CHAPTER 1

DIFFERENTIATING METABOLIC, TRAUMATIC AND INFECTIOUS BONE DISEASE

Melissa Robitaille, DPM
Craig Camasta, DPM

Differentiating inflammatory bone diseases is a diagnostic challenge to the physician. Metabolic, traumatic, and infectious bone disease often manifest with similar clinical and imaging characteristics. Clinically, they may share similar signs and symptoms: erythema, edema, and pain. Radiographically and microscopically, they present as marrow edema and increased bone turnover, reflective of a similar reparative process.

Advances in diagnostic imaging has increased the sensitivity to identify a pathologic process, however, accurate diagnosis (specificity) is unreliable in 10-20% of the cases in question. Just as no test or combination of tests is truly specific for any disease process, non-invasive imaging is of limited use in the lower extremity. Radiologic interpretation, surrounding soft tissue inflammation, temporally variable and evolving presentation of a healing process, poor spatial differentiation and tissue averaging, limited sampling size, and extremes in variation of blood flow (hyper- versus avascular), lead to ambiguous and unreliable reports which can further confuse an already difficult diagnosis.

Differentiation between traumatic, necrotic, neuropathic, and infected bone ultimately requires a bone biopsy, and in many instances this can be successfully achieved without compromising the structural integrity or function of the limb. In certain instances, a definitive diagnostic and therapeutic procedure is warranted (distal digital disarticulation for diabetic ulcer with clawtoe) as it will both solve the problem and provide a definitive diagnosis. In other instances, a fine-needle bone biopsy and culture are recommended over en-block resection of a bony segment, as the later can violate the structural integrity of the weight-bearing limb.

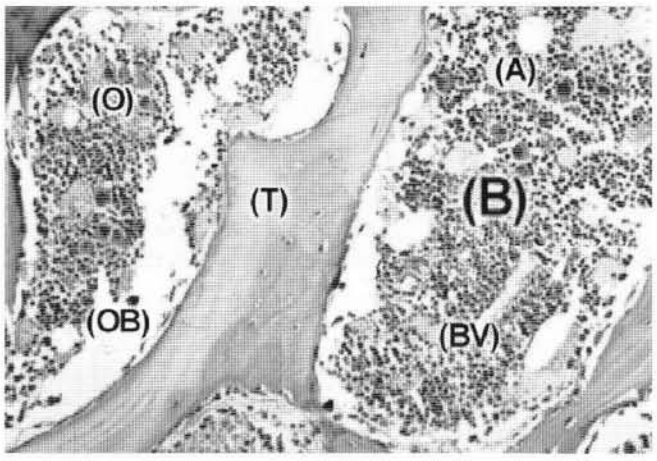

Figure 1. Normal anatomy of cancellous bone. There are several elements in the slide; bone trabeculae (T), bone marrow (BM) which contains adipose cells (A), blood cells (BV) and osteogenic cells (O). Osteoblast (OB) can also be seen and are lined up along the edge of the trabeculae.

Several presumptive diagnoses can be made based on key clinical and radiographic findings. If bone is exposed within an infected or necrotic wound, then the assumption should be made for osteomyelitis, until followed-up via bone biopsy and culture. If a wound has a chronic draining sinus with adequate vascularity, then one should assume either a retained foreign body or chronic osteomyelitis. If a patient has a warm and swollen foot with radiographic reactive bone changes, but no constitutional signs/symptoms of infection, and no history of open wound to the foot, then regardless of scintigraphy or MRI findings, one should be very hesitant to assume osteomyelitis. Also, laboratory findings alone should not be relied upon to assume an infectious process, as any acute phase of inflammation can present with leukocytosis and an elevated ESR/CRP.

The astute clinician must be suspicious of critical clinical findings, directed by plain radiographs, tempered with special studies, and reliant only upon the results of a biopsy, in order to accurately diagnose and treat the patient with inflammatory bone disease.

HISTOLOGY

Normal Bone

A short review of the normal anatomy of bone and the cellular response of inflammation is necessary to understand the pathogenesis of bone disease, and will aid in diagnosing these entities. The normal anatomy of the mature bone includes an outer cortical or compact bone and a central spongy or cancellous bone (Figure 1). Compact bone contains haversian canals, which are

vascular channels oriented longitudinal to the cortical surface, and Volkmann's canals, which are oriented obliquely (Figure 2, 3). Cancellous bone is supplied by end arteries, a network of anastomosing vessels, and a nutrient artery, entering the spongy bone at mid-shaft. Cortical bone is surrounded by periosteum, which consists of an outer fibrous layer and an inner cambium layer of fibroblast and osteoblast cells. The inner layer also contains proprioceptive and sensory nerve fibers. An understanding of the blood supply of bone may help to explain the extent and limitation of certain pathologic conditions.

Osteoblast is a bone-producing cell derived from mesenchymal osteogenic cells which are housed within the marrow. They have a high content of alkaline phosphatase, which can be elevated in the serum of patients who suffer from several metabolic bone diseases. When the osteoblasts are incorporated into the bone matrix, they house in a lacunae and are called osteocytes. Osteoclasts are multinucleated giant cells responsible for bone resorption (Figure 4). Osteoblast and osteoclast are part of the reparative process and are present in the majority of bone diseases. Osteoid is the unmineralized organic precursor matrix of bone. It is composed of collagen and proteins including bone morphogenetic protein. Bone is formed through mineralization of the organic matrix of the osteoid. Normal skeletal growth results from a balance between bone matrix synthesis and resorption, which can be disturbed in several pathological conditions.

