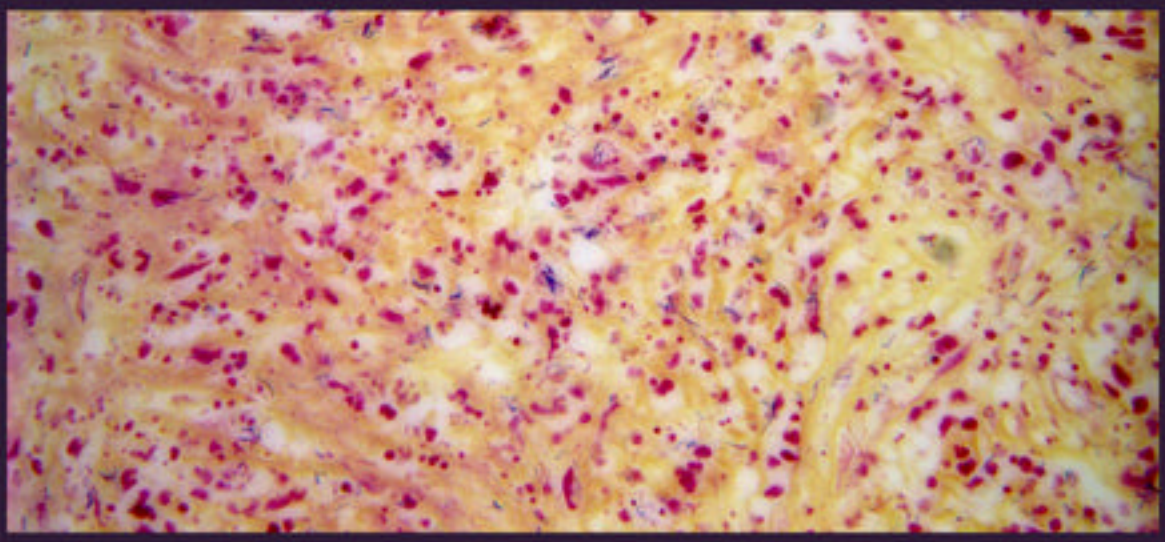
INFECTIONS IN THE IMMUNOSUPPRESSED PATIENT

AN ILLUSTRATED CASE-BASED APPROACH

edited by Pranatharthi H. Chandrasekar



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An Illustrated Case-Based Approach

EDITED BY

PRANATHARTHI H. CHANDRASEKAR

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PREFACE

I came across this quote from the French embryologist, Jean Rostrand, "What a profession this is-this daily inhalation of wonder". I am sure readers can relate to this as they get immersed in the daily care of patients with weakened immune systems. This book, "Infections in the Immunosuppressed Patient", is a product of that wonder. With stark, indelible memories I dedicate this book to the thousands of patients who generously taught me the fundamental principles of management of their ailments. Their lives are not wasted, to say the least.

The Book consists of five Sections – areas recognized as common clinical categories of patients with impaired immunity. Case stories included are carefully handpicked not to describe the extraordinary or esoteric, but to highlight the varied presentations of common as well as unique pathogens. Despite the pathogen often being the same, dramatically different perspectives and presentations are demonstrated across the Sections. The overlap of pathogens seen among the different Sections is intentional to emphasize the subtle variations in presentations seen among the different hosts. The goal of the book is for the reader to appreciate and hopefully adopt the appropriate approaches toward common clinical scenarios that are played out daily around the world, in the ambulatory clinics and in the hospital wards caring for patients with uniquely compromised immune systems.

Almost through each case history in the Book, six fundamental concepts for successful management are repeated. Firstly, it is critical to recognize the roles played by the underlying illness of the host, the robustness or frailty of the host immunity and the therapies administered, in the etiology of infection; consideration of such factors need to be attended to in diagnosis as well as therapy. Secondly, unlike in the competent host, both common and uncommon pathogens are at play in the compromised host, thus making the list of differential diagnoses long and establishing an early accurate diagnosis difficult. Thirdly, several non-infectious entities may mimic clinical syndromes of infection. Failure to recognize this possibility frequently leads to unnecessary diagnostic invasive and non-invasive procedures and administration of potentially toxic medications, further compromising the health of the already frail host. Fourthly, choice of the appropriate diagnostic or therapeutic procedures, invasive or non-invasive, requires clinical wisdom. The urgency of establishing an accurate diagnosis needs to be weighed against the risks involved with the procedure(s). "Econotoxitiy" from hospitalization, cost of procedures and cost of medications is not to be trivialized. Fifthly, it is always wise to avoid empiricisms in therapy; however, in critically ill patients or in whom invasive procedures may be precluded, empiricism may be the smart or only choice. While recognizing that antimicrobial resistance is widespread in wards housing compromised hosts, broad spectrum empiric therapy may often is inevitable. Under such circumstances, the duration of empiric therapy needs to be questioned incessantly. Finally, timing of appropriate intervention based on sound clinical judgement is crucial for a good outcome – not too early, not too late.

By design, the book does not include infections in the HIV-infected population and in patients with primary immunodeficiencies. Hopefully, these may be addressed in the future.

I am most indebted to the Section Editors. These are experts with tremendous insight and wisdom and have carefully chosen the "perfect" cases. My sincere thanks to the case authors for their lucid descriptions combined with wonderful illustrations.

The publisher, Oxford University Press, was most supportive of this project, right from its inception. I am grateful for their encouragement, help and most importantly, patience.

ABOUT THE EDITOR

Pranatharthi H. Chandrasekar, MD, was born in Colombo, Sri Lanka. After earning his medical degree from the Christian Medical College, Vellore, South India, he immigrated to the United States. He continued his medical training residency at the University of Louisville, Kentucky, and Fellowship in Infectious Diseases at the Hahnemann University Hospital in Philadelphia, Pennsylvania. Since 1983, Dr. Chandrasekar has served in the Division of Infectious Diseases, Department of Medicine at Wayne State University. His major interest has been the management of infections in the immunocompromised hosts.

CONTRIBUTORS

Faten Aberra, M.D., M.S.C.E.
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

George J. Alangaden, M.D.
Henry Ford Hospital, Detroit, MI

Maha Alhusseini, M.D.
Wayne State University, Detroit, MI

Marwan Al-Hajeili, M.D.
Karmanos Cancer Institute, Wayne State University, Detroit, MI

Yuki Aoyagi, M.D., M.P.H., M.A.
Geisel School of Medicine at Dartmouth, NH

Jennifer M. Babik, M.D., Ph.D.
University of California, San Francisco, CA

Sara Bares, M.D.
University of Nebraska Medical Center, Omaha, NE

Todd Barton, M.D.
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Elena Beam, M.D.
Mayo Clinic, Rochester, MN

Ashish Bhargava, M.D.
Wayne State University, Detroit, MI

Emily A. Blumberg, M.D.
University of Pennsylvania, Philadelphia, PA

R. Gregory Bociek, M.D.
University of Nebraska Medical Center, Omaha, NE

Cristina Brickman, M.D.
University of California, San Francisco, CA

Jackrapong Bruminhent, M.D.
Mayo Clinic, Rochester, MN

Dana D. Byrne, M.D.
Cooper Medical School of Rowan University, Camden, NJ

Stephen Castro, M.D.
New York Presbyterian-Weill Cornell Medical Center, New York, NY

Pranatharthi H. Chandrasekar, M.D.
Wayne State University, Detroit, MI

Jasmin Chaudhary, M.D.
Oregon Health and Science University, Portland, OR

David Crockett, M.D.
University of Nebraska Medical Center, Omaha, NE

Paul J. Deziel, PA-C
Mayo Clinic, Rochester, NY

Christine M. Durand, M.D.
Johns Hopkins University, Baltimore, MD

Ignacio A. Echenique, M.D.
Northwestern University, Chicago, IL

Glenn Eiger, M.D.
Einstein Medical Center, Philadelphia, PA

Graeme N Forrest, M.B.B.S.
Oregon Health and Science University, Portland
VA Medical Center, Portland, OR

Alison G. Freifeld, M.D.
University of Nebraska Medical Center,
Omaha, NE

Deepak Garg, M.D.
St. John Hospital and Medical Center,
Detroit, MI

Ige Abraham George, M.D.
Washington University School of Medicine,
St. Louis, MO

Murat Gonulalan, M.D.
Henry Ford Hospital, Detroit, MI

Rachel Gormley, M.D.
Perelman School of Medicine at the University
of Pennsylvania, Philadelphia, PA

Charitha Gowda, M.D.
Perelman School of Medicine at the University
of Pennsylvania, Philadelphia, PA

Jamie S. Green, M.D.
University of California San Diego, La Jolla, CA

Melissa A. Grilliot, M.D.
Miami Valley Hospital, Wright State University
School of Medicine, Dayton, OH

Ambar Haleem, M.D.
University of Iowa Hospital and Clinics,
Iowa City, IA

Morgan Hakki, M.D.
Oregon Health and Science University,
Portland, OR

Keith Hamilton, M.D.
Perelman School of Medicine at the University
of Pennsylvania, Philadelphia, PA

Joshua A. Hill, M.D.
Fred Hutchinson Cancer Research Center
& University of Washington, Seattle, WA

David Holtzman, M.D.
Global Health Corps Physician, Baylor
International Pediatric AIDS Initiative,
Houston, TX

Jack Hsu, M.D.
University of Florida, College of Medicine,
Gainesville, FL

Dilek Ince, M.D.
University of Iowa Carver College of Medicine,
Iowa City, IA

Michael G. Ison, M.D., M.S.
Northwestern University Feinberg School
of Medicine, Chicago, IL

Samantha E. Jacobs, M.D.
New York Presbyterian-Weill Cornell Medical
Center, New York, NY

Janice Jou, M.D., M.H.S.
Oregon Health and Science University,
Portland VA Medical Center, Portland, OR

Deborah Kahal, M.D., M.P.H.
Perelman School of Medicine at the University
of Pennsylvania, Philadelphia, PA

Vandana Khungar, M.D., M.Sc.
Perelman School of Medicine at the University
of Pennsylvania, Philadelphia, PA

Karen Krok, M.D.
Penn State Hershey Medical Center
and Penn State College of Medicine, Hershey, PA

Steven J. Lawrence, M.D., MSC
Washington University, St. Louis, MO

Erika D. Lease, M.D.
University of Washington, Seattle, WA

Ajit P. Limaye, M.D.
University of Washington, Seattle, WA

Kieren Marr, M.D.
Johns Hopkins University, Baltimore, MD

Matthew McCarthy, M.D.
New York Presbyterian-Weill Cornell Medical
Center, New York, NY

Ryan McConnell, M.D.
University of California, San Francisco, CA

Rachel Miller, M.D.
University of Iowa, Carver College of Medicine, Iowa City, IA

Elizabeth Ann Misch, M.D.
University of Washington, Seattle, WA

Kailash Mosalpuria, M.D.
University of Nebraska Medical Center, Omaha, NE

Kate Mullane, D.O., Pharm.D.
University of Chicago Medical Center, Chicago, IL

Allison L. Nazinitsky, M.D.
Washington University, St. Louis, MO

Kari Neemann, M.D.
University of Nebraska Medical Center, Omaha, NE

Maxim Norkin, M.D.
University of Florida, College of Medicine, Gainesville, FL

Robbe Peetz, P.A.
University of Nebraska Medical Center, Omaha, NE

Edwin C. Pereira, M.D.
University of Minnesota, Minneapolis, MN

Christopher D. Pfeiffer, M.D., M.H.S.
Oregon Health and Science University, Portland VA Medical Center, Portland, OR

Amy Pruitt, M.D.
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Robert M. Rakita, M.D.
University of Washington, Seattle, WA

Raymund R. Razonable, M.D.
Mayo Clinic, Rochester, MN

Misha Rosenbach, M.D.
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Priscilla Rupali, M.D., D.T.M. & H.
Christian Medical College and Hospital, Vellore, South India

Rahul Sampath, M.D.
Baylor College of Medicine, Houston, TX

Michael J. Satlin, M.D., M.S.
New York Presbyterian-Weill Cornell Medical Center, New York, NY

Audrey N. Schuetz, M.D., M.P.H.
New York Presbyterian-Weill Cornell Medical Center, New York, NY

Susan Seo, M.D.
Memorial Sloan Kettering Cancer Center, New York, NY

Katie A. Sharff, M.D.
Oregon Health and Science University, Portland, OR

Nicole Shonka, M.D.
University of Nebraska Medical Center, Omaha, NE

Rosemary Soave, M.D.
New York Presbyterian-Weill Cornell Medical Center, New York, NY

Bryan Steussy, M.D.
University of Iowa, Carver College of Medicine, Iowa City, IA

Lynne Strasfeld, M.D.
Oregon Health and Science University, Portland, OR

Naasha J. Talati, M.D., M.S.C.R.
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Pavan Kumar Tandra, M.D.
University of Nebraska Medical Center, Omaha, NE

Patrick Tang, M.D.
University of Nebraska Medical Center, Omaha, NE

Jessie Torgersen M.D.
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Gaurav Trikha, M.D.
University of Florida, College of Medicine, Gainesville, FL

Shawn Vasoo, M.D.
Mayo Clinic, Rochester, MN

Jason Van Winkle, M.D.
Oregon Health and Science University, Portland, OR

Thomas J. Walsh, M.D.
New York Presbyterian-Weill Cornell Medical Center, New York, NY

Nancy L. Wengenack, Ph.D.
Mayo Clinic, Rochester, MN

Matthew Whitson, M.D.
Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

John R. Wingard, M.D.
University of Florida, College of Medicine, Gainesville, FL

Richard A. Zuckerman, M.D., M.P.H.
Geisel School of Medicine at Dartmouth, NH

SECTION 1

Infections in Cancer Patients

ALISON G. FREIFELD

An Introduction: Infections in Solid Tumor, Lymphoma, and Leukemia Patients (Nonhematopoietic Stem Cell Transplantation Recipients)

ALISON G. FREIFELD, MD

Solid tumors, lymphomas, and leukemias represent a widely diverse array of cancers. Until recently, the general approach to treating all of them was to administer cytotoxic anticancer drugs that damage proliferating cells by interfering with mitosis and other essential steps in cellular replication. As a consequence of their high proliferative index, many high-grade leukemias and lymphomas can be cured with aggressive cell-killing chemotherapies. Low-grade hematologic tumors can often be controlled over a period of many years by maintenance dosing strategies of these drugs that cause minimal toxicities. However, relapse of hematologic cancers carries a poor prognosis, often due to drug resistance, and further chemotherapies may not achieve durable remission. Localized solid tumors are largely treated by surgical resection and radiotherapy, with cytotoxic chemotherapy being commonly used adjunctively or in cases of metastatic disease.

A major drawback of this approach has been the lack of specificity in that cytotoxic drugs will destroy actively dividing normal cells as well as malignant cells. As a result, achieving maximum tumor killing by high doses of anticancer drugs is often offset or prohibited by collateral damage to normal tissues. Two common adverse effects are profound neutropenia, due to disruption of hematopoiesis in the bone marrow, and mucositis, resulting from injury to the gastrointestinal mucosal barrier. Mucositis potentiates the translocation of normal and colonizing gastrointestinal flora into the bloodstream. In the setting of neutropenia, where there is a paucity of effector cells to contain serious infections, bacteremias may cause severe morbidity and increased mortality. Chemotherapy-related neutropenia (defined when the absolute neutrophil count is less than 500 cells/μL) is, in fact, considered the single most significant risk factor for the development of invasive bacterial and fungal infections in the cancer patient. The degree of infection risk depends on the depth and duration of neutropenia. Neutropenic periods lasting as long as several weeks may be seen with induction therapy for acute myelogenous leukemia (AML), and they are associated with increased risk for bacterial blood stream infections and pneumonias as well as invasive mold infections (e.g. aspergillosis and mucormycosis), which typically occur when neutropenia lasts for 14 days or more. Treatment of solid tumor or lymphomas is generally associated with a briefer neutropenic period, lasting from a few days to a week, depending on the type and dose of cytotoxic chemotherapy, and severe infections are less common than during treatment of AML.

The "shotgun approach" of using intensive cytotoxic chemotherapies has been the mainstay of cancer treatment for at least 6 decades. More recently, various strategies have been developed to achieve a more targeted antitumor effect, based on the identification of genetic mutations or abnormal signaling pathways involved in cancer cell proliferation and/or the emergence of drug resistance. Rational drug design aimed at abnormal mechanistic, genetic, or structural features of tumor cells has generated a host of new agents that are increasingly used with or without conventional cytotoxic chemotherapy. New classes of therapeutic interventions have consequently evolved, including angiogenesis inhibitors, epigenetic modifiers, immunotherapies, hormone therapies, monoclonal antibodies, and targeted molecules

TABLE 1. ANTICANCER AGENTS

Class	Mechanism	Common Examples	Main Side Effects (Drugs in Same Class May Have Very Variable Effects)
Alkylating agents	Form covalent bonds with cellular DNA, causing DNA breaks and strand cross-linking that prevent replication	Melphalan Cyclophosphamide Carmustine (BCNU) Bendamustine Temozolomide Procarbazine	• Neutropenia • Gonadal dysfunction • Secondary cancers
Anthracyclines	Several known mechanisms: DNA intercalation, proteasome, or p53 gene binding to promote apoptosis, and interference with gene expression	Daunorubicin Doxorubicin (Adriamycin) Idarubicin Epirubicin	• Neutropenia • Gastrointestinal complaints • Mucositis (esp doxorubincin) • Cardiotoxicity
Antimetabolites	Induce cell death during the S phase of cell growth when incorporated into RNA and DNA; some will inhibit enzymes needed for nucleic acid production	Methotrexate Cytosine arabinoside (cytarabine, araC) Gemcitabine Fluorouracil (5FU) Fludarabine	• Neutropenia • Mucositis (esp methotrexate and araC)
Platinum compounds	Cross-link DNA strands to prevent replication	Cisplatin Carboplatin	• Neutropenia • Nephrotoxicity • Gastointestinal complaints • Peripheral neuropathy
Topoisomerase inhibitors	Bind topoisomerase enzymes that are required for DNA synthesis	Topotecan Irinotecan Etoposide	• Neutropenia • Gastrointestinal complaints • Mucositis (esp etoposide)
Tubulin-binding drugs	Bind tubulin and prevent spindle fiber formation that is critical to cell division; also may inhibit angiogenesis	Vincristine Taxanes (paclitaxel, docetaxel, taxotere)	• Neutropenia • Gastrointestinal complaints • Peripheral neuropathy
Tyrosine kinase inhibitors	Inhibit tyrosine kinases or their receptors (such as vascular endothelial growth factor [VGEF] or other growth factor receptors [i.e. fibroblast, epidermal, platelet-derived, etc]) involved in tumor angiogenesis and growth	Sorafenib Sunitinib Regorafinib Bortezomib Imatinib Ibrutinib Idelalisib	• Neutropenia • Hepatic enzyme elevation • Gastrointestinal complaints • Hand-food syndrome (rash, swelling)
Epigenetic modifiers	Alter regulation of oncogenes or tumor suppressor genes through histone modifications and DNA methylation or demethylation	Azacitidine Decitabine Vorinostat Romidepsin (many more in development)	• Neutropenia • Gastrointestinal complaints
Monoclonal antibodies: ligand	Block a wide variety of tumor-promoting cell functions by attaching to specific cell receptors	Rituximab: CD20 Alemtuzumab: CD52 Bevacizumab: VEGF	Various, depending on type of cell blocked

such as tyrosine kinase inhibitors. A brief description of both older and newer antitumor classes and their effects on the host are shown in Table 1. The oncologist and the infectious diseases consultant should be familiar with the potential (and often unique) infectious complications that may arise from these treatments.

Finally, in addition to the tissue damage and immunomodulating effects of anticancer drugs, it should be remembered that cancers themselves may increase the chances for infection. For example, multiple myeloma and chronic lymphocytic leukemia (CLL) may both be associated with hypogammaglobulinemia and the attendant risk of recurrent sinopulmonary infections due to encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. On the other hand, solid tumors can grow through normal tissue planes and obstruct tubular or hollow viscus structures, allowing for post-obstructive infections. Pneumonia in the setting of bronchogenic carcinoma or cholangitis from obstructing hepatobiliary tumors are examples. In sum, the patients' underlying cancer and their treatment regimen may each contribute to the risk for and type of infection observed in this population.

1.1

Leg Edema Woes

EDWIN C. PEREIRA, MD

CASE PRESENTATION

A 58-year-old man with a history of metastatic rectal adenocarcinoma presented to the emergency department with fevers, chills, and redness over his right thigh. On exam, temperature was 101.9°F, blood pressure 117/63 mm Mercury, heart rate 92/minute, and respirations 14/minute. The patient had blanching erythema and warmth over the entire right thigh, extending from the knee to the groin, and into the right flank (Figures 1.1.1 and 1.1.2). There was no involvement of the penis or scrotum.

Rectal adenocarcinoma had been diagnosed three years before presentation and treated with local resection and chemotherapy. His disease course was complicated by metastatic disease to his liver and bones. Palliative radiation therapy to his right femur occurred one year before his presentation. He has a history of deep venous thrombosis of the right common iliac vein and stenting of the right iliac vein. He suffers from chronic right lower extremity edema. He is receiving panitumumab due to progression of cancer on other regimens. One week before presentation, he had an ingrown toenail removed on his right foot.

QUESTIONS

- What organisms are typically responsible for this type of infection?
- How does the patient's medical history affect initial treatment choices?
- What, if any, diagnostic studies should be done?

DIFFERENTIAL DIAGNOSIS

Localized erythema should raise concerns for a superficial skin infection such as cellulitis or erysipelas. A deeper infection such as necrotizing fasciitis or gas gangrene should also be considered if signs such as pain out of proportion to touch, skin necrosis, or crepitus are seen. This is a medical emergency requiring immediate surgical evaluation. Fever or a systemic inflammatory response syndrome can indicate a disseminated infection, necessitating systemic work-up (e.g. blood cultures). Noninfectious considerations include deep or superficial venous

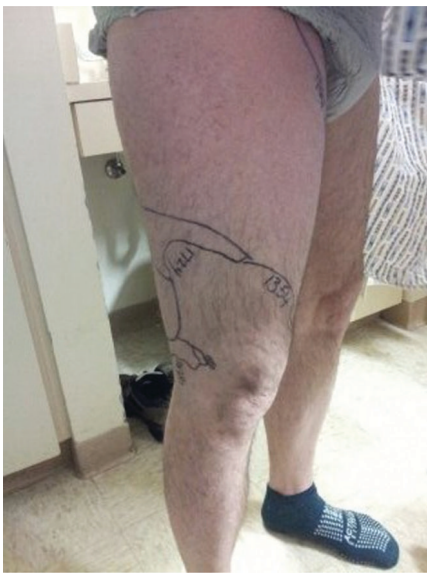


FIGURE 1.1.1: Faint erythema of the right thigh without distinct borders.

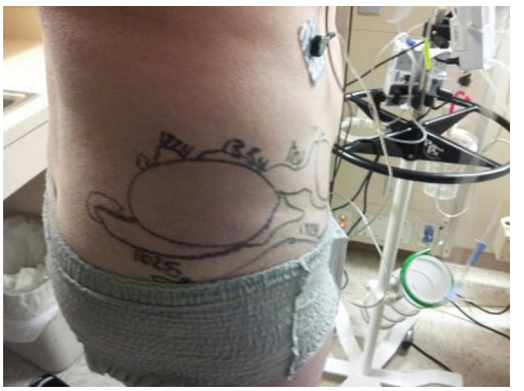


FIGURE 1.1.2: Erythema extending to the right flank. Note markings on the skin to document the edge of the rash which continued to advance after initial presentation.

thrombosis, dermatitis, fixed drug reaction, foreign body, or lymphedema [1, 2].

ADDITIONAL DATA

Blood cultures were from a venous access subcutaneous port and a peripheral site grew β-hemolytic group B *Streptococcus*. The isolate demonstrated inducible clindamycin resistance, but it was sensitive to penicillin, ceftriaxone, and vancomycin. The site from the ingrown toenail removal was examined and did not appear infected. A doppler ultrasound of the thigh showed no signs of deep venous thrombosis.

Final Diagnosis: Group B streptococcal cellulitis and bacteremia

TREATMENT AND OUTCOME

The patient was immediately started on intravenous broad spectrum antibiotics to cover both Gram-positive and Gram-negative bacteria. Antibiotic coverage was narrowed to ceftriaxone based on susceptibility testing on the isolate. Symptoms improved after a two-week course of antibiotics.

Cellulitis to the right thigh recurred on two separate occasions over the next seven months. The presentation was similar in each episode with diffuse, blanching erythema over the right thigh extending to the groin. Multiple blood cultures on each admission grew β-hemolytic group B *Streptococcus* with identical susceptibility patterns. On the second hospital admission, a venous access subcutaneous port was removed as a possible source for recurring infection. However, cultures from the catheter tip were negative. Symptoms rapidly improved with the administration of antibiotics on each admission. After completion of antibiotics and resolution of cellulitis, the patient was started on prophylactic penicillin VK for recurrent cellulitis. He was also referred to a lymphedema clinic for management of his chronic lymphedema with compressive wraps.

RECURRENT CELLULITIS

Discussion

Cellulitis is usually an acute infection involving the subcutaneous tissue and dermis, typically caused by *Staphylococcus aureus* or β-hemolytic streptococci. Cancer patients are at increased risk for cellulitis. The resulting immunosuppression makes this population susceptible to atypical organisms for cellulitis such as Gram-negative bacteria, nontuberculous mycobacteria, fungi, and viruses.

Risk Factors

Lymphedema and tinea pedis are known risk factors for developing cellulitis in the general population [3, 4]. Cancer patients develop deficiencies in their systemic and cutaneous immune system, often as a result of radiation and chemotherapy. These therapies can alter the structural and functional integrity of the skin, serving as a portal of entry for colonizing pathogens. Medications, such as the epidermal growth factor receptor inhibitors (e.g. panitumumab), used in the treatment of solid organ tumors, can adversely affect the skin, causing papulopustular rash and xerosis [5]. Malnutrition, often associated with cancer and chemotherapy, can contribute to skin breakdown and poor healing. Radiation therapy and lymph node resection can contribute to lymphedema, making recurrent cellulitis more common [2].

Clinical Presentation

Cellulitis can appear as a localized area of erythema, swelling, and warmth, typically on the extremities. The margins of cellulitis are usually ill-defined, whereas erysipelas (an infection of the upper dermis) has distinct margins. A point of entry may or may not be seen with cellulitis. Systemic symptoms are usually absent, but they are more likely in the immunocompromised patient and may indicate deeper or disseminated infection [2, 6].

Management

Evaluating for signs of an abscess, necrosis, or gas is an important part of the evaluation of cellulitis because treatment will require surgical debridement. A fluctuant, raised area may suggest an abscess. However, clinical signs of an abscess can be masked in neutropenic patients who lack the ability to mount an inflammatory response. Subcutaneous fluid can be seen by ultrasound if the presence of an abscess is uncertain. If there is concern for myonecrosis or gas gangrene, then urgent surgical consultation is required. A magnetic resonance image can be useful in diagnosing these serious conditions; however, surgical exploration provides a definitive diagnosis and is an important element in treatment.

If debridement is not required, treatment with antibiotics is appropriate, targeting potential pathogens. Cancer patients, who are immunocompromised, usually require broad-spectrum antibiotics, to include coverage for Gram-negative bacteria and nosocomial-acquired resistant microorganisms [7]. Intravenous antibiotics should be started in rapidly spreading cellulitis

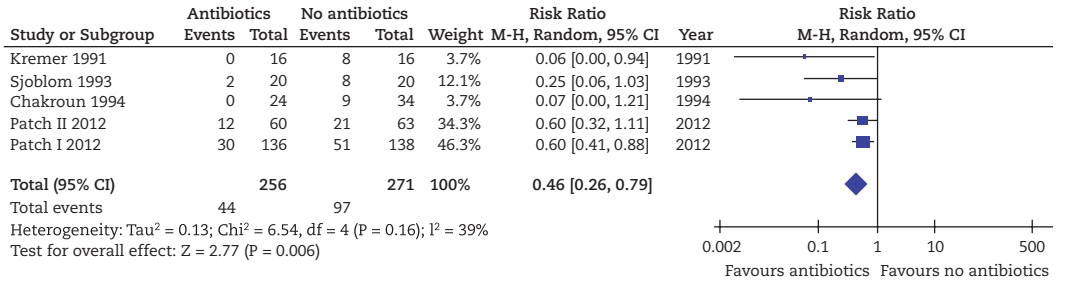


FIGURE 1.1.3: Comparison and analysis of studies evaluating the use of prophylactic antibiotics for recurrent cellulitis. Reproduced from *J Infect*. 2014;69:26.

or if the patient is systemically ill. Efforts should be made to determine the cause of cellulitis, given the broad differential in immunocompromised patients, especially in nonresolving cases. Blood cultures may be of use in the immunocompromised patient or if there are signs of systemic illness. Studies examining the use of blood cultures in cellulitis in the general population have shown a yield of approximately 2%–4% [8, 9]. A Thai study of 150 hospitalized patients with cellulitis compared immunocompetent with immunocompromised patients and showed that blood cultures were positive in 8.3% compared with 21.3% of cases, respectively; however, this difference was not statistically significant [10]. In cases not responding to empiric therapy, in which atypical organisms are suspected, local aspiration or skin biopsy may be considered; however, the yield is considered low at 10% and 20%, respectively, among non-immunocompromised adults presenting to the emergency department [8].

Prevention

Cellulitis can predispose patients to subsequent episodes due to localized lymphatic inflammation [7]. When chronic lymphedema is present, recurrences are more common [3, 11]. Recurring cellulitis is a known complication in breast cancer patients who suffer upper extremity lymphedema following axillary lymph node dissection [12, 13]. Treatment of underlying risk factors, when feasible, is preferred. Protracted courses of antibiotics in cases of recurring cellulitis in breast cancer patients has been recommended [13].

Prophylactic antibiotics to prevent recurrent cases of cellulitis have been recommended with reservation due to conflicting data [7]. Prospective trials have not been done in cancer populations, and the choice of antibiotics has focused on antibiotics that target penicillin-sensitive streptococci. A systematic review and meta-analysis of the use of prophylactic antibiotics for preventing recurrent cellulitis was performed by Oh et al [14]. The meta-analysis included five randomized controlled trials [15–19]. Prophylactic regimens included twice daily penicillin VK 250 mg, phenoxymethylpenicillin 1–2 g, erythromycin 250 mg, or intramuscular injection of penicillin G 1.2 million units every 15 days. The use of antibiotics to prevent the recurrence of cellulitis was shown to be beneficial with a risk ratio of 0.46 (Figure 1.1.3) [14]. This analysis was not large enough to comment on which antibiotic or antibiotic formulation was superior. The PATCH I trial was the largest study included in this analysis and included a total of 274 patients with recurrent cellulitis. Thirty (22%) of 136 patients receiving penicillin VK developed cellulitis during a 12-month prophylaxis period compared with 51 (37%) of 138 patients receiving placebo (hazard ratio, 0.55; 95% confidence interval, 0.35–0.86; $P = .01$). Both a body mass index of 33 or higher and history of three or more previous episodes of cellulitis were significantly associated with a poor response to treatment. The benefit of penicillin did not extend beyond the period of prophylaxis. There was no significant difference in adverse events between the two groups [19]. The smaller PATCH II trial studied patients with at least one previous case of cellulitis who were randomized to either six months of penicillin VK prophylaxis (n = 60) or placebo (n = 63). This trial failed to show a significant difference in time to the first recurrence or risk of recurrence during the treatment and follow-up period [18].

KEY POINTS

- Cancer patients are prone to developing cellulitis due deficiencies in their systemic and cutaneous immune system.
- Cellulitis must be differentiated from necrotizing fasciitis or gas gangrene, which are more aggressive infections and require surgical debridement.

- Broad-spectrum antibiotics are required for the initial treatment of cellulitis. Diagnostic studies (e.g. tissue or blood cultures) may be necessary to guide treatment in difficult cases.
- Prophylactic antibiotics may be beneficial in cancer patients who are prone to recurring streptococcal cellulitis due to associated conditions such as lymphedema.

REFERENCES

1. Falagas ME, Vergidis PI. Narrative review: diseases that masquerade as infectious cellulitis. Ann Intern Med. 2005;142:47.
2. Swartz MN. Clinical practice. Cellulitis. N Engl J Med. 2004;350:904.
3. Dupuy A, Benchikhi H, Roujeau JC, et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. BMJ. 1999;318:1591.
4. Roujeau JC, Sigurgeirsson B, Korting HC, et al. Chronic dermatomycoses of the foot as risk factors for acute bacterial cellulitis of the leg: a case-control study. Dermatology 2004;209:301.
5. Gandhi M, Brieva JC, Lacouture ME. Dermatologic infections in cancer patients. Cancer Treat Res. 2014;161:299.
6. Lopez FA, Lartchenko S. Skin and soft tissue infections. Infect Dis Clin North Am. 2006;20:759.
7. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis. 2005;41:1373.
8. Hook EW, Hooton TM, Horton CA, et al. Microbiologic evaluation of cutaneous cellulitis in adults. Arch Intern Med. 1986;146:295.
9. Perl B, Gottehrer NP, Raveh D, et al. Cost-effectiveness of blood cultures for adult patients with cellulitis. Clin Infect Dis. 1999;29:1483.
10. Kulthanan K, Rongrungruang Y, Siriporn A, et al. Clinical and microbiologic findings in cellulitis in Thai patients. J Med Assoc Thai. 1999;82:587.
11. Cox NH. Oedema as a risk factor for multiple episodes of cellulitis/erysipelas of the lower leg: a series with community follow-up. Br J Dermatol. 2006;155:947.
12. Simon MS, Cody RL. Cellulitis after axillary lymph node dissection for carcinoma of the breast. Am J Med. 1992;93:543.
13. Cheema F, Agloria M, Mills GM, et al. Recurring breast and arm cellulitis in patients with early breast cancer. In: Meeting was the 2013 ASCO Annual Meeting in Chicago, Illinois, May 31–June 4, 2013. http://meetinglibrary.asco.org/content/117756-132 (Abstract 31:e20600).
14. Oh CC, Ko HC, Lee HY, et al. Antibiotic prophylaxis for preventing recurrent cellulitis: a systematic review and meta-analysis. J Infect. 2014;69:26.
15. Kremer M, Zuckerman R, Avraham Z, Raz R. Long-term antimicrobial therapy in the prevention of recurrent soft-tissue infections. J Infect. 1991;22:37.
16. Sjöblom AC, Eriksson B, Jorup-Rönström C, et al. Antibiotic prophylaxis in recurrent erysipelas. Infection 1993;21:390.
17. Chakroun M, Ben Romdhane F, Battikh R, et al. Benzathine penicillin prophylaxis in recurrent erysipelas. Méd Mal Infect. 1994;24: 894–897. doi: http://dx.doi.org/10.1016/S0399-077X(05)80579-7
18. Thomas K, Crook A, Foster K, et al. Prophylactic antibiotics for the prevention of cellulitis (erysipelas) of the leg: results of the UK Dermatology Clinical Trials Network's PATCH II trial. Br J Dermatol. 2012;166:169.
19. Thomas KS, Crook AM, Nunn AJ, et al. Penicillin to prevent recurrent leg cellulitis. N Engl J Med. 2013;368:1695.

1.2

Doctor, I'm Sick Again and Again

PATRICK TANG, MD AND R. GREGORY BOCIEK, MD

CASE PRESENTATION

A 63-year-old woman with a history of chronic lymphocytic leukemia (CLL) presented to the outpatient clinic with sinus congestion and purulent nasal discharge for two days. She was febrile at 38.6°C. Her blood pressure was 128/75 mm mercury with a heart rate of 86 bpm and respiratory rate of 14 breaths per minute. Physical exam was remarkable for tenderness to palpation and percussion of the left maxillary sinus region. Laboratory data were significant for leukocytosis of 65 600/μL with 19% neutrophils, 4% bands, and 76% lymphocytes. Other hemogram indices were within normal limits. Computed tomography of the sinuses showed dense opacification of the left maxillary sinus (Figure 1.2.1). She reports that this is her third sinus infection this year. Two years prior to the present illness, she was hospitalized initially in the intensive care unit for sepsis syndrome with a lobar pneumonia (Figure 1.2.2). She was again hospitalized one year later for a community-acquired pneumonia, during which *Streptococcus pneumoniae* was isolated from her sputum.

Her CLL was diagnosed incidentally during evaluation for an absolute lymphocytosis 5 years prior to her current presentation. A bone marrow biopsy with aspirate confirmed the usual immunophenotype for CLL. Imaging studies showed no radiographic evidence of lymphadenopathy or organomegaly, and she had no constitutional symptoms or cytopenias related to the chronic leukemia. Cytogenetic studies on marrow demonstrated none of the commonly associated abnormalities seen in CLL. She had Rai stage 0 disease and had no indication for treatment. Other than recurrent sinus infections and pneumonias in recent years, she had no other significant illnesses and no other relevant past medical history.

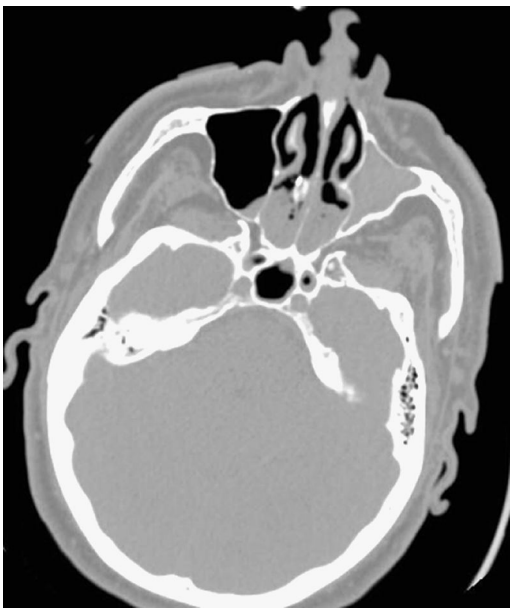


FIGURE 1.2.1: Computed tomography images of sinus, axial view, opacification of left maxillary sinus.

QUESTIONS

- What diagnoses should be considered in a patient with recurrent sinopulmonary infections?
- What pathogens are commonly associated with these infections?
- What role does CLL have in pathogenesis of recurrent infections?

DIFFERENTIAL DIAGNOSIS

Recurrent sinopulmonary infections could be due to a secondary (acquired) hypogammaglobulinemia in which B cells are unable to produce adequate amounts of circulating antibodies (such as immunoglobulin [Ig]G, IgM, and/or IgA). Common variable immune deficiency is the most common clinically significant primary antibody deficiency disorder in adults. Secondary hypogammaglobulinemia is associated with lymphoproliferative disorders and plasma cell dyscrasias such as CLL, multiple myeloma, and Waldenstrom's macroglobulinemia [1, 2]. Hypogammaglobulinemia is also seen in postallogeneic hematopoietic stem cell

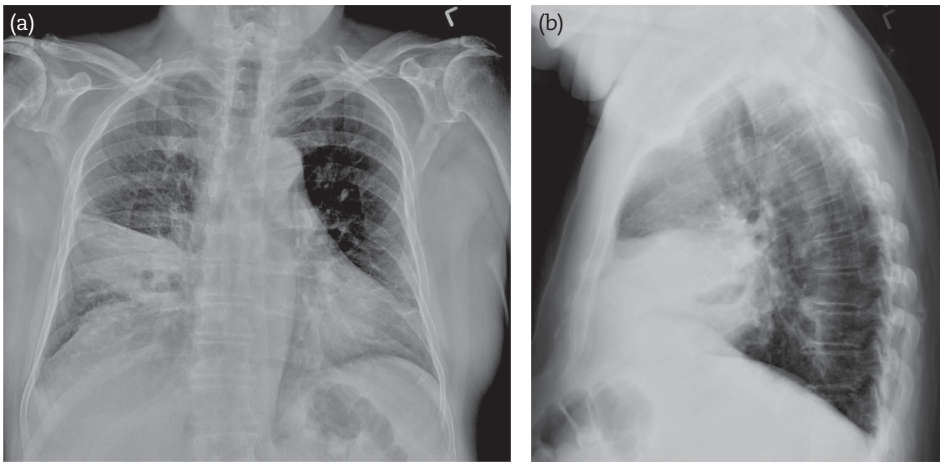


FIGURE 1.2.2: Chest X-Ray images of chest, posterior/anterior and lateral view, right middle lobe infiltrate.

transplant recipients [3]. Pathogens to consider in these settings are primarily encapsulated bacteria such as *S pneumoniae* and *Haemophilus influenza* [1, 4, 5]. Mycoplasma infections are commonly seen as well. Viral infections also occur with increased frequency in patients with hypogammaglobulinemia.

ADDITIONAL DATA

Quantitative Igs levels are shown (Table 1.2.1)

DIAGNOSIS

Acute rhinosinusitis was diagnosed by clinical and radiographic findings, but in the context of two hospitalizations for severe pulmonary infections (including one potentially life-threatening illness requiring hospitalization), there was a strong suspicion for hypogammaglobulinemia. Quantitative Ig levels confirmed this diagnosis. Recurrent sinopulmonary infections in a patient with secondary hypogammaglobulinemia in association with CLL was the final diagnosis.

TREATMENT AND OUTCOME

The patient received 12 monthly infusions of intravenous Ig (IVIG) prophylaxis and has not had a serious infection requiring hospitalization during that time. Intravenous Ig therapy was discontinued, and she remained free of infections for the following two years. She had routine follow-up visits with occasional monitoring of her peripheral blood counts as well as serum quantitative Ig levels. Her IgG levels remained above 400 mg/dL.

TABLE 1.2.1. QUANTITATIVE IMMUNOGLOBULIN LEVELS AT DIAGNOSIS OF HYPOGAMMAGLOBULINEMIA

Serum Quant Assay	Level (mg/dL)	Reference Range (mg/dL)
IgG	324	700–1600
IgA	176	70–400
IgM	17	40–230

DISCUSSION

Hypogammaglobulinemia

Clinical manifestations of insufficient antibody levels are primarily recurrent bacterial sinopulmonary infections including pneumonia and sinusitis, although bacterial sepsis and meningitis may occur. Infections with encapsulated bacteria, primarily *H influenzae* and *S pneumoniae*, are most common. Manifestations are not limited to sinopulmonary infections, because chronic *Giardia lamblia* diarrhea, gastrointestinal lymphoid hyperplasia, polymyositis, autoimmune cytopenias, and chronic arthritis also occur [6, 7].

Chronic lymphocytic leukemia is the most common malignancy associated with hypogammaglobulinemia, occurring in 25%–70% of patients diagnosed with CLL [8, 9]. Beyond secondary hypogammaglobulinemia, the immunodeficiency associated with CLL is complex. This is in part evident from the observation that 10%–15% of patients with CLL will develop autoimmune disorders such as hemolytic anemia and immune thrombocytopenia during the course of the illness [10]. The more directly measurable immune abnormalities involve several facets of the immune system and include B-cell hypoproliferation and poor response to antigen challenges (such as vaccines), abnormal T-cell numbers, and function including increased numbers of regulatory T cells (which may dampen

normal immune responses to infectious stimuli), natural killer cell abnormalities with deficient killing ability, and neutrophil defects (e.g. diminished function and impaired migration and chemotaxis). Of note, although this patient population is susceptible to opportunistic infections, infection with cytomegalovirus (CMV) is rare in the absence of exposure to profoundly immunosuppressive agents such as alemtuzumab. It is interesting to note that patients with CLL frequently appear to have normal or increased levels of functional T cells specific to CMV, possibly because chronic low levels of CMV antigenemia may be sufficient to create a stimulus for increased CMV T cell-specific immunity in the host [11]. Despite previously described poor response to vaccines, small observational series suggest that patients with CLL can derive a reasonable degree of measurable protection after vaccines such as influenza [12] and encapsulated organisms [13], and these vaccines should be administered to these patients based on published guidelines (i.e. annual influenza and appropriate pneumococcal vaccinations are recommended). It is generally recommended that this patient population not receive live-attenuated vaccines such as the varicella and zoster vaccines and the measles/mumps/rubella (MMR) vaccine.

The immunodeficiency associated with CLL appears to deepen over time, and the additive effects of immunosuppressive therapies such as nucleoside analog combinations and alemtuzumab that may be required in these patients likely contribute a significant element as well. It is not clear that treatment of the underlying CLL improves these immune defects over time, even when less immunosuppressive therapies (e.g. alkylating agents) are used [14].

Risk Factors

In CLL, the degree of hypogammaglobulinemia correlates with duration and stage of disease. Likewise, the likelihood of recurrent infection correlates with serum levels of Ig [8, 9, 15], particularly IgG [5]. Patients with serum IgG levels lower than 50% of normal were found to be at risk of bacterial infection and can be protected by administration of Ig [16]. Rituximab therapy has been associated with the development of low levels of IgG in 39% (69 of 179) of B-cell lymphoma patients, which led to recurrent sinopulmonary infections requiring IVIG in 6.6% of patients (14 of 211) [17].

Diagnosis of Secondary Hypogammaglobulinemia

Current guidelines for diagnosing and treating hypogammaglobulinemia require prolonged severe deficiency of Ig levels (IgG <400 mg/dL) and a history of recurrent or severe infections [18–22].

Management and Prevention

Evidence supports use of IVIG therapy for patients with acquired hypogammaglobulinemia secondary to malignancy such as CLL and multiple myeloma [2, 3, 18, 21, 23, 24]. Patients are typically treated with IVIG infusions of 400 mg/kg every 3–4 weeks for one year, typically to maintain IgG serum trough levels of 500–800 mg/dL in

BOX 1.2.1 RECOMMENDATIONS ON USE OF PROPHYLACTIC IVIG IN ACQUIRED HYPOGAMMAGLOBULINEMIA IN ADULTS. ADAPTED FROM CONSENSUS RECOMMENDATIONS FROM NATIONAL ADVISORY COMMITTEE ON BLOOD AND BLOOD PRODUCTS OF CANADA AND CANADIAN BLOOD SERVICES, ANDERSON ET AL [18]

- IVIG is recommended for infectious prophylaxis in adults with malignant hematologic disorders associated with hypogammaglobulinemia or dysfunctional gammaglobulinemia and either of the following:
  - (i) a recent episode of a life-threatening infection that is reasonably thought to be caused be low levels of polyclonal immunoglobulins
  - (ii) recurrent episodes of clinical significant infections (e.g. pneumonia) thought to be caused by low levels of polyclonal immunoglobulins.
- Typical dose of IVIG is 400 mg/kg every three weeks for one year
- Re-evaluation of therapy every four–six months

an effort to prevent infections [21, 25]. Guidelines advocate re-evaluation of therapy every 4–6 months [18] (Box 1.2.1). Routine replacement of IVIG in asymptomatic individuals with secondary hypogammaglobulinemia is not currently recommended [2], and it may not be cost effective [26]. It is also important to recognize that IVIG therapy has many potential adverse effects. Although anaphylaxis is rare, mild hypersensitivity reactions are fairly common. Patients may experience pyrexia, rigors, dyspnea, and headache. Renal failure, aseptic meningitis, hemolytic anemia, neutropenia, and dermatitis are several of many other recognized potential toxicities [27].

KEY POINTS

- The immune deficiency associated with lymphoproliferative disorders such as CLL is complex and multifaceted.
- Patients with CLL and other lymphoproliferative disorders or plasma cell dyscrasias are at risk of developing secondary hypogammaglobulinemia.
- Secondary hypogammaglobulinemia can result in recurrent sinopulmonary infections, typically from encapsulated bacteria such as *S pneumoniae* and *H influenzae.*
- Diagnosis requires prolonged IgG levels of less than 400 mg/dL and a history of recurrent or severe infections.
- IVIG infusions every three to four weeks for one year can be considered as therapy in patients who meet diagnostic criteria.

REFERENCES

1. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92:34.
2. Raanani P, Gafter-Gvili A, Paul M, et al. Immunoglobulin prophylaxis in chronic lymphocytic leukemia and multiple myeloma: systematic review and meta-analysis. Leuk Lymphoma 2009;50:764.
3. Raanani P, Gafter-Gvili A, Paul M, et al. Immunoglobulin prophylaxis in hematopoietic stem cell transplantation: systematic review and meta-analysis. J Clin Oncol. 2009; 27:770.
4. Roifman CM, Rao CP, Lederman HM, et al. Increased susceptibility to Mycoplasma infection in patients with hypogammaglobulinemia. Am J Med. 1986;80:590.
5. Umetsu DT, Ambrosino DM, Quinti I, et al. Recurrent sinopulmonary infection and impaired antibody response to bacterial capsular polysaccharide antigen in children with selective IgG-subclass deficiency. N Eng J Med. 1985;313:1247.
6. Baldovino S, Montin D, Martino S, et al. Common variable immunodeficiency: crossroads between infections, inflammation and autoimmunity. Autoimmun Rev. 2013; 12:796.
7. Oksenhendler E, Gerard L, Fieschi C, et al. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis. 2008;46:1547.
8. Rai KR, Sawitsky A. A review of the prognostic role of cytogenetic, phenotypic, morphologic, and immune function characteristics in chronic lymphocytic leukemia. Blood Cells 1987;12:327.
9. Rozman C, Montserrat E, Vinolas N. Serum immunoglobulins in B-chronic lymphocytic leukemia. Natural history and prognostic significance. Cancer 1988;61:279.
10. Moreno C, Hodgson K, Ferrer G, et al. Autoimmune cytopenia in chronic lymphocytic leukemia: prevalence, clinical associations, and prognostic significance. Blood 2010;116:4771.
11. Pourgheysari B, Bruton R, Parry H, et al. The number of cytomegalovirus-specific CD4+ T cells is markedly expanded in patients with B-cell chronic lymphocytic leukemia and determines the total CD4+ T-cell repertoire. Blood 2010;116: 2968.
12. Rapezzi D, Sticchi L, Racchi O, et al. Influenza vaccine in chronic lymphoproliferative disorders and multiple myeloma. Eur J Haematol. 2003;70:225.
13. Sinisalo M, Vilpo J, Itala M, et al. Antibody response to 7-valent conjugated pneumococcal vaccine in patients with chronic lymphocytic leukaemia. Vaccine 2007;26:82.
14. Young JA. Epidemiology and management of infectious complications of contemporary management of chronic leukemias. Infect Disorders Drug Targets 2011;11:3.
15. Fairley GH, Scott RB. Hypogammaglobulinaemia in chronic lymphatic leukaemia. Br Med J. 1961;2:920.
16. Intravenous immunoglobulin for the prevention of infection in chronic lymphocytic leukemia. A randomized, controlled clinical trial. Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia. N Eng J Med. 1988;319:902.
17. Casulo C, Maragulia J, Zelenetz AD. Incidence of hypogammaglobulinemia in patients receiving rituximab and the use of intravenous immunoglobulin for recurrent infections. Clin Lymphoma Myeloma Leuk 2013;13:106.
18. Anderson D, Ali K, Blanchette V, et al. Guidelines on the use of intravenous immune globulin for hematologic conditions. Transfus Med Rev. 2007;21:S9.
19. Centers for Disease Control and Prevention, Infectious Disease Society of America, American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections

among hematopoietic stem cell transplant recipients. MMWR Recomm Rep. 2000;49:1.
20. Orange JS, Hossny EM, Weiler CR, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006;117:S525.
21. Shehata N, Palda V, Bowen T, et al. The use of immunoglobulin therapy for patients with primary immune deficiency: an evidence-based practice guideline. Transfus Med Rev. 2010;24:S28.
22. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biology of blood and marrow transplantation: J Amer Soc Blood Marrow Transplantation 2009;15:1143.
23. Boughton BJ, Jackson N, Lim S, Smith N. Randomized trial of intravenous immunoglobulin prophylaxis for patients with chronic lymphocytic leukaemia and secondary hypogammaglobulinaemia. Clin Lab Haematol. 1995;17:75.
24. Molica S, Musto P, Chiurazzi F, et al. Prophylaxis against infections with low-dose intravenous immunoglobulins (IVIG) in chronic lymphocytic leukemia. Results of a crossover study. Haematologica 1996;81:121.
25. Darabi K, Abdel-Wahab O, Dzik WH. Current usage of intravenous immune globulin and the rationale behind it: the Massachusetts General Hospital data and a review of the literature. Transfusion 2006;46:741.
26. Weeks JC, Tierney MR, Weinstein MC. Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia. N Eng J Med. 1991;325:81.
27. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. Transfus Med Rev. 2003;17:241.

1.3

What's Lurking Beyond the Barricade?

ALLISON L. NAZINITSKY, MD AND STEVEN J. LAWRENCE, MD, MSC

CASE PRESENTATION

A 59-year-old man who had a history of chronic obstructive pulmonary disease presented with fever, cough productive of purulent sputum with intermittent hemoptysis, singultus, right-sided pleuritic chest pain, and hypoxia. He was diagnosed with undifferentiated small cell lung cancer, stage T3N2M0, three months before admission. He was undergoing radiation therapy and was status-post two cycles of cisplatin and etoposide, with the last cycle given 20 days before admission.

Upon admission, he was in moderate distress with fever to 38.4°C and tachycardia from 100–110 beats per minute. His blood pressure was 110/67 mm mercury, respiratory rate was 24 per minute, and oxygen saturation was 92%–96% on a new oxygen requirement of 6 liters per minute via nasal cannula. On exam, he was diaphoretic and dyspneic and unable to speak in full sentences. Head and neck exam was notable for temporal wasting and poor dentition. Cardiac exam showed tachycardia, regular rhythm, and no murmurs. Pulmonary exam was significant for dullness to percussion and decreased breath sounds throughout the right lung field. Egophony was elicited in the right upper lobe.

Laboratory data included white blood cell count (WBC) of 8800/ μL (84% neutrophils), hemoglobin of 8.5g/dL, and platelets of 339 000/ μL. Serum sodium was 135 mEq/L, creatinine was 0.59 mg/dL, liver enzymes were normal, and albumin was 2.5g/dL.

A chest radiograph revealed extensive right upper lung cavitary consolidation with elevation of the right hemidiaphragm (Figure 1.3.1). The left lung was clear.

A chest computed tomography (CT) scan showed a thick-walled cavitary mass (9.1 × 8.7 cm) centered in the right upper lobe extending into the mediastinum and encasing the right main stem bronchus and subsequent branches with associated mediastinal adenopathy, the largest in the subcarinal distribution (2.4 × 1.2 cm) (Figure 1.3.2). The right pulmonary artery and superior pulmonary vein were compressed by the adenopathy. A small right pleural effusion and pleural thickening extended up the mediastinum. This had progressed from a previous scan prior to his chemotherapy.

QUESTIONS

- What pathogens should be considered in the differential diagnosis?
- What diagnostic approach should be taken?
- What are the risk factors for development of this infection?

DIFFERENTIAL DIAGNOSIS

At the top of the differential in this patient with known lung cancer is postobstructive pneumonia, which is generally caused by bacteria (typical and atypical). Mycobacterial or fungal pathogens are other uncommon etiologies. Cavitary and necrotizing pneumonia may develop without obstruction; however, the CT findings in this case suggest consolidation distal to a section of right main stem bronchus that is compressed by either tumor or adenopathy. Noninfectious considerations include radiation pneumonitis, vasculitis, alveolar hemorrhage, atelectasis, bronchiolitis obliterans organizing pneumonia, pulmonary emboli with lung infarctions, and sarcoidosis.

ADDITIONAL DATA

Urinalysis was unremarkable. Blood cultures, human immunodeficiency virus serology, *Histoplasma* urinary antigen, interferon gamma release assay for *Mycobacterium tuberculosis*, and serum galactomannan were all negative.

A thoracentesis was performed obtaining slightly cloudy fluid with 700 WBC (53% neutrophils, 13% lymphocytes, 23% monocytes, 11% mesothelial cells), 111 red blood cells (RBC), pH 7.46, lactate dehydrogenase (LDH) 101, protein 3.2. The serum LDH was 234, and serum total protein was 6.9. The Gram stain and culture were negative.

Bronchoscopy was performed, which showed a friable mass in the right main stem bronchus.

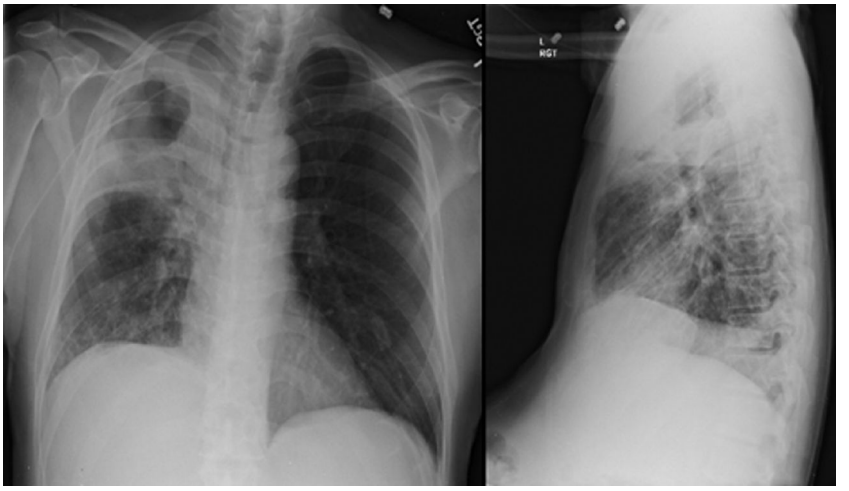


FIGURE 1.3.1: Posterioranterior and lateral chest radiographs demonstrating right upper lobe cavitary consolidation.

Bronchoalveolar lavage (BAL) performed on the right upper lobe revealed pink hazy fluid with 8617 WBC (90% neutrophils, 1% lymphocytes, 6% macrophages), and 10 000 RBC. Gram stain showed normal respiratory flora along with Gram-negative bacilli as the predominant organism. Culture grew normal flora and *Achromobacter xylosoxidans* susceptible to meropenem, piperacillin-tazobactam, and trimethoprim-sulfamethoxazole.

Pathology from a transbronchial biopsy specimen revealed reactive epithelial cells arranged in clusters with mildly enlarged nuclei with smooth nuclear borders and abundant cytoplasm on a background of abundant neutrophils. A Gomori methenamine silver stain was negative for fungal elements.

Final Diagnosis: Given the clinical symptoms of fever, cough, respiratory distress along with imaging and bronchoscopy findings and BAL culture results, the patient was diagnosed with a postobstructive pneumonia.

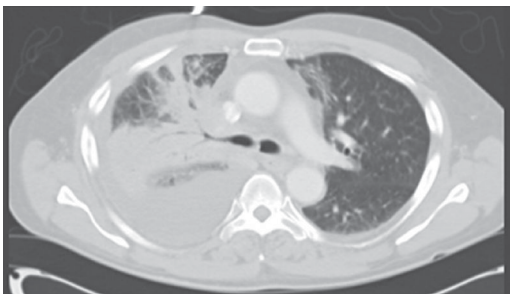


FIGURE 1.3.2: Chest computed tomography scan demonstrating large right upper lobe cavitary mass and mediastinal lymphadenopathy.

TREATMENT AND OUTCOME

Based on the Gram stain and culture results from the BAL specimen, along with the consideration of polymicrobial infection, the patient was treated with meropenem, leading to defervescence and weaning of oxygen to 2 liters per minute via nasal cannula at discharge. Goals of care were addressed, and he was subsequently transitioned to hospice because of his progressive advanced lung cancer.

DISCUSSION

Postobstructive Pneumonia

Malignant and nonmalignant conditions can obstruct the central airways (trachea, mainstem bronchi, and lobar bronchi). Primary lung cancer can affect the central airways in up to 20%–30% of cases and is most associated with squamous cell carcinoma and small cell carcinoma [1–3]. Obstruction of the central airway can lead to consolidation and cause atelectasis, bronchiectasis, mucus plugging, and parenchymal inflammation with or without infection [4].

Differentiating infectious and noninfectious airway changes distal to an obstructing tumor may be clinically and radiographically difficult. Many nonresolving radiologic opacifications may be secondary to physical or chemical effects of airway blockage and can represent tumor necrosis, intra-alveolar fluid, interstitial pneumonitis, and interstitial fibrosis [5]. Many patients undergoing resection of a primary lung cancer may not have histologic evidence of infection distal to the tumor [6].

Few studies have attempted to identify specific pathogens in postobstructive pneumonia

because it is difficult to obtain appropriate specimens. However, when causative organisms are isolated, they are often polymicrobial and include Gram-negative bacilli (*Pseudomonas aeruginosa, Klebsiella pneumoniae, Hemophilus influenzae*), anaerobes (*Peptostreptococcus* spp, *Bacteroides* spp), *Staphylococcus aureus* (including methicillin-resistant isolates), and *Streptococcus* species [3, 7–9]. Invasive tests such as transthoracic needle biopsy and bronchoscopy are more likely to yield a microbiologic diagnosis than sputum Gram stain and culture, which are limited by poor sensitivity and difficulty in distinguishing between a true lower respiratory tract pathogen and colonization of the oropharynx or upper airways [7].

BOX 1.3.1 GENERAL LIST OF BACTERIAL PATHOGENS THAT MAY BE INVOLVED IN A POSTOBSTRUCTIVE PNEUMONIA

Bacteria
Enterobacteriaceae
- *Klebsiella* spp
- *Escherichia coli*
- *Serratia marcescens*
- *Proteus* spp
- *Citrobacter* spp
- *Enterobacter* spp

Other Gram-Negative Rods
- *Achromobacter* spp
- *Acinetobacter* spp
- *Pseudomonas* spp
- *Stenotrophomonas maltophila*
- *Haemophilus influenza*

Anaerobes
- *Actinomyces* spp
- *Bacteroides* spp
- *Fusobacterium* spp
- *Peptostreptococcus* spp
- *Prevotella* spp

Staphylococcus
- Methicillin-sensitive *Staphylococcus aureus*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)

Streptococcus
- Viridans Streptococci
- *Streptococcus milleri*
- *Streptococcus pneumoniae*

Mycobacterium
- *Mycobacterium tuberculosis*
- Non-tuberculous Mycobacteria

Atypical bacteria
- *Legionella pneumophila*

Risk Factors

Patients with obstructing lung cancer have several risk factors that can lead to postobstructive pneumonia, but the unique risk factor is the anatomical obstruction itself. Other risk factors can be divided into individual host factors, immunologic factors and iatrogenic factors, which can be observed in many underlying conditions, especially other oncologic diagnoses [11–13].

BOX 1.3.2 RISK FACTORS THAT MAY BE ASSOCIATED WITH POSTOBSTRUCTIVE PNEUMONIA

HOST FACTORS

Age (especially >65)
Comorbidities
- Chronic obstructive pulmonary disease/bronchiectasis
- Neurologic disorders, dysphagia, absent cough reflex
- Alcoholism
- Poor dentition
- Chronic kidney disease/dialysis

Residence in skilled nursing facility

IMMUNOLOGIC FACTORS

Chemotherapy-induced neutropenia, mucositis
Steroid-mediated immunosuppression
Malnutrition

IATROGENIC FACTORS

Sedating medications (narcotics, benzodiazepines, anticholinergics)
Healthcare exposures (colonization with MDR pathogens)
Prior antibiotic exposure
Antacids (raise gastric pH causing colonization with gram negative rods)
Mechanical ventilation

Clinical Presentation

Postobstructive pneumonias can present several ways. One scenario is a patient with recurrent pneumonia and incomplete clinical or radiographic resolution despite antibiotic therapy. Clinical suspicion for a mass, obstruction, or abscess should be high and should prompt more advanced imaging to further evaluate for malignancy and/or anatomical obstruction [10]. Another scenario is a patient with a known malignancy (lung primary, metastases, lymphoma, etc) in which the tumor itself or corresponding lymphadenopathy can cause obstruction. As the inflammatory process continues, the lung becomes necrotic and can form cavitations.

Diagnosis

Important clinical history includes fevers, chills, pleuritic chest pain, hiccups, worsening dyspnea, cough, or wheezing. Fever has been shown to be associated with the ability to identify a microbiological pathogen [5]. Cough may be secondary to the mass itself or due to the infectious process. Foul-smelling sputum may also be a sign of aspiration and anaerobic bacterial pathogens.

Routine laboratory tests are typically unremarkable, although an elevated WBC may be seen.

A chest radiograph, preferably including posteroanterior and lateral views, should be obtained in patients presenting with a clinical history of pneumonia. However, radiographic findings alone may not always be sufficient for making a diagnosis of postobstructive pneumonia. For patients with a known history of primary lung cancer or metastatic disease in the lungs, it may be difficult to distinguish tumor from infiltrate or atelectasis on standard chest radiographs, even when comparison is made to prior studies. Computed tomography scans of the chest usually provide enough resolution to confirm an obstructing mass and associated distal consolidation.

Blood cultures may yield a predominant pathogen and should be obtained from febrile patients. Sputum specimens are generally of low diagnostic yield but may identify drug-resistant bacteria that could alter antibiotic therapy. Yields are higher for pre-antibiotic, deep cough, purulent specimens that are obtained by coaching the patient or by induction [12]. Parapneumonic pleural effusions should be sampled for Gram stain and cultures, and to exclude an empyema that would require drainage.

Bronchoscopy is often performed in patients with a pneumonia that is not responding to seemingly appropriate therapy to evaluate for airway obstruction and to obtain specimens that could identify drug-resistant organisms. As with sputum samples, bronchoscopically obtained specimens may not identify the causative agent(s) but may indicate organisms colonizing the respiratory tract [12].

Management

A multidisciplinary approach including oncologic treatment (chemotherapy and radiation) to palliatively reduce tumor mass, pulmonary interventions to open airways or obtain invasive samples, and infectious disease input to assist with antibiotic management may be necessary.

Once a diagnosis of postobstructive pneumonia is suspected, patients require empiric antibiotic therapy guided towards likely pathogens (Box 1.3.1) while any microbiologic diagnostic tests are pending. The diagnosis of "healthcare-associated pneumonia (HCAP)" has streamlined broad-spectrum antibiotic administration given the risk for colonization and infection with multidrug-resistant (MDR) pathogens. Antibiotics are tailored to cover polymicrobial pathogens described in Box 1.3.1. It is important to consider using antibiotics with anaerobic coverage regardless of whether the culture has anaerobes present, particularly if the patient exhibits poor dentition, has foul-smelling sputum, or a cavity is seen on imaging. See Box 1.3.3 for a list of examples of empiric therapy.

Antibiotics are typically given for several weeks, depending on response to therapy and whether the obstruction persists. If the airway obstruction is treated, a shorter course of therapy may be used. Relieving airway obstruction to obtain and maintain airway patency can be accomplished by airway dilatation, tracheobronchial stents, ablation, radiotherapy, or cryotherapy. Surgical resection may be necessary in some situations however it may be associated with higher risk of morbidity, mortality, and complications including bronchopleural fistula [14]. If obstruction is unable to be cleared, a longer course of antibiotics may be necessary. Clinical response should be followed closely.

The decision on when to resume chemotherapy and/or radiation treatments can be challenging. Because patients are likely to require weeks of antibiotic therapy, there may be a benefit to early radiation to relieve the obstruction to assist with source control and expectoration. Postobstructive pneumonia develops typically in advanced lung cancer that is noncurable, and goals of care are important to consider.

BOX 1.3.3 EXAMPLES OF EMPIRIC ANTIBIOTIC THERAPY FOR POSTOBSTRUCTIVE PNEUMONIA

MILD INFECTIONS OR TRANSITIONING TO ORAL

Amoxicillin/clavulanate 875 mg po q12hours
Ciprofloxacin 500–750 mg po BID OR levofloxacin 750 mg po q24hours PLUS anaerobic coverage (see below)
Moxifloxacin 400 mg po q24hours

MODERATE TO SEVERE INFECTIONS WITH LOW CONCERN FOR PSEUDOMONAS

Ampicillin/sulbactam 3 grams IV q6hours
Ceftriaxone 1–2 grams IV q24hours PLUS anaerobic coverage (see below)
Ertapenem 1 gram IV q24hours
Moxifloxacin 400 mg po q24hours

CONFIRMED OR MODERATE TO HIGH SUSPICION FOR PSEUDOMONAS

Piperacillin/tazobactam 4.5 grams IV q6hours
Cefepime 2 grams IV q8hours PLUS anaerobic coverage (see below)
Meropenem 2 grams IV q8hours OR imipenem 500–1000 mg IV q6–8hours
Ciprofloxacin 400 mg IV q8hours OR levofloxacin 750 mg IV q24hours PLUS anaerobic coverage (see below)
Aztreonam 2 grams IV q8hours PLUS anaerobic coverage (see below)

ANAEROBIC COVERAGE

Clindamycin 600–900 mg IV q8hours or 450–600 mg po q8hours
Metronidazole 500 mg IV or po q8hours

FOR CONFIRMED OR MODERATE TO HIGH SUSPICION FOR MRSA, ADD THE FOLLOWING:

Vancomycin (goal trough 15–20)
Linezolid 600 mg IV or PO q12hours*
Ceftaroline 600 mg IV q12hours

PATHOGEN-DIRECTED THERAPY

TMP/SMX for Stenotrophomonas maltophila 5 mg/kg IV/PO q8hours

**Need to monitor for toxicity when used for prolonged period of time*
Note: Drug dosages are based on normal kidney and liver function.

Prevention

Postobstructive pneumonia may be difficult to prevent in patients with large obstructive tumors, although this can sometimes be preemptively addressed by placing endobronchial stents in the early stages of bronchial obstruction. Mitigation of reversible risk factors listed in Box 1.3.2 may be important, particularly avoidance of sedating drugs to prevent aspiration.

KEY POINTS

- Postobstructive pneumonia is a clinical diagnosis that relies on symptoms and usually occurs with presence of fever.

- Microbiologic specimens may be difficult to obtain and may be unreliable or not represent the actual pathogen(s).
- A multidisciplinary treatment approach is used depending on goals of care.
- Management includes antibiotics and treating anatomical obstruction (stenting, radiation).
- Broad-spectrum antibiotics covering methicillin-resistant *Staphylococcus aureus* (MRSA), anaerobes, and Gram-negative rods are used to treat symptomatic patients and are typically continued for several weeks.

Acknowledgements: Gram stain courtesy of Morgan Pence, PhD.

REFERENCES

1. Williamson JP, Phillips MJ, Hillman DR, Eastwood PR. Managing obstruction of the central airways. Intern Med J. 2010;40:399.
2. Collins LG, Haines C, Perkel R, Enck RE. Lung cancer: diagnosis and management. Am Fam Physician 2007;75:56.
3. Kohno S, Koga H, Oka M, et al. The pattern of respiratory infection in patients with lung cancer. Tohoku J Exp Med. 1994;173:405.
4. McDonald JR, Harrington SW, Clagett OT. Obstructive pneumonitis of neoplastic origin; an interpretation of one form of so-called atelectasis and its correlation according to presence of absence of sputum. J Thorac Surg. 1949;18:97.
5. Liao WY, Liaw YS, Wang HC, et al. Bacteriology of infected cavitating lung tumor. Am J Respir Crit Care Med. 2000;161:1750.
6. Burke M, Fraser R. Obstructive pneumonitis: a pathologic and pathogenetic reappraisal. Radiology 1988;166:699.
7. Liaw YS, Yang PC, Wu ZG, et al. The bacteriology of obstructive pneumonitis. A prospective study using ultrasound-guided transthoracic needle aspiration. Am J Respir Crit Care Med. 1994;149: 1648.
8. Hsu-Kim C, Hoag JB, Cheng GS, Lund ME. The microbiology of postobstructive pneumonia in lung cancer patients. J Bronchology Interv Pulmonol. 2013;20:266.
9. Rolston KV. The spectrum of pulmonary infections in cancer patients. Curr Opin Oncol. 2001; 13:218.
10. Rome L, Murali G, Lippmann M. Nonresolving pneumonia and mimics of pneumonia. Med Clin North Am. 2001;85:1511.
11. Poch DS, Ost DE. What are the important risk factors for healthcare-associated pneumonia? Semin Respir Crit Care Med. 2009;30:26.
12. Polverino E, Torres A. Diagnostic strategies for healthcare-associated pneumonia. Semin Respir Crit Care Med. 2009;30:36.
13. Nagata N, Nikaido Y, Kido M, et al. Terminal pulmonary infections in patients with lung cancer. Chest. 1993;103:1739.
14. Haraguchi S, Koizumi K, Tanimura S, et al. Surgical results of lung cancer associated with postobstructive pneumonia. Ann Thorac Cardiovasc Surg. 2009;15: 297.

1.4

Alimentary Antimicrobial Apocalypse

KATHLEEN M. MULLANE, DO, PHARMD

CASE PRESENTATION

A 46-year-old woman presented with complaints of fever to 100.8°F, nausea, and diarrhea of twenty-four hours duration.

Several months earlier, she had presented with right leg pain and swelling of two weeks duration. Bilateral duplex of the extremity was negative; however, she was found to have white blood cell (WBC) count of 19 600/mL with 38% blasts. A bone marrow biopsy was performed and was found to be consistent with acute myelomonocytic leukemia (AML) with eosinophilia (with inv(16), CBFB-MYH11 positive, FLT3/CEBPA negative). Cytoreduction therapy with hydroxyurea was initiated followed by induction chemotherapy (cytarabine/hydroxyurea/idarubicin) with complete remission and then desatinib for 21 days. Her initial course was uncomplicated by abdominal complaints or diarrhea but was complicated by sinusitis that was treated initially with clindamycin. On sinus surgery, she was found to have a fungal ball without evidence of invasive fungal sinusitis, and cultures returned positive for *Pseudomonas aeruginosa* for which she was treated with ciprofloxacin. She remained neutropenic for a prolonged period.

Eight weeks later, she was admitted for second consolidation chemotherapy with cytarabine followed by desatinib. She received antimicrobial prophylaxis with acyclovir, micafungin (chosen due to drug interaction with desatinib and azole antifungals), and oral levofloxacin. Her course was complicated by neutropenic fever and *Streptococcus mitis* bacteremia for which she was treated with cefepime and vancomycin while neutropenic and was transitioned to ceftriaxone when counts recovered, completing three weeks of antimicrobial therapy. Follow-up blood cultures off antimicrobials and prior to her second course of consolidation chemotherapy documented resolution of bacteremia. For her second consolidation, antibacterial prophylaxis was changed to amoxicillin/clavulanate plus ciprofloxacin, as well as acyclovir and micafungin.

Two weeks after completion of the second consolidation course, she presented with complaints of fever to 100.8°F, nausea, and diarrhea of 24 hours duration. There was no report of sick contacts or eating undercooked meat or fish. The patient reported drinking only bottled water. She denied excursions outside her home since her recent discharge. On admission, blood pressure was 141/70 mm mercury, pulse was 71 beats per minute, and respiratory rate was 16 breaths per minute. Physical examination was without localizing findings.

The patient was neutropenic (absolute neutrophil count 10/μL), anemic (hematocrit 20.7), and thrombocytopenic (10 000/μL). Serum chemistries were within normal limits including the creatinine. Therapy was initiated with cefepime per institutional neutropenic fever protocol.

QUESTIONS

- What infectious etiologies should be considered to explain this patient's diarrheal illness?
- What diagnostic approach should be taken?
- What are the risk factors for development of infection?

DIFFERENTIAL DIAGNOSIS

Diarrhea is common in cancer patients and may be related to paraneoplastic syndromes, chemotherapeutic agents, radiation therapy, antimicrobial agents, as well as infections. Infections to consider in an immunosuppressed cancer patient include viral pathogens (enteroviruses, Norwalk virus, rotavirus, adenovirus, and less likely cytomegalovirus [CMV]), *Clostridium difficile*, enteric pathogens (*Campylobacter, Escherichia coli, Salmonella, Shigella, Vibrio* spp, *Yersinia*), and, if exposure history suggests, parasites (*Cryptosporidia, Cyclospora, Entamoeba histolytica, Giardia*). By far, however, *C*

difficile is the most likely cause of infectious diarrhea in this patient population.

ADDITIONAL DATA

Blood and urine cultures were obtained, and stool was sent for culture and *C difficile* polymerase chain reaction (PCR) testing. Because the stool was formed, *C difficile* testing was not performed by the laboratory. Stool culture returned negative, ova and parasite examination was negative, PCR testing for CMV and adenovirus in blood and for adenovirus 40/41 (associated with gastroenteritis) in the stool were negative. The patient continued to complain of "explosive diarrhea" associated with nausea and cramping as well as rectal pain occurring every thirty minutes. On hospital day 4, a stool (liquid) specimen was sent for *C difficile* PCR and returned positive.

TREATMENT AND OUTCOME

Oral metronidazole 500 mg administered every eight hours was started. Her frequency of diarrhea increased, and oral vancomycin 500 mg every six hours was added. The frequency and volume of diarrhea improved, and the patient was discharged on oral vancomycin 500 mg every six hours to complete a fourteen-day course of therapy. She was admitted seven days later for consolidation cycle 3. One week after discharge, she presented with neutropenic fever and diarrhea. Therapy was started with cefepime and metronidazole, and stool *C difficile* PCR was sent and returned positive, constituting her first relapse. Metronidazole was discontinued and oral vancomycin was initiated. She was discharged on a planned four-week course of oral vancomycin.

She was admitted for consolidation cycle 4 one week later. The patient was maintained on desatinib therapy for her AML, and oral vancomycin was continued for the next eight weeks and was tapered off over three weeks. The patient had a second relapse of *Clostridium difficile* infection (CDI) three weeks later and was again treated with a vancomycin taper over eight weeks. She relapsed one week later, for the third time, and was referred to an Infectious Diseases consultant who treated her with oral vancomycin for three weeks, with resolution of diarrhea, followed by a two-week course of fidaxomicin 200 mg orally twice daily. Three weeks after completion of fidaxomicin, a fourth relapse of *C difficile* occurred [1]. The patient was treated with a fidaxomicin for three weeks followed by an enema-delivered fecal microbiota transplant (FMT). She has remained CDI free for over one year.

DISCUSSION

In adult cancer patients, CDI occurs in 5%–9% of chemotherapy courses and 5%–20% of patients, respectively [2–4]. In the stem cell transplant population, this rate increases to as high as 30%. Clinically defined "chemotherapy-associated bowel syndrome" predicts severe complications and death in cancer patients. In a multicentered survey of 11 cancer centers, hospitalized cancer patients acquired CDI at twice the rates reported for all US hospitalized patients (15.8 vs 7.4 per 10 000 patient days), regardless of diagnostic assay used [5]. Not only do cancer patients have higher rates of CDI than the general hospital population, cancer patients have lower cure rates and longer time to resolution of diarrhea with CDI therapy than patients without cancer [6]. In addition, cancer patients with CDI have been reported to have prolonged hospitalizations, interruption or withdrawal of curative chemotherapy and radiation therapy, and death due to CDI [7].

Risk Factors

Risk factors for CDI include prior antimicrobial use (especially clindamycin, fluoroquinolones, and broad-spectrum cephalosporins), chemotherapy (especially antimetabolites such as methotrexate, 5-fluorouracil, capcitabine, and cyclophosphamide; topoisomerase inhibitors; anthracyclines; taxanes; and vinca alkaloids), advanced age, exposure to *C difficile* as noted in long-term and acute healthcare settings where the population is enriched with patients colonized with the organism, prolonged length of hospital stay, inflammatory bowel disease, chronic kidney disease, and possibly use of proton-pump inhibitors [7–10].

Cancer patients provide the perfect storm in risk for CDI. Whether the profound immunological changes due to cancer alone without chemotherapy can lead to CDI is not known. Risk factors for CDI common in the oncology population include depressed function of immune response (specifically neutropenia and lower antibody production directed against clostridial toxins A and B), recurrent and prolonged hospitalizations, and repeated antibiotic and chemotherapeutic treatments. Because both chemotherapeutic agents and antibiotics can induce CDI, it is often difficult to distinguish which is the culprit. Both antibiotics and chemotherapeutic agents can alter the intestinal microbiome for prolonged periods after treatment has concluded. In addition, chemotherapeutic agents promote inflammatory changes in the gut and may induce intestinal

necrosis and an anaerobic, protein-enriched environment conducive to *C difficile* proliferation while inhibiting degradation of *C difficile* toxins [11]. Although classically described as a nosocomial process, community-acquired CDI is now more common than previously reported and in populations previously considered at low risk for infection [12, 13]. Cancer patients have frequent healthcare-associated clinic visits, frequent antibiotic courses (as in the case described), and recurrent chemotherapeutic interventions, even in the outpatient setting, and this population is one uniquely at risk for CDI.

Diagnosis

Because diarrhea is a common complaint in cancer patients, healthcare personnel should have a high index of suspicion of CDI and access to rapid, sensitive, and specific testing to rule out CDI as the cause of diarrhea. *Clostridium difficile* infection is defined as having symptoms of diarrhea (>3 unformed bowel movements in 24 or fewer consecutive hours) and having a diagnostic test positive for the presence of *C difficile* toxins or toxigenic *C difficile* or colonoscopic/histopathologic findings demonstrating pseudomembranous colitis. Testing for *C difficile* or its toxins should only be performed on unformed stool, unless ileus due to *C difficile* is suspected [14]. Stool culture is the most sensitive test, but it is not clinically practical due to difficulties in culturing techniques and slow turn around time. Enzyme immunoassay (EIA) testing for clostridial toxins A and/or B is rapid and specific but not sensitive. Enzyme immunoassay sensitivity has been reported to range from 35% to 85% [15]. Given its low positive predictive value and increased risk of false-positive tests on repeat specimen testing, there is no additional advantage to sending multiple specimens for EIA analysis in order to diagnose CDI. However, because false-negative results on EIA are frequent, negative results in a strongly suspected case of CDI may warrant testing by another more sensitive method. To enhance sensitivity, some institutions utilize a two-step method testing specimens first for glutamate dehydrogenase by EIA, a sensitive but nonspecific test, with specimens screening positive then tested using a cell toxin-specific EIA, cytotoxicity assay, toxigenic culture, or PCR [16]. Polymerase chain reaction testing for the genes that code for the production of toxin A and/or B is rapid, sensitive (93.3%), and specific (97.4%) [17]. However, because individuals may have asymptomatic carriage of *C difficile* possessing the toxin-producing genetic locus as part of their normal gut microbiome, in order to diagnose CDI, testing must be done on unformed fecal specimens.

Because individuals may harbor preformed toxin or toxigenic *C difficile* spores, repeat testing during the same episode of illness or as test of cure should not be undertaken. Studies have shown that ≥50% of hospitalized patients colonized by *C difficile* are symptomless carriers.

Management

In the management of diarrhea in cancer patients, empirical therapy for *C difficile* is not recommended, when diagnostic testing is available, unless the patient is severely ill (hemodynamically unstable and/or ileus, and/or toxic megacolon) or has been diagnosed with CDI in the recent past, because even in an epidemic setting, only 30% of patients with antibiotic-associated diarrhea will have proven CDI [14, 18–20].

There is little prospective and validated data relating clinical predictors of outcome for CDI, but the factors that appear to correlate best with risk of recurrences, complications of CDI, and mortality from CDI include fever >38.5°C, presence of an ileus or megacolon, leukocytosis (>15 000/μL), serum albumin <3 mg/dL, renal failure and/or a rise of serum creatinine >50% of baseline, age ≥65 years, severe underlying comorbid illness (cancer, altered mental status, cardiopulmonary disease, inflammatory bowel disease, hypogammaglobulinemia), and the need for concurrent antimicrobial therapy. *Clostridium difficile* infection should be judged to be severe if two or more of these risks factors are present (Boxes 1.4.1 and 1.4.2).

Although these factors have been used to differentiate mild, moderate, and severe cases of CDI, these factors have not been validated in the immunocompromised patient population.

Primary therapy for patients suspected or diagnosed as having CDI is discontinuation of any unnecessary antimicrobial agents. Fluid and electrolyte replacement therapy should be initiated, and antiperistaltic agents to control diarrhea should avoided, whereas use of agents that suppress stomach acid secretion should be reviewed for necessity.

The current Infectious Diseases Society of America/Society of Healthcare Epidemiologists (IDSA/SHEA) developed before the release of fidaxomicin in 2011 advocates oral metronidazole in cases of mild to moderate disease, oral vancomycin for serious CDI, and combination therapy with enteral vancomycin and intravenous metronidazole in cases of ileus or toxic

BOX 1.4.1 RISK FACTORS FOR SEVERE CDI (CDI IS JUDGED TO BE SEVERE WHEN ONE OR MORE FACTORS PRESENT)

CONSTITUTIONAL

Age >65 years
Fever >38.5°C
Hemodynamic instability/shock
Respiratory failure
Severe underlying disease comorbidity or immunodeficiency

PHYSICAL EXAMINATION

Signs and symptoms of peritonitis
Signs and symptoms of ileus

LABORATORY

Leukocytosis (WBC count >15 000 cells/μL with >20% band forms)
Rise in serum creatinine >1.5 times baseline value
Albumin <3.0 mg/dL

COLONOSCOPY

Presence of pseudomembranous colitis

RADIOGRAPHIC FINDINGS

Distention of the large bowel (>6 cm in transverse width)
Colonic wall thickening
Pericolonic fat stranding
Ascites without other known causes

Adapted from:
Clin Microbiol Infect. 2014;S2:1; Infect Control Hosp Epidemiol. 2010;5:431.

BOX 1.4.2 RISK FACTORS FOR RISK OF RELAPSE/ RECURRENT CDI

Age >65 years
Need for concomitant antibiotic therapy
History of more than one recurrence of CDI
Severe underlying disease/ immunodeficiency
Chronic kidney disease
Use of stomach acid suppressing agents (i.e. proton pump inhibitors)
Initial disease severity

megacolon [14, 21] (Table 1.4.1). For first relapse, these guidelines recommend using the same therapy as the initial regimen unless the WBC count is ≥15 000 cells/μL or in cases where there is a rising creatinine; in the latter case, vancomycin is recommended. The American Society of Gastroenterology guidelines mirror the published IDSA/SHEA guidelines for treatment of initial and recurrent CDI with the additional recommendation of FMT for third recurrence of CDI [19]. In the latest guidelines published by the European Society of Clinical Microbiology and Infectious Diseases, treatment with metronidazole, vancomycin, or fidaxomicin is recommended as initial oral antimicrobial therapy of "non-severe" disease [20]. Vancomycin or fidaxomicin is recommended for treatment of severe CDI, and intravenous metronidazole is recommended for those subjects who are unable to have orally administered therapy.

There are many small uncontrolled studies evaluating different agents in managing second CDI recurrence or subsequent episodes (Table 1.4.2); however, there is only one published randomized clinical trial, and based on these data, tapering or pulsed dosing of vancomycin is currently recommended for management of these cases in published treatment guidelines [22]. Fecal microbiota transplant has also been reported as a treatment option in individuals with recurrent CDI. Fecal microbiota transplant is a procedure in which stool from a healthy donor is delivered into the duodenum or colon of the patient. Fecal microbiota transplant has been shown to be an effective treatment for recurrent CDI [23]. Duodenal infusion of donor feces after a three-day course of vancomycin in individuals with recurrent CDI in whom vancomycin had failed was compared with a fourteen-day course of vancomycin with or without bowel lavage by van Nood et al [24]. Subjects in the study arm who received donor fecal infusion had significantly higher (81%) cure rates than either of the vancomycin arms (31% vancomycin alone and 23% vancomycin plus bowel lavage).

TABLE 1.4.1. TREATMENT OF CDI

Clinical Definition	Recommended Therapy
Initial episode with mild to moderate CDI	A Metronidazole 500 mg po q8H for 10–14 days B Vancomycin 125 mg po qid for 10 days *OR* Fidaxomicin 200 mg po bid for 10 days
Initial episode with severe CDI	A Vancomycin 125 mg po qid for 10 days B Vancomycin 500 mg po qid for 10 days *OR* Fidaxomicin 200 mg po bid for 10 days
Initial episode, severe complicated CDI (hypotension, ileus, megacolon)	Vancomycin 500 mg po/NG tube every 6 hours *PLUS* metronidazole 500 mg q8H. If complete ileus consider vancomycin rectal enemas* If complete ileus or evidence of an acute abdomen consider surgical consultation
First recurrence	Same a initial episode
Second recurrence or more	Consider Infectious Diseases consultation Vancomycin tapered and/or pulsed regimen If greater than 2 recurrences, consider fecal microbial transplant based on degree of immunosuppression of patient

A, primary recommendation; B, secondary recommendation.
Adapted from: *Infect Control Hosp Epidemiol*. 2010;31:431, *Am J Gastroenterol*. 2013;108:478, *Clin Microbiol Infect*. 2014;20(Suppl 2):1.
*Vancomycin rectal enema: 0.5–1.0 grams vancomycin in 1000cc NS instilled as a retention enema.

TABLE 1.4.2. AVAILABLE ANTIBIOTICS FOR THE MANAGEMENT OF CDI

Agent	Dose	Relative Efficacy/ Recurrence Risk	Adverse Events
Metronidazole	500 mg po tid × 10 d or 250 mg po qid × 10–14 d	++ / ++	Nausea, neuropathy, abnormal taste in mouth. (Not an FDA-approved indication.)
Fidaxomicin	200 mg po bid × 10 d	+++ / +	Not absorbed, therefore systemic symptoms unlikely. Abdominal pain, nausea, vomiting, anemia, neutropenia, bowel obstruction and GI hemorrhage.
Vancomycin	Initial therapy: 125 mg po qid × 10 d Recurrence therapy: "tapering dose" 125 mg po qid × 10–14 d, then 125 mg po bid per day × 1 wk, then 125 mg po once daily × 1 wk, then 125 mg po every 2–3 d for 2–8 wks.	+++ / ++	Not absorbed, therefore systemic symptoms unlikely. Nausea

Other agents reported to have activity against CDI without FDA-approved indication

Agent	Dose	Relative Efficacy/ Recurrence Risk	Adverse Events
Nitazoxanide	500 mg po bid × 10 d	++ / ++	Nausea, diarrhea, abdominal pain.
Rifaximin	400 mg po tid × 10 d or "chaser" regimen 400 mg po bid × 14 d	++ / +?	Headaches, abdominal pain, nausea, flatulence, not absorbed.
Teicoplanin	400 mg po bid × 10 d	+++ / ++	Not absorbed so systemic symptoms unlikely.
Tigecycline	50 mg iv every 12 hrs × 10 d	++? /?	Nausea, vomiting, diarrhea.
Bacitracin	25000 units po qid × 10 d	+ / +++	Minimal absorbed, poor taste.
Fusidic acid	250 mg po tid × 10 d	++ / ++	Nausea, vomiting, epigastric pain, anorexia.

Adapted from: *Clin Microbiol Infect*. 2012;18 (Suppl 6):28 and *Clin Infect Dis*. 2012;55:S71.

Prevention

Because of lag in specimen collection, testing, and reporting, some institutions preemptively place hospitalized individuals with diarrhea in contact isolation (meaning that all healthcare workers and visitors must practice hand hygiene and wear gloves and gown on entry and discard these before exiting the patient room). Because alcohol does not destroy *C difficile* spores, hand washing with soap and water for hand hygiene over alcohol-based preparations should be emphasized when caring for individuals with CDI because the mechanical action of scrubbing and drying has been shown to reduce carriage of spores in healthcare workers. Contact precautions should be continued until diarrhea has resolved and the patient is not incontinent.

Chlorine-containing cleaning agents or other sporicidal agents should be used to clean the patient environment, and disposable thermometers, blood pressure cuffs, and stethoscopes should be used in patient care. Terminal room cleaning should be performed as well with a chlorine-containing cleaning agent or sporicidal agent.

Although a difficult issue in the immunocompromised population, minimization of the frequency of use and duration of antimicrobial therapy and the number of agents prescribed can reduce CDI risk. There are limited data to support the use of currently available probiotics as primary prevention of CDI, and in the immunocompromised patient population there is a risk of blood stream infection from use of these agents; therefore, probiotics cannot be routinely recommended.

KEY POINTS

- Diarrhea is common in individuals undergoing chemotherapy, and the differential should include CDI.
- To prevent nosocomial spread of CDI, all patients with diarrhea should be placed on contact precautions until an infectious etiology for the diarrhea is ruled out. Empiric treatment for CDI is discouraged if testing is readily available and the patient is hemodynamically stable.
- Oncology patients receiving chemotherapy with or without antimicrobial agents are at high risk for the development of severe CDI and for relapse after CDI-directed therapy.
- For mild to moderate risk patients with an initial episode of CDI and without having risk factors for relapse, metronidazole remains the treatment of choice.
- For those patients with mild to moderate CDI with two or more risk factors for relapse, those with severe CDI, and those who are first relapse of CDI, vancomycin or fidaxomicin is superior to metronidazole.
- For second relapse of CDI, a prolonged course of vancomycin or fidaxomicin (pulsed or tapered therapy) should be considered.
- For multiple relapses, FMT could be considered depending on the degree of immunosuppression experienced by the patient.

REFERENCES

1. Johnson S, Gerding D. Fidaxomicin "chaser" regimen following vancomycin for patients with multiple *Clostridium difficile* recurrences. Clin Infect Dis. 2013;56:309.
2. Vehreschild MJ, Meissner AM, Cornely OA, et al. Clinically defined chemotherapy-associated bowel syndrome predicts severe complications and death in cancer patients. Haematologica 2011;96:1855.
3. Gorschluter M, Glasmacher A, Hahn C, et al. *Clostridium difficile* infection in patients with neutropenia. Clin Infec Dis. 2001;33:786.
4. Chopra T, Chandrasekar PH, Salimnia H, et al. Current epidemiology of *Clostridium difficile* associated disease (CDAD) in hematopoietic stem cell transplant recipients (HSCT). In: 45th Annual Meeting Infectious Diseases Society of America (IDSA); October 4–7, 2007; San Diego, CA.
5. Kamboj M, Son C, Cantu S, et al. Hospital-onset *Clostridium difficile* infection rates in persons with cancer of hematopoietic stem cell transplant: a C3IC network report. Infect Control Hosp Epidemiol. 2012;33:1162.
6. Cornely OA, Miller MA, Fantin B, et al. Resolution of *Clostridium difficile*-associated diarrhea in patients with cancer treated with fidaxomicin or vancomycin. J Clin Oncol. 2013;31:2493.
7. Hautmann MG, Hipp M, Kolbl O. *Clostridium difficile* associated diarrhea in radiooncology: an underestimated problem for the feasibility of radiooncological treatment? Radiat Oncol. 2011;6:1.
8. Mullane K. Fidaxomicin in *Clostridium difficile* infection: latest evidence and clinical guidance. Ther Adv Chronic Dis. 2014;5:69.
9. Chopa T, Alangaden GJ, Chandrasekar P. *Clostridium difficile* infection in cancer patients and hematopoietic stem cell transplant recipients. Expert Rev Anti Infec Ther. 2010;8:1113.
10. Kamthan AD, Bruckner HW, Hirschman SZ, Agus SG. *Clostridium difficile* diarrhea induced by cancer chemotherapy Arch Intern Med. 1992;152:1715.

11. Anand A, Glatt AE. *Clostridium difficile* infection associated with antineoplastic chemotherapy: a review. Clin Infect Dis. 1993;17:109.
12. Lessa FC, Gould CV, McDonald LC. Current status of *Clostridium difficile* infection epidemiology. Clin Infect Dis. 2012;55:S65.
13. Khanna S, Pardi D, Aronson S, et al. The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. Am J Gastroenterol. 2012;107:89.
14. Cohen SH, Gerding DN, Johnson S, et al. Guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society of Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol 2010;31:431.
15. Peterson LR, Robicsek A. Does my patient have *Clostridium difficile* infection? Ann Intern Med. 2009;151:176.
16. Eastwood K, Else P, Charlett A, Wilcox M. Comparison of nine commercially available *Clostridium difficile* toxin detection assays, real time OCR assay for *C. difficile tcdB*, and a glutamate dehydrogenase detection assay to cytotoxin testing and cytotoxigenic culture methods. J Clin Microbiol. 2009;47:3211.
17. Peterson LR, Manson RU, Paule SM, et al. Detection of toxigenic *Clostridium difficile* in stool samples by real time polymerase chain reaction for the diagnosis of *C. difficile*-associated diarrhea. Clin Infect Dis. 2007;45:1152.
18. Bartlet JG. Clinical practice. Antibiotic-associated diarrhea. N Engl J Med. 2002;346:334
19. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment and prevention of *Clostridium difficile* infection. Am J Gastroenterol. 2013;108:478.
20. Debast AB, Bauer MP, Kuijper EJ; European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. Clin Microbiol Infect 2014;20:1.
21. Bauer MP, Kuijper EJ, van Dissel JT; European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for *Clostridium difficile* infection (CDI). Clin Microbiol Infect. 2009;15:1067.
22. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. Am J Gastroenterol. 2002;97:1769.
23. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. Clin Infect Dis. 2011;53:994.
24. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med. 2013; 368: 407.

1.5

Not Appendicitis in a Neutropenic Host

KARI NEEMANN, MD

CASE PRESENTATION

A 68-year-old female with a one-month history of marginal cell lymphoma with leptomeningeal involvement presented with a two-day history of worsening, diffuse abdominal pain and two to three episodes/day of loose, blackish stools. Her chemotherapy regimen at presentation had included three doses of intrathecal (IT) methotrexate (MTX), two doses of rituximab, decadron, and one day prior to admission she had received one dose of IT cytarabine for failure to improve on MTX alone. Her infection prophylaxis consisted of oral trimethoprim/sulfamethoxazole twice weekly. She denied history of blood in stool, minimal nausea, and no emesis. She had a past history of breast cancer status-post chemoradiation and resection, melanoma, and basal cell carcinoma status-post Mohs procedure, hypertension, type II diabetes, and gout.

On initial exam, the patient appeared ill, was moaning, inattentive, and only oriented to person. Her temperature was 37.0°C, heart rate 114 bpm, and blood pressure 72/49 mm mercury. Abdominal exam was notable for moderate distension, rare bowel sounds, and severe tenderness to palpation of the bilateral lower quadrants with rebound tenderness. Laboratory results revealed a white blood count (WBC) of 300 cells/mm^3 (0% neutrophils), a dramatic decrease from the WBC documented one day prior to admission (WBC 4800 cells/mm^3 with 94% neutrophils). The hemoglobin was 8.9 g/dL and platelet count was 81 000/mm^3. Serum creatinine was elevated from baseline at 1.3 mg/dL (range, 0.7–0.9 mg/dL). Coagulation studies were remarkable for an elevated ***prothrombin time***, international normalized ratio, and ***partial thromboplastin time*** (51 seconds, 4.5 seconds, and 39.5 seconds, respectively). ***Aspartate aminotransferase*** and ***alanine aminotransferase*** were normal at 23 U/L and 37 U/L, respectively. Blood cultures were obtained. Computed tomography (CT) scan of abdomen and pelvis revealed a pancolitis with colonic wall thickening of the distal transverse, splenic flexure, descending colon, and sigmoid colon concerning for an infectious or inflammatory colitis. Ischemia was believed less likely due to the distribution, and no free air was seen to suggest perforation (Figure 1.5.1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of an immunocompromised patient presenting with abdominal pain with associated diarrhea is numerous because

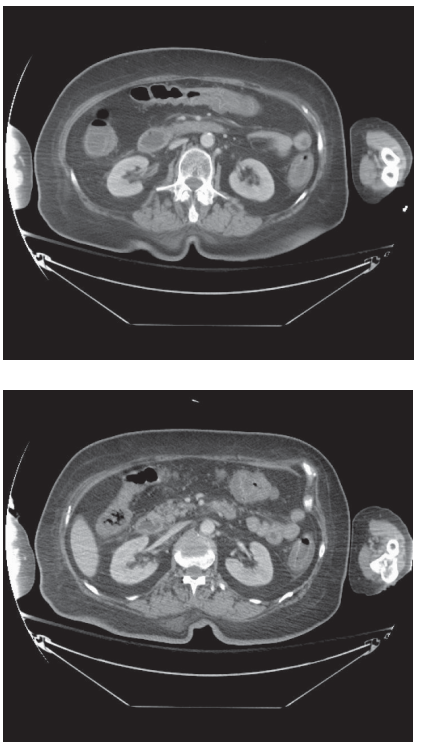


FIGURE 1.5.1: Computed tomography of abdomen/pelvis with pancolitis noted; with colonic wall thickening of the distal transverse, splenic flexure, descending colon, and sigmoid colon.

several conditions present with similar clinic findings. Conditions that may present in a similar fashion to the described patient include bacterial (*Salmonella, Campylobacter, Shigella*, enterotoxigenic *Escherichia coli*) and viral (norovirus, rotavirus, adenoviruses, astrovirus) gastroenteritis, neutropenic enterocolitis (NE), *Clostridium difficile* colitis, intussusception, diverticulitis, ischemic colitis, and appendicitis. If this was a post-allogeneic hematopoietic stem cell transplant patient, then cytomegalovirus (CMV) infection and graft-versus-host disease (GHVD) would also need to be considered. High-quality imaging is critical in that it allows us to narrow the differential. In the patient presented, the CT was able to demonstrate a diffuse colonic thickening that, along with her neutropenia and recent frequent medical access, put NE and *C difficile* colitis at the top of the differential.

INITIAL MANAGEMENT

The patient was admitted to the intensive care unit for fluid resuscitation and vasopressor support. Empiric broad-spectrum antibacterial coverage consisted of cefepime, vancomycin, and metronidazole. Antifungal therapy with micafungin and treatment with granulocyte colony-stimulating factor (G-CSF) were also initiated on admission. Blood component replacement therapy was begun to manage the disseminated intravascular coagulation. Stool enzyme immunoassay tests for *C difficile* A/B toxin and glutamate dehydrogenase were negative, indicating that *C difficile* was not causing the illness observed. She was made NPO, and surgical consult was obtained for suspected impending perforation, but surgical intervention was declined by the family.

Final Diagnosis: Neutropenic enterocolitis with likely perforation of the bowel

TREATMENT AND OUTCOME

Over the following forty-eight to seventy-two hours, the patient had deterioration of her mental status and required mechanical ventilation and increasing vasopressor support. She continued with several episodes of melenic stools daily and persistent rebound tenderness of the entire abdomen, with distention. On the third day of hospitalization, supportive care was discontinued and the patient died.

DISCUSSION

Neutropenic Enterocolitis

Patients receiving chemotherapy for malignancy will frequently develop infections of the intestinal tract, especially during periods of neutropenia. Several syndromes that overlap in clinical presentation have been described during this period and include the following: cholecystitis, diverticulitis, CMV infection, *C difficile*-associated colitis, GHVD, and NE. These entities are often difficult to distinguish based on clinical manifestations alone because they all can present with fever, abdominal pain, distension, and diarrhea. Neutropenic enterocolitis was classically called "typhlitis" (typhlon or cecum, from the Greek word typhlos meaning blind or closed) in reference to the cecum as the most frequent location of the inflammation, although, in practice, the inflammation can be seen throughout the colon [1]. The disease varies in its clinical severity from mild, or nonnecrotizing, form to a severe transmural process that often foreshadows a poor prognosis, including death. The incidence has ranged from 2.35%–6% in acute leukemia [2–5], 5.3% (266 of 5058; 95% confidence interval, 4.7%–5.9%) in patients hospitalized for hematological malignancies, or for high-dose chemotherapy in solid tumors or for aplastic anemia [6]; it is approximately 12% in post autologous stem cell transplant [7]. Neutropenic enterocolitis typically occurs five to fourteen days after commencement of chemotherapy, during the neutropenic phase [8, 9].

The pathogenesis of NE is thought to result from a combination of mucosal injury secondary to cytotoxic drugs, neutropenia, and impaired host defense to intestinal organisms. The initial insult appears to be disruption of the bowel mucosa from either the cytotoxic effect of chemotherapy or the leukemic infiltrates themselves. The disruption of the mucosa in combination with either overgrowth of microbial species native to the gut or from acquisition of nosocomial flora associated with concurrent empiric broad-spectrum (usually prophylactic) antibiotic administration often promotes bacterial invasion of the bowel wall, aided by decreased defense mechanisms associated with neutropenia and cytoreductive chemotherapy. Lastly, the bacterial endotoxins produced can lead to increased necrosis and hemorrhage [10–13]. Organisms commonly associated with NE include *Clostridium* species, *Pseudomonas* species, *E coli*, and Candida species, although a broad range of pathogens may be involved [12, 14, 15]. On autopsy or surgical pathology specimens, the gross appearance of the bowel demonstrates a dilated, edematous, and frequently hemorrhagic external appearance [15]. Microscopically, there is edema of the mucosa or the entire intestinal wall, mucosal ulcerations, focal hemorrhage, and mucosal or transmural necrosis [9, 15].

BOX 1.5.1 CHEMOTHERAPEUTIC AGENTS LINKED TO NEUTROPENIC ENTEROCOLITIS

cytosine-arabinoside	methotrexate
etoposide	vincristine
daunorubicin	carboplatin
doxorubicin	prednisone
capecitabine	paclitaxel
5-fluorouracil	docetaxel

BOX 1.5.2 DIAGNOSTIC CRITERIA FOR NEUTROPENIC ENTEROCOLITIS[a]

Major	Finding
	Neutropenia
	ANC <500 × 109 cells/L
	Bowel wall thickening on CT or US
	>4 mm thickening in any segment of bowel
	Fever
	>38.3°C
Minor	Abdominal pain
	Abdominal cramping
	Abdominal distention
	Diarrhea
	Lower GI bleeding

Abbreviations: ANC, absolute neutrophil count; GI, gastrointestinal.
[a] *Adapted from Eur J Haematol. 2005;75:1.*

Risk Factors

Neutropenic enterocolitis was first described in pediatric patients receiving therapy for various malignancies but primarily acute leukemia [16]. It is interesting to note that case reports exist of NE as the presenting clinical syndrome of acute leukemia and in individuals with aplastic anemia and cyclic neutropenia who have not received chemotherapeutic agents [17, 18]. Agents most commonly associated with typhlitis include cytosine-arabinoside, etoposide, and daunorubicin. Other implicated agents include doxorubicin, capecitabine, 5-fluorouracil, MTX, vincristine, carboplatin, and prednisone [19–25]. Most recently, taxanes (paclitaxel, docetaxel) therapy alone or in combination with other therapy frequently used for solid tumors has been demonstrated as an additional risk factor for NE [26–29] (Box 1.5.1).

Clinical Presentation and Diagnosis

Patients with NE may present with fever, abdominal pain (often localized to the right lower quadrant), distention, diarrhea, bloody stools, nausea, and vomiting [11, 14]. Paralytic ileus may develop occasionally, but it is relatively uncommon. Serial abdominal exams to evaluate for progression of disease should be performed until resolution of symptoms, often beyond the recovery from neutropenia. These clinical manifestations are nonspecific and could be associated with a number of other abdominal processes [30]. Gorschlüter et al [6] have proposed the following case definition including both clinical and radiological criteria: neutropenic fever, abdominal pain, and any bowel wall thickening >4 mm detected by ultrasonography (US) or CT (Box 1.5.2).

Computed tomography of abdomen is the current radiological investigation of choice because it provides for a clearer delineation among multiple disorders capable of causing differing degrees of bowel wall thickening [1, 5]. Suggestive features include colonic mural thickening (>4 mm in a distended bowel segment) with low-density areas representing edema and/or necrosis, pericolic inflammation (evidenced by fat stranding), ascites, pneumatosis intestinalis, and free air in the presence of underlying mural necrosis and perforation [9]. Mural thickness of >10 mm has been associated with poorer outcome among patients with NE [5, 31]. Ultrasound imaging, which has the advantage of being performed bedside, has also been found to be more useful in monitoring the clinical course of NE than in diagnosing by demonstrating measurable reduction in bowel wall thickening in patients who are responding to therapy [5].

In addition to imaging, the following laboratory tests should also be obtained: a complete blood count to assess for degree of neutropenia, anemia, or thrombocytopenia and a comprehensive metabolic panel to assess renal and hepatic function. Blood cultures should be obtained to assess for bacteremia, and stool for *C difficile* screening should be completed because *C difficile*-associated disease is in the differential diagnosis.

TABLE 1.5.1. ANTIBIOTICS FOR EMPIRIC TREATMENT OF NEUTROPENIC ENTEROCOLITIS

Antibiotics for Empiric Treatment	Dosages
Monotherapy	
Piperacillin-tazobactam	3.375 g IV q6h
Meropenem	1 g IV q8h
Dual-Therapy	
Cefepime	2 g IV q8h *or*
Ceftazidime	1 g IV q8-12h *plus*
Metronidazole	500 mg IV q6h

Treatment

The management of NE is primarily conservative, consisting of bowel rest, parenteral nutrition, fluid resuscitation, and nasogastric suction if needed in combination with broad-spectrum antibiotics and early surgical consultation to monitor for acute abdomen with perforation or ischemia [8, 32]. Treatment should be directed against the major pathogens that are typically isolated in patients with NE, including *Clostridium* species, *Pseudomonas* species, *E coli*, and *Candida* species [12, 14, 15]. Due to the limited efficacy of cephalosporins against Clostridial species, it is recommended to include anaerobic coverage (i.e. metronidazole) in addition to enteric Gram-negative coverage to the antibiotic regimen [6, 33–35] (Table 1.5.1).

Gorschlüter et al [36] found that the frequency of invasive fungal NE is probably approximately 5% but that the mortality was approximately 70%–80%. Therefore, these authors concluded that antimycotic therapy should be considered in patients with NE with persistent fevers [36] (Figure 1.5.2). The role of G-CSF has not been well studied, but the American Society of Clinical Oncology does support its use in patients with fever and neutropenia who are at high risk for infection-associated complications, or those who have prognostic factors that are predictive of poor clinical outcomes. High-risk features included expected prolonged (10 days) and profound neutropenia, age greater than 65 years, uncontrolled primary disease, pneumonia, hypotension and multiorgan dysfunction (sepsis syndrome), invasive fungal infection, or being hospitalized at the time of the development of fever [10, 37].

The following criteria for surgical intervention have been proposed: gastrointestinal bleeding that persists after improvement of neutropenia, thrombocytopenia, and coagulopathy; free air in the intraperitoneal cavity (intra-abdominal perforation); clinical deterioration during medical therapy, such as uncontrollable sepsis (hypotension, organ perfusion impairment); or development of symptoms of an intra-abdominal process in the absence of neutropenia that would usually require surgery, such as acute appendicitis [38]. Perforated or necrotic bowel must undergo surgical correction, although mortality is extremely high in this setting. If surgical correction is needed, it has been recommend that primary bowel anastomosis should not be attempted in the face of ongoing leukopenia; that resection and diversion should be performed [39]. Supportive care and antimicrobial therapy should be continued until resolution of clinical signs of infection occurs, including normalization of temperature and the absolute neutrophil count and return of gastrointestinal function.

Prognosis

Historically, mortality rates associated with NE have been high, ranging from 50%–100%, although with good medical management the rate has now been reported to be as low as 20% [11]. Cartoni's [5] retrospective case series on NE revealed an overall mortality of 29.5%, but patients with bowel wall thickness of more than 10 mm had a significantly higher mortality rate (60%) than did those with bowel wall thickness <10 mm (4.2%; $P < .001$).

KEY POINTS

- Neutropenic enterocolitis is commonly seen in the ileocecal region but can be observed throughout the colon.
- The pathogenesis of NE probably involves a combination of factors, including mucosal injury by cytotoxic drugs, profound neutropenia, and impaired host defense to invasion by microorganisms.
- Diagnosis should be suspected when the following are present: neutropenic fever, abdominal pain, and any bowel wall thickening >4 mm detected by US or CT.
- Antibacterial therapy should be targeted against enteric Gram-negative pathogens and anaerobes, and the addition of anti-fungal therapy should be considered in those individuals who have persistent fever.
- Early surgical consultation should be sought to evaluate for the development of an acute abdomen.

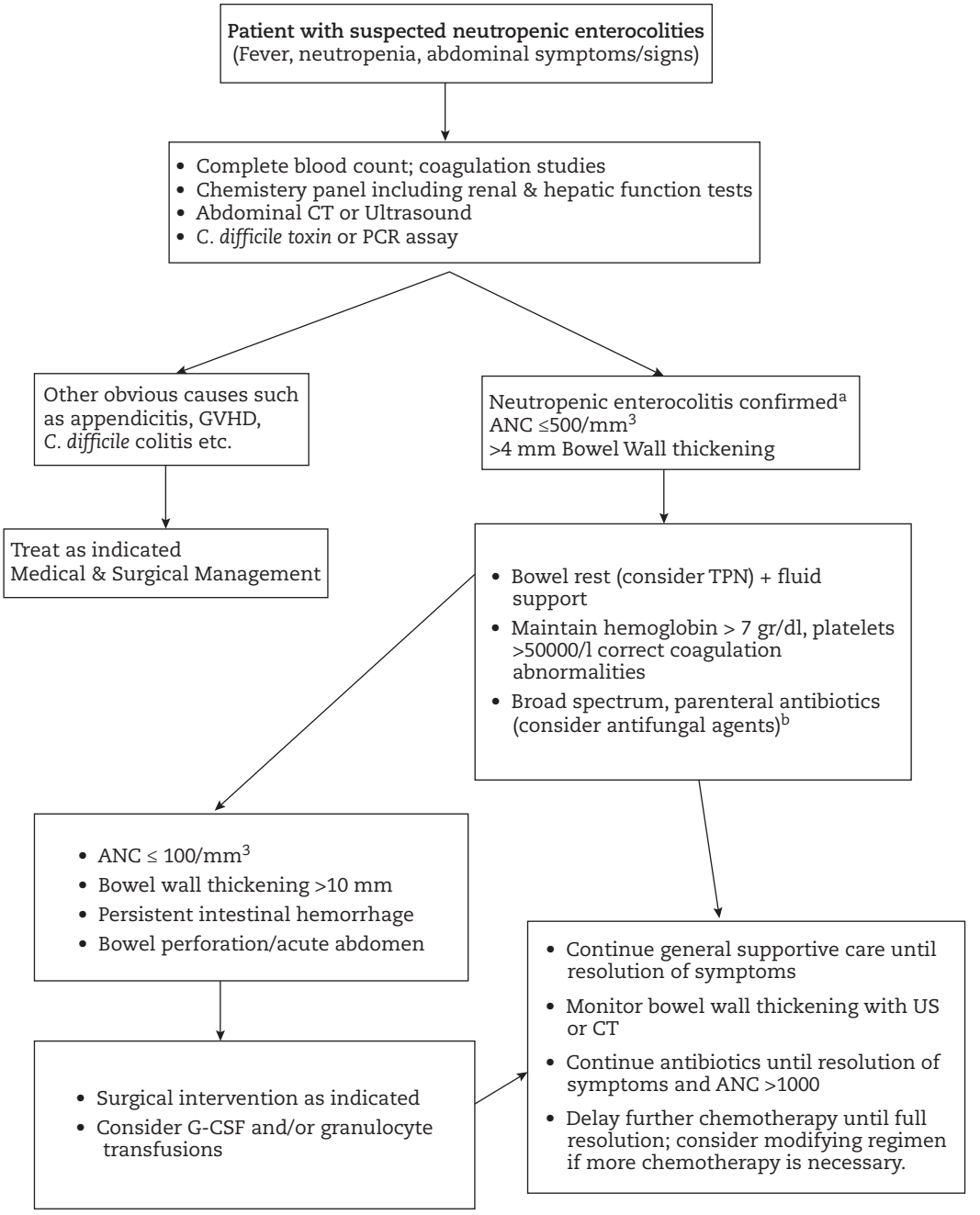


FIGURE 1.5.2: Treatment Algorithm (Adapted from Nesher et al.[30]).

Abbreviations: ANC, absolute neutrophil count; CT, computerized tomography; G-CSF, granulocyte colony stimulating factor; GVHD, graft versus-host disease; PCR, polymerase chain reaction; tpn, total parenteral nutrition; US, ultrasound.

REFERENCES

1. Kirkpatrick ID, Greenberg HM. Gastrointestinal complications in the neutropenic patient: characterization and differentiation with abdominal CT. Radiology 2003;226:668.
2. Gorschlüter M, Glasmacher A, Hahn C, et al. Severe abdominal infections in neutropenic patients. Cancer Invest. 2001;19:669.
3. Gorschlüter M, Marklein G, Höfling K, et al. Abdominal infections in patients with acute

leukaemia: a prospective study applying ultrasonography and microbiology. Br J Haematol. 2002;117:351.
4. Aksoy DY, Tanriover MD, Uzun O, et al. Diarrhea in neutropenic patients: a prospective cohort study with emphasis on neutropenic enterocolitis. Ann Oncol. 2007;18:183.
5. Cartoni C, Dragoni F, Micozzi A, et al. Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. J Clin Oncol. 2001;19:756.
6. Gorschlüter M, Mey U, Strehl J, et al. Neutropenic enterocolitis in adults: systematic analysis of evidence quality. Eur J Haematol. 2005;75:1.
7. Gil L, Poplawski D, Mol A, et al. Neutropenic enterocolitis after high-dose chemotherapy and autologous stem cell transplantation: incidence, risk factors, and outcome. Transpl Infect Dis. 2013;15:1.
8. Wach M, Dmoszynska A, Wasik-Szczepanek E, et al. Neutropenic enterocolitis: a serious complication during the treatment of acute leukemias. Ann Hematol. 2004;83:522.
9. Cronin CG, O'Connor M, Lohan DG, et al. Imaging of the gastrointestinal complications of systemic chemotherapy. Clin Radiol. 2009;64:724.
10. Urbach DR, Rotstein OD. Typhlitis. Can J Surg. 1999;42:415.
11. Gomez L, Martino R, Rolston KV. Neutropenic enterocolitis: spectrum of the disease and comparison of definite and possible cases. Clin Infect Dis. 1998;27:695.
12. Bremer CT, Monahan BP. Necrotizing enterocolitis in neutropenia and chemotherapy: a clinical update and old lessons relearned. Curr Gastroenterol Rep. 2006;8:333.
13. Deitch EA. Role of bacterial translocation in necrotizing enterocolitis. Acta Paediatr Suppl. 1994;396:33.
14. Sloas MM, Flynn PM, Kaste SC, Patrick CC. Typhlitis in children with cancer: a 30-year experience. Clin Infect Dis. 1993;17:484.
15. Katz JA, Wagner ML, Gresik MV, et al. Typhlitis. An 18-year experience and postmortem review. Cancer 1990;65:1041.
16. Cooke JV. Acute leukemia in children. JAMA 1993;101:432.
17. Quigley MM, Bethel K, Nowacki M, et al. Neutropenic enterocolitis: a rare presenting complication of acute leukemia. Am J Hematol. 2001;66:213.
18. Hopkins G, Kushner JP. Clostridial species in the pathogenesis of necrotizing enterocolitis in patients with neutropenia. Am J Hematol. 1983;14:289.
19. Gordon VL, Harding GA, Czaykowski P. Capecitabine-induced, nonneutropenic enterocolitis. J Gastrointest Cancer 2011;42:278.
20. Kronawitter U, Kemeny NE, Blumgart L. Neutropenic enterocolitis in a patient with colorectal carcinoma: unusual course after treatment with 5-fluorouracil and leucovorin—a case report. Cancer 1997;80:656.
21. Gamboa-Dominguez A, Velazquez-Cecena JL, Reyes-Gutierrez E. Neutropenic enteropathy associated with multiple myeloma. Rev Gastroenterol Mex. 1995;60:94.
22. Uzuka Y, Saito Y, Takahashi H, et al. Neutropenic enterocolitis in adults with acute leukemia. Rinsho Ketsueki 1989;30:980.
23. Kelly KM, Hutchinson RJ, Sposto R, et al. Feasibility of up front dose-intensive chemotherapy in children with advanced-stage Hodgkin's lymphoma: preliminary results from the Children's Cancer Group Study CCG-59704. Ann Oncol. 2002;13(Suppl 1):107.
24. Pestalozzi BC, Sotos GA, Choyke PL, et al. Typhlitis resulting from treatment with taxol and doxorubicin in patients with metastatic breast cancer. Cancer 1993;71:1797.
25. Vlasveld LT, Ten Bokkel Huinink WW, Rodenhuis S. Neutropenic enterocolitis in a patient with ovarian cancer after treatment with high-dose carboplatin and granulocyte macrophage-colony stimulating factor (GM-CSF). Neth J Med. 1990;37:158.
26. Kouroussis C, Samonis G, Androulakis N, et al. Successful conservative treatment of neutropenic enterocolitis complicating taxane-based chemotherapy: a report of five cases. Am J Clin Oncol. 2000;23:309.
27. D'Amato G, Rocha Lima C, Mahany JJ, et al. Neutropenic enterocolitis (typhilitis) associated with docetaxel therapy in a patient with non-small-cell lung cancer: case report and review of literature. Lung Cancer 2004;44:381.
28. Fisherman JS, Cowan KH, Noone M, et al. Phase I/II study of72 h infusional paclitaxel and doxorubicin with granulocyte colony-stimulating factor in patients with metastatic breast cancer. J Clin Oncol. 1996;14:774.
29. Fisherman JS, McCabe M, Noone M, et al. Phase I study of Taxol, doxorubicin, plus granulocyte-colony stimulating factor in patients with metastatic breast cancer. J Natl Cancer Inst Monogr. 1993;15:189.
30. Nesher L, Rolston KV. Neutropenic enterocolitis, a growing concern in the era of widespread use of aggressive chemotherapy. Clin Infect Dis. 2013;56:711.
31. Dietrich CF, Hermann S, Klein S, Braden B. Sonographic signs of neutropenic enterocolitis. World J Gastroenterol. 2006;12:1397.
32. Zuckerman T, Ganzel C, Tallman MS, Rowe JM. How I treat hematologic emergencies in adults with acute leukemia. Blood 2012;120:1993.

33. Rampling A, Warren RE, Berry PJ, et al. Atypical *C* difficile colitis in neutropenic patients. Lancet 1982;2:162.
34. Barie PS, Vogel SB, Dellinger EP, et al. A randomized, double-blind clinical trial comparing cefepime plus metronidazole with imipenem-cilastatin in the treatment of complicated intra-abdominal infections. Cefepime Intra-abdominal Infection Study Group. Arch Surg. 1997;132:1294.
35. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133.
36. Gorschlüter M, Mey U, Strehl J, et al. Invasive fungal infections in neutropenic enterocolitis: a systematic analysis of pathogens, incidence, treatment and mortality in adult patients. BMC Infect Dis. 2006;26;6:35.
37. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006;24: 3187.
38. Shamberger RC, Weinstein HJ, Delorey MJ, Levey RH. The medical and surgical management of typhlitis in children with acute nonlymphocytic (myelogenous) leukemia. Cancer 1986;57:603.
39. Wade DS, Nava HR, Douglass HO Jr. Neutropenic enterocolitis. Clinical diagnosis and treatment. Cancer 1992;69:17.

1.6

Lung Lesions, Skin Lesions, Brain Lesions . . . Oh My

PATRICK TANG, MD AND R. GREGORY BOCIEK, MD

CASE PRESENTATION

A 71-year-old woman with history of chronic lymphocytic leukemia (CLL) initially presented to her primary care physician at an outside institution with a two-month history of progressively worsening cough and dyspnea with associated fevers. A computed tomography (CT) imaging study of her chest (Figure 1.6.1) identified a new 4.5 cm noncalcified solid mass with areas of gas in superior segment of right lower lobe with surrounding pulmonary nodules. She was treated for community-acquired pneumonia with oral levofloxacin 750 mg daily, but symptoms persisted leading to an ultrasound-guided biopsy of a right lung lesion. Fite stain of the lung tissue showed a Gram-positive branching, beaded, filamentous bacilli (Figure 1.6.2), but Gomori's methenamine silver (GMS) stain and acid-fast stains were negative. Confirmative cultures were not sent, and thus a pathogen was not identified. She was again treated empirically with an extended course of oral levofloxacin for five weeks followed by two weeks of azithromycin, again without clinical improvement.

On evaluation at our center, after seven weeks of oral antibiotics, she reported progressive shortness of breath and fatigue that was worse with activity. She denied headaches, visual changes, night sweats, weight loss, or difficulty sleeping. She appeared distressed, diaphoretic, and pale. Her blood pressure was 137/61 mm mercury with a pulse of 94 bpm and oral temperature of 38.4°C. Remarkable physical exam findings included decreased breath sounds over the right lung base and an 18–20 mm nodular red-purplish raised skin lesion on her right lower extremity below the knee.

Her CLL had previously been treated with oral chlorambucil monotherapy for six months, discontinued four years ago due to complications including febrile neutropenia, pulmonary emboli, and lobar pneumonia. Since then, no further chemotherapy was given. Six months prior to presentation, she was hospitalized with *Legionella* pneumonia, atrial fibrillation, and recurrent pulmonary emboli. She also has a history of rheumatoid arthritis that is well controlled on prednisone 5 mg daily for many years.

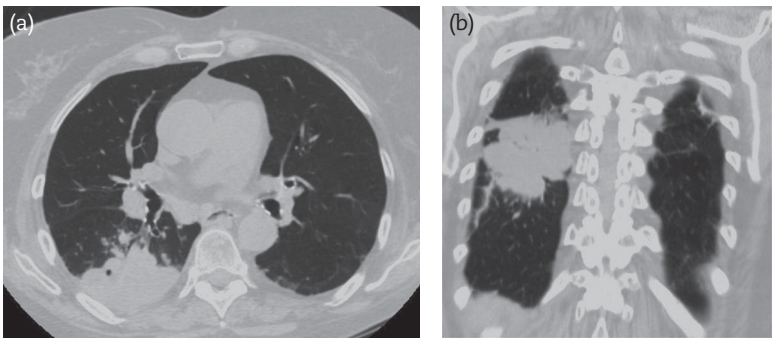


FIGURE 1.6.1: Computed tomography images of chest, axial and coronal views, right lower lobe mass.

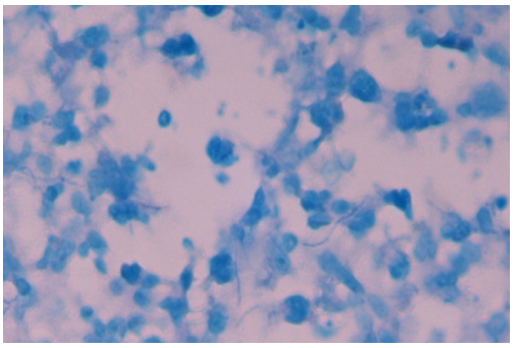


FIGURE 1.6.2: Fite stain, Gram-positive branching, beading, filamentous bacilli.

QUESTIONS

- What infectious etiologies should be considered in this context of chronic pneumonia?
- What further diagnostics should be considered?
- What are the risk factors for developing a chronic pneumonia in a patient who is not neutropenic?

DIFFERENTIAL DIAGNOSIS

Infections to consider in an immunosuppressed host presenting with pulmonary symptoms, fever, and noncalcified lung mass should include the following:

- Fungal—*Aspergillus* spp, *Cryptococcus neoformans, Pneumocystis jirovicii*, endemic fungal infections such as histoplasmosis, coccidioidomycosis, or blastomycosis
- Mycobacterial—*Mycobacterium tuberculosis, Mycobacterium avium-intracellulare, Mycobacterium kansasii*
- Bacterial—*Streptococcus pneumoniae, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae, Nocardia* spp

Obtaining the appropriate diagnosis is essential to targeting appropriate treatment for any patient with a pulmonary infiltrate. Bronchoalveolar lavage is a moderately sensitive method to isolate a pulmonary pathogen and is usually a first step in the approach to immunosuppressed patients with pulmonary infiltrates. However, a tissue biopsy may increase sensitivity by providing histopathologic specimens. Because this patient had a large mass on CT scan, a lung biopsy was deemed the most direct way to obtain tissue for histopathology and cultures.

ADDITIONAL DATA

Initial workup included a sputum culture that grew only a colonizing *Candida albicans* species and was negative for growth of routine bacterial pathogens or acid-fast bacilli on smear. Serologic studies were nonrevealing, including the following: histoplasma urine antigen, 1,3-β-D-glucan serum antigen, *Cryptococcus* serum antigen, *Mycoplasma pneumoniae* immunoglobulin (Ig)M, and serum *Aspergillus* galactomannan. Serum quantitative Ig levels were as follows: IgG 591 mg/dL (normal 700–1600 mg/dL), IgA 67 mg/dL, and IgM 39 mg/dL.

An excisional biopsy of the right lower leg skin/soft tissue lesion showed acute and chronic inflammation and granulation tissue formation on histopathology. Tissue Gram stain showed branching filamentous bacteria, which grew in Sabouraud dextrose agar and was later identified as *Nocardia* species. A modified acid-fast stain was positive. Antimicrobial susceptibility and molecular sequencing were most consistent with the organism *Nocardia exalbida,* a very rare species of *Nocardia* [1, 2]. A typical antimicrobial susceptibility pattern of *Nocardia asteroides* type I, a common nocardial pathogen, is shown in Table 1.6.1 [3, 4].

With suspicion for disseminated nocardiosis, a brain magnetic resonance imaging study (Figure 1.6.3) was performed to evaluate for central nervous system (CNS) involvement. This revealed multifocal ring enhancing lesions involving the right parasagittal frontal lobe, left caudate, left posterior temporal/parietal lobe, left inferior temporal lobe, and right cerebellum. There was also evidence of right sigmoid dural venous sinus thrombosis extending into the proximal internal jugular vein.

Final Diagnosis: Disseminated nocardiosis involving lung, brain, and skin

TREATMENT AND OUTCOME

The patient initially received empiric piperacillin/tazobactam. After report of *Nocardia* spp, with its antimicrobial sensitivities, she received high-dose oral trimethoprim-sulfamethoxazole ([TMP-SMX] 10 mg/kg per day divided into three daily doses = two tablets three times a day) for one year and intravenous ceftriaxone (2 grams twice a day) for the first six weeks of treatment. She was seen regularly in follow up with interval imaging studies and had gradual improvement of pulmonary symptoms and radiographic findings over the course of therapy.

DISCUSSION

Nocardia Infections

Nocardia species are a group of aerobic Gram-positive bacteria that commonly reside in soil,

TABLE 1.6.1. TYPICAL IN VITRO CULTURE AND SUSCEPTIBILITY PATTERN OF *NOCARDIA ASTEROIDES* TYPE IV

Antibiotic	Sensitivity	Minimum Inhibitory Concentration
Amikacin	Susceptible	<1
Amoxicillin/Clavulanate	Susceptible	<1
Ceftriaxone	Susceptible	<1
Ciprofloxacin	Resistant	>8
Clarithromycin	Intermediate	4
Linezolid	Susceptible	<1
Minocycline	Susceptible	<1
Tobramycin	Susceptible	<1
Trimethoprim/sulfamethoxazole	Susceptible	<0.25
Imipenem	Susceptible	<1

organic material, water, compost vegetation, and other environmental sources. The organism enters the body via either inhalation or contamination of a wound. It is an uncommon infection but has been reported worldwide. Localized or disseminated systemic disease may involve the lung (in over half of cases), CNS, skin, and other extrapulmonary sites [1, 3, 5, 6].

More than 100 species of *Nocardia* are currently identified, many of which have been recognized as causes of human infections [7]. The most important pathogenic species for humans and animals are *N asteroides* complex, *Nocardia brasiliensis, Nocardia pseudobrasiliensis, Nocardia otitidiscaviarum*, and *Nocardia transvalensis* [1]. *Nocardia asteroides* complex includes types I–VI. Type III is called *Nocardia nova* and type V, *Nocardia farcinica* [8].

Risk Factors

Nocardiosis is considered an opportunistic infection; however, it affects immunocompetent hosts in approximately one third of all cases [5]. Risk of infection due to *Nocardia* spp is increased in a variety of chronically immunocompromised hosts, including those with human immunodeficiency virus infection, solid organ or hematopoietic stem cell transplant, chronic lung disease, alcoholism, malignancy, and diabetes [5, 9–13]. History of prolonged steroid therapy is a particularly significant risk factor, seen in 50% or more of all cases [11, 14].

Clinical Presentation

Nocardiosis may present as either an acute or chronic, often disseminated suppurative or granulomatous infection, most commonly in the lung. Clinical

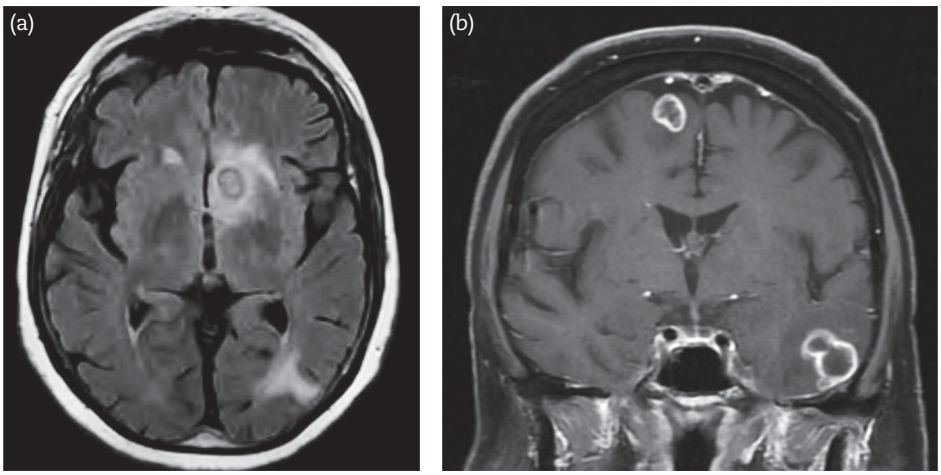


FIGURE 1.6.3: Magnetic resonance images of brain, axial and coronal views, multifocal ring enhancing lesions.

manifestations of nocardiosis are widely variable and can affect many tissue sites. Although primary infection of the lung is characteristic, nearly half of all pulmonary cases disseminate to sites outside the lung, most commonly the skin and brain [5, 6, 15].

Signs and symptoms of pulmonary nocardiosis are not specific and vary in acuity of onset and severity. Some frequent presenting symptoms include fever, cough, dyspnea, hemoptysis, pleuritic chest pain, night sweats, anorexia, nausea, vomiting, and weight loss [3, 6, 11, 15, 16]. Accordingly, presentation with chronic respiratory symptoms and a chronic pneumonia should raise the possibility of *Nocardia* spp pulmonary infection as well as tuberculosis and endemic fungal infections such as histoplasmosis. Radiographic findings vary as well, and they can appear as nodules (multiple or single), a mass (with or without cavitation), infiltrates, consolidations, subpleural plaques, or pleural effusions [3, 5].

Approximately one third of nocardial infections present with systemic disease involving 2 or more sites, including CNS involvement in 44% of disseminated cases and 20% of all cases [5]. Clinical findings of CNS involvement are nonspecific, and they are often clinically silent. Possible presenting symptoms may include fever, headache, nausea, vomiting, seizures, meningismus, and focal neurologic deficits [5, 9, 17]. In general, CNS lesions appear as parenchymal abscesses with ring-enhancement and may involve any region of the brain. *Nocardia meningitis* is rare, and it is often associated with brain abscesses [18].

Cutaneous involvement of nocardiosis is usually due to dissemination from a lung focus. Local ulcerations, subcutanesous abscesses, or cellulitis are most common manifestations. Mycetomas may manifest as areas of local edema or swelling with erythema and draining sinus tracts and is usually due to *N brasiliensis* [1, 6, 15].

Diagnosis

Definitive diagnosis of *Nocardia* spp infection requires isolation and identification of organism from clinical specimen, which often requires an invasive procedure. *Nocardia* spp histologically appear as thin, beaded, branching Gram-positive bacilli and are positive by modified acid-fast stain (and may be weakly acid-fast positive) and typically stain positive by GMS (silver) stain [19]. *Nocardia* sp are strict aerobes that demonstrate slow growth on solid or liquid media, requiring five to twelve days of incubation for tissue or blood cultures to turn positive [5, 6, 19]. In our case, biopsy of both pulmonary and cutaneous lesions was necessary to obtain definitive diagnosis. Speciation is difficult, and it is typically based on antimicrobial susceptibility profile and polymerase chain reaction.

Management

Without treatment, pulmonary and disseminated nocardiosis are typically fatal. Among patients who are treated with appropriate antibiotics, the mortality rate may be as high as 50% or greater in immunocompromised patients with disseminated infections. Mortality rate is approximately 10% in immunocompetent patients with localized lung infection, and overall excellent outcomes are associated with limited skin disease.

Sulfonamides are the mainstay of *Nocardia* therapy. Empiric therapy for nocardiosis should always include a sulfonamide, and TMP-SMX has traditionally been the most readily available formulation and has consistently shown clinical efficacy against most species. Initial dose of TMP-SMX should be 10–15 mg/kg of the trimethoprim component per day divided into two to four doses. Therapeutic drug monitoring is recommended in severe cases, to target serum sulfonamide level of 100 to 150 mcg/mL measured two hours after dose administration [3]. Combination therapy is reserved for cases of severe or disseminated infection, especially if the CNS is involved. The choice of additional drugs (to a cornerstone of TMP-SMX) is based on in vitro susceptibility testing because susceptibility patterns vary among *Nocardia* species.

Combination therapy may include initial parenteral agents along with TMP-SMX, such as amikacin (7.5 mg/kg intravenously every twelve hours), imipenem (500 mg intravenously every six hours), or a third-generation cephalosporin [3]. Again, susceptibility testing is essential to ultimately choose effective agents.

Although linezolid is effective in vitro across all *Nocardia* spp tested, its use is limited by potential myelosuppression and peripheral neuropathy when given for long periods [23].

Once antimicrobial susceptibility results are available and the patient clinically improves (usually after three to six weeks), treatment can be switched to oral monotherapy. Prolonged therapy for six to twelve months or longer in immunosuppressed patients is recommended due to treatment failure and relapse [3].

KEY POINTS

- *Nocardia* spp infections are considered opportunistic but up to one third of cases occur in immunocompetent hosts.

- Lung is the most common infection site, but CNS, skin, and other sites may occur.
- CNS disease is very common, occurring in up to 50% of pulmonary cases, and often clinically silent; CNS imaging is mandatory if pulmonary nocardiosis is diagnosed.
- Isolation and identification often requires a tissue biopsy; growth in culture is slow.
- Sulfonamides are the mainstay of therapy, usually given as oral TMP-SMX; however, in vitro susceptibility patterns may vary depending on strain.
- Long durations of therapy are typically required to treat *Nocardia* infections (≥6 months) in immunocompromised patients.

REFERENCES

1. Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ Jr. Clinical and laboratory features of the *Nocardia* spp. based on current molecular taxonomy. Clin Microbiol Rev. 2006;19:259.
2. Iida S, Kageyama A, Yazawa K, et al. *Nocardia exalbida* sp. nov., isolated from Japanese patients with nocardiosis. Int J Syst Evol Microbiol. 2006;56:1193.
3. Lerner PI. Nocardiosis. Clin Infect Dis. 1996;22: 891.
4. Wallace RJ Jr, Steele LC, Sumter G, Smith JM. Antimicrobial susceptibility patterns of *Nocardia asteroides*. Antimicrob Agents Chemother. 1988;32:1776.
5. Beaman BL, Beaman L. *Nocardia* species: host-parasite relationships. Clin Microbiol Rev. 1994;7:213.
6. Lederman ER, Crum NF. A case series and focused review of nocardiosis: clinical and microbiologic aspects. Medicine 2004;83:300.
7. Parte AC. LPSN—list of prokaryotic names with standing in nomenclature. Nucleic Acids Res. 2014;42:D613.
8. Clinical and Laboratory Standards Institute. *Susceptibility Testing of Mycobacteria, Nocardiae, and other Aerobic Actinomycetes*. Second Edition ed. Wayne, PA; 2011.
9. Anagnostou T, Arvanitis M, Kourkoumpetis TK, et al. Nocardiosis of the central nervous system: experience from a general hospital and review of 84 cases from the literature. Medicine 2014;93:19.
10. Castro JG, Espinoza L. *Nocardia* species infections in a large county hospital in Miami: 6 years experience. J Infect. 2007;54:358.
11. Martinez Tomas R, Menendez Villanueva R, Reyes Calzada S, et al. Pulmonary nocardiosis: risk factors and outcomes. Respirology 2007;12:394.
12. Peleg AY, Husain S, Qureshi ZA, et al. Risk factors, clinical characteristics, and outcome of *Nocardia* infection in organ transplant recipients: a matched case-control study. Clin Infect Dis. 2007;44:1307.
13. Saubolle MA, Sussland D. Nocardiosis: review of clinical and laboratory experience. J Clin Microbiol. 2003;41:4497.
14. Palmer DL, Harvey RL, Wheeler JK. Diagnostic and therapeutic considerations in *Nocardia asteroides* infection. Medicine 1974;53:391.
15. McNeil MM, Brown JM. The medically important aerobic actinomycetes: epidemiology and microbiology. Clin Microbiol Rev. 1994;7:357.
16. Uttamchandani RB, Daikos GL, Reyes RR, et al. Nocardiosis in 30 patients with advanced human immunodeficiency virus infection: clinical features and outcome. Clin Infect Dis. 1994;18:348.
17. Mamelak AN, Obana WG, Flaherty JF, Rosenblum ML. Nocardial brain abscess: treatment strategies and factors influencing outcome. Neurosurgery 1994;35:622.
18. Bross JE, Gordon G. Nocardial meningitis: case reports and review. Rev Infect Dis. 1991;13:160.
19. Conville PS, Murray PR, Zelazny AM. Evaluation of the integrated database network system (IDNS) SmartGene software for analysis of 16S rRNA gene sequences for identification of *Nocardia* species. J Clin Microbiol. 2010;48:2995.
20. Ambrosioni J, Lew D, Garbino J. Nocardiosis: updated clinical review and experience at a tertiary center. Infection 2010;38:89.
21. Brown-Elliott BA, Biehle J, Conville PS, et al. Sulfonamide resistance in isolates of *Nocardia* spp. from a US multicenter survey. J Clin Microbiol. 2012;50:670.
22. Uhde KB, Pathak S, McCullum I Jr, et al. Antimicrobial-resistant nocardia isolates, United States, 1995–2004. Clin Infect Dis. 2010;51:1445.
23. Brown-Elliott BA, Ward SC, Crist CJ, et al. In vitro activities of linezolid against multiple *Nocardia* species. Antimicrobi Agents Chemother. 2001;45:1295.

1.7

Lung Mass in a Neutropenic Patient With Leukemia: Beyond Aspergillosis

MICHAEL J. SATLIN, MD, MS, STEPHEN CASTRO, MD, AND THOMAS J. WALSH, MD

CASE PRESENTATION

A 65-year-old woman from China with relapsed acute myeloid leukemia (AML) was evaluated for recurrent fever in the setting of neutropenia while receiving salvage therapy with decitabine. She was initially diagnosed with AML one year prior to this presentation, previously achieved a complete remission with idarubicin and cytarabine, and received numerous courses of consolidation chemotherapy. During these treatments, she developed scattered nodular opacities that resolved after starting voriconazole, although a microbiologic diagnosis for these lesions was never obtained.

She was found to have relapsed leukemia based on the identification of myeloblasts in her peripheral blood and was admitted to the hospital for treatment with ten days of intravenous decitabine. Given her history of a possible invasive fungal infection, she received voriconazole for antifungal prophylaxis. Nineteen days after starting decitabine, she developed fever and neutropenia and cefepime was initiated. The fever resolved after one day and blood cultures did not yield organisms. Nine days later, she began a second ten-day cycle of decitabine. During the fourth day of this cycle, she developed fever, and cefepime was changed to meropenem. She defervesced by the next day, but developed another fever on the last day of her decitabine infusion. She did not have visual changes, pain, cough, dyspnea, vomiting, diarrhea, or dysuria. She had been neutropenic for four weeks. Blood cultures were obtained and vancomycin was added to meropenem.

On physical exam, she was comfortable-appearing and alert, but she had a temperature of 39.4°C and a heart rate of 116 bpm. She had a normal blood pressure, respiratory rate, and oxygen saturation on room air. There were no plaques or mucosal erosions in her oropharynx. Her lungs were clear to auscultation, her heart rate was regular, her abdomen was soft and nontender, and she had no skin lesions. She had a peripherally inserted central catheter in her left arm that had no erythema or tenderness at the insertion site.

Laboratory data were notable for white blood cell count 1400 cells/mm^3, of which 85% were lymphocytes and 6% were neutrophils, hemoglobin 10.3 g/dL, and platelet count 40 000/mm^3. Her serum creatinine was 0.7 mg/dL, and her liver function tests and urinalysis were normal. A non-contrast computed tomography (CT) scan of the chest and sinuses was obtained and revealed a new 5.6 × 4.4 cm mass-like focus of consolidation with surrounding ground-glass attenuation in the apex of the right upper lobe and no abnormalities in the sinuses or orbits.

QUESTIONS

- What are the possible infectious etiologies of this patient's fever and lung mass?
- How is this differential diagnosis influenced by her prophylactic antifungal and empirical antibacterial therapy?
- What diagnostic approach should be taken?

DIFFERENTIAL DIAGNOSIS

Infectious etiologies of a well circumscribed lung mass in a patient with a hematological malignancy and prolonged neutropenia include invasive moulds, such as *Aspergillus* spp, Mucorales, and *Fusarium* spp, *Nocardia*, and mycobacteria. Occasionally, large lung nodules or masses can also be caused by more typical causes of bacterial pneumonia, such as *Pseudomonas aeruginosa, Klebsiella pneumoniae*, and *Legionella* spp. The finding of a dense, well circumscribed nodule or mass with surrounding ground-glass attenuation

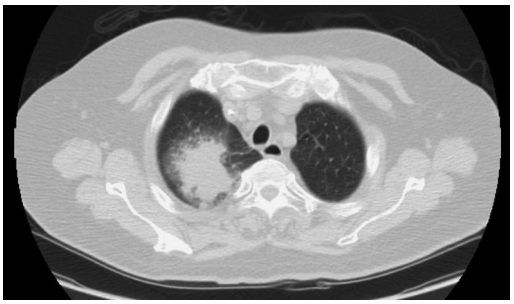


FIGURE 1.7.1: Chest CT demonstrating a dense, well-circumscribed apical mass, with surrounding ground glass attenuation (halo sign).

is suggestive of a mould infection and is classically associated with aspergillosis.

ADDITIONAL DATA

Given the appearance of a lung mass in a neutropenic patient despite voriconazole prophylaxis, therapy with 5 mg/kg of daily liposomal amphotericin B (LAMB) was initiated to cover potential breakthrough fungal pathogens and voriconazole was discontinued. Her fever resolved after two days. Vancomycin was discontinued, but she continued to receive meropenem for fever and neutropenia. Serum (1–>3)-β-D-glucan and *Aspergillus* galactomannan enzyme immunoassay tests were negative.

She subsequently had a CT-guided, fine-needle aspirate (FNA) and core biopsy of the lung mass five days after starting LAMB. Gram, calcofluor white/potassium hydroxide, and acid-fast (Kinyoun) stains of the biopsy specimens did not reveal any organisms. A Papanicolaou stain

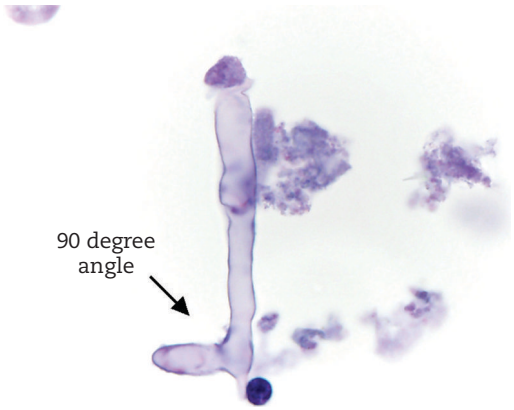


FIGURE 1.7.2: Oil immersion of a ThinPrep Papanicolaou stain that demonstrates a broad hyphal structure with 90-degree branching and only one septum, 100×.

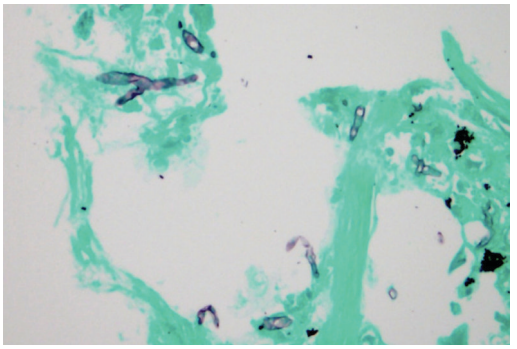


FIGURE 1.7.3: Lung tissue biopsy with Gomori methenamine silver stain highlighting large, hyposeptate, and ribbon-like hyphae amidst infarcted lung parenchyma, 40×.

of the FNA cytology revealed broad, relatively aseptate hyphae with right-angle branching in a background of necrosis, few macrophages, and scattered reactive epithelial cells. The core biopsy revealed infarcted lung parenchyma and Gomori methenamine silver stain revealed hyphal forms resembling those identified in the FNA. The bacterial, fungal, and mycobacterial cultures did not yield any pathogens.

Final Diagnosis: Pulmonary mucormycosis in a neutropenic patient with AML who was receiving prophylactic voriconazole

TREATMENT AND OUTCOME

She continued to receive 5 mg/kg of daily LAMB. Her neutropenia resolved and she remained afebrile. Her meropenem was discontinued, and she was discharged to home on daily LAMB infusions twelve days after the biopsy. She developed hypokalemia and required daily oral potassium supplementation. After completing six weeks of LAMB, she developed acute kidney injury, leading to discontinuation of LAMB and initiation of 200 mg of oral posaconazole suspension four times daily with food. A follow-up chest CT was performed 2.5 months after starting antifungal therapy and showed that the lesion had decreased in size from 5.6 × 4.4 to 3.6 × 1.0 cm. She received three more cycles of decitabine, but her leukemia ultimately progressed, requiring the initiation of other salvage regimens. Posaconazole was initiated during all episodes of neutropenia, and the lung lesion continued to decrease in size. She ultimately died of refractory leukemia ten months after she was diagnosed with pulmonary mucormycosis.

DISCUSSION

Pulmonary Mucormycosis in Patients With Hematologic Malignancies

Epidemiology and Risk Factors

The term mucormycosis describes infections caused by fungi of the order Mucorales. The genera that most commonly cause human infections are *Rhizopus, Mucor*, and *Cunninghamella* [1]. These organisms are found in decaying vegetation and soil, and exposure to their sporangiospores is common during normal human activities. Despite the fact that these moulds are ubiquitous, invasive disease is limited to patients with compromised innate immunity. Among patients with cancer, the vast majority of mucormycosis occurs in patients with hematological malignancies, and particularly in patients with AML [2]. Mucormycosis has emerged as the third most common invasive fungal infection, after candidiasis and aspergillosis, in patients with AML [2–3]. The use of voriconazole for antifungal prophylaxis, as in the case patient, has been identified as a risk factor for pulmonary mucormycosis in patients with cancer, because voriconazole protects against invasive aspergillosis but does not have activity against fungi that cause mucormycosis [4].

Clinical Manifestations

Invasive mucormycosis leads to invasion of vasculature by fungal hyphae, followed by thrombosis and subsequent tissue necrosis [2]. Although the most common clinical presentation overall is rhino-orbital-cerebral infection, patients with hematological malignancies most often present with pulmonary mucormycosis [1]. The clinical features of pulmonary mucormycosis in this patient population are nonspecific and cannot be reliably distinguished from those of pulmonary aspergillosis [2]. Pulmonary mucormycosis can also involve the sinuses, spread to the mediastinum and heart, and disseminate hematogenously to other organs. Patients typically present with fever that is not responsive to broad-spectrum antibacterial agents in the setting of prolonged neutropenia. A nonproductive cough is common (although not seen in the case patient), and occasionally patients will also have hemoptysis, pleuritic chest pain, and dyspnea.

A chest CT is typically more informative than a chest radiograph in evaluating for a fungal pneumonia in neutropenic patients, because lung nodules are often not seen on routine radiographs. However, CT findings of pulmonary mucormycosis do not reliably distinguish this infection from pneumonia caused by other moulds. The most common radiographic findings are well circumscribed nodules or masses, with our without cavitation or abscess, or consolidation [5]. Although the halo sign (a ground-glass opacity that surrounds a nodule or mass) is classically associated with pulmonary aspergillosis, this finding can also be seen in mucormycosis, as in the case patient. In a study of CT findings in cancer patients with either pulmonary aspergillosis or mucormycosis, the presence of ≥10 nodules, sinus involvement, and pleural effusion were independent predictors of having mucormycosis [4]. A reversed halo sign (a focal round area of ground-glass attenuation that is surrounded by a ring of consolidation) is another finding that is more common in patients with pulmonary mucormycosis than other types of fungal pneumonia [6].

Diagnosis

Establishing the diagnosis of mucormycosis in a timely manner is of critical importance because early treatment prevents hematogenous dissemination and extension of this infection into additional sites, reduces the need for or extent of surgical resection, and decreases morbidity and mortality [7]. In fact, an observational study of 70 patients with a hematologic malignancy and mucormycosis demonstrated that delayed therapy was associated with a two-fold increase in mortality and was an independent predictor of poor outcome [8]. The need for early diagnosis is also of heightened importance because antifungal agents that are commonly used for empirical therapy, such as voriconazole and echinocandins, do not have activity against Mucorales.

The diagnosis of pulmonary mucormycosis is difficult to establish based on clinical and radiographic findings alone, because the presentation is similar to that of aspergillosis and other angioinvasive moulds. These nonspecific manifestations highlight the need for an aggressive approach to evaluating pulmonary nodules and infiltrates in neutropenic patients with hematologic malignancies. Reasonable approaches include performing bronchoscopy to obtain bronchoalveolar lavage (BAL) fluid or, if platelet counts can be maintained at a sufficient level, obtaining a radiography-guided percutaneous needle aspirate or biopsy or a transbronchial biopsy of involved lung tissue. Biopsy and BAL fluid specimens should be submitted to the microbiology laboratory and to either the histopathology or cytopathology laboratories, as appropriate. The decision of whether to first perform a bronchoscopy and BAL or a percutaneous needle aspirate or biopsy

typically depends on the size of the lesion(s), whether it is peripherally or centrally located, and the patient's platelet count. Although core needle biopsies are thought to have the highest yield among these procedures, it should be noted that none of these approaches have sufficient sensitivity such that a negative result rules out mucormycosis. In fact, even an open lung biopsy may be falsely negative because of sampling error.

Direct microscopic examination of BAL fluid, aspirate, or biopsy specimens should be performed by the microbiology laboratory to evaluate for the presence of fungal hyphae. The hyphae of Mucorales have a unique appearance of being broad, ribbonlike, and irregularly shaped with right-angle branching and rare or no septations [7]. These characteristics usually allow them to be distinguished from hyphae of other filamentous fungi, such as *Aspergillus* and *Fusarium* spp, which typically are slender, dichotomously branching, and septated. The addition of a chitin-binding stain, such as calcofluor, and fluorescent microscopy may increase the likelihood of identifying fungal hyphae, compared with potassium hydroxide wet mount preparations alone [9]. In addition to the routine hematoxylin-eosin stain, the cytopathology and histopathology laboratories should also perform a Gomori methenamine silver and/or Periodic acid-Schiff stain because the hyphae are more easily observed with these stains.

In addition to direct examinations, specimens should also be submitted for fungal culture. Although Mucorales organisms are ubiquitous and their identification in culture can represent laboratory contamination, their isolation from BAL fluid or bronchial or lung tissue in a high-risk patient with a hematological malignancy and compatible clinical manifestations should be considered strong evidence of infection [10]. However, it should also be noted that the sensitivity of culture of BAL fluid for mucormycosis may be as low as 25% [10]. This sensitivity may be further compromised if the patient receives treatment with amphotericin B before specimen collection, as in the case patient. This low sensitivity underscores the importance of obtaining biopsy specimens where feasible. Furthermore, the microbiology laboratory should be alerted about the consideration of mucormycosis, because the yield of tissue culture for these fragile organisms is decreased if specimens are ground or homogenized before they are inoculated onto media (a common practice for tissue culture). Similar to *Aspergillus*, Mucorales organisms are angioinvasive, but they are virtually never associated with positive blood culture results using either standard or lysis centrifugation ("fungal") blood culture systems.

Although Mucorales organisms have predictable susceptibility patterns and are typically easy to distinguish from other fungi on direct stains, identifying the genus and species by growth on culture still has valuable therapeutic and prognostic implications. For example, *Rhizopus oryzae*, the most common cause of mucormycosis, tends to have higher minimum inhibitory concentrations (MICs) to posaconazole [11], whereas *Cunninghamella* species tend to have higher MICs to amphotericin B and a higher associated mortality [12, 13]. Furthermore, fungal isolates can be sent to reference laboratories for antifungal susceptibility testing to obtain MICs that can guide therapy.

Given the limited yield of culture and the difficulties of obtaining ample tissue for histopathology in thrombocytopenic patients with hematologic malignancies, molecular methods to diagnose mucormycosis would be a welcome advance. Quantitative Mucorales polymerase chain reaction assays have been developed and have shown promise when applied to plasma and BAL fluid in rabbit models [13]. Further research is needed to evaluate and establish a role for these molecular methods.

Treatment

As previously outlined, early treatment of mucormycosis is associated with improved outcomes. Lipid formulations of amphotericin B remain the drugs of choice for initial antifungal therapy. Liposomal amphotericin B and amphotericin B lipid complex showed similar efficacy in a neutropenic murine model of mucormycosis, although the former agent may be associated with a lower rate of toxicity [14]. Daily doses of at least 5 mg/kg of these lipid formulations are recommended [15]. Despite the favorable in vitro activity of amphotericin B, recovery from neutropenia is essential for successful outcome. Granulocyte transfusions, although not proven in randomized clinical trials, may be useful in certain situations to stabilize the infection until neutrophil recovery [16].

Posaconazole may have a role as stepdown therapy after a favorable clinical response has been achieved with many weeks of treatment with lipid formulations of amphotericin B. Posaconazole tablets are an improvement compared with the oral suspension for this indication, because the tablets achieve higher serum concentrations, can be dosed once daily, and their absorption is not markedly affected by food [17]. Therapy should continue until there is clinical resolution of the signs and symptoms of infection and of

radiographic signs of active disease. Even after this has been achieved, posaconazole should be considered for any subsequent episodes of neutropenia. Posaconazole has also been used successfully as salvage therapy in patients who are refractory to or intolerant of lipid formulations of amphotericin B [18]. However, given (1) the lack of supportive data for the newer tablet and intravenous posaconazole formulations and (2) animal models that suggest the efficacy of posaconazole is inferior to amphotericin B [19], posaconazole is not currently recommended for primary therapy.

Although surgery has a critical role in the treatment of rhino-orbital-cerebral mucormycosis, its role in pulmonary zygomycosis in patients with hematologic malignancies is less clear [15]. Disease involving multiple lung lobes and thrombocytopenia may limit the ability for surgical resection. However, in the appropriate setting, surgical resection of pulmonary mucormycosis that is limited to a single lobe should be considered.

The poor outcomes of oncology patients with mucormycosis who are treated with amphotericin B suggest a potential role for combination therapy [20]. Although echinocandins do not have in vitro activity against the Mucorales in standard susceptibility testing, *Rhizopus oryzae* expresses the target enzyme for echinocandins, suggesting that these agents may have clinical utility [21]. Two murine models and a small observational clinical study of rhino-orbital-cerebral mucormycosis demonstrated that combination therapy with amphotericin B and an echinocandin improved survival compared to treatment with amphotericin B alone [22, 23]. These limited supportive data, combined with the favorable toxicity profile for echinocandins, provide rationale for considering the addition of an echinocandin to LAMB for the treatment of mucormycosis in appropriate cases.

Data supporting other combination regimens for the treatment of mucormycosis are even more limited. Murine models have not demonstrated a benefit of adding posaconazole to liposomal amphotericin B, and clinical data to support this combination are sparse [24]. Deferasirox, an orally available iron chelator, was previously considered a promising therapy for mucormycosis, because it has in vitro activity against Mucorales and demonstrated synergistic activity with LAMB in a murine model [25]. Unfortunately, a small randomized clinical trial demonstrated a higher mortality rate in patients who received deferasirox and LAMB for the treatment of mucormycosis compared with those who received LAMB alone, and thus iron chelation therapy is not recommended [26].

Prognosis

In a review of 224 reported cases from 1940 to 2003 of pulmonary mucormycosis and 154 reported cases of mucormycosis overall in patients with malignancies, the mortality rate was 76% and 66%, respectively [1]. More recent single-center reports have demonstrated lower mortality rates for mucormycosis in patients with hematologic malignancies, although the numbers of cases in these reports are relatively small [27–28]. Irrespective of the antifungal therapy that is administered, recovery from neutropenia is essential for a favorable outcome.

