are generally associated with focal neurological deficits and widespread lesions on imaging studies, these studies are frequently initially normal.

Prophylactic and preemptive use of antimicrobial and antiviral agents has reduced the number of life-threatening infections. Clinical presentation and signs may be as minimal as fever, headaches, or a very mild change in level of consciousness (all too easily attributed to medication or psychological factors). Archetypical signs such as neck stiffness are frequently absent, as are focal neurological deficits. Along with routine CSF analysis, techniques such as polymerase chain reaction (PCR) may be needed for detection of the various infectious agents. However, it should again be strongly emphasized that absence of abnormalities on CT and even MR scans in an HSCT recipient with "only" a febrile headache should not be interpreted as incompatible with a CNS infection *(79,80)*. Varicella zoster virus (VZV), Epstein-Barr virus (EBV) *(81)*, and adenovirus *(82)* may give rise to a severe and sometimes fatal meningoencephalitis with only minimal abnormalities of CT and MRI scans. Similarly, meningitis from bacteria such as *Stomatococcus mucilaginosus (83), Listeria monocytogenes (84), Streptococcus pneumoniae (85)*, or from *Acanthamoeba (86)*, albeit distinctly uncommon, may not result in imaging abnormalities. It has been hypothesized that the immunosuppressed conditions during which these infections characteristically occur—frequently during chronic GVHD—result in an attenuated immunologic-inflammatory response with less severe disruption of the blood-brain barrier.

Another prime example of a neurologically devastating pathogen causing very little abnormality on neuroimaging studies is human herpes virus-6 (HHV-6). This member of the herpesvirus family has been increasingly studied over the last decade and is the causative agent of childhood diseases as exanthema subitum and febrile illness. After the initial infection this lymphotropic and neurotropic virus persists indefinitely and may flare up in a spectrum of diseases in the immunocompromised patient. Following HSCT, HHV-6 infection has been documented in 38–60% of patients *(87)*. It has been implicated as the causative agent of increased incidence of other viral infections such as Epstein-Barr or CMV, interstitial pneumonitis, or bone marrow suppression and exacerbating graft-vs-host disease *(87–90)*. It may occur through reactivation of the latent virus, infection from the donor *(91)*, or via exogenous infection. Variant B is most commonly involved, but variant A may be more virulent. In addition, HHV-6 is supposedly the most neuroinvasive member of the herpes virus family *(92)*. After the initial report in 1994 of a case of fatal encephalitis caused by HHV-6 in a 37-yr-old female following allogeneic bone marrow transplantation *(93)*, 10 other cases have been reported since 1998. Singh and Paterson *(90)* suggested that HHV-6 as etiologic agent of posttransplantation encephalitis (both in the HSCT and solid organ transplant populations) might be underreported *(94,95)*. Clinical similarity with the neurotoxicity of cyclosporine and tacrolimus was noted: both produce altered mental status, headache, visual and speech disturbances, usually in the absence of fever. Both syndromes occur in the early post-transplantation period (most within the first 90 d). Differences between the two clinical syndromes are that seizures are much more common (75 vs 25%) in immunosuppression-associated neurotoxicity and, perhaps most importantly, that neuroradiological abnormalities on CT and MR scans in HHV-6 encephalitis are usually absent (CT abnormalities in only 1 of 11 patients, MRI abnormalities in 2 of 8 cases). Antiviral prophylaxis with acyclovir, ganciclovir or valacyclovir frequently did not prevent HHV-6 encephalitis. Further complicating the differential diagnosis is the fact that pleocytosis or elevated protein in the CSF may be absent or only minimal with HHV-6. The diagnosis of HHV-6 encephalitis should be based on demonstration of HHV-6 DNA in the CSF by means of PCR or a shell vial culture assay. Treatment consists of either ganciclovir or foscarnet, as acyclovir is ineffective both prophylactically and in established infection due to the absence of a thymidine kinase in HHV-6. It appears that these drugs should be given for at least 1 wk, possibly longer. Six of the 11 patients reported thus far survived, but one of these died 32 d later from bleeding *(94)*. Residual neurologic deficits were not mentioned or specified in the surviving cases, but impaired memory might occur, as HHV-6 has a predilection for the hippocampus and limbic system.

## OTHER INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

A brief review of opportunistic infections in HSCT will be provided in this section, concentrating on patients with focal lesions on MRI scan (Table 5).

Nocardiosis has been reported in immunocompromised patients including solid organ transplant patients (heart, heart-lung, liver, kidney) *(96)*. *Nocardia asteroides* is a branching gram-positive rod and usually establishes infection through inhalation of the aerosolized organism. Following pulmonary infection, hematogenous spread may occur, predominantly to skin, bone, and CNS. Meningitis, cerebritis, or meningocerebritis may all be seen, with symptoms and signs of fever with headaches, altered mentation, seizures, and focal deficits depending on location. However, in HSCT patients it is a rare opportunistic infection, with only 11 cases reported, of which likely five involved the brain *(96,97)*. Four of these five patients received an allogeneic HSCT, one an autologous HSCT. All patients with allogeneic HSCT were receiving treatment for chronic GVHD. *Nocardia asteroides* was found in the cultures of sputum and broncho-alveolar lavage in four, whereas *Nocardia nova* was cultured from a stereotactic aspirate from a solitary left temporal lobe lesion in the only neurologically symptomatic patient (headache, visual blurring and slow mentation). The other patients presented with fever (up to 103°F) and other signs of a respiratory infection. CT or MRI scans of the brain

**Table 5**
**MRI Characteristics of Focal CNS Infections in HSCT Patients**

| *Infections* | *Preferential location* | *Number of lesions* | *T1* | *T2/FLAIR* | *Enhancement* |
|---|---|---|---|---|---|
| Nocardiosis | Any site | Multiple > solitary | ↓ | ↑ | + |
| Aspergillosis | Subcortical cerebral/cerebellar hemispheres; basal ganglia | Multiple | ↓; hemorrhagic | ↑ | + |
| Toxoplasmosis | Basal ganglia; cortical medullary junction of cerebral/ cerebellar hemispheres | Multiple | ↓ or =; hemorrhagic | ↑ or = | + |
| Herpes virus infections (HSV; HHV-6) | Medial temporal; multiple lobes | Solitary (uni/bilateral) or multiple | ↓ | ↑ | – |
| Progressive multifocal leukoencephalopathy | Cerebral subcortical white matter at any site, deep white matter later | Multiple | ↓ | ↑ | + or – |

↓, Decreased signal intensity; ↑, increased signal intensity; =, isointense; +, present; –, absent.

were obtained as part of the evaluation for disseminated disease. Imaging studies in these five patients were variable, with multiple and enhancing lesions. CT scan in some of these cases was unremarkable, or showed only a solitary lesion. One patient demonstrated abnormalities on T2 weighted images of the brain, and was found to have both *Blastomyces dermatitis* and *Nocardia asteroides* infection of the lungs; two other patients were found at autopsy to have *Aspergillus fumigatus* infection of the lungs and brain but no residual nocardiosis. In these circumstances nocardiosis may then be a marker in HSCT patients for susceptibility to infection with other opportunistic pathogens. Treatment should include trimethoprimsulfamethoxazole for 6–12 mo. If the patient is allergic to these agents, a multitude of other drug combinations have anecdotally been reported to be successful e.g. imipenem/amikacin, imipenem/cefotaxime and amikacin/cefotaxime, as well as minocycline, ampicillin and chloramphemicol *(96,98)*.

*Mycobacterium tuberculosis* infections in HSCT patients are, contrary to what might be expected, uncommon. Incidences of between 0.5–3.0% have been reported *(99)*, mainly in T-cell depleted allogeneic graft recipients and those with chronic and severe GVHD. Even more uncommon is CNS involvement due to *M. tuberculosis*: only four cases have been reported in the English literature *(17,99–101)*. Graus and coauthors *(17)* included a case of fatal *M. tuberculosis* in their prospective series of patients with leukemia treated with allogeneic or autologous HSCT. No further details were provided. Two other cases involved patients with tuberculous meningitis, with no abnormalities *(100)* or only ventricular dilatation on CT scan *(101)*. This last patient developed a focal lesion on a CT scan 48 h later. The fourth patient *(99)* presented with a tuberculoma of the temporal lobe 3 mo after diagnosis of pulmonary tuberculosis and while on tuberculostatic therapy. In this patient CSF cultures prior to biopsy of the lesion were negative for acid-fast bacilli. The typical presentation is an insidious meningitis with headaches, fever, decreased level of consciousness, sixth or third cranial nerve palsies, and papilledema. CSF abnormalities may initially reveal a polymorphic pleocytosis after which the classic lymphocytic pleocytosis, hypoglycorrhacia, and elevated protein are found. No reports with atypical mycobacterium species in HSCT patients could be retrieved. Three of four reported patients with CNS tuberculosis have died. Treatment of CNS tuberculosis requires multiple drug therapy—isoniazid, rifampin, and pyrazinamide—for the first 2 mo, then the first two drugs for the next 12–24 mo. Resistance requires addition of other drugs, e.g., ethambutol or streptomycin.

*Aspergillus fumigatus* and *Aspergillus flavum* are responsible for the most common fungal infections of the CNS in HSCT patients. In 25–50% of patients with invasive aspergillosis, the CNS is involved at the time of diagnosis of the systemic infection. In a series of 655 patients who had undergone BMT (allogeneic, autologous, or syngeneic) or peripheral blood stem cell transplantation (PBSCT), 27 patients (4%) developed opportunistic CNS infections. Five of these 27 (18%) had *Aspergillus* encephalitis *(102)*. Patients with neoplastic diseases, particularly leukemia and lymphoma, without or with granulocytopenia, have long been known to be at risk for *Aspergillus* infections. Systemic use of corticosteroids is an additional risk factor *(103)*, particularly if given in the setting of acute or chronic GVHD. Inhalation of excessive amounts of *Aspergillus* spores in contaminated air is the usual route of infection. Bronchopneumonia, and rarely invasive disease of the nasal sinuses, results, which may be followed by tissue infarction, hemorrhage and hematogenous dissemination due to blood vessel invasion. Pulmonary symptoms and signs include dyspnea with cough, pleurisy, or hemoptysis. Once the brain parenchyma is invaded, this same pathophysiologic mechanism will result in the development of arterial occlusion due to hyphal elements blocking the artery, with infarction and frequently secondary hemorrhagic conversion. These lesions may be localized in the subcortical areas of the cerebral hemispheres or the cerebellum *(103)* (Fig. 3). Rarely, the formation of a mycotic aneurysm with resultant subarachnoid hemorrhage has been seen. Involvement of the meninges in the inflammatory process is distinctly uncommon. The invasion of subcortical blood vessels with subsequent thromboses, infarction and hemorrhage ex-

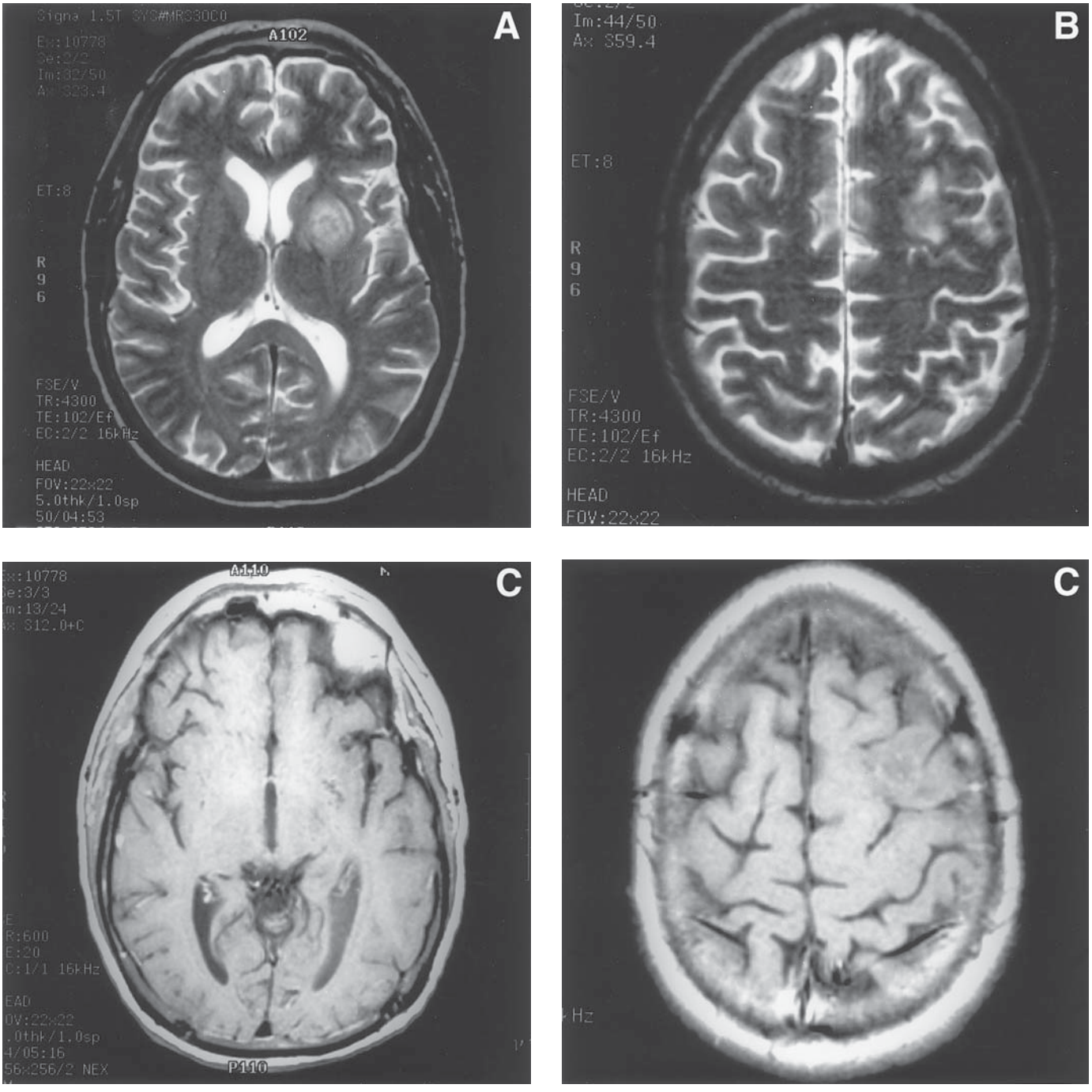



**Fig. 3.** Axial MRI, T2 weighted (**A** and **B**) and T1-weighted post-gadolinium (**C** and **D**) of *Aspergillus flavus* lesions in the brain of a 31-yr-old male 10 mo after allogeneic bone marrow transplantation for AML. He was admitted 1 mo prior to death with respiratory insufficiency, and developed generalized tonic-clonic seizures 2 wk later. Autopsy confirmed the presence of *A. flavus* from a right temporal lesion. Note the very faint enhancement of the left basal ganglia and left frontal lesions.

plains the high frequency of focal neurological deficits (hemiparesis, unilateral cranial nerve palsies, intention tremor, and dysmetria) in most series *(103,104)*. Seizures and headaches may be presenting symptoms. Altered mental status, with or without fever, is uncommon *(105)*. Nuchal rigidity is extremely rare because of the sparing of the meninges. This lack of meningeal signs relates to the relative paucity of CSF abnormalities: pleocytosis, usually a mix of polymorphonuclear and mononuclear cells, is usually less than 100/mm$^3$, CSF protein content is only mildly elevated, and glucose level is normal or mildly decreased. CSF cultures for *Aspergillus* are rarely positive *(104)*. Although CT scan of the brain may show low-density lesions, usually without significant mass effect or enhancement, MR scans are clearly the imaging modality of choice. Miaux and coauthors described two different patterns: one with non-enhancing lesions located in the basal ganglia representing small infarctions; the other pattern represents large cerebral artery infarctions with early intravascular and

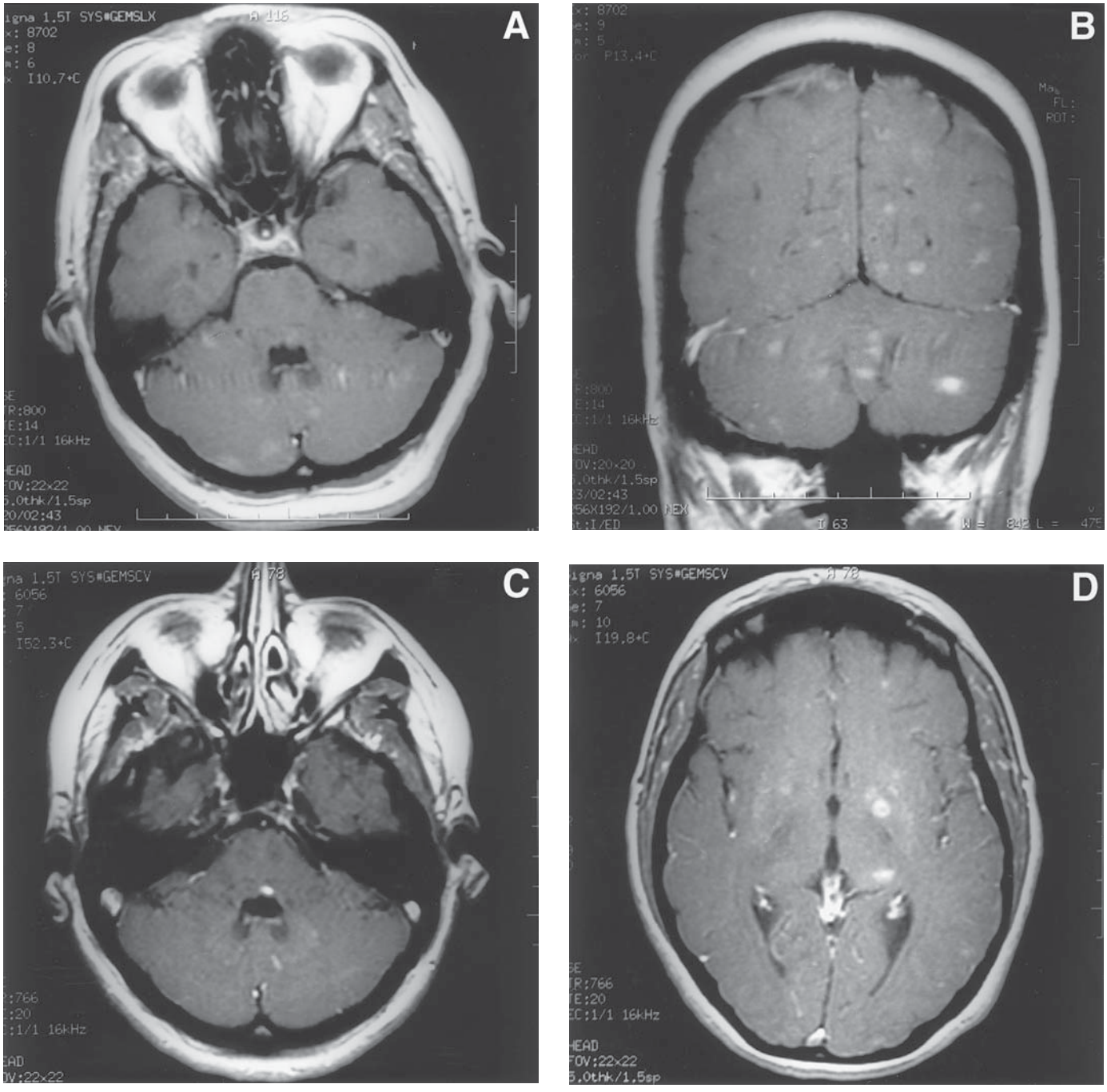



**Fig. 4.** Multiple lesions in both cerebral and cerebellar hemispheres (**A** and **B**) in a 46-yr-old female 8 mo after allogeneic bone marrow transplantation for chronic myelogenous leukemia. She presented with dizziness, ataxia, nystagmus, and diplopia. Mild right upper motor neuron facial palsy and right upper extremity weakness were found. CSF analysis including toxoplasmosis IgG and IgM was normal; however, serum toxoplasmosis IgG, IgM and IgG quantitative index were elevated. After prolonged treatment (>4 mo) with pyrimethamine, sulfadiazine, and leucovorin, there has been significant clinical improvement but only incomplete neuroradiological response (**C** and **D**).

meningeal enhancement *(104)*. T2-weighted images showed inhomogeneous high signal intensity lesions, with a low-signal peripheral rim if hemorrhage had occurred. MRI detected multiple lesions in four of six patients, CT in only two of five. Maschke and coworkers found similar abnormalities on MR scans in their five patients with *Aspergillus* infections. However, they noted ring enhancement of the lesions (two of which had undergone hemorrhagic transformation) in all patients. All patients died from their CNS aspergillosis. The importance of early diagnosis has been emphasized by many authors, since an almost 100% mortality in most series has been reported *(103,104)*, and only recently have reports on HSCT patients surviving CNS aspergillosis been published *(27,105,106)*. If invasive aspergillosis has been established by means of biopsy of a lung lesion and a characteristic brain MR scan, treatment should begin. However, occasionally biopsy of a cerebral lesion may be necessary *(105,106)* to document fungus. Treatment of CNS aspergillosis consists of amphotericin B, usually

at 1.0–1.5 mg/kg/d intravenously. Lipid formulations are now being increasingly given as initial therapy (at >5 mg/kg/d) because of increased efficacy and significantly less nephrotoxicity. A second drug such as rifampin (600–900 mg/d in divided doses) is frequently added in CNS aspergillosis patients given their dismal prognosis. Duration of treatment is unknown but should probably be continued for 2–3 mo after the MR scan as normalized. Prevention of aspergillosis is very important, and includes clear air supply by high-efficiency particulate air filters on the hospital ward; prevention of CMV infection (which seems to predispose to invasive aspergillosis); and pre-emptive therapy with amphotericin B once colonization of airways with Aspergillus species has been found.

Fungal infections with *Coccidioidomyces immitis*, *Cryptococcus neoformans* and *Histoplasma capsulatum*, although not uncommon in the solid organ transplant population, are extremely uncommon in HSCT patients *(98)*. Similarly, a fairly common fungal pathogen such as *Candida*, with a systemic infection rate in HSCT patients of 12.5% *(107)*, rarely leads to CNS involvement (2 out of 70 patients had positive CSF cultures). Mortality from systemic *Candida* infections for these patients was high (79% in the early post-transplant period); no data were provided about possible CNS involvement established by autopsy. Another retrospective series of 58 HSCT patients, however, identified 19 patients with *Candida* abscesses (15 *Candida albicans*, 2 *Candida tropicalis*, 2 unknown species). Only one of these survived (but died from congestive heart failure) *(108)*. In a recently published review by Maschke and collaborators *(102)* one patient (4%) developed *Candida* encephalitis, 24 d after BMT. MR scan demonstrated multiple lesions, hypointense on T1 weighted sequences, intermediate signal on T2-weighted images, and ring-enhancing after gadolinium administration. They were localized in the basal ganglia and cerebellum. The patient died after 19 d from respiratory failure *(102)*.

Other rare fungi that occasionally result in brain abscess in HSCT patients, usually under the predisposing circumstances of neutropenia and corticosteroid use, are saprophytes of the *Zygomycetes* group, most notably *Rhizopus, Absidia* and *Mucor*. These species are responsible for a rhinocerebral zygomycosis, with or without concomitant pulmonary infection. A total of 12 patients were recently reviewed *(109)*. Invasion directly from the involved nasal sinuses is usually seen. In addition to neutropenia and immunosuppression by corticosteroids, ketoacidosis due to hyperglycemia is a predisposing factor. Prognosis is as grim as with the previously discussed fungal CNS infections, in spite of treatment with conventional or liposomal amphotericin B and surgical debridement of the nasal sinuses *(98,109)*. Finally, a unique and again fatal case of *Microascus cinereus (110)* brain abscess in a 28-yr-old female recipient of an allogeneic HSCT was recently reported *(110)*.

*Toxoplasma gondii* seropositivity is fairly common in the population scheduled for any organ transplantation, and a prevalence of 43–68% in allogeneic bone marrow recipients has been estimated *(111,112)*. However, clinical manifestations of disseminated toxoplasmosis after HSCT are rare. Following a mononucleosis-like prodromal stage (not unlike CMV infection), disseminated toxoplasmosis involving lungs, liver, bone marrow and brain is seen. Toxoplasma encephalitis usually occurs within the first 6 mo post-HSCT, as early as 9 d and the majority within 3 mo; rare cases of late cerebral toxoplasmosis have also been reported *(112–116)*. Clinical disease in HSCT patients usually results from reactivation of latent disease in the recipient during immunosuppression, particularly with concurrent GVHD; rarely, it occurs as a primary infection acquired from the allograft into the seronegative recipient *(111)*. The incidence of toxoplasmic encephalitis was less than 2% in one series *(112)*. Clinical symptoms and signs include headaches, low-grade fever, lethargy, seizures (focal, without or with secondary generalization), and focal motor, sensory or cerebellar deficits depending on the location of the lesions.

Given this nonspecific clinical presentation, additional diagnostic tests are indicated. Serological tests measuring IgG antibodies against *T. gondii* in blood (and CSF) are of limited value given the prevalence of latent infection. Increased IgM levels may indicate recent activation of infection, but false-positive and false-negative cases have been reported *(111,113,117,118)*. Routine CSF parameters such as cell count and protein level are either normal or mildly elevated due to the immunosuppressed state of the patient. PCR assay of blood and CSF has recently proved to be of significant use in the early detection of *T. gondii* genes or antigens *(120)*. Occasionally, however, even PCR assay in the CSF may be negative, at least early in the infection *(112)*. Definitive proof of *T. gondii* infection of the CNS relies upon demonstration of tachyzoites of *T. gondii* in histologic sections of brain tissue acquired by means of a biopsy *(113,116,119)*.

MRI scans typically will show multiple lesions in the basal ganglia and at the cortico-medullary junction of the cerebral and cerebellar hemispheres with low/isointense signal on T1 and isointense/high signal on T2-weighted MR images representing central coagulation necrosis *(116)*. Enhancement after gadolinium administration may or may not be present, depending on the ability of the patient's immune system to muster a meaningful inflammatory response *(116)* (Fig. 4). Leptomeningeal enhancement is rare *(120)*, as is the presence of hemorrhage within the toxoplasmic lesion *(121,122)*. Differential diagnosis based on MRI characteristics would include other opportunistic infections such as aspergillosis, mucormycosis, as well as progressive multifocal leukoencephalopathy and posttransplant lymphoproliferative disorders/primary CNS lymphoma. Additional techniques such as positron emission tomography (PET), single-photon emission CT (SPECT), or MR spectroscopy (MRS) may be useful for differentiation between these possibilities. Prophylactic treatment with low-dose trimethoprim-sulfamethoxazole (80 mg/400 mg once per d) in seropositive HSCT patients may be sufficient, given for the first 6 mo post-HSCT. However, if during that period severe GVHD develops in a seronegative HSCT recipient of a graft from a seropositive donor this prophylactic regimen may fail and clinically symptomatic disease may still develop.

Treatment should consist of pyrimethamine (50–100 mg/d) and a sulfonamide (2–4 g/d) (which may also be the regimen of intensified prophylaxis in high-risk patients as mentioned above). Intolerance to sulfonamides (allergic reactions, gastrointestinal symptoms) is not uncommon, at which time drugs

such as clindamycin, atovaquone, azithromycin or clarithromycin will need to be given.

Prognosis of patients with toxoplasmic encephalitis is poor, with only 1 in 10 patients surviving. Early detection with PCR assays offers hope of improving on this dismal prognosis.

Herpesvirus infections in HSCT patients affecting the CNS are uncommon, undoubtedly the consequence of the prophylactic use of acyclovir after HSCT. Rare cases of herpes simplex encephalitis have been reported. Two fatal cases, both after mucocutaneous herpes infections, have been documented in an autopsy series *(20)*. In one of the patients, bilateral leg pain and perineal pain preceded the encephalitis. CSF was normal in one patient, HSV was cultured antemortem from the CSF in the other. Histopathological findings were in the classic locations such as medial temporal lobes, insula, and inferior frontal area but also in the lower spinal cord. No reports on CT or MR studies in HSCT patients with herpes simplex encephalitis are available. One may expect a focal pattern of abnormalities as seen in the adult nonimmunocompromised population, although enhancement may be absent due to the immunosuppressed status of HSCT patients. Varicella zoster virus (VZV) encephalitis may or may not give a similar pattern of multifocal abnormalities on T2-weighted and FLAIR images with a preference for the deep white matter. Usually, it follows a cutaneous herpes zoster infection occurring between 2–5 mo post-HSCT. Whereas a 4% incidence of VZV encephalitis in HSCT patients with active zoster or varicella infection was still seen in the 1970s *(123)*, this complication has become uncommon in the current age of acyclovir prophylaxis. Various patterns of dermatomal involvement (cranial, cervical and lumbosacral) may result in concomitant meningoradiculitis *(27)*.

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disorder caused by a subacute infection of glial tissue, predominantly oligodendroglial cells. JC virus, a neurotropic polyomavirus of the Papovaviridae family, has been identified as the infectious agent. JC virus and the related BK polyomavirus are endemic in humans, with seroconversion up to 90% in adults *(124)*. Both viruses have been demonstrated in normal brain in immunocompetent patients and can establish a latent infection in the kidney. In HSCT patients they may thus cause clinical symptoms of a hemorrhagic cystitis. However, PML after HSCT is extremely rare, and only seven cases have been reported to date *(124–130)*. Clinical symptomatology is non-specific but dramatic with personality changes, confusion, or dementia, as well as more localizing signs such as aphasia, apraxia, hemiparesis, cerebellar dysfunction, or visual processing abnormalities. MR scan is the imaging modality of choice, usually demonstrating multifocal areas of high-signal abnormalities on T2 weighted and FLAIR images. As the disorder's name suggests, these are mostly located in the white matter but may extend into the gray matter. Enhancement is variable, and some of the changes may indicate vasogenic edema. Diagnosis is based on demonstration of JC virus in CSF by means of PCR assay, *in situ* hybridization, or immunohistochemistry; however, PCR is negative in approx 25% of cases of PML *(125)*. Treatment is empirical, and successes have been reported with intrathecal cytarabine, subcutaneous interferon, subcutaneous IL-2, or combinations of these. However, prognosis remains very poor with a median survival of less than 6 mo. Long-term survivors (more than one year) have been noted in HSCT patients *(124,130)*. In these cases, a relatively prominent inflammatory response in the biopsied brain tissue was found. Spontaneous remission of PML lesions may also occur.

## IDIOPATHIC HYPERAMMONEMIA (IHA)

This usually fatal complication of HSCT presents as a progressive encephalopathy characterized by acute onset of lethargy, confusion, disorientation and agitation, and may be accompanied by seizures and cerebellar dysfunction. Rapid deterioration to coma and death frequently follow, sometimes within 24 h of the first symptoms *(131)*. Laboratory findings include: elevated plasma ammonia levels (>70 μmol/L) in the presence of normal or only mildly elevated serum bilirubin and hepatocellular enzyme concentrations, respiratory alkalosis and tachypnea, and normal plasma amino acid levels. Usually these patients have a profound leukopenia. Neuroimaging studies of the brain are normal or demonstrate nonspecific findings (Fig. 5), and EEG shows nonspecific abnormalities consistent with a metabolic encephalopathy (diffuse slow background activity).

IHA is rare, occurring in 0.5% *(132)* to 1.2% *(133)* of patients at large HSCT centers. In addition, it has been seen during and shortly after high-dose chemotherapy only *(133,134)*, when the patient is neutropenic (absolute neutrophil count $< 5 \times 10^8$/L). The etiology of IHA remains unclear. There are clinical similarities to Reye's syndrome, fulminant hepatic failure, and inherited defects of urea synthesis. Autopsy studies have indeed confirmed the presence of diffuse cerebral edema due to astrocytic swelling. However, no ultrastructural abnormalities of the mitochondria have been found in IHA as have been for Reye's syndrome, and the other two pathophysiologic mechanisms have been ruled out by usually normal (or mildly abnormal) laboratory findings and autopsy findings *(131)*. Heterozygosity for ornithine carbamoyltransferase deficiency has to be excluded. Finally, IHA may be caused by asparaginase *(135)* and valproic acid *(136)*. Absolute levels of plasma ammonia do not correlate well with the severity of the clinical findings, and there are no data in IHA patients regarding glutamine levels in the CSF which have been found to correlate with mental status changes in hepatic encephalopathy (glutamine is the primary metabolic product of ammonia in the brain). The most recent hypothesis on the origin of IHA involves a multifactorial etiology of gastrointestinal hemorrhage in an acutely ill and pancytopenic patient who is highly catabolic *(132)*. In addition, the duration of elevated ammonia level may be important. Treatment should consist of reduction of exogenous nitrogen load (discontinue parenteral nutrition, treat gastrointestinal bleeding), as well as hemodialysis and ammonia-trapping therapy to increase nitrogen excretion. Ammonia-trapping treatment consists of infusion of sodium benzoate or sodium phenylacetate with the resultant compounds hippurate or phenylacetylglutamine, respectively, being excreted in the urine without further metabolism. Although a reversible stage of coma in IHA has been postulated and some HSCT patients survive this complication, most patients progress into an irreversible coma and die (seven of nine patients in Mitchell's

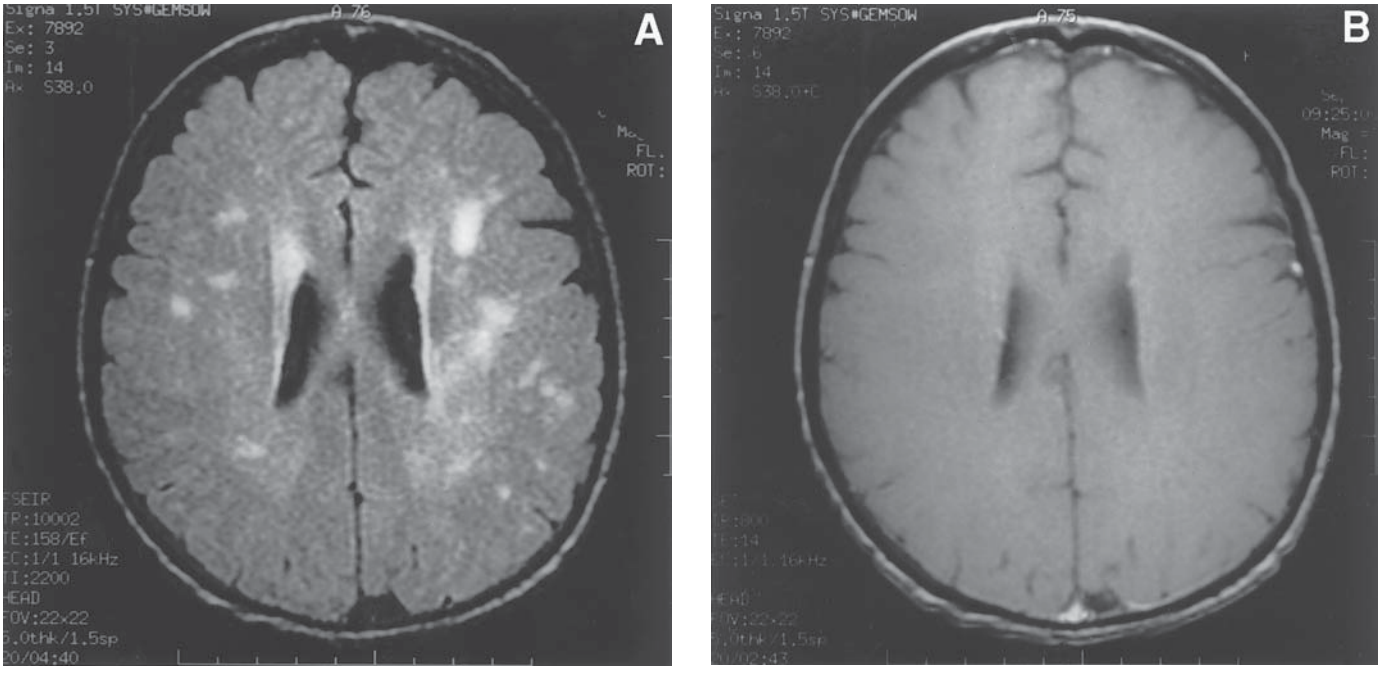



**Fig. 5.** Nonspecific multiple small high-intensity lesions (FLAIR images, **A**), nonenhancing (T1-weighted, with gadolinium, **B**) compatible with ischemic small vessel disease on a MRI scan in a 51 yr-old female 5 mo after allogeneic bone marrow transplant for recurrent NHL. She also had a 4 yr history of hypertension. She had developed chronic GVHD. Rapidly progressive coma (<48 h) set in, with respiratory alkalosis. Serum ammonia level was 451 mmol/L, liver enzymes were only mildly elevated, liver biopsy was normal. Treatment with lactulose resulted in decreased ammonia level (61 mmol/L) and improved neurological status. Within 1 wk, however, her ammonia level was again up to 376 mmol/L. Generalized seizures developed, and she expired in spite of treatment with phenylacetate/benzoate.

series, one after recurrent IHA; 10 of 12 patients in Davies' series). Therefore, early recognition of IHA may prevent this dismal prognosis. We would recommend measuring plasma ammonia levels in every patient presenting with an unexplained encephalopathy, particularly if combined with respiratory alkalosis and tachypnea.

## OTHER YET UNCLASSIFIED SYNDROMES WITH FOCAL MRI LESIONS IN HCST

A delayed and transient encephalopathy with focal MRI abnormalities mainly involving cerebral and cerebellar hemispheric white matter has been described in four patients *(137)*. These patients developed a subacute onset of confusion, lethargy, global aphasia, and generalized seizures 1 to 2 mo after either autologous or allogeneic HSCT. All recovered without specific therapy within weeks, and their MRI scans normalized within 2 to 3 mo. EEG and CSF showed nonspecific abnormalities, and a search for an infectious agent was negative. An etiological role for chemotherapeutic agents was felt to be highly unlikely. However, no mention of possible GVHD was made. We recently saw a similar syndrome in a patient without GVHD 9 mo after allogeneic HSCT for chronic lymphocytic leukemia. High signal nonenhancing abnormalities developed in the tegmentum pontis and dorsal medulla oblongata on MR scan, but disappeared within 2 wk after presentation with a subacute encephalopathy progressing to coma, seizures, and fever (Fig. 6). No infectious agent was identified, and the patient recovered spontaneously.

The spinal cord has only rarely been the predominantly involved portion of the CNS in HSCT patients. Five cases of myelopathy have been reported *(138–141)*. In two of these patients *(139,140)* radiation therapy appeared to be the cause although standard doses and fractionation were given. In the other three patients, the presence of GVHD and the response to corticosteroids or plasmapheresis suggested an immune-mediated mechanism. In one patient optic neuritis developed and resolved. MRI in these patients demonstrated abnormalities, frequently contrast-enhancing, at various levels of the spinal cord.

## NEUROLOGIC MANIFESTATIONS ASSOCIATED WITH GVHD

GVHD, the clinical manifestations of an immunological attack by donor lymphocytes on recipient tissues, generally occurs in allogeneic HSCT (rarely in syngeneic, i.e., genetically identical, or autologous HSCT). Acute GVHD develops within 100 d, usually 30–40 d after allogeneic HSCT, but may evolve into chronic GVHD. Acute GVHD describes a syndrome of dermatitis, enteritis, and hepatitis; chronic GVHD is an autoimmune-like syndrome targeting multiple organs and organ systems *(142,143)*. Both forms are still incompletely understood but require complex interactions of immunocompetent donor cells (T lymphocytes, monocytes, dendritic cells) and cytokines (e.g., tumor necrosis factor-alpha, IL- 1 and -6, interferon-gamma, released by both donor and recipient tissue, the latter induced by conditioning of the transplant recipient by

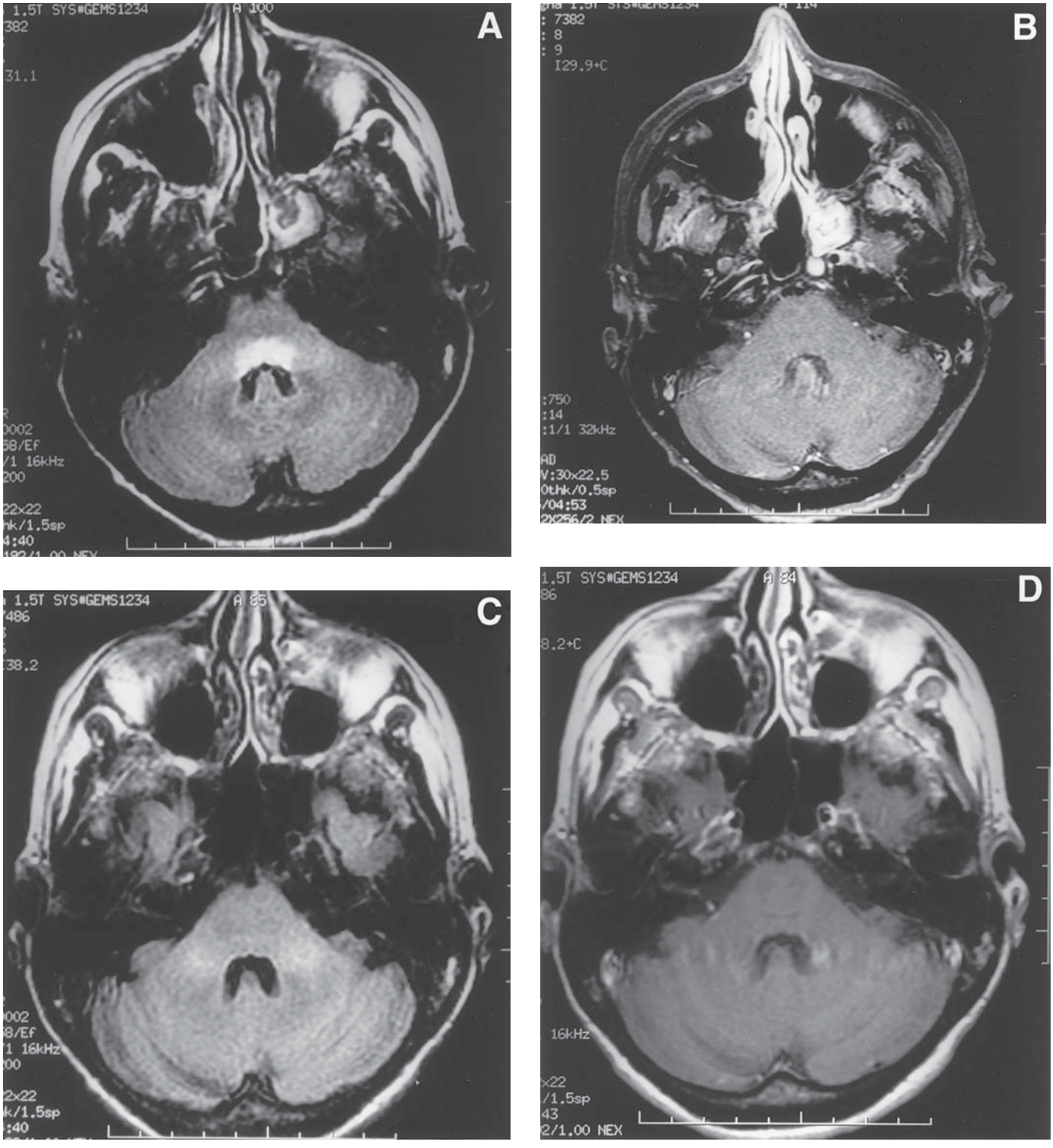



**Fig. 6.** Axial MRI scan (FLAIR images, **A)** of a 48 yr old female 9 mo after match-related T-cell depleted bone marrow transplant for CLL (T1-weighted with gadolinium, **B**). An episode of headaches, fever, nausea, and vomiting preceded mental status changes, somnolence, and coma. Hyperintense lesions in the tegmentum pontis and dorsal portion of medulla oblongata were noted at that time. All metabolic and infectious studies in serum and CSF were unremarkable. Tonic-clonic seizures developed and were treated with phenytoin. Spontaneous clinical and radiographic recovery were seen after 1 wk (**C** and **D**).

means of chemotherapy or total body irradiation). Adhesion molecules also appear to play a role *(142)*. The incidence of acute GVHD varies widely depending on HLA subtype mismatching and adequate prophylaxis, but may be as low as 10% during optimal conditions and as high as 90% in severely mismatched unrelated transplants. Patients with acute GVHD may subsequently develop chronic GVHD, but this autoimmune disease (with clinical similarities to Sjögren's syn-

drome, scleroderma, biliary cirrhosis, and bronchiolitis obliterans *(14)* may develop in about 20% of the patients without preceding acute GVHD. Prophylaxis against acute GVHD requires (except in T-cell depleted marrow grafts) an immunosuppressive drug regimen consisting of cyclosporine, prednisone, low-dose methotrexate, or combinations thereof. Antithymocyte globulin (ATG) is also occasionally used but may cause thrombocytopenia. These drugs have their own set of neurotoxic side effects and in addition may aggravate neutropenia, thus increasing the risk of infections in allogeneic HSCT patients. Chronic GVHD may require treatment with increased doses of cyclosporine, prednisone, thalidomide, psoralen with UVA irradiation, or photophoresis.

Whereas GVHD seems an established cause of peripheral nervous system disorders, it is questionable at best if GVHD ever affects the CNS. In an infant with severe combined immune deficiency (SCID) who received a maternal haploidentical transplant at 3 wk of age, acute and chronic GVHD developed. This patient died after multiple complications. At autopsy, the brain stem and right hippocampus showed focal lymphohistiocytic aggregates similar to those found in the cardiac conduction system and diaphragm. The authors raise the alternative explanation of a very early stage of a lymphoproliferative process (e.g., Epstein-Barr-virus driven B-cell lymphoma), rather than chronic GVHD *(144)*. Similarly, a case report of seizures in a patient with chronic GVHD following allogeneic HSCT for chronic myelogenous leukemia documented hyperintense lesions on T2-weighted MR images involving the posterior white matter around the lateral ventricles; no tissue diagnosis was provided *(145)*. Extremely rare are cases of immune-mediated myelopathy after allogeneic HSCT *(138,141)*; in these instances a relationship with GVHD has been postulated. The relation between GVHD and CNS disorders clearly requires further study.

## WERNICKE'S ENCEPHALOPATHY AFTER ALLOGENEIC AND AUTOLOGOUS HSCT

Side effects from HSCT and its preparative regimens may include nausea, vomiting, mucositis and diarrhea, thus necessitating total parenteral nutrition (TPN) to meet demands of caloric and nutrient intake. Thiamine (Vitamin $B_1$) is a water soluble vitamin which, via phosphorylation to thiamine pyrophosphate (TPP) and thiamine triphosphate (TTP), plays a crucial role in transketolation and oxidative carboxylation of carbohydrates. Thiamine deficiency leads to Wernicke's encephalopathy (WE), classically characterized by the triad of ataxia, ophthalmoplegia, and altered mental status. Several authors *(146,147)* have described WE as a consequence of thiamine deficiency caused by a lack of thiamine supplementation in the TPN regimens of HSCT patients. Bleggi-Torres and coworkers *(147)* described the development of severe metabolic acidosis in eight patients between the second and fourth week after allogeneic HSCT. Encephalopathy was preceded by the appearance of a raspberry tongue and was rapid in onset with confusion, papilledema, nystagmus, blindness, and eventually coma and death. Autopsy studies demonstrated petechial hemorrhages in the periventricular gray matter, medulla oblongata, and hypothalamus, but surprisingly none in the mamillary bodies. The appearance of a raspberry tongue and decreased level of consciousness should alert physicians to the possibility of iatrogenic WE.

## NEUROPATHIES AFTER HSCT

The potential consequences to the peripheral nervous system from chemotherapeutic agents are discussed elsewhere in this monograph (*see* Chapter 15).

As in other types of transplantation, peripheral nerves can be damaged by catheter placement, immobilization and cachexia, or herpes zoster infection. Peripheral neuropathy may be seen concomitantly with GVHD *(148)*. However, the literature on this putative association is rife with incompletely documented reports. Additionally, patients with disabling axonopathies are difficult to tease out from patients with sepsis-associated critical illness polyneuropathy *(149,150)*. In many of these cases, the crucial issue is whether the association is causal or coincidental. Openshaw is credited with the most comprehensive overview of the subject *(151)*.

Polyneuropathies have been noted following both autologous and allogeneic HSCT. Guillain-Barré like syndromes *(152)* as well as more protracted CIDP have been described. Their association with HSCT is problematic due to paucity of pathologic confirmation and uncertainty regarding its pathophysiologic mechanism. The degree of the immune response directed against the peripheral nerve, if any, is unclear. In some instances, a change (mostly reduction) in immunosuppression has preceded the ictus. This may indicate a breakthrough immunologic response.

Clinical presentation of demyelinating polyneuropathy follows a typical scenario with progressive motor weakness, inability to support weight, potentially resulting in a bed-bound state. Muscle cramps and prickling sensations are present. Progression in the few reported cases does not seem to involve the respiratory muscles. Pure autonomic neuropathy is on record as well following allogenic bone marrow transplantation *(153)*.

Symptoms resolved after resolution of GVHD or after treatment with glucocorticosteroids and azathioprine, both abandoned therapies for typical GBS and CIDP *(154,155)*. A recent case presenting three years after autologous BMT responded very well to ten treatments with plasma exchange *(156)*, as did three of the four patients presented by Wen and coworkers *(152)*.

Other impressive neuromuscular disorders have been myasthenia gravis *(157)* and polymyositis *(158,159)*, both observed in patients with chronic forms of graft-vs-host disease (palmar erythema, xerostomia, oral mucosae lichen). Myasthenia gravis has not been associated with thymoma in these patients, and acetylcholine receptor antibodies may be negative despite characteristic increased jitter on EMG *(160)*. Treatment has been traditional with corticosteroids and pyridostigmine *(162–164)*. Rituximab was successful in one refractory patient with myasthenia gravis *(161)*.

## CONCLUSIONS

The field of bone marrow transplantation has been firmly established and continues to shape the treatment of hematologic and solid cancers. This paradigm shift in the management of these neoplasms has introduced opportunities of studying neu-

rologic complications. New developments as immune reconstitution after autologous HSCT *(165)* and the identification and application of so-called "facilitating cells" to promote allogeneic stem cell engraftment *(166)* may improve antitumor efficacy and reduce complication rates. Nevertheless, the consultant neuro-oncologist or any neurologist with specific interest in this area should anticipate complex presentations, nondiagnostic neuroimaging tests, and incomplete understanding of mechanisms. Prospective clinical registries should be designed to address the magnitude of the problem.

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# 18 Central Nervous System Infections in Cancer Patients

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## INTRODUCTION

Infections of the nervous system occur more frequently in patients with cancer than in the general population, but they are one of the least common neurologic complications of malignancy. Central nervous system (CNS) infections were diagnosed in only 0.05% of the patients admitted to a large cancer hospital *(1,2)*. CNS infections are more common in certain clinical settings: Hodgkin's disease, non-Hodgkin's lymphoma, leukemias, severe neutropenia, immunosuppressive treatment, bone marrow transplantation, and following neurosurgery *(1,3)*. In one study CNS infections occurred in 2.7% of patients with Hodgkin's disease, 2.5% of patients with chronic lymphocytic leukemia (CLL), and 0.6% of patients with non-Hodgkin's lymphoma *(4)*.

The spectrum of organisms responsible for CNS infections in cancer patients differs from that seen in immunocompetent individuals *(3,4)*. *Cryptococcus neoformans* and *Listeria monocytogenes* are the most common causes of meningitis while enteric Gram negative bacilli, fungi, and *Toxoplasma gondii* are the major causes of brain abscesses in patients with cancer *(3)*. *Neisseria meningitidis* and *Haemophilus influenzae* rarely cause meningitis, and anaerobic organisms seldom cause brain abscesses in the cancer population.

The presence of fever accompanied by headache, altered mental state (lethargy, irritability, delirium, stupor, or coma) or focal neurologic signs should prompt a careful search for a CNS infection. However, the typical characteristics of CNS infection are often blunted in patients with cancer. Fever may be absent, neck stiffness is uncommon even in the presence of meningitis, and headache may be mild *(3–5)*. A change in mental state is the most consistent sign of CNS infection in cancer patients *(3,5)*. Evidence of systemic infection is an important clue that neurologic symptoms and signs may be the result of a CNS infection. However, in about 40% of patients with concurrent systemic and CNS infections, the CNS is infected with a different organism from the one causing the systemic infection. Multiple pathogens may infect the CNS simultaneously or sequentially *(4)*. Fever and mental state changes may be wrongly attributed to a concurrent systemic infection or a metabolic encephalopathy.

Magnetic resonance imaging (MRI), computerized tomography (CT), and examination of the cerebrospinal fluid (CSF) are usually required to establish the presence of a CNS infection and to identify the cause. Complications of the underlying malignancy and its treatment may hinder diagnostic procedures. There is a risk of developing a spinal subdural hematoma following lumbar puncture in patients with coagulation defects. Biopsy of the meninges, brain, and other organs may be hampered by the risk of poor wound healing, bleeding from coagulation defects, and the patient's general debility. Stereotactic procedures have reduced the morbidity of a brain biopsy.

The treatment of CNS infections is less successful than it is in immunocompetent patients. In one study, 85% of neutropenic patients with a CNS infection died despite appropriate treatment *(5)*. Survival largely depends on bone marrow recovery. Even when antimicrobial treatment results in a clinical cure, relapse and superinfection are common.

## PATHOGENESIS OF NERVOUS SYSTEM INFECTIONS

CNS infections in patients with cancer often arise from an abnormality of host defenses, either due to the cancer itself or its treatment (Table 1) *(1–4)*. Disruption of skin, mucous membrane, or epithelial barriers to infection by tumor infiltration, chemotherapy-induced mucositis, surgery, vascular cannulae, and urinary and epidural catheters provide a portal of entry for microorganisms. Previous antimicrobial treatment may change the normal flora and facilitate growth of microorganisms better suited to penetrate these barriers. Barriers to CNS infection may be breached during cranial and spinal surgery, or by infiltrating tumors in the skull base. Defects in the immune system

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**Table 1**
**Pathogenesis of CNS Infections in Patients with Cancer**

| *Neutrophil defects*[a] | *Disorders of cell-mediated immunity*[b] | *Abnormal B-lymphocyte function*[c] | *Hyposplenism* | *Barrier disruption* |
|---|---|---|---|---|
| Bone marrow infiltration<br>Acute leukemia<br>Lymphoma | Hodgkin's disease<br>Non-Hodgkin's lymphoma | Multiple myeloma<br>Chronic lymphocytic leukemia | Splenectomy<br>Hyposplenism | Head, spine surgery<br>Infiltrating tumor in skull, spine |
| Bone marrow suppression<br>Chemotherapy<br>Radiotherapy | Corticosteroids<br>Other immunosuppressive drugs | Combined CT/RT[d] for advanced Hodgkin's disease | | CSF shunt<br>Intraventricular reservoir |
| Bone marrow transplantation (early) | Bone marrow transplantation (late) | Bone marrow transplantation | | |

[a]Most commonly neutropenia (<1000/mm$^3$).
[b]Disorders of T-lymphocyte and macrophage function.
[c]Decreased immunoglobulin production.
[d]CT/RT, Chemotherapy and radiotherapy.

hinder eradication of these organisms and permit a previously suppressed organism to cause disease.

## CLINICAL PATTERNS OF INFECTION

Each organism tends to cause a specific pattern of infection (Table 2), but some pathogens can present in several ways.

**MENINGITIS** Meningitis accounts for 70% of the CNS infections in the cancer population *(3)*. Fever, headache, and neck stiffness are the cardinal clinical features *(6)*, but in patients with cancer the clinical presentation may be subtle. Fever may be present already, usually from a systemic infection, and some patients are afebrile. Headache is often present, but it may be mild. Nuchal rigidity is present initially in only 20% of patients, but it eventually develops in 60% *(3)*. An alteration in mental state may be the only clue to the presence of meningitis *(4,5)*. Focal neurologic signs and seizures are uncommon early manifestations, but they can occur if cerebral infarction develops secondary to vasculitis. Cranial nerve palsies may occur with basilar meningitis.

Examination of the CSF is the key investigation if meningitis is suspected. Enough CSF should be collected for a cell count and differential, measurement of the protein and glucose concentrations, Gram stain and culture for bacteria and fungi. The CSF typically has a pleocytosis, but 50% of neutropenic patients do not have a CSF pleocytosis despite the presence of bacterial or fungal meningitis *(3)*. Collection of a large volume of CSF increases the chance of determining the pathogen *(3)*. Cytologic examination of the CSF is often required to distinguish between CNS infection and malignant infiltration of the leptomeninges. Cultures from other sites, such as blood and urine, are commonly positive in patients with bacterial or *Candida albicans* meningitis. CT and MRI may be normal, or show hydrocephalus, cerebral edema, and enhancement of the leptomeninges and ependyma *(6)*.

The neuropathologic changes of meningitis in neutropenic patients differ from those seen in immunocompetent hosts. Neutrophilic inflammatory exudates are typically absent from the leptomeninges, but vasculitis and ischemic necrosis are unusually prominent and may explain the severe encephalopathy associated with meningitis in neutropenic patients *(5)*.

**BRAIN ABSCESS** In relation to meningitis, brain abscesses are relatively more common causes of CNS infection in patients with cancer than in immunocompetent hosts *(3)*. Brain abscesses constitute about 25% of the CNS infections occurring in a cancer hospital *(3)* and most commonly occur in the setting of leukemia, bone marrow transplantation, or recent neurosurgery. Patients typically present with headache, nausea, vomiting, and altered mental state. Focal neurologic signs are present in only 30–50% and fever is often absent *(7)*. CT and MRI are useful in identifying brain abscesses (Fig. 1), but the lesions may be mistaken for cerebral metastases *(7)*. The CSF is either normal or shows a pleocytosis and a high protein content. CSF cultures are positive only if there is a coincident meningitis. Enteric Gram negative bacilli, *Staphylococcus aureus* and *Candida albicans* often can be isolated from blood cultures. *Toxoplasma gondii* DNA often can be detected by polymerase chain reaction (PCR) in the CSF. *Nocardia asteroides* and fungal pathogens frequently cause a coexistent lung infection, and *Aspergillus* species and *N. asteroides* may be cultured from the sputum. A brain biopsy is usually required to confirm a diagnosis of aspergillosis or mucormycosis.

**MENINGOENCEPHALITIS** Viruses can cause CNS infection in patients with impaired cell-mediated immunity. Most patients present with encephalitis or meningoencephalitis. Neck stiffness may be absent, but delirium, myoclonus and seizures are prominent. Focal signs may arise secondary to direct viral invasion of the brain or vasculitis with secondary infarction. The CSF typically contains a lymphocytic pleocytosis, but the glucose level is usually normal. Detection of viral DNA or RNA by PCR is helpful in the diagnosis of many types of encephalitis. Encephalitis may be confused with more common neurologic complications of cancer, especially a metabolic encephalopathy or brain metastases.

**MICROABSCESSES** *S. aureus*, *C. albicans*, and *T. gondii* produce multiple microabscesses in patients with leukemia or

**Table 2**
**Main Patterns of CNS Infection and Common Pathogens**

| | *Neutrophil defects* | *Disorders of cell-mediated immunity* | *Abnormal B-lymphocyte function* | *Hyposplenism* | *Head, spine surgery* | *CSF shunt* |
|---|---|---|---|---|---|---|
| Meningitis | Enteric GNB*<br>*Candida**<br>*Aspergillus*<br>*Listeria*<br>*S. pneumoniae* | *Cryptococcus**<br>*Listeria**<br>*Nocardia*<br>*Toxoplasma*<br>*Strongyloides*<br>*Coccidioides*<br>*Histoplasma* | *S. pneumoniae**<br>*H. influenzae*<br>*N. meningitidis* | *S. pneumoniae**<br>*H. influenzae*<br>*N. meningitidis* | Enteric GNB*<br>*S. epidermidis**<br>*S. aureus**<br>*Corynebacteria*<br>*Candida* | *S. epidermidis**<br>*S. aureus* |
| Brain abscess | Enteric GNB*<br>*Aspergillus**<br>*Mucoraceae**<br>*Candida** | *Nocardia**<br>*Toxoplasma**<br>*Listeria*<br>*Cryptococcus*<br>*Histoplasma* | | | Enteric GNB | |
| Meningo-encephalitis | | Varicella zoster*<br>JC virus*<br>Cytomegalovirus<br>Herpes simplex | | | | |
| Microabscesses | *Candida**<br>*Aspergillus* | Toxoplasma* | | | | |
| Stroke | *Aspergillus**<br>*Mucoraceae** | Varicella zoster* | | | | |
| Invasive sinusitis | *Mucoraceae**<br>*Aspergillus** | | | | | |

*Most common pathogens.
GNB, Gram-negative bacilli.

lymphoma. The clinical presentation resembles encephalitis with fluctuating confusion, reduced level of consciousness, and focal signs *(8)*. The lesions are often too small to be seen on CT or MRI *(7)* and the CSF cell count is usually normal. The organism is not recovered from the CSF, but blood cultures may be positive.

**STROKE** CNS infection in cancer patients can have a stroke-like presentation with sudden onset of focal neurologic signs in three settings. *Aspergillus* and the *Mucoraceae* invade cerebral blood vessels, causing hemorrhagic infarction, intracerebral hemorrhage (Fig. 2), or subarachnoid hemorrhage *(9)*. Patients with bacterial meningitis can develop a vasculitis which causes cerebral infarction *(10)*. Cerebral vasculitis also can appear after an episode of herpes zoster *(11)*.

**INVASIVE SINUSITIS (RHINOCEREBRAL INFECTION)** Invasive sinusitis occurs in the setting of severe neutropenia and acute leukemia. The most common pathogens are the *Mucoraceae* and species of *Aspergillus (12,13)*. Less common causes are *Fusarium* species, *Pseudomonas aeruginosa*, and *Pseudallescheria boydii*. Infection begins in the nasopharynx and spreads into the paranasal sinuses, orbit, and intracranial cavity by invading blood vessels or by direct extension. Early manifestations include persistent fever, periorbital pain, facial swelling, facial numbness, epistaxis, and necrotic ulceration of the nasal epithelium and the palate. Extension into the orbit is heralded by proptosis, ophthalmoplegia, visual loss, and periorbital cellulitis. Intracranial extension leads to meningitis, cavernous sinus thrombosis, cerebral infarction secondary to thrombosis of the internal carotid artery, or a frontal lobe abscess.

**MYELOPATHY** Many of the organisms that cause brain abscesses in immunocompromised patients also can cause epidural, subdural, or intramedullary spinal cord abscesses. Spinal infections often occur in the setting of disseminated infection with hematogenous spread, but epidural abscesses also can develop by direct extension from vertebral osteomyelitis or a paraspinal abscess. Epidural and subdural spinal abscesses typically present with localized back pain followed by the development of radicular pain, weakness, sensory level, and sphincter dysfunction. Pain may be less severe with an intramedullary spinal cord abscess. Fever is not a consistent finding. The clinical features resemble spinal cord compression by a metastatic tumor. MRI is the most appropriate method of imaging. Blood cultures may yield the pathogen, but CSF cultures are usually negative. Epidural, subdural, and intramedullary spinal cord abscesses should be treated with surgical drainage and intravenous antibiotics.

Varicella zoster, herpes simplex, and cytomegalovirus may cause a myelitis, which typically presents with the acute onset of severe weakness, a sensory level, and sphincter dysfunction. Back and radicular pain may be present. There is a CSF pleocytosis, and MRI shows changes in the signal intensity in the spinal cord. The pathogen may be identified by amplification of viral DNA in the CSF by the PCR.

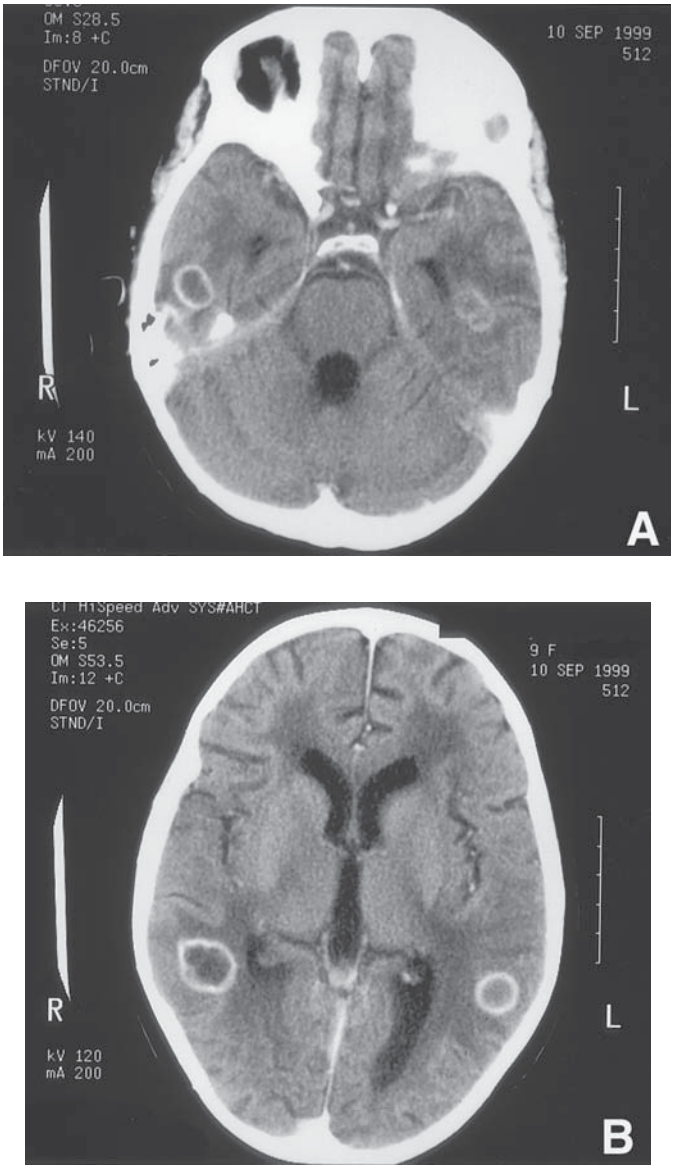


**Fig. 1. (A,B).** Enhanced CT showing ring-enhancing cerebral abscesses in a 9-yr-old girl with disseminated aspergillosis following bone marrow transplantation for acute lymphoblastic leukemia.

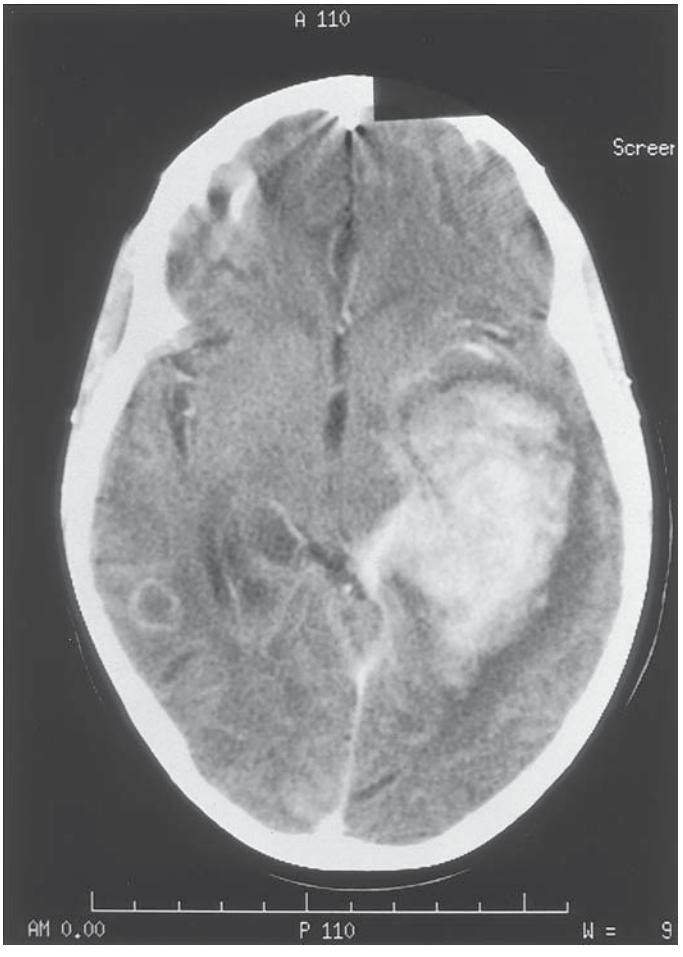


**Fig. 2.** Large intracerebral hemorrhage in a 12-yr-old girl with acute lymphoblastic leukemia and cerebral aspergillosis. Note ring-enhancing lesion in the right cerebral hemisphere.

## BACTERIAL INFECTIONS

**LISTERIA MONOCYTOGENES** *L. monocytogenes* is an aerobic Gram-positive bacillus, which causes infections in patients with lymphomas or other hematologic malignancies, bone marrow transplant recipients, and patients who have been treated with corticosteroids or other immunosuppressive agents *(14–17)*. Meningitis is the most common form of CNS infection. Symptoms usually develop over 2–10 d, but the course may be more fulminant in severely immunocompromised patients. Fever, altered mental state, and headache are the most common manifestations, but neck stiffness is uncommon. Seizures occur in 25%. The CSF pleocytosis may show a predominance of neutrophils or lymphocytes. The CSF glucose concentration is decreased in 40% of patients and the protein level is usually elevated. Gram stain is positive in only 30% *(17)*. Visible organisms may be mistaken for diphtheroids and dismissed as contaminants. *Listeria* usually grows from the CSF, and blood cultures are positive in 75%.

Meningitis may be associated with microabscesses in the brainstem, but this complication is uncommon in immunocompromised patients *(18)*. These patients develop asymmetric cranial nerve palsies, ataxia, nystagmus, hemiparesis, and hemisensory signs. Rare neurologic manifestations of listeriosis are diffuse or focal cerebritis, brain abscesses, and spinal cord abscesses *(17,19)*.

Meningitis should be treated with either intravenous ampicillin 2 g every 4 h or penicillin 2MU every 4 h, plus either intravenous or intrathecal gentamicin for at least 3 wk *(17,20)*. Trimethoprim and sulfamethoxazole can be used if the patient is allergic to penicillin, but third-generation cephalosporins are inactive against *L. monocytogenes*. In patients with a brain abscess, antibiotics should be continued for at least 6 wk. Well-localized abscesses may require surgical drainage *(17)*. CNS infection with *Listeria* is associated with a 50–65% mortality in cancer patients *(1)*, but most patients respond to treatment unless treatment is delayed or the patient has advanced malignancy *(15)*.

**NOCARDIA ASTEROIDES** *N. asteroides* is an aerobic actinomycete, which causes disease in patients with impaired cell-mediated immunity *(21–23)*. Infection usually begins in

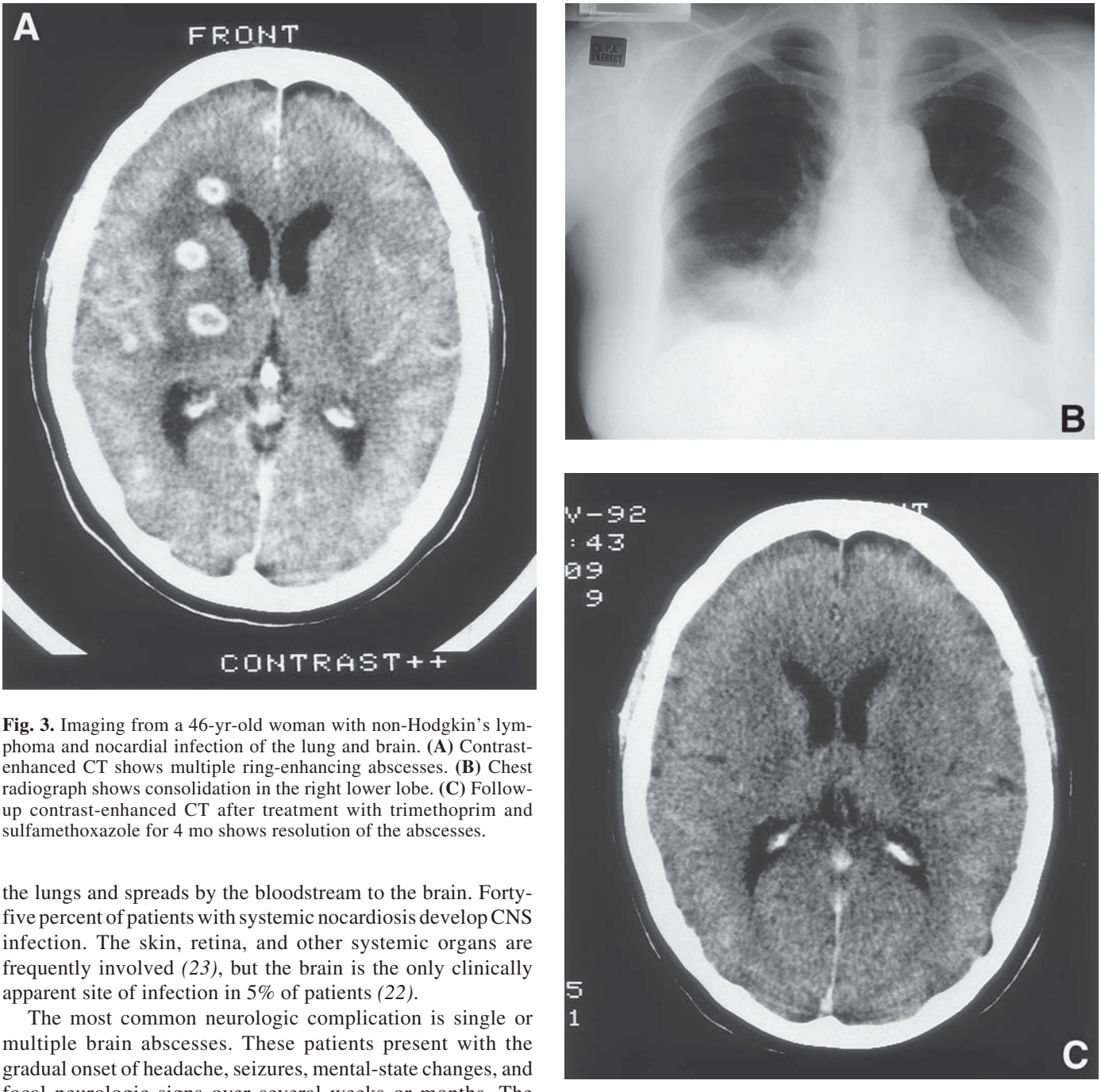


**Fig. 3.** Imaging from a 46-yr-old woman with non-Hodgkin's lymphoma and nocardial infection of the lung and brain. **(A)** Contrast-enhanced CT shows multiple ring-enhancing abscesses. **(B)** Chest radiograph shows consolidation in the right lower lobe. **(C)** Follow-up contrast-enhanced CT after treatment with trimethoprim and sulfamethoxazole for 4 mo shows resolution of the abscesses.

the lungs and spreads by the bloodstream to the brain. Forty-five percent of patients with systemic nocardiosis develop CNS infection. The skin, retina, and other systemic organs are frequently involved *(23)*, but the brain is the only clinically apparent site of infection in 5% of patients *(22)*.

The most common neurologic complication is single or multiple brain abscesses. These patients present with the gradual onset of headache, seizures, mental-state changes, and focal neurologic signs over several weeks or months. The course may be more rapid in severely immunocompromised patients. Fever is often absent. Ring-enhancing lesions are visible with CT and MRI (Figs. 3 and 4), but the radiologic appearances are not specific for *Nocardia (23)*. The organism grows from CSF cultures in only 20% of patients. Identification of *Nocardia* in sputum is a convenient method of confirming the diagnosis in patients with lung disease, but the organism is more consistently identified in pus or necrotic tissue obtained by stereotactic aspiration or biopsy of a cerebral lesion.

*Nocardia* also can cause a subacute or chronic meningitis secondary to hematogenous seeding of the meninges *(24)*. These patients present with headache, nausea, vomiting, altered mental state, neck stiffness and fever. Focal signs are uncommon. The CSF typically shows a neutrophilic pleocytosis, low glucose level, and high protein content. Gram stain of the CSF is not usually diagnostic, but CSF cultures are typically positive. The yield from the CSF may be improved by obtaining multiple large-volume specimens. Several weeks may be required before the organism is isolated and cultures should not be prematurely discarded *(23)*.

Nocardial infections of the CNS are usually treated with trimethoprim 10–20 mg/kg/d and sulfamethoxazole 50–100 mg/kg/d for at least 1 yr. Antibiotics should be administered intravenously for the first 3–6 wk. Sulfadiazine or sulfisoxazole 6–12 g/d in 4-6 divided oral doses after a loading dose of 4 g appears to have similar efficacy to trimethoprim and sulfamethoxazole *(23)*. Broad-spectrum cephalosporins, minocycline, imipenem, and amikacin have also been used

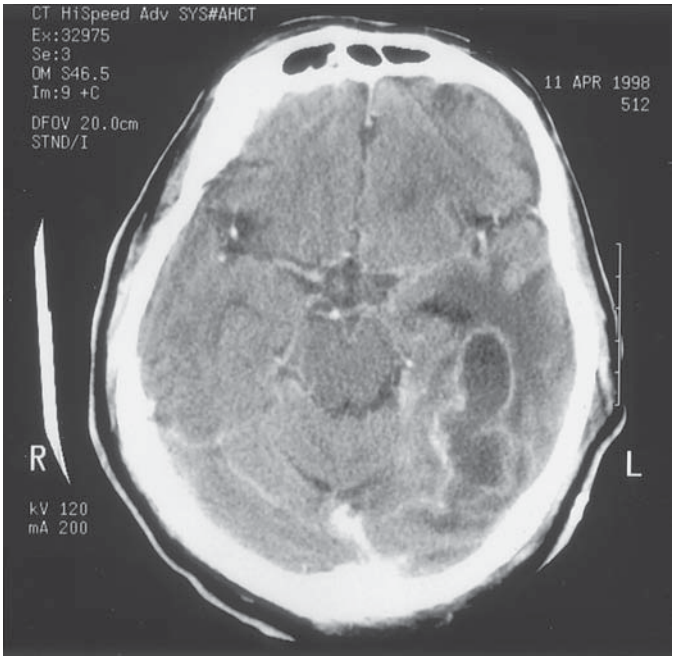


**Fig. 4.** Single, large abscess in left temporal lobe in 63-yr-old man. *Nocardia asteroides* was isolated from pus aspirated from the abscess.

successfully. Excision of a multiloculated abscess may be beneficial *(25)*. In immunocompromised patients the mortality of CNS nocardial infection exceeds 80% *(22)* and relapses may occur after completing apparently successful treatment.

**STREPTOCOCCUS PNEUMONIAE** *S. pneumoniae* and, less commonly other encapsulated bacteria, can cause meningitis after splenectomy and in patients with functional hyposplenism, multiple myeloma or CLL *(26)*. Polyvalent pneumococcal vaccine should be given to patients before splenectomy *(27)*, but the vaccine does not consistently prevent pneumococcal sepsis. Meningitis is often a component of a community-acquired disseminated infection. An initial prodrome consisting of mild flu-like symptoms is followed by the fulminant onset of fever, rigors, and shock *(28)*. Headache and mental state changes are common, but most patients do not have neck stiffness. The CSF usually shows a polymorphonuclear pleocytosis, low glucose level, and raised protein concentration, but early in the illness the cell count and chemical constituents may be normal. The CSF Gram stain usually reveals large numbers of bacteria and the pneumococcal capsular antigen is detectable. The pathogen usually grows from CSF and blood cultures. Pneumococcal meningitis commonly causes vasculitis and cerebral infarction resulting in seizures and focal neurologic deficits. An increasing proportion of strains of *S. pneumoniae* are resistant to penicillin. Patients with suspected or proven pneumococcal meningitis should be treated with intravenous vancomycin 1 g every 12 h, plus either penicillin or ceftriaxone until the identity of the infecting organism and its antimicrobial susceptibility have been determined. Treatment should be continued for at least 7 d.

**GRAM-NEGATIVE BACILLI** Patients with neutropenia are prone to infection with enteric Gram-negative bacilli, especially *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae (5)*. Occasionally these organisms cause infections in patients with impaired cell-mediated immunity. Gram-negative bacilli usually cause a hospital-acquired meningitis, which develops during bacteremia. Brain abscesses are less common. The gastrointestinal and urinary tracts are the usual portals of entry, but Gram-negative bacillary meningitis can arise from a contiguous site of infection or develop after neurosurgery (29).

Patients with Gram-negative bacillary meningitis present with new onset of fever and an acute deterioration in mental state. Headache may be present, but nuchal rigidity is rare. Seizures occur in 40%. The pathogen is often visible on a Gram stain and it is readily grown from the CSF *(3,5)*. Treatment is usually with a third generation cephalosporin (e.g., ceftriaxone 2 g every 12 h or ceftazidime 2 g every 8 h) for at least 3 wk. Ceftazidime is the only cephalosporin with adequate activity against *P. aeruginosa (30)*. The addition of an aminoglycoside (e.g., amikacin 7.5 mg/kg 12 hourly) may improve the outcome. Fewer than 20% of patients with cancer and a CNS infection due to Gram-negative bacilli survive *(1)*, but postoperative Gram-negative bacillary meningitis has a lower mortality rate.

In patients with Gram-negative bacillary abscesses, the pathogen often can be isolated from blood cultures, but stereotactic aspiration of an abscess may be required to establish the diagnosis. The initial treatment is with antibiotics, but excision of an abscess must be considered if there is no clinical or radiologic improvement, and if the patient is in good condition.

**STAPHYLOCOCCI** In patients who have had a ventricular shunt or reservoir inserted, meningitis is usually caused by *Staphylococcus epidermidis* or less commonly, *S. aureus* and other skin organisms *(31,32)*. There is a high prevalence of methicillin resistance in both *S. epidermidis* and *S. aureus*. Until the antibiotic sensitivity of the organism is known, patients with a staphylococcal shunt infection should be treated initially with intravenous vancomycin 1 g every 12 h plus an isoxazolyl penicillin (e.g., oxacillin 2 g every 6 h). Vancomycin can be discontinued if the organism is methicillin-sensitive. Treatment should be continued for at least 2 wk and infected shunts should be removed. Staphylococci also can cause CNS infection after other neurosurgical operations.

## FUNGAL INFECTIONS

*Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Coccidioides immitis* typically cause community-acquired chronic meningitis in patients with impaired cell-mediated immunity *(33)*. *Candida*, *Aspergillus*, and the *Mucoraceae* are common pathogens in patients with neutropenia. Fungi with hyphal elements (*Aspergillus* and *Mucoraceae*) cause abscesses or hemorrhagic infarcts, while *Candida* most commonly produces multiple microabscesses *(34)*. A wide range of other fungal pathogens occasionally cause meningitis or brain abscesses in immunocompromised patients *(35–37)*.

**CRYPTOCOCCUS NEOFORMANS** *C. neoformans* is a yeast-like fungus that causes a meningoencephalitis in patients with lymphoma or CLL *(38,39)*. Corticosteroids and other immunosuppressive agents also predispose to the development

of cryptococcal meningitis *(39)*. Disseminated infection arises from the lungs.

Cryptococcal infection usually presents with subacute or chronic meningitis *(40)*. The symptoms usually begin insidiously over several weeks or months, but a more rapid onset over 1–2 wk occurs with severe immunosuppression. Early symptoms are often mild and include headache, low-grade fever, nausea, unsteady gait, and a change in mental state. Seizures are uncommon until the later stages. Examination may show mental state changes, papilledema, ataxia, and hyperreflexia, but neck stiffness is uncommon. Cranial nerve palsies occur in about 20%, but other focal neurologic signs are uncommon. Neuroimaging may be normal, or show hydrocephalus and contrast enhancement of the leptomeninges and the cortical gyri. Pathologic examination of the brain reveals granulomatous inflammation of the leptomeninges, which is especially prominent at the base of the brain. Small lesions containing clusters of cryptococci with little inflammatory response are often present in the Virchow-Robin spaces and the brain parenchyma *(41)*. Skin lesions may be an important clue to the diagnosis. The chest radiograph may show lung infiltrates, but most cryptococcal pulmonary infections are asymptomatic. Five percent of patients with cryptococcal meningitis develop one or more enhancing or nonenhancing mass lesions in the brain (cryptococcomas), but these lesions are rare in immunocompromised patients.

The CSF cell count may be normal, but it usually shows a lymphocytic pleocytosis and an increased protein content. The CSF glucose level is often low. Cryptococci are visible in centrifuged CSF samples in about 50% of patients, but India ink or nigrosin preparations may yield false-positive results. The cryptococcal polysaccharide capsular antigen is present in the CSF in more than 90% of patients and may be detected despite negative India ink preparations and CSF cultures. False-positive antigen results are rare. *C. neoformans* usually grows from CSF cultures, but large specimens may be needed and it takes several days to grow. Cisternal CSF may yield positive cultures when the lumbar CSF is negative. The organism also can be isolated from the sputum, blood, or urine even when there is no clinical evidence of infection at these sites. The cryptococcal antigen can be detected in serum from most patients.

Immunocompromised patients are usually treated with intravenous amphotericin B 0.7 mg/kg/d and oral flucytosine 100 mg/kg/d in four divided doses for the first 2 wk, followed by oral fluconazole 400 mg/d for the next 8 wk *(42,43)*.

Combined intraventricular and intravenous amphotericin B may be curative in severe cryptococcal meningitis *(44)*. Only 43% of patients with cancer and cryptococcal meningitis are cured or improved 6 mo after diagnosis *(39)*. The median survival is only 2 mo and relapses are common among survivors. Maintenance treatment with fluconazole 200–400 mg/d is required if cell-mediated immunity is persistently impaired *(45,46)*.

**COCCIDIOIDOMYCOSIS** Patients with impaired cell-mediated immunity and a history of travel or residence in an endemic area may develop disseminated infection with *C. immitis*. Infection may involve the leptomeninges and the underlying brain and spinal cord *(47,48)*. These patients usually present with chronic meningitis. Brain abscesses are uncommon. Headache, nausea, vomiting, and confusion are typical manifestations, but nuchal rigidity and focal neurologic signs are uncommon. The CSF shows a mononuclear pleocytosis, low glucose concentration, and an elevated protein level. *C. immitis* is seldom isolated from the CSF, and antibody responses may be blunted. Sputum, bone marrow aspirates, and skin lesions may yield positive cultures. Initial treatment may include intrathecal amphotericin B. Relapses are common if treatment is stopped, and lifelong treatment with fluconazole or itraconazole is required *(49)*.

**HISTOPLASMOSIS** Disseminated histoplasmosis may cause chronic meningitis, intracerebral granulomas, brain abscesses, or vasculitis in immunocompromised patients *(50)*. The diagnosis is made on the basis of positive cultures from the CSF, blood, or bone marrow, or serologic tests for antibodies in the blood and CSF. Several weeks are needed to identify *H. capsulatum* in cultures, and multiple CSF specimens may be required to obtain positive cultures. Detection of the *Histoplasma* polysaccharide antigen in serum, urine, or CSF may be a sensitive and specific indicator of disseminated infection and provides a more rapid diagnosis. Disseminated histoplasmosis is treated with high doses of amphotericin B, but relapses are common *(50)*.

**ASPERGILLOSIS** *Aspergillus* species, most commonly *A. fumigatus (9,51)*, cause invasive infection in patients with severe prolonged neutropenia and either acute leukemia or another hematologic malignancy *(51,52)*. Other risk factors include diabetes mellitus, bone marrow transplantation, and corticosteroids *(9,53–55)* .

Cerebral aspergillosis usually follows hematogenous dissemination from the lung *(9,51,54,55)*. The brain is involved in 10–20% of patients, but isolated CNS disease is rare. The most common pathogenic process is fungal invasion and thrombosis of cerebral blood vessels causing solitary or multiple subcortical ischemic or hemorrhagic infarcts *(9)*. Neurologic symptoms typically develop in the setting of unremitting fever and pulmonary infiltrates despite antibiotic therapy *(53,55)*. The most common presentation is with abrupt onset of focal neurologic signs and seizures followed by progressive confusion and loss of consciousness over the next few days *(9)*. Headache and meningeal signs are uncommon. Aspergillosis also may present with subarachnoid hemorrhage secondary to rupture of a mycotic aneurysm, solitary or multiple brain abscesses, microabscesses, meningitis, or invasive sinusitis *(13,56)*.

Imaging may show infarcts, hemorrhages or ring-enhancing abscesses (Figs. 1, 2, and 5) *(9, 57,58)*. The CSF may be normal, or show a mildly elevated protein level, a mononuclear pleocytosis, and erythrocytes. *Aspergillus* rarely grows in CSF or blood cultures. The usual method of confirming the diagnosis is identification of *Aspergillus* in pus or tissue, but a brain biopsy may not be feasible because of the patient's clinical state or the presence of coagulation abnormalities. In patients with pulmonary infection *Aspergillus* may be isolated from the sputum or a lung biopsy. Detection of galactomannan in the serum, or *Aspergillus* DNA in the blood or CSF by PCR, promise to be useful methods of diagnosing aspergillosis *(51,59,60)*.

The mortality of cerebral aspergillosis exceeds 95% *(55)*. Successful treatment is seldom possible if neutropenia is

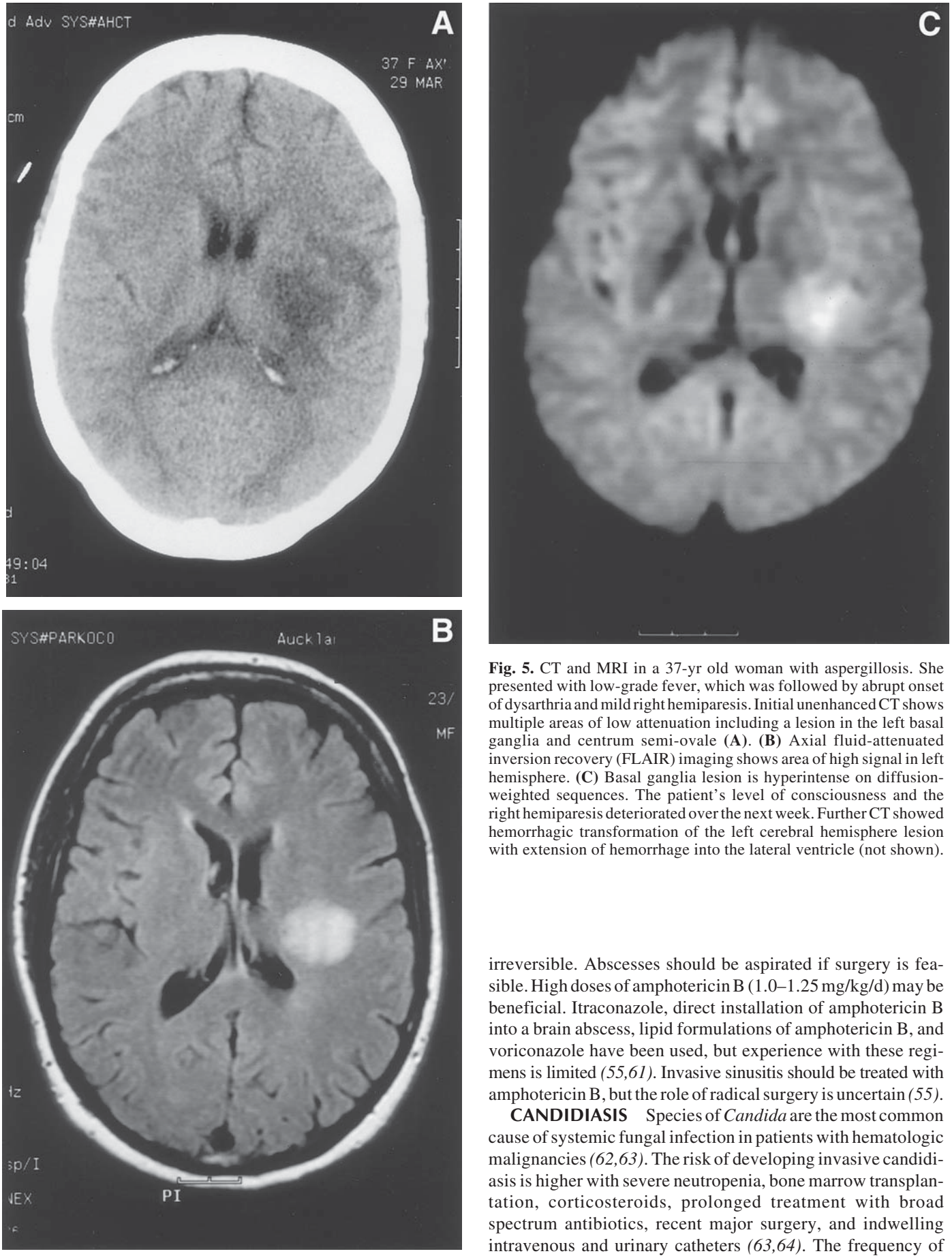


**Fig. 5.** CT and MRI in a 37-yr old woman with aspergillosis. She presented with low-grade fever, which was followed by abrupt onset of dysarthria and mild right hemiparesis. Initial unenhanced CT shows multiple areas of low attenuation including a lesion in the left basal ganglia and centrum semi-ovale **(A)**. **(B)** Axial fluid-attenuated inversion recovery (FLAIR) imaging shows area of high signal in left hemisphere. **(C)** Basal ganglia lesion is hyperintense on diffusion-weighted sequences. The patient's level of consciousness and the right hemiparesis deteriorated over the next week. Further CT showed hemorrhagic transformation of the left cerebral hemisphere lesion with extension of hemorrhage into the lateral ventricle (not shown).

irreversible. Abscesses should be aspirated if surgery is feasible. High doses of amphotericin B (1.0–1.25 mg/kg/d) may be beneficial. Itraconazole, direct installation of amphotericin B into a brain abscess, lipid formulations of amphotericin B, and voriconazole have been used, but experience with these regimens is limited *(55,61)*. Invasive sinusitis should be treated with amphotericin B, but the role of radical surgery is uncertain *(55)*.

**CANDIDIASIS** Species of *Candida* are the most common cause of systemic fungal infection in patients with hematologic malignancies *(62,63)*. The risk of developing invasive candidiasis is higher with severe neutropenia, bone marrow transplantation, corticosteroids, prolonged treatment with broad spectrum antibiotics, recent major surgery, and indwelling intravenous and urinary catheters *(63,64)*. The frequency of

CNS involvement in systemic candidiasis varies from 11–50% in different studies *(62,64,65)*. *Candida* reaches the CNS by hematogenous spread from the bowel, lungs, genitourinary tract, or heart *(65)*. Other clinical manifestations of systemic candidiasis include pulmonary infiltrates, skin lesions, hepatosplenomegaly, myositis, and retinal abnormalities *(62)*.

Multiple microabscesses are the most common neurologic complication of systemic candidiasis *(64)*. These patients present with persistent fever despite antibiotic treatment, headache, seizures, fluctuating focal neurologic signs, and an encephalopathy. CT and MRI are often normal *(7)*.

*Candida* also causes an acute or chronic meningitis *(66)*. In this condition the CSF shows a polymorphonuclear or lymphocytic pleocytosis, increased protein, and reduced glucose concentrations. CSF smears identify the yeast in 17–40% of patients *(65,66)*. Cultures of the CSF are initially positive in less than 50% of patients, but with repeated lumbar punctures *C. albicans* is eventually cultured from the CSF in more than 80% *(66)*. Less common neurologic manifestations of disseminated candidiasis include macroabscesses, noncaseating granulomas, hemorrhagic infarction following invasion of blood vessels, and intracerebral hemorrhage after rupture of a mycotic aneurysm *(64,65)*.

*Candida* can be isolated from the blood, urine, oropharynx, or skin lesions *(65)*. Although *Candida* can be isolated from blood cultures in 30–70% of patients, cultures may not become positive until late in the disease *(62)*. Tissue biopsy may be required to confirm the diagnosis. The role of tests that detect fungal nucleic acids by PCR, cell wall or cytoplasmic antigens, or antibodies directed against *Candida* antigens is unclear *(67)*.

CNS candidiasis is treated with intravenous amphotericin B 0.6–1.0 mg/kg/d, which is sometimes combined with oral flucytosine 100–150 mg/kg/d in four divided doses for at least 6 wk. Large solitary abscesses should be drained if surgery is feasible. The mortality of disseminated candidiasis in neutropenic patients exceeds 90%, but the prognosis is better for meningitis than with other types of CNS candidiasis.

**MUCORMYCOSIS** Members of the Mucorales order of fungi cause fulminant infections in patients with hematologic malignancies and severe neutropenia *(68–71)*. The risk of infection is increased by poorly controlled diabetes mellitus, metabolic acidosis, renal failure, iron overload, corticosteroid therapy, and organ transplantation.

In patients with hematologic malignancies, mucormycosis is usually a disseminated infection *(68)*. Most of these patients present with fever and pulmonary infiltrates, which progress despite antibiotic treatment *(70,71)*. The CNS is involved in 27% of patients with disseminated mucormycosis *(70)*. Organisms reach the brain by hematogenous spread and have a propensity for invasion of blood vessels *(68)*. Neurologic manifestations of disseminated mucormycosis include cerebral infarction, subarachnoid hemorrhage following rupture of a mycotic aneurysm, and brain abscesses *(69)*. Typical presenting features include altered mental state, lethargy, focal neurologic signs, and headache. Disseminated mucormycosis is difficult to diagnose, as there are no specific clinical or radiologic features and the organism cannot be cultured from the sputum, blood, or CSF. The diagnosis usually requires identification of fungi in a tissue biopsy. Management should include prolonged treatment with intravenous amphotericin B 1.0 mg/kg/d and, if appropriate, surgical debridement and reduction of immunosuppressive treatment *(69,70)*. Three-quarters of patients with a hematologic malignancy and mucormycosis die within a few weeks *(70)*. A good outcome depends on reversal of the neutropenia.

Mucormycosis also can cause infection in the paranasal sinuses without evidence of disseminated infection *(68)*. Most of these patients are diabetic or have been treated with corticosteroids *(12)*. Cultures obtained from the CSF and the infected sinuses are often sterile, and confirmation of the diagnosis requires histologic demonstration of hyphae in the infected tissue. Rhinocerebral mucormycosis is treated with intravenous amphotericin B, extensive surgical debridement, and rigorous diabetic control *(12)*.

## PARASITIC INFECTIONS

**TOXOPLASMOSIS** Latent infection with *T. gondii* is present in many adults. Cerebral toxoplasmosis usually results from recrudescence of a latent infection when cellular immunity is impaired. Toxoplasmosis can develop following chemotherapy for Hodgkin's disease and other hematologic malignancies *(72–75)*. Fever and the gradual onset of neurologic symptoms characterize the clinical presentation. Three clinicopathologic syndromes occur. Some patients present with a clinical picture of diffuse encephalitis with headache, lethargy, mental state changes, myoclonus, seizures, and sometimes neck stiffness. Pathologic examination of the brain in these patients reveals multiple microabscesses in the gray matter *(73,76)*. These lesions may not be visible with neuroimaging. Other patients with cerebral toxoplasmosis have symptoms and signs of an intracranial mass lesion with headache, altered mental state, focal signs, seizures, vomiting, and papilledema. CT and MRI shows single or multiple diffusely enhancing or ring-enhancing lesions with a predilection for the cerebral cortex, thalamus, and basal ganglia *(75)*. Histologic examination of the brain reveals large abscesses surrounded by inflammatory cells, tachyzoites, and encysted bradyzoites *(73,76)*. *Toxoplasma* also may cause an acute or subacute meningitis. Neurologic symptoms may be accompanied by skin rash, chorioretinitis, myocarditis, and pneumonitis.

The CSF may be normal or show a mildly raised protein content and a mononuclear pleocytosis *(73–75)*. Most patients have elevated titers of anti-toxoplasma antibody in the serum, but serologic tests cannot distinguish between previous infection and active disease. There is no readily available method of culturing *Toxoplasma* from the CSF. Detection of *T. gondii* DNA in the CSF or blood by PCR is highly specific for toxoplasmosis, but the sensitivity is only 50–80% *(77)*. If necessary, the diagnosis can be confirmed with a brain biopsy.

Treatment can be successful if it is started promptly *(73,75)*. Patients are treated with pyrimethamine (75 mg/d for the first 3 d followed by 25–50 mg/d) plus sulfadiazine (1.0–1.5 g four times daily). Folinic acid 10–20 mg/d may ameliorate the bone marrow toxicity that commonly complicates pyrimethamine therapy. Pyrimethamine and clindamycin 600–1200 mg four times daily can be used in patients who cannot tolerate sulfadi-

azine. Treatment should be continued for at least 4–6 wk after clinical recovery *(75),* and maintenance treatment is required if cellular immunity is persistently impaired.

**STRONGYLOIDIASIS** *Strongyloides stercoralis* is a nematode that mainly occurs in tropical and subtropical regions *(78–80)*. It is also endemic in parts of Europe and the United States. In immunocompetent hosts *S. stercoralis* causes a chronic benign bowel infection. In patients with hematologic malignancies, and in patients who have been treated with corticosteroids, larvae can spread by the bloodstream to other organs including the meninges and the CNS. Disseminated strongyloidiasis can develop many years after exposure to the parasite.

The most common neurologic complication of disseminated infection is bacterial meningitis. Gram-negative bacilli and other enteric organisms are transported into the bloodstream by the larvae causing recurrent bacteremia, meningitis, peritonitis, or endocarditis. Hematogenous larval invasion of the brain may result in occlusion of multiple small blood vessels producing a clinical picture resembling cerebral vasculitis. A petechial rash and atypical pulmonary infiltrates also occur with disseminated infection. Disseminated strongyloidiasis should be suspected if a patient with Gram-negative bacillary meningitis has unexplained gastrointestinal symptoms (mild abdominal pain, diarrhea, and weight loss) and a peripheral-blood eosinophilia. Larvae can be detected in feces, duodenal aspirates, or sputum *(80)*, but they are seldom isolated from the CSF. There is a high mortality from secondary bacterial infections *(78)*. Oral thiabendazole 25 mg/kg twice daily for 2–3 wk may be beneficial if treatment is started early, but the optimal duration of treatment is uncertain *(80)*. Albendazole 400 mg/d or ivermectin 200 µg/kg/d are alternatives. Patients who have lived in or travelled to an endemic area should have a stool examination before immunosuppressive treatment is started *(78,79)*.

## VIRAL INFECTIONS

**VARICELLA ZOSTER VIRUS (VZV)** Reactivation of latent VZV infection in cranial nerve and dorsal root ganglia can occur during immunosuppression *(81)*. Both localized and disseminated VZV infections are more common in patients with cancer than in immunocompetent hosts *(81–83)*. More than 50% of patients with Hodgkin's disease develop VZV infections *(84)*, most commonly in the first 6 mo after treatment with radiotherapy and chemotherapy. The incidence of VZV infection is also increased in bone marrow transplant recipients and in patients with non-Hodgkin's lymphoma, CLL, acute leukemia, and solid tumors that have been treated with chemotherapy *(85,86)*. Radiotherapy may trigger herpes zoster in an irradiated dermatome *(82)*, and spinal metastases can reactivate VZV before signs of spinal cord compression appear. Disseminated infection occurs in less than 2% of cases of herpes zoster in the general population, but dissemination occurs in up to 25% of immunocompromised patients.

**Varicella** Varicella has a high rate of visceral dissemination in children with cancer. Acute cerebellar ataxia, meningoencephalitis, and other neurologic complications of varicella are more common in children with malignancies than in immunocompetent individuals *(87)*.