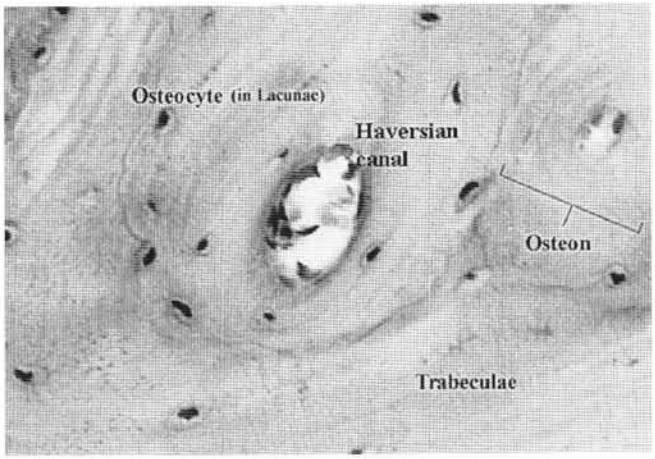

Figure 2. Normal anatomy of the compact bone containing haversian canals and osteocytes.

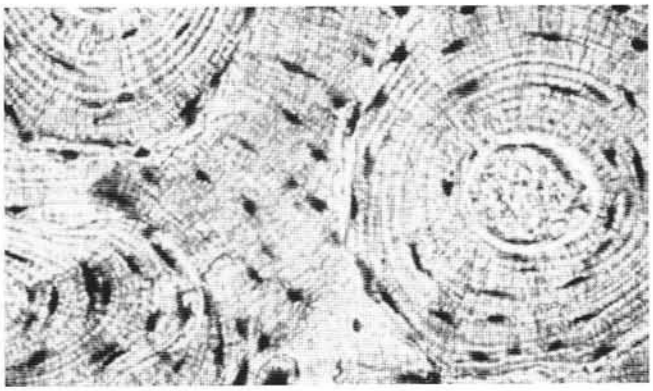

Figure 3. Haversian Canal is a vascular channel oriented longitudinal to the cortical surface.

PATHOLOGIC BONE

Neurotrophic Osteoarthropathy

Any disease which causes a loss of the sensory nerve function, which includes diabetes, syringomyelia, leprosy, Vitamin B12 deficiency associated peripheral neuropathy, and Charcot Marie Tooth disease, may lead to the development of neurotrophic osteoarthropathy. Diabetic neuropathy is the most common cause for a neuropathic joint in the foot and ankle. Leprosy seems to affect both the upper and lower extremities. Syringomyelia is a significant cause for neuropathic shoulder, elbow, and wrist joint disease.

Pathologic tissue analysis in the developmental or acute stage of a neuropathic joint will demonstrate fractures of the joint surface. As the disease progresses, pieces of cartilage and bone are ground up and shed into the joint space. In a neuropathic joint, once a fracture has occurred, the normal healing response with callus

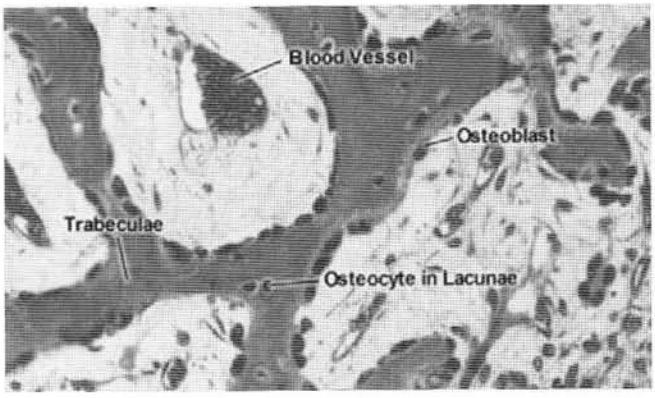

Figure 4. Reparative process of bone: Osteoblasts originates from osteoprogenitor cells which lay down bone matrix and stain pink. When they have secreted enough matrix to surround themselves in lacunae, they are called osteocytes. Osteoblastas and osteoclasts are part of the reparative process and are present in the majority of bone disease.

formation can be observed. However, in a normal joint, progressive healing will occur, but in a neuropathic joint, which frequently is not treated in its acute stage, further fracturing occurs. Thus, continued trauma causes continued fracture formation. There is continued healing, but deformity results. When deforming mechanical stresses are greater than the healing ability, the deformity progresses. Reparative and continued destructive changes are found in a specimen of a neuropathic joint. Undoubtedly, osteonecrotic fragments can also be seen because of the traumatic disruption of blood supply to a portion of the joint surface. A very reactive hyperemic synovium is also seen microscopically between the fragments of bone. This microscopic feature is typical for this disease, but may also be seen in cases of osteomyelitis and osteonecrosis.

In the coalescence or sub-acute stage of the disease, dense bone is observed and is a result of new bone formation. The late neuropathic joint (reconstructive stage) may be difficult to recognize as a joint. All the cartilage may be resorbed or fragmented, and the bone is sclerotic, rounded, and irregular. If visible, marked fibrous thickening of the joint lining is noted. The soft tissues around a neuropathic joint are stretched and torn. Chronic ligamentous instability results and the primary stabilizers of a joint may be lost completely. The dense bone observed is usually a prominent feature of theses cases. Both radiographically and pathologically, the bone is sclerotic.

