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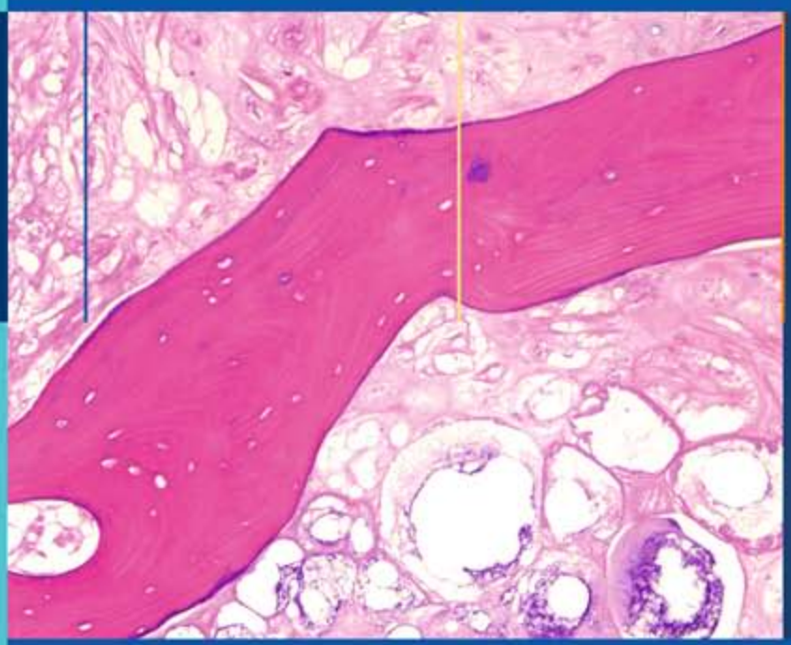

Essentials in Bone and Soft-Tissue Pathology

Springer

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Preface

This book is a short text directed primarily at residents in pathology. The aim is to provide a short text that captures the salient points of the most common problems in bone and soft-tissue pathology. The book does not replace the other more voluminous texts and references on the subject. With this aim in mind, the editors have included only the most important or diagnostic features of common musculoskeletal lesions with emphasis on established information. Newer but less established reports, papers, tests and data based upon limited numbers of cases or ongoing research have not been included. For brevity, the editors have not included references.

The book follows a systematic approach for instruction in bone pathology. Chapter 1 starts with anatomy that is pertinent to the understanding of bone pathology and includes some information on bone biology. Chapter 2 includes some of the most common specimens that a practicing pathologist is likely to see. Chapter 3 discusses arthropathies and has been written with a strong focus on the radiological aspects, since this is how the diagnosis on most arthropathies is made. Chapter 4 discusses bone infections. Chapter 5 introduces the complexities of metabolic bone disease to the reader and suggests several excellent texts which delve into the minutiae of how bone histomorphometric analysis is conducted. The last two chapters are focused on bone and soft-tissue tumors and contain the most important entities a resident or a practicing pathologist need to know.

Despite the focus on knowledge needed by residents in pathology, the book will also be of value to other individuals interested in the field of orthopedic pathology, including medical students, orthopedic surgeons, radiologists and practicing pathologists who do not see these cases on a day to day basis.

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Contents

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Chapter 1
Bone Structure, Development and Bone Biology

Jasvir S. Khurana and Fayez F. Safadi

The Skeleton

The skeleton serves as a structural support system. It has mechanisms to grow and change in shape and size to suit varying mechanical forces. It is involved in the calcium/phosphate balance and in the detoxification of heavy metals.

Bone tissue is continuously formed and remodeled throughout life. This is necessary since otherwise it would cross its tolerance limit after the repetitive stress and torsion it faces on a nearly daily basis.

Initially, the bone achieves its increase in size and shape through *growth* (increase in size) and subsequent *modeling*. In late childhood and adulthood there is continuous renewal of the skeleton, by a process termed *remodeling*. Both modeling and remodeling *require* two separate processes namely bone resorption and bone formation to *occur simultaneously* to be effective. This requirement is known as "coupling."

Bone Formation and Degradation

The major functions of bone cells include matrix *formation* (*osteogenesis*), *mineralization*, and *degradation* (*resorption*). Formation and resorption can and generally do occur simultaneously. During the first two decades of life when the skeleton is growing, bone formation exceeds its degradation. With aging, the rate of bone formation declines to a slightly greater extent than the rate of resorption, resulting in a progressive bone loss as bone remodeling continues.

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Bone Architecture

Bone is a composite tissue consisting of mineral, matrix, cells, and water. The mineral is an analog of the naturally occurring crystalline calcium phosphate, hydroxyapatite. The outer cortices of various bones are fashioned in the form of a hollow tube or a bilaminar plate. The architecture is strengthened by internal "struts" of trabecular bone that follow the lines of stress. This kind of design is known in engineering terms as "composite" and allows bone to take advantage of the strength of components. Thus, bone resists mechanical compression and can deform a great deal before failing.

Gross Morphology

There are four kinds of bones: long bones (femur, tibia, ulna and radius), short bones (carpal and tarsal bones), flat bones (skull, sternum and scapula) and irregular shaped bones (vertebra and ethmoid). These bones form through different mechanisms during embryonic development. The majority of long bones form by endochondral and the flat bones by intramembranous bone formation. Some bones, like the clavicle have both kinds of bone formation. Both long and flat bones are organized with a hard, but relatively thin, outer region composed of dense, *compact* bone called the *cortex* or *cortical* bone. Inside the cortex is the marrow cavity containing hematopoietic elements, fat and spongy spicules of bone. The bone spicules are also referred to as *trabecular* or *cancellous* bone.

Parts of a Long Bone

Epiphysis: This term refers to the end of a tubular bone, lying between the physeal plate (in developing bone) and the articular cartilage (Fig. 1.1). In adults, the physeal plate is absent. The portion of the bone that the epiphysis would have occupied in the growing skeleton is arbitrarily referred to by the same name.

Physis or epiphyseal plate: The physis (growth plate) is the region of bone elongation in children. Injuries or other disruptions of the growth plate such as infections, can seriously affect the subsequent size and shape of the bone.

Metaphysis: This refers to the widened portion of bone occupying the area between the cylindrical diaphysis and the physis/epiphysis. Several tumors have an epicenter in the metaphysis.

Diaphysis (shaft): This refers to the middle, cylindrical portion of a tubular bone. There is a thick cortex surrounding a marrow space. The latter contains trabecular bone, hematopoietic elements and fat in varying compositions, the proportions of which change with age.

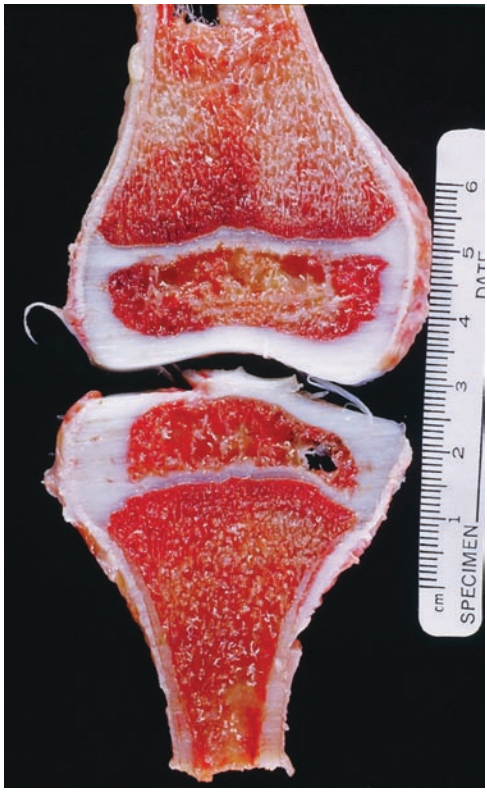

Fig. 1.1 The picture shows a cut section of the knee joint, with femur above and tibia below. Facing the centrally located joint space is the white articular cartilage of both bones (lining the femoral condyle and tibial plateau). Adjacent to this is the red marrow and trabecular bone of the epiphysis seen in both the bones. Immediately adjacent to the epiphysis is the physis (growth plate) visible in both these bones (indicating that the bones are from a skeletally immature individual). Moving further away from the physis is the metaphysis which gradually becomes the shaft or diaphysis of the bone. Surrounding the cancellous bone in all these areas is the cortex (a hard shell of compact bone). The cortex is in turn surrounded by a periosteum

Bone marrow: The medullary cavity is filled with varying proportions of hematopoietic marrow, fat and trabecular bone. The marrow is most prevalent in younger age groups and in the metaphyseal region of long bones. The diaphysis contains mainly fat in adults. In comparison to the appendicular (limb) skeleton, the axial skeleton has a greater proportion of bone marrow.

Periosteum: The periosteum is composed of an *outer fibrous* layer and an *inner cambium* (cellular) layer. The cambium layer is cellular and contains osteoprogenitor cells and fibroblasts. When tendons insert into bone, the collagen fibers (Sharpey's fibers) pass through the periosteum and then into the bone lamellae (see below).

Endosteum: The endosteum is composed of a resting layer of marrow at its interface with bone. This is not a morphologically recognizable layer of tissue at the light or electron microscopic level. It is, however, a convenient concept that explains the functional changes seen in physiologic and pathologic alterations in bone at the bone medullary cavity interface.

Microscopic Features of Bone

Microscopically too, bone tissue can be either compact (cortical) or spongy (trabecular or cancellous) (Fig. 1.2a, b) and can be classified based on collagen fibers arrangements into two different types: woven bone and lamellar bone (Fig. 1.3).

Woven (streamer/immature) bone: This form of bone consists of randomly oriented collagen fibers, with large numbers of osteoblasts (osteoprogenitor cells) alongside. Under polarized light it can be recognized as having a haphazard structure. It occurs in regions of rapid growth, such as in the growing skeleton especially in the embryo, fracture callus, fibrous dysplasia, osteosarcoma and several other tumors.

Lamellar bone: Lamellar bone is the mature form of adult bone. It is readily identified on polarized light microscopy as parallel lines of deposited bone. Studies have shown this bone to have a well-organized arrangement of collagen fibers. Lamellar bone is formed when the rate of deposition is slow. In general, it is formed only on pre-existing bone.

Secondary organization is a hallmark of lamellar bone. In the cortex, the lamellae are arranged in circumferential as well as tubular arrangements. The tubular arrangement is called an osteon. Under the microscope, these tubes can look like circles or parallel sheets depending on how they are cut to make histologic sections. The central part of the tube is the Haversian canal, which contains blood and lymphatic vessels and nerves. Bone cells called osteocytes are located between lamellae.

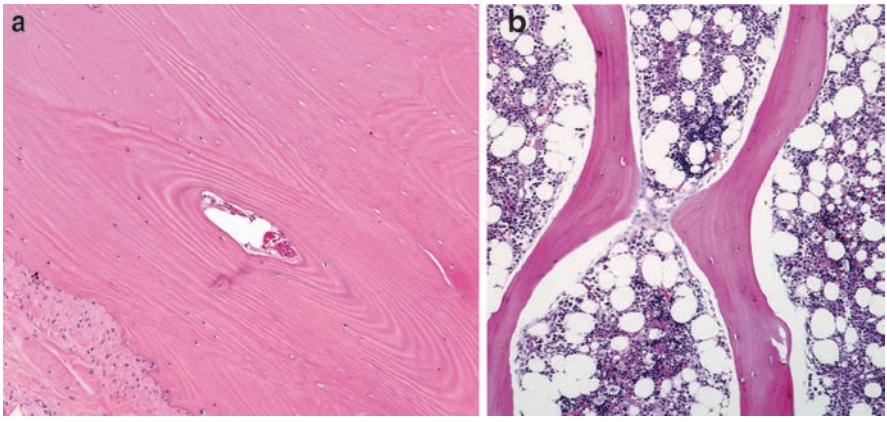

Fig. 1.2 (**a**) Microscopic section of dense (cortical or compact) bone from the cortex of a long bone. (**b**) Microscopic section of trabecular (cancellous or spongy) bone from the metaphysis of a long bone

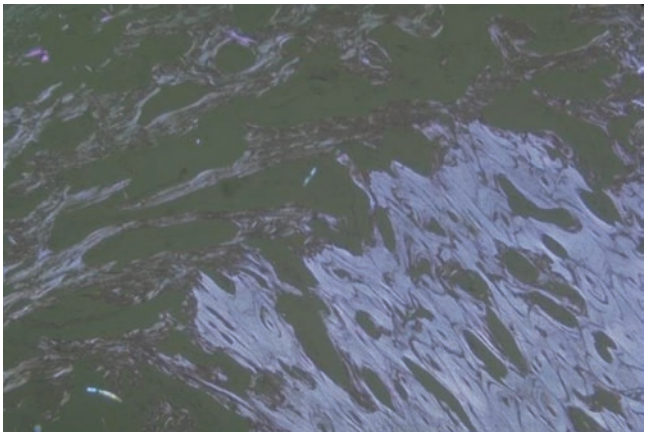

Fig. 1.3 A section taken from a bone undergoing Ilizarov distraction taken under semi-polarized light. The pre-existing cortical bone is of the lamellar type (with well organized lamellae) and emanating from this are woven bone streamers seen in the upper part of the picture

Blood Supply of Bone

Bone has a rich vascular supply. It receives 10–20% of the cardiac output. Blood supply varies with different types of bones. The diaphyseal nutrient artery is the most important supply of arterial blood to a long bone. This divides into an ascending and descending branch, which supply the inner two thirds of the cortex and medullary cavity. There are also numerous metaphyseal and epiphyseal arteries supplying the ends of bones. They arise mainly from the arteries that supply the adjacent joints. They anastomose with the diaphyseal capillaries and terminate in bone marrow, cortical bone, trabecular bone, and articular cartilage. In growing bones, these arteries are separated by the epiphyseal cartilaginous plates. Finally, periosteal arterioles are vessels that supply the outer layer of cortical bone. Blood is drained from bone through veins that accompany the arteries and frequently leave through foramina near the articular ends of the bones. Lymph vessels are abundant in the periosteum.

Nerve Supply of Bones

Nerves fibers accompany the blood vessels to the interior of the bones and to the perivascular spaces of the Haversian canals. The periosteal nerves are sensory nerves, some of which are pain fibers. Therefore, the periosteum is especially sensitive to tearing or tension. Accompanying the arteries inside the bones are vasomotor nerves, which control vascular constriction and dilation. Bone is also innervated by sympathetic fibers.

Bone Cells

The cells important in bone biology are osteoprogenitor cells, osteoblasts, osteocytes and osteoclasts. Osteoblasts and osteocytes, are thought to be derived from the primitive mesenchymal cells (the osteoprogenitor cells). Osteoclasts are thought to owe their lineage to cells of the hematopoietic bone marrow related to macrophages/monocytes.

Osteoprogenitor Cells

These are undifferentiated mesenchymal cells, and have the properties of stem cells, that is, the potential for proliferation and a capacity to differentiate. These cells have the potential to differentiate into osteoblasts, chondroblasts, bone marrow stromal cells, or fibroblasts depending on the nature of the stimulus, and perhaps the local microenvironment. They are present in the inner layer of the periosteum and the endosteum lining marrow cavities, osteonal (Haversian) canals and the perforating (Volkmann's) canals. Osteoprogenitor cells persist throughout postnatal life as bone-lining cells; they are reactivated in adults during the repair of bone fractures and other injuries.

Osteoblasts

Osteoblasts are derived from the osteoprogenitor cells. Osteoblasts have a cuboidal or columnar shape and vary in size from barely detectable by light microscopy to up to 50 μm when activated (Fig. 1.4). Osteoblasts produce collagen type I and glycosaminoglycans. The phenotype and morphologic characteristics of osteoblasts however depend on their stage of development and differentiation. Osteoblasts also secrete receptor activator of nuclear factor kappa B (RANK) ligand, a receptor important for the differentiation of osteoclasts (see below). Osteoblasts also secrete variety of collagenous and non-collagenous proteins such as osteocalcin, osteopontin, bone sialoprotien and osteonectin, as well as a variety of cytokines and colony stimulating factors (CSF), transforming growth factor-beta (TGF-β) and bone morphogenetic proteins (BMPs).

Osteoblasts respond to mechanical stimuli to mediate changes in bone size and shape. Perhaps this is modulated by a piezo-electric effect of the calcium hydroxylapatite crystal. Constant mechanical stress is essential for the maintenance of bone mass and strength.

Osteocytes

Osteocytes are cells within the substance of bone and are derived from osteoblasts. They are said to be involved in cell signaling and maintaining the viability of the bone matrix. It is possible, that these cells are important in the translation of mechanical loads to cellular events such as bone formation.

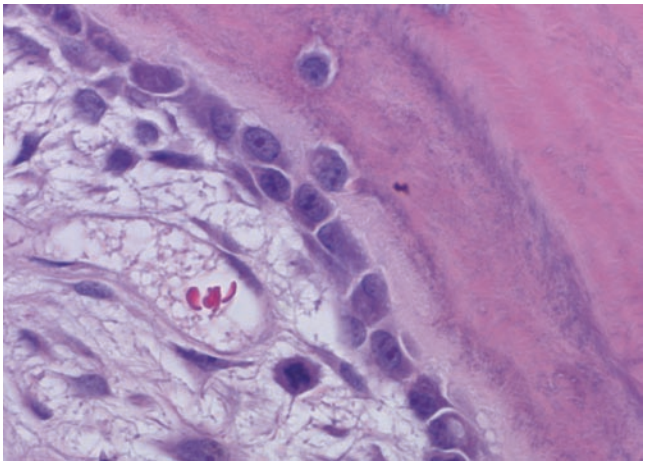

Fig. 1.4 Osteoblasts are seen lining woven bone. This is generally considered to be a "benign" feature and is seen in reactive woven bone and sometimes in benign bone tumors. Tumor bone as seen in osteosarcoma is generally devoid of lining osteoblasts of this type. This statement however should not be taken to be an absolute truth

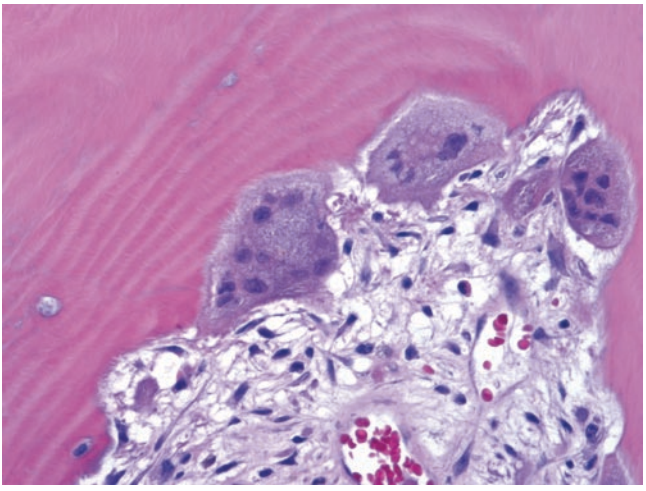

Fig. 1.5 Osteoclasts eroding bone in a patient with hyperparathyroidism

Osteoclasts

These are multinucleated cells with 2–100 nuclei per cell (Fig. 1.5). Osteoclasts arise from monocyte/macrophage hematopoietic progenitor cells. Their genesis requires a variety of hematopoietic cytokines, such as interleukins 1, 3, 6, and 11, tumor necrosis factor (TNF), parathyroid hormone (PTH), and 1,25-dihydroxyvitamin D_3. Calcitonin inhibits the formation of osteoclasts.

Osteoclasts are the primary bone resorbing cells: Osteoclasts are mostly found at sites where resorption is taking place, within "eaten out" cavities known as *Howship's lacunae*. The cells can tunnel through cortical bone creating channels. The cells are polarized (the nuclei congregate away from the resorbing bone surface). The cytoplasm of the cell between the nuclei and the ruffled border is rich in carbonic anhydrase and in tartrate resistant alkaline phosphatase (TRAP). By electron microscopy, there is an abundance of mitochondria, lysozomes and free ribosomes in the cytoplasm. Activated osteoclasts show an infolding of the plasma membrane (ruffled border). At the point where the cell membrane is close to the bone, a ring like perimeter called clear zone or sealing zone. This zone contains abundant microfilaments (actin filaments) but lacks other organelles. The formation of the sealing zone is a participation of actin filaments together with $\alpha_v\beta_3$ integrin. Into the space bounded by the ruffled border and bone, resorptive substances can be secreted .

Mechanism of osteoclast-mediated bone resorption: The mechanism of bone resorption involves protons (hydrogen ions) secreted by an ATP driven proton pump in the ruffled border of osteoclasts. The enzyme carbonic anhydrase II is essential in the generation of hydrogen ions. Simultaneously, acid hydrolases are released from lysosomes. Osteoclasts can move over the bone surface, creating many such resorptive pits. These pits are well visualized by scanning electron microscopy, and correspond to the Howships' lacunae in routine sections.

A combination of the acid created by the hydrogen ions, and the proteolytic enzymes, provides optimal conditions for the resorption of bone and degradation of collagen.

Osteoclasts have calcitonin (but not PTH or vitamin D) receptors. They are stimulated by IL-6 (perhaps in combination with IL-1, IL-3 and IL-11) and RANK-ligand. These cytokines are produced locally by cells of the osteoblast lineage under the influence of PTH, vitamin D_3, TGF-β, IL-1 and TNF. The regulation of osteoclast differentiation is a subject of intense ongoing study with implications for the treatment of a variety of diseases ranging from osteoporosis to skeletal dysplasias such as osteopetrosis. It involves numerous cytokines including macrophages colony-stimulating factor (M-CSF), RANK-ligand (present on osteoblasts), RANK receptor (present on osteoclast precursors) and osteoprotergrin (OPG), a decoy protein.

Bone Matrix

Bone matrix, consists of an organic and an inorganic or mineral component. Forty percent of the dry weight is composed of the organic component, called osteoid. This includes collagen, proteoglycans, glycoproteins, phospholipids and phosphoproteins (Table 1.1).

The inorganic component makes up the remaining 60% of the dry weight of bone and is composed primarily of calcium hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$.

Table 1.1 Bone proteins

Collagens
Type I collagen – woven and lamellar bone
Type II collagen – cartilage
Type III collagen found in certain pathologic conditions
Non collagenous proteins (synthesized mainly from osteoblasts)
Calcium binding – osteonectin, bone sialoprotein
Adhesion proteins – osteopontin, fibronectin, thrombospondin
Mineralization proteins – osteocalcin
Enzymes – collagenase, alkaline phosphatase, metalloproteinases
Cytokines – PG, IL-1 and -6
Growth factors – IGF-1, TGF-β, PDGF
The hydrated (muco)polysaccharide gels

Collagen

Connective tissues contain varying amounts of collagen, elastin (a related fibrous protein) glycosaminoglycans and proteoglycans. Of these, collagen is the most abundant.

Several different types of *fibrillar, basement membrane and short chain* collagens are recognized. These are the types I to XIII collagens. Type I collagen is found in bone, skin, meniscus, tendon, ligament, annulus fibrosis and joint capsules. Type II collagen is located mainly in hyaline cartilage, the vitreous humor of the eye and the nucleus pulposus of the intervertebral disk. The other fibrillar collagens are the "minor" collagens, Type III occurs in association with Type I and also in tissue undergoing repair.

Urinary excretion of hydroxyproline (found exclusively in collagen) and other products of collagen degradation (cross-linked products such as pyridinoline and deoxypyridinoline), act as a marker for collagen breakdown. These measurements reflect the amounts of bone turnover.

Enzymes

Alkaline Phosphatase

Although not generally thought of as a matrix component, this enzyme is an osteoblast product (such as osteocalcin and osteonectin). There are three related isozymes that are tissue related and are associated with three separate genes. These are the *placental, intestinal and tissue nonspecific* forms. The last is seen in high levels in a variety of tissues such as bone, liver, kidney and skin. The form of enzyme, which is important in bone, is the tissue non-specific form.

The role on alkaline phosphatase in biomineralization is still speculative. Serum alkaline phosphatase activity is increased in growing children, pregnancy, healing fractures, Paget's disease, rickets, osteomalacia, hyperparathyroidism, bone-forming tumors and certain skeletal metastases. It is reduced in hypophosphatasia.

The Hydrated (Muco)Polysaccharide Gels

The functional units of bone extracellular matrix "gels" are the glycosaminoglycans (GAGs). Of the several GAGs, four main groups are present. Hyaluronic acid, chondroitin and dermatan sulfates, heparan sulfate and heparin, and keratan sulfate. The majority are aggregated to a protein core to form a *proteoglycan*. Prior to release from the synthesizing cell, GAGs (except hyaluronic acid) are sulfated. This step allows a net negative charge on these molecules. In turn, this charge serves two functions. Firstly it keeps the molecules extended, increasing the volume to weight ratio. Secondly, by attracting osmotically charged cations, it attracts water. This mechanism creates a gel with very high swelling pressures and tremendous resistance to compression.

The highly viscous hyaluronic acid is a major constituent of synovial fluid, where it helps in lubrication. Additionally, it may impede bacteria, by its physical and chemical properties.

Factors Important in Mineralization

Collagen	Collagen provides oriented support for the newly formed crystals. The post-translational changes in collagen type I make it possible for diffusion of large hydrated ions such as calcium phosphate into the fibril.
Calcium binding proteins	Phosphoproteins and sialoproteins in the bone matrix may bind calcium to promote crystal deposition and growth, thus acting as nucleators. Crystal growth could then depend upon the conformational change in these proteins after deposition. The initiation of mineralization is coincident with the deploymerization of proteoglycan molecules. Proteoglycans may inhibit calcification by a number of mechanisms including shielding of collagen, chemical interaction with collagen side chains, sequestering calcium or phosphate ions or occupying critical space in the molecule. Different phosphoproteins have varying importance in mineralization.
Pyrophosphate	This is a naturally occurring inhibitor of calcification. It has a short half-life due to its rapid degradation by pyrophosphatases. Pyrophosphates are present in body fluids and increase the stability of the solution phase of calcium phosphate. Diphosphonates are pyrophosphate analogs, and are powerful inhibitors of calcification in large doses.
Bone Gla proteins	Osteocalcin is a highly conserved protein which is abundant in the bone matrix. Because of the Gla residues, it is able to bind calcium however its role in mineralization is controversial.
Lipids and proteolipids	Within bone there are acid phospholipids that form complexes with calcium phosphate and could thereby influence mineralization. These substances have the capacity to bind to calcium.

Alkaline phosphatase	This is an ectoenzyme produced by osteoblasts and is likely to be involved with the mineralization process. Patients with decreased amounts of enzyme (hypophosphatasia) have impaired mineralization (see rachitic syndromes in metabolic bone disease). Alkaline phosphatase may be involved in the degradation of inorganic pyrophosphate, thus providing a sufficient level of organic phosphate for mineralization to proceed.

The Regulation of Bone and Cartilage

Bone is regulated by hormones (such as parathyroid hormone, calcitonin, vitamin D, vitamin A, estrogens, androgens and growth hormone. It is also under the influence and regulation of many paracrine and autocrine factors such as proteoglycans, glyco and phosphoproteins, gama-carboxyglutamic acid proteins, preteolipids, growth factors and cytokines such as interleukins.

Parathyroid Hormone

Parathyroid hormone (PTH) is an 84 amino acid, single chain polypeptide (called PTH 1-84). It is synthesized in the parathyroid gland from a biosynthetic precursor pro-PTH. PTH acts on bone, intestine and kidney. In the latter two it enhances calcium resorption. It is also involved in the metabolism of phosphate, bicarbonate, ammonium, magnesium and in the regulation of acid–base homeostasis in the body. The action of PTH are influenced by several factors such as 1,25-dihydroxyvitamin D_3, IL-1, TGF-α, and EGF. The production of several of these substances is in turn under the control of PTH in a complicated interrelated web.

The best known effect of PTH is osteoclast activation and subsequent bone resorption. Receptors for PTH are found on pre-osteoblasts, osteoblasts and chondrocytes. They are not, however present on osteoclasts. This supports the notion, that the action of PTH on the latter is dependent on the osteoblasts. This effect is mediated via substances such as IL-1, IL-6 and prostaglandins of the E series. The net result is osteoclast activation and the initiation of bone resorption leading to calcium release from bone.

Additionally, there is evidence to suggest, that in certain situations PTH stimulates bone formation. When administered continuously, it increases osteoclastic resorption and suppresses bone formation. When administered in low doses, intermittently, it stimulates bone formation without resorption. This bone forming effect of PTH has been termed the anabolic effect. This anabolic effect too (like the resorptive effect) is probably indirect, and mediated via substances such as IGF-1 and TGF-β.

Calcitonin

Calcitonin peptide hormone produced by the thyroid parafollicular C cells. Its synthesis and secretion is under the influence of extracellular calcium levels, and certain gastrointestinal hormones such as gastrin. It is encoded by a complex gene that undergoes alternate splicing. This gene is responsible for several other peptides such as a calcitonin gene related peptide.

Calcitonin causes a short lived fall in plasma calcium. It acts via a receptor to stop the resorption of bone. These receptors are present on osteoclasts, preosteoclasts, monocytes and certain tumor cells. The major effect on blocking of bone resorption however is probably via the mature osteoclast. The mechanism of action is via enhancement of adenylate cyclase and stimulating cAMP accumulation. There may likewise be a mitogenic effect of calcitonin on bone cells. Calcitonin also promotes renal calcium excretion. Its effects on calcium homeostasis are lost after 24–48 h. This loss of effectiveness can be reduced by simultaneous administration of corticosteroids. A possible role in the body is to maintain normocalcemia after a large calcium containing meal.

The absence of significant changes in bone mineral density caused by decline or overproduction o calcitonin in humans has raised the question, whether the pharmacological action of calcitonin as an inhibitor of bone resorption is also of physiological relevance.

Calcitonin has a role in the therapy of hypercalcemia of malignancy, in Paget's disease and in osteoporosis. In this reference it should be mentioned that there is evidence to suggest that the osteoclasts of Paget's patients are hyperresponsive to calcitonin, and do so for longer periods of time than do control cells. The molecular mechanisms for this hyperresponsivity is unknown.

Vitamin D

Ergosterol and 7-dehydrocholesterol are the precursors for this hormone/vitamin. These compounds are stored in the skin, transported in the body via an alpha-globulin binding protein or vitamin D binding protein (DBP) and become activated by ultraviolet light of 315 nm. This activation generates calciferol and cholecalciferol respectively. These substances are hydroxylated in the liver to yield 25-hydroxy-vitamin D in the presence of magnesium, and then converted further in the proximal tubule of the kidney to its active form: 1,25-dihydroxyvitamin D. This hormone/vitamin is one of the prime controllers of calcium metabolism in the gut, proximal tubule and bone. Reduced calcium and increased PTH are the signals for increasing 1,25-dihydroxyvitamin D production.

The action of 1,25-dihydroxyvitamin D include stimulation of calcium binding proteins, effect on osteocalcin production, osteoclastic resorption, monocytic maturation, myelocytic differentiation, skin growth and insulin secretion. Lack of vitamin D results in impaired mineralization of newly formed bone – the clinical disease resulting from this is known as rickets in children, and osteomalacia in

adults. In both these conditions, the proteinaceous bone matrix accumulates, but does not mineralize. Excess of vitamin D leads to increases in bone resorption and hypercalcemia.

The action of vitamin D is via the vitamin D receptors. Receptor sites of 1,25-dihydroxyvitamin D have been identified on several cells. Gene errors in several forms of rickets have been found to occur within these nuclear receptors. There is also a suggestion that postmenopausal osteoporosis may be genetically predetermined by the polymorphisms present on the vitamin D receptor gene.

Vitamin A

Retinoids, in excess, decrease the formation of bone and cartilage matrix. A deficiency of vitamin A has the opposite effect. Several years ago, it was discovered that an imbalance of vitamin A during embryonic development has dramatic teratogenic effects. These effects have since been attributed to vitamin A's most active metabolite, retinoic acid (RA), which itself profoundly influences the development of multiple organs including the skeleton. Retinoid signaling involves several components, including the skeletogenic master regulatory factors, Sox9 and Cbfa1.

Estrogens

In experimental situations, reduced estrogen leads to bone loss. This may be a direct effect on osteoblasts and possibly osteoclasts, although it could be mediated via PTH and calcitonin.

Androgens

These act to maintain bone mass through action via receptors on osteoblasts. There is an inhibition of the action of PTH and calcitonin.

Growth Hormone

The effect of growth hormone on bone is mostly mediated via insulin like growth hormone (IGF). There may however be a direct effect through growth hormone receptors on osteoblasts and chondrocytes.

Proteolipids

These are membrane proteins complexed with acidic phospholipids. They cause hydroxyapatite deposition. They have a high concentration in the matrix vesicles,

where they are thought to have a role in the export of protons and the import of calcium and phosphate.

Growth Factors

Transforming Growth Factor-Beta

Initially isolated from "transformed" neoplastic cells in tissue culture studies. Two "factors" were isolated and named TGF-α and -β. TGF-α is not found in bone and is now called epidermal growth factor. TGF-β is one of five closely related compounds that include the bone morphogenetic proteins. There are three human isoforms, the largest store being in bone matrix. The current hypothesis is that TGF-β induces bone formation during remodeling. The action of TGF-β in bone induction may however be only in conjunction with other factors such as the BMPs.

Bone Morphogenetic Proteins

A bone inducing principal was first postulated in 1952 by Marshall Urist et al. Since then, at least ten proteins with this property have been extracted from *demineralized bone*, the amino acid sequence has been characterized and synthesized by recombinant DNA technology. These have been named bone morphogenetic proteins 1–10. Purified BMPs have been used to promote bone repair. Several trials have shown their efficacy in experimental models.

Other Growth Factors

These include insulin like growth factors, epithelial growth factor, acid and basic fibroblast growth factors and platelet derived growth factors (A and B). They are thought to be particularly important in bone remodeling. PDGFs are heterodimers of A and B chains, and function via specific receptors. Mutations in the fibroblast growth factors have thought to play a role in certain kinds of skeletal deformities, including achondroplasia, Apert's syndrome, Cruzon syndrome, Pfeiffer syndrome, and the Jackson–Weiss syndrome.

Prostaglandins: Prostaglandins have been shown to have multiple effects on bone cells, and sometimes opposite effects on different species. They are powerful bone resorbers in certain culture studies (especially true of the E series). Prostaglandins are produced by monocytes under appropriate stimuli. It is possible that part of the effects of interleukins are mediated by prostaglandins.

IL-6: This is produced by osteoblasts and bone marrow stromal cells in response to PTH, vitamin D_3, TGF-β, IL-1 and TNF, etc. Human osteoclastoma cells respond to this cytokine. It is still unclear, whether normal mature osteoclasts respond to

IL-6. It has a pathogenetic role in diseases such as multiple myeloma, Paget's disease, rheumatoid arthritis and Gorham's disease (vanishing bone disease). Experimentally, estrogens and androgens inhibit the production of IL-6 by osteoblasts, and additionally, there is evidence to suggest that osteoclastic activity may be inhibited by anti IL-6 antibodies.

Mechanosensory Systems and Stretch Studies (Wolff's Law)

Wolff's law: Every change in *form and function* of bones, is followed by changes in *the internal architecture and external conformation*, in strict accordance with mathematical laws (Julius Wolff, 1882).

Wolff's law has been confirmed by experimental studies. However only recently have there been studies to investigate the basis of the law at *a molecular level*. It is clear, that mechanical forces have some definite effects on the skeleton. For example, individuals who lift weights tend to develop bigger and stronger bones. If use of a limb is stopped, it undergoes "disuse" osteoporosis. Children with malunited limb fractures, frequently remodel into almost normal bones. If, on the other hand, they are unable to bear weight, or use the limb owing to a disease such as poliomyelitis, then the limbs stay malunited. Paraplegics or quadriplegics with a spastic form of paresis have exuberant callus, if however, they have a flaccid paresis they fail to develop such an exaggerated response. Weightlessness in space causes rapid decrease in bone mass reflecting the need for constant force in maintaining skeletal bone.

All these examples illustrate the close linkage of mechanical forces with skeletal response and bone formation. What is poorly understood however is how forces get translated into cellular events. It is likely, that signaling mechanisms, such as electricity or chemical messengers, such as certain cytokines mediate these responses. Investigations into the mechanisms have suggested the presence of stretch sensitive ion channels and stretch dependent DNA synthesis in certain cells. Additionally, there are stream generated potentials are created when fluid flowing through the matrix carries along a species of ion and a "piezo-electric" effect as a result of compression of the hydroxyapatite crystal – all various methods by which Wolff's law might operate.

Suggested Readings

Principles of Bone Biology, Edited by John P. Bilezikian, Lawrence G. Raisz and Gideon A. Rodan. Academic Press, 1996

Histology for Pathologists, Third edition, Edited by Stacy E. Mills. Lippincott Williams and Wilkins (Wolters Kluwer), 2007

Chapter 2
Common Problems in Orthopedic Pathology Including Trauma, Reactive Conditions and Necrosis of Bone

Jasvir S. Khurana and Edward F. McCarthy

The pathology and pathophysiology of bone healing is important from several aspects. For the surgical pathologist, it is critical to be able to distinguish normal fracture healing in bone from disordered healing and from bone neoplasms. For the orthopedic surgeon and the scientific investigator, the histologic appearances of healing allow a qualitative and quantitative assessment of the process. This permits, for example, the comparison of different methods of treatment. Additionally, an understanding of the cellular signals operating in bone healing, allows the clinician to manipulate and promote or modify osseous union.

Healing of Bone

Traumatic disruption of bone, such as in fractures or surgical osteotomies, can have several different end points. The result is dependent on the mechanism of disruption, the pattern of fracture/osteotomy, the type of fixation utilized and the mechanical and biologic environment to which the bone is subject. For instance, fractures under semi-rigid conditions go on to form an external and internal callus and re-unite via a cartilage model. Under several unfavorable conditions (for example: interposed soft-tissues, avascularity, excessive motion, presence of a foreign body, tumor or infection), this process may get disrupted and go on to "nonunion." Under rigidly fixed conditions, there may be no visible external callus and no transitional cartilage formation. If there are tensile forces acting such as in callotasis, or distraction osteogenesis, then a different sequence of events follows. The cellular mechanisms that operate in these different situations have only recently begun to be elucidated.

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Fracture Union

Under semi-rigid conditions there are three recognizable stages of healing. These are termed the inflammatory, reparative and remodeling stages. With disruption of the blood supply, and the formation of a hematoma at the fracture site, there is a variable amount of necrosis of tissues in the immediate vicinity of the fracture, the start of the inflammatory stage. Blood and plasma infiltrate the surrounding tissues which become swollen and friable. The necrotic tissue chemotactically attracts primitive mesenchymal elements, which differentiate into osteoblasts and chondrocytes. These produce collagen II and collagen III, contributing to the external callus. This is the start of the reparative stage. The majority of the proliferating osteoblasts appear to localize under the periosteum with a smaller number at the endosteum. Depending upon how much movement there is between the fragments, a variable amount of cartilage is formed (Fig. 2.1). Soon thereafter, collagen I predominates. At this point, the two collars of bone from each fractured end of bone advance towards each other and a "bridge" of initial union is complete (external callus). The cartilage of the initial callus is completely replaced by a bone. This is referred to as the remodeling stage. The internal callus (endosteal callus) is the chief source of union between the fragments as the external callus disappears. This callus is predominantly made up of woven bone and the collagen species localizable is collagen I. With the passage of time, the entire callus gets remodeled, and woven bone gives way to mature (lamellar) bone.

Under conditions of rigid internal fixation, repair occurs by the internal (endosteal) callus alone. The kind of union seen in rigidly fixed fractures resembles

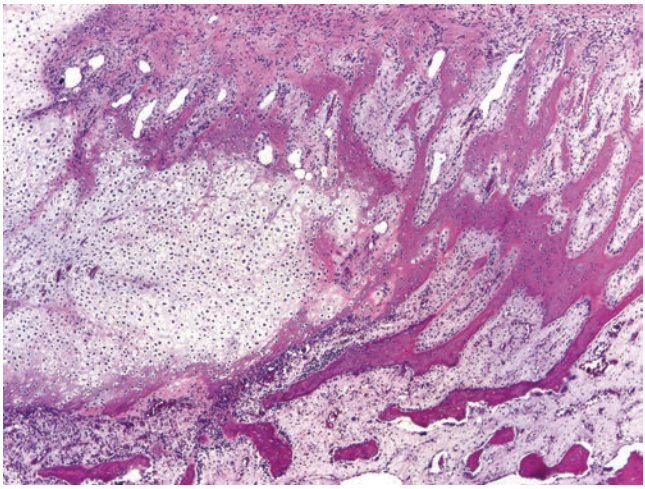

Fig. 2.1 Fracture callus showing reactive woven bone and cartilage. The presence of cartilage indicates that some amount of motion has occurred between the fragments. In completely immobilized fractures (such as after compression plating) there is no cartilage and union is by direct conversion of fibrous tissue at the endosteum to bone (primary union)

the physiologic process of remodeling. It is important to note that bone resembling native bone histologically does not automatically translate into strong union biomechanically. There may be a certain time lag when this callus consolidates and achieves the strength of original bone.

Complications

Nerve and vascular injuries can occur at the time of initial injury, during closed reduction maneuvers, and during operative fixation. Blood loss externally or internally into the fracture hematoma is common in the orthopedic trauma patient. Compartment syndrome is a condition in which the pressure within a tissues that are tightly enclosed within a fascia or bone boundary (compartment) rises to a level that decreases the perfusion gradient across tissue capillary beds, leading to cellular anoxia, muscle ischemia, irreversible muscle damage. Fat embolism is the extravasation of fatty marrow into the venous system upon fracture and can be worsened during introduction surgical instruments and implants into the intramedullary canal. Deep venous thrombosis (DVT) is quite prevalent in patients admitted for orthopedic fractures and, like fat embolism, it can be fatal. Nonunion is the absence of bony union within a defined amount of time. Typically this is 6 months, but can be up to a year for certain fractures such as the femoral neck fracture. Two types of nonunion exist. Atrophic nonunions occur when little or no callus is formed and are often attributed to a lack of blood supply. Hypertrophic nonunions are characterized by a large volume of callus without union. These often develop due to inadequate fixation and motion that exceeds the limit required for bony union. Several adverse conditions can occur that delay or prevent union. These conditions include the presence of an extensive gap between the fragments (or interposition of soft-tissues), loss of blood supply, or abnormal biomechanics such as increased mobility or the presence of shearing forces. Additional problems may be contributory to these such as infection or a pathologic fracture, extensive comminution or the presence of a systemic metabolic disturbance. Malunion is bony union with a deviation from the anatomic length, alignment, and rotation. Infection is a risk in open fractures and in operative fixation of fractures. Reflex sympathetic dystrophy and heterotopic bone may occur and are discussed below.

Distraction Osteogenesis (Callotasis/Ilizarov Lengthening)

This is a technique of achieving bone transport or lengthening. The technique involves, creating a cortical disruption (often with preservation of the endosteum), waiting for a primary callus to form, and then gradually moving the two ends of the bone away. This results in an increase in length of the bone and its' surrounding soft-tissues. An important histologic difference from fracture healing is the absence

of cartilage formation in distraction osteogenesis. In fact, if the pathologist visualizes cartilage, it can be inferred that instability of the construct or fracture of the regenerate bone may have occurred.

Heterotopic Ossification

This refers to the presence of bone formation within the soft-tissues. It is to be distinguished from the metastatic calcification that occurs in conditions such as hyperparathyroidism. It must also be distinguished from traumatic ossification (myositis ossificans). The site of most concern to the orthopedic surgeon is the hip, in the context of post-operative ossification following total hip arthroplasties. The prevalence of heterotopic ossification varies from 2 to 90% depending upon the population operated and the diagnostic criteria used. Severe heterotopic ossification results in restriction of movement and an unsatisfactory result.

Myositis Ossificans

This is a time honored term, and continues to be used despite being neither a muscle nor an inflammatory disorder. It refers to the reaction to trauma, seen most often in soft-tissues, but also in a subperiosteal location (subperiosteal hematoma). The entity most often represents a localized tissue disruption, followed by a hematoma. This hematoma gets organized in a fashion similar to a healing fracture. Ossification commences from the outside to within. Eventually, the entire mass may get ossified. From the point of the surgical pathologist, the diagnosis of this lesion can present a problem, since it generally present as a painful mass and is biopsied under the clinical impression of it being a soft-tissue tumor. In these situations the central fibroblastic repair reaction can be alarming.

Mistakes can be avoided by paying attention to the characteristic radiologic and histologic clues. By CT scan, it is often possible to see a peripheral rim of bone formation (Fig. 2.2). This sign may be absent very early or very late in the evolution of the lesion. When present, however, it is a valuable sign and serves to differentiate it from bone forming tumors such as extraskeletal osteosarcomas. Osteosarcomas however tend to have bone formation centrally or more haphazardly placed.

Histologically, myositis shows a zonation phenomenon. This corresponds to the peripheral rim of ossification seen radiologically, and is its microscopic equivalent. The finding of mature tissues situated in an organized fashion on the outer side of the lesion, with a fibroblastic or immature, reactive, spindle-cell center is extremely suggestive of myositis ossificans (Fig. 2.3). The center of the lesion can be alarmingly cellular and mitotically active. There may also be scattered osteoclast like giant cells and extravasated blood similar to a solid aneurysmal bone cyst. Recent studies show that there might be a deeper relationship

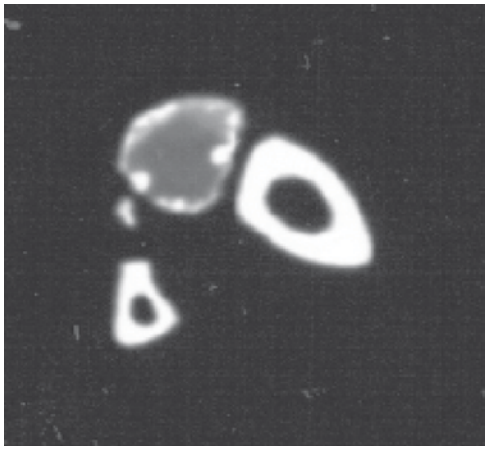

Fig. 2.2 A peripheral rim of bone is seen around a soft-tissue mass. The radiological features are characteristic of myositis ossificans. Extra-skeletal osteosarcoma would not show this zonation

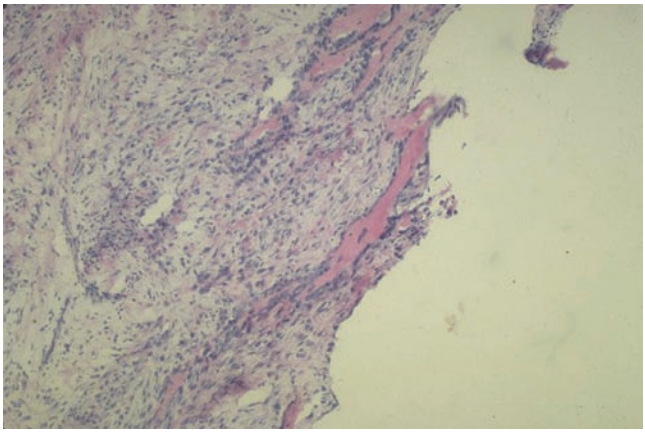

Fig. 2.3 Photomicrograph from a frozen section slide of a case of myositis ossificans showing a very cellular center and woven bone in the periphery (the histological equivalent of zonation). Biopsies taken from the center run the risk of misinterpretation as malignant if they are taken out of context

between these two entities, in that, some cases from both lesions have shown translocations involving the USP 6 gene.

Reflex Sympathetic Dystrophy (Sudeck Dystrophy or Algodystrophy)

This term refers to a condition of severe regional, patchy, osteopenia and often pain, following trauma. The condition is associated with trophic skin changes (such as hair loss and shiny skin), edema of the extremity and psychological disturbances in

the afflicted patients. Most often, a peripheral portion of an extremity is involved (hand or foot), but proximal parts of the appendicular skeleton, and the axial skeleton are not immune. Occasionally, the condition can arise in the absence of trauma, and rarely, in association with pregnancy. The condition is infrequent, and afflicts a minority of post-trauma patients, but can prove severely disabling.

Reflex sympathetic dystrophy must be differentiated from other forms of osteopenia such as bone marrow edema, transient osteoporosis, migratory osteolysis and idiopathic regional osteoporosis. These latter entities are benign, self-limited forms of osteopenia that are not accompanied by loss of function of the limb, or by pain. The underlying path-physiology, however may perhaps be related. In cases where this condition is suspected, MR imaging can prove a sensitive tool for early detection (loss of signal on T1 weighted images, along with an increased signal on T2 weighted images). Rest, analgesics, sympathetic blockade and core-decompression have been used to treat the condition. Histologically, there is a proliferation of fibroblasts within the marrow space, but there is little that is characteristic or diagnostic of the condition. Some authors have noted bone necrosis and new bone formation as well.

Bizzare Parosteal Osteochondromatous Proliferation (BPOP or Nora Lesion)

BPOP is an exophytic outgrowth from the cortex, consisting of a mixture of cartilage, fibrous tissue and bone. The lesion is clinically benign, but microscopically disturbing. The lesions have a predilection for the bones of the hands and feet. There is a wide age range, but most cases are in the third decade.

Radiologically, the outgrowth mimics an osteochondroma or a parosteal osteosarcoma, in that it arises directly from the cortex, and has an identifiable pedicle. The lack of continuity with the cortex helps distinguish it from an osteochondroma. The lesions range from about 0.5 to 3.0 cm. The location of the lesion, when present in the hands or feet, is away from the nail-bed. This helps to distinguish it from a subungual exostosis.

Grossly, the lesions have a stalk and may have a well-defined cartilage cap. The mass may sometimes show lobulations. Microscopically, there is a mixture of cartilage, bone and spindle cells. The cartilage may form a cap and is often very cellular, with enlarged, bizarre nuclei. The chondrocytes often show bi- or multinucleation. The interface with the underlying bone is irregular and there is an admixture of bone and cartilage prominent at this junction. At times, there is no cap, and the cartilage is admixed with bone and the spindle cells. The bone may show considerable osteoblastic prominence, and is more irregular than what is typically seen in osteochondromas. A helpful feature, in the diagnosis, is the blue tinctorial quality of the bone in routine sections (Fig. 2.4). Fibrous tissue and osteoclast type giant cells may be intermixed.

Myositis ossificans and fracture callus are other entities that enter the differential, but unlike Nora's lesion these show a well defined pattern of zonation.

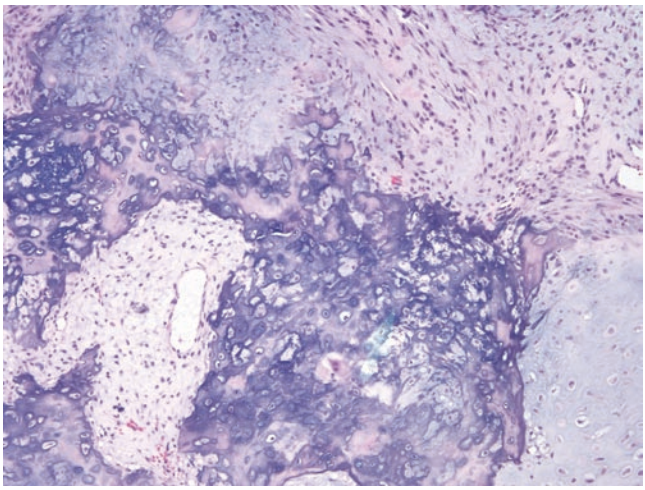

Fig. 2.4 Nora lesion (BPOP) showing a mixture of blue bone, fibrous tissue and cartilage

Parosteal osteosarcoma is an important differential to exclude. However, parosteal osteosarcomas are extremely infrequent in the bones of the hands and feet. More importantly, they show a mild spindle cell atypia which is not seen in Nora lesion. Moreover, parosteal osteosarcomas often have a parallel arrangement of trabecular bone, a feature very different from Nora lesion.

Management: Marginal excision suffices in most cases. Recurrences should be treated with wide excision.

Osteonecrosis

Osteonecrosis (bone infarction) results from the interruption of the blood supply of bone. Three mechanisms may cause this: First, bone may be deprived of blood vessels due to an infiltrative process such as secondary infection of a fracture. Second, trauma may disrupt blood vessels. Third, there may be intra-vascular coagulation.

Trauma may interrupt the blood supply in two manners. First, necrosis may follow displaced fracture, such as femoral neck fracture in which the blood supply through the posterior retinacular vessels (branches of the profunda femoris) is directly damaged either by tearing of the vessels or by compression. Second, severe joint trauma may shear off a portion of articular cartilage and bone, a condition known as osteochondritis dissecans.

The second form of traumatic bone death, osteochondritis dissecans, affects adolescents. In this disorder, joint trauma shears from the joint surface a portion of articular cartilage and underlying bone, together known as an osteochondral fragment. The trauma, probably an excessive rotary force, usually detaches the osteochondral

fragment from the bone, and it becomes a loose body in the joint cavity. Occasionally, however, the fragment remains partly attached.

In addition to infiltrating processes and trauma, primary intra-vascular occlusion also causes segmental bone death. The resulting changes are known as osteonecrosis or bone infarction. Until a few years ago, this disorder was called aseptic necrosis or avascular necrosis (AVN). However, the preferred term currently is the more encompassing term osteonecrosis. Osteonecrosis of bone is a process similar to infarction in other organs such as the heart or brain. Unlike infarcts in other organs, however, which are usually caused by atherosclerotic occlusion of arteries, bone infarction results from intravascular coagulation in small arterioles or venules. It is a common disorder and often leads to significant disability.

Osteonecrosis can occur anywhere in any bone. However, the subchondral areas of bone are predilected because these regions have little or no collateral circulation. The most common site is the femoral head, but the distal femur, proximal humerus, talus, and scaphoid are also frequently involved (Fig. 2.5). In addition to subchondral regions, the medullary canal in the shafts of long bones, particularly the femur and tibia, may also become infarcted.

Osteonecrosis rarely occurs in a healthy patient; usually an underlying medical problem is present. These problems include previous steroid therapy, alcoholism, sickle cell disease, dysbarism (decompression sickness), and Gaucher disease.

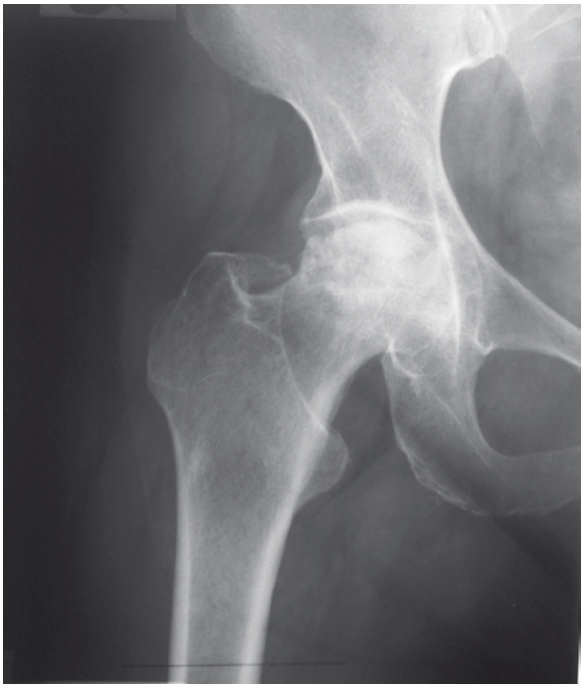

Fig. 2.5 Plain radiograph of osteonecrosis of the femoral head. The infarct shows segmental collapse and compression into the lower part of the femoral head

Bone infarction unassociated with an underlying disease was formerly called "idiopathatic" avascular necrosis. However, the idiopathic category is shrinking because close investigation of affected patients often reveals preexisting, but not clinically obvious, abnormalities. For example, many patients with so called "idiopathic" necrosis have been found to have hypercoagulable blood.

The initial pathophysiologic events leading to osteonecrosis depend on the underlying disease state. However, the various underlying diseases all lead to a final common pathway: focal intravascular coagulation, either in terminal arterioles or postsinusoidal venules.

Many predisposing factors lead to the final common pathway of intravascular thrombosis. These factors include vascular stasis, fat embolism, and hypercoagulability of blood. In addition, increased intraosseous pressure due to fat swelling or marrow edema also compromises blood flow.

The first factor, vascular stasis, contributes to the development of most bone infarcts. The microanatomy of the blood supply to the ends of long bones predisposes to vascular stasis. For example, the subchondral bone of the femoral head, the most common site of osteonecrosis, is supplied by endarterioles. Because the ends of long bones are encased by articular cartilage, there is almost no collateral circulation to these areas. In the femoral head, the endarterioles blend into vascular arcades which make 180° turns beneath the subchondral plate. This microanatomy favors vascular stasis and predisposes to fibrin thrombosis.

The next predisposing factor, fat embolism and hyperlipidemia, plays a major etiologic role in many cases of osteonecrosis. In these cases, fat emboli to subchondral bone may be the initial event which triggers intravascular coagulation. The fat emboli may originate by several mechanisms – disrupted marrow fat, mobilization of fat from a fatty liver, or coalescence of serum lipids. Whatever their origin, the fat emboli are trapped in the endarterioles of subchondral bone where they damage the endothelium and initiate the clotting cascade.

Increased intraosseous pressure, well documented in osteonecrosis of the hip is another important contributing factor to bone infarction. When caused by bone marrow edema or hemorrhage, increased intraosseous pressure probably occurs secondarily in all cases of osteonecrosis and further compromises blood supply. However, in certain circumstances, such as fat cell swelling secondary to steroid therapy, the increased intraosseous pressure may be the primary cause of bone death. Just as steroids cause fat swelling in the face and trunk (so-called "cushingoid" features), they also cause swelling of bone marrow fat cells. However, fat swelling in the rigid, non-expansile compartment of bone increases the intraosseous pressure and compresses the microvasculature. The local bone architecture may exaggerate this effect. For example, trabecular bone is most concentrated in weight-bearing, subchondral areas. Therefore, these areas are the most rigid and are the most susceptible to damage by increased intraosseous pressure. Indeed, osteonecrosis is most common in these weight-bearing areas, e.g., the antero-lateral portion of the femoral head.

A final systemic factor which may predispose to bone infarction is hypercoagulability of blood, a finding in many patients who develop osteonecrosis. Altered hemostasis and capillary sludging was first described in patients with osteonecrosis

in 1970. More recently, specific syndromes of congenital and acquired hypercoagulability have been documented. Among these syndromes are protein C and protein S deficiency. Reduction of these proteins, which are inhibitors of the clotting cascade, causes hypercoagulability and a tendency for thrombosis to occur. These conditions are not uncommon. For example, protein C deficiency, an autosomal dominant disorder, may be present in as many as 1 in 60 adults. Blood hypercoagulability may also be caused by hypofibrinolysis, a condition which may be either congenital or acquired. Congenital hypofibrinolysis, a familial disorder, is due to high levels of plasminogen activator inhibitor. Acquired hypofibrinolysis occurs in several conditions, such as pregnancy or certain malignancies. Various hypofibrinolytic syndromes have, in fact, been documented in patients with osteonecrosis.

Osteonecrosis occurs more frequently in certain clinical settings: alcohol abuse, steroid therapy, sickle cell disease and dysbarism. Of these alcoholism and steroid therapy account for 90% of the reported associated conditions. Alcoholism may even account for some of the remaining 10% of cases because some patients give an inaccurate drinking history.

In addition to alcoholics, patients receiving steroids are also at risk to develop osteonecrosis. As with alcoholism, many of these patients are predisposed to fat embolism secondary to fatty liver or hyperlipemia, both known complications of steroid therapy. The risk of bone necrosis correlates with the amount of steroids. However, a critical dose level that correlates with an increased risk of necrosis is difficult to establish.

Persons who work in environments of compressed air, such as divers and caisson workers, are also predisposed to bone infarction. Rapid return to normal atmospheric pressure results in dysbarism and, occasionally, bone infarcts. Osteonecrosis in compressed air workers is initiated by the formation of nitrogen bubbles in tissue. Rapid decompression allows nitrogen, which has been dissolved in the tissues, to come out of solution and form bubbles. Bubbles which form in the marrow cavity disrupt fat cells and lead to fat embolism.

Bone necrosis has also been reported in many of the common variants of the sickle cell disorder. The sickled erythrocytes cause capillary sludging and vascular thrombosis. Infarcts are most common in SC disease, occurring in 20–68% of patients. A lower incidence is reported with SS disease, presumably because patients with this disease have a decreased life expectancy. In patients with sickle cell anemia, acute infarcts may be very difficult to distinguish from osteomyelitis, another complication of this disorder. However, bone infarction is at least 50 times more common in these patients than bacterial osteomyelitis. Patients with sickle cell disease develop both subarticular and medullary bone infarcts. Infarcts also occur in unusual locations such as the vertebral bodies and phalanges.

The histologic features of necrotic bone are uniformly empty osteocyte lacunae and fat necrosis of the marrow (Fig. 2.6). All the lacunae in a zonal area of trabecular bone must be empty, a feature which remains constant. However, histologic changes evolve in the marrow. For the first few weeks after an infarct, the marrow shows only fat necrosis. The nuclei of the lipocytes are absent, and their cellular membranes are indistinct. In addition, foam cells, multinucleated giant cells, and a few lipid-filled

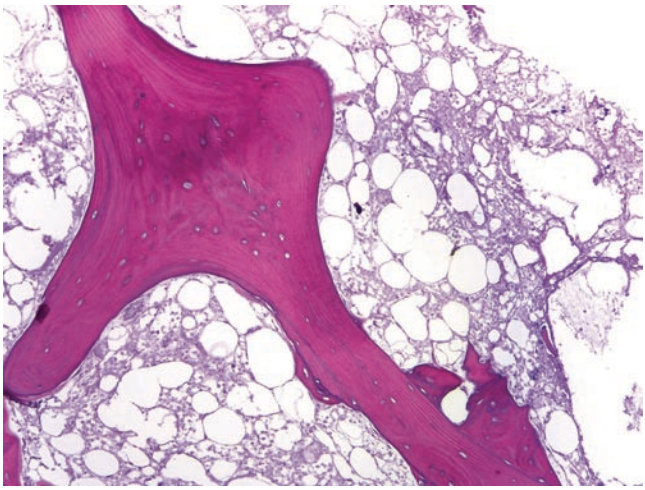

Fig. 2.6 Photomicrograph of dead bone showing empty lacunae and necrotic fat

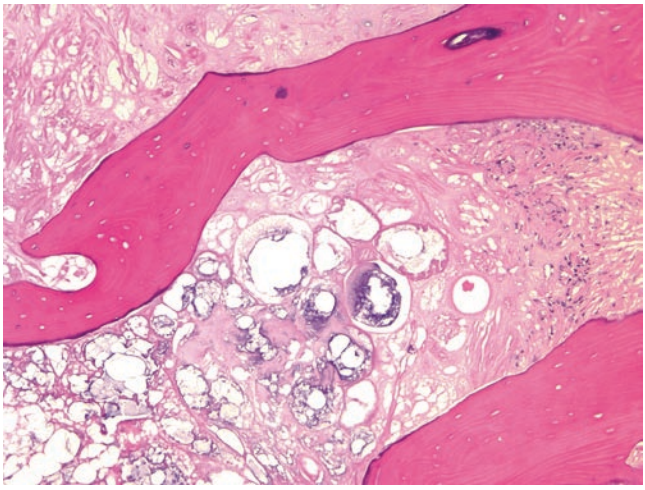

Fig. 2.7 Photomicrograph of an infarct showing dead bone and necrotic fat with dystrophic calcification

cysts are present. Eventually, the marrow space is filled with amorphous acellular debris, and small particles of dead bone are surrounded by foreign body giant cells. Sometimes, focal dystrophic calcification occurs in the necrotic fat of the marrow space (Fig. 2.7).

The viable bone at the margin of the infarct shows reactive changes and is the source of repair of the infarct. First, these marginal areas show bone marrow edema. Faintly eosinophilic edema fluid is present between the marrow fat cells, and small

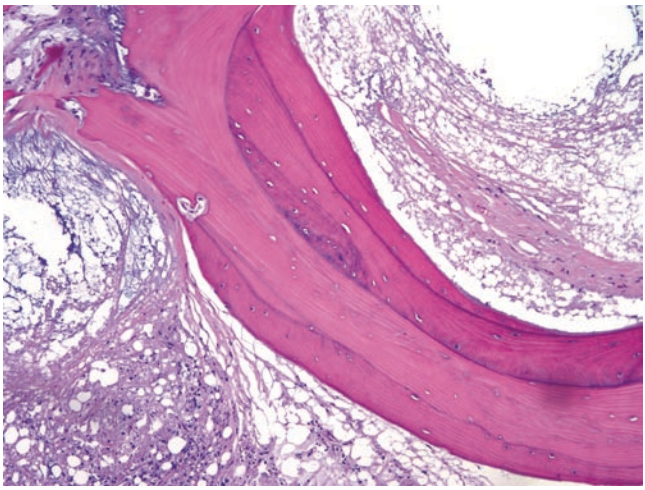

Fig. 2.8 Photomicrograph of dead bone with layers of reparative bone which contain viable osteoblasts

blood vessels are dilated and congested. The trabeculae in this region show mild osteoclastic resorption.

After several weeks, a reparative reaction begins. First, a zone of granulation tissue develops at the interface between viable and dead bone. This tissue often contains scattered mononuclear inflammatory cells. Then, gradual encroachment of reparative tissue into the necrotic zone replaces dead fat with a highly collagenized fibrous tissue. Osteoblasts, having differentiated from the granulation tissue, deposit seams of appositional bone on the dead trabecular bone. The new bone, containing viable osteocytes, is sharply demarcated from the necrotic bone which shows only empty lacunae (Fig. 2.8). New viable bone also forms in resorption cavities within the dead bone, a process known as creeping substitution. Weakened by osteoclastic resorption at the margin of the infarct, the dead trabeculae eventually fracture beneath the subchondral plate. This process, leading to collapse of the articular surface, correlates with the crescent sign seen radiographically.

Bone infarction may occur in the medullary portion of the bone or adjacent to an articular surface, particularly the femoral head. Medullary infarcts occur in the metaphyseal and diaphyseal regions of a bone. This manifestation of osteonecrosis frequently occurs in patients with sickle cell disease or patients treated with steroids, and usually, the femur or tibia is involved. During the early phases of medullary infarction, bone pain may be present, and the process may be misdiagnosed as infection or neoplasm. Most medullary infarcts, however, are asymptomatic and are discovered incidentally during imaging procedures for other areas of bone or joint pain.

The radiologic features of an old medullary infarct are characteristic. A well-defined, mottled radiodensity involves a 2–10 cm segment of the medullary canal.

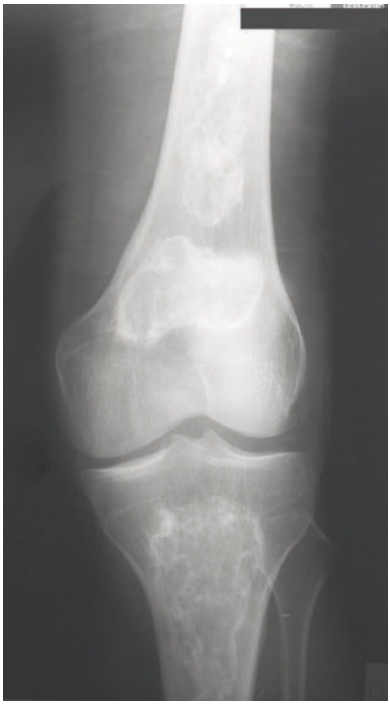

Fig. 2.9 Plain radiograph of the knee showing medullary infarcts in the tibia and femur. There are radiodensities in the pattern of "smoke rings"

The radiodensities, due to calcification of dead marrow and reparative new bone, assume a "smoke-ring" shape (Fig. 2.9). Very old infarcts may show partial or complete cystic change.