KEY POINTS

- With expanded use of drugs lacking good activity against mucormycosis (voriconazole and echinocandins) as prophylaxis and as empirical therapy, mucormycosis has emerged as the third most common invasive fungal infection in patients with AML.
- Early diagnosis and treatment of mucormycosis is essential for optimal outcome, but recovery of the absolute neutrophil count is critical for survival.
- Clinical manifestations and radiographic features do not reliably distinguish pulmonary mucormycosis from aspergillosis and other invasive mould infections; unlike aspergillosis, there are no established biomarkers for mucormycosis.
- Diagnostic evaluation of suspicious pulmonary lesions in patients with hematologic malignancies should include bronchoscopy with BAL and transbronchial biopsy (where appropriate) and/or radiography-guided FNA or core needle biopsy.
- The three pillars of the management of mucormycosis are primary treatment with amphotericin B, reversal of underlying immunosuppression, and surgical resection, where appropriate.

REFERENCES

1. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41:634.
2. Petrikkos G, Skiada A, Lortholary O, et al. Epidemiology and clinical manifestations of mucormycosis. Clin Infect Dis. 2012;54:S23.
3. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356:348.

4. Chamilos G, Marom EM, Lewis RE, et al. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis. 2005;41:60.
5. Georgiadou SP, Sipsas NV, Marom EM, Kontoyiannis DP. The diagnostic value of halo and reversed halo signs for invasive mould infections in compromised hosts. Clin Infect Dis. 2011;52:1144.
6. Wahba H, Troung MT, Lei X, et al. Reversed halo sign in invasive pulmonary fungal infections. Clin Infect Dis. 2008;46:1733.
7. Walsh TJ, Gamaletsou MN, McGinnis MR, et al. Early clinical and laboratory diagnosis of invasive pulmonary, extrapulmonary, and disseminated mucormycosis (zygomycosis). Clin Infect Dis. 2012;54:S55.
8. Chamilos G, Lewis RE, Kontoyiannis DP. Delaying amphotericin B-based frontline therapy significantly increases mortality among patients with hematologic malignancy who have zygomycosis. Clin Infect Dis. 2008;47:503.
9. Monheit JG, Brown G, Kott MM, et al. Calcofluor white detection of fungi in cytopathology. Am J Clin Pathol. 1986;85:222.
10. Kontoyiannis DP, Wessel VC, Bodey GP, Rolston KV. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis. 2000;30:851.
11. Sun QN, Fothergill AW, McCarthy DI, et al. In vitro activities of posaconazole, itraconazole, voriconazole, amphotericin B, and fluconazole against 37 clinical isolates of zygomycetes. Antimicrob Agents Chemother. 2002;46:1581–2.
12. Almyroudis NG, Sutton DA, Fothergill AW, Rinaldi MG, Kusne S. In vitro susceptibilities of 217 clinical isolates of zygomycetes to conventional and new antifungal agents. Antimicrob Agents Chemother. 2007;51:2587.
13. Kasai M, Harrington SM, Francesconi A, et al. Detection of a molecular biomarker for zygomycosis by quantitative PCR assays of plasma, bronchoalveolar lavage, and lung tissue in a rabbit model of experimental pulmonary zygomycosis. J Clin Microbiol. 2008;46:3690.
14. Wingard JR, White MH, Anaissie E, et al. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. L Amph/ABLC Collaborative Study Group. Clin Infect Dis. 2000;31:1155.
15. Spellberg B, Walsh TJ, Kontoyiannis DP, et al. Recent advances in the management of mucormycosis: from bench to bedside. Clin Infect Dis. 2009;48:1743.
16. Quillen K, Wong E, Scheinberg P, et al. Granulocyte transfusions in severe aplastic anemia: an eleven-year experience. Haematologica 2009;94:1661–8.
17. Krishna G, Ma L, Martinho M, O'Mara E. Single-dose phase I study to evaluate the pharmacokinetics of posaconazole in new tablet and capsule formulations relative to oral suspension. Antimicrob Agents Chemother. 2012;56:4196.
18. Van Burik JA, Hare RS, Solomon HF, et al. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis. 2006;42:e61.
19. Ibrahim AS, Gebremariam T, Schwartz JA, et al. Posaconazole mono- or combination therapy for treatment of murine zygomycosis. Antimicrob Agents Chemother. 2009;53:772.
20. Spellberg B, Ibrahim A, Roilides E, et al. Combination therapy for mucormycosis: why, what, and how? Clin Infect Dis. 2012;54 (Suppl 1):S73.
21. Ibrahim AS, Bowman JC, Avanessian V, et al. Caspofungin inhibits *Rhizopus oryzae* 1,3-beta-D-glucan synthase, lowers burden in brain measured by quantitative PCR, and improves survival at a low but not a high dose during murine disseminated zygomycosis. Antimicrob Agents Chemother. 2005;49:721.
22. Ibrahim AS, Gebremariam T, Fu Y, et al. Combination echinocandin-polyene treatment of murine mucormycosis. Antimicrob Agents Chemother. 2008;52:1556.
23. Reed C, Bryant R, Ibrahim AS, et al. Combination polyene-caspofungin treatment of rhino-orbital-cerebral mucormycosis. Clin Infect Dis. 2008;47:364.
24. Ibrahim AS, Gebremariam T, Schwartz JA, et al. Posaconazole mono- or combination therapy for treatment of murine zygomycosis. Antimicrob Agents Chemother. 2009;53:772.
25. Ibrahim AS, Gebremariam T, Fu Y, et al. The iron chelator deferasirox protects mice from mucormycosis through iron starvation. J Clin Invest. 2007;117:2649.
26. Spellberg B, Ibrahim AS, Chin-Hong PV, et al. The Deferasirox-AmBisome therapy for mucormycosis (DEFEAT Mucor) study: a randomized, double-blinded, placebo-controlled trial. J Antimicrob Chemother. 2012;67:715.
27. Hammond SP, Baden LR, Marty FM. Mortality in hematologic malignancy and hematopoietic stem cell transplant patients with mucormycosis, 2001 to 2009. Antimicrob Agents Chemother. 2011;55:5018.
28. Lewis RE, Georgiadou SP, Sampsonas F, et al. Risk factors for early mortality in haematological malignancy patients with pulmonary mucormycosis. Mycoses 2014;57:49.

1.8

When an Uncommon Atypical Bacillus Goes Mainstream

JACKRAPONG BRUMINHENT, MD, NANCY L. WENGENACK, PHD, AND RAYMUND R. RAZONABLE, MD

CASE PRESENTATION

A 60-year-old female was diagnosed with symptomatic chronic lymphocytic leukemia in 2005. She received chemotherapy with fludarabine, cyclophosphamide, and rituximab and achieved complete remission. Two years later, in 2007, she developed progressive disease and required a combination therapy of alemtuzumab and rituximab for relapsed disease. One month later, she was admitted to the hospital because of fever and chills. Other than feeling unwell, she did not have any localizing symptoms such as cough, dyspnea, headache, and gastrointestinal or genitourinary symptoms.

On physical examination, she looked ill and was in mild distress. She had an oral temperature of 101.2°F, heart rate of 105 beats per minute, blood pressure of 100/84 mmHg, and respiratory rate of 18 breaths per minute. Physical examination was significant for mild redness at the insertion site of the Hickman catheter in her right anterior chest wall, but with no fluctuance or drainage. Her maxillary and mastoid sinuses were not tender, lungs were clear, and heart had no murmur. The rest of the physical examination was unremarkable.

Laboratory examinations revealed neutropenia with white blood cell count of $0.4 \times 10^3/\ \mu L$ (neutrophils, 100), hemoglobin of 7.9 gm/dL, platelet count of 45 000/μ L, and serum creatinine 0.9 mg/dL. Urinalysis was negative. Chest radiography showed no evidence of parenchymal disease.

After blood cultures were obtained from the Hickman catheter and from peripheral venipuncture, she was started empirically on intravenous (IV) cefepime therapy. Vancomycin was added on her second hospital day due to persistent fever and over concern for the mild erythema at the Hickman insertion site. On the fifth day of her hospitalization, the laboratory reported that her blood cultures obtained on the day of admission, taken from the lumens of the Hickman catheter and from a peripheral venipuncture, grew a beaded Gram-positive, rod-shaped organism. The growth of the organism in culture is shown in Figure 1.8.1, and the microbial stain is shown in Figure 1.8.2. No other organisms were recovered from blood cultures.

QUESTIONS

- What infectious etiologies should be considered as the cause of this patient's bloodstream infection?
- What are the risk factors for this infection?
- What diagnostic approaches should be undertaken to make the diagnosis?
- How do you manage this bloodstream infection?

DIFFERENTIAL DIAGNOSIS

This patient was diagnosed to have central line-associated bloodstream infection (CLABSI).

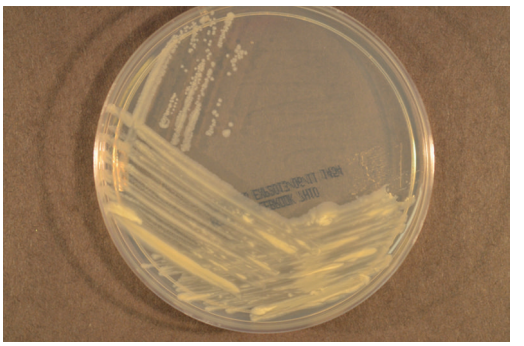


FIGURE 1.8.1: Middlebrook 7H10 agar revealed a colony with whitish to gray in color consistent with the morphology of *Mycobacterium fortuitum*.

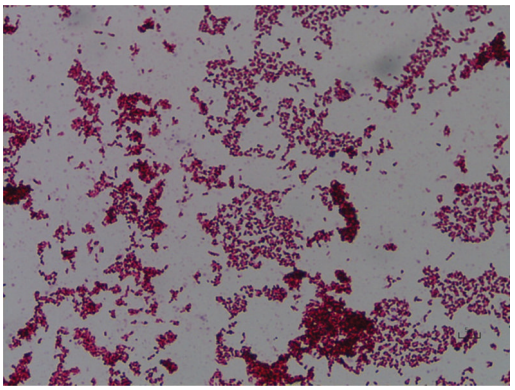


FIGURE 1.8.2: Carbol-Fuchsin stain revealed acid-fast organisms at 1000× magnification.

There is a wide array of infectious etiologies considered as potential cause of CLABSI in immunosuppressed cancer patients. Most common culprits are Gram-positive bacteria (e.g. coagulase-negative Staphylococci, *Staphylococcus aureus, Enterococcus* sp, *Corynebacterium* spp), and Gram-negative bacteria (*Escherichia coli, Klebsiella* spp, *Pseudomonas* spp). Less common are fungal pathogens, particularly *Candida* spp. In rare cases, mycobacteria have been identified as pathogens causing CLABSI. Among them, the rapidly growing mycobacteria (RGM) such as *Mycobacterium mucogenicum, Mycobacterium fortuitum*, and *Mycobacterium abscessus/ Mycobacterium chelonae* have been reported with increasing frequency in cancer patients.

DIAGNOSIS

The diagnosis of the offending organism is established by isolation and identification through culture, genetic sequencing, and antimicrobial susceptibility testing. In this particular case, *M fortuitum* was identified by 16S rRNA gene sequencing analysis. The clinical and microbiologic diagnosis of *M fortuitum* CLABSI was made based on blood culture results and the erythema noted on the Hickman catheter insertion site.

TREATMENT AND OUTCOME

The Hickman catheter was immediately removed. Vancomycin and cefepime were discontinued, and the patient was started empirically on IV imipenem, oral clarithromycin, and oral moxifloxacin while awaiting species identification and antimicrobial susceptibility testing. Intravenous imipenem was subsequently discontinued upon clinical stability and when the results of the antimicrobial susceptibility testing revealed that the organism was susceptible to clarithromycin and moxifloxacin. She completed four weeks of combined oral clarithromycin and moxifloxacin therapy. Repeated blood cultures were negative after Hickman catheter removal and initiation of effective antimicrobial therapy.

DISCUSSION

Gram-negative bacteria were the leading pathogens causing CLABSI before the 1980s, but, later on, this was replaced by Gram-positive bacteria, most commonly coagulase-negative Staphylococci, and *S aureus. Candida* spp has also increased in frequency in recent years as a cause of catheter-related bloodstream infection. The reasons for the rise in Gram-positive bacteria and fungal pathogens as causes of CLABSI have been postulated to be the increasing use of central venous catheter and the broad-spectrum antibiotic prophylaxis (directed mainly towards Gram-negative pathogens) during periods of neutropenia in hematologic malignancy patients. In recent studies, RGM have also emerged as pathogens causing bloodstream infection in cancer patients with indwelling vascular catheters.

Rapidly growing mycobacteria are environmental pathogens, and they often contaminate water supplies. They are called rapid growers because they characteristically show mature growth within seven days on a culture plate, which distinguishes them from the slowly growing mycobacterial species. There are numerous species of RGM, but the most clinically significant species causing human disease are *M mucogenicum, M fortuitum, M abscessus, M chelonae*, and *Mycobacterium neoaurum*. These RGM organisms cause a wide variety of clinical disease states especially in immunosuppressed patients. In a case series and literature review from a US cancer center, patients with hematologic malignancy (like our patient presented here) have the highest risk of CLABSI among cancer patients, with the mean incident rate of 2.9 cases per 100 000 patient-days [1]. The most common species causing RGM CLABSI in this population is *M mucogenicum* followed by *M fortuitum, M chelonae*, and *M abscessus* [1, 2].

Risk Factors

The risk factors for CLABSI have been classified into host- and catheter-related factors. Hematologic malignancy and neutropenic patients appear to have higher risk of CLABSI due to underlying immune dysfunction, and they generally have indwelling central vascular catheters for

prolonged periods of time [1]. In a case series and literature review of cancer patients with a diagnosis of RGM CLABSI, 50% of the patients had an absolute lymphocyte count of <500 cells/mL, and 97% had chemotherapy during the preceding three months [1]. The presence of central venous catheter and the prolonged duration of catheterization appear to be significant risk factors. RGMs have the ability to produce biofilm on the surface of indwelling vascular catheters, and this has been proposed in the pathogenesis of CLABSI, specifically accounting for the difficulty in its treatment without vascular catheter removal [3, 4].

Clinical Presentation

Rapidly growing mycobacteria have been associated with a wide spectrum of clinical syndromes in cancer and other immunocompromised patients and immunocompetent hosts. In cancer patients, RGM may cause respiratory tract, bloodstream, localized skin, or disseminated infections [1]. Bloodstream infection with RGM usually occurs in the presence of a focus of infection elsewhere, such as the lungs or an indwelling vascular catheter. Other less common clinical syndromes involve the central nervous system (meningitis), endovascular (endocarditis), and ophthalmologic (keratitis) infections [5].

Central line-associated bloodstream infection due to RGM can manifest with mild localized skin infection, or tunneled infection, and may progress to a complicated bloodstream infection. In contrast to the case presented above, where only mild erythema was observed at the insertion site, some patients present with pain, swelling, erythema, warmth, or drainage at a catheter insertion site or along subcutaneous tract of the tunnel. Systemic symptoms such as fever or chills may be observed, especially among patients with bacteremia. Although rare, disseminated disease may occur. Central line-associated bloodstream infection due to RGM has been reported to be less virulent in its clinical presentation compared with typical CLABSI pathogens such as Gram-positive or Gram-negative bacteria [6].

Diagnosis

Even if RGMs are frequently found in the environment, their recovery from blood culture should not be considered as a contaminant, especially in immunocompromised hosts [7]. The most important part of diagnosis of RGM infection is to identify the species and its antimicrobial susceptibility pattern. Rapidly growing mycobacteria usually grows in routine blood cultures, but the recovery can be enhanced by using the Isolator method with lysis and centrifugation of the blood and by prolonged incubation [8]. Gram stain reveals beaded Gram-positive rod-shaped organism, and this can be confirmed as mycobacteria by use of an acid-fast stain. Further species identification can be performed using molecular methods such as 16S rRNA gene sequencing analysis or matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Furthermore, antimicrobial susceptibility testing should be performed on all isolates due to variability of susceptibilities among each species [9].

Management

According to the guideline from the Infectious Disease Society of America, CLABSI caused by RGM should be managed with removal of the infected vascular catheter [10]. The rationale for this strong recommendation relates to the biofilm production by RGM on the surface of indwelling catheter. This biofilm could prevent antimicrobial penetration to the infected site, and it serves as a site of persistent infection during and after antimicrobial therapy. In some circumstances, control of localized (isolated) catheter infection, in the absence of true bloodstream infection, may be achieved by catheter removal alone. Patient with tunneled infection alone may be treated with surgical excision alone [11]. However, successful treatment of CLABSI due to RGM is more likely achieved by a combination of catheter removal and antimicrobial therapy. The patients whose vascular catheters remain in place have higher risk of relapse [10].

There are no controlled clinical trials to support a general recommendation for RGM treatment. Moreover, the antimicrobial susceptibility patterns for the RGMs are highly variable. Hence, the choice of antimicrobial therapy should be determined based on susceptibility testing result. The summary of antimicrobial susceptibility results for RGM species collected from cancer patients at our institution over a 2.5-year period is shown in Table 1.8.1. Testing was performed using a microbroth dilution method following the Standard set by the Clinical and Laboratory Standards Institute for RGM. First-line antituberculous medications are not active against RGM and should not be used for treatment. The RGM species are generally susceptible to amikacin. *Mycobacterium abscessus* is usually susceptible to macrolides but generally resistant to fluoroquinolones. On the other hand, *M neoaurum* is usually susceptible fluoroquinolones but resistant to

TABLE 1.8.1. SUSCEPTIBILITY RESULTS OF RAPIDLY GROWING MYCOBACTERIA FROM CANCER PATIENTS AT MAYO CLINIC IN ROCHESTER, MN FROM NOVEMBER 2011 TO APRIL 2014*

	%Susceptible [14]		
Antibiotic	*Mycobacterium fortuitum* (n = 8)	*Mycobacterium abscessus* (n = 18)	*Mycobacterium chelonae* (n = 11)
Amikacin	100%	94%	90.9%
Cefoxitin	0%	0%	0%
Ciprofloxacin	100%	0%	0%
Clarithromycin	0%	76.5%	90.9%
Doxycycline	50%	0%	18.2%
Imipenem	100%	11.8%	9.1%
Linezolid	87.5%	23.5%	81.8%
Moxifloxacin	100%	0%	9.1%
Trimethoprim-sulfamethoxazole	100%	5.9%	0%
Tobramycin	0%	0%	72.7%

*Antimicrobial susceptibility testing was performed using microbroth dilution according to the Clinical and Laboratory Standards Institute guideline M24-A2 [14].

macrolides, whereas *M mucogenicum* is often susceptible to both medications. By far, *M fortuitum* is the most susceptible pathogen among RGM. *Mycobacterium fortuitum* is usually susceptible to amikacin, fluoroquinolones, sulfonamides, imipenem, linezolid, cefoxitin, doxycycline, and clarithromycin. However, approximately one third of *M fortuitum* isolates may contain an inducible erythromycin methylase (*erm)* gene, which confers clarithromycin resistance [2, 12]. Hence, clarithromycin monotherapy should be avoided, and the pathogen should be tested for the presence of this *erm* gene. The general recommendation for treatment is to use at least two systemic antimicrobial therapies pending susceptibility results. Intravenous amikacin is a good choice, although there is hesitance to its use due to nephrotoxicity. This is often combined with either oral fluoroquinolones or macrolides as part of the empiric regimen. The optimal pathogen-directed therapy should be modified according to susceptibility results. At least two active antimicrobial drugs should be used for the duration of treatment. However, the optimal duration of antimicrobial therapy is not defined and should be guided by clinical and microbiological responses. Successful outcome has been reported in cancer patients who were treated with four to eight weeks of pathogen-directed antimicrobial therapy [1, 2]. However, the duration of therapy may need to be prolonged based on type of infections and complications and the clinical state of the host. Overall, RGM CLABSI usually has a good outcome, when treated accordingly with antibiotics and catheter removal [1, 13].

Prevention

Because RGM can be found in the environment, there should be caution to avoid or limit contact between the intravascular catheters and tap water. Use of multidose injection vials should be avoided in an effort to prevent CLABSI due to RGM and other pathogens.

KEY POINTS

- RGM are emerging pathogens that causes a wide spectrum of clinical syndromes in immunosuppressed patients, including the respiratory tract, bloodstream, skin and soft tissue, and disseminated infections.
- RGM should be suspected as a cause of central line-associated bloodstream infection in cancer patients with indwelling central venous catheter and no clearly identified source of bacteremia.
- The diagnosis of RGM is made using culture of the specific organism and molecular methods for species identification.
- Key management for RGM CLABSI consists of catheter removal combined with antimicrobial therapy. Susceptibility testing should be performed on all isolates to guide the choices of antibiotic therapy, because there is significant inter- and intraspecies variability in the susceptibility pattern among RGM.

REFERENCES

1. Redelman-Sidi G, Sepkowitz KA. Rapidly growing mycobacteria infection in patients with cancer. Clin Infect Dis. 2010;51:422.
2. El Helou G, Hachem R, Viola GM, et al. Management of rapidly growing mycobacterial bacteremia in cancer patients. Clin Infect Dis. 2013;56:843.
3. Esteban J, Martin-de-Hijas NZ, Kinnari TJ, et al. Biofilm development by potentially pathogenic non-pigmented rapidly growing mycobacteria. BMC Microbiol. 2008;8:184.
4. Hall-Stoodley L, Lappin-Scott H. Biofilm formation by the rapidly growing mycobacterial species *Mycobacterium fortuitum*. Fems Microbiol Lett. 1998;168:77.
5. Brown-Elliott BA, Wallace RJ Jr. Clinical and taxonomic status of pathogenic nonpigmented or late-pigmenting rapidly growing mycobacteria. Clin Microbiol Rev. 2002;15:716.
6. El Helou G, Viola GM, Hachem R, et al. Rapidly growing mycobacterial bloodstream infections. Lancet Infect Dis. 2013;13:166–74.
7. De Groote MA, Huitt G. Infections due to rapidly growing mycobacteria. Clin Infect Dis. 2006;42: 1756.
8. Brown-Elliott BA, Wallace RJ Jr, Petti CA, et al. *Mycobacterium neoaurum* and *Mycobacterium bacteremicum* sp. nov. as causes of mycobacteremia. J Clin Microbiol. 2010;48:4377.
9. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Resp Crit Care 2007;175:367.
10. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;49:1.
11. Raad, II, Vartivarian S, Khan A, Bodey GP. Catheter-related infections caused by the *Mycobacterium fortuitum* complex: 15 cases and review. Rev Infect Dis. 1991;13:1120.
12. Nash KA, Zhang Y, Brown-Elliott BA, Wallace RJ Jr. Molecular basis of intrinsic macrolide resistance in clinical isolates of *Mycobacterium fortuitum*. J Antimicrob Chemother 2005;55:170.
13. McCracken D, Flanagan P, Hill D, Hosein I. Cluster of cases of *Mycobacterium chelonae* bacteraemia. Eur J Clin Microbiol Infect Dis. 2000;19:43.
14. CLSI. *Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard—Second Edition*. CLSI document M24-A2. Wayne, PA; Clinical and Laboratory Standards Institute; 2011.

1.9

What's Wrong With My Right Side, Doc?

SUSAN K. SEO, MD

CASE PRESENTATION

A 32-year-old man with recently diagnosed acute myelogenous leukemia (AML) presented with fever and mild right upper quadrant tenderness after induction chemotherapy. He had been otherwise healthy until development of fever and sore throat that did not resolve despite an antibiotic trial. He was admitted to the hospital where evaluation showed circulating blasts in peripheral blood. A bone marrow biopsy showed a hypercellular marrow in which normal hematopoietic elements were replaced by sheets of myeloblasts. The patient was diagnosed with AML and underwent standard induction chemotherapy with idarubicin and cytarabine. Bone marrow biopsy on hospital day (HD) 22 demonstrated 20% myeloblasts, so he was reinduced with idarubicin and cytarabine, and repeat bone marrow evaluation on HD 44 was finally compatible with remission. His hospital course was notable for prolonged fever, neutropenia, and mucositis for which he was supported with broad-spectrum antimicrobial therapy for almost his entire hospitalization. With regard to antifungal coverage, he initially received liposomal amphotericin B (3 mg/kg per day), but due to hypokalemia, this was switched to caspofungin (70 mg load on day 1, then 50 mg daily thereafter) before second induction. He experienced neutrophil recovery and was discharged home on HD 51 on no antibiotics. While at home, the patient continued to have daily fever to 101.2°F, and he was readmitted five days later. On exam, he had some tenderness to palpation of the right upper abdomen but no guarding. Pertinent laboratory findings included elevated white blood cell count ([WBC] 20.8, 83% N) and alkaline phosphatase ([AP] 247) but normal total bilirubin (0.6), aspartate aminotransferase (94), and alanine aminotransferase (40). Computed tomography (CT) scan of the chest and abdomen demonstrated multiple round, low attenuation lesions with peripheral enhancement scattered throughout the liver (Figures 1.9.1 and 1.9.2).

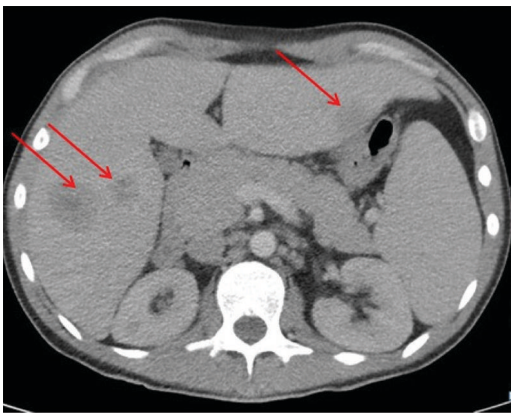


FIGURE 1.9.1: CT of liver showing multiple round low attenuation lesions.

QUESTIONS

- What is the most likely diagnosis to explain the patient's liver lesions?
- What diagnostic approach should be taken?

DIAGNOSIS

Although tumor or microabscesses due to bacteria, mycobacteria (e.g. miliary tuberculosis), or other fungi (e.g. *Aspergillus, Trichosporon beigelii*) can be entertained, the clinical and radiological picture is highly suggestive of chronic disseminated candidiasis (CDC), also called hepatosplenic candidiasis. Definitive diagnosis is established by biopsy, which can show granulomas and with special staining, yeasts, and hyphal forms. Tissue cultures may be negative, particularly if the patient has been exposed to antifungal therapy, but a negative culture does not rule out the diagnosis.

CASE PRESENTATION (CONTINUED)

The patient underwent fine-needle aspiration of one of the liver lesions. Cytology was negative

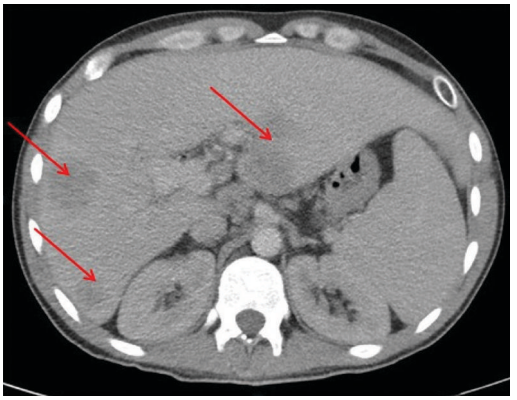


FIGURE 1.9.2: Wet mount showing yeast with pseudohyphae.

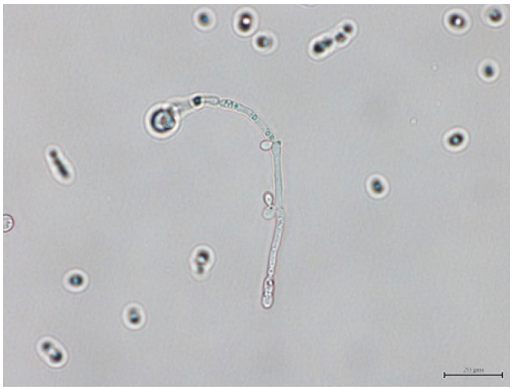


FIGURE 1.9.4: CT of liver showing other low attenuation lesions.

for malignant cells. Pathology showed "aggregates of epithelioid histiocytes in a background of purulent inflammation and blood," and Gomori methenamine silver (GMS) stain was positive for pseudohyphae and spores suggestive of *Candida* species. Germ-tube positive yeast was recovered from tissue culture (Figures 1.9.3 and 1.9.4) and identified as *Candida albicans*. Smear and culture for acid-fast bacilli were negative. The patient was empirically given voriconazole, but he was discharged home on fluconazole 400 mg orally daily once antifungal sensitivities were available.

QUESTIONS

- What should the duration of therapy be?
- How does one follow treatment response?

DURATION OF THERAPY

Antifungal duration is highly individualized. Patients with acute leukemia generally undergo further cycles of chemotherapy and/or undergo hematopoietic stem cell transplantation (HSCT), so antifungal treatment for CDC should be continued through these periods of risk to avoid relapse.

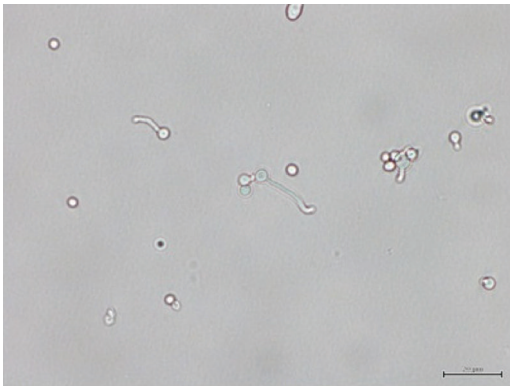


FIGURE 1.9.3: Germ-tube positive yeast.

MONITORING THERAPEUTIC RESPONSE

Factors to follow include resolution of symptoms, normalization of AP, and serial imaging. Antifungal treatment is generally continued until there is resolution or calcifications of the lesions. Of note, hepatic and/or splenic lesions can wax and wane as the patient's neutrophil count rises and falls, but these findings do not correlate with failure or success of antifungal treatment. Although there is some evidence that 1–3-β-D-glucan (BD glucan) can be used adjunctively for diagnosis of invasive fungal disease (e.g. CDC), it remains to be seen whether it has utility for disease follow-up.

CASE PRESENTATION (CONTINUED)

Within three weeks of starting azole therapy, the patient defervesced, and the right upper abdominal discomfort improved. Serum fungal markers were not checked until three weeks after initial diagnosis of hepatic candidiasis, and a BD glucan was noted to be 140 pg/mL (negative, <31). Repeat CT imaging after one month of fluconazole showed that many of the liver lesions had decreased in size. Six weeks after CDC diagnosis, the patient was maintained on fluconazole through first consolidation chemotherapy with high-dose cytarabine and later a brief admission for neutropenic fever. After 11 weeks of therapy, a repeat liver CT showed that some of the hepatic lesions had enlarged, AP remained in the 120s, and BD glucan was >300 pg/mL. Table 1.9.1 depicts the trends of WBC, AP, serum fungal markers, and serial liver imaging. Repeat liver

TABLE 1.9.1. LABORATORY AND RADIOGRAPHIC TRENDS AFTER DIAGNOSIS OF CDC*

Time After CDC Diagnosis (Weeks)	Course	White Blood Cell	Alkaline Phosphatase (Units/L)	1–3-β-D glucan (pg/mL)	Serum Galactomannan Antigen	Liver Imaging
0	Fluconazole started	20.8	247	N/A	N/A	Multiple round hepatic low attenuation lesions with peripheral enhancement involving both hepatic lobes
3		11.8	158	140	0.276	Slight decrease in size of some hepatic lesions, others are stable. Overall, mild disease improvement.
8	Admit for F&N after first consolidation	0.2	102	366	0.123	Several bilobar hypoattenuating abscesses with poorly defined surrounding enhancement, now smaller
11	Repeat liver biopsy, fluconazole changed to voriconazole	6.1	126	312	0.072	Multiple solid hepatic nodules consistent with abscesses with slight increase in some of these
15	2nd consolidation	10.4	122	221	0.121	Several hepatic lesions increased in size, other lesions are stable.
16	Admit for F&N	0.3	80	319	N/A	N/A
28	T cell- depleted HSCT	<0.1 (Day 0)	69	171	N/A	Stable hypoattenuating hepatic masses
30	Engraftment	4.2	128	61	0.160	No new hepatic lesions. Existing hepatic abscesses are stable.
39		N/A	103	31	N/A	Decrease in size of numerous hepatic lesions that no longer demonstrate any significant enhancement
68	Azole narrowed to fluconazole	4.4	113	45	N/A	Decrease in size of one lesion, others stable

Abbreviations: CDC, chronic disseminated candidiasis; F&N, fever and neutropenia; HSCT, hematopoietic stem cell transplantation; N/A, not applicable.

biopsy was performed to see whether there was evidence for uncontrolled CDC or other coinfection not treated by fluconazole. The result was compatible with organized abscess formation; no fungal spores or hyphae were identified by GMS stain; and cultures for bacteria, fungi, and mycobacteria were negative. It was thought possible that the results reflected immune reconstitution postneutrophil recovery. Nevertheless, the patient was switched to voriconazole to cover for the possibility of fluconazole-resistant *Candida* or *Aspergillus* sp, and this was maintained through his second consolidation cycle (week 15 post-CDC diagnosis), receipt of T cell-depleted HSCT (week 28 post-CDC diagnosis), and posttransplant course. By week 39 post-CDC diagnosis, liver imaging showed that numerous liver lesions had decreased in size, and there was no longer any significant peripheral enhancement. In addition, BD glucan dropped to 31, and AP decreased to 103. By week 68 post-CDC diagnosis, voriconazole was switched back to fluconazole. Antifungal therapy was finally discontinued by week 97 on the basis of stable or shrunken liver lesions and evidence for immune reconstitution. The patient was able to return to work full time.

Final Diagnosis: Chronic hepatic candidiasis in a patient following neutrophil recovery after AML induction chemotherapy

DISCUSSION

Chronic disseminated candidiasis, or hepatosplenic candidiasis, is a distinct syndrome predominantly involving the liver, spleen, and occasionally the kidneys and other organs and is seen almost exclusively in patients with hematologic malignancies who have just recovered from chemotherapy-induced neutropenia [1].

Epidemiology

Reported rates of CDC in the published literature range between 4.5% and 29% for patients with acute leukemia [2, 3] and between 3% and 9% in HSCT recipients [4, 5]. Although fluconazole prophylaxis has been shown to reduce hepatic candidiasis in HSCT recipients [6], there are no clear-cut data for leukemic patients in non-HSCT settings, although one would expect a similar finding. In one meta-analysis, prophylactic fluconazole in non-HSCT patients seemed to be effective only when the incidence of systemic fungal infection was expected to be >15% [7]. Further epidemiologic studies of severely neutropenic patients with acute leukemia are needed.

Prolonged neutropenia has been cited as the primary risk factor for CDC. In one study, absolute neutrophil count <500 μL lasting >15 days, younger age, and prophylactic quinolones were found to be independent risk factors for development of infection in patients with acute leukemia [8]. It is thought that younger patients are more likely to be treated aggressively and thus have longer, more profound neutropenic periods. In addition, severe mucositis as a consequence of cytotoxic chemotherapy and the change in the composition of gut flora by quinolones may potentiate the risk.

Pathogenesis

The pathogenesis is not well understood, but the most likely sequence of events starts with prolonged neutropenia and mucosal damage of the gastrointestinal tract, followed by local invasion and subsequent entry of *Candida* sp into the hepatosplenic circulation [9]. Because the portal system likely receives the largest inoculum, the disease tends to be prominent in the liver. Dysregulation of the host adaptive immune response certainly plays a role in pathogenesis because symptoms and radiographic findings manifest when the patient experiences neutrophil recovery. It is now thought that chemotherapy destabilizes the balance between pro- (Th1/Th17) and anti-inflammatory (Th2/Treg) pathways and a predominantly anti-inflammatory state conducive to the survival of *Candida* ensues. Once the WBC rises, there is a shift favoring the Th1/Th17 response that leads to an immune reconstitution inflammatory syndrome (IRIS) [10].

There is at least one clinical study investigating the use of adjunctive corticosteroids to decrease the inflammatory response associated with IRIS. A retrospective, multicenter study assessed the efficacy of oral glucocorticoids in ten children and adults who had ongoing symptomatic probable or proven CDC despite appropriate antifungal therapy [11]. Steroids were started a mean of 33.8 days after initiation of antifungal treatment. Patients received a prednisone equivalent of ≥0.5 mg/kg per day for at least three weeks and experienced resolution of fever and abdominal pain (median of four to five days) and normalization of C-reactive protein within fourteen to thirty days. Further studies will be needed to determine the safety and efficacy of adjuvant steroids for this indication.

Clinical Manifestations

Classically, patients have persistent fever >100.4°F that fails to respond to conventional antibiotics [3, 12–14]. Right upper quadrant or abdominal pain is the second most common finding [3, 12–14]. Liver function tests typically show an elevated AP as high as ten-fold the normal value and, less commonly, elevated serum transaminases [12–14]. Inflammatory markers such as C-reactive protein are often elevated but are nonspecific [15].

Radiographic imaging reveals multiple lesions representing microabscesses in the liver, spleen, and sometimes the kidneys. Magnetic resonance imaging (MRI) appears to be superior to CT scan and ultrasound for identification of disease with sensitivity of 100% and specificity of 96% [16]. Lesions compatible with the acute phase of infection are round and are markedly hyperintense on T2-weighted images. Sometime between two weeks to three months after initiation of antifungal therapy, a dark ring surrounding the initial lesions and a nonenhancing center on gadolinium images may be seen [16]. Chronic healed lesions have irregular margins with disappearance of the central area; the time to appearance of healed fungal foci ranges between three months and more than one year [16]. Although the sensitivity of CT is lower than that of MRI (57%–90%) [17], it is used more frequently because it is less expensive

and simpler to perform [18]. The hypodense lesions are typically described as "bull's eye" or target-like lesions. Biphasic liver imaging seems to be the ideal CT modality, because a characteristic pattern of central enhancement with a peripheral double ring has been described in the arterial phase [19]. In comparison with MRI or CT, ultrasound has the lowest sensitivity (33%–75%) and is dependent on the experience of the radiologist [17]. One drawback of imaging is the inability to visualize fungal lesions during the neutropenic phase because of the lack of inflammatory response essential to form the focal infiltrate [20]. Thus, radiographic imaging alone should not dictate treatment duration.

Diagnosis

Diagnosis of CDC requires a high index of suspicion and is typically established after neutrophil recovery in 85% of patients with acute leukemia [3]. Although modern imaging techniques have an important role in early identification and recognition of the disease, tissue biopsy is considered to be the gold standard [21]. However, it is not always possible to identify fungal elements if the sampling is less than optimal, and tissue cultures have historically been positive in ~50% of cases, even when fungal elements are visible on microscopic examination [1, 15, 22]. The most common *Candida* sp recovered from liver biopsy samples are *C albicans* (>50%), followed in decreasing order by *Candida tropicalis, Candida glabrata*, and *Candida parapsilosis* [18]. Historically, laparoscopy has been preferred because it allowed for better sampling of hepatic focal lesions [22]. However, ultrasound- or CT-guided percutaneous biopsy is generally well tolerated with few complications and is becoming the norm.

It is worth mentioning that the BD glucan is a component of the cell wall of many fungi, including *Candida* sp, and there is moderate evidence that its detection in the blood may be a useful diagnostic adjunct for invasive candidiasis [23, 24]. The BD glucan may also be useful to monitor treatment response, although further study is warranted [24].

Treatment

Randomized trials evaluating the efficacy of antifungal drugs in the treatment of CDC have not been performed. The clinical approach has been based on anecdotal case reports and open-label series with the bulk of the experience being with amphotericin B deoxycholate (AmB-d), lipid formulations of amphotericin (LFAmB), and fluconazole [25–30]. Caspofungin, an echinocandin, and voriconazole, a broader-spectrum azole, have also been used in primary or salvage therapy for CDC [31–35].

According to the Infectious Diseases Society of America candidiasis guidelines [36], AmB-d (0.5–0.7 mg/kg intravenously daily) or LFAmB (3–5 mg/kg intravenously daily) is recommended for acutely ill patients or patients with refractory disease. Induction therapy with AmB-d or LFAmB for one to two weeks is then followed by oral fluconazole (400 mg daily). Echinocandins (anidulafungin 200 mg loading dose, then 100 mg intravenously daily; caspofungin 70 mg loading dose, then 50 mg intravenously daily; or micafungin 100 mg intravenously daily) can be used as alternative induction therapy, followed by oral fluconazole when clinically appropriate. Clinically stable patients may be started with oral fluconazole at a dosage of 400 mg daily.

Clinical signs generally improve within two to eight weeks after starting treatment. Normalization of AP can lag behind clinical and radiographic response [3]. Antifungal therapy should be continued for weeks to months, until calcifications occur or lesions resolve. Patients with CDC who receive further chemotherapy for their underlying malignancy or who undergo HSCT should continue to receive appropriate antifungal treatment through these periods of risk to prevent relapse [29, 37].

KEY POINTS

- CDC, or hepatosplenic candidiasis, is seen predominantly in patients with hematologic malignancies who have just recovered their neutrophils.
- Although definitive diagnosis is established by biopsy, the classic features (persistent fever, right upper quadrant abdominal pain, elevated AP) combined with abdominal imaging showing multiple lucencies in the liver and/or spleen are characteristic of this disease.
- Most cases are due to *C albicans*, but other *Candida* species have been reported.
- Duration of antifungal therapy is individualized to the patient, can take weeks to months, and ends with resolution or calcification of lesions.

REFERENCES

1. Kontoyiannis DP, Luna MA, Samuels BI, Bodey GP. Hepatosplenic candidiasis. A manifestation of chronic disseminated candidiasis. Infect Dis Clin North Am. 2000;14:721.

2. Grois N, Mostbeck G, Scherrer R, et al. Hepatic and splenic abscesses—a common complication of intensive chemotherapy of acute myeloid leukemia (AML). A prospective study. Ann Hematol. 1991;63:33.
3. Sallah S, Semelka RC, Wehbie R, et al. Hepatosplenic candidiasis in patients with acute leukaemia. Br J Haematol. 1999;106:697.
4. Bjerke JW, Meyers JD, Bowden RA. Hepatosplenic candidiasis—a contraindication to marrow transplantation. Blood 1994;84:2811.
5. Rossetti F, Brawner DL, Bowden R, et al. Fungal liver infection in marrow transplant recipients—prevalence at autopsy, predisposing factors, and clinical features. Clin Infect Dis. 1995;20:801.
6. van Burik JH, Leisenring W, Myerson D, et al. The effect of prophylactic fluconazole on the clinical spectrum of fungal diseases in bone marrow transplant recipients with special attention to hepatic candidiasis. An autopsy study of 355 patients. Medicine (Baltimore) 1998;77:246.
7. Kanda Y, Yamamoto R, Chizuka A, et al. Prophylactic action of oral fluconazole against fungal infection in neutropenic patients. A meta-analysis of 16 randomized, controlled trials. Cancer 2000;89:1611.
8. Sallah S, Wan JY, Nguyen NP, et al. Analysis of factors related to the occurrence of chronic disseminated candidiasis in patients with acute leukemia in a non-bone marrow transplant setting: a follow-up study. Cancer 2001;92:1349.
9. Cole GT, Lynn KT, Seshan KR. Evaluation of a murine model of hepatic candidiasis. J Clin Microbiol. 1990;28:1828.
10. Rammaert B, Desjardins A, Lortholary O. New insights into hepatosplenic candidosis, a manifestation of chronic disseminated candidosis. Mycoses 2012;55:e74.
11. Legrand F, Lecuit M, Dupont B, et al. Adjuvant corticosteroid therapy for chronic disseminated candidiasis. Clin Infect Dis. 2008;46:696.
12. Haron E, Feld R, Tuffnell P, et al. Hepatic candidiasis: an increasing problem in immunocompromised patients. Am J Med. 1987;83:17.
13. Talbot GH, Provencher M, Cassileth PA. Persistent fever after recovery from granulocytopenia in acute leukemia. Arch Intern Med. 1988;148:129.
14. Thaler M, Pastakia B, Shawker TH, et al. Hepatic candidiasis in cancer patients: the evolving picture of the syndrome. Ann Intern Med. 1988;108:88.
15. Anttila VJ, Ruutu P, Bondestam S, et al. Hepatosplenic yeast infection in patients with acute leukemia: a diagnostic problem. Clin Infect Dis. 1994;18:979.
16. Semelka RC, Kelekis NL, Sallah S, et al. Hepatosplenic fungal disease: diagnostic accuracy and spectrum of appearances on MR imaging. AJR Am J Roentgenol. 1997;169:1311.
17. Anttila VJ, Lamminen AE, Bondestam S, et al. Magnetic resonance imaging is superior to computed tomography and ultrasonography in imaging infectious liver foci in acute leukaemia. Eur J Haematol. 1996;56:82.
18. Masood A, Sallah S. Chronic disseminated candidiasis in patients with acute leukemia: emphasis on diagnostic definition and treatment. Leuk Res. 2005;29:493.
19. Rudolph J, Rodenwaldt J, Ruhnke M, et al. Unusual enhancement pattern of liver lesions in hepatosplenic candidiasis. Acta Radiol. 2004;45:499.
20. Pestalozzi BC, Krestin GP, Schanz U, et al. Hepatic lesions of chronic disseminated candidiasis may become invisible during neutropenia. Blood 1997;90:3858.
21. Johnson TL, Barnett JL, Appelman HD, Nostrant T. Candida hepatitis. Histopathologic diagnosis. Am J Surg Pathol. 1988;12:716.
22. Anttila VJ, Farkkila M, Jansson SE, et al. Diagnostic laparoscopy in patients with acute leukemia and suspected hepatic candidiasis. Eur J Clin Microbiol Infect Dis. 1997;16:637.
23. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1-->3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis. 2005;41:654.
24. Marchetti O, Lamoth F, Mikulska M, et al. ECIL recommendations for the use of biological markers for the diagnosis of invasive fungal diseases in leukemic patients and hematopoietic SCT recipients. Bone Marrow Transplant 2012;47:846.
25. Anaissie E, Bodey GP, Kantarjian H, et al. Fluconazole therapy for chronic disseminated candidiasis in patients with leukemia and prior amphotericin B therapy. Am J Med. 1991;91:142.
26. Kauffman CA, Bradley SF, Ross SC, Weber DR. Hepatosplenic candidiasis: successful treatment with fluconazole. Am J Med. 1991;91:137.
27. Gokhale PC, Barapatre RJ, Advani SH, et al. Successful treatment of disseminated candidiasis resistant to amphotericin B by liposomal amphotericin B: a case report. J Cancer Res Clin Oncol. 1993;119:569.
28. de Pauw BE, Raemaekers JM, Donnelly JP, et al. An open study on the safety and efficacy of fluconazole in the treatment of disseminated *Candida* infections in patients treated for hematological malignancy. Ann Hematol. 1995;70:83.
29. Walsh TJ, Whitcomb PO, Revankar SG, Pizzo PA. Successful treatment of hepatosplenic candidiasis through repeated cycles of chemotherapy and neutropenia. Cancer 1995;76:2357.

30. Walsh TJ, Whitcomb P, Piscitelli S, et al. Safety, tolerance, and pharmacokinetics of amphotericin B lipid complex in children with hepatosplenic candidiasis. Antimicrob Agents Chemother. 1997;41:1944.
31. Sora F, Chiusolo P, Piccirillo N, et al. Successful treatment with caspofungin of hepatosplenic candidiasis resistant to liposomal amphotericin B. Clin Infect Dis. 2002;35:1135.
32. Hubel K, Chemnitz J, Brochhagen HG, Cornely OA. Successful treatment of chronic disseminated candidiasis with caspofungin and itraconazole in a patient with progressive acute leukemia and prolonged neutropenia. Int J Hematol. 2004;79:289.
33. Cornely OA, Lasso M, Betts R, et al. Caspofungin for the treatment of less common forms of invasive candidiasis. J Antimicrob Chemother. 2007;60:363.
34. Kontny U, Walsh TJ, Rossler J, et al. Successful treatment of refractory chronic disseminated candidiasis after prolonged administration of caspofungin in a child with acute myeloid leukemia. Pediatr Blood Cancer 2007;49:360.
35. Ostrosky-Zeichner L, Oude Lashof AM, Kullberg BJ, Rex JH. Voriconazole salvage treatment of invasive candidiasis. Eur J Clin Microbiol Infect Dis. 2003;22:651.
36. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503.
37. Poon LM, Chia HY, Tan LK, et al. Successful intensive chemotherapy followed by autologous hematopoietic cell transplantation in a patient with acute myeloid leukemia and hepatosplenic candidiasis: case report and review of literature. Transpl Infect Dis. 2009;11:160.

1.10

A Budding Headache in a Patient with Hematological Malignancy

SAMANTHA E. JACOBS, MD, MS, ROSEMARY SOAVE, MD, AUDREY N. SCHUETZ, MD, MPH, AND THOMAS J. WALSH, MD

CASE PRESENTATION

A 62 year-old man with chronic lymphocytic leukemia (CLL) was admitted to the hospital with fever and headache. The patient was diagnosed with CLL in 2008 when leukocytosis was noted on a routine complete blood count. He did not require treatment until 2013, when he developed cervical, axillary, and intra-abdominal lymphadenopathy with anemia. He underwent six cycles of fludarabine, cyclophosphamide, and rituximab that were completed seven months before admission. Three months before admission, he developed a rising white blood cell count (WBC) and facial rash that was biopsied revealing leukemia cutis. He received rituximab and five days of high-dose methylprednisolone. Despite an initial response, he had rapid progression of his disease, including lymphadenopathy, thrombocytopenia, anemia, and a rising lymphocyte count. Two months before admission, he initiated therapy with the tyrosine kinase inhibitor ibrutinib.

One month before admission, the patient was hospitalized for nine days with fevers, nasal congestion, cough, and a facial rash. He was found to have respiratory syncytial virus (RSV) pneumonia and facial cellulitis. His respiratory symptoms and facial rash resolved with supportive care and intravenous (IV) antibiotics; however, low-grade fevers persisted. He was discharged home with outpatient follow-up for additional fever work-up.

After discharge, the patient continued to have fevers and developed night sweats. He also developed nausea and an "achy" frontal headache that was exacerbated by laying supine. A positron emission tomography-computed tomography (PET-CT) was scheduled to evaluate for Richter's transformation. However, on the day of admission, the patient had a worsening headache and episode of vomiting, prompting his presentation to the Emergency Department for further evaluation. Medications included ibrutinib, valacyclovir, and trimethoprim-sulfamethoxazole.

On physical exam, he was a thin male, chronically ill appearing but nontoxic. He preferred to keep his eyes closed because the light exacerbated his headache. The temperature was 39.1°C, the heart rate was 105 beats per minute, and blood pressure, respiratory rate, and oxygen saturation were within normal range. He was alert and oriented, and the remainder of the physical exam, including the neurologic exam, was normal.

Laboratory studies were remarkable for a WBC count of 122 000 cells/μL (from 85 000 cells/μL three weeks prior) with 90% lymphocytes, hemoglobin 8.5 g/dL (baseline 8–9 g/dL), and serum albumin 2.8 g/dL. The platelet count, serum electrolytes and creatinine, and liver function tests were normal. Chest radiograph revealed a right lower lung zone airspace opacity of similar appearance to a film three weeks prior when RSV was detected. A CT scan of the head showed no infarct, hemorrhage, or mass lesion. Magnetic resonance imaging of the brain showed subtle areas of sulcal T2/FLAIR hyperintensity along the right frontal sulci (Figure 1.10.1).

A lumbar puncture was performed. The opening pressure was 360 mm of cerebrospinal fluid (CSF), and the CSF was clear and colorless. There were 48 WBCs/μL (58% lymphocytes, 31% segmented neutrophils, 7% monocytes, and 3% bands), 3 red blood cells/μL, 44 mg/dL protein, and 47 mg/dL glucose. The CSF Gram stain showed many WBCs and yeast (Figure 1.10.2). A KOH preparation showed many yeast-like elements.

PET-CT was performed after the lumbar puncture. It revealed new focal uptake along the right lateral aspect of the prostate gland (Figure 1.10.3). Otherwise, there was a significant decrease in

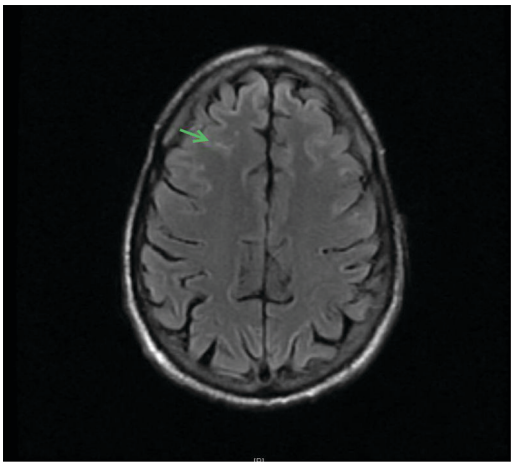


FIGURE 1.10.1: Subtle areas of sulcal T2/FLAIR hyperintensity along the right frontal sulci can be seen in the setting of meningitis.

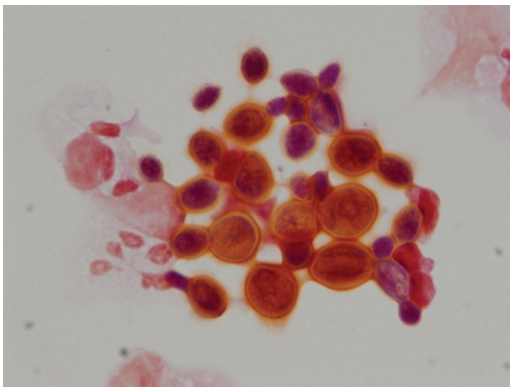


FIGURE 1.10.2: Gram stain of CSF, 1000× magnification: Cluster of yeast forms variable in size (4–15 microns) and neutrophils. The yeast forms stain gram-positive with a mottled appearance.

fluorodeoxyglucose (FDG) uptake in the cervical, axillary, and abdominopelvic lymphadenopathy consistent with the patient's known CLL.

QUESTIONS

- What is the differential diagnosis for fungal meningitis when yeast are visualized on CSF Gram stain?
- How did this patient's immune impairment contribute to his risk for this fungal infection?
- What are the initial steps in management of this patient's fungal infection?
- What factors are critical to optimizing outcome in this type of fungal infection?

DIFFERENTIAL DIAGNOSIS

Invasive fungal infections (IFIs) of the central nervous system (CNS) are an uncommon but potentially devastating complication in patients with hematologic malignancy. Manifestations of IFIs of the CNS include single or multiple brain abscesses (e.g. *Aspergillus* species, Mucorales, *Trichosporon* species), meningitis (e.g. *Cryptococcus neoformans, Candida* species, *Coccidioides* species, *Histoplasma capsulatum*), and vascular injury causing cerebral infarcts, subarachnoid hemorrhage, or mycotic aneurysms. The CNS may be the primary site of IFI, or infection may occur secondarily due to hematogenous seeding from extracranial sites (most often the lungs) or contiguous spread from the cranial bones or sinuses [1].

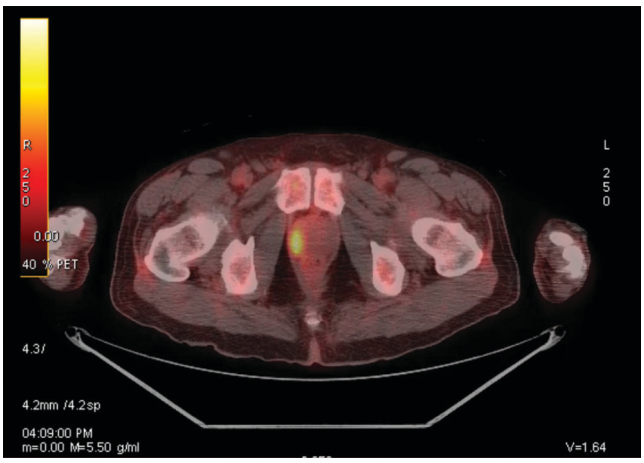


FIGURE 1.10.3: New focal uptake along the right lateral aspect of the prostate gland observed on PET-CT. The prostate may serve as a reservoir for cryptococcal infection (6).

In this patient with clinical and radiographic evidence of meningitis, the differential diagnosis for yeast seen on CSF Gram stain includes *Cryptococcus* species, *Candida* species, *Blastomyces dermatitidis*, or *Histoplasma capsulatum*. *Candida* meningoencephalitis may have a subacute presentation as seen in this patient. However, as a manifestation of disseminated candidiasis, *Candida* meningoencephalitis is much more common in neonates and children. Among adults, *Candida* meningitis often occurs as a postoperative complication of neurosurgery, particularly ventriculoperitoneal shunt placement. Blastomycosis of the CNS is also a consideration, especially if the patient lived recently in the north central, southeastern, or mid-Atlantic portions of the United States; the yeast forms also have distinctive broad-based budding. Histoplasmosis involving the CNS is usually associated with symptoms of disseminated infection, plus the patient had no history of residence or travel to endemic areas. Moreover, the yeast forms of *H capsulatum* are relatively small at 3 micron diameter, whereas *Cryptococcus* species are more variable in size and larger at 4–20 micron diameter. A diagnosis of cryptococcal meningitis is most compelling given the clinical presentation and markedly elevated CSF opening pressure in a patient with profound deficiency in cell-mediated immunity.

ADDITIONAL DATA AND DIAGNOSIS

The CSF and serum cryptococcal antigen titer were 1:8192 and 1:2048, respectively. Cerebrospinal fluid and blood cultures grew *C neoformans*. The diagnosis was cryptococcal meningitis and bloodstream infection.

MANAGEMENT AND OUTCOME

Liposomal amphotericin B 5 mg/kg IV every 24 hours and flucytosine 25 mg/kg orally every 6 hours were initiated. The flucytosine peak serum concentration was measured at 41 mcg/mL (therapeutic range, 25–100 mcg/mL). To manage the patient's increased intracranial pressure, therapeutic lumbar puncture was performed every one to two days for thirteen days until the opening pressure was less than 250 mm of CSF for two consecutive days. The CSF fungal culture had no growth after eleven days of antifungal therapy. The patient gradually improved and was discharged home on hospital day 27. He completed six weeks of liposomal amphotericin B and flucytosine at home and was transitioned to fluconazole 400 mg daily for the consolidation phase of treatment. Throughout this time, he continued ibrutinib for CLL treatment. PET-CT performed three months after the diagnosis of cryptococcosis showed continued interval decrease in size of numerous cervical, thoracic, and abdominopelvic lymph nodes, none of which demonstrated FDG avidity. In addition, the focal FDG uptake along the lateral aspect of the prostate gland had resolved.

DISCUSSION

Cryptococcal infection in patients with hematological malignancies is a well described [2–4] but still relatively uncommon complication, perhaps due to routine use of prophylactic fluconazole or the absence of symptomatic disease. *Cryptococcus neoformans* is typically isolated from soils enriched in the droppings of birds, especially pigeons, turkeys, and chickens. Most cryptococcal infections are acquired primarily by inhalation of infectious propagules. After inhalation, *C neoformans* likely causes a focal pneumonitis that may or may not be symptomatic or disseminated depending on the host's immune status. Of the 19 *Cryptococcus* species, *C neoformans* most commonly causes clinical disease, followed by *Cryptococcus albidus* and *Cryptococcus laurentii*. Since the late 1990s, infections due to *C gatti* have been reported primarily in immunocompetent hosts, predominantly in tropical and subtropical areas including Hawaii, Brazil, Australia, Southeast Asia, and Central and sub-Saharan Africa as well as outbreaks in Vancouver and the northwestern United States. More recently, a genetically distinct strain of *C gattii* has been described in several states outside the Pacific Northwest, affecting both healthy and immunocompromised adults [5].

Risk Factors

Neutropenia per se does not predispose patients with hematological malignancies to cryptococcosis. Rather, an impairment of cellular immunity, such as that associated with corticosteroids or graft-versus-host disease prophylaxis, increases the risk for cryptococcosis. For example, patients with acute lymphoblastic leukemia or Hodgkin's lymphoma have a greater risk of pulmonary and CNS cryptococcosis than those patients with acute myelogenous leukemia, who do not usually receive corticosteroids. The risk of cryptococcosis may also increase with the use of cell-mediated immune inhibitors such as fludarabine and alemtuzumab that yield profound lymphopenia lasting from months to two to three years after treatment. In the present case, impaired cell-mediated immunity

due to underlying CLL or previous treatment with fludarabine were likely contributing factors.

Clinical Presentation

Many patients are exposed to *Cryptococcus* during childhood and then develop reactivated disease during periods of immunosuppression. Similar to patients with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome, clinical manifestations include neurologic and pulmonary disease, as well as disseminated disease to the gastrointestinal tract, skeletal system, and skin. Central nervous system disease most commonly occurs as meningitis or meningoencephalitis but occasionally may lead to cryptococcomas. Patients may present with fever, headache, photophobia, altered mental status, and/or seizures. Osseous cryptococcosis occurs in up to 10% of disseminated cases. The lesions are lytic and may involve bony prominences, cranial bones, and vertebrae. The prostate may serve as a reservoir for infection [6]. The abnormal FDG uptake in the prostate gland on PET-CT imaging is suggestive of cryptococcal infection in the present case; however, confirmatory fungal cultures of prostatic secretions and urine were not obtained.

Diagnosis

All immunocompromised patients with pulmonary or bloodstream infection with cryptococcosis should undergo lumbar puncture to evaluate for CNS disease. The detection of cryptococcal capsular polysaccharide antigen in spinal fluid is the method of choice for diagnosing patients with cryptococcal meningitis. India ink staining of exudates or body fluids, used more commonly in resource-poor settings, may demonstrate a characteristic-wide gelatinous capsule (Figure 1.10.4). On Gram stain of spinal fluid, the yeast usually stains gram-positive with stippling and are often round with budding. In culture, the yeast forms are cream-colored, mucoid colonies that grow in three to five days. Serum cryptococcal antigen testing is less useful for diagnosis of cryptococcosis in non-HIV-immunocompromised patients because the sensitivity is approximately 56% and 86% in pulmonary and CNS disease, respectively [7].

Treatment

Recommended induction therapy for most non-HIV-related immunocompromised patients with CNS, pulmonary, or disseminated disease is deoxycholate amphotericin B or lipid formulation amphotericin B plus flucytosine for at least four weeks' duration. This is followed by fluconazole consolidation for eight weeks (400 mg orally daily) in adults or 12 mg/kg per day in children, then fluconazole maintenance (200 mg orally daily in adults or 6 mg/kg per day in children) [8]. Monitoring of the height of the CSF or serum cryptococcal antigen titer is not useful in evaluating response to therapy. Serial quantitative cultures of CSF are becoming more widely used as a marker of therapeutic response. Management of increased intracranial pressure is critical to outcome in cryptococcal meningitis. In the setting of symptoms and persistent pressure elevation >25 cm of CSF, daily lumbar puncture should be performed until symptoms and CSF pressure have normalized for at least two days [8]. Some patients may require temporary percutaneous lumbar drains or ventriculostomy. Older studies have generally observed that non-HIV-immunocompromised patients have higher short-term mortality rates than HIV-positive patients [7]. However, this finding was not confirmed in a more recent analysis, perhaps due to more timely diagnosis, aggressive management, and use of nonmyeloablative chemotherapy [9].

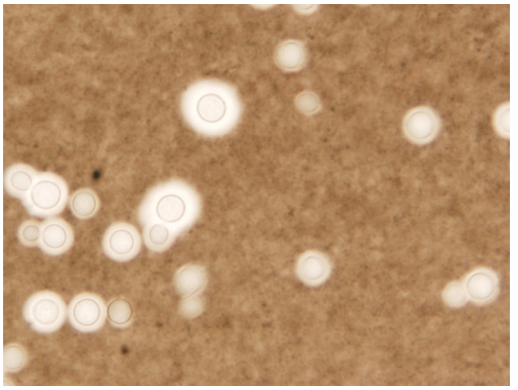


FIGURE 1.10.4: India ink stain of Cryptococcus spp., 1000× magnification. Round yeasts with capsules that do not take up the stain and occasional narrow-based buds are seen.

REFERENCES

1. Caira M, Falcucci P, Fianchi L, Pagano L. Fungal CNS infections in patients with hematologic malignancy. Expert Rev Anti Infect Ther. 2005;3:775.
2. Kaplan MH, Rosen PP, Armstrong D. Cryptococcosis in a cancer hospital: clinical and pathological correlates in 46 patients. Cancer 1977;39:2265.
3. Pagano L, Fianchi L, Caramatti C, et al. Cryptococcosis in patients with hematologic malignancies. A report from GIMEMA-infection program. Haematologica 2004;89:852.

4. Kontoyiannis DP, Peitsch WK, Reddy BT, et al. Cryptococcosis in patients with cancer. Clin Infect Dis. 2001;32:E145.
5. Harris JR, Lockhart SR, Park BJ. *Cryptococcus gattii* infections in multiple states outside the U.S. Pacific Northwest. Emerg Infect Dis. 2013;19: 1621.
6. Larsen RA, Bozzette S, McCutchan JA, et al. Persistent *Cryptococcus neoformans* infection of the prostate after successful treatment of meningitis. California Collaborative Treatment Group. Ann Intern Med. 1989;111:125.
7. Pappas PG, Perfect JR, Cloud GA et al. Cryptococcosis in HIV-negative patients in the era of effective azole therapy. Clin Infect Dis. 2001;33:690.
8. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:291.
9. Brizendine KD, Baddley JW, Pappas PG. Predictors of mortality and differences in clinical features among patients with cryptococcosis according to immune status. PLoS One 2013;8:e60431.

1.11

Shocking Revenge of the Weak Gram-Positive Cocci

ELENA BEAM, MD AND RAYMUND R. RAZONABLE, MD

CASE PRESENTATION

A 52-year-old male patient with chronic neutrophilic leukemia (CNL), a rare blood disorder characterized by proliferation of mature granulocytes in the bone marrow and other organs, complicated by its transformation into acute myelogenous leukemia (AML) was admitted to the intensive care unit (ICU) for sepsis syndrome.

He was diagnosed with CNL one year ago and received treatment with hydroxyurea. Six months later, he developed progressive anemia and splenomegaly and was treated with ruxolitinib. Surveillance bone marrow biopsy later showed transformation to AML, and hence the patient received induction therapy with daunorubicin and ara-C. Because of persistent disease, the patient was treated with a second induction regimen consisting of mitoxantrone and etoposide. During these treatments, the patient developed severe oral mucositis and prolonged neutropenia.

During a few days after the second cycle of induction chemotherapy, while receiving voriconazole, acyclovir, and levofloxacin prophylaxis, he developed fever and hemodynamic instability that required admission to the ICU. On physical examination, he appeared chronically ill and was in mild distress. He had a temperature of 39.8°C. He had sinus tachycardia, with heart rate ranging between 150–170 beats per minute. His blood pressure was 90/55 mmHg (normally 130/70 mm mercury) and respiration rate was 20 breaths per minute. The oral cavity was notable for moderate mucositis but without active bleeding or lesions. Scattered crackles were heard on both lung fields. The insertion site and tunnel of the indwelling Port-A-Cath were not inflamed or tender.

Blood cultures were obtained. Laboratory tests revealed pancytopenia (white blood cell count $0.1 \times 10^3/\mu L$, with too few cells for adequate differential; hematocrit, 17.7% and platelet count, 12 000/μL). His serum creatinine and liver biochemical studies were normal. His lactate level was elevated to 4.5 mmol/L.

Therapy was immediately started empirically with intravenous cefepime and vancomycin. In addition, the patient received aggressive fluid resuscitation. Later in the day, he was observed to have increasing oxygen requirements from 2 liters by nasal cannula to 10 liters via closed facemask. He failed a trial of noninvasive pressure ventilation, and he subsequently required endotracheal intubation and mechanical ventilation, with FiO2 requirements of 50% for adequate saturation and a P/F ratio of 150.

Chest radiograph showed diffuse bilateral pulmonary infiltrates, which had progressed compared with a surveillance radiograph performed one week before admission (Figure 1.11.1). Computed tomography scan of the chest demonstrated bilateral diffuse ground-glass opacities (Figure 1.11.2). Transthoracic echocardiogram showed mildly diminished left ventricular ejection fraction of 47% with new mild right ventricular (RV) enlargement and moderately decreased RV function.

QUESTIONS

- What infectious etiologies should be strongly considered to account for this patient's neutropenic fever, hemodynamic instability and sepsis?
- What are the risk factors for this specific infection?
- When should the empiric management of neutropenic fever include broader coverage for possible drug-resistant Gram-positive organisms?

DIFFERENTIAL DIAGNOSIS

The case presented here is one of fever with neutropenia (febrile neutropenia [FN]), which is a common complication of cytotoxic chemotherapy for the treatment of cancer. Prior to the use of antibiotic

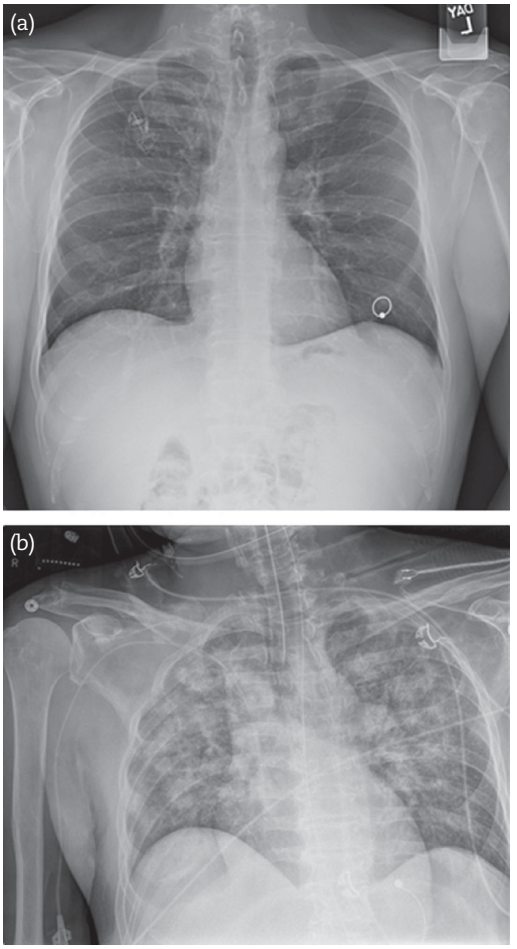


FIGURE 1.11.1: Chest radiograph shows diffuse bilateral infiltrates.

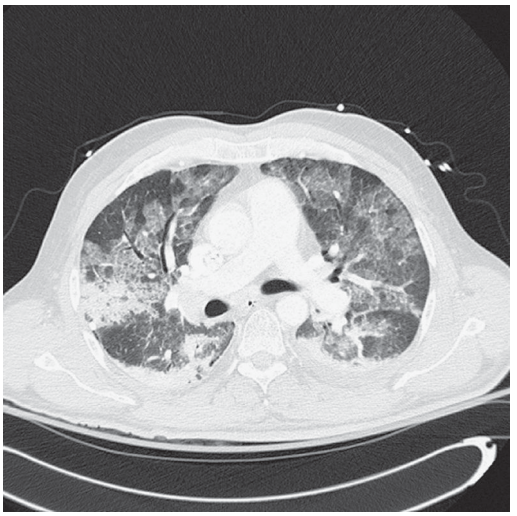


FIGURE 1.11.2: CT scan of the chest shows diffuse bilateral ground-glass opacities.

prophylaxis, infections were major causes of FN in cancer patients. The direct cytotoxic effects of chemotherapy on mucosal surfaces and the immune deficits from chemotherapy and underlying malignancy contribute to the heightened risk of infection as a cause of FN, especially when neutropenia is profound (<100/mm^3) and prolonged (longer than seven days). However, in the current era when antibiotic prophylaxis is standard of care in high-risk patients, the majority of episodes of FN in patients with cancer no longer have a defined infectious etiology [1]. High-risk patients that benefit from antimicrobial prophylaxis for FN include those patients with an expected duration of severe absolute neutropenia (<100 cells/μL, although some include <500 cells/μL) for seven days or longer.

Documented infections currently account for only approximately 20%–30% of FN episodes, with bacterial pathogens as the predominant etiologic agents. Only approximately 10%–25% of FN cases have an identified bloodstream infection. Before the 1980s, Gram-negative bacilli, especially *Pseudomonas aeruginosa*, were the predominant pathogens and were associated with serious complications. Subsequently, fluoroquinolones such as ciprofloxacin and levofloxacin were introduced as antibacterial prophylaxis during the high-risk period of neutropenia in patients with hematologic malignancies. With this practice, and with the increasing use of indwelling plastic venous catheter devices, Gram-positive bacteria, most commonly coagulase-negative staphylococcus, *Staphylococcus aureus*, and streptococci, have emerged as the most common causes, accounting for up to 75% of microbiologically confirmed bloodstream infections during FN episodes. The vast majority of these bacterial pathogens are part of endogenous flora. In this regard, the destruction in gastrointestinal mucosal protective barrier (e.g. mucositis) serves as a portal of entry of endogenous oral and gastrointestinal flora to gain access to the bloodstream. Viridans group streptococci (VGS) are among the predominant bacteria in the oral and gastrointestinal tract that can translocate to cause bloodstream infection during periods of severe mucositis. Viridans group streptococci accounts for up to 18% of all bloodstream infections in patients with FN [2]. The clinical presentation of severe mucositis, septic shock, and acute respiratory distress syndrome (ARDS) early in the clinical course of FN, as in the clinical case presented here, are characteristic of VGS bloodstream infection in cancer patients with FN [3–7]. Another diagnostic consideration in this patient would be a central line-associated (Port-A-Cath) bloodstream

infection due to *S aureus*, coagulase-negative staphylococcus, enterococcus, other streptococci, and Gram-negative bacterial pathogens such as *P aeruginosa, Klebsiella pneumonia,* and *Escherichia coli*. However, there were no physical findings suggestive of tunnel or line-associated infection. Nonetheless, we emphasize that close evaluation of all indwelling vascular lines should be performed during assessment of the patients with FN, including a detailed physical examination and culture of the blood and the vascular line. Other potential causes of sepsis, such as community-acquired or nosocomial pneumonia (especially in this patient with pulmonary findings), urinary tract infection, and other opportunistic infections due to viruses and fungi should also be considered and evaluated. Indeed, herpes infections and oral candidiasis could complicate the mucosal inflammation in patients with severe mucositis (hence, the use of acyclovir and antifungal prophylaxis during this period). Fungal infections are generally rarely implicated as the cause of FN during the first seven days of fever. However, these pathogens, especially *Candida* spp and *Aspergillus* spp, should be considered in high-risk patients (i.e. those with prolonged and profound neutropenia) especially when the fever persists beyond one week.

The Infectious Disease Society of America (IDSA) recommends empiric therapy of FN with cefepime, piperacillin-tazobactam, or the anti-pseudomonal carbapenems (meropenem and imipenem). These agents have broad-spectrum coverage to include many Gram-positive bacteria and Gram-negative organisms including *P aeruginosa*. In general, additional antibiotics with enhanced Gram-positive activity such as vancomycin and daptomycin are not recommended as initial therapy because the antibacterial coverage of cefepime, piperacillin-tazobactam, or the anti-pseudomonal carbapenems are broad enough to be active against the major pathogens causing FN. Some indications for the addition of antibiotics with enhanced activity against Gram-positive organisms (such as vancomycin and daptomycin) to the empirical regimen of FN are listed in Table 1.11.1. In addition to cefepime, our patient received vancomycin due to sepsis and the consideration of pneumonia. Because of unremarkable physical findings, the vascular catheter was not suspected to be the source of his FN.

ADDITIONAL CASE DATA

At 17 hours, the blood cultures obtained by venipuncture and through the Port-A-Cath were positive for *Streptococcus mitis* group (see Figure 1.11.3 for Gram stain and culture). The organism was susceptible to cefepime (minimum inhibitory concentration [MIC], <0.5), ceftriaxone (MIC, <0.5),

TABLE 1.11.1. CLINICAL INDICATIONS FOR THE ADDITION OF VANCOMYCIN OR OTHER ANTIBIOTIC WITH ENHANCED GRAM-POSITIVE BACTERIAL ACTIVITY TO THE EMPIRIC THERAPY OF NEUTROPENIC FEVER (MODIFIED FROM [1])

Indication for Gram-Positive Antibiotics to the Empiric Regimen for Neutropenic Fever	Clinical Reasoning
Severe sepsis/septic shock	To cover for organisms such as *S aureus*, which has been implicated to cause more serious infections and complications such as septic shock. To cover for possible penicillin-resistant viridans group streptococcal sepsis in the setting of severe sepsis.
Clinical documentation or suspicion of pneumonia, and skin/soft tissue infection	To cover for possible MRSA as the cause of pneumonia and skin/soft tissue infections. Recommendations are based on microbiology of such infection, again including MRSA.
Clinical documentation or suspicion of catheter-related infection	Catheter-related infections are often due to *S aureus* and coagulase-negative staphylcococcus and enterococcus, hence the empiric use of antibiotics with added Gram-positive activity.
Presence of severe mucositis, especially with previous use of fluoroquinolone/ceftazidime	Additional Gram-positive coverage for the potential for penicillin-resistant viridans group streptococcal sepsis.
Known colonization with drug-resistant organisms—methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococcus, or penicillin-resistant *Streptococcus pneumoniae*	Known colonization with such organisms increases the chance of invasive infection with the same drug-resistant organisms; therefore, empiric coverage against these organisms is recommended during period of neutropenic fever.

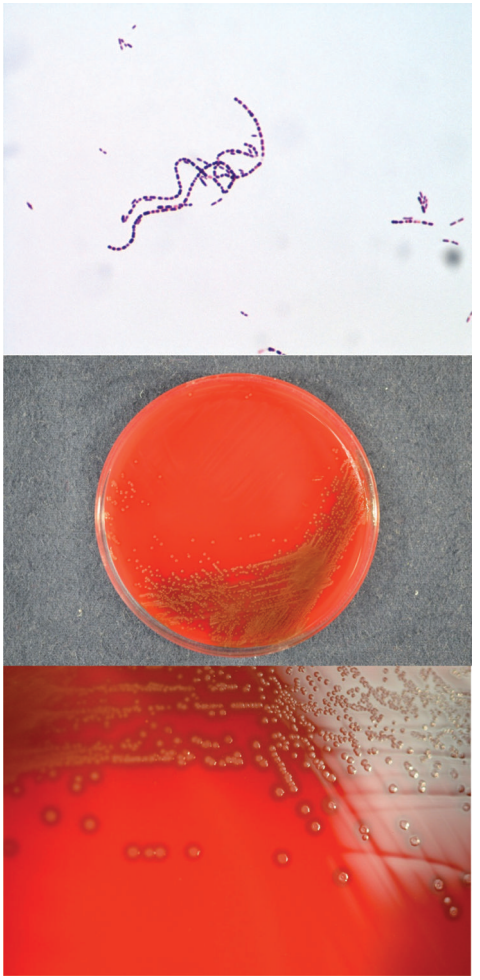


FIGURE 1.11.3: Top, Gram stain showing Gram-positive cocci in chains; Bottom, Blood agar plate showing growth of *Streptococcus mitis*.

meropenem (MIC, <0.25), and vancomycin (MIC, <1), intermediate to penicillin (MIC, 1) and resistant to levofloxacin (MIC, >4). Because of diffuse bilateral pulmonary infiltrates, the patient underwent bronchoscopy with bronchoalveolar lavage, but the microbiologic work up was unremarkable for any bacterial, fungal, or viral pathogens. Given the negative bronchoscopy work-up, he was suspected to have VGS-associated adult respiratory distress syndrome and was provided mechanical ventilation using lung-protective ARDS strategy.

Final Diagnosis: Neutropenic fever due to *S mitis* group bloodstream infection complicated by septic shock and ARDS

TREATMENT AND OUTCOME

The patient's hemodynamics and pulmonary function gradually stabilized during the aggressive management at the ICU. He was extubated after four days. Vancomycin was eventually discontinued when no other pathogens were isolated on multiple evaluations, and the patient completed two weeks of intravenous cefepime therapy. Blood cultures were negative after two days of effective antibiotic therapy. He subsequently underwent allogeneic hematopoietic stem cell transplant to treat his underlying illness.

DISCUSSION

Viridans Group Streptococcal Bloodstream Infections During Neutropenia

Risk Factors

Risk factors for VGS bloodstream infections in patients with NF are as follows: (1) prophylaxis with fluoroquinolones (such as ciprofloxacin and levofloxacin, as in this case) and trimethoprim-sulfamethoxazole, and empiric therapy with ceftazidime (drugs with poor in vitro activity against VGS); (2) certain chemotherapeutic agents (including high-dose cytosine arabinoside); and (3) severe oral and gastrointestinal mucositis (see Box 1.11.1). Our patient was receiving levofloxacin prophylaxis and developed moderate to severe mucositis during the prolonged period of severe neutropenia. As discussed above, the most common source of

BOX 1.11.1 RISK FACTORS FOR VGS BLOODSTREAM INFECTIONS IN CANCER PATIENTS WITH FEBRILE NEUTROPENIA

Risk factors implicated in VGS infections causing fever with neutropenia

1. Use of trimethoprim/sulfamethoxazole prophylaxis during neutropenia
2. Use of fluoroquinolone prophylaxis during neutropenia
3. Use of ceftazidime as empiric FN management
4. Presence of oral and gastrointestinal mucositis, especially if severe
5. Use of certain cytotoxic chemotherapy, specifically Cytarabine (Ara-C)
6. Age (more severe VGS infection in pediatric FN cases) [12]

VGS to cause FN in patients with cancer is the oral cavity and the alimentary tract, especially in context of severe mucosal damage from use of cytotoxic chemotherapy. His VGS was also found to be penicillin resistant. Among the risk factors for bloodstream infection with a penicillin-resistant VGS strain that have been reported include the following: (1) underlying acute leukemia, (2) mucocutaneous lesions, and (3) breakthrough bacteremia during prophylaxis with β-lactams. Previous exposure to β-lactam therapy (such as ceftazidime) is also a risk factor for cephalosporin-resistant VGS cases [8]. It is interesting to note that one study reported that exposure to trimethoprim-sulfamethoxazole is also associated with reduced susceptibility to penicillins [9], whereas those receiving levofloxacin prophylaxis, like the case presented here, are expectedly at risk for the selection of fluoroquinolone-resistant strains [10, 11].

Clinical Presentation

The majority of cases of VGS bloodstream infection in cancer patients with chemotherapy-induced FN presents with fever alone. However, VGS bloodstream infection may be complicated by septic shock syndrome and ARDS in 7%–39% of cases, with mortality rates that could exceed 20% [4, 5, 7, 8, 13–17]. *Streptococcus mitis* is the most common VGS group responsible for NF, and in some studies, this group was associated with worse clinical outcomes and complications (such as ARDS and VGS shock syndrome) compared with less commonly encountered non-*S mitis* strains (*Streptococcus oralis, Streptococcus infantis/australis, Streptococcus sanguinis, Streptococcus anginosus, Streptococcus salivarus/vestubularis*) [4, 18, 19]. In a review of neutropenic cancer patients with primary bacteremia, 58 of 72 cases (81%) of the cases of VGS bacteremias were due to *S mitis* [18]. It is interesting to point out that children have been reported to have a higher occurrence of a more severe disease [12], although a more recent study did not confirm this observation [7].

Diagnosis

The diagnosis of VGS bloodstream infection in patients with FN is established using blood cultures. It is especially important to emphasize that blood samples be obtained for cultures as soon as possible after clinical presentation, preferably within two hours, and before the initiation of broad-spectrum antibiotic therapy. As illustrated in this case, VGS may be complicated by ARDS. Bronchosocpy may be performed to rule out other pathogens. In VGS-associated ARDS, no additional organisms are isolated on the bronchoalveolar lavage fluid cultures.

Management

Per the IDSA guidelines, monotherapy with cefepime, carbapenems (meropenem or imipenem), and piperacillin-tazobactam continue to be recommended as the first-line regimen for the empiric therapy for FN. All of these agents are generally effective against the vast majority of VGS isolates and are therefore also used for the targeted treatment of VGS bloodstream infection [1].

The vast majority of cases do not require addition of vancomycin [1]. However, the emergence of penicillin and β-lactam resistance among VGS isolates has been a driver behind the addition of vancomycin for empiric treatment of FN and VGS bloodstream infection in some centers. The rates of β-lactam and penicillin resistance vary from a low of 5% of isolates [4, 19] to as high as 17% [20]. A recent study [20] identified current use of β-lactam prophylaxis, receipt of β-lactam antimicrobial within past 30 days, and nosocomial-acquired VGS bloodstream infections as independent predictors of penicillin resistance. Cases of penicillin-resistant VGS infections have been implicated to cause more severe disease in earlier studies [14], although this has not been observed in more recent studies [4, 7]. However, this observation led to an increase in use of drugs with enhanced Gram-positive activity such as vancomycin and daptomycin early in the treatment course for many patients with FN. In one study, the addition of vancomycin early in the treatment course has led to improved outcomes in VGS infections [21]. However, a Cochrane Systematic Review failed to show improved outcomes with the addition of Gram-positive antibiotics to the empiric regimen of FN in patients with cancer [22]. Likewise, a meta-analysis of all FN cases failed to show any improvement in all-cause mortality with the addition of empiric Gram-positive antibiotics [23]. Therefore, vancomycin is not recommended as a part of the initial empiric regimen for FN. Furthermore, the vast majority of VGS isolates, including those with penicillin resistance, remain susceptible to the cefepime, piperacillin-tazobactam, and meropenem (the first-line therapy of FN). Indeed, as illustrated in the case described here, although the *S mitis* was not susceptible to penicillin, it remained susceptible to the first-line drugs (cefepime, meropenem, and piperacillin-tazobactam) recommended for empiric treatment of FN.

Prevention

The prevention of invasive VGS infections causing FN remains controversial. Fluoroquinolones have poor to modest activity against VGS, and thus explaining the association between VGS bacteremia and fluoroquinolone prophylaxis. Accordingly, some centers have added penicillin (or other β-lactams) to fluoroquinolone prophylaxis to reduce VGS infections during periods of neutropenia [24]. However, this has not been associated with reduction in VGS and ARDS, and, more importantly, there is significant concern for the emergence of resistance to β-lactams with this strategy [14]. Indeed, there have been a number of reports of increasing rates of antimicrobial resistance for *S mitis* and other VGS strains in neutropenic patients receiving penicillin prophylaxis [4, 15, 16, 19, 25]. Therefore, current guidelines do not recommend this strategy. Instead, prompt empiric therapy is recommended for patients who present to the clinic with FN.

KEY POINTS

- Microbiologically defined infections account for only up to 30% of cases of FN, and VGS accounts for a minority of bacteremia causing FN.
- Infections should be suspected and treated early in the course of FN to reduce the risk of complications such as sepsis and death.
- Bloodstream infection due to VGS account for only a minority of cases of infection-related FN, but it can lead to severe sepsis, septic shock, and ARDS.
- Risk factors for VGS bloodstream infections include gastrointestinal mucositis, cytotoxic chemotherapy such as cytarabine, empiric ceftazidime treatment, and prophylaxis with fluoroquinolone and trimethoprim-sulfamethoxazole.
- The majority of VGS remain susceptible to the first-line empiric therapy for neutropenic fever such as cefepime, meropenem, and piperacillin-tazobactam.
- Vancomycin and other Gram-positive active drugs are not recommended for empiric therapy of FN, but they should be used only as empiric therapy of FN in certain situations, such as suspicion for resistant bacteria, pneumonia, sepsis, and skin and soft tissue infections.

REFERENCES

1. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011;52:e56.
2. Kwon JC, Kim SH, Choi JK, et al. Epidemiology and clinical features of bloodstream infections in hematology wards: one year experience at the Catholic Blood and Marrow Transplantation Center. Infect Chemother. 2013;45:51.
3. Shenep JL. Viridans-group streptococcal infections in immunocompromised hosts. Int J Antimicrob Ag. 2000;14:129.
4. Marron A, Carratalà J, González-Barca E, et al. Serious complications of bacteremia caused by Viridans streptococci in neutropenic patients with cancer. Clin Infect Dis. 2000;31:1126.
5. Gassas A, Grant R, Richardson S, et al. Predictors of viridans streptococcal shock syndrome in bacteremic children with cancer and stem-cell transplant recipients. J Clin Oncol. 2004;22:1222.
6. Paganini H, Staffolani V, Zubizarreta P, et al. Viridans streptococci bacteraemia in children with fever and neutropenia: a case-control study of predisposing factors. Eur J Cancer 2003;39:1284.
7. Han SB, Bae EY, Lee JW, et al. Clinical characteristics and antimicrobial susceptibilities of viridans streptococcal bacteremia during febrile neutropenia in patients with hematologic malignancies: a comparison between adults and children. BMC Infect Dis. 2013;13:273.
8. Marron A, Carratalà J, Alcaide F, et al. High rates of resistance to cephalosporins among viridans-group streptococci causing bacteraemia in neutropenic cancer patients. J Antimicrob Chemother. 2001;47:87.
9. Westling K, Julander I, Ljungman P, et al. Reduced susceptibility to penicillin of viridans group streptococci in the oral cavity of patients with haematological disease. Clin Microbiol Infect. 2004;10:899.
10. Razonable RR, Litzow MR, Khaliq Y, et al. Bacteremia due to viridans group Streptococci with diminished susceptibility to Levofloxacin among neutropenic patients receiving levofloxacin prophylaxis. Clin Infect Dis. 2002;34:1469.
11. Prabhu RM, Piper KE, Baddour LM, et al. Antimicrobial susceptibility patterns among viridans group streptococcal isolates from infective endocarditis patients from 1971 to 1986 and 1994 to 2002. Antimicrob Agents Chemother. 2004;48:4463.
12. Martino R, Subirá M, Manteiga R, et al. Viridans streptococcal bacteremia and viridans streptococcal shock syndrome in neutropenic patients: comparison between children and adults receiving chemotherapy or undergoing bone marrow transplantation. Clin Infect Dis. 1995;20:476.
13. Han SB, Bae EY, Lee JW, et al. Clinical characteristics and antibiotic susceptibility of viridans

streptococcal bacteremia in children with febrile neutropenia. Infection 2013;41:917.
14. Spanik S, Trupl J, Kunova A, et al. Viridans streptococcal bacteraemia due to penicillin-resistant and penicillin-sensitive streptococci: analysis of risk factors and outcome in 60 patients from a single cancer centre before and after penicillin is used for prophylaxis. Scand J Infect Dis. 1997;29:245.
15. Husain E, Whitehead S, Castell A, et al. Viridans streptococci bacteremia in children with malignancy: relevance of species identification and penicillin susceptibility. Pediatr Infect Dis J. 2005;24:563.
16. Bochud PY, Eggiman P, Calandra T, et al. Bacteremia due to viridans streptococcus in neutropenic patients with cancer: clinical spectrum and risk factors. Clin Infect Dis. 1994;18:25.
17. Lewis V, Yanofsky R, Mitchell D, et al. Predictors and outcomes of viridans group streptococcal infections in pediatric acute myeloid leukemia: from the Canadian infections in AML research group. Pediat Infect Dis J. 2014;33:126.
18. Shelburne SA, Sahasrabhojane P, Saldana M, et al. *Streptococcus mitis* strains causing severe clinical disease in cancer patients. Emerg Infect Dis. 2014;20:762.
19. Lyytikäinen O, Rautio M, Carlson P, et al. Nosocomial bloodstream infections due to viridans streptococci in haematological and non-haematological patients: species distribution and antimicrobial resistance. J Antimicrob Chemother. 2004;53:631.
20. Shelburne SA, Sahasrabhojane P, Saldana M, et al. Development and validation of a clinical model to predict the presence of beta-lactam resistance in viridans group streptococci causing bacteremia in neutropenic cancer patients. Clin Infect Dis. 2014;59:223.
21. Elting LS, Lu C, Escalante CP, et al. Outcomes of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. Clin Infect Dis. 1997;25:247.
22. Paul M, Dickstein Y, Borok S, et al. Empirical antibiotics targeting Gram-positive bacteria for the treatment of febrile neutropenic patients with cancer. Cochrane Database Syst Rev 2014;1:CD003914.
23. Paul M, Borok S, Fraser A, et al. Empirical antibiotics against Gram-positive infections for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2005;55:436.
24. Timmers GJ, Simoons-Smit AM, Leidekker ME, et al. Levofloxacin vs. ciprofloxacin plus phenethicillin for the prevention of bacterial infections in patients with haematological malignancies. Clin Microbiol Infect. 2007;13:497.
25. Han XY, Kamana M, Rolston KV. Viridans streptococci isolated by culture from blood of cancer patients: clinical and microbiologic analysis of 50 cases. J Clin Microbiol. 2006;44:160.

1.12

Upper Respiratory Symptoms During Febrile Neutropenia

MICHAEL G. ISON, MD, MS

CASE PRESENTATION

The patient is a 72-year-old white male with follicular lymphoma who presents 2 weeks after his 4th cycle of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in late January with new fevers and fatigue since the night prior to evaluation; he also notes a slightly runny nose. Lymphoma, predominately restricted to the gastrointestinal tract and spleen, was diagnosed in October, and he has undergone therapy with R-CHOP in 21-day cycles starting in early November. He received a seasonal influenza vaccine in late September, before being diagnosed with lymphoma, although he was having significant B symptoms attributed to the lymphoma at the time. He has generally been healthy before his diagnosis of lymphoma. His treatment course was uncomplicated for the first 3 cycles without significant fever or infection during neutropenia. The patient reported no recent sick contacts that he is aware of and his wife also received her influenza vaccine.

On presentation he appeared mildly ill. His temperature was 38.2°C, pulse 98/minute, his blood pressure was 134/64 mm Mercury, and his respiratory rate was 14/minute with pulse oximetry of 96% on room air. On examination, his oral mucosa was slightly dry and he had no conjunctival injection; his heart was regular rate without murmurs, gallops, or rubs; his lungs were clear to auscultation; his abdomen was nontender with normal bowel sounds; he had no obvious skin rashes or lesions. Laboratory results revealed a white blood cell count (WBC) of 1200 cells/mL (absolute neutrophil count was 800 cells/mL), hemoglobin of 8.9 g/dL, and a platelet count of 112 000/dL. His electrolyte panel was within normal limits with a creatinine of 0.9 mg/dL. Chest radiograph is demonstrated in Figure 1.12.1.

QUESTIONS

- What diagnostic testing would you perform on this patient?
- What therapy would you initiate in this patient?

DIFFERENTIAL DIAGNOSIS

The patient is presenting with fever and neutropenia during the winter respiratory viral season. The differential diagnosis of causes of fever in this patient are relatively broad, although the most common causes include bacteremia, candidemia, intra-abdominal infection, *Clostridium difficile* colitis, pneumonia, catheter-related infection, and respiratory viral infections [1]. Current guidelines recommend careful physical examinations, collection of 2 sets of blood cultures, urine analysis and culture, and respiratory viral testing; in addition, tests for *C difficile* toxin assay should be sent in patients with diarrhea, cerebrospinal fluid tests should be sent in patients with concern for meningitis or encephalitis, skin biopsies should be obtained for new skin lesions, and respiratory specimens (sputum or bronchoalveolar lavage [BAL]) should be obtained for patients with cough or abnormalities on chest imaging [1].

INITIAL MANAGEMENT

This patient is likely at low risk for complications because his neutropenia is anticipated to last ≤7 days and his MASCC score is >21, he is clinically stable, and he has no significant medical clinical comorbidities. As such, the patient could be treated as an outpatient with oral ciprofloxacin and amoxicillin-clavulanate, or even with levofloxacin, with observation for four to twenty-four hours in the clinic before going home; alternatively, he could be admitted for intravenous (IV) antibiotics [1]. Because the patient has respiratory viral symptoms, initiating oseltamivir to his

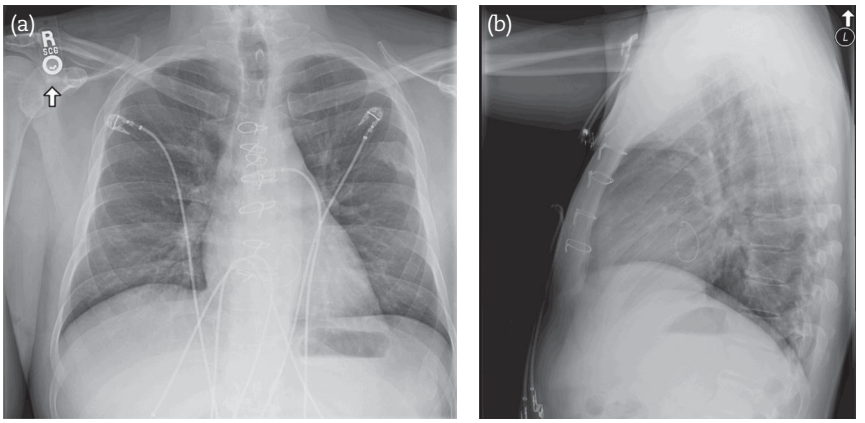


FIGURE 1.12.1: Chest radiograph of patient on presenation.

empiric regimen should be considered until testing for influenza can be completed when influenza is circulating in the community.

ADDITIONAL DATA

The patient was treated with a single dose of ciprofloxacin 750 mg, amoxicillin-clavulanate 875 mg, and oseltamivir 150 mg with food. He tolerated the therapy and remained clinically stable for six hours while receiving IV fluids in clinic; a rapid influenza antigen test was negative for influenza. He was discharged on each of the three antimicrobials twice daily and asked to return to clinic the following day. His WBC was increasing the following day (absolute neutrophil count [ANC] = 900/mm^3), his blood and urine cultures were negative, and his respiratory viral panel (RVP) polymerase chain reaction (PCR) performed on a nasal swab was positive for influenza B. The patient stated that he felt substantially better with no further fevers.

Final Diagnosis: Influenza B infection

TREATMENT AND OUTCOME

The patient was continued on oseltamivir 150 mg BID while ciprofloxacin and amoxicillin-clavulanate were discontinued. The patient was prescribed a ten-day course of oseltamivir and was asked to return at day eight for repeat testing. His RVP was still positive for influenza B and an additional five days of oseltamivir were prescribed. On day fourteen of therapy, he returned and RVP was negative for influenza. The patient completed his next cycle of R-CHOP chemotherapy one week later and recovered from the associated neutropenic period uneventfully, without recurrent fever or influenza.

Discussion

A wide range of viruses cause infections of respiratory tract, including influenza, respiratory syncytial virus (RSV), human metapneumovirus (hMPV), parainfluenza (PIV), rhinovirus (RV), coronavirus, and adenovirus. Influenza, RSV, and hMPV typically cause infections in the winter months (November–April in the Northern Hemisphere), RV and coronaviruses typically cause infections in the fall and spring, and adenovirus and PIV cause infections throughout the entire year. Infections with respiratory viruses often have milder symptoms and more prolonged shedding in patients undergoing chemotherapy than otherwise healthy adults and children. Likewise, progression from the upper airway to the lower airway is more common in patients with hematologic malignancy, lymphopenia, and patients actively receiving chemotherapy. The clinical presentation, prevention, and management of influenza will be discussed in detail in this case.

Clinical Presentation

Clinically, it is challenging to make a diagnosis of influenza, particularly in patients with hematologic malignancy, because typical signs and symptoms are often mild to absent. Most clinical signs and symptoms of influenza infection are the result of cytokine release in response to local replication of influenza in the respiratory mucosa [2]. Defects in number and function of lymphocytes (absolute lymphocyte count ≤100 cells/mL is associated with the greatest risk for progressive influenza pneumonia) are common among patients undergoing chemotherapy. In addition, many patients undergoing chemotherapy receive

steroids and other anti-inflammatory agents as part of the chemotherapy regimen or to mitigate against adverse effects of chemotherapy. Together, the lymphocyte defects and immunosuppressive agents are responsible for the reduced severity and frequency of typical influenza symptoms, including fever, myalgias, arthralgias, cough, and sore throat [3]. As such, clinicians should have a very high clinical suspicion for respiratory viruses at times when viruses are circulating and a patient presents with any respiratory symptoms.

Diagnosis

Because influenza circulates at a time when several other viruses may cause a clinical picture that is indistinguishable, diagnostic tests are required to confirm that a patient is infected with influenza virus [4]. Available diagnostic strategies include serology or testing of material from the respiratory tract (nasal swab, nasal wash, or BAL) by rapid antigen detection, direct fluorescent antibodies, culture, and molecular diagnostics [5]. Rapid antigen testing has the clear advantage of speed, but it lacks sensitivity [5, 6]. Direct fluorescent antibody testing is a relatively rapid and effective diagnostic that may screen for a large number of viruses, although commercially available antibodies are not available for all clinically significant viruses [5]. Traditionally, cell culture, using either long tubes or spin-enhanced shell-vial techniques, had been previously considered the gold standard. Given the need for two to five days of incubation for cultures, these techniques are now rarely used; with improved sensitivity, ease, and wide availability, PCR methods are preferred [5, 7, 8]. Most contemporary molecular assays (i.e. PCR) have excellent sensitivity and rapid turn-around times (usually measured in hours), and they test for a wide range of potential pathogens in a single assay. Nonetheless, even molecular assays may miss infection in patients. Up to 20% of patients with influenza pneumonia will have negative results from PCR of nasal swabs; as a result, lower airway specimens, obtained by non-bronchoscopic or bronchoscopic alveolar lavage, may be required to confirm a diagnosis of lower airway infection [9]. Likewise, attention must also be paid to the collection of adequate specimens; inadequate collection of nasal swabs may result in false-negative results.

Prevention

Influenza can be prevented through the use of vaccination. Current guidelines suggest that all patients with underlying medical conditions, such as hematologic malignancies, and their close contacts receive the inactivated, injectable influenza vaccine annually [10, 11]. Because of the risk of replication and disease, use of the live, attenuated inhaled vaccine is contraindicated in immunocompromised patients and discouraged for close contacts [11]. Although antibody responses to influenza vaccine are reduced in patients currently receiving chemotherapy, influenza vaccine has consistently been associated with clinical benefit. Available data suggest that influenza vaccination is associated with reduction in influenza-like illness, confirmed influenza rates, pneumonia, hospitalization, and mortality in adult patients with cancer [12, 13]. The studies have consistently failed to demonstrate any life-threatening or persistent adverse effects from vaccination [12].

The optimal timing of influenza vaccination has not been definitively established. Studies have suggested that response is best after completing therapy, but this may leave patients at risk if therapy is initiated at the start of influenza season. Various recommendations include vaccinating patients two weeks before initiation of therapy and vaccinating patients when the ANC is ≥1000 cells/mL [12, 14]. Greater responses occur if vaccine is given between cycles [14, 15]. Nonetheless, because vaccination is safe and appears to be more effective in preventing influenza and its complications, it is critical to attempt to vaccinate patients if chemotherapy is given during the influenza season and the patient is not previously vaccinated [14, 15]. There may be benefit to vaccinating patients again after chemotherapy is completed if the influenza season is still ongoing. Because of this slightly decreased response to vaccine, all close contacts of transplant patients, including associated healthcare workers, should be vaccinated; inactivated vaccine is preferred in patients at close contact with immunosuppressed patients but live, attenuated intranasal vaccines can be used in close contacts of oncology patients, although they should be avoided in transplant recipients [11].

Influenza antiviral therapy has been demonstrated to be safe, well tolerated, and effective in preventing influenza in high-risk patients [16]. The adamantanes, which are M2 ion channel inhibitors, amantadine and rimantadine, should not be used for the prevention of influenza because all circulating strains are resistant to this class of antiviral. Antiviral prophylaxis after exposure or seasonal antiviral prophylaxis has lost favor in most instances because of the concern for emergence of antiviral resistance [17]. If antivirals are to be considered for postexposure prophylaxis

of at-risk oncology patients, most experts recommend empiric treatment (full treatment doses) of the patient instead of lower-dose prophylaxis with oseltamivir.

Treatment

Available influenza antivirals include the M2 ion channel inhibitors (amantadine and rimantadine) and the neuraminidase inhibitors (oseltamivir and zanamivir). Due to widespread resistance in all circulating strains, the M2 inhibitors should not be used [16].

Antiviral therapy has been proven to reduce the duration and severity of influenza in otherwise healthy ambulatory adults when started within forty-eight hours of symptom onset (see Table 1.12.1) [16, 18]. Likewise, antiviral therapy is associated with improved recovery, reduced progression to the lower airway, and lower mortality rates in patients requiring hospitalization when therapy is started within five days of symptom onset; there may be benefit for treating patients beyond five days, but the number of patients with significantly delayed treatment is too small to draw definitive conclusions [19, 20]. Randomized controlled studies have not been conducted to prospectively define the optimal treatment in patients with cancer. Nonetheless, treatment should be started as soon as possible after symptom onset to maximize outcomes. Antiviral therapy, therefore, should be started as soon as influenza infection is considered and should not wait for confirmation by diagnostic testing. In patients who are heavily immunosuppressed, neutropenic, or hospitalized, consideration should be given to treating all patients with documented influenza [8, 21]. Oseltamivir is less active against influenza B viruses, and higher doses may be associated with improved outcomes in these patients [22]. Higher doses of oseltamivir may be associated with lower rates of resistance emergence during treatment, which occurs more commonly in immunosuppressed patients [21–23]. Likewise, prolonged shedding has been demonstrated in patients that are immunosuppressed, who are receiving corticosteroids; as a result, longer durations of therapy (greater than the five days of therapy used in otherwise healthy ambulatory adults and children) are generally recommended for patients who are treated for influenza and are currently receiving chemotherapy [21]. Several experts recommend continuing therapy until viral replication has been documented to be resolved, although the optimal duration of therapy has not been prospectively defined for immunosuppressed patients. Clinical progression despite antiviral therapy should warrant consideration for resistance or a secondary superinfection. Resistance testing is not widely available, and consultation with an expert in the diagnosis and management of influenza is recommended.

KEY POINTS

- Respiratory viral infections are common causes of infection in patients undergoing chemotherapy.
- Oncology patients receiving chemotherapy may have few or often mild symptoms when they present with influenza.
- PCR-based testing has the highest sensitivity for detecting influenza and other respiratory viruses, but false-negative results can occur with improper sampling or in sampling only the upper airway in patients with pneumonia.
- Influenza vaccine is safe and effective in oncology patients undergoing chemotherapy; vaccination should be given

TABLE 1.12.1. AGENTS USED TO PREVENT AND TREAT INFLUENZA

	Usual Adult Dosage			
Drug	**Prophylaxis**	**Treatment**	**Dose Adjustment State**	**Suggested Dosage**
Zanamivir[†]	2 puffs	2 puffs	No dose adjustment needed	
Oseltamivir[‡]	75 mg q24h	75 mg q12h	CrCl <30 mL/min[§]	Treatment: 75 mg q24h Prophylaxis: 75 mg every other day
			≤15 kg	30 mg q12h
			15–23 kg	45 mg q12h
			23–40 kg	60 mg q12h
			>40 kg	75 mg q12h

[†] Zanamivir is indicated for prophylaxis in children ≥5 years old and for treatment in children ≥7 years old.
[‡] Oseltamivir is indicated for treatment in children ≥2 weeks of age and older and in children ≥1 year of age for prophylaxis.

to all oncology patients, optimally between cycles or after chemotherapy is completed.
- Influenza vaccination should be given to all close contacts of patients undergoing chemotherapy.
- Antiviral therapy should be initiated as soon as influenza is considered and should not wait for diagnostic confirmation.
- Higher doses of oseltamivir and duration of therapy longer than five days are recommended by many experts for the treatment of influenza in patients undergoing chemotherapy.

REFERENCES

1. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2011;52:e56.
2. Kaiser L, Fritz RS, Straus SE, et al. Symptom pathogenesis during acute influenza: interleukin-6 and other cytokine responses. J Med Virol. 2001;64:262.
3. Peck AJ, Englund JA, Kuypers J, et al. Respiratory virus infection among hematopoietic cell transplant recipients: evidence for asymptomatic parainfluenza virus infection. Blood 2007;110:1681.
4. Monto AS, Gravenstein S, Elliott M, et al. Clinical signs and symptoms predicting influenza infection. Arch Intern Med. 2000;160:3243–7.
5. Ison MG, Rosenberg ES. Respiratory viruses. In: Hayden RT, Carrol KC, Tang YW, Wolk DM, eds. *Diagnostic Microbiology of the Immunocompromised Host*. Washington, D.C.: ASM Press; 2008.
6. Uyeki TM, Prasad R, Vukotich C, et al. Low sensitivity of rapid diagnostic test for influenza. Clin Infect Dis. 2009;48:e89.
7. Kuypers J, Campbell AP, Cent A, et al. Comparison of conventional and molecular detection of respiratory viruses in hematopoietic cell transplant recipients. Transpl Infect Dis. 2009;11:298.
8. Engelhard D, Mohty B, de la Camara R, et al. European guidelines for prevention and management of influenza in hematopoietic stem cell transplantation and leukemia patients: summary of ECIL-4 (2011), on behalf of ECIL, a joint venture of EBMT, EORTC, ICHS, and ELN. Transpl Infect Dis. 2013;15:219.
9. Feikin DR, Njenga MK, Bigogo G, et al. Additional diagnostic yield of adding serology to PCR in diagnosing viral acute respiratory infections in Kenyan patients 5 years of age and older. Clin Vaccine Immunol. 2013;20:113.
10. Baluch A, Pasikhova Y. Influenza vaccination in oncology patients. Curr Infect Dis Rep. 2013;15:486.
11. Centers for Disease Control and Prevention (CDC). Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices—United States, 2013–2014. MMWR Recomm Rep. 2013;62:1.
12. Eliakim-Raz N, Vinograd I, Zalmanovici Trestioreanu A, et al. Influenza vaccines in immunosuppressed adults with cancer. Cochrane Database Syst Rev 2013;10:CD008983.
13. Beck CR, McKenzie BC, Hashim AB, et al. Influenza vaccination for immunocompromised patients: systematic review and meta-analysis by etiology. J Infect Dis. 2012;206:1250.
14. Pollyea DA, Brown JM, Horning SJ. Utility of influenza vaccination for oncology patients. J Clin Oncol. 2010;28:2481.
15. Ortbals DW, Liebhaber H, Presant CA, et al. Influenza immunization of adult patients with malignant diseases. Ann Intern Med. 1977;87:552.
16. Fiore AE, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60:1.
17. Centers for Disease Control and Prevention (CDC). Oseltamivir-resistant 2009 pandemic influenza A (H1N1) virus infection in two summer campers receiving prophylaxis—North Carolina, 2009. MMWR Recomm Rep. 2009;58:969.
18. Moscona A. Neuraminidase inhibitors for influenza. New Eng J Med. 2005;353:1363.
19. Lee N, Ison MG. Editorial commentary. "Late" treatment with neuraminidase inhibitors for severely ill patients with influenza: better late than never? Clin Infect Dis. 2012;55:1205.
20. Louie JK, Yang S, Acosta M, et al. Treatment with neuraminidase inhibitors for critically ill patients with influenza A (H1N1)pdm09. Clin Infect Dis. 2012;55:1198.
21. Casper C, Englund J, Boeckh M. How I treat influenza in patients with hematologic malignancies. Blood 2010;115:1331.
22. Lee N, Hui DS, Zuo Z, et al. A prospective intervention study on higher-dose oseltamivir treatment in adults hospitalized with influenza a and B infections. Clin Infect Dis. 2013;57:1511.
23. South East Asia Infectious Disease Clinical Research N. Effect of double dose oseltamivir on clinical and virological outcomes in children and adults admitted to hospital with severe influenza: double blind randomised controlled trial. BMJ. 2013;346:f3039.

1.13

Multiple Skin Lesions in a Neutropenic Patient With Leukemia: Connecting the Dots

MATTHEW MCCARTHY, MD, AUDREY N. SCHUETZ, MD, MPH, AND THOMAS J. WALSH, MD

CASE PRESENTATION

A 55-year-old man with chronic lymphocytic leukemia complicated by Richter's transformation presented to his outpatient physician with diffuse myalgias and cutaneous lesions of unclear etiology. The patient was day + 15 s/p chemotherapy with hyperfractionated cyclophosphamide/vincristine/doxorubicin/dexamethasone (cycle 1B) and was pancytopenic from disease and chemotherapy at the time of presentation.

On the day prior to presentation, the patient noted a red, tender area on the right lower leg as well as a painful right fourth toe. He reported possible trauma to the toe while walking the previous day. His medical history is notable for coronary artery disease, hyperlipidemia, sleep apnea, and asthma. Pertinent medications at the time of presentation included oral fluconazole 400 mg daily, valacyclovir 500 mg q twice daily, and enoxaparin 120 mg (subcutaneous) daily.

The patient works in finance and lives in New Jersey with his wife of thirty years. He denied recent travel but reported daily walks in the country at night with his wife. He has never smoked and reported consuming one or two glasses of wine daily. He was in good health until the previous year when his cardiologist noted lymphocytosis and a small growth on his neck. The patient underwent lymph node biopsy and subsequent bone marrow biopsy, which revealed an atypical chronic lymphocytic leukemia with a complex karyotype including 17p deletion, Zap 70 positive.

Physical exam was notable for an ill-defined 2 cm erythematous, mildly edematous tender noncircumscribed plaque with central 1-cm atrophic shiny macule along the mid-anterior aspect of the right leg, and an erythematous patch on the right fourth toe with two pinpoint erosions secondary to trauma from adjacent rubbing of sharp dystrophic fifth nail. The lesions were suspicious for bruising given the patient's use of anticoagulation, and the decision was made to monitor the lesions with close dermatologic follow-up.

Over the next four days, new lesions appeared on the legs, face, neck, and scalp, and the lesions on right lower leg (Fig. 1.13.1) and right fourth toe (Fig. 1.13.2) became more erythematous, painful, and swollen with new dark areas. The patient also reported diffuse myalgias and weakness but denied fever, chills, chest pain, dyspnea, or diarrhea.

Laboratory results revealed a white blood cell count of 2900 cells/mm^3 (99% lymphocytes), hemoglobin of 8.3 g/dL, and a platelet count of 41 000/mm^3. Serum creatinine was 0.79 mg/dL, calcium 8.5 mg/dL (range, 8.9–10.3mg/dL), and albumin 3.3 g/dL (range, 3.5–4.8 g/dL). Synthetic liver function tests were unremarkable. Chest radiograph revealed no focal consolidations or pleural effusions. The cardiomediastinal silhouette was within normal limits. Punch biopsies (3 mm) of the lesions on the right leg and lower neck were performed.

QUESTIONS

- While awaiting results from the microbiology laboratory, which fungal infections should be considered to explain this patient's presentation?
- How does the use of fluconazole prophylaxis impact your differential diagnosis?

DIFFERENTIAL DIAGNOSIS

This is a patient with neutropenia and multiple tender, erythematous skin lesions. The differential is broad and includes infectious and noninfectious etiologies

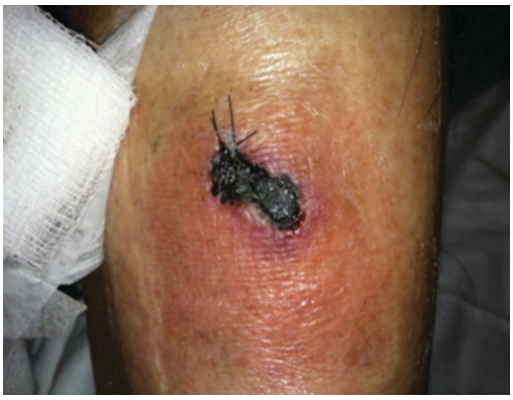


FIGURE 1.13.1: Right lower extremity after punch biopsy. The initial 3cm x 4cm skin lesion was tender and hyperpigmented. A violaceous nodule within the lesion was biopsied and sent for culture.

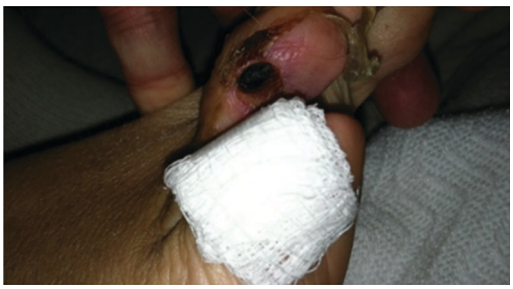


FIGURE 1.13.2: Right 4th toe: A 1cm x 2cm non-tender necrotic ulceration was noted on the lateral aspect of the right 4th toe.

Both skin lesions resolved after a prolonged course of voriconazole.

TABLE 1.13.1. DIFFERENTIAL DIAGNOSIS

Noninfectious	Infectious
Neoplastic • Leukemia cutis • Lymphoma • T-cell leukemia • Sézary syndrome	**Bacteria** • *Pseudomonas aeruginosa* • *Stenotrophomonas maltophilia* • *Aeromonas hydrophila* • Enterobacteriaceae • *Staphylococcus aureus*
Vasculitis • Polyarteritis nodosa • Cryoglobulinemia • Systemic lupus erythematous	**Fungi** • *Candida* spp • *Cryptococcus* spp • Mucorales • *Aspergillus* spp • *Fusarium* spp • *Histoplasma* spp
Coagulopathy • Heparin-induced bleeding • Disseminated intravascular coagulation	**Less Common Pathogens** • Majocchi granuloma (*Trichophyton* spp, *Microsporum* spp,) • *Nocardia* spp • *Malassezia* spp

(Table 1.13.1). Noninfectious causes include neoplastic and paraneoplastic syndromes, various forms of vasculitis, and coagulation-associated skin lesions. Infectious etiologies include ecthyma gangrenosum, which is traditionally caused by *Pseudomonas aeruginosa* but may also be seen in disseminated infection with *Stenotrophomonas maltophilia, Aeromonas hydrophila*, and Enterobacteriaceae (*Escherichia coli, Serratia marcescens*, etc) [1]. Various fungal species including *Fusarium* spp, Mucorales, *Aspergillus* spp, *Trichosporon asahii, Candida* spp, *and Cryptococcus neoformans* may also produce disseminated cutaneous lesions in the immunocompromised host [2]. Less common pathogens, such as the dermatophytes (*Epidermophyton floccosum, Microsporum canis, Trichophyton* spp), *Malassezia* spp, and *Nocardia* spp are also within the differential diagnosis.

The epidemiologic context and the clinical presentation, which includes multiple erythematous, painful, rapidly evolving skin lesions in the absence of fever or pulmonary symptoms, make many of these organisms very unlikely. The use of fluconazole prophylaxis may further narrow the diagnosis, making certain yeasts such as *Candida albicans, Candida tropicalis*, and *T asahii* less likely and certain moulds (*Fusarium* spp, *Aspergillus* spp, Mucorales) more likely. Among these three moulds, *Fusarium* spp are more likely to cause multiple disseminated painful cutaneous lesions.

INITIAL MANAGEMENT

The patient was admitted to the hospital's Lymphoma Service and an Infectious Disease consultation was obtained. Based on the outpatient antimicrobials, the decision was made to empirically treat the patient with cefepime and voriconazole while biopsy results were pending. Blood cultures as well as serum *Aspergillus* galactomannan and cryptococcal antigen were obtained. The patient was empirically treated with corticosteroids given recent outpatient steroid taper. A Rheumatology consultation was obtained given possible paraneoplastic syndrome in the setting of myalgias and possible myositis.

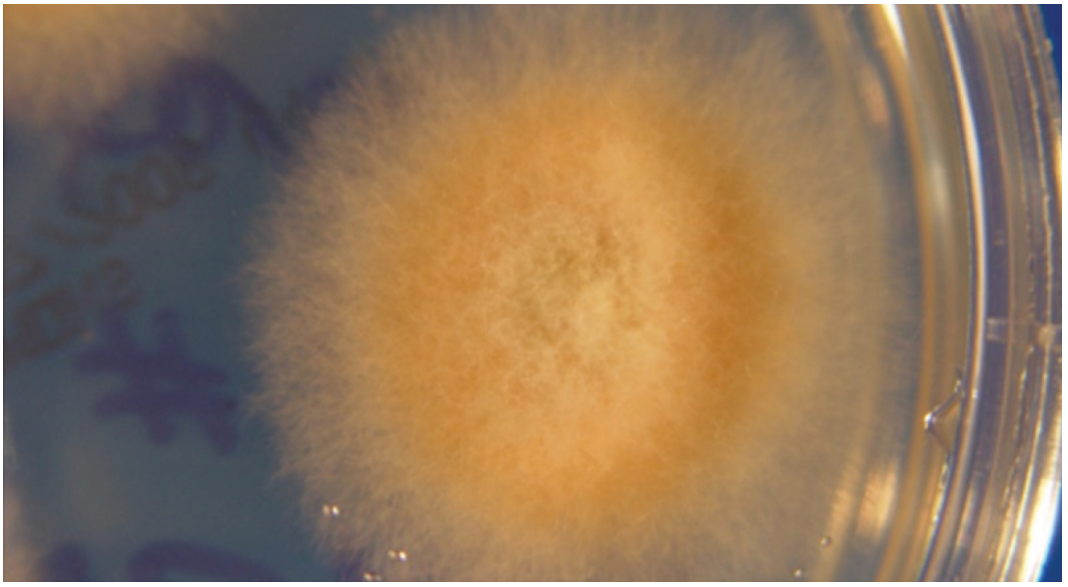


FIGURE 1.13.3: Peach-colored colony of *Fusarium* sp on Sabouraud dextrose agar.

On hospital day three, the patient developed right eye pain and blurry vision and an Ophthalmology consultation was obtained. Exam revealed scleritis, likely secondary to recent corticosteroid taper, and subconjunctival hemorrhage, possibly secondary to thrombocytopenia. On hospital day four, vitreous tap and intravitreal injection of vancomycin, ceftazidime, and amphotericin was administered given the concern for infectious endophthalmitis.

On hospital day five, blood culture and punch biopsy were found to have fungal elements consistent with mould. Given the concern for *Fusarium* spp, liposomal amphotericin B 5 mg/kg intravenously q24hr was added while identification and antimicrobial susceptibilities were pending. Growth was obtained from the skin biopsy and blood culture (Fig. 1.13.3), and the isolate was confirmed by morphology to be *Fusarium* spp. (Fig. 1.13.4).

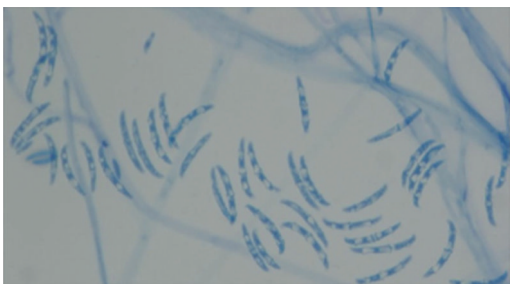


FIGURE 1.13.4: Lactophenol cotton blue stain, 400× magnification. Characteristic sickle-shaped, septate macroconidia of *Fusarium* sp obtained b tease preparation of colony.

ADDITIONAL DATA

Over the next week, the patient's cutaneous lesions continued to improve while his vision deteriorated. The patient received multiple injections of amphotericin B and voriconazole in both eyes as empirical treatment for fungal endophthalmitis. He then underwent right pars plana vitrectomy on hospital day fourteen. He subsequently underwent left pars plana vitrectomy and lensectomy on hospital day seventeen. The patient was ultimately found to have disseminated *Fusarium* spp infection with the following antimicrobial susceptibility profile:

Amphotericin = 4 μg/mL
Voriconazole >16 μg/mL
Posaconazole >1 μg/mL

After three weeks of therapy, the patient developed acute renal failure. Amphotericin B was discontinued and the renal function returned to baseline. Therapy with voriconazole was continued. The patient was later found to have chronic retinal detachment and a cataract in his right eye. Left eye was found to have corectopia with an iris membrane in a silicone oil filled eye. Although cutaneous lesions resolved with antifungal therapy, vision did not return to baseline.

Final Diagnosis: Disseminated *Fusarium* spp infection

TREATMENT AND OUTCOME

Once identification and antimicrobial susceptibility profiles were obtained, the patient was started on combination therapy of amphotericin B and voriconazole. These drugs were initiated despite the fact that the organism appeared to be resistant to both agents by in vitro testing, but there were no other treatment options. However, the patient eventually developed renal failure that was thought to be at least partly due to liposomal amphotericin B. This antifungal treatment was discontinued, and the patient was treated with a prolonged course of voriconazole. The cutaneous lesions ultimately resolved while the patient's vision continued to deteriorate. After ten weeks of hospitalization, the patient was discharged on voriconazole so that he could travel to another state to participate in an experimental monoclonal antibody clinical trial for treatment of his lymphoma.

DISCUSSION

This case illustrates the challenges of rapidly diagnosing a disseminated fungal infection in an immunocompromised host and highlights the importance of rapidly evolving cutaneous lesions in a patient with neutropenia and broad-spectrum antimicrobial agents. *Fusarium* species are widely distributed in soil, subterranean and aerial plant parts, plant debris, and other organic substrates and are present in water worldwide as part of water structure biofilms and cause superficial, locally invasive, and disseminated infections in humans [3]. The clinical form of fusariosis depends largely on the immune status of the host and the portal of entry, with superficial and localized disease occurring mostly in immunocompetent patients and invasive and disseminated disease affecting immunocompromised patients, as was the case here [4].

Our case illustrates the most common presentation of disseminated fusariosis, which includes a combination of characteristic cutaneous lesions and positive blood cultures, with or without lung or sinus involvement. *Fusarium* spp infections are difficult to treat and have a high mortality rate, in some cases as high as 60% [4]. *Fusarium* isolates are typically highly drug-resistant organisms, often with high minimum inhibitory concentrations for many antifungal agents including newer azoles as noted in the patient presented. *Fusarium* is intrinsically resistant to glucan synthesis inhibitors, (i.e. the echinocandins,) while *Fusarium solani* is often resistant to all available antifungal agents. The appropriate regimen of voriconazole or liposomal amphotericin B (or possibly both) and duration of therapy remain controversial, and an infectious disease consultation is often necessary to determine the appropriate course of treatment.

Risk Factors

The primary risk factors for fusariosis relate to immune system impairment and include prolonged neutropenia and T-cell deficiency, especially in hematopoietic stem cell transplant (HSCT) recipients with severe graft-versus-host disease [4]. Disseminated fusariosis may also be seen in patients with chronic granulomatous disease [5]. Disseminated fusariosis is occasionally seen in immunocompetent hosts, usually as a result of trauma [6].

Treatment

Treatment options include the lipid formulations of amphotericin B, voriconazole, and posaconazole. Antifungal susceptibility cannot be reliably predicted from the species of *Fusarium*. Combination therapy is often used while awaiting susceptibility profiles. The optimal treatment and duration of therapy have not been established. Depending on disease burden and antifungal resistance pattern, treatment of fusariosis may include surgical debulking. The role of granulocyte transfusions remain controversial, but they are often used in persistently neutropenic patients to stabilize the infection until recovery from neutropenia.

Prognosis

Disseminated fusariosis carries a high mortality and often depends on the extent of infection and degree of immunosuppression. One recent case series reported the mortality rates for patients with disseminated, skin, and pulmonary fusariosis at 50%, 40%, and 37.5%, respectively [7]. There is virtually a 100% death rate among persistently neutropenic patients with disseminated disease [4].

Prevention

Reversal of immunosuppression and minimizing exposure are crucial for prevention of fusariosis in the immunocompromised host. This includes discontinuation or tapering of corticosteroids

and other immunosuppressive agents as well as shortening the duration of neutropenia by using nonmyeloablative conditioning regimens for allogeneic HSCT. For hospitalized patients, exposure to organism can be minimized with the use of HEPA filters and by avoiding contact with known reservoirs of *Fusarium* spp such as tap water [8].

KEY POINTS

- *Fusarium* infection may present as superficial or disseminated infection.
- There are two major portals of entry: respiratory tract and skin.
- The classic cutaneous portal of entry is via traumatic inoculation of the toe, particularly in an immunocompromised host.
- In contrast to most disseminated fungal infections, recovery of the organism from blood culture is common.
- Mortality of disseminated infection is largely a function of the degree and duration of immunosuppression as well as the extent of infection.
- There is nearly 100% mortality for persistently neutropenic patients with disseminated disease.

REFERENCES

1. Fino P, Fioramonti P, Diego M. et al. Non healing leg ulcers infected with *Stenotrophomonas maltophilia*. Ann Ital Chir. 2013;12:84.
2. Le Clech L, Hutin P, Le Gal S, et al. Skin nodules in a patient with acute lymphoblastic leukaemia. BMJ Case Rep. 2014;9:2014.
3. Elvers KT, Leeming K, Moore CP, Lappin-Scott HM. Bacterial-fungal biofilms in flowing water photoprocessing tanks. J Appl Microbiol. 1998;84:607.
4. Nucci M, Anaissie E. *Fusarium* infections in immunocompromised patients. Clin Microbiol Rev. 2007;20:695.
5. Bassiri-Jahromi S, Doostkam A. Fungal infection and increased mortality in patients with chronic granulomatous disease. J Mycol Med. 2012;22:52.
6. Testerman GM, Steagald MK, Colquitt LA. Disseminated *Fusarium* infection in a multiple trauma patient. South Med J. 2008;101:320.
7. Muhammed M, Anagnostou T, Desalermos A, et al. *Fusarium* infection: report of 26 cases and review of 97 cases from the literature. Medicine (Baltimore) 2013;92:305.
8. Anaissie EJ, Kuchar RT, Rex JH, et al. Fusariosis associated with pathogenic *Fusarium* species colonization of a hospital water system: a new paradigm for the epidemiology of opportunistic mold infections. Clin Infect Dis. 2001;33:1871.

1.14

The New "Red Tide": Multidrug-Resistant Gram-Negative Infections in the Compromised Host

RAHUL SAMPATH, MD, RAYMUND R. RAZONABLE, MD, AND SHAWN VASOO, MD

CASE PRESENTATION

A 60-year-old man was brought to the emergency room by his wife because of high-grade fever and altered mental function. He traveled from India to the United States four months ago to seek treatment of chronic myeloid leukemia. His medical history includes diabetes mellitus and benign prostatic hypertrophy (BPH). Five months ago, he had urinary retention that required transient urinary catheterization, but this had since resolved.

He was started on imatinib treatment two weeks ago. For the past 3 days, he complained of dysuria, lower abdominal pain, and fever. On physical examination, he was somnolent but oriented to person and place. He was febrile to 39°C, with a pulse rate of 120/minute, a mean arterial pressure (MAP) of 60, and a respiratory rate of 22/minute with normal oxygenation on room air. Examination of his lungs was unremarkable. His extremities were warm to touch. There was mild tenderness over his suprapubic region and left costovertebral angle.

His laboratory examination was significant for marked leukocytosis (120 000 white blood cells [WBCs]/mm^3 with 95% neutrophils) and a platelet count of 500 000/mm^3, which are approximately 10% above his most recent blood counts. He had serum creatinine of 3.4 mg/dL, and serum lactate level was 2.3 mmol/L. Urinalysis showed >100 WBCs/high-power field, with few red cells and numerous bacteria.

QUESTIONS

- What infectious syndromes and potential etiologies could account for this patient's sepsis?
- What initial empiric treatment should be instituted?
- What are the risk factors for development of this infection?

DIFFERENTIAL DIAGNOSIS

The patient's clinical and hemodynamic presentation indicates a systemic inflammatory response syndrome that is most likely caused by infection. His clinical symptoms point to the urinary tract as the primary infectious focus. Urinary tract infections (UTIs) are uncommon in men without anatomic abnormalities or obstructive uropathy, and hence, by definition are complicated. Given the history of BPH and recent instrumentation, an underlying prostatitis should also be considered. The physical findings of costovertebral and suprapubic tenderness suggest possible pyelonephritis or obstructive uropathy with pyonephrosis.

The most common uropathogens are members of the Enterobacteriaceae (predominantly *Escherichia coli*, but also includes other Gram-negative bacilli such as *Klebsiella pneumoniae, Proteus* sp), although Gram-positive bacteria such as coagulase-negative staphylococcus and *Enterococcus* sp have also caused many cases of UTI. In patients with extensive healthcare exposure (such as this patient) or those with indwelling catheters/devices, nonfermenters such as *Pseudomonas aeruginosa* and *Acinetobacter* sp, *Staphylococci* sp, and *Candida* may also be pathogens. Given the patient's extensive healthcare exposure and receipt of medical care overseas in an area endemic for multidrug-resistant organisms, he is at increased risk of UTI caused by fluoroquinolone-resistant, extended-spectrum β-lactamase (ESBL) or carbapenemase-producing Gram-negative bacilli. All of these considerations should be kept in mind when formulating an empiric antimicrobial therapy, especially in the setting of sepsis.

ADDITIONAL DATA

The patient received aggressive volume resuscitation with 3 liters of intravenous fluids and his MAP transiently improved. After urgent collection of two sets of blood cultures and urine specimen for bacterial culture, he was started on empiric therapy with intravenous piperacillin-tazobactam and vancomycin.

He was admitted to the intensive care unit, where his urine output progressively declined. He became hypotensive and required vasopressors. A computed tomography scan of his abdomen and pelvis showed left-sided hydronephrosis, and an obstructing calculus was seen at the vesico-ureteric junction. A percutaneous nephrostomy was emergently placed.

Six hours after admission, blood cultures were positive for a Gram-negative bacillus. A single dose of intravenous gentamicin was added to his regimen, and piperacillin-tazobactam was switched to meropenem. Urine and blood cultures eventually yielded the growth of an extensively drug-resistant (XDR) *K pneumoniae*, which had a positive modified Hodge test (Figure 1.14.1, Table 1.14.1). On molecular testing, the organism was positive for the New Delhi metallo-β-lactamase (NDM) gene (bla_{NDM}).

Final Diagnosis: Carbapenemase (New Delhi metallo-β-lactamase)-producing, multidrug-resistant *K pneumoniae* complicated UTI with pyonephrosis secondary to an obstructing ureteric calculus

TREATMENT AND OUTCOME

The patient's antimicrobial regimen was adjusted to intravenous colistin forty-eight hours after his blood cultures flagged positive. His kidney function further deteriorated, necessitating dose reduction of colistin. With targeted antibiotic therapy and aggressive hemodynamic support, he eventually improved clinically over the next week. He completed a fourteen-day course of intravenous colistin. His renal function recovered. One month later, he underwent transurethral removal of his ureteric calculus, with colistin used as perioperative prophylaxis.

DISCUSSION

Early goal-directed therapy for UTI-associated sepsis should include the prompt initiation of effective antimicrobial therapy, source control (as in the patient described, with a percutaneous nephrostomy), and fluid resuscitation. Urine and blood cultures are essential to guide targeted antibiotic treatment. In contrast to the outpatient management of uncomplicated UTI, where treatment is empiric and urine cultures are not routinely obtained,

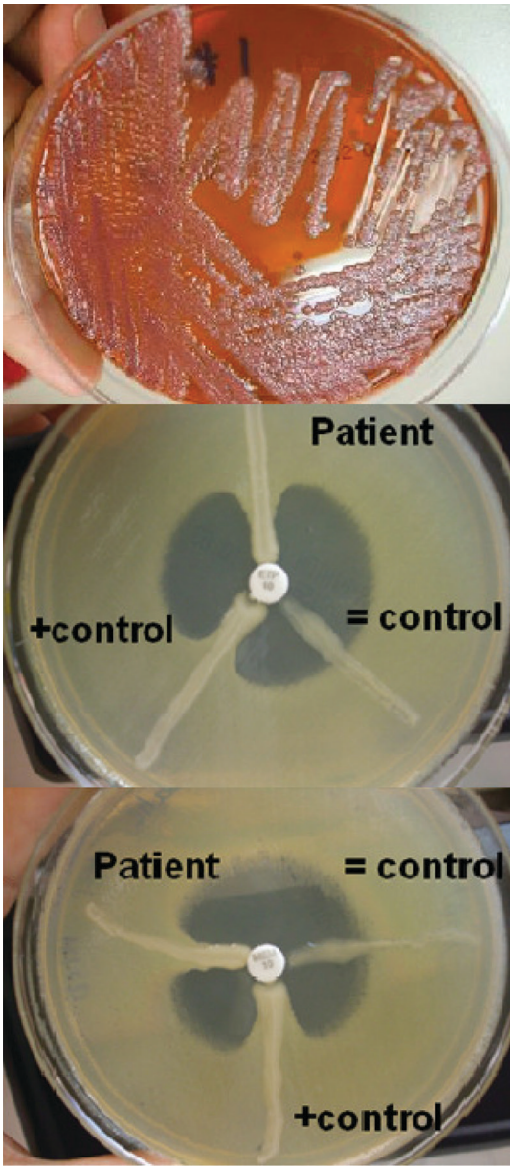


FIGURE 1.14.1: Plate morphology and modified Hodge Test of NDM-positive *Klebiella pneumoniae* isolate.

Top figure: Plate morphology showing the lactose-fermenting *Klebsiella pneumoniae* isolate on an eosin-methylene blue plate. Middle and bottom figures: Modified Hodge Test using an ertapenem and meropenem disk, respectively; + control: positive control with an isolate producing a carbapenemase; = control: Negative control, isolate not producing a carbapenemase; "Patient" = patient's *K pneumoniae* isolate. The positive control isolate, negative control isolate, and the patient's isolate are the radial streaks that are inoculated in a straight line outwards from the carbapenem disk in the center of a Mueller-Hinton agar (MHA) plate, on a background of susceptible *E. coli* plated as a lawn on the MHA plate. Carbapenemase production in the clinical and positive control isolate allows for growth of the *E coli* toward the carbapenem disk in an indentation resembling a "clover-leaf" pattern, indicating a positive test. There is no indentation with the negative control.

TABLE 1.14.1. ANTIMICROBIAL SUSCEPTIBILITY OF THE PATIENT'S *KLEBSIELLA PNEUMONIAE* ISOLATE

Antimicrobial	Minimum Inhibitory Concentration (mcg/mL)	Interpretation*
Ampicillin	>16	Resistant
Ampicillin/sulbactam	>16/8	Resistant
Piperacillin/tazobactam	>64/4	Resistant
Ticarcillin/clavulanate	>64/2	Resistant
Cefazolin	>16	Resistant
Cefepime	>16	Resistant
Ceftazidime	>16	Resistant
Ceftriaxone	>32	Resistant
Ertapenem	>4	Resistant
Meropenem	>8	Resistant
Ciprofloxacin	>2	Resistant
Levofloxacin	>4	Resistant
Amikacin	>32	Resistant
Gentamicin	>8	Resistant
Tobramycin	>8	Resistant
Tigecycline	4	Intermediate (US Food and Drug Administration [FDA] breakpoints)
Trimethoprim/sulfamethoxazole	>2/38	Resistant
Colistin	≤2	European Committee on Antimicrobial Susceptibility Testing (EUCAST)
Nitrofurantoin	≤32	Susceptible

* Interpretive criteria as per the Clinical Laboratory and Standards Institute (CLSI), unless otherwise stated [1].

complicated UTI should be guided by urine culture. In addition, urine cultures are recommended to guide pathogen-directed therapy in the following circumstances: (1) sepsis, (2) need for hospitalization, (3) pregnancy, (4) inability to tolerate first-line antibiotic therapy, (5) failure to respond to initial empiric therapy, (6) suspicion or documented for pyelonephritis, (7) healthcare-associated UTIs, and (8) risk factors for drug-resistant organisms, e.g. travel from an endemic area.

Radiologic imaging is not usually obtained in most UTIs. However, it should be considered in patients who are septic, those who have risk factors for complicated infection (e.g. the immunocompromised), and in whom etiologies such as renal abscesses, calculi, hydronephrosis, BPH, prostatic abscesses, an elevated postvoid residual urine volume, or other causes of pain (e.g. abdominal, flank, or back) need to be ruled out.

Emergence of Multidrug-Resistant Gram-Negative Bacilli

Gram-negative bacilli account for the vast majority of UTIs. As illustrated in this chapter, the management of UTI due to Gram-negative bacilli has recently become more complicated due to the emergence of drug resistance. In the 1990s, Gram-negative bacilli harboring extended spectrum β-lactamases emerged, and in the late 1990s–2000s, carbapenemase-producing Enterobacteriaceae (CPE) such as those that harbor *K pneumoniae* carbapenemases (KPCs) and NDMs emerged and grabbed global attention as the new "superbugs." The epicenter for KPCs was originally in the Northeast United States, but it subsequently spread globally. New Delhi metallo-β-lactamases were first described from a Swedish patient of Indian origin who had received healthcare in the Indian subcontinent [1], and this is also now being recognized globally. The reader is referred to several reviews for further background [1–4].

Definitions and Classification

Drug resistance due to β-lactamases is of major concern because the β-lactams are the "workhorse" antibiotics for treating many bacterial infections. The β-lactamase enzymes vary according to their substrate affinities, and they are classified based on the molecular Ambler system (classes A to D), based on their amino acid sequences and residue needed at the enzyme's active site (serine for classes A, C, and D, and zinc for class B enzymes, which are metallo-β-lactamases). We highlight salient definitions and points, which are of importance to the practicing clinician (see also Table 1.14.2).

1. **β-lactamases:** enzymes that hydrolyze the β-lactam ring. The **β**-lactamases can be narrow (e.g. penicillinases) or broad (e.g. ESBLs or cephalosporinases) in spectrum.
2. **Cephalosporinases:** these enzymes are usually referred to as class C cephalosporinase (AmpC) β-lactamases (Ambler Class C), which are inherently carried on the chromosomes of certain

TABLE 1.14.2. SUMMARY OF CHARACTERISTICS OF B-LACTAMASES (EXTENDED SPECTRUM B-LACTAMASES, AMPC CEPHALOSPORINASES, AND CARBAPENEMASES)

Ambler Class	A	B	C	D
Active site residue	Serine	Zinc	Serine	Serine
Resistance gene location	Plasmid usually	Plasmid usually	Chromosomal, occasionally plasmid	Plasmid usually
Examples*	ESBLs (e.g. CTX-M) KPCs	NDMs	AmpC (e.g. inherently in *Enterobacter, Serratia, Citrobacter*) Plasmid AmpC	OXA-48 group
Inactivates†	ESBLs: 1GC to 4GC, aztreonam, older BLIs KPCs: as above, plus carbapenems	1GC to 4GC, older BLIs and carbapenems	1GC to 3GC, older BLIs	1GC to 4GC, although 3/4 GC may be hydrolyzed poorly; carbapenems
Potential treatment options††	ESBLs: Carbapenems KPCs: colistin, tigecycline, aminoglycosides, ceftazidime-avibactam Novel agent (investigational): Plazomicin	Colistin, tigecycline, aztreonam Novel agent (investigational): Aztreonam-avibactam	Cefepime, carbapenems	More data needed. Would depend on susceptibility testing. 3GCs, e.g. ceftazidime, may retain activity and may be preferable to carbapenems (even if isolate tests carbapenem susceptible)

* AmpC, class C cephalosporinase; BLI, β-lactam/β-lactamase inhibitors (older BLIs being amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam, and ticarcillin-clavulanate); ESBL, extended spectrum β-lactamases; KPC, *Klebsiella pneumoniae* carbapenemases; NDM, New Delhi metallo-β-lactamase.
† 1GC to 4 GC, 1st-generation cephalosporin to 4th-generation cephalosporin; 3GC, 3rd-generation cephalosporin.
Ceftazidime-avibactam and aztreonam-avibactam are novel BLIs [2].
†† Treatment must be individualized, considering susceptibility results, site of infection, pharmacokinetic/dynamic considerations, and patient factors (allergies/intolerances) [3].

species of Enterobacteriaceae (e.g. *Enterobacter* sp, *Serratia* sp, *Citrobacter* sp). These enzymes may be become de-repressed or induced during therapy with β-lactams (e.g. broad-spectrum cephalosporins) and manifest phenotypically during treatment. This is especially an issue with *Enterobacter* sp. In general, bacterial isolates carrying this inducible enzyme initially test as susceptible (in vitro susceptibility test), but they have the potential to become resistant within days of β-lactam therapy. Sometimes, AmpC β-lactamases can be plasmid-borne and may be found in other Enterobacteriaceae: one study reported an incidence of 4% of *E coli* isolates in the United States [5]. Class C cephalosporinase β-lactamase hydrolyzes penicillins, first- to third-generation cephalosporins, and cephamycins (e.g. cefoxitin), monobactams (e.g. aztreonam), and the β-lactam/β-lactamase inhibitor (BLI) combinations (e.g. amoxicillin-clavulanate, piperacillin-tazobactam). However, they usually remain susceptible to cefepime (fourth generation cephalosporin) and carbapenems, which are the treatment of choice for these infections. Alternative treatment choices are fluoroquinolones and trimethoprim-sulfamethoxazole, should susceptibility be confirmed by formal testing.

3. **ESBL:** these β-lactamases (Ambler Class A) hydrolyze and confer resistance to penicillins, cephalosporins, and aztreonam. β-lactamase inhibitor combinations (e.g., piperacillin-tazobactam) can inhibit ESBLs (which distinguishes them from AmpC β-lactamases), and the isolates may test susceptible in vitro, but treatment with these BLI agents is controversial and not always reliable. The treatment of choice for ESBL infections is a carbapenem (meropenem, imipenem, ertapenem). Other alternative options for treatment of ESBL infections are fluoroquinolones,

trimethoprim-sulfamethoxazole, fosfomycin, and nitrofurantoin, if susceptible. Extended-spectrum β-lactamases are carried on plasmids and may be transferred among members of the Enterobacteriaceae group. Several ESBLs have been described, and the most common is the CTX-M-type in *E coli* and *K pneumoniae*.

4. **Carbapenemases:** these are carbapenem-hydrolyzing β-lactamases that confer resistance to all β-lactams and carbapenems. The two most prominent carbapenemases are KPC (Ambler Class A) and NDM (Ambler Class B). They are plasmid-borne and can be transferred among bacterial isolates. *Klebsiella pneumoniae* carbapenemases have become endemic in certain parts of the United States (North East and areas in the Midwest); they are also endemic in Israel, China, Greece, Europe, and parts of South America [2]. New Delhi metallo-β-lactamases have been reported in at least 15 states in the United States [6], they are endemic in India, and they are also rapidly disseminating worldwide [1, 3]. It is interesting to note that NDM and the metallo-β-lactamases do not hydrolyze aztreonam, so this may be effective for treatment. However, most of the isolates also carry other resistance-determinant genes, including ESBLs, and, hence, they also generally test nonsusceptible to aztreonam. Another carbapenemase that has emerged in the Mediterranean and the Middle East is OXA-48 (Class D). Carbapenemases have also been found in nonfermenting Gram-negative bacteria such as *Acinetobacter* sp and *Pseudomonas* sp.
5. **Other mechanisms of carbapenem resistance:** even in the absence of carbapenemases, the ESBL or AmpC-producing Enterobacteriaceae may develop carbapenem resistance as a result of decreased porin expression. Porins are structural pores in the outer membranes of bacteria, which serve as a permeability barrier but also allow for the entry of antimicrobials into the cell.

Multidrug Resistance, Extensive Drug Resistance, and Pan-Drug Resistance

Beyond β-lactam resistance, ESBL-harboring enteric organisms, and CPEs are also often resistant to other antibiotic classes, including fluoroquinolones and aminoglycosides. Multidrug-resistant Enterobacteriaceae (MDRE) have been variously defined in the literature, but a recent consensus statement defines multidrug resistance (MDR) as resistance to at least one agent in three or more antimicrobial classes; extensive drug resistance (XDR) is defined as nonsusceptibility to one or more agents in all but two or less antimicrobial categories; and pan-drug resistance (PDR) is defined as resistance to all antimicrobial agents, including the polymyxins [7]. Most CPEs belong to the XDR or PDR category.

Epidemiology and Risk Factors for Multidrug-Resistant Enterobacteriaceae

The rates of drug-resistant Gram-negative bacteria are rising. In a five-center United States study, community-onset ESBL-producing *E coli* infection rates ranged from 1.8% to as high as 6.7%. Of the 291 patients with community onset ESBL-producing *E coli* infection, 36.8% had no healthcare-associated risk factors, suggesting its spread in the community [8]. A study in Chicago described a 19% rate of MDRE among bacteria causing UTI in patients presenting to the Emergency Department; levofloxacin resistance rate for *E coli* was 16%, but it rises to 39% among patients with healthcare associated UTIs [9, 10]. Carbapenem-resistant isolates account for 10.8% of all *Klebsiella* spp isolates implicated in device-related infections in a National Healthcare Safety Network survey [11].

Risk factors for MDRE infection and colonization with carbapenemase and/or ESBL-producing bacteria are as follows: (1) prior and recent antibiotic (especially fluoroquinolone) use; (2) healthcare-associated risks including residence in long-term acute-care facilities, presence of feeding tubes, mechanical ventilation, or a central venous catheter; (3) obstructive uropathy; (4) increased age; (5) receiving healthcare in, or travel to, endemic areas; and (6) organ and stem cell transplantation [9, 12–18]. The patient presented in this chapter possesses many of these risk factors.

Diagnostic Considerations

Bacterial identification and susceptibility testing is key in the diagnosis and management of drug-resistant (e.g. ESBL/CPE) Gram-negative bacterial infections. In this case presented, the *K pneumoniae* isolate showed an XDR phenotype, because it was resistant to all antibiotics tested, with the exception of colistin and nitrofurantoin (Table 1). On occasion, ESBL-producing Gram-negative

organisms and CPEs may test susceptible or show only modest increases in their minimum inhibitory concentrations to extended spectrum cephalosporins or carbapenems, respectively.

Clinicians should be familiar with how susceptibility testing is performed in their laboratory, and they should be aware as to whether screening and confirmatory testing are performed for ESBL/CPEs, such as the modified Hodge test for CPEs. In the Hodge test, a meropenem or ertapenem disk is placed in on an agar plate with a lawn of susceptible *E coli*. On this plate, a positive control CPE isolate (usually a KPC producer), a negative control isolate (a carbapenem resistant but non-CPE isolate), and the clinical isolate in question are radially streaked from the carbapenem disk in the center. Carbapenemase production in the clinical strain allows for growth of the susceptible strain toward the carbapenem disk, giving the appearance of a clover-leaf (Figure 1).

Although the modified Hodge test is useful as a phenotypic screening test for carbapenemases (e.g. KPCs), it is not as sensitive for NDMs. Molecular confirmation of the specific resistance gene is considered the gold standard. Confirmatory testing for the ESBLs/CPEs is important in the broader context of infection prevention and control, so that outbreaks from the spread of these infections can be avoided [19].

As exemplified in this case, the relatively slow turnaround time for bacterial culture and susceptibilities is a major barrier to the initiation of early and appropriate therapy. Early effective therapy has a direct bearing on survival in the setting of MDR/XDR bloodstream infections. Emerging technologies for the direct detection of ESBLs and CPEs directly from clinical specimens (e.g. blood cultures) either by molecular or rapid chromogenic methods should be more widely adopted to overcome this hurdle [20–22].

Treatment Considerations

The treatment options for MDREs are limited due to multiclass resistance that is usually conferred by multiple resistance genes co-located on plasmids. As illustrated here, choosing an effective empiric antibiotic treatment may be difficult. If ineffective, this can lead to devastating consequences, especially in immunosuppressed hosts. In patients with hematologic malignancies, the mortality rates for these infections can be as high as 65%, with many patients dying even before effective treatment is started, if MDRE infection is not initially suspected and treated [4]. The choice of empiric treatment should be guided by the patient's history for MDRE infection or colonization or if there are risk factors for MDRE carriage (see above). A new episode of sepsis in a patient who is already receiving extended-spectrum cephalosporins or a carbapenem should also prompt consideration of infection with MDREs. In the clinical setting, such as a patient with risk factors and where local epidemiology indicates a high incidence of MDRE, the empiric treatment for bacterial sepsis may include a carbapenem, an aminoglycoside, and a polymyxin (polymyxin B and colistin [polymyxin E]).

Definitive treatment of drug-resistant, Gram-negative bacilli should be guided by antimicrobial susceptibility testing. For significant infections (e.g. bacteremia and other invasive infections) with ESBL-producing organisms, carbapenems are the treatment of choice. Quinolones may also be used, if the isolate is susceptible, in less severe types of infections. For CPEs, treatment choices are very limited and should always be guided by antimicrobial susceptibility testing. Often, the antimicrobials with efficacy are colistin, tigecycline, fosfomycin, nitrofurantoin, and occasionally aminoglycosides (gentamicin seems to retain the most efficacy against KPCs, whereas NDMs are usually aminoglycoside-resistant). There are no randomized trials for the comparative efficacy of any of these agents for CPEs. In the case presented, colistin monotherapy and prompt source control (i.e. relief of ureteral obstruction) led to gradual clinical improvement. There are increasing data for improved outcomes with combination therapy. For infection with KPC-producing bacteria, combination treatment with polymyxin, tigecycline, and a carbapenem (despite the presence of carbapenemase) has been reported to result in improved outcomes [4, 23]. Combination of these antimicrobials with rifampin may also be considered, and this is supported by an in vitro data demonstrating potential synergy with polymyxin, carbapenem, and rifampin combination [4]. Although active in vitro, tigecycline generally achieves only low to modest blood and urinary concentrations, and it should not be used as monotherapy in bloodstream infections and, ideally, not as a single agent for treatment of UTI. Other strategies that could be used include the use of high-dose, extended infusion therapy with carbapenems in combination with other antimicrobials, such as colistin/polymyxin B.

The dilemma in treating drug-resistant Gram-negative bacteria calls for the "fast-track" development of new antimicrobials. A novel BLI,

avibactam, combined with ceftazidime or aztreonam, have shown activity against KPCs and NDMs, respectively. This ceftazidime-avibactam combination has been approved by the US Food and Drug Administration in 2015. In addition, plazomicin, a novel aminoglycoside in phase III clinical trials, has activity against KPC isolates. However, there are limited data for these agents against *P aeruginosa* and *Acinetobacter* sp. Nonetheless, novel agents, if clinically proven to be safe and efficacious, will be a welcome addition to the currently limited options for CPE. More importantly, these cases should call for (1) attention to antimicrobial stewardship and (2) aggressive infection control measures to stem the tide of MDREs.

KEY POINTS

- Drug resistance among Gram-negative bacilli is increasing globally; ESBL and CPEs are major concerns.
- Mortality among immunocompromised hosts, such as those with cancer and hematologic malignancies, with these infections is high.
- The resistance determinants are often plasmid-borne and can easily spread among the Gram-negative bacterial isolates. Infection control measures, such as hand hygiene and barrier precautions, are important in preventing the spread of these organisms in a healthcare setting, especially among immunocompromised hosts.
- In devising the empiric therapy for a patient with suspected Gram-negative bacterial sepsis, risk factors for the acquisition of MDRE should be considered.
- Limited evidence indicates that, at least currently, given our limited options for therapy for CPE, combination of antibiotics may improve the outcome of CPE infections.
- New antimicrobials with activity against CPE and novel rapid diagnostics for CPE are needed to improve outcomes for patients with such infections.

REFERENCES

1. Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis. 2010;10:597.
2. Munoz-Price LS, Poirel L, Bonomo RA, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. Lancet Infect Dis. 2013;13:785.
3. Nordmann P, Naas T, Poirel L. Global spread of carbapenemase-producing Enterobacteriaceae. Emerg Infect Dis. 2011;17:1791.
4. Satlin MJ, Jenkins SG, Walsh TJ. The global challenge of carbapenem-resistant enterobacteriaceae in transplant recipients and patients with hematologic malignancies. Clin Infect Dis. 2014;58:1274.
5. Alvarez M, Tran JH, Chow N, Jacoby GA. Epidemiology of conjugative plasmid-mediated AmpC beta-lactamases in the United States. Antimicrob Agents Chemother. 2004;48:533.
6. Centers for Disease Control and Prevention. Carbapenemase-producing CRE in the United States. Available at: http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html. Accessed 30 April 2014. 2012.
7. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18:268.
8. Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum beta-lactamase-producing *Escherichia coli* infection in the United States. Clin Infect Dis. 2013;56:641.
9. Khawcharoenporn T, Vasoo S, Singh S. Urinary tract infections due to multidrug-resistant Enterobacteriaceae: prevalence and risk factors in a Chicago emergency department. Emerg Med Int. 2013;258517.
10. Khawcharoenporn T, Vasoo S, Ward E, Singh K. High rates of quinolone resistance among urinary tract infections in the ED. Am J Emerg Med. 2012;30:68.
11. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis. 2011;53:60.
12. Banerjee R, Strahilevitz J, Johnson JR, et al. Predictors and molecular epidemiology of community-onset extended-spectrum beta-lactamase-producing *Escherichia coli* infection in a Midwestern community. Infect Control Hosp Epidemiol. 2013;34:947.
13. Lin MY, Lyles-Banks RD, Lolans K, et al. The importance of long-term acute care hospitals in the regional epidemiology of *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae. Clin Infect Dis. 2013;57:1246.
14. Pop-Vicas AE, D'Agata EM. The rising influx of multidrug-resistant gram-negative bacilli into a tertiary care hospital. Clin Infect Dis. 2005;40:1792.
15. Prabaker K, Lin MY, McNally M, et al. Transfer from high-acuity long-term care facilities is associated with carriage of *Klebsiella pneumoniae* carbapenemase-producing Enterobacteriaceae: a multihospital study. Infect Control Hosp Epidemiol. 2012;33:1193.

16. Vasoo S, Madigan T, Cunningham SA, et al. Prevalence of rectal colonization with multidrug-resistant Enterobacteriaceae among international patients hospitalized at Mayo Clinic, Rochester, Minnesota. Infect Control Hosp Epidemiol. 2014;35:182.
17. Schechner V, Kotlovsky T, Kazma M, et al. Asymptomatic rectal carriage of blaKPC producing carbapenem-resistant Enterobacteriaceae: who is prone to become clinically infected? Clin Infect Dis. 2013;19:451.
18. Patel G, Huprikar S, Factor SH, et al. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol. 2008;29:1099.
19. Snitkin ES, Zelazny AM, Thomas PJ, et al. Tracking a hospital outbreak of carbapenem-resistant *Klebsiella pneumoniae* with whole-genome sequencing. Sci Transl Med. 2012;4:148ra116.
20. Altun O, Almuhayawi M, Ullberg M, Ozenci V. Clinical evaluation of the FilmArray blood culture identification panel in identification of bacteria and yeasts from positive blood culture bottles. J Clin Microbiol. 2013;51:4130.
21. Dortet L, Bréchard L, Poirel L, Nordmann P. Rapid detection of carbapenemase-producing Enterobacteriaceae from blood cultures. Clin Microbiol Infect. 2014;20:340.
22. Tojo M, Fujita T, Ainoda Y, et al. Evaluation of an automated rapid diagnostic assay for detection of gram-negative bacteria and their drug-resistance genes in positive blood cultures. PLoS One. 2014;9:e94064.
23. Lee GC, Burgess DS. Treatment of *Klebsiella pneumoniae* carbapenemase (KPC) infections: a review of published case series and case reports. Ann Clin Microbiol Antimicrob. 2012;11:32.

1.15

Cough and Dyspnea in a Sarcoma Patient: Appetite for Infection

DAVID CROCKETT, MD AND NICOLE SHONKA, MD

CASE PRESENTATION

A 47-year-old male with a history of metastatic liver sarcoma currently receiving systemic chemotherapy presents to his oncology clinic for follow-up with a new complaint of dry cough. He was diagnosed five months earlier with a presentation of reflux symptoms and general indigestion. Esophagoduodenoscopy was unremarkable so it was followed by imaging of his liver that revealed a 15 × 13 × 11 cm mass in the left hepatic lobe. He underwent partial hepatectomy with pathology revealing high-grade undifferentiated sarcoma. Two months after surgery, he developed lung metastasis and began doxorubicin and ifosfamide chemotherapy at that time. He progressed after two cycles and has been on second-line gemcitabine and docetaxel for the last six weeks with disease response.

At a clinic visit, he complained of poor appetite, low-grade fevers, and a nonproductive cough that began one week earlier. He denied any hemoptysis, chills, nausea, or vomiting. His weight, although initially down after starting chemotherapy, has been stabilizing over the last several weeks. Due to concerns about poor appetite and weight loss, his primary doctor had started him on dexamethasone 4 mg BID for the prior six weeks.

He was normotensive at 112/76 mm mercury but tachycardic to 117 beats per minute, with a temperature of 36.2°C, respiratory rate 18/minute, and oxygen saturation 96% on room air. There was no increased subjective work of breathing. He appeared thin but comfortable, and his exam was unremarkable except for slight inspiratory crackles worse on right than left.

Laboratory data were notable for a white blood cell count of 46.2 10^3/mL with absolute neutrophilia (thought to be secondary to pegfilgrastim), hemoglobin 10.1 g/dL (hematocrit 29.7), and platelet count of 328 10^3/μL. Complete metabolic panel was unremarkable apart from mild hyponatremia of 130 mmol/L. A chest computed tomography (CT) scan was obtained for staging, which showed new multifocal pulmonary ground-glass opacities in addition to known metastatic disease findings.

QUESTIONS

- What infectious causes should be considered to explain the patient's cough and radiological findings?
- What should be done to further work up the diagnosis?
- What specific risk factors exist for this infection?