Osteomyelitis

Acute. Acute osteomyelitis is defined as a clinically evident bone infection of a few days or weeks duration. If not treated, it may progress to chronic osteomyelitis, which may persist for a long time, even the lifetime of the patient. Except for mycobacterium and brucella species, bacterial osteomyelitis does not demonstrate characteristics features related to each specific organism. Ordinarily, multiple small abscesses are observed in a specimen of acute osteomyelitis. Necrosis of trabeculae may be oddly distributed within the microscopic examination. Abscesses may become confluent causing the formation of larger abscesses. The typical cells observed near the pyogenic infection are polymorphonuclear leukocytes (PMN), macrophages, and lymphocytes are also present in large numbers. Blood vessels are engorged with erythrocytes as well as increased numbers of white blood cells. One may also see small hemorrhages, probably due to the toxic injury to the blood vessel cells themselves. Granulation tissue is observed around the site of infection. Bone resorption induce by osteoclastic cells can also be seen in a specimen of osteomyelitis. This resorption can be quite dramatic and may explain the rapid dissolution of bone tissue observed radiographically. Cortical bone may become quite porotic in some cases. Resorption occurs around normal vascular canals throughout the cortex. These resorbed canals permit the formation of subperiosteal abscesses, which occur commonly with osteomyelitis. Resorption of bone creates the space for abscess cavities within cancellous bone

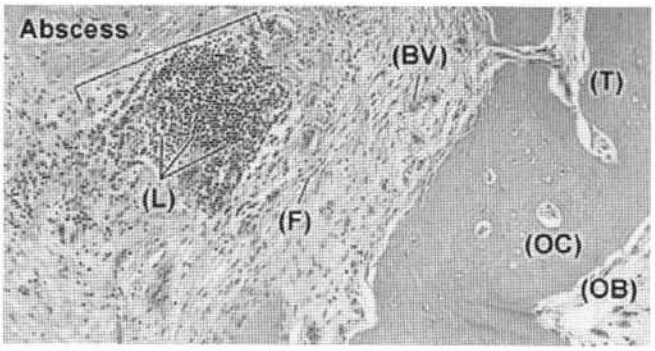

Figure 5. Chronic Osteomyelitis. Note the fibrosis (F) of the marrow as the infection becomes dormant. Chronic inflammatory cells are present which are predominantly lymphocytes (L). A walled off abscess is noted. Trabeculae (T), Osteoblast (OB) and osteocytes in lacunae (OC) are also noted.

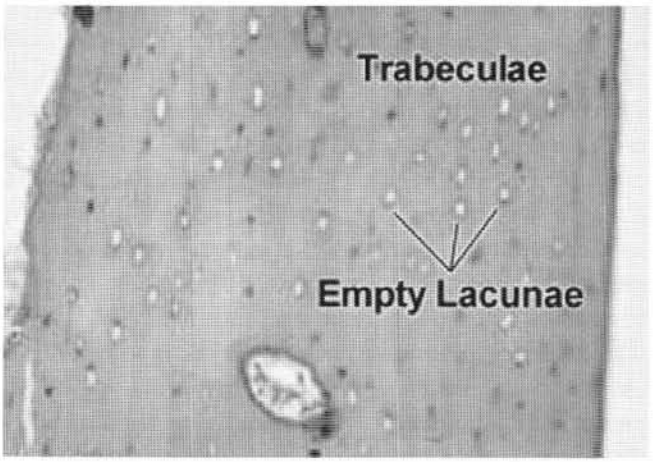

Figure 6. Osteonecrosis. Dead bone is indicated by the necrotic osteocytes with empty lacunae.

tissue. Where bone is alive, a reactive bone marrow is observed. Reactive resorption of bone may also be seen at a distant site from the site of infection. As seen in osteonecrosis, the bony sclerosis observed in osteomyelitis is a reparative response to reinforce the weakened bone. Pathologic fracture may occur through weakened bone.

The process of infection yields a rapid formation of pus, which is a combination of necrotic leukocytes, bacteria, tissue debris, surrounded by inflammatory granulation. The accumulation of these byproducts may interfere with the circulation of involved segments of bone. Necrosis of normal tissue in an important pathologic feature of infection, and necrotic bone in combination with the presence of bacteria and defense cells will reflect the pathogenesis. In soft tissue, the necrotic portion of the involved organ turns into a semi-liquid structure, which can be walled-off from normal tissue by fibroblastic tissue. Until the infection has been controlled, the mass of expanding necrotic debris is an enlarging abscess. Bone is different from all other tissues because of its three dimensional mineralized structure that persists even when the tissue cells lose their blood supply. Necrotic bone can become a honeycomb in which bacteria reside, separated from defense cells indefinitely. This special characteristic of bone permits chronic osteomyelitis to persist for extended lengths of time. On the other hand, cartilagenous tissue is only slightly more resistant than bone to the effects of infection. Ordinarily, infection passes into the joint by traveling around the edges of the articular cartilage, rather than through the articular surface as in the case of a septic joint.

Infection may occur via different routes and because of the periosteal circulation around the bone, soft tissue infection can pass into the bone from the periosteum, and vice-versa. The susceptibility to osteomyelitis depends on a number of factors, including the age and general health of the patient, the capability of the body to mount an immune response, the size of the bacterial inoculum, tissue injury and coverage, vascular viability of the bone and surrounding soft tissues, and the presence of a retained foreign body.

Chronic. Chronic osteomyelitis is defined as an area where the infection becomes dormant within the bone. In chronic osteomyelitis, revascularization is marked by the presence of granulation tissue, similar to the reparative process that occurs when the marrow of a subchondral bone infarct becomes revascularized. Dead bone is resorbed by osteoclasts and other dead tissue is removed by mononuclear phagocytic cells. Some fibrosis occurs, but dense scar indicates persistent infection. Histologic sections of chronic osteomyelitis may vary with the location from which the tissue is obtained and the type of bone which is affected. If cortical bone is affected, there may be resorption of bone with enlarged vascular channels (which parallel the normal longitudinal and oblique orientation of haversian channels). Such changes can sometimes be detected in cortical bone radiographically as osteopenic intra-cortical tunneling. Bone marrow contains a considerable number of inflammatory cells and appears to be hypervascular and reactive. Necrotic leukocytes and pus may be present. PMNs are replaced by lymphocytes and plasmocytes in well establish cases (Figure 5). Again, both active bone resorption and new bone formation can be identified in all but the most chronic cases. Fibrosis of the bone marrow is a feature of older more quiescent disease in which the hypervascularity of a more active infection has resolved. Microscopic foci of bone necrosis may still be present. If a cavity has formed, it will be lined with scar tissue containing pockets of inflammatory cells. A chronic bone abscess which has been walled-off by sclerotic bone usually contains both necrotic and viable white blood cells.