**Herpes Zoster** Intravenous acyclovir 5–10 mg/kg every 8 h should be started as soon as possible and continued for 7–10 d. Early treatment accelerates the healing of skin lesions and reduces the incidence of disseminated infection, but it has little effect on the incidence or severity of postherpetic neuralgia *(88,89)*. The efficacy of valaciclovir, famciclovir, and oral acyclovir in immunosuppressed patients is uncertain *(83)*. Corticosteroids shorten the duration of pain, but they do not prevent postherpetic neuralgia *(90)*. Steroids should be avoided in immunosuppressed patients because they may facilitate dissemination of VZV.

**Post-Herpetic Neuralgia** The risk of developing postherpetic neuralgia is not increased in immunocompromised patients *(90)*. Amitryptiline, nortryptiline, and desimipramine reduce the constant burning pain of postherpetic neuralgia, while carbamazepine and phenytoin lessen lancinating pain *(90)*. Gabapentin is beneficial and has fewer side effects than the tricyclic antidepressants and the other anticonvulsants *(91)*. Opioid analgesics and neurosurgical procedures are sometimes used as a last resort.

**Segmental Motor Weakness** Segmental motor weakness may be more frequent in patients with cancer than in immunocompetent people *(92)*. Weakness and loss of tendon reflexes can develop in muscles innervated by the nerve root or cranial nerve affected by zoster. Adjacent nerve roots and cranial nerves are also often affected. Sphincter function may be affected if the sacral dermatomes are involved. Eighty-five percent make a complete or partial recovery, but a few patients suffer permanent paralysis.

**Central Nervous System Infections with Varicella Zoster Virus** VZV infections of the CNS typically appear 2–3 wk after the onset of herpes zoster, but occasionally they precede the rash or develop without an antecedent rash. The CSF usually contains a mild mononuclear pleocytosis, VZV DNA, and antibodies to VZV, but similar findings occur in uncomplicated herpes zoster *(81)*. Treatment with intravenous acyclovir 10–15 mg/kg every 8 h for 10 d is recommended *(81)*, although there is only anecdotal evidence that it is beneficial.

**Myelitis** Spread of VZV from the dorsal root ganglia to the adjacent spinal cord is more likely to occur in immunocompromised hosts than in immunocompetent patients *(93)*. These patients develop signs of a unilateral or bilateral asymmetric spinal cord lesion. Pain may be an early feature. The neurologic deficit often progresses over a few weeks leading to paraplegia, a sensory level, and sphincter dysfunction. The level of the neurologic deficit may ascend, and most immunocompromised patients die. MRI shows enhancing lesions in the spinal cord. Pathologic examination of the spinal cord reveals inflammation, viral inclusions, viral antigen, and VZV DNA. In some patients there are areas of demyelination and necrotizing vasculitis.

**Large Vessel Vasculitis (Granulomatous Arteritis)** A necrotizing granulomatous arteritis can develop when VZV spreads along the trigeminal nerve to the ipsilateral intracranial arteries. These patients present with transient ischemic attacks, stroke, and mental changes several weeks or months after a bout of herpes zoster ophthalmicus *(11)*. Imaging reveals bland or hemorrhagic infarcts in one cerebral hemisphere and seg-

mental narrowing of the ipsilateral internal carotid artery and its branches. A large vessel vasculitis can follow herpes zoster in other sites. Treatment with intravenous acyclovir for 10 d and prednisone 60–80 mg/d for 3–5 d is recommended *(81)*.

**Meningoencephalitis** A subacute progressive meningoencephalitis can develop in immunosuppressed hosts, including patients with lymphoma *(81)*. Typical clinical features are headache, fever, vomiting, mental changes, seizures, and focal signs *(81,94)*. The mortality rate is high. MRI shows multiple spherical white matter lesions that are not associated with edema *(95,96)*. The lesions are smaller and more discrete than the abnormalities associated with progressive multifocal leukoencephalopathy. Pathologic examination of the brain reveals multiple areas of demyelination, hemorrhagic necrosis, astrocytosis, and macrophage infiltration *(95,96)*. This form of VZV encephalitis may be caused by a vasculopathy.

**Necrotizing Ventriculitis** Necrotizing ventriculitis is less common than the other CNS infections with VZV. These patients typically present with a gait disorder, and imaging shows hydrocephalus and periventricular enhancing lesions.

**HERPES SIMPLEX VIRUS** The incidence of herpes simplex encephalitis is not thought to be increased in patients with cancer, but its true incidence in immunocompromised patients may be underestimated *(97)*. The clinical presentation in immunocompromised patients is usually typical of herpes simplex encephalitis with the acute onset of fever, headache, mental-state changes, partial or generalized seizures, focal neurologic signs, and a CSF pleocytosis. MRI shows lesions in the basal frontal and medial temporal lobes.

The clinical and pathologic features of herpes simplex encephalitis may be modified in immunosuppressed patients. The course may be slowly progressive or relapsing *(98)*. Inflammatory cell infiltrates and hemorrhagic necrosis may be absent *(98)*, but neuronal destruction, inclusion bodies and diffuse involvement of the brain (including the brainstem) may be observed *(97)*. Detection of herpes simplex virus DNA in the CSF by PCR is a sensitive and specific method of diagnosing herpes simplex encephalitis, and brain biopsy is seldom necessary. Intravenous acyclovir 10 mg/kg every 8 h should be started as soon as the diagnosis is suspected and treatment should be continued for 2–3 wk *(99)*.

**HUMAN HERPES VIRUS-6 (HHV-6)** Infection with HHV-6 is commonly acquired in early childhood. More than 90% of healthy adults harbor antibodies to HHV-6 *(100)*.In immunocompromised patients most HHV-6 infections are caused by reactivation of latent virus, but occasionally infection is acquired by donor organ transmission. HHV-6 infection occurs in 40–60% of bone marrow transplant recipients, usually 2–4 wk after transplantation.

HHV-6 causes an encephalitis *(101)*, which is characterized by mental state changes, headache and, in some patients, focal neurologic deficits and seizures *(102)*. Encephalitis may be accompanied by bone marrow suppression, interstitial pneumonitis, skin rash and fever *(100)*. Neuroimaging may show focal lesions and the EEG reveals focal slowing and epileptogenic activity *(102)*. The CSF contains a mononuclear pleocytosis. Viral DNA can be detected in the CSF by PCR *(100,102)*, but this may not distinguish between latent infection and active viral replication. The diagnosis can be confirmed by isolating HHV-6 from the CSF or by an increase in serum antibodies. Treatment with ganciclovir is preferred if there is renal dysfunction, but foscarnet should be used in patients with bone marrow suppression *(100)*. HHV-6 is resistant to acyclovir.

**MEASLES** Asymptomatic spread to the brain probably occurs in many patients with measles, but immunocompromised patients may fail to eliminate the measles virus from the brain after primary infection. A subacute encephalitis caused by the measles virus occurs in children with acute lymphoblastic leukemia (ALL) *(103)* and in adults with Hodgkin's disease or other tumors *(104)*. Encephalitis develops 1–10 mo after primary measles infection, but in 30% there is no clinically apparent preceding measles infection or exposure to measles. Measles encephalitis often develops when the malignancy is in remission. The clinical picture is characterized by a progressive deterioration in mental state, myoclonus, refractory focal and generalized seizures, and focal motor and sensory signs *(104)*. Patients usually develop coma and die within a few weeks of the onset. Headache and fever are often absent. Encephalitis may be accompanied by retinal lesions, pneumonia or hepatitis. MRI shows focal or widespread cortical abnormalities, and the EEG reveals generalized slowing, multifocal epileptogenic activity and periodic complexes *(104)*. The CSF cell count and chemical constituents are normal in three-quarters of patients. Neither measles virus nor viral RNA can be detected in the CSF. Measles antibody may be absent from the serum and CSF, and if present the titer may be low. Brain biopsy is required for diagnosis. Inclusion bodies containing paramyxovirus nucleocapsids, measles virus antigen, and viral RNA are present in the brain *(104)*, but the virus can be isolated from the brain in only one-quarter of the patients. Treatment is usually unsuccessful, but survival after treatment with intravenous ribavirin has been reported *(104)*.

**PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)** PML is a lytic infection of oligodendrocytes that arises either by invasion of the brain by B-lymphocytes infected with the JC virus or reactivation of a latent infection in glial cells *(105)*. The JC virus is not usually pathogenic. Seventy percent of adults harbor antibodies to JC virus *(106)*. Latent infection persists in the kidneys, B lymphocytes, and the brain *(105)*.

PML develops in patients with lymphoma or CLL, and in patients who have been treated with immunosuppressive agents *(106,107)*. It presents with the insidious onset of an altered mental state, weakness (hemiparesis or quadriparesis), ataxia, dysarthria, visual field defects, dysphasia, and agnosia. Headache and seizures are uncommon, and fever, neck stiffness, and signs of intracranial hypertension do not occur. The course is steadily progressive, and most patients die within 4–6 mo. Occasionally there is a spontaneous remission or stabilization of the clinical course. MRI shows one or more lesions in the cerebral, cerebellar, or brainstem white matter (Fig. 6). Faint enhancement of some of the lesions may be seen, although the disease is typically nonenhancing *(108)*. The CSF is usually normal although the CSF protein concentration may be mildly elevated. JC virus DNA can be detected in the initial CSF in 75–92% of patients with PML. Serial CSF sampling increases the

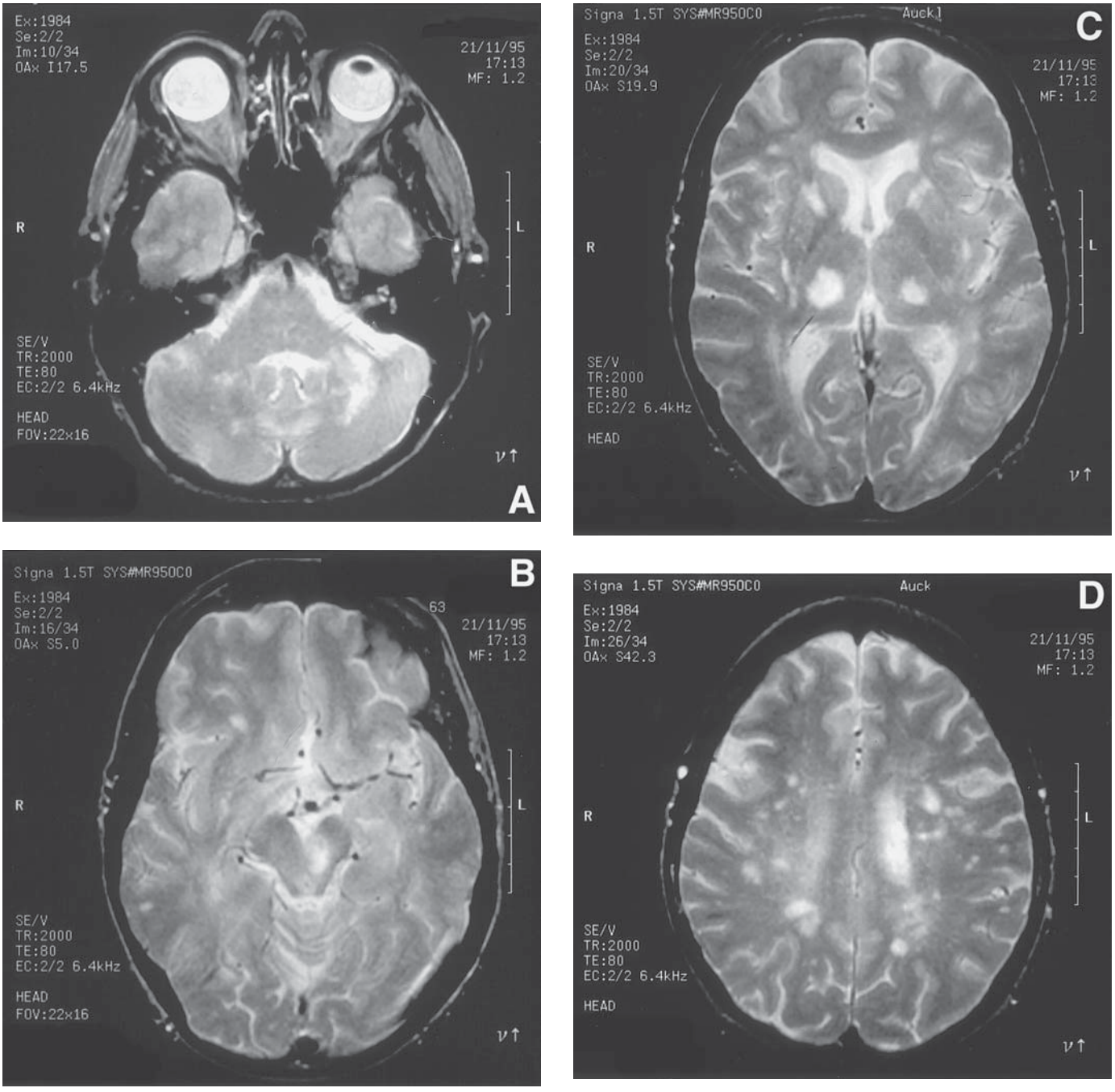


**Fig. 6. (A–D).** T2-weighted MRI in a 63-yr-old woman with non-Hodgkin's lymphoma and PML shows multiple white matter lesions in the cerebellar peduncles, cerebellum, brain stem and white matter of the cerebral hemispheres. Lesions in PML occasionally involve the thalamus (C).

frequency of positive results *(109,110)*. The PCR assay is highly specific for the JC virus, and a brain biopsy is not required if JC virus DNA is present in the CSF. Detection of JC virus DNA in peripheral blood or urine is not specific for PML.

Pathologic examination of the brain shows multiple demyelinating lesions, abnormal oligodendrocytes with nuclear inclusions, and bizarre hyperchromatic astrocytic nuclei *(106)*. There is little or no inflammatory reaction. Papovavirus virions are present in oligodendroglial nuclei, and JC virus antigens can be detected with immunostaining.

Treatment is usually ineffective. Where possible, immunosuppressive treatment should be minimized. Remissions have been reported after treatment with intravenous or intrathecal cytosine arabinoside, but there was no benefit from cytosine arabinoside in a controlled trial *(111)*.

**CYTOMEGALOVIRUS (CMV)** CMV infection of the CNS is widely recognized among patients with human immunodeficiency virus (HIV) infections, but it is much less common in other immunocompromised patients. There are two main forms of CMV encephalitis: microglial nodule encepha-

**Table 3**
**Diagnosis of Bacterial, Fungal, and Parasitic Infections of the CNS in Patients with Impaired Cell-Mediated Immunity**

| | *Typical pattern* | *Duration of illness* | *CSF* | *Special features* |
|---|---|---|---|---|
| *Listeria monocytogenes* | Meningitis | Acute (2–10 d) | Neutrophils/lymphocytes<br>Gram stain +ve (30%)<br>Cultures usually +ve | ± Rhombencephalitis<br>+ve Blood cultures |
| *Cryptococcus neoformans* | Meningitis | Subacute or chronic (wk–mo) | Lymphocytes<br>India ink stain +ve (50%)<br>Cryptococcal antigen +ve >90%<br>+ve Cultures >90% | Asymptomatic lung infection<br>Skin lesions |
| *Nocardia asteroides* | Abscess | Acute/subacute | Cultures +ve 20% | Lung infection<br>Chorioretinitis<br>Skin lesions |
| *Toxoplasma gondii* | Abscess | Acute/subacute | Toxoplasma DNA | Chorioretinitis<br>Rash<br>Pneumonitis<br>CT/MR-predilection for basal ganglia |
| *Toxoplasma gondii* | Microabscesses | Acute/subacute | Toxoplasma DNA | CT/MR often normal |

+ve, positive.

litis and necrotizing ventriculoencephalitis *(112)*. Both forms are usually associated with evidence of systemic CMV infection. Microglial nodule encephalitis occurs in bone marrow transplant recipients. Most of these patients present with delirium or psychomotor slowing *(113)*. Necrotizing ventriculoencephalitis is found almost exclusively in patients with advanced HIV infection, but it has been reported in a patient with Hodgkin's disease. Viral cultures of the CSF are usually sterile, but detection of viral DNA in the CSF by PCR is a sensitive and specific test for both forms of CMV encephalitis *(114)*. CMV encephalitis is usually treated with intravenous ganciclovir, foscarnet, or both, but the efficacy of treatment is uncertain *(112)*.

**ADENOVIRUS** Adenovirus causes a fatal meningoencephalitis in patients with lymphoma or acute leukemia and in bone marrow transplant recipients *(115,116)*. These patients present subacutely with headache, confusion, focal seizures, and progressive obtundation. The neurologic symptoms may be associated with pneumonia, hepatitis, and nephritis. CSF and imaging studies show nonspecific abnormalities. Adenovirus can be isolated from the CSF or from the brain. At autopsy these patients have a hemorrhagic meningoencephalitis involving the temporal lobes, amygdala, anterior hypothalamus, and brain stem nuclei.

## THE CLINICAL APPROACH

Infections of the CNS may be rapidly progressive, and antimicrobial treatment often must be started before the pathogen has been identified. However, it is often possible to predict the likely pathogen from the clinical pattern of the illness and the underlying defect in host defenses. This may be more difficult when patients have multiple defects of host defenses.

**PATIENTS WITH T-LYMPHOCYTE AND MONONUCLEAR PHAGOCYTE DEFECTS** *L. monocytogenes* and *C. neoformans* are the most common causes of meningitis in patients with impaired cell-mediated immunity and a normal blood neutrophil count (Table 3). *Listeria* is the most likely cause if meningitis has an acute onset, but *S. pneumoniae* must be considered if the patient has had a splenectomy, especially if the onset is fulminant. *Listeria* may not be visible in the CSF with a Gram stain, but the organism usually can be isolated from blood and CSF cultures. Cryptococcal meningitis typically has a more gradual onset and the diagnosis can be confirmed by detecting the cryptococcal antigen in the CSF or visualization of cryptococci in the CSF with an India ink stain. In the setting of meningitis and impaired cellular immunity, ampicillin should be started immediately. Antifungal treatment usually can be withheld until the cryptococcal antigen assay and the India ink stain have been completed. If the patient is neutropenic, the possibility of Gram-negative bacillary meningitis should be covered with a third-generation cephalosporin until the results of CSF cultures are available.

*N. asteroides* and *T. gondii* are the most common causes of a brain abscess in patients with impaired cell-mediated immunity (Table 3). Both types of CNS infection may be associated with infection in the lung, skin or retina. It is sometimes possible to isolate *Nocardia* from the sputum or from skin lesions. The diagnosis of cerebral toxoplasmosis may be confirmed by detecting *T. gondii* DNA in the CSF, but false-negative results are not uncommon. If toxoplasmosis is the most likely diagnosis, a therapeutic trial with pyrimethamine and sulfadiazine can be attempted. It may be necessary to proceed to a stereotactic biopsy of a brain lesion if the patient does not improve with treatment for toxoplasmosis.

Viral infections of the CNS also must be considered in patients with a defect in cell-mediated immunity. The clinical setting, clinical features and MRI help to predict the likely viral pathogen (Table 4). PML has a distinctive clinical and radiologic presentation, while VZV infections of the CNS are usually heralded by an episode of herpes zoster. The diagnosis of other forms of viral meningoencephalitis is more difficult. Viral cultures of the CSF are nearly always negative, but detection of viral DNA or RNA by PCR is a specific and sensitive method of identifying many viral infections. Brain biopsy is not usually required unless CSF studies are negative. Herpes

**Table 4**
**Diagnosis of CNS Viral Infections in Patients with Impaired Cell-Mediated Immunity**

| *Virus* | *Typical setting* | *Clinical features* | *MRI* | *CSF* | *Treatment* |
|---|---|---|---|---|---|
| Varicella zoster virus (VZV) | Preceding herpes zoster or varicella | Myelitis | Enhancing spinal cord lesions | | Acyclovir |
| | | Granulomatous arteritis | Cerebral infarcts<br>Segmental arterial narrowing | | Acyclovir + prednisone |
| | | Subacute meningoencephalitis | Multiple subcortical white matter lesions | VZV antibody<br>VZV DNA | Acyclovir |
| | | Necrotizing ventriculitis | Hydrocephalus<br>Periventricular white matter lesions | | Acyclovir |
| Herpes simplex virus (HSV) | | Acute/subacute encephalitis<br>Focal features | Medial temporal, basal frontal-lobe lesions | HSV DNA | Acyclovir |
| Human herpes virus-6 (HHV-6) | BM transplant | Encephalitis<br>Pancytopenia<br>Pneumonitis<br>Skin rash | Focal lesions | HHV-6 DNA | Ganciclovir or foscarnet |
| Measles | Children<br>Acute leukemia | Subacute encephalitis<br>Refractory epilepsy | Focal/diffuse cortical abnormalities | Acellular CSF<br>Viral RNA absent | ? Ribavirin |
| JC Virus (PML) | Lymphoma<br>CLL<br>Steroids | Slow onset<br>Dementia<br>Focal signs<br>Afebrile | Multiple white matter lesions | Acellular CSF<br>JCV DNA | |
| Cytomegalovirus | BM transplant | Encephalopathy<br>± Retinitis | Nonspecific | CMV DNA | Ganciclovir or foscarnet |
| Adenovirus | Lymphoma<br>Leukemia<br>BM transplant | Subacute encephalitis | Nonspecific | Nonspecific | |

BM, bone marrow.
PML, progressive multifocal leukoencephalopathy.
CLL, chronic lymphocytic leukemia.

**Table 5**
**Diagnosis of CNS Infections in Patients with Neutrophil Defects**

| *Organism* | *Clinical pattern* | *CSF* | *Special features* |
|---|---|---|---|
| Enteric Gram-negative bacilli | Acute meningitis | Normal or polymorphs<br>Gram-stain +ve<br>Cultures +ve | |
| *Candida albicans* | Acute or chronic meningitis | Polymorphs or lymphocytes<br>Gram stain +ve 20–40%<br>Culture +ve 80% | Blood cultures +ve<br>Pulmonary infiltrates<br>Skin, retinal lesions<br>Myositis |
| | Microabscesses | Nonspecific | Blood cultures +ve<br>Normal CT/MR |
| | Brain abscess | Nonspecific | Blood cultures +ve |
| *Aspergillus* species | Brain abscess<br>Cerebral infarct<br>Intracerebral hemorrhage<br>Invasive sinusitis | Normal or lymphocytes<br>Cultures –ve | Pulmonary infiltrates |
| Mucormycosis | Brain abscess<br>Cerebral infarct<br>Intracerebral hemorrhage<br>Invasive sinusitis | Cultures –ve | Pulmonary infiltrate<br>Diabetes mellitus<br>Metabolic acidosis |

+ve, positive; –ve, negative

simplex encephalitis must be considered in any patient presenting with acute encephalitis, especially if there are focal symptoms and signs; intravenous acyclovir should be started pending the results of investigations. The clinical presentation of *T. gondii* microabscesses in the brain may resemble viral encephalitis.

**NEUTROPHIL DEFECTS** CNS infections in neutropenic patients usually develop in hospital in the setting of severe systemic illness and prolonged antibiotic treatment. Enteric Gram-negative bacilli and *Candida* are the usual causes of meningitis (Table 5). Gram-negative bacilli are often visible with a Gram stain and are readily grown from CSF or blood cultures. *Candida* is more difficult to identify in CSF smears, and initial CSF cultures are positive in less than 50% of cases. A third-generation cephalosporin should be started while the results of the CSF examination are pending.

Species of *Aspergillus*, Mucoraceae, *Candida* species, and Gram-negative bacilli are the most common causes of brain abscesses in neutropenic patients. The cause is often obvious from the clinical and radiologic abnormalities. Most patients with disseminated aspergillosis or mucormycosis have clinical or radiographic signs of pulmonary infection. *Aspergillus* and the Mucoraceae tend to invade cerebral blood vessels. These patients present with a stroke-like onset of symptoms and imaging often shows ischemic or hemorrhagic lesions. The same fungi can cause paranasal sinus and orbital infection. CNS infection with *Candida* usually presents with multiple microabscesses. CNS candidiasis should be suspected in a patient who presents with a fluctuating encephalopathy, a source of infection in the lungs, heart, gastrointestinal tract or a wound, normal imaging of the brain, and positive blood cultures for *C. albicans*.

**SPLENECTOMY** Patients who have undergone a splenectomy and patients who have impaired immunoglobulin production may develop an overwhelming infection due to encapsulated bacteria, especially *S. pneumoniae (28)*. Vancomycin and either penicillin or ceftriaxone should be started as soon as the diagnosis is suspected.

**CSF SHUNTS AND RESERVOIRS** *S. epidermidis* is the most common cause of meningitis associated with an intraventricular shunt or reservoir. Other causes include *S. aureus*, *Corynebacteria*, Gram-negative bacilli and *Propionobacterium acnes (31,32)*. Shunt-associated meningitis probably results from perioperative wound contamination *(31)*. Perioperative prophylactic antibiotics reduce the rate of shunt-associated infections *(117)*. Shunt-associated meningitis starts insidiously within 1–2 mo of insertion of the device with lethargy, nausea, headache, change in mental state and low-grade fever. Often there is no neck stiffness. The CSF pleocytosis usually shows a predominance of mononuclear cells, but the cellular and chemical abnormalities in the CSF may be wrongly attributed to the surgery. The organism usually can be grown from ventricular CSF, CSF aspirated from a shunt reservoir *(31)*, or from the blood in patients with a ventriculoatrial shunt. These patients should be treated initially with intravenous vancomycin and oxacillin, but vancomycin can be stopped if the organism proves to be methicillin-sensitive. Intraventricular vancomycin can be tried if the patient does not respond to intravenous antibiotics. Cure of shunt-associated meningitis usually requires removal of the shunt, but an intraventricular reservoir only needs to be removed if antibiotics fail to eradicate the organism from the CSF *(32)*.

**POST-OPERATIVE INFECTIONS** Gram-negative bacilli and staphylococci are the main causes of meningitis after other types of neurosurgery *(31)*. Wound contamination at the time of surgery is the usual source of infection. Postoperative meningitis develops within a few weeks of surgery and it may be

difficult to distinguish from the aseptic meningitis that may follow neurosurgical operations *(31)*. The onset of postoperative meningitis may be insidious, but persistent fever and prolonged impairment of consciousness after an operation should suggest the diagnosis. The CSF contains neutrophils and a low glucose concentration. The pathogen can be readily found in the CSF. Empiric treatment for postoperative meningitis should include vancomycin and a third-generation cephalosporin, pending the results of the CSF examination *(31)*. Ceftazidime is preferred if *P. aeruginosa* is the possible pathogen. Subdural or epidural abscesses following neurosurgery are usually due to staphylococci or aerobic microaerophilic streptococci *(31)*. Postoperative brain abscesses are rare *(7)*.

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# Part VI Diagnostic Studies

# 19 Imaging Neurologic Manifestations of Oncologic Disease

CAROLYN C. MELTZER, MD AND MELANIE B. FUKUI, MD

## INTRODUCTION

The advent of more effective chemotherapeutic regimens for systemic malignancies, which has afforded increased patient survival, has also resulted in a rise in the frequency of central nervous metastases and late disease complications. We are now seeing a wider variety of tumor types causing brain lesions in patients, where previously locally aggressive disease would have proved fatal *(1,2)*. Metastatic brain disease now affects 80,000–170,000 persons annually in the United States *(3)*. The success of a variety of treatment approaches for single or limited brain metastases, including surgical resection, whole brain radiation, and stereotactic radiosurgery (SR), relies heavily on sensitive imaging tools. The main diagnostic tools are enhanced computed tomography (CT) or magnetic resonance imaging (MRI). However, the rapid development and refinement of structural and functional imaging acquisition and postprocessing technology have also permitted imaging approaches to be increasingly used, not only for diagnosis, but also for therapeutic planning and monitoring.

## IMAGING THE ONCOLOGY PATIENT

### BRAIN IMAGING

**Detection of Metastatic Disease** The majority of cases of brain metastases are attributed to a handful of malignancies, such as lung cancer, breast cancer, and melanoma. Indeed, occult metastases are common in lung cancer, warranting early screening. A recent study evaluating the effectiveness of MRI for the detection of brain metastases in nonsmall cell lung cancer staging supported the utility of contrast-enhanced MR in clinically operable tumors of greater than 3 cm *(4)*. Conversely, in patients who present with brain metastases as their sole manifestation of disease, the search for a primary tumor usually reveals the tissue of origin to be the lung *(5,6)*. In this setting, conventional body CT imaging may be supplemented by whole body positron emission tomography (PET) imaging for identifying the primary tumor site and detecting additional lesions *(7,8)*. However, effective new systemic therapies responsible for longer survival times have been associated with the appearance of brain metastases arising from tumors for which they had been distinctly rare *(9)*. This supports a higher degree of vigilance on the part of the clinician for evidence of symptoms referrable to central nervous system (CNS) lesions in nearly all oncology patients.

It is generally regarded that MRI is superior to CT in detecting metastatic brain disease *(10)*; however, CT is still frequently used in the metastatic work-up of patients with systemic malignancy. Schellinger et al. *(11)* reported that in 55 patients with a CT diagnosis of solitary brain metastasis, 17 (31%) had multiple lesions by MRI. In a larger prospective comparison of enhanced CT and MRI in 332 patients with potentially operable nonsmall cell lung cancer, there was a trend toward a higher rate of preoperative detection with MRI relative to CT *(12)*. MRI also affords substantially increased sensitivity over CT in the detection of meningeal-based neoplastic disease. Beam-hardening and other artifacts near bony structures may be in part responsible for the difficulty in detecting superficial metastatic disease and abnormal meningeal enhancement with CT. Also, experimental evidence suggests that gadolinium-DTPA-enhanced MRI results in more intense enhancement in areas of blood-brain barrier (BBB) disruption than CT with iodinated contrast *(13,14)*. Although the size of lesions identified with MRI may be significantly smaller than those detected with CT, interestingly, both Yokoi et al. *(12)* and Mastronardi et al. *(10)* found no significant difference in survival rates between those screened with MRI vs CT. Therefore, although contrast-enhanced MRI is the examination of choice for suspected brain metastases, CT may be considered an acceptable, less costly alternative.

Technical factors that impact on the sensitivity of MRI for detecting metastatic disease include pulse sequence parameters, magnetic field strength, contrast dose, and imaging plane selection *(15–18)*. Greater contrast between enhancing metastatic

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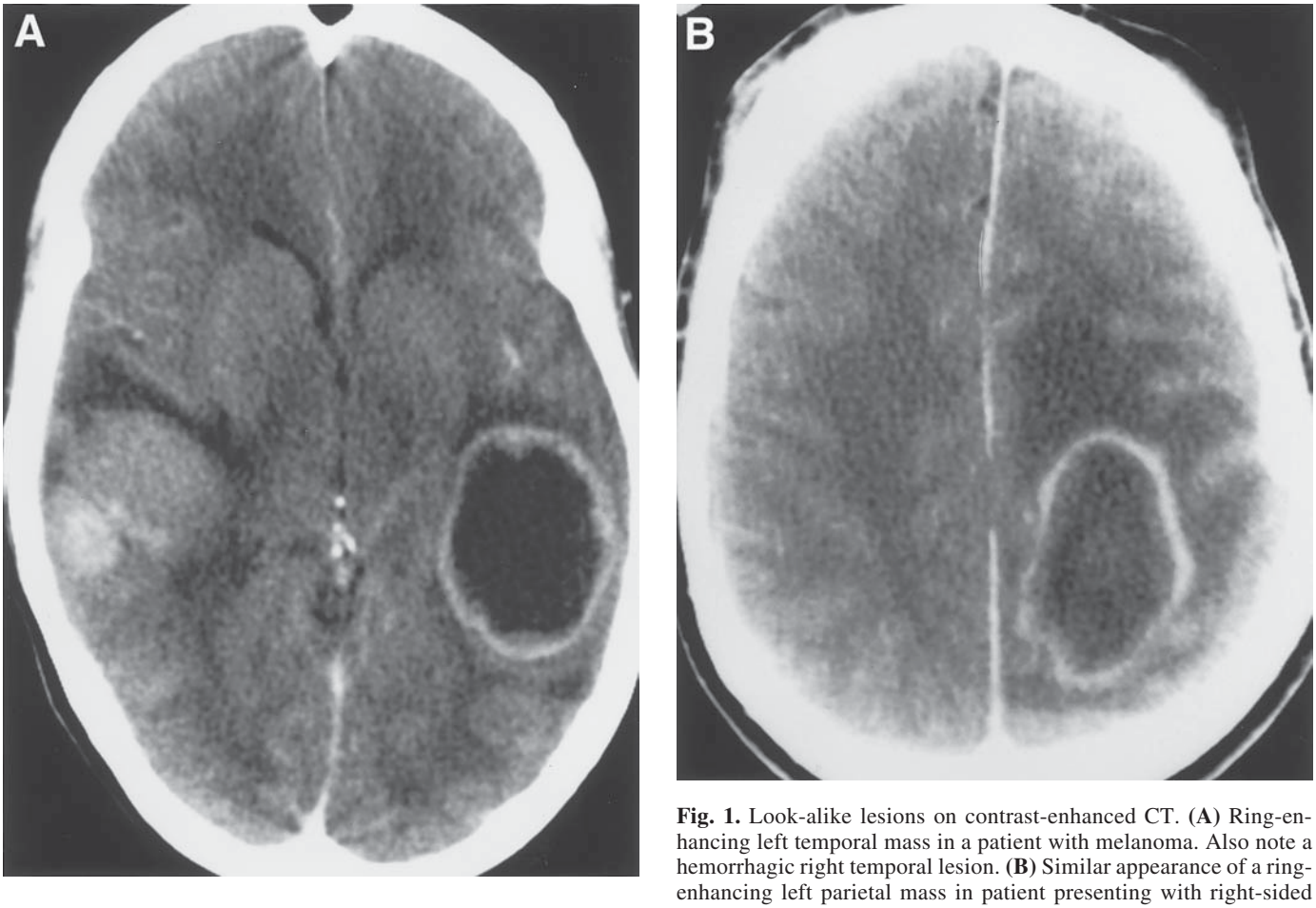



**Fig. 1.** Look-alike lesions on contrast-enhanced CT. **(A)** Ring-enhancing left temporal mass in a patient with melanoma. Also note a hemorrhagic right temporal lesion. **(B)** Similar appearance of a ring-enhancing left parietal mass in patient presenting with right-sided numbness, hemiplegia, and aphasia. CT-guided drainage confirmed pyogenic material.

lesions and surrounding brain is achieved with 1.5 Tesla relative to lower strength magnets and with heavily T1-weighted images. The ability with MRI to visualize a small suspicious lesion in two orthogonal planes can increase confidence in making the diagnosis of metastatic disease. Furthermore, coronal images are preferable to axial MRI data in evaluating meningeal enhancement concentrated over the cerebral convexity.

Enhancement of metastatic brain lesions is dependent on tumor neovascularity and BBB disruption. Since enhancement characteristics largely determine the sensitivity of CT and MRI for detection of brain metastases, strategies for augmenting tumor enhancement have been explored. It is well-known that longer delay times can increase the conspicuity of enhancing lesions *(19)*. Double- and triple-dosing of paramagnetic contrast agents have demonstrated improved detection of parenchymal lesions with MRI *(17–19)*, which may be particularly important where the number of lesions influences the triage of patients into different therapeutic categories. There is evidence to support a similar dose effect for enhanced MRI of meningeal disease *(20,21)*. However, high-dose strategies have also been associated with an increased rate of false-positive readings for both parenchymal and meningeal disease *(22,23)*. Further, it has been argued that the relatively small added benefit does not justify the expense of triple-dose contrast administration for routine screening MRI examinations *(22)*. Another effective strategy is to use magnetization transfer (MT) imaging to enhance the conspicuity of pathological parenchymal and meningeal enhancement with MRI by suppressing signal from adjacent gray matter *(24–26)*. Since the performance of single-dose MT is comparable to that of triple-dose conventional spin-echo T1 imaging, the former is a more cost-effective technique *(18)*. Fast fluid-attenuated inversion recovery (FLAIR) images provide particularly high sensitivity for many pathologies, and, when used with contrast agents, may offer superior tumor-to-background contrast relative to standard clinical-imaging sequences *(27)*.

**Imaging Features of Secondary Neoplastic Disease**

Hematogenously-spread parenchymal brain lesions tend to deposit in characteristic brain locations due to flow patterns and physical properties of the vasculature. Metastatic lesions have a predilection for the gray-white matter junction and vascular border zones, which present areas of acute change in the caliber of small vessels *(28)*. Multiple enhancing lesions at the supratentorial gray-white matter junction are highly typical, but not pathognomonic, of metastatic lesions *(29)*. Indeed, hematogeneous deposition of infectious material at the gray-white junction can result in a similar appearance for multiple abscesses (Fig. 1). A highly vascular tissue lacking a BBB, the choroid plexus is also a common site for hematogenous spread of tumor *(30,31)*. Detection of lesions in this location, however, may be

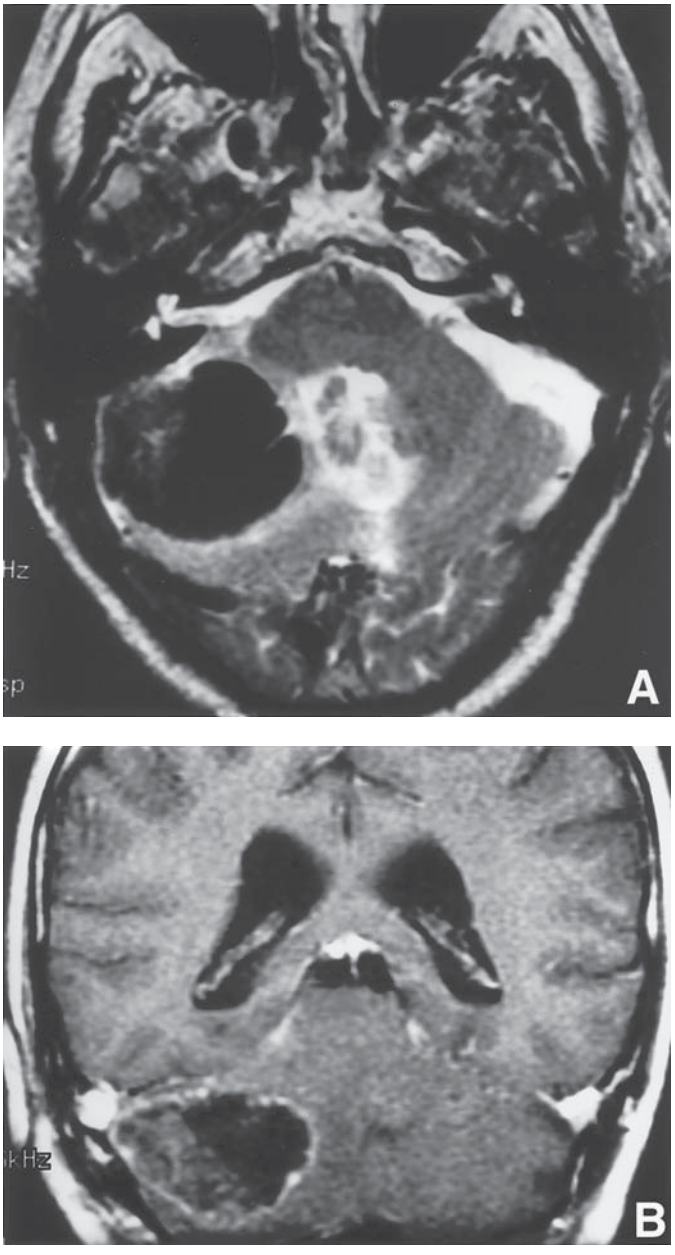



**Fig. 2.** Axial T2 **(A)** and coronal contrast-enhanced T1 **(B)** images in a 78-yr-old patient with history of colon cancer presenting with progressive dizziness and difficulty walking. A large ring-enhancing right cerebellar mass is notable for particularly low T2 signal, sometimes seen in mucinous tumors. Histopathology confirmed metastatic adenocarcinoma.

challenging due to the intense normal enhancement of choroid plexus and its often heterogeneous appearance on CT and MRI.

Most nonhemorrhagic metastases will appear mildly hypointense on T1-weighted and bright on T2-weighted, proton-density, and FLAIR sequences. Lack of T2 hyperintensity is associated with certain tumors, including lymphoma and colon cancer metastases *(32,33)*. Mucinous metastases, in particular, tend to lack signal on T2 sequences *(34)* (Fig. 2). Melanoma may exhibit the unique features of relative T1 hyperintensity and T2 hypointensity, which are attributed to its melanin content. Radiologic-pathologic correlation, however, is lacking *(35)*. It seems that this "characteristic" MRI appearance of melanoma, seen most often in those tumors with more than 10% melanin-containing cells, is the exception rather than the rule *(36)*. Enhancement patterns in metastatic lesions may vary from ring-like to solid. A ring-enhancing pattern is associated with cystic or centrally necrotic lesions. A variable degree of surrounding vasogenic edema with its characteristic finger-like projections along white matter tracts and associated mass effect may be observed, and typically relates to the size and rapidity of growth of lesions.

Tumors that are particularly prone to a hemorrhagic presentation include melanoma, renal cell carcinoma, choriocarcinoma, and thyroid cancer (Fig. 3). Due to its high incidence rather than a particular propensity to hemorrhage, lung cancer is another common cause of hemorrhagic metastatic disease to the brain. Acute and subacute hemorrhage are easily recognized as hyperdense on CT images. The appearance of parenchymal blood on MRI is more complex, but its characteristic progression of signal over time permits more precise characterization of the age of hemorrhagic lesions. Disruption of the regular pattern of concentric rings of varying signal associated with bland parenchymal hemorrhage suggests an underlying neoplastic process *(37)* and thus warrants follow-up imaging.

When brain metastates are solitary, the diagnosis may be difficult. This is particularly so in patients with no known malignancy. The differential diagnosis of an enhancing mass lesion also includes primary brain neoplasm, abscess, demyelinating disease, and infarction. A common clinical scenario is a single cerebellar mass, which is most often due to metastatic disease in adults. Other considerations include primary brain tumors such as hemangioblastoma, or subacute infarction. Diffusion-weighted MRI can help distinguish between tumor and infarction, with restricted diffusion most characteristically found in stroke. However, some tumors may display restricted diffusion, which is thought to be a function of their protein content and structural organization *(38)*. Relatively higher apparent diffusion coefficients have been noted in metastases relative to high-grade gliomas *(39)*; however, the clinical diagnostic value of this finding has yet to be evaluated. Also, higher apparent diffusion coefficients may be found in abscesses relative to necrotic or cystic tumors *(40)*, which is a difficult distinction to make using conventional MRI techniques alone. MRI spectroscopy may be effectively used to distinguish metastatic disease from other entities such as infection *(41)*.

Extraaxial metastases may be evaluated with a combination of MRI, CT, and bone scintigraphy. Dural metastases (epidural and subdural), which are most commonly secondary to breast and prostate carcinoma, may mimic meningioma in location, enhancement pattern, and presence of a dural tail *(42–44)*. Vertebral bone metastases may spread through Batson's plexus directly to the dural venous sinuses *(45)*. Indeed, patients with disseminated breast cancer are as likely to have dural metastases as they are to have parenchymal brain metastases. Rarely, lymphoma (usually non-Hodgkin's) may involve the dura in patients with disseminated systemic disease, or less commonly, as a primary extraaxial lesion *(46)*. A typically densely cellular tumor, lymphoma may demonstrate T2 shortening (i.e.,

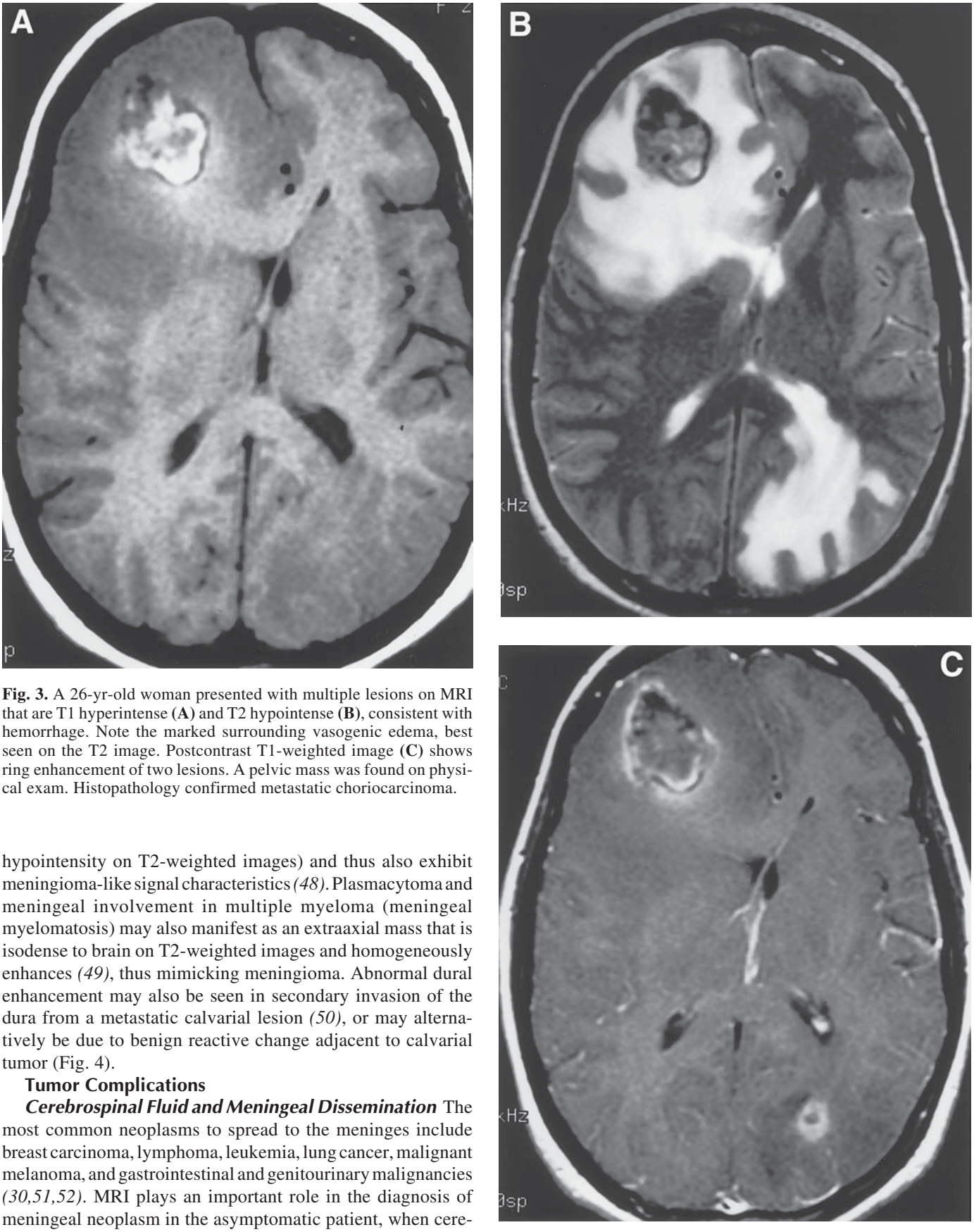



**Fig. 3.** A 26-yr-old woman presented with multiple lesions on MRI that are T1 hyperintense **(A)** and T2 hypointense **(B)**, consistent with hemorrhage. Note the marked surrounding vasogenic edema, best seen on the T2 image. Postcontrast T1-weighted image **(C)** shows ring enhancement of two lesions. A pelvic mass was found on physical exam. Histopathology confirmed metastatic choriocarcinoma.

hypointensity on T2-weighted images) and thus also exhibit meningioma-like signal characteristics *(48)*. Plasmacytoma and meningeal involvement in multiple myeloma (meningeal myelomatosis) may also manifest as an extraaxial mass that is isodense to brain on T2-weighted images and homogeneously enhances *(49)*, thus mimicking meningioma. Abnormal dural enhancement may also be seen in secondary invasion of the dura from a metastatic calvarial lesion *(50)*, or may alternatively be due to benign reactive change adjacent to calvarial tumor (Fig. 4).

### Tumor Complications

***Cerebrospinal Fluid and Meningeal Dissemination*** The most common neoplasms to spread to the meninges include breast carcinoma, lymphoma, leukemia, lung cancer, malignant melanoma, and gastrointestinal and genitourinary malignancies *(30,51,52)*. MRI plays an important role in the diagnosis of meningeal neoplasm in the asymptomatic patient, when cerebrospinal fluid (CSF) cytology is equivocal, or if lumbar puncture is contraindicated *(2,53,54)*. The limited sensitivity of CSF cytology continues to be a significant obstacle and reinforces

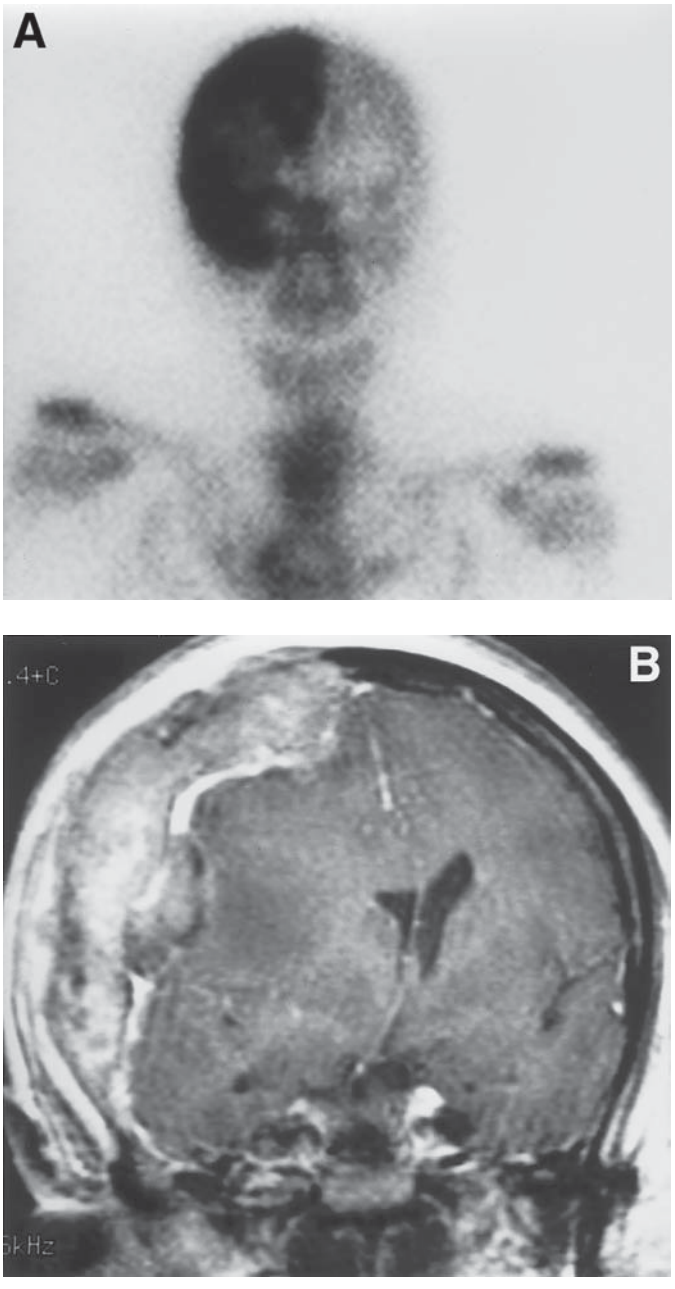



**Fig. 4.** This 68-yr-old patient noted a "bulging" in the right scalp region and a firm breast mass for 8 mo. **(A)** Whole-body bone scintigraphy shows substantial radionuclide uptake in the right calvaria. **(B)** This breast cancer metastasis corresponds to the enhancing mass on MRI that is centered in the diploic space, but traverses the dura and arachnoid to invade the subjacent brain parenchyma and produces significant mass effect with subfalcine herniation.

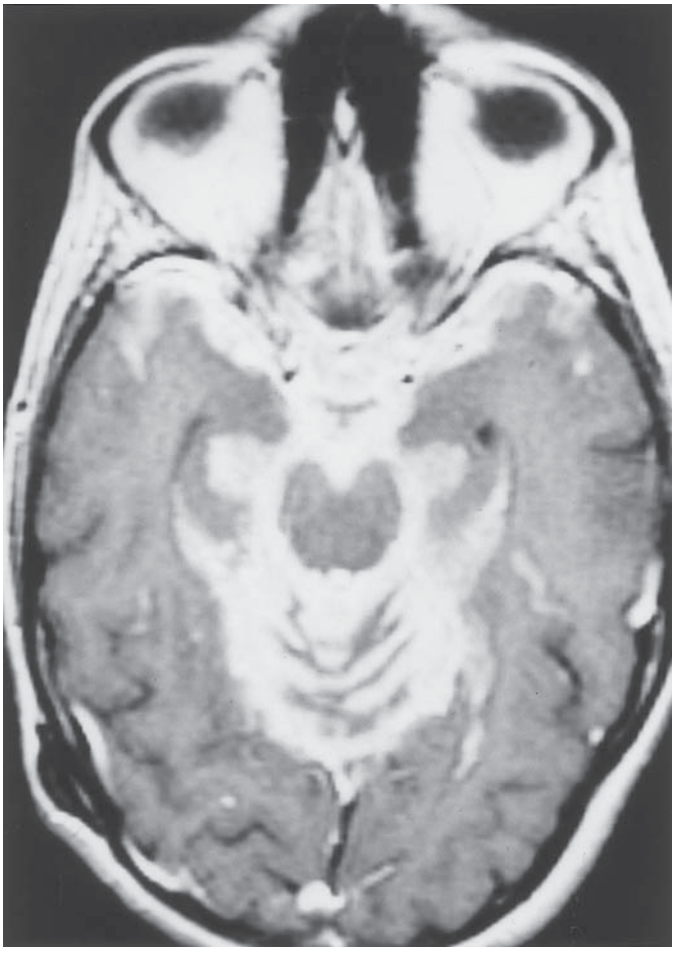
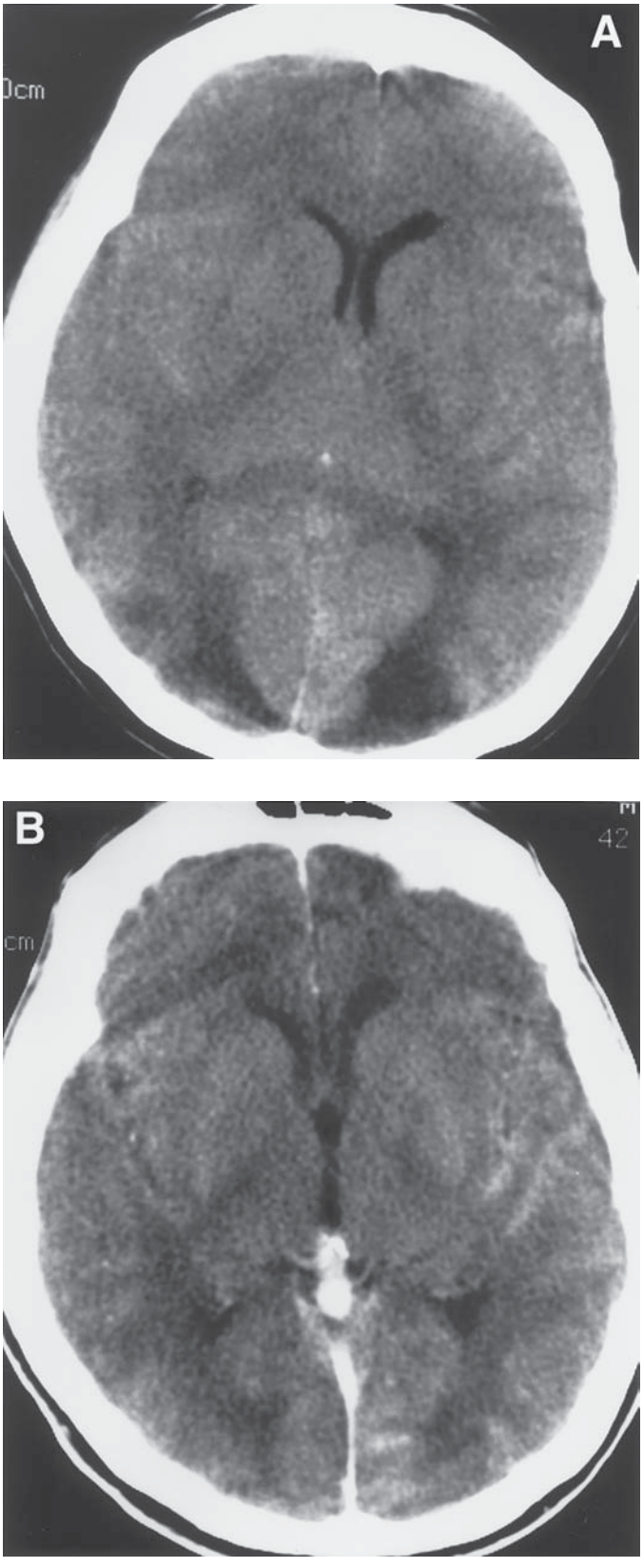


**Fig. 5.** Contrast-enhanced MRI shows thick basilar meningeal enhancement, the differential diagnosis for which includes meningeal carcinomatosis, granulomatous meningitis (e.g., sarcoid), or tuberculous meningitis. Histopathologic examination revealed a poorly differentiated CNS neoplasm consistent with pineoblastoma.

the complementary role of imaging *(55)*. In cases of meningeal metastases from non-CNS neoplasms, CSF cytology was positive in 45% after single lumbar puncture, and 80% with multiple taps *(30)*. Another large series of non-CNS neoplasms with meningeal disease confirms these data *(52)*.

A Memorial Sloan-Kettering Cancer Center study showed an increased rate of detection of leptomeningeal carcinomatosis when the patient cohort was not restricted to those with positive cytology *(54)*. CT and MRI studies of 137 patients with signs and symptoms of meningeal disease were evaluated for the presence of hydrocephalus and enhancement of the dura, leptomeninges, or cranial nerves. Leptomeningeal metastases were diagnosed in 77 of 137 patients. In 31% of those cases, the diagnosis was based on the clinical and imaging findings alone. Abnormal imaging findings were reported in 90% of solid tumor primaries and 55% of hematological neoplasms. MRI is less sensitive in detecting spread of hematologic malignancies, as opposed to solid tumors, to the meninges *(54,56,57)*. In the appropriate clinical setting, imaging is a vital tool in the diagnosis of meningeal neoplasm along with CSF examination to exclude infection or noninfectious processes of the meninges.

The main imaging findings of meningeal or subarachnoid space neoplasm are hydrocephalus, dura/arachnoid enhancement, pia/subarachnoid space enhancement, and ependymal enhancement *(53,54,57–59)* (for review, *see* ref. *42*) (Fig. 5). Hydrocephalus may or may not be associated with enhancement of the meninges or ependyma. In this setting, hydrocephalus implies a resorptive block to CSF flow and is more likely in the presence of leptomeningeal invasion, rather than neoplasm limited to the dura *(60)*. Enhancement of the



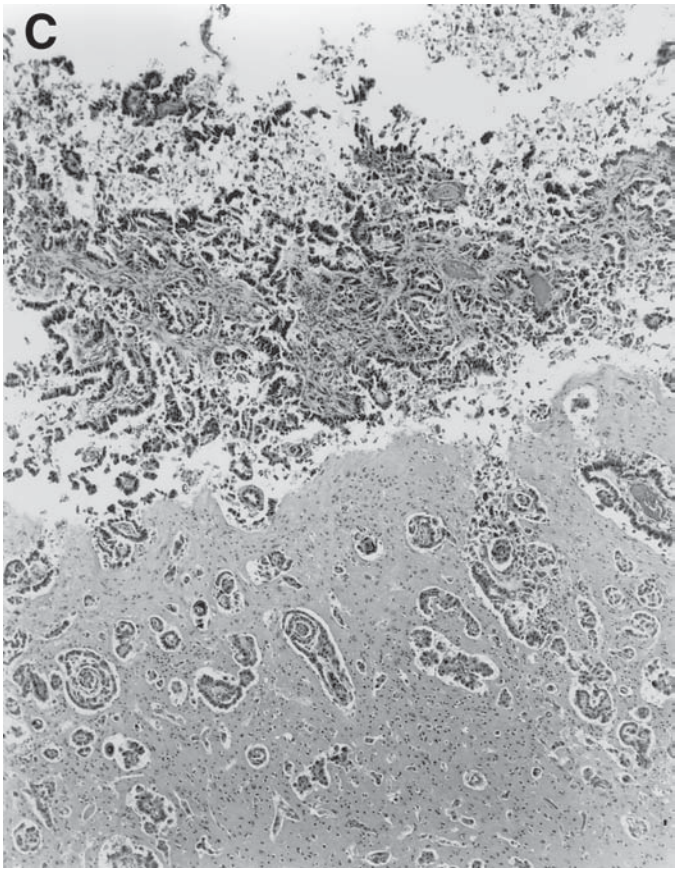




**Fig. 6.** Carcinomatous encephalitis. This 42-year-old patient presented with a 4 mo history of seizures. The patient had suffered intermittent vomiting and a 30 pound weight loss; multiple cranial nerve palsies were noted on exam. Clinically, a basilar inflammatory process, such as sarcoidosis, was suspected. CT demonstrates hypoattentuation in the occipital lobes **(A)** with minimal enhancement in the pia/subarachnoid space **(B)**. Autopsy revealed a poorly differentiated adenocarcinoma of the lung with leptomeningeal carcinomatosis and multiple cerebral infarcts. **(C)** The histology shows extensive neoplasm in the subarchnoid space with many neoplastic cells invading the perivascular spaces.

meninges may occur in the spine or brain. Meningeal or subependymal enhancement may be focal or diffuse and may have either a smooth or nodular contour. Diffuse leptomeningeal involvement heralds a worse prognosis than does focal disease *(61)*. Although a nodular pattern of enhancement may suggest neoplasm, it is not specific since nonneoplastic entities such as sarcoidosis may also produce nodular thickening of the meninges.

Prolonged survival *(9,30,62,63)* and the presence of other metastatic foci *(45,61,63)* enhance the probability of meningeal spread from non-CNS primary neoplasms. Viadana et al. *(64)* analyzed the pathways of metastases from a variety of non-CNS tumors and concluded that dissemination of neoplasia is a multistep process. This "cascade" phenomenon describes spread of the primary tumor to at least one intervening organ, from which widespread dissemination may occur *(64)*. The propensity of tumors to spread initially to an intermediate organ substantiates the observation that vertebral body (especially in breast cancer), bone marrow, and liver metastases (especially in lung cancer) are often present in cases of meningeal carcinomatosis *(45,61,63)*. Primary sites of solid tumors that have a propensity to metastasize to the leptomeninges are breast, lung, melanoma, and stomach *(30,51,52)*. Hematological neoplasms such as leukemia and lymphoma are also prone to CSF dissemination.

***Vascular Complications of Metastatic Neoplasm*** After CSF seeding has occurred, neoplasm has the potential to spread throughout the arachnoid and pia mater, through the perivascular (Virchow-Robin) spaces, or along the root sleeves of cranial and spinal nerves *(65)*. Invasion of the perivascular spaces or partial obstruction of the vessel lumen by tumor cells can result in ischemic complications of leptomeningeal carcinomatosis *(30,52)*. The rare occurrence of diffuse perivascular (Virchow-Robin space) infiltration producing ischemia is termed "carcinomatous encephalitis" *(51,66)* (Fig. 6).

***Paraneoplastic Syndromes*** Neurological paraneoplastic syndromes are most frequently encountered in association with small cell lung cancer, but have also been reported in a variety of malignancies, including testicular, breast, and gynecologic neoplasms *(67–69)*. There are relatively few reports of imaging correlates in these unusual manifestations of cancer. When paraneoplastic syndromes present prior to the detection of malignancy, the diagnosis may be especially perplexing. Paraneoplastic cerebellar degeneration due to anti-Purkinje cell antibodies expressed by the tumor results in subacute cerebellar symptoms *(70,71)*. MRI may demonstrate progressive cerebellar atrophy. Other paraneoplastic syndromes include paraneoplastic limbic encephalitis and subacute sensory neuropathy. Shavit et al. *(72)* recently reported MRI findings in three patients with paraneoplastic syndromes who presented with epilepsia partialis continua. Focal T2 hyperintensity in cortical areas was noted in two patients, with autopsy confirmation of inflammatory infiltrates and neuronal loss in one case. A recent study of 50 patients with limbic encephalitis associated with a variety of primary neoplasms including lung, testis, and breast was performed at Memorial Sloan-Kettering Cancer Center *(73)*. In 60% of patients in this series, neurological symptoms predated the diagnosis of cancer by a median of 3.5 mo. Of the 44 patients who underwent MRI, 25 (57%) had limbic distribution signal abnormalities.

**Role of Imaging in Treatment Planning** The success of aggressive approaches to treating brain metastatic disease has served to expand the role of imaging in therapeutic planning. Biopsy and surgical resection of solitary metastases may require advanced imaging techniques, particularly when eloquent areas of cortex are at risk. Three-dimensional reconstructions of volumetric MRI data can provide highly detailed anatomic maps with surface landmarks. Frameless stereotaxy is possible with both CT and MRI. Although MRI suffers from geometric distortion, this may be minimized with careful sequence planning and acceptable accuracy obtained *(74–77)*. The accessibility of CT, limitations of MRI compatibility of stereotactic frames, and geometric distortions in MRI have restricted its widespread use in planning radiotherapy. However, the anatomical detail and superior soft tissue contrast available with MR makes it a preferred imaging tool for therapeutic planning. Indeed, MR has been successfully applied to guide radiotherapy of brain tumors on a limited basis, with spatial distortions minimized by employing smaller field-of-view, increased bandwidth, and fast spin-echo (FSE) sequences *(76)*. Accurate approaches to stereotaxy are also needed to facilitate delivery systems for targeting new gene therapies *(78,79)*.

Although not yet in widespread use, intraoperative MRI can provide real-time guidance for localizing tumor margins and adjacent anatomic structures *(80–82)*. Initial reports have been favorable for augmenting the yield of biopsies and improved accuracy of tumor resection *(80,82)*. Black and colleagues *(80)* evaluated the performance of an open-configuration 0.5 Tesla MRI scanner in aiding 60 craniotomies for tumor resection, including eight metastatic lesions. In over a third of cases, intraoperative imaging demonstrated residual tumor when conventional surgical assessment did not. One important caveat is that surgically induced contrast enhancement may occur and can lead to overestimation of residual tumor *(83,84)*. Intraoperative MRI requires substantial changes in surgical instrumentation, since MRI-compatible instruments, drills, and surgical microscope must be developed, with significant cost implications *(85)*.

Both PET and functional MRI (fMRI) are effective for mapping motor and somatosensory cortices and language areas prior to surgery in order to minimize the risk of permanent adverse neurologic sequelae *(86,87)*. PET imaging with [O-15]water has been used to localize the cerebral blood flow response to a motor or sensory stimulus. Recently, blood oxygenation level dependent (BOLD) imaging with fMRI—which measures the change in the relative proportion of deoxy- and oxyhemoglobin that results from local increases in blood flow in activated cortex—has been shown to correlate moderately well with PET blood-flow studies *(86)* and direct cortical stimulation *(88)*. FMRI is generally more widely available than [O-15]water PET imaging and has the advantage of superior temporal and spatial resolution. The results of presurgical functional mapping have been shown to be useful for determining feasibility of surgery, as an aid to surgical planning, and to select patients for whom invasive surgical functional mapping may be needed *(89)*. Occasional difficulty in identifying the motor or somatosensory cortex with fMRI has been attributed to vascular compression or distortion by the tumor *(90)*. Magnetoencephalography (MEG) may also be used for presurgical localization of the central sulcus *(90,91)*. Passive motor stimuli have been used to adapt these techniques to cortical mapping in pediatric or sedated patients *(92)*.

**Therapeutic Monitoring** The volume of the enhancing portion of a tumor is generally used as a quantitative measure of therapeutic response. Various approaches, including hand tracing, semi-automated, and automated methods, may be used with variability in precision *(74,93–95)*. Visual assessment by an experienced neuroradiologist is practical for routine evaluation of tumor response with serial imaging; however, computer-driven segmentation methods generally offer a mild advantage in reliability for quantitative measurements of tumor progression, with lower inter-rater variation *(95,96)*. In primary brain tumors, CT or MRI-determined doubling time is superior to histologic grade in predicting patient prognosis *(97)*. However, enhancing lesion volume may be influenced by steroid use and temporal proximity to radiation, especially SR *(98)*.

SR is increasingly used for local control of metastatic brain lesions, and has been shown to be a beneficial, and potentially safer and more cost-effective alternative to surgical resection

and whole brain radiotherapy *(99,100)*. One-year local control rates of up to 75% have been reported *(101,102)*. The expected course of the imaging response to SR may differ from that produced by whole brain irradiation due to the small territory and rapid peripheral gradient. Peterson et al. *(98)* examined the time course and imaging features of 78 metastatic lesions followed with serial enhanced MRI. A greater than 50% decrease in lesion volume in the first 3 mo was associated with a long-term favorable prognosis for continued local disease control. Interestingly, they observed a transient increase in lesion size in several cases 4–24 wk posttreatment. Others have observed a reversible increase in the extent of T2 signal alterations in the subacute (3–6 mo) post-SR period *(102)*. These observations indicate that initial increases in the size of the enhancing lesion or extent of associated T2 signal abnormalities do not necessarily portend a poor prognosis following SR. The pathophysiology of this phenomenon is uncertain; it may be to radiation-induced inflammatory changes, analogous to a "flare reaction" observed posttherapy on bone scintigraphy. Also, lesions exhibiting a homogeneous, rather than a ring-like, pattern of enhancement at baseline tended to exhibit a relatively better SR response *(98)*. As may be expected, smaller tumors are more likely to respond to SR than those larger than 2.5 cm *(103)*.

In the immediate postoperative period following resection of intracranial lesions, a noncontrast CT image typically suffices to exclude immediate complications, such as intracranial hemorrhage, hydrocephalus, and evidence of edema/herniation. However, surgical intervention interferes with the subsequent use of anatomical imaging for disease detection. Indeed, one of the major limitations of structural MRI or CT imaging is the confounding effect of postsurgical and postradiation tissue distortion, enhancement, and edema on detection of early recurrent disease *(104,105)*.

The interpretation of posttreatment imaging may be further confounded by reactive meningeal changes. Physical disruption of the integrity of the meninges resulting from surgical tumor resection or intracranial catheter placements may result in benign meningeal enhancement. Postoperative enhancement typically manifests as localized or diffuse dural enhancement, and may persist indefinitely *(106,107)*. Thus, a craniotomy performed for tumor resection may render subsequent imaging unable to distinguish normal, reactive postoperative enhancement from meningeal tumor involvement. This is especially problematic since there is evidence to suggest that surgery for brain metastases increases the risk of leptomeningeal recurrence *(108)*. However, certain imaging features, such as nodular dural enhancement, prominent pial enhancement, or progression of meningeal enhancement with serial imaging, should increase suspicion of neoplastic disease *(109)*. Although lumbar puncture can result in dural enhancement, this is quite rare unless complicated by intracranial hypotension *(47,110)*.

The recent rise in aggressive treatment approaches to brain metastatic disease, including surgical resection and SR, have led to renewed interest in nuclear medicine techniques for diagnosis and monitoring of intracranial metastases. Metabolic imaging with PET has been used to distinguish posttherapeutic changes from persistent or recurrent malignant tissue, but due to high background uptake of FDG in normal brain tissue is more useful for highly metabolically active lesions such as high-grade glial tumors or primary CNS lymphoma *(111)*. Variability of metabolic activity in brain metastases limits the sensitivity of PET in this setting *(112)*. However, in the specific case of SR, Mogard et al. *(113)* showed a clear advantage of FDG PET over MRI and CT in providing prognostic information on 11 patients following SR of cerebral metastases. Although rarely performed, acquisition of a baseline pretreatment "metabolic fingerprint" can be of substantial value in later determining whether a tumor is responding to therapy. Also, fusion of structural images with functional image data can further improve the accuracy of image interpretation. Although the optimal posttherapeutic interval for functional imaging has yet to be clearly determined, a paradoxical rise in FDG uptake of primary and metastatic neoplasms has been observed in the immediate (4 h–2 d) period following conventional radiotherapy or SR, with uptake returning to baseline levels by 1 wk *(114,115)*. This hyperacute rise in glucose utilization may be prognostically useful in predicting a favorable response to SR *(115)*. Therefore, imaging too soon following therapy may lead to confusing results. Based on the preponderance of evidence, one to three months posttreatment appears to be a generally ideal interval for obtaining reliable prognostic information on tumor reponse *(116,117)*. Co-registration with MRI can further aid in both the diagnostic accuracy of FDG PET and for biopsy planning of recurrent or residual disease *(118,119)*. Due to the limited spatial resolution of PET and single-photon emission tomography (SPECT), sensitivity is diminished for evaluating very small lesions, typically those below 1–2 cm.

### Imaging Treatment Complications

***Neurotoxicity Associated with Chemotherapy and Radiation*** Neurotoxicity may occur following the use of chemotherapy agents used in the treatment of neoplasm or from immunosuppressive drugs used to maintain bone marrow transplants as part of a treatment regimen. Confusion, memory loss, dysarthria, visuospatial disorganization, broad-based gait, and hemiparesis are part of the clinical spectrum of neurotoxicity *(120)*. The route of drug delivery may influence the time course and severity of toxicity, with intrathecal administration producing a more rapid and deleterious result *(121)*. Resulting imaging findings include ventricular enlargement, white matter hypoattenuation and parenchymal calcification on CT *(120)*, with multiple chemotherapeutic agents (including cisplatin, methotrexate, BCNU, cytosine arabinoside [Ara-C], 5-fluorouracil, levamisole, fludarabine, thioTEPA, interleukin-2 [IL-2], procarbazine) producing a similar appearance *(120–124)*. With a shorter course than radiation-induced bran injury, imaging manifestations of neurotoxicity due to chemotherapy may be observed as early as 1 wk following intrathecal agents.

Demyelination has been reported as a manifestation of neurotoxicity with multiple agents including methotrexate, Ara-C, and thioTEPA *(123,125)*. Demyelination stemming from impaired methylation of the myelin sheath has been proposed as a pathogenic mechanism in the neurotoxicity of patients with small cell lung cancer treated with methotrexate and procarbazine *(120)*. Vasculopathy has been proposed as a cause of the necrosis observed following high-dose BCNU adminis-

tration *(122)*. Price and Jamieson *(125)* examined CNS autopsy specimens of 13 cases of leukoencephalopathy after treatment of acute lymphoblastic leukemia with radiation therapy (>2000 rads) and systemic methotrexate. Diffuse reactive astrocytosis, varying stages of demyelination, multiple necrotic foci, and mineralized cellular debris characterized the histopathologic examination.

The response of brain tissue to radiation therapy is dependent on the total dose, fractionation schedule, and field selection *(126–129)*. A lower total radiation dose, increased fractionated delivery, and three-field (rather than two-field) technique are associated with reduced risk of radiation tissue effects *(128)*. Also, accelerated fractionation schedules for whole brain radiation may enhance the likelihood of late radiation toxicity *(127)*. Radiation-induced complications are often classified in three stages: (1) acute, (2) early delayed, and (3) late delayed reactions *(130)*. Acute reactions are those occurring during or immediately following radiotherapy. These are characterized clinically, have no recognized neuroimaging correlates, and resolve without sequelae. Early delayed reactions occur several weeks to months posttreatment and are generally transient and responsive to steroids. Reversible deficits in verbal memory function may accompany early delayed radiotherapy reactions *(131)*. MRI or CT imaging may demonstrate multiple enhancing lesions that may mimic multiple sclerosis (MS).

The imaging features of late delayed reactions most commonly include those associated with diffuse white matter injury and focal radiation necrosis. A diffuse pattern of white matter lucency by CT imaging or T2 hyperintensity with MRI is a hallmark of postradiation change. This appearance of radiation white matter changes may be distinguished from vasogenic edema due to tumor regrowth by its periventricular or geographic distribution and the absence of associated mass effect. Focal radiation necrosis is characterized by a ring-enhancing mass lesion, which is virtually indistinguishable from tumor regrowth on conventional CT or MRI. Other late radiation complications are often related to radiation induced vascular injury including induction of vascular malformations (e.g., aneurysm, telangiectasia), hemorrhage, mineralizing microangiopathy, and radiation injury to large arteries *(130,132–134)*.

Concomitant chemotherapy can exacerbate the toxic effects of radiotherapy on brain tissue *(129)*. Disseminated necrotizing leukoencephalopathy (DNL) is a form of late radiation white matter injury seen in patients receiving both radio- and chemotherapy (particularly for childhood leukemia) and is associated with cognitive dysfunction, especially common in children and the elderly *(135,136)*. Increased permeability of the BBB in the face of radiotherapy may be responsible for the augmented toxicity of chemotherapy drugs in this setting *(125)*. DNL tends to occur earlier than diffuse radiation-induced white matter changes, but appears similar on imaging. CT will demonstrate extensive lucency of the supratentorial white matter. The extent of involvement may be shown to best advantage with MRI, in which involved areas will appear hyperintense on relatively T2-weighted sequences (Fig. 7).

Not surprisingly, the developing brain appears to be particularly vulnerable to the adverse effects of radiation and chemotherapy. Indeed, cognitive deficits are frequently observed in pediatric patients exposed to radiotherapy for childhood brain tumors *(137)*. In children treated for brain tumors, MRI spectroscopy demonstrates significant neurochemical disturbances in brain tissue remote from the tumor site *(138)*. A decline in the ratio of N-acetylaspartate (NAA) to creatine (Cr) was noted in children exposed to chemotherapy with and without whole brain radiation. Similarly, perfusion defects have been shown in normal brain areas treated with external beam radiotherapy *(139)*. Craniospinal radiation and chemotherapy has been shown to result in reduced white matter volumes that correlated with loss of intellectual function in childhood medulloblastoma survivors *(140)*.

Another late complication of cranial irradiation with obvious neuroimaging implications is the development of secondary neoplasms, including meningiomas, sarcomas, non-Hodgkin's lymphoma, and gliomas *(141,142)*. This risk is particularly notable in childhood leukemia survivors. Among 1612 consecutive pediatric patients treated for acute lymphoblastic leukemia at St. Jude Children's Research Hospital between 1967 and 1988, 22 brain tumors were diagnosed after an average latency of 12.6 yr (143). High-grade gliomas developed with a shorter mean latency than meningiomas (9.1 yr vs 19 yr) and

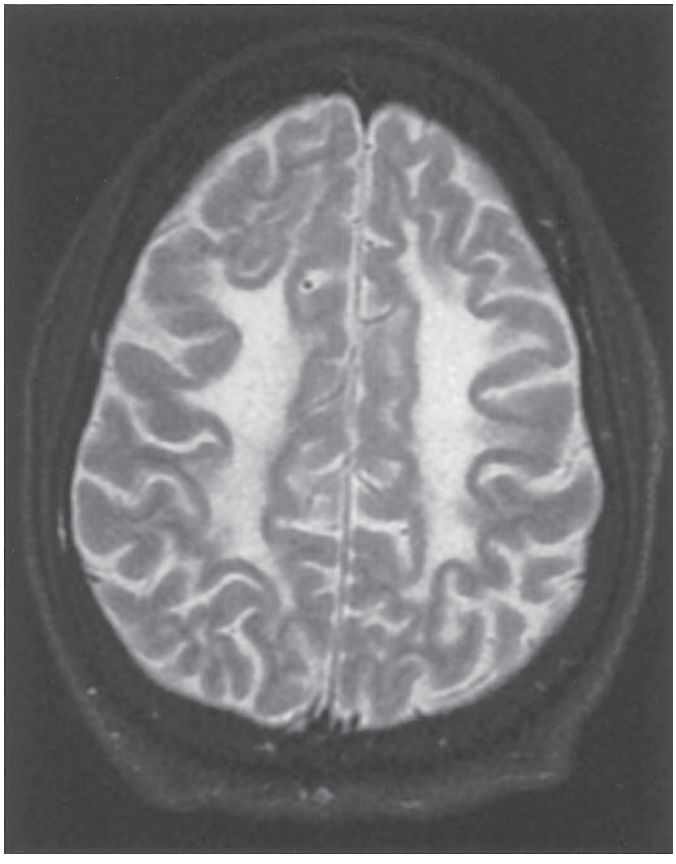


**Fig. 7.** This 22-yr-old patient had a history of acute lymphoblastic leukemia. The patient was treated with radiation (2400 cGy) and chemotherapy, in addition to intrathecal methotrexate, 4 yr previously and now has cognitive impairment. T2-weighted imaging of the brain demonstrates diffuse white matter signal abnormality characteristic of neurotoxicity following radiation and chemotherapy (disseminated necrotizing leukoencephalopathy, DNL).

were most often seen in those patients who were under age six at the time of cranial irradiation. The tumorigenic effect of radiotherapy has been shown to be dose-dependent by some *(143),* but not all, investigators *(144)*.

***Immunosuppression Neurotoxicity*** Immunosuppression-associated leukoencephalopathy should be distinguished from irreversible forms of treatment sequelae in oncology patients undergoing bone marrow transplantation. Tacrolimus and cyclosporine A, among the most common immunosuppressive agents, produce a well-characterized neurological syndrome *(145–147)*. Immunosuppression-associated leukoencephalopathy is felt by some to represent a demyelinating syndrome, which shares clinical features with other pathological processes including ischemia, infection, and metabolic abnormalities, and cannot be readily distinguished from them on clinical grounds alone *(148)*. Common clinical features include headache, focal neurological findings, encephalopathy, seizures, and cortical blindness.

MRI is superior to CT for demonstrating the characteristic parieto-occipital white matter lesions of immunosuppression-associated leukoencephalopathy, which are typically patchy, bilateral, and predominately subcortical areas of hyperintensity on T2-weighted images *(149–151)*. Lesion conspicuity is especially high on FLAIR sequences *(152,153)*. These imaging findings are identical among various agents despite differing proposed mechanisms, and are similarly reversible upon withdrawal of the causative agent *(145,153–156)*. The differential diagnosis for immunosuppression-associated leukoencephalopathy includes infections such as progressive multifocal leukoencephalopathy (PML) *(157,158)* and potentially human herpesvirus infection *(159)*. The key to the diagnosis of immunosuppression-associated leukoencephalopathy is the characteristic reversibility and location of imaging findings in the posterior subcortical white matter (Fig. 8). Recognition of these diagnostic features typically obviates the need for biopsy confirmation.

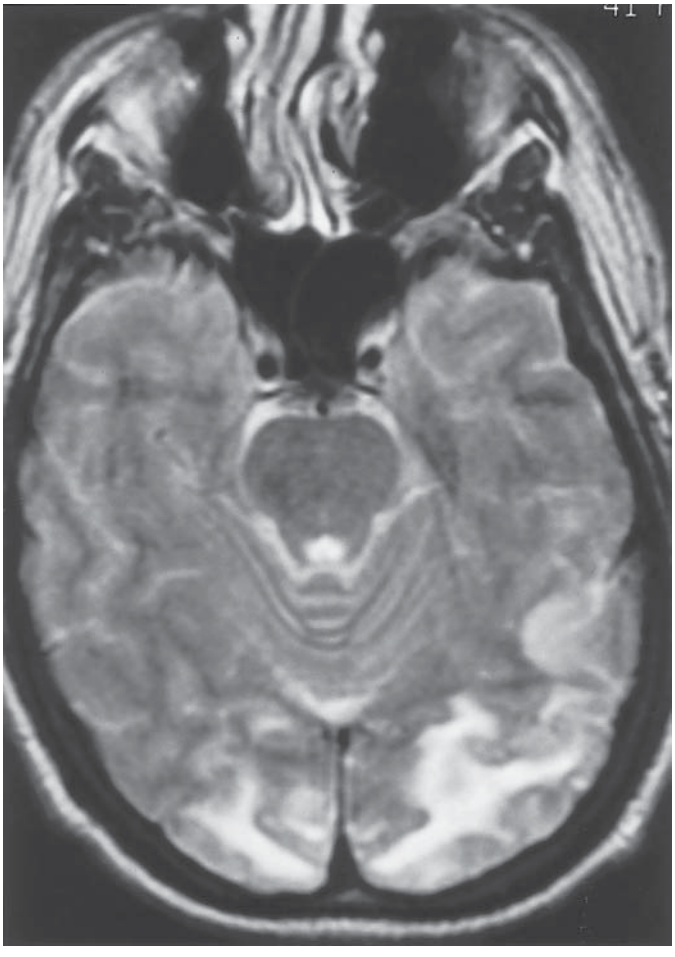


**Fig. 8.** This 51-yr-old patient developed decreased visual acuity 3 d after commencing cyclosporine therapy. The patient had recently undergone bone marrow transplantation for chronic myelogenous leukemia. T2-weighted MRI shows a pattern of bilateral increased signal in the subcortical occipital white matter typical of cyclosporine toxicity.

Hypertension has been invoked as a factor in both cyclosporine A and tacrolimus-associated leukoencephalopathy *(145,150)*. Since the reversible posterior leukoencephalopathy seen in hypertensive encephalopathy is indistinguishable from immunosuppression-associated leukoencephalopathy on imaging *(160)*, this is a compelling theory. Schwartz et al. *(150)* and Bonham et al. *(145)* documented hypertension in the majority of their cases of immunosuppression-associated leukoencephalopathy, providing further evidence to support this link. Neuropathological findings have been variable: myelin pallor and astrocytosis or edema without evidence of demyelination *(155,156,161)*.

***Infectious Complications*** Immunocompromised patients—such as those on chemotherapy, steroids, or immunosuppressive therapy associated with treatment regimens, or individuals with hematological malignancies—are at increased risk of acquiring CNS infection from a wide variety of bacterial, viral, fungal, and parasitic pathogens. Among those with brain abscesses, a third are patients with cancer *(162)*. MRI is the preferred imaging modality in suspected CNS infection *(163)*. In particular, FLAIR sequences should be acquired for improved detection of meningoencephalitis and brain abscesses over conventional spin-echo images *(164)*. Preliminary evidence suggests that when the diagnosis is in doubt, diffusion-weighted MRI may be useful in differentiating cystic or necrotic metastases from cerebral abscesses, the latter displaying a reduced apparent diffusion coefficient *(40,165)*. Proton MRI spectroscopy may also be helpful in this setting *(41)*. The distinct metabolic spectra of pyogenic abscesses are notable for the prominence of lactate and cytosolic amino acids (e.g., leucine, isoleucine, valine, and alanine).

*Aspergillus* is among the more common infectious agents to cause brain lesions in the immunocompromised host, and is the dominant form of fungal disease in this patient population *(166)*. In a review of eight years' experience at the Fred Hutchinson Cancer Research Center in Seattle, 58 patients developed brain abscesses following bone marrow transplantation *(167)*. Ninety-two percent of these were attributed to fungal infection, most commonly *Aspergillus* (58%) or *Candida* (33%). With a variable imaging appearance, systemic invasive aspergillosis infests the CNS by hematogenous dissemination. Lesions tend to be multiple, irregularly ring-enhancing, and demonstrate a predilection for the basal ganglia and thalami

*(168–170)*. Characteristic of cerebral abscesses in general, the enhancing ring tends to be hypointense on T2-weighted images. As with other fungal infections, hemorrhage is not uncommon. Invasive aspergillosis may also manifest as aggressive infection of the paranasal sinuses, calvarium, or orbit *(168)*. Vascular complications of *Aspergillus* are a notable source of morbidity and mortality *(171)*. Fungal spinal osteomyelitis, which may occur in immunocompromised patients, may lack the T2 hyperintensity in the intervertebral disk that is characteristic of bacterial spine infections *(172)*.

Pyogenic abscesses are distinctly less common than fungal infections in the immunocompromised host *(167)*. When present, bacterial infections are typically due to *Listeria, Pseudomonas,* and *Enterobacter (171)*.

Parasitic infection with toxoplasmosis, most commonly found in the acquired immunodeficiency syndrome (AIDS) population, may also occasionally develop in the oncology patient *(173)*. This association is most often noted in patients with Hodgkin's disease, but is also reported in the setting of other tumors treated with antineoplastic therapy. Multiple ring-enhancing lesions in the basal ganglia is a typical imaging presentation of toxoplasmosis, although occasional lack of enhancement may make the diagnosis particularly challenging *(173,174)*. When unrecognized, toxoplasmosis is accompanied by a high morbidity and mortality.

Viral infections, typically encountered in patients with T-lymphocyte deficits, include varicella zoster virus (VZV) and herpes simplex encephalitis *(171,175)*. CNS involvement with disseminated VZV produces multifocal, plaque-like subcortical lesions that enhance with contrast *(176–178)*. Hemorrhage may be seen later in the disease progression. Pathologic examination reveals an active demyelinating process *(177)*. The MRI appearance of herpes simplex encephalitis is well-recognized, with its characteristic bilateral, asymmetric involvement of limbic gray matter *(179)*; hemorrhagic signal abnormalities, and gyriform enhancement are variable features.

Since CNS infection is a significant source of morbidity and mortality in oncology patients *(167,171,174)*, early recognition and institution of appropriate therapy is extremely important. MRI should be promptly performed in immunosuppressed patients in whom CNS complications are suspected. Particular vigilance is required because of the often subtle nature of the clinical presentation, which may include only fever or headache *(171)*. Imaging features may suggest specific diagnoses; however, CSF analysis and culture and brain biopsy often are needed to direct the proper therapeutic course. The presence of multiple infectious agents should also be considered in this patient population.

## SPINE IMAGING

**Metastatic Disease of the Spine** Vertebral metastases constitute 39% of all skeletal metastases *(180)*. Primary sites of metastases to the vertebral column include breast, lung, genitourinary (especially prostate and renal), lymphoma, melanoma, and gastrointestinal and sarcoma *(181–186)*. The spinal epidural soft tissue may be secondarily invaded by adjacent vertebral metastases, or may be involved in the absence of bony disease, especially in non-Hodgkin's lymphoma *(46)*. Between 5 and 8% of patients who die with cancer have cord compression *(181)*. Pain is the most common presenting symptom of spinal cord compression from metastatic disease, followed by motor or sensory deficits *(182,183)*. Metastatic disease to the spine is most often to the epidural compartment with bone involvement, but CSF or meningeal neoplasm also can involve the intradural, extramedullary compartment. Metastases to the cord substance, however, are uncommon.

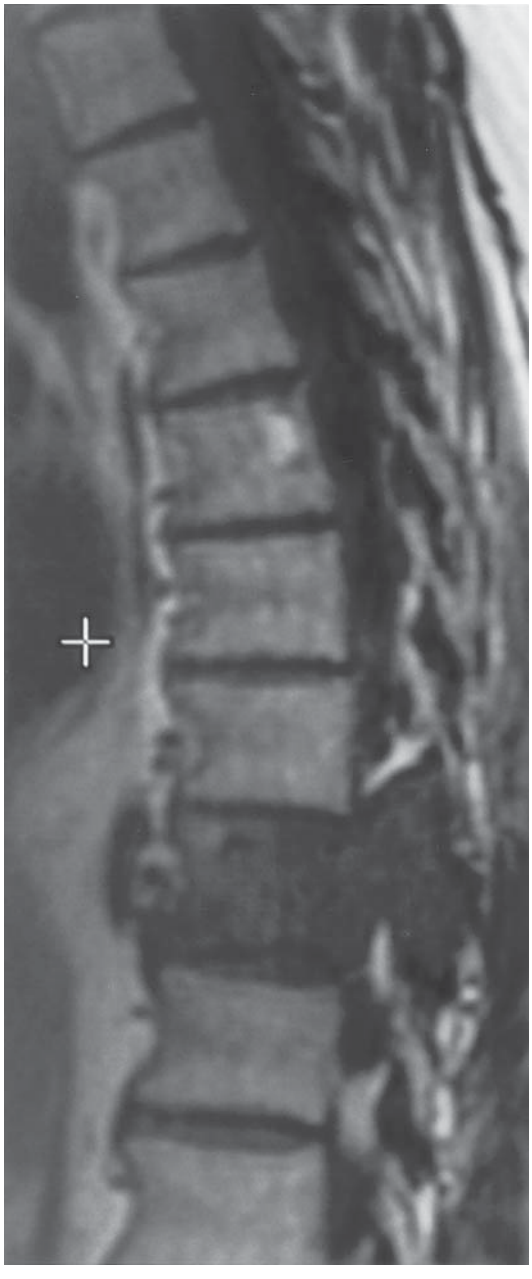


**Fig. 9.** This 54-yr-old patient was diagnosed with metastatic renal cell carcinoma 4 yr previously. MRI obtained for routine surveillance of spinal metastases demonstrates a low signal intensity T-9 lesion that replaces the normal bright marrow fat on T1-weighted imaging and extends into the posterior elements.

**Detection of Metastatic Spine Disease** Plain film radiographs are relatively insensitive to bone metastases, since more than 50% of cancellous bone content must be lost before a lesion is evident *(187)*. Bone scintigraphy with planar (that is,

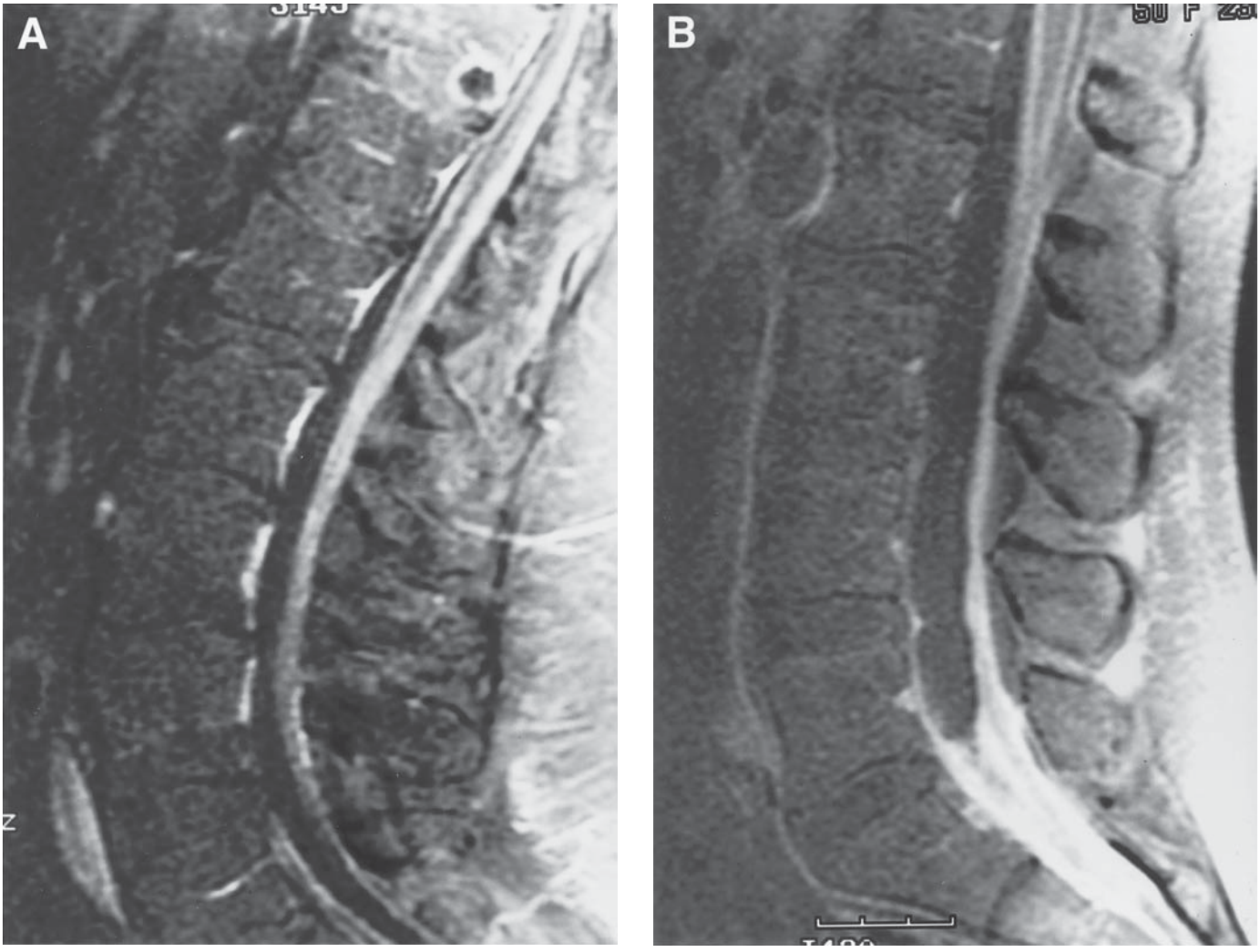



**Fig. 10.** Look-alike spine lesions. **(A)** This 45-yr-old patient presented with headache and back pain. Opening pressure on lumbar puncture was 50 cm of water. MRI obtained after gadolinium administration with fat saturation demontrates a round hypointense focus in the T-9 vertebra and thick pial and nerve root enhancement. Vertebral body biopsy confirmed a sclerotic adenocarcinoma metastasis of unknown primary. **(B)** This 50-yr-old patient had low back pain treated with multiple epidural steroid injections 6 mo earlier. She presented to the emergency room with severe low back pain and fever. Sagittal, enhanced MRI shows thick enhancement of the nerve roots of the cauda equina, mimicking carcinomatosis. CSF cultures grew *Neisseria sicca*.

nontomographic) imaging is a sensitive, but not specific technique to evaluate the entire skeletal system for metastases *(188,189)*. The pattern of abnormal uptake on SPECT has added to the specificity of radionuclide imaging of metastatic disease to the spine *(185,190)*. Abnormal uptake in the vertebral body and pedicle or pedicle alone most likely represents tumor (73–83%). Conversely, abnormal uptake in the vertebral body and posterior elements with an intervening normal pedicle or isolated facet disease are patterns most likely to result from a benign etiology (93–100%) *(185,190,191)*.

The superior sensitivity and specificity of MRI over other imaging techniques, including planar bone scintigraphy and CT myelography, in the evaluation of spinal metastatic disease has been established in a body of literature since 1985 *(188,192–194)*. MRI is more sensitive than CT myelography for the detection of vertebral metastases, as well as paravertebral extension *(194)*. Indeed, a noninvasive technique is preferable to myelography for evaluation of suspected spinal cord compression because of the risk of neurological deterioration after puncture below the level of a complete block *(195)*. Although MRI is generally considered to be more sensitive that planar bone scintigraphy, it may be equivalent to SPECT scintigraphy in the detection of vertebral metastases *(196)*. The advantage of MRI over scintigraphic studies, however, is the ability to provide soft tissue contrast that permits detection of epidural and paravertebral extension of bony disease, spinal cord compression *(184,194)*, and carcinomatosis of the meninges. Newer MRI sequences such as short-inversion-time inversion recovery (STIR) and inversion recovery fast spin echo (IRFSE) are even more sensitive than conventional T1-weighted and fat-saturation FSE imaging for detecting vertebral metastases *(197)*. T1-weighted, FSE, and fat-saturated FSE, however, were superior to STIR and IRFSE for epidural disease in one series *(197)*.

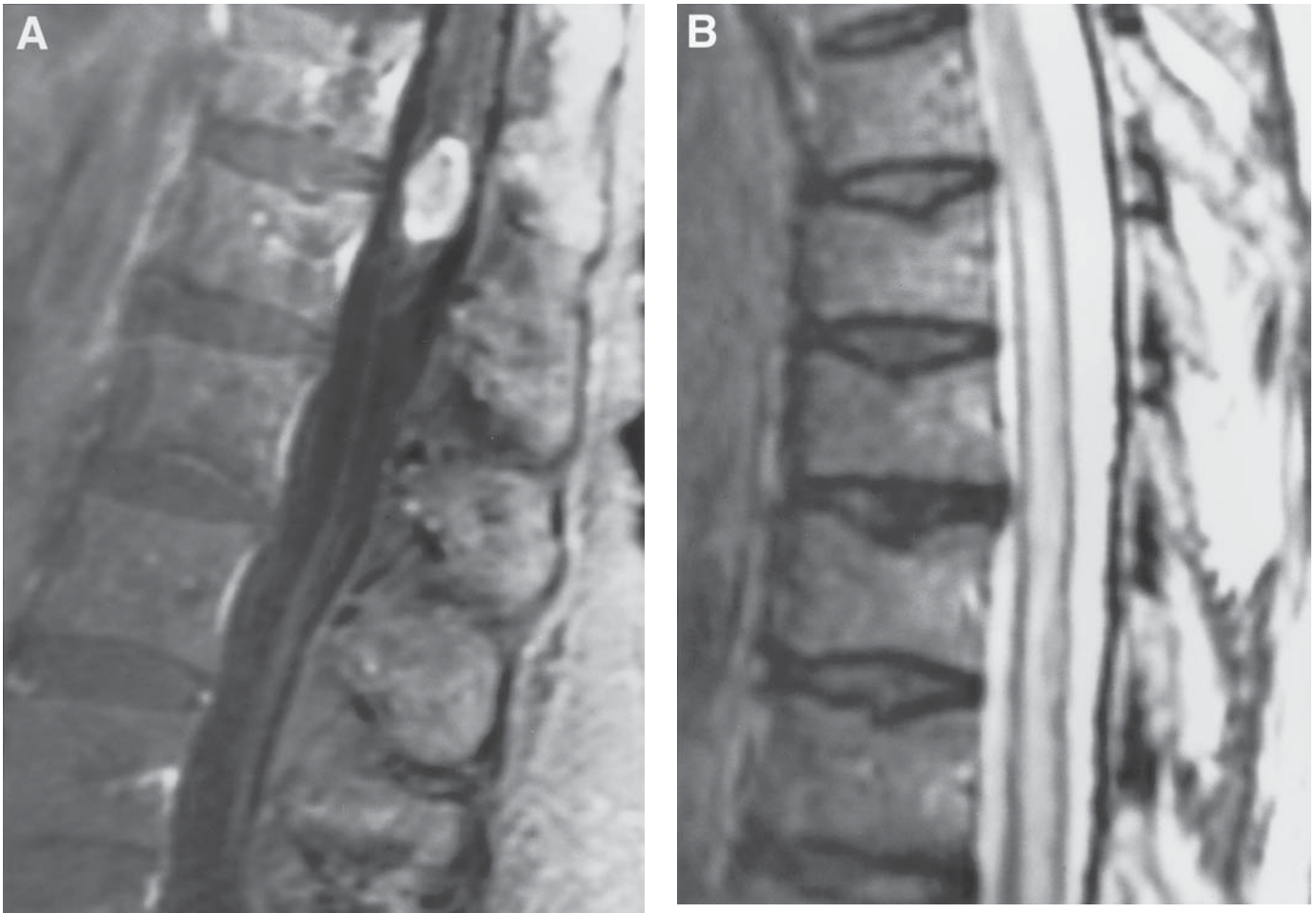



**Fig. 11. (A)** This 66-yr-old patient with nonsmall cell carcinoma metastatic to the brain presented with lower extremity weakness and bladder dysfunction. Physical exam showed loss of reflexes at the knee and below. MRI of the spine with gadolinium shows an enhancing metastasis to the conus. T2-weighted imaging **(B)** demonstrates a syrinx extending proximally in the cord.

### Imaging Features of Secondary Neoplastic Disease

***Extradural Metastases*** Vertebral metastases produce findings of marrow replacement on MRI *(193)*. MRI features of vertebral neoplasm include hypointensity on T1-weighted imaging, hyperintensity on T2-weighted imaging, altered vertebral body contour, and epidural and paravertebral extension *(193,194)* (Fig. 9). Metastases usually enhance with gadolinium and may occasionally be hypointense on T2-weighted imaging, particularly when sclerotic.