DIFFERENTIAL DIAGNOSIS

Infections to consider in patients with solid tumors undergoing chemotherapy and long-term steroids who present with a dry cough and ground-glass opacities include bacterial, viral, and fungal pneumonias. Atypical pneumonia caused by *Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella pneumophila*, or *Haemophilus influenza* should be considered. Viral pneumonia from influenza, adenovirus, parainfluenza, respiratory syncytial virus, or human metapneumovirus infection should also be considered. Fungal pneumonia due to *Aspergillus* species or *Cryptococcus neoformans* would be highly unlikely in a solid tumor patient but would be a consideration for patients with chronic neutropenia. Cytomegalovirus pneumonia is most commonly seen in patients with graft-versus-host disease after an allogeneic stem cell transplant. *Pneumocystis jiroveci* is a consideration with immunosuppression and especially lymphocytopenia. Although rare in the United States, tuberculosis should also be considered.

ADDITIONAL DATA AND DIAGNOSIS

A serum 1,3-β-D-glucan returned positive at >500 pg/mL (upper limit of normal 80 pg/mL).

CASE DIAGNOSIS

The clinical, radiographic, and laboratory findings are strongly compatible with a presumptive diagnosis of *Pneumocystis jirovecii* pneumonia ([PJP] formerly *Pneumocystis carinii* pneumonia). A definitive diagnosis typically requires direct visualization on a diagnostic specimen and was not obtained in this case.

TREATMENT AND OUTCOME

Trimethoprim-sulfamethoxazole (TMP-SMX) was begun at 15 mg/kg per day (trimethoprim component) and given for six weeks due to a persistently elevated 1,3-β-D-glucan value. His dexamethasone was tapered off over the first ten days. He did require ondansetron thirty minutes prior to his doses to combat antibiotic-induced nausea. After one month, he could no longer tolerate treatment doses of TMP-SMX so he was switched to atovaquone liquid 750 mg BID. He recovered and after six weeks, he switched to a *Pneumocystis* prophylactic dose with dapsone 100 mg daily (Fig. 1.15.1).

DISCUSSION

Consideration for PJP and its prophylaxis should be given in the clinical context of long-term steroid exposure, chemoradiation with temozolomide, human immunodeficiency virus infection (HIV), and patients receiving immunotherapy such as alemtuzumab or potentially antitumor necrosis factor alpha agents or methotrexate. Infections may present with an insidious onset of dry cough more common in HIV-associated disease, or infection may rapidly progress to acute respiratory failure

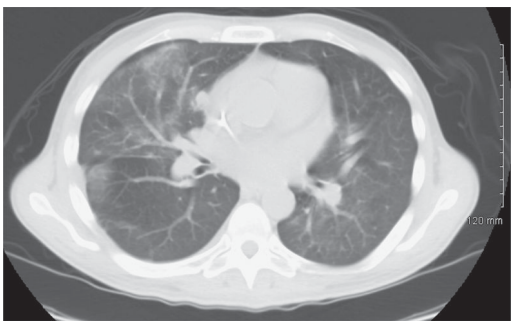


FIGURE 1.15.1: computed tomography of chest showing multifocal,ground-glass opacities besides previously known metastases.

frequently seen in those without HIV. The presence of hypoxia indicates a moderate to severe infection requiring hospital admission, intravenous (IV) therapy with TMP-SMX, and prophylaxis after recovery. Identifying patients at risk for infection is the most important step for prevention.

Risk Factors

Although diminishing in incidence due to antiretroviral therapy and routine prophylaxis, the classical risk factor for infection would be in HIV-infected adults, including those who are pregnant and those on antiretroviral therapy, when CD4 counts are less than 200 cells/μL. Apart from HIV infection, the most common risk factor for PJP is corticosteroid use [1]. There is some debate regarding the dose and duration of corticosteroid that confers risk. According to National Comprehensive Cancer Network guidelines, patients receiving doses equivalent to 20 mg of prednisone daily or greater for at least four consecutive weeks or longer should be given primary prophylaxis [2]. Additional risk factors are related to impaired or decreased lymphocyte counts (<500 cell/μL) and include patients with hematologic or solid organ transplantation, inherited immunodeficiency syndromes, or those receiving immunosuppression with or without corticosteroids for various inflammatory or rheumatologic conditions.

Clinical Presentation

The clinical presentation is different in HIV-infected patients and patients not infected with HIV, notably those with cancer. For those with HIV infection, the clinical presentation is often insidious with subtle findings of progressive dyspnea, and dry cough and will not occur with a CD4 count above 200 cells/μL. Although there are more pneumocystis organisms found in the lungs of an HIV-infected individual, there are fewer neutrophils and overall less inflammation contributing to this type of presentation. Among cancer patients (and other immunosuppressed individuals), symptoms onset is usually more abrupt in the manner of a few days with dyspnea, hypoxia, dry cough, and low-grade fevers. Pleuritic chest pain or sudden onset of dyspnea should raise suspicion for a pneumothorax.

Mild cases may be difficult to detect on plain chest radiograph, whereas CT better elucidates diagnostic details. Typical findings include bilateral perihilar interstitial infiltrations with increasing amounts of ground-glass opacification as the infection progresses. Pneumocele or pneumothorax along with cystic lesions may

develop in later stages of the disease, thus a wide variation in radiographic findings due to PJP is possible.

Diagnosis

The diagnosis of PJP is largely based on clinical and radiographic findings in a vulnerable or at-risk patient, because the organism cannot be cultured. Obtaining the gold standard of microscopic visualization of the organisms is difficult, and staining of sputum, oropharyngeal, or bronchoalveolar wash samples may not be definitive. Newer methods of diagnosis include polymerase chain reaction (PCR) techniques and the use of monoclonal antibody staining. The use of PCR in bronchoalveolar wash yields sensitivity and specificity of 98.3% and 91.0%, respectively, far exceeding much lower estimates of sputum staining methods [3]. There remains some concern about the threshold of a positive test and reliability of detection in HIV versus non-HIV patients and those receiving prophylaxis. Nevertheless, bronchoscopy with bronchoalveolar lavage should be considered when sputum staining is negative but a strong clinical suspicion remains.

Supportive laboratory evidence exists in a serum assay for fungal wall carbohydrates in the form of 1,3-β-D-glucan. A commercial test (Fungitell) has been available since 2003 and has been used for invasive fungal infections from candidiasis or *Aspergillus*. β-D-glucan should be used as a screening tool for PJP because its sensitivity is 96% and specificity is 84% [4]. When coupled with the appropriate clinical situation, this test represents a fairly reliable noninvasive modality that can prevent further invasive and costly work-ups if the test is negative.

Management

Pneumocystis is a fungus that is extremely resistant to traditional fungal agents such as amphotericin, and the azole family and is best treated with TMP-SMX 15–20 mg/kg per day (trimethoprim) and 75–100 mg/kg per day (sulfamethoxazole) divided into four daily doses. This can be delivered PO or IV and is given to all infected patients for a minimum of three weeks. Clinical improvement is not typically seen for at least seven to ten days [5]. Second-line agents for treatment include primaquine 30 mg/day with clindamycin 600 mg TID, or atovaquone 750 mg BID, or IV pentamidine 4 mg/kg per day (Table 1.15.1). There are case reports of salvage therapy with caspofungin given as 70 mg IV loading dose followed by 50 mg IV daily.

TABLE 1.15.1. TREATMENT FOR *PNEUMOCYSTIS* PNEUMONIA

Drug	Dose	Route
Trimethoprim-sulfamethoxazole	15–20 mg/kg 75–100 mg/kg daily in 4 divided doses	Oral or intravenous
Primaquine plus	30 mg daily	Oral
clindamycin	600 mg TID	Oral
Atovaquone	750 mg BID	Oral
Pentamidine	4 mg/kg daily 600 mg daily	Intravenous Aerosol

In general, reduction or removal of immunosuppression such as stopping corticosteroids should be undertaken (as much as possible in the context of the underlying disease) to allow reconstitution of the immune system and lymphocyte recovery. However, using steroids to suppress the associated inflammation of a moderate to severe respiratory infection with hypoxia may be a beneficial strategy. There is prospective evidence that adding corticosteroids at an initial dose of 40 mg of prednisone BID followed by a steroid taper over several weeks improves survival in patients infected with HIV; there is no solid evidence for a benefit of steroids in non-HIV-infected patients [6, 7]. In fact, one recent study has shown a detrimental effect [8].

Outcomes can be good with early recognition and appropriate treatment. However, if intubation is required, mortality can approach 60% [9]. There is some retrospective data that suggest non-HIV-infected patients with acute respiratory failure may do worse with a 67% in-hospital mortality rate. Adverse prognostic factors include intubation delay, longer duration of positive pressure ventilation, and pneumothorax [10]. This could be due to slower recognition because one review found a four-day delay of appropriate antibiotics in non-HIV-infected patients [11].

Prevention

As with any opportunistic infection, primary prophylaxis in the properly recognized cancer situation (Table 1.15.2) can be highly effective. Most patients with acute leukemia, allogeneic, and autologous bone marrow transplant recipients should be considered for prophylaxis. A meta-analysis of PJP prophylaxis in non-HIV-infected patients including solid organ and bone marrow-transplanted patients showed (1) the use of TMP-SMX resulted in a 91%

TABLE 1.15.2. CANCER TREATMENT SITUATIONS REQUIRING *PNEUMOCYSTIS JIROVECII* PNEUMONIA PROPHYLAXIS

Situation	Duration
Acute lymphocytic leukemia	During entire leukemia treatment
Allogeneic stem cell transplant	Minimum of 6 months and while getting immunosuppressive therapy
Autologous stem cell transplant	3–6 months after transplant
Alemtuzumab	2 months after treatment and until CD4 >200
Fludarabine or other purine analogs	Until CD4 >200
Temozolomide and radiation	Until absolute lymphocyte counts have normalized
Prednisone 20 mg or equivalent for >4 weeks	Until steroids discontinued or below the 20 mg threshold

reduction in PJP with a number needed to treat of 15 and (2) a statistically significant reduction in mortality [12]. In addition, TMP-SMX is also active for several other common bacterial and opportunistic infections such as listeria, nocardia, and toxoplasmosis. Common medications used during cancer care requiring consideration for prophylaxis also include alemtuzumab, fludarabine, prolonged corticosteroids, and concurrent temozolomide and radiation therapy.

There are typically four prophylactic regimens proven effective in preventing PJP (Table 1.15.3): TMP-SMX (1 double-strength tablet 160/800 mg daily), dapsone 100 mg daily, atovaquone 750 mg twice daily, or aerosolized pentamidine 300 mg every 4 weeks. Both TMP-SMX and dapsone were superior to pentamidine for HIV-infected patients with CD4 counts below 100 and is the prophylaxis of choice for both PJP and toxoplasmosis [6]. To improve tolerability, several dose modifications to TMP-SMX have been studied. Doses of 80/400 mg daily, 160/800 mg every other day, or 160/800 mg daily three times a week all are equally effective in preventing PJP [12, 13]. Trimethoprim-sulfamethoxazole can be given safely with methotrexate without significant concern for side effects such as marrow suppression [14]. Thus, this antibiotic is a preferred category 1 recommendation for prophylaxis.

KEY POINTS

- Recognition of patients infected and at risk for infection with pneumocystis is vital for proper management.
- Antineoplastic therapies such as alemtuzumab, temazolamide, etc are notable risk factors for PJP.
- Prolonged steroid use, no matter the underlying indication, should raise concern for pneumocystis in the non-HIV-infected patient
- Onset may be rapid in cancer patients.
- Serum 1,3-β-D-glucan is an excellent surrogate marker for PJP in the proper setting.
- TMP-SMX remains the cornerstone for prophylaxis and treatment.

TABLE 1.15.3. PROPHYLACTIC REGIMENS FOR *PNEUMOCYSTIS* PNEUMONIA

Drug	Dose	Comments
Trimethoprim-sulfamethoxazole	Double-strength tablet daily Single-strength tablet daily Double-strength tablet every other day Double-strength tablet 3 days a week	1st-line agent with several dosing regimens to help with tolerability
Dapsone	100 mg daily	Testing for G6PD recommended to avoid hemolysis
Atovaquone	750 mg BID	High-fat meals improve absorption
Pentamidine (aerosolized)	300 mg monthly	Least preferred agent

REFERENCES

1. Worth L, Dooley M, Seymour J, et al. An analysis of the utilisation of chemoprophylaxis against *Pneumocystis jirovecii* pneumonia in patients with malignancy receiving corticosteroid therapy at a cancer hospital. Br J Cancer 2005;92:867.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology for Cancer-Related Infections, version 2.2013. Accessed 30 April 2014. www.nccn.org
3. Fan LC, Lu HW, Cheng KB, et al. Evaluation of PCR in bronchoalveolar lavage fluid for diagnosis of *Pneumocystis jirovecii* pneumonia: a bivariate meta-analysis and systematic review. PLoS One 2013;8:e73099.
4. Onishi A, Sugiyama D, Kogata Y, et al. Diagnostic accuracy of serum 1,3-beta-D-glucan for *Pneumocystis jiroveci* pneumonia, invasive candidiasis, and invasive aspergillosis: systematic review and meta-analysis. J Clin Microbiol. 2012;50:7.
5. Limper AH, Knox KS, Sarosi GA, et al. An official American Thoracic Society statement: Treatment of fungal infections in adult pulmonary and critical care patients. Am J Respir Crit Care Med. 2011;183:96.
6. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. N Engl J Med. 1995;332:693.
7. Pareja JG, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV *Pneumocystis carinii* pneumonia. Chest 1998;113:1215.
8. Lemiale V, Debrumetz A, Delannoy A, et al. Adjunctive steroid in HIV-negative patients with severe *Pneumocystis* pneumonia. Respir Res. 2013;14:87-9921-14.
9. Mansharamani NG, Garland R, Delaney D, Koziel H. Management and outcome patterns for adult *Pneumocystis carinii* pneumonia, 1985 to 1995: comparison of HIV-associated cases to other immunocompromised states. Chest 2000;118:704.
10. Festic E, Gajic O, Limper AH, Aksamit TR. Acute respiratory failure due to *Pneumocystis* pneumonia in patients without human immunodeficiency virus infection: outcome and associated features. Chest 2005;128:573.
11. McKinnell JA, Cannella AP, Kunz DF, et al. *Pneumocystis* pneumonia in hospitalized patients: a detailed examination of symptoms, management, and outcomes in human immunodeficiency virus (HIV)-infected and HIV-uninfected persons. Transpl Infect Dis. 2012;14:510.
12. Green H, Paul M, Vidal L, Leibovici L. Prophylaxis of *Pneumocystis* pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc. 2007;82:1052.
13. Di Cocco P, Orlando G, Bonanni L, et al. A systematic review of two different trimetoprim-sulfamethoxazole regimens used to prevent *Pneumocystis jirovecii* and no prophylaxis at all in transplant recipients: appraising the evidence. Transplant Proc. 2009;41:1201.
14. Langford CA, Talar-Williams C, Barron KS, Sneller MC. Use of a cyclophosphamide-induction methotrexate-maintenance regimen for the treatment of Wegener's granulomatosis: extended follow-up and rate of relapse. Am J Med. 2003;114:463.

1.16

Breaking Bad: Breakthrough Fungemia

JAMIE S. GREEN, MD

CASE PRESENTATION

A 60-year-old Mexican male living in San Diego, California developed neutropenic fever while being treated for Burkitt's lymphoma. His initial cancer presentation was in 2006 with left cervical lymphadenopathy. For two years, he was managed with alternative and experimental therapy while participating on a clinical trial in Mexico. In 2008, he developed progressive fatigue, anorexia, and weight loss. By 2009, there was rapid enlargement of several cervical and abdominal lymph nodes with pain and tracheal impingement (Figure 1.16.1), necessitating intubation for airway protection. After transfer to a tertiary hospital in San Diego, given the large tumor burden, chemotherapy with cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HCVAD) was administered with a good initial response.

Three days after chemotherapy, absolute neutropenia (absolute neutrophil count [ANC] <0.4 cells/mL) ensued and persisted for more than ten days. Prophylactic antibiotics included trimethoprim-sulfamethoxazole and acyclovir. Micafungin 100 mg daily was initiated at the start of neutropenia. On the eleventh day after chemotherapy, fevers occurred up to 38.4°C. He remained intubated for airway protection on minimal ventilator settings with fraction of inspired oxygen (FiO_2) of 40% and minimal suction requirements. Initial work up for neutropenic fever included blood cultures, chest radiograph, bronchoalveolar lavage, and initiation of empiric broad-spectrum antibiotics (meropenem). Over the next few days, computed tomography scans of the neck, chest, abdomen, and pelvis were repeated. They were notable for decreased cervical and abdominal lymphadenopathy and persistence of bilateral pleural effusions, with decreased lung volumes and no new parenchymal infiltrates (Figure 1.16.2).

Mental status had been steadily improving over time (intensive care unit delirium), and he was regaining strength. Physical exam at the time of initial fevers was notable for a very thin, cachectic male without skin rashes. Heart exam was normal, lungs had decreased breath sounds at the bases, no notable crackles or wheeze, right subclavian triple lumen central-line catheter was without erythema or tenderness, and abdomen was nontender with little change to his palpable abdominal mass (Figure 1.16.3).

Laboratory evaluation was notable for absolute neutropenia with a white blood cell count <0.4 cells/mL. Blood cultures drawn during febrile episodes were pending. Despite the lack of parenchymal pulmonary infiltrates, a bronchoalveloar lavage was performed for evaluation of persistent fevers, which grew methicillin-resistant *Staphylococcus aureus, Klebsiella pneumoniae*, and *Achromobacter* spp. Fevers persisted after six days of broad-spectrum antibiotics (vancomycin and meropenem) and thirteen days of

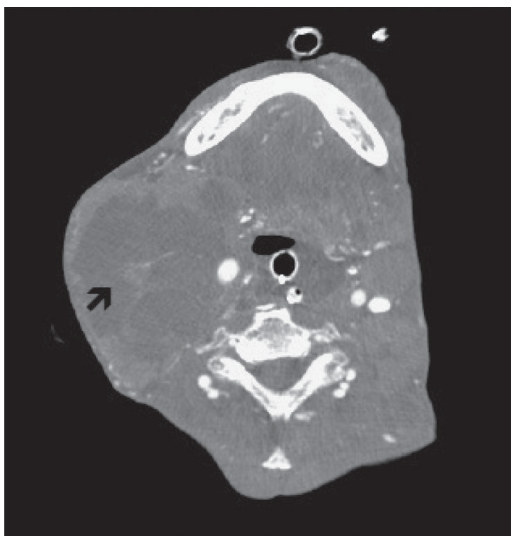


FIGURE 1.16.1: Computed tomography neck. Black arrow denoting large cervical lymphadenopathy.

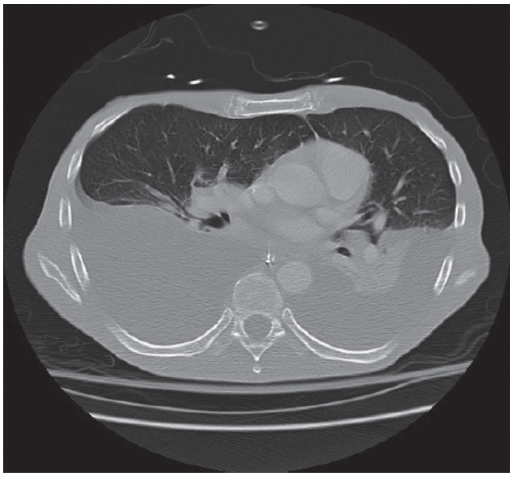


FIGURE 1.16.2: CT chest at the time of neutropenic fevers. Large bilateral pleural effusions without overt parenchymal infiltartes.

micafungin. A blood culture drawn at the onset of fevers grew a filamentous yeast on the sixth day of incubation (Figure 4a), at which time the central line was removed. Repeat daily blood cultures continued to grow this yeast on six consecutive days (Table 1.16.1).

QUESTIONS

- What fungal pathogens can be resistant to echinocandins?
- What types of fungi can cause fungemia in a neutropenic patient?
- What changes to antifungal therapy should be made after the yeast was identified in blood culture?
- What are this patient's risk factors for fungemia?
- What is the prognosis and outcome of breakthrough fungemia?

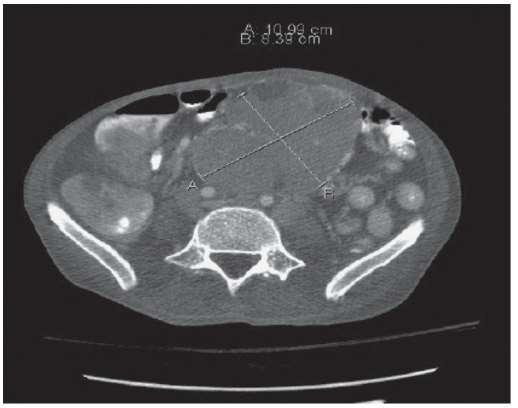


FIGURE 1.16.3: Computed tomography abdomen. White lines denoting large abdominal mass 10.99cm X 8.39 cm.

TABLE 1.16.1. MICROBIOLOGY DATA

	Blood Culture*	Yeast Identified as *Trichosporon asahii,* MICs
Day 1**	Positive for yeast	Fluconazole 2.0
Day 2**	Positive for yeast	Voriconazole 0.065
Day 4**	Positive for yeast	Micafungin >8
Day 6**	Positive for yeast	

Abbreviations: MICs, minimal inhibitory concentrations (μg/mL).
*From central line, arterial line. and peripheral draw.
**Blood cultures drawn coinciding with the onset of fevers (day 1). Cultures were not obtained on day 3 or 5.

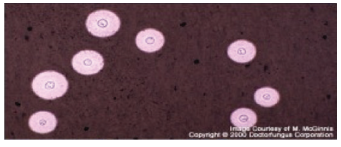
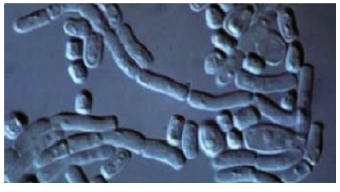
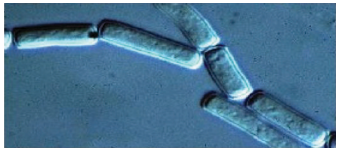
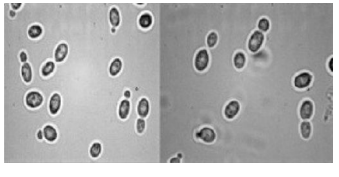
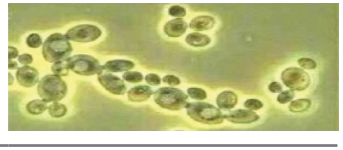
DIFFERENTIAL DIAGNOSIS

In this case, we describe a patient with Burkitt's lymphoma and neutropenic fevers with breakthrough yeast fungemia while on micafungin. *Candida* spp represent the most common blood yeast isolate [1], with the incidence of non-*albicans Candida* species increasing over time (cohort from 2005 to 2007 compared with 1997 to 2000) [2]. Some species of *Candida* can develop echinocandin resistance such as *Candida glabrata* or *Candida parapsilosis*. In this case, the yeast morphology (Figure 4a) suggested a non-*Candida* yeast. Endemic fungi can be a consideration in a patient with sepsis and fungemia breakthrough on echinodandin therapy. The most common endemic fungus known to grow in blood would be disseminated histoplasmosis. This patient would have been at risk for other endemic fungi such as paracoccidioidomycosis and coccidioidomycosis because he was native to Mexico. Other than *Histoplasma*, these tend to present with pulmonary infiltrates or lymphadenopathy and are often diagnosed from tissue biopsy samples, not from blood cultures. The morphology of the yeast in this case (Figure 4) was not consistent with an endemic fungus. Finally, we must consider non-*Candida* opportunistic yeast. These non-*Candida* opportunistic yeasts are often resistant to echinocandins and are known to cause fungemia in cancer patients. Included among them are *Cryptococcus, Trichosporon, Saccharomyces, Rhodotorula*, and *Geotrichum*. The morphology (Figure 4a) of our isolate most closely resembles *Trichosporon* or *Geotrichum* (Table 1.16.2). Infections with *Geotrichum* geographically occur in Europe (Italy, Spain, and France), whereas *Trichosporon* is distributed worldwide [3].

INITIAL RECOMMENDATIONS

On the first day the yeast was isolated, voriconazole was initiated (6 mg/kg every twelve hours

TABLE 1.16.2. COMPARISON OF NON-CANDIDA YEASTS

Yeast	Clinical Features	Microbiologic Features	Antifungal Susceptibilities	
Cryptococcus	Pneumonia, meningitis, dissemination, sepsis	Round, budding yeast. No true hyphae	Sensitive to amphotericin, azoles, often combination with flucytosine is used. Resistant to echinocandins	
Trichosporon	Fungemia, dissemination, pneumonia	Hyphae (septate), pseudohyphae, barrel-shaped arthroconidia, pleomorphic budding yeast (blastoconidia)	*Trichosporon asahii* susceptible to voriconazole and posaconazole. Reduced sensitivity to fluconazole Resistant to echinocandins and amphotericin.	
Geotrichum	Fungemia, dissemination, pneumonia	Arthroconidia are unicellular, in chains, rectangular or barrel shape. True hyphae	Sensitive to amphotericin and voriconazole. Reduced susceptibility to fluconazole and itraconazole.	
Rhodotorula	Fungemia, central catheter-associated infections	Unicellular blastoconidia, globose to elongated in shape. No hyphae or pseudohyphae	Sensitive to amphotericin, itraconazole, and voriconazole. Reduced susceptibility to echinocandins and other azoles.	
Sacchromyces	Fungemia, probiotic-associated	Unicellular. globose, and ellipsoid to elongated blastoconidia. Multipolar budding. Hyphae are absent.	Sensitive to amphotericin Variable minimal inhibitory concentrations to azoles.	

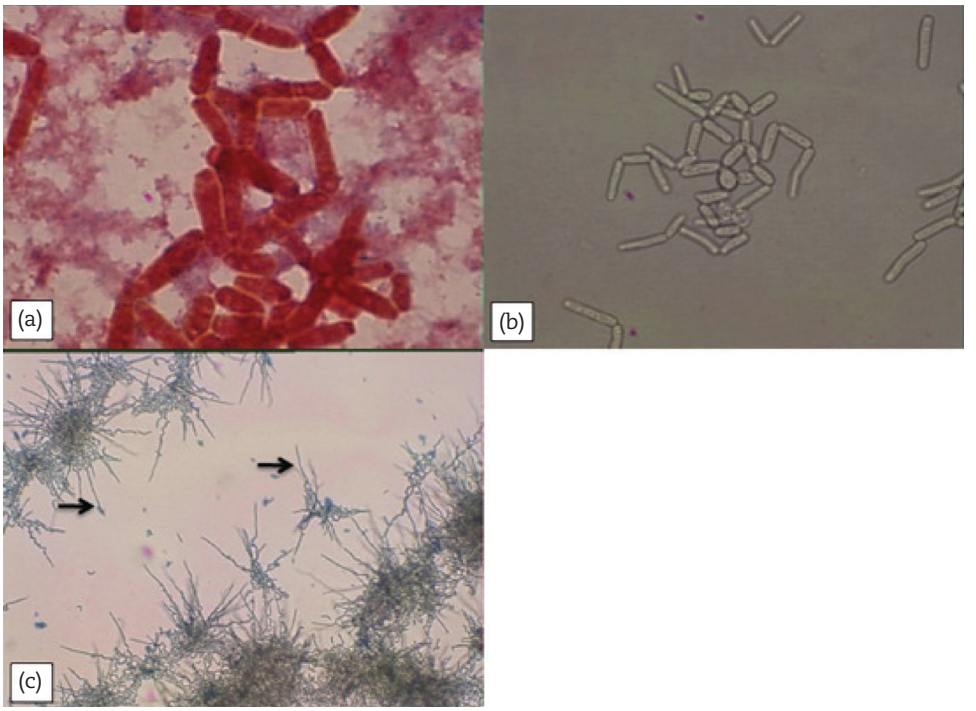


FIGURE 1.16.4: Panel A: Blood culture gram stain with elongated filamentous yeast. Panel B: Potassium hydroxide (KOH) prep showing Trichosporon arthroconidia, some with terminal and oval conidia. Panel C: Lactophenol cotton blue tease prep showing hyphal forms (black arrows).

for two doses, then 4 mg/kg every twelve hours) in place of micafungin. Recommendations were also made that any change in clinical status would trigger the use of a lipid amphotericin product. That evening he developed hypotension requiring vasopressor support. Liposomal amphotericin B (AmBisome) was then started in place of voriconazole.

ADDITIONAL DATA, MANAGEMENT, AND OUTCOME

Based on morphologic data, the yeast was identified as *Trichosporon asahii* (Figure 4b and c, Table 2). This included identification of elongated yeast forms with hyphae in blood culture (Figure 4a), arthroconidia with some terminal and oval conidia on potassium hydroxide preparation (Figure 4b), and hyphal forms on lactophenol cotton blue tease preparation (Figure 4c). Once *T asahii* was identified, voriconazole was added back, in addition to continuing AmBisome. The minimal inhibitory concentrations (MICs) of the *Trichosporon* resulted sensitive to voriconazole at 0.065 (Table 1). Despite antifungal therapy, this patient's condition continued to decline, and he was transitioned to comfort care. He remained profoundly neutropenic throughout his course. Blood cultures were documented positive for *Trichosporon* for six days, until his death, without clearance despite six days of voriconazole therapy (Table 1).

DISCUSSION

Non-*Candida* Opportunistic Yeast

Invasive non-*Candida* yeast infections are emerging opportunistic pathogens with high mortality among immunocompromised patients. Non-*Candida* yeast infections represented <5% of all yeast isolates in the ARTEMIS Global Antifungal Surveillance Study, the largest worldwide collection of over 205 000 yeast isolates over 8.5 years. Of the non-*Candida* yeast (8821 isolates), *Cryptococcus neoformans, Saccharomyces* spp, *Trichosporon* spp, and *Rhodotorula* spp were most commonly identified, representing 33%, 11.3%, 10.7%, and 4.2%, respectively [1].

Classification of *Trichosporon*

Trichosporon is an environmental yeast found in soil and decaying material. For over 50 years *Trichosporon* was recognized as *Trichosporon beigelii* and *Trichosporon cutaneum*. The previous classification of *Trichosporon* was redefined using data from new molecular techniques and environment niches, which included six species: *T cutaneum, T asahii, Trichosporon*

asteroides, Trichosporon mucoides, Trichosporon inkin, and *Trichosporon ovoides* [4]. Currently, 50 species of *Trichosporon* are recognized, 16 species of which have clinical relevance [4]. In general, invasive disease has been associated with *T asahii, T mucoides*, and *T asteroides*, whereas superficial cutaneous infections are more commonly due to *T inkin, T cutaneum, T ovoides*, and *Trichosporon loubieri* [4]. The association of *T asahii* with invasive disease comes from several case reports and case series. In fact, most of the cases of invasive *Trichosporon* infections are reported at *Trichosporon* spp and do not identify the organism down to the subspecies level. Virulence factors that could impact the ability of a subspecies of *Trichosporon* to cause invasive or superficial disease have not been elucidated or systemically studied.

Colonization and Risk Factors

Colonization with *Trichosporon* can occur in healthy adults on the skin, in the gastrointestinal and genitourinary tracts, and in the respiratory tree of humans. *Trichosporon* colonization was found in 11% of patients admitted to the intensive care unit. The majority of isolates were *T cutaneum* and *T asteroides*, with *T asahii* representing less than 10% [5]. Haupt et al [6] prospectively studied surveillance cultures from blood, urine, and stool in 353 immunocompromised oncology patients. Thirteen patients (3.7%) were colonized with *Trichosporon* spp, and three of these subjects (25% of those colonized) went on to develop invasive disease [6]. Given the severity of *Trichosporon* infections in immunocompromised patients, the isolation of *Trichosporon* from a clinically relevant sample should not be interpreted as colonization or contamination.

Risk factors for invasive *Trichosporon* infections include neutropenia and acute leukemia [3, 7, 8], with severe neutropenia being associated with disseminated disease and breakthrough infections (fungemia developing after receiving 7 days of an antifungal agent) [9]. In a series of *Trichosporon* infections in 17 cancer patients (which included use of fluconazole as prophylaxis), 70% of infections were related to central catheters [8]. The largest compilation of *Trichosporon* infections included 287 cases worldwide, with an even distribution of cases across all continents [3]. The most common underlying conditions in this series included hematologic diseases, peritoneal dialysis, and solid tumors. Of the 167 cases that occurred in patients with hematologic malignancies, 68% had acute leukemia and 85% received cytotoxic chemotherapy [3]. It is interesting that the vast majority of cases occurred in patients with acute leukemia receiving chemotherapy as opposed to stem cell transplant. This has also been reported in another smaller study of *Trichosporon* infections [8].

Presentation and Diagnosis

The most common presentation of trichosporonosis is fungemia (fever, sepsis, and positive blood cultures) [3]. Disseminated disease can involve any organ, with pneumonia [3] and cutaneous lesions being common manifestations. *Trichosporon* is the second most common non-*Candida*, non-*Cryptococcus* yeast bloodstream infection among cancer patients [9] and third most common non-*Candida* yeast isolated in the ARTEMIS Global Antifungal Surveillance Study [1]. Although candidemia and trichosporonosis can present with similar syndromes among immunocompromised patients (fever and fungemia), there are some notable differences. Compared with candidemia, *Trichosporon* is less commonly associated with catheter infections, has a higher propensity for invasive tissue disease, and is isolated in blood in over 70% of cases [3].

Diagnosis of most non-*Candida* yeast infections is based on culture recovery of the organism from a sterile specimen from a body site (blood, tissue, etc). Morphologic and biochemical characteristics are used to identify the yeast by clinical microbiology laboratories [10]. *Trichosporon* produces blastoconidia with hyphae, which differentiates it from *Geotrichum* (Table 2). There is an array of molecular and immunologic tests for *Trichosporon*, riddled with various limitations, and in general these tests are not available for clinical real-time use. Commercial immunoassays for *Trichosporon* cross-react with *Cryptococcus* [11]. In fact, our patient did have a positive cryptococcal antigen test of 1:256, which was interpreted as a false-positive result. Molecular identification using nucleic acid testing and monoclonal antibodies is very promising [7] but not yet available for real-time clinical use.

Treatment and Outcome

Data on management of *Trichosporon* infections are confounded by a lack of studies linking in vitro susceptibilities with in vivo treatment responses. As such, there is no standardized therapy for *Trichosporon* infections. However, azoles (specifically voriconazole) seem to be the best currently available treatment option. Prior to azoles, use of amphotericin resulted in a 76%–93% mortality of

Trichosporon infections in cancer patients [3, 12]. Studies of *Trichosporon* infections in neutropenic rabbits [13] and in vitro testing of clinical isolates of *Trichosporon* [14] showed high MICs to amphotericin. Amphotericin is not fungicidal against *Trichosporon*. Another class of antifungals, echinocandins, is ineffective against *Trichosporon* and should not be used for therapy.

Clinical and in vitro studies suggest that the azoles, voriconazole and posaconazole, have the greatest effectiveness [15]. Hazirolan et al [16] evaluated the inhibitory and fungicidal effects of the triazoles (fluconazole, voriconazole, posaconazole, and isavuconazole) on 90 clinical isolates of *T ashaii*. This study showed that voriconazole was the most active triazole in vitro against *T asahii*. Itraconazole, posaconazole, and isavuconazole showed similar antifungal activity, which was lower than voriconazole. Fluconazole had the lowest activity of all the azoles tested. Using time-kill experiments, they this study assessed the fungicidal status of these azoles. Although none of the azoles were fungicidal, the lowest concentrations at which killing activity begins was for voriconazole and highest for fluconazole [16]. There are numerous case reports of successful treatment of invasive *Trichosporon* infections in immunocompromised patients with voriconazole. In summary, voriconazole is the current drug of choice in managing these infections.

The mortality of *Trichosporonosis* ranges from 34% to 84% [3, 8, 9, 12]. This variation is likely related to infections described in years past, when limited antifungal medications were available. Breakthrough *Trichsoporon* infections (fungemia developing after receiving seven days of an antifungal agent) are associated with high mortality [9], and they have been reported to occur with use of all classes of antifungal medications (especially echinocandins). The use of antifungal prophylaxis (most commonly fluconazole) in neutropenic patients may impact the incidence or severity of *Trichosporon* infections, but this has not been systemically studied.

Summary

This case demonstrates many classic findings in severe disseminated *Trichosporon* infections. Risk factors in our patient included a refractory oncologic condition heavily treated with chemotherapy, severe neutropenia (depth, ANC <100, and duration, greater than seven days), and antifungal prophylaxis with an echinocandin. Our patient remained neutropenic and fungemic until the time of death. The lack of recovery of neutrophils contributes to the mortality associated with fungal infections. Unlike *Candida, Trichosporon* should not be considered a colonizing organism in the immunocompromised population. Voriconazole remains the treatment of choice because *Trichosporon* is considered resistant to amphotericin and echinocandins.

Often in clinical medicine, we are challenged with optimization of empiric antifungal therapy prior to definitive identification of a yeast organism. This is an area where guidelines are lacking, and treatment of life-threatening infections before identification relies on the art of medicine. Use of one versus two antifungal agents as either empiric or targeted treatment is not yet fully delineated. The toxicities and side effects of the available agents often contribute to the decision of which agent to use for empiric antifungal therapy. Common themes among non-*Candida* yeast infections are that most yeast (*Rhodotorula* excluded) remain sensitive to voriconazole or other higher generation azoles, some yeast are resistant to echinocandins, and some yeast may have variable sensitivity to amphotericin products [1].

KEY POINTS

- Opportunistic yeasts other than *Candida* species can cause severe disseminated disease among cancer patients, with high mortality.
- Long-term neutropenia and acute leukemia are important risk factors for *Trichosporon* infection.
- *Trichosporon* can cause severe disseminated disease in cancer patients with high mortality.
- In the immunocompromised population, *Trichosporon* should not be considered a colonizing organism.
- In the setting of breakthrough fungemia on antifungal prophylaxis, it is important to understand the resistance patterns of opportunistic yeast when choosing empiric antifungals for treatment.
- At this time, voriconazole appears to be the most effective therapy for *Trichosporon* infections.

REFERENCES

1. Pfaller MA, Diekema DJ, Gibbs DL, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance study, 1997 to 2005: an 8.5-year analysis of susceptibilities of *Candida* species and other yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. J Clin Microbiol. 2007;45:1735.

2. Pfaller MA, Diekema DJ, Gibbs DL, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-year analysis of susceptibilities of *Candida* species to fluconazole and voriconazole as determined by CLSI standardized disk diffusion. J Clin Microbiol. 2010;48:1366.
3. Girmenia C, Pagano L, Martino B, et al. Invasive infections caused by *Trichosporon* species and *Geotrichum capitatum* in patients with hematological malignancies: a retrospective multicenter study from Italy and review of the literature. J Clin Microbiol. 2005;43:1818.
4. Colombo AL, Padovan AC, Chaves GM. Current knowledge of *Trichosporon* spp. and trichosporonosis. Clin Microbiol Rev. 2011;24:682.
5. Messias Silvestre AJ, Alexandre Bandeira Rampazzo Miranda M, Pires de Camargo Z. Species isolated from the perigenital region, urine and catheters of a Brazilian population. Braz J Microbiol. 2010;41:628.
6. Haupt HM, Merz WG, Beschorner WE, et al. Colonization and infection with *Trichosporon* species in the immunosuppressed host. J Infect Dis. 1983;147:199.
7. Davies GE, Thornton CR. Differentiation of the emerging human pathogens *Trichosporon asahii* and *Trichosporon* asteroides from other pathogenic yeasts and moulds by using species-specific monoclonal antibodies. PLoS One 2014;9:e84789.
8. Kontoyiannis DP, Torres HA, Chagua M, et al. Trichosporonosis in a tertiary care cancer center: risk factors, changing spectrum and determinants of outcome. Scand J Infect Dis. 2004;36:564.
9. Chitasombat MN, Kofteridis DP, Jiang Y, et al. Rare opportunistic (non-*Candida*, non-*Cryptococcus*) yeast bloodstream infections in patients with cancer. J Infect. 2012;64:68.
10. Silva JO, Franceschini SA, Lavrador MA, Candido RC. Performance of selective and differential media in the primary isolation of yeasts from different biological samples. Mycopathologia 2004;157:29.
11. Fonseca FL, Frases S, Casadevall A, et al. Structural and functional properties of the *Trichosporon asahii* glucuronoxylomannan. Fungal Genet Biol. 2009;46:496.
12. Hoy J, Hsu KC, Rolston K, et al. *Trichosporon beigelii* infection: a review. Rev Infect Dis. 1986;8:959.
13. Walsh TJ, Lee JW, Melcher GP, et al. Experimental *Trichosporon* infection in persistently granulocytopenic rabbits: implications for pathogenesis, diagnosis, and treatment of an emerging opportunistic mycosis. J Infect Dis. 1992;166:121.
14. Walsh TJ, Melcher GP, Rinaldi MG, et al. *Trichosporon beigelii*, an emerging pathogen resistant to amphotericin B. J Clin Microbiol. 1990;28:1616.
15. Miceli MH, Diaz JA, Lee SA. Emerging opportunistic yeast infections. Lancet Infect Dis. 2011;11:142.
16. Hazirolan G, Canton E, Sahin S, Arikan-Akdagli S. Head-to-head comparison of inhibitory and fungicidal activities of fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole against clinical isolates of *Trichosporon asahii*. Antimicrob Agents Chemother. 2013;57:4841.

1.17

Painful Sores All Over My Body

KAILASH MOSALPURIA, MD, MPH AND SARA BARES, MD

CASE PRESENTATION

A 56-year-old African American female with a past medical history of multiple myeloma and chronic kidney disease presented with a painful rash involving her bilateral upper and lower extremities, chest, abdomen, and back. The patient first developed pain in her left arm approximately three days prior to presentation. She was evaluated in clinic and physical exam was unrevealing, so she was managed conservatively for presumptive musculoskeletal pain with oral analgesics. Approximately three days after the onset of the left arm pain, the patient developed a rash involving her left upper arm, chest, and back. Upon presentation to clinic for repeat evaluation, she was noted to have a disseminated vesicular rash and was referred for admission for further diagnostic evaluation and treatment.

The patient has a history of multiple myeloma complicated by chronic kidney disease and had undergone induction treatment with four cycles of bortezomib and dexamethasone with partial response followed by melphalan and autologous stem cell transplant five months prior. Prophylactic antimicrobials included acyclovir (initiated during treatment with bortezomib and continued until count recovery after autologous stem cell transplant) and fluconazole (initiated at time of autologous stem cell transplant and continued until count recovery). At the time of presentation, she was receiving maintenance therapy with lenalidomide.

The patient resides in Omaha, Nebraska and lives at home with her husband. She has no pets and denied any recent travel. She did report a childhood history of chickenpox but denied any history of shingles. She denied fevers, chills, headache, sick contacts, eye pain, vision changes, chest pain, shortness of breath, abdominal pain, nausea, vomiting, or diarrhea. On arrival, she was anxious but otherwise well appearing. Temperature was 37.4°C, blood pressure 126/77, and pulse oximetry was 97% on room air. There were numerous coalescing clusters of vesicular lesions in different stages of healing in a dense pattern over the patient's left arm (Figure 1.17.1). Likewise, there were scattered vesicular lesions over her right arm, back, chest, bilateral lower extremities, and face (Figure 1.17.2). Her neck was supple and she had no signs of meningismus.

Laboratory results revealed a white blood cell count of 4800 cell/mm^3 (neutrophils of 63%), hemoglobin of 13.1 g/dL, and a platelet count of 209, 000/mm^3. Serum creatinine was 1.45 mg/dL (range, 0.7–1.2 mg/dL), total bilirubin 0.4 mg/dL (range, 0.3–1.2 mg/dL), aspartate transaminase 20 U/L (range, 15–41 U/L), alanine aminotransferase 16 U/L (range, 14–54 U/L), and alkaline phosphatase 69 U/L (range, 32–91 U/L). Quantitative immunoglobulins (Igs) were as follows: IgG 565 mg/dL (700–1600 mg/dL), IgA 51 mg/dL (70–400 mg/dL), and IgM of 35 mg/dL (40–230 mg/dL). A chest radiograph revealed normal lung fields.

QUESTIONS

- What infectious etiologies should be considered to explain this patient's rash?

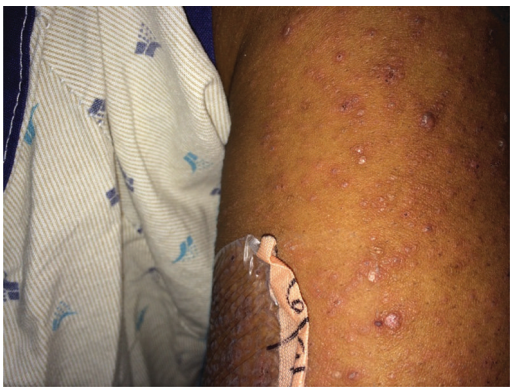


FIGURE 1.17.1: Left arm with vesicular lesions in different stages of healing.

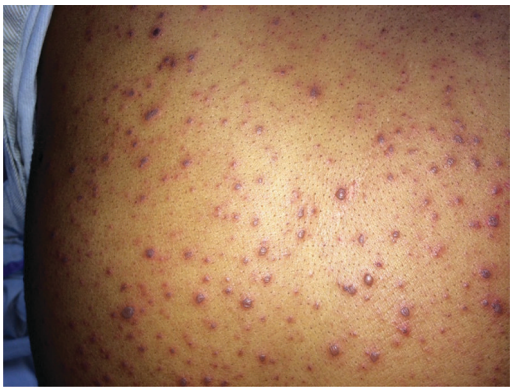


FIGURE 1.17.2: Back with vesicular lesions in different stages of healing.

- What diagnostic approach should be taken?
- What are the risk factors for development of this infection?

DIFFERENTIAL DIAGNOSIS

This is a disseminated painful vesicular rash in multiple stages of healing in an immunocompromised patient. In this context, disseminated herpes zoster should be at the top of the differential diagnosis. Other diagnostic considerations include primary infection with varicella-zoster virus (VZV), disseminated herpes simplex, drug eruption, enteroviruses including coxsackie virus, as well as rare eruptions such as rickettsialpox and monkeypox.

INITIAL MANAGEMENT

Given concern for disseminated herpes zoster, the patient was admitted to the hospital for additional diagnostic evaluation to confirm the suspected diagnosis, rule out visceral disease, and initiate empiric treatment with intravenous acyclovir.

ADDITIONAL DATA

On day one of hospitalization, slides of material obtained from the base of a fresh vesicle were sent for VZV direct fluorescent antibody (DFA) testing. Varicella-zoster virus DFA returned positive within a few hours, thus confirming the diagnosis of disseminated zoster virus. On day two of hospitalization, the patient developed fever of 38.4˚C and was noted to have multiple new vesicular lesions on her trunk, extremities, and right upper eyelid. Ophthalmology was consulted and ophthalmologic evaluation confirmed the presence of disseminated zoster involving the ophthalmic branch of the right trigeminal nerve, but there was no evidence of ocular involvement including keratoconjunctivitis, uveitis, or papillitis. She did not develop any mental status changes, shortness of breath, abdominal pain, elevated liver function tests, or other signs or symptoms of visceral dissemination.

Final Diagnosis: Disseminated herpes zoster virus

TREATMENT AND OUTCOMES

The patient was started on intravenous (IV) acyclovir 10 mg/kg every twelve hours (dose adjusted for the patient's renal insufficiency) on arrival to the hospital. The acute neuritis associated with her rash was managed with topical lidocaine, gabapentin, and opioid analgesics as needed. She was placed on contact and droplet precautions. The IV acyclovir was dose-adjusted for the patient's underlying renal insufficiency and was initiated along with IV fluids to prevent crystallization in the urine and worsening of her underlying nephropathy. By hospital day five, she had defervesced and the majority of her lesions were crusted, so she was discharged home with instructions to complete a three-week course of oral valacyclovir 1 gram twice daily (dose adjusted for the patient's renal insufficiency).

DISCUSSION

Immunocompromised patients are at risk for developing complicated herpes zoster infections characterized by cutaneous dissemination and/or visceral involvement. Cutaneous dissemination typically presents with numerous vesicular lesions in a generalized distribution affecting a number of dermatomes and crossing the midline. Visceral organ involvement often presents acutely in the form of a rapidly evolving pneumonia, hepatitis, or encephalitis. Disseminated VZV has been documented in patients with hematologic malignancies undergoing chemotherapy as well as in bone marrow and solid organ transplant recipients.

Risk Factors

Factors related to the host, underlying malignancy, antineoplastic therapies, and degree of immunosuppression affect the risk of VZV reactivation in oncology patients. Hematopoietic stem cell transplant (HSCT) in particular significantly increases the risk of both dermatomal and complicated zoster. The ten-year overall incidence of dermatomal zoster after HSCT is approximately 62%, whereas that of complicated zoster is approximately 30% (including central nervous system encephalitis, disseminated zoster, and visceral zoster) [1]. In particular, zoster can develop

in one-third of patients undergoing autologous stem cell transplant patients and approximately two-thirds of patients undergoing allogeneic stem cell transplant [2]. However, the estimated two-year cumulative incidence of VZV reactivation in allogeneic-HSCT is 34% and that of autologous-HSCT is 22% [2]. Other factors associated with increased risk of VZV reactivation are radiation before bone marrow transplant, VZV seropositive patients, absence of any antiviral prophylaxis (acyclovir/ganciclovir), suppressed lymphocyte subsets, substantial cell-mediated immune defects, and compromised humoral immune response [1, 3, 4].

In patients with multiple myeloma, the increased susceptibility to VZV reactivation results from the interplay between myeloma itself, antineoplastic therapies, and age- and disease-related complications. Cell-mediated immunity (CMI) plays a large role in the prevention of VZV reactivation, and bortezomib, a proteasome inhibitor with inhibitory effects on T-cell proliferation and dendritic cell function, has been associated with a significantly increased incidence of herpes zoster infection (13% with bortezomib versus 5% with dexamethasone) [5–8]. Treatment with alemtuzumab and other purine analogs also poses an increased risk of zoster, as does graft-versus-host disease (GVHD) treated with steroids.

Clinical Presentation

Primary infection occurs during childhood where the transmission occurs by droplet infection subsequently leading to infection involving the reticuloendothelial system. It becomes latent in the cranial nerve and dorsal root ganglia during primary infection and frequently reactivates with increasing age or immunosuppression [9]. More than 90% of adults are latently infected with VZV, so true primary infection (varicella-chicken pox) characterized by a diffuse maculopapular rash, vesicles in various stages of evolution, low-grade fever, and generalized malaise occurs primarily in pediatric patients.

The initial presentation of herpes zoster in immunocompromised hosts is similar to that seen in the immunocompetent host. Neuralgic pain in the involved dermatome often precedes the onset of a vesicular dermatomal rash by hours to a few days. Multidermatomal involvement is observed more frequently in bone marrow transplant recipients than in immunocompetent hosts [10]. Potential complications of herpes zoster include postherpetic neuralgia, cutaneous scarring, and bacterial superinfection of skin lesions.

Zoster sine herpete is a rare pain syndrome in which no cutaneous rash occurs but a segmental pain syndrome is transiently present and associated with serological evidence of varicella infection.

Herpes zoster ophthalmicus is linked to VZV reactivation in the trigeminal nerve and can result in blindness if not recognized in a timely fashion. Vesicular lesions on the tip of nose (Hutchinson's sign) are associated with an increased risk of herpes zoster ophthalmicus, and their presence warrants an urgent slip lamp examination.

The major otologic complication of VZV reactivations is Ramsay Hunt syndrome, which is characterized by painful vesicular lesions that appear in the external auditory canal along with hypoguesia involving the anterior two-thirds of the tongue and ipsilateral facial palsy. Facial paralysis in the absence of vesicles may be a sign of *zoster sine herpete*, which can be mistaken for Bell's palsy. Hematogenous dissemination to the eye can result in acute retinal necrosis and blindness. Approximately 15%–30% of bone marrow transplant patients who initially present with localized dermatomal zoster develop cutaneous dissemination, and rates of cutaneous dissemination are higher among those undergoing allogeneic HSCT recipients than in those undergoing autologous HSCT. Cutaneous dissemination is not associated with increased mortality but is associated with an increased risk of visceral infection such as VZV pneumonitis, hepatitis, pancreatitis, and/or meningoencephalitis. Studies in bone marrow transplant recipients have shown that approximately one third of HSCT recipients with dermatomal zoster and cutaneous dissemination subsequently develop visceral infection [11, 12]. Thus, it is important to obtain a chest radiograph and liver function tests in all immunocompromised patients presenting with cutaneous dissemination in order to document the presence or absence of visceral involvement.

A rare but potentially fatal manifestation of herpes zoster in the immunocompromised host is "abdominal zoster", in which patients present with severe abdominal pain that often precedes the appearance of the cutaneous rash by hours to days. Because the diagnosis of herpes zoster is not usually considered until the typical skin vesicles begin to appear, abdominal zoster can be associated with delays in diagnosis and poor outcomes despite the initiation of appropriate antiviral therapy [9, 13–15].

Diagnosis

The diagnosis of herpes zoster infection is usually a clinical one based on the dermatomal distribution

TABLE 1.17.1. COMPLICATIONS OF HERPES ZOSTER

Cutaneous	Cutaneous dissemination
	Bacterial superinfection
	Scarring
Neurologic	Postherpetic neuralgia
	Motor neuropathy
	Cranial neuritis
	Meningoencephalitis
	Transverse myelitis
Ophthalmic	Keratitis
	Iritis
	Retinitis
Visceral	Pneumonitis
	Hepatitis
	Pancreatitis

of vesicular lesions in different stages of healing with associated neuralgic pain, but additional diagnostic testing is recommended in cases of atypical rashes in immunocompromised hosts or if there is concern for visceral disease in an immunocompromised host without cutaneous lesions. Varicella-zoster virus can be isolated in culture from a swab of a fresh vesicular lesion or sterile body fluid, but culture techniques are insensitive, time consuming, and associated with a low yield compared with DFA testing and real-time polymerase chain reaction assays (PCR).

A rapid diagnosis can be made by using DFA testing on scrapings obtained from of the base of an unroofed, fresh vesicle. The DFA test is widely available and is associated with a rapid turnaround time [16]. Polymerase chain reaction is a useful technique that provides rapid and sensitive confirmation of VZV from clinical specimens obtained from active skin lesions and other body sites such as cerebrospinal fluid and bronchoalveolar lavage fluid. Serologic assays are helpful for determining patient susceptibility to VZV but are not typically useful in the diagnosis of acute infection.

Treatment

The widespread availability of safe and effective antiviral drugs has reduced the mortality associated with VZV infections in immunocompromised hosts [17]. Balfour et al [17] first demonstrated that IV acyclovir speeds viral clearance and halts disease progression when used in the treatment of localized or disseminated herpes zoster in immunocompromised patients in 1983. Subsequent studies in HSCT recipients have shown that acyclovir is effective not only in stimulating more rapid disease resolution but also in preventing and treating VZV dissemination [18, 19].

Oral therapy with either acyclovir (800 mg five times daily), valacyclovir (1000 mg three times daily), or famciclovir (500 mg three times daily) are all reasonable treatment options for less severely immunocompromised patients (e.g. autologous HSCT recipients) with localized herpes zoster. All agents are equally efficacious in accelerating healing and resolution of zoster-associated pain, but valacyclovir and famciclovir provide the additional benefit of reduced frequency of drug administration when compared with acyclovir.

Intravenous acyclovir is the therapy of choice for disseminated VZV, suspected visceral VZV, or localized herpes zoster in severely immunocompromised patients (e.g. allogeneic HSCT within four months of transplantation, allogeneic HSCT patients with GVHD, or any immunocompromised host requiring aggressive immunosuppression or antirejection therapy). In addition, immunocompromised patients presenting with herpes zoster involving the first division of the trigeminal nerve are at high risk for ocular complications (herpes zoster ophthalmicus). These patients should receive treatment with IV acyclovir and undergo evaluation by an ophthalmologist. The recommended dose of IV acyclovir is 10 mg/kg every eight hours, and this should be dose-adjusted for any underlying renal insufficiency. Treatment should be continued until clinical signs and

TABLE 1.17.2. TREATMENT OF HERPES ZOSTER

	Drug and Dose	**Duration**
Localized dermatomal cutaneous zoster (shingles)	Acyclovir 800 mg PO 5×/day* Famciclovir 500 mg PO TID* Valacyclovir 1 gram PO TID*	7–10 days
Disseminated cutaneous zoster or visceral disease	Acyclovir 10–15 mg/kg IV q8h* until clinical improvement is noted, then switch to one of the oral antiviral agents listed above	10–14 days or until signs and symptoms have resolved, whichever is longer

* Acyclovir, famciclovir, and valacyclovir require dose adjustments for renal impairment,

symptoms have resolved or for a minimum of ten to fourteen days, whichever is longer.

Resistance to acyclovir is rare in stem cell recipients but when clinically suspected or microbiologically documented, therapy should be changed to foscarnet for preemptive treatment.

Prognosis

Prompt diagnosis and initiation of effective antiviral therapy has been associated with a reduction in the mortality rate associated with VZV infection in immunocompromised hosts. Nonetheless, occasional deaths from disseminated VZV still occur.

The most common and challenging complication of herpes zoster infection is postherpetic neuralgia (PHN), which can be pronounced in immunocompromised patients (41%) [20]. Postherpetic neuralgia can last for several years and may reduce quality of life [2, 4]. Tricyclic antidepressants (nortriptyline and desipramine), selective serotonin and norepinephrine reuptake inhibitors (duloxetine, venlafaxine), calcium channel $\alpha_2\delta$ ligands (gabapentin, pregabalin), and topical lidocaine have demonstrated efficacy in pain control in PHN and peripheral neuropathy [21]. Oral opioid analgesics are considered as second-line agents [21].

Prevention

The two-year cumulative incidence of VZV reactivation is approximately 22% in patients receiving autologous stem cell transplant patients, with the majority (~95%) occurring within the first year [2]. Antiviral agents are used prophylactically for the prevention of VZV reactivation in seropositive VZV patients undergoing HSCT [22, 23]. It is interesting to note that acyclovir can also suppress the development of VZV-specific immunity. Thus, its administration for only six months after transplantation does not prevent zoster from occurring when treatment is stopped. Administration of low doses of acyclovir for one entire year after transplantation is effective and may eliminate most cases of posttransplantation zoster [23, 24]. Continuation of prophylaxis beyond one year is considered in patients with ongoing systemic immunosuppression [25].

TABLE 1.17.3. VZV PROPHYLAXIS IN CANCER PATIENTS [28, 29]

Overall Risk of VZV Reactivation	Disease/Therapy Examples	Antiviral Prophylaxis	Duration
Intermediate	• Autologous HSCT • Lymphoma • Multiple myeloma • CLL • Purine analog therapy (e.g. fludarabine)	Acyclovir 800 mg PO BID* (Preferred by IDSA) Valacyclovir 500 mg PO BID* (Alternative per IDSA) Famciclovir 250 mg PO BID*	Consider for at least 1 year after HSCT During neutropenia with aggressive lymphoma regimens Until 3 months after discontinuation of purine analog therapy
High	• Allogeneic HSCT • GVHD requiring steroid therapy • Proteasome inhibitor therapy (e.g. bortezomib) • Alemtuzumab therapy		Start with conditioning regimen for allogeneic HSCT and continue for 1 year Until resolution of severe GVHD Until discontinuation of proteasome inhibitor Until at least 2 months after discontinuation of alemtuzumab AND CD4 ≥200 cells/mm^3

Abbreviations: AMMI, Association of Medical Microbiology and Infectious Diseases Canada; ASBMT, American Society of Blood and Marrow Transplantation; CBMTG, Canadian Blood and Marrow Transplant Group; CDC, Centers for Disease Control and Prevention; CIBMTR, Center for International Blood and Marrow Transplant Research; CLL, chronic lymphocytic leukemia; EBMP, European Blood and Marrow Transplant Group; GVHD, graft-versus-host disease; HRSA, Health Resources and Services Administration; HSCT, hematopoietic stem cell transplant; IDSA, Infectious Disease Society of America; NMDP, National Marrow Donor Program; SHEA, Society for Healthcare Epidemiology of America; VZV, varicella-zoster virus.

*Acyclovir, famciclovir and valacyclovir require dose adjustments for renal impairment.

Adapted from the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for the Prevention and Treatment of Cancer-Related Infections as well as the Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients cosponsored by multiple groups including the CIBMTR, NMDP, EBMP, ASBMT, CBMTG, IDSA, SHEA, AMMI, CDC, and HRSA.

Varicella-zoster virus-seronegative family members, visitors, and healthcare workers should be vaccinated before being allowed direct contact with a HSCT recipient [24]. Stem cell transplant recipients requiring immunosuppressive therapy for longer than two years should receive either varicella zoster immune globulin (VZIG) within ninety-six hours after being exposed to either chickenpox or shingles or initiate antiviral therapy using acyclovir or valacyclovir, regardless of pre-transplant VZV serologies [24].

It has recently been shown that routine prophylaxis using acyclovir in patients with multiple myeloma receiving bortezomib, lenalidomide, or undergoing stem cell transplant (autologous/allogeneic) has been associated with a lower incidence of VZV infection [23, 26, 27]. Although antiviral prophylaxis is typically continued for one year after HSCT as mentioned above, there is no clear consensus regarding how long prophylaxis should be continued after completion of bortezomib, lenalidomide, alemtuzumab, or purine analogs such as fludarabine.

KEY POINTS

- Older age and ongoing immunosuppression are important predictors of herpes zoster.
- CMI plays an important role in the prevention of VZV reactivation.
- The diagnosis of herpes zoster is clinical based on the presence of vesicular lesions in different stages of healing, often in an atypical dermatomal distribution but sometimes disseminated.
- Confirmatory testing with either VZV DFA or PCR should be performed in cases of atypical rashes in immunocompromised hosts. Serum PCR testing can be performed if there is a concern for visceral disease in the absence of cutaneous lesions.
- Intravenous acyclovir is the therapy of choice for disseminated VZV, suspected visceral VZV, or localized herpes zoster in severely immunocompromised patients. Oral therapy with acyclovir, valacyclovir, or famciclovir is recommended for less severely immunocompromised patients with localized herpes zoster.
- Prophylactic oral acyclovir is recommended for one year after allogeneic (and some experts would advocate after autologous) HSCT to prevent recurrent VZV infection. Continued acyclovir prophylaxis should be considered in cases of ongoing immunosuppression after one year.
- Prophylaxis is also recommended in multiple myeloma patients receiving bortezomib or lenalidomide and in leukemia or lymphoma patients receiving alemtuzumab.

REFERENCES

1. Han CS, Miller W, Haake R, Weisdorf D. Varicella zoster infection after bone marrow transplantation: incidence, risk factors and complications. Bone Marrow Transplant. 1994;13:277.
2. Onozawa M, Hashino S, Haseyama Y, et al. Incidence and risk of postherpetic neuralgia after varicella zoster virus infection in hematopoietic cell transplantation recipients: Hokkaido Hematology Study Group. Biol Blood Marrow Transplant. 2009;15:724.
3. König C, Kleber M, Reinhardt H, et al. Incidence, risk factors, and implemented prophylaxis of varicella zoster virus infection, including complicated varicella zoster virus and herpes simplex virus infections, in lenalidomide-treated multiple myeloma patients. Ann Hematol. 2014;93:479.
4. Steer CB, Szer J, Sasadeusz J, et al. Varicella-zoster infection after allogeneic bone marrow transplantation: incidence, risk factors and prevention with low-dose aciclovir and ganciclovir. Bone Marrow Transplant. 2000;25:657.
5. Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol. 2008;26:4784.
6. Kröger N, Zabelina T, Ayuk F, et al. Bortezomib after dose-reduced allogeneic stem cell transplantation for multiple myeloma to enhance or maintain remission status. Exp Hematol. 2006;34:770.
7. Tong Y, Qian J, Li Y, et al. The high incidence of varicella herpes zoster with the use of bortezomib in 10 patients. Am J Hematol. 2007;82:403.
8. Wu KL, van Wieringen W, Vellenga E, et al. Analysis of the efficacy and toxicity of bortezomib for treatment of relapsed or refractory multiple myeloma in community practice. Haematologica 2005;90:996.
9. Gnann JW Jr. Varicella-zoster virus: atypical presentations and unusual complications. J Infect Dis. 2002;186:S91.
10. Atkinson K, Meyers JD, Storb R, et al. Varicella-zoster virus infection after marrow transplantation for aplastic anemia or leukemia. Transplantation 1980;29:4750.
11. Locksley RM, Flournoy N, Sullivan KM, Meyers JD. Infection with varicella-zoster virus after marrow transplantation. J Infec Dis. 1985;152:1172.
12. Schuchter LM, Wingard JR, Piantadosi S, et al. Herpes zoster infection after autologous bone marrow transplantation. Blood 1989;74:1424.

13. Yagi T, Karasuno T, Hasegawa T, et al. Acute abdomen without cutaneous signs of varicella zoster virus infection as a late complication of allogeneic bone marrow transplantation: importance of empiric therapy with acyclovir. Bone Marrow Transplant. 2000;25:1003.
14. Verdonck LF, Cornelissen JJ, Dekker AW, Rozenberg-Arska M. Acute abdominal pain as a presenting symptom of varicella-zoster virus infection in recipients of bone marrow transplants. Clin Infect Dis. 1993;16:190.
15. Rogers SY, Irving W, Harris A, Russell NH. Visceral varicella zoster infection after bone marrow transplantation without skin involvement and the use of PCR for diagnosis. Bone Marrow Transplant. 1995;15:805.
16. Drew W, Mintz L. Rapid diagnosis of varicella-zoster virus infection by direct immunofluorescence. Am J Clin Pathol. 1980;73:699.
17. Balfour HH Jr, Bean B, Laskin OL, et al. Acyclovir halts progression of herpes zoster in immunocompromised patients. N Eng J Med. 1983;308:1448.
18. Meyers JD, Wade JC, Shepp DH, Newton B. Acyclovir treatment of varicella-zoster virus infection in the compromised host. Transplantation 1984;37:571.
19. Shepp DH, Dandliker PS, Meyers JD. Treatment of varicella-zoster virus infection in severely immunocompromised patients. N Eng J Med. 1986;314:208.
20. Koc Y, Miller KB, Schenkein DP, et al. Varicella zoster virus infections following allogeneic bone marrow transplantation: frequency, risk factors, and clinical outcome. Biol Blood Marrow Transplant. 2000;6:44.
21. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132:237.
22. Shepp DH, Newton BA, Dandliker PS, et al. Oral acyclovir therapy for mucocutaneous herpes simplex virus infections in immunocompromised marrow transplant recipients. Ann Intern Med. 1985;102:783.
23. Truong Q, Veltri L, Kanate AS, et al. Impact of the duration of antiviral prophylaxis on rates of varicella-zoster virus reactivation disease in autologous hematopoietic cell transplantation recipients. Annal Hematol, 2014;93:677.
24. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Bone Marrow Transplant. 2009;44:453.
25. Erard V, Wald A, Corey L, et al. Use of long-term suppressive acyclovir after hematopoietic stem-cell transplantation: impact on herpes simplex virus (HSV) disease and drug-resistant HSV disease. J Infect Dis. 2007;196:266.
26. Fukushima T, Sato T, Nakamura T, et al. Daily 500 mg valacyclovir is effective for prevention of varicella zoster virus reactivation in patients with multiple myeloma treated with bortezomib. Anticancer Res. 2012;32:5437.
27. Minarik J, Pika T, Bacovsky J, et al. Low-dose acyclovir prophylaxis for bortezomib-induced herpes zoster in multiple myeloma patients. Br J Haematol. 2012;159:111.
28. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Bone Marrow Transplant. 2009;44:453.
29. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Prevention and Treatment of Catheter-Related Infections. Version 1.2014. Available at: http://www.nccn.org/professionals/physician_gls/PDF/infections.pdf. Accessed June 1, 2014.

1.18

Wounds in Cancer Patients: Watch for the Drugs!

PAVAN KUMAR TANDRA, MD AND NICOLE SHONKA, MD

CASE PRESENTATION

A 47-year-old male patient presented with right foot pain and associated swelling of his right leg during a routine follow up of an anaplastic astrocytoma diagnosed sixteen months earlier.

He reported that five weeks earlier, he developed a callus on the lateral side of his right foot. He soaked his foot in warm water for one hour at home, and he removed the callus himself using a knife. Over the last three weeks, he noted increased redness, swelling, sharp pain, and blister formation. When initially evaluated four weeks ago, there was a calloused area noted over the lateral mid foot bone with a scab in the center. No drainage, periwound fluctuance or bogginess was noted. The wound care nurse recommended Aquaphor ointment twice daily to feet and lower extremities to soften dry skin and calloused area. He did not notice expanding ulceration. He had pain in his foot and he was unable to weight bear. He denied any fever or systemic symptoms.

The diagnosis of brain tumor was made sixteen months earlier, when he experienced a grand mal seizure, and imaging revealed a left frontal, primarily noncontrast-enhancing tumor. He underwent total resection, and the pathology was consistent with grade III anaplastic astrocytoma with focal vascular endothelial changes suggestive of but not diagnostic of grade IV. One month later, he began concurrent chemoradiation therapy with temozolomide. Magnetic resonance imaging (MRI) and positron emission tomography scan performed nine months ago confirmed progressive disease. He began bevacizumab (BV) at 10 mg/kg intravenously q2 weeks approximately eight months prior to the current presentation. His last dose was four days before admission.

His past medical history was significant for neuroendocrine tumor of the pancreas, diabetes mellitus type II, hypertension, cholecystectomy, and gastroparesis of uncertain etiology with chronic abdominal pain requiring percutaneous endoscopic gastrostomy tube insertion. His surgical history consisted of distal pancreatectomy and splenectomy seven years ago.

At admission, his blood pressure was 145/81 mm mercury, pulse rate was 71 per minute, temperature was 36.6°C (oral), and respiratory rate was 16. His height was 1.829 meters, weight was 100 kg, and his SpO_2 was 94% on room air. His right foot was inflamed, tender, and expressed pus. The wound showed an area of cellulitis around it, and, when probed, the bone was palpable. His laboratory tests showed hemoglobin of 10.9 g/dL, mean corpuscular volume of 94.8 femtoliters, platelet count of 410 000/μL, and white blood cell count of 10 300/μL with a normal differential count. His absolute neutrophil count was 4400/μL. His C-reactive protein was 6.7 mg/L, and his erythrocyte sedimentation rate was 98 mm/hour.

QUESTIONS

- How do we manage a nonhealing ulcer in patients with cancer?
- Identify the risk factors for development of a foot ulcer in this patient?
- What issues we need to consider in treating underlying malignancy in future?

WORK UP

An MRI of the foot showed (1) osteomyelitis of the base of the fifth metatarsal and (2) a sinus tract extending from the plantar aspect of the foot to the base of the fifth metatarsal with adjacent soft tissue swelling. Wound culture grew group B streptococcus and methicillin-resistant *Staphylococcus aureus*. His ankle brachial pressure indices were normal bilaterally.

Final Diagnosis: Osteomyelitis of the right fifth toe at the site of excised callus

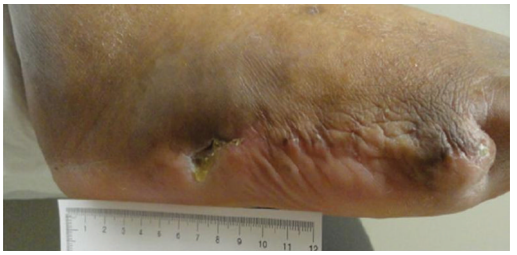


FIGURE 1.18.1: Patient's healed wound: at the time of re initiation of Bevacizumab.

TREATMENT COURSE AND OUTCOME

He was started on vancomycin and piperacillin-tazobactam for suspected foot cellulitis and osteomyelitis. His right fifth toe and metatarsal was amputated five days later, and the margins appeared viable. The bone culture grew vancomycin-susceptible *Enterococcus fecalis*. The pathology was consistent with osteomyelitis. Piperacillin-tazobactam was discontinued, and a six-week course of vancomycin was recommended because it was resistant to ampicillin. Bevacizumab was withheld to optimize wound healing.

Due to erratic serum vancomycin levels secondary to his worsening renal insufficiency, antibiotic treatment was changed to daptomycin after four weeks. A brain MRI at that time showed his astrocytoma to be stable. He completed a total of six weeks of antibiotics (vancomycin for four weeks and daptomycin for two weeks) for osteomyelitis.

He required continued wound care over the next several months because his wound healed slowly. Decision was made to hold BV until his astrocytoma progressed. It took five months for the wound to heal completely.

An MRI six months later showed mild increased enhancement peripherally along left frontal lobe resection cavity extending into the genu of corpus callosum consistent with recurrent glioma. At that time, BV was restarted. As of now, he continues on BV without further wound complications.

DISCUSSION

Pathogenesis

Bevacizumab is a humanized monoclonal antibody that selectively binds vascular endothelial

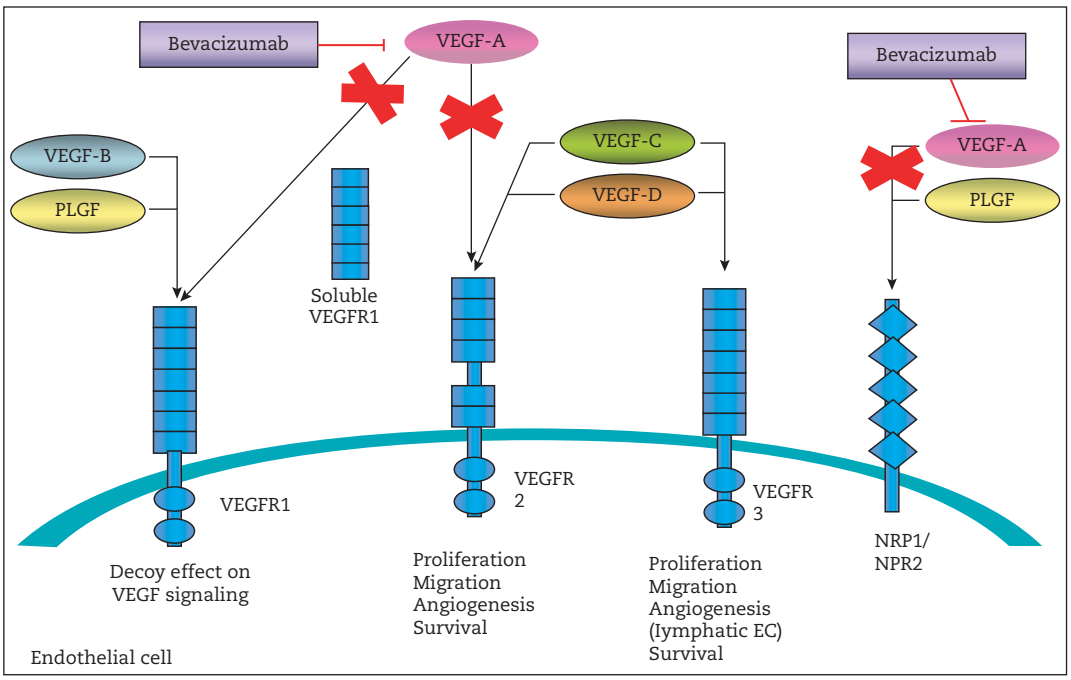


FIGURE 1.18.2: With permission. Shonka N, Gilbert M. Molecularly Targeted Therapy for Malignant Brain Tumors "http://www.cyberrounds.com/" www.cyberrounds.com 2010. http://www.cyberounds.com/cmecontent/art467.html. Mechanism of action of Bevacizumab.

VEGF: Vascular Endothelial Growth Factor ; VEGFR: Vascular Endothelial Growth Factor Receptor ;PLGF: Placental Growth Factor; NRP: Neuropilin

TABLE 1.18.1. WOUND HEALING AND BEVACIZUMAB[#] – CLINICAL TRIALS

Cancer	Bibliography reference number	Study Type (Number of Patients	Timing	Interval	WHC Rate
Glioblastoma multiforme	Friedman et al (13)	Prospective (84)	Adjuvant	Not reported	6%
	Clark et al (14)	Retrospective (23 neoadjuvant and 18 adjuvant)	Neoadjuvant Adjuvant	30 days (median) 43 days (median)	35% 6%
	Gutin et al (15)	Nonrandomized prospective (25)	Adjuvant	28 days	4%
Metastatic colorectal carcinoma	Scappaticci et al (4)	Retrospective (75 neoadjuvant and 230 adjuvant)	Neoadjuvant Adjuvant	<60 days 28–60 days	13% 1.3%
	Kozloff et al (16)	Prospective (521)	Neoadjuvant	Variable no.	4.4%
	Allegra et al (17)	Prospective (1326)	Adjuvant	46 days (median)	1.7%
Breast cancer	Miles et al (18)	Prospective (499)	Neoadjuvant	Not reported	0.4%
Advanced renal cell carcinoma	Escudier et al* (19)	Prospective (337)	Adjuvant	Not reported	1%

[#] Bevacizumab-surgery interval and WHC(Wound healing complications) rate: 0 to 13 days (9.7%),14 to 27 days (3.2%) 28-41 days (3.0%),48 to 55 days (5.9%) and >56 days(2.2%)

[*]Study did not report what proportion of patients receiving Bevacizumab – containing chemotherapy regimens underwent surgery.
This table was adapted from "Bevacizumab and Wound- Healing Complications , Mechanisms of action, Clinical Evidence, and Management Recommendations for the Plastic Surgeon" by Ketan Sharma etal (3)

growth factor (VEGF)-A to prevent its interaction with surface VEGF receptors (VEGFRs) thereby inhibiting VEGFR signaling [1] and inhibiting angiogenesis. The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue). It was approved by the US Food and Drug Administration for the treatment of metastatic colon, kidney, ovary, lung, and grade IV gliomas. Bevacizumab carries a specific adverse reaction profile including hypertension and proteinuria and risk of chronic kidney disease, hemorrhage, gastrointestinal perforation, venous and arterial thromboembolic events, reversible posterior leukoencephalopathy, and impaired wound healing [2, 3]. Activated platelets, monocytes, and fibroblasts release VEGF. Vascular endothelial growth factor plays multiple roles in wound healing. It helps recruit fibroblasts, macrophages, and endothelial cells. It also increases microvascular permeability, allowing granulocytes to clear bacteria and macrophages to clear wound debris. Fibroblasts deposit collagens types I and III to form new extracellular matrix [3]. As a consequence of these multiple effects, BV can inhibit wound healing.

Clinical Evidence

In one study of patients with colorectal cancer who underwent emergent surgery, wound healing complications occurred in 13% of patients who had BV and chemotherapy compared with 3.4% after chemotherapy alone within sixty days of surgery [4]. The frequency of wound complications of all grades in patients with glioblastoma treated with BV ranges from 0% to 6% [5–8]. In one retrospective review, patients receiving preoperative BV developed significant wound healing complications (35%) compared with non-BV-treated patients (10%; $P = .004$) [9].

Many cancer patients require placement of venous access ports, and the effect of BV on healing tissue is a common clinical issue. In one study, wound dehiscence was significantly higher in those patients receiving BV within ten days of port placement [10]. In a retrospective analysis, patients treated with BV within one day of port placement had a 2.4% absolute risk of wound dehiscence requiring removal of the port [4]. In another study, the risk of wound dehiscence was inversely proportional to the interval between BV therapy and the port placement, with significantly higher risk seen when the interval was less than fourteen days [11].

Management

The optimal interval from interruption of VEGF blockers has not been determined. It depends on various factors including the type of surgery and, more importantly, the half-life of these agents. The long half-life of BV of twenty days (range, eleven to fifty days) [1] results in a more extended risk of wound healing compared with

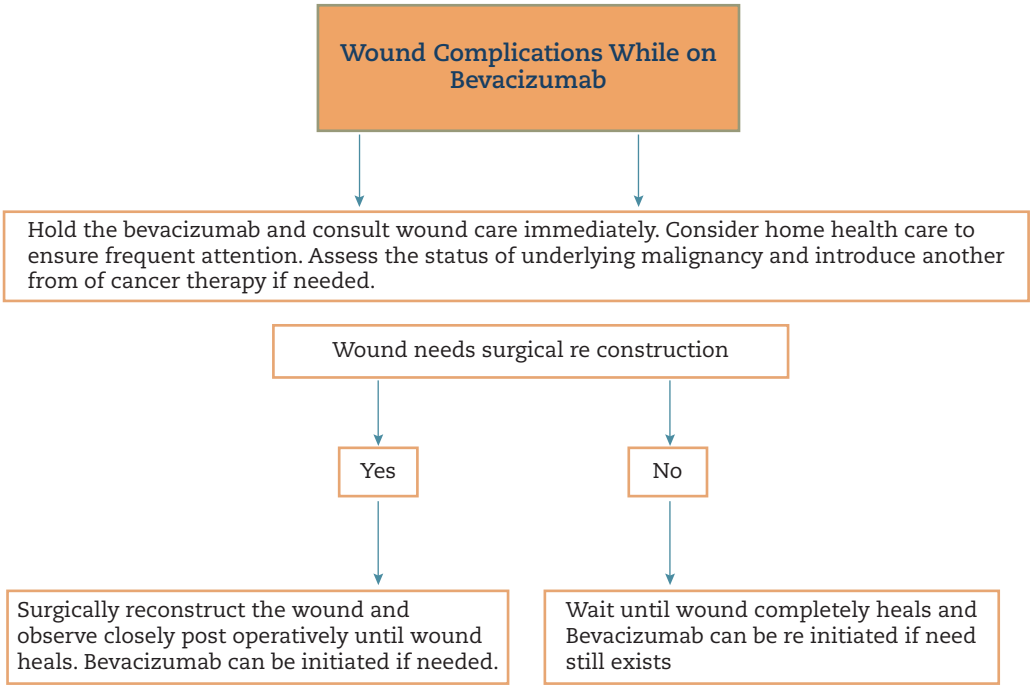


FIGURE 1.18.3: Wound care measures: regular cleaning, appropriate dressing changes, negative pressure vacuum assisted wound therapy, wound cultures if wound looks infected and appropriate antibiotic therapy for any evidence of infection, surgical debridement for any necrosis.

VEGF tyrosine kinase inhibitors (TKIs), which have a short half-life. Sunitinib (Sutent), sorafenib (Nexavar), pazopanib (Votrient), and imatinib (Gleevec) are some of the TKIs used in oncology. Clinicians should also consider patients' other comorbidities that can also impair wound healing such as collagen disorders, vitamin deficiencies, and chronic diseases such as peripheral arterial disease, peripheral neuropathy, and diabetes. A multidisciplinary management team is needed in complex patients.

It is currently recommended that the BV should not be given for twenty-eight days before and after elective surgery (sixty-day window for liver surgery) [4, 12], should not be initiated until all wounds are fully healed, and permanently discontinued for wound dehiscence. In cases such as this one, the permanent discontinuation of BV without rechallenge may not be reasonable. We propose a simplified management algorithm in managing wound complications in patients taking VEGF monoclonal antibodies or TKIs.

KEY POINTS

- Wound-healing complications of VEGF and VEGFR targeting monoclonal antibodies and TKIs are diverse and include delayed primary wound closure, impaired wound healing, prolonged seromas, wound dehiscence, bowel perforation, fistula, abscesses, and hemorrhage.
- Current guidelines are empiric and recommend that BV be withheld for four to six weeks before elective surgery. Small molecule TKIs have short half-lives and typically a short "wash out" period of one week is sufficient.
- Advise patients to refrain from self-surgery, particularly when they are receiving these agents.

REFERENCES

1. Shih T, Lindley C. Bevacizumab: an angiogenesis inhibitor for the treatment of solid malignancies. Clin Ther. 2006;28:1779.
2. Kamba T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. Br J Cancer 2007;96:1788.
3. Sharma K, Marcus JR. Bevacizumab and wound-healing complications: mechanisms of action, clinical evidence, and management recommendations for the plastic surgeon. Ann Plast Surg. 2013;71:434.
4. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in

metastatic colorectal cancer patients treated with bevacizumab. J Surg Oncol. 2005;91:173.
5. Lai A, Filka E, McGibbon B, et al. Phase II pilot study of bevacizumab in combination with temozolomide and regional radiation therapy for up-front treatment of patients with newly diagnosed glioblastoma multiforme: interim analysis of safety and tolerability. Int J Radiat Oncol Biol Phys. 2008;71:1372.
6. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009;27:4733.
7. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol. 2007;25:4722.
8. Raizer JJ, Grimm S, Chamberlain MC, et al. A phase 2 trial of single-agent bevacizumab given in an every-3-week schedule for patients with recurrent high-grade gliomas. Cancer 2010; 116:5297.
9. Clark AJ, Butowski NA, Chang SM, et al. Impact of bevacizumab chemotherapy on craniotomy wound healing. J Neurosurg. 2011;114:1609.
10. Zawacki WJ, Walker TG, DeVasher E, et al. Wound dehiscence or failure to heal following venous access port placement in patients receiving bevacizumab therapy. J Vasc Interv Radiol. 2009;20:62.
11. Erinjeri JP, Fong AJ, Kemeny NE, et al. Timing of administration of bevacizumab chemotherapy affects wound healing after chest wall port placement. Cancer 2011;117:1296.
12. Avastin(bevacizumab) [package insert]. San Francisco, CA: Genentech Inc; 2008.

1.19

The Dangers of Dirt: Pulmonary Infiltrates and Skin Ulcers in a Farmer

PAUL J. DEZIEL, PA-C AND RAYMUND R. RAZONABLE, MD

CASE PRESENTATION

A 62-year-old man with a six-month history of myelodysplastic syndrome (MDS) with refractory cytopenias and multilineage dysplasia was referred to our hospital because of fever, cough, and ulcerative skin lesions. His MDS did not respond to initial treatment with prednisone and he was recently started on decitabine. He completed the second five-day cycle of decitabine chemotherapy three weeks before the onset of his current symptoms. He developed severe chemotherapy-associated neutropenia during the first and second cycles of decitabine and was receiving levofloxacin and acyclovir prophylaxis.

The patient works as a farmer in Indiana. Two weeks before his admission, while neutropenic, he sustained several lacerations on his left arm, right index finger, and neck while working at grain bins where corn and soybeans were kept. The skin lacerations did not heal, and during the following week they progressed into weepy nonhealing ulcerations. His local physician started him empirically on oral amoxicillin-clavulanic acid but with no clinical improvement. Three days ago, he started to complain of cough productive of yellowish sputum. He also reported low-grade fever during the day prior to his admission.

On physical examination, he had a temperature of 38°C, blood pressure of 119/62 mmHg, heart rate of 75 beats/minute, and respiratory rate of 24/minute. He looked chronically ill with wasting and pallor. He had no oral lesions. His lung examination showed scattered crackles bilaterally. Heart was without murmur. Skin examination demonstrated multiple areas of black eschar over his left neck, left forearm, right hand, and right index finger.

His peripheral white blood cell count was 0.9×10^9 /L (with 2% neutrophils). He had hemoglobin of 7.6 g/dL, hematocrit of 22.0 %, and platelet count of 8000/mm^3. Serum creatinine was 1.0 mg/dL. Serum electrolytes and liver enzymes were normal. A chest x-ray showed right lung haziness (Figure 1.19.1), which corresponded to the chest computed tomography (CT) scan finding of dense right upper and middle lobe consolidation with air-bronchograms and ground-glass opacification (Figure 1.19.2). A survey of his chest CT scan showed multiple smaller nodular lesions scattered bilaterally.

QUESTIONS

- What are the most common infections that should be considered in this patient?
- What are the risk factors for this infection?
- How would you proceed with establishing a definitive diagnosis?
- What are the treatment regimens available for this infection?
- How do you prevent this infection?

DIFFERENTIAL DIAGNOSIS

Infection is the most likely cause of this clinical syndrome consisting of fever, productive cough,

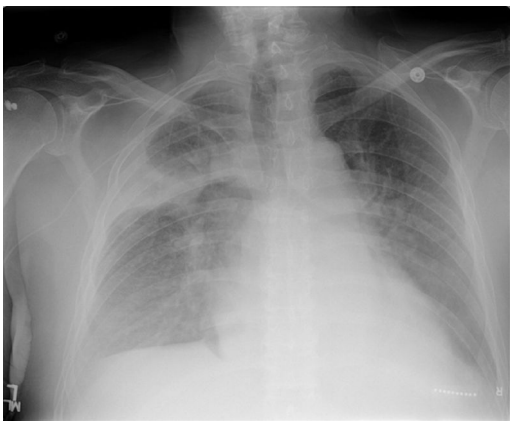


FIGURE 1.19.1: Chest radiograph shows infiltrates in the right lung fields.

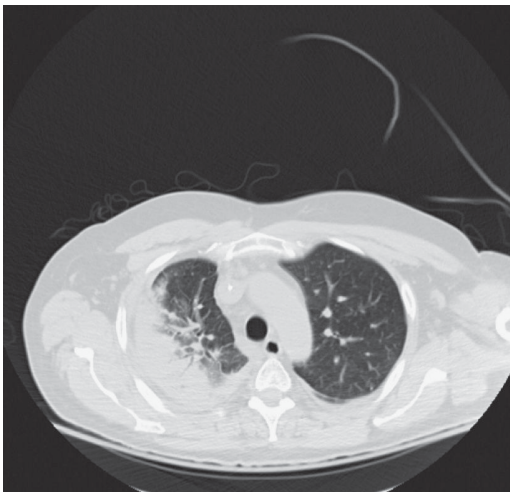


FIGURE 1.19.2: CT scan of the chest shows ground-glass opacities and consolidation with air-bronchogram.

pulmonary nodules, and skin lesions in the setting of refractory MDS with prolonged and profound neutropenia and pancytopenia. Risk factors for infection in this immunocompromised patient include underlying hematologic malignancy (refractory MDS), prolonged and profound neutropenia, lymphopenia, use of broad-spectrum antimicrobial therapy (levofloxacin), and chemotherapy including corticosteroids and decitabine. Among the pathogens that are most likely to cause this clinical syndrome are fungi (such as *Aspergillus* species, *Mucor* species, *Fusarium* species, *Scedosporium* species, and other mycelial fungi, and some endemic fungi such as *Histoplasma capsulatum*, and *Blastomyces dermatitidis*) and atypical bacteria (such as *Nocardia* species and members of the nontuberculous mycobacteria). Many of these pathogens are ubiquitous in the environment, and the patient most likely acquired the infection during the course of his farming activities. Notably, the onset of his clinical illness coincided with him working at grain bins where he had kept corn and soybean. Fungal pathogens such as *Aspergillus* species are especially commonly encountered with farming activities, including working in moist grain storage bins, and should be considered highly likely in this case. However, several other mycelial fungi can cause invasive infections that are indistinguishable from invasive aspergillosis on clinical and radiographic findings alone. These include members of the *Mucorales* group, *Fusarium* species, and *Scedosporium* species. The major risk factors for these invasive fungal infections are similar to those of invasive aspergillosis. Hence, the definitive microbiologic diagnosis of this infection will require culture of clinical samples.

ADDITIONAL DATA

Serum galactomannan antigen index value was 4 (negative, <0.5), whereas serum β-D-glucan assay was >500 pg/mL (negative, <60 pg/mL). Skin biopsy was sent for histopathology and culture. A flexible diagnostic bronchoscopy was performed with bronchoalveolar lavage (BAL) from the right upper lobe. Because of profound thrombocytopenia, transbronchial biopsy was deemed too risky and was not performed. Culture of the BAL fluid is shown in Figure 1.19.3, and stain of the culture is shown in Figure 1.19.4. The offending pathogen was identified as *Aspergillus fumigatus*.

Final Diagnosis: Multifocal invasive aspergillosis with pulmonary and skin involvement

TREATMENT AND OUTCOME

Upon admission, there was a high clinical suspicion for invasive fungal infection, and the patient was started on a combination of intravenous liposomal amphotericin B and voriconazole. Due to progressive necrosis, the right index finger required surgical amputation. The histopathology of the amputated index finger demonstrated fungal structures suggestive of invasive aspergillosis. He also underwent debridement of necrotic skin ulcers in his right hand and left forearm.

Perioperatively, the patient developed right middle cerebral artery infarction that presented clinically with left facial droop and left arm weakness. A magnetic resonance image of the brain showed multifocal cerebral embolic infarcts in multiple vascular territories including bilateral frontal lobes and left cerebellum. Transesophageal echocardiogram did not reveal any endovascular lesions.

FIGURE 1.19.3: 2-day old plate morphology of *Aspergillus fumigatus* on inhibitory mold agar.

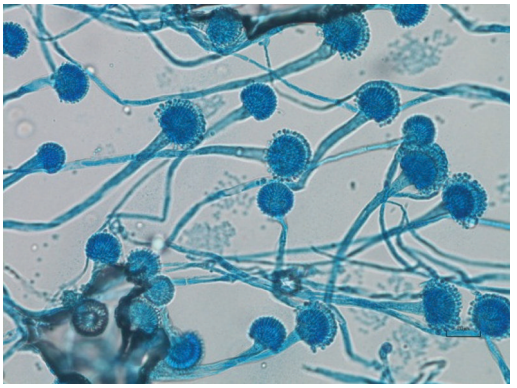


FIGURE 1.19.4: Tape preparation of fungal culture showing *Aspergillus fumigatus.*

After the identification of *A fumigatus* and the availability of its antifungal susceptibility pattern, which demonstrated susceptibility to voriconazole, liposomal amphotericin B was later discontinued. Three weeks into oral voriconazole treatment, a dense right lung consolidation persisted, albeit with radiographic improvement compared with baseline imaging. His skin lesions started to improve. He is currently maintained on oral voriconazole, with serum trough drug levels measured at 3.6 mcg/mL. He is undergoing aggressive physical rehabilitation, although his overall prognosis is poor due to underlying refractory MDS.

DISCUSSION

Aspergillus species causes serious and potentially life-threatening opportunistic fungal infection in patients with hematologic malignancy. *Aspergillus* species are ubiquitous in nature, and inhalation of fungal spores into the sinuses and the lungs occurs commonly [1]. However, inhalation of spores does not have any significant untoward consequence in healthy individuals, because pulmonary macrophages and neutrophils ensure clearance of inhaled pathogen. In patients with compromised immunity, however, *Aspergillus* species can lead to invasive disease. The most common site of involvement are the lungs and the sinuses, but the infection can locally spread or potentially disseminate to extrapulmonary sites including the brain and other parts of the body. *Aspergillus fumigatus* is the most commonly encountered species causing invasive disease, with *Aspergillus flavus, Aspergillus niger*, and *Aspergillus terreus* as less common pathogens [2].

Aspergillus species is the most common invasive fungal infection in patients with hematological malignancies, and it has surpassed *Candida* spp in the current era of routine fluconazole prophylaxis [3]. The estimated incidence of invasive aspergillosis is between 5% and 10% in patients with acute myelogenous leukemia, with the rates varying depending on the immune status of the individual and other risk factors.

Risk Factors

The risk factors for invasive aspergillosis in patients with cancer are (1) severe and prolonged neutropenia and (2) receipt of glucocorticoids and chemotherapy that impair cellular immunity [1]. The risk of invasive aspergillosis increases directly with the duration of neutropenia (more than fourteen days of persistent neutropenia) and the severity of neutropenia [4]. Neutropenia of $<0.5 \times 10^9$/L for a duration longer than ten days is one of the major host factors that predispose to invasive fungal infection [4]. Among the underlying malignancies, those with acute myelogenous leukemia and refractory MDS, like the patient discussed in this chapter, are at highest risk. Receipt of an allogeneic hematopoietic stem cell transplant is also a population at high risk of invasive fungal disease. The risk is lower among patients with chronic leukemia, lymphomas, and multiple myeloma. The number of cycles of chemotherapy and the number of chemotherapeutic agents is directly correlated with the risk of invasive aspergillosis, and it is especially increased with the use of agents that suppress T-cell immunity such as glucocorticoids, antithymocyte globulin, alemtuzumab, fludarabine, and cladribine. Patients with prior history of aspergillosis are also at higher risk of recurrent disease. The amount of airway exposure to the fungus is also directly associated with the risk of invasive aspergillosis. The classic examples of these types of high-burden exposure are in the setting of construction and farming. Our patient possessed many of the risk factors including prolonged and profound neutropenia, refractory MDS, multiple cycles of chemotherapy and use of corticosteroids, and high-burden exposure such as his farming activities. More recently, mutations in innate immune genes, such as Toll-like receptors and mannose binding lectin, have been described as risk factors for invasive fungal disease in patients with hematologic malignancies [5, 6].

Diagnosis

The diagnosis of invasive aspergillosis is based upon the demonstration of the organism in an individual at risk of disease and who presents with compatible clinical symptoms [4]. Radiographic

imaging is an essential component in the evaluation of patients with suspected invasive aspergillosis, with chest radiographs and CT scans as the most commonly used modalities. Chest x-ray is not very sensitive for detecting the early stages of invasive pulmonary aspergillosis, and CT scan may assist in this setting when invasive aspergillosis is clinically suspected [7, 8]. The type of radiographic abnormalities in invasive aspergillosis vary widely, depending on the host and the time of clinical presentation, from single to multiple nodules, infiltrates, consolidation, and other opacities with or without cavitation. Aspergillosis is classically associated with the halo sign, which is a lung nodule surrounded by an area of hypoattenuation. The nodule may eventually cavitate to form the air-crescent sign (Figure 1.19.5). Computed tomgraphy scans of the sinuses, the abdomen, and the brain may also be performed, depending on the clinical presentation of the patients [9].

The fungus can be demonstrated by direct examination of clinical specimens, such as sputum, BAL fluid, other respiratory secretions, or cytology preparations. With calcofluor white or Gomori methenamine silver stains, *Aspergillus* species appear as septated hyaline hyphae with dichotomous 45° acute-angle branching. *Aspergillus* species grow rapidly in culture, which will allow for confirmation of its genus and species and will allow performance of antifungal susceptibility testing [10].

Because *Aspergillus* species are frequently inhaled into the airways, its culture isolation from the respiratory tract (e.g. sputum or BAL) does not necessarily indicate clinical disease. To provide definitive evidence of invasive aspergillosis, one should ideally demonstrate hyphal elements in tissue biopsy. *Aspergillus* species can be observed on biopsy specimens stained with Gomori methenamine silver or periodic acid-Schiff staining as septated hyaline hyphae with dichotomous acute-angle branching. The histopathology will also demonstrate vascular invasion resulting in infarction and tissue necrosis. However, biopsy is not always performed because many patients at risk of fungal disease have other comorbidities (such as thrombocytopenia) that heighten their risk of complications from transbronchial biopsies. Such was the case in this patient, where transbronchial biopsy was deemed too risky due to severe thrombocytopenia. The invasive nature of the infection was later confirmed with histopathology and culture of the amputated index finger. In the absence of such histopathologic evidence, culture of *Aspergillus* species from respiratory specimens generally provides adequate evidence for invasive aspergillosis in patients with risk factors and clinical and radiographic features suggestive of invasive aspergillosis [4].

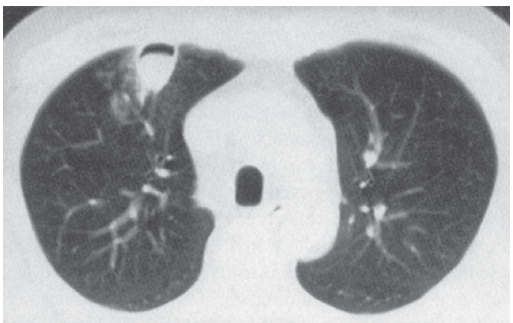


FIGURE 1.19.5: Air crescent sign of invasive pulmonary aspergillosis.

Detection of biomarkers, such as galactomannan and 1,3-β-D-glucan, in the serum (and other clinical specimens) have emerged as adjunctive tools for the diagnosis of invasive aspergillosis [11, 12]. Galactomannan is a major polysaccharide component of *Aspergillus* species and can be detected in the serum, BAL fluid, and other clinical specimens (such as cerebrospinal fluid) of patients with invasive aspergillosis. The sensitivity of serum and BAL galactomannan testing varied widely depending on the patient population and the severity of clinical disease. The sensitivity is better among high-risk patients with established disease. The sensitivity of serum galactomannan test for the diagnosis of invasive aspergillosis is also reduced with concurrent antifungal therapy [13]. Hence, a single negative serum galactomannan test does not exclude the diagnosis of invasive aspergillosis. Indeed, serial galactomannan determination is recommended when patients are considered at high risk of invasive fungal disease. False-positive galactomannan results have been notably reported with the use of some β-lactam antibiotics, such as piperacillin-tazobactam (although this is no longer observed with current formulations), and with infections with other fungi such as *Fusarium* species, *Penicillium* species, and *H capsulatum* [14]. The 1,3 β-D-glucan is a cell wall component of many fungi, and its detection in the blood has also been used as an adjunct for the diagnosis of invasive fungal disease including aspergillosis [15–17]. Because 1,3-β-D-glucan is present in many fungi, it is not specific for *Aspergillus* species and can be detected in cases of other fungal infection such as invasive candidiasis and *Pneumocystis jiroveci* infections. Detection of *Aspergillus* species DNA in clinical

specimens by polymerase chain reaction is also emerging as another adjunctive tool but with varied sensitivity and specificity.

Depending on the strength of the evidence, the diagnosis of invasive aspergillosis is classified into proven, probable, or possible. This classification is recommended to ensure consistency in clinical and epidemiological studies, but it does not have any effect on treatment recommendations [4]. All patients with suspected invasive aspergillosis should be initiated on treatment as soon as possible in order to reduce its significant morbidity and mortality, regardless of whether it is a proven, probable, or possible diagnosis [4].

Treatment

Treatment of invasive aspergillosis should involve the use of antifungal drugs, reduction in iatrogenic immunosuppression, if possible, and occasionally surgical debulking or excision of infected sites [18, 19]. Three classes of antifungal agents are available for treatment of invasive aspergillosis: the polyenes, azoles, and echinocandins (Table 1.19.1). However, the two drugs specifically approved by the US Food and Drug Administration for the primary treatment of invasive aspergillosis are voriconazole and amphotericin B deoxycholate. The duration of antifungal treatment should be individualized based on the disease severity and the immune status of the host, and it should be continued until all evidence of clinical disease has resolved.

Voriconazole is the preferred drug for the initial treatment for invasive aspergillosis. Clinical trials have demonstrated that voriconazole is superior for treatment of invasive aspergillosis compared with amphotericin B deoxycholate [20]. In an open-label, unblinded clinical trial of patients including those with hematologic malignancies, treatment with voriconazole resulted in higher rates of clinical response and lower rates of adverse effects and mortality, compared with amphotericin B deoxycholate [20]. This clinical trial provided support for the use of voriconazole as initial primary therapy for invasive aspergillosis [20]. There have been no large controlled trials comparing voriconazole with lipid formulations of amphotericin B. Serum voriconazole concentration should be measured at day five to seven of treatment to ensure therapeutic levels [21]. The recommended serum voriconazole trough concentrations is >1 to <5.5 mcg/mL. Voriconazole use is associated with visual complaints (in up to 18% of patients), neurologic symptoms (in up to 3.0% of patients), and liver toxicities (in up to 20% of patients); these generally resolve with discontinuation of therapy.

Amphotericin B deoxycholate and its lipid preparations (liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B cholesteryl sulfate complex) remain as alternatives for the treatment of invasive aspergillosis [22]. They are indicated mainly for patients with invasive aspergillosis who are intolerant to voriconazole. Amphotericin B is also recommended when coinfection with *Mucor* species is suspected (because voriconazole is not active against *Mucor* species), and it is also recommended in patients who developed breakthrough aspergillosis during voriconazole prophylaxis. Nephrotoxicity is the primary adverse effect related to amphotericin B deoxycholate. The lipid formulations of amphotericin B are associated with lower risk for renal toxicity and have been the formulations most often used for treatment (even if not licensed for primary treatment of invasive aspergillosis).

Although voriconazole monotherapy is recommended by the Infectious Disease Society of America and the American Thoracic Society for the primary treatment of invasive aspergillosis, there is increasing use of combination therapy with voriconazole and an echinocandin (or amphotericin B) [23–26]. Combination therapy is especially used as initial therapy in cancer patients with severe fungal disease and prior to the availability of antifungal susceptibility pattern. There is some anecdotal evidence from small clinical trials that combination therapy with liposomal amphotericin B and caspofungin was more effective than monotherapy with liposomal amphotericin B. Combination therapy is also used as salvage treatment of invasive aspergillosis nonresponsive to initial treatment with voriconazole or amphotericin B [27].

Monotherapy with nonapproved drugs, such as posaconazole and echinocandins (caspofungin, micafungin, and anidulafungin), is not currently recommended as first-line treatment of invasive aspergillosis. These drugs are often used as part of combination therapy (as discussed above) or as salvage treatment in patients who are not responsive to standard voriconazole or amphotericin B treatment. Lipid amphotericin B formulations, itraconazole, posaconazole, and caspofungin are licensed for salvage treatment of invasive aspergillosis [28]. In an open-label clinical trial for the treatment of invasive aspergillosis in patients intolerant to conventional therapy, posaconazole treatment was better compared with a control group of patients who received licensed antifungal

TABLE 1.19.1. ANTIFUNGAL DRUGS FOR THE TREATMENT OF INVASIVE ASPERGILLOSIS

Drug	Dose	Route	Indications	Class	Selected Adverse Effects	Other Comments
Preferred Drugs						
Voriconazole	Loading dose of 6 mg/kg q12hr for 1 day, then 4 mg/kg q12hr	IV	Primary treatment of invasive aspergillosis in patients 12 yrs of age and older	Triazole	Photosensitivity Visual disturbances Hallucinations Hyperfluorosis and periostitis	Measure drug level at day 5–7 of treatment. Drug-drug interactions.
	200 mg q12 hr	PO	Primary treatment of invasive aspergillosis in patients 12 yrs of age and older	Triazole	Photosensitivity Visual disturbances Hallucinations Hyperfluorosis and periostitis	Should be taken 1 hour before meals. Measure drug level at day 5–7 of treatment. Drug-drug interactions.
Amphotericin-B deoxycholate (AMB-D)	0.5–1.0 mg/kg per day	IV	Life-threatening fungal infections including *Aspergillus*	Polyene	Nephrotoxicity Fever and infusion reactions Hypotension Headache Muscle and joint pains	Maximum dose is 1.5 mg/kg per day. Avoid rapid infusions. Manage electrolyte abnormalities. Adjust dose according to renal function.
Lipid formulations of Amphotericin-B (ABCD, LAMB, ABLC)	3–6 mg/kg per day	IV	Fungal infection, systemic Fungal infection, empirical Salvage treatment of invasive aspergillosis	Polyene	Nephrotoxicity Infusion reactions Electrolyte abnormalities	Less nephrotoxicity then AMB-D. Avoid rapid infusions. Manage electrolyte abnormalities. Adjust dose according to renal function.
Alternative Drugs						
Posaconazole	Suspension 200 mg 4 times daily or 400 mg twice daily	PO	No FDA indication for primary treatment of invasive aspergillosis Off-label use—salvage treatment of invasive *Aspergillosis*	Triazole	Peripheral edema Diarrhea Rash Hyperbilirubinemia Increased ALT	Needs to be taken with meals of high fatty content to aid absorption. Monitor drug levels. Drug-drug interactions.
	Extended release tablet 300 mg twice daily on day one, then 300 mg once daily	PO	No FDA indication for primary treatment of invasive aspergillosis Off-label use—salvage treatment of invasive *Aspergillosis*	Triazole	Peripheral edema Diarrhea Rash Hyperbilirubinemia Liver function abnormalities	Taken with meals, but high fatty content is not necessary. More stable absorption compared with suspension. Monitor drug levels. Drug-drug interactions.

(*continued*)

TABLE 1.19.1. (CONTINUED)

Drug	Dose	Route	Indications	Class	Selected Adverse Effects	Other Comments
Caspofungin	70 mg loading dose then 50 mg daily	IV	Salvage therapy of invasive aspergillosis	Echinocandin	Rash Liver function test abnormalities Diarrhea Hypotension	Adjust in moderate hepatic impairment. No dosage adjustments with renal impairment.
Micafungin	100–150 mg per day	IV	FDA off-label; Invasive aspergillosis, initial, and salvage therapy	Echinocandin	Rash Liver function test abnormalities Diarrhea Hypotension	
Anidulafungin	200 mg on day 1, then 100 mg daily	IV	Not FDA approved for treatment of *Aspergillosis* but used off-label for salvage therapy	Echinocandin	No significant hepatotoxicity	
Itraconazole	200 mg every 12 hr	PO	Off-label use for invasive aspergillosis	Triazole	Peripheral edema Diarrhea Increase in liver enzymes	Multiple drug-drug interactions. Measure drug levels.

Abbreviations: ABCD, amphotericin B colloidal dispersion; ABLC, amphotericin B lipid complex (Abelcet); ALT, alanine aminotransferase; AMD-D, amphotericin B deoxycholate; FDA, US Food and Drug Administration; IV, intravenous; LAMB, liposomal amphotericin B; PO, per orem.

TABLE 1.19.2. ANTIFUNGAL DRUGS FOR PREVENTION OF INVASIVE ASPERGILLOSIS

Drug	Dose	Route	Indications	Comments
Voriconazole	200 mg every 12 hr	PO	FDA off-label; antifungal prophylaxis	Taken 1 hour before meals. Drug-drug interactions.
Posaconazole	Suspension 200 mg three times daily Extended release tablet 300 mg twice daily on day 1, then 300 mg once daily thereafter	PO	Prophylaxis against invasive aspergillosis in high-risk patients	Suspension to be taken with full meal and acid beverage to aid absorption. Delayed release tablets cannot be used interchangeably with suspension. Note dosage differences.
Itraconazole	Capsules 200 mg every 12 hr Solution 200 mg every 12 hr	PO	FDA off-label; prophylaxis against invasive aspergillosis in high-risk patients	Capsules and solution are not interchangeable. Capsules must be taken with food (acid dependent). Solution should be taken on an empty stomach.

Abbreviations: FDA, US Food and Drug Administration; PO, per orem.

drugs such as amphotericin B formulations, voriconazole, and echinocandins [29]. Micafungin and anidulafungin have in vitro activity against aspergillosis, but they have not been licensed for treatment of invasive aspergillosis. Because there is no theoretical reason to assume that they would have efficacy different from caspofungin, both micafungin and anidulafungin have been used by clinicians for the treatment of invasive aspergillosis in situations when use of licensed and first-line agents is not possible. Fluconazole has no activity against *Aspergillus* species and should not be used for treatment or prophylaxis of invasive aspergillosis or other mold infections.

Surgery is indicated to debride necrotic tissue and remove infected tissue, if they are accessible [30]. In our patient's case, amputation of the right index finger and debridement of accessible extremity lesions was performed. The need for surgery should be assessed in the context of its risk, becasue many infected patients have conditions that increase their risk for surgical complications such as excessive bleeding from thrombocytopenia. Surgical excision of infected bone in osteomyelitis, sinus debridement in those with sinusitis, resection of pulmonary cavitating mass, among others, has been performed, on a case-by-case basis. Involvement of the central nervous system is managed most commonly with antifungal drug therapy alone, and most do not require surgical intervention [31].

PREVENTION

The strategies for preventing invasive aspergillosis in high-risk patients with cancer are antifungal prophylaxis and preemptive therapy [32, 33]. This is a controversial area, and there is wide variation in clinical practices among cancer centers. However, it is suggested that antifungal prophylaxis with antimold agent be used when the estimated incidence rate of invasive aspergillosis is at least 6%. The two malignant conditions for which antifungal prophylaxis has been demonstrated to be very beneficial during chemotherapy are acute myelogenous leukemia and advanced MDS.

The antifungal drugs that can be used for prevention of invasive aspergillosis are voriconazole and posaconazole [34] (Table 1.19.2). In one large randomized multicenter trial, posaconazole was more effective than fluconazole or itraconazole in preventing invasive fungal infection, including invasive aspergillosis, in patients with acute myeloid leukemia or MDS undergoing induction chemotherapy [34]. There was also survival advantage in patients who received posaconazole prophylaxis [34]. A meta-analysis of several clinical trials indicate that mold-active antifungal prophylaxis was associated with significant reduction in the number of invasive fungal diseases, including aspergillosis, with reduction in mortality due to invasive fungal disease. However, there was no demonstrable benefit in terms of all-cause mortality, and there was higher rate of adverse

events resulting in discontinuation of antifungal prophylaxis [35]. The other alternative antifungal agents for prevention of invasive aspergillosis are amphotericin B products, itraconazole, and echinocandins [36–38]. The duration of antifungal prophylaxis should be individualized based on the clinical status of the patient.

The second strategy for prevention is preemptive therapy. Using this approach, high-risk patients are routinely screened, using galactomannan and β-D-glucan test, or serial CT scanning [39, 40]. Once there is evidence of infection, as indicated by a positive antigen test or suspicious radiographic finding, antifungal therapy (most often voriconazole) is administered to prevent the progression of infection into invasive disease.

KEY POINTS

- Invasive aspergillosis causes significant morbidity and mortality in patients with cancer undergoing chemotherapy.
- The lungs and sinuses are the most common sites of involvement, although *Aspergillus* species can disseminate to distant organs.
- Risk factors are prolonged and profound neutropenia, steroid use and chemotherapy, acute myelogenous leukemia, refractory MDS, and high-burden exposures such as farming and construction.
- The diagnosis of invasive aspergillosis can be categorized as proven, probable, or possible based upon diagnostic, clinical, and radiographic findings. A proven case of invasive aspergillosis would require the demonstration of the fungus invading tissues, the identification of the fungus in culture, and compatible clinical findings in a high-risk host.
- Galactomannan and β-D-glucan tests have emerged as important biomarkers to diagnose invasive fungal disease, including aspergillosis. Detection of aspergillus DNA by polymerase chain reaction is also emerging as another tool for diagnosis.
- The first-line treatment of invasive aspergillosis is voriconazole, and amphotericin B products are alternative for patients intolerant to voriconazole. There is increasing use of combination therapy especially in patients with suspected coinfections, those with severe clinical disease, and prior to the identification of the offending organism and its susceptibility pattern.
- Prevention of invasive aspergillosis in high-risk individuals can be in the form of voriconazole or posaconazole prophylaxis or preemptive antifungal therapy guided by serum biomarkers (galactomannan and β-D-glucan) and serial radiographic imaging.

REFERENCES

1. Segal BH. Aspergillosis. N Engl J Med. 2009; 360:1870.
2. Marr KA, Carter RA, Crippa F, et al. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. Clin Infect Dis. 2002;34:909.
3. Chamilos G, Luna M, Lewis RE, et al. Invasive fungal infections in patients with hematologic malignancies in a tertiary care cancer center: an autopsy study over a 15-year period (1989–2003). Haematologica 2006;91:986.
4. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/ Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008;46:1813.
5. Bochud PY, Chien JW, Marr KA, et al. Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. N Engl J Med. 2008;359:1766.
6. Lambourne J, Agranoff D, Herbrecht R, et al. Association of mannose-binding lectin deficiency with acute invasive aspergillosis in immunocompromised patients. Clin Infect Dis. 2009;49:1486.
7. Horger M, Hebart H, Einsele H, et al. Initial CT manifestations of invasive pulmonary aspergillosis in 45 non-HIV immunocompromised patients: association with patient outcome? Eur J Radiol. 2005;55:437.
8. Stanzani M, Battista G, Sassi C, et al. Computed tomographic pulmonary angiography for diagnosis of invasive mold diseases in patients with hematological malignancies. Clin Infect Dis. 2012;54:610.
9. Ashdown BC, Tien RD, Felsberg GJ. Aspergillosis of the brain and paranasal sinuses in immunocompromised patients: CT and MR imaging findings. AJR Am J Roentgenol. 1994;162:155.
10. Horvath JA, Dummer S. The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. Am J Med. 1996;100:171.
11. Marr KA, Balajee SA, McLaughlin L, et al. Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. J Infect Dis. 2004;190:641.

12. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis. 2006;42:1417.
13. Marr KA, Laverdiere M, Gugel A, Leisenring W. Antifungal therapy decreases sensitivity of the *Aspergillus* galactomannan enzyme immunoassay. Clin Infect Dis. 2005;40:1762.
14. Vergidis P, Razonable RR, Wheat LJ, et al. Reduction in false-positive *Aspergillus* serum galactomannan enzyme immunoassay results associated with use of piperacillin-tazobactam in the United States. J Clin Microbiol 2014;52:2199.
15. Pickering JW, Sant HW, Bowles CA, et al. Evaluation of a (1->3)-beta-D-glucan assay for diagnosis of invasive fungal infections. J Clin Microbiol. 2005;43:5957.
16. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, et al. beta-D-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. Clin Infect Dis. 2011;52:750.
17. Koo S, Bryar JM, Page JH, et al. Diagnostic performance of the (1-->3)-beta-D-glucan assay for invasive fungal disease. Clin Infect Dis. 2009;49:1650.
18. Limper AH, Knox KS, Sarosi GA, et al. An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients. Am J Respir Crit Care Med. 2011;183:96.
19. Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008;46:327.
20. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002;347:408.
21. Pascual A, Calandra T, Bolay S, et al. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis. 2008;46:201.
22. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clin Infect Dis. 2007;44:1289.
23. Aliff TB, Maslak PG, Jurcic JG, et al. Refractory *Aspergillus* pneumonia in patients with acute leukemia: successful therapy with combination caspofungin and liposomal amphotericin. Cancer 2003;97:1025.
24. Kontoyiannis DP, Hachem R, Lewis RE, et al. Efficacy and toxicity of caspofungin in combination with liposomal amphotericin B as primary or salvage treatment of invasive aspergillosis in patients with hematologic malignancies. Cancer 2003;98:292.
25. Caillot D, Thiebaut A, Herbrecht R, et al. Liposomal amphotericin B in combination with caspofungin for invasive aspergillosis in patients with hematologic malignancies: a randomized pilot study (Combistrat trial). Cancer 2007;110:2740.
26. Singh N, Limaye AP, Forrest G, et al. Combination of voriconazole and caspofungin as primary therapy for invasive aspergillosis in solid organ transplant recipients: a prospective, multicenter, observational study. Transplantation 2006;81:320.
27. Baddley JW, Pappas PG. Antifungal combination therapy: clinical potential. Drugs 2005;65:1461.
28. Maertens J, Glasmacher A, Herbrecht R, et al. Multicenter, noncomparative study of caspofungin in combination with other antifungals as salvage therapy in adults with invasive aspergillosis. Cancer 2006;107:2888.
29. Walsh TJ, Raad I, Patterson TF, et al. Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial. Clin Infect Dis. 2007;44:2.
30. Baron O, Guillaume B, Moreau P, et al. Aggressive surgical management in localized pulmonary mycotic and nonmycotic infections for neutropenic patients with acute leukemia: report of eighteen cases. J Thorac Cardiovasc Surg. 1998;115:63; discussion 8.
31. Schwartz S, Ruhnke M, Ribaud P, et al. Improved outcome in central nervous system aspergillosis, using voriconazole treatment. Blood 2005;106:2641.
32. Cornely OA, Bohme A, Buchheidt D, et al. Primary prophylaxis of invasive fungal infections in patients with hematologic malignancies. Recommendations of the Infectious Diseases Working Party of the German Society for Haematology and Oncology. Haematologica 2009;94:113.
33. Maertens J, Marchetti O, Herbrecht R, et al. European guidelines for antifungal management in leukemia and hematopoietic stem cell transplant recipients: summary of the ECIL 3--2009 update. Bone Marrow Transplant. 2011;46:709.
34. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med. 2007;356:348.
35. Ziakas PD, Kourbeti IS, Voulgarelis M, Mylonakis E. Effectiveness of systemic antifungal prophylaxis in patients with neutropenia after chemotherapy: a meta-analysis of randomized controlled trials. Clin Ther. 2010;32:2316.
36. Glasmacher A, Prentice A, Gorschluter M, et al. Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: evidence from a meta-analysis of 3,597 patients. J Clin Oncol. 2003;21:4615.

37. Kelsey SM, Goldman JM, McCann S, et al. Liposomal amphotericin (AmBisome) in the prophylaxis of fungal infections in neutropenic patients: a randomised, double-blind, placebo-controlled study. Bone Marrow Transplant. 1999;23:163.
38. Penack O, Schwartz S, Martus P, et al. Low-dose liposomal amphotericin B in the prevention of invasive fungal infections in patients with prolonged neutropenia: results from a randomized, single-center trial. Ann Oncol. 2006;17:1306.
39. Cordonnier C, Pautas C, Maury S, et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. Clin Infect Dis. 2009;48:1042.
40. Morrissey CO, Chen SC, Sorrell TC, et al. Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial. Lancet Infect Dis. 2013;13:519.

1.20

A Red Hot Mess

ROBBE PEETZ, PA AND ALISON G. FREIFELD, MD

CASE PRESENTATION

A 56-year-old female with a past medical history of asthma, obesity, hypertension, and stage II infiltrating ductal carcinoma of the left breast presented with fever, erythema, and pain of the right breast approximately two months following bilateral mastectomy. She is a retired teacher and resides with her husband in a suburban home.

With the mastectomy procedure, bilateral first-stage breast reconstruction was performed including placement of tissue expanders under regenerative tissue matrix implants. Five days later, the right breast surgical site demonstrated swelling and erythema, but the patient was afebrile and felt otherwise well. The wound was surgically opened and serous fluid was drained, but cultures were not obtained. Oral clindamycin 300 mg every eight hours was started for a twenty-day course, and the wound partially closed secondarily. There was resolution of surrounding erythema over the next few days. Subsequently, adjuvant chemotherapy with dose-dense cyclophosphamide and doxorubicin was given at standard dosages, with granulocyte colony-stimulating factor support. She tolerated the chemotherapy well and received another cycle three weeks later.

Approximately four weeks after the initial breast cellulitis presentation and eight days after cycle two of chemotherapy, the patient developed fever with increasing erythema and pain at the surgical site. She was noted to have a white blood cell count of 1.7 cells/mm^3 and an absolute neutrophil count of 800 cells/mm^3. Notably pegfilgrastim support was given following the most recent antineoplastic treatment in an effort to abrogate the duration of neutropenia. She was admitted for tissue expander removal, and initial vital signs were as follows: blood pressure 108/66, pulse 100F, temperature 38.1°C, respirations 16, and oxygenation 97% on room air. Physical exam showed the right side mastectomy site with an approximately 6 × 2 cm wound, packing in place, and a circumferential area of 1 cm erythema at the wound edges. Laboratory values revealed hemoglobin 9.4 g/dL, platelet count of 172 000/mm^3, sodium 139 mmol/L, potassium 4.4 mmol/L, blood urea nitrogen 9 mg/dL, creatinine 1.53 mg/dL (elevated from baseline of 0.60 mg/dL), and random glucose 169 mg/dL.

QUESTIONS

- What are the risk factors for breast cellulitis complicating mastectomy and expander implant?
- What organisms should be considered as pathogens and what empiric antibiotics are indicated in this case?
- What are the key principles in managing this patient's soft tissue infection?

DIFFERENTIAL DIAGNOSIS

This patient presents with fever, increased pain, and erythema at the right breast surgical site and a history of recent antibiotic therapy for breast wound infection. Taken together, the signs and symptoms are obviously indicative of local skin and soft tissue infection (SSTI) complicated by the presence of foreign material, the tissue expander. Skin and soft tissue infections in adults, including those who are immunocompromised, are most commonly attributable to the most prominent skin-colonizing bacteria, either *Staphylococcus aureus* or β-hemolytic *Streptococcus* species. Indeed, these are the likely pathogens given her initial improvement with a course of clindamycin during the prior month. However, it is important to consider that her recurrent symptoms are now occurring eight days after receiving cytoreductive chemotherapy. At this time, it should be assumed that her neutrophil count is declining or is already in the range of neutropenia. In neutropenic patients, it is rare that a Gram-negative organism may cause cellulitis, and the diagnosis is occasionally made by positive blood cultures.

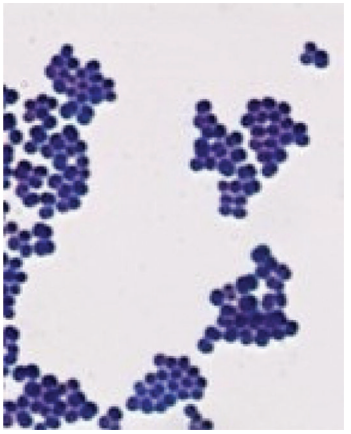


FIGURE 1.20.1: Gram stain of gram positive cocci in clusters.

Reactivations of herpes zoster (i.e. shingles) may present with cutaneous erythema and pain that can mimic a bacterial cellulitis. Invasive fungal infections and atypical mycobacterial infections may also cause these symptoms in severely immunocompromised patients.

INITIAL MANAGEMENT

On admission, blood cultures, chest x-ray, and urinalysis were obtained, and the patient was started on empiric intravenous (IV) vancomycin 1 gram every twelve hours and IV cefepime 2 grams every eight hours. She was then taken to the operating room for surgical debridement and washout of the wound and removal of the tissue expander. Gram stain of tissue showed Gram-positive cocci in clusters. The wound was left open postoperatively with application of a wound vacuum device initially. Culture of tissue obtained at surgery grew methicillin-susceptible *S aureus* (MSSA).

Final Diagnosis: MSSA infection of breast related to the presence of a tissue expander

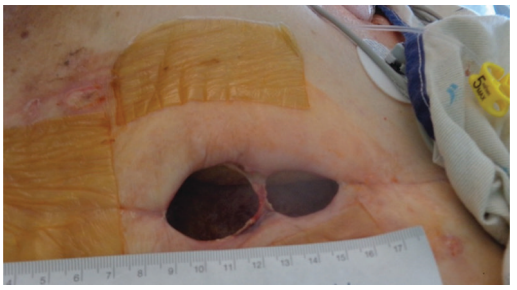


FIGURE 1.20.2: Right breast wound after packing removed, prior to surgical washout.

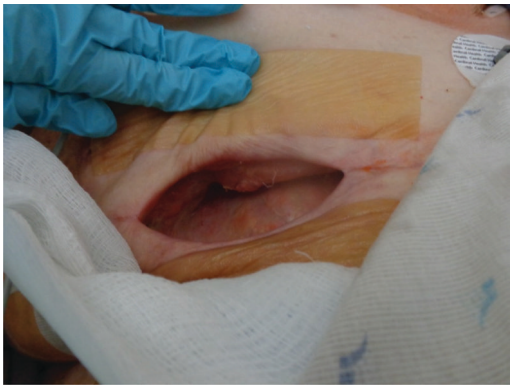


FIGURE 1.20.3: Right breast wound post-op day #2.

TREATMENT AND OUTCOME

Final cultures revealed MSSA that was resistant to clindamycin and penicillin but susceptible to semisynthetic penicillins and cephalosporins. Initial *IV* antibiotics (vancomycin and cefepime) were switched to oxacillin IV for several days until discharge. A wound vacuum was not tolerable to the patient so daily wound packing was used. Oral cephalexin 500 mg four times daily for fourteen days was prescribed at discharge. Chemotherapy was delayed until one week after completion of antibiotic therapy, and there was no recurrence of infection. The wound was very slow to heal due to both the location under the reconstruction skin flap and ongoing cytotoxic chemotherapy, but there was no recurrence of infection.

DISCUSSION

Tissue expander placement followed by prosthetic breast implants is the most common postmastectomy reconstruction modality in breast cancer patients [1–4]. Periprosthetic infections with both the expanders and the implants are a common and debilitating complication, often requiring hospitalization for IV antibiotics, reoperation for expander removal, and additional procedures to reconstruct the breast. Staphylococcal and streptococcal skin commensals are the most common pathogens causing such infections, although Gram-negative bacilli have been identified as the cause in approximately one-third of cases [4]. No organisms are isolated in a minority of cases.

Risk Factors

The incidence of periprosthetic infections reported in the recent literature ranges from 1.9% to 6%, during the tissue expansion phase [1, 5, 6]. Obesity and smoking have both been identified as key predictors of infection following breast

reconstruction surgery [1, 2, 5, 7]. In addition, age >65 years, location of the foreign body under a reconstructive skin flap, ongoing chemotherapy, prior radiation therapy, lymph node dissection, larger breast size, diabetes, and hypertension may also contribute to infection risk [1, 2, 4, 5]. Controversy exists regarding whether there is increased risk associated with immediate tissue expanders at time of mastectomy compared with patients in whom reconstruction is delayed [6, 8]. Ready-to-use sterile acellular dermal matrix used in immediate implant-based breast reconstruction has been found to reduce the risks of infectious complications compared with aseptic acellular dermal matrix [9].

Clinical Presentation

Periprosthetic infections in breast cancer patients undergoing mastectomy with tissue expander placement most commonly occur at or around the surgical site and surrounding soft tissue [3]. Infections occur at an average of approximately 120 days after tissue expander or implant placement and present with a warm, painful, and erythematous breast, accompanied by low-grade fever and chills [6]. Patients may also have enlarged axillary lymph nodes depending on the severity of the infection. Physical exam will reveal tenderness to palpation of the affected breast, erythema surrounding the surgical site, warmth, and occasionally purulence. It is important to remember that in the setting of a neutropenia, symptoms of cellulitis may be significantly attenuated, pus is often absent, and fever may be minimal due to the lack of a robust inflammatory response [10].

Diagnosis

Diagnosis of cellulitis is usually clear from the clinical history and physical exam, which shows a spreading erythema of the skin with tenderness and warmth at the site. This presentation is typical for β-hemolytic streptococcal infection, although occasionally *S aureus* may be the cause. The presence of a furuncle or purulent discharge from a tender nodule is suggestive of *S aureus* involvement. Ultrasound can be helpful to identify underlying abscess. Culture of any wound drainage or purulent discharge and especially cultures taken at surgical explant of the expander or implant are essential to making a bacteriologic diagnosis. In the non-immunocompromised patient, blood cultures are not routinely recommended, but wound cultures should be performed if applicable. Immunosuppressed patients should be evaluated with a complete blood count, blood cultures, and culture of any wound discharge [11]. If blood cultures are positive for *S aureus*, then transesophageal echocardiography should be performed to rule out endocarditis. It is best to obtain wound cultures before initiation of antibiotic therapy in hopes of attaining a high yield of organisms. However, in the case presented, since this cancer patient is febrile and nearly neutropenic, there is the possibility of an occult bacteremia causing fever. For this reason, antibiotic coverage for both Gram-positive and Gram-negative pathogens (including *Pseudomonas aeruginosa*) is warranted as initial empiric therapy, even prior to going to the operating room [10]. Antibiotics should be continued in this case, at least until recovery of the absolute neutrophil count and possibly longer, as clinical judgment dictates. Cultures and Gram stain obtained at the time of surgical removal of the foreign body are also essential to guide empiric antibiotic therapy. Once culture results from blood and tissue samples are available, antibiotic coverage can be tailored.

Treatment

Treatment of SSTIs will be dictated by severity of illness, likely pathogens, overall clinical picture, and immune deficiency status. Empiric treatment with antibiotics that are active against methicillin-resistant *S aureus* (MRSA) and streptococci are initially indicated for all patients with severe purulent (primarily *S aureus* or MRSA) or nonpurulent (primarily streptococci) skin infections, until culture and susceptibility results become available. Incision and drainage is the standard of care for purulent processes. Immunosuppressed patients with significant SSTIs may need to be hospitalized for broad-spectrum empiric IV antibiotic therapy with a spectrum covering MRSA and Gram- negative pathogens [11]. Methicillin-resistant *S aureus* coverage is achieved with vancomycin or linezolid in most cases, although daptomycin or one of several recently approved drugs such as oritavancin, televancin, tedizolid, or ceftaroline may be considered. If susceptible *S aureus* is isolated, it should be treated with IV oxacillin (or nafcillin) or cephalothin. Gram-negative agents with activity against *P aeruginosa* should be considered in highly immunocompromised patients or those who are neutropenic, and they include cefepime, meropenem/imipenem, or piperacillin-tazobactam [11]. Oral antimicrobials can be used once an identification of an organism has been reached and/or clinical improvement has been achieved (clindamycin or trimethoprim-sulfamethoxazole). Duration of

therapy is five days, at minimum, but depends on the patient's response and immune status.

Surgical explant of breast tissue expanders or prosthetics is essential in clearing most infections of this type. Occasionally, limited local infections may be addressed by antibiotics alone [4].

Prognosis

With proper antibiotic therapy and surgical removal of foreign material in most cases, the overall prognosis of tissue expander-related infections of the breast is excellent. Occasionally, recurrent episodes of cellulitis may occur, particularly if lymph node dissection has compromised local clearance of skin pathogens [12].

Prevention

Attention to patient characteristics such as obesity and larger breast size, smoking cessation, and use of certain surgical methods (based on above-mentioned risk factors) may reduce the incidence of tissue-expander and breast reconstruction-related infections, although studies have not been done to confirm these suggestions [1, 2]. In a recently published report [4], an aggressive standardized protocol of peri- and postoperative chlorhexidine washes and IV antibiotics, immersion of the tissue expander in triple antibiotic solution prior to placement, and continuation of postoperative antibiotics until all drains were removed was associated with a reduction in infectious complications (18.4%–11.6%; $P = .042$) in patient groups treated before and during the protocol. It is not clear which specific protocol interventions were key to the improved outcome, but it is notable that the extended use of antibiotics beyond intraoperative administration is strongly discouraged by current guidelines [13].

KEY POINTS

- Breast reconstruction with the use of tissue expanders followed by implants is complicated by infection in approximately 1%–5% of cases.
- *S aureus* and streptococci are most common pathogens, but Gram-negative bacilli may be identified in a significant minority.
- Blood and tissue cultures are required to make a bacteriologic diagnosis.
- Empiric antibiotic treatment should be primarily directed against MRSA and streptococci, but in neutropenic or severely immunosuppressed patients, Gram-negative coverage is also required.
- Surgical drainage and/or explant of foreign material is often necessary for resolution of infection.
- Good outcomes are expected with early diagnosis, appropriate cultures, drainage as needed, and antibiotic coverage.

REFERENCES

1. Fischer JP, Nelson JA, Serletti JM, et al. Peri-operative risk factors associated with early tissue expander (TE) loss following immediate breast reconstruction (IBR): a review of 9305 patients from the 2005–2010 ACS-NSQIP datasets. J Plast Reconstr Aesthet Surg. 2013;66:1504.
2. McCarthy CM, Mehrara BJ, Riedel E, et al. Predicting complications following expander/implant breast reconstruction: an outcomes analysis based on preoperative clinical risk. Plast Reconstr Surg. 2008;121:1886.
3. Frassica DA, Bajaj GK, Tsangaris TN. Treatment of complications after breast-conservation therapy. Oncology (Williston Park) 2003;17:1118.
4. Khansa I, Hendrick RG Jr, Shore A, et al. Breast reconstruction with tissue expanders: implementation of a standardized best-practices protocol to reduce infection rates. Plast Reconstr Surg. 2014;134:11.
5. Kato H, Nakagami G, Iwahira Y, et al. Risk factors and risk scoring tool for infection during tissue expansion in tissue expander and implant breast reconstruction. Breast J. 2013;19:618.
6. Nahabedian MY, Tsangaris T, Momen B, et al. Infectious complications following breast reconstruction with expanders and implants. Plast Reconstr Surg. 2003;112:467.
7. Goodwin SJ, McCarthy CM, Pusic AL, et al. Complications in smokers after postmastectomy tissue expander/implant breast reconstruction. Ann Plast Surg. 2005;55:16.
8. Ota D, Fukuuchi A, Iwahira Y, et al. Clinical outcome of reconstruction with tissue expanders for patients with breast cancer and mastectomy. Clin Breast Cancer 2014;14:339.
9. Weichman KE, Wilson SC, Saadeh PB, et al. Sterile "ready-to-use" AlloDerm decreases postoperative infectious complications in patients undergoing immediate implant-based breast reconstruction with acellular dermal matrix. Plast Reconstr Surg. 2013;132:725.
10. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52:e56.
11. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of

skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59:147.
12. Peled AW, Stover AC, Foster RD, et al. Long-term reconstructive outcomes after expander-implant breast reconstruction with serious infectious or wound-healing complications. Ann Plast Surg. 2012;68:369.
13. Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm. 2013;70:195.

SECTION 2

Infections in Solid Organ Transplant Recipients

AJIT P. LIMAYE AND LYNNE STRASFELD

Introduction: Infections in Solid Organ Transplant Recipients

AJIT P. LIMAYE, MD AND LYNNE STRASFELD, MD

Solid organ transplantation (SOT) is undertaken to restore organ function for patients with failing or end-stage disease of the liver, heart, lung, kidneys, and/or pancreas or to re-establish function in patients with short gut or other disorders of the intestinal tract. Organ transplantation requires lifelong maintenance immune suppression to prevent organ rejection. The degree of immune suppression must be carefully balanced, weighing risk of rejection with risk for infection.

Infection can be related to donor transmission, reactivation from latency in the recipient, or acquisition de novo posttransplant. Important host factors that impact risk for infection include exposure status, including both prior exposure to infections that have the ability to establish latency (eg. herpesviruses, tuberculosis, toxoplasmosis, various endemic fungi, etc) and the type and intensity of exposure to infectious agents in the community or environment, as well as the "net state of immune suppression", a composite of immunosuppressive medications and other underlying host immune factors (e.g. granulocyte and lymphocyte count or function, human immunodeficiency virus status, etc).

Infections in the early (<1 month) posttransplant period, soon after initiation of immune suppression, are typically either related to technical aspects of the procedure (e.g. surgical wound infections, central-line associated bacteremia, etc) and/or donor-transmitted infection. The period of one to six months posttransplant is characterized by opportunistic infection, with risk for such impacted by antimicrobial prophylaxis strategies (e.g. cytomegalovirus, *Pneumocystis*, etc), as well as community-type infections (e.g. community respiratory viruses). In the late (>6 month) posttransplant period, infections are either "late onset" opportunistic infection (e.g. late cytomegalovirus infection occurring after antiviral prophylaxis has been completed) or community-type infections, with opportunistic pathogens more often occurring in patients who require augmentation of immune suppression for management of rejection.

The evaluation of suspected infection in SOT recipients is guided by the clinical presentation, with likelihood shaped by prophylaxis strategies, host factors, and exposure history. Prompt evaluation is critical, often requiring multimodality imaging, microbiologic testing with cultures and molecular diagnostics, and invasive diagnostics or biopsy. Challenges to evaluation of suspected infection in SOT recipients include the broad differential diagnostic considerations—including both opportunistic and "typical" or community-type infections, the occurrence of mixed or multiple infections contemporaneously, and the often attenuated clinical presentation of infection in the context of immune suppression. Decisions regarding empiric or directed antimicrobial therapy must take into account potential drug interactions with immunosuppressive agents. Laboratory monitoring for antimicrobial side effects and toxicity is often necessary, with such effects, at times, dose limiting.

Prevention of infection in SOT recipients draws on the pretransplant assessment (history, selected laboratory screening) and involves education on mitigating exposure risk ("safe living after transplant") as well as prophylactic and preemptive and monitoring strategies for selected infections (e.g. *Pneumocystis*, cytomegalovirus, fungal infections, etc). Prophylactic strategies must balance risk for and of infection with the cost and potential toxicity of antimicrobial agents.

Ultimately, through use of biomarkers and indicators of pathogen-specific immune competence as well as better laboratory assessment of overall immune competence, a more granular

identification of those SOT recipients at highest risk for infection will allow for optimization of prophylaxis and other infection prevention strategies. More selective immune suppressive agents will serve to decrease the collateral risk for infection implicit in current strategies to prevent allograft rejection. Improved pathogen-directed testing, with greater sensitivity and specificity, will enhance the ability to make a timely and accurate diagnosis, ideally by less invasive means. Lastly, antimicrobial agents with greater efficacy and fewer dose-limiting toxicities and drug interactions will facilitate the safe prevention and treatment of infection in SOT recipients.

2.1

Breathless in Seattle

ERIKA D. LEASE, MD

CASE PRESENTATION

A 24-year-old woman underwent bilateral lung transplant due to end-stage cystic fibrosis (CF)-associated bronchiectasis. Prior to transplant, she was chronically colonized with *Pseudomonas aeruginosa*, methicillin-sensitive *Staphylococcus aureus* (MSSA), and *Aspergillus fumigatus*. Other past medical history included CF-related pancreatic exocrine dysfunction, chronic sinusitis, and gastroesophageal reflux disease. The patient was not working prior to transplant and lived with her fiancé and 3-year-old daughter. There were no pets at home. She was a nonsmoker with no other reported substance use. Her family history included a sister who had undergone liver transplant due to CF-related liver disease.

The patient had an uneventful postoperative course and was maintained on routine immunosuppression including tacrolimus, mycophenolate mofetil, and prednisone. Prophylactic antimicrobials on discharge included valganciclovir (cytomegalovirus D+/R+), clotrimazole troche, and trimethoprim-sulfamethoxazole. One month following transplantation, she underwent bronchoscopy due to a lack of improvement in spirometry as expected post-transplant. At the time, the patient endorsed a mild nonproductive cough but no dyspnea or fever. Her physical exam revealed rare scattered bibasilar crackles on auscultation of her chest and a well healing clamshell incision but was otherwise normal. Radiographic images were unremarkable. Bronchoscopic evaluation revealed granulation tissue at the anastomotic sites and copious purulent secretions throughout the tracheobronchial tree. Bronchoalveolar lavage (BAL) cultures grew *P aeruginosa* and MSSA. An appropriate course of antibiotics was completed. Her spirometry showed mild improvement in her forced expiratory volume in 1 second (FEV_1) from 1.48 to 1.76 liters.

One month later, the patient returned with progressive dyspnea, a scant productive cough with the feeling of being unable to expectorate her secretions, as well as a sensation of wheezing in her chest. Physical exam was notable for a normal temperature as well as both inspiratory and expiratory large-airway wheezes heard best on the left side. Her spirometry had a mild decline in FEV_1 from 1.76 to 1.44 liters. Radiographic images were unremarkable. A repeat bronchoscopy demonstrated normal caliber airways with inspissated mucus and grayish tan-brown granulation tissue predominantly in the left mainstem bronchus at the anastomotic site as well as the right mainstem bronchus and bronchus intermedius (Figure 2.1.1).

QUESTIONS

- What diagnoses should be considered to explain this patient's bronchoscopic findings?
- What diagnostic testing would be appropriate?

DIFFERENTIAL DIAGNOSIS

Given the findings on bronchoscopy, infections to consider include *Aspergillus* tracheobronchitis, other fungal tracheobronchitis, and bacterial infection of necrotic anastomotic debris. Noninfectious considerations include ischemia-reperfusion injury or acute rejection.

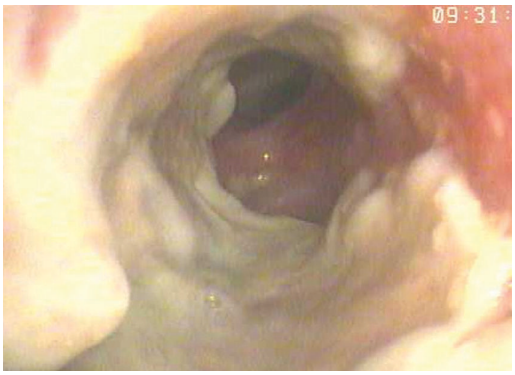


FIGURE 2.1.1: Bronchoscopic photograph of the left mainstem bronchus revealing a thick gray-tan pseudomembrane. (Photo courtesy Kamran Mahmood, MD, MPH.)

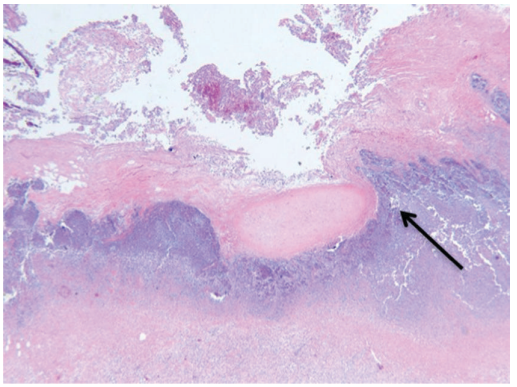


FIGURE 2.1.2: Biopsy hematoxylin and eosin stain of pseudomembranous material showing transmural necrosis. (Photo courtesy Rodney A. Schmidt, MD.)

ADDITIONAL DATA

The pathologic samples showed granulation tissue with transmural necrosis (Figure 2.1.2) and extensive hyphal elements on special staining (Figure 2.1.3) consistent with *Aspergillus*. Bronchoalveolar lavage cultures grew *A fumigatus*.

Final Diagnosis: *Aspergillus* tracheobronchitis

TREATMENT AND OUTCOME

The patient was initiated on treatment with voriconazole and eventually had a full recovery.

DISCUSSION

Epidemiology

Aspergillus tracheobronchitis and other forms of invasive pulmonary *Aspergillus* infection are most common in patients who are immunocompromised. Absolute or functional neutropenia, hematopoietic stem cell transplant, solid organ transplant (SOT), human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), and prolonged corticosteroid use are all risk factors for the various forms of invasive pulmonary aspergillosis. *Aspergillus* tracheobronchitis is a unique presentation, affecting primarily the large airways as opposed to the lung parenchyma, in approximately 8% of patients with invasive pulmonary *Aspergillus* infection [1]. Lung transplant patients, in particular, are at high risk and constitute nearly 40% of all cases [2]. *Aspergillus* tracheobronchitis appears to be the most common presentation of invasive pulmonary *aspergillus* infection in lung transplant patients, comprising 40%–80% of all invasive pulmonary *Aspergillus* infections in this population [3, 4]. There are a number of factors that likely contribute to the increased risk in lung transplant recipients including continuous exposure of the transplanted organ to environmental *Aspergillus* spores, ischemic injury at the anastomotic sites, disruption of lymphatic drainage, impaired airway clearance due to absence of the cough reflex, general airway inflammation with episodes of acute rejection, and overall higher levels of immunosuppression than other organ transplant recipients [5, 6].

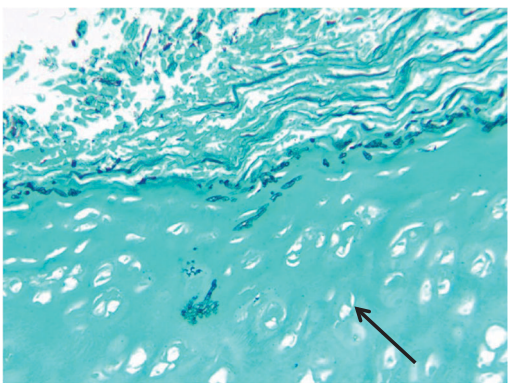


FIGURE 2.1.3: Biopsy Gomori methenamine silver stain showing fungal elements consistent with *Aspergillus*. (Photo courtesy Rodney A. Schmidt, MD.)

Clinical Presentation

In a recent review of reported cases [2], cough, dyspnea, and fever were the most common presenting symptoms in patients with *Aspergillus* tracheobronchitis. Many lung transplant recipients may present asymptomatically, however, with findings only present on routine posttransplant surveillance bronchoscopy. Unilateral wheezing should raise suspicion for *Aspergillus* tracheobronchitis; however, it is present in less than 25% of patients. Nearly half of patients have normal radiographic images. The remaining half may have nonspecific changes such as patchy pulmonary infiltrates, nodules, or atelectasis. A small number, approximately 15%, may have evidence of tracheobronchial wall thickening. Although the timing of *Aspergillus* tracheobronchitis varies by underlying predisposing condition, the majority of lung transplant patients develop the infection within the first three months following transplantation [6].

Aspergillus tracheobronchitis has historically been divided into three forms based on gross bronchoscopic appearance: pseudomembranous, ulcerative, and obstructive [7]. More recently,

however, it has been speculated that these may be different stages of the same disease process [8].

Diagnosis

Due to the lack of reliable clinical signs or symptoms, the diagnosis of *Aspergillus* tracheobronchitis relies primarily upon visual inspection of the airways via bronchoscopy, pathologic evidence of invasive fungal elements in the airway mucosa, and positive microbiologic cultures with *Aspergillus* species. Fernandez-Ruiz et al [2] found nearly 80% of cases had histologic findings of invasive septate hyphae and 90% had a positive microbiologic culture. As in other forms of invasive pulmonary aspergillosis, the majority of cases of *Aspergillus* tracheobronchitis are due to *A fumigatus*.

Newer fungal diagnostics including serum and BAL galactomannan, serum (1→3)-β-D-glucan, and BAL *Aspergillus* polymerase chain reaction (PCR) have not been evaluated extensively in the diagnosis of *Aspergillus* tracheobronchitis. However, the use of these tests in the diagnosis of invasive pulmonary aspergillosis has shown variable results, particularly in lung transplant recipients. Recognizing the limitations of serum galactomannan testing in SOT recipients, in a meta-analysis by Pfeiffer et al [9], serum galactomannan has been shown to have a sensitivity of 22% and a specificity of 84% in SOT patients. BAL galactomannan and BAL *Aspergillus* PCR appear to have greater sensitivity than serum galactomannan and have been shown specifically in the lung transplant population to have utility in diagnosing *Aspergillus* infections [10, 11]. A positive test result, however, only confirms the presence of *Aspergillus* and does not necessarily definitively distinguish between invasive pulmonary aspergillosis, aspergilloma, tracheobronchitis, or *Aspergillus* colonization.

Treatment

Treatment of *Aspergillus* tracheobronchitis should include a multipronged approach, consisting of systemic antifungal therapy, reduction in immunosuppression as feasible, and may include debridement of necrotic tissue and/or stenting of stenoses. Voriconazole is considered the antifungal agent of choice for *Aspergillus* tracheobronchitis, given a more tolerable side effect profile than amphotericin and as extrapolated from studies in other immunosuppressed populations. Voriconazole has been shown to have a similar mortality as amphotericin B in the treatment of *Aspergillus* tracheobronchitis in lung transplant patients, although this result is based on a small group of patients [6]. There appears to be excellent penetration of voriconazole into lung tissue with appropriate therapeutic concentrations [12]. Because systemic antifungal therapy might result in limited penetration into necrotic tissue at the poorly vascularized anastomotic site, adjunctive use of nebulized amphotericin has been utilized but has not been subjected to rigorous clinical study. The duration of treatment must be tailored to the clinical course and depends on clinical, radiographic, and bronchoscopic improvement.

Prevention

For lung transplant recipients, many centers provide postoperative antifungal prophylaxis in the immediate posttransplant period with either aerosolized amphotericin B as topical therapy to prevent *Aspergillus* colonization of the anastomotic sites or with systemic therapy such as with a triazole.

Outcomes

Mortality following *Aspergillus* tracheobronchitis ranges from 20% in lung transplant recipients [6] to nearly 90% in neutropenic patients [2]. Complications arise from the development of invasive parenchymal pulmonary aspergillosis and disseminated aspergillosis, as well as from invasion of the circulatory system resulting in hemoptysis. Destruction of the anastomotic site in lung transplant patients may also result in anastomotic dehiscence and necrosis of the transplanted airways (Figure 2.1.4). Obstructive *Aspergillus* tracheobronchitis may result in acute respiratory failure.

KEY POINTS

- *Aspergillus* tracheobronchitis is an unusual form of invasive pulmonary *Aspergillus* infection that occurs most frequently in lung transplant recipients and generally involves the bronchial anastamotic site.

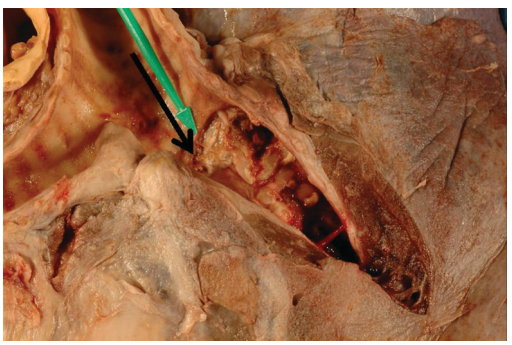


FIGURE 2.1.4: Sharp demarcation at the anastomotic site showing necrotic bronchial tissue in the transplanted lung. (Photo courtesy Corinne Fligner, MD.)

- Physical exam and general laboratory/radiographic findings are often nonspecific, thus diagnosis relies on visual inspection via bronchoscopy with microbiologic and pathologic assessment.
- Treatment relies on reduction of immunosuppression if possible and systemic and local antifungal therapy.

REFERENCES

1. Young RC, Bennett JE, Vogel CL, et al. Aspergillosis: the spectrum of disease in 98 patients. Medicine 1970; 49:147.
2. Fernandez-Ruiz M, Silva JT, San-Juan R, et al. *Aspergillus* tracheobronchitis: report of 8 cases and review of the literature. Medicine 2012; 91:261.
3. Husain S, Kwak EJ, Obman A, et al. Prospective assessment of Platelia *Aspergillus* galactomannan antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. Am J Transplant. 2004;4:796.
4. Hosseini-Moghaddam SM, Husain S. Fungi and molds following lung transplantation. Semin Respir Crit Care Med. 2010;31:222.
5. Nunley DR, Gal AA, Vega JD, et al. Saprophytic fungal infections and complications involving the bronchial anastomosis following human lung transplantation. Chest 2002;122:1185.
6. Singh N, Husain S. *Aspergillus* infections after lung transplantation: clinical differences in type of transplant and implications for management. J Heart Lung Transplant. 2003;22:258.
7. Denning DW. Commentary: unusual manifestations of aspergillosis. Thorax 1995;50:812.
8. Wu N, Huang Y, Li Q, et al. Isolated invasive *Aspergillus* tracheobronchitis: a clinical study of 19 cases. Clin Microbiol Infect. 2010;16:689.
9. Pfeiffer CD, Fine JP, and Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis. 2006;42:1417.
10. Luong ML, Clancy CJ, Vadnerkar A, et al. Comparison of an *Aspergillus* real-time polymerase chain reaction assay with galactomannan testing of bronchoalveolar lavage fluid for the diagnosis of invasive pulmonary aspergillosis in lung transplant recipients. Clin Infect Dis. 2011;52:1218.
11. Pasqualotto AC, Xavier MO, Sanchez LB, et al. Diagnosis of invasive aspergillosis in lung transplant recipients by detection of galactomannan in the bronchoalveolar lavage fluid. Transplantation 2010;90:306.
12. Segal BH. Aspergillosis. N Engl J Med. 2009; 360;1870.

2.2

Red Snapper Cough

ROBERT M. RAKITA, MD

CASE PRESENTATION

A 52-year-old woman presented with cough and worsening pulmonary infiltrates. One year earlier she had undergone bilateral lung transplantation for severe chronic obstructive pulmonary disease. She was both cytomegalovirus (CMV) and Epstein-Barr virus seropositive at the time of transplant. She had done relatively well postoperatively, with only one episode of suspected pneumonia four months prior. However, she reported increasing cough over the course of two to three weeks. This was mostly nonproductive, associated with mild shortness of breath, but without chest pain, fever, chills, or sweats.

Maintenance immunosuppression included tacrolimus, mycophenolate, and prednisone, and she took trimethoprim-sulfamethoxazole and acyclovir as prophylaxis against pneumocystis pneumonia and herpes simplex virus infection, respectively. Her other medical history was only notable for prior deep vein thromboses and pulmonary emboli, and she took warfarin chronically for anticoagulation. She lived in the Pacific Northwest and had no history of foreign travel. She had spent time in the Midwestern United States (Kansas) a few years earlier. She had dogs but no other animal exposures. She denied any known recent ill contacts. She had a forty-pack- year smoking history but had quit eight years prior to transplant.

Physical exam revealed a temperature of 36.5°C, heart rate 90 beats per minute, and blood pressure 101/56 mm mercury. She required 2 liters of oxygen by nasal cannula to maintain her oxygen saturation at 98%. She was not acutely ill appearing. Lungs examination was notable for mild crackles at both bases. She had a soft systolic murmur, which was not new, and the rest of her exam was unremarkable.

Laboratory studies were notable for serum creatinine of 0.9 mg/dL, white blood cell count of 9700/μL, hemoglobin 9.5 g/dL, and platelet count 501 000/μL. Liver enzymes were normal. Tacrolimus level was 8 ng/mL.

Pulmonary function testing revealed that her forced expiratory volume in 1 second had declined from her posttransplant baseline of 1.67 liters (72% of predicted) to 1.30 (55% of predicted). Chest x-ray showed new patchy consolidation in the lower lung fields. Computed tomography (CT) scan of her chest (Figure 2.2.1) showed patchy bilateral peribronchial and bronchovascular consolidations especially at the bases.

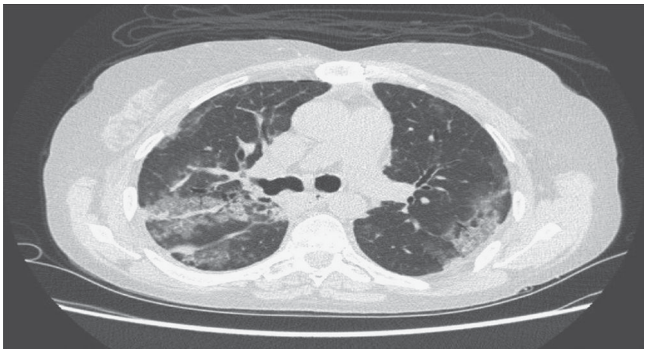


FIGURE 2.2.1: Chest computed tomography scan demonstrating patchy bilateral peribronchial and bronchovascular consolidations.

Cytomegalovirus DNA was not detectable in plasma by polymerase chain reaction (PCR). Blood cultures were negative. Fiberoptic bronchoscopy revealed grossly normal airways, but bronchoalveolar lavage (BAL) fluid was cloudy, and no biopsies were performed due to her anticoagulation. Bacterial cultures from the BAL fluid grew scant "normal oral flora". A *Pneumocystis* stain was negative, and cultures for *Legionella* and fungi were negative. Polymerase chain reaction testing for *Aspergillus fumigatus*, respiratory viruses, and CMV was negative.

DIFFERENTIAL DIAGNOSIS

The array of infectious agents that can cause pulmonary infiltrates in the lung transplant population is extensive (Table 2.2.1). One must consider common causes of pneumonia in the general, non-immunocompromised population (etiologic agents of community-acquired pneumonia—both typical and atypical, healthcare-associated pneumonia, and aspiration pneumonia), along with organisms more specifically related to the immunosuppressed state of lung transplant patients. The latter includes various bacteria, viruses, fungi, mycobacteria, and less commonly parasites. Many lung transplant patients are chronically colonized with various organisms as a consequence of their underlying lung disease, such as cystic fibrosis; organisms commonly seen in that situation include *Staphylococcus aureus, Pseudomonas aeruginosa, Burkholderia cepacia* complex, *A fumigatus*, and *Scedosporium apiospermum*, amongst others. In addition, a number of noninfectious etiologies should be considered (Box 2.2.1). Acute rejection in the transplanted lung is always a concern, as are malignancies such as posttransplant lymphoproliferative disease, inflammatory conditions such as organizing pneumonia, and medication-related causes.

TABLE 2.2.1. SELECTED INFECTIOUS AGENTS CAUSING PULMONARY INFILTRATES IN LUNG TRANSPLANT PATIENTS

Bacteria	Common agents in community-acquired pneumonia
	Streptococcus pneumoniae
	Haemophilus influenzae
	Staphylococcus aureus
	Enterobacteriaceae
	Common agents in the atypical pneumonia syndrome
	Mycoplasma spp
	Chlamydophila spp
	Legionella spp
	Others
	Pseudomonas aeruginosa
	Stenotrophomonas maltophilia
	Mixed anaerobic bacteria
	Nocardia spp
Mycobacteria	*Mycobacterium tuberculosis*
	Nontuberculous mycobacteria
Fungi	Endemic fungi:
	Histoplasma capsulatum
	Coccidioides spp
	Blastomyces dermatitidis
	Cryptococcus spp
	Pneumocystis jirovecii
	Aspergillus spp
	Scedosporium spp
	Agents of mucormycosis
Viruses	Respiratory viruses
	Influenza
	Respiratory syncytial virus
	Adenovirus
	Parainfluenza
	Human metapneumovirus
	Herpesviruses
	Cytomegalovirus
	Herpes simplex virus
	Varicella-zoster virus
Parasites	*Toxoplasma gondii*
	Strongyloides stercoralis

ADDITIONAL RESULTS AND TREATMENT

An acid-fast bacillary stain from the BAL showed acid-fast organisms (Figure 2.2.2) and culture grew *Mycobacterium abscessus* subspecies *massiliense*. A subsequent BAL two weeks later again grew the same organism. She was treated with intravenous amikacin, inhaled amikacin, intravenous imipenem, and oral azithromycin. Unfortunately, after approximately two months of treatment, she developed hearing loss and the amikacin was stopped. Linezolid was substituted for azithromycin based on susceptibility results. Repeat CT scan showed worsening of multiple infiltrates, and repeat BAL did not yield any mycobacteria but did have both CMV and *A fumigatus*. Despite treatment for the latter agents, she had progressive clinical deterioration and subsequently died.

Final Diagnosis: Pulmonary infection due to *M abscessus* subspecies *massiliense*

DISCUSSION

Characteristic epidemiologic and clinical manifestations of nontuberculous mycobacteria (NTM)

BOX 2.2.1 NONINFECTIOUS CAUSES OF PULMONARY INFILTRATES IN LUNG TRANSPLANT PATIENTS

Acute rejection
Ischemia-reperfusion lung injury
Posttransplant lymphoproliferative disease
Alveolar hemorrhage
Organizing pneumonia
Heart failure
Pulmonary emboli
Drug-related
Graft-versus-host disease
Recurrence of primary lung disease

in the solid organ transplant (SOT) population are described in Box 2.2.2.

Diagnosis

A high level of suspicion is required because NTM are typically found using culture techniques specific for mycobacteria, although PCR directly from clinical samples may be an option. However, because these agents are commonly found in the environment or as airway colonizers, sorting out true infection from contamination or colonization is a vexing problem. Criteria for the diagnosis of pulmonary NTM disease have been developed for use in the non-immunosuppressed population [6]. A key point is that NTM isolated from a single sputum sample should not be considered diagnostic. Positive cultures from multiple sputum samples or from a single BAL or lung biopsy, in conjunction with a compatible clinical presentation and appropriate radiographic findings, would meet American Thoracic Society/Infectious Disease Society of America criteria for disease. However, these criteria have not been systematically assessed in lung transplant recipients. One study demonstrated that colonization with NTM in the lung transplant population is common, but a positive culture often does not warrant treatment because there was no long-term deterioration due to the NTM [3].

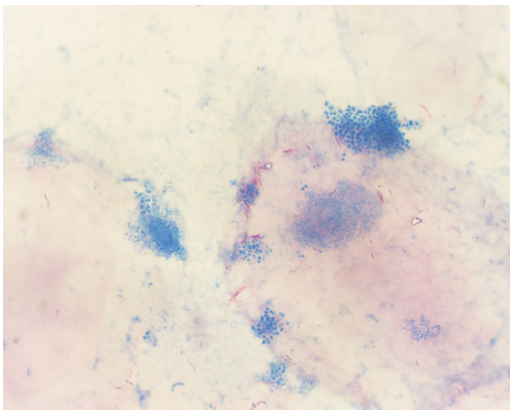


FIGURE 2.2.2: Kinyoun stain showing multiple acid-fast positive organisms.
(Photo courtesy of Carolyn K. Wallis.)

Treatment

One of the guiding principles in approaching treatment of mycobacterial infection is combination therapy to prevent the development of resistance. Three-drug regimens are commonly used for treatment of *Mycobacterium avium intracellulare* (MAC), typically including a macrolide, a rifamycin (rifampin or rifabutin), and ethambutol [6].

Although susceptibility testing of NTM is available, the correlation between in vitro results and clinical outcomes has only been reasonably well defined for certain species and drugs [7]. These include susceptibility of MAC to macrolides, *Mycobacterium kansasii* to rifampin, and rapidly growing NTM to several drugs. *Mycobacterium abscessus* is often resistant in vitro to a variety of agents. *Mycobacterium abscessus* ssp. *abscessus* are typically resistant to macrolides due to the inducible methylase gene erm(41), whereas *M abscessus* ssp *massiliense* have an inactivating deletion in that gene and are usually susceptible to macrolides [7]. This in vitro finding has correlated with better treatment outcomes with macrolides for *M abscessus* ssp *massiliense* infections [8].

As to length of therapy for NTM infections, again there are guidelines for use in the non-immunosuppressed population that could be used [6], but those should be taken to represent a minimum treatment course. For NTM lung infections, treatment should continue for at least twelve to eighteen months; an even longer course could be used, dependent on clearance of the organism, the level of immunosuppression, and other patient factors; in cutaneous or disseminated disease, the course should be six months or longer. However, despite extended treatment regimens, one may see relapse after treatment has stopped and thus a high level of suspicion should be maintained.

Several of the agents used to treat NTM interact with common immunosuppressive drugs.

BOX 2.2.2 EPIDEMIOLOGIC AND CLINICAL MANIFESTATIONS OF NONTUBERCULOUS MYCOBACTERIA IN SOLID ORGAN TRANSPLANT RECIPIENTS

EPIDEMIOLOGY

Environmental organisms, found in soil and water.

Commonly acquired by inhalation, although also can be via direct inoculation due to surgical site infection or contaminated penetrating wounds [1].

Incidence 0.2%–3% [2], although higher in the lung transplant population [3]. Higher risk in single lung transplant.

More commonly presents late after lung transplant.

M abscessus ssp *massiliense* can be transmitted from person to person and cause outbreaks [4].

Person-to-person transmission of other NTM not described.

MOST COMMON CLINICAL MANIFESTATIONS

Lung

Most common site in lung transplant recipients.
Common symptoms are chronic cough and shortness of breath ± fever.
Radiology—variable, including consolidation, cavity formation, nodules, or bronchiectasis.
Organisms—MAC, *M kansasii*, and *M abscessus* [1–5].

Skin

Painful subcutaneous nodules, which may subsequently suppurate and drain.
May also develop tenosynovitis and joint involvement.
Organisms—*Mycobacterium fortuitum, Mycobacterium chelonae*, and *M abscessus*.

Clarithromycin inhibits cytochrome P450, so tacrolimus, cyclosporine, and sirolimus metabolism is impaired and drug levels correspondingly increase. Azithromycin is a less potent inhibitor, and thus it may be preferred when a macrolide is part of the treatment regimen. In contrast, rifampin increases the metabolism of both calcineurin inhibitors and sirolimus with resultant decrease in levels. Rifabutin may be an alternative, and it has less severe interactions with calcineurin inhibitors.

Outcome of NTM infection in SOT patients is quite variable and likely depends on the organ transplanted, the level of immunosuppression, and the organ involved with the infection [2]. In lung transplant patients in particular, some studies have found significantly worse outcomes overall in those patients infected with NTM [9], whereas others have not [3].

Pretransplant Infection

Some studies reported that isolation of *M abscessus* (but not other NTM) before lung transplant was associated with worse posttransplant outcomes [10]. It is not clear what the best management approach is when NTM are isolated pretransplant; options include treatment prior to transplant, peritransplant prophylactic therapy, or no treatment at all.

KEY POINTS

- NTM pulmonary infection can be a cause of significant morbidity in lung transplant recipients.
- In general, the same diagnostic criteria used for establishing clinically significant infection in nontransplant patients have been extrapolated to lung transplant recipients, but they have not been systematically evaluated in this setting.
- Susceptibility testing should be performed for certain organism-drug combinations where there are data for correlation between clinical outcomes and in vitro results.
- Treatment regimens for NTM should include more than one drug to prevent the development of resistance.
- Pretransplant isolation of *M abscessus* in lung transplant candidates may be associated with worse outcome after

transplant, although this may not be the case with other NTM species.

REFERENCES

1. Piersimoni C. Nontuberculous mycobacteria infection in solid organ transplant recipients. Eur J Clin Microbiol Infect Dis. 2012;31:397.
2. Doucette K, Fishman JA. Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients. Clin Infect Dis. 2004;38:1428.
3. Knoll BM, Kappagoda S, Gill RR, et al. Nontuberculous mycobacterial infection among lung transplant recipients: a 15-year cohort study. Transpl Infect Dis. 2012;14:452.
4. Aitken ML, Limaye A, Pottinger P, et al. Respiratory outbreak of *Mycobacterium abscessus* subspecies *massiliense* in a lung transplant and cystic fibrosis center. Am J Respir Crit Care Med. 2012;185:231.
5. Chernenko SM, Humar A, Hutcheon M, et al. *Mycobacterium abscessus* infections in lung transplant recipients: the international experience. J Heart Lung Transplant. 2006;25:1447.
6. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367.
7. Brown-Elliott BA, Nash KA, Wallace, RJ. Antimicrobial susceptibility testing, drug resistance mechanisms, and therapy of infections with nontuberculous mycobacteria. Clin Microbiol Rev. 2012;25:545.
8. Koh WJ, Jeon K, Lee NY, et al. Clinical significance of differentiation of *Mycobacterium massiliense from Mycobacterium abscessus*. Am J Respir Crit Care Med. 2011;183:405.
9. Huang HC, Weigt SS, Derhovanessian A, et al. Non-tuberculous mycobacterium infection after lung transplantation is associated with increased mortality. J Heart Lung Transplant. 2011;30:790.
10. Chalermskulrat W, Sood N, Neuringer IP, et al. Non-tuberculous mycobacteria in end stage cystic fibrosis: implications for lung transplantation. Thorax 2006;61:507.

2.3

Spots on the Lung

JOSHUA A. HILL, MD

CASE PRESENTATION

A 51-year-old man underwent orthotopic heart transplantation (OHT) for ischemic cardiomyopathy. Both donor and recipient were human cytomegalovirus (CMV) seropositive. The immediate posttransplant course was uncomplicated, and he was discharged on a regimen of tacrolimus 2 mg by mouth (PO) twice a day (BID), mycophenolate 720 mg PO BID, prednisone 15 mg PO BID, trimethoprim-sulfamethoxazole single-strength tablet once a day, and valganciclovir 900 mg PO BID. Valganciclovir was discontinued after three months.

Six months after OHT, he developed generalized malaise and fever. Evaluation at that time was notable for CMV viremia, and he was prescribed valganciclovir 900 mg PO BID with symptomatic improvement. Seven months after OHT, the patient had a chest x-ray (CXR) after routine endomyocardial biopsy to screen for rejection, at which time he was noted to have new pulmonary nodules in the left lung compared with a CXR one month prior (Fig. 2.3.1A). He did not have any symptoms and specifically denied fever, chills, sweats, malaise, headache, cough, shortness of breath, chest pain, abdominal pain, diarrhea, and rash.

The patient's past medical history was also notable for three-vessel coronary artery bypass grafting five years prior to OHT, left ventricular assist device implantation six months prior to OHT, pulmonary hypertension, type 2 diabetes mellitus, hypertension, and hyperlipidemia. His medications included amlodipine, hydralazine, pravastatin, sildenafil, torsemide, and insulin. The patient lived with his wife in Idaho and worked as a web designer. He had traveled extensively throughout the United States, including the Southwest years ago. He had no risk factors for *Mycobacterium tuberculosis* and did not have any significant animal exposures. He had a thirty-pack per year smoking history, drank alcohol occasionally, and denied other recreational or injection drug use.

Examination revealed a healthy appearing man in no distress. His vital signs were as follows: blood pressure 126/75 mm mercury, heart rate 100 beats per minutes, respirations 14 per minute, and temperature 37.2°C, and he was breathing comfortably on room air. His lungs were clear to auscultation without adventitious sounds, and the rest of his exam was unremarkable. Basic laboratory studies were notable for normal complete metabolic panel, mild leukopenia with white blood cell count 3500 cells/μL, and normal differential. His serologies were positive for herpes simplex virus 1, CMV, Epstein-Barr virus (EBV), and varicella-zoster virus, and the donor was seropositive for CMV and EBV. Serum galactomannan was negative. Pretransplant QuantiFERON-TB Gold and *Coccidioides* immunodiffusion testing were negative. Computed tomography (CT) scan of the chest revealed multiple bilateral nodular densities, the largest approximately 1 × 2 cm, without any associated ground glass change, cavitation, lymphadenopathy, or pleural effusions (Figure 2.3.1B).

QUESTIONS

- What is the differential diagnosis of pulmonary nodules after solid organ transplantation (SOT)?
- What additional workup should be performed?

DIFFERENTIAL DIAGNOSIS

Pulmonary nodules in SOT recipients can be due to both infectious and noninfectious causes. Infections to consider include common nosocomial bacterial pathogens, including *Staphylococcus aureus* and *Pseudomonas aeruginosa*; atypical bacteria, such as Actinomycetes (especially *Nocardia* and *Rhodococcus*), *Legionella* (especially *Legionella micdadei*), *Pneumocystis jirovecii*, tuberculous and nontuberculous mycobacterial species; fungi, particularly *Aspergillus* and *Cryptococcus*, as well as other endemic mycoses (e.g. histoplasmosis and

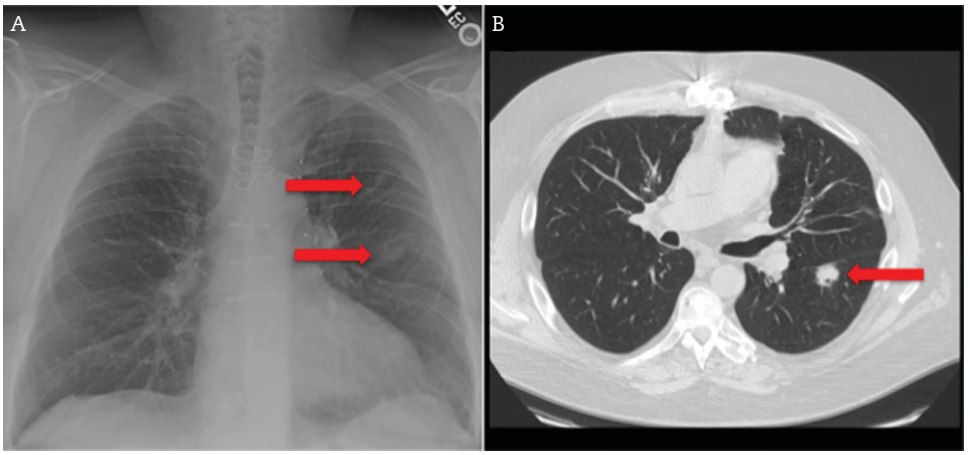


FIGURE 2.3.1: (A) Chest x-ray demonstrating two nodules in the upper and lower lobes of the left lung. (B) Chest computed tomography image demonstrating a nodular density in the superior segment of the left lower lobe.

coccidioidomycosis). Noninfectious etiologies to consider include posttransplant lymphoproliferative disorder (PTLD), other primary or metastatic malignancies, and abnormalities such as calcifications, pulmonary embolism, or atelectasis.

ADDITIONAL EVALUATION

The patient's workup included blood cultures and serum testing for *Cryptococcal* antigen, as well as CMV and EBV DNA by quantitative polymerase chain reaction (PCR). Urine was sent for *Legionella* and *Histoplasma* antigen detection. Bronchoalveolar lavage (BAL) was performed, and specimens were sent for bacterial, fungal, mycobacterial, and *Nocardia* stains and culture; *Legionella* culture; *P jirovecii* direct fluorescent-antibody stain; galactomannan; PCR testing for viral respiratory pathogens; and CMV shell vial culture. Because the results of BAL were nondiagnostic, he underwent CT-guided biopsy of one of the nodules, and specimens were sent for microbiologic testing in addition to histopathologic evaluation.

FINAL DIAGNOSIS AND OUTCOME

Histopathology of the lung biopsy specimens demonstrated necrotizing granulomas associated with fungal organisms showing frequently septate, narrow-angle branching hyphae (Fig. 2.3.2). Final cultures eventually grew *Aspergillus fumigatus*. He was treated with voriconazole and had complete resolution of the pulmonary nodules over the subsequent three months.

DISCUSSION

Pulmonary nodules in immunocompromised patients pose diagnostic and therapeutic challenges given the broad differential diagnosis and sometimes limited diagnostic approaches. Pulmonary nodules occur in approximately 10% of patients after SOT and are associated

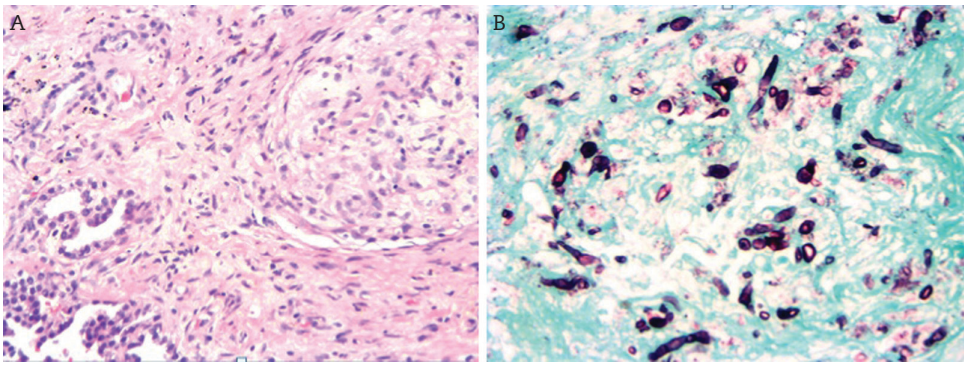


FIGURE 2.3.2: (A) Hematoxylin and eosin stain of specimen from pulmonary nodule biopsy demonstrating granulomatous inflammation. (B) Gomori methenamine silver stain revealing fungal forms with septate hyphae.

with significant morbidity and mortality [1–7]. A study of thirty-three heart transplant recipients with pulmonary nodules demonstrated significantly worse survival compared with a matched control group, and one third of affected patients were deceased within a few years of follow up [2]. Accordingly, aggressive evaluation and treatment is required.

Clinical Manifestations

Pulmonary nodules are often incidentally identified on CXR and may be asymptomatic in up to 60% of patients, irrespective of the cause [5]. The most common symptoms were fever (67%) and cough (50%) in one series. Radiographic appearance of pulmonary nodules on CT imaging, including number, size, distribution, and other characteristics did not correlate with etiology in a diverse cohort of fifty-five SOT patients, although evidence of consolidation was strongly associated with infectious etiology [1]. Important clues to the cause may come from other aspects of the history or clinical presentation, such as skin manifestations of disseminated *Cryptococcus* or *Nocardia* [6–8].

Risk Factors and Etiology

Timing, epidemiologic factors, and the degree of immunosuppression are important considerations in all cases. In a large series of SOT recipients with pulmonary nodule(s), the etiology was infectious in approximately 60% of cases [1]. Pooled data from eight published studies of pulmonary nodules in SOT recipients demonstrate infections due to bacteria in 22%, fungi in 31%, and viruses (CMV) in 5% of patients (Table 2.3.1). The most common pathogens are *Aspergillus* (typically within ninety days after transplant) and *Nocardia.* Prior exposure to the American Southwest or Midwest might raise the possibility of endemic mycoses, such as coccidioidomycosis or histoplasmosis, respectively. *Pneumocystis* should be considered in patients not receiving prophylactic medications but is an unusual cause of larger discrete pulmonary nodules. Septic pulmonary emboli with nosocomial pathogens should be considered in the appropriate clinical setting [3, 6, 8]. Noninfectious causes of pulmonary nodules account for approximately 30% of cases and are primarily due to EBV-associated PTLD and malignancy (Table 2.3.1). Recipient EBV seronegativity and lung transplantation have both been associated with an increased risk for PTLD [1].

Diagnostic Evaluation

Early and aggressive diagnostic evaluation of pulmonary nodules in SOT recipients is recommended, because the differential diagnosis is broad and empiric treatment has the potential for toxicity and drug-drug interactions [1, 6, 7]

TABLE 2.3.1. POOLED PERCENTAGES OF PUBLISHED STUDIES OF PULMONARY NODULES IN SOT RECIPIENTS

	Pooled Data*	Comments
Number of Subjects	242	Heart, lung, kidney, liver, kidney/pancreas
Infectious	59%	
Bacterial	22%	
Nocardia	11%	Usually more than 90 days after transplant
Other	4%	Mycobacteria, *Legionella*, and other
Fungal	31%	
Aspergillus	25%	Usually within the first 90 days after transplant
Other	6%	*Cryptococcus, Coccidioides*, and other
Viral—CMV	5%	Usually associated with CMV viremia
Noninfectious	33%	
PTLD	10%	Usually associated with EBV viremia
Malignancy	16%	Especially recurrent HCC after liver transplantation
Other†	7%	
Unknown	6%	

Abbreviations: CMV, human cytomegalovirus; EBV, Ebstein-Barr virus; HCC, hepatocellular carcinoma; PTLD, posttransplant lymphoproliferative disorder.
*Data are pooled from the following studies: End et al 1995 [3]; Paterson et al 1998 [6]; Copp et al 2006 [1]; Schulman et al 2000 [7]; Hsu et al 2012 [9]; Muñoz et al 2000 [5]; Kocher et al 2001 [2]; Lee et al 2004 [4].
†Other noninfectious etiologies such as calcifications, pulmonary embolism, artifacts, or atelectasis.

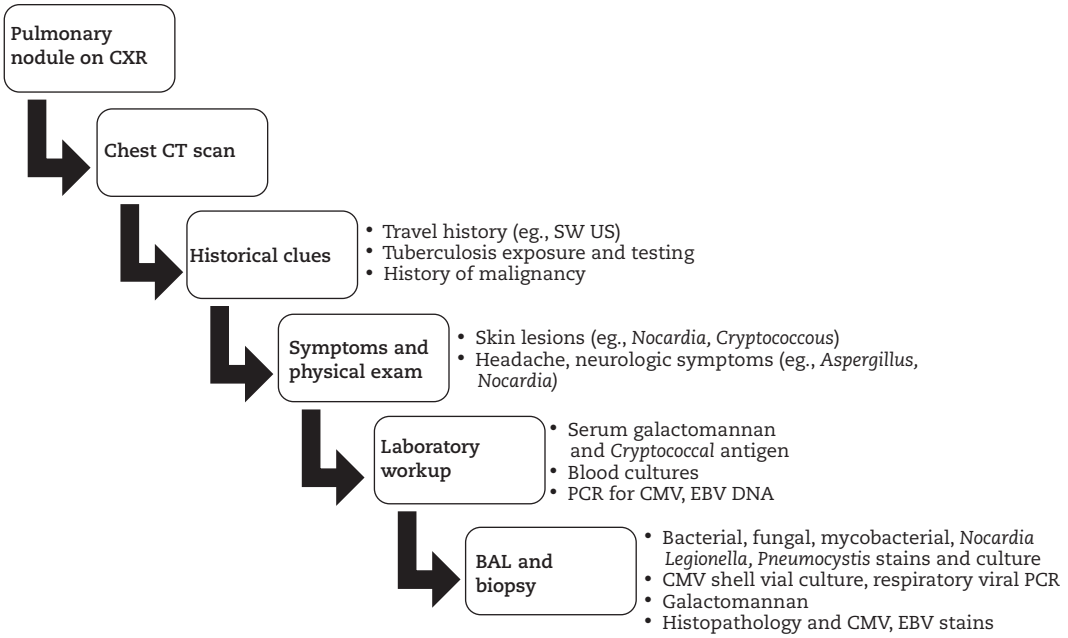


FIGURE 2.3.3: Algorithm for evaluation of pulmonary nodules in solid organ transplantation recipients.

BAL, bronchoalveolar lavage; CMV, human cytomegalovirus; CT, computed tomography; CXR, chest X-ray; EBV, Epstein-Barr virus; PCR, polymerase chain reaction; SW, Southwest. Adapted from Paterson et al 1998 [6].

(Figure 2.3.3). Chest CT imaging is important to consider in most patients with pulmonary symptoms and suggestive changes on CXR. Initial noninvasive laboratory tests such as galactomannan, *Cryptococcal* antigen, CMV and EBV PCR, and blood cultures may provide diagnostic clues. Bronchoscopy with BAL and/or biopsy should be considered if the diagnosis remains unclear after noninvasive testing. A small study of thirteen heart transplant recipients revealed a diagnostic yield of 60% for transtracheal aspiration and 70% for BAL and/or transbronchial biopsy [5]. Tissue diagnosis should be considered when less invasive testing is nondiagnostic. CT-guided biopsy of pulmonary nodules in SOT recipients was demonstrated to be a safe and procedure in a retrospective analysis of 45 biopsies [9]. Although the overall diagnostic yield was only 53%, the sensitivity was 75% for invasive fungal disease and malignancy, two of the most common causes of pulmonary nodules in this patient population. The complication rate of 13% was primarily due to asymptomatic pneumothoraces. Video-assisted thoracoscopic surgery or open biopsy may be reasonable if other approaches are nondiagnostic. Samples should be sent for bacterial, fungal, mycobacterial and *Nocardia* stains and culture, *Legionella* culture, CMV shell vial culture, and histopathology with staining for CMV and EBV. Additional tests may be indicated on a case-by-case basis.

A variety of tests are available for diagnosis of invasive aspergillosis and have varied utility. Proven invasive disease is established by tissue evidence of narrow (3 to 6 microns wide), septate hyaline hyphae with dichotomous acute angle (45°) branching invading tissues plus culture of the organism [10]. However, microscopic examination and culture are insensitive, and one study found the predictive value of positive cultures in SOT recipients with proven or probable disease to be 58% [11]. In a large meta-analysis, serum galactomannan, a constituent of *Aspergillus* cell walls, had a sensitivity and specificity of 22% and 84% among SOT patients with proven or probable aspergillosis, respectively [12]. In BAL fluid, the sensitivity of galactomannan testing is estimated to exceed 70% [13]. An assay to detect 1,3-β-D-glucan, a cell wall component of many fungi, has sensitivity and specificity ranging from 55% to 95% and 77% to 96%, respectively. It may have utility in distinguishing patients with proven or probable invasive fungal infection from patients without, but it is infrequently used in SOT recipients [14]. Both galactomannan antigen and 1,3-β-D-glucan testing require careful interpretation, because they can be falsely positive due to a variety of exposures

causing cross-reactivity. Finally, investigational PCR assays for *Aspergillus* DNA in BAL specimens have shown very heterogeneous results and are of unclear clinical value at this time [15].

KEY POINTS

- Pulmonary nodules are relatively common in SOT recipients and have a broad infectious and noninfectious differential diagnosis.
- Pulmonary nodules in SOT recipients require aggressive workup.
- Diagnostic evaluation may involve both noninvasive and invasive methods as appropriate, including blood tests, BAL with or without transbronchial biopsy, CT-guided biopsy, and video-assisted thoracoscopic surgery or open biopsy

REFERENCES

1. Copp DH, Godwin JD, Kirby KA, Limaye AP. Clinical and radiologic factors associated with pulmonary nodule etiology in organ transplant recipients. Am J Transplant. 2006;6:2759.
2. Kocher AA, Funovics M, Khazen C, et al. Etiology of pulmonary nodules after heart transplantation. Transplant Proc. 2001;33:2757.
3. End A, Helbich T, Wisser W. The pulmonary nodule after lung transplantation. Cause and outcome. Chest 1995;107:1317.
4. Lee P, Minai OA, Mehta AC, et al. Pulmonary nodules in lung transplant recipients: etiology and outcome. Chest 2004;125:165.
5. Muñoz P, Palomo J, Guembe P, et al. Lung nodular lesions in heart transplant recipients. J Heart Lung Transplant. 2000;19:660.
6. Paterson DL, Singh N, Gayowski T, Marino IR. Pulmonary nodules in liver transplant recipients. Medicine (Baltimore) 1998;77:50.
7. Schulman LL, Htun T, Staniloae C, et al. Pulmonary nodules and masses after lung and heart-lung transplantation. J Thorac Imaging 2000;15:173.
8. Cabot RC, Scully RE, Mark EJ, et al. Case 29–2000. N Engl J Med. 2000;343:870.
9. Hsu JL, Kuschner WG, Paik J, et al. The diagnostic yield of ct-guided percutaneous lung biopsy in solid organ transplant recipients. Clin Transplant. 2012;26:615.
10. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the european organization for research and treatment of cancer/invasive fungal infections cooperative group and the national institute of allergy and infectious diseases mycoses study group (eortc/msg). Clin Infect Dis. 2008;46:1813.
11. Horvath JA, Dummer S. The use of respiratory-tract cultures in the diagnosis of invasive pulmonary aspergillosis. Am J Med. 1996;100:171.
12. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis. 2006;42:1417.
13. Husain S, Clancy CJ, Nguyen MH, et al. Performance characteristics of the platelia aspergillus enzyme immunoassay for detection of aspergillus galactomannan antigen in bronchoalveolar lavage fluid. Clin Vaccine Immunol. 2008;15:1760.
14. Karageorgopoulos DE, Vouloumanou EK, Ntziora F, et al. β-d-glucan assay for the diagnosis of invasive fungal infections: a meta-analysis. Clin Infect Dis. 2011;52:750.
15. Mengoli C, Cruciani M, Barnes RA, et al. Use of PCR for diagnosis of invasive aspergillosis: systematic review and meta-analysis. Lancet Infect Dis. 2009;9:89.

2.4

Spots on the Brain

ELIZABETH ANN MISCH, MD

CASE PRESENTATION

A 63-year-old Hispanic female presented with a chief complaint relayed by her daughter of "lethargy," decline in mental alertness, headaches, shaking chills, and fever for approximately two weeks. She also reported trouble keeping up with work, right-sided headaches, blurry vision, and a recent episode of thrush. She denied shortness of breath or cough, but she was observed by her daughter to be short of breath with minor exertion.

Five and a half months prior to this presentation she had received a liver transplant for cryptogenic cirrhosis. Basiliximab (anti-CD25 monoclonal antibody) and high-dose steroids were used for induction immunosuppression, with mycophenolic acid and tacrolimus for maintenance immunosuppression. Her past medical history included cirrhosis, which was complicated by ascites, spontaneous bacterial peritonitis, and esophageal varices, and a history of tuberculosis (TB), for which she had received treatment in a sanatorium at the age of 7 (in the late 1950s). Details of the prior TB treatment regimen were unknown. Past surgeries included tubal ligation and appendectomy. She denied foreign travel. She did not smoke, drink alcohol, or use illicit drugs, she had no pets or farm exposures, and she did not consume unpasteurized or raw cheeses. A tuberculin skin test ([TST] purified protein derivative [PPD]) three years prior to transplant was negative. Cytomegalovirus [CMV] serostatus was donor-positive, recipient-negative. Medications included tacrolimus, mycophenolate, trimethoprim-sulfamethoxazole, aspirin, vitamin D, a multivitamin, calcium, magnesium, pantoprazole, and acetaminophen.

On physical examination, the temperature was 38.9°C, pulse was 117 per minute, respirations were 18 per minute, and the blood pressure was 112/69 mmHg. Oxygen saturation was 98% on room air. She appeared lethargic. Pupils were equal, round, and reactive to light. There was no thrush. Lungs were clear to auscultation and percussion. There was a regular tachycardia. The extremities were warm and well perfused. There was no rash and no lymphadenopathy. She responded to questions slowly but appropriately. Cranial nerves were intact, strength in the upper and lower extremities was normal, with normal reflexes, bulk, and tone. Visual fields were not assessed.

Laboratory investigation revealed a sodium of 129 meq/L (reference range [ref], 136–145 meq/L), a normal anion gap, blood urea nitrogen of 46 (ref, 8–21 mg/dL), creatinine of 2.2 (ref, 0.2–1.1 mg/dL), and a calculated glomerular filtration rate of 30 mL/min (ref, ≥60 mL/min). The white blood cell count was $3.73 \times 10^3/\mu L$ (ref, $4.3–10 \times 10^3/\mu L$) with 93% neutrophils (ref, 41%–71%) and no bands. The hemoglobin was 8.3 g/dL (ref, 11.5–15.5 g/dL) and platelets were 103 000/μL (150 000–400 000/μL). The albumin was 3.1 g/dL (ref, 3.5–5.2 g/dL). Serum immunoglobulin (Ig) G and IgM for *Toxoplasma gondii* measured after transplant were negative (pretransplant serologies were not performed). Chest computed tomography scan (Figure 2.4.1) showed subtle peribronchial infiltrates. Magnetic resonance imaging of the brain (Figure 2.4.2) showed a mass measuring 1.7 × 1.6 × 2.0 cm in the right subinsular white matter and basal ganglia region with extensive surrounding edema, producing mild downward transtentorial herniation and right-to-left midline shift. Two additional masses were noted in the left occipital region and the left cerebellar vermis, respectively.

QUESTIONS

- What is the differential diagnosis of central nervous system (CNS) mass lesion(s) in an organ transplant patient?
- Which elements of this patient's prior history are relevant as risk factors?

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of CNS mass lesions after solid organ transplantation (SOT) can be divided into infectious and noninfectious causes. *Toxoplasma gondii, Nocardia asteroides, Listeria*

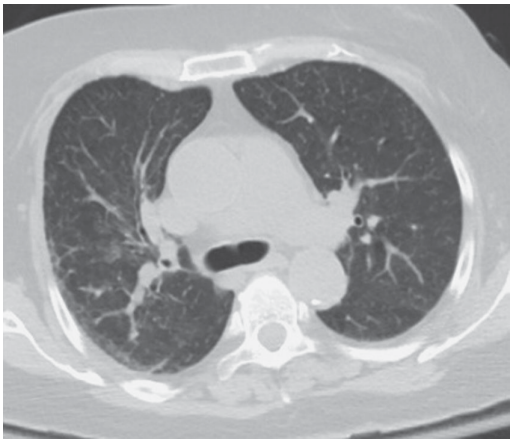


FIGURE 2.4.1: Chest CT scan showing nodules with "tree-in-bud" pattern in bilateral upper lobes.

monocytogenes, Mycobacterium tuberculosis (Mtb), C*ryptococcus, Candida* species, *Aspergillus*, members of the *Mucoraceae* order of Zygomycetes, and John Cunningham virus-related progressive multifocal leukoencephalopathy are important considerations in the infectious category [1]. The noninfectious category includes primary CNS lymphoma, posttransplant lymphoproliferative disorder, and metastatic cancer. Although often cited, Mtb is a very infrequent cause of CNS lesions after transplant [1]. Pyogenic bacteria are also rarely implicated in brain abscesses in SOT recipients, although common in normal hosts [1].

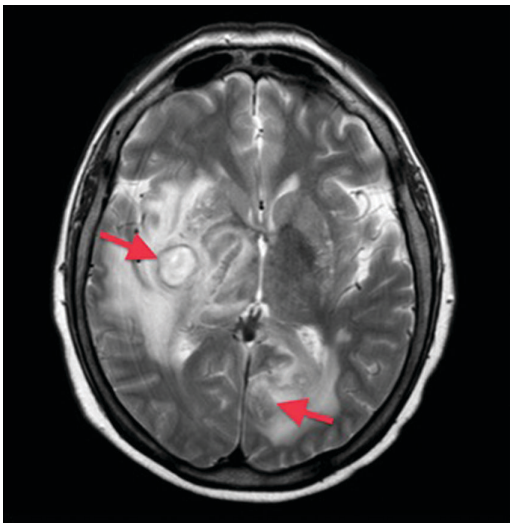


FIGURE 2.4.2: T1 weighted brain MRI image demonstrating right insular/basal ganglia and left occipital lesions, and surrounding edema.

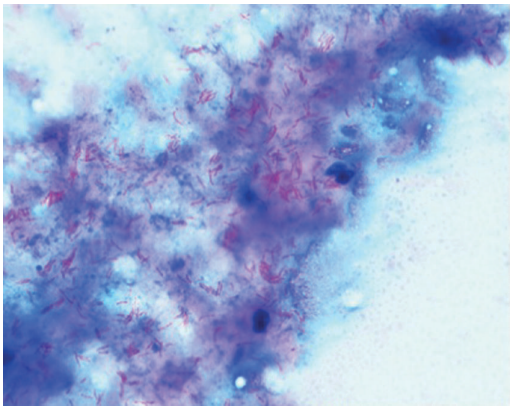


FIGURE 2.4.3: Acid-fast (Kinyoun) stain of brain biopsy showing numerous acid-fast bacill(magnification 1000x).

ADDITIONAL FINDINGS

Cerebrospinal fluid (CSF) examination revealed 11 red blood cells/μL, and 1 nucleated cell/μL (differential: 6% neutrophils, 17% lymphocytes, and 77% macrophages), 46 mg/dL, glucose and 63 mg/dL protein (ref, 15–45 mg/dL). Cerebrospinal fluid bacterial and fungal stains and culture were negative. Polymerase chain reaction (PCR) testing of the CSF for bacterial, mycobacterial, and fungal DNA was negative. Brain biopsy revealed 4+ acid-fast bacilli on Kinyoun stain (Figure 2.4.3), with *M tuberculosis* detected by PCR of brain tissue. Subsequently, *M tuberculosis* was cultured from brain tissue, tracheal aspirate, and sputum. All isolates were susceptible to isoniazid (INH), rifampin, ethambutol, streptomycin. and pyrazinamide.

Final Diagnosis: Disseminated tuberculosis with brain abscess

TREATMENT AND OUTCOME

Treatment was initiated with INH, ethambutol, pyrazinamide, rifabutin, and prednisone. Mycophenolate was discontinued and tacrolimus dosing was reduced. Rifabutin was discontinued after approximately seven weeks due to severe drug interaction with tacrolimus. The patient then continued therapy with INH and pyrazinamide and moxifloxacin. She eventually completed a total of twenty months of therapy without relapse.

DISCUSSION

The majority of TB occurs within one year of transplant (median, nine months). Rare instances of donor allograft transmission of active or latent infection as well as de novo acquisition after transplant have also been described [2, 3].

Pathophysiology

Most cases of posttransplant TB arise from reactivation of latent infection in the setting of suppressed T-cell immunity. In TB-endemic countries, however, it is speculated that a greater proportion of cases arise from de novo infection after transplant, although this has not been well documented. Lung transplant recipients from donors with latent or active TB appear to have a particularly high risk of developing donor-derived TB compared with recipients of nonlung organs. M. tuberculosis reaches the CNS hematogenously, usually from a primary focus in the lungs. Intracranial TB abscess is quite rare, but it may arise from a tuberculoma in the brain parenchyma or by contiguous spread from the meninges.

Clinical Manifestations

The presenting symptoms and signs of TB after SOT are frequently nonspecific and may be "atypical." For example, cough and hemoptysis may be absent. In one series from Spain, 72% of patients had fever and/or constitutional symptom, such as night sweats or weight loss. Most (89%) had abnormal chest imaging [4], with pleural effusion found in 13%–44%, miliary disease in 11%–22%, and interstitial infiltrates in 5%–22%. Cavitary lesions are rare (4%–6%) [3, 4]. Dissemination and extrapulmonary disease seem to be more frequent in SOT, occurring in 9%–50% of transplant recipients versus 3%–21% in the general population [3–6]. Unusual presentations include cutaneous manifestations, genitourinary or hepatobiliary disease, colitis, pyomyositis, and tenosynovitis [2].

Tuberculosis is a very infrequent cause of CNS lesions after organ transplant. In a review of TB manifestations in SOT recipients, only 1% (5 of 476) had brain abscess [3]. In immunocompetent persons, fever and headache are the most frequent clinical signs of CNS TB (mostly meningitis cases); seizures and confusion are uncommon. Intracranial TB abscess often presents clinically as a focal neurologic deficit with one or more ring-enhancing, supratentorial or cerebellar lesions.

Risk Factors

The risk of active TB after SOT is estimated to be twenty to seventy-four times that of the general population, and it appears greatest in lung and kidney transplant recipients [7]. Proposed risk factors for the development of TB after SOT include the use of T cell-depleting antibodies (e.g. anti-CD3 antibodies), heightened immunosuppression (e.g. treatment of rejection), use of mycophenolate or tacrolimus, latent TB infection, radiography consistent with prior untreated or healed TB, renal failure, diabetes, advanced age, lung transplantation, hepatitis C virus infection, chronic liver disease, and coexisting infections, including CMV, *Pneumocystis jiroveci*, and *Nocardia* [5,8]. These predisposing conditions are in addition to risk factors for TB in normal hosts.

Diagnosis

Because TB may present nonspecifically, diagnosis in a transplant patient requires a high index of suspicion. Tuberculosis should be strongly considered in patients with fever of unknown origin, especially when there is a history of residence in a TB-endemic country, prior treated or untreated disease, or abnormal chest imaging. Cultures of sputum, blood, urine, or bronchoalveolar lavage should be obtained. Biopsy of the lung or other suspected sites (liver, kidney, lymph node, skin, CSF, or brain) may also be required. Specimens should be submitted for stain and culture for acid-fast bacilli and histopathology for acid-fast organisms. Skin testing (PPD) or interferon gamma release assays do not contribute significantly to the diagnosis of active TB in immunosuppressed patients.

Management

Tuberculosis treatment in SOT follows the guidelines recommended for the general population. However, drug interactions between the rifamycins (rifampin, rifabutin, rifapentine) and immunosuppressive agents (tacrolimus, cyclosporine, and rapamycin) complicate the selection of anti-TB drugs (see below). Treatment duration is another unsettled issue. Data suggest that treatment for less than nine to twelve months may be associated with a higher risk of recurrence or death [8]. Nonetheless, European guidelines for kidney transplant recipients recommend two months of INH, rifampin, and pyrazinamide therapy, followed by four months of INH and rifampin [9]. American guidelines recommend daily INH, rifampin/rifabutin, pyrazinamide, and ethambutol for the initial two months of treatment, followed by daily INH and rifampin for an additional eighteen weeks [2, 10]. For CNS disease, nine to twelve months of therapy, with adjunctive corticosteroids given in a tapering dose for the first several months, is appropriate.

Complications of TB and its therapy include interactions between immunosuppressive and anti-mycobacterial drugs, hepatitis, immune reconstitution syndrome, and death. The

rifamycins—in particular, rifampin—induce cytochrome P450 (P450) 3A4, increasing metabolism of calcineurin inhibitors, rapamycin, corticosteroids, and mycophenolate mofetil. In contrast, steroids may reduce serum levels of INH. Rejection and graft loss have been reported with the concomitant use of rifampin and tacrolimus or cyclosporine, due to the potent drug interaction between these drugs [4, 8]. Tacrolimus, cyclosporine dose should therefore be increased when rifampin is used, with close monitoring of calcineurin inhibitor levels [2, 3, 8]. Rifabutin causes less P450 3A4 induction compared with rifampin and rifapentine, and so it is often the rifamycin of choice in this setting. Use of rifamycins (rifabutin) is generally recommended in US guidelines because of this class's ability to sterilize TB-infected tissues, but must be weighed against the risk for serious drug interactions [2]. In contrast, Spanish guidelines do not list rifamycins as first-line therapy for nondisseminated disease [8], and some authors recommend against their use. Hepatic toxicity has been frequently reported with INH and rifampin use [8]. In several studies from Spain, hepatitis was reported in (1) 33%–39% of subjects overall, (2) 50%–71% of liver transplant recipients, and (3) 20%–37% of kidney transplant recipients [4, 8]. The immune reconstitution syndrome is a sudden inflammatory response to pathogens when immune suppression is tapered. This syndrome is well described in human immunodeficiency virus and TB-coinfected patients and occurs as antiretroviral treatment restores T cell immune function. It has also been described in the setting of TB in SOT recipients.

Prevention

The cornerstone of TB prevention remains detection of latent TB infection (LTBI) before transplant. Tests for LTBI include the TST (or PPD) or a TB-specific interferon-gamma release assay (IGRA). The presence of classic risk factors (country of origin, social and medical risk factors, and history of exposure) [2] should raise the suspicion for occult active or latent disease, even if testing is negative. Guidelines recommend presumptive treatment of LTBI for individuals with geographic risk factors, unclear or incomplete treatment history, or imaging suggestive of TB even if TST or IGRA results are negative [2, 8]. Because many transplant candidates have cutaneous anergy, some experts recommend applying another TST seven to fourteen days after the first one if it is negative. Alternatively, an IGRA may be followed by a TST, to avoid a false-positive IGRA test result due to a recall response to the TST [2]. Treatment of LTBI should ideally be completed before transplant if feasible and tolerated, although treatment can be initiated or continued after transplant, particularly if decompensated liver disease precludes safe pretransplant treatment, as is commonly the case in liver transplant candidates. Daily INH for nine months or daily rifampin for four months are recommended; weekly INH and rifapentine for twelve weeks may also be an option, although without data from the literature to guide use in transplant candidates [2]. Donors should routinely be assessed for active TB, and organs from donors with suspected or proven active TB should not be used. Because of various logistical limitations, testing for latent TB infection in donors is not routinely done.

KEY POINTS

- Manifestations of TB in SOT recipients are often nonspecific, but fever is almost always present with disseminated disease.
- TB is an infrequent cause of CNS lesions in SOT.
- Diagnosis may require biopsy of suspect lesions.
- Treatment is complicated by drug interactions, hepatic toxicity, and the potential for immune reconstitution syndrome.
- Diagnosis and treatment of LTBI is key to preventing reactivation disease posttransplant.

REFERENCES

1. Selby R, et al. Brain abscess in solid organ transplant recipients receiving cyclosporine-based immunosuppression. Arch Surg. 1997;132:304.
2. Subramanian AK, Morris MI, *Mycobacterium tuberculosis* infections in solid organ transplantation. Am J Transplant. 2013;13:68.
3. Singh N, Paterson DL. *Mycobacterium tuberculosis* infection in solid-organ transplant recipients: impact and implications for management. Clin Infect Dis.1998;27:1266.
4. Bodro M, Sabé N, Santín M, et al. Clinical features and outcomes of tuberculosis in solid organ transplant recipients. Transplant Proc. 2012;44:2686.
5. Torre-Cisneros J, Doblas A, Aguado JM, et al. Tuberculosis after solid-organ transplant: incidence, risk factors, and clinical characteristics in the RESITRA (Spanish Network of Infection in Transplantation) cohort. Clin Infect Dis. 2009;48:1657.
6. Centers for Disease Control and Prevention. US Department of Health and Human Services. Atlanta, GA, 2011.

7. Horne DJ, Narita M, Spitters CL, et al. Challenging issues in tuberculosis in solid organ transplantation. Clin Infect Dis. 2013;57:1473.
8. Aguado JM, Torre-Cisneros J, Fortún J, et al. Tuberculosis in solid-organ transplant recipients: consensus statement of the group for the study of infection in transplant recipients (GESITRA) of the Spanish Society of Infectious Diseases and Clinical Microbiology. Clin Infect Dis. 2009;48:1276.
9. EBPG Expert Group on Renal Transplantation. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.7.2. Late infections. Tuberculosis. Nephrol Dial Transplant. 2002;17:39.
10. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603.

2.5

A Purplish Skin Lump

CHRISTINE M. DURAND, MD AND KIEREN MARR, MD

CASE PRESENTATION

A 56-year-old man presented with a slowly enlarging skin lesion on his right thigh. He had a history of adult polycystic kidney disease and had received a living unrelated kidney transplant two years prior. Five months prior to the presentation, he was found to have proteinuria and evidence of focal segmental glomerulosclerosis on kidney biopsy, for which he was treated with rituximab and was undergoing serial plasmapheresis treatments.

One month prior to presentation, he had noted a 1 cm red nodule on the lateral aspect of his right thigh. He denied any antecedent trauma, and the lesion was nontender without associated induration, pruritus, or drainage. Over the course of four weeks, the area of erythema extended to approximately 6 × 6 cm, at which time he presented for evaluation.

He reported no fevers or chills, no weight loss, no respiratory symptoms. A comprehensive review of systems was otherwise negative. His past medical history was significant for osteoarthritis, gout, and hyperlipidemia. He was cytomegalovirus seronegative as was his kidney donor.

He was married and lived with his wife in New Jersey, with a pet dog and cat. He was a construction site supervisor, and he had recently been overseeing the clearance of destroyed homes in the aftermath of a severe hurricane in the Northeast. His work required contact with standing water, soil, and hurricane debris. He did not consistently wear a mask during this work. He reported no international travel and had never lived outside of the Northeastern United States. He reported no substance abuse.

His medications included mycophenolate mofetil 1000 mg twice daily, tacrolimus 2 mg twice daily, and prednisone 5 mg daily. He was not on any prophylactic antimicrobials.

On physical exam, he was afebrile and appeared comfortable. His sclera were nonicteric and his oropharynx was without lesions or thrush. He had no palpable lymphadenopathy. His cardiac exam demonstrated regular rate and rhythm and no murmurs were appreciated. His chest was clear to auscultation. His abdomen was soft and nontender. On his right thigh, he had a solitary 6 × 6 cm reddish-brown indurated lesion with poorly defined borders, with some palpable subcutaneous nodularity (Figure 2.5.1). The lesion was nontender, slightly warm, and without associated ulceration or drainage. There were no other skin lesions identified.

Laboratory evaluation showed a white blood cell count of 6600 cells/cu mm, hemoglobin of 14.2 g/dL, platelet count of 233 000/cu mm, and creatinine of 1.4 mg/dL. Serum transaminases were normal.

DIFFERENTIAL DIAGNOSIS (INFECTIOUS)

Fungal

- Phaeohyphomycosis
- Blastomycosis
- Coccidiomycosis

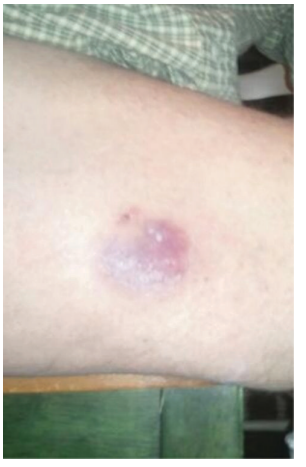


FIGURE 2.5.1: Skin lesion, right thigh, lateral aspect.

- Histoplasmosis
- Cryptococcosis
- Aspergillosis
- Zygomycosis
- Sporotrichosis

Bacterial

- Nocardiosis
- Nontuberculous mycobacteria

Many infections can present with focal skin lesions, either at the primary site of inoculation or as a manifestation of disseminated infection (e.g. cutaneous dissemination in the context of pulmonary infection). Given the insidious nature of presentation and lack of systemic symptoms, the differential in this case is weighted towards slow-growing "atypical" organisms, such as mycobacteria and *Nocardia*, and fungi. Other, noninfectious diagnoses (e.g. skin cancer) would also need to be entertained.

ADDITIONAL DATA

Bacterial, mycobacterial, and fungal cultures of the blood were without growth. Serum cryptococcal antigen was negative. A computed tomography scan of the chest did not show any pulmonary nodules, calcifications, or adenopathy.

In an examination of skin biopsy, the following result was revealed: on hematoxylin-eosin stain, granulomatous infiltrate with suppurative inflammation was seen, including histiocytes, multinucleated giant cells, neutrophils, eosinophils, and lymphocytes. Pigmented hyphal forms were visualized within the granuloma (Figure 2.5.2a), septated hyphal forms were highlighted with Grocott's methenamine silver stain (Figure 2.5.2b), Fontana-Masson stain confirmed the presence of melanin in the hyphae (Figure 2.5.2c), and culture of skin tissue grew *Exophiala dermatitidis*.

Final Diagnosis: Cutaneous phaeohyphomycosis, caused by *Exophiala dermatitidis*

TREATMENT AND OUTCOME

No surgical intervention was performed. The patient was treated with posaconazole and over three months had regression of the lesion.

DISCUSSION

Phaeohyphomycosis refers to a spectrum of disease caused by filamentous fungi that have cell walls containing melanin. These dark molds, also known as dematiaceous fungi, are ubiquitous in the environment. Many genera of fungi are included in this group of dark molds. The most common genera reported to cause disease include *Alternaria, Bipolaris, Cladophialophora, Curvularia, Exophiala, Exserohilum*, Ochronosis, *Phaeoacremonium, Phialophora, Scedosporidium*, and *Wangiella* [1].

These pathogens rarely cause invasive disease in normal hosts but can cause opportunistic infection in immunocompromised individuals such as solid organ transplant recipients or stem cell transplant recipients [2–4]. The dematiaceous fungi are most commonly known for causing localized cutaneous disease, but they have also been reported to cause sinus and pulmonary disease, joint infections, and central nervous system (CNS) infections [1].

The ubiquitous nature of the organisms in soil and other environmental sources explains the epidemiologic patterns of exposures and disease. Serial studies suggest that observed rates of disease are variable and depend on geography. For instance, cutaneous phaeohyphomycosis have been reported most frequently in people residing in warmer climates such as India [5]. In 2012, the dematiaceous mold, *Exserohilum rostratum*, has drawn attention as the predominant cause of CNS and articular infections associated with injection of corticosteroids contaminated during drug compounding [6].

Clinical Presentation

Cutaneous phaeohyphomycosis typically manifests as a single cutaneous or subcutaneous lesion that enlarges slowly over time. Infection usually arises through trauma to the skin with direct inoculation of the organism and resulting skin lesion(s) at the site. Local deeper invasion may occur, but systemic dissemination appears to be relatively uncommon. Systemic symptoms of infection (fever, sweats, etc) are uncommon [1, 2].

Diagnosis

With no pathognomonic physical exam findings, tissue biopsy is critical. Exposures such as those for the patient in this case (significant occupational exposure due to his construction work and extensive contact with soil and decaying plant material) combined with skin lesions should raise the suspicion for the diagnosis. A definitive diagnosis can be made through examination of tissue biopsy, with the characteristic histologic finding of thick-walled, dark brown bodies known as sclerotic bodies or "copper pennies." These forms represent individual fungal cells that stain positive for melanin in the cell walls with Fontana-Masson stain as seen in Figure 2c. Species can be identified

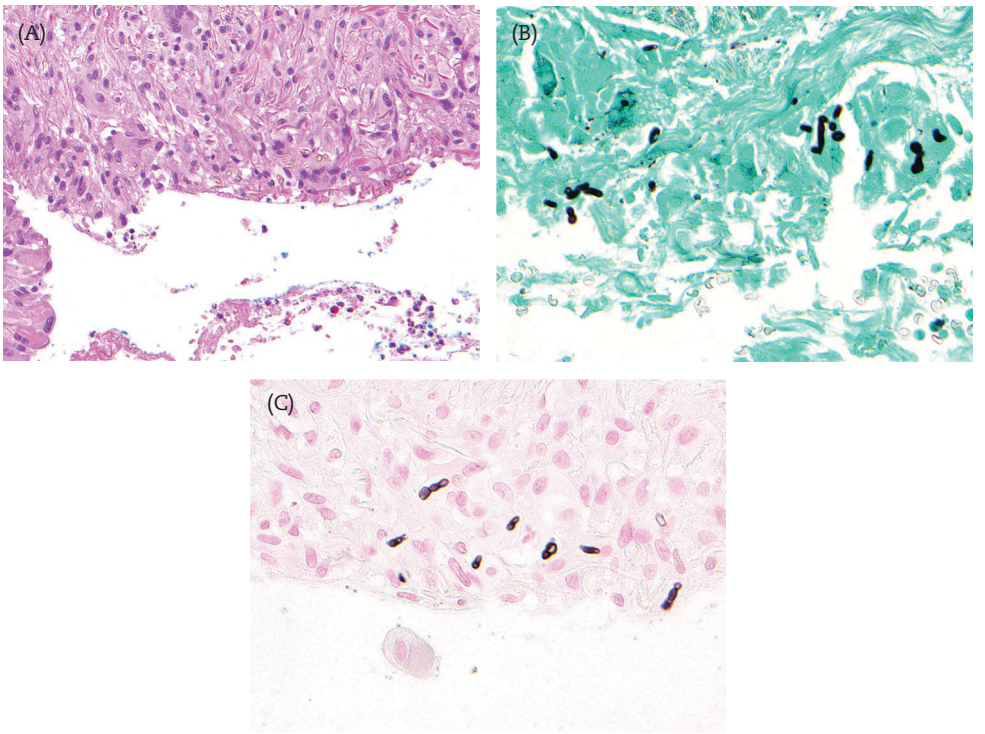


FIGURE 2.5.2: A) Pigmented hyphae in skin tissue, hematoxylin and eosin stain B) Septated hyphal forms, Grocott's methenamine silver stain C) Melanin in hyphae, Fontana-Masson stain.

through fungal culture based on colony and microscopy morphology. Direct molecular detection techniques have been described to be useful but are not standardized [1].

In addition, it is also critical to determine whether the lesion represents isolated cutaneous infection or whether it is a sign of disseminated infection. In particular, in cases in which there is no history of traumatic inoculation, imaging of the lungs to evaluate for pulmonary infection as a potential portal of entry should be considered.

Treatment

In cases of localized cutaneous phaeohyphomycosis, outcomes are very good. There are no clinical trials to guide treatment, because this is a relatively rare infection. Surgical resection alone, treatment with antifungal therapy alone, or a combination of surgical and medical management have all been described. For *Exophiala* species, itraconaozle, voriconazole, and posaconazole have all been shown to have in vitro activity [1, 2]. Reported cure rates are very high and recurrences rare.

KEY POINTS

- Phaeohyphomycosis refers to disease caused by dematiaceous fungi (or dark molds).
- Localized cutaneous disease is the most common presentation.
- The diagnosis is made through tissue biopsy, with the classic finding of thick dark-walled "copper pennies" that are positive for melanin on Fontana-Masson stain.
- Mortality is very low with localized cutaneous disease.
- Surgical resection alone, systemic antifungal therapy alone, or combined surgical and systemic antifungal therapy have been reported to be effective.
- Most of the triazole antifungal medications demonstrate in vitro activity, and clinical responses to itraconaozle, voriconazole, and posaconazole have all been reported in the literature.

REFERENCES

1. Pappas PG. Dematiaceous fungal infections. In: Goldman L and Schafer A, eds. *Goldman's Cecil Medicine*. 24th ed. Philadelphia: Elsevier Saunders; 2012: 343:2101–2103.
2. Revankar SC. Dematiaceous fungi. Mycoses 2007;50:91.
3. Lief MH, Caplivski D, Bottone EJ, et al. *Exophiala jeanselmei* infection in solid organ transplant

recipients: report of two cases and review of the literature. Transpl Infect Dis. 2011;13:73.
4. Vermeire SE, de Jonge H, Lagrou K, Kuypers DR. Cutaneous phaeohyphomycosis in renal allograft recipients: report of 2 cases and review of the literature. Diagn Microbiol Infect Dis. 2010; 68:177.
5. Sharma NL, Mahajan V, Sharma RC, Sharma A. Subcutaneous pheohyphomycosis in India: a case report and review. Int J Dermatol. 2002;41:16
6. Kainer, MA, Reagan DR, Nguyen DB, et al. Fungal infections associated with contaminated methylprednisolone in Tennessee. N Engl J Med. 2012;367:2194.

2.6

To Accept or Not To Accept?

IGNACIO A. ECHENIQUE, MD AND MICHAEL G. ISON, MD, MS

CASE PRESENTATION

A 55-year-old female with a remote history of alcohol abuse and cirrhosis is evaluated for liver transplantation after receiving an offer from a potential donor organ from the local organ procurement organization (OPO). She is blood type O and is currently the highest listed potential recipient at your institution with a Model for End-Stage Liver Disease score of 32. Past medical and surgical histories are otherwise unremarkable. Her daily medications include lactulose and rifaximin. She has no known drug allergies. She was afebrile, hemodynamically stable, and had stigmata of end-stage liver disease.

The potential donor is a 24-year-old male who was admitted four days prior with bacterial meningitis complicated by anoxic brain injury (Figure 2.6.1). He had no previously known past medical history. He was otherwise in his usual state of health until two days before admission noting fever, lethargy, and headache. Upon presentation to an outside institution, evaluation was notable for obtundation and nuchal rigidity. He required intubation for failure to protect his airway. After resuscitative measures and diagnostic testing including cerebrospinal fluid testing, *Streptococcus pneumoniae* meningitis was identified. His fevers resolved with empiric antibiotic treatment. Magnetic resonance imaging of the brain demonstrated diffuse gray matter injury consistent with anoxic brain injury. His next of kin have elected to withdraw care with consent for organ and tissue donation. He took no medications routinely. He worked as a forest ranger in a local nature preserve up until the days he became symptomatic. Social history was otherwise notable for one pack of cigarettes weekly, two beers a night, and no known illicit substance use. No animal exposure was reported. He occasionally enjoyed hunting for sport. He was born and raised in a suburb of Chicago. He has never traveled outside of the country. Laboratory evaluation included isolation of *S pneumoniae* from cerebrospinal fluid cultures, notable for a minimum inhibitory concentration to penicillin of ≤0.06 mcg/mL. His donor screening tests include negative human immunodeficiency virus (HIV) antigen/antibody combination testing and viral load, negative hepatitis A, B, and C serologies, and negative hepatitis B and C viral loads.

QUESTIONS

- What are the risks of donor-derived infection?
- What are the risks of transmission of bacterial meningitis to the recipient?
- With informed consent, would it be appropriate to accept the offer for liver transplantation?

DISCUSSION

Donor-derived infections are divided into those that are expected or unexpected. To mitigate against donor-derived disease transmission, all donors are screened according to Organ Procurement and Transplantation Network (OPTN) policy (Box 2.6.1), with some donors having supplemental testing at the discretion of the accepting OPO and transplant center [1, 2]. Past exposure to certain infections (e.g. cytomegalovirus), particularly those with potential for latency, is an indication for prophylactic therapy or preemptive monitoring. Other infections (e.g. HIV) preclude transplantation altogether. More importantly, although the objective of pretransplant screening is to reduce the risk of unexpected disease transmission, elimination of such risk is often not feasible. It is estimated that the risk of donor-derived disease transmission complicates 0.2% of all donations [3].

Unfortunately, disease may be present that is not recognized at the time of donation and inadvertently transmitted to the recipients from the donor. Organ Procurement and Transplantation Network policy requires the OPO or transplant center

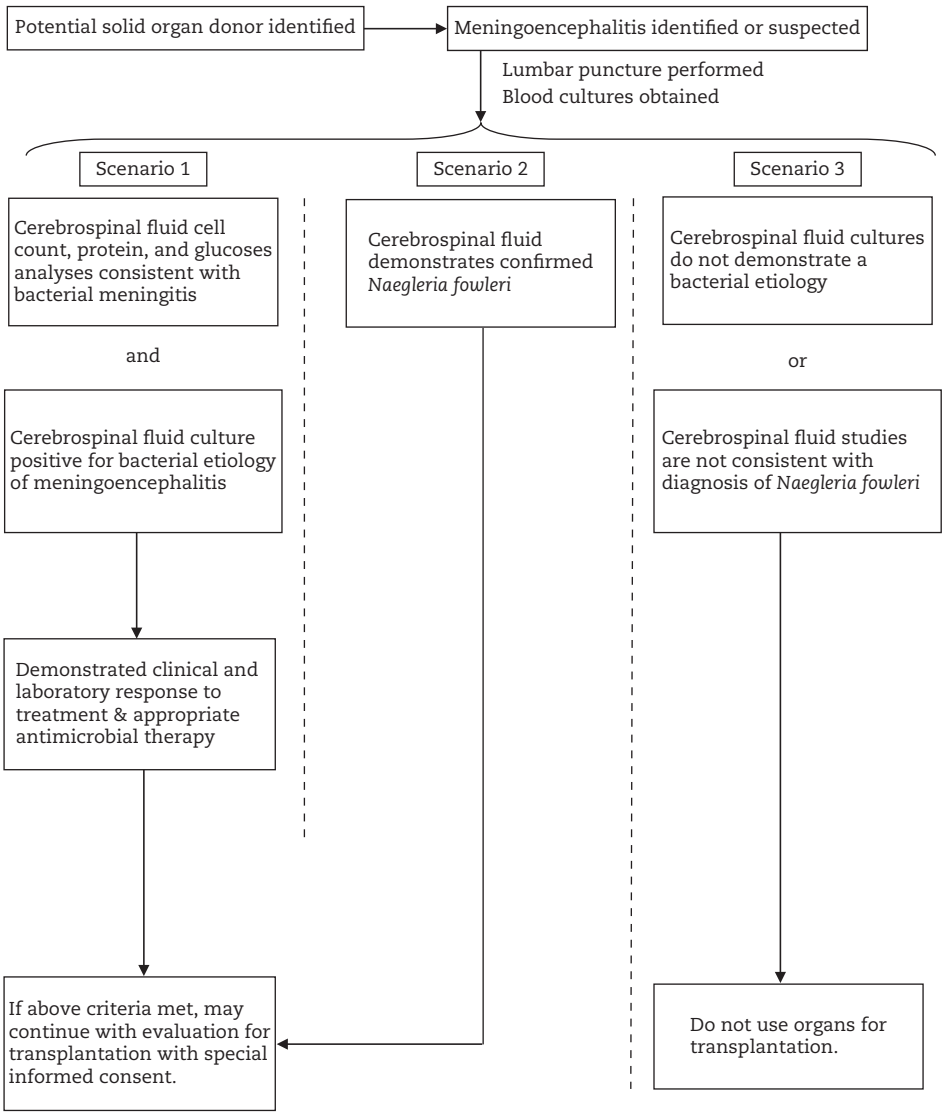


FIGURE 2.6.1: Left knee medial aspect with demonstration of *ecthyma gangrenosum*, a hallmark of bacteremia, most often associated with *Pseudomonas Aeruginosa* among other gram-negative bacilli, although not exclusively.

to promptly report (within twenty-four hours) any concern for an unexpected donor-derived disease transmission. The potential transmission events are reviewed and categorized by the OPTN/United Network for Organ Sharing Disease Transmission Advisory Committee [3, 8]. Potential donor-derived infectious disease transmissions have involved viruses (hepatitis B virus, hepatitis C virus, HIV, West Nile virus, rabies, lymphocytic choriomeningitis virus [LCMV], and others), bacteria (*Acinetobacter, Brucella, Enterococcus, Klebsiella, Staphylococcus aureus* including methicillin-resistant *S aureus, Pseudomonas, Syphilis*, bacterial meningitis), fungi (*Aspergillus, Candida, Coccidioides immitis, Cryptococcus neoformans, Histoplasma capsulatum*, and agents of mucormycosis), *Mycobacterium tubcerculosis*, and parasitic infections (*Trypanosoma cruzi*, schistosomiasis, *Strongyloides*) [3, 8].

All donors are screened for bacteremia by blood culture, according to OPTN policy. Bacterial infections of the donor may be recognized, and care should be used in assessing the risk of disease transmission from donors with confirmed bacterial infections. Ongoing uncontrolled bacteremia represents a potential risk for transmission, and experts recommend treating the donor with antibacterials that are known to be effective against the cultured

BOX 2.6.1 REQUIRED AND RECOMMENDED DONOR INFECTIOUS DISEASES SCREENING TESTS

OPTN-required deceased donor screening [4]

- Anti-HIV I, II*
- Hepatitis screen serological testing, including:
  - HBV surface antigen
  - HBV core antibody
  - HCV antibody
- Venereal Disease Research Laboratory or Rapid Plasma Reagin (RPR)†
- CMV antibody
- Epstein-Barr virus antibody
- Blood and urine cultures
- Chest x-ray
- For potential deceased lung donors: sputum Gram stain

PTN-required living organ donor screening [5]

- Testing as per Deceased Donor Screening Requirements
  - For syphilis screening, RPR alone
  - In addition, HBV surface antibody (HBsAb)
- Purified protein derivative or interferon gamma release assay for latent tuberculosis infection
- Testing for HIV, HBV, and HCV within 30 days, but optimally within 14 days, of the organ donation procedure
- If the donor is from an endemic area (as determined by the transplant center), testing for the relevant pathogen must be included [5].
  - Strongyloides
  - *T cruzi*
  - West Nile virus

Screening tests recommended by some experts/in certain scenarios but not required by OPTN policy

- HIV, HCV, and/or HBV nucleic acid test (NAT)
- Human T-cell lymphotropic virus-I/II antibody
- Herpes simplex virus immunoglobulin G antibody
- HBsAb
- Toxoplasma antibody (usually only for heart donors)
- Varicella-zoster virus antibody
- For donors from endemic areas
  - Coccidioides serology
  - Strongyloides serology
  - *T cruzi* serology
  - West Nile virus NAT

**Only US Food and Drug Administration (FDA)-licensed testing for screening prior to organ donation acceptable; diagnostic testing not acceptable.*

† FDA-approved diagnostic tests are acceptable.

Note: US Public Health Service guidelines for defining increased risk donors and their evaluation have been published [6]. Centers should always review current OPTN policy to stay abreast of any changes [7].

bacteria and to assess for metastatic foci. Once the donor has evidence of clinical, and optimal microbiologic, response to initial treatment, donors may be utilized with appropriate therapy given to the recipient for a duration consistent with the infection in the donor (i.e. donors with simple bacteremias, treatment of recipients for two weeks is generally recommended). Recipients from donors with infection of a single organ in the absence of bacteremia (e.g. pneumonia or urinary tract infection) require treatment if the respective infected organ was transplanted (i.e. lung or kidney, respectively).

One unique bacterial infection that warrants particular attention is the donor with bacterial meningitis. First and foremost, it is essential to determine that the donor truly has bacterial meningitis, because cerebrospinal fluid abnormalities consistent with meningitis without positive cultures can be associated with other transmissible diseases, including viral encephalitis and malignancy, particularly leukemias and lymphomas. The donor with documented bacterial meningitis should be treated for the identified organism, given presumed presence of concurrent occult bacteremia. With appropriate antibiotics and a clinical response in the donor (e.g. defervescence, improvement in leukocytosis) and antibiotic therapy in the recipient, transplantation of organs from a donor with bacterial meningitis does not appear to compromise graft function or recipient outcomes (Table 2.6.1) [1, 9–11].

It is critical to remember that the recipient must be informed about the presence of any transmissible disease. In the presence of confirmed or suspected infections, special informed consent must be obtained prior to the use of such affected organs according to OPTN policy [12].

Final Diagnosis: *Streptococcus pneumoniae* meningitis

Treatment and Outcome

The risks are discussed with your patient and family, and they provide consent to undergo liver transplantation from the donor with *S pneumoniae* meningitis. After review of the susceptibilities of the *S pneumoniae* cultured from the donor, the liver recipient is treated for fourteen days at the recommendation of the Transplant Infectious Diseases team. The recipient did not experience fever or alterations in mental status, and she recovered without complication after fourteen days of intravenous antibiotics.

QUESTION

- If the etiology of the donor's meningoencephalitis was of uncertain etiology, would this affect acceptance of the offer for transplantation?

SUMMARY

Donors with meningoencephalitis likely represent the subset with the highest risk of having

TABLE 2.6.1. OUTCOMES OF RECIPIENTS OF ORGANS FROM DONORS WITH BACTERIAL MENINGITIS

Reference	Comment
Cantarovich et al. [16]	Case report of a single donor with *Neisseria meningitidis* meningitis. No reported complications in the two renal allograft recipients.
Lopez-Navidad et al. [10]	Reviewed 5 solid organ donors with bacterial meningitis and the associated 16 recipients. No infectious complications were reported.
Paig i et al. [9]	Reviewed 7 solid organ donors with bacterial meningitis. No infectious complications in the recipients were reported.
Satoi et al. [11]	Reviewed 33 donors with bacterial meningitis liver allografts donated to 34 recipients. There were no differences in patient and graft survival among matched-groups at 60 months.
Issa et al. [17]	Commentary paper with literature review. Does not advise transplant candidacy for donors with bacterial meningitis due to *Listeria monocytogenes* citing a concern for a high risk of relapse.
Mirza et al. [18]	Surveyed pediatric transplant centers including a unit in England and 3 U.S. centers, all of whom reported successful use of liver allografts from donors with bacterial meningitis, without observed increased morbidity.
Bahrami et al. [19]	Reviewed 39 cadaveric heart and lung donors with bacterial meningitis. No reported related infectious complications or deaths.
Caballero et al. [20]	Case-report of a single donor with postneurosurgical *Escherichia coli* meningitis. No transmission to 3 recipients.

an unexpected transmissible infection. As such, donors with clinical suspicion for meningoencephalitis without proven and treated bacterial cause should generally not be utilized [3, 9, 10]. A range of infections, including but not limited to West Nile virus, LCMV, rabies [13], and *Balamuthia mandrillaris*, have been transmitted from donors with unexplained meningoencephalitis. These transmitted infections have significant clinical consequences including recipient death. The one potential exception to this rule is a donor with proven *Naegleria fowleri* meningoencephalitis. In the few donors with proven *N fowleri*, organs have been safely utilized without transmission [14, 15].

KEY POINTS

- In recipients of organs from bacteremic donors, antimicrobial therapy guided by susceptibility should be initiated without delay. Review of donor cultures (which might only be available after organ procurement) is essential to guide appropriate antimicrobial therapy in the recipient.
- In donors with confirmed bacterial meningoencephalitis who are receiving appropriate antibiotic therapy (except *M tuberculosis*), use of organs for transplantation appears to be associated with a low risk for transmission of infection, as long as appropriate antibiotics are continued in the recipient.
- In donors with suspected meningoencephalitis not documented to be caused by bacterial meningitis or *N fowleri* encephalitis, organ transplantation is not recommended due to the risk of disease transmission with severe sequelae in the recipient.

REFERENCES

1. Fischer SA, Lu K. Screening of donor and recipient in solid organ transplantation. Am J Transplant. 2013;4:9.
2. Garzoni C, Ison MG. Uniform definitions for donor-derived infectious disease transmissions in solid organ transplantation. Transplantation 2011;92:1297.
3. Ison MG, Nalesnik MA. An update on donor-derived disease transmission in organ transplantation. Am J Transplant. 2011;11:1123.
4. OPTN Policy 2.0 Minimum procurement standards for an organ procurement organization (OPO). Available at: http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_2.pdf. Accessed 31 August 2013.
5. OPTN Policy 12.0 Living donation. Available at: http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_172.pdf. Accessed 31 August 2013.
6. Seem DL, Lee I, Umscheid CA, Kuehnert MJ. PHS guideline for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission through organ transplantation. Public Health Rep. 2013;128:247.
7. OPTN Policies. Available at: http://optn.transplant.hrsa.gov/policiesAndBylaws/policies.asp. Accessed 1 September 2013.
8. Ison MG, Hager J, Blumberg E, et al. Donor-derived disease transmission events in the United States: data reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. Am J Transplant. 2009;9:1929.
9. Paig i JM, Lopez-Navidad A, Lloveras J, et al. Organ donors with adequately treated bacterial meningitis may be suitable for successful transplantation. Transplant Proc. 2000;32:75.
10. Lopez-Navidad A, Domingo P, Caballero F, et al. Successful transplantation of organs retrieved from donors with bacterial meningitis. Transplantation 1997;64:365.
11. Satoi S, Bramhall SR, Solomon M, et al. The use of liver grafts from donors with bacterial meningitis. Transplantation 2001;72:1108.
12. OPTN Policy 4.0 Identification of transmissible diseases in organ recipients. Available at: http://optn.transplant.hrsa.gov/PoliciesandBylaws2/policies/pdfs/policy_16.pdf. Accessed 31 August 2013.
13. Vora NM, Basavaraju SV, Feldman KA, et al. Raccoon rabies virus variant transmission through solid organ transplantation. JAMA 2013;310:398.
14. Kramer MH, Lerner CJ, Visvesvara GS. Kidney and liver transplants from a donor infected with *Naegleria fowleri*. J Clin Microbiol. 1997;35:1032.
15. Bennett WM, Nespral JF, Rosson MW, McEvoy KM. Use of organs for transplantation from a donor with primary meningoencephalitis due to *Naegleria fowleri*. Am J Transplant. 2008;8:1334.
16. Cantarovich M, Tchervenkov J, Loertscher R. Transplantation of kidneys from a donor with *Neisseria meningitides* infection. Am J Nephrol. 1993;13:171.
17. Issa NC, Patel R. Potential for expansion of the donor pool using liver allografts from donors with bacterial meningitis. Liver transplantation. 2002;8:977–9.
18. Mirza D, Hastings M, Reyes J, et al. Organ donation from children with meningitis. Pediatr Infect Dis J. 2003;22:475.
19. Bahrami T, Vohra HA, Shaikhezai K, et al. Intrathoracic organ transplantation from donors with meningitis: a single-center 20-year experience. Ann Thorac Surg. 2008; 86: 1554.
20. Caballero F, Puig M, Santos JA, et al. Successful transplantation of organs from a donor with post-neurosurgical meningitis caused by *Escherichia coli*. Translantation. 2012;93:e11.

2.7

Fuzzy Vision and Balance Problems

YUKI AOYAGI, MD, MPH, MA AND RICHARD A. ZUCKERMAN, MD, MPH

CASE PRESENTATION

A 56-year-old man presented with progressive right eye visual loss, confusion, and ataxia. He has a history of combined kidney and pancreas transplant two years ago for diabetic nephropathy (cytomegalovirus [CMV] serology, donor negative/recipient negative; herpes simplex virus [HSV] serology, recipient positive for HSV-1; Epstein-Barr virus serology, donor negative/recipient negative; varicella-zoster virus [VZV] serology, recipient positive). His posttransplant course was complicated by antibody-mediated rejection, treated with plasmapheresis, increased immunosuppression and rituximab. He is currently on maintenance immunosuppression with tacrolimus, sirolimus, and prednisone. Baseline creatinine is 1.3 mg/dL and his glucose levels are well controlled without insulin. He is currently not taking prophylactic antimicrobials. His past medical history is significant also for hypertension and hyperlipidemia.

He is an elementary school teacher and lives with his wife. He quit smoking cigarettes three years ago and has no history of illicit drug use. He has a cat but no farm animals and no recent insect bites. Apart from a trip to Mexico five years ago, he has no other history of foreign travel.

Approximately one month ago he went back to work, and soon after he developed symptoms of upper respiratory tract infection with dry cough and rhinorrhea. He was diagnosed with human metapneumovirus infection. These symptoms subsided spontaneously within a few days, but the following week he developed fatigue with weakness bilaterally in his lower extremities. He also noticed blurry vision of the right eye, for which he was seen and evaluated by an ophthalmologist. His fundoscopic exam showed evidence of inflammatory optic neuropathy (Figure 2.7.1). His vision in the right eye became progressively diminished over the ensuing days, and he started experiencing mental status changes with mild confusion and short-term memory loss. He also complained of problems with balance while walking. He denied headache, nausea, vomiting, diarrhea, or rash.

On presentation, the patient was awake, alert, and oriented to place and person only. His temperature was 100.8°F. His heart rate was 90/minute and blood pressure was 136/56 mmHg. His oxygen saturation was 96% on room air. During the exam, his right pupil was not reactive to light, and the left pupil was sluggish. Other cranial nerve functions were unremarkable. He was noted to have a wide-based ataxic gait with truncal instability, as well as mild bilateral distal lower extremity weakness, which was more prominent in the left side with a brisk deep tendon reflex. His conjunctiva and oral mucus membranes were normal. His neck was supple without lymphadenopathy. Chest auscultation revealed normal breath sounds bilaterally, and no murmurs were appreciated. His

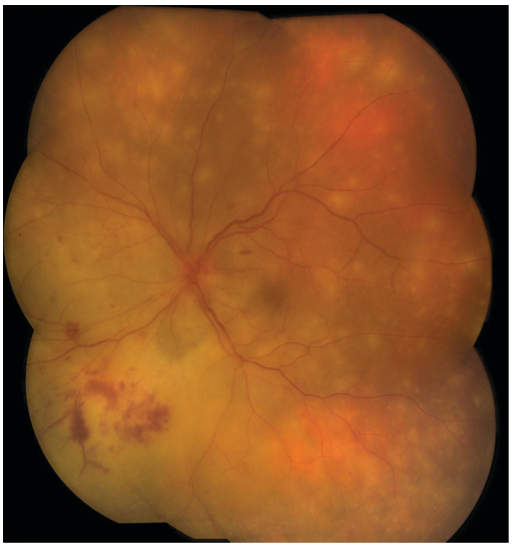


FIGURE 2.7.1: Retinal examination findings in a 56 year old transplant recipient with visual loss showing retinitis and retinal vasculitis with associated acute retinal necrosis.

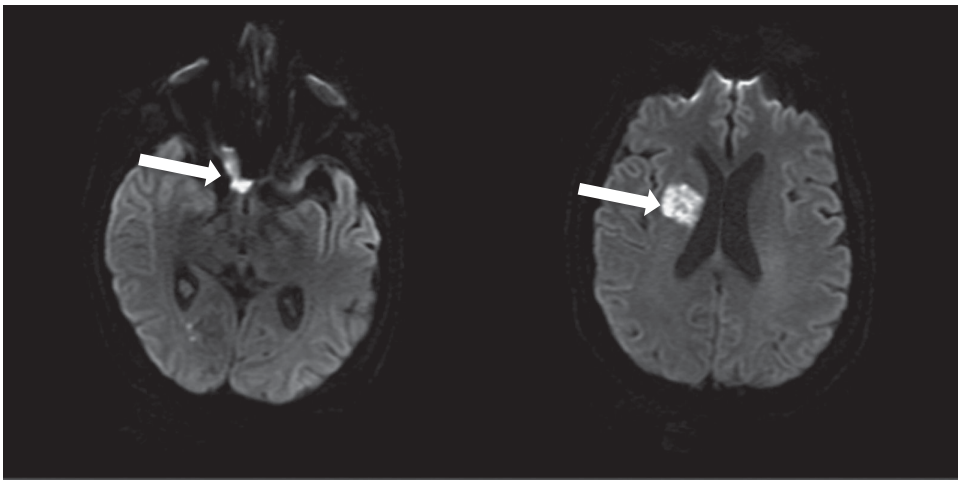


FIGURE 2.7.2: Diffusion-weighted brain MRI images showing involvement of the a) right optic nerve and chiasm, and b) right basal ganglia.

abdominal grafts were not tender and no bruits were detected above them. He did not have rash.

Laboratory evaluation showed white blood cell count (WBC) of 6500 per mm^3, hemoglobin 13.1 g/dL, and platelet count of 230 000/mm^3. Serum electrolytes, creatinine, and liver enzymes were normal. Cerebrospinal fluid analysis showed lymphocytic pleocytosis (WBC 38/μL with 85% lymphocytes, protein 123 mg/dL, glucose 60 mg/dL). Cerebrospinal fluid Gram stain showed moderate WBC but no organisms. Tacrolimus and sirolimus trough levels were therapeutic. Chest x-ray was normal. A magnetic resonance image of the brain revealed optic nerve enhancement on the right and a right basal ganglia infarct (Figure 2.7.2).

QUESTIONS

- What are the possible causes of this syndrome?
- What is the best diagnostic test for this disease?

DIFFERENTIAL DIAGNOSIS

Progressive visual loss in an immunocompromised host with central nervous system (CNS) involvement raises concern for infection with herpes viruses. Optic neuritis and/or acute retinal necrosis (ARN) or progressive outer retinal necrosis (PORN) due to VZV, HSV, or CMV should be considered. *Toxoplasma* and *Bartonella* infections must be considered with the history of cat exposure. Arboviruses infections such as West Nile virus, Eastern equine encephalitis virus, and Western equine encephalitis virus should also be considered in patients with relevant exposure history. Tickborne disease, such as Lyme, is associated with cranial nerve symptoms but is not usually associated with visual loss. Cryptococcal meningitis with cryptococcoma could possibly cause the focal findings, but it is usually not also associated with the ocular findings described in this case. Neurosyphilis should always be in differential diagnosis for patients presenting with CNS symptoms and ocular involvement. Noninfectious causes including medication toxicity (i.e. posterior reversible leukoencephalopathy syndrome from calcineurin inhibitors), stroke, CNS vasculitis, and paraneoplastic syndromes should be considered as well.

Additional Data: Cerebrospinal fluid VZV polymerase chain reaction (PCR) was positive.

Final Diagnosis: Varicella-zoster virus meningoencephalitis with vasculitis

TREATMENT AND OUTCOME

The patient was started on high-dose acyclovir and eventually received steroids due to progressive CNS vasculitis. His condition further deteriorated and he suffered an acute hemorrhagic stroke. He died after two months of hospitalization.

DISCUSSION

Varicella-zoster virus (or human herpesvirus type 3) is associated with a variety of clinical syndromes; immunocompromised hosts are prone to both typical and atypical presentations [1]. The majority of patients receiving solid organ transplant (SOT) have either been infected naturally with VZV or were immunized [1, 2]. Varicella-zoster

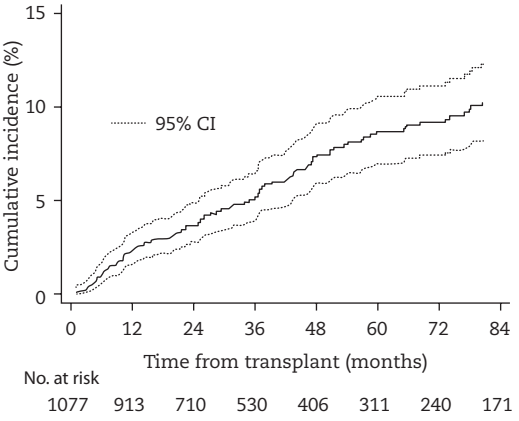


FIGURE 2.7.3: Herpes zoster cumulative incidence in solid organ transplant recipients (Pergam et al. 2009).

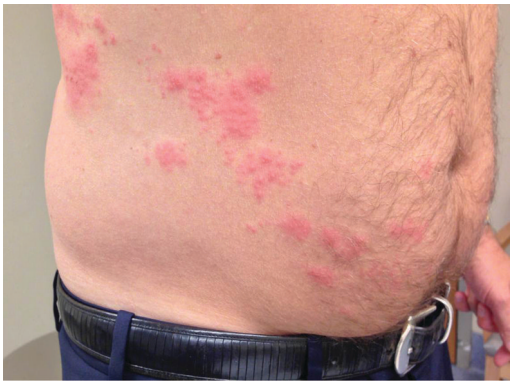


FIGURE 2.7.4: Vesicular dermatomal rash of Herpes Zoster ("Shingles").

virus reactivation after transplantation occurs at a relatively consistent rate over time (Figure 2.7.3).

Pathophysiology

Varicella-zoster virus is a pathogenic human α-herpes virus. Chickenpox develops as a result of primary infection and is usually seen in healthy, unvaccinated children infected via the respiratory route. Although rare, immunocompromised individuals may also be at risk for disseminated chickenpox-like disease from re-infection [3]. After primary infection, VZV establishes latency in the dorsal root ganglia. Herpes zoster (HZ), often referred to as shingles, occurs as a result of reactivation of latent VZV [4]. Varicella-zoster virus-specific cell-mediated immunity is important to prevent reactivation, so administration of potent T-cell active agents in the setting of SOT can potentially decrease immune control of latent VZV, predisposing to HZ [3, 4].

Clinical Manifestations

Chickenpox presents as a disseminated pruritic rash that often starts on the face and spreads down the trunk, with relative sparing of the hands and soles of the feet. New lesions continue to appear for several days, and so patients with chickenpox have lesions at various stages (papules, vesicles, and crusted lesions) at the same time. Mucosal involvement (e.g. buccal, pharyngeal, urogenital) is common. Prodromal symptoms of nausea or anorexia can precede the exanthem in adults or adolescent patients. Immunosuppressed patients may have severe primary infection with rapid progression and multiorgan failure [5].

Herpes zoster most often presents as a painful vesicular rash that involves ≤2 adjacent unilateral dermatomes (Figure 2.7.4). Secondary complications of HZ include bacterial superinfection and postherpetic neuralgia (PHN), or chronic neuropathic pain at the site of the skin lesions [4]. Approximately 20%–40% of transplant recipients with HZ will develop PHN, significantly greater than the rate in the general population [5].

Disseminated HZ usually occurs as a reactivation disease, and it is defined by (1) a distribution of greater than two dermatomes or (2) involvement of two noncontiguous dermatomes and lesions that may mimic primary disease [5]. The most common sites of visceral infection include the lung (pneumonitis), liver (hepatitis), and gastrointestinal tract [4, 5]. Central nervous system meningoencephalitis is often accompanied by localized CNS vasculitis, which can be quite morbid [5]. Herpes zoster ophthalmicus, ARN, and PORN are sight-threatening emergencies that require prompt ophthalmologic evaluation and treatment [4, 6]. A vesicular rash on the nose (Hutchinson's sign) should prompt consideration of opththalmic involvement, because the nasociliary nerve innervates the tip of the nose and the globe.

Risk Factors

Varicella-zoster virus is highly infectious to seronegative persons and is primarily transmitted through droplet or airborne route but can also be spread through direct contact with active skin lesions [5]. In rare instances, virus may be aerosolized from patients with active skin lesions and transmitted to mucosal surfaces [7]. Donor transmitted infection is possible but extremely rare [5]. Varicella-specific antibody likely provides some protection against primary infection, but humoral immunity is less important for protection against VZV reactivation

[8]. Intact VZV-specific cell-mediated immunity is essential to keep the virus from reactivating [8].

Patients with previous natural VZV infection or VZV vaccination are at risk for the development of HZ, although it appears that vaccinated individuals are less likely to develop HZ than those infected naturally [8]. Heart and lung transplant patients and African American patients appear to be at a higher risk for HZ compared with other organ transplant recipients [1, 5].

Diagnosis

Patient history and clinical findings serve to guide the diagnosis of VZV infection. Because of the varied nature of clinical presentation in transplant recipients, however, supportive diagnostics including direct fluorescent assays and PCR are often useful and necessary [5]. Direct fluorescent assay is performed on scrapings taken from the base of a lesion or other tissue specimen [4, 5]. Polymerase chain reaction testing is the most sensitive test, and IT can also be done on blood and other fluids (e.g. cerebrospinal, bronchoalveolar lavage, and vitreous) [4, 5]. Shell vial culture is less sensitive than PCR, but it is very specific and usually available within forty-eight hours. Tissue histopathology can be helpful with immunocytochemistry for VZV.

Management

Primary, disseminated, CNS and visceral varicella requires the early initiation of intravenous (IV) acyclovir 10 mg/kg every eight hours (and adjusted according to renal function). In the setting of severe ophthalmic involvement such as ARN or PORN, intravitreal injections of antiviral agents may be required. Although some experts support reduction in immunosuppression, there have been no controlled trials of this approach. Varicella-zoster virus-specific immune globulin is costly, difficult to obtain, and lacks evidence in efficacy in the setting of evident disease [5].

Mild, localized cutaneous HZ can be treated with oral acyclovir (800 mg five times a day), valcyclovir (1 gram three times a day), or famciclovir (500 mg three times a day). Treatment is given for a minimum of seven days and until all lesions have crusted, which may be longer in immunocompromised hosts. Adjunctive therapies to prevent PHN have not been studied in SOT patients. Patients with localized disease involving the face (trigeminal and geniculate ganglions) should be considered for IV acyclovir therapy (10 mg/kg every eight hours) given the potential for ocular (HZ ophthalmicus) and facial nerve (Ramsay-Hunt syndrome) complications [5].

Prevention

When used as universal prophylaxis for CMV prevention, valganciclovir and ganciclovir also appear to prevent VZV reactivation [5]. However, the risk for VZV reactivation persists for years after transplant, and the relative benefits of extended duration therapy have not been established in this population. Thus, short duration of VZV-specific prophylaxis is not likely to prevent the majority of cases of HZ. Intensification of immunosuppression for organ rejection has been associated with VZV reactivation [5]. Resumption of prophylaxis during rejection episodes is thus warranted.

Varicella-zoster virus seronegative organ transplant candidates without contraindications should be vaccinated with a live-attenuated Oka varicella vaccine (Varivax) prior to transplantation [5]. Serology should be checked after immunization and subsequent doses given for patients who do not respond to the initial series. The "shingles vaccine", Zostavax, has not been studied specifically in transplant candidates as a strategy to reduce the incidence of posttransplant zoster. Because Zostavax is a live vaccine it is contraindicated after transplant. Zostavax can be given more than four weeks before transplant in those who are otherwise eligible to receive it. Other adjuvant and inactivated vaccines that can be given posttransplant are in clinical trials.

Varicella-zoster virus is highly transmissible, and it is therefore important to ensure all close contacts are protected from acquiring primary VZV and potentially exposing the SOT recipient. Isolation precautions, both airborne (including negative pressure room) and contact, are used in hospital settings for transplant patients with zoster [5].

KEY POINTS

- In adult SOT recipients, VZV disease is most commonly due to reactivation, and it typically presents with dermatomal rash.
- Immunosuppressed patients, including transplant recipients, are at risk for severe and/or disseminated infection.
- CNS involvement with VZV is highly morbid.
- History and examination are important methods for a diagnosis of VZV disease.
- PCR is the most rapid sensitive laboratory test.
- IV high-dose acyclovir is the mainstay of treatment for severe disease.
- Airborne and contact isolation precautions are important to prevent the spread of VZV from hospitalized transplant patients.

REFERENCES

1. Gourishankar S, McDermid JC, Jhangri GS, Preiksaitis JK. Herpes zoster infection following solid organ transplantation: incidence, risk factors and outcomes in the current immunosuppressive era. Am J Transplant. 2004;4:108.
2. Pergam SA, Forsberg CW, Boeckh MJ, et al. Herpes zoster incidence in a multicenter cohort of solid organ transplant recipients. Transpl Infect Dis. 2011;13:15.
3. Lauzurica R, Bayes B, Frias C, et al. Disseminated varicella infection in adult renal allograft recipients: role of mycophenolate mofetil. Transplant Proc. 2003;35:1758.
4. Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster. N Engl J Med. 2002;347:340.
5. Pergam SA, Limaye AP. Varicella zoster virus (VZV) in solid organ transplant recipients. Am J Transplant. 2009;9:S108.
6. Volpi A. Severe complications of herpes zoster. Herpes 2007;14:35.
7. Suzuki K, Yoshikawa T, Tomitaka A, et al. Detection of aerosolized varicella-zoster virus DNA in patients with localized herpes zoster. J Infect Dis. 2004;189:1009.
8. Papaloukas O, Giannouli G, Papaevangelou V. Successes and challenges in varicella vaccine. Ther Adv Vaccines 2014;2:39.

2.8

More Than a Green Thumb

JASMIN CHAUDHARY, MD

CASE PRESENTATION

A 57-year-old woman with a history of heart transplantation (cytomegalovirus [CMV] seropositive recipient) nine years ago presented with new bilateral upper lobe lung nodular opacities, some of which appeared cavitary.

The patient had reported several months of anorexia, a 20-pound weight loss, malaise, and early satiety, prompting further evaluation with a computed tomography (CT) scan, then with subsequent bronchoscopy and bronchoalveolar lavage (BAL). For prophylaxis of allograft rejection, she was maintained on three-drug immune suppression with mycophenolate mofetil, tacrolimus, and prednisone 5 mg daily, with no recent augmentation of immune suppression. Her posttransplant course was complicated by posttransplant lymphoproliferative disease two years prior, for which she received six cycles of rituximab-cyclophosphamide, etoposide, procarbazine, and prednisone chemotherapy.

At the time of evaluation, she reported mild dyspnea on exertion, fatigue, and an occasionally productive cough. Specifically, she denied fevers, chills or sweats. She mentioned having a splinter of her right second finger a number of weeks before the onset of symptoms, for which she underwent incision and drainage (I&D) with removal of the splinter by her local healthcare provider.

Exposure history was notable for the fact that she was an avid gardener and reported smoking marijuana four to five times per week. She resides in the Pacific Northwest, with last travel to Hawaii six months prior and a trip to California three years prior. She has dogs and cats at home but denied any bites or scratches. Skin testing for *Mycobacterium tuberculosis* was negative prior to transplantation and no known tuberculosis exposure history was elicited.

On presentation she was afebrile and comfortable, with a heart rate of 102 beats per minute, blood pressure of 125/74 mm mercury, respiratory rate of 15 breaths per minute, and room air oxygenation saturation of 95%. No lymphadenopathy was appreciated. Her lungs were clear and there was no heart murmur. Her thoracotomy scars were clean and well-healed. Her abdominal exam was unremarkable. The prior I&D site on her right finger was noted to be mildly indurated, although with no active drainage or purulence (Figure 2.8.1).

Laboratory evaluation revealed a normal white blood cell count (4500/mm^3) and normal electrolytes and liver function tests. The chest CT was notable for multiple cavitary nodules in both lungs, the largest measuring 2.6 × 1.9 cm in the left upper lobe (Figure 2.8.2). The airways were reportedly normal in appearance on bronchoscopy, with scant secretions but no purulence. Cultures and other studies from the bronchoscopy with BAL were pending.

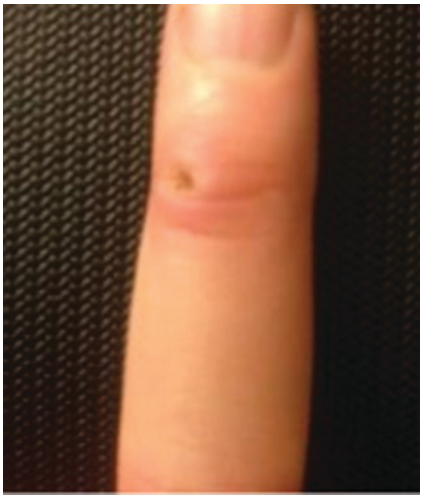


FIGURE 2.8.1: Right second finger demonstrating small ulceration and local induration at site of prior splinter.

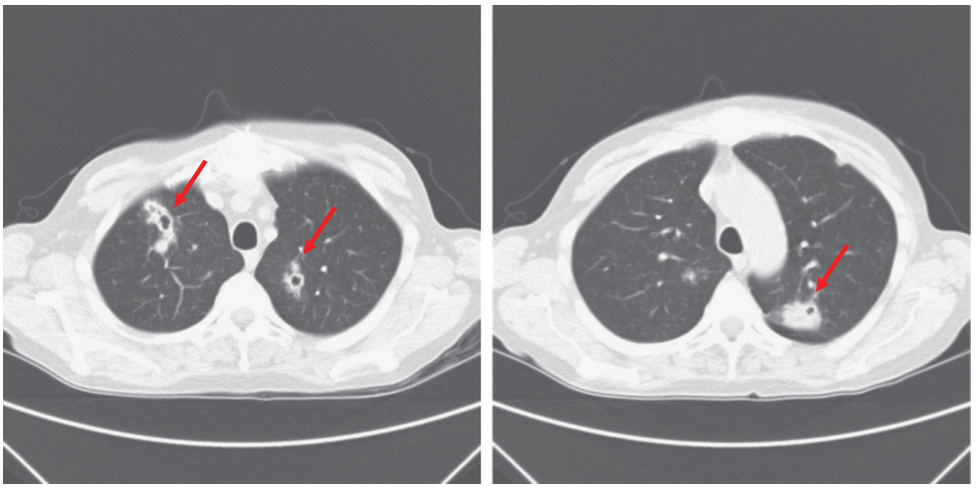


FIGURE 2.8.2: CT chest demonstrating bilateral multifocal cavitary pulmonary nodules.

Over the ensuing week and while awaiting microbiologic data from the BAL, the patient noted increased swelling and pain of her right second finger at the prior I&D site, accompanied by new fever, pleurisy, and headache prompting admission for further evaluation. A repeat chest CT demonstrated further progression of bilateral cavitary nodules; magnetic resonance imaging (MRI) of the brain was unremarkable. A plain film of the right hand was notable for soft tissue swelling overlying the distal phalanx of the right second digit, with no evidence of osteomyelitis and no foreign body. Surgery was consulted for repeat I&D of the involved finger. The prospect of a surgical lung biopsy was considered, but ultimately the BAL cultures yielded growth of an organism on day fourteen of incubation.

QUESTIONS

- What is the differential diagnosis of cavitary pulmonary nodules in this heart transplant recipient?
- What is the first-line antibiotic for this infection?

DIFFERENTIAL DIAGNOSIS

In an immune suppressed host with rapid evolution and progression of nodular pulmonary consolidations, some of which appear cavitary, an infectious etiology is likely. Relevant exposures in this patient include gardening, marijuana use, and residence in the Pacific Northwest. Fungi to consider include *Aspergillus* as well as other environmental molds (mucormycosis, etc), *Cryptococcus* (both *C neoformans* as well as *C gattii* in this geographic region), and the dimorphic fungi. *Nocardia* species as well as mycobacteria should also be considered, though *M tuberculosis* is less likely in the absence of known latent infection or exposure history.

ADDITIONAL DATA

Cryptococcal antigen (serum), *Aspergillus* galactomannan (serum and BAL), urine *Legionella* antigen, serum QuantiFERON-TB Gold, and CMV polymerase chain reaction (plasma) testing were negative. Blood cultures were negative. Bronchoalveolar lavage fluid yielded growth of *Nocardia* species, later identified as *Nocardia asteroides*. On hospital day two, the patient was evaluated by the hand surgery service and was noted to have a 0.5 cm abscess over the dorsal aspect of the right second finger, adjacent to the distal interphalangeal joint; an I&D was performed, with material obtained for culture. Approximately seven days later, the wound culture also grew *N asteroides*.

Final Diagnosis: Disseminated nocardiosis

TREATMENT AND OUTCOME

Therapy with trimethoprim/sulfamethoxazole ([TMP/SMX] 15 mg/kg per day in three divided doses) was initiated. She ultimately completed nine months of TMP/SMX therapy, with resolution of chest CT findings as well as the soft tissue infection of her finger.

DISCUSSION

Microbiology and Epidemiology

Nocardia species are strictly aerobic, Gram-positive, weakly acid-fast, filamentous,

branching bacteria, distributed widely in soil and decaying vegetable matter [1]. There are more than eighty species of *Nocardia*, thirty-three of which have been implicated in human disease [1]. Common species implicated in invasive disease include *N asteroides sensu stricto, N nova complex, N cyriacigeorgica, N abscessus, N farcinica*, and *N brasiliensis* [2]. More species are likely to be identified with the increasing use of molecular diagnostics. The route of transmission is predominately inhalation, with inoculation and ingestion less frequent modes of entry.

The majority of *Nocardia* infections occur in immune suppressed hosts, such as human immunodeficiency virus-seropositive patients (typically with CD4 count <100/mm^3), transplant recipients, and patients on high-dose corticosteroids, highlighting the importance of cell-mediated immunity to host defense [3]. The frequency of infection ranges from 0.7% to 3.5% in solid organ transplant (SOT) recipients [4]. A large single-center study completed over ten years identified lung recipients to be at highest risk (3.5% incidence), followed by heart (2.5%), intestine (1.3%), kidney (0.2%), and liver recipients (0.1%) [5]. In the same study, the following risk factors were associated with *Nocardia* infection: CMV disease, high-dose prednisone in the preceding six months, and elevated calcineurin inhibitor levels in the preceding thirty days [5]. Infection typically occurs in the first year posttransplant but has been reported as early as twenty-eight days to as late as eleven years posttransplant [3, 6].

Clinical Manifestations

In SOT patients, pulmonary infection is the most common disease manifestation, with 60% to 70% of cases involving the lung [2, 3, 6]. Extrapulmonary disease is present in approximately 50% of cases, and so diagnosis of pulmonary infection should prompt evaluation for disseminated disease [4]. *Nocardia* species have a tropism for the central nervous system (CNS), with 44% of patients with nocardiosis developing cerebral abscesses [1, 7]. Meningitis and spinal cord abscesses are less common [7]. Cutaneous lesions have been reported in 20% to 30% of SOT recipients with nocardiosis [8]. While pulmonary, CNS and cutaneous involvement are some of the more common manifestations, *Nocardia* has been reported to involve virtually every organ system—for example, the liver, spleen, kidneys, and adrenal glands, epididymis/testicles, and pericardium [4, 7, 9].

Diagnosis

The gold standard for diagnosis of *Nocardia* infection is isolation and identification of the organism from a clinical specimen. Biopsy of lung, brain, or other involved tissue is often required for diagnosis. Because the pathogenesis of pulmonary nocardiosis involves lymphocytes and macrophages, a suppurative response is usually seen, but granulomas have also been observed on histopathology [9].

In the microbiology laboratory, *Nocardia* colonies may appear on plates within three to five days, but this organism tends to be slow growing and often requires incubation of two weeks or more [10]. In a retrospective cohort study of 577 lung transplant patients between January 1991 and May 2007, 1.9% of whom had a nocardial infection, growth of organism from culture occurred at a mean of nine days from the time of sampling [11]. Growth occurs under aerobic conditions, is inhibited at 50°C, and can be enhanced by utilizing selective media such as modified Thayer-Martin [4]. *Nocardia* appear as filamentous Gram-positive branching rods and display weak acid-fast staining, which can often aid in the differentiation from *Actinomyces* species (Figures 2.8.3 and 2.8.4). More recently, molecular diagnostic technology has aided in the diagnosis and speciation of *Nocardia* infections, although with continued reliance on isolation of the organism to provide antimicrobial susceptibility data.

In a predisposed host, imaging can be suggestive of nocardiosis. A review by Bargehr et al [7], demonstrated the radiological features of nocardiosis in SOT patients—multifocal air space

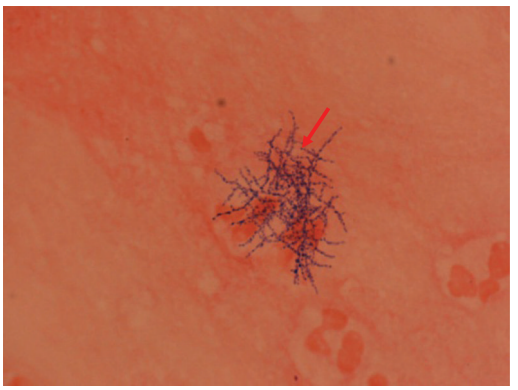


FIGURE 2.8.3: Gram stain, demonstrating branching, filamentous rods
(Image courtesy of Dr. Susan Sharp, Kaiser Permanente NW, Portland, OR).

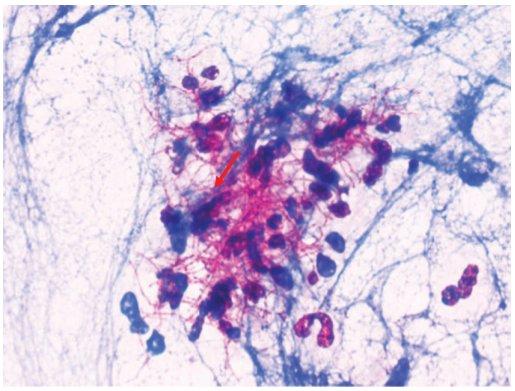


FIGURE 2.8.4: Modified acid fast stain, demonstrating the weakly acid fast staining property of *Nocardia* species (Image courtesy of Dr. Susan Sharp, Kaiser Permanente NW, Portland, OR).

consolidation with or without cavitation was most common (64%), followed by nodules (57%), masses (21%), pleural effusion (28%), and hilar/mediastinal lymphadenopathy (15%). CT is superior to plain chest radiography in demonstrating disease. For suspected CNS involvement, MRI is the modality of choice, classically demonstrating ring-enhancing lesions and surrounding edema [7]. Given the relative frequency of CNS involvement, all immune compromised hosts with documented *Nocardia* infection should have CNS imaging.

Treatment

Antimicrobial treatment is standard of care for *Nocardia* infections. Surgical management, in conjunction with antimicrobial(s), may be necessary for cerebral involvement not responding to therapy and/or for localized soft tissue infection. Generally speaking, TMP/SMX is first-line therapy, given broad susceptibility across species as well as high achievable drug concentration in lung, bone, brain, and skin. Serum sulfonamide drug level monitoring is typically advised, targeting a serum level of between 10 and 15 mg/dL, to ensure adequacy of absorption and to mitigate against drug-related toxicity, given that high doses of TMP/SMX have been associated with adverse drug reactions such as renal toxicity and marrow suppression [4]. However, certain species of *Nocardia* may be resistant to TMP/SMX [8]. Owing to significant variation in susceptibility patterns among *Nocardia* species, there is a role for in vitro antibiotic susceptibility testing is, particularly for more resistant species (eg., *N farcinica* or *N abscessus*) and/or if non-sulfa-based therapy is intended or anticipated. Combination therapy is recommended in disseminated infection, in critically ill patients, or patients who have CNS disease. There is in vitro data to suggest that certain antibiotic combinations have improved bactericidal activity or even display synergy in the treatment of *Nocardia* [2]. Recent guidelines suggest using imipenem in conjunction with amikacin, or in a three-drug combination with TMP/SMX, as initial therapy for CNS or disseminated disease pending susceptibility testing [4]. Ulitmately, most patients who have an initial response can be transitioned to oral monotherapy. Acceptable alternatives in patients with allergy or other contraindications to first-line medications include linezolid, ceftriaxone, cefotaxime, and/or minocycline [4].

Optimal duration of treatment is unknown, but because of the tendency for *Nocardia* to relapse, long treatment courses are typically used [12]. In general, pulmonary and soft tissue infections should be treated for six months; for CNS and disseminated nocardiosis, treatment for up to twelve months or longer is preferred [4]. Clinical and radiographic improvement should be demonstrated before stopping treatment. Mortality ranges from 20% to 60%, but it can be up to 80% with CNS involvement [13]. Relapsing infection has been observed in SOT recipients but typically with shorter initial treatment duration [7, 12].

Prevention

There are no definitive recommendations regarding prevention or prophylaxis for *Nocardia* infection in SOT recipients. Some reports have shown efficacy of daily TMP/SMX prophylaxis in preventing *Nocardia* infections in the first six months posttransplant [4]. Breakthrough cases of nocardiosis have been demonstrated in patients taking TMP/SMX thrice weekly, as opposed to daily [5]. There are no clear guidelines regarding secondary prophylaxis after initial treatment of nocardiosis; some centers use lifelong, daily TMP/SMX.

KEY POINTS

- Nocardiosis should be considered in transplant recipients presenting with cavitary lung lesions, skin lesions, and/or CNS disease.
- Diagnosis is by detection of *Nocardia* in a clinical specimen, either by culture and/or molecular diagnostic studies.
- Most *Nocardia* species are susceptible to TMP/SMX and infections limited to the lungs can be treated with monotherapy. For

disseminated infection, particularly with CNS involvement, combination therapy can be used initially.

- In vitro susceptibility testing should be considered, particularly with treatment failures, when non-sulfa-based treatment is intended, or with certain species of *Nocardia* that are resistant to many antimicrobials.

REFERENCES

1. Mandell G, Bennett JE, and Dolin R. *Nocardia* species. In: *Principles and Practice of Infectious Diseases*, 7th ed. 2010; pp 3199.
2. Tripodi MF, Durante-Mangoni E, Fortunato R, et al. In vitro activity of multiple antibiotic combinations against *Nocardia*: relationship with a short-term treatment strategy in heart transplant recipients with pulmonary nocardiosis. Transplant Infectious Dis. 2011;13:335.
3. Minero MV, Marin M, Cercenado E, et al. Nocardiosis at the turn of the century. Medicine 2009;88:251.
4. Clark NM, Reid GE. *Nocardia* infections in solid organ transplantation. Am J Transplant. 2013;13:83.
5. Peleg AY, Husain S, Qureshi ZA, et al. Risk factors, clinical characteristics, and outcome of *Nocardia* infection in organ transplant recipients: a matched case-control study. Clin Infect Dis. 2007;44:1307.
6. Peraira JR, Segovia J, Fuentes R, et al. Pumonary nocardiosis in heart transplant recipients: treatment and outcome. Transplant Proc. 2003; 35:2006.
7. Bargehr J, Flors L, Leiva-Salinas C, et al. Nocardiosis in solid-organ transplant recipients: spectrum of imaging findings. Clin Radiol. 2013;68:e266.
8. Husain S, McCurry K, Dauber J, et al. *Nocardia* infection in lung transplant recipients. J Heart Lung Transplant. 2002;21:354.
9. Beaman BL, Beaman L. *Nocardia* species: host-parasite relationships. Clin Microbiol Rev. 1994;7:213.
10. Murray PR, Herren RL, Niles AC. Effect of decontamination procedures on recovery of *Nocardia* spp. J Clin Microbiol. 1987;25:2010.
11. Poonyagariyagorn HK, Gershman A, Avery R, et al. Challenges in the diagnosis and management of *Nocardia* infections in lung transplant recipients. Transplant Infect Dis. 2008;10:403.
12. Arduino RC, Johnson PC, Miranda AG. Nocardiosis in renal transplant recipients undergoing immunosupression with cyclosporine. Clin Infect Dis. 1993;16:505.
13. Santos M, Gil-Brusola A, Morales P. Infection by *Nocardia* in solid organ transplantation: thirty years of experience. Transplant Proc. 2011;43:2141.

2.9

Oh My Aching Head

GRAEME N. FORREST, MBBS

CASE PRESENTATION

A 57-year-old kidney transplant recipient presents with syncope and altered mental status, in the context of a one-week history of bilateral headache with photophobia. The patient has type 2 diabetes mellitus complicated by end-stage renal disease and received a deceased donor kidney transplant four months earlier (cytomegalovirus D+/R+, Epstein-Barr virus D+/R+). Induction immunosuppression was with antithymocyte globulin (ATG), followed by maintenance immunosuppression with prednisone, mycophenolate mofetil, and tacrolimus. Prophylactic antimicrobials included valganciclovir (for one month posttransplant) and trimethoprim-sulfamethoxazole (for three months posttransplant).

The patient resides in Oregon and previously worked as a truck driver for a logging company, with frequent travel through California and Arizona. He lives on a farm and has contact with horses, chickens, and a dog.

He was well until the onset of new headaches, described as diffuse and generally worse in the mornings, with accompanying nausea and lethargy. At an outside hospital, a fine nodular pneumonia was seen on chest radiograph, with a peri-allograft collection noted on abdominal ultrasound. On day two of hospitalization, a "yeast-like organism" was reported to be growing in blood cultures. Before transfer, he was begun on empiric ceftriaxone, azithromycin, and caspofungin.

On arrival to the transplant center, the patient was noted to be somnolent with periods of agitation. He had photophobia with pinpoint pupils. Temperature was 36.8°C, blood pressure was 198/93 mmHg, and pulse oximetry was 89% on room air. Neck was supple without meningismus. Chest auscultation revealed bilateral fine rales. Neurologic examination was limited due to somnolence, with no gross motor deficits but with bilateral upgoing plantar reflexes. Skin examination revealed multiple firm, nontender 5 mm umbilicated nodules on elbows, abdomen, and knees.

Laboratory results revealed a white blood count (WBC) of 18 800 cells/mm^3 (95% neutrophils), hemoglobin of 13.7 g/dL, and a platelet count of 301 000/ mm^3. Serum creatinine was elevated from baseline at 1.9 mg/dL (range, 0.7–1.2 mg/dL), lactate dehydrogenase was elevated at 646 U/L (range, 155–250 U/L), and both total (2.2 mg/dL; range, 0.3–1.2 mg/dL) and direct bilirubin were elevated (0.4 mg/dL; range, 0–0.2 mg/dL). A chest radiograph revealed a diffuse hazy bilateral nodular infiltrate (Figure 2.9.1). Computed tomography (CT) chest scan revealed a nodular right upper lung consolidation with hilar adenopathy and thymic enlargement (Figure 2.9.2). A noncontrast CT scan of the head demonstrated maxillary sinusitis and mild ventricular enlargement.

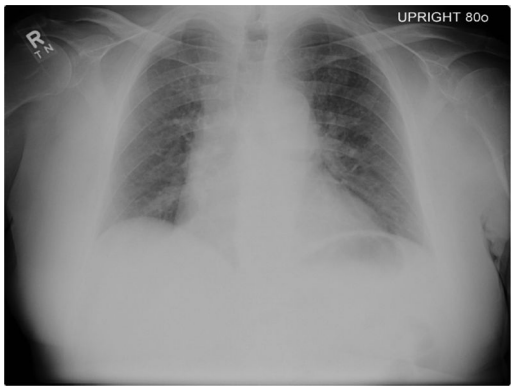


FIGURE 2.9.1: Chest radiograph demonstrating diffuse hazy bilateral nodular infiltrate.

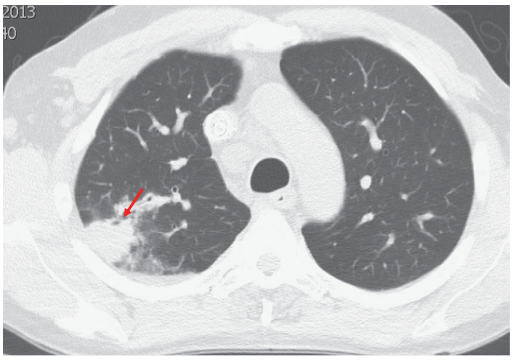


FIGURE 2.9.2: CT chest revealing nodular right upper lobe consolidation.

QUESTIONS

- While awaiting results from the microbiology laboratory, which fungal infections should be considered to explain this patient's presentation?
- What are the key principles in managing this patient's fungal infection?

DIFFERENTIAL DIAGNOSIS

This is a pulmonary/central nervous system (CNS) syndrome in a solid organ transplant (SOT) recipient, which, to some extent, helps to focus the differential diagnosis. In this context, and knowing yeast is present in the blood cultures, concern for cryptococcosis should quickly come to mind. Other diagnostic considerations include the endemic mycoses such as histoplasmosis and coccidioidomycosis, especially with reported travel through the southwest United States. *Malassezia, Trichosporon, Rhodotorula*, and *Saccharomyces* are yeasts that can, on rare occasion, present as bloodstream infection in an immunocompromised host, often related to intravascular catheters or as a result of dissemination from cutaneous infection. The epidemiologic context and the clinical picture in this case, however, make these organisms very unlikely. Molds such as *Aspergillus* rarely result in positive blood cultures and would not be reported out as yeast.

INITIAL MANAGEMENT

A serum cryptococcal antigen is an important quick and easy test to perform, with a turnaround time that can provide a key to diagnosis within hours. Presuming neuroimaging does not contraindicate it, the critical next step is a lumbar puncture (LP), with cerebrospinal fluid (CSF) for diagnostic studies and measurement of opening pressure. If opening pressure is elevated (>25 cm water), therapeutic removal of CSF targeting closing pressure of ≤25 cm water is indicated. Cerebrospinal fluid should be sent for Gram stain, bacterial and fungal culture, cell count, glucose, protein, and cryptococcal antigen, with storage of any remaining fluid for additional testing as indicated. India ink is less sensitive than cryptococcal antigen and should only be performed if there is no access to rapid-turnaround CSF antigen testing.

ADDITIONAL DATA

The LP opening pressure was >50 cm water, necessitating large volume CSF removal. Cerebrospinal fluid analysis revealed WBC of 4 (100% lymphocytes), glucose 84 mg/dL (simultaneous serum glucose 210 mg/dL), protein 40 mg/dL (range, 15–45 mg/dL), budding yeast organisms on KOH stain, and a cryptococcal antigen titer of 1:2048. Magnetic resonance imaging (MRI) of the brain demonstrated ventricular dilatation and hyperintense FLAIR signal in the subarachnoid space consistent with meningitis but no intraparenchymal abnormalities to suggest brain abscess/cryptococcoma (Figure 2.9.3). Blood, CSF, and sputum cultures ultimately grew *Cryptococcus neoformans*.

Final Diagnosis: Disseminated cryptococcal infection

TREATMENT AND OUTCOME

The patient was begun on liposomal amphotericin B and 5-flucytosine (5FC) a few hours after arrival to the transplant center. He required daily LPs for management of elevated intracranial pressure. On hospital day five, he had further neurologic

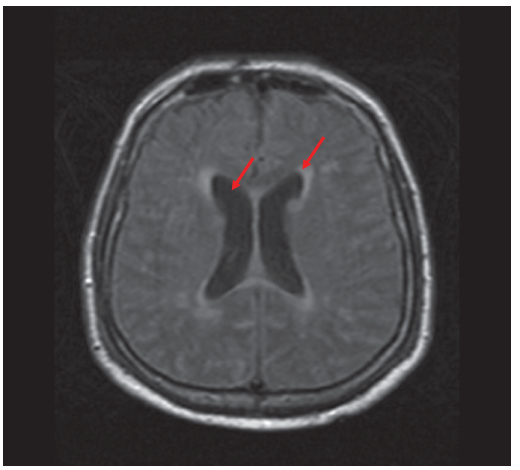


FIGURE 2.9.3: MRI brain demonstrating ventricular enlargement and periventricular enhancement.

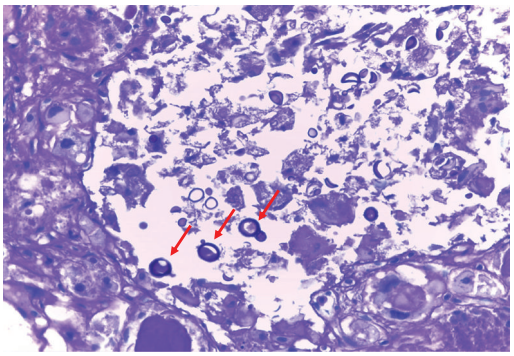


FIGURE 2.9.4: Peribronchial lymph node tissue demonstrating typical yeast forms of *Cryptococcus*, Periodic acid-Schiff stain, 40×.

deterioration; MRI of the brain showed dilated ventricles and peduncular herniation, prompting placement of an external ventricular drain. He never recovered neurologically and ultimately died ten days later. A post mortem examination demonstrated widespread cryptococcal disease involving the brain, spleen, thyroid, thymus, lungs, hilar nodes, spleen, liver, skin, and prostate (see Figures 2.9.4 and 2.9.5).

DISCUSSION

Cryptococcosis is the third most common fungal infection in SOT recipients, after *Candida* spp and *Aspergillus*. The incidence of infection in SOT recipients ranges from 0.2% to 5% [1, 2].

Acquisition of infection is through inhalation of the yeast or basidiospore form, with propensity for dissemination to the CNS. The two main *Cryptococcus* species that cause human infection are *C neoformans* and *C gattii*, an emerging infection in the Pacific Northwest. The ecologic niche for these two species are distinct; *C neoformans* is found in soil contaminated with bird droppings and *C gattii* is found in association with certain trees in isolated regions of the world (especially the Pacific Northwest and Australia).

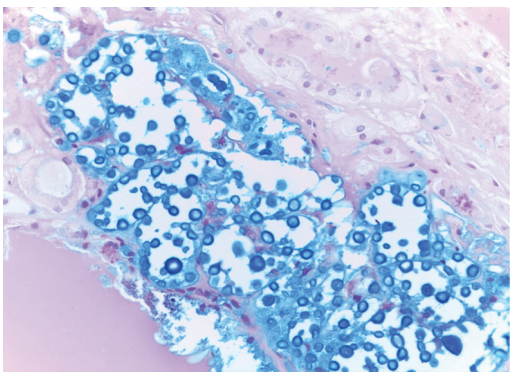


FIGURE 2.9.5: Thymus tissue demonstrating typical yeast forms of *Cryptococcus*, Alcian blue stain, 40×.

Risk Factors

The use of T cell-depleting agents such as ATG or alemtuzumab has been associated with an increased risk of cryptococcosis [3]. These agents can result in prolonged T-cell immunodeficiency, with a resultant increase in risk for a variety of infections. Corticosteroids have also been associated with an increased risk for cryptococcosis in SOT recipients, although without a clear threshold dose.

Clinical Presentation

Disease onset ranges from days to many years after transplantation and can represent primary infection, reactivation of quiescent infection, or even donor-derived infection. Very early posttransplant infection (<30 days posttransplant) appears to occur preferentially in liver recipients and is more likely to involve unusual sites, such as the transplanted allograft or the surgical site. It is suspected that these very early onset infections are the result of either undetected pretransplant infection or donor-derived infection [4].

Cryptococcosis may have an insidious onset. Presentation is characteristically with neurologic symptoms such as chronic headache and blurry vision, focal neurologic signs, altered mental states, and/or seizures. As many as 75% of patients have disseminated disease at time of presentation, with skin and soft tissue, osteoarticular, and prostate being the most common sites [2, 5]. Pulmonary presentations can include single or multiple pulmonary nodules/masses as well as widespread interstitial involvement. Cryptococcomas are reported to occur in 33% of organ transplant recipients and more frequently with *C gattii* infection [6]. Up to 40% will have fungemia on presentation, more often in patients with CNS disease [2, 5]. Cutaneous lesions can present as nodules, papules, ulcers, or cellulitis [7].

Diagnosis

Timely diagnosis requires a high index of suspicion, with pulmonary and/or CNS symptoms raising concern for this infection. After a diagnosis is established, evaluation to determine the extent of disease is imperative, specifically whether CNS infection is present because this has significant implication for therapy.

Cryptococcus species are yeast, often budding, and are encapsulated in a thin layer of glycoprotein, the characteristic capsule seen on India ink staining. The cryptococcal antigen test can be performed on serum and CSF, with results available within one hour; traditional methodologies include latex agglutination or enzyme immunoassay from CSF or serum, although a recently introduced lateral flow immunoassay may offer greater convenience of use and more rapid turnaround. Serum antigen testing is very sensitive (approximately 90%) in the setting of CNS cryptococcal disease. Antigen testing of CSF has a sensitivity of over 90% in patients with cryptococcal meningitis and is preferred over India ink, which has a sensitivity of approximately 60% from CSF [2, 5]. Cryptococcemia (isolation of *Cryptococcus* in blood cultures) occurs in approximately 30% to 40% of patients with cryptococcal infection and is more common in those with CNS disease. *Cryptococcus gattii* can be differentiated from *C neoformans* by growth features on canavanine-glycine-bromothymol blue agar or by molecular testing [8].

An LP should be performed in all patients with suspected/proven cryptococcosis, including in patients with focal pulmonary disease without accompanying neurologic symptoms, because this will help to guide therapy. Brain imaging should be performed before LP to determine whether there are mass lesions or hydrocephalus that would contraindicate this exam. Opening pressure should be measured, with fluid sent for Gram stain, culture, cell count, protein, glucose, and cryptococcal antigen testing.

Treatment

The suggested treatment regimens for SOT recipients are largely the same as those used to treat human immunodeficiency virus (HIV)-positive individuals and are part of the American Society of Transplantation Infectious Diseases Community of Practice Guidelines [6, 9].

An amphotericin B product and flucytosine (5FC) are recommended induction therapy for all SOT recipients with disseminated and/or CNS disease. Although most large prospective studies draw on the HIV-positive population, failure to include 5FC in the induction regimen is associated with increased treatment failure at two weeks in SOT recipients [10]. Combination therapy with an amphotericin B product (specifically, use of a lipid amphotericin B as a less toxic alternative) and 5FC is associated with improved clinical outcomes [6]. Duration of induction therapy can vary based on response to treatment as well as emergent drug-related toxicities, but a minimum of two weeks is generally recommended. After induction therapy, the usual practice is to transition to oral fluconazole for consolidation (approximately eight weeks) and then maintenance (typically six to twelve months) phases. In patients with non-severe isolated pulmonary, prostatic or cutaneous disease, without CNS involvement, fluconazole can be used from the outset [9]. Importantly, the echinocandin antifungals (e.g. anidulafungin, caspofungin, and micafungin) have no activity against *Cryptococcus* species.

As highlighted in this case, therapeutic removal of CSF in patients with elevated opening pressure is a key aspect of management, often requiring serial LPs, and at times placement of a shunt. If the initial opening pressure is elevated (>25 cm water), daily LP should be performed until the opening pressure is controlled and clinical symptoms suggest improvement [6].

Reduction in immunosuppressive therapy can be a critical component of treatment, although with the caveat that rapid reduction can precipitate immune reconstitution inflammatory syndrome (IRIS) and/or allograft rejection. IRIS is an increasingly recognized phenomenon whereby the restoration of host immunity upon reduction of immunosuppression is associated with clinical worsening (e.g. meningismus with aseptic meningitis), a representation of immune response to inciting infection. Care is generally supportive, with use of corticosteroids reserved for severe neurologic compromise [6].

Prognosis

The mortality rate for cryptococcosis in SOT recipients is approximately 14% but can be as high 40% for those with CNS disease [2, 9]. Risk factors associated with increased mortality include altered mental status or seizure on presentation, cryptococcal antigen titer >1:512, low WBC and low glucose in the CSF, and cryptococcemia [5, 9, 11].

Prevention

Routine primary antifungal prophylaxis for *Cryptococcus* is not advised. In patients with a history of cryptococcosis prior to transplantation or infection associated with a failed allograft, secondary prophylaxis with fluconazole after transplant or re-transplant, respectively, should be considered.

KEY POINTS

- *Cryptococcus* is an environmentally acquired yeast that can present insidiously

in transplant recipients, often with pulmonary and/or CNS disease.
- The serum/CSF cryptococcal antigen assays are an important rapid diagnostic test.
- Evaluation for disseminated/CNS disease should be undertaken, with cultures, LP, imaging as appropriate, and consideration of biopsy of mass lesions.
- Diagnostic LP with measurement of opening pressure should be performed on all proven and suspect cases of cryptococcal infection.
- Combination therapy with amphotericin B (specifically, use of a lipid amphotericin B as a less toxic alternative) and 5FC is the mainstay of induction therapy for CNS, disseminated, or severe pulmonary disease, with transition to fluconazole for consolidation and maintenance phases of therapy. Mild to moderate pulmonary disease can be managed with fluconazole.

REFERENCES

1. Baddley JW, Schain DC, Gupte AA, et al. Transmission of *Cryptococcus neoformans* by organ transplantation. Clin Infect Dis. 2011; 52:e94.
2. Husain S, Wagener MM, Singh N. *Cryptococcus neoformans* infection in organ transplant recipients: variables influencing clinical characteristics and outcome. Emerg Infect Dis. 2001;7:375.
3. Peleg AY, Husain S, Kwak EJ, et al. Opportunistic infections in 547 organ transplant recipients receiving alemtuzumab, a humanized monoclonal CD-52 antibody. Clin Infect Dis. 2007;44:204.
4. Sun HY, Alexander BD, Lortholary O, et al. Unrecognized pretransplant and donor-derived cryptococcal disease in organ transplant recipients. Clin Infect Dis. 2010;51:1062.
5. Wu G, Vilchez RA, Eidelman B, et al. Cryptococcal meningitis: an analysis among 5,521 consecutive organ transplant recipients. Transplant Infect Dis. 2002;4:183.
6. Baddley JW, Forrest GN. Cryptococcosis in solid organ transplantation. Am J Transplant. 2013;13(Suppl 4):242.
7. Sun HY, Alexander BD, Lortholary O, et al. Cutaneous cryptococcosis in solid organ transplant recipients. Med Mycol. 2010;48:785.
8. Harris JR, Lockhart SR, DeBess E, et al. *Cryptococcus gattii* in the United States: clinical aspects of infection with an emerging pathogen. Clin Infect Dis 2011;53:1188.
9. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:291.
10. Dromer F, Bernede-Bauduin C, Guillemot D, Lortholary O. Major role for amphotericin B-flucytosine combination in severe cryptococcosis. PLoS One 2008;3:e2870.
11. Brizendine KD, Baddley JW, Pappas PG. Predictors of mortality and differences in clinical features among patients with cryptococcosis according to immune status. PLos One 2013;8:e60431.

2.10

It's That Time of Year Again

MORGAN HAKKI, MD

CASE PRESENTATION

A 46-year-old man underwent a deceased donor kidney transplant (cytomegalovirus [CMV] D-/R-) with daclizumab induction that was complicated by delayed graft function requiring thymoglobulin. Two months after transplant, in February, he presented with two days history of dry cough, pleuritic chest pain, increasing shortness of breath, chills, fever, rhinorrhea, and myalgias. He had no known sick contacts. His maintenance immunosuppressive medications included mycophenolate delayed release 720 mg twice daily, prednisone 30 mg daily, and tacrolimus 9 mg twice daily. His antimicrobial prophylaxis consisted of thrice weekly double-strength trimethoprim-sulfamethoxazole (TMP-SMX). He is an accountant but has not returned to work since transplant. He is married, has no children, and has not had any recent travel or unusual exposures. He has a dog but denies other animal exposures.

Exam findings on presentation were notable for ill appearance, with fever of 38.3°C, tachypnea with respiratory rate 22 breaths per minute, tachycardic with heart rate of 110 beats per minute, and hypoxia with a room air oxygen saturation of 89%. Blood pressure was 130/65 mm mercury. He had mild conjunctival injection bilaterally. Chest auscultation revealed diminished breath sounds at the right base and rales at the left base. His abdomen was soft and nontender, with an unremarkable appearing surgical wound, and with no tenderness overlying the allograft. No rash was present. Neurological examination was unremarkable.

A chest x-ray revealed bilateral diffuse central airway thickening but no focal consolidation (Figure 2.10.1).

QUESTIONS

- What disease entities should be considered to explain this patient's clinical syndrome of acute respiratory illness?
- How should a diagnosis be pursued?
- Are there any specific isolation precautions relevant to this case?

DIFFERENTIAL DIAGNOSIS

This patient is presenting with a constellation of signs and symptoms that point to a community-acquired respiratory virus infection (CARVI). The most commonly encountered pathogens are similar to those seen in immunocompetent adults, primarily rhinovirus, and coronaviruses. Parainfluenza, influenza, respiratory syncytial virus (RSV), adenovirus, and human metapneumovirus have all been associated with similar disease manifestations. It can be difficult to distinguish one from another based solely on clinical grounds. Sometimes, the time of the year can offer a clue, with RSV and influenza being the most "seasonal" (late winter/early spring) viruses. CMV infection as a cause for this patient's pulmonary findings is unlikely given negative donor/recipient serostatus at the time of transplant, although primary community-acquired CMV can occur. Likewise, *Pneumocystis jirovecii* pneumonia

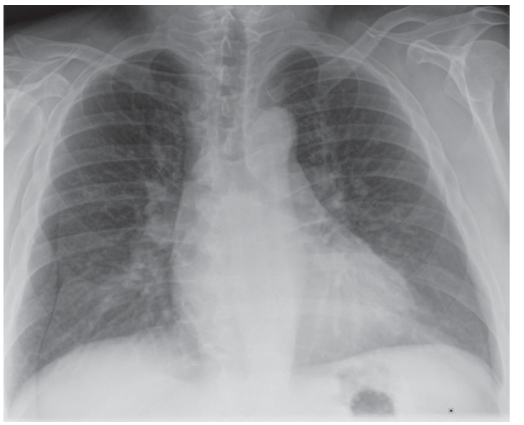


FIGURE 2.10.1: Chest x-ray demonstrating bilateral diffuse central airway thickening.

would be unusual in the setting of compliance with TMP-SMX prophylaxis and would not be associated with upper respiratory symptoms such as rhinorrhea.

ADDITIONAL DATA

A nasal swab was obtained and submitted for multiplex panel respiratory virus polymerase chain reaction testing. The following day it was reported as positive for influenza A, further identified by subtyping as influenza A/H3N2. No other respiratory viruses were detected as part of the multiplex testing. The results of blood, urine, and sputum bacterial cultures were all negative.

Final Diagnosis: Seasonal influenza upper respiratory tract infection, with probable lower respiratory tract involvement

TREATMENT AND OUTCOME

Due to the fact that this patient was presenting with a syndrome compatible with a CARVI, at a time of year when influenza was prevalent in the community, he was started empirically on the neuraminidase (NA) inhibitor oseltamivir and was admitted to the hospital with contact/droplet precautions in place. Over the following two days his condition was stabilized, and he ultimately was discharged from the hospital to complete a five-day course of oseltamivir.

DISCUSSION

Epidemiology and Pathogenesis

Influenza virus strains are named according to their genus, species from which the virus was isolated (if from a nonhuman source), geographic location of the isolate, isolate number, year of isolation, and the hemagglutinin (HA) and NA subtypes (for influenza A viruses). At least fifteen distinct HA and nine distinct NA subtypes are described in animals, although infection in humans is generally composed of one of three major subtypes of HA (H1, H2, and H3) and two subtypes of NA (N1 and N2). Subtypes H1N1 and H3N2 represent the majority of cases of human influenza A infection, whereas influenza B lineages B/Victoria and B/Yamagata are the predominant circulating influenza B viruses [1]. Circulating influenza strains may develop variations due to either antigenic drift, which involves H and/or N mutations, or antigenic shift, in which genetic reassortment occurs between animal and human influenza viruses infecting the same cell [1]. Whereas antigenic drift is associated with localized outbreaks of variable degree due to the subtle nature of the genetic changes involved, antigentic shift may result in the emergence of epidemic and pandemic strains.

Transmission of influenza occurs through aerosolized viral particles, large droplets, fomites, or contact with respiratory secretions. Respiratory tract mucosa is the initial site of replication, resulting in tracheobronchial inflammation, edema, and hemorrhage in severe cases. The outcome of infection is determined by both strain-specific properties of the virus and the host antiviral immune response. The immunosuppressed patient may shed virus for weeks or months.

Clinical Presentation

Symptoms associated with influenza in the transplant recipient largely overlap with those seen in the immunocompetent host, including fever, headache, rhinorrhea, myalgias, fatigue, gastrointestinal symptoms such as diarrhea, and chills. During the appropriate time of year, influenza infection should be considered in all patients presenting with such symptoms, in addition to recognizing that the immunosuppressed host may not manifest these "classical" symptoms, and therefore a high degree of suspicion must be maintained.

Complications of influenza infection include lower respiratory tract infection (LRTI)/pneumonia with potential for bacterial superinfection, central nervous system involvement manifest primarily as encephalitis, and myocarditis. Solid organ transplant (SOT) recipients are at higher risk for complications compared with the general population, with pneumonia occurring in anywhere from 22% to 49% of cases and infection-attributable mortality ranging from 4% to 8% [2]. In addition, influenza infection has been associated with allograft dysfunction and acute rejection [3].

The risk of infection after SOT may vary according to the type of organ transplanted, with lung transplant recipients described in one study as having the highest rates of infection [4]. Risk factors for poor outcome of infection based on data from 2009 pandemic influenza A H1N1 infection include pediatric patients, delayed initiation of antiviral therapy, a history of anti-thymocyte globulin administration, the presence of LRTI at the time of presentation, time from transplant <3 months, the presence of bacterial and/or fungal copathogens, and diabetes [3, 5].

Diagnosis

The diagnosis of influenza virus infection has evolved rapidly over the past several years

TABLE 2.10.1. METHODS FOR DIAGNOSING INFLUENZA INFECTION*

Test	Turnaround Time	Specificity	Sensitivity
Shell vial culture	2–3 days	+++	+
Standard culture	3–10 days	+++	+
EIA†	10–20 minutes	++	+
DFA	2–4 hours	++	++
PCR	1–2 hours	+++	+++

Abbreviations: DFA, direct fluorescent antibody; EIA, enzyme immunoassay; PCR, polymerase chain reaction.
*For use on nasopharyngeal swabs and nasopharyngeal or bronchial washings.
†Not performed on bronchial washing.

(Table 2.10.1). Historically, viral culture in combination with direct fluorescent antibody (DFA) testing was the laboratory gold standard. However, viral culture takes too long for clinical purposes and DFA is labor intensive and not amenable to automation. Rapid point-of-care antigen testing kits, which use monoclonal antibodies to detect viral antigens, are available but were found to be of poor sensitivity (10%–50%) during the 2009 pandemic [6]. Polymerase chain reaction-based diagnostics have largely supplanted other methodologies, given their rapid turnaround time, automation, increased sensitivity compared with culture and DFA, and ability to identify virus at the strain/subtype level and to detect NA resistance mutations.

Treatment

During the 2009 pandemic influenza outbreak, the early use of antiviral therapy (e.g. oseltamivir) was associated with a reduced rate of influenza-associated complications, such as need for admission to intensive care unit, need for mechanical ventilation, and death among SOT recipients [3, 5, 7–9]. In suspected cases of influenza infection, the SOT recipient should receive prompt empirical antiviral therapy pending further diagnostic evaluation. Despite the documented benefits of early therapy, all symptomatic SOT recipients with influenza infection should be treated, regardless of time from onset.

There are two classes of antiviral agents currently approved by the US Food and Drug Administration (FDA) for the treatment of influenza infection (Table 2.10.2). The adamantanes (amantadine, rimantadine) function as inhibitors of influenza A M2 ion channel; they have no effect on influenza B. Although resistance among seasonal influenza A/H1N1 is variable, the high rate of resistance among seasonal influenza A/H3N2 (~95%) and the 2009 pandemic H1N1 influenza A strain (100%) has limited their utility and so they are no longer recommended as first-line agents for the treatment of influenza.

The NA inhibitors (oseltamivir, zanamivir, and peramivir) are analogs of sialic acids that block viral release from the host cell by inhibiting the sialidase activity of NA. They are effective against different NA subtypes of both influenza A and B viruses. Zanamivir and oseltamivir have been approved for the prophylaxis and treatment of influenza A and B since 1999 in the United States, whereas peramivir is undergoing phase 3 clinical trials in the United States. The efficacy of oseltamivir therapy in the SOT recipient was highlighted during the 2009 pandemic H1/N1 outbreak [3, 5, 7–9]. Whether differences in efficacy exist among the NA inhibitors is not currently known but is undergoing evaluation in clinical trials.

The optimal duration of therapy is unknown. At least five days are recommended as in the general population; acknowledging that the immunosuppressed host may shed virus for longer periods of time, some experts advocate extending therapy to ten days.

Resistance due to mutations in NA, most commonly H275Y (or H274Y, depending on the amino acid numbering used), was reported worldwide during 2007–2008 among seasonal influenza A H1N1 strains. More recently, resistance among seasonal and pandemic influenza A/H1N1 strains has remained relatively low (approximately 1%–2%) in the United States. The H275Y mutation confers resistance to oseltamivir and peramivir but not zanamivir. Close attention to local and seasonal resistance patterns is therefore required to guide antiviral therapy.

Prevention

The cornerstones of influenza prevention in the immunocompromised host are vaccination and compliance with infection control policies. Adherence to principles of hand hygiene reduces transmission of influenza and other respiratory

TABLE 2.10.2. ANTIVIRAL AGENTS FOR THE TREATMENT OF INFLUENZA

Agent	Activity*						Adult Treatment Dose	Toxicities/ Side Effects
	Seasonal H1N1†	2009 Pandemic H1N1	Seasonal H3N2	vH3N2	H7N9	Influenza B/C		
Oseltamivir	+	+	+	+	+	+	75–150 mg po bid	GI
Zanamivir	+	+	+	+	+	+	10 mg bid	Bronchospasm
Peramivir	+	+	+	+	+	+	600 mg IV qd	GI, neutropenia
Rimantidine/ amantidine	+/–	–	–	–	–	–	100 mg po bid	CNS, GI

Abbreviations: CNS, central nervous system; FDA, US Food and Drug Administration; GI, gastrointestinal; IV, intravenous.
*Review local influenza surveillance data to determine which types and subtypes of influenza are circulating, as well as their resistence patterns.
†Emergence of H275Y NA mutation in 2007–2008 seasonal H1N1 conferred resistance to oseltamivir and peramivir but not zanamivir.

viruses, whereas early recognition of patients with suspected influenza is critical to effective hospital infection control practices. Patients with suspected or confirmed influenza infection should be placed in droplet and contact isolation while symptomatic. Infection control practices for prolonged, asymptomatic shedders remain controversial.

Influenza vaccination is strongly recommended for all SOT recipients before or three to six months after transplant [10]. During periods of high influenza activity vaccine can be given as early as one month posttransplant, with revaccination if influenza remains active in the community at three to six months posttransplant, recognizing the reduced likelihood of eliciting protection this early after transplant [10]. There are two types of vaccine available for use in the general population: inactivated vaccine (either trivalent or quadrivalent) and a live-attenuated vaccine (LAIV). The inactivated trivalent vaccine is safe and well tolerated in the SOT recipient, whereas LAIV is contraindicated in transplant recipients. Given the relatively recent introduction of the quadrivalent vaccine, there is limited experience on use of this formulation in SOT recipients. Rates of seroconversion after vaccination tend to be lower among the immunocompromised compared with the general population, although with an increasing appreciation of benefits of influenza vaccination in the SOT population [11, 12]. There are no clear and convincing data to support strategies to enhance vaccine efficacy in this population, such as giving a booster dose or higher doses of the vaccine. Vaccination of close contacts of transplant recipients as a way of "cocooning" the SOT recipient, preferably with inactivated vaccine, is strongly recommended.

Both oseltamivir and zanamivir have been found to effectively prevent influenza illness when administered as chemoprophylaxis. Although not broadly recommended, the use of antiviral prophylaxis can be considered on a case-by-case basis (e.g. in scenarios where vaccine is contraindicated, exposure to a documented case has occurred, and risks of infection are high).

KEY POINTS

- Influenza infection in SOT recipients most often presents with a syndrome similar to that seen in the general population, but it is associated with a higher rate of complications (LRTI, etc).
- Molecular diagnostic tests are the gold standard for diagnosis of influenza and other CARVIs in SOT recipients.
- NAs are the first-line treatment for influenza virus infection in symptomatic SOT recipients and should be initiated when there is suspicion for influenza, while awaiting diagnostic testing, and regardless of timing from symptom onset.
- Mainstays of influenza prevention include hand hygiene and isolation precautions, vaccination, and chemoprophylaxis.

REFERENCES

1. Wright PF, Neumann G, Kawaoka Y. Orthomyxoviruses. In: Knipe DM, Howley PM, eds. *Fields Virology*. Vol 2. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2007:pp1691.
2. Manuel O, Estabrook M. RNA respiratory viruses in solid organ transplantation. Am J Transplant. 2013;4:212.

3. Cordero E, Perez-Romero P, Moreno A, et al. Pandemic influenza A(H1N1) virus infection in solid organ transplant recipients: impact of viral and non-viral co-infection. Clin Microbiol Infect. 2012;18:67.
4. Vilchez RA, McCurry K, Dauber J, et al. Influenza virus infection in adult solid organ transplant recipients. Am J Transplant. 2002;2:287.
5. Kumar D, Michaels MG, Morris MI, et al. Outcomes from pandemic influenza A H1N1 infection in recipients of solid-organ transplants: a multicentre cohort study. Lancet Infect Dis. 2010;10:521.
6. Ginocchio CC, Zhang F, Manji R, et al. Evaluation of multiple test methods for the detection of the novel 2009 influenza A (H1N1) during the New York City outbreak. J Clin Virol. 2009;45:191.
7. Low CY, Kee T, Chan KP, et al. Pandemic (H1N1) 2009 infection in adult solid organ transplant recipients in Singapore. Transplantation 2010;90:1016.
8. Ng BJ, Glanville AR, Snell G, et al. The impact of pandemic influenza A H1N1 2009 on Australian lung transplant recipients. Am J Transplant. 2011;11:568.
9. Smud A, Nagel CB, Madsen E, et al. Pandemic influenza A/H1N1 virus infection in solid organ transplant recipients: a multicenter study. Transplantation 2010;90:1458.
10. Kumar D, Morris MI, Kotton CN, et al. Guidance on novel influenza A/H1N1 in solid organ transplant recipients. Am J Transplant. 2010;10:18.
11. Hurst FP, Lee JJ, Jindal RM, et al. Outcomes associated with influenza vaccination in the first year after kidney transplantation. Clin J Am Soc Nephrol. 2011;6:1192.
12. Schuurmans MM, Tini GM, Dalar L, et al. Pandemic 2009 H1N1 influenza virus vaccination in lung transplant recipients: coverage, safety and clinical effectiveness in the Zurich cohort. J Heart Lung Transplant. 2011;30:685.

2.11

How Low Did the Hemoglobin Go?

MORGAN HAKKI, MD

CASE PRESENTATION

A 67-year-old-man with end-stage renal disease due to IgA nephropathy underwent a living related kidney transplant (cytomegalovirus [CMV] R+/D+, Epstein-Barr virus [EBV] R+/D-) after basiliximab induction. His immediate posttransplant course was uncomplicated. He presented to clinic for a routine visit two months posttransplant with had no complaints apart from one week of fatigue and postural lightheadedness. His immunosuppressive regimen consisted of mycophenolate mofetil, prednisone 25 mg daily, and tacrolimus. He took trimethoprim-sulfamethoxazole prophylaxis and he received valganciclovir prophylaxis for one month after transplant.

On examination, he appeared comfortable and in no acute distress. Vital signs were notable only for tachycardia (108 beats per minute), with normal room air oxygen saturation and no fever. Conjunctival pallor was noted. Lungs were clear and the cardiac examination was normal. Abdominal examination was normal, with no tenderness and a well healing surgical wound at the site of the kidney allograft. Skin examination revealed no rash and no edema was present.

Routine posttransplant laboratory studies were notable for anemia, with hemoglobin (Hgb) of 7.5 g/dL (prior baseline for this patient 8.9–9.4 g/dL); the rest of his cell lines were normal. Allograft function was stable (serum creatinine 1.4 mg/dL).

QUESTIONS

- What processes should be considered in a solid organ transplant (SOT) recipient presenting with isolated anemia?
- How should a diagnosis be pursued?

DIFFERENTIAL DIAGNOSIS

Up to 40% of renal transplant recipients develop anemia (defined as Hgb <14 g/dL in males and <12 g/dL in females) within the first year after transplant [1]. As for infectious etiologies of isolated anemia, Parvovirus B19 infection should be considered; other entities such as babesiosis, malaria, clostridial sepsis, and EBV related posttransplant lymphoproliferative disorder are possible, although most often accompanied by other laboratory abnormalities as well as signs and/or symptoms of systemic illness. Noninfectious entities to consider include drugs (particularly azathioprine and mycophenolate), decreased erythropoietin production due to a failing allograft, gastrointestinal bleed, and malignancy.

ADDITIONAL DATA

This patient was found to have a serum iron of 251 μg/dL (reference range, 40–150 μg/dL), serum iron binding capacity of 288 μg/dL (reference range, 245–410 μg/dL), transferring saturation 87% (20–50%), ferritin of 1733 ng/mL (18–460 ng/mL), and a reticulocyte count of 0.2%. There were no schistocytes, parasites, or evidence of hemolysis on review of the blood smear. Polymerase chain reaction (PCR) for Parvovirus B19 performed on blood was positive (quantitative PCR 12 500 copies/mL). No evidence of CMV or EBV reactivation was found. A bone marrow aspirate demonstrated markedly enlarged erythroblasts with viral inclusions, (Figure 2.11.1). White blood cell and platelet precursors were normal.

Immunohistochemical staining for Parvovirus B19 performed on a core marrow biopsy sample was positive (Figure 2.11.2).

Final Diagnosis: Parvovirus B19-induced pure red cell aplasia

CLINICAL COURSE

Ultimately, this patient's Hgb reached a nadir of 6.2 g/dL. Once the diagnosis of Parvovirus

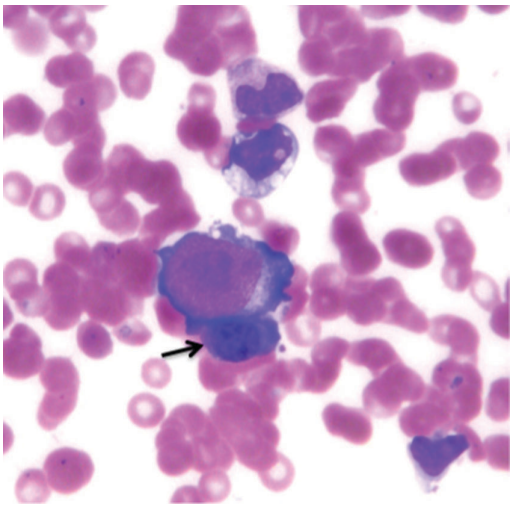


FIGURE 2.11.1: Bone marrow aspirate demonstrating an enlarged erythroblast with a viral inclusion (arrow) adjacent to normal-sized hematopoietic cells, Wright-Giemsa stain (Image courtesy of Dr. Daphne Ang, Department of Pathology, Oregon Health and Science University, Portland, OR).

B19-induced red cell aplasia was established, he received intravenous immune globulin (IVIG) 400 mg/kg × 5 doses. By three weeks after treatment his Hgb recovered and remained stable thereafter.

DISCUSSION

Parvovirus B19 (B19) is a member of the family *Parvoviridae*, genus *Erythrovirus*. The first published report of B19 infection after transplantation appeared in 1986, describing persistent anemia in a renal transplant recipient [2]. Since then, B19 infection has come to be a recognized as an uncommon but potentially serious infectious complication of SOT.

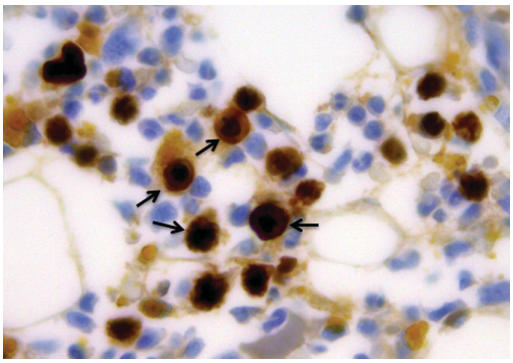


FIGURE 2.11.2: Bone marrow core biopsy showing B-19 infected erythroblasts by immunoperoxidase stain (arrows) (Image courtesy of Dr. Daphne Ang, Department of Pathology, Oregon Health and Science University, Portland, OR).

EPIDEMIOLOGY/ PATHOGENESIS

The seroprevalence of B19 increases with age and by adulthood approximately 70% to 90% of persons are seropositive. Transmission is thought to occur via nasopharyngeal and upper airway secretions. Infection can also be conveyed with blood product transfusions and is suspected to occur through donor organ transmission. The incidence of B19 infection after transplantation is less than 1% [3]. Chronic red cell aplasia results from prolonged B19 infection due to failure to produce neutralizing antibodies in immunodeficiency states.

CLINICAL PRESENTATION

Clinical syndromes associated with B19 infection depend in large part on the host (Table 2.11.1).

The classic presentation of B19 infection in transplant recipients is anemia. Anemia is present in nearly 99% of transplant recipients with active B19 infection [3]. Most cases of B19-associated pure red cell aplasia occur within the first year posttransplant, with a median time to diagnosis of seven weeks posttransplant [3–7], when immune suppression is maximal. B19 infection has been demonstrated in 23% to 38% of kidney transplant recipients presenting with anemia [5, 8]. Testing for B19 should be strongly considered in transplant recipients with otherwise unexplained anemia.

Apart from anemia, other cell lines are less likely to be affected during B19 infection, with leukopenia occurring in 38% and thrombocytopenia in 21% [3]. Fever is observed in approximately 25% of SOT recipients with B19 infection [9]. Immune complex-mediated phenomena such as rash and arthralgia occur infrequently in the SOT population. Proven or suspected accompanying organ-invasive disease has been described in 11% of transplant recipients, including myocarditis, pneumonitis, hepatitis, and glomerulonephritis [3]. Death due to B19 is rare but is uniformly due to myocarditis when it does occur [3].

DIAGNOSTICS

Diagnosis of B19 infection can be made by detection of viral DNA by PCR in clinical samples or by histopathologic assessment of bone marrow, in the setting of anemia. Serology is unreliable in this patient population. In a

TABLE 2.11.1. CLINICAL PRESENTATION OF PARVOVIRUS B19, BASED ON HOST IMMUNE STATUS AND AGE

Patient Population	Clinical Manifestation
Children	Erythema infectiosum ("fifth disease")
Pregnant women	Hydrops fetails
Immunocompetent adults	Polyarthropathy syndrome
Persons with red cell disorders	Transient aplastic crisis
Immunocompromised host	Pure red cell aplasia
	End organ disease (myocarditis, hepatitis, pneumonitis, encephalitis)
	Allograft dysfunction

large review, 29% of transplant recipients were found to have negative IgM at disease onset [3]. Polymerase chain reaction testing to detect B19 DNA in whole blood, plasma, and/or bone marrow is the recommended diagnostic approach in the transplant recipient. Given the lack of specificity for active or acute disease, however, PCR-based testing requires careful clinical interpretation. The value of following PCR to monitor response to treatment is unclear, given that viremia can persist for months despite clinical response. Bone marrow examination may reveal giant, multinucleated erythroblasts and pronormoblasts, with near complete absence of late normoblasts; confirmation is provided by in situ hybridization or immunohistochemical staining. B19 is not easily cultured and therefore culture-based methods are not used to diagnose infection.

TREATMENT

There are no antiviral drugs available for the treatment of B19 infection. There have been numerous reports on the utility of IVIG in transplant recipients and other immunocompromised hosts [3, 8, 10–12] and this has become standard-of-care. However, no placebo-controlled trials have been performed to stringently evaluate the efficacy of this intervention.

Based largely on expert opinion and accepted standard practice, 400 mg/kg per day of IVIG for five days is the usual approach. In a large case series/review of published cases, relapse of infection after treatment with immune globulin, defined by the reappearance of signs and symptoms of infection after completion of treatment, was observed in 28% of SOT recipients [3]. Relapses can be treated with a second course of immune globulin [9], barring dose-limiting toxicities [3]. There are also reports of patients who have cleared infection solely with reduction in immunosuppression; this measure, as an adjunct to immune globulin therapy, should be considered [3].

PREVENTION

Given the lack of specific preventative strategies and the relative rarity of B19 infection in transplant recipients, there are no recommendations for screening. It is noteworthy, however, that patients with B19 viremia are considered infectious, and so standard and droplet precautions should be implemented in the hospital setting to prevent transmission to other at-risk individuals.

KEY POINTS

- Testing for B19 should be considered in transplant recipients with otherwise unexplained hypoproliferative anemia.
- Although molecular diagnostic testing with PCR is the mainstay of rapid B19 diagnosis in SOT recipients, careful clinical interpretation is critical, given that prolonged viremia can occur after infection.
- IVIG is the standard approach to management of B19-associated red cell aplasia in transplant recipients.

REFERENCES

1. Vanrenterghem Y, Ponticelli C, Morales JM, et al. Prevalence and management of anemia in renal transplant recipients: a European survey. Am J Transplant. 2003;3:835.

2. Neild G, Anderson M, Hawes S, Colvin BT. Parvovirus infection after renal transplant. Lancet 1986;2:1226.
3. Eid AJ, Brown RA, Patel R, Razonable RR. Parvovirus B19 infection after transplantation: a review of 98 cases. Clin Infect Dis. 2006;43:40.
4. Beske F, Modrow S, Sorensen J, et al. Parvovirus B19 pneumonia in a child undergoing allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2007;40:89.
5. Cavallo R, Merlino C, Re D, et al. B19 virus infection in renal transplant recipients. J Clin Virol. 2003;26:361.
6. Laurenz M, Winkelmann B, Roigas J, et al. Severe parvovirus B19 encephalitis after renal transplantation. Pediatr Transplant. 2006;10:978.
7. Yango A Jr, Morrissey P, Gohh R, Wahbeh A. Donor-transmitted parvovirus infection in a kidney transplant recipient presenting as pancytopenia and allograft dysfunction. Transpl Infect Dis. 2002;4:163.
8. Egbuna O, Zand MS, Arbini A, et al. A cluster of parvovirus B19 infections in renal transplant recipients: a prospective case series and review of the literature. Am J Transplant. 2006;6:225.
9. Eid AJ, Chen SF. Human parvovirus B19 in solid organ transplantation. Am J Transplant. 2013; 134:S201.
10. Corbett TJ, Saw H, Popat U, et al. Successful treatment of parvovirus B19 infection and red cell aplasia occurring after an allogeneic bone marrow transplant. Bone Marrow Transplant. 1995;16:711.
11. Frickhofen N, Abkowitz JL, Safford M, et al. Persistent B19 parvovirus infection in patients infected with human immunodeficiency virus type 1 (HIV-1): a treatable cause of anemia in AIDS. Ann Intern Med. 1990;113:926.
12. Moudgil A, Shidban H, Nast CC, et al. Parvovirus B19 infection-related complications in renal transplant recipients: treatment with intravenous immunoglobulin. Transplantation 1997;64:1847.

2.12

The "Achilles' Heel" of Liver Transplantation

JANICE JOU, MD, MHS AND CHRISTOPHER D. PFEIFFER, MD, MHS

CASE PRESENTATION

A 51-year-old man with a history of ulcerative colitis and primary sclerosing cholangitis (PSC) complicated by end-stage liver disease requiring orthotopic liver transplantation (OLT) presented with acute onset shaking chills and low-grade fevers. Graft function and immunosuppressive regimen had been stable at the most recent clinic visit, one week before presentation. He denied nausea, vomiting, abdominal pain, diarrhea, confusion, headache, cough, rhinorrhea, chest pain, shortness of breath, or change in weight.

He underwent transplantation (cytomegalovirus [CMV] D-/R-with Roux-en-Y (choledochojejunostomy) anastomosis four months before presentation. Medications included tacrolimus, mycophenolate mofetil, prednisone 5 mg daily, and mesalamine. Posttransplant course was unremarkable leading up to this presentation.

He was married and lived in an urban setting. His wife had recently recovered from an upper respiratory infection one week prior to his acute illness. He had no pets, no recent travel, and no history of illicit drug use.

Vital signs on presentation revealed a temperature of 101.2°F, pulse 98 beats per minute, respirations 14 breaths per minute, blood pressure 137/99 mm mercury, and a room air oxygen saturation of 97% He did not appear to be in acute distress was alert and fully oriented. Chest was clear to auscultation bilaterally and heart was regular with a 2/6 systolic ejection murmur best heard over the left upper sternal border (murmur documented previously). The abdomen was soft, nontender, and nondistended, with normal bowel sounds. There was no rash and his prior abdominal incisions were well healed.

Laboratory data revealed a white blood cell (WBC) count of 9900/mm^3 and abnormal liver tests: total bilirubin 3.9 mg/dL (reference range, 0.3–1.2 mg/dL), alkaline phosphatase 306 IU/L (53–128 IU/L), aspartate aminotransferase (AST) 259 IU/L (15–41 IU/L), alanine aminotransferase (ALT) 122 IU/L (12–60 IU/L), and albumin 3.4 g/dL (3.5–4.7 g/dL). Urinalysis was normal and blood cultures were obtained.

QUESTIONS

- What entities should be considered to explain this patient's acute presentation, with fever, chills, and new liver test abnormalities?
- Should the absence of right upper quadrant abdominal pain or tenderness influence your differential diagnosis?
- What empiric management and additional diagnostic studies are indicated?

DIFFERENTIAL DIAGNOSIS

Acute cholangitis was suspected, with other possibilities including biliary stricture, recurrent PSC, hepatic artery thrombosis, drug-related liver toxicity or acute organ rejection.

ADDITIONAL DATA

A liver ultrasound revealed new intrahepatic biliary ductal dilation and increased resistive indices in the hepatic artery, indicative of hepatic artery thrombosis. The patient was admitted, two sets of blood cultures were obtained, and empiric piperacillin-tazobactam was begun. Both sets of blood cultures grew pan-susceptible *Klebsiella oxytoca*. Computed tomography (CT) of the abdomen and pelvis revealed extensive bilateral intrahepatic biliary ductal dilation, left greater than right, with inflammatory changes in the common hepatic duct concerning for cholangitis and stricture.

Final Diagnosis: Cholangitis, as a consequence of biliary duct strictures resulting from ischemia due to hepatic artery thrombosis

TREATMENT AND OUTCOME

The patient underwent endoscopic retrograde cholangiopancreatography (ERCP), at which time a stent was placed in the common bile duct. On hospital day four, liver tests remained elevated and it was suspected that drainage of the biliary tree was inadequate. Ultimately, a percutaneous transhepatic cholangiogram (PTC) was performed, a persistent stricture was identified, and a percutaneous biliary drain/stent was placed (Figures 2.12.1a, 2.12.1b).

FOLLOW-UP

Fevers resolved by hospital day three and all subsequent blood cultures were negative. By hospital day six, liver tests were improved (total bilirubin 1.6 mg/dL, alkaline phosphatase 230 IU/L, AST 94 IU/L, ALT 26 IU/L). Piperacillin-tazobactam was transitioned to oral ciprofloxacin and the patient was discharged with a plan to complete the balance of two weeks of antibiotic therapy. Over time, he continued to have biliary strictures with recurrent cholangitis. He was temporized with percutaneous biliary drain placements and exchanges until he was successfully re-transplanted two years later.

DISCUSSION

Biliary infections, including acute cholangitis and infected bilomas, are important complications of OLT. The risk of infection is largely determined by graft perfusion as well as the type and adequacy of the biliary anastomosis, the latter of which has been called the "Achilles' heel" of OLT [1]. The biliary system is vulnerable to ischemic injury in so far as it lacks a redundant vascular supply—whereas the liver parenchyma is supported by the portal vein and hepatic artery, the bile ducts are supplied solely by the hepatic artery.

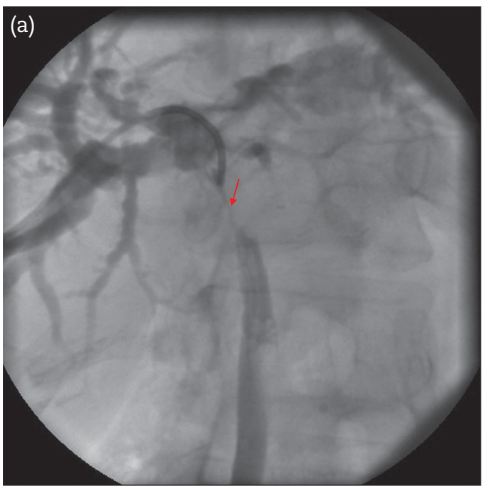


FIGURE 2.12.1a: PTC demonstrating markedly dilated intrahepatic biliary ducts and a stricture in the common hepatic duct (see arrow).

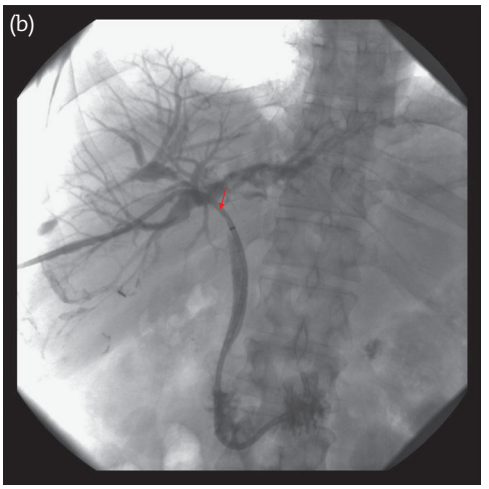


FIGURE 2.12.1b: PTC demonstrating a biliary drain (see arrow) traversing the stricture in the common hepatic duct.

The types of biliary anastomoses used in OLT include: (1) choledocho-choledochostomy (CC), which is a direct duct-to-duct anastomosis of the donor and recipient common bile ducts, and (2) choledocho-jejunostomy (Roux-en-Y), whereby the donor common bile duct is connected directly to the recipient's jejunum. Choledocho-choledochostomy is used most commonly; the advantages of this technique include a shorter operating time and preservation of the recipient Sphincter of Oddi, thereby maintaining some degree of protection against ascending cholangitis as well as endoscopic accessibility to the biliary system. The Roux-en-Y approach is typically used only when CC is either technically infeasible (e.g. re-transplantation, donor-recipient size mismatch) or relatively contraindicated (e.g. PSC). Routine perioperative biliary T-tube use has been associated with increased rates of cholangitis and other complications, and so this practice has been largely abandoned [2, 3].

The timeline of biliary complications after OLT is summarized in Figure 2.12.2 [3].

Bile Leaks

Bile leaks, when they occur, typically arise within the first thirty days after transplant and are related

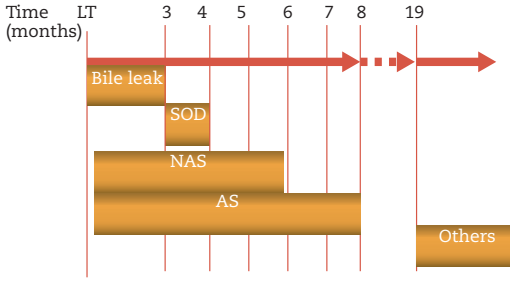


FIGURE 2.12.2: Post OLT biliary complications timeline (adapted from Ayoub *et al.*[3]).

LT, Liver transplantation; SOD, sphincter of Oddi dysfunction; NAS, non-anastomotic stricture; AS, anastomotic stricture; Others includes biliary stones, sludge, and casts.

to technical biliary anastomotic issues. The clinical presentation varies from pauci- or asymptomatic to frank peritonitis. Management entails endoscopic or percutaneous stenting, with surgical revision of the anastomosis reserved for refractory cases. Placement of a stent distal to the leak creates a pressure gradient, allowing bile to flow freely into the duodenum; as such, stenting across the leak is often not necessary [1]. Antibiotics are used as adjunctive therapy for cases complicated by cholangitis or peritonitis.

Biliary Strictures

Biliary strictures occur in 5% to 15% of OLT recipients, typically arising within the first five to eight months posttransplant. Clinical presentation is variable, ranging from asymptomatic liver test elevation to cholangitis with fulminant sepsis [3]. Graft ischemia (e.g. hepatic artery thrombosis) is the most common cause of nonanastomotic stricturing; other risk factors include recurrence of primary disease (e.g. PSC), receipt of organ that was donated after cardiac death, CMV infection, prolonged cold and warm ischemia times, ABO incompatibility, and chronic rejection [1–4].

Diagnosis is by visualization of the biliary tree, either with ERCP or magnetic resonance cholangiopancreatography (MRCP) (Figures 2.12.3a, 2.12.3b, 2.12.3c). Strictures are classified as either anastomotic or nonanastomotic. Anastomotic strictures are usually discrete strictures at the biliary anastomosis site and are caused by either technical surgical issues or graft ischemia. These strictures are often amenable to management by stenting, either endoscopically or percutaneously. On the other hand, nonanastomotic strictures are more challenging to treat because they are often

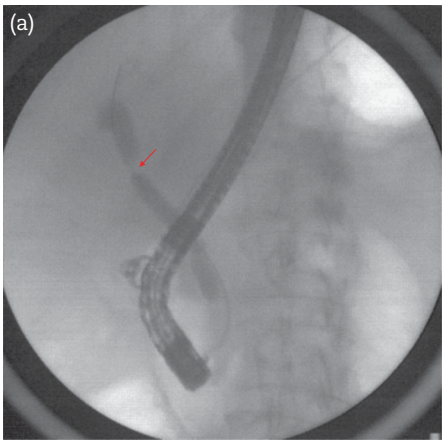


FIGURE 2.12.3a: Anastomotic stricture (see arrow) as seen on ERCP.

diffuse, may be intrahepatic, and are less responsive to stenting.

Bilomas

Bilomas arise when bile ducts rupture and form intrahepatic or perihepatic bilious fluid collections. Bilomas may become infected if nonsterile bile creates the initial collection or if a sterile collection becomes superinfected. In a study evaluating 492 OLT recipients, risk factors for the 51 (12%) patients in whom an infected biloma was diagnosed included hepatic artery thrombosis (odds ratio [OR] = 91), hepatic artery stenosis (OR = 13), and Roux-en Y reconstruction (OR = 6) [5]. In that same study, the most common initial organisms recovered from infected bilomas included enterococci (37%, half of which were vancomycin-resistant), coagulase-negative *Staphylococcus* species (26%, most of which were associated with presence of a T-tube), *Candida* species

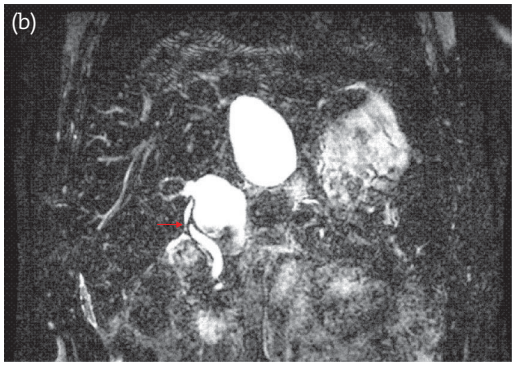


FIGURE 2.12.3b: Anastomotic stricture (see arrow) as seen on MRCP.

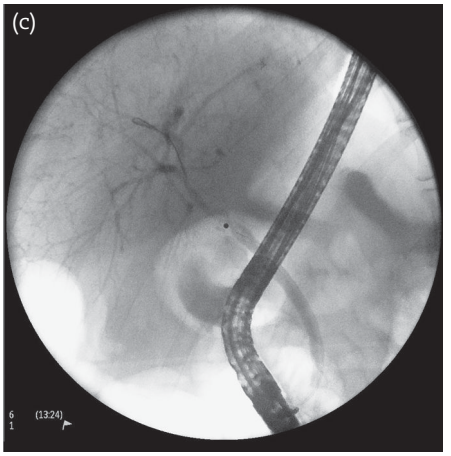


FIGURE 2.12.3c: Diffuse, non-anastomotic structuring as seen on ERCP.

(26%), enteric Gram-negative bacilli (10%), and *Pseudomonas* species (5%). Although small sterile bilomas that remain in contiguity with the biliary tree may resolve spontaneously, treatment of an infected biloma includes percutaneous drainage as well as prolonged, targeted antibiotic therapy [6, 7].

In addition to the special circumstances relevant to biliary complications in the OLT recipient as discussed above, common causes of biliary tract disease in the postcholecystectomy state remain, including biliary stones, sludge, and casts.

Diagnosis and Management

When a biliary complication is suspected in an OLT recipient, Doppler ultrasound of the liver is a practical, noninvasive first-line test. Based on the results, either cross-sectional imaging (e.g. CT, magnetic resonance imaging) or more specific biliary tree visualization (e.g. MRCP, ERCP, PTC) can be obtained to clarify the presence of a bile leak, biliary stricture, biliary ductal dilation, or biloma(s).

Once a biliary issue or complication is identified, the main interventional goal is stenting of strictures and drainage of fluid collections, either endoscopically or percutaneously. The advantage of ERCP or PTC is ability to intervene with biliary stenting at the time of diagnostic cholangiogram. Therefore, if the suspicion for biliary obstruction is high, then ERCP or PTC is preferable to MRCP.

The role for antimicrobial therapy in the setting of a biliary complication is adjunctive to biliary decompression. Empirical antimicrobial recommendations for acute cholangitis in immunocompromised patients with bilio-enteric anastomoses are outlined in practice guidelines coauthored by the Surgical Infection Society and Infectious Diseases Society of America [8]. The guidelines recommend antibiotics with a spectrum of activity that includes coverage for biliary and gut flora (e.g. enteric Gram-negative rods, enterococci, and anaerobes), while accounting for any prior growth of multidrug-resistant organisms and local antimicrobial susceptibility patterns. Empiric choices should be adjusted based on culture data and clinical response.

KEY POINTS

- It is not uncommon for biliary complications to present atypically in OLT recipients, often with absence of classical right upper quadrant pain as a result of allograft denervation.
- The diagnosis of biliary infection in OLT recipients requires awareness and recognition of the clinical syndromes as well as an appreciation of the anatomy and technical considerations that place this patient population at risk for such infections.
- Once the root cause of the biliary infection is identified, a multidisciplinary approach is often required to optimize the care of these often complicated cases.
- In approaching biliary complications in the OLT recipient, antibiotics are typically adjunctive to biliary decompression and/or drainage.

REFERENCES

1. de la Mora-Levy JG, Baron TH. Endoscopic management of the liver transplant patient. Liver Transpl. 2005;11:1007.
2. Kochhar G, Parungao JM, Hanouneh IA, Parsi MA. Biliary complications following liver transplantation. World J Gastroenterol. 2013;19:2841.
3. Ayoub WS, Esquivel CO, Martin P. Biliary complications following liver transplantation. Dig Dis Sci. 2010;55:1540.
4. Koneru B, Sterling MJ, Bahramipour PF. Bile duct strictures after liver transplantation: a changing landscape of the Achilles' heel. Liver Transpl. 2006;12:702.
5. Said A, Safdar N, Lucey MR, et al. Infected bilomas in liver transplant recipients, incidence, risk factors and implications for prevention. Am J Transplant. 2004;4:574.

6. Romero FA, Razonable RR. Infections in liver transplant recipients. World J Hepatol. 2011;3:83.
7. Safdar N, Said A, Lucey MR, et al. Infected bilomas in liver transplant recipients: clinical features, optimal management, and risk factors for mortality. Clin Infect Dis. 2004;39:517.
8. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis. 2010;50:133.

2.13

The Troll of Transplantation Rears Its Head

KATIE A. SHARFF, MD

CASE PRESENTATION

A 56-year-old man with a history of heart transplantation eight months earlier presents with three weeks of fatigue, sweats, and abdominal pain. The patient underwent a heart transplant (cytomegalovirus [CMV] D+/R−) for nonischemic cardiomyopathy. His induction immune suppression was basiliximab and his current immune suppression consists of mycophenolate mofetil, prednisone 5 mg daily, and tacrolimus. Prophylactic antimicrobials included valganciclovir for six months and trimethoprim-sulfamethoxazole for three months.

Eight months after transplantation the patient presents to the outpatient clinic with several weeks of fatigue, sweats, and abdominal discomfort. He endorses multiple watery stools with occasional hematochezia over the past week. Bowel movements are associated with abdominal pain and cramping. He denies fevers, chills, nausea or vomiting. He denies history of foreign travel or consumption of unpasteurized dairy products or undercooked meat or fish. There is no report of recent ill contacts.

On the day of presentation, the patient appears to be in mild distress. He has a low-grade fever, with temperature of 38.2°C; other vital signs are normal, with heart rate of 102 beats per minute, blood pressure of 110/74 mm mercury, and respiratory of 16 breaths per minute. Physical exam is remarkable for a soft abdomen that is mildly distended and diffusely tender to palpation, with no rebound tenderness or guarding. He has active bowel sounds in all quadrants without masses or shifting dullness. The sternotomy wound is well healed, heart rate is regular with no murmurs, and lungs are clear to auscultation.

Laboratory data are notable for acute kidney injury with a serum creatinine of 1.49 mg/dL (baseline creatinine 0.8–0.9 mg/dL), new mildly elevated hepatic aminotransferases (aspartate aminotransferase of 138 U/L and alanine aminotransferase of 94 U/L), and new cytopenias (white blood cell count of 2200/mm^3, hematocrit of 37.1%, and platelets of 123 000/mm^3). Serum amylase, total and direct bilirubin, and serum bicarbonate were normal. An abdominal x-ray revealed dilated loops of large bowel, although without differential air fluid levels or transition point to suggest an obstruction. Abdominal computed tomography demonstrated a featureless colon with circumferential mural thickening and colonic hyperemia compatible with pancolitis (Figure 2.13.1).

QUESTIONS

- What infectious etiologies should be considered to explain this patient's colitis?
- What diagnostic approach should be taken?
- What are the risk factors for development of this infection?

DIFFERENTIAL DIAGNOSIS

Infections to consider in a solid organ transplant (SOT) recipient with an inflammatory colitis include CMV *Clostridium difficile*, other enteric pathogens (*Campylobacter, Shigella, Salmonella, Escherichia coli, etc.*), and, if exposure history is suggestive, *Entamoeba histolytica*. Less

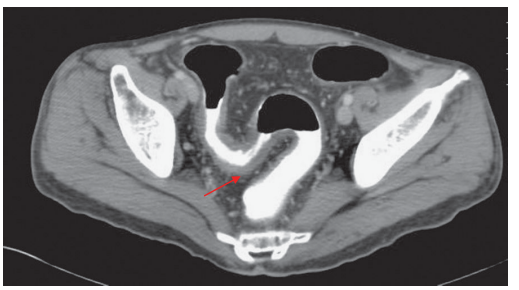


FIGURE 2.13.1: CT demonstrating circumferential mural thickening and hyperemia, consistent with pancolitis.

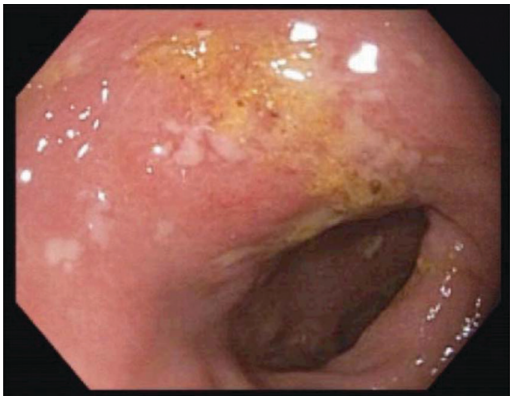


FIGURE 2.13.2: Flexible sigmoidoscopy with diffusely erythematous mucosa with loss of normal vascular pattern and several areas of superficial ulceration.

commonly adenovirus can be a cause of colitis in immunosuppressed hosts.

ADDITIONAL DATA

Stool culture, ova and parasite examination and *C difficile* polymerase chain reaction (PCR) assay were negative. Plasma CMV PCR was 98 000 IU/mL. Flexible sigmoidoscopy revealed diffusely erythematous mucosa in the rectum and sigmoid colon with loss of normal vascular pattern (Figure 2.13.2). Histopathology demonstrated mucosal inflammation and enlarged cells containing eosinophilic intranuclear and basophilic intracytoplasmic inclusions (Figure 2.13.3a).

Final Diagnosis: Late-onset CMV colitis in a high-risk SOT recipient

TREATMENT AND OUTCOME

The patient was treated with intravenous ganciclovir for two weeks, with subsequent improvement in abdominal pain and resolution of loose stools. Therapy was then transitioned to oral valganciclovir 900 mg BID, with weekly monitoring of CMV viral load (plasma PCR). After four weeks, the CMV PCR was undetectable and valganciclovir was discontinued, with no recurrence of gastrointestinal symptoms thereafter.

DISCUSSION

In SOT, CMV infection can be acquired through a number of routes, including transmission from the donor organ or blood products, reactivation of latent infection, or via acquisition of a primary infection from close contact with a CMV-infected individual [1].

Risk Factors

There are several factors related to the host, the virus, and the transplantation procedure that increase the risk of CMV disease in transplant recipients. Cytomegalovirus serostatus is the single most important predictor of CMV disease after SOT (Table 2.13.1).

Solid organ transplant recipients who are CMV-seronegative before transplantation and receive an organ or blood products from a CMV-seropositive donor (D+/R−) are at highest risk. Without prophylaxis, 80% to 100% of D+/R− SOT recipients will develop CMV infection and 50% to 70% of these will develop CMV disease. Solid organ transplant recipients who are CMV seropositive before transplantation (D+/R+, D−/R+) are at intermediate risk, and CMV infection or disease occurs in up to 20% of intermediate risk recipients who are not treated with lymphocyte depleting agents and

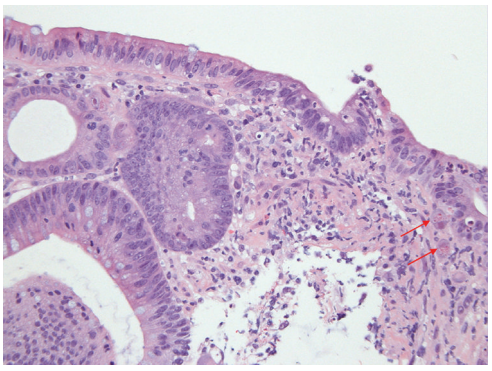


FIGURE 2.13.3a: Histopathology from colon biopsy demonstrating CMV inclusion bodies, hematoxylin & eosin stain, 200×.

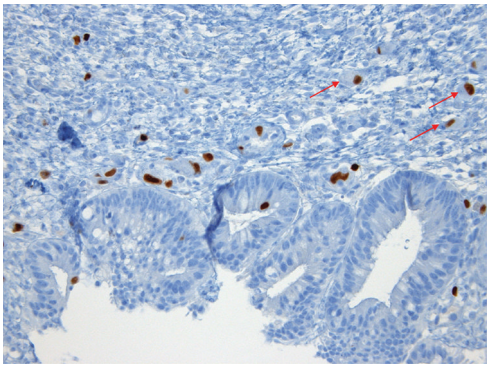


FIGURE 2.13.3b: CMV immunostaining, immunohistochemical stain, 200×.

(Images courtesy of Dr.David Sauer, Department of Pathology, Oregon Health and Science University, Portland, OR.)

TABLE 2.13.1. CMV RISK BY SEROSTATUS AND PROPHYLAXIS STRATEGIES FOR SOT RECIPIENTS

CMV Serostatus	Risk Category	Risk of CMV Infection Without Antiviral Therapy	Prophylaxis	Duration of Prophylaxis
D+/R–	High risk	80%–100%	Valganciclovir*; IV ganciclovir	3–6 months; 12 months for lung recipients
D–/R+, D+/R+	Intermediate risk	20%	Same as above	3 months; 3–6 months for heart or intestine recipients; 6–12 months for lung or heart/lung recipients
D-/R-	Low risk	Low risk	None (presuming use of CMV seronegative or leukocyte-depleted blood products)	None

Abbreviations: CMV, cytomegalovirus; FDA, US Food and Drug Administration; IV, intravenous; SOT, solid organ transplant.
*FDA caution with valganciclovir in liver transplant.

who do not receive preventative antiviral therapy. Cytomegalovirus-seronegative recipients who receive an organ from a CMV-seronegative donor (D–/R–) are considered to be at low risk for CMV disease, presuming CMV-negative or leukocyte-depleted blood products are used [2]. Lung and small bowel transplant recipients are at highest risk for CMV infection and disease, largely owing to the degree of immune suppression and the amount of lymphoid tissue associated with the transplanted organ [3]. Other risk factors include the type and intensity of immunosuppressive agents, with high risk associated with the use of lymphocyte depleting agents [4].

Clinical Presentation

Cytomegalovirus infection is defined as the presence of CMV replication, regardless of symptoms, whereas CMV disease is defined as evidence of infection accompanied by clinical signs and symptoms. Cytomegalovirus disease is then categorized as (1) CMV syndrome, which may present with fever, malaise, leukopenia, and/or thrombocytopenia; or (2) tissue-invasive CMV disease [5]. Tissue-invasive CMV disease can manifest as gastrointestinal disease, pneumonitis, hepatitis, nephritis, mycocarditis, retinitis, or other tissue inflammation. Cytomegalovirus has a predilection for affecting the allograft, presumably related to aberrant immune response within the graft [3]. Indirect effects of CMV include predisposition to other opportunistic infections, acute and chronic allograft rejection, and reduced graft and patient survival posttransplant. Without the use of a preventative strategy, CMV disease typically occurs within the first three months after transplant, but it is delayed in patients receiving CMV prophylaxis [6, 7].

Diagnosis

Several tests are available for diagnosis of CMV disease, including viral culture, antigen-based assays, molecular assays, and histopathology (Table 2.13.2) [8].

Management

The first-line antiviral drugs for treatment of CMV disease include intravenous ganciclovir and valganciclovir, the oral prodrug of ganciclovir (Table 2.13.3). Intravenous ganciclovir is recommended for severe, life- or site-threatening disease and for patients with barriers to enteral absorption. Valganciclovir is an effective therapy for mild to moderate CMV disease. Patients should receive a minimum of two weeks of induction dose antiviral therapy, and until resolution of clinical signs and symptoms of disease and virologic clearance (documentation of one or two consecutive negative samples). Cytopenias, particularly neutropenia, are an important and common toxicity of ganciclovir and valganciclovir. Foscarnet is an alternative CMV-active antiviral that can be considered in patients with severe and dose-limiting toxicity to ganciclovir or valganciclovir, though

TABLE 2.13.2. APPLICATIONS AND LIMITATIONS OF TESTING MODALITIES FOR DIAGNOSIS OF CMV INFECTION OR DISEASE

	Specimen Source	Uses/Advantages	Limitations
Serology (CMV IgG)	Blood: pretransplant from donor and recipient	Donor/recipient serostatus guides posttransplant prophylaxis	Not useful for diagnosis of active CMV infection or disease
Culture (rapid shell vial culture)	Nonblood clinical specimens (eg. BAL fluid, tissue, cerebrospinal fluid, etc)	Contributes to diagnosis of CMV end-organ disease	Must interpret significance of positive culture—infection vs shedding Turnaround time of ~48 hours
Antigen test (CMV pp65 antigen)	Blood	Detection of CMV viremia, with quantitation	Unreliable in neutropenic patients* Requires subjective interpretation Less sensitive than PCR-based testing
PCR	Whole blood or plasma, nonblood clinical specimens (e.g. BAL fluid, cerebrospinal fluid, etc)	Detection of CMV viremia, with quantitation Automated and rapid (quantitative real-time PCR)	Significant lab-to-lab variability, based on testing platform (introduction of WHO International Reference Standard in 2010 should ameliorate this problem)
Histopathology, with CMV immunohistochemistry	Tissue	Gold standard for confirmation of end-organ disease	Barriers to tissue biopsy in certain scenarios (in particular, lung biopsy in morbidly ill patients)

Abbreviations: BAL, bronchoalveolar lavage; CMV, cytomegalovirus; Ig, immunoglobulin; PCR, polymerase chain reaction; WHO, World Health Organization.
*The CMV pp65 antigenemia assay uses tagged monoclonal antibodies specific to the CMV pp65 protein to allow for the detection of CMV proteins in peripheral blood leukocytes.

with the caution that this drug is associated with nephrotoxicity and electrolyte wasting.

Patients who develop CMV disease after prolonged courses of ganciclovir or valganciclovir or who do not respond to standard first-line therapy (e.g. increasing viral load after >2 weeks on appropriately dosed antiviral therapy) should be suspected of having ganciclovir-resistant virus and genotypic testing for resistance should be considered. In the setting of ganciclovir-resistant CMV due to mutations in the UL97 gene, foscarnet and cidofovir are possible alternative therapies. Mutations in UL54 may result in resistance to all of the above therapies, and so treatment should be guided by genotypic assays [3].

Prevention

Most transplant centers use antiviral drugs, in the form of either prophylactic or preemptive therapy, for the prevention of CMV disease in SOT recipients. Antiviral prophylaxis, the administration of drug therapy to all patients who are at risk, is the strategy most often used at SOT centers in the United States. Preemptive therapy entails the administration of antiviral drug to asymptomatic patients with evidence of CMV infection, as detected by PCR or antigen-based assays, to prevent progression to CMV disease. There are advantages and disadvantages to both approaches, and in a limited number of randomized trials in predominantly kidney recipients both were effective for CMV disease prevention [9]. Although preemptive therapy has lower drug costs and fewer associated toxicities, it requires frequent laboratory testing and coordination of care that can be difficult for patients living at a distance from the transplant center. In contrast, prophylaxis entails higher drug costs and greater potential for drug toxicity as well as risk for late-onset CMV disease, but it is associated with improved patient and allograft survival in high-risk groups and decreased rates of opportunistic infection [3, 10].

Ganciclovir and valganciclovir are the antiviral drugs used for prophylaxis and are generally considered comparable in efficacy [11]. Valganciclovir has supplanted oral ganciclovir as the drug of choice for CMV prophylaxis given its lower

TABLE 2.13.3. ANTIVIRAL THERAPY FOR TREATMENT AND PROPHYLAXIS OF CMV DISEASE

Drug	Treatment	Prophylaxis
Valganciclovir	900 mg PO twice daily*	900 mg PO once daily*
Oral ganciclovir	Not recommended due to poor oral absorption (no longer available in United States)	
IV ganciclovir	Induction: 5 mg/kg IV every 12 hours* Maintenance: 5 mg/kg IV every 24 hours	5 mg/kg IV every 24 hours*
Foscarnet	Induction: 60 mg/kg IV every 8 hours* or 90 mg/kg every 12 hours* Maintenance: 90 mg/kg every 24 hours*	Not recommended
Cidofovir	5 mg/kg once weekly × 2 doses*, then every 2 weeks thereafter	Not recommended

Abbreviations: CMV, cytomegalovirus; IV, intravenous.
*Renal dose adjustment as indicated.

pill burden and higher bioavailability, although with the caveat that it is not US Food and Drug Administration-approved for prophylactic use in liver transplant recipients. Late-onset CMV disease, occurring once prophylaxis has been completed, is a significant problem in high-risk recipients (CMV D+/R−). The IMPACT study evaluated 200 versus 100 days of valganciclovir prophylaxis in D+/R− kidney recipients and demonstrated decreased incidence of CMV disease in the group receiving 200 days of prophylaxis (at two years of follow-up, 21.3% vs 38.7%) [7]. In lung recipients the risk of CMV infection and disease is high with less than six months of prophylaxis; one multicenter trial showed significantly lower rates of CMV disease and viremia in lung transplant recipients receiving twelve months versus three months of valganciclovir prophylaxis (4% disease and 10% viremia vs 34% and 64%, respectively) [12].

KEY POINTS

- CMV is an important cause of morbidity in SOT recipients.
- CMV serostatus is the most important predictive factor for the development of CMV disease after SOT.
- Most transplant centers use antiviral medications for the prevention of CMV disease (prophylaxis), particularly in CMV high-risk recipients (D+/R-); preemptive management is an alternative approach.
- Late-onset CMV disease, after completion of antiviral prophylaxis remains a challenge, particularly for CMV high-risk recipients.
- Ganciclovir and valganciclovir are the first-line drugs for treatment of CMV disease and neutropenia is the most common toxicity.

REFERENCES

1. Zamora MR. Cytomegalovirus and lung transplantation. Am J Transplant. 2004;4:1219.
2. Schnitzler MA, Lowell JA, Hardinger KL, et al. The association of cytomegalovirus sero-pairing with outcomes and costs following cadaveric renal transplantation prior to the introduction of oral ganciclovir CMV prophylaxis. Am J Transplant. 2003;3:445.
3. Razonable RR, Humar A. Cytomegalovirus in solid organ transplantation. Am J Transplant. 2013;13 Suppl 4:93.
4. Portela D, Patel R, Larson-Keller JJ, et al. OKT3 treatment for allograft rejection is a risk factor for cytomegalovirus disease in liver transplantation. J Infect Dis. 1995;171:1014.
5. Ljungman P, Griffiths P, Paya C. Definitions of cytomegalovirus infection and disease in transplant recipients. Clin Infect Dis 2002;34:1094.
6. Arthurs SK, Eid AJ, Pedersen RA, et al. Delayed-onset primary cytomegalovirus disease and the risk of allograft failure and mortality after kidney transplantation. Clin Infect Dis. 2008;46:840.
7. Humar A, Limaye AP, Blumberg EA, et al. Extended valganciclovir prophylaxis in D+/R- kidney transplant recipients is associated with long-term reduction in cytomegalovirus disease: two-year results of the IMPACT study. Transplantation 2010;90:1427.
8. Razonable RR, Paya CV, Smith TF. Role of the laboratory in diagnosis and management of cytomegalovirus infection in hematopoietic stem cell and solid-organ transplant recipients. J Clin Microbiol. 2002;40:746.

9. Khoury JA, Storch GA, Bohl DL, et al. Prophylactic versus preemptive oral valganciclovir for the management of cytomegalovirus infection in adult renal transplant recipients. Am J Transplant. 2006;6:2134.
10. Kalil AC, Levitsky J, Lyden E, et al. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. Ann Intern Med. 2005;143:870.
11. Paya C, Humar A, Dominguez E, et al. Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant. 2004;4:611.
12. Palmer SM, Limaye AP, Banks M, et al. Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation: a randomized, controlled trial. Ann Intern Med. 2010;152:761.

2.14

Sometimes It's the Drug, Rather Than the Bug

LYNNE STRASFELD, MD

CASE PRESENTATION

A 40-year-old man presented with fever and chills accompanied by dry cough and dyspnea on exertion. He has a history of congenital heart disease and underwent heart transplant (cytomegalovirus [CMV] D+/R−) seven months earlier. Induction immune suppression was with antithymocyte globulin; maintenance immune suppression was initially with prednisone, mycophenolate, and tacrolimus, then tacrolimus was changed to sirolimus (3 mg daily) two months post-transplant in the context of rising serum creatinine. There is no history of rejection. Antimicrobial prophylaxis, now completed, included six months of valganciclovir and trimethoprim-sulfamethoxazole.

He reported low-grade fever and chills for two weeks preceding admission, then a fever of 103.8°F on the day before admission. Additionally, he had dry cough and progressive dyspnea on exertion, which caused him to limit his activities. He denied recent ill contacts. He has no pets and had not traveled recently. He received an influenza vaccination four months prior.

He appeared nontoxic but notably dyspneic after talking for an extended period. He was febrile with a temperature of 39.9°C and tachycardic with heart rate of 120 beats per minute. Oxygen saturation was 93% on room air at rest and 88% with exertion. Lungs were clear to auscultation, Heart rate was regular, with no appreciable cardiac murmur. Laboratory evaluation was notable for white blood cell count (WBC) 12 400/mm^3 (88% neutrophils), hemoglobin 9.9 g/dL, and platelet count 364 000/mm^3. Serum creatinine was 1.79 mg/dL (at baseline). Liver function tests were normal. Serum lactate dehydrogenase was 151 U/L (range, 110–205 U/L). Sirolimus level was 15.2 mg/dL. Echocardiogram revealed normal cardiac function. Computed tomography (CT) chest revealed ill-defined ground-glass opacities throughout the lungs, more evident on the right relative to the left (Figure 2.14.1).

DIFFERENTIAL DIAGNOSIS

Infectious considerations include CMV pneumonitis, particularly in this CMV high-risk (CMV D+/R−) solid organ transplant (SOT) recipient, as well as respiratory viruses (influenza, respiratory syncytial virus [RSV], parainfluenza, etc), *Pneumocystis jirovecii* pneumonia, and atypical bacteria (e.g. *Mycoplasma pneumoniae, Chlamydophila pneumoniae*, and *Legionella*). Drug toxicity should be kept in mind (e.g. to sirolimus), albeit a diagnosis of exclusion.

QUESTIONS

- How should a diagnosis be pursued?
- How should this syndrome be managed

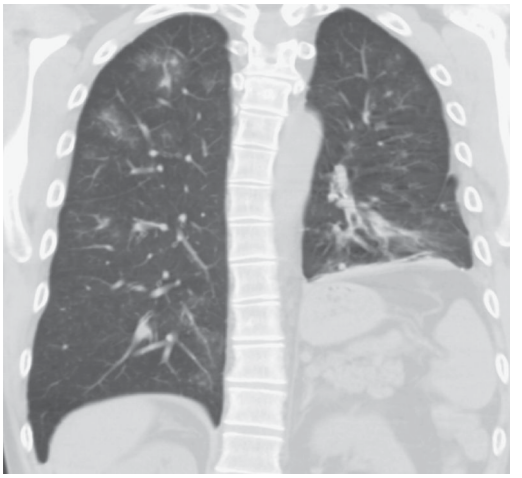


FIGURE 2.14.1: CT chest (coronal view) revealing patchy areas of ground glass opacification, right > left with elevation of the left hemidiaphragm.

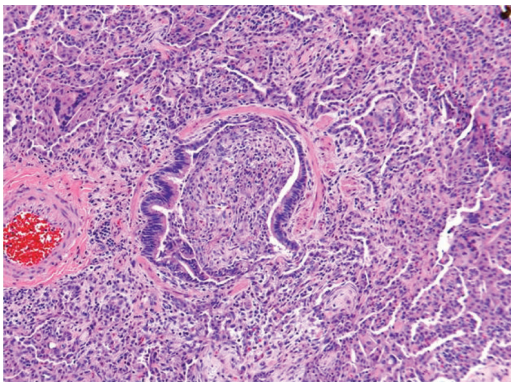


FIGURE 2.14.2: Lung biopsy demonstrating alveolar and small airway organizing changes with reactive pneumocytes and dispersed lymphocytes, hematoxylin and eosin stain

(Image courtesy of Dr. David Sauer, Department of Pathology, Oregon Health and Science University, Portland, OR.)

ADDITIONAL DATA

In pursuit of a diagnosis, bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy was undertaken. All microbiologic studies from the BAL fluid were negative, including stains and culture for bacteria, fungi, and mycobacteria; CMV and herpes simplex virus culture; respiratory virus polymerase chain reaction (PCR) multiplex panel (influenza, RSV, parainfluenza, metapneumovirus, adenovirus, rhinovirus); *Legionella* PCR; *M pneumoniae* PCR; and *Pneumocystis* direct fluorescent antibody. Bronchoalveolar lavage cell count demonstrated 356/mm^3 WBCs (49% macrophages, 27% lymphocytes, and 5% polymorphonuclear cells). Cytologic examination revealed rare ferruginous bodies and pulmonary macrophages loaded with iron pigment and no organisms on Gomori methenamine silver stain. Histologic evaluation of the biopsy revealed alveolar and small airway organizing change with reactive pneumocytes and dispersed lymphocytes (Figure 2.14.2).

Presumptive Diagnosis: Sirolimus-associated pulmonary toxicity

TREATMENT AND OUTCOME

While awaiting results from the bronchoscopy, this patient received empirical levofloxacin, which was subsequently discontinued in light of the negative cultures and other studies from bronchoalveolar lavage fluid. Suspicion was high for drug toxicity and, sirolimus was discontinued, with subsequent introduction of cyclosporine to the immunosuppressive regimen. Over the course of the ensuing two to three weeks, the patient had marked clinical improvement, ultimately with resolution of cough, fever, and dyspnea. Follow-up chest imaging three months after presentation revealed complete resolution of previously seen infiltrates.

DISCUSSION

Sirolimus (rapamycin), a potent immunosuppressive drug, suppresses T-lymphocyte activation through inhibition of mammalian target of rapamycin. Not long after the adoption of sirolimus as an immunosuppressive agent for prevention of rejection in 1999, pulmonary toxicity was recognized as a potential adverse effect [1].

Epidemiology and Risk Factors

The incidence of sirolimus-associated pulmonary toxicity is not well defined. A large single-center series from a hospital in France reported an incidence of 11% for the development of pneumonitis in 217 kidney transplant recipients who received sirolimus over the course of seven years. Of the 600 transplant recipients observed at that center over the same period who did not receive sirolimus, none developed similar pneumonitis/lymphocytic alveolitis [2].

The duration of sirolimus therapy prior to presentation is variable, with reports of onset as early as one month and as late as fifty-one months (median of 5.5 months); approximately 50% of cases occur within the first six months of therapy [2, 3]. There is suggestion of a dose-dependent relationship in some but not all reports [4, 5]. Champion et al [2] reported a median sirolimus trough of 20 ng/mL (range 12–30 ng/mL) prior to onset of pneumonitis. A number of series report a higher incidence of pulmonary toxicity when sirolimus is used as switch therapy from a calcineurin inhibitor (e.g. in the context of renal insufficiency), compared with de novo use post-transplant [2–6]. This association raises the possibility that higher drug levels, as a byproduct of reduced renal clearance, is contributory.

Clinical Presentation

There is significant variability in severity of clinical presentation, from mild and insidious to fulminant and rapidly progressive. The most common presenting symptoms are nonproductive cough, fatigue, fever, and dyspnea, with hemoptysis in a minority of patients [1–7]. Hypoxia is observed in many but not all patients. Chest radiography and CT imaging often reveal bilateral patchy or diffuse alveolo-interstitial infiltrates, typically with

lower lobe predominance, described as resembling bronchiolitis obliterans-organizing pneumonia [1–7]. Lung disease attributed to sirolimus toxicity has been categorized as interstitial pneumonitis, bronchiolitis obliterans with organizing pneumonia (BOOP), or as alveolar hemorrhage.

PATHOPHYSIOLOGY

Although the pathophysiology of sirolimus-associated pulmonary toxicity is not clear, it is theorized to be related either to cell-mediated immune response to exposed cryptic antigens, which in turn induces an autoimmune response resulting in lymphocytic alveolitis and interstitial pneumonitis [8], or possibly related to direct cellular toxicity as manifested by alveolar hemorrhage [7].

Diagnosis

Sirolimus-associated pulmonary toxicity is a diagnosis of exclusion, made after thorough evaluation to exclude infectious etiologies and other pulmonary disease. Bronchoscopy with BAL most characteristically reveals a lymphocytic alveolitis, with an excess of CD4-positive cells by some reports, and occasional report of hemosiderin-laden macrophages typical of alveolar hemorrhage [2, 6–8]. Lung biopsy, when obtained, has been characterized by findings consistent with BOOP, with interstitial lymphocytic infiltrate [3, 5, 6, 8].

The diagnosis of sirolimus-associated pulmonary toxicity rests largely on the temporal relationship between sirolimus exposure and onset of pulmonary symptoms, in the absence of a definable infectious or other etiology, despite thorough evaluation, and with associated clinical and radiographic improvement after sirolimus discontinuation. Morelon et al [8] proposed the following criteria for the diagnosis of sirolimus-induced pulmonary toxicity: (1) exposure to sirolimus preceding the onset of pulmonary symptoms; (2) exclusion of infection, alternative pulmonary disease, and drug toxicity other than sirolimus; (3) resolution of symptoms after sirolimus cessation or dose-reduction; and (4) lymphocytic alveolar cellular profile.

TREATMENT

The mainstay of management of sirolimus-associated pulmonary toxicity is discontinuation of sirolimus, with dose-reduction reported to be variably successful. There are reports of favorable outcomes with use of high-dose corticosteroids [1–5, 7], although there are no controlled trials of this approach. The large majority of patients make a full recovery after cessation or dose reduction of sirolimus. However, there are a few reports of SOT recipients with residual pulmonary fibrosis despite sirolimus discontinuation [3, 4]. Mortality is infrequent, although deaths have been reported [5, 6]. One review cites two deaths, both in heart transplant recipients, among 62 patients with known status at follow-up (4.8% mortality) [6].

KEY POINTS

- The immunosuppressive agent sirolimus lacks the nephrotoxicity associated with calcineurin inhibitors, but can be associated with pulmonary toxicity.
- Sirolimus-associated pulmonary toxicity is characterized by dry cough, fever, and dyspnea, with radiographs revealing bilateral patchy or diffuse alveolo-interstitial infiltrates that can mimic many infectious processes.
- Sirolimus-associated pulmonary toxicity is a diagnosis of exclusion; critically, diagnostic evaluation must include appropriate testing for infectious entities.
- The mainstay of management of sirolimus-associated pulmonary toxicity is discontinuation of sirolimus.

REFERENCES

1. West ML. Bronchiolitis obliternas and organizing pneumonia in renal transplant recipients. Transplantation 2000;69:1531.
2. Champion L, Stern M, Israel-Biët D, et al. Sirolimus-associated pneumonitis: 24 cases in renal transplant recipients. Ann Intern Med. 2006;144:505.
3. Pham PT, Pam PC, Danovitch GM, et al. Sirolimus-associated pulmonary toxicity. Transplantation 2004;77:1215.
4. Haydar AA, Denton M, West A, et al. Sirolimus-induced pneumonitis: three cases and a review of the literature. Am J Transplant. 2004;4:137.
5. Lindenfeld JA, Simon SF, Zamora MF, et al. BOOP is common in cardiac transplant recipients switched from a calcineurin inhibitor to sirolimus. Am J Transplant. 2005;5:1392.
6. Garrean S, Massad MG, Tshibaka M, et al. Sirolimus-associated interstitial pneumonitis in solid organ transplant recipients. Clin Transplant. 2005;19:698.
7. Vlahakis NE, Rickman OB, Morgenthaler T. Sirolimus-associated diffuse alveolar hemorrhage. Mayo Clin Proc. 2004;79:541.
8. Morelon E, Stern M, Israel-Biët D, et al. Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. Transplantation 2001;72:787.

2.15

While the T Cells Were Sleeping

LYNNE STRASFELD, MD

CASE PRESENTATION

A 41-year-old woman presented with fever, night sweats, and a tender left-sided neck mass. She has a history of type 1 diabetes mellitus, and six months ago she underwent a simultaneous pancreas kidney transplant (cytomegalovirus [CMV] D−/R−, Epstein Barr virus [EBV] D+/R−). Induction immunosuppression was with antithymocyte globulin (ATG) and maintenance immunosuppression for prevention of allograft rejection with prednisone 5 mg daily, tacrolimus, and mycophenolate mofetil.

Her course had been remarkable for a brief readmission approximately six weeks after transplant for evaluation of fevers. During that hospital stay she had an extensive evaluation for source of fever (blood cultures negative, computed tomography [CT] abdomen without abscess, influenza polymerase chain reaction [PCR] negative) and was found to have a right lower extremity deep vein thrombosis, for which she was begun on warfarin anticoagulation. Thereafter, she felt well for a number of months, with good allograft function and no new problems. Five months posttransplant, she began to experience low-grade fevers (temperature 99.2–100°F) with drenching night sweats and chills, followed a few weeks later by new lower back pain. At six months posttransplant, she noted a tender left neck mass, accompanied now by high-grade fevers (103.2°F). She was admitted for further evaluation.

She works as an accountant and just recently returned to work. She is single and lives alone. She denies illicit substance use. She has an 8-year-old cat at home, although as instructed by her renal transplant coordinator she has not been changing the kitty litter since transplant. She has not been sexually active recently and denies ill contacts. She has always resided in the Pacific Northwest and has no history of international travel.

On presentation the patient appeared mildly uncomfortable but not toxic. Her temperature was 101.1°F. She was noted to have a firm, nonmobile 3 cm left-sided neck mass with mild tenderness to palpation but no fluctuance or overlying erythema. There were no other enlarged lymph nodes. Heart was regular in rate and rhythm with no appreciable murmur, and lungs were clear to auscultation. The abdominal surgical scar was well healed and there was no tenderness overlying the allografts. She had mild tenderness to palpation of the lumbar spine, although without specific point tenderness. Neurologic examination was normal without demonstrable weakness.

Laboratory evaluation revealed a white blood count of 8500/mm^3 (59% neutrophils, 24% bands, 4% lymphocytes, and 12% monocytes), hemoglobin 11.3 g/dL, and platelet count of 301 000/mm^3. Serum lactate dehydrogenase was elevated at 350 U/L (reference range, 110–205 U/L). Serum electrolytes and liver function tests were normal, with serum creatinine (Cr) 0.98 mg/dL and serum glucose ranging 70–114 mg/dL. A CT of the neck and chest revealed a 3 cm left jugular chain/posterior triangle mass, a 3 cm paratracheal lymph node, a mass-like opacity of the right middle lobe near the major fissure, and rim-enhancing hepatic lesions (Figures 2.15.1 and 2.15.2). Magnetic resonance

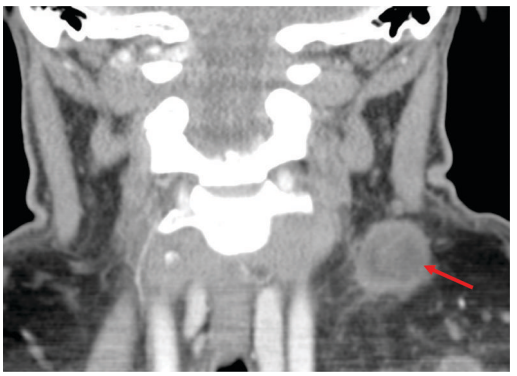


FIGURE 2.15.1: CT neck demonstrating 3 cm left jugular chain/posterior triangle mass (see arrow).

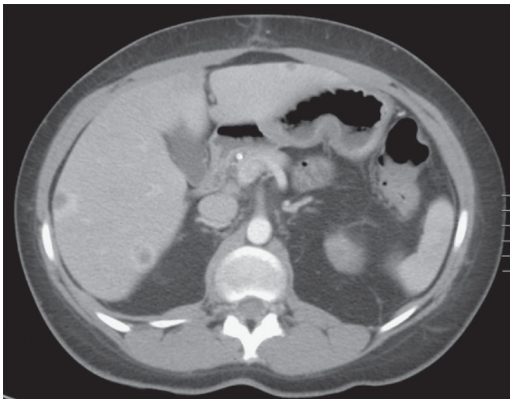


FIGURE 2.15.2: CT demonstrating multiple rim-enhancing hepatic lesions.

imaging of the thoracic and lumbar spine revealed multiple enhancing lesions in the spine and left ilium, concerning for metastatic disease or lymphoma.

QUESTIONS

- What disease entities should be considered to explain this patient's clinical syndrome?
- How should a definitive diagnosis be pursued?

DIFFERENTIAL DIAGNOSIS

Both infection and malignancy are possibilities. Infections to consider in a transplant recipient with fever and adenopathy include the herpesviruses (specifically CMV and EBV, human herpesvirus-8), toxoplasmosis, human immunodeficiency virus (HIV), bartonellosis, endemic mycoses (e.g. histoplasmosis, coccidioidomycosis), and mycobacterial infection (both *Mycobacterium tuberculosis* and the nontuberculous mycobacteria).

ADDITIONAL DATA

Cytomegalovirus PCR (plasma) was undetected. Blood cultures and urine culture were negative. Epstein-Barr virus PCR (plasma) was 120 000 copies/mL. A left neck mass (lymph node) excisional biopsy was performed. Stains and cultures for bacteria, fungi, and mycobacteria from the biopsy were negative. Lymph node histopathology revealed sheets of plasma cells with diffuse CD20 staining (Figure 2.15.3) and immunohistochemical staining positive for EBV (Figure 2.15.4).

Final Diagnosis Posttransplant lymphoproliferative disorder (PTLD)

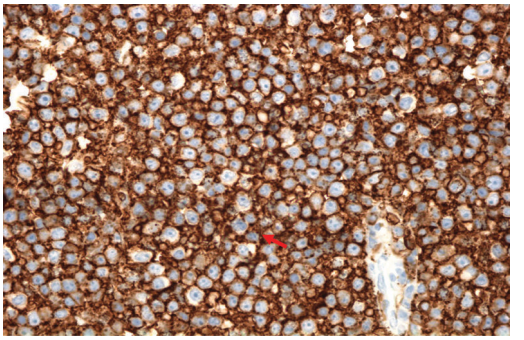


FIGURE 2.15.3: Lymph node biopsy with diffuse CD20 staining, immunoperoxidase stain
(Image courtesy of Dr. Ken Gatter, Department of Pathology, Oregon Health and Science University, Portland, OR).

TREATMENT AND OUTCOME

In light of the new diagnosis of PTLD, immune suppression was tapered, with discontinuation of mycophenolate and dose reduction of tacrolimus. She was seen by oncology and received six cycles of rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisolone. In the context of decreased immune suppression she experienced rejection of both allografts, ultimately losing function of the pancreas. Now three years after the diagnosis of PTLD, she has no evidence of residual PTLD and is on two-drug immune suppression (prednisone and tacrolimus) with serum Cr of 2.5 mg/dL.

DISCUSSION

Epstein-Barr virus, a gammaherpes virus, is a common infection transmitted by exposure to infected body fluids (e.g. saliva). Although the

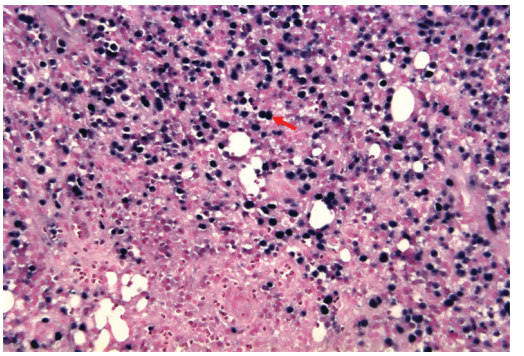


FIGURE 2.15.4: Lymph node biopsy positive for EBV by EBER in situ hybridization (dark blue staining is positive for EBV)
(Image courtesy of Dr. Ken Gatter, Department of Pathology, Oregon Health and Science University, Portland, OR).

most frequent clinical manifestation of primary EBV infection in immunocompetent individuals is a mononucleosis syndrome (fever, pharyngitis, cervical lymphadenopathy, hepatosplenomegaly, and atypical lymphocytosis), young infants and children often experience asymptomatic infection. Up to 90%–95% of adults are EBV-seropositive, indicative of prior infection [1]. Once primary infection has occurred, EBV enters a latent phase, lying dormant in B lymphocytes.

Pathophysiology

Epstein-Barr virus is a transforming virus and has been associated with the development of a number of malignancies (e.g. Burkitt lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma in the HIV population, nasopharyngeal carcinoma, etc). In transplant recipients on chronic immunosuppression, EBV-related PTLD can occur, most often of recipient B cell origin [2]. The pathophysiology of this process is EBV infection (either transmitted via latently infected lymphocytes from a seropositive donor, by blood products, through primary exposure in the community, or as a consequence of reactivation of latent EBV under the pressure of immune suppression) and unchecked replication in the context of decreased immune surveillance. Intensive immune suppression blunts the development an adequate population of EBV-specific cytotoxic $CD8^+$ T lymphocytes (CTLs), thereby increasing the risk for PTLD related to uncontrolled EBV-driven B-cell proliferation [2, 3].

Risk Factors

Risk factors for EBV-associated PTLD in solid organ transplant (SOT) recipients include profound T-cell suppression, particularly in the setting of anti-lymphocyte antibody preparations such as OKT3 and ATG, and primary EBV infection posttransplant [3]. The prevalence of EBV-associated PTLD in SOT recipients ranges from 1% to 20%, depending on organ type (multivisceral > intestinal > heart-lung > lung > heart > liver > kidney), EBV donor/recipient serostatus (D+/R− highest risk for early posttransplant PTLD), and recipient age [2]. Given that primary EBV infection is a major risk factor, pediatric transplant recipients are at higher risk of developing PTLD.

Clinical Presentation

The manifestations of posttransplant EBV infection range from asymptomatic viremia to a mononucleosis-like syndrome to lymphoproliferative disorder, which can be either polyclonal or monoclonal in nature [2]. Posttransplant lymphoproliferative disorder can present in a variety of ways, symptomatic or asymptomatic, indolent or fulminant, with nodal or extranodal disease, and often with involvement of the transplanted organ(s). Central nervous system involvement, when it occurs, seems to be associated with an overall poorer prognosis [4]. Although most PTLD is EBV-associated, a small but increasing number of cases are EBV-negative; EBV-negative PTLD generally presents later (>5 years posttransplant) [5].

Diagnosis

Although detection of EBV by PCR in blood is often sensitive, it is not sufficiently specific for the diagnosis of PTLD. There is significant variability in EBV viral load measurements depending on the compartment assayed (e.g. serum vs plasma vs whole blood) and a lack of standardization between laboratory tests, resulting in substantial laboratory-to-laboratory variability [6]. As such, there is no clear consensus on what threshold viral load should prompt additional diagnostic evaluation for PTLD or therapeutic intervention. Definitive diagnosis requires tissue biopsy for histopathologic and immunophenotypic characterization. In situ hybridization for Epstein-Barr encoding region, a marker of EBV-infected cells, is key to the diagnosis of EBV-associated PTLD; CD20 status has significant bearing on the therapeutic approach, and most EBV-associated PTLD are CD20 positive.

Management

Central to management of PTLD is the reduction or cessation of immune suppression. Although acyclovir and ganciclovir both inhibit lytic DNA replication in vitro, neither has activity against latently infected B cells, nor is there been proven efficacy of antivirals for the treatment of EBV-associated PTLD. Rituximab, a humanized chimeric monoclonal CD20 antibody, has an established role in the treatment of CD20-positive EBV-associated PTLD [4]. The use of standard cytotoxic chemotherapy is generally reserved for individuals with advanced, monomorphic PTLD. Adoptive immunotherapy with the use of EBV-specific CTLs has been used more successfully in PTLD after stem cell transplantation, where the donor remains available to provide T cells. Intriguing are the encouraging results reported from clinical trial whereby healthy blood donors served to generate a bank of EBV-specific CTLs for SOT recipients with PTLD unresponsive to other treatment approaches [7].

Prevention

In high-risk scenarios (e.g. EBV D+/R−), antivirals (e.g. acyclovir or ganciclovir) are often used as prophylaxis, although the evidence to support this practice is limited. Preemptive strategies using regular monitoring of EBV viral loads have been used in high-risk settings, with adjustment of the immunosuppressive regimen in response to viremia; there is some literature suggesting that this strategy may be successful in decreasing the incidence of EBV disease and PTLD [8].

KEY POINTS

- EBV is a common herpesvirus virus with oncogenic potential.
- Risk for PTLD is highest in SOT recipients who experience primary EBV infection (e.g. EBV D+/R−) and in those who have received potent T-cell immune suppression.
- Although molecular diagnostic tests (e.g. EBV PCR on blood) can suggest the possibility of PTLD, they are nonspecific and definitive diagnosis requires tissue biopsy.
- Management of PTLD includes reduction of immune suppression and, when frank monomorphic lymphoma is present, consideration for conventional chemotherapy if and when functional status allows.
- The value of preemptive monitoring of EBV viral load in high-risk patients as a strategy to reduce the incidence of PTLD is uncertain.

REFERENCES

1. Cohen JI. Epstein-Barr virus infection. N Engl J Med 2000;343:481.
2. Green M, Michales MG. Epstein-Barr virus infection and posttransplant lymhoproliferative disorder. Am J Transplant. 2013;13:41.
3. Paya CV, Fung JJ, Nalesnik MA, et al. Epstein-Barr virus-induced posttransplant lymphoproliferative disorders. ASTS/ASTP EBV-PTLD Task Force and The Mayo Clinic Organized International Consensus Development Meeting. Transplantation 1999;68:1517.
4. Evens AM, David KA, Helenowski I, et al. Multicenter analysis of 80 solid organ transplantation recipients with post-transplantation lymphoproliferative disease: outcomes and prognostic factors in the modern era. J Clin Oncol. 2010;28:1038.
5. Callard S, Lamy FX, Quelen C, et al. Epidemiology of posttransplant lymphoproliferative disorders in adult kidney and kidney pancreas recipients: report of the French registry and analysis of subgroups of lymphomas. Am J Transplant. 2012;12:682.
6. Preiksaitis JK, Pang XL, Fox JD, et al. Interlaboratory comparison of Epstein-Barr virus viral load assays. Am J Transplant. 2009;9:269.
7. Haque T, McAulay KA, Kelly D, Crawford DH. Allogeneic T-cell therapy for Epstein-Barr virus-positive posttransplant lymphoproliferative disease: long-term follow-up. Transplantation 2010;90:93.
8. Lee TC, Savoldo B, Rooney CM, et al. Quantitative EBV viral loads and immunosuppression alterations can decrease PTLD incidence in pediatric liver transplant recipients. Am J Transplant. 2005;5:2222.

2.16

An Ounce of Prevention

JASON VAN WINKLE, MD

CASE PRESENTATION

A 41-year-old man presents with fever, shaking chills, and a dry cough. He has type 1 diabetes mellitus and received a simultaneous kidney pancreas transplant (cytomegalovirus [CMV] D+/R−) five years earlier. Induction immune suppression was with daclizumab, and maintenance regimen is tacrolimus, azathioprine, and prednisone 5 mg daily; he was treated with a pulse of steroids one month earlier for mild renal allograft rejection. His posttransplant course had been otherwise complicated by CMV reactivation three years ago, treated with valganciclovir.

He reported feeling unwell for approximately one week prior to presentation, with fever to 101°F associated with shaking chills and a dry cough. He denied chest pain, rhinorrhea, headache, nausea, vomiting, or abdominal pain.

He is married, has no children and is unemployed. He denies illicit drug or tobacco use. He resides in the Pacific Northwest, traveled to Texas recently, but he has no history of international travel and has no known exposure to tuberculosis. He has no pets. He is monogamous with his wife and denies high-risk sexual exposures. He denies recent ill contacts.

On presentation, he appeared fatigued and chronically ill. He was able to speak in full sentences. He was afebrile with a blood pressure of 82/45 mm mercury and oxygen saturation of 89% on room air. On chest auscultation, rales were appreciated at the right lung base, without wheezing or dullness to percussion. Laboratory evaluation was notable for a normal white blood count (6800/mm^3) and anemia (hemoglobin 10.9 g/dL); lactate dehydrogenase was markedly elevated at 887 U/L (reference range, 110–205 U/L), and serum creatinine was above baseline at 1.29 mg/dL (baseline creatinine 0.7 mg/dL). An arterial blood gas revealed hypoxemia, with pO2 of 57 mmHg. Chest radiography demonstrated diffuse left upper and right lower lobe ground-glass opacities (Figure 2.16.1).

QUESTIONS

- What infectious entities should be considered to explain this patient's clinical syndrome?
- How should a definitive diagnosis be pursued?

DIFFERENTIAL DIAGNOSIS

This patient's clinical syndrome is one of fever, nonproductive cough and hypoxia, with diffuse ground-glass opacities on imaging, in a solid organ transplant (SOT) recipient with recent augmentation of immune suppression. Infectious considerations include community respiratory virus infection (e.g. influenza, respiratory syncytial virus, parainfluenza), CMV pneumonitis, atypical bacterial pathogens (e.g. *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*), *Pneumocystis jirovecii* pneumonia (PCP), and possibly other fungi such as *Cryptococcus* and endemic mycoses (e.g. *Histoplasma* and *Coccidioides*).

ADDITIONAL DATA

Respiratory virus polymerase chain reaction (PCR) multiplex panel from nasopharyngeal swab

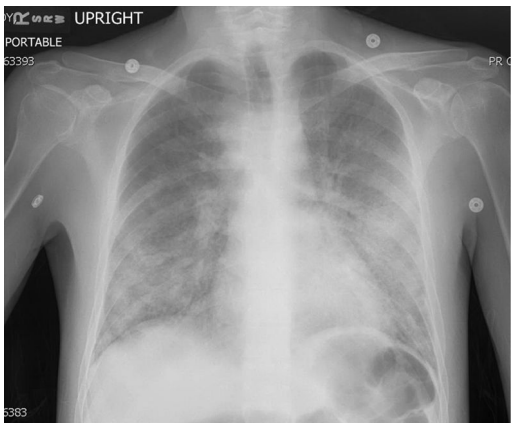


FIGURE 2.16.1: Chest X-ray demonstrating bilateral ground glass opacities.

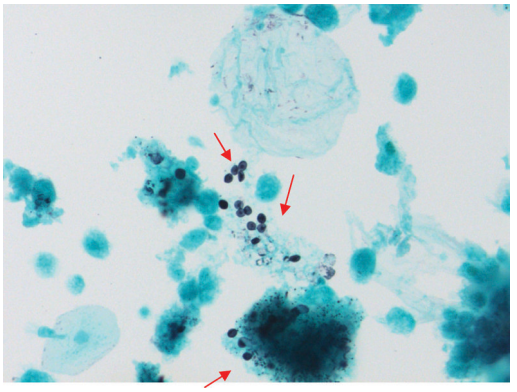


FIGURE 2.16.2: PCP cysts (arrows), Gomori methenamine silver stain

(Image courtesy of Dr. David Sauer, Department of Pathology, Oregon Health and Science University, Portland, OR).

was negative. Cytomegalovirus PCR (plasma) was negative. Sputum gram stain/culture and blood cultures were negative. Sputum silver stain for *Pneumocystis* was negative.

The patient underwent bronchoscopy with bronchoalveolar lavage. Cultures were negative. Silver stain performed on the lavage fluid revealed *P jirovecii* cysts (Figure 2.16.2).

Final Diagnosis: *Pneumocystis jirovecii* pneumonia

TREATMENT AND OUTCOME

The patient was treated with high-dose trimethoprim-sulfamethoxazole (TMP-SMX) and adjunctive corticosteroid therapy (prednisone 40 mg twice daily for five days, followed by 40 mg daily for five days, 20 mg daily for eleven days, and then resumption of 5 mg daily dosing for prophylaxis of allograft rejection). He was progressively hypoxic and required prolonged intubation. Despite a complicated course notable for multiple pneumothoraces, he gradually improved and ultimately returned to his baseline clinical status.

DISCUSSION

Pneumocystis jirovecii, formerly known as *P. carinii*, is a ubiquitous fungus that almost all humans are exposed to by a very young age. It is a cause of pneumonia in individuals with compromised cellular immunity, including SOT recipients.

Pathogenesis

Studies in animals and humans suggest that *pneumocystis* is transmitted through person-to-person spread by the airborne route [1]. Although previously thought to represent reactivation, more contemporary epidemiologic and animal data suggests that infection is related to new infection, with asymptomatic lung colonization in immunocompetent individuals common and serving as a reservoir for spread of *Pneumocystis* to susceptible individuals [2].

Epidemiology and Risk Factors

The overall risk for the development of PCP after SOT has been reported to be in the range of 5% to 15% without prophylaxis and is highest in those with combined heart-lung transplantation [3]. Risk for development of PCP is greatest in the first six months posttransplant and after augmentation of immune suppression. Broadly speaking, risk relates to the overall net state of immune suppression rather than to a specific immunosuppressive agent.

In the era of routine application of effective posttransplant prophylaxis, cases of PCP are presenting at increasingly late time points after transplantation, as with this case. A recent review demonstrated that the median time to presentation was two years posttransplant, with a range of eight months to eleven years [4]. Apart from immune suppression with SOT, PCP has been associated with human immunodeficiency virus (HIV), high-dose corticosteroid use and malnutrition. Cytomegalovirus infection has also been associated with the development of PCP co-infection, and so dual infection should be entertained.

Clinical Presentation

The usual presentation of PCP is one predominated by cough, fever, and shortness of breath, with hypoxia often out of proportion to symptoms. In HIV-negative individuals PCP is characterized by a more abrupt, rather than indolent, picture, with an overall shorter duration of symptoms leading up to presentation. Duration of symptoms are, on average, slightly greater than one week for those without HIV compared with just over two weeks for those with HIV (Table 2.16.1) [24].

Diagnosis

Plain radiographs characteristically reveal a diffuse interstitial pattern that is often bilateral [5]. However, plain chest radiography may appear normal and high-resolution computed tomography (CT) imaging is more sensitive for the diagnosis. Classic findings on CT include ground-glass attenuation, interstitial infiltrates, and thin-walled cysts (Figure 2.16.3) [6]. At least in the HIV-positive population, CT imaging has been noted to have

TABLE 2.16.1. DURATION OF SYMPTOMS AT PRESENTATION, FOR HIV-NEGATIVE AND HIV-POSITIVE INDIVIDUALS WITH PCP*

Duration of Symptoms at Hospitalization		
	Non-HIV PCP	**HIV PCP**
Cough	9.86 ± 1.70 days	15.2 ±1.72 days
Fever	8.05 ± 1.57 days	15.4 ± 3.67 days
Dyspnea	9.88 ± 1.54 days	17.3 ± 1.91 days

Abbreviations: HIV, human immunodeficiency virus; PCP, *Pneumocystis jirovecii* pneumonia.
*Adapted from [2].

a very high sensitivity and a high negative predictive value for *Pneumocystis* [7].

Pneumocystis jirovecii cannot be grown in culture, and so diagnosis is based on direct visualization of the organism from a respiratory specimen or lung tissue. Gomori methenamine silver, Giemsa, Wright, and Calcafluor stains have been the traditional methodologies for detecting the presence of cysts. Use of monoclonal fluorescent antibodies has been shown to be more sensitive than traditional stains to detect *Pneumocystis* in samples from induced sputum and bronchoalveolar lavage fluid [8].

It is appreciated that the burden of infection in patients without HIV is often lower than in those with HIV, which has important implication for diagnostic strategies in approaching HIV-seronegative patients suspected to have PCP. The sensitivity for diagnosis increases with the invasiveness of the procedure; direct lung tissue biopsies demonstrate higher yield (sensitivity > 95%) than that from bronchoalveolar lavage (sensitivity 80% to 95%), which is in turn more sensitive than induced sputum (sensitivity 30% to 55%, higher with immunofluorescent antibody staining) [9].

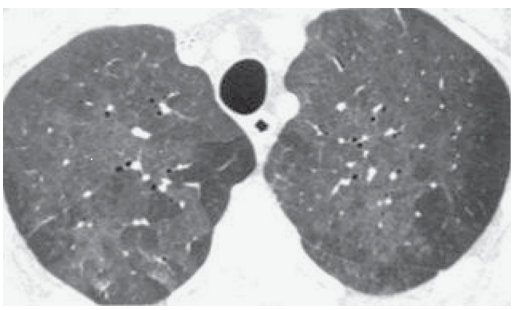


FIGURE 2.16.3: CT chest demonstrating typical diffuse bilateral ground glass opacities.

Serum (1–3)-β-D-glucan has been examined as a noninvasive strategy for PCP diagnosis. A prospective study found serum (1–3)-β-D-glucan to have a sensitivity of 86% and a specificity of 89% in 31 HIV-seronegative patients, including 17 SOT recipients [10]. In a study of 448 patients with pulmonary infiltrates and possible PCP, 21 of whom were renal transplant recipients, PCR performed on respiratory secretions had a sensitivity of 92% and a specificity of 87% [11]. Polymerase chain reaction remains a promising diagnostic modality but genomic targets are not yet standardized.

Treatment

The preponderance of prospective trial data on treatment of PCP derives from the HIV literature. As such, therapy recommendations for treatment of PCP in SOT recipients have largely been extrapolated from studies in HIV-infected patients. The treatment of choice for PCP is TMP-SMX, dosed at 15–20 mg/kg of the trimethoprim component divided q6–q8 hours (dose adjustment as indicated for renal insufficiency) for at least 14 days, and up to 21 days in the context of severe infection. Overlapping toxicities with antirejection regimens (e.g. renal insufficiency with calcineurin inhibitors and cytopenias with antimetabolites) are at times dose-limiting. Alternatives to TMP-SMX include intravenous pentamidine as well as combination clindamycin and primaquine, with debate as to which second-line regimen is more effective.

Use of adjunctive corticosteroids in hypoxic HIV-positive patients with PCP has been shown to decrease risk for respiratory failure and mortality. Limited, retrospective data in HIV-negative patients has demonstrated a decrease in duration of mechanical ventilation and length of intensive care unit admission with use of corticosteroid therapy, although with no mortality benefit [12]. In the context of moderate to severe disease, adjunctive corticosteroids should be considered; for patients with PaO_2 <70 mmHg and/or an alveolar-arterial oxygen gradient >35 mmHg and/or hypoxemia on pulse oximetry, prednisone (40 mg po twice daily days one to five, then 40 mg po daily for days six to ten, and then 20 mg po daily for days eleven to twenty-one) can be considered in combination with antimicrobial therapy.

Prevention

The routine administration of antimicrobial prophylaxis has led to a dramatic decrease in the incidence of PCP after SOT. *Pneumocystis* prophylaxis

should be considered for all SOT recipients for the first three to twelve months posttransplant, when immune suppression is maximal, and should be extended beyond that period in certain circumstances. Extending or restarting prophylaxis should be considered in patients who require augmented immune suppression for treatment of rejection as well as receipt of corticosteroids with a prednisone equivalent of 20 mg daily for more than two to three weeks.

Trimethoprim-sulfamethoxazole is the first-line agent for PCP prophylaxis and should be used in the absence of documented allergy or dose-limiting toxicity. Advantages of TMP-SMX include its broad spectrum of activity (offering some protection against other opportunistic infections such as *Toxoplasma gondii, Nocardia*, *Listeria monocytogenes*, as well as urinary tract infection in kidney recipients), low cost, and availability in a variety of formulations. Various dosing regimens have been shown to be effective in preventing PCP in SOT recipients, including daily double strength (DS) or single strength, DS thrice weekly, and DS with twice daily dosing twice weekly.

Trimethoprim-sulfamethoxazole is the first-line drug for prophylaxis against PCP and the practitioner should be wary of abandoning TMP-SMX for minor side effects or intolerances. Alternatives to TMP-SMX include dapsone, pentamidine, and atovaquone. These second-line agents have been shown to be slightly less effective than TMP-SMX in preventing PCP and are all accompanied by potential for drug-related or other side effects [13]. In patients with true TMP-SMX allergy the cross-reactivity to dapsone is approximately 50%, and so dapsone should not be used in patients with severe or life-threatening TMP-SMX (sulfa) allergy or in patients with glucose-6-phosphate dehydrogenase deficiency. Pentamidine has traditionally been administered monthly by inhalation when given for prophylaxis, although this can precipitate bronchospasm; there is some limited data on the use of pentamidine for prophylaxis by monthly intravenous infusion. Atovaquone, although likely as effective as the other second-line agents, is disadvantaged by a comparably high cost as well as associated dysgeusia and other gastrointestinal side effects.

Lastly, given reports of clusters of infection in the healthcare setting and the accumulating data to suggest person-to-person airborne transmission of PCP, infection control practices warrant consideration. Although some centers segregate patients with PCP (e.g. avoiding placement of susceptible hosts in the rooms of patients with *P carinii* pneumonia) or recommend use of facemasks to prevent transmission, no formal infection prevention recommendations can be made in the absence of definitive data [3].

KEY POINTS

- SOT recipients are at risk for PCP, a risk that is mitigated by antimicrobial prophylaxis and increased with augmentation of immune suppression.
- Less invasive diagnostic modalities such as examination of induced sputum may not be sensitive enough to exclude PCP in SOT recipients.
- TMP-SMX is the drug of choice for prevention and treatment of PCP.
- Prophylaxis, preferably with TMP-SMX, is typically given for three to twelve months after transplantation.

REFERENCES

1. Choukri F, Menotti J, Sarfati C, et al. Quantification and spread of Pneumocystis jirovecii in the surrounding air of patients with Pneumocystis pneumonia. Clin Infect Dis. 2010;51:259.
2. Ponce CA, Gallo M, Bustamante R, Vargas SL. Pneumocystis colonization is highly prevalent in the autopsied lungs of the general population. Clin Infect Dis. 2010;50:347.
3. Martin S, Fishman J; AST Infectious Diseases Community of Practice. *Pneumocystis* pneumonia in solid organ transplantation. Am J Transplant. 2013;13:272.
4. McKinnell JA, Cannella AP, Kunz DF, et al. *Pneumocystis* pneumonia in hospitalized patients: a detailed examination of symptoms, management, and outcomes in human immunodeficiency virus (HIV)-<?font ?>infected and HIV<?font aid:cstyle="crs_Minion Pro"?>-uninfected persons. Transpl Infect Dis. 2012;14:510.
5. DeLorenzo LJ, Huang CT, Maguire GP, Stone DJ. Roentgenographic patterns of Pneumocystis carinii pneumonia in 104 patients with AIDS. Chest 1987;91:323.
6. Fujii T, Nakamura T, Iwamoto A. *Pneumocystis* pneumonia in patients with HIV infection: clinical manifestations, laboratory findings, and radiological features. J Infect Chemother. 2007;13:1.
7. Hidalgo A, Falcó V, Mauleón S, et al. Accuracy of high-resolution CT in distinguishing between Pneumocystis carinii pneumonia and non-*Pneumocystis carinii* pneumonia in AIDS patients. Eur Radiol. 2003;13:1179.
8. Kovacs JA, Ng VL, Masur H, et al. Diagnosis of *Pneumocystis carinii* pneumonia: improved

detection in sputum with use of monoclonal antibodies. N Engl J Med. 1988;318:589.
9. Rodriguez M, Fishman JA. Prevention of infection due to *Pneumocystis* spp. in human immunodeficiency virus-negative immunocompromised patients. Clin Microbiol Rev. 2004;17:770.
10. de Boer MG, Gelinck L, van Zelst BD, et al. β-D-glucan and S-adenosylmethionine serum levels for the diagnosis of Pneumocystis pneumonia in HIV-negative patients: a prospective study. J Infect. 2011;62:93.
11. Azoulay E, Bergeron A, Chevret S, et al. Polymerase chain reaction for diagnosing pneumocystis pneumonia in non-HIV immunocompromised patients with pulmonary infiltrates. Chest 2009;135:655.
12. Pareja JG, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV *Pneumocystis carinii* pneumonia. Chest 1998;113:1215.
13. Fishman JA. Prevention of infection caused by *Pneumocystis carinii* in transplant recipients. Clin Infect Dis. 2001;33:1397.

2.17

Cruise Ship Souvenir

ROBERT M. RAKITA, MD

CASE PRESENTATION

A 35-year-old woman presented with worsening watery diarrhea of three weeks' duration. Seven years earlier, she had small bowel and colon necrosis due to superior mesenteric vein thrombosis, requiring removal of most of her small bowel and total colectomy. After being maintained on total parenteral nutrition, two years later she underwent a small intestinal transplant, with direct ileorectal anastomosis. She was both cytomegalovirus (CMV) and Epstein Barr virus (EBV) seropositive at the time of transplant. She did well thereafter, except for development of mild chronic kidney disease related to calcineurin-inhibitor toxicity. Maintenance immunosuppression included tacrolimus and hydrocortisone, and she took monthly inhaled pentamidine for *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis (due to a prior sulfa allergy).

She had three to four bowel movements per day at baseline. However, over the course of three weeks she had worsening diarrhea, with up to ten to fifteen bowel movements per day. Her stools were watery and malodorous, were not oily, did not float, and were without gross blood or mucus. She had nausea and headache, with occasional emesis. She denied fever, chills, or significant abdominal pain.

She lived in the Pacific Northwest and had no history of foreign travel. She had not eaten anything unusual recently, and she specifically denied eating raw meat or shellfish or drinking unpasteurized milk. She was a preschool teacher and was thus exposed to many small children, but she did not recall any with a recent diarrheal illness.

Physical exam revealed temperature of 36.5°C, heart rate 88 beats per minute, and blood pressure 115/76 mm mercury. She was not acutely ill appearing, although she appeared dehydrated. Her throat was dry without lesions, there was no palpable lymphadenopathy, the lungs were clear, and abdominal exam revealed hyperactive bowel sounds and was soft and mildly tender to palpation in the epigastrium, without guarding or rebound.

Laboratory studies were notable for mild hyponatremia with a serum sodium 130 meq/L, creatinine 2.6 mg/dL (up from her baseline of 1.6), white blood cell count of 4700/μL, lymphocyte count slightly low at 900/μL, hemoglobin 13.2 g/dL, and platelet count 114 000/μL (at baseline for her). Liver enzymes were normal. Tacrolimus level was 8 ng/mL.

Abdominal computed tomography (CT) showed normal bowel loops (Figure 2.17.1). Cytomegalovirus and EBV DNA were not detectable in plasma by polymerase chain reaction (PCR). Stool studies, including culture for enteric pathogens, ova, and parasite exam, *Clostridium difficile* toxin testing by PCR, auramine stain for *Cryptosporidium, Cyclospora*, and *Cystoisospora*, and trichrome stain for *Microsporidia* were all negative. Stool antigen testing for rotavirus, adenovirus, and *Giardia* were also negative. Flexible sigmoidoscopy revealed grossly normal mucosa of the transplanted small bowel (Figure 2.17.2), and pathology of random biopsies showed only rare apoptotic bodies without evidence for rejection

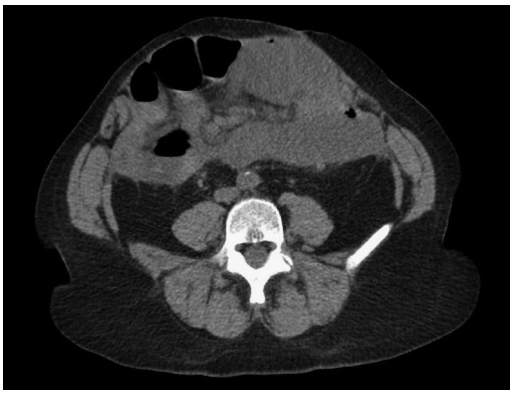


FIGURE 2.17.1: Abdominal CT showing normal loops of bowel.

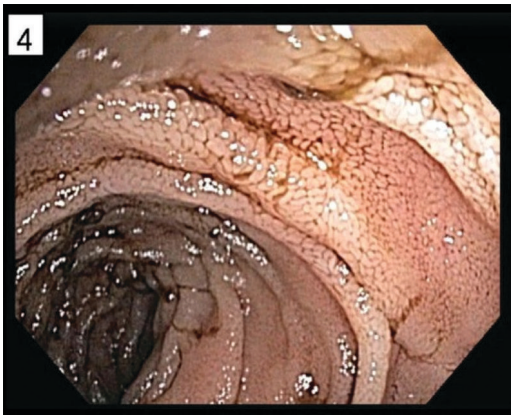


FIGURE 2.17.2: View of ileum from sigmoidoscope, showing normal appearing mucosa.

(Figure 2.17.3), with immunostaining for CMV and viral cultures negative.

She was treated with intravenous fluids, and her symptoms improved over the course of two to three days. However, over the next three months she had multiple episodes of recurrent diarrhea requiring hospitalization for elevated creatinine and volume depletion. All of the above studies were repeated at least twice, without any change in the results. Additional studies included anti-endomysial immunoglobulin (Ig)A, which was negative, and total serum IgG, IgA, and IgM levels, which were normal. Empiric treatment with methylprednisolone for possible rejection also did not seem to alter the course of her recurrences.

QUESTIONS

- What infectious and noninfectious etiologies of diarrhea should be considered in solid organ transplant (SOT) recipients?

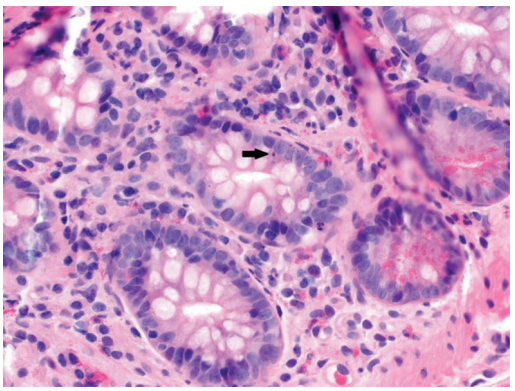


FIGURE 2.17.3: Biopsy of small intestine with rare apoptotic body (arrow) and normal crypt architecture.

(Courtesy of Matthew M. Yeh, MD, PhD)

- What diagnostic evaluations should be pursued in SOT patients with persistent or recurrent diarrhea?

DIFFERENTIAL DIAGNOSIS

A wide variety of infectious agents can cause diarrhea in the SOT population (Table 2.17.1) [1]. These include bacterial enteropathogens, parasites, viruses, and occasionally fungi and mycobacteria. In addition, a number of noninfectious etiologies should be considered (Table 2.17.2) [2]. Malignancy may be found, particularly posttransplant lymphoproliferative disease (PTLD). In addition, one must always consider medication-related causes, which in this population often includes mycophenolate. Another common etiology specific to patients with intestinal transplant is acute rejection.

ADDITIONAL RESULTS AND TREATMENT

Reverse transcriptase-PCR (RT-PCR) from stool was positive for norovirus group 2. She was treated

TABLE 2.17.1. INFECTIOUS AGENTS CAUSING DIARRHEA IN SOLID ORGAN TRANSPLANT PATIENTS

Bacteria	Pathogenic *Escherichia coli* (Enterotoxigenic *E coli*, enteroinvasive *E coli*, enteropathogenic *E coli*, enteroaggregative *E coli*, enterohemorrhagic *E coli*)
	Other common enteropathogens (*Salmonella* spp, *Shigella* spp, *Campylobacter* spp, *Vibrio* spp, *Yersinia enterocolitica, Aeromonas* spp)
	Clostridium difficile
Mycobacteria	*Mycobacterium tuberculosis*
	Mycobacterium avium complex
Parasites	*Cryptosporidium* spp
	Entamoeba histolytica
	Giardia lamblia
	Cystoisospora belli
	Cyclospora spp
	Strongyloides stercoralis
Viruses	Cytomegalovirus
	Herpes simplex virus
	Adenovirus
	Astrovirus
	Rotavirus
	Norovirus
Fungi	*Microsporidia* spp
	Histoplasma spp

TABLE 2.17.2. NONINFECTIOUS CAUSES OF DIARRHEA IN SOLID ORGAN TRANSPLANT PATIENTS

Drug-induced	Antibiotics
	Mycophenolate
	Azathioprine
	Cyclosporine
	Sirolimus
	Tacrolimus
	Others (e.g. magnesium)
Other	Posttransplant lymphoproliferative disease (PTLD)
	Graft-versus-host disease
	Rejection (in intestinal transplant)
	Inflammatory bowel disease
	Ischemic colitis

with nitazoxanide 500 mg po bid for five days with marked improvement in her diarrhea. However, approximately one month later, she had relapse of diarrhea and nausea. She was treated with oral Ig 1.5 g (25 mg/kg) every six hours for eight doses, again with resolution of her symptoms, but had multiple subsequent relapses despite repeated courses of the above therapies. Norovirus continued to be detectable in her stool by RT-PCR ten months later, but it was not associated with clinical symptoms.

Final Diagnosis: Recurrent diarrhea due to norovirus

DISCUSSION

Noroviruses are now recognized as one of the most common causes of gastroenteritis in the general population [3]. First identified as the cause of a school-related outbreak in 1968 in Norwalk, Ohio (and thus originally named the Norwalk virus), these single-stranded RNA, nonenveloped viruses in the family *Caliciviridae* now consist of at least 35 genotypes [1, 3]. Characteristics of the epidemiology and clinical manifestations of norovirus-related disease are listed in Box 2.17.1.

Epidemiology

Noroviruses are common causes of diarrhea in immunocompromised patients [1] and in the SOT population in particular [4]. One study found that norovirus was the primary enteric pathogen in over one third of kidney transplant patients with severe diarrhea [5], and it is commonly found in hematopoietic stem cell transplant recipients as well.

Clinical Manifestations

Although disease is self-limited in the normal population, in immunocompromised hosts norovirus infection can result in prolonged clinical disease and extremely protracted viral shedding [1]. Thus, in SOT patients, this can be an unrecognized cause of chronic or recurrent gastroenteritis. In addition, disease due to norovirus in immunocompromised patients may be more severe than that due to other enteropathogens [4].

Diagnosis

The standard diagnostic technique is RT-PCR from stool (or vomitus) [3]. This is a very sensitive technique and can detect small quantities of virus.

BOX 2.17.1 EPIDEMIOLOGY AND CLINICAL MANIFESTATIONS OF NOROVIRUS

Occurs throughout the year, although higher rate in the winter.
Easily transmitted; infectious dose is ~18 viral particles, whereas amount in diarrhea is ~100 billion/gram feces.
Peak shedding at day 1–3 of illness, but may continue to shed for average of 4 weeks in normal population. Prolonged shedding (many months) in the immunocompromised host.
Temperature stable. Can persist on surfaces.
Resistant to commonly used disinfectants; bleach is preferred.
Incubation period is 0.5–2 days.
Sudden onset nausea, vomiting, diarrhea or some combination.
Fever in up to 50%. May have headache or myalgias.
Self-limited illness, resolves in 1–3 days in the normal population. Common cause of chronic or recurrent episodes in the immunocompromised host.

TABLE 2.17.3. POSSIBLE TREATMENT OPTIONS FOR NOROVIRUS IN IMMUNOCOMPROMISED PATIENTS

Nitazoxanide	Antiviral activity in normal hosts. One patient after hematopoietic stem cell transplant improved [7].
Oral human immunoglobulin	Dose of 25 mg/kg every 6 hrs × 8 doses. Retrospective case control study showed less stool output at 7 days, but no change in time to resolution of symptoms [8].
mTOR inhibitors	Case reports of symptom improvement and viral clearance after change from calcineurin inhibitor to sirolimus or everolimus [9].

However, viral RNA may be detected for a prolonged period after infection, which is of unclear significance. In addition, in patients appreciated to have very prolonged shedding, such as transplant recipients, it may be difficult to determine whether ongoing or recurrent symptoms are due to norovirus infection or to an alternative cause. Enzyme immunoassay kits are available for detection of norovirus in stool; although their specificity is fairly high, their sensitivity is only moderate. Enzyme immunoassay should not be relied on for routine diagnosis, although it may be useful as a screening test in outbreak situations [6]. Solid organ transplant recipients with diarrhea that is of uncertain etiology despite comprehensive stool evaluation may require upper and/or lower endoscopy, particularly to look for pathogens such as CMV. Intestinal histopathology from patients with norovirus enteritis may be similar to that seen in acute allograft rejection in intestine transplants, with apoptotic bodies present, adding to the difficulty in distinguishing these entities.

Treatment

No well defined specific treatment for infection with norovirus has been described. Because the disease is self-limited in normal hosts, supportive therapy with volume and electrolyte repletion is all that is typically required. In the immunocompromised/transplant population, where patients may have prolonged or recurrent symptoms [1], small studies have suggested a few pharmacologic approaches (Table 2.17.3). However, in the SOT population, the most important factor in managing norovirus infection may be a reduction in the level of immunosuppression, particularly in those patients with chronic or relapsing illness, but must be carefully balanced with the risk for rejection.

Prevention

Hand hygiene is a key factor in preventing transmission. The effectiveness of alcohol-based hand sanitizers is not clear; studies of these agents using surrogate viruses (such as animal caliciviruses) have shown some activity, but this is dependent on both the type of sanitizer and the type of virus [6]. Enteric contact precautions for hospitalized individuals is important, particularly during the most infectious period, which includes the duration of the illness and for one to two days thereafter. Disinfection of surfaces preferably should be with chlorine bleach solution at 1–5000 ppm.

Immunity to noroviruses is not well defined. Duration of immunity after infection may be relatively short lived (< 2 years) [3], but immunity in the SOT population has not been examined. Vaccine development has been challenging, in part due to the many potential infecting genotypes. However, an experimental nasal vaccine using virus-like particles, which are self-assembled capsid proteins that have been expressed in eukaryotic cells, had some benefits when volunteers were challenged with a homologous viral strain [10], and similar vaccines using other strains are in clinical trials.

KEY POINTS

- Noroviruses are very common causes of diarrhea in both the general population and immunocompromised hosts.
- In the SOT population, chronic or recurrent diarrhea may result from norovirus infection.
- Diagnosis is by RT-PCR from stool.
- Treatment is supportive, although small reports have described a few potentially effective therapies (nitazoxanide, oral human Ig, mammalian target of rapamycin [mTOR] inhibitors), and reduction of immunosuppression is likely important in chronic illness.
- Hand hygiene and bleach disinfection of surfaces are critical to prevent transmission.

REFERENCES

1. Bok K, Green KY. Norovirus gastroenteritis in immunocompromised patients. N Engl J Med. 2012;367:2126.

2. Krones E, Hogenauer C. Chronic diarrhea in the immunocompromised patient. Gastro Clin N Amer. 2012;41:677.
3. Glass RI, Parashar UD, Estes MK. Norovirus gastroenteritis. N Engl J Med. 2009;361:1776.
4. Roos-Weil D, Ambert-Balay K, Lanternier F, et al. Impact of norovirus/sapovirus-related diarrhea in renal transplant recipients hospitalized for diarrhea. Transplantation 2011;92:61.
5. Coste JF, Vuiblet V, Moustapha B, et al. Microbiological diagnosis of severe diarrhea in kidney transplant recipients by use of multiplex PCR assays. J Clin Microbiol. 2013;51:1841.
6. Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Updated norovirus outbreak management and disease prevention guidelines. MMWR Recomm Rep 2011;60:1.
7. Siddiq DM, Koo HL, Adachi JA, Viola GM. Norovirus gastroenteritis successfully treated with nitazoxanide. J Infect. 2011;63:394.
8. Florescu DF, Hermsen ED, Kwon JY, et al. Is there a role for oral human immunoglobulin in the treatment for norovirus enteritis in immunocompromised patients? Pediatr Transplantation 2011;15:718.
9. Boillat Blanco N, Kuonen R, Bellini C, et al. Chronic norovirus gastroenteritis in a double hematopoietic stem cell and lung transplant recipient. Transpl Infect Dis. 2011;13:213.
10. Atmar RL, Bernstein DI, Harro CD, et al. Norovirus vaccine against experimental human Norwalk virus illness. N Engl J Med. 2011;365:2178.

SECTION 3

Infections in Hematopoietic Stem Cell Transplant Recipients

SECTION EDITOR, JOHN R. WINGARD

Introduction: Infections in Hematopoietic Stem Cell Transplant Recipients

JOHN R. WINGARD, MD

The goal of allogeneic stem cell transplantation is the establishment of donor hematopoiesis and immunity in the recipient to treat an antecedent marrow failure disorder or to achieve a graft-versus-cancer effect to treat a neoplastic disease. Profound changes in immune competence take place involving all arms of innate and adaptive immunity and host barriers. The immune changes occur abruptly in some types of transplants and gradually in other types depending on the intensity of the conditioning regimen and type of stem cell graft. For example, myeloablative conditioning regimens cause abrupt abrogation of hematopoiesis and substantial damage to mucosal barriers, resulting in profound neutropenia and mucositis during the first several weeks after transplant. Reduced intensity regimens, in contrast, result in less severe and shorter neutropenic periods and less mucosal injury. Peripheral blood grafts typically contain more hematopoietic and lymphocyte precursors than bone marrow grafts, and both the time to engraftment is shorter and the pace of lymphoid recovery tends to occur more quickly. Lymphoid reconstitution under the best of circumstances takes months to a year or longer but occurs more slowly in recipients of cord blood grafts, T cell-depleted grafts, and mismatched donor grafts. The occurrence of graft-versus-host disease (GVHD) profoundly disturbs the pace of both B and T cell recovery, and lymphoid recovery may persist for years.

The goal of autologous hematopoietic stem cell transplant (HSCT) is very different from allogeneic HSCT. In autologous HSCT, the goal of the graft is simpler: it is to rescue the myelotoxic effects of high-dose chemotherapy. Neutropenia is shorter, cellular immunodeficiency is less profound, and immune reconstitution is quicker. Thus, early on, the types and risk for infection mirrors allogeneic HSCT early, but the risk for infection is much less after neutrophil recovery. How robust the immune recovery is depends mostly on the types and duration of therapies given for the underlying malignancy before the transplant and whether the patient receives posttransplant therapies that impede hematopoietic or immune recovery. For example, monoclonal anti-B cell antibodies or purine analogs that suppress T cell function given before the transplant (particularly in patients transplanted for lymphoid malignancies) may have long-lasting effects that will persist after autologous HSCT. The use of immunomodulatory drugs after transplant (increasingly used after transplant for multiple myeloma) may likewise suppress immune reconstitution. Poor recovery of hematopoiesis after transplant due to myelotoxic drugs given before HSCT may also predispose patients to infection.

Infectious exposures before transplant play an important role after transplant. Although an infection may be effectively treated and under good control before transplant, reactivation may occur after transplant. This has been most dramatically seen with herpesviruses, hepatitis, and invasive fungal infections, but there are notable examples with many other pathogens as well. Accordingly, careful screening as part of the pretransplant evaluation and continued close monitoring after transplant is important.

Three periods of immune deficiency are generally recognized after HSCT: pre-engraftment (the first two to four weeks after transplant), early postengraftment (second and third month after transplant), and late postengraftment (beyond three months). The types of infectious syndromes that occur vary according to the period. The pre-engraftment period is characterized by neutropenia and mucosal injury. Breaches in the mucosal barrier allows seeding of commensal organisms (principally Gram-negative bacteria and *Candida*) into the bloodstream, and the lack of a second-line of defense (neutrophils

and macrophages) provides these organisms the opportunity to progress and lead to life-threatening consequences. The use of implanted vascular catheters predispose to skin-colonizing, Gram-positive cocci. The early postengraftment period is characterized by profound deficiency in cellular immunity. Cytomegalovirus (CMV), *Aspergillus*, and *Pneumocystis jirovecii* are the principal opportunistic organisms that exploit the lack of protective cellular responses during this period to cause serious disease, but a variety of other pathogens can also pose serious threats. During the late postengraftment period, immune recovery is gradual and infectious risk is much less. However, if chronic GVHD occurs, there are profound and long-lasting disturbances in humoral and T cell immunity that are associated with risks of varicella-zoster, *P jirovecii, Aspergillus*, and recurrent and serious infection by encapsulated bacteria.

The search for risk factors that can identify individuals at greatest risk for various types of infection has led to the identification of neutropenia, lymphopenia (or low $CD4^+$ cell counts), low levels of immunoglobulin, and GVHD, prior infection by organisms that may persist in the recipient or donor, and a number of other factors in certain situations. However, it is important to note that normal numbers of lymphocytes and normal immunoglobulin levels provide little reassurance of effective functioning of various subsets of lymphocytes required for protective anti-infective immunity or the ability to mount serologic responses to vaccines or new pathogens. Unfortunately, although the presence of the above risk factors identifies groups of patients who are at risk, there are no reliable markers of immune competence in individual patients.

Many of the infectious syndromes mimic non-infectious complications of HSCT. One of the biggest challenges is distinguishing infection from some other noninfectious etiology of a syndrome. For example, the patient with diarrhea may have *Clostridium difficile*, typhlitis, medication toxicity, or mucositis from the conditioning regimen during the pre-engraftment period, or CMV, *C difficile*, medication toxicity, or GVHD during the early postengraftment period. A new diffuse pulmonary infiltrate early after transplant may be due to fluid overload, toxicity from the conditioning regimen, or a respiratory virus. The infectious disease consultant must have a comprehensive knowledge of the possible etiologies, both infectious and noninfectious, and a clear diagnostic algorithm to reach a diagnosis to provide optimal anti-infectious care to the HSCT recipient.

3.1

A Bad Case of the Trots: Diarrhea Early in the Course of Transplantation

JACK HSU, MD

CASE PRESENTATION

A 45-year-old woman with acute myelogenous leukemia presents thirty days after allogeneic stem cell transplant from his 10/10 human leukocyte antigen-matched unrelated donor after cyclophosphamide/total body irradiation conditioning. Postgraft immunosuppression consisted of tacrolimus and methotrexate. Her posttransplant course was complicated by neutropenic fevers requiring broad-spectrum antibiotics. She had prompt neutrophil engraftment starting at day twenty-one of transplant, and she was discharged to the clinic two days later. She sees you today with complaints of abdominal cramping and loose bowel movements. Temperature was 38.1°C; other vital signs were normal. Abdominal exam revealed moderate discomfort with deep palpation in the right lower quadrant. Bowel sounds were hyperactive. No masses were palpated. No ecchymosis or petechiae were seen.

DIFFERENTIAL DIAGNOSIS

The differential for diarrhea early into the course of allogeneic transplant is very broad. A considerable number of infectious and noninfectious etiologies may be responsible for the diarrhea. Potential infectious causes include neutropenic enterocolitis, diverticulitis, *Clostridium difficile*, enteric viral pathogens, adenovirus, cytomegalovirus (CMV), or parasites. Noninfectious etiologies include drug toxicities and acute graft-versus-host disease (GVHD).

In this situation, the lack of broad-spectrum antibiotic use or new medications does not favor *Clostridium difficile* or drug toxicity. Isolated gut GVHD is unusual but possible. The recovery of neutrophils excludes neutropenic colitis. An infectious etiology is favored. Blood and stool cultures should be obtained to identify infectious causes. A computed tomography (CT) of the abdomen will help in looking for inflammatory foci.

Complete blood counts and a chemistry panel were found to be within normal limits. Blood cultures and stool cultures were negative. Peripheral blood CMV DNA polymerase chain reaction (PCR) was negative. Stool examination for ova and parasites as well as *C difficile* toxin were negative. Stool was noted to be brownish liquid with semi-formed elements. Quantitation of stool output was <500 mL/day. Computed tomography of the abdomen revealed no abnormalities.

The negative stool and blood cultures reduces the possibility of a bacterial etiology. A negative CT scan does not exclude the possibility of GVHD or viral colitis. Referral to gastroenterology for upper and lower endoscopy with biopsy can assist with identifying an etiology.

The Gastroenterology service was consulted, and the patient underwent upper and lower endoscopy with biopsy. Gross visual inspection showed essentially normal gastric and colonic mucosa (Figure 3.1.1). Random biopsies were obtained. Microscopic examination of the colonic mucosa revealed inclusion bodies within the mucosal cells. Immunohistochemical stains showed these inclusions were positive for CMV (Figure 3.1.2). There

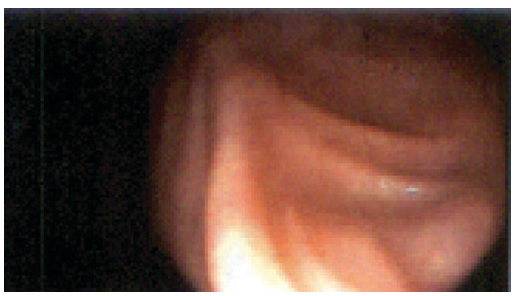


FIGURE 3.1.1: Normal colonoscopic appearance of colonic mucosa.

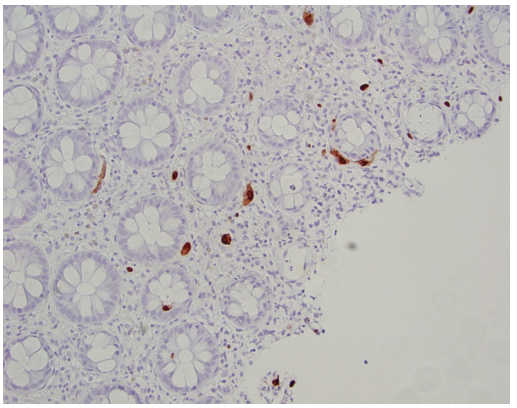


FIGURE 3.1.2: CMV inclusions by positive immunochemical stain of colon biopsy.

was crypt dropout and apoptosis in association with CMV-infected cells. No apoptosis was seen in areas not associated with CMV-infected cells.

The biopsy confirmed the diagnosis of CMV colitis. Although GVHD can also cause crypt dropout and apoptosis, the fact that these findings were only seen in association with infected cells favors the diagnosis of CMV colitis.

TREATMENT AND FOLLOW-UP

Therapy was started with intravenous ganciclovir. After several days of therapy, her diarrhea began to improve and her fever and abdominal cramping resolved. She was continued on intravenous ganciclovir for three weeks, and she had no recurrence of symptoms after cessation of therapy.

Final Diagnosis: Cytomegalovirus colitis

DISCUSSION

Cytomegalovirus is a DNA virus in the herpesvirus family. Infections with this virus are common in the general population with latent infection rates of approximately 40%–60% in industrialized nations. After primary infection, the virus remains in a latent state and can be reactivated by immune compromise. Infections in the HSCT patient can be caused by either endogenous reactivation from a latent virus or in a seronegative patient, newly acquired from transfusion of blood products or from an organ graft from a seropositive donor. The CMV status of the recipient is the primary risk factor for the development of CMV infection in the allotransplant population. Prior to the use of CMV seronegative blood product support, the incidence of CMV infection was similar between seronegative and seropositive patients [1]. With the use of seronegative blood products, the incidence of CMV infection in seronegative recipients dropped to 10%–15% [2]. Most serious CMV infections in HSCT patients manifest as interstitial pneumonia.

Cytomegalovirus enterocolitis is an increasingly important problem in allogeneic stem cell transplant recipients. The overall incidence of CMV enteritis in this population has been constant at 2% [3]. However, for transplant patients who develop significant gastrointestinal complaints, CMV enteritis is the second most common cause comprising 11% of cases [4]. The median time of onset is 91 days and is associated with a two-year overall survival rate of 35%. Approximately two thirds of cases are preceded by viremia, a median of twenty-five days prior to the development of enteritis. Thus, testing of blood for CMV viremia is an important diagnostic test in patients with diarrhea, but negative blood CMV PCR does not exclude the diagnosis. Because of the nonspecific nature of its symptoms, diagnosis usually requires biopsy.

The optimal method of treatment of CMV enteritis is unknown. Ganciclovir is the preferred treatment. The addition of intravenous immunoglobulin (as is done in the treatment of CMV pneumonitis) has not been found to be beneficial in the treatment of CMV enteritis [5], despite some antiviral activity [5]. Foscarnet is an additional option for treatment, particularly in patients who are cytopenic or who have resistance to ganciclovir.

REFERENCES

1. Wingard JR, Piantadosi S, Burns WH, et al. Cytomegalovirus infections in bone marrow transplant recipients given intensive cytoreductive therapy. Rev Infect Dis. 1990;7:S793.
2. Winston DJ, Ho WG, Champlin RE. Cytomegalovirus infections after allogeneic bone marrow transplantation. Rev Infect Dis. 1990;7:S776.
3. Van Burik JA, Lawatsch EJ, DeFor TE, Weisdorf, DJ. Cytomegalovirus enteritis among hematopoietic stem cell transplant recipients. Biol Blood Marrow Transplant. 2001;7:674.
4. Schulenburg A, Turetschek K, Wrba F, et al. Early and late gastrointestinal complications after myeloablative and nonmyeloablative allogeneic stem cell transplantation. Ann Hematol. 2004;83:101.
5. Reed EC, Wolford JL, Kopecky KJ, et al. Ganciclovir for the treatment of cytomegalovirus gastroenteritis in bone marrow transplant patients. A randomized, placebo-controlled trial. Ann Intern Med. 1990;112:505.

3.2

An Unexpected Trouble

MAXIM NORKIN, MD

CASE PRESENTATION

A solitary lung nodule was found in a 65-year-old man with acute myeloid leukemia (AML) during evaluation for allogeneic hematopoietic stem cell transplantation (HSCT).

History of Present Illness

The patient developed dyspnea on exertion and rapidly progressing fatigue three months ago. A complete blood count showed pancytopenia with white blood cell count (WBC) 1800 cells/mm^3, hemoglobin 8.4 g/dL, platelet count 17 000/mm^3, and absolute neutrophil count (ANC) 700 cells/mm^3. A subsequent bone marrow evaluation revealed extensive marrow involvement by AML with complex karyotype abnormalities. The patient received induction chemotherapy with idarubicin and cytarabine. Antimicrobial prophylaxis with fluconazole, levofloxacin, and valacyclovir was given, and his ANC remained <500 cells/mm^3. A postinduction hospital course was complicated by neutropenic fever due to vancomycin-resistant enterococcal bacteremia, which was successfully treated with linezolid and vascular access device. A repeat bone marrow evaluation showed no detectable immunophenotypic or morphologic evidence of AML. Because of the adverse prognosis of the cytogenetic profile, HSCT was recommended in first hematologic remission. Donor search was initiated, and one cycle consolidation therapy with high-dose cytarabine was given to maintain his remission status. He tolerated consolidation therapy well, received daily injections of granulocyte-colony stimulating factor and antimicrobial prophylaxis with fluconazole, levofloxacin and valacyclovir while his ANC remained <500 cells/ mm^3. Pretransplant evaluation was initiated when a suitable human leukocyte antigen-matched unrelated donor was identified, and the patient presented to the clinic to discuss its results. He felt generally well; however, he reported mild nonproductive cough started five days previously but no dyspnea, hemoptysis, or chest wall pain. He also complained of mild subjective fevers during last two nights, but he reported no chills, sweats, abdominal pain, or bowel symptoms or urinary problems.

On physical examination, the temperature was 37.4°C, the blood pressure 127/67 mm mercury, the pulse 79 beats per minute, and the respiratory rate 15 breaths per minute. The oxygen saturation 94% while he was breathing an ambient air. The physical examination was entirely normal.

Laboratory data revealed normal serum levels of electrolytes, serum creatinine, and protein. His complete blood counts and liver function tests were also within normal levels. A routine chest radiograph, which was done as a part of the pretransplant evaluation, showed a new 3 cm round consolidation in the right lower lobe superior segment without cavitation, pleural effusion, or other focal infiltrates (Fig. 3.2.1). Chest radiograph from two weeks earlier had shown no abnormalities. A computed tomography (CT)

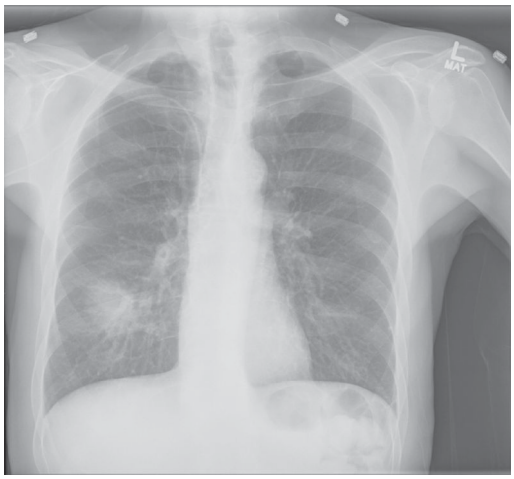


FIGURE 3.2.1: Chest radiograph before transplant with fever and cough.

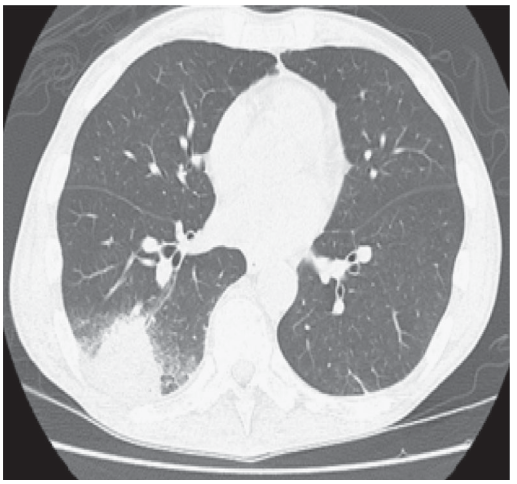


FIGURE 3.2.2: Chest CT.

of the chest without intravenous contrast was performed, which showed a focal wedge-shaped pleural-based opacity in the right lower lobe with surrounding ground-glass opacity (Fig. 3.2.2). There were multiple calcified granulomas and calcified mediastinal/hilar lymph nodes consistent with prior granulomatous disease. The patient had no prior CTs available for comparison; however, the rapid development of right lower lobe abnormality on chest x-ray was consistent with an acute process.

The patient was admitted to the hospital and empiric therapy with cefepime was initiated. On the third hospital day, the patient developed persistent fever, worsening dyspnea on exertion, and blood tinged sputum. Nasal swabs showed no evidence of respiratory viruses. Blood cultures remained negative and urinalysis was normal. His complete blood counts continued to be within normal limits.

DIFFERENTIAL DIAGNOSIS

Development of a pulmonary nodule in an immunocompromised patient can occur due to noninfectious and infectious causes. Infectious causes include chronic infectious granuloma; bacterial infection by either Gram-positive and Gram-negative organisms; and acute invasive fungal infections (IFIs) due to *Aspergillus*, the agents of *Mucormycosis*, or other molds. Noninfectious causes include (1) AML recurrence with development of leukemic infiltrates, (2) secondary malignancy particularly primary lung cancer or lymphoma, and (3) lung infarction due to thromboembolism.

Case Continued

Serum galactomannan (GM) assay was low-level positive with an index value of 0.54 (>0.5 is considered positive). A fiber optic bronchoscopy was performed and showed the presence of old blood in the posterior basal segment of the right lower lobe without any obstruction of the airway. Bronchoalveolar lavage (BAL) fluid was sent for cell count, bacterial culture, viral smears and culture, fungal and acid-fast bacilli (AFB) analysis, and galactomannan assay. Gram stain showed few polymorphonuclear cells and no organisms. Fungus stain was negative for yeasts and other fungal elements. No AFB were seen on both direct and concentrated smears. Pneumocystis was not identified on silver stain. No cytologic changes consistent with viral infection were identified. Lactophenol cotton blue staining revealed the presence of fungal organisms morphologically consistent with *Aspergillus* spp (Fig. 3.2.3). Galactomannan assay from BAL fluid returned with a positive index value of 8.6. Therapy was started with intravenous voriconazole and fever quickly subsided. Transplantation was delayed. Therapy was transitioned to oral voriconazole, and he was discharged in stable condition. Computed tomography scan after five weeks of treatment with voriconazole showed significant interval improvement in the right lower lobe pneumonia.

DISCUSSION

Rapid onset of a solitary lung nodule in an immunocompromised patient along with the presence of positive mycologic tests are diagnostic of IFI, particularly invasive aspergillosis (IA). Leukemic infiltration rarely causes nodular pulmonary

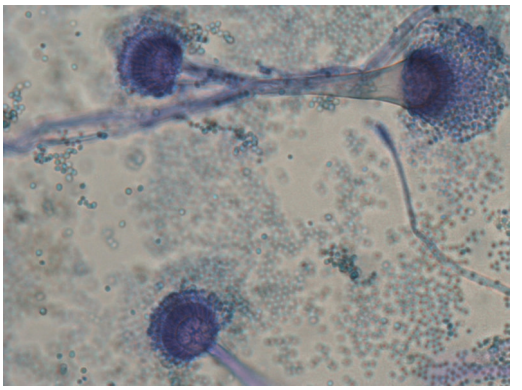


FIGURE 3.2.3: Lactophenol cotton blue staining of BAL sample revealing the presence of fungal organisms morphologically consistent with *Aspergillus* spp.

abnormalities. There were no laboratory or clinical signs of relapsed leukemia, which makes leukemic lung infiltrates in this patient highly unlikely. Although malignancy can be incidentally identified on routine imaging of the chest during pretransplant evaluation, in this patient the clinicoradiological characteristics and quick progression suggested infectious rather than a neoplastic process. Most frequently, nodular infiltrates in immunocompromised patients are caused by bacterial and/or fungal infections. Although *Aspergillus* (mostly pulmonary) and *Candida* (mostly bloodstream) are the most common fungal pathogens in patients with acute leukemia, endemic mycoses such as coccidioidomycosis, histoplasmosis, and blastomycosis are relatively common in certain high-risk geographic locations. Computed tomography of the chest has higher sensitivity over plain radiograph for detection of IFI. Plain radiographs lead to false-negative results in 10% of patients with IA, whereas chest CT is falsely negative in only 3% of such patients [1]. Sensitivity and negative predictive value of high-resolution CT scans are both >85%, and CT scan gives an average time gain of five days over plain radiograph in diagnosis of IFI [2, 3]. Blood cultures are rarely ever positive in disseminated aspergillosis [4], and in patients with pulmonary involvement, *Aspergillus* spp can occasionally be isolated from sputum; however, BAL increases the diagnostic yield to 45%–62% [5], particularly if the BAL is tested for galactomannan. The serum GM test was low-level positive in this case; however, the GM assay from BAL was strongly positive. In a meta-analysis, the serum GM assay in patients with hematologic malignancy had a pooled specificity of 70% and sensitivity of 92% [6]. Compared with serum GM assay, BAL GM assay has higher specificity and sensitivity. In patients with proven or probable IA, BAL GM has specificity of 79%–94% and sensitivity of 90%–94% [7, 8], which exceeds the sensitivity and specificity of culture and microscopy [8].

Delay in proceeding to HSCT during the treatment of the acute infection, as was done in this case, is advisable to avoid a high risk of reactivation and death from aspergillosis. Even after control of the infection, antifungal therapy should be continued after HSCT to reduce the risk for recurrence [9].

REFERENCES

1. Chamilos G, Marom EM, Lewis RE, et al. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis. 2005;41:60
2. Barloon TJ, Galvin JR, Mori M, et al. High-resolution ultrafast chest CT in the clinical management of febrile bone marrow transplant patients with normal or nonspecific chest roentgenograms. Chest 1991;99:928
3. Heussel CP, Kauczor HU, Heussel GE, et al. Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high-resolution computed tomography. J Clin Oncol. 1999;17:796
4. Reimer LG, Wilson ML, Weinstein MP. Update on detection of bacteremia and fungemia. Clin Microbiol Rev. 1997;10:444
5. Paterson DL, Singh N. Invasive aspergillosis in transplant recipients. Medicine (Baltimore) 1999;78:123
6. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis. 2006;42:1417
7. Guo YL, Chen YQ, Wang K, et al. Accuracy of BAL galactomannan in diagnosing invasive aspergillosis: a bivariate metaanalysis and systematic review. Chest 2010;138:817
8. Maertens J, Maertens V, Theunissen K, et al. Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. Clin Infect Dis. 2009;49:1688
9. Cordonnier C, Rovira M, Maertens J, et al. Voriconazole as secondary antifungal prophylaxis in stem cell transplant recipients. Haematologica 2011;96:e9.

3.3

A Swollen Eye

JOHN R. WINGARD, MD

CASE PRESENTATION

A 63-year-old man underwent allogeneic hematopoietic stem cell transplantation (HSCT) for myelodysplastic syndrome (refractory anemia with excess blasts) from an 8/8 human leukocyte antigen-matched sibling donor after busulfan plus cyclophosphamide conditioning. Postgraft immunosuppression consisted of tacrolimus and methotrexate. On the fourth day of neutropenia, fever occurred and he was placed on cefepime. He defervesced and remained afebrile. Fourteen days after transplant, he complained of pain and swelling of his left eye. He denied trauma. On exam, his temperature was 38.4°C and there was erythema and puffiness of the left lower orbit. The conjunctiva of the left eye was injected. On palpation, the area of swelling and over the maxillary sinus was tender. The nares and oral cavity are normal. You are consulted.

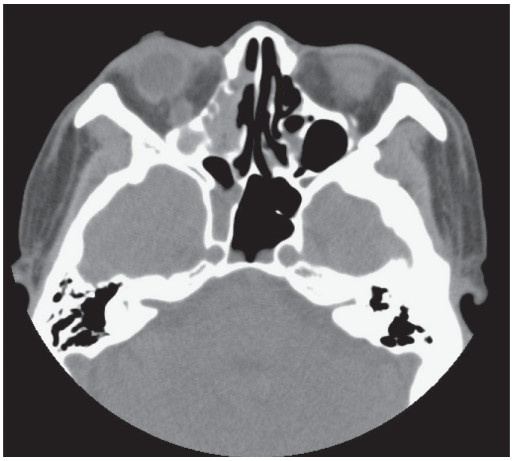


FIGURE 3.3.1: Sinus CT scan demonstrating maxillary fluid, soft tissue swelling into the orbit, and possible bony destruction.

DIFFERENTIAL DIAGNOSIS

The differential for orbital swelling in the HSCT patient is cellulitis from bacterial or mold infection. An allergic reaction or viral conjunctivitis could also be considered.

TREATMENT AND FOLLOW-UP

Serum galactomannan assays have been monitored and are negative. You recommend a computed tomography (CT) scan and consult an otolaryngologist, Nose, and Throat Specialist for further evaluation. While the diagnostic assessment proceeds, you add a lipid formulation of amphotericin B to cover suspected aspergillosis and mycormycosis and add vancomycin for coverage against Gram-positive bacteria. The sinus CT scan demonstrated maxillary fluid, soft tissue swelling into the orbit, and possible bony destruction (Figure 3.3.1).

Nasal endoscopy demonstrated necrotic tissue, which was debrided. Examination of the resected tissue demonstrated branching filamentous forms invading tissue with tissue necrosis. The forms were aseptate and wide, morphologically consistent with mucormycosis. Culture later confirmed *Rhizopus* species. Lipid form of amphotericin B was continued, and debridement was performed at three-day intervals over the next two weeks. The patient had neutrophil recovery on day twenty-two. Clinically, the patient had resolution of the orbital inflammation. Antifungal treatment continued daily for one month, it was then reduced to twice weekly until day 100.

Final Diagnosis: Rhizopus sinusitis and orbital cellulitis

DISCUSSION

Mucormycosis after HSCT is infrequent, but it can be deadly when it occurs [1]. Most commonly, it can present as pneumonia, sinusitis, a deep, penetrating oral ulceration, or as a disseminated infection. It can mimic aspergillosis in many ways, but

there are several clinical and radiologic differences that can be useful in distinguishing the two entities. Involvement of the sinuses, greater numbers of pulmonary nodules, the presence of a pleural effusion, and the prior use of voriconazole (which is not active against the agents of mucormycosis) are more commonly seen with mucormycosis compared with aspergillosis [2, 3]. Although discrete, dense pulmonary nodules (with or without a halo) are common, as with aspergillosis, less characteristic radiologic findings can also be seen, as with aspergillosis [4]. Although a reversed halo sign was once thought to strongly suggest mucormycosis, it is now recognized that tuberculosis and other etiologies can also be causes of the reversed halo sign [5, 6]. Bony destruction of the sinuses and orbit should strongly suggest a fungal etiology rather than bacterial infection. However, absence of bone destruction does not exclude the diagnosis. Even an unremarkable CT scan does not exclude the diagnosis, and nasal endoscopy should be performed. Aggressive antifungal and surgical therapy is necessary [7]. An amphotericin B formulation is the preferred antifungal agent in any patient with sinusitis while diagnostic assessment proceeds, and treatment should be continued until or unless mucormycosis is excluded since death or disfigurement can result if appropriate therapy is delayed. The course of therapy must be prolonged until both infection is controlled and immunity has been restored.

REFERENCES

1. Park BJ, Pappas PG, Wannemuehler KA, et al. Invasive non-*Aspergillus* mold infections in transplant recipients, United States, 2001–2006. Emerg Infect Dis. 2011;17:1855.
2. Chamilos G, Marom EM, Lewis RE, et al. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis. 2005;41:60.
3. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis. 2005;191:1350.
4. Nucci M, Noue´r SA, Grazziutti M, et al. Probable invasive aspergillosis without prespecified radiologic findings: proposal for inclusion of a new category of aspergillosis and implications for studying novel therapies. Clin Infect Dis. 2010;51:1273.
5. Georgiadou SP, Sipsas NV, Marom EM, Kontoyiannis DP. The diagnostic value of halo and reversed halo signs for invasive mold infections in compromised hosts. Clin Infect Dis. 2011; 52:1144.
6. Marchiori E, Zanetti G, Irion KL, et al. Reversed halo sign in active pulmonary tuberculosis: criteria for differentiation from cryptogenic organizing pneumonia. AJR Am J Roentgenol. 2011;197:1324
7. Kontoyiannis DP, Lewis RE. How I treat mucormycosis. Blood 2011;118:1216.

3.4

Breathless in the Transplant Unit

JOHN R. WINGARD, MD

CASE PRESENTATION

A 48-year-old cytomegalovirus (CMV) seropositive man with acute myelogenous leukemia presents 60 days after allogeneic hematopoietic stem cell transplantation (HSCT) from a 7/8 human leukocyte antigen-matched unrelated donor after cyclophosphamide/total body irradiation conditioning. Postgraft immunosuppression consisted of tacrolimus and methotrexate. He engrafted and was discharged. He developed a cutaneous rash over 60% of his body surface area without diarrhea or liver function abnormalities on day forty-six. A skin biopsy revealed graft-versus-host disease (GVHD) and therapy was started with prednisone. The rash improved over the next week and the prednisone dose was reduced. On day sixty, he developed a nonproductive cough and low grade fever (temperature 38.0°C). He denied sinus congestion, sore throat, or myalgias. Chest exam was unremarkable. There were no signs of congestive heart failure. Chest radiograph did not reveal abnormalities. The O_2 saturation was 94%. Weekly CMV polymerase chain reaction (PCR) assays had been negative. A nasopharyngeal swab was sent for respiratory viruses by PCR. The next day, the patient described dyspnea climbing stairs. The O_2 saturation was 88%. A chest computed tomography scan was performed and demonstrated diffuse infiltrates bilaterally (Figure 3.4.1). The patient was admitted and you are consulted.

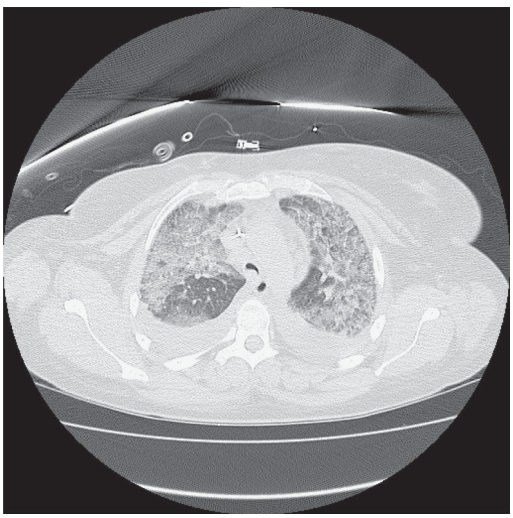


FIGURE 3.4.1: CT scan demonstrating diffuse bilateral infiltrates.

DIFFERENTIAL DIAGNOSIS

The differential for diffuse pulmonary infiltrates in the early period (first three months) after engraftment for allogeneic transplant includes both infectious and noninfectious etiologies. Pulmonary toxicity from intensive conditioning regimens occurs most commonly in this interval. Infections that commonly cause diffuse pulmonary infiltrates include respiratory viruses, CMV, *Pneumocystis jirovecii*, and less commonly *Mycoplasma, Legionella*, and *Strongyloides*.

TREATMENT AND FOLLOW-UP

The patient was presumptively treated with ganciclovir for CMV pneumonia/and trimethoprim-sulfamethoxazole for *Pneumocystis pneumonia* while further diagnostic assessment proceeded. Bronchoscopy with bronchoalveolar lavage (BAL) was performed. The plasma quantitative PCR for CMV was positive with 2800 copies/mL. The BAL was negative for *Pneumocystis*. Nasopharyngeal and BAL samples for respiratory viruses were negative. Bronchoalveolar lavage was positive for CMV. Therapy with intravenous immunoglobulin was added. The prednisone taper was accelerated. The patient's respiratory status improved, and the patient completed her antiviral course of therapy and was discharged.

Final Diagnosis: Cytomegalovirus pneumonia

DISCUSSION

Historically, CMV has represented the most common life-threatening infection after allogeneic HSCT, with up to one third of seropositive patients dying from CMV infection [1]. The most common clinical manifestation is pneumonia, with bilateral diffuse infiltrates being characteristic [2]. The median time of onset historically was two months after transplant. Without treatment, more than 80% of cases resulted in respiratory failure and death. Cytomegalovirus seropositivity of the HSCT recipient and the occurrence of GVHD have been the most common risk factors [3]. Cytomegalovirus viremia commonly was noted to occur one to two weeks prior to onset of pneumonia.

The development of active antivirals (ganciclovir, foscarnet, and cidofovir), sensitive and specific blood and BAL diagnostics (shell vial cultures, PCRs, and immunohistochemistry stains), and the testing of both prophylaxis and preemptive therapy triggered by the detection of viremia have dramatically changed the landscape of CMV infection and disease [4]. Today, CMV-seropositive patients are routinely monitored for detection of CMV in plasma samples by PCR [5]. If positive, therapy is instituted with ganciclovir (or foscarnet if the patient is leukopenic). Treatment is continued for two weeks and stopped if negative, or treatment is continued longer if needed until it is negative. After cessation of therapy, monitoring is continued because up to one third of patients will have a recurrence that requires retreatment. This preemptive approach is highly effective, but failures occasionally occur, since some pneumonia cases occur at the same time as viremia, or rarely, in the absence of viremia. An alternative, less commonly used approach is prophylaxis. Since ganciclovir is myelotoxic and CMV disease is rare before engraftment, prophylaxis is generally started after neutrophil engraftment and sometimes is also given before transplant. Some centers use prophylaxis in high-risk patients (mismatched or cord blood transplants or use of T cell depletion, alemtuzumab, or antithymocyte globulin) while relying on monitoring and preemptive therapy in lower-risk patients. Better-tolerated brincidofovir and letermovir are undergoing clinical trials for the prevention of CMV reactivation in transplant recipients. With the advent of routine prophylaxis and, to a lesser extent, preemptive therapy, late-onset CMV disease (beyond three months posttransplant) has increased [6].

Bronchoalveolar lavage testing for CMV has a high sensitivity and specificity, each exceeding 90%. Transbronchial biopsy for examination of tissue does not materially add to the yield and increases the risk of bleeding or pneumothorax and is not advised. Occasionally, co-infection by Gram-negative bacteria, staphylococci, or *Aspergillus* can occur, and testing for these pathogens should be performed on BAL samples.

Treatment consists of ganciclovir or, alternatively, foscarnet [7]. Intravenous immunoglobulin is added as well based on nonrandomized studies, which suggest an additive benefit. Treatment should be prompt and should be initiated presumptively in patients with suspected CMV pneumonia to optimize treatment outcomes. Once the diagnostic assessment is completed, if an alternative diagnosis is made, then the anti-CMV therapy can be withdrawn.

REFERENCES

1. Ljungman P. Beta-herpes virus challenges in the transplant recipient. J Infect Dis. 2002;186:S99.
2. Wingard JR, Hsu J, Hiemenz JW. Hematopoietic stem cell transplantation: an overview of infection risks and epidemiology. Infect Dis Clin North Am. 2010;24:25.
3. Wingard JR, Piantadosi S, Burns WH, et al. Cytomegalovirus infections in bone marrow transplant recipients given intensive cytoreductive therapy. Rev Infect Dis. 1990;7:S793.
4. Boeckh M, Nichols G, Papanicolaou G, et al. Cytomegalovirus in hematopoietic stem cell transplant recipients: current status, known challenges, and future strategies. Biol Blood Marrow Transplant. 2003;9:543.
5. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143.
6. Boeckh M, Leisenring W, Riddell SR, et al. Late cytomegalovirus disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and T-cell immunity. Blood 2003;101:407.
7. Wingard JR, Leather HL. Viral infections in patients with hematological malignancies. Chapt. 51. In: Wiernik PH, Goldman JM, Dutcher JP, Kyle RA, eds. *Neoplastic Diseases of the Blood*. 4th edition. Cambridge: Cambridge University Press; 2003; pp 968–1005.

3.5

Learning From Our Failures: Stubborn Aspergillosis That Does Not Get Better

JOHN R. WINGARD, MD

CASE PRESENTATION

A 52-year-old woman underwent allogeneic hematopoietic stem cell transplantation (HSCT) for acute lymphoblastic leukemia in first complete remission from an 8/8 human leukocyte antigen-matched unrelated donor after busulfan plus cyclophosphamide conditioning. Posttransplant immunosuppression consisted of tacrolimus and methotrexate. He engrafted and was discharged. He developed graft-versus-host disease (GVHD) of the skin and liver on day thirty-three and was treated with prednisone. The GVHD improved over the next week and the prednisone dose was reduced. On day forty-two, he developed a nonproductive cough and low-grade fever (temperature 38.1°C). Chest exam was unremarkable. Chest radiograph did not reveal abnormalities. The O_2 saturation was 94%. A nasopharyngeal swab was sent for respiratory viruses by polymerase chain reaction (PCR). Four days later, the patient described pleuritic pain. A chest computed tomography (CT) scan was performed and demonstrated two dense nodules, one with a halo (Figure 3.5.1). Serum galactomannan was sent. The patient was admitted and you are consulted.

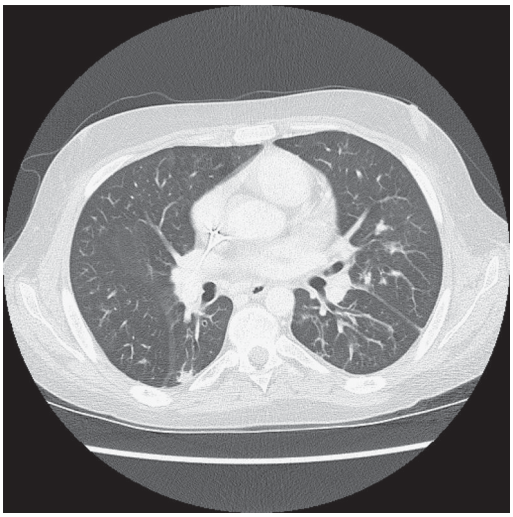


FIGURE 3.5.1: Chest CT scan demonstratying 2 dense nodules, one with a halo.

DIFFERENTIAL DIAGNOSIS

The differential for nodular pulmonary infiltrates in the early period (first three months) after engraftment for allogeneic HSCT includes both infectious and noninfectious etiologies [1]. Infections predominate with bacterial and mold fungal pathogens being the most common. Less likely, posttransplant lymphoma, associated with Epstein-Barr virus infection, is another consideration.

TREATMENT AND FOLLOW-UP

The patient was presumptively treated with antibiotics for bacterial pneumonia (vancomycin plus cefepime) and voriconazole for *Aspergillus*, while further diagnostic assessment proceeded. The dose of steroids was tapered. Bronchoscopy with bronchoalveolar lavage (BAL) was performed, and both serum and BAL galactomannan were positive, confirming the suspicion of pulmonary aspergillosis. Voriconazole was continued but antibiotics were discontinued. The patient's respiratory status did not improve, fever persisted, and one week later, the CT scan showed a worsening infiltrate (Figure 3.5.2). You are again consulted.

DIFFERENTIAL DIAGNOSIS

The differential for worsening aspergillosis should consider immune reconstitution syndrome,

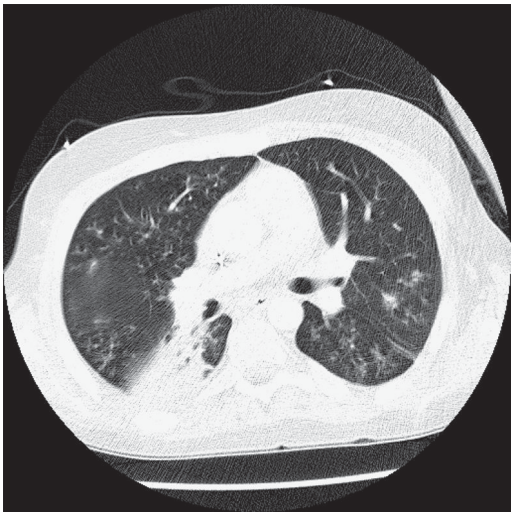


FIGURE 3.5.2: Follow-up CT scan one week later.

resistance, incorrect diagnosis, or superinfection by viral, bacterial, or another mold pathogen. False-positive galactomannan test results have been noted in the past, particularly in patients receiving piperacillin or amoxicillin and could mislead one to believe that there is aspergillosis, but this seems less likely in this case because the implicated antibiotics were not used in this patient and recent reports suggest that the false-positive test results are no longer being seen with these antibiotics.

Continued Treatment and Follow-Up

Repeated serum galactomannan tests indicated a reduction in the galactomannan index values. A repeat bronchoscopy was performed. Bronchoalveolar lavage galactomannan index was also lower. Cultures of BAL grew *Pseudomonas aeruginosa*. Cefepime was reintroduced and voriconazole was continued. Two weeks later, the patient was much improved.

Final Diagnosis: *Aspergillus* pneumonia with bacterial superinfection

DISCUSSION

Assessing response to antifungal therapy can be very challenging [2, 3]. Radiologically, infiltrates typically worsen during the first week of therapy, even in patients who eventually respond [4], and cannot be reliable gauges of response during the first or second week of therapy. Worsening clinical status may be related to neutrophil recovery or improved cellular immunity [5], rather than failure of antifungal response. When positive, the serum galactomannan can be followed during therapy; a falling value during therapy suggests a good antifungal response and has been shown to predict antifungal outcome [6]. Thus, monitoring the galactomannan can be particularly helpful in deciding whether a patient, such as this case, is truly failing from inadequate antifungal therapy or other reasons should be pursued. Superinfections are frequent in patients with documented invasive aspergillosis [7], and clinicians must be on the alert to detect these. In one series [7], nearly half of patients with documented aspergillosis had co-infections. In some cases, the other infection was present concomitantly with the aspergillosis diagnosis, underscoring the importance of bronchoscopic evaluation at the outset, even if the serum galactomannan is positive [8, 9]. Bacterial co-infections are most frequent, as with our patient, with three fourths due to Gram-negative rods. Viral copathogens are next in frequency with CMV and respiratory viruses being the most common. A small percentage may become co-infected by other fungi or mycobacteria. Azole resistance in *Aspergillus* isolates remains infrequent to date, but there are troubling reports in Europe of growing azole resistance in clinical isolates, with possible links to agricultural use of antifungals [10]. Inadequate therapy can be due to inadequate blood levels of the antifungal. This is mainly a problem with oral azole therapy, where multiple studies have shown variable blood levels of itraconazole, voriconazole, and posaconazole. Thus, initial therapy should be provided by intravenous administration, and, if switched to oral therapy after clinical response, therapeutic drug level monitoring should be considered, especially if response is suboptimal.

REFERENCES

1. Wingard JR, Hiemenz JH, Jantz M. How I manage pulmonary nodular lesions and nodular infiltrates in patients with hematologic malignancies or undergoing hematopoietic cell transplantation. Blood 2012;120:1791.
2. Nucci M, Perfect JR. When primary antifungal therapy fails. Clin Infect Dis. 2008;46:1426.
3. Wingard JR. Learning from our failures: the antifungal treatment conundrum. Clin Infect Dis. 2008;46:1434.
4. Caillot D, Couaillier JF, Bernard A, et al. Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. J Clin Oncol. 2001;19:253.

5. Miceli MH, Maertens J, Buve K, et al. Immune reconstitution inflammatory syndrome in cancer patients with pulmonary aspergillosis recovering from neutropenia: proof of principle, description, and clinical and research implications. Cancer 2007;110:112.
6. Woods G, Miceli MH, Grazziutti ML, et al. Serum *Aspergillus* galactomannan antigen values strongly correlate with outcome of invasive aspergillosis: a study of 56 patients with hematologic cancer. Cancer 2007;110:830.
7. Georgiadou SP, Kontoyiannis DP. Concurrent lung infections in patients with hematological malignancies and invasive pulmonary aspergillosis: how firm is the *Aspergillus* diagnosis? J Infect. 2012;65:262
8. Shannon VR, Andersson BS, Lei X, et al. Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. Bone Marrow Transplant. 2010;45:647.
9. Wingard JR. Have novel serum markers supplanted tissue diagnosis for invasive fungal infections in acute leukemia and transplantation? Best Pract Res Clin Haematol. 2012;25:487.
10. Verweij PE, Snelders E, Kema GH, et al. Azole resistance in *Aspergillus fumigatus*: a side-effect of environmental fungicide use? Lancet Infect Dis. 2009;9:789.

3.6

Mr. Sniffles Strikes Again

GAURAV TRIKHA, MD

CASE PRESENTATION

A 67-year-old man with a history of acute myelogenous leukemia presented during the Fall season for pretransplant evaluation. His last cycle of chemotherapy (re-induction chemotherapy for relapse) was six weeks earlier. He was doing well until three days prior to presentation when he developed fever, sinus fullness, new onset sore throat, and a nonproductive cough. He was recently visited by his grandsons, aged two and three years, who attend day care centers but were doing well. Positive findings on exam were temperature 38.2°C, maxillary sinus tenderness, pharyngeal erythema, and postnasal drainage. Initial laboratory investigations disclosed leukocyte count of 6300/cu mm, with normal neutrophil count (2600/cu mm) and lymphocyte count 1762/cu mm and thrombocytopenia (130 000/cu mm); his serum creatinine was 1.3 mg/dL. Blood cultures and a nasopharyngeal swab for direct viral antigen testing and viral respiratory polymerase chain reaction (PCR) panel were performed. Chest radiograph showed no abnormalities. He was hospitalized and therapy was started with empiric levofloxacin. Transplant evaluation was delayed.

DIFFERENTIAL DIAGNOSIS

The differential diagnostic possibilities considered were seasonal allergic rhinitis and sinusitis, viral upper respiratory infection (URI) including influenza, viral respiratory infection with secondary bacterial sinusitis, bacterial pharyngitis, bacterial or fungal sinusitis.

CLINICAL COURSE

Nasopharyngeal swab was reported positive for respiratory syncytial virus (RSV) by PCR.

TREATMENT OUTCOME

Patient defervesced in thirty-six hours, antibiotic therapy was discontinued, and the patient was discharged from the hospital but continued to have sinus fullness and sore throat for five to six days. The clinical symptoms resolved, and the patient's condition was re-evaluated in the clinic two weeks later; there was complete resolution of his symptoms and a repeat chest x-ray showed no parenchymal process. Transplant evaluation was resumed.

Final Diagnosis: Respiratory syncytial virus: upper respiratory tract infection

DISCUSSION

Upper respiratory symptoms after a potential exposure (grandchildren attending day care center) is suggestive of a viral URI. During winter months in temperate climate, influenza, RSV, parainfluenza, and rhinovirus are the most common viruses presenting with the above symptomatology. Fever and absence of atopic medical history make seasonal allergy unlikely. In the absence of pharyngeal exudate, cervical lymphadenopathy and clinical improvement without antibiotics, bacterial pharyngitis is unlikely. Patients with leukemia are at risk of invasive fungal infection, but our patient was nonneutropenic and in remission, so fungal infection is less likely.

Respiratory syncytial virus is one of the most common respiratory viruses in cancer patients. In the United States, RSV infections occur in the fall, winter, and spring, with an attack rate up to 10% during winter [1, 2]. Respiratory syncytial virus infection may present as URIs, such as pharyngitis or laryngitis, or a potentially fatal lower respiratory tract infection, such as pneumonia. It is generally accepted that the first step in RSV replication is attachment of the viral

BOX 3.6.1 RISK FACTORS FOR PROGRESSION TO PNEUMONIA IN LEUKEMIA PATIENTS WITH RSV INFECTION

- High APACHE II score at the time of the first evaluation
- Persistent lymphocytopenia
- Corticosteroid use within one month of the onset of RSV infection
- Sex (Males > Females)

particle to the nasal epithelium, and then the infection progresses down into the lower respiratory tract and causes pneumonia, particularly in immunocompromised patients [3]. In one of the largest retrospective review of leukemia patients diagnosed with RSV respiratory infection, several risk factors associated with progression of URI to lower respiratory infection (LRI) and eventual increase in mortality were identified (Box 3.6.1) [4]. Neutropenia was not significantly associated with progression to pneumonia, whereas persistent lymphocytopenia seemed to be related to such an event, in accordance with previous studies in hematopoietic stem cell transplantation recipients [4, 5]. Because this case did not have any of the risk factors, anti-RSV treatment was not initiated.

Rapid diagnosis of RSV infection can be made by direct antigen testing on clinical specimens (i.e. direct immunofluorescence staining), shell vial culture technique, which provides results within 48 hours, with a sensitivity of 93% and a specificity of 97%, and by real-time PCR assay for detection of RSV RNA with a higher sensitivity and specificity [6-8]. At our institution's Bone Marrow Transplant Unit, any patient presenting with URI symptoms gets screened by direct viral antigen testing and, if necessary followed by viral respiratory PCR (Figure 3.6.1).

Prevention of RSV transmission in a hospital setting, especially where immunosuppressed patients are housed, is considered a basic standard of care in most hospitals. Strict infection control measures to prevent spread within a hospital ward include respiratory isolation of infected patients, hand washing before and after contact with patients, and educational efforts targeting healthcare workers and family members (Figure 3.6.2). For RSV infection, control practices required are standard and contact precautions. Patients can be roomed with other RSV patients as long as there are no other significant organisms present (i.e. methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, etc)

Management of RSV infection should target (1) viral replication, (2) virus-induced lung inflammation, (3) co-infections or superimposed infections, and (4) respiratory dysfunction.

Available therapies that have been used for treatment of RSV infections are limited to ribavirin, intravenous immunoglobulin, and palivizumab. The lack of well designed, randomized controlled trials leaves clinicians with little information, mostly retrospective and from single centers, as the only available clinical data.

The aerosolized form of ribavirin was approved by the US Food and Drug Administration in 1986 for treatment of RSV LRI in hospitalized high-risk infants and young children, and it is still the only drug approved for this indication.

The lack of controlled trials makes treatment decisions about RSV URI difficult. Regardless of the form or duration of therapy or the addition of an immunomodulator, the rate of progression to LRI and mortality rate appear to be lower in high-risk patients who received ribavirin than in patients who did not receive any form of RSV therapy [4, 9–12]. In

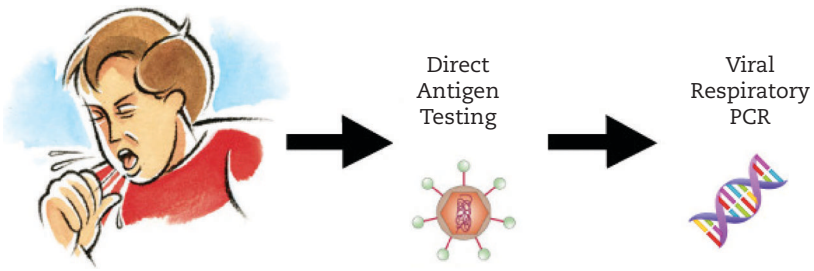


FIGURE 3.6.1: Sequential evaluation of patients suspected to have RSV infection.

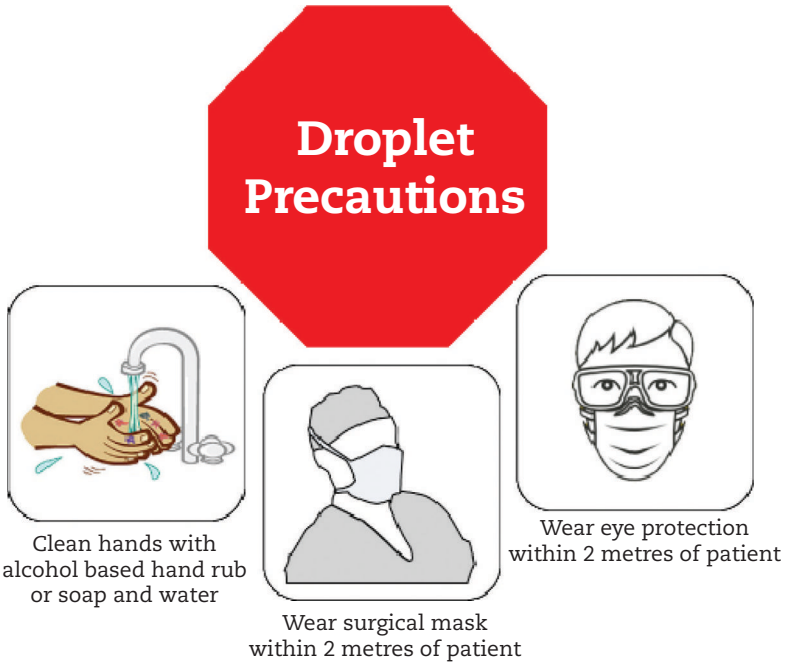


FIGURE 3.6.2: Infection control measures to minimize transmission.

a meta-analysis comparing various combination regimens [13], better outcomes were seen in patients treated with aerosol ribavirin and an immunomodulator than in those treated with ribavirin alone. Among patients whose infection progressed to LRI, those treated with aerosolized ribavirin and an immunomodulator had a lower mortality rate of 24% than those treated with aerosol ribavirin alone (50%) or with intravenous or oral ribavirin with or without an immunomodulator 54% [13].

REFERENCES

1. Nichols WG, Gooley T, Boeckh M. Community-acquired respiratory syncytial virus and parainfluenza virus infections after hematopoietic stem cell transplantation: the Fred Hutchinson Cancer Research Center experience. Biol Blood Marrow Transplant. 2001;7:11S.
2. Welliver RC. Pharmacotherapy of respiratory syncytial virus infection. Curr Opin Pharmacol. 2010;10:289.
3. Black CP. Systematic review of the biology and medical management of respiratory syncytial virus infection. Respir Care 2003;48:209.
4. Torres HA, Aguilera EA, Mattiuzzi GN, et al. Characteristics and outcome of respiratory syncytial virus infection in patients with leukemia. Haematologica 2007;92:1216.
5. Ljungman P, Ward KN, Crooks BN, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant. 2001;28:479.
6. Kuypers J, Campbell AP, Cent A, et al. Comparison of conventional and molecular detection of respiratory viruses in hematopoietic cell transplant recipients. Transpl Infect Dis. 2009;11:2.
7. Kuypers J, Wright N, Ferrenberg J, et al. Comparison of real-time PCR assays with fluorescent-antibody assays for diagnosis of respiratory virus infections in children. J Clin Microbiol. 2006;44:2382.
8. Ohm-Smith MJ, Nassos PS, Haller BL. Evaluation of the Binax NOW, BD Directigen, and BD Directigen EZ assays for detection of respiratory syncytial virus. J Clin Microbiol. 2004;42:2996.
9. Ebbert JO, Limper AH. Respiratory syncytial virus pneumonitis in immunosuppressed adults: clinical features and outcome. Respiration 2005;72:263.
10. Boeckh M, Englund J, Li Y, et al. Randomized controlled multicenter trial of aerosolized ribavirin for respiratory syncytial virus upper respiratory tract infection in hematopoietic cell transplant recipients: NIAID Collaborative Antiviral Study Group. Clin Infect Dis. 2007;44:245.

11. McColl MD, Corser RB, Bremner J, et al. Respiratory syncytial virus infection in adult BMT recipients: effective therapy with short duration nebulised ribavirin. Bone Marrow Transplant. 1998;21:423.
12. Bowden RA. Respiratory virus infections after marrow transplant: the Fred Hutchinson Cancer Research Center experience. Am J Med. 1997;102:27.
13. Shah JN, Chemaly RF. Management of RSV infections in adult recipients of hematopoietic stem cell transplantation. Blood 2011;117:2755.

3.7

Mucormycosis: An Uncommon but Deadly Foe

MAXIM NORKIN, MD

CASE PRESENTATION

A 52-year-old man developed acute onset right sided pleuritic chest pain on day +55 status postallogeneic hematopoietic stem cell transplant (HSCT) for relapsed acute myeloid leukemia (AML). The patient described the pain as sharp, worsening at inspiration, and radiating towards the epigastrium. He also reported low-grade fevers and mildly productive cough over the last four days.

The patient's oncologic history dates back five months when he was found to have severe anemia with a hemoglobin of 6.5 g/dL and an absolute neutrophil count (ANC) of 1300 cells/mm^3. Subsequent bone marrow evaluation was consistent with high-grade myelodysplastic syndrome, for which he was started on azacitidine. This treatment was complicated by severe neutropenia requiring administration of filgastrim and antimicrobial prophylaxis. After two cycles of azacitidine, the patient developed a rapidly increasing white blood cell count with abundant circulating blasts on peripheral blood smear. Repeat bone marrow evaluation confirmed transformation to AML. The patient underwent induction chemotherapy with idarubicin and cytarabine, which he tolerated well, but he had a slow ANC recovery. He received prophylaxis with levofloxacin, fluconazole, and acyclovir while ANC remained <500 cells/mm^3. The patient recovered his peripheral blood counts after five weeks and had no evidence of residual leukemia on the bone marrow evaluation. Then, he underwent HSCT from a related donor with myeloablative conditioning with cyclophosphamide and total body irradiation. The posttransplant period was complicated by febrile neutropenia, which was empirically treated with cefepime. On day +41 posttransplant, the patient developed histologically proven acute graft-versus-host-disease of the skin requiring administration of a high dose of systemic steroids. The skin rash rapidly responded to steroid therapy, and he was discharged on a slow tapering steroid schedule and prophylactic levofloxacin, fluconazole, and acyclovir.

Physical examination revealed the temperature 38.3°C, the blood pressure 145/87 mm mercury, the pulse 110 beats per minute, and the respiratory rate 18 breaths per minute. The oxygen saturation was 91% on ambient air. The physical examination was normal except for respiratory crackles over the right lower lobe. Laboratory data revealed normal serum levels of electrolytes, serum creatinine, and protein. His complete blood counts and liver function tests were also within normal levels.

Computed tomography (CT) scan of the chest demonstrated two nodular areas of airspace disease each surrounded by a halo of ground-glass opacity in the right lung (Fig. 3.7.1). The patient was started on empiric cefepime, vancomycin, and voriconazole. Blood cultures showed no growth. Serum galactomannan (GM) assay was negative with an index value of 0.4. Over next two days, the patient continued to be febrile and started complaining of frontal headache, nasal congestion, and pain. On day +59 posttransplant,

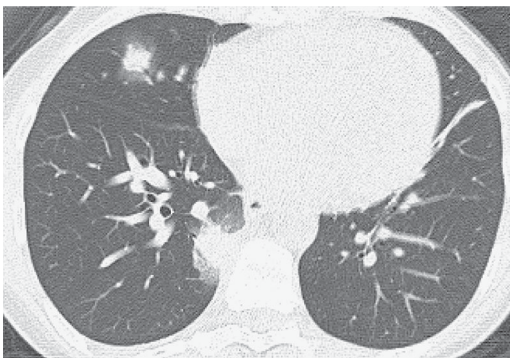


FIGURE 3.7.1: Chest CT demonstrating 2 nodular areas of airspace disease each with halo.

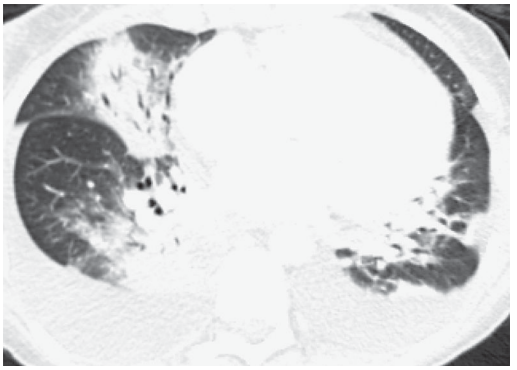


FIGURE 3.7.2: Followup CT scan 6 days later showing progression.

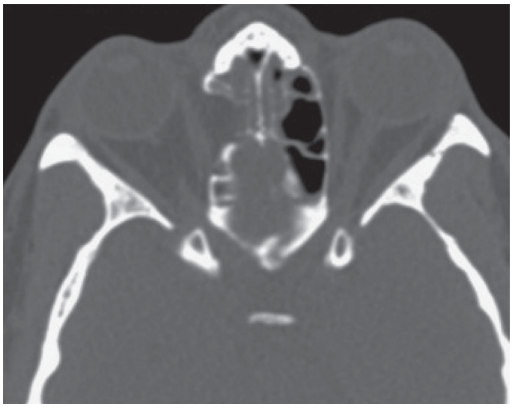


FIGURE 3.7.3: CT scan of the sinuses showing the presence of diffuse mucoperiosteal thickening throughout the paranasal sinuses with abnormal extension into the pterygoid palatine fossa through the sphenopalatine foramen on the right side more than the left.

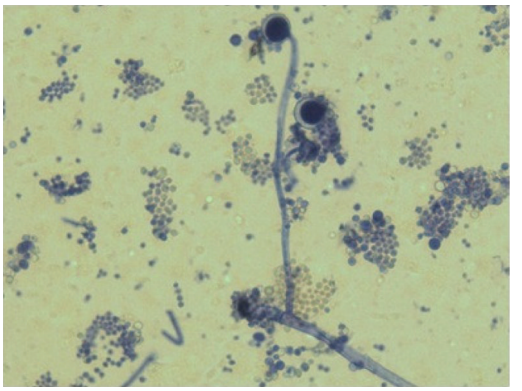


FIGURE 3.7.4: Pathologic sample demonstrating presence of fungal elements morphologically consistent with mucormycosis.

he developed severe respiratory distress, metabolic acidosis, and worsening hypoxemia requiring intubation. Repeat chest CT scan of the chest showed marked interval progression of lung disease compared to chest CT six days ago (Fig. 3.7.2). The patient underwent urgent bronchoscopy, which revealed the presence of an area of inflamed mucosa in the superior segment of the right lower lobe. Bronchoalveolar lavage (BAL) fluid was and sent for cell count, bacterial culture, viral studies and culture, fungal and acid-fast bacilli analysis, and GM assay. The patient continued to be febrile and deteriorated clinically with a development of septic shock despite broad antimicrobial coverage. Blood and BAL cultures continued to be negative. Serum and BAL were negative.

DIFFERENTIAL DIAGNOSIS

Development of air space consolidation, ground-glass and nodular infiltrates, and pleuritic pain in an immunocompromised patient can be caused by an infectious, inflammatory, or neoplastic process. Among infections, bacterial pathogens such as *Mycobacterium tuberculosis, Klebsiella* spp, *Staphylococcus* spp, *Nocardia* spp, and fungal pathogens such as *Aspergillus* spp and the agents of mucormycosis are most frequently associated with the development of pulmonary cavities in these patients.

Case Continued

On day +62, he developed sinus tenderness on physical examination. Computed tomography scan of the sinuses showed the presence of diffuse mucoperiosteal thickening throughout the paranasal sinuses with abnormal extension into the pterygoid palatine fossa through the sphenopalatine foramen on the right side more than the left. (Fig. 3.7.3) These findings were thought to be suspicious for invasive fungal sinus disease. Voriconazole was stopped, and therapy with amphotericin B lipid complex was started. The patient underwent a nasal endoscopy that showed multiple ulcerations and necrotic mucosa followed by debridement of the sinus cavities. The review of the pathology specimen showed the presence of fungal elements morphologically consistent with mucormycosis (Fig. 3.7.4). In spite of appropriate antibiotic therapy, the patient died.

DISCUSSION

In this case, clinical and laboratory findings do not support the diagnosis of recurrent leukemia, secondary malignancy or inflammatory processes

such as bronchiolitis obliterans organizing pneumonia, pulmonary infarction, granulomatous disease, or vasculitis. The presence of fever and rapidly progressive pulmonary infiltrates make an infectious process as the most probable cause. Progression of disease despite broad-spectrum antimicrobial coverage, the presence of nodular infiltrates with halo sign, and concomitant sinusitis are highly suspicious for invasive fungal infection. *Aspergillus* spp is the most frequent pathogen causing approximately 90% of mold pneumonias, followed by the agents of mucormycosis, which are identified in approximately 10% of mold cases [1]. Specific radiologic signs of fungal pneumonia include a "halo sign", when the central nodular area is surrounded by a ground-glass appearing hemorrhage, and a "crescent sign", which develops later as a consequence of lung tissue necrosis and cavitation. The presence of sinusitis and pleural effusion, multiple (>10) nodules, and a history of prior voriconazole exposure are more frequently associated with mucormycosis than aspergillosis [2, 3]. Microscopic examination and culture are the only methods allowing identification of mucormycosis because serologic tests such the galactomannan assay or the β-glucan test do not detect the agents of mucormycosis [4–6]. Blood cultures are almost never positive in disseminated mucormycosis [7]. Sputum cultures are positive in only one quarter of all cases of pulmonary mucormycosis, and BAL typically does not increase the diagnostic yield [5]. In tissue, wider, ribbon-like, aseptate or pauci-septate hyphae help to distinguish mucormycosis from *Aspergillus* spp. Voriconazole lacks activity against the agents of mucormycosis. As soon as mucormycosis is suspected, high doses (≥5 μg/kg per day) of liposomal amphotericin B [6] or amphotericin B lipid complex [8] should be empirically initiated while the definitive diagnosis is being pursued. Surgical debridement of necrotic tissue along with antifungal therapy is associated with improved survival compared with antifungal therapy alone. Posaconazole appears beneficial as salvage therapy or step-down therapy for mucormycosis [9, 10].

REFERENCES

1. Wingard JR, Hsu J, Hiemenz JW. Hematopoietic stem cell transplantation: an overview of infection risks and epidemiology. Hematol Oncol Clin North Am. 2011;25:101
2. Chamilos G, Marom EM, Lewis RE, et al. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis. 2005;41:60
3. Kontoyiannis DP, Lionakis MS, Lewis RE, et al. Zygomycosis in a tertiary-care cancer center in the era of Aspergillus-active antifungal therapy: a case-control observational study of 27 recent cases. J Infect Dis. 2005;191:1350
4. Kontoyiannis DP, Wessel VC, Bodey GP, et al. Zygomycosis in the 1990s in a tertiary-care cancer center. Clin Infect Dis. 2000;30:851
5. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1–>3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis. 2005;41:654
6. Pagano L, Offidani M, Fianchi L, et al. Mucormycosis in hematologic patients. Haematologica 2004;89:207
7. Reimer LG, Wilson ML, Weinstein MP. Update on detection of bacteremia and fungemia. Clin Microbiol Rev. 1997;10:444
8. Perfect JR. Treatment of non-*Aspergillus* moulds in immunocompromised patients, with amphotericin B lipid complex. Clin Infect Dis. 2005;6:S401
9. van Burik JA, Hare RS, Solomon HF, et al. Posaconazole is effective as salvage therapy in zygomycosis: a retrospective summary of 91 cases. Clin Infect Dis. 2006;42:e61
10. Greenberg RN, Mullane K, van Burik JA, et al. Posaconazole as salvage therapy for zygomycosis. Antimicrob Agents Chemother. 2006;50:126

3.8

Something's in the Air

GAURAV TRIKHA, MD

CASE PRESENTATION

A 68-year-old male with a history of a matched related donor allogeneic stem cell transplantation (performed in September 2010) for acute myelogenous leukemia presented in October 2012 with a history of malaise, headache, new onset sore throat, and nonproductive cough. The patient's posttransplant course had largely been uneventful with no overt infectious or graft-versus-host disease complications. On admission, vital signs showed blood pressure 180/98, mm mercury temperature 35.6°C, pulse 84 per minute, and respirations 14 per minute. Initial laboratory investigations disclosed leukocyte count 5300/cu mm, with normal neutrophil and lymphocyte counts and mild thrombocytopenia (127 000/cu mm); his serum creatinine was 1.2 mg/dL (baseline 0.8–1.0 mg/dL). Blood cultures and a nasopharyngeal (NP) swab for influenza were performed, and an admission chest radiograph was normal. The patient was admitted, and therapy was started with empiric intravenous levofloxacin and standard respiratory precautions were instituted. The following morning, his temperature rose to 38.5°C and he had persistent myalgia and lethargy; he denied any shortness of breath, and on room air, his oxygen saturation >95%.

DIFFERENTIAL DIAGNOSIS

Seasonal allergic rhinitis and sinusitis, viral upper respiratory infection (URI) including influenza, viral respiratory infection with secondary bacterial sinusitis, bacterial pharyngitis.

HOSPITAL COURSE

Nasopharyngeal swab was reported positive by polymerase chain reaction for influenza A (IFV A). Other tests were negative. Subsequently, therapy was started with oseltamivir 75 mg orally twice daily, and the patient was placed under droplet isolation precautions. On the third day of hospitalization, he complained of cough with yellow-colored phlegm. His other symptoms started to improve, and he was finally discharged on the sixth day of hospitalization. He completed a five-day course of oseltamivir and required no antibacterial drugs.

During his hospitalization, on the fourth day, three other patients in the same unit developed new onset fever with intense myalgias and subsequent sore throat and nonproductive cough. They were checked for influenza and their NP swabs returned positive for IFV A.

Final Diagnosis: Influenza A upper respiratory infection

DISCUSSION

Nosocomial transmission of community-acquired respiratory viruses (CRVs) is common, and widespread hospital outbreaks of CRVs have occurred with sometimes devastating sequelae. Hematopoietic cell transplantation (HCT) centers should maintain appropriate precautions and infection control measures for preventing the transmission of CRV among hospitalized HCT recipients and candidates undergoing conditioning therapy [1–5]. Hematopoietic cell transplantation recipients or candidates with URI or lower respiratory tract infection symptoms due to community respiratory viruses should be placed on contact plus droplet precautions until a specific pathogen has been identified. (Figure 3.8.1 and 3.8.2) Pathogen-specific CRV isolation precautions can be instituted after the organism has been identified. For influenza, droplet precautions should be used.

The influenza syndrome is similar in patients with cancer and HCT recipients, but high fever and myalgias may be less prominent. Two major complications that can occur are viral pneumonia and secondary bacterial pneumonia. The degree of risk for influenza complications are influenced by the depth of immunosuppression. Factors

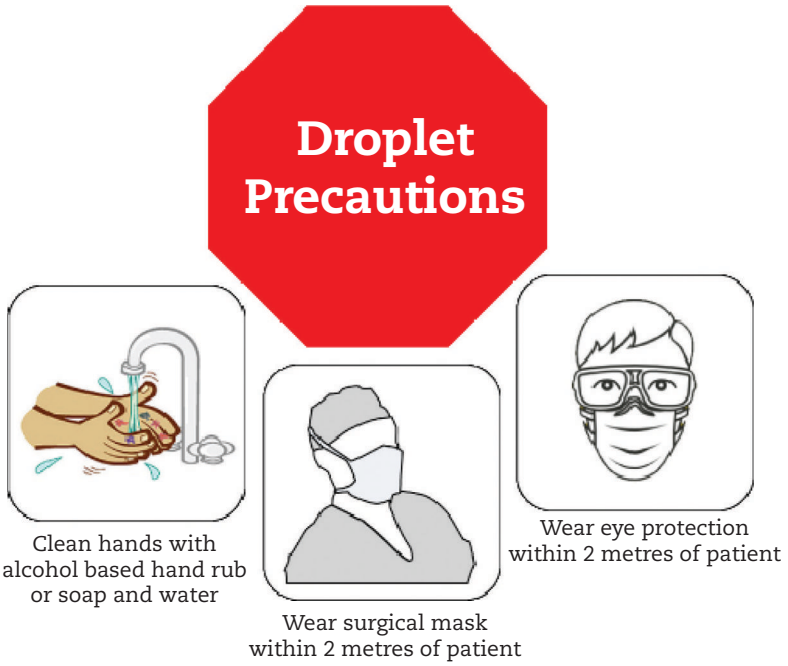


FIGURE 3.8.1: Precautions against Inflenza.

associated with a greater risk for progression to pneumonia are enumerated in Box 3.8.1.

Death has been noted in 15%–30% of patients with pneumonia. Even in survivors of influenza, residual sequela may include long-lasting pulmonary impairment [6].

In the setting of an outbreak, equal emphasis should be given to treatment and containment of influenza via transmission prevention and infection control practices.

Lifelong seasonal influenza vaccine is recommended for all HCT candidates and recipients. Inactivated influenza vaccine should be administered beginning at least six months after HCT and annually thereafter for the life of the patient [7]. A dose of inactivated influenza vaccine can be given as early as four months after HCT, but a second dose should be considered in this situation. Two doses are recommended routinely for the initial vaccination for all children receiving influenza vaccine for the first time.

Data demonstrating efficacy of inactivated (killed) influenza virus vaccines for HCT recipients are limited. The protective effect is lower in HCT patients in general, and one study reported 29% protective antibody levels to IFV A H1/N1 serotype in the recipients. It is widely accepted that transplant-to-vaccination interval has an important impact on vaccine immunogenicity [8]. A study in pediatric allogeneic HCT recipients showed higher response rates

*Continue annually thereafter for the life of the patient
†If administered as early as 4 months, a second dose should be considered after 6 months and thereafter annually

FIGURE 3.8.2: Timetable for Inflenza vaccine after transplant.

BOX 3.8.1 FACTORS ASSOCIATED WITH A GREATER RISK FOR PROGRESSION TO PNEUMONIA

Age >65 years
Severe neutropenia
Severe lymphopenia*

**Associated with a higher risk for death*

in patients >1 year post-HCT, but patients were found to have increasing antibody responses even at six months post-HCT. A correlation of CD4 counts and response to vaccination has been inconsistent [9]. One small study reported a correlation of naive-CD4 cells and antibody response [10].

REFERENCES

1. Chemaly RF, Ghosh S, Bodey GP, et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. Medicine (Baltimore) 2006;85:278.
2. Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep. 2004;53:1.
3. Lee I, Barton TD. Viral respiratory tract infections in transplant patients: epidemiology, recognition and management. Drugs 2007;67:1411.
4. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143.
5. Wingard JR. Influenza: preparedness for an inevitable "Emergency" for oncology and BMT units. J Natl Compr Canc Netw. 2008;6:215.
6. Nichols WG, Guthrie KA, Corey L, et al. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis. 2004;39:1300.
7. American Academy of Pediatrics. Immunization in special clinical circumstances. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS. eds. *Red Book: 2009 Report of the Committee on Infectious Diseases*. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.
8. Avetisyan G, Aschan J, Hassan M, et al. Evaluation of immune responses to seasonal influenza vaccination in healthy volunteers and in patients after stem cell transplantation. Transplantation 2008;2:257.
9. Karras NA, Weeres M, Sessions W, et al. A randomized trial of one versus two doses of influenza vaccine after allogeneic transplantation. Biol Blood Marrow Transplant. 2013;19:109.
10. Mohty B, Bel M, Vukicevic M, et al. Graft-versus-host disease is the major determinant of humoral responses to the AS03-adjuvanted influenza A/09/H1N1 vaccine in allogeneic hematopoietic stem cell transplant recipients. Haematologica 2011;96:896.

3.9

Take My Breath Away

GAURAV TRIKHA, MD

CASE PRESENTATION

A 62-year-old man with a history of a matched unrelated donor allogeneic hematopoietic stem cell transplantation (HSCT) for acute myelogenous leukemia presented two years after transplant with a history of malaise, headache, new onset sore throat, and a nonproductive cough. The patient's posttransplant course had been complicated by chronic graft-versus-host-disease (GVHD) involving the skin and liver, which required ongoing treatment with immunosuppressive drugs (mycophenolate mofetil, prednisone 25 mg daily, and tacrolimus). On admission, he was afebrile with normal vital signs, and there were no cardiorespiratory findings. Initial laboratory investigations revealed leukocyte count 5300/cu mm, with significant lymphopenia (110 lymphocytes/cu mm) and thrombocytopenia (120 000 platelets/cu mm); his creatinine was elevated at 2.3 mg/dL (baseline 1.3 mg/dL). Blood cultures and a nasopharyngeal swab for viral respiratory polymerase chain reaction (PCR) were performed, and admission chest radiograph showed no consolidation or increased interstitial markings. Empiric therapy was started with intravenous levofloxacin.

The following morning, he developed a fever of 38.4°C, increased shortness of breath, and tachypnea with progressive oxygen requirement. A repeat chest radiograph demonstrated new bibasilar opacities. A computed tomography (CT) chest scan without contrast confirmed bibasilar consolidation with bilateral ground-glass opacities (Figure 3.9.1).

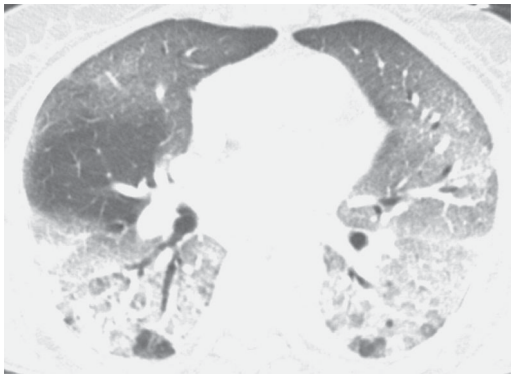


FIGURE 3.9.1: Chest CT scan demonstrating bibasilar consolidation with bilateral ground-glass opacities.

DIFFERENTIAL DIAGNOSIS

Possible infectious etiologies include community-acquired bacterial pneumonia (including atypical pneumonia), respiratory virus infection, postinfluenza pneumonia (commonly caused by *Staphylococcus* spp or *Staphylococcus pneumoniae*), *Pneumocystis jiroveci*, invasive fungal pneumonia, *Nocardia* pneumonia, or the noninfectious syndrome of cryptogenic organizing pneumonia.

HOSPITAL COURSE

Nasopharyngeal swab was reported positive for parainfluenza virus (PIV) by PCR. Subsequently, therapy was started with aerosolized ribavirin (AR).

His respiratory status continued to decline, and despite maximal oxygen therapy he required intubation. Antibiotic therapy was empirically changed to vancomycin and cefepime. The next day, he underwent a diagnostic bronchoscopy, which showed evidence of alveolar hemorrhage. His bronchoalveolar lavage fluid was positive for PIV and fungal stain was positive for hyphae. Bronchoalveolar lavage fluid culture grew *Aspergillus fumigatus*. Intravenous immunoglobulin (IVIG) and voriconazole were administered.

His respiratory status continued to worsen with progressive and persistent hypoxemia requiring maximal ventilatory support. On day fourteen, his endotracheal secretions were still positive for PIV. He eventually developed an ileus,

cardiac dysrhythmia, and his care was eventually transitioned to comfort measures. He died on day eighteen of his hospital stay.

Before diagnosis and throughout his hospitalization, the patient's lymphocyte count remained persistently at <250 cells/cu mm. An autopsy demonstrated bilateral pulmonary consolidation, hemorrhage with diffuse alveolar damage, and patchy fibrosis.

Final Diagnosis: Parainfluenza pneumonia, with possible *Aspergillus* co-infection

DISCUSSION

Recipients of HSCT routinely receive immune suppressants to prevent and treat GVHD. The occurrence of acute or chronic GVHD intensifies the immunodeficiency and prolongs the time to immune reconstitution. Respiratory viral infections in this population can be potentially fatal especially when they involve the lower respiratory tract and predispose to co-infection or superinfection by bacteria and fungi. In this case, the clinical and radiologic picture is most consistent with human parainfluenza virus (HPIV) pneumonia, but with the recovery of *Aspergillus*, even though the European Organization for Research in the Treatment of Cancer radiologic criteria for documentation of an invasive fungal infection are not met, co-infection (which commonly occurs) is possible. Studies have shown nonclassical radiologic patterns can also be seen with invasive aspergillosis [1]. Thus, the prudent clinician would presumptively add anti-*Aspergillus* treatment to the therapeutic regimen.

Human Parainfluenza Virus

Human parainfluenza virus infections occur throughout the year, with infections occurring primarily in the spring, summer, and fall. Human parainfluenza virus infections encompass four serotypes that cause mostly mild upper respiratory infection throughout the year with seasonal increases in fall and spring in children [2]. Several studies have documented a high occurrence of HPIV type III infection in HSCT recipients [3, 4]. In adult and pediatric leukemia and HSCT patients, symptomatic HPIV infections have been reported to range from 2% to 7%, of which at least one third manifest as lower respiratory infection [5–7]. Most cases of HPIV type III infection occur in spring and summer. A single center study showed that type of transplant influenced the likelihood of progression to HPIV pneumonia during the first 100 days after transplant (Figure 3.9.2)

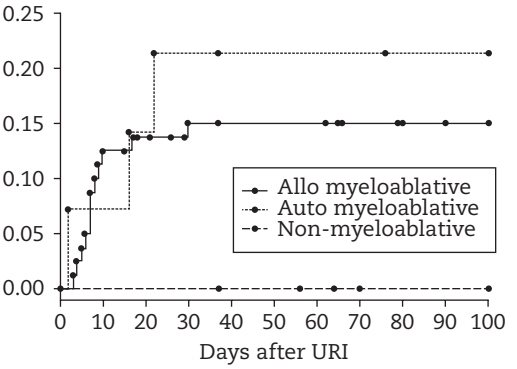


FIGURE 3.9.2: Rates of progression to lower respiratory tract infection after HPIV URI (7).

[8]. Serotype 1 was more likely to be associated with lower tract progression. Lymphopenia was also a risk factor for progression from upper to lower respiratory infection [8].

The role of treatment is limited by the lack of effective agents and randomized intervention trials. Treatment with AR and/or IVIG has not prevented progression to pneumonia and has not affected duration of illness or survival. A novel oral agent, GS-5806, that interferes with RSV entry by blocking viral-envelope fusion with the host cell membrane has recently been shown to be effective in modulating RSV infection in healthy adults [9]. Another drug currently under investigation, DAS181, is a recombinant fusion protein containing the catalytic domain of actinomyces viscosus sialidase, which effectively removes sialic acids from the surface of respiratory epithelial cells, thereby inhibiting infection by different HPIV strains. In cultured human airway epithelial cells and in a cotton rat HPIV infection model, DAS181 has been shown to remove sialic acid receptors, inhibit PIV genome replication and progeny virion formation, and significantly reduce viral titers in the infected lungs. In vitro treatment of infected LLC-MK2 cells at the known $TCID_{50}$ with serially diluted concentrations of DAS181 showed that the concentration of DAS181 needed to inhibit viral infection was between 10 and 100 nmol/L (Figure 3.9.3), whereas LLC-MK2 cells treated with 0.1–1 nmol/L DAS181 exhibited viral spread similar to that of the no-drug control [10]. Experience with DAS181 for the treatment of HPIV infections in humans is limited.

Human parainfluenza virus infection is the cause of significant morbidity and mortality, not only in recipients of HSCT but also in patients with leukemia. Multiple nonmodifiable risk

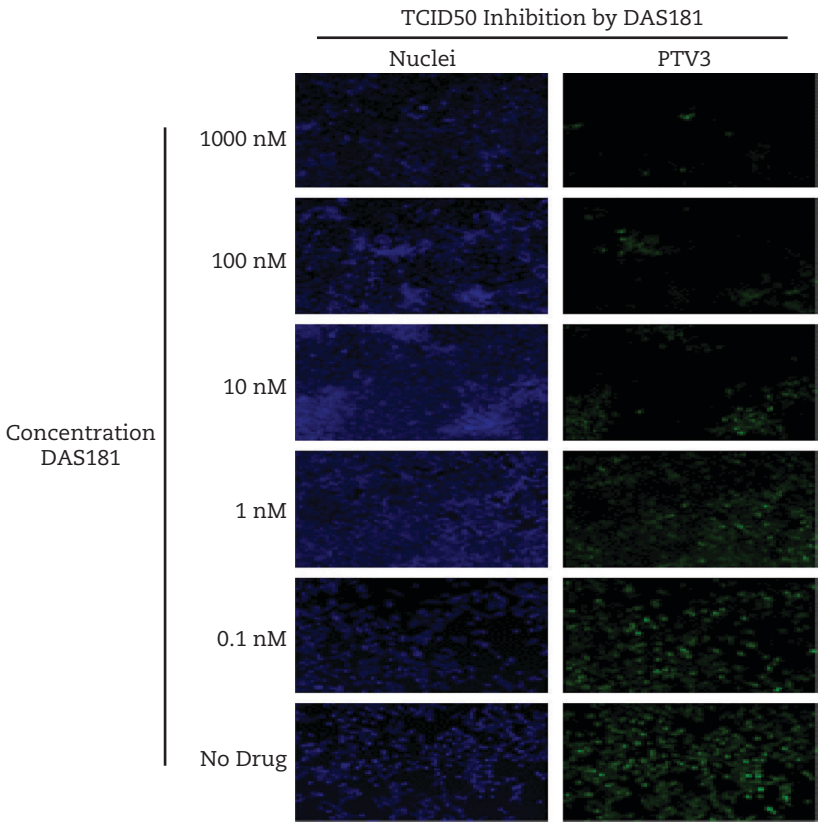


FIGURE 3.9.3: Concentrations of DAS181 that inhibit HPIV in vitro.

factors are independently associated with progression to pneumonia and mortality. Aerosolized ribavirin, with or without IVIG, do not appear to improve the duration of illness, length of hospitalization, or survival of patients with leukemia and recipients of HSCT. Because existing therapeutic options are inadequate, infection control strategies continue to be the cornerstone for preventing the spread of this infection among susceptible patients.

REFERENCES

1. Nucci M, Nouér SA, Grazziutti M, et al. Probable invasive aspergillosis without prespecified radiologic findings: proposal for inclusion of a new category of aspergillosis and implications for studying novel therapies. Clin Infect Dis. 2010;51:1273.
2. Hall, CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med. 2001;344:1917
3. Harrington RD, Hooton TM, Hackman RC, et al. An outbreak of respiratory syncytial virus in a bone marrow transplant center. J Infect Dis.1992;165:987.
4. Fox JP, Brandt CD, Wassermann FE, et al. The virus watch program: a continuing surveillance of viral infections in metropolitan New York families. VI. Observations of adenovirus infections: virus excretion patterns, antibody response, efficiency of surveillance, patterns of infections, and relation to illness. Am J Epidemiol. 1969;89:25.
5. Whimbey E, Champlin RE, Couch RB, et al. Community respiratory virus infections among hospitalized adult bone marrow transplant recipients. Clin Infect Dis. 1996;22:778.
6. Martino R, Porras RP, Rabella N, et al. Prospective study of the incidence, clinical features, and outcome of symptomatic upper and lower respiratory tract infections by respiratory viruses is adult recipients of hematopoietic stem cell transplants for hematologic malignancies. Biol Blood Marrow Transplant. 2005;11:781.
7. Klimov AI, Rocha E, Hayden FG, et al. Prolonged shedding of amantadine-resistant influenza A viruses by immunodeficient patients: detection by polymerase chain reaction-restriction analysis. J Infect Dis.1995;172:1352.

8. Schiffer JT, Kirby K, Sandmaier B, et al. Timing and severity of community acquired respiratory virus infections after myeloablative versus non-myeloablative hematopoietic stem cell transplantation. Haematologica 2009;94:1101.
9. DeVincenzo JP, Whitley RJ, Mackman RL, et al. Oral GS-5806 activity in a respiratory syncytial virus challenge study. N Engl J Med. 2014; 371:711
10. Chen Y, Driscoll JP, McAfee S, et al. Treatment of parainfluenza 3 infection with DAS181 in a patient after allogeneic stem cell transplantation. Clin Infect Dis. 2011;53:e77.

3.10

Unfinished Business: Prior Aspergillosis

JOHN R. WINGARD, MD

CASE PRESENTATION

A 46-year-old man was referred for allogeneic hematopoietic stem cell transplantation (HSCT). The patient was diagnosed with acute myelogenous leukemia two years ago. He underwent induction chemotherapy with idarubicin plus cytarabine. He required two courses of chemotherapy to achieve remission. Other than oral mucositis, culture-negative diarrhea, and neutropenic fever treated with empiric cefepime, he did well and entered complete remission. He then received consolidation chemotherapy with three courses of high-dose cytarabine. Five months after completing consolidation, he was noted to have a rising leukocyte count. A repeat bone marrow biopsy showed relapse. He underwent re-induction chemotherapy at an outside hospital. Fever occurred seven days later and was treated with cefepime. Fever persisted, and he developed a cough. Chest computed tomography (CT) reportedly demonstrated a localized infiltrate in the right lower lobe. The patient received empiric voriconazole and had no additional evaluation. He defervesced and blood counts recovered. Voriconazole was given for four weeks and stopped because his fever and cough had resolved. He was referred for transplant evaluation, now seven weeks after neutrophil recovery. An unrelated donor matched at A, B, C, and Drb1 loci was identified.

On physical examination the temperature was 37.0°C, the blood pressure was 124/69 mm mercury, the pulse 72 beats per minute, and the respiratory rate 12 breaths per minute. The oxygen saturation was 96% on room air. The physical examination was unrevealing. Laboratory testing revealed normal complete blood counts and liver function tests were also within normal levels. A chest CT revealed a nodular infiltrate in the left lung without cavitation or pleural effusion (Figure 3.10.1), which was decreased from the infiltrate seen on the earlier CT. Serum galactomannan (GM) assay was negative.

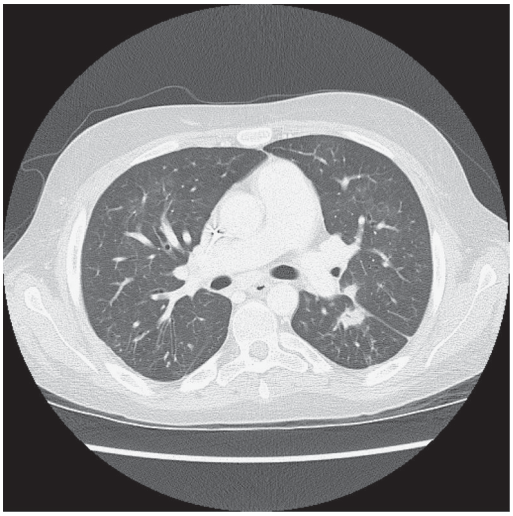


FIGURE 3.10.1: Chest CT showing a nodular infiltrate in the left lung without cavitation or pleural effusion.

DIFFERENTIAL DIAGNOSIS

Development of new nodular infiltrates during induction chemotherapy for acute leukemia are most likely to be due to bacteria or *Aspergillus*. Less commonly, mucormycosis or other mold infections may be the etiology.

Case Continued

The patient was referred to the Pulmonary Service for bronchoscopy. Bronchoalveolar lavage (BAL) fluid testing was negative for multiple infectious pathogens, and BAL GM was negative. A transbronchial biopsy was not done during bronchoscopy. With the clinical response to

the prior pneumonia, therapy with voriconazole was resumed. After completion of the transplant evaluation, the patient underwent a reduced intensity conditioning regimen with a peripheral blood graft from the matched, unrelated donor. Voriconazole was stopped prior to the conditioning regimen but resumed after completion of the conditioning regimen. The patient developed grade 2 acute graft-versus-host disease (GVHD), which resolved with corticosteroid therapy; the steroid therapy was weaned off after six weeks. Therapy with voriconazole was stopped on day 100. After six months, the immunosuppressive therapy was weaned off.

Final Diagnosis: Presumed prior invasive aspergillosis

Discussion

The etiology of the nodular infiltrate that occurred during re-induction is unclear. Between one third and two thirds of nodular infiltrates in this setting are due to invasive Aspergillosis (IA) [1]. Recurrence rates of IA historically have been so high that prospective HSCT candidates were routinely excluded due to IA.

Several studies have found that so-called "secondary" prophylaxis with anti-*Aspergillus* agents given posttransplant can allow such patients with prior IA to successfully undergo HSCT. The mold-active azoles have been best studied because their ability to be given orally lend themselves to prolonged administration to cover the extended period of risk. The most experience is with voriconazole. In a multinational voluntary registry study, voriconazole was found to be well tolerated and there was a break-through rate of only 7% [2]. Today, such patients are routinely offered transplantation. Still, with greater experience, recurrences of IA do occur. In a retrospective study of the European Group for Blood and Marrow Transplantation, recurrences were observed in 22% of patients with probable or proven IA [3]. Risk factors for IA recurrence were prolonged neutropenia, advanced disease status of the underlying malignancy, and less than six weeks between start of antifungal therapy and transplant. Risk factors for early recurrence (the first month) and late recurrence (after the first month) were examined separately. Early relapses were seen more commonly in patients who received myeloablative conditioning regimens. Late recurrences were seen more commonly in patients who developed cytomegalovirus disease, use of marrow or cord blood as stem cell source, and moderate to severe grades of acute GVHD. Patients with none or only one of the seven risk factors stated above were at low risk of IA recurrence (6%), whereas the presence of two to three risk factors was associated with a 27% risk for recurrence, and the presence of four or more risk factors was associated with a recurrence rate of 72%. Although voriconazole was the antifungal most commonly used as prophylaxis, other drugs were also occasionally used with similar rates of protection. A short time interval between treatment of infection and transplant may lead to relapse of infection, which, in large part, relates to inadequate control of the infection [4].

In recent years, a number of other factors have also been associated with the occurrence of IA after HSCT. Iron overload, prior immunosuppressive therapies including the purine analogs (eg, fludarabine, cladrabine, pentastatin) or monoclonal antibodies (eg, antithymocyte globulin or alemtuzumab), and persistent neutropenia are increasingly recognized as factors that can set the patient up for IA.

One of the challenges faced during the transplant evaluation is knowing whether a patient truly had IA prior to referral. Unfortunately, many patients, as with this patient, have had inadequate evaluation without mycological confirmation of IA but are judged to have IA based on clinical or radiological criteria. Although additional evaluation before transplant, as was performed in this patient, is important both for determining whether there may be another etiology as well as to ensure adequacy of treatment, the evaluation is often negative and one is left with considerable uncertainty. In such a situation, assuming the worst is the best option. Because of potential deleterious interaction with high-dose chemotherapy, especially cyclophosphamide, omission of the voriconazole during the conditioning regimen is advisable. Antimold therapy with an echinocandin during the conditioning is an option to consider.

REFERENCES

1. Wingard JR, Hiemenz JW, Jantz MA. How I manage pulmonary nodular lesions and nodular infiltrates in patients with hematologic malignancies or undergoing hematopoietic cell transplantation. Blood 2012;120:1791.
2. Cordonnier C, Rovira M, Maertens J, et al. Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. Haematologica 2010;95:1762.

3. Martino R, Parody R, Fukuda T, et al. Impact of the intensity of the pretransplantation conditioning regimen in patients with prior invasive aspergillosis undergoing allogeneic hematopoietic stem cell transplantation: a retrospective survey of the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Blood 2006;108:2928.
4. Cordonnier C, Rovira M, Maertens J, et al. Voriconazole as secondary antifungal prophylaxis in stem cell transplant recipients. Haematologica 2011;96:e9.

3.11

When the Levee Breaks

MAXIM NORKIN, MD

CASE PRESENTATION

A 30-year-old female with history of acute myeloid leukemia (AML) developed acute respiratory distress on day +17 after allogeneic hematopoietic stem cell transplant (HSCT).

History of Present Illness

Five months earlier, the patient developed an upper respiratory infection and was found to have an elevated white blood cell count (WBC) of 36 000 cells/mm^3 with abundant blasts. Subsequent bone marrow evaluation was consistent with AML. The patient received induction chemotherapy with idarubicin and cytarabine, which she tolerated well. Bone marrow evaluation after neutrophil recovery revealed persistence of residual leukemic blasts, and she received re-induction with high-dose cytarabine. Re-induction chemotherapy was complicated by the development of a peripherally inserted central catheter line-associated thrombus, requiring systemic anticoagulation. The patient received antimicrobial prophylaxis with fluconazole, levofloxacin, and valacyclovir during neutropenia. After neutrophil recovery, bone marrow evaluation showed no evidence of residual leukemia. She subsequently underwent a matched unrelated donor HSCT with myeloablative conditioning of cyclophosphamide and total body irradiation. She tolerated the conditioning regimen and stem cell infusion well. When her absolute neutrophil count (ANC) dropped to <500 cells/mcL she received prophylaxis with levofloxacin, voriconazole, and valacyclovir. On day +16 after the HSCT, the patient developed a neutropenic fever with the temperature of 38.8°C.

At the time of first fever spike, her blood pressure was 100/45 mm mercury, pulse was 120 beats per minute, respirations were 22 per minute, and oxygen saturation was 90% on ambient air. Two liters of supplemental oxygen was administered and oxygen saturation improved to 94%. On physical examination, the patient was in mild respiratory distress with tachypnea. The patient did not use accessory muscles to breathe and did not have visible cyanosis. Inspiratory crackles and rhonchi were appreciated bilaterally on auscultation. Cardiovascular examination demonstrated tachycardia but did not reveal any pulse irregularities, murmur, gallop, or rub. The patient did not have an elevated jugular venous distention or lower extremity edema. Inspection of the central line revealed no visible erythema or tenderness at the insertion site. Laboratory data revealed normal serum levels of electrolytes, serum creatinine, and liver function tests. Brain natriuretic peptide level was <100 picograms/mL. The complete blood count showed pancytopenia with WBC 300 cells/mm^3, hemoglobin 7.9 g/dL, platelet count 32 000/mm^3, and ANC 200 cells/mm^3. Chest radiograph showed development of perihilar interstitial opacities but no focal consolidation, effusion, or pneumothorax. Blood and urine cultures were obtained, and the patient was started on empiric cefepime and continued on prophylactic voriconazole and valacyclovir. During the next twelve hours, the patient continued to be febrile and showed deterioration of the respiratory status with worsening tachypnea and increasing requirements for supplemental oxygen. Computed tomography (CT) examination of the chest demonstrated multiple new rounded parenchymal opacities bilaterally surrounded by a component of ground-glass opacification (Figure 3.11.1). Vancomycin and amphotericin B lipid complex were added to empiric antimicrobial coverage, dropping the prophylactic voriconazole; however, the patient's respiratory status continued to deteriorate, and she remained hypoxic despite administration of high concentration of oxygen via a non-rebreather mask. The systolic blood pressure fell to 75 mm Hg and heart rate increased to 140 beats per minute. Analysis of arterial blood at that time showed that the partial

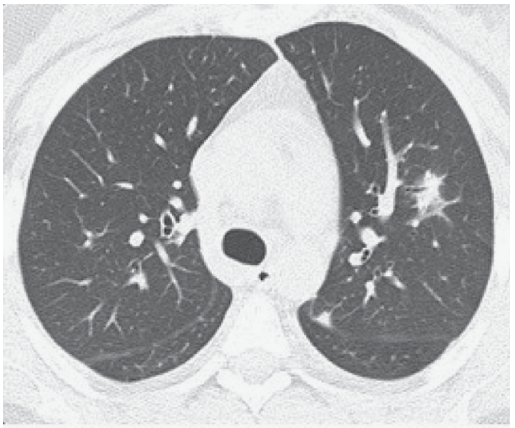
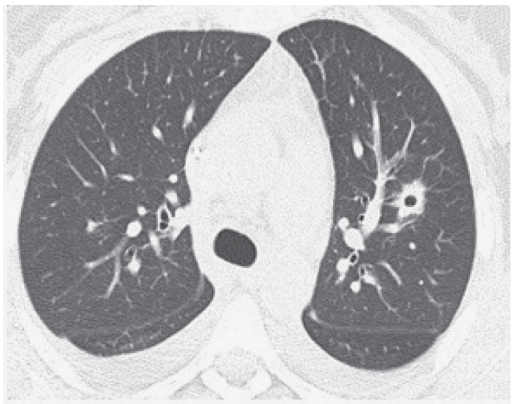
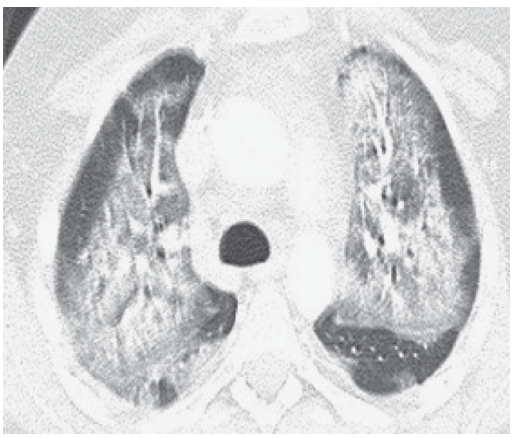


FIGURE 3.11.1: Chest CT demonstrating multiple new rounded parenchymal opacities bilaterally surrounded by a component of ground- glass opacification.





FIGURES 3.11.2 AND 3.11.3: Repeat chest CTs in the next 12 twelve days showed development of ill-defined pulmonary nodules, some of which exhibited cavitation, most prevalent in the upper lobes bilaterally progressing to bilateral diffuse infiltrates.

pressure of oxygen was 82 mm mercury, the partial pressure of carbon dioxide was 62 mm mercury, and the pH was 7.10. An urgent insertion of an endotracheal tube was performed. Repeat chest CTs in the next twelve days showed development of ill-defined pulmonary nodules, some of which exhibited cavitation, most prevalent in the upper lobes bilaterally progressing to bilateral diffuse infiltrates (Figures 3.11.2 and 3.11.3) in a few days.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of rapidly progressing pulmonary opacities in the post-HSCT setting includes both noninfectious and infectious causes. The most frequent infectious causes are bacterial infections with Gram-positive and Gram-negative organisms particularly with *Klebsiella* spp, *Legionella*, and *Staphylococcus aureus*; invasive fungal infections with *Aspergillus*, the agents of mucormycosis, and other molds. Noninfectious causes include congestive heart failure, volume overload, adult respiratory distress syndrome (ARDS), engraftment syndrome, diffuse alveolar hemorrhage (DAH), leukemic infiltrates; thromboembolism with subsequent lung infarction; and bronchiolitis obliterans organizing pneumonia.

Blood cultures (both from central line and peripheral access and drawn at different times) were positive for methicillin-resistant *S aureus* (MRSA) sensitive to vancomycin and linezolid. A fiber optic bronchoscopy showed no apparent bleeding but significant erythema of the distal lobar segments. The Gram stain of a sample of bronchoalveolar lavage (BAL) fluid revealed the presence of numerous Gram-positive cocci in clusters (Figure 3.11.4), which were later identified as MRSA. Galactomannan assay from BAL fluid was negative. The central line was promptly removed. Transthoracic and transesophageal echocardiography showed no valve vegetations. Despite aggressive supportive care and broad-spectrum antimicrobial coverage, the patient continued to have persistently positive blood cultures for MRSA and developed worsening hypoxemia with copious, blood-tinged secretions. She was also noted to have progressive decline in mean arterial pressure despite continued infusion of multiple vasopressors and inotropes. Repeated CT of the chest revealed progression with interval development of multifocal areas of mosaic attenuation and ground-glass opacification in all lobes of the lung with persistent nodular opacities, some of which demonstrated central cavitation (Figure 3.11.3).

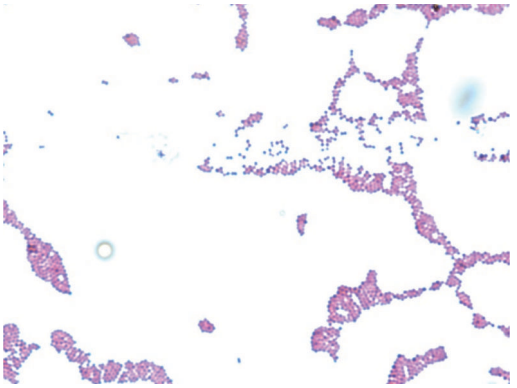


FIGURE 3.11.4: Gram stain of a sample of bronchoalveolar lavage (BAL) fluid revealed the presence of numerous Gram-positive cocci in clusters.

The patient died from multiple organ dysfunction syndrome. No autopsy was performed.

Final Diagnosis: *Staphylococcus aureus* bacteremia with pulmonary abscesses and multiorgan failure

DISCUSSION

The acute onset of respiratory failure at the time of engraftment can be due to infectious or noninfectious causes (especially the engraftment syndrome). The development and rapid progression of multiple cavitary pulmonary nodules, persistent fever, and hypotension with subsequent multiple organ dysfunction syndrome in severely immunocompromised patients indicate the likely presence of a life-threatening infection rather than a noninfectious process and makes the engraftment syndrome, ARDS, or DAH unlikely, which usually produce a diffuse infiltrate. The clinical and radiologic findings do not support the diagnosis of lung infarction due to thromboembolism. The formation of cavitary lesions occurs as a result of complex interactions between host and pathogen, which are often associated with development of infarction or necrosis. In HSCT recipients, mold infections, particularly by *Aspergillus* spp, are frequent causes of cavitary pulmonary lesions. In patients with invasive pulmonary, aspergillosis cavities are observed in 20% of cases [1]. This patient had received prophylactic voriconazole and had negative fungal biomarker testing, which makes invasive pulmonary aspergillosis less likely and increases the probability of mucormycosis or bacterial infection rather than invasive aspergillosis. Bacterial pathogens can cause pulmonary cavities by two mechanisms: (1) by inducing a necrotizing process or abscess at the site of pathogen inoculation or (2) by producing septic emboli due to hematogenous dissemination. Among bacterial pathogens, *Klebsiella pneumoniae* is most frequently associated with extensive pyogenic lung necrosis and cavitation [2]. *Staphylococcus aureus* is another bacterial pathogen that can lead to the development of necrotizing pneumonia with cavitary lesions. Lung cavitation from tissue necrosis and abscess formation is also frequently seen in pulmonary nocardiosis (which usually occurs much later after HSCT) [3] but infrequent in patients with *Pneumocystis jirovecii* pneumonia. Lung cavities can also develop in HSCT recipients with bronchiolitis obliterans organizing pneumonia [4]; however, that too occurs much later after transplant, and the clinical or radiographic manifestations in this patient do not support this diagnosis. In HSCT recipients with respiratory distress and nodular pulmonary abnormalities, empiric therapy should be initiated to cover a wide spectrum of bacterial and mold pathogens while aggressive diagnostic assessment proceeds.

REFERENCES

1. Wingard JR, Hiemenz JW, Jantz MA. How I manage pulmonary nodular lesions and nodular infiltrates in patients with hematologic malignancies or undergoing hematopoietic cell transplantation. Blood 2012;120:1791.
2. Moon WK, Im JG, Yeon KM, et al. Complications of *Klebsiella pneumonia*: CT evaluation. J Comput Assist Tomogr. 1995;19:176.
3. Feigin DS. Nocardiosis of the lung: chest radiographic findings in 21 cases. Radiology 1986;159:9.
4. Gadkowski LB, Stout JE. Cavitary pulmonary disease. Clin Microbiol Rev. 2008;21:305.

3.12

A Bump in the Neck

JACK HSU, MD

CASE PRESENTATION

A 27-year-old man underwent a four of six antigen-matched unrelated cord blood transplantation using a conditioning regimen of fludarabine, cyclophosphamide, and rabbit antithymocyte globulin (ATG) for refractory, recurrent Hodgkin's disease. The postgraft immunosuppression consisted of tacrolimus and mycophenolate mofetil. He is currently thirty-five days after transplantation. Overnight, he has noted the start of low-grade fevers with the appearance of palpable swellings in the neck. He denies any upper respiratory symptoms, urinary symptoms, or rash. In the clinic, he is found to have a temperature of 38.3°C. Physical exam reveals a normal oral and oropharyngeal exam, normal lung exam, and small, shotty lymph nodes in the right cervical chain. There were no other significant physical findings.

DIAGNOSTIC CONSIDERATIONS

The sudden onset of fever in patients early in the transplant course raises the concern about bacterial infections. With the cervical adenopathy, oral and oropharyngeal bacterial or viral infections should be strongly considered. In addition, because of the use of both cord blood as the stem cell source, mismatching of donor and recipient, and the use of ATG in the transplant conditioning regimen—factors that are associated with delay in T cell immune reconstitution—he is at risk for reactivation of viral infections, such as cytomegalovirus (CMV), human herpes virus-6 (HHV6), and Epstein-Barr virus (EBV). In addition to blood cultures, and immunoassays/polymerase chain reaction (PCR) testing for respiratory viruses, serum PCR tests for CMV, HHV6, and EBV should be obtained. Given his history of refractory lymphoma, early recurrence is also a consideration.

Case Continued

A complete blood count reveals normal neutrophil count and hemoglobin level. The platelet count was 57 000/mm^3 but stable. Serum PCR for CMV was negative; however, the EBV DNA was elevated at 649 copies/mL.

Comment

The positive EBV DNA PCR raises the concern for EBV lymphoproliferative disease (LPD). However, recurrence is still a consideration. This patient should have a computed tomography (CT) scan to look for evidence of increased adenopathy, and if any enlarged nodes are seen, a biopsy should be performed to look for EBV DNA in the atypical cells.

Case Continued

A CT scan of neck revealed enlarged nodes in the right anterior cervical chain, the largest node was approximately 2.3 cm in size. A fine-needle aspirate was obtained of the node, which revealed many atypical large lymphoid cells intermixed with small lymphocytes and histiocytes. Immunostain showed that the majority of the atypical large cells are positive for CD20 and PAX5, with variable reactivity for CD45. Many of the large cells are also positive for EBV (Figure 3.12.1).

Final Diagnosis: Epstein-Barr virus-associated lymphoproliferative disease

TREATMENT AND FOLLOW-UP

The patient was started on a weekly course of rituximab for four weeks. He tolerated the infusions without problems, except for the first dose when he developed fever and hypotension, which resolved with fluids, steroids, and reduction in the rate of infusion. Epstein-Barr virus DNA level dropped to 204 copies/mL after completion of therapy. Restaging scans after completion of

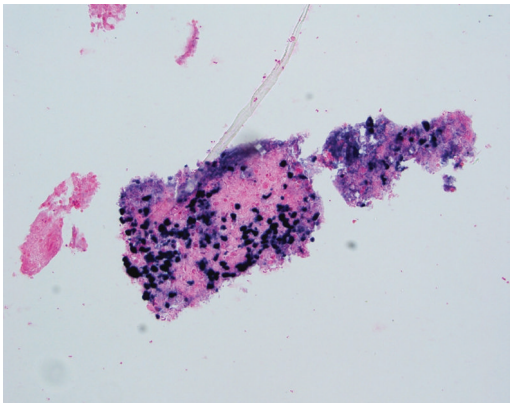


FIGURE 3.12.1: Immunostain of fine needle aspirate sample showed that the majority of the atypical large cells are positive for CD20 and PAX5, with variable reactivity for CD45. Many of the large cells are also positive for Epstein Barr virus.

therapy showed a mild increase in the size of the cervical node; however, restaging three months later showed a mild decrease in node size with a nondetectable EBV DNA level.

DISCUSSION

Epstein-Barr virus is an enveloped, DNA gammaherpesvirus that is ubiquitous in all adult human populations. It has a tropism for B lymphocytes, although it can also infect monocytes and epithelial cells. In immunocompetent patients, it is associated with the syndrome of infectious mononucleosis. However, in immunosuppressed patients, EBV is associated with LPD. Epstein-Barr virus LPD occurs in approximately 1%–3% of myeloablative hematopoietic stem cell transplant recipients [1]. Most cases of LPD are diagnosed within the first six months after transplantation [2]. Risk factors include T-cell depletion, use of unrelated or mismatch related donors, use of ATG in prophylaxis or treatment of graft-versus-host disease (GVHD), and use of anti-CD3 monoclonal antibodies for the treatment of acute GVHD [3]. The greater number of the risk factors present, the more likely EBV-LPD is. Epstein-Barr virus LPD is generally preceded by a rising plasma EBV DNA level associated with a relatively high positive predictive value [4].

The incidence of positive EBV DNA level varies depending upon the source of the donor cells and the intensity of the conditioning regimen. In the myeloablative setting, the incidence of positive EBV DNA was 14% overall. Ten percent of patients who received an human leukocyte antigen-identical sibling donor graft eventually developed positive EBV DNA compared with 20%–30% of patients who received an unrelated donor graft [5]. Risk factors for seroconversion were patients who received ATG for any reason or who developed grade III–IV acute GVHD. In comparison, non-myeloablative (NMA) conditioning regimens appear to be associated with an increased risk of EBV seroconversion (35% vs 8%), possibly due to the increased use of ATG in NMA conditioning regimens [6]. In the setting of unrelated cord blood transplants, there was an increased risk of positive EBV DNA in patients who received NMA conditioning regimens that contained ATG (21% vs 2%) [7]. A more limited impact of ATG was seen in the myeloablative setting (3.3% vs 0%).

Therapy of EBV-LPD is primarily preventative because EBV-LPD can rapidly progress into aggressive lymphoma, requiring intensive treatment. Weekly screening of high-risk populations, such as this case, is advised. Preemptive therapy is usually initiated at a predefined EBV DNA level and consists of either reduction or withdrawal of immunosuppression, if possible [8], or rituximab [9]. Early intervention may result in overtreatment; however, it can significantly reduce the development of LPD (49% vs 16%) and its associated mortality (26% vs 0%).

Treatment of overt EBV-LPD is not as effective. Antiviral drugs, such as acyclovir and ganciclovir, are not expected to have any effect because overt EBV-LPD is the result of autonomously proliferating B cells, initiated by latently infected B cells that have acquired secondary events. Small, single institution studies of rituximab found complete response rates from 66% to 100% with an overall survival ranging from 66% to 100%. A report of rituximab given in the standard four-dose weekly schedule in forty-three solid organ transplant recipients with EBV-LPD revealed an overall response rate of 44% with twelve complete responders [10]. The overall survival rate at one year was 67%. Adoptive T-cell immunotherapy using donor lymphocytes can also effectively induce complete remissions in EBV-LPD [11].

REFERENCES

1. Meijer E, Slaper-Cortenbach IC, Thijsen SF, et al. Increased incidence of EBV-associated lymphoproliferative disorders after allogeneic stem cell transplantation from matched unrelated donors due to a change of T cell depletion technique. Bone Marrow Transplant. 2002;29:335.

2. Ocheni S, Kroeger N, Zabelina T, et al. EBV reactivation and post transplant lymphoproliferative disorders following allogeneic SCT. Bone Marrow Transplant. 2008;42:181.
3. Curtis RE, Travis LB, Rowlings PA, et al. Risk of lymphoproliferative disorders after bone marrow transplantation: a multi-institutional study. Blood 1999;94:2208.
4. Van Esser JW, van der Holt B, Meijer E, et al. Epstein-Barr virus (EBV) reactivation is a frequent event after allogeneic stem cell transplantation (SCT) and quantitatively predicts EBV-lymphoproliferative disease following T-cell-depleted SCT. Blood 2001;98:972.
5. Juvonen E, Aalto S, Tarkkanen J, et al. Retrospective evaluation of serum Epstein Barr virus DNA levels in 406 allogeneic stem cell transplant patients. Haematologica 2007;92:819.
6. Cohen J, Gandhi M, Naik P, et al. Increased incidence of EBV-related disease following paediatric stem cell transplantation with reduced-intensity conditioning. Br J Haematol. 2005;129:229.
7. Brunstein CG, Weisdorf DJ, DeFor T, et al. Marked increased risk of Epstein-Barr virus-related complications with the addition of antithymocyte globulin to a nonmyeloablative conditioning prior to unrelated umbilical cord blood transplantation. Blood 2006;108:2874.
8. Cesaro S, Murrone A, Mengoli C, et al. The real-time polymerase chain reaction-guided modulation of immunosuppression enables the pre-emptive management of Epstein-Barr virus reactivation after allogeneic haematopoietic stem cell transplantation. Br J Haematol. 2005;128:224.
9. Van Esser JW, Niesters HG, van der Holt B, et al. Prevention of Epstein-Barr virus-lymphoproliferative disease by molecular monitoring and preemptive rituximab in high-risk patients after allogeneic stem cell transplantation. Blood 2002;99:4364.
10. Choquet S, Leblond V, Herbrecht R, et al. Efficacy and safety of rituximab in B-cell post-transplantation lymphoproliferative disorders: results of a prospective multicenter phase 2 study. Blood 2006;107:3053.
11. O'Reilly RJ, Small TN, Papadopoulos E, et al. Biology and adoptive cell therapy of Epstein-Barr virus-associated lymphoproliferative disorders in recipients of marrow allografts. Immunol Rev. 1997;157:195–216.

3.13

A Really Bad Yeast Infection

JOHN R. WINGARD, MD

CASE PRESENTATION

A 42-year-old man underwent allogeneic hematopoietic stem cell transplant for recurrent acute myelogenous leukemia from a 6/6 human leukocyte antigen-matched sibling donor following cyclophosphamide plus total body irradiation conditioning. Therapy was started with levofloxacin, acyclovir, and fluconazole prophylaxis. Postgraft immunosuppression consisted of tacrolimus and methotrexate. On day four, he developed oral mucositis with ulcerations, necessitating morphine as continuous infusion. On day seven, the patient developed a neutropenic fever that was treated with cefepime. Blood cultures were negative and the patient defervesced. On day sixteen, the patient developed a temperature of 38.4°C. The oral mucosa still demonstrated ulcerations. The central venous catheter did not demonstrate inflammation. The remainder of the exam failed to demonstrate any signs suggestive of an infectious focus. Blood cultures were drawn. Two days later, the laboratory notifies the clinicians that yeasts are growing from the blood cultures. You are consulted.

DIFFERENTIAL DIAGNOSIS

The setting of persistent or recurrent neutropenic fever and the blood culture findings are consistent with *Candida* bloodstream infection. Because the patient is on fluconazole prophylaxis, *Candida albicans* is not likely. More likely are fluconazole-resistant non-*albicans* species, such as *Candida krusei* or *Candida glabrata*.

TREATMENT AND FOLLOW-UP

You recommended stopping fluconazole and changing therapy to a lipid amphotericin formulation. The yeasts are subsequently identified as *C krusei.* The fungemia persisted for four days, and you recommended removal of the central venous catheter. The fungemia cleared and the neutrophil count recovered on day twenty-one.

Final Diagnosis: *Candida krusei* fungemia emerging during fluconazole prophylaxis

DISCUSSION

Candidemia is a cause of persistent or recurrent fever in neutropenic patients, accounting for 15%–30% of persistent neutropenic fevers [1]. However, antifungal prophylaxis is protective with a substantially reduced risk for candidemia after hematopoietic stem cell transplantation (HSCT). Consensus guidelines recommend fluconazole prophylaxis after HSCT [2]. Unfortunately, with the routine use of fluconazole prophylaxis, the emergence of less susceptible non-*albicans* species has occurred, principally *C krusei and C glabrata* [3–5].

Switching to a different class of antifungal agents, such as an echinocandin or polyene, is advisable when a breakthrough infection is suspected while on fluconazole prophylaxis [6]. A lipid formulation of amphotericin B is a good choice [6]. An alternative would be an echinocandin, but recent studies suggest a lower likelihood of susceptibility [7]. A number of studies have suggested that early removal of central venous catheters have been associated with quicker clearing of fungemia and improved outcomes, but a reanalysis of these studies suggest that in cancer patients, routine early removal of the catheter is not necessarily associated with improved outcomes [8]. The rationale is that many candidemia episodes in patients receiving cytotoxic therapies associated with intestinal mucosal injury are caused by commensal organisms entering the bloodstream via the gut lumen rather than via the venous catheter. In any event, persistence of candidemia despite appropriate antifungal therapy is sufficient justification for catheter removal, as in this case, because biofilms frequently form on catheters and may prevent penetration of the antifungal drug to the fungus and may cause persistent fungemia. Thus, the catheter was removed in this case.

REFERENCES

1. Wingard JR, Leather HL. Empiric antifungal therapy for the neutropenic patient. Oncology (Williston Park) 2001;15:351.
2. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143.
3. Wingard JR, Merz WG, Rinaldi MG, et al. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N Engl J Med. 1991;325:1274.
4. Wingard JR, Merz WG, Rinaldi MG, et al. Association of *Torulopsis glabrata* infections with fluconazole prophylaxis in neutropenic bone marrow transplant patients. Antimicrob Agents Chemother. 1993;37:1847.
5. Wingard JR. The changing face of invasive fungal infections in hematopoietic cell transplant recipients. Curr Opin Oncol. 2005;17:89.
6. Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. Infectious Diseases Society of America. Clin Infect Dis. 2000;30:662
7. Orasch C, Marchetti O, Garbino J, et al. *Candida* species distribution and antifungal susceptibility testing according to European Committee on Antimicrobial Susceptibility Testing and new vs. old Clinical and Laboratory Standards Institute clinical breakpoints: a six-year prospective candidemia survey from the Fungal Infection Network of Switzerland. Clin Microbiol Infect. 2013;20:6988.
8. Nucci M, Anaissie E, Betts RF, et al. Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. Clin Infect Dis. 2010;51:295.

3.14

Proceed or Not to Proceed: Evaluation of the Transplant Candidate With Prior Hepatitis

JACK HSU, MD

CASE PRESENTATION

You are asked to evaluate a 33-year-old woman awaiting transplantation. She was diagnosed with acute myeloid leukemia, monocytic subtype (AML-M5) with normal cytogenetics. She has a history of alcohol abuse and has a sacral tattoo, which was placed several years before her diagnosis of AML. She received induction chemotherapy with idarubicin and cytarabine induction. The chemotherapy course was complicated by neutropenic fevers with negative cultures and profound cytopenias requiring transfusions of blood and platelets. She recovered her counts and was found to be in complete remission on recovery bone marrow biopsy.

She subsequently received consolidation chemotherapy with two cycles of high-dose cytarabine. During this time, a human leukocyte antigen-identical unrelated donor was identified. During her pretransplant assessment, she was noted to have a normal physical exam and normal metabolic profile (including transaminases) and complete blood count. Her vital organ functions were normal. On viral screening, her hepatitis panel revealed the following:

Hepatitis B Core Antibody (HBcAb): Negative

Hepatitis B Core Antibody Immunoglobulin M (HBcAb IgM): Negative

Hepatitis B Surface Antibody (HBsAb): Negative

Hepatitis B Surface Antigen (HBsAg): Positive

Hepatitis C Antibody (HCAb): Negative

DIFFERENTIAL DIAGNOSIS

The above hepatitis panel in this patient is concerning for an active hepatitis B virus (HBV) infection. The patient should have her HBsAg confirmed as well as hepatitis B DNA (HBV DNA) titer by polymerase chain reaction sent.

FURTHER CLINICAL COURSE

Confirmatory testing for HBsAg was positive, and her HBV DNA titer was 4.4 (normal is undetectable). Referral to gastroenterology was made, and she had a liver biopsy which found minimal portal inflammatory cell infiltrate without apparent interface or lobular hepatitis (Figure 3.14.1). Minimal portal fibrosis was seen. Immunostains for hepatitis B antigen was negative. Therapy was started with entecavir, and she now returns to you to discuss her biopsy findings.

Final Diagnosis: Chronic hepatitis B infection

TREATMENT AND FOLLOW-UP

After review of her liver workup, the patient was cleared to proceed towards a matched unrelated

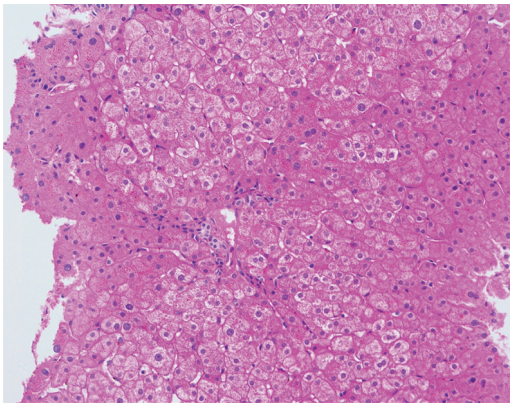


FIGURE 3.14.1: Liver biopsy showing portal inflammatory cell infiltrate without apparent interface or lobular hepatitis with minimal portal fibrosis.

donor allogeneic transplant using a reduced intensity conditioning regimen. She received a conditioning regimen of fludarabine, melphalan, and antithymocyte globulin. She was maintained on entecavir throughout her entire transplant course without difficulty. Her postgraft immunosuppression consisted of tacrolimus and short course methotrexate where she received all four planned doses. Her posttransplant course was complicated by profound cytopenias requiring transfusions of blood and platelets, neutropenic fever controlled by broad-spectrum antibiotics, and serum transaminitis up to five times the upper limit of normal. Her clinical course after engraftment was uneventful, immunosuppression was tapered and stopped at six months. She was HBsAg negative at six months after transplant. Entecavir was stopped, and long-term follow-up by gastroenterology found she was still HBsAg negative with normal liver functions.

DISCUSSION

This patient's hepatitis panel is consistent with chronic persistent hepatitis B infection with elevated HBV DNA titer. No significant fibrosis was seen on liver biopsy. The patient is at high risk for development of liver-related complications after transplant, such as sinusoidal obstruction syndrome (otherwise known as hepatic veno-occlusive disease) or liver graft-versus-host disease (GVHD). She received an allogeneic transplant; however, a reduced intensity conditioning regimen was used to minimize hepatic toxicity and harmful effects resulting from impaired hepatic metabolism of chemotherapeutic drugs.

Hepatitis viruses are DNA (hepatitis B) or RNA (hepatitis A, C) enteric pathogens, which can be transmitted via fecal-oral route, sexual contact, or through infected blood products. In hematopoietic stem cell transplantation (HSCT) recipients, active hepatitis infection is associated with increased morbidity and mortality after transplantation. The rate of reactivation of hepatitis B is approximately 20% in patients with isolated HBcAb [1, 2]. Patients who are HBsAg or HBV DNA positive are at even higher risk of reactivation with rates up to 50% [3]. Risk factors include treatment with corticosteroids and acute GVHD.

Guidelines have been established for the screening and management of hepatitis B in stem cell transplant recipients [4]. Testing both recipients and potential donors for evidence of active or past HBV infection is critical to preventing HBV exposure and disease in transplant recipients. The HBsAG, HBsAb, and HBcAb are appropriate screening assays. All recipients who are positive for HBcAb or HBsAg should be tested for HBV DNA. In addition, HBV naive recipients should not receive transplants from HBsAg- or HBV DNA-positive donors, if possible.

Management of HSCT candidates with evidence of prior exposure to HBV varies depending on the serologic findings. Recipients who are HBcAb and HBsAb positive are at risk of reactivation following prolonged immunosuppressive treatment. These patients should have HBV DNA titers examined if there are elevations in serum alanine aminotransferase, and preemptive treatment should be started if there is a positive HBV DNA viral load [5]. Alternatively, prophylactic antiviral treatment starting before transplantation and continuing for at least one to six months has been explored. Duration of therapy for HBV DNA-positive recipients is unclear; however, it is generally advised to continue therapy for at least six months after cessation of immunosuppressive drugs, because flares of hepatic injury can occur with tapering of immunosuppressive therapy [6].

Candidates with evidence of active HBV replication (HBsAg or HBV DNA positive) should have a liver biopsy prior to transplantation to exclude cirrhosis and hepatic fibrosis, because they can alter metabolism of the drugs used in the transplant conditioning regimen and result in increased treatment-related morbidity and mortality. A recent trial comparing entecavir and lamivudine prophylaxis in hepatitis B-infected patients treated with chemotherapy for non-Hodgkin lymphoma showed lower rates of HBV hepatitis and HBV reaction with entecavir [7]. These patients should receive antiviral therapy prior to conditioning, and, if transplant is not urgent, three to six months of therapy should be administered prior to the start of the conditioning regimen. Candidates who are HBcAb positive only should be tested for HBV DNA and, if undetectable, should receive HBV vaccination prior to transplantation. If they are HBV DNA positive, then preemptive antiviral therapy should be given.

For hepatitis C (HCV)-infected recipients, morbidity and mortality rates between HCV-infected and noninfected patients are similar up to ten years after transplant [8]. However, there is an increased risk of progression to cirrhosis with a cumulative incidence of biopsy-proven cirrhosis of 11% and 24% at 15 and 20 years posttransplant, respectively, with a median onset of eighteen years compared with forty years for non-HCT HCV-infected patients [9].

It is recommended that all transplant candidates should be screened for anti-HCV antibodies, and those who are positive or at high-risk for HCV infection should be tested for HCV RNA. Liver biopsy to assess for chronic liver disease is warranted in cases with associated iron overload, history of excessive alcohol intake, history of HCV >10 years, and with clinical evidence of chronic liver disease. Patients with evidence of cirrhosis or hepatic fibrosis should be reassessed as candidates for transplantation, because the risk of fatal sinusoidal obstruction syndrome is 15%–25% with cyclophosphamide-based myeloablative conditioning regimens [8]. Prior cirrhosis is associated with increased mortality risk even when reduced intensity conditioning regimens are selected [10].

Antiviral treatment should be considered in all HCV-infected recipients and, in the past, generally consisted of a combination of pegylated interferon and ribavirin [11]. However, interferon is contraindicated within the first six months of transplantation because of an associated risk of GVHD and mortality, and ribavirin monotherapy has been shown to be ineffective in the general population [12]. If treatment is not possible with these agents, it does not preclude transplantation because the course of HCV-mediated chronic liver disease is slow for at least ten to twenty years. New antiviral agents will alter our approach in the upcoming future but require study in the HSCT setting.

REFERENCES

1. Matsue K, Aoki T, Odawara J, et al. High risk of hepatitis B-virus reactivation after hematopoietic cell transplantation in hepatitis B core antibody-positive patients. Eur J Haematol. 2009;83:357.
2. Hammond SP, Borchelt AM, Ukomadu C, et al. Hepatitis B virus reactivation following allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2009;15:1049.
3. Lalazar G, Rund D, Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. Br J Haematol. 2007;136:699.
4. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143.
5. Lau GK, He ML, Fong DY, et al. Preemptive use of lamivudine reduces hepatitis B exacerbation after allogeneic hematopoietic cell transplantation. Hepatology 2002;36:702.
6. Shibolet O, Ilan Y, Gillis S, et al. Lamivudine therapy for prevention of immunosuppressive-induced hepatitis B virus reactivation in hepatitis B surface antigen carriers. Blood 2002;100:391.
7. Huang H, Li X, Zhu J, et al. Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. JAMA 2014;312:2521.
8. Strasser SI, Myerson D, Spurgeon CL, et al. Hepatitis C virus infection and bone marrow transplantation: a cohort study with 10-year follow-up. Hepatology 1999;29:1893.
9. Peffault de Latour R, Lévy V, Asselah T, et al. Long-term outcome of hepatitis C infection after bone marrow transplantation. Blood 2004;103:1618.
10. Hogan WJ, Maris M, Storer B, et al. Hepatic injury after nonmyeloablative conditioning followed by allogeneic hematopoietic cell transplantation: a study of 193 patients. Blood 2005;103:78.
11. Peffault de Latour R, Asselah T, Lévy V, et al. Treatment of chronic hepatitis C virus in allogeneic bone marrow transplant recipients. Bone Marrow Transplant. 2005;36:709.
12. Morton AJ, Gooley T, Hansen JA, Appelbaum, et al. Association between pretransplant interferon-alpha and outcome after unrelated donor marrow transplantation for chronic myelogenous leukemia in chronic phase. Blood 1998;92:394.

3.15

An All Too Common Abdominal Catastrophe in the Transplant Patient

GAURAV TRIKHA, MD

CASE PRESENTATION

A 55-year-old man with stage IIIA immunoglobulin G kappa multiple myeloma had an elective admission for autologous hematopoietic stem cell transplant (HSCT) with high-dose melphalan as conditioning regimen. On the third day post-transplant, the patient developed abdominal pain and was found to have perforated sigmoid diverticulitis for which he underwent an exploratory laparotomy and Hartmann's procedure. Antibiotic therapy included cefepime and metronidazole. On postoperative day twelve, the patient had persistent fever with multiple temperature spikes >38.5°C, worsening diffuse abdominal pain, and a change in the consistency of his bowel movements from formed to semisolid and later to watery diarrhea. On physical exam, he was noted to be in severe distress; vital signs were as follows: temperature 38.1°C, pulse 100/minute, respirations 20/minute, and blood pressure 160/96 mm mercury. His oral mucosa was dry, the anterior abdominal wall incision was healing well, but the abdomen was distended with diffuse tenderness. His colostomy was draining watery, green-colored stool. Laboratory data showed leukocytosis of 11 300/cu mm (was neutropenic earlier) and serum creatinine of 0.80 mg/dL. Abdominal computed tomography scan showed partial small bowel obstruction (Figures 3.15.1 and 3.15.2). Stool was sent for *Clostridium difficile* polymerase chain reaction (PCR) and oral vancomycin was administered. The patient continued to have multiple temperature spikes >38.5°C, with increasing abdominal girth, nausea, and increasing colostomy output with watery, green-colored stool.

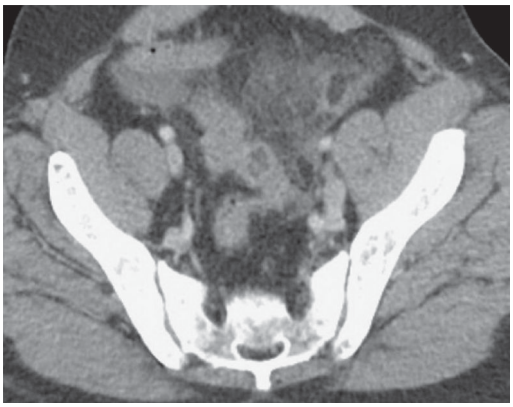


FIGURE 3.15.1: Inflammation of the sigmoid colon.

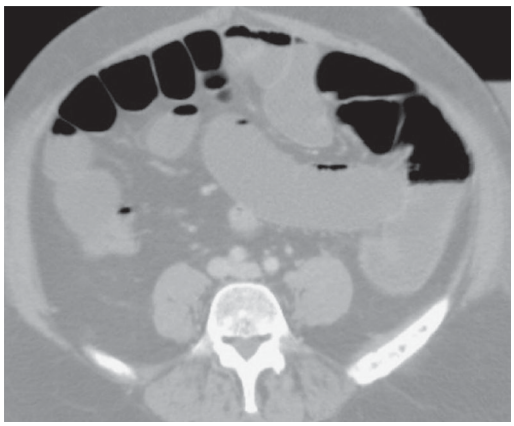


FIGURE 3.15.2: Multiple loops of minimally dilated small bowel filled with air and fluid.

DIFFERENTIAL DIAGNOSIS

Given the recent history of perforated sigmoid diverticulitis and exposure to broad-spectrum antibiotics, worsening sepsis in the setting of abdominal discomfort is concerning for an intra-abdominal leak and abscess, ischemic bowel, or antibiotic-associated infection such as *C difficile* colitis.

TREATMENT OUTCOME

Vancomycin 500 mg every six hours per nasogastric tube (NGT) was started empirically. Subsequently, stool for *C difficile* PCR test returned positive. Approximately twelve hours after starting vancomycin per NGT, fever subsided, and over the next twelve hours there was an interval decrease in the diarrhea with improving consistency of the stool. Over the next three days, white blood cell count improved and other concurrent antibiotics, cefepime and metronidazole, were discontinued.

Final Diagnosis: *Clostridium difficile* colitis

DISCUSSION

Clostridium difficile is the leading cause of infectious diarrhea among hospitalized patients and is an increasing concern in patients who are recipients of HSCT. *Clostridium difficile* infection (CDI) is defined by the presence of symptoms (usually diarrhea) and either (1) a stool test positive for *C difficile* toxin or toxigenic *C difficile* or (2) colonoscopic or histopathologic findings revealing pseudomembranous colitis [7]. Because most centers in the United States have only recently started testing via *C difficile* PCR, the actual incidence of CDI might be higher. The rate of CDI relapse after correctly administered treatment, the frequency of complications, as well as the rate of mortality remains unknown in this setting. Historically, the incidence of CDI after HSCT was 5% [1-3], but recent studies suggest an increasing incidence 9.2%–14% [4-6]. In one study, 50% of CDI occurred during the first month and 95% occurred during the first six months after HSCT. The median time to develop CDI was 25 days after HSCT (range from 3 days before transplantation to 276 days after transplantation) [4] (Figure 3.15.3). Another study showed recipients of autologous transplant developing CDI predominantly in the first month posttransplant (median time, 6.5 days; interquartile range [IQR], day –1 to day 21) and in recipients of allogeneic transplant, the median time to infection was 33 days (IQR, 5–70 days) [6].

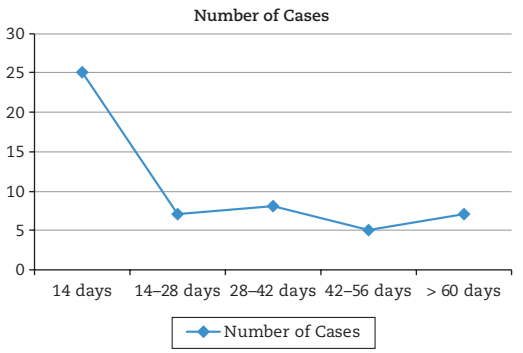


FIGURE 3.15.3: Incidence of C difficile colitis is greatest during the first month after HCT and lower thereafter.

TABLE 3.15.1. COMMON RISK FACTORS ASSOCIATED WITH DEVELOPMENT OF *CLOSTRIDIUM DIFFICILE* COLITIS

Standard Risk Factors for the Development of CDI	HSCT Recipients: Special Risk Factors for the Development of CDI
• Broad-spectrum antibiotic • Length of hospitalization • Altered integrity of the intestinal mucosa • Immunodeficiency	• Acute GVHD • Cord blood as the source of stem cells • Total body irradiation • Primary diagnosis of acute myelogenous leukemia/ myelodysplastic syndrome • Receipt of myeloablative conditioning • Vancomycin-resistant enterococci colonization

After HSCT, patients are exposed to several well recognized risk factors for the development of CDI (Table 3.15.1) [8–9]. In HSCT recipients with CDI, there were additional risk factors noted (Table 3.15.1). In one study of allogeneic recipients with CDI, pre-existing graft-versus-host disease (GVHD) was present in approximately half (18 of 39) of the cases, and most of these patients (13 of 18) had GVHD of the gastrointestinal tract [5].

Clinical expression of CDI is highly variable, and the immunocompromised status of HSCT patients limits the value and the specificity of clinical symptoms. The classic symptom complex of cramping abdominal pain, fever, and watery diarrhea with leukocytosis seen in the majority of immunocompetent patients is rarely seen in HSCT recipients, with fever and abdominal pain seen in 8%–29% and diarrhea in up to 49% [4–6].

REFERENCES

1. Cox GJ, Matsui SM, Lo RS, et al. Etiology and outcome of diarrhea after marrow transplantation: a prospective study. Gastroenterology 1994;107:1398.
2. Van Kraaij MG, Dekker AW, Verdonck LF, et al. Infectious gastro-enteritis: an uncommon cause

of diarrhoea in adult allogeneic and autologous stem cell transplant recipients. Bone Marrow Transplant. 2000;26:299.
3. Avery R, Pohlman B, Adal K, et al. High prevalence of diarrhea but infrequency of documented *Clostridium difficile* in autologous peripheral blood progenitor cell transplant recipients. Bone Marrow Transplant. 2000;25:67.
4. Willems L, Porcher R, Lafaurie M, et al. *Clostridium difficile* infection after allogeneic hematopoietic stem cell transplantation: incidence, risk factors, and outcome. Biol Blood Marrow Transplant. 2012;18:1295.
5. Chopra T, Chandrasekar P, Salimnia H, et al. Recent epidemiology of *Clostridium difficile* infection during hematopoietic stem cell transplantation. Clin Transplant. 2011;25:E82.
6. Cohen S, Gerding D, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31:431.
7. Issa M, Ananthakrishnan AN, Binion DG. *Clostridium difficile* and inflammatory bowel disease. Inflamm Bowel Dis. 2008;14:1432.
8. Anand A, Glatt AE. *Clostridium difficile* infection associated with antineoplastic chemotherapy: a review. Clin Infect Dis. 1993;17:109.
9. Gorschlu€ter M, Glasmacher A, Hahn C, et al. *Clostridium difficile* infection in patients with neutropenia. Clin Infect Dis. 2001;33:786.

3.16

Female Troubles After Transplantation

JACK HSU, MD

CASE PRESENTATION

You are asked to see a 44-year-old woman who is complaining of painful urination. She was diagnosed with Stage II diffuse large B-cell non-Hodgkin's lymphoma and was treated with six cycles of rituximab, cyclophosphamide, doxorubicin, prednisone, and vincristine chemotherapy and was found to be in complete remission. Her disease relapsed one year later, and she was subsequently treated with two cycles of rituximab, iphosphamide, carboplatin, etoposide chemotherapy and found to be in complete remission. She underwent an autologous transplantation without any complications and was observed routinely until two years later when she relapsed. She received two cycles of bendamustine plus rituximab chemotherapy followed by a matched-related allogeneic transplant after cyclophosphamide/total body irradiation conditioning regimen. Postgraft immunosuppression consisted of tacrolimus with a short course of methotrexate of four planned doses. She engrafted in a timely fashion and is currently forty-three days after transplant. Two days ago, she noted pain on urination. She does not note any fevers or blood in urination. The pain gradually became more severe and is associated with a sensation of fullness in the bladder and urinary frequency. There was no evidence of graft-versus-host (GVHD) disease on exam, her creatinine was normal, platelet count was normal, and at her last clinic visit, she was found to have a therapeutic tacrolimus level and negative cytomegalovirus (CMV) DNA titer by polymerase chain reaction (PCR).

DIFFERENTIAL DIAGNOSIS

The sudden onset of painful micturition is suspicious for either an infectious etiology or hemorrhagic cystitis (HC). The lack of fever does not rule out bacterial infections because she is still relatively early in her transplant course and is on immunosuppressive medications. Viral etiologies, such as adenovirus, CMV, or BK virus (BKV), should be considered. Bacterial urine culture, urine analysis, and PCR test for BK, CMV, and adenovirus should be sent to help distinguish between the possible etiologies. With her sensation of fullness, a bladder ultrasound should be considered to look for urinary retention or obstructive uropathy.

CLINICAL COURSE

Urinalysis demonstrated microscopic hematuria. Urine cultures were negative for bacteria. Polymerase chain reaction testing for urinary viruses was negative for CMV, adenovirus, but it was positive for >12 million copies of polyoma BKV. A bladder ultrasound found mild urinary retention but no obstruction.

Final Diagnosis: Hemorrhagic cystitis with polyoma BK virus infection

TREATMENT AND FOLLOW-UP

The patient was encouraged to increase oral hydration to prevent development of clots and obstruction. Therapy was started with ciprofloxacin in an attempt to suppress BKV replication. She was closely observed in the clinic, where her pain and hematuria eventually resolved after several weeks.

DISCUSSION

Hemorrhagic cystitis is a clinical syndrome characterized by painful hematuria due to hemorrhagic inflammation of the urinary bladder mucosa. Manifestations range from microscopic hemorrhage to severe bladder hemorrhage leading to clot formation and urinary obstruction [1]. In the HSCT population, HC can be divided into pre- and postengraftment subtypes [2]. Pre-engraftment HC is related to uroepithelial toxicity from the conditioning regimen. This is primarily related to either cyclophosphamide or irradiation in the conditioning regimen. Other risk factors include prior pelvic irradiation [3]

and use of busulfan [4]. Pre-engraftment HC is generally mild and self-limiting and does not pose significant risk to patients.

However, postengraftment HC often results in increased morbidity and prolonged hospitalization after transplantation. It generally occurs one month after engraftment and may last for weeks to months [5]. Risk factors of postengraftment HC include allogeneic stem cell transplant, unrelated donors, busulfan containing myeloablative conditioning regimens, and GVHD. Frequently, viral particles in the urine are identified with the onset of HC, implying viral infection may have a pathogenic role. The most common virus associated with HC is the polyoma BKV. Other viruses that have been associated with HC include adenovirus and CMV.

The polyoma BKV is a nonenveloped DNA virus of the genus *Polyomaviridae*. Over 80% of the adult population has been exposed to BKV. It has been associated with neoplastic transformation, pneumonitis, HC, and even multiorgan failure [6]. Primary infection in healthy individuals is mostly asymptomatic, with the virus remaining dormant in the uroepithelum. In the immunocompromised population, it is felt that most infections from BKV in the HSCT setting are generally from reactivation of latent virus.

Association between BKV and HC has been extensively reported based on the detection of viral particles in the urine by cytology, electron microscopy, and PCR techniques. However, asymptomatic BKV shedding occurs frequently, both in immunocompromised and normal hosts. It is still unclear whether this association is causal or coincidental. Proponents of a causal link theorize the combination of mucosal damage and immunosuppression that occurs in transplant recipients lead to conditions that favor viral reactivation and result in an alloimmune attack by donor lymphoid cells against BKV antigens, resulting in continued mucosal damage [7].

There are no effective therapies for the treatment of postengraftment HC. Treatment is generally supportive with use of phenazopyridine and opiates to relieve the painful hematuria. In all cases, correction of thrombocytopenia and coagulopathy can ameliorate the severity of hematuria. If a specific infectious agent is identified, additional therapy can be directed towards the virus. Cidofovir is active against BKV, CMV, and adenovirus; however, it is associated with severe myelotoxicity and nephrotoxicity, which limits its use in the transplant population. Ganciclovir can be used in CMV-related HC; however, it causes myelosuppression. There is evidence of quinolone antibiotics suppressing BKV replication in vitro; however, their activity is modest and may be more appropriate in the prophylactic rather than therapeutic setting [8]. Persistent, gross hematuria can be treated by bladder irrigation to prevent obstruction by blood clots. Urology should also be consulted in severe cases for consideration of cystoscopy and cauterization. Sclerotherapy, cystectomy, and vesical artery embolization may be considered in refractory, life-threatening situations.

REFERENCES

1. Bedi A, Miller CB, Hanson JL, et al. Association of BK virus with failure of prophylaxis against hemorrhagic cystitis following bone marrow transplantation. J Clin Oncol. 1995;13:1103.
2. Leung AY, Mak R, Lie AK, et al. Clinicopathological features and risk factors of clinically overt haemorrhagic cystitis complicating bone marrow transplantation. Bone Marrow Transplant. 2002;29:509.
3. Sell A, Bertelsen K, Andersen JE, et al. Randomized study of wholeabdomen irradiation versus pelvic irradiation plus cyclophosphamide in treatment of early ovarian cancer. Gynecol Oncol. 1990;37:367.
4. Tsuboi K, Kishi K, Ohmachi K, et al. Multivariate analysis of risk factors for hemorrhagic cystitis after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2003;32:903.
5. McCarville MB, Hoffer FA, Gingrich JR, Jenkins JJ 3rd. Imaging findings of hemorrhagic cystitis in pediatric oncology patients. Pediatr Radiol. 2000;30:131.
6. Hirsch HH, Steiger J. Polyomavirus BK. Lancet Infect Dis. 2003;3:611.
7. Leung AY, Yuen KY, Kwong YL. Polyoma BK virus and haemorrhagic cystitis in haematopoietic stem cell transplantation: a changing paradigm. Bone Marrow Transplant. 2000;36:929.
8. Leung AY, Chan MT, Yuen KY, et al. Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. Clin Infect Dis. 2005;40:528.

3.17

If at First You Do Not Succeed, Try, Try, Again

JOHN R. WINGARD, MD

CASE PRESENTATION

A 42-year-old man underwent allogeneic hematopoietic stem cell transplantation (HSCT) for recurrent acute myelogenous leukemia from a 6/6 human leukocyte antigen-matched sibling donor following cyclophosphamide plus total body irradiation conditioning. Postgraft immunosuppression consisted of tacrolimus and methotrexate. On day seven, the patient developed a neutropenic fever that was treated with cefepime. After engraftment, he developed acute graft-versus-host disease (GVHD) of skin and liver, which was treated with prednisone at a dose of 2 mg/kg per day. Persistent hyperbilirubinemia required continuation of high-dose prednisone, and after one week antithymocyte globulin was added. Weekly plasma cytomegalovirus (CMV) polymerase chain reaction (PCR) testing had been negative; however, the quantitative PCR showed rising levels, initially 500 copies/mL, later 1800 copies/mL. The patient was placed on oral valganciclovir. After one week of therapy, the PCR had risen to 4200 copies/mL. The patient was placed on intravenous ganciclovir. The PCR rose to 9400 copies/mL one week later. You are consulted.

DIFFERENTIAL DIAGNOSIS

Possible explanations for rising CMV viremia despite ganciclovir are antiviral resistance and inadequate host response due to profound immunosuppression.

TREATMENT AND FOLLOW-UP

You recommended antiviral resistance testing and reduction of immunosuppressive therapy as judiciously as possible. While awaiting test results, you recommend a change of therapy to foscarnet. The CMV PCR continues to rise for an additional week, peaking at 14 000 copies/mL, then started to fall, and after four weeks was negative. The virus was found to have no resistance mutations.

Final Diagnosis: Refractory cytomegalovirus viremia due to host immunosuppression

DISCUSSION

A true increase or decrease in the viral load is generally regarded as >0.5 $\log_{10}$—approximately a three-fold difference [1]. Failure of a fall in the CMV DNA level during the first week or two after institution of ganciclovir is not uncommon [2, 3], occurring in 30%–40% of patients. Rises by two-fold in the CMV level in one study [3] occurred in nearly 40% and by five-fold in almost 30%. In multivariate analysis, the use of high-dose steroids (prednisone >1 mg/kg per day) was highly associated with the likelihood of increasing CMV viremia. Antiviral susceptibility testing indicated resistance was rarely the cause of rising levels (<5%). Cytomegalovirus disease occasionally occurred in some patients, but it mostly occurred in patients whose ganciclovir dosing was dropped from 5 mg/kg twice daily to once daily. These findings are consistent with the observations in this case, indicating host failure, rather than antiviral failure due to viral resistance, accounting for the rising viral levels as with most HSCT patients with refractory CMV viremia. Antiviral resistance to ganciclovir can occur. The most common setting is with patients receiving prolonged courses of ganciclovir and in those whose T-cell immunity before and after HSCT is profoundly suppressed. An example of this would be a patient with T-cell lymphoma who had been exposed to multiple T-cell immunosuppressants (purine analogs and corticosteroids) before HSCT and after HSCT, multiple T-cell immunosuppressive drugs to treat refractory GVHD; such a patient is a setup for challenges to control the CMV infection. Children with immunodeficiency syndromes and recipients of mismatched or cord blood transplants are also groups of patients who are at greater risk for persistent CMV infections [4, 5].

Antiviral resistance occurs most commonly by mutations in the UL97 gene region [6, 7], but resistance can also occur in the U54 gene (DNA polymerase) region as well. Foscarnet is the preferred therapy for resistant CMV infection [8]. Drugs with alternate mechanisms of action are needed. One investigational option for resistant CMV infection is the use of infusions of CMV-specific T cells, which have proven to be safe, and phase 2 studies suggest benefit [9].

REFERENCES

1. Boeckh M, Nichols G, Papanicolaou G, et al. Cytomegalovirus in hematopoietic stem cell transplant recipients: current status, known challenges, and future strategies. Biol Blood Marrow Transplant. 2003;9:543.
2. Almyroudis NG, Jakubowski A, Jaffe D, et al. Predictors for persistent cytomegalovirus reactivation after T-cell-depleted allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis. 2007;9:286.
3. Nichols WG, Corey L, Gooley T, et al. Rising pp65 antigenemia during preemptive anticytomegalovirus therapy after allogeneic hematopoietic stem cell transplantation: risk factors, correlation with DNA load, and outcomes. Blood 2001;97:867
4. Eckle T, Prix L, Jahn G, et al. Drug-resistant human cytomegalovirus infection in children after allogeneic stem cell transplantation may have different clinical outcomes. Blood 2000;96: 3286.
5. Eckle T, Lang P, Prix L, et al. Rapid development of ganciclovir-resistant cytomegalovirus infection in children after allogeneic stem cell transplantation in the early phase of immune cell recovery. Bone Marrow Transplant. 2002;30:433.
6. Emery VC, Griffiths PD. Prediction of cytomegalovirus load and resistance patterns after antiviral chemotherapy. Proc Natl Acad Sci U S A 2000;97:8039.
7. Chou S, Guentzel S, Michels R et al. Frequency of UL97 phosphotransferase. Mutations related to ganciclovir resistance in clinical cytomegalovirus isolates. J Infect Dis. 1995;172:239.
8. Razis E, Cook P, Mittelman A, Ahmed T. Treatment of ganciclovir resistant cytomegalovirus with foscarnet: a report of two cases occurring after bone marrow transplantation. Leuk Lymphoma 1994;12:477.
9. Leen AM, Bollard CM, Mendizabal AM, et al. Multicenter study of banked third-party virus-specific T cells to treat severe viral infections after hematopoietic stem cell transplantation. Blood 2013;121:5113.

3.18

An Enemy Awakened

MAXIM NORKIN, MD

CASE PRESENTATION

Chief Complaint

A 59-year-old female developed persistent fever and rash at the time of neutrophil engraftment after an umbilical cord blood transplant.

The oncologic history dates back six years when she was diagnosed with low-grade follicular lymphoma. She had initially been under clinical surveillance for two years and then received multiple lines of chemotherapy due to progressive and refractory disease. The first-line of therapy included four cycles of cisplatin, doxorubicin, cyclophosphamide, and etoposide followed by an autologous vaccine therapy as a part of clinical trial. The patient achieved a complete remission lasting for two years and upon progression, she was enrolled in another clinical trial using a combination of monoclonal antibodies galiximab and rituximab, but with an inadequate response. Next, she received therapy with rituximab, cyclophosphamide, vincristine, and prednisone and achieved a second complete remission; however, a subsequent relapse was treated with six cycles of bendamustine and rituximab. This therapy led to a partial response, and she underwent double umbilical cord transplant with a nonmyeloablative conditioning using cyclophosphamide, fludarabine, and total-body irradiation. The patient tolerated the conditioning regimen well, but she experienced a slow neutrophil engraftment despite daily injections of filgastrim, and early signs of absolute neutrophil count (ANC) engraftment only were noted on day +32. She received antimicrobial prophylaxis with fluconazole, levofloxacin, and valacyclovir while her ANC remained <500 cells/mm^3. The patient developed neutropenic fever and rapidly progressive generalized pruritic rash on day +35. She reported no chills, cough, dyspnea, hemoptysis, chest wall pain, abdominal pain or bowel symptoms, no urinary problems, or tenderness around the central line.

On physical examination, the temperature was 39.2°C, the blood pressure was 102/45 mm Hg, the pulse 112 beats per minute, and the respiratory rate 12 breaths per minute. The oxygen saturation was 97% on ambient air. The skin examination revealed a generalized palpable purpura with round 1–3 mm solitary and coalescent lesions (Fig. 3.18.1). Rash involved mostly both lower extremities and lower abdomen. The remainder of the physical examination was normal. There was no tenderness or erythema at the central line insertion site. Laboratory data revealed normal serum levels of electrolytes, except for mild hyponatremia with a sodium at 131 mEq/L, normal creatinine, and total protein. Her complete blood count was significant for white blood cell count 670 cells/mcL, hemoglobin 7.8 g/dL, platelet count 21 000/mmol, ANC 350 cells/mcL, and absolute lymphocyte count 470 cells/mcL. Liver function tests showed alanine aminotransferase 125 U/L, aspartate aminotransferase 160 U/L, alkaline phosphatase 123 U/L, total bilirubin 1.5 mg/dL, and direct bilirubin 1.1 mg/dL. Levofloxacin was discontinued, and the

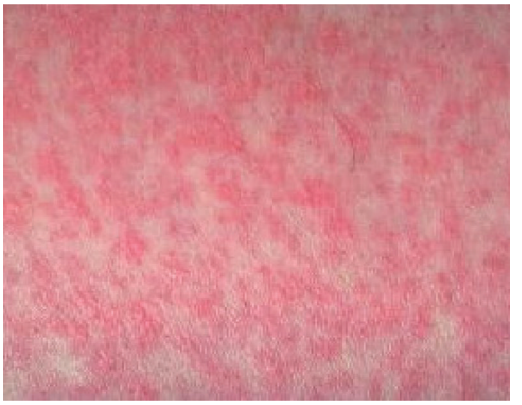


FIGURE 3.18.1: Picture of the skin showing purpura with round 1–3 mm solitary and coalescent lesions.

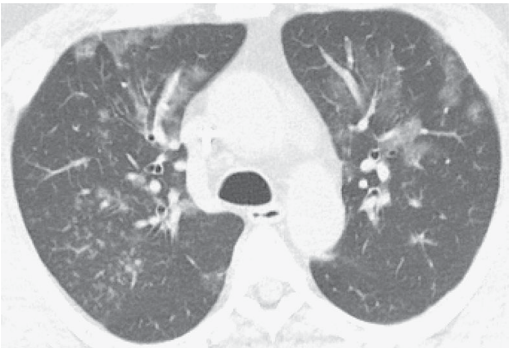


FIGURE 3.18.2: Cheat CT showing mutifocal areas of ground-glass opacity.

patient was started on cefepime for neutropenic fever, which later was changed to piperacillin tazobactam, because she developed an allergic reaction to cefepime. Chest radiograph was negative. Initial blood and urine cultures were negative as well. Despite broad empiric antimicrobial therapy, the patient continued having persistent fevers and worsening rash and later developed abdominal pain with loose, nonbloody diarrhea. Computed tomography (CT) scan of the chest, abdomen, pelvis was obtained and showed multifocal areas of ground-glass opacity involving all lobes and most prominent in the right upper, left lower lobes and mild thickening of the descending colon (Fig. 3.18.2).

DIFFERENTIAL DIAGNOSIS

Both noninfectious and infectious causes should be considered. Infectious causes include bacterial infections, particularly with Gram-positive organisms, invasive fungal, and viral infections with either reactivation of latent viruses or new onset viral infection. Noninfectious causes include pulmonary edema, pulmonary hemorrhage, toxicity from the conditioning regimen, engraftment syndrome, acute graft-versus-host disease (GVHD), drug toxicity, and relapsed malignancy.

Case Continued

Further diagnostic studies included bacterial and fungal blood cultures, serologic tests for *Aspergillus* and parasites, as well as polymerase chain reaction (PCR) analysis of nasopharyngeal samples for respiratory viral pathogens and of blood for cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), Epstein-Barr virus, and varicella-zoster virus. A stool sample was sent for *Clostridium difficile* toxin test, bacterial, and viral cultures. All of these studies returned negative with the exception of HHV-6 PCR, which detected 128 000 copies/mL. After initiation of foscarnet, fever quickly subsided, the rash disappeared on day six, and HHV-6 viremia became undetectable on day ten of therapy. Foscarnet was discontinued after two undetectable HHV-6 measurements, and HHV-6 level was followed by serial PCRs on weekly basis. Repeat chest CT showed resolution of ground-glass opacities and no additional abnormalities.

DISCUSSION

Persistent fever not responding to broad-spectrum antibiotics in patients at the time of neutrophil engraftment raise suspicion for infection by fungal or viral pathogens. Clinical and radiologic signs of localized infectious processes, such as pulmonary infiltrates, skin and perineal cellulitis/abscesses, or colitis may become clinically apparent at the time of neutrophil recovery when leukocytes start to enter infected areas to mount an inflammatory response. Presence of persistent fever, generalized purpura, leukopenia, and serum transaminitis in the early posttransplant period raises suspicion for generalized infection, particularly a viral process, or acute GVHD. Engraftment syndrome is less likely in this patient given the neutrophil recovery two weeks earlier, absence of diffuse erythrodermatous skin rash, and lack of clinical signs of noncardiogenic pulmonary edema. The patient did not receive any new medications preceding these clinical symptoms, which makes drug-induced fever and rash less likely. She had no clinical signs of recurrent malignancy and never experienced similar symptoms in the past, which make the diagnosis of recurrent malignancy also unlikely.

Primary HHV-6 infection typically occurs at an early age, and the virus continues to be laten, but can reactivate when immune surveillance is compromised. In hematopoietic stem cell transplantation (HSCT) recipients, HHV-6 reactivation often occurs close to neutrophil engraftment [1] and can be detected by PCR in 56% of HSCT recipients at a median of twenty-three days. The incidence of detectable HHV-6 viremia is even higher (69%) in recipients of umbilical cord blood [2]. Human herpesvirus 6 reactivation is often associated with unexplained fever and rash; high-level HHV-6 viral load (≥25 000 copies/mL) can lead to the development of culture-negative pneumonitis [2]. Other clinical presentations of HHV-6 reactivation include myelosuppression, encephalitis, gastroduodenitis, and CMV

reactivation [3, 4]. Treatment options in HSCT recipients with HHV-6 reactivation include foscarnet, ganciclovir, or cidofovir, which lead to resolution of HHV-6 viremia in the majority of patients within two weeks. The impact of HHV-6 viremia on clinical outcomes is not entirely clear because survival at three months is similar in treated compared with untreated patients with HHV-6 viremia [2].

REFERENCES

1. Ogata M, Kikuchi H, Satou T, et al. Human herpesvirus 6 DNA in plasma after allogeneic stem cell transplantation: incidence and clinical significance. J Infect Dis. 2006;193:68.
2. Betts BC, Young JA, Ustun C, et al. Human herpesvirus 6 infection after hematopoietic cell transplantation: is routine surveillance necessary? Biol Blood Marrow Transplant. 2011;17:1562.
3. Hentrich M, Oruzio D, Jager G, et al. Impact of human herpesvirus-6 after haematopoietic stem cell transplantation. Br J Haematol. 2005;128:66.
4. Vu T, Carrum G, Hutton G, et al. Human herpesvirus-6 encephalitis following allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant. 2007;39:705.

3.19

A Heat Wave

JOHN R. WINGARD, MD

CASE PRESENTATION

A 52-year-old man underwent an allogeneic hematopoietic stem cell transplantation for recurrent lymphoma from a 6/6 human leukocyte antigen-matched sibling donor following cyclophosphamide plus total body irradiation conditioning. He was started on levofloxacin, acyclovir, and fluconazole prophylaxis. Postgraft immunosuppression consisted of tacrolimus and methotrexate. On day four, he developed neutropenic fever, which was treated with cefepime. Cultures were negative, but the patient had persistent fever. Chest x-ray and repeated blood and urine cultures were negative. The central venous catheter site did not demonstrate inflammation. The remainder of the exam failed to demonstrate any signs suggestive of an infectious focus. On day twelve (eighth day of fever), you are consulted.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for persistent or recurrent neutropenic fever includes bacterial infection due to organism resistant to the antibiotics (e.g. Gram-positive bacteria or an extended-spectrum β-lactamase (ESBL)-resistant Gram-negative organism), a viral pathogen (e.g. cytomegalovirus [CMV], adenovirus, or a respiratory virus), or fungus (an azole-resistant *Candida* or *Aspergillus* or other mold). Another consideration includes a noninfectious etiology such as a drug fever.

TREATMENT AND FOLLOW-UP

You recommended obtaining blood cultures, serum β-glucan and galactomannan test, and a chest computed tomography (CT) scan to evaluate for fungal infection. You order polymerase chain reaction tests for CMV and adenovirus in blood. The serum galactomannan assay is negative. The chest CT demonstrates a small nodular lesion (Figure 3.19.1).

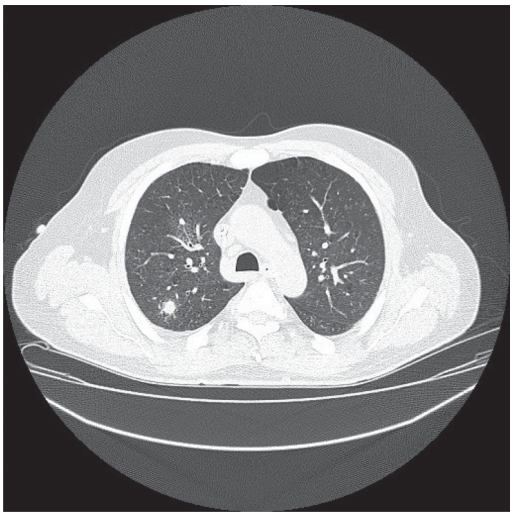


FIGURE 3.19.1: CT scan demonstrates a small dense nodule in the peripheral of the lung. The nodule in the right lung has a halo surrounding it.

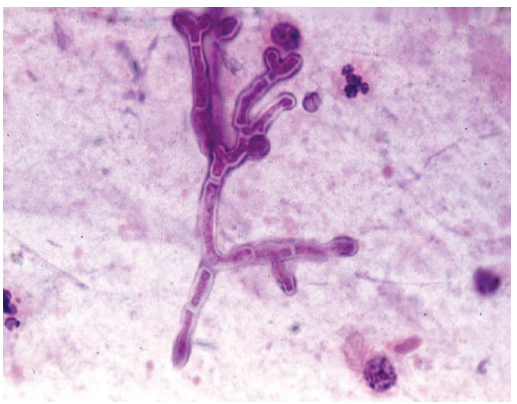


FIGURE 3.19.2: Branching hyphae are noted in BAL fluid.

You perform bronchoscopy and hyphae are noted on a sample of bronchoalveolar lavage fluid (BAL) (Figure 3.19.2).

You initiate voriconazole for aspergillosis. Culture subsequently grew *Aspergillus fumigatus* and the BAL fluid was positive for galactomannan. Voriconazole was initiated and the fever gradually abated.

Final Diagnosis: Persistent fever due to pulmonary aspergillosis

DISCUSSION

Persistent or recurrent neutropenic fever is a common problem faced by clinicians [1]. The diagnostic assessment should be guided by identifying occult sites of infection. Careful history and physical exam should emphasize oral, sinus, lung, skin, catheter, intra-abdominal, and perianal sources of infection. Cultures are the key tests to detect antibiotic resistant bacteria. Surveillance cultures of stool or throat can sometimes be helpful in identifying patients at risk for infection by the resistant colonizing organism, such as vancomycin-resistant enterococci or ESBL producing Gram-negative organisms. However, empiric antibiotics targeting colonizing organisms is controversial and should be avoided in general, except in patients who show signs of sepsis or are rapidly deteriorating. In the past, fungal infections accounted for 15%–30% of persistent neutropenic fever [1]. However, today with routine use of fluconazole [2] or other antifungal prophylaxis, *Candida* infections are much less likely. However, there is a small possibility that less susceptible non-*albicans* species, principally *Candida krusei* and *Candida glabrata*, can occur and be difficult to detect. The β-glucan test can be helpful and is more sensitive than fungal blood cultures for *Candida* [3]. More likely is the possibility of a pulmonary mold infection. Most mold infections are due to *Aspergillus*, with approximately 10% due to the agents of mucormycosis, and a small number due to *Fusarium, Scedosporium*, and other infrequent molds. The serum galactomannan assay is helpful in the diagnosis of aspergillosis [4] but not mucormycosis. Empiric antifungal therapy is an age-old accepted practice and is still widely used. Its disadvantage is that most individuals on antifungal prophylaxis are not infected by a fungus and do not need it. More recently, the routine use of twice weekly galactomannan and β-glucan testing has been advocated as an alternative with a positive test result used to trigger focused antifungal therapy [5, 6]. This latter strategy requires further clinical study. It is important to note that a chest CT scan is more sensitive to detect pulmonary infiltrates than chest radiograph and is preferred [7]. Because the characteristics of the infiltrates are helpful but not diagnostic, further evaluation by bronchoscopy is advisable. In this case, the BAL microscopy and galactomannan assays were diagnostic. Several studies and meta-analyses indicate the utility of BAL galactomannan testing [8, 9]. Important to note is that the BAL galactomannan may be positive even when the serum galactomannan is negative.

REFERENCES

1. Wingard JR, Leather HL. Empiric antifungal therapy for the neutropenic patient. Oncology (Williston Park) 2001;15:351.
2. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143.
3. Ostrosky-Zeichner L, Alexander BD, Kett D, et al. Multicenter clinical evaluation of the (1-->3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. Clin Infect Dis. 2005;41:654.
4. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis. 2006;42:1417
5. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. Clin Infect Dis. 2005;41:1242.
6. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guidelines for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis. 2011;52:427.
7. Wingard JR, Heimenz JH, Jantz M. How I manage pulmonary nodular lesions and nodular infiltrates in patients with hematologic malignancies or undergoing hematopoietic cell transplantation. Blood 2012;120:1791.
8. Zou M, Tang L, Zhao S, et al. Systematic review and meta-analysis of detecting galactomannan in bronchoalveolar lavage fluid for diagnosing invasive aspergillosis. PLoS One. 2012;7:e43347
9. Heng SC, Morrissey O, Chen SC, et al. Utility of bronchoalveolar lavage fluid galactomannan alone or in combination with PCR for the diagnosis of invasive aspergillosis in adult hematology patients: a systematic review and meta-analysis. Crit Rev Microbiol. 2015;41:124.

3.20

A Bellyache Seven Months After Transplant

JOHN R. WINGARD, MD

CASE PRESENTATION

A 56-year-old-man underwent allogeneic hematopoietic stem cell transplantation (HSCT) for acute myelogenous leukemia from an 8/8 human leukocyte antigen-matched sibling donor following busulfan plus cyclophosphamide conditioning. Postgraft immunosuppression consisted of tacrolimus and methotrexate. After engraftment, he developed acute graft-versus-host-disease (GVHD) of the skin, which was controlled with high-dose prednisone, which was tapered after initial control. He had a flare of GVHD that required reinstitution of high-dose prednisone. The taper was performed more slowly and was discontinued four months after transplant. Tacrolimus dose was tapered, and he discontinued immunosuppressive therapy at six months with no signs of active GVHD. He had been given trimethoprim-sulfamethoxazole for pneumocystis pneumonia prophylaxis and acyclovir for zoster prophylaxis. He stopped both treatments at six months when his immunosuppressive therapy was stopped. He was doing well but presented to the emergency room seven months after transplant with sudden onset of diffuse abdominal pain. On exam, his temperature was 38.4°C, but other vital signs were normal. He had no rash or skin lesions. His abdomen was diffusely tender and there was guarding. Bowel sounds were hypoactive. Complete blood count showed leukocytosis with a shift to the left. Blood chemistries showed a dramatic elevation of serum transaminases and elevated amylase. Serum bilirubin was only mildly elevated. Blood cultures were sent and broad-spectrum antibiotics were started. Computed tomography scans of abdomen and pelvis were ordered. You are consulted.

DIFFERENTIAL DIAGNOSIS

The differential for abdominal pain after HSCT is wide and includes all the same etiologies that one might see in noncompromised patients. In particular, with fever, acute viral hepatitis, acute cholecystitis, pyelonephritis, enterocolitis, diverticulitis, and pancreatitis should be considered. One serious threat, which is rare, is visceral zoster.

TREATMENT AND FOLLOW-UP

You recommended intravenous acyclovir while evaluation proceeded. Computed tomography scan was performed. No signs of bile duct or ureteral obstruction were noted. There was no evidence of a perforated viscus. No diverticuli were seen. No findings consistent with an abscess were noted. Some stranding in the pancreatic bed was noted. Hepatitis serologies were negative. Cutaneous vesicles developed on the third hospital day. The hepatic enzyme levels stabilized and pancreatic enzyme levels normalized over the ensuing seven days. Abdominal pain improved and the patient was discharged. Acyclovir at prophylaxis doses were continued.

Final Diagnosis: Visceral zoster

DISCUSSION

Most cases of varicella-zoster virus (VZV) infection after HSCT are reactivation of latent infection. Historically, approximately 40% of seropositive patients developed zoster [1, 2]. Reactivation occurs at a median of five months, much later than with other herpesvirus infections, such as herpes simplex virus (three weeks) and cytomegalovirus (two months). Dermatomal zoster is the most common manifestation. Dissemination can occur in 30%–40% of patients. Cutaneous dissemination is the most common form of dissemination. Pneumonia is the most common form of visceral VZV disease.

Rarely, intra-abdominal VZV infection, manifested as fulminant hepatitis, gastritis, or pancreatitis, can occur and lead rapidly to shock and death [3]. In one series, onset was approximately

nine months after transplant [4] and many had chronic GVHD. Cutaneous vesicular lesions did not appear in most for several days after abdominal pain (median three days). Presumptive antiviral therapy was very effective with most patients surviving, in contrast to delayed initiation (after appearance of the cutaneous vesicles).

Prophylaxis with acyclovir (or valacyclovir) is effective in preventing reactivation of VZV infection. Consensus guidelines recommend twelve months of prophylaxis [5]. Shorter courses of prophylaxis demonstrate protection during prophylaxis, but recurrences occur after discontinuation at similar cumulative rates to patients not given prophylaxis [6]; in contrast, twelve months of prophylaxis has been associated with fewer cumulative infections [7, 8]. This patient discontinued his prophylaxis at six months, whereas twelve months would have been much preferred.

REFERENCES

1. Locksley RM, Flournoy N, Sullivan KM, Meyers JD Infection with varicella-zoster virus after marrow transplantation. J Infect Dis. 1985;152:1172.
2. Atkinson K, Meyers JD, Storb R, et al Varicella-zoster virus infection after marrow transplantation for aplastic anemia or leukemia. Transplantation. 1980;29:47.
3. Schiller GJ, Nimer SD, Gajewski JL, Golde D. Abdominal presentation of varicella-zoster infection in recipients of allogeneic bone marrow transplantation. Bone Marrow Transplant. 1991;7:489.
4. Doki N, Miyawaki S, Tanaka M. et al. Visceral varicella zoster virus infection after allogeneic stem cell transplantation. Transpl Infect Dis. 2013;15:314.
5. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplant recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143.
6. Ljungman P, Wilczek H, Gahrton G, et al. Long-term acyclovir prophylaxis in bone marrow transplant recipients and lymphocyte proliferation responses to herpes virus antigens in vitro. Bone Marrow Transplant. 1986;1:185.
7. Boeckh M, Kim HW, Flowers ME, et al. Long-term acyclovir for prevention of varicella zoster virus disease after allogeneic hematopoietic cell transplantation—a randomized double-blind placebo-controlled study. Blood. 2006;107:1800.
8. Erard E, Guthrie KA, Varley C, et al. One-year acyclovir prophylaxis for preventing varicella-zoster virus disease after hematopoietic cell transplantation: no evidence of rebound varicella-zoster virus disease after drug discontinuation. Blood. 2007;110:3071.

SECTION 4

Infections in Patients Receiving Immunosuppressive Drugs

EMILY A. BLUMBERG

Introduction: Infections in Patients Receiving Immunosuppressive Drugs

EMILY A. BLUMBERG, MD

Immunosuppressive medications are a mainstay of treatment for diverse immunologically mediated conditions. The impact of these medications on the risk for infection is variable and sometimes difficult to determine. Many of the recipients of these drugs have underlying conditions that independently increase their risk for diverse infections, including those due to opportunistic pathogens. Immunosuppressive agents can be divided into a heterogeneous set of classes with unique effects on the immune system; the risks for infections reflect the specific immunological perturbation associated with the medication. The degree of immune dysregulation and specific risk may vary over the duration of administration; notably, this can outlast the specific dosing period. Finally, these medications are often administered in combination, complicating the assessment of infection risk associated with individual medications.

The list of disease-modifying drugs (DMARDS) includes medications that have been used for decades (conventional DMARDs including glucocorticoids and cytotoxic agents) and the newer biologic therapies. The latter group comprises agents that target cytokine expression (tumor necrosis factor [TNF] blockers, anti-interleukin agents), those targeting B lymphocytes, and those affecting T-cell function. It is notable that agents in the same class may have diverse effects both in terms of the specific disease associations as well as the chronology of infection. In many instances, patients who fail to respond to a conventional DMARD will then receive a biologic agent, potentially increasing the risk for infection due to additive and synergistic immunologic effects; the diversity of underlying diseases further complicates this assessment. Because the biological agents appear to have a more profound impact on infection risk than conventional DMARDs, these chapters will primarily focus on infections seen more frequently in recipients of those medications.

The most extensively studied biologic agents are the TNF-α blockers. These agents have been available in the United States since the release of infliximab in 1998, and the risks for infection have been identified both through clinical trials as well as postmarketing surveillance. Because TNF is critical for both differentiation and activation of macrophages, recruitment of inflammatory cells, activation of phagosomes, and granuloma formation and maintenance, these agents have been associated with an increase in infections associated with granuloma formation and intracellular pathogens, including mycobacteria, mycoses, listeria, leishmania, malaria, herpes zoster, and hepatitis B. Pharmacodynamics and binding kinetics are important cofactors that determine the likelihood of developing specific infections. Some TNF-α blockers (infliximab, adalimumab, and golimumab) bind to both soluble and cell surface TNF and have a more durable effect with a greater risk of reactivation of or severe infection due to these pathogens. Other agents bind more specifically to fragment antigen (Fab) (certolizumab) or to the soluble receptor (etanercept), resulting in shorter, more limited anti-TNF activity with reduced infection-associated risk.

Agents with anti-interleukin (IL)-1 activity (anakinra, rilonacept) inhibit binding to IL-1, an important component of the febrile reaction to infection, inhibiting B-cell activation, the induction of IL-2, and cytokine (TNF-γ, IL-6, and IL-8) secretion. These medications have been associated with a small increase in serious bacterial infections.

T-cell function may be inhibited by blocking costimulation (abatacept), T-cell migration (natalizumab), or binding to CD2 receptors on T lymphocytes (alefacept). The impact on infection risk varies with the medication because the impact on T-cell function differs with each medication. Natalizumab has been associated with the

rare development of progressive multifocal leukoencephalopathy. Possibly because alefatacept does not affect naive T-cell responses, inhibit T cell-dependent humoral responses, or responses to recall antigens, serious infections do not appear to be increased and opportunistic infections are rare.

Rituximab is an example of a B cell active agent. More frequently used for the treatment of lymphomas than immunologic disorders, it is a human chimeric monoclonal that depletes B lymphocytes for six to nine months, with limited impact on cellular immunity and relative preservation of immunoglobulin levels. Nevertheless, some opportunistic and serious infections have been reported, especially progressive multifocal leukoencephalopathy, mycobacterial infections, disseminated varicella, and reactivation of hepatitis B.

Currently, guidelines have been published recommending specific preventive measures to limit the likelihood that these immunosuppressive agents will be associated with infection. These guidelines are based on case reports and series and clinical trials and specify patient screening for latent infections (e.g. tuberculosis), timely immunizations, and prophylactic antimicrobials (e.g. for *Pneumocystis jirovecii* prevention and to prevent hepatitis B reactivation). Unfortunately, there are no large-scale prospective trials to specifically categorize risk; consequently, all recommendations are based on lower-grade evidence. Future study will be important to develop algorithms to define risk and specify appropriate preventive interventions.

REFERENCES

1. Koo S, Marty FM, Baden LT. Infectious complications associated with immunomodulating biologic agents. Infect Dis Clin N Am. 2010;24:285.
2. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275.
3. Novosad SA, Winthrop KL. Beyond tumor necrosis factor inhibition: the expanding pipeline of biologic therapies for inflammatory diseases and their associated infectious sequelae. Clin Infect Dis. 2014;58:1587.
4. Furst DE, Keystone EC, Braun J, et al. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2010. Ann Rheum Dis. 2011;70:i2.

4.1

Consternation About Induration

RYAN A. MCCONNELL, MD AND NAASHA J. TALATI, MD

CASE PRESENTATION

A 23-year-old African American woman with Crohn's enteritis presented to an infectious diseases specialist for evaluation of a positive QuantiFERON-TB Gold In-Tube (QFT) interferon-gamma release assay (IGRA).

She was diagnosed with Crohn's disease three years ago, when she presented with epigastric pain, loose stools, low-grade fevers, 8-pound weight loss, and oral aphthous ulcers. Colonoscopy revealed aphthous ulcerations of the terminal ileum, and computed tomography (CT) enterography findings were consistent with the diagnosis. The patient's symptoms failed to improve with oral 5-aminosalicylate therapy, so she was treated with oral corticosteroids. Baseline tuberculin skin test (TST) with purified protein derivative (PPD) and QFT—both performed while the patient was on steroids—were negative. Chest x-ray demonstrated clear lungs. The patient received a 5 mg/kg dose of intravenous infliximab, a monoclonal antibody against tumor necrosis factor (TNF)-α. However, severe abdominal pain recurred three weeks later when steroids were tapered, and the patient was found to have an ileal perforation requiring ileocecectomy and temporary ileostomy. Surgical pathology was notable for ileal mucosal ulcerations and rare, poorly formed granulomas.

Over the ensuing thirty months, the patient received an additional sixteen infusions of infliximab. Her course was complicated by an anastomotic stricture requiring dilation, anal fissure treated with metronidazole, low vitamin D, and low vitamin B12 requiring parenteral supplementation. After the seventeenth infliximab infusion, repeat QFT was positive at 0.4 IU/mL (upper limit of normal is 0.34 IU/mL). Tuberculin skin test was negative and chest x-ray remained clear. The patient was asymptomatic and had gained 15 pounds since starting infliximab.

The patient was a full-time student. She does not smoke, consume alcohol, or use drugs. She and her parents were born and raised in urban New York and have not traveled internationally. The patient's brother was treated for active pulmonary tuberculosis (TB) three years ago while incarcerated. She cannot recall how much time she spent with her brother while he was symptomatic.

On physical exam, she was a thin but well-nourished woman. She was afebrile with normal vital signs, clear lungs, and a well healed abdominal surgical scar. Her exam was otherwise unremarkable.

The patient's diagnostic testing was notable for a TST with zero millimeters of induration forty-eight hours after intradermal PPD injection, positive QFT at 0.4 IU/mL, normal complete blood count and comprehensive metabolic panel, negative human immunodeficiency virus antibody, and clear lungs without scarring on chest x-ray.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for the patient's discrepant TST and QFT results includes two clinical scenarios: (1) latent TB infection (LTBI) with a true-positive QFT and a false-negative TST, or (2) a false-positive QFT with a true-negative TST.

FINAL DIAGNOSIS AND TREATMENT OUTCOME

QuantiFERON-TB Gold In-Tube was repeated and spontaneously reverted to negative without intervention. However, due to the patient's possible close contact with active TB and the increased risk of reactivating TB with TNF-α inhibitor use, she was treated for latent TB with nine months of isoniazid. It was recommended that infliximab be discontinued until the patient completed at least four weeks of isoniazid prophylaxis. She was educated to remain vigilant for symptoms of active TB.

DISCUSSION

Mechanisms of Increased Tuberculosis Risk With Tumor Necrosis Factor-α Inhibitors

The development of TNF-α antagonists has revolutionized the treatment of multiple immune-mediated inflammatory diseases (IMIDs), including rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriasis, and psoriatic arthritis. However, these therapies are associated with increased risk of granulomatous infections, including TB. The mechanism of this heightened risk likely relates to the critical importance of TNF-α in promoting and maintaining the immune response to these intracellular pathogens.

It is estimated that one third of the world's population is infected with *Mycobacterium tuberculosis* [1]. However, the lifetime risk of developing active TB among immunocompetent individuals is only 5%–10% [2]. The vast majority of infected individuals enter an asymptomatic state of LTBI, during which the granulomatous, T-helper 1-type cellular immune response, contains the infection. Tumor necrosis factor-α, which exists in membrane-bound and soluble forms, is a key cytokine produced by macrophages and T cells in response to *M tuberculosis* infection. By stimulating chemokine production and adhesion molecule expression, TNF-α recruits inflammatory cells to the site of infection and maintains granuloma organization and structural integrity [3–6]. Together with interferon-γ, TNF-α activates macrophages to enhance phagocytosis and intracellular killing. By inducing apoptosis, TNF-α also regulates immune cell survival and turnover within the granuloma [4, 5]. Suppression of a normal TNF response abrogates host control mechanisms, increasing the risk of TB reactivation even years after the primary infection.

Experimental models provide support for the mechanisms of increased TB risk with TNF-α inhibition. Tumor necrosis factor-α knockout mice infected with TB demonstrate delayed inflammatory cell recruitment and fail to form organized granulomas [6]. Tumor necrosis factor-α inhibition has been shown to prevent macrophage phagosome maturation, reduce interferon-γ production, stimulate apoptosis of TB-reactive T cells while interfering with monocyte apoptosis, and cause granuloma regression leading to mycobacterial multiplication [4].

Differential Risk Amongst the Tumor Necrosis Factor-α Inhibitors

Tumor necrosis factor-α inhibitors increase the relative risk of active TB 1.6–25 times [3]. This heightened risk is a class effect and has been reproducibly demonstrated in North America, Europe, and Asia [2, 3, 7]. The wide range of reported attributable risk likely results from the significant variability in rates of TB infection in different countries and patient populations. For example, the risk of TB is two to sixteen times higher in rheumatoid arthritis patients relative to the general population, independent of TNF-α inhibitor use [3]. This may be due to the disease itself and the use of nonbiological immunosuppressive medications. In contrast, active TB is observed less frequently in patients with inflammatory bowel disease, probably because these patients tend to be younger and have lower rates of LTBI [6]. Furthermore, the frequency of screening for and treating LTBI before initiating TNF-α antagonist therapy has increased over time, because the risk of active TB associated with these drugs became recognized.

There are five TNF-α inhibitors in clinical use. Four are monoclonal antibody-based drugs, namely infliximab, adalimumab, certolizumab pegol, and golimumab. Etanercept, the fifth agent, is a soluble TNF receptor 2. The differential risk of TB amongst these drugs correlates with their differing activity against granulomatous inflammatory disorders, with the monoclonal drugs carrying approximately three to four times higher TB risk than etanercept [2, 3]. The timing of active TB onset is also significantly different. Active infection develops a median of three to six months after starting infliximab, but it appears approximately three to five times later with etanercept [8] (Figure 4.1.1). Etanercept-associated cases are also more uniformly distributed over time. These data suggest a higher risk of reactivation of LTBI with the monoclonal drugs compared with etanercept but a more equal risk of acquiring a new infection while on therapy. Infliximab and etanercept have been in clinical use since 1998 and 1999, respectively, and most of the data comes from studies of these agents. However, rates and timing of TB with adalimumab are similar to infliximab, supporting the heightened risk profile of the monoclonal antibody-based agents [2, 7].

The increased risk with monoclonal antibody- based drugs likely relates to key differences in pharmacodynamics and drug-binding kinetics [4]. Etanercept binds soluble TNF-α

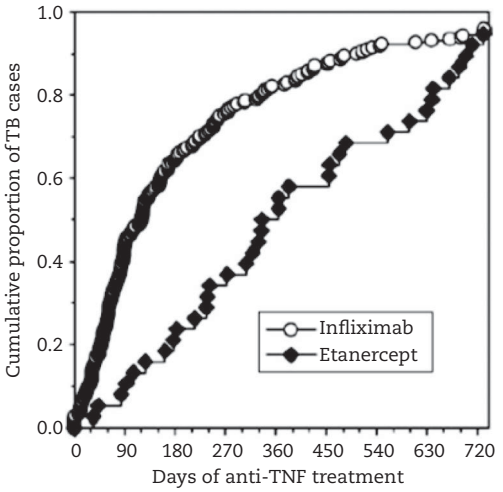


FIGURE 4.1.1: Cumulative proportion of active TB cases in relation to the start of TNF-α inhibitor therapy. Each symbol represents a case reported to the US Food and Drug Administration Adverse Event Reporting System from 1998 to 2003. There were 248 cases of infliximab-associated TB and thirty-nine cases of etanercept-associated TB reported. Reproduced from: Wallis RS. Reactivation of latent tuberculosis by TNF blockade: the role of interferon gamma. *J Investig Dermatol Symp Proc*. 2007;12:16.

trimers and transmembrane TNF-α at a ratio of 1:1. This binding is reversible, with 50% of soluble TNF-α and 90% of transmembrane TNF-α released within ten minutes of etanercept binding [9]. The antibody-based drugs form much more stable complexes with both monomeric- and trimeric-soluble TNF-α and can bind two TNF-α molecules at a time, allowing the formation of immune complexes and cross-linking of transmembrane TNF-α. Drug binding to transmembrane TNF-α is thought to be a key factor contributing to the differential risk of TB, because this binding suppresses cytokine production from the affected cell via a process known as reverse signaling [2, 5]. Cross-linking of transmembrane TNF-α, which is unique to the antibody-based drugs, causes apoptosis of the affected cell. In whole blood cultures stimulated with *M tuberculosis*, infliximab reduced the proportion of TB-responsive $CD4^+$ T cells and suppressed interferon-γ production by 70%, whereas etanercept did not [8]. Because etanercept does not entirely block TNF-α bioactivity, it is hypothesized that this drug allows for more preservation of granulomas and macrophage antimicrobial function.

Clinical Presentation of Active Tuberculosis in Patients Treated With Tumor Necrosis Factor-α Inhibitors

Up to 75% of active TB cases occur within the first ninety days of TNF-α inhibitor treatment, suggesting that they are likely due to reactivation of LTBI [6]. However, patients taking TNF-α inhibitors remain at elevated risk of acquiring active TB as a result of new infection as well.

The clinical characteristics of active TB in this population often differ from those seen in immunocompetent persons. Although active TB has been reported in TNF-α inhibitor patients of all ages, the median age is the late 50s. Many patients are taking additional immunosuppressive medications, such as methotrexate and/or corticosteroids [7]. Active TB tends to progress rapidly and is frequently extrapulmonary and disseminated (Figure 4.1.2). Extrapulmonary disease is reported in 33%–75% of case patients and disseminated disease is reported in 12%–36%, compared to 18% and <2% in immunocompetent hosts, respectively [6, 10, 11]. Because TNF-α is responsible for some of the clinical manifestations of active TB, including weight loss and night sweats, TNF-α inhibition may mask some of the signs and symptoms of TB and contribute to delays in diagnosis [10]. A US study found that patients receiving TNF-α blocking therapy who developed active TB were twice as likely to have diabetes, four times as likely to have chronic kidney disease, and were more likely to be non-white compared to uninfected patients [7].

Diagnosing active TB can be challenging. Infected patients receiving TNF-α inhibitors have a lower rate of positive acid-fast bacilli staining [11]. Some patients may have poorly organized or absent granulomas, although others do form more classic-appearing caseating granulomas [10]. These findings highlight the need to remain vigilant, educate patients, and recognize that typical symptoms may not be present due to immunosuppression.

Treatment is with standard four-drug therapy. The TNF-α inhibitor should be stopped for the duration of therapy, or at least until the patient demonstrates clinical improvement and drug-resistant TB has been excluded. There are rare reports of immune reconstitution inflammatory syndrome after stopping TNF-α inhibitor therapy. There is conflicting data on whether treatment outcomes are worse compared to the general population, and mortality may be increased (the reported mortality in several studies ranges from

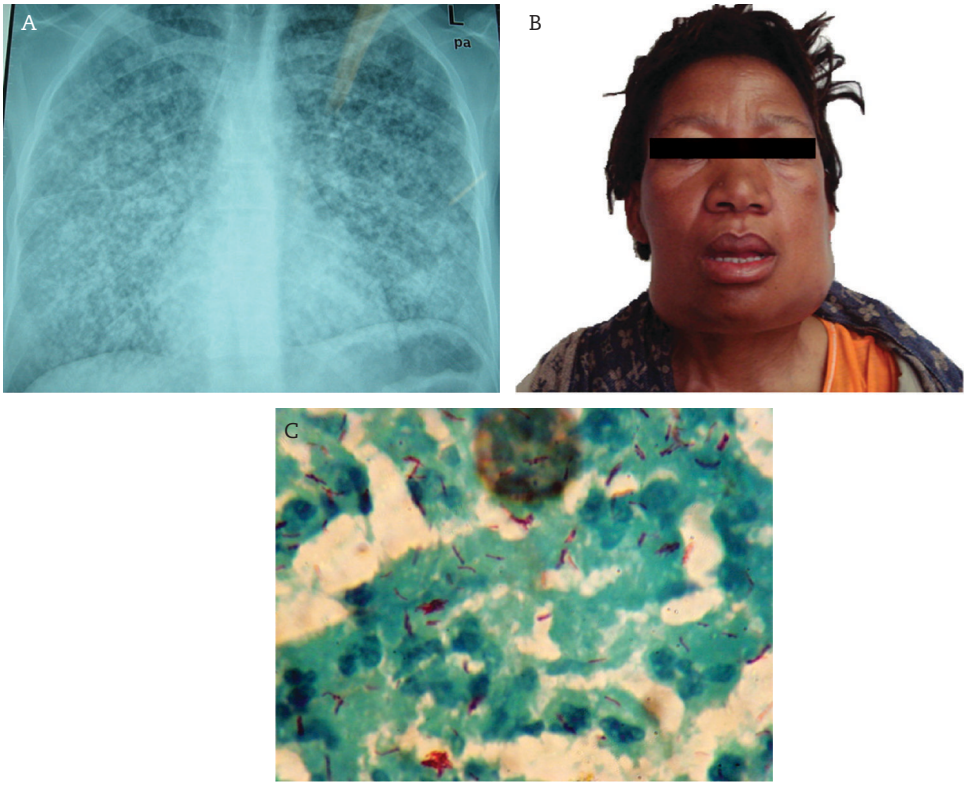


FIGURE 4.1.2: Extrapulmonary and disseminated TB occur more frequently in patients receiving TNF-α inhibitors. Shown here are miliary tuberculosis (A), tuberculous lymphadenitis (B), and positive acid-fast bacilli staining from an infected lymph node aspirate (C).

0% to 19%) [7, 10, 11]. Limited data exist regarding the safety of resuming TNF-α inhibition following successful TB treatment, although seven patients in Spain and Portugal resumed therapy without TB recurrence [11, 12].

Screening for Latent Tuberculosis Infection Before Initiating Tumor Necrosis Factor-α Inhibitor Therapy

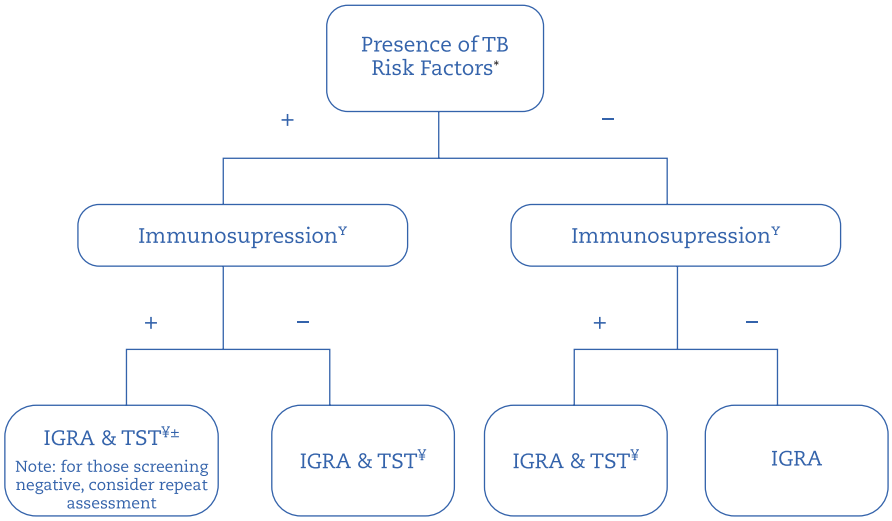
Screening for LTBI is recommended for all patients before starting TNF-α inhibitor therapy. Traditionally, diagnosis of LTBI relied on the TST. Patients with IMID have a high rate of false-negative TST results, due to anergy [3, 6]. Up to 80% of TNF-α inhibitor candidates are already taking other immunosuppressive therapy, and studies demonstrate anergy rates over 80% in patients receiving steroids or nonbiological immunosuppressants [6].

A new generation of blood tests is now available, the IGRAs [1]. In patients previously exposed to TB, T cells recognize the TB-specific peptides and release interferon-γ. Two IGRAs are commercially available: QFT, which measures the amount of interferon-γ released using an enzyme-linked immunosorbent assay, and TSPOT.TB (TSPOT), which uses enzyme-linked immunospot technology to identify the number of T cells producing interferon-γ. Both QFT and TSPOT have been shown to correlate with risk factors for TB exposure, such as country of birth and close contact with a known case.

Interferon-gamma release assays have a mitogen stimulus that is used as a positive control to assess general T-cell responsiveness. A reduced mitogen response is reported as "indeterminate" and may help discriminate true-negative responses from anergy. Patients with IMID on immunosuppressive medications (particularly steroids) tend to have increased rates of indeterminate results with QFT but not with TSPOT, suggesting that TSPOT may be a better IGRA to use for patients on immunosuppressive medications at the time of testing [3]. Clinical studies provide conflicting results regarding whether the presence of an IMID reduces the overall rate of positive IGRAs, and the IGRAs are probably at least as sensitive as TST in diagnosing LTBI. However, the positive

predictive value of IGRA responses for the subsequent development of active TB in patients receiving TNF-α inhibitor therapy is unknown.

Discordance between IGRAs and TST is common in patients with IMID, particularly those on steroids, regardless of Bacillus Calmette-Guérin (BCG) vaccination status. When TST and IGRAs are applied simultaneously, there is little overlap in patients who test positive by either method. In fact, several recent studies demonstrate that only approximately 20% of IMID patients testing positive to either TST or IGRA test positive to both tests [13, 14]. In addition, the overlap between positive QFT and TSPOT is also low, with one third of patients testing positive by either IGRA failing to test positive by both. This means that each test is picking up a different subset of patients. There is no gold standard for the diagnosis of LTBI, so when test results are discordant it is difficult to know which test is falsely positive and which is falsely negative. Given the high risk of TB reactivation in patients receiving TNF-α inhibitors, the increased sensitivity gained by screening with both a TST and IGRA may justify screening with both types of tests [11, 15]. The Centers for Disease Control and Prevention (CDC) guidelines state that for immunocompromised populations at high risk of disease progression, both a TST and IGRA may be performed [1]. Boosting of the IGRA has been reported when performed sequentially after placement of a TST [1]. Therefore, if both tests are used, it is recommended to either perform them simultaneously or perform the IGRA



*TB risk factors include: a history of contact to a case of active TB; birth or extended living (>3 months) in regions where TB is prevalent (crude incidence ≥20/100,000 per year); history of working or living in jails, prisons, healthcare facilities providing care to TB patients, or homeless shelters; or history of intravenous drug use.

^YImmunosupression includes poorly controlled rheumatoid arthritis or other systemic inflammatory, immune-mediated diseases, current use of biologic or non-biologic disease modifying therapies, or current use of corticosteriods, and other conditions [e.g. HIV].

^¥In regions of BCG use (or individuals with BCG history), consider a dual strategy of using both commercially available IGRAs (QuantiFERON-TB Gold In-Tube and TSPOT.TB) in lieu of the TST.

^±For patients with TB risk factors who are immunosuppressed in whom false negative results are more likely, consider repeat screening with one or both tools if their initial screening results are negative

Note: IGRA and TST can be performed on the same day. Alternatively, one test can precede the other. Using a TST prior to IGRA could potentially improve subsequent IGRA sensitivity in those truly infected, and such sequential testing (i.e performing the second test if the first test is negative) would be advantageous with regards to screen cost.

TB: tuberculosis; IGRA: interferon-gamma release assay; TST: tuberculin skin test

FIGURE 4.1.3: Proposed algorithm for latent TB infection testing in patients with IMIDs about to receive a TNF-α inhibitor. Reproduced from: Winthrop KL, Weinblatt ME, Daley CL. You can't always get what you want, but if you try sometimes (with two tests—TST and IGRA—for tuberculosis) you get what you need. *Ann Rheum Dis*. 2012;71:1757.

first. When there are discrepant results, it is reasonable to interpret a single positive test as evidence of LTBI. Figure 4.1.3 is a proposed testing algorithm.

The ideal timing to test patients for LTBI is prior to initiation of any immunosuppressive medications. However, the lack of evidence to clearly support IGRAs or TST for the diagnosis of LTBI has resulted in discrepant guidelines from different national organizations (Table 4.1.1) [2]. There are multiple reports of patients developing active TB after receiving TNF-α inhibitors despite a negative initial screening test, highlighting the adverse clinical implications of false-negative screening tests as well as the risk of new TB exposures after screening. Therefore, in addition to testing for LTBI, all TNF-α inhibitor candidates require a careful clinical history to assess for TB exposure risk factors. Screening chest x-ray may also be considered in certain situations. Although

TABLE 4.1.1. EXAMPLES OF GUIDELINES FOR LTBI SCREENING AND MANAGEMENT IN PATIENTS WITH IMIDS.

Country or Organization	TST as Part of Screening	IGRA as Part of Screening	Preferred TB Prophylaxis Regimen
United States (CDC)	Recommended. Cutoff ≥5 mm if immunosuppressed.	Supplement if TST is negative in immunosuppressed patients with potential poor outcome. Negative IGRA does not exclude LTBI.	9 months INH
United Kingdom (British Thoracic Society)	Recommended. Cutoff >5 mm in those without and >15 mm in those with BCG history. Unreliable in immunosuppressed.	Consider in immunosuppressed patients with history of BCG, but decision for prophylactic treatment takes the clinical risk profile into account.	6 months of INH or 3 months of INH+Rifapentine
Canada	Recommended. Cutoff >5 mm if immunosuppressed.	Supplement with TSPOT if false-negative TST suspected. Intermediate or negative IGRA does not exclude LTBI.	9 months of INH
Switzerland	Not used.	Recommended as first-line screening test.	9 months of INH or 4 months of rifampin
Spain	Recommended. Cutoff >5 mm.	Consider in negative TST.	9 months of INH
Europe: TBNET	Recommended. Cutoff ≥10 mm in those without BCG.	Preferred in patients with BCG history.	9–12 months of INH or 3 months of INH+Rifapentine
European Crohn's and Colitis Organisation	Recommended along with risk assessment and CXR. Cutoff ≥5 mm.	Supplement in patients with BCG history.	Per local guidelines
European Centre for Disease Prevention and Control	Recommended along with risk assessment.	Recommended along with risk assessment.	Per local guidelines

Abbreviations: CXR, chest x-ray; INH, isoniazid.
Adapted from: To KW, Reino JJ, Yoo DH, Tam LS. Tumour necrosis factor antagonist and tuberculosis in patients with rheumatoid arthritis: an Asian perspective. *Respirology* 2013;18:765.

chest x-ray is abnormal in only 10%–20% of patients with LTBI, such patients are more likely to reactivate TB [6].

Although screening for LTBI is recommended annually in most high-risk populations, there is no clear guidance on how frequently patients on TNF-α inhibitors should be screened for LTBI. Serial IGRA testing in healthcare workers demonstrates that spontaneous conversions and reversions do occur without clear exposure to TB. These changes in test results tend to occur more frequently when the interferon-γ responses are close to the cutoff for positivity. Little is known regarding within-subject variation and the significance of conversion or reversion with respect to the development or clearance of LTBI. Therefore, patients who have conversions on serial testing with no apparent exposure to TB and an interferon-γ value close to the cutoff should be evaluated closely to determine whether treatment for LTBI is warranted.

Preventive Treatment of Latent Tuberculosis Infection

Patients with a positive screening test should undergo chest x-ray, physical exam, and symptom screen to rule out active TB. Once active TB has been excluded, all patients with a positive screening test should be offered chemoprophylaxis (options are shown in Table 1). Patients with significant past TB exposure should also be considered for prophylaxis, even if tests for LTBI are negative. There is no guidance on when to begin or re-initiate TNF-α inhibitors in patients with LTBI.

Preventive therapy is generally considered to be highly effective. Several studies report that isoniazid prophylaxis in patients with IMID prior to initiating TNF-α inhibitor therapy is associated with an approximately 75%–90% reduction in the incidence of active TB, with TB rates approaching the background rate for patients not receiving TNF-α inhibitor therapy [3, 6]. However, one study found that patients positive on screening who received nine months of isoniazid still had a 19% risk for active TB when treated with TNF-α inhibitors [6].

SUMMARY

Tumor necrosis factor-α is a key cytokine in the formation and maintenance of granulomas and control of TB infection. In patients on TNF-α inhibitors, the risk of TB is increased 1.6–25 times, and active disease often occurs within the first ninety days of therapy. Patients frequently have disseminated disease and may not present with characteristic signs and symptoms. High index of suspicion for active TB and early diagnosis and treatment may aid in achieving better outcomes. Screening for LTBI using a detailed history and potentially more than one screening test is key. Screening prior to use of any immunosuppressive agents would likely increase test sensitivity. Treatment of LTBI with preventive therapy markedly decreases the risk of developing active TB on TNF-α inhibitors.

REFERENCES

1. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using interferon gamma release assays to detect *Mycobacterium tuberculosis* infection—United States, 2010. MMWR Recomm Rep. 2010;59(RR-5):1.
2. To KW, Reino JJ, Yoo DH, Tam LS. Tumour necrosis factor antagonist and tuberculosis in patients with rheumatoid arthritis: an Asian perspective. Respirology. 2013;18:765.
3. Solovic I, Sester M, Gomez-Reino JJ, et al. The risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. Eur Respir J. 2010;36:1185.
4. Harris J, Keane J. How tumour necrosis factor blockers interfere with tuberculosis immunity. Clin Exp Immunol. 2010;161:1.
5. Fallahi-Sichani M, Flynn JL, Linderman JJ, Kirschner DE. Differential risk of tuberculosis reactivation among anti-TNF therapies is due to drug binding kinetics and permeability. J Immunol. 2012;188:3169.
6. Theis VS, Rhodes JM. Review article: minimizing tuberculosis during anti-tumour necrosis factor-alpha treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2008;27:19.
7. Winthrop KL, Baxter R, Liu L, et al. Mycobacterial diseases and antitumour necrosis factor therapy in USA. Ann Rheum Dis. 2013;72:37.
8. Wallis RS. Reactivation of latent tuberculosis by TNF blockade: the role of interferon gamma. J Investig Dermatol Symp Proc. 2007;12:16.
9. Ehlers S. Why does tumor necrosis factor targeted therapy reactivate tuberculosis? J Rheumatol Suppl. 2005;74:35.
10. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med. 2001;345:1098.
11. Abreu C, Magro F, Santos-Antunes J, et al. Tuberculosis in anti-TNF-α treated patients remains a problem in countries with an intermediate incidence: analysis of 25 patients matched with a control population. J Crohns Colitis. 2013;7:e486.

12. Jauregui-Amezaga A, Turon F, Ordás I, et al. Risk of developing tuberculosis under anti-TNF treatment despite latent infection screening. J Crohns Colitis. 2013;7:208.
13. Mariette X, Baron G, Tubach F, et al. Influence of replacing tuberculin skin test with ex vivo interferon γ release assays on decision to administer prophylactic antituberculosis antibiotics before anti-TNF therapy. Ann Rheum Dis. 2012;71:1783.
14. Hsia EC, Schluger N, Cush JJ, et al. Interferon-γ release assay versus tuberculin skin test prior to treatment with golimumab, a human anti-tumor necrosis factor antibody, in patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis. Arthritis Rheum. 2012;64:2068.
15. Winthrop KL, Weinblatt ME, Daley CL. You can't always get what you want, but if you try sometimes (with two tests—TST and IGRA—for tuberculosis) you get what you need. Ann Rheum Dis. 2012;71:1757.

4.2

A Game of Cat and Mouse

AMBAR HALEEM, MD AND BRYAN STEUSSY, MD

CASE PRESENTATION

A 71-year-old white male with autoimmune disease on chronic immunosuppressive therapy presented to our infectious disease clinic for evaluation of a three-week history of pain and swelling of his right upper extremity. The swelling was located on the posterior aspect of the shoulder and was painful and fluctuant (Figure 4.2.1). Pain radiated from the shoulder to the middle three fingers and was exacerbated by laying supine. There was no associated erythema or restricted range of motion of the shoulder. The patient denied a history of fevers, chills, and night sweats, but did endorse persistent fatigue over the previous month. The patient denied any recent weight changes. Review of other systems was unrevealing. There was no history of preceding trauma or infection in the right upper extremity.

The patient underwent aspiration of the shoulder swelling with retrieval of 14 cc of yellowish-brown, cloudy fluid. The fluid showed a string sign that indicated increased viscosity. Fluid analysis is demonstrated in Table 4.2.1. Fluid Gram stain and auramine-rhodamine stain for mycobacteria did not show white blood cells or microorganisms.

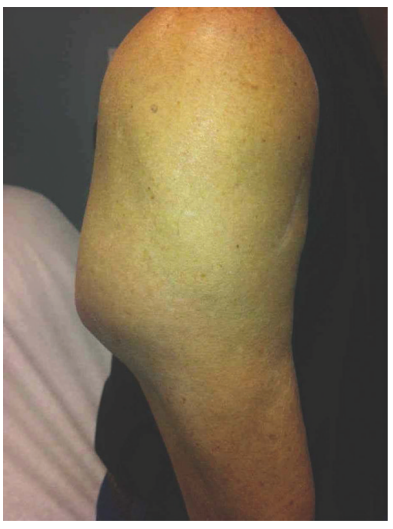


FIGURE 4.2.1: Right upper extremity mass.

On evaluation in infectious diseases clinic, vital signs were within normal limits. The patient appeared frail and ill. Exam of the shoulder revealed a tender, fluctuant subcutaneous mass, approximately 6 cm in diameter on the posterolateral aspect of the right arm distal to the shoulder joint. The overlying skin had a violaceous hue. Passive shoulder movement was painful. The remaining exam was unchanged from previous exams.

He was anemic (hemoglobin 8.7 g/dL) with slightly elevated inflammatory markers (erythrocyte sedimentation rate was 19 mm/h and C-reactive protein was 0.6 mg/L). White blood cell count, platelet count, electrolytes, and liver function tests were within normal limits.

The patient's history of autoimmune disease included seronegative rheumatoid arthritis (RA) and Crohn's disease with partial bowel obstruction requiring a procto-colectomy with ileostomy creation in the past. His Crohn's disease was successfully controlled on prednisone for >20 years. He had tried multiple, other disease-modifying medications for Crohn's disease and RA in the

TABLE 4.2.1. FLUID ANALYSIS OF SHOULDER MASS

Clarity	Turbid
Color	Orange
Total nucleated count	8505 cells/mm^3
Red blood cell count	9000 cells/mm^3
Neutrophil count	3487 cells/mm^3
Lymphocyte count	2892 cells/mm^3
Mononucleated cell count	2126 cells/mm^3

past without success, including hydroxychloroquine, sulfasalazine, and tumor necrosis factor (TNF)-blockade agents (infliximab, rituximab, and abatacept). Tumor necrosis factor-blocking drugs had last been used several years earlier; since then, he had been maintained only on 20 mg of prednisone daily. As a result of RA and chronic steroid usage, he had developed degenerative joint disease with resultant partial arthroplasty of right shoulder, bilateral total arthroplasties of hips and knees, and fusion of the left wrist.

His past medical history was also notable for a right prosthetic knee joint infection from *Mycobacterium avium intracellulare* (MAI) complex in the previous three years. For this infection, he had undergone a two-stage revision knee arthroplasty and a prolonged course of triple-drug therapy comprising clarithromycin, rifampin, and ethambutol. Intraoperative cultures obtained at prosthesis reimplantation had been negative for MAI. During his course of MAI therapy, approximately one year after his knee revision surgery, he had developed severe back pain and was diagnosed with T5/6 osteomyelitis/discitis with epidural extension and cord compression. He underwent spinal cord decompression and T4/7 posterior spinal fusion. Surgical culture grew MAI (susceptible to macrolides). It was thought that the spinal infection had, most likely, been present subclinically at the time of the knee infection and, as such, had not represented a failure of MAI therapy. Therefore, his triple-drug MAI therapy was continued without modification. The intention was to treat him at full-drug dose strength for at least twelve months from the time of his spinal surgery and then de-escalate therapy to a maintenance regimen for an indefinite duration. However, the patient could not tolerate the treatment due to gastrointestinal distress and discontinued it himself after ten months. Gastrointestinal symptoms resolved thereafter. He then remained asymptomatic for six to eight months until he presented with a shoulder mass.

The patient had retired many years previously from work at a pig slaughter house. He was a former heavy smoker. He had no history of alcohol or illicit drug use. His history was negative for out-of-state travel, outdoor recreational activities, animal exposure (including farm animals), or consumption of raw meat or unpasteurized dairy products. There was no history of tuberculosis infection or exposure.

DIFFERENTIAL DIAGNOSIS

Infectious etiologies for bone and joint infections in an immune suppressed individual cover a broad array of microorganisms. The spectrum includes bacteria, fungi, and mycobacteria.

Bacteria such as Gram-positives (staphylococci, streptococci) and Gram-negatives typically cause a more robust clinical picture than seen in this case. Anaerobic skin and soft tissue infections in immune compromised populations typically occur as a result of a breach of gut mucosa, obstruction/stasis, trauma, or vascular insufficiency. Because the patient's Crohn's disease had been well controlled for years, there was no reason to suspect bacterial translocation from the gut and subsequent, hematogenous dissemination to the shoulder joint.

Slow-growing bacteria such as *Brucella, Bartonella*, and *Nocardia* can cause an indolent skin and soft tissue infection in both immune competent and immune suppressed patients. The patient denied exposures typically associated with brucellosis and bartonellosis—farm environment and consumption of unpasteurized dairy products for *Brucella* and feline exposure for *Bartonella*.

Fungi and mycobacteria, with their environmental prevalence, intracellular survival, slow growth, and diverse immune-evasive strategies, are well suited to infecting the immune suppressed population. Typical fungi in this setting include *Cryptococcus, Aspergillus, Histoplasma, Blastomyces*, and *Sporothrix*. Differentials for non-infectious etiologies in this patient were pseudotumor or joint space cyst.

DIAGNOSTIC TESTS

Blood cultures were negative. Fungal serologies were negative for *Aspergillus, Histoplasma, Coccidioidomyces, Blastomyces*, and *Cryptococcus*. Bacterial and fungal tissue cultures were negative.

Acid-fast bacilli (AFB) cultures from the shoulder mass aspirate grew *Mycobacterium avium-intracellulare* complex after twelve days of incubation.

In light of his prior history of vertebral osteomyelitis, a magnetic resonance image (MRI) of the spine with and without contrast was repeated. No new foci of osteomyelitis or fluid collections were found on MRI.

SURGICAL INTERVENTION

The patient underwent surgical excision of the right upper arm mass [Figure 4.2.2]. There was a communicating sinus tract between the mass and shoulder joint. Multiple tissue samples were submitted for bacterial, fungal, and mycobacterial stains and cultures.

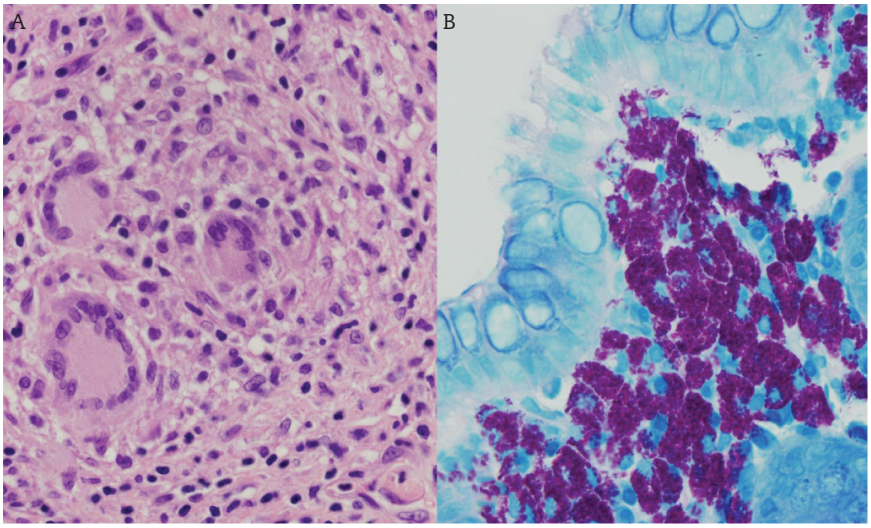


FIGURE 4.2.2: (A) Granulomatous inflammation present in the tissue sections from the shoulder mass in this patient. (B) AFB stain from a separate case demonstrating MA1 in a tissue section. (The direct gram stain and AFB stain on tissue in this case were negative.)

MICROBIOLOGY

Mycobacterial cultures (*Mycobacterium* growth indicator tube [MGIT]) turned positive after thirteen days [Figure 4.2.3], and subsequent stains confirmed the presence of mycobacteria species [Figure 4.2.4 and 4.2.5]. The *Mycobacterium* was confirmed to be MAI by rRNA probes for MAI complex. *Mycobacterium avium* complex was also inoculated onto solid media [Figure 4.2.6].

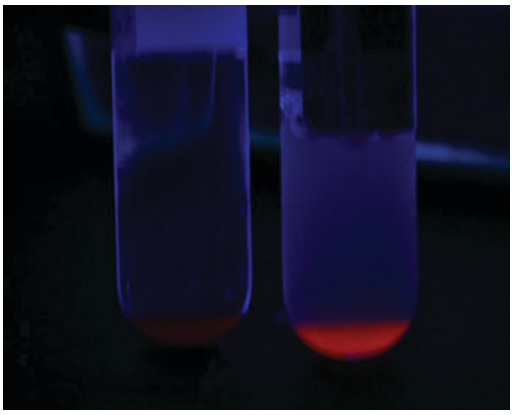


FIGURE 4.2.3: The MGIT fluorescence under a woods lamp—a negative tube is shown on the left with a positive tube on the right. The fluorescence occurs as oxygen is used up in the tube by the *Mycobacterium*.

TREATMENT

The MAI isolate was found to be susceptible to clarithromycin (minimum inhibitory concentration [MIC], 0.5 μg/mL), resistant to linezolid (MIC, 32 μg/mL), and intermediately susceptible to moxifloxacin (MIC, 2 μg/mL). In light of recurrent and severe disease, he was treated with a four-drug therapy regimen comprising clarithromycin 500 mg BID, rifabutin 300 mg daily, and ethambutol 900 mg daily and three times weekly parenteral streptomycin. Pretreatment ophthalmologic and audiology tests were performed to monitor for ethambutol and aminoglycoside-induced ocular and ototoxicity, respectively.

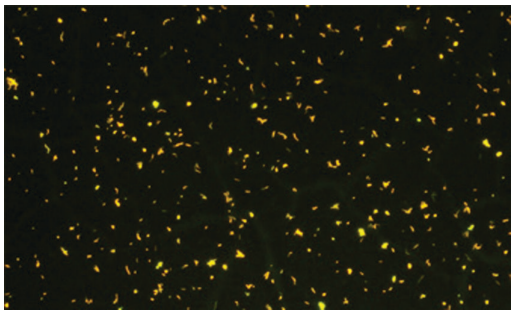


FIGURE 4.2.4: Auramine-Rhodamine Stain. This low-power view demonstrates the *Mycobacterium* staining golden-orange. This photo is of the *Mycobacterium* isolated from the MGIT in this case.

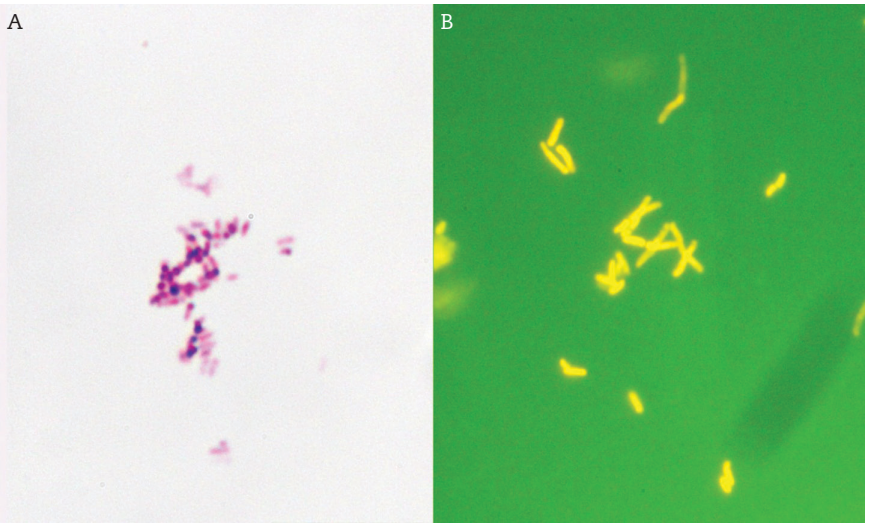


FIGURE 4.2.5: Kinyoun (AFB stain) and suramine-rhodamine stain. (A) 100× magnification showing the AFB as demonstrated by a kinyoum stain. (B) 100× magnification showing the same AFB as they appear under fluorescence using an suramine-rhodamine stain.

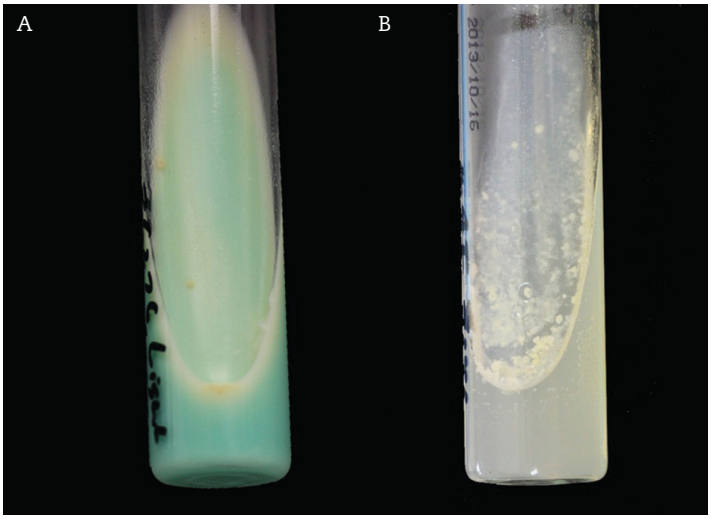


FIGURE 4.2.6: MAI grows as buff-colored colonies as demonstrated on (A) Lowenstein-Jensen agar and (B) Middlebrook agar.

CLINICAL OUTCOME

The patient received four-drug therapy for eleven weeks without suffering another relapse or adverse drug effects. At eleven weeks of therapy, parenteral streptomycin was discontinued and he was maintained thereafter on oral clarithromycin 500 mg BID, rifampin 600 mg daily, and ethambutol 900 mg daily for an indefinite duration. Since the last relapse one year ago, his disease has remained quiescent.

DISCUSSION

Nontuberculous mycobacteria (NTM) are a large, diverse group of environmental organisms that are ubiquitous in water and soil. *Mycobacterium avium intracellulare* is the commonest NTM species causing human disease in most series, but many NTM species have been implicated as pathogens [4, 9]. Recent reports indicate rising rates of NTM disease, especially in populations receiving TNF-α antagonist therapies [Figure 4.2.7] [1].

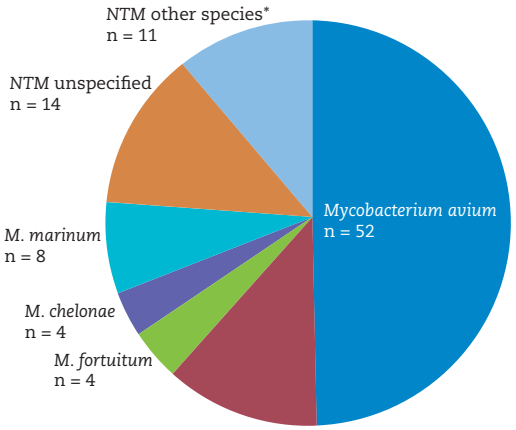


FIGURE 4.2.7: Reported causes of 105 confirmed and probable NTM infections associated with anti-TNF-α agents (US Food and Drug Administration MedWatch database, 1999–2006). *Other species include *Mycobacterium kansasii* (n = 3), *Mycobacterium xenopi* (n = 3), *Mycobacterium haemophilum* (n = 2), and *Mycobacterium mucogenicum* (n = 1) [1].

However, because NTM diseases are not communicable, they are not reportable in the United States. Nontuberculous mycobacteria disease can also be more insidious and difficult to diagnose than *Mycobacterium tuberculosis* because NTM are environmental organisms with marked geographic variability and propensity to colonize airway and gastrointestinal mucosal surfaces as well as to contaminate cultures. Nontuberculous mycobacteria disease ranges from asymptomatic colonization, symptomatic, localized disease (pulmonary, lymphatic, cutaneous, osteoarticular) to life-threatening, disseminated disease. In patients on TNF antagonist therapy, extrapulmonary NTM disease is reported to be more common than in patients with RA not receiving anti-TNF therapy [1, 9].

The critical anti-mycobacterial immune cell types are macrophages, natural killer cells, and CD4 T-helper type 1 cells [2]. After phagocytosis of mycobacteria, macrophages respond with production of interleukin (IL)-12 and TNF-α. These cytokines are crucial to activation of the innate and adaptive immune systems for eradication of intracellular pathogens, such as mycobacteria. Tumor necrosis factor-α is also essential for granuloma formation and its maintenance. Tumor necrosis factor-α is up-regulated in a variety of autoimmune diseases, including RA, inflammatory bowel disease, and psoriasis. Immunomodulator therapy, including anti-TNF drugs, paradoxically increases risk for granulomatous infectious diseases [3]. Both *M tuberculosis* and NTM infections have been reported with immunosuppressive therapy. Implicated drugs include biologic TNF-α inhibitors (infliximab, etanercept, adalimumab), rituximab, an anti-CD20$^+$ peripheral B cell-depleting antibody, and nonbiologic drugs, such as corticosteroids that suppress cell-mediated immunity primarily by inhibiting the transcription of cytokines (IL-1–8 and TNF-α) [3, 4].

Nontuberculous mycobacteria disease manifestations depend on host immune competence and the local tissue environment. Pulmonary disease is the commonest manifestation of NTM disease [1, 9]. From a primary inoculation site, mycobacteria can invade locally or disseminate hematogenously to multiple foci. Osteoarticular infection typically results from direct inoculation during trauma or surgery and can manifest in a myriad of ways (e.g. bursitis, tenosynovitis, arthritis, or osteomyelitis [5]). The NTM species causing bone and joint infection often depends on the environmental exposure. Nontuberculous mycobacteria have a predilection for infection of foreign devices, such as prosthetic joints and intravascular catheters [6, 7]. Clinical presentation of NTM bone and joint disease is similar to that of *M tuberculosis* in that it can be indolent, nonspecific, and therefore liable to be missed early, which can result in significant local damage. Nontuberculous mycobacteria can cause acute disseminated disease in patients with the-acquired immune deficiency syndrome (AIDS) , Most published reports of osteoarticular NTM disease involve chronic, localized infection of skin, tendon, or bone and joints [8]. Local pain or swelling is the most frequent presenting complaint. Cutaneous fistulae, abscesses, and joint deformity usually develop with advanced disease. Systemic symptoms, such as fever, night sweats, or weight loss are most often seen with disseminated infection in AIDS patients. Disseminated NTM disease is almost always a manifestation of underlying immunologic dysfunction, as with human immunodeficiency virus/AIDS, organ transplantation, immunosuppressive therapies, or genetic defects in the interferon-γ/IL-12 pathway [9].

Differential Diagnoses

In the immunocompromised host, clinicians need to have a high index of suspicion for unusual, slow-growing organisms. Recalcitrant musculoskeletal symptoms despite standard antibacterial therapy or recurrent, culture-negative

tenosynovitis or joint disease should raise suspicion for an atypical microorganism. This is especially significant in the context of immunomodulator therapy where cytokine defects predispose to infection from slow-growing, intracellular organisms, including mycobacteria, fungi (*Cryptococcus, Aspergillus, Histoplasma, Blastomyces, Coccidioidomyces, Sporothrix*) as well as bacteria (*Listeria, Nocardia, Bartonella, Salmonella*). A careful history of recent exposures (trauma, surgery, animals, travel), occupation, and recreational activities usually provides important clues to the diagnosis.

Diagnosis

When suspecting an atypical, indolent infection (especially in an immunosuppressed host), obtaining deep tissue for bacterial, fungal, and mycobacterial culture and histopathology is crucial to making a diagnosis. In the case of bone and joint infection, multiple tissue cultures should be submitted from synovium, tendon sheath, synovial fluid, and bone. Obtaining multiple deep samples is especially important in case of NTM infections because these organisms can also be culture contaminants. Nontuberculous mycobacteria have variable, interspecies antimicrobial susceptibilities, and empiric treatment is difficult to prescribe. For NTM, culture remains the gold standard despite the protracted time to grow the organism. (On average, it took thirteen days for mycobacteria to grown in multiple cultures from this patient and even longer for a definitive identification as MAI.) Certain NTM species have special culture requirements, and the microbiology laboratory should be alerted if the specialist suspects such species (e.g. *Mycobacterium marinum, Mycobacterium hemophilum*). Molecular methods have been shown to be more sensitive than both AFB stains and culture for *M tuberculosis* on direct specimens and lead to faster identification of the bacteria; however, test expense and inability to discriminate between live and dead organisms has hindered its broader adoption [10].

Treatment

The 2007 American Thoracic Society guidelines for treatment of NTM infections recommends a combined surgical and medical treatment approach to extrapulmonary *M avium* disease localized to the musculoskeletal system [9]. Aggressive surgical debridement of the affected osteoarticular structure and removal of foreign devices provides the best chance of cure. This is especially relevant because mycobacteria may persist on foreign bodies in biofilms, despite appropriate antimicrobial therapy. The recommended antimicrobial therapy for bone and joint MAI disease is the same as for MAI pulmonary disease, i.e. a multidrug regimen (two to three drugs) with a macrolide backbone (clarithromycin or azithromycin) guided by the isolate's antibiotic susceptibility profile. It is necessary to combine macrolide therapy with one to two other drugs (albeit drugs with less activity against MAI) to prevent the emergence of macrolide resistance. Macrolides should never be used as monotherapy for treatment of MAI disease. If there is a large MAI disease burden or prior treatment failure, a regimen of three oral drugs in combination with parenteral aminoglycoside is recommended. The optimal drug regimen and duration of treatment for MAI disease remains unknown, and drug toxicity can be severely limiting.

Our patient was especially challenging because he had a high disease burden, multiple affected osteoarticular foci, and had experienced relapse despite appropriate treatment courses (although the relapse occurred upon discontinuation of treatment). De-escalation or discontinuation of immunosuppressive therapy is typically recommended with active fungal or *M tuberculosis* infection. There are no similar guidelines for NTM disease in patients receiving immunomodulator therapy; presumably, the same approach would apply. Unfortunately, our patient's Crohn's disease was controlled only on steroid dose of 20 mg/day and did not permit any modification of immunosuppressive therapy.

Latency and reactivation under immunosuppression is not known to occur with NTM. In our patient, we believe that most likely the initial MAI infection could not be eradicated due to profound immune suppression resulting in bacterial persistence in 1 or more "sanctuary sites" (such as the spine or prosthetic knee) from where it "escaped" to seed other sites after anti-mycobacterial therapy was discontinued. Unfortunately, the patient was a poor surgical candidate for removal of his prosthetic joints. In conclusion, this case was a prime example of a "cat and mouse" game where the MAI bacteria simply "kept getting away" from maximal therapeutic measures.

REFERENCES

1. Winthrop KL, Yamashita S, Beekmann SE, et al. Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case

finding through the Emerging Infections Network. Clin Infect Dis. 2008;46:1738.
2. van de Vosse E, Hoeve MA, Ottenhoff TH. Human genetics of intracellular infectious diseases: molecular and cellular immunity against mycobacteria and salmonellae. Lancet Infect Dis. 2004;4:739.
3. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis. 2004;38:1261.
4. Keystone EC. Does anti-tumor necrosis factor-α therapy affect risk of serious infection and cancer in patients with rheumatoid arthritis? A review of longterm data. J Rheumatol. 2011;38:1552.
5. Piersimoni C, Scarparo C. Extrapulmonary infections associated with nontuberculous mycobacteria in immunocompetent persons. Emerg Infect Dis. 2009;15:1351.
6. Wang SX, Yang CJ, Chen YC, et al. Septic arthritis caused by *Mycobacterium fortuitum* and *Mycobacterium abscessus* in a prosthetic knee joint: case report and review of literature. Intern Med. 2011;50:2227.
7. Gupta A, Clauss H. Prosthetic joint infection with *Mycobacterium avium* complex in a solid organ transplant recipient. Transpl Infect Dis. 2009;11:537
8. Patel R, Roberts GD, Keating MR, Paya CV. Infections due to nontuberculous mycobacteria in kidney, heart, and liver transplant recipients. Clin Infect Dis. 1994;19:263
9. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367
10. Lawn SD, Mwaba P, Bates M, et al. Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. Lancet Infect Dis. 2013;13:349

4.3

Beware the Fish Tank

DILEK INCE, MD

CASE PRESENTATION

A 39-year-old woman with a history of psoriasis and psoriatic arthritis and on etanercept and methotrexate presented with a painful nodule on the dorsum of her right fourth finger of two months' duration. She had been applying antibiotic ointment and moisturizers to the area without benefit. The lesion had enlarged over time and she developed pain over the whole finger, especially with movement. She had no fevers, chills, night sweats, or weight loss. Past medical history was significant for psoriasis and psoriatic arthritis of twelve years' duration. She had received multiple tumor necrosis factor (TNF)-α inhibitors over this period, most recently etanercept for the last four years. Social history revealed she had a fish tank at home. Upon further questioning, she reported she might have cut her right fourth finger at the site of the lesion when she turned on the fish tank light, a few weeks prior to the development of the lesion.

On initial examination, she had a 1.5 cm nodule on the dorsum of the right fourth finger over the proximal interphalangeal joint (PIP) (Figure 4.3.1). There was small central crusting and erythema, but no drainage. Range of motion was preserved. There were small erythematous, scaly plaques over the lower extremities, consistent with psoriasis. Her laboratory values were remarkable for a slight elevation in white blood cell count (13 000 cells/mm^3) with 9000 cells/mm^3 polymorphonuclear cells.

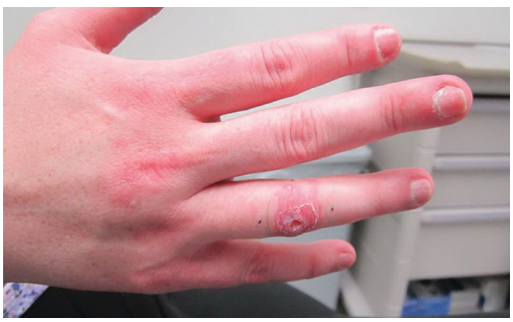


FIGURE 4.3.1: Nodular lesion on the PIP of the fourth finger on initial examination.

DIFFERENTIAL DIAGNOSIS

The chronicity and the appearance of lesion were most concerning for nodular lymphangitis, typically due to organisms such as *Sporothrix schenckeii, Nocardia* sp, *Mycobacterium marinum*, systemic mycoses, tularemia or leishmaniasis, *Sporotrichosis*, and primary cutaneous nocardiosis are commonly associated with gardening injuries. The patient's social history did not reveal such an exposure, nor did it reveal travel to a leishmania endemic area. Tumor necrosis factor inhibitors are commonly associated with infections due to atypical mycobacteria or endemic fungi, such as histoplasmosis in the Midwest. Given the fish tank exposure, highest on the differential was *M marinum* infection. A biopsy was performed, after which she was empirically started on clarithromycin and ethambutol for probable *M marinum* infection. Etanercept and methotrexate were discontinued. Anatomic pathology showed spongiosis with superficial and deep perivascular and perieccrine inflammation, suggestive of perniosis. Gram stain, acid-fast bacilli stain, and fungal stain were negative.

One week after starting treatment, she presented with worsening pain over the right 4th PIP joint and a new erythematous nodule with fluctuance at the base of her 3rd and 4th digits (Figure 4.3.2). A magnetic resonance image of the right hand showed increased cutaneous and subcutaneous T2 signal and postcontrast enhancement along the dorsum of the hand along the mid/distal second to fourth metatarsals and along the dorsal aspect of the ring finger at the PIP joint. There was no evidence

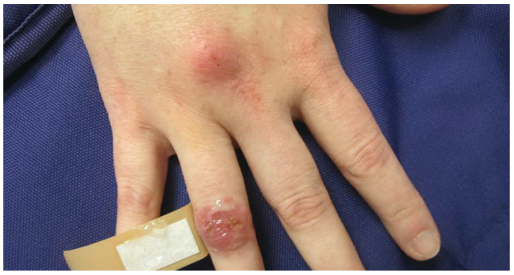


FIGURE 4.3.2: New nodule at the base of the third and fourth digits one week after initiation of treatment.

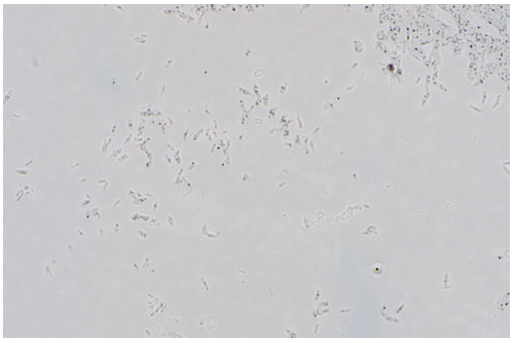


FIGURE 4.3.4: Gram stain of lesion aspirate. Ghost-like beaded rods seen in the stain are suggestive of mycobacterial infection.

of abscess, synovitis, or septic arthritis (Figure 4.3.3). A Gram stain of an aspirate of the fluctuant lesion over the third metacarpal area showed ghost-like beaded rods, suggestive of nontuberculous mycobacterial infection (Figure 4.3.4). Acid-fast bacilli smear was also positive. Both the initial biopsy sample and the aspirate eventually grew *M marinum*. Clarithromycin and ethambutol were continued.

Approximately one month after starting treatment, she presented with worsening pain and new satellite lesions around the lesion on her fourth finger (Figure 4.3.5). She also had new nodular lesions over the anterolateral wrist and arm, tracking up toward the elbow. Incision and drainage of the two hand lesions were performed to decrease bacterial load, and rifampin was added to the antimicrobial regimen. Approximately one month later, subcutaneous abscesses on the wrist and arm were still getting larger. Surgical debridement was performed for these lesions. Anatomic pathology showed poorly developed granulomas and culture again grew *M marinum.* Over the course of her treatment, all surgical sites healed well (Figure 4.3.6). Nine months after starting treatment, etanercept was restarted due to inability to control psoriatic arthritis with other therapies. Her antimycobacterial therapy was continued for an additional three months to complete a year of therapy, with full resolution of her lesions. When seen in follow up four months after cessation of anti-mycobacterial therapy, there was no evidence of relapse despite continuation of etanercept.

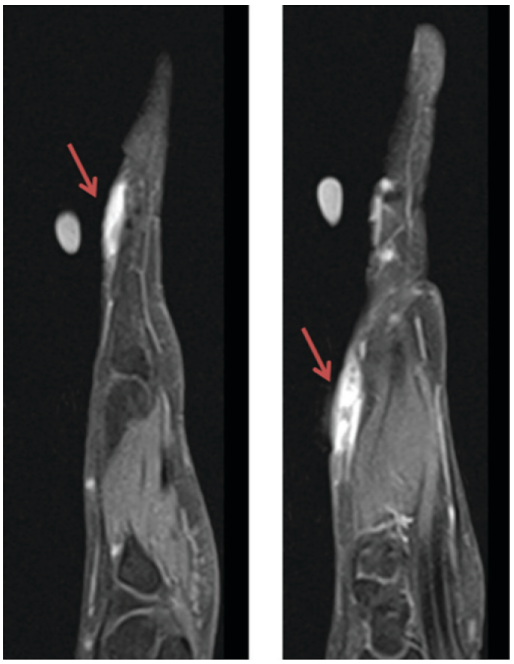


FIGURE 4.3.3: MRI of the right hand showing cutaneous and subcutaneous inflammation without evidence of abscess or septic arthritis.

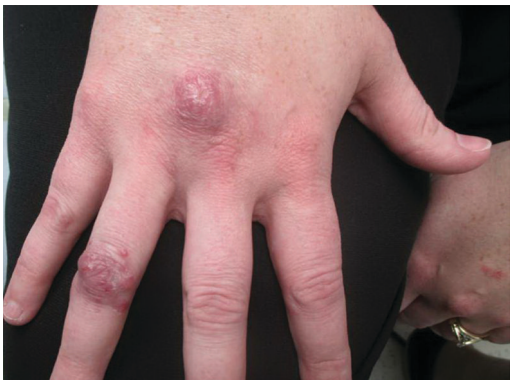


FIGURE 4.3.5: New satellite lesions on the fourth finger despite one month of antimicrobial therapy for *M. marinum*.

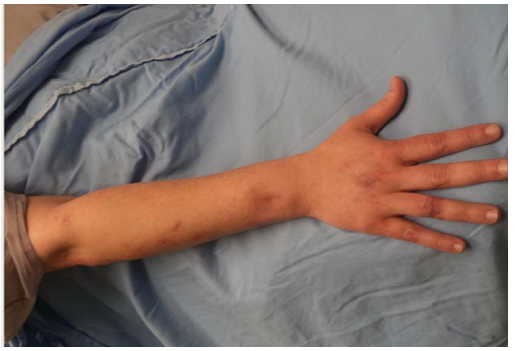


FIGURE 4.3.6: Resolution of nodular lesions after surgery medical therapy.

DISCUSSION

Epidemiology of Nontuberculous Mycobacteria

Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms, which are found in water and soil [1]. They are opportunistic pathogens that can lead to a wide variety of infections, the majority of which involve pulmonary disease [2]. In the United States, most pulmonary NTM disease is caused by *Mycobacterium avium* complex, *Mycobacterium kansasii*, or *Mycobacterium abscessus* [3]. It almost exclusively occurs in individuals over age forty-five, with a predilection for women and those with underlying lung disease [3]. Nontuberculous mycobacteria also cause skin and soft tissue infections, bone and joint infections, lymphadenitis, and, disseminated disease, which is usually in the immunocompromised host [4].

Mycobacterium marinum is commonly isolated from fresh and salt water, and it can cause granulomatous soft tissue or bone disease when contaminated water is exposed to traumatized skin, leading to "swimming pool" or "fish tank" granuloma [5]. Lesions are usually solitary but ascending lesions can occur, leading to "sporotrichoid disease". Cutaneous disease can be seen in both immunocompetent and immunocompromised persons, whereas disseminated disease with bursa, tendon, or bone involvement is more common in immunocompromised persons [6].

Tumor Necrosis Factor Inhibitors and Nontuberculous Mycobacteria

Tumor necrosis factor-α plays an essential role in in host defense against intracellular pathogens [7]. An initial review by the US Food and Drug Administration postmarketing surveillance system (MedWatch) in 2004 for reports of granulomatous disease occurring on anti-TNF therapy found that mycobacterial disease was more common than other granulomatous diseases [8]. In regions with low tuberculosis (TB) incidence, NTM infection may be a more frequent complication of anti-TNF therapy [9]. In a large cohort of anti-TNF users from Northern California, NTM disease rates were found to be ten-fold higher than that in the unexposed rheumatoid arthritis and general population [10]. In this cohort, NTM disease occurred more frequently and a greater proportion of NTM patients died. With good adherence to screening for TB prior to use, anti-TNFs NTM has become more common than TB. Extrapulmonary disease, disease dissemination, and mortality have also been reported to be higher in patients on anti-TNF therapy [4, 10].

Mycobacterium marinum infection, similar to other NTM infections, has been reported with anti-TNF therapy as well as steroid use. Review of PubMed does not reveal increased incidence of *M marinum* infections with disease-modifying antirheumatic drugs.

Diagnosis of *M marinum* infections is usually delayed by weeks to months, with the time from clinical presentation to correct diagnosis varying from one to twenty-seven months, with a mean interval of seven months [11, 12]. Atypical pathogens, including *M marinum*, are usually only considered when these infections do not respond to treatment for typical bacterial infections. In the presence of compatible exposure history, diagnosis should be confirmed by histology and bacteriology. Histology can be nonspecific during early stages of infection [11, 13]. Acid-fast bacilli staining of skin and soft tissue specimens is positive in only 9%–13% of cases of localized cases, but it can yield higher results in disseminated cases [13]. Culture from a tissue biopsy is the gold standard for diagnosis, with reports of 70%–80% positivity with rapid transportation and processing of specimens and appropriate culture conditions [14]. It is important to notify the microbiology laboratory that *M marinum* infection is suspected because optimal growth temperature is 30–32°C.

Treatment and Prevention

Nontuberculous mycobacteria infections in patients on anti-TNF therapy may show delayed response to therapy and cause significant morbidity and mortality [15]. The optimal anti-mycobacterial combinations and duration of therapy are unknown. Although there are

multiple reports of successful treatment with a single agent (doxycycline, clarithromycin, or trimethoprim-sulfamethoxazole), the American Thoracic Society/Infectious Disease Society of America guidelines recommend treating *M marinum* infections with two active agents for one to two months after resolution of symptoms [5]. Clarithromycin and ethambutol combination is probably the most effective and best tolerated combination, with the addition of rifampin for deep tissue infections. In a review of *M marinum* arthritis cases, average treatment was eight months with a range of three to twelve months [6]. Use of second-line agents, such as amikacin or streptomycin, has been reported in cases of progressive cutaneous or joint involvement [6]. In most patients, surgery is not necessary and may be contraindicated due to possible extension of infection to deeper tissues or to the creation of wounds that do not heal for prolonged periods [16]. Although there are no criteria for timing of surgical intervention, debridement may be necessary for disease involving closed spaces of the hand or disease that fails to respond to antimicrobial therapy alone [5, 6].

There are many reports of NTM disease progression on aggressive antimicrobial therapy while anti-TNF therapy is continued. Given the morbidity and mortality associated with these infections, discontinuation of anti-TNF therapy is recommended when NTM infection is diagnosed [17, 18]. There are reports of reinitiation of anti-TNF therapy with or without recurrence of NTM disease after treatment with antimicrobials [18, 19]. It is not known when and in which patients it might be safe to reinitiate anti-TNF. There are few reports of NTM infections in patients on disease-modifying drugs and steroids. Animal models suggest other biologic agents, such as tocilizumab and abatacept, might carry less mycobacterial risk than anti-TNFs. It might be reasonable to start a disease-modifying drug or second-line biologic agent rather than anti-TNF, especially if the NTM infection has taken a prolonged period of time to be cured [3]. If anti-TNF is definitely needed, in the absence of definite criteria, it seems reasonable to continue atypical mycobacterial therapy for a few months to ensure NTM disease will not relapse.

Unlike TB, NTM does not cause reactivation disease; consequently, most NTM disease on anti-TNF therapy reflects newly acquired disease. In rare cases, pulmonary NTM disease may be due to progression of active disease that had not been diagnosed before initiation of anti-TNF therapy. There are no evidence-based recommendations for screening patients for pulmonary NTM prior to initiation of TNF blockers, but chest computed tomography scan or culture of respiratory specimens might be considered in patients with abnormalities on chest-ray or chronic cough [10, 20]. A complete social history could also help physicians identify risk factors for NTM disease. Specific activities that should be queried for *M marinum* infection include aquarium care, fishing, or handling of saltwater fish, shrimp, fins, and other marine life, and swimming in nonchlorinated pools. Patients can then be counseled about avoiding these activities or, if not possible, to use skin protection such as gloving to decrease the likelihood of exposures that might lead to NTM disease [15, 19].

In conclusion, NTM infections, including *M marinum* infection, are more common and can be more severe in patients on anti-TNF. Enhanced suspicion is required for diagnosis, and treatment can be more challenging, occasionally necessitating surgical intervention.

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REFERENCES

1. Falkinham JO 3rd. Ecology of nontuberculous mycobacteria—where do human infections come from? Semin Respir Crit Care Med. 2013;34:95.
2. Tortoli E. Microbiological features and clinical relevance of new species of the genus *Mycobacterium*. Clin Microbiol Rev. 2014;27:727.
3. Winthrop KL, Iseman M. Bedfellows: mycobacteria and rheumatoid arthritis in the era of biologic therapy. Nat Rev Rheumatol. 2013;9:524.
4. Winthrop KL, Chang E, Yamashita S, et al. Nontuberculous mycobacteria infections and anti-tumor necrosis factor-alpha therapy. Emerg Infect Dis. 2009;15:1556.
5. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367.
6. Danko JR, Gilliland WR, Miller RS, Decker CF. Disseminated *Mycobacterium marinum* infection in a patient with rheumatoid arthritis receiving infliximab therapy. Scand J Infect Dis. 2009;41:252.
7. Clay H, Volkman HE, Ramakrishnan L. Tumor necrosis factor signaling mediates resistance to mycobacteria by inhibiting bacterial growth and macrophage death. Immunity. 2008;29:283.
8. Wallis RS, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor

necrosis factor blockade: correction. Clin Infect Dis. 2004;39:1254.
9. Winthrop KL, Yamashita S, Beekmann SE, et al. Mycobacterial and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case finding through the Emerging Infections Network. Clin Infect Dis. 2008;46:1738.
10. Winthrop KL, Baxter R, Liu L, et al. Mycobacterial diseases and antitumour necrosis factor therapy in USA. Ann Rheum Dis. 2013;72:37.
11. Dodiuk-Gad R, Dyachenko P, Ziv M, et al. Nontuberculous mycobacterial infections of the skin: a retrospective study of 25 cases. J Am Acad Dermatol. 2007;57:413.
12. Adhikesavan LG, Harrington TM. Local and disseminated infections caused by *Mycobacterium marinum*: an unusual cause of subcutaneous nodules. J Clin Rheumatol. 2008;14:156.
13. Dolenc-Voljc M, Zolnir-Dovc M. Delayed diagnosis of *Mycobacterium marinum* infection: a case report and review of the literature. Acta Dermatovenerol Alp Pannonica Adriat. 2010;19:35.
14. Safdar N, Abad CL, Kaul DR, Saint S. Clinical problem-solving. Skin deep. N Engl J Med. 2012;366:1336.
15. Ferreira J, Grochowsky J, Krakower D, et al. *Mycobacterium marinum*: an increasingly common opportunistic infection in patients on infliximab. Am J Gastroenterol. 2012;107:1268.
16. Huminer D, Pitlik SD, Block C, et al. Aquarium-borne *Mycobacterium marinum* skin infection. Report of a case and review of the literature. Arch Dermatol. 1986;122:698.
17. Levesque BG, Sandborn WJ. *Mycobacterium marinum* infection in the setting of antitumor necrosis factor alpha therapy for Crohn's disease. Inflamm Bowel Dis. 2011;17:1443.
18. Kump PK, Hogenauer C, Wenzl HH, Petritsch W. A case of opportunistic skin infection with *Mycobacterium marinum* during adalimumab treatment in a patient with Crohn's disease. J Crohns Colitis. 2013;7:e15.
19. Bakker CV, Kardaun SH, Wilting KR, et al. Why you should ask your patients about their fishing hobbies. The Neth J Med. 2013;71:366.
20. Iseman MD. Mycobacterial infections in the era of modern biologic agents. Am J Med Sci. 2011;341:278.

4.4

The Perils of Processed Foods

JESSIE TORGERSEN, MD AND TODD BARTON, MD

CASE PRESENTATION

A 56-year-old female presented to the emergency room with one day history of word-finding difficulties and right-sided weakness. Her past medical history was notable for ulcerative colitis treated with infliximab for over one year, sarcoidosis on chronic prednisone at 30 mg daily, seizure disorder treated with phenobarbital, and history of completed therapy for latent tuberculosis infection. In the emergency room, she was afebrile and normotensive, but she subsequently sustained three witnessed right-sided partial seizures with secondary generalization. Seizures were aborted with lorazepam, and her postictal exam was notable only for somnolence and mild right leg and arm weakness. Initial laboratory data revealed leukocytosis with white blood cell (WBC) count of 15 300 cells/μL, normal comprehensive metabolic panel, therapeutic phenobarbital levels, and negative urinalysis and urine toxicology screen. A subsequent computed tomography scan of the head noted no acute process, and cerebrospinal fluid (CSF) fluid analysis was remarkable for absence of all cells, mildly elevated protein at 63 mg/dL, and normal glucose at 50 mg/dL.

Therapy was started empirically with intravenous acyclovir for herpes encephalitis, and she was given therapeutic doses of antiepileptics as well. A magnetic resonance image (MRI) of the brain performed on hospital day two did not note obvious pathology, but it was significantly limited by motion artifact. She continued to have intermittent partial seizures and, on hospital day four, became febrile to 103.9°F and progressed to status epilepticus requiring intubation and midazolam infusion. An MRI of the brain noted abnormal signal intensity in the left parietal lobe on T2 (Figure 4.4.1) and diffuse cortical hyperintensity on FLAIR imaging. Therapy with vancomycin, cefepime, and metronidazole was started for aspiration pneumonia, yet the patient remained febrile with negative cultures to date.

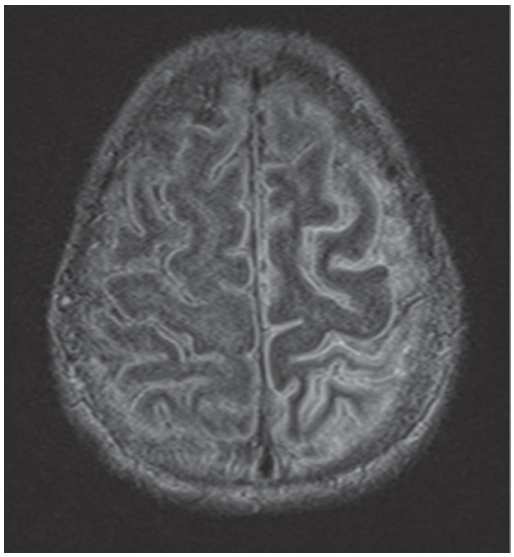

FIGURE 4.4.1: MRI image showing left parietal lobe signal intensity.

Additional CSF studies including paraneoplastic panel and herpes simplex virus (HSV) polymerase chain reaction were negative. Acyclovir was discontinued, and extensive evaluation to uncover etiology of febrile seizures was continued. Repeat CSF analysis on hospital day seven showed 1830 WBC/μL with 86% neutrophils, 120 red blood cells/μL, elevated protein at 186 mg/dL, and low glucose at <20 mg/dL while CSF cytology was nondiagnostic, revealing acute and chronic inflammation.

DIFFERENTIAL DIAGNOSIS

Meningoencephalitis in an immunosuppressed patient is an infectious disease emergency and warrants empiric broad-spectrum antimicrobials while a thorough evaluation is undertaken. Immune suppression induced by tumor necrosis factor (TNF)-α antagonists can increase the

risk of infection due to community-acquired, opportunistic, and environmental organisms. Typical central nervous system (CNS) pathogens such as *Streptococcus pneumoniae* and *Neisseria meningitidis* should be considered as well as members of the *Herpesviridae* family, including HSV, varicella-zoster virus, and cytomegalovirus. Opportunistic infections with CNS manifestations, including tuberculosis, toxoplasmosis, and cryptococcosis should also be part of the differential diagnosis. Additional environmental organisms to consider include those with CNS tropism, such as *Nocardia* species and *Listeria monocytogenes*. On hospital day nine, the patient's CSF cultures were growing Gram-variable bacilli, prompting change of antibiotic regimen to ampicillin and gentamicin. Cerebrospinal fluid cultures later identified the organism as *Listeria monocytogenes*. After a prolonged hospitalization, the patient recovered with minimal neurologic sequelae and was discharged to a rehabilitation center.

DISCUSSION

Listeria meningoencephalitis: Clinical Features

Listeria monocytogenes is a Gram-positive motile bacillus that is found widely throughout the environment, often in decaying vegetation. It also has been isolated from a host of food products including processed meats and soft cheeses. A well known, albeit rare foodborne pathogen, *Listeria*, is generally associated with gastrointestinal illness, occurring one to ten days after ingestion (mean six days), which is self-limited with symptoms abating in one to three days [1]. Although the Centers for Disease Control and Prevention estimates that major foodborne pathogens cause 9.4 million cases of gastroenteritis in the United States annually, only 1591 cases and 255 deaths are attributable to *Listeria* [2].

Invasive listeriosis can manifest as bacteremia, septic arthritis, meningoencephalitis, or brain abscess. This disease predominantly affects the very young, elderly, and immunosuppressed populations. Invasive disease likely follows ingestion of the organism, and although incubation periods are not clearly established, estimates range from eleven to seventy days (mean thirty-one days) [1].

Listeria has a tropism for the CNS and is one of the most common causes of bacterial meningitis in adults >50 years old [3]. It is thought that *Listeria* enters the CNS via three pathways: hematogenously, direct spread along cranial nerves, or via intracellular passage with leukocytes [4]. Affected patients often present with encephalitis and focal neurological deficits. The intracellular nature of this pathogen often complicates recovery of the organism in culture with case series of meningoencephalitis reporting positive CSF cultures in approximately 40% of cases [1]. There are no findings of CNS listeriosis that are pathognomonic. Cerebrospinal fluid profiles can vary but commonly have normal glucose with neutrophilic pleocytosis, and, despite the species nomenclature, monocytosis is an unusual finding in human disease [5, 6]. Rare manifestations, including subcortical abscesses in thalamus or brainstem and rhomboencephalitis, have been highly associated and should prompt one to consider *Listeria* infection.

Since the licensing of the first TNF-α antagonists in the United States in 1998, several case reports of invasive listeriosis have been reported in patients receiving such therapies, offering insight into pathogenesis of systemic disease (Table 4.4.1) [7]. Tumor necrosis factor-α is an important component of cell-mediated immunity, released from macrophages in response to proinflammatory stimuli and leading to a cascade culminating in T- and B-cell activation. Tumor necrosis factor-α similarly is an important cytokine involved in immune defense against intracellular pathogens through granuloma formation and maintenance. Inhibition of TNF-α has been shown to increase the incidence of infection by several intracellular organisms, and murine models have demonstrated a clear susceptibility to CNS *Listeria* in TNF-deficient mice [8]. Although these agents have revolutionized the treatment of inflammatory and autoimmune diseases, the increased number of invasive listeriosis cases in patients on such therapy led the US Food and Drug Administration (FDA) to require that package inserts include increased risk of infection with *Listeria* in patients treated with TNF-α antagonists.

The absolute risk of invasive listeriosis conferred by TNF-α antagonists has not been delineated, likely due to the overall low incidence of disease and the concomitant use of various immunosuppressive agents. Several postlicensing studies published to date have provided some estimates of disease risk where incidence estimates range from 1.8 to 15.5 cases of listeriosis per 100 000 treated people [9]. Most cases published to date have been associated with infliximab, one of the first TNF-α antagonists to be licensed. This has led some investigators to suggest that infection

TABLE 4.4.1. DESCRIPTION OF TNF-α ANTAGONISTS LICENSED IN UNITED STATES

TNF-α Antagonists		
Name	Year of FDA approval	Mechanism of Action
Etanercept	1998	Recombinant DNA-derived fusion protein of TNF receptor and Fc portion of human immunoglobulin (Ig)G1
Infliximab	1998	Chimeric IgG1κ monoclonal antibody (Ab) against TNF-α
Adalimumab	2002	Recombinant human monoclonal IgG1 Ab against TNF-α
Certolizumab pegol	2008	Humanized Fab' fragment of monoclonal Ab against TNF-α conjugated to polyethylene glycol
Golimumab	2009	Human monoclonal IgG1κ Ab against TNF-α

risk may be agent-specific, varying by mechanism of action and relative level of TNF-α suppression [10]; however, additional investigation is required to determine incidence of infection by specific agent.

Diagnosis and Treatment

Diagnosis of invasive listeriosis requires a high index of suspicion and is largely dependent upon recovery of the organism by culture. Standard culture media is adequate to support growth of *Listeria*. Colonies are often identified as Gram-positive bacilli or coccobacilli with characteristic tumbling motility on wet mount; however, the small colonies can be initially mistaken for diphtheroids. Empiric therapy for invasive listeriosis should be considered in all immunosuppressed patients presenting with meningoencephalitis, including patients treated with TNF-α antagonists.

No randomized clinical trials have been performed to identify the optimal antibiotic agent against *Listeria*, yet clinical experience is greatest with ampicillin and trimethoprim-sulfamethoxazole. In severe infections, such as endocarditis or CNS infections, or in patients with severely impaired T-cell function, ampicillin with gentamicin is recommended given findings of in vitro synergy [4]. Duration of treatment is generally prolonged with recommended duration of *Listeria* meningitis ≥3 weeks. Ongoing TNF-α antagonist therapy should be carefully considered in the setting of an acute serious infection, such as *Listeria* meningoencephalitis. Although it is likely that deferring ongoing therapy would be beneficial for treatment of the infection, no specific data are available to assess this, and the risks of either holding immunosuppression or substituting alternative immunosuppression must be considered for each

TABLE 4.4.2. STANDARD INFECTION PREVENTION MEASURES OF FOOD HANDLING IN IMMUNOCOMPROMISED [12]

Wash	• Wash hands before eating and between preparing produce and raw meats • Rinse or scrub all produce with clean brush in tap water before eating
Clean	• Utensils, countertops, and cutting boards used to prepare raw meats should be cleaned thoroughly after each use • Juices from raw or refrigerated meats should be cleaned promptly to avoid contamination of other foods
Prepare	• Cook meat, poultry, and seafood to internal temperature over 165°F or until steaming
Store	• Keep refrigerator below 40°F and freezer below 0°F to limit bacterial growth • Produce and raw meats should be stored separately to avoid contamination • Discard foods near or past expiration date • Promptly refrigerate or freeze foods; use leftovers within 3 days
Avoid	• Unpasteurized dairy products and soft cheeses • Raw foods • Processed meats, hot dogs, cold cuts, and refrigerated meats/fish unless cooked to internal temperature above 165°F

individual. Despite antibiotic treatment, CNS *Listeria* is associated with significant morbidity and mortality of 11%–30% [9]. Standard infection prevention measures should be discussed with patients receiving TNF-α antagonists, and consideration of dietary restrictions to reduce exposure to *Listeria* should also be taken into account (Table 4.4.2) [11, 12].

REFERENCES

1. Lorber B. Listeriosis. Clin Infect Dis. 1997;21:1.
2. Scallan E, Hoekstra R, Angulo F, et al. Foodborne illness acquired in the United States—major pathogens. Emerg Infect Dis. 2011;17:7.
3. Thigpen M, Whitney C, Messonnier N, et al. Bacterial meningitis in the United States, 1998–2007. N Engl J Med. 2011;364:2016.
4. Clauss H, Lorber B. Central nervous system infection with *Listeria monocytogenes*. Curr Infect Dis Rep. 2008;10:300.
5. Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with *Listeria monocytogenes*. 33 years' experience at a general hospital and review of 776 episodes from the literature. Medicine. 1998;77:313.
6. Stanley NF. Studies on *Listeria monocytogenes*. 1. Isolation of a monocytosis-producing agent (MPA). Aust J Exp Bio Med Sci. 1949;27:123.
7. Wallis R, Broder M, Wong J, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis. 2004;38:1261.
8. Virna S, Deckert M, Lutjen S, et al. TNF is important for pathogen control and limits brain damage in murine cerebral listeriosis. J Immunol. 2006;177:3972.
9. Bodro M, Paterson D. Listeriosis in patients receiving biologic therapies. Eur J Clin Microbiol Infect Dis. 2013;32:1225.
10. Ehlers S. Tumor necrosis factor and its blockade in granulomatous infections: differential modes of action of infliximab and etanercept? Clin Infect Dis. 2005;41:S199.
11. Davies R, Dixon WG, Watson KD. Influence of anti-TNF patient warning regarding avoidance of high risk foods on rates of listeria and salmonella infections in the UK. Ann Rheum Dis. 2013;72:461.
12. Centers for Disease Control and Prevention (CDC). Outbreak of invasive listeriosis associated with the consumption of hog head cheese--Louisiana, 2010. MMWR Morb Mortal Wkly Rep. 2011;60:401.

4.5

When the Dust Settles

JENNIFER M. BABIK, MD, PHD

CASE PRESENTATION

A 75-year-old woman with rheumatoid arthritis presented to her rheumatologist with left eye pain and decreased visual acuity. She was found to have sight-threatening scleritis with scleral perforation. She had previously been on leflunomide alone and at that visit was changed to prednisone 60 mg daily, low-dose weekly methotrexate, and infliximab 5 mg/kg every eight weeks. Screening interferon-gamma release assay (for latent tuberculosis infection) and chest x-ray were negative before starting infliximab. She had excellent improvement in her joint and eye disease, and the prednisone was tapered down to 10 mg PO daily over the next few months. She was continued on methotrexate and infliximab. Nine months after her initial presentation with scleritis, the patient was admitted to the hospital with a one-month history of severe fatigue, anorexia, and weight loss. She had lost fifteen pounds in the last month due to fatigue that was so profound she felt she did not have the energy to prepare food. She complained of multiple new painful, mildly pruritic skin lesions on her face, chest, and arms that had developed over the last few weeks. She otherwise denied fevers, chills, night sweats, shortness of breath, cough, hemoptysis, headache, abdominal pain, diarrhea, dysuria, or new joint symptoms.

The patient's other medical history was unremarkable except for mild hypertension, for which she was taking hydrochlorothiazide. She was on no other medications aside from the immunosuppression, as mentioned, and she had no drug allergies. She was white and was born in San Jose, California but had been living in Fresno, California for the past 20 years. She lived in an apartment complex that had been undergoing construction of new units over the last year. She had not traveled outside of California for many years and had not spent significant periods of time in the midwestern or eastern United States. Her only prior international travel was to Mexico on vacation while she was a college student. She had no known risk factors for tuberculosis. She owned a cat but had no other animal exposures. She did not consume any unpasteurized milk or cheese products. She had no sick contacts.

On admission to the hospital, she was febrile to 39˚C and tachycardic to 110 beats per minute. Other vital signs were normal. Her exam was notable for scattered wheezes as well as skin lesions on the face, arms, and trunk (Figure 4.5.1). The remainder of the physical exam was normal. Initial laboratory studies were significant for a white blood cell count of 11.3×10^9 cells/L with a neutrophil predominance (9.7×10^9 cells/L) and slightly elevated eosinophil count (0.46×10^9 cells/L). She had a hemoglobin of 11 g/dL, which was her baseline, and a normal creatinine. Her total bilirubin was normal, but aspartate transaminase, alanine transaminase, and alkaline phosphatase were all mildly elevated at 50 U/L, 86 U/L, and 206 U/L, respectively. Her sedimentation rate was >100 mm/hour. A chest radiograph was normal but computed tomography (CT) of the chest revealed innumerable tiny nodules distributed throughout the lungs in a random pattern with marked mediastinal adenopathy (Figure 4.5.2). An abdominal ultrasound was normal.

DIFFERENTIAL DIAGNOSIS

This woman's history of recently augmented immunosuppression including infliximab, fever, fatigue, weight loss, skin lesions, and a miliary pattern on chest CT were highly concerning for a disseminated infection. Framing the differential broadly, infections that can cause concomitant skin and pulmonary disease include endemic mycoses (*Histoplasma, Coccidioides, Blastomyces*), *Cryptococcus*, mycobacteria (both tuberculosis and nontuberculous mycobacteria), *Nocardia*, and endocarditis. The initiation of a tumor necrosis factor (TNF) antagonist in the

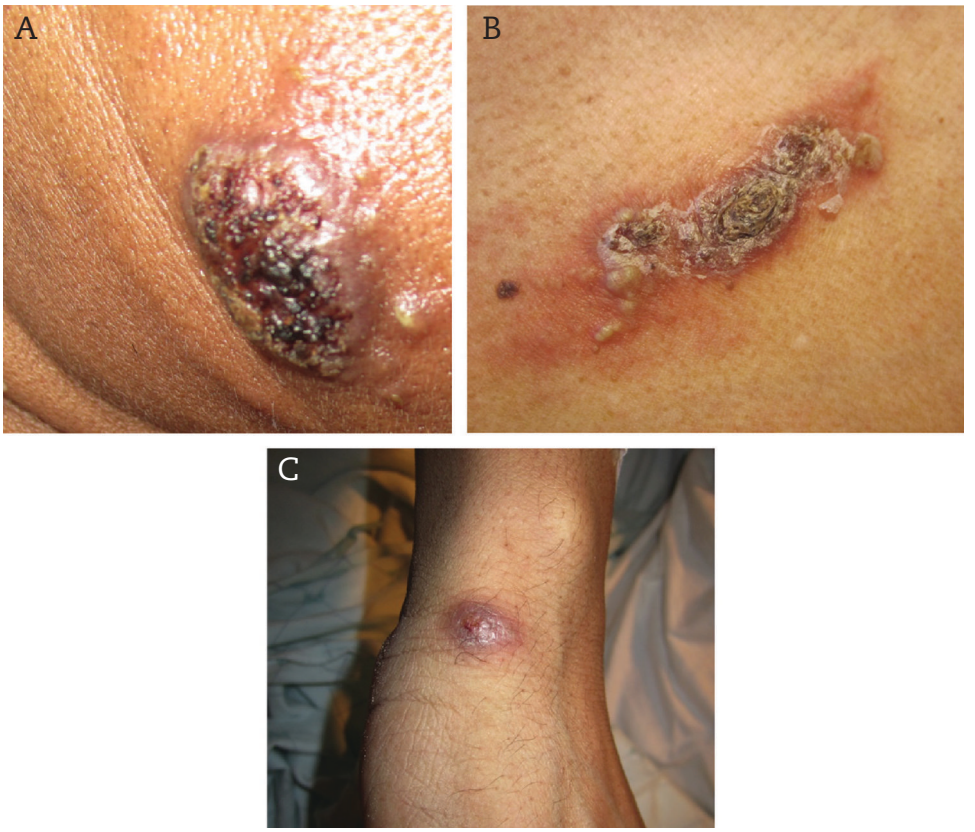

FIGURE 4.5.1: Photos of the patient's rash on the cheek (A), trunk (B), and wrist (C). Photos courtesy of Roberto R. Ricardo-Gonzalez, MD, PhD.

last year raises significant concern for granulomatous disease, in particular tuberculosis, histoplasmosis, and coccidioidomycosis—all of which can cause a miliary pattern on chest CT. Tumor necrosis factor blockers also increase the risk of *Legionella, Listeria, Salmonella*, and other fungi such as *Pneumocystis, Cryptococcus, Aspergillus*, and *Candida*. Of these, only cryptococcal infection would be consistent with the clinical picture described here. Given the patient's residence in the San Joaquin Valley and low-grade eosinophilia, disseminated coccidioidomycosis is the most likely diagnosis.

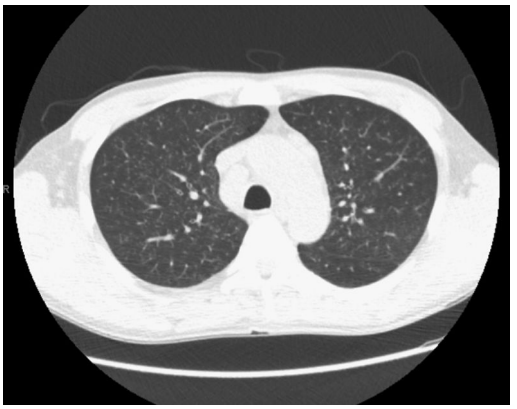

FIGURE 4.5.2: Computed tomography of the chest showing innumerable tiny nodules distributed in a random (miliary) pattern.

ADDITIONAL TESTING

Histopathologic examination of a skin biopsy from the right wrist lesion showed suppurative and granulomatous inflammation with *Coccidioides* spherules (Figure 4.5.3). Microbiologic examination of the skin biopsy showed spherules containing endospores, and fungal cultures grew *Coccidioides immitis* (Figure 4.5.4). Bacterial and mycobacterial stains and cultures were negative. In addition, one of four blood cultures (in standard bacterial culture bottles) grew *C immitis*. Serum *Coccidioides* immunodiffusion testing for immunoglobulin (Ig) G/IgM was positive, and complement fixation titers

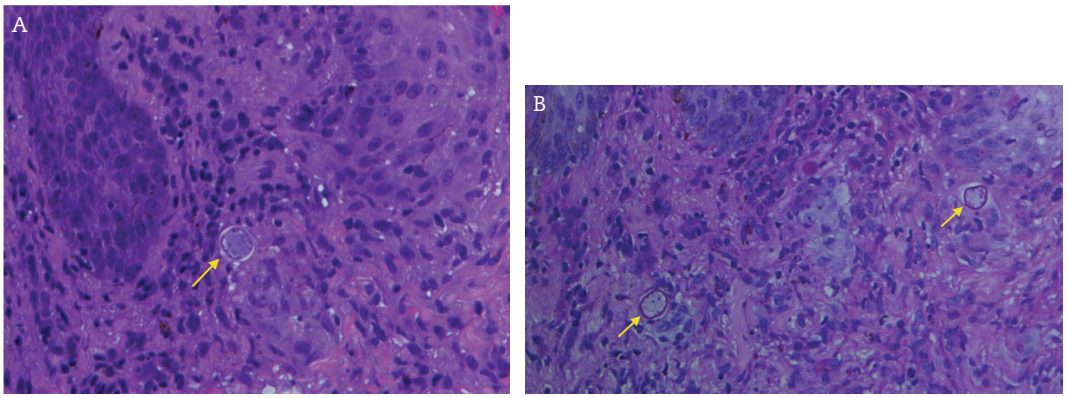

FIGURE 4.5.3: Skin biopsy from the right wrist lesion. (A) Hematoxylin and eosin stain, which shows suppurative and granulomatous inflammation and *Coccidioides* spherules. (B) Periodic acid-Schiff-diastase (PAS-D) stain, which highlights the fungal cell wall of the spherule. Photos courtesy of Philip E. LeBoit, MD.

were 1:256. A lumbar puncture was performed and showed a white blood cell count of 2×10^6 cells/L with no red blood cells and normal protein and glucose. Cerebrospinal fluid fungal culture and *Coccidioides* immunodiffusion and complement fixation assays were negative. Urine *Histoplasma* antigen and serum galactomannan were negative. β-D-glucan was >500 pg/mL. One sputum was smear and culture negative for acid-fast bacilli, and a mycobacterial blood culture was also negative.

TREATMENT OUTCOME

The patient was treated with high-dose fluconazole (800 mg by mouth daily) and began to improve slowly over the next several weeks. Her infliximab and methotrexate were held on admission and prednisone was continued. Her mild eosinophilia and liver enzymes eventually normalized. She will continue on fluconazole for a prolonged course, possibly lifelong given her need for continued immunosuppression for her rheumatoid arthritis. She was not restarted on infliximab.

Final Diagnosis: Disseminated coccidioidomycosis

DISCUSSION

Coccidioidomycosis is caused by *C immitis* and *Coccidioides posadasii*, which live in the soil of the

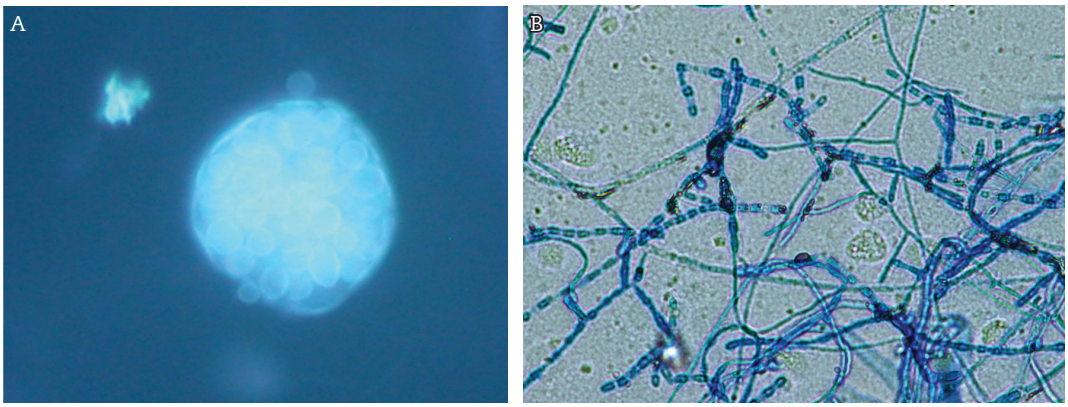

FIGURE 4.5.4: Microbiological examination of the skin biopsy from the right wrist lesion. **(A)** Direct examination of a biopsy specimen by calcofluor white staining, which shows a *Coccidioides* spherule containing endospores. **(B)** Lactophenol cotton blue stain of fungal colonies grown on brain heart infusion agar, which shows septate hyphae and thick-walled arthroconidia. This illustrates that *Coccidioides* is a dimorphic fungus: it grows as a yeast form (spherule) when infecting an animal host at body temperature, but grows as a mold (hyphae with arthroconidia) when outside the body at lower temperatures, such as in the environment or when incubated on media. Photos courtesy of the UCSF Clinical Microbiology Laboratory.

arid areas of southwestern United States, Mexico, and Central and South America. *Coccidioides* spp are highly endemic in the San Joaquin Valley of California, hence the moniker "Valley Fever," and south-central Arizona (Figure 4.5.5). In fact, more than 95% of cases in the United States are reported from Arizona and California, and the incidence has been increasing over the past decade [1]. The arthroconidia of *Coccidioides* are easily released into the air by disruption of the soil, for example, during construction or from heavy winds, where they can then be inhaled and cause infection [2].

Approximately 60% of *Coccidioides* infections are asymptomatic. In the remaining 40% of patients, symptoms develop after an incubation period of one to three weeks. The most common manifestation of primary *Coccidioides* infection is a self-limited pneumonia similar to community-acquired pneumonia. This illness may be associated with erythema nodosum, headache, prominent fatigue, and arthralgias ("desert rheumatism"). Pulmonary sequelae such as nodules or thin-walled cavities develop in ~5% of patients [3]. A small proportion of patients may progress to develop diffuse pulmonary disease, chronic pulmonary disease, or extrapulmonary (disseminated) disease.

Disseminated coccidioidomycosis can manifest in any organ, but the most common sites are the skin, skeletal system, and meninges. Patients at risk for disseminated disease include those of African or Asian (especially Filipino) ancestry, pregnant women in the third trimester, and immunocompromised patients such as those who are human immunodeficiency virus-positive, recipients of solid organ transplants, or those receiving high-dose corticosteroids or TNF antagonists. Immunocompromise is a major risk factor for disseminated disease: although dissemination usually occurs in <1% of all infections, it has been reported to occur in up to 30%–50% of infections in immunosuppressed patients [2, 3].

Tumor necrosis factor antagonists include the soluble TNF receptor etanercept and the anti-TNF monoclonal antibodies infliximab, adalimumab, golimumab, and certolizumab. Use of these biologics increases the risk of several infections, but, in particular, there is an increased risk for granulomatous infections such as tuberculosis, histoplasmosis, and coccidioidomycosis [4, 5]. This is because these agents interfere with granuloma formation and weaken the integrity of existing granulomas. The risk of granulomatous infection is approximately two- to seven-fold higher with infliximab and adalimumab compared with etanercept, and, specifically, the risk of coccidioidomycosis is six-fold higher [4, 5]. The biological basis for this difference in infection risk is not entirely clear, although it likely relates to differences between the soluble TNF receptor and the monoclonal antibodies in terms of their mechanism of action and pharmacokinetics. When compared with etanercept, infliximab and adalimumab achieve higher peak and steady-state levels, have more binding sites for TNF, and can cause antibody-mediated cytotoxicity of monocytes and

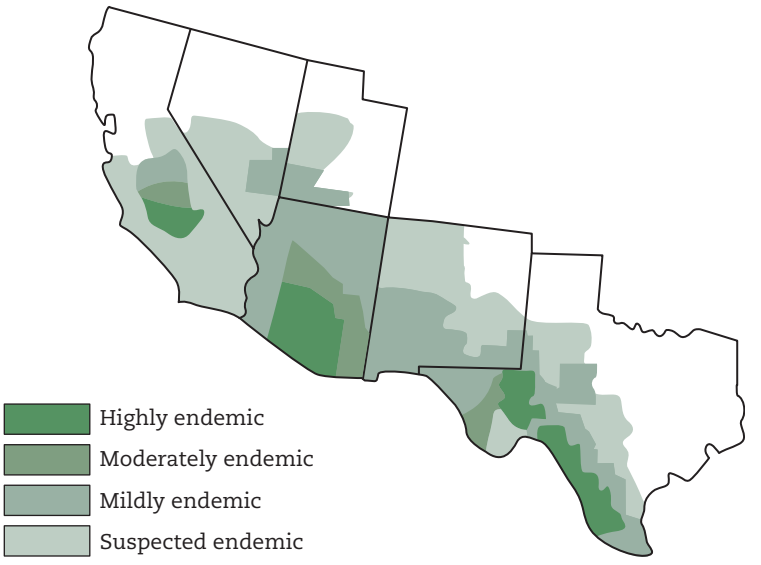

FIGURE 4.5.5: Map showing the areas in the southwestern United States that are endemic for *Coccidioides* [12].

T cells; taken together, these differences may lead to a more prolonged and/or robust TNF inhibition in conjunction with effector cell death, all of which could contribute to the increased infectious risk seen with these agents [4].

There are two case series of coccidioidomycosis in rheumatologic patients residing in endemic areas of the Southwest who were taking TNF blockers [6, 7]. Of the twenty patients described, eighteen were taking infliximab and two were taking etanercept. All patients had pulmonary disease and 25% had disseminated disease. One study calculated the incidence of coccidioidomycosis in rheumatologic patients receiving infliximab at 2.8%, compared with 0.5% for those receiving other therapies, yielding a relative risk of 5.23 [6]. In that study, the cases clustered at two different time points: within three months and approximately forty weeks after starting anti-TNF therapy. The basis for this bimodal distribution is not entirely clear. It does not appear to simply reflect reactivation at the earlier time point versus acute infection at the later time point, because the cases of presumed reactivation and acute infection were distributed equally between the two clusters. Five patients who were diagnosed with coccidioidomycosis by positive serology while on infliximab had negative serologies before anti-TNF therapy initiation. This appears to represent acute infection rather than reactivation, although it is possible that these patients had falsely negative pretreatment serologies in the setting of immunosuppression. Taken together, these results suggest that a significant proportion of *Coccidioides* cases in the setting of anti-TNF inhibition may represent acute infection and would therefore not be detected by serologic screening before anti-TNF therapy initiation [6]. This is in contrast to tuberculosis infection, which is thought to be largely due to reactivation of latent disease given the clustering of cases within the first three months after starting anti-TNF therapy [4].

The diagnosis of coccidioidomycosis is usually made based on a combination of serologic, microbiologic, and histopathologic analysis. Detection of IgM and IgG is usually made by either immunodiffusion or enzyme immunoassay, which have a sensitivity of approximately 70% and 80%, respectively [2]. The IgG titers are measured by complement fixation assay, which has a sensitivity of ~60% [2]. Complement fixation titers can be used to follow disease course over time and are predictive of disease burden; a titer ≥1:16 raises concern for disseminated infection. Sensitivity of serologic testing is lower before the second or third week of symptoms and in some immunosuppressed patients. In solid organ recipients, for example, the sensitivity of a single serologic test is only 21%–56%, but this can be increased to 77% by sending a battery of serologic tests and increased up to 92% by rechecking serologies approximately one month later [8]. It is interesting to note that serologies were positive in >85% of rheumatologic patients taking TNF blockers who developed *Coccidioides* infection [6, 7]. Nevertheless, is important to note the limited sensitivity of serologic assays in immunosuppressed patients, and, as such, negative serologic testing cannot exclude *Coccidioides* infection. When *Coccidioides* infection is suspected, multiple test modalities—including different types of serologic assays as well as cultures of respiratory, skin, or other tissue specimens—should be used [8]. Coccidioides antigen testing is a promising new modality, especially in cerebrospinal fluid. Lumbar puncture should be performed in patients with persistent or progressively severe headaches, mental status changes, meningeal signs, persistent nausea/vomiting, evidence of increased intracranial pressure, or focal neurologic deficits [3, 9]. In addition to routine studies, cerebrospinal fluid should be sent for fungal culture, which is only ~30% sensitive, as well as *Coccidioides* antibodies, which are ~60%–70% sensitive [9]. Clinicians should notify the microbiology laboratory when *Coccidioides* is suspected so that laboratory personnel can be sure to take appropriate precautions to prevent inadvertent inhalational exposure.

Although not all immunocompetent patients with acute pulmonary coccidioidomycosis require treatment, all immunosuppressed patients should be treated given their risk of progression to diffuse pulmonary disease or dissemination. Fluconazole is the treatment of choice in most situations, although amphotericin B may be chosen in some cases where there is rapid progression of disease [3]. Therapy is usually prolonged, and possibly lifelong, depending on the site of infection and need for continued immunosuppression. Patients who develop *Coccidioides* infection while taking a TNF blocker should stop anti-TNF therapy. Whether these patients can safely resume their anti-TNF therapy is unclear. Restarting a TNF blocker would need to be undertaken carefully in the setting of frequent serologic monitoring and likely continued antifungal prophylaxis [10, 11]. Some experts recommend avoiding rechallenge of anti-TNF therapy in patients with prior central nervous system (CNS) *Coccidioides* given the consequences of relapsed CNS disease [10].

There are no official guidelines for *Coccidioides* screening before initiation of a TNF antagonist in patients living in endemic areas. Patients should be screened for symptoms, and a chest x-ray should be obtained to rule out active disease. Some experts recommend obtaining a *Coccidioides* serology before starting therapy, but there are no studies evaluating this approach, and the benefit is not clear given that many patients are already on immunosuppression before starting anti-TNF therapy (impacting the sensitivity of the screening test) and many infections in this setting appear to be acute [6, 10, 11]. At the very least, patients in endemic areas on TNF blockers should be closely monitored for signs of *Coccidioides* infection and counseled to avoid dust storms and high-risk activities that can disrupt soil [10, 11].

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Increase in reported coccidioidomycosis—United States, 1998–2011. MMWR Morb Mortal Wkly Rep. 2013;62:217.
2. Saubolle MA, McKellar PP, Sussland D. Epidemiologic, clinical, and diagnostic aspects of coccidioidomycosis. J Clin Microbiol. 2007;45:26.
3. Galgiani JN, Ampel NM, Blair JE, et al. Coccidioidomycosis. Clin Infect Dis. 2005;41:1217.
4. Wallis RS, Broder MS, Wong JY, et al. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clin Infect Dis. 2004;38:1261.
5. Wallis RS, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: correction. Clin Infect Dis. 2004;39:1254.
6. Bergstrom L, Yocum DE, Ampel NM, et al. Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum. 2004;50:1959.
7. Mertz LE, Blair JE. Coccidioidomycosis in rheumatology patients: incidence and potential risk factors. Ann N Y Acad Sci. 2007;1111:343.
8. Mendoza N, Blair JE. The utility of diagnostic testing for active coccidioidomycosis in solid organ transplant recipients. Am J Transplant. 2013;13:1034.
9. Mathisen G, Shelub A, Truong J, Wigen C. Coccidioidal meningitis: clinical presentation and management in the fluconazole era. Medicine (Baltimore). 2010;89:251.
10. Smith JA, Kauffman CA. Endemic fungal infections in patients receiving tumour necrosis factor-α inhibitor therapy. Drugs. 2009;69:1403.
11. Winthrop KL, Chiller T. Preventing and treating biologic-associated opportunistic infections. Nat Rev Rheumatol. 2009;5:405.
12. Centers for Disease Control and Prevention. Valley fever: awareness is key. Available at: http://www.cdc.gov/features/valleyfever/. Accessed 14 September 2013.

4.6

A Tough Pill to Swallow

MATTHEW WHITSON, MD AND VANDANA KHUNGAR, MD MSC

CASE PRESENTATION

A 56-year-old woman with a history of psoriasis with psoriatic arthritis and hepatitis C presented for an initial hepatology consultation after being referred by her primary care doctor to consider new hepatitis C therapies. Her previous treatment history included an attempt with pegylated interferon in 2008, which was truncated after three months due to the development of new onset psoriasis. Initially, the rash was thought to be secondary to the hepatitis C virus itself, but during tapering of steroids for inflammatory arthritis, she experienced a severe flare of skin plaques on her hands, feet, palms and soles, torso, and buttocks. This was recognized as psoriasis, and her dermatologist prescribed adalimumab, an anti-tumor necrosis factor-alpha (TNF)-α medication, with subsequent improvement in her psoriatic plaques.

The patient presented to a hepatologist for evaluation of hepatitis C, but during her appointment, a thorough gastrointestinal review of systems uncovered a complaint of odynophagia. The patient reported that the odynophagia had begun suddenly to both solids and liquids. She denied any fevers, chills, cough, or any other sign of recent infection. Initial physical examination was most notable for psoriatic lesions on her upper and lower extremities and a normal oropharyngeal examination. When asked whether she had previously experienced thrush or a whitish coating on her tongue, she revealed that her primary care physician had given her nystatin swish and spit two weeks prior that cleared up her oropharyngeal thrush but did not resolve her odynophagia. The decision was made to treat her empirically for *Candida* esophagitis (CE) with a two-week course of fluconazole and schedule an esophagogastroduodenoscopy (EGD) at the end of that period in case symptoms did not improve. The patient's symptoms did not resolve with a full two-week course of fluconazole 200 mg orally daily.

DIFFERENTIAL DIAGNOSIS

At this time, a broader differential of odynophagia in an immunocompromised patient was considered. This includes *CE* that has been incompletely or inadequately treated, viral ulcerations (specifically, cytomegalovirus and herpes simplex virus), medication-induced esophagitits (nonsteroidal anti-inflammatory drugs, bisphosphonates, and antibiotics are the most common), or even reflux esophagitits. The decision was made to continue with the planned EGD given the need for direct visualization of the esophagus and potentially for biopsies.

On EGD, she was found to have significant white and yellow exudates throughout the esophagus and atop the tongue [Figure 4.6.1a, 4.6.1b]. Brushings were taken during the procedure. The brushings demonstrated *Candida* species on pathology (further speciation and minimum inhibitory concentration were unable to be provided by pathology) [Figure 4.6.2a, 4.6.2b,]. She was treated with a two-week course of voriconazole because she likely had a fluconazole-resistant *Candida*, and she experienced complete resolution of her symptoms.

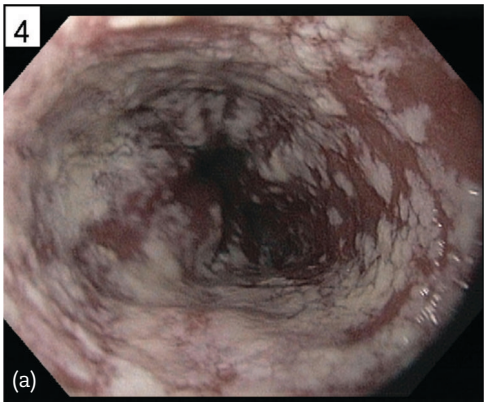

FIGURE 4.6.1a: Whitish yellow exudate at 20 cm into esophagus

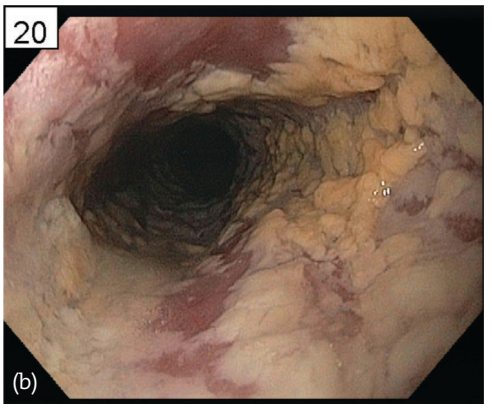

FIGURE 4.6.1b: Whitish yellow exudate at 35 cm into esophagus

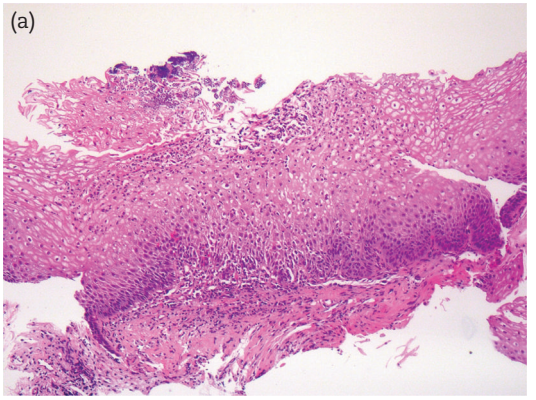

FIGURE 4.6.2a: Low power view of candida

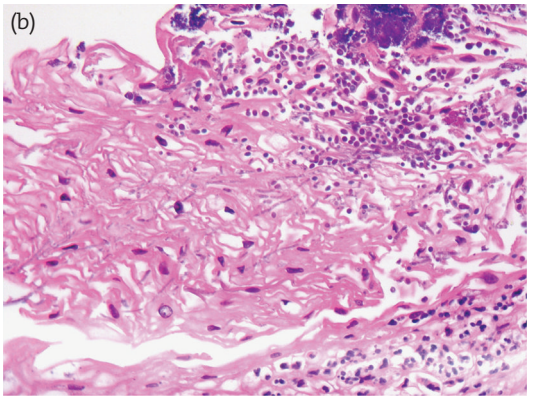

FIGURE 4.6.2b: Low power view of candida

Special thanks to Dr. David Braxton and Dr. Emma. Fourth of pathology for providing figures 4.6.2a and b

MICROBIOLOGY

The *Candida* species are native to the gastrointestinal tract of humans. There are more than 350 separate species within this genus, with at least thirteen different species of *Candida* that have been documented to cause infection in humans. The most common type of *Candida* to cause infection in humans is *Candida albicans*. Infections involving *Candida* can range from life-threatening blood stream infections to relatively benign mucocutaneous infections. *Candida* spp are commonly present in low concentrations in the oral cavity but rarely causes symptoms unless patients are on antimicrobial therapy or are immunocompromised hosts.

Candida esophagitis is a mucocutaneous infection predominantly caused by *Candida albicans*, although there have been case reports of *Candida glabrata* and *Candida krusei* as the predominant pathogen involving the esophagus [1]. Some studies examining the microbiome of patients with inflammatory bowel disease have successfully cultured other strains of Candida compared with normal hosts, including the following: *Candida tropicalis, Candida guilliermondii, Candida kefir*, and *Geotrichum candidum* [2].

RISK FACTORS FOR *CANDIDA* ESOPHAGITIS

There are multiple factors that put patients at an increased risk for CE: human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), various medications, esophageal motility disorders, malignancy, diabetes, alcohol use, and reflux [3]. The medications that may increase the risk for CE include proton pump inhibitors, histamine-2 antagonists, corticosteroids, and immunosuppressant drugs. Tumor necrosis factor (TNF)-α antagonists (infliximab, adalimumab, certolizumab pegol, golimumab, and etanercept) also have been demonstrated to increase the risk of CE. Anti-TNF-α agents are one of the major modalities to treat a variety of illnesses including psoriasis, rheumatoid arthritis, and inflammatory bowel disease. These medications are monoclonal antibodies (chimeric, partly humanized, or fully humanized) that bind to TNF-α and therefore interfere with endogenous TNF-α activity.

Tumor necrosis factor-α has multiple activities in the body including induction of interleukins (ILs), enhancement of leukocyte migration, and the activation of neutrophils and eosinophils. Mechanisms of *Candida* infection in patients receiving anti-TNF-α drugs can be hypothesized. It may be that during anti-TNF-α therapy, patients are more susceptible to fungal infections because their immune systems cannot recognize fungal antigens through Toll-like receptor

signaling; in particular through Toll-like receptor 4 host cells (dendritic cells and macrophages). Blocking TNF-α could inhibit the production of interferon gamma, leading to defective activation of phagocytosis and killing of intracellular pathogens. Tumor necrosis factor-α inhibition could affect E-selectin, vascular cell adhesion molecule-1, and IL-8, which recruit leukocytes at the site of fungal infection. It could also increase apoptosis of peripheral blood monocytes [4]. Regardless of the true mechanism of action, clinically an increased risk of CE is seen with these medications.

A large meta-analysis involving over 7000 patients with inflammatory bowel disease demonstrated a statistically significant increase in oral and esophageal candidiasis (0.03% vs 0.15%) in patients undergoing anti-TNF-α treatment [5]. This increase was seen with each of the varied agents in the class. The relative risk of developing any opportunistic infection was significantly higher with anti-TNF-α therapy (2.05; 95% confidence interval [CI], 1.10–3.85, number needed to harm = 500; 95% CI, 200–1567).

Candidal infections are not specific to anti-TNF-α therapy in the setting of inflammatory bowel disease alone. A case-control study conducted in psoriatic patients being treated with anti-TNF-α agents aimed to study oral *Candida* colonization in this population [6]. In this study, the group treated with anti-TNF-α drugs had more frequent colonization with *Candida* (61.5% vs 41.2% in the nonimmune suppressed group).

DIAGNOSIS AND TREATMENT

Although patients with CE may present with no symptoms, they often have typical symptoms of abdominal pain, odynophagia, dysphagia, or heartburn [7]. Complications can arise in patients with CE including stricture, hemorrhage, perforation, and tracheoesophageal fistula formation. With a high index of clinical suspicion (for example, new onset odynophagia in a patient with AIDS and a low CD4 count), CE is often treated as a presumptive diagnosis. In the right clinical context, a presumptive diagnosis is all that is needed before initiating first-line therapy. A definitive diagnosis of CE requires endoscopic evaluation. Visually, one can see white plaques throughout the esophagus (as seen in our case patient) as well as potential fistulas or strictures as complications. Microscopic diagnosis is confirmed with biopsy and or cytology collection. This is usually sufficient and further culturing is not routinely performed. As resistance patterns continue to change, there may be a future role for culture and susceptibility testing.

Candida esophagitis requires systemic therapy; topical agents have not been shown to be effective treatment for CE. First-line therapy is oral fluconazole for fourteen to twenty-one days. With an increasing pattern of resistance, other antifungal therapies are often considered for second-line therapy, specifically itraconazole and voriconazole. Itraconazole has been shown to successfully treat up to 80% of fluconazole-resistant cases of CE in some studies. Voriconazole is less favored secondary to adverse events. Patients requiring intravenous formulations have also been treated with amphotericin, caspofungin, and micafungin [8].

SUMMARY

There does appear to be a clinically significant increased risk in esophageal candidiasis for patients undergoing anti-TNF-α treatment regardless of the indication. Other immunosuppressed disease states, such as HIV, can also predispose patients to CE. Symptoms such as odynophagia in an immunosuppressed population on anti-TNF-α treatment should prompt clinicians to consider esophageal candidiasis. An empiric trial of systemic therapy with fluconazole is an appropriate first step in managing these patients, because topical treatments such as nystatin swish and swallow will not treat esophageal candidiasis. An endoscopy is warranted if symptoms are not completely resolved after empiric treatment to evaluate for alternative causes or fluconazole-resistant candidiasis.

REFERENCES

1. Sangeorzan JA, Bradley SF, He X, et al. Epidemiology of oral candidiasis in HIV-infected patients: colonization, infection, treatment, and emergence of fluconazole resistance. Am J Med. 1994;97:339.
2. Trojanowska D, Zwolinska-Wcisio M, Tokarczyk M, et al. The role of Candida in inflammatory bowel disease. Estimation of transmission of *C. albicans* fungi in gastrointestinal tract based on genetic affinity between strains. Med Sci Monit. 2010;16:CR451.
3. Underwood JA, Williams JW, Keate RF. Clinical findings and risk factors for *Candida esophagitis* in outpatients. Dis Esophagus. 2003;16:66.
4. Tsiodras S, Samonis G, Boumpas DT, et al. Fungal infections complicating tumor necrosis factor alpha blockade therapy. Mayo Clin Proc. 2008;83:181.

5. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-alpha therapy in inflammatory bowel disease. Am J Gastroenterol. 2013;108:1268.
6. Corazza M, Zauli S, Ricci M, et al. Does anti-tumour necrosis factor-alpha increase oral candida colonization? A case-control study in psoriatic patients. Acta Derm Venereol. 2013;93:352.
7. Asayama N, Nagata N, Shimbo T, et al. Relationship between clinical factors and severity of esophageal candidiasis according to Kodsi's classification. Dis Esophagus. 2014;27:214.
8. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503.

4.7

A Construction Hazard

RACHEL MILLER, MD

CASE PRESENTATION

A 33-year-old woman with rheumatoid arthritis, treated with adalimumab, presented to her primary care physician with a two-week history of progressive fatigue, myalgias, fever, and nausea. She was admitted to the hospital and initiated on empiric antibacterial therapy pending evaluation. Over the course of the next five days, she continued to have fevers of 102–103°F with the development of cough, diarrhea, and hepatic dysfunction. Given her clinical decline, she was transferred to a tertiary care center for further management.

She was diagnosed with rheumatoid arthritis two years previously based on synovitis involving multiple joints and a markedly positive rheumatoid factor and anticyclic citrullinated peptide antibody. Because she was pregnant at the time of diagnosis, she was treated with low-dose prednisone. Methotrexate was added after her delivery. Persistently active disease prompted the addition of adalimumab, which she received monthly for four months before the onset of her present illness. She had no other significant medical history.

The patient is married with a 9-month-old child and works as a realtor in Eastern Iowa. Her child attends day care. She frequently gardened in her yard and noted that there was new construction ongoing in her neighborhood. She had no animal exposure, ill contacts, or significant travel history.

Physical exam revealed an ill-appearing female in mild respiratory distress with temperature of 38.9°C, blood pressure 100/62 mm mercury, pulse 110 beats per minute, respirations 22 per minute, and oxygen saturation 93% on 2 liters of oxygen by nasal cannula. Her exam was otherwise notable for coarse crackles at the lung bases bilaterally and mild hepatosplenomegaly. She had no abdominal tenderness, lymphadenopathy, or rash. Her laboratory studies were remarkable for the following: white blood cell count 2400/mm^3, hemoglobin 10.9 g/dL, platelets 110 000/mm^3, aspartate aminotransferase (AST) 540 U/L, alanine aminotransferase (ALT) 294 U/L, alkaline phosphatase 891 U/L, total bilirubin 6.3 mg/dL, and direct bilirubin 5.4 mg/dL. Abdominal ultrasound imaging confirmed the enlarged liver (20.9 cm) and spleen (13.9 cm). A chest x-ray revealed right lower lobe consolidation (Figure 4.7.1). Additional chest computed tomography imaging also showed right lower lobe consolidation with several patchy areas of focal airspace disease in the left lower lobe and associated bilateral effusions, as well as enlarged pretracheal and subcarinal lymph nodes (Figure 4.7.2).

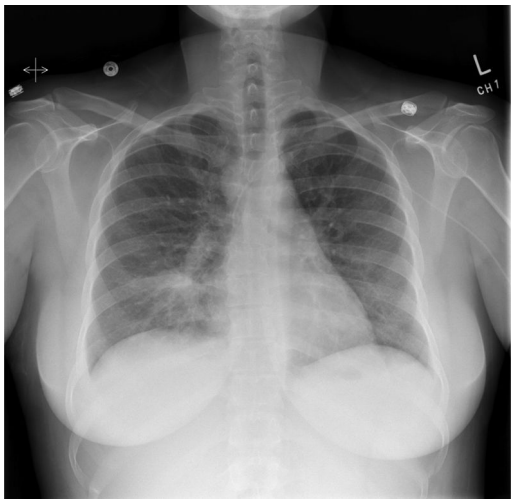

FIGURE 4.7.1: Chest X-ray (PA view) showing right lower lobe consolidation.

DIFFERENTIAL DIAGNOSIS

This patient presented with a subacute, progressive, multisystem illness characterized by fever, constitutional symptoms, cough, diarrhea, hepatic dysfunction, and mild pancytopenia.

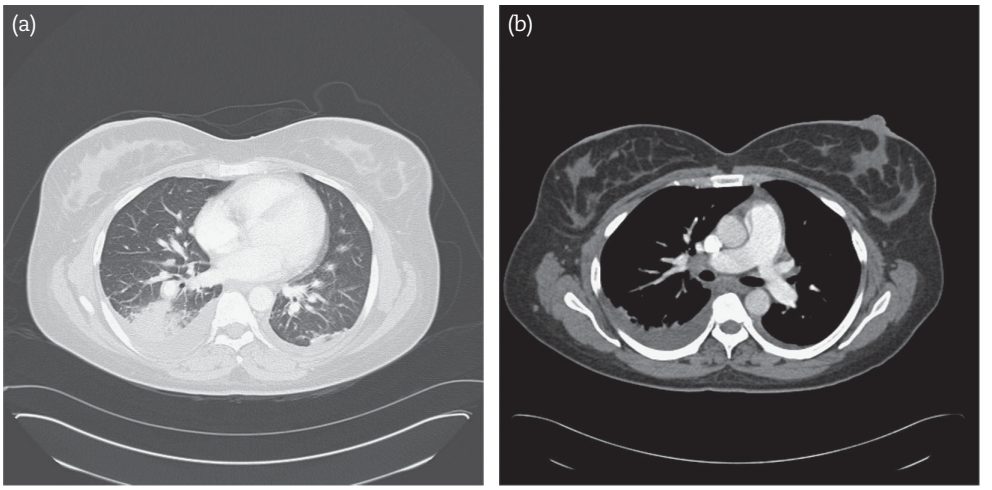

FIGURE 4.7.2: Chest CT imaging, a. Lung windows showing right lower lobe consolidation with several patchy areas of focal airspace disease in the left lower lobe and associated bilateral effusions. b. Mediastinal windows showing a conglomeration of several enlarged subcarinal lymph nodes (2.6 × 1.8 cm).

Her preceding and concurrent immunosuppressive therapy implicates a higher susceptibility to opportunistic pathogens, as well as a higher likelihood for more severe manifestations of common infections. The recent addition of adalimumab therapy, a tumor necrosis factor (TNF) antagonist, and the most potent immunosuppressive agent in her regimen raises heightened concern for a granulomatous infection. Infections that could manifest with nearly all of these findings include tuberculosis (TB), nontuberculous mycobacterial infections, endemic fungal infections, legionellosis, cytomegalovirus (CMV) infection, and adenovirus infection. Her lack of TB risk factors and geographic area of residence with proximity to a construction zone make endemic fungal infection, particularly histoplasmosis, more likely among the other possible granulomatous infections. Her child's daycare attendance raises suspicion for viral infections, specifically CMV and adenovirus infection. *Legionella* infection is associated with exposure to and/or inhalation of contaminated aerosols, whether in the community or hospital setting, and is more common in immunocompromised hosts.

ADDITIONAL DIAGNOSTIC TESTING AND CLINICAL COURSE

A liver biopsy showed nonnecrotizing granulomatous inflammation with fungal organisms morphologically consistent with *Histoplasma* (Figure 4.7.3 and 4.7.4). A urine *Histoplasma* antigen assay was positive at 8.95 ng/mL, and fungal blood cultures returned positive for *Histoplasma capsulatum* three weeks later. *Histoplasma* serology was negative. A urine *Legionella* antigen assay, QuantiFERON-Gold assay, CMV/adenovirus polymerase chain reaction assays, and stool studies were negative. Based on these results, she was diagnosed with disseminated histoplasmosis, and therapy was initiated with liposomal amphotericin 5 mg/kg daily. She continued to have fevers but with a downward trend over the next five days. She received fourteen days of liposomal amphotericin therapy before transitioning to oral itraconazole solution 200 mg daily. All immunosuppressive

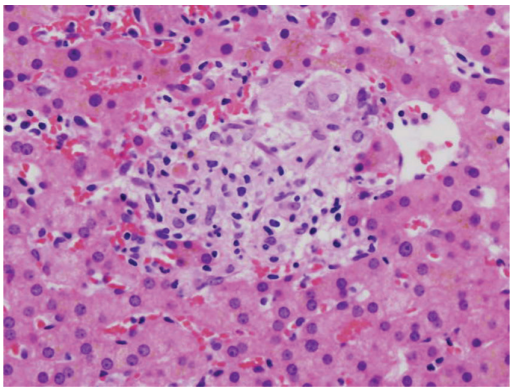

FIGURE 4.7.3: Hematoxylin and eosin stain of a liver biopsy specimen identifying a nonnecrotizing granuloma.

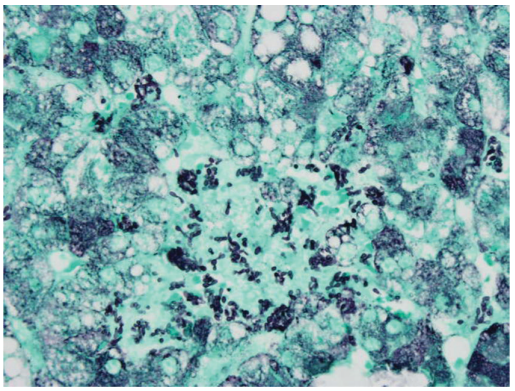

FIGURE 4.7.4: Grocott's methenamine silver (GMS) stain of liver tissue with fungal forms morphologically consistent with *Histoplasma* (3–5 μm, round/oval narrowly budding yeast).

therapy for her rheumatoid arthritis was held during and after her admission.

At a follow-up clinic visit three weeks into her treatment course, she noted gradual improvement of all of her symptoms. Concurrent liver function tests were the following: AST 43 U/L, ALT 41 U/L, alkaline phosphatase 389 U/L, total bilirubin 1.8 mg/dL, and direct bilirubin 0.9 mg/dL. She remained anemic, but her other blood counts normalized. The urine *Histoplasma* antigen level fell to 5.02 ng/mL. Her rheumatoid arthritis therapy was resumed five months into her histoplasmosis treatment course, necessitating initiation of rituximab and leflunomide to control her symptoms. Despite the resumption of immunosuppressive therapy, her infection-related symptoms and laboratory abnormalities continued to resolve over the next several months, with her first negative urine *Histoplasma* antigen assay occurring nine months into her treatment course. Itraconazole was continued to complete a year of antifungal therapy, without relapse after discontinuation of treatment and ongoing immunosuppressive therapy.

DISCUSSION

Histoplasma capsulatum is a dimorphic fungus widely distributed in nature and endemic to the Ohio and Mississippi River valleys in the United States (Figure 4.7.5). Primary infection occurs via inhalation of *H capsulatum* mycelia, typically found in high concentrations in excavated soil and in avian or bat droppings in endemic areas. Exposure to disrupted soil around construction or agricultural areas, caves where bats reside, or buildings inhabited by birds or bats pose particular risk. The clinical spectrum of infection ranges from a self-limited febrile illness to severe multiorgan dysfunction, depending on the size of the host inoculum and immune status of the infected individual. Intact immunity is critical to containing and eradicating *Histoplasma* infection. In addition to other host defense factors, TNF plays a critical role in the host's immune response to *H. capsulatum* and other pathogens whose infections are characterized by granulomatous inflammation [1]. Tumor necrosis factor antagonists impair macrophage activation, which leads to ineffective granuloma formation, with subsequent inability to compartmentalize viable organisms. Tumor necrosis factor inhibition also disrupts the orderly induction of macrophage apoptosis, which further perpetuates the organism's intracellular sanctuary and viability.

Postmarketing surveillance of patients receiving TNF antagonist therapy identifies an increased rate of granulomatous infections among this population. Of these, histoplasmosis is the most commonly reported endemic fungal infection. Individuals with rheumatoid arthritis and other autoimmune diseases, who receive corticosteroid therapy and/or other disease-modifying antirheumatic agents, are also at higher risk for more severe histoplasmosis. In 2008, the US Food and Drug Administration (FDA) issued a warning notifying healthcare providers of this increased risk among individuals on TNF antagonist therapy based on their review of 240 reported cases of histoplasmosis in this population, including twelve deaths [2]. Late recognition of infection was associated with a poor outcome. Since that time, histoplasmosis complicating TNF antagonist therapy has been increasingly recognized [3–5]. Several reports indicate that the incidence of granulomatous infections among individuals treated with TNF antagonists varies depending on which agent is used (infliximab, etanercept, adalimumab, or certolizumab). Differences in both drug kinetics and mechanisms of action may explain this variability [6]. Among accumulated reports of histoplasmosis in the setting of TNF antagonist therapy, infliximab is the mostly commonly associated agent with far fewer reports with concomitant adalimumab or etanercept therapy [2–5]. There are only isolated reports of histoplasmosis associated with certolizumab therapy, which likely reflects lesser clinical experience with this agent given its more recent FDA approval relative to the other TNF antagonists.

Early clinical symptoms of histoplasmosis are nonspecific, which usually include fever and constitutional symptoms. As the infection progresses,

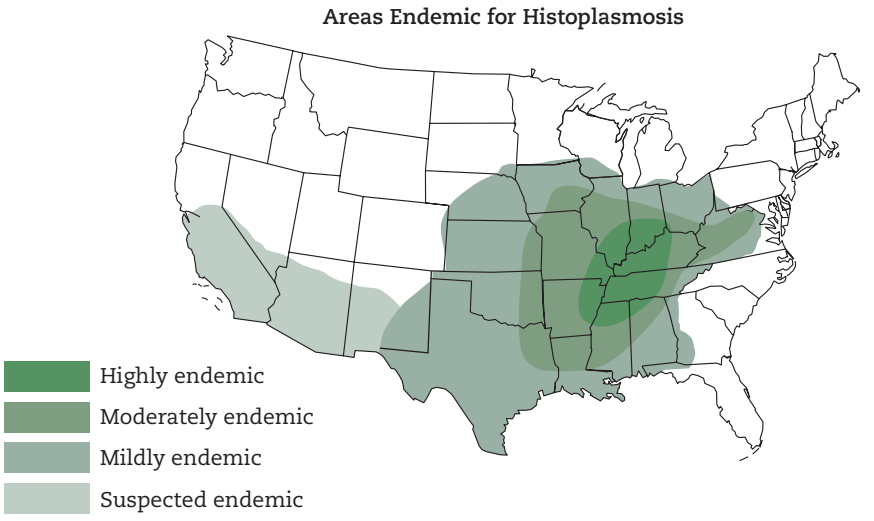

FIGURE 4.7.5: Areas endemic for histoplasmosis in the United States. http://www.cdc.gov/fungal/pdf/histoplasmosis-lifecycle508c.pdf. Accessed Mar 7, 2014.

usually over two to four weeks, associated clinical findings include hepatosplenomegaly, pneumonia, gastrointestinal involvement, pancytopenia, hepatic dysfunction, mucosal/skin lesions, and/or weight loss. Pulmonary involvement is common with imaging findings showing single-lobar or multilobar infiltrates, reticulonodular infiltrates, cavitary lesions, and/or pleural effusions. Individuals on immunosuppressive therapy frequently have disseminated infection at the time of presentation, so a high index of suspicion is necessary to identify the infection before it becomes severe.

Evaluation of symptomatic patients should include fungal blood cultures and urine and serum *Histoplasma* antigen assays. Histopathologic examination of biopsy specimens from suspected sites of involvement, including liver, lung, skin, lymph nodes, and bone marrow, can also expedite diagnosis. Direct visualization of *H. capsulatum* yeast forms with or without granulomas and/or a positive culture in involved tissues is confirmatory of the diagnosis. Although serologic testing is beneficial for the diagnosis of histoplasmosis in the normal host, the effects of immunosuppressive agents on the humoral immune response may blunt the serologic response to infection, decreasing the sensitivity of serology in individuals treated with these agents [7].

Empiric treatment with antifungal agents should be considered while awaiting results of diagnostic tests for individuals with compatible epidemiologic and clinical features. Once the diagnosis is confirmed, antifungal treatment is indicated for all patients, according to published guidelines [8]. For moderate to severely ill patients, a lipid formulation of amphotericin is recommended initially with transition to itraconazole to complete the treatment course. For mildly ill patients, itraconazole may be used for the entire course. In general, treatment should be continued for at least twelve months. Limited experience suggests that cautious reintroduction of immunosuppressive therapy, including TNF antagonist agents, can proceed with low risk of infection relapse if the clinical manifestations of histoplasmosis have resolved, even if the individual is still completing the course of antifungal therapy. Itraconazole prophylaxis may be considered for individuals who have had active histoplasmosis during the previous two years if immunosuppressive therapy is continued or intensified, although the duration of prophylaxis is unclear.

Education of patients and physicians is the most important approach for histoplasmosis prevention. Before the initiation of TNF antagonist therapy, patients should be asked about travel or residence in endemic regions, with particular emphasis on high-risk exposures such as old buildings, bird roosts/coops, wood piles, and caves. In addition, a thorough patient review of past infections (especially pneumonia) and suggestive symptoms of past or current histoplasmosis should be performed. This provides an opportunity to discuss histoplasmosis risk factors and common presenting symptoms with the

patient, as well as identify individuals that may have active infection. Screening asymptomatic individuals with serology or antigen detection before or during immunosuppressive therapy is not recommended, because most histoplasmosis infections are the result of exogenous exposure rather than reactivation of latent infection [4].

Tumor necrosis factor antagonists are now frequently used in the management of autoimmune diseases, often in combination with other disease-modifying immunosuppressive agents. Histoplasmosis is an increasingly recognized infectious complication of this therapy, particularly among individuals from endemic areas with at-risk environmental exposures. Clinicians must maintain vigilance to recognize the often subtle manifestations early, to pursue prompt diagnostic and treatment interventions to minimize morbidity and optimize outcomes.

REFERENCES

1. Smith JA, Kauffman CA. Endemic fungal infections in patients receiving tumour necrosis factor-α inhibitor therapy. Drugs. 2009;69:1403.
2. FDA alert. Tumor necrosis factor-alpha blockers (TNF blockers), Cimzie (certolizumab pegol), Enbrel (etanercept), Humira (adalimumab) and Remicade (infliximab). Available at: URL:http://www.fda.gov/Safety/MedWatch/Safety Information/SafetyAlertsforHumanMedicalProducts/ucm163195.htm. Accessed 7 March 014.
3. Tsiodras S, Samonis G, Bounpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor α blockade therapy. Mayo Clin Proc. 2008;83:181.
4. Hage CA, Bowyer S, Tarvin SE, et al. Recognition, diagnosis and treatment of histoplasmosis complicating tumor necrosis factor blocker therapy. Clin Inf Dis. 2010;50:85.
5. Olson TC, Bongartz T, Crowson CS, et al. Histoplasmosis infection in patients with rheumatoid arthritis, 1998–2009. BMC Infect Dis. 2011;11:145.
6. Furst DE, Wallis R, Broder M, Beenhouwer DO. Tumor necrosis factor antagonists: different kinetics and/or mechanisms of action may explain differences in the risk for developing granulomatous infection. Semin Arthritis Rheum. 2006;36:159.
7. Kauffman CA. Diagnosis of histoplasmosis in immunosuppressed patient. Curr Opin Infect Dis. 2008;21:421.
8. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America, 2007. Clin Infect Dis. 2007;45:807.

4.8

The Dyspneic Diplomat

IGE ABRAHAM GEORGE, MD AND GLENN EIGER, MD

CASE PRESENTATION

A 67-year-old woman with rheumatoid arthritis (RA) was admitted during the summer with a two-week history of fever, cough, and shortness of breath. She also complained of worsening pain in her knees and small joints of her hands. Her cough was predominantly dry and she denied any pleurisy or hemoptysis. Her primary care physician prescribed oral levofloxacin ten days prior to admission with no relief. A chest x-ray (CXR) taken during that visit that was normal (Figure 4.8.1).

Her past medical history was significant for RA for the past twenty years, and she had been on methotrexate (MTX) at 20 mg weekly for the past ten months and prednisone 10 mg daily for over one year with no recent change in dose. In addition, she was started on etanercept by her rheumatologist eight weeks before admission. She was a nonsmoker of Pakistani origin but has been residing in the United States for the past two years and had served as a diplomat to several eastern European nations. Her tuberculin skin tests (TSTs) were always negative with the most recent one done early this year. She denied any sick contacts and had no known significant exposure to tuberculosis.

On examination, she appeared dyspneic on conversation and mildly cushingoid. Her vitals included a blood pressure of 102/68 mm Hg, heart rate 102 beats per minute, and respiratory rate 24 breaths per minute with an oxygen saturation of 85% on room air. She had no evidence of digital clubbing or cyanosis. Auscultation revealed bilateral crepitations in all lung fields with a normal cardiovascular system examination. Wrists and ankles revealed synovitis with diffuse tenderness over most joints and muscles. Admission CXR suggested new bilateral alveolar and reticulonodular infiltrates (Figure 4.8.2), and a chest computed tomography (Figure 4.8.3) revealed scattered-ground glass opacities with interstitial infiltrates. Her respiratory status declined rapidly, and she required intubation and mechanical ventilation on the second day of admission.

Her white blood cell count was 3500/mm^3 (Neutrophils 72% Lymphocytes 16%) and

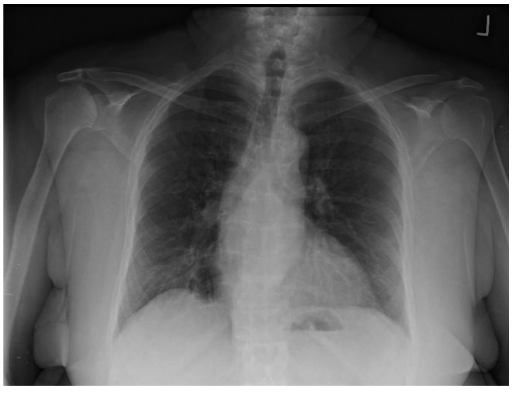

FIGURE 4.8.1: Initial Chest X-Ray.

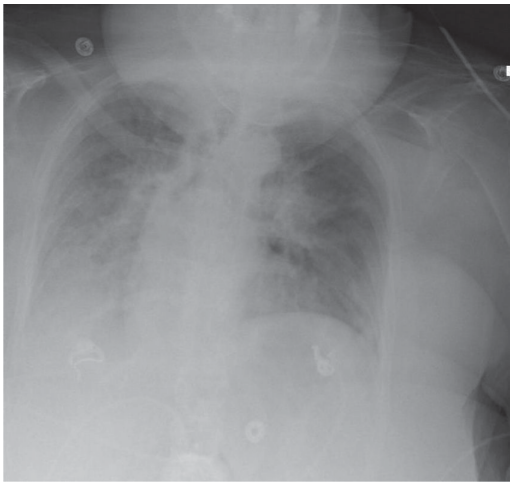

FIGURE 4.8.2: Chest X-ray on admission.

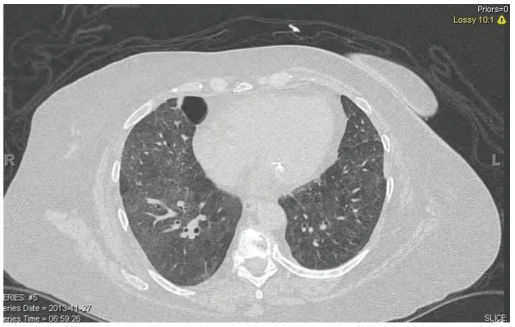

FIGURE 4.8.3: CT Chest with B/L scattered ground glass opacities and interstitial infiltrates.

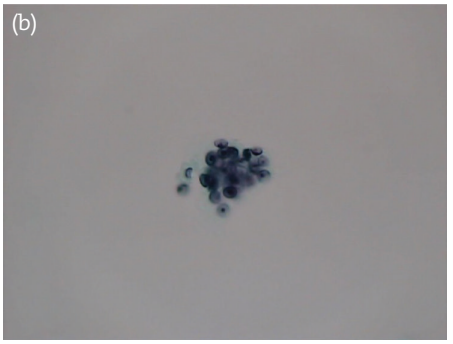

FIGURE 4.8.4b: *P. jirovecii* stained with modified toluidine blue.

hemoglobin was 9.2 g/dL with normal renal and hepatic function tests. Serum lactate dehydrogenase was 126 U/L. Her human immunodeficiency virus (HIV) enzyme-linked immunosorbent assay and TST were negative.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses in this immune-compromised patient with hypoxia and bilateral interstitial lung infiltrates included infectious and noninfectious etiologies. Atypical bacterial, viral, or pneumocystis pneumonia and other fungal or mycobacterial diseases could lead to this presentation. Rheumatoid arthritis-related interstitial lung disease or drug-induced pneumonitis are noninfectious etiologies to be considered.

Hospital Course

The patient underwent a fiber optic bronchoscopy, and the bronchoalveolar lavage (BAL) stained positive with methylamine and toluidine for *Pneumocystis jirovecii* (Figure 4.8.4). She was treated with trimethoprim-sulfamethoxazole (TMP-SMX) (dosed at 20 mg/kg TMP daily), and her chronic dose of corticosteroids (10 mg of prednisone daily) was continued. She improved symptomatically and was discharged home on the tenth hospital day. She was advised to continue the prophylactic dose of TMP-SMX after her treatment duration of 21 days.

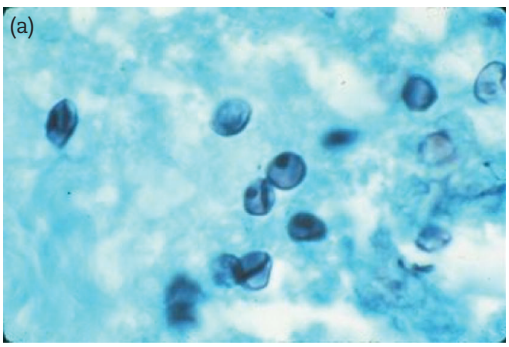

FIGURE 4.8.4a: Cysts of *P. jirovecii* in BAL, stained with methenamine silver.

DISCUSSION

Over the past decade, *Pneumocystis jirovecii* pneumonia (PCP) has been increasingly recognized to cause disease in non-HIV patients, whereas its incidence in HIV-infected patients has steadily declined. This is due to widespread use of prophylaxis and better immune recovery in patients with acquired immune deficiency syndrome with potent antiretrovirals. In contrast, the number of patients receiving hematopoietic stem cell and solid organ transplants and those receiving novel therapeutic agents for the control of malignancies and inflammatory and rheumatologic diseases has increased [1]. Common risk factors for PCP amongst non-HIV patients are hematologic malignant disorders (30.2%), organ transplantation (25.0%), inflammatory disorders (22.4%), solid tumors (12.9%), and other miscellaneous immune compromised states (9.5%) [2]. Before the era of disease-modifying agents, especially biologic therapies, PCP had an incidence of 1%–2% amongst patients with rheumatologic conditions and approximately 90% of them while on corticosteroids. A higher risk for PCP was seen in patients on a prednisolone dose greater than 20 mg/day for more than four weeks and in patients diagnosed with granulomatosis with polyangiitis (formerly known as Wegener's Granulomatosis) [3].

The risk of PCP is higher with the increased use of biological agents such as tumor necrosis

factor (TNF)-α inhibitors (infliximab, etanercept, and adalimumab) and anti-CD monoclonal antibodies. Tumor necrosis factor blockade prevents both clearance and control of the pneumocystis by the host defense system and results in more severe infection by their inhibitory effect on macrophage and phagosome activation, as well as neutrophil and cytokine recruitment [4]. Postmarketing surveillance studies from Japan report the risk of developing PCP to be 0.4% among infliximab-treated patients, 0.3% with adalimumab, and 0.18% with etanercept, and these studies show a ten-fold higher incidence of PCP after the introduction of biological medications [5, 6]. In the United States, 84 cases of PCP following infliximab therapy were identified in a review of the US Food and Drug Administration data between 1998 and 2003 [7].

The most frequent symptoms are fever, nonproductive cough, and shortness of breath. Often, symptoms develop during a period of corticosteroid dose reduction. Chest radiographs typically reveal bilateral infiltrates, although atypical presentations can be seen. Diagnosis is most often confirmed by bronchoscopy. The clinical presentation of PCP in non-HIV patients is characterized by a more fulminant course, shorter duration of symptoms, and a higher mortality rate. This difference in presentation and outcomes may be related to the significantly lower parasite burden in the lower respiratory tract as reflected in BAL specimens and a superior capacity for inflammation in the non-HIV group (Table 4.8.1) [3, 14]. However, a higher prevalence of *P jirovecii* colonization in BAL specimens (up to 44%) has been noted in non-HIV patients who receive corticosteroids equivalent to >20 mg of prednisone per day [9]. Hence, clinical findings and laboratory data should be considered when confirming a diagnosis.

Treatment: Pneumocystis Pneumonia in Patients on Immunosuppressive Agents

Trimethoprim-sulfamethoxazole, administered orally or intravenously, is the first-line agent for the treatment of any form or severity of PCP. Trimethoprim-sulfamethoxazole has a synergistic effect with MTX, inactivating dihydrofolate reductase and increasing free MTX levels and thereby inducing pancytopenia. Reducing the dose of MTX when using TMP-SMX concomitantly should be considered [10]. Unlike in HIV-infected patients, there are no randomized controlled trials in non-HIV patients with PCP that clearly demonstrate that adjunctive corticosteroids in moderate-to-severe disease accelerate symptomatic and physiologic improvement and prolong survival. Small retrospective studies have shown no significant difference in mortality, respiratory failure, or pulmonary co-infection with the use of adjunctive corticosteroids [11]. It is argued that in patients on corticosteroids for their primary rheumatologic disease, the dose should not be reduced, but whether the dose should be increased is unknown.

There are no strict guidelines on when to offer prophylaxis to patients on immunosuppressive agents without HIV. Universal prophylaxis is unrealistic because of the long-term nature of the anti-RA therapy, adverse effects related to TMP-SMX, and the potential for development of resistance to *Pneumocystis*. Experts recommend that prophylaxis is warranted for patients

TABLE 4.8.1. CLINICAL PRESENTATION AND OUTCOMES OF PCP IN PATIENTS WITH AND WITHOUT HIV[a]

	HIV	Non-HIV
Median duration of symptoms prior to diagnosis (in days) [3]	28	5
Degree of hypoxia on room air (PaO2 in mm) [3, 8]	69	52
Marker for susceptibility	CD4 <200 a good marker	No reliable laboratory marker
BAL parasite burden [14]	High	Low
Survival [3, 8]	Survival approaches 90%	40%–70%

[a]Adapted from Sepkowitz KA. Opportunistic infections in patients with and patients without acquired immunodeficiency syndrome. *Clin Infect Dis*. 2002;34:1098, Gripaldo R, Lippmann ML. Pneumocystis pneumonia in HIV-negative patients: a review of the literature. *Clin Pulm Med*. 2012;19:5, and Limper AH, Offord KP, Smith TF, Martin WJ 2nd. *Pneumocystis carinii* pneumonia. Differences in lung parasite number and inflammation in patients with and without AIDS. *Am Rev Respir Dis*. 1989;140:1204.

with rheumatologic diseases receiving ≥20 mg of prednisone daily for one month or longer in combination with a second immunosuppressive drug or if the risk of PCP is >3.5% during the period of immunodeficiency [12]. A recent study identified age >65 years, coexisting pulmonary disease, and the use of glucocorticoids as risk factors for PCP in RA patients being treated with biologics. Trimethoprim-sulfamethoxazole prophylaxis in this high- risk group reduced the incidence of PCP from 0.93 to 0.00 per 100 person years [13]. However, further trials addressing prophylaxis in at-risk patients are warranted. Although widely prescribed, there are no data on secondary prophylaxis in this population either.

REFERENCES

1. Kovacs JA, Masur H. Evolving health effects of pneumocystis: one hundred years of progress in diagnosis and treatment. JAMA. 2009;301:2578.
2. Roblot F, Godet C, Le Moal G, et al. Analysis of underlying diseases and prognosis factors associated with *Pneumocystis carinii* pneumonia in immunocompromised HIV-negative patients. Eur J Clin Microbiol Infect Dis. 2002;21:523.
3. Sepkowitz KA. Opportunistic infections in patients with and patients without acquired immunodeficiency syndrome. Clin Infect Dis. 2002;34:1098.
4. Haroon N, Inman RD. Infectious complications of biological therapy. Curr Opin Rheumatol. 2009;21:397.
5. Mori S, Sugimoto M. *Pneumocystis jirovecii* infection: an emerging threat to patients with rheumatoid arthritis. Rheumatology (Oxford). 2012;51:2120.
6. Tanaka M, Sakai R, Koike R, et al. *Pneumocystis jirovecii* pneumonia associated with etanercept treatment in patients with rheumatoid arthritis: a retrospective review of 15 cases and analysis of risk factors. Mod Rheumatol. 2012;22:849.
7. Kaur N, Mahl TC. *Pneumocystis jiroveci* (*carinii*) pneumonia after infliximab therapy: a review of 84 cases. Dig Dis Sci. 2007;52:1481.
8. Gripaldo R, Lippmann ML. Pneumocystis pneumonia in HIV-negative patients: a review of the literature. Clin Pulm Med. 2012;19:5.
9. Maskell NA, Waine DJ, Lindley A, et al. Asymptomatic carriage of *Pneumocystis jiroveci* in subjects undergoing bronchoscopy: a prospective study. Thorax. 2003;58:594.
10. Al-Quteimat OM, Al-Badaineh MA. Methotrexate and trimethoprim-sulphamethoxazole: extremely serious and life-threatening combination. J Clin Pharm Ther. 2013;38:203.
11. Moon SM, Kim T, Sung H, et al. Outcomes of moderate-to-severe pneumocystis pneumonia treated with adjunctive steroid in non-HIV-infected patients. Antimicrob Agents Chemother. 2011;55:4613.
12. Green H, Paul M, Vidal L, Leibovici L. Prophylaxis of pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc. 2007;82:1052.
13. Katsuyama T, Saito K, Kubo S, et al. The prophylaxis for pneumocystis pneumonia in patients with rheumatoid arthritis treated with biologics, based on risk factors found in a retrospective study. Arthritis Res Ther. 2014;16:R43.
14. Limper AH, Offord KP, Smith TF, Martin WJ 2nd. *Pneumocystis carinii* pneumonia. Differences in lung parasite number and inflammation in patients with and without AIDS. Am Rev Respir Dis. 1989;140:1204.

4.9

Take One's Breath Away

DANA D. BYRNE, MD, MISHA A. ROSENBACH, MD, AND KEITH W. HAMILTON, MD

CASE PRESENTATION

A 54-year-old Cambodian woman with rheumatoid arthritis and recent diagnosis of interstitial lung disease presented to the emergency department with a week of worsening abdominal pain, nausea, and vomiting accompanied by fevers, chills, cough, and diarrhea. The patient had seen her primary doctor for abdominal pain and nausea approximately two weeks prior to presentation and had been prescribed a proton pump inhibitor with no improvement. In the emergency room, her temperature was 101.7°F, pulse was 120 per minute, and blood pressure was 94/54 mmHg. Her oxygen saturation was 90% on room air and 99% on 2 liters of oxygen. Physical examination was significant for moderate distress, pallor, a macular rash on the abdomen, diffuse scattered wheezing bilaterally on pulmonary examination, diffuse upper abdominal tenderness to palpation without rebound, and a normal rectal examination. Routine laboratory tests were significant for anemia with hemoglobin 8.5 g/dL (baseline was 11.0 g/dL three months earlier) and normal white blood cell and platelet counts. Chemistry and liver function tests were normal. A computed tomography (CT) scan of the abdomen and pelvis showed "nonspecific colitis" with thickening of the small bowel. A CT scan of the chest showed extensive bilateral pulmonary infiltrates (Figure 4.9.1).

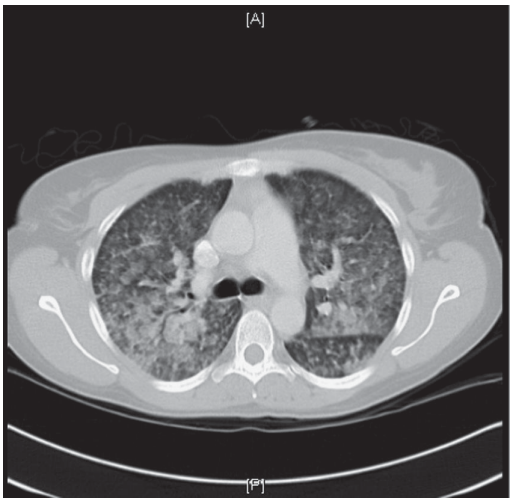

FIGURE 4.9.1: Non-contrast computed tomography of the chest showed extensive bilateral pulmonary infiltrates.

The patient was diagnosed with rheumatoid arthritis thirty years ago. She was treated with methotrexate, hydroxychloroquine, and most recently was on etanercept and 5 mg of prednisone daily. She recently completed a pulse of high-dose prednisone (0.5 mg/kg per day) prescribed by her pulmonologist because of concern for rheumatoid arthritis-induced interstitial lung disease. However, her symptoms worsened. Other significant medical history included treated latent tuberculosis. Her initial abdominal pain was thought to be due to gastritis from prednisone. At the time of presentation, she had resided in Albuquerque, New Mexico for approximately two years. She last traveled to Cambodia approximately one year prior to presentation and had traveled back to the area approximately once every two to three years to visit family. She was a retired restaurant worker.

DIFFERENTIAL DIAGNOSIS

In this case, the most salient features were enteritis, pulmonary infiltrates, and rash. Because of the patient's chronic condition and immunosuppression, these symptoms could have been caused by more than one etiology. Rheumatoid arthritis can cause pulmonary as well as skin manifestations. However, the rash described in this case would be atypical. Rheumatoid arthritis would also be an unlikely explanation for this patient's prominent enteritis. Therefore, alternative explanations would have to be implicated for

some of these findings. Disseminated tuberculosis or coccidioidomycosis could explain many of the features of this case and should be considered, given the patient's history of latent tuberculosis, residence in the American Southwest, and immunosuppressed state. Several parasitic infections endemic to many tropical and subtropical regions can cause enteritis, pulmonary infiltrates, and rash, so these should be strong considerations in this case. These infections include schistosomiasis, strongyloidiasis, and infections with the hookworms *Ancylostoma duodenale* and *Necator americanus*. Noninfectious conditions such as polyarteritis nodosa (PAN) can also cause multiorgan involvement. Because of the high prevalence of hepatitis B in Cambodia and its association with PAN, PAN should be considered.

The patient was admitted to the hospital and started on vancomycin and cefepime empirically. She subsequently developed respiratory distress and was transferred to the intensive care unit and intubated. A bronchoalveolar lavage was performed for her persistent respiratory failure.

The bronchoalveolar lavage revealed numerous filariform larvae. A skin biopsy also demonstrated larval forms (Figure 4.9.2). Subsequent stool microscopy and serum antibody were positive for *Strongyloides stercoralis* (Figure 4.9.3). The patient was treated successfully with daily ivermectin.

DISCUSSION

Strongyloides affects more than 10 million persons worldwide and is an especially important parasitic infection to recognize in immunocompromised hosts [1]. It is more common in warm, humid climates where sanitation is poor, but it is endemic to many more moderate climates as well, including the Southeastern United States, Southern Europe, and Japan [2]. The lifecycle of *Strongyloides* can result in an autoinoculation syndrome, which allows the infection to persist with little or no symptoms in immune competent hosts. When the host becomes immunosuppressed or when an immunosuppressed host acquires the infection, a severe form of the infection, called "hyperinfection syndrome" can occur. Hyperinfection syndrome results in mortality rates as high as 50%, making it important to recognize and treat early [3].

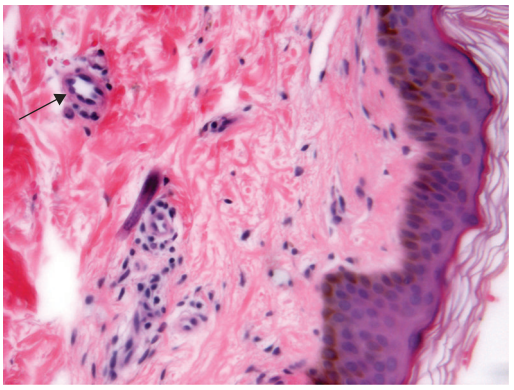

FIGURE 4.9.2: Skin biopsy demonstrated larval forms of Strongyloides.

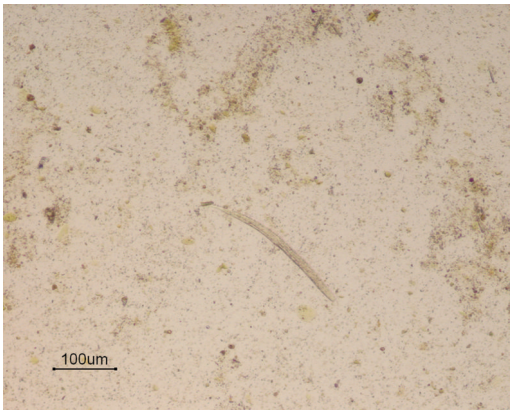

FIGURE 4.9.3: Stool microscopy demonstrated larval forms of Strongyloides.

Strongyloides Infection in the Immunocompromised Host

In immunocompromised patients, *Strongyloides* most commonly occurs as reactivation of chronic subclinical infection. When the immune system becomes suppressed for the treatment of medical conditions such as rheumatologic diseases, cancer, or transplantation, symptoms can become severe [4]. Glucocorticoids in particular have been associated with risk for *Strongyloides* infection, although other immunosuppressive agents and disease-modifying antirheumatic drugs (DMARDs) are also considered risk factors. There have been several reports of *Strongyloides* infection or hyperinfection after treatment with tumor necrosis factor (TNF)-α inhibitors such as etanercept [5, 6]. This class of medications is often administered in the setting of other concomitant immunosuppressive and immunomodulatory drugs, so isolating the risk for individual medications is difficult [4–6].

Nonetheless, hyperinfection syndrome has a plausible association with TNF-α inhibitors, especially when added to other immunosuppressive agents [5, 6]. The Th2 $CD4^+$ T cells are important for the immune control of *Strongyloides* as well as other helminthic infections, and TNF-α plays an essential role in T-cell communication. By suppressing response to TNF-α, TNF-α inhibitors alter cellular immunity and can increase the susceptibility to infection with *Strongyloides* [4, 7].

Clinical Manifestations Associated With the Life Cycle of *Strongyloides*

Initial infection occurs after cutaneous contact with *Strongyloides* larvae in contaminated soil [2]. After the larvae penetrate the skin, they migrate to the lungs through the vasculature where they ascend the trachea and are eventually swallowed. They then travel to the small intestine to lay eggs, which hatch into larvae that are excreted in the stool. Common symptoms of infection in immune competent hosts include skin rash at the site of inoculation or perirectal area, pulmonary symptoms such as cough, and gastrointestinal symptoms such as abdominal pain and diarrhea [2, 8].

Autoinfection occurs when the larvae in the small intestine penetrate the wall of the bowel or the rectum and reinitiate the infection process. In an immune competent individual, autoinfection can cause chronic strongyloidiasis, which is often asymptomatic and can persist for decades. Approximately two thirds to three quarters of these individuals have peripheral eosinophilia and/or elevated immunoglobulin E levels. However, eosinophilia may not be apparent in immunosuppressed hosts. Some individuals may have nonspecific gastrointestinal symptoms or may develop urticaria or larva currens, a linear pruritic rash usually on the lower body [4, 8, 9]. Larvae can migrate in a retrograde fashion to portosystemic anastomoses, causing purpuric macules to appear in a periumbilical distribution due to extravasation of red blood cells. This finding is known as thumbprint purpura and is pathognomonic for the diagnosis of strongyloidiasis [10].

When the autoinfection process occurs rapidly, often in the setting of immunosuppression, such as in patients on steroids or DMARDs, hyperinfection syndrome can occur. Hyperinfection syndrome can lead to intestinal obstruction or bacteremia from the frequent and rapid penetration of the larvae through the bowel wall. Hyperinfection can also lead to disseminated strongyloidiasis, in which the parasites can migrate to organs other than the gastrointestinal tract and airways. In humans, *Strongyloides* can disseminate to the lung parenchyma, skin, and central nervous system [4, 11, 12].

Diagnosis

Diagnosis of *Strongyloides* infection can be made in several ways. The most common diagnostic method is direct stool examination by microscopy; however, this test can be insensitive because parasites and eggs can be excreted intermittently in cases of more mild infection. In hyperinfection syndrome, the parasite burden is high, and the sensitivity of stool microscopy as well as the microscopy of specimens from other involved body sites, such as sputum or surgical aspirates, becomes higher [13]. Stool can also be plated on an agar plate and incubated so that if larvae are present, they will make bacterial growth patterns on the plate. Other modalities for diagnosis include duodenal aspiration, which is usually reserved for children or immunocompromised patients with a high parasite burden. Skin exam can sometimes confirm the diagnosis when thumbprint purpura is present. Even when this skin finding is not present, skin biopsy can reveal the presence of *S stercoralis* larvae, confirming the diagnosis. Serology with enzyme-linked immunosorbent assay can also be useful, but it can be falsely negative in patients with immunosuppression [13, 14].

Treatment

For uncomplicated infection, ivermectin 200 mcg/kg doses administered either on two consecutive days or two weeks apart is considered standard and cost-effective therapy [15, 16]. In general, immunocompromised patients require more intensive treatment, although there is no consensus amongst experts on an optimal regimen. For hyperinfection syndrome, daily ivermectin at a dose of 200 mcg/kg is often administered until symptoms resolve and stool tests have been negative for at least two weeks (one autoinfection cycle) or longer if the patient remains immunosuppressed. Effective treatment also involves holding or decreasing immune-modulating agents if possible, and patients with ongoing immunosuppression are often treated with maintenance monthly doses of ivermectin for approximately six months, although the ultimate duration is not clearly defined [17]. There are also reports of using combination therapy with albendazole and ivermectin, subcutaneous ivermectin, and a veterinary formulation of intravenous ivermectin for successful treatment of hyperinfection syndrome [18–22].

Prevention

Because of the association between *Strongyloides* hyperinfection syndrome and immune-

modulating agents, patients from endemic areas likely should be screened for *Strongyloides* before initiation of DMARDs. Data to guide this recommendation is not strong, but screening has been mandated in special immunosuppressed populations based on the ease with which the infection is treated in immune competent individuals, coupled with the severity of disease in those patients with hyperinfection syndrome [23]. In most cases, latent infection can be identified by serologic testing. In some immunosuppressed hosts, serology may be negative and stool ova and parasites may help identify infected individuals. If *Strongyloides* infection is found, a treatment course should be administered before initiation of DMARD therapy.

REFERENCES

1. Coster LO. Parasitic infections in solid organ transplant recipients. Infect Dis Clin North Am. 2013;27:395.
2. Olsen A, van Lieshout L, Marti H, et al. Strongyloidiasis: the most neglected of the neglected tropical diseases? Trans R Soc Trop Med Hyg. 2009;103:967.
3. Roxby AC, Gottlieb GS, Limaye AP. Strongyloidiasis in transplant patients. Clin Infect Dis. 2009;49:1411.
4. Keiser PB, Nutman TB. *Strongyloides stercoralis* in the immunocompromised population. Clin Microbiol Rev. 2004;17:208.
5. Boatright MD, Wang BWE. Clinical infection with *Strongyloides stercoralis* following etanercept use for rheumatoid arthritis. Arthritis Rheum. 2005;52:1336.
6. Krishnamurthy R, Dincer HE, Whittemore D. *Strongyloides stercoralis* hyperinfection in a patient with rheumatoid arthritis after anti-TNF-alpha therapy. J Clin Rheumatol. 2007;13:150.
7. Maurice MM, van der Graaff WL, Leow A, et al. Treatment with monoclonal anti-tumor necrosis factor α antibody results in an accumulation of Th1 CD4+ T cells in the peripheral blood of patients with rheumatoid arthritis. Arthritis Rheum. 1999;42:2166.
8. Siddiqui AA, Berk SL. Diagnosis of *Strongyloides stercoralis* infection. Clin Infect Dis. 2001;33:1040.
9. Smith JD, Goette DK, Odom RB. Larva currens. Cutaneous strongyloidiasis. Arch Dermatol. 1976;112:1161.
10. Weiser JA, Scully BE, Bulman WA, et al. Periumbilical parasitic thumbprint purpura: *Strongyloides* hyperinfection syndrome acquired from a cadaveric renal transplant. Transpl Infect Dis. 2011;13:58.
11. Marcos LA, Terashima A, Dupont HL, Gotuzzo E. *Strongyloides* hyperinfection syndrome: an emerging global infectious disease. Trans R Soc Trop Med Hyg. 2008;102:314.
12. Gotuzzo E, Terashima A, Alvarez H, et al. *Strongyloides stercoralis* hyperinfection associated with human T cell lymphotropic virus type-1 infection in Peru. Am J Trop Med Hyg. 1999;60:146.
13. Sudarshi S, Stümpfle R, Armstrong M, et al. Clinical presentation and diagnostic sensitivity of laboratory tests for *Strongyloides stercoralis* in travellers compared with immigrants in a non-endemic country. Trop Med Int Health. 2003;8:728.
14. Carroll SM, Karthigasu KT, Grove DI. Serodiagnosis of human strongyloidiasis by an enzyme-linked immunosorbent assay. Trans R Soc Trop Med Hyg. 1981;75:706.
15. Muennig P, Pallin D, Challah C, Khan K. The cost-effectiveness of ivermectin vs. albendazole in the presumptive treatment of strongyloidiasis in immigrants to the United States. Epidemiol Infect. 2004;132:1055.
16. Zaha O, Hirata T, Kinjo F, et al. Efficacy of ivermectin for chronic strongyloidiasis: two single doses given 2 weeks apart. J Infect Chemother. 2002;8:94.
17. Segarra-Newnham M. Manifestations, diagnosis, and treatment of *Strongyloides stercoralis* infection. Ann Pharmacother. 2007;41:1992.
18. Marty FM, Lowry CM, Rodriguez M, et al. Treatment of human disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin. Clin Infect Dis. 2005;41:e5.
19. Turner SA, Maclean JD, Fleckenstein L, Greenaway C. Parenteral administration of ivermectin in a patient with disseminated strongyloidiasis. Am J Trop Med Hyg. 2005;73:911.
20. Pacanowski J, Dos Santos M, Roux A, et al. Subcutaneous ivermectin as a safe salvage therapy in Strongyloides stercoralis hyperinfection syndrome: a case report. Am J Trop Med Hyg. 2005;73:122.
21. Pornsuriyasak P, Niticharoenpong K, Sakapibunnan A. Disseminated strongyloidiasis successfully treated with extended duration ivermectin combined with albendazole: a case report of intractable strongyloidiasis. Southeast Asian J Trop Med Public Health. 2004;35:531.
22. Keiser PB, Nutman TB. *Strongyloides stercoralis* in the immunocompromised population. Clin Microbiol Rev. 2004;17:208.
23. Levi ME, Kumar D, Green M, et al. Considerations for screening kidney donors for endemic infections: a viewpoint on the UNOS policy. Am J Transplant. 2014;14:1003.

4.10

Wielding a Double-Edged Sword

CHARITHA GOWDA, MD, MPH AND MELISSA A. GRILLIOT, MD

CASE PRESENTATION

A 76-year-old man with a history of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) overlap syndrome, complicated by lupus nephritis, presented with chronic diarrhea for two months. The patient first noticed a change in his bowel habits two months earlier. He characterized his bowel movements as "large volume," "watery," and "nonbloody." He did not have any associated abdominal pain, cramping, nausea, or vomiting. By the time he presented to the hospital, his frequency of bowel movements had steadily increased and he was noting diarrhea occurring more than hourly. After he began to note fecal urgency and inability to get to the bathroom before losing bowel control, he presented to the emergency department. He denied any fevers, chills, or night sweats, but complained of decreased appetite and generalized weakness. He also had noted an approximately fifteen-pound weight loss since the onset of his symptoms. He had initiated mycophenolate mofetil (MMF) after the onset of his symptoms, but given the close temporal association with the onset of diarrhea, the MMF was held upon admission. However, the patient did not experience any significant improvement in his symptoms with discontinuation of the drug. A comprehensive laboratory and microbiological workup was conducted, and esophagogastroduodenoscopy and flexible sigmoidoscopy were performed.

The patient's complex autoimmune disease history included seropositive RA for over twelve years, primarily manifest as swelling of his metacarpophalangeal joints, wrists, and proximal interphalangeal joints bilaterally. He had a positive rheumatoid factor and cyclic citrullinated peptide antibody, and he had been treated previously with various antirheumatic agents including methotrexate, hydroxychloroquine, sulfasalazine, and more recently with cyclophosphamide. He was also noted to have high positive antinuclear antibodies with a titer of 1:1280, as well as positive antibodies to double-stranded DNA and antineutrophil cytoplasmic antibodies. During the fall of the previous year, he had developed worsening renal function with hematuria and proteinuria and was ultimately diagnosed with membranous nephritis secondary to SLE. After initiation of cyclophosphamide and prednisone, renal function returned to baseline and prednisone was tapered to 10 mg daily. Cyclophosphamide was discontinued and he was transitioned to MMF less than two months ago.

In addition to the history above, he had been diagnosed with hypothyroidism, benign prostatic hypertrophy, and had a history of a congenital solitary kidney. His complete medication list at time of presentation included levothyroxine, MMF, prednisone, ranitidine, cotrimoxazole double-strength tablet daily, and tamsulosin. He had no known drug allergies. He was a retired docking pilot, having spent most of his career working in the Northeast. He had a remote twelve-pack per year history of tobacco use, had one to two alcohol drinks a day, and denied any illegal drug use. There was no known family history of autoimmune, vascular, and renal diseases or malignancies.

On physical exam, he was afebrile and other vital signs were stable. He was an elderly man in no acute distress. His head and neck exam was unremarkable including normal oropharynx and no cervical or supraclavicular lymphadenopathy. He had a normal cardiopulmonary examination. His abdomen was tender to deep palpation diffusely but with normoactive bowel sounds and no hepatosplenomegaly. On musculoskeletal exam, he had no evidence of synovitis, joint swelling, or tenderness.

Laboratory data were notable for a white blood cell count of 3800 cells/μL (normal: 4000–11 000), hemoglobin of 10.3 g/dL (normal: 13.5–17.5), and platelets of 137 000

cells/μL (normal: 150 000–400 000). Electrolytes and serum creatinine were within the normal range. Liver function tests demonstrated an elevated aspartate transaminase of 72 U/L (normal: 15–41) and alanine transaminase of 141 U/L (normal: 17–63), as well as elevated alkaline phosphatase of 316 U/L (normal: 38–126). Total bilirubin was normal at 0.7 mg/dL (normal: 0.3–1.2). Albumin was low at 2.0 g/dL (normal: 3.5–4.8). Thyroid stimulating hormone and free T4 were within the normal range, as was adrenal corticotropin hormone. Microbiology data including stool culture for *Salmonella, Shigella, Campylobacter, Pleisomonas*, and *Aeromonas* were negative. *Clostridium difficile* stool polymerase chain reaction (PCR) test was negative. Stool examination of ova and parasites was negative for cryptosporidia, giardia, and microsporidia. Additional stool studies demonstrated elevated fecal α1-antitrypsin (1050 mg/dL; normal: 0–62 mg/dL) and normal qualitative fecal fat testing. Antibody testing for human immunodeficiency virus (HIV) and celiac disease were negative.

Esophagogastroduodenoscopy demonstrated normal esophagus and stomach. A small (<5 mm) clean-based punctate ulcer was identified in the second portion of the duodenum. Multiple cold forceps biopsies were obtained from the duodenum. Flexible sigmoidoscopy was notable for internal hemorrhoids with overlying ulcerated mucosa. Otherwise, normal mucosa was seen up to the rectosigmoid junction, and multiple cold forceps biopsies were obtained. Histopathological examination of small bowel biopsy demonstrated viral inclusions consistent with cytomegalovirus (CMV) (Figure 4.10.1). Subsequently, quantitative serum CMV PCR was found to be 41 158 copies/mL (normal: < 150).

DIFFERENTIAL DIAGNOSIS AND TREATMENT

The differential diagnosis for chronic diarrhea is broad and can be classified into inflammatory, watery, or fatty diarrhea. Infectious diseases, including invasive bacterial, parasitic, and viral infections, typically cause an inflammatory diarrhea, although bacterial toxins can produce a watery diarrhea [1]. Other common etiologies of inflammatory diarrhea are ischemic colitis, neoplasia, diverticulitis, and radiation colitis. Inflammatory bowel diseases can be associated with either inflammatory or watery diarrhea. Watery diarrhea can also be produced by osmotic laxatives, medications, motility disorders such as diabetic autonomic neuropathy or irritable bowel syndrome, endocrinopathies, or vasculitides [2]. In this patient, the initial differential diagnosis included medication-induced, protein-losing enteropathy, adrenal insufficiency, or an infectious etiology. Based on the histopathology demonstrating viral inclusions characteristic of CMV, the patient was diagnosed with CMV enteritis and started on intravenous ganciclovir. He responded promptly to treatment, with a reduction in stool frequency within three days and transition to formed bowel movements after five days of treatment. After a week of intravenous ganciclovir, he was transitioned to PO valganciclovir and completed four weeks total of antiviral therapy. Regarding his immunosuppression, MMF was held and prednisone was tapered slowly. He had complete resolution of his abdominal symptoms and was not transitioned to prophylactic

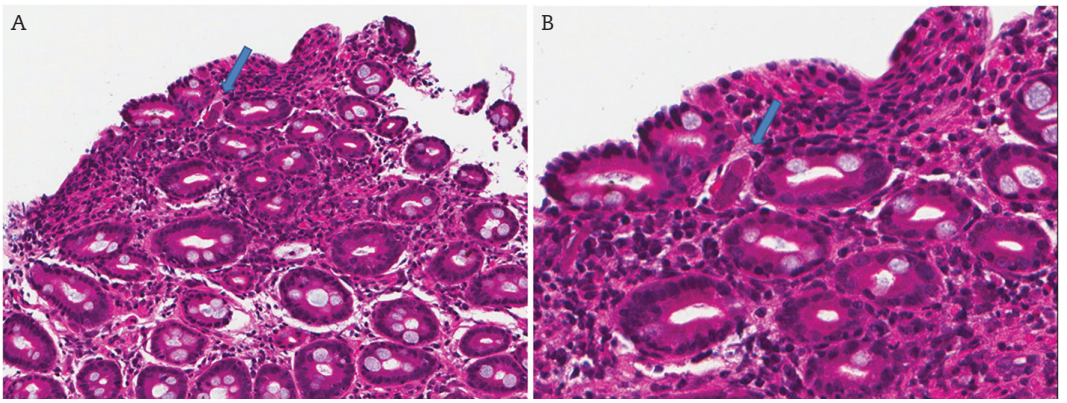

FIGURE 4.10.1: Duodenal mucosal biopsy (A: H&E stain 200× magnification; B: 400×) reveals characteristic intranuclear inclusions (arrows) consistent with Cytomegalovirus infection.

valganciclovir therapy. Subsequently, given his stable renal function and minimal arthritic pain, he has been closely monitored off all maintenance immunosuppression.

DISCUSSION

Most cases of infectious diarrhea are acute and self-limited, with a narrow list of infectious pathogens implicated in chronic diarrhea in the immunocompetent person. However, the clinical presentation of infectious diarrhea among immunosuppressed patients is often more severe. Furthermore, chronic diarrhea can result from infections that are classically associated with acute disease in healthy hosts [3]. In this case, our patient had a complex autoimmune disease for which he was taking several immunosuppressive medications including high doses of corticosteroids, cyclophosphamide, and mycophenolate. As a result, the potential list of infectious pathogens was broader and required an extensive evaluation looking for bacterial, viral, and parasitic agents (Table 4.10.1). In addition to evaluating for common bacterial pathogens, as performed in this case with stool culture and *C difficile* PCR testing, multiple stool specimens were examined for ova and parasites including cryptosporidia and microsporidia, which may be associated with chronic and more severe disease in patients with immune compromise. Finally, endoscopic evaluation was performed with tissue sampling that culminated in the diagnosis.

Cytomegalovirus is an important example of an opportunistic pathogen implicated in gastrointestinal disease. As a member of the *Herpesviridae* family, CMV typically produces a self-limited viral syndrome during acute infection before going on to establish latency within the immunocompetent host. However, CMV reactivation or even primary infection in patients with acquired defects of cellular immunity can manifest clinically as severe disease with significant morbidity. The pathogenic potential of CMV has been increasingly recognized with the advent of organ transplantation and the acquired immune deficiency syndrome (AIDS) epidemic. For example, CMV is the most common viral opportunistic infection in AIDS patients, primarily manifesting in patients with CD4 counts below 50 cells/μL. In transplant recipients, the harsh immunosuppressive regimens designed to prevent organ rejection invariably predispose to severe CMV disease [4].

Systemic corticosteroids, although notable for their inhibitory effects on both the innate

TABLE 4.10.1. LIST OF INFECTIOUS PATHOGENS IMPLICATED IN DIARRHEA IN IMMUNOCOMPROMISED PATIENTS

Acute Diarrhea	Chronic Diarrhea
Bacterial Pathogens	
Enterotoxigenic *Escherichia coli*	Enteroaggregative *Escherichia coli*
Enterohemorrhagic *Escherichia coli*	Enteropathogenic *Escherichia coli*
Clostridium difficile	*Yersinia enterocolitica*
Salmonella spp	*Aeromonas hydrophilia*
Shigella spp	*Plesiomonas shigelloides*
Campylobacter spp	*Clostridium difficile*
Vibrio spp	*Mycobacterium tuberculosis*
Listeria monocytogenes	*Mycobacterium avium complex*
Yersinia enterocolitica	*Tropheryma whipplei*
Small intestinal bacterial overgrowth	Small intestinal bacterial overgrowth
Viral Pathogens	
Rotavirus	Cytomegalovirus
Norovirus	HIV
Adenovirus	
Herpes simplex virus	
Astrovirus	
Parasitic Pathogens	
Giardia lamblia	*Entamoeba histolytica*
	Giardia lamblia
	Cyclospora
	Isospora belli
	Cryptosporidia
	Microsporidia
	Blastocystis
	Balantidium coli
	Strongyloides stercoralis
	Ascaris lumbricoides
	Ancylostoma duodenale
	Necator americanus
	Trichuris trichiura
	Taenia saginata and *Taenia solium*
	Diphyllobothrum latum
	Hymenolopsis nana
Miscellaneous	
	Candida albicans
	Histoplasmosis
	Brainerd diarrhea (unknown etiologic agent but presumed infectious)

and acquired immune system, likely predispose to reactivation of CMV infection and gastrointestinal disease through the impairment of cell-mediated immunity. In particular, glucocorticoid therapy leads to rapid reductions in circulating effective T lymphocytes by impairing dendritic cell maturation, inhibiting important cytokine and growth factor signaling for y differentiation, and inducing lymphocyte apoptosis. Glucocorticoids render dendritic cells less functional as antigen-presenting cells by preventing the up-regulation of major histocompatibility complex class II and costimulatory molecules, thereby impairing the ability for a T-cell response to infection. In addition, by inhibiting interleukin-12 secretion, glucocorticoids block lymphocyte differentiation and secretion of cytokines interferon-γ and tumor necrosis factor-α involved in the T-helper cell type 1 (Th1) immune response. Furthermore, supraphysiologic doses of glucocorticoids can induce T-cell apoptosis [5]. Taken together, these effects can lead to profound cellular immunodeficiency and impaired defense against opportunistic pathogens.

Given the onset of gastrointestinal symptoms after the initiation of corticosteroids and prior to MMF use in this patient, corticosteroids were implicated as the most likely predisposing factor for the development of CMV disease. However, subsequent MMF use may have exacerbated his symptoms further. It is unknown whether there is a minimum dose or duration of corticosteroid therapy that is associated with CMV disease. Although most clinical reports describe high doses of steroids, including pulse-dosing initially, with slow tapers planned over months, even low-dose steroid therapy has been associated with severe CMV disease [6–8]. The timing of CMV disease can range from weeks to months after the initiation of steroids. Given the lack of consensus on the timing and dose of steroids associated with CMV disease, there are no indications for CMV prophylaxis in the setting of corticosteroid therapy. However, a diagnosis of CMV should be entertained in these patients presenting with systemic and organ-specific complaints. Finally, treatment of CMV disease includes not only antiviral therapy but also tapering of corticosteroids and other immunosuppression as tolerated by the patient. Reintroduction of immunosuppression should be accompanied with close monitoring for recurrence of symptoms and/or CMV viremia.

Glucocorticoids are a classic double-edged sword wielded by physicians. Despite serving a therapeutic benefit in the management of autoimmune conditions such as RA or SLE, they can unfortunately induce a profound cellular immunodeficiency that leaves patients vulnerable to intracellular and opportunistic infections. Thus, a thorough evaluation for common and uncommon bacterial and viral and parasitic pathogens should be undertaken when confronted with a patient who develops chronic diarrhea in the setting of chronic corticosteroid use.

REFERENCES

1. Kaiser L, Surawicz CM. Infectious causes of chronic diarrhea. Best Pract Res Clin Gastroenterol. 2012;26:563.
2. Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. Gastroenterology. 1999;116:1464.
3. Schiller LR. Definitions, pathophysiology and evaluation of chronic diarrhea. Best Pract Res Clin Gastroenterol. 2012;26:551.
4. Baroco AL, Oldfield EC. Gastrointestinal cytomegalovirus disease in the immunocompromised patient. Curr Gastroenterol Rep. 2008;10:409.
5. Franchimont D. Overview of the actions of glucocorticoids on the immune response. Ann NY Acad Sci. 2004;1024:124.
6. Buckner FS, Pomeroy C. Cytomegalovirus disease of the gastrointestinal tract in patients without AIDS. Clin Infect Dis. 1993;17:644.
7. Ohashi N, Isozaki T, Shirakawa K, et al. Cytomegalovirus colitis following immunosuppressive therapy for lupus peritonitis and lupus nephritis. Intern Med. 2003;42;362.
8. Aukrust P, Moum B, Farstad IN, et al. Fatal cytomegalovirus (CMV) colitis in a patient receiving low dose prednisolone therapy. Scand J Infect Dis. 1991;23:495.

4.11

Don't Judge a Book by Its Cover

DEBORAH KAHAL MD, MPH AND FATEN N. ABERRA MD, MSCE

CASE PRESENTATION

A 29-year-old female with ulcerative colitis (on 6-mercaptopurine [6MP]), stage V chronic kidney disease secondary to mesalamine-induced acute interstitial nephritis, and on the renal transplantation list initially presented to an outside hospital with coryza, a mild sore throat, persistent and progressively higher fevers, productive cough with scant hemoptysis, nausea, vomiting, and a new whole body rash that began nearly one week earlier while on vacation in Las Vegas. The patient worked with children in a school but denied any sick contacts, pets, or animal exposures.

After receipt of an outpatient prescription for levofloxacin without improvement in her symptoms, the patient sought medical care five days into the course of her illness. Multifocal pneumonia was diagnosed on the basis of cross-sectional imaging, and therapy was started with empiric broad-spectrum antibiotics for her unrelenting cough and ongoing high fevers up to 103.4^{0}F. Seven days into her admission, the patient was transferred to our institution with diagnoses of fever of unknown origin (FUO) and pancytopenia.

At the time of transfer, she had a temperature of 99.4°F with a heart rate of 115 beats per minute, blood pressure 115/77 mm mercury, respiratory rate of 18 beats per minute, and oxygen saturation of 97% on room air. Physical exam was notable for lack of adenopathy, anicteric sclera, conjunctival pallor, clear oropharynx without oral lesions or palatal petechiae, a normal respiratory examination, tachycardia without murmurs, no lower extremity edema, a palpable spleen tip but otherwise benign abdominal examination, a nonfocal neurological examination, and a diffuse erythematous maculopapular rash involving her bilateral upper and lower extremities with sparing of the palms and soles.

She had progressive pancytopenia with a white blood cell count nadir of 1300/mm^3 (4000–11 000/mm^3), absolute neutrophil count (ANC) of 820/mm^3 (1800–7500/mm^3), hemoglobin of 8.0 g/dL (12.0–16.0 g/dL), and platelet count of 90 000/mm^3 (150 000–400 000/mm^3). A viral respiratory panel and serial blood cultures were negative.

Her initial chest x-ray (CXR) revealed increased interstitial markings, with a follow-up CXR and computed tomography chest scan revealing patchy opacities in the mid and lower right lung and in the left lung base suggestive of pneumonia (see Figure 4.11.1).

Monospot, urine legionella antigen, serum cryptococcal antigen, serologies for tick-borne illnesses (Rocky Mountain spotted fever, Lyme disease, *Ehrlichia, Anaplasma*), parvovirus, and human immunodeficiency virus (HIV) were negative. Adenovirus DNA polymerase chain reaction (PCR) and human herpesvirus-6 DNA PCR were both negative. Antinuclear antibodies (ANAs) were positive at 1:160, and her antineutrophil cytoplasmic antibody serology was also weakly positive. Serial blood cultures and a urine culture were negative. Given her pancytopenia, she underwent a bone marrow biopsy with demonstration of a hypocellular marrow and no other abnormalities including hemophagocytosis. She had serum ferritin 17 000 ng/mL (13–150 ng/mL), triglyceride 532 mg/dL (25–150 mg/dL), fibrinogen 305 mg/dL (170–410 mg/dL), sedimentation rate 60 mm/hour (0–25 mm/hour), creatinine 4.25 mg/dL (0.44–1.03 mg/dL), albumin 2.2 mg/dL (3.5–4.8 mg/dL), as well as transaminitis with alanine transaminase 79 U/L (14–54 U/L), aspartate aminotransferase 61 U/L (15–41 U/L), and alkaline phosphatase 148 U/L (38–126 U/L). Viral hepatitis (A, B, C) serologies were negative. Quantitative cytomegalovirus (CMV) PCR from serum was markedly elevated at >130 350 copies/mL. Epstein-Barr virus (EBV) serologies were consistent with acute infection with a highly positive EBV capsid antigen immunoglobulin (Ig)M of 117.9 U/mL (0–43.9 U/mL) and IgG of >749.9 U/mL (0–21.9 U/mL) and antibody to EBV

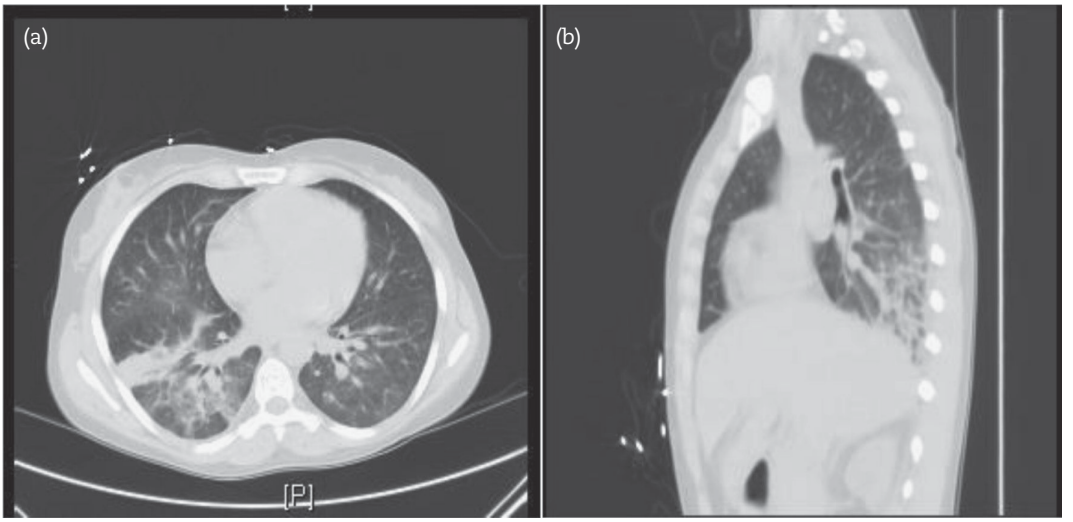

FIGURE 4.11.1: CT chest showing interstitial edema and right greater than left lower lobe consolidation likely from CMV and EBV. 1a transverse view 1b. sagittal view.

nuclear antigen of 7.0 Index Value (IV) (0–0.8IV). Quantitative EBV PCR was detectable in serum, and her soluble interleukin-2 receptor alpha level was 43 200 pg/mL (0–1033 pg/mL). After consultation with rheumatology, the patient was determined to not have a primary rheumatologic diagnosis in the setting of a weakly positive ANA.

DIFFERENTIAL DIAGNOSES

The differential diagnoses for an immunosuppressed patient presenting with FUO and multisystem disease, rash, cough, hepatitis, and pancytopenia is very broad and may be divided into infectious, neoplastic, autoimmune-mediated, and iatrogenic etiologies. The most likely infectious diagnoses include acute or reactivation of viral infections (adenovirus, CMV, EBV, HIV, parvovirus), tick-borne infections (Rocky Mountain spotted fever, Lyme disease, *Ehrlichia, Anaplasma*), disseminated bacterial infections (syphilis, *Legionella*, tuberculosis, nontuberculous mycobacteria), and disseminated fungal infections (*Cryptococcus* and dimorphic fungal infections such as *Histoplasmosis, Blastomycosis*, and *Coccidiodes*). Also meriting consideration are primary hematologic neoplasms such as lymphomas and acute leukemias as well as solid tumor metastatic disease. Immune dysregulatory etiologies include, but are not limited to, drug-induced systemic lupus erythematosus, adult-onset Still's disease, hemophagocytic lymphohistiocytosis (HLH), and drug reaction with eosinophilia and systemic symptoms.

DIAGNOSIS

On the basis of the patient's clinical presentation and accompanying serologic and radiographic data, the patient was diagnosed with acute CMV and EBV infection. Given the additional findings of fever, splenomegaly, peripheral blood cytopenia of at least two cell lines with hemoglobin <9 g/dL and platelet count <100 000/μL, hypertriglyceridemia, ferritin level >500 ng/mL, and an elevated soluble interleukin-2 receptor alpha level, she was diagnosed with HLH.

TREATMENT

A high-dose dexamethasone taper was initiated for HLH treatment, and intravenous ganciclovir was concomitantly initiated for the treatment of CMV viremia, pneumonia, and CMV-associated HLH. After steroid initiation and CMV treatment, her fevers resolved, and her transaminases, ferritin, and triglycerides all trended toward normal with concomitant improvement of her pancytopenia by the time of discharge three weeks later. At the time of discharge, her outpatient 6MP was withheld and a slow steroid taper was continued along with trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* pneumonia prophylaxis.

CLINICAL FEATURES AND DIAGNOSIS

Thiopurines, 6MP and azathioprine, are used to treat patients with inflammatory bowel disease (IBD), Crohn's and ulcerative colitis are types of inflammatory bowel disease. Thiopurines

suppress T cells and cell-mediated immunity that may increase the risk for viral infections such as EBV and CMV. Of the cases of HLH reported in patients with IBD, most were on thiopurine therapy and had either CMV or EBV acute infection [1–5]. Inflammatory bowel disease patients in particular are at risk for the development of HLH as a result of chronic systemic inflammation as well as exposure to immune-suppressing therapies [2]. Primary infection with EBV and EBV reactivation are well appreciated precipitants of HLH in pediatric and adult populations, respectively [1, 2, 6]. Cytomegalovirus-associated HLH has been described in both immune-competent and immune-suppressed patients [6].

Hemophagocytic lymphohistiocytosis is a rare disorder with current estimates suggesting an incidence of 1.2 cases per million individuals annually [6, 7]. Hemophagocytic lymphohistiocytosis may present as either primary or secondary disease. Primary HLH, familial HLH, is an autosomal recessive disease that is often diagnosed in early infancy via genetic testing [8]. Secondary HLH may present in either the pediatric or adult population, with underlying infection, hematologic malignancy, autoimmune disease, or immunosuppression serving as potential precipitants for the development of HLH [7, 8]. Hemophagocytic lymphohistiocytosis is a result of intense immune activation and inappropriately activated macrophages and lymphocytes leading to the phagocytosis of all bone marrow-derived cells [1, 2, 6, 8]. The Histiocyte Society developed the first prospective international treatment protocol, HLH-94, in 1994. These diagnostic guidelines underwent revision in 2004 leading to HLH-2004, which remains the standard guidelines for HLH diagnosis and treatment [8]. Diagnosis with HLH requires either a molecular diagnosis consistent with HLH or fulfillment of at least five of the following eight diagnostic criteria: (1) fever ≥38.5°C; (2) splenomegaly; (3) peripheral blood cytopenia involving at least two cell lines with a hemoglobin <9 g/dL, platelet count <100 000/μL, and ANC <1000/μL; (4) hypertriglyceridemia with fasting triglycerides >265 mg/dL or hypofibrinogenemia with a fibrinogen <150 mg/dL; (5) hemophagocytosis of bone marrow, spleen, lymphatic, or hepatic tissue; (6) ferritin >500 ng/mL; (7) a soluble interleukin-2 receptor alpha level (also known as soluble CD25) >2 standard deviations above age-adjusted, laboratory-specific norms; and (8) low or absent natural killer cell activity (the latter three criteria were added as part of HLH-2004) [8].

TREATMENT AND PREVENTION

The five-year survival rate from HLH in the late twentieth century was 55% on the basis of HLH-1994 treatment protocols. With the implementation of HLH-2004 diagnostic and treatment guidelines, the five-year survival rate from HLH has greatly improved to be over 80% [3]. The HLH-2004 protocol includes treatment recommendations that do not discriminate on the basis of whether an infection precipitated the HLH, although there are some data to suggest that this protocol is particularly successful in patients with EBV-associated HLH [4, 8]. Present guidelines do not provide recommendations on how to manage those patients on immunomodulating agents at time of diagnosis. This specific patient's thiopurine was held due to her pancytopenia and the immunosuppression causing EBV and CMV infection. The thiopurine was not restarted after her pancytopenia resolved due to the sensitivity of developing pancytopenia with the standard treatment dose for ulcerative colitis. Of note, there have been case reports of HLH in IBD patients taking other immunosuppressants that do not typically cause leukopenia, such as infliximab and corticosteroids used in the setting of severe disease or chronic use [1]. Of these cases, an infectious pathogen was usually detected, mostly CMV or EBV and one case associated with histoplasmosis [1].

Treatment recommendations for HLH are based on controlling the cytokine storm and impressive cellular proliferation that mark HLH [6]. The HLH-2004 protocol suggests initial treatment during weeks 1 through 8 with a combination of a high-dose dexamethasone taper in conjunction with cyclosporin A, etoposide (VP-16), and consideration of intrathecal chemotherapy with methotrexate or corticosteroids in the case of refractory central nervous system involvement [6, 8]. Salvage therapy recommendations in cases of recurrent, refractory, or persistent severe disease are not specifically delineated in the HLH-2004 guidelines and are deferred to the discretion of the treating clinicians or subspecialty center, including consideration for possible hematopoietic stem cell transplantation [8]. In patients with CMV, treatment of CMV with hyperimmune globulin, ganciclovir, or foscarnet can help with recovery from HLH [6].

Although there is no definitive prophylaxis to protect against the development of HLH, patients with HLH are at increased risk of secondary viral, fungal, and bacterial infections. Prophylaxis with trimethoprim-sulfamethoxazole

and consideration for treatment with intravenous immunoglobulin during the initial phase of treating HLH have been recommended [8].

REFERENCES

1. Biank VF, Sheth MK, Talano J, et al. Association of Crohn's disease, thiopurines, and primary Epstein-Barr virus infection with hemophagocytosis lymphohistiocytosis. J Pediatr. 2011;159:808.
2. Viridis F, Tacci S, Messina F, Varcarda, M. Hemophagocytic lymphohistiocytosis caused by primary Epstein-Barr virus in patient with Crohn's disease. World J of Gastro Surg. 2013;5:306.
3. Fitzgerald, MP, Armstrong L, Hague R, Russell RK. A case of EBV driven haemophagocytic lymphohistiocytosis complicating a teenage Crohn's disease patient on azathioprine, successfully treated with rituximab. J Crohns Colitis. 2013;7:314.
4. Horne AC, Janka G, Egeler RM, et al. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis. Br J Haematol. 2005;129:622.
5. N'Guyen Y, Baumard S. Cytomegalovirus associated hemophagocytic lymphohistiocytosis in patients suffering from Crohn's disease treated by azathioprine: a series of four cases. Inflamm Bowel Dis. 2011;17:E116.
6. Maakaroun NR, Moanna A, Jacob JT, Albrecht H. Viral infections associated with haemophagocytic syndrome. Rev Med Virol. 2010;20:93.
7. Atim-Oluk M. Cytomegalovirus associated haemophagocytic lymphohistiocytosis in the immunocompetent adult managed according to HLH-2004 diagnostic using clinical and serological means only. Eur J Microbiol Immunol (Bp). 2013;3:81.
8. Henter JI, Horne A, Arico M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer. 2007;48:124.

4.12

Hitting the Bull's Eye: Target Lesions

RACHEL GORMLEY, MD AND MISHA ROSENBACH, MD

CASE PRESENTATION

A 39-year-old woman with history of rheumatoid arthritis, on adalimumab (HUMIRA), presented with crusted painful lips and a new rash on her hands, feet, arms, and legs. Preceding her rash, she had noted a "cold sore" on her lower lip and she described getting cold sores a few times per year for many years. In the year prior to presentation, she noted two episodes of cold sores followed within a week by eruption of similar but slightly milder version of her current skin eruption, with lesions accentuated on the palms and soles. She denied any urinary discomfort, vaginal or anal erosions, or ulcerations. She had no known history of genital herpes simplex virus (HSV). She denied any new medications. Due to the severity of the most recent eruption, she presented to the emergency room, where she was admitted for further workup and management. Her medications at the time of presentation included albuterol, gabapentin, montelukast, and adalimumab.

On physical exam, she was noted to have tender, round, well defined, violaceous-to-red macules, some with a target appearance with three distinct zones involving her legs, hands, and feet (Figure 4.12.1). Focal lesions demonstrated central bullae formation. Her lips were crusted, and ulcerated and ulcerations were also present on the tongue and buccal mucosa (Figure 4.12.2). The differential diagnosis for her mucocutaneous findings included Stevens-Johnson syndrome (SJS), erythema multiforme (EM), and small vessel vasculitis.

Workup included a normal complete blood count, complete metabolic profile, including liver function tests, and urinalysis. Viral culture from one of the vesicular lesions on the arm was negative. Herpes simplex immunoglobulin (Ig)M was positive. She was evaluated by ophthalmology and determined to have slight epicanthal edema but no involvement of the cornea or sclera. She

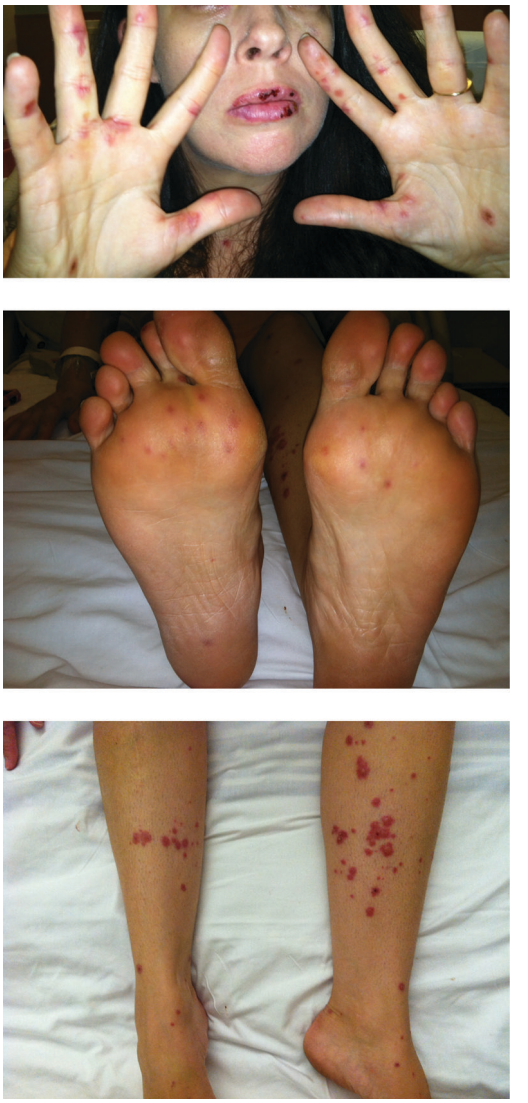

FIGURE 4.12.1: Cutaneous exam. Hands and feet with tender, round and focally target shaped macules. Legs with non-blanching, violaceous-to-red macules with focal bullae formation.

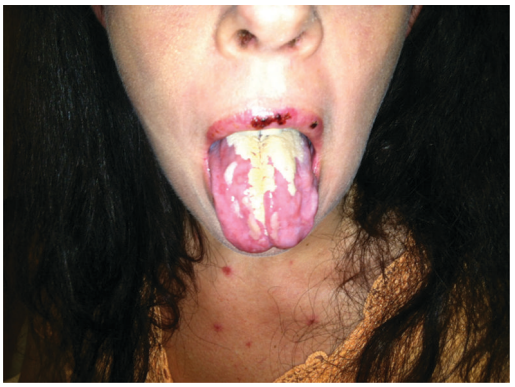

FIGURE 4.12.2: Oral findings. Lips with hemorrhagic crusting and extensive, painful ulcerations coalescing on the tongue.

was started on valacyclovir 500 mg twice daily along with prednisone, and her adalimumab was discontinued. She rapidly improved and had full resolution of her skin lesions.

DISCUSSION

Erythema multiforme is an acute, self-limited, type IV hypersensitivity reaction associated with certain infections, most commonly HSV, as well as some medications. In up to 50% of cases, no identifiable cause can be found [1]. The herpes simplex-associated form of EM is called "Herpes Simplex Associated EM" (HAEM). The HAEM may present with recurrent episodes in the context of flares of genital or oral HSV.

The degree of severity can vary; some patients present with only a few scattered lesions on the palms and soles, and others present with many exuberant lesions and extensive mucosal involvement. Severe mucosal involvement may lead to difficulty with oral intake and severe pain. The degree of mucosal involvement in this patient raised concern for SJS, prompting inpatient dermatology consultation. Although EM is now generally considered separate and distinct from SJS and toxic epidermal necrolysis (TEN) by most experts, these entities were previously felt to have overlap, and some experts discussed them as a spectrum of severity. Nevertheless, distinguishing these entities can be challenging. Stevens-Johnson syndrome almost always has two mucous membrane sites involved, with marked conjunctival involvement classically and "targetoid" or two-colored nonblanching spots. Toxic epidermal necrolysis involves multiple mucous membrane sites and sheets of epidermal necrosis. Stevens-Johnson syndrome and TEN exist on a spectrum. Erythema multiforme generally has one site of inflamed mucous membrane (often the lips, particularly if oral HSV is present), and skin lesions are generally limited and distinct, with target lesions (three zones of color) symmetrically on acral sites. It is important to note that our patient demonstrated involvement of only her oral mucosa without involvement of the genitals or eyes, thus lacking involvement of two or more sites of mucosal membranes for the definition of SJS.

It is also important to note that bullous lesions of EM can occur, as seen in the leg lesions of this patient. If the inflammatory infiltrate is brisk enough, pseudovesiculation or true vesiculation may occur. It is noteworthy that clinically available HSV culture and polymerase chain reaction assays may not detect HSV viral DNA in peripheral skin lesions, because these represent a host immune response to a localized HSV infection; some studies have demonstrated the presence of fragments of HSV DNA and expression of virally encoded antigens on keratinocytes within cutaneous target lesions [2, 3].

Adalimumab is a recombinant human IgG monoclonal antibody tumor necrosis factor (TNF)-α inhibitor. The occurrence of EM occurring in patients being treated with adalimumab as well as with other TNF-α inhibitors, including etanercept and infliximab, have been reported in multiple patients [1, 4–7]. There are total of eight reported cases of severe skin reactions to adalimumab in the literature [1]: five cases of EM, two cases of SJS, and one case classified as concurrent EM and SJS [1]. There are additional reports in the literature of EM associated with other TNF-α inhibitors including infliximab [5, 6] and etanercept [7].

In patients on TNF-α inhibitors, it has been suggested that immunosuppression induced by TNF-α inhibitors may lead to increased susceptibility to HSV infections and flares, consequently promoting eruptions of HAEM [1]. Immune compromise caused by TNF-α inhibition specifically decreased levels of proinflammatory cytokines such as interleukin (IL)-1 and IL-6, inhibition of leukocyte migration, and decreased activation of neutrophil functional activity [1]. This may provide an opportunity for viral DNA fragments to be disseminated peripherally into the circulation with subsequent development of HAEM. Widespread use of TNF-α inhibitors has led to the observation that there may be frequent latent virus reactivation in patients on these medications. Patients on

TNF-α inhibitors seem to be at an increased risk for developing reactivation varicella-zoster virus infection as well HSV.

Immunosuppressed patients, overall, are at higher risk for developing EM. Patients with human immunodeficiency virus infection, corticosteroid exposure, history of bone marrow transplantation, systemic lupus erythematosus, graft-versus-host disease, and inflammatory bowel disease, and those undergoing radiation, chemotherapy, or neurosurgery for brain tumors have all been shown to be at higher risk for development of EM [8].

Most cases of EM are self-limited, with lesions evolving over a few weeks, followed by spontaneous resolution and healing without scarring. Recurrence may occur and is a particular problem for patients with HAEM. Recurrent episodes are often associated with flares of oral or genital herpes, as in this patient with recurrent cold sores, but recurrence may also be seen with subclinical HSV disease in absence of lesions recognized by patients or their providers.

In severe cases of EM, a one- to three-week course of oral prednisone at 0.5 to 1 mg/kg daily may be used. In cases of HAEM, patients should also be treated with acyclovir. For those patients who experience recurrent episodes, daily suppressive therapy (with acyclovir, valacyclovir or famciclovir) should be considered. For comfort and symptom management, topical therapy including topical antiseptics and local anesthetic solutions may be useful.

REFERENCES

1. Ahdout J, Haley JC, Chiu MW. Erythema multiforme during anti-tumor necrosis factor treatment for plaque psoriasis. J Am Acad Dermatol. 2010;62:874.
2. Darragh TM, Egbert BM, Berger TG, Yen TS. Identification of herpes simplex virus DNA in lesions of erythema multiforme by the polymerase chain reaction. J Am Acad Dermatol. 1991;24:23.
3. Aslanzadeh J, Helm KF, Espy MJ, et al. Detection of HSV-specific DNA in biopsy tissue of patients with erythema multiforme by polymerase chain reaction. Br J Dermatol. 1992;126:19.
4. Beuthien W, Mellinghoff HU, von Kempis J. Skin reaction to adalimumab. Arthritis Rheum. 2004;50:1690.
5. Soliotis F, Glover M, Jawad AS. Severe skin reaction after leflunomide and etanercept in a patient with rheumatoid arthritis. Ann Rheum Dis. 2002;61:850.
6. Vergara G, Silvestre JF, Betlloch I, et al. Cutaneous drug eruption to infliximab: report of 4 cases with an interface dermatitis pattern. Arch Dermatol. 2002;138:1258.
7. Kain T, MacGregor D, Buchanan RR, et al. Erythema multiforme with tumour necrosis factor inhibitors: a class effect? Ann Rheum Dis. 2008;67:899.
8. Plaza J, James WD. Erythema multiforme. eMedicine. http://emedicine.medscape.com/article/1122915-overview, unsure of exact date approx. June 1, 2013.

4.13

Multiple Sclerosis Treatments: Friend and Foe

DAVID HOLTZMAN, MD, MSC AND AMY PRUITT, MD

CASE PRESENTATION

A 55-year-old woman with relapsing remitting multiple sclerosis (MS) in remission on monthly natalizumab infusions for the past three years presented with several days of difficulty focusing and subtle cognitive difficulties. She stated that she felt uncertain about everything she tried to do but could not pinpoint any other specific symptoms. She denied any weakness, vertigo, ataxia, or other symptoms that have typically appeared with her prior MS flares.

Her other medical problems included gastroesophageal reflux, hypertension, and neuropathic pain due to her MS. The medications she was taking at the time of her initial presentation included aspirin, baclofen, gabapentin, hydrochlorothiazide, omeprazole, valsartan, and natalizumab. Her last natalizumab infusion was three weeks before the onset of her current symptoms.

Physical Exam and Data

She was afebrile and normotensive. Her general physical examination was unremarkable. Neurologic examination revealed fluent speech, normal prosody and articulation, and intact comprehension. Her attention span, memory, and affect were normal. Her cranial nerve exam was normal except for optic pallor bilaterally on fundoscopic examination. Her motor strength was 5/5 in all extremities. Her coordination and gait were normal. She had decreased vibratory sensation in both feet, but her sensory examination was otherwise normal. Her deep tendon reflexes were 3+ in the upper extremities and 2+ in the lower extremities. Plantar responses were flexor.

Basic serum chemistries, liver functions panel, and a complete blood count were normal. A lumbar puncture demonstrated a normal opening pressure and normal glucose and protein with 1 white blood cell/μL. Magnetic resonance image (MRI) of the brain revealed stable appearance of numerous foci of increased signal intensity in the subcortical, deep and periventricular white matter, splenium, and left brachium pontis in keeping with the diagnosis of MS. However, new compared with her MRI of the brain from four months earlier was a confluent, nonenhancing T2 hyperintensity with corresponding T1 hypointensity in the left frontal and parieto-occipital white matter involving the subcortical U fibers (Figure 4.13.1).

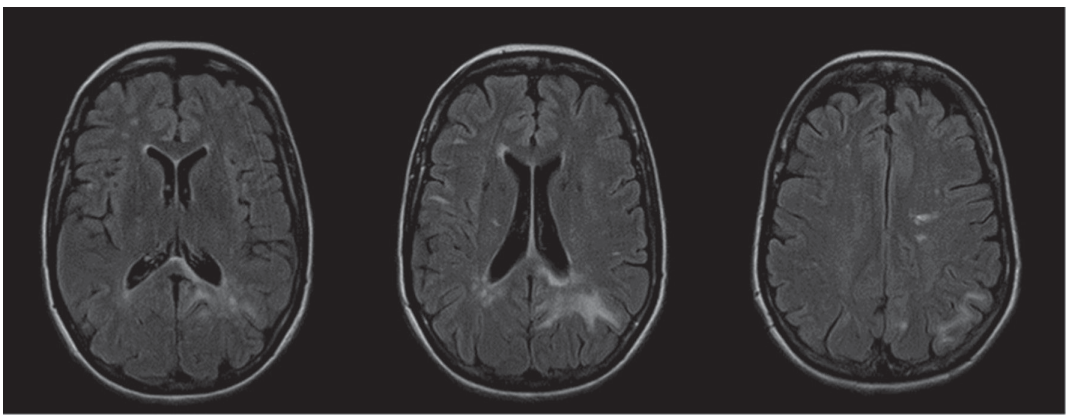

FIGURE 4.13.1: Initial MRI after onset of new neurologic symptoms (fluid attenuated inversion recovery [FLAIR] sequence). The lesions did not enhance with gadolinium on T1 sequences (not shown).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of nonenhancing white matter lesions is broad and includes neurologic disorders (MS, neuromyelitis optica, acute disseminated encephalomyelitis); infections (progressive multifocal leukoencephalopathy [PML], human immunodeficiency virus [HIV] encephalopathy); primary glial neoplasms; vascular disease (stroke, vasculitis, posterior reversible encephalopathy syndrome [PRES]); metabolic disorders; toxic exposures (methotrexate and other drugs), and genetic syndromes (leukodystrophies).

DIAGNOSIS

An initial polymerase chain reaction (PCR) for JC virus (JCV) DNA from a cerebrospinal fluid (CSF) sample was indeterminate, but a second CSF sample collected eleven days later and tested at a different laboratory demonstrated a CSF JCV DNA viral load of 2427 copies/mL, confirming the diagnosis of PML.

TREATMENT OUTCOME AND FOLLOW-UP

The patient underwent urgent plasmapheresis to remove natalizumab and to decrease the binding of any remaining drug from its receptor. Mefloquine and mirtazapine were administered for potential inhibitory effects on JCV replication. She was discharged from the hospital nineteen days after her presentation with minimal symptoms but presented four days later with the acute onset of expressive aphasia and gait instability. A repeat MRI of the brain redemonstrated the confluent areas of increased T2 and fluid-attenuated inversion recovery (FLAIR) signal intensity in the left frontal, parietal, and occipital lobes without significant change from her recent MRIs. An electroencephalogram showed periodic lateralized epileptiform discharges, and herpes simplex virus-1 infection was excluded by CSF PCR. Phenytoin, levetiracetam, and lacosamide were required to control seizure activity, and high-dose corticosteroids (methylprednisolone 1000 mg intravenously for seven days) were given for presumed immune reconstitution inflammatory syndrome (IRIS) associated with the discontinuation of natalizumab. Over the course of the following six weeks, her symptoms of expressive and receptive aphasia, right-sided weakness, and right homonymous hemianopsia waxed and waned before slowly beginning to improve. She was placed on a slowly tapering course of oral steroids and discharged to an acute rehabilitation facility for ongoing therapies. Clinical symptoms gradually resolved, and she was left with minimal right-sided weakness and language impairment.

Over this same period of time, serial MR imaging of her brain showed significant progression of the left hemispheric white matter lesions due to PML and development of enhancement consistent with IRIS that appeared approximately five weeks after her initial presentation and four weeks after receiving plasmapheresis (Figure 4.13.2). The PML lesions and enhancement due to IRIS began to slowly improve by eight weeks after her initial presentation (Figure 4.13.3). A repeat CSF JCV DNA PCR was negative six months later.

DISCUSSION

Overview of Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy is a demyelinating disease caused by infection of myelin-producing oligodendrocytes with JCV. JC virus is a large polyoma virus that infects the majority of the population by early adulthood. Primary infection is essentially asymptomatic, and the exact mechanism of transmission is unknown. JC virus persists in the bone marrow, kidneys, and lymphoid tissues [1]. B lymphocytes are felt to be the primary agents of dissemination during primary infection and periods of reactivation, which are frequent and asymptomatic. Wild-type JCV is not able to infect and replicate within the central nervous system (CNS), but JCV isolated from persons with PML has been shown to undergo genetic rearrangement, enabling it to productively infect oligodendrocytes and propagate [2].

Epidemiology

Before the beginning of the HIV epidemic in the 1980s, PML was a rare disease that had only been described in immunocompromised patients with malignancies (chronic lymphocytic leukemia and Hodgkin's lymphoma), bone marrow and solid organ transplants, or systemic lupus erythematosus. Human immunodeficiency virus is now the predominant cause of PML with HIV-infected patients, accounting for approximately 80% of PML cases [1]. Progressive multifocal leukoencephalopathy occurs in HIV-infected persons with an overall prevalence of 4% among those with a CD4 count below 200 cells/mL [2]. Human immunodeficiency virus-associated PML can also present after the initiation of antiretroviral therapy (ART) as a manifestation of IRIS.

Progressive multifocal leukoencephalopathy has been associated with the use of immunosuppressive

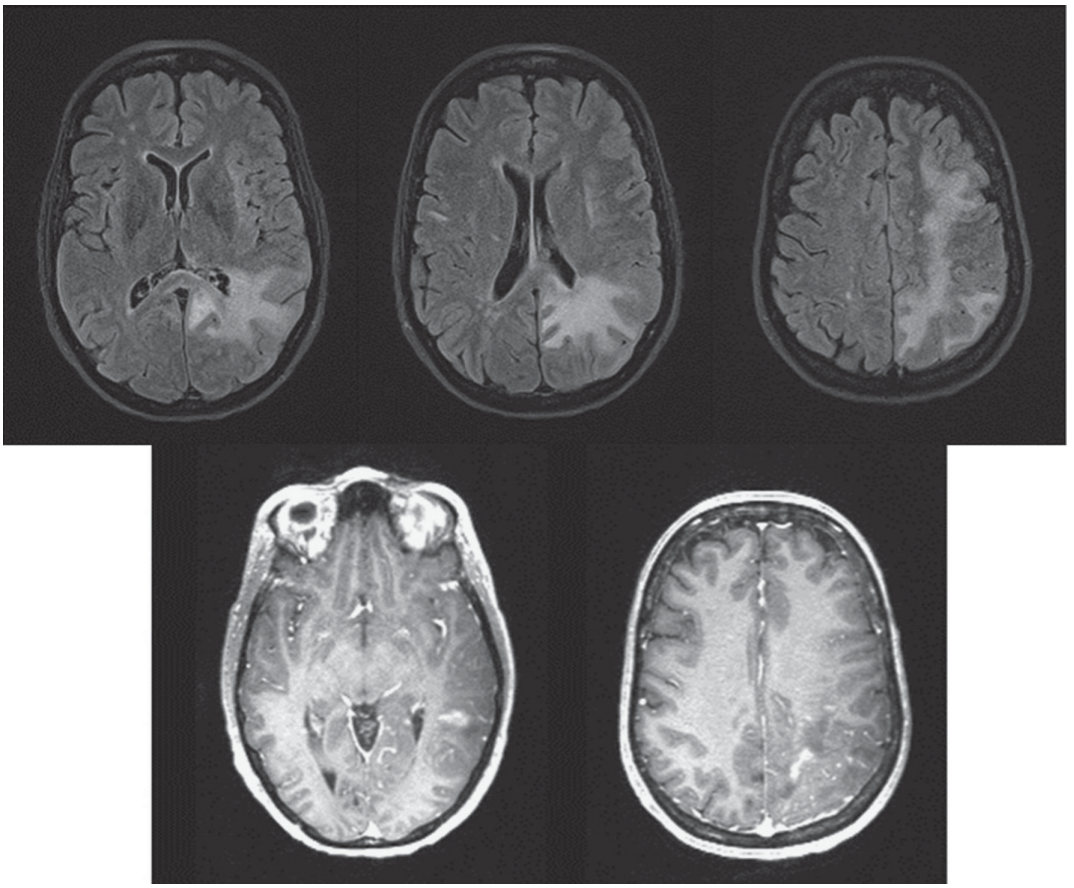

FIGURE 4.13.2: MRI 5 weeks after presentation, 4 weeks after plasmapheresis (top row-FLAIR sequence, bottom row–T1 post-gadolinium sequence). The extent of FLAIR abnormality has increased since Figure 1 and there is now patchy contrast enhancement.

medications for several decades in solid organ and bone marrow transplant recipients and certain chemotherapeutics, especially fludarabine [1]. The introduction and rapidly expanded use of biologic medications since the mid-1990s has led to a notable increase in medication-associated PML cases. That PML has been associated with certain immune-modulating biologics and not others has also shed light on how latent JCV infection may reactivate, spread to and gain access to the CNS, and then infect oligodendrocytes to produce the characteristic changes of PML.

Clinical Presentation

The most common presenting symptoms of PML reflect lesions in supratentorial and posterior fossa locations and typically involve changes in cognition and personality, motor weakness and gait abnormalities, speech and language difficulties, visual field deficits, and incoordination. Seizures are an uncommon presenting symptom [3].

Two other forms of PML have been described. (1) Granule cell neuronopathy is the result of JCV infection of the granule cells of the cerebellum and presents with cerebellar and brainstem findings. (2) A fulminant JCV encephalopathy involving infection of the cortical pyramidal neurons has also been described [3].

Radiographic Findings

Both computed tomography and MRI can detect PML brain lesions, but MRI is more sensitive. Progressive multifocal leukoencephalopathy lesions are hypointense on T1-weighted MRIs and hyperintense on T2-weighted and FLAIR sequence images [3]. In HIV-associated PML, gadolinium enhancement is present in approximately 10% of patients, although this proportion increases in HIV-infected persons who develop PML after initiating ART due to restoration of immune function that may be accompanied by worsening symptoms of IRIS. Immune

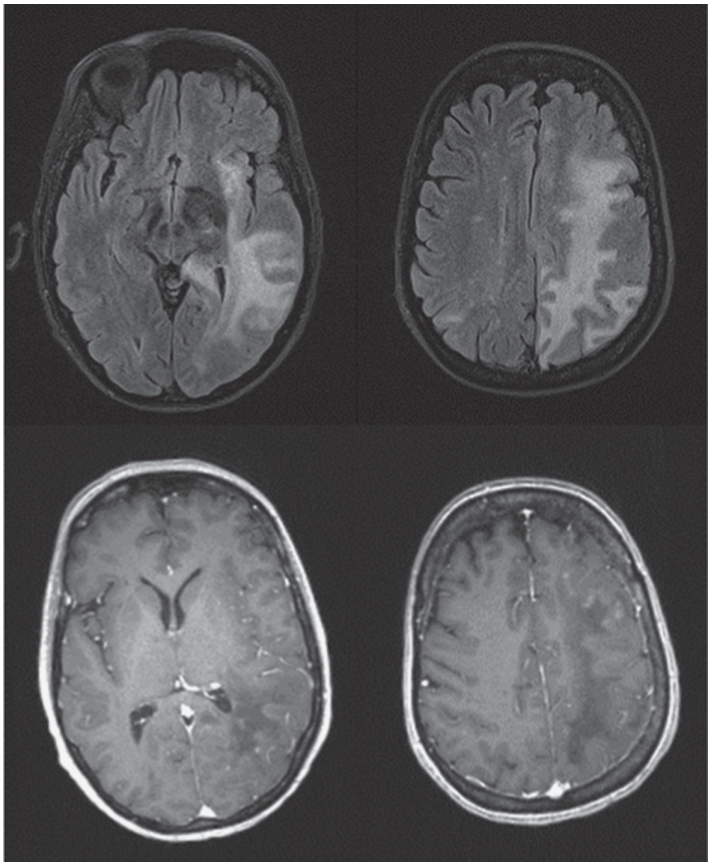

FIGURE 4.13.3: MRI 8 weeks after presentation (top row-FLAIR sequence, bottom row–T1 post-gadolinium sequence). While the FLAIR abnormalities are slightly more extensive than in Figure 2, the decrease in gadolinium contrast enhancement after corticosteroid therapy indicates resolving IRIS.

reconstitution inflammatory syndrome is more severe and more common in MS patients with natalizumab-associated PML, approximately one half of whom have enhancing lesions at presentation [3]. Radiographic evidence of IRIS occurs in essentially every MS patient as the effects of natalizumab wane [4, 5].

Association of Progressive Multifocal Leukoencephalopathy With Immune-Modulating Medications

Table 4.13.1 lists the immune-modulating medications that have been reported to be associated with PML. Natalizumab, rituximab, mycophenolate, brentuximab, and efalizumab all have "black box" warnings on their package inserts mandated by the US Food and Drug Administration (FDA). Efalizumab was voluntarily withdrawn worldwide in 2009 after four patients out of 1200 on the medication developed PML. Natalizumab, rituximab, and mycophenolate are highlighted below because of the strength of their association with PML or their frequent use among immune-modulating medications.

Natalizumab

Natalizumab is a humanized immunoglobulin (Ig)G_4 monoclonal antibody. It is a selective adhesion molecule (SAM) blocker and targets the α_4 subunit of the very late antigen-4 (VLA-4) integrin, which is used by lymphocytes to bind to vascular cell adhesion molecule 1 on endothelial cells. The primary mechanism theorized by which PML develops in patients receiving natalizumab is that the drug leads to decreased immune surveillance of the CNS due to its inhibitory effect on T-cell trafficking into the CNS. It is approved for use in MS and Crohn's disease.

Cases of PML were identified during clinical trials of natalizumab when combined with other immune-modulating medications [6–8]. As a result, it was approved for monotherapy use only, but cases of PML continue to be associated with its use. As of April 2013, approximately seven

TABLE 4.13.1. IMMUNE-MODULATING MEDICATIONS ASSOCIATED WITH PML

Drug	Molecular Target	Disease Indications
Adalimumab	TNF-α	Anklylosing spondylitis* Inflammatory bowel disease* Juvenile idiopathic arthritis* Psoriasis* Rheumatoid arthritis*
Alemtuzumab	CD52	B-cell chronic leukocytic leukemia* Chronic graft-versus-host disease Multiple sclerosis Solid organ transplant immunosuppression Hematopoietic stem cell transplant conditioning chemotherapeutic
Azathioprine	Antimetabolite, purine analog	Chronic immune thrombocytopenia Dermatomyositis Inflammatory bowel disease Lupus nephritis Myasthenia gravis Neuromyelitis optica Pemphigus vulgaris Polymyositis Rheumatoid arthritis* Sjogren's syndrome Solid organ transplant immunosuppression* Vasculitis
Brentuximab†	CD30	Anaplastic large cell lymphoma* Hodgkin lymphoma*
Cyclophosphamide	Alkylating agent	Acute lymphoblastic leukemia* Acute myelocytic leukemia* Autoimmune hemolytic anemia Breast cancer* Chronic lymphocytic leukemia* Chronic myelocytic leukemia* Cutaneous T-cell lymphoma* Hodgkin lymphoma* Idiopathic thrombocytopenic purpura Lupus nephritis Multiple myeloma* Multiple sclerosis Myasthenia gravis Nephrotic syndrome in children* Neuroblastoma* Non-Hodgkin lymphoma* Ovarian cancer* Retinoblastoma* Severe rheumatologic diseases Various solid organ cancers
Cyclosporine	Calcineurin inhibitor	Focal segmental glomerulosclerosis Graft-vs-host disease (prophylaxis and treatment) Psoriasis* Rheumatoid arthritis* Solid organ transplant immunosuppression* Systemic lupus erythematosus Ulcerative colitis

(*continued*)

TABLE 4.13.1 (CONTINUED)

Drug	Molecular Target	Disease Indications
Efalizumab[†,‡]	CD11a	Psoriasis*
Fludarabine	Antimetabolite, purine analog	Acute lymphocytic leukemia in children Acute myeloid leukemia B-cell chronic leukocytic leukemia* Hematopoietic stem cell transplant conditioning chemotherapeutic Non-Hodgkin lymphoma Waldenstrom's macroglobulinemia
Ibritumomab	CD20	B-cell non-Hodgkin lymphoma* Follicular non-Hodgkin lymphoma*
Infliximab	TNF-α	Anklylosing spondylitis* Inflammatory bowel disease* Psoriasis* Rheumatoid arthritis* Sarcoidosis
Methotrexate	Folate analog inhibitor	Acute lymphoblastic leukemia* Acute promyelocytic leukemia Bladder cancer Breast cancer* CNS tumors Cutaneous T-cell leukemia* Dermatomyositis Graft-versus-host disease (prophylaxis) Head and neck cancer (epidermoid)* Juvenile idiopathic arthritis* Lung cancer* Non-Hodgkin lymphoma* Osteosarcoma* Polymyositis Rheumatoid arthritis* Psoriasis* Soft tissue sarcoma Systemic lupus erythematosus Takayasu arteritis
Mycophenolate[†]	Inosine-5′-monophosphate dehydrogenase inhibitor	Autoimmune hepatitis Autoimmune glomerular disease Graft-vs-host disease (prophylaxis and treatment) Lupus nephritis Myasthenia gravis Neuromyelitis optica Psoriasis Solid organ transplant immunosuppression*
Natalizumab[†]	α_4 integrin CD49d	Crohn's disease* Multiple sclerosis*
Rituximab[†]	CD20	Autoimmune hemolytic anemia in children Chronic immune thrombocytopenia Chronic lymphocytic leukemia* Chronic graft-versus-host disease Granulomatosis with polyangitis*

(*continued*)

TABLE 4.13.1 (CONTINUED)

Drug	Molecular Target	Disease Indications
		Inflammatory myositis Lupus nephritis Membranous nephropathy Microscopic polyangitis* Multifocal motor neuropathy Multiple sclerosis Myasthenia gravis Nephrotic syndrome in children Neuromyelitis optica Non-Hodgkin lymphoma* Pemphigus vulgaris Posttransplant lymphoproliferative disease Rheumatoid arthritis* Thrombotic thrombocytopenic purpura Waldenstrom's macroglobuliemia
Tacrolimus	Calcineurin inhibitor	Graft-vs-host disease (prophylaxis and treatment) Solid organ transplant immunosuppression*

Abbreviations: FDA, US Food and Drug Administration; TNF, tumor necrosis factor.
*FDA-approved indication.
†Black-label warning mandated by FDA regarding risk of PML associated with medication.
‡Voluntarily withdrawn from market worldwide in 2009. Table adapted from Schmedt N, Andersohn F, Garbe E. Signals of progressive multifocal leukoencephalopathy for immunosuppressants: a disproportionality analysis of spontaneous reports within the US Adverse Event Reporting System (AERS). *Pharmacoepidemiol Drug Saf*. 2012;21:1216, Bosch X, Saiz A, Ramos-Casals M, BIOGEAS Study Group. Monoclonal antibody therapy-associated neurological disorders. *Nat Rev Neurol*. 2011;7:165, and Berger JR. Progressive multifocal leukoencephalopathy and newer biological agents. *Drug Saf*. 2010;33:969.

years after becoming available for prescription, 347 cases of confirmed PML have been reported in persons receiving natalizumab.

The estimated risk of developing PML is 1 case for every 1000 patients receiving natalizumab. Three risk factors identified with the highest risk of developing PML are as follows: (1) the prior use of immunosuppressive medications, such as azathioprine, methotrexate, mitoxantrone, cyclophosphamide, or mycophenolate; (2) a positive JCV serology; and (3) natalizumab monthly treatment for more than two years. Individuals with all three risk factors have an estimated risk of developing PML of 11 per 1000 persons [9].

Rituximab

Rituximab is a chimeric IgG_1 anti-CD20 monoclonal antibody that depletes $CD20^+$ B and pre-B cells. It is used in a wide range of disease states, including neurologic disorders, malignancies, and autoimmune diseases. Cases of PML have been observed in patients receiving rituximab across this entire spectrum of diseases, including diseases such as rheumatoid arthritis where PML does not occur in untreated patients [10]. This observation strongly suggests that rituximab itself is associated with an increased risk of PML.

The mortality rate of reported rituximab-associated PML cases is 90%, with a median time to death of two months [11]. This mortality rate is higher than the observed rate of death in PML cases attributed to other immune-modulating drugs, such as natalizumab, and is likely because the majority of rituximab-associated PML cases occur in patients with leukemia or lymphoma. These patients often are receiving additional immune-modulating chemotherapeutics that may decrease their ability to survive PML.

Mycophenolate

Mycophenolate is a selective, noncompetitive, reversible inhibitor of inosine-5'-monophosphate dehydrogenase, which is the first of two enzymes responsible for conversion of inosine monophosphate to guanosine monophosphate. Depletion of guanosine and deoxyguanosine metabolites inhibits B and T cell proliferation. Although patients taking mycophenolate typically receive

additional immunosuppressive medications, an increased incidence of PML has been observed in patients on mycophenolate-containing immunosuppressive regimens compared with patients on mycophenolate-sparing regimens [12].

DIFFERENTIAL DIAGNOSIS

It is crucial that PML be considered in the differential diagnosis of any patient receiving an immune-modulating medication associated with PML and presenting with new neurologic symptoms. An MRI of the brain should be obtained promptly, and evidence of JCV infection in the CNS should be investigated. Differential diagnosis depends on the patient's underlying disease and immune-compromising regimen.

It can be difficult to ascertain the etiology of neurologic symptoms in MS patients receiving natalizumab. Multiple sclerosis and PML both cause demyelinating lesions, and half of natalizumab-associated PML cases present with some degree of enhancement on MRI, a typical finding in MS. Corticosteroids can improve symptoms attributable to PML IRIS, thus further confounding the picture because steroids are also a mainstay of treatment for MS exacerbations.

In MS patients on natalizumab, comparison of MRIs obtained after the onset of new neurologic symptoms with prior MRIs is important. Certain features can help discern between demyelinating lesions caused by PML or MS. Multiple sclerosis lesions often occur in a periventricular pattern, so-called "Dawson's fingers", in contrast to PML lesions, which frequently appear in the subcortical white matter or the gray-white matter junction. Progressive multifocal leukoencephalopathy lesions are rarely found in the optic nerves or spinal cord, but MS lesions preferentially affect these locations [13].

Two additional diagnoses that should be considered in oncology patients and bone marrow or solid organ transplant recipients presenting with new neurologic symptoms are posterior reversible encephalopathy syndrome (PRES) and posttransplant lymphoproliferative disorder (PTLD). Posterior reversible encephalopathy syndrome is associated with immunosuppressive medications frequently used in transplant populations, including tacrolimus, cyclosporine, sirolimus, and rituximab. Posterior reversible encephalopathy syndrome presents as acute onset of confusion, seizures, headache, and visual disturbances. Brain imaging reveals a primarily posterior cerebral hemispheric process with imaging features consistent with vasogenic edema [13]. Posttransplant lymphoproliferative disorder is caused by a proliferation of B lymphocytes that is driven by Epstein-Barr virus reactivation in the setting of immune suppression. Some of these B lymphocytes may undergo mutations leading to B-cell lymphoma. Most patients with PTLD present with extranodal masses and 20%–25% have CNS disease.

Diagnosis of Progressive Multifocal Leukoencephalopathy

There are two main approaches to establishing the diagnosis of PML: (1) demonstration of characteristic histopathologic changes consistent with JCV infection or (2) correlating clinical and radiographic criteria for PML with the identification of JCV in CSF [3]. Before the development of PCR techniques to identify JCV DNA, brain biopsy was the primary means of confirming the diagnosis of PML. Biopsies of PML lesions demonstrate a unique triad of histopathologic changes consisting of white matter inflammation and demyelination; enlarged, reactive, so-called "bizarre" astrocytes; and enlarged basophilic oligodendrocytes that stain positive for JCV SV40 antigen [3].

Identification of JCV DNA via PCR in CSF combined with the presence of characteristic clinical and/or radiographic findings of PML is the more common diagnostic approach used now. The sensitivity of various commercial laboratories' JCV PCR tests varies, and false-negative results can occur because CSF JCV viral loads can be low early in the course of PML. The research laboratory at the National Institutes of Health can reliably detect 10 copies of viral DNA/mL, and CSF samples can be sent to this laboratory in the situation of a suspected false-negative CSF JCV PCR [3]. Aside from the detection of JCV DNA in CSF, the CSF profile of patients with PML in the absence of IRIS is typically normal with the majority of patients having only a few white blood cells and a modest elevation in protein levels at most.

JC virus serology is not useful in diagnosing PML given the frequency of JCV infection by adulthood. Likewise, detection of JCV DNA in plasma or urine has not been shown to directly correlate with development of PML [14, 15].

Treatment

Reconstitution of the immune system is the mainstay of PML treatment, because there is no drug that has proven to be effective in combating JCV infection. In natalizumab-associated PML, immune reconstitution is accomplished

by stopping the drug and performing plasma exchange transfusion (PLEX) or immunoadsorption. Plasma exchange transfusion and immunoadsorption serve to rapidly decrease the levels of natalizumab remaining in the body. They also decrease the drug's binding to lymphocytes' α_4 subunit of the VLA-4 integrin, thus minimizing further interference with lymphocytes trafficking into the CNS [4, 5].

Immune reconstitution inflammatory syndrome predictably occurs several days to weeks after PLEX in natalizumab-associated PML. Patients with IRIS after PLEX typically present with subacute progression of their prior PML symptoms [5]. High-dose corticosteroids (dexamethasone 32 mg daily in four divided doses for two weeks or methylprednisolone 1 gram daily for five days) are often administered for several days when patients present with IRIS symptoms followed by a slow taper of oral steroids. Immune reconstitution inflammatory syndrome symptoms can last up to several months and, in certain circumstances, prove to be fatal. Despite the potential worsening of symptoms due to IRIS, it is vital to reconstitute the immune system as soon as possible given the natural progression of PML in the setting of ongoing immune suppression.

Several medications have been studied in the treatment of PML, but none has proven clinically beneficial. Mirtazapine blocks the entry of JCV into cells in vitro via its 5-hydroxytryptamine$_{2A}$ serotonin receptor blockade but has not been shown to stop PML disease progression in clinical experience [16]. Mefloquine inhibits JCV replication within cells in vitro after a virion has entered but also has not demonstrated any positive effect on disease outcomes [17]. Cytarabine was found to prevent JCV replication in vivo, but a placebo-controlled trial in patients with HIV-associated PML showed no benefit [18]. Cidofovir has in vitro activity against JCV but has not been found to affect PML morbidity or mortality [19]. CYT107, a recombinant form of human interleukin-7 that serves as a T-lymphocyte growth factor, received orphan drug designation for the treatment of PML in the United States and Europe, but its development was suspended when the pharmaceutical company developing it declared bankruptcy.

Prevention

Several strategies have been proposed for preventing PML associated with immune-modulating medications. Risk-stratifying recipients of immune-modulating drugs based on JCV seropositivity can be useful because 90%–100% of natalizumab-associated PML occurs in JCV-seropositive patients [15]. However, the high rates of JCV seropositivity in the general population suggest that few patients would be exempted from closer monitoring due to being seronegative.

Routine surveillance for JCV DNA in urine, plasma, and peripheral blood mononuclear cells does not seem to be a useful screening tool. No significant differences were found in the detection rates of JCV viremia and viruria between people exposed and unexposed to natalizumab. Moreover, there were no significant differences found in JCV DNA detection over time in people receiving natalizumab. In addition, JCV DNA was unable to be isolated from the blood of five patients who developed PML while on natalizumab [15].

Surveillance magnetic resonance brain imaging is another recommended surveillance approach for any patient receiving an immune-modulating drug that has been associated with PML. Comparison with baseline MRIs is particularly important among patients with MS given the difficulties distinguishing the etiology of white matter lesions.

Drug holidays from agents such as natalizumab have also been used to allow for at least partial immune reconstitution. However, the risk of a patient's underlying disease recurring during the drug holiday is significant, and the magnitude of any potential benefit of reducing the risk of PML is offset by the risk of IRIS. Prevention of IRIS by prophylactic administration of corticosteroids after PLEX for PML or discontinuation of natalizumab for indications other than suspected PML is not advised because steroids may blunt effective anti-JCV cell response [20].

Prompt assessment of patients with new neurologic symptoms or MRI findings who are receiving immune-modulating drugs associated with PML remains the most crucial intervention. Drug safety databases and registries of patients receiving particular immune-modulating medications are important data repositories for better understanding the risk factors for developing PML associated with these drugs as well as patient outcomes and responses to various treatments.

REFERENCES

1. Carson KR, Focosi D, Major EO, et al. Monoclonal antibody-associated progressive multifocal leucoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a review from the Research on Adverse Drug Events and Reports (RADAR) Project. Lancet Oncol. 2009;10:816.

2. Keene DL, Legare C, Taylor E, et al. Monoclonal antibodies and progressive multifocal leukoencephalopathy. Can J Neurol Sci. 2011;38:565.
3. Berger JR, Aksamit AJ, Clifford DB, et al. PML diagnostic criteria: consensus statement from the AAN Neuroinfectious Disease Section. Neurology. 2013;80:1430.
4. Clifford DB, De Luca A, Simpson DM, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. Lancet Neurol. 2010;9:438.
5. Tan IL, McArthur JC, Clifford DB, et al. Immune reconstitution inflammatory syndrome in natalizumab-associated PML. Neurology. 2011; 77:1061.
6. Van Assche G, Van Ranst M, Sciot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med. 2005;353:362.
7. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med. 2005;353:369.
8. Langer-Gould A, Atlas SW, Green AJ, et al. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med. 2005;353:375.
9. US Food and Drug Administration. New risk factor for progressive multifocal leukoencephalopathy (PML) associated with Tysabri (natalizumab). 2012. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm288186.htm. Accessed July 29, 2013.
10. Clifford DB, Ances B, Costello C, et al. Rituximab-associated progressive multifocal leukoencephalopathy in rheumatoid arthritis. Arch Neurol. 2011;68:1156.
11. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. Blood. 2009; 113:4834.
12. Schmedt N, Andersohn F, Garbe E. Signals of progressive multifocal leukoencephalopathy for immunosuppressants: a disproportionality analysis of spontaneous reports within the US Adverse Event Reporting System (AERS). Pharmacoepidemiol Drug Saf. 2012;21:1216.
13. Horger M, Beschorner R, Beck R, et al. Common and uncommon imaging findings in progressive multifocal leukoencephalopathy (PML) with differential diagnostic considerations. Clin Neurol Neurosurg. 2012;114:1123.
14. Major EO, Frohman E, Douek D. JC viremia in natalizumab-treated patients with multiple sclerosis. N Engl J Med. 2013;368:2240.
15. Tyler KL. Progressive multifocal leukoencephalopathy: can we reduce risk in patients receiving biological immunomodulatory therapies? Ann Neurol. 2010;68:271.
16. Marzocchetti A, Tompkins T, Clifford DB, et al. Determinants of survival in progressive multifocal leukoencephalopathy. Neurology. 2009; 73:1551.
17. Clifford DB, Nath A, Cinque P, et al. A study of mefloquine treatment for progressive multifocal leukoencephalopathy: results and exploration of predictors of PML outcomes. J Neurovirol. 2013;19:351.
18. Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. AIDS Clinical Trials Group 243 Team. N Engl J Med. 1998;338:1345.
19. De Luca A, Ammassari A, Pezzotti P, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. AIDS. 2008;22:1759.
20. Antoniol C, Jilek S, Schluep M, et al. Impairment of JCV-specific T-cell response by corticotherapy: effect on PML-IRIS management? Neurology. 2012;79:2258.
21. Bosch X, Saiz A, Ramos-Casals M, BIOGEAS Study Group. Monoclonal antibody therapy-associated neurological disorders. Nat Rev Neurol. 2011;7:165.
22. Berger JR. Progressive multifocal leukoencephalopathy and newer biological agents. Drug Saf. 2010;33:969.

4.14

"B" Prepared When Using Biologic Agents

CHARITHA GOWDA, MD, MPH AND KAREN KROK, MD

CASE PRESENTATION

A 35-year-old woman with a longstanding history of Crohn's disease presented to the gastroenterology office for evaluation of abdominal pain and diarrhea that had been getting progressively worse over the last six months. She reported frequent, loose bowel movements, requiring trips to the bathroom as often as every two to three hours, as well as significant fatigue. She had lost over ten pounds in the preceding three months.

The patient had been diagnosed with Crohn's disease in her late 20s after an initial presentation of fatigue, abdominal pain, and diarrhea. Upper and lower endoscopy revealed ileocolonic disease, and pathology confirmed the diagnosis of Crohn's disease. Her disease had been quiescent on mesalamine, and she was otherwise healthy requiring no other daily medications. She was born in Korea but subsequently raised in Philadelphia after being adopted at age one year. She denied any tobacco, alcohol, or drug use. She had a negative human immunodeficiency virus (HIV) test at the time of her Crohn's diagnosis.

Physical examination revealed a well developed, thin woman in no significant distress. Her head and neck exam was notable for pale conjunctivae and was without oropharyngeal lesions or cervical lymphadenopathy. Cardiopulmonary exam was normal. She was diffusely tender to palpation throughout her abdomen, and assessment of organomegaly was limited by pain. Rectal examination revealed hemoccult-positive stool in the rectal vault, and no fissures or ulcers were visible on perianal exam.

Laboratory data were notable for a white blood cell count of 11 000 cells/mm^3 (normal: 4000–11 000), hemoglobin of 9.6 g/dL (normal: 13.5–17.5), and platelets of 196 000 cells/mm^3 (normal: 150 000–400 000). Serum creatinine was normal with no derangement of her electrolytes. Liver function tests demonstrated an elevated aspartate transaminase of 56 U/L (normal: 15–41) and alanine transaminase of 75 U/L (normal: 17–63), with normal alkaline phosphatase and total bilirubin levels. Albumin level was mildly depressed at 3.2 mg/dL (normal: 3.5–4.8). Erythrocyte sedimentation rate was 69 mm/hour (normal: 0–40). Initial workup for the chronic diarrhea was negative including thyroid studies, serologic testing for Celiac disease, *Clostridium difficile* stool polymerase chain reaction testing, and microbiologic stool cultures.

Colonoscopy was subsequently performed. Endoscopic findings included multiple small ulcers with surrounding erythema as well as serpiginous, deeper ulcers involving the ileum and primarily right side of the colon. It was noted that the rectum was spared with normal-appearing mucosa. Biopsies from the colon and ileum revealed acute and chronic inflammation with occasional granulomas. These findings confirmed the diagnosis of active Crohn's disease.

The severity of disease activity prompted a discussion about the use of immunomodulatory agents to achieve disease control and provide symptomatic relief for the patient. The patient was amenable to more aggressive therapy since her symptoms had been progressively worsening without any symptom abatement. The patient's gastroenterologist hoped to start the patient on infliximab, but he was troubled by the patient's elevated liver function tests. As part of the initial workup for hepatitis and in preparation for possible initiation of infliximab, the patient underwent serologic testing for HIV and hepatitis B and C. She also had a Mantoux tuberculin skin test placed for tuberculosis screening, which was read as negative at seventy-two hours. Antibody testing for HIV and hepatitis C were all negative. Screening tests for hepatitis B virus (HBV) were as follows: hepatitis B surface antigen (HBsAg) positive, hepatitis B core antibody (HBcAb) positive, and hepatitis B surface antibody (HBsAb) negative. Subsequent testing revealed that a serum

HBV DNA level was elevated at 2100 IU/mL (normal: < 20), hepatitis B e antigen was negative, and hepatitis B e antibody was positive.

DISCUSSION

The use of immunomodulatory agents has revolutionized the management of autoimmune diseases such as inflammatory bowel diseases, rheumatoid arthritis, and psoriasis [1–3]. Disease pathogenesis in these conditions has been linked to enhanced proinflammatory activity by the cytokine tumor necrosis factor (TNF)-α. Blockade of this cytokine's activity with TNF-α inhibitors has dramatically altered disease progression and improved clinical outcomes for these patients. However, the immunosuppression induced by these biologic agents carries substantial infection risk, particularly the reactivation of latent infections [4–6]. Hepatitis B virus is one such infection, where inhibition of TNF-α can lead to reactivation and potentially life-threatening hepatitis or liver failure.

Tumor necrosis factor-α is an important proinflammatory cytokine that exerts multiple effects on both the innate and adaptive immune response. Synthesized and secreted by activated macrophages and T lymphocytes, TNF-α is responsible for stimulating the release of other proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8 and granulocyte-macrophage colony-stimulating factor, up-regulating endothelial adhesion molecules, recruiting neutrophils and macrophages, as well as coordinating granuloma formation and maintenance [7, 8]. Tumor necrosis factor-α seems to have multiple functions in the eradication and control of HBV infection including down-regulation of HBV replication in hepatocytes and promotion of the apoptosis of infected hepatocytes. Reduction in TNF-α secretion is associated with diminished proliferation of HBV-specific cytotoxic T lymphocyte activity and subsequent impairment of HBV clearance [9, 10]. Thus, use of TNF-α inhibitors could be associated with the loss of immune control in chronic or occult HBV infection, leading to reactivation [11, 12].

Since the first TNF-α inhibitor, infliximab, received initial approval by the US Food and Drug Administration (FDA) in 1998, multiple drugs have been introduced, with important structural differences within the class (Table 4.14.1). Most of the available agents, including infliximab, adalimumab, certolizumab, and golimumab, are monoclonal antibodies that bind TNF-α, preventing subsequent binding of TNF-α to its receptor and activation of downstream signaling pathways. Although infliximab is a chimeric monoclonal

TABLE 4.14.1. CHARACTERISTICS OF THE DIFFERENT TNF-α INHIBITORS CURRENTLY AVAILABLE

TNF-α Inhibitor (Brand Name)	Structure	Route	Specific Features
Infliximab (Remicade)	Chimeric monoclonal antibody	IV	• Can fix complement → cytolysis • Greater immunogenicity compared with other monoclonal antibodies and etanercept
Adalimumab (Humira)	Fully human monoclonal antibody	SC	• Can fix complement → cytolysis
Golimumab (Simponi)	Fully human monoclonal antibody	SC*	• Can fix complement → cytolysis
Certolizumab (Cimzia)	Pegylated humanized monoclonal antibody (lacks Fc portion of the antibody)	SC	• Unable to fix complement • Reduced immunogenicity compared to other monoclonal antibodies
Etanercept (Enbrel)	Recombinant human protein mimic of TNF-α receptor	SC	• Able to bind and neutralize lymphotoxin (TNF-β) • Forms less stable complexes with TNF-α, compared with monoclonal antibodies • Unable to fix complement

Abbreviations: IV, intravenous; SC, subcutaneous.
*Has FDA approval for intravenous administration in rheumatoid arthritis.

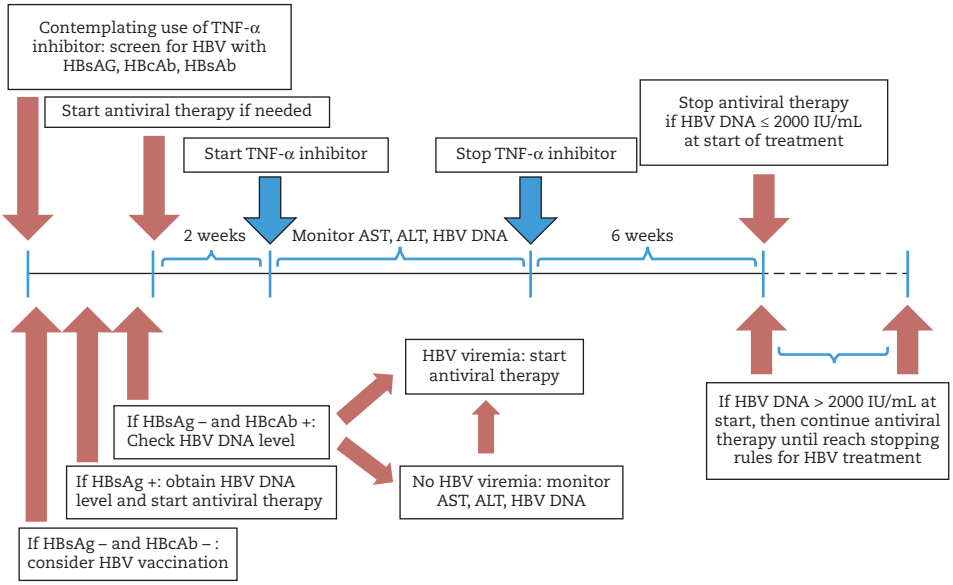

FIGURE 4.14.1: Managing the potential reactivation of hepatitis B infection in the setting of initiation of TNF-α inhibitors.

antibody derived from human and murine components, adalimumab and golimumab are fully humanized. Certolizumab differs slightly in that it is a humanized monoclonal antibody coupled to polyethylene glycol, which is thought to reduce immunogenicity and prolong the drug's half-life. In contrast, etanercept is a recombinant human protein that mimics the soluble TNF-α receptor, thereby preventing TNF-α from binding functional receptors. Such structural variation may have mechanistic implications that, along with differences in routes of administration, may portend differential infection risk profiles for these drugs [13]. Postmarketing drug studies have suggested that infliximab may carry a higher risk of HBV reactivation compared with the other drugs, possibly owing to its uniqueness as an intravenously administered and chimeric agent. However, it is also postulated that currently observed higher infection rates simply may be driven by the longer history and more widespread use of infliximab [14].

Hepatitis B virus is one of the most common chronic viral infections worldwide, with over 350 million people chronically infected [15]. Thus, with more widespread use of TNF-α inhibitors, the potential for activation of HBV infection will likely become more clinically important. Currently, providers from multiple specialties—gastroenterology, rheumatology, and dermatology—prescribe TNF-α inhibitors, but to date no consensus has been established as to how best to manage these patients [16]. The American Association for the Study of Liver Diseases (AASLD) has expanded its recommendations on antiviral prophylaxis for HBV carriers who receive immunosuppressive or cytotoxic chemotherapy to apply to patients receiving TNF-α inhibitors as well [17].

Drawing from the AASLD guidelines [17], Figure 4.14.1 depicts a simplified algorithm for the management of antiviral prophylaxis for HBV infection in the setting of therapy with a TNF-α inhibitor. Prior to the initiation of a TNF-α inhibitor, the first priority should be to determine HBV infection status by measuring HBsAg, HBsAb, and HBcAb. Interpretation of these laboratory tests will allow for identification of patients with chronic, occult, or resolved infection; each of these disease states carry a different risk for disease reactivation or flare. Negative HBsAg and HBcAb testing essentially rules out the possibility of previous or current HBV infection, and these patients should be offered HBV vaccination if not previously administered. Unfortunately, adherence to these screening guidelines is poor.

Patients who test positive for HBsAg should be started on antiviral therapy regardless of being categorized as active or inactive carriers. Among those with a negative HBsAg who test positive for HBcAb, further testing should be performed to determine the presence of HBV viremia. Those with detectable viremia should be treated with antiviral therapy, as in the case

of the HBV carriers. The risk of reactivation in patients without detectable viremia, classified typically as occult hepatitis B, is considered low enough that prophylactic therapy is not routinely recommended in the setting of TNF-α inhibitors. Instead, these patients should be closely observed with routine monitoring of liver function tests and HBV DNA levels and subsequent initiation of antiviral therapy if laboratory abnormalities arise. An important exception is patients with occult hepatitis B who will receive rituximab, a chimeric monoclonal antibody targeting B lymphocytes, because these patients should be prophylactically started on antiviral therapy. This recommendation is driven by the profound, long-lasting depletion of the B-cell population induced by rituximab, which leads to dysregulation in HBV immunity and contributes to a substantially increased risk of HBV reactivation. Loss of B cells leads to failure in HBV antigen presentation, allowing the virus to evade cytotoxic T lymphocyte control and ultimately leading to viral reactivation [18].

Prophylactic antiviral therapy generally should be started one to two weeks prior to the initiation of TNF-α inhibitors and continued for at least six months after cessation of the immunosuppressive regimen. All patients initiated on treatment should have a baseline HBV DNA level drawn and receive routine monitoring of serum liver function tests and HBV DNA levels. Patients with HBV DNA levels >2000 IU/mL should continue antiviral therapy until they reach therapeutic goals for chronic hepatitis B, which vary depending on their HBV infection status but generally consist of achieving sustained undetectable HBV DNA levels and possibly HBsAg clearance. Most studies on prophylactic antiviral therapy during courses of immunosuppression have focused on lamivudine, but alternative treatment with tenofovir or entecavir could be used. These alternatives may be preferred in patients who will be receiving a long duration of immunosuppressive therapy and thus may be at higher risk of developing resistance to lamivudine. Interferon-based therapy should be avoided.

Tumor necrosis factor-α inhibitors have become important agents in our armamentarium of drugs against autoimmune diseases. However, given the immunosuppression induced by these drugs, their safe application mandates careful, ongoing evaluation of a patient's infection risk and adoption of prophylactic strategies as applicable. The availability and ease of use of antiviral therapy for HBV infection should help prevent life-threatening complications of HBV infection from becoming a reality in the era of TNF-α inhibitors.

REFERENCES

1. Ma X, Xu S. TNF inhibitor therapy for rheumatoid arthritis. Biomed Rep. 2013;1:177.
2. Bandzar S, Gupta S, Platt MO. Crohn's disease: a review of treatment options and current research. Cell Immunol. 2013;286:45.
3. Tobin AM, Kirby B. TNF alpha inhibitors in the treatment of psoriasis and psoriatic arthritis. BioDrugs. 2005;19:47.
4. Targownik LE, Bernstein CN. Infectious and malignant complications of TNF inhibitor therapy in IBD. Am J Gastroenterol. 2013;108:1835.
5. Jain A, Singh JA. Harms of TNF inhibitors in rheumatic diseases: a focused review of the literature. Immunotherapy. 2013;5:265.
6. Desai SB, Furst DE. Problems encountered during anti-tumour necrosis factor therapy. Best Pract Res Clin Rheumatol. 2006;20:757.
7. Koo S, Marty FM, Baden LR. Infectious complications associated with immunomodulating biologic agents. Infect Dis Clin N Am. 2010;24:285.
8. Roach DR, Bean AG, Demangel C, et al. TNF regulates chemokine induction essential for cell recruitment, granuloma formation, and clearance of mycobacterial infection. J Immunol. 2002; 168:4620.
9. Calabrese LH, Zein N, Vassilopoulos D. Safety of antitumour necrosis factor (anti-TNF) therapy in patients with chronic viral infections: hepatitis C, hepatitis B, and HIV infection. Ann Rheum Dis. 2004;63:ii18.
10. Guidotti LG, Ishikawa T, Hobbs MV, et al. Intracellular inactivation of the hepatitis B virus by cytotoxic T lymphocytes. Immunity. 1996;4:25.
11. Esteve M, Saro C, Gonzalez-Huix F, et al. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. Gut. 2004;53:1363.
12. Ostuni P, Botsios C, Punzi L, et al. Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid arthritis treated with infliximab and low dose methotrexate. Ann Rheum Dis. 2003;62:686.
13. Mpofu S, Fatima F, Moots RJ. Anti-TNF-alpha therapies: they are all the same (aren't they?). Rheumatology. 2005;44:271.
14. Carroll MB, Forgione MA. Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. Clin Rheumatol. 2010;29:1021.
15. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging

prevention and control measures. J Viral Hepat. 2004;11:97.
16. Ferri C, Govoni M, Calabrese L. The A, B, Cs of viral hepatitis in the biologic era. Curr Opin Rheumatol. 2010;22:443.
17. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology. 2009;50:661.
18. Mastroianni CM, Lichtner M, Citton R, et al. Current trends in management of hepatitis B virus reactivation in the biologic therapy era. World J Gastroenterol. 2011;17:3881.

4.15

Can We Inject to Protect

CRISTINA BRICKMAN, MD

CASE PRESENTATION

A 60-year-old woman with rheumatoid arthritis presented with five days of fever and left ear pain. She had been diagnosed with rheumatoid arthritis at age 45 after developing arthralgias, morning stiffness, and fatigue. She was treated with methotrexate and hydroxychloroquine but required progressively longer courses of steroids to alleviate her symptoms, ultimately becoming dependent on 20 mg of prednisone daily after a few years. By age 55, she had developed progressive joint deformities of the metacarpal joints as well as steroid-induced diabetes mellitus. A decision was made to start therapy with infliximab, a tumor necrosis factor (TNF)-α inhibitor. A tuberculin skin test was negative, and she received pneumococcal polysaccharide and tetanus-diphtheria-acellular pertussis vaccines prior to therapy. Immunization with live herpes zoster vaccine (Zostavax, Merck) was contraindicated given her longstanding steroids and methotrexate [1]. The patient responded quickly to infliximab and was maintained on this along with methotrexate: steroids were tapered and ultimately discontinued. Although she still noted mild stiffness and occasional arthralgias, these did not significantly impact her daily activity.

At age 60, she was in her usual state of health until one week prior to admission when she noted left ear pain and swelling. Her primary care provider diagnosed otitis externa and prescribed ciprofloxacin otic drops, but symptoms did not improve. On the day prior to admission, she developed subjective fevers, dizziness, and gait instability, eventually prompting her husband to bring her to the emergency department (ED).

In the ED, she had a temperature of 39.2°C, blood pressure of 166/72 mmHg, and heart rate of 100 beats per minute. Physical exam was notable for a mild left-sided facial droop and a grossly inflamed, erythematous ear with copious grayish yellow exudate (Figure 4.15.1). Two small, clear vesicles were present along the antihelix of the ear. She was started on broad-spectrum antibiotics for possible malignant otitis media externa, but a magnetic resonance image did not show evidence of bony or deep tissue involvement. She was then noted to have several scattered, crusted erythematous papules on her left anterior neck (Figure 4.15.2). A lumbar puncture was significant for 60 white blood cells/μL (65% lymphocytes), 18 red blood cells/μL, protein 127 mg/dL, and glucose 59 mg/dL. Gram stain was negative for organisms.

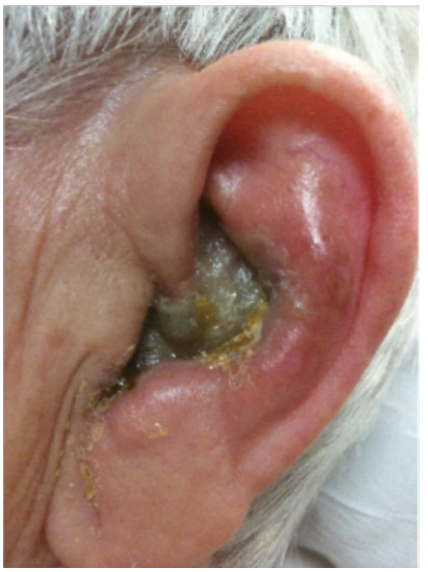

FIGURE 4.15.1: Swollen and erythematous left ear with grayish yellow exudate. Several small vesicles are visible within the antihelix of the ear.

Based on her rash, cerebrospinal fluid pleocytosis, and underlying immunocompromised status, a variety of diagnoses were considered. Although the pattern of involvement suggested herpes zoster, other potential diagnoses included herpes simplex and enteroviral infections. Her

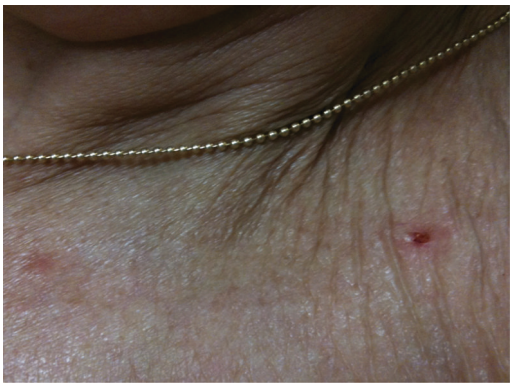

FIGURE 4.15.2: Scattered, crusted, erythematous papules along the skin of the left anterior neck.

neurologic findings might have been consistent with other diagnoses, such as cytomegalovirus, tuberculous meningitis, endemic mycoses (e.g. *Coccidioides*), and Lyme disease; however, the cutaneous manifestations were inconsistent with these diagnoses. The Infectious Diseases consultant suspected disseminated zoster and recommended high-dose acyclovir.

The patient improved clinically over the next few days with resolution of her pain and vertiginous symptoms. She reported a history of childhood varicella-zoster, prompting a diagnosis of disseminated herpes zoster with facial nerve involvement (Ramsey-Hunt syndrome) and central nervous system involvement. Polymerase chain reaction from her cerebrospinal fluid was positive for varicella-zoster virus, confirming the diagnosis. She received a fourteen-day course of acyclovir 10 mg/kg intravenously every eight hours along with seven days of vancomycin and piperacillin-tazobactam for superimposed bacterial infection of her ear, and she recovered completely.

DISCUSSION

The widespread use of immunosuppressive agents in transplant recipients and patients with autoimmune conditions has led to a steady increase in the number of people living with immunosuppression [2]. Immunosuppressive agents can be divided into three categories: glucocorticoids, nonbiologic immunomodulators, and biologic agents. Nonbiologic immunomodulators include potent anti-inflammatory agents such as the calcineurin inhibitors and mycophenolate mofetil, as well as the antimetabolites, which have less marked effects on the immune system. Antimetabolites such as methotrexate, azathioprine, and 6-mercaptopurine comprised the mainstay in treatment of rheumatologic disease and inflammatory bowel disease (IBD) until the advent of biologic agents. Due to their clear efficacy, biologics such as the TNF-α inhibitors are now front-line agents in the treatment of many rheumatic diseases and IBD despite the associated risk of serious infection [3].

Given the association between immunosuppression and infection, the Centers for Disease Control and Prevention (CDC) and the Academy for Immunization Practices recommend that persons on immunosuppressive drugs receive inactivated trivalent influenza vaccine as well as all age-appropriate polysaccharide-based vaccines (e.g. pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine, meningococcal conjugate vaccine or meningococcal polysaccharide, and *Haemophilus influenza* type b vaccine) [1]. However, the safety and/or effectiveness of this practice has not been completely established.

In addition, live vaccines such as herpes zoster vaccine (Zostavax) are currently contraindicated due to the theoretical risk of developing clinical disease from the attenuated virus [1]. This decision arises primarily from the absence of data rather than from evidence that live vaccines actually harm immunosuppressed patients. Therefore, it is also important to address whether live vaccines can be used in patients on immunosuppressive therapy.

Inactivated Vaccines in Patients Receiving Immunosuppressive Drugs

A recent review evaluated all prospective controlled trials that measured pre- and postimmunization titers of vaccines for children and adults on immunosuppressive therapy [4]. Only fifteen trials were identified, all of which measured antibody titers to the influenza vaccine and/or the pneumococcus polysaccharide vaccine.

None were powered to detect differences in the risk of infection, and none evaluated live vaccines or other inactivated vaccines such as hepatitis A, hepatitis B, TDaP, pneumococcus conjugate, or *H influenzae* type B.

The studies were notable for the heterogeneity in underlying medications and disease processes: eight included subjects with rheumatic disease, three with IBD, and four with a solid organ transplant. Two conclusions can be gleaned despite this diversity. First, vaccines were well tolerated and not associated with disease flares or graft rejection. Second, although the response to the influenza and

pneumonia polysaccharide vaccine was reduced by immunosuppressants, the majority of subjects still attained seroprotective levels. Although true efficacy data is lacking, it is reasonable to infer that patients with evidence of seroprotection may be protected against actual infection.

Whether biologics inhibit vaccine responses more than nonbiologic immunomodulators has not been clearly answered. Of the trials that addressed this question, six found that vaccine responses were more impaired by biologics compared with nonbiologic immunomodulators. However, all six were cohort studies that did not account for confounding by indication: that is, the studies did not consider whether subjects with the most severe immune dysregulation were more likely to receive biologics. Thus, patients may fail to respond to vaccines because of differences in baseline immune function and not from the direct effect of biologics. In fact, the only two available randomized trials that addressed the specific role of biologics did not find a statistically significant difference compared with nonbiologic immunomodulators, although it is unclear whether they were powered appropriately.

In summary, there is substantial evidence that inactivated vaccines are safe and immunogenic in patients on immunosuppressive medications, although the exact impact of biologic agents remains to be determined. Furthermore, given the short follow-up time of the available studies, the long-term effects of vaccination and whether immunosuppressed patients would benefit from more frequent boosting are unknown.

The Live Herpes Zoster Vaccine in Patients Receiving Immunosuppressive Drugs

With approximately 1 million people in the United States affected each year, herpes zoster is exceedingly common. Although rarely lethal, 25% of cases develop complications that result in significant morbidity, including chronic pain, scarring, vision loss, and hospitalization [5]. Patients on immunosuppressive drugs are at increased risk for herpes zoster due to impaired cellular immunity. For example, patients with rheumatic disease have a two-fold risk of herpes zoster compared with the general population, and those treated with TNF- α inhibitors have a 75% greater risk than patients on nonbiologic agents [6]. Patients on biologics are also nine times more likely to be hospitalized for herpes zoster than the general population [7].

The live herpes zoster vaccine is derived from the same strain used to develop the varicella-zoster vaccine (Varivax, Merck), but it is fourteen times more potent; a stronger dose is used to boost host cellular immunity and allow recipients to maintain viral latency. A 2005 randomized controlled trial demonstrated its efficacy in preventing both the incidence of herpes zoster and its complications in an older patient population, but subjects on immunosuppressant medications were excluded [8]. Although inactivated zoster vaccines have shown promise in clinical trials, they are not yet available [9, 10]. Hence, patients on immunosuppressive agents are both particularly vulnerable to herpes zoster and paradoxically excluded from the potential benefits of immunization.

The most compelling evidence that Zostavax can be used in patients on immunosuppressive drugs comes from a 2012 study of Medicare claims data [6]. Of 463541 subjects with rheumatic diseases or IBD, 4% received Zostavax from 2006 to 2009. The incidence of herpes zoster or varicella-zoster within the first forty-two days, an endpoint used to determine safety, was the same as in the unvaccinated cohort. No cases of zoster or varicella were observed among the 663 patients who were vaccinated while on biologic therapy. The hazards ratio for herpes zoster in vaccinated patients was 0.61 (0.52–0.71) over a median follow-up of two years. These data strongly suggest that the vaccine can be given safely and that it is effective in patients on immunosuppressive medications.

However, the work is subject to the inherent limitations of a retrospective study that was based on claims data, and it is insufficient to change practice guidelines by itself. It also does not address whether the varicella-zoster vaccine is safe for patients with severe rheumatic disease or IBD patients who require very high levels of immunosuppression, nor does it address the potential differential risk with different disease-modifying agents. It does, however, draw attention to the fact that avoiding live vaccines in patients on immunosuppressive drugs may be an outdated practice, and it highlights the need for clinical trials in this area.

In summary, there is substantial evidence to indicate that immunization with inactivated vaccines is safe and potentially effective in immunosuppressed hosts, but there is insufficient information regarding the administration of live vaccines. The recommendations for immunizations in the immunosuppressed host are modified and updated regularly on the CDC Morbidity and Mortality Weekly Report website as new

data become available [1]. Prior to starting any immunosuppressive therapy, all patients should undergo a review of their vaccination history, and the appropriate immunizations should be administered to maintain currency of their vaccine status. Annual reviews while on disease-modifying agents should also be conducted to ensure that appropriate preventive strategies are enlisted to prevent complications in this particularly vulnerable population.

REFERENCES

1. National Center for Immunization and Respiratory Diseases. General recommendations on immunization—recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2011;60:1.
2. Lobermann M, Boršo D, Hilgendorf I, et al.. Immunization in the adult immunocompromised host. Autoimmun Rev. 2012;11:212.
3. Kroesen S, Widmer AF, Tyndall A, Hasler P. Serious bacterial infections in patients with rheumatoid arthritis under anti-TNF-alpha therapy. Rheumatology (Oxford). 2003;42:617.
4. Agarwal N, Ollington K, Kaneshiro M, et al. Are immunosuppressive medications associated with decreased responses to routine immunizations? A systematic review. Vaccine. 2012;30:1413.
5. Harpaz R, Ortega-Sanchez IR, Seward JF. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2008;57:1.
6. Zhang J, Xie F, Delzell E, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA. 2012; 308:43.
7. Garcia-Doval I, Pérez-Zafrilla B, Descalzo MA, et al. Incidence and risk of hospitalisation due to shingles and chickenpox in patients with rheumatic diseases treated with TNF antagonists. Ann Rheum Dis. 2010;69:1751.
8. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005; 352:2271.
9. Mullane KM, Winston DJ, Wertheim MS, et al. Safety and immunogenicity of heat-treated zoster vaccine (ZVHT) in immunocompromised adults. J Infect Dis. 2013;208:1375.
10. Chlibek R, Bayas JM, Collins H, et al. Safety and immunogenicity of an AS01-adjuvanted varicella-zoster virus subunit candidate vaccine against herpes zoster in adults >=50 years of age. J Infect Dis. 2013;208:1953.

SECTION 5

Infections in Patients With Immunosuppression Due to Miscellaneous Conditions

GEORGE J. ALANGADEN AND PRANATHARTHI H. CHANDRASEKAR

5.1

Why Won't My "Infection" Go Away?

GEORGE J. ALANGADEN, MD

CASE PRESENTATION

A 77-year-old man with prostate cancer and myelodysplastic syndrome for two years underwent placement of an artificial urinary sphincter and suprapubic catheter for incontinence. Three weeks later, he developed severe pain at the surgical site and dehiscence of the surgical wound. Debridement of the wound and removal of the artificial urinary sphincter and suprapubic catheter were done. The patient was sent home with an urethral urinary catheter and a seven-day course of oral ciprofloxacin. Three days later, the patient was readmitted with increasing pain and worsening of wound and fevers of up to 103°F. There were no other associated systemic symptoms.

The patient was being treated for hypothyroidism, hypertension, and gastroesophageal reflux disease. His medications included synthyroid, amlodipine, omeprazole, and ciprofloxacin. The patient has a history of generalized rash to penicillin. He was a retired accountant who does not smoke nor drink alcohol.

On examination, his temperature was 101.3°F, blood pressure was 134/78 mm Hg, heart rate was 92 beats per minute, and respiratory rate was 18 breaths per minute. The patient was in mild distress. A faint ejection systolic murmur was present in the aortic area radiating to carotids. An indwelling urinary catheter was present. Linear wound was present in the suprapubic region, with surrounding erythema, induration and warmth, and minimal purulent discharge (Figure 5.1.1). The reminder of the systemic examination was normal.

The white blood cell count was 9800/μL (neutrophils 52%), hemoglobin was 8 g/dL, and platelet count was 58 000/μL. Blood and urine cultures were obtained.

Therapy was started with empiric intravenous cefepime, vancomycin, and metronidazole, and additional surgical debridement of the wound was performed. All microbiological cultures were negative. After debridement, there appeared to be further worsening and enlargement of the wound.

QUESTIONS

- What is the etiology of the patient's wound?
- What additional tests should be performed?
- What therapies should be discontinued?

DIFFERENTIAL DIAGNOSIS

In a patient with a nonhealing, rapidly progressive ulcer, one should consider a complicated skin and soft tissue infection with unusual organisms including mycobacteria or fungi, vasculitis, or noninfectious entity such as pyoderma gangrenosum.

ADDITIONAL DATA

Wound swabs showed few polymorphonuclear cells, moderate red blood cells, and rare Gram-positive bacilli. Few *Corynebacterium* spp, few *Enterobacter cloacae*, few *Enterococcus faecalis*, and rare *Candida tropicalis* were isolated on culture.

Skin biopsy of the lesion demonstrated skin and subcutaneous tissue with acute ulceration, focal necrosis, granulation tissue, and focally marked acute and chronic inflammation. There was no evidence of malignancy.

Final Diagnosis: Pyoderma gangrenosum

TREATMENT AND OUTCOME

The antibiotic therapy was discontinued after ten days and surgical debridement was stopped.

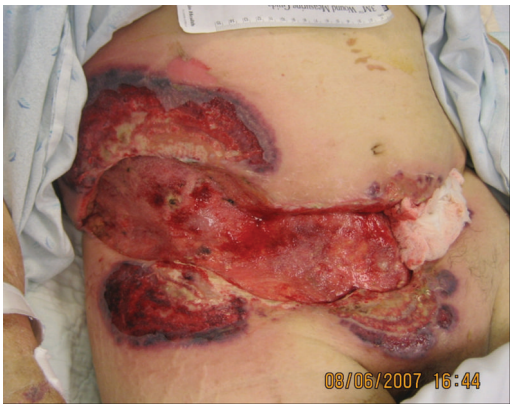

FIGURE 5.1.1: Necrolytic cutaneous ulcer with an irregular, violaceous undermined border.

The patient was initiated on oral prednisone 40 mg daily. Two weeks later, the ulcer had improved significantly (Figure 5.1.2). Prednisone was tapered off and stopped over the next four weeks.

DISCUSSION

The causes of inflammatory cutaneous ulcers are shown in Box 5.1.1.

Pyoderma gangrenosum is an inflammatory ulcerative condition first described in 1930 and was believed to be due hematogenous dissemination of bacterial infection, hence the misnomer "pyoderma". Pyoderma gangrenosum is now believed to be an inflammatory reactive disorder. It is thought to be caused by neutrophil dysfunction that occurs as a consequence of immune dysregulation, as suggested by the association of pyoderma gangrenosum with autoimmune inflammatory diseases [1, 2]. It is estimated that approximately three to ten cases of pyoderma gangrenosum occur per million persons per year, and the average age of affected patients is about 50 years with more cases occurring in women [1–5].

Approximately half of patients have an underlying systemic disorder: approximately 20% have seropositive of negative arthritis; approximately 35% have inflammatory bowel disease ([IBD] ulcerative colitis or Crohn's disease); and approximately 20% have monoclonal gammopathy, hematological disorders (myelodysplastic syndrome, leukemias) [1–5]. Pyoderma gangrenosum is also associated with the inherited pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa, also known as PAPASH syndrome [6].

Pyoderma gangrenosum commonly presents as painful, inflammatory pustule that develops into an ulcer. The margins of the lesions are boggy and bluish, undermining, peripheral zone of erythema, center fibrinoid mucopurulent exudate (Figure 5.1.1). In patients with hematological disorders, it can present as bullous lesions as was seen in our patient [5]. Pustular and vegetative forms are other variants that can occur. Pyoderma gangrenosum most often affects the legs, although lesions can occur on other cutaneous sites, genitalia, or at the site of intestinal stoma [3–5, 7]. Pathergy, the rapid extension of margins often as a consequence of trauma such as surgical debridement (as in our patient), may be present in approximately 20%–30% of patients [3, 4]. Healing of the pyoderma gangrenosum ulcerations leads to atrophic and cribriform scarring (Figure 5.1.2).

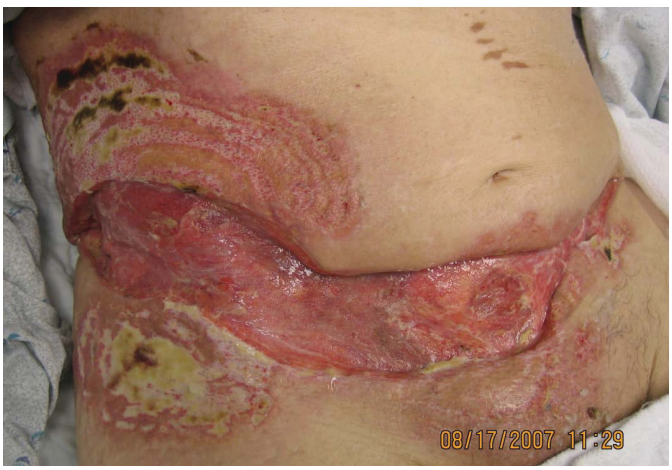

FIGURE 5.1.2: Cutaneous ulcer healing with atrophic and cribriform scarring.

BOX 5.1.1 COMMON CAUSES OF INFLAMMATORY CUTANEOUS ULCERS

CAUSES OF INFLAMMATORY CUTANEOUS ULCERS

Pyoderma gangrenosum
Infections (bacterial, mycobacterial, fungal, viral)
Vasculitis (e.g. Wegener's granulomatosis, polyarteritis nodosa)
Vascular insufficiency (venous and arterial)
Antiphospholipid antibody syndrome
Cryoglobulinemia
Necrobiosis lipoidica diabeticorum
Medication reaction e.g. warfarin-induced skin necrosis
Calciphylaxis
Cutaneous malignancy
Factitious ulceration

References [1, 2]

Although there is no established definition for the diagnosis of pyoderma gangrenosum, the following major and minor criteria have been proposed [8]. The major criteria are (1) rapid progression of a painful necrolytic cutaneous ulcer with an irregular, violaceous and undermined border and (2) other causes of cutaneous ulceration have been excluded. The minor criteria include the following: (1) history of pathergy or clinical finding of cribriform scarring; (2) presence of systemic diseases associated with pyoderma gangrenosum; (3) histopathologic findings of sterile dermal neutrophilia with or without mixed inflammation, with or without lymphocytic vasculitis; and (4) treatment response (rapid response to systemic steroids) [8]. Diagnosis requires the presence of both one major and at least two minor criteria.

EVALUATION OF PATIENT WITH SUSPECTED PYODERMA GANGRENOSUM

The evaluation of a patient with suspected pyoderma gangrenosum should include a comprehensive history and examination, to define the evolution of the lesions and to identify any underlying conditions associated with pyoderma gangrenosum [1, 2].

Additional studies are as follows:

a) Biopsy of the lesions for histopathology and microbiological studies. The histology is often nonspecific (as described above) but primarily helps exclude other potential causes.
b) Laboratory studies are primarily directed at identifying conditions associated with pyoderma gangrenosum. These include a complete blood count and differential, peripheral smear, rheumatoid factor, antinuclear antibody, antineutrophilic cytoplasmic antibody, antiphospholipid antibody, cryoglobulins, protein immunoelectrophoresis, viral hepatitis profile, studies of gastrointestinal tract, and venous and arterial function studies.

TREATMENT OF PYODERMA GANGRENOSUM

Wound care is important and should consist of gentle cleansing followed by application of a suitable antiseptic or occlusive nonadherent dressing. Surgical debridement should be limited given the propensity for pathergy [9, 10].

In general, there are no well controlled clinical trials to guide the therapy of pyoderma gangrenosum. Commonly used therapies are summarized in Table 5.1.1.

The initial therapy should be directed at any associated underlying condition [9, 10]. The tumor necrosis factor (TNF)-α inibitors infliximab, adalimumab, and etarnacept may be particularly effective in IBD-associated pyoderma gangrenosum [9–13]. In patients with poor response to therapy of the underlying disease or if no associated condition is identified, then systemic or topical therapy of pyoderma gangrenosum is necessary. For small stable limited lesions, topical or intralesional steroids or topical tacrolimus have been used with success. Systemic therapy is indicated for large, multiple, or progressive lesions. The agents used most commonly are systemic corticosteroids e.g. 0.5–1 mg/kg per day of methylprednisolone. Cyclosporine in a dose of 5 mg/kg per day has also been used as first-line therapy with success [9, 10]. Combination therapy has been used in refractory cases.

Response to corticosteroid therapy is often rapid, as was seen in our patient. Many patients need maintenance therapy for the underlying associated disease.

TABLE 5.1.1. COMMON AGENTS USED FOR THE TREATMENT OF PYODERMA GANGRENOSUM

Disease Severity	Agents	Comments
Limited disease	Topical corticosteroids	First-line
	Topical tacrolimus	Alternative
Extensive and severe disease	Systemic corticosteroids	First-line
	Cyclosporine	First-line steroid sparing
	Infliximab	Alternative,
	Adalimumab	first-line if underlying inflammatory disease
	Etarnecept	
	Mycophenolate, azathioprine	Alternative
	Dapsone	

References [9–13]

KEY POINTS

- Pyoderma gangrenosum should be suspected if painful progressive ulcers occur in patients with IBD, inflammatory arthritis, or hematological malignancies.
- Pathergy is an important clue to the diagnosis.
- It is important to exclude other causes of inflammatory ulcers before the diagnosis of pyoderma gangrenosum is established.
- Investigations should be directed to identify any underlying conditions associated with pyoderma gangrenosum.
- Initial treatment should be directed at any underlying inflammatory disease.
- Topical steroids or tacrolimus can be used in limited cases. Systemic corticosteroids, cyclosporine, or TNF inhibitors may be necessary to treat more extensive disease.

REFERENCES

1. Ruocco E, Sangiuliano S, Gravina AG, et al. Pyoderma gangrenosum: an updated review. J Eur Acad Dermatol Venereol. 2009;23:1008.
2. Ahronowitz I, Harp J, Shinkai K. Etiology and management of pyoderma gangrenosum: a comprehensive review. Am J Clin Dermatol. 2012;13:191.
3. Binus AM, Qureshi AA, Li VW, Winterfield LS. Pyoderma gangrenosum: a retrospective review of patient characteristics, comorbidities and therapy in 103 patients. Br J Dermatol. 2011;165:1244.
4. Saracino A, Kelly R, Liew D, Chong A. Pyoderma gangrenosum requiring inpatient management: a report of 26 cases with follow up. Australas J Dermatol. 2011;52:218.
5. Bennett ML, Jackson JM, Jorizzo JL, et al. Pyoderma gangrenosum. A comparison of typical and atypical forms with an emphasis on time to remission. Case review of 86 patients from 2 institutions. Medicine (Baltimore). 2000;79:37.
6. Marzano AV, Trevisan V, Gattorno M, et al. Pyogenic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PAPASH): a new autoinflammatory syndrome associated with a novel mutation of the PSTPIP1 gene. JAMA Dermatol. 2013;149:762.
7. Sheldon DG, Sawchuk LL, Kozarek RA, Thirlby RC. Twenty cases of peristomal pyoderma gangrenosum: diagnostic implications and management. Arch Surg. 2000;135:564.
8. Su WP, Davis MD, Weenig RH, et al. Pyoderma gangrenosum: clinicopathologic correlation and proposed diagnostic criteria. Int J Dermatol. 2004;43:790.
9. Miller J, Yentzer BA, Clark A, et al. Pyoderma gangrenosum: a review and update on new therapies. J Am Acad Dermatol. 2010;62:646.
10. Reichrath J, Bens G, Bonowitz A, Tilgen W. Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients. J Am Acad Dermatol. 2005;53:273.
11. Brooklyn TN, Dunnill MG, Shetty A, et al. Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo controlled trial. Gut. 2006;55:505.
12. Li J, Kelly R. Treatment of pyoderma gangrenosum with mycophenolate mofetil as a steroid-sparing agent. J Am Acad Dermatol. 2013;69:565.
13. Argüelles-Arias F, Castro-Laria L, Lobatón T, et al. Characteristics and treatment of pyoderma gangrenosum in inflammatory bowel disease. Dig Dis Sci. 2013;58:2949.

5.2

Why Do I Have a Groin Lump?

PRISCILLA RUPALI, MD, DTM&H

CASE PRESENTATION

A 43-year-old man underwent a pancreas transplant in 2007 and had been on stable immunosuppression with mycophenolate mofetil 720 mg BID, tacrolimus 3 mg BID, and prednisolone 5 mg once daily. He presented with a one-week history of fever, chills, weight loss, and a painful red swelling in his left groin. He did not recall any trauma, scratches, or abrasions. He was a type 1 diabetic with numerous vascular complications. He had a myocardial infarction in 2008 and recurrent osteomyelitis of his feet resulting in the loss of all toes of both feet. He was divorced for ten years and has not had sexual contact since then. There was no history of incarceration or intravenous drug use. He was tested for human immunodeficiency virus (HIV). He did not have pets but did report that his neighbor had a cat. He did not remember being scratched by the cat or contact with any other animals. He was a funeral home director.

The patient was admitted to an outside hospital for evaluation of fever and left inguinal lymphadenopathy. Blood cultures were negative; however, therapy was empirically started with intravenous vancomycin and cefepime. Fine-needle aspiration cytology of the left inguinal lymph node was done, and it revealed pleomorphic lymphocytes, scattered neutrophils, and monocytes. Because suspicion for malignancy was high, a core biopsy of the lymph node was done, which demonstrated areas of fibrosis and acute necrotizing inflammation. Stains for bacterial and fungal organisms were negative. He was referred to our institution for further evaluation.

On examination, the patient was a thin frail individual with a temperature of 36.9°C, blood pressure of 141/81 mm mercury, heart rate of 80 beats per minute, and respiratory rate of 18 breaths per minute. There was a healed scabbed over lesion in the left leg with no surrounding erythema or tenderness (Figure 5.2.1a). There was a mildly erythematous, left inguinal indurated mass that was tender to palpation, with the biopsy site covered by adhesive tape (Figure 5.2.1b). There was no discharge. The rest of the examination was normal.

The white blood cell count was 8400/μL (neutrophils 54%), hemoglobin was 9.1 g/dL, platelet count was 149 000/μL, and serum creatinine was 0.78 mg/dL. Blood and urine cultures were obtained. The patient had been treated with intravenous cefepime and vancomycin without clinical response. Blood and urine cultures were negative.

QUESTIONS

- What is the differential diagnosis for this clinical presentation?
- What additional tests should be performed?
- What therapy should be started?

DIFFERENTIAL DIAGNOSIS

The differential diagnoses considered are lymphogranuloma venereum and chancroid among the sexually transmitted infections. Cat-scratch disease (CSD) would be considered in case

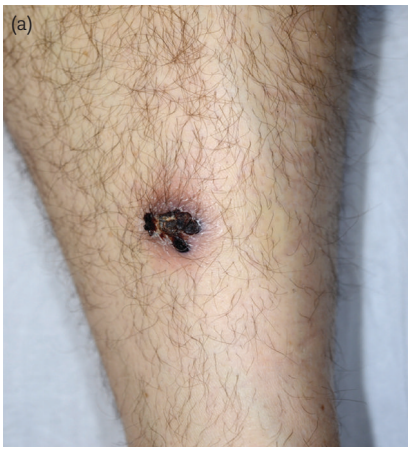

FIGURE 5.2.1a: Skin lesion left leg.

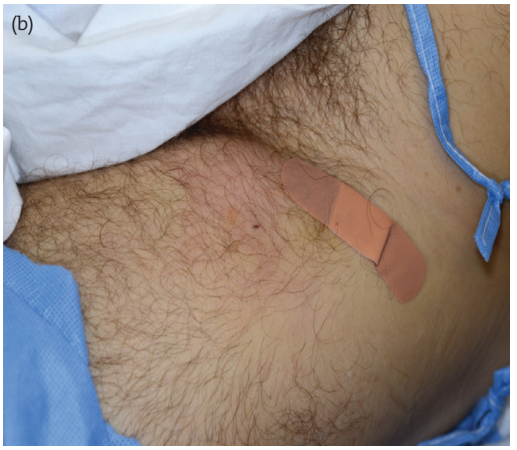

FIGURE 5.2.1b: Enlarged lymphnodes left inguinal region.

of exposure to a cat bite or a cat scratch. Given the history of solid organ transplantation on long-term immunosuppression, tuberculosis and posttransplant lymphoproliferative disorder would also be considered possibilities.

ADDITIONAL DATA

A computed tomography scan of the abdomen and pelvis revealed enlarged lymph nodes localized to the left pelvic and inguinal regions.

Human immunodeficiency virus and syphilis serologies were negative. *Aspergillus* galactomannan, β-D-glucan assay, and cryptococcal and histoplasma antigen tests were negative. Skin biopsy of the lesion on the left leg did not demonstrate any inflammation, and bacterial, fungal, and mycobacterial stains including the Warthin Starry stain were negative. A left inguinal excisional biopsy demonstrated lymphoid proliferation, necrosis, granulation tissue, and Epstein-Barr virus-positive staining of the cells. Lymph node biopsy cultures sent for bacterial, mycobacterial, and fungal cultures were negative. Serum *Bartonella henselae* immunoglobulin (Ig)G increased from 1:256 to 1:1024 over one week, and the *B henselae* IgM increased from indeterminate to 1:256. Polymerase chain reaction (PCR) testing detected *B henselae* DNA in the lymph node tissue.

TREATMENT AND OUTCOME

The patient was diagnosed to have CSD caused by *B henselae*. His therapy consisted of oral azithromycin for three weeks. The lymph nodes suppurated requiring surgical incision and drainage. Two weeks later, the inguinal adenopathy improved significantly (Figure 5.2.3).

DISCUSSION

It is estimated that approximately 60% of all US households had at least one pet [1]. Pets serve as valuable adjuncts to medical treatment in the treatment of chronic medical conditions such as high blood pressure and hyperlipidemia while improving feelings of loneliness and increasing the chances of outdoor activities, exercise, and social interaction [2]. Even in transplant recipients, having pets improves the quality of life and psychological well being [3].

However, having pets is not without its problems and can present zoonotic risks, especially for immunocompromised hosts [4, 5]. The most common route of infection related to pet contact is through bites or scratches, especially in children. Multiple outbreaks of enteric disease associated with animal exposure have also been noted in public settings such as fairs, farms, and petting zoos. Transmission related to pets can occur due to the following [4, 5]:

- Bites or infectious saliva or other body fluids contaminating skin abrasions or mucus membranes

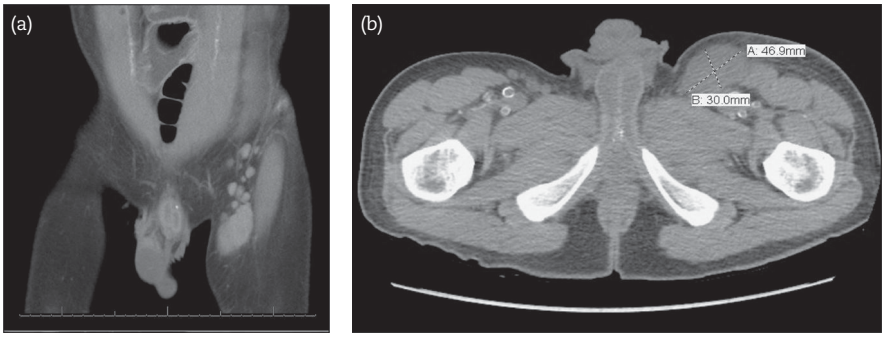

FIGURE 5.2.2: Computerized tomography scan of abdomen and pelvis demonstrating enlarged pelvic and inguinal lymphnodes.

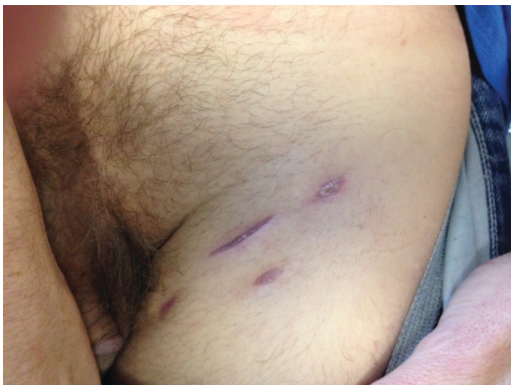

FIGURE 5.2.3: Resolution of enlarged lymphnodes in the left inguinal region.

- Insect bites due to vectors carried by pets
- Aerosols from body fluids of pets
- Contamination of objects put into mouth by animals

Common diseases transmitted from animals are shown in Table 5.2.1.

CAT-SCRATCH DISEASE

Cat-scratch disease is caused by *B henselae*. Cats serve as the natural reservoir for this organism, which causes intraerythrocytic bacteremia that can persist for up to one year in cats [6]. After inoculation of *B henselae*, humans may develop localized disease with lymphadenopathy, but a few patients can develop disseminated disease with neuroretinitis and visceral organ involvement.

Clinical manifestations start with a cutaneous inoculation lesion that evolves through a vesicular, erythematous papular phase to enlargement and suppuration of regional lymphadenopathy approximately two weeks later. Visceral organ involvement occurs with fever, abdominal pain, weight loss, and hepatosplenomegaly and can present with a fever of unknown origin, especially in children. Ocular manifestations include neuroretinitis, papillitis, and optic neuritis and

TABLE 5.2.1. COMMONLY TRANSMITTED INFECTIONS FROM PETS

Animals	Pathogens	Method of Transmission	Clinical Presentation in Humans
Cats	*Bartonella henselae*	Cat bite, scratch or contamination of abrasion by infectious saliva	Cat scratch disease
	Pasteurella multocida		Visceral larva migrans
	Toxocara cati	Ingestion of eggs from contaminated hands, soil, fomites	
	Toxoplasma gondii	Ingestion of cysts from raw or undercooked meat or cat faeces	Toxoplasmosis
Dogs	*Rhabdovirus*	Dog bite/scratch	Rabies
	Capnocytophaga canimorsus		Fulminant sepsis or meningitis
	Bordetella bronchoseptica	Aerosols from infected cats or dogs	Pneumonia or respiratory illness
Horses	*Salmonella*	Fecal-oral transmission	Gastroenteritis
	Campylobacter		
	Cryptosporidium		
	Rhodococcus equi	Aerosol transmission	Suppurative pneumonia
Birds	*Chlamydophila psittaci*	Exposure to bird feces and nasal discharge	Psittacosis
	Cryptococcus neoformans		Cryptococcal pneumonia or meningitis
	Histoplasma capsulatum		Pulmonary histoplasmosis
Reptiles	*Salmonella* spp	Fecal-oral transmission	Salmonellosis
	Edwardsiella tarda		Gastroenteritis
Monkeys	Herpes B virus	Bites or contact with feces or secretions	Fatal encephalomyelitis
	Rabies virus		

Adapted from: Elliot DL, Tolle SW, Goldberg L, Miller JB. Pet associated illness. *N Engl J Med*. 1985;313:985; Kotton CN. Zoonoses in solid-organ and hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2007;44:857; Spach DH, Kaplan SL. Microbiology, epidemiology, clinical manifestations and diagnosis of cat scratch disease. Available at: http://www.uptodate.com/contents/microbiology.

usually present with fever, malaise, and unilateral blurred vision. Neurological manifestations of CSD include encephalopathy, transverse myelitis, radiculitis, and cerebellar ataxia. In rare cases, myalgia, arthralgia, and arthritis can occur.

The diagnosis of CSD is based on positive serology (enzyme immunoassay or indirect immunofluorescence assay) with a titer >1:64, sterile pus/tissue positive for *B henselae* PCR, or a biopsy consistent with CSD/positive with Warthin-Starry silver stain. Histopathological features in CSD include lymphoid hyperplasia and stellate granulomas. The centers of these are acellular and necrotic, and histiocytes and lymphocytes surround these and lead to the formation of microabscesses. Warthin-Starry stain may demonstrate delicate pleomorphic *B henselae* bacilli in clumps, chains, or filaments within areas of necrosis of involved lymph nodes. The diagnosis of CSD in our patient was based on the history of pet exposure, compatible clinical syndrome, and positive serology and PCR.

Treatment of CSD is based on the presenting clinical syndrome. Studies of lymphadenitis in immunocompetent adults revealed that treatment with azithromycin decreased lymph node size significantly compared with those who did not receive the same treatment [7]. Hepatosplenic disease with prolonged fever is often treated with rifampicin combined with gentamicin or trimethoprim-sulfamethoxazole or even azithromycin [8]. Neuroretinitis is generally treated with doxycycline and rifampicin for four to six weeks [9].

Cat-scratch disease can also occur in immunocompromised patients (HIV, solid organ transplantation) and can produce bacillary angiomatosis, peliosis hepatis, and splenitis in these individuals. These have been most commonly described in HIV-infected recipients. In a case series of 29 *B henselae* infections in solid organ transplant recipients [10], twenty-one had disseminated disease, whereas eight had localized CSD. Two of these patients died due to endocarditis. All of them were treated with azithromycin, doxycycline, levofloxacin, aminoglycosides, or a combination of any of these for a duration ranging from two weeks to twelve months.

KEY POINTS

- Exposure to animals can result in transmission of potential pathogens that can cause disease in transplant recipients.
- CSD should be suspected in patients with localized tender lymphadenopathy.
- Special stains, serial serological testing, and PCR can help confirm the diagnosis of CSD.
- Transplant patients should be counseled in safe-living strategies related to exposure to animals [11].

REFERENCES

1. U.S. Pet Ownership & Demographics Sourcebook 2012. Available at: https://www.avma. org/kb/ resources/ statistics/pages/ market-research-statistics-us-pet-ownership-demographics-sourcebook.aspx?utm_ source=avma-at-work&utm_medium=web&utm_campaign=pet-demo. Accessed 15 February 2015.
2. Anderson WP, Reid CM, Jennings GL. Pet ownership and risk factors for cardiovascular disease. Med J Australia. 1992;157:298.
3. Irani S, Mahler C, Goetzmann L, et al. Lung transplant recipients holding companion animals: impact on physical health and quality of life. Am J Transplant. 2006;6:404.
4. Elliot DL, Tolle SW, Goldberg L, Miller JB. Pet associated illness. N Engl J Med. 1985;313:985.
5. Kotton CN. Zoonoses in solid-organ and hematopoietic stem cell transplant recipients. Clin Infect Dis. 2007;44:857.
6. Spach DH, Kaplan SL. Microbiology, epidemiology, clinical manifestations and diagnosis of cat scratch disease. Available at: http://www.uptodate.com/ contents/microbiology-epidemiology-clinical manifestations and-diagnosis-of-cat-scratch-disease. Accessed February 20, 2015.
7. Bass JW, Freitas BC, Freitas AD, et al. Prospective randomized double blind placebo-controlled evaluation of Azithromycin for treatment of CSD. Pediatr Infect Dis J. 1998;17:447.
8. Arisoy ES, Correa AG, Wagner ML, Kaplan SL. Hepatosplenic cat-scratch disease in children: selected clinical features and treatment. Clin Infect Dis. 1999;28:778.
9. Reed JB, Scales DK, Wong MT, et al. *Bartonella henselae* neuroretinitis in cat scratch disease. Diagnosis, management and sequelae. Opthalmology. 1998; 105:459.
10. Psarros G, Riddell J 4th, Gandhi T, et al. *Bartonella henselae* infections in solid organ transplant recipients: report of 5 cases and review of literature. Medicine. 2012;91:111.
11. Avery RK, Michaels MG, AST Infectious Diseases Community of Practice. Strategies for safe living after solid organ transplantation. Am J Transplant. 2013;4:304.

5.3

Driveline Infection, Pocket Infection, or Endocarditis?

GEORGE J. ALANGADEN, MD

CASE PRESENTATION

A 58-year-old man with refractory idiopathic nonischemic cardiomyopathy underwent implantation of a left ventricular assist device (LVAD) as a bridge to cardiac transplantation. Three months after the LVAD implantation, the patient presented with a two-day history of fever, chills, and abdominal pain. There were no other associated systemic symptoms.

The patient was being treated for hypertension, hyperlipidemia, gastroesophageal reflux disease, and atrial fibrillation. His medications included carvedilol, lisinopril, aldactone, amiodarone, warfarin, and omeprazole. He was a retired autoworker who did not smoke or drink alcohol.

On examination, his temperature was 38.4°C, the blood pressure and heart rate could not be recorded due to the LVAD, and the respiratory rate was 18 breaths per minute. The patient appeared well. Tenderness was present over the epigastrium. The exit site of the driveline of the LVAD had no erythema or discharge. The hum of the LVAD was heard on auscultation. The reminder of the systemic examination was normal.

The white blood cell count was 12 000/μL (neutrophils 82%), hemoglobin was 12 g/dL, and platelet count was 152 000/μL. Blood and urine cultures were obtained. A chest radiograph showed a dilated heart and the LVAD.

QUESTIONS

- What is the etiology of his symptoms?
- What additional tests should be performed?
- What empiric antimicrobial therapy should be initiated?

DIFFERENTIAL DIAGNOSIS

In a patient with LVAD and fever, clinicians should consider the possibility of driveline infection, LVAD-pocket infection, and LVAD endocarditis. The presence of abdominal pain and tenderness suggests the possibility of a LVAD-pocket infection.

ADDITIONAL DATA

Therapy was initiated with empiric antibiotics including intravenous (IV) vancomycin and cefepime. Methicillin-susceptible *Staphylococcus aureus* was isolated from the blood cultures. A computerized tomography (CT) scan of the abdomen demonstrated a localized fluid collection beneath the anterior abdominal wall (Figure 5.3.1). An ultrasound-guided needle aspiration of the fluid collection obtained 5 mL serosanguineous fluid. Methicillin-susceptible *S aureus* was isolated from culture of the fluid.

Final Diagnosis: Left ventricular assist device infection and bacteremia due to methicillin-susceptible *Staphylococcus aureus*

TREATMENT AND OUTCOME

Cefepime and vancomycin were discontinued and therapy was switched to IV nafcillin (2 grams q 4 hours) and oral rifampin (600 mg daily). The bacteremia resolved on day five of antibiotic therapy. The patient completed six weeks of therapy with these antibiotics. He was then placed on suppressive therapy with oral trimethoprim-sulfamethoxazole (160 mg-800 mg twice daily) until cardiac transplantation.

DISCUSSION

Left ventricular assist devices are an increasingly used effective therapeutic option that improves both functional status and survival in patients with end-stage heart failure. Although initially used as a bridge to cardiac transplantation, LVADs are now being considered as a permanent treatment option or destination therapy for patients with heart failure refractory to medical therapy.

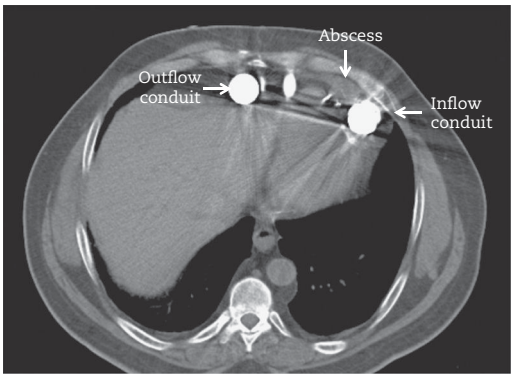

FIGURE 5.3.1: CT scan demonstrating LVAD infection with abscess formation.

Newer continuous-flow LVADs are now being used instead of the old pulsatile LVADs. The components of an implantable LVAD are shown in Figure 5.3.2. The inflow conduit connected to the left ventricle directs the blood through the implanted pump that directs the blood through an outflow conduit to the aorta. The LVAD is connected to an external controller and power source through the tunneled driveline that exits through the anterior abdominal wall.

Infections complicating LVADs can occur in 18%–60% of patients, the wide range being the result of varying definitions of LVAD infection used in studies [1–4]. The newer continuous-flow LVADs are less likely to be complicated by infection compared with the older pulsatile-flow LVADs [5, 6]. The 2013 report of the Interagency Registry for Mechanical Assisted Circulatory Support on continuous-flow LVAD noted an early (<3 months after implantation) infection rate of 2.09 per 100 patient months and a late (>3 months) infection rate of 2.94 per 100 patient months [6]. Left ventricular assist device infections are generally subdivided into (1) driveline infection, (2) pump-pocket infections, and (3) LVAD-associated pump/cannula (LVAD infective endocarditis), with frequent overlap among these infections [7]. Overall driveline infections are the most common (3.43 per 100 patient months), pocket infections (0.75 per 100 patient months), pump infections (0.10 per 100 patient months), and cannula infections (0.05 per 100 patient months) [6]. The predominant pathogens isolated from LVAD infections are the Gram-positive bacteria: *S aureus* (20%–44%), coagulase-negative staphylococci (7%–40%), *Enterococcus* spp (5%–30%), *Corynebacterium* spp (2%–20%), and *Propionibacterium* [1–2, 5, 8–10]. Gram-negative infections occur as well and are caused by *Pseudomonas* spp (5%–28%) and other enteric Gram-negative bacteria (0%–30%), whereas *Candida* spp (0%–10%) has been occasionally reported. The relative distribution of these pathogens may vary depending on the site of the LVAD infection.

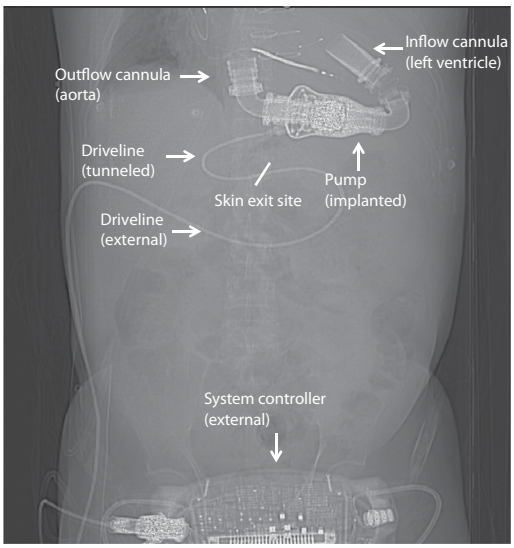

FIGURE 5.3.2: Graphic shows the LVAD.

Predisposing risk factors for LVAD infections include both host factors and device-related factors. Older age, diabetes, high body mass index, and associated metabolic syndrome, renal failure, malnutrition, lymphopenia, and T cell-related defects may contribute to infections [8, 10, 11]. The smaller sized pump and driveline line of the newer continuous-flow LVADs are less likely to be complicated by infection compared with the older pulsatile-flow LVADs.

The clinical features of VAD-specific infections are summarized in Table 5.3.1. In addition, in patients with LVADs, bloodstream infection with no focus of infection is presumed to be LVAD-related. Similarly infective endocarditis or mediastinitis in a patient with LVAD should be considered to be LVAD-related [7].

The workup for LVAD infections are summarized in Table 5.3.1. Specimens for microbiological studies should be obtained before initiation of empiric antibiotic therapy. Imaging studies should be done to evaluate the extent of infection and to identify any deep-seated abscesses. Ultrasound or CT scans are commonly used, but metallic artifacts caused by the LVAD can compromise study quality. Leukocyte single photon-emission CT scan (SPECT) has been shown to be an accurate imaging

TABLE 5.3.1. CLINICAL FEATURES AND MANAGEMENT OF VENTRICULAR ASSIST DEVICE INFECTIONS

VAD-Specific Infection	Features	Investigations	Treatment
Driveline infection	• Erythema • Warmth • Tenderness at exit site or over tunnel • Purulent discharge • Fever	• Complete blood count and differential • ESR and C-reactive protein • Blood culture × 3 sets • Aspirate of purulent discharge for Gram stains, fungal stains, and cultures • TTE, if negative obtain TEE • Chest radiograph • If pocket infection or abscess suspected obtain US, CT, leukocyte SPECT scan	• Empiric IV antibiotic therapy to treat Gram-positive and Gram-negative bacteria e.g. vancomycin and cefepime • Modify based on culture and susceptibility results • Duration 2–4 weeks, 4–6 weeks if BSI • Surgical debridement may be needed for tunnel and deep infection • Need for chronic suppressive therapy individualized decision based on recurrent infection, or if destination therapy
Pocket infection	• Above • Radiographic evidence of abscess • Microbiological evidence of infection on fluid aspirate	• Above tests • US, CT scan of thorax and abdomen • Leukocyte SPECT scan	• Above • Surgical debridement • Surgical revision and pump replacement may be needed • Chronic suppressive therapy until VAD exchange or transplantation
Pump/cannula infection (VAD endocarditis)	• Above • Multiple positive blood cultures and no other foci of infection • TTE or TEE demonstrating vegetation noted on implanted material, abscess, or dehiscence of outflow cannula • Embolic phenomena of infective endocarditis	• Above tests • TEE	• Above • 6 weeks or longer IV therapy • Explantation of VAD or transplantation • Chronic suppressive therapy until VAD exchange or transplantation

Abbreviations: BSI, bloodstream infection; ESR, erythrocyte sedimentation rate; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; US, ultrasound.
References: 1–2, 7.

modality that may be superior to CT scan [12]. Echocardiography should be done to detect if pump/cannula infection (LVAD-endocarditis) is suspected, although its utility is limited in this setting.

The management of LVAD infections is summarized in Table 5.3.1. There are no randomized controlled studies that have examined the optimal regimens and duration of antibiotic therapy for LVAD infections. Initial empiric IV antibiotic therapy should be broad-spectrum to cover staphylococci including methicillin-resistant *S aureus* (MRSA) and Gram-negative infections including *Pseudomonas* spp [1–3]. Subsequent antibiotic therapy should be pathogen-directed and guided by the microbiology results. In addition to systemic antibiotics, incision and drainage of driveline site infections and replacement of the driveline may be needed in refractory complicated infections. Likewise, pump-pocket infection may require surgical drainage of the pocket infections. In LVAD-associated endocarditis or refractory pump-infection, explantation

of the device and all hardware may be required [13]. The duration of initial antibiotic therapy for uncomplicated driveline infections is two to four weeks with longer durations for infections associated with bloodstream infections [1–2]. Most other LVAD infections are treated initially for four to six weeks. Because it is difficult to eradicate infection without the removal of the pump and drivelines, chronic suppressive oral antibiotic therapy is often used until cardiac transplantation. However, given that LVADs are used as destination therapy, chronic suppressive therapy is often used in such patients if the hardware cannot be replaced. Despite chronic suppressive therapy, breakthrough infections can occur.

Antimicrobial prophylaxis is used perioperatively during LVAD implantation. The optimal antimicrobial regimens and duration are unknown. Regimens have included coverage for MRSA, Gram-negative infections, and *Candida* [14]. In general, prophylaxis at a minimum should cover staphylococci; cefazolin is reasonable, with vancomycin as an alternative if MRSA coverage is needed [1]. The drug should be administered within one hour of incision and for not more than forty-eight hours postoperatively. Because driveline infections are the most common LVAD infection, various strategies to decrease driveline infections have been used. These include longer tunneling of drivelines and secure anchoring of the driveline to avoid traction-related trauma at the exit site. Meticulous care of the exit site of the driveline is recommended. This includes cleaning of the site using chlorhexidine and the use of silver-coated dressings [1–2]. Routine antibiotic prophylaxis during dental procedures is not addressed in prevention of endocarditis guidelines; however, it needs to be considered for patients with LVAD [15].

Patients with LVAD-associated infection and LVAD-associated endocarditis have lower survival rates. However, LVAD infection is not a contraindication to transplantation and does not significantly affect survival after transplantation [11–12, 16].

KEY POINTS

- Infection is an important cause of morbidity in patients with LVADs.
- Infection of the LVAD should be considered in the presence of fever and bloodstream infection.
- Investigation should include blood cultures and imaging to identify deep-seated infection and LVAD endocarditis.
- Empiric therapy should be broad-spectrum to cover both Gram-positive and Gram-negative pathogens.
- Chronic suppressive therapy until transplantation may be required for complicated driveline, pocket, and pump/cannula infections if hardware cannot be removed.
- Perioperative antibiotic prophylaxis and meticulous care of the driveline exit site is important to prevent LVAD infections.

REFERENCES

1. Koval CE, Rakita R, AST Infectious Diseases Community of Practice. Ventricular assist device related infections and solid organ transplantation. Am J Transplant. 2013;13:348.
2. Nienaber JJ, Kusne S, Riaz T, et al. Clinical manifestations and management of left ventricular assist device-associated infections. Clin Infect Dis. 2013;57:1438.
3. Califano S, Pagani FD, Malani PN. Left ventricular assist device-associated infections. Infect Dis Clin North Am. 2012;26:77.
4. Gordon RJ, Weinberg AD, Pagani FD, et al. Prospective, multicenter study of ventricular assist device infections. Circulation. 2013;127:691.
5. Topkara VK, Kondareddy S, Malik F, et al. Infectious complications in patients with left ventricular assist device: etiology and outcomes in the continuous-flow era. Ann Thorac Surg. 2010;90:1270.
6. University of Alabama at Birmingham, Interagency Registry of Mechanically Assisted Circulatory Support. INTERMACS Summaries. https://www.uab.edu/medicine/intermacs/statistical-summaries. Accessed 7 April 2014.
7. Hannan MM, Husain S, Mattner F, et al. Working formulation for the standardization of definitions of infections in patients using ventricular assist devices. J Heart Lung Transplant. 2011;30:375.
8. Schaffer JM, Allen JG, Weiss ES, et al. Infectious complications after pulsatile-flow and continuous-flow left ventricular assist device implantation. J Heart Lung Transplant. 2011;30:164.
9. Bomholt T, Moser C, Sander K, et al. Driveline infections in patients supported with a HeartMate II: incidence, aetiology and outcome. Scand Cardiovasc J. 2011;45:273.
10. Monkowski DH, Axelrod P, Fekete T, et al. Infections associated with ventricular assist devices: epidemiology and effect on prognosis after transplantation. Transpl Infect Dis. 2007;9:114.
11. Simon D, Fischer S, Grossman A, et al. Left ventricular assist device-related infection: treatment and outcome. Clin Infect Dis. 2005;40:1108.

12. Litzler PY, Manrique A, Etienne M, et al. Leukocyte SPECT/CT for detecting infection of left-ventricular-assist devices: preliminary results. J Nucl Med. 2010;51:1044.
13. Levy DT, Guo Y, Simkins J, et al. Left ventricular assist device exchange for persistent infection: a case series and review of the literature. Transpl Infect Dis. 2014;16:453r.
14. Acharya MN, Som R, Tsui S. What is the optimum antibiotic prophylaxis in patients undergoing implantation of a left ventricular assist device? Interact Cardiovasc Thorac Surg. 2012;14:209.
15. Findler M, Findler M, Rudis E. Dental treatment of a patient with an implanted left ventricular assist device: expanding the frontiers. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;111:e1.
16. Schulman AR, Martens TP, Russo MJ, et al. Effect of left ventricular assist device infection on post-transplant outcomes. J Heart Lung Transplant. 2009;28:237.

5.4

Delirium During Treatment for Pneumonia

MURAT GONULALAN, MD

CASE PRESENTATION

A 65-year-old woman with hypertension, and end-stage renal disease was diagnosed with lung cancer. She underwent lung resection and had completed adjuvant chemoradiation approximately four weeks ago. The patient was maintained on hemodialysis three times a week. During a dialysis session, she was noted to have shortness of breath. The dialysis was interrupted and the patient was transferred to the hospital for evaluation.

On presentation, her temperature was 98.2°F, blood pressure was 131/82 mmHg, heart rate was 115 beats per minute, respiratory rate was 20 breaths per minute, and O_2 saturation was 96% on room air. Lung examination revealed basilar crackles. The hemodialysis tunneled catheter was functioning well and the exit site was clean; the rest of the examination was unremarkable.

The patient's white blood cell count was 12 600/μL (with neutrophils 62%), hemoglobin was 8.5 g/dL, and platelet count was 154 000/μL. Serum blood urea nitrogen was 50 mg/dL, and creatinine was 7.26 mg/dL. Chest radiograph demonstrated evidence of lung resection and atelectasis in the lung bases.

The patient was admitted, and treatment was initiated for possible healthcare-associated pneumonia with intravenous (IV) vancomycin 500 mg 1 dose (to be redosed after dialysis), cefepime 1 gram once daily, and azithromycin 500 mg once daily. On the day after admission, the patient did not complete the hemodialysis session due to tachypnea. On third day of hospital stay, the patient was noted to be confused and delirious. Neurological examination revealed pupils equal and reactive to light, symmetric facial grimaces to supraorbital pain, movements of all extremities to painful stimuli, symmetric deep tendon reflexes, and down-going plantar reflexes. There was no photophobia or nuchal rigidity noted, and the rest of physical examination was unremarkable.

QUESTIONS

- What are the causes of acute encephalopathy in this patient?
- What diagnostic tests should be done?
- Which medication should be discontinued?

DIFFERENTIAL DIAGNOSIS

The acute encephalopathy in this patient could be due to multiple etiologies. These include azotemia, anoxia, drug-related toxicity, meningitis or encephalitis, cerebrovascular accident, and seizure disorder.

ADDITIONAL DATA

The rest of the biochemical panel was within normal limits. Computerized tomography of the brain did not reveal any abnormalities. Electroencephalogram (EEG) revealed diffuse, periodic, broad-based waveforms with a triphasic morphology and a prominent second downward component, an EEG pattern observed with toxic-metabolic encephalopathies (Figure 5.4.1). The patient was diagnosed to have nonconvulsive status epilepticus seizures and was initiated on IV phenytoin.

MANAGEMENT AND OUTCOME

All antibiotics were stopped because the patient had no symptoms or signs of infection. A lumbar puncture could not be performed due to the patient's agitation. Hemodialysis was continued daily. The patient's mental status improved over four to five days. Repeat EEG showed a marked improvement in the frequency of the discharges compared with the previous study. Phenytoin was stopped, and the lumbar puncture was cancelled due to clinical improvement. The patient made a full recovery and was discharged home on day seven of hospitalization.

FINAL DIAGNOSIS

Cefepime-induced neurotoxicity was considered the most likely diagnosis. The temporal

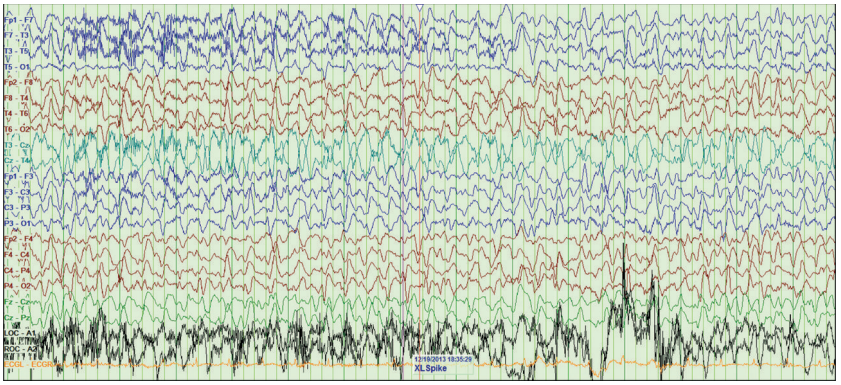

FIGURE 5.4.1: Abnormal EEG with triphasic waves.

relationship of the acute onset of encephalopathy and abnormal EEG after initiation of cefepime and the dramatic clinical improvement and normalization of the EEG after stopping cefepime were consistent with this diagnosis.

DISCUSSION

Cefepime is a fourth-generation cephalosporin with good activity against Gram-negative bacteria including *Pseudomonas aeruginosa*, and it is widely used to treat hospital-acquired infections. Neurotoxicity has been associated with the use of β-lactam antibiotics including penicillins, cephalosporins, and carbapenems. Although it is uncommon, there have been several recent reports of neurotoxicity associated with the use of cefepime [1–4].

The onset of neurotoxicity generally occurs within five days of initiation of cefepime. The clinical manifestations of neurotoxicity can vary and include impaired consciousness, encephalopathy, myoclonus, seizures, nonconvulsive status epilepticus, myoclonus, global aphasia, asterixis, and coma [1–5]. Clinical resolution occurs within a few days of stopping cefepime.

Advanced age and impaired kidney function are the most important risk factors associated with cefepime-induced neurotoxicity. Neurotoxicity is reported more frequently in patients without appropriate dose adjustments for impaired renal function, although it can occur in patients with dose adjustments as well [2, 6–7]. Cefepime has good penetration through the blood-brain barrier, and renal impairment can result in higher serum and cerebrospinal fluid levels.

The mechanism of cephalosporin-induced neurotoxicity is believed to be due to decrease of the inhibitory neurotransmitter γ-aminobutyric acid from the nerve terminals, resulting in increased excitatory neurotransmission and lowering of the seizure threshold [8]. Cefepime-induced neurotoxicity is basically a diagnosis of exclusion. Initial investigation should address the more common etiologies of encephalopathy, including metabolic causes, electrolyte imbalance, anoxia, infection, and stroke. Electroencephalogram findings, although not characteristic, can be suggestive of the diagnosis [9]. The EEG patterns described include diffuse delta slow-wave activity or periodic discharges. The pattern of triphasic waves associated with cefepime-induced neurotoxicity can be seen in many metabolic encephalopathies. A high degree of clinical suspicion of this condition is required to prevent delay in the diagnosis.

The primary management of cefepime-induced neurotoxicity is discontinuation of cefepime. In some instances, hemodialysis has been used to hasten clearance of cefepime [10], and it may have played a role in our patient. Antiseizure medications such as phenytoin or benzodiazepines have been used temporarily to treat cases of cefepime-induced nonconvulsive status epilepticus [9].

KEY POINTS

- Cefepime-induced neurotoxicity, although uncommon, should be considered in the differential diagnosis of acute encephalopathy in the appropriate clinical context.
- Neurotoxicity is more likely to occur in the elderly and in patients with renal impairment without appropriate dose adjustment of cefepime.
- The clinical manifestations include encephalopathy, myoclonus, or nonconvulsive status epilepticus.

- EEG abnormalities are useful in supporting the diagnosis.
- Discontinuation of cefepime generally results in prompt reversal of symptoms.

REFERENCES

1. Chow KM, Szeto CC, Hui AC, et al. Retrospective review of neurotoxicity induced by cefepime and ceftazidime. Pharmacotherapy. 2003;23:369.
2. Fugate JE, Kalimullah EA, Hocker SE, et al. Cefepime neurotoxicity in the intensive care unit: a cause of severe, underappreciated encephalopathy. Crit Care. 2013;17:R264.
3. McNally A, Pithie A, Jardine D. Cefepime: a rare cause of encephalopathy. Intern Med J. 2012;42: 732.
4. Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. Pharmacotherapy. 2006;26:1169.
5. Thabet F, Al Maghrabi M, Al Barraq A, Tabarki B. Cefepime-induced nonconvulsive status epilepticus: case report and review. Neurocrit Care. 2009;10:347.
6. Sonck J, Laureys G, Verbeelen D. The neurotoxicity and safety of treatment with cefepime in patients with renal failure. Nephrol Dial Transplant. 2008;23:966.
7. Gangireddy VG, Mitchell LC, Coleman T. Cefepime neurotoxicity despite renal adjusted dosing. Scand J Infect Dis. 2011;43:827.
8. Sugimoto M, Uchida I, Mashimo T, et al. Evidence for the involvement of GABA(A) receptor blockade in convulsions induced by cephalosporins. Neuropharmacology. 2003;45:304.
9. Grill MF, Maganti R. Cephalosporin-induced neurotoxicity: clinical manifestations, potential pathogenic mechanisms, and the role of electroencephalographic monitoring. Ann Pharmacother. 2008;42:1843.
10. Chatellier D, Jourdain M, Mangalaboyi J, et al. Cefepime-induced neurotoxicity: an underestimated complication of antibiotherapy in patients with acute renal failure. Intensive Care Med. 2002;28:214.

5.5

Construction of a Bone Marrow Transplant Unit

GEORGE J. ALANGADEN, MD

CASE PRESENTATION

A tertiary care hospital is expanding their Cancer Center. The plans include the construction of a twenty-bed unit within the Cancer Center to house patients who will be undergoing bone marrow transplantation (BMT) and hematopoietic stem cell transplantation (HSCT). As the Medical Director of Infection Control and Prevention for the hospital, you have been consulted for advice on various aspects of the design of the new BMT Unit.

QUESTIONS

In particular you have been asked for your recommendation on the following:

- Specifications for room ventilation for the new BMT unit.
- Infection control precautions to be taken during the construction of the unit.

DISCUSSION

Patients undergoing allogeneic HSCT are at risk for aspergillosis and mold infections. The risk is greatest during the pre-engraftment period of neutropenia and then again during therapy with high-dose corticosteroids for the treatment of graft-versus-host disease. Aspergillosis and mold infections are primarily acquired by inhalation of fungal spores. Most cases of invasive aspergillosis are sporadic; however, outbreaks of aspergillosis in the hospital settings have been reported [1]. The majority of these outbreaks occurred in patients undergoing treatment for hematological malignancies and in allogeneic HSCT recipients [1]. Most of these outbreaks were associated with renovation or construction in or around the healthcare facility (HCF). Outbreaks of aspergillosis in the hospital environment have also been associated with malfunctioning ventilation systems, contaminated air filters, and water damage causing mold contamination [2].

Recommendations by the Centers for Disease Control and Prevention and the Healthcare Infection Control Practices Advisory Committee provide guidance to minimize exposure to airborne environmental fungal spores within the hospital environment in high-risk patients [2–3].

The Protective Environment

The provision of a protected environment (PE) is recommended for housing the high-risk allogeneic HSCT patients [2]. The main components of the PE are summarized in Box 5.5.1.

Patients should limit time spent outside PE. When patients have to leave the PE areas, they should preferably wear an N95 mask and should avoid areas where there is ongoing construction [4]. Other recommendations include frequent monitoring of room pressure differentials, appropriate maintenance and removal of particulate matter, and excess moisture from the ventilator systems in the PE areas [2–5].

BOX 5.5.1 PROTECTIVE ENVIRONMENT

COMPONENTS OF PROTECTIVE ENVIRONMENT FOR HSCT UNITS

Well sealed patient rooms that are kept closed.
Use of HEPA filters with 99.97% efficiency for removing particles ≥0.3 μm.
Directed airflow, air intake at 1 side, and air exhaust at the opposite side of the room.
Positive air pressure differential between room and corridor (≥2.5 Pa).
Maintenance of ≥12 air changes per hour [2].

BOX 5.5.2 MEASURES TO MINIMIZE EXPOSURE TO ENVIRONMENTAL AIRBORNE FUNGI DURING CONSTRUCTION

Perform an ICRA before construction begins.
Build rigid impermeable airtight barriers to keep dust out of patient care areas.
Maintain negative air pressure in construction areas. Place HEPA filter units between the construction areas and patient care units if negative pressure cannot be maintained.
Direct construction traffic away from patient care areas.
Avoid transport of patients or patient care equipment through construction areas.
Daily thorough cleaning of dust in patient care areas.
Prompt cleanup and repair of water leaks to prevent mold growth.
Monitor for any cases of nosocomial aspergillosis during periods of construction [2, 3, 5, 6].

Infection Control Measures During Construction

In addition the above engineering measures, additional precaution to minimize exposure to fungal spores are necessary during construction within the HCF. The Infection Control team should be an integral member of the multidisciplinary team involved with the construction project.

Before construction begins, an infection control risk assessment (ICRA) should be performed by the Infection Control team to assess potential exposure of patients to dust and fungal spores. Education should be provided to construction crew and staff in PE areas regarding dust and airborne fungal infections [2, 6–8]. Proactive measures should be implemented to ensure safe air handling including installation of dust barriers, maintenance of negative pressure in construction areas, and assessment for water damage. Surveillance should be maintained for possible outbreaks of nosocomial aspergillosis and mold infection in high-risk patients. Epidemiologic investigation and corrective measures should be performed if nosocomial invasive mold infections are identified.

Other Measures

Other measures to minimize environmental exposure to fungal spores in PE areas include avoidance of fresh flowers and potted plants, no carpeting, and no upholstered furniture in patient care areas. Daily cleaning should be done to remove dust in these areas using measures to minimize dust dispersion such as wet-dusting and vacuuming using vacuum cleaners fitted with high-efficiency particulate air (HEPA) filters [2, 4]. In addition to these measures that minimize the risk of exposure to airborne fungal pathogens, high-risk allogeneic HSCT patients should also receive appropriate antifungal prophylaxis during high-risk periods [5].

KEY POINTS

- Allogeneic HSCT patients are at high-risk for aspergillosis and other airborne invasive mold infections.
- Outbreaks of aspergillosis have been associated with construction in and around HCFs.
- Protective environment is recommended for housing allogeneic HSCT recipients to minimize exposure to airborne fungal spores.
- Barriers to dust, safe air handling, and environmental cleaning are essential to minimize exposure of HSCT patients to dust and fungal spores during hospital construction.

REFERENCES

1. Vonberg RP, Gastmeier P. Nosocomial aspergillosis in outbreak settings. J Hosp Infect. 2006;63:246.
2. Sehulster L, Chinn RY. Guidelines for environmental infection control in health-care facilities. Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep. 2003;52:1.
3. Tablan OC, Anderson LJ, Besser R, et al. Guidelines for preventing health-care—associated pneumonia, 2003: recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep. 2004;53:1.
4. Raad I, Hanna H, Osting C, et al. Masking of neutropenic patients on transport from hospital rooms is associated with a decrease in nosocomial aspergillosis during construction. Infect Control Hosp Epidemiol. 2002;23:41.

5. Tomblyn M, Chiller T, Einsele H, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143.
6. Alangaden GJ. Nosocomial fungal infections: epidemiology, infection control, and prevention. Infect Dis Clin North Am. 2011;25:201.
7. Berthelot P, Loulergue P, Raberin H, et al. Efficacy of environmental measures to decrease the risk of hospital-acquired aspergillosis in patients hospitalised in haematology wards. Clin Microbiol Infect. 2006;12:738.
8. Kidd F, Buttner C, Kressel AB. Construction: a model program for infection control compliance. Am J Infect Control. 2007;35:347.

5.6

Clostridium difficile Keeps Coming Back: Liver Transplant Recipient

GEORGE J. ALANGADEN, MD

CASE PRESENTATION

A 54-year-old woman with end-stage liver disease due to hepatitis C received an orthotopic liver transplant. She was on stable immune suppression with tacrolimus and mycophenolate. The patient was being treated for hypertension and gastroesophageal reflux disease. Her medications included lisinopril, omeprazole, tacrolimus, and mycophenolate. Five months posttransplant, she was treated for a urinary tract infection with a seven-day course of oral ciprofloxacin. The following week, she developed diarrhea, five to six loose bowel movements that was associated with abdominal cramping. *Clostridium difficile* toxin was detected on testing a stool specimen. The patient was treated with a ten-day course of oral metronidazole with complete resolution of her diarrhea and abdominal cramps. Three weeks later, the diarrhea and abdominal symptoms recurred, and a repeat stool examination was positive for *C difficile* toxin. The patient was treated with a fourteen-day course of oral vancomycin with resolution of her symptoms. She presented two weeks later with diarrhea and abdominal cramps, and *C difficile* toxin was detected in her stool sample.

On examination, her temperature was 38.2°C, her blood pressure was 134/80 mm Hg, her heart rate was 92 beats per minute, and her respiratory rate 16 breaths per minute. The patient appeared in mild distress, due to abdominal cramps. Mild distension and tenderness to palpation without rebound or guarding was noted over her lower abdomen. The remainder of the systemic examination was normal. The white blood cell count (WBC) was 9000/μL (neutrophils 52%), hemoglobin was 12 g/dL, and platelet count was 152 000/μL.

QUESTIONS

- What is the differential diagnosis of her recurrent diarrhea?
- What is the likelihood of further recurrences of *C difficile* infection (CDI) in this patient?
- What is the optimal management of recurrent CDI?

DIFFERENTIAL DIAGNOSIS

In this patient with recent CDI, it is very likely that diarrhea and abdominal cramps are due to a relapse of the CDI. Cytomegalovirus (CMV)-related colitis is less likely given that the patient is at low risk for CMV reactivation given the stable immune suppression and CMV seropositive status of both donor and recipient.

ADDITIONAL DATA

A repeat stool test was positive for *C difficile* toxin. A computerized tomography (CT) scan of her abdomen was performed given the abdominal distension and tenderness. The CT scan demonstrated distension of the colon and diffuse thickening of the colonic wall (Figure 5.6.1).

Final Diagnosis: Recurrent *Clostridium difficile* infection

TREATMENT AND OUTCOME

The patient was treated with a twenty-eight-day tapering course of oral vancomycin therapy with resolution of her diarrhea and abdominal cramps. However, approximately three weeks later, her symptoms recurred, and the repeat *C difficile* toxin assay on a stool specimen was positive. She received a fecal microbiome transplant (FMT) administered via nasogastric tube using stool provided by her sister. The symptoms resolved within forty-eight hours, and the patient was symptom-free at six months of follow-up.

DISCUSSION

Approximately 15%–20% of patients with CDI will experience a second episode of infection

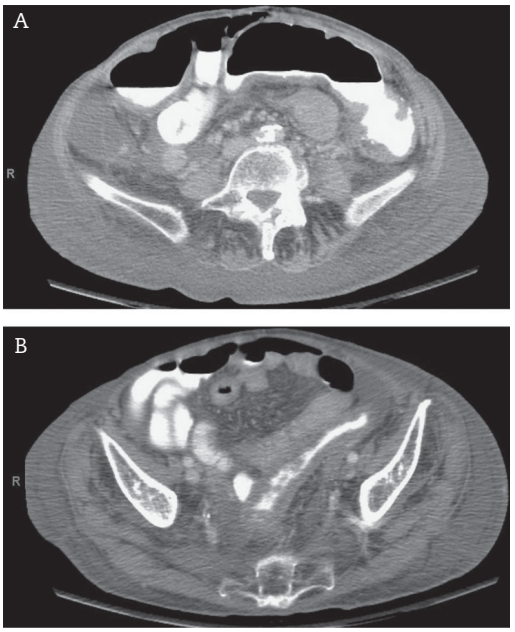

FIGURE 5.6.1: Computerized tomography scan demonstrating (A) distension of the colon and (B) diffuse thickening of the colonic wall.

within four weeks of completion of therapy with oral metronidazole or oral vancomycin [1]. In patients with recurrence, the risk of a second and third recurrence is estimated to be 40% and 60%, respectively [2].

The potential risk factors for recurrent CDI include advanced age (>65 years), repeat hospitalization, continued exposure to antibiotics, use of proton pump inhibitors, and presence of cancer or receipt of organ transplant as in our patient [2–3]. Recurrence generally occurs due to persistent disruption of the normal gut microbiome and resulting loss of "colonization resistance" to spores of *C difficile* [4]. Recurrence may also be due to the inability of the host to develop an adequate antibody response *to C difficile* toxins [5]. Furthermore, hypervirulent NAP-1 strains of *C difficile* have also been associated with higher rates of recurrence [4]. Recurrence of CDI is not due to the development of resistance of metronidazole or vancomycin.

The general approach to prevention of recurrence of CDI includes avoidance of antibiotics and possibly H2 blockers or proton pump inhibitors (Table 5.6.1). Most patients will respond to a second course of the therapy that was used initially, namely metronidazole or oral vancomycin [6]. Therapy with fidaxomicin may be considered, because it is associated with half the rate of recurrence compared with oral vancomycin [7]. A second recurrence is generally managed with a tapering course of oral vancomycin therapy.

Fecal microbiome transplant should be considered for the treatment of patients with three or more recurrences of CDI. The use of FMT to treat recurrent CDI is based on the premise that the diversity of the disrupted gut microbiome in patients with CDI is restored with the infusion into the gut of stools from healthy donors [4]. In retrospective uncontrolled studies, the efficacy of FMT for the treatment of recurrent CDI is approximately >90% [8–9]. The first prospective randomized study of FMT for the treatment of recurrent CDI was performed using a duodenal infusion of donor stool. The overall efficacy of FMT was 91% compared with 30% for oral vancomycin [10].

Initial reports suggested better response rates with related stool donors of 93% compared with 84% with unrelated donors [8–9]. However, recent reports suggest efficacy of 92% of FMT done using unrelated donor stools that are frozen and thawed for use compared with 70% using related donors [11]. All CDI-related antibiotic therapy and other antibiotic therapies should be discontinued twenty-four hours before FMT, and antibiotics should be avoided after FMT.

Stool donors should be healthy with no gastrointestinal illness, no recent use of antibiotics (three to six months), and no high-risk behaviors for HIV infection. The screening tests for selection of donors include serology for HIV, hepatitis A, B and C, and syphilis. Stools of the donors should be tested for toxigenic *C difficile* (preferably polymerase chain reaction test), enteric pathogens, ova, and parasites. Some centers recommend more expanded stool testing [12].

The donor stool sample is blended in water and administered via nasogastric tube placed in the duodenum or by enema or colonoscopy. In approximately 75% of the published reports, FMT was done via enema or colonoscopy. In general, a single infusion is sufficient to achieve a response generally within three days. The reported adverse effects are mild and may include transient irritable bowel-like symptoms [8–10, 12]. The long-term adverse effects of FMT are unknown. There are currently ongoing clinical trials that are evaluating the efficacy and safety of FMT for recurrent and refractory CDI.

A recent retrospective multicenter study evaluated the safety and efficacy of FMT for recurrent or refractory CDI in eighty immunocompromised patients, including nineteen solid organ transplant recipients. The overall cure rate in the study

TABLE 5.6.1. MANAGEMENT OF RECURRENT CDI

Episodes of CDI	Management
Initial episode of CDI	• Stop inciting antibiotic • Assess severity of CDI* • Treatment: (a) Mild or moderate disease -oral metronidazole (500 mg q 8 h) × 10–14 d (b) Severe disease† -oral vancomycin 125 mg q 6 h × 10–14 d (c) Severe complicated disease‡ -oral vancomycin 500 mg q 6 h × 10–14 d + -IV metronidazole 500 mg q8 h × 10–14 d
First recurrence of CDI	As above
Second recurrence of CDI	• Stop inciting antibiotic • Treatment (a) Vancomycin tapering regimen -125 mg q 6 h × 14 d -125 mg q 12 h × 7 d -125 mg q daily × 7 d -125 mg every 2 –3 d × 2–8 wks or (b) Consider oral fidaxomicin 200 mg q 12 h × 10 d
Third recurrence of CDI	• Stop all antibiotics • Treatment -Fecal microbiome transplant

*Severity of CDI.
†Severe disease: WBC >15 000/mm^3, serum creatinine >1.5 × baseline.
‡Severe complicated disease: hypotension, shock, ileus, megacolon [6–7, 12].

was 89%, with a 78% cure rate after a single infusion. One death occurred due to aspiration during sedation for a colonoscopic FMT. None of the patients had FMT-related infections [13].

KEY POINTS

- Immunosuppressed transplant recipients are at risk for recurrent CDI.
- Patients who are unresponsive to standard therapy including oral vancomycin taper should be considered for FMT.
- FMT is a well tolerated therapeutic option for recurrent CDI with a response rate of >90%.
- FMT may be a safe and effective option even in immunocompromised patients.

REFERENCES

1. McFarland LV, Surawicz CM, Rubin M, et al. Recurrent *Clostridium difficile* disease: epidemiology and clinical characteristics. Infect Control Hosp Epidemiol. 1999;20:43.
2. Kelly CP. Can we identify patients at high risk of recurrent *Clostridium difficile* infection? Clin Microbiol Infect. 2012;6:21.
3. Zilberberg MD, Reske K, Olsen M, et al. Development and validation of a recurrent *Clostridium difficile* risk-prediction model. J Hosp Med. 2014;9:418.
4. Lawley TD, Clare S, Walker AW, et al. Targeted restoration of the intestinal microbiota with a simple, defined bacteriotherapy resolves relapsing *Clostridium difficile* disease in mice. PLoS Pathog. 2012;8:e1002995.
5. Kyne L, Warny M, Qamar A, Kelly CP. Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A. N Engl J Med. 2000;10;342:390.
6. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31:431.

7. Cornely OA, Miller MA, Louie TJ, et al. Treatment of first recurrence of *Clostridium difficile* infection: fidaxomicin versus vancomycin. Clin Infect Dis. 2012;2:S154.
8. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. Clin Infect Dis. 2011;53:994.
9. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for *Clostridium difficile* infection: systematic review and meta-analysis. Am J Gastroenterol. 2013;108:500.
10. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. N Engl J Med. 2013;368:407.
11. Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent *Clostridium difficile* infection. Am J Gastroenterol. 2012;107:761.
12. Brandt LJ. American Journal of Gastroenterology Lecture: Intestinal microbiota and the role of fecal microbiota transplant (FMT) in treatment of *C. difficile* infection. Am J Gastroenterol. 2013;108:177.
13. Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of *Clostridium difficile* infection in immunocompromised patients. Am J Gastroenterol. 2014;109:1065.

5.7

Idiopathic CD4⁺ Lymphocytopenia: Dizziness and Headaches

ASHISH BHARGAVA, MD AND PRANATHARTHI H. CHANDRASEKAR, MD

CASE PRESENTATION

A 63-year-old woman presented with worsening dizziness, new onset diplopia, and slurring of speech. Her initial symptom of dizziness started six weeks earlier, but it progressed to recurrent headaches and motion sickness despite symptomatic treatment. Magnetic resonance imaging (MRI) showed a 3 mm focal, nodular-enhancing lesion in the left cerebellar hemisphere. She was given a short course of prednisone without any clinical improvement four weeks prior to her presentation. She had a history of hyperlipidemia, and she had no history of tobacco, alcohol, or intravenous drug abuse. She had no pets, and she had no recent travel history. Her current medication was only simvastatin.

On presentation, she was afebrile. She had bilateral horizontal nystagmus, worse on the left side, wide-based gait, significant vertigo, moderate dysmetria, and dysdiadochokinesia on the left side. Her sensory and motor examinations were unremarkable as was the rest of the examination.

LABORATORY DATA

Her white blood cell count was 5200/μL with morphed lymphocytopenia (neutrophils 3800/μL, lymphocyte 700/μL, monocytes 500/μL). Serum electrolytes, hemoglobin level, and platelet count were normal. Renal and liver function tests were unremarkable.

Magnetic resonance imaging of brain on T2-weighted image showed a 3 × 3 cm bright enhancing mass lesion in left cerebellar hemisphere. There were no additional lesions in the cerebrum, brainstem, or rest of the cerebellum. There was no significant perilesional vasogenic edema, mass effect or hydrocephalus, or any leptomeningeal enhancement.

The following additional studies for lymphocytopenia were performed:

- $CD4^+$ lymphocyte: 10 cells/μL
- $CD8^+$ lymphocyte count: 12 cells/μL
- Human immunodeficiency virus (HIV) 1 and 2 (enzyme immunoassays) serology, HIV viral load, and serum rapid plasma reagin: negative

A lumbar puncture was done for cerebrospinal fluid (CSF) analysis. The CSF was unremarkable; Gram stain and acid-fast bacilli smears were negative. Bacterial, fungal and viral cultures were negative. In addition, herpes viral polymerase chain reaction (PCR) (herpes simplex virus ½, vesicular stomatitis virus, cytomegalovirus, and Epstein-Barr virus) was negative.

DIFFERENTIAL DIAGNOSIS

Central Nervous System Lesions With Mass Effects

A brain abscess is usually a focal collection within the brain parenchyma, which can arise from direct or hematogenous spread. Clinical manifestations can vary, depending upon the involved brain area. Magnetic resonance imaging shows ring-enhancing lesions. Absence of any prior dental procedure, ear or sinus infections, negative blood culture, and absence of focal lesions on MRI makes this diagnosis unlikely.

Toxoplasma encephalitis is a reactivation disease from prior infection. Affected patients usually present with fever, headache, altered mental status, and/or focal neurological deficit. Lesions are generally multiple and have ring enhancement. If clinical suspicion is high with a single lesion, then empiric therapy is initiated. A brain biopsy is recommended in patients without any clinical or radiological improvement.

Malignancy (primary lymphoma) can present with focal neurological signs and symptoms, confusion, or seizures. It is commonly associated with fever, night sweats, and weight loss. It can be solitary or have multiple lesions that commonly have peripheral enhancement.

Tuberculomas frequently present as focal lesions without evidence of systemic illness or meningeal infection. They originate during hematogenous dissemination. Absence of exposure and negative epidemiology makes the diagnosis unlikely.

Granulomatous conditions (sarcoidosis and fungal disease such as *Histoplasma, Cryptococcus*, and *Coccidioidomyces*): Presence of a single lesion without any evidence of disseminated infection makes them less likely.

Neurocysticercosis usually presents with seizures or focal neurological findings. Cystic or enhancing lesions are the most common form. Absence of these characteristics radiologically and no travel history to endemic areas makes this diagnosis less likely.

VIRAL ENCEPHALITIS (HERPES SIMPLEX VIRUS, VARICELLA-ZOSTER VIRUS): NEGATIVE CEREBROSPINAL FLUID POLYMERASE CHAIN REACTION TESTS MAKE THESE ENTITIES UNLIKELY

Central Nervous System Lesions Without Any Mass Effect

Demyelinating condition (progressive multifocal leukoencephalopathy [PML]) is a demyelinating disease and characteristically presents with rapidly progressive focal neurological deficits including aphasia, ataxia, hemiparesis, and cognitive impairment. Areas of demyelination are usually bilateral, asymmetric, and located mostly in the periventricular or subcortical white matter. Surrounding edema or mass effect on surrounding structures is absent.

Human immunodeficiency virus encephalopathy usually presents with a classic triad of depressive symptoms, movement disorder, and memory and psychomotor speed impairment. On MRI, multiple bilaterally symmetrical, nonenhancing lesions are seen. Negative HIV serology makes it an unlikely diagnosis in this patient.

Cytomegalovirus encephalitis is an opportunistic infection in immunosuppressed patients, most commonly seen in those with acquired immune deficiency syndrome (AIDS). Patients usually present with altered mental status and focal neurologic abnormalities. Magnetic resonance imaging can either show diffuse micronodules in cortex, brainstem, and basal ganglia or periventricular enhancement.

DIAGNOSTIC PROCEDURE

An open needle biopsy specimen revealed marked atypia in the astrocytes and rare nuclei with abnormal inclusion-like material. Electron microscopy confirmed demyelinating process along with the presence of intranuclear virus particles. Cerebrospinal fluid PCR testing showed 32 700 copies/mL of JC virus (JCV).

HOSPITAL COURSE

Her neurological condition rapidly declined after hospital admission. By the tenth admission day, she was unable to eat or follow simple commands. She received one dose of cidofovir (357 mg, IV), after confirmed diagnosis, but her condition continued to decline. On nineteenth day, she developed acute left cerebellar hemorrhage with noncommunicating hydrocephalus and midline shift. She expired secondary to cardiac complications. At autopsy, demyelinating lesions associated with viral inclusion consistent with PML were noted in the brain.

Final Diagnosis: Progressive multifocal leukoencephalopathy in idiopathic CD4 lymphocytopenia

Progressive multifocal leukoencephalopathy is a rare and usually fatal demyelinating viral disease of the brain, caused by reactivation of JCV. It typically occurs in immunosuppressive states and is characterized by rapid neurological deterioration, associated with progressive inflammation of the white matter at multiple locations.

Primary infection with JCV usually occurs in childhood and is asymptomatic. Proposed sites of latency included tonsillar tissue, kidneys, bone marrow, and brain. Immunosuppression allows JCV to reactivate. It infects the oligodendrocytes and astrocytes in the central nervous system (CNS) causing PML, possibly through 5HT2A serotonin receptors. Human immunodeficiency virus/AIDS and drugs such as natalizumab and rituximab are among the commonest predisposing conditions. Other illnesses include myeloproliferative states (e.g. chronic lymphocytic leukemia), carcinoma, granulomatous conditions (tuberculosis, sarcoidosis), stem cell or organ transplantation, connective tissue diseases (systemic lupus erythematosus), and other immune suppressive states (idiopathic CD4 lymphocytopenia) [1].

The Centers for Disease Control and Prevention (CDC) defines idiopathic CD4 lymphocytopenia as $CD4^+$ T cells <300/μL or a $CD4^+$ cell count <20% of the total T cell on two occasions, with no evidence of infection on HIV testing and absence of any defined immunodeficiency or therapy associated with depressed levels of $CD4^+$ T cells. An extensive review of cases from the CDC conducted by Ho et al [2] shows that PML in the setting of idiopathic CD4 lymphocytopenia is an exceedingly rare clinical occurrence.

Progressive multifocal leukoencephalopathy causes multifocal demyelination of white matter of CNS resulting in behavioral, speech, cognitive, motor, and visual impairment. An MRI is the imaging modality of choice and shows areas of hyperintensity on T2-weighted and FLAIR images. Cerebrospinal fluid is usually normal, but protein may be slightly elevated. Detection of JCV DNA in CSF (by PCR amplification) has high sensitivity (72%–92%) and specificity (92%–100%) [3]. After a negative JCV PCR test result, one or more lumbar punctures are indicated if clinical suspicion of PML persists [3]. Brain biopsy remains the gold standard for diagnosis of PML. No specific treatment exists for PML.

Correction of an underlying condition of immune suppression has been associated with clinical improvement in these patients [4]. Immunotherapies boosting the immune system have been tried as treatment modality with limited success. Cytarabine showed some efficacy in one clinical trial [5]. Cidofovir, mirtazapine, and mefloquine have shown in vitro potential to control JCV infection [6].

KEY POINTS

- PML is a demyelinating disease of the brain caused by reactivation of JCV.
- PML is commonly seen in patients with HIV/AIDS and in patients receiving natalizumab and rituximab.
- Presentation is usually characterized by fever, mental status changes, and focal neurologic defects usually in immunocompromised patients.
- MRI is the imaging modality of choice.
- Brain biopsy remains the gold standard for diagnosis of PML.
- The most effective treatment for PML is the restoration of the immune system.
- Prognosis is very poor unless immune function can be restored; even when immune function improves, neurologic deficits may persist.

REFERENCES

1. Smith DK, Neal JJ, Holmberg SD. Unexplained opportunistic infections and CD4+ T-lymphocytopenia without HIV infection. An investigation of cases in the United States. The Centers for Disease Control Idiopathic CD4+ T-lymphocytopenia Task Force. N Engl J Med. 1993;328:373.
2. Ho DD, Cao Y, Zhu T, et al. Idiopathic CD4+ T-lymphocytopenia: immunodeficiency without evidence of HIV infection. N Engl J Med. 1993;328:380.
3. Koralnik IJ. Progressive multifocal leukoencephalopathy revisited: has the disease outgrown its name? Ann Neurol. 2006;60:162.
4. Mascarello M, Lanzafame M, Lattuada E, et al. Progressive multifocal leukoencephalopathy in an HIV patient receiving successful long-term HAART. J Neurovirol. 2011;17:196.
5. Aksamit AJ. Treatment of non-AIDS progressive multifocal leukoencephalopathy with cytosine arabinoside. J Neurovirol. 2001;7:386.
6. Patel A, Patel J, Ikwuagwu J. Treatment of progressive multifocal leukoencephalopathy and idiopathic CD4+ lymphocytopenia. J Antimicrob Chemother. 2010;65:2489.

5.8

Confused: A Patient With Melanoma

MAHA ALHUSSEINI, MD, DEEPAK GARG, MD, MARWAN AL-HAJEILI, MD, AND PRANATHARTHI H. CHANDRASEKAR, MD

CASE PRESENTATION

A 35-year-old woman with a history of advanced melanoma, on treatment with a monoclonal antibody against cytotoxic T lymphocyte-associated antigen ([CTLA-4]; ipilimumab), was admitted with fever and altered mentation for one day. The patient had complained of progressively worsening headache for the prior one week. On examination, her temperature was 38.8°C, pulse was 125 per minute, respiration was 16 per minute, and blood pressure was 109/60 mm mercury. She was not oriented to time, place, or person and was confused; her neck was supple, and there was no focal neurological deficit. The rest of the examination was normal. Complete blood counts, serum electrolytes, and renal and liver function tests were normal. A computed tomography head scan (without contrast) done on admission was unremarkable. Initial management included cerebrospinal fluid (CSF) examination and empiric broad-spectrum antibiotics (vancomycin and cefepime). With persistent fever and worsening mentation, she was transferred to the intensive care unit. Empiric antimicrobial therapy included ceftriaxone, vancomycin, ampicillin, and acyclovir. Her chest x-ray and blood and urine cultures were negative. Lumbar puncture showed normal opening pressure; CSF exam revealed 10 white blood cells (mostly lymphocytes), 0 red blood cells, glucose 59 mg/dL, and protein 48 mg/dL. Cerebrospinal fluid Gram stain, acid-fast bacilli, fungal stains, Venereal Disease Research Laboratory test, bacterial and fungal cultures, and cryptococcal antigen were negative. Cerebrospinal fluid polymerase chain reaction for herpes simplex virus (HSV) and varicella-zoster virus (VZV) and CSF West Nile virus immunoglobulin (Ig)M were negative.

A magnetic resonance image (MRI) of the brain showed diffuse enlargement of the pituitary gland with homogeneous enhancement. An MRI of the head obtained three months earlier was normal (Figure 5.8.1). The rapid rate of growth of the lesion with no evidence of intracranial neoplastic changes raised the possibility of an inflammatory process.

Based on the two MRIs, a diagnosis of lymphocytic hypophysitis was entertained by the radiologist. Hypophysitis is not a commonly encountered entity by oncologists, endocrinologists, or infectious disease physicians. The clinical features of fever and altered mentation combined with CSF pleocytosis rendered a diagnosis of meningoencephalitis.

Final Diagnosis: Lymphocytic hypophysitis and meningoencephalitis

DISCUSSION

This patient, with metastatic melanoma, on ipilimumab, presented with fever and altered mental status. Her condition quickly deteriorated and required admission to the critical care unit, and a multidisciplinary team was also involved in her assessment. There was a strong suspicion for an infectious etiology initially; however, workup for the involvement of HSV, VZV, West Nile virus, *Cryptococcus*, or bacteria were negative. Antibiotic therapy was stopped. A diagnosis of lymphocytic hypophysitis prompted a hormonal workup, which revealed depressed levels of ACTH, cortisol, thyroid-stimulating hormone, free T4, luteinizing hormone, and follicle-stimulating hormone. Therapy was started with prednisone 20 mg daily, and within twenty-four hours, fever and tachycardia resolved, and her mentation was back to baseline. In a two-week follow-up appointment postdischarge, while still on corticosteroids and thyroid hormone replacement, repeat laboratory tests showed normalized cortisol and free T4.

Lymphocytic hypophysitis is a rare autoimmune inflammatory disorder of the pituitary gland, mostly reported in women in late

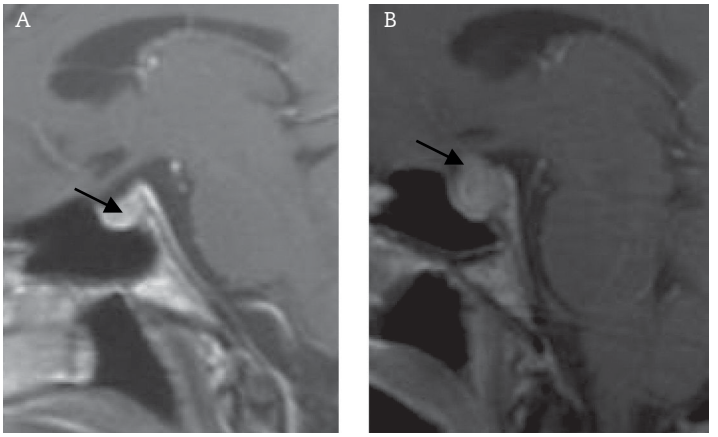

FIGURE 5.8.1: MRI of brain before initiation of ipilimumab (A) and three months posttherapy (B).

pregnancy or after menopause [1]. Lymphocytic adenohypophysitis involves anterior pituitary dysfunction that occurs in association with autoimmune diseases and pregnancy, and lymphocytic infundibuloneurohypophysitis affects the posterior pituitary, leading to diabetes insipidus. The most frequent presentation is pituitary dysfunction: from pan hypopituitarism to a single hormone deficiency. Suprasellar extension may lead to compression of the optic chiasm. Headaches, visual field disturbances, and hyperprolactinemia are common. More than half of the patients also present with secondary hypoadrenalism. Other reported presentations include febrile syndrome and aseptic meningitis [2, 3]. Lymphocytic hypophysitis is commonly a subacute process with atypical symptoms resulting in diagnostic delay. Magnetic resonance imaging findings are nonspecific and are typically characterized by diffuse enlargement of the pituitary gland with loss of normal posterior pituitary signal intensity on the precontrast images and variable enlargement of the infundibulum [4]. Pathology consists of destruction of the pituitary acini by plasma cells and T lymphocytes. Some studies suggest that the lymphocytic subpopulation is represented mainly by cytotoxic T lymphocytes ($CD8^+$) underscoring the role of T cell-mediated cytotoxicity in the pathogenesis of this disorder [5].

Ipilimumab is an IgG1 monoclonal antibody against CTLA-4, a negative regulator of T cells. It augments unrestrained T-cell activation. It is currently approved for unresectable and metastatic melanoma because the drug has been shown to improve survival [6–8]. As a result of overstimulation of T cells, this class of drugs is commonly associated with immune-related adverse effects including hypophysitis, colitis, rash, fever, hepatitis, pancreatitis, iridocyclititis, and nephritis [9]. Most of the immune-related adverse events are reversible upon drug discontinuation and respond well to corticosteroids. Hypopituitarism appears to be the only potentially irreversible event.

Lymphocytic hypophysitis is reported in 0%–17% of patients receiving ipilimumab and is often associated with thyroid and adrenal insufficiency. Whether increased incidence of infections occurs with this new class of novel drugs is unclear. Early recognition of immune-related adverse events caused by this class of drugs is important because the events can lead to death if left unattended.

REFERENCES

1. Ng WH, Gonzales M, Kaye AH. Lymphocytic hypophysitis. J Clin Neurosci. 2003;10:409.
2. Suzuki K, Izawa N, Nakamura T, et al. Lymphocytic hypophysitis accompanied by aseptic meningitis mimics subacute meningoencephalitis. Intern Med. 2011;50:2025.
3. Katoh N, Machida K, Satoh S, et al. A clinically diagnosed lymphocytic hypophysitis presenting as recurrent meningitis. Rinsho Shinkeigaku. 2007;47:419.
4. Carpenter KJ, Murtagh RD, Lilienfeld H, et al. Ipilimumab-induced hypophysitis: MR imaging findings. Am J Neuroradiol. 2009;30:1751.
5. Torino F, Barnabei A, De Vecchis L, et al. Hypophysitis induced by monoclonal antibodies to cytotoxic T lymphocyte antigen 4: challenges from a new cause of a rare disease. Oncologist. 2012;17:525.
6. Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind,

multicentre, phase 2, dose-ranging study. Lancet Oncol. 2010;11:155.
7. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363:711.
8. Juszczak A, Gupta A, Karavitaki N, et al. Ipilimumab: a novel immunomodulating therapy causing autoimmune hypophysitis: a case report and review. Eur J Endocrinol. 2012;167:1.
9. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012;30:2691.

5.9

Infected Donor—What Do I Do?

ASHISH BHARGAVA, MD AND PRANATHARTHI H. CHANDRASEKAR, MD

CASE PRESENTATION

A 45-year-old man with end-stage renal disease underwent a renal transplant from a cadaveric donor. His donor was a Hispanic male from Mexico, who died of intracranial hemorrhage following head trauma. Posttransplant day five, the donor's serum specimen was found to have positive serology for Chagas disease; the test was performed at the Centers for Disease Control and Prevention ([CDC] Atlanta, GA). Indirect fluorescence antibody titer against Chagas disease was 1:32, and enzyme immunoassay was positive. The transplant recipient was doing well without any chest or abdominal pain, nausea, vomiting, dysuria, diarrhea, fever, chills, or shortness of breath. Another transplant recipient who received his kidney from the same deceased donor was doing well. Liver of the deceased donor was sent for research purposes, and no other organ donation was made from the deceased donor.

You are consulted for advice in managing the seronegative recipient who received a kidney from a seropositive, otherwise asymptomatic donor.

CHAGAS DISEASE

Chagas disease is caused by a protozoan, *Trypanosoma cruzi.* It is endemic throughout parts of South and Central America. Most infections are transmitted through skin breaks contaminated with feces of infected triatomine insects, but the parasite can be acquired through contaminated food, blood transfusion, organ transplantation, and vertical transmission from mother to child. Most acute infections in endemic areas are acquired during childhood and are asymptomatic. The signs of portal of entry of *T cruzi* through the skin (chagoma) or via the ocular mucous membranes (Romañ a sign) are characteristic in vector-borne transmission. Twenty to 30% of the patients' infection progresses to chronic phase involving the cardiovascular system most commonly, followed by gastrointestinal tract, and to a lesser extent the central nervous system [1]. Clinical presentation of cardiac involvement includes arrhythmias or cardiomyopathy. Megaesophagus and megacolon are common gastrointestinal manifestations. Demonstration of *T cruzi* in wet preparations of blood or buffy coat establishes acute diagnosis. After eight to twelve weeks, the parasitemia becomes undetectable by microscopy. Serologic testing is the mainstay for the diagnosis of chronic Chagas disease. Most immune competent patients with acute, indeterminate, and chronic disease are treated with antiparasitic therapy consisting of nifurtimox and benznidazole for 90 to 120 days.

CHAGAS DISEASE IN SOLID ORGAN TRANSPLANTATION

In solid organ transplantation, Chagas disease could be a donor-derived infection. Uninfected recipients who receive an organ from *T cruzi*-infected donor may develop acute *T cruzi* infection. In endemic areas, Chagas disease could result from a new infection or reactivation of chronic infection in the presence of intense immune suppression. A study from Argentina showed reactivation of chronic Chagas disease in five (21.7%) of twenty-three recipients and development of acute *T cruzi* infection in three (18.7%) of sixteen non-chagasic recipients [2]. Transplantation of any organ from donors with acute Chagas disease is contraindicated [3]. In chronically infected patients, the heart is an important reservoir of *T cruzi* organisms. Heart transplantation from *T cruzi* seropositive donors is currently not recommended [3]. In view of shortage of organs, other organs (kidney, liver, lung, pancreas, and intestines) can be transplanted from donors with positive serostatus after obtaining informed consent from the prospective recipient. In a case series, risk for transmission of *T cruzi* was noted in the following order: heart (3 of 4; 75%), liver (2 of 10; 20%), kidney (2 of 15;

13%), combined liver-kidney (0 of 1 = 0), combined kidney and pancreas (1 of 1; 100%), and bilateral lung (1 of 1; 100%) [4].

Universal testing of all potential donors is performed in endemic countries [5]. In an endemic area, if the donor is known to have Chagas disease, the diagnosis should be confirmed with serological tests. In nonendemic countries, targeted testing with *T cruzi* serology is an effective screening strategy for all organ donors [3]. This testing is recommended for organ donors from an endemic country or patients with a prolonged stay (three to six months), or those who had extensive travel history in the endemic country, especially when in close contact with people from lower socioeconomic ranks and those in poor housing and rural areas. The Ortho EIA and Abbott Prism Chagas test are the two US Food and Drug Administration-approved systems for blood donor screening [3].

Recipients of organs from a seropositive donor should be monitored for clinical signs and symptoms of acute Chagas disease or its reactivation. Symptoms of acute *T cruzi* infection in a transplant recipient are generally nonspecific, including fever, malaise, myocarditis, meningoencephalitis, and cutaneous lesions, or the symptoms may mimic transplant rejection. The incubation period for *T cruzi* transmitted via organ transplantation has been reported to be longer (two to three months) compared with vector-borne infections (three weeks) [1, 2]. The period can be delayed as long as six months. So, signs and symptoms of *T cruzi* infection can appear much later than those of more common infections conveyed via allograft. Current recommendations are for preemptive monitoring of infections in recipients and prompt treatment with antitrypanosomal therapy if donor-derived *T cruzi* occurs [3, 4, 6]. The patient described in this report had no clinical signs, symptoms of *T cruzi* infection, or positive polymerase chain reaction (PCR) screening test throughout the one-year recommended period of follow up. A prophylactic treatment strategy is not recommended because antitrypanosomal agents have significant side effects and do not lead to cure of the chronic infection.

Laboratory monitoring for *T cruzi* includes microscopy of buffy coat blood sample, Giemsa-stained peripheral blood smears, and whole blood testing by PCR [3]. Due to intense immune suppression posttransplant, serological testing may be less useful. Microscopy of peripheral smears and buffy coat preparations detects circulating trypomastigotes. Polymerase chain reaction is the most sensitive tool because it detects infection before parasitemia develops [7]. It is the best tool to diagnose acute Chagas disease as well as for monitoring reactivation of chronic Chagas disease in the immunosuppressed host. *Trypanosoma cruzi* infections in transplant recipients are treated with benznidazole or nifurtimox. Benznidazole is preferred over nifurtimox among transplant recipients due to fewer drug interactions. Posaconazole and allopurinol have been found to have some antitrypanosomal activity but has not yet shown any promising results. In the United States, medication for Chagas disease is available only through the CDC. The CDC should be contacted as soon as Chagas infection is recognized in the donor.

REFERENCES

1. Bern C, Montgomery SP, Herwaldt BL, et al. Evaluation and treatment of Chagas disease in the United States: a systematic review. JAMA. 2007;298:2171.
2. Riarte A, Luna C, Sabatiello R, et al. Chagas' disease in patients with kidney transplants: 7 years of experience 1989–1996. Clin Infect Dis. 1999;29:561.
3. Chin-Hong PV, Schwartz BS, Bern C, et al. Screening and treatment of Chagas disease in organ transplant recipients in the United States: recommendations from the Chagas in transplant working group. Am J Transplant. 2011;11:672.
4. Huprikar S, Bosserman E, Patel G, et al. Donor-derived Trypanosoma cruzi infection in solid organ recipients in the United States, 2001–2011. Am J Transplant. 2013;13:2418.
5. de Andrade JP, Marin-Neto JA, de Paola AAV, et al. Latin America guidelines for the diagnosis and treatment of Chagas' heart disease: executive summary. Arq Bras Cardiol. 2011;96:434.
6. Fischer SA, Avery RK. Screening of donor and recipient prior to solid organ transplantation. Am J Transplant. 2009;9(Suppl 4):S7.
7. Schijman AG, Vigliano C, Burgos J, et al. Early diagnosis of recurrence of *Trypanosoma cruzi* infection by polymerase chain reaction after heart transplantation of a chronic Chagas' heart disease patient. J Heart Lung Transplant. 2000;19:1114.

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