Chronic osteomyelitis is usually associated with intermittent episodes of active inflammation. Ackerman describes that osteomyelitis may be acute, subacute, or chronic, and the designation is made based on the duration of the disease rather than the microscopic composition of the inflammatory infiltrate, since one may find PMN cells in a specimen of early chronic osteomyelitis. In the more chronic cases, the majority of inflammatory cells usually seen are lymphocytes. Bone necrosis (sequestrum) can also be seen in a specimen of chronic osteomyelitis, and this sequestrum can be surrounded by reactive new bone, which may form a thick shell around dead bone. In a chronic draining ulcer, the sinus tract by which the drainage leaves the bone may become epithelialized from the skin, and a thick layer of keratin can form along the tract because of chronic irritation. In some case, chronic irritation and continuous drainage is associated with the development of squamous cell carcinoma. Squamous cell carcinoma can present as bone destruction present along the sinus tract.

Trauma

Vascularized. Injury to bone can occur in any location and through a variety of causes, either via a macro-traumatic event in which there is obvious cortical disruption, or through a more subtle stress injury to the bone. Even the most occult fracture can be seen microscopically. In a specimen of fractured bone, a hematoma both within the bone and surrounding the fracture site

can be seen. The inflammatory cells observed at acute frature sites include PMNs, lymphocytes, macrophages, mast cells, plasma cells, and giant cells. Fibroblasts are also a component of the vascular granulation tissue. The cells of the hematoma also include progenitor cells which differentiate into osteoblasts and chondroblasts. While phagocytic cells are removing the injured tissue and non-cellular debris, osteogenic repair tissue is forming from the surfaces of bone, bone marrow, and surrounding soft tissue. These osteogenic cells proliferate and migrate into the fracture to form three types of callus - periosteal, intracortical, and endosteal. Both bone and cartilage callus are formed. Cartilage is formed within that portion of the callus where motion is present. Microscopic bridging of the fracture gap is necessary for healing to occur. As healing occurs, mineralization of the cartilaginous and osseous callus develops to stiffen the fracture site. With time, this osseous tissue will convert to lamellar bone.

As discussed, an acute injury to a major cortical bone affects not just the bone itself but the surrounding soft tissue and circulation. Fortunately, there are many anastamotic channels bringing circulation to bone (including the periosteal cells), such that major devascularization of bone occurs uncommonly in closed fracture.

Avascular. Osteonecrosis of bone is an important component of many different forms of bone disease, including neurotrophic osteoarthropathy, osteomyelitis, and trauma. Infarcted bone is an ideal site for localization of an infection, and it may be difficult to differentiate whether a bone infarction preceded or followed an associated infection. Bone infarct can occur in the subchondral plate around a joint, in the medullary canal, and also intracortically, which as the least common occurrence. Histological changes of bone necrosis are cellular swelling, necrotic osteocytes with empty lacunae, calcification of fat tissue surrounding the infarct, and intravascular thrombosis (Figure 6). The articular cartilage overlying the infarct is normal except in the later stages of the disease. Microscopically, during the reparative process, it is typical to see osteoclastic activity on one side of the dead trabeculae and osteoblastic activity on the other.

Revascularization of necrotic bone involves an invasion of the necrotic bone marrow by fibroblastic granulation tissue, which contains cells that can differentiate into osteoclasts (to remove dead bone), osteoblasts (to produce new live bone), and macrophages (to remove soft tissue debris). Spontaneous revascularization across a fracture line in dead tissue is rare because revascularization appears to be blocked by the fracture gap. A fibrocartilagenous callus may form to partially immobilize the dead segment, but it is usually not sufficient to permit blood vessel invasion into the dead bone. Surgical bone grafting and immobilization can permit stability and revascularization of the infarcted bone.

Inflammatory cells (PMNs and lymphocytes) can be found in a specimen of bone necrosis, similar to that which is seen in acute and chronic osteomyelitis, however, in osteonecrosis and in chronic osteomyelitis there is a predominance of lymphocytes over PMNs, whereas in acute osteomyelitis or acute trauma there is a predominance of PMNs. In osteonecrosis the inflammatory cells can lose their nuclear activity/staining due to their sensitivity to ischemia, whereas in osteomyelitis there may be osteonecrosis as well, but the majority of inflammatory cells will remain viable and maintain their nuclear activity/staining. A loss of staining of nuclear structure can be noted around 2 weeks following bone necrosis, therefore, the correct diagnosis of osteonecrosis is made only after pathologic examination of the excised specimen.

CLINICAL SIGNS AND SYMPTOMS

In an acute setting, traumatic, necrotic, neuropathic, and infectious bone disease can share similar signs and symptoms: erythema, edema, and pain. Although pain is often a presenting feature with any of theses bone disease, it is typically less marked than the degree of involvement in the neuropathic patient. While these patients present with sensory deficits, they may also have acute pain, which is distinguishing and noteworthy in a previously neuropathic patient who may also have an adjacent, asensate, neurotrophic ulceration. Acute bone pain is often not a presenting complaint of AVN of the medullary and intracortical bone. On the other hand, a subchondral plate infarct can be noticeably painful for the patient, especially with joint usage. One exception to this is found in the sickle cell patient who may have severe acute bone pain for any given location of the infarct. In an infectious process, systemic signs including fever, chills, and nausea may be noted, although theses signs tend to be more insidious in the immune compromised patient. In the foot, local signs of inflammation will be present, however, fever and/or leukocytosis is less common, and will only be noteworthy in approximately 33% of cases.