***Intradural Metastases*** Carcinomatosis of the meninges has been discussed in the previous section on brain imaging. Characteristic features of neoplastic CSF and meningeal involvement in the spine include thickening and enhancement of nerve roots *(42)* (Fig. 10A). Infection may mimic neoplastic subarachnoid tumor, but is usually excluded on the basis of CSF data (Fig. 10B).

***Intramedullary (Spinal Cord) Metastases*** Metastases to the spinal cord are uncommon *(198)*, although may result from a wide variety of primary neoplasms, including lung cancer, breast cancer, lymphoma, colorectal cancer, melanoma, renal cell cancer, thyroid cancer, endometrial cancer, bladder cancer, and head and neck cancer *(198,199)*. Intramedullary spinal cord metastases accounted for 6% of myelopathies in cancer patients in one large series (40 patients) *(199)*, and was frequently accompanied by the clinical manifestation of asymmetric spinal cord dysfunction (45%). MRI is the accepted imaging modality for imaging cord lesions. In a series of 18 cases (26 lesions) studied with MRI, 46% of lesions were in the lumbosacral spinal cord, 27% were thoracic, and 27% were cervical *(198)*. Most patients (67%) had solitary lesions. Typical MRI features included a long segment (greater than two vertebral bodies) of signal abnormality on T2-weighted imaging, isointensity with surrounding spinal cord on T1-weighted imaging, and focal enhancement with gadolinium (Fig. 11).

### Tumor Complications

***Pathologic Fractures*** Bone marrow signal characteristics on spin-echo and STIR imaging may also help to distinguish between chronic and acute pathologic compression fractures. Baker et al. *(191)* found that pathologic fractures tended to have more extensive signal abnormality than bland fractures, although they conceded that biopsy or serial imaging may still be required to make the distinction definitively. More recently,

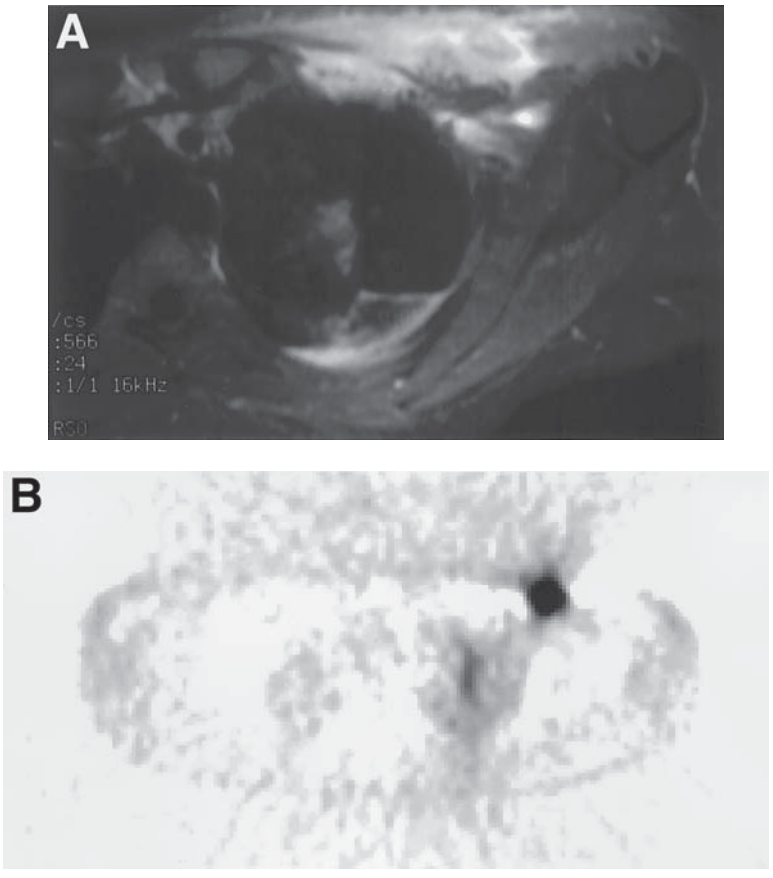



**Fig. 12. (A)** Axial T2-weighted MRI with fat saturation in 34-yr-old woman previously treated with radiation for metastatic involvement of the left brachial plexus. Diffuse increased T2 signal in the irradiated tissue makes it difficult to distinguish posttreatment changes from recurrent disease. **(B)** Transverse image from FDG PET study clearly shows markedly elevated FDG uptake in the brachial plexus indicative of active tumor.

diffusion-weighted imaging has been used to differentiate between benign and pathologic compression fractures in the spine. In a study of 39 vertebral compression fractures in 30 patients, all pathologic fractures demonstrated increased signal on diffusion-weighted imaging (i.e., restricted diffusion), whereas the benign fractures showed iso- to hypointensity suggestive of increased diffusion of free water *(186)*. The increase in free water diffusion in vertebral marrow in the setting of benign compression fracture is attributed to hemorrhage and edema, producing expansion of the extracellular volume fraction. Conversely, restricted diffusion in the pathologic fractures is credited to a reduction in extracellular free water as a result of densely packed tumor cells in bone marrow. One potential limitation is that diffusion-weighted imaging is particularly prone to susceptibility artifacts produced by flow, motion and perfusion *(200)*.

## Treatment Effects and Therapeutic Monitoring

***Role of Imaging in Treatment Planning*** The importance of MRI in documenting both bony and soft tissue tumor involvement before planning surgical decompression of the spinal cord is well established *(201)*. Schiff et al. *(202)* emphasized the necessity of scanning the entire spine in cases of suspected cord compression. In their series, management was altered as a result of the relatively high incidence (approx 30%) of multiple spinal epidural metastases detected on complete spine imaging. Colletti et al. *(184)* examined the impact of spinal MRI on treatment planning in a group of 130 patients with suspected spinal metastases. Of the 100 cases examined retrospectively at 0.5 Tesla, management was altered in 47 cases as a result of findings on MRI; 31 patients had cord compression from metastases, and 16 patients had vertebral metastases without cord compression. In addition, 30 patients were evaluated prospectively at 1.5 Tesla; of these, 12 (40%) had therapy directed by the results of MRI. Overall, MRI resulted in altered treatment planning in 45% of cases.

***Radiation Myelopathy*** Radiation myelopathy is characterized by subacute signs and symptoms corresponding to the irradiated cord segment in the absence of neoplastic disease *(203)*. The presence of associated vertebral necrosis is also strong, but rare, supportive evidence of radiation myelopathy *(204)*. Radiation myelopathy has been reported after radiation for multiple primary tumors, including lung cancer, head and neck malignancies, lymphoma, nasopharyngeal cancer, and medulloblastoma *(204)*. Symptoms developed 20–50 mo after completion of radiation with 70–72 Gy for nasopharyngeal cancer *(205–207)*. The dose to the cord in cases of radiation

myelopathy is usually more than 40 Gy *(208,209)*. MRI typically shows initial long segment cord signal abnormality on T1-weighted images (decreased signal) and with T2-weighting (increased signal), with eccentric contrast enhancement (with or without cord swelling) seen within 8 mo of symptom onset *(205,207,209)*. Cord atrophy is a later finding. Histopathology reports of findings in radiation myelopathy are scarce, although demyelination, swollen astrocytes, and hyalin changes of arteriolar walls have been demonstrated *(208,210)*.

***Insufficiency Fractures*** Sacral insufficiency fractures may develop as a complication of radiation therapy, usually for primary pelvic malignancy, and produce back pain *(211,212)*. The primary importance of insufficiency fractures is that they may mimic vertebral metastases both clinically and by imaging features *(211)*. Lower back pain may occur between 2 and 16 mo following irradiation (with an average dose to sacrum of 50 Gy); MRI abnormalities were detected an average of 5 mo after symptom onset, in one series *(211)*. The MRI appearance of sacral insufficiency is that of signal abnormality in parallel to the sacroiliac joint with indistinct margins, bilaterality (usually), involvement of the anterior pelvis, enhancement with contrast, and lack of an associated soft tissue mass. These characteristics should permit distinction of insufficency fractures from metastases, the latter being typically associated with a discrete soft tissue mass. Sacral CT imaging may also confirm the characteristic configuration of insufficiency fractures oriented parallel to the sacroiliac joints *(211)*.

***Vertebroplasty*** Vertebroplasty is a relatively new technique for treatment of pain from vertebral body lesions and bland compression fractures. Acrylic glue (methyl methacrylate) is injected percutaneously into the vertebral body under fluoroscopic or CT guidance. Bone packing with acrylic glue may prevent pathologic compression fractures in addition to relieving pain *(213)*.

### BRACHIAL PLEXUS IMAGING

**Imaging Approach and Disease Detection** Brachial plexopathy in cancer patients may result from either radiation fibrosis, tumor compression, or infiltration of nerves *(214–216)*. Other potential causes of brachial plexopathy include injury at operation, edema following lymph node dissection, paralytic brachial neuritis, hematoma from catheter placement and, rarely, acute ischemia from vascular occlusion *(214,217–219)*. The clinical features of brachial plexopathy from radiation or tumor may overlap, although pain is more often associated with neoplasm *(220)*.

Imaging evaluation of the brachial plexus should include the entire brachial plexus: roots, trunks, and cords. Metastatic disease to the cervical spine and epidural space with spinal-cord compression may be missed if the cervical spine is excluded. The MRI findings of radiation fibrosis include diffuse thickening and enhancement of the brachial plexus and low signal intensity, typically on both T1- and T2-weighted imaging *(215,216,221,222)*. Since both tumor infiltration and radiation change in the brachial plexus can be associated with increased signal on T2-weighted imaging, the most reliable feature to distinguish tumor from radiation change is the presence of a mass in or adjacent to the plexus**.** PET imaging may be helpful in this setting to distinguish recurrent or residual tumor from posttreatment change (Fig. 12).

## CONCLUSION

The development of more effective therapies for a variety of systemic malignancies has influenced the scope and imaging appearance of CNS disease in the oncology patient. Tumors previously rarely metastasizing to brain are more commonly encountered. Additionally, infectious complications of the prolonged immunocompromised state and treatment-related disorders are increasingly observed. MRI is the preferred modality for evaluating and monitoring brain and spine disease associated with oncologic disease. Newer imaging sequences and advanced MRI techniques such as MRI spectroscopy, fMRI, FLAIR and diffusion-weighted imaging, and MRI-based tumor volumetrics can supplement the imaging tools available to guide patient management. Brain and whole body PET imaging may also provide complementary metabolic information on disease activity.

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# Part VII Neuro-Oncologic Complications of Specific Malignancies

# 20 Neuro-Oncologic Complications of Lung Cancer

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## INTRODUCTION

**EPIDEMIOLOGY** *(1)* Lung cancer is the most frequent form of cancer to be diagnosed in humans and is the leading cause of cancer-related mortality in the world. In the United States, it is the second leading cause of cancer in both men and women and is the number one cause of cancer-related mortality. In 1999, there were 171,600 new cases of lung cancer, comprising 14% of cancer diagnoses. The incidence is higher in men than women, but while the incidence rates of lung cancer among men have dropped by 2.5% since 1973, the incidence has increased among women by 123%. Concomitantly, mortality rates have been increasing in women more than men. The lifetime risk of developing lung cancer is 8.3% among female smokers and 14.6% among male smokers. Among ethnic groups, blacks have the highest incidence rates (117 per 100,000) while Native Americans have the lowest (14 per 100,000). Lung cancer rarely occurs before the age of 40, but thereafter a sharp increase in rates occurs. The median age at diagnosis is 65–70 yr.

Fifteen percent of patients are initially diagnosed with localized lung cancer, 23% have regional spread of disease, while the majority (48%) have distant metastases. The 5-yr survival rate has changed little over time, but there has been some improvement in 2-yr survival rates since 1975, from 34.3% to 41%. The 5-yr survival for all patients is 15%.

Lung cancer is unique among cancers in that its etiology has been attributed to a single, strong risk factor: smoking. The increasing incidence among women is thought to be due to the lag of 20 yr in the prevalence of smoking among women compared to men.

**TUMOR CLASSIFICATION** *(1)* Lung cancer is a generic term used to describe cancer arising from the trachea, bronchi, bronchioles, and alveoli. According to the World Health Organization (WHO), 20% of lung cancer is small cell cancer (SCLC or oat-cell cancer) and 80% is nonsmall cell lung cancer (NSCLC).

NSCLC is subdivided into three groups: (1) adenocarcinoma (40% of all lung cancer), (2) squamous cell or epidermoid carcinoma (30%), and (3) large cell undifferentiated carcinoma (10%). These three subgroups are often combined under the heading of NSCLC because they frequently coexist in a single tumor, are hard to distinguish from each other when poorly differentiated, and because their overall prognosis and treatment is the same (Table 1) *(1,2)*.

The revised international staging classification of lung cancer (1997) divides NSCLC into four stages (Table 2) *(2–4)*. This chapter is primarily focused on neurological complications arising from stage IV lung cancer.

### GENERAL ONCOLOGIC MANAGEMENT

**Small Cell Lung Cancer (SCLC)** *(2,5)* Two-thirds of patients with SCLC have distant metastatic disease at presentation. Patients with stage I or II disease are candidates for surgical resection, but surgery can be also considered as part of combination therapy. The standard approach to these patients is multi-agent chemotherapy, which has an initial response rate of 75–95% *(2)*. Complete responses (CR) are seen in 50–60% of patients with limited disease. These responses, however, are usually short-lived, resulting in overall median survival of less than 1 yr. Twenty to thirty percent of patients with limited stage disease survive 2 yr.

In patients with limited stage disease, adjuvant radiotherapy is also beneficial *(2)*. Combination therapy has been shown to moderately improve median survival compared to patients who receive only chemotherapy. Meta-analysis of clinical trials has confirmed this benefit. Timing of radiotherapy may be important, as early therapy may destroy drug-resistant clones that might otherwise survive *(2)*. Prophylactic cranial irradiation (PCI) will be discussed later in this chapter.

**Nonsmall Cell Lung Cancer** *(2)* Surgery for stage I NSCLC results in a 5-yr survival of 40–67% *(2)*. In this group, many of the "recurrences" turn out to be second primary cancers. Irradiation is used in patients who do not undergo

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**Table 1**
**WHO Classification of Lung Cancer[a]**

| *Type of cancer* | *Incidence* |
|---|---|
| Small cell lung cancer (SCLC) | 20% |
| Nonsmall cell lung cancer (NSCLC) | 80% |
| Adenocarcinoma (40%) | |
| Squamous cell carcinoma or epidermoid carcinoma (30%) | |
| Large cell undifferentiated carcinoma (10%) | |

[a]Adapted with permission from refs. *1,2.*

**Table 2**
**Staging of NSCLC[a]**

| *Stage* | *TNM subset[b]* |
|---|---|
| 0 | Carcinoma *in situ* |
| IA | T1N0M0 |
| IB | T2N0M0 |
| IIA | T1N1M0 |
| IIB | T2N1M0 |
| | T3N0M0 |
| IIIA | T3N1M0 |
| | T1N2M0 |
| | T2N2M0 |
| | T3N2M0 |
| IIIB | T4N0M0 |
| | T4N1M0 |
| | T4N2M0 |
| | T1N3M0 |
| | T2N3M0 |
| | T3N3M0 |
| | T4N3M0 |
| IV | Any T, any N, M1 |

[a]Adapted with permission from refs. *2,3.*
[b]TNM: T = Tumor size/invasion, N = nodal involvement, M = metastasis. T1 = tumor size less than or equal to 3 cm, invasion confined to the lobar bronchus. T2 = any of the following: tumor size greater than 3 cm, invasion of the visceral pleura, involvement of the mainstem bronchus greater than or equal to 2 cm distant to the carina, association with obstructive pneumonitis or atelectasis extending to the hilum. T3 = tumor in main bronchus within 2 cm of the carina or extension into specified adjacent surrounding tissues. T4 = tumor involving the mediastinum, heart, or other specified adjacent structures, or the presence of maligant pleural effusion. N0 = no nodal involvement. N1 = No nodal involvement outside of the pleura. N2 = involvement of ipsilateral mediastinal or subcarinal lymph nodes. N3 = involvement of contralateral lymph nodes. M0 = no distant metastasis. M1 = distant metastasis.

surgery. Radiotherapy alone has a 25% cure rate in stage I NSCLC.

Surgical resection is considered the definitive therapy in stage II NSCLC *(2,6)*. Adjuvant radiation or chemotherapy does not improve survival. In patients with stage II NSCLC the 5-yr survival is 25–55% *(2,6)*.

Stage IIIA cancer is treated with a combination of chemotherapy, surgery, and radiation, while stage IIIB is treated with chemotherapy and radiation alone *(2,6)*. A recent Phase III comparison of sequential vs concurrent chemoradiation for unresected stage III NSCLC suggested improved median survival with the concurrent treatment strategy *(7)*. In stage IIIB NSCLC, there is often recurrence of disease locally, with median survivals of 10 mo or less and a 5-yr survival of between 5–10%.

Stage IV cancer is present in 40–50% of patients at initial diagnosis of NSCLC. Both randomized trials and meta-analysis support the use of palliative chemotherapy in patients with a good performance status. Compared with supportive care alone, chemotherapy improves quality of life and can increase both median and 1 yr survival.

### PATTERNS OF SPREAD TO THE CNS

**Small Cell Lung Cancer** A retrospective study of the autopsy findings of 537 patients with SCLC found a 35% incidence of brain metastases and an 8% incidence of leptomeningeal metastases (LM) *(8)*. Brain metastases are detected clinically in 12% of patients prior to starting treatment. Patients with a complete response (CR) to therapy had a higher rate of brain metastases (60 vs 40%) and LM (24 vs 10%) than patients with a partial response (PR).

**Nonsmall Cell Lung Cancer** Autopsy studies in NSCLC show a 41% incidence of brain metastases and a 9% incidence of LM *(9)*. In patients with LM there is usually coexistence of parenchymal brain metastases. Overall, the metastatic pattern seen in NSCLC does not differ from that of SCLC *(8)*.

## DIRECT COMPLICATIONS OF LUNG CANCER (TABLE 3)

Most studies dealing with neurological complications of systemic cancer include patients with a wide variety of primary tumor types, making it somewhat difficult to draw conclusions about primary-specific complications. However, because lung cancer is a common cause of neurologic complications, it generally comprises a plurality or majority of cases in studies. In this chapter we have attempted to provide as much lung cancer specific information as possible, but the reader should be aware of the general nature of much of this discussion.

### PARENCHYMAL BRAIN METASTASES

**Incidence** Brain metastases are a common finding in patients with lung cancer. They are present in 10% of patients with SCLC at the time of diagnosis and increase to 20% during therapy and 35% at time of autopsy *(10–12)*. At 2 yr postdiagnosis the cumulative risk of brain metastasis is 47% for patients with limited disease and 69% for those with extensive disease *(12)*.

Patients with NSCLC have a 20% incidence of brain metastases, which increases to 40% at time of autopsy *(10)*. Brain metastases are the initial manifestations of disease in as many as 10% of patients with lung cancer. Some experts advocate the routine use of brain computed tomography (CT) or magnetic resonance (MR) scan to detect asymptomatic metastases prior to planned curative thoracic resections. Since MR scanning reveals brain metastases in only 3% of asymptomatic patients, the role of neuroimaging in this setting is arguable *(13)*.

**Manifestations**

***Symptoms*** Presenting symptoms of cerebral metastases can be generalized or focal. Headache is one of the most common symptoms, occurring in up to 50% of patients *(14,15)*.

**Table 3**
**Neurologic Complications of Lung Cancer**

| *Metastatic complications* | *Paraneoplastic syndromes* |
|---|---|
| Parenchymal brain metastases | Encephalomyelitis |
| Leptomeningeal metastases | Cerebellar syndrome |
| Epidural metastases | Sensory neuronopathy |
| Skull base metastases | Autonomic neuropathy |
| Intramedullary spinal cord metastases | LEMS |
| | Polymyositis/dermatomyositis |
| Plexopathy | |

Patients complain of a mild, constant, dull headache, which usually responds well to analgesics. The classic "brain tumor headache," which is worse in the morning or with Valsalva maneuver, is less common *(14)*. Other symptoms of increased intracranial pressure include impairment of consciousness, nausea and vomiting, and blurring of vision secondary to papilledema *(14,16)*.

Cognitive disturbances occur in 20–40% of patients and can include such general symptoms as depression, personality change, and memory loss, as well as more focal symptoms such as aphasia, alexia, acalculia, agnosia, and apraxia *(14,17)*. Generalized cognitive disturbances are more common in patients with multiple metastases or with increased intracranial pressure. These symptoms may masquerade as psychiatric disease and can lead to delay in diagnosis.

Focal weakness is a common finding *(15,17)*. Since tumor-associated edema may also result in brain dysfunction, the pattern of weakness may not accurately reflect the precise location of a cerebral metastasis. Focal or generalized seizures are the presenting complaint in about 20% of patients *(15,17)* and occur in 30–40% of patients at some point during the course of the disease *(14)*. Ataxia as a presenting symptom is common with cerebellar or brainstem metastases, although gait ataxia may also result from large frontal lobe metastases or hydrocephalus *(14,15)*.

***Signs*** Findings on the neurological examination are typically in excess of the presenting complaints. Cerebellar metastases are an exception, as patients often complain of being more unsteady than actually detected on examination *(14)*. Mental status testing is abnormal in up to 75% of patient with cerebral metastases *(14)*. When present, focal findings will typically identify the neuroanatomic location of metastases or tumor-associated edema.

### Radiologic Findings

***CT*** Cranial CT scanning is a valuable imaging modality in the diagnostic evaluation of cerebral metastases, although it is less sensitive than magnetic resonance imaging (MRI) in the detection of small or infratentorial lesions. Cerebral metastases are usually hypodense on pre-contrast scans, unless the lesions are hemorrhagic or of extremely high cell density *(14,18)*. Metastases become hyperdense after administration of intravenous contrast.

***MRI*** Gadolinium-enhanced cranial MRI is the most sensitive test available for the detection of cerebral metastases *(14,18)*. An MRI should be considered in patients with lung cancer who have the symptoms or signs noted previously or are at high risk for brain metastases. Metastases tend to be isointense or mildly hypointense on T1 precontrast images when compared to gray matter. T2 images show increased signal in the tumor and surrounding gray and white matter. Almost all cerebral metastases enhance after administration of intravenous gadolinium. Technical advances such as magnetization transfer, MR diffusion, and MR spectroscopy are being investigated.

### Diagnosis

***Surgical*** Biopsy of a lesion with a typical radiographic appearance, in the setting of known metastatic cancer, is usually not indicated. Brain biopsy should be considered in patients without known cancer, with a remote history of lung cancer, or with indolent, limited stage disease. In one study from the CT era, 11% of the patients with known cancer and a solitary intracranial lesion had diagnoses other than metastases at brain biopsy *(19)*.

***Other Tests*** Biochemical markers such as calcitonin, bombesin, and B2-microglobulin have been examined as possible screening tests in CSF for parenchymal metastases in patients with small cell lung cancer *(20,21)*. Although the specificity of these tests was high, sensitivity was only about 50%, thereby limiting their usefulness as screening measures.

### Management

***Glucocorticoids*** Glucocorticoids are effective in the management of cerebral edema associated with metastatic lesions *(22)*. Symptomatic response to glucocorticoids is an important prognosticator of response to further therapy and survival *(23)*.

Dexamethasone is the most commonly used glucocorticoid because of its potent effect on cerebral edema and its low mineralocorticoid activity *(22)*. Dexamethasone is often started with a loading dose of 10 mg followed by 4–6 mg qid. In patients who fail to respond, the dose can be increased up to 40 mg/d. As the patient responds to other treatment modalities, glucocorticoids are slowly tapered off to minimize side effects such as steroid myopathy, diabetes, and immunosuppression. Trimethoprim/sulfamethoxazole prophylaxis against *Pneumocystis carinii* pneumonia should be considered in patients on dexamethasone for longer than 2 mo *(24)*.

***Antiepileptic Drugs (AEDs)*** Antiepileptic agents should be administered to patients with intracranial metastases who have seizures *(22)*. Phenytoin is a commonly used AED with few side effects; other advantages are once a day dosage and the possibility of intravenous administration. Carbamazepine, valproic acid, and other AEDs are also effective.

In randomized trials AED prophylaxis have shown no benefit *(22)*. Therefore, AEDs should be withheld from patients with brain metastases until a first seizure.

***Surgery*** The impact of surgical resection of brain metastases has been difficult to assess due to bias in the selection of patients. In one study, median survival after surgery for brain metastases from lung cancer was 11.6 mo *(25)*. Survival rates were 24% at 1 yr and 8% at 2 yr. Performance status after surgery improved in 36% of patients, remained the same in 53%, and became worse in 11%. Favorable prognostic factors included stable systemic disease, good initial performance

scores, histologic diagnosis of adenocarcinoma, solitary brain metastases, and receipt of adjuvant therapy.

***Role of Surgery in Single and Multiple Metastases*** Single brain metastases occur in one-quarter to one-third of patients, and about half of metastases are resectable *(26,27)*. Unlike the situation in infiltrative gliomas, metastases are well-demarcated from the surrounding brain tissue, making complete resection possible. Resection of a single brain lesion followed by whole brain radiation (WBRT) appear to improve survival and quality of life and delay recurrence compared with WBRT alone *(19,28)*. In these studies, there was no survival benefit in patients with active extracranial disease. Patients with resection of a single lesion may be able to discontinue their glucocorticoids more rapidly, thereby lowering the incidence of side effects. Patients with single metastases from primary tumors that are highly sensitive to radiotherapy (e.g., SCLC) may be less likely to benefit from resection.

A retrospective cohort study of 231 patients with NSCLC who underwent surgical resection of their brain metastases reported a median survival of 11 mo *(29)*. Significant positive prognostic factors were female sex ($p < 0.02$), single metastases (11 vs 8.5 mo median survival, $p < 0.02$), high KPS, complete resection of primary tumor, and age < 60 yr. About one-third of the cohort died of neurological complications while another third died of a combination of systemic and neurological causes. These latter statistics are similar to those of all patients with CNS metastases, suggesting that surgery did not reduce the long-term risk from neurological complications.

It has been suggested that surgical removal of two or three lesions improves survival (14 vs 6 mo) and quality of life similar to that in patients undergoing excision of a single lesion *(30)*. However, another study has found no benefit of surgery for multiple metastases, with median survival of 5 mo in this group compared to 12 mo for the patients with single intracranial metastases *(31)*. These results do not permit definite recommendations regarding the role of surgery in patients with multiple metastases *(22)*. Currently, therefore, accessible lesions that are symptomatic, large, or life-threatening are those most often considered for surgery.

***Recurrent Brain Metastases*** A retrospective study of 214 patients has shown that re-resection of recurrent brain metastases in patients with NSCLC may prolong survival *(32)*. The median survival of patients who underwent a second operation was 15 mo from time of the first operation compared to 10 mo for those who did not undergo an additional surgery ($p < 0.001$). Positive predictive factors were female sex, histology of the primary tumor (adenocarcinoma associated with a better survival), disease stage, and extent of resection of the primary tumor. Almost half the patients were reirradiated after surgery. The median survival of those reirradiated after surgery was 24 mo compared to 14.4 mo for those who were not re-irradiated ($p = 0.48$). A third operation was performed in some patients. The median period until a third recurrence was 4 mo. Median survival after this third surgery was 10.5 mo. These survival statistics strongly suggest that patients were highly selected for those with limited, indolent disease and that in such patients an aggressive approach to management of CNS disease can produce remarkably long survival.

**Radiation** Radiation therapy (RT) is a standard treatment for patients with single brain metastases from lung cancer *(22)*. Randomized trials have shown a benefit in survival and quality of life with the addition of RT, even after complete excision of a single metastasis *(19,28,33)*. RT reduces local recurrence rates and may effectively eradicate small metastases.

***Whole Brain Radiation*** Whole brain radiation is the standard form of treatment for brain metastases, employing external beam, fractionated megavoltage radiation of approx 3600 cGy given over 2–3 wk *(14)*. Hyperfractionated treatments with twice daily fractions offer no benefit over the conventional schedule *(22)*. Administration over shorter periods of time may actually lead to poorer survival rates *(14,22)*. Median survival after WBRT ranges from 3–6 mo with 1 yr survival of 5–10%. The patients in this latter group tend to be the ones with high functional status. In patients with a solitary metastasis treated with WBRT who have their primary site under control, the most likely cause of death is recurrence of the brain metastasis *(14,22)*. Those patients whose lung cancer is not controlled at its primary site have significantly poorer survival despite palliative WBRT compared to those whose primary site is under good control *(34)*.

Overall, about 60% of patients respond to radiotherapy with improvement or stabilization in their symptoms *(35)*. Median survival was 4.7 mo in these patients compared to 1.6 mo in non-responders. Treatment has been shown to be more effective when started early *(22)*. Response to radiation is often delayed, with about 50–60% of the patients having a partial response (i.e., at least 50% shrinkage in the tumor) at 6 wk after the completion of WBRT *(14)*.

***Focal Radiation*** Stereotactic radiosurgery (SR) has gained increased importance in the management of brain metastases from lung cancer. Its role is more important in NSCLC than in SCLC given the latter's sensitivity to WBRT. SR has been utilized as an adjuvant boost to WBRT for oligometastatic disease and as a salvage therapy for recurrence following WBRT or resection. In the largest reported series, 77 patients underwent RS with the gamma knife apparatus; 37 as an adjuvant to WBRT, 34 at progression after prior WBRT or surgery, and 6 as isolated initial strategy *(36)*. Median survival following radiosurgery was 10 mo and was unaffected by the number of brain metastases (patients with up to four metastases were eligible). Median survival was 12 mo in patients with stable systemic cancer and only 2 mo in those with systemic progression at time of RS. Local tumor control was achieved in 85% of tumors. These impressive results raise the question of whether patients with oligometastatic brain disease from NSCLC should be treated with RS initially, reserving WBRT for failure. Radiosurgery is limited to neoplasms ≤ 3 cm in diameter.

***Prophylactic Cranial Irradiation (PCI)*** SCLC, though initially responsive to chemotherapy, progresses with distant metastases occurring early in the course of the disease *(11)*. With combined treatment producing thoracic CR, the risk of thoracic recurrence decreases, and brain becomes an important region of tumor failure. It has been presumed that the brain is a pharmacologic sanctuary in which microscopic tumor is protected against typical systemic chemotherapy for SCLC which does not penetrate the intact blood-brain barrier (BBB).

This has led to numerous trials designed to test whether PCI would decrease the incidence of brain relapse and improve survival in patients who achieved systemic CR. Typically, 24–36 Gy WBRT has been administered in 2–2.5 Gy fractions. These studies commonly demonstrated that PCI decreased risk of brain metastasis and typically showed an insignificant trend towards survival benefit *(37,38)*. A recently published meta-analysis of these studies indicated that PCI cut the risk of subsequent brain metastasis in half and modestly increased 3-yr survival from 15.3% to 20.7% ($p = 0.01$) *(39)*.

Controversy still remains over whether the benefits of PCI outweigh its toxicities. Short-term side effects of PCI are usually benign and consist mostly of headache, loss of hair, transient lack of appetite, decreased hearing, decreased taste, and fatigue *(11)*. Potential long-term side effects of PCI include leukoencephalopathy and dementia that can occur about a year after radiation is completed. Milder forms of neuropsychological impairment are a long-term complication of cranial radiation recently recognized in adults *(40)*. Two large prospective randomized trials of PCI did not document increased neuropsychological deficits among PCI recipients *(37,38)*. Others have argued that the small numbers of long-term survivors in these trials precluded accurate assessment of the risk of leukoencephalopathy *(41)*, and that since PCI benefitted only about one-quarter of its recipients it should not be considered standard of care *(42)*.

While PCI has not been evaluated in NSCLC, randomized trials to evaluate its potential benefit in locally advanced (stages IIIA and IIIB) disease have been proposed *(10)*.

### Chemotherapy

***Small Cell Lung Cancer*** The chemosensitivity of systemic SCLC has led to interest in treatment of brain metastases with chemotherapy. Frequently these patients have had prior WBRT and have multiple metastases as well as systemic relapse, making radiosurgery or surgery unattractive. Postmus has carefully reviewed the results with various chemotherapy regimens *(10)*. In general, multidrug regimens have led to radiographic responses in about half of patients, with less impressive results from single-agent trials. He concluded that chemotherapy's efficacy is roughly comparable to that of WBRT.

The utility of chemotherapy alone in SCLC patients with brain metastases who had not received prior WBRT was recently evaluated *(43)*. Patients in this Phase III trial were randomized to teniposide alone vs teniposide plus WBRT. The rationale was that WBRT alone was inappropriate since almost all these patients have or will shortly have systemic relapse. The radiographic response rate (57%; 30% CR and 27% PR) was significantly higher in the combined-therapy group than in the chemotherapy group (22%, 8% CR; and 13% PR). Patients receiving teniposide alone had a significantly higher chance of failing in the brain, and median time to brain progression was longer in the combined modality group (11 vs 7 wk). The median survival in the two groups was identical: 3.2 vs 3.5 mo. The disappointing results in both arms of this trial may be partly attributable to some patients having had prior exposure to etoposide. Perhaps newer agents or combinations such as carboplatin/paclitaxel might improve on these results. The authors argue that because of the extremely poor prognosis of this subgroup of patients, it is questionable whether WBRT should be given to patients with progressive disease outside the brain that does not respond to second-line chemotherapy, since most patients will die within a few weeks.

***Nonsmall Cell Lung Cancer*** Various single-agent and multidrug regimens have been tested in small series of patients with brain metastases from NSCLC. Although occasional responses have been reported, generally response rates, time to progression, and survival have been disappointing *(10)*. Development of more active regimens for systemic metastases from NSCLC will be necessary to improve treatment of brain metastases with this therapeutic modality.

***Approach to Progressive or Recurrent Disease*** Radiosurgery may be administered as the focal therapy for symptomatic, progressive lesions 3 cm or less in diameter. Retreatment with standard WBRT may also be considered. In a retrospective study of 86 patients who were reirradiated for recurrent brain metastases, two-thirds had partial resolution or complete resolution of their neurologic symptoms, whereas one-third had no benefit or had progression after reirradiation. Most of the patients had no significant short-term side effects from retreatment. Favorable prognostic factors were solitary brain metastases without extracranial metastases and a reirradiation dose greater than 20 Gy *(44)*.

In a retrospective study, patients with NSLC who were reirradiated after repeat resection for recurrent metastases showed a trend towards increased survival *(32)*.

Chemotherapy may also be considered in patients with SCLC whose cancer is progressing in the brain but have stable systemic disease. Temozolomide, topotecan, or platinum can be administered in the salvage setting.

**Prognosis *(23,25,34)*** In two large retrospective studies, median survival of lung cancer patients after diagnosis of metastases to the brain was 3 mo with 1-yr survival of about 10% *(23,45)*. Performance status is the major determinant of survival in patients with brain metastases from cancer. Histologic subtype of lung cancer does not appear to be correlated with survival, although some studies have suggested that adenocarcinomas have a more favorable prognosis than other types *(25,26,45)*. Patients older than 70 yr had poorer survivals than younger patients, even after correction for treatment differences *(23,25)*. Progressive systemic disease from the lung cancer is a negative prognostic factor *(34)*. In this study the presence of multiple brain metastases did not have the impact on survival that has been seen in some other studies ($p < 0.0001$) *(45)*.

Sen et al. suggested that response to glucocorticoids was a positive prognostic factor *(35)*. Patients who responded to steroids showed a median survival of 4.3 mo compared to only 1.6 mo in nonresponders. The authors concluded that a "good" prognostic group included patients with inactive systemic tumor, high performance status, and response to steroids.

## LEPTOMENINGEAL METASTASES (LM) (TABLE 4)

**INCIDENCE BY TUMOR TYPE** LM complicate 1–15% of cancer cases *(46,47)*. Autopsy studies in lung cancer have found LM in about 10% of cases *(8,9,12,48,49)*. The incidence of LM has been increasing in solid tumors as the overall survival

**Table 4**
**Presenting Symptoms and Signs in Patients with Leptomeningeal Metastases[a]**

| | *Patients with all primary types (n = 40) (50)* | *Patients with NSCLC (n = 32) (46)* |
|---|---|---|
| Headache | 19 | 11 |
| Nausea/vomiting | – | – |
| Seizure | 5 | – |
| Confusion | 2 | – |
| Paresthesia | – | – |
| Weakness | 2 | |
| Cranial neuropathy | 16 | 9 |
| Meningismus | 3 | 2 |
| Cauda equina syndrome | 2 | 3 |
| Myelopathy | 2 | 3 |
| Back pain or radiculopathy | 1 | 2 |
| Ataxia | 3 | 5 |

[a]Adapted with permission from ref. *86*.

for these patients has risen *(46,47)*. In patients with SCLC who have survived for 3 yr the incidence of LM will increase to 25% *(48)*. Almost half of patients with SCLC who relapse in the CNS do so in the meninges, which is the sole site of relapse in about 25% *(14)*.

Risk factors associated with the development of LM disease in SCLC are presence of metastases in other parts of the neuraxis, extensive systemic disease, no response or partial response to therapy for the primary cancer, and male sex *(48)*.

**MANIFESTATIONS** In general, findings on neurologic examination tend to exceed the patient's symptoms *(47,50)*. The multifocal nature of leptomeningeal dissemination means there may be signs and symptoms at multiple different levels of the neuraxis. Combinations of mental status changes, cranial nerve palsies and spinal nerve root signs are suggestive of the diagnosis in cancer patients *(47,50)*. The neurological signs and symptoms of LM patients with SCLC are similar to those found in other malignancies *(48)*. About half of the patients will have signs and symptoms involving different levels of the nervous system, with almost all developing further CNS metastases during the course of their disease *(48)*.

**SYMPTOMS**

**Parenchymal** Headache occurs in approx 25% of patients with LM *(13,48)*. Episodic headache accompanied by nausea and vomiting may indicate the presence of plateau waves from increased intracranial pressure *(47)*. Bifrontal cerebral dysfunction from hydrocephalus or parenchymal invasion may result in cognitive changes and gait apraxia *(14)*. Cognitive dysfunction occurs in 25–33% of patients with LM, while seizures are a presenting symptom in only 3–12% of cases.

**Cranial Nerves** Cranial nerve symptoms include loss of visual acuity, diplopia, dysarthria, dysphagia, and hoarseness *(47,50)*. Visual changes may occur in patients with cancer involving the optic chiasm or tract *(14,50)*. Sudden hearing loss and vertigo may be seen with involvement of the VIIIth cranial nerve *(14,50)*. Cranial nerve involvement is seen in almost 20% of SCLC patients with LM disease *(48)*.

**Spinal Cord/Nerve Root** Spinal cord and nerve root symptoms occur in more than 50% of patients with LM and can be divided into radicular and leptomeningeal patterns of involvement *(14,50)*. A higher incidence is seen in patients with SCLC, where two-thirds have spinal cord and nerve root symptoms including radicular pain and sensory loss, weakness (lower extremities more often than upper extremities), and autonomic failure with sexual dysfunction and sphincter disturbances *(45)*. Leptomeningeal infiltration results in neck or back pain with nuchal rigidity.

**SIGNS**

**Parenchymal** Signs of parenchymal brain dysfunction, such as aphasia, hemiparesis, and hemisensory loss are uncommon and when present suggest coexisting cerebral metastases or significant invasion of tumor cells into brain along Virchow-Robin spaces *(14)*. Mental status abnormalities are discovered in approx 50% of patients. In SCLC patients with LM disease, 60% were found to have either limb weakness or mental-status changes. None of the patients had seizures *(48)*. Isolated cortical signs or symptoms occur in almost 30% of patients *(48)*.

**Cranial Nerves** Cranial nerve signs discovered during examination are usually mild and involve paresis of extraocular muscles, decreased facial sensation, facial paresis, and hearing loss *(14,51)*.

**Spinal Cord/Nerve Roots** When tumor cells infiltrate the parenchyma of the spinal cord, the presentation may be predominantly of upper motor neuron type (weakness, spasticity, hyperreflexia and Babinski signs). Lower motor neuron findings (weakness, hypotonia, areflexia and fasciculations) are from spinal nerve root infiltration. The lower extremities are more commonly involved than the upper extremities, reflecting the lengthy course of the nerves of the cauda equina. Isolated spinal symptoms occur in almost 30% of patients with SCLC *(48)*.

**RADIOLOGIC FINDINGS** MRI is more sensitive than computed tomography (CT) in detecting LM *(47)*. Both have a high false-negative rate, and the radiographic findings are often nonspecific *(52,53)*. The best use of MRI is the detection of bulky disease *(54)*. It may also be of benefit in the detection of focal leptomeningeal disease, where CSF cytology may have a higher false-negative incidence *(55)*.

Contrast enhancement may be seen diffusely or as multiple subarachnoid nodules, especially along the cauda equina. Double-dose gadolinium may increase the sensitivity of MRI *(52–54)*. The presence of communicating hydrocephalus is a nonspecific but suggestive finding.

When considering patient eligibility for intrathecal chemotherapy, the demonstration of CSF flow patency or the reversibility of its obstruction should be taken into account *(56,57)*. Radionuclide cisternography, which examines CSF flow, can be used to exclude the presence of subarachnoid blocks due to LM disease *(56,57)*.

**DIAGNOSIS** Dural puncture and CSF analysis is the definitive diagnostic test for LM. Cerebral metastases with mass effect and obstructive hydrocephalus are relative contraindications to dural puncture *(58)*. All patients being screened for LM should first undergo brain CT or MR scans to exclude such conditions. An adequate volume of CSF (≥ 5 mL)

should be obtained and delivered promptly to the laboratory to maximize diagnostic yield on cytopathology.

Opening pressure is elevated due to impaired CSF absorption in approx 60% of SCLC patients with LM. The cell count reveals a mild pleocytosis with a lymphocytic predominance in most cases *(14,48)*. Subarachnoid hemorrhage is uncommon in LM. Protein is typically increased because of BBB disruption. Hypoglycorrhachia is present in 68% of SCLC patients with LM *(48)*.

CSF cytology is the definitive diagnostic test for LM, but only 50% of patients with LM will have a positive result on the first lumbar puncture *(14,47)*. With serial dural punctures, malignant cells can be identified in up to 90% of patients. In patients with a negative first LP and a high degree of clinical suspicion, at least two additional lumbar punctures should be performed over several days to increase diagnostic yield *(14,48)*. A presumptive diagnosis of leptomeningeal metastases may occasionally be made in the absence of positive cytology in patients with decreased glucose, increased protein, lymphocytic pleocytosis, and negative microbiological studies. In such circumstances, neuroimaging may be useful in supporting the presumptive diagnosis. There is some evidence that cervical-level punctures are more sensitive than lumbar-level punctures in the diagnosis of LM in breast cancer patients *(47,50)*.

**Other Tests** Monoclonal antibodies (MAbs) to specific tumor proteins can increase the detection of malignant cells by about 10% *(14,47,51)*. Biochemical markers are generally not useful for patients with lung tumors *(47,50,51)*. Creatinine kinase BB may be useful as a screening test for leptomeningeal disease in patients with SCLC. In one series it was found to have a sensitivity of 88% and a specificity of 100% *(20)*.

Flow cytometry, though still under investigation, is occasionally helpful when a routine cytology is negative *(14,50,51)*. Abnormal results include the detection of aneuploid cells *(59)* and the presence of CEA on cell surfaces.

**MANAGEMENT** Treatment of LM should begin as soon as possible after the diagnosis is established *(47)*. Since the disease involves the subarachnoid space, it can extend from the cerebral convexities to the lumbar cistern, making treatment of the entire neuraxis of concern. In general, focal radiation is employed for treatment of bulky, nodular disease and sites of rapidly progressive symptoms (usually of cranial nerve or cauda equina origin). Intrathecal chemotherapy is used to treat the entire subarachnoid space *(48,50,60)*.

**Radiation** Focal external beam RT is an effective means of alleviating LM symptoms *(14,50)*. Irradiation of the entire neuroaxis is usually ill-advised due to the amount of bone marrow (40% of the body's total) affected by this approach. RT should be employed for sites of focal symptoms and sites of bulky disease seen on MRI *(14,50)*. Focal radiation to the skull base can be employed in place of WBRT in patients with cranial nerve symptoms. WBRT is indicated for patients with hydrocephalus, seizures, or other signs of brain parenchymal involvement *(14)*. PCI, which prevents parenchymal metastases, is not effective in preventing LM in SCLC *(14)*.

**Intrathecal Chemotherapy** LM is usually treated with administration of chemotherapy directly into the CSF. This allows a high concentration of drug to be delivered to the site of disease *(14,50,60)*. Treatment with systemically administered chemotherapy is usually ineffective as most antineoplastic agents penetrate the blood CSF barrier poorly.

Intrathecal chemotherapy may be administered by lumbar puncture (LP) or via an Ommaya reservoir that connects to the lateral ventricle by a cannula. Ommaya reservoirs are generally preferred because of ease of administration of the drug and better distribution throughout the entire CSF system *(50)*. Complications of intraventricular catheter insertion occur in about 5% of cases and mainly involve infection *(50)*.

The most commonly used intrathecal chemotherapy agents are methotrexate (MTX), thiotepa, and cytosine arabinoside (ara-C). A liposomal form of ara-C has recently become available. Agents such as mafosphamide (a derivative of cyclophosphamide), MAbs, interferon (IFN), and interleukin-2 (IL-2) are under investigation. Single-agent therapy is usually employed, because combination chemotherapy is not more efficacious and is also associated with a higher incidence of side-effects *(14,47,50,60)*. MTX is usually administered at a dose of 12 mg twice a week until the CSF cytology becomes negative or patients experience symptomatic improvement, at which point the frequency is gradually decreased to once every 2–4 wk. Treatment is continued for at least 3–6 mo in patients who respond *(14,47)*. Oral leucovorin should be administered to patients who develop mucositis or are receiving concurrent systemic chemotherapy.

Ara-C is given at a dose of 50 mg twice a week on the same schedule as MTX. Liposomal ara-C has the advantage that it is administered every 2 wk; however, it has a much higher rate of chemical meningitis than does standard formulation ara-C.

It is difficult to know when to recommend intrathecal chemotherapy in an individual patient. Treatment is most often considered in patients with SCLC, in patients with good performance and relatively indolent systemic disease, and in patients without bulky LM on neuroimaging. A retrospective study found that a combination therapy of intrathecal methotrexate and irradiation to symptomatic regions of the neuraxis cleared the CSF of malignant cells in 50% of SCLC patients. Half of these patients had complete or nearly complete resolution of signs or symptoms of their disease. Four out of five patients treated only with intrathecal MTX cleared their CSF of malignant cells, but only one had symptomatic relief of signs and symptoms *(48)*.

**Ventricular Peritoneal Shunting (VPS)** VPS is used for the treatment of symptomatic hydrocephalus. The existence of the shunt is problematic if intrathecal chemotherapy is planned, as the drug will drain out of the ventricle into the abdominal cavity. However, the risk that a VPS may introduce cancer cells into the peritoneal cavity has proven negligible in clinical practice *(14)*. The presence of hydrocephalus also raises concern regarding the distribution of intrathecal chemotherapy. Therefore, the combination of VPS and WBRT is commonly employed.

**PROGNOSIS** Average survival of patients with untreated LM is 1.5–2 mo after initial diagnosis *(14,47)*. LM from SCLC is usually more responsive than other histologies. Seventy-five percent of these patients will experience symptomatic improve-

ment with a concomitant improvement in their CSF results. Approximately 25% of all patients will have some neurological improvement *(47)*. Nonetheless, the overall median survival after treatment for LM disease in SCLC is only 6 wk *(48)*.

## EPIDURAL SPINAL CORD COMPRESSION (ESCC)

**INCIDENCE** The incidence of clinically diagnosed ESCC in patients with systemic cancer is approx 5% *(61,62)*. There are approx 18,000 cases of symptomatic ESCC in the United States each year *(61)*. Danish investigators reported a 5–15% incidence of ESCC in patients with all types of lung cancer. The incidence of ESCC in SCLC is reported to be 3–8% *(12,63,64)*.

ESCC is the initial presentation of cancer in up to 20% of patients with this syndrome *(61,62)*. Patients with lung cancer, hematological malignancies, and cancer of unknown primary are especially likely to present with symptoms and signs of ESCC *(14)*. Patients with SCLC have a tendency to develop ESCC early after diagnosis of their primary cancer (87% within the first 3 mo) whereas a similar percentage is achieved after 30 mo in patients with NSCLC.

In about 60% of patients with ESCC, vertebral metastases occur in the thoracic spine; 25% in the lumbar spine and the remainder in the cervical spine *(65–67)*. Virtually identical figures pertain to ESCC specifically from lung cancer *(63)*. A large retrospective study found that 29% of patients with ESCC from lung cancer have multiple, synchronous epidural lesions *(63)*.

### MANIFESTATIONS

#### Signs and Symptoms

***Pain*** Back pain is the initial symptom in the majority of lung cancer patients with ESCC, occurring in 77%. Pain was either localized to the spine (37%) or radicular in nature (40%) *(62,63,68)*. Pain occurs when vertebral metastases invade the pain-sensitive periosteum, dural, or paravertebral soft tissues. Pain can also be caused by compression of the spinal nerve roots from tumor or bone fragments from pathologic fractures. Secretion of prostaglandins by the tumor can promote tumor invasion and cause increased pain sensitivity. Pain may occur 1–2 mo before the onset of other symptoms and signs *(62)*. Treatment is most effective when pain is the only symptom.

Pain localized to the affected vertebral body is usually steady, aching, and midline. It may be exacerbated by Valsalva maneuver or movement in the case of spinal instability and is usually more severe at night and in the supine position. By contrast, pain from a herniated intervertebral disk or compression fracture is usually alleviated in the supine position. Localized tenderness to palpation is useful but not precise in identifying the affected spinal level *(14)*.

Radicular pain is caused by epidural extension or vertebral collapse with compression of the nerve roots within the spinal canal or as they exit through the intervertebral foramen. Cervical root compression may produce pain or paresthesias in one or both arms. Thoracic compression may cause a tight band around the chest or abdomen, while patients with lumbar nerve-root compression have radiation of pain down one or both legs *(14)*. Neck movement and straight leg raising may exacerbate radicular pain. Percussion of the spine helps to localize the involved vertebral body.

***Weakness*** Weakness is the next most common symptom of ESCC *(61,62)*. At presentation, about two-thirds of lung cancer patients have profound motor symptoms and are unable to walk *(63)*. Upper motor neuron weakness occurs with compression of the corticospinal tracts and is usually associated with other signs of myelopathy including hyperreflexia and Babinski signs. Myelopathy usually develops weeks after onset of pain and may progress rapidly within a few days of onset *(51)*. Initially there is symmetrical, proximal leg weakness, producing difficulty climbing stairs and arising from the seated position.

Acute weakness may occur on occasion with sudden onset paraplegia, flaccid muscle tone, and areflexia in a "spinal shock" pattern of cord injury. This presentation is often secondary to acute hemorrhage in the epidural tumor, or to collapse of an involved vertebral body. Recovery of ambulation is unlikely to occur in patients presenting in this manner.

Lower motor neuron weakness (LMN) occurs when the cauda equina is compressed. Symptoms include decreased muscle tone and absent reflexes *(14)*. Weakness from compression of the cauda equina is usually patchy in distribution and more distal than proximal.

***Sensory Loss*** Sensory loss usually occurs simultaneously with weakness, but is rarely disabling. Symptoms may include decreased sensation or paresthesias in the limbs or trunk below the level of cord compression *(62)*. Two-thirds of lung cancer patients had a sensory level below the area of ESCC, with 10% retaining normal sensory function *(63)*. However, it should be noted that the sensory level cannot be used to accurately predict the site of ESCC.

Cauda equina lesions may result in painful paresthesias of the feet and lower legs. With cord compression, the earliest sensory changes are proprioceptive and vibratory loss *(62)*. Lhermitte's sign is an electrical sensation that, upon neck flexion, radiates from the cervical region down the spine and into the legs. In cancer patients this sign may be due to a cervical epidural metastasis, prior irradiation to the cervical spine, or a side effect of certain chemotherapeutic drugs.

***Autonomic Dysfunction*** Bowel or bladder dysfunction, sweating abnormalities, and impotence are rare as isolated or initial manifestations of ESCC *(14,62)*. However, patients with ESCC affecting the tip of the conus medullaris (often secondary to a T11–T12 vertebral metastasis) may have bowel or bladder changes before weakness sets in. In lung cancer patients, 59% had severe bladder dysfunction (usually urinary retention) requiring catheterization; another 12% had milder symptoms of urgency *(63)*. Sphincter disturbances can produce retention or incontinence, the former being more common. Patients may not be aware of severe urinary retention because of sensory loss. Urinary retention may result in frequent episodes of small volume voiding as bladder compliance is exceeded. Urinary retention is usually seen in more rapidly evolving cases of ESCC and is associated with marked sensory and motor losses in the legs *(14)*. Examination of anal tone and assessment of bladder function (postvoid residual) can be useful to assess sphincter function when ESCC is suspected.

***Ataxia*** Spinocerebellar signs, including gait ataxia, are often obscured by weakness and sensory loss, and can persist

after weakness has improved with treatment. Cerebellar signs suggest that the spinocerebellar tracts of the spinal cord may be involved *(14)*. On rare occasions, ataxia may be the only sign in ESCC, and a diagnostic delay may occur while the cause of cerebellar dysfunction is sought.

### RADIOLOGIC FINDINGS AND DIAGNOSIS

**MRI** MRI is the most sensitive and specific test for spinal metastases *(14)*. Because MRI is sensitive to changes in the bone marrow, this technique is able to detect the presence of metastatic disease within the vertebral bodies. The addition of gadolinium is not crucial for the identification of epidural metastases, and may mask bony involvement as T1 hypointense metastases may become isointense after contrast administration *(69,70)*. Because synchronous epidural metastases occur at multiple levels in approx 20–30% of cases, the entire vertebral column should be imaged *(62,69)*.

**Plain X-Rays** Plain X-rays may be useful for identifying vertebral body metastases *(14)*. Abnormalities include erosion of a pedicle and collapse of the vertebral body. Plain X-rays are suggestive of epidural extension in a vertebral body collapse of more than 50% or pedicle erosion *(14,62)*.

**CT** CT scans are more sensitive than plain X-rays or bone scans for identifying vertebral metastases, and like MRI, can image paravertebral disease.

**Myelography** MRI has replaced myelography as the definitive radiographic test for epidural metastases *(14,70)*. However, if the patient is unable to tolerate MRI because of claustrophobia or severe pain, or if there is a strong clinical suspicion of cord compression despite a negative MRI of poor quality, CT-myelography can be useful. The entire spinal canal should be imaged.

### MANAGEMENT

**Glucocorticoids** Glucocorticoids can improve the symptoms of ESCC, especially pain. In addition, patients treated with high-dose dexamethasone plus RT have a better functional outcome than patients treated with RT alone *(14,71)*.

**Surgery** Surgery should be considered for diagnostic purposes in patients without known cancer, in patients with ESCC in the setting of limited or indolent systemic disease, in cases of RT failure, or in cases of spinal instability *(14)*.

Vertebral body resection allows for complete removal of tumor. Bone graft or a synthetic cement replaces the resected vertebrae. Stabilization of the spinal column is necessary and requires intact vertebral bodies above and below the lesion. Laminectomy can be employed for patients with compression of the spinal cord by metastases to posterior spinal elements *(14)*.

**Radiation** RT should be implemented soon after diagnosis is made in patients who do not receive surgery. The radiation port is centered on the site of ESCC and includes two vertebral bodies above and below.

**Approach to Recurrent Disease** Retrospective series of patients with ESCC put the incidence of recurrence between 13–20%, with half of the recurrences occurring at a different level than the original site *(67,72)*. Half of the patients who survived 2 yr after diagnosis and nearly all of the patients at 3 yr had recurrence of their disease. Reirradiation of recurrent ESCC may preserve ambulation with low risk of radiation injury to those patients with limited duration of expected survival *(73)*.

**PROGNOSIS** The best results from treatment are for pain control, with two-thirds of patients with ESCC from all cancers having durable improvement of pain *(66)*. This figure may be even higher for patients with SCLC treated with radiotherapy *(74)*. This likely reflects the radiosensivity of this histology. The majority of patients with ESCC from all cancers who are ambulatory at the initiation of treatment remain so a year later *(14,65,66)*. In lung cancer patients, the number of ambulatory patients improved from 41–52% after treatment. If the patient was paraplegic at the beginning of treatment, the chances of walking again are poor *(63)*. However, rare patients have regained ambulation several weeks to months after RT despite severe weakness at initiation of treatment. Patients with SCLC again may be particularly likely to improve *(74)*. Patients with ESCC from all cancers who are paraparetic at start of therapy have a 25–70% chance of being ambulatory after treatment *(14,65,66)*. Patients who do not regain ambulation have shorter survivals. There were no significant improvements in bladder function in lung cancer patients after treatment of ESCC *(63)*.

Prognostic factors for survival and function include tumor histology (lung cancer is an unfavorable histology), good initial performance status, complete surgical removal of the metastasis, and cervical location of the metastasis *(65–67)*. Patients with multiple epidural metastases had a shorter median survival than patients with a single, spinal metastasis *(67)*.

Patients with SCLC showed no difference in outcome regardless of mode of treatment. However, the NSCLC patients did significantly better when treated with the combination therapy of laminectomy and then RT. Only 39% of these patients improved with RT alone, 47% with laminectomy alone, while 82% improved with combined therapy ($p = 0.03$) *(63)*. Survival also improved in the combined therapy group (median of 3.5 mo, with range of 0–132 mo) compared with the RT group (median of 1 mo, range of 0–59 mo) or the laminectomy group (median of 1.5 mo, range 0–32 mo) *(63)*.

Although there is no significant difference in survival between different lung cancer histologies, the trend shows survival for squamous cell carcinoma to be the worst (median of 1 mo, range of 0–32 mo) and SCLC being the best (median of 2.5 mo, range of 0–132 mo) *(63)*. Overall, only 9% of lung cancer patients survived more than 1 yr *(63)*.

## INTRAMEDULLARY SPINAL CORD METASTASES (ISCM)

Lung cancer accounts for about 50% of ISCMs, and SCLC accounts for about 60% of ISCM associated with lung cancer *(75)*. In a large unselected series, ISCM developed in 3/203 SCLC patients (1.5%). In another series of 50 patients, ISCM developed in 6/50 (12%). ISCM and leptomeningeal carcinomatosis frequently co-exist in SCLC patients (between 17 and 54% of cases) *(75,76)*.

Clinical features and diagnosis of ISCM in lung cancer patients do not differ from these issues in other malignancies and are discussed in Chapter 9. ISCM in patients with SCLC is particularly responsive to radiotherapy and may be undetect-

able at autopsy in irradiated patients *(77)*. As with ISCM from other malignancies, early diagnosis and rapid institution of radiotherapy offer the best hopes of maintaining or improving neurologic function.

## BASE OF SKULL METASTASES

Skull-base metastases can invade the bones surrounding the middle cranial fossa, as well as the parasellar regions, orbits, occipital condyle, and jugular foramen. Lung, breast, and prostate cancer are the primary tumors that most commonly produce metastases to the base of the skull *(15)*. Clinical syndromes and management are fully discussed in Chapter 8.

## PLEXUS AND PERIPHERAL NERVE METASTASES

### BRACHIAL PLEXUS

#### Manifestations

***Symptoms*** Pancoast tumor is a term used to describe tumors that originate in the apex of a lung and compress or invade the brachial plexus. As the tumor grows into the plexus from below, the C8 and T1 fibers (which become the ulnar nerve) are usually first affected.

Pain, the most common initial symptom, rapidly progresses from a dull, throbbing feeling in the back or lateral part of the shoulder to involve the medial portions of the upper arm, elbow, and forearm. Involvement of the C8 and T1 fibers also results in numbness and tingling in the fourth and fifth fingers, although these symptoms are usually less noticeable by the patient.

Weakness in the intrinsic muscles of the hand makes it difficult for the patient to grasp small items. As the tumor spreads to involve the rest of the plexus, involvement of the medial and radial nerve occur, resulting in weakness in the flexors and extensors of the hand and wrist and in the extensors of the elbow. Involvement of muscles innervated by the upper plexus, such as the biceps and brachioradialis, is a late-stage development. Medial progression of the tumor to involve the sympathetic trunk may cause a partial Horner's with ptosis, miosis, and anhydrosis.

***Signs*** The neurological examination may be normal at an early stage despite sensations of numbness and tingling. Visual and tactile examination may show smoothing of the well-defined clavicular boundaries with supraclavicular or axillary adenopathy. Percussion of these areas may reproduce the sensory symptoms in the arm. Extension of the brachial plexus with full range of motion of the arm can also reproduce these symptoms.

#### Radiologic Findings

***Chest X-Ray*** Apical views can be obtained for examination of the superior part of the lung.

***CT and MRI*** Imaging of the brachial plexus with either CT or MRI generally demonstrates tumor. Extension of the tumor into the spinal canal via the neural foramina, may also be revealed.

**Diagnosis** Diagnosis is usually made by typical radiographic findings. EMG can document involvement of the plexus but is rarely indicated.

#### Treatment

***Radiation*** Radiation can provide effective pain relief and stabilize or improve motor function. Full recovery can occur if the syndrome is diagnosed early. However, restoration of neurologic function is less likely if the symptoms are advanced. Chemotherapy may result in alleviation of symptoms and signs.

***Analgesics*** Treatment for pain usually includes the use of analgesic agents including opioids. Newer agents such as gabapentin, which are specific for neuropathic pain, should also be employed.

***Surgery*** Failure to control pain may result in consideration of rhizotomy or cordotomy. Alternatively, in the setting of a reflex sympathetic dystrophy syndrome, blocking the stellate ganglion may produce some benefit.

### RECURRENT LARYNGEAL NERVE

**Manifestations** The recurrent laryngeal nerve, a distal branch of the vagal nerve, innervates the muscles of the larynx. Its compression by metastatic deposits of lung cancer causes a weak cough and hoarseness secondary to vocal cord paralysis. Dysphagia can occur, with aspiration of liquids.

**Treatment** Treatment of the lung cancer by radiation and chemotherapy can occasionally improve the symptoms. Aspiration may be reduced by laryngoplasty of the paralyzed vocal cord.

**ATYPICAL FACIAL PAIN** As discussed in Chapter 4, patients with lung cancer may describe constant aching unilateral facial pain often located around the ear. The pain is invariably ipsilateral to the thoracic tumor and is likely attributable to intrathoracic vagus nerve compression. Local management with surgery or radiotherapy usually alleviates the symptom.

## INDIRECT COMPLICATIONS OF LUNG CANCER (TABLE 3)

### PARANEOPLASTIC NEUROLOGIC SYNDROMES

The neurologic paraneoplastic syndromes constitute a group of rare disorders that may affect the nervous system at all levels, and not uncommonly involve multiple sites within a single individual *(14)*. SCLC appears to have the highest incidence among all cancers of associated paraneoplastic neurologic syndromes; approx 3% of SCLC patients have antibody-associated paraneoplastic disorders *(12,14,78)*. In contrast, clinically significant paraneoplastic neurologic syndromes probably occur in fewer than 1% of all cancer patients *(14,79)*.

#### Manifestations

***Encephalomyelitis*** Paraneoplastic limbic encephalomyelitis (PLE) is characterized by memory loss, confusion, personality changes, and hallucinations *(80)*. Less commonly, involvement of the brainstem results in cranial nerve symptoms (such as deafness, vertigo, and diplopia), weakness, central respiratory failure, or involvement of the autonomic system. MRI abnormalities consist of T2-weighted changes in the medial temporal lobes and brainstem that do not enhance. Neuropathological findings show multifocal inflammatory infiltrates *(78)*.

In a recent review of 50 patients with PLE *(80)*, lung cancer was the most commonly associated malignancy, making up 50% of the cases. In 60% of patients the neurological symptoms preceded the diagnosis of cancer, by a median interval of 3.5 mo. One-half of MRIs showed changes in the limbic system. Sixty percent had positive antineuronal antibodies, and 18 of

these patients had anti-Hu. In the patients with anti-Hu antibodies, 94% had SCLC. Thirty-eight percent of the anti-Hu patients showed clinical improvement over time, compared with 64% of the patients without anti-Hu antibodies. Treatment directed against the primary tumor was more effective than immunosuppressive therapy.

***Paraneoplastic Cerebellar Degeneration (PCD)*** Symptoms of PCD begin as mild truncal ataxia, evolving over the course of several weeks to months to include the limbs and trunk. Dysarthria, nystagmus, vertigo, diplopia, and oscillopsia are common symptoms. After a period of subacute progression, the disease usually stabilizes, leaving the patient severely disabled. Signs are bilateral, though one side can be more affected than the other *(14,78)*.

Although signs and symptoms are primarily confined to the cerebellar system, other areas of the nervous system may be affected, producing altered mental status, extrapyramidal signs, hearing loss, hyperreflexia, and peripheral neuropathy *(14)*.

The most common association with PCD is lung cancer *(14)*. In patients with SCLC, this syndrome may exist in combination with a widespread encephalomyeloneuritis *(81)*. Detection of anti-Hu or anti-Yo antibodies in serum or CSF can be useful to confirm the clinical suspicion and to help the search for a primary tumor. Anti-Hu is associated with SCLC whereas anti-Yo is associated with breast and gynecologic cancers in women *(81)*. Over time, neuroimaging shows cerebellar atrophy. At autopsy, there is specific loss of Purkinje cells *(78,81)*.

***Subacute Sensory Neuronopathy (SSN)*** This syndrome occurs in patients with SCLC or with autoimmune diseases such as Sjögren's syndrome. Serum from affected patients usually contains the anti-Hu antibody *(82,83)*. Anti-Hu antibodies have a sensitivity of 82% and specificity of 99% in confirming the diagnosis of SSN *(84)*.

The syndrome starts with burning dysesthesias involving the legs and progressing over days and weeks to involve the arms and the face. A severe sensory ataxia results that mimics cerebellar dysfunction. Both small and large neurons are affected, which helps to differentiate SSN from the large fiber neuropathy due to cisplatin. Muscle-stretch reflexes are lost whereas normal muscle strength is maintained *(14,78)*.

CSF findings include an inflammatory pleocytosis and high titer of anti-Hu antibody. EMG/NCS studies show normal motor nerve findings but small or absent sensory potentials. Pathologically, there is inflammation of the dorsal root ganglion with loss of neuronal cell bodies *(14,78)*. Evidence suggests that the neuronal damage is mediated by cellular immunity with the anti-Hu antibodies serving as a marker for the condition *(84)*.

***Autonomic Neuropathy*** Autonomic neuropathy is a rare entity that can exist by itself or in combination with other sensory neuropathies. It is primarily associated with SCLC, usually as part of the anti-Hu syndrome. Typical symptoms include orthostatic hypotension, gastroparesis, neurogenic bladder, and pupillary asymmetries. Symptoms are usually progressive, but may stabilize with successful treatment of the primary cancer *(14,82)*.

***Lambert-Eaton Myasthenic Syndrome (LEMS)*** LEMS is a paraneoplastic disorder of the neuromuscular junction (NMJ) that occurs in patients with SCLC or autoimmune conditions. Patients complain of increasing weakness and fatigability in the proximal musculature. Weakness can involve respiratory muscles, but unlike myasthenia gravis (MG), the oculobulbar muscles are usually spared. Another difference compared to MG is that strength increases with initial effort before the weakness returns. These patients have other cholinergic disturbances such as impotence, constipation, and a dry mouth. Freeze-fracture electron micrographs show loss of voltage-gated calcium channels (VGCC) in the presynaptic active zone *(14,78)*. Antibodies to VGCC at the presynaptic terminal are pathogenic.

Electromyography is used to diagnose LEMS, with a decrement of the compound muscle action potential (CMAP) at slow rates of stimulation but an increment at faster rates. This is in contrast to normal musculature, which has a similar size CMAP at slow or fast rates or to MG, which has a decremental response to both *(14)*.

***Polymyositis (PM)/Dermatomyositis (DM)*** Both of these disorders are inflammatory myopathies of autoimmune origin, and are only rarely associated with an underlying malignancy. DM is more likely than PM to be associated with cancer. Lung cancer is a frequent cause of the paraneoplastic form of this disease. Laboratory findings include autoantibodies (e.g., anti-Jo) and increased serum creatinine kinase level. EMG confirms the presence of a myopathy. The conditions respond to immunosuppressive therapy. Dermatologic and muscle symptoms improve in some patients when the underlying primary cancer is treated *(14)*.

**Management**

***Treatment of Primary Cancer*** Treatment directed at the primary lung tumor stabilizes or partially improves paraneoplastic syndromes in approx 1/4 of patients. These improvements have been observed between 3 wk and 3 mo after surgery *(85)*.

***Immunosuppressive Therapies*** Because of the apparent role of autoimmunity in many of the paraneoplastic conditions, there has been an attempt to employ immunosuppressive therapies. In general, these approaches have yielded little in the way of benefit, but may be considered in patients for whom other options, such as removal of the primary tumor are not effective or possible *(81,84,85)*. Treatments have included administration of glucocorticoids, intravenous immunoglobulin, and plasmapheresis.

In an analysis of cases published in the literature, 22% of patients with a variety of paraneoplastic neurologic disorders appeared to respond to plasmapharesis. Patients with LEMS have responded to glucocorticoids and plasmapharesis. Dermatomyositis responds to glucocorticoids *(85)*.

***Manipulation of Neuromuscular Transmission*** Pyridostigmine has some activity in patients with LEMS. Acetylcholine release can be enhanced by blocking potassium channels involved in terminating the action potential, prolonging the time available for calcium entry into the cell, and enhancing acetylcholine release. 4-aminopyridine improves muscle strength but is associated with an unacceptable lowering of the seizure threshold. 3,4-diaminopyridine (3,4-DAP) has been shown to increase strength and is associated with a

much lower incidence of seizures. The medication is well-tolerated and is very effective, but is at present only available as an investigational agent. Efforts are being made to make it commercially available.

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# 21 Neuro-Oncologic Complications of Breast Cancer

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## INTRODUCTION

Breast cancer arises from the epithelial cells that line the ducts and lobules of the mammary gland. Its incidence has increased gradually (1–2%/yr for the last three decades), but recently the incidence has leveled off and mortality has even decreased slightly. At present, about 1 out of every 10 females in the United States and Western Europe will develop breast cancer. The risk of breast cancer rises steadily from about the age of 25, with some slowing of increase after menopause. Obviously, hormones are important promoters of the disease. Length of menstrual life and the fraction until first pregnancy are established risk factors of breast cancer. Other factors include exposure to radiotherapy (RT) before the age of 30, and to some extent long-term postmenopausal estrogen replacement. A family history of breast cancer is the most important risk factor *(1)*. About 5–10% of all breast cancers occur in high-risk families, including families with the Li-Fraumeni syndrome (mutation in p53) and families with mutation in the tumor suppressor gene BRCA 1 or BRCA 2 (lifetime risk of breast cancer up to 85%). In sporadic breast cancer p53 mutation is found in 40% of the patients and overexpression of the oncogene erb B2 (HER-2/neu) in a quarter of the patients *(2)*.

At diagnosis about 50% of the patients with breast cancer have clinically local disease, 40% regional disease, and 10% distant metastases *(3)*. The estimated 5-yr survival rates for local, regional, and distant metastatic disease at diagnosis are approx 85, 55, and 10%, respectively *(3)*. Almost half of the patients with breast cancer will eventually die of their disease. Recently, mortality of breast cancer has somewhat declined, presumably because of screening women over the age of 50 yr, and the extended use of adjuvant systemic therapy *(4)*. A quarter of the women who would otherwise die of their metastatic disease will remain disease-free with appropriate adjuvant systemic therapy. Tumor relapse and overall survival are dependent on prognostic factors, including age, menopausal status, tumor size, tumor grade, lymph node status, lymphovascular invasion, and hormone receptor status. High expression of erb B2 and mutated p53 also signify a bad prognosis.

Half of the patients who will get a relapse develop metastatic disease more than 5 yr after the diagnosis of the primary tumor. The first site of relapse is soft tissue (skin, lymph nodes), bone, or viscera (lung, liver, brain), each accounting for a third of the relapses. The median survival from diagnosis of relapse is about 2 yr; patients with visceral metastases have the worst prognosis. Patients with bone metastases as sole site of relapse often have hormone receptor-positive tumors and a relatively indolent course of their disease. Visceral metastases more often develop in relatively young patients with hormone receptor-negative tumor. The response rate to hormonal therapy of tumors with positive estrogen and progesteron receptors is 70%, and still 30–50% to second-line hormonal therapy. Patients with hormone receptor negative tumors, patients with life-threatening visceral metastases, and patients refractory to hormonal therapy should receive chemotherapy, if necessary combined with local treatment (RT, surgery) for disabling local disease. Response rates for the combination regimen cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) are 40–60%; response rates with anthracycline-based regimens such as CAF or FEC slightly higher with generally acceptable toxicity *(5)*. Patients may respond to CMF for metastatic disease even after previous adjuvant CMF. Tumors with high expression of erb B2 oncogene are more aggressive and resistant to chemotherapy, but often responsive to anthracyclines *(6)*. The taxoids are the most promising new drugs in metastatic breast cancer with little cross-resistance with anthracyclines and relatively high activity in visceral disease. Several Phase II studies have reported a high response rate to high-dose chemotherapy in combination with autologous stem cell transplantation in patients with metastatic breast cancer. Survival benefit, however, has not been demonstrated in the published randomized studies *(7,8)*.

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**Table 1**
**Neurologic Symptoms Due to Metastatic Breast Cancer and Its Treatment**

| *Symptom* | *Cause* |
|---|---|
| Headache | Metastasis: BM, LM, dural, skull, skull base |
| | Treatment-related: – intrathecal chemotherapy |
| | – RT (edema, encephalopathy) |
| | Postlumbar puncture |
| | Vascular: sinus thrombosis, subdural hematoma/hygroma |
| Seizures | Metastasis: BM, LM, dural |
| | Treatment-related: – intrathecal MTX |
| | – RT (encephalopathy, radiation necrosis) |
| | Vascular: sinus thrombosis, subdural hematoma / hygroma |
| | Metabolic (hypercalcemia) |
| Encephalopathy | Metastasis: BM, LM, dural |
| | Metabolic (hypercalcemia, liver metastasis) |
| | Drug-induced (opioids, corticosteroids, anticonvulsants) |
| | Treatment-related: – intrathecal chemotherapy |
| | – RT (encephalopathy) |
| Visual disturbances | |
| – decreased visual acuity, blurred vision | Metastasis: choroid, optic nerve, orbit, LM, retro-orbital/pituitary |
| | Treatment-related: – intrathecal MTX, tamoxifen |
| | – RT (eye, optic nerve) |
| | – corticosteroids |
| – metamorphopsia | Metastastis: choroid |
| – diplopia | Metastasis: ocular, orbit, retro-orbital/parasellar, LM, brainstem |
| | Increased intracranial pressure (metastasis, edema) |
| | Paraneoplastic: PCD (anti-Yo) |
| | Anticonvulsants, opioids |
| – oscillopsia | Metastasis: brainstem |
| | Paraneoplastic: PCD (anti-Yo), OMS (anti-Ri) |
| – cortical blindness | Metastasis: LM, BM, bilateral occipital |
| | Vascular: sinus thrombosis |
| Arm/leg weakness | Metastasis: cranial dural, BM, LM, ISCM, SEM, plexus |
| | RT-induced (ischemic) plexopathy |
| Tetra/paraparesis | Metastasis: multiple BM, ISCM, SEM |
| | Treatment-related: – MTX |
| | – Ara-C myelopathy |
| | – RT myelopathy |
| | Vascular: sinus thrombosis |
| | Corticosteroids: myopathy (proximal), epidural lipomatosis |
| | Hypercalcemia (proximal) |
| | Polymyositis (proximal) |
| Lhermitte's sign | Metastasis: SEM |
| | RT myelopathy (transient) |
| | Docetaxel |
| Sensory disturbances | Metastasis: ISCM, LM, SEM |
| | Taxoid-induced polyneuropathy |
| | RT myelopathy |
| | Paraneoplastic sensory neuropathy |

BM, Brain metastasis; ISCM, Intramedullary spinal cord metastasis; LM, Leptomeningeal metastasis; SEM, Spinal epidural metastasis; RT, Radiotherapy; MTX, Methotrexate; PCD, paraneoplastic cerebellar degeneration; OMS, opsoclonus–myoclonus syndrome.

**Table 2**
**Treatment of Metastases from Breast Cancer**

| | | *Neurological response* | | |
|---|---|---|---|---|
| *Metastatic site* | *Treatment modality* | *Rate* | *Median duration* | *Median survival (mo)* |
| Brain | Corticosteroids | 75% | 1 mo | 1–2 |
| | WBRT (+ steroids) | 75% | 3 mo | 4 |
| | Radiosurgery + WBRT | 90% | 75% 1 yr | |
| | Surgery + WBRT | >90% | 75% 1 yr | 9–18 |
| | Chemotherapy | 50% | 3–7 mo | 3–6 |
| Leptomeningeal | Intraventricular chemoth. + RT symptomatic site | 50% | 1–2 mo | 3–4 |
| | Systemic chemotherapy + RT symptomatic site | 50% | | 3–4 |
| Intramedullary spinal cord | RT | Sporadically | | 1 |
| Spinal epidural | RT (+/– laminectomy) | ± 80% | ± 12 mo | 9 |
| | Systemic chemotherapy | 55% | | 7 |
| | Surgery + RT (vertebrectomy + stabilization) | >90% | >12 mo | |
| Skull base/orbit | RT | 50% | | 12–24 |
| | Systemic therapy | | | |
| Brachial plexus | RT | 50–75% | | |
| | Systemic therapy | <50% | | |

Overall, despite major improvements in treatment of advanced breast cancer, the median survival of patients with metastatic disease has changed little over the last decades, remaining approx 2 yr. However, the expansion of therapeutic options and increased knowledge of pathogenesis and prognostic factors of metastatic disease enable the physician to refine the management of the individual patient, often leading to long term palliation and meaningful quality of life. This also holds true for central nervous system (CNS) metastasis. CNS metastasis is one of the most dreaded complications in metastatic disease. Longer survival of patients with metastatic disease and increased use of adjuvant systemic therapy may lead to a higher incidence of CNS metastasis. The clinical diagnosis of CNS metastasis is made in about 15% of patients with breast cancer. Autopsy studies report an incidence of CNS metastases in more than 30% of patients dying of breast cancer, of whom about 10% have metastatic disease exclusively in the CNS *(3,9)*. Five to ten percent of the patients with breast cancer will die primarily of CNS failure *(10)*. Like CNS involvement in other solid tumors, CNS metastasis in breast cancer is usually associated with widespread systemic disease. Systemic disease in breast cancer is, however, often more amenable to treatment than in other solid tumors. In addition, CNS involvement may be the only site of clinical disease in a small but clinically important proportion of patients with breast cancer *(9)*. This explains why in breast cancer the outcome of patients with CNS metastases often depends primarily on the treatment response of the neurological disease.

## METASTATIC COMPLICATIONS

**BRAIN METASTASIS** Approximately 20% of breast cancer patients have brain metastases (BM) at autopsy, whereas the clinical diagnosis of BM is made before death in 5–10% of patients with breast cancer *(11,12)*. BM is associated with ductal carcinoma, a short cancer history (6 mo shorter than patients dying without BM), young age (on average 5 yr younger than patients dying without BM), estrogen receptor-negative tumor, and the presence of lung metastases. In about 20% of the patients with BM the brain is the first site of relapse *(13,14)*. An autopsy study reported that in 13% of the patients with CNS involvement no other metastases were found *(9)*. In contrast to lung cancer, BM only rarely is the first clinical manifestation of breast cancer. An increased incidence of the brain as first site of relapse has been associated with use of adjuvant chemotherapy *(14)*. The median disease-free interval in these patients seems the same as in patients without adjuvant treatment who develop systemic metastases, suggesting that chemotherapy administered when the blood-brain barrier (BBB) is intact does not prevent the development of cerebral micrometastases, whereas it suppresses effectively the development of extracranial metastatic disease. About 40% of BM in breast cancer are single lesions. Symptoms and signs of BM are related to the site of the lesion(s) and accompanying edema (Table 1). Half of patients complain of headache that may be associated with vomiting and drowsiness. A third of patients present with focal signs and 20% with seizures *(15)*. The diagnosis of BM is confirmed with CT or preferably MRI using intravenous contrast. The lesion(s) may be indistinguishable from primary brain tumors, vascular lesions, infectious processes, radionecrosis, or demyelinating lesions. In general, the correlation between BM and aggressive tumor activity is reflected in the poor outcome with a median survival after treatment of BM of 3–5 mo; 10–20% survive more than a year; and half of the patients die of their neurological disease *(13,14,16)*. Absence of extracranial metastatic disease and a solitary BM appear the most important prognostic factors. A Karnofsky index of more than 70 and a

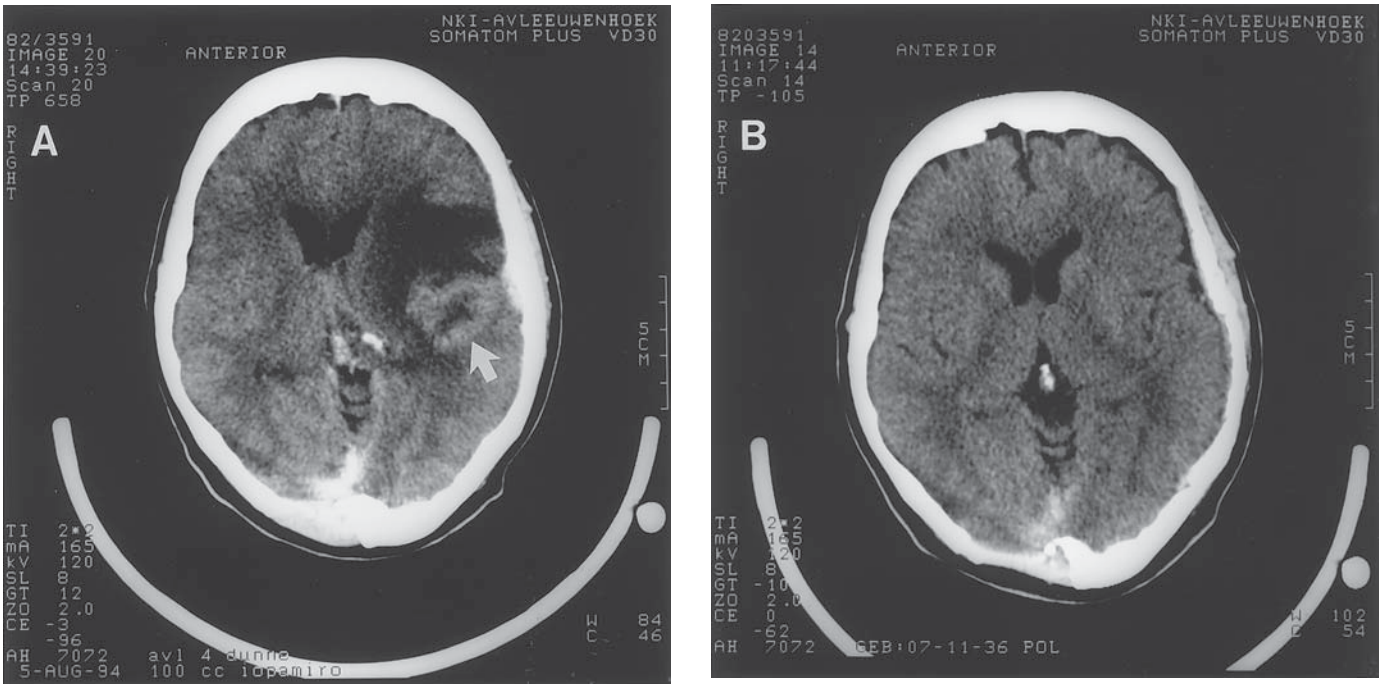


**Fig. 1.** Brain metastasis; complete remission following systemic chemotherapy. Pretreatment CT scan **(A)** shows contrast enhancing lesion (arrow) with surrounding edema. Complete remission after CMF chemotherapy **(B)**, that persisted until death due to systemic disease after 19 mo.

neurological history of more than a month prior to the diagnosis of BM are less significant prognostic factors *(13,14,16,17)*.

Radiotherapy (RT) is the mainstay of treatment of BM. Median survival after RT is about 4 mo (Table 2) *(13,14,16)*. RT is usually combined with steroids. Steroids induce neurological improvement in about 75% of the patients. There is no correlation between the extent of edema and degree of clinical improvement, nor between response to steroids and survival *(18)*. The optimal dose of steroids is not defined. In patients without imminent herniation a dose of 4 mg/d is as effective as 16 mg, while causing less side effects *(19)*. The RT fractionation scheme and total dose have no significant influence on the rate and duration of response *(18,20,21)*, although in patients with favorable prognostic factors some increase of survival has been suggested with a RT scheme with low fraction size (≤ 3 Gy). Boost RT and the use of radiosensitizers do not result in better outcome, even in the absence of systemic disease *(20)*. Clinical response following steroids and RT is seen in about 80% of patients with a median duration of response of 3 mo *(18)*. At time of death half of patients treated with RT are neurologically improved or stable *(13,14,18)*.

Radiosurgery and surgery also play a role in selected cases of BM. Radiosurgery of BM provides good local tumor control, low morbidity and mortality, low rate of steroid dependence, and high rate of functional independence, comparable with results of surgical resection *(22,23)*. Radionecrosis is a rare complication that predominantly occurs following whole brain RT (WBRT) and in lesions larger than 3 cm. After radiosurgery without WBRT the risk of cerebral recurrence distant from the irradiated lesion is increased, but these recurrences can be treated successfully again with radiosurgery *(23)*. Patients with brainstem metastases without acute neurologic symptoms may achieve effective palliation after radiosurgery *(24)*. Small lesions (<3 cm) are treated with radiosurgery probably as effective as with surgical resection. Patients with larger but operable lesions without active systemic disease should be treated with surgical resection. Postoperative WBRT significantly reduces relapse at the site of the original metastases, as well as at other sites in the brain *(25)*. Median survival of patients treated with surgery and postoperative WBRT is about 9–18 mo *(13,14,26)*; most of these patients die of systemic disease without evidence of cerebral relapse. In a retrospective analysis of patients with a solitary BM as first site of relapse, operated patients had a clearly better outcome (median survival 23 mo) than patients treated with RT or chemotherapy (median survival 9 mo) *(27)*. Outcome of patients undergoing resection of multiple, accessible BM appears the same as in patients with a single operated BM *(26,28)*.

Since it is recognized that the BBB is impaired or absent in large areas of BM because metastatic tumor vasculature lacks the structure of normal brain capillaries, evidence has accumulated that systemic chemotherapy can be an effective treatment in BM from breast cancer (Fig. 1). Phase II studies demonstrated an objective response of 50% or more and an overall median survival of about 6 mo after primary treatment with standard systemic chemotherapy, comparing favorably to the treatment results of WBRT *(29,30)*. Responses of extracranial disease paralleled the cerebral response in those patients. Chemotherapy including cisplatin and etoposide followed by consolidation WBRT in a number of patients resulted in an objective response rate of 38%, stabilization in 12%, and overall median survival of 7 mo *(31)*. The benefit of consolidation WBRT following chemotherapy-induced response of BM instead of reserving RT for local cerebral relapse has not been

established. Response of BM to hormonal therapy has been reported occasionally *(32,33)*, although it is assumed that hormonal treatment usually will act too slowly to prevent serious neurological deterioration in patients with symptomatic BM.

Recurrence of BM in stable or absent extracranial disease is not uncommon in breast cancer patients. A second course of RT or second line chemotherapy after previous systemic treatment of BM will result only occasionally in a meaningful response. However, systemic chemotherapy after previous RT or surgery of BM may induce stabilization or response in more than half of the patients *(30,34)*. In selected cases radiosurgery and also re-resection offer a local tumor control for 6–12 mo in about 75% of the cases *(23,26,27)*.

In conclusion, if the variety of therapeutic options including surgery, RT, radiosurgery, and systemic therapy is appropriately put into practice, long term and meaningful palliation may be possible, with survival extending a year or more.

**PITUITARY METASTASIS** Pituitary metastasis seems a relatively frequent finding at autopsy. It was found in 9% of patients dying with breast cancer *(35)*. It is associated more frequently with bone metastasis than with lung metastasis *(9)*. The pituitary gland may be invaded by extension from a bone metastasis in the sella, by hematogenous spread, or from leptomeningeal metastasis (LM). Symptoms include headache, anterior hypopituitarism, visual field loss, and rapidly progressive oculomotor weakness in cases of cavernous sinus invasion. Diabetes insipidus develops infrequently. Treatment consists of RT, but systemic chemotherapy may also be effective *(36)*.

**INTRAMEDULLARY SPINAL CORD METASTASIS** Intramedullary spinal cord metastasis (ISCM) is an infrequent complication of breast cancer that will be diagnosed presumably more often by the use of magnetic resonance imaging (MRI) scanning. Enhancement of ISCM at T1 weighted images is a reliable finding reflecting disruption of the blood spinal-cord barrier. T2-weighted images are particularly sensitive in detecting ISCM. ISCM usually develops in patients with widespread metastatic disease, including parenchymal BM. Most of ISCM result from hematogenous dissemination and occur in the gray matter because of its greater arterial perfusion. Sometimes ISCM is caused by direct infiltration of tumor cells from LM along the perivascular space into the cord. There are no clinical features characteristic for ISCM by which it can be distinguished with certainty from an extradural compressive lesion. Pain is the initial symptom in the majority of the reported cases; it usually begins as back pain that often soon becomes radicular. The clinical picture of ISCM usually is that of a rapidly progressive myelopathy, initially often asymmetric, leading to a complete loss of cord function in the course of days or a few weeks. Treatment consists of RT with corticosteroids. Treatment results are poor. Reported median survival of patients with symptomatic ISCM is < 3 mo. In our experience, early diagnosis and prompt start of treatment may lead to symptomatic improvement lasting a few months.

**LEPTOMENINGEAL METASTASIS** Among solid tumors breast cancer is the primary tumor most frequently associated with LM. About 2–5% of patients with metastatic breast cancer will experience LM, usually late in the course of their disease *(37)*. It is relatively more common in lobular carcinoma *(38)*. Relation with aggressive tumor activity including a short recurrence-free interval is a matter of controversy *(37–39)*. In breast cancer LM is associated with bone metastases. Spread of tumor cells from vertebral metastases perivascularly along the radicular veins seems the major route of entrance of tumor cells into the subarachnoid space *(40)*. Direct extension from a subependymal or cortical metastasis, from a paravertebral mass, or by direct seeding from a metastasis in the choroid plexus are occasional causes of LM. LM usually is multifocal. It often forms macroscopic tumor masses, sometimes with a local inflammatory reaction. This may cause obliteration of the subarachnoid space with CSF compartmentalization and hydrocephalus. There is a predilection for tumor sedimentation at the base of the brain and in the cauda equida. Tumor cells may infiltrate the nerve or form a cuff surrounding nerve roots. Tumor cells in the leptomeninges may extend into the perivascular spaces penetrating the brain or spinal cord parenchyma. Concomitant cortical tumor is more likely a late effect of LM than the source of LM. The most common symptoms and signs of LM include headache, confusion, cranial nerve involvement (most commonly cranial nerves III, VI, VII, VIII) and spinal root dysfunction particularly at the lumbosacral level. Differential diagnosis includes a variety of diseases such as metabolic encephalopathy, infectious meningo-encephalitis, paraneoplastic disease, brain metastasis, epidural metastasis, intervertebral disc disease, and peripheral neuropathy. The diagnosis of LM is established by demonstration of malignant cells in the CSF. In LM from breast cancer cytology is falsely negative in <10% on the first lumbar puncture *(37,38)*. Cisternal CSF cytology may be more sensitive than lumbar CSF in patients with cerebral symptoms *(41)*. Flow cytometry and immunocytochemistry are no better to cytology in detecting tumor cells in CSF of patients with LM from breast cancer *(42,43)*. *In situ* hybridization of CSF cells correlated better than cytology with the course of disease *(44)*, but its relevance in diagnosing LM still must be established. The chemical profile of CSF (protein, glucose, LDH), the cell count, or CSF pressure almost always show abnormalities in LM *(37)*. A variety of specific and nonspecific tumor markers have been detected in the CSF, but their clinical relevance is uncertain and CSF cytology is clearly more sensitive and specific in establishing the diagnosis. However, vascular endothelial growth factor (VEGF) may be a useful marker for both the diagnosis and evaluation of treatment response in LM *(47)*. Myelography and CT brain show abnormalities suggestive of LM in about 25% of patients. These abnormal findings include meningeal or ependymal enhancement, hydrocephalus, and nodular filling defects. About 10–20% show concomitant but clinically unsuspected parenchymal BM. Contrast-enhanced MRI of the brain is abnormal in 70% and spinal MRI in about 30% of patients with LM (Fig. 2). It should be noted that any condition with irritation of the meninges can produce meningeal enhancement. This includes local tumor infiltration, but also infectious meningitis and even postlumbar puncture CSF hypotension syndrome *(48)*. Occasionally MRI reveals meningeal infiltration concurrent with repeatedly tumor negative cytology of the CSF. Thus, CSF cytology and MRI may be complementary in the diagnosis of

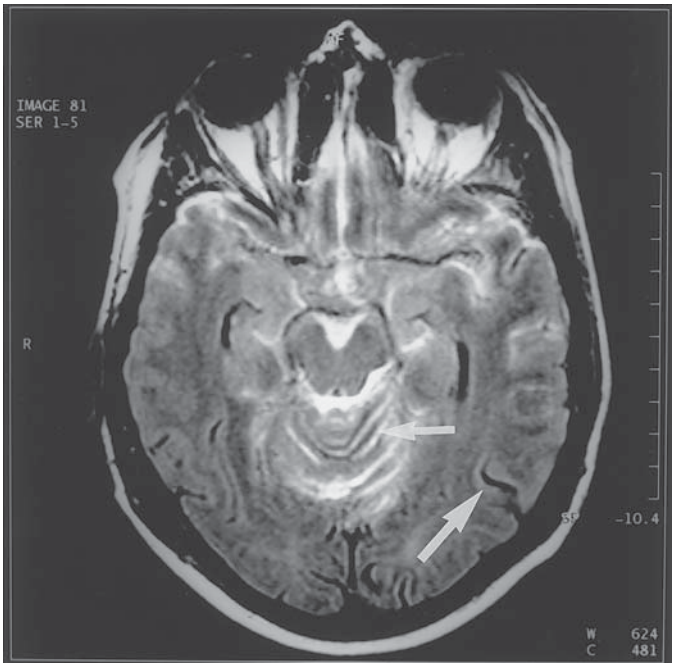


**Fig. 2.** Leptomeningeal metastasis; MRI FLAIR image. Hyperintensity of arachnoid and pia (white, small arrow) signifies leptomeningeal seeding. Uninvolved arachnoid is hypointense (black, large arrow).

LM. In patients with a normal neurological examination, imaging studies have a low yield of detecting abnormalities.

In line with the experience with LM from hematologic malignancies, intraventricular administration of chemotherapy in combination with RT to the symptomatic area has become the recommended treatment of LM from breast cancer. The alternative of intralumbar administration of chemotherapy is inconvenient for the patient and does not reliably achieve therapeutic ventricular drug concentrations *(49)*. Intraventricular administration via an Ommaya reservoir is associated with infection, misplacement or occlusion of the catheter in about 10% of the patients *(37,50,51)*. Methotrexate (MTX) is the drug of choice, and given as a single agent it is less toxic and as effective as multi-agent treatment *(52)*. Other agents for intraventricular use are Cytarabine (Ara-C) and Thiotepa. Ara-C is used as a second-line agent after failure to MTX. The benefit of intraventricular Thiotepa is questionable *(53)*: TEPA, an active metabolite of Thiotepa that crosses the BBB, is formed when Thiotepa is given intravenously, whereas it is not formed when Thiotepa is given intraventricularly.

The response rate following intraventricular treatment in combination with clinically involved field RT was more than 50% in several early studies with a median survival of about 6 mo as compared to rapid clinical deterioration and a median survival of 4–6 wk for historical controls *(45,54,55)*. However, poor responses and a short median survival of only one or a few months despite similar, or even more intensive therapy were described in more recent studies *(37,52,56,57)*. Selection of patients may have played a role *(45)*. In a randomized study comparing the efficacy of intraventricular MTX and Thiotepa in combination with involved field RT, not a single patient in either treatment arm with a fixed neurological deficit showed neurological improvement and median survival was 15 wk *(56)*. In all studies at least one-third of the patients die within a few weeks despite intensive treatment. Based on prognostic factors these patients should preferably be excluded from extensive therapy. Negative prognostic factors are age over 55 yr, low-performance status, extensive visceral metastatic disease, cranial nerve involvement, and a decreased CSF glucose concentration *(37,38)*. Normal CSF protein has been associated with a better prognosis, but a markedly increased CSF protein (>1.0 g/L) does not necessarily imply a short survival *(37,52)*. A markedly increased protein may be related to spinal involvement and a relatively better prognosis *(37,39,51)*. In addition to uncertainty about the actual efficacy of intraventricular treatment, there are no data concerning the effect of dose of MTX, nor from duration of treatment. No differences in efficacy were seen in schedules that included 5, 10, or 20 mg of MTX per injection. A 12 hourly administration of 1 mg was as effective but less toxic than 10 mg MTX twice a week *(58)*. In most studies intraventricular treatment is intensive as long as CSF cytology is tumor positive, and continued throughout the patient's life. Larger studies show that continuation of intraventricular therapy beyond 6 wk does not improve survival, but increases the risk of neurotoxicity *(37,51)*. It should be noted that treatment of LM is purely palliative. A lasting complete remission of LM from solid tumors is hardly ever obtained. The clinical status after the first 6 wk of treatment is a better predictor of outcome than CSF cytology *(37)*. Patients may have tumor-positive CSF cytology for many months, while they are in a stable clinical condition, even without prolonged intraventricular treatment. Lack of efficacy of intraventricular MTX has been ascribed to compartmentalization and flow disturbances of the subarachnoid space *(59,60)*. However, cytotoxic levels of MTX can be found in CSF compartments with a partial block *(61)*.

Acute and subacute neurologic side effects of intraventricular MTX, including aseptic menigitis, myelopathy, and encephalopathy, are usually mild and transient (Table 3). On occasion, however, they are progressive and fatal. Slow but sustained absorption of MTX from the CSF into the plasma may lead to systemic side effects including myelosuppression and mucositis; the use of leucovorin protects against these complications. Late neurotoxicity consisting of leukoencephalopathy was reported only occasionally in early studies, but more recent studies report that this serious complication with progressive ataxia and dementia develops in as many as half of long-term survivors *(37,51)*. High peak levels of MTX, a high cumulative dose of MTX, and cranial RT are associated with an increased risk of leukoencephalopathy *(62,63)*. In this respect flow disturbances in the subarachnoid space may play a role *(59)*. Ara-C is the second most frequently used drug for intrathecal therapy.The usual dose is 50 mg twice a week, although in vitro analysis suggests that it should be given daily to maintain active concentrations *(125)*. Depo Ara-C given once per 2 wk results in continuously cytotoxic CSF concentration, but in LM from breast cancer its efficacy and toxicity still remain to be determined. Intrathecal Ara-C in combination with RT to the

**Table 3**
**Neurologic Complications of Intraventricular Methotrexate**

| | |
|---|---|
| Related to Ommaya reservoir | Bacterial meningitis |
| | Intracranial hemorrhage |
| | Subdural hematoma/hygroma |
| | Focal leukoencephalopathy due to CSF leakage along the reservoir |
| Related to Methotrexate +/– RT | Aseptic meningitis (transient) |
| | Seizures (very rare) |
| | Acute encephalomyelopathy (rare) |
| | Subacute encephalopathy (usually mild and transient) |
| | Optic neuropathy/radiculopathy |
| | Myelopathy |
| | Late leukoencephalopathy (progressive, 50% of long survivors) |

spinal cord is associated with serious myelopathy *(64)*. Efficacy and toxicity of the recently introduced 5-fluoro-2-deoxyuridine has to be studied more extensively *(65)*. Despite anecdotal reports of success, other investigational intrathecal therapies such as monoclonal antibodies (MAbs) conjugated with toxins or radioisotopes, and intraventricular immunotherapy have not yet been demonstrated to be effective in LM from breast cancer *(66,67)*.

Radiotherapy to the symptomatic area often results in stabilization and sometimes in improvement of neurologic deficit, but probably does not influence survival. Some authorities report a better outcome with the administration of RT to asymptomatic sites of macroscopic meningeal infiltration *(51)*. Radiotherapy to the site of CSF block as demonstrated on flow studies may restore CSF flow *(59,60)*. Radiotherapy to the complete neuraxis is not feasible in most patients because of effects on bone marrow and the requirement for a protracted treatment course in a disease with short median survival.

Studies of experimental LM have demonstrated that LM are well-vascularized with highly permeable blood vessels *(68,69)*. Contrast enhancement of LM on MRI scanning supports this observation. Penetration of chemotherapy from the CSF space into these tumors is only a few cell layers. Theoretically, therefore, these tumor deposits may be treated more effectively with intravenous chemotherapy than with drugs dissolved in CSF. Patients with LM treated with intraventricular chemotherapy seem to have a better neurological response and a longer survival when they also receive systemic chemotherapy *(37,51,57)*. A few nonrandomized studies showed that patients treated with systemic chemotherapy and involved field RT have the same response, median survival, and proportion of long-term survivors as patients treated with intraventricular chemotherapy combined with RT, without the serious neurotoxicity associated with intraventricular treatment (Fig. 3) *(37,70)*. In selected patients even hormonal therapy can induce a long-term response and survival in LM from breast cancer *(71)*. However, most of the patients who present with LM have previously received systemic therapy, which reduces the chance of a successful systemic treatment of LM.

In summary, the treatment results of LM in breast cancer are not better than 20 yr ago. However, the accumulating evidence showing that outcome and survival are not primarily dependent on intraventricular chemotherapy presumably will alter the management of patients with LM considerably. Intensive intraventricular chemotherapy, at least with currently available agents, will be applied less frequently and as a consequence debilitating neurotoxicity, it is hoped, will become a rare phenomenon. Meanwhile, new therapeutic approaches are urgently needed to improve the overall poor outcome and median survival of only 3 mo in breast cancer patients with LM.

**CRANIAL DURAL METASTASIS** Cranial dural metastasis includes metastases that involve either or both the epidural or subdural space. Epidural cranial metastasis usually occurs through direct extension from calvarial metastatic lesions, or occasionally hematogenously through the external carotid artery or the vertebral veins. Cranial epidural tumor often appears to spread over a much larger area than the adjacent osseous metastasis from which it originates. It may invade the cranial dura to cause a diffuse thickening of the dura, whereas it only rarely transgresses the dura to give rise to a subdural tumor. Subdural metastasis may also occur as a solitary lesion without adjacent epidural tumor (Fig. 4). It may develop in the falx cerebri where it must be differentiated from a meningioma. Subdural tumor may invade the adjacent leptomeninges to produce LM. Overall, dural and subdural metastasis constitute only a minor clinical problem because of rare symptomatic occurrence *(12)*. At autopsy, however, cranial dural metastasis can be found in 15% of patients who die of breast cancer *(11)*. Symptoms of cranial dural metastasis include contralateral weakness, signs of intracranial hypertension, and cranial nerve involvement (Fig. 5). Abrupt onset of focal neurological deficit and seizures suggest direct parenchymal invasion through perivascular spaces, hemorrhage, or venous sinus occlusion. MRI is the most accurate diagnostic method. Its advantages over CT scanning include multiplanar capability and identification of sinus occlusion. Symptomatic cranial dural or epidural metastasis is usually treated with RT, but in our experience systemic therapy as single treatment can also be successful. Occasionally surgical resection followed by RT is the treatment of choice for a large dural metastasis. As cranial dural metastasis is associated with bone metastasis, survival after treatment is usually better than in patients with parenchymal brain metastasis.