The MRI, however, is the most sensitive tool to diagnose early bone infarction. Signal abnormalities may appear as early as a few days after infarction. Typically, an inhomogeneous signal change is present in a well-demarcated zone with serpiginous borders. Infarcts usually show low-signal intensity on T1 weighted images and an intermediate- or high-signal intensity on T2 weighted images (Fig. 2.10). The T2 weighted images often show the "double-line sign," a pattern highly characteristic of necrosis. This double line is thought to represent a zone of hypervascular granulation tissue at the interface between viable and necrotic bone.

Osteonecrosis of the femoral head (ONFH), a common disease which often leads to significant disability, is the most important clinical syndrome of bone infarction. In the United States, approximately 10,000–20,000 new cases occur each year. Unlike medullary infarcts which are usually asymptomatic, the subchondral location of an infarct in the femoral head causes hip pain. Osteonecrosis of the femoral head most commonly affects patients between the ages of 20 and 40. Usually, the disease leads to structural failure of the femoral head, and a total hip arthroplasty is required. However, hip arthroplasty for osteonecrosis is problematic. Results of total hip surgery in these patients are less satisfactory than in patients

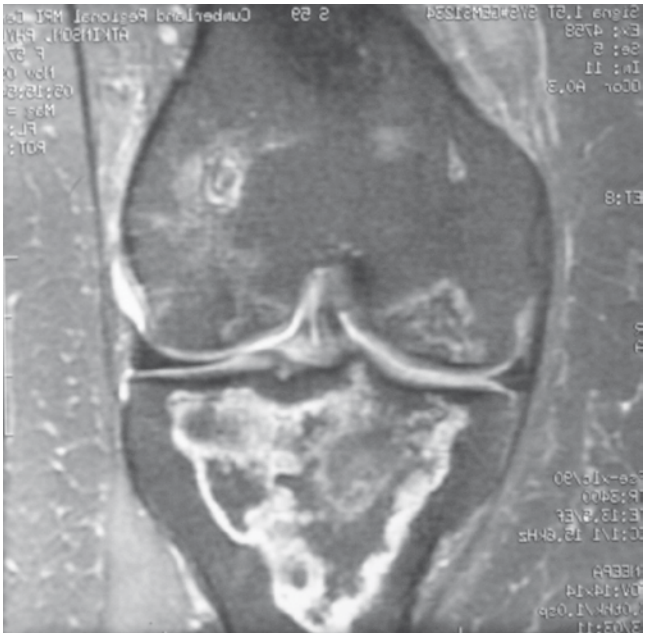

Fig. 2.10 A T2 weighted MRI showing infarcts of both the femur and tibia. The tibial infarct shows a high signal demarcating the area of dead bone

with primary osteoarthritis. There are reasons for this. First, patients with osteonecrosis require hip arthroplasty earlier, the average age being only 38. It is, therefore, unlikely that a total hip prosthesis will last the remainder of the person's life. Second, hip arthroplasties fail earlier in these patients. This early failure may be due to the systemic disease which led to the necrosis or an increased activity level of this younger age group. The failure rate of total hip arthroplasty for osteonecrosis may be as high as 25%, significantly higher than the 5% failure rate of this procedure for primary osteoarthritis.

Suggested Readings

Pathology of Bone and Joint Disorders with Clinical and Radiographic Correlation, Edward F. McCarthy and Frank J. Frassica. W.B. Saunders, 1998

Orthopaedic Pathology, Vincent J. Vigorita. Lippincott Williams and Wilkins (Wolters Kluwer), 2007

Bone Pathology, Jasvir S. Khurana. Humana Press, 2009

Chapter 3
Arthropathies

William R. Reinus and Jasvir S. Khurana

Common Features of Arthropathies

Arthropathies, by definition, are joint-centered processes. If the bone surface on only one side of the joint is affected, the disease process is unlikely to be a primary arthropathy.

Hyaline cartilage that lines the articular bone along the joint surface is critical for proper function of the joint. Its loss is a common finding in most arthropathies, whether productive or inflammatory in nature. Radiographically, this loss is seen as reduction in joint space.

With loss of cartilage, the denuded ends of the bones that make up the joint rub against one another, leading to new bone formation (termed eburnation when described grossly and seen as subchondral new bone formation on radiographs). In addition, osteophytes form, as a response to abnormal stresses across the joint. The radiographic sine qua non for osteoarthritis (whether primary or secondary to other arthritidies or disease processes) is the trio of joint space narrowing, subchondral sclerosis and osteophyte formation.

Radiological Aspects of Arthropathies

From a radiological point of view, then, there are four possible appearances of arthritis: destructive, productive, both destructive and productive and those that are neither. Two of these appearances: those that are productive, the osteoarthroses, and those that are destructive, the inflammatory arthropathies account for the vast majority of cases.

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Radiologic diagnosis of arthopathies and evaluation of the extent and severity of the disease relies on assessment of: *A*lignment, *B*ones, *C*artilage spaces, *D*istribution of disease, other *E*xtraordinary findings and the *S*oft-tissues: the so-called ABCDES of arthritis.

Alignment

Misalignment of bones may occur in a consistent and predictable fashion in some arthritidies as a result of inflammation induced destruction or dysfunction of tendons, ligaments and muscles. For example in rheumatoid arthritis (RA), ulnar deviation of digits in the hands is common. Swan-neck and boutonnière deformities are other examples of mal-alignments and are often seen in inflammatory arthritidies, especially rheumatoid arthritis.

Bones

Bones may develop either osteopenia from disuse or inflammation induced hypervascularity (for example rheumatoid arthritis) or sclerosis (as seen in the phalanges in psoriasis). Periosteal reaction may also occur along the diaphysis of bones affected by some inflammatory arthropathies, particularly psoriatic arthritis and Reiter's disease (also now called reactive arthritis).

Cartilage

Cartilage space narrowing is seen as an end result of most arthropathies. Erosions are often seen in the cartilage space as the result of inflammatory destruction of the underlying bone. Some diseases, for example rheumatoid arthritis, initially cause marginal erosions while others, such as erosive osteoarthritis, show uniform erosive changes across the articular surface. In general, inflammatory arthropathies tend to be destructive and as such show erosions along the joint margins within the cartilage space. In gout the erosions start juxtaarticularly in the metaphysis and give rise to a peculiar clasp like erosion with overhanging edges (Fig. 3.1), so-called Granger's overhanging edges. In psoriatic arthritis, there is often a total obliteration of the cartilage space and ankylosis. In other conditions (collectively referred to as the chondrocalcinoses) there is calcification of joint cartilage. Such conditions include calcium pyrophosphate dehydrate deposition disease (pseudogout), hyperparathyroidism, hemochromatosis and alkaptonuria (ochronosis).

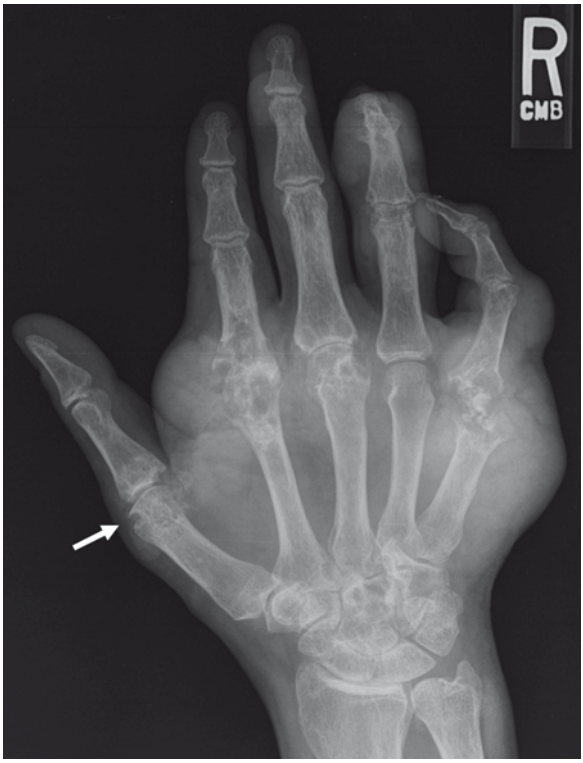

Fig. 3.1 PA radiograph showing severe gout of the hand in a 55-year-old man. Note the hyperdense tophi in the soft-tissues and the destructive changes at the first, second, third and fifth MCP joints. A classic overhanging edge erosion is present at the first metacarpal head (*arrow*). Multiple other erosions with overhanging edges are also present. Lytic changes are present in the hamate and capitate, likely from intraosseous tophi

Distribution

Knowing the distribution of disease is critical in diagnosis. The spondyloarthropathies and alkaptonuria both primarily involve the spine; the spondyloarthropathies also involve the sacroiliac joints. Gout predominates in the distal parts of the appendicular skeleton (the acral skeleton, and frequently involves the feet and knees). Rheumatoid arthritis tends to be symmetrically distributed whereas psoriatic arthritis and Reiter's disease tend to asymmetry. Infections and gout may affect a single joint while the other inflammatory arthritidies tend to involve more than one joint. Thus, a bilaterally symmetric destructive arthropathy involving the carpi and the metacarpophalangeal joints strongly suggests rheumatoid arthritis. Productive arthritis involving the patellofemoral joint out of proportion to other compartments of the knee joint may indicate calcium pyrophosphate dihydrate deposition arthropathy (CPPD). Similarly, a productive arthritis that involves primarily the second

and third metacarpophalangeal joints and shows large radial hook-like osteophytes suggests the possibility of hemochromatosis or CPPD.

Extraordinary Findings

In addition, peculiarities of the radiographic appearance and distribution of some arthropathies help to narrow the differential and lead to definitive diagnosis. For example, the presence of spontaneous joint ankylosis or an ivory phalanx is strongly suggestive of psoriatic arthritis. Chondrocalcinosis, though caused by many conditions, is frequently although not always present in CPPD deposition disease. Atlantoaxial subluxation is common in RA but unusual in psoriatic arthritis and Reiter's disease. Finally, interstitial lung disease is common in some of the conditions associated with arthritis, e.g. RA and ankylosing spondylitis.

Soft-Tissues

Soft-tissues may be involved in the form of capsular or joint swelling or masses as seen in gout, rheumatoid arthritis or multicentric reticulohistiocytosis (a form of histiocytic proliferation). There may also be considerable soft-tissue atrophy in such diseases as rheumatoid arthritis or lupus.

Specific Arthritidies

The Productive Arthritidies

Osteoarthritis

Osteoarthritis (pejoratively called degenerative joint disease) is the prototypical productive arthropathy. It may be the end result of one of several arthritidies (secondary osteoarthritis) or occur in the absence of other known arthritis (idiopathic or primary osteoarthritis). Osteoarthritis is considered to be one of the most important contributors to old age morbidity and medical expense.

Pattern of involvement: Overall, primary osteoarthritis is most common in the major weight-bearing joints, the hip, knee and to a lesser degree the ankle. It is also common in the frequently used small joints of the hands and wrists, particularly the first carpometacarpal joints at the base of the thumbs (Fig. 3.2a, b). Often the dominant hand is more severely affected than the non-dominant hand. The facet joints of the cervical and lumbar spine are also commonly affected. Typically, the shoulder and elbow are relatively spared.

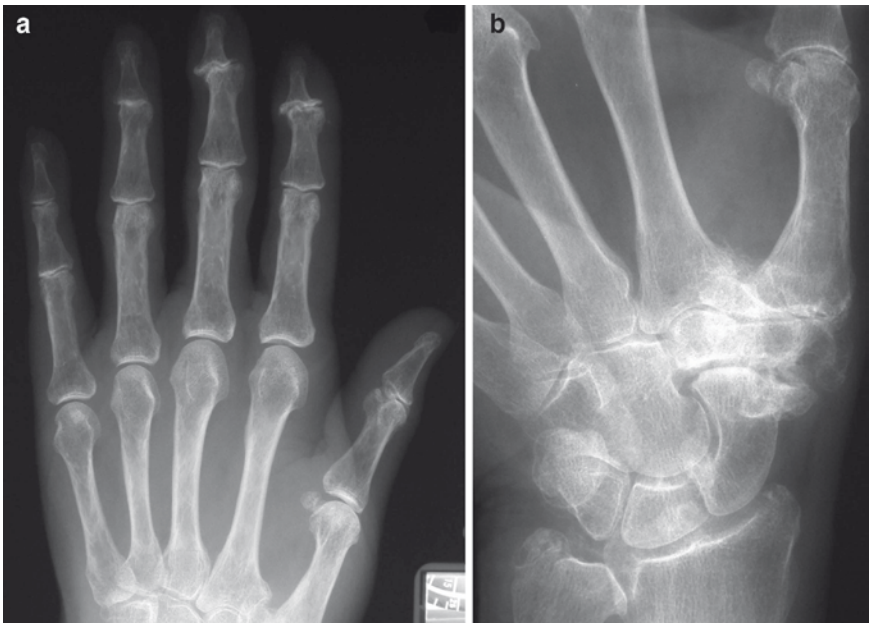

Fig. 3.2 (**a**, **b**) PA radiographs of the hand in a 59-year-old woman showing changes of osteoarthritis with joint space narrowing involving the first CMC joint and second through fifth DIP joints. Osteophyte formation is evident at the CMC joint and the second and third DIP joints. Some joint space narrowing is evident at the first MCP joint as well

Clinical presentation: Clinically patients with osteoarthritis complain of joint pain, crepitus and stiffness with use after periods of inactivity. Normally the pain is relieved by rest but may become continuous late in the disease.

Osteoarthritis undergoes relative periods of symptomatic improvement and worsening, the latter related to periods of reactive synovitis and joint effusion. Advanced disease is often accompanied by disuse atrophy of muscles. As the disease progresses, the joints begin to show clinical enlargement. In the fingers these enlarged areas are known as Heberden's and Brouchard's nodes in the distal and proximal interphalangeal joints respectively. With enlargement of the facet joints in the spine, the neuroforamina may become encroached resulting in radiculopathy or development of spinal stenosis.

Etiology: Various causes of osteoarthritis have been investigated. Obesity, trauma, joint incongruity due to congenital conditions and repetitive joint use are all risk factors for (secondary) osteoarthritis, which also can be seen as an end result from other arthritidies as well as many deposition and endocrine diseases. Patients with ochronosis accumulate homogentisic acid polymers that cause stiffening of the cartilage. In osteopetrosis stiffness of the subchondral trabeculae occurs.

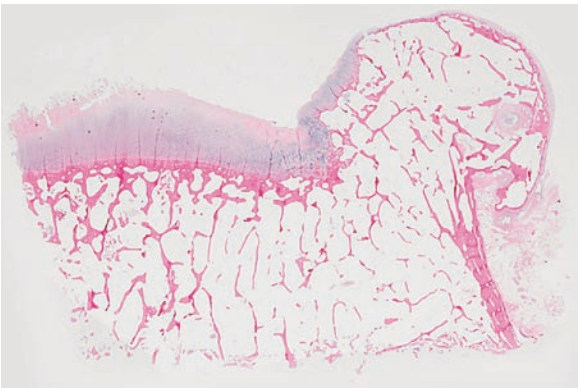

Fig. 3.3 Osteoarthritis with osteophyte formation

In both severe degeneration of cartilage is present by 40 years of age. The etiology of primary osteoarthritis is less well characterized. A genetic basis appears possible.

Surgical pathology: The most striking changes are usually seen in load bearing areas of the articular cartilage. In the early stages the cartilage is thicker than normal but with progression of the disease, the joint surface thins, the cartilage softens, the integrity of the surface is breached and vertical clefts develop. This gives the cartilage a resemblance to velvet and is termed fibrillation. Deep cartilage ulcers, extending to bone, may appear. Areas of fibrocartilaginous repair may develop. Fibrocartilage, however, is inferior to the original hyaline articular cartilage in its ability to withstand mechanical stress. The articular cartilage is metabolically very active and the chondrocytes replicate forming clusters – a finding called "cloning." Later the cartilage becomes hypo cellular and eventually gets entirely eroded (Fig. 3.3). Remodeling and hypertrophy of bone are also major features. Appositional bone growth occurs in the subchondral region leading to an opaque rim seen radiologically. The abraded bone under a cartilage ulcer may take on the appearance of ivory or of shiny wood and is termed "eburnation." Growth of cartilage and bone at the joint margin leads to osteophytes (spurs), which alter the contour of the joint restricting movement (Fig. 3.4). Thickening of the joint capsule along with chronic synovitis also occur in some cases, but the inflammation is not usually very prominent.

Neuropathic Arthropathy (Charcot's Joints)

Neuropathic arthritis is an extreme form of post-traumatic osteoarthritis. In neuropathic arthropathy the involved joints lack proprioception and deep sensation. As a result joint movement is not inhibited and tends to undergo unintentional repetitive minor trauma. Ultimately this constant trauma causes repetitive fracture and fragmentation of the joint and eventually biomechanical instability and severe osteoarthritis (Fig. 3.5).

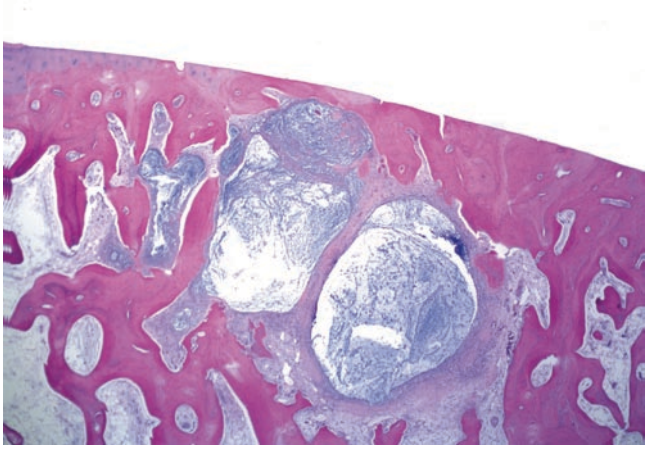

Fig. 3.4 Severe osteoarthritis with erosion of articular cartilage, thickening of subchondral bone and subchondral cyst formation

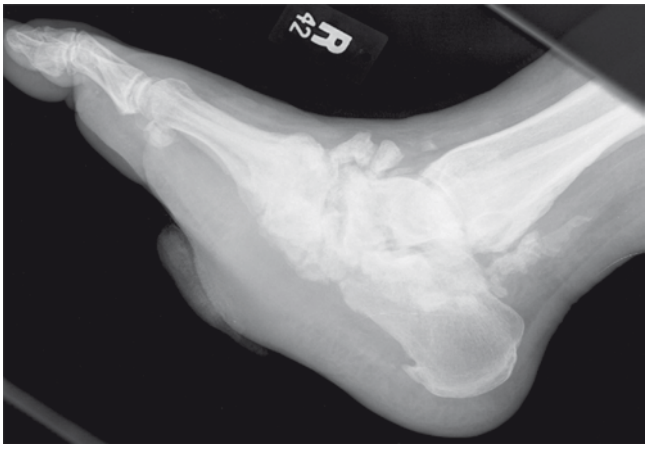

Fig. 3.5 Lateral foot radiograph in a 41-year-old diabetic man showing mid foot neuropathic changes, essentially severe osteoarthritis with disorganization and fragmentation of the joint. This configuration is known as a rocker bottom foot. Note dystrophic ossification posterior to the tibia and the ulcer on the sole of his foot

With the decline of tertiary syphilis other causes, such as, diabetes (especially the foot and ankle), syringomyelia (in the shoulder), amyloid, alcoholic neuropathies and leprosy have increased in importance. The commonest cause in the United States is diabetes.

Surgical pathology: Pathologic findings neuropathic arthropathy, include severe degeneration and fragmentation of the joint surfaces with extensive detiritic synovitis resulting from particles of bone and cartilage embedded in the synovium.

Calcium Pyrophosphate Dihydrate Crystal Deposition Disease (CPPD)

In calcium pyrophosphate dihydrate deposition arthropathy (CPPD) there is excess calcium and pyrophosphate solute with the joint such that crystal precipitates out into the joint spaces and is deposited within the synovium and articular cartilage (Figs. 3.6a, b and 3.7). This material causes an inflammatory reaction within the joint that leads to destruction of the articular cartilage and symptomatic joint effusion.

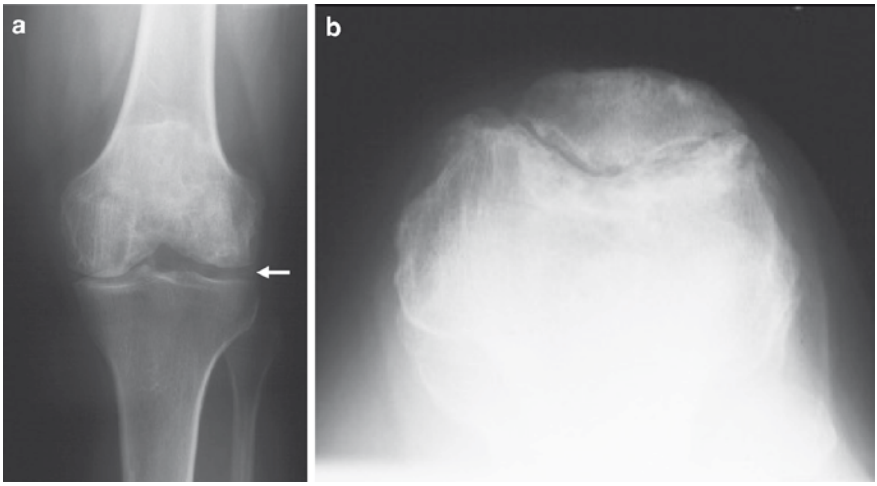

Fig. 3.6 (**a**, **b**) showing AP (**a**) and skyline (**b**) radiographs of the knee in a 50-year-old man with CPPD arthritis. Note that the arthropathy is productive and similar to osteoarthritis, but that the patellofemoral joint is disproportionately affected, a characteristic of CPPD arthritis. Also note the chondrocalcinosis in the lateral joint space outlining the lateral meniscus (*arrow*, **a**)

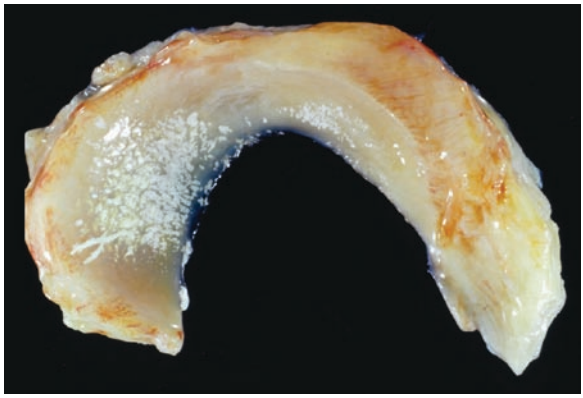

Fig. 3.7 Chondrocalcinosis involving the menisci of the knee with calcium deposits (*brown*) on cartilage

Clinically, CPPD affects a similar population to that of OA. It becomes more prevalent with age and affects about 5% of the population. There are three types – sporadic, hereditary and secondary types. The secondary form occurs in conditions such as hyperparathyroidism, hemochromatosis, hypomagnesemia, hypophosphatasia, gout, X-linked hypophosphatemic rickets, hypothyroidism, ochronosis and diabetes.

The clinical features in many cases are very similarly to osteoarthritis: joint pain, crepitus and stiffness after prolonged rest. CPPD also has a tendency to present with occasional flares where patients develop acute inflammation in the joint, swelling from a joint effusion and erythema. This presentation may be very similar to gout and has been referred to clinically as pseudogout.

Radiology: The deposition of calcium pyrophosphate within the articular structures, primarily the hyaline cartilage and the meniscal fibrocartilage, can become radiographically visible. This disease also is associated with a productive arthritis. This arthropathy resembles osteoarthritis except that more often affects a particular subset of joints, including the patellofemoral, scaphotrapeziotrapezoidal, radioscaphoid, second and third metacarpophalangeal and talonavicular joints.

Surgical pathology: There is calcification of joint cartilage. There may be crystals seen in joint fluid or tissues. The crystals are 0.5–5 μm in the greatest diameter. They first develop in the articular matrix, menisci and intervertebral discs. The deposits later enlarge into large chalky white friable masses. They are distinguishable from gout by their positive birefringence under polarized light (gout contains uric acid crystals that are needle-like and negatively birefringent).

Hemophilia

Hemarthroses occur in 75–90% of patients with hemophilia. The knee, ankles and elbows are the joints most commonly affected. For obscure reasons, joints distal to the elbow and ankle are rarely affected. Patients may also develop hemorrhage into their marrow space resulting in pseudotumors of bone. These typically appear as isolated lytic lesions with well-defined margins that may be confused radiographically with other true neoplastic lesions of bone. There have been disastrous instances where these pseudotumors were amputated in the belief that the patient had an osteosarcoma.

Radiology: Recurrent hemorrhage into a target joint leads to immediate inflammation and eventual deposition of ferritin within the joint. Magnetic resonance imaging is extremely sensitive to this intraarticular hemosiderin deposition since the iron alters the local magnetic field and causes signal loss. Episodes of hemorrhage cause (generally beginning around the age of 2 years) increased blood flow to the bone around the joint. This increased flow in turn causes overgrowth of the adjacent epiphyses and leg length discrepancies. Overgrowth of the femoral condyles leads to widening of the intercondylar notch and overgrowth of the patella causes the appearance of squaring of its inferior pole. Eventually these patients develop

secondary osteoarthritis secondary to loss of their articular cartilage and abnormal biomechanics.

The Destructive (Inflammatory) Arthritidies

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is considered to be an autoimmune disease that may involve multiple organ systems. Joint involvement predominates in most patients. The disease occurs more often in women than men in a ratio of about 2–3:1. It may appear at any time during life but has its peak incidence between 35 and 50 years of age.

The majority of patients afflicted with rheumatoid arthritis have ongoing, progressive disease with periods of reduced activity. Since the severity and behavior of RA varies from patient to patient, diagnosis can be difficult. The American College of Rheumatology has established a set of clinical criteria to establish the diagnosis.

Etiology: Rheumatoid arthritis (RA) is a systemic disease that manifests as a synovial arthropathy. An antigen–antibody reaction, initiates the inflammatory process. The joint destruction is aided by the elaboration of cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin 1 (IL-1) which also activate osteoclasts.

Clinical features: Rheumatoid arthritis is a symmetrical multi-joint inflammatory arthropathy, potentially involving every joint in the body with the exception of the distal interphalangeal (DIP) joints. There are usually accompanying constitutional symptoms such as stiffness, fatigue, malaise, anorexia and weight loss. Other organs and systems can be involved in the inflammatory process including the formation of rheumatoid nodules which are pathognomic of the condition. Increased rheumatoid factor and anti cyclic citrullinated antibody titers are helpful in confirming the diagnosis.

Radiological features: RA is a destructive arthritis, with the most prominent radiographic initial changes being erosions in the bone at the periphery of the involved joint(s). With progression of disease the central articular cartilage of the joints erodes, and the subchondral bone shows erosions and subchondral cysts (Fig. 3.8). The distribution of RA is generally symmetrical. The one exception to this rule is in paralyzed patients where, for unknown reasons, the disease tends not to involve the paralyzed limb. Despite long standing disease, ankylosis of joints usually does not occur – the major exception being the wrist.

Subcutaneous nodules can also be seen clinically and by radiological imaging, and are a pathognomic feature if seen. Tendon and ligament inflammation often lead to joint misalignment including prominent ulnar drift at the metacarpophalangeal joints of the hands (the feet may also show similar deformities). Boutonniere deformities (flexion deformity at the PIP and hyperextension at the DIP) and swan neck deformities (hyperextension at the PIP and flexion at the DIP) also occur frequently.

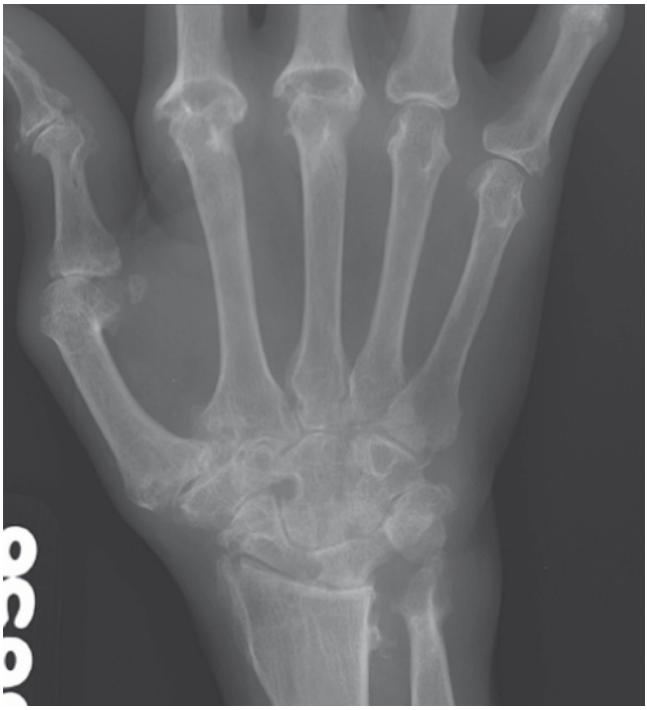

Fig. 3.8 PA view of the left wrist in a 68-year-old woman with long standing rheumatoid arthritis. Note the destruction of the second and third metacarpophalangeal joints, the erosions in the carpus and the whittling of the distal ulna, all without much productive change

The bone adjacent to involved joints shows marked osteopenia caused by increased local blood flow, so called periarticular osteopenia. Periosteal reaction, while common in psoriatic arthritis, is rare in RA.

Surgical pathology: In the early stages of RA, the capsule of the joint especially the juxta-synovial layer shows nonsuppurative chronic inflammation. This is characterized by hypertrophy and hyperplasia of the synovial cells resulting grossly in a papillary pattern on the surface of the synovium.

Marked increase in vascularity occurs and the tissue is edematous and infiltrated with large numbers of cells, especially plasma cells and lymphocytes, the former frequently containing eosinophilic inclusions of gamma globulin (Fig. 3.9). These cells form "rosettes" or cuffs around blood vessels and may form lymphoid follicles (Allison-Ghormeley bodies). In time, the collections of lymphocytes often develop germinal centers. Synovial villi can get engulfed in the lymphocytes; also, the hypertrophic synoviocytes can develop into giant cells.

Immature mesenchymal cells proliferate. There is fibrinous exudation at the surface and within the synovium (rice bodies). Disruption of the synovial border of

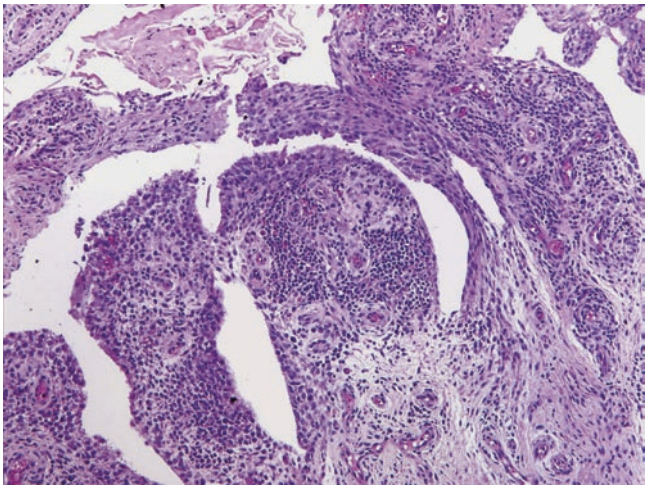

Fig. 3.9 Chronic synovitis in a patient with rheumatoid arthritis. In some cases, germinal center formation is prominent

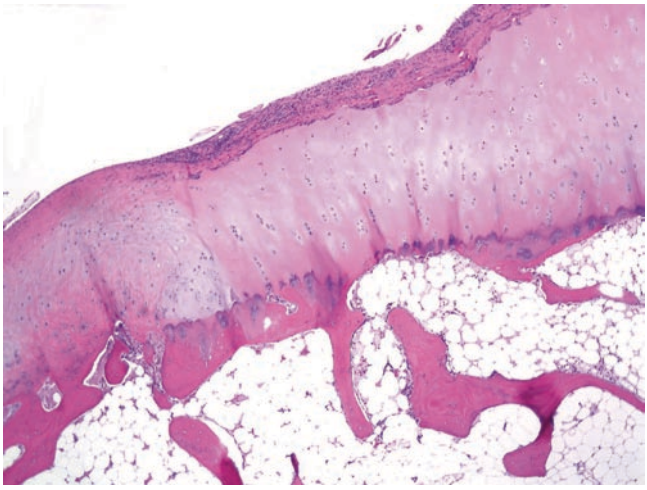

Fig. 3.10 Inflammatory pannus growing over the articular cartilage

the inner aspect of the capsule occurs and there is extravasation of inflammatory cells into the joint. The amount of joint fluid is markedly increased.

Later, a pannus forms. This is a combination of proliferating mesenchymal cells and granulation tissue starting at the periphery of a joint and invading it covering and destroying the articular cartilage and the subchondral marrow spaces beneath the articular cartilage (Fig. 3.10)

Juvenile Rheumatoid Arthritis (Juvenile Chronic Arthritis)

Juvenile rheumatoid arthritis (JRA) is usually seen in individuals before the age of 16. As with adult RA, it affects girls more often than boys in a 2:1 ratio. It often resolves with age but may leave significant residual joint damage. JRA has three main forms: pauciarticular (less than 5 joints involved), polyarticular and Still's disease.

Septic Arthritis

Infectious arthritis is a serious problem in spite of the wide range of potent antibiotics that are available (Fig. 3.11). Sometimes these infections arise in individuals who are immune compromised. In some cases, the joint infection is secondary to overwhelming infection primary to some other system of the body. In other cases there may be contiguous infection or a penetrating injury into the joint. The problem of infectious arthritis is further aggravated by poor diffusion of antibiotics into the joint space. Septic arthritis may cause considerable morbidity if treatment is delayed. Early intervention in the form of arthrotomy or arthrocentesis for diagnosis and therapeutic washout is important.

Besides direct involvement of the joint by a pathogen arthritis may occur from an immune response to a pathogen causing a reactive arthritis as is seen in

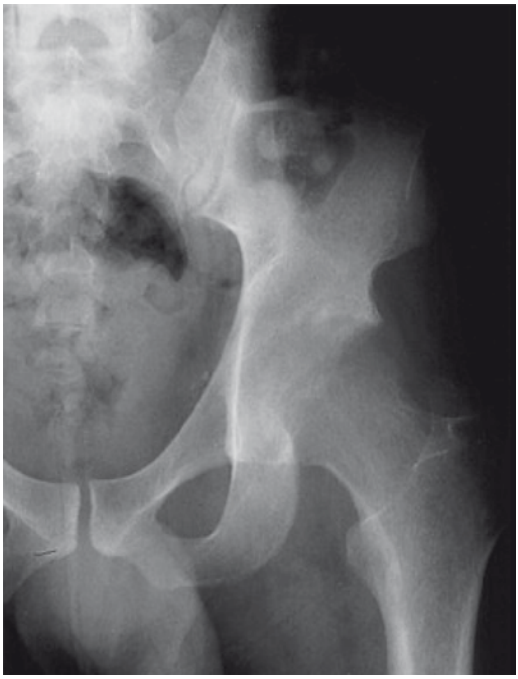

Fig. 3.11 AP hip radiograph of the left hip in a 14-year-old boy showing destruction and periarticular osteopenia in a septic hip

Chlamydial (Reiter's syndrome/REactive Arthritis), some enteric, and sometimes with treponemal and fungal systemic infections. These immune forms of arthritis (including Lyme arthritis) are generally discussed separately and excluded from discussion of infectious arthritis and discussed.

Pathogenesis: Infection reaches the joint by hematogenous or lymphatic routes. The hematogenous route is common in most forms of arthritis including viral. Infection of the joint may also be by direct spread from neighboring soft-tissue or bone. Penetrating injuries are especially important as a cause of fungal septic arthritis.

Pathology: The basic inflammatory process in infection of the joint is marked by hyperemia of the synovium, infiltration by leukocytes, lymphocytes and macrophages and plasma cells. An associated exudate develops which may be purulent, serous or fibrinous. With persisting infection and inflammation, granulation tissue (pannus) results and subsequently adhesions occur. Pyogenic infections may result in pyoarthrosis which is extremely resistant to antibiotic therapy and requires surgical drainage or repeat arthrocentesis – often emergently.

The sequelae of septic arthritis can be severe and leave lasting scars. These are fibrinous adhesions and fibrous ankylosis, articular erosion by pannus (chondrolysis), destruction of the stabilizing ligaments, and intraarticular disks. Erosion of the articular cartilage by pannus may extend to the subchondral bone and lead to secondary osteoarthritis. Lasting damage is frequent in bacterial and fungal arthritis.

The type of organism and pattern of joint involvement often depends upon the age (the elderly are at greater risk) of the patient, pre-existing arthropathy, immune status and habits such as intravenous drug abuse. Dermal nosocomial bacteria are the most frequent pathogens (Staphylococci, Streptococci, Pseudomonas) and Enterobacteriacae less so. *Neisseria gonorrhea* is suspected most often in septic arthritis in young sexually active individuals, particularly females. Mycobacterial arthritis is often diagnosed late and is very destructive. Spinal tuberculosis can form abscesses (psoas abscess) that can extend considerable distances (Fig. 3.12a–c). Fungal and parasitic arthritis are rare, but well documented.

Infection can also complicate prosthetic joints. In this case it may be acute (pyogenic and enteric bacteria) or chronic (coagulase negative staphylococci or diptheroids, etc.). The diagnosis in such cases can be difficult, and requires clinical, laboratory and radiological input (Table 3.1).

Gout

Gout affects about 2 million individuals in the US, roughly the same number as are afflicted by RA. Primary gout is predominantly a disease of adult men with a 4:1 male to female ratio.

Gout arises from precipitation of urate crystals into joint spaces, the marrow and the soft-tissues. The first causes an inflammatory arthropathy within the joint, the second causes intraosseous tophi that may lead to paraarticular erosive changes, and the last causes soft-tissue tophi and inflammatory masses in the soft-tissues. Some patients with chronic gout also develop urate nephropathy.

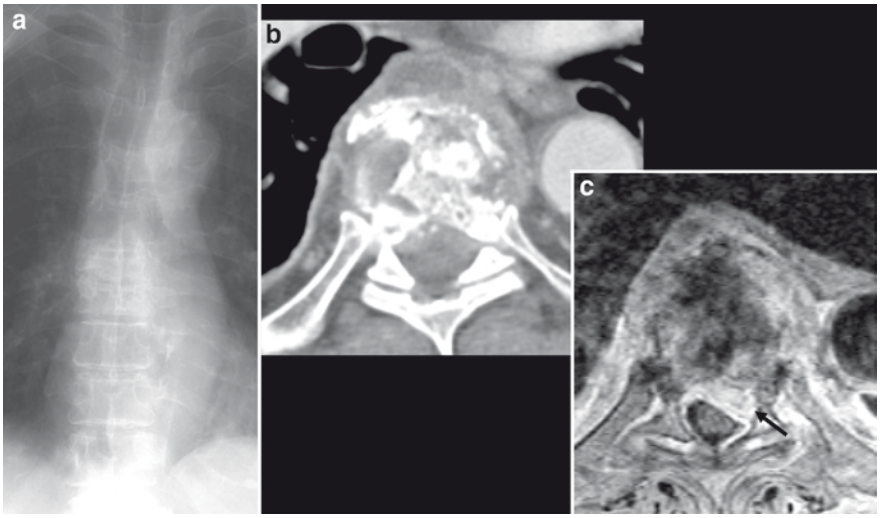

Fig. 3.12 (**a**–**c**): AP T-spine radiograph (**a**), CT (**b**) and post gadolinium axial T1W MRI (**c**) through T8-9 disc level showing destruction of the adjacent vertebral bodies and paraspinous abscess formation in this patient with TB discitis. Note also the epidural abscess on the MRI (*arrow*, **c**)

Table 3.1 Frozen section for loosening of arthroplasty components

Loosening of endoprosthetic components can occur from a variety of causes (infection, metal reaction, rejection, wear reaction, etc.). Separating infection from all the other non-infectious causes is important, since the foreign material acts as a nidus for infection and perpetuates it in a vicious cycle. Removing the endoprosthesis is often considered an important part of the management. It may subsequently be replaced later or a procedure such as an excision or interposition arthroplasty be used instead (such as a Girdlestone arthroplasty of the hip). Estimation and quantization of the acute inflammatory response is the usual way of diagnosing infection. Tissue from around the prosthesis is taken. The number of polymorphs per 40× field (400× magnification) are counted and averaged over at least five fields (taking care to avoid counting cells within vessels, fibrin and inflammatory exudate). Counts of five polys/high-power field are very suggestive of infection ("Mirra's criteria"). Counts of ten polys/high-power field are, however, much more likely to be infection. Whether or not this method still applies in specialized situations such as patients with rheumatoid arthritis is uncertain.

Uric acid (urate) crystallizes at a level that exceeds 6.8 mg/dL (with slight variation for temperature and pH). High concentrations of uric acid may result from under-excretion or from over-production of uric acid. The former, known as primary gout, accounts for 90% of cases. Over-production most commonly results from high rates of tissue degradation as one may see in patients on chemotherapy for neoplasms or myeloproliferative diseases or ethanol abuse. This form of gout is secondary and accounts for only 10% of patients. Some rare enzymatic deficiencies result in over-production of uric acid. These include patients with Lesch–Nyhan

syndrome (hypoxanthine-guanine phosphoribosyl transferase deficiency), Von Gierke's disease (glucose-6-phosphatase deficiency) and patients with PP-ribose-P synthetase variants. Synovial fluid is a poor solvent of monosodium urate crystals because of a low pH. Thus urate in joint fluids become supersaturated much before plasma does especially in peripheral joints where the temperature is lower (such as the foot, where gout is prone to manifest).

Radiology: Gout classically affects the first metatarsophal phalangeal joint of the feet, a condition known as podagra. It also often affects other joints in the feet as well as the wrist and small joints of the hand. The knee and elbow are less commonly affected. Typical early gout shows deposition of mildly hyperdense material in the soft-tissues adjacent to joints. These represent soft-tissue tophi. Over time and with repeated attacks, the bones may develop paraarticular erosions related to osseous tophi that punch out into the surrounding tissues. At the same time intracapsular urate deposition leads to an inflammatory synovitis and destructive changes within the joint. The appearance of clasp-like erosions in a distribution that is typical for gout are nearly pathognomonic (Fig. 3.1). The disease does not always follow a classic course, however, and may give myriad less typical appearances.

Surgical pathology: The progress of gout can be divided into (1) asymptomatic hyperuricemia, (2) acute arthritis, (3) inter-critical periods, (4) chronic tophaceous arthritis and (5) gouty nephropathy.

Acute arthritis: The synovium and the synovial fluid show a dense infiltrate of polymorphonuclear leukocytes. The synovium and neutrophils may show small clusters of mono-sodium urate crystals. These are slender, long, needle like and negatively birefringent (Fig. 3.13a, b). In response to the inflammation there is edema and congestion of the synovium. Besides the dense neutrophil aggregates some lymphocytes, plasma cells and macrophages are also seen. The acute attack abates when the crystals go into solution and as a result the inflammatory response ceases.

Chronic tophaceous arthritis: Repeated acute attacks lead to precipitation of monosodium urate crystals until visible deposits form. The synovium in response becomes progressively more fibrotic and thickened, with pannus formation. This pannus destroys the underlying bone. The fibrosis and articular destruction progress to progressive articular functional impairment. Since uric acid crystals are water soluble, when tissue is placed in 10% formalin they will dissolve out (and so polarization microscopy will not reveal the crystals). Diagnosis can still often be made by identifying the needle-shaped empty spaces where the crystals once resided. If visualizing the crystals is needed, the tissue should be fixed in ethanol.

Tophi: A tophus is an aggregate of mono-sodium urate crystalline material with its accompanying inflammation including foreign body type of giant cells. This is the pathognomonic hallmark of this disorder (Fig. 3.14). Tophi can be see in the articular cartilage, periarticular ligaments, bone, tendons, and soft-tissue such as olecrenon and patellar bursae, kidneys, nasal cartilage, skin of the finger tips, palms and soles. They may cause superficial swelling if large enough, overlying ulceration.

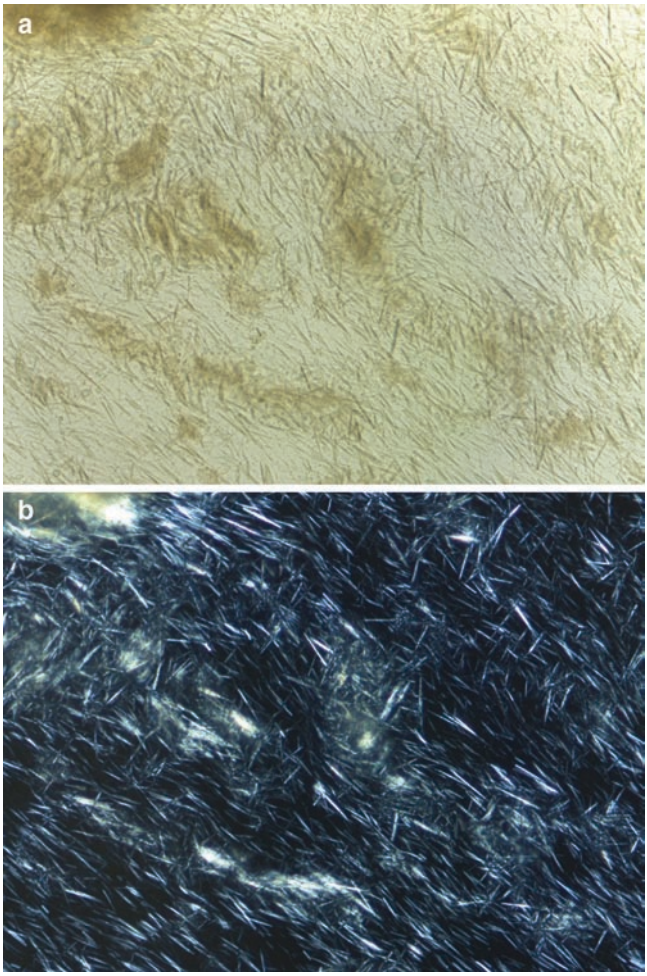

Fig. 3.13 (**a**, **b**): Uric acid crystals in joint fluid (**a**) and under polarization microscopy (**b**)

Psoriatic Arthritis

About 5–10% of patients with cutaneous psoriasis develop arthropathy, a subset of which may be severe, deforming and progressive. In some cases the arthropathy precedes the skin disease, and in some cases of familial psoriasis, the skin manifestations may be entirely absent for a generation. Psoriatic arthritis can be asymmetric and involves the distal small joints (including the DIP joints). It may involve the spine.

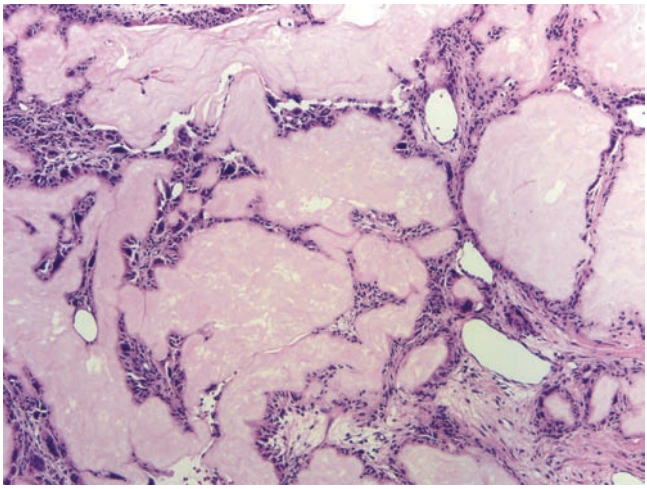

Fig. 3.14 Gouty tophus. The uric acid crystals are no longer seen since they have been dissolved during the fixation and processing. The empty needle like spaces however are consistent with gout

Reactive Arthritis

Reactive arthritis occurs more commonly in young adults (20–40 years) with a male predominance and is strongly associated with HLA-B27. The syndrome consists of inflammatory arthritis, mucosal lesions, conjunctivitis, urethritis or cervicitis, skin rash, and keratodermia blenorrhagicum (a rash that occurs on the soles of the feet and the palms of the hands that resembles pustular psoriasis). The condition is called reactive arthritis because it frequently follows dysentery or a sexually transmitted disease. Several bacterial triggers have been identified, that may initiate the onset of disease. These include Shigella, Salmonella, Yersinia *enterocolitica*, Chlamydia *trachomitis*, Campylobacter *jejuni*, and Lymphogranuloma *venereum*.

Radiographically, reactive arthritis is virtually indistinguishable from psoriatic arthritis.

Ankylosing Spondylitis

Ankylosing spondylitis most common of the spondyloarthropathies and has the highest association with the HLA-B27 antigens (over 95% of patients are HLA B27 positive). As with many arthropathies, it is a systemic disease so it affects not only the spine and SI joints, but also causes aortitis and aortic insufficiency late in the disease in about 5–10% of patients, rare upper lobe predominant interstitial restrictive pulmonary disease (1%) and iridocyclitis (25%) or uveitis (20%). About 10% of AS patients will develop secondary amyloidosis.

Ankylosing spondylitis is insidious in onset and usually begins between ages 16 and 45 years, although 10% of patients may have had an earlier onset in a juvenile form of the disease. It progresses to significant disability in about 20% of those affected. Clinically, it affects men nine times more often than women, but radiographic survey studies have shown an equal prevalence, suggesting that women are less symptomatic. Patients complain of low back pain, morning stiffness and fatigue. They may have intermittent fever. Many patients have enthesopathy/tendonitis. Typically, ankylosing spondylitis starts in the sacroiliac joints (from inferior to superior with later fusion of the joint) and slowly ascends the spine. There may be reactive bone formation in the ring apophyses with erosions of the margins and later, squaring of the bodies of the vertebrae. There is a prominent calcification of the posterior longitudinal ligament of the spine. There is prominent vertebral syndesmophyte formation. In late stages the spine may appear fused, with a fixed kyphosis (the so-called bamboo spine).

Pigmented Villonodular Synovitis

Pigmented villonodular synovitis (PVNS) is considered to be the diffuse counterpart of giant cell tumor of tendon sheath, with which it shares morphological and genetic features. It is an uncommon proliferative disease of the synovium that arises most frequently in patients aged 20–50 years. This disease may affect the synovium of the joints, bursae and tendon sheaths and is most common in the hips, knees and ankles. Rare cases have occurred in the temporomandibular joint and the facet joints of the spine. Extra-articular tumors of the soft-tissue and muscle have also been described. Typically it causes nodular synovitis throughout the joint but rarely may give rise to a focal nodular form. The proliferative nodules have a tendency to bleed, and over time hemosiderin is deposited in the joint giving rise to the characteristic pigmentation of the nodules and the "crank case oil" appearance of the affected joint fluid. Clonal abnormalities and the capacity for autonomous growth have supported PVNS as being a true neoplasm.

Early in the disease the nodules may cause recurrent hemarthroses, saucerized erosions and subchondral cysts on either side of the joint. Radiographically, these phenomena are seen as hyperdense effusions and smooth corticated saucerizations with relative preservation of the joint space. MRI has proven very useful to make the diagnosis because of the paramagnetic effects of hemosiderin (dark on T1 and T2). MRI shows joint effusion with dark signal lining the synovium and internal structures of the joint (Fig. 3.15). This material shows susceptibility effects on gradient echo imaging resulting in "blooming" of the low signal. Calcification is rare in cases of PVNS and if present, alternative diagnoses should be considered, particularly synovial sarcoma.

Surgical pathology: The tumors are large (often more than 5 cm), red or brown, and a villous pattern can often be seen grossly. Microscopically, one can see variably cellular, diffuse, expansile and somewhat infiltrative sheets small ovoid or spindle cells admixed with larger and a few multinucleated cells (Fig. 3.16). Cleft like spaces and

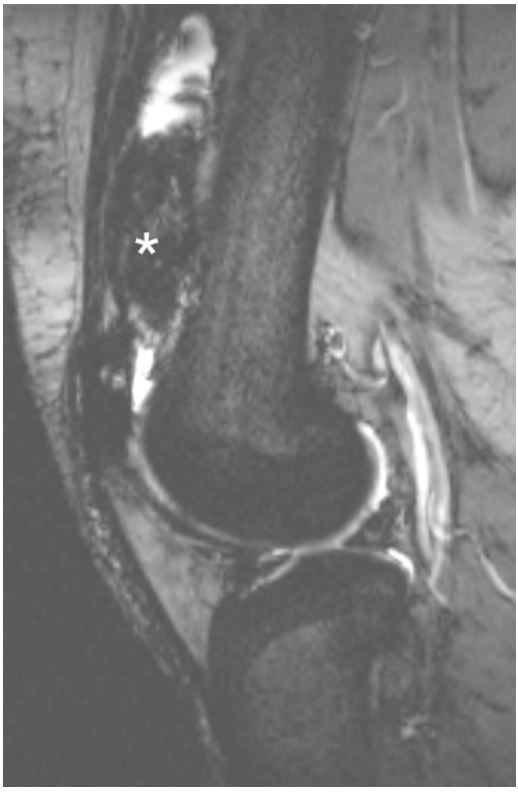

Fig. 3.15 Sagittal GRE MR image from a 49-year-old woman with the nodular form of PVNS. Note the low signal mass within the suprapatellar bursa (*), and low signal material layering along the synovial surfaces and the menisci consistent with hemosiderin

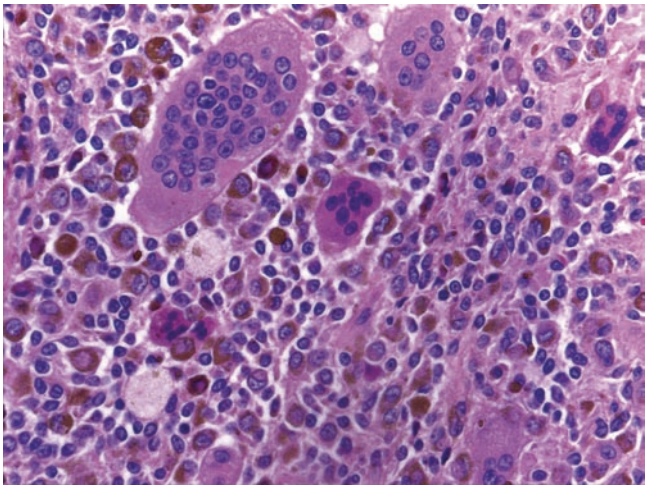

Fig. 3.16 Pigmented villonodular synovitis showing mononuclear cells, pigment laden cells and multinucleate giant cells. Occasional foamy histiocytes are also seen

blood filled spaces are generally prominent. The smaller cells are histiocyte like and often display grooved nuclei. The larger mononuclear cells frequently have a densely eosinophilic cytoplasm and sometimes have a peripheral rim of hemosiderin granules. Sheets of foam cells can also be observed. There is variable amount of fibrosis and lymphocytic infiltrate. Mitoses can be quite frequent. Rare malignant cases have shown very frequent mitotic activity (more that 20 per 10 HPF) and necrosis; although there are no definite histological criteria for malignancy, since some histologically banal cases have metastasized. Both the mononuclear and multinucleate cells can be positive for CD 68. There may be focal desmin positivity.

Chromosomal studies show that translocations involving chromosome 1p11–13 are common in PVNS and giant cell tumor of tendon sheath. More recent studies have found the over expression of colony stimulating factor 1 receptor (CSF1R) in both these lesions (the location for CSF1 is chromosome 1). It is currently thought that many cases have translocations involving CSF1 and the collagen gene COL6A3 (which resides on chromosome 2q35).

PVNS is considered a benign disease, the treatment usually consists of synovectomy. The disease has a tendency to recur (around 20–30%), sometimes requiring extensive synovectomy and total arthroplasty. Malignant (metastasizing) PVNS is extremely rare (a few case reports). If left untreated, PVNS eventually causes joint destruction and secondary osteoarthritis.

Productive and Destructive Arthropathies

This class of arthropathies shows both erosive and productive changes together in the same joint. Erosive osteoarthritis is the prototype of this type of arthritis. A similar imaging pattern becomes apparent is in cases of old burned out destructive arthropathies where, for reasons of altered biomechanics, the joints develop secondary osteoarthritis. Gout, too, though typically destructive, may give an appearance of a combination of destruction and production. This may, in part, be the result of bone production in the healing phase between acute attacks, the loss of hyaline cartilage to synovitis and bone production induced by urate. On the other side of the coin, neuropathic arthritis may cause so much joint disintegration that it may appear destructive as well as productive.

Nondestructive and Nonproductive Arthropathies

Although these diseases do not actually cause morphological alterations in joint architecture and hence technically are not arthropathies, a few conditions are traditionally placed in this category. These include the joint-related abnormalities of systemic lupus erythematosis (SLE), scleroderma, Ehlers Danlos syndrome, agammaglobulinemia and those associated with rheumatic fever, Jaccoud's arthropathy.

Miscellaneous Joint-Related Conditions

Though not actually arthropathies a few conditions occur around joints or bursae, i.e. diffuse idiopathic skeletal hyperostosis (Forestier's disease), Haglund's disease (retrocalcaneal bursitis) or within the joint space with the potential to lead to arthritis, i.e. synovial chondromatosis, osteochondritis dissicans and chondromalacia patella.

Osteochondritis Dissecans

More frequently seen in males, this lesion is characterized by variable number of (but fewer compared to synovial chondromatosis) loose bodies composed of bone and cartilage within the joint cavity often referred to as joint mice. They can measure up to 2 cm. The articular surface shows grooves and discontinuities in the articular margins probably from where the bodies were detached. The underlying bone is sclerotic. The knee is most frequently involved followed by hip, elbow and shoulder joints. Although a trauma history is frequently elicited, the role of developmental and circulatory factors can not be ignored. It is believed, that the lesions can heal in skeletally immature individuals, but not in adults.

Synovial Chondromatosis (Synovial Chondrometaplasia)

Synovial chondromatosis is a benign nodular cartilaginous proliferation arising in the synovium of joints, bursae or tendon sheaths. It occurs often in adults. Joints involved include the knee and less commonly the hip, elbow, wrist, ankle, shoulder or the temporomandibular joint (Fig. 3.17a, b). Presentation is with pain, mass or both.

Grossly, there are multiple (many) nodules of cartilage either free within the joint or attached to the synovium that vary from a few millimeters to a few centimeters (Fig. 3.18). The nodules are variably cellular with the chondrocytes present in clusters, a very characteristic finding (Fig. 3.19a, b). Mitoses are uncommon. There may be ossification.

Chondromalacia Patella

Chondromalacia patella occurs in younger often female patients and is a form of chondrolysis. The patellar cartilage surface becomes softened and may develop fissures or be lost altogether. MRI has become a useful tool to evaluate the hyaline cartilage in joints and on the posterior aspect of the patella. Most believe that chondromalacia patella is the final common pathway to a number of problems including

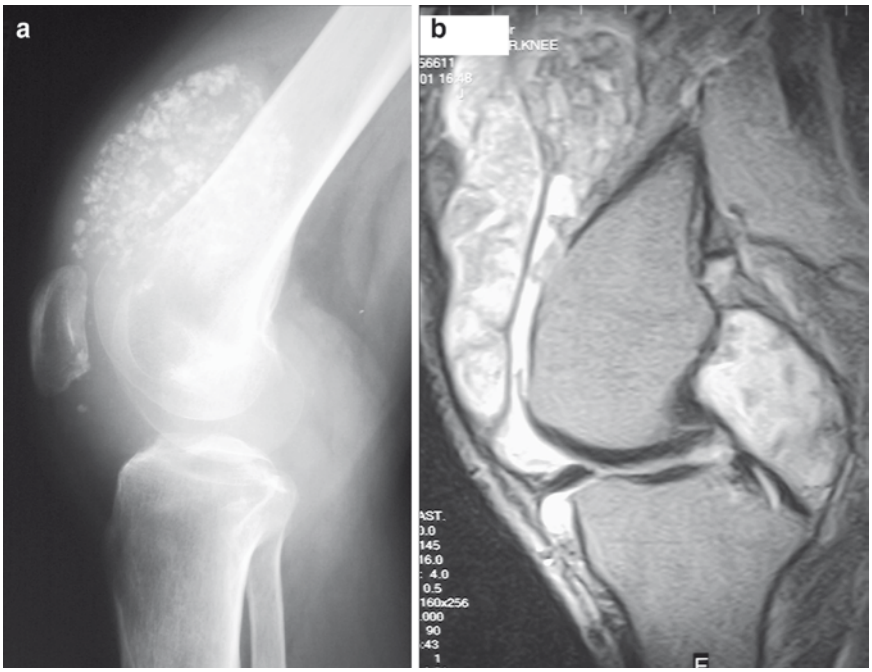

Fig. 3.17 (**a**, **b**): Lateral radiograph (**a**) of the knee from a 40-year-old man showing increased density about the joint and multiple calcified loose bodies within the synovial space. The sagittal T2W MR image (**b**) shows fluid within the joint and multiple lower signal loose bodies both in the suprapatellar bursa and the posterior portion of the joint

Fig. 3.18 Synovial chondromatosis showing multiple yellow cartilaginous bodies

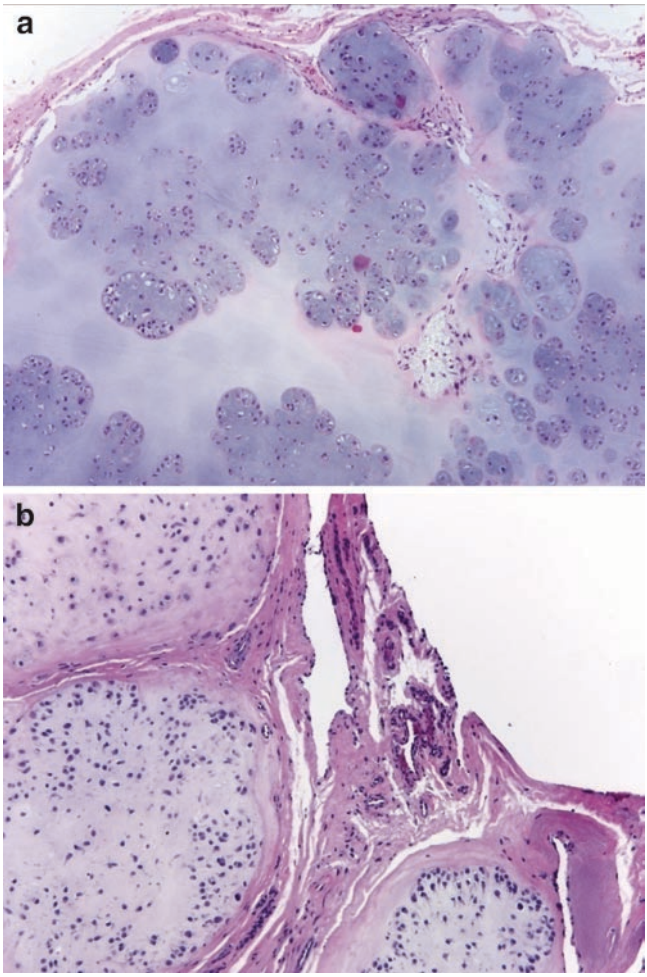

Fig. 3.19 (**a**, **b**): Low-power photomicrograph of synovial chondromatosis showing embedded cartilage bodies within synovium (**a**). At a higher power (**b**) the characteristic clustering of chondrocytes is more apparent

trauma, patellar tracking abnormalities, chronic muscle imbalance about the knee and patellar hypermobility.

Suggested Readings

Diagnostic Imaging of Musculoskeletal Diseases: A Systematic Approach, Akbar Bonakdarpour, William R. Reinus, Jasvir S. Khurana (Eds.), Humana Press, 2009
Bone Pathology, Jasvir S. Khurana, Humana Press, 2009

Chapter 4
Infections of Bones

Edward F. McCarthy

Osteomyelitis, or infection in bone, has a wide variety of radiologic and histologic features. Early acute osteomyelitis may present as an aggressive lytic lesion. Chronic osteomyelitis produces extensive reactive change.

Microorganisms find their way into bone by two mechanisms, via the bloodstream or via direct invasion. When bone is infected via the bloodstream, a syndrome known as *hematogenous osteomyelitis*, organisms originate elsewhere in the body. In direct invasion, often referred to as *secondary osteomyelitis* organisms are inoculated directly into bone from an adjacent soft-tissue infection or, as in some open fractures, from a source outside the patient.

Bone infections are usually caused by bacteria, though they may result from any kind of microorganism. The clinical syndrome associated with the initial invasion of microorganisms is known as *acute osteomyelitis*. If the infection is not completely eradicated, a continuous interaction of microbial growth and reactive bone formation results in *chronic osteomyelitis*. On occasion, an episode of acute osteomyelitis is subclinical. A patient's defenses confine the infection to a localized zone of the bone. This presentation is called *subacute osteomyelitis*.

The initial phase in the pathogenesis of osteomyelitis is bone destruction with an abscess formation. Cytokines, released from the inflammatory cells, activate osteoclasts to resorb bone. These cytokines include tumor necrosis factor (TNF), interleukin-1 (IL-1), prostaglandin E_2, and others. Although osteoclasts are responsible for resorption of viable bone in all physiologic and pathologic states, there is some evidence that inflammatory cells may be able to resorb necrotic bone.

In addition to osteoclast-mediated bone destruction, the integrity of the bone is further compromised by the growing subperiosteal abscess. The elevated periosteum over the abscess disrupts blood vessels, and this causes segmental cortical necrosis. These necrotic segments are known as *sequestra*. In contrast, the periosteum, which has an external blood supply, remains viable and produces reactive new bone. This reactive bone, known as an *involucrum*, encases the abscess and the sequestra.

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DOI 10.1007/978-0-387-89845-2_4,

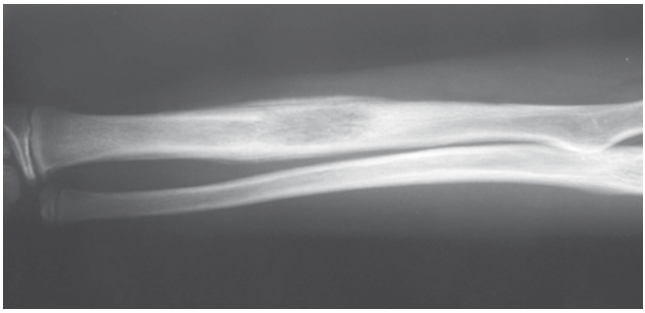

Fig. 4.1 Plain radiograph of acute osteomyelitis. There is an aggressive lytic lesion in the mid-shaft of the radius of a child. This radiograph would be indistinguishable from an aggressive malignant tumor

Patients with acute osteomyelitis present with pain, fever and an elevated E.S.R. The most sensitive indicator of acute osteomyelitis is the bone scan, an imaging modality which is positive within 48–72 h after the onset of symptoms. The bone scan, however, is non-specific. Other processes, such as neoplasms, can cause similar changes.

The plain radiograph is more specific, but the changes are not apparent until 10–14 days after the onset of symptoms. The first change is usually the appearance of a poorly defined lytic area in the metaphysis adjacent to the physis (Fig. 4.1). Usually, the amount of lucency seen on the plain radiograph does not reflect the total amount of bone tissue involved by the inflammatory process. A sequestrum, if present, appears as a radiodensity within the area of bone destruction.

Appearing about the same time as the lytic area, a thin line of periosteal new bone forms on the adjacent cortex. Generally, the amount of periosteal new bone parallels the amount of medullary bone destruction. This characteristic radiographic pattern of acute osteomyelitis helps distinguish it from other permeative processes in which the amount of bone destruction and periosteal reaction are not equivalent.

Occasionally, the body's defense mechanisms are able to contain but not eradicate the initial infection of hematogenous osteomyelitis. In this event, patients may be asymptomatic. Usually, however, mild symptoms, such as vague pain and low-grade fever, are present for months. This syndrome is known as subacute osteomyelitis or a *Brodie's abscess*. Plain radiographs show a well-defined metaphyseal lytic area surrounded by a rim of reactive bone (Fig. 4.2). It is most commonly seen in the tibia, but the femur and tarsal bones are also favored sites.

Chronic osteomyelitis is the symptomatic, long-term infection of bone due to failure to eradicate hematogenous or secondary osteomyelitis. This condition is associated with marked disability and is always difficult, sometimes impossible, to eradicate. Most cases of chronic osteomyelitis result from open fracture-related secondary osteomyelitis. In fact, 5% of open fractures result in this syndrome. In addition, 5% of cases of acute hematogenous osteomyelitis also become chronic

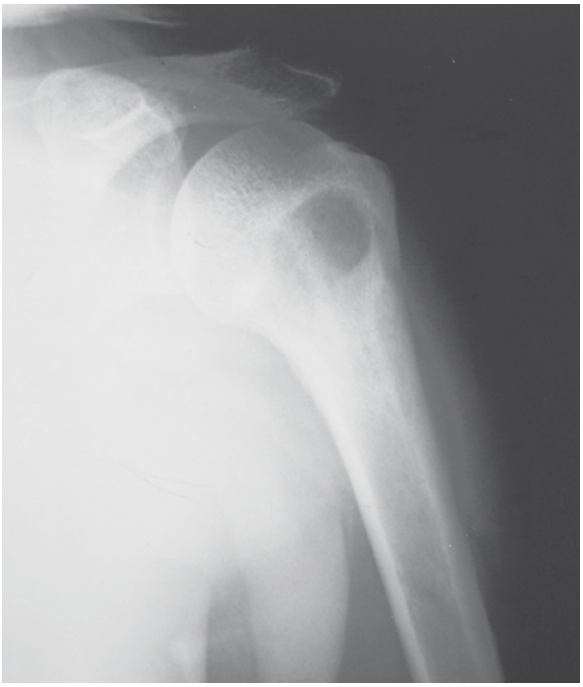

Fig. 4.2 Plain radiograph of sub-acute osteomyelitis in the proximal humerus. There is a well defined lytic lesion surrounded by a rim of reactive bone

bone infections. The progression usually becomes clinically evident within 1 year of the primary infection, although an 80-year interval has been reported.

The characteristic feature of chronic osteomyelitis is the tenacious persistence of microorganisms. These organisms cause continuous, smoldering bone destruction and sequestration. The dead bone fragments harbor the microorganisms and insulate them from both host defense mechanisms and antibiotics. In addition, continuous reactive bone formation makes surgical debridement difficult. As a result, infection persists for many years, and sometimes it lasts for the remainder of a patient's life.

Plain radiographs show evidence of continuous bone destruction and repair, processes which alter the shape of the bone. Multiple ill-defined radiolucent areas alternate with radiodense reactive bone (Fig. 4.3). Also, there is extensive periosteal new bone formation which increases the diameter of the bone. This periosteal bone reaction may be extensive and markedly distort the bone contour. Small radiodense areas, representing sequestra, may be present within the radiolucent areas. A CT scan is often necessary to localize these sequestra.

Osteomyelitis is characterized by bone destruction, the replacement of bone marrow by inflammatory tissue, and reparative new bone formation. The inflammatory tissue is similar to that seen in infection in any other organ (Fig. 4.4). The pathologist must be aware of two diagnostic principles: (1) the diagnosis of osteomyelitis

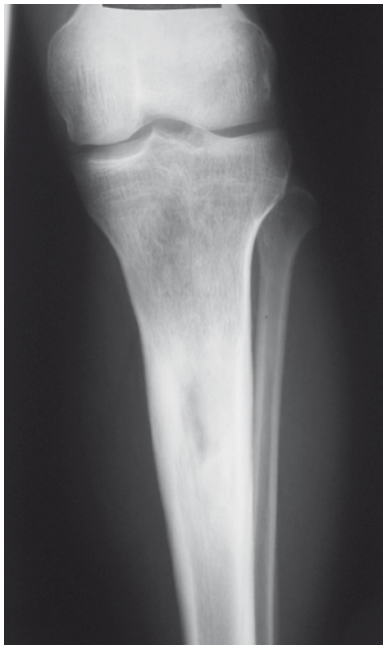

Fig. 4.3 Chronic osteomyelitis of the tibia. There is a dense zone of reactive bone indicating long standing repair. This surrounds an area of lucency

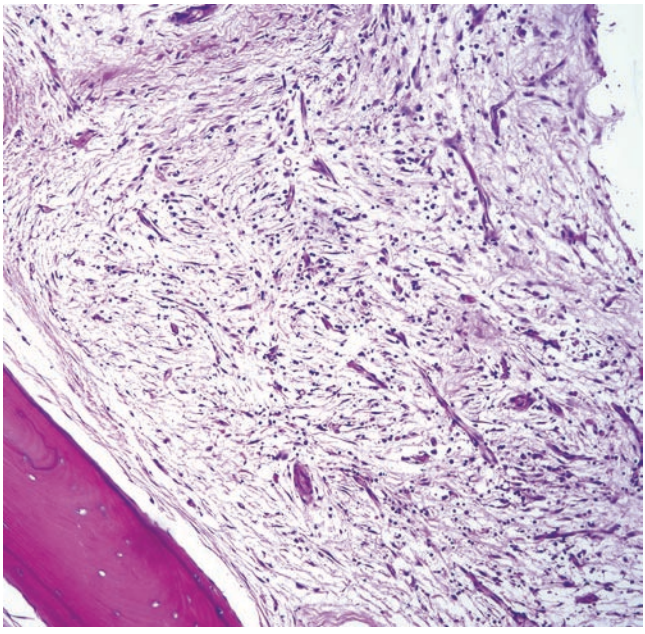

Fig. 4.4 Osteomyelitis, medium power photomicrograph. There is inflamed granulation tissue replacing the bone marrow. This pattern would be present in both acute and chronic osteomyelitis. Therefore, the distinction between acute and chronic osteomyelitis cannot be made on histologic grounds alone

should only be made in the proper clinical and radiographic setting, and (2) the various syndromes of osteomyelitis – acute, subacute, and chronic – cannot usually be distinguished histologically.

The first principle is based on the fact that in the bone marrow, inflammation is not synonymous with infection. Marrow fibrosis with an inflammatory cell infiltrate is a non-specific reactive change which occurs focally or diffusely in many other clinical settings. For example, inflammation of the marrow is present in healing fractures, osteoarthritis, inflammatory arthritis, and in bone adjacent to neoplasms or infarcts. Therefore, the unequivocal diagnosis of osteomyelitis should only be made in a clinical and radiographic setting consistent with the disease. In ambiguous cases, the pathologist should suggest that an unexplained inflammatory reaction in bone be correlated with the radiographs, clinical history, or microbiologic cultures.

The second principle in the diagnosis of osteomyelitis is that the various syndromes – acute, subacute, and chronic osteomyelitis – are clinico-radiologic entities. Because the microscopic features of inflammatory reactions in these syndromes overlap, they cannot be distinguished histologically. For example, tissue from an active focus of chronic osteomyelitis may contain an acute purulent exudate, a feature commonly seen in acute osteomyelitis. The pathologist should only render a diagnosis of osteomyelitis.

Despite overlapping histologic features, certain patterns of inflammation are suggestive of each syndrome, though they should never be used to render diagnoses of specific syndromes. In acute osteomyelitis, for example, suppuration in the marrow is common, and there is extensive osteoclastic bone resorption. In subacute osteomyelitis, acute purulent inflammation is less prominent. The marrow is replaced by edematous granulation tissue containing, in addition to neutrophils, a mixture of lymphocytes and plasma cells. In chronic osteomyelitis, there is usually marrow fibrosis with varying numbers of chronic inflammatory cells. Often, native trabecular bone is encased by layers of appositional reactive bone, a feature leading to radiodensity. Although focal bone necrosis is present in all syndromes of osteomyelitis, necrotic bone is especially prominent in chronic osteomyelitis.

Tubercular, Viral, Fungal and Parasitic Osteomyelitis. With the advent of travel and prevalence of a large number of patients with reduced immunity due to a variety of reasons (transplants, drug therapy, HIV infections) etc. several cases of unusual organisms causing bone infections are being seen. Tubercular osteomyelitis is often seen in the form of reactivation of a primary focus. In the developing world, it is often seen in children however in the richer countries it is seen in the setting of reduced immunity (sometimes with atypical mycobacteria). Classical tuberculosis is divided into the "granular" and "exudative" forms depending on the amount of pus formed. Caries sicca is a particularly dry form often involving the shoulder. Pott spine is tuberculosis of the spine, generally seen involving the disc space and portions of the immediately adjacent anterior vertebral bodies, clinically creating a gibbus deformity. Histologically, a granulomatous inflammation is seen and quite often (but not always) mycobacterial organisms are seen with the use of special stains such as the Ziehl–Neelsen or auramine–rhodamine). Cultures are usually positive. Syphilitic osteomyelitis due to Treponema pallidum is no longer a world-wide disease and is currently

seen only in pockets where significant infection persists. Like pyogenic osteomyelitis it starts as a metaphyseal infection but it is characteristically a low-grade disease. Histologically it is characterized by lymphocytes, plasma cells and granulomas (gumma). It may also occur as a congenital infection. Fungal infection of bone is very uncommon. Blastomycosis, Coccidiodomycosis, Actinomycosis, Maduramycosis and Sporotrichosis are the more common infections seen. Blastomycosis may be relatively more frequently seen in the mid-western parts of the United States, but is still very rate. Often these infections involve the hands, feet or the craniofacial skeleton. The AIDS epidemic has changed the face of such infections considerably, and increased their incidence. Identification of the organisms using standard pathologic techniques (such as silver or periodic acid Schiff stains) and standard culture techniques in the laboratory form the basis of diagnosis. Although rare in the west, parasitic osteomyelitis is not infrequently encountered in certain pockets of the world. In parts of the Middle East, South Asia and certain African countries there is a high incidence of hydatid disease of bone. Viral osteomyelitis and bone infection due to unusual organisms such as the cat-scratch bacillus is rare but reported.

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Edward F. McCarthy and Frank J. Frassica. W.B. Saunders, 1998, Pathology of Bone and Joint Disorders with Clinical and Radiographic Correlation. Bone Pathology: Jasvir S Khurana, Humana Press, 2009

Chapter 5
Metabolic Bone Disorders

Edward F. McCarthy

Metabolic bone diseases are a group of disorders caused by alterations in the chemical milieu of the body. In almost all cases, the end result is decreased skeletal mass. This is known as osteopenia or, in its more pronounced form, osteoporosis. Severe osteoporosis can lead to structural failure of the skeleton. This concept of organ failure is just as valid in the skeletal system as it is in the heart, the kidney, etc. Early stages of metabolic bone disease may be difficult to diagnose because 30% of the bone mass must be removed before the change can be appreciated on plain radiographs. Therefore, patients may be evaluated with a DEXA scan, a very sensitive radiographic study which determines bone loss.

Metabolic bone disease may be divided into four categories: focal osteoporosis, specific endocrine abnormalities, primary osteoporosis, and secondary osteoporosis.

Focal osteoporosis results from disuse of the skeleton. This may be of a single extremity or it may be of the entire skeleton. Traumatic disorders or joint disease may lead to non-weight bearing, and this may cause decrease in bone mass. Weight bearing and the use of the skeleton is necessary to preserve healthy bones. This is mediated by electric potentials which are generated when the bone is deformed during use. Total osteoporosis may result from prolonged bed rest or weightless environments.

There are two specific endocrine abnormalities which cause distinctive histologic changes. The first is hyperparathyroidism. Hyperparathyroidism may be seen in parathyroid adenomas (primary hyperparathyroidism) or in renal failure (secondary hyperparathyroidism). Primary hyperparathyroidism is the third most common endocrine disorder. Nowadays, cases are diagnosed very early on routine screening studies, and, as a result, clinical bone disease is extremely rare in primary hyperparathyroidism. Evidence of bone changes are most commonly seen in the secondary hyperparathyroidism of chronic renal failure. In fact, almost all patients with chronic renal disease will have skeletal manifestations. The most sensitive radiographic change is seen in the distal phalanges where there may be erosion

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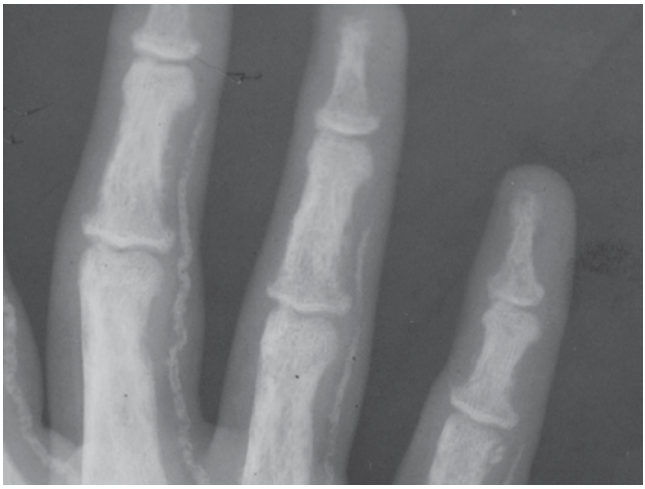

Fig. 5.1 Plain radiograph of the hand in very early hyperparathyroidism. There is sub-periosteal resorption along the ulnar aspect of the phalanges

of the tufts of the distal phalanges (Fig. 5.1). Excess PTH activity cause generalized skeletal resorption due to indirect activation of osteoclasts. The pattern of resorption is very distinctive and is known as tunneling resorption. Each trabecula is hollowed out by a cutting cone of osteoclasts followed by loose fibrous tissue (Fig. 5.2). Eventually there is marrow fibrosis and woven bone (Fig. 5.3). Long standing renal disease will result in severe skeletal abnormalities. In addition to the osteopenia produced by tunneling resorption, lytic skeletal lesions occur due to large areas of resorption (Fig. 5.4). These lesions, composed of giant cells, fibroblasts and reactive bone, are known as giant cell reparative granulomas. Because many of these lesions contain abundant hemosiderin, they are sometimes called "brown tumors of hyperparathyroidism" (Fig. 5.5).

The other specific endocrine abnormality is vitamin D deficiency resulting in rickets in children and osteomalacia in adults. Osteomalacia means soft bones. Vitamin D is necessary for the absorption of calcium in the bowel. If the calcium levels in the body are not sufficient, the bone is not mineralized. In children, the bone formed at the epiphyseal plate is not mineralized resulting in skeletal deformity and short stature. In adults, bones produced in normal bone turnover are not mineralized resulting in soft bones. Osteomalacia is extremely common. Thirty-three percent of institutionalized patients and 50% of homebound elderly patients may have osteomalacia. This is a result of poor diet and inadequate sun exposure. Radiographically, patients are osteopenic and often have multiple stress fractures (Fig. 5.6). The characteristic histologic change of osteomalacia can only be seen in undecalcified preparations of bone. Thus, the diagnosis cannot be made in routine surgical pathology practice. The change is reflected as very *wide osteoid seams* (Fig. 5.7). These osteoid seams are unmineralized osteoid.

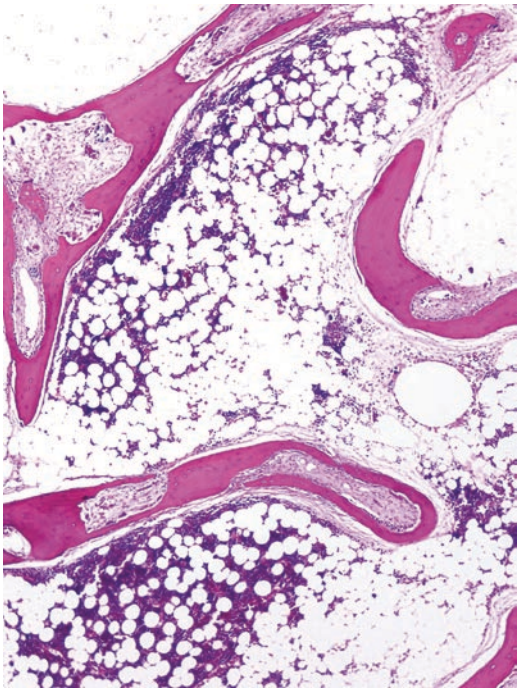

Fig. 5.2 Photomicrograph showing tunneling resorption. Each trabeculae is hollowed out by a cone of osteoclasts and fibrous tissue

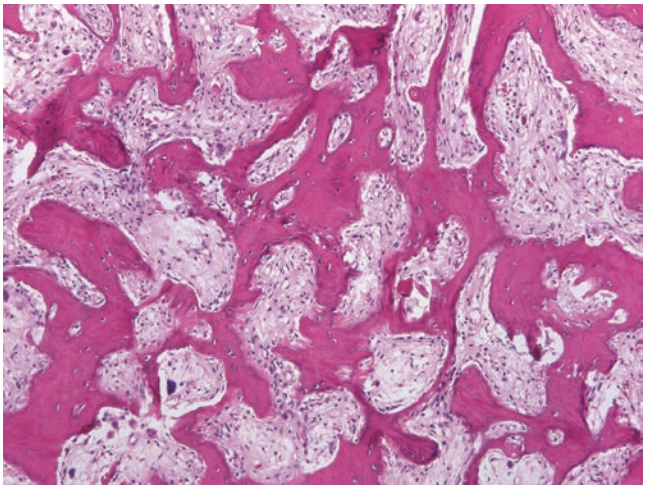

Fig. 5.3 Photomicrograph showing extensive marrow fibrosis with woven bone

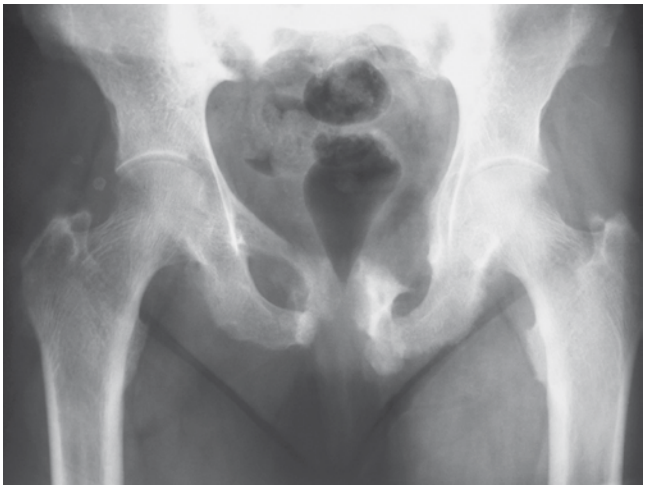

Fig. 5.4 Plain radiograph of the pelvis in a patient with renal osteodystrophy. There is a lytic lesion of the left pubic ramus. This is a giant cell reparative granuloma

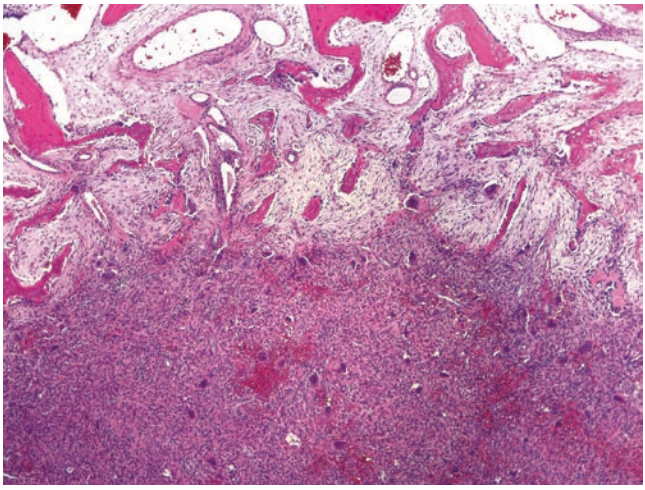

Fig. 5.5 Photomicrograph of giant cell reparative granuloma. There are multi-nucleated giant cells, extravasated red cells, and fibroblasts surrounded by a zonal pattern of reactive bone

Primary osteoporosis is the third pattern of metabolic bone disease. Primary osteoporosis may be divided into senile osteoporosis and post-menopausal osteoporosis. It is said that osteoporosis is a geriatric disease that begins in childhood. People reach their peak bone mass at about age 28 or 29. From thereafter all patients undergo a gradual decrease in their bone mass. If this decrease is extremely rapid, patients may reach the zone of skeletal failure before dying. They may sustain

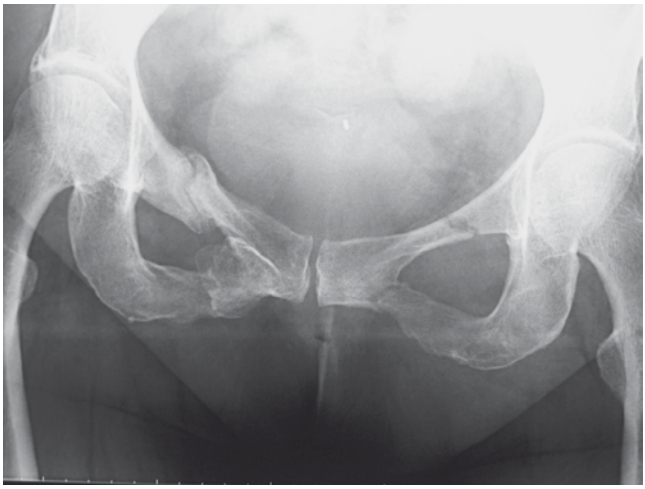

Fig. 5.6 Plain radiograph of a patient with osteomalacia. There are multiple stress fractures of the anterior portion of the pelvis including the pubic and ischial rami

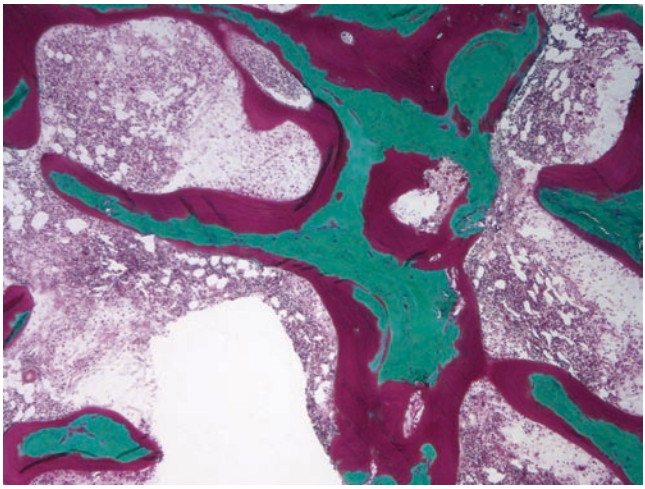

Fig. 5.7 Photomicrograph of an undecalcified bone section stained with a tri-chrome stain. The *red* represents unmineralized osteoid. There are extensive wide osteoid seams consistent with a mineralization defect

multiple fractures. Particularly they suffer fractures of the hip, spine and wrist. These fractures are very common in the elderly population (Fig. 5.8).

Senile osteoporosis is a gradual loss of bone secondary to *osteoblast senescence*. The remodeling rate is normal. Senile osteoporosis occurs in all patients in all cultures throughout all periods of history. This may be contrasted with post-menopausal

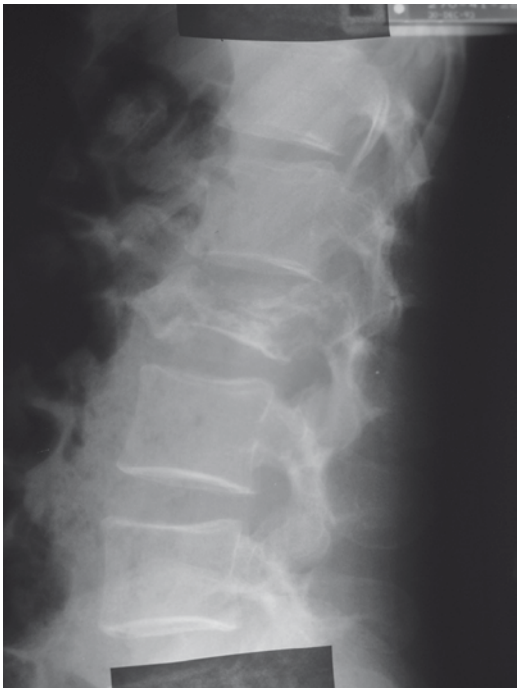

Fig. 5.8 Severe osteoporosis with a compression fracture of a lumbar vertebrae

osteoporosis which is a rapid decrease of skeletal mass which occurs to some women around menopause. Some women are exquisitely sensitive to estrogen withdrawal. Estrogen withdrawal releases cytokines which stimulate osteoclastic bone turnover. The increased turnover results in a more rapid incremental bone loss.

Secondary osteoporosis is a pattern of generalized bone loss that occurs in patients who are not yet pre-menopausal or not in the old age group. Generalized bone loss in a middle age person is generally referred to as secondary osteoporosis and is usually related to a specific problem. The most common causes are steroid therapy or amenorrhea. Steroid therapy may be seen in patients on long term steroids for organ transplants or auto-immune disorders. Approximately 30% of patients on long-term steroids will have vertebral crush fractures. Amenorrhea is another cause of secondary osteoporosis. Young women with eating disorders may develop severe osteoporosis. Similarly, women who have had their ovaries removed may develop osteoporosis as well.

The histopathologic features of senile or postmenopausal osteoporosis are not distinctive except for decreased cortical thickness and decreased cancellous bone volume (Fig. 5.9).

Paget disease is characterized by *focal or multifocal chaotic and increased bone remodeling*. The end result is architectural distortion of the bones. Although bones are denser than normal, they are more fragile. Paget disease occurs primarily in older people. Approximately 10% of people over 60 in the US and UK have some evidence

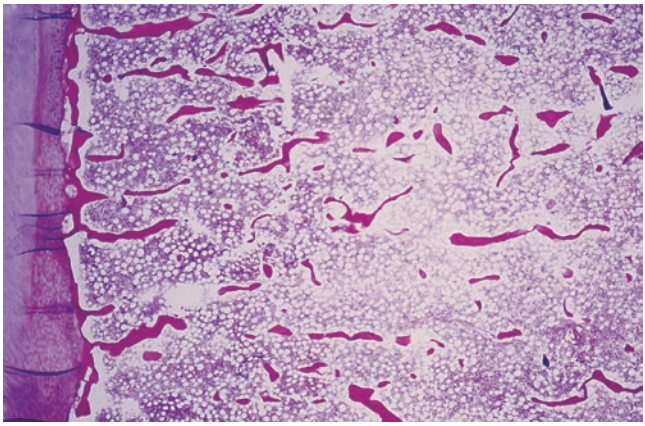

Fig. 5.9 Photomicrograph of a patient with severe post-menopausal osteoporosis. The section is from a vertebral body. There is marked thinning of the subchondral plate as well as thinning of trabeculae. The bone is otherwise unremarkable

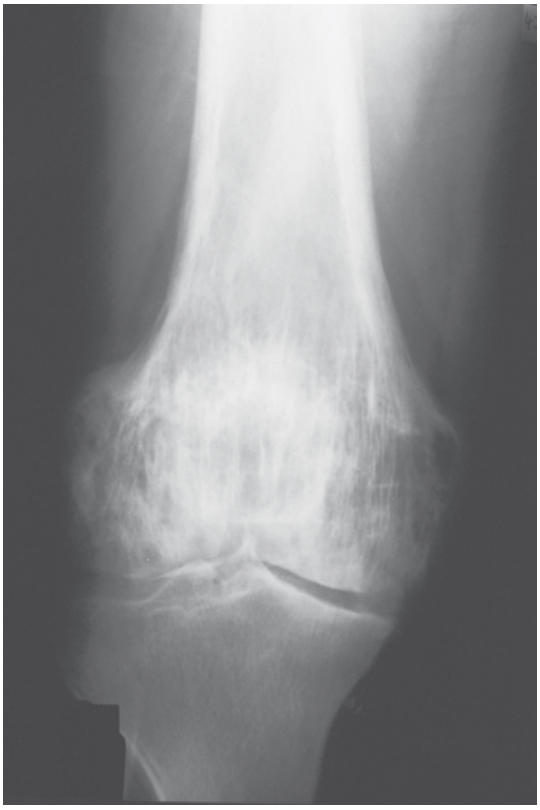

Fig. 5.10 Paget disease involving the distal femur showing a V-shaped lytic lesion with mild expansion of the bone along with a periosteal reaction, thickening of the cortices and the trabeculae (which are prominent) and slight blurring of the cortico-medullary junction

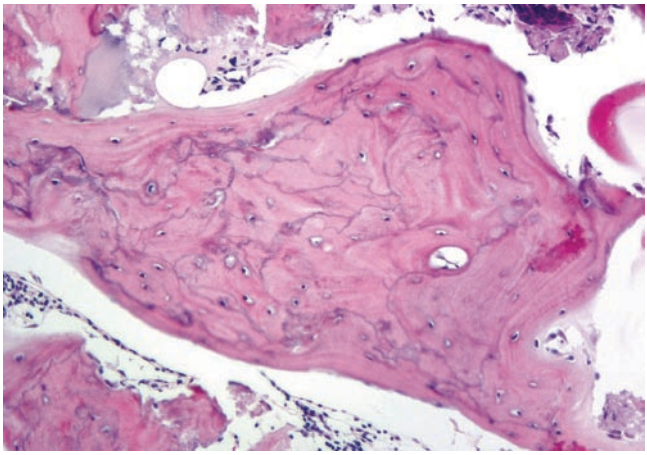

Fig. 5.11 Paget disease showing very prominent blue cement lines. The bone bounded by these lines is mostly lamellar with the lamellae arranged haphazardly. The overall effect is that of a jig-saw puzzle. In other areas prominent osteoclastic and osteoblastic activity was seen along with fibrosis and increased vascularity of the marrow

of Paget disease. It favors the axial skeleton. The skull, spine and pelvis are the most common locations.

Paget disease occurs primarily in people of Northern European descent. It also tends to cluster in families. Very likely Paget disease is caused by a slow virus that one acquires in young adulthood or childhood and only finds pathologic expression in older age. In fact, viral material is visible in the osteoclasts of Paget disease.

Radiographically, Paget disease is characterized by thickening of the bones with increase radiodensity. The most prominent radiographic feature is coarsening of the trabeculae. There is also blurring of the cortical medullary junctions (Fig. 5.10). Deformity of the bones is common due to stress microfractures. Histologically, there is evidence of increased bone remodeling in the form of an increased number of blue remodeling lines. The number of remodeling lines is so increased and interconnected that it resembles a mosaic. This is known as the "*mosaic pattern*" of remodeling lines (Fig. 5.11).

The complications of Paget's disease are usually a result of the skeletal deformities and fragilities. Patients also have pain and cranial nerve palsy. Sometimes they have cardiac failure due to high output demands. The most dreaded complication is a sarcoma that complicates approximately 2% of patients with Paget's disease.

Suggested Readings

Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, Clifford Rosen, Editor. American Society of Bone and Mineral Research, Seventh Edition, 2008

Pathology of Bone and Joint Disorders with Clinical and Radiographic Correlation, Edward F. McCarthy and Frank J. Frassica. W.B. Saunders, 1998

Chapter 6
Tumors and Tumor-Like Lesions of Bone

Jasvir S. Khurana and Edward F. McCarthy

Malignant bone tumors are rare. The lack of familiarity on a day to day basis and the need to utilize clinical and imaging information in their diagnosis and management creates a feeling of difficulty in the team involved with their management including pathologists, radiologists and surgeons. The following discussion lists the most important lesions and their salient radiological and pathological features.

Bone Cysts

Bone cysts are fluid-filled cavities with a connective tissue lining and varying numbers of septae. There are three important types of bone cyst, and each contains a characteristic fluid. The first is the unicameral bone cyst, also known as a simple bone cyst. This type of cyst results from a temporary failure of bone formation during skeletal growth. The unicameral bone cyst usually has a single chamber and is filled with yellow, serous-like fluid. The second type of cyst, the aneurysmal bone cyst, is thought by many to result from a focal hemodynamic alteration in normal bone (primary aneurysmal bone cyst) or in a preexisting bone lesion (secondary aneurysmal bone cyst). Emerging studies have suggested that at primary aneurysmal bone cysts might be true neoplasms. An aneurysmal bone cyst contains many locules filled with blood. The third type of cyst is the subchondral cyst. Cysts in this category include osteoarthritic cysts, intraosseous ganglia, and post-traumatic cysts. Subchondral cysts occur adjacent to joints and contain mucoid or jelly-like material.

Bone cysts are radiolucent lesions and may therefore masquerade as solid neoplasms. However, the MRI, which readily recognizes their fluid content, has become an important tool in the diagnosis of these lesions. Although the fluid-filled nature of

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these cysts may now be recognized preoperatively, the pathologist must pay careful attention to the cyst's radiographic setting and the characteristics of its fluid to make the correct diagnosis.

Unicameral Bone Cyst

A unicameral bone cyst forms in childhood as a result of temporary cessation of medullary bone formation by the epiphyseal plate. This developmental failure results in a single-chambered, fluid-filled cyst in the metaphyseal portion of the bone. While the cyst is forming, a so-called "active" lesion, the cavity is adjacent to the epiphyseal plate. After medullary bone formation resumes, the cyst migrates into the diaphysis and is separated from the epiphyseal plate by normal cancellous bone. An important clinical feature of this lesion is its predilection for two locations: the proximal humerus (50% of cases) and the proximal femur (about 30% of cases).

Unicameral bone cysts almost always present in childhood or adolescence. In fact, 85% of lesions are diagnosed in patients under age twenty. The walls of a unicameral bone cyst are very thin, so many patients present with a pathologic fracture. Non-fractured lesions often present as incidental findings during radiologic studies for other conditions. Undoubtedly, many unicameral bone cysts are never diagnosed because most lesions are asymptomatic.

Unicameral bone cysts are usually diagnosed radiologically. Plain radiographs show a central and symmetric radiolytic lesion present in the metaphysis. The cortices are often thin and expanded. With actively growing cysts, the lytic area abuts the epiphyseal plate. Inactive cysts are separated from the epiphyseal plate by normal cancellous bone (Fig. 6.1). A unicameral bone cyst is characteristically equal or slightly greater in diameter to that of the epiphyseal plate. However, depending on the duration of activity, the length may vary from 3 to 13 cm. In about 20% of cases, a fractured cortical fragment falls into the distal portion of the cyst producing the "*fallen leaf*" sign (Fig. 6.2). In addition, some unicameral bone cysts contain faint granular or ring-shaped radiodensities.

Usually an MRI confirms the diagnosis of a simple bone cyst. The study shows a well-defined zone of very bright, uniform signal in T_2-weighted images. This finding confirms the high water content of the lesion. The signal from this zone is much less intense in T_1-weighted images.

Histologically, the lining membrane of unicameral bone cyst consists of bland fibrous tissue and occasional spicules of reactive bone (Fig. 6.3). A few osteoclast-like giant cells are usually present. In addition, approximately 10% of lesions contain cementum-like spherules in the lining membrane (Fig. 6.4). These eosinophilic bodies are thought to be either old fibrin coagula or osteoid. They frequently calcify and correspond to the granular densities seen on plain radiographs.

Surgery is no longer the prime therapy for unicameral bone cysts. Treatment is with intralesional injection of steroids or other sclerosing agents.

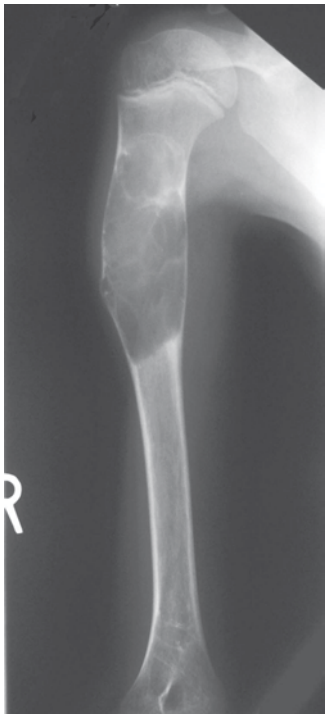

Fig. 6.1 Plain radiograph of an unicameral bone cyst. There is a lytic lesion in the proximal humeral metaphysis with symmetrical cortical expansion. There is a zone of normal bone between the top of the cyst and the epiphyseal plate

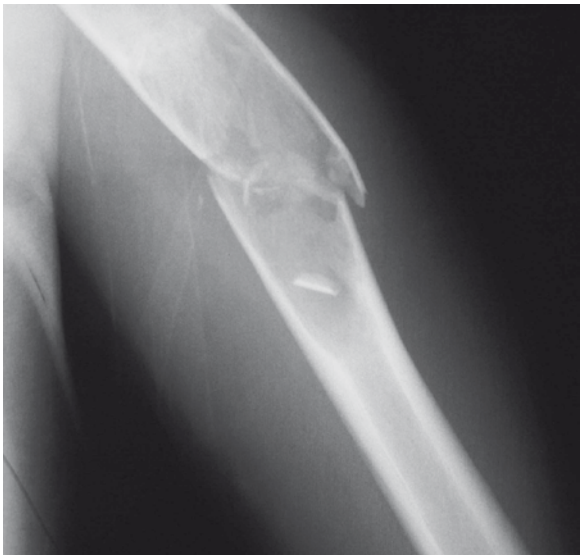

Fig. 6.2 Plain radiograph of an unicameral bone cyst with a fracture. A small fragment of cortex is present in the bottom of the cyst, the so called "fallen leaf sign"

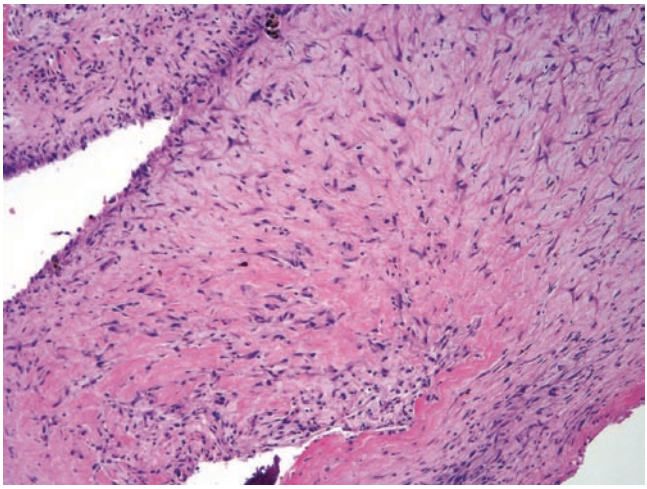

Fig. 6.3 Unicameral bone cyst, histology. The lining consists of a membrane of bland fibrous tissue

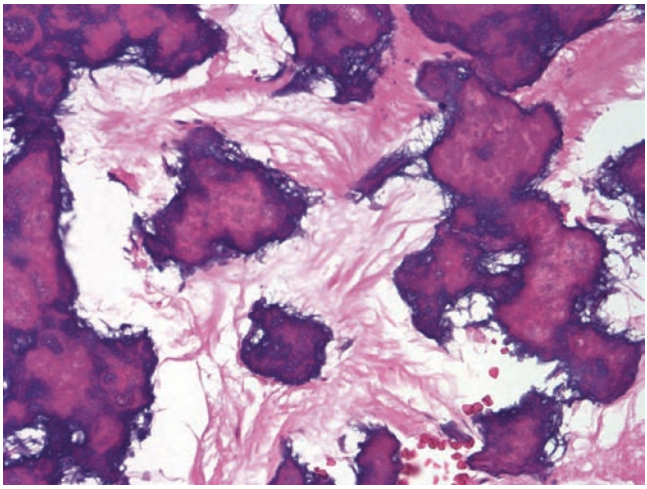

Fig. 6.4 Unicameral bone cyst, histology. Amorphous, cementum like material is often present in the lining of the cyst

Aneurysmal Bone Cyst

Aneurysmal bone cyst is a destructive, expansile bone lesion characterized by a reactive proliferation of connective tissue containing multiple blood-filled cavities. The cyst may arise de novo in bone (primary) or is engrafted on preexisting bone lesions (secondary), histologically identifiable in 30% of cases. The incidence of an

underlying preexisting lesion may be higher because the aneurysmal bone cyst process can totally efface the histologic features of the original lesion. In this event, the clinical and radiographic setting may be the only clue to the preexisting lesion. Neoplasms most frequently associated with aneurysmal bone cyst are chondroblastoma, giant cell tumor, chondromyxoid fibroma, and fibrous dysplasia. Lesional tissue from primary aneurysmal bone cysts generally contains translocations leading to the upregulation of the USP 6 gene.

Aneurysmal bone cysts occur at any age, although 60–85% of patients are under age 20. The distal femur and proximal tibia are the most common locations, followed by the posterior elements of the vertebrae. Any bone, however, including the cranium and facial bones, may be involved. In the long bones, the metaphysis is the most commonly affected area.

Aneurysmal bone cysts have a wide range of radiographic appearances. Some have a benign radiologic pattern with well-circumscribed margins, although they usually lack a sclerotic rim. By contrast, other aneurysmal bone cysts have an aggressive, permeative pattern. These lesions show marked cortical expansion, and sometimes a soft-tissue mass is present which is best visualized with MRI, is present (Fig. 6.5). The MRI of aneurysmal bone cysts shows multiple fluid-filled cavities. These cavities often show distinct fluid lines representing the interface between blood and serum, a feature best seen on T_2-weighted images (Fig. 6.6).

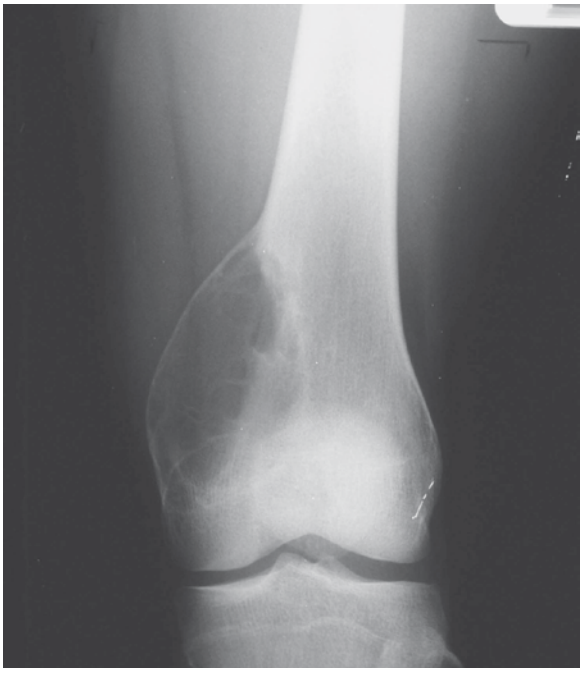

Fig. 6.5 Plain radiograph of aneurysmal bone cyst. There is an expansile lytic lesion in the distal femoral metaphysis

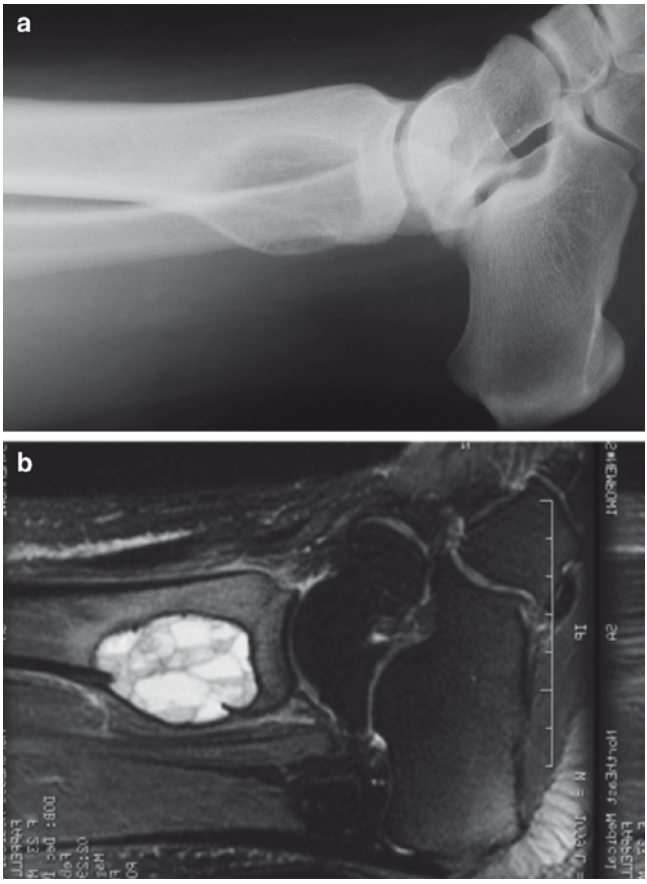

Fig. 6.6 (**a**) Plain radiographs of an aneurysmal bone cyst of the distal tibia. There is a well defined expansile lytic lesion. (**b**) A T_2-weighted MRI of the lesion. There are multiple locules with fluid/fluid lines

At surgery, the gross appearance of an aneurysmal bone cyst is a pulsatile mass with multiple blood-filled cavities. Heavy bleeding often follows a biopsy, and curettage produces abundant, spongy soft-tissue. The characteristic microscopic feature of aneurysmal bone cyst, best seen on low-power examination, is multiple blood-filled cavities of varying sizes (Fig. 6.7). The cavities lack an endothelial lining, and the stroma of the intervening septae consists of proliferating fibroblasts and scattered multinucleated giant cells (Fig. 6.8). Reactive bone, usually in broad bands, and fibromyxoid cartilage are often abundant. The stromal cells sometimes show many mitotic figures; however, the stromal cells are uniform and atypical mitoses are not present.

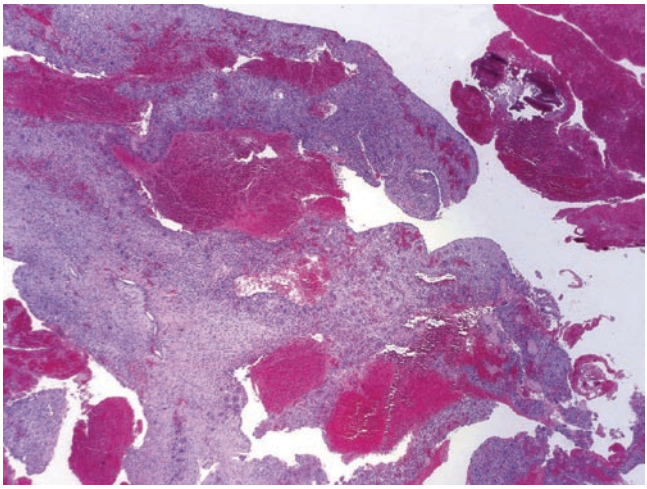

Fig. 6.7 Aneurysmal bone cyst, histology. Cellular membranes contain numerous blood filled lakes

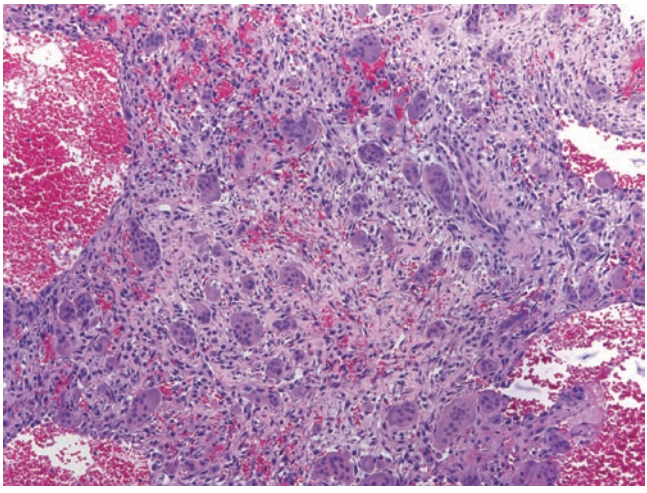

Fig. 6.8 Aneurysmal bone cyst, histology. The membrane of the aneurysmal bone cyst contains zones with numerous multi-nucleated giant cells

Subchondral Cysts

Acquired subchondral bone cysts, known by a variety of names depending on clinical and radiographic features, are probably all caused by trauma to the joint surface. These lesions include osteoarthritic cysts, intraosseous ganglia, and post-traumatic cysts. Injury to the articular cartilage stimulates granulation tissue proliferation in

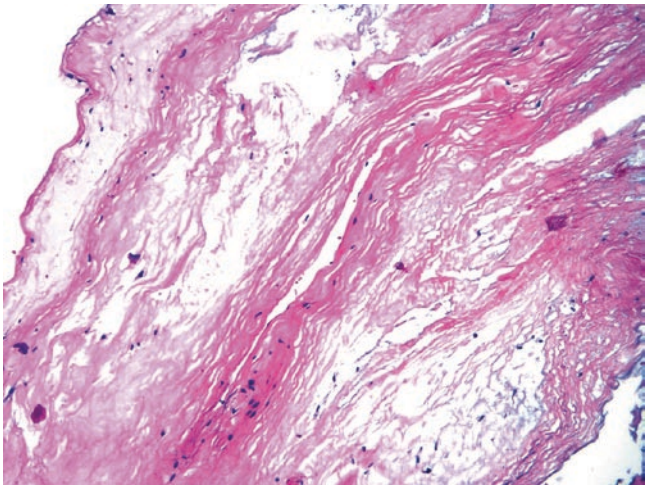

Fig. 6.9 Subchondral cyst, histology. Fibrous membranes with numerous areas of myxomatous degeneration

the marrow spaces of the subchondral bone. Then, foci of myxomatous change appear in the granulation tissue (Fig. 6.9). Finally, due to enlargement and coalescence of these foci, a cyst forms and causes local bone resorption. Regardless of the clinical setting, the result of this process is a subchondral radiolytic defect filled with granulation tissue and acellular myxoid material.

Osteoarthritic Cysts

Osteoarthritic cysts are a component of the degenerative changes of osteoarthritis. Patients are in their 50s and 60s, the usual age range for the onset of osteoarthritis. The subchondral cysts usually occur adjacent to areas of maximal joint space narrowing and are often present on both sides of a joint. The hip and knee are the most common joints to develop these cysts because these joints are most frequently involved by osteoarthritis (Fig. 6.10). Osteoarthritic cysts vary in size from a few millimeters to several centimeters.

Diagnostic problems occasionally arise because a subchondral cyst may develop when other radiologic features of osteoarthritis are minimal or even absent. In this event, a large cyst may radiographically mimic a bone neoplasm, particularly giant cell tumor. This diagnostic problem is most frequently encountered in osteoarthritic cysts of the proximal tibia. However, careful radiographic study usually demonstrates subtle changes of osteoarthritis. For example, patients may have small osteophytes or joint space narrowing visible only on weight bearing films. In addition, tiny cysts may be present on the other side of the joint. Finally, the MRI will correctly identify the fluid-filled cystic nature of these subchondral lesions.

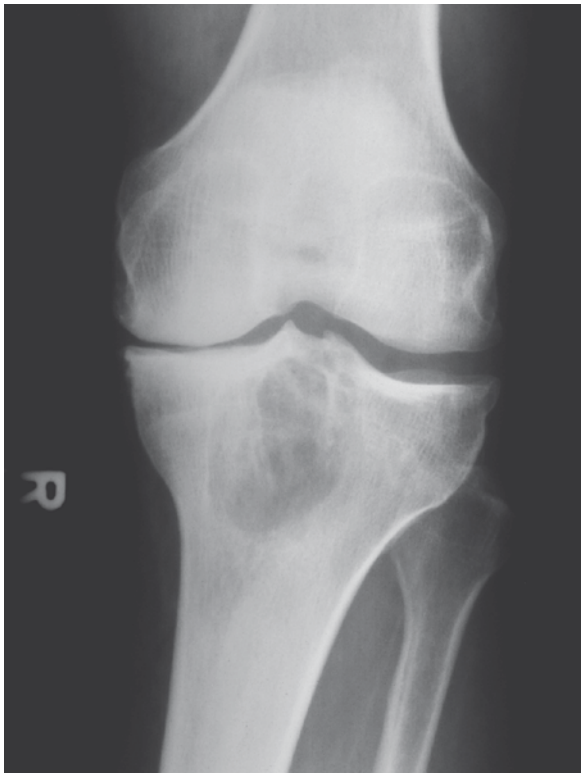

Fig. 6.10 Plain radiograph of an osteoarthritic cyst. In the proximal tibia there is a zone of radio-lucency adjacent to joint space narrowing

Intraosseous Ganglion

Intraosseous ganglia, although sharing histologic features with osteoarthritic cysts, are regarded as a distinct entity because patients lack other clinical and radiographic features of osteoarthritis. For example, trabecular thickening of the subchondral bone and joint space narrowing, characteristic features of osteoarthritis are not present with intraosseous ganglia.

However, most intraosseous ganglia are probably early manifestations of osteoarthritis before clinical and other radiographic features occur.

Intraosseous ganglia occur in middle-aged patients (mean age, 42 years) and most frequently involve the medial malleolus of the distal tibia, the proximal tibia, the carpal bones, and the acetabulum. Radiographically, these lesions are well-defined lytic defects in the epiphysis beneath the subchondral plate (Fig. 6.11).

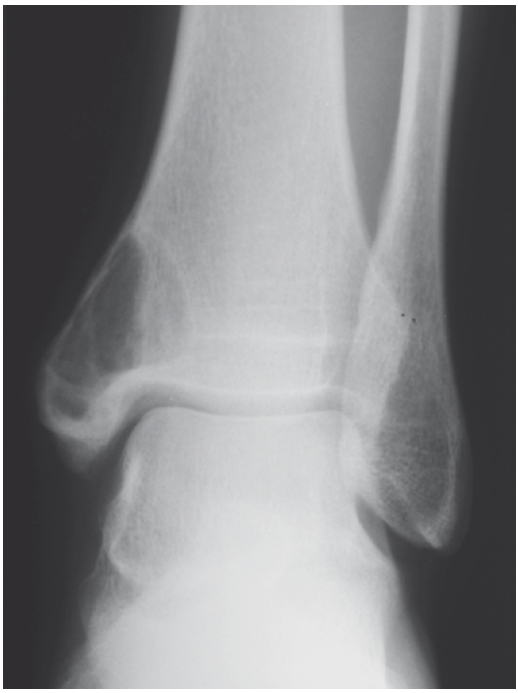

Fig. 6.11 Plain radiograph of intraosseous ganglion. In the epiphyseal/metaphyseal area of the distal tibia there is a well defined lytic lesion

Cartilage Forming Tumors

Cartilage lesions may be broadly divided into two categories: lesions of fetal cartilage and lesions of mature hyaline cartilage. The lesions of fetal cartilage are intraosseous radiolytic lesions that most commonly occur in children and young adults. Lesions of mature hyaline cartilage are characterized by radiographic ring and stippled radio densities on plain radiographs. They may occur on the surface of the bone or within the medullary cavity.

Chondroblastoma

The two fetal cartilage lesions are chondroblastoma and chondromyxoid fibroma. Chondroblastoma is a benign tumor of immature cartilage cells (chondroblasts). It generally occurs in the epiphyses of skeletally immature patients (although several cases of older patients and unusual locations have been reported). Most cases involve the long tubular bones; but cases have been described in short bones, flat bones, vertebrae and the craniofacial skeleton. The clinical presentation may be

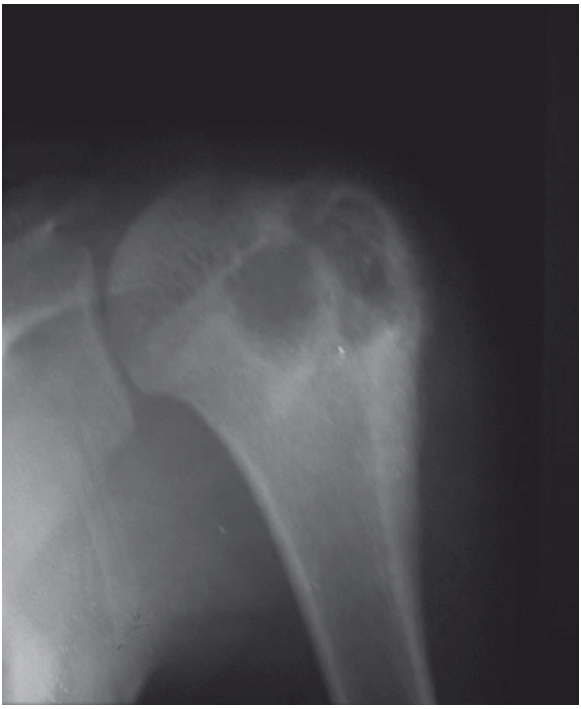

Fig. 6.12 Plain radiograph of chondroblastoma of the proximal humerus. The lesion is epiphyseal, does not expand the bone and is well delineated by a sclerotic rim

with pain or mass effects (such as tinnitus in temporal bone lesions). Radiologically, the lesions are lytic, epiphyseal, small (generally less than 5 cm) and sharply demarcated (sometimes with a sclerotic rim). There is generally no expansion of bone or periosteal reaction (except in large lesions in flat bones) (Fig. 6.12). Microscopically, the characteristic cell is the chondroblast. It is a uniform epitheloid cell with an oval nucleus showing a prominent groove. Variable numbers of osteoclasts may be present as may be a background chondroid matrix. A network of fine pericellular "chicken wire" calcification may be seen (Fig. 6.13a, b). A few typical mitoses are acceptable. Secondary aneurysmal bone cyst formation is common. The chondroblasts generally express S-100 protein and vimentin. Chondroblastomas are benign tumors. Marginal or intra-lesional procedures (curettage and cryotherapy or bone grafting) have been successful in many cases. A few benign chondroblastomas have "passively" metastasized. The metastases in these cases have responded well to excision. It is hypothesized that rather than representing a true metastasis, the tumor may have got passively carried to the lung by "falling into" adjacent peritumoral veins.

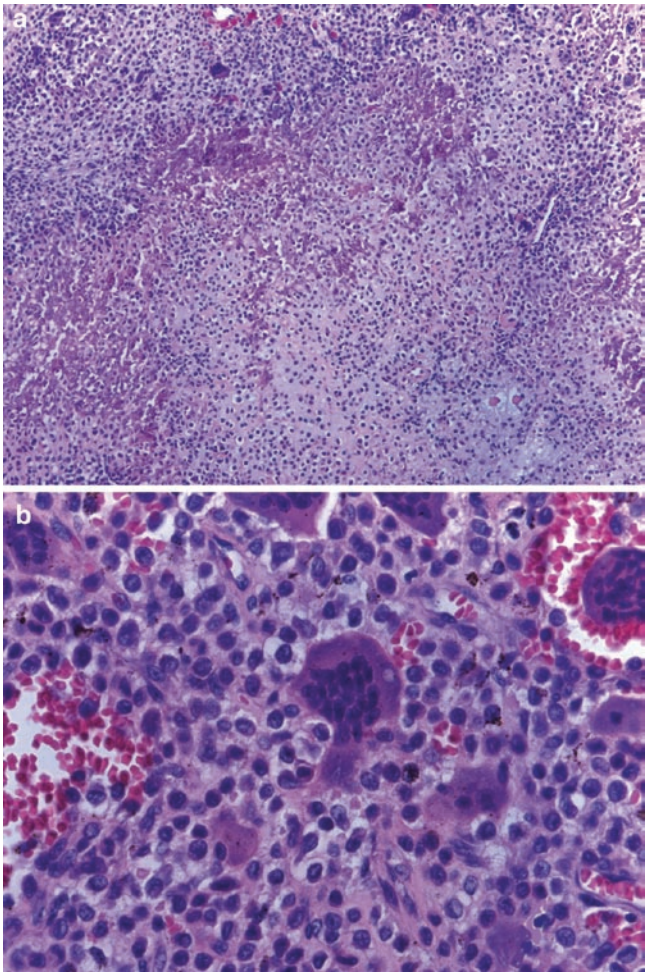

Fig. 6.13 (**a**) Low power photomicrograph showing a proliferation of uniform cells in a chondroid matrix. There is focal pericellular calcification seen. (**b**) The chondroblasts can be seen as uniform cells with round or oval nuclei, some showing grooves. The cells have abundant eosinophilic cytoplasm. Several multinucleated giant cells are seen

Chondromyxoid Fibroma

Chondromyxoid fibroma is a rare tumor composed of lobules of spindle shaped cells with abundant intercellular myxoid or chondroid material. The lobules are classically hypocellular centrally with a condensation of cells in the periphery of the lobules. Some cases show areas that merge into chondroblastoma like morphology.

The tumor occurs most frequently in the second or third decades. It is a metaphyseal tumor in the long bones (where it is most frequent), but flat bones and the

bones of the hands and feet may also be involved. Radiologically, the lesions are metaphyseal, eccentric and sharply delineated. In the small bones of the hands and feet there may be bony expansion. There may also be focal cortical breakthrough and extension into soft-tissue (Fig. 6.14a, b). Microscopically the tumor is well demarcated, and there is no evidence of infiltration into the Haversian system or entrapment of bone. The growth pattern is lobular with the lobules showing condensation of the cells to the periphery. Myxoid change, chondrocyte atypia or significant mitotic activity are absent. Osteoclast like giant cells may be present and there may be a secondary aneurysmal bone cyst change (Fig. 6.15a, b).

Osteochondroma

Lesions of mature hyaline cartilage can be divided into surface and medullary lesions. There are both benign and malignant lesions in each location. The most common surface benign cartilage lesion is the osteochondroma. An osteochondroma is a cartilage capped bony projection on the external surface of bone. By definition, the cortex of the underlying bone is continuous with that of the osteochondroma, as is the marrow cavity it encloses. Osteochondromas are very common lesions, many series suggest that they comprise about a third of all benign bone tumors. However, since many are asymptomatic, the true incidence is unknown and may be much higher. Osteochondromas may be solitary, or multiple, the latter is generally seen in a familial setting with an autosomal dominant inheritance (Fig. 6.16). There is evidence to suggest that genetic alterations may be responsible for osteochondromas. Certain alterations (EXT 1 genes) have been identified in

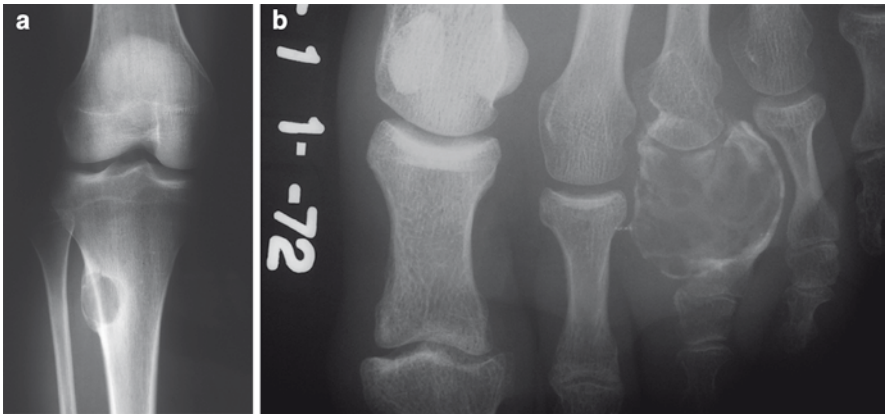

Fig. 6.14 (**a**) Chondromyxoid fibroma involving the proximal tibial metaphysis. The lesion is well demarcated and surrounded by a rim of sclerotic bone. (**b**) Chondromyxoid fibroma involving a short tubular bone of the foot (proximal phalanx). The bone is expanded by a lytic lesion that is well demarcated

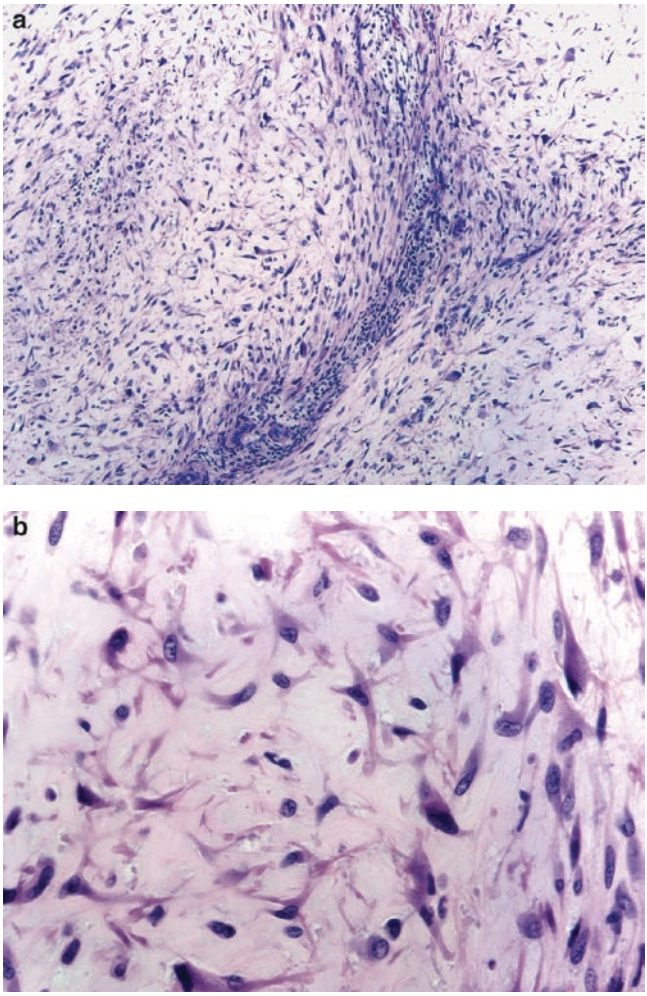

Fig. 6.15 (**a**) Chondromyxoid fibroma showing spindle cells in a myxoid background with a characteristic growth pattern of a hypocellular center and hypercellular periphery (**b**) The spindle cells are seen at a higher power. The nuclear membranes are smooth and the chromatin is evenly dispersed. There may be mitoses in many cases, but no atypical mitoses should be seen

sporadic and hereditary lesions. Symptoms are often related to size, mechanical obstruction or complications such as bursitis, fracture of the stalk, nerve impingement, pseudoaneurysm or infarction (Fig. 6.17). Rarely, a secondary chondrosarcoma can develop on a long standing osteochondroma (in about 1–3% of cases). Typically, secondary chondrosarcomas show a thick cartilage cap (over 2 cm), made up of myxoid, lobulated cartilage and may show evidence of infiltration into the adjacent soft-tissues. Osteochondromas generally arise on long tubular bones (rare cases are seen in short bones, phalanges, iliac wings or vertebrae). They may be sessile or

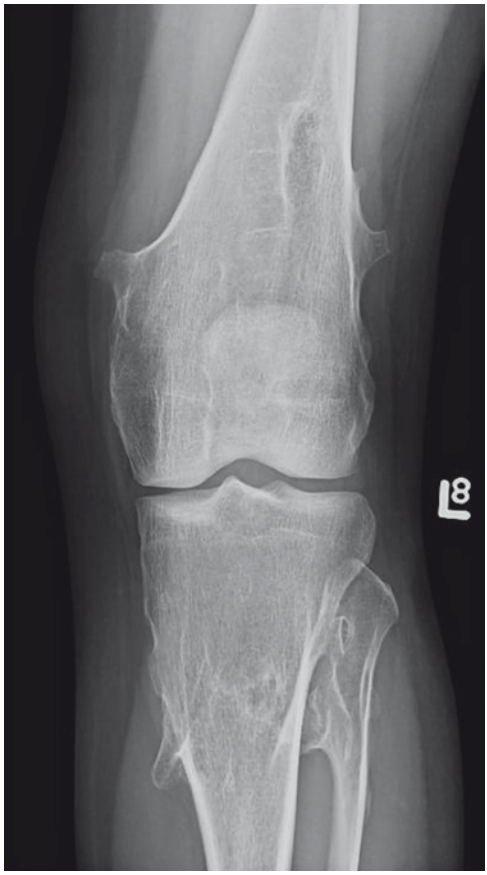

Fig. 6.16 Multiple osteochondromas in a patient with hereditary disease. An associated remodeling defect shows the characteristic widening of the metaphyses in these patients

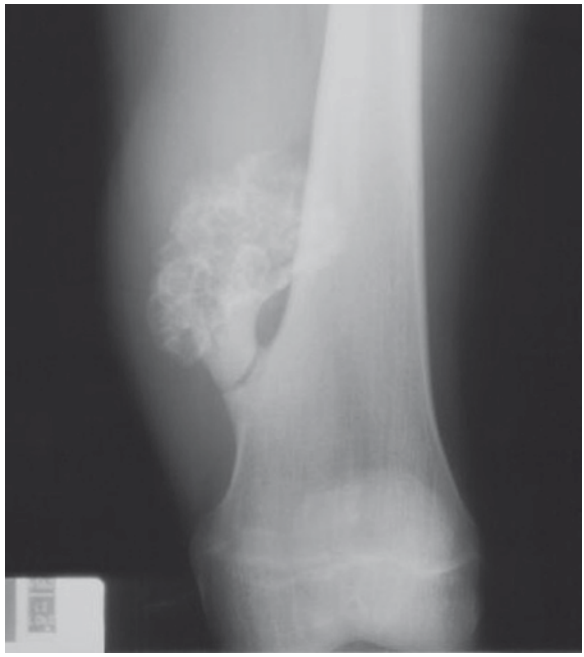

Fig. 6.17 A pedunculated osteochondroma with fracture through the stalk

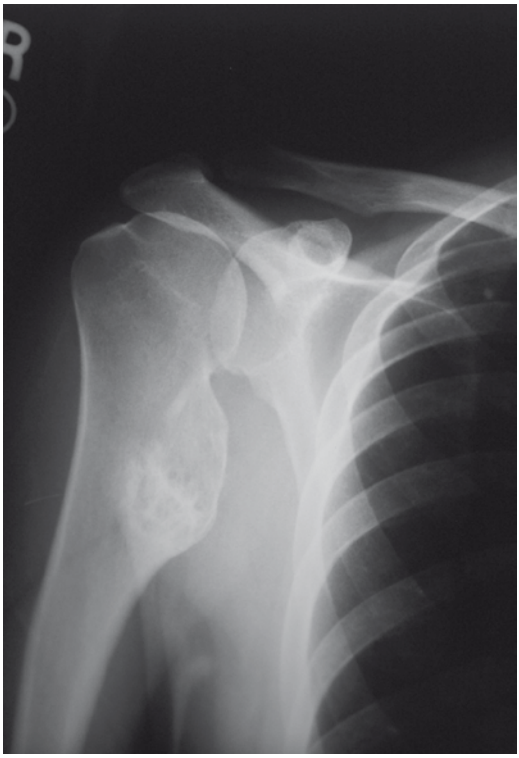

Fig. 6.18 Sessile osteochondroma. Unlike the example in Fig. 6.17, this osteochondroma attaches by a broad base rather than a thin stalk

pedunculated (Fig. 6.18). Magnetic resonance imaging shows continuity of the marrow signal between the lesion and the underlying bone and is helpful in assessing the thickness of the cartilage cap (which is generally less than 1.5 cm and decreases with age). Grossly, the lesions are stalk-like bone, capped by cartilage. The lesions should be sectioned perpendicularly to the cartilage cap to determine the thickness (Fig. 6.19). A cap with a thickness greater than 2 cm may be indicative of malignancy. Microscopically, the lesion is composed of hyaline cartilage, enclosed by perichondrium on one end and bounded by bone on the other. There is often evidence of endochondral ossification at the junction of the cartilage and bone (Fig. 6.20).

Chondroma

Chondromas are benign lesions of hyaline cartilage. If entirely within the medullary cavity of bone, they are referred to as enchondromas; if entirely on the surface, they are called periosteal chondromas. Rare lesions that are partly intramedullary and partly surface are called enchondroma protuberens. Enchondromas are common tumors and

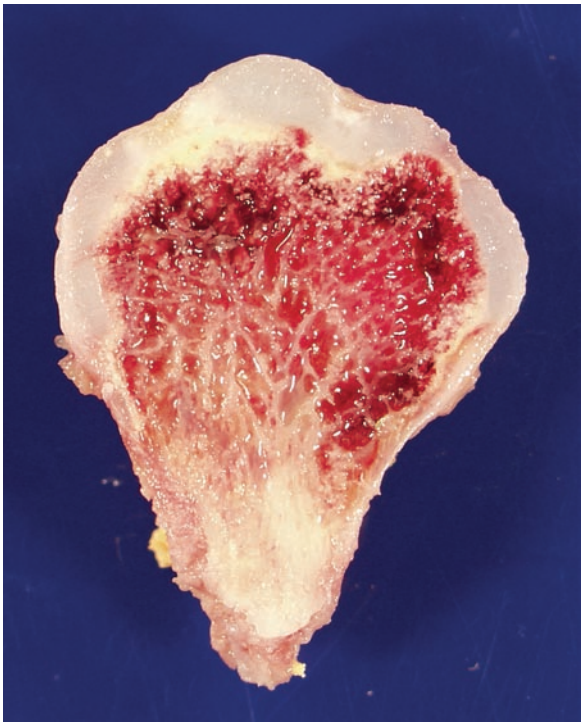

Fig. 6.19 Gross picture of osteochondroma showing a thin cap of cartilage on top of a bony protuberance. The osteochondroma has been sectioned perpendicular to the surface of the cartilage

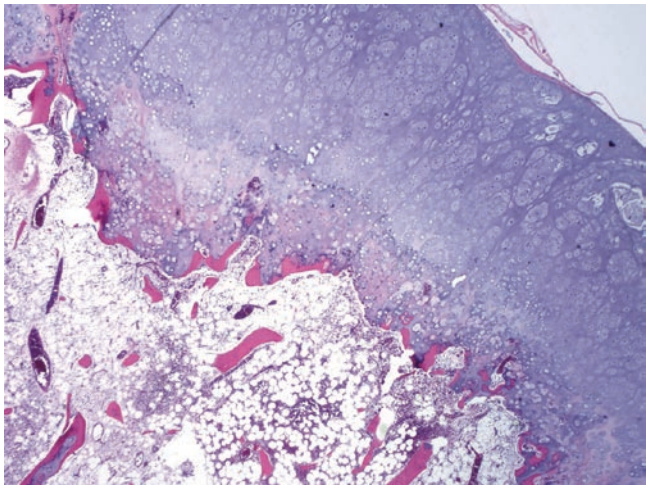

Fig. 6.20 Microscopic picture of osteochondroma showing a hyaline cartilage cap and underlying bone marrow and trabecular bone. Endochondral ossification is seen at the junction

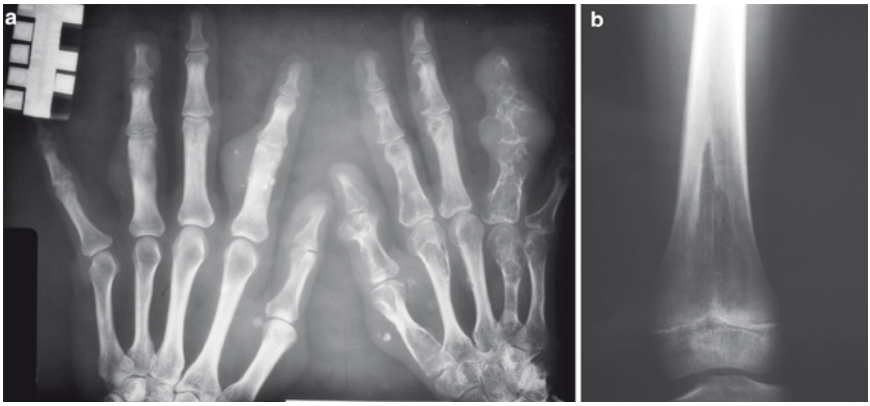

Fig. 6.21 (**a**) Maffuci syndrome showing enchondromas. There are soft-tissue masses with calcifications – these are hemangiomas with focal calcifications. (**b**) A flare like remodeling defect, commonly seen in patients with multiple enchondromas

may affect any bone, especially the short tubular bones of the hands and feet, humerus, femur and tibia. There is a wide age distribution. Lesions may be solitary or multiple (multiple enchondromatosis or Ollier disease). One of the problem areas in surgical pathology is distinguishing them from low-grade chondrosarcomas. Multiple enchondromas can be wide-spread or unilateral. If associated with a remodeling defect, the condition is called Ollier disease. Occasionally there may be associated soft-tissue or visceral hemangiomas called Maffuci syndrome (Fig. 6.21a, b). The hemangiomas may be of the cavernous or spindle cell types. The risk of secondary malignancy (often chondrosarcoma, occasionally other high grade sarcomas) is reported to be high in Ollier's disease and Maffuci's syndrome (and may be as high as 25% of affected patients). Some patients have been shown to have mutations in the parathyroid hormone receptor (PTHR) or parathyroid hormone related protein (PTHrP). Clinically, enchondromas are usually painless, asymptomatic lesions discovered incidentally (although lesions of the hands and feet can be painful and associated with a fracture). Pain and pathological fracture (except in the hands and feet) is a worrisome feature and may indicate a secondary chondrosarcoma arising on an enchondroma.

Radiographically, enchondromas are small (often less than 3 cm), metadiaphyseal, well demarcated and are sometimes surrounded by a rind of sclerotic bone (Fig. 6.22). Enchondromas of the hands and feet may expand the bone and be associated with a periosteal reaction and can occasionally be associated with a pathological fracture (Fig. 6.23). A pathological fracture in a long bone however is very unusual and raises the possibility that the lesion is a chondrosarcoma. Mineralization within the tumor can be quite characteristic in the form of C's and O's (the so-called popcorn calcification). Excessive scalloping of the internal edge of the lesion is a worrisome feature and may indicate aggressive behavior. Cortical destruction should not be seen. Enchondromas are characteristically hot

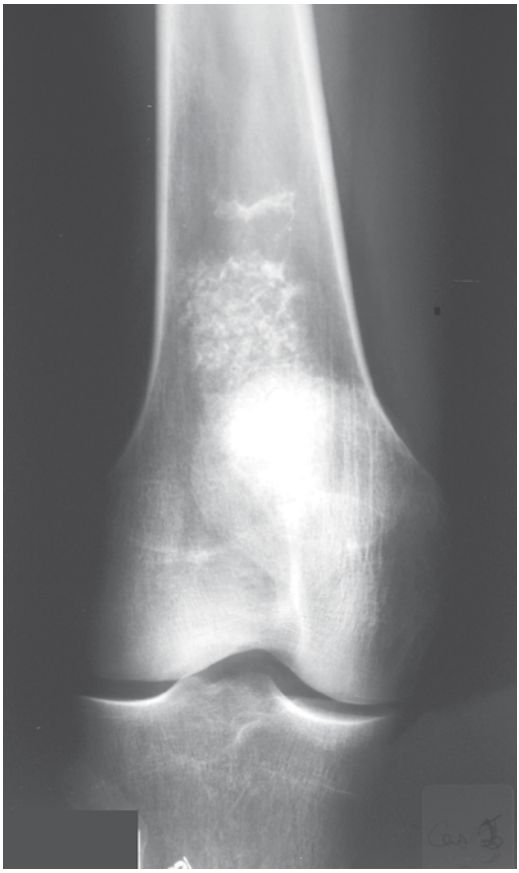

Fig. 6.22 Enchondroma of the distal femur. The cartilage is calcified in the form of C's and O's (popcorn calcification). The lesion is well demarcated, although a sclerotic rim is not evident in this particular example

on Technetium bone scans. Grossly enchondromas are lobulated lesions. They should be composed of glistening solid appearing cartilage. A myxoid (watery) appearance may indicate a malignancy, although tumors from patients with Ollier's disease can often have prominent myxoid change. Microscopically, the lesions are well demarcated and grow in lobules (Fig. 6.24a). Cortical breakthrough, extension into the soft-tissues (in the absence of fracture), are indicators of malignancy in the long bones. Extension along Haversian or Volkman's canals or the entrapment of medullary bone (trabeculae) should not be seen in benign enchondromas and is indicative that the lesion is a chondrosarcoma. The lesions are usually hypocellular (although tumors from the hands and feet can be very cellular especially so in the setting of multiple enchondromatosis or Ollier's disease) (Fig. 6.24b). There can be one or more chondrocytes in each lacuna, but true bi-nucleation is not commonly seen. Cytological atypia and mitotic activity are indicators of malignancy. Markers of cell proliferation (such as K1-67 or Mib1) should be low (less than 5% staining). Infarct like necrosis is acceptable in enchondromas and does not necessarily indicate

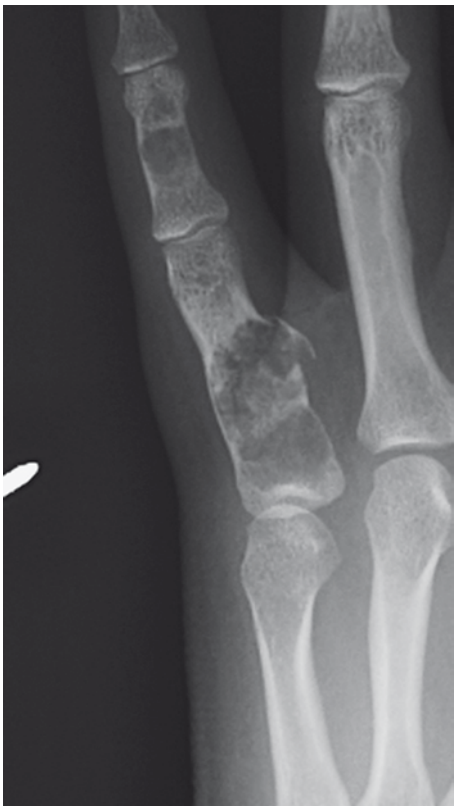

Fig. 6.23 Enchondroma of a proximal phalanx with a pathological fracture

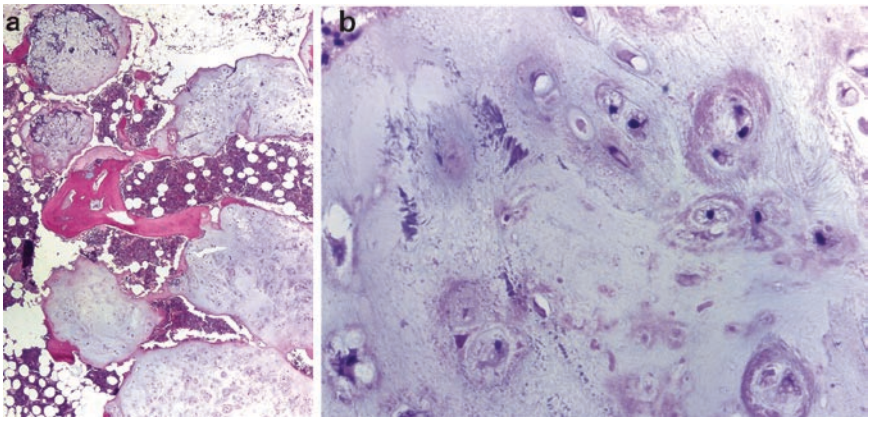

Fig. 6.24 (**a**) Enchondroma composed of lobules of hyaline cartilage. (**b**) High power microphotograph showing hypocellular cartilage with one or two chondrocytes within a lacuna along with some calcification of the matrix

malignancy. Correlation with radiographs is essential to avoid undercalling or overdiagnosing low-grade chondrosarcoma.

Periosteal chondromas are rare lesions and occur in a wide age range. They occur in the long tubular bones (such as humerus) and are also frequent in the short tubular bones of the hands and feet. Radiologically and grossly they are sharply demarcated from the underlying bone and are usually small tumors (less than 5 cm) (Fig. 6.25). Microscopically, they can be cellular with the chondrocytes showing prominent clustering, similar to a pattern seen in synovial chondromatosis (Fig. 6.26).

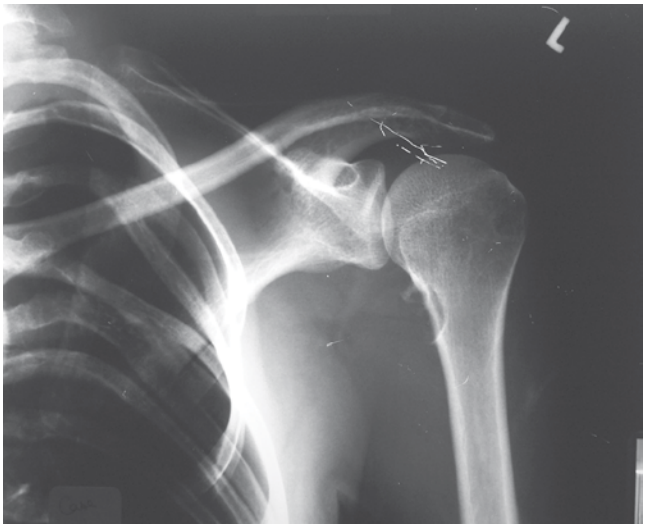

Fig. 6.25 Periosteal chondroma forming a small, geographic, scooped out surface lesion of the proximal humerus

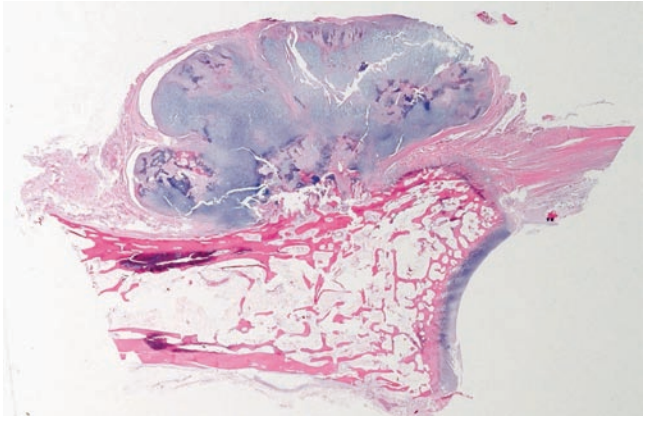

Fig. 6.26 Low-power photomicrograph showing the architecture and non-infiltrative nature of a periosteal chondroma

Chondrosarcoma

Chondrosarcoma is the malignant counterpart of hyaline cartilage tumors. This lesion may occur on the bone surface or in the medullary cavity. Chondrosarcoma is a term used to describe a variety of tumors with varying morphologies and behavior. The lesions may be primary (arising on previously normal bone) or secondary (arising on a pre-existing benign tumor, generally either an osteochondroma or enchondroma). Apart from the primary intramedullary chondrosarcoma (also called conventional), there are also some variants – mesenchymal clear cell and de-differentiated chondrosarcoma. Periosteal chondrosarcoma is also considered to be a variant of chondrosarcoma, although many if not all cases are considered to be secondary (arising on osteochondroma) where the primary lesion is not always discernable. The lesion is included in the discussion of secondary chondrosarcoma in this chapter.

Conventional Chondrosarcoma

Conventional chondrosarcoma accounts for about a fifth of all malignant bone tumors. It is a tumor of adults; the peak incidence is fifth to seventh decades. Common sites of involvement include the pelvis, femur, humerus and sternum.

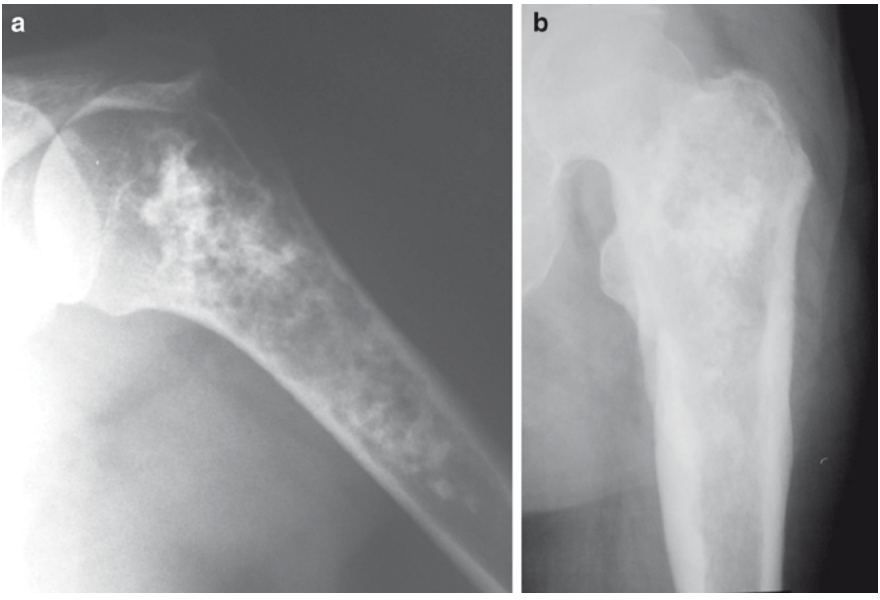

Fig. 6.27 (**a**) Conventional chondrosarcoma involving the proximal humerus. The lesion extensively scallops the endosteum and shows a cartilaginous matrix in the form of C's and O's of calcification. (**b**) Conventional chondrosarcoma involving the proximal femur. There is a prominent periosteal reaction to the tumor. Once again, the popcorn-like calcification can be appreciated

Clinical presentation is with pain or a mass. Radiographically, the tumors are metaphyseal or diaphyseal. There is often a host response in the form of bone expansion, thickening or periosteal reaction (Fig. 6.27a, b). Cortical erosion or destruction is often present. The tumor matrix shows the typical popcorn type calcification seen in cartilage tumors (in the form of C's and O's). Grossly, the tumors may be lobulated and often show areas of mucoid material (where the cartilage is watery and runs). Chalky yellow-white areas of calcification often occur. Erosion of the cortex, cortical breakthrough and extension in to soft-tissues are often present (Fig. 6.28).

Microscopically, the tumor may exhibit a lobular growth, sometimes separated by wide fibrous bands. There is often permeation into the cortical bone and the marrow space with entrapment of bony trabeculae (Fig. 6.29). The cellularity of chondrosarcomas can vary considerably, with low-grade, well-differentiated tumors being difficult to separate from enchondromas, (this is especially true in the hands and feet where enchondromas can be quite cellular). The chondrocytes may display obvious atypia and mitotic activity in the high grade tumors. Necrosis and myxoid change

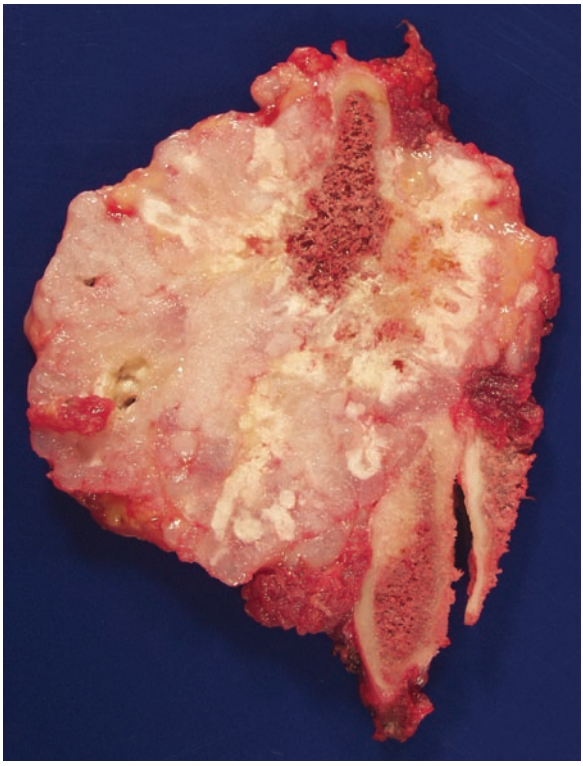

Fig. 6.28 Gross photograph of a pelvic chondrosarcoma showing a *bluish* appearance of the hyaline cartilage. The tumor has broken through the cortices and extended into the soft-tissues

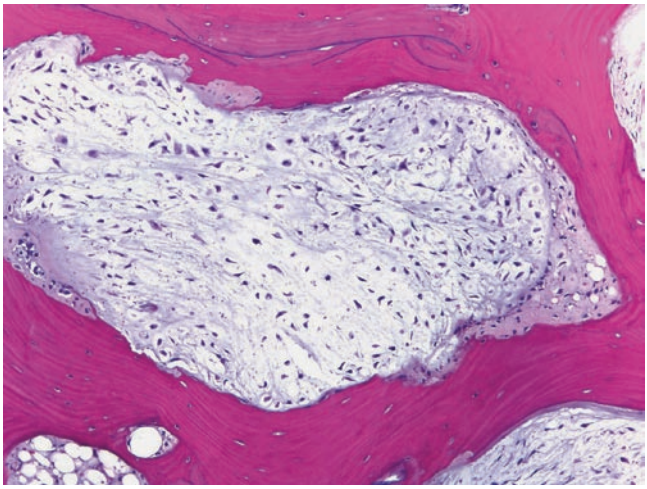

Fig. 6.29 Conventional chondrosarcoma showing a relatively hypercellular cartilage tumor with a myxoid background scalloping and entrapping trabeculae of bone

(cystification or liquefaction) can be prominent. Most authors grade chondrosarcomas into three grades, with grade 1 resembling enchondromas, but showing features such as permeation and grade 3 showing obvious malignant features such as atypia and frequent mitoses.

Chondrosarcoma Variants

There are four important variants of chondrosarcoma: mesenchymal chondrosarcoma, clear cell chondrosarcoma, dedifferentiated chondrosarcoma and secondary chondrosarcoma.

Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma is a rare neoplasm that has a bimorphic pattern microscopically. There is well-differentiated (low-grade) cartilage, sharply delineated from an undifferentiated round cell tumor that typically shows a prominent hemangiopericytomatous vascular pattern. Mesenchymal chondrosarcomas have a wide distribution; involvement of the craniofacial skeleton, ribs, pelvic bones and vertebrae are not infrequent. Some cases involve the extraskeletal

soft-tissues and meninges. Pain and swelling are common clinical presentations; although some cases of oncogenic osteomalacia (tumor induced osteomalacia due to a phosphate regulating factor called phosphatonin, possibly FGF 23) have also been described. Radiologically, the lesions are generally lytic destructive and poorly marginated. Some cases show the typical popcorn calcification of cartilage tumors (in the form of C's and O's). Changes such as bony expansion, cortical breakthrough, sclerosis and cortical thickening occur in a variable number of cases (Fig. 6.30). Grossly, the tumors may show hemorrhage and necrosis. In a few cases there is gross evidence of cartilage. Microscopically, there is an undifferentiated round cell malignancy which shows a prominent vascular pattern with branched vessels. There are also sharply delineated islands of low-grade cartilage (Fig. 6.31a, b). The round cells can be positive for CD99 (mic2), but generally in a cytoplasmic rather than a membranous pattern. The 11:22 translocation is not seen in mesenchymal chondrosarcoma and the fusion gene product EWS-FLI1 or EWS-ERG is lacking. Mesenchymal chondrosarcoma is a malignant tumor. Some cases are fatal rapidly; others can show metastases after long delays (over 20 years).

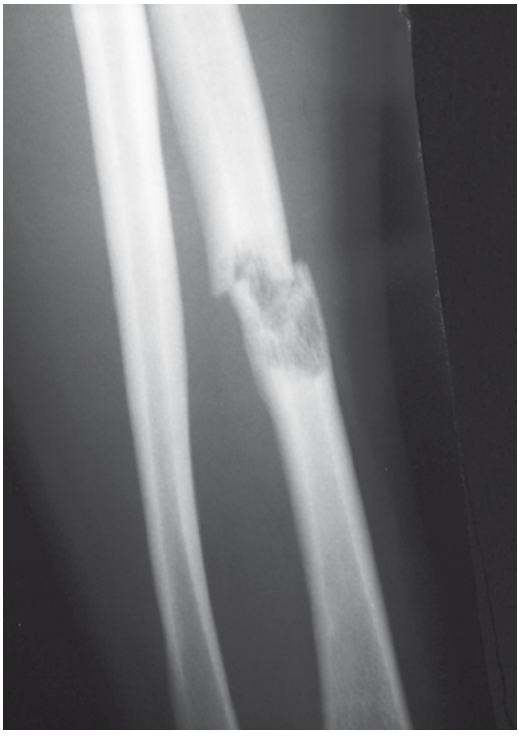

Fig. 6.30 Mesenchymal chondrosarcoma involving the radius. The lesion is lytic and associated with a pathological fracture

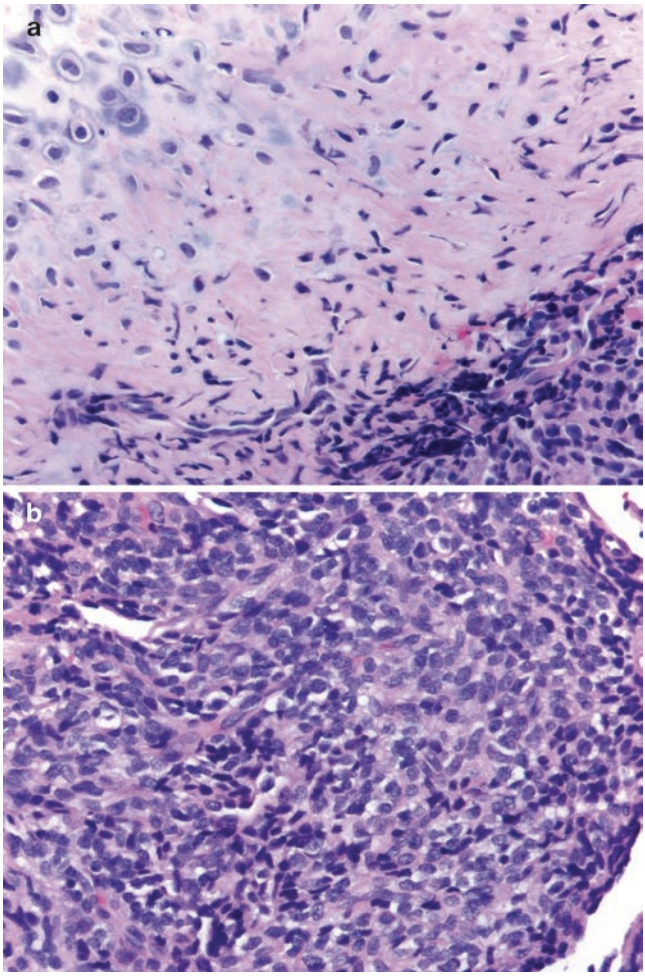

Fig. 6.31 (**a**) Mesenchymal chondrosarcoma showing a component of low-grade cartilage sharply demarcated from a round cell component which can be seen in the *bottom right corner*. (**b**) The round cell component is better seen in this picture. There are is a prominent slightly flattened vessel seen, resembling those seen in hemangiopericytoma

Clear Cell Chondrosarcoma

Clear cell chondrosarcoma is a rare tumor that has a predilection for the epiphyses of long bones and contains chondrocytes with clear cytoplasm. The tumor is seen in adults (although rare cases have been described in teen-agers), with a

male preponderance. Clinically the patients present with pain. Radiologically there is usually a well-defined lytic lesion in the epiphysis, sometimes with a sclerotic rim. There may be some stippled pop-corn like calcification. The radiological features therefore overlap with chondroblastoma (Fig. 6.32). Grossly the tumors may be gritty and sometimes contain cystic areas. Cartilage is not often seen grossly. Microscopically, the characteristic cell is a chondrocyte with clear cytoplasm and distinct cytoplasmic membrane. Some cells have a pale pink cytoplasm (similar to chondroblastoma). Osteoclast type giant cells are often present (one of the few chondrosarcomas to have giant cells although benign cartilage tumors like chondroblastoma or chondromyxoid fibroma characteristically have these cells). Woven bone is frequently present, as are some areas of conventional (hyaline cartilage) chondrosarcoma (Fig. 6.33a, b). En-bloc excision is often curative, whereas intra-lesional procedures are often followed by recurrences and metastases.

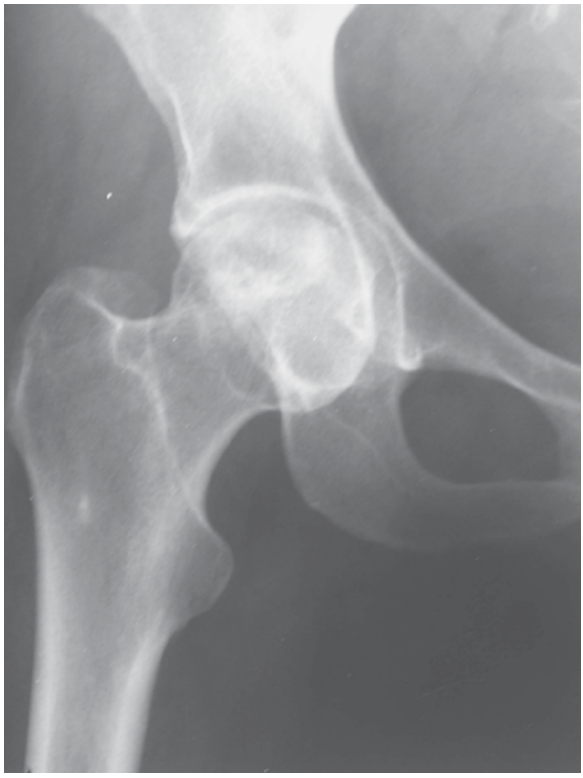

Fig. 6.32 Clear cell chondrosarcoma involving the femoral head in an adult, skeletally mature individual

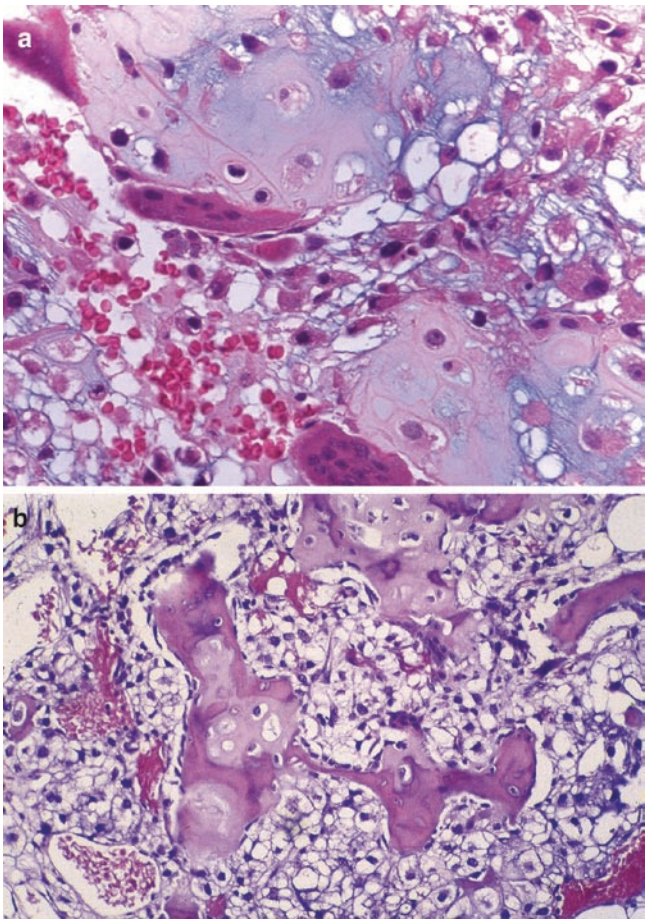

Fig. 6.33 (**a**) Chondrocytes with a clear cytoplasm along with multinucleated giant cells in a typical case of clear cell chondrosarcoma. (**b**) Metaplastic bone and giant cells in a background of clear chondrocytes in a patient with clear cell chondrosarcoma

Dedifferentiated Chondrosarcoma

Dedifferentiated chondrosarcoma contains two clear defined components – a high-grade sarcoma and sharply delineated from it, a low-grade cartilage component. The tumor comprises about 10% of all chondrosarcomas in most series. The average age of presentation is between 50 and 60 years. The common sites of involvement are pelvis, femur and humerus. Radiologically, the lesions are often aggressive with moth-eaten or permeative margins. In some cases a clear-cut cartilaginous component with the characteristic C's and O's of calcification are also seen (Fig. 6.34). MRI scans can be helpful, in that they have different signals from the two components. Grossly, the high-grade sarcoma shows areas of hemorrhage and necrosis. Cartilage

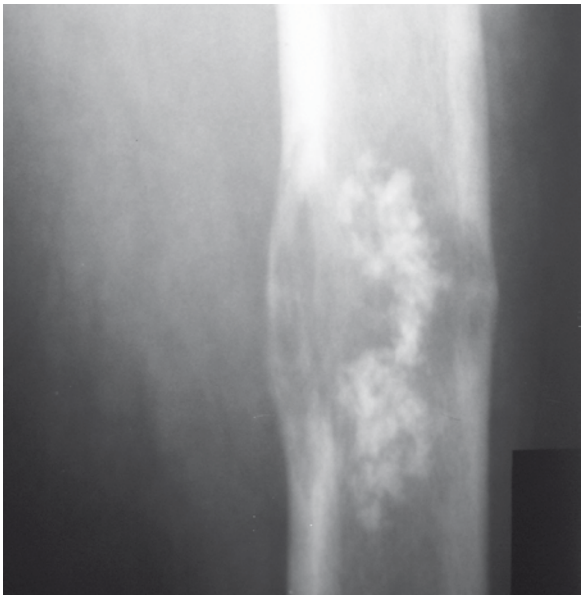

Fig. 6.34 De-differentiated chondrosarcoma showing a cartilaginous type matrix centrally with popcorn like calcification. The margins however are aggressive and show a lysis surrounding the cartilage with permeative margins

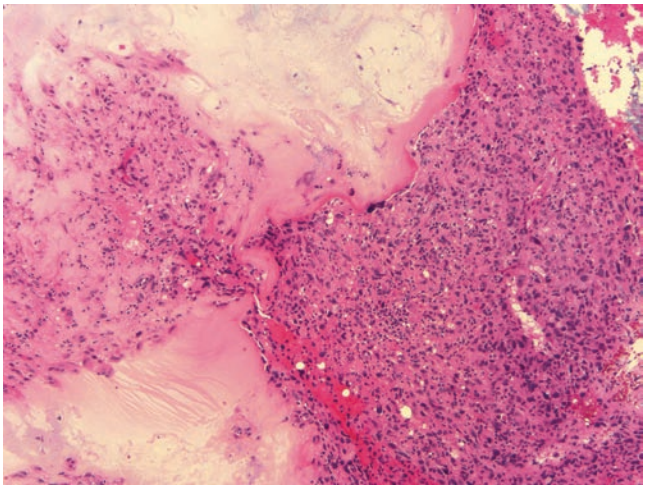

Fig. 6.35 De-differentiated chondrosarcoma photomicrograph showing low-grade cartilage, sharply delineated from a high-grade sarcoma

may be present in varying amounts. Microscopically, the high grade component can take on a variety of sarcoma patterns, although pleomorphic sarcoma (malignant fibrous histiocytoma) and osteosarcoma are more common. There is an abrupt transition to low-grade cartilage (Fig. 6.35). There are no specific genetic changes associated

with dedifferentiated chondrosarcoma, although there is some support for the idea that both components (cartilage and sarcoma) have a common genetic origin. The outcome of dedifferentiated chondrosarcoma is dismal, with most patients (around 90%), dying within 2 years.

Secondary Chondrosarcoma

Secondary chondrosarcoma refers to chondrosarcoma arising on a pre-existing (usually benign) precursor lesion (most often an osteochondroma or enchondroma). The risk of developing chondrosarcoma varies from about 2% in solitary osteochondroma or enchondroma up to about 25% in multiple enchondromatosis (Ollier or Maffuci syndromes). Although any bone may be involved, the most common sites of secondary chondrosarcoma appear to be the girdle bones of the shoulder and pelvis. Clinically the onset of chondrosarcoma is often heralded by a change in symptoms – for example increased pain in a previous osteochondroma or enchondroma, or a pathological fracture in an enchondroma. Radiologically, the tumors are sometimes obviously malignant with the benign enchondroma being discovered only histologically. In other cases the changes can be more subtle – for example MRI evidence suggesting a thick or growing cartilage cap on an osteochondroma, or the evidence of focal scalloping or aggressive borders on an otherwise well-delineated cartilage lesion (Fig. 6.36). Grossly, the

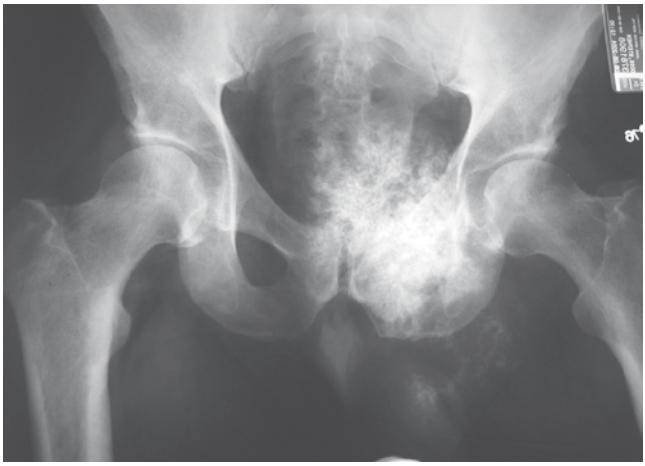

Fig. 6.36 Secondary chondrosarcoma/periosteal chondrosarcoma arising on the surface of bone. The tumor is made up of lobules of cartilage, the thickness of which was 3 cm. There was a suggestion of an underlying osteochondroma, but it was better appreciated radiologically rather than in this gross cut section

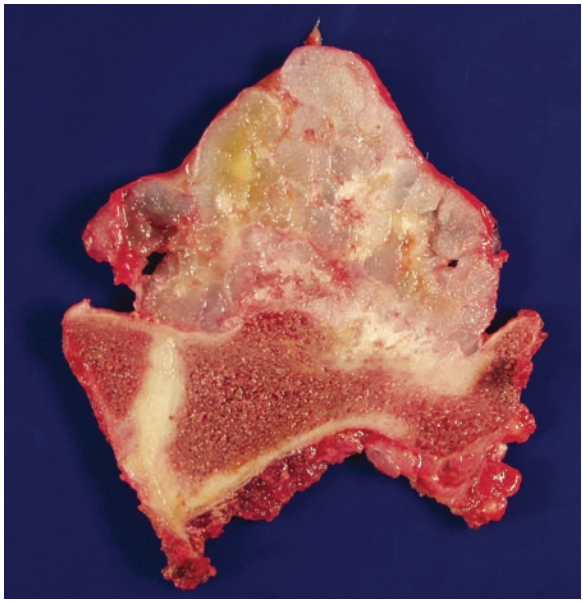

Fig. 6.37 Secondary chondrosarcoma of the pelvis extending into soft-tissues

sarcomatous portion may be obvious (showing myxoid change, fluid filled cysts or watery cartilage) along with other areas of more typical solid blue glistening cartilage (Fig. 6.37). Microscopically, secondary chondrosarcomas are often low-intermediate grade with the sarcomatous portion being of low cellularity but showing evidence of soft-tissue extension or permeation of underlying bone or entrapment or bone trabeculae. The diagnosis of secondary chondrosarcoma can be challenging in the bones of the hands and feet, or in multiple enchondromatosis (Ollier or Maffuci disease), where the enchondroma is often alarmingly cellular and should not be interpreted as a malignancy based on that feature alone. Definite evidence of soft-tissue extension or permeative growth must be sought for. The prognosis of secondary chondrosarcomas is similar to equivalent primary chondrosarcoma matched by site and stage.

Bone Forming Lesions

Bone Island

A bone island is a well-defined focus of dense compact bone within the medullary cavity. This lesion, also known as an enostosis, most probably results from a remodeling error during skeletal growth. Although it is a developmental abnormality,

a bone island may be mistaken radiographically for a neoplasm. Patients are asymptomatic. Therefore, a bone island is almost always discovered incidentally when a patient is X-rayed for other reasons.

A bone island has diagnostic plain radiographic features. A well-defined round or oval radiodensity is present in the medullary canal, usually in the metaphysis. The degree of radiodensity is comparable to the cortex (Fig. 6.38). Most lesions are 1 mm to 2 cm in diameter. However, some may reach several centimeters in diameter. Often a bone island blends with the endosteal surface of the cortex.

Histologically, a bone island is a well-defined island of lamellar compact bone identical to the cortex (Fig. 6.39). Also, mature Haversian canals are usually present.

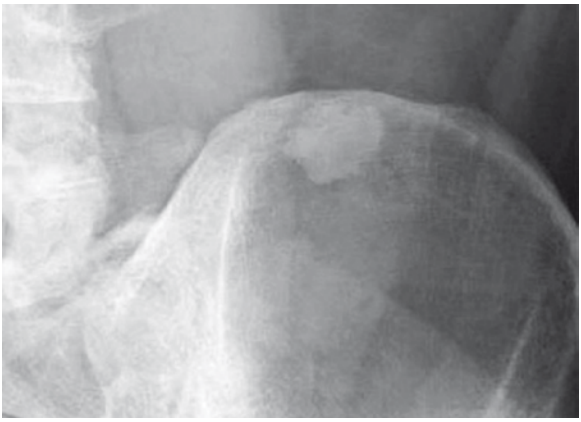

Fig. 6.38 Bone island. A well-defined uniform zone of radiodensity in the iliac wing

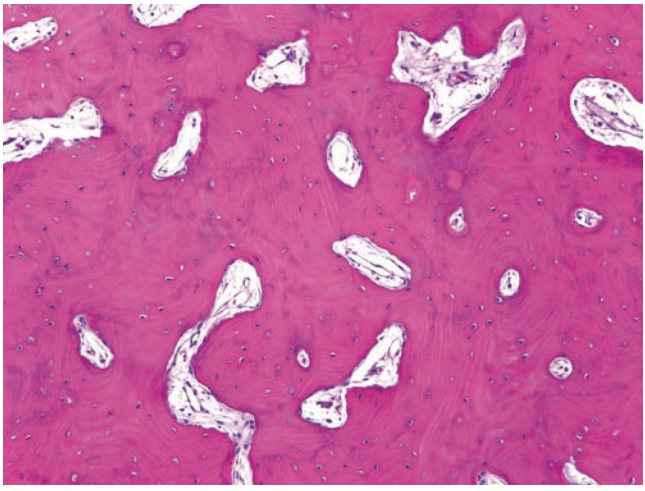

Fig. 6.39 Bone island histology. Dense uniform compact bone

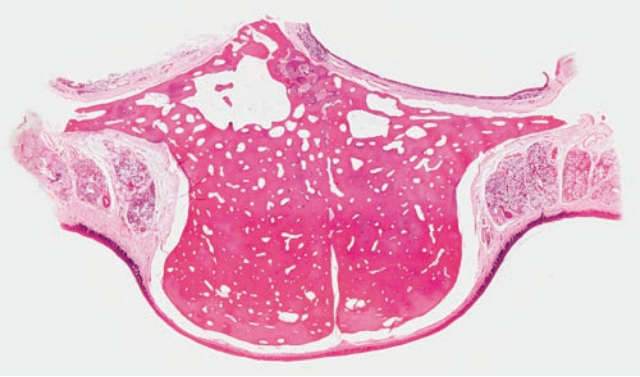

Fig. 6.40 Osteoma. A well define symmetrical projection of compact bone extending from the hard palate

Osteoma

Osteomas are dense, slow-growing, bony projections which arise from the bone surfaces. These non-neoplastic lesions most commonly arise in the craniofacial bones where they project into the oral cavity or sinus, usually the frontal sinus (Fig. 6.40). They vary in size from 1.5 to 3 cm and can be discovered in 3% of patients requiring sinus radiographs.

On rare occasions, an osteoma may occur in the post-cranial skeleton where it is called a *parosteal osteoma*. The long bones are usually affected, but the pelvis or vertebrae may also be involved. Of the long bones, the tibia and femur are most commonly involved. Parosteal osteomas tend to be larger than those in the craniofacial skeleton; some may reach a diameter of 6–8 cm.

Histologically, osteomas consist of dense compact lamellar bone which shows evidence of remodeling. Many mature Haversian systems are present.

Osteoid Osteoma

Osteoid osteomas are benign osteoid-producing neoplasms with three important characteristics: a small size, self-limited growth, and a tendency to cause extensive reactive changes in adjacent tissues. The lesional tissue of an osteoid osteoma, known as a *nidus*, is almost always only 1 cm or less in diameter. Despite its small size, the lesional tissue causes intense pain and provokes an exuberant periosteal reaction, a reaction which often obscures the small nidus.

Like most other primary bone tumors, osteoid osteomas affect children and young adults. Most cases present between the ages of 10 and 35, with the average being 19 years. Rarely, children under age 5 or adults over age 35 may be affected.

Patients invariably present with pain. Characteristically, the pain is worse at night and dramatically relieved by aspirin. This feature is present in more than 75% of cases and is an important diagnostic clue.

Osteoid osteomas may occur in any bone, but lesions in the femur and tibia account for 50% of cases. Other sites of predilection include the posterior elements of the spine (the vertebral body is a very rare location).

Osteoid osteomas have a very characteristic radiographic appearance. A small radiolucent nidus is surrounded by dense reactive bone. The nidus may be subperiosteal, intracortical, or subcortical. On rare occasions, the nidus is deep in the medullary canal. Occasionally, the reactive bone may be so dense that it obscures the nidus (Fig. 6.41). In this situation, a CT or MRI scan, usually identifies the small radiolucent focus in the center of the radiodense area (Fig. 6.42). Osteoid osteomas are uniformly hot on Technetium bone scans; this is often used to locate lesions in difficult areas such as within joints where they may be missed on radiograms because of obscuring bones.

Histologically, osteoid osteomas are characterized by thin interconnecting seams of osteoid or woven bone which are lined by osteoblasts (Fig. 6.43). The osteoid

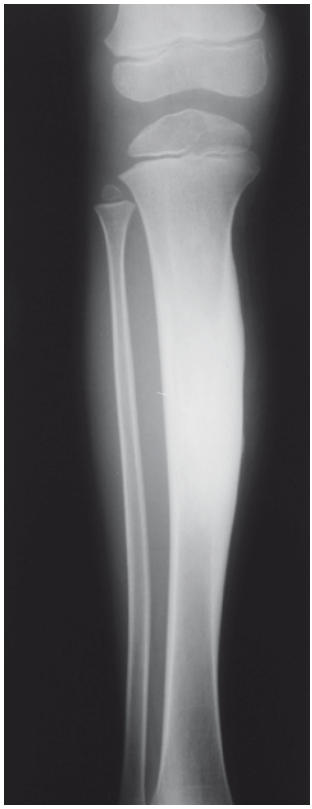

Fig. 6.41 Plain radiograph of osteoid osteoma. A zonal pattern of radiodensity of the mid-shaft of the tibia. The nidus is not apparent on the plain film

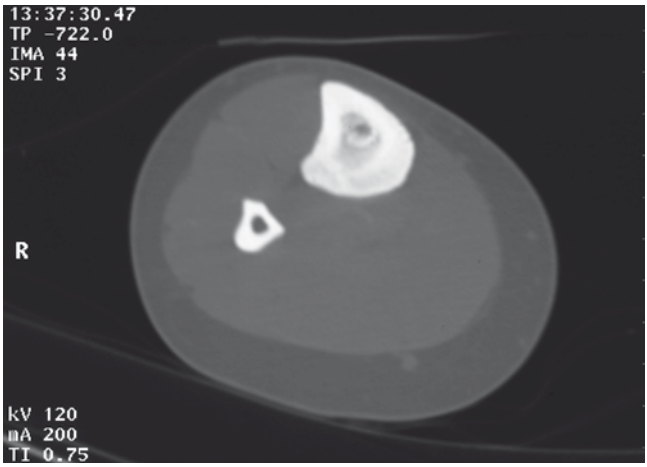

Fig. 6.42 Osteoid osteoma CT scan. The nidus is visible in the medullary canal of the tibia

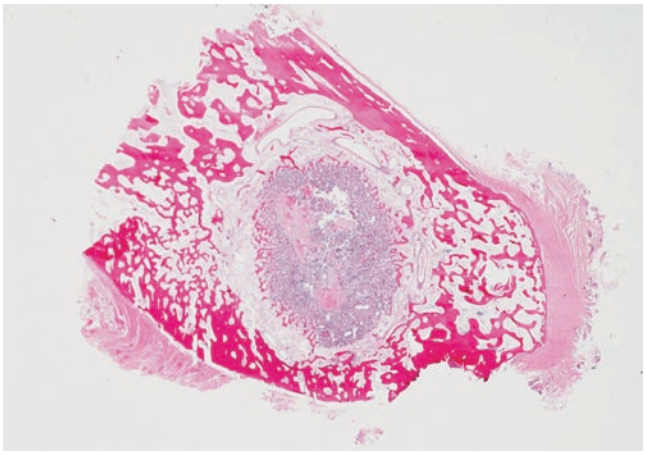

Fig. 6.43 Osteoid osteoma, low-powered photomicrograph. A well defined zone of cellularity is surrounded by reactive bone

seams are separated by a loose fibrous stroma with prominent vascularity. This lesional tissue is sharply demarcated from the dense surrounding bone (Fig. 6.44). Often, a few thick-walled blood vessels are present in the tissue between the surrounding reactive trabeculae. Surgical excision of the osteoid osteomas is followed by relief of pain. Currently microwave ablation of the lesion after confirmatory biopsy is becoming an alternative method of management.

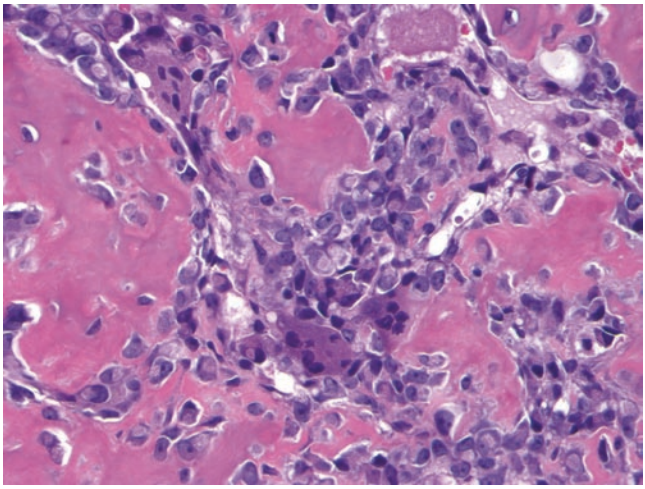

Fig. 6.44 Osteoid osteoma, high-powered photomicrograph. Benign osteoblasts and occasional giant cells surrounding deposits of new bone

Osteoblastoma

Osteoblastomas are benign bone forming neoplasms that share many histologic features with osteoid osteomas. However, these neoplasms differ in several important ways. First, osteoblastomas are rare neoplasms, unlike osteoid osteomas which are relatively common. Second, osteoblastomas are larger than osteoid osteomas. Third, unlike the self-limited growth of osteoid osteomas, osteoblastomas grow progressively. In fact, some grow very aggressively and may be mistaken for osteosarcomas. Fourth, osteoblastomas lack the highly irritative effect of osteoid osteomas.

Osteoblastomas may occur at any age, however 80% occur between the ages of 10 and 25. Patients usually present with pain, and some have local swelling and tenderness. Any bone may be involved including the calvarium and the small bones of the hands and feet. The spine, however, is the most common location, accounting for about a third of reported cases. In this location, the vertebral posterior elements are the principle site of involvement, but occasionally, the vertebral body may also be involved. In the appendicular skeleton, the diaphysis or metaphysis of long bones, particularly the femur or tibia, are the most common locations.

Radiographically, osteoblastomas are expansile, lytic lesions with variable amounts of fluffy mineralization. Reported lesions have ranged from 1 to 11 cm. Most are well-circumscribed, and occasionally they have a sclerotic rim. Many osteoblastomas expand the cortex and are bounded by a thin shell of reactive bone.

Osteoblastomas of the spine are best visualized by a CT or MRI scan (Fig. 6.45). In this location, as in the appendicular skeleton, a lesion may vary from 1 to 15 cm, the average size being 3.5 cm.

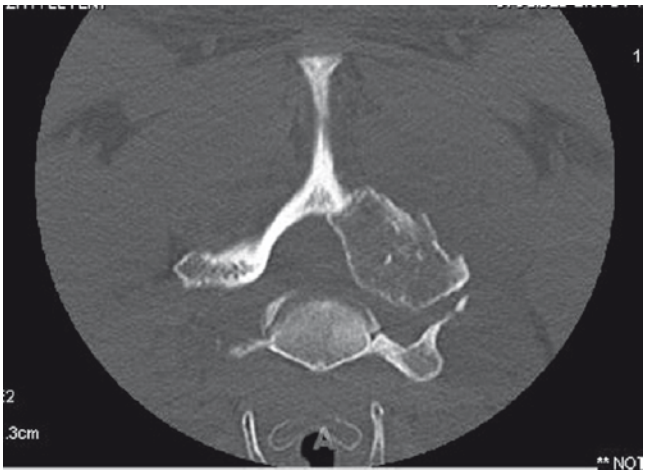

Fig. 6.45 Osteoblastoma, plain radiograph. A well-defined lytic expansile lesion in the posterior elements of the vertebrae

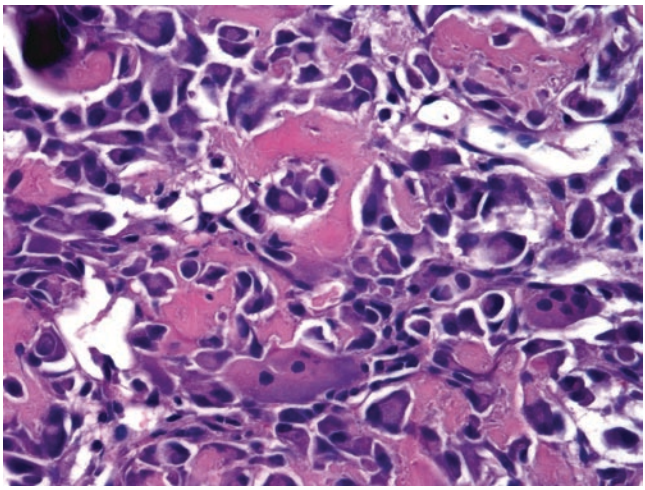

Fig. 6.46 Osteoblastoma histology. Plump osteoblasts are associated with newly deposited pink osteoid

Osteoblastomas share many histologic features with osteoid osteomas (Fig. 6.46). Irregular anastamosing seams of osteoid or woven bone are lined by a single layer of bland osteoblasts. Occasionally, broad sheets of osteoid are produced which entrap individual cells. A few osteoclasts are evenly scattered adjacent to the osteoid. The seams of osteoid are separated by a loose fibrovascular stroma containing occasional mitotic figures.

Osteosarcoma

Osteosarcoma (osteogenic sarcoma), the most common primary malignant bone tumor, usually affects children and young adults. By definition, an osteosarcoma is a neoplasm in which osteoid is synthesized by malignant cells.

Osteosarcomas have a wide range of radiographic and histologic patterns. For example, osteosarcomas may be radiolucent or very radiodense. Some originate and grow on the bone surface and others are confined to the medullary cavity. Some arise on normal bone (de novo osteosarcoma) others arise in the setting of Paget disease or radiation (secondary osteosarcoma). Most arise in genetically normal individuals but rare cases have been seen in patients various genetic syndromes (such as Rothmund–Thomson, Li Fraumani and Retinoblastoma gene mutation). The vast majority, are solitary lesions, rare cases of multifocal osteosarcoma have been reported. Histologically, some osteosarcomas show extensive cartilage differentiation and others contain abundant fibrous tissue. In addition, osteosarcomas may be of any histologic grade. For example, some contain many pleomorphic cells and mitotic figures, and others may be difficult to recognize as malignant neoplasms.

Some osteosarcomas have very specific histologic, radiographic, and clinical features. Lesions with these features have been identified as osteosarcoma variants. The most important variants are parosteal osteosarcoma, periosteal osteosarcoma, and telangiectatic osteosarcoma.

Conventional Osteosarcoma

Conventional osteosarcoma accounts for 90% of all osteosarcomas. It begins in the medullary canal and often penetrates the cortex and invades the adjacent soft-tissues. Most patients with conventional osteosarcoma are adolescents or young adults. About 85% of patients are under age 30, the peak incidence being from age 20 to 25. This neoplasm is extremely rare under age 10. Older adults may also develop conventional osteosarcoma, although many cases in adults are actually *secondary osteosarcoma* arising on predisposing factors such as Paget disease or prior radiation therapy. In younger patients, conventional osteosarcoma most commonly occurs around the knee, the distal femur accounting for one-third of all cases. Pain, tenderness, and swelling, rarely present for more than a few months, are the usual presenting symptoms.

The radiographic features of conventional osteosarcoma are diagnostic in two-thirds of cases. The lesion is a poorly circumscribed medullary lucency with mottled areas of radiodensity (Fig. 6.47). Occasionally, a lesion may be entirely radiodense. Cortical destruction is usually present, and there is often a focally mineralized soft-tissue mass (Fig. 6.48). Benign, periosteal reactive bone forms a Codman's triangle adjacent to the soft-tissue mass.

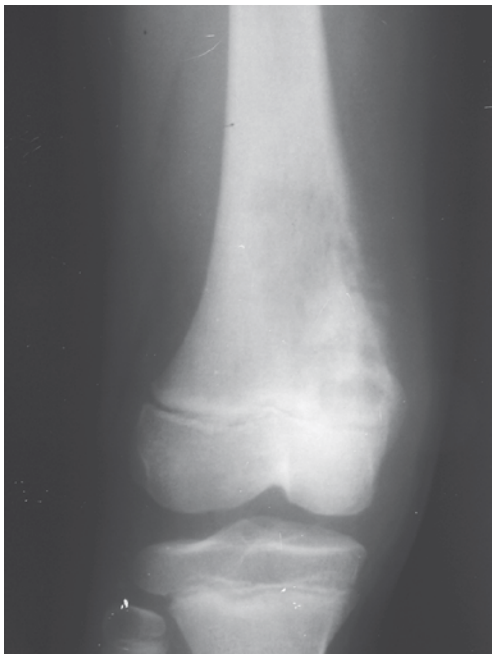

Fig. 6.47 Plain radiograph of conventional osteosarcoma. A poorly defined mixed lytic and radiodense zone in the distal femoral metaphysis. There is destruction of the cortex and a periosteal reaction

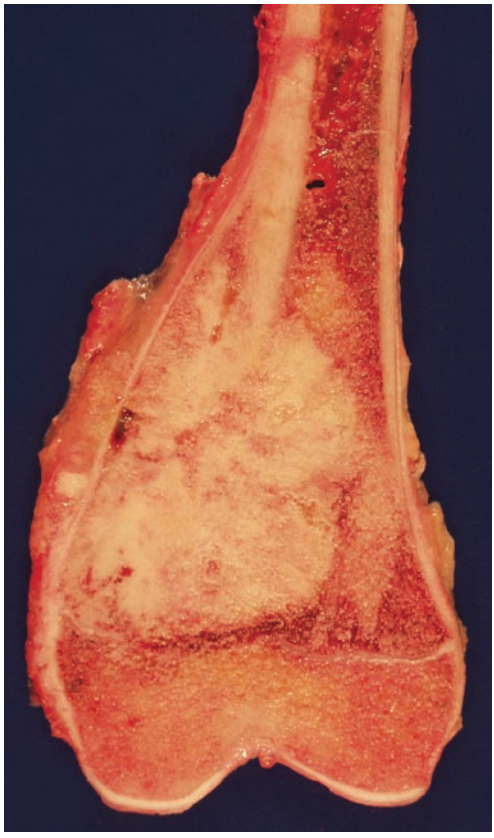

Fig. 6.48 Osteosarcoma, gross photograph. A white fleshy neoplasm is destroying bone in the femoral metaphysis. The cortex is destroyed, and the periosteum is elevated

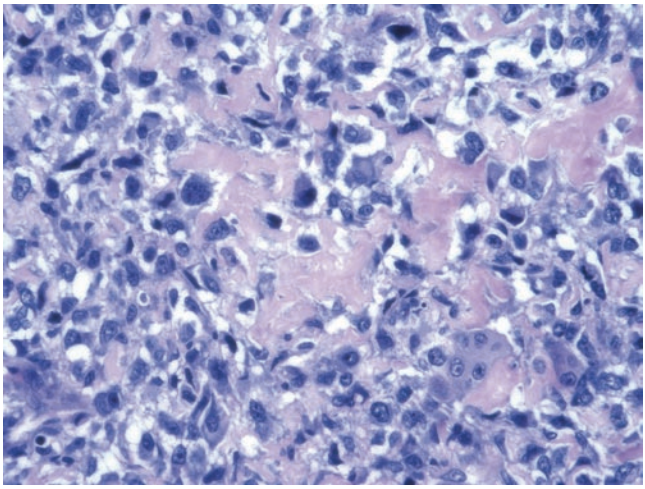

Fig. 6.49 Osteosarcoma histology. Sheets of pleomorphic osteoblasts associated with lace-like pink osteoid deposition

Conventional osteosarcoma is usually an osteoblastic neoplasm. Seams or sheets of eosinophilic osteoid are distributed in a sarcomatous stroma (Fig. 6.49). The stromal cells of conventional osteosarcoma are usually high-grade. They show varying degrees of atypia and numerous mitotic figures. The pattern and distribution of osteoid is often variable. In some areas, osteoid is deposited in fine lace-like seams. In other areas, broad sheets of osteoid may entrap single neoplastic. In some cases, there may be cartilage within the tumor that blends into the sarcomatous portion (chondroblastic osteosarcoma). In still other cases, osteoid may be very sparse (fibroblastic osteosarcoma).

Parosteal Osteosarcoma

The most common osteosarcoma variant is parosteal osteosarcoma. It accounts for only 5% of osteosarcoma. Parosteal osteosarcoma is a low-grade, slow-growing neoplasm which originates from the surface of the cortex and forms a bony mass in the soft-tissue. Patients present with a slow-growing painless swelling which is often present a year or more before they seek medical attention. Some have symptoms for as long as 10 years. Although this neoplasm may arise at any age, 75% of patients are between ages 20 and 45. An unusual feature of parosteal osteosarcoma is its predilection for one particular site, the posterior aspect of the distal femur.

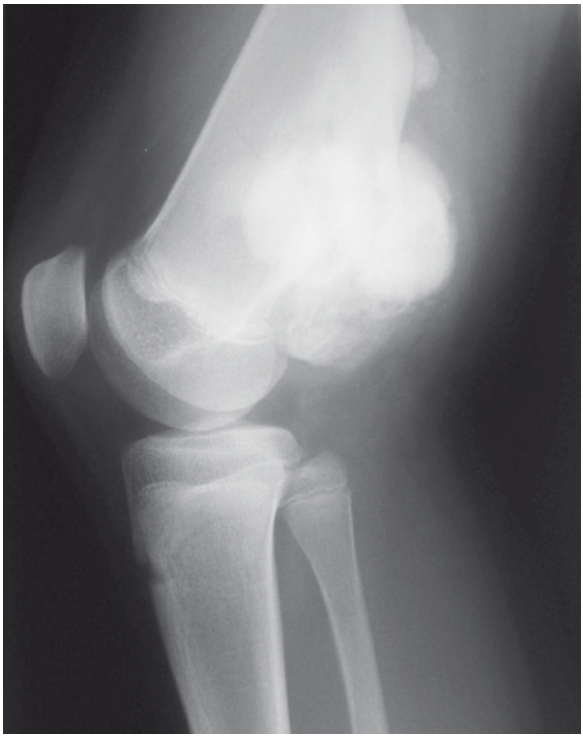

Fig. 6.50 Plain radiograph of parosteal osteosarcoma of the distal femur. An ill defined lumpy surface radiodensity in the posterior aspect of the distal femur

This location accounts for 75% of patients. The proximal tibia and proximal humerus are the next most frequently involved sites.

Radiographically parosteal osteosarcoma is a radiodense lobulated mass attached to the cortex with a broad base (Fig. 6.50). The medullary canal is typically uninvolved but may occasionally show a radiodense process continuous with the surface mass. Most parosteal osteosarcomas are from 4 to 6 cm in diameter when diagnosed, although some may reach 10 cm or more. Usually, the bony mass is homogeneous.

Histologically, parosteal osteosarcomas are a well-differentiated fibro-osseous neoplasm. Broad seams of osteoid lie in a bland, fibrous stroma (Fig. 6.51). The osteoid may mature and develop a lamellar pattern. The hypocellular fibrous stroma usually shows only minimal cytologic atypia (Fig. 6.52).

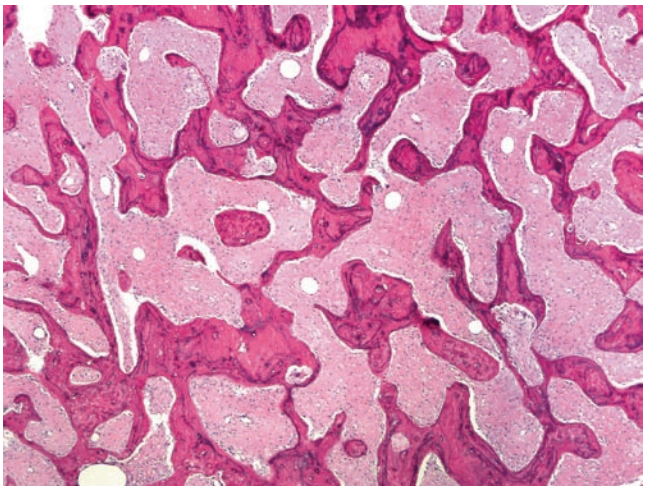

Fig. 6.51 Parosteal osteosarcoma, low-powered photomicrograph. Anastamosing strands of bone separated by fibrous tissue

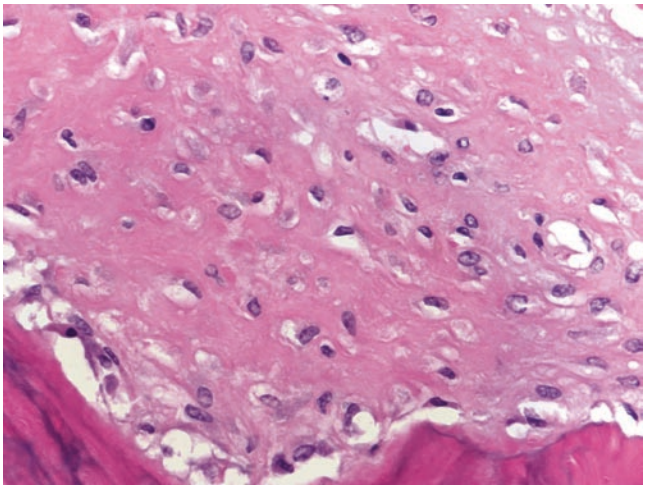

Fig. 6.52 Parosteal osteosarcoma, high-powered photomicrograph. Sheets of bland fibroblasts associated with bone production

Periosteal Osteosarcoma

Periosteal osteosarcoma is another, but much rarer, surface variant of osteosarcoma. Unlike parosteal osteosarcoma, which extends from the cortex like a bony knob, periosteal osteosarcoma tightly encases the bone like a glove. As with most

osteosarcomas, patients are usually between 15 and 25 years of age and present with pain. However, unlike other osteosarcomas which usually develop in the metaphyseal portion of bone, periosteal osteosarcoma tends to involve the diaphysis. The tibia and femur are most frequently affected. Other long bones may also be involved, but involvement of the flat bones is rare.

Radiographically, periosteal osteosarcoma is a circumferential surface mass which is less radiodense than parosteal osteosarcoma (Fig. 6.53). Mineralization occurs as ring-shaped radiodensities or as streaks of reactive bone radiating from the cortex. The cortex may be focally eroded, but the medullary canal is usually not involved. Lesions can best be visualized by a MRI scan (Fig. 6.54).

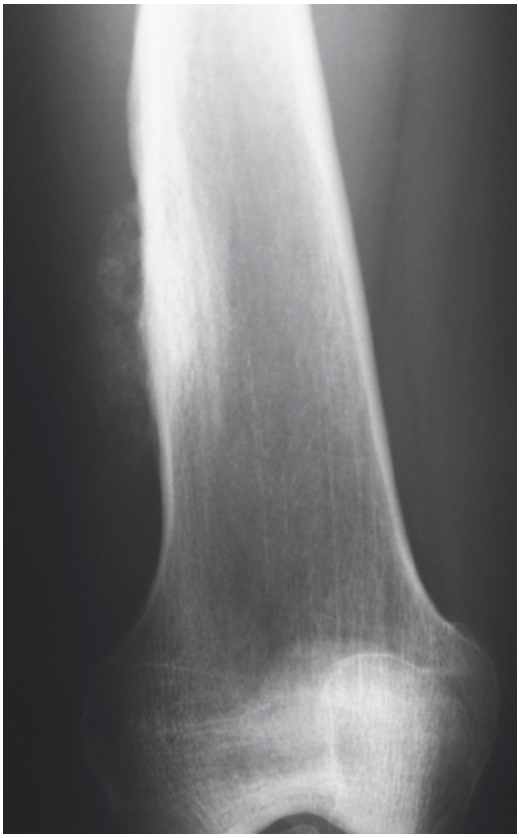

Fig. 6.53 Plain radiograph of periosteal osteosarcoma. An ill defined surface lesion on the distal femoral cortex. There is slight erosion of the bone and a periosteal reaction

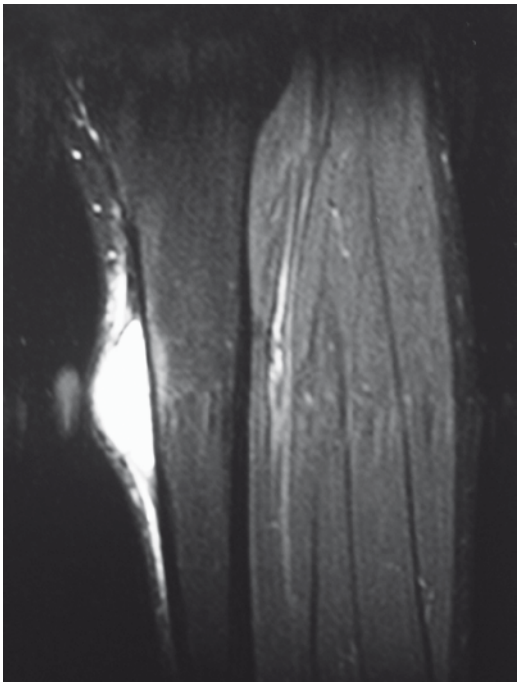

Fig. 6.54 Periosteal osteosarcoma T_2-weighted MRI scan. A sub-periosteal lesion on the surface of the mid-shaft of the tibia. The signal is *bright white* indicating its high cartilage content

Periosteal osteosarcoma is a chondroblastic neoplasm (Fig. 6.55). It consists almost entirely of lobules of cellular, atypical cartilage separated by thin bands of fibrous tissue. Often there is condensation of chondrocytes at the margin of the lesion (Fig. 6.56). Careful study of the fibrous bands reveals seams of neoplastic osteoid, usually at the outer surface of the neoplasm (Fig. 6.57). This osteoid, often difficult to find, distinguishes this lesion from a surface chondrosarcoma. The cartilage shows focal calcification, and reactive bone forms between the cartilage lobules.

Telangiectatic Osteosarcoma

The third important osteosarcoma variant is telangiectatic osteosarcoma. Telangiectatic osteosarcomas are high-grade intramedullary osteosarcomas which have undergone total, or near total aneurysmal bone cyst like change. This rare variant, accounting for only 4% of all osteosarcomas is completely lytic on plain

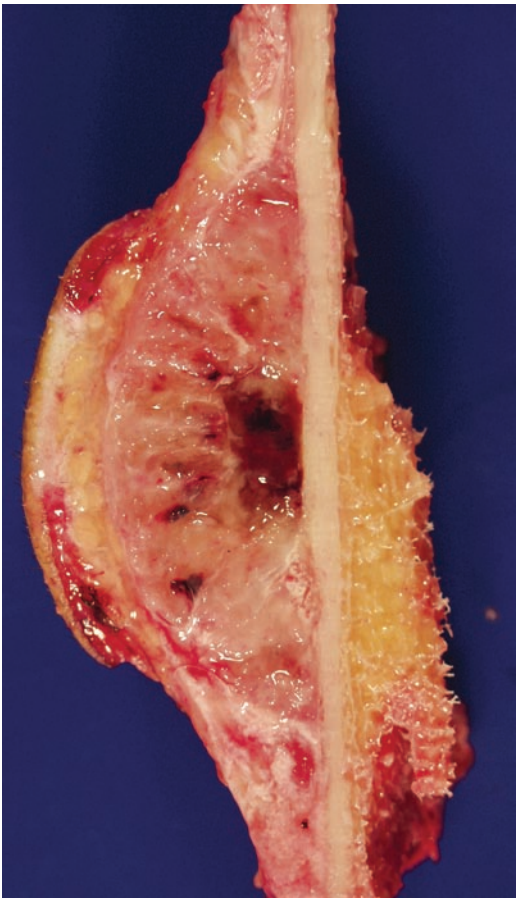

Fig. 6.55 Gross specimen of the lesion in Fig. 6.54. There is a jelly-like and hemorrhagic fleshy mass underneath the periosteum adjacent to the tibial cortex

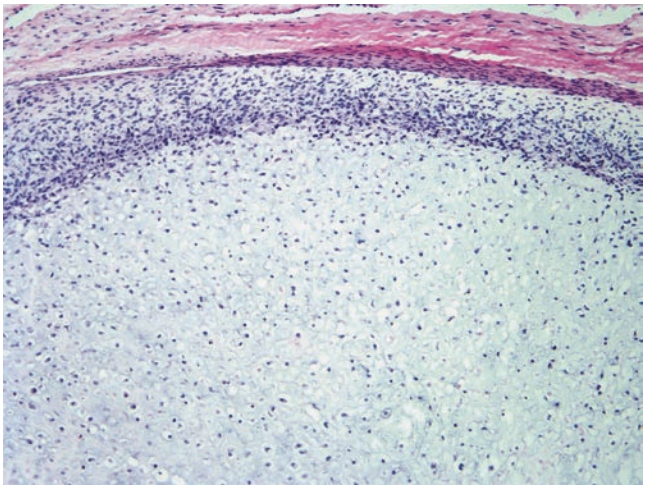

Fig. 6.56 Periosteal osteosarcoma, low-powered photomicrograph. A cartilaginous lesion with peripheral condensation of chondroblasts

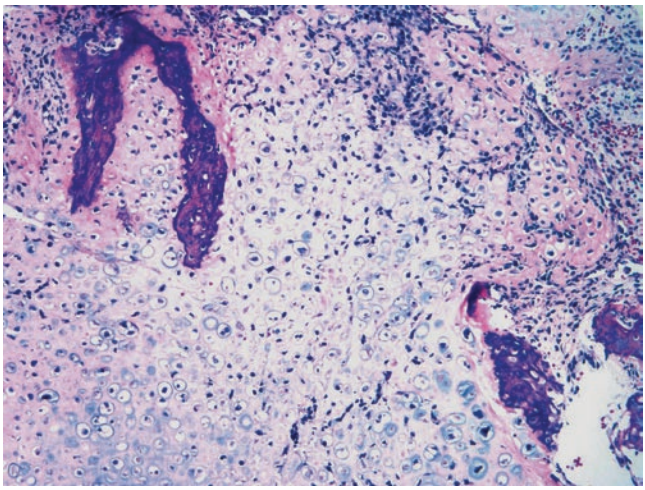

Fig. 6.57 Periosteal osteosarcoma, high-powered photomicrograph. Abundant cartilage and areas of neoplastic osteoid production consistent with a chondroblastic osteosarcoma

radiographic images. Histologically, these lesions contain many blood-filled spaces, a feature of the aneurysmal bone cyst process.

Although patients may be any age, most, as in conventional osteosarcoma, are in the second decade of life. Pain and rapid swelling are the presenting symptoms. Because this neoplasm is highly destructive, 25% of patients present with pathologic fracture. Over 60% of cases occur in the distal femur or proximal tibia. The humerus is also a common location. Additionally, the osteosarcomas that complicate long-standing Paget disease are frequently the telangiectatic variant.

Telangiectatic osteosarcomas are lytic lesions with no radiographic mineralization (Fig. 6.58). Therefore, unlike other osteosarcomas, the clue to its osteoid producing nature is lacking. In fact, the radiographic pattern may be identical to an aneurysmal bone cyst engrafted on a benign process. There is extensive cortical expansion or destruction and often a soft-tissue mass. A periosteal new bone reaction is present in over 75% of cases. The MRI often shows multiple fluid-filled locules, a pattern identical to aneurysmal bone cyst.

Histologically, telangiectatic osteosarcomas are characterized by many blood-filled cystic cavities and areas of hemorrhagic necrosis (Fig. 6.59). Areas of stroma resembling benign aneurysmal bone cyst are present. These areas are cellular with numerous mitotic figures. In addition, many benign osteoclast-like giant cells are present, a feature characteristic of almost all telangiectatic osteosarcomas.

The diagnostic feature of telangiectatic osteosarcoma is the presence of areas of high-grade sarcoma (Fig. 6.60). Markedly atypical pleomorphic cells and many

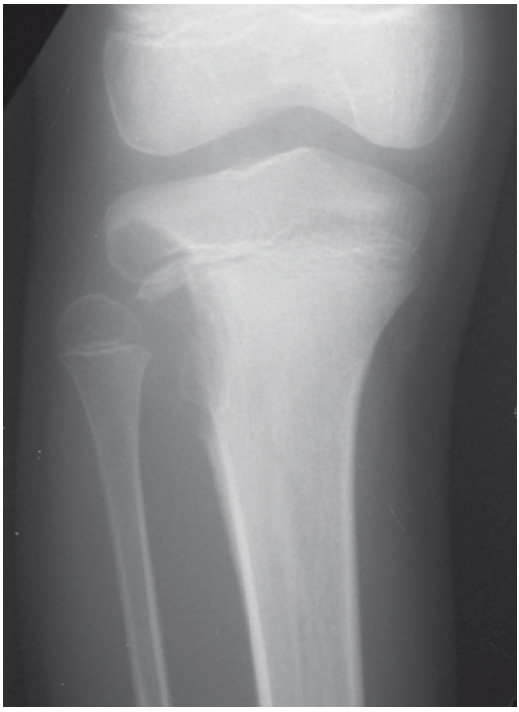

Fig. 6.58 Plain radiograph of telangiectatic osteosarcoma. A lytic lesion in the proximal tibia involving both the epiphysis and the metaphysis. There is cortical destruction

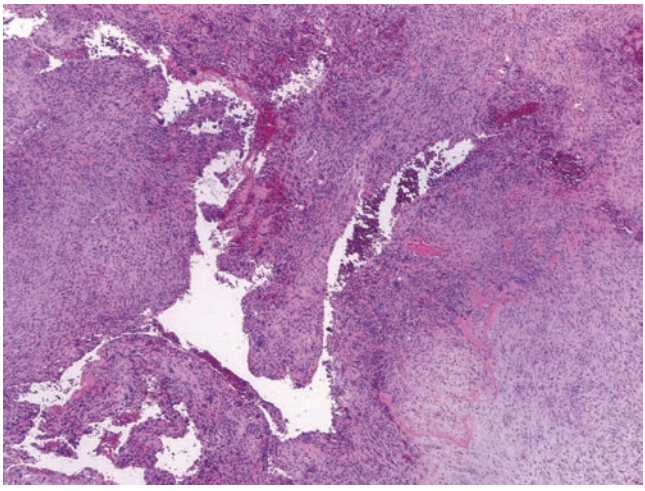

Fig. 6.59 Telangiectatic patterned osteosarcoma, low-powered photomicrograph. There are areas of blood filled lakes with features of an aneurysmal bone cyst

atypical mitotic figures are present. These areas, although only focally present, are easily recognized as malignant and can almost always be found if the entire specimen is meticulously examined histologically. Tumor osteoid may be scarce in telangiectatic osteosarcomas and is often not present in small biopsy specimens. Where present, this osteoid has a fine, lace-like pattern.

Other Variants of Osteosarcoma

There are other less common variants of osteosarcoma. One variant is the well differentiated interosseous osteosarcoma. This very rare variant is the medullary equivalent to parosteal osteosarcoma. It is a low-grade fibroblastic osteosarcoma and is histologically identical to parosteal osteosarcoma. However, when involving the medullary canal this variant may be confused with fibrous dysplasia. However, the mild atypia present in this variant distinguishes it from fibrous dysplasia.

Another variant of osteosarcoma is small cell osteosarcoma. This is a small round cell neoplasm that makes neoplastic osteoid. It has an identical radiographic appearance to most conventional osteosarcomas. However, histologically the tumor shows sheets of small round blue cells. These areas may be confused with Ewing sarcoma but the presence of osteoid is diagnostic (Fig. 6.61). Occasionally, stains for CD99 are positive, similar to Ewing sarcoma. However, the Ewing sarcoma translocation is absent in small cell osteosarcoma.

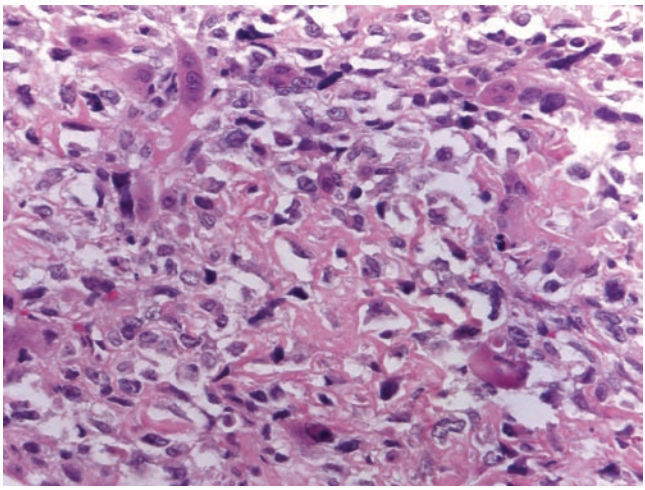

Fig. 6.60 Telangiectatic osteosarcoma, high-powered photomicrograph. Solid areas of the lesion show features typical of high-grade conventional osteosarcoma with abundant pleomorphic cells and lace-like osteoid

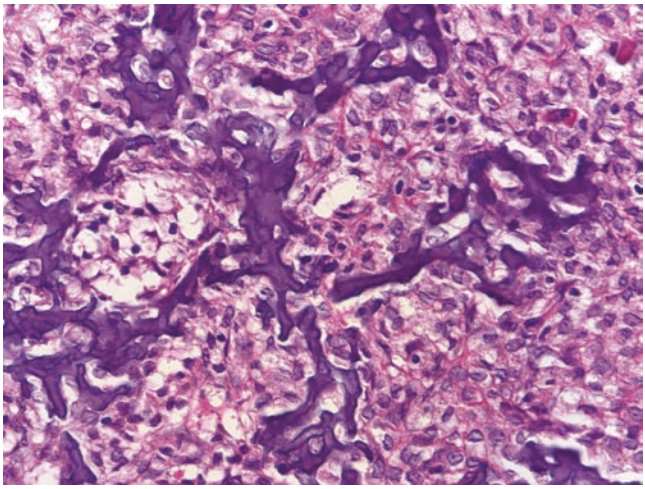

Fig. 6.61 Small cell osteosarcoma, high power photomicrograph. Sheets of small round blue cell are separated by seams of osteoid

Three other osteosarcoma variants can be confused with benign bone tumors. These are the osteoblastoma-like osteosarcoma, chondroblastoma-like osteosarcoma, and the giant cell rich osteosarcoma. These may be confused respectively with osteoblastoma, chondroblastoma, and giant cell tumor. These osteosarcoma variants can be distinguished from their benign counterparts by three important factors. First, they all show permeation of the native bone trabeculae, a feature characteristic of malignant lesions. Second, they all show varying degrees of atypia which is not present in their benign counterparts. Finally, they all have aggressive radiographic patterns which would be uncharacteristic for benign tumors.

Osteosarcoma may also occur as a complication of other skeletal diseases, particularly Paget disease and radiation osteodysplasia. Approximately 1–2% of patients with Paget disease may develop a sarcoma (Paget sarcoma). Very often this sarcoma is an osteosarcoma. The sarcoma develops in sites involved by Paget disease. Patients, who have had radiation therapy for other malignancies, may develop radiation bone damage. Approximately 2% of patients with radiation dysplasia may develop a sarcoma in the irradiated bone. Usually, patients have had 50–70 grays. The average latency period between the radiation and the development of a sarcoma is 14 years. However, sarcomas have developed in as little an interval as 2 years after therapy. Although osteosarcoma may occur de novo in bone in older people, any older adult with an osteosarcoma should be evaluated for pre-existing Paget disease or radiation dysplasia.

Fibrous and Fibrohistiocytic Tumors

Nonossifying Fibroma

Nonossifying fibromas are common developmental proliferations of fibrous tissue which occur in the metaphyseal region of long bones. Although the cause of these lesions is unknown, they are probably due to exaggerated subperiosteal osteoclastic resorption during metaphyseal remodeling. Small lesions are known as fibrous cortical defects (Fig. 6.62).

Nonossifying fibromas most commonly involve the distal femur and the distal or proximal tibia, sites which account for 80% of lesions. Many nonossifying fibromas are asymptomatic and are discovered incidentally on radiographs taken for other reasons. Undoubtedly, many are never diagnosed. Large nonossifying fibromas may cause pain, and some present with pathologic fracture. Symptoms, when present, usually develop when patients are in their mid teens.

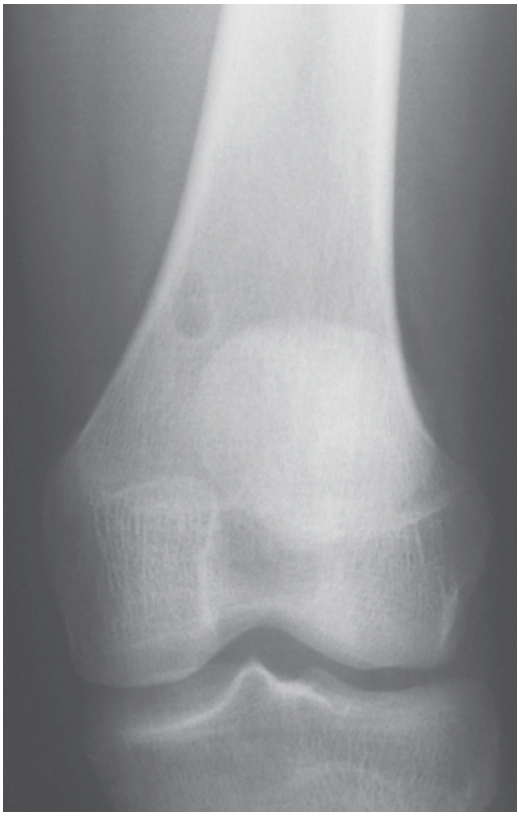

Fig. 6.62 Plain radiograph of a fibrous cortical defect. There is a well defined lytic lesion in the femoral metaphysis

Radiographically, nonossifying fibromas are lytic metaphyseal lesions. Characteristically, lesions are eccentric in the medullary canal and are juxtaposed to one cortex (Fig. 6.63). In addition, the margins are scalloped and there usually is a sclerotic rim. Nonossifying fibromas in older patients often have intralesional radiodensity, a manifestation of healing.

Histologically, nonossifying fibromas consist of a spindle cell stroma with scattered small multinucleated giant cells, although the giant cells may be scarce (Fig. 6.64). Characteristically, the spindle cells are arranged in a whorled or storiform pattern. Occasionally, the stroma is very cellular, and the spindle cells often have plump hyperchromatic nuclei (Fig. 6.65).

Small asymptomatic nonossifying fibromas need no therapy. Most heal spontaneously over a period of several years. Larger lesions, particularly those that expand the cortex or present with pathologic fracture, should be treated by curettage and bone grafting. Recurrence after treatment is very rare.

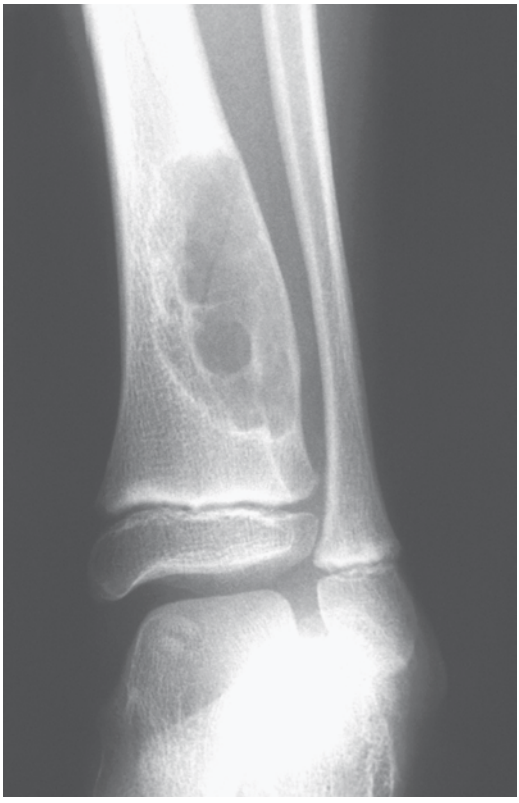

Fig. 6.63 Plain radiograph of nonossifying fibroma. There is a well defined eccentric lytic lesion eccentric in the distal tibial metaphysis. There is a sclerotic rim

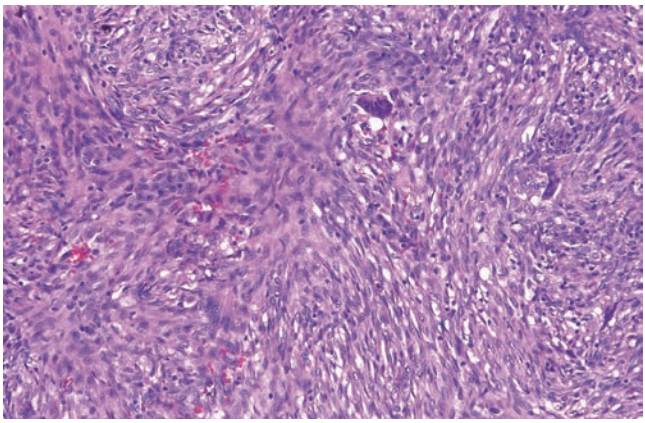

Fig. 6.64 Non-ossifying fibroma, low-powered histology. Uniform spindle cells in a storiform pattern

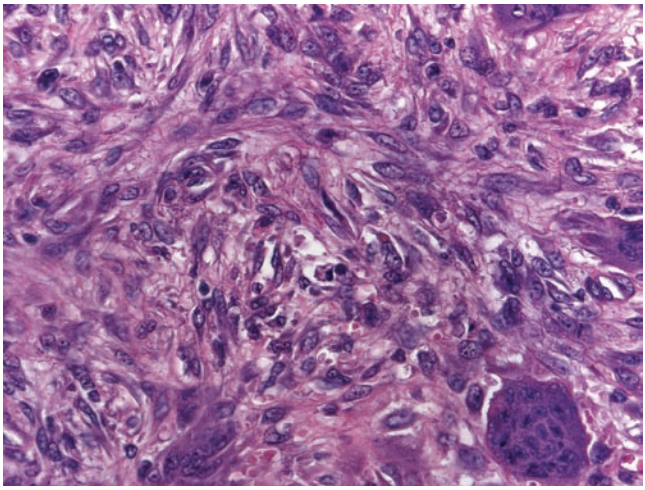

Fig. 6.65 Non-ossifying fibroma, high-powered photomicrograph. Bland spindle cells mixed with multi-nucleated giant cells

Fibrous Dysplasia

Fibrous dysplasia is a common skeletal lesion characterized by a proliferation of fibro-osseous tissue in the medullary canal. This tissue proliferates during skeletal growth and, in some cases, continues to grow during adulthood. Bone involvement in fibrous dysplasia exhibits a wide spectrum of severity. In about 80% of cases, only a small focus of one bone is affected, a presentation known as monostotic

fibrous dysplasia. Multiple bones are involved in the remainder of patients, the so-called polyostotic fibrous dysplasia.

Fibrous dysplasia may occur in any bone. The axial skeleton, the craniofacial bones and ribs are the most common sites. The tibia and proximal femur are the preferred sites in the appendicular skeleton. Fibrous dysplasia is often asymptomatic – lesions are discovered on plain radiographs taken for other reasons. Although lesions develop during skeletal growth, 25% of cases are not diagnosed until after age 30.

Some patients with severe polyostotic fibrous dysplasia also have pigmented skin lesions and endocrine abnormalities. Patients with this syndrome, known as the McCune–Albright syndrome, have severely deformed bones and are usually symptomatic before age 10. This syndrome is now known to be a genetic mutation caused by a mosaic state of an activating mutation in the GNAS1 gene. This gene codes for an adenosinediphosphate (ADP) dependent G protein. In addition, over expression of the C-fos proto-oncogene has been noted in the bones of some patients with polyostotic fibrous dysplasia. Some patients with fibrous dysplasia also have soft-tissue myxomas, a combination called Mazabraud syndrome. The myxomas have also been shown to harbor activating mutations of GNAS1.

The radiologic features of fibrous dysplasia are often diagnostic. In the appendicular skeleton, fibrous dysplasia is typically an elongated lesion with symmetrical cortical thinning and expansion – the characteristic "long lesion in a long bone." Although most lesions have a "ground glass" texture, some may be entirely radiolytic; others may be radiodense (Fig. 6.66). Lesions of polyostotic fibrous dysplasia are similar (Fig. 6.67). The bones involved by fibrous dysplasia often become deformed. A characteristic deformity known as the "shepherd's crook," occurs in the proximal femur (Fig. 6.68).

Histologically, fibrous dysplasia shows irregular seams of woven new bone in a cellular fibrous stroma. The seams of bone are thin and disconnected and are arranged in curved shapes reminiscent of "Chinese letters" or "alphabet soup" (Fig. 6.69). Although osteoblasts are occasionally adjacent to the seams of woven

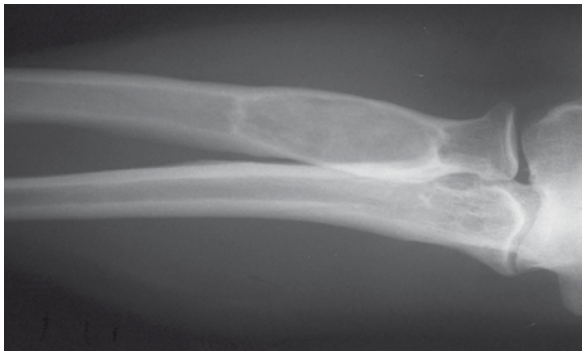

Fig. 6.66 Plain radiograph of fibrous dysplasia. There is a symmetrical long lesion in the proximal radius. There is a "ground glass" pattern to the medullary canal

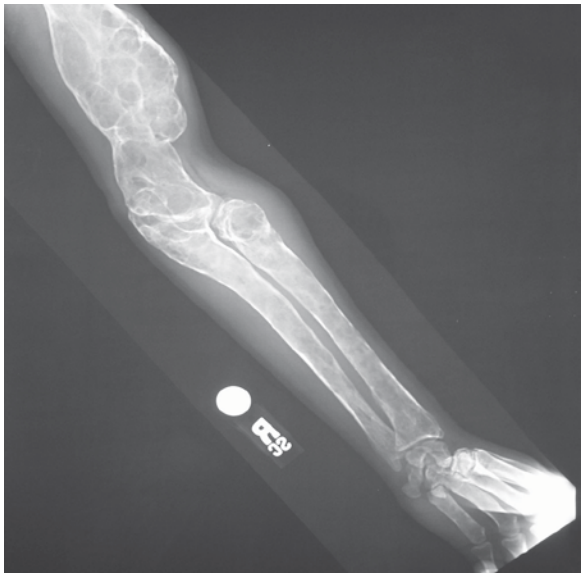

Fig. 6.67 Plain radiograph of polyostotic fibrous dysplasia. There is extensive involvement of the humerus, the radius, and the ulna

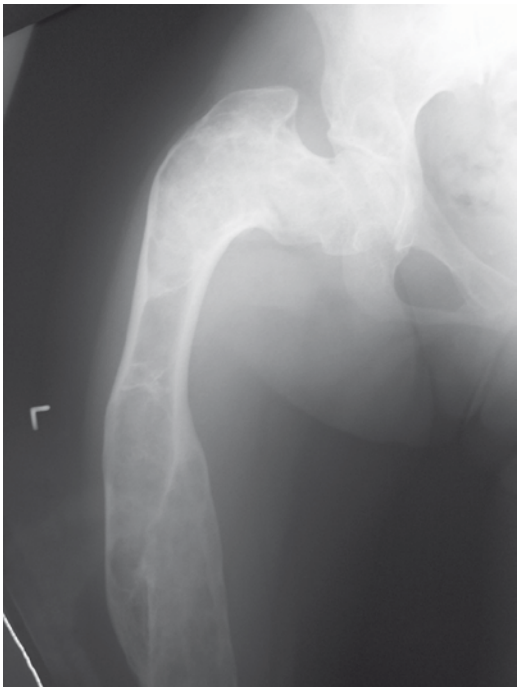

Fig. 6.68 Plain radiograph of fibrous dysplasia of the femur. There is deformity of the proximal femur in the pattern of the so called "shepherd's crook" deformity

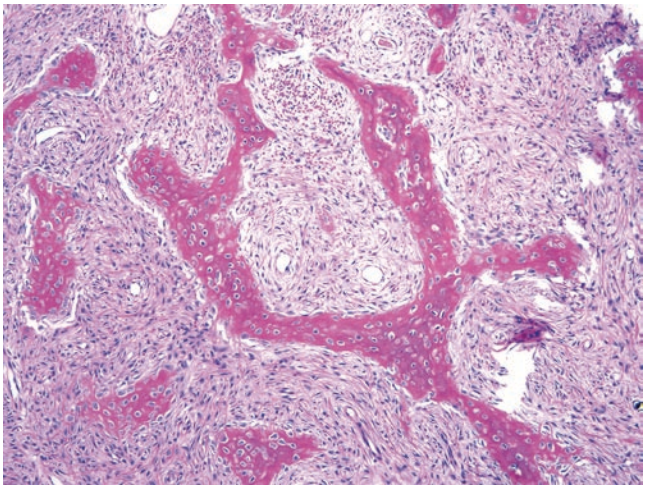

Fig. 6.69 Low-powered photomicrograph of fibrous dysplasia. Anastamosing bands of woven osteoid mixed with bland spindle cells

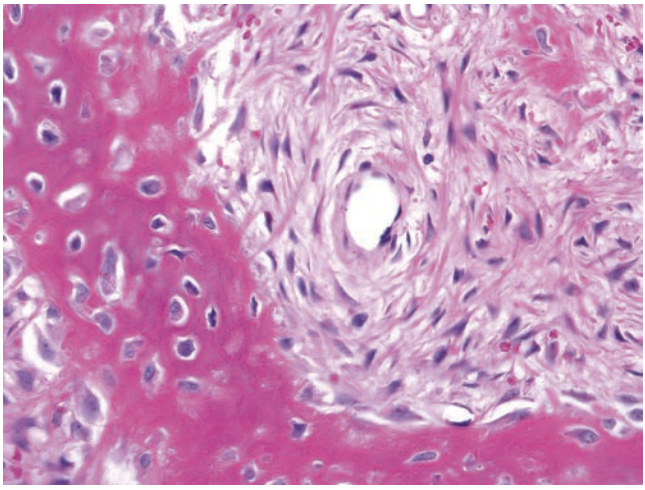

Fig. 6.70 Fibrous dysplasia, high-powered photomicrograph. Bland spindle cells and new bone. The bone lacks a lining of differentiated osteoblasts

bone, orderly osteoblastic rimming, characteristic of reactive or neoplastic bone, is not present (Fig. 6.70). Hyaline cartilage nodules are present in some lesions of fibrous dysplasia.

Treatment is unnecessary for asymptomatic lesions of fibrous dysplasia which have no potential for pathologic fracture. Large or symptomatic lesions may be

treated by curettage and bone grafting. Recurrences are due to incomplete removal of lesional tissue. Rare instances of malignant transformation of fibrous dysplasia have been reported.

Osteofibrous Dysplasia

Osteofibrous dysplasia (Campanacci disease, cortical fibrous dysplasia) is a rare, self-limited fibro-osseous lesion involving the cortex of long bones. The lesion has a very strong predilection for the mid-shaft of the tibia in skeletally immature individuals (the vast majority of cases). Rare cases of other bone involvement (fibula, ulna and radius) have been reported. Occasional cases of bilateral tibial involvement have also been reported.

Radiologically, the lesions are geographic and often have a sclerotic soap-bubble like rim. The cortex is occasionally expanded. The lesions may be single, multiple or confluent within the tibia (Fig. 6.71). The lesions are hot on Technetium bone scans.

The lesions bear microscopic resemblance to fibrous dysplasia and are composed of fibrous tissue and woven bone rimmed by osteoblasts (Fig. 6.72). Isolated cytokeratin positive cells can be seen (Fig. 6.73). Molecular studies have shown various abnormalities including trisomy 7 and 8 but not activating mutations of GNAS1 (which are seen in fibrous dysplasia).

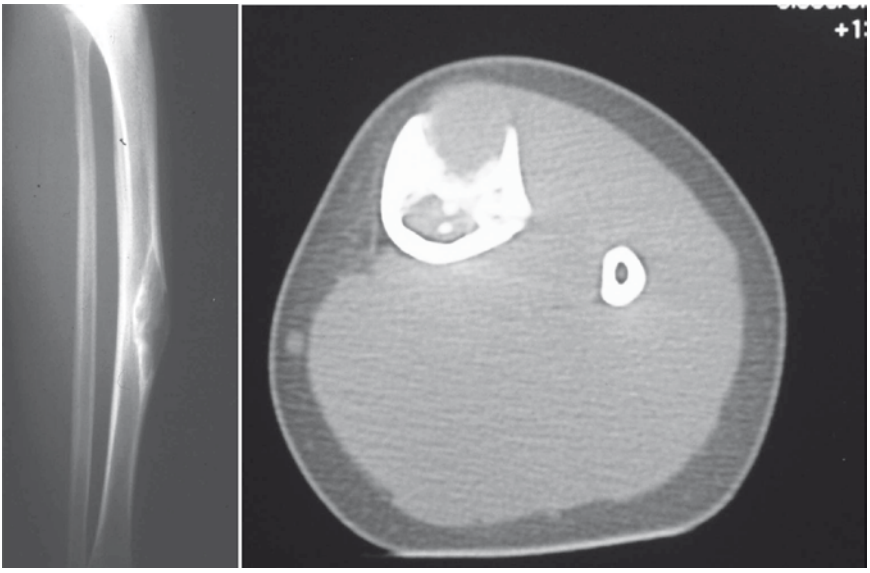

Fig. 6.71 A classic example of osteofibrous dysplasia involving the tibia of a skeletally immature patient. The plain radiograph shows a geographic lesion that is surrounded by sclerotic bone. The CT scan illustrates nicely the cortical nature of the lesion

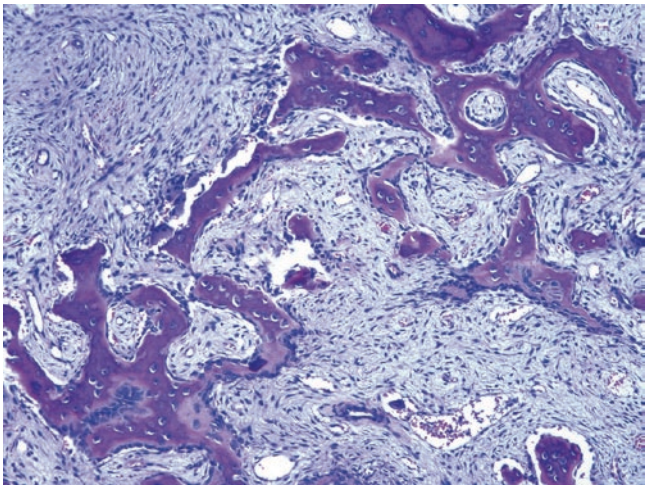

Fig. 6.72 Microphotograph from a patient with osteofibrous dysplasia. There are trabeculae of woven bone embedded in a fibrous background. There is prominent osteoblastic rimming around the trabeculae of bone

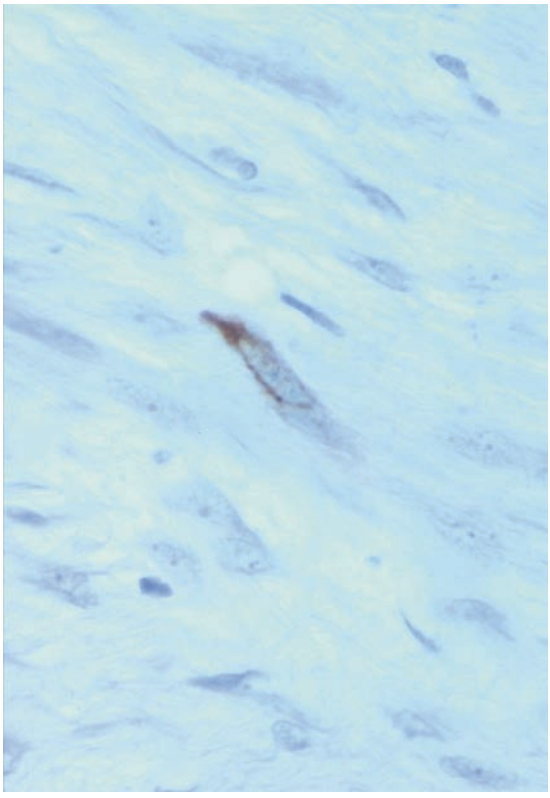

Fig. 6.73 Osteofibrous dysplasia: An immunostain for cytokeratin can sometimes show occasional positive spindle cells

The natural history of the disease is one of growth, followed by stabilization and then healing. There is an uncertain relationship with adamantinoma with some reports of lesions that are intermediate between the two entities. Some cases have been reported with pseudarthrosis of the tibia, which is often very recalcitrant to treatment.

Desmoplastic Fibroma

Desmoplastic fibromas, the intraosseous equivalent of soft-tissue fibromatosis, are extremely rare neoplasms which most commonly involve the jaw, femur, and tibia. Although patients may be any age, almost one-half are between the ages of 10 and 20. Patients present with pain, often present for several years, which suggests lesional growth.

Desmoplastic fibromas are radiolytic lesions, usually well-defined and centered in the metaphyseal portion of the bone. A multicystic, expansile pattern is typical (Fig. 6.74). The cortex is often focally destroyed, and a soft-tissue mass, best visualized on MRI, may be present. Twelve percent of patients present with a pathologic fracture. Histologically, desmoplastic fibromas show a patternless proliferation of benign-appearing fibroblasts with a densely collagenized stroma (Fig. 6.75). The fibroblasts have bland, oval, or elongated nuclei, usually without a nucleolus, and mitotic figures are extremely rare. The fibroblastic proliferation has an infiltrative growth pattern, often entrapping native trabeculae. Unlike fibromatosis of soft-tissue,

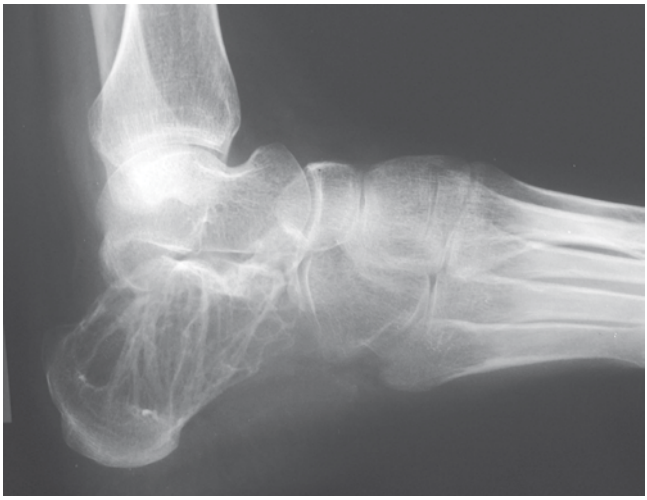

Fig. 6.74 Plain radiographs of desmoplastic fibroma of the calcaneus. There is a poorly defined radiolytic zone in the calcaneus

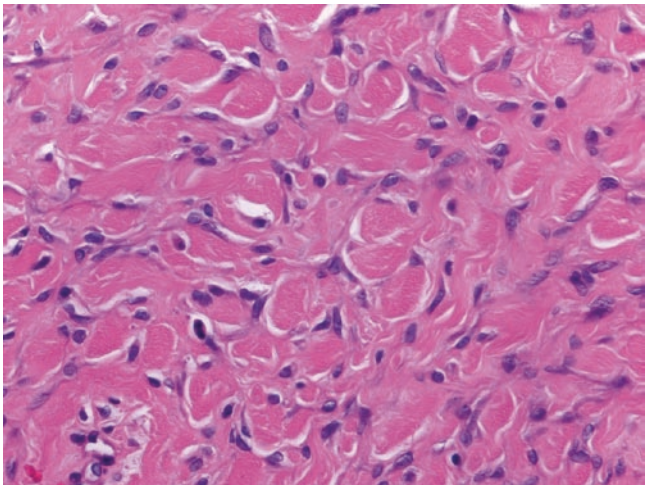

Fig. 6.75 Desmoplastic fibroma, photomicrograph. Spindle cells are mixed with bands of collagen

desmoplastic fibroma of bone is β-catenin negative. Desmoplastic fibromas are locally aggressive neoplasms that do not metastasize. However, 50% of lesions recur after curettage. Therefore, wide surgical excision with negative margins is the preferred treatment. Patients with extensive bone involvement may require amputation.

Fibrosarcoma of Bone

Fibrosarcomas of bone are neoplasms of varying malignant potential which may occur de novo in bone or, in 25% of cases, as a complication of other conditions such as Paget's disease or radiation osteitis. Like desmoplastic fibromas, these neoplasms are also rare. Many cases originally diagnosed as fibrosarcoma have been reclassified as malignant fibrous histiocytoma. Patients may be any age, and they present with pain. Any bone may be involved, but the femur, tibia, and pelvis are the most common sites.

Fibrosarcomas, although also radiolytic lesions, are usually poorly defined (Fig. 6.76). The lytic process typically involves the central portion of the medullary canal, although occasional lesions may be centered on the cortex and have a significant soft-tissue mass.

The histologic features of fibrosarcoma are similar to fibrosarcoma in other tissues. Bundles of spindle cells are present with varying amounts of extracellular collagen (Fig. 6.77). Often the spindle cells are arranged in a "herringbone pattern." There are varying degrees of nuclear atypia.

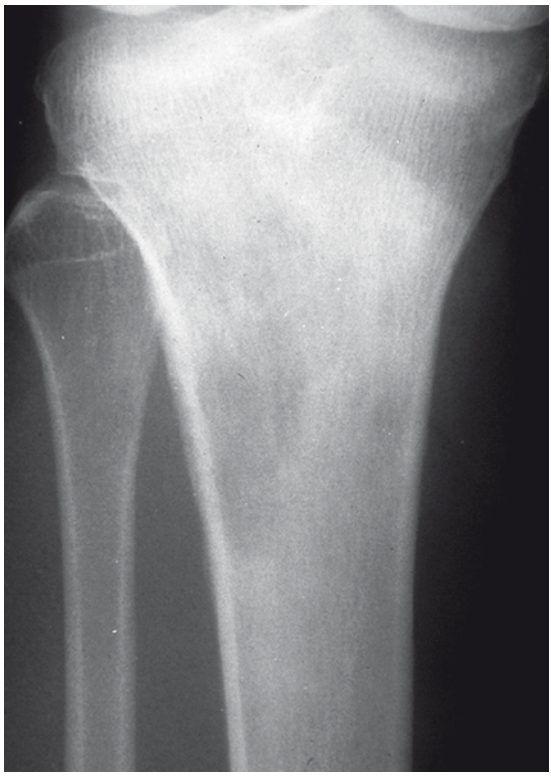

Fig. 6.76 Plain radiograph of fibrosarcoma. There is a poorly defined aggressive lytic lesion in the proximal tibia

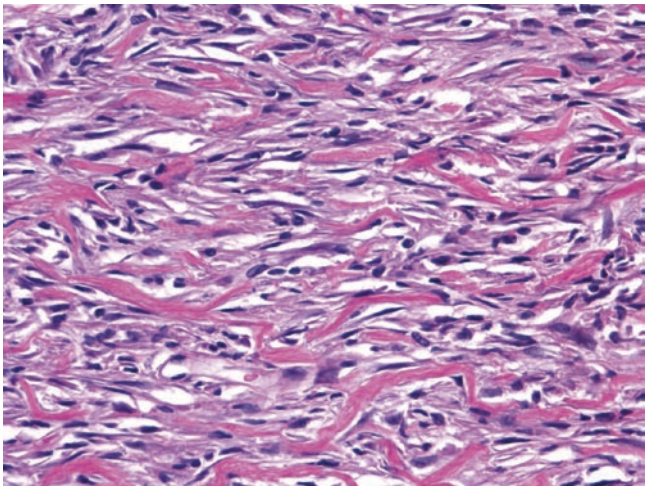

Fig. 6.77 Fibrosarcoma, photomicrograph. Atypical spindle cells imbedded in a highly collagenized extracellular matrix

Malignant Fibrous Histiocytoma

Malignant fibrous histiocytomas are high-grade pleomorphic sarcomas. In addition to occurrence in bone as a primary lesion, this neoplasm is the most common sarcoma to complicate preexisting osseous lesions such as radiation damage, Paget's disease, and cartilaginous neoplasms.

Primary malignant fibrous histiocytomas may involve any bone. However, the femur is the most common site (one-third of cases), followed by the tibia and humerus. Patients range in age from 6 to 81 years, but more than 50% of cases occur in patients older than 40 years. Patients present with pain, and 67% present with swelling or a mass. Some patients present with a pathologic fracture.

Radiographically, malignant fibrous histiocytomas are poorly defined radiolytic lesions, often with extensive cortical destruction, a periosteal new bone reaction is unusual (Fig. 6.78). An MRI often shows an associated soft-tissue mass. Malignant fibrous histiocytoma most commonly involves the metaphyseal region of bone. However, secondary involvement of the epiphysis is common.

Malignant fibrous histiocytomas are composed of spindle cells, histiocytic cells, or an intermingled combination of the two in varying proportions. The spindle cells are arranged in a storiform pattern, the most characteristic feature of malignant fibrous histiocytoma. The nuclei are oval and vesicular with moderate to severe pleomorphism (Fig. 6.79). At the other end of the spectrum, malignant fibrous histiocytomas may have a histiocytic differentiation. In contrast to the uniform spindle cells, the histiocytic cells are usually pleomorphic and bizarre. These cells are

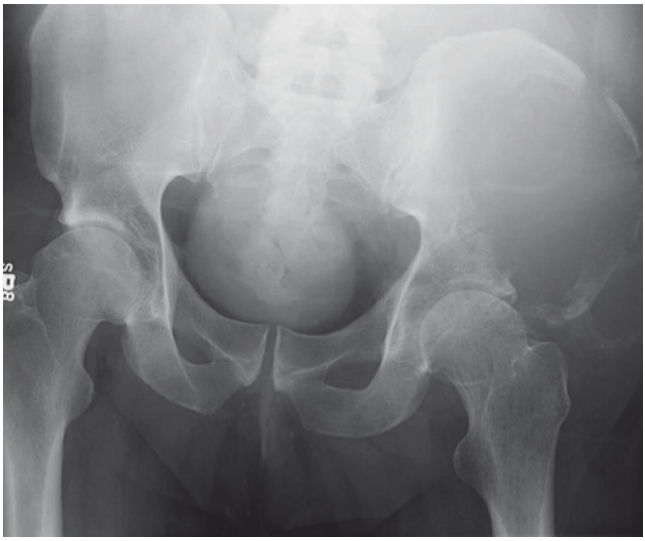

Fig. 6.78 Plain radiograph of a malignant fibrohistiocytoma of the iliac wing. A very aggressive destructive lytic lesion occupying a majority of the iliac wing

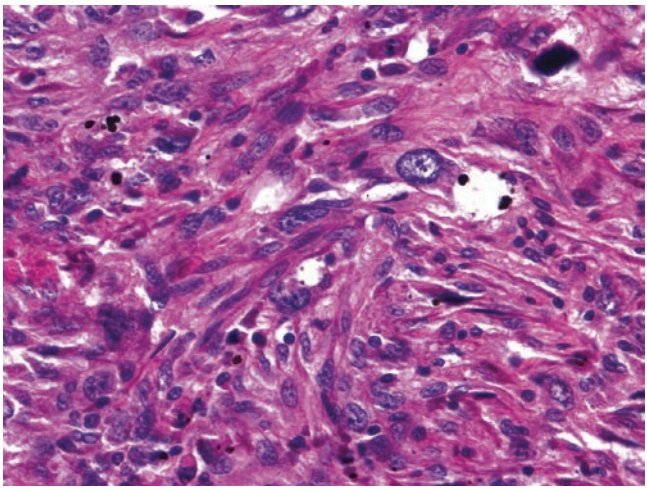

Fig. 6.79 Malignant fibrohistiocytoma, photomicrograph. Atypical, pleomorphic spindle cells arranged in a storiform pattern

rounded and have large, oval or lobulated nuclei, often with a prominent eosinophilic nucleolus. Some of the histiocytic cells contain hemosiderin or lipid. Lesions with predominantly histiocytic differentiation contain multinucleated giant cells with bizarre nuclei. Bland, osteoclast-like giant cells may infrequently be present.

Ewing Sarcoma

The neoplasm takes its name after James Ewing (1921) who considered it an endothelioma. After several years of controversial search for its histogenesis and its relationship with peripheral neuroectodermal tumors (PNETs), some facts about its molecular defects have emerged. It is now considered to be one of the less differentiated tumors from the group of neoplasms with neuroectodermal differentiation. Tissue culture studies in the presence of differentiation agents have showed that the tumor develops neural features.

Ewing's sarcoma tends to afflict patients at young ages. The majority of patients are in the first two decades of life. Patients above the age of 30 are exceedingly rare. In children below 5 years of age, metastatic neuroblastoma should be conscientiously excluded. Localized pain and a mass are the most common presenting symptoms. There may be fever, leukocytosis and a raised sedimentation rate. These bring up the clinical differential of acute osteomyelitis, an entity which can mimic Ewing's tumor both clinically and radiologically. Upto 10% of patients may have skeletal metastases at the time of presentation.

The tumor involves the long tubular bones such as the femur as well as some flat bones like the pelvis and ribs in greater frequencies than the short tubular bones of the hands and feet or sites such as skull, vertebrae or sternum, however any bone may be affected. Although diaphyseal location is more common, tumors may also occur in the metaphysis. Epiphyseal location, even though reported, is rare.

Radiologically, the lesions are ill defined, lytic with permeative margins (Fig. 6.80). A periosteal reaction is not often seen, but if present is of the onion-skin, sunburst or other rapidly growing type (Fig. 6.81). A soft-tissue component

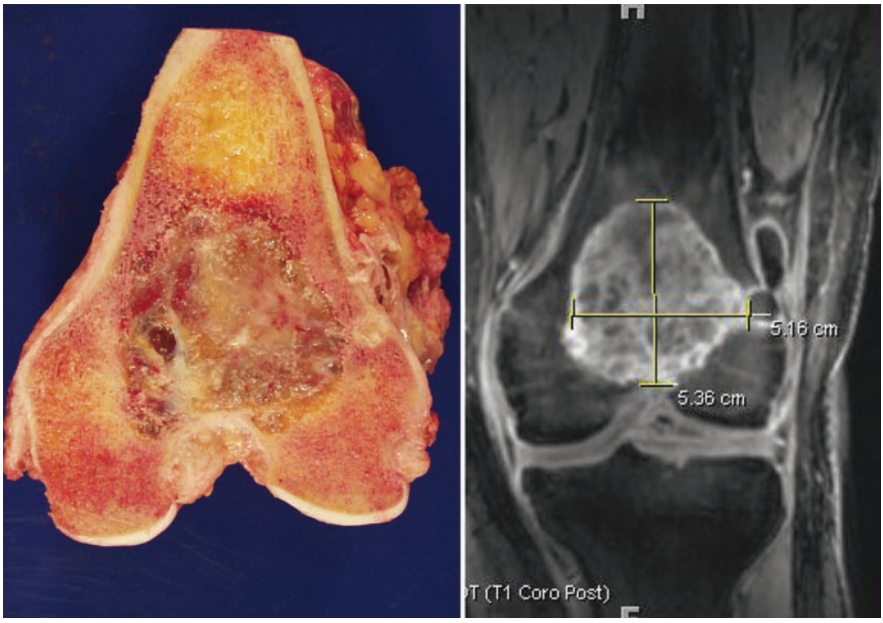

Fig. 6.80 Ewing tumor, gross specimen and MR correlation. The tumor is post treatment

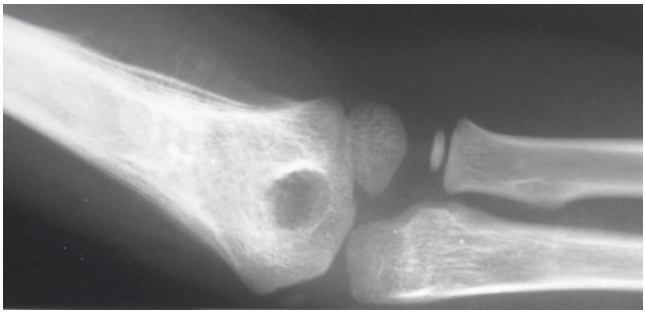

Fig. 6.81 Ewing sarcoma distal humerus. The lesion is barely perceptible since it is very permeative, but shows an onion-skin type of periosteal reaction

is often present and is well detected by CT or MR scans. The extent of involvement by MR is frequently far greater than that demonstrated by plain X-rays. Rare cases of surface (periosteal) Ewings, producing a saucerization effect are on record.

Grossly, the tumor may be firm or glistening, or more friable, mimicking pus. Hemorrhage and cystic change may be evident. Microscopically, the classic form is very cellular, and consists of sheets and large nests of uniform, small, round to polygonal cells with scanty cytoplasm. The chromatin is finely dispersed usually with no nucleoli and a variable number of mitotic figures (Fig. 6.82a). Perivascular cuffing may be evident in areas of necrosis. Rosettes are seen in a small minority of cases, and may cause a misdiagnosis of the lesion as a metastatic neuroblastoma.

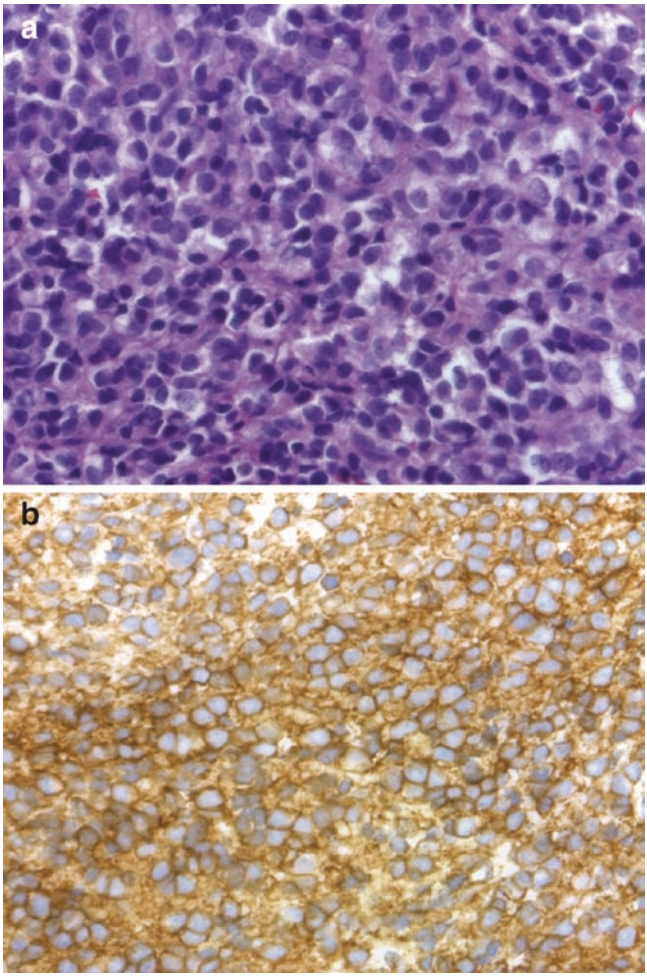

Fig. 6.82 (**a**) Ewing tumor photomicrograph showing small round cells. (**b**) Ewing tumor CD99 (mic2) stain showing a membranous pattern

Reticulin is scant in most cases of Ewing's sarcoma. Cytoplasmic glycogen demonstrated by the PAS stain is evident in many (but not all) cases; the demonstration is better and more consistent if the tumor is fixed in 80% alcohol (or other non aqueous based fixatives) rather than formalin.

An immunohistochemical stain, Mic2 (CD99) marking the protein of a pseudoautosomal gene located on the X- and the Y-chromosomes is available. It shows membranous positivity in the large majority (if not all cases) of Ewing's sarcoma and PNETs (Fig. 6.82b). This immuno-marker also stains the cells from some rhabdomyosarcomas, and cells from acute lymphoblastic leukemia, however these tumors tend to show cytoplasmic rather than membranous staining. Another marker FLI has recently become available, but experience with it is limited. Ewing's sarcoma cells also usually express vimentin. Occasional cases may express weak-focal staining for cytokeratin. A case with strong positivity for keratin with epithelial islands has been reported (adamantinom-like Ewing sarcoma). Neuron specific enolase and other neural specific markers may be positive. Leukocyte common antigen, markers of muscle and blood vessel differentiation should be absent.

Variants from this classic pattern include a large-cell type and a filigree pattern. In the large cell type, the cells are larger and have nucleoli. The filigree pattern refers to a bi-cellular architecture, separated by stroma. Patient's with tumors showing a filigree pattern have been reported to have a poorer outcome. Some authors recognize on morphologic basis, an "atypical" Ewing's sarcoma characterized by one or more of the features – lack of glycogen, brisk (over 2 per high power field) mitoses, neoplastic vascular formation, spindling at the periphery of the tumor, some amount of extracellular matrix, lobular architecture or alveolar pattern.

Ultrastructurally, the features include a lack of visible differentiation along with varying amounts of glycogen. The latter is often present in the form of "lakes." Occasional intermediate filaments might be seen as may primitive cell junctions, but cell processes and dense core granules, by definition should be absent.

Ewings tumors show a characteristic t(11;22) chromosomal translocation. By molecular methods, this chromosomal abnormality corresponds to the EWS/FL1 gene fusion. The EWS gene (located on chromosome 22 at q12) is translocated to the FL1 (a gene of the ETS family located on chromosome 11). This results in the formation of a chimerical protein product, and is seen in about 85% of patients. A second translocation has been identified in about 15% of patients. This is the t(21;22) translocation, which fuses the EWS gene with a different member of the ETS family, the ERG gene located on chromosome 21q22. This gives a hybrid EWS/ERG product. Whether these two kinds of Ewing's sarcoma behave differently clinically is unknown. These two kinds cannot be distinguished at the light microscopic level. Diagnostically, this is a convenient method of confirming or establishing the diagnosis of Ewing's tumor in selected cases. The most important differential diagnoses include small cell osteosarcoma, lymphoma and metastatic neuroblastoma.

Ewing tumors are highly malignant and are currently treated with multiple modalities including chemotherapy, radiation therapy and surgery.

Giant Cell Lesions

Giant Cell Tumor

Giant cell tumor of bone, sometimes referred to as conventional giant cell tumor, is a benign locally aggressive neoplasm which usually affects young adults; about two-thirds of patients are between ages 20 and 40. Giant cell tumors may occasionally occur in the elderly – a patient age 74 has been documented. However, these neoplasms are extremely rare in growing children. Less than 2% of giant cell tumors affect patients under age 15.

Giant cell tumors occur most commonly in the distal femur, proximal tibia, and distal radius. These locations account for about 65% of cases. Other common locations include the pelvis, vertebral bodies, and proximal femur. Patients almost always present with pain, and a few present with a pathologic fracture. On rare occasions, giant cell tumor may be multicentric; as many as nine foci may occur either synchronously or metachronously.

Giant cell tumors, when they occur in the long bones, have a diagnostic radiographic pattern. A well-defined lytic lesion involves both the epiphysis and the metaphysis and almost always extends to the subchondral bone (Fig. 6.83). The epiphyseal plate is almost always closed. Although well-circumscribed, giant cell tumors usually lack a sclerotic rim. At least one cortex is thin and may also be expanded or destroyed. In the flat bones, giant cell tumors are also well-defined lytic lesions without a sclerotic rim.

Histologically, giant cell tumors consist of multinucleated giant cells admixed with mononuclear stromal cells (Fig. 6.84). The stromal cells are polygonal or slightly elongated mitotic figures in the stromal cells are numerous. The multinucleated giant cells, often numerous, resemble osteoclasts (Fig. 6.85). Formerly, particularly in the British literature, giant cell tumors were called osteoclastomas due to the abundance of these cells. Mature cartilage or chondroid matrix is not present in giant cell tumors.

Immunohistochemical studies of giant cell tumors have clarified the relationship of the stromal cells to the giant cells. These studies suggest that there are two populations of stromal cells. One population, thought to be the neoplastic component, consists of spindle-shaped cells. The other population is the polygonal cell which resembles a macrophage. These two populations are immunohistochemically distinguishable – the polygonal cells stain for macrophage associated antigens, particularly CD11a, CD18 and CD13, while the spindle cells do not. Many antigen profiles have supported this distinction. However, we have found this differential staining to be most striking with the KP1 stain. With this stain, the giant cells stain identically to the macrophage-like cells. This strongly suggests that the giant cells originate from fusion of the macrophage-like cells and not the neoplastic spindle cells. Giant cells also stain for acid phosphatase, a reaction also exhibited by bone resorbing osteoclasts. These histochemical observations suggest that giant cells are of macrophage origin and are very similar to true osteoclasts. However, they do not result from fusion of the neoplastic cells.

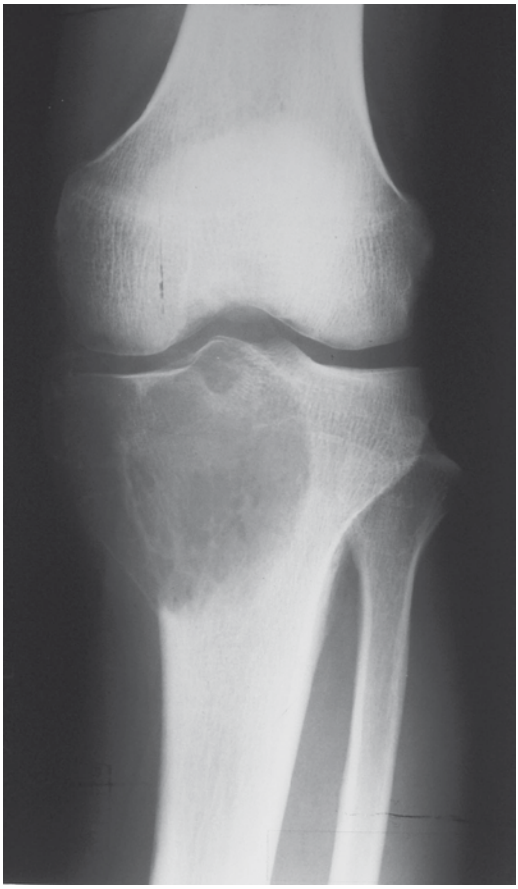

Fig. 6.83 Giant cell tumor of the proximal tibia showing a well defined lytic lesion which involves both the epiphysis and the metaphysis

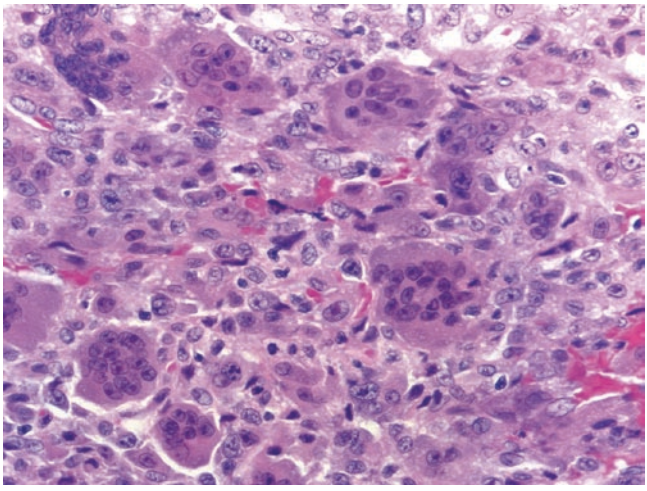

Fig. 6.84 Photomicrograph showing osteoclast-like giant cells mixed with mononuclear stromal cells

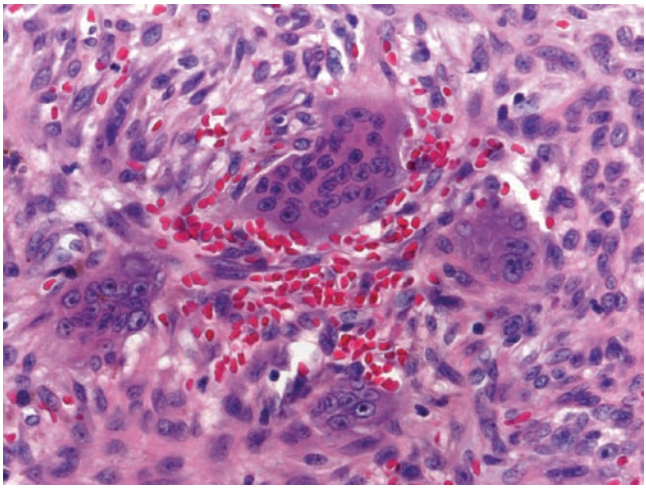

Fig. 6.85 High-power photomicrograph of a group of giant cells which show many nuclei

In addition to the typical histologic features of giant cells and stromal cells, giant cell tumors frequently undergo secondary histologic changes, and these changes often lead to diagnostic confusion. There may be zones of necrosis, fibrohistiocytic repair, reactive bone, and aneurysmal bone cyst. Sometimes the stromal cells may show nuclear atypia. However, abnormal mitotic figures are absent.

A rare behavior of conventional giant cell tumor, present in 1–2% of cases is pulmonary metastasis, the so-called benign metastasizing giant cell tumor. The pulmonary metastases are usually detected a few years after surgery and probably result from tumor embolization. In these unusual cases, the primary bone lesion is identical in all clinical, radiologic, and histologic respects to other conventional giant cell tumors. Also, the pulmonary metastases are histologically benign. This complication does not indicate an unfavorable prognosis. Pulmonary lesions grow very slowly and may be surgically resected. In fact, some pulmonary lesions remain stationary or even resolve. However, approximately 10% of patients with these "benign" lung metastases die of their disease.

Malignant giant cell tumor is a high-grade sarcoma developing in association with conventional giant cell tumor. This combination, when identifiable at the time of the initial presentation, is known as primary malignant giant cell tumor. Alternatively, secondary malignant giant cell tumor is the late development of a sarcoma after radiotherapy or curettage of a giant cell tumor. Both manifestations of malignant giant cell tumor are extremely rare and account for about 7% of all giant cell tumors.

Malignant giant cell tumors, both primary and secondary, occur in the same radiographic setting as the conventional variant – the epiphyseal end of a long bone.

The radiographic pattern of a primary malignant giant cell tumor may be identical to a conventional lesion. Most, however, are poorly circumscribed. A large volume of sarcomatous tissue may cause significant cortical destruction and soft-tissue invasion. By contrast, secondary malignant giant cell tumors, occurring years after the original lesion, have a more destructive pattern. The location at the end of a long bone may be the only clue to its relationship to the original conventional giant cell tumor.

Giant Cell Reparative Granuloma

Giant cell reparative granuloma (solid aneurysmal bone cyst) shares many histologic features with conventional giant cell tumor of bone. There is emerging data, that at least some of these lesions might be related to aneurysmal bone cysts, in that they have translocations involving the USP 6 gene (similar to usual aneurysmal bone cyst). This relationship had been made several decades earlier by Sannerkin on morphological grounds.

Giant cell reparative granuloma arises in three clinical settings: hyperparathyroidism, a lytic lesion in the jaw, a lesion in the hands and feet, and Paget disease. Giant cell reparative granuloma occasionally occurs in patients with advanced hyperparathyroidism. In this setting, the giant cell reparative granuloma is known as a *brown tumor* due to lesional hemosiderin deposition. Multiple lesions are typical, and the femur and tibia are the most common sites. Because advanced primary hyperparathyroidism is rare nowadays, brown tumors are usually only seen in secondary hyperparathyroidism due to chronic renal failure. Molecular studies have not found translocations involving USP 6 in brown tumors.

Giant cell reparative granuloma associated with hyperparathyroidism is a well-defined lytic lesion which may involve any portion of the bone. In the long bones, usually the metaphysis or diaphysis is involved (Fig. 6.86). Multiple lesions are often present. Initially, lesions lack a sclerotic rim. However, after parathyroidectomy, lesions show perilesional and intralesional sclerosis, a manifestation of healing.

The second setting for giant cell reparative granulomas is a lytic lesion in jaw or face in the absence of hyperparathyroidism. Giant cell reparative granuloma in this setting most commonly (two-thirds of cases) affects the anterior portion of the mandible. The maxilla, maxillary sinus, or sphenoid sinuses are other sites of involvement. Although patients range in age from 7 to 67 years, most are between 10 and 20 years. The characteristic radiographic pattern is a lytic expansile lesion with a loculated or “soap bubble” pattern. The cause of this lesion is unknown, although trauma has been implicated in some cases.

A curious syndrome of multiple giant cell reparative granulomas affecting the mandible in children is known as *cherubism*. In this autosomal dominant disorder, the multiple jaw lesions cause a puffy swelling of the lower face, a feature characteristic

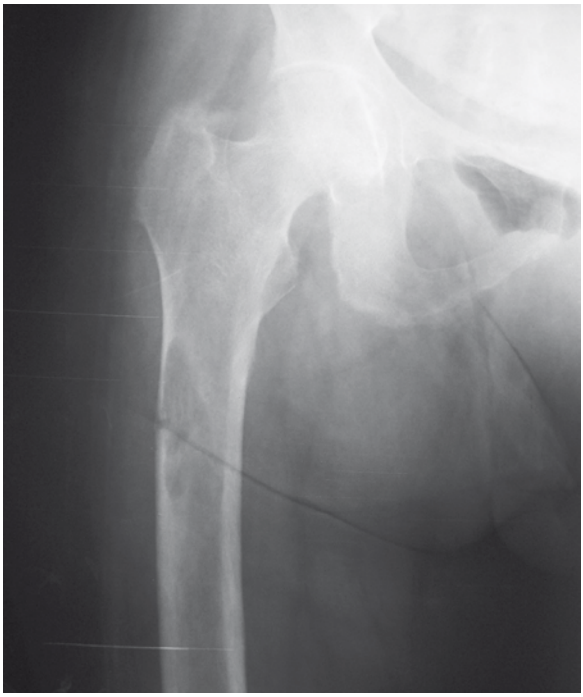

Fig. 6.86 Giant cell reparative granuloma of the femoral shaft in a patient with renal osteodystrophy. The lesion is a poorly defined lytic lesion in the subtrochanteric area. In this setting a giant cell reparative granuloma is known as a brown tumor of hyperparathyroidism

of the faces of cherubs in Renaissance paintings. The lesions are symmetrical and begin to appear at about age two. They grow until the patients are in their early teens and then begin to regress.

The third setting for giant cell reparative granuloma is in the bones of the hands and feet, also in the absence of hyperparathyroidism. In this setting, there is occasionally a history of trauma, but patients usually have no prior medical problems.

Giant cell reparative granuloma of the hands and feet is a lytic lesion which usually affects the metaphysis or diaphysis (Fig. 6.87). The tubular bones of the hands and feet are more commonly involved than the carpal or tarsal bones. These lesions may appear aggressive and occasionally destroy one cortex.

The histologic features of giant cell reparative granuloma are identical in all clinical settings. Stromal cells are admixed with osteoclast-like giant cells. The most important histologic feature of the lesion is a zonal pattern. The clusters of giant cells aggregate around red blood cells (Fig. 6.88). The giant cells are

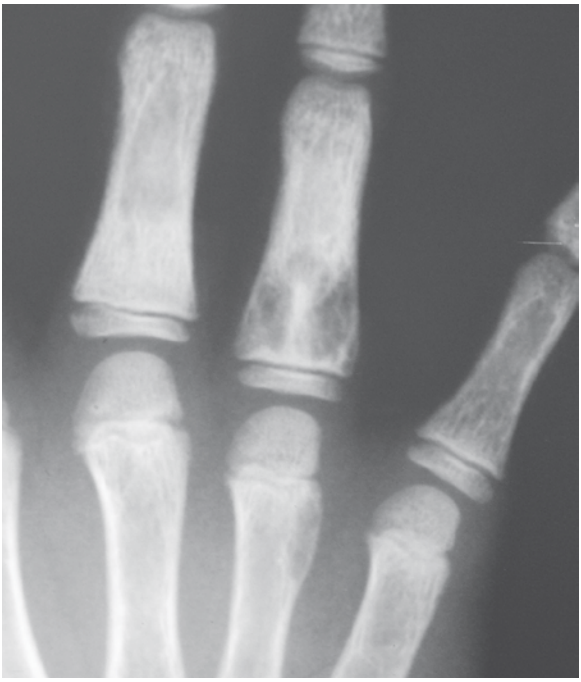

Fig. 6.87 Giant cell reparative granulomas of the metacarpal and the phalanx. The lesion is a moderately well defined lucency

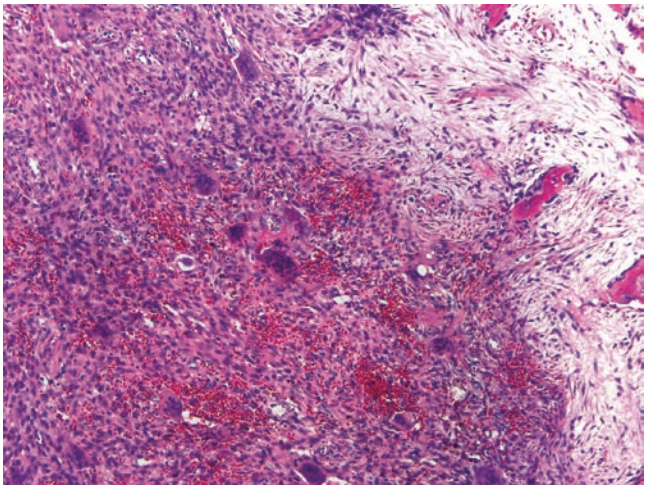

Fig. 6.88 Photomicrograph of a giant cell reparative granuloma showing giant cells adjacent to many extravasated red blood cells

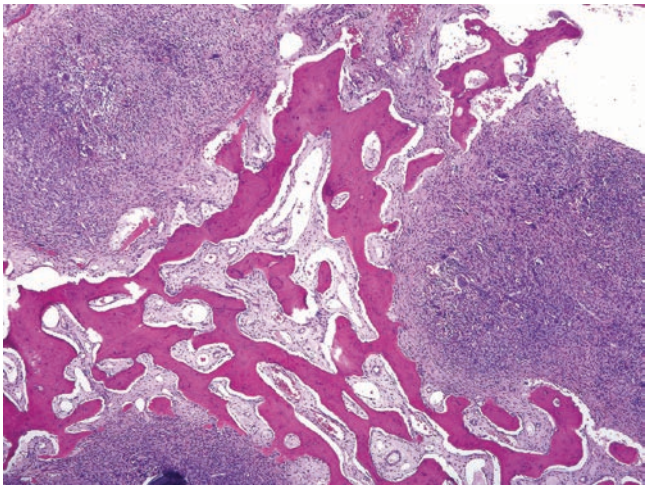

Fig. 6.89 Photomicrograph showing the zonal pattern of reparative granuloma. Clusters of giant cells and stromal cells are separated by walls of reactive bone

surrounded by a zone of reactive fibrosis which, in turn, is bounded by reactive bone. This pattern repeats itself numerous times in any low-power field (Fig. 6.89). Giant cell reparative granuloma may also undergo focal aneurysmal bone cyst change. Particularly in this case, the term solid aneurysmal bone cyst is apt.

Giant cell reparative granuloma presents an important problem of differential diagnosis – it is often confused with giant cell tumor of bone. It is imperative to distinguish these lesions because giant cell tumor of bone is an aggressive neoplasm whereas giant cell reparative granuloma is an indolent process, often cured by simple curettage.

These two lesions may be distinguished by clinico-radiographic and histologic means. Although giant cell tumor may rarely be multicentric, multiple giant cell lesions are more likely to be brown tumors of hyperparathyroidism. Serum calcium and parathormone levels should be checked.

Differences in location also aid in distinguishing these lesions. For example, giant cell tumor rarely occurs in the jaw; lesions in this location are probably reparative granulomas. In the long bones, giant cell tumor is centered in the epiphysis and extends into the metaphysis; patients are skeletally mature. By contrast, giant cell reparative granuloma is usually metaphyseal or diaphyseal; patients may be skeletally immature.

Histological differences are also present. Although both lesions contain giant cells and stromal cells, giant cell tumor lacks the zonal pattern characteristic of giant cell reparative granuloma.

Adamantinoma

Adamantinoma is considered to be a low-grade malignant biphasic neoplasm, with epithelial and mesenchymal differentiation, which arises in patients, somewhat older than those with osteofibrous dysplasia, but shares the same predilection for the tibia.

It has an uncertain and controversial relationship with Campanacci disease or osteofibrous dysplasia. Some authors have suggested a pretibial origin and a possible relationship to cutaneous eccrine carcinomas.

Some authors recognize a classic (or aggressive form, with a tendency to occur in older age groups) and a well-differentiated form (or indolent, non-metastasizing form occurring in younger age groups). This distinction needs to be confirmed on larger series before being adopted.

Patients display a wide age range, but most cases occur in the third and fourth decades. Presentation can be with pain, fracture or be discovered incidentally.

Radiologically, most lesions affect the tibial diaphysis (Fig. 6.90). A very small number of cases have involved bones other than the tibia, these bones include the fibula, femur, other long bones, pelvis and the short tubular bones. The lesions are often diaphyseal, eccentric, epicentered in the cortex, with a "soap-bubble" appearance. Primary intra-medullary origin or cortical breakthrough is seen in a small number of cases. The lesions usually show a geographic margin, which is only rarely sclerotic.

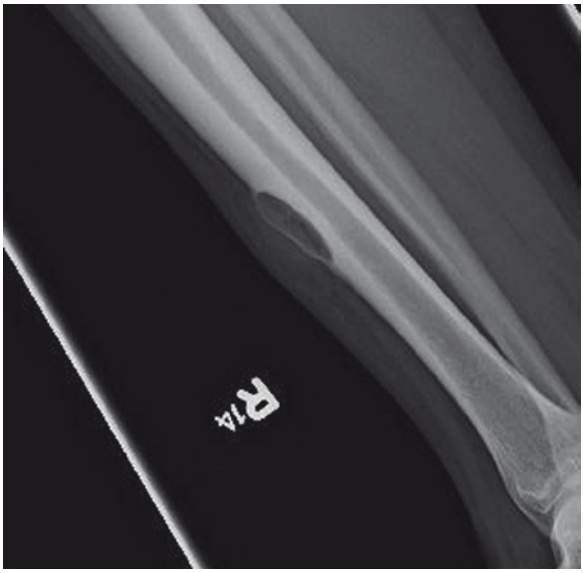

Fig. 6.90 Adamantinoma of the tibia

Grossly, the tumor is well demarcated in resection specimens. A lobular growth pattern may be evident. Cystic spaces and hemorrhage are common. Microscopically, the tumor consists of epithelial islands in a fibrous stroma (Fig. 6.91a, b). The nuclei of adamantinoma are usually bland and the mitotic rate is usually low in most cases. A variety of growth patterns may be evident in the epithelial component. These include spindled, basaloid, tubular and squamoid. The spindle pattern in particular, can be difficult to recognize as epithelial, in the absence of immunohistochemical stains. Anastamosing spaces, with the appearance of vascular channels are seen in some cases.

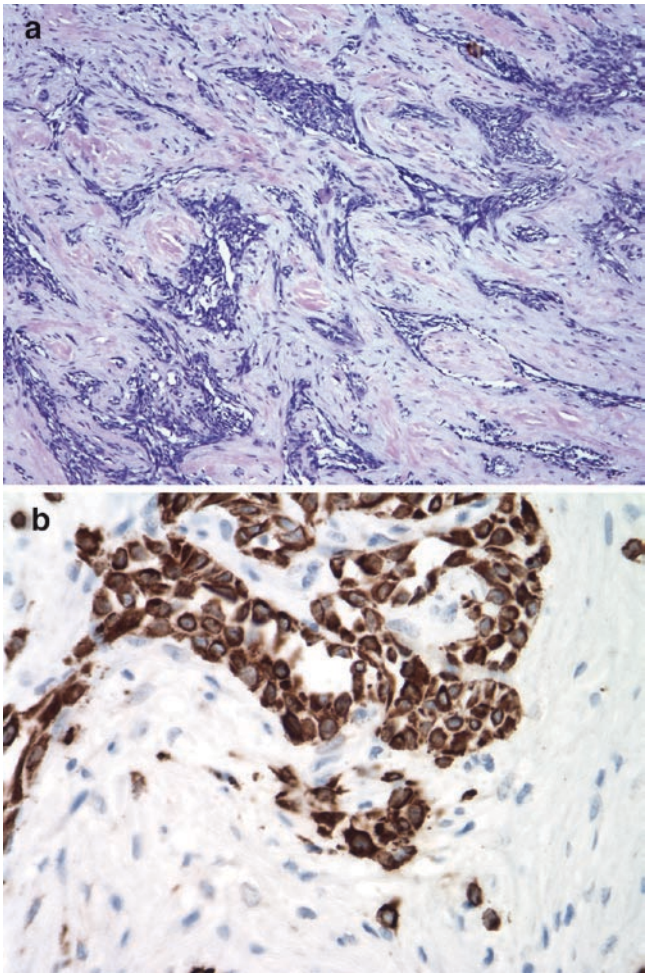

Fig. 6.91 (**a**) Adamantinoma. Seen are epithelial islands in a fibrous background. (**b**) Cytokeratin stain staining the epithelial islands

Notochordal Tumors

Chordoma

Chordomas, thought to arise from notochordal rests, are slow growing malignant neoplasms which occur exclusively along the spinal axis. The two ends of the spinal axis, inside the skull and the sacrococcygeal region, are the most common locations. Half of all chordomas arise in the sacrococcygeal region where they present with pain and, occasionally, bladder dysfunction (Fig. 6.92). At the other end of the spine, intracranial chordomas, accounting for 40% of lesions, involve bones at the base of the skull. When chordomas occur in this region, patients present with headache and neurologic impairment. The remaining 10% of chordomas involve the vertebral column. These locations correlate with the distribution of notochordal rests found by meticulous study of adult and developing spines. Most patients with a chordoma are over age 40, although intracranial lesions occur in somewhat younger patients.

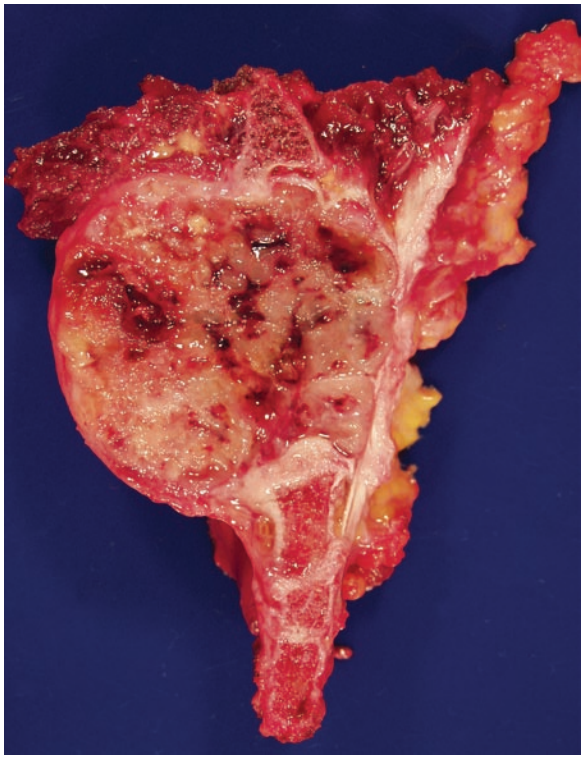

Fig. 6.92 Gross photograph of a chordoma of the sacrum period. There is a heterogeneous mass involving the sacrum and extending anteriorly

Radiologically, sacral chordomas are intraosseous destructive lesions which often expand into the soft-tissues . Chordomas are best studied with the CT scan (Fig. 6.93) or MRI (Fig. 6.94). Intracranial chordomas may destroy the sella tursica, and they often invade the petrous or sphenoid bone.

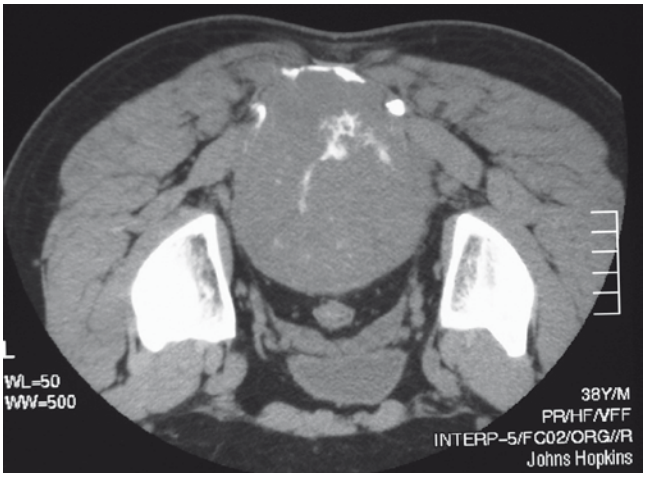

Fig. 6.93 CT scan of a sacral chordoma showing a mass destroying the sacrum extending anteriorly. The mass contains areas of irregular radiodensity

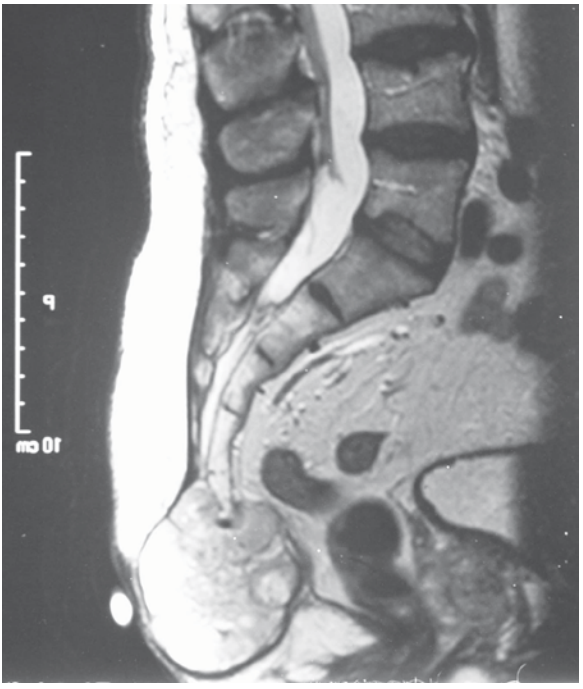

Fig. 6.94 T_1-weighted MRI image showing a chordoma arising from the tip of the coccyx

The histologic features of chordomas are distinctive. On low power, a lobular growth pattern, similar to cartilage neoplasms, is apparent. Cords and sheets of cells are embedded in an abundant, pale extracellular matrix (Fig. 6.95). Higher power study reveals two types of cells. One type is a square to oblong cell with a round central nucleus and an eosinophilic cytoplasm. The other type contains a round nucleus but has a bubbly cytoplasm (physaliferous cell) (Fig. 6.96). Chordomas show little nuclear pleomorphism, and mitotic figures are rare. Occasionally, the extracellular matrix of chordomas in the sphenooccipital region have a chondroid matrix. This may lead to the misdiagnosis of chondrosarcoma. Chordomas, particularly in the sacral

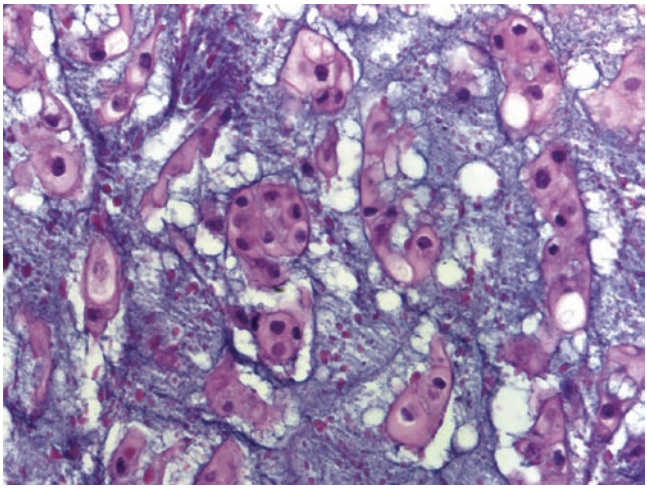

Fig. 6.95 Photomicrograph showing cords of chordoma cells in a basophilic extracellular matrix

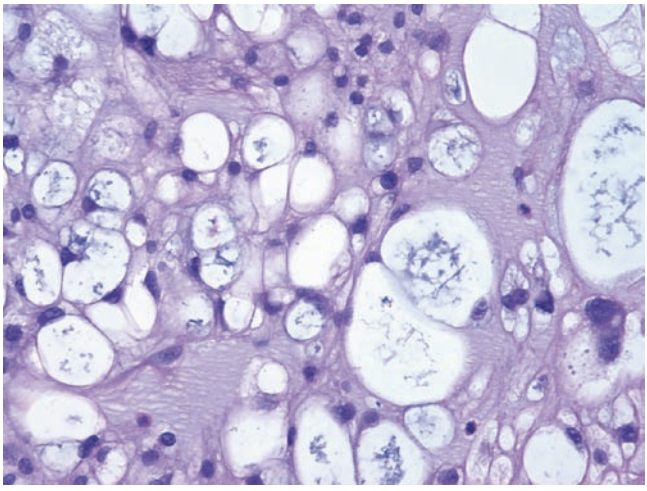

Fig. 6.96 Photomicrograph showing the cells of a chordoma with bubbly cytoplasm

region, may dedifferentiate. The dedifferentiated component is a high-grade pleomorphic sarcoma or an osteosarcoma.

Immunohistochemical stains facilitate the diagnosis of chordomas. They are epithelial neoplasms and are strongly positive for cytokeratin. Stains for epithelial membrane antigen and S-100 protein are also positive. However, the stain for S-100 protein is usually only weakly positive. Even the cells in the chondroid areas of chondroid chordomas stain with these epithelial markers suggesting that this tissue is not true cartilage. Stains for brachyury seem to be specific for chordoma, but experience with these antibodies is limited.

Chordomas must be distinguished from other spinal neoplasms. The presence of cytokeratin rules out chondrosarcoma. Metastatic adenocarcinoma may be ruled out by the presence of S-100 protein and acid mucin, substances found in chordomas but not in metastatic carcinomas. Also, chordomas do not form glandular lumens. One difficult problem is distinguishing a small chordoma from a large notochordal rest. These lesions are histologically and immunohistochemically identical. In this situation, only evidence of destructive growth can identify a chordoma.

Benign Notochordal Cell Rest

Benign notochordal cell rests have been recently separated from true chordoma. Although the lesional cells are notochordal, and hence, histologically and immunohistochemically similar to those of chordoma, the growth pattern is sufficiently different to allow a diagnosis. These rests do not have a myxoid matrix. The cells often contain hyaline globules. They are often seen in sheet like aggregates and do not form cords. They are well demarcated and often surrounded by sclerotic bone trabeculae. Unlike notochordal vestiges, but like chordoma, these lesions are negative for cytokeratin 18. These lesions are thought to be benign, although some cases have progressed to frank chordoma.

Vascular Neoplasms

The nomenclature of vasoformative bone lesions has been confusing. Terms such as epithelioid hemangioma, hemangioendothelioma and hemangioendothelial sarcoma create artificial categories which can possibly lead to improper therapy. A particularly confounding problem, in the categorization of vascular neoplasms, is that they are often multifocal. It therefore is difficult and sometimes impossible to decide if a lesion is a second primary or a metastasis. This is particularly problematic in intermediate grade vascular tumors. Nevertheless, vascular lesions of bone are best subdivided into three major categories: hemangioma (including angiomatosis and epitheloid hemangioma), epithelioid hemangioendothelioma, and angiosarcoma.

Hemangioma

Hemangiomas in the skeleton may be solitary or multiple. Solitary hemangiomas usually affect a vertebral body or the calvarium. Small lesions can be found at autopsy in 11% of carefully examined spines. Most spinal hemangiomas are asymptomatic and are discovered incidentally on radiographs taken for other reasons. Some patients, however, present with back pain due to a compression fracture. Hemangiomas of the calvarium usually present as a slowly growing mass. Hemangiomas may be discovered at any age, but most patients are in their 40s.

Radiographically, vertebral hemangiomas are lytic lesions with coarse vertical striations, the so-called "jail bar" pattern (Fig. 6.97). These dense striations on cross-sectional CT images appear as spots of dense bone. Lesions in the calvarium bulge the outer cortical table and have a "sunburst" appearance of reactive bone (Fig. 6.98).

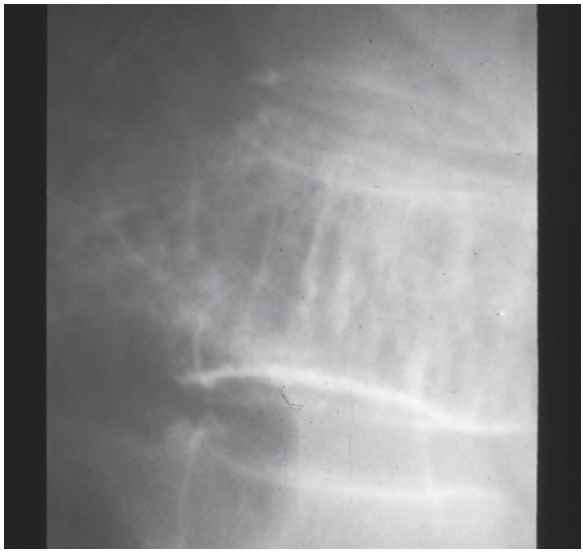

Fig. 6.97 Plain radiograph of a vertebral hemangioma. There are coarse vertical trabeculae

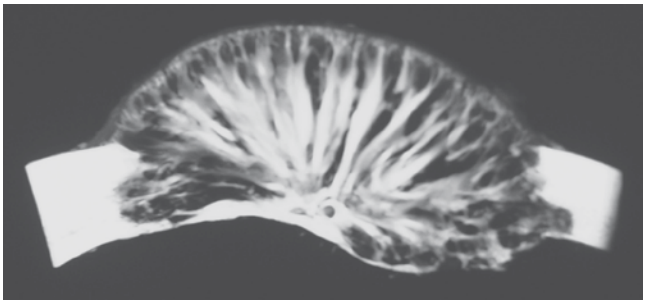

Fig. 6.98 Specimen X-ray of a calvarial hemangioma showing a sunburst appearance

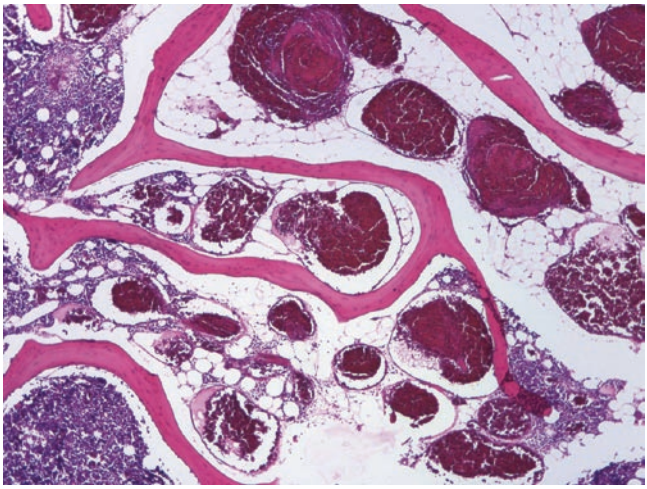

Fig. 6.99 Photomicrograph of a hemangioma. Dilated vascular spaces are separated by marrow and trabecular bone

Histologically, hemangiomas show multiple blood-filled cavities, separated by marrow elements or loose fibrous tissue. The vascular spaces may also be found between trabeculae (Fig. 6.99). The cavities may be dilated as in a cavernous hemangioma, or they may be small as in capillary hemangioma. The spaces are lined by a single layer of flattened endothelial cells.

Epithelioid Hemangioma

This lesion is similar to its soft-tissue counterpart (angiolymphoid hyperplasia with eosinophilia or histiocytoid hemangioma). The lesions have a lobular architecture with larger vessels lined by epitheloid cells centrally and smaller vessels in the periphery of the lobules. The epitheloid endothelial cells have grooved nuclei with abundant eosinophilic cytoplasm. There is often an inflammatory background rich in eosinophils. A myxoid matrix is not present.

Lesions with this characteristic morphology have been recognized as epitheloid hemangioma by many authors (including the WHO sponsored consensus group); the entity is however somewhat controversial since other authors have suggested that these lesions cannot be well separated from epitheloid hemangioendothelioma (a low-grade malignancy) and that lesions with the exact same morphology have "metastasized" to bone, lung, lymph node, etc. The problem of differentiating multifocality from metastasis has been used by each of these groups to support their counter claims as to the biological behavior and hence the terminology.

Angiomatosis

Cystic angiomatosis is a syndrome of multiple hemangiomas of bone and, occasionally, extraosseous sites. The lesions are hamartomatous proliferations of simple endothelial-lined spaces, similar to hemangiomas in other locations. Patients may have as many as 20 lesions, and any bone may be affected (Fig. 6.100). Usually, like solitary hemangiomas, cystic angiomatosis is usually asymptomatic, and lesions are found on radiographs taken for other reasons. Cystic angiomatosis shows microscopic features identical to those of solitary hemangioma of bone. Occasionally, skeletal angiomatosis can involve the soft-tissues (skeletal-extraskeletal angiomatosis). Some of these lesions can be symptomatic and difficult to treat because of a propensity to recurrence.

Massive Osteolysis

Massive osteolysis (Gorham disease) is a term given to a particularly aggressive form of hemangioma or angiomatosis that involves the resorption of most or almost

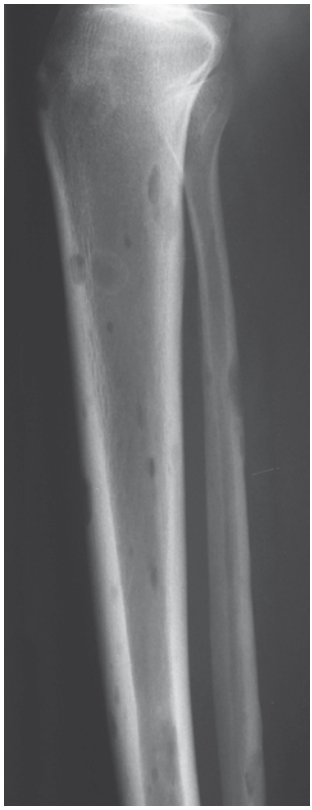

Fig. 6.100 Cystic angiomatosis showing multiple punched out lytic lesions of the tibia and fibula

all the bone locally. It is often seen in the appendicular skeleton involving one (or sometimes two contiguous bones). Microscopically, there is a proliferation of benign vascular channels similar to hemangioma. The essential difference with hemangioma or angiomatosis is that of extent and aggressiveness. Additionally, most cases occur below 35 years. Pain is a frequent presenting symptom. There is a predilection for mandible, rib, femur, scapula, humerus and sternum. Radiologically, there is a lucent change in the medullary region, or alternatively, a concentric destruction of the cortex with tapering at ends ("sucked candy effect"). About three quarters of the cases show involvement of contiguous bones.

Hemophilic Pseudotumor

Although this is not a vascular proliferation, it is discussed here since it forms a tumor like lesion and may mimic several aggressive bone neoplasms.

Pseudotumors can cause massive bone destruction. They arise secondary to the large amounts of hemorrhage that occurs in bleeding disorders. This hemorrhage is often intra-articular, and is associated with reactive synovitis and degenerative bone disease. Less often, the patients develop soft-tissue or skeletal pseudotumors. When located subperiosteally, they can cause considerable periosteal lifting and demonstrate convincing Codman's triangles on X-rays.

The presentation is most often in males (owing to the X-linked nature of the disease), and can occur at any age. Painless enlarging masses, are the most common, however, pain and neural deficits are sometimes present. Any site can be involved, but the buttocks and lower extremities are the most commonly affected. Radiologically, there are geographic lytic lesions, sometimes with well-defined margins mimicking an aneurysmal bone cyst. Occasionally, more aggressive margins that mimic malignant bone tumors may be seen. Bony expansion can be seen in some lesions. Grossly, the masses may mimic thrombus or hematomas and are often confined by the periosteum. Microscopically, there is reactive woven bone, fibrous tissue and repair reaction at the periphery of the lesion. More centrally, there is often blood in various stages of degeneration. A zonation phenomenon similar to myositis ossificans or fracture callus can often be seen.

Epithelioid Hemangioendothelioma

Epithelioid hemangioendotheliomas are indolent neoplasms characterized by the proliferation of plump, histiocytoid endothelial cells. Most epithelioid hemangioendotheliomas of bone are diagnosed in patients between ages 10 and 30, although older patients may also develop this lesion. The femur, pelvis and tibia are the most common sites. Patients usually present with pain or pathologic fracture. A distinctive feature of epithelioid hemangioendothelioma, present in 65% of patients, is

involvement of multiple sites. Curiously, multicentric lesions tend to involve the bones of one extremity. Although any bone may be involved, the bones of the lower extremity are favored sites.

Epithelioid hemangioendothelioma of bone is usually a well-circumscribed radiolytic defect ranging in size from 2.5 to 15 cm in maximum dimension (Fig. 6.101). A mildly sclerotic border is sometimes present. On rare occasions, lesions may be predominantly sclerotic. Cortical expansion and extension into the soft-tissue may occasionally occur.

Epithelioid hemangioendotheliomas of bone are characterized by nests, cords, or sheets of plump, round or polygonal cells with abundant eosinophilic cytoplasm (Fig. 6.102). Their nuclei are round and moderately hyperchromatic. These "histiocytoid" cells, which show little pleomorphism, often contain intracytoplasmic lumina which may coalesce with similar structures in an adjacent cell. Often, the cell nests form well-developed vascular lumina which contain red cells. In some areas, the clusters of histiocytoid endothelial cells are separated by a fibrovascular stroma containing lymphocytes, plasma cells, and often, many eosinophils. The well-formed neoplastic vessels in the fibrous stroma have the appearance of granulation tissue. Many cases have a prominent myxoid background.

Epithelioid hemangioendotheliomas of bone are slow-growing neoplasms with a protracted clinical course. Lesions should be totally removed, either by complete curettage or by limb-sparing resection. Radiotherapy may be of value if complete excision is impossible. Lesions with more than mild mitotic activity may be more aggressive. Patients with epithelioid hemangioendothelioma should be evaluated for multifocal lesions. These patients have an equally good, perhaps better, prognosis. Rare reports of metastasis of epithelioid hemangioendothelioma may be cases of multifocal lesions rather than metastases.

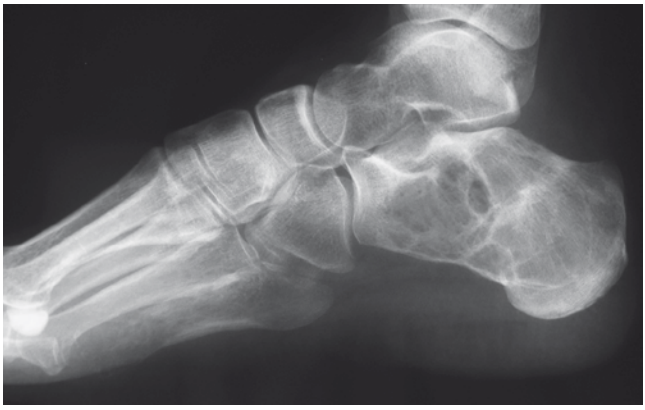

Fig. 6.101 Epithelioid hemangioendothelioma of the calcaneus. There is a moderately defined lytic lesion

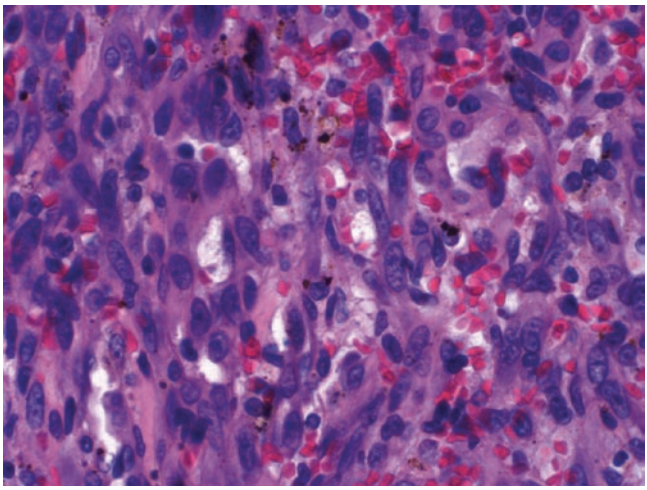

Fig. 6.102 Photomicrograph of epithelioid hemangioendothelioma. Multiple rounded cells with vesicular nuclei are present. Some have cytoplasmic lumina. There are many extravasated red blood cells

Angiosarcoma of Bone

Angiosarcomas of bone are very rare, highly malignant neoplasms which occur in patients from age 10 to 70. Most, however, are over age 30. Pain of several weeks to a few months duration is the usual presenting symptom. Angiosarcomas most commonly involve the femur and tibia.

Angiosarcomas of bone show a radiographic pattern of an aggressive, high-grade malignant bone tumor. Lesions are radiolytic with poorly defined margins, and cortical expansion and cortical destruction are usually present (Fig. 6.103).

Histologically, these lesions show anastamosing blood-filled clefts and slits. These spaces are lined by large cells with abundant eosinophilic cytoplasm (Fig. 6.104). Unlike the uniform cells of epithelioid hemangioendotheliomas, the cells of angiosarcomas show marked pleomorphism. Large, bizarre, hyperchromatic nuclei are common, and mitotic figures are numerous. Papillary tufts of the pleomorphic cells often project into the neoplastic vascular lumina.

Hematopoietic Tumors

These entities are usually discussed in texts specializing in hematopathology. However, these lesions are important in the differential diagnosis of bone tumors and so will be discussed briefly.

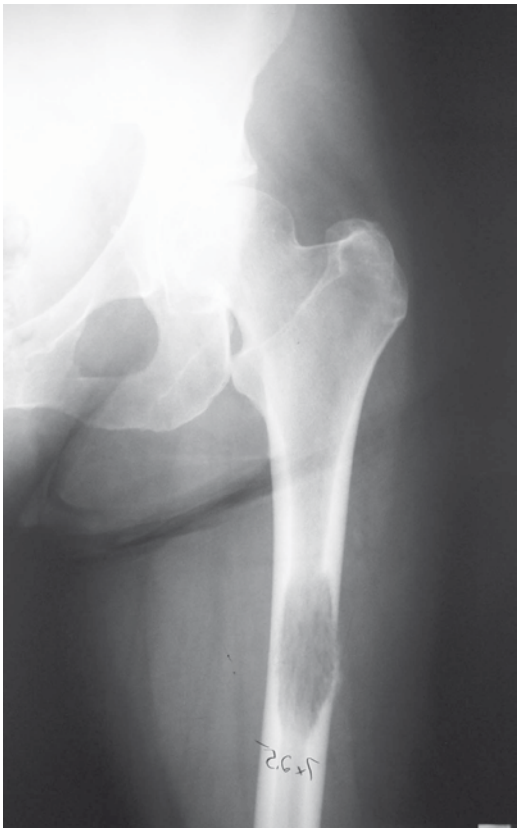

Fig. 6.103 Angiosarcoma of the mid-shaft of the femur. There is a poorly defined, aggressive lytic lesion

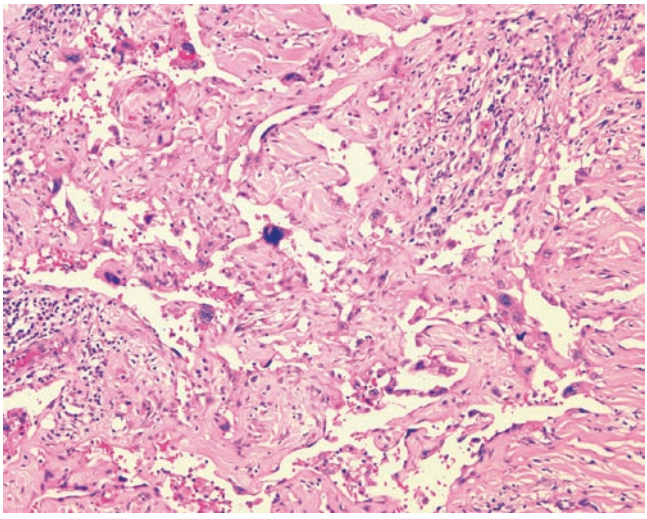

Fig. 6.104 Photomicrograph of angiosarcoma. Numerous slit like vascular spaces are lined by highly atypical endothelial cells

Plasma Cell Neoplasms (Plasma Cell Myeloma and Plasmacytoma)

Plasma cell neoplasms constitute one of the most frequent neoplasms to affect bone and bone marrow, especially so in the older age groups. These tumors results from the expansion of a single clone of immunoglobulin secreting, plasma cells. The spectrum includes a generalized bone marrow disorder with osteolytic lesions and a serum monoclonal protein (plasma cell myeloma) as well as a solitary lesion composed of a clonal proliferation of plasma cells (plasmacytoma). In a variant (POEMS) there may be sclerotic bone lesions along with polyneuropathy, organomegaly, endocrine disturbances and skin changes.

Radiological findings: In the typical case of plasma cell myeloma, there are lytic bone lesions (punched out defects), which are not necessarily hot on bone scans and generalized osteoporosis. The most common bones affected include: vertebral column, ribs, skull, and the pelvis.

Grossly, the tissue is soft, pink or gray. Microscopically, the lesions are composed of sheets or aggregates of mature to immature, pleomorphic or anaplastic plasma cells. Less differentiated examples, may show prominent nucleoli immature or "plasmablastic" morphology. Amyloid deposition may be seen in some cases. The plasma cells are usually positive for CD38, CD56, CD79a, CD138 and an immuno-globulin light chain (κ or λ). In the very poorly differentiated or anaplastic examples, there may be difficulty in distinguishing from lymphoma and other non-hematopoietic disorders and immunohistochemical stains to establish clonality (κ and λ) may be required.

Granulocytic Sarcoma

Most cases of granulocytic sarcoma are diagnosed in patients with established leukemia. In rare cases however the initial presentation is with osseous lesions composed of blasts.

Radiological findings: The lesions are usually permeative and metaphyseal-diaphyseal which may mimic Ewing tumor or osteomyelitis. The microscopic appearance of these tumors consists of a proliferation of blasts. Auer rods and/or Azurophilic granules may be present in some myeoblasts. Immunophenotypic studies by flow cytometry or immunohistochemistry for myeloid and lymphoid markers and cytochemical stains (non-specific esterase) are useful in the diagnosis. The differential diagnosis includes small round cell tumors: Ewing's sarcoma, metastatic neuroblastoma, small cell osteosarcoma, mesenchymal chondro-sarcoma, rhabdomyosarcoma and occasionally osteomyelitis.

Non Hodgkin Lymphoma

Bone lymphoma is more common as a *secondary* involvement of bone in a patient with nodal or extra-nodal lymphoma, rather than a primary form of involvement. Most cases of primary bone lymphomas are of the diffuse large cell variety. In the United States, the majority of these are B-cell lymphomas. In Japan, about 10% may be of T-cell. Primary bone lymphomas tend to occur more frequently in the appendicular skeleton (reverse of secondary lymphomas which are more common in the axial skeleton).

Radiological findings: Lymphoma lesions can be lytic, blastic. Secondary involvement is generally extensive. The microscopic appearance can be either a diffuse (majority) or nodular (rare) lymphoid proliferation. There is often considerable variability of tumor cells, a feature that helps distinguishing lymphoma from Ewing's sarcoma. Rare cases can show spindling or even a signet ring form. Immunophenotypic studies by flow cytometry or immunohistochemical stains are useful in the diagnosis. A panel to both establish the diagnosis, and classify it often includes CD45 (leukocyte common antigen or LCA), B and T cell markers, and other markers to differentiate lymphoma from its mimics such as Ewing's tumor.

Hodgkin Lymphoma

Similar to other hematopoietic malignancies, secondary involvement in patients with stage IIIB or IV Hodgkin's disease is not uncommon. Presentation as bone involvement as the initial or only site is distinctly uncommon or rare. There is a slight predilection to axial skeletal involvement.

Radiological findings: Hodgkin lymphoma can show lytic, blastic or mixed lesions. Microscopically, nodular sclerosing or mixed cellularity type subtypes are the most frequently seen in bone, a pattern similar to that seen in lymph nodes. Immunohistochemical studies for CD15, CD30, CD45 (LCA) and PAX-5 are the most helpful.

Langerhans Cell Histiocytosis

LCH is a proliferation of cells showing differentiation towards activated Langerhans cells and are related to histiocytes. Terms such as histiocytosis X, Eosinophilic granuloma, Letterer–Siewe, Hand–Schuller–Christian disease, etc. have in the past been used for some of these proliferations depending upon the clinical presentation and extent of involvement.

Langerhans cells bear ultrastructural resemblance to Langerhan's cells of the skin, and have the characteristic "Birbeck" granules. Immunohistochemically, they

express S-100 protein and CD1a. LCH is generally considered to be a neoplasm because it is clonal, although in prior years it had been considered to be a reactive condition.

The disease can affect several organ systems in addition to bone, and a staging system for the entity has been developed by the histiocytosis society. The disease is more common in the first three decades of life, although no age is completely exempt. Pain and swelling are the most frequent presentations for patients with disease limited to osseous involvement. In systemic disease a variety of symptoms can occur depending upon the organ involved including diabetes insipidus, exophthalmos and skin lesions. Solitary skeletal involvement outnumbers visceral involvement by a factor of at least 2 to 1, and is the most frequent site. Almost any bone and any location within the bone can be involved.

Radiologically, the lesions are lytic, geographic and may occasionally show bony expansion.

The gross appearance is non specific. Microscopically, the lesions comprise of a proliferation of histiocytoid cells, with variable amounts of cytoplasm. The cell borders may be well defined or syncytium-like. The nuclei have characteristic "grooves" and may be reniform or coffee-bean like. Multinucleated giant cells may be present. A variable number of mitotic figures may be seen. There is frequently an accompanying inflammatory response, often rich in eosinophils. Lipid laden histiocytes are sometimes seen. The Langerhan histiocytes stain with S-100 protein and CD1a. The show variable staining with CD68.

Erdheim Chester Disease

This is a condition of unknown cause, but may be related to Langerhans cell histiocytosis. Most patients are male, and present either asymptomatically or with weight loss and bone pain.

Radiologically, the characteristic finding is of a bilateral, symmetric sclerosis of the meta-diaphyseal regions of the long bones. In some patients, the disease progresses to systemic involvement of deep organs such as the lung or pituitary.

Surgical pathology: Microscopic exam of the involved tissue shows an infiltration by foamy macrophages and lymphocytes. True Langerhan's cells are not seen, but the involvement of bone and pituitary suggests the relationship.

Other Hematopoietic Disorders

Several other hematologic entities can involve the skeleton usually, secondarily. Entities such as systemic mastocytosis or sinus histiocytosis with massive lymphadenopathy can occasionally show involvement of the bone as the first presentation. The features of most of these in bone are similar to the visceral, soft-tissue or lymph node counterparts.

Suggested Readings

Dahlin's Bone Tumors: General Aspects and Data on 10,165 Cases. K. Krishnan Unni, Carrie Inwards, Editors, Lippincott-Raven, Sixth Edition, 2009

World Health Organization Classification of Tumors: Pathology and Genetics, Tumors of Soft Tissue and Bone, Christophe Fletcher, K. Krishnan Unni, Fredrik Mertens, Editors, IARC Press, 2002

Chapter 7
Tumors and Tumor-Like Lesions of the Soft-Tissues

Paul J. Zhang

Soft-Tissue Tumors

Most soft-tissue tumors are benign, of which the majority are lipomas. Malignant sarcomas account for about 1% of all malignant tumors. Most sarcomas arise in the deep soft-tissues of the extremities, the incidence increasing with age. With current treatment, about one third of patients die of their disease, largely because of lung metastases. Currently, most authors recognize the categories of benign, locally aggressive, rarely metastasizing and frankly malignant tumors.

Vascular Tumors

Capillary Hemangioma (Pyogenic Granuloma)

Capillary hemangioma commonly occurs in skin of the head and neck region and the periparotid soft-tissues of young patients (juvenile hemangioma) shortly after birth as well as in mucosa of the head and neck region and skin of older age groups associated with ulceration and granulation tissue-like growth (pyogenic granuloma).

The lesion is multilobulated and composed of a proliferation of capillary sized small vessels with small or inconspicuous lumina that are lined by flat endothelial cells (Fig. 7.1). The vessels are often associated with some degree of pericyte proliferation. A striking lobular architecture is typically seen in both lobular capillary hemangioma and pyogenic granuloma (Fig. 7.2). Occasional mitotic figures can be seen but not atypia or pleomorphism.

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DOI 10.1007/978-0-387-89845-2_7,

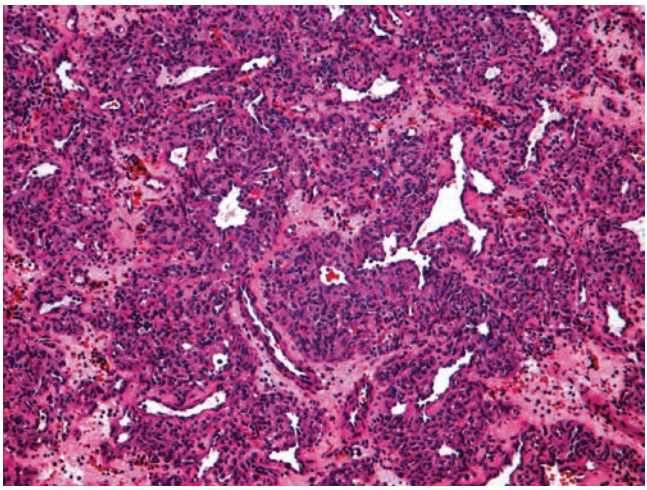

Fig. 7.1 Multilobulated proliferation of plump to flat endothelial cells forming capillary-size caliber vascular spaces in capillary hemangioma

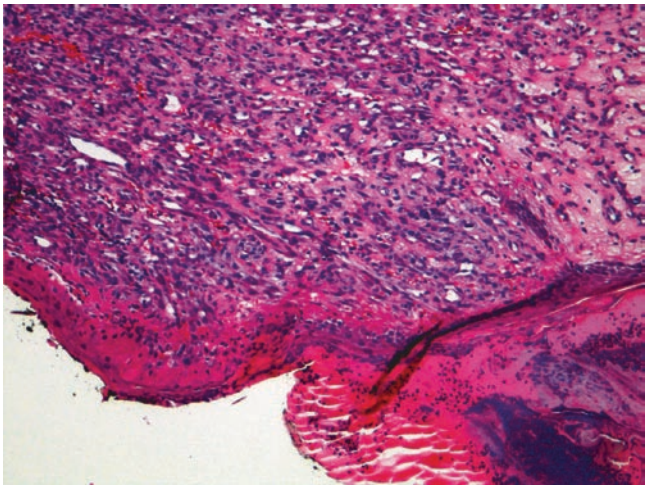

Fig. 7.2 Pyogenic granuloma ulcerating mucosa and morphologically similar to granulation tissue

Cavernous Hemangioma

This is the second most common vascular lesion of childhood after capillary hemangioma. It is usually seen in the deep soft-tissues of the upper body.

The lesion is composed of a cluster of thin-walled, medium to large caliber blood filled spaces lined by flat endothelium (Figs. 7.3 and 7.4).

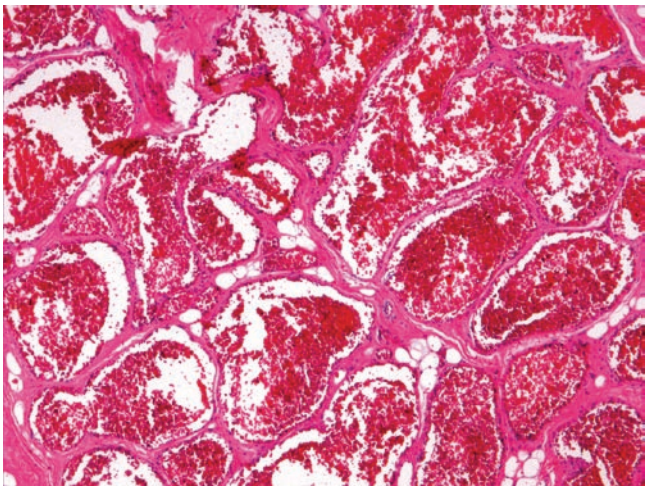

Fig. 7.3 Thin-walled, medium to large caliber vein-like, blood filled vessels in cavernous hemangioma

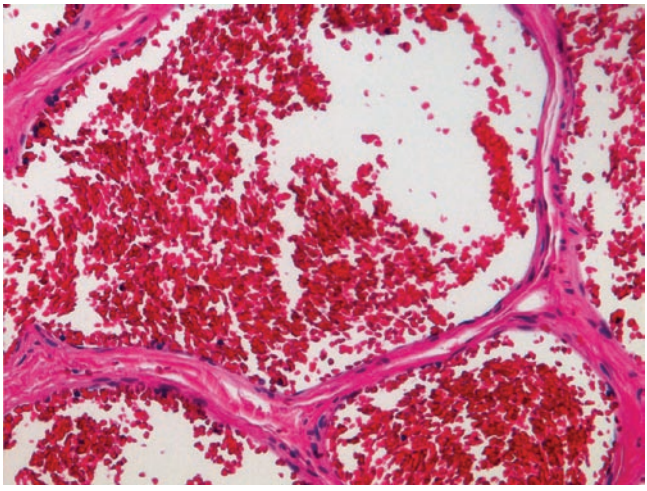

Fig. 7.4 The vascular spaces of cavernous hemagnioma are lined by flat endothelium

Histocytic (Epithelioid) Hemangioma (Angiolymphoid Hyperplasia with Eosinophilia)

This is a well-known skin lesion, but can also occur in the soft-tissues. In this location, it is generally seen as a slowly growing, superficial, painless nodule in the head and neck region or the distal extremities.

The lesion is characterized by well-defined small-sized vessels lined by plump, polygonal endothelial cells with amphophilic or eosinophilic cytoplasm in a background of prominent lymphoid and eosinophilic inflammatory reaction (Figs. 7.5 and 7.6).

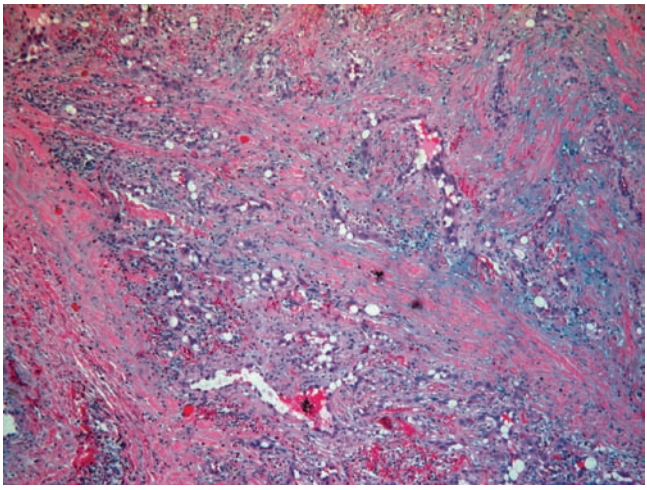

Fig. 7.5 Well-defined small-sized vessels lined by epithelioid endothelial cells in epithelioid hemangioma

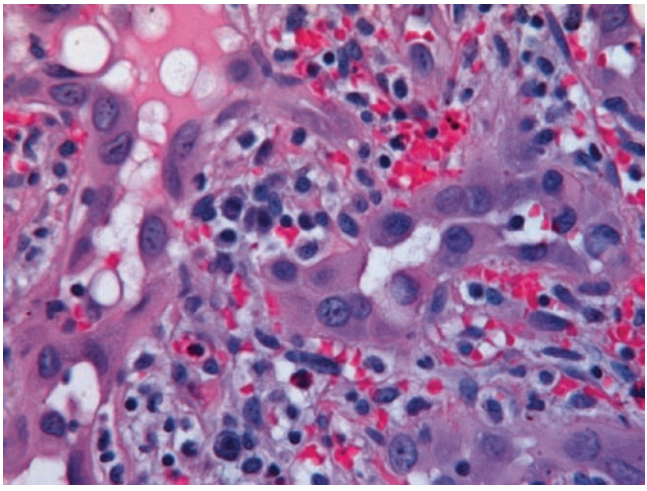

Fig. 7.6 The epithelioid endothelial cells are plump and polygonal with amphophilic or eosinophilic cytoplasm in a background of prominent lymphoid and eosinophilic inflammatory reaction

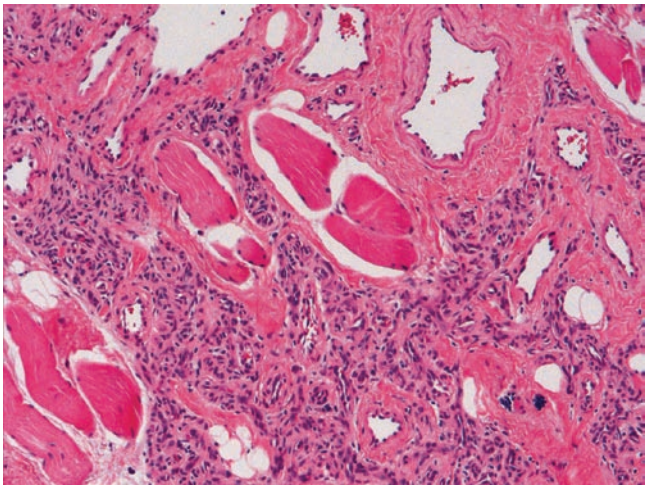

Fig. 7.7 Mixed type vascular proliferation within skeletal musculature and associated with variable amount of mature adipose tissue in intramuscular hemangioma

Intramuscular Hemangioma (Intramuscular Angiolipoma)

This lesion is usually seen in young adults. It is commonly located in the thigh followed by head and neck, upper extremities and trunk. It typically presents as a long-standing, painful, deep-seated mass which radiographically appears to be hypervascular.

The lesional tissue can be a capillary, cavernous or a mixed type of hemangioma present within skeletal muscle. The margins are somewhat poorly defined. It is often associated with some amount of mature adipose tissue (Fig. 7.7).

Venous Hemangioma

Venous hemangiomas are related to vascular malformations. They are deep seated soft-tissue masses with superficial varicosities only visible by venography.

There is a collection of large irregular and disorganized veins with partially muscular walls loosely "infiltrating" the soft-tissue, usually adipose tissue (Figs. 7.8 and 7.9). Intraluminal thrombosis is common.

Angiomatosis

Angiomatosis is a benign vascular proliferation that involves a large area of the body such as limbs and visceral organs. It is more common in infants and children. The affected areas might become enlarged or hypertrophic, frequently with discoloration.

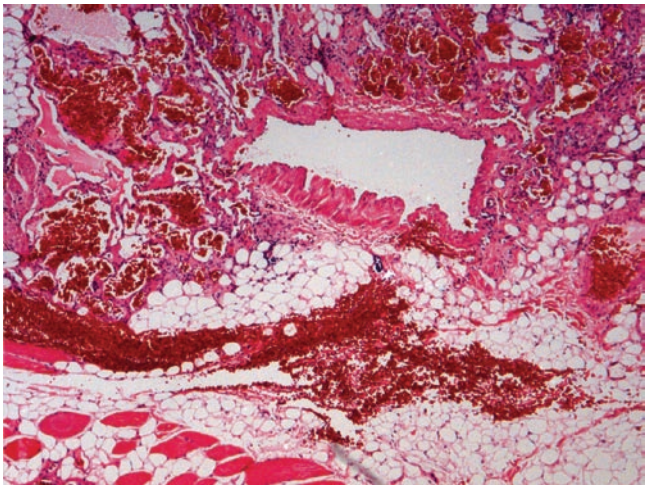

Fig. 7.8 Collection of large irregular and disorganized veins with partially muscular walls loosely "infiltrating" the soft-tissue in venous hemangioma

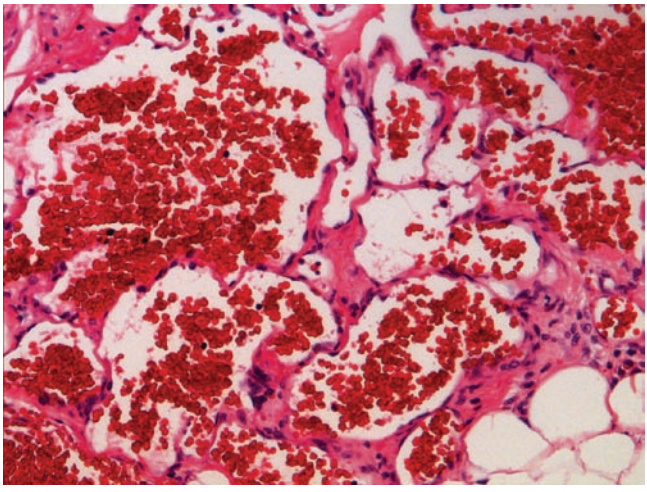

Fig. 7.9 Flat and bland endothelial cells in venous hemagnioma

The lesion is composed of a diffuse proliferation of small to medium sized, irregular thin-walled vessels in dermis, subcutis, skeletal muscle and/or visceral organs.

The endothelial cells are bland with little mitotic activity and nuclear atypia (Fig. 7.10). Some mature fat and/or lymphoid tissue is generally associated.

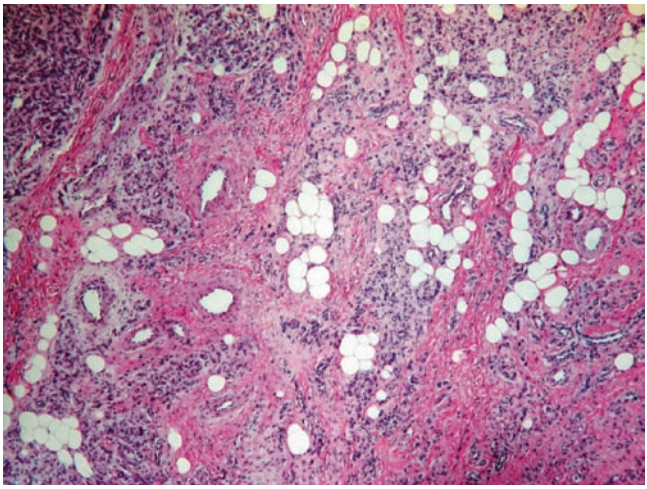

Fig. 7.10 Diffuse proliferation of small to medium sized, irregular thin-walled vessels in angiomatosis

Arteriovenous Hemangioma (AV Malformation)

This condition may be seen in the deep soft-tissues of the head and neck, the lower extremities of younger patients and submucosa and subcutis of adult patients. It is usually associated with arteriovenous shunting. Radiographic correlation to identify the arterial and venous components is necessary to confirm the diagnosis.

Medium to large caliber arteries and abnormal and twisted veins with a thickened intima and media are seen (Figs. 7.11 and 7.12). Capillary and cavernous hemangioma-like areas can also be seen.

Papillary Endothelial Hyperplasia (Intravascular Vegetant Hemangioendothelioma of Masson)

This is a mass-forming organizing thrombus within or around a vessel commonly in superficial veins of the head and neck, fingers and trunk.

The lesion is characteristically a well-defined intravascular proliferation of endothelial cells forming interanastomosing channels and papillae (Fig. 7.13). The endothelial cells may have enlarged and hyperchromatic nuclei and occasional mitotic figures. The stroma or the papillary cores can be fibrinous or hyalinized.

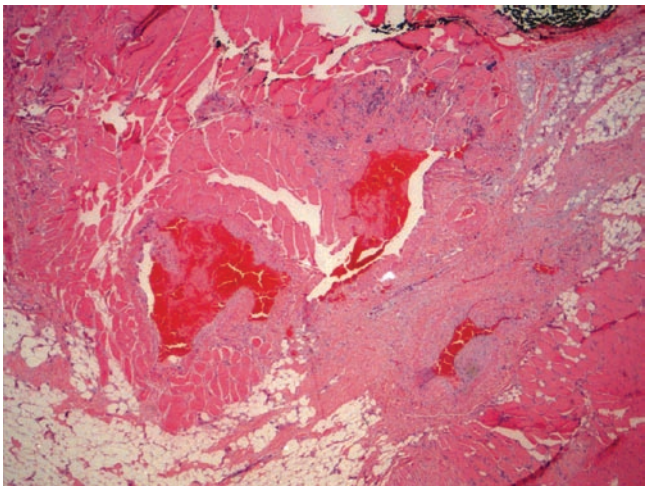

Fig. 7.11 Twisted and tangled medium to large caliber arteries and abnormal veins in AVM

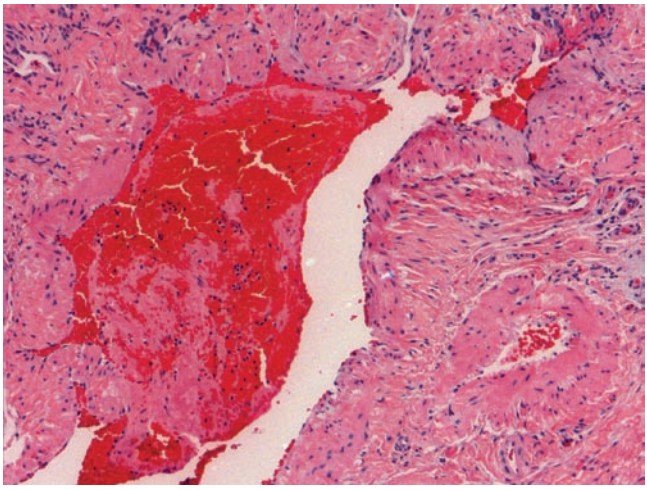

Fig. 7.12 An abnormal vein with thicken intima and media in AVM

Spindle Cell Hemangioma (Spindle Cell Hemangioendothelioma)

A benign vascular tumor (once considered to be of borderline malignancy), this lesion typically occurs in the dermis and subcutis of the distal extremities of young adults. Some cases are associated with multiple enchondromas, possibly a variant of Muffucci syndrome.

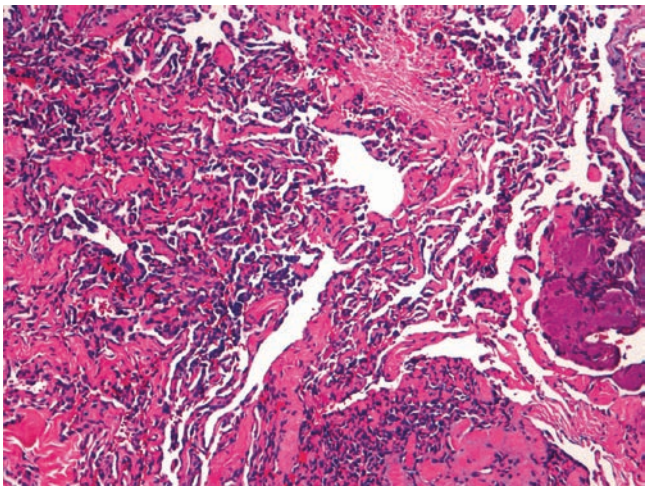

Fig. 7.13 Proliferation of bland endothelial cells forming interanastomosing channels and papilla in papillary endothelial hyperplasia

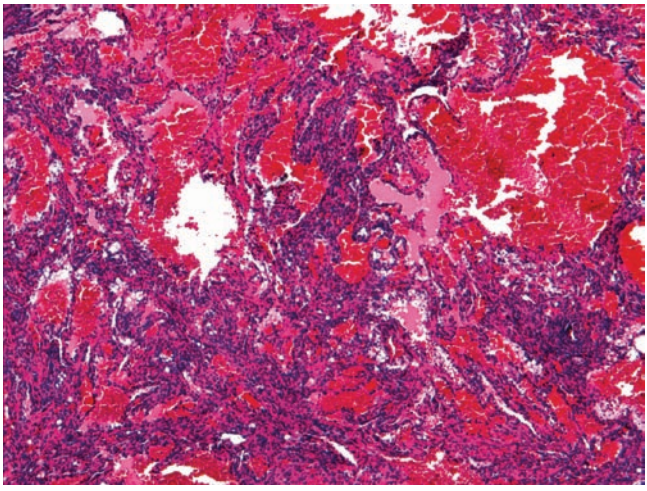

Fig. 7.14 Spindle cell proliferation in between cavernous-like or irregular gaping vascular channels lined by epithelioid endothelial cells in spindle cell hemangioma

The lesion is a multinodular growth of bland spindle cells are seen between cavernous-like or irregular gaping vascular channels lined by epithelioid endothelial cells (Figs. 7.14 and 7.15).

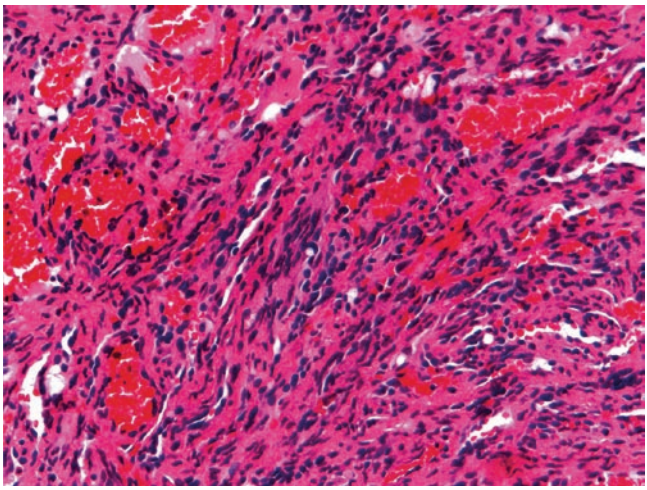

Fig. 7.15 Both the endothelial cells and spindle cells are very bland in spindle cell hemagnioma

Lymphangioma

This is composed of lymphatic vessels and occurs frequently in axilla, groin, oral cavity and other sites. It has typical cystic presentation in the neck of patients with Turner syndrome. In many cases, the lesion presents at or shortly after, birth. It is a slow-growing painless swelling or cystic mass containing watery and milky fluid.

Variable-sized, thin-walled vessels lined by flat endothelial cells are feature of lymphangioma. The open vascular spaces are empty or filled with proteinaceous fluid and some lymphocytes (Fig. 7.16). Podoplanin/D2-40 highlights the lymphatic endothelium.

Kaposiform Hemangioendothelioma

This vascular tumor occurs mainly in children, but several cases have been reported in adults. The location is usually the retroperitonium or skin followed by the head and neck region, mediastinum and deep soft-tissue of trunk and extremities. Despite the similar name, no association with HIV infection or HHV8 has been identified.

The lesion is composed of poorly defined and infiltrative growth of vaguely lobular vascular structures composed of interspersed capillary-sized vessels and bland spindle cells in between the vessels. The vessels are usually lined by plump endothelial cells (Fig. 7.17). Similar to true Kaposi sarcoma, fragmented red blood cells and fibrin thrombi in the vascular spaces and the slit-like spaces are seen.

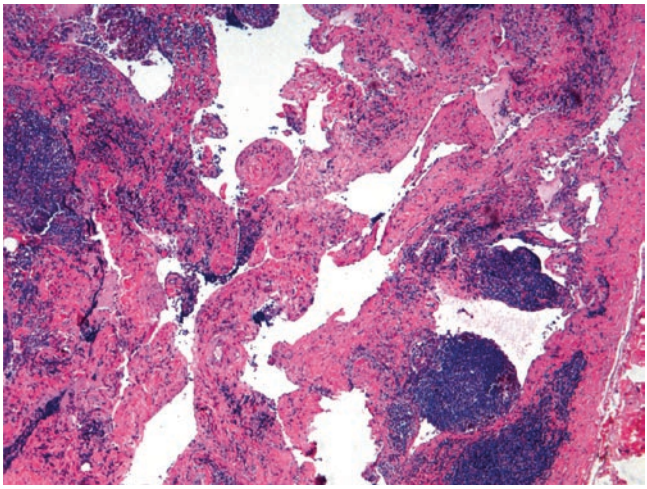

Fig. 7.16 Variable-sized, thin-walled vessels lined by flat endothelial cells in lymphangioma with lymphocytes in vascular spaces and lymphoid aggregates in the interstitium

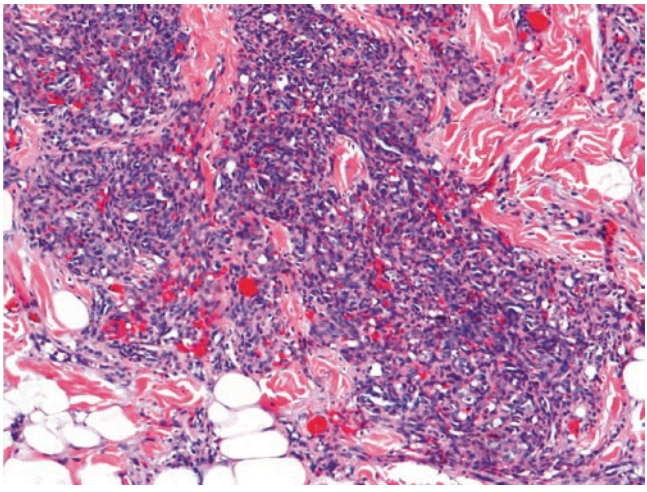

Fig. 7.17 Poorly defined and infiltrative growth of vaguely or irregularly lobular vascular structures composed of interspersed capillary-sized vessels in KS form hemangioendothelioma

Epithelioid Hemangioendothelioma (Intravascular Bronchioloalveolar Tumor)

This is low grade or borderline vascular tumor and is the most common type of hemangioendothelioma which can affect all age groups and both sexes. It often presents as painful solitary nodule in superficial or deep soft-tissue of the extremities.

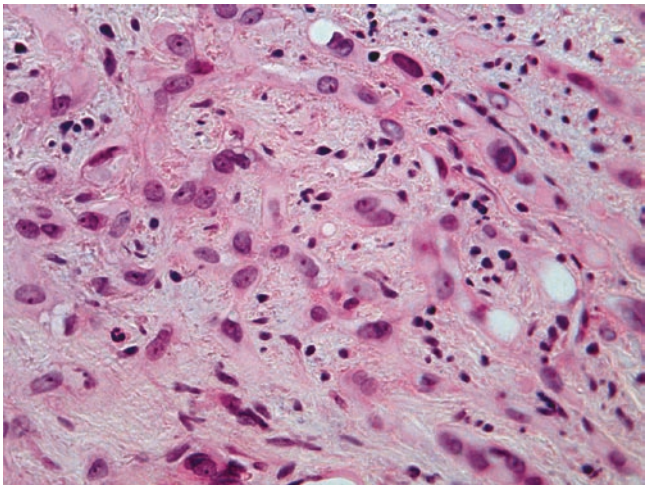

Fig. 7.18 Poorly-defined growth of short cording and nesting of epithelioid or short spindle endothelioid cells with glassy cytoplasm in myxohyaline stroma in EHE

It may also present as multiple lesions in viseral organs such as lung, liver and bone. Pulmonary lesions are called intravascular bronchioloalveolar tumor and generally affect young females. Soft-tissue lesions are thought to derive from a vessel, usually a vein.

The tumor is characterized by poorly defined, intravascular growth of short cords and nests of epithelioid or short spindle endothelial cells in myxohyaline stroma with perivascular extension (Fig. 7.18). The epithelioid endothelial cells have eosinophillic granular to glassy cytoplasm with frequent intracytoplasmic lumina containing red blood cells.

Hobnail Hemangioendothelioma (Dabska Tumor, Papillary Intralymphatic Angioendothelioma)

This is a very rare low-grade vascular tumor usually seen in pediatric patients. About 25% of cases occur in adults. Limbs are most the frequently involved site, followed by the trunk. Clinically, it presents as a slow-growing, painless, ill-defined, cutaneous plaque or nodule.

The lesion consists of poorly defined and diffuse proliferation of cavernous, thin-walled vascular channels. The channels have prominent intraluminal papillary tufts that are formed by hyaline cores and are lined by hobnail endothelial cells (Fig. 7.19).

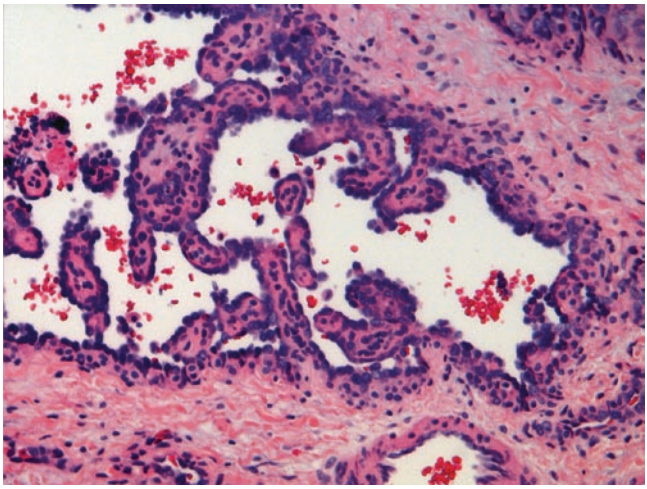

Fig. 7.19 Prominent intraluminal papillary tufts lined by hobnail endothelial cells in hobnail hemangioendothelioma

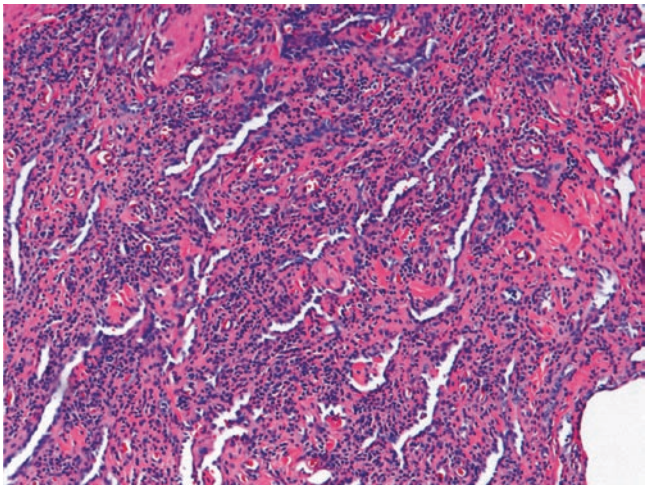

Fig. 7.20 Poorly-defined growth of elongated and arborizing vascular channels resembling to the rete testis in retiform hemangioendothelioma

Retiform Hemangioendothelioma

This is a variant of hobnail hemangioendothelioma which occurs typically in the skin and subcutis of the distal extremities of young adults as a slow-growing plaque or nodule.

It is a poorly-defined growth of elongated and arborizing vascular channels lined by plump or hobnail endothelial cells resembling the rete testis (Fig. 7.20).

The hobnail cells have scant cytoplasm and hyperchromatic nuclei but no pleomorphism and very rare mitotic figures.

Kaposi Sarcoma

Kaposi sarcoma can occur in four different clinical settings: (1) classic indolent form in elderly men of Mediterranean or eastern European decent; (2) endemic African form in middle-aged and children of Equatorial Africa; (3) iatrogenic form in solid organ transplant patients or any patients received immunosuppressive agents for various diseases; (4) in the setting of acquired immunodeficiency syndrome (AIDS associated form in HIV-1 infected individuals).

All forms are associated with a herpesvirus (HHV-8) infection. The skin is the most common site of involvement but mucosa, lymph node and visceral organs may also be affected either along with skin lesions or by themselves.

The same histologic features are seen in all four forms. In the early stage (patch stage), there is a subtle increase in slightly irregular vascular channels lined by flat and mildly atypical endothelial cells. Later, variable numbers of poorly-formed vascular channels characterized as slit-like spaces, lined by attenuated or spindle endothelial cells are seen in a dissecting pattern of growth, usually accompanied by extravasated red blood cells.

In later (plaque) stage, slightly raised lesion in skin or mucosa with more exaggerated histologic features of patch stage is seen with more siderophages and hyaline globules. The globules are thought to be destroyed red blood cells. In the nodular stage, there are even more dominant slit-like spaces and spindle cell proliferation in intersecting fascicles; nuclear pleomorphism and frequent mitotic figures (Fig. 7.21).

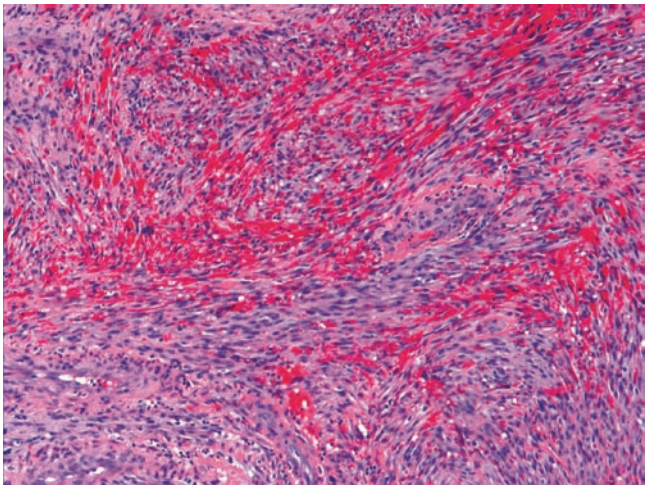

Fig. 7.21 Slit-like spaces and spindle cell proliferation in intersecting fascicles with nuclear atypia and frequent mitotic figures in KS

Lymphatic endothelial marker D2-40 and HHV-8 are positive in both spindle cells and endothelial cells.

Angiosarcoma

Angiosarcoma is the malignant form of vascular tumors. It may occur de novo, but may also be seen in the setting of patients with chronic lymphedema (post-mastectomy), radiation exposure, synthetic vascular grafts, and exposure to carcinogenic agents such as Thorotrast, arsenic compounds or vinyl chloride. The skin of the head and neck in elderly patients is the most common site for patients without any predisposing factors. Less than a quarter of cases arise in deep soft-tissue of extremities, trunk and head and neck in adult patients. It typically occurs as a poorly-defined, usually multicentric, rapidly growing mass.

The tumor is composed of irregularly shaped, interanatomosing, sinusioidal-like vascular channels lined by atypical endothelial cells in a dissecting growth pattern (Fig. 7.22). There are frequent intraluminal tufts and papillary proliferations. When poorly differentiated, the neoplastic endothelial cells become more epithelioid or more spindle appearance with little vascular channel formation (Fig. 7.23). Occasionally the only morphological evidence of vascular origin may be intracytoplasic lumina containing red blood cells. Nuclear pleomorphism and mitotic figures are minimal in well differentiated tumor and more apparent in less differentiated ones.

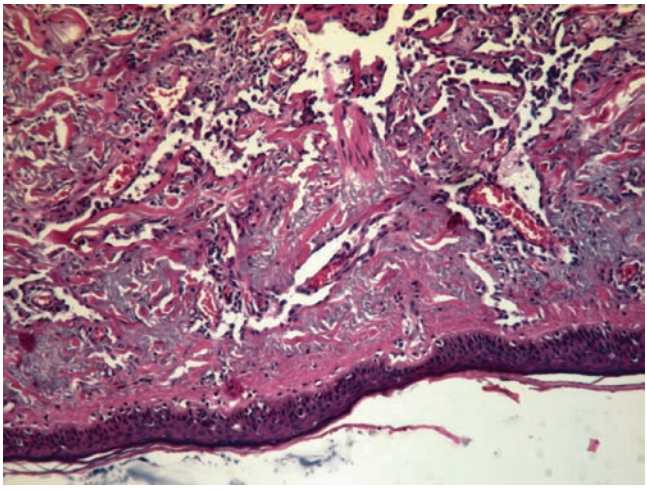

Fig. 7.22 Irregularly shaped interanatomosing, sinusioidal-like vascular channels lined by atypical endothelial cells in a dissecting growth pattern in angiosarcoma

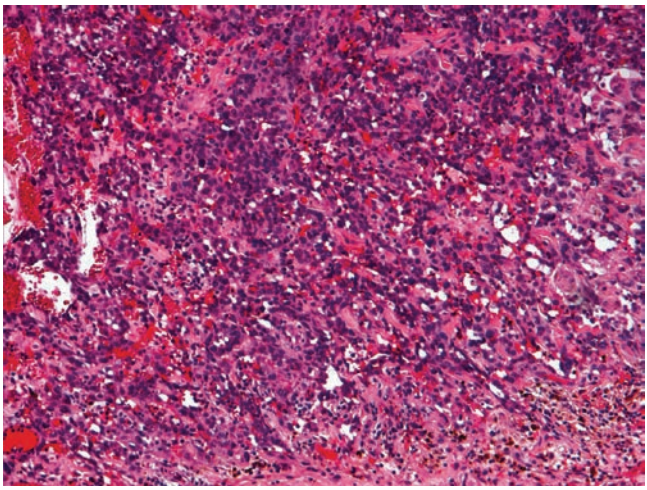

Fig. 7.23 When poorly differentiated, the neoplastic endothelial cells become more epithelioid appearance with little vascular channel formation in angiosarcoma

Tumors of Adipose Tissue

Lipoma

Lipoma is the most common of all the soft-tissue tumors. It most frequently affects adult patients in their fifth and sixth decades of life and is rare in the pediatric age group. It can occur superficially in subcutis or deeply in soft-tissue. Superficial lipoma is usually solitary and more common in shoulder, back, neck and abdomen. It generally presents as a slowly-growing, painless mass. Multiple lipomas are present in about 5% of the cases. Deep lipomas occur within or between skeletal muscle (intramuscular or intermuscular lipoma), on the surfaces of bone (parosteal lipoma), in tendon sheath (lipoma of tendon sheath) or around nerve (perineural lipoma) and are often seen in younger patients. They are less circumscribed and larger as compared to superficial lipomas and may be painful in some cases due to nerve compression.

Lipomas are composed of mature adipose tissue with little or no difference from normal mature fat. Sometimes there is a slight irregularity in the size and shape of adipocytes, or a subtle loss of normal lobulation and architecture. Generally there is presence of a thin capsule in intact specimens (Fig. 7.24). Variable myxoid, chondroid and fibrous tissue are present in some cases (myxoid lipoma, chondroid lipoma and lipofibroma) (Fig. 7.25). When present in a deep location, entrapment of the surrounding normal tissue can be seen and leads to an impression of infiltrative growth pattern as seen intramuscular lipoma.

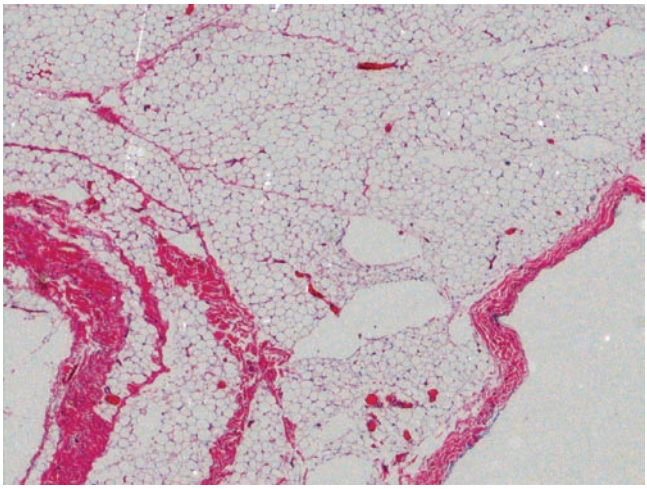

Fig. 7.24 Expansile growth of mature adipose tissue with presence of thin capsule in lipoma

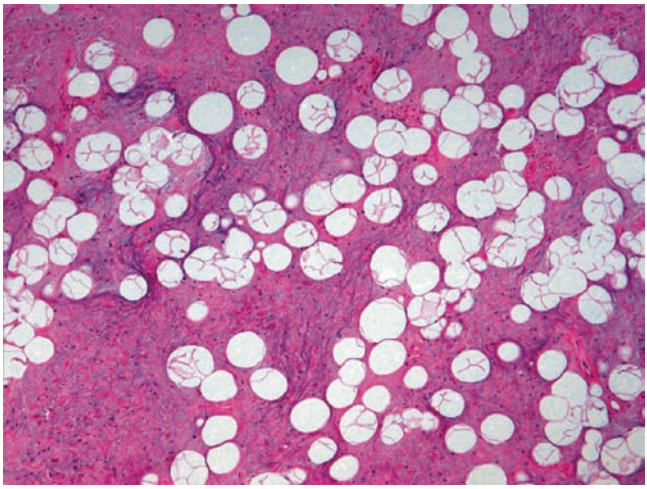

Fig. 7.25 Increased myxoid matrix in myxoid lipoma

Lipomatosis

Idiopathic diffuse lipomatosis occurs in early childhood involving large areas of the trunk and extremities. Idiopathic pelvic lipomatosis occurs more in young to middle-aged black male patients. Cervical symmetric lipomatosis occurs in middle-aged men

with history of liver disease or extensive alcohol consumption. Steroid lipomatosis occurs in the face and mid-upper back of patients who are receiving steroid therapy or have increased endogenous production of adrenocortical steroids. HIV lipodystrophy occurs in visceral organs, breast and cervical fat pads of AIDS patients treated with protease inhibitors or patients receiving other forms of antiretroviral therapy.

Massive and diffuse accumulation of the fat in the affected areas can sometimes be symptomatic due to compression of the vital structures or organs in the regions.

This lesion shows completely normal appearing mature adipose tissue replacing and entrapping the surrounding normal tissues, structures or organs.

Angiolipoma

Angiolipoma typically presents as a painful subcutaneous nodule in the extremities and trunks of young adults. Multiple lesions are seen in two thirds of cases. A small numbers of patients (5%) have a familial history of angiolipoma(s). The lesions are usually circumscribed and less than 2 cm in size.

The lesion is composed of lipomatous and vascular components. The vascular component is that of branching capillary-sized vessels frequently containing fibrin thrombi, a feature that is more prominent in the periphery of the lesion (Fig. 7.26). The proportion of the adipose tissue and vascular tissue varies from case to case and histologic appearance ranges from a lipoma with few vessels at one end to almost a capillary hemangioma at the other end.

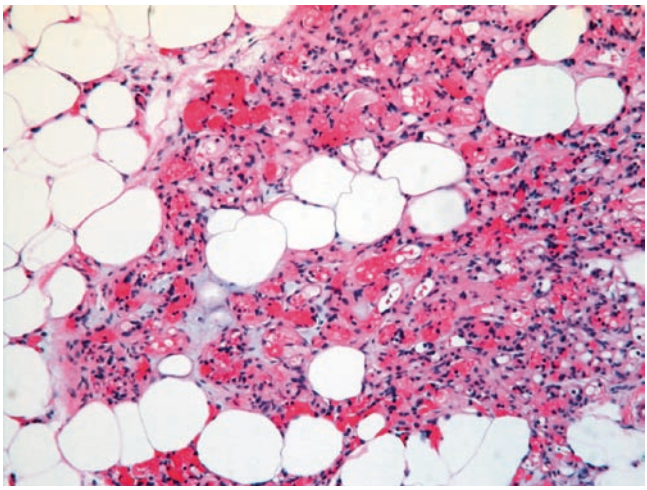

Fig. 7.26 Proliferation of branching capillary-sized vessels in angiolipoma

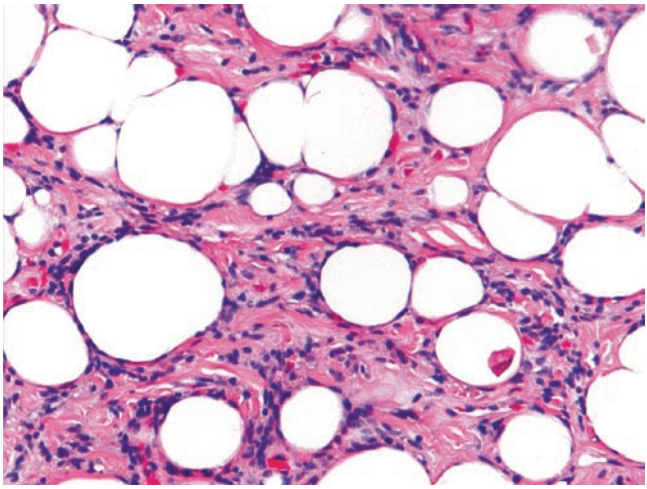

Fig. 7.27 Bland and uniform short spindle cells in spindle cell lipoma

Spindle Cell Lipoma/Pleomorphic Lipoma

These two entities are two ends of a histologic spectrum of a distinct fatty tumor. Typically, these lesions present as a painless, slow-growing, well-defined subcutaneous nodule in the posterior neck or shoulder of men over the fourth decades of life. Rare cases of multiple lesions and familial history have been reported.

The tumor is usually well circumscribed with a variable amount of mature adipose tissue. Within the lesion, there is a proliferation of bland, uniform short spindle cells that are associated with thick rope-like collagen fibers along with some degree of myxoid change in the classic spindle cell lipoma (Fig. 7.27). Hyperchromatic floret-like multinucleated giant cells are present in addition to the short spindle cells in pleomorphic lipoma (Fig. 7.28). Several cases have mixed histologic features of these two histologic spectrums. Both variants are positive for CD34 and negative for muscle and nerve sheath markers.

Hibernoma

Hibernoma is commonly seen in thigh, scapular region, chest wall, and inguinal and axillary regions of young patients. It is a slow-growing, painless mass in subcutis and occasionally in intramuscular region.

Lobules of polygonal brown fat cells are seen with abundant multivacuolated eosinophilic cytoplasm with a small central nucleus (Fig. 7.29). The amount of brown fat cells varies significantly and mixes with mature adipocytes.

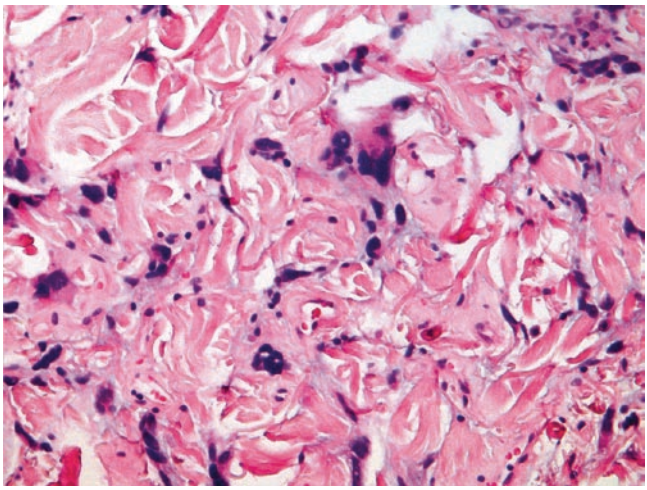

Fig. 7.28 Hyperchromatic floret-like multinucleated giant cells in addition to the short spindle cells in pleomorphic lipoma

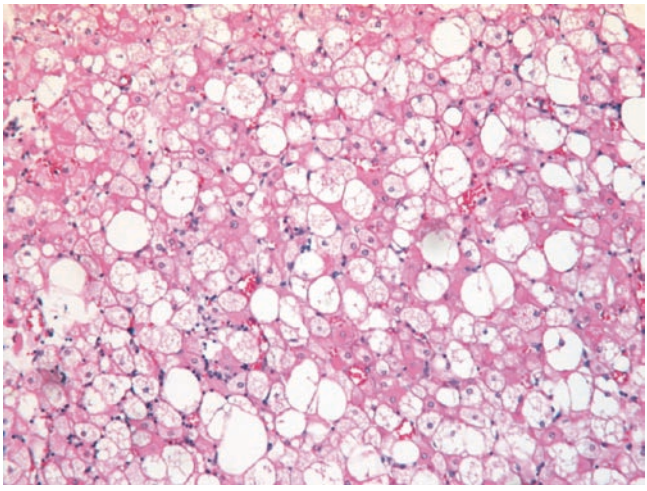

Fig. 7.29 Brown fat cells with abundant multivacuolated eosinophilic cytoplasm and a small central nucleus in hibernoma

Liposarcoma

The liposarcoma is the most common type of soft-tissue sarcomas in adults. The tumor occurs primarily in the fifth through seventh decades of life. There are four types of liposarcomas as defined by their clinico-pathological features. These are

the *well differentiated liposarcomas/atypical lipomatous tumor, myxoid liposarcomas/round cell liposarcomas, pleomorphic liposarcomas and de-differentiated liposarcoma*.

Well-Differentiated Liposarcomas/Atypical Lipomatous Tumor

Well-differentiated liposarcoma and atypical lipomatous tumor have the same histologic and karyotypical characteristics. The tumor is preferentially called atypical lipomatous tumor when superficially located in subcutis, and well-differentiated liposarcoma when located in a deep location, particularly the retroperitoneum. These well-differentiated liposarcomas occur most frequently in the extremities followed by the retroperitoneum, the paratesticular areas and the mediastinum.

There are four histologic subtypes of well-differentiated liposarcoma: lipoma-like, sclerosing type, inflammatory type and spindle cell type.

Lipoma-like liposarcoma bears similarities to benign lipoma, but contains several atypical adipocytes with enlarged, irregular and hyperchromatic nuclei (Fig. 7.30).

Sclerosing liposarcomas is characterized by pleomorphic hyperchromatic stromal cells usually in multinucleated forms, more frequently seen in the fibrous septa or in a hyaline fibrous stroma. The sclerosing fibrous element sometimes dominates the tumor with little fat (Fig. 7.31). Spindle cell type of liposarcomas is the least common, characterized by the presence of bland spindle cells in myxoid fibrous

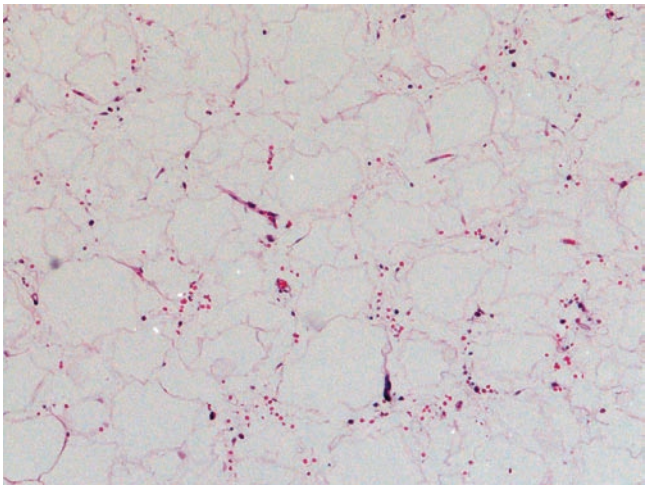

Fig. 7.30 Lipoma-like liposarcoma with only rare atypical adipocytes

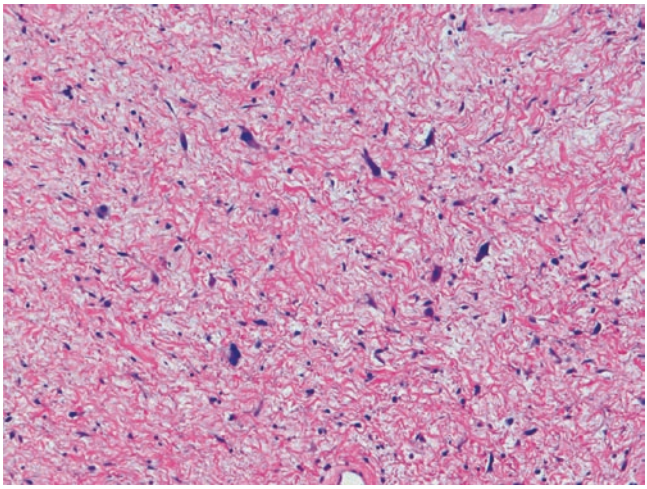

Fig. 7.31 Pleomorphic cells, some in multinucleated forms, in a fibrous stroma in sclerosing liposarcoma

background associated with lipoma-like liposarcoma. Inflammatory type liposarcoma has chronic inflammatory infiltrates composed of lymphoplasmacytic cells.

Tumors with mixed features of the above histologic variants are not infrequent.

Myxoid/Round Cell Liposarcoma

These are the two ends of a histologic spectrum of the same disease identified by presence of t(12;16)(q13;p11) and *FUS–CHOP* fusion gene formation. They are frequently located in the deep soft-tissues of the extremities. They may also occur very rarely in retroperitoneum or in the superficial location. They affect patients of fourth to fifth decades of life, a decade younger than the other types of liposarcoma. Clinically, they present as a painless swelling in the deep soft-tissues of the involved limb.

These tumors have a wide range of monotonous round cells at different stage of differentiation ranging from primitive round cells to vacuolated lipoblasts.

In myxoid liposarcomas, the tumor cells are present in a myxoid stroma with a rich delicate arborising, short branching capillary vessels ("chicken wire vessels" (Fig. 7.32)).

When poorly differentiated (round cell type), the primitive round cells are closely-packed. The cells have a high nucleus to cytoplasmic ratio. Mitotic figures and necrosis are frequently seen. Additionally, there is little or a complete lack of

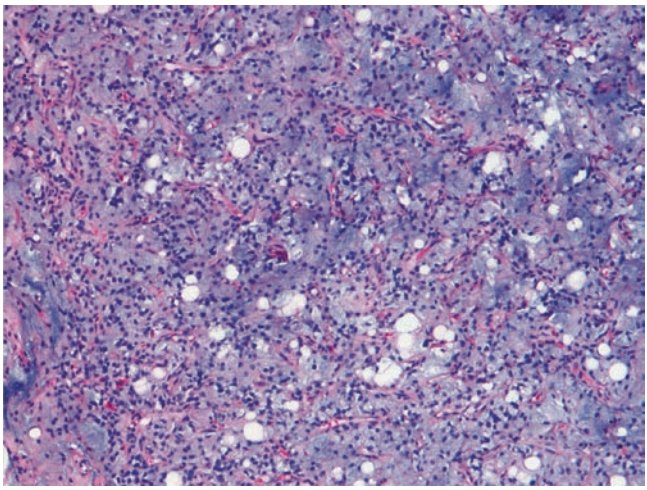

Fig. 7.32 Scattered round tumor cells in a myxoid stroma with a rich delicate arborizing, short branching capillary vessels in a "chicken-wire" pattern referred as "chicken wire" in myxoid liposarcoma

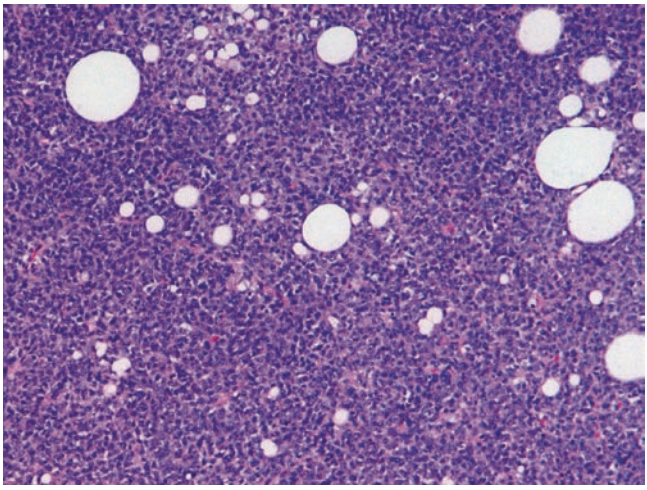

Fig. 7.33 Closely-packed primitive round cells with higher nucleus to cytoplasm ratio, prominent mitotic activity and foci of necrosis; along with little or complete lack of myxoid stroma in round cell liposarcoma

myxoid stroma (Fig. 7.33). More often, both myxoid and round cell features are present in the same case. Cytogenetic and molecular evaluation of t(12;16)(q13;p11) and *FUS–CHOP* fusion is helpful in diagnosis.

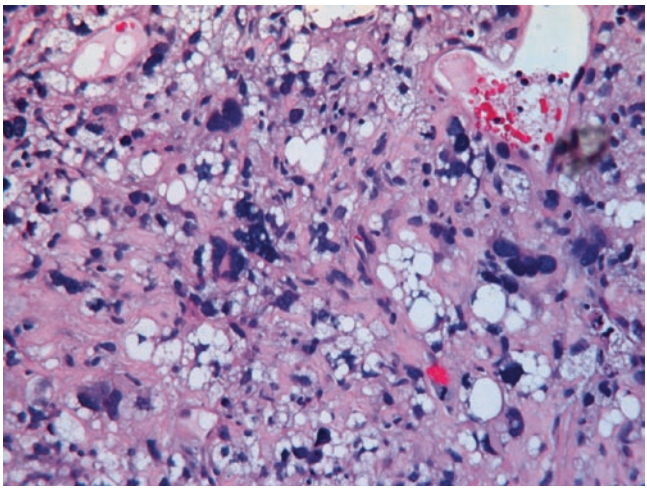

Fig. 7.34 Pleomorphic cells with hyperchromatic nuclei, many recognized as lipoblasts by the presence of cytoplasmic multivacuolation in pleomorphic liposarcoma

Pleomorphic Liposarcoma

This is the rarest form of liposarcoma. It is usually in deep soft-tissue of the extremities and rarely in superficial locations. Many of the patients are over 50 years old. Clinically, patients present with a history of a rapidly growing firm mass.

There are numerous pleomorphic cells with hyperchromatic nuclei, many recognized as lipoblasts by the presence of cytoplasmic multivacuolation (Fig. 7.34).

Other tumor cells are less pleomorphic with spindle to round hyperchromatic nuclei in a fibrous background. Mitotic figures and tumor necrosis are common.

De-differentiated Liposarcoma

The incidence of dedifferentiation is 10% in well-differentiated liposarcoma overall, and is more common in deep seated or retroperitoneal lesions. It typically occurs as any recent episodes of rapid growth of an otherwise long lasting and stable soft-tissue mass.

The diagnosis is made if there are non-lipogenic neoplastic elements juxtaposed with well-differentiated liposarcoma (Fig. 7.35). The non-lipogenic elements can be fibrosarcomatous, chondroblastic, osteogenic, myogenic, angiomatous and neural (Fig. 7.36). The dedifferentiated elements could be histologically high or low grade.

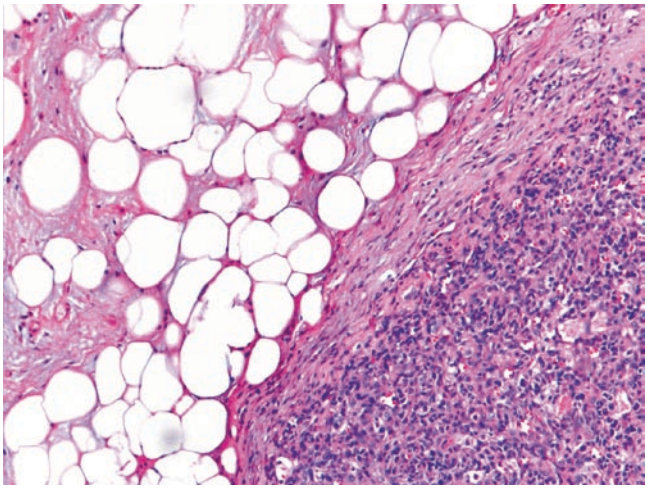

Fig. 7.35 Non-lipogenic neoplastic elements juxtaposition to the well-differentiated liposarcoma

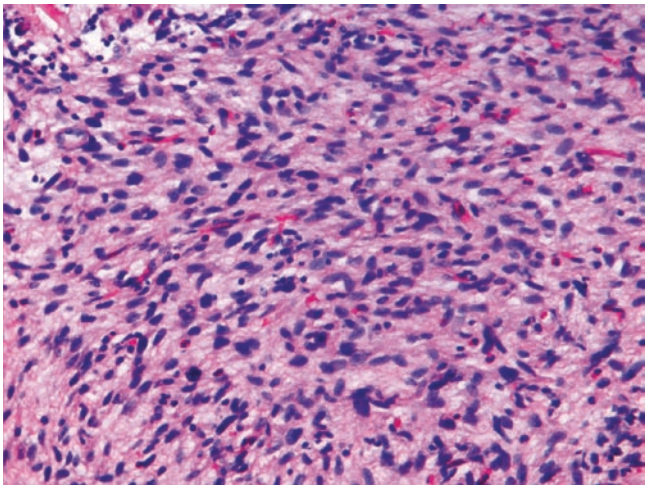

Fig. 7.36 Non-lipogenic fibrosarcomatous element in a dedifferentiated liposarcoma

Fibrous Tumors

Elastofibroma

This is a rare soft-tissue lesion, seen almost exclusively in the deep soft-tissue between the lower scapula and the chest wall. It is usually ill-defined and adherent to the underlying periosteum. It affects elderly individuals, particularly those with long history of manual labor and has a female predilection.

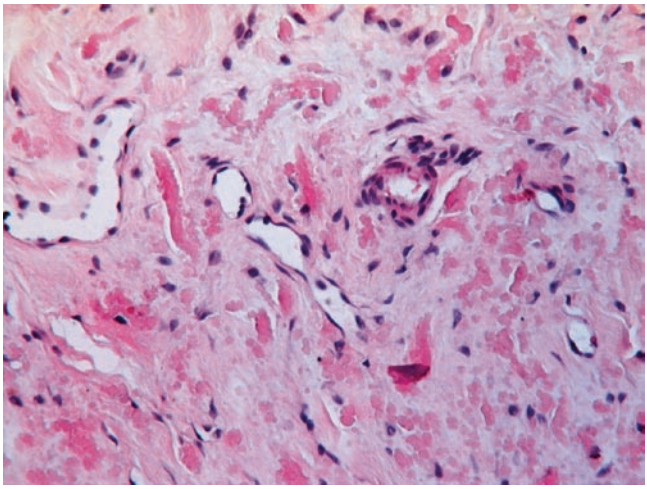

Fig. 7.37 Large, coarse and intensively eosinophilic elastic fibers which can be fragmented into variable lengths and globules in elastofibroma

The lesion is composed of hyalinized collagenous stroma and abundant large, coarse, intensively eosinophilic elastic fibers which can be fragmented into variable lengths and globules (Fig. 7.37). Elastic stain highlights a dense core and irregular serrated margins in these fibers.

Soft-Tissue Myxoma (Intramuscular Myxoma, Juxta-Articular Myxoma, Cutaneous Myxoma)

A benign tumor frequently occurs in intramuscular location adjacent to large joints and in subcutaneous site. It is usually asymptomatic. Some cases of multiple intramuscular myxomas have been associated with fibrous dysplasia and Albright syndrome (the combination of myxoma and fibrous dysplasia is known as the Mazabraud syndrome). Most (about 90%) of myxomas of Mazabraud syndrome and many (about 60%) of non-syndromic (sporadic) myxomas harbor activating mutations of GNAS1 (similar to those seen in lesions of fibrous dysplasia).

Myxomas are characterized by loosely situated, bland spindle or stellate cells with tapering, weakly eosinophilic and fibrillary cytoplasm scattered in abundant myxoid matrix with very scant vasculature (Fig. 7.38). The lesion can have poorly defined periphery with a short distance of infiltration into the adjacent skeletal muscle or other tissues in some cases. Cellularity is increased in cellular myxoma but there are no mitoses, nuclear atypia or necrosis.

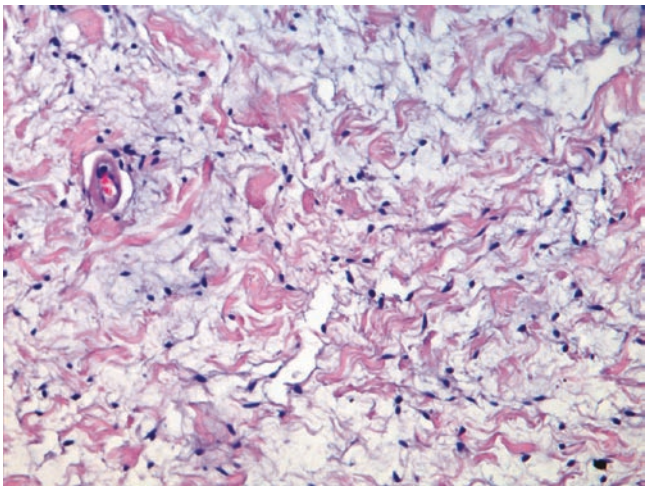

Fig. 7.38 Loosely situated, uniform bland spindle and stellate shaped cells with weakly eosinophilic and fibrillary cytoplasm scattered in abundant myxoid matrix in a soft-tissue myxoma

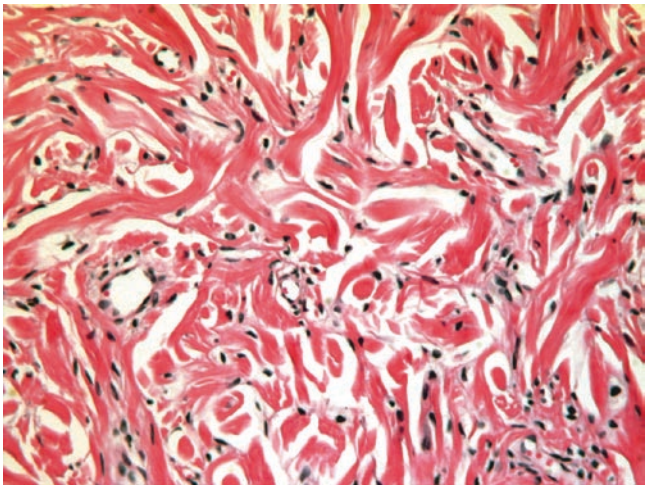

Fig. 7.39 Paucicellular dense collagenous fibers haphazardly arranged in thick strands or bundles and hyaline amorphous sheets in nuchal fibroma

Nuchal Fibroma

This benign soft-tissue tumor has a predilection for the subcutis of interscapular and upper paraspinous regions of adults and is more common in men. It is usually asymptomatic and about 40% of patients have diabetes mellitus.

Microscopically these lesions are paucicellular. There is dense collagenous tissue that grows in haphazardly arranged thick strands or within a hyaline background (Fig. 7.39). It is a poorly defined process with frequent entrapment of the mature adipocytes in subcutis.

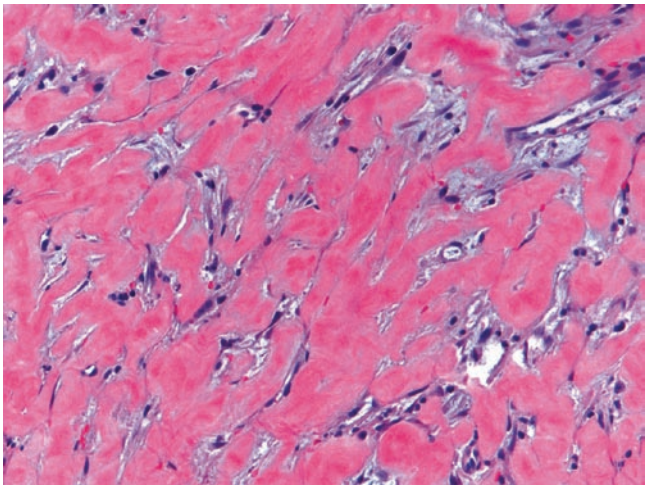

Fig. 7.40 Glassy or amorphous, hyalinized coarse bundles or strands of collagen tissue in haphazard arrangement in keloid

Keloid

This is a cutaneous scar-like fibrous overgrowth with predilection for blacks and is possibly familial in some patients. It typically affects the upper body and head and neck region and occurs at the sites of recent trauma or surgery. It presents as raised nodular/multinodular firm cutaneous lump.

The lesion is characterized by multinodular growth of glassy or amorphous, hyalinized coarse bundles of collagen in haphazard arrangement. A few slender bland fibroblasts are seen scattered between the collagenous strands (Fig. 7.40).

Fibroma of tendon sheath

This lesion typically presents as a small firm painless nodule attached to the tendons of the hands and feet in adults.

It is a well-demarcated, multilobated proliferation of dense collagen fibers and scattered bland spindle fibro/myofibroblasts in variable cellularity. The lesion is usually associated with tendon. Cleft-like spaces are seen between the lobules within the lesion (Fig. 7.41). Giant cells are not seen.

Desmoplastic Fibroblastoma

Desmoplastic fibroblastoma occurs in older individuals in various sites such as arm, shoulder, lower extremities and the back. It presents as a superficial painless

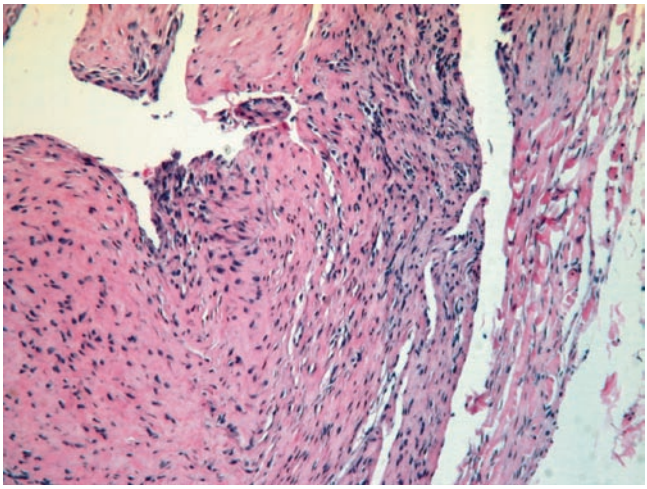

Fig. 7.41 Dense collagenous fibers and scattered bland spindle fibro/myofibroblasts with cleft spaces within fibroma of tendon sheath

nodule which occasionally reaches the fascia and may even extend into the skeletal muscle.

It is composed of abundant delicate collagenous fibers in haphazard pattern with scattered slender or stellate-shaped fibroblasts and myofibroblasts with inconspicuous vascularity.

Calcifying Aponeurotic Fibroma

A benign lesion that usually affects the distal extremities of younger individuals as a poorly-defined painless mass associated with aponeuroses and tendons.

The lesion is characterized by poorly-defined and hypercellular fibrous tissue with central serpiginous zones of calcification and adjacent hyaline and chondroid changes. There are round to plump fibroblasts palisading around the calcified areas or arranged in cords. Hyaline stromal tissue is present between the calcified and cellular areas. Rare osteoclast-like multinucleated giant cells are present in some cases.

Fibromatoses

Superficial fibromatosis is a benign condition and occurs in the fascia or the aponeuroses of the hand (palmar fibromatosis, Dupuytren disease), foot (plantar fibromatosis, Lederhose disease) and knuckle pads. It presents as a painless firm

nodule in the palmar and plantar aspects of the hands or feet respectively. In some cases there is a cord-like thickening leading to flexion contractures. It is bilateral in 50% of the cases, and up to 20% patients with palmar fibromatosis also have a concurrent plantar lesion.

Deep fibromatosis, also called desmoid tumor, is a locally aggressive lesion. It occurs in intraabdominal sites in middle aged female patients (intraabdominal fibromatosis), about 50% of the patients with history of recent pregnancy and prior abdominal surgery. It may also occur in extraabdominal sites in younger age (extraabdominal fibromatosis) with shoulder being the most commonly site followed by chest wall and thigh. Mesenteric fibromatosis occurs in patients with Gardner syndrome (familial polyposis associated with mesenteric fibromatosis). It presents as a slow-growing, poorly defined, firm mass, initially asymptomatic and later present with various symptoms due to involvement of adjacent anatomic structures and organs. The lesion is significantly larger than superficial fibromatoses at the time of surgery.

All fibromatoses (both deep and superficial) are characterized by a proliferation of bland and uniform fibroblasts that are typically spindle or fusiform with cytologically bland nuclei, very small nucleoli, and scant fibrillary eosinophilic cytoplasm. In the background, there is characteristic wavy collagenous stromal matrix (Fig. 7.42). The lesional cells may focally arrange in fascicles or bundles mimicking those seen in normal tendon, ligament or fascia in some cases. Based on the different phases or age of the lesion, the cellularity and the amount of collagenous matrix may vary. Difference between deep and superficial fibromatoses is only quantitatively apparent under low power magnification for the size and the degree

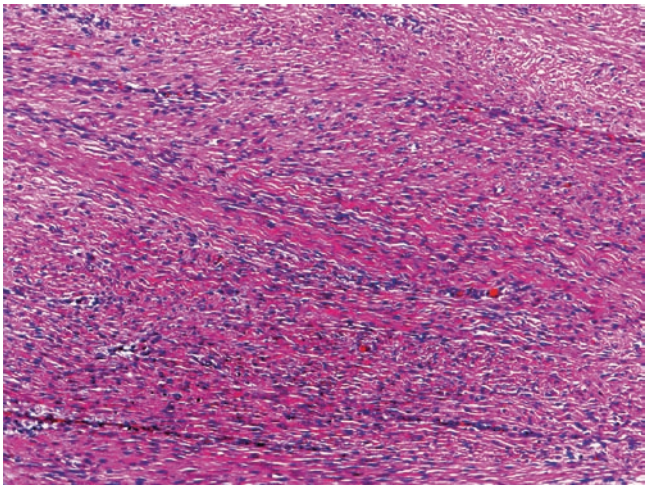

Fig. 7.42 Proliferation of bland and uniform fibroblastic type stromal cells in a characteristic fascicular and wavy pattern

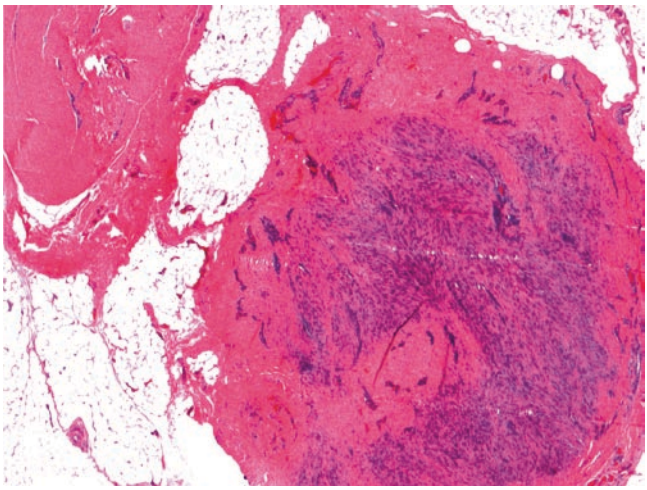

Fig. 7.43 Less infiltrative growth in a palmar fibromatosis

of infiltration into surrounding tissue or organ (Fig. 7.43). Nuclear beta-catenin immunoreactivity has been reported by some authors to be positive in deep but not superficial disease. We have found this feature to be difficult to use or unreliable in practice. Mutations of the beta-catenin gene (CTNNB1) have been identified in 85% of patients with desmoid tumors (deep fibromatosis).

Solitary Fibrous Tumor

Solitary fibrous tumors (SFTs) were initially described as a distinct tumor arising in a pleuropulmonary location. Subsequently, they have been described in a number of sites. In extrapulmonary sites, these tumors can occur in the head and neck, chest wall, mediastinum, retroperitoneum, abdominal cavity, extremities, thyroid, meninges, liver, adrenal, urinary bladder, prostate and testes. Clinically, it presents as a slow growing painless mass. Typically, it behaves in a low grade fashion in most of the cases and malignant in rare cases which might or might not show malignant histologic features.

The tumor is composed of stromal cells usually believed to be of fibroblastic origin. Typically the spindle tumor cells are arranged in so-called patternless pattern with variable collagenous matrix. The cellularity can be quite variable from case to case and within a case from area to area. There is often a hemangiopericytoma like vascular pattern which leads many to believe that cases of hemangiopericytoma diagnosed in the past are in fact solitary fibrous tumor (Figs. 7.44 and 7.45). There is lack of significant nuclear pleomorphism, necrosis and active mitotic activity in majority of the cases.

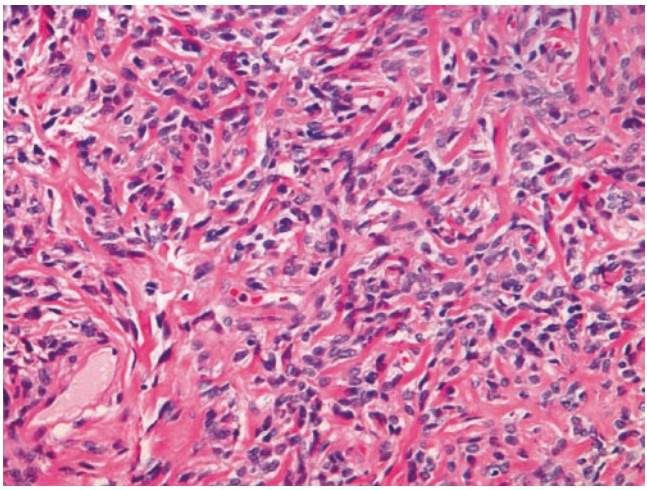

Fig. 7.44 The patternless pattern of spindle cell proliferation in collagenous fibrous background in SFT

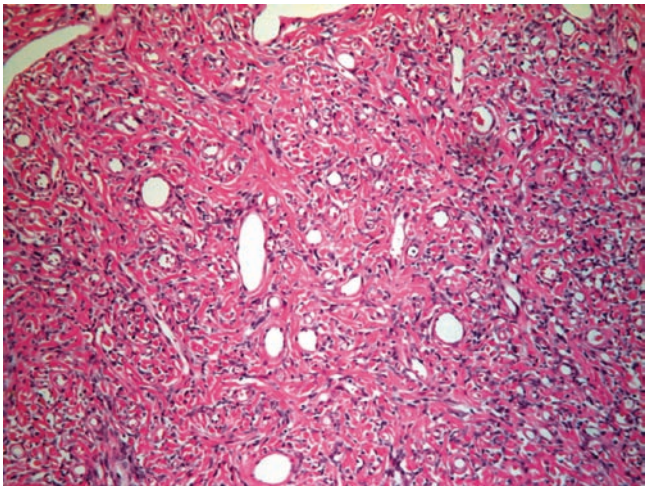

Fig. 7.45 HPC-like vasculature in SFT

Malignant Solitary Fibrous Tumor

It arises from high-grade transformation in typical SFT or de novo. It shows diffuse or focal increased cellularity, significant nuclear pleomorphism, tumor necrosis and high mitotic activity (>2 mitotic figures/10 hpf). Focal areas of typical SFT are seen in cases of high grade transformation (Fig. 7.46).

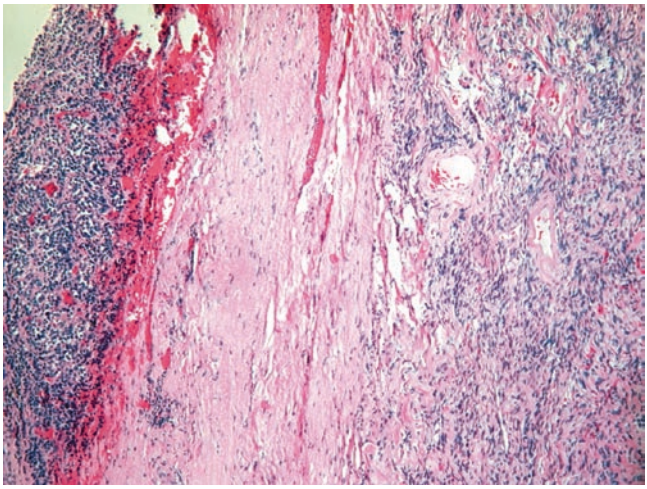

Fig. 7.46 The interface of the high grade nodule (*left*) and the typical SFT (*right*)

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuburans (DFSP) is a locally aggressive soft-tissue tumor that commonly occurs in dermis and subcutis of the trunk and extremities of young to middle aged adults. It presents as a cutaneous plaque and small nodule initially and later becomes a multinodular dermal and subcutaneous mass (protuberant stage).

The lesion is mainly centered in deep dermis and subcutaneous tissue with an infiltrative growth pattern. It is characteristically composed of monotonous fibroblast-like spindle cells with slender nuclei with weak fibrillary eosinophilic cytoplasm arranged in uniform storiform pattern throughout the lesion with little intervening collagenous stroma (Fig. 7.47).

Typically, the infiltrative growth pattern is seen as arrays of long and narrow projections in lateral as well vertical directions into the subcutis or other adjacent structures. In general, there is lack of nuclear hyperchromasia, pleomorphism, frequent mitotic figures and tumor necrosis. High-grade transiformation can be seen in small number of the cases, particularly in recurrent cases, characterized by loss of storiform pattern and presence of fascicular pattern with larger and/or pleomorphic tumor nuclei, hyperchromasia and more active mitotic activity. The tumor is CD34 positive, factor XIIIa negative and D2-40 negative. t(17;22)(q22;q13) with *COL1A1–PDGFB* fusion has been reported in the tumor.

Low Grade Myxofibrosarcoma (Myxoid Malignant Fibrous Histiocytoma)

It is one of the most common sarcomas in elderly patients. It occurs most commonly in limbs and is extremely rare in the retroperitoneum or the abdominal

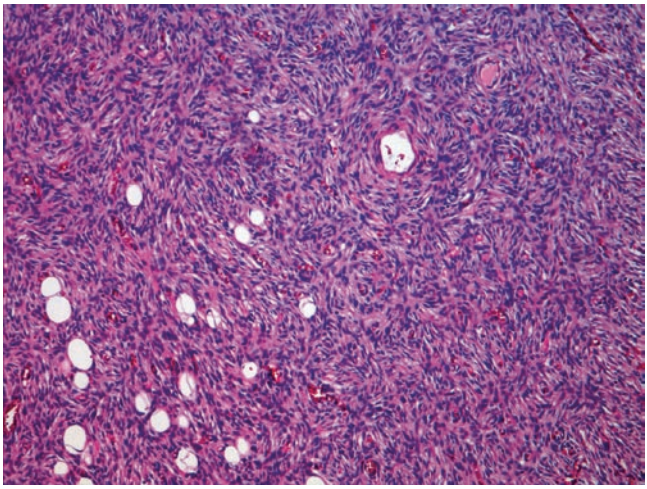

Fig. 7.47 Uniform storiform pattern throughout the lesion with little intervening collagenous stroma in DFSP. Note the entrapped adipocytes from the subcutis

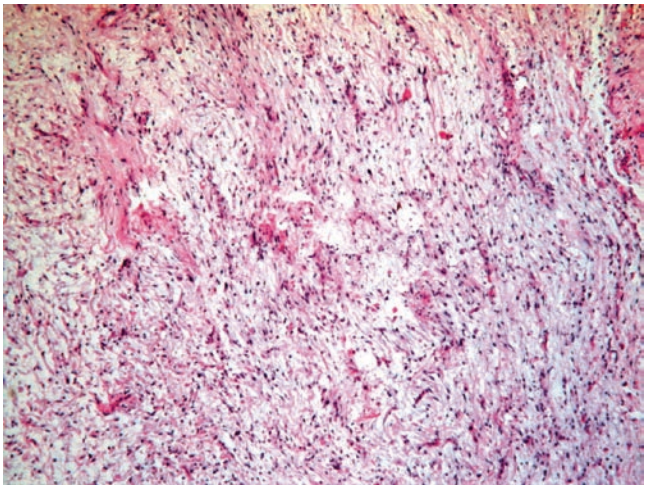

Fig. 7.48 Characteristic myxoid and fibrous background with the distinct curvilinear vasculature in low grade myxofibrosarcoma

cavity. It grows slowly but persistently as a painless mass in dermis and subcutis in 2/3 of cases and deep fascia and deep soft-tissue in the remaining cases.

Under low magnification, the tumor is an irregular myxoid nodule with incomplete fibrous septae and distinct curvilinear, elongated thin-walled, capillary-sized blood vessels (Fig. 7.48). The tumor cells are spindle, or stellate shaped with mild to moderate nuclear pleomorphism (Fig. 7.49). They are present individually within a myxoid

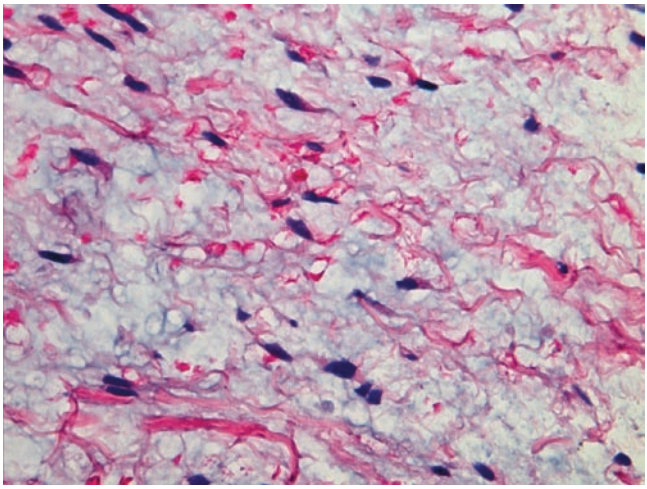

Fig. 7.49 Spindle, or stellate-shaped cells with mild to moderate nuclear pleomorphism in myxoid matrix with loose fibrous strands

matrix or loosely packed into vague fascicles in more cellular areas. Occasionally, a few large tumor cells with vacuolated cytoplasm mimicking lipoblasts and bizarre multinucleated giant cells are seen.

Low Grade Fibromyxoid Sarcoma (Hyalinizing Spindle Cell Tumor with Giant Rosettes)

This is a rare malignant soft-tissue tumor that typically affects the subfascial location of proximal extremities and trunk of young to middle aged adults. It presents as slow-growing painless mass in deep soft-tissue.

The tumor is characterized by uniformly bland, mitotically inactive fibroblast-type spindle cells loosely arranged in rich myxoid and fine collagenous fibrous stroma (Fig. 7.50). The cellularity is low in general. There is little striking pattern but short fascicular and whorling pattern can be seen in some cases. There are only scant curvilinear small blood vessels or thick-walled arteriole-like vessels. Giant rosettes characterized by hyalinized collagenous core rimmed by epithelioid fibroblasts are seen in some cases. t(7;16)(q33;p11) with *FUS–CREB3:2* fusion has been reported in the tumor.

Adult Fibrosarcoma

Currently this tumor comprises about 1–3% of all adult sarcomas due to the use of very strict diagnostic criteria and the wide-spread availability and use of

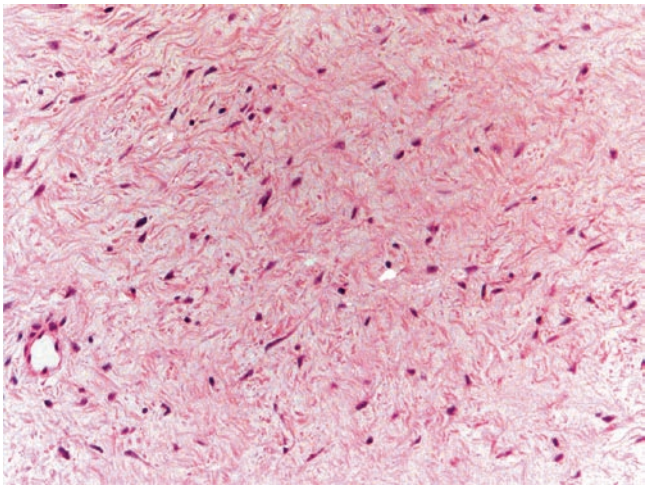

Fig. 7.50 Uniformly bland, mitotically inactive fibroblast-type spindle cells in rich myxoid and fine collagenous fibrous stroma with little vasculature in low grade fibromyxoid sarcoma

immunohistochemistry. Fibrosarcomas are typically located in the deep soft-tissues of the extremities, trunk, and head and neck region of middle-aged and older adults. They may also arise in pre-existing low-grade fibroblastic tumors such as DFSP or SFT. Fibrosarcomas can also be seen in scar, after burns or in areas exposed to radiation.

The tumor is composed of relatively uniform spindle cells with fusiform and hyperchromatic nuclei with variable-sized nucleoli (Fig. 7.51). The tumor cells are arranged in fascicles (the herringbone pattern). A storiform pattern is not seen. Mitotic figures are common but not necrosis.

Malignant Fibrohistiocytoma and Pleomorphic Undifferentiated Sarcoma

Malignant fibrohistiocytoma (MFH) used to be the most commonly diagnosed adult soft-tissue sarcoma. Many such tumors are now reclassified differently according to their lineages. Tumors with no other specific mesenchymal lineage other than fibroblastic/myofibroblastic origin are reclassified preferentially as myxofibrosarcoma, pleomorphic undifferentiated sarcoma or pleomorphic fibrosarcoma.

The tumor is typically composed of pleomorphic cells. The cells may be spindle, polygonal or bizarre giant mononuclear or multinucleated cells (Fig. 7.52). A storiform pattern is characteristic with some poorly organized collagenous

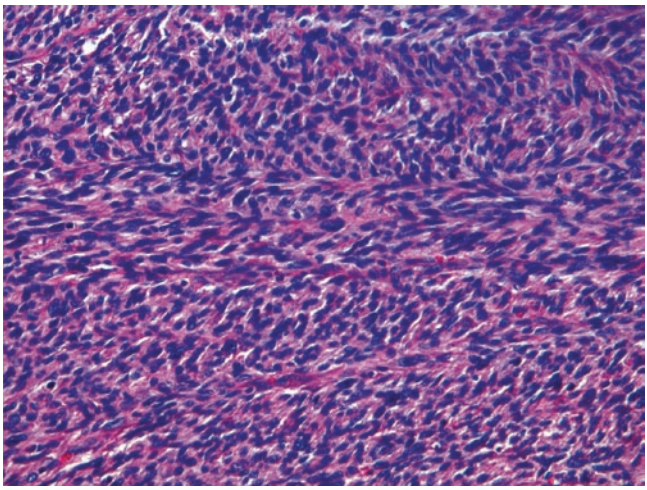

Fig. 7.51 Relatively uniform spindle cells with fusiform and hyperchromatic nuclei closely packed together with little intervening cytoplasm and stroma in classic herringbone or fascicular pattern in fibrosarcoma

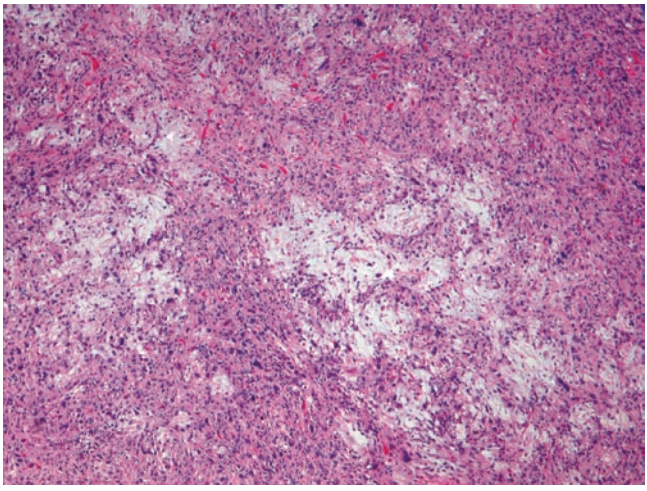

Fig. 7.52 Pleomorphic cell population, ranging from spindle, polygonal to bizarre giant mononuclear or multinucleated cells in MFH. Note the focal storiform pattern

stroma and myxoid change. Numerous osteoclast-like multinucleated giant cells are seen in same cases (giant cell MFH). Extensive inflammatory infiltrates composed of histiocytes, neutrophils, eosinophils, lymphocytes and plasma cells are present in cases called inflammatory MFH.

Myogenic Tumors

Leiomyoma (Soft-Tissue)

Leiomyoma is generally seen in a superficial or cutaneous location in young or middle-aged adults and rarely in deep location of extremites, retroperitoneum, abdominal and pelvic cavity. There is a female predilection.

The tumor is composed of spindle cells of smooth muscle type with cigar-shaped nuclei with nuclear membrane indentation or inward folding along the short axis and eosinophilic fine fibrillary cytoplasm with variable cytoplasmic vacuoles (Fig. 7.53).

Epithelioid cellular morphology can be seen in some cases. The tumor cells form well-organized intersecting fascicles. Nuclear atypia should be minimal and mitotic figures should be less than one in fifty high-power fields (less than 5/50 high-power fields in retroperitoneal and pelvic peritoneal lesions in females). There should be no coagulative tumor necrosis although areas of hyalinization (hyaline necrosis), myxoid change, cystic change and calcification are common in larger tumors. The histologic criteria for leiomyoma are more stringent in soft-tissue as compared to those occurring in viscera.

Rhabdomyoma (Non-cardiac)

Soft-tissue (non-cardiac) rhabdomyoma is a benign soft-tissue tumor with skeletal muscle differentiation. There are adult, fetal, and genital types. The adult type is common in the head and neck of young to middle-aged adults with a 3:1 male

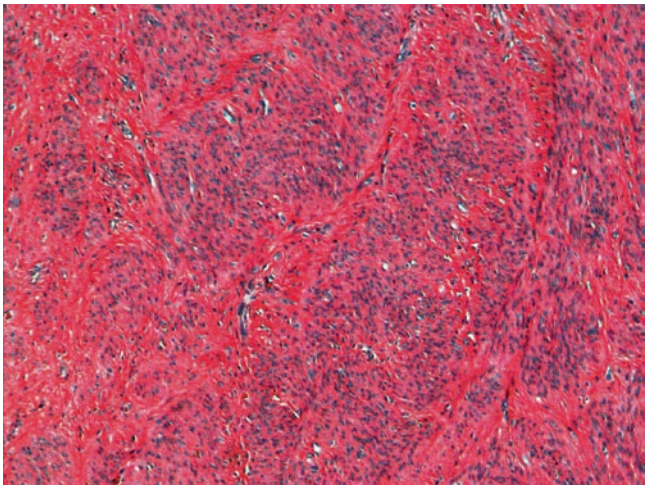

Fig. 7.53 Cigar-shaped nuclei with nuclear membrane indentation or inward folding along the short axis; and eosinophilic fine fibrillary cytoplasm in well-organized intersecting fascicular pattern in leiomyoma

predilection. It presents with airway obstruction or as a asymptomatic mucosal or soft-tissue mass. The genital type is very rare and presents as a polypoid mass in the vagina, vulva or cervix of young females. The fetal type is common in younger age (median age 4 years) with similar male predilection; and affects the soft-tissue and mucosal sites of the head and neck region. Unlike cardiac rhabdomyoma there is no association with tuberous sclerosis.

Adult type is characterized by closely packed, uniform, large polygonal rhabdoid cells with single round nucleus, abundant eosinophilic, granular cytoplasm and distinct cytoplasmic membrane (Fig. 7.54). Variably vacuolated cytoplasm is seen in some cells rendering a "spider" appearance.

Genital type is usually polypoid and composed of round or strap-like mature rhabdomyoblasts with more abundant intercellular fibrous stroma and dilated vein-like vascular spaces.

Fetal type is composed of bland fetal type rhabdomyoblasts as either primitive spindle cells with little cytoplasm or long strap cells with more eosinophilic cytoplasm.

The spindle cells have haphazard and loose arrangement in abundant myxoid stroma.

Some cases show rhabdomyoblasts with more advanced cytoplasmic differentiation toward adult type rhabdomyomas (intermediate, juvenile or cellular type).

Leiomyosarcoma

Leiomyosarcoma is usually seen in older adults but also rarely in children with HIV infection. There are three types according to anatomic locations: retroperitoneum/

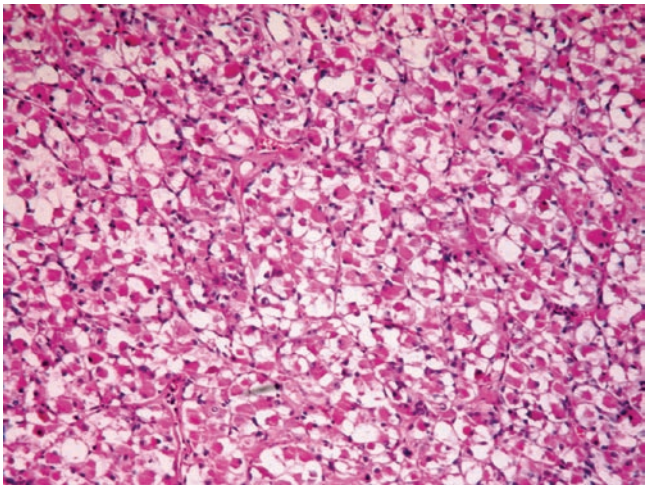

Fig. 7.54 Closely packed, uniform, large polygonal rhabdoid cells with single round nucleus, abundant eosinophilic, granular cytoplasm and distinct cytoplasmic membrane in rhabdomyoma

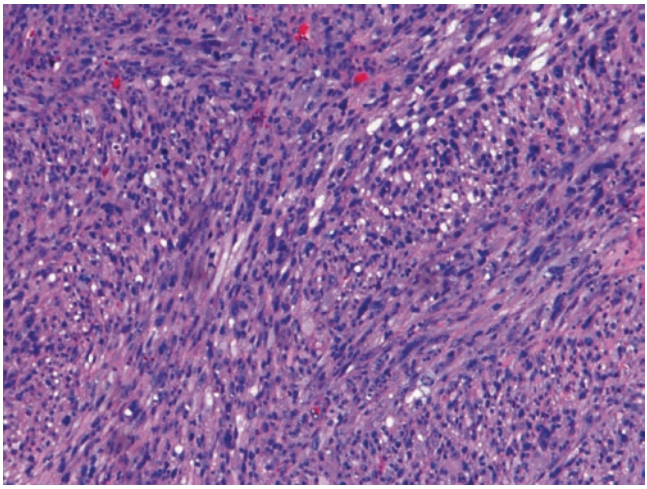

Fig. 7.55 Spindle cells similar to those in leiomyoma but with hyperchromatic or vesicular nuclei, more pleomorphism and less organized pattern in leiomyosarcoma

intraabdominal type, cutaneous/subcutaneous type and major vessel type. There is a female predilection in retroperitoneal and inferior vena cava locations.

Clinical presentations depend upon the size and location and usually presents as palpable or deep mass with symptoms related to mass effect on the adjacent organs or structures such as urogenital tract, gastrointestinal tract and major large blood vessels.

The tumor is composed of spindle cells similar to those seen in leiomyoma but with hyperchromatic or vesicular nuclei and at least some degree of pleomorphism. An intracytoplasmic vacuole at one end of the spindle-shaped nucleus and transverse nuclear indentations and inward nuclear envelope folding are characteristic but not pathognomonic for smooth muscle differentiation. Some cases show an epitheloid morphology. The overall arrangement of the spindle cells may be of a whirling, storiform or even a palisading type (Fig. 7.55). Mitotic activity is frequent with several atypical mitotic figures. Coagulative tumor necrosis is frequently seen.

Rhabdomyosarcoma

Rhabdomyosarcoma is the malignant version of rhabdomyoma. It is subclassified to embryonal, alveolar and pleomorphic types. It is the most common sarcoma of pediatric population. Embryonal type accounts for 75% of all rhabdomyosarcomas and occurs primarily in children younger than 15 years old. It typically affects the head and neck region, paratesticular area, urinary tract and biliary tract. Alveolar type is commonly seen in the deep soft-tissue of limbs and less commonly in the paranasal sinuses, paraspinal and perineal regions. It can be seen at all ages but is

seen more often older children or young adults. Pleomorphic type is extremely rare after excluding other sarcomas with rhabdomyoblastic differentiation. It is almost always seen in adults older than 45 years old and affects the deep soft-tissue of the lower extremities. Clinically all present as rapid growing mass with symptoms usually related to the mass effects to adjacent organs and structures.

Embryonal type has a diverse histological appearance. The tumor cells can be round, spindle and/or strap shape with hyperchromatic and vesicular nuclei (Figs. 7.56 and 7.57). They may have a scant amphophilic or an abundant fibrillary

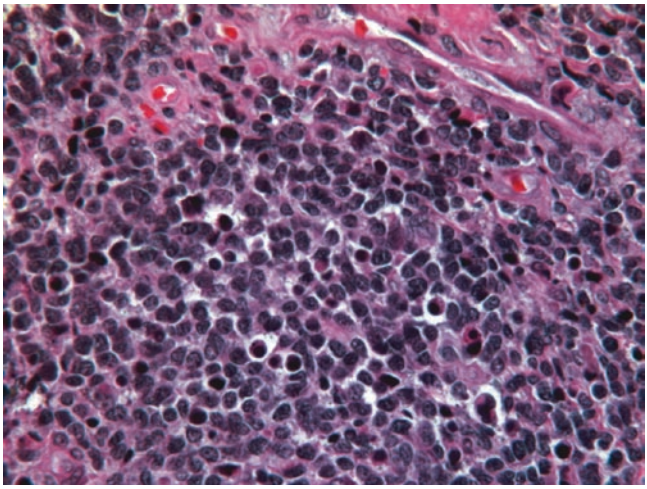

Fig. 7.56 Primitive undifferentiated round cells in embryonal rhabdomyosarcoma

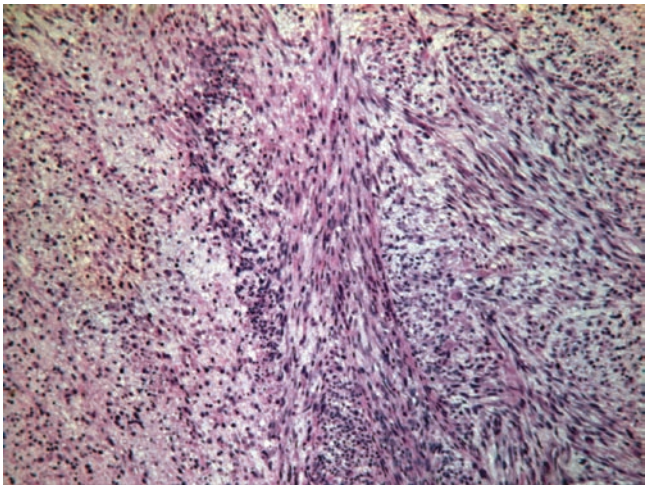

Fig. 7.57 Spindle cells and rare strap cells with hyperchromatic and vesicular nuclei and scant amphophilic to abundant fibrillary eosinophilic cytoplasm in embryonal rhabdomyosarcoma

eosinophilic cytoplasm dependent upon the degree of myoid differentiation. The tumor cells have haphazard arrangement with alternating hypercellular and myxoid hypocellular zones. Rare multinucleated giant tumor cells are seen in some cases.

Alveolar type has more uniform round cells in an alveolar growth pattern resulting from a loss of extracellular matrix in a nest of round rhabdomyoblasts. Often, there are fibrovascular septae around such nests (Fig. 7.58). Solid sheet or nest of tumor cells are present when alveolar pattern is not apparent in some tumors (Fig. 7.59).

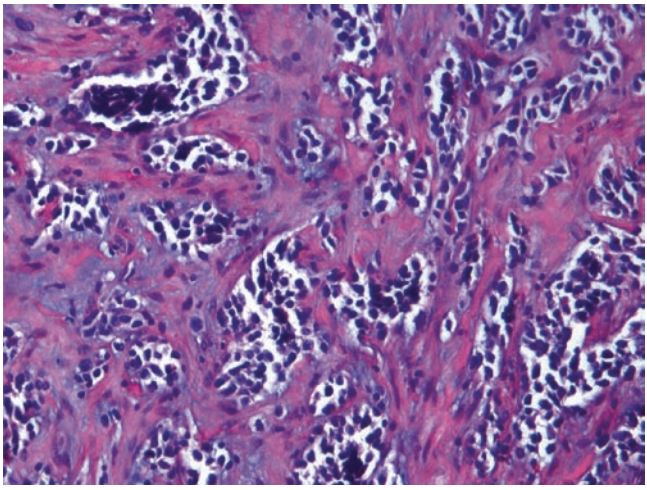

Fig. 7.58 More uniform round cells in an alveolar growth pattern in alveolar rhabdomyosarcoma

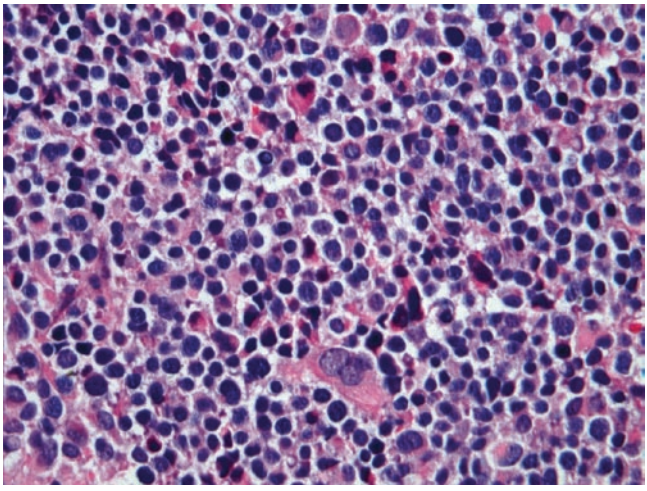

Fig. 7.59 The round tumor cells are very hyperchromatic and have a high N/E ratio in alveolar rhabdomyosarcoma

Pleomorphic type is composed of numerous large and pleomorphic, globoid, spindle and/or tadpole appearing cells with hyperchromatic nuclei and abundant eosinophilic cytoplasm. Despite the rhabdoid cellular appearance, cross-striation is extremely rare.

All tumor types are positive for myoD, myogenin and myoglobin. Alveolar rhabdomyosarcoma is also characterized by t(2;13)(q35;q14) or t(1;13)(p36;q14); presence of *PAX 3* or *PAX 7–FHKR* fusion.

Neural Tumors

Traumatic Neuroma

A benign condition usually arises from the proximal stump of the severed nerve at a site of previous trauma or surgery. It presents as a painful nodule.

Microscopically, there is a disorganized proliferation of nerve bundles or fascicles composed of axon, Schwann cells and perineurial cells in a fibrocollagenous stroma with a myxoid change (Fig. 7.60).

Schwannoma (Neurilemoma)

This is a benign nerve sheath tumor with exclusive schwannian differentiation. It is more commonly seen in adults and occurs associated with the peripheral nerves of

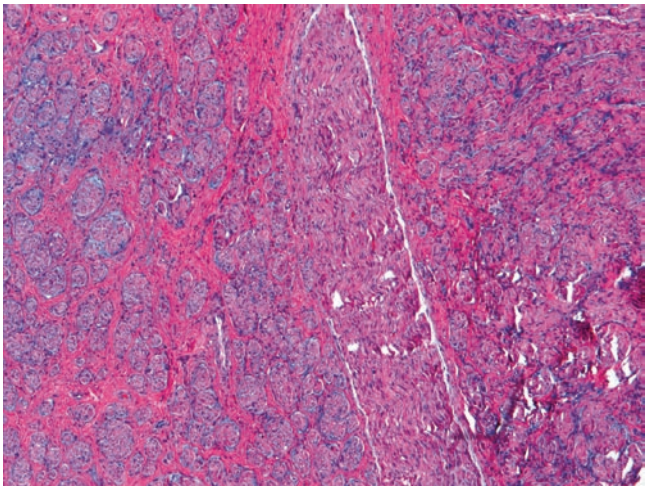

Fig. 7.60 Disorganized proliferation of nerve bundles or fascicles in traumatic neuroma

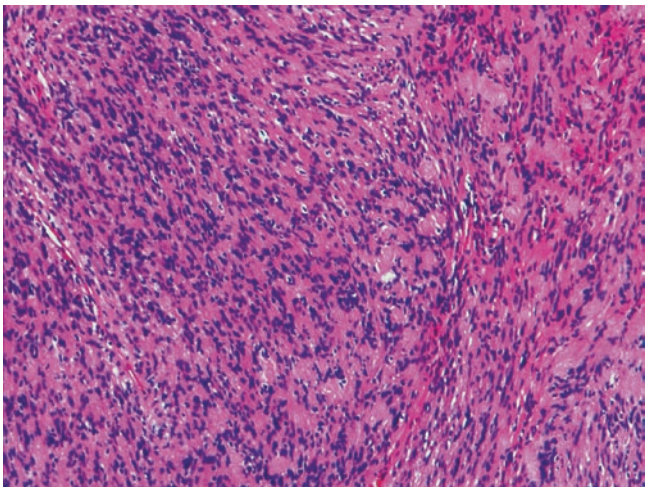

Fig. 7.61 Cellular areas (Antoni A areas) characterized by short fascicles, swirls and/or palisading pattern (Verocay bodies)

the head and neck, extremities, mediastinum, retroperitoneum and paraspinal region. It presents as a slow-growing mass with symptoms associated with pressure on adjacent structures.

The spindle cells of schwannoma are typically angulated, comma-shaped or bullet shaped nuclei with fine chromatin, and ill-defined eosinophilic fibrillary cytoplasm (Fig. 7.61). Cellularity alternates from area to area. There is often a myxoid or hyaline stromal change. The cellular areas (Antoni A areas) are characterized by short fascicles, swirls and/or palisading nuclei (Verocay bodies). The hypocellular areas (Antoni B areas) are characterized by myxoid and hyaline stroma. Various degenerative/reactive changes are common: hemorrhage, hemosiderin deposition, organizing thrombi, inflammatory infiltrate, xanthomatous infiltrate, pseudocyst formation, calcification, and necrosis. There are very characteristic hyalinized thick-walled vessels in the lesion. Pleomorphic and hyperchromatic nuclei are seen randomly in cases with extensive degenerative changes (ancient schwannoma) but mitotic figures are rare.

Neurofibroma

Neurofibroma is nerve sheath tumor composed of Schwann cells, fibroblasts, and axonal processes of neurons. Localized neurofibromas are usually sporadic and seen in early adulthood as a painless, slow-growing mass usually in the superficial location closely associated with a nerve trunk. Multiple neurofibromas are usually associated with von Recklinghausen's disease (NF-1) with larger, more diffuse and

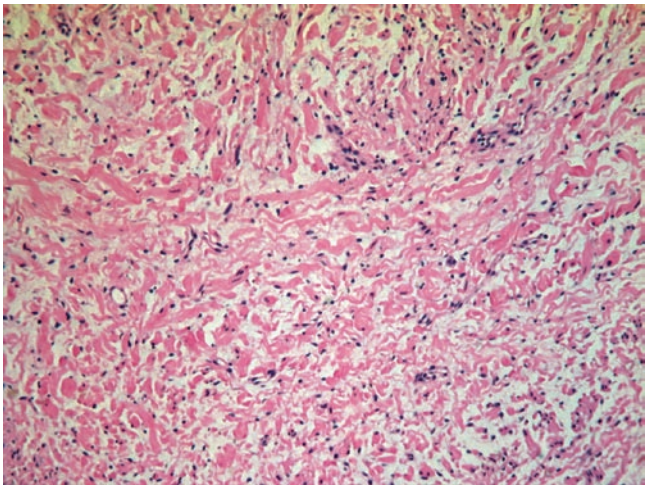

Fig. 7.62 Wavy spindle cells with features of Schwann cell, fibroblast and perineurial cell in neurofibroma

multiple lesions in deep and superficial locations, frequently with plexiform growth pattern involving the nerve trunk (plexiform neurofibroma).

The tumor is usually associated with a nerve. It can be encapsuled (localized neurofibroma), plexiform appearance (plexiform neurofibroma), or diffuse and poorly demarcated growth without capsule (diffuse neurofibroma). The tumor contains wavy spindle cells with features of Schwann cell, fibroblast and perineurial cell in fascicular, whorling, storiform and/or haphazard patterns. In general, there is more diffuse pattern with less organioid feature in neurofibroma than in schwannoma (Fig. 7.62). Axons, if seen (usually by neurofilament immunostain), are very characteristic in neurofibromas. Nerve sheath proliferation is confined to the perineurium in plexiform neurofibromas (Fig. 7.63). Scattered hyperchromatic pleomorphic cells and increased cellularity are seen in some cases these are not associated with increased mitotic activity.

Granular Cell Tumor (Granular Cell Schwannoma, Granular Cell Myoblastoma)

Granular cell tumor is a benign tumor of nerve sheath origin with schwannian differentiation. It is usually a superficial mass in the tongue, chest wall and arms of adults and rarely occurs in visceral organs.

The tumor is characterized by proliferation of round, polygonal or sometimes even spindle cells with uniform central nuclei and abundant, coarse granular eosinophilic cytoplasm (Fig. 7.64). The tumor cells form nests, strands, cords and

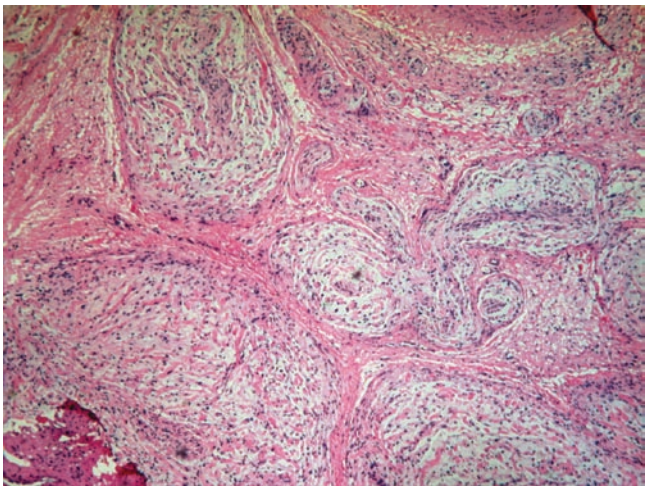

Fig. 7.63 Nerve sheath proliferation is primarily confined within the perineurium of numerous disorganized nerve fascicles in a plexiform growth pattern in plexiform neurofibroma

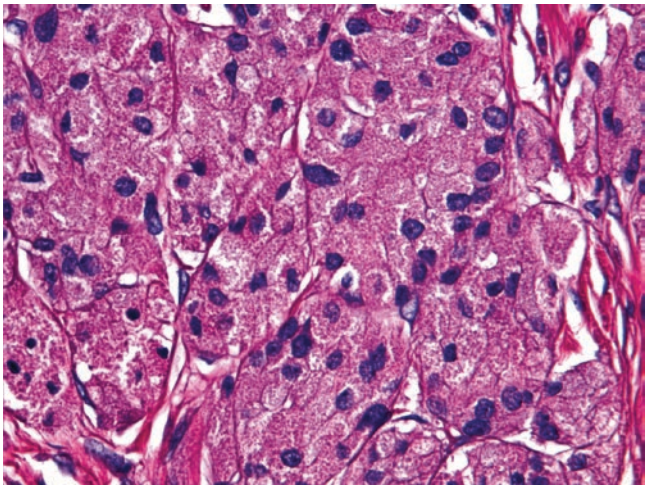

Fig. 7.64 Round, polygonal or sometimes even spindle cells with uniform central nuclei and abundant, coarse granular eosinophilic cytoplasm in granular cell tumor

sheets, generally in a well circumscribed fashion, although occasionally the lesion can show an alarmingly infiltrative growth pattern. Hyperplastic epithelial change is seen in some cases. There is no significant nuclear pleomorphism or mitotic activity in majority of the cases. Malignant potential should be considered when there is presence of three of the following features: marked cellularity, pleomorphism, high nucleus to cytoplasm ratio, nucleolar prominence, increased mitoses, prominent spindling of the cells, frequent necrosis.

The tumor is positive for S100 but negative for melanocytic, myoid and epithelial markers.

Malignant Peripheral Nerve Sheath Tumor (MPNST, Malignant Schwannoma, Neurofibrosarcoma)

MPNST is a very rare sarcoma and accounts for 5% of all soft-tissue sarcomas.

It can be classified as classic type and contemporary type according to the different clinical criteria applied to the diagnosis. Classic type occurs usually in young adults, many with NF-1 in a period of 10–20 years. It typically affects large and medium-sized nerves in the proximal limbs and trunk with sciatic nerve being most frequently affected. Symptoms of nerve compression are commonly seen. In a NF-1 patient, pain or rapid enlargement of a neurofibroma may herald malignant transformation. Contemporary type does not meet the classic requirement for NF-1 background and the diagnosis is purely based on morphological, immunohistochemical and/or ultrastructural evidence of nerve sheath differentiation.

The tumor is usually associated with neurofibroma or nerve trunk in classic cases. It shows various morphologies and variable degree of peripheral nerve sheath differentiation. Typically, the tumor cells are oval to spindle and have wavy or angulated nuclei with one tapered end and coarse chromatin pattern with scant to moderate amount of weakly eosinophilic, poorly defined cytoplasm. Tumor cells form fascicles and whorls, with rare rosettes and may show a palisading pattern (Fig. 7.65). Mitotic activity is high with atypical mitotic figures. Geographic necrosis is common with perivascular tumor preservation. S100 is usually weak and focal or negative.

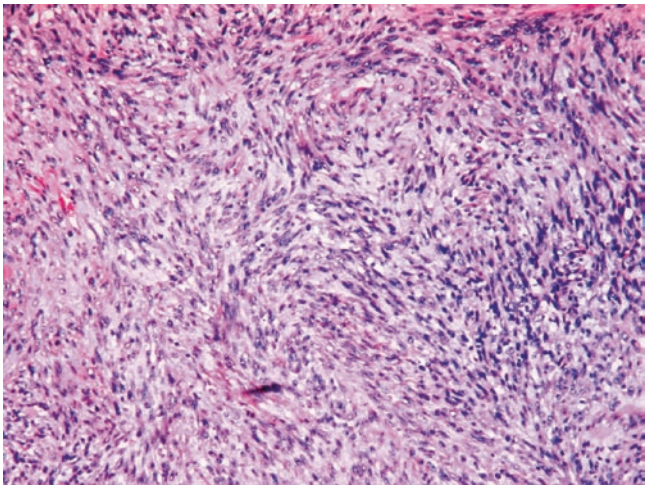

Fig. 7.65 Oval to spindle cells with coarse nuclear chromatin, scant to moderate amount of weakly eosinophilic, and poorly defined cytoplasm arranged in fascicular and whorling pattern in MPNST

Tumors with Pericytic or Modified Perivascular Cell Differentiation

Glomus Tumor

This is a rare benign soft-tissue tumor which morphologically simulates the glomus bodies in the dermis of distal extremities, subungual region of the digits and in the precoccygeal soft-tissue (glomus coccygeum). It is characteristically painful lesion that may be exacerbated by temperature change. Typically it is small and solitary. Rarely multiple lesions called glomangiomatosis are seen in patients with autosomally dominant inheritance.

The lesional cells are uniform round to ovoid simulating those seen in glomus body. They have a bland chromatin with inconspicuous nucleoli (Fig. 7.66). The tumor cells form nests and trabeculae cuffing around thin-walled, capillary-sized vessels. According to the proportion of the glomus-like cells, the degree of smooth muscle differentiation and vascular element, glomus tumors can be subcategorized as solid glomus tumor and glomangioma and glomangiomyoma. Tumors with the following features are considered malignant: large size (>2 cm), deep location, moderate to high nuclear grade, increased mitotic rate (>5/10 high power fields) and presence of atypical mitotic figures.

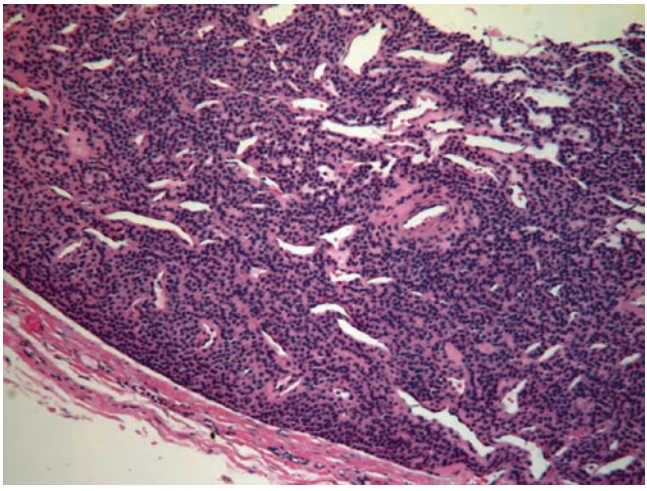

Fig. 7.66 Uniform round to ovoid epithelioid cells (glomus-like cells) with bland chromatin pattern, absent or inconspicuous nucleoli n glomus tumor

Myopericytoma

A benign tumor shows histologic differentiation towards perivascular myoid cells.

It is a slow growing cutaneous and subcutaneous nodule occurring most commonly in middle-aged adults.

The tumor is composed of monotonous oval-spindle cells with myoid-like eosinophilic cytoplasm arranged concentrically around variably-sized, short branching, gaping, thin-walled vessels. Histologic spectrum can span among myofibroma, angioleiomyoma, infantile hemangiopericytoma, and glomangiomyoma.

Hemangiopericytoma

Hemangiopericytomas have a characteristic vascular pattern that dominates and often defines them – however this pattern can be seen in a variety of soft-tissue tumors such as solitary fibrous tumor, gastrointestinal stromal tumor, monophasic synovial sarcoma and myopericytoma. It is very likely, that some of these tumors were diagnosed as hemangiopericytoma in the past.

After careful exclusion of all the above entities, only small number of tumors fit well into true soft-tissue hemangiopericytoma. The dural and head and neck hemangiopericytomas share many features with soft-tissue hemangiopericytomas but will not be discussed here.

The histologic hallmark of hemangiopericytoma are thin-walled, ramifying and gapping vessels in staghorn-like pattern with perivascular proliferation of monotonous round to oval mesenchymal cells (pericytes) (Fig. 7.67).

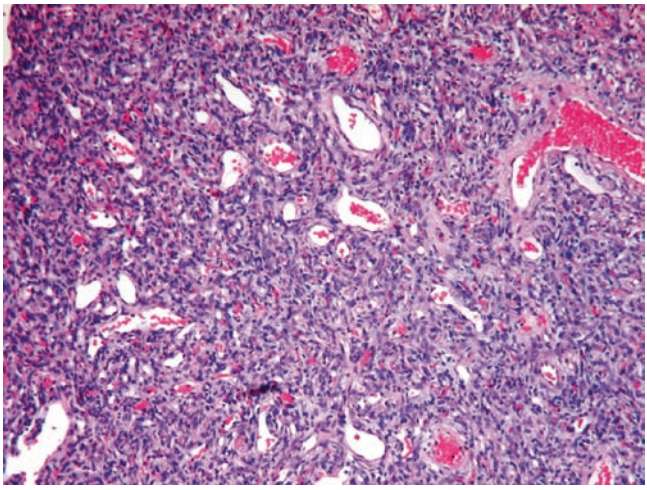

Fig. 7.67 Thin-walled, ramifying and gaping vessels in staghorn-like pattern in low magnification in HPC

Tumors of Uncertain Histogenesis and Differentiation

Clear Cell Sarcoma of Soft-Tissue (Malignant Melanoma of Soft Part)

Clear cell sarcoma is a rare sarcoma which occurs usually in young adults, most commonly in the extremities, typically attached to aponeuroses and tendons as slow-growing mass frequently with pain and tenderness.

Under low magnification, the tumor is characterized by a nested or fascicular pattern separated by delicate fibrous septa giving a multilobulated appearance (Fig. 7.68). The tumor is composed of polygonal or spindle cells with eosinophilic or clear cytoplasm and vesicular nuclei with prominent nucleioli. Clear cell sarcoma is positive for a wide range of melanocytic markers such as S100, HMB45, melan-A, MITF, and MAGE. The tumor is cytogenetically and molecularly characterized by t(12;22)(q13;q12) or *EWS–ATF1* fusion which can be used to differentiate them from melanoma.

Angiomatoid Fibrous Histiocytoma

This is an indolent tumor that frequently affects the subcutis and deep dermis of the upper extremities of young adults. It presents as a slow-growing mass occasionally associated with systemic symptoms such as fever, anemia and weight loss.

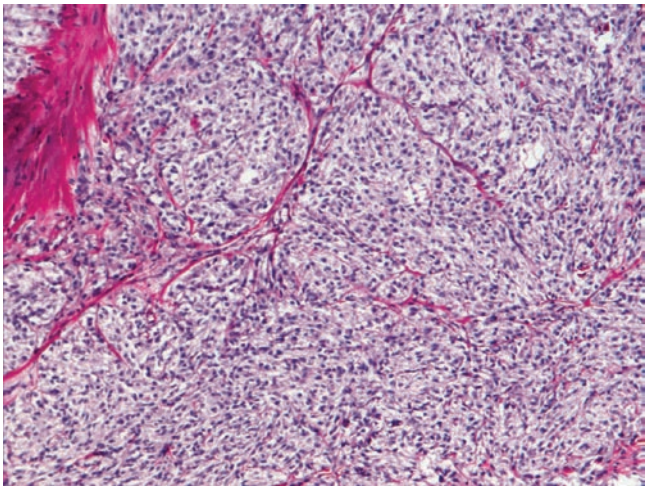

Fig. 7.68 The nesting growth of epithelioid cells with clear cytoplasm and vesicular nuclei with prominent nucleoli are very characteristic of clear cell sarcoma

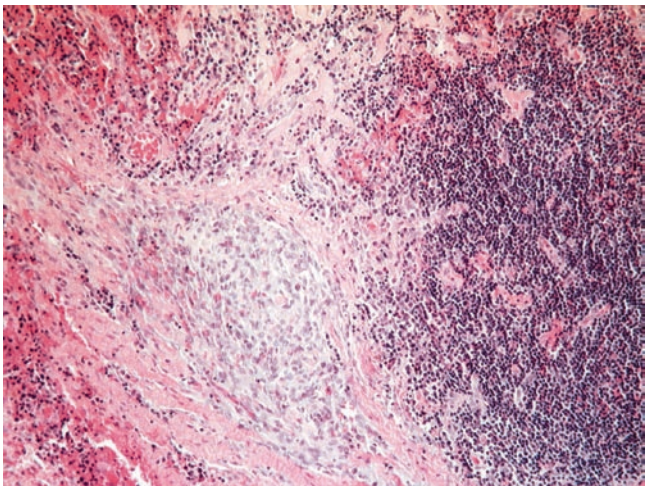

Fig. 7.69 Aggregates of uniform histiocytoid/myoid cells and cuff of dense lymphocytes and plasma cells in angiomatoid FH

The tumor is characterized by multinodular proliferation of relatively uniform histiocytoid/myoid cells with vesicular nuclei and eosinophillic cytoplasm. There are pseudoangiomatoid or cystic hemorrhagic areas without endothelial lining in the center of the lesion and peripheral cuff of dense lymphocytes and plasma cells sometimes with germinal center formation (Fig. 7.69). T(12;16)(q13;q12) with *EWS–CREB1* fusion has been reported in this tumor recently.

Ossifying Fibromyxoid Tumor

The histogenic origin of this rare soft-tissue tumor is still unclear. A peripheral nerve origin has been suggested in the past. It occurs usually in adults in their 50s with majority (70%) of the cases occurring in the lower extremities followed by trunk (20%) and head and neck (10%). It frequently attaches to underlying tendons and deep fascia. The tumor shows a peripheral calcification or ossification around a well-circumscribed mass that can be seen on plain film radiographs.

The tumor is composed of multilobulated and well-circumscribed proliferation of monotonous round and oval cells with scant eosinophilic cytoplasm (Fig. 7.70). The tumor cells form cords, nests and trabeculae in a fibromyxoid matrix. There is a characteristic ossification, usually forming lamellar bone, as a partial shell. Occasionally the ossification may occur within rather than around the tumor. The stroma can be extremely myxoid or fibrous in different cases. The tumor is positive for S100 and desmin.

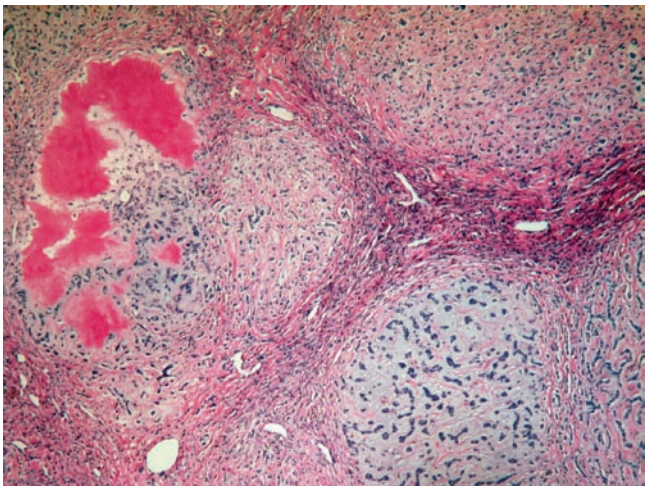

Fig. 7.70 Multilobulated and well-circumscribed growth with ossification in ossifying fibromyxoid tumor. The tumor cells are monotonous round and oval with scant eosinophilic cytoplasm forming cords, nests and trabeculae in a fibromyxoid matrix

Synovial Sarcoma

It accounts for 5–10% of all soft-tissue sarcoma. It occurs frequently in the deep soft-tissue adjacent to joints or tendons of extremities and less commonly the head and neck region, rarely in visceral organs. Clinically, it presents as a slow-growing mass not infrequently associated with pain. Bone involvement and calcification are seen in less than one third of cases.

The tumor is typically biphasic with both epithelial and spindle cell elements. Epithelial cells form of glandular structures or solid nests. The mesenchymal type spindle cells have scant cytoplasm and indistinct cell borders in between the epithelial elements (Fig. 7.71). Monophasic variant is composed of only monotonous short spindle cells with formation of vague fascicular, whorling and rarely palisading patterns (Fig. 7.72). A hemangiopericytoma-like vascular pattern is common but usually focal. Extracellular matrix varies from myxoid in hypocellular area to more fibrous in cellular area. Both epithelial and spindle cells are positive for cytokeratin, EMA. An antibody thought to be sensitive but not specific for synovial sarcoma has been reported (TLE-1). The presence of t(X;18)(p11;q11) karyotype or positive detection of *SYT–SSX1* or *SSX2* fusion gene product is diagnostic for synovial sarcoma.

Extraskeletal Myxoid Chondrosarcoma (Chordoid Sarcoma)

A very rare sarcoma typically occurs in deep soft-tissue or musculature of adults in their 50s–60s as a slowing growing mass. Lower extremities and the limb girdles are the most common site followed by the trunk and upper extremities.

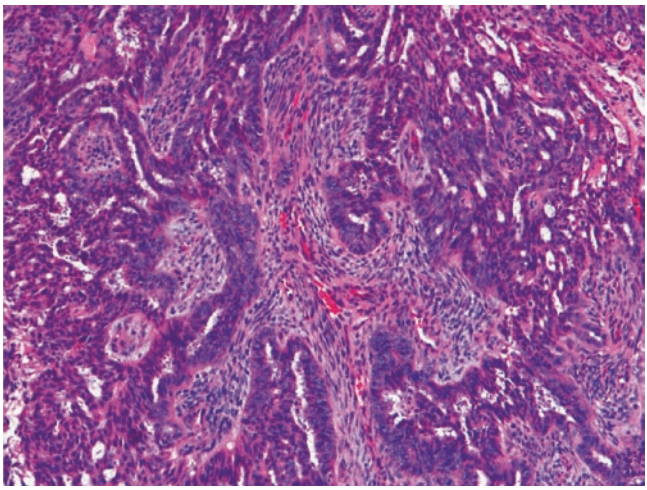

Fig. 7.71 Biphasic synovial sarcoma composed of epithelial cells forming glandular structures and mesenchymal type spindle cells with scant cytoplasm, hyperchromatic nucleus and indistinct cell border in between the epithelial elements

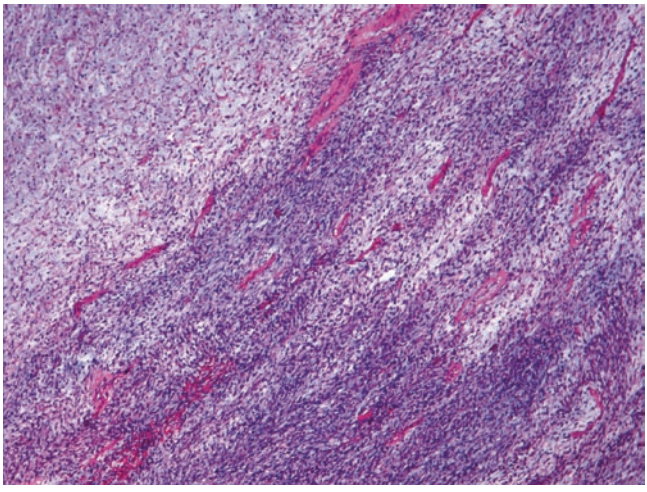

Fig. 7.72 Monophasic synovial sarcoma dominated by uniform spindle mesenchymal type cells growing in a loose or vague fascicular pattern

Except for the myxoid matrix, the tumor has little similarity with chondrosarcoma of the bone. It shows well-defined, multilobulated growth of polygonal and oval primitive tumor cells with eosinophilic cytoplasm forming clusters, cords, irregular trabeculae and cribriform nests divided by fibrous septa in myxoid matrix (Fig. 7.73). There is hardly hyaline cartilage and lacula formation. Mitotic activity is usually low but increased in cellular type and epithelioid/anaplastic variant.

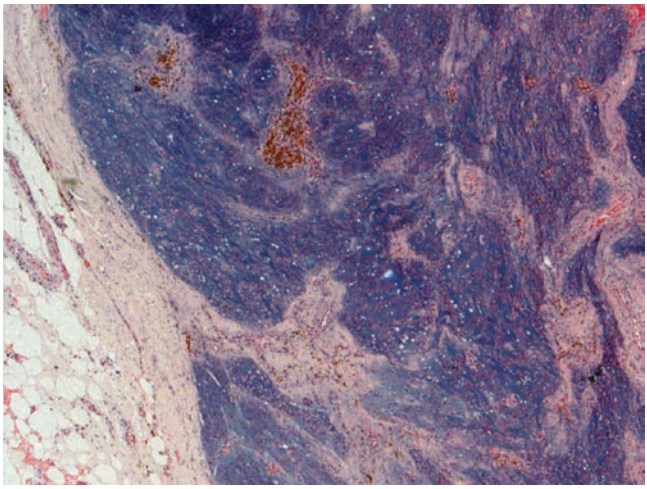

Fig. 7.73 Multilobulated myxoid mass divided by fibrous septa in extraskeletal myxoid chondrosarcoma. Tumor cells form clusters, cords, irregular trabeculae and cribriform nests in myxoid matrix

Alveolar Soft Part Sarcoma

This is a very rare soft-tissue sarcoma that occurs mainly in young adults with female predilection. It usually affects lower extremities and the head and neck region and presents as a slow-growing, painless mass. One third of patients present with metastatic lesion in lung, brain or bone even before diagnosis of the primary lesion.

The tumor shows organoid growth of relatively uniform and large polygonal cells with abundant, granular, eosinophilic cytoplasm. The tumor cells form nests and islands separated by delicate fibrovascular tissue exhibiting a paraganglioma-like pattern or pseudoalveolar appearance attributed to loss of cellular adherence in tumor cells (Fig. 7.74). Vascular invasion is common. The tumor is positive for TEF-3 and shows a t(X;17)(p11;q25) with *ASPS–TEF3* fusion.

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is a rare and very aggressive tumor of undetermined histogenesis. It primarily affects children and young adults and has a strong male predilection. The most common site is the peritoneal surface of the abdomen. It usually presents with rapid development of abdominal distention, acute abdomen and ascites.

The tumor is characterized by nests of uniform small round cells with high nuclear/cytoplasmic ratio and hyperchromatic nuclei in a strikingly desmoplastic

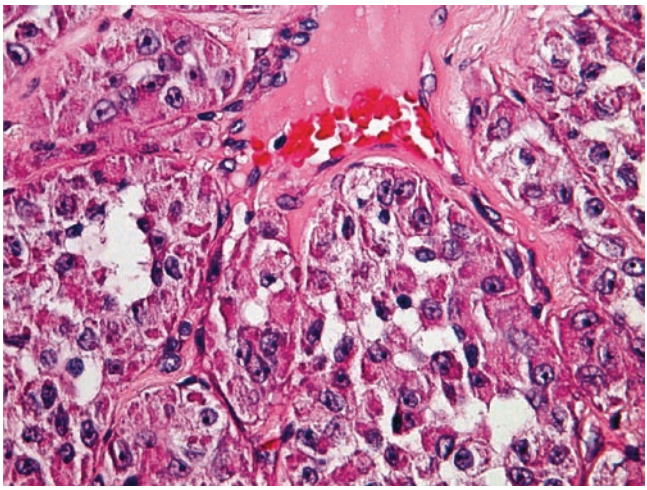

Fig. 7.74 Striking organoid nests and islands of tumor cells separated by delicate fibrovascular tissue in alveolar sarcoma of soft part. Tumor cells are relatively uniform, large and polygonal with abundant, granular, eosinophilic cytoplasm

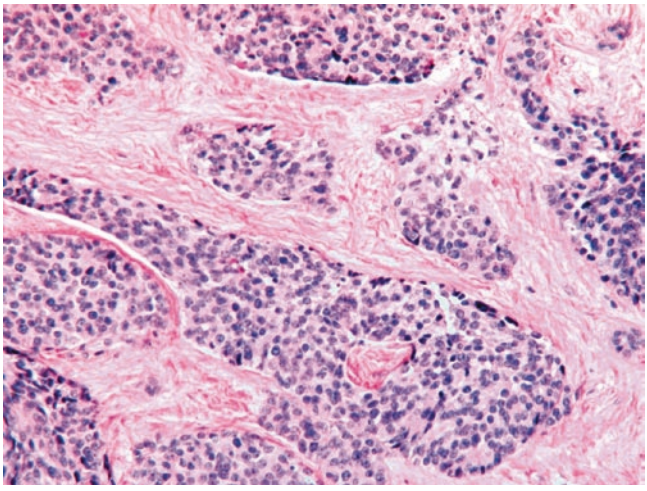

Fig. 7.75 Variably shaped and sized nests of blue and round cells with high nuclear/cytoplasmic ratio and hyperchromatic nuclei in desmoplastic stroma in DSRCT

stroma (Fig. 7.75). Mitotic figures and tumor necrosis are common. The tumor is positive for cytokeratin, desmin and WT-1. Cytogenetic and molecular tests reveal characteristic t(11;22)(p13;q12) and *EWS–WT1* fusion.

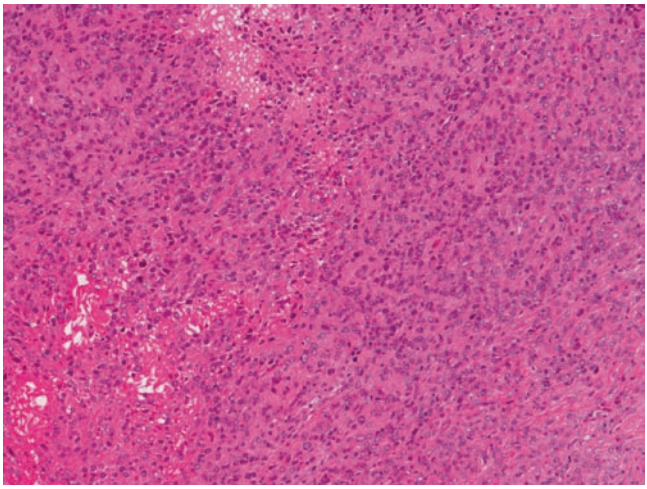

Fig. 7.76 Coalescing nodular composed of polygonal to short spindle cells with strong eosinophilic cytoplasm in epithelioid sarcoma

Epithelioid Sarcoma

Epithelioid sarcoma typically occurs in the distal extremities of young adults. It presents as painless and slow-growing solitary or multiple nodules in the skin, subcutis, fascia or tendon with tumor progression toward the proximal extremity.

The tumor shows a coalescing nodular or multinodular growth of polygonal to short spindle cells with strong eosinophilic to somewhat clear cytoplasm arranged around an amorphous hyaline or necrotic area simulating granuloma (Fig. 7.76). There is little pleomorphism. The tumor is positive for cytokeratin, EMA and vimentin and characteristically negative for INi1 immunohistochemically.

Non-neoplastic Conditions Frequently Misdiagnosed as Sarcoma (Pseudosarcoma)

Nodular Fasciitis

Nodular fasciitis is a reactive myofibroblastic proliferation that is prone to misdiagnosis as sarcoma. It frequently involves extremities, trunk and head and neck region of young adults. It may also involve the scalp (cranial fasciitis) in infants.

It is typically a rapid-growing subcutaneous or less frequently intramuscular mass, sometimes with tenderness. The lesion is usually about 2 cm and no larger than 5 cm in adults and can be larger in size in some cranial lesions eroding the skull.

The lesion is typically a non-encapsulated nodular proliferation of spindle fibroblastic or myofibroblastic cells, usually associated with fascia underneath the subcutis. The lesional cells are characteristically fusiform or stellate shape with plump spindle nuclei arranged haphazardly, or in vaguely whorled or storiform pattern in a variably myxoid matrix (Figs. 7.77 and 7.78). The cellularity is quite variable. Mitotic activity is not uncommon in hypercellular area but there is lack of nuclear

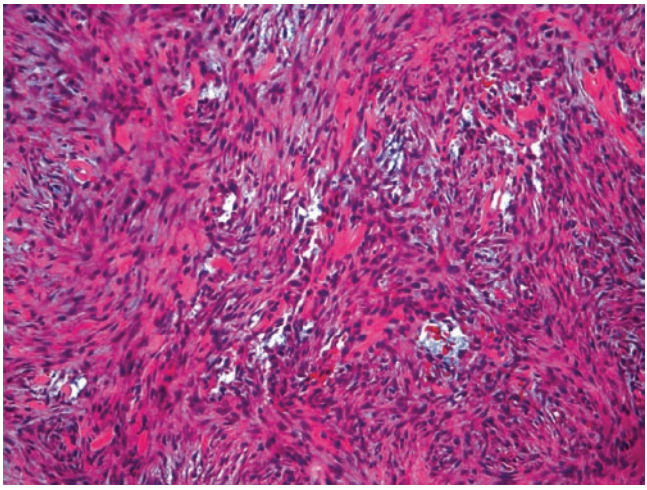

Fig. 7.77 Proliferation of fibroblastic or myofibroblastic type spindle cells in a haphazard, vaguely whorled or storiform pattern in a variably myxoid matrix

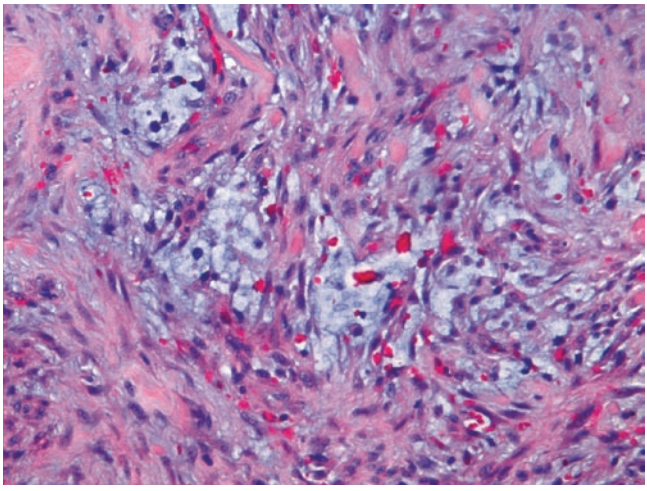

Fig. 7.78 The fusiform or stellate shaped lesional cells with plump spindle nuclei loosely arranged in myxoid matrix simulating fibroblasts in cell culture

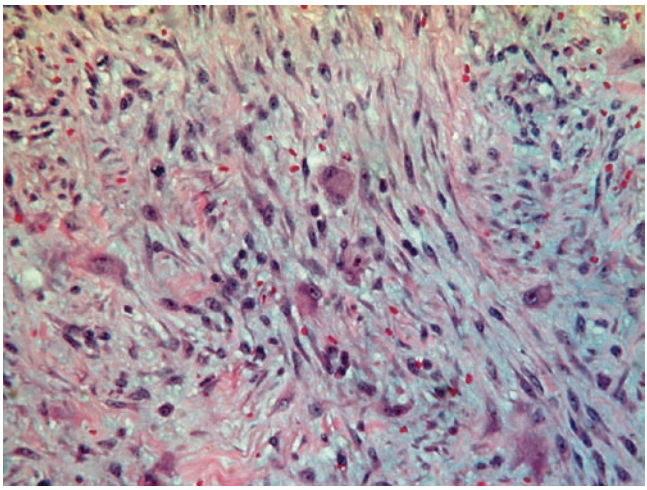

Fig. 7.79 Large ganglion cell-like fibroblasts in proliferative fasciitis

hyperchromasia, atypia or atypical mitotic figures. The lesion is commonly associated with extravasated red cells, chronic inflammatory cells and osteoclast-like giant cells.

Proliferative Fasciitis/Myositis

This benign fibroblastic/myofibroblastic entity is similar to nodular fasciitis in nature but is much less common than nodular fasciitis. It occurs in deep fascia and subcutis (proliferative fasciitis) or skeletal muscle (proliferative myositis). Clinical presentation is similar to that of nodular fasciitis.

The hallmark of this lesion is the presence of large ganglion cell-like fibroblasts in addition to other features seen in nodular fasciitis (Fig. 7.79). Atrophic multinucleated skeletal muscle cells are frequent. It is also less demarcated and more cellular than nodular fasciitis.

Suggested Readings

Enzinger and Weiss's Soft-Tissue Tumors, Sharon W. Weiss and John R. Goldblum, Editors, Mosby, 5th edition, 2008

World Health Organization Classification of Tumors: Pathology and Genetics, Tumors of Soft Tissue and Bone, Christophe Fletcher, K. Krishnan Unni, and Fredrik Mertens, Editors, IARC Press, 2002

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