In the chronic setting, traumatic, necrotic, neuropathic, and infectious bone disease can differ in its clinical presentation, and the degree to which the injury has or has not healed will influence the appearance of the extremity. In a traumatic situation, the fracture will

eventually heal, and less pain, swelling, and warmth will be noted. On the other hand, the most frequent presenting sign in chronic osteomyelitis is a persistent sinus or ulceration with drainage, pain, and swelling. Small pieces of dead bone (sequestrum) may be discharged spontaneously from the sinus tract. Patients with fever or acute inflammatory signs can have an acute flare-up of cellulitis over the chronically infected bone.

LABORATORY FINDINGS

An elevated white cell count, a shift of the differential to the left, and an elevated ESR or CRP are pertinent laboratory findings that could be found in all acute inflammatory processes such as traumatic, necrotic, neuropathic and infectious bone diseases. As the disease progresses the signs and symptoms will decrease with the exception with chronic osteomyelitis where the ESR and CRP tends to stay elevated. The demargination of WBC from the vessel wall into the blood stem is responsible in part for the elevated WBC seen after an acute inflammatory process.

RADIOGRAPHY

Neurotrophic Osteoarthropathy

In the pre-developmental stage of neurotrophic osteoarthropathy, radiographs may only show an increase in soft tissue density. An acute fracture may be present with a history of trauma. In the developmental phase, subtle changes in the alignment of the foot/ankle can be noted if comparison is made with previous radiographs. Fracturing of bones around a joint with associated soft tissue swelling may be noted and progressive fragmentation of a particular bone may develop, but other fractures may heal. In the coalescence phase, the loose pieces of broken bone that are shed into the joint become attached to the very reactive hyperemic synovial lining of the joint. Together with the reattachment and resorption of bone fragments by the joint lining is the formation of new bone. Marked sclerosis of the residual bone which borders the joint is eventually seen. Continuous remodeling and bone sclerosis is noted in the later reconstructive phase of the disease. Disuse osteoporosis may occur in certain individuals after NWB treatment.

Osteomyelitis

Acute. Early diagnosis of osteomyelitis should be based on the history and clinical suspicion rather than radiographs. After a thorough history and physical examination, conventional radiography should be the initial modality for the work-up of osteomyelitis because it can, at minimum, determine whether another underlying, more obvious pathologic condition exists (ie fracture). The earliest radiographic finding is deep soft tissue swelling that may cause obliteration of tissue planes. In cases in which osteomyelitis is the result of spread of infection from a contiguous source, the initial radiographic manifestation is a periosteal reaction. Other diagnoses to consider when viewing a periosteal reaction include post-traumatic periosteal reaction and non-specific periosteal reaction (e.g. chronic venous stasis. Radiographs do not show bone abnormalities in cases of osteomyelitis until the infection has been present for at least ten days after the onset of infection, because a 30 % to 50% loss of bone density must occur before a radiograph becomes abnormal. Periosteal elevation, disuse osteoporosis, and destructive resorptive changes in the original bone are seen as the disease progresses.

Chronic. In chronic osteomyelitis, radiographs demonstrate a decrease in soft tissue swelling and relatively dense sequestrated dead bone, and the thick organized shell of new reactive bone, the involucrum, that forms around it.

Plain films have a lower sensitivity than other methods, but a specificity that is comparable to bone scans. False-positive radiographs are often associated with neuropathic joints, stress injury to bone, or degenerative or inflammatory arthritis.

Computed tomography (CT) can be a useful adjunct to conventional radiography for selected patients who have osteomyelitis. CT studies provide for the reliable detection of cortical destruction, periosteal proliferation, and soft tissue extension, and may be useful even when radiographs are normal. CT is especially helpful in detection of bony sequestra in chronic osteomyelitis. Osseous manifestations of inflammatory conditions that can be seen on CT images include hyper-attenuation of the medullary cavity, destruction of cortical bone, new bone formation, sequestra, and intraosseous gas, but the increase in intramedullary density seen on CT is nonspecific and may be seen in conjunction with infections, hemorrhage, neoplasm, stress fracture, or radiation. Of added benefits is spiral CT which permits high-resolution 3-D and multi-planar reconstruction artifacts.

Trauma

Vascularized. Conventional radiographs are adequate for the detection and staging of the majority of foot and ankle fractures. Other imaging methods may be useful when high quality plain films are negative and clinical suspicion for acute fracture remains high. The radiographic changes seen are dependent on the age of the lesion, and in the acute setting obvious cortical disruption may be seen. As the fracture heals, progressive calcification of the callous will form, and bridging of the fracture gap and disappearance of the radiolucent fracture line will be evident. Fractures which are treated by rigid internal fixation will most likely exhibit less callous with direct bone healing of the fracture. After bridging has occurred radiographically a period of remodeling of the bone occurs. This remodeling can be identified on radiographs by radiolucency and radiopacity signifying bone resorption and new bone formation respectively.

Avascular. The radiographic changes seen with avascular necrosis depend on the age of the lesion and the degree of reparative activity of the bone. The early degenerative process of a bone infarct may induce no radiographic changes and may not reveal abnormalities for several months. Early detection can only be done through special imaging or histological examination. The second stage is the creation of a reactive border, which separates the infarct from the live bone. Radiographically, this can be seen as an increase in bone density. The third stage, revascularization, is caused by the surrounding live osteogenetic cells that proliferate, and circulatory hyperemia occurs, and the dead bone is replaced with new bone. This reparative process can often be seen on radiographs and presents as a transient local osteoporosis or decrease in bone density. New bone formation growing in apposition to dead trabeculae (creeping substitution) leads to an increase in bone density on radiographs. The process of re-ossification is often irregular, and the combination of incomplete resorption of dead bone and focal deposition of new bone can result in a mottled and irregular radiograph appearance.

A bone infarct, as opposed to other organ infarcts in the body, may completely revascularize and resume a normal tissue structure. For this reason, it is important to protect the bone from structural stress when avascular necrosis is suspected. If no revascularization occurs, a very sclerotic wide band of bone, which can be seen radiographically, forms between the viable and non-viable bone, and may fracture.