**SPINAL EPIDURAL METASTASIS** Spinal epidural metastasis (SEM) in breast cancer is considered of utmost clinical importance because of its high incidence and risk of

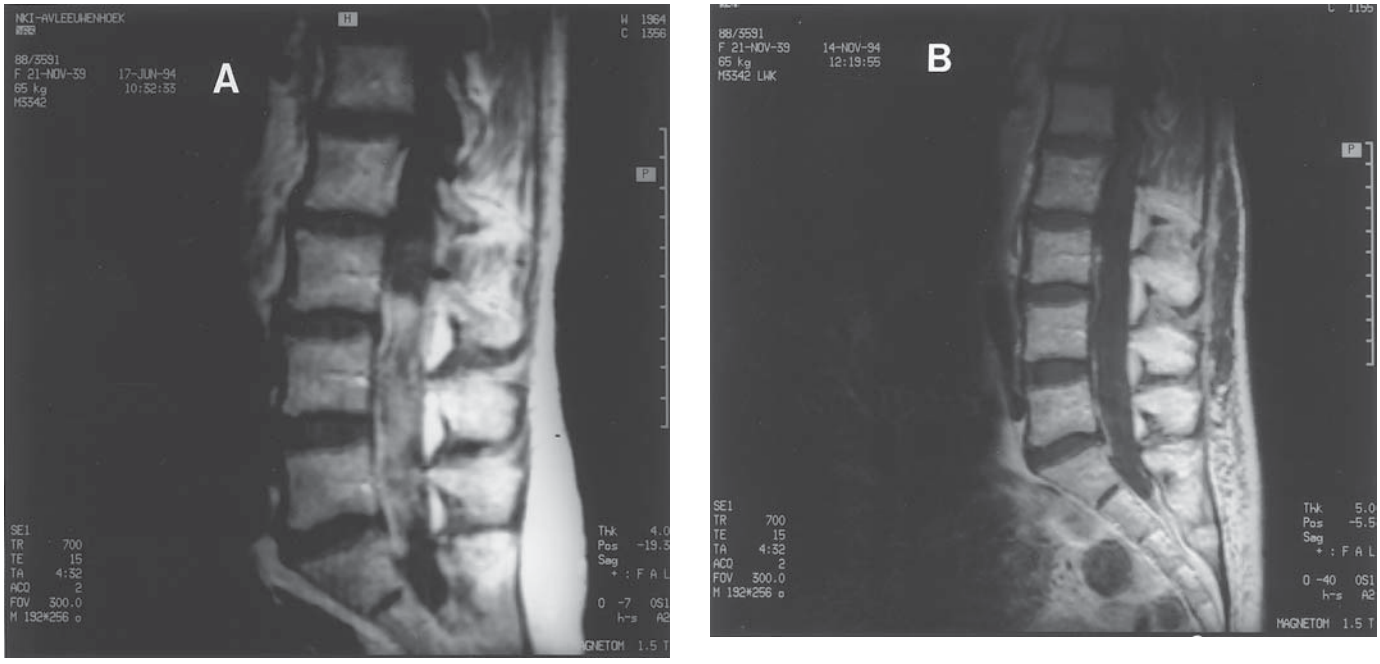


**Fig. 3.** Leptomeningeal metastasis; response to local RT and systemic chemotherapy. The pretreatment postcontrast T1, weighted MRI **(A)** shows that the lumbar subarachnoid space is filled with tumor with thickening of the nerve roots. After local RT and systemic CMF chemotherapy near-complete disappearance of intradural tumor **(B)**. The patient survived 48 mo with only slight residual neurological impairment without intrathecal treatment.

spinal-cord or cauda equina compression. In breast cancer SEM is usually caused by extension of a vertebral metastasis through the bony cortex into the extradural space. Vertebral bone marrow apparently is a suitable environment for tumor growth: 60% of patients with breast cancer develop vertebral metastases, predominantly in the posterior part of the vertebral bodies. The majority of SEM is found at the lower thoracic and lumbar level. Fewer than 10% develop in the cervical spine. SEM extends over one vertebra in half of the patients, over two vertebrae in a quarter, and over three or more vertebrae in another quarter *(72)*. Multiple SEM (MSEM) occur in at least 20% of patients suspected of SEM *(72,73)*. These MSEM are usually asymptomatic, but of course may influence the further course of disease. Asymptomatic SEM rarely occur in the cervical region, so it is recommended that at least the thoracic and lumbosacral spinal canal are imaged in patients suspected of SEM. Neurological symptoms of SEM are the result of direct compression of spinal roots and cord by tumor or bone fragments, and of changes in blood flow and vascular permeability in the spinal cord. Back pain at the site of the vertebral metastasis is nearly always the initial symptom *(74)*. Usually a few months later radicular signs develop due to epidural extension or vertebral collaps. The pain associated with SEM often increases with recumbency. Signs of myelopathy due to spinal cord compression develop an average of 1 mo after the first signs of radiculopathy, but may also develop rapidly or even may be the first manifestation of SEM. The risk of rapid development of paraplegia is great once signs of myelopathy are present. Physicians and patients should be familiar with early symptoms of myelopathy in order to institute adequate treatment promptly. The pretreatment ambulatory status is the critical prognostic factor for neurological outcome and thus for the quality of life. In contrast to SEM from other primaries *(73)*, the degree of spinal block and presence of MSEM are not prognostic for outcome *(72)*. In acute spinal cord injury as occurs with spinal instability the damage develops within hours in the center of the cord, with hemorrhage in the gray matter followed by decreased blood flow and necrosis. In chronic cord compression the damage is mainly in the lateral columns with relatively few changes in the gray matter. Thus, the rate of progression of myelopathy can be important for neurological outcome: occasionally functional recovery may occur after prolonged development of paraplegia, even if complete paralysis exists for more than 24 h *(126)*.

Plain films of the vertebral column are the first diagnostic procedure in patients suspected of SEM. A vertebral collaps of 50% or more carries a 50% risk of SEM *(76)*. However, more than 30–70% bony destruction is required before a plain spinal X-ray becomes abnormal. Consequently, normal plain films do not exclude SEM. Plain films did not accurately localize the site of epidural lesion in a third of patients with breast cancer. In addition, clinical data were not localizing in another third of SEM *(72)*. Thus, in patients suspected of SEM the entire spinal canal, or at least the thoracic and lumbar area should be imaged, preferably by MRI. If MRI is contraindicated, myelography or CT-scanning with intrathecal or bolus intravenous contrast are alternative techniques *(77)*. Myelography has the added advantage of CSF examination: in 9% of breast cancer patients who underwent myelography for SEM, CSF disclosed LM *(72)*.

The aim of treating SEM is to relieve pain, to maintain or restore neurological function and spinal stability, and to achieve local tumor control. Whether asymptomatic SEM should be

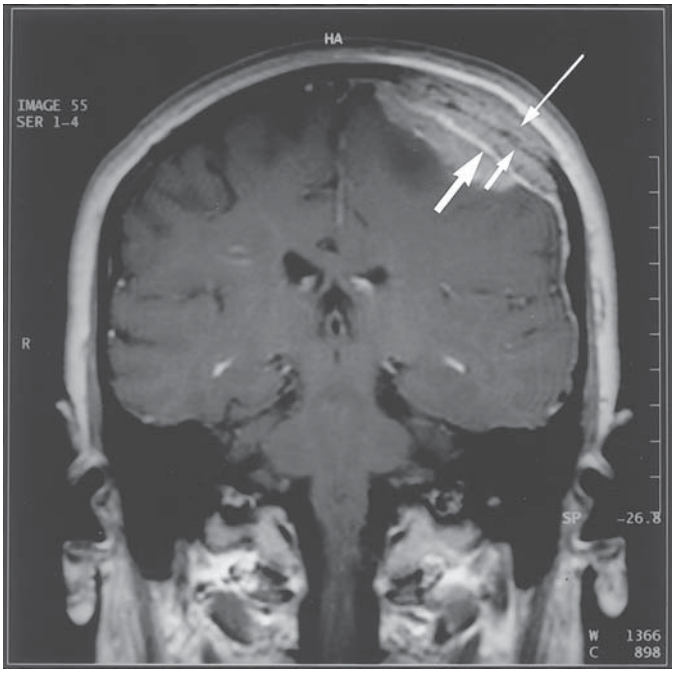


**Fig. 4.** Calvarial metastasis with epidural and subdural tumor. The postcontrast T1-weighted MRI shows contrast enhancement of the calvarial lesion and epidural as well as subdural tumor extension. Contrast enhanced dura, thick arrow. Tabula externa, thin arrow. Tabula interna, small arrow.

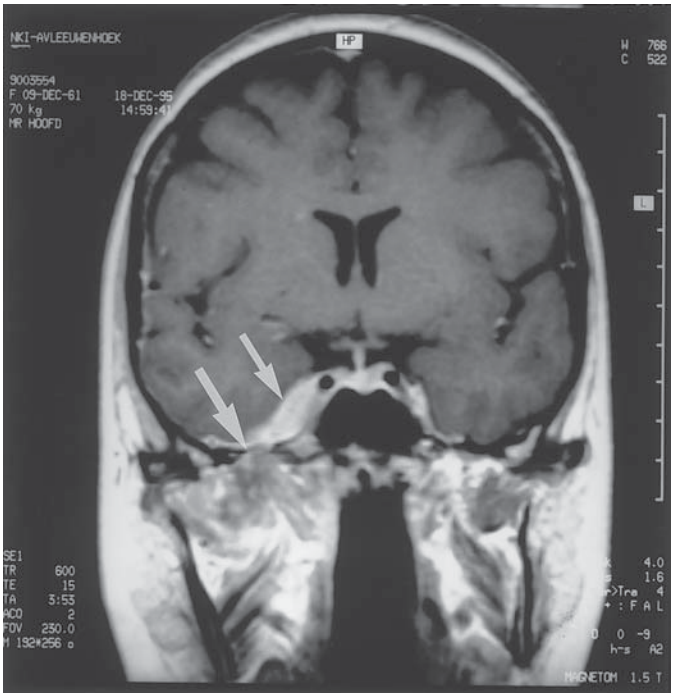


**Fig. 5.** Parasellar epidural metastasis (small arrow) extending through the foramen ovale (large arrow) into the lateral pterygoid muscle in a patient with pain and swelling of the right cheek.

treated is uncertain *(73,75)*. Compared to BM from breast cancer, SEM occurs in older patients and is related to bone metastases, implying some longer median survival. Median survival of SEM from breast cancer is 6–9 mo, and the 1 yr survival 40% *(72,78)*. Unsurprisingly, nonambulatory patients have a significantly worse prognosis *(72)*. Radiotherapy in combination with corticosteroids is the standard treatment of SEM. Corticosteroids are an important adjuvant treatment in the early stage *(79,80)*. Most patients experience dramatic relief of pain at the first day of steroid treatment, and neurological outcome is significantly better than without steroids *(80)*. Experimental studies showed a dose-dependent effect of Dexamethasone on the reduction of spinal cord edema *(81)*, so high dose Dexamethasone of 100 mg/d is recommended in patients with severe or rapidly progressive neurologic deficit. Usually, after an initial bolus of 10 mg Dexamethasone, 4 mg four times a day is given during the first 3–7 d and then tapered off over 1–2 wk. The chance of major side effects is small when it can be discontinued within 3 wk, even after doses of 100 mg during the first 3 d *(79,80)*. More than 90% of the ambulatory patients treated with RT for SEM from breast cancer remain ambulatory, whereas one-third of the paraparetic patients regain walking ability. Restoration of sphincter dysfunction is achieved in one-third of the patients. Usually RT ports are two vertebrae above and below SEM. Smaller RT fields were associated with increased risk of local recurrence *(82)*. Overall, recurrent SEM occurs in about 20% of patients, more often in long survivors: recurrent SEM occurs in a third of the patients surviving 6 mo, and in half of the patients surviving 2 yr *(83)*. About one-half of recurrent SEM develops at the same level as the previous SEM. Influence of total RT dose or fraction size on local tumor control of SEM has not been demonstrated.

Recurrent SEM is treated with RT, surgery, or systemic therapy. Re-irradiation carries only a small risk of radiation myelopathy, whereas half or more of the patients remain ambulatory after re-irradiation at 1 yr follow-up *(84)*. A third recurrence occurs in half of the patients with a second recurrence, most of whom will remain ambulatory after repeated and timely treatment, which confirms the importance of continuous neurological observation *(83)*. As MSEM occur as frequently in recurrent SEM as in initial SEM, imaging of as much of the spinal canal as possible is required also in recurrent SEM. Surgery is reserved for instability of the spine, bony compression of the spinal cord, serious clinical deterioration while on RT, and for recurrent EM in patients that have received the maximum tolerated dose of RT. Surgery should be performed at the site of the offending tumor. Since at least 85% of SEM invade the spinal canal anteriorly of the cord, an anterior approach including tumor and vertebral body resection and stabilization instrumentation will be the usual procedure. For this technique nonmetastatic adjacent vertebrae are required. Nonrandomized studies using this technique show prolonged clinical improvement in the vast majority of patients with a high proportion of nonambulatory patients regaining ability to walk *(85,86)*. However, vertebral resection is a major surgical procedure in patients with metastatic disease, with at least 5% postoperative mortality *(85,87)*.

Systemic therapy can be given adjuvantly to RT or surgery. As a single treatment it is generally considered inadequate

because it will take too long to induce tumor reduction. We used chemotherapy and hormonal therapy as primary treatment in a few patients with SEM, predominantly in recurrent SEM after RT, with rate and duration of response being comparable to RT results *(72,88)*. Thus, early recognition of (recurrent) SEM may permit successful treatment by systemic therapy.

**SKULL AND SKULL BASE METASTASIS** Metastasis to the skull usually is asymptomatic if it is confined to the pain-insensitive bone marrow. It may become palpable by expanding the tabula interna and externa. Pain occurs if the tumor breaks through the bony cortex. Rarely, skull metastasis may cause increased intracranial pressure or local infarction by compression of draining veins or sinus. Contrast enhanced MRI is superior to CT with bone window setting for detecting subtle intradiploic metastases. It is also the best technique for evaluation of the patency of the dural sinuses that are adjacent to calvarial lesions. Computer tomography is a sensitive method to identify lesions confined to the bone particularly when the metastasis is osteoblastic, whereas MRI is sensitive in identifying tumor growth along the nerve sheaths and into the extradural space. Occasionally, skull base metastasis is visible on technetium SPECT scan when both MRI and CT are negative *(89)*. Skull base metastasis is more likely than LM to cause cranial nerve involvement in patients without macroscopic intracranial lesions *(90)*. Cranial nerves V and VII are involved most frequently. Sporadically isolated cranial nerve involvement occurs without LM or adjacent bone metastasis. It is presumably caused by hematogenous spread and is predominantly found in cranial nerves II and V *(15)*. The numb chin syndrome, which is associated in particular with breast cancer and characterized by numbness restricted to the distribution of the mental nerve, is usually caused by bone metastasis in the mandible or at the base of the skull and less frequently by LM *(91)*. Improvement of cranial nerve involvement from skull base metastasis can be expected in at least half of the patients following local RT or systemic therapy. Improvement is more likely to occur in recently developed cranial nerve dysfunction.

**ORBITAL AND OCULAR METASTASIS** Breast cancer may metastasize both to bone and to soft tissue of the orbit. Orbital metastases develop an average of 5 yr after the diagnosis of the primary tumor. Presenting symptoms are proptosis, ptosis, pain, and diplopia. Orbital RT is the treatment of choice, but systemic treatment may also be successful. Orbital metastases are associated with bone metastases and as a consequence median survival of patients with orbital metastasis is relatively long, being about 1.5 yr. Ocular metastasis probably is associated with a less favorable prognosis than orbital metastasis *(92)*. The majority of choroidal metastases remain asymptomatic. Symptoms of choroidal metastasis include decreased visual acuity, metamorphopsia, diplopia, and less frequently pain, and photophobia. RT is the treatment of choice. Except in unusual cases of anteriorly located lesions, RT to the lens can be avoided. Improvement following RT is obtained in about 70% of the patients, although vision may deteriorate for a few weeks following RT because of subretinal fluid and retinal detachment. Response of choroidal metastasis following systemic therapy has been documented; if the patient can be carefully observed by an ophthalmologist and shows no progression, such treatment can also be adequate.

## TUMOR-INDUCED PLEXOPATHY

**Brachial Plexopathy** Despite the proximity of the draining lymph nodes of the breast, tumor involvement of the brachial plexus is relatively uncommon. Lymph node metastases most frequently develop in the axillary region, so the lower trunk (root level C8 and T1) is usually involved. Involvement of the upper plexus (root level C5 and C6) due to supraclavicular lymph node metastasis is less common. The clinical picture of tumor-induced and radiation-induced plexopathy may be similar, but usually the two conditions can be differentiated after a careful history and neurological examination. The most prominent clinical difference is the frequency and intensity of pain as initial symptom. In tumor-induced plexopathy pain is almost always the first and dominant symptom *(15)*. Initially it usually is located in and around the shoulder, irrespective of the site of plexus involvement. After a few weeks or months pain and paraesthesias radiate into the arm and hand, and motor signs develop corresponding to the site of plexus involvement. Medial extension of tumor along the lower trunk may induce a Horner's syndrome and subsequently may progress into the epidural space at the level of C7-T1 and T1-T2.

Physical examination often reveals a palpable mass in the axilla or in the supraclavicular fossa. Compression of the subclavian vein may cause an increased venous pattern around the shoulder. Lymphedema of the arm sometimes occurs when tumor infiltrates in a previously irradiated brachial plexus. Imaging of the brachial plexus including the paraspinal and epidural space by CT scan or MRI scan is required to determine the cause and the extension of the lesion. A CT scan should preferably include both the symptomatic and asymptomatic plexus for comparison. A CT scan reveals soft-tissue density changes in the brachial plexus and paraspinal extension of the tumor. Limitations of CT, in comparison with MRI are only a single imaging plane, artifacts from bone, and inaccuracy to distinguish vascular structures from nervous tissue. In addition, MRI is superior in imaging the epidural space. Tumor is best demonstrated on T1-weighted images. With early enhancement after bolus intravenous contrast tumor can be differentiated from radiation fibrosis *(93)*. Loss of fat planes and local increased signal on T2-weighted images are not helpful in differentiating tumor from radiation injury. Overall MRI diagnoses the nature of the plexus lesion correctly in more than 80% *(94)*. In a selected group of 16 patients with tumor plexopathy MRI was not diagnostic in 2 of the 16 patients, and CT in 6 of the 16 patients. Theoretically PET scanning may be a useful technique to differentiate between local tumor and a radiation lesion, but until now PET scanning has appeared less accurate than MRI in defining the nature of the lesion. Particularly in diffusely infiltrating tumor, imaging techniques may be inconclusive. In these instances, electrophysiologic studies, close follow-up, or eventually surgical exploration may be required. There are no electrophysiological features pathognomonic for tumor induced plexopathy. Motor or sensory nerve conduction abnormalities are found in the majority of patients but do not differentiate between tumor-induced and radiation-induced

plexopathy. Similarly, needle examination may reveal fibrillation potentials and fasciculations in both conditions. Myokymic discharges (pseudomyotonia) occur in about half of the patients with radiation-induced plexopathy and only very rarely in tumor-induced plexopathy, and represent the only electrophysiologic finding possibly useful in distinguishing the two conditions *(95,96)*. Occasionally the clinical picture, imaging studies, and electrophysiologic studies cannot define the nature of the plexus lesion. The differential diagnosis includes also idiopathic neuralgic amyotrophy and ischemic brachial plexopathy. Ischemic brachial plexopathy results from a radiation-induced thrombotic occlusion of the subclavian artery *(97)*. The clinical picture of acute paresis and paresthesias with absence of peripheral arterial pulsations and signs of ischemia is usually well-distinguishable from the other causes of plexopathy. Idiopathic plexus amyotrophy is characterized by acute and severe pain over the shoulder. After 1 or 2 wk paresis develops, particularly in the muscles of the shoulder girdle, and pain subsides spontaneously. Paresis recovers gradually and usually completely within a few weeks or months.

Dependent on the severity of pain and neurological deficit, the actual tumor state and the therapeutic possibilities in case of local tumor, close clinical follow-up or occasionally surgical exploration might be considered. However, a negative exploration does not reliably exclude tumor. Moreover, a clearly beneficial effect of resection of metastatic tumor infiltrating the brachial plexus may not be expected. Therefore, surgery should be considered only rarely and predominantly to differentiate between metastatic and primary or radiation-induced tumor; the 10-yr actuarial risk of radiation-induced sarcoma is estimated to be 0.8%.

Treatment of tumor-induced plexopathy consists of control of tumor and relief of pain. In unirradiated patients RT is the treatment of choice. Local tumor control and pain relief is achieved in about 50–75% of the patients. In previously irradiated patients surgery, systemic chemotherapy or hormonal therapy will offer the only chance for tumor control, but this will be achieved only in a minority of the patients. Prompt and adequate treatment of pain is essential, also to prevent the development of a chronic pain syndrome and pain-induced dysfunction including frozen shoulder and dystrophy of the arm. Corticosteroids are required in epidural tumor, but in our experience are also of some benefit in tumor-induced brachial plexopathy.

**Lumbosacral Plexopathy** Tumor involvement of the lumbosacral plexus in patients with breast cancer is caused by extension from bone metastases, particularly of the sacral bone. It usually starts with asymmetrical low back pain, radiating into the buttock and the posterior aspect of one leg. Pain often increases with recumbency. Bilateral radiating pain with incontinence indicates epidural tumor extension into the sacral spinal canal. At neurological examination pure sacral plexopathy often can be distinguished from leptomeningeal metastasis and epidural metastasis by absence of radicular signs and normal or only slightly abnormal motor, sensory and bladder function. The diagnosis is confirmed by CT or MRI scan of the sacral area. MRI is superior to CT in demonstrating epidural extension of tumor. Local RT is the treatment of choice.

## NONMETASTATIC COMPLICATIONS

### PARANEOPLASTIC NEUROLOGIC DISORDERS

Paraneoplastic neurological disorders (PND) are very rare in patients with breast cancer. Presumably these disorders arise when the primary tumor expresses antigens that are normally found only in neural tissue (onconeural antigens). The pathogenesis of PND is attributed to the immune response elicited by the tumor antigens, which is also directed to the parts of the nervous system that share the same antigen *(15,98)*. This explains why the tumor status associated with PND is usually limited; often the neurological signs precede the diagnosis of the primary tumor. Antibodies against discrete onconeural antigens are found in serum and CSF in a number of patients with PND, but with the exception of the antibodies in Lambert-Eaton myasthenic syndrome (LEMS) in patients with small cell lung cancer, these antibodies do not appear to be pathogenic. In breast cancer patients a few distinct clinico-pathological paraneoplastic syndromes are recognized.

Paraneoplastic cerebellar degeneration (PCD) is the most common syndrome, with an estimated incidence of one in 3000 patients. The cerebellar disease is usually subacute in onset and stabilizes after a couple of weeks. Dysarthria and truncal ataxia are prominent. Most patients are unable to walk, write, or read because of diplopia or oscillopsia. Once stabilized, the illness does not change despite possibly successful treatment of the primary tumor. Histopathology shows loss of Purkinje cells with diffuse lymphocytic infiltration. Specific antibodies against cytoplasmic Purkinje cell antigens (Anti-Yo) are found in serum and CSF of a substantial proportion of patients with PCD, but therapy directed against antibody activity does not affect the course of the disease *(99)*. Cytotoxic T lymphocytes reactive with the onconeural antigen were demonstrated in blood and CSF of patients with PCD, indicating that a T cell-mediated autoimmune response probably is responsible for the Purkinje cell degeneration. Tacrolimus, whose effect is directed against activated T cells, might be effective provided that it is given in the very early stage of disease *(100)*. The differential diagnosis of PCD includes metastasis in the posterior fossa, Wernicke disease, infectious or postviral encephalitis, multiple sclerosis (MS), and spinocerebellar atrophy. Additionally, the paraneoplastic opsoclonus myoclonus syndrome (OMS) may somewhat resemble PCD. Saccadic eye movements and opsoclonus are often associated with truncal ataxia, dysarthria, and vertigo. Symptoms of OMS may fluctuate spontaneously or react to cancer treatment, and sometimes respond to treatment with steroids or benzodiazepines, suggesting a functional rather than structural neural damage *(101,102)*. MRI is normal, and CSF is normal or may show some pleocytosis. OMS in breast cancer patients is associated with antibodies (anti-Ri) that react with virtually all neuronal nuclei of CNS. Cerebellar and brainstem dysfunction without opsoclonus do not rule out the possibility of anti-Ri associated paraneoplastic disorder *(101)*.

Stiff-man syndrome is a very rare paraneoplastic disorder described in a few patients with breast cancer. It is characterized by axial rigidity with painful spasms that responds to intravenous benzodiazepines and disappears during sleep. Anti-amphiphysin antibodies have been identified in the serum of

these patients *(98)*. These antibodies react with synapses of CNS neurons.

Paraneoplastic sensory neuropathy (PSN) predominantly occurs in patients with small cell lung cancer, but sometimes is associated with breast cancer. Histopathology shows degeneration of the dorsal root ganglion neurons with perivascular inflammatory infiltrates. Symptoms are painful paresthesias and numbness in arms or legs of asymmetric distribution. Cranial nerves may be involved leading to facial numbness, loss of taste, or deafness. Patients may become wheelchair-bound because of sensory ataxia, although the course of disease in breast cancer often appears less severe than in patients with small cell lung cancer. Anti-Hu antibodies may be found in patients with PSN, both in serum and in CSF. Electrophysiologic studies show decreased or absent sensory potentials and markedly decreased sensory conduction velocity, while motor nerve conduction is usually normal. The differential diagnosis includes chemotherapy-induced sensory neuropathy (taxoids), pyridoxine intoxication, and immune mediated sensory neuropathy, particularly Sjögren's syndrome. Patients with Sjögren's syndrome do not harbor anti-Hu antibodies unless they also have cancer and PSN.

Polymyositis (PM) and dermatomyositis (DM) are inflammatory, probably immune-mediated muscle diseases that may occur more frequently in patients with breast cancer *(15)*. Patients usually present with proximal muscular weakness. Muscle tenderness is somewhat less common. Symptoms often precede identification of tumor. There is no absolutely diagnostic laboratory test. ESR and creatinine kinase are usually elevated but may be normal. EMG changes include spontaneous fibrillation and polyphasic activity. Treatment consists of steroids and other immunosuppressants.

**CEREBROVASCULAR COMPLICATIONS** Patients with breast cancer appear to have some increased risk of cerebrovascular complications *(103)*. A number of factors have been implicated as possible etiologic mechanism. These include a tumor-related hypercoagulable state, nonbacterial thrombotic endocarditis, consumptive coagulopathy, and tumor-related thrombocytopenia. In addition, chemotherapy may be associated with an increased risk of thromboembolic complications *(104)*. Protein C and protein S deficiency have been found during CMF chemotherapy *(105)*. Other possible risk factors for stroke during chemotherapy are hypovolemia due to vomiting and a hypercoagulable state because of release of procoagulant tissue factors derived from tumor cells, or because of injury of endothelial cells. Deficiency of protein C and antithrombin III has been described in patients receiving tamoxifen. On the other hand, use of tamoxifen is associated with a decrease of LDL cholesterol. A clear increase in risk of stroke is not observed in patients receiving tamoxifen *(106)*. Overall, some increase of stroke is observed in patients with breast cancer, often occurring during chemotherapy, however with a total incidence of less than 1%. There are no laboratory tests specific for the hypercoagulable state in these patients. Treatment of these thrombotic events is the same as in patients without cancer.

Intracranial hemorrhages are rare in patients with breast cancer, despite the high incidence of BM and occurrence of tumor or treatment-related thrombocytopenia. Hemorrhages into cerebral metastases occur in fewer than 1% of patients with BM. Bleeding is usually from veins or small arterioles and often superficial. The prognosis for immediate survival and functional recovery is usually better than in hypertensive cerebral hemorrhage. In general, management and outcome of hemorrhagic brain metastases is the same as in nonhemorrhagic brain metastases. Subdural hematoma is usually caused by bleeding into a dural metastasis or by rupture of small vessels due to venous obstruction caused by dural tumor, with or without cancer-induced coagulopathy *(103)*. Occasionally, insertion of an Ommaya reservoir for the treatment of LM is complicated by a subdural hematoma or hygroma. Subdural hematoma may be asymptomatic and an incidental finding on CT or MRI brain or at autopsy. Asymptomatic or small subdural hematomas or hygromas may be treated conservatively. Progressive lesions will require surgical evacuation and, in case of (sub)dural tumor, RT to prevent recurrence. Sinus thrombosis is a rare complication in patients with breast cancer, occurring when a metastatic tumor compresses the sinus. Treatment-induced protein C or protein S deficiency is apparently not associated with an increased risk of sinus thrombosis.

**INFECTION** Infections of the nervous system are uncommon in patients with breast cancer. Patients who are immunocompromised from chemotherapy or chronic use of corticosteroids are accordingly susceptible to the usual microorganisms. About 5–10% of the patients treated for leptomeningeal metastasis with intraventricular chemotherapy develop infectious meningitis *(37,50)*. Staphylococcus epidermidis usually is the infecting organism. With appropriate intravenous and intraventricular antibiotics the Ommaya reservoir can be preserved in the majority of cases. Infectious meningitis may run a fulminant and fatal course, particularly in patients receiving corticosteroids.

**METABOLIC DISORDERS** Metabolic CNS dysfunction is a common complication in patients with cancer. In a survey of neurological complications in patients referred to the Memorial Sloan-Kettering Cancer Center, more than 10% of patients had an admitting diagnosis of metabolic encephalopathy. In 61% of these patients metabolic or drug-related encephalopathy was the cause of mental disturbance *(107)*. The most common causes are use of opioids, sepsis, and electrolyte imbalance. Often the clinical picture results from multiple systemic factors. Both overdose and withdrawal of drugs can cause a confusional state or delirium. An adrenal crisis with decreased consciousness may be the result of withdrawal after prolonged use of steroids.

Attention deficit usually is the first symptom of metabolic encephalopathy. The clinical picture is further dominated by confusion and decreased consciousness, or delirium. Sometimes motor signs, like asterixis and myoclonus, and focal or generalized convulsions occur. Hypercalcemia probably is the most important cause of metabolic encephalopathy in breast cancer patients, usually associated with extensive bone metastasis. It can also cause proximal weakness and diminished reflexes. Prompt diagnosis of metabolic encephalopathy is important because the often serious clinical dysfunction is usually reversible if the cause is treated adequately.

## NEUROLOGIC COMPLICATIONS OF TREATMENT

### NEUROLOGIC COMPLICATIONS OF CYTOSTATIC DRUGS

**Central Nervous System Toxicity** Systemic chemotherapy regimens as employed in patients with breast cancer are not associated with specific acute complications of the CNS. Mild long-term CNS toxicity consisting of some cognitive impairment was observed in breast cancer patients treated adjuvantly with high-dose chemotherapy *(108)*, and also after standard CMF *(109)*. Severe chemotherapy induced toxicity of the CNS in breast cancer patients is predominantly observed after intrathecal (IT) chemotherapy, usually administered via an Ommaya reservoir. Use of IT MTX can be complicated by acute, subacute, and late neurotoxicity *(110)* (Table 3). Acute aseptic meningitis may develop within a few hours or days after IT MTX. Symptoms are usually mild and self-limiting if treatment is discontinued. Rarely, and sometimes concurrent with MTX meningitis the patient may develop transient or progressive encephalopathy or myelopathy. Rapidly fatal cases have been considered idiosyncratic, but in patients with a subacute course axonal swelling and demyelination were found, similar to the findings in late leukoencephalopathy. Spinal roots and cranial nerves may be involved *(111)*. Mild and transient subacute encephalopathy seems related to development of late and progressive leukoencephalopathy *(63)*. Leukoencephalopathy is the most important late neurologic complication of IT MTX. It usually occurs after combined treatment of cranial RT and IT MTX, but it may also develop after IT MTX alone *(62,63)*. The first symptoms of subcortical dementia and ataxia usually are noted between 4 and 6 mo after IT MTX. Recovery is observed only very rarely. The beneficial effect of leukovorin is uncertain. The risk of leukoencephalopathy is related to the dose of WBRT, the cumulative dose of MTX, and the presence of CSF flow disturbances. Histopathology shows foci of demyelination and coagulation necrosis, axonal swelling, and relative absence of inflammatory reaction. The pathogenesis of these changes is still unknown. Damage to endothelial cells, oligodendrocytes, and microglia, but also primarily to the neuron itself, have been postulated. Myelopathy has also been observed following IT Ara-C and IT Thiotepa. The combination of spinal RT and previous IT MTX administration increases the risk of Ara-C myelopathy, which is clinically and histopathologically indistinguishable from MTX myelopathy *(64)*. The combination of IT Ara-C and cranial RT may be complicated by optic neuropathy *(112)*.

Hormonal agents are very rarely associated with neurotoxicity. Optic neuropathy, retinopathy, and reversible encephalopathy have been reported following Tamoxifen *(110,113)*.

**Peripheral Neuropathy** The taxoids (paclitaxel and docetaxel) are the cytostatic drugs that cause peripheral neuropathy in breast cancer patients. These agents interact with microtubule activity and so affect axoplasmic transport. Paclitaxel induces a predominantly sensory, symmetrically distributed distal polyneuropathy. Paresthesias, numbness, and sometimes pain in feet and hands are early symptoms. Myalgia and arthralgia are transient disabling symptoms, especially occurring with high doses. Neurotoxicity is uncommon at doses below 200 mg/m$^2$ per course until a cumulative dose of about 1500 mg/m$^2$ is administered. In diabetics, neurotoxicity may be dose-limiting at 175 mg/m$^2$ *(114)*. Motor signs are mild; some weakness may develop at doses of 250 mg/m$^2$. Optic nerve toxicity causing transient scotomas has been reported at doses between 175 and 225 mg/m$^2$ *(115)*. Paclitaxel neuropathy is at least partly reversible. Agents to prevent this toxicity have not been successful.

Neuropathy due to docetaxel is usually mild, with acral paresthesias and numbness, and occasionally with Lhermitte's sign *(116)*. Symptoms may become seriously disabling with cumulative doses of more than 600 mg/m$^2$. Predominantly proximal motor weakness has also been reported *(117)*. Taxoid-induced neuropathy may deteriorate the first weeks after cessation of treatment.

### NEUROLOGIC COMPLICATIONS OF RADIOTHERAPY

Serious neurologic complications of RT are uncommon in patients with breast cancer. Occasionally WBRT is followed within 2 mo by somnolence, anorexia, and irritability. This early delayed reaction is attributed to damage of the oligodendrocytes *(118)*. CT or MRI may show some increased subcortical hypodensity. Usually, this syndrome recovers completely within a few weeks or months. Late reactions are caused by vascular injury in combination with demyelination and usually, but not always, are irreversible. They may develop with conventional RT schemes. Symptoms range from some neuropsychological impairment to severe dementia and brain herniation. Pathological changes include atrophy, hydrocephalus, leukoencephalopathy, and focal necrosis, not necessarily at the site of the irradiated BM and not always restricted to the white matter. These complications, occurring a median of 12 mo after WBRT, are rare in our experience, although one study estimated their occurrence in almost 20% of long survivors treated with conventional RT *(127)*.

Transient paresthesias and Lhermitte's sign may develop a few months after RT that included the spinal cord. It is attributed to RT induced demyelination of the posterior columns. Late RT myelopathy is irreversible and progresses to a complete paraplegia in half of the patients. Vascular injury is the pathogenic factor, initially affecting the posterior columns. Because paraplegia is such a debilitating complication, the threshold of tolerance is usually set at a low dose level of 50 Gy in 2.0 Gy fractions or 33 Gy in 3.0 Gy fractions. Clinical practice shows that re-irradiation of the spinal column for recurrent EM, with a cumulative dose well above this threshold is only rarely complicated by radiation myelopathy *(84)*. Moreover, the average interval of 5–6 mo to onset of RT myelopathy after re-irradiation should be weighed against the expected survival of the patient with recurrent EM.

Brachial plexopathy is a well-known complication of radiation therapy in breast cancer patients. Two distinct entities are identified: an early, transient, and usually mild plexopathy, and the more common delayed and often progressive plexopathy.

Early and transient plexopathy has been reported in only two series of patients *(119,120)*. Symptoms usually are mild and consist of paresthesias, mild shoulder and axilla pain. Weakness occurred in about half of the patients. Symptoms develop a few months after radiation therapy and usually resolve com-

pletely within 1 yr. The incidence of this mild and reversible plexopathy was 1% and 1.4% in the two series. No definite relationship was found with RT dose. Concurrent chemotherapy might be a contributing factor *(120)*. Occasionally such early and reversible plexopathy has a more serious and prolonged course. The pathogenesis of this apparently distinct syndrome of transient plexopathy is unclear.

Classic radiation-induced brachial plexopathy is caused by perineural fibrosis. Epineural vessel wall thickening occurs that may eventually result in vascular occlusion. Surgical dissection contributes to the extent of fibrosis and microvascular damage. The development of plexus fibrosis and its course are related to the total dose of RT and fraction size. Stoll in 1966 reported an incidence of plexus injury in 73% of the patients who had received a total dose of 56.7 Gy in large fractions of 4.7 Gy *(121)*. The fraction size appears the crucial factor. In a randomized study with 45 Gy in 15 fractions vs 54 Gy in 30 fractions the incidence of radiation-induced brachial plexus injury was 5.9 and 1.0%, respectively *(122)*. Obviously overlap of radiation fields will increase the risk of plexus injury. In a retrospective analysis adjuvant chemotherapy and younger age (premenopausal) harbored an increased risk of plexopathy *(123)*. Clinical symptoms usually occur 1–4 yr from RT, but may vary from a few months to >15 yr. Paresthesias are the presenting symptom in the vast majority of patients. Pain, usually described as dull and mildly disabling, is an initial symptom in a quarter of the patients. Gradually weakness develops. The predominant level of clinical involvement is the upper trunk or the entire plexus in most of the patients *(123)*. It has been suggested that the clavicle may spare the lower plexus to some extent to radiation injury. Horner's syndrome is extremely rare in radiation injury of the plexus. Lymphedema of the arm is found in a substantial proportion of patients, but it probably does not influence the further course of disease. The natural history is highly variable; weakness may stabilize or increase to complete paralysis. Occurrence of severe pain is uncommon and should lead to further investigation for recurrent tumor. In addition to the patient's history and neurological examination CT or MRI scan should be performed to differentiate between tumor-induced and radiation-induced plexopathy. Myokymic discharges on EMG are highly suggestive of radiation-induced plexopathy *(95,96)*. There is no treatment that can reverse the neurologic damage. Surgery may be associated with worsening of fibrosis and vascular damage. The effect of anticoagulants or antiplatelet drugs has not been investigated. Treatment consists of measurements to manage subluxation of the shoulder and lymphedema of the arm and physical therapy to try to improve or maintain residual strength.

**NEUROLOGIC COMPLICATIONS OF SURGERY** Axillary lymph node dissection may be complicated by a chronic deafferentiation pain due to a lesion of the intercostobrachial nerve *(124)*. Pain usually develops days or weeks after surgery with disturbed sensation of the lateral chest wall, in the axilla, and over the inner area of the upper arm. Shoulder movement increases the pain, and frozen shoulder can develop. Tricyclic antidepressants, carbamazepine, or topical lidocaine or capsaicin are the recommended treatments but usually are only moderately effective. Neuro-ablative techniques are not effective in deafferentiation pain, and may lead to increase of pain distributed over a larger skin area.

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# 22 Neurologic Complications of Genitourinary Malignancies

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## INTRODUCTION

Tumors of the genitourinary system (including the prostate, kidneys, bladder, and testicles) account for almost one-fourth of internal malignancies. Tumors specific to the female genitourinary tract are discussed in Chapter 27. Tumors of these organs are associated with disparate neurologic manifestations. For example, prostate cancer produces most of its neurologic morbidity through its propensity for bony metastasis, whereas renal cell carcinoma and testicular germ cell tumors frequently metastasize to brain parenchyma. These tumors additionally span a wide range of treatment responsiveness that impacts on neurologic as well as on overall prognosis. In this chapter, we will provide an overview of the neurologic complications associated with each of these tumors, emphasizing the syndromes commonly seen.

## PROSTATE CANCER

Adenocarcinoma of the prostate is the most common internal malignancy in men, with approx 198,000 new diagnoses and 31,500 fatalities each year in the United States *(1)*. Although prostate cancer can spread by direct extension and via lymphatics to pelvic lymph nodes, hematogenous spread is responsible for most neurologic morbidity. Metastases to bone are so common that radionuclide bone scan is routinely performed in newly diagnosed patients with prostate-specific antigen (PSA) > 10 *(2)*.

The risk of prostate cancer is strongly tied to age. The risk of developing invasive prostate cancer between the ages of 40 and 59 is 1 in 103, and between 60 and 69 1 in 8 *(3)*. Most patients with advanced prostate cancer ultimately die from or experience substantial morbidity from their disease *(4)*. Management strategies must weigh treatment morbidity heavily. Treatment options for localized prostate cancer include radical prostatectomy, external beam radiotherapy, brachytherapy, or observation. Management of locally recurrent or metastatic disease generally starts with androgen deprivation either through pharmacologic means or surgical means via bilateral orchiectomy. Pharmacologic approaches include gonadotropin-releasing hormone (GnRH) analogs such as leuprolide and goserelin acetate, nonsteroidal antiandrogens like flutamide, bicalutamide, or nilutamide, and estrogens like diethylstilboestrol. Prostate cancer is usually radiosensitive, and thus radiotherapy is often utilized for palliation of symptomatic metastases. Systemic cytotoxic chemotherapy does not appear to improve survival, although agents such as mitoxantrone and glucocorticoids lower PSA, diminish pain, and improve quality of life.

Most of the time, prostate cancer produces neurologic complications from its proclivity to metastasize to bones. Spinal cord compression is the most common reason for neurologic consultation. Prostate cancer is also a relatively common cause of metastasis to the skull base, producing cranial neuropathies. Other complications such as brain and leptomeningeal metastasis and paraneoplastic syndromes are unusual.

**EPIDURAL SPINAL CORD COMPRESSION** Epidural spinal cord compression (ESCC) is the most common neurologic complication in patients with prostate cancer and is associated with significant morbidity. ESCC tends to occur in patients with advanced stage disease and poorly differentiated tumors. Prostate cancer accounts for approx 15–20% of all cases of ESCC and is the second most common cause of cord compression in men after lung cancer. In older series, ESCC affected up to 7% of patients with prostate cancer and was the presenting symptom in 10–25% of these patients. The introduction of screening tests such as PSA has resulted in patients being diagnosed increasingly at an earlier stage, and it is likely that a lower percentage of patients with prostate cancer develop ESCC. Nonetheless, ESCC remains a common problem in patients with prostate cancer. It is important to have a high index of suspicion since ESCC is treatable when diagnosed early but is associated with a poor outcome once neurologic function is affected. A recent study utilizing total spine MR

From: *Cancer Neurology in Clinical Practice* (D. Schiff and P. Y. Wen, eds.), © Humana Press Inc., Totowa, NJ.

imaging to screen patients with prostate cancer and known bone metastases without neurologic deficits found that 32% of patients had epidural metastases. Extensive disease on bone scan (≥20 metastases) and increasing length of time on continuous hormonal therapy were significant risk factors for epidural disease. Back pain was present slightly more often in patients with ESCC than in those without but was not a reliable discriminator. If the screening MR scan was negative for ESCC, the risk of developing ESCC in the subsequent year was only 3%; by 2 yr this figure increased to 14%. The authors concluded that even in the absence of symptoms a screening magnetic resonance (MR) scan should be considered in patients with >20 discrete bone metastases on bone scan *(5)*.

The pathophysiology, symptoms, signs, and work-up of suspected ESCC in prostate cancer do not differ from ESCC in general (discussed in Chapter 9).

For most patients with prostate cancer, fractionated external beam radiotherapy is the treatment of choice for ESCC. No dose-fractionation schema has proven superior to others. Most patients receive 2500–4000 cGy in 10–20 fractions over 2–4 wk, with 3000 cGy in 10 fractions being a particularly popular regimen. For prostate cancer patients with poor performance status and a short life expectancy, a radiotherapy regimen of two fractions of 800 cGy given 1 wk apart apparently produces comparable outcomes to more conventional fractionation schedules *(6)*. As prostate cancer is generally radiosensitive, patients with ESCC from prostate cancer have a higher chance of regaining neurologic function than do patients with other primary tumors.

There are several anecdotal reports of ESCC from prostate cancer responding to hormonal manipulation alone *(7–10)*. Hormonal therapy for prostate cancer is arguably the most effective therapy for any adult epithelial cancer except germ cell tumors. Response rates are ≥90% with median duration of response 2–3 yr. Thus, for previously untreated patients androgen deprivation is an absolutely required part of the therapy of ESCC. GnRH analogs alone are to be avoided because of the possibility of bony flares. Hormonal manipulation may also have a role the treatment of ESCC in combination with other therapies *(11)*. In one study, 37 men with prostate cancer and ESCC were treated with laminectomies. Fifteen of these men were also treated with hormonal manipulation. Of these patients, 80% were ambulatory following therapy compared to only 42% of historical controls who had received prior hormonal therapy and were treated only with surgery *(11,12)*. Unfortunately, 57–82% of prostate cancer patients who develop ESCC have already had prior hormonal therapy *(11–14)*, limiting the usefulness of this approach.

Bisphosphonates like clodronate and pamidronate are of proven benefit in reducing bone pain in patients with prostate cancer *(15,16)*, but they have not yet been shown to decrease the incidence of ESCC. Bisphosphonates block bone resorption by inhibiting osteoclast activity *(17)*.

The prognosis of prostate cancer patients with ESCC is generally poor with a median survival of approx 4-9 mo and 13–25% 2-yr survival *(14,18,19)*. The poor prognosis derives from the fact that most patients have androgen-independent prostate cancer when they develop ESCC. The prognosis is significantly better for those patients with no prior hormone therapy (median survival of 16–21 mo) *(14,19)*. Other favorable prognostic factors include a single level of compression and a young age (<65 yr) *(19)*. One study found that patients with poorly differentiated tumors had a worse prognosis but another study could not confirm this association *(18,20)*.

**CALVARIAL METASTASES** Prostate metastases reach the skull either through arterial hematogenous spread or via Batson's venous plexus. Calvarial metastases are common and usually asymptomatic, although they may occasionally cause pain or present as a palpable mass. Less often they may compress the underlying brain and produce neurologic symptoms. Rarely, calvarial metastases may compress the sagittal or lateral sinus *(21)*. This may lead to increased intracranial pressure with headaches and papilledema. Occasionally, the sinuses become occluded and venous infarction of the brain results with headaches, seizures, and focal neurologic deficits. There has been a report of a patient with prostate cancer and venous sinus thrombosis who subsequently developed dural arteriovenous malformations *(22)*. Asymptomatic calvarial metastases may not require treatment. Symptomatic lesions usually respond to radiotherapy; however, surgery may occasionally be necessary to remove a large lesion, especially if it is compressing the underlying brain. Metastases to the orbit produces pain behind the eye or supraorbital or periorbital pain. The pain is dull and constant and worse with eye movement or when the patient lies down. Proptosis, visual loss and disorders, or cranial nerves II, IV, V1, V2, and VI may occur.Treatment usually consists of fractionated radiotherapy. Metastases to the dura or leptomeninges may affect the mandibular division of the trigeminal nerve in the foramen ovale and result in numbness over the ipsilateral chin ("numb chin syndrome"). However, this syndrome is more commonly caused by metastases to the jaw involving the mental or inferior alveolar branch of the mandibular nerve ("mental neuropathy"). There may be associated pain and swelling, but painless involvement of the mental nerve can also occur. Plain X-rays or bone scans may be helpful in making the diagnosis, but often these tests are negative.

**INTRACRANIAL METASTASES** Intracranial metastases, including dural, leptomeningeal, and parenchymal brain metastases, occur in fewer than 5% of patients with prostate cancer *(23–25)*. Many of these are asymptomatic and detected only at postmortem *(23)*. The majority of these intracranial metastases are located in the dura; metastases to the brain parenchyma are relatively uncommon *(25–29)*.

**DURAL METASTASES** Metastases to the dura usually arise either by direct extension from the adjacent skull or by hematogenous spread. Carcinoma of the prostate, together with lung and breast cancer, is one of the most common causes of dural metastases *(30,31)*. Dural metastases may act as a mass lesion, compressing the underlying brain, producing seizures, headaches, and focal neurologic deficits. The adjacent bone is usually involved. Involvement of the skull base and resulting cranial neuropathies are discussed in Chapter 8.

MR imaging is the most sensitive test for detecting dural metastases. Occasionally bone scans or CT scans with bone windows may help with skull-based lesions. Most patients can

be successfully treated with corticosteroids and standard external beam radiotherapy. Surgery is rarely feasible or necessary. For single isolated dural metastases or tumor that has recurred after standard external beam radiotherapy, stereotactic radiosurgery (SR) may have a role. In general, cranial neuropathies tend to respond poorly to treatment *(31,32)*. Treatment of symptoms within one month of onset and higher doses of radiotherapy (36 Gy) are associated with slightly better outcome *(31)*.

Rarely, a dural metastasis may cause symptoms by exuding fluid into the subdural space, producing a subdural hematoma or effusion *(33,34)*. Patients may be asymptomatic, but as the fluid or blood collection increases in size they usually experience headaches, lethargy, and focal neurologic deficits. Rarely, patients may present acutely as a result of the subdural hematoma *(33)*. The diagnosis of multiple dural metastases in a patient with metastatic prostate cancer is usually straightforward. However, it can be difficult to differentiate dural-based metastases from meningiomas if there are only one or two lesions.

**BRAIN METASTASES** Parenchymal brain metastases occur in fewer than 1% of patients with prostate cancer in most autopsy series *(25,27)*. The majority of these metastases are asymptomatic *(25)*. The management is similar to other brain metastases and includes corticosteroids, surgery for single or symptomatic lesions, and whole brain radiotherapy (WBRT). Radiosurgery may be useful for recurrent metastases, although this intervention is rarely required.

**LEPTOMENINGEAL METASTASES (CARCINOMATOUS MENINGITIS)** Leptomeningeal metastases from prostate cancer are extremely uncommon, with only a few reported cases *(35)*. The response to treatment is generally poor.

**PERIPHERAL NERVE DYSFUNCTION** Prostate cancer tends to metastasize to the spine and produce neurologic symptoms in the lower extremities by compressing the cauda equina or the lumbosacral nerve roots. Rarely, the tumor will infiltrate the lumbosacral plexus directly, producing pain, weakness and parasthesias in the legs *(36)*.

Patients with advanced cancer, including prostate cancer, are at risk of developing peroneal neuropathies, characterized by foot drop and numbness over the anterolateral aspect of the shin and the dorsum of the foot. This condition results from compression of the common peroneal nerve at the level of the fibular head. Predisposing factors include weight loss, prolonged bed rest, leg crossing, and chemotherapy. In general, the prognosis is good and the neuropathy improves in the majority of patients *(37)*.

**STROKE** The majority of strokes in patients with prostate cancer are due to atherosclerosis and are unrelated to the neoplasm *(38,39)*. However, some of these strokes may be caused by the hypercoagulable state present in many patients with metastatic prostate cancer. These patients may develop nonbacterial thrombotic endocarditis (NBTE) characterized by the formation of platelet-fibrin vegetations on heart valves. These vegetations can embolize to cerebral vessels of any size, typically producing focal deficits or less often an encephalopathy without focal features. Echocardiography will sometimes demonstrate the vegetations, but they are often small and undetectable. Some of these patients experience concomitant systemic venous thromboembolic disease. The absence of controlled studies makes treatment recommendations problematic. When feasible, treatment directed at the underlying tumor is indicated. Heparin has been of anecdotal benefit in NBTE.

Chronic disseminated intravascular coagulation (DIC) may co-exist with NBTE or can occur in its absence. Typically it produces an encephalopathy with little in the way of focal findings. Chronic DIC may be very difficult to diagnose, as the usual hematologic parameters such as prothrombin time, partial thromboplastin time, and platelet count (which are abnormal in acute DIC) are often normal; however, fibrin degradation products and D-dimer should be detectable. However, these laboratory abnormalities are often present in cancer patients without central nervous system (CNS) complications from DIC. As with NBTE, heparin has occasionally been of anecdotal benefit.

Rarely, prostate metastases to the dura will cause venous sinus thrombosis and hemorrhagic infarction of the brain *(33)*. In general, however, cerebral hemorrhage is very uncommon in patients with prostate cancer. As discussed earlier, metastases to the dura may result in subdural hematomas. Rarely, patients may present after hemorrhage into a cerebral metastasis *(40)*.

**PARANEOPLASTIC SYNDROMES** Paraneoplastic neurologic disorders are most commonly associated with small cell lung cancer. Nonetheless, they occasionally occur in conjunction with prostate cancer, and are probably most common in patients with a small cell component *(41)*. Hypercalcemia and a low PSA are also associated with small cell prostate cancer.

One of the most common paraneoplastic syndromes associated with prostate cancer is defined by the presence of an antibody that binds to neuronal nuclei in both the central and peripheral nervous system. This antibody is known as anti-Hu or anti-neuron nuclear antibody type I (ANNA-I). About 80% of patients with neurologic symptoms associated with the anti-Hu antibody have small cell lung cancer, but 2–3% have prostate cancer *(42)*. Neurologic manifestations of the anti-Hu syndrome may include sensory neuronopathy, limbic encephalitis, brainstem encephalitis, or myelitis. This entity is discussed extensively in Chapter 13.

Two patients have been reported with a unique paraneoplastic syndrome thus far exclusively associated with prostate carcinoma *(41)*. These patients developed loss of horizontal eye movements, facial and pharyngeal spasms, and mild gait unsteadiness. Although no antineuronal antibodies were detected, both patients had evidence of chronic brainstem inflammation on post mortem.

Prostate cancer is a rare cause of paraneoplastic cerebellar degeneration *(43)*. In one large series, 3 of 199 cases of cerebellar degeneration were associated with prostate cancer *(43)*. Cerebellar degeneration tends to occur with small cell prostate cancer and may be associated with the anti-Hu antibody, as discussed above *(44)*.

There have been rare reports of amyotrophic lateral sclerosis in patients with prostate cancer but it is likely that these associations are fortuitous *(45)*.

The Lambert-Eaton myasthenic syndrome (LEMS) is typically associated with small cell lung cancer but it has been reported with both adenocarcinoma *(46)* and small cell carcinoma of the prostate *(47)*.

Perhaps 10% of cases of inflammatory myopathies such as dermatomyositis and polymyositis are associated with systemic cancer. This association appears strongest with dermatomyositis and increases with age. There are case reports of both dermatomyositis and polymyositis associated with prostate cancer *(48–50)*.

Paraneoplastic retinal degeneration or cancer-associated retinopathy (CAR syndrome) is usually associated with small cell lung cancer, but has been reported with prostate cancer *(51)*.

**COMPLICATIONS OF TREATMENT** Obturator nerve injury occurs in 1.3% of radical retropubic prostatectomies, usually associated with dissection of a large fixed lateral tumor. If the nerve is completely transected it should be repaired primarily. Occasionally the lateral femoral cutaneous nerve or genitofemoral nerve is injured in extensive resections, producing paresthesias in the superolateral thigh or groin and scrotum.

Impotence was an almost invariable accompaniment to radical retropubic prostatectomies prior to the advent of nerve-sparing surgery. Injury to the neurovascular bundle crossing along the posterolateral aspect of the prostate bilaterally interfered with autonomic supply to the corpus cavernosa. With nerve-sparing surgery adequate erectile function is preserved in about two-thirds of patients.

External-beam radiation therapy for prostate cancer is frequently associated with bowel and genitourinary complications, including an approx 50% incidence of impotence, but more extensive injury to the lumbosacral plexus is extremely uncommon *(52)*. Rarely, radiation therapy for epidural spinal cord compression may result in radiation myelopathy. Radiation may also produce erectile dysfunction, but this is believed to occur on the basis of a vasculopathy.

## TESTICULAR CANCERS

Testicular germ cell tumors are responsible for approx 1% of cancers in men; about 7000 cases are diagnosed yearly in the United States. Testicular cancer is the leading cause of cancer in males between 15 and 35 yr old. Germ cell tumors occasionally arise in extragonadal locations, including the sacrum, retroperitoneum, mediastinum, hypothalamus, and pineal gland.

Germ cell tumors may be comprised of several histologic subtypes, including seminoma, embryonal cell carcinoma, choriocarcinoma, yolk sac tumors, and teratoma. Seminomas are the single most common histologic subtype, accounting for 40%. Mixtures of the subtypes occur as well. Nongerm cell neoplasms may rarely arise in the testes: leukemia, lymphoma, Sertoli cell tumors, and adenocarcinoma account for < 5% of testicular neoplasms.

Germ cell tumors may spread by hematogenous or lymphatic routes. The pattern of spread is neither stepwise nor predictable. Choriocarcinoma in particular has a propensity to spread hematogenously early in its course.

Management and prognosis in testicular germ cell tumors depend on histologic subtype and stage. Staging generally consists of testicular ultrasound and CT scan of the chest, abdomen, and pelvis. Serologic evaluation of tumor markers including alpha fetoprotein, beta-human chorionic gonadotropin, and lactate dehydrogenase is also performed. Elevation of alpha fetoprotein and substantial elevation of beta-human chorionic gonadotropin suggest a nonseminomatous germ cell tumor. Seminomas have the most favorable prognosis: 98% of tumors localized to the testis and 90% of metastatic tumors are curable. Nonseminomas, in contrast, are fatal in approx 20%. Seminomas are highly radiosensitive, and known or suspected retroperitoneal lymph node spread is often successfully treated with relatively low doses of radiation therapy. Nonseminomas are less radiosensitive. Both tumors are usually chemosensitive; most chemotherapy regimens include either carboplatin or cisplatin. Bleomycin, vinblastine, and etoposide are also frequent components. In refractory cases, high-dose chemotherapy with peripheral blood stem cell transplant is often utilized.

Brain metastasis is the most common substantial neurologic complication of testicular cancer. Chemotherapy-related neuropathies are also quite common but produce less morbidity. Paraneoplastic syndromes and complications of surgery and radiation are infrequent but may result in profound neurologic deficits.

**BRAIN METASTASES** Brain metastases are a common complication of testicular tumors, occurring in 15–25% of patients with disseminated germ cell tumors *(53,54)*. Concomitant lung metastases are present in as many as 89% of patients *(55)*. An autopsy series similarly revealed brain metastases in 31% of patients, almost always associated with systemic metastases *(56)*. Choriocarcinoma is particularly likely to produce brain metastases (which are frequently hemorrhagic), and seminoma is relatively unlikely to do so *(55,56)*.

The brain is a fairly common site of relapse in patients who achieve a complete response of systemic tumor to chemotherapy *(57,58)*, suggesting the brain may function as a sanctuary from systemically effective chemotherapy. Some physicians have argued that brain relapse is a marker of imminent systemic relapse and that such patients require systemic chemotherapy for control of systemic tumor.

The overall median survival of patients with brain metastases from germ cell tumors is 6 mo *(55)*. Patients with brain metastases as initial manifestation of germ cell tumor have the best prognosis *(55,59)*, whereas patients developing brain metastases while receiving systemic chemotherapy have the worst prognosis. Overall, about 1 in 4 patients are 2-yr survivors after brain metastases *(55)*. Most series include patients undergoing individualized treatment with a variety of modalities including radiation, surgery and chemotherapy. Patients treated with both chemotherapy and radiation have a median survival of 12 mo compared to 2–3 mo with single modality management *(55)*. Aggressive management including surgery, radiation, and sometimes chemotherapy for patients with isolated brain relapse following systemic chemotherapy produced long-term control in a majority of patients *(55,58,59)*. However, patients who develop brain metastases while on systemic chemotherapy have a median survival of only 3 mo and appear best treated with radiation therapy alone *(55,59)*. The small size and nonrandomized nature of these treatment series limit the definitiveness of these conclusions.

One series has utilized chemotherapy as the sole treatment modality for brain metastases *(60)*. In this report, 10 patients with brain metastases from nonseminomatous germ cell tumors

were treated with combination chemotherapy (POMB/ACE). Eight were alive without evidence of active disease 3–54 mo (mean 32 mo) after therapy. Several had residual abnormalities on CT scan; resection in one case revealed only gliosis. Five patients were without evidence of relapse after 18 mo, suggesting these patients were cured. Nine of these patients had very high serum HCG supporting the diagnosis of choriocarcinoma. The authors suggested that WBRT might be unnecessary for long-term control of brain metastases; no confirmatory series have been published to date.

**PARANEOPLASTIC SYNDROMES** Several paraneplastic neurologic syndromes have been associated with testicular tumors. The two most common syndromes appear to be limbic encephalitis and brainstem encephalitis. Cortical cerebellar degeneration has also been reported *(61)*. Patients with limbic encephalitis typically present with depression, memory loss, seizures, or hallucinations. MR scanning generally reveals T2 hyperintensity in one or both temporal lobes and sometimes in the diencephalon as well. Contrast enhancement in these regions may be seen on postgadolinium T1 images. This syndrome has been seen with both seminomatous and nonseminomatous neoplasms. Many of these patients have a serum and CSF antibody known as anti-Ta; this antibody is not found in controls without testicular cancer or in patients with testicular cancer but without paraneoplastic syndrome. The antibody recognizes a protein called Ma2, which is normally found only in brain but which was expressed in these patients' tumors. Paraneoplastic brainstem and cerebellar degeneration have also been associated with anti-Ma2 antibodies *(62)*. A similar protein, Ma1, is expressed in normal brain and testicular germ cells. Anti-Ma antibodies recognizing both Ma1 and Ma2 have been reported in patients with colon, breast, and parotid tumors and paraneoplastic brainstem and cerebellar degeneration; curiously, however, anti-Ma1 antibodies have not been associated with testicular tumors *(63)*. Brain biopsy in one testicular cancer patient with anti-Ma2 antibodies revealed CD8+ lymphocytes clustered around neurons, suggesting that cytotoxic T cells, rather than the anti-Ma2 antibody, explain syndrome pathogenesis. As with most other paraneoplastic syndromes, this syndrome usually antedates testicular tumor detection. In most cases the neurologic syndrome stabilizes and may even improve; too few cases have been studied to identify any association of neurologic outcomes with antitumor or immunosuppressive therapy.

**MENINGEAL DISEASE** Leptomeningeal disease is exceedingly rare in testicular tumors *(53,64,65)*. Dural metastasis of seminoma and choriocarcinoma producing subdural hematoma has been reported *(66)*.

**SPINAL DISEASE** Spinal cord compression is a rare complication of testicular germ cell tumors. In a series of 297 patients with metastatic germ cell tumors, only 16 (5%) had bone metastases and only 2 (0.7%) developed epidural spinal cord compression. These authors noted that back pain was often due to retroperitoneal lymphadenopathy rather than osseous metastases *(67)*. The chemosensitivity of these tumors makes chemotherapy a viable treatment option for spinal cord compression when radiation is contraindicated *(68)*. Patients should be monitored for the possibility of vertebral collapse related to rapid tumor lysis *(67)*.

**PERIPHERAL NERVE COMPRESSION** This is an exceedingly rare complication of germ cell tumors. A case of recurrent laryngeal nerve paralysis manifesting as hoarseness was recently reported in a young man with mediastinal seminoma *(69)*. The paralysis and mass resolved with chemotherapy. Phrenic nerve palsy and brachial plexopathy from compressive masses have also been observed *(70,71)*.

**COMPLICATIONS OF TREATMENT** Radiation therapy to abdominopelvic lymph nodes has been associated with delayed neurologic dysfunction. Kristensen reported 4 patients with nonseminomatous germ cell testicular tumors treated with fractionated radiotherapy totaling 5300–5700 cGy in 27–30 fractions from T11 through the lumbosacral spine to cover paraaortic lymph nodes who 4–14 mo later developed bilateral lower extremity weakness of lower motor neuron type, diminished to absent lower extremity reflexes, with preserved sensation and sphincters *(72)*. Epidural tumor was excluded with myelogram. Neurophysiologic testing and the absence of fasciculations suggested the anterior horn cell was not the main site of injury. Bowen reported 6 similar cases with an overwhelmingly motor, asymmetric disorder (although minor sensory symptoms were noted by all patients) *(73)*. Mild bladder dysfunction developed in half. The disorder gradually worsened over time in most patients. Electrophysiologic studies and neuropathology (in one patient) localized the lesion to the nerve roots in the cauda equina. These findings point to a radiation-induced lumbosacral radiculopathy. Radiation-induced peripheral nerve sheath tumors have also been reported *(74)*.

Chemotherapy for management of testicular cancer often includes drugs such as cisplatin and vinblastine known to produce peripheral neuropathy. Paresthesias are very common during treatment with these medications, and several years later most patients have demonstrable sensory loss and electrophysiologic evidence of peripheral neuropathy and hearing loss *(75)*. Cisplatin has also been associated with the development of Lhermitte's sign in the absence of spinal radiation or compressive lesion *(76)*. Most such patients have concomitant peripheral neuropathy.

Retroperitoneal lymphadenectomy is sometimes utilized for accurate staging and treatment of nonseminomatous germ cell tumors. Femoral neuropathy has been reported following retroperitoneal and pelvic lymphadenectomy for testicular cancer *(77)*. Patients experience weakness of knee extension and sensory loss in the anteromedial thigh and medial calf; the patellar reflex is usually absent. The presumptive cause of nerve injury in most cases is compression in the psoas muscle from self-retaining retractors. Most patients gradually recover satisfactorily. A more serious complication of retroperitoneal lymph node dissection is spinal cord ischemia. In one study this complication followed 4 of 712 postchemotherapy surgeries but none of 735 prechemotherapy procedures *(78)*. Extensive residual tumor after chemotherapy, advanced age, and prior surgery were risk factors. The typical findings were asymmetric paraparesis, hyporeflexia, neurogenic bladder, and variable sensory loss. In this report all patients recovered at least partially. Finally, extensive bilateral retroperitoneal lymph node dissection damages the sympathetic innervation to the smooth muscle of the vas deferens, prostate, and seminal

vesicles. The consequence for many patients is ejaculatory incompetence.

## BLADDER CANCER

Bladder cancer is the fifth most common cancer among American men and eighth most common cancer in women (reflecting its 3:1 male predominance). 54,500 cases were estimated to occur in the United States in 1998, with 11,000 fatalities. Transitional cell carcinoma accounts for most cases, although squamous cell carcinoma may arise in patients with chronic bladder irritation, e.g., chronic indwelling catheters. Whereas many cases are superficial and successfully managed with transurethral resection and intravesical chemotherapy or immunotherapy, invasion of the muscularis propria portends potentially lethal disease and may require cystectomy, chemotherapy, or radiation. Adjuvant systemic chemotherapy for high-risk patients may delay time to progression and may improve survival. The most commonly used regimen, MVAC, consists of methotrexate, vinblastine, doxorubicin, and cisplatin. Frequent sites of metastasis include lymph nodes, bone, liver, and lung. Radiotherapy is often used to palliate locally advanced tumors. MVAC is also sometimes used in this setting; when utilized for recurrent disease it achieves complete responses in 13% and partial responses in 26% of patients. Median survival in this setting is approx 1 yr. The combinations of carboplatin with paclitaxel and cisplatin with gemcitabine also are active against bladder cancer.

Although neurologic complications of bladder cancer are uncommon, brain metastases are seen increasingly frequently. Lumbosacral plexopathy is the second common reason for consultation.

**BRAIN METASTASES** Brain metastases were formerly a rare complication of bladder cancer; Whitmore reported only five cases (1%) in a cohort of 451 patients treated in the 1950s and 1960s *(79)*. Recently, however, this complication has become more commonly recognized. Dhote reported 8 patients developing brain metastases in a cohort of 50 patients treated with MVAC for systemic metastases *(80)*. All had achieved systemic response after starting MVAC a median of 21 mo earlier, but 4 had systemic relapse at the time of brain metastsis detection. Sternberg similarly reported a 16% incidence of brain metastases in patients treated with MVAC, with half occurring in the setting of systemic relapse. In this series median time to brain failure was 12 mo *(81)*. Thus, it appears that aggressive therapy has altered the pattern of failure and increased the incidence of brain metastases. No MR data on bladder metastases have been reported, although CT data suggest most patients have single metastases.

The outcome of patients with brain metastases from bladder cancer does not differ substantially from patients with other sources of brain metastases. In one study of the outcome of treatment in 19 patients with brain metastases from transitional cell carcinoma, the median survival was 4 mo *(82)*. Mean survival among the 13 patients with single metastasis was 14 mo, markedly better than the 3-mo mean survival in 6 patients with multiple brain metastases. Patients treated with surgery and fractionated WBRT had mean survival of 19 mo compared to 6 mo with radiotherapy alone, but only patients with single brain metastases underwent surgery, biasing these results in favor of surgery. No radiosurgery series for brain metastases from bladder cancer has been reported. With brain metastasis now a common site of treatment failure, some oncologists have recommended routine brain imaging as part of the assessment of response to chemotherapy.

**LEPTOMENINGEAL METASTASES** Leptomeningeal carcinomatosis is a rare complication of transitional cell carcinoma, with fewer than 10 cases reported *(83,84)*. As with parenchymal brain metastases, this complication occurs primarily in patients with systemic metastases, sometimes in the setting of successful control of systemic disease with chemotherapy.

**PARANEOPLASIA** Paraneoplastic neurologic disorders are a rare complication of bladder cancer, with only scattered case reports. One patient has been reported with a syndrome of tunnel vision, diplopia, tongue induration, and a hyperactive gag associated with transitional cell carcinoma *(85)*. The syndrome resolved when the primary was resected, returned when the tumor recurred, and remitted when the tumor was successfully treated with chemotherapy. No serologic workup was performed for this case of presumed paraneoplastic brainstem encephalitis. Dermatomysoitis *(86,87)* and polymyositis *(88)* have also been reported. A hypercoagulable state producing multiple cerebral infarcts as well as venous thromboembolism has been reported with locally advanced bladder cancer *(89)*. Sensory peripheral neuropathy remitting with resection of a renal pelvis transitional cell carcinoma has been noted *(90)*. One patient with bladder cancer has been noted to have opsoclonus-myoclonus and anti-Ri antibodies *(43)*. Finally, one case of paraneoplastic cerebellar degeneration associated with anti-Yo antibody was detected in a woman with transitional cell carcinoma and an extensive negative workup for breast or gynecologic cancer *(91)*.

**SPINAL DISEASE** Spinal cord compression is an extremely uncommon occurrence in bladder cancer despite the tumor's predilection for producing bone metastases. Only one patient developed this complication out of 685 bladder cancer patients seen over one decade *(92)*.

**PERIPHERAL NERVE DISEASE** Locally progressive bladder cancers or lymph node metastases have proximity to the lumbosacral plexus, and malignant plexopathy is an occasional consequence. In one large series, 3 of 85 cases of malignant lumbosacral plexopathy were attributable to bladder cancer *(93)*. Typically both the upper and lower plexus are involved, resulting in both proximal and distal ipsilateral lower extremity weakness as well as neuropathic pain. The "malignant psoas" syndrome has been reported with bladder cancer *(94)*. This entity consists of an upper lumbosacral plexopathy (L1-L4) associated with painful fixed flexion of the hip, pain on attempted hip extension, and infiltration of the psoas muscle with tumor.

Local extension of bladder cancer has rarely produced obturator mononeuropathy *(95)*. Patients present with pain in the groin and sometimes upper or medial thigh. Weakness of hip adductors or flexors is seen as is hyperesthesia or hypesthesia on the upper anteromedial thigh. Ipsilateral leg edema is a variable finding, presumably from lymphatic obstruction. Although EMG is confirmatory, the clinical features and the

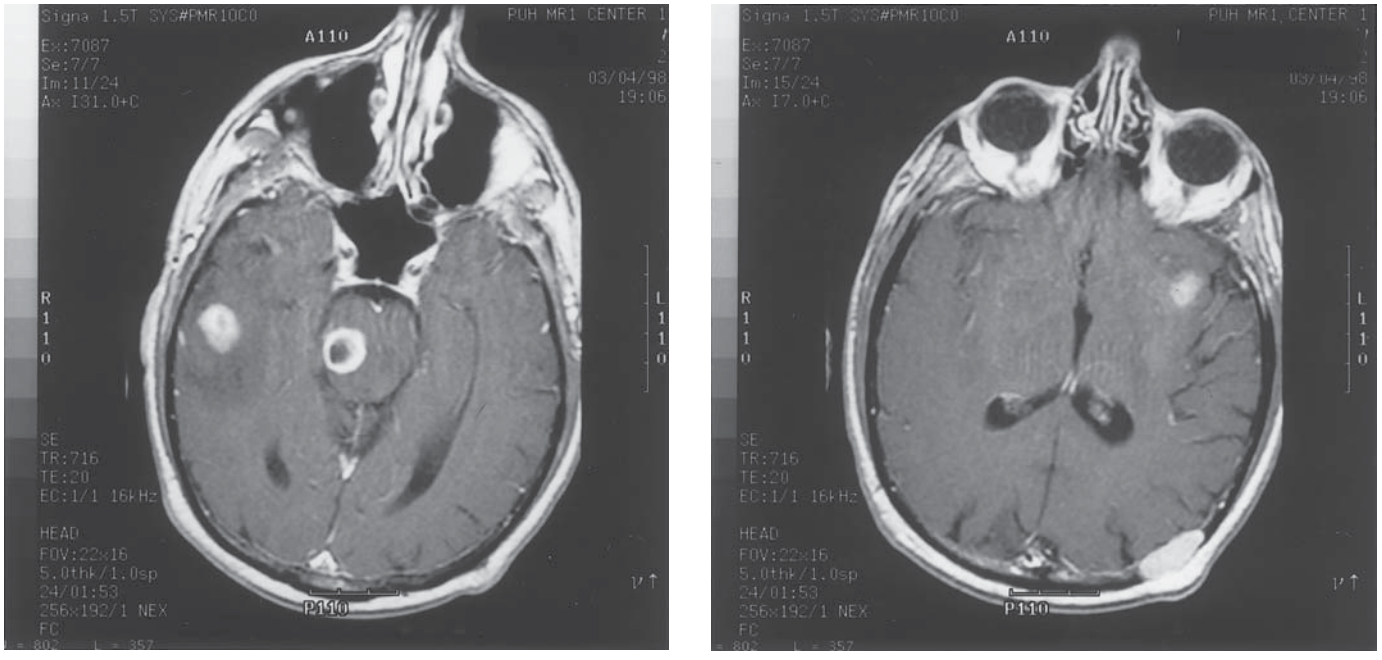


**Fig. 1.** Multiple intracranial metastases from renal cell carcinoma. These gadolinium-enhanced MR images demonstrate three parenchymal and one calvarial metastasis. The left frontal parenchymal metastasis demonstrated precontrast T1 shortening and extracellular methemoglobin on other sequences indicative of hemorrhage.

presence of a pelvic mass on CT or MR scan are sufficient for diagnosis. Successful antineoplastic therapy of the mass with radiation or chemotherapy usually results in clinical improvement.

**COMPLICATIONS OF TREATMENT** As with testicular cancer, pelvic lymphadenectomy for bladder cancer has been reported to produce femoral neuropathy *(96)*. Ligation of both internal iliac arteries to reduce bleeding during radical cystectomy has produced cauda equina ischemia manifesting as distal lower extremity weakness and numbness *(97)*. The posterior trunks of these vessels help supply the cauda equina via the ileolumbar and lateral sacral arteries.

## RENAL CELL CARCINOMA

Renal cell carcinoma accounts for 12,000 fatalities and 30,000 new cases of cancer each year in the United States. 45% of patients are diagnosed with localized disease, 25% with locally advanced tumors, and 30% with metastatic disease. Median survival with metastatic disease is 18 mo with 2–18% of patients alive at 5 yr *(98)*. The lung is the most common site of metastatic disease (75% of patients); soft tissue (36%), bone (20%), liver (18%), and skin metastases (8%) are also common *(3)*. Radical nephrectomy is standard management of localized renal cell carcinoma, with partial nephrectomy occasionally undertaken in patients with bilateral renal cell carcinoma or tumor in a solitary kidney. Conventional cytotoxic chemotherapy is of minimal benefit for metastatic disease; response rates are < 10%. Immunologic therapies are of somewhat more benefit; for example, interferon-α (IFN-α) has up to a 40% response rate for pulmonary metastases (albeit lower rates for other sites). Interleukin-2 (IL-2) has a 15% response rate, and complete responses may be durable for >18 mo. Metastases from renal cell carcinoma may rarely undergo complete spontaneous regression, and partial regression or stabilization of untreated tumors is not rare.

Neurologic complications of renal cell carcinoma occur frequently. Both brain and spine are common sites of metastasis, and with the advent of MRI intramedullary spinal cord metastasis is no longer a rare diagnosis.

**Brain Metastases (Fig. 1)** Brain metastases occur in about 10% of patients with metastatic renal cell carcinoma *(99)*. Brain metastases from renal cell carcinoma hemorrhage in one-quarter to one-half of cases *(99,100)* and accounted for 20% of all hemorrhagic brain metastases in one study *(101)*. In 92% of cases the primary tumor has been diagnosed before the patient presents with brain metastases *(102)*. Between 3% and 7% of patients with metastatic renal cell carcinoma without neurologic symptoms will have brain metastases detected with CT scan *(103,104)*. No consensus exists on whether or how often asymptomatic patients should be screened for this entity.

Brain metastases from renal cell carcinoma traditionally have been thought to be highly radioresistant. Clinical improvement has been noted in only one-quarter of patients with brain metastases treated with fractionated radiotherapy alone, compared to two-thirds of brain metastases in general *(105)*. Radiographic response rates are also much lower than with brain metastases from other primary tumors. Works reviewed the outcome in 119 patients treated with fractionated radiotherapy alone at MD Anderson from 1976–1993 *(99)*. Median survival was 4 mo. In a multivariate model, only single brain metastasis, lack of other systemic metastases at time of brain metastasis (42% of patients), KPS > 60, and tumor diameter ≤ 2 cm were good prognostic factors. More than three-quarters of patients died of neurologic progression, a much higher percentage than

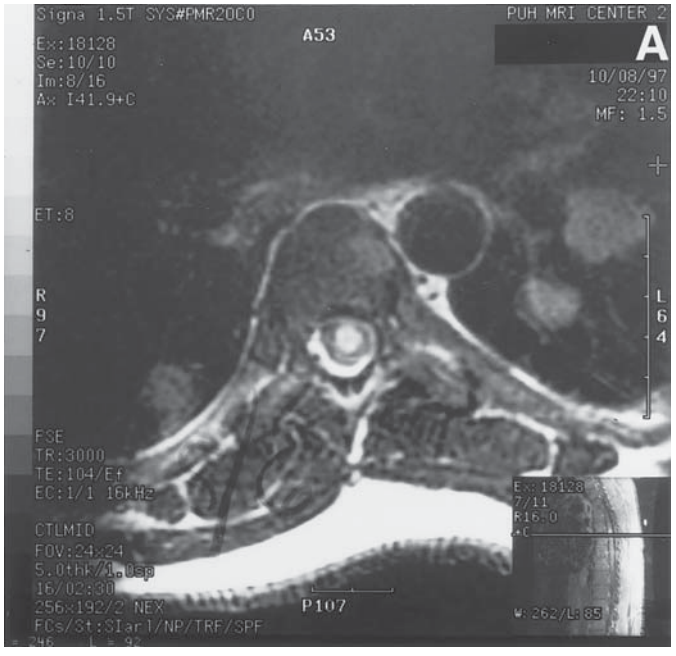


**Fig. 2.** Intramedullary spinal cord metastasis from renal cell carcinoma. A 2 cm enhancing mass is seen within the spinal cord at the T5-6 level on postcontrast axial **(A)** and sagittal **(B)** images. Increased signal on the T2-weighted images **(C)** is seen in the central portion of the cord extending superiorly and inferiorly from the mass consistent with a tumor-associated syrinx. This patient developed paraplegia 3 wk after diagnosis of a small frontal lobe metastasis.

the 40% seen in patients with brain metastases of all tumor sites combined. The conclusion was that fractionated radiotherapy was an unsatisfactory treatment modality for brain metastases from renal cell carcinoma. A French report suggested a slightly more optimistic outcome with radiotherapy, with a median survival of 7 mo *(106)*. Interestingly, symptomatic improvement with radiotherapy alone was seen in 38/50 patients (76%), though 0/32 had radiographic response.

For many years, neurosurgeons have noted occasional prolonged survival following resection of brain metastasis from renal cell carcinoma. Five decades ago, Stortebecker published a series of 17 patients with resected brain met from 1922–1950. Two patients survived for 14 and 4.5 yr *(107)*. Later reports noted survivals of 7 and 10+ yr following resection of brain metastases without use of other therapies *(108,109)*.

The first large surgical series from the modern neuroimaging era reviewed the Memorial Sloan-Kettering experience through 1986 and also supported the benefits of surgery. Indications for surgery were nonmoribund state and <3 accessible metastases. 2/22 patients died postoperatively; the remaining 20 had a median survival of 21 mo. Most had either previously received WBRT or were irradiated postoperatively. Eight had CNS relapse, 3 locally and 5 distantly. Thus, local control was achieved in 85%, a major improvement over radiotherapy alone *(110)*. An update of the Memorial experience in 50 patients through 1993 revealed a median survival following craniotomy of 12.6 mo. Patients receiving postoperative WBRT demonstrated no survival advantage. Survival rates at 3 and 5 yr were 22 and 8.5%, respectively. In multivariate analysis only the resection of lung metastasis, supratentorial location of met, left sided primary kidney involvement, and lack of neurologic deficit before craniotomy were the significant good prognostic factors *(111)*. Other surgical series have reported similar results *(112)*. Thus, patients with limited or slowly progressive systemic disease and surgically accessible brain metastases may do better with surgery than without.

The advent of radiosurgery has provided an exciting treatment option for patients with renal cell carcinoma. In general,

radiosurgery appears to work as well for metastases resistant to fractionated radiotherapy as for those sensitive to it. The renal cell carcinoma experience bears this out (*see* Chapter 7, Fig. 4). In one series, 23 patients with 44 brain metastases underwent gamma-knife radiosurgery. Three-quarters of the patients improved symptomatically within 3 wk. Only three patients required chronic corticosteroids. Twenty-two of twenty-three patients had radiographic tumor control, 95% of patients having tumor shrinkage at 3 mo. The median survival was 11 mo, comparable to most surgical series. Eight patients ultimately underwent a second radiosurgical procedure, seven for distant brain failure *(113)*. Another series reported 35 patients with 52 brain metastases undergoing gamma knife radiosurgery. The median survival again was 11 mo and local control rate 90%. The addition of WBRT did not affect distant failure rate although it did improve local control *(114)*.

Fractionated stereotactic radiotherapy, the use of stereotactic principles with cranial immobilization devices to deliver repeated doses of highly focal radiation to specified targets, has also been explored in the management of brain metastases from renal cell carcinoma *(115)*. Preliminary results suggest local control rates similar to stereotactic radiosurgery series. The advantages of this approach compared to radiosurgery are as yet unclear.

Metastases of renal cell carcinoma to meningiomas *(116)* and to the leptomeningeal edge of a glioblastoma *(117)* have rarely been observed. Intraventricular metastasis simulating a meningioma has also been reported *(118)*. Rare cases in which untreated (unbiopsied) cerebral metastases have spontaneously regressed (sometimes in association with regression of pulmonary metastases) have also been noted *(119,120)*. IFN-$\alpha$, which induces systemic tumor responses in approx 10% of patients, is generally ineffective as treatment for brain metastases. However, one case of a pineal metastasis as well as lung metastases responding completely to this agent has been published *(121)*. The lack of a blood-brain barrier (BBB) in the pineal gland may explain this unusual response. Leptomeningeal carcinomatosis in renal cell carcinoma is exceedingly rare; to our knowledge a single rapidly fatal case has been reported *(122)*.

**SPINAL CORD DISEASE** Bony metastases are a common complication of renal cell carcinoma, occurring in 20–40% of patients with metastatic disease. One study examining the effectiveness of palliative radiation for bone metastases from renal cell carcinoma noted that 59% of patients reported some pain relief at 2 wk but only 12% had complete relief of pain at 8 wk *(123)*. No large series has examined the results of fractionated radiotherapy for epidural spinal cord compression from renal cell carcinoma. Sundaresan reported neurologic improvement in 5/11 patients treated with RT and corticosteroids without surgery. Nonetheless, approx half the patients died of complications of paraplegia, emphasizing the relatively transient salutary effects of fractionated radiotherapy in this setting *(124)*.

There is precedent in the orthopedic oncology literature for resection of bone metastases from renal cell carcinoma. Durr reported 49% 1-yr survival after resection of bony metastasis (one-third of which arose from the spine) *(125)*. Patients with a solitary bone metastasis fared best, with a median survival > 2 yr. Multiple bone metastases or the presence of visceral metastases were prognostically ominous factors on multivariate analysis; a long interval from diagnosis of primary tumor to detection of bone metastasis was a good prognostic factor.

One report has focused on the results of surgery for epidural metastasis from renal cell carcinoma, with results appearing beneficial in selected cases *(124,126)*. Eleven patients underwent laminectomy with tumor resection after failing radiotherapy, while 21 patients received vertebral body resection (7 prior to and 14 following radiotherapy). Five patients (all on high-dose steroids) had complications, including excessive hemorrhage (four) and wound breakdown (two). Median survival of patients undergoing surgery was 13 mo, which compared favorably to the median survival of 3 mo in patients undergoing radiotherapy alone. Neurologic improvement was seen in 7/7 patients undergoing up-front surgery and 15/25 for postradiotherapy surgery. In general, neurologic improvement paralleled preoperative status; severely paraparetic patients were least benefited. Additional surgery for recurrent compression at the same or other sites was required in eight patients. Pain was improved postoperatively in 78% of patients. Spinal angiography with embolization was used to reduce hemorrhage. Embolization as the sole therapy has provided a few months of neurologic improvement or stabilization in several patients *(127,128)*.

In accordance with its propensity to metastasize to brain parenchyma, renal cell carcinoma occasionally metastasizes to the spinal cord itself (Fig. 2). The management of this complication does not differ from the general guidelines to treating intramedullary spinal cord metastasis discussed in Chapter 9.

**PARANEOPLASTIC SYNDROMES** Paraneoplastic neurologic disorders are notably uncommon with renal cell carcinoma. Several patients with RCC and motor neuron disease have been reported *(129,130)*. While an association between cancer and motor neuron disease is controversial, the dramatic response of several patients to nephrectomy differentiates these cases from coincidental cases of motor neuron disease in cancer patients and suggests this association, albeit rare, is real. One case of paraneoplastic cerebellar degeneration *(43)* and one of polymyositis *(131)* have been reported.

**COMPLICATIONS OF TREATMENT** Neurologic complications of immunotherapy for treatment of metastatic renal cell carcinoma are covered in Chapter 16.

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# 23 Melanoma

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## MELANOMA INCIDENCE AND AGE GROUPS

Throughout the world, cases of melanoma are increasing at a rate of 5% per year *(1)*. Over the last decade, the estimated lifetime risk of developing melanoma in the United States has increased from 1 in 105 to 1 in 75 *(2,3)*. In the year 2000, an estimated 28,600 cases of *in situ* melanoma and 47,700 new cases of malignant melanoma were diagnosed in the United States *(3)*. During that year, 7700 deaths were attributed to this disease. Overall, melanoma is the fifth most common cancer among men and the sixth most common cancer among women *(3)*.

The median age at diagnosis of malignant melanoma is 53 yr *(4)*. While melanoma affects adults of all age groups, it is uncommon in the pediatric population. Fewer than 3% of patients with this malignancy are younger than 21 yr of age *(5–7)*. The occurrence of melanoma in prepubertal children is particularly rare, representing between 0.4% and 1% of cases *(8–10)*.

## RISK FACTORS AND EARLY DETECTION

Factors associated with the development of malignant melanoma include fair skin, history of excessive sun exposure and blistering burns, family or personal history of melanoma, increased number of common acquired nevi, and history of dysplastic nevi or large congenital nevi. The detection of cutaneous melanoma is facilitated by melanocyte pigment production in over 95% of primary lesions. The majority of cutaneous melanomas evolve through a predictable sequence of growth beginning with a visually recognizable but biologically indolent phase of radial growth. Melanoma confined to the epidermal skin layer, or that associated with superficial invasion of the papillary dermis (melanoma *in situ*), has no capacity to metastasize. During this phase of growth melanoma is surgically curable, with 5-yr survival rates approaching 100%. Once a melanoma enters its vertical growth phase through the dermal skin layers, a significant decline in 5-yr survival is seen. Characteristic changes in pigmented lesions on visual inspection of the skin and the potential for cure with early detection underscore the importance of surveillance in at risk populations.

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## STAGING AND TREATMENT OVERVIEW

Once a diagnosis of malignant melanoma has been established, several prognostic factors have been identified to help guide treatment. The staging system recently adopted by the American Joint Committee on Cancer determines the T-stage on the less favorable of the Clark level and the Breslow thickness *(11)*. The Clark microstaging method characterizes the histologic level of invasion through the skin, while the Breslow depth measurement quantitates tumor thickness (*see* Table 1). Patients with stage I melanoma have a low incidence of nodal metastases at presentation, and subsequent nodal failure is rare *(12)* (*see* Table 2). A limited staging evaluation and treatment with surgical resection alone is warranted. Nodal metastases are found in 20–25% of patients with stage II disease, and are present in over 60% of patients with stage III disease. The presence of nodal metastases correlates with incidence of systemic metastases. Patients with stage II disease have less than a 25% incidence of systemic metastases, whereas patients with stage III disease have more than a 70% incidence of occult distant metastases at the time of initial presentation. Traditionally, elective node dissection was undertaken in patients with stage II disease to determine the presence or absence of occult nodal metastases. Recently, however, the sentinel node biopsy has emerged as a less invasive alternative. Sentinel node biopsy refers to sampling of the first draining node from a melanoma primary lesion, and has been shown to reflect the status of the remaining lymph nodes within a drainage basin *(12)*. Patients with positive nodal disease require further therapy with regional lymph node dissection and adjuvant or neoadjuvant chemotherapy. Stage IV disease has a uniformly poor prognosis, with a median survival of 7.5–7.9 mo *(13,14)*. Therapeutic approaches to metastatic melanoma include supportive care

**Table 1**
**American Joint Committee on Cancer Staging System for Melanoma**

| Stage | | Clark level | Breslow depth | T-stage T | T-stage N | T-stage M | 5-yr Survival |
|---|---|---|---|---|---|---|---|
| 0 | Melanoma *in situ* | | | | | | |
| I | Localized melanoma | Level II: invasion up to the papillary dermis | ≤0.75 mm | T1 | 0 | 0 | 87–96% |
| | Localized melanoma | Level III: invasion into the papillary dermis | 0.76–1.5 mm | T2 | 0 | 0 | |
| II | Localized melanoma | Level IV: invasion into the reticular dermis | 1.5–4 mm | T3 | 0 | 0 | 47–75% |
| III | Localized melanoma | Level V: invasion into the subcutaneous layer | >4 mm | T4 | 0 | 0 | 10–46% |
| | Limited nodal metastases | | | Any | N1 | 0 | |
| | Advanced regional metastases or in-transit metastases | | | Any | N2 | 0 | |
| IV | Distant metastases | | | Any | Any | M1 | 1–2% |

only, surgical resection with or without adjuvant radiation, systemic chemotherapy, regional chemotherapy with isolated limb perfusion, immunotherapy, or experimental drug trials. According to SEER summary stage categories, over the time period of 1989–1995, 82% of patients had localized disease at presentation, 8% regional disease, and 4% distant metastases *(3)*.

## PATTERNS OF DISTANT METASTASES

Melanoma can metastasize to virtually any organ of the body. At the initial diagnosis of stage IV disease, 18–36% of patients have disease within the lung, 14–20% within the liver, and 12–20% within the brain. Distant sites of metastases found at autopsy in decreasing order of frequency are lung, liver, bowel, brain, kidneys, and bone *(15)*. Brain involvement usually manifests late in the disease course, occurring at disease relapse or progression. At malignant melanoma relapse, brain metastases are the first site of distant metastasis in 12–20% of patients *(15)*.

## METASTATIC MELANOMA OF UNKNOWN PRIMARY

In large series of metastatic malignant melanoma, patients with an unknown primary tumor constitute 2–6% of patients with metastatic disease although figures as high as 15% have been reported *(16–22)*. About two-thirds of patients with occult primary melanoma have regional lymph node metastases. The remaining one-third have distant metastases involving skin, subcutaneous tissue, lung, or brain *(23)*. Patients presenting with "primary" cerebral melanoma invariably develop multiple systemic metastases *(24,25)*. Outcomes are similar between these patients and those patients with known primary sites when matched for prognostic factors *(23)*.

## FAMILY HISTORY AND GENETIC FACTORS

At least 10% of all melanoma cases are familial *(26)*. While some melanomas are derived from an autosomal dominant heritable syndrome of atypical moles *(27,28)*, the pattern of inheritance in malignant melanoma appears to be multifactoral or polygenic. Cutaneous malignant melanomas have been associated with other tumors arising from neural crest derivatives including neurofibromas *(29,30)*, meningiomas *(31)*, and gliomas *(32)*. Reports of family kindreds with a high incidence of malignant melanoma postulate genetic linkage of malignant melanoma to essential myoclonus *(33)* and Charcot-Marie-Tooth neuropathy *(34)*. In rare instances, melanoma is associated with other genetic diseases, such as xeroderma pigmentosum and neurocutaneous melanosis *(30)*.

## CNS METASTASES

**INCIDENCE** As treatment advances increase survival times in some types of cancer, the frequency of cerebral metastases is escalating *(35–37)*. Malignant melanoma is the fourth most common cause of central nervous system (CNS) metastases after lung and breast carcinomas and unknown primary tumors *(38–40)*. Clinical data from large databases report an incidence of CNS metastases in patients with malignant melanoma of 6–10% *(25,41,42)*. However, if the data from smaller series is incorporated, the incidence ranges from 6–43% *(39,43–47)*. Autopsy series report brain metastases in 12–74% of patients succumbing to metastatic melanoma *(44,46,48–54)*.

**CO-EXISTENT EXTRACRANIAL DISEASE** Brain metastasis in malignant melanoma generally occurs in patients with concurrent extracranial disease. However, the brain is the only site of distant metastases in 20–60% of malignant melanoma patients with brain metastasis *(55–59)*. In one case series, isolated brain metastases occurred in less than 5% of cases *(60)*. The presence or absence of extracranial disease appears related to the multiplicity of brain metastases. While the majority of patients with metastatic brain disease have multiple lesions, 20–60% of patients will have single metastatic deposits *(25,60–68)*. Forty to forty-five percent of patients with single brain metastases have co-existing systemic disease compared with 80% of patients with multiple brain metastases *(57,68)*.

**Table 2**
**Incidence of Nodal and Systemic Metastases by Stage *(12)***

| *Melanoma stage* | *Incidence of nodal metastases* | *Incidence of systemic metastases* |
|---|---|---|
| Stage I | 5% | Rare |
| Stage II | 20–25% | <25% |
| Stage III | >60% | >70% |
| Stage IV | — | 100 % |

Adapted with permission from ref. *12*.

**RISK FACTORS FOR DEVELOPING CNS METASTASES IN MALIGNANT MELANOMA** Several factors have been associated with the development of CNS disease in malignant melanoma. Primary melanomas involving the head and neck regions are the most likely to spread to the CNS *(53,61,65, 69,70)*. Brain metastases are more common in males than females *(56,59,64,65,69,71)*, perhaps because primary melanoma lesions in males more often develop in the head, neck, and trunk regions. The presence of lymph node or visceral metastases at the time of diagnosis is associated with a higher risk of developing brain metastasis *(25)*. Nearly one-half of patients with multiple visceral metastases have concomitant brain involvement or will subsequently develop CNS metastasis. Specific features of primary melanoma lesions that are associated with the development of brain metastases include acral lentiginous or nodular histological types *(25)*, deeply invasive primary lesions or primary lesions located on mucosal surfaces *(25,61)*, and primary lesions that are ulcerated or have large superficial diameters *(25)*. Overall, these factors identify a population at risk for the widespread metastatic dissemination of disease rather than specifically delineating a population at risk for brain metastases *(25)*.

**INTERVAL BETWEEN INITIAL DIAGNOSIS AND BRAIN METASTASES** CNS metastases rarely herald the diagnosis of malignant melanoma. Instead, they typically occur later in the disease course and often represent the first metastatic focus *(66,72,73)*. The interval between the diagnosis of a primary skin lesion and the first appearance of CNS involvement varies according to the initial site of the primary lesion, occurring earlier in those patients with head and neck primary tumors. The first appearance of neurological signs or symptoms of CNS involvement typically manifests 2–4 yr after diagnosis *(25,68,69,74)*.

## PARENCHYMAL BRAIN METASTASES

**GENERAL** In general, patients with brain metastases have advanced, widespread, and uncontrolled systemic cancer. Not surprisingly, more than 70% of patients with brain metastases from grouped histologies eventually succumb to their systemic disease. In contrast, brain metastases from malignant melanoma directly contribute to patient death in up to 95% of patients *(25)*. Moreover, compared to patients with other forms of brain metastasis, patients with melanoma tend to be younger (<50 yr), often have excellent performance scale scores, and have a longer disease-free survival between the initial diagnosis and development of metastatic disease *(24)*. Because patients with brain metastases from melanoma usually die from neurological sequelae, most clinical research trials exploring treatments for metastatic melanoma exclude patients with brain metastases. It is notable that rare case reports describe long-term survivals of patients with melanomatous brain metastases, ranging between 3 and 18 yr *(56,75–79)*.

Brain metastases carry the worst prognosis of all distant metastases in patients with melanoma *(59,80–82)*. CNS metastases occur in up to 75% of all patients who die from melanoma and contribute to morbidity and mortality in one-half of all patients with disseminated disease *(23,25,50,53, 54,69)*. Of patients with brain metastases from malignant melanoma, those with metastatic disease limited to the brain have the best outcomes *(25,59,68,69,72,83,84)* and those with widely disseminated disease the worst *(25,57)*. However, the complete surgical resection of metastases at other visceral sites may improve survival *(59,80,85–89)*. Patients with brain metastases and concomitant single-organ extracranial disease have survival rates comparable to patients with brain involvement alone. Exceptions are coexistent lung or liver metastases, which result in a significantly worse prognosis compared to other sites of single organ involvement *(25,59,69)*. General negative prognostic indicators derived from a recursive partitioning analysis of prognostic factors in patients with brain metastases from all cancers include poor performance status, the presence of systemic tumor activity, and age over 70 yr *(90,91)*. In addition, there is some data suggesting that patients who do not improve neurologically with steroid therapy have poorer response rates to radiotherapy and decreased overall survival rates *(91)*.

**CLINICAL PRESENTATION** The majority of brain metastases are symptomatic during the lifetime of the patient. The signs and symptoms of brain metastases vary according to tumor growth rate and localization. Tumors can produce symptoms directly via destruction of neurons or by the compression of surrounding brain structures. Indirect tumor effects include seizures related to the focal irritation of neurons, mass effect related to vasogenic edema surrounding the tumor, or hydrocephalus produced by obstruction of ventricular outflow. Brain metastases from melanoma are associated with seizures in nearly half of patients, which is considerably higher than the 25% incidence seen with brain metastases from other primaries *(60)*. Other common presenting symptoms include headache, focal weakness, cognitive impairment, and behavioral disturbances. Symptoms inconsistent with tumor location on imaging studies should raise suspicion for leptomeningeal spread or multifocal tumor.

Similar to other primary tumors, brain metastases from malignant melanoma have a predilection for localization to the gray-white matter junction and are distributed roughly in proportion to brain volume and blood flow distribution. As such, 80–85% of metastatic lesions involve the cerebrum, 10–15% the cerebellum, and 3–5% the brainstem *(64,71,92–94)*. Compared to other primary tumors, melanoma has the highest tendency to produce multiple lesions *(45,51,78,95)*.

The superiority of gadolinium-enhanced magnetic resonance imaging (MRI) over contrast-enhanced computerized tomography (CT) in the diagnosis of brain metastases is unquestioned. MRI is particularly sensitive in the detection of

smaller metastatic deposits and infratentorial lesions *(96–98)*. Melanoma metastases are often heterogeneous in appearance, demonstrating contrast enhancement as well as necrosis and hemorrhage within individual lesions. These tumors characteristically show increased signal intensity on noncontrast T1-weighted imaging sequences as a consequence of methemoglobin and melanin. Intraoperatively, the hyperpigmented lesions of melanoma metastases grossly appear well-demarcated from the surrounding brain tissue. However, microscopically these tumors can display infiltrative tendencies *(99)*. Microscopic invasion may play an important role in recurrence after gross total resection of single metastasis.

**INTRATUMORAL HEMORRHAGE** Acute bleeding into a metastasis represents a small proportion of intracerebral hemorrhage. 0.6 to 1% of hematomas in neurosurgical series *(100)* and 5.5% in one autopsy series *(101)* are attributable to intratumoral hemorrhage. Despite this, intratumoral hemorrhage can be a significant factor in the management of some types of brain metastases. Up to 20% of adult patients with brain metastases may have a catastrophic event secondary to intracranial bleeding *(94,102)*. Neoplastic hemorrhage is most common in patients with malignant melanoma and germ cell tumors *(100,103–109)*. Clinical series report intratumoral hemorrhage in 25–50% of patients with brain metastases from malignant melanoma *(24,39,60,74,94,102,105,110)*.

The majority of patients with intratumoral hemorrhage present with subacute progressive symptoms typical of nonhemorrhagic brain metastases *(105)*. In some patients, the clinical presentation may mimic an evolving stroke with abrupt onset of headache followed by progressive obtundation and focal neurologic signs. Other patients exhibit acute worsening of preexisting neurological symptoms *(105,109,111,112)*. In one series, a significant proportion of patients were asymptomatic *(103)*. Medical conditions often associated with intracerebral hemorrhage, such as hypertension or thrombocytopenia, do not appear to contribute to intratumoral hemorrhage in malignant melanoma brain metastases *(110)*.

Up to 80% of brain metastases from melanoma have evidence of macroscopic bleeding *(24,105)*. When multiple metastases are present, simultaneous bleeding into most or all metastases is more common than an isolated hemorrhage *(105)*. Histopathologic evidence of prior hemorrhage is found in up to 25% of presumptive nonhemorrhagic metastases *(24)*. Hemorrhage may be confined to the metastatic brain tumor itself, occur in the area immediately adjacent to the tumor, or exist as an intracerebral hematoma intermixed with scattered tumor fragments. Both peripherally located and deep tumors can rupture to the surface of the brain or intraventricularly *(109)*. The mechanism of intratumoral hemorrhage is multifactorial, involving loss of vessel integrity associated with inter- and intratumoral necrosis and neovascularization *(110)*. Lesion size appears unrelated to bleeding tendency. Hemorrhagic metastatic tumors range in size from microscopic tumor deposits to 8 cm in diameter *(109)*.

Imaging characteristics suggestive of intratumoral hemorrhage, as opposed to hemorrhage unrelated to underlying tumor, include the presence of additional noncontiguous enhancing lesions, hemorrhage occurring outside of the basal ganglia region *(113,105)*, and enhancement adjacent to the blood clot *(105,111)*. Brain MRI may help differentiate neoplastic from nonneoplastic hemorrhages. Neoplastic lesions do not display the usual pattern of hematoma resolution on serial imaging studies and often have a heterogeneous intensity pattern on spin-echo sequences *(114)*.

**SUBDURAL HEMATOMA** One case series reports subdural hematoma in approx 50% of patients with cerebral melanoma *(115)*, but this is not typical. Subdural hematoma is symptomatic in only one-fourth of patients. Most commonly, nonspecific symptoms of acute confusion and lethargy are present. Fewer than 10% of patients have focal neurologic signs or symptoms *(105)*.

In patients with subdural hematomas associated with carcinomatous brain metastases, neoplastic infiltration of the dura at the level of the hematoma is common *(105)*. Brain metastases from melanoma do have a proclivity to spread peripherally. Furthermore, tumor contact with the leptomeninges is known to facilitate the development of an arterial supply from meningeal vessels *(112,116)*. It has been postulated that neovascularization at this level is an etiological factor in the development of metastatic subdural hematomas. Thrombocytopenia is rarely associated with subdural hematomas of nonleukemic origin *(105)*.

**TREATMENT OVERVIEW AND PROGNOSIS** Without treatment, the median survival of patients with brain metastases from malignant melanoma is 3 wk to 2 mo *(64,65,117,118)*. Whole brain radiation therapy (WBRT) may alleviate neurological symptoms and improve quality of life; however, it has a limited impact on life expectancy, improving median survival rates to between 2 and 6 mo *(56,60,64,69,72,119,120–125)*. Surgical resection of isolated or symptomatic brain metastases increases median survival to between 5 and 22 mo *(47,55,56,60,65,69,80,82,117,122,126–130)*. Similar if not better results are seen with radiosurgery *(57,60,68,84,91,118, 122,133–138)*. Whole brain irradiation following surgical resection or radiosurgery is of uncertain benefit. Some reports suggest a delay in time to neurologic disease progression and an overall trend towards improved regional disease control and survival *(57,102)*. The role of chemotherapy, immunotherapy, and tumor vaccines in the treatment of brain metastases from melanoma is poorly defined.

**WHOLE BRAIN RADIATION THERAPY FOR BRAIN METASTASES** Palliation of neurological symptoms is the primary treatment goal of whole brain irradiation. While this treatment modality essentially doubles the median survival compared to supportive care, the overall survival benefit is modest. Median survival is only between 2 and 6 mo *(56,60,64,69,72,119–125)*. WBRT addresses both gross tumor as well as microscopic tumor deposits within seemingly normal brain tissue. However, the large treatment volume limits the total radiation dose, potentially compromising local tumor control in this characteristically radioresistant tumor. Relative contraindications to radiation therapy include prior whole brain irradiation, active intracranial infection, and severe collagen vascular or cerebrovascular disease *(139)*. High rates of local recurrence are reported with WBRT. Over one-half of patients demonstrate local failure, which ultimately contributes to patient death *(123,140,141)*.

Acute neurological side effects occurring during radiation therapy usually result from increased perilesional vasogenic edema. Corresponding symptoms include headaches, nausea, lethargy, and increased intracranial pressure. Early delayed side effects resulting from damage to myelin manifest as a self-limited fatigue syndrome 1–4 mo following completion of radiation. A significant proportion of surviving patients will develop late effects of radiation. Symptoms result from radiation damage to normal brain tissue and usually occur 6–12 mo after whole brain irradiation. Approximately 11% of 1-yr survivors and up to 50% of 2-yr survivors develop dementia *(142,143)*. Other potential late effects include radiation necrosis, cerebral atrophy, and leukoencephalopathy *(142–144)*.

**SURGERY FOR BRAIN METASTASES** The goals of surgical resection are improvement or resolution of neurological deficits and increased survival. Surgical management of brain metastases is generally limited to those patients with a solitary brain lesion or patients with multiple metastases in which one dominant lesion is symptomatic. Selected patients with multiple brain metastases may be treated successfully with surgery. Similar survival rates have been reported for patients undergoing resection of solitary vs multiple brain metastases in one series *(145)*. Gross total resection is essential to fully realize the benefits of surgical intervention *(59,68,84,92,117)*. Symptomatic improvement is reported in 30–100% of patients undergoing surgical resection *(59,68,84,117)*. Thirty-one to forty-eight percent of surgically treated patients will develop recurrence in the brain *(143,145–147)*. For these patients, second resections may provide symptomatic relief *(25,59)* and can result in increased survival time *(148)*.

Surgical morbidity and mortality associated with resection of brain metastasis is low but not negligible. Fewer than 3% of patients die during surgery or in the immediate postoperative period *(143)*. Increased postoperative neurologic deficits are seen in less than 5% of patients *(55,143,145,149)*. Other complications, including infections and hematomas, occur in 8–9% of all craniotomies for brain metastases *(55,143,145,149)*. An estimated 10% of surgically treated will develop thromboembolic complications postsurgery *(150)*.

Three prospective randomized studies have evaluated the role of surgery as an adjunct to WBRT for patients with a single brain metastasis from grouped histologies *(131,149,151)*. Overall, patients treated with surgical resection followed by whole brain irradiation lived longer, had fewer local recurrences within the CNS, and had fewer neurological symptoms referable to brain metastases compared to patients receiving radiation therapy alone *(147,149,152)*. The most significant favorable prognostic factor was the absence of extracranial disease *(131,149)*.

The administration of postoperative radiation therapy specifically for patients with brain metastases from malignant melanoma remains controversial. Several retrospective studies have found increased survival in those patients treated with surgical resection followed by WBRT *(57,68,84,130)*. However, the survival benefit was limited and did not reach statistical significance. In patients with limited or no systemic disease at the time of craniotomy, one study reported a median survival of almost 20 mo when postoperative radiation doses ranged between 4000 and 5000 cGy *(57)*. This result is not confirmed in other series. Based on the results of these series, some propose a more aggressive approach in younger patients who present with a single brain lesion without evidence of progressive extracranial disease.

**RADIOSURGERY FOR BRAIN METASTASES** Radiosurgery is an external irradiation technique that provides a single high dose of radiation to a small target volume. Three types of high-energy radiation technologies are utilized—high-energy X-rays produced by linear accelerators, gamma rays produced by radioactive cobalt in the gamma knife, and charged particles such as protons produced by cyclotrons. The hallmark of these radiation techniques is the rapid fall-off of radiation dose at the target edge, minimizing dose delivery to the surrounding normal brain. Target lesions are usually less than 3 cm in maximal dimension and should be at least several millimeters removed from critical structures such as the optic chiasm.

Many patients with brain metastases are not candidates for surgical resection because of lesion location, multiplicity of tumors, or confounding medical issues. Radiosurgery is an appealing treatment option under these conditions. Retrospective studies of patients with metastatic brain tumors treated with radiosurgery report crude local control rates of 73–98% with median follow-up of 5–26 mo *(118,137,153–155)*. Three studies report analyses based on actuarial local control rates *(135,156,157)*. These studies combined show a 1-yr actuarial freedom from progression rate of greater than 80%. There is no apparent correlation between local control and number of lesions treated or type of histology *(156)*. Radiosurgery may provide better tumor control in relatively radioresistant tumor types, such as melanoma or renal cell carcinoma, compared to other tumor histologies *(135,136)*. However, in one report, univariate analysis found no differences between melanoma and adenocarcinoma, and multivariate subset analysis for differences in radiosurgical parameters and other prognostic factors showed significantly worse freedom from progression for melanomas *(157)*.

Improved local control does not necessarily equate to prolonged survival. Statistically insignificant trends toward improved survival are reported in most radiosurgical series. While lesion multiplicity is not related to local control rates, it may be linked to survival. Patients with multiple lesions may fare worse than patients with single lesions *(139)*. One report suggests that ring-enhancing and heterogeneous patterns of lesion enhancement at the time of radiosurgery correlate negatively with both radiographic response and freedom from progression *(157)*.

Several small retrospective case series address the provision of radiosurgery for malignant melanoma brain metastases. Treatment was limited to radiosurgery in only one report. In this series, 35 patients with one to three brain metastases either with or without extracranial disease were treated at presentation with radiosurgery alone *(158)*. Fifty-six of the 70 treated lesions were evaluable for response at 3 mo due to early patient death. The corresponding response rate was 98%. It is notable that 7 of the 35 patients survived more than 12 mo. Another series reported on 23 patients with primarily solitary metastases treated with WBRT and adjuvant gamma knife radiosurgery

*(102)*. With a mean follow-up of 12 mo, they reported a 97% local control rate and a median survival after radiosurgery of 7 mo (range 4–8 mo). A recent gamma knife series similarly reported a local control rate of 97% and a median survival of 8 mo following radiosurgery for metastatic melanoma *(159)*.

The most promising results are from a series of 40 patients treated at initial presentation or at disease recurrence with radiosurgery alone or adjuvant radiosurgery following surgery and whole-brain irradiation *(139)*. A total of 97 lesions were targeted with radiosurgery. In this heterogeneously treated group, the overall median survival was 46 wk after the diagnosis of brain metastases and 35 wk after radiosurgery. The actuarial survival probability at 1 yr following radiosurgery was 32%. The actuarial median freedom from progression analyzed by lesion was 111 wk. The median time to intracranial progression, including local failures and the development of new brain lesions was 21 wk, and the 1 yr actuarial freedom from development of new brain metastases was 45%. A statistically insignificant increase in survival was observed in patients with solitary brain metastases (37 wk) compared to those with multiple metastases (33 wk). Overall, this group had limited neurological deficits and control of extracranial disease prior to radiosurgery, which may partially explain the improved survival compared to other reports.

**RADIOSURGERY VS SURGICAL RESECTION** Radiosurgery and surgery are both local therapies. Surgery has an advantage over radiosurgery in immediately relieving neurological signs and symptoms secondary to tumor mass effect. Radiosurgery, on the other hand, offers reduced morbidity and decreased healthcare costs *(160)*. Both of these treatment modalities offer means of achieving local tumor control. This is of particular advantage for patients being considered for study protocols which exclude patients with uncontrolled CNS disease. Local tumor control rates for radiosurgery equals or surpasses those reported for surgical resection with or without fractionated radiotherapy *(124,135,149,159,161)*. The combination of whole brain irradiation with either radiosurgery or surgical resection improves local tumor and regional disease control but not survival *(131,135,149,157,162,163)*. Moreover, combination therapy delays the time to neurologic relapse within distant sites of the brain and the leptomeninges *(57)*. The effect of WBRT on local tumor control in the setting of recurrent metastases following radiosurgery remains uncertain *(135)*. A direct comparison of radiosurgery and surgical resection for the treatment of solitary brain metastases is not likely, as a randomized trial designed to address this issue was closed early due to poor patient accrual *(156)*.

Complications of radiosurgery occur in <10% of patients reported on in the published literature *(164)*. Most studies do not report significant side effects from the radiosurgical treatment of brain metastases, likely partially attributable to the relatively short survival period following treatment. When reported, early radiation reactions are the most common. Brain edema can result in transient worsening of preexisting neurologic symptoms, increased intracranial pressure, and breakthrough localization related seizures. These symptoms generally resolve with conservative management, including corticosteroid therapy and anticonvulsant medications. The incidence of acute effects is not known, but small retrospective studies suggest that 3–8% of patients experience acute side effects *(139)*.

Radiation necrosis is estimated to occur in less than 3% of patients with brain metastases. Isolated reports suggest that the actual incidence may be higher. In one study, the development of symptomatic radiation necrosis requiring reoperation for increasing mass effect and steroid dependency occurred in 6% of patients *(136)*. Misinterpretation of radiation necrosis as progressive tumor on imaging studies may further confound the issue. Risk factors for developing radiation necrosis include tumor volumes greater than 3 $cm^3$ and prior WBRT to doses greater than 40 Gy *(153)*.

**CHEMOTHERAPY** In contrast to surgery and radiation therapy, which are focal therapies, chemotherapy is a global therapy. In theory, it has the potential to address macroscopic and microscopic disease throughout the CNS as well as concurrent systemic disease. In reality, however, with the exception of germ cell tumors and possibly breast carcinoma and small cell lung cancer, chemotherapy for the treatment of brain metastases has not been shown to manifest meaningful response rates or improve patient survival *(165–170)*.

Throughout the world, dacarbazine (DTIC) is considered to be the single most efficacious chemotherapy agent for the systemic treatment of metastatic melanoma. Combination chemotherapy regimens containing DTIC are frequently used; however, studies have not shown increased response rates or improved survival with the combination regimens compared with DTIC monotherapy. Responses to chemotherapy in metastatic melanoma are disease site-dependent. Patients with skin, subcutaneous tissue, and lymph node involvement respond most frequently to DTIC with responses in 25–35% of cases, compared to 15% in patients with lung metastases, and 5–10% in those patients with bone, liver, and brain metastases. *(171)* The median duration of response is 3–6 mo. Other single agents with activity, the platinum compounds, nitrosureas, and tubular toxins, all show similar activity, with systemic response rates of 10–15% *(172)*. Scant isolated reports of metastatic brain melanoma responses to these agents exist, but these results are often contradicted in other publications *(173)*. Systemic disease response rates of fotemustine are similar to those obtained with other nitrosourea compounds. However, fotemustine has greater ability to cross the blood-brain barrier (BBB), and produces responses in 25% of patients with brain metastases from malignant melanoma *(174)*. Some have proposed that fotemustine is a viable alternative to whole brain irradiation for melanoma brain metastases; however, this approach has not gained widespread acceptance.

Biochemotherapeutic regimens, or the combination of multiagent cytotoxic chemotherapy and biologic response modifiers such as interleukin-2 (IL-2) and interferon-alpha (IFN-$\alpha$), are increasingly provided for metastatic melanoma. In clinical studies, response rates in systemic disease of greater than 50% have been achieved, with duration of responses from 5 to greater than 12 mo *(175)*. Biochemotherapy has not been specifically studied for the treatment of melanoma brain metastases. However, a recent report of combination chemotherapy (carmustine, cisplatin, dacarbazine) with IL-2 and IFN-$\alpha$ observed partial radiographic responses in 7 (47%)

of 15 patients with melanoma brain metastases. The median time to disease progression and median survival in this subgroup was 6 and 6.5 mo, respectively *(176)*.

Temozolomide is a pro-drug of monomethyl 5-triazeno imidazole carboxamide (MTIC), which is the active metabolite of DTIC. A large randomized Phase III study comparing temozolomide with dacarbazine in metastatic melanoma found similar response rates between the two groups and a nonstatistically significant favorable trend toward improved survival in the temozolomide treatment group *(177)*. This study confirmed the findings of an earlier Phase II trial and demonstrates that temozolomide is at least equal in efficacy to DTIC for metastatic melanoma *(178)*. Patients with CNS disease were excluded from these initial studies. However, temozolomide does penetrate the BBB and has demonstrated efficacy in the treatment of primary brain tumors.

The incidence of CNS relapse in patients with advanced melanoma who had previously responded to either temozolomide or DTIC was examined in a retrospective case-controlled study of 40 patients *(179)*. Preliminary results showed fewer CNS relapses in patients who were treated with temozolomide; however, small patient numbers preclude specific conclusions. Further exploration of the potential for temozolomide plus combination immunotherapy to prevent brain metastases in metastatic melanoma was a major objective of another clinical study *(180)*. At a median follow-up of 10 mo, none of the patients who achieved a response or maintained stable disease developed brain metastases. This suggests that therapeutic agents with activity against melanoma and reasonable penetration of the BBB may prevent or delay the time to CNS relapse. Preliminary results from two Phase II trials evaluating the efficacy of temozolomide for the treatment of brain metastases from solid tumors did not show significant responses in five melanoma patients *(181,182)*. Further studies are needed to define the role of chemotherapy in the management of brain metastases from malignant melanoma.

## LEPTOMENINGEAL METASTASES

Up to 19% of cancer patients with neurologic signs and symptoms will have evidence of meningeal involvement at autopsy *(183)*. Melanoma is the third most common solid tumor to metastasize to the leptomeninges after breast and lung carcinoma *(183–186)*. It accounts for 6–18% of all leptomeningeal carcinomatosis in large series *(183,185–187)*. Alternatively, approx 23% of patients with melanoma will develop leptomeningeal metastases *(188)*. One-half of patients with meningeal carcinomatosis have concomitant brain relapse *(57)*.

Clinical manifestations of leptomeningeal carcinomatosis result from obstruction of normal CSF flow, infiltration of nerves or occlusion of pial blood vessels within the subarachnoid space, irritation or invasion of underlying brain parenchyma, and alteration of CNS metabolism. The initial presentation is headache in up to one-half of patients and cranial nerve dysfunction in one-third of patients *(186)*. Mental status changes, seizures, back or radicular pain, incontinence, lower motor neuron weakness, and sensory abnormalities are also common symptoms. In one clinical series, the most common neurological examination finding was the asymmetric loss of deep tendon reflexes in 70% of patients, followed by cranial nerve abnormalities in 55%, cauda equina syndrome in 33%, and cognitive abnormalities in 31% *(186)*. Neurologic dysfunction at multiple levels of the neuraxis is found in most patients *(184–186,189,190)*.

Diagnostic confirmation of leptomeningeal carcinomatosis can be difficult. Definitive diagnosis relies upon the finding of malignant cells in cerebrospinal fluid (CSF), tumor nodules on nerve roots at myelography, or convincing evidence of leptomeningeal tumor with MRI. Malignant cells are found in the CSF at the first examination in 45–77% of cases with the diagnostic yield increasing up to 94% if multiple CSF samples are taken at different times or from differing locations *(186,189, 191,192)*. The diagnostic utility of biochemical markers in CSF has yet to be realized in this disease. Elevated CSF levels of lactate dehydrogenase (LDH) and LDH isoenzyme-5 are often present in patients with leptomeningeal involvement from melanoma *(193–196)*; however, these markers lack specificity and can be seen in nonmalignant conditions such as stroke, bacterial meningitis, and head trauma *(197)*.

Radiographic abnormalities are found in approx 50% of patients with spinal symptoms from leptomeningeal carcinomatosis *(186,198)*. Findings include meningeal enhancement along the cortical convexities or basilar cisterns, enlarged enhancing nerve roots, or hydrocephalus in the absence of ventricular obstruction. While these findings are suggestive of leptomeningeal carcinomatosis, they are nonspecific and of limited diagnostic utility. In contrast, multiple nodular enhancing subarachnoid masses on CT myelography or MRI are highly suggestive if not diagnostic of leptomeningeal carcinomatosis. Most imaging manifestations are better visualized with gadolinium enhanced MRI than contrast-enhanced CT *(199,200)*. Imaging also provides additional information that may impact diagnostic evaluation and/or treatment recommendations. It serves to exclude concurrent intraparenchymal or epidural metastases, identify areas of bulky disease, and demonstrate potential contraindications for lumbar puncture such as obstructive hydrocephalus or spinal block. In the appropriate clinical setting, imaging findings and relatively nonspecific spinal fluid abnormalities, such as an elevated protein or pleocytosis, are sufficient for a clinical diagnosis of leptomeningeal carcinomatosis.

Treatment of leptomeningeal carcinomatosis must address widespread tumor within the CSF space, bulky tumor deposits, and tumor spread within nerve root sleeves and Virchow-Robin spaces. Craniospinal irradiation adequately targets all sites of disease, but this treatment modality is limited by the relative radioresistance of melanoma as well as side effects inherent to this approach such as myelosuppression. Intrathecal chemotherapy does not adequately penetrate into bulky subarachnoid tumor masses, and its distribution within the CSF may be impeded by alterations in CSF bulk flow *(201)*. Radionuclide CSF flow scans demonstrate abnormalities in as many as 70% of patients with solid tumors *(202,203)*. Local irradiation to areas of symptomatic disease and abnormal CSF flow in combination with intrathecal chemotherapy provides treatment encompassing all disease sites, and is the mainstay of current therapy. Antineoplastic agents available for intrathecal

administration, mainly methotrexate, thiotepa, and cytosine arabinoside (Ara-C), have not demonstrated significant activity against melanoma.

Overall the response to therapy in leptomeningeal carcinomatosis from malignant melanoma is poor. Most evidence suggests that untreated, clinically evident leptomeningeal carcinomatosis produces precipitous neurological decline and death from neurologic disease with a median survival of 4–6 wk *(184–186)*. Treatment is palliative, and rarely results in effective local control. Diffuse brain symptoms, such as altered mental status, respond to therapy more often than focal neurological deficits. Even with aggressive treatment, between 35% and 76% of patients die as a direct consequence of their neoplastic meningitis rather than of their systemic disease *(186,191,192)*.

## SPINAL METASTASES

Spinal cord compression due to metastatic malignant melanoma occurs infrequently, and accounts for approx 1.5-5% of cases of spinal cord compression *(204,205)*. Patients with epidural spinal cord compression present with pain in 83–96%, sensory loss in 51–90%, weakness in 76–94%, and autonomic dysfunction in 57–69% *(206)*.

Spinal cord compression due to epidural metastases has a poor prognosis. As such, the primary goal of treatment is functional improvement or stabilization of neurological deficits. Small retrospective case series reviewing symptomatic spinal metastases from melanoma report neurological improvement in 20–71% of patients treated with radiation therapy alone *(130,204,207)*. Similar results are noted with surgical intervention *(122,208–212)*. The benefit of postoperative radiation therapy is unclear. In one report, radiation therapy alone was as effective as the combination of surgery and radiotherapy in radioresistant tumors. The provision of postoperative radiation therapy did not improve overall response in another series *(122)*. The median survival for patients with symptomatic spinal metastases undergoing surgical decompressive laminectomy is approx 1.5 mo *(208–213)*.

There are no randomized studies addressing whether or not surgical decompression provides better or more durable neurological responses compared to radiation therapy alone. Treatment recommendations must take into consideration the risk and recovery period of an extensive operative procedure in light of the uncertainty of clinical improvement and overall poor prognosis. Surgery may be justified in selected patients with good general health and no evidence of visceral or other distant metastases.

## INTRAMEDULLARY SPINAL CORD METASTASES

Metastases from melanoma comprise approx 6% of intramedullary spinal cord tumors *(214)*. Intramedullary metastases are often accompanied by disease at other levels of the neuraxis. Fifty to sixty percent of patients will have a history of prior brain metastases or simultaneous brain metastases *(206,215,216)*. Fifteen to forty-four percent have coexistent leptomeningeal disease *(206)*.

The presenting symptoms of intramedullary spinal cord metastases are similar to those of epidural spinal metastases: pain, sensory loss, weakness, and autonomic dysfunction. However, the presence of asymmetric spinal cord dysfunction in the pattern of Brown-Sequard syndrome or pseudo-Brown-Sequard syndrome, implicates intramedullary disease *(206)*.

Symptomatic intramedullary spinal cord metastases are most often treated with spinal irradiation. Radiation therapy with concurrent corticosteroids can stabilize or alleviate neurological dysfunction. As is the case with epidural spinal metastases, the loss of ambulatory capacity at presentation portends poor prognosis for neurological recovery.

## PLEXUS/PERIPHERAL NERVE METASTASES

Cutaneous melanoma itself rarely metastases to nerve root/peripheral nerve. However, a variant of melanoma, desmoplastic neurotropic melanoma, has a unique proclivity to extend along small peripheral nerves. This entity is synonymous with spindle cell malignant melanoma with neurotropism, desmoplastic melanoma, and neurotropic melanoma. Desmoplastic neurotropic melanoma usually occurs in the head and neck region, but it can be located in the extremities *(217,218)*. Typically patients present in their seventh decade and have precursor lentigo maligna *(219)*. The primary differential diagnosis is malignant peripheral nerve sheath tumors (MPNST), which can simulate desmoplastic neurotropic melanoma clinically and histologically *(220–224)*. Both types of tumors may express S-100 protein, and neural proteins may stain both Schwann cells and melanocytes. While melanoma-associated antigen HMB-45 is commonly found in melanoma, it can be rarely expressed in MPNSTs *(220)*. In the setting of immunohistochemical ambiguity, the pattern of disease involvement may help differentiate between these two entities. In particular, the presence of lymph node metastases implicates malignant melanoma *(225)*.

The mechanism of neurotropism in malignant melanoma is poorly understood. The nerve growth factor (NGF)/NGF-receptor system likely plays a role *(226)*. In vitro studies have demonstrated that the binding of NGF to its receptor can stimulate melanoma cell proliferation *(227)*. NGF is produced in peripheral nerves by Schwann cells. NGF receptors are rarely expressed in conventional epithelioid melanomas, but are highly expressed in neurotropic melanoma.

## PARANEOPLASTIC DISORDERS

**MELANOMA-ASSOCIATED RETINOPATHY** Photoreceptor degeneration as a paraneoplastic syndrome in patients with malignant melanoma has been recently reported. Melanoma associated retinopathy (MAR) is a rare condition characterized by abrupt onset of night blindness, photopsias, and peripheral or central visual loss. A male sex predominance exists *(228)*. Diagnostic studies reveal an electroretinopathy (ERG) pattern showing rod dysfunction with relatively normal cone function, and circulating antibodies to retinal bipolar cells. The corresponding antigen has not yet been identified. In most reported cases, the onset of visual symptoms occurs after the diagnosis of malignant melanoma has been established, either heralding or following the development of metastatic disease *(228–236)*. However, there is an isolated report of MAR night blindness preceding the diagnosis of melanoma *(237)*. Immunosuppressive therapy, such as steroids or plasmapheresis, has not been successful in restoring vision *(229,234)*.

**ANTI-HU RELATED ENCEPHALOMYELITIS** A high titer of anti-Hu antibody, also known as type 1 antineuronal nuclear autoantibody or ANNA-1, generally implies the presence of small cell lung cancer. However, it is rarely associated with other tumors, including melanoma *(238)*. Malignant melanoma can express the Hu antigen *(238)*, and isolated cases of anti-Hu paraneoplastic disorders have been reported in malignant melanoma patients *(239)*. In a group of ANNA-1 positive patients, one series found a 13% frequency of an unrelated primary malignany coexisting with small cell lung cancer *(239)*. This in conjunction with the overwhelming association of anti-Hu paraneoplastic disorders with small cell lung cancer underscores the importance of vigilance for SCLC in melanoma patients with anti-Hu antibodies.

**CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY** Isolated reports have proposed an association between malignant melanoma and chronic inflammatory demyelinating polyneuropathy *(240,241)*. This concept is supported by the rare observation of an inflammatory demyelinating polyneuropathy in patients receiving melanoma immunotherapy, in particular following the administration of monoclonal anti-GD2 antibodies or intradermal vaccinia melanoma cell lysates for metastatic melanoma *(242,243)*. Both peripheral nerve Schwann cells and melanocytes are derived from the neural crest and may share common antigenic components.

## NEUROLOGIC COMPLICATIONS RELATED TO THERAPY

**IFN-α THERAPY** Biochemotherapy, which is becoming the mainstay of treatment for metastatic melanoma, is not without side effects. Neurotoxicity is the major dose-limiting factor for IFN-α therapy. Although symptoms can occur at any time throughout treatment, 90% of side effects occur within 3 mo of starting treatment, 60% within 1 mo, 40% within 2 wk, and 20% within 1 wk *(244)*. Systemically administered IFN-α can produce subacute, reversible symptoms of impaired concentration, memory loss, cognitive slowing, reduction in goal directed behavior, and frontal lobe dysfunction. Incoordination and gait disturbance can also occur *(245–252)*. Subsequently, dysphoria, helplessness, and anhedonia may manifest *(253)*. Suicidal ideation and severe dysphoria can occur at the beginning of treatment or at the time of dose escalation *(253)*. For the majority of patients, discontinuation of IFN therapy results in remission of side effects in 2–3 wk *(254)*, although persistent symptoms have been reported up to 3 yr after treatment *(255)*. Long-term IFN therapy is associated with prominent dose-limiting fatigue *(260)*. In patients with leptomeningeal carcinomatosis, intraventricular administration of IFN-α at a cumulative dose from $14 \times 10^6$ IU to $54 \times 10^6$ IU was associated with a subacute reversible progressive wakeful vegetative state resembling catatonia. Prior brain irradiation may have potentiated neurotoxicity in this patient population *(256)*.

## CONCLUSION

Several characteristics distinguish melanoma brain metastases from brain metastases of other tumors. Brain metastases from melanoma have a strong tendency for both macroscopic and microscopic intratumoral hemorrhage. CNS metastases from malignant melanoma carry the worst prognosis of all sites of distant metastases in this disease. While the majority of patients with brain metastases from grouped histologies die from uncontrolled systemic disease, patients with brain metastases from melanoma usually succumb to a neurologic death. For this reason, patients with CNS disease are usually excluded from clinical trials for metastatic melanoma. Preliminary study results suggest that improved disease control at the initial management of metastatic melanoma may decrease the incidence of CNS disease. While palliative therapy is reasonable in patients with concurrent widely disseminated disease, more aggressive multiple modality treatment approaches are warranted in those patients with good performance status and absent or limited extracranial disease. Management decisions must consider both quality and quantity of life.

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# 24 Leukemia

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## INTRODUCTION

Neurologic complications are relatively common in patients with leukemia. They occur either as a result of direct dissemination of leukemia to the nervous system, or indirectly as a consequence of treatment. Leukemic cells usually infiltrate the leptomeninges, but rarely the brain parenchyma and peripheral nerves may be affected. Neurologic complications may also result from treatment-related neurotoxicity or bone marrow aplasia. This chapter focuses principally on the direct neurologic complications of leukemia, particularly leptomeningeal disease.

## DIRECT NERVOUS SYSTEM INVOLVEMENT

**CNS LEUKEMIA** Leukemia may directly invade any part of the central or peripheral nervous system (CNS/PNS), but most commonly involves the leptomeninges.

Leptomeningeal leukemia is an important complication of acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML), but occurs only rarely in plasmocytoma, multiple myeloma, chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML). For many years the French-American-British (FAB) classification of acute leukemias was used. This is a system based on morphology and histochemistry *(1)* which recognizes several subtypes of AML (M0-M7) and three types of ALL (L1 to L3). Newer immunocytochemical, immunophenotypical, cytogenetic, and molecular techniques are being used to subtype leukemias. These developments may provide better insight into the prognosis of subgroups of leukemia and help define more specific therapies *(2)*.

At the time of diagnosis of ALL, asymptomatic meningeal leukemia is present in cerebrospinal fluid (CSF) in 5–10% of patients. Meningeal leukemia occurs less frequently in AML. It occurs most commonly in patients with the myelomoncytic and monocytic subtypes (M4 and M5 of the FAB classification) where up to 20% of patients may have positive CSF cytology. Patients with chromosome 16 abnormalities are particularly prone to having CNS involvement, and there have even been reports of these patients with primary CNS leukemia *(3)*. In addition to leptomeningeal disease, intracerebral tumor nodules may also be found *(4)*. During the years prior to the routine use of CNS prophylaxis, isolated meningeal relapses were frequently encountered. In most cases hematological relapse usually followed shortly afterwards. With continuing improvements in the management of acute leukemia and the introduction of CNS prophylaxis, CNS dissemination is now much less common.

Uncontrollable leukemia affects the CNS in several ways. A high white blood cell (WBC) count can cause sludging within the small cerebral vessels, leading to hemorrhage or infiltration of the brain parenchyma by malignant cells. Patients with uncontrolled leukemia frequently also have severe thrombocytopenia, which can cause intracranial hemorrhages. Many of these patients will also have leptomeningeal and dural dissemination. Before the availability of effective cytotoxic drugs these complications were common. An overview of the natural course of these diseases without treatment can be found elsewhere *(5)*. Today, in the era of intensive systemic chemotherapy, dissemination in the leptomeninges occurs mainly in the setting of uncontrolled systemic disease or systemic relapse.

ALL is a disease of childhood and young adults and is found less often in the older age groups. The cure rate is especially high between the age of 2–10 yr. Adverse prognostic factors are a high initial WBC, organomegaly, B-cell leukemia, and cytogenetic abnormalities, such as a Philadelphia chromosome or translocation (t 4;11). Male and black patients fare worse. In contrast, a complete remission (CR) achieved within 4–6 wk is a good prognostic factor. Although 80–90% of adults can attain a CR on current treatment regimens, long-term survival is only 20–35%. More than half of the adults relapse within 2 yr *(6)*. It has been suggested that initial CNS disease carries a poor prognosis. However, this may have changed with the more intensive chemotherapy regimens. For example, Kantarjian et

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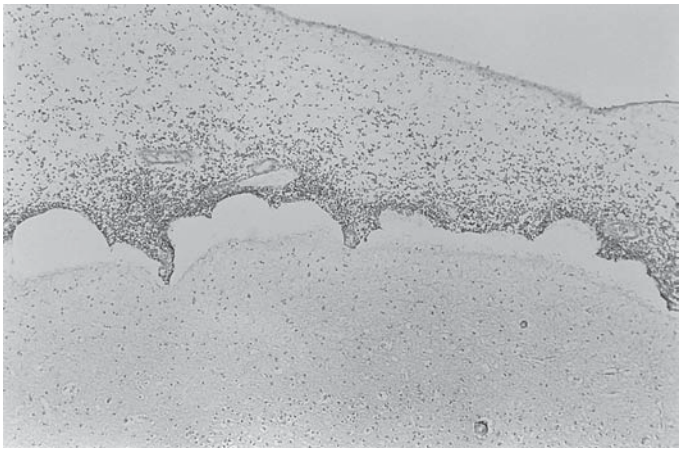

**Fig. 1.** Infiltration of the arachnoid over the cerebral cortex.

al. found no correlation between CR rates or survival with the presence of CNS leukemia at diagnosis *(7)*.

AML occurs more frequently in adults than in children. The incidence increases with age *(8)*. More intensive chemotherapy tailored to specific subtypes has improved the long-term survival to approx 35% in those under 65 yr. Bone marrow transplantation (BMT) in patients who achieve a CR reduces the relapse rate, but this is counterbalanced by a higher risk of death. More randomized trials are needed to define the exact benefit of BMT.

AML may give rise to solid tumors consisting of myeloid leukemic blasts called granulocytic sarcomas or chloromas. The term chloroma results from the greenish color of the tumors, similar to gaseous chlorine, caused by the presence of myeloperoxidase. These lesions occasionally develop before the diagnosis of acute leukemia is made and may be misdiagnosed. Rarely, they are associated with other myeloproliferative disorders. They usually have a dural attachment *(9,10)*, although parenchymal granulocytic sarcomas have been reported *(11,12)*. They are often hyperdense on precontrast CT scan, and typically enhance homogenously on CT and MR scan *(11,12)*. Neurologic findings depend on location. The development of granulocytic sarcoma usually heralds impending blast crisis. Since the intracranial lesions are highly radiosensitive, survival after diagnosis generally depends on control of extracranial disease with chemotherapy. Granulocytic sarcomas most commonly arise in bone, skin, or soft tissues. Rarely they occur in the vertebral column, where they potentially can cause epidural spinal cord compression *(13–15)*.

CML can undergo lymphoblastic transformation, which may then seed the leptomeninges. The meninges can also be infiltrated by CLL, but this is usually asymptomatic. Multiple myeloma can involve the skull and the skull base. Extension of these myeloma tumors can compromise adjacent cranial nerves and the brain. Meningeal dissemination has been described in myeloma but is extremely rare.

Adult T-cell leukemia is caused by the human T-cell lymphotropic virus type I. This virus can also cause tropical spastic paraparesis. Leukemic involvement of the CNS is characterized by infiltration by blast cells accompanied by multi-

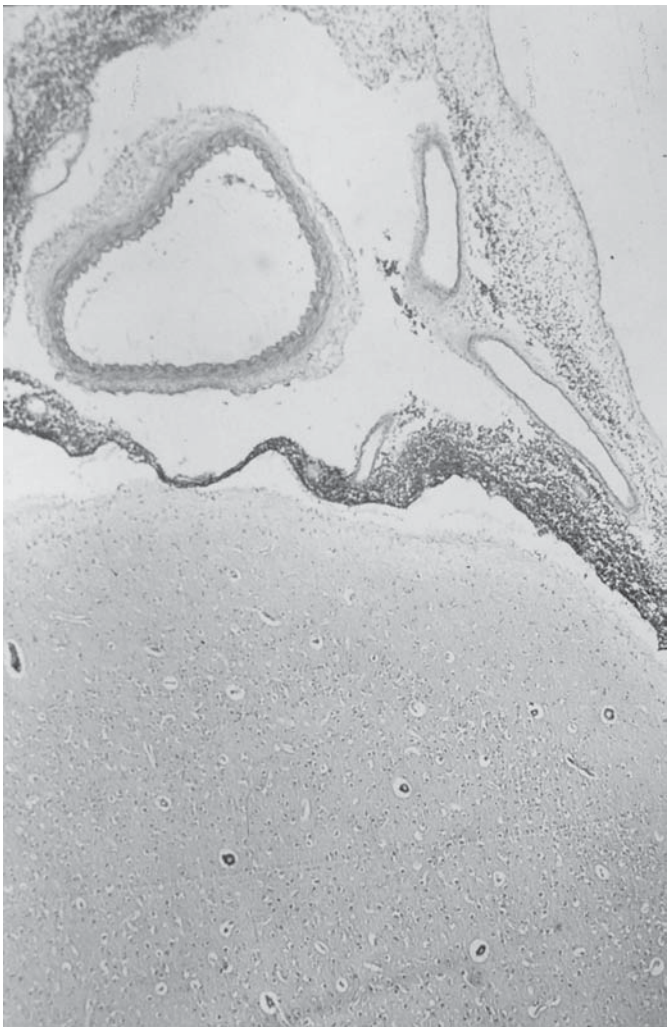

**Fig. 2.** Leukemic infiltrate around arteries in the arachnoid.

nucleated giant cells, reminiscent of findings in acquired immunodeficiency syndrome (AIDS) *(16)*.

In hairy cell leukemia, meningeal or cerebral infiltration are very uncommon *(17,18)*. The disease is rarely associated with a necrotizing vasculitis and may occur as an isolated cerebral event *(19,20)*.

**Leptomeningeal Leukemia after Introduction of Systemic Chemotherapy** After the introduction of cytotoxic drugs for acute leukemia in the 1960s an increased incidence of CNS relapse became evident. Malignant cells disseminated behind an intact blood-brain barrier (BBB) prior to treatment initiation presumably escaped the systemically administered chemotherapy. At the same time survival improved, so that patients remained at risk for longer periods of time. Price and Johnson described in detail the consecutive stages of this dissemination *(21)*. Malignant cells egress from the walls of the superficial arachnoidal veins to form perivenous infiltrates (Fig. 1). First they infiltrate the trabeculae of the arachnoid and encase the arteries (Figs. 2 and 3). Gradually the deeper parts of the arachnoid are invaded. Initially the infiltrate remains extraneural (Fig. 4). Whether malignant cells can be found in the CSF depends on cell shedding in the CSF, which does not always occur. Vascular structures, cranial nerves and spinal

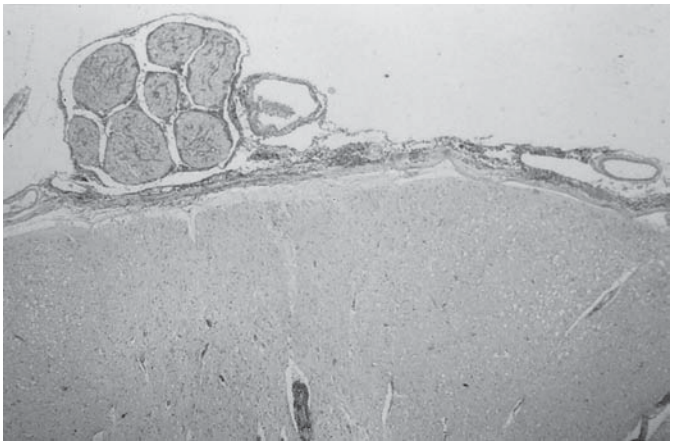

**Fig. 3.** Leptomeningeal leukemic infiltrate at the level of cauda equina and spinal cord.

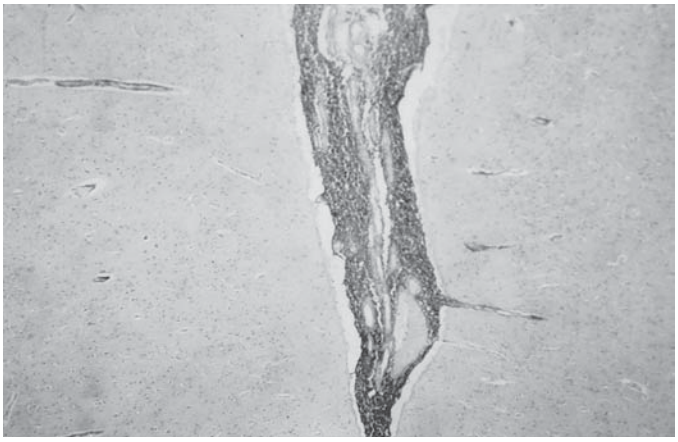

**Fig. 4.** Leptomeningeal infiltrate in the depth of a cerebral sulcus. No invasion of the brain parenchyma.

roots may become compressed. Finally the glia limitans is penetrated and blast cells may be found in the neural parenchyma (Figs. 5 and 6). These end stages are rarely seen nowadays with advances in the therapy for leukemias, especially the introduction of "CNS prophylaxis" during the 1970s and 1980s. Leukemic cells can also invade the dura, usually along venous channels. This gives rise to petechial hemorrhages, which is followed by fibrosis. With time, chronic subdural hematomas can develop *(22)*.

## SYMPTOMS AND SIGNS OF CNS LEUKEMIA

Leptomeningeal leukemia is a multifocal disease that can produce three types of neurologic dysfunction.

The first category consists of cranial nerve or spinal root dysfunction and is frequently seen in the early stages of the disease. Pain, paraesthesias, or myokymia may be present, but eventually functional loss predominates. Although all cranial nerves can be infiltrated, the facial nerve, abducens nerve, oculomotor, and trigeminal nerves are most frequently involved. Motor deficits can develop very rapidly, sometimes becoming complete in 1 or 2 d. This is explained by the fact that the malignant cells produce not only compression of the nerves, but may also involve the vasa nervorum, resulting in hemorrhages and infarction of the cranial nerves and nerve roots.

A second category is characterized by symptoms and signs resulting from involvement of the leptomeninges. Headache, nuchal rigidity, and a positive straight leg raising test may be present, although these signs may be very mild or absent.

A third category of clinical features results from involvement of cortical vessels and CSF flow by the leptomeningeal infiltrate. Transient ischemic attacks can occur as a result of hypoperfusion of cortical vessels, and there may be difficulty in reaching the correct diagnosis. Hydrocephalus may result from obstruction of the CSF pathways or diminished reabsorption of CSF.

Today, hematologist-oncologists and neurologists are aware that CNS disease should be considered in patients with acute leukemia who present with neurologic symptoms, even when they may be in remission. As a result of this increased awareness, patients with advanced disease are seen much less frequently than in the past. There are certain differences in presentation between children and adults. Early on, children may present with convulsions and papilledema, whereas adults usually present with vague headaches, subtle mood changes, and mild cranial nerve dysfunction. The older literature also reports hypothalamic and hypophyseal dysfunction in children. Hydrocephalus in meningeal leukemia patients is less prominent than in meningeal carcinomatosis *(23)*. This may be the result of the effectiveness of systemic treatment and the way "CNS prophylaxis" is administered. When initial (asymptomatic) meningeal seeding is treated by CNS directed chemotherapy, further dissemination in the meninges can be prevented and normal CSF flow can be retained or restored *(24)*.

## OTHER NEUROLOGIC MANIFESTATIONS OF LEUKEMIA

Epidural leukemic tumors adhering to the spinal roots are often misdiagnosed for some time. These patients frequently present with radicular symptoms, which are commonly attributed to a herniated disc. Most cases of epidural leukemia are caused by AML. Because of the location outside the BBB they are usually managed with systemic treatment, or when necessary, radiation therapy.

Thrombocytopenia occurs commonly in patients with leukemia either as a consequence of bone marrow infiltration or cytotoxic drugs. In leukemic patients hemorrhages usually occur when the platelet count falls below $20 \times 10^9$/L. Intracerebral, subarachnoid, and subdural bleeding may occur simultaneously. The subcortical brain structures are preferentially involved because of the tortuous vessels with thin walls in these areas *(25)*. AML-M3 patients are especially at risk because of an associated tendency for disseminated intravascular coagulation and subsequent hemorrhagic infarction. An underdiagnosed complication is oozing of blood within the subarachnoid space following routine movements of the spine. Patients may complain of upper thoracic back pain, that shifts to the lumbar region after a couple of days. The low platelet count often precludes a spinal tap and the diagnosis may have to be made clinically. The amount of blood is small in contrast with an aneurysmal subarachnoid hemorrhage. In the appropriate setting,

**Fig. 5.** Some perivascular leukemic invasion of the brain, thickened meninges.

evaluation for intracerebral aneurysms is unnecessary. If CSF is subsequently analyzed there will be macrophages laden with hemosiderin and degradation products of hemoglobin.

Patients with uncontrolled leukemia and high levels of circulating blast cells ($>100 \times 10^9$/L) may also be at risk of hemorrhage resulting from stasis within the blood vessels, followed by rupture of the ischemic vessel walls.

Patients with leukemia are also at risk of neurologic complications resulting from opportunistic infections. The disease itself produces a disturbed immune system. In addition, bone marrow aplasia due to chemotherapy and the influence of glucocorticosteroids, radiation therapy, and BMT are also important factors. Prevention of infection with appropriate antibiotics during critical periods may be helpful.

Peripheral nerve dysfunction in patients with leukemia are usually caused by drugs such as vincristine. Hemorrhages or infarction of peripheral nerves are extremely rare. Infiltration of these nerves by leukemic cells has only been reported in a limited number of cases in ALL, T-cell leukemia, AML-M4, acute megakaryocytic leukemia, acute myelomonoblastic leukemia, CLL, CML, and chronic promyelocytic leukemia *(26–33)*. Malignant cells are found around blood vessels in the endoneurium or perineurium and are considered to have escaped the effects of cytotoxic drugs behind the blood-nerve barrier. Very rarely patients presents with a rapidly progressive neuropathy resembling the Guillain-Barré syndrome. These cases may have an autoimmune basis and represent a form of paraneoplastic syndrome *(34)*. However, in general paraneoplastic syndromes are a rare cause of neuropathies in patients with leukemias.

## DIAGNOSTIC PROCEDURES

**Cerebrospinal Fluid** Overt meningeal leukemia may be accompanied by elevated CSF pressure, lymphocytic pleocytosis, increased total protein, and reduced glucose, but these findings are not specific and are of little importance for making an early presymptomatic diagnosis.

The gold standard for the diagnosis of meningeal leukemia is positive CSF cytology. However, the diagnosis cannot always be made in this way. CSF analysis should be part of the initial work-up in patients with ALL and AML, since these patients

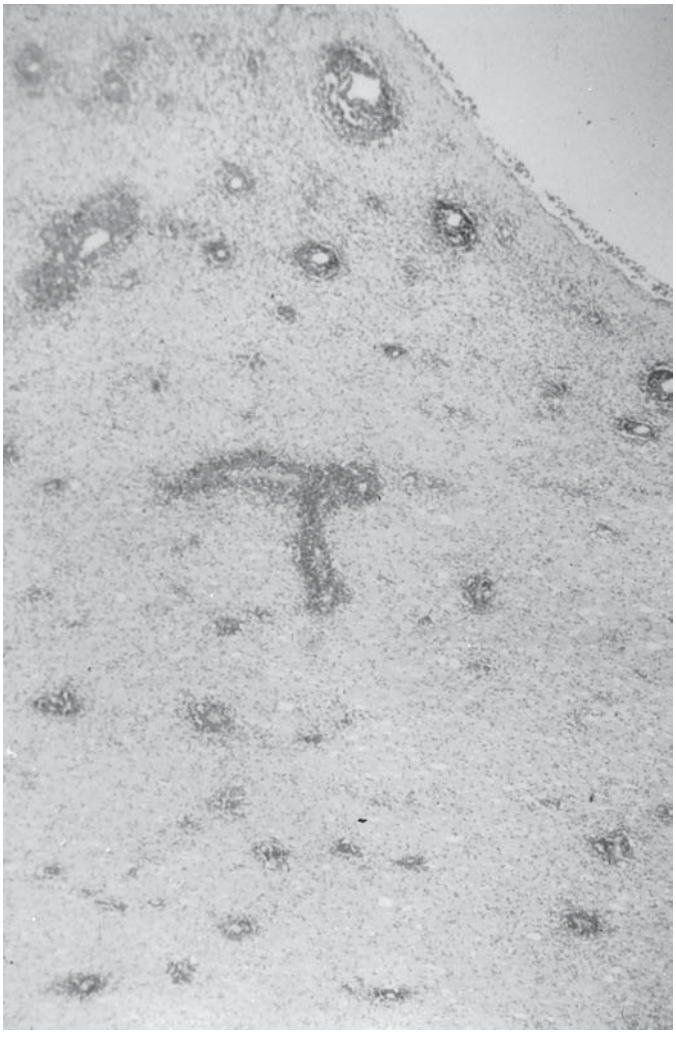

**Fig. 6.** Extensive leukemic infitration of the brain.

are at risk for CNS dissemination. CSF analysis should also be considered at the time of a systemic relapse and whenever meningeal relapse is suspected. Frequently, patients with meningeal recurrence will have suggestive clinical features. In the early stages of meningeal leukemia, CSF cytology is often positive while neuroimaging studies may be negative. As a result, CSF analysis is the procedure of choice. Neuroimaging studies should be performed first only when focal lesions that could potentially increasing the risk of lumbar puncture are suspected.

Accidental contamination of the CSF with leukemic peripheral blood or bone marrow cells can be prevented by administering the first dose of intrathecal (IT) cytotoxic treatment immediately after sampling the CSF. As long as the platelet count is $\geq 20 \times 10^9$/L, lumbar punctures are safe. Platelet transfusions are necessary if a lumbar puncture is required in a patient with a lower platelet count. In my experience, over a period of more than 25 yr, no postlumbar puncture intraspinal hemorrhage or headaches were observed when adhering to these rules (Haaxma-Reiche, unpublished observations). Patients undergoing placement of an Ommaya reservoir require a platelet count of $\geq 70 \times 10^9$/L at the time of the procedure and a value of $\geq 20 \times 10^9$/L during the first two postoperative weeks.

**Table 1**
**CSF Criteria for CNS Disease in Leukemia**

| | |
|---|---|
| CNS-1 | No blast cells present |
| CNS-2 | < 5 WBC's/μL with blast cells |
| CNS-3 | ≥ 5 WBC's/μL with blast cells or cranial nerve palsy |

***CSF Cytology*** If the initial CSF cytology is inconclusive a second lumbar puncture may be useful. Newer techniques such as immunocytochemistry or gene amplification may also help with the diagnosis of meningeal leukemia if the initial cytology is equivocal. In the past, the diagnosis of meningeal leukemia depended on the number of blasts in the CSF *(35,36)*. Currently, the CSF criteria for diagnosing meningeal leukemia is divided into three categories (Table 1). CNS-1: no malignant cells in the CSF; CNS-2: blast cells are present, but the WBC is <5/μL; CNS-3: WBC ≥5/μL with blast cells present or cranial nerve palsy. CNS-3 is compatible with a diagnosis of meningeal leukemia. The exact significance of a CNS-2 status is still a subject of discussion *(37–39)*. It is likely that these patients are at increased risk for developing CNS disease, although early intensive CNS-directed treatment may prevent this. The significance of this category may also differ in the different subgroups of ALL. Occasionally, leukemic cells adhere to the meninges and are not detected in the CSF. Although these patients have negative CSF cytology, they show clinical features of leptomeningeal leukemia. Frequently, CSF protein is increased and neuroimaging studies may show meningeal enhancement. In these patients, reexamination of the CSF after 1–4 wk may be helpful.

***CSF Pleocytosis*** Meningeal dissemination can be diagnosed when the cell count is elevated and the cells are predominantly blasts. Sometimes lymphocytes predominate. Only when 40–60% of these cells are blast cells can meningeal leukemia be diagnosed *(40)*. Otherwise a blast-like reaction due to a viral infection or a contamination with leukemic peripheral blood or bone marrow should be considered. In the appropriate setting it can be interpreted as a reaction to prior radiation or intrathecal chemotherapy. Rarely, an immune reaction to an Ommaya reservoir can cause a pleocytosis. Another explanation is a reaction to the systemic leukemia, without any CNS involvement. Reactive WBCs in the ventricular CSF due to a malfunctioning catheter may be a source of confusion. The simultaneous presence of reactive ependymal cells, multinucleated giant cells and histiocytes will lead to the correct explanation.

***Immunocytochemistry*** Subtyping of B and T cells is becoming increasingly refined. The use of double or triple labeling with fluorescence microscopy or flow cytometry can help distinguish malignant cells from inflammatory and reactive cells *(41)*.

***Gene Amplification*** Minimal residual (meningeal) leukemia can be detected by this technique, which requires only a minute amount of DNA *(42,43)*.

**Conclusions and Recommendations** For optimal diagnosis of leptomeningeal leukemia, it is important that the CSF specimen be delivered promptly to the laboratory and analyzed immediately. Obtaining CSF from a site with known disease may be helpful in meningeal carcinomatosis, but is less important with meningeal leukemia.

If newer laboratory tests are not available, one has to rely on the older diagnostic criteria, outlined in Table 1. The interpretation of these findings can be difficult. One should be aware that negative CSF cytology does not preclude meningeal leukemia. Alternatively, a positive cytology does not always indicate a diagnosis of leptomeningeal leukemia.

**Neuroimaging** The contribution of neuroimaging studies to the diagnosis of CNS leukemia is limited. They may be helpful for diagnosing leukemia dissemination in the brain, meninges, spinal roots, cranial nerves, and peripheral nerves. Intra-axial leukemic deposits in the CNS appear as hypodense lesions with surrounding edema which enhance peripherally after intravenous contrast on computerized tomographic (CT) or magnetic resonance imaging (MRI) scans of the brain. Other lesions may be isodense or slightly hyperdense on CT scans and enhance homogenously. These appearances are not specific. The differential diagnosis includes infections, hemorrhage, or treatment-related changes (e.g., acute necrotizing leukoencephalopathy *[44]*). In children and young adults, late sequelae of radiotherapy and chemotherapy, such as cerebral atrophy, leukoencephalopathy, and calcifications, may be present.

Leptomeningeal leukemic infiltrates are less likely to enhance than leptomeningeal lymphoma or meningeal carcinomatosis (*45*, Haaxma-Reiche, unpublished data). Only 6% of patients with leptomeningeal leukemia with a positive CSF cytology have cranial and spinal MRI abnormalities *(46)*. The use of glucocorticosteroids does not explain the lack of enhancement in most patients. Early leptomeningeal seeding may appear as asymmetric obliteration of sulci and cisterns *(47)*. Patients with advanced meningeal leukemia may show enhancement of cranial nerves, tentorium, sulci, and cisterns. There may also be hydrocephalus and ependymal enhancement. Late effects of glucocorticoid use and irradiation are reflected in diffuse atrophy of the whole brain.

Because the enhancing areas can be subtle in leptomeningeal leukemia, there may be confusion with other causes of leptomeningeal enhancement. These include transient postsurgical enhancement following placement of an Ommaya reservoir, enhancement following IT chemotherapy, intracranial hypotension following lumbar punctures, or reaction to subarachnoid bleeding in thrombocytopenic patients or in relation to small infarcts. In patients with leukemia, several of these causes may be present simultaneously. The significance of the enhancement will depend on the clinical context and the results of CSF examination *(48)*.

Dural infiltrates are often focal and may be mistaken for artifacts because of their location next to the skull *(49)*. Spinal epidural leukemic tumors are best detected by contrast-enhanced MRI. MRI and CT-myelography are useful for detecting intradural extramedullary nodules in the spinal canal. These nodules are isointense on T1- and T2-weighted MRI images and enhance minimally, but they appear as irregular filling defects especially along the cauda equina on CT-myelography *(50)*. In patients with more diffuse leukemic involvement, contrast-enhanced MRI will show thickened nerve roots and encasement of the spinal cord.

Leukemic infiltration of peripheral nerves may occasionally be visible on T2-weighted MRI. When the cause of a mononeuropathy cannot be localized by imaging the peripheral nerve, it is sometimes worthwhile investigating the proximal nerve trunk *(31)*.

**Conclusions** Neuroimaging can sometimes be helpful in diagnosing leukemic involvement of the nervous system but its role is limited. The findings are often subtle and easily overlooked. The diagnosis of leukemic dissemination in the nervous system should never be discounted because of normal neuroradiological studies.

## PRESYMPTOMATIC TREATMENT OF SUBCLINICAL LEUKEMIA IN THE CENTRAL NERVOUS SYSTEM

**Developments in Childhood ALL** Childhood ALL was the first acute leukemia to be successfully treated with systemic chemotherapy. The events that followed the introduction of this treatment were sobering. It became apparent that early in the course of the disease leukemic cells spread to the CNS, where they can proliferate, sheltered from cytotoxic drugs by the BBB. After a variable period up to 80% of these patients developed overt meningeal leukemia, even when they had a complete systemic response to treatment. To deal with this problem "CNS prophylaxis" was developed. Although grammatically incorrect, this term has been used for many years and since a good short alternative is lacking, it is still in use. Other terms used include "treatment for the prevention of meningeal relapse," "preventive CNS-directed treatment," and the heading above. The goal is eradication of disseminated malignant cells in the meninges in order to prevent subsequent isolated meningeal relapses. In addition to meningeal relapses, patients may also relapse simultaneously in the bone marrow or in other systemic organs such as the testes. If a CNS relapse occurs only 1–2 mo before the systemic relapse, this should not be seen as a failure of prophylactic treatment. This can be explained by the fact that a small leukemic burden may produce signs and symptoms earlier in the CNS than elsewhere.

The first "CNS prophylaxis" regimen consisted of cranial irradiation together with a number of lumbar IT injections with methotrexate (MTX) and prevented CNS relapses fairly well. However, this was achieved at the expense of considerable delayed neurotoxicity and an increased risk of radiation-induced neoplasms, especially brain tumors *(51)*. When antimetabolites were given concurrently with the radiation, the incidence of complications was especially high. A contributing factor may be a genetically determined deficiency of thiopurinemethyltransferase, an enzyme that inactivates 6-mercaptopurine, a drug commonly used in ALL *(52)*. In an attempt to reduce the incidence of neurological, neuropsychological and endrocrine sequelae in long-term survivors of leukemia while preventing meningeal relapse, several different therapeutic regimens have been evaluated in clinical trials *(53)*.

There has been a gradual change from one form of "CNS prophylaxis" for all ALL cases to preventive treatment tailored to specific ALL subgroups and certain risk categories defined by age, initial tumor load, WBC count, and initial response to prednisone. This has been made possible by the availability of ALL subtyping.

The developments in childhood ALL have provided the basis for the treatment schedules currently used for adults. The experience in children will be described first.

**Radiotherapy Plus Intrathecal Methotrexate** One of the earliest regimens used for "CNS prophylaxis" consisted of cranial radiation with 24 Gy and concurrent treatment with five doses of lumbar IT MTX 12 mg/m$^2$, administered soon after patients entered remission. This reduced the incidence of isolated meningeal relapse to ± 10% and remained the "gold standard" for some time *(54)*. Radiotherapy of the entire neuraxis was also effective but produced myelosuppression, which restricted the amount of chemotherapy that could be subsequently administered *(55)*. Since the brains of very young children are especially vulnerable to radiatiotherapy, subsequent studies evaluated the efficacy of reduced doses of radiation. A reduction in the dose of radiation therapy to 18 Gy *(56)* was found to be as effective as 24 Gy. Subsequently, with more intensive systemic treatment, a reduction of the radiation dose to 12 Gy became feasible *(57)*.

**Intrathecal and Intraventricular Chemotherapy** Neurotoxicity is increased when a patient receives more than one treatment modality, especially when whole brain radiation is followed by either IT or intravenous (IV) MTX. By calculating the dose of IT chemotherapy according to age instead of weight, it became possible to administer larger doses of drug. Administration of these increased doses of chemotherapy over longer periods of time allowed cranial irradiation to be omitted *(58,59)*. Other approaches that have been evaluated included combination therapy with IT MTX, cytosine arabinoside (ara-C), and hydrocortisone (HC) *(60)*, and administration of lumbar IT MTX injections over extended periods of time *(61,62)*. The results of these studies were disappointing, probably because of the unpredictable distribution of drugs administered into the lumbar CSF, resulting in subtherapeutic levels in the ventricles and intracranial subarachnoid space *(63)*. This problem can be largely circumvented by using an Ommaya reservoir to administer drug into the ventricles *(64)*. The distribution of the drug is much more physiological, and therapeutic drug levels can be achieved throughout the entire CSF compartment *(65)*. The Ommaya reservoir also allows frequent monitoring of CSF cytology and long-term maintenance treatment on an out-patient basis. Long-term treatment is necessary because of the slow kinetics of leukemic cells in the CSF. Another advance has been the use of oral dexamethasone instead of prednisone. The bioavailability of oral dexamethasone is better than prednisone is the CSF *(66)*, and the use of dexamethasone in several regimens has been associated with a reduced incidence of meningeal leukemia *(67)*.

**Intermediate or High-Dose Intravenous Chemotherapy** Regimens using intermediate dose IV MTX with concomitant IT MTX and can also prevent meningeal dissemination *(68)*. Other regimens currently in use include high dose IV MTX and ara-C, which results in therapeutic levels in the CNS. These high-dose regimens have prevented meningeal relapses, while treating other sanctuaries at the same time. Intrathecal MTX and occasionally ara-C are also part of several newer and more complex regimens. Increasingly, therapeutic regimens are being developed specifically for different subtypes of ALL taking into account patient risk factors.

**RESULTS IN CHILDHOOD ALL** The working groups on ALL had varying definitions of risk categories and different inclusion criteria for their trials, leading to conflicting results in earlier studies. More recent agreement on the definition of subtypes of ALL and recognition of risk factors have made it easier to evaluate newer treatments *(69)*. However, evaluation criteria remain variable, and the distinction between isolated CNS relapse and combined systemic and CNS relapse has not always made. These differences make it difficult to compare the results of different treatment regimens. Recently, most investigators have divided patients into two risk groups: high and low (or nonhigh, or standard). The various therapeutic regimens all attempt to reduce or eliminate the need for cranial irradiation from the CNS disease-preventing schedules.

An initial good response to prednisone is a favorable prognostic factor in ALL *(57)*. In B-precursor ALL other good prognostic parameters are an initial WBC count less than $50 \times 10^9$/L and age of 1–9 yr *(70)*. All other B-lineage ALL cases are classified as high risk. These patients currently receive combinations of high-dose systemic treatment based on the regimens from the Berlin-Frankfurt-Münster (BFM) Group *(71)*.

The success of IT prophylactic therapy is correlated with early treatment during induction of remission and continuation of the therapy for at least 1–2 yr *(72,73)*. Even in precursor B-cell patients cranial radiation can be replaced by alternating drugs (MTX, ara-C) or IT triple drug treatment *(74,75)*. Several studies indicate that this is also effective for B-ALL *(76–78)*.

There is no consensus on the risk designation of patients with T-cell ALL who have a high risk of developing meningeal leukemia *(79)*. In those children with T-cell ALL with WBC's up to $100 \times 10^9$/L and a good response to prednisone, cranial radiation can probably be omitted *(80)*. Other T-cell ALLs, including those with a hyperleukocytosis and those harboring a Philadelphia chromosome, still require cranial irradiation. Others consider that all patients with T-cell ALL require cranial irradiation.

Infants represent a very poor risk group. The number of isolated CNS relapses can be kept low, but bone marrow relapse occurs in nearly half of the patients *(81)*.

Currently the "gold standard" for the prevention of meningeal seeding is a CNS relapse rate of <5%. A number of issues remain unresolved, including the protective role of IT MTX for late bone marrow relapses and the possible effects of cranial RT on spreading of leukemic blasts from the CNS to elsewhere in the body.

Intensive IT MTX without cranial RT, together with systemic treatment such as the modified BFM regimen or Total Therapy from study XIIIA as used by the St. Jude Children's Research Hospital Group, also provides adequate presymptomatic CNS therapy for a large set of children with ALL, even for those with unfavorable presenting features *(82,83)*.

**PRESYMPTOMATIC CNS DIRECTED TREATMENT IN ADULTS WITH ALL** Adults with ALL fall automatically into the high-risk category, if only because of their age. The effects of preventive measures are much less well-studied in adults than in children.

The conventional "CNS prophylaxis" regimen (cranial radiation and five or six lumbar IT MTX doses) or treatment with IT drugs for more than 2 yr is successful in reducing the incidence of primary CNS relapses to less than 5–10% *(84–86)*. In patients with initial WBCs of more than $20 \times 10^9$/L, a schedule of early IT drugs, followed by intraventricular drugs for 3 yr, was equally effective *(64)*. A course of preventive treatment via an Ommaya reservoir for 6 mo is also sufficient in adult ALL cases *(87)*. High-dose ara-C with IT MTX was also an effective method, even without IT maintenance *(88)*. The same holds true for treatment with hyper-CVAD, another combination of high-dose cytotoxic drugs *(7)*.

A difference between children and adults is the higher relapse rate in the latter. A systemic relapse means that the meninges are again at risk for dissemination, negating the effect of any prior prophylaxis. This requires a preventive regimen that can easily be repeated, carries little neurotoxicity, and preferably can be administered in the outpatient setting.

If the original treatment involved 24 Gy or less of cranial radiation, radiotherapy can be repeated. Although the brain is less vulnerable in adults than in children, the eventual neuropsychological impairment limits the usefulness of this option. Brain irradiation may also impose certain restrictions on further systemic chemotherapy. It is becoming clear that in the older age group the use of chemotherapy alone should also be favored. Cranial radiation should be reserved for the treatment of meningeal leukemia, which cannot be treated with drugs alone. One option is to give only appropriate IV high-dose drugs or to combine the systemic treatment with additional intrathecal drugs, preferentially intraventricular or initially IT and subsequently intraventricular. For intrathecal chemotherapy to be effective, it should be administered on a long-term basis. It is important to start the treatment soon after diagnosis and to give frequent doses during induction treatment and to continue during the consolidation and a large part of the maintenance phase, with intraventricular injections administered at increasing intervals *(89)*. Although newer systemic regimens have reduced the incidence of meningeal dissemination, adult ALL still needs intraCSF prevention. It is appropriate to tailor the intensity of treatment to the risk group.

Adult ALL already falls into the high-risk group, but certain patients are considered to have even greater chances of developing meningeal leukemia. They have the following risk factors: serum LDH >600 U/L, a high proliferative index, initial WBC's $>5 \times 10^9$/L or the presence of a Philadelphia chromosome, the need for more than one chemotherapy course to achieve complete response (CR), and B-cell ALL. The more risk factors a patient has, the greater the chance for a CNS relapse.

There is currently no consensus on the best prophylactic schedule. Table 2 presents some of the options. In choosing a treatment, one should strike a balance between a low CNS relapse rate, minimal acute and late neurotoxicity, acceptance by the patient, and ease of administration in an outpatient setting. In the future, better systemic regimens may be developed based on improved understanding of the pharmacokinetics of cytotoxic drugs, especially in relation to the BBB. The DNA

**Table 2**
**Options for Prevention of Meningeal Relapse in ALL**

1. MTX or ara-C or triple drugs IT early during induction, frequency depending on classification and risk factors; cranial radiotherapy (12–18 Gy) plus IT MTX × 5–6, when systemic remission is reached.
2. The same as 1) with maintenance IT MTX q 8-12 wk up to 2 yr
3. Induction: IT MTX × 3, followed by intermediate dose IV MTX (500 mg/m$^2$) plus IT MTX q 3 wk × 3
4. High-dose IV MTX (3–10 g/m$^2$) + leucovorin rescue
5. High-dose IV ara-C 3 g/m$^2$/12h/3 d
6. Hyper-CVAD
7. MTX or ara-C IT early during induction, frequency depending on classification and risk factors, continued intraventricular via an Ommaya reservoir as maintenance q 4 wk × 6; repeated with a systemic relapse.

MTX regular dose IT or intraventricular in adults: 12 mg/m$^2$, max. 15 mg (usual dose 12 mg). Children: ≤1 yr 6 mg, 1–2 yr 8 mg, 2–3 yr 10 mg, 3–8 yr 12 mg, ≥ 9 yr 15 mg. Ara-C regular dose IT or intraventricular in adults: 50–100 mg; children: 30 mg/m$^2$, max. 30–50 mg. IntraCSF MTX can be alternated or substituted with ara-C. Triple drugs: MTX, ara-C, HC. HC regular intraCSF dose equal to MTX dose. Hyper-CVAD: cyclophophamide, vincristine, doxorubicin, dexamethasone.

index and cytogenetics will play a role in determining the criteria for using specific regimens.

**AML: IS THERE A PLACE FOR PRESYMPTOMATIC CNS DIRECTED TREATMENT?** Meningeal seeding in AML occurs slightly less often than ALL *(90)*. When CSF is examined at the time of diagnosis 20% of AML patients have a positive cytology. Some subtypes (M4–M5) have the highest rate *(91–93)*. Over the years it has been demonstrated that with the currently available systemic therapy, development of isolated meningeal relapses is rare.

There has been a gradual change in the preventive treatment regimens used for patients with AML. In the 1980s systemic treatment was less intensive and "CNS prophylaxis" had a beneficial effect *(94)*. Just as in ALL, cranial radiation with some IT drugs and long-term IT or intraventricular chemotherapy were used. Short courses of treatment were ineffective *(92)*. Overall outcome in AML is worse than in ALL. In 1993, the 3-yr event-free survival in adolescents and adults was approx 30%. This was slightly inferior to childhood results *(95)*. With more intensive drug treatment, and later allogeneic BMT, the rate improved to about 48%. Part of this latter regimen is total body irradiation, which may have an impact on the prevention of meningeal disease. Some favor cranial radiation when patients are not eligible for BMT. Others prefer IT ara-C as addition to systemic chemotherapy *(96–98)*. The incidence of isolated CNS relapse (approx 4%) is similar with the various treatment regimens. Others rely on high-dose systemic ara-C and omit specific "CNS prophylaxis." It has been shown that the initial positive CSF cytology in asymptomatic AML patients can clear completely with this kind of treatment.

## TREATMENT OF ESTABLISHED MENINGEAL LEUKEMIA

***General Principles*** The management of meningeal leukemia has evolved and is influenced by when meningeal seeding occurs during the course of the disease. Malignant cells that are present in the meninges or CNS when the diagnosis of leukemia is made are still drug-sensitive and easier to eradicate than CNS relapses occurring later in the disease course. Primary CNS relapses also respond well to treatment, especially when the first remission has lasted at least 18 mo *(99)*. Asymptomatic patients with CSF leukemic blast cells are more likely to achieve CNS remission and have a longer duration of remission than symptomatic patients. Those patients whose CSF clears rapidly also have a favorable prognosis. The response to treatment of meningeal dissemination in AML is in general better than in ALL. One consequence of the intensified multiagent schedules currently in use for both ALL and AML is that drug resistance may develop, making it more difficult to eradicate the malignant cells in the CNS at a later time. This is true both for early (within 18 mo) meningeal relapses and late uncontrollable disease.

**The Use of an Ommaya Reservoir** With lumbar intrathecal injections the circulation of drugs is unpredictable. After a few injections, spinal arachnoiditis and fibrosis may develop and interfere with the flow of the drug. As a result, it is generally preferable to administer drugs through an Ommaya reservoir. The reservoir also has other advantages, including easy access to the CSF space and a more even distribution of the drug throughout the entire CSF space *(100,101)*. The Ommaya reservoir also makes the procedure more convenient for the patients, especially now that regimens include a large number of intrathecal injections over an extended period. In younger children, where head growth must be considered, the device is probably less useful.

Meticulous attention should be paid to prevent infection during implantation and subsequent puncturing of the dome of the reservoir. This will effectively prevent contamination even in leukopenic patients. When reservoirs were first introduced there were concerns about the frequency of infectious complications. However, this is unwarranted with strict adherence to sterile techniques. Most of the inadvertent infections are caused by skin flora. Bacteria such as Staphylocccus epidermidis and Propionibacterium acnes can be managed without removal of the reservoir *(102)*. Antibiotics administered intravenously and into the reservoir can eliminate the infection in most cases. Bacterial cultures will guide the choice of the most appropriate antibiotic. In most adults, daily courses of antibiotics into the reservoir for approx 1 wk are sufficient, in combination with a more prolonged course of systemic antibiotics. The usual intraventricular antibiotics include cephalosporins such as cephradine (50 mg), cefuroxime (20–50 mg), and ceftazidime (10–20 mg), vancomycin (10–20 mg), or netilmycin (1–5 mg).

Centers with neurosurgical expertise in the insertion of the reservoir generally have fewer complications *(103,104)*. Usually the device is placed on the right side of the skull with the catheter tip in the ipsilateral frontal horn of the ventricle. Occasionally the catheter becomes obstructed and may produce a cellular reaction in the CSF. Interpretation of the cytology of the CSF obtained from another site may be confusing. Reactive ependymal cells can contribute to the correct differentiation between catheter malfunction and leukemia *(105)*. When the catheter is obstructed, administration of MTX may result in pericatheter leukoencephalopathy. A malpositioned catheter may cause even more damage. A prerequisite for any injection is a smooth flow. Whenever this does not occur the injection must be interrupted to detect and correct the blockage *(106)*. Sampling CSF through the Ommaya reservoir must be done slowly to prevent aspirating the choroid plexus or pulling on a collapsing ventricle wall *(107)*. Positioning the patient on his or her side can help to let these structures float away from the catheter side ports. Injecting sterile saline may help to push away the tissues (Haaxma-Reiche, unpublished data). When there is doubt about adequate CSF flow through the entire CSF compartment, a radioisotope ventriculography is often helpful in detecting any obstructions *(108,109)*. Treatment of these obstructions with radiotherapy may help restore normal CSF flow. Studies in patients with meningeal carcinomatosis suggest that patients with CSF flow obstructions generally have a worse prognosis. It is unclear whether the presence of CSF obstruction is also an adverse prognostic indicator in patients with meningeal leukemia, where bulky disease occurs much less frequently.

Patients cured of acute leukemia may ask for the reservoir to be removed. It is difficult to determine when the risk of relapse has decreased sufficiently to allow this to occur. Patient factors and the estimated risk of recurrence will help in the decision. Removal carries a small risk of hemorrhage from choroid plexus wrapped around the catheter tip.

Because MTX in the CSF penetrates only 2–3 mm into the underlying parenchyma, deeper-situated leukemic infiltration cannot be cured by intraventricular drugs alone and must be treated by radiation therapy or high-dose chemotherapy.

## HISTORY OF DEVELOPMENTS IN TREATMENT OF LEPTOMENINGEAL LEUKEMIA

**Radiotherapy** CNS leukemia is radiosensitive. Meningeal leukemia can be controlled by irradiation of the whole neuraxis in most cases. The disadvantage is that it causes a severe myelosuppression, which limits further intensive chemotherapy. In children, spinal growth is also affected. The current trend is to defer radiation for half a year, or even to postpone it until all drug options have been exhausted. Sporadically, tumor nodules in the meninges may obstruct the CSF flow. As discussed previously, the application of focal radiotherapy prior to intrathecal chemotherapy may restore free CSF flow and prevent build-up of high drug concentrations and neurotoxicity.

### Induction of CNS Remission by Intrathecal or Intraventricular Chemotherapy

Usually treatment starts with IT or intraventricular MTX or ara-C, or a combination of both drugs, together with HC every 3–4 d. This is continued until the CSF is free of leukemic cells. Without additional treatment the CNS remission usually lasts only 3–4 mo. Continuation of treatment at increasing intervals will double this period *(110)*. The effectiveness of drugs administered into an Ommaya reservoir is greater than that of drugs administered into the lumbar CSF *(100,111,112)*.

**CNS Remission Consolidation** It is clear that consolidation therapy is needed after achieving intraCSF drug-induced CNS remission. Previously this consisted of radiotherapy (cranial 24–30 Gy, spinal 0–18 Gy) *(113)*. This usually benefited patients with a first CNS relapse, but the role of radiotherapy for subsequent relapses is limited. While additional doses of 10 Gy to the spine has acceptable toxicities, an additional dose of 30 Gy to the brain will lead to significant neurotoxicity and adversely impact neuropsychological functions *(114)*.

In the 1970s and 1980s, continuous CRs were only achieved in 25–50% of patients. Although neuraxis irradiation was effective for the CNS, many patients failed in the bone marrow. During the 1990s intensified systemic therapy has improved outcome. Event-free survival (EFS) of four or five yr has been reported in 45–70% of ALL patients, even when craniospinal radiation was delayed for a couple of months. In one recent study, children with ALL with an isolated CNS relapse were treated with triple IT therapy for 6 mo plus systemic chemotherapy. This was followed by craniospinal radiation (24 Gy/15 Gy) and 18 mo of systemic maintenance treatment. 100% of the patients achieved a CR, while the 4-yr EFS was 71%. Children with an initial systemic remission longer than 18 months fared twice as well as those with a shorter one. Using this regimen, the long-term prognosis for children with isolated CNS relapse in the good prognostic group (first complete remission of 18 mo or more), was comparable to the outcome of those with meningeal leukemia at the time of the original diagnosis of ALL *(99)*. Additional trials defining the optimal treatment schedule are still ongoing.

**Combination of IntraCSF Cytotoxic Drugs and Low-Dose Radiation** Another approach involves the combination of IT/intraventricular treatment and low-dose neuraxis irradiation *(70)*. CNS remission is initially induced with intrathecal chemotherapy. Low-dose neuraxis irradiation (6–9 Gy) is then administered, while alternating intrathecal and intraventricular therapy is continued for a period of 3 yr *(70)*. In another study, children with CNS ALL were treated with intensive systemic and intraCSF chemotherapy, while radiation was delayed for ± 14 mo. This reduced the risk of neurotoxicity and made it possible to give 18 Gy to the brain and 12 Gy to the spine as consolidation. The CNS leukemia was brought under control in 90% of patients *(115)*. There is also a report that long-term intermittent low-dose craniospinal radiation and IT MTX for more than 2 yr also resulted in good disease control *(116)*.

For most patients with a second or subsequent CNS relapses the treatment of the CNS leukemia has to be modified to take into account prior therapies. The prior use of radiation therapy for CNS prophylaxis or treatment of a first relapse poses a particularly difficult problem.

**"Concentration × Time" Regimen** In 1978, Bleyer et al. reported on a regimen in which 1 mg of MTX was injected into

**Table 3**
**Treatment Options in Meningeal Leukemia**

| | | |
|---|---|---|
| 1. (a) | Induction: | Intraventricular (and/or IT) MTX, ara-C or alternating, or triple drugs, until CSF is cleared of blast cells.<br>MTX 12 mg/m$^2$ (max. 15 mg), lower doses in patients over 60 yr and with CSF flow obstructions; ara-C 50–100 mg; hydrocortisone 15 mg/m$^2$ (max. 15 mg),<br>If necessary focal radiotherapy. |
| (b) | Consolidation | |
| (c) | Maintenance: | Chemotherapy alone<br>(b) intraCSF q wk × 4, q 2 wk × 4<br>(c) intraCSF q 4 wk × 6 or q 3 mo for 3 yr<br>Or radiotherapy alone<br>(b) cranial 25 Gy and spinal 10 Gy<br>Or combined<br>(b) neuraxis 6 Gy plus<br>(c) intraventricular (and alternating IT) MTX or ara-C monthly for 3 yr<br>Or 1 yr of intensive systemic and IT chemotherapy followed by cranial radiation (24 Gy) |
| or | | |
| 2. | C × T regimen | Induction: intraventricular MTX 1 mg/12 h/3 d, q 7–10 d until CNS remission,<br>Consolidation: q 2 wk, × 3<br>Maintenance: monthly for 2 yr;<br>Desired CSF MTX level after 12 h $5 \times 10^{-7}$ min |
| | Alternative C × T regimen | Induction: intraventricular MTX 2 mg/24 h/3 d q 10 d until CNS remission<br>Consolidation: ara-C 15 mg/24 h/3 d, alternating with MTX 2 mg/24 h/3 d, every 2 wk;<br>Total of 4 courses<br>Maintenance: ara-C and MTX the same as during consolidation, every 4 wk, until CNS relapse |
| or | | |
| 3. | Craniospinal radiotherapy | In cases with additional intraparenchymal tumor, in cases failing intraventricular chemotherapy, or in multiple meningeal recurrences |

an Ommaya reservoir every 12 h for six doses. This resulted in therapeutic MTX levels *(117)* which were maintained much longer than after a single standard dose of 12 mg/m$^2$. The procedure was continued every 7–10 d until remission was achieved. The frequency of administration was tapered during a consolidation phase of 6 wk and a maintenance phase of 2 yr. Since elevated MTX levels in the CSF were avoided, the risk of MTX toxicity was reduced. However, this treatment is obviously more difficult for the patient.

A recent variation of this regimen involves injections of MTX or ara-C daily for 3 d, initially every 10 d, then every 2 wk, and finally every 4 wk *(118)*. In some patients it was maintained for more than 3 yr. These patients also received systemic therapy. The outcome was very good; 93% of patients achieved a CR in the CNS. The median CNS remission duration was 15 mo and there were some long-term survivors. It was also well-tolerated in heavily pretreated patients, in whom the CNS had been exposed to prior radiation and IT chemotherapy.

**Intraventricular Chemotherapy for First CNS Recurrences** In most adult patients with meningeal leukemia intraventricular treatment alone can result in CNS remission. Ara-C administered for 9.5 mo will produce CNS remissions in AML patients *(94)*. MTX can produce CNS remissions in ALL patients, but these are usually less durable than those in patients with AML *(87)*.

A slow-release formulation of ara-C, DepoCyt, has recently become available for the treatment of meningeal disease *(119)*. This has been evaluated mostly in patients with meningeal lymphoma and carcinomatosis; only a few leukemia patients have been treated. The advantages are predictable: fewer injections, better quality of life, cytotoxic drug levels maintained for more than 14 d, and a higher response rate. The exact value and place for this slow-release drug in the preventive and therapeutic setting of CNS leukemia remains to be determined in additional studies *(119)*. There are reports that radioactive monoclonal antibodies are beneficial in meningeal leukemia, but the use of these agents remain experimental *(120)*.

**High-Dose Intravenous Chemotherapy** As discussed previously, high-dose systemic chemotherapy plays an important role in the treatment of CNS disease. High-dose IV

MTX achieved complete CNS remissions in 80% of patients and partial ones in the others *(121,122)*. The efficacy of high dose ara-C is well known, and high-dose IV 6-mercaptopurine seems promising as well. These results were obtained during an era when patients received less intensive systemic chemotherapy. With the current intensive drug regimens, it is unclear whether leukemic cells in the meninges remain chemosensitive or whether they are becoming more resistant.

**Definition of Complete CNS Remission** CSF remission is achieved if there is negative cytology in two consecutive CSF samples 4 wk apart, together with improvement or at least stabilization of neurological signs and symptoms. Some patients have disparate cytologic results between their lumbar and ventricular CSF. In such cases CSF from both sites must be free of leukemic cells. When the diagnosis is made on clinical grounds and neuroimaging studies are suggestive of meningeal disease, CNS remission will be defined by normalization or stabilization of clinical signs.

**Second and Successive CNS Relapses** The use of alternating drugs can be helpful in controlling these recurrences. Radiation is rarely needed for meningeal dissemination in AML and only occasionally in subsequent CNS relapses in ALL. In the latter it is a last resort for end-stage disease.

**SUMMARY OF TREATMENT OPTIONS FOR CNS RELAPSE** In the preceding paragraphs several treatment approaches have been discussed. In determining the optimal treatment, it is important to take into account the severity of the meningeal dissemination and the point of time in the disease course. One should keep in mind whether the patient has: (1) an initial asymptomatic CNS-2 or CNS-3 status in the CSF; (2) initial symptomatic meningeal leukemia (e.g., cranial-nerve palsy, cauda equina syndrome); (3) a first isolated CNS relapse; (4) a combined bone marrow/systemic and CNS relapse; (5) successive CNS recurrences; or (6) treatment-refractory systemic and meningeal disease. The therapy should fit the type of meningeal leukemia in the particular patient. Table 3 represents an outline of several options.

1. Although the meaning of a CNS-2 status for prognosis has not been resolved, current intensive systemic regimens with or without special CNS-directed therapy can achieve complete remission in cases with CNS-2 findings. Asymptomatic meningeal leukemia with CNS-3 status warrants intensive treatment of the CNS.

2. The neurological deficits are a sign of advanced and aggressive disease for which special CNS-directed treatment is needed. In B- and T-cell leukemia such a presentation is frequently encountered, and tends to progress rapidly.

3. and 4. The first isolated CNS relapse is usually readily treatable, although it requires intensive intrathecal and systemic treatment. Radiation should be delayed as long as possible to make optimal use of the available systemic therapy. In this way systemic relapses are managed simultaneously.

5. Previous treatment will dictate second-line therapy.

6. In the palliative setting craniospinal radiation can be included.

**CNS LEUKEMIA: COMPLICATIONS OF TREATMENT** The success that has been achieved in treating patients with CNS leukemia has come with a price. The use of multimodality therapy has been associated with a number of neurologic complications (*see also* Chapters 12, 14–17). Over the years treatment regimens have been modified in an attempt to reduce the severity of these complications. Recent studies have started to improve our understanding of the mechanisms for the neurotoxicity, as well as to provide insight into intrinsic or acquired drug resistance *(123,124)*. This knowledge will improve the choice, dose, and timing of drugs in the near future.

Only a few drugs can be administered directly into the CSF. For ALL the first drug of choice is MTX and in AML, it is ara-C. Monitoring of drug level is worthwhile with MTX, but not needed with ara-C. Sometimes HC is added. Preservative-free solutions must be used, followed by flushing with either NaCl 0.9% or autologous CSF. Second line treatment can be given with mitoxantrone *(125,126)*. Its neurotoxicity is not well known.

**Methotrexate** The neurotoxicity related to MTX can be acute, subacute, and delayed. The dose, route of administration, and the variable elimination rate in patients play a role *(59,65,127–129)*. Prior or concurrent CNS irradiation increases the severity of the complication.

Acute, transient focal cerebral dysfunction is seen after (very) high-dose IV MTX, especially in patients with osteogenic sarcoma, but is uncommon in leukemia. An acute meningeal reaction can develop several hours following IT/intraventricular treatment, and usually resolves after 1–2 d. After a couple of injections this reaction usually diminishes in most patients.

A subacute encehalomyelopathy occurs when the MTX level in the CSF is high, especially if this persists for a long time. This complication may be caused even by standard doses of IV MTX in patients who have received cranial irradiation. The addition of IT medication increases the risk. Seizures are a common presentation in children. Mental status changes and headache predominate in adults. In symptomatic patients brain CT and MRI will show white matter changes. This complication may be reversible when it is mild.

Chronic MTX neurotoxicity is characterized by a progressive leukoencephalopathy with or without calcifications. The more treatment modalities used in a patient, the higher the risk. The youngest patients are the most vulnerable. Poor academic achievement and psychsocial functioning have been reported in long-term survivors of ALL who received the standard "CNS prophylaxis" with cranial irradiation and IT MTX in the 1970s *(130)*. Before the age of 5 yr IT MTX causes structural and functional effects on the developing neocerebellar-frontal subsystem. These effects are measurable on morphometry and neuropsychological testing *(131)*.

The balance between therapeutic exposure to MTX in the CSF and the hazard of neurotoxicity can be difficult. It is reasonable to aim for a CSF MTX level of $10^{-6}$ mol/L for at least 72 h. This is the approximate duration of the cell cycle. Newer preventive regimens are being developed with the aim of minimizing long-term neurologic sequelae.

**Cytosine Arabinoside** Very high-dose or prolonged high-dose ara-C damages Purkinje cells, resulting in severe cerebellar ataxia *(132)*. As a result, lower doses are generally used today. Nonetheless, reversible generalized cerebral dysfunction

and transient cerebellar syndromes may occur in those over 60 yr of age or with hepatic and renal impairment. A demyelinating polyneuropathy may rarely occur. The demyelination may be caused by a direct toxic effect on Schwann cells or is due to an immune-mediated process triggered by the high-dose ara-C *(133)*. Ara-C administered into the CSF may result in arachnoiditis or myelopathy, but these are relatively uncommon.

**Corticosteroids** These drugs have an oncolytic effect on leukemic cells. Some authors also use HC as part of intrathecal chemotherapy to prevent a meningeal reaction to MTX. However, this is controversial as HC comes with a preservative that may itself induce an inflammatory reaction *(134)*. In vitro HC even inhibits MTX accumulation in L1210 leukemic cells *(135,136)*. Prednisolone initially played an important role in induction treatment. However, the CSF/plasma ratio of dexamethasone is higher than that of prednisolone, because of differences in plasma protein binding *(66)*. In addition, dexamethasone appears to be more effective than prednisolone as a preventive measure against CNS dissemination *(137)*. As a result, dexamethasone is usually incorporated into treatment schedules for children and adults *(7,71)*.

**Bone Marrow Transplantation** Allogeneic and autologous BMTs are increasingly used to treat leukemia. The conditioning regimen consists of high-dose chemotherapy and frequently, total body irradiation, to eradicate the remaining leukemic cells. When the hematopoietic stem cells come from an HLA-matched donor (allogeneic BMT) immunosuppression is obligatory to avoid rejection of the graft and also to minimize graft-versus-host disease (GVHD). Neurologic complications are common with bone marrow transplantation, *(138)* (*see* Chapter 17). Metabolic encephalopathy occurs frequently and is mostly a consequence of GVHD, because several major organs will be involved. Seizures occur frequently as a result of metabolic abnormalities, infections, and drugs such as busulfan in the conditioning regimen or cyclosporine given for immunosuppression. Patients receiving autologous BMT may be at increased risk of intracranial hemorrhages, especially subdural hematomas. This is often caused by thrombocytopenia and is a particular problem in AML patients because of defects in the magakaryocyte progenitor cells *(4)*. Opportunistic infections also occur frequently. Minor problems such as headache and tremor may result from cyclosporine *(139)*. The peripheral nervous system is only rarely involved. Nonspecific polyneuropathies and mononeuropathies may occur. Sporadically intraneural hemorrhage can be occasionally be demonstrated. Patients with GVHD may develop myasthenia gravis, polymyositis, or chronic inflammatory polyneuropathy. Myopathy may also be caused by corticosteroids. Patients without any complications from BMT tend to have a better prognosis for overall survival.

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# 25 Neurologic Complications of Hodgkin's Disease and the Non-Hodgkin's Lymphomas

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## INTRODUCTION

Lymphomas are malignant neoplasms of the hematopoietic system, specifically lymphocytes. They are a diverse group of disorders clinically, histologically, immunophenotypically, and genotypically that vary in their natural history, treatments, response to therapy, and survival rates. The most common and most prevalent subtypes in the United States are Hodgkin's disease (HD) and the non-Hodgkin's lymphomas (NHL). These two forms will be the foci of this chapter.

Lymphomas arise in lymph nodes or in lymphoid tissue but also may involve extranodal tissues such as liver, lungs, and the central nervous system (CNS). Most NHL originate from a monoclonal population of B-lymphocytes. T-cell derived NHL are less common. HD is characterized by a unique cell, the Reed-Sternberg cell.

Multiple classification schemes have been proposed for both subtypes. The most recent, and most widely used, classification for NHL is the World Health Organization (WHO) Classification which was developed from the "Revised European American Lymphoid Neoplasms (REAL)" Classification *(1)*. Similarly the latest international classification system for HD is the Cotswalds' modification of the Ann Arbor Classification *(2)*. Treatment varies with the histologic classification, type of presentation, extent of disease, new vs relapsed disease, and, if relapsed, prior treatment. A new prognostic classification, the International Index *(3)* has been developed for intermediate and high-grade NHL. Patients with a high risk based on this index are less likely to obtain a complete response (CR) to chemotherapy and have a higher relapse rate following a CR.

Apropos this discussion there is wide variation in the incidence, frequency, and type of neurologic involvement in the lymphomas. In 1980 Cairncross and Posner described the differing neurologic manifestations of hematologic malignancies and, in particular, described the differing manifestations of HD and NHL *(4)*. For example, in the former dural involvement is common and leptomeningeal and parenchymal (intradural) disease rare; the opposite is true for NHL. Table 1 summarizes the differences between the neurologic complications of HD and NHL

Five caveats relate to this variability in neurologic involvement. First, the lymphomas occur by clonal expansion of normal lymphocytes. Thus, the malignant lymphocytes may retain some or most properties of normal lymphocytes at least temporarily (undoubtedly they lose these characteristics as they becomes progressively more dedifferentiated). This characteristic is best exemplified by the "ghost tumor" response, i.e., lymphocyte apoptosis in response to corticosteroids (v.i. *[5,6]*). Second, these patients may have simultaneous or sequential disease involving multiple sites in the central and peripheral nervous systems, and the deficits associated with these disorders may be amplified by the effects of previous therapy and, since these patients are often older, co-morbidity *(7)*. Third, by inference, lymphoma occurs in hosts who have alterations in their immunocompetence *(8)*. Thus, patients may have neurologic disease not only directly related to lymphomatous involvement; they may also have neurologic disorders that are dysimmune in origin. For example, we have had examples of patients developing corticosteroid-responsive idiopathic thrombocytopenic purpura and Hashimoto's thyroiditis many years after complete remission of the presenting cancer. Fourth, biologic differences themselves likely contribute to the inter- and intratumoral phenotypic variation discussed two decades ago by Cairncross and Posner *(4)*. As a corollary, sustained control or cure of neurologic disease will only occur if systemic disease can be successfully treated. Fifth, although some of these complications may be the presenting symptoms of systemic lymphoma, they typically are late phenomena and their occurrence correlates with high-grade, widespread and especially extranodal disease, and bone marrow involvement *(9,10)*.

This chapter reviews the neurologic complications of HD and the NHL. In so doing I have made several arbitrary decisions. First, I have chosen to describe those conditions as a

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**Table 1**
**Neurologic Complications of HD and NHL**

| | *Hodgkin's disease* | *Non-Hodgkin's lymphoma* |
|---|---|---|
| Intradural | | |
| • Parenchymal CNS | Not reported | Rare |
| • Neoplastic meningitis | Very rare | Common; may be presenting syndrome |
| • Other | Eosinophilic meningitis | Intravascular lymphoma |
| | Lymphomatoid granulomatosis | Pituitary lymphoma |
| Dural and extradural | | |
| • Dural | Common | Common |
| • Epidural spinal cord compression | Common | Common |
| • Other | | Neurolymphomatosis |
| Paraneoplastic | Cerebellar degeneration | Subacute motor neuronopathy |

result of actual lymphomatous involvement of the nervous system and those directly related to the disease, such as paraneoplastic disorders. Second, based on nearly 15 yr of consultation on neurologic problems of patients with these diseases, I have chosen to highlight concepts by examples from my own experience. Third, neurologic complications of treatment such as encephalopathy and neuropathy are purposely underdeveloped. Reviews of these are widely available from multiple sources, especially Posner's excellent monograph, *Neurologic Complications of Cancer (11)*. Of course, specific examples are noted when appropriate such as in the differential diagnosis of plexopathies. Finally, controversy exists over whether primary central nervous system non-Hodgkin's lymphoma (PCNSL) is a brain tumor that happens to be a lymphoma or a lymphoma that happens to be in the brain. Conventional thinking treats PCNSL as a unique entity and thus it will not be specifically discussed in this chapter.

The vast majority of the neurologic complications of the lymphomas occur in the NHL and of these the diffuse large B-cell type (DLC NHL). In one series 98% of the neurologic complications occurred in DLC NHL *(12)*. Nevertheless these are relatively uncommon overall. Liang and colleagues estimated a 6% risk of neurologic complications in 833 NHL cases diagnosed in the modern neuroimaging era *(13)*. No case of low-grade lymphoma developed neurologic involvement. However, 6.5% and 16.7% of patients with intermediate and high-grade lymphomas, respectively, had involvement. Stage IV disease, an elevated serum LDH, presence of circulatory lymphoma cells, and the presence of B symptoms were also associated with an increased risk of CNS disease *(9,10,13)*. The majority of cases had either epidural spinal cord compression or leptomeningeal lymphoma. In the Liang series a significantly higher incidence of CNS disease was seen in patients with lymphoma involving orbit (43%), testis (40%), peripheral blood (33%), bone (29%), nasal/paranasal sinuses region (23%), and bone marrow (20%).

Approximately 10% of all NHL are T-cell lymphoma (TCL). In contrast to B-cell lymphomas, Kaufman and colleagues *(14)* reviewed the incidence of neurologic complications in TCL and found that the overall rate of neurological complications was 7.9%. The frequency of neurological complications in peripheral TCL and cutaneous TCL was 17 and 3%, respectively, with at least half of the neurological complications in both conditions due to direct involvement of the nervous system (leptomeningeal and parenchymal involvement). Unlike the situation in B-cell NHL there were no cases of epidural spinal cord disease.

In HD precise figures are lacking. One can only conclude that this is partly because of its rarity. In one series of more than 2000 patients with HD, none presented with direct neurologic involvement *(15)*. Neurologic disease, when present, was usually seen with advanced HD *(16)*. In preparation for this chapter I conducted a review of the *Medline* resource over the entire time period of its existence, January 1966–December 2000. Only 82 citations were retrieved when "Hodgkin's disease" and "neurologic disease" were used as key words. The vast majority of these citations described indirect complications, that is, neurotoxic and infectious complications; were from the 1970s and 1980s; and arose mostly from the London group of Henson and Currie. The reader is referred to the superb text *Cancer and the Nervous System* by Henson and Urich *(17)*.

## CENTRAL NERVOUS SYSTEM (INTRADURAL)

There are no reports of primary intradural parenchymal HD. Even when reported as such, careful analysis shows that every example had a dural component. Thus it is reasonable to conclude that these infrequent reports (for example, ref. *18*) support the hypothesis of centripetal extension of HD (v.i.). Unusual forms of parenchymal disease do occur in HD but are not thought to be due to the actual presence of malignant lymphocytes. These include eosinophilic meningitis *(19)* and granulomatous angiitis *(20)*. These are not documented in NHL and this may be explainable by inherent biologic differences as to how these two lymphomas effect the nervous system.

Intradural NHL, though not common, does occur. The mechanism of direct spread of NHL intradurally remains a puzzle. In the early part of the 20th century intradural NHL was variously described as reticulum cell sarcoma, microglioma, and perithelial sarcoma since it was thought to arise from nonlymphocytic microglial cells, or dedifferentiation of multi-potential cells in the perivascular spaces of the CNS *(21)*. It has only been in the past two decades that intradural NHL is viewed as a unique extranodal form. Specifically, by histologic, ultrastructural, and immunophenotypic criteria intradural malignant lymphocytes are identical to malignant lymphocytes elsewhere *(22–24)*.

A special consideration for prophylactic treatment is relevant here. The CNS has been assumed to be a "sanctuary" site for systemic chemotherapy. As with acute lymphocytic lymphoma (ALL), a high incidence of intradural "failure" has been described in NHL at certain sites such as sinus and testicular lymphomas, and Burkitt's lymphoma *(25–27)*. Furthermore, this failure occurs at a time in the patients' illness atypical for NHL at large (that is, early in their course or even at presentation, or at a time later in their illness when they are well). A large literature has accumulated about the issue of preventive treatment of the intradural nervous system, its type of treatment (or treatments), their timing, and indications *(10,13,28,29)*. The assumption is that prophylaxis is necessary to prevent CNS relapse and even systemic reseeding. Since many of the reports upon which these recommendations preceded the modern neuroimaging era, it is not clear whether patients had been properly staged. Since even with prophylaxis a substantial number of patients will develop CNS disease and as prophylactic therapy may be neurotoxic *(29,30)*, based on our experience with testicular lymphoma we have taken a cautious view towards prophylaxis *(27)*.

To our view prophylaxis requires an understanding of intradural NHL involvement. However, there is still only speculation as to how these cells get intradurally. The various theories include blood-borne "metastases," entry of malignant lymphocytes via normal lymphocyte flux in and out of the CNS, and lymphocyte "homing" *(31–33)*. Any insight into mechanism will be related to focused clinical experience, improvements in imaging and further advances in molecular biology. Indeed the very divisions employed in this chapter may ultimately be as obsolete as the term "reticulum cell sarcoma."

**BRAIN** With the exception of PCNSL brain parenchymal involvement is unusual in NHL. In an autopsy series that provides the most convincing data, Schaumberg and colleagues at Massachusetts General Hospital found that 2 of 121 consecutive postmortem examinations of NHL patients harbored parenchymal lymphomatous deposits *(34)*. More recent studies have confirmed the rarity. Conversely, we reviewed the Mayo Lymphoma Database for all patients who presented as PCNSL and had staging for the presence of occult systemic disease. 3.9% had systemic lymphoma, which was typically present in intra-abdominal or intra-pelvic lymph nodes *(35)*. Since our population is a highly selected one, the actual incidence is probably much lower.

When parenchymal lymphoma has been diagnosed it has usually been as a late complication, occurring at a time that there is widespread systemic disease and bone marrow involvement *(9,10)*. A special situation involves "Richter's Transformation." Others and we have described parenchymal lymphoma occurring some years after another hematologic malignancy, including systemic NHL and HD *(36,37)*. In some cases no treatment for the original tumor had been administered, thus excluding a treatment-induced second malignancy. In other patients the histology of the original lymphoma and the parenchymal disease have been discordant. Siegal and colleagues demonstrated molecular genetic differences between the two tumors of similar histology (e.g., large cell lymphoma *[38]*). Thus there appear to be convincing data now supporting the contention that these are in fact "second malignancies" rather than "recurrence." In fact the imaging features of these instances of Richter's transformation are similar to those seen in "*de novo*" PCNSL.

The treatment decision ultimately rests with the responsible clinician and is based on realistic goals and expectations. Treatment may be supportive care, palliative radiotherapy, or salvage attempts with "penetrating" chemotherapy *(39)*, typically high-dose intravenous methotrexate *(40)* or high-dose intravenous cytarabine *(41)*. In some ways the actual therapy decisions are similar whether the issue is PCNSL or parenchymal NHL as a site of intradural disease. To that end a large retrospective review published recently by Reni and colleagues included discussion of bone marrow and stem cell transplantation might be relevant *(42)*. This is rarely indicated in general practice where if treatment is to be given it is usually whole brain or focused external beam irradiation.

**SPINAL CORD** Cord involvement has been demonstrated far less frequently than brain parenchymal disease. Except for the special circumstance of cord involvement in the context of leptomeningeal lymphoma (v.i.) the mechanism is unknown. No doubt this is an underrecognized complication of systemic lymphoma. Since cord lymphoma rarely expands the cord, a myelogram would be unlikely to give diagnostic information *(43)*. The more recent widespread use of magnetic resonance imaging (MRI) scanning of the spine has contributed to the increased number of reports in the past decade compared to the two decades prior *(44,45)*. Furthermore it is likely that a certain number of enhancing cord masses without significant mass effect occurring in the context of systemic NHL have been assumed to be infectious, inflammatory, or postirradiation. Last, these have often occurred as end-of-life illnesses and an aggressive work up may not have been considered. Again treatment decisions rest with the responsible clinician and are based on realistic goals and expectations. Treatment may be supportive care, palliative radiotherapy, or salvage attempts. Only anecdotal reports support the use of one over another.

**CRANIAL AND SPINAL NERVES** Three specific forms are encountered clinically: encasement by leptomeningeal lymphoma (which is by definition intradural); centripetal spread intradurally from contiguous extradural sites of lymphoma; and neurolymphomatosis, a unique intraneural tumor that may be intra- or extradural (I have arbitrarily decided to discuss this here). Cavernous sinus lymphoma, a not uncommon phenomenon in systemic lymphoma, is discussed in the section on the Peripheral Nervous System (v.i.).

**Lymphomatous Meningitis (LM)** This entity is common; in some series it occurs in as many as 5% of patients overall with large cell lymphoma *(46)*. Furthermore, 10–30% of all patients are diagnosed at the time of initial presentation of the lymphoma *(16)*. In B-cell lymphomas this entity comprises nearly half of the neurologic complications *(13)*. However it may be as common in T-cell lymphomas. In the Kaufman series

*(14)* 2.4% of T-cell lymphoma cases overall had leptomeningeal syndromes comprising 36.8% of the neurologic complications (7/19 patients). LM is typically seen in patients with no or insufficient control of systemic disease and high-grade disease.

Pathogenesis of LM is uncertain. Most reports associate the development of lymphomatous meningitis with direct entry of malignant lymphocytes into the CSF rather than dural invasion (as mentioned in the section on extradural disease our experience is that even with aggressive dural lymphoma CSF involvement is uncommon). LM is an especially dreaded complication of systemic lymphoma because its diagnosis may be so elusive during which disability is progressive and additive. Current treatment regimens are rarely curative and may produce additional neurologic toxicity, thus adding to the disease burden.

Diagnosis requires a high index of suspicion, especially when lymphoma has not yet been discovered. The differential diagnosis is broad and includes dysimmune states, opportunistic infections, and other malignancies. Malignant lymphoma cells tend to cluster (presumably by stasis) at the basilar meninges and the cauda equina. Thus patients typically present with meningeal and/or radicular pain, and cranial and spinal neuropathies *(47)*. A few unusual syndromes have been described including optic neuropathy *(29)* and nonconvulsive status epilepticus presenting as a confusional state *(48)*. Sometimes, if cells obstruct cerebrospinal fluid (CSF) pathways a communicating hydrocephalus syndrome may be superimposed. Invasion along the Virchow-Robin spaces may give focal or multifocal CNS parenchymal signs including frank myelopathy due to spinal cord invasion *(50)*. As many as 10% of cases are asymptomatic *(28)*.

A careful neurologic examination may reveal disease at several levels even if the patient presents with symptoms referable to only one cranial or spinal nerve. Usually the diagnosis is secured by CSF analysis. CSF cytology may be abnormal in the first lumbar puncture (or ventricular fluid if an extraventicular drain is inserted because of hydrocephalus), but in approx half the cases at least three CSF examinations are necessary *(49)*. CSF analysis may be problematic. The "gold standard" is the demonstration of malignant lymphocytes in the CSF. However, CSF lymphocytes obtained from either the ventricular fluid or the lumbar fluid may be deceptively normal *(50)*. Sometimes it is necessary to obtain fluid from both sites *(51)*. Demonstration of surface immunoglobulin monclonality had been assumed to be an acceptable surrogate. However, others and we have had patients with inflammatory disorders of the CNS (e.g., multiple sclerosis [MS]) who have had small numbers of CSF lymphocytes demonstrating monoclonality. Thus the issue now is whether there is a monoclonality threshold for the diagnosis of lymphomatous meningitis. At the time of this writing this has not been settled. Lastly, some investigators consider "atypical" lymphocytes to be equivalent to malignant lymphocytes *(52)*. Since morphology is dependent on many factors our approach has been to make treatment decisions on the presence of "positive" CSF cytology.

In some cases CSF cytology remains negative despite multiple spinal taps. In these cases, a meningeal biopsy is required for diagnosis. Cheng and colleagues reviewed the Mayo experience of the use of such biopsies in 37 patients with chronic meningitis of unknown cause seen during the MRI era *(53)*. A definitive diagnosis was made in 16 of 41 biopsies (39%), but in cases where enhancement was present and the enhancing meninges were biopsied, a diagnosis was obtained in 80% (12 of 15 cases). In some patients who presented with a cauda equina syndrome and had contrast enhancement only in the lumbosacral spine a "mini"-hemilaminectomy was performed to remove an involved rootlet and its coverings. Cancer was diagnosed in over half of these cases. Only 2 of 22 biopsies (9%) from nonenhancing regions were diagnostic. The authors emphasized that a well-coordinated approach between clinician, surgeon, radiologist, and pathologist will assure the best results with the lowest morbidity.

Treatment, as with all decisions regarding these patients, is predicated on the overall status of the patient and consensus between the responsible clinician, the patient, and the patient's family. Several treatment algorithms have been published *(11,16)*. Most of these focus on some variation of intrathecal administration of short-acting, water-soluble chemotherapy such as methotrexate or cytarabine, usually combined with irradiation to the symptomatic area(s). Administration options include intralumbar administration, intraventricular administration via an Ommaya reservoir, and the use of three way ventricular catheters that allows CSF diversion to be suspended for a period of time while drug permeates the CSF. If intralumbar administration is chosen for treatment some advocate the concomitant use of corticosteroids and some advocate alternate use of methotrexate and cytarabine *(54)*. Control of systemic disease is a prerequisite for successful treatment *(16)*.

Intra-Ommaya treatment is the preferred route of administration if the CSF is to be directly treated. It "goes with the flow" (that is, administered drug follows normal CSF circulation), it permits frequent administrations of chemotherapy without the need for repeated lumbar punctures, and it allows CSF to be sampled as a means of monitoring therapy. Usually a radionuclide flow study is performed first to be certain that there is free communication between the intracranial and intraspinal compartments *(55)*. If there is a hindrance to flow, drug may accumulate in the CSF, increasing the risk of neurotoxicity *(56)*.

A slow-release formulation of cytarabine designed to maintain cytotoxic CSF concentrations for more than 14 d is now available for clinical use *(57)*. This agent (DepoCyt) is purported to produce a high response rate and a better quality of life as measured by Karnofsky score relative to that produced by free drug given by intralumbar injection twice a week. However, time to neurologic progression and survival was not significantly different between the two arms. A cost-analysis and comparison of the new agent to standard drug administered via an Ommaya reservoir have not yet been provided. Newer therapies now entering clinical trials include the use of radiolabeled monoclonal antibodies (MAbs) *(58)*.

Some unusual but nevertheless serious complications of Ommaya reservoir placement and use have been described. First, if ventriculomegaly is not present, freehand placement of the ventricular end may be difficult. Obviously multiple passes through brain cortex exposes the patient to immediate and longer-term complications such as hemorrhage, epilepsy, and

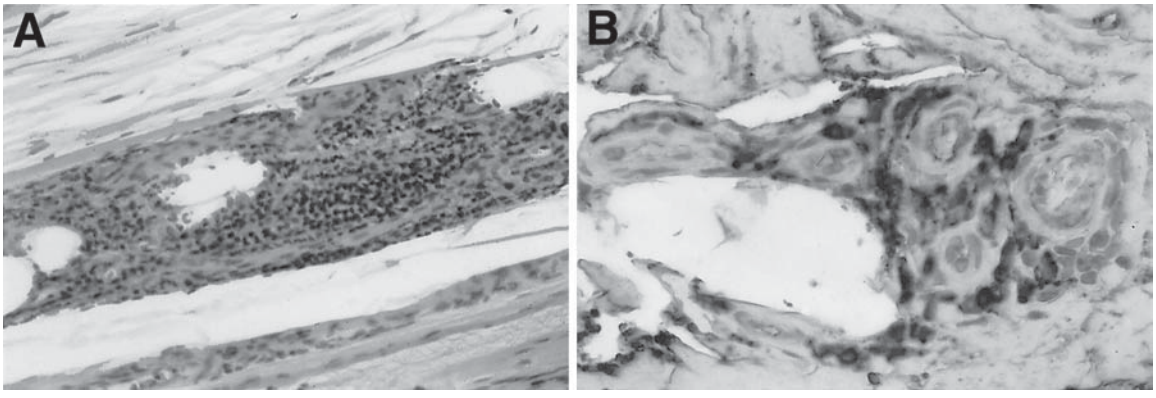


**Fig. 1.** Nerve biopsy of 45-yr-old woman who presented with a mononeuritis multiplex syndrome 24 yr after treatment and complete remission of Stage IIA HD. Biopsy demonstrates thick epineural lymphoplasmocytic infiltrate **(A)** that displayed IgG kappa predominance **(B)**.

intracranial infection. In 1987 Hagen and colleagues described the use of stereotaxy to simplify the insertion of catheters into the lateral ventricle *(59)*. Second, most surgeons advise waiting several days after placement before introducing drug. However some patients may literally add to disease burden day by day; any time lost before treatment onset could be clinically significant. Third, systemic lymphoma patients are highly vulnerable to infection and bleeding. Thus, as with shunts, the placement of an intraventricular catheter may increase the patients' risks of serious complications such as seizures, hemorrhage, and infection. Lastly, pericatheter necrosis is a rare and potentially devastating complication *(60)*. This is thought to arise by capillary movement of drug along the outside of the Ommaya tubing thus exposing the contiguous brain tissue to high concentrations of drug. Early diagnosis is critical since the necrosis may progress after cessation of treatment. Most neurosurgeons do not recommend removal of such catheters for fear of removing brain tissue with it, but if infection is suspected removal will be necessary.

Systemic administration of high-dose chemotherapy that "penetrates" the blood-brain barrier (BBB) is now viewed by many to be the preferred means of treating leptomeningeal lymphoma *(61)*. In the past 2 yr we have not placed an Ommaya reservoir for treatment of neoplastic meningitis. Instead, for those patients thought salvagable we have employed high-dose systemic chemotherapy. Obviously this decision is individualized based on the patient's prior treatment history and the primary tumor. Usually therapy has consisted of high-dose (3.5 g/m$^2$ and higher) methotrexate (MTX) administered intravenously or high-dose (1–3 g/m$^2$) intravenous Ara-C. Studies compared CSF levels from intra-lumbar, intra-Ommaya, and intravenous administrations and have found the latter to be equivalent to those directly introduced *(62)*. Since the myelosuppressive effect of MTX can be abrogated by the administration of leucovorin, patients with active systemic disease may be able to continue to receive their systemic chemotherapy; an important factor in overall patient outcome. Although a devastating MTX-induced leukoencephalopathy has been described, the risks of this are less if the drug is given intravenously without, or at least before, head irradiation *(57,63)*. In our experience, high-dose intravenous MTX is usually sufficient to treat disease.

**Centripetal Spread** Since retroperitoneal adenopathy is common in both HD and in systemic NHL, involvement of adjacent peripheral nervous system (PNS) structures should occur. However, intradural extension via centripedal spread occurs only with NHL. Again biologic differences probably account for this observation. Lymphoma may dissect intradurally along nerve fibers from contiguous sites extradurally such as the dorsal root ganglia and spinal roots. Although the mechanism of centripetal spread is only partly understood it probably reflects the ability of malignant lymphocytes to transgress across endothelia *(64)* or to migrate within myelinated structures *(65)*. This has been well-documented in MS and appears to be mediated by integrins and adhesion molecules *(66)*. This may be much more common than recognized clinically. In one autopsy series, invasion of peripheral nerves was noted in over one-third of cases *(67)*.

**Neurolymphomatosis** Primary localization of malignant lymphoma to a peripheral nerve is rare (v.i.). No series has been presented and fewer than 10 case reports are in the literature. A more common situation, but no more clearly understood phenomenon, is neurolymphomatosis (NL). Diaz-Arrastia and colleagues *(68)* described a clinicopathologic syndrome characterized as "a clinical disorder with signs of peripheral neuropathy that is confirmed by histopathologic evidence of lymphomatous infiltration of the nerves as seen by nerve biopsy or at autopsy." The lymphocytes have the appearance of those of NHL rather than HD; only 1 of 40 patients studied had HD. Their review defined four clinical syndromes: an acute sensorimotor illness similar to Guillain-Barre syndrome; a subacute progressive neuropathy; a mononeuropathy syndrome; and a cauda equina syndrome. Only one patient was asymptomatic. More than one-half (52%) had no known lymphoma at presentation. Only nerve biopsy allowed correct diagnosis during life. Treatment when given usually involved systemic chemotherapy; Batchelor and colleagues have reported success with high-dose MTX *(69)*. Our experience is limited but similar. A recent patient is described in Fig. 1. This 45-yr-old woman presented with a mononeuritis multiplex syndrome 24 yr after treatment and complete remission of stage

IIA HD. After a sural nerve biopsy confirmed neruolymphomatosis, she had a complete response to fludarabine.

**OTHER** Some unusual intradural syndromes have been described. Although rare they may pose diagnostic and therapeutic challenges. Four such syndromes have been selected for further discussion: eosinophilic meningitis and granulomatous angiitis from HD and pituitary lymphoma and intravascular lymphoma from NHL.

**Eosinophilic Meningitis** Eosinophilic meningitis can occur from parasitic and autoimmune causes. In 1981, Patchell and Perry described CSF eosinophils in an autopsy proven case of HD *(70)*. A more detailed report in 1988 by Mulligan and colleagues described a 31-yr-old man in remission after radiotherapy for HD who developed meningitis characterized by an eosinophilic pleiocytosis *(19)*. A neoplastic cause was suspected because of 'variant' Reed-Sternberg cells in the CSF. The patient promptly responded to oral dexamethasone and intrathecal methotrexate. Systemic relapse occurred 10 mo later. As of this writing it is not resolved whether this entity represents a true neoplastic meningitis.

**Granulomatous Angiitis** A paraneoplastic vasculitis has been described in HD *(16)*. In some cases, an infectious cause was suspected because of the ultrastructural demonstration of what were felt to be viral particles in brain capillary endothelia. Inwards and colleagues reported a 28-yr-old man who had a 5-mo history of focal and generalized neurologic symptoms culminating in a thoracic myelopathy. Evaluation revealed granulomatous angiitis of the spinal cord in association with occult nodular sclerosing HD *(20)*. Other cases reported involved brain parenchyma. Successful therapy for HD may result in marked improvement of associated granulomatous angiitis, whereas the lack or failure of therapy results in a uniformly fatal outcome. Definitive antemortem diagnosis of granulmatous angiitis requires a biopsy of involved tissue. The cause of granulomatous angiitis, as well as the nature of its association with HD, remains unexplained.

**Pituitary Lymphoma** In 1983 Kimmel et al. described 25 patients with diabetes insipidus (DI) on the basis of systemic cancer *(71)*. This represented 14% of all cases of DI diagnosed at Mayo Clinic during the period of study. DI was the initial presentation of the cancer in 11 of the 25, and 4 of these 11 were due to systemic lymphoma. Anterior pituitary and visual system involvement was uncommon. Although skull X-rays were usually normal, computed tomography (CT) was abnormal, demonstrating pituitary stalk enlargement, suprasellar masses, or both. These findings have not been updated although there are a small number of corroborating case reports from the modern neuroimaging era, which included MR findings.

**Intravascular Lymphoma (IVL)** Intravascular lymphoma (also known as malignant angioendotheliomatosis or angiotropic lymphoma) is an unusual systemic lymphoma with a predilection for the CNS *(72)*. Typically patients present with multifocal and progressive neurologic involvement in the setting of silent or occult systemic involvement. Stroke syndromes are the most common. A cauda equina syndrome with paraparesis, pain, and incontinence; a mononeuritis multiplex syndrome involving cranial and/or spinal nerves; and a subacute encephalopathy syndrome with confusion and/or delirium syndromes have been reported *(73)*.

The unexplained development of one or more of these syndromes, and especially a multi-infarct syndrome, should alert the clinician to the possibility of IVL. "B" symptoms, and adenopathy are usually absent. A careful general physical examination may reveal splenomegaly and petechial hemorrhages in the skin, which if biopsied may prove diagnostic. Abdominal scanning may not only confirm splenic enlargement but may also demonstrate adrenal gland enlargement, another nearly pathognomonic feature.

It is not clear whether the entity represents actual intravascular proliferation of B-lymphocytes or homing to the luminal surface of endothelia and then blockage of these vessels by malignant lymphocytes. Unlike the imaging in "primary" and "secondary" CNS lymphoma the imaging is nonspecific. Thus CT and MR scanning will demonstrate one or more infarcts and angiography may show single or multiple occlusions. Often a cerebrovascular biopsy is necessary and if it is we have found it helpful to obtain a large enough sample to include leptomeninges, pial vessels, and adjacent cortex. Staging procedures usually follow to exclude occult systemic disease (staging tests are usually positive). Treatment when given has usually involved systemic chemotherapy *(74)*.

## PERIPHERAL NERVOUS SYSTEM (DURAL AND EXTRADURAL)

Involvement of the peripheral nervous system by HD and NHL is more intuitively obvious. It usually occurs by direct extension from contiguous sites such as calvarial lymphoma extending from skin through bone to dura, and epidural spinal cord compression extending from nodes in the paraspinal "gutter" to the epidural space. Epidural spinal cord compression may be the initial presentation of systemic HD or NHL, although more a likely occurrence with NHL. As such the diagnosis of either should *always* lead to a search for occult systemic disease.

Listing these following disorders under "Peripheral Nervous System" may prove to have been as arbitrary and too simplistic as the classification for "Central Nervous System." Clearly calvarial lymphoma may transgress the dura and give an intradural component. As already mentioned "neurolymphomatosis" seems to encompass a syndrome that has both "central" and "peripheral" (that is, intra- and extradural) components. Mechanisms that underlie these complications may be similar for intra- and extradural disorders. For example, malignant lymphocytes seem to be able to transgress the "blood-nerve barrier" just as they may the "blood-brain barrier" *(64)*. Indeed, the particular phenotype may not be simply due to invasion from a contiguous area but may be biologically preordained. Nevertheless we will use a traditional classification system for the PNS disorders.

**Dural Syndromes** Unlike the situation intraspinally, the intracranial epidural space is a virtual one. The dura is relatively impenetrable, so that invasion when it does occur is an extremely poor prognostic sign.

**Calvarial Lymphoma and Other Forms of Dural Lymphoma** Herkes and colleagues described two patients who had focal neurological deficits as the initial manifestation of a malignant lymphoma involving the skull *(75)*. Soft tissue

masses and variable bone destruction were the predominant computed tomographic findings. MRI studies revealed meningeal involvement in one case and sinus thrombosis in the other (Fig. 2). Systemic lymphomas initially appearing in the skull are rare, but these lesions should be considered in patients with a rapidly developing scalp mass and invasion should be suspected in anyone who has focal neurological signs.

In another report Isla and colleagues described the imaging similarity of cranial vault lymphoma to meningioma. They reviewed other reports of patients not known to have lymphoma where the diagnosis was surgically confirmed *(76)*. Since presumptive meningiomas are increasingly treated with radiosurgery (where the diagnosis is based on clinical and imaging characteristics) it becomes even more important to recognize the bony component of calvarial lymphoma to avoid misdiagnosis.

In some instances calvarial lymphoma occurred in well-established patients who were in complete remission. We have experience with eight such patients. MR was used to explore the extent of centripetal spread (including parenchymal disease), and, if not contraindicated, a lumbar puncture was performed to exclude meningeal disease. None of these eight were foung to have evidence of neoplastic meningitis although two had parenchymal swelling and pial enhancement adjacent to the involved dura. Assuming that the dura has not been broached we assume that these patients have disease "outside" the BBB and proceed with systemic chemotherapy *(77,78)*. If they are nonresponsive or if chemotherapy is not indicated, involved-field radiotherapy is employed.

**Cavernous Sinus Lymphoma** A not uncommon presentation of both HD and NHL is lymphomatous involvement of the cavernous sinus dura. Patients may present with pain in the distribution of one of the branches of the trigeminal nerve (typically V1) and/or extraocular muscle palsies and local ophthalmic signs such as chemosis. When this is the presentation of lymphoma the differential diagnosis is broad but typically includes cavernous sinus meningioma and inflammatory conditions (Fig. 3). Although cavernous sinus is one of the skull base syndromes initially described by Deck and Greenberg in 1980 *(79)*, most of these syndromes occurred with solid tumors such as breast and prostate carcinoma that frequently metastasize to bone. In patients with solid tumors, bony disease is usually apparent on skull X-rays, bone scan or CT scan with bone windows. In contrast, bone changes from lymphoma are unusual and a tissue diagnosis is usually required. In our experience an imaging-guided (usually CT) needle biopsy often will quickly and safely provide the diagnosis.

**Dural Sinus Thrombosis (DST)** Dural invasion by HD or NHL adjacent to a venous sinus may lead to thrombosis. This may occur by either compression or intraluminal invasion. The likelihood of subsequent thrombosis may be enhanced by such "procoagulant" factors as dehydration and dysproteinemia. In fact DST is more common without apparent sinus invasion by cancer and is usually attributable to a "hypercoagulable state" (although many of the clinical reports did not include postmortem inspection of the sinuses).

In superior sagittal sinus thrombosis, patients may present with seizures, headache, obtundation, focal and/or multifocal signs, and increased intracranial pressure *(80)*. Imaging with MR is useful particularly if MR venography is performed. DST is a potentially lethal situation when a major sinus is involved such as the superior sagittal sinus, the cavernous sinus, or the transverse sinus. Controversy exists over whether these patients should receive anticoagulation *(81)* but some form of anti-lymphoma therapy is usually employed. Again, treatment decisions rest with the responsible clinician and are based on realistic goals and expectations.

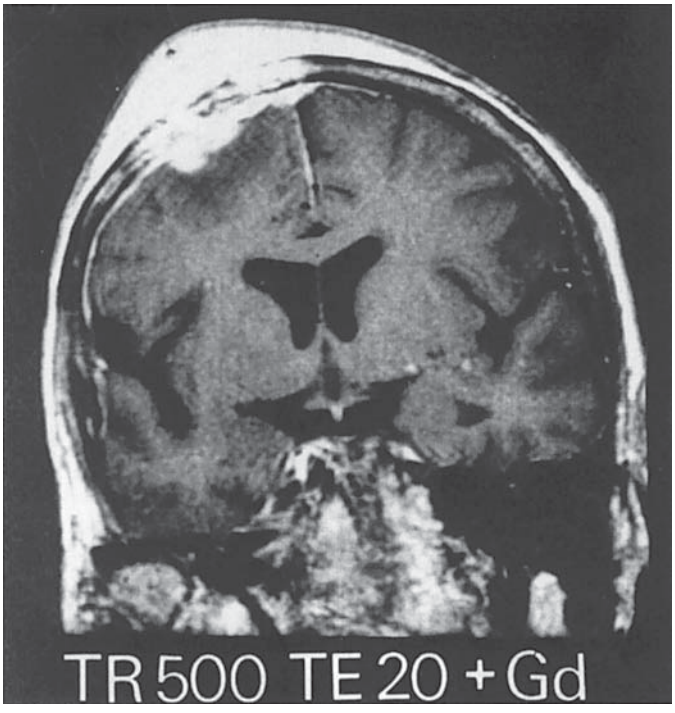


**Fig. 2.** Enhanced MRI scan of head in 62-yr-old man whose NHL presented as an enlarging skull mass followed by focal seizures.

**Epidural Syndromes** Intraspinally the epidural space is a true space with traversing veins, arteries, and epidural fat. The dura reflects back on itself at the dorsal root ganglion so that this structure is technically extraspinal but intradural. Here too the dura is relatively impenetrable so that invasion when it does occur is an extremely poor prognostic sign.

**Epidural Spinal Cord Compression (ESCC)** Since ESCC could be demonstrated by myelography (and thus not dependent on modern neuroimaging), an extensive literature describes this entity. Indeed, seminal reports on this condition date back to the early 1970s *(82,83)*. Nevertheless, MR has clearly contributed to improved knowledge about ESCC. For example, MR can tell us about the tissue components of the mass (e.g., bone fragments, blood clot, tumor tissue), the relationship of the mass with extra- and juxtaspinal structures, and whether there is abnormal signal within adjacent spinal cord parenchyma, a harbinger of poor neurologic outcome. Moreover, Schiff and colleagues demonstrated how MR could accurately define the number of other spinal lesions in patients presenting with ESCC *(84)*. In that study, 32% of patients with ESCC and complete spinal MRI had multiple epidural metastases; however, lymphoma (HD and NHL) patients were

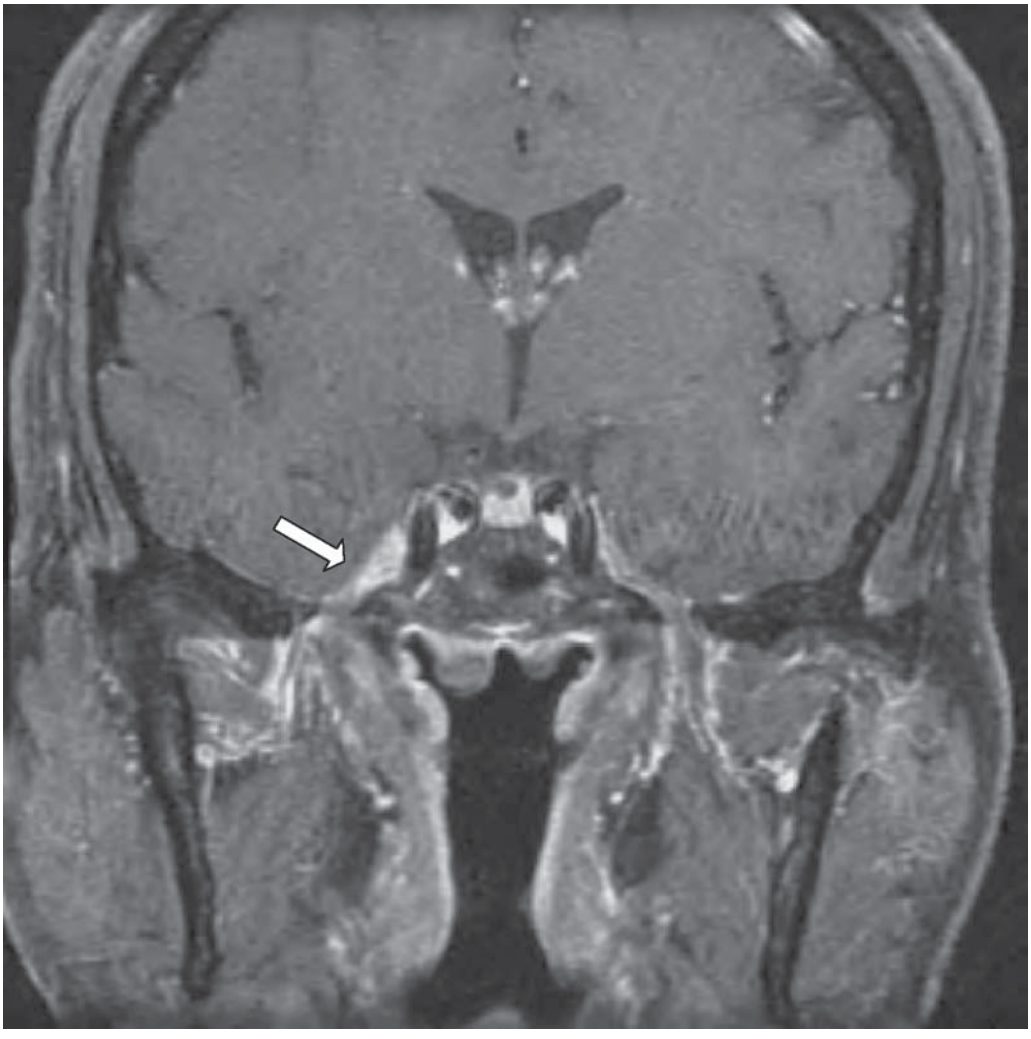

**Fig. 3.** A 68-yr-old man presented with retro-orbital pain, ipsilateral decreasing vision, neuralgic pain and paresthesias in the distribution of the supraorbital nerve, and then double vision. MRI suggested an invasive meningioma. Biopsy confirmed NHL.

much more likely than solid tumor patients to have only a single lesion (only 16% had multiple epidural metastases).

There are other ways that ESCC from solid tumors differ from lymphomatous ESCC. In ESCC of solid tumor origin (e.g., metastatic adenocarcinoma of the prostate) the classic presentation consists of bone pain followed by monoradicular pain then asymmetric myelopathy or cauda equina syndrome. Symptoms of bony instability may also be present relative to the status of the involved vertebral body. In lymphomatous ESCC this presentation is often modified. First, since malignant lymphocytes may access the spinal epidural space from retroperitoneal lymph nodes, bone pain may be absent. Second, the syndromic "time line" is usually short. The mean duration of symptoms of ESCC of all tumors is 6–8 wk from onset to diagnosis. A more abrupt presentation may occur because of vertebral body collapse and pathologic fracture and cord ischemia. In lymphomatous ESCC the course is often very subacute even without vertebral body collapse; we have had patients whose ESCC occurred within 24 h. Third, the corticosteroid benefit seem in ESCC from solid tumor is usually much more dramatic in lymphomatous ESCC. This is probably because of corticosteroid induced lymphocyte apoptosis (the so-called "ghost tumor" effect *[6]*) *(5,85)*.

Lymphoma patients may present with ESCC although it is more commonly seen in later stages of the disease *(4)*. Schiff and colleagues reviewed the Mayo Clinic records of 337 patients with ESCC *(86)*. In that study 20% of these patients presented with ESCC. However, nearly half of the lymphoma patients (44%) who developed ESCC presented with ESCC. We have also had experience with several unusual variations on this theme. In 1992 and 1996 we described a group of patients who presented with ESCC and never developed other sites of disease *(87,88)*. There were no distinguishing features between these patients and the more typical patient presenting with ESCC. These papers, and subsequent papers from our group, made the argument for percutaneous CT-guided needle biopsy (v.s.). Lastly, even within NHL there is variation. In the previously cited Kaufman paper on neurologic complications of T-cell NHL none had ESCC *(14)*.

MR is the preferred modality for evaluation of the patient suspected to have ESCC. MR reveals T2 signal change in cord parenchyma, which has been shown to correlate with a poor

outcome; it defines the tissue characteristics of the compressing mass; it can reveal other clinically occult lesions; it can demonstrate complications of therapy such as radiation myelitis; and it can show the response to therapy and pattern(s) of failure. In addition MR can give information about spine integrity and the extent of paraspinal disease. In patients in whom MR is not feasible, CT/myelogram will be the next best thing. Unfortunately CT/myelography has not been shown to be comparable to MR in displaying tissue characteristics of the compressing mass, occult other disease, and cord parenchymal change.

Apropos lymphoma presenting as ESCC, a tissue confirmation is required and it has been our practice to first consider a CT-guided biopsy *(86)*. We have found this to be safe, efficient, and reliable with little or no "down time" so that therapy can commence as soon as the diagnosis is established. Since lymphomatous masses appear to respond as well to chemotherapy as they do to radiotherapy and since there does not seem to be an advantage (and perhaps a disadvantage) to surgical debulking we now avoid neurosurgical procedures if at all possible. Under certain circumstances CT-guided biopsy should also be considered in those patients with known lymphoma who develop a spinal syndrome, and whose imaging demonstrates a compressing mass. These circumstances include long disease-free interval, atypical presentation, and low-grade histology. As an example we have had the experience of a patient with follicular NHL who after a long period of stable disease developed a subacute myelopathy. A CT-guided biopsy showed the compressing mass to be NHL, diffuse large cell type due to "Richter's Transformation."

As stated previously, treatment is predicated on the overall status of the patient and consensus between the responsible clinician, the patient and the patient's family. Traditionally radiotherapy (RT) has been employed for treating HD and NHL ESCC *(89)*. However, RT has important disadvantages to this group of patients, more so than in ESCC from solid tumors. First, since most cases of ESCC occur within the thoracolumbar spine, RT will impact active bone marrow. Since these patients typically have active disease and are more likely to receive concurrent or subsequent chemotherapy, RT could limit treatment options. Furthermore, previous treatment might either limit the amount of RT a person may receive or produce more intensive side effects because of the cumulative myelosuppression. Second, even though HD and NHL were less likely than solid tumors to have other occult sites of ESCC a commitment to employ RT for the symptomatic lesion could imply that the additional sites would also need to receive RT (thus potential cumulative myelosuppression). Third, RT has its own menu of local and neurologic side effects including radiation myelitis. Avoidance of additional spinal disease burden intuitively seems to be a realistic goal.

For these reasons Burch and Grossman *(90)* and Wong and colleagues *(91)* described a satisfactory and satisfying response of ESCC to chemotherapy alone in HD and NHL, respectively. In the former, two HD patients responded "dramatically" to systemic chemotherapy. In the latter report, seven episodes of ESCC from NHL were analyzed. Five episodes were asymptomatic at presentation; one patient had back pain, leg numbness, and tingling; and one had radicular pain and mild leg weakness. After chemotherapy alone, five of seven episodes showed radiographic resolution of ESCC and improvement of neurologic deficits. One patient received consolidation radiotherapy (2700 cGy) to the spine after chemotherapy and had a complete response. One patient had progression of systemic lymphoma and ESCC despite chemotherapy. Our experience has been similar.

As both NHL and HD are highly sensitive to both RT and chemotherapy, surgery is usually only employed to obtain tissue for histologic diagnosis in patients without known lymphoma or when the diagnosis is in doubt. Unlike the case in ESCC of solid tumor origin vertebral body resection and stabilization *(92)* is rarely required. In patients who have recurrent ESCC after a course of radiotherapy adequate palliation can be achieved with a course of reirradiation. Schiff and colleagues reported 54 patients who underwent two or more courses of radiotherapy to the same segment of the spinal column with radiographically documented epidural disease at the time of reirradiation to determine outcome as measured by the ability to walk and by survival. They concluded that for patients with progressive epidural disease following radiotherapy, reirradiation frequently preserves ambulation and carries minimal risk of radiation myelopathy during the patient's lifetime *(93)*.

## NERVE ENTRAPMENT SYNDROMES

**Numb Chin Syndrome** In 1970 Simpson described mental neuropathy and coined the term "numb chin syndrome" *(94)*. Since then more than 30 reports describe this syndrome in patients with metastatic cancer including lymphoma. The frequency and stereotypy of this phenomenon has led to its recognition as being due to "cancer until proven otherwise." The syndrome is attributed to entrapment of the mental nerve by tumor as it passes through its foramen in the mandible involved with blastic metastases (breast, prostate *[95]*) or marrow overgrowth as in lymphoma, and leukemia *(96)*. Usually a plain radiograph (panorex views) will demonstrate an abnormal foramen. Sometimes a similar syndrome can occur with more proximal disease such as involvement of the alveolar nerve along its interosseous course in the mandible *(97)*. Numb chin syndromes from disease at the level of the trigeminal ganglion and even intradurally have been described *(98)*. Thus if neither panorex views and mandible views displays the responsible pathology we usually will do an enhanced MR scan and, if there is no contraindication, a lumbar puncture. In some cases a CT scan with bone windows will give additional information. Treatment is usually defined by the status of the responsible malignancy but often consists of involved field radiotherapy.

**Root Entrapment at Cranial and Spinal Nerve Foramina** A process similar to the "numb chin syndrome" may occur at one or several bony egresses. Blastic lesions (the so-called "ivory" vertebra; Fig. 4) and less commonly fractures with encroachment on the foramen can cause a mononeuropathy (or multiple mononeuropathy) syndrome *(99)*. The typical setting is a painful spinal mononeuropathy without cord or cauda signs. A simple yet helpful clue is the "winking owl" sign of a destroyed pedicle ipsilateral to the radiculopathy. A CT/myelogram and/or MR is usually performed for suspicion of an

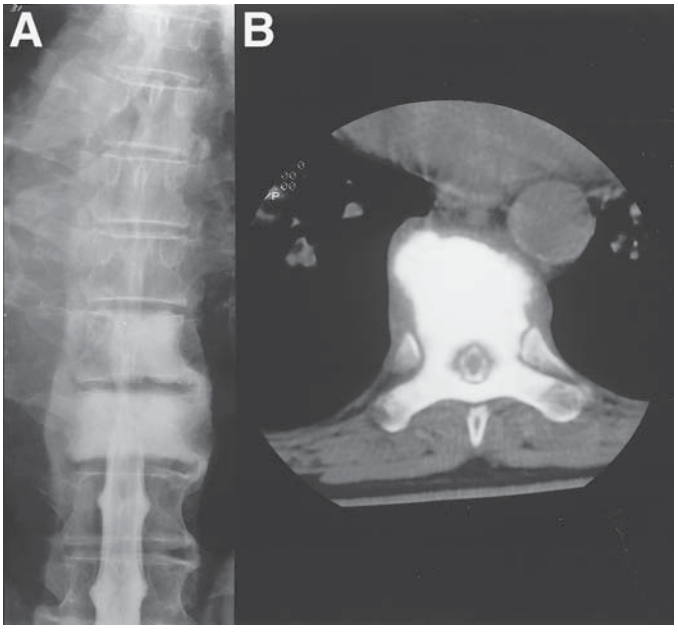


**Fig. 4.** A 39-yr-old with HD presented with new back pain. A sclerotic thoracic vertebral body typical of the "ivory vertebra" of HD is shown on plain X-ray **(A)** and bone CT **(B).**

epidural lesion and demonstrates a normal epidural space. However, careful views of the foramen will usually display the responsible pathology. One MR pitfall is the variability in epidural fat so that the changes at the root exit are not seen.

In 1981, Greenberg and colleagues published their classic paper describing 43 patients with skull base metastases from systemic cancer *(79)*. In that paper they identified five clinical syndromes: orbital, parasellar, middle fossa, jugular foramen, and occipital condyle. Frontal headache, diplopia, and first-division trigeminal sensory loss characterized the orbital and parasellar syndromes. Proptosis occurred with the orbital but not the parasellar syndrome. Facial pain or numbness exemplified the middle fossa syndrome. The jugular foramen syndrome was distinguished by hoarseness and dysphagia, with paralysis of the ninth through eleventh cranial nerves. Unilateral occipital pain and unilateral tongue paralysis defined the occipital condyle syndrome. In our experience a common pitfall in the evaluation of the patient is the all-too-quick ascription of a cranial nerve palsy to lymphomatous meningitis. Disease at the skull base is an important differential point since by definition it is "outside" the BBB. Although localized RT is usually employed, systemic chemotherapy is not unreasonable in selected patients. As was mentioned in the section on "entrapment neuropathies" careful and individualized imaging is key *(100)*.

A recurring clinical problem is the failure of standard CT/myelography and MR to adequately image the lower sacral nerve roots in cases of suspected root entrapment. For example, a patient may present with S2 to S5 symptoms and signs. Standard MRI typically goes no further than S1 or the S1-2 interspace. Again, discussion with the radiologist will avoid missing the responsible pathology or having to repeat the study. For the sacrum we have found simple bone X-rays to be invaluable. The bony "struts" that arch over the foramina bilaterally at each level are usually well seen. Although the "winking owl" sign does not apply (because of the different architecture of the sacrum) the same principle that the foramina should be displayed symmetrically holds. An EMG may be useful if sufficient time has elapsed since the onset of the syndrome since proximal denervation changes may not be apparent until a minimum of 14 d after injury *(101)*. Options for treatment include surgery, chemotherapy, and radiotherapy. The same surgical concerns that were discussed under epidural disease apply here.

## PERIPHERAL NERVE SYNDROMES

**Plexopathies** As with solid tumors, brachial and crural plexopathies may be of malignant origin in systemic lymphoma *(102–104)*. However, the diagnosis may be more elusive than with solid tumors. In lymphomatous plexopathies neuroimaging is less likely to show a discrete mass; moreover, inflammatory plexopathies of dysimmune origin may occur and simulate the symptoms of plexopathies of malignant origin *(105)*. EMG may help differentiate between an intra- and an extradural process, and in the case of the latter localize the process to the plexus rather than the proximal nerve. Often a biopsy is necessary to establish the diagnosis. It is our practice to obtain a CSF sample and spinal MR in lymphoma patients presenting with plexopathy since as many as a third of patients may have coincident intradural disease *(4)*. Whether this occurs as a manifestation of "neurolymphomatosis" or simply multifocal disease is uncertain.

Usually lymphomatous plexopathies occur in the context of adjacent malignant lymphadenopathy. I recently evaluated a 53-yr-old man who had an explosive return of large cell NHL and began experiencing neuropathic pain along the anterior surface of the left thigh followed by leg weakness and quadriceps atrophy. Pelvis MRI demonstrated enormous adenopathy and the involvement of the adjacent plexus. Treatment with systemic chemotherapy resulted in significant improvement in both the adenopathy and the plexopathy. RT is often deferred in such patients to avoid marrow suppression that might hinder the use of subsequent chemotherapy. Patients can usually be salvaged with external beam radiotherapy.

When adjacent nodes appear normal and especially when the patient is disease-free alternate diagnoses need to be considered. We had the experience of a 36-yr-old man who was disease-free and presented with brachial plexus symptoms over 8 wk. Imaging and electrodiagnostic testing were inconclusive. A brachial plexus exploration and biopsy revealed inflammatory cells only *(106)*. Treatment with corticosteroids resulted in a complete remission and the patient remains disease-free 5 yr later.

Obviously the slow development of plexus symptoms and signs, especially without pain, in the distribution of an irradiated plexus raises the spectrum of radiation-induced plexopathies. Cascino and colleagues have reported on the imaging and electrophysiologic features of these conditions *(107,108)*. Both diagnostic tests may reveal distinctive features; electromyography (EMG) may reveal myokymia and MRI can demonstrate wispy enhancement without a discrete mass or adjacent adenopathy. Although not exact, the window for development of postirradiation plexopathy is sufficiently

reliable. If plexus symptoms slowly develop many years (typically a hiatus of at least a decade) after irradiation one needs to consider a radiation induced nerve sheath tumor *(109)*.

**Peripheral Nerve Lymphoma** As mentioned in the section on neurolymphomatosis primary localization of malignant lymphoma to a peripheral nerve is rare. No series has been presented and less than 10 case reports are in the literature. Interestingly, T-cell lymphoma and the sciatic location predominate in these *(110,111)*. Since some of these reports preceded modern neuroimaging it is possible that these reports represent cases of centripetal spread from an intradural site or cases of neurolymphomatosis. However, a carefully worked up case by Kanamori and colleagues described a purely intraneural lesion *(110)*. Nevertheless, the rarity of such cases means that such patients have disease elsewhere until proven otherwise. Treatment must be individualized. Nonetheless, extrapolation from parenchymal lymphoma and neurolymphomatosis would suggest that, because of the "blood nerve barrier" chemotherapy that "penetrates" such as high-dose systemic methotrexate could be considered.

## PARANEOPLASTIC DISORDERS IN THE LYMPHOMAS

Every paraneoplastic disorder can also be seen without known malignancy, but with clinical and paraclinical features of a dysimmune disorder *(112)*. These syndromes presumably occur by some dysimmune process of which certain malignancies are the most common trigger. As with other malignancies, paraneoplastic disorders associated with the lymphomas have been amply described in the literature. Unlike other malignancies, however, the lymphoma-associated disorders are almost exclusively neurologic. Comprehensive and current reviews are plentiful (especially the recent monograph by Dropcho) *(113)*. However, two of these lymphoma-associated syndromes are sufficiently distinctive to merit special attention: cerebellar degeneration associated with HD and subacute motor neuronopathy associated with NHL.

**SUBACUTE CEREBELLAR DEGENERATION ASSOCIATED WITH HD** In 1951 Brain first described the association of a subacute cerebellar degeneration syndrome and cancer *(114)*. This syndrome was further clarified in the 1980s by the identification of specific anti-neuronal autoantibodies to Purkinje cells and other neurons *(115,116)*. The syndrome now known as paraneoplastic cerebellar degeneration (PCD) is profoundly disabling, often precedes the initial diagnosis of or the recurrence of a malignancy, and by clinical phenotype and antibody characteristic may predict the type of malignancy *(113)*. Hammack and colleagues described a group of HD-associated PCD including five patients whose PCD heralded tumor recurrence and two patients who had significant spontaneous neurologic improvement. The report also described a specific autoantibody, later named anti-Tr *(117)*. For unknown reasons PCD is not characteristic of NHL.

**SUBACUTE MOTOR NEURONOPATHY ASSOCIATED WITH NHL** Schold and colleagues described a group of 10 patients with a subacute lower motor neuron syndrome associated with lymphoma. It may occur prior to the discovery of the lymphoma or after a complete remission *(118)*. The syndrome as initially described was principally characterized by muscle weakness, often asymmetric, and purely lower motor neuron in type. Spontaneous improvement of neurological function occurred in 7/10 patients and improvement was independent of the activity of the underlying neoplasm. In two patients, postmortem examinations revealed prominent neural degeneration restricted to the anterior horns of the spinal cord and mild posterior demyelination. The mechanism is unknown.

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# 26 Neurologic Disorders in Benign and Malignant Plasma Cell Dyscrasias

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## INTRODUCTION

Plasma cell dyscrasias (PCD) and their accompanying monoclonal proteins (M-protein [MP]) or immunoglobulins are frequently associated with neurologic diseases *(1)*. These syndromes may be distinctive and, in some cases, appear to be due to the direct effects of the MP on peripheral nerves (paraneoplastic syndromes) *(2)*. This chapter will outline our current knowledge in this field and provide a clinical approach to these patients.

## BACKGROUND

A plasma cell dyscrasia, synonymous with monoclonal gammopathy (Table 1), is defined as a proliferation of a single clone of plasma cells, either neoplastic or non-neoplastic, and is usually associated with a monoclonal serum or urine protein *(1,3)*. Monoclonal proteins consist of a single heavy chain (M, G, or A) and a single light chain (kappa or lambda) *(1)*. Polyclonal gammopathies contain both light chains and generally more than one heavy chain and are usually a non-neoplastic reaction to inflammatory disease or neoplasia. Occasionally, in a monoclonal gammopathy, only the light chain or heavy chain may be secreted (light or heavy chain disease) either in serum or urine (Bence-Jones protein). Formerly, M-proteins were thought to be biologically inert. Recently, however, these proteins have been found to possess activity directed at specific antigens, likely accounting for most of the remote effects of these disorders *(4)*.

## LABORATORY SCREENING

The M-protein is detected by screening patients with serum protein (cellulose acetate) electrophoresis (SPEP) *(1)*. In cases where a suspicious peak is seen on SPEP and in all cases where a monoclonal gammopathy is suspected, such as idiopathic polyneuropathy or atypical motor neuron disease, serum immunoelectrophoresis (IEP) or immunofixation electrophoresis (IFE) should be performed, even with a normal SPEP *(3)*. IEP and IFE are more sensitive than SPEP for the presence of a small M-protein and allow characterization of the single heavy and light chain, thus verifying the monoclonal nature of the immunoglobulin *(3)*. Of these two, IFE is more sensitive and will occasionally detect M-proteins when IEP and SPEP are negative. A concentrated urine specimen should also be examined since monoclonal light chains may appear in urine when serum is normal, suggesting either a malignant PCD or light chain amyloidosis (AL).

After identification and characterization of an M-protein in serum or urine, further hematologic evaluation should be done to classify the PCD (Table 2) *(1,5)*. If a diagnosis of MGUS is made, M-protein levels should be monitored on a yearly basis since a sudden increase can indicate malignant transformation of a benign plasma cell dyscrasia, which can occur in up to 20% of cases *(6)*.

## CLINICAL SYNDROMES

**BENIGN PLASMA CELL DYSCRASIAS** Monoclonal gammopathy of undetermined significance (MGUS), rather then benign monoclonal gammopathy, is now the preferred term for patients with small monoclonal gammopathies but without evidence of an underlying malignancy *(1,6)*. These disorders are often associated with peripheral neuropathies *(3,5)*. IgM-MGUS is the most likely to cause neuropathy, accounting for 50% or more in most series. These syndromes are not uniform and are best approached by dividing them into IgM-MGUS and non-IgM-MGUS (IgG or IgA) (Tables 3 and 4).

**IgM-MGUS** Roughly 50% of MGUS neuropathies occur in patients with an IgM gammopathy *(4,7)*. Since the percentage of IgM gammopathies in the general population is very low, investigators have suspected an etiologic link between neuropathies and gammopathies. Subsequent studies have borne this out and we now know that sera from some, but not all, IgM-MGUS neuropathies display anti-nerve antibody activity. Anti-

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**Table 1**
**Classification of Common Plasma Cell Dyscrasias**

| *Disorder* | *Diagnostic criteria* |
|---|---|
| Monoclonal gammopathy of undetermined significance | MP in serum <3 g/dL and no malignancy or amyloid |
| Osteosclerotic myeloma | Solitary or multiple plasmacytomas with osteosclerotic features |
| Multiple myeloma | >10% abnormal plasma cells in bone marrow or plasmacytoma and MP in serum or urine or osteolytic lesions |
| Waldenstrom's macroglobulinemia | IgM-MP >3 g/dL; >10% lymphs or plasma cells in bone marrow |
| Primary systemic amyloidosis | Light-chain amyloid by histology |
| Gamma-heavy chain disease | Monoclonal heavy chain in serum or urine |

Abbreviations: MP, monoclonal protein.
Adapted with permission from ref. *7*.

MAG associated polyneuropathies are the most common and the prototype for this group.

***Anti-MAG Neuropathy (Latov's Syndrome)*** This disorder accounts for about 25% of the neuropathies associated with MGUS and was first described by Latov and colleagues in 1980 *(2)*. Later studies by this group *(8)* showed that the MP was an IgM antibody directed at myelin-associated glycoprotein (MAG) and other glycosphingolipids *(9)* in the myelin sheath. This led to the discovery of other anti-nerve antibodies *(10,11)* (Table 5), most of which appear to be of uncertain clinical significance.

(1) Clinical manifestations: Anti-MAG neuropathy has a fairly homogenous clinical presentation *(4,12–16)*. Typically, these patients are older (6th through 9th decades) and present with a slowly progressive sensory neuropathy. Unlike many of the mild and painful benign neuropathies of late life, these are relatively painless. Patients instead complain of numbness and paresthesias of the feet and distal legs and gradually increasing unsteadiness due to sensory ataxia. Weakness is less prominent although, as the disease progresses, it becomes more evident. Rare patients may present with mainly weakness, resembling chronic inflammatory demyelinating polyneuropathy, although I have not seen such a case. An action tremor of the hands is also prominent in some patients *(17)*.

Examination reveals that these patients have striking discriminative sensory loss, including loss of vibration sense in feet and impaired position sense, accounting for their sensory ataxia. A classically positive Romberg sign accompanies this. Cutaneous sensory modalities are less severely affected and autonomic dysfunction rarely occurs, helping to separate this disorder from amyloidosis. Motor strength is often impaired distally to a much lesser extent. Reflexes tend to be absent in legs and depressed in arms. Nerves are often thickened and firm to palpation. The symptoms are very chronic, often for months or years, and slowly progressive. Some patients are relatively stable for several years but most progress slowly. In severe cases, patients are unable to walk mostly due to sensory ataxia with varying degrees of weakness.

(2) Laboratory tests: The most helpful neurologic test is the EMG *(14,18)*, which shows, in all but the earliest cases, the classical findings of a demyelinating polyneuropathy with marked slowing of motor conduction velocities, very prolonged distal latencies and areas, or conduction block and dispersion on proximal stimulation with secondary axonal degenerative changes. Sensory potentials are absent or attenuated. These findings, suggestive of a demyelinative process, greatly simplify the differential diagnosis. Cerebrospinal fluid (CSF) shows a high protein concentration with nonspecific features and a normal sugar and cell count. Nerve biopsy is almost pathognomonic, showing IgM deposition on the myelin sheath using immunofluorescent techniques and splitting and separation of the outer layers of compacted myelin with electron microscopy *(4,19–21)*. General laboratory and hematological tests are negative in these patients, which helps to exclude the more serious gammopathies. The SPEP usually shows a small monoclonal spike in the gamma region. However, negative SPEP may occur and should not obviate further testing for anti-nerve antibodies in the appropriate setting. IEP or IFE confirms the presence of an IgM gammopathy, usually with kappa light chains. Further testing using enzyme-linked immunosorbent assay (ELISA) and Western blot shows that the IgM antibody reacts with MAG and other sphingoglycolipid epitopes *(9,10,15)*, thus establishing the diagnosis.

(3) Treatment: Treatment is problematic in these patients, since the monoclonal protein is difficult to eliminate. Plasmapheresis should theoretically work but the marked chronicity of this disorder would necessitate frequent and lifelong pheresis, which is not practical. However, it can be used to rapidly lower the concentration of IgM at the onset of treatment. Likewise, intravenous gamma globulin and corticosteroids are generally not helpful *(7,22–25)*. Cytotoxic drugs such as cyclophosphamide and fludarabine have been shown to be helpful in some patients *(13,19,26,27)*, presumably due to the lowering of the M-protein level in serum. However, some patients also sometimes respond without lowering of the M-protein level *(27)*; therefore, the mechanism of action of these drugs is unclear.

**Table 2**
**Hematologic Diagnosis of 28 Patients with PCD and Polyneuropathy**

| *Diagnosis* | *Number* |
|---|---|
| Monoclonal gammopathy of undetermined significance | 16 |
| Primary systemic amyloidosis | 7 |
| Multiple myeloma (includes osteosclerotic myeloma) | 3 |
| Waldenstrom's macroglobulinemia | 1 |
| Gamma-heavy chain disease | 1 |

Abbreviation: PCD, plasma cell dyscrasia.
Adapted with permission from ref. *5*.

Toxicity with cytotoxic drugs is the limiting factor, especially in elderly patients. Generally, monthly intravenous therapy is thought to have less toxicity than daily oral therapy. Careful consideration in each case must be given to whether or not to treat and, if so, how aggressively to treat. Many patients with mild disease should not be treated aggressively unless their disease accelerates *(7)*. A recent preliminary study found that interferon alpha (IFN-α) seemed to help some patients *(28)*. There is as yet no definitive proof of efficacy of these toxic drugs since there have been no controlled trials. However, it would be difficult to mount a controlled trial since these patients are uncommon even at academic medical centers. Clearly, better and less toxic treatments will be developed when we better understand the molecular pathology of these disorders.

(4) Pathophysiology: There is now overwhelming evidence that the MP causes the neuropathy. There is a close relationship between the clinical and laboratory manifestations of this syndrome and the presence in serum of IgM anti-MAG antibodies. However, small studies comparing IgM-MP patients with and without anti-MAG antibody activity could not demonstrate a difference in attributes of neuropathy between the two groups *(25,29,30)*. Laboratory data is much more convincing. The anti-MAG antibodies are deposited in the layers of the myelin where there is complement-mediated damage to the myelin sheath *(4,19,21)*. Separation of the outer lamellae of myelin occurs *(4,19)*, which is presumably due to the specificity of these antibodies for the adhesion molecules of the myelin sheath. In addition, although intraneural injections of serum to rats have not demonstrated pathologic changes comparable to those in humans, injection systemically into higher animals has demonstrated identical changes *(31)*. Also, although there are exceptions, clinical improvement is generally associated with a reduction of the MP level in serum *(13,26)*. Additionally, presence of anti-MAG antibodies predicts future development of neuropathy *(32)*. Variability of the clinical course and time of onset in individual patients may be related to differing binding affinities of the anti-MAG proteins *(33)*. Thus, most investigators now accept anti-MAG neuropathy as an autoimmune disease although further work needs to be done to elucidate the specific epitopes affected and the exact mechanism of myelin damage.

## NON-MAG MGUS NEUROPATHY SYNDROMES

These represent the other 75% of the neuropathies associated with MGUS *(5)*. These neuropathies tend to be more heterogeneous in type *(1,15,34)* including those resembling anti-MAG neuropathy but without anti-MAG activity and many with mostly axonal features. In addition, rare cases are associated with vasculitis, some with type 1 or 2 cryoglobulinemia *(35)*.

**IgM Non-MAG Neuropathies** This group accounts for about 25% of the MGUS neuropathies. The patients with anti-MAG negative IgM neuropathies cannot be separated from the IgM anti-MAG cases without serological testing *(25,29,30)*. Clinical manifestations *(25,29)* are similar to those described above for anti-MAG neuropathy. Occasionally, these patients have IgM antibody activity directed at other antigens, such as sulfatides *(10)*. The significance of this antibody activity is uncertain since non-MAG patients are less likely to respond to immunosuppressive or cytotoxic treatments and the pathologic data is less compelling.

Occasional reports have appeared of patients with a motor neuron disease (MND)-like illness and monoclonal gammopathies. These usually fall into one of three categories. The first are those patients with ALS who also have a small IgG or IgA monoclonal protein in their blood (MGUS). These are likely the chance co-occurrence of the MP and ALS in the same elderly patient and are not thought by most workers to play an etiologic role. The second group are those with a monoclonal protein (usually IgG or A and MGUS) who actually have multifocal motor neuropathy (MMN), which can superficially resemble motor neuron disease. The diagnosis is clarified by the restricted nature of the findings, lack of upper motor neuron involvement and characteristic EMG changes in MMN. The third are rare cases with an apparent clinical MND and an IgM gammopathy sometimes with anti-nerve activity against neural antigens (Table 5). These are likely restricted motor neuropathies or polyradiculopathies and not true motor neuron disorders and generally can be separated by lack of upper motor neuron involvement and careful EMG and clinical studies. Thus, the consensus now is that true MND or ALS is not caused by a monoclonal gammopathy.

Treatment consists of immunosuppression or cytotoxic drugs. In general, these patients respond less well to these treatments than do the MAG patients *(13)* but there have been no controlled studies of this group. However, most patients with severe and progressing neuropathies deserve a trial of therapy. More work needs to be done on this group, with careful separation of cases, to determine if there are homogeneous groups with specific pathophysiology and if target antigens on myelin or axons can be identified.

**IgG and IgA Neuropathies** This group accounts for approx 50% of MGUS neuropathies *(5)*. In general, these patients are quite heterogeneous. Anti nerve antibody activity is infrequently found and is of unclear significance *(36)*.

(1) These patients can present with a syndrome resembling chronic inflammatory demyelinating polyneuropathy *(37)* with a subacute or chronic progressive or relapsing and remitting motor dominant polyradiculoneuropathy. EMG typically shows changes of a demyelinating neuropathy in most. CSF shows the typical albumino-cytologic dissociation. Nerve

**Table 3**
**Features of Dysproteinemia Polyneuropathy Syndromes**

| *Class* | *Weakness* | *Sensory* | *Autonomic* | *CSF* | *MNCV* |
|---|---|---|---|---|---|
| MGUS-IgM | + | +++ | – | ++ | D |
| MGUS-IgG,A | ++ | ++ | – | + | D |
| Amyloidosis | +/++ | +++ | +++ | + | A or D |
| OSM | +++ | ++ | – | +++ | D |
| WM | ++ | ++ | – | ++ | D or A |

Abbreviations: CSF, cerebrospinal fluid protein concentration; MNCV, motor nerve conduction velocity; MGUS, monoclonal gammopathy of undetermined significance; OSM, osteosclerotic myeloma; WM, Waldenstrom's macroglobulinemia; D, segmental demyelination pattern; A, axonal degeneration pattern.

Adapted with permission from ref. *7*.

**Table 4**
**Major Electrodiagnostic Features of PN Associated with PCD**

| *Type of PN* | *Demyel* | *Axonal* | *CTS* | *Pure sensory* | *Other* |
|---|---|---|---|---|---|
| MGUS-IgM | +++ | + | – | ++ | + |
| MGUS-IgG,A | ++ | ++ | – | + | + |
| OSM | +++ | + | – | – | – |
| PSA | – | +++ | ++ | + | +++* |
| MM | + | ++ | + | + | ++# |

Abbreviations: PN, polyneuropathy; PCD, plasma cell dyscrasia; CTS, carpal tunnel syndrome superimposed on polyneuropathy; MGUS, monoclonal gammopathy of undetermined significance; OSM, osteosclerotic myeloma; PSA, primary systemic amyloidosis; MM, multiple myeloma; *, autonomic involvement; #, root involvement and polyradiculoapthies superimposed on PN.

Adapted with permission from ref. *1*.

biopsy is nonspecific with mixed axonal and demyelinating changes with or without inflammatory cell infiltration. However, a recent patient had an IgA gammopathy with IgA and complement deposition on the myelin sheath associated with splitting of the myelin sheath lamellae, similar to anti-MAG neuropathy, but without detectable anti-MAG or other glycolipid reactivity *(38)*. Otherwise, serological testing rarely identifies antinerve antibodies in these patients. Therapy is similar to CIDP, requiring long-term immunosuppresants. These patients generally respond well and have a good prognosis if treated early before severe axonal damage occurs.

(2) Sensory neuropathy in the setting of a small IgG or IgA MP is the most frequent syndrome detected in MGUS patiennts *(29,39)*. This neuropathy is generally fairly mild but symptoms are disturbing *(1,39)*. These patients are usually older and complain of painful dysesthesias with or without autonomic disturbances. Motor manifestations are usually mild. This neuropathy causes considerable discomfort and often keeps the patient awake at night. Progression is usually very slow and symptoms are more of a nuisance than a real impairment. As such, it closely resembles the many cases of idiopathic sensory neuropathy that occur in elderly patients.

Generally, laboratory tests, with the exception of the protein studies and EMG, are normal. The presence of anemia, an elevated sedimentation rate, proteinuria, or other findings should raise the question of amyloidosis or malignant PCD *(1)*. The SPEP typically shows a small spike and IFE confirms an IgA or G monoclonal gammopathy with a low concentration and no suppression of the gamma globulin fraction. EMG shows a mild axonal neuropathy with predominant sensory involvement. Nerve biopsy and CSF exam are not helpful and are generally not indicated. Pain control is the main goal of treatment. These patients require analgesics and other pain control medications especially at night, when the discomfort keeps them awake. If mild non-narcotic analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDS) are not helpful, then the tricyclic antidepressants such as amitriptyline in a dose of 25–75 mg at bedtime should be tried. For patients in whom this is not helpful or the side effects are limiting, gabapentin, in doses of 300–1200 mg three times a day, can often help and does not produce unpleasant side effects in most. Other treatments such as capsaicin are occasionally helpful and sometimes a low dose of a long-acting narcotic at bedtime, in a medically stable and reliable patient, can help a great deal. This syndrome is usually very slowly progressive. Immunosuppression seldom helps and is not indicated in these patients. The cause of this syndrome is unknown. Some patients have antisulfatide antibodies *(10,11)* or antibodies against other nerve antigens. However, the relevance of these antibodies to the nerve damage is unestablished and may represent the chance co-occurrence of PCD and idiopathic sensory neuropathy of the elderly.

(3) Others: This group consists of a number of other disorders, which occur rarely in association with IgA or G monoclonal proteins. A number of these are discussed below. They include primary systemic amyloidosis, which, in early stages, may be difficult to separate from sensory polyneuropathies associated with IgG and IgA MGUS. Rapid progression, marked pain and autonomic involvement, other organ dysfunction, and abnormal laboratory studies are a clue to that diagnosis. Other rare patients have myeloma, lymphoma, or cryoglobulinemia. Occasional reports cite the occurrence of a GBS-like syndrome in these patients.

**MULTIPLE MYELOMA (MM)** Multiple myeloma is a malignant PCD with high serum and urinary concentrations of MP, infiltration of bone marrow by malignant plasma cells, and multiple bony plasmacytomas *(3)*. Most neurologic complications are due to secondary effects of the tumor (hypercalcemia, infections) or to malignant infiltration of vertebrae with secondary compression of spinal cord or nerve roots due to vertebral fractures and collapse. Remote effects are much less common.

**Direct Effects of Myeloma** Most neurologic symptoms associated with MM are due to malignant infiltration of the vertebral column or metabolic and toxin manifestations of the malignancy or its treatment. Patients with spinal involvement usually present with segmental spinal pain and symptoms of spinal cord or cauda equina disruption below that level. Local pain is due to infiltration of the vertebrae with collapse. Unless the cord or roots are involved, this pain is usually localized to the region of the vertebra and does not radiate into the trunk or

**Table 5**
**Antibody Activities of Monoclonal IgM in Peripheral Nerve Disorders**

| *Antibody activity* | *Clinical syndrome* | *Pathology* |
|---|---|---|
| MAG | Sensory > motor polyn. | SD |
| Acidic glycolipids | Polyneuropathy | ? |
| Gangliosides GM1 and GD1b | Motor neuron disease | SD, ?AD |
| Chondroiton sulfate C | Sensory polyneuropathy | AD |
| Intermediate filaments | Polyneuropathy | SD |
| Neurofilament | Polyenruopathy | AD |
| Sulfatide | Sensory polyn. | AD |

Abbreviations: MAG, myelin-associated glycoprotein; SD, segmental demyelination; AD, axonal degeneration.
Adapted with permission from ref. *11*.

extremities. There may be tenderness to percussion over the vertebra; the pain is aggravated by spinal movements and is often worse at night when the patient is supine. If there is no clinical evidence of root or cord compression, plain X-ray or computed tomography (CT) is often adequate for diagnosis, although subsequent magnetic resonance imaging (MRI) may be warranted to judge whether there should be concern for later epidural encroachment and cord compression. Treatment of uncomplicated vertebral involvement consists of adequate pain control, localized radiation therapy and chemotherapy. The patient needs to be followed carefully for development of cord compression.

Root and spinal cord compression cause local pain plus a radicular or cord syndrome or both, depending on the level and extent of compression. If the compression is in the thoracic region, the patient may have girdle pain around the flanks and into the chest or abdomen due to root involvement, which may suggest cardiac or abdominal disease initially. In addition, if the cord is compressed, leg symptoms and signs appear. These may be subtle at first, consisting only of mild weakness, sensory symptoms or even isolated ataxia. Without rapid diagnosis and treatment, these patients progress to bilateral leg weakness or paralysis, dense sensory loss to the spinal level of compression, and bladder and bowel paralysis. Patients with lesions in the cervical or lumbar area have added limb radicular symptoms and signs, which may in some cases be the only finding early on. These patients have root pain, lost reflexes, weakness and dermatomal sensory loss in affected root distributions. If the cord is compressed in the cervical area, patients develop involvement of legs and arms with upper motor neuron signs in a distribution depending on the level of involvement of the cord. The cord syndrome may be asymmetrical in cases of mild or early compression but is generally more symmetrical in advanced cases. In the lumbar region, since the cord terminates normally at L1, root, and cauda equina symptoms and signs predominate. In this setting, there is no evidence of an upper motor neuron deficit such as Babinski signs, hyperreflexia and long tract sensory loss. Patients instead have lost reflexes, weakness and atrophy of muscles, radicular pain, and sensory loss in root distributions with bladder and bowel involvement if the conus medullaris is affected or the roots (cauda equina) are affected severely and bilaterally.

Diagnosis is suspected by the association of local symptoms (spinal pain, radicular pain, and findings) and/or a spinal cord pattern of involvement of the lower extremities. Diagnosis is urgent in these cases to prevent further worsening. Urgent MRI is warranted with imaging of the suspected area. Since incomplete spinal lesions are often difficult to carefully localize with confidence, a sagittal screening MRI of the entire spine is often helpful as an initial step to detect suspicious areas allowing careful localized imaging. In patients who cannot have MRI, spinal plain films and radionuclide bone scans can be helpful in localizing collapsed vertebrae and eroded pedicles, thus suggesting the level of compression. This can be followed by CT of this area to look for an epidural mass. If the findings fit with the clinical picture, treatment can commence without myelography. However, since the lesion seen on CT may not the proximate cause, careful follow-up must be maintained and any worsening should prompt urgent CT myelography.

Treatment generally consists of high-dose corticosteroids, pain control, localized irradiation of the area, and chemotherapy. As mentioned earlier, careful monitoring is necessary to detect deterioration which may necessitate surgical decompression, although usually this is not necessary if treatment is commenced promptly. Surgery is complicated, in addition, by the frequent involvement of adjacent vertebrae, which may render the postoperative spine unstable. Outcome usually depends on speed of diagnosis, rapidity of commencing treatment, and the neurologic status before treatment. Severe pretreatment impairment usually predicts a poor result.

Neuropathies or plexopathies due to localized deposits in the peripheral nerves are quite uncommon. Direct involvement of plasma cell disorders in the intracranial compartment is also rare but well-documented. Leptomeningeal myelomatosis typically occurs in advanced cases of MM and is managed according to the usual guidelines for leptomeningeal leukemia *(40)*. Myelomatous infiltration of the dura occurs rarely, presumably the result of spread from contiguous bone. This entity has responded favorably to radiation therapy *(41)*. Solitary extramedullary plasmacytomas also rarely involve the dura and are successfully managed with surgery and radiotherapy *(42)*. Parenchymal brain plasmacytomas are exceedingly uncommon *(43)*.

**Metabolic, Toxic, and Infectious Effects of Myeloma**

Metabolic, toxic and infectious disorders can also cause neurologic syndromes in myeloma. These patients can develop encephalopathy, sometimes with seizures, from renal insufficiency, dehydration, hypercalcemia, and associated metabolic failure. Light-chain deposition can cause a rapidly progressive nephropathy. Anemia, immunosuppression, and secondary infections are common. In patients with IgM myeloma, hyperviscosity syndrome with CNS changes (Bing-Neel Syndrome) can present (*see* below). In evaluation of encephalopathic patients with PCD, thorough metabolic screening with careful review of medications is indicated. If the patient is febrile or no obvious metabolic or toxic cause is found, evaluation for infection should be carried out including CSF exam for bacteria, fungi, and tuberculosis. Brain imaging with CT or MRI and EEG are indicated in all cases where cause is not clear. These patients generally do well once the cause is

found and the underlying problem reversed, but recovery to baseline often takes several days or longer.

**Remote Effects of Myeloma** Remote effects of myeloma consist mostly of peripheral neuropathies of various types. Other remote effects, such as paraneoplastic cerebellar ataxia, are vanishingly rare.

***Typical Lytic Multiple Myeloma*** These polyneuropathies are uncommon *(44,45)*. They occur in only a few percent of MM patients and are diverse in nature, similar to the polyneuropathies associated with other malignancies. The exception is osteosclerotic myeloma, discussed separately below. Neuropathies associated with typical lytic MM include distal sensorimotor axonopathy, a chronic inflammatory demyelinating polyneuropathy (CIDP)-like syndrome, and a sensory neuropathy resembling carcinomatous sensory neuropathy. In addition, these patients may also develop amyloid polyneuropathy, also know as primary systemic amyloid (PSA) neuropathy or AL neuropathy, due to deposition of light chain-derived amyloid in nerve and other tissue. In one series, 20% of neuropathies associated with MM were due to AL *(44)*. Superimposed root involvement in occasional patients may confuse the clinician by mistakenly suggesting a picture of mononeuritis multiplex. The root- and cord-compressive syndromes should be managed by conventional means as discussed earlier. The neuropathies should be separately classified by the usual techniques and treated according to type. Electromyography can be very helpful in properly classifying these disorders. Of the four types mentioned previously, only the CIDP-like neuropathy is amenable to treatment using conventional immunosuppression.

***Osteosclerotic Myeloma (OSM) and Polyneuropathy (and Related Syndromes) (44,46)*** Osteosclerotic myeloma is a rare and relatively benign variant of MM. Fewer than 3% of untreated myeloma patients have sclerotic bony lesions. In addition, while polyneuropathy is rare with typical MM, it occurs in 50% or more of reported cases with OSM. In addition, in contrast to typical MM, patients with OSM are usually not systemically ill. They present because of the neuropathy or other remote effects of the malignancy rather than as a direct effect of the malignancy. Anemia, hypercalcemia, and renal insufficiency are uncommon is OSM, the bone marrow is rarely infiltrated with malignant plasma cells, and the serum M-protein concentration is low. Finally, the course of OSM is indolent and these patients have prolonged survivals even without treatment. Thus, there is something singular about the syndrome of OSM and its paraneoplastic accompaniments. For these reasons, the syndrome can be difficult to diagnose even by experienced clinicians.

Clinical Features Unlike MM, the polyneuropathy accompanying OSM is distinctive and homogeneous *(46)*. Deficits are mainly motor and slowly progressive without sudden changes in severity or tempo of progression. Patients present with the onset of weakness, mostly in distal limbs initially, with gradual proximal spread accompanied by reflex loss. Sensory loss is typically less striking and tends to affect the larger sensory fibers disproportionately with greater loss of discriminative than cutaneous sensation. Pain and autonomic dysfunction, with the exception of impotence (actually due to endocrine insufficiency), are very uncommon. Nerves are often palpably thickened. The deficit is usually very symmetrical and the speed of progression slow, often over months to years. In keeping with the nature of the underlying disorder, general laboratory studies are usually relatively uninformative. The best clue to the diagnosis is the presence of a serum M-protein, which is present in about 75–80% of patients. However, the M-protein may be very small and obscured by the normal serum protein components in the electrophoresis, emphasizing the importance of IEP or IFE in all patients with idiopathic polyneuropathy. The M-protein is characteristically IgG or IgA with a lambda light chain (occasionally kappa), and rarely present in the urine, as opposed to MM and AL.

Laboratory Studies Neurodiagnostic studies are helpful but nonspecific *(46)*. Nerve biopsy studies disclose a reduced concentration of myelinated fibers with changes of mixed demyelination and axonal degeneration *(46)*. There may be mild foci of mononuclear cells in the epineurium surrounding blood vessels. These changes are nonspecific and characteristic of a number of neuropathies, including CIDP and diabetic polyneuropathy. The EMG (Table 4) reveals a mixed axonal and demyelinating picture, which is also nonspecific but helpful in categorizing the neuropathy into the group with clear-cut demyelinating features *(14,46)*. This feature is helpful since the differential diagnosis of demyelinating neuropathies is very limited. CSF typically discloses a normal cell count but a very high protein concentration, generally greater than 100 mg per dl and sometimes as high as several hundred mg per dL. Since all these findings are nonspecific, the diagnosis often hinges on the discovery of the characteristic bony lesions and subsequent bone biopsy. The osteosclerotic lesions may be solitary or multiple *(46)*. They tend to affect the axial skeleton and very proximal long bones but spare the distal long bones and skull. They may be purely sclerotic or mixed sclerotic and lytic. Radioactive bone scans, although more sensitive than radiographs as a rule in detecting spinal metastases, are not as sensitive as X-rays in detecting typical MM and especially OSM lesions, probably due to the indolent nature and relative paucity of osteoclastic activity of these plasmacytomas *(46–48)*. Thus, all patients with unexplained polyneuropathies that fit the clinical profile as previously described should be screened with a radiographic skeletal survey, even in the absence of a serum or urine MP. On occasion, these lesions are misinterpreted by radiologists who are unfamiliar with their appearance and significance. Three of our patients were felt to have benign osteosclerotic lesions (fibrous dysplasia in a rib in two and a vertebral hemangioma in one) with negative radionuclide bone scans. We insisted on biopsy because of the clinical picture and the presence of a serum M-protein and plasmacytomas were discovered, leading to effective treatment. Thus, if there is any question of the significance of a bony lesion in a patient with a suggestive clinical picture, the neurologist and the radiologist should review the X-rays and the lesion should be biopsied if doubt remains. Open biopsy has been preferable to needle biopsy in our experience.

Pathogenesis The cause of the polyneuropathy is not known but most theories of pathogenesis have focused on some secretory product of the tumor, most likely the M-protein itself.

However, other secretory or autoimmune products are possible including cytokines. A recent study suggested that cytokines interleukin (IL)-1β, tumor necrosis factor-α (TNF-α), and IL-6 may play a role in pathogenesis *(49)*. Studies of anti-nerve antibody activity in the serum of these patients and immunocytochemical studies of nerves have been negative to date, although a recent study showed some deposition of antibody in the endoneurium in 3 of 4 cases *(50)*. The pathogenesis of nerve damage in this disorder and whether or not it is an axonopathy or a primary demyelinating disorder remains unresolved at this time.

TREATMENT The diagnosis of this disorder is of more than academic interest since these patients may be helped by tumoricidal treatment. Patients with solitary lesions do best. Radiation therapy in tumoricidal doses to the lesion or surgical excision results in elimination of the M-protein from the serum and gradual recovery of the neuropathy and other symptoms over the ensuing months in most patients. However, these patients should continue to be followed since they have a tendency to relapse with the development of new lesions months to years later. This is usually heralded by the return of the neuropathy and other symptoms and the reappearance of the serum M-protein. Patients with multiple lesions are more difficult to treat. Radiation therapy is generally not an option due to the risk of toxicity. In some cases, aggressive chemotherapy, with or without local radiation therapy to large lesions, can help these patients *(46,51,52)* but in general the outcome is less favorable than for solitary lesions. Treatment usually requires large doses of steroids and alkylating agents. Treatments that are usually effective in autoimmune inflammatory neuropathies, such as steroids, azathioprine, plasmapheresis, and IV-Ig, are typically ineffective in these patients.

SYSTEMIC FEATURES This disorder is also of considerable interest since many of these patients develop a multisystem syndrome which goes by a variety of names including the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-protein, skin changes) *(53)* or the Crow-Fukase syndrome *(54)*. These patients have, in addition to polyneuropathy, other features (Table 6) suggesting the presence of an underlying endocrinopathy or malignancy *(46,53–55)*. The reason for the endocrinopathy is unclear. Limited data suggests a disturbance of the hypothalamic-pituitary axis rather than primary end-organ failure, possibly due to antibody activity against pituitary tissue. The organomegaly is usually nonspecific pathologically. Biopsy of affected lymph nodes generally discloses hyperplastic changes, sometimes resembling the pathologic findings in the syndrome of angiofollicular lymph node hyperplasia (Castleman's disease), which is a benign localized or generalized hyperplastic lymph node syndrome of unknown etiology. Of interest, patients with generalized angiofollicular lymph node hyperplasia without bony lesions may also have the manifestations of Crow-Fukase syndrome associated with serum M-proteins or polyclonal gammopathies. Thus, it is likely that the main pathogenetic determinant of these syndromes is the presence of a serum product, most likely the IgG or IgA lambda M-protein or polyclonal antibodies with similar specificity, directed against neural and other tissue. The term POEMS syndrome for these patients, however, is not entirely accurate and focuses attention on a small number of these patients to the exclusion of others *(46,55)*. For example, of the patients with OSM polyneuropathy, most have features other than neuropathy which are fragments of a multisystemic disorder but only a few would qualify for the term POEMS (Table 7). Also, patients without myeloma may develop all the features of the POEMS syndrome. Thus, I prefer the term Crow-Fukase syndrome when referring to patients with polyneuropathy and multisystemic disorder, as suggested by Nakanishi and colleagues *(54)*.

**PRIMARY SYSTEMIC AMYLOIDOSIS** PSA can occur in the setting of MM *(44)* or Waldenstrom's macroglobulinemia *(26)* although most commonly it presents in the absence of a malignant plasma cell dyscrasia *(56–59)*. It should always be considered when a patient develops a neuropathy in the setting of a malignant or apparently benign plasma cell dyscrasia or in any patient who presents with a predominantly pain small fiber neuropathy with attendant autonomic symptoms.

**Clinical Presentation** This syndrome is perhaps the best characterized of the polyneuropathies associated with M-proteins and accounts for up to one-quarter of cases in some series *(5)*. This neuropathy characteristically occurs in older men and is very rare prior to the sixth decade. Most cases are unassociated with an underlying illness but a few are associated with hematologic malignancies such as myeloma and Waldenstrom's macroglobulinemia. PSA generally presents as a multisystem disease due to the deposition of fragments of the variable portion of a monoclonal light chain, most often lambda, in tissue *(57–59)*. Patients present with a medical disease with associated (sometimes incidental) polyneuropathy (60%) or severe polyneuropathy with minimal organ involvement (40%) *(58)*. A similar illness can occur in a variety of inherited amyloid polyneuropathies due to an abnormal circulating prealbumin (transthyretin) protein with a single amino acid substitution. Polyneuropathy does not occur in amyloidosis secondary to chronic inflammatory disease or familial CNS amyloidosis.

Medical syndromes (Table 8) include the nephrotic syndrome due to amyloid infiltration of the kidneys, cardiac failure due to amyloid cardiomyopathy, chronic diarrhea with wasting due to amyloid infiltration of the gut wall, and autonomic neuropathy with prominent orthostatic hypotension *(58)*. General laboratory studies reflect the medical syndromes with proteinuria occurring in a high percentage, elevated erythrocyte sedimentation rate in about half, and a mild increase in benign appearing plasma cells in bone marrow in many. Up to 90% have an M-protein in serum or a monoclonal light chain in urine when thoroughly screened with serum and urine IFE. Those patients lacking an M-protein may have inherited amyloid neuropathy. However, most have primary systemic amyloidosis and are called nonsecretory, assuming the lack of a secreted M-protein. In fact, immunocytologic studies of their tissue disclose amyloid derived from single (monoclonal) light chains. Presumably, the serum concentration is too low to detect the light chains in these patients. The light chains are deposited in tissue, where they are digested by macrophages with the production of amyloid fibrils, which are insoluble.

The polyneuropathy has been well characterized *(58,59)*. Sensory symptoms are typically most prominent and the earliest to appear. Almost all present with numbness of the hands

**Table 6**
**Nonneurologic Abnormalites in 16 Patients with OSM and Polyneuropathy**

| *Abnormality* | *Patients* |
|---|---|
| Gyneomastia | 2 |
| Hepatomegaly | 5 |
| Splenomegaly | 2 |
| Hyperpigmentation | 5 |
| Edema | 3 |
| Lymphadenopathy | 2 |
| Papilledema | 4 |
| Digit clubbing | 3 |
| White nails | 2 |
| Hypertrichosis | 3 |
| Atrophic testes | 3 |
| Impotence | 4 |
| Polycythemia | 5 |
| Leukocytosis | 3 |
| Thrombocythemia | 12 |
| Hypotestosterone | 5 |
| Hyperestrogogen | 3 |
| Hypothyroid | 2 |
| Hyperglycemia | 1 |

Abbreviation: OSM, osteosclerotic myeloma.
Adapted with permission from ref. *46*.

**Table 7**
**Results of Biopsy in Primary Amyloidosis with Neuropathy**

| *Site* | *Number of patients* | *Percent positive* |
|---|---|---|
| Rectum | 25 | 88 |
| Kidney | 4 | 75 |
| Liver | 2 | 100 |
| Small intestine | 2 | 100 |
| Bone marrow | 21 | 33 |
| Sural nerve | 10 | 100 |
| Other (skin, gingiva) | 2 | 100 |

Adapted with permission from ref. *58*.

and legs with complaints such as burning, aching, stabbing, and shooting pains. In greater than half of patients, cutaneous sensation (light touch, pain, temperature) are more frequently and severely affected than discriminative sensation (vibration and position sense). Occasional patients (about 20%) present with the typical symptoms of carpal tunnel syndrome due to amyloid infiltration of the flexor retinaculum of the wrist before distal neuropathy symptoms appear. Rare patients present with symptoms of autonomic dysfunction without symptoms of somatic sensory dysfunction. Symptoms and signs of weakness generally follow. These are usually less prominent than the sensory findings although rare patients may present with predominantly motor findings *(60)*. Occasional patients with amyloid infiltrative myopathy present with proximal muscle weakness and patients with malignant plasma cell dyscrasias, such as myeloma, may present with additional compressive radiculopathies, which can mimic mononeuropathies or plexopathies. Otherwise the findings tend to be symmetric and predominant distally with gradual proximal spread. Most patients soon complain of autonomic dysfunction with orthostatic lightheadedness and syncope, bowel and bladder disturbances, impotence, and sweating disturbances. Hypoactive pupils and orthostatic blood pressure drop with a fixed heart rate are the most easily detected autonomic signs at the bedside.

**Lab Studies** Electrophysiologic studies (Table 4) confirm the presence of a distal axonopathy, which is maximal in the legs *(58)*. Motor conduction velocities in the "demyelinating" range (<60% of the mean normal for that nerve) occur rarely and then only in severely affected nerves where the evoked compound muscle action potential is very low in amplitude. Sensory nerve action potentials are usually absent. Often, there is evidence of carpal tunnel syndrome, which can suggest the diagnosis. Needle EMG shows the changes expected of a distal axonopathy, with abundant signs of distal denervation and reinnervation. CSF is usually acellular and there are usually mild elevations of protein levels, in the 50–70 mg per dL range. Diagnosis is dependent on the discovery of amyloid in tissue. Sural nerve biopsy is very useful in detection of amyloid in virtually all cases, although occasionally it has to be sought through multiple sections. One study, however, reported that 6 of 10 patients with PSA neuropathy had negative nerve biopsies *(61)*, so it is often advisable to biopsy more than one tissue. Amorphous deposits of amyloid on Congo red or cresyl violet stains typically appear in the perivascular regions of the epineurium or occasionally in the endoneurium. Amyloid is classically defined by its appearance under polarized light where the Congo red stained deposits emit an apple green birefringence. Electron microscopy can also be used to identify the characteristic beta-pleated fibrils. Immunofluorescent staining for monoclonal light chain fragments is helpful but is technically more demanding and should be limited to experienced labs. Other useful tissues to biopsy (Table 7) include rectum, fat pad aspiration (reported to be 82% sensitive *[62]*) and other affected organs. Teased fiber studies show predominant axonal degeneration. The reason for nerve fiber damage, however, is not always readily apparent in all cases. In some instances, marked axonal degeneration appears with minimal amyloid infiltration, possibly caused by more proximal amyloid, perhaps at the level of the dorsal root ganglion.

**Pathogenesis** These findings have led to many theories of the pathogenesis of the neuropathy including vascular and pressure changes by the amyloid deposits. However, direct toxic effects of the amyloid fibrils on nerve fibers and dorsal root ganglion cells seems more likely *(58)*.

**Treatment** Treatment is problematic. The amyloid fibrils are insoluble once deposited in tissue. Thus, it is unlikely that much improvement would appear, even with cessation of amyloid deposition. Thus far, the neuropathy has resisted all attempts to halt its progression with combinations of anti-inflammatory medications including steroids, alkylating agents such as melphalan and cyclophosphamide designed to slow production of the light chains, and even prolonged plasmapheresis aimed at lowering the light chain concentration in serum *(58,63,64)*. However, the nephropathy due to light chain depo-

**Table 8**
**Medical Syndromes in Amyloid Polyneuropathy**

| *Syndrome* | *Percent frequency* |
|---|---|
| Orthostatic hypotension | 42% |
| Nephrotic syndrome | 23% |
| Cardiac failure | 23% |
| Malabsorption | 16% |

Adapted with permission from ref. *58.*

sition has been shown to be at least partially reversible with a combination of melphalan and prednisone *(63,64)*. These patients usually progress inexorably with increasing numbness and pain, autonomic failure and weakness with added multiorgan failure in many cases. Death usually occurs in 2–4 yr from time of diagnosis and is generally due to major organ failure, cardiac most commonly. Diagnosis is delayed most in patients with relatively pure neuropathies without significant organ failure (median 26 mo) *(58,65)*. The disease has a dismal prognosis and 85% are dead within 25 mo *(58)*. The role of high dose chemotherapy and stem cell rescue in this disorder is yet to be determined.

### MISCELLANEOUS SYNDROMES

**Waldenström's Macroglobulinemia (WM)** It is sometimes difficult to separate WM from IgM-MGUS and the latter may evolve into WM over time *(66)*. Thus, similar polyneuropathy syndromes occur. The most frequent polyneuropathy encountered is probably that associated with anti-MAG antibodies *(15)*. This syndrome has the same features and clinical course as in IgM-MGUS since, despite the presence of a malignant plasma cell dyscrasia, the anti-MAG antibody determines the type of neuropathy. One patient with anti-MAG neuropathy and WM was reported to respond to bone marrow transplantation *(66)*. Other patients may have a CIDP-like picture, a distal axonal neuropathy, typical amyloid polyneuropathy, or even the sensory neuronopathy syndrome usually seen with small cell cancer of the lung. Rare patients develop CNS symptoms due to hyperviscosity, requiring urgent lowering of viscosity via plasmapheresis. These patients present with encephalopathy with or without seizures. Treatment is based on rapid lowering of IgM levels, hydration, and chemotherapy to lower IgM production. The prognosis is often poor unless the patient is treated promptly before there is significant neurologic deterioration.

**Cryoglobulinemia** This disorder is usually divided into 3 types *(35,67)*. In type 1, the M-protein itself is a cryoglobulin in the setting of a plasma cell disorder. In type 2, the cryoglobulin is a mixture of an M-protein of IgM type with rheumatoid factor activity against polyclonal immunoglobulins, usually occurring in the setting of a lymphoproliferative disorder. Type 3 occurs in the setting of a collagen-vascular or other chronic inflammatory disease and the cryoglobulin consists of polyclonal immunoglobulins. The polyneuropathy in all these syndromes is painful, symmetrical or asymmetrical, sensorimotor, and axonal in nature. Purpura occurs in distal limbs in a high percentage of patients and the neuropathy is generally considered to be due to a vasculopathy or vasculitis of skin and vasa nervorum.

**Lymphoma, Leukemia, Cancer** These disorders can be associated with MP and polyneuropathy *(15)*. In lymphoma with IgM M-protein, the IgM may have anti-MAG activity with the usual clinical and pathological features. Other syndromes without clear anti-nerve activity in the M-protein fraction may respond to ablation of the malignancy. Still other have an unclear relation to the malignancy and show little response to tumoricidal treatment or to lowering of the M-protein concentration in serum.

## CONCLUSION

The topic of plasma cell dyscrasias and neurologic disease has been a fruitful area for active research over the last decade or so. These patients frequently develop and even present with neurologic disease and an organized approach, as presented in this review, aids diagnosis. Prompt treatment can reverse many of these syndromes. The neuropathy patients especially are of great importance to recognize since treatment may lead to remission in some cases and careful study of these patients may lead to a better understanding of the pathogenesis of polyneuropathies and possibly motor neuron disease. This may in turn lead to effective treatment for conditions for which there are now no effective treatments. Therefore, despite their relative infrequency, increased recognition of these neuropathies will continue to be a high priority for both peripheral nerve specialists and for general neurologists.

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# 27 Female Reproductive Tract Cancers

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## INTRODUCTION

Neurologic problems in patients with gynecologic malignancy may be the result of treatment, metastatic disease, paraneoplastic syndromes, or coincidental neurologic disease (*see* Table 1). Gynecologic cancers are uncommon causes of brain metastases and neurologic paraneoplastic syndromes are rare, but the full spectrum of neurologic complications in these patients is more common than generally appreciated. Metabolic encephalopathies and secondary neurologic complications are common in patients with cancer and are the most common reason for neurologic consultation. In particular, patients with pelvic tumors are at high risk to develop obstructive renal failure with uremia, mental status changes, and seizures. This chapter will review the common malignancies of the female reproductive tract and the specific neurologic problems encountered as a result of these tumors or their treatment.

## OVARIAN CANCER

Ovarian cancer is the most deadly of the female reproductive tract malignancies with only 39% of all women surviving for 5 yr. Approximately 24,000 new cases are diagnosed and 13,600 deaths attributed to ovarian cancer annually *(1)*. Oral contraceptives may reduce the risk of ovarian cancer, but infertility treatments have been associated with an increased risk. Family history is the most significant risk factor, and there are several familial ovarian cancer syndromes that include associations with breast, endometrial, and colorectal cancer.

The disease is often clinically silent in its early stages. Increasing abdominal girth with or without abdominal pain or bloating is the most common initial symptom, usually a manifestation of advanced disease. As many as 85% of tumors are malignant at diagnosis and may spread via local extension, lymphatic invasion, peritoneal implants, and hematogenous metastasis.

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Tumor markers such as lactate dehydrogenase (LDH), human chorionic gonadotropin (HCG), and alpha-fetoprotein (AFP) are useful in distinguishing germ cell tumors from ovarian carcinoma. Serum CA-125 is a valuable marker of disease activity in serous ovarian carcinoma.

Ovarian cancer is treated with a combination of surgery and adjuvant therapy. The role of surgery is twofold. First, methodical surgical procedure is critical to accurately stage patients; second, optimal debulking and cytoreduction are therapeutic. Pelvic or abdominal radiotherapy is important adjuvant therapy for patients with stage II and III disease. Chemotherapy, most commonly regimens incorporating either paclitaxel or a platinum-based chemotherapy, is used for patients with advanced stage disease and may be used preoperatively to decrease tumor size and allow optimal debulking. Ovarian germ cell tumors are a relatively uncommon subset of ovarian cancer seen most often in young women. A combination of chemotherapy and conservative surgery may be used in select patients in an effort to preserve fertility.

## OTHER GYNECOLOGIC CANCERS

**ENDOMETRIAL CANCER** Endometrial cancer is the most common cancer of the female reproductive tract and ranks as the fourth most common cancer of women behind breast, lung, and colorectal carcinoma. In 1994 there were 31,000 new cases of endometrial cancer and 5900 deaths *(1)*. The median age at diagnosis is 58 yr and most patients are postmenopausal; however, 25% of cases occur in premenopausal women. Risk factors include obesity, diabetes, nulliparity, unopposed estrogen exposure, pelvic irradiation, and late menopause *(2)*. Unopposed endogenous or exogenous estrogen appears to play the most important role in pathogenesis.

The vast majority of patients present with postmenopausal bleeding and the older the patient the greater the likelihood that cancer is the cause of the bleeding. Locally, endometrial cancer metastasizes to the vagina, peritoneum, and inguinal lymph nodes, while hematogenous spread results in metastases to the

**Table 1**
**Incidence of Neurologic Complications in Gynecologic Malignancy**

| *Tumor-related* | *Incidence* |
|---|---|
| Brain metastases | 0–20% |
| Spine metastases and cord compression | <1% |
| Leptomeningeal carcinomatosis | <1% |
| Lumbosacral plexopathy | 2% |
| Paraneoplastic disorders | <1% |
| *Treatment-related* | |
| Surgical complications | |
| Peripheral nerve injury | 1% |
| Radiotherapy complications | |
| Lumbosacral plexopathy | 0.2% |
| Chemotherapy complications | |
| Peripheral neuropathy | Up to 60% |
| Ifosfamide encephalopathy | Up to 30% |

lungs, liver, and bones. Elevated levels of CA-125 at diagnosis are highly correlated with advanced, metastatic disease.

Total abdominal hysterectomy with bilateral salpingo-oophorectomy (TAH/BSO) is standard treatment; the removal of the ovaries is important as these often contain micrometastatic disease. Furthermore, the ovaries are a source of estrogen production that may stimulate growth of residual tumor. Adjuvant radiotherapy is recommended for all patients with advanced-stage disease or any known risk factor for more aggressive tumor. Advanced endometrial cancer should be treated with a multimodality approach including surgery, radiation, chemotherapy, and/or progestin therapy. The most common chemotherapeutic agents used are cisplatin and doxorubicin.

**CERVICAL CANCER** Cervical cancer is diagnosed in approx 15,000 women annually and accounts for 4600 cancer-related deaths *(1)*. Risk factors include lower socioeconomic status, history of multiple sexual partners, intercourse at a young age, and a large number of pregnancies *(3)*. It is rare in sexually inactive or nulliparous women. Human papillomavirus and several oncogenes, including *c-myc* and *ras*, have been strongly implicated in the pathogenesis of cervical cancer *(4–6)*.

Cervical cancer spreads by local extension and lymphatic invasion; tumor infiltrates locally to involve the upper vagina, parametria, bladder, and rectum. The typical clinical presentation is a complaint of vaginal bleeding, including heavy menses, intermenstrual bleeding, and postcoital bleeding. Hydronephrosis and uremia are late or end-stage symptoms. Distant metastases are relatively uncommon.

The treatment of cervical cancer is based on the clinical stage of the disease. Surgical resection, radical hysterectomy, is recommended for locally confined disease and has an associated 5 year survival of 90%. Locally invasive tumors (stage IIB–IV) are routinely treated with postoperative radiotherapy to a total dose of 4500–5000 cGy with 5-yr survivals ranging between 45 and 65%. Neoadjuvant chemotherapy may be useful in consolidating local disease to allow a safe radical hysterectomy and decreasing the frequency of regional lymph node metastases.

**OTHER GYNECOLOGIC MALIGNANCY** Other primary gynecologic malignancies are rare and include fallopian tube cancer, vulvar malignancies, and vaginal carcinomas. These are primarily tumors that spread by local extension. Surgery and radiotherapy are the primary treatment modalities. Choriocarcinoma, a gestational trophoblastic tumor, is an aggressive germ cell tumor of particular neurologic interest as it frequently metastasizes to the brain. The prognosis for patients with this tumor has improved dramatically with the use of multiagent chemotherapy; however, up to 50% of deaths from choriocarcinoma are related to intracranial metastases *(7)*.

## NEUROLOGIC COMPLICATIONS OF TUMOR

**BRAIN METASTASES** Brain metastases are relatively uncommon in patients with cancer of the female reproductive tract. However, an autopsy series from Memorial Sloan Kettering Cancer Center found that 7% of patients with tumors of the female genital tract had intracranial metastasis; therefore, an estimated 1764 patients with female genital tract tumors and intracranial tumor in the United States died in 1994 *(8,9)*. While brain metastases can develop in any lobe of the brain, these pelvic tumors may have a predilection to metastasize to the posterior fossa *(10)*.

There has been concern that the incidence of brain metastases secondary to ovarian cancer may be increasing as a result of prolonged survival from improved treatment of systemic disease. Eradication of systemic tumor is increasingly successful, but the brain can act as a sanctuary site for tumor cells which then lead to central nervous system (CNS) metastases. Longitudinal studies of ovarian cancer estimate that brain metastases occur in 0.29–4% of patients *(11–16)*. Metastases may be single or multiple and can occur at any time during the course of the disease. Median survival following a diagnosis of brain metastases ranges from 1–6 mo; however, aggressive multimodality therapy incorporating surgery, radiotherapy, and/or chemotherapy has been demonstrated to result in an improved overall survival *(17,18)*. A recent study looking at the role of stereotactic radiosurgery plus whole brain radiotherapy (WBRT) for these patients reported a 69% radiographic response rate and a 60% 2-yr survival *(19)*. Response to chemotherapy alone has been clearly documented (Fig. 1) and may be an important treatment alternative for patients previously treated with cranial radiation or for those patients in whom radiation may confer an unacceptable risk of neurologic morbidity.

Fewer than 1% of patients with endometrial or cervical cancer develop symptomatic brain metastases although autopsy series report rates as high as 10% *(20,21)*. Metastases usually develop in the setting of widely disseminated disease although they are rarely the presenting symptom of the underlying tumor. Therefore, the diagnosis of brain metastases in a patient with cervical or endometrial cancer should prompt systemic restaging. WBRT is the standard of care; however, patients with single lesions may be candidates for surgical resection or stereotactic radiosurgery.

Choriocarcinoma is the gynecologic malignancy most likely to metastasize to the brain and comprises up to 35% of all brain metastases ascribed to gynecologic malignancies *(20)*. These metastases are particularly prone to hemorrhage and may be the presenting feature of the primary malignancy. The presence of

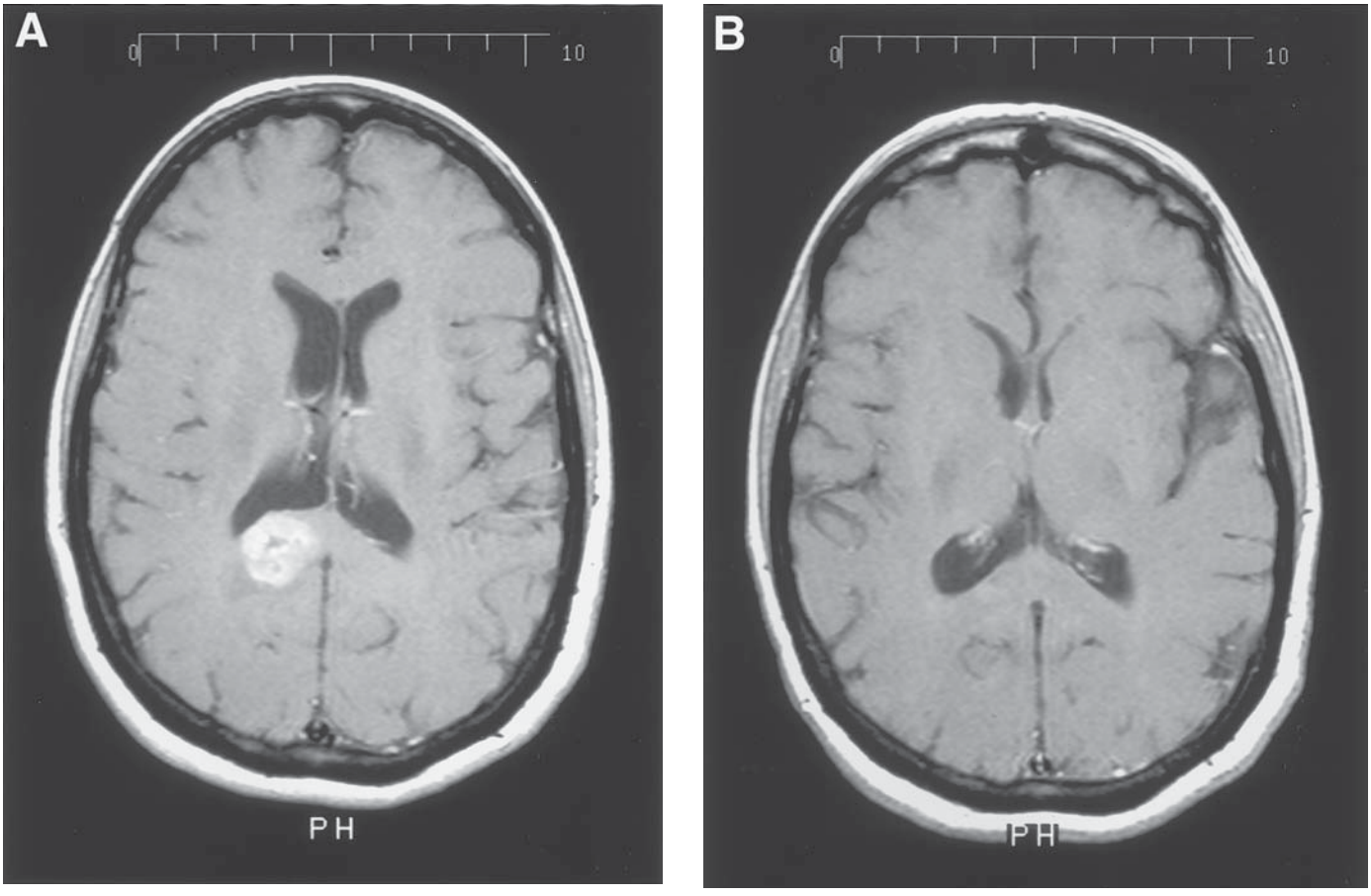


**Fig. 1.** Gadolinium enhanced MRI scan of a 50-yr-old ovarian cancer patient with a brain metastasis treated with ifosfamide. **(A)** is pretreatment and **(B)** is after 4 cycles of chemotherapy. This patient was felt to be a poor candidate for radiotherapy as she also had a diagnosis of multiple sclerosis.

pulmonary metastases, histologic invasion into surrounding tissue, and an increase in urine HCG levels during treatment are associated with an increased risk of brain metastases *(7)*. Gadolinium-enhanced magnetic resonance imaging (MRI) of the brain should be performed in every patient with choriocarcinoma to evaluate the extent of disease. Unlike other brain metastases, these are often exquisitely sensitive to chemotherapy and whole-brain radiation, allowing for the possibility of prolonged remission or even cure in a subset of patients. Therefore, these patients should have an aggressive multimodality approach to treatment including neurosurgical decompression in those patients with evidence of increased intracranial pressure. The use of corticosteroids to treat increased intracranial pressure may be relatively contraindicated in these patients as there are reports of steroids stimulating tumor growth *(7,22)*.

**SPINE METASTASES AND CORD COMPRESSION** A review of more than 23 series of patients suggests that gynecologic malignancies account for 3% or less of all epidural metastases causing spinal cord and cauda equina compression *(23)*. However, pelvic tumors may metastasize directly to the lumbar vertebral bodies via Batson's venous plexus without having evidence of other distant metastases, and autopsy series suggest that as many as 20% of women with tumors of the genitourinary tract have metastatic disease in the vertebral column *(24)*. In addition, back pain is a common symptom of pelvic tumors and is the most common presenting symptom of spinal cord compression. Therefore, patients with back pain merit careful neurologic evaluation and consideration of epidural tumor. Diagnostic neuroimaging should be obtained in those patients with an abnormal neurologic evaluation or symptoms suggestive of spinal tumor (increased pain when lying flat, urinary retention, radiculopathy, etc.). Prompt treatment with corticosteroids and radiation therapy is critical to preserve neurologic function in patients with spinal cord compression.

In a series of neurologic consultations performed on patients with ovarian cancer there were only four with a vertebral body metastasis, all of whom presented with pain *(17)*; none had evidence of spinal cord compression. A report of seven ovarian cancer patients with neurologic complications included four with epidural spinal cord compression *(25)*. Three patients presented with leg weakness and sphincter dysfunction with compression at the level of the conus medullaris, the fourth had cervical cord compression with myelopathy. Two of the four patients had significant improvement following radiation therapy and one attained a remission lasting at least 44 mo. A single patient with ovarian cancer and an intramedullary spinal cord metastasis has been reported *(26)*. This patient had a cervical cord lesion presenting with progressive paraparesis

and left arm weakness following treatment for brain metastases. She improved with focal radiotherapy and died 6 mo later from progressive systemic tumor.

Spinal cord metastasis or cord compression are rare complications of cervical cancer with only two reported cases in a review of 2261 patients *(21)*. However, Robinson et al. reported five patients with cervical cancer and spinal cord compression, two of whom were not known to have cancer; a thorough history revealed a complaint of abnormal vaginal bleeding in both patients *(27)*. This series highlights the importance of considering pelvic malignancy in the patient whose presenting tumor symptom is spinal cord compression.

**LEPTOMENINGEAL CARCINOMATOSIS** Meningeal carcinomatosis complicating malignant gynecologic neoplasms is extremely rare. However, the incidence of leptomeningeal metastases appears to be increasing as more effective systemic treatments are developed. Diagnosis is usually established by the demonstration of malignant cells in the cerebrospinal fluid (CSF) or unequivocal leptomeningeal tumor visualized on cranial or spinal MRI scan. For patients with ovarian cancer, CA-125 can be assayed in the CSF and may be useful in the diagnosis and monitoring of leptomeningeal tumor. Treatment options include WBRT, radiation to symptomatic sites of disease, intrathecal chemotherapy, and systemic chemotherapy. In spite of these treatments prognosis is generally poor, with patients rarely surviving more than a few months *(28,29)*.

**LUMBOSACRAL PLEXOPATHY** Lumbosacral plexopathy was the most common neurologic complication in a review of 2261 cervical cancer patients at the University of Kentucky, affecting 50 patients (2%) *(21)*. All patients with plexopathy had a diagnosis of squamous cell cancer. Patients developed plexopathy on average 20 mo after the diagnosis of cervical cancer. Pain was the most common presenting symptom. Computed tomography (CT) or MR scan demonstrated local compression by a retroperitoneal mass (tumor or lymphadenopathy) in the majority of patients. Half had extension of tumor into adjacent lumbar or sacral vertebrae and most had ipsilateral hydronephrosis. Survival was less than 6 mo in all patients with plexopathy. Radiation therapy was helpful in controlling pain in approximately one-third of patients treated; however, no patient had improved neurologic function as a result of radiation.

A review of 85 patients with malignant lumbosacral plexopathy included 12 (14%) with tumors of the female reproductive tract (6 cervical cancer, 3 ovarian cancer, and 3 uterine cancer) *(30)*. In this series pain preceded any clinical neurologic signs by weeks to months. Patients with genitourinary tumors were more likely to develop a panplexopathy with pain primarily localized in the lumbosacral region and variable radicular or referred pain. Sensory loss and paresthesias were typically seen in the anterior thigh and foot with weakness of knee flexion, ankle dorsiflexion, and inversion. Nearly half of patients studied also had evidence of epidural spinal tumor. Treatment provided symptomatic relief to only about a third of patients and median survival was 5.5 mo, emphasizing the need for aggressive pain and palliative-care management of these patients.

**PARANEOPLASTIC DISORDERS** Paraneoplastic cerebellar degeneration is the most common and best characterized of the neurologic paraneoplastic disorders. Patients with gynecologic malignancy develop a particular type of paraneoplastic cerebellar degeneration characterized by the anti-Yo antibody. In a report of 55 patients with anti-Yo associated paraneoplastic cerebellar degeneration, 26 had a diagnosis of ovarian cancer, and 8 had other gynecologic malignancies including endometrial, fallopian tube, and mesovarium carcinoma *(31)*. Another patient developed typical paraneoplastic cerebellar degeneration with anti-Yo antibodies and an elevated CA-125 that decreased to normal levels following TAH/BSO despite the absence of tumor on detailed pathologic examination. In addition, a number of patients with gynecologic malignancy and paraneoplastic cerebellar degeneration have been described with other autoantibodies directed against the cytoplasm of Purkinje cells or other neurons.

Most patients present with an acute to subacute onset of neurologic symptoms preceding the diagnosis of malignancy. The typical patient develops a pancerebellar syndrome characterized by axial and appendicular ataxia, dysarthria, and nystagmus. The nystagmus often has a downbeat component. These symptoms stabilize within weeks to months leaving the patient with severe neurologic disability; most patients are unable to read or watch television because of oscillopsia and many are wheelchair-bound as a result of gait ataxia. Treatment of the underlying malignancy often results in oncologic cure but the patient does not improve neurologically. Specific therapies aimed at treating the neurologic disease have been unsuccessful although there are a few individual reports of transient clinical improvement following plasmapharesis *(32)*, high-dose corticosteroids *(31)*, or other immunosuppressive agents. Although the neurologic disability often stabilizes, many patients die as a result of complications of immobility. Persistent anti-Yo antibody titers can be detected years after diagnosis and treatment in patients in remission from their cancer and with stable neurologic disability.

The pathogenesis of paraneoplastic cerebellar degeneration is unknown. The presence of high-titer antibody suggests an autoimmune etiology but there is no direct evidence for either a humoral or cell-mediated immune reaction. Attempts to use paraneoplastic antibodies to create an animal model have been unsuccessful to date. The anti-Yo antibody interacts with the *cdr2* antigen expressed in the cytoplasm of Purkinje cells. This onconeural antigen is also expressed by many breast and ovarian cancers including tumors in neurologically normal patients *(33)*. There is evidence that patients with paraneoplastic cerebellar degeneration have expanded populations of *cdr2* specific cytotoxic T lymphocytes in their blood and CSF, leading to the hypothesis that these lymphocytes may play an important role in the etiology of paraneoplastic cerebellar degeneration as well as mediating anti-tumor immunity *(34)*. Ongoing clinical investigations will try to diminish this T-cell population in patients with active paraneoplastic cerebellar degeneration in an effort to decrease Purkinje cell destruction and minimize neurologic dysfunction *(35)*.

Other neurologic paraneoplastic disorders have been reported in patients with gynecologic malignancy including limbic encephalitis, retinal degeneration, and opsoclonus associated with the anti-Ri antibody *(36)*. There is also a single case

report of a patient with a mixed mullerian tumor of the uterus developing myasthenia gravis with a positive Tensilon test and elevated acetylcholine receptor antibodies *(37)*. Interestingly, her tumor contained a mesenchymal element with striated muscle differentiation.

**CEREBROVASCULAR DISEASE** Cerebrovascular disease was more common than anticipated in a series of ovarian cancer patients, accounting for 12% of neurologic consults *(17)*. Large retrospective series indicate that 15% of all cancer patients have cerebrovascular lesions at autopsy; only half are ever symptomatic and the pathogenesis of cerebrovascular disease is usually cancer-related. Ovarian cancer patients suffering a cerebrovascular event were older than the average patient and most had risk factors for stroke that were not related to their cancer. However, all of the patients had active advanced-stage ovarian cancer, and in more than one-third the etiology of the cerebrovascular event was related to the tumor or treatment. Volume depletion, electrolyte abnormalities, and alteration in baseline blood pressure are all potential side effects of abdominal surgery and chemotherapy, and may increase the risk of stroke in patients with preexisting cerebrovascular risk factors. Hypercoaguable states and nonbacterial thrombotic endocarditis are complications of disseminated cancer, and patients with the mucinous form of ovarian cancer are particularly prone to develop a coagulopathy. Hemorrhagic stroke or cerebral sinus thrombosis may occur following chemotherapy.

Choriocarcinoma may result in formation of a neoplastic aneurysm via tumor embolization to the brain presenting with subarachnoid or intracerebral hemorrhage. Neoplastic aneurysm should be considered in the differential diagnosis of subarachnoid hemorrhage in women of childbearing age *(38)*. Neonates with intracerebral hemorrhage secondary to metastatic choriocarcinoma originating in the placenta have also been reported. The treatment should include combined chemotherapy and radiation in conjunction with definitive treatment of the aneurysm. The role of neurosurgery must be decided on a case by case basis *(39,40)*. Some patients may benefit from neurosurgical decompression of a large hematoma with improvement in neurologic function as well as their ability to tolerate chemotherapy or cranial radiotherapy. The benefit of resecting or clipping an unruptured neoplastic aneurysm is unclear although some authors report improved survival *(41)*.

## NEUROLOGIC COMPLICATIONS OF TREATMENT

### SURGICAL COMPLICATIONS

**Peripheral Nerve Injury** Patients undergoing hysterectomy or radical pelvic surgery for tumor debulking are at risk for peripheral nerve injury *(42,43)*. There are no good prospective studies that assess the risk of neuropathy, but the available reports in the literature suggest that the risk is quite low. Femoral neuropathy is the most common injury reported, but damage to any of the individual nerves or lumbosacral plexus may occur. The most likely etiology is compression either as a result of self-retaining retractors or the positioning of the patient in stirrups. Excessive flexion or external rotation of the hip may result in stretch injury to the femoral nerve. Surgical ligation or severe vascular injury is rare. Co-morbidities such as diabetes mellitus or uremia play an important role in patient susceptibility and prognosis. Most patients have a gradual recovery of neurologic function over weeks to months. Delayed neuropathies, particularly of the ilioinguinal or iliohypogastric nerve, can also be the result of surgery if the nerve becomes entrapped secondary to postoperative scar tissue or adhesions.

**Other** An unusual case of a vaginal CSF leak was seen in a 42-yr-old woman with endometrial cancer following pelvic exenteration. In the postoperative period the patient complained of clear colorless fluid leaking from her vagina after assuming an upright posture. She subsequently developed a postural headache consistent with intracranial hypotension. A nuclear medicine study confirmed leakage of CSF into her pelvis and onto a sanitary napkin. A myelogram demonstrated a fistula of her S3–4 nerve root. The patient was managed conservatively with bed rest and placement of a lumbar drain and had complete resolution of her symptoms at the time of discharge. This complication has not previously been reported following gynecologic surgery but is a known complication of thoracic procedures *(44)*.

### RADIOTHERAPY COMPLICATIONS

**Plexopathy** Radiation-induced lumbosacral plexopathy is a risk for patients treated with local radiotherapy to the pelvic organs *(45)*. It is distinguished from metastatic plexopathy by the absence of tumor on imaging studies, the presence of bilateral signs and symptoms, predominant motor dysfunction, and the long survival of afflicted patients. Radiation induced plexopathy may develop from months to years after treatment with cases reported up to 14 yr. Patients typically develop a flaccid painless weakness of the legs without bowel or bladder dysfunction; sensory symptoms are present in roughly half of patients. MRI or CT scanning should be used to exclude recurrent tumor. Myokymic discharges seen on electromyogram differentiate radiation induced plexopathy from a compressive etiology. No effective treatment exists, but patients may benefit from physical therapy.

### CHEMOTHERAPY COMPLICATIONS

**Peripheral Neuropathy** Cis-platinum and paclitaxel alone or in combination are commonly used in the treatment of gynecologic malignancy and account for the majority of peripheral neuropathies seen in these patients. Cis-platinum typically produces a large fiber neuropathy with loss of vibratory and position sense, while paclitaxel affects all sensory fibers and may also cause a proximal motor neuropathy. Either concomitant or sequential administration of cis-platinum and paclitaxel enhances neurotoxicity and can result in debilitating peripheral neuropathy *(46,47)*.

The only available intervention for chemotherapy-induced peripheral neuropathy is to discontinue the chemotherapy. This may be difficult with cisplatin, which may cause a progressive neuropathy after discontinuation of the agent; maximal nerve damage may have occurred without the patient or physician realizing it during the course of treatment. However, if debilitating neuropathy develops during therapy, stopping or reducing the dose of the offending agent is often necessary. This is a difficult decision if the drug is having a beneficial anti-cancer effect. The neurologist must eliminate other potential causes of peripheral neuropathy so that effective chemotherapy is not

stopped unnecessarily. Several potential neuroprotective and therapeutic agents (Org 2766, nerve growth factors, and amifostine) are in different stages of preclinical and clinical evaluation *(48–50)*.

**Ifosfamide Encephalopathy** Ifosfamide is an alkylating agent used in the treatment of both cervical and ovarian carcinoma. Up to 30% of patients treated with ifosfamide will develop an encephalopathy. The risk of encephalopathy is increased by oral administration or rapid intravenous infusion; therefore, ifosfamide is administered over a 5 d interval. In addition, patients with renal dysfunction, hypocalcemia, or those receiving sedatives are at increased risk of encephalopathy. The clinical picture ranges from mild somnolence to an agitated delirium to deep coma; cerebellar dysfunction, hallucinations, and seizures are common. The encephalopathy is usually reversible within 3–4 d, but prolonged symptoms and death have been reported. Methylene blue has been reported as an effective treatment in shortening the duration of symptoms and may be used prophylactically in patients who need to be retreated with ifosfamide after developing an encephalopathy *(51)*.

**Other** Intraarterial chemoembolization has been used in the treatment of predominantly unilateral cervical cancer in an attempt to minimize the sequelae of systemic chemotherapy administration. In one study utilizing a combination of cisplatin and collagen injected into the internal iliac artery, three patients developed significant neurologic toxicity *(52)*. All three patients had evidence of an acute femoral neuropathy thought to be ischemic in origin; in two of the three the sciatic nerve was also affected. In each patient the onset of symptoms began abruptly within 12 h of the chemoembolization procedure. Neurologic recovery occurred over a period of several months.

## CONCLUSION

Neurologic complications of female reproductive tract tumors are more common and more diverse than usually recognized. In particular, patients with pelvic tumors are at high risk of local neurologic complications, including compression of the lumbosacral plexus or peripheral nerves, metastasis to the spinal column, and neurologic sequelae of obstructive hydronephrosis. As systemic treatment of gynecologic malignancy improves, it is likely that neurologists will encounter increasing numbers of patients with metastasis to the central nervous system. Studies of neurologic paraneoplastic syndromes may provide important clues to tumor immunology and its therapeutic potential.

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# 28 Neurologic Complications of Gastrointestinal Malignancies

DEBORAH T. BLUMENTHAL, MD AND RICHARD H. WHEELER, MD

## INTRODUCTION

Gastrointestinal malignancies as a group are the third most common systemic cancer and make up almost 20% of all new cancer diagnoses. The majority of these cases are colorectal adenocarcinomas, with much smaller numbers of other digestive system malignancies contributing to the total. This chapter will review the cancers of the digestive tract, their therapy, and neurologic complications related to the disease or treatment thereof.

## COLON AND RECTAL

**EPIDEMIOLOGY/PATH** In 2001 there were an estimated 150,000 new cases of colon and rectal cancer diagnosed in the United States. Colorectal cancers are the third most common causes of new cancer in both sexes and have the third-highest mortality rate (following lung and prostate in males and lung and breast in females) with 56,000 annual deaths (10% of all cancer fatalities). Mortality rates have slightly declined over the past 20 yr. Incidence rates declined by 1.6% between 1985 and 1997, possibly as a result of increased screening and polypectomy. One and five-yr survival rates for individuals developing colorectal cancer are 82 and 61%, respectively. The 5-yr survival rate drops to 8% when distal metastases are present at diagnosis *(1,2)*.

Adenocarcinoma is the most common histological type. Poorly differentiated and mucin-producing tumors are generally most aggressive.

Carcinoid tumors are most frequently found in the appendix and rectum. Those of rectal origin rarely metastasize. Anal cancers are typically epidermoid, with inguinal nodes the most frequent site of regional metastasis.

**FAMILIAL CONDITIONS/RISKS** The risk for colorectal cancer is highest in individuals with a diet high in red meats, high fat, and low fiber intake. Increased risk has also been associated with daily alcohol intake and obesity.

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Familial polyposis (FAP, familial adenomatous polyposis) is a success story for colonoscopic screening and prevention. The condition consists of multiple colonic polyps, with a high propensity for the polyps to develop into adenocarcinoma. Inheritance is autosomal dominant, but many cases can be detected at early stages, improving outcome. Those who have the gene will eventually require large bowel resection, which is now possible without sacrificing sphincter function (modified Parks procedure).

Turcot's syndrome is a rare heritable disease manifested by multiple polyps of the colon which frequently undergo malignant transformation to carcinoma, and associated central nervous system (CNS) neoplasms, including glioblastoma multiforme, astrocytoma, medulloblastoma, and ependymoma. Inheritance is typically recessive, but dominant and sporadic cases have also been cited *(3)*.

Inflammatory bowel disease (Crohn's and ulcerative colitis) are associated with an increased risk of colon cancer. Ten years of active ulcerative colitis carries an increased risk of colon cancer of about 1% annually. These figures may influence an individual's decision for preventive surgery.

Recent studies have shown a role for COX-2 in the pathway of colon carcinogenesis, possibly related to APC tumor suppressor mutation. Inhibition of COX-2 may block development of malignancies from premalignant states and can impact colon cancer prognosis. Nonsteroidal anti-inflammatory drugs (NSAIDS) may be useful in the prophylaxis of colon cancer and polyps by reducing the inflammatory stimuli, which can initiate the cascade of events leading to malignancy *(4)*.

**Screening** For the general population, digital rectal examination and occult blood test should be performed annually beginning at age 50, with flexible sigmoidoscopy every 3–5 yr. (Colonoscopy is recommended for those with first-degree relatives with colon cancer or adenomatous polyps.) Screening in these higher risk individuals should begin at age 40 or 10 yr prior to the age the relative developed cancer, whichever is earlier.

**Treatment** Surgery is the primary therapy for colon and rectal adenocarcinoma. Stage II and III rectal carcinomas

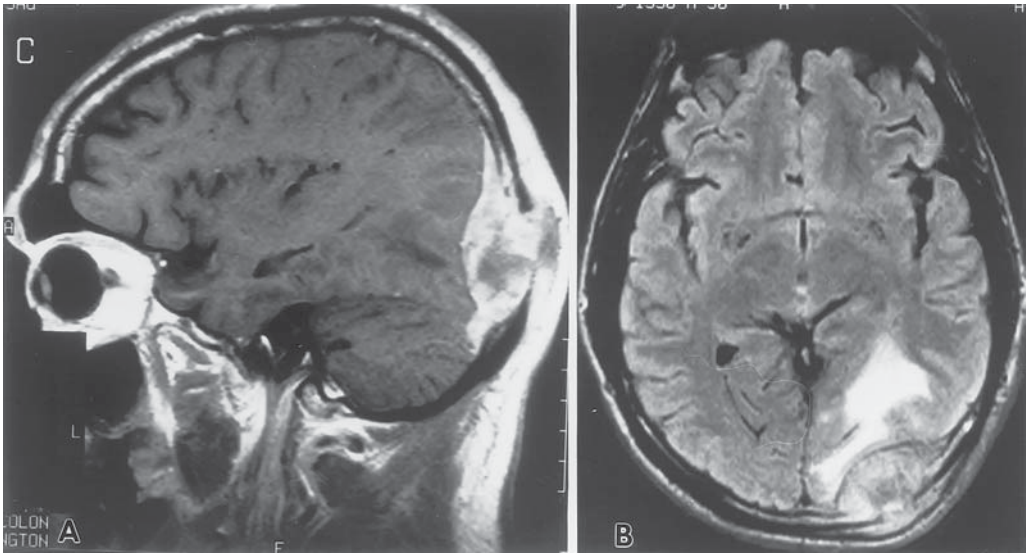


**Fig. 1.** Fifty yr old man with well-differentiated adenocarcinoma of the colon. **(A)** T1 weighted, gadolinium-enhanced, sagittal MRI shows enhancing dural-based metastasis with central hypointensity, corresponding to necrosis found at resection. Tumor invaded the brain microscopically and invaded the outer skull cortex and subcutaneous tissues externally. **(B)** Axial FLAIR MRI shows invasive dural-based metastasis, with hyperintense signal in the underlying parenchyma, related to mass effect and microscopic tumor invasion.

appear to benefit from concurrent radiation and chemotherapy, usually continuous infusion 5-fluorouracil (5-FU), following surgery *(5)*. Current practice for treatment of rectal cancer may instead combine radiation with 5-FU given preoperatively to limit the need for a colostomy. Low anterior resection ("anal-sparing surgery") can then be performed.

Standard postoperative therapy for higher stage colon adenocarcinoma includes adjuvant chemotherapy. A study from the North Central Cancer Treatment Group first demonstrated that stage III colon cancer patients had improved survival when treated postoperatively with the combination of 5-FU and levamisole, compared (historically) to surgery alone *(6).* Subsequent studies have shown that 6 mo postoperative treatment with 5-FU plus leucovorin gives the same improvement in survival as 1 yr of 5-FU with either levamisole or leucovorin, but is superior to 6 mo of 5-FU and levamisole *(7)*. Two recent studies in patients with metastatic colorectal disease have shown improved objective response and modest increase in median survival with the three drug combination of CPT-11 (irinotecan), 5-FU, and leucovorin compared to 5-FU and leucovorin alone *(8,9)*. This combination is currently under evaluation as postoperative therapy. The NSABP (National Surgical Adjuvant Breast and Bowel Project) has completed a number of studies in stage II or III colon cancers. These studies suggest that standard chemotherapy regimens benefit and should be considered standard care for both stages of disease. A current postoperative NSABP trial is comparing 5-FU/ LV plus oxaliplatin to 5-FU/ LV alone *(10)*.

Eighty to ninety percent of recurrences of colon and rectal adenocarcinomas occur within 2–3 yr. Liver and lung are the most common sites of spread, and less so, bone and brain. Even isolated liver or lung metastases can be cured in over 20% of patients if all the metastatic disease can be resected surgically. Once metastatic disease is widespread, the role of current treatment modalities is primarily palliative.

Patients with metastatic colorectal cancer have traditionally been treated with 5-FU by continuous infusion or with leucovorin. As noted earlier, the drug combination of CPT-11, 5-FU and leucovorin is more effective, particularly in high performance status patients, and represents the new standard for treatment. Oxaliplatin (Eloxatin) is a new platinum compound with a possible role in first- and second-line therapy for advanced and metastatic colorectal cancer. It inhibits DNA synthesis by causing inter- and intrastrand DNA crosslinks. It does not appear to have cross-resistance with other platinum chemotherapies. It is not associated with nephrotoxicity or ototoxicity as seen with other platinum drugs. However, it can cause a cold-sensitive, hyperpathic sensory neuropathy. This neuropathy is a dose-limiting toxicity associated with cumulative oxaliplatin administration and appears to be largely reversible once therapy is stopped. (The mechanism may be an increase in the refractory period of peripheral nerves via voltage-gated Na channels). An acute laryngeal reaction can be seen, also cold-triggered and probably more prevalent in the winter in colder regions. Mild-moderate nausea and vomiting and diarrhea are seen, as well as typically mild myelosuppression *(11–14)*.

Colorectal cancer that is refractory to 5-FU and irinotecan may show response to chemotherapy with monoclonal antibody to epidermal growth factor receptor (EGFR). Activation of these receptors may be critical for the growth of some epithelial cancers. A study of 121 patients with refractory cancer positive for EGFR treated with cetuximab plus CPT-11 showed partial response in 21 patients (17%), and stable disease in 37 (31%) *(15)*.

**BRAIN METASTASES (FIG. 1)** From a group of 210 patients with brain metastases at Memorial Sloan-Kettering Cancer Center, only 14 had primary tumors of the gastrointestinal system (8 colon; 4 esophagus; and 1 each of gastric and pancreatic origin) *(16)*.

Cerebral metastases arise in 0.3–6% of colon cancer patients and comprise about 8% of all brain metastases *(17)*. They often present concurrent with metastases to the lung or liver.

A study of patients from Memorial Sloan-Kettering Cancer Center (1977–1980) revealed 40 colon cancer patients with brain metastases, (an incidence of 4% of all colon cancer patients). The majority of patients had known colon cancer at the time of their brain metastases (median 24.5 mo since diagnosis). Thirty-seven of the 40 had concurrent advanced systemic spread of cancer at time of brain metastasis. The prognosis for these patients was poor. Median survival after whole brain radiation was only 9 wk (32 patients), compared to 37 wk in 7 patients who underwent surgical resection *(1)*.

Another study of 20 colon cancer patients with brain metastases similarly suggested that selected patients had improved survival with combined surgery and radiation therapy. Only 5 of 14 (36%) treated with radiation alone had symptomatic/palliative improvement. Five patients (25%) in this group had brain as the first site of metastasis. Fifty percent had solitary brain metastases. Overall median survival in this group was only 51 d; 1-yr survival rate was 6%. Metastatic disease outside of the CNS seemed to be the most important prognostic factor *(19)*.

The best reported prognosis for colorectal metastases to brain comes from a study of 73 patients resected at Memorial Sloan–Kettering Cancer Center. Median survival from craniotomy was 8.3 mo, with 1- and 2-yr survival rates of 31.5 and 6.8%, respectively. Surgical resection appeared to increase survival. Infratentorial location of metastasis was associated with a poorer survival compared with supratentorial tumor (5.1 vs 9.1 mo) *(20)*.

**SKELETAL METASTASES** Skeletal metastases from colorectal cancer are fairly uncommon, and when they do occur they are typically a late manifestation of disease. A 25-yr retrospective review from the Saskatchewan Cancer Registry reported 355 patients with skeletal metastases out of 5352 total cases of primary colorectal cancer. Sixty had skeletal metastases only and had a 38% 5-yr survival, while the majority (295) had concurrent brain, lung, or hepatic metastases, and had a 5-yr survival rate of only 16%. Radiation therapy was the most effective treatment modality *(21)*.

**LUMBOSACRAL PLEXOPATHY (LSP) AND EPIDURAL SPINAL CORD COMPRESSION** Colorectal cancer is a common cause of lumbosacral plexopathy. Patients present with severe pain in the back and leg and later develop weakness and sensory loss in the affected areas of distribution. Of 85 patients with LSP from Memorial Sloan-Kettering Cancer Center, 17 had colorectal cancer as their primary tumor, and 2 had gastric cancer. Patients with colorectal cancer presented most commonly with radicular pain radiating down the posterior aspect of the leg from lower plexus involvement. Coccygeal plexus involvement with perineal sensory loss and sphincter weakness was seen in rectal tumors. There were 3 colorectal cancer patients (of 13 patients overall) who achieved reduced tumor size from radiation and/or chemotherapy treatment at a median of 6.5 mo. Overall prognosis of the 85 patients was poor, with mean survival only 5.5 mo from the time of LSP diagnosis *(22)*.

Radiation plexopathy can present months to years after pelvic radiation. It is differentiated from neoplastic plexus involvement by painless weakness, eventual stabilization of deficits, and occasionally by clinical or electromyographic evidence of myokymia *(23)*.

Epidural spinal cord compression is seen in small number of colon and gastric cancers *(24)*. Lumbosacral epidural metastases may present with back or leg pain. A retrospective review from Memorial Sloan-Kettering Cancer Center of 235 patients with metastatic epidural spinal cord involvement revealed only 9 to have a primary GI tumor. This relatively low incidence is thought to be related to the low incidence of vertebral metastases in colon and gastric cancers *(25)*. A study of 34 colorectal cancer patients with spinal cord compression found 55% of these cases in the lumbar area (unlike the majority of other metastatic cancers to the epidural space which occur chiefly in the thoracic spine). Patients were treated with external beam radiation therapy. The patients with rectal cancer survived a median of 7.9 mo, which was significantly longer than those with colon cancer (2.7 mo). As seen in other cases of epidural spinal compression, patients who were ambulatory at the start of therapy largely remained so, while only a small number (2 of 9) who had lost ambulation prior to treatment were able to regain the ability to walk *(26)*.

**LEPTOMENINGEAL METASTASES** Autopsies of 311 patients with gastrointestinal cancers showed 3 to have leptomeningeal cancer (1%) *(27)*. Survival with carcinomatosis from colorectal cancer is typically poor.

**PARANEOPLASTIC SYNDROMES** Paraneoplastic sensorimotor neuropathy has been rarely reported in colon cancer *(28)*.

One patient with metastatic colon adenocarcinoma developed mononeuritis multiplex, with biopsy-proven vasculitis. Although the patient had no active tumor at the time of his neurologic presentation, the cancer reappeared with systemic metastases following diagnosis and treatment of the vascultits *(29)*.

The association of dermatomyositis with colon cancer may be as high as 6–35% of dermatomyositis cases. Resection of the cancer may result in regression of the dermatomyositis, with reappearance heralding recurrence of the malignancy *(30)*.

**PARANEOPLASTIC CEREBELLAR DEGENERATION (PCD)** PCD is seen primarily in lung, ovarian, lymphoma, and breast cancers, but it has been reported less commonly in GI cancers. In a study of neoplasms associated with PCD in 199 patients, 6 were colon cancer, 2 gastric, 1 rectal (and another rectal and bronchus), and 1 uterine and colon concurrently *(27)*.

Cerebellar syndrome with myoclonus (no opsoclonus) has been described as the presenting subacute symptom leading to diagnosis of a colon adenocarcinoma in a 72-yr-old man. Paraneoplastic antibodies were not found. High-dose steroids resulted in improvement of the neurologic symptoms, and complete recovery occurred following surgical resection of the cancer *(31)*.

Cerebellar degeneration with limbic encephalitis was reported in a 55 yr old woman, in whom a microscopic adenocarcinoma in a polyp was found. She recovered from the encephalitis, but ataxia persisted following polypectomy. Immunoblots showed

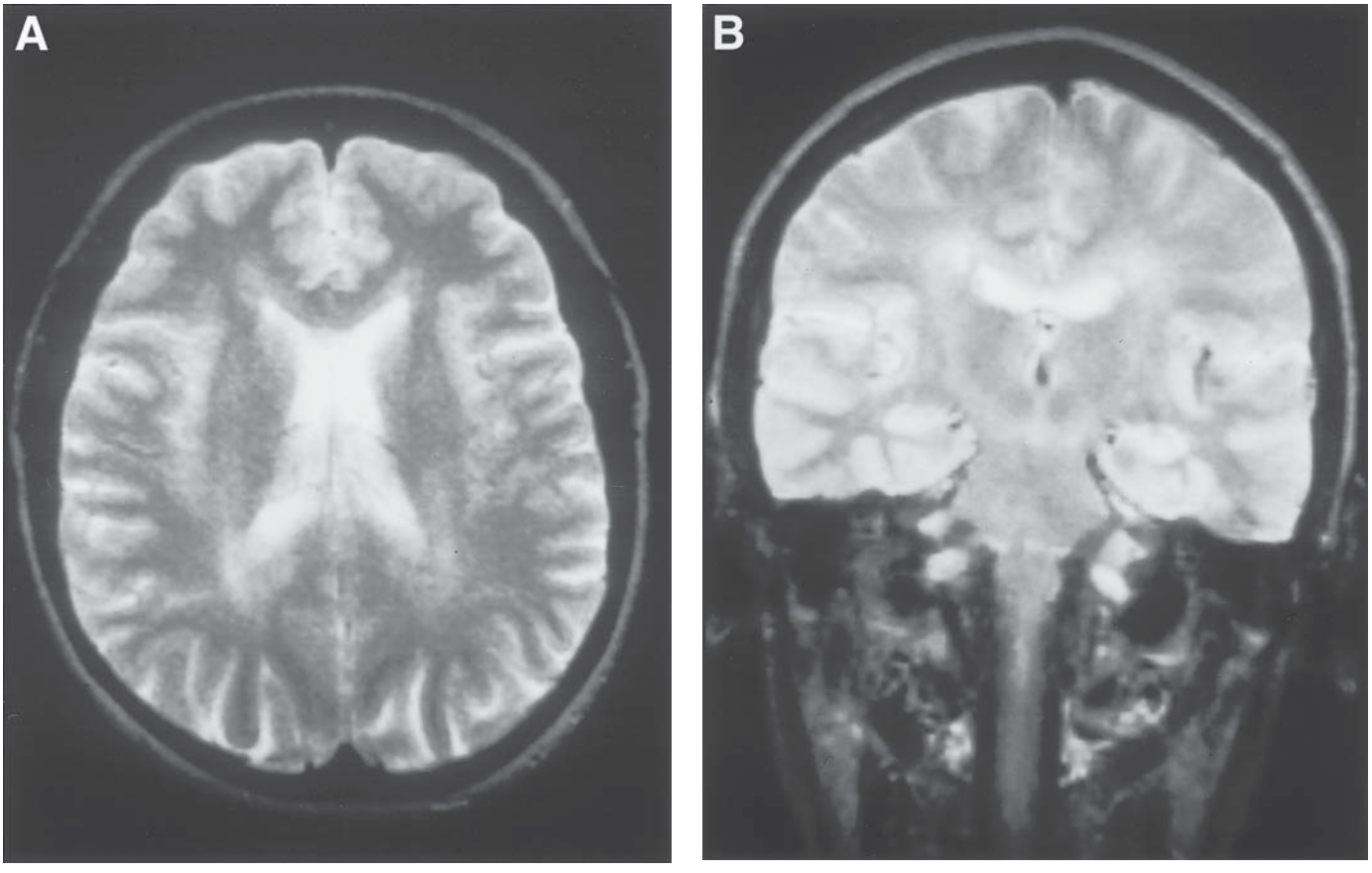


**Fig. 2.** Leukoencephalopathy in a woman with colon adenocarcinoma treated with 5-FU and leucovorin. She presented with ataxia and confusion. She was found later to have profound DPD deficiency with no detectable enzyme activity. **(A)** T2-weighted axial MRI shows hyperintensity in periventricular white matter. **(B)** Coronal MRI shows periventricular white matter changes, as well as involvement of the deeper white matter and corticospinal tracts, sparing U-fibers. (Figures courtesy of Robert Diasio MD, Chairman, Department of Pharmacology & Toxicology, University of Alabama at Birmingham.)

a 41 kDa protein band, with high antineuronal antibody titers resembling anti-Hu by serum immunohistochemistry *(32)*.

**NEUROLOGIC COMPLICATIONS OF TREATMENT (CHEMOTHERAPY)** 5-fluorouracil (5-FU) and leucovorin with or without irinotecan are the accepted standard chemotherapy regimen for Stage III or IV colon carcinoma. 5-FU, a pyrimidine analogue, is also used in the treatment of head and neck, breast, and ovarian cancers. 5-FU has been reported to cause a pan-cerebellar dysfunction, encephalopathy, and peripheral neuropathy *(33)*.

There have been several reports of leukoencephalopathy (white matter damage) with focal neurologic symptoms resulting from one or both of these treatments, primarily in the colon cancer population. Patients may present with cognitive changes, ataxia, and dysarthria *(34)*. Clinical features may be slowly progressive *(35)*. MRI in these cases may reveal multifocal, enhancing, diffuse periventricular white matter lesions. One case report documented resolution of the lesions when levamisole was stopped (despite continued administration of 5-FU). At autopsy, the abnormal areas in this case showed demyelination, reactive gliosis and macrophages positive for Class II antigens, interleukin-6 (IL-6) and IL-1 alpha. Perivascular T cells were noted as well, without evidence of metastatic tumor *(36)*. Thus, these lesions appear to have immunologic activity, similar to demyelinating lesions seen in multiple sclerosis (MS). This may be related to the immunomodulatory effects of levamisole. The differential considerations of multifocal inflammatory lesions in patients with (colorectal) cancer being treated with chemotherapy should include metastatic disease, multifocal glioma, or opportunistic conditions such as primary CNS lymphoma, progressive multifocal leukoencephalopathy (PML), and toxoplasmosis. Ancillary imaging tests may be useful, and in the proper context may be substituted for biopsy. Thallium SPECT (single photon-emission computed tomography) used in one such case revealed the lesions in question to be "cold" (inconsistent with metastases) *(37)*. PET or MR spectroscopy may also prove to be useful modalities for noninvasive differentiation from metastatic disease. Clinical and radiographic improvement typically occurs weeks to months after stopping the chemotherapy, with or without a limited course of corticosteroids.

5-FU neurologic toxicity to white matter in some individuals may be related to deficient dihydropyrimidine dehydrogenase (DPD) activity *(38)* (*see* Fig. 2). DPD is the rate-limiting enzyme in the breakdown of 5-FU. Severe neurologic toxicity, along with particularly severe mucositis, dermatitis, and prolonged myelosuppression, was reported in a colon cancer patient who subsequently was found to have extremely low

levels of DPD activity *(39)*. In vitro studies of 5-FU derivatives (tegafur and carmofur) show direct myelin injury from splitting and destruction resulting in vacuolation *(40)*.

## PANCREAS

**EPIDEMIOLOGY** Pancreatic cancer is the second most common abdominal malignancy. It is the fourth leading cause of cancer mortality in the United States. In 2001 there were an estimated 29,200 new cases and 28,900 deaths. Pancreatic cancer is more common in the industrialized world, (in populations with diets high in fat). Cigarette smoking may carry an elevated relative risk of 2.6 *(41)*.

Studies of geographic distribution suggest a role for high fat diet, possibly via cholecystokinin release. Lovastatin, which lowers cholesterol, inhibits pancreatic cancer growth in vitro. There is an inverse relationship with high fiber, fruits, and fresh vegetables. Risk increases with age. Mean age at diagnosis is 63, with a slight male predominance.

Although less than 15% of the pancreas is made of ductal tissue, more than 90% of pancreatic cancers arise from ductal epithelium, most from the pancreas head. Mucin-producing adenocarcinomas are most common. Mutation in Ki-*ras* codon 12 may be seen in 89% of pancreas cancers *(42)*.

Diagnosis is often late in the course of disease, accompanied by weight loss, abdominal pain, and jaundice/pruritis from biliary obstruction. Thrombophlebitis may be seen as an early sign, and depression can predate diagnosis by more than 6 mo. CT scan is the diagnostic test of choice.

**TREATMENT** Surgery provides the best chance of cure, but only 20% of patients are eligible for surgery at the time of diagnosis. Five-year survival rate for resectable patients is 10% with a median survival of 12–18 mo. 40% present with locally advanced disease, and another 40% with distant metatases. Unresectable patients survive 6 mo *(43)*.

Patients who undergo a Whipple resection (pancreaticoduodenectomy) may benefit from adjuvant therapy. The Gastrointestinal Tumor Study Group showed extended median survival to 20 mo for such patients treated with 5-FU and two courses of radiation at 20 Gy each; median survival of the control group was 11 mo *(44)*.

The combination of 5-FU and irradiation has also been shown to be better than irradiation alone in patients with unresectable pancreatic cancer *(45)*. There may be a role for neoadjuvant chemoradiation, prior to pancreaticoduodenectomy. In a study from MD Anderson Cancer center, 132 patients received preoperative radiation with concurrent infusion of 5-FU, paclitaxel, or gemcitabine. Overall median survival was 21 mo, suggesting a possible benefit *(46)*.

For palliation of jaundice and pruritis, surgical biliary bypass or endoscopic stenting can be effective. The antimetabolite gemcitabine has been shown to improve survival and quality of life compared to 5-FU and is the standard therapy for patients with metastatic pancreatic cancer. The therapeutic gain, however, is small. A study of gemcitabine in combination with inhibitors of farnesyl transferase is ongoing. Farnesylation is necessary for ras gene (which is found mutated in pancreatic and other cancers) activation, as well as activation of other components in signaling pathways. A study of 63 patients with metastatic or locally advanced pancreatic cancer showed the possible activity of SCH 66336, a farnesyl transferase inhibitor, with less toxicity, but shorter median survival (only 3.3 vs 4.4 mo) compared to gemcitabine *(47)*. Combinations of farnesyl transferase inhibitors with other agents are underway. An early trial of the monoclonal chimeric antibody C225 to EGFR in combination with gemcitabine suggests a potential role for this strategy in the treatment of advanced pancreatic cancer *(49)*.

**METASTATIC DISEASE** Pancreatic cancer most frequently metastasizes to regional lymph nodes, liver, lung, and peritoneal surfaces. Bone metastases from pancreatic carcinoma are less common, although involvement of the bone marrow with consequent hematologic compromise has been reported *(49,50)*.

### PARANEOPLASTIC NEUROLOGIC SYMPTOMS

**Insulinomas** Insulinomas make up 75% of islet cell tumors and are typically benign. As they secrete excess insulin and can cause marked hypoglycemia, patients may present with neurologic symptoms including change in level of consciousness, coma, seizures, perturbation of vision, and confusion. Any of these symptoms in the presence of "Whipple's triad" (symptomatic hypoglycemia during fasting or exercise, blood sugar < 50, or reversal of neurologic symptoms after administration of IV glucose) should raise suspicion of an insulinoma. Diagnostic tests include radioimmunoassay measurement of proinsulin and C-peptide. Imaging is difficult, as most of these tumors are small. Angiography can be helpful for preoperative localization. Intraoperative ultrasound can show hyperechogenic masses. Patients are treated successfully with surgical resection.

**Depression** Many cancer patients suffer from depression and anxiety related to their circumstances, pain, or treatment, but depression is seen in a significantly higher percentage of patients with pancreatic cancer than other malignancies. These symptoms can present even months before the cancer is diagnosed in as many as half of those who will later be found to have the disease *(51)*. A patient has been reported who presented with panic attacks preceding her diagnosis with pancreatic cancer; her symptoms resolved following resection of the tumor *(52)*.

Compared with a group of 111 patients with advanced gastric cancer, 107 patients with advanced pancreatic cancer had significantly higher rates of depression, anxiety, fatigue, and mood disturbance *(53)*.

**Thrombosis/Cerebrovascular Accident** Stroke due to hypercoagulability is a potential risk in pancreatic cancer. Migratory thromboplebitis, mesenteric vein thrombosis, and pulmonary emboli are well-described in patients with pancreatic cancer. One young patient presented with transient stroke and paraneoplastic thrombocytosis as the initial manifestation of her pancreatic cystadenocarcinoma *(54)*.

**Other Syndromes** Delayed gastric emptying without evidence of obstruction has been seen in patients with pancreatic cancer. One such patient's serum showed immunofluorescent staining of Purkinje cells, possibly representing a paraneoplastic syndrome *(55)*.

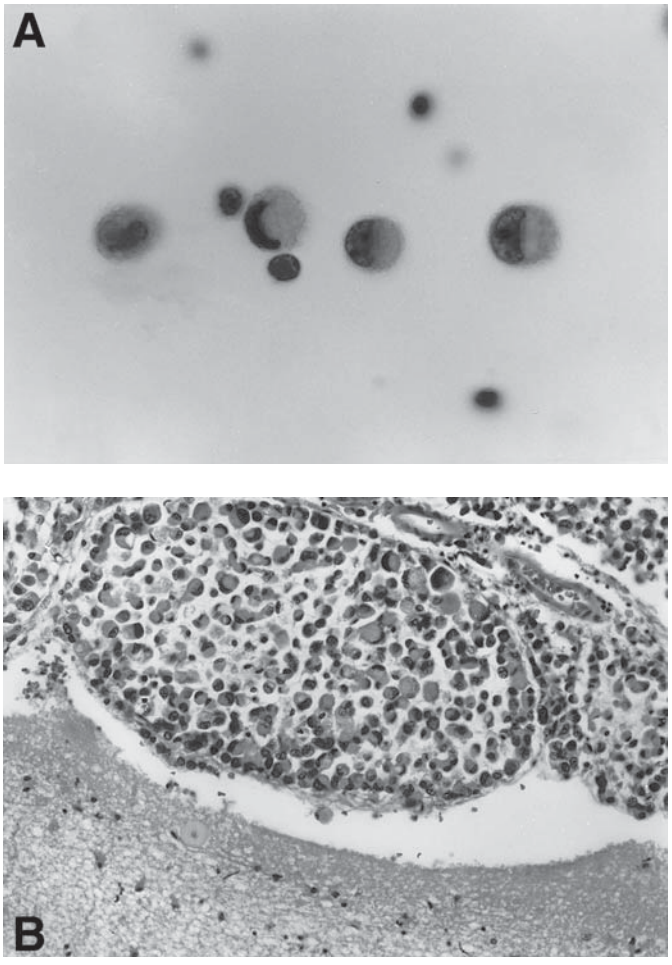


**Fig. 3.** Fifty-two-yr-old woman with gall-bladder adenocarcinoma, presenting with ataxia from leptomeningeal carcinomatosis. **(A)** Cerebrospinal fluid sample showing signet-ring cells with pleomorphic nuclei. **(B)** Autopsy tissue specimen of the brain showing sheets of signet-ring adenocarcinoma involving the leptomeninges. (Figures courtesy of Evelyn Gopez MD, Department of Pathology, University of Utah.)

### DIRECT NEUROLOGIC SYMPTOMS

**Brain Metastases** There are very few reports of pancreatic cancer metastases to the brain. Outcome is very poor in these cases *(56)*.

## GALLBLADDER CARCINOMA

**EPIDEMIOLOGY** Gallbladder carcinoma makes up 0.5% of all malignancies; it is the fourth most common GI cancer in the United States (6900 cases of gallbladder and other biliary cancers in 2001). There is a slight female preponderance, with peak incidence in the late 60s and early 70s. Seventy to eighty percent of cases are associated with chronic gallstone disease. Adenocarcinomas make up 90% of the histologies. Spread is typically by direct invasion into the liver, duodenum, colon, and abdominal wall. Three and a half percent of patients undergoing cholecystectomy are found to have a carcinoma *in situ* of the gall bladder. Distal spread typically occurs only after locally advanced disease.

**Prognosis** Early (stage I and II) lesions have a good prognosis and do not require further treatment after surgery. Survival with advanced disease is weeks to months. Adjuvant therapy has not been shown to have a significant impact on survival, and there is no established, effective systemic treatment for metastatic disease.

**Leptomeningeal Carcinomatosis** There have been five reports of neurologic symptoms (headaches, psychosis, dysarthria, ataxia), leading to diagnosis of leptomeningeal carcinomatosis from an occult cancer postmortem, or rarely a premortem primary gallbladder carcinoma. Signet-ring carcinomas may have an increased propensity to spread to the leptomeninges *(57–59)* (*see* Fig. 3).

**PARANEOPLASTIC SYNDROMES** At least one case of paraneoplastic opsoclonus associated with gallbladder cancer has been reported *(60)*.

## CHOLANGIOCARCINOMA (BILE DUCT CARCINOMA)

**EPIDEMIOLOGY** Cholangiocarcinoma is relatively rare, with 4500 cases occurring annually in the United States. In contrast, cholangiocarcinoma is the most common cause of malignant cholestasis in southeast Asia. Mean survival is 6-12 mo. Lesions with location at or near the confluence of the hepatic ducts have a resectability rate of 20%. Unresectable lesions in this location have survival of only 3–5 mo. Radiation therapy using doses above 40 Gy may control tumor growth and can be useful for palliation. Small series have reported partial responses of 20–30% with 5-FU and doxorubicin.

**BRAIN METASTASES** There is a single report of metastatic cholangiocarcinoma to the cerebellum (with hydrocephalus as the presenting symptom) *(61)*.

**LEPTOMENINGEAL CARCINOMATOSIS** There is one case report in the literature of a patient with cholangiocarcinoma who developed multiple progressive neurologic symptoms postoperatively and was found to have leptomeningeal carcinomatosis *(62)*.

## LIVER

**EPIDEMIOLOGY** Incidence of primary hepatic tumors (including benign tumors) in the United States is 3 in 100,000, while as high as 30–100/100,000 in Africa and Asia. Hepatic tumors are the most common solid organ tumor worldwide. 16,200 cancerous tumors were anticipated in the United States for 2001, with 14,100 deaths.

Benign hepatic tumors include hemangiomas, adenomas, and focal nodular hyperplasias. Hepatocellular carcinoma is the most common malignant hepatic tumor, and is four to eightfold more common in males. The fibrolamellar variant of hepatocellular carcinoma occurs in younger individuals, and is seen with equal frequency in males and females. It is much less likely to be associated with cirrhosis or hepatitis B, is generally alpha-fetoprotein (AFP) negative, is well-circumscribed, more amenable to resection, and is associated with a better prognosis.

Risk factors for hepatocellular carcinoma include hepatitis B infection, alcohol-induced cirrhosis, certain drugs (immunosuppressants), and pesticides. Cirrhosis is often a pre-existing feature. Hemochromatosis of the liver carries a 13% risk of

malignancy in cirrhotic livers; and alpha$_1$-antitrypsin deficiency carries a risk as high as 40%. Hepatocellular cancers are usually diagnosed only when the primary tumor has reached large size. Presentation is often with upper (right) abdominal pain, and jaundice, gastrointestinal bleeding, or hepatic decompensation are not uncommon. Elevated AFP serum levels are seen in 75–90% of these carcinomas, and these tend to be more aggressive than AFP-negative tumors (median survival of 5 mo vs 10.5 mo). Surgical resection (and transplant) are the only chances for cure, but are only indicated in fewer than 15% of cases. Partial hepatectomy produces a 5-yr survival of more than 30%, but location, invasion of vascular systems, and function of the remaining liver (if cirrhotic) may preclude surgery. Liver transplantation may offer benefit above that of resection, but is limited by morbidity, cost, and availability of livers for transplant.

Only limited options are available to unresectable patients with hepatocellular cancer, with little data that survival is improved by any intervention. Local or systemic therapies and radiation can be offered for palliation. Hepatocellular carcinomas are notoriously poorly responsive to systemic chemotherapy, with no evidence that combination drug therapy is more effective than single agents. The use of systemic chemotherapy as adjuvant, neoadjuvant, or in unresectable patients is most appropriate in the setting of a clinical trial.

Hepatic arterial infusion has been reported to produce responses of over 50% in selected series *(63,64)*. Chemoembolization may provide comparable or more frequent responses, and generally provides temporary palliation *(65,66)*. However, a clear improvement in survival has not been documented *(67,68)*. Whole liver radiation has minimal efficacy, although hyperfractionated external beam radiotherapy in combination with hepatic arterial FUDR or cisplatin has shown benefit in limited trials *(69)*.

**METASTATIC DISEASE** Although the majority of patients with hepatocellular cancer present and die with tumor confined to the liver, distant metastases are not infrequent. The clinical impact of distant disease is most frequently seen in patients undergoing partial hepatic resection or transplantation. The most frequent sites of metastases are lung, lymph nodes, adrenal gland, and bone.

**Skeletal Metastases** A study of 323 cases of hepatocellular carcinoma from Japan showed bone metastases in only 12 (3.7%), 58% of which were in the vertebral bone. With radiation or surgical treatment 1-yr survival was 74% *(70)*. Estimates of the incidence of bone metastases in autopsy series range 4–14%, most commonly to the vertebral column *(71)*.

Hepatocellular carcinoma metastatic to the vertebral column occasionally results in epidural spinal cord compression *(72)*.

**BRAIN METASTASES** Rarely does hepatocellular cancer metastasize to the brain. Of only 10 cases cited in the literature up to 1990, 9 of these presented with intracranial-intratumoral hemorrhage *(73,74)*.

**PARANEOPLASTIC SYNDROMES** There is one case report of presumed paraneoplastic sensorimotor neuropathy as the presenting symptom in a man with hepatic cirrhosis and hepatocellular cancer *(75)*. Hypercalcemia, which can present with weakness and mental status changes, is another paraneoplastic phenomenon seen in hepatocellular carcinoma. Finally, fulminant liver failure in advanced hepatic cancer can present with encephalopathy.

## GASTRIC CANCER

**EPIDEMIOLOGY** The mortality rate for gastric cancer in the United States has declined for more than 50 yr despite a dearth of novel treatment options. Incidence for 2001 in the United States is 21,700, with a mortality rate of 12,800. Nonetheless, gastric cancer is the second most common cancer worldwide. Epidemiology plays an important role in this disease, with mortality rates in Japan, Chile, and Iceland being five times higher than those in the United States. Changes in methods of food preservation, specifically the decreased use of nitrites, which can lead to formation of nitrosamines (shown to produce gastric cancer in experimental animals), may be partly responsible for these changes in US incidence. *Helicobacter pylori* infection is associated with gastric cancer, as are conditions such as atrophic gastritis, also of higher incidence in the aforementioned countries with high rates of gastric cancer. Studies of Japanese immigrants suggest that environmental factors play more of a causative role than genetic ones.

Recent studies provide conflicting reports regarding the possible influence of green tea consumption and protection against developing gastric cancer. A large, prospective study involving over 26,000 residents of northern Japan used a questionnaire format to study green tea consumption in addition to other dietary and alcohol practices. Of 419 patients who ultimately developed gastric cancer, Cox regression analysis did not show any increased relative risk for developing stomach cancer, based on amount of green tea consumption *(76)*. However, a population-based control study performed in China with 133 cases with stomach cancer and 433 controls suggested an inverse relationship between green tea drinking and stomach cancer risk as well as risk of developing chronic gastritis. In this study, there even appeared to be a dose-response related to years of green tea drinking *(77)*.

The majority of gastric cancers are adenocarcinomas that occur in the distal portion of the stomach. Spread may be by direct invasion to other visceral organs, via the peritoneum, regional lymphatics, or hematogenously via the portal circulation.

Diagnosis can be made by upper GI endoscopy or radiography. In early gastric cancer (limited to the mucosa or submucosa) 5-yr survival may be even higher than 90%. Overall 5-yr survival rate for patients with gastric cancer is only 10–15%.

**TREATMENT** Surgery is the only curative treatment and helpful for palliation in patients diagnosed at later stages. A recently completed intergroup randomized study in the United States has demonstrated improved survival with chemotherapy plus irradiation compared to surgical resection alone. Postoperative radiation (45 Gy) and chemotherapy (5-FU and leucovorin) showed improved survival in 603 patients with stomach and gastroesophageal junction adenocarcinoma, 85% of whom had nodal metastases. Three-yr overall survival was 52% for combined treatment and 41% ($p = .03$) for the observation only group *(78)*. Another study of node-positive gastric adenocarcinoma randomized surgery alone to surgery with adjuvant chemotherapy of epidoxorubicin, leucovorin, and 5-FU. Median survival was 18 mo with surgery alone and 31 mo ($p < 0.01$)

with the addition of chemotherapy. Five-yr survival rates were 13% with surgery alone and 30% with adjuvant treatment *(79)*. If surgery is not feasible, radiation is rarely curative. Combination regimens have not shown clear superiority compared to single agent use.

**NEUROLOGIC SEQUELAE** Partial or more commonly total gastrectomy may result in the "dumping syndrome," loss of the physiologic delay of food transport to the small intestine (from loss of functional pylorus).

Anemia can develop early postgastrectomy from decreased iron absorption, and later related to decreased B12 absorption from loss of intrinsic factor. This can be a delayed problem (years after the procedure), with complications involving both the peripheral and central nervous systems, known as subacute combined degeneration of the spinal cord *(80)*. This syndrome consists of loss of myelin sheaths and axons in the posterior and lateral columns of the spinal cord. Patients may exhibit (primarily in the lower extremities) vibratory and position sense loss, sensory ataxia, and eventually (as the peripheral neuropathy manifests) loss of tendon stretch reflexes with extensor plantar response to noxious stimuli *(81)*. If this complication is detected, vitamin $B_{12}$ replacement should be administered immediately (1000 μg of cyanocobalamin IM every day while hospitalized, then weekly for 1 mo, and monthly indefinitely). Improvement is more likely if treatment is initiated within 3 mo of gait disturbance, and recovery may be complete if the deficiency is recognized and treated within a few weeks of symptom onset *(82)*.

**LUMBOSACRAL PLEXOPATHY** See the section on lumbosacral plexopathy in colon cancer.

**LEPTOMENINGEAL METASTASES** Gastric carcinoma can rarely involve the leptomeninges, usually with poor outcome *(83)*.

**PARANEOPLASTIC** Uncommonly, paraneoplastic cerebellar degeneration has been associated with gastric adenocarcinoma. (This syndrome is more commonly associated with ovarian and breast cancers.) A case has been reported with high serum antibody titers found by immunohistochemistry, which decreased after resection of the gastric tumor *(84)*. Opsoclonus-myoclonus syndrome has also been associated with one case of gastric adenocarcinoma. As in other opsoclonus paraneoplastic cases, there is no identified antineuronal antibody, calcium-channel antibody, nor specific immunoreactivity to brainstem or cerebellar tissues *(85)*.

Anti-Ri antibody associated paraneoplastic cerebellar degenration has been reported in a patient presenting with severe cerebellar ataxia without opsoclonus, with a mixed poorly differentiated adenocarcinoma and neuroendocrine carcinoma of the stomach. The serum was reactive with the neuroendocrine portion of the tumor only *(86)*. The case of a man with metastatic gastric cancer (high CEA and AFP titers) with necrotizing arteritis along the sciatic nerve was reported. The patient's serum reacted to the affected endothelial vessels, suggesting an autoimmune mechanism for the arteritis *(87)*.

## CANCER OF THE ESOPHAGUS

**EPIDEMIOLOGY** There are an estimated 13,000 new US cases of esophageal cancer annually, with 12,500 fatalities. A much higher prevalence is found in other areas of the world. Male to female ratio is 3:1. The highest incidence is seen in the seventh and eighth decades. The disease is more common in black than white males. It is the seventh leading cause of cancer deaths in males.

The ethanol and nicotine in alcohol and tobacco are thought to interact synergistically to increase the risk of esophageal cancer. Other recognized predisposing factors include achalasia (7 × greater risk), caustic esophagus injury (1000 × greater risk), and Barrett's esophagus (8.6–50% prevalence). Other risk factors include gastroesophageal reflux.

Dysphagia is the most common presenting complaint, initially occurring with solid foods, then later with liquids.

Esophageal radiography can be used for diagnosis. Esophagoscopy can be used for diagnosis and usually provides histologic confirmation. Improved staging can be provided by the combination of ultrasound with esophagoscopy. A CT scan of the chest and abdomen completes the staging evaluation. Two-thirds of cases are of squamous cell origin. Adenocarcinoma is seen most often with Barrett's esophagus. Histology has no clear impact on treatment selection or patient survival.

Untreated, the median survival is only 4 mo. Surgery has impact on survival and cure for earlier stage cancers as staged by endoscopic ultrasound. Improved surgical mortality rates and increased resectability have enhanced long-term survival rates *(88)*. Five-year survival rates now average 20–25% for curatively resectable disease. Surgery can be helpful for palliation of dysphagia in advanced disease. Although postoperative irradiation is frequently used, its value has not been demonstrated by randomized trial. In more advanced patients, median survival with radiation alone may reach 12 mo, and radiation may be palliative for severe dysphagia. Randomized studies have clearly established the improvement in survival with the combination of irradiation and chemotherapy compared to radiation therapy alone. One study of combined 5-FU, mitomycin C, and radiation compared to radiation alone showed improved 2- and 5-yr survival rates with chemoradiation therapy (27 and 9% vs 12 and 7% with radiation alone). Median survival (14.8 mo) was also better with chemoradiation than with radiation alone (9.2 mo) *(89)*. Another trial demonstrated similar superiority for the use of cisplatin and 5-FU with irradiation compared to radiation therapy alone *(90)*. The proper roles for radiotherapy, surgery, and chemotherapy in node-negative, or early stage disease are unclear.

Response rates with chemotherapy agents range from 10–40%, but there is questionable impact on median survival. Multiple single agents and combinations have been used, with no "standard" therapy recognized. Active agents include cisplatin, 5-FU, bleomycin, paclitaxel, mitomycin, vinorelbine, irinotecan, gemcitabine, and methotrexate *(91)*.

**BRAIN METASTASES** Metastases to the brain in primary esophageal cancer are relatively rare. Review of 334 esophagectomy cases (230 adenocarcinoma and 104 squamous) from 1984–1993, identified 10 patients with adenocarcinomas and 2 squamous carcinomas who developed brain metastases. Preoperative head CT screening was done on 240 patients, with no metastases shown. This cohort showed an incidence of 3.6% of brain metastases, and indicated that head CT screening in

asymptomatic patients was not indicated. Large size of the primary tumor correlated with risk of brain metastases *(92)*.

**PARANEOPLASTIC SYNDROMES** Paraneoplastic vasculitis has been reported in a man with both gastric and esophageal cancers who presented with fever and leg numbness for 3 mo predating diagnosis. Symptoms persisted following gastric carcinoma resection, but disappeared after esophagectomy. The esophageal cancer was a well-differentiated squamous cell carcinoma with positive lymph nodes. Vasculitis was confirmed histologically in the resected organs and serratus anterior muscle *(93)*.

An unusual case of paraneoplastic cerebellar degeneration with anti-Yo neuronal antibodies has been reported in a man with esophageal adenocarcinoma. The antigen was expressed in the primary tumor, but not in a frontal lobe metastasis *(94)*.

**NEUROLOGIC COMPLICATIONS OF TREATMENT (CHEMOTHERAPY)**

These are described in the colon cancer section, as well as in Chapters 15 and 16.

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# 29 Neuro-Oncologic Complications of Sarcomas

LARA J. KUNSCHNER, MD

## INTRODUCTION

Tumors that arise from mesenchymal tissue rarely occur within the central nervous system (CNS). Sarcomas develop from a wide variety of tissues types: fat, smooth or striated muscle, vascular tissue, and peripheral nerve. The sarcomas are an extremely heterogeneous group of rather rare tumors that comprise fewer than 1% of adult malignancies and approx 15% of pediatric malignancies.

Estimates of incidence suggest that perhaps 0.1% of intracranial tumors are sarcomas *(1)*. Some tumors previously designated as sarcomas have been renamed due to advances in histopathologic technique; for example, reticular sarcoma is now recognized as malignant lymphoma, and cerebellar arachnoidal sarcoma is recognized as desmoplastic medulloblastoma. According to current criteria proposed by Scheithauer and the 1993 World Health Organization (WHO) classification system, several tumors comprise the class of malignant mesenchymal, nonmeningothelial tumors of the CNS *(2)*. Table 1 outlines the malignant tumors in this category, the relative incidence with respect to other members of the category, and typical age at presentation. Paulus et al. examined the histopathologic diagnosis of 25,000 intracranial tumors and found 19 sarcomas: 6 malignant fibrous histiocytoma, 3 leiomyosarcoma, 2 rhabdomyosarcomas and angiosarcomas, and 1 each of fibrosarcoma, mesenchymal chondrosarcoma, differentiatied chondrosarcoma, fibromyxoid sarcoma, malignant ectomesenchymoma, and Ewing's sarcoma *(1)*. This list highlights the relative scarcity of any one tumor type within the class.

Neurological effects of sarcoma are more often the result of tumors outside of the CNS. A paraspinal mass may occur due to any tumor in the family, although certain tumors predominate in patients of different ages. In early childhood, neuroblastoma is more common than sarcoma, but causes radicular or spinal symptoms in only 4% of patients. A young child found to have a spinal extradural lesion in the latter half of the first decade is more likely to have a sarcoma than a neuroblastoma *(3)*. The incidence of spinal cord compression in childhood sarcoma is 12–15% *(4,5)*. As long-term survival rates in childhood sarcoma improve, reports of neurological complications have increased *(6)*.

From: *Cancer Neurology in Clinical Practice* (D. Schiff and P. Y. Wen, eds.), © Humana Press Inc., Totowa, NJ.

## CHONDROSARCOMA

Chondrosarcoma is a rare tumor consisting of malignant chondrocytes with variable mesenchymal components such as atypical cartilage and vascular tissue (Fig. 1). Infrequently they occur in the head and neck, where it is felt they arise from cartilaginous remnants in the petro-clival, spheno-occipital, and fronto-parietal synchondroses. When involving the CNS, they usually arise from an extradural origin and have imaging characteristics suggesting a meningioma; rare tumors are intradural. These tumors often arise in locations typical for meningioma, largely from the skull base. The distribution of intracranial chondrosarcoma in the largest series published to date, including 177 cases, listed location as petrous bone 37%, occipital bone/clivus 23%, sphenoid 20%, frontal/ethmoid/parietal 14% and any intradural location 6% *(7)*. When these tumors are midline, the differential diagnosis also includes chordoma, which can be differentiated using immunohistochemical stains for cytokeratin and epithelial membrane antigen which will be positive in chordoma but not chondrosarcoma. Rare orbital cases (17 to date) with intracranial extension have been reported *(8)*.

Several case reports and a small series of 21 cases reveal that the tumor usually is attached to the dura, though very rarely may be found intraparenchymally in the frontoparietal region *(9–11)*. The tumor appears as a contrast enhancing, lobulated mass on standard computed tomography (CT) and magnetic resonance imaging (MRI) imaging. Imaging often reveals bony destruction and variable degrees of intratumoral calcification; however, angiography typically reveals the tumor to be relatively hypovascular. Rare chondrosarcomas are extensively vascular, with the appearance of an arteriovascular malformation on imaging *(7)*.

**Table 1**
**Malignant Mesenchymal, Nonmeningothelial Tumors of the CNS and Relative Incidence**

| *Tissue of origin* | *Tumor* | *Age at diagnosis* | *Incidence* |
|---|---|---|---|
| Fibrohistiocytic and fibrous tissue | Fibrosarcoma | Adult | ++ |
| | MFH | 50–60 yr | +++ |
| Adipose tissue | Liposarcoma | Adult | + |
| Muscle tissue | Leimyosarcoma | Child | + |
| | Rhabdomyosarcoma | Child | +++ |
| Blood vessels | Angiosarcoma | Young adult | +++ |
| | Hemangiopericytoma | Adult | |
| Cartilage and bone | Chondrosarcoma | Adult | ++++ |
| | Osteosarcoma | Adolescent | + |
| Pluripontential mesenchyme | Ectomesenchymoma | Adolescent | + |
| Uncertain origin | Ewing's sarcoma | Child to young adult | ++ |
| | Rhabdoid tumor | Young child | ++ |
| | Meningeal sarcomatosis | Infant or child | ++ |
| Unclassified | Sarcoma ONS | | |

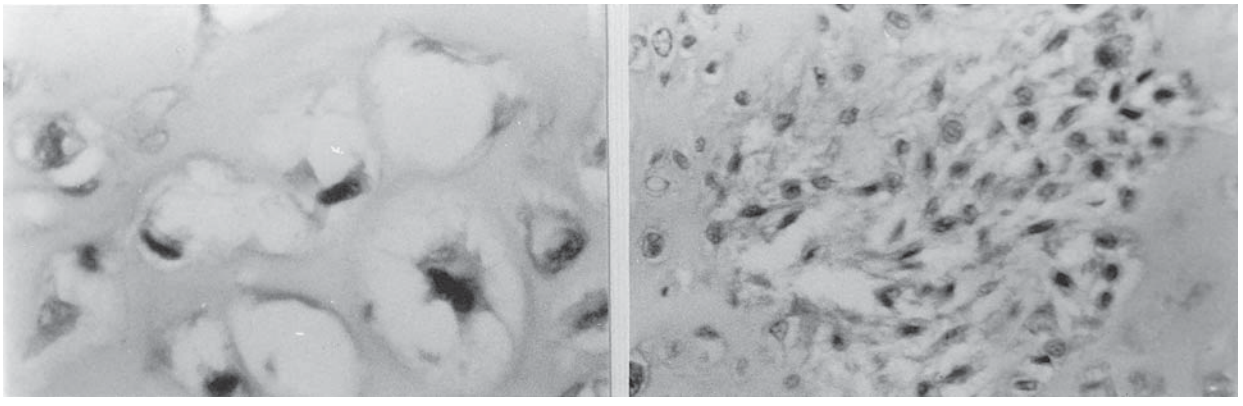

**Fig. 1.** Intracranial chondrosarcoma. **(A)** H and E at high power showing hyaline cartilage surrounding isolated polymorphic small cells. **(B)** intracranial chondrosarcoma at lower power demonstrating typical small cell component. (Figure courtesy of Henry Brown, M.D., Allegheny General Hospital, Pittsburgh, PA.)

Chondrosarcoma has been reported in a wide range of patients, ages 5–51 yr, with no true peak in incidence. A mean age of 37 and no predisposition for either sex was seen in the series reported by Korta et al. *(7)*. Intracranial chondrosarcoma can occur in the setting of Maffuci's syndrome (multiple enchondromas and subcutaneous hemangiomas) and Ollier's disease (multiple skeletal enchondromas) *(12,13)*. A patient with Goldenhar syndrome of multiple facial, vertebral, and jaw anomalies also developed an intracranial mesenchymal chondrosarcoma, initially misdiagnosed as meningioma *(14)*.

Typical presenting clinical features reflect the common localization of the tumor. The most common reported symptoms are oculomotor dysfunction and diplopia (51%), headache (31%), and auditory/vestibular dysfunction such as decreased hearing, dizziness, and tinnitus (21%) *(7)*. Clinical features in patients with chordoma and chondrosarcoma overlap considerably. Both entities produce diplopia or visual impairment as the initial symptom in approx 50% of patients, but multiple cranial neuropathies are more common in chondrosarcoma while most patients with chordoma have normal neurological examinations at presentation *(15)*.

These tumors vary in malignant potential, although the majority appears to have slow growth. Survival appears to correlate with the degree of differentiation of the tumor, as well as the degree of initial tumor resection *(10)*. Treatment includes surgical resection, either complete resection alone or followed by focal radiotherapy if resection is incomplete. Regrowth after surgery is common, reported by Korta et al. in 53% of patients treated with surgery alone *(6)*. Treatment with surgical resection alone resulted in 1- and 3-yr overall survival of 81 and 45%, respectively, in spinal meningeal chondrosarcoma *(16)*. Fractionated focal radiotherapy has been used with prolonged overall survival and time to progression in low-grade chondrosarcoma *(17)*. Estimated 5-yr survival of 83–94%, and local control at 5 yr of 78–91% reported after radiation therapy suggest a standard role for this modality in the adjuvant setting *(7)*. Chemotherapy has been used in both the adjuvant setting for higher-grade chondrosarcomas and at recurrence. Too few tumors have been reported to determine the role of chemotherapy is this tumor.

## MALIGNANT FIBROUS HISTIOCYTOMA

Malignant fibrous histiocytoma (MFH) is the most common adult soft tissue sarcoma, commonly occurring in the lower

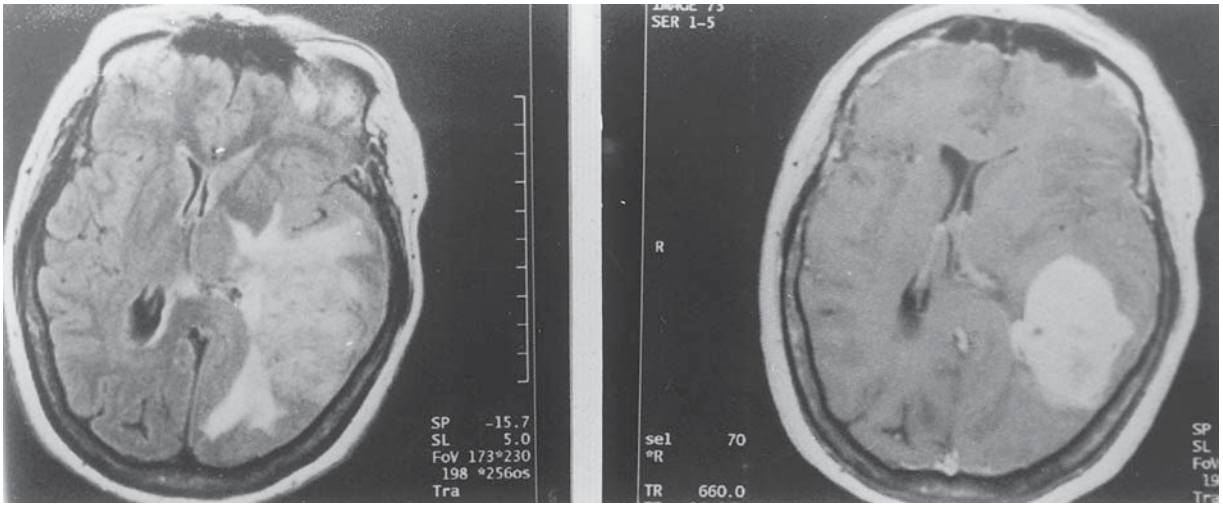


**Fig. 2.** Intracranial hemangiopericytoma in a 48-yr-old woman. **(A)** T2 weighted image. **(B)** T1 gadolinium contrasted image demonstrates a large, well-circumscribed, homogeneously enhancing mass with relatively modest surrounding edema and mass effect. The tumor extends to the dural surface as a small tail only at the inferolateral edge of the mass.

extremities, less often in the upper extremities or retroperitoneum. MFH is a malignant tumor characterized by spindled, pleomorphic giant cells in a storiform background. This tumor is seen mostly in middle age adults, typically 50–70 yr of age, with a slight male predominance.

It is extremely rare (<3% of cases) to identify a MFH arising in the CNS. MFH has been reported both as an intracranial primary tumor and as cerebral metastasis from systemic primary tumors. Two cases of primary leptomeningeal MFH have been reported *(18)*. Several case reports in middle-age adults of primary intracranial MFH suggest a possible etiology of previous radiation or trauma, but true etiologic correlation is difficult to assess *(19)*.

Neurological involvement due to MFH is more often seen as an indirect effect by peripheral nerve compression secondary to tumor. Retroperitoneal MFH typically presents with constant, moderately severe back pain. Compression of peripheral nerves of the lumbar or sacral plexus may occur within the retroperitoneum, and in the extremity an isolated peripheral nerve compression may occur.

Treatment for both intracranial and systemic MFH involves surgical resection. Prognosis is usually quite poor, with rapid local recurrence and very rare survival 2 yr after diagnosis *(19)*.

## HEMANGIOPERICYTOMA

Hemangiopericytoma (HPC) is a rare vascular tumor that may arise anywhere in the body, and rarely within the CNS where it is usually in close approximation to the leptomeninges. Formerly, intracranial hemangiopericytoma was classified as angioblastic meningioma. The 1993 WHO classification reclassified the tumor as a distinct entity, as it is now recognized to arise from pericapillary mesenchymal cells. They are very vascular and highly cellular tumors.

The majority of hemangiopericytomas occur in adults, with a mean age at diagnosis of 40–50 yr old. Children account for only 10% of intracranial HPC. The tumor usually is found attached to the dura without infiltration into the brain or spine parenchyma, although it does have a tendency to metastasize outside of the CNS. The primary location typically reflects the usual distribution of meningiomas: supratentorially over the convexities, along the petrous ridge, along the tentorium, and less often in the posterior fossa or spinal canal.

Hemangiopericytoma shares many imaging characteristics of the more common meningioma and therefore is commonly not recognized prior to surgical resection. Features that may differentiate HPC from meningioma are that it often is multilobulated with a narrow dural tail, may show bony erosion but not hyperostosis, and lacks intratumoral calcification *(20)*. Figure 2 demonstrates nonetheless that the imaging features may closely mimic meningioma or metastatic tumors. In children, however, meningiomas are quite uncommon and several tumors may mimic meningioma on standard imaging. A recent series by Demirtas et al. reported that in a series of apparent childhood meningioma on MRI seven (38.8%) out of 18 tumors showed anaplastic features, including two hemangiopericytomas, one mesenchymal chondrosarcoma, and one pleomorphic sarcoma *(21)*. Papillary meningiomas with hemangiopericytoma-like solid areas were seen frequently (15.3%). Angiography typically shows small corkscrew vessels in a densely stained tumor.

Treatment of HPC consists of complete surgical extirpation, if possible, followed by focal radiation therapy. Surgery is sometimes preceded by embolization of the tumor to partially devascularize these very vascular tumors, since HPC has been known to bleed extensively perioperatively. Despite this, the usual course of adult HPC is one of frequent local recurrence, estimated at 27% at 5 yr and 67% at 10 yr *(22)*. Radiosurgery has been attempted in small series to enhance local control with modest apparent success. Using gamma knife technology, Payne et al. reported that 4 of 9 tumors shrank an average of 22 mo after treatment *(23)*. Distant metastasis throughout the CNS and to multiple systemic sites, including bone, pancreas, liver, and heart, have been reported. The role of chemotherapy for recurrent and metastatic HPC has not been clarified; however,

one series reported improved survival at 24 mo, 90 vs 60%, in patients treated with adjuvant radiation or chemotherapy vs surgery alone *(24)*.

An infantile form of HPC is recognized with a quite benign clinical course despite a histopathological appearance that in an adult would be associated with a malignant course *(25)*. The infantile form typically presents within days of birth as a large mass within the cerebral hemispheres. With aggressive surgical removal the tumor usually follows a very indolent clinical course *(26)*.

## RHABDOMYOSARCOMA

Rhabdomyosarcoma (RMS) is an embryonal sarcoma derived from primitive mesenchymal cells throughout the body that shows evidence for muscle differentiation within the mass. It is the most common soft tissue sarcoma in children. Two histological types are seen, embryonal and alveolar rhabdomyosarcoma. Only embryonal RMS has been reported in the CNS.

RMS is a childhood tumor with a median age of 10–10.5 yr. Usually seen sporadically, it can be associated with neurofibromatosis type 1, the Li-Fraumeni syndrome, and Beckwith-Weideman syndrome. Most childhood rhabdomyosarcomas occur in the head and neck region, typically in the orbit, paranasal sinuses, pterygopalatine fossa, the infratemporal fossa, middle ear, and the parotid gland. Skull base RMS in this region is usually an invasive tumor, often extending intracranially and producing a neoplastic meningitis *(27)*. Infiltration of the leptomeninges has been estimated to occur in one-third of patients *(28)*. Primary intracranial RMS is very rare, with most cases occurring in children as well *(29)*. Fewer than 50 cases of primary intracranial RMS and fewer than 10 cases of primary meningeal RMS have been reported to date *(30,31)*. Brain metastasis from systemic RMS are uncommon, usually only seen concurrent with or following developing after lung metastasis.

Patients with RMS may have a very short duration of symptoms prior to diagnosis. Presenting neurological symptoms largely reflect the location of the mass and frequently include headache, visual disturbance because of orbital tumor, hearing loss, and rarely unilateral facial paralysis due to middle ear tumor. Occasionally, RMS will present with a pseudotumor cerebri-like syndrome due to tumor in or compressing the jugular vein from extrapharyngeal areas or tumor in the heart causing venous congestion. Rarely, an intracranial mass will present with seizure or acute focal neurologic symptoms. This presentation usually signals hemorrhage into a brain metastasis. RMS is one of the metastatic tumors prone to bleeding.

Treatment for head and neck RMS has been developed according to International Rhabdomyosarcoma Society protocols that take into consideration several risk factors identified for development of leptomeningeal involvement with tumor. One or more of the following factors increases this risk: skull base erosion, cranial nerve palsy, and intracranial extension. Current recommendations are that concomitant combination chemotherapy and focal radiation therapy be administered if one or more of the risk factors is present *(27)*. Radiation is delivered to a 2 cm margin around the gross tumor to a dose of approx 50.4 Gy. Combination chemotherapy includes ifosphamide or melphalan, followed by vincristine, adriamycin, and cyclophosphamide. If no risk factors are present the radiation therapy is held until after completion of chemotherapy.

Multimodality therapy for head and neck RMS has resulted in excellent long-term survival in most patients. Wharam reported 5-yr progression-free survival of 71% for parameningeal RMS *(27)*. Intracranial extension and meningeal involvement, however, portend a shorter survival than those cases without the aforementioned risk factors. Late effects of treatment are relatively common in patients treated for RMS. These effects include frequent abnormal facial growth, neuroendocrine abnormalities, hearing loss, visual disturbances, and cognitive loss (especially in children who receive whole brain radiation for meningeal involvement) *(32)*.

In rare instances, distant cerebral metastases occur from systemic RMS (2% of cases) with ominous implications. The median survival, only 2.7 mo in one large series, has been extremely short despite aggressive therapy *(33)*. Primary intracranial RMS has also had a poor prognosis, and most reported cases had survivals of only months after diagnosis *(33)*.

## LEIOMYOSARCOMA

Leiomyosarcoma is a previously extremely rare smooth muscle derived tumor that is becoming somewhat more frequent as an acquired immunodeficiency syndrome (AIDS) related tumor. The most common soft tissue site is the retroperitoneum, although the tumor is commonly found in the gastrointestinal tract and uterus. Any age group can be affected. Long clinical latency of this tumor is one hallmark. Tumors are often large and unresectable at diagnosis. Examples of longstanding radicular type extremity pain due to pelvic leiomyosarcoma exist *(34)*.

In children with AIDS the tumor is usually seen in the chest or abdomen; however, several case reports of intracranial leiomyosarcoma exist in AIDS patients. The majority of these have involved young adult AIDS patients found to have leiomyosarcoma in the sellar or suprasellar region, though cases have been reported in the pontine cistern and the spinal canal *(35,36)*. The AIDS-related tumors have been found to be Epstein-Barr Virus (EBV)-positive by *in situ* hybridization, suggesting that re-activation of the virus may have a role in the development of these tumors *(35,37)*. Interestingly, a single case of a 14-yr-old with common variable immunodeficiency syndrome with a temporal lobe leiomyosarcoma has been reported, in which *in situ* hybridization revealed extensive EBV infection in the tumor *(38)*.

Fewer than 5 cases of non-AIDS related intracranial leiomyosarcoma have been reported, all in children less than 10 yr old with uniformly poor outcome *(39)*. Non-AIDS related cases of leiomyosarcoma more commonly impact the nervous system by extrinsic compression of peripheral nerves by a systemic tumor. Pelvic tumors, for example, may produce lower back pain and lumbosacral plexus dysfunction with unilateral leg weakness or numbness.

Treatment of intracranial leiomyosarcoma has been largely surgical resection alone, although focal radiation therapy has been administered in a few cases. The benefit of radiation therapy remains undefined due to small numbers of cases treated. Systemic tumors, likewise, are surgically resected as

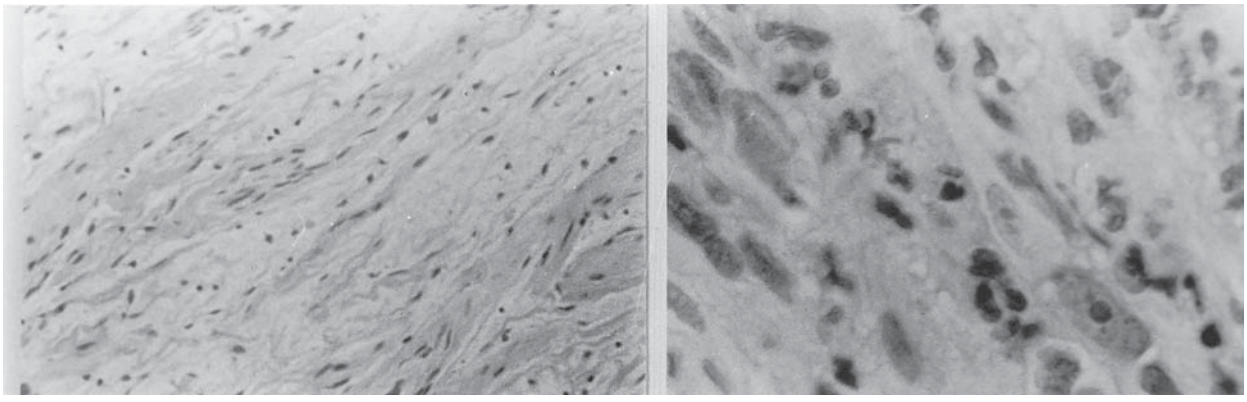

**Fig. 3. (A)** Neurofibroma. Ovoid to spindle-shaped, curved cells in a matrix of collagen fibers showing very rare mitoses and **(B)** Malignant nerve sheath tumor. Spindle-type cells showing marked nuclear pleomorphism and frequent mitotic figures in a disorganized background. (Figure courtesy of Henry Brown, M.D., Allegheny General Hospital, Pittsburgh, PA.)

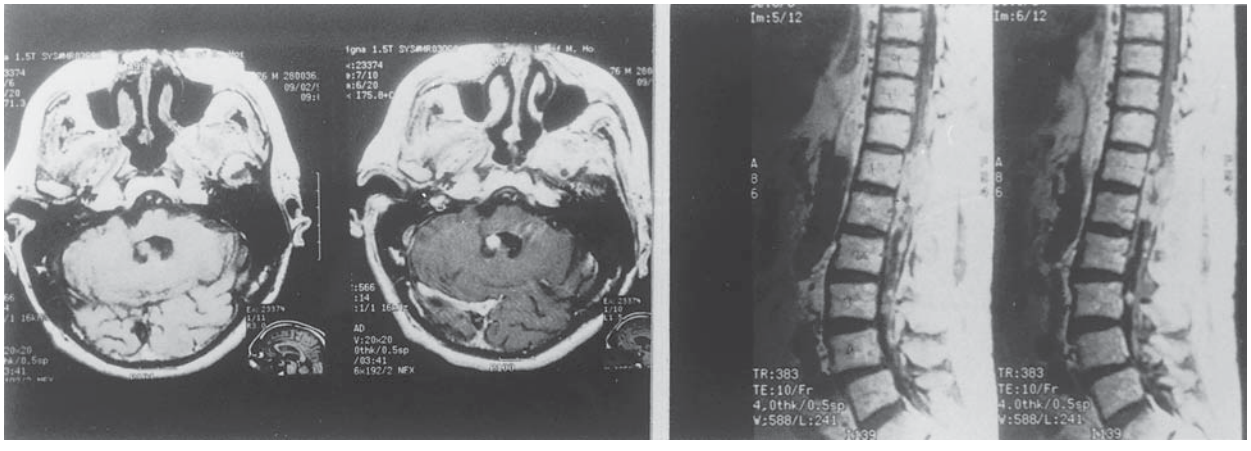


**Fig. 4.** MPNST arising within the spinal canal, compressing the lower thoracic spinal cord. A fourth ventricular mass was noted to be a metastasis from the lesion in this patient without evidence for Neurofibromatosis type 1.

primary treatment. Recurrence occurs in 40–60% of cases, and repeat resection is often the treatment. The role of radiation and chemotherapy remains unclear.

## MALIGNANT PERIPHERAL NERVE SHEATH TUMOR

Malignant peripheral nerve sheath tumor (MPNST) makes up 5–10% of soft tissue sarcomas. MPNST can be divided into four groups; sporadic MPNST, MPNST related to neurofibromatosis type 1 (NF-1), MPNST resulting from prior ionizing radiation exposure, and MPNST arising within ganglioneuroma or carcinoid tumor. MPNSTs are a wide group of tumors with neural differentiation that most commonly present as a spindle cell neoplasm. A retrospective institutional review of MPNST of the buttock and extremity over 35 yr revealed that 53% of patients had NF-1 *(40)*. In general, risk of death due to NF-1 is largely related to the development of malignant neoplasms, the most common of which is MPNST. There is a 7–10% lifetime chance of malignant peripheral nerve sheath tumor in NF-1 patients *(41)*. A large population-based Finnish study identified an 8% risk of NF-1 related malignancy, the most common of which was malignant peripheral nerve sheath tumors leading directly to the patient's death in most cases *(42)*. A retrospective series from St. Jude's Hospital of 28 patients with 29 MPNSTs found a 5-yr overall survival of 39% *(43)*. MPNSTs are very aggressive tumors in most cases.

MPNST often appears histologically as a spindle cell neoplasm with tightly packed cells, marked pleomorphism, numerous mitotic figures, and geographic necrosis. Variants exist with glandular, epitheliod, and rhabdomyoloid differentiation. Most MPNST arise within benign neurofibromas; 81% did so in cases of NF-1 associated and 41% of sporadic cases in a series from the Mayo Clinic. Plexiform neurofibromas appear to have a greater predisposition to malignant transformation than do standard neurofibromas. Histopathologic differences between neurofibroma are highlighted in Fig. 3. Progression from benign to a malignant nerve sheath tumor is poorly understood. Malignant transformation in NF-1 may be related to genetic changes leading to gains of 17q or loss of 13q, which can be identified in multiple MPNSTs in NF-1 but not in sporadic MPNST *(44)*. Allelic loss of both the short and long arm of 17 has been reported for MPNST, as well as loss of heterozygosity of 17p in a patient with concurrent gliosarcoma *(45)*.

Distinguishing a benign from a malignant PNST on imaging studies can be difficult. Both tumors can cause neural foramen

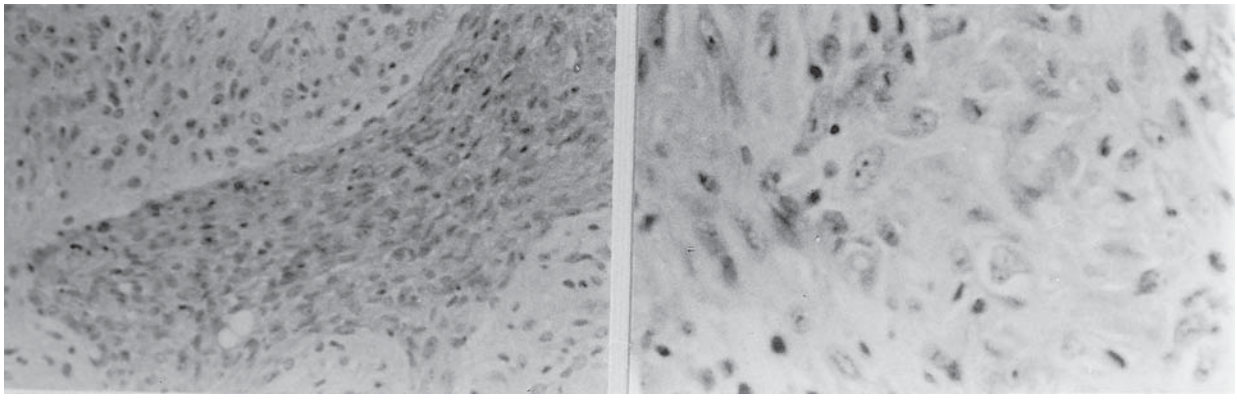

**Fig. 5.** Gliosarcoma: histopathological appearance. **(A)** Biphasic tumor with clear demarcation between glial and mesenchymal cells. **(B)** Higher-powered view of sarcomatous tissue showing spindle cells with pleomorphic nuclei. (Figure courtesy of Henry Brown, M.D., Allegheny General Hospital, Pittsburgh, PA.)

widening due to a dumbbell shaped tumor extending through the foramen. The "target sign" on T2-weighted MR images—round lesions with a central hypointensity and a hyperintense rim—is helpful in distinguishing a neurofibroma. MPNST very rarely display the target sign, whereas neurofibroma usually will *(46)*.

Clinical presentation of MPNST varies depending on location of the mass. Tumors of the cranial nerves, spinal nerve roots, and peripheral nerves and plexuses have been reported. Spinal nerve sheath tumors along the dorsal nerve roots are commonly found in NF-1 and NF-2. One of the more common presentations of MPNST is extradural spinal cord compression from MPNST either arising within the spinal canal or extending into the canal through a neural foramen (Fig. 4). MPNSTs arising from peripheral nerves result less frequently in neurological signs and symptoms, despite their ability to grow to quite large size along medium to large nerves. The common presentation is of an enlarging mass in an extremity with or without neurological symptoms.

MPNST is a very aggressive tumor. Low-grade tumors occur in only 10–15% cases. A recent review estimated the overall 5-yr survival ranges from 34–52% *(47)*. The most significant prognostic factor identified in MPNST associated with NF-1 was extent of initial resection. Patients with a gross total resection had 65% 5-yr overall survival, those with subtotal resection had poorer survival, with no patient alive greater than 25 mo *(43)*. Distant metastasis, 18% in one series, have been reported to multiple systemic sites, including lung and brain *(48–50)*. Outcome has been extremely poor after development of metastasic disease from MPNST.

Treatment includes surgical resection followed by focal radiation therapy; however, rapid regrowth is not uncommon.

## OSTEOGENIC SARCOMAS

Osteosarcoma is the most common primary malignancy of bone. This tumor has typical sarcomatous features, but also has direct bone formation within the tumor. The usual sites of occurrence are distal femur, proximal tibia, humerus and pelvis. Primary osteosarcoma of the vertebral coloumn is rare. Fewer than 100 cases, mostly in the thoracic and lumbar spine, have been reported to date *(51)*. Osteosarcoma arising from the spine can present as acute spinal cord compression due to local kyphosis and vertebral body collapse. Brain metastases are uncommon, usually only seen in concert with lung metastasis. Isolated brain metastasis without lung involvement has only been convincingly shown in a case of a boy with a patent foramen ovale that permitted bypass of the lung vasculature by metastasis *(52)*.

Osteosarcomas of the skull are rare. Risk factors include Paget's disease and prior radiotherapy. Prior radiotherapy is also a risk factor for development of fibrosarcoma of the skull *(53)*. In contrast to sarcomas of long bones, which frequently metastasize, postradiation sarcomas of the skull rarely do so. Local progression results in headache and the development of neurologic symptoms related to compression of underlying brain. Treatment includes aggressive resection and fractionated radiotherapy, but such tumors are usually fatal within a few years.

## EWING'S SARCOMA

Ewing's sarcoma of the spine is an extremely rare condition with a typical clinical triad of local back pain, neurological deficit, and a palpable mass *(54)*. Back pain not relieved by conservative measures, especially with symptoms suggesting sciatica, a cauda equina syndroma, or a conus medullaris syndrome has been reported in multiple teenagers as presenting symptoms of Ewing's sarcoma *(55)*. Rarely, spinal cord compression has been the presenting symptom. Ewing's sarcoma may also be complicated by cerebral metastasis both in children and in adults *(33,56)*.

## GLIOSARCOMA

Gliosarcoma is a variant of glioblastoma that has clear biphasic areas of glial and mesenchymal differentiation within the tumor. Approximately 2% of glioblastoma meet WHO criteria for gliosarcoma *(57)*. Histologically, the sarcomatous portion of the tumor is demarcated from the glial portion and may show differentiation along cartilaginous, bony, or smooth muscle lines (Fig. 5). The gross appearance may be firmer and more discrete than usual for glioblastoma.

Gliosarcoma tends to mimic the clinical characteristics of glioblastoma, with regards to presentation, imaging, and response to treatment. There does not seem to be a survival difference between glioblastoma and gliosarcoma *(58)*.

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# 30 Neurologic Complications of Head and Neck Cancer

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## BACKGROUND

Head and neck cancer accounts for approx 4–5% of all newly diagnosed cases of cancer in the United States, with estimated numbers of diagnoses and deaths in 2000 were 40,300 and 11,700, respectively *(1)*. Worldwide, more than 600,000 new cases are projected annually *(2)*. More than 90% of head and neck cancer is squamous cell carcinoma in histology, and the majority of tumors are associated with smoking and alcohol use *(3)*. Repeated exposure of the upper aerodigestive tract from the oral cavity to the bronchial trees leads to epithelial damage (condemned mucosa syndrome) and initiation of carcinogenesis *(4–6)*.

Biological processes of tumorigenesis in the aerodigestive tract are thought to be a multistep process where tumor is arising in this field at risk *(7)*. Biological understanding of tumorigenesis of second primary tumors is extremely important to prevent relapse or multiple primary tumors after definitive therapy is delivered *(8)*. Over the last two decades, development of molecular biology has made major contributions to basic understanding of tumorigenesis processes and identified multiple genes involved in the tumorigenesis process (i.e., p53 mutations/overexpression, erbB family, 9p deletion, 11q13 amplification, 17p loss, 3p loss, etc.) *(9–16)*. Direct DNA analysis has shown that cyclin D1, located at 11q13, is amplified in one-third of squamous cell carcinoma of the head and neck (SCCHN) *(17)*. Although other genes (INT2 and HST1) located nearby may be contained within the amplified DNA segment, only cyclin D1 is amplified consistently and may correlate also with histopathologic progression in SCCHN *(18)*. Chromosome 3p loss is seen in approx 60% of SCCHN. The target(s) of 3p loss is critical because these losses are among the earliest events in progression of SCCHN *(19)*. Loss of chromosome 17p was also observed in more than 50% of primary tumors and had been extensively studied since p53 locates within this region *(20)*. Mutations of p53 increase with tumor progression in SCCHN, occurring in approx 40–60% of invasive tumors *(12,21)*. The p53 protein appears to be ubiquitously involved in multiple cellular functions including cell cycling, apoptosis, DNA repair, and responsiveness to cytotoxic therapy *(22)*. Studies have also shown that p53 expression increases from normal epithelium adjacent to tumors to premalignant lesions to invasive carcinoma in a multistep fashion *(12)*. The functional implication of p53 gene is an important rationale for p53-based gene therapy, which has also been investigated *(23–25)*.

Clinical presentations and detection of SCCHN are varied according to tumor location. Tumors of oral cavity and oropharynx present with swelling or ulcer, dysphagia, odynophagia, or otalgia, while laryngeal tumors are associated with hoarseness, stridor, dyspnea, or pain depending on the size and/or invasion to adjacent structures *(3)*. Tumors in the nasopharynx (NPC) are frequently associated with epistaxis, obstructive symptoms, otitis media, and also present with cranial nerve neuropathy when the tumors invade the base of the skull (*vide infra*). Exophthalmos with facial swelling is usually associated with tumor of the paranasal sinuses.

## SURGICAL THERAPY

For surgical resection in the context of effective surgical management, the single most important principle is the adequate preoperative assessment of disease extent. Adequate preoperative assessment provides optimal intraoperative exploration of disease. The surgeon should consider appropriate means to achieve an optimal operative exposure. The choice of incision and ability to mobilize surrounding anatomical structures to achieve adequate exposure should be considered for each anatomical subset *(26)*.

For oral cavity cancer, the majority of surgeons prefer to do radical resection, although there is an effort to minimize surgical extent to preserve organ function as well as anatomical structures *(27,28)*. However, obtaining negative tumor mar-

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gins is very important to prevent recurrence. There is a general trend for the oropharynx including base of tongue to be considered for nonsurgical methods such as radiation therapy or concurrent chemotherapy and radiation therapy followed by neck dissection if necessary. The neck dissection is an important modality to control cervical lymph node metastases *(29)*. The radical neck dissection involves complete removal of the lymphatic channels in the neck. To assure complete extirpation, anatomical structures including the sternocleidomastoid muscle, spinal accessory nerve, and jugular vein are routinely sacrificed. However, a recent development in the management of the cervical lymph nodes involves more conservative procedures such as modified neck dissection or selective neck dissection. These procedures differ from the classic radical neck dissection in sparing of specific anatomical structures *(30)*. The value of selective neck dissection in patients without clinical evidence of cervical node involvement is still controversial *(31)*. Studies are preliminary and more conclusive studies are required. More minimal surgical approaches sparing organ structure and functions are desirable in the future practice of surgical approaches for head and neck cancer patients. Reconstructive surgery in conjunction with radical surgery is an important modality in terms of improving the functional, anatomical, and cosmetic outcome.

**RADIATION THERAPY** In addition to surgical resection, radiation therapy is an important treatment modality for head and neck cancer. Selection of treatment modality must be individualized to each patient and must consider issues such as cosmetic and functional outcome, quality of life, speed of which treatment can be completed, sequelae of each modality, patient reliability, risk of subsequent cancers, and effectiveness of salvage therapy *(32)*. For advanced head and neck cancer, surgery and radiation therapy are frequently combined. In the postoperative setting, radiation therapy is very important to prevent recurrence. In planning treatment for advanced disease, it is essential to consider both the primary site and the neck and to integrate a management strategy that encompasses both locoregional control and quality of life. It is likely that the primary site can be managed by radiation therapy alone if the primary tumor is small. The neck should receive combination therapy with surgery and radiation therapy *(33)*. However, neoadjuvant or adjuvant chemotherapy in this setting has not shown any survival benefit in these patients although the organ can be preserved *(34,35)*. In terms of postoperative therapy, there is a trend to give concurrent chemotherapy and radiation, particularly for those patients who have involved lymph nodes at one or more levels, extracapsular extension, high risk of contralateral nodal metastases, and risk of disease in the lower neck. Recent studies demonstrate that concurrent chemotherapy and radiation therapy achieves better local control than radiation therapy alone in either the postoperative setting or the primary treatment of disease in which the patient is not a candidate for surgical resection *(36,37)*. There is also evolving evidence that concurrent chemotherapy and radiation therapy provides more survival benefit than chemotherapy followed by radiation therapy *(38)*.

**CHEMOTHERAPY** Chemotherapy can be utilized in two different settings: in the locally advanced previously untreated patients, and in the recurrent or metastatic disease. The most active single agents in recurrent or metastatic head and neck cancers are methotrexate, bleomycin, cisplatin, carboplatin, 5-fluorouracil (5-FU), paclitaxel, docetaxel, and ifosfamide *(39)*. These single chemotherapeutic agents produce tumor responses in 15–30% of patients. However, combination chemotherapy regimens have been developed and used more frequently for recurrent or metastatic head and neck cancer.

In the early 1980s, researchers at Wayne State University reported a response rate of 70% and a complete response (CR) rate of 27% using cisplatin and 5-FU. Several randomized trials have been conducted to compare single agents with combination chemotherapy for recurrent/metastatic squamous cell carcinoma of the head and neck. Three large multicenter trials reported by Jacobs et al. compared cisplatin and infusional 5-FU to the single agents cisplatin, 5-FU, or methotrexate (MTX). The response rate of cisplatin plus 5-FU was 32% in two of the trials and 31% in the third; all studies demonstrated a significantly higher response rate for cisplatin plus 5-FU compared to the single agents. However, there were no differences in median survival rates for any of the treatment arms *(40–42)*.

The activity of paclitaxel or docetaxel as a single agent in the treatment of head and neck cancer has stimulated intense interest in the use of these drugs in combination with other active agents for treatment of this disease. Because of the established activity of platinum and its synergy with taxanes, several studies have examined the various combinations in the treatment of head and neck cancer. The Eastern Cooperative Oncology Group (ECOG) compared a high dose of paclitaxel (200 mg/m$^2$) with a low-dose paclitaxel (135 mg/m$^2$) on d 2 to treat patients with recurrent and metastatic head and neck cancer. The ECOG study showed similar response rates in the high-dose and low-dose paclitaxel arms (34 vs 35%, respectively). Survival rates did not appear to differ, and side effects also were similar between the two arms. This study concluded that no advantage was observed by using the higher dose of paclitaxel *(43)*. We conducted two consecutive studies using paclitaxel, ifosfamide, mesna, and cisplatin (called TIP) *(44)*; and paclitaxel, ifosfamide, plus carboplatin (TIC) *(39)*. The improved overall response rates noted with TIP and TIC regimens (58 and 59%, respectively) compared favorably with the rate of 32% reported for 5-FU/cisplatin or paclitaxel/cisplatin studies; the superior antitumor activity associated with the TIP and TIC regiments may be related to the addition of ifosfamide. However, other factors such as early patient dropouts in the ECOG trial, the relative number of patients treated, and a single institution vs a cooperative group trial need to be considered carefully when making the comparison.

## NEUROLOGIC COMPLICATIONS OF HEAD AND NECK CANCER

**DIRECT EXTENSION OF PRIMARY TUMOR** Direct extension and spread via lymphatics are the principal means of metastasis for carcinomas of the head and neck. Tumor may follow peripheral nerves through neural foramina in the skull base, utilize other openings in the skull base such as the foramen lacerum, or may erode bone to enter the skull or orbit.

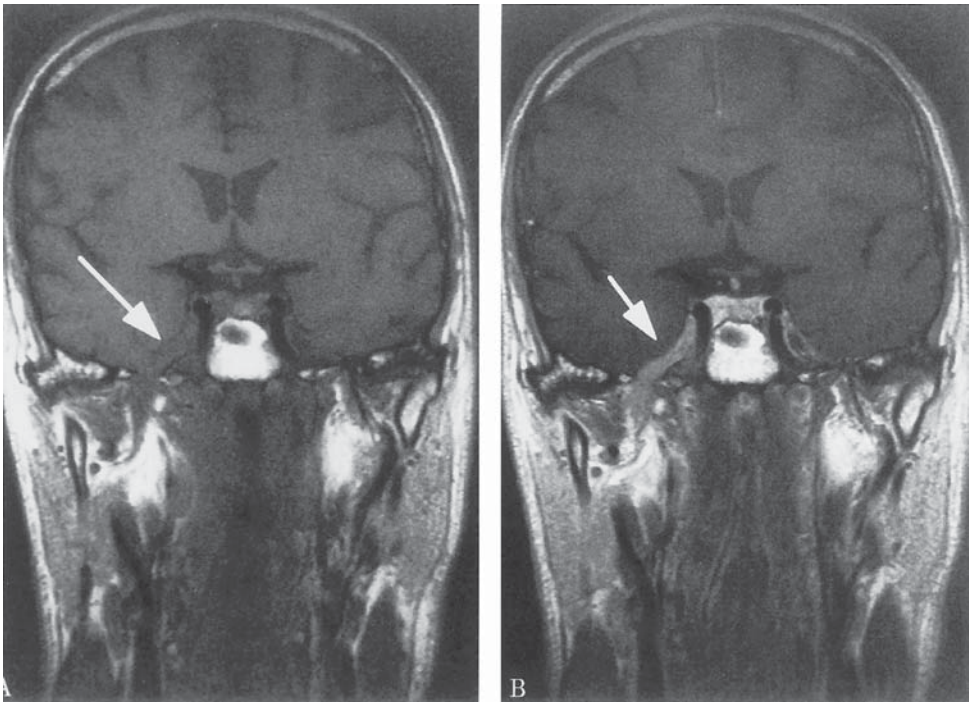

**Fig. 1.** This 37-yr-old female was previously treated with surgery and radiation for adenoid cystic carcinoma of the right maxilla. Six years later she presented with neuropathic pain in the right V2 distribution. Coronal T1-weighted spin echo image before **(A)** and after **(B)** gadolinium administration demonstrate enhancement of the mandibular trigeminal nerve within the oval foramen (arrow). Adapted with permission from ref. *45*.

Almost by definition, perineural spread of head and neck cancer is difficult to detect because the tumor cells grow linearly rather than forming a mass. Although some patients are asymptomatic, many complain of burning or lancinating pain often for months before the tumor becomes apparent. Paresthesias or hypesthesias are also common. Of head and neck tumors, adenoid cystic carcinoma of the nasopharynx, oropharynx, salivary glands, or paranasal sinuses is particularly prone to present in this manner. The pace of growth is often sufficiently slow that enlargement of the mandibular canal, foramen ovale, or other bony foramen is an important radiographic clue to neural extension. More recently, postgadolinium coronal magnetic resonance (MR) scanning has documented utility in demonstrating perineural enhancement along the mandibular division of the trigeminal nerve, extending through the skull base (*see* Fig. 1). In some cases this leads to development of a metastatic mass in the cavernous sinus *(46)*.

Perineural spread of cutaneous squamous and (less commonly) basal cell carcinomas tends to follow a slightly different pattern *(47)*. As with adenoid cystic carcinomas, tumor cells are capable of invading the perineural space and spreading axially many centimeters proximal to the primary tumor. Because trigeminal and facial nerve branches are anatomically closely related in the skin, both nerves are commonly involved. When tumors arise in the distribution of the ophthalmic or maxillary divisions of the trigeminal nerve, orbital nerves are often the next to be affected with masses growing in orbit. The tumor can break out of the perineurium and form a mass lesion along the course of the trigeminal nerve some distance from the primary site.

The incidence of perineural spread of skin cancer ranges from 5–14% of cases *(48)*. The finding of radiographically visible perineural spread on preradiotherapy CT or MR scan worsens the prognosis with these tumors. Some experts have recommended that all patients with either clinical or pathological evidence of perineural spread should undergo pretreatment MR scanning to assist in planning of optimal radiation ports *(48)*.

When SCCHN has spread intracranially along cranial nerves, treatment may include surgery, fractionated radiotherapy, or radiosurgery. Some neurosurgeons advocate radical resection of adenoid cystic carcinoma metastases in the cavernous sinus *(49)*, although patients may suffer disfiguring cranial nerve palsies and as well as strokes from internal carotid artery manipulation. Preliminary reports suggest radiosurgery may provide effective local control with less morbidity *(50)*. For large or diffuse intracranial spread, or patients with limited anticipated survival, fractionated radiotherapy may be preferable.

Erosion through bone offers another means of head and neck cancers to produce neurologic symptoms. The bony structures between the sinuses, skull, and orbits are thin, offering little resistance to cancer spread. Masses in the ethmoid sinus or superior nasal cavity may grow through the cribiform plate into the anterior cranial fossa, producing anosmia, cerebrospinal fluid (CSF) leak, or frontal lobe syndromes. For example, esthesioneuroblastomas (also known as olfactory neuroblastomas) are rare tumors arising from bipolar neurons of the olfactory epithelium in the superior nasal cavity. Erosion through bone is common; such erosion can include the cribiform plate, other parts of the skull base, or orbit. Intracranial involvement is seen in 20–30% of patients *(51)*. Carcinomas of the sphenoid sinus may grow into the middle cranial fossa or the cavernous

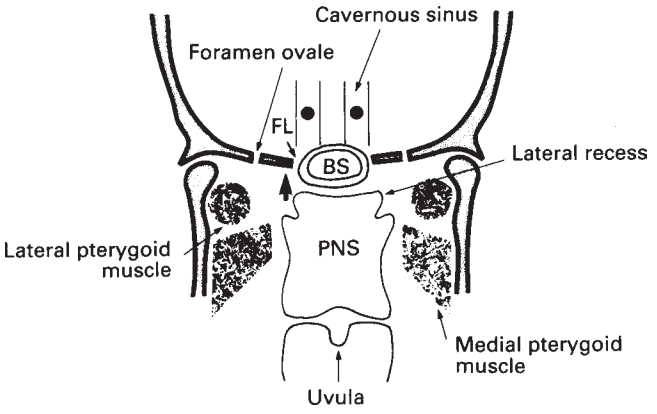


**Fig. 2.** The proximity of the nasopharynx to the skull base, foramen ovale, and cavernous sinus. Diagram based on coronal sections to illustrate the upward path of tumors from the postnasal space. Lateral recess: Fossa of Rosenmuller. PNS: postnasal space. FL: Foramen lacerum. BS: basisphenoid. Adapted with permission from ref. *53*.

sinus via the inferior orbital nerve. Patients may complain of diplopia, proptosis, or trigeminal paresthesias.

Nasopharyngeal tumors are another tumor occasionally presenting with neurologic symptoms. These tumors usually arise in the clinically silent fossa of Rosenmuller. They may present with metastatic neck masses or with symptoms of nasal obstruction, but one-quarter of patients will present with symptoms of intracranial involvement. The old teaching was that these tumors tracked through the foramen lacerum along the carotid artery to gain access to intracranial contents, involving sympathetic and cranial nerves in the process. A recent MR study of 150 cases demonstrated skull base invasion in 63% of cases at diagnosis *(52)* and suggested an alternative process: invasion of the sphenoid bone and clivus each occurred in 47% of cases. The authors suggested that direct invasion through bone was more important than passage through the foramen lacerum or along perineural pathways (*see* Fig. 2). Regardless of the pathway, intracranial spread of nasopharyngeal carcinomas commonly involves the trigeminal nerve, resulting in unilateral facial pain and sometimes sensory loss and paresthesias. Involvement of the VIth nerve results in diplopia, the second most common complaint. Orbital invasion can involve cranial nerves III and IV or produce exophthalmos. Invasion of brain parenchyma or leptomeninges is rare.

**ORBITAL TUMOR** Given the proximity of the nasal cavity and paranasal sinuses to the orbit, it is unsurprising that 59% of tumors arising from these structures invade the orbit *(54)*. Three-quarters of the offending tumors are squamous cell carcinomas, with maxillary sinus tumors particularly likely to involve the orbit. While orbital invasion may be an asymptomatic radiographic diagnosis, the majority of patients have symptoms including proptosis, decreased vision, eyelid edema, diplopia, and decreased ocular motility. Symptoms related to orbital invasion may be the initial complaint related to SCCHN; thus, neurologists and ophthalmologists need to be cognizant of this presentation *(54)*. Tumors that are posterior or retrobulbar in the orbit are of particular neurologic interest as they may displace, compress, or invade the optic and extraocular muscle-related nerves.

Although not a complication of SCCHN, metastases from other systemic tumors to the orbit produce similar symptoms and are logically reviewed here. Several case series suggest that breast cancer accounts for more than one-half of cases, with prostate and lung cancer other relatively common causes *(55,56)*. In children, metastatic neuroblastoma is the most common cause. Diplopia, proptosis, and extraocular muscle motility disturbances are the most common findings. Visual failure stems from pressure on the globe, circulatory disturbances in the choroid retina or optic nerve. When diplopia or extraocular palsy is the only finding, the differential diagnosis includes leptomeningeal tumor or skull base metastasis. Computed tomography (CT) or MR scanning is generally diagnostic for orbital metastasis. Management typically consists of radiotherapy, although systemic chemotherapy or surgery may be appropriate in selected cases

**SKULL BASE PARAGANGLIOMAS** Another tumor frequently manifesting neurologic symptoms is paraganglioma of the head and neck. These tumors are synonymous with chemodectomas or glomus tumors. The cell of origin, which has chemoreceptive properties, derives from the neural crest; these tumors rarely secrete catecholamines. Approximately 20% are familial; a likely responsible tumor suppressor gene has recently been identified. Transmission is far more likely when the father carries the disease, a manifestation of parental imprinting. Women predominate in sporadic cases. These tumors are typically slow-growing, infrequently metastasize, and produce most of their problems through local invasion

Glomus tympanicum tumors arise from paraganglia associated with the tympanic branch of the glossopharyngeal nerve. They arise in the middle ear and usually produce pulsatile tinnitus and eventually conductive hearing loss over a few years. An audible bruit may be detected. Otoscopy usually demonstrates a reddish-blue retrotympanic lesion *(57,58)*. Glomus jugulare tumors arise from the jugular bulb and may involve cranial nerves IX, X, and XI in the jugular foramen. They can extend rostrally into the middle ear and mimic glomus tympanicum tumors or compress cranial nerves VII and VIII in the internal auditory canal. Glomus vagale tumors arise from the inferior ganglion of the vagus nerve, sitting behind the internal carotid artery high in the neck. Patients usually have a neck mass, frequently associated with hoarseness and vocal cord paralysis *(59)*. Treatment of all these tumors usually involves an attempt at gross total surgical resection, sometimes preceded by embolization given their highly vascular nature. Stereotactic radiosurgery has been used with some success *(60)*, though the slow growth rate of these tumors mandates longer follow-up. Metastasis of these neoplasms is uncommon.

**METASTATIC DISEASE**

**Leptomeningeal Metastasis** The incidence of carcinomatous meningitis in SCCHN is about 1–2%, or somewhat less than the 5% incidence that is generally stated as the overall incidence of meningeal metastases in cancer patients *(61–63)*. Perineural invasion appears to be the predominant route of spread to the meninges *(61,64,65)*. In comparison with meningeal dissemination by other solid tumors, spinal cord and spinal nerve root involvement are uncommon. Systemic methotrexate is an active agent against squamous cell carcinomas of the head and

neck, and intrathecal MTX may produce a response in patients with meningeal involvement by this neoplasm. In four patients treated by Redman et al., two patients had significant responses and two had stable disease with a median survival of 10 mo *(61)*. This exceeds the median survival of patients treated for meningeal involvement by breast cancer.

**Parenchymal Brain Metastases** Parenchymal brain metastases are generally hematogenous in origin, and for many cancers are strongly associated with lung involvement *(66,67)*. The lungs are the most frequent site of distant metastases from head and neck cancers. Thus, it is not surprising that the brain is occasionally the site of distant metastasis by SCCHN. In an autopsy study of 2452 patients performed at the Memorial Sloan-Kettering Cancer Center, 3% of all intracranial metastases were observed in patients with SCCHN. In that report, 7 of 118 (6%) SCCHN patients had intracerebral metastases *(66)*. In another postmortem series, brain lesions accounted for 5 of 71 metastatic sites documented in 63 SCCHN patients *(68)*. More recently, brain metastases were detected in 13% of terminally ill SCCHN patients *(69)*. Treatment approaches rely on extrapolation of results obtained with the solid tumors more commonly associated with brain metastases and probably have a similar efficacy. Brain metastases appearing in a patient with SCCHN following a long disease-free interval should raise suspicion regarding a second primary neoplasm.

**Epidural Spinal Cord Compression** Compared to other solid tumors like lung and breast cancer, metastatic dissemination of SCCHN beyond the cervical lymph nodes (10% or less at diagnosis and 30% with advanced disease) is relatively uncommon. Similarly, involvement of the spinal epidural space occurs much less frequently than with many other solid tumors *(68,70)*. The most common sites of distant metastasis in SCCHN are lung and bone, accounting for 50 and 20% of distant sites, respectively *(68,70)*. Approximately 80% of distant metastases are detected within 2 yr of diagnosis of the primary cancer. As spinal epidural metastasis is the sequela of vertebral bone involvement in 80–85% of cases, most studies of epidural metastases include a small percentage of patients with head and neck primaries. In two large studies from the Memorial Sloan-Kettering Cancer Center, 6% had head and neck primaries *(71,72)*. A more recent study found that SCCHN accounted for only 1.5% of all cases of spinal epidural metastasis *(73)*. Conversely, epidural spinal cord compression occurs in only 1% of patient with SCCHN *(74)*. No differences in treatment outcome with cord compression from SCCHN and other tumors have been reported. Given the relative rarity of these metastases, epidural involvement in a head and neck cancer patient without any other evidence of active disease, and particularly if more than 2 yr from the initial diagnosis, should raise the suspicion of a second primary neoplasm.

**Brachial Plexopathy** Involvement of the brachial plexus is occasionally observed in patients with advanced SCCHN, usually in the setting of cervical lymph node involvement with capsular extension and involvement of adjacent tissues. Capsular extension producing truly fixed lymph nodes is rare in nodes smaller than 6 cm *(73)*. In large series, about 7% of patients have truly fixed nodes at diagnosis. The incidence is higher for cancers of the oropharynx and hypopharynx than for other primary sites. However, in 23 surgically treated patients with fixed nodes reported by Stell et al., none had involvement of the brachial plexus *(75)*. Conversely, in two series reported from the Memorial Sloan-Kettering Cancer Center including more than 75 patients with brachial plexopathy due to neoplastic infiltration, 4 patients had head and neck cancers *(76,77)*.

**Syncope and Glossopharyngeal Neuralgia** Glossopharyngeal neuralgia is a rare complication of SCCHN *(78,79)*. As in idiopathic cases, patients complain of lancinating pain in the throat or ear, sometimes triggered by swallowing, coughing, or suctioning. Syncope may accompany both idiopathic and tumor-related glossopharyngeal neuralgia. Probably more common in SCCHN patients is syncope unrelated to glossopharyngeal neuralgia *(80,81)*. This phenomenon occurs almost exclusively in patients with metastatic cervical node involvement, either at diagnosis or more commonly at recurrence. Pain prior to syncope is common, but in many cases the duration, quality, or location of pain is atypical for glossopharyngeal neuralgia. Most patients have bradycardia during most attacks; however, a majority of patients occasionally have hypotension without bradycardia. Moreover, cardiac pacemakers and atropine are only of partial benefit, whereas vasoconstrictors like norepinephrine are useful during an attack *(82)*. Presumably, the causes include tumoral invasion of the carotid sinus, the carotid sinus nerve (nerve of Hering), or the main branch of the glossopharyngeal nerve *(80)*. About half of affected patients will have convulsive jerks as part of the syncopal episode. Carbamazepine, anticholinergics such as atropine, and radiotherapy are all sometimes successful; glossopharyngeal sectioning in refractory cases is reliably successful.

**Paraneoplastic Neurologic Syndromes** SCCHN rarely accounts for neurologic paraneoplastic syndromes. Thymomas may present in the supraclavicular region and are associated with myasthenia gravis (MG) in 50% of cases. One to three percent of glomus tumors secrete catecholamines or histamines, producing headaches among other systemic symptoms. Several head and neck tumors, including squamous cell carcinoma and adenoid cystic carcinoma, are exceptionally associated with inappropriate secretion of antiduretic hormone; the resulting hyponatremia may produce encephalopathy and seizures. Similarly, paraneoplastic hypercalcemia, the most common paraneoplastic syndrome of SCCHN, includes confusion and fatigue among its manifestations *(83)*.

**NEUROLOGICAL SEQUELAE OF SURGERY** Resection of primary head and neck cancers often requires sacrifice of terminal branches of sensory nerves to the face, oral, and nasal cavity (trigeminal nerve), the oropharynx and hypopharynx (glossopharyngeal nerve), or dermatomal branches of the upper cervical nerve roots. The subsequent development of neuropathic pain syndromes can be a major clinical problem. Referred pain involving the ear is another common sequela. Such pain syndromes require careful re-examination and repeated imaging to exclude recurrent tumor, particularly with perineural extension, which is often difficult to demonstrate. Pain syndromes with burning dysesthetic sensations or lancinating pains that appear confined to the territory of a peripheral nerve may be treated with amitriptyline or anticonvulsants such as gabapentin or carbamazepine.

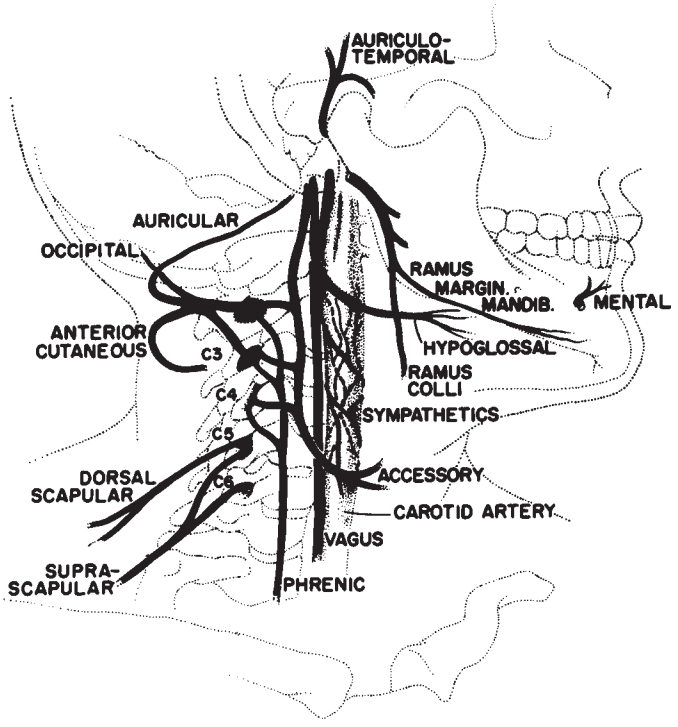


**Fig. 3.** Neural structures in the neck which might be involved by radical neck dissection. Adapted with permission from ref. *85*.

The most characteristic postoperative neurological complications seen in patients with head and neck cancer are those related to neck dissection. The standard radical neck dissection involves removal of the sternocleidomastoid, digastric, and stylohyoid muscles, the internal and external jugular veins, the submaxillary gland, and the spinal accessory nerve. Swift examined 24 pts who had undergone 33 radical neck dissections *(84)*. The accessory nerve, cervical plexus, and supraclavicular nerves were invariably sacrificed. Sympathetic fibers were lesioned in 33% of surgeries, the hypoglossal nerve in 39%, the mandibular branch of the facial nerve in 67%, the vagus nerve in 15%, and the glossopharyngeal and phrenic nerves in 10% (*see* Fig. 3). Vagus nerve lesions led to persistent hoarseness. Most patients admitted to shoulder weakness, although only 24% raised this as a complaint. All patients had shoulder drooping related to accessory nerve sacrifice. Lack of stabilization of the scapula led to apparent deltoid weakness. Although a surprisingly large hypesthetic area could often be demonstrated on examination, only one pt complained of sensory loss (*see* Fig. 4). The greater the surgical manipulation of the carotid sheath, the greater was the postoperative risk of Horner's syndrome. Two-thirds of patients have distortion of the corner of the mouth. Burning dysesthetic pain occurs due to the interruption of the anterior cervical nerve roots with subsequent neuroma formation. This is the most common posttreatment complaint in patients who have undergone radical neck dissection.

Carotid exposure and rupture represent another means of neurological complication from the neck dissection *(86)*. Invasion of the carotid artery by neoplasm is more often seen at the time of recurrence than at initial diagnosis. Many surgeons favor resection of the tumor along with the involved carotid artery. This is accompanied by reconstruction of the vessel. Ligation of the carotid appears to have a higher incidence of cerebrovascular events and a higher mortality than reconstruction.

Carotid artery rupture, often called "carotid blowout," may occur either as a surgical complication in 3–5% of aggressive SCCHN resections or in the setting of postradiotherapy tumor recurrence *(87,88)*. Untreated patients may exsanguinate in as little as 3 min. Mortality of this complication is 40%. Until recently the only therapy was emergency ligation of the common carotid artery or proximal internal carotid artery; major stroke was a common sequela. When patients can be stabilized, the current tendency is to perform an emergency angiogram with balloon test occlusion whenever feasible. Patients tolerating balloon test occlusion undergo permanent balloon occlusion. What to do with patients who fail balloon test occlusion remains problematic *(88)*.

Sacrifice of or injury to the internal jugular vein in neck dissection may adversely affect intracranial pressure. Venous drainage from the brain occurs through the internal jugular veins and internal and external vertebral venous plexuses. Cerebral edema may ensue following simultaneous (more likely) or staged (less likely) radical neck dissections. Symptoms may include facial edema and venous congestion as well as cerebral edema producing seizures and obtundation. These symptoms are often worse with recumbency. Staged operations allow for the intervening development of venous collaterals.

Unilateral neck dissection has also been associated with the development of the syndrome of benign intracranial hypertension, with headache, papilledema, and decreased vision *(89)* through the mechanism of cranial venous obstruction producing dural sinus hypertension. Rarely a hypoplastic contralateral jugular vein or transverse sinus has been implicated *(90)*. Temporizing medical management is generally satisfactory, as patients eventually develop collateral venous circulation ameliorating the condition.

Functional or "conservation" neck dissections in which the sternocleidomastoid muscle, internal jugular vein, and spinal accessory are left intact have gained wide acceptance as the surgical approach to the patient with clinically negative or very limited cervical lymph node involvement *(28)*.

**COMPLICATIONS OF RADIOTHERAPY** Radiotherapy for head and neck cancers typically involves the administration of doses between 55 and 70 Gy in daily fractions of 180–225 cGy to ports that include the primary site and all tissues at risk of involvement. In selected primary sites interstitial implantation may be used. Treatment of hypopharyngeal and laryngeal primaries and patients with advanced nodal disease (i.e., N2 or N3) includes substantial radiation doses to the cervical spine. Bilateral parallel opposed fields are frequently used and generally include 5–15 cm. of the cervical spine. With limited neck disease a single anterior posterior field with a midline block is sometimes used. Field reductions at 45–50 Gy can also be used to limit the dose to the spinal cord depending on the location of the primary neoplasm. Primary tumors in the nasopharynx necessitate inclusion of the base of the skull and frequently portions of the anterior and middle cranial fossa.

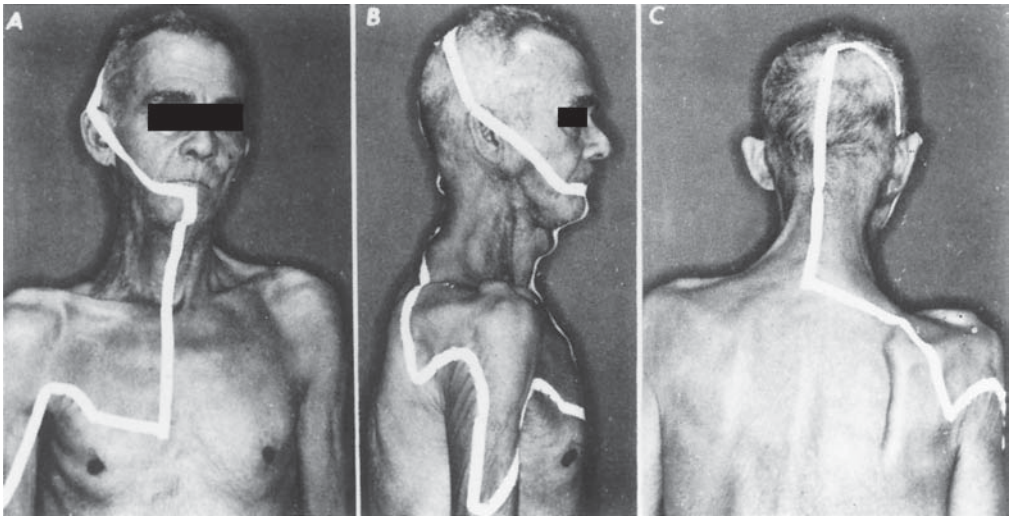


**Fig. 4.** Sensory loss after radical neck dissection. **(A)** Anterior view. Sensory loss extends to the outer boundary of the marking line throughout. **(B)** Lateral view. Sensory loss extends midway down the humerus and to the occiput, including the pinna of the ear. **(C)** Posterior view. Sensory loss extends slightly beyond the midline to the opposite side. Shoulder droop and scapular winging are also clearly seen. Adapted with permission from ref. *85*.

Acute neurologic complications associated with radiotherapy are rare. The major neurotoxicities are categorized temporally as early- and late-delayed radiation toxicities. The most common early-delayed effect is Lhermitte's sign. The incidence of Lhermitte's sign in head and neck cancer patients is about 4% *(91)*. In most patients this is transient, lasting a few weeks. In the absence of pain or other signs of myelopathy, close follow-up is all that is needed. However, occasionally these patients will go on to develop more serious late-delayed sequelae or radiation myelopathy *(91)*.

Late-delayed radiation myelopathy is characterized by small vessel thrombosis with parenchymal necrosis, inflammation, and eventual atrophy of the affected segment. There is subsequent degeneration of the involved nerve-fiber tracts. The latent period following irradiation is usually 6 mo and often more than 1 yr. There is not an absolute relationship between total dose and the likelihood of myelopathy; however, the incidence increases progressively with doses above 5500 cGy. In addition, high-dose fractions (e.g., 300 cGy/fraction) and longer lengths of irradiated spinal cord are associated with an increased risk of radiation myelopathy. The incidence in head and neck cancer patients is probably 0.5–1%, although some series report figures as high as 5% *(91,92)*. Clinical features of radiation myelopathy are discussed in Chapter 14.

Delayed cerebral radionecrosis has been reported following treatment of a variety neoplasms originating in the head and neck region *(93)*. Frontal and temporal masses with evidence of microvascular injury are seen. These lesions behave as progressive space-occupying masses and must be distinguished from malignant gliomas or metastatic tumors.

Cranial neuropathy is a relatively rare sequela of radiation therapy. The latent period to the development of cranial neuropathies is generally greater than 2 yr. This interval is inversely related to the dose of radiation. For patients with SCCHN the twelfth nerve is most commonly affected, followed by the tenth *(94)*. The distinction from recurrent tumor is often difficult and requires serial observations.

Vasculopathy is another important sequela of radiation therapy for head and neck cancers that can result in neurological symptoms. Cerebral radionecrosis largely results from endothelial and small vessel damage. Large vessel injury has also been associated with radiation *(95)*. Carotid stenosis and carotid occlusion have both been reported following radiation, often in the absence of coronary or peripheral vascular disease *(96,97)*. Atherosclerosis following radiation occurs with a long latent period, and thus is not a complication seen with high incidence in the head and neck cancer patients. The frequency of atherosclerotic changes appears to be inversely related to vessel size based on comparisons of intracranial vs extracranial carotid artery disease *(96)*. These changes evolve slowly. The latency to onset of symptoms is up to 4 yr for intracranial carotid disease as compared to 19 yr for extracranial carotid disease *(96)*. Distal carotid stenosis or occlusion following radiation is often associated with the development of a moyamoya-like abnormality.

Despite compelling laboratory and clinical evidence that radiation produces vascular injury, its significance in head and neck cancer patients is unclear. This population has multiple risk factors for atherosclerosis and stroke. Among 52 patients surviving an average of 5.5 yr after treatment for a head and neck cancer reported by Lopez et al., stroke risk factors included: male gender (84%), smoking (92%), hypertension (17%), diabetes (8%), and coronary artery disease (23%). Of those 52 patients, 28 who had received radiation underwent carotid duplex scanning. Five carotid stenoses of 50–75%, and 3 greater than 75% were detected. In six nonirradiated patients, two asymptomatic carotid stenoses of 50–75% were detected. Two of 34 patients studied had symptomatic cerebral ischemia, both of whom had received radiation and had 50–75% stenosis *(98)*. While demonstrating the multiplicity of stroke risk factors

common to head and neck cancer patients, the size of this study is too small to assess the significance of radiation as an added risk factor. These authors do not recommend carotid doppler studies as part of the routine long-term follow-up evaluation of head and neck cancer patients *(98)*.

**NEUROLOGIC TOXICITY FROM CHEMOTHERAPY**

Cisplatinum produces dose-related ototoxicity and peripheral neuropathy. It occasionally causes Lhermitte's sign *(99)*. Chemotherapy protocols for head and neck cancers using cisplatinum rarely achieve the cumulative dose of cisplatinum sufficient to produce a high incidence of peripheral neuropathy (cumulative dose > 400 mg/m$^2$). The incidence of severe ototoxicity is generally less than 5%. Severe neuropathy is reported as 1% or less. Central nervous system (CNS) complication such as radiation myelopathy and cerebral radionecrosis are reported even less commonly in the large randomized trials despite the evidence that cisplatinum and radiation may have synergistic effects in the production of neurotoxicity *(100,101)*. Notably, the concurrent use of cisplatinum/5-FU in moderate doses with radiation resulted in no instances of myelopathy or other CNS complications *(102)*.

The principal neurotoxicity associated with 5-FU is an acute, transient cerebellar syndrome which is seen in 2–7% of patients *(103)*. Less commonly encephalopathy, Parkinsonism, and other neurological syndromes are observed. These problems are most frequent when high doses (e.g., > 1 g/m$^2$) are administered by intravenous bolus. Neurotoxicity is rarely associated with continuous infusion of 5-FU, which is the usual method of administration in SCCHN.

Newer chemotherapeutic agents including paclitaxel and docetaxel have been identified as active drugs for head and neck cancer *(104,105)*. Taxanes may produce peripheral neuropathy, particularly with cumulative administration or in combination with cisplatin *(104,105)*. Several studies have addressed paclitaxel-induced peripheral neuropathy, which is considered to be dose-dependent *(106)*. When paclitaxel was combined with cisplatin, peripheral neuropathy became more frequent and severe, and a significant number of patients developed dose-limiting toxicity *(107)*. Paclitaxel-induced peripheral neuropathy also has been associated with muscle weakness, predominantly affecting proximal muscles *(108)*. Electromyographic studies suggested that distal axonopathy occurred in some patients and proximal denervation in others *(108)*. We investigated a combination of paclitaxel (Taxol), ifosfamide, and cisplatin (TIP regimen) for recurrent head and neck cancer *(44)*. The response and median survival rates were 59% and 9.1 mo, which were quite remarkable for recurrent or metastatic head and neck cancer. However, the TIP regimen had an apparently higher incidence of peripheral neuropathy and fatigue. When cisplatin was replaced with carboplatin in the regimen (TIC), these side effects decreased substantially, and thus TIC was better tolerated in this regard, while the antitumor activities and the survival rates of the TIC regimen were as high as the TIP regimen *(39)*.

## ACKNOWLEDGMENT

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# 31 Neurologic Complications in Children with Systemic Cancer

NUNO LOBO ANTUNES, MD

## INTRODUCTION

Neurologic complications are common in children with cancer. This population is at risk for the neurologic disorders that can affect healthy children, but is also susceptible to central nervous system (CNS) metastases, iatrogenic complications of medical and surgical cancer therapy, and paraneoplastic disorders. With longer survival from more intensive therapies, neurologic complications will probably became even more common. An excellent monograph on the neurologic complications of cancer in adults has been published *(1)*, but neurologic complications in children with cancer differs from those in adults because of the particular susceptibilities of the developing brain and the differences in the types of tumors that affect children and adults *(2)*. This chapter reviews the most common chief complaints resulting in pediatric neuro-oncologic consultation and provides an approach to their assessment.

## HEADACHES

Headache is the most common reason for a neurologic consultation in children with cancer (Table 1). If the neurological examination is abnormal, urgent radiological investigation is mandatory. If the headache is severe enough to justify a consultation but the neurologic examination is normal, the decision to perform an imaging study is more difficult. Unless the cause is obvious, we believe that structural disease must be excluded even in the absence of localizing signs in children being actively treated for cancer and complaining of acute headache, since 15% will have structural disease (Table 2). In 28 children with chronic headaches, none had structural disease and psychogenic factors seemed to be the basis for the complaint in almost half. Structural disease is less common as a cause of acute headache in cancer survivors. In 13 such cases, the neuroradiological studies were negative in all but one, who presented with multiple brain metastases 4 mo after completing her treatment for Ewing's sarcoma.

From: *Cancer Neurology in Clinical Practice* (D. Schiff and P. Y. Wen, eds.), © Humana Press Inc., Totowa, NJ.

## NONSTRUCTURAL CAUSES

Headaches resulting from low intracranial pressure after a lumbar puncture (LP) are common. One prospective study found an 8% incidence of post-LP headache in pediatric oncology patients *(3)*, the frequency in adolescents reaching 50%. The diagnosis is easy if one obtains a history of clear improvement by recumbency. Occasionally low intracranial pressure causes subdural hematomas or hygromas *(4)*. That diagnosis should be suspected when the headache is no longer relieved by assuming the supine position. Magnetic resonance imaging (MRI) of low pressure headache often reveals a diffuse linear dural enhancement, probably resulting from compensatory venous distension that should not be mistaken for metastatic leptomeningeal disease *(5)*. The administration of intrathecal medication does not affect the incidence of post-LP headaches although it may cause nonpostural headaches from chemical meningitis *(6)*. Chemical aseptic meningitis occurs in about 10% of patients that receive intrathecal methotrexate *(1)*. Although polymorphonuclear pleocytosis of the cerebrospinal fluid (CSF) may be present *(7)*, fever, headache, and meningeal signs usually develop 2–4 h after the administration of the drug, helping to distinguish chemical from iatrogenic bacterial meningitis that usually takes at least 24 h to develop *(1)*.

A child with anemia may develop a severe throbbing headache that resolves after a blood transfusion.

Headaches often occur in children with febrile illnesses. Fever-induced headache is not rare in patients with fever and neutropenia but meningitis must also be considered. The marked improvement when the patient becomes afebrile may be a clue to the cause of the headache, but the analgesic effect of most antipyretics may raise questions as to the significance of the improvement. The absence of encephalopathy, or the onset of fever immediately after accessing a central venous catheter, makes meningitis unlikely. In most patients with meningitis, nuchal rigidity is a helpful sign; however, if the

**Table 1**
**Reason for Neurologic Evaluation: 487 Consultations (626 Complaints)[a]**

| *Complaint* | *Number* | |
|---|---|---|
| Headache | 109 | (17%) |
| Acute | 81 | |
| Chronic | 28 | |
| Pain syndromes | 99 | (16%) |
| Back | 37 | |
| Neck | 11 | |
| Upper extremity | 14 | |
| Lower extremity | 27 | |
| Both | 5 | |
| Other locations | 5 | |
| Paroxysmal events | 56 | (9%) |
| Seizures | 36 | |
| Syncope | 4 | |
| Other paroxysmal events | 16 | |
| Motor weakness | 46 | (7%) |
| Hemiparesis | 5 | |
| Upper extremity | 11 | |
| Lower extremity | 30 | |
| Sensory abnormalities | 27 | (4%) |
| Dysesthesias | 13 | |
| Paresthesias | 9 | |
| Numb chin | 3 | |
| Lhermitte's sign | 2 | |
| Altered mental status | 49 | (8%) |
| Somnolence | 19 | |
| Stupor | 18 | |
| Delirium/confusion | 12 | |
| Visual complaints | 42 | (7%) |
| Movement disorders | 15 | (2%) |
| Baseline neurologic evaluations | 21 | (3%) |
| "Dizziness" | 14 | (2%) |
| Urinary retention/incontinence | 14 | (2%) |
| Nausea/vomiting | 9 | (1%) |
| Cord compression? | 8 | (1%) |
| Other complaints | 117 | (19%) |

[a]Included are some adult patients that were diagnosed with cancer before age 21, or had tumors that usually occur in children and were thus being treated by pediatricians.

child is markedly neutropenic the absence of meningeal signs is not reassuring, because the ability to mount the inflammatory response that causes meningeal signs may be impaired. The absence of meningeal signs may also be due to the use of glucocorticoids so common in this population. When in doubt, a LP is indicated. Occasionally the neurologist is called upon to arrange for a computerized tomography scan (CT) or to perform a fundoscopic examination before a LP, as a means of excluding elevated intracranial pressure in a child with the suspicion of meningitis, because of fear of cerebral herniation. The absence of papilledema does not exclude elevated intracranial pressure, and a scan is normal in a third of patients with meningitis who subsequently herniate *(8)*. A LP should be performed immediately when there is a suspicion of meningitis if the patient is awake and without lateralizing signs. Mild CSF pleocytosis and increased protein values in the absence of infection occur in 25–50% of children with acute lymphoblastic leukemia (ALL) months after allogeneic bone marrow transplantation *(9)*, and CSF pleocytosis after intravenous cytarabine has been described *(10)*. In a patient with sepsis and a ventriculo-peritoneal shunt a "shunt tap" is not indicated unless there are good reasons to suspect a CSF infection.

Admission to the hospital often changes life style: adolescents may develop vascular headaches due to caffeine withdrawal when their intake of coffee and other beverages containing caffeine is abruptly curtailed.

In the cancer population antiemetics are used frequently. The administration of the new 5-HT3 antagonists has been associated with headaches in a substantial number of patients.

One-third of children with cancer and acute headache suffer from migraine. That percentage increases further if one looks at the etiology of headaches in children who are long-term survivors of systemic cancers (Table 3).

**STRUCTURAL CAUSES** The most common structural cause of headache in this population is metastatic disease followed by infections like abscess and meningitis. Intracranial hemorrhage and unsuspected primary intracranial tumors are less frequent.

Brain metastases in children with solid tumors differ from those in adults *(11)*: (1) In children, brain metastases do not occur as a form of initial presentation of systemic cancer. (2) They occur in the context of widely disseminated disease. (3) Single metastases from sarcomas are rare. (4) If the primary tumor is chemosensitive, extended survival and even cure may be seen with chemotherapy. In our series intracranial metastases developed in 35 (4.9%) of 709 patients treated for solid tumors. The most common were neuroblastoma followed by rhabdomyosarcoma and Ewing's sarcoma. The median time from diagnosis of systemic cancer to the development of intracranial metastases was 13 mo. Systemic metastases were present in 27 patients (77%) when intracranial metastases were diagnosed. Multiple metastases were present in 19 patients (54%). There are no data to help decide the best approach to a child with brain metastases. If feasible, surgical extirpation followed by whole brain radiation is the traditional approach. The role of radiosurgery for the treatment of pediatric brain metastases has not been explored, although it has been used in the treatment of arteriovenous malformations in children with minimal short term side-effects. In children with sensitive tumors, there may be a place for chemotherapy instead of whole brain radiation. Intraparenchymal metastases from Ewing's sarcoma or rhabdomyosarcomas have a poor prognosis, while metastases from neuroblastoma or systemic germ cell tumors may sometimes be cured. In our experience, metastases from germ cell tumors and sarcomas are frequently hemorrhagic (Fig. 1), and if surgery is planned it should be performed as soon as possible. Radiation to localized skull metastases offers significant palliation, particularly when there is invasion of the base of the skull causing cranial nerve dysfunction (Fig. 2).

Subdural hematomas develop in 9% of patients undergoing intensive chemotherapy for acute myeloid leukemia (AML) *(12)*. They also occur in 10.3% of children who died of ALL *(13)* and in 5% of patients with leukemia following bone marrow transplant. Subdural hematomas were not seen in 198 patients with other malignancies or nonmalignant indications for bone marrow transplant *(14)*. Lumbar puncture may be responsible for this complication, perhaps in combination with coagulation abnormalities or leukemic infiltration of vessel walls.

**Table 2**
**Acute Headaches in Children with Active Cancer: Etiology ($n$ = 69)[a]**

| | |
|---|---|
| *Normal neurologic examination* | ($n$ = 55) |
| Migraine | 21 |
| Tension | 4 |
| Systemic causes | 13 |
| Post-LP | 3 |
| Metastases | 5 |
| CNS infections | 2 |
| Hydrocephalus | 1 |
| Unclear etiology | 4 |
| *Abnormal neurologic examination* | ($n$ = 13) |
| Metastases | 5 |
| Meningitis | 2 |
| Abscess | 2 |
| Hypertensive encephalopathy | 2 |
| "Pressure waves" | 1 |
| Migraine | 1 |

[a]Included are some adult patients that were diagnosed with cancer before age 21, or had tumors that usually occur in children and were thus being treated by pediatricians.

**Table 3**
**Headaches in Children Who Finished Treatment for Systemic Cancer: Etiology[a]**

| | |
|---|---|
| Acute ($n$ = 13) | |
| Migraine | 7 |
| Tension | 4 |
| Metastases | 1 |
| Unclear | 1 |
| Chronic ($n$ =19) | |
| Migraine | 10 |
| Tension | 9 |

[a]Included are some adult patients that were diagnosed with cancer before age 21, or had tumors that usually occur in children and were thus being treated by pediatricians.

Subdural hygromas after bone marrow transplantation were found in 18% of patients followed prospectively with CT scans performed before and 1 mo after transplant. All hygromas resolved without treatment after a median of 60 d after diagnosis *(15)*.

Brain abscesses generally occur in children who are severely immunosuppressed, particularly after bone marrow transplant. Fungi such as *Aspergillus* are frequent pathogens *(16)*. *Aspergillus* infection of the brain usually follows infection of the lungs or paranasal sinuses; it is extremely unusual to culture the organism from the blood. Headaches due to fungal abscesses are often misdiagnosed as "sinusitis" until lateralizing signs became obvious. Sinusitis should never be accepted as an explanation for headaches until other diagnoses have been convincingly excluded.

The MRI appearance of *Aspergillus* abscess is quite variable ranging from a single large lesion to multiple miliary abscesses or lesions indistinguishable from ischemia *(17)*. Enhancement is also variable with some patients presenting with an enlarging mass without ring enhancement. When the lesion is large, small hemorrhages on the periphery reinforce *Aspergillus* as the causative organism (Fig. 3). Surgical aspiration of the abscess will establish the responsible organism; if the patient's condition does not allow surgery, empirical medical therapy that includes an antifungal agent at maximal doses is occasionally successful *(16)*. Lumbar puncture usually does not provide useful information. Glucocorticoids should not be given unless the mass effect threatens survival, since they may impair lymphocytic and fibroblastic responses, delay collagen deposition, and decrease antibiotic efficacy. Prophylactic anticonvulsants are not indicated in patients with either brain metastases or abscesses.

The child with cancer may be immunocompromised due to the underlying malignancy and its therapy. Disruption of the skin and mucosa, foreign bodies, and poor nutrition further increase the risk of infection *(20)*. Because the nature of the immune defect varies, so does the type of infection: patients with lymphoma often have abnormalities of the cellular immune system that increase their risk for viral infections, patients with acute leukemia are most often subject to infection with Gram-negative bacteria as a result of granulocytopenia. There is a lag of at least 1 mo between the introduction of immunosuppressive therapy and the occurrence of opportunistic infections.

Meningo-encephalitis in immunosuppressed children may be caused by unusual opportunistic organisms. Symptoms may be subtle because patients are unable to mount an appropriate inflammatory response. Mild intermittent headaches may be the only complaint for days until a seizure or change in mental status leads to the performance of a lumbar puncture. The mortality in children with meningitis, immunosuppressed to prevent graft rejection approaches 50% *(21)*, and it is possible that a delay in diagnosis is partially to blame.

The neurologist can often help to make an empiric diagnosis as to the responsible organism before the results of the cultures are available; for example, brainstem dysfunction suggests *Listeria* infections *(22)*. MRI abnormalities may be helpful in the diagnosis of viral encephalitis: (1) Varicella-zoster leukoencephalitis usually show clustered subcortical round or plaque-like lesions (a result of rapid demyelination); the active lesions enhance with intravenous administration of contrast medium. Edema and hemorrhage develop as the infection evolves *(23)*. (2) Herpesvirus 6 infection is characterized by multifocal selective involvement of the gray matter *(24)*. (3) Herpes simplex involves one or both temporal lobes frequently with hemorrhagic changes *(25)*. (4) Cytomegalovirus encephalitis causes periventricular enhancement often with ventricular enlargement *(26)*. (5) Progressive multifocal leukoencephalopathy shows decreased attenuation on CT scans and an increased signal on T2-weighted MRI images. The lesions most often involve periventricular and subcortical white matter with rare enhancement and absence of mass effect, although exceptions occur *(27)*.

The neurology consultant is often called upon to give advice regarding the management of complications like secondary hydrocephalus, seizures, or stroke. Hydrocephalus may sometimes be difficult to diagnose when due to metastases from solid cancers, since it may be of sudden onset with only mild

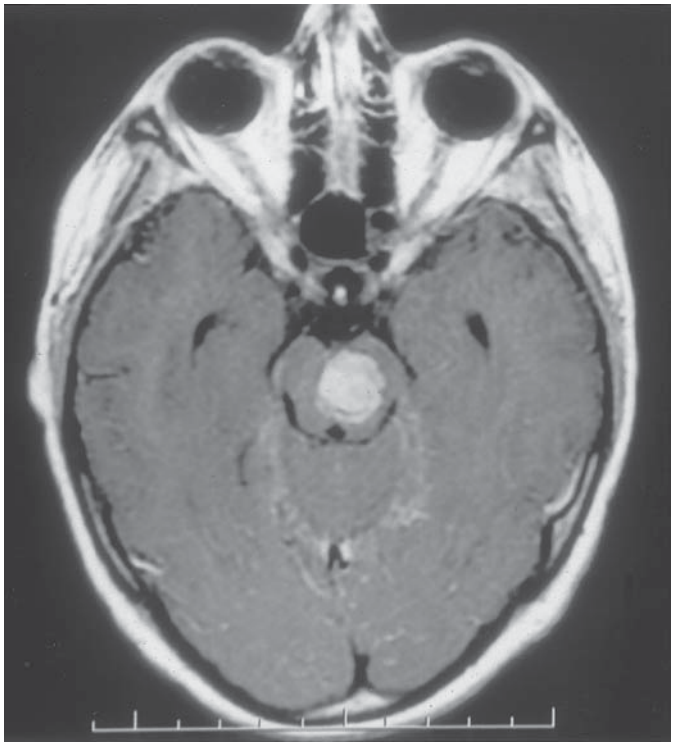

**Fig. 1.** MRI of the brain showing a hemorrhagic metastasis from choriocarcinoma in the mesencephalic region (T1 weighted image after gadolinium injection).

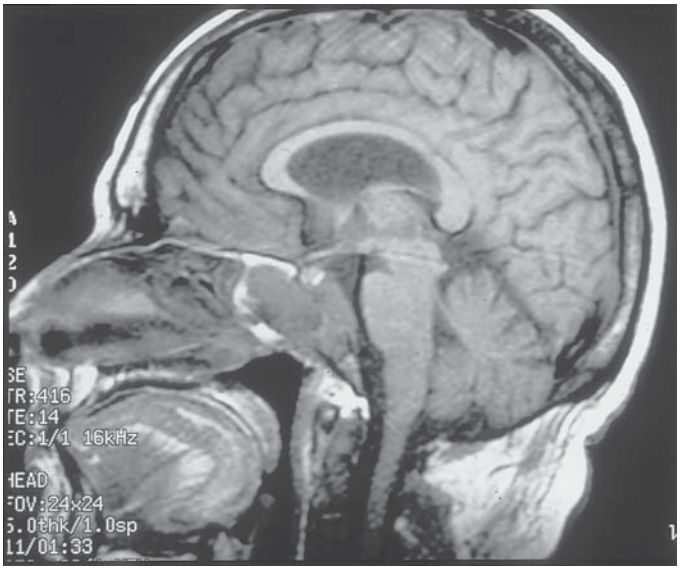


**Fig. 2.** Metastatic involvement of the clivus by Ewing's sarcoma in patient presenting with diplopia and VI nerve palsy.

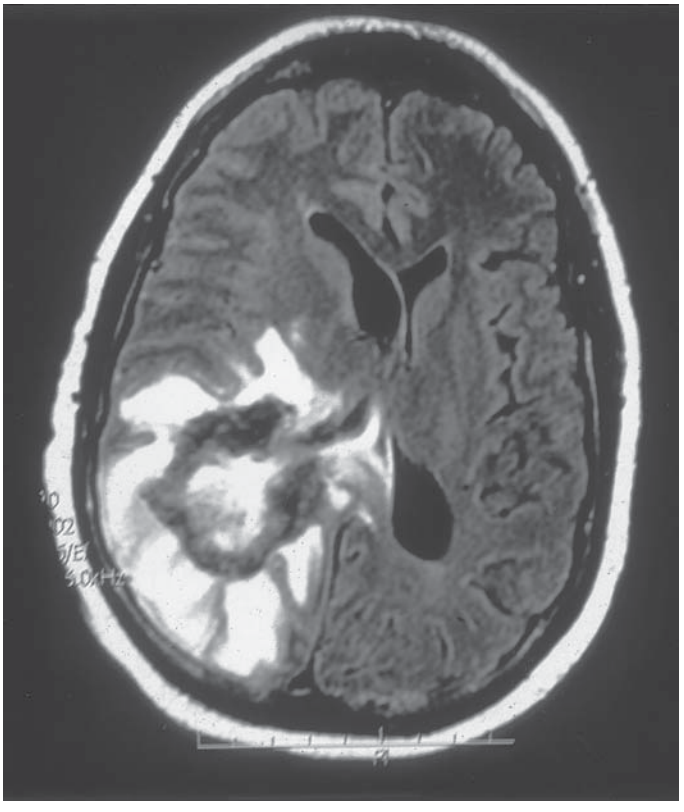

**Fig. 3.** FLAIR image showing the characteristic hemorrhagic ring of an *Aspergillus* abscess.

enlargement of the ventricular system (Fig. 4). Under those circumstances, somnolence rather than headache may dominate the clinical picture. The management of hydrocephalus may be difficult due not only to severe neutropenia and thrombocytopenia but also to the possible development of large subdural hygromas after shunt placement (Fig. 5). Ventriculomegaly in children with leukemia may result from treatment-related leukoencephalopathy as well as from communicating or obstructive hydrocephalus

Headaches in children who previously underwent radiation to the brain or nearby structures may be attributable to the development of a primary brain tumors. Radiation-induced primary brain tumors are defined by the presence of a different histology from the previous cancer occurring after an interval of several years within the radiation field (Fig. 6). Low-dose radiation usually produces extra-axial tumors, particularly meningiomas. Higher doses (>1000 cGy), are more likely to induce intraparenchymal malignant tumors such as gliomas. A 2.3% incidence of second primary brain tumors was found in a cohort of 468 survivors of ALL *(28)* treated with chemotherapy and radiation therapy. It is possible that radiation-induced malignant gliomas have a worse prognosis than those of children with primary gliomas *(29)*. One should have a low threshold for obtaining neuroradiological studies when a patient with a known history of radiation to the brain complaint of headaches of recent onset.

## SEIZURES

Seizures occur in children with: (1) solid tumors, (2) hematologic cancers, (3) bone marrow transplants. Seizures in the absence of a mass lesion occur in 8–10% of children with leukemia and lymphoma *(30,31)* or after bone marrow transplant. Our experience with 36 children with cancer who developed seizures is shown in Table 4. Neurologic conditions such as mental retardation antedating new onset seizures in a child with leukemia increase the risk for chronic seizure disorder, while children with normal development and neurologic examination usually have isolated seizures and do not require long-term treatment. After bone marrow transplant approx 10% of

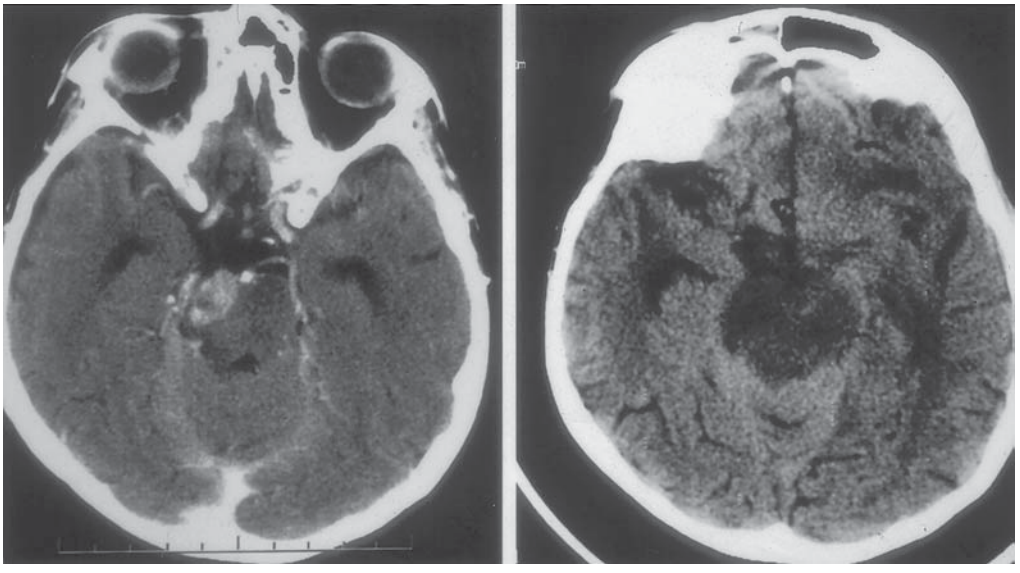

**Fig. 4.** Acute obstructive hydrocephalus from an extra-parenchymal metastasis from rhabdomyosarcoma (left). A follow-up CT scan shows brainstem ischemia and generalized atrophy (right).

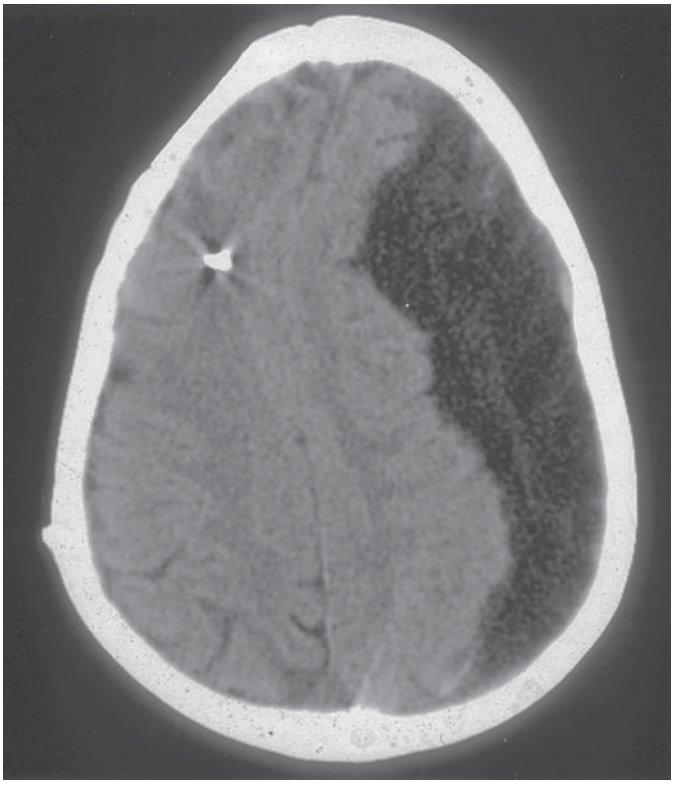

**Fig. 5.** Large subdural hygroma after a ventriculo-peritoneal shunt placement in a child with leukemia and leukoencephalopathy.

patients have seizures, and one-third of these will develop epilepsy.

The emergency treatment of an acute seizure is the same as in children without cancer. Electrolyte abnormalities, drug-related seizures (imipenem, cyclosporine) *(32)*, and structural causes from infectious to metastatic are common. Thus the child with cancer and and new onset of seizures often requires a thorough metabolic work-up, neuroradiological studies, and LP. However, because only a minority of such patients will develop a chronic seizure disorder, anticonvulsants are unnecessary if no underlying neurological abnormality is found and the seizure seems related to an acute event that might be avoided in the future. The many pharmacologic interactions between phenytoin (usually the drug of choice to treat the acute seizure) and medications used to treat cancer or to provide supportive care are one impetus to eschew prolonged anticonvulsant use. It is often difficult to maintain adequate serum levels of phenytoin in patients who receive other drugs that induce liver enzymes, or that interfere with the absorption or protein-binding of the phenytoin. Under these circumstances the measurement of the free fraction may be useful. Phenytoin affects the serum levels of other important medications as cyclosporine and paclitaxel *(33,34)*. Phenytoin may also complicate management due to the relatively high risk of allergic rash (it may be difficult to pinpoint the responsible agent on a child taking multiple drugs) as well as drug fever *(35)*.

Seizures sometimes occur in patients on cyclosporine therapy, the so-called reversible posterior encephalopathy or cyclosporine-associated encephalopathy *(37)*. The pathophysiology of this disorder is unclear, and cyclosporine-associated encephalopathy has been related to hypocholesterolemia, hypomagnesemia, and high levels of cyclosporine *(38)*. Although cyclosporine is known to induce neuronal apoptosis and selective oligodendrocyte death in cortical cultures *(39)*, the selective involvement of the structures perfused by the posterior circulation (Fig. 7) and the usually rapid reversibility of symptoms point to a loss of vasculoregulatory control of the vertebrobasilar system *(40)*, known to have a relatively sparse sympathetic innervation. Many patients have a significant concomitant elevation of the blood pressure *(41)*, and we believe that adequate correction of the blood pressure abnormalities is a fundamental, if not the most important aspect of treating these children. Rarely, irreversible lesions may develop *(42)*. Diffusion-weighted MRI may be helpful in showing a tissue stage of permanent brain injury. A similar syndrome has been associated

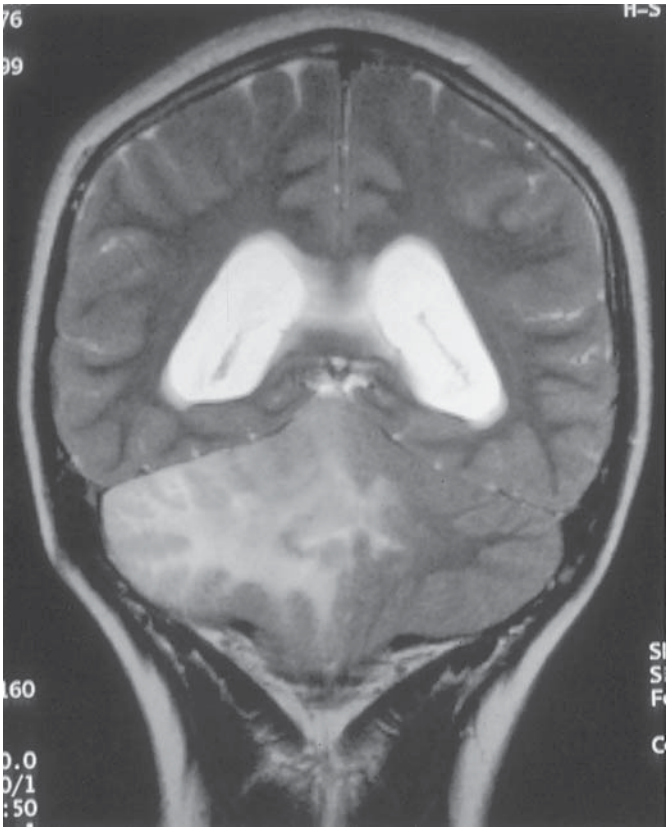

**Fig 6.** Large right cerebellar anaplastic astrocytoma resulting in obstructive hydrocephalus (T2-weighted MR scan). The patient had undergone radiotherapy for a nasopharyngeal rhabdomyosarcoma 18 yr prior to the diagnosis of the current tumor.

with tacrolimus, another immunosuppressant *(43)*. The majority of children with cancer and a seizure related to cyclosporine/hypertension do not require long-term anticonvulsants as long as hypertension is under good control. A recent study found the electroencephalogram to be useful in predicting which patients have a high risk of seizure recurrence *(44)*.

Many bone marrow transplant protocols utilize "prophylactic" anticonvulsants (phenytoin, clonazepam) at the time of high dose chemotherapy (e.g., busulfan) *(45)*; to our knowledge, the effectiveness of this approach has never been documented in a randomized study, and it is possible that phenytoin may alter busulfan pharmacokinetics and pharmacodynamics. Seizures related to chemotherapy are well-known. A retrospective study of 17 patients with leukemia and seizures found that 16 were receiving antileukemic treatment and related the convulsions particularly to methotrexate and L-asparaginase, but many other chemotherapeutic agents have been associated with seizures *(46–49)*.

DiMario and Packer reported 45 children with systemic cancer and seizures who had an identifiable etiology: metastatic disease was the most frequent cause followed by metabolic disturbances, coagulopathy, infarction, hypertension, leukoencephalopathy, medications, infection, and secondary brain tumors *(50)*.

## BACK PAIN

Back pain, the most common reason for neurologic consultation in adults with cancer, is also common in children. Metastatic disease from solid tumors or leukemic expansion of the vertebrae is common; other causes include osteomyelitis, epidural hematoma after lumbar puncture, and referred pain from bowel obstruction, retroperitoneal tumor, or pleural effusion. Pain presumably of musculoskeletal origin was found in 25% of our patients. Pain induced by drugs, particularly Vincristine and G-CSF, may be quite severe and simulate more serious conditions *(51–53)*.

Back pain in any child must be taken seriously *(54)*, particularly so in children with cancer because metastatic disease, potentially leading or associated with spinal cord compression, is the cause in about 50% (Tables 5 and 6). Spinal cord compression in children differs in several ways from that in adults. Firstly, the prognosis is better in children. One series reported that 50% of the children that presented with paraparesis ultimately recovered independent ambulation *(55)*. Complete paraplegia for more than 2 wk can resolve to the point of independent ambulation (Fig. 8). The rate at which weakness develops is more important than the degree of impairment: children who develop the paraparesis slowly recover better than when the deficit evolves rapidly. Secondly, the underlying tumor type differs: neuroblastoma, sarcomas, and lymphomas are common in children while breast, lung, and prostate are common in adults. In one series of 21 patients with cord compression *(55)*, sarcomas were the most common underlying cancer (12 patients) followed by neuroblastoma (5) and lymphoma (3). Thirdly, the therapy of cord compression is also different *(56–58)*. Whereas radiotherapy is the first treatment for most adults with cord compression, chemotherapy is often the initial treatment for pediatric cord compression from lymphoma, germinoma, and stage IV neuroblastoma. Surgery is the initial treatment in unknown primary tumors, evolving neurologic deficit while on chemotherapy, or rapidly developing neurologic deficit. Posterior decompressive laminectomy is the usual procedure. Late development of spinal deformities is a complication of this procedure, depending on the age of the patient and the extent and level of laminectomy. Spinal deformities occur more frequently in young children, when the cervical spine is involved and when multi-level surgery is necessary. At Memorial Hospital surgery is also the preferred treatment for loco-regional neuroblastoma. Lastly, the mechanism of cord compression in adults is usually from epidural extension of a vertebral body metastasis; in children invasion of the vertebral canal through the intervertebral foramina by a paraspinal mass is the most frequent mechanism (Fig. 9).

A child with spinal cord compression should receive dexamethasone. Adults receive 16 mg as an intravenous bolus followed by 4 mg q.i.d.; with severe pain a 100 mg bolus is sometimes recommended *(1)*. It is unclear if the "megadose" of steroids offers any advantage although it may provide better pain relief *(59)*. The ideal pediatric dose has not been established, but 0.5–0.75 mg /kg/d seems reasonable, using the "low" adult dose (16 mg/d) for children weighing more than 20 kg.

## ALTERED MENTAL STATUS AND COGNITIVE DEFICITS

Stupor and delirium are common in adults with cancer. In contrast, these are uncommon reasons for pediatric neuro-

**Table 4**
**Seizures in Children with Systemic Cancer**
**(Patients = 36)[a]**

| *Underlying cancer* | | *Etiology* | |
|---|---|---|---|
| *Hematologic cancer (23)* | | | |
| Acute Lymphocytic Leukemia | 14 | Nonstructural | 8 |
| Acute Myelocytic Leukemia | 2 | Hypertension/cyclosporin | 5 |
| Chronic Myelocytic Leukemia | 2 | CNS infections | 1 |
| Non-Hodgkin Lymphoma | 2 | Leukoencephalopathy | 5 |
| Other hematologic diseases | 3 | Other | 4 |
| *Solid cancers (13)* | | | |
| Neuroblastoma | 7 | Nonstructural causes | 7 |
| Retinoblastoma | 2 | Metastases | 5 |
| Fibrosarcoma | 1 | Hypertension/cyclosporine | 1 |
| Leiomyosarcoma | 1 | | |
| Rhabdoid Tumor | 1 | | |
| Lymphangioma | 1 | | |

[a]One patient with leukemia also had lymphoma. Included are some adult patients that were diagnosed with cancer before age 21, or had tumors that usually occur in children and were thus being treated by pediatricians.

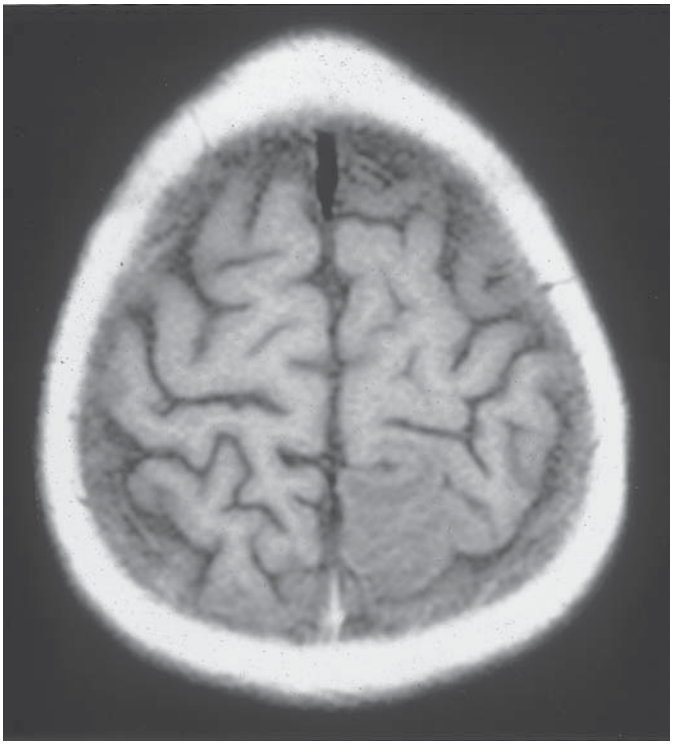

**Fig. 7.** Signal changes in the left occipital lobe of a patient with cyclosporine/hypertensive encephalopathy. Although often bilateral it is not uncommon for the MRI changes to be asymmetric.

oncology consultation. In our pediatric department, after excluding post-ictal states, fewer than 10% of consultations were for stupor/delirium. We found that about 75% of delirious or stuporous children suffer from metabolic-toxic encephalopathy while the rest have an underlying structural disease (Tables 7 and 8). The distinction between the two etiologic categories is not easy because metabolic disorders may present with lateralizing signs (e.g., hypoglycemia) while structural disease in "silent" areas of the brain or multifocal in nature (e.g., meningitis) may be indistinguishable from a toxic-metabolic encephalopathy. In every child presenting with an altered mental state, neuroimaging studies and CSF evaluation should be considered in addition to a "metabolic work-up," particularly when headaches, lateralizing signs, neck stiffness, or progressive nonfluctuating deterioration in mental status are present. Conversely, asterixis, marked diurnal variations of alertness, or hallucinations make a toxic-metabolic encephalopathy more likely. The cause of delirium in severely immunosuppressed patients, particularly following bone marrow transplant, is often difficult to identify; patients are commonly receiving several potential offending medications. Moreover, CNS infection in immunosuppressed patients may cause only a limited inflammatory response, and leukoencephalopathy from prior chemotherapy often limits "cerebral reserve" and makes the child more sensitive to a metabolic/toxic insult.

Drugs, particularly opioids, are the most frequent cause of delirium or stupor in our population. Myoclonus, blurred vision, and difficulty initiating micturition may accompany the delirium. Other drugs include steroids *(60)*, benzodiazepines *(61)*, H2 blockers *(62)*, antihistaminics *(63)*, antibiotics *(64)*, and acyclovir *(65)*. Although drug intoxication usually causes quiet delirium in children, atropine given during anesthesia may cause extreme agitation. Some chemotherapeutic agents that cause delirium are ifosfamide *(66)* and high-dose thiotepa *(67)*. Ifosfamide toxicity may be related to the formation of chloracetaldehyde and may be improved by methylene blue, although our experience has not been convincing *(68)*. Hallucinations associated with ifosfamide are usually frightening or disturbing and occur when the patient has eyes closed. Progressive brain atrophy with cessation of cranial growth has also been described in an infant *(69)*. High-dose thiotepa is associated with somnolence and confusion, exacerbated by the utilization of opioids for severe mucositis. An acute or subacute encephalopathy, sometimes irreversible, has been described with amphotericin B *(70)*. Neuroimaging studies show diffuse nonenhancing abnormalities of the white matter due to a noninflammatory leukoencephalopathy *(71)*.

**Table 5**
**Back Pain in Children with Systemic Cancer**
**($n$ = 48)[a]**

| *Underlying cancer* | | *Etiology* | |
|---|---|---|---|
| *Hematologic cancer (17)* | | | |
| ALL | 5 | Muscle/Skeletal | 7 |
| Hodgkin's | 6 | Metastases/Recurrence | 5 |
| NHL | 4 | Infections | 2 |
| Other | 2 | Other | 3 |
| *Solid cancer (31)* | | | |
| Ewing's Sarcoma | 14 | Muscle/Skeletal | 5 |
| Neuroblastoma | 7 | Metastases/Recurrence | 20 |
| Osteosarcoma | 4 | Infections | 1 |
| Desmoplastic | 3 | Other | 5 |
| Other | 3 | | |

[a]Included are some adult patients that were diagnosed with cancer before age 21, or had tumors that usually occur in children and were thus being treated by pediatricians.

**Table 6**
**Cord Compression/Epidural Disease**
**Underlying Cancer ($n$ = 23)[a]**

| | |
|---|---|
| Neuroblastoma | 10 |
| Ewing's sarcoma | 5 |
| Osteosarcoma | 3 |
| Non-Hodgkin's lymphoma | 1 |
| Melanoma | 1 |
| Rhabdomyosarcoma | 1 |
| Teratoma | 1 |

[a]Included are some adult patients that were diagnosed with cancer before age 21, or had tumors that usually occur in children and were thus being treated by pediatricians.

Organ failure as a major factor contributing to delirium is less common in children than adults. However, sepsis and electrolyte imbalance in our population often contribute to an altered mental status. In some children the sudden onset of stupor due to sepsis precedes the development of fever and other signs of infection by a few hours *(72)*. We have encountered three such cases.

Two unusual conditions must be kept in mind when discussing the differential diagnosis of a child with cancer and stupor: thiamine deficiency (Wernicke's encephalopathy), and hyperammonemic encephalopathy after chemotherapy. Both conditions are usually seen after bone marrow transplant; the first, in malnourished children often with protracted vomiting, is associated with ataxia and eye movement abnormalities *(73,74)*. The MR scan may show abnormal signal in the thalami, mammillary bodies, and periaqueductal gray matter. The cause of hyperammonemia associated with bone marrow transplant is obscure. Although these patients often have normal liver function testing, the condition may be suspected clinically by the presence of unexplained hyperventilation *(75)*. Dialysis and treatment with sodium benzoate and sodium phenylacetate should be instituted promptly *(76)*.

When structural disease is found, CNS infection and metastatic disease are frequent culprits. In our series, unsuspected hydrocephalus due to one of the aforementioned conditions was also found. Usually described in adults, thrombotic microangiopathy may be the explanation for an encephalopathy with fleeting neurologic signs *(77)*. This complication has been associated with the use of chemotherapeutic agents including cisplatin and carboplatin.

The deleterious long-term effects on the nervous system of whole brain radiation and intrathecal chemotherapy are some of the most feared consequences of the treatment of CNS leukemia. The literature on radiation-induced cognitive dysfunction, although extensive, is fraught with methodological problems. It seems certain, however, that the dose of radiation, the age of the child, and the addition of intrathecal methotrexate are relevant factors to cognitive outcome. Prospective studies involving children who received as little as 1800 cGy of craniospinal irradiation and intrathecal drugs showed a significant decline in cognitive functioning at 4–5-yr follow-up period *(78)*. Children treated at a young age for ALL with cranial irradiation and chemotherapy demonstrate poor subsequent scholastic performance when compared to their siblings *(79)*, perhaps due more to inattention and poor memory than low intellectual level *(80)*. Cognitive deficits seem to be particularly pronounced when radiation is given before age 7 *(81)*. White matter changes that may evolve into generalized atrophy with dystrophic calcifications particularly in the basal ganglia and gray-white matter interface are seen on neuroradiological studies. MRI is more sensitive than CT in demonstrating treatment-related neurologic damage *(82)*. It seems clear that the addition of intrathecal methotrexate (MTX) increases neurotoxicity, particularly when given after CNS radiation *(83)*. The combination of intravenous and intrathecal methotrexate without radiation has also been associated with encephalopathy *(84)*. MRI abnormalities involving signal changes in the white matter are not rare in patients receiving intrathecal methotrexate. The clinical relevance of those changes has not been clearly established, as some are reversible and do not correlate well with neuropsychological functioning or academic achievement *(85)*.

## MOTOR ABNORMALITIES

Two forms of weakness are common in children with cancer: hemiparesis and leg weakness either unilateral or bilateral.

**HEMIPARESIS** The majority of children with solid cancers who present with a hemiparesis have metastatic disease. Other structural diseases of the brain that cause a hemiparesis are abscess, cerebrovascular occlusion, and intracranial hemorrhage. Nonstructural etiologies include migraine, conversion reactions, and transient hemiparesis related to methotrexate *(86,87)*.

Arterial ischemic stroke in children with cancer is rare *(88)*. It can occur from direct damage to the vessel wall from meningitis, leptomeningeal metastatic disease, radiotherapy, or cardiac emboli from cardiomyopathy or marantic endocarditis. L-asparaginase causes cerebrovascular events, particularly thrombosis of the superior sagittal sinus, probably related to a reduction in the production of coagulation inhibitor factors such as anti-thrombin III and protein C and S *(89,90)*. Dural sinus thrombosis occasionally occurs during maintenance treatment for ALL *(91,92)*, or the initial phase of therapy for non-Hodgkin lymphoma without L-asparaginase, or its synthetic congener

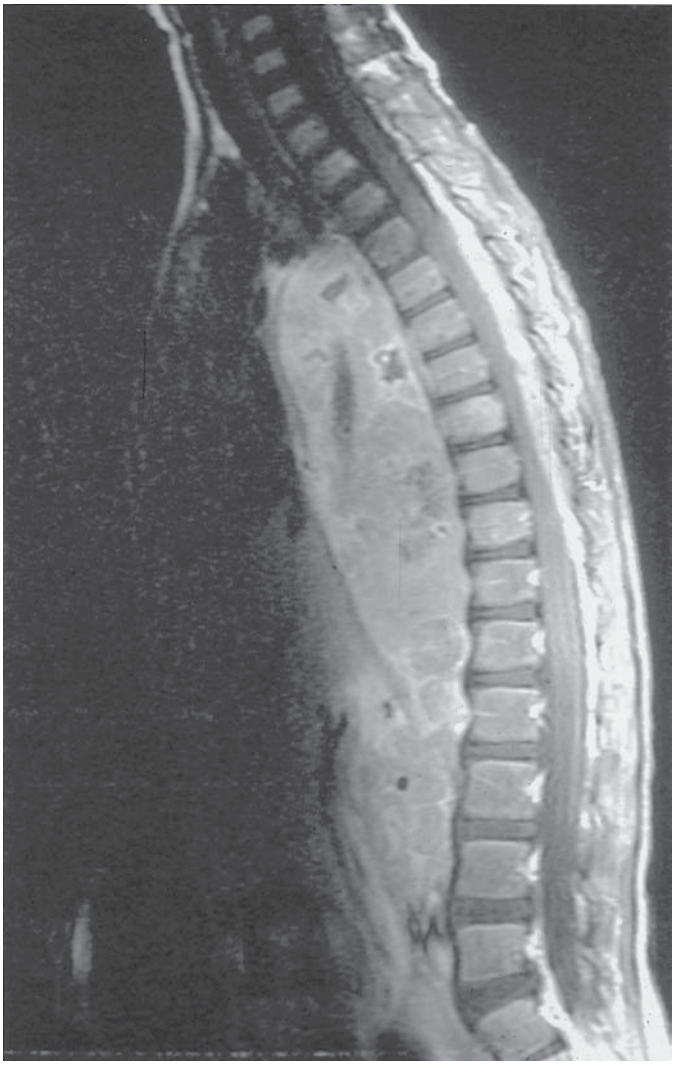

**Fig. 8.** Large neuroblastoma, placed anteriorly to the spine, invading the spinal canal and causing severe cord compression. This girl was paraplegic for 2 wk but recovered independent ambulation after treatment with chemotherapy and surgery.

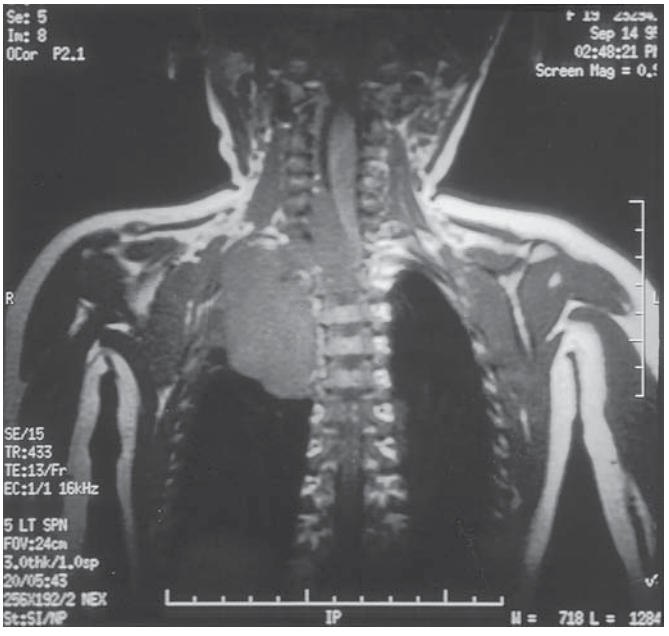


**Fig. 9.** Paraspinal neuroblastoma invading the spinal canal through the intervertebral foramina and causing cord compression.

pegaspargase *(93)*. The clinical presentation is generally seizures or hemiparesis, although pseudotumor cerebri is also a known consequence of superior sagittal sinus thrombosis. The most common radiological picture is one of hemorrhagic infarction usually posteriorly located and involving the gray matter (Fig. 10). A magnetic resonance venogram establishes the diagnosis that may have been suspected on a CT scan by the presence of a filling defect on the area of the sagittal sinus ("empty delta sign") *(94)*. The prognosis is usually good even without specific treatment, although heparin and transfusion of fresh frozen plasma have been suggested *(95)*. Direct compression by tumor particularly neuroblastoma or lymphoma may occlude the sagittal sinus *(96)*.

Intracerebral hemorrhage may complicate: (1) platelet counts below $20{,}000 \times 10^{-9}$/mL; (2) promyelocytic leukemia with its associated coagulation abnormalities *(97)*; (3) invasion of the vessel wall by leukemic cells *(98)*; (4) the development of cavernous angiomas after cranial radiation. The incidence of cavernous angiomas after cranial radiation for the treatment of CNS leukemia is unknown. Using the MRI technique known as reverse echo we have been impressed by its frequent occurrence and the multiplicity of the lesions (Fig. 11). They can present with recurrent localized headaches, possibly the result of rebleeding, or with seizures or focal signs. One of our patients developed acute deafness due to a hemorrhage resulting from a brainstem radiation-induced cavernous angioma. A few patients have had acute bleeds after taking medications (e.g., aspirin), that affect coagulation.

Chronic subdural hematomas are found at necropsy in 10% of children with ALL *(13)*. Some are caused by thrombocytopenia, intracranial hypotension, or trauma but in others no cause is found. Subdural hematoma also complicates acute myeloid leukemia with a monoblastic component *(99)*, and a 5% incidence after bone marrow transplant for leukemia has been reported *(14,100)*.

The incidence of transient neurological deficits including weakness and visual loss seems to be increased in patients with cancer, particularly with Hodgkin's disease *(101)*. Transient hemiparesis or other lateralizing signs may complicate high-dose MXT therapy. This usually occurs in the initial phases of treatment. Originally described in patients with osteosarcoma treated with high-dose MXT *(102)*, hemiparesis has been seen in patients with other malignancies and with different methotrexate regimens *(103)*. The pathophysiology is unclear although it is possibly related to the effects of homocysteine on the vessel wall *(104)* causing endothelial cell injury due to oxidative stress; tumor emboli or transient demyelination have also been proposed as possible mechanisms *(105)*. The onset is characterized by sudden weakness, often alternating sides, and confusion. The signs usually clear in 48–72 h. Neuroradiological studies are usually unremarkable. Of interest, many patients have tolerated the reintroduction of the drug.

**Table 7**
**Somnolence/Stupor in Children with Systemic Cancer**
**(Patients = 37)[a]**

| *Underlying cancer* | | *Etiology* | | | |
|---|---|---|---|---|---|
| *Hematologic cancers (23)* | | | | | |
| Acute lymphocytic leukemia | 15 | Toxic-metabolic | 14 | CNS recurrence | 1 |
| Acute myelocytic leukemia | 3 | CNS infections | 2 | Hydrocephalus | 1 |
| Chronic myelocytic leukemia | 1 | Subdural collections | 2 | Hyperviscosity | 1 |
| Other hematologic diseases | 4 | Strokes | 2 | | |
| *Solid cancers (14)* | | | | | |
| Neuroblastoma | 6 | Toxic-metabolic | 10 | | |
| Retinoblastoma | 3 | Metastases | 2 | | |
| Teratoma | 2 | Hydrocephalus | 1 | | |
| Other | 3 | Concussion | 1 | | |

[a]Included are some adult patients that were diagnosed with cancer before age 21, or had tumors that usually occur in children and were thus being treated by pediatricians.

**Table 8**
**Delirium/Confusion in Children with Systemic Cancer**
**(Patients = 13)[a]**

| *Underlying cancer* | | *Etiology* | |
|---|---|---|---|
| *Hematologic cancers (5)* | | | |
| Acute lymphocytic leukemia | 4 | Intoxication | 4 (opioid) |
| Non-Hodgkin's lymphoma | 1 | Psychogenic | 1 |
| *Solid cancers (8)* | | | |
| Osteosarcoma | 4 | Intoxication[b] | 7 |
| Rhabdoid | 1 | Psychogenic | 1 |
| Desmoplastic small cell | 1 | | |
| Teratoma | 1 | | |
| Ewing sarcoma | 1 | | |

[a]Included are some adult patients that were diagnosed with cancer before age 21, or had tumors that usually occur in children and were thus being treated by pediatricians.
[b]Opioids, diphenhydramine, thiotepa, atropine.

Complicated migraine-like episodes have been described following cranial irradiation and chemotherapy *(106)*. Although reported in children treated for intracranial tumors, they may occur in children with other forms of cancer who have undergone similar therapy. Conversion disorder manifested as a motor deficit is a rare occurrence in this population.

**PARAPARESIS** Progressive weakness of one or both legs with sparing of the arms is usually the result of metastatic disease involving the spinal cord, cauda equina, or lumbosacral plexus. Cord compression may result from non-neoplastic causes such as spinal epidural hematoma (usually related to LP *[107]*), abscess or empyema, or epidural lipomatosis in patients treated with steroids *(108)*. Other causes include steroid myopathy, spinal cord abscess, and treatment-related myelitis.

It is recommended that a LP not be performed with a platelet count below 20,000 and preferably below 50,000 *(109)* unless absolutely necessary (e.g., bacterial meningitis), in which case the LP should be performed while platelets are being transfused *(110)*. The risk is the development of a spinal epidural hematoma with back pain followed by leg weakness. Relatively small epidural hematomas are probably not rare in patients without coagulopathies who undergo LP and complain afterwards of severe back pain. In children with cancer the hemostatic abnormalities may allow these collections to grow further. Surgical treatment is difficult because of the thrombocytopenia, but may become necessary if weakness develops or progresses despite platelet transfusions. Spontaneous epidural hematomas have been reported *(111)*.

Infection of the spinal epidural space may complicate placement of an epidural catheter for treatment of pain *(112)*. The disorder may also follow osteomyelitis of the vertebrae of bacterial or fungal origin *(113)*. Symptoms consist of severe back pain and fever followed by signs of cord compression. A combination of surgical evacuation followed by antibiotic treatment is the usual approach, although successful treatment with medical therapy alone has been reported *(114)*.

Spinal epidural lipomatosis is rare in the pediatric population but has been described in children treated with glucocorticoids for prolonged periods of time *(115)*. Much more commonly steroids often cause severe leg weakness from myopathy. The child often complains of difficulty climbing stairs and rising from a low sitting position such as the toilet or couch without using his or her arms. The diagnosis is usually easy when weakness is demonstrated in other proximal seg-

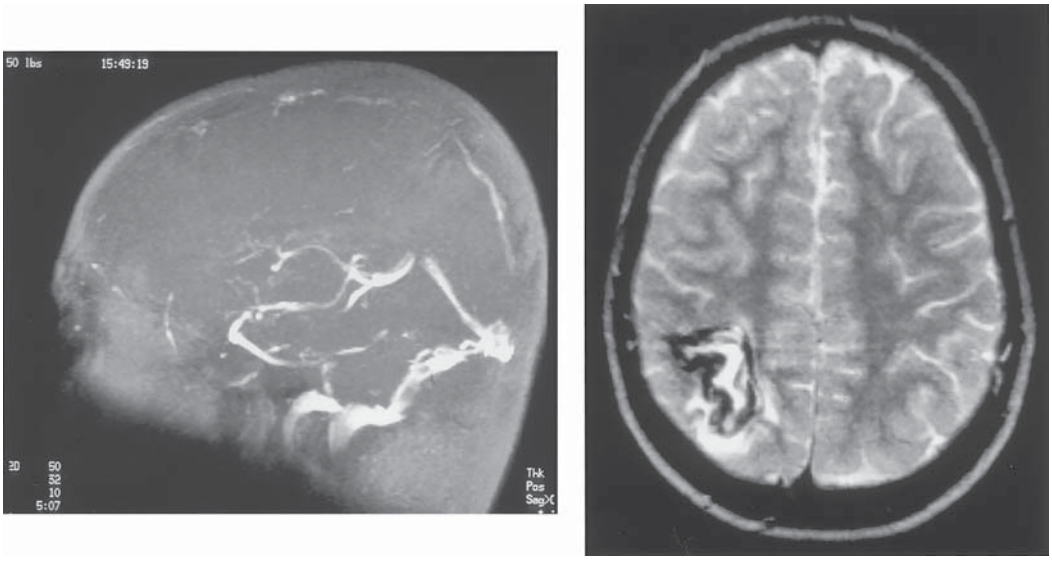


**Fig. 10.** MRI showing the typical posteriorly located hemorrhagic infarct associated with superior sagittal sinus thrombosis (right). An MRV confirmed the thrombosis on this patient being treated with L-Asparaginase (left).

**Table 9**
**Visual Complaints in Children with Systemic Cancer ($n$ = 42)[a]**

| *Complaint* | | *Etiology* | |
|---|---|---|---|
| "Blurred vision" | 7 | Toxic | 12 |
| Decreased vision | 3 | Metastatic | 11 |
| Diplopia | 4 | Stroke | 4 |
| Strabismus | 2 | Migraine | 3 |
| Anisocoria | 4 | Physiologic anisocoria | 3 |
| Ptosis | 4 | Other | 9 |
| Horner's | 2 | | |
| Proptosis | 3 | | |
| Eye pain | 2 | | |
| Other | 11 | | |

[a]Included are some adult patients that were diagnosed with cancer before age 21, or had tumors that usually occur in children and were thus being treated by pediatricians.

ments, particularly neck flexor muscles. Weakness of the neck muscles may also develop years after mantle radiation for Hodgkin's disease. The muscle atrophy may be quite striking and has been attributed to motor neuronopathy associated with vascular disease.

Acute myelopathy is a feared complication of intrathecal chemotherapy. Patients may have received either or both methotrexate and Ara-C therapy *(116)*. Clinically the patient presents with back pain followed by signs of transverse myelopathy, usually within 48 h of injection but occasionally up to 2 wk later. Some patients recover, but most do not. It is possible that the prognosis is better for the early onset cases; no effective treatment is available. Some reports suggest that at least on occasion there is an elevation of the myelin basic protein before development of paraplegia *(117)*. Demyelination is an important component of the pathologic findings in the cases brought to autopsy *(118)*. Rarely, acute myelopathy may ascend to cause an encephalopathy, which may be severe, irreversible, and fatal *(119)*. An anterior lumbosacral radiculopathy, presenting with flaccid paraparesis without sensory deficits, has also been described following intrathecal chemotherapy *(120)*. MRI of the spine in such cases may show enhancement of the nerve roots of the cauda equina, and treatment with methylprednisone has been suggested. Myelopathy may also be caused by radiation or the interaction between radiation and the sensitizing effects of some chemotherapy agents *(121)*. The disorder is uncommon in children, but we have seen such a case.

Leptomeningeal disease may produce a cauda equina syndrome resulting in leg weakness as well as numbness and incontinence. Outside of leukemia and primary brain tumors, leptomeningeal disease in children is primarily seen in patients with parenchymal brain metastases. Findings of multifocal, multilevel CNS dysfunction (e.g., the combination of cranial neuropathy and nerve root dysfunction) suggest the diagnosis. The adult experience teaches us that the reliability of the CSF cytology depends on the volume of CSF examined as well as how fast the sample is processed *(1)*.

Leg weakness may be attributable to polyneuropathy. Vincristine is the most common pediatric etiologic agent. Children complain of dysesthesias in the fingertips and later the toes followed by bilateral wrist and foot drop. The hand weakness is more bothersome to a child because it interferes with proficiency in computer games. Bilateral ptosis, often subtle, is common, and the voice may become hoarse. Although one may be tempted to advise the use of high top sneakers as a means to provide support to the ankle, we have found that they are too heavy to be useful; light shoes are better tolerated. We have been impressed by the number of children who are survivors of cancer who complain of subtle motor dysfunction years after treatment. One may speculate that this is due to irreversible long-term effects of some chemotherapeutic agents. Vincristine seems to cause longstanding axonal injury throughout the nervous system and demyelination within the spinal cord *(122)*.

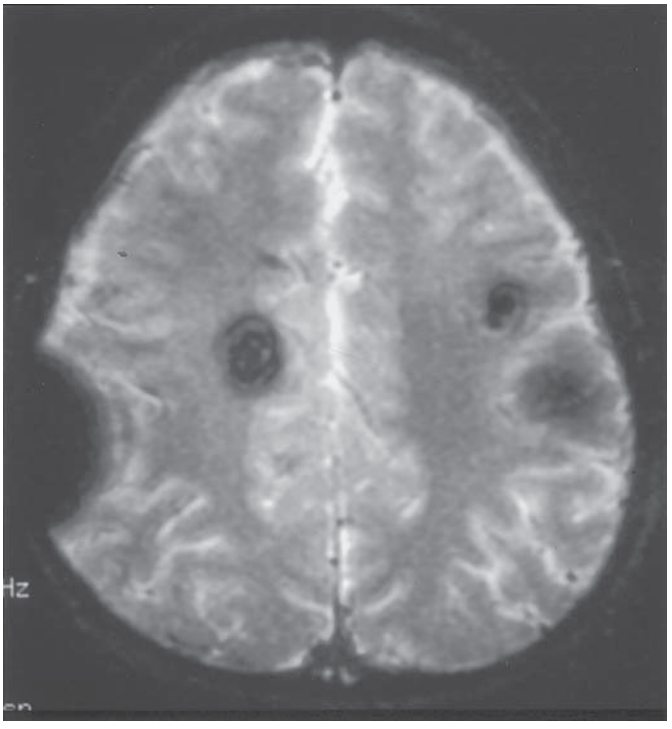

**Fig. 11.** Multiple radiation-induced cavernous angiomas. The concentric signal voids probably represent hemorrhages of different ages as the lesions enlarge.

Neuromuscular disorders that complicate bone marrow transplant include myositis, Guillain-Barré syndrome, chronic inflammatory demyelinating neuropathy, and myasthenia gravis (MG) *(123)*.

The peripheral neuropathy associated with transplantation is diffuse with variable sensory loss and associated with graft-versus-host disease (GVHD). Increased CSF protein without pleocytosis has usually been present. Patients improve with immunosuppressive therapy *(124)*. Myositis has been reported with and without graft versus host disease (GVHD), and response to immunosuppressants has also been good.

Guillain-Barré syndrome has been described after allogeneic and autologous bone marrow transplant. It is possible that dysfunction of the immune system and an increased susceptibility to infection may play a role. Posttransplant Guillain-Barré syndrome may have distinct pathophysiology in autologous versus allogeneic transplants; in the former it occurs in the immediate posttransplant period as compared to months following allogeneic transplant *(125)*.

MG after allogeneic bone marrow transplant is associated with anti-acetylcholine receptor antibodies, tends to occur after tapering or at low doses of prednisone, and may be due to the formation of antibodies against the recipient's different acetylcholine receptors. Patients seriously ill, especially with sepsis, who require ventilatory support and the use of neuromuscular blocking agents and steroid therapy are at increased risk for critical illness myopathy or polyneuropathy. Flaccid tetraplegia with inability to wean from the ventilator is the usual clinical presentation, and recovery in strength usually occurs over a period of weeks to months *(126)*.

## SENSORY DISTURBANCES

Numbness and dysesthesias may accompany motor weakness or be independent of it. Symmetric dysesthesias are usually caused by chemotherapy although spinal cord disease should be considered and carefully excluded. Vincristine and cisplatin are the most common offending agents. While vincristine tends to affect first fingers and then toes, the reverse is true with cisplatin *(1)*. Vincristine also causes weakness; cisplatin does not. Cisplatin neuropathy selectively affects the large myelinated fibers, sparing pain and temperature sensation. When the sensory abnormalities are asymmetric, root or nerve lesions due to surgical trauma, leptomeningeal disease, or compression neuropathy should be considered.

Malnutrition and chemotherapy-induced polyneuropathy makes children with cancer particularly susceptible to compression neuropathies. Peroneal nerve palsy (presenting clinically as foot drop with preserved foot inversion), is the most common; others include meralgia paresthetica *(127)* and superficial peroneal nerve compression. When surgical trauma is responsible for the problem, the temporal relationship often makes the diagnosis obvious, although at times due to prolonged postsurgery analgesia the patient does not complain until a week or two have elapsed. Axillary vein thrombosis associated with vascular catheters may simulate brachial plexus injury. The edema of the arm plus the intense nonradicular pain makes one suspect the diagnosis that may be confirmed by venous ultrasound *(128)*.

Two sensory syndromes of particular significance in cancer patients are worth mentioning: Lhermitte's sign is characterized by a sudden electric shock-like sensation, uncomfortable but not painful, traveling down the spine to the arms and legs upon flexion of the neck. Initially described in multiple sclerosis, it can result from a number of diseases affecting the spinal cord including metastatic cord compression *(129)*. Lhermitte's sign has also been described in association with radiation myelitis, following bone marrow transplant *(130)* and as a complication of cisplatin therapy *(131)*. Numb chin syndrome is characterized by numbness of the chin and lower lip, areas innervated by the inferior alveolar nerve. It is typically unilateral and may be due to metastatic disease involving the base of the skull, leptomeninges, or mandible *(132)*. It is often a sign of progressive or recurrent skeletal disease, despite normal results of bone scan and mandibular radiographs. Usually described in adults with lymphoproliferative diseases and breast cancer, it is probably underrecognized in the pediatric population. We have seen it in association with progressive Ewing's sarcoma *(133)*.

## VISUAL DISTURBANCES

Visual complaints include decreased visual acuity, diplopia, and asymmetry of ocular structures (Table 9). When a child with cancer complains of "not seeing well" or of "blurred vision," he/she may be describing diplopia rather than poor vision. If the problem persists with either eye closed, diplopia is excluded and chances are that the complaint is due to drugs. Of all the drugs frequently used in this population, opioids are probably the most common to cause "blurred" vision, followed by glucocorticoids. Anticonvulsants, particularly phenytoin and carbamazepine at toxic levels, are also possible offending drugs. Almost all chemotherapeutic agents can cause ocular

toxicity. Children on cyclophosphamide complain of blurred vision on occasion. Blindness during treatment for ALL or even during remission may occur in the absence of leptomeningeal involvement as a consequence of neurotoxicity from the combination of radiation and chemotherapy *(134,135)*.

Diplopia is caused by drugs, especially anticonvulsants, metastatic disease to the orbit, base of the skull (particularly clivus), or leptomeninges. Other frequent causes of oculomotor palsies in this population are cavernous sinus thrombosis from metastatic invasion or infection *(136)*. Increased intracranial pressure may cause a nonlocalizing VI nerve palsy.

Parents may note pupillary asymmetry or unilateral ptosis. The two usual causes are Horner's syndrome and constitutional pupillary asymmetry. Horner's syndrome consists of miosis and palpebral fissure narrowing with or without facial anhidrosis. The miosis is often more apparent in dim light. In children with cancer Horner's syndrome is usually the result of surgical intervention on the apical region of the lung or pulmonary metastases to the same area. We have seen transient Horner's syndrome as a complication of lumbar epidural anesthesia for an abdominal intervention. Isolated pupillary asymmetry without diplopia, with normal light response and maintaining the same relative degree under different lightning conditions, is likely physiologic, of no clinical significance and seen in approx 20% of normal individuals. Sometimes opioids may cause anisocoria, due perhaps to different sensitivity of each eye to the miotic effect of the drug. Unilateral ptosis can sometimes occur as a side effect of vincristine therapy *(137)*.

Other common eye-related complaints are abnormal spontaneous eye movements, particularly opsoclonus, consisting of chaotic, rapid, involuntary, repetitive conjugate saccadic eye movements in all directions, not a rare accompaniment of neuroblastoma *(138)*. Under those circumstances, opsoclonus is often accompanied by ataxia, myoclonus, and behavioral changes. This clinical picture may precede the diagnosis of neuroblastoma. Oculogyric crisis, an acute upward deviation of the eyes is often due to neuroleptics or antiemetics, and tics may be exacerbated by the stress of the disease or its treatment.

## MISCELLANEOUS

**MOVEMENT DISORDERS** Abnormal movements include tremors, dystonia, myoclonus, choreoathetosis, and tics as well as hypokinetic syndromes. Most are caused by drugs. Cyclosporine therapy causes tremors that abate as the drug is reduced or discontinued *(139)*. Tremors may also complicate polyneuropathy. Dystonic reactions may occur as a result of many of the drugs given for supportive care, including antihistamines, antidepressants, antiemetics, and even possibly chemotherapy *(140,141)*. Myoclonus is a component of the opsoclonus-myoclonus syndrome that in children accompanies some cases of neuroblastoma but in the general population is seen more frequently as a toxic effect of opiate therapy or metabolic derangements *(142)*. It can also occur as part of the serotoninergic syndrome, a potential side effect of the serotonin reuptake inhibitors *(143)*. Chorea may be seen with neuroleptics and anticonvulsants *(144,145)*. An akinetic rigid syndrome has been described in association with cytarabine, bone marrow transplant, and amphotericin B *(146–148)*.

**DIZZINESS AND SYNCOPE** Transient loss of consciousness may be caused by a seizure or by syncope. With a syncopal episode the loss of consciousness is not abrupt and there are changes in skin color and increased perspiration antedating the event. Clonic movements and spontaneous micturition may occur in both conditions *(149)*. Syncopal episodes are not uncommon in children with cancer given the combination of neuropathy (vincristine can cause marked autonomic dysfunction) *(150)*, dehydration, malnutrition, anemia, and marked deconditioning. Dizziness (in opposition to true vertigo), often has a similar explanation. Tumors of the neck invading the vagus nerve may be a cause of syncope.

**BEHAVIORAL DISTURBANCES** The most common behavioral disturbances in children with cancer have already been discussed under the "mental status changes" heading. On occasion a child with partial complex seizures is misdiagnosed as acute psychosis, but the reverse has also been true. Conversion disorders often present with neurologic symptoms such as visual disturbances, motor or gait abnormalities, or pseudoseizures. Ten percent of adolescents with cancer have a depressive mood disorder due to a combination of illness and treatment factors, compounded by external stressors such as poor family support *(151)*. A detailed neurologic examination is sometimes difficult in adolescents with negativistic, hostile, and defiant behavior. Being introduced by a trusted member of the staff will often facilitate the work of the consultant.

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# Cancer Neurology in Clinical Practice

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Neurologic complications of systemic cancer and its treatment often present complex diagnostic and management problems, commonly have a great impact on quality of life, and are a major factor in the death of cancer patients. In *Cancer Neurology in Clinical Practice,* leading neuro-oncologists from around the world comprehensively review the neurologic symptoms that cancer patients experience, and show how these symptoms should be interpreted and evaluated. Organized by both symptom and type of cancer, the book carefully describes each diagnostic neurologic entity—from symptomatology, to diagnostic studies, to management and prognosis—and presents each major type of cancer in terms of its neurologic problems and how they should be handled. This dual organization allows physicians quickly to obtain neurologic guidance on either a diagnostic problem (e.g., confusion and delirium) or on the neurologic problems and treatments associated with a specific type of cancer (e.g., lung cancer). The role of surgery, radiation, chemotherapy, and other palliative measures are considered for each type of problem.

Multidisciplinary and up-to-date, *Cancer Neurology in Clinical Practice* explains to the busy physician treating cancer patients all the latest findings in neuro-oncology that will help sharpen their differential diagnoses, diagnostic strategies, and treatment plans for those patients with neurologic symptoms and findings.

- **Cutting-edge review of the diagnosis and treatment of neurologic complications of cancer**
- **Organized for quick reference by symptom or specific disease**
- **Discussion of surgery, radiation, chemotherapy, and other palliative measures**
- **Written to illuminate the neurologic complications of cancer treatment**

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