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

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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

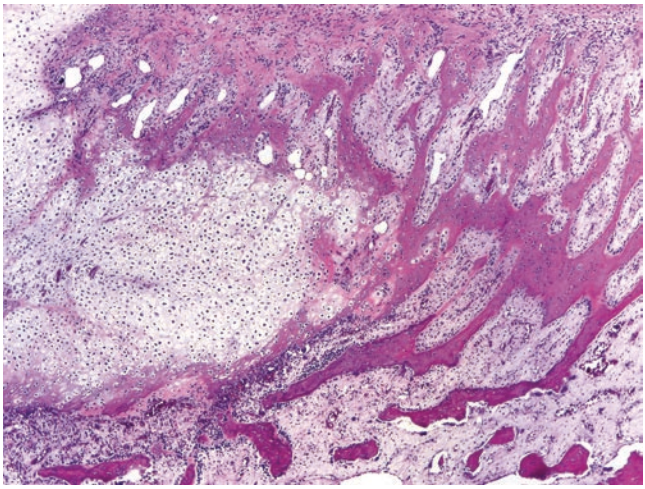

Fig. 2.1 Fracture callus showing reactive woven bone and cartilage. The presence of cartilage indicates that some amount of motion has occurred between the fragments. In completely immobilized fractures (such as after compression plating) there is no cartilage and union is by direct conversion of fibrous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

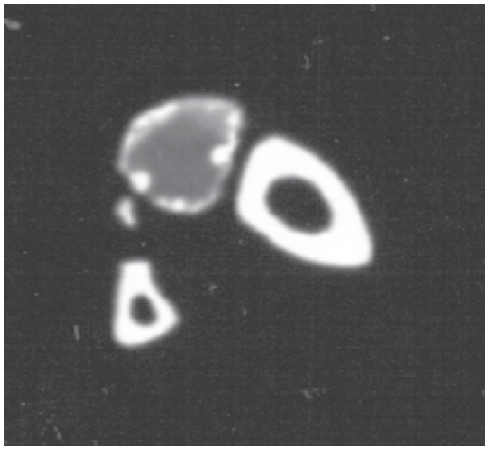

Fig. 2.2 A peripheral rim of bone is seen around a soft-tissue mass. The radiological features are characteristic of myositis ossificans. Extra-skeletal osteosarcoma would not show this zonation

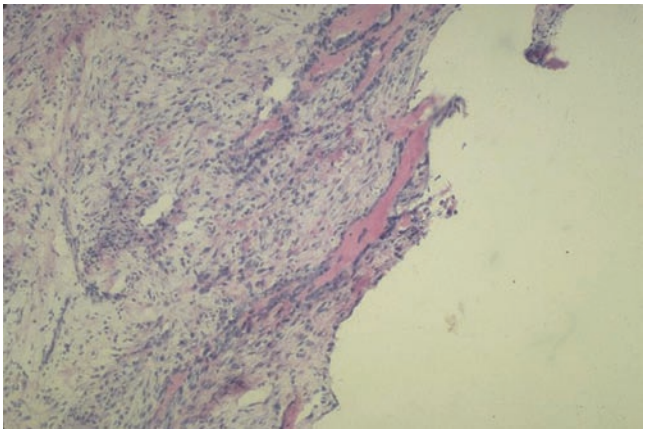

Fig. 2.3 Photomicrograph from a frozen section slide of a case of myositis ossificans showing a very cellular center and woven bone in the periphery (the histological equivalent of zonation). Biopsies taken from the center run the risk of misinterpretation as malignant if they are taken out of context

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.

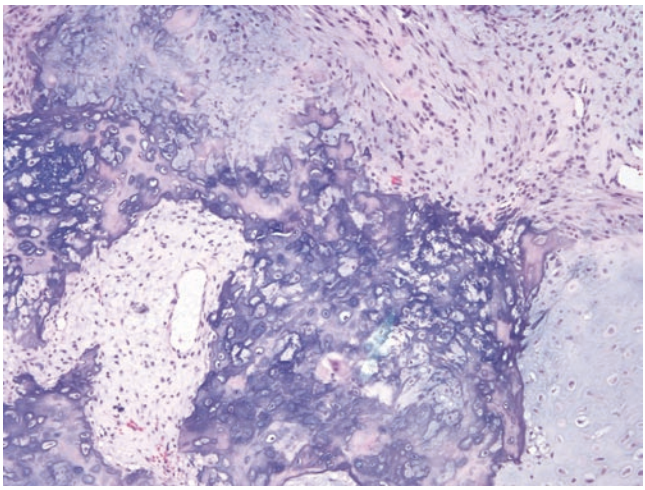

Fig. 2.4 Nora lesion (BPOP) showing a mixture of blue bone, fibrous tissue and cartilage

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.

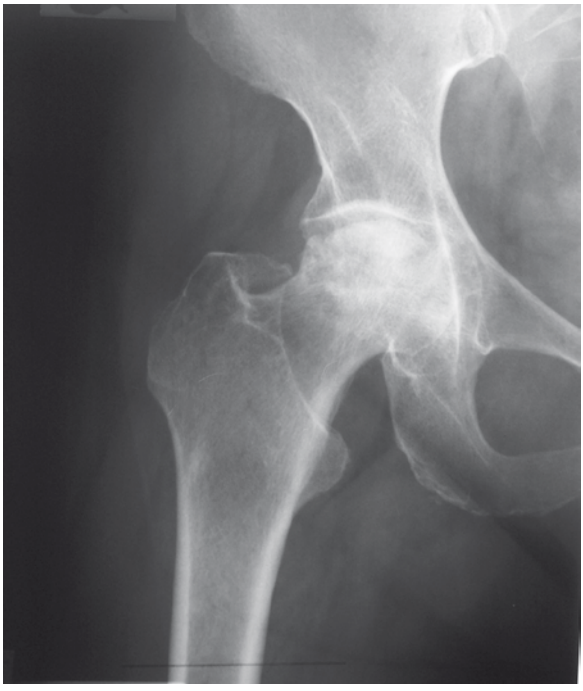

Fig. 2.5 Plain radiograph of osteonecrosis of the femoral head. The infarct shows segmental collapse and compression into the lower part of the femoral head

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

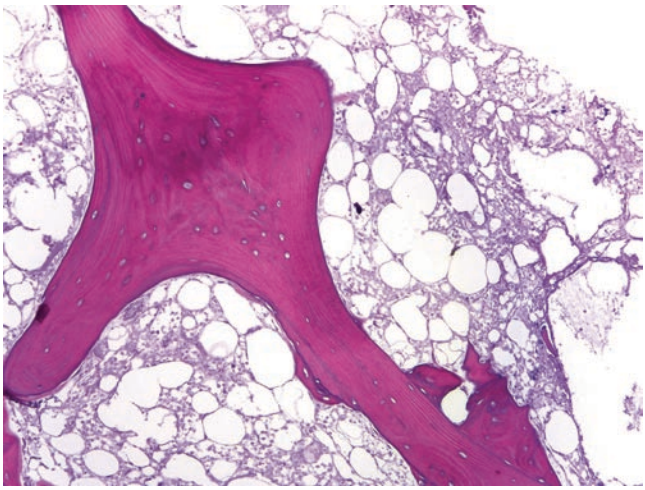

Fig. 2.6 Photomicrograph of dead bone showing empty lacunae and necrotic fat

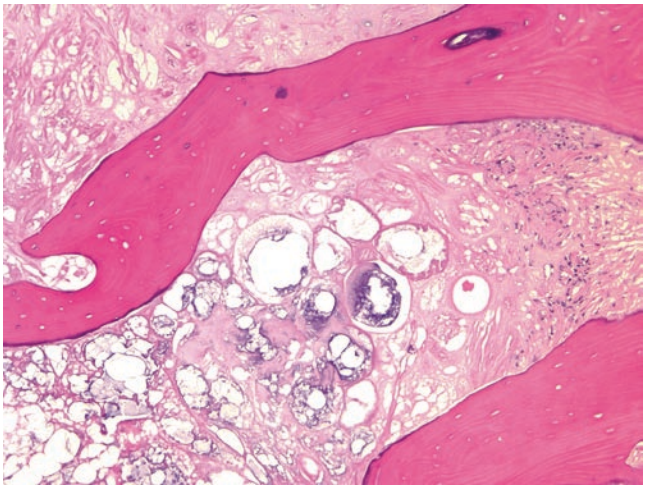

Fig. 2.7 Photomicrograph of an infarct showing dead bone and necrotic fat with dystrophic calcification

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

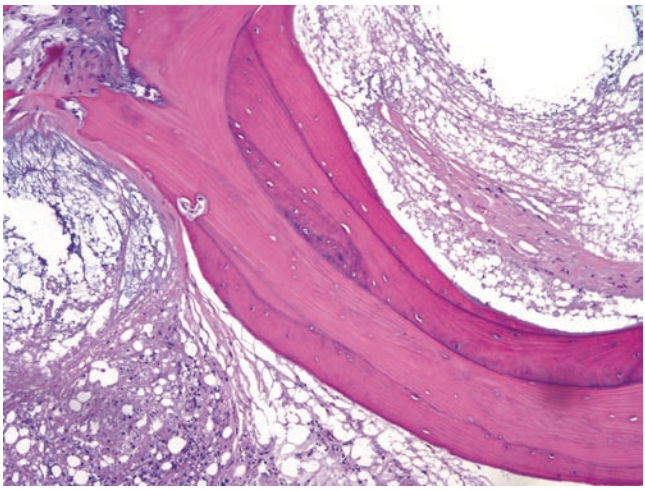

Fig. 2.8 Photomicrograph of dead bone with layers of reparative bone which contain viable osteoblasts

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.

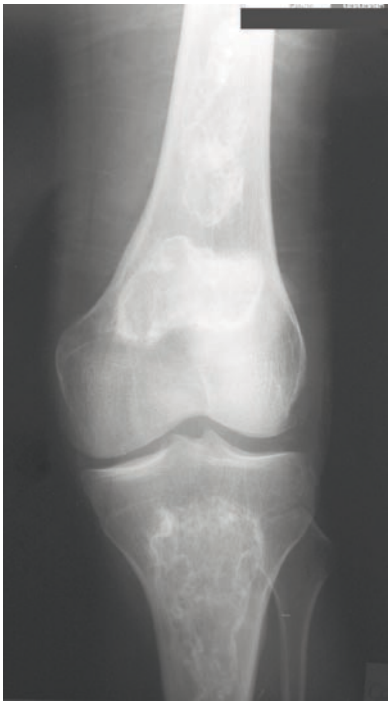

Fig. 2.9 Plain radiograph of the knee showing medullary infarcts in the tibia and femur. There are radiodensities in the pattern of "smoke rings"

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

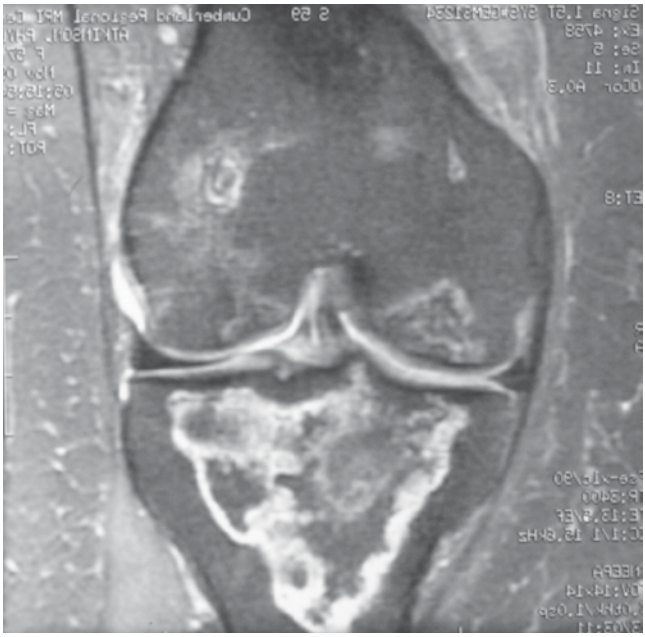

Fig. 2.10 A T2 weighted MRI showing infarcts of both the femur and tibia. The tibial infarct shows a high signal demarcating the area of dead bone

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

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