And finally in the later stages of osteonecrosis, one may observe osteoarthritic changes in an affected joint with concomitant cartilage collapse and osteophyte formation. A serial sequence of radiographs is important to demonstrate the different stages of the disease, and without prior radiographs, it might be quite difficult to identify the original disease process underlying the osteoarthritis.

SCINTIGRAPHY

Any form of bone imaging scan which is sensitive to the cellular and metabolic response of inflammation will be non-specific in differentiating between traumatic, neuropathic, and infectious bone diseases. Although newer techniques and methods of analysis gain in specificity, none alone or in combination approach the specificity of a bone biopsy, lending to the possibility of a false positive result.

It is also noteworthy to point out that any imaging scan requires a minimal degree of vascularity and appropriate immune response, and any diminution in either requirement (adequate blood flow and immunogenicity) will impair the results of such study, possibly leading to a false negative result.

Neurotrophic osteoarthropathy

Three classes of tracers are predominantly used to diagnose bone disease: 1) technetium 99m diphosphonates; 2) gallium 67 citrate , and 3) autologous leukocytes labeled with indium 111 or technetium 99m hexamethylpropylenamine oxime(HMPAO). The four phases bone scan are 1) the flow or angiogram phase; 2) blood pool phase; 3) 3-hour delayed image; and 4) 24-hour delayed image. The three-phase bone scan can suffice for the detection of Charcot arthropathy if an infectious process is not suspected. During the developmental and coalescence phase of neurotrophic osteoarthropathy, an increase uptake will be present in the first three phases with a progressive and focal concentration of the bone involved in the 3-hour delayed image. In the late reconstructive phase of the disease, an increase uptake will still be noted in all three phase with a more diffuse uptake of the involved bone signifying a more quiescent remodeling of bone. The specificity of bone scintigraphy varies greatly and on a bone scan, neurotrophic osteoarthropathy can not be distinguished from stress fracture, gout, degenerative joint disease, postsurgical changes, healing fracture, or noninfectious inflammatory reaction or even osteomyelitis. Basically, bone scan can not distinguish between any bone pathology that involves reactive bone or bone turnover.

For detecting osteomyelitis versus neurotrophic

osteoarthropathy, one study used a combined bone scan and 111In-WBC. Their study involved 35 patients who had radiographic evidence of neuropathic joint disease and clinically suspected osteomyelitis. The results indicated 100% sensitivity for 111In-Wbc detecting osteomyelitis and 83% specificity. The authors concluded that since Indium 111 leukocytes do not generally accumulates in area of increased bone turnover, they do not accumulate in uninfected neurotrophic osteoarthropathy. They recommend using the combined bone scan and 111In-WBC study for the detection and localization of infection to soft tissue or bone in patients with neurotrophic osteoarthropathy disease. Tc 99 HMPAO can also be used as a radiolabeled WBC agent if osteomyelitis is suspected. The drawbacks in using labeled WBC are: the labeling process is complex, and there is a high dose of radiation when using Indium 111 labeled WBC; and Tc 99 labeled WBC is less stable and can be excreted which could obscure the abdominal cavity.

Osteomyelitis

Acute. Acute osteomyelitis causes an increased uptake in the earlier phases of a bone scan and a focal intense uptake of the involved bones on delayed images. When a suspected case of osteomyelitis is superimposed on an abnormality that causes an increase in bone turnover, a three phase bone scan loses specificity, and a leukocyte labeled WBC (In 111-, Tc 99 HMPAO) study should be considered. Since leukocyte labeled WBCs are not usually incorporated into an area of increased bone turnover, they are reported to be specific for infection. The combination of bone scan and leukocytes labeled WBC (In-111 or Tc-99 HMPAO) have shows to be useful for the detection of osteomyelitis in complicated cases where an increase bone turnover may be superimposed on the infection. In a study of 22 diabetic patients with clinical suspicion of foot/ ankle infection, using biopsy for culture and clinical course for reference, the combination of three-phase 99m Tc-MDP and 111 In-WBC scan had the highest diagnostic efficacy (100% sensitivity, 80% specificity, and 91% accuracy), followed closely by 111In-WBC alone (100% sensitivity, 70% specificity, and 86% accuracy).

Another challenge is to determine whether an infection is localized to bone or soft tissue only. Cellulitis is characterized on bone scan by initial soft tissue uptake in the flow and blood pool phases, with mild and diffuse uptake in the third phase. Schauwecker conclude that for diabetic patients with clinical suspicion of osteomyelitis but no radiographic findings of the disease, 111In-WBc alone is an appropriate nuclear medicine evaluation to detect infection. However, in an area of 111In-WBC uptake is present, a simultaneous 99 Tc-MDP scan is often helpful in providing the anatomic correlation to differentiate osteomyelitis from infection that is limited to soft tissue.

The accuracy of combined 99 Tc-MDP and 111 In-WBC scans for detecting infection varies with the age and location of the infection. It is very useful in the peripheral skeleton that could be an advantage to the podiatric physician. Lesions with high WBC uptake tend to be acute osteomyelitis, and the sensitivity of the WBC scan is 98%. One study concluded that a definitive WBC abnormality in diabetics patients with ulcers with abnormal bone scan and plain films had a sensitivity of 73%, a specificity of 91%, and positive predictive value of 89% for osteomyelitis. One study concluded that MPD-WBC scanning is more specific in possibly infected Charcot arthropathy than MR imaging. Yu mentions that a positive 111In or HMPAO scan should be considered a false positive for osteomyelitis unless positive uptake is demonstrated at 24 hours.

Chronic. Chronic osteomyelitis is especially difficult to localize on a bone scan because of the fibrosis, decreased vascularity, and less avid localization of leukocyte labeled WBCs, making the sensitivity and specificity of WBC scanning less favorable, approximately 50%. Chronic osteomyelitis will cause a slight increased isotope uptake in all phase of a bone scan and leukocyte labeled WBC. Several studies show that the images of acute osteomyelitis are more intense than those of chronic osteomyelitis, because of the quiescent phase of the disease.

Trauma

Vascularized. The site of a recent trauma usually shows an increase radionuclide accumulation. The uptake of tracer steadily increases with time due to the increase vascularity and bone turnover at the fracture site. Within 72 hours, all fractures are demonstrable on bone scan. The integrity of osseous blood supply to regions distal to a fracture site may also be evaluated on a bone scan. In areas where the blood supply has been compromised, decreased radionucleotide accumulation will be noted. In an old injury or as the fracture heals, the concentration of isotope at the fracture site should decrease, and eventually return to normal in 6-18 months. Bone scans prove valuable in localizing the site of a suspected stress fracture, where plain films are often negative. Persistent uptake at the fracture site beyond 18-24 months after injury suggests a non-union

Avascular. A "cold spot" is a photopenic zone or isotope-deficient zone that is caused by interruption of blood flow to the area. This can be seen in cases of

avascular necrosis secondary to trauma, chronic infection, sickle cells disease, or any disease that could potentially affect the circulation. It should be noted that an increased uptake of the isotope around the "cold spot"/photopenic zone can be seen and is secondary to concentration of the isotope surrounding the lesion because of reactive hyperemic bone.

MRI

Charcot

The diagnosis of Charcot osteoarthropathy is readily accomplished through physical examination and plain film radiography. The role of MRI is commonly reserved for concurrent complications such as infection with associated bone fragmentation, periosteal changes, articular disruption, and soft tissue involvement. The early changes of neurotrophic osteoarthropathy seen on MRI are manifested as a decrease in signal intensity confined to the marrow on T-1 and slight increase signal intensity on T-2 weighted sequence, and marked increase on STIR sequences. As the disease progresses, the signal for T-2 and STIR weighted images will not be as intense. Bone fragmentation and coalescence will also be seen with articular disruption in the later stages. The differentiation of neuropathic osteoarthropathy from associated infection is difficult, but can be accomplished by analysis of cortical bone and periosteum, where cortical bone and periosteal disruption are more commonly seen in infection.

Osteomyelitis

Acute. Magnetic resonance imaging (MRI) evaluation of osteomyelitis generally uses T-1 and T-2 weighted images, often supplemented with short-tau inversion recovery (STIR) or fat saturated fast spin echo T2-weighted sequences. MRI is sensitive for the early detection of osteomyelitis because of the contrast it typically provides between the abnormal and normal bone marrow. Although MRI is extremely helpful in differentiating soft tissue edema, inflammation, and cellulites, from osteomyelitis in long bones, it should be noted that other conditions, such as noninfectious inflammatory and metabolic conditions of osseous tissue, bone contusion, healing fracture, osteonecrosis, and metastasis can simulate T-1 and T-2 signal alterations to those seen in osteomyelitis.

Characteristically, a focus of osteomyelitis demonstrates low signal intensity on T-1 weighted images and high signal intensity on T-2 weighted, STIR, or fat-saturated sequences. This contradistinction, in cellulites, the edema is confined to soft tissue and is not associated with bone marrow signal alterations. The STIR pulse sequence is considered highly sensitive for abnormalities, with a negative predictive value for acute osteomyelitis approaching 100%. Sensitivity and specificity of MRI for osteomyelitis range from 60% to 100% and 50% to 90%, respectively. A study using MR to detect osteomyelitis in the diabetic foot had a sensitivity of 90% and specificity of 71%, all confirmed by histological diagnosis. They concluded that marrow edema could not be reliably distinguished from osteomyelitis with MRI. The results were not improved by the use of a contrast medium.

Of all the available imaging modalities, MRI has the highest accuracy for diagnosing osteomyelitis in the diabetic foot. MRI showed a sensitivity and specificity of 82% and 80%, respectively, in diagnosing osteomyelitis in diabetics, and 89% and 94%, respectively, in nondiabetics. Although in many instances the diagnosis of osteomyelitis may readily be made on long bones, this diagnosis may pose a challenging task in the small long bones of the distal extremities in patients with severe anemia and other marrow replacing conditions. It should be cautioned that the bone marrow finding of acute osteomyelitis on MRI is nonspecific. However, the more profound the T-2 signal intensity in the bone marrow is, the more likely the abnormality is acute osteomyelitis. In addition, the use of MRI for following an infection's response is limited and remains to be defined.

Chronic. As mentioned earlier, chronic osteomyelitis is described as an area of dormant infection in which bone remodeling and marrow fibrosis occurs. Sequestrum and sinus tracts may also be present. On MRI, theses findings are identified as follows: a sequestrum will show an area of decrease signal intensity (similar to cortical bone), and a sinus tract will be identified as a linear area of increase signal on T-2 weighted sequence that extend from the bone to the skin surface. A foci of chronic osteomyelitis may also demonstrate a "rim sign" which consists of fibrous tissue that is identified as a well-defined rim of decreased signal intensity surrounding the area of focal, active, disease. However, this sign was demonstrated in 93% of chronic osteomyelitis cases secondary to trauma, not diabetes. An area of acute infection is distinguishable from fibrous marrow by signal characteristics described for acute osteomyelitis. The fibrous marrow found in a chronic disease appears as a decreased signal intensity on T-1 and slight increase signal intensity on T-2.

Trauma

Vascularized. The role of MRI in the detection and characterization of occult injuries plays a role in a sense that it has the advantage of evaluating the soft tissues, including growth plate disturbances, as well as the bony structures. The classic appearance of a stress fracture on MRI is a linear decrease in signal intensity on T-1 surrounded by a diffuse area of lower signal intensity. Typically, the linear component remains dark on a T-2 sequence but the surrounding zone becomes bright. As healing occurs, callous formation may be seen bridging the fracture, and appears as an intermediate signal.

Avascular. The hallmark of medullary bone infarction on MRI is the appearance of a reactive interface between the viable and non-viable tissue. This interface is demonstrated as a well-defined low signal intensity line at the margin of the necrotic bone on T-1 weighted image. This line is actually represents granulation tissue that replaces the fat in the medullary bone. On a T-2 weighted image, a " double-line" sign appears, which is though to represent a layer of granulation tissue and mineralization. This double-line or serpentine line has high signal intensity in its inner margin and low signal intensity in its outer margin. Staging systems using MRI has been proposed in the literature to better understand the pathophysiology of osteonecrosis. Three stages are described: Class A demonstrates a necrotic segment of bone that is similar to fat tissue - high signal on T-1 and intermediate signal on T-2; Class B MRI demonstrates a sub-acute hemorrhagic segment and shows a pattern on MRI that is similar to blood - high signal on both T-1 and T-2; Class C shows a decrease signal in T-1 and high signal on T-2 because of the accumulation of fluids within the necrotic tissue segment, and finally as the disease progresses, fibrosis and sclerosis predominates in the segment of bone and demonstrates decreased signal intensity on T-1 and T-2 weighted images.

CLINICAL RELEVANCE AND RECOMMENDATIONS

Many diagnostic tools are available to the clinician, the most important of which are clinical acumen based on experience and common sense. Accurate history and physical examination, combined with plain radiography, will be most useful in formulating a treatment plan that is most prudent and cost-effective. At the same time, the judicious use of special studies should add useful information that directly influences the treatment plan, rather than cloud the diagnosis.

At best, the clinical usefulness of special imaging studies remains speculative. Most authors and reports focus on sensitivity and specificity, and although the accuracy for diagnostic reliability has increased in recent years, there still remains a significant number of false positive and false negative results. Differentiating traumatic bone diseases (neuropathic, vascularized and avascular traumatic) from infectious bone disease remains the highest priority in clinical practice, as the treatment courses diverge irreparably. In clinical practice, the decision-making dilemmas lie in the difficult to diagnose cases, not the obvious. Therefore, a summary of the literature of the past quarter century demonstrates the following shortcomings:

- The inaccuracy of plain films alone in diagnosing acute osteomyelitis is 95-97%.
- The inaccuracy of plain films alone in diagnosing chronic osteomyelitis is 30%.
- The inaccuracy of bone scan alone in diagnosing acute osteomyelitis is 40%.
- The inaccuracy of bone scan alone in diagnosing chronic osteomyelitis is 39-50%.
- The inaccuracy of labeled WBC alone in diagnosing acute osteomyelitis is 14-30%.
- The inaccuracy of labeled WBC alone in diagnosing chronic osteomyelitis is 39%.
- The inaccuracy of combined bone scan + labeled WBC in diagnosing acute osteomyelitis is 9-20%.
- The inaccuracy of MRI in diagnosing acute and chronic osteomyelitis is 10-20%.
- The inaccuracy of MRI in diagnosing chronic osteomyelitis secondary to trauma is 7%.
- The inaccuracy of combined MRI + labeled WBC in diagnosing chronic osteomyelitis is 11%.

No study to date has demonstrated a false positive or negative correlation for acute or chronic osteomyelitis. Therefore, the inaccuracy of a bone biopsy in diagnosing bone infection is 0%, continuously reaffirming bone biopsy as the gold standard for diagnosing and differentiating metabolic and traumatic from infectious bone disease.

In clinical practice, the authors have concluded the following tenets of assessment of a suspected bone infection:

- If bone is exposed in a necrotic or infected wound, the presumptive diagnosis can be made for acute or chronic osteomyelitis.
- An avascular limb cannot mount an inflammatory or immunologic response, therefore, the usefulness of special studies is questionable at best.

- If there is radiographic evidence of reactive bone changes (ie periosteal or hypertrophic, or osteolytic), but NO constitutional signs or symptoms of infection (fever, chills, sweats, malaise, leukocytosis or elevated ESR after several days), and NO draining sinus or history of open wound, then REGARDLESS of MRI or SCINTIGRAPHY/BONE SCAN findings, the diagnosis of osteomyelitis is highly unlikely.
- If there is a chronic or recurring draining sinus tract that probes beneath the superficial fascia, then presume: foreign body, neoplasm, or osteomyelitis.
- Strong consideration should be given to performing a diagnostic and therapeutic biopsy/end-bone resection when there is no functional or architectural impairment as a result (ie. distal symes/digital end-disarticulation).
- Fine needle biopsy and culture is recommended when suspicion is strong for osteomyelitis, especially where the structural, architectural, integrity of a weight-bearing segment is in question.
- Reliance on any radiologic report for "making" a diagnosis is strongly discouraged, and that NO radiologic study is diagnostic in and of itself.
- Delay in diagnosis and treatment is common when performing multiple adjunctive non-diagnostic studies.

BIBLIOGRAPHY

A Clinical Manual of Nuclear Medicine. Walker JM, Margouleff D. Appleton;1984. p. 214-217.

Banks AS. Avascular Necrosis of the First Metatarsal Head. A Different Perspective. *J Am Podiatry Med Assoc* 1999;89:441-53.

Craig JG, et al. Osteomyelitis of the Diabetic Foot: MR Imaging-Pathologic Correlation. *Radiology* 1997;6:850-5.

Cicchinelli LD, Corey SV. Imaging of the infected foot. Fact or Fancy? *JAPMA* 1993;83:576-94.

Deutsch AL, Mink JH, Kerr R. MRI of the Foot and Ankle.Lippincott-Raven.

Kaim A, et al. Chronic Post-Traumatic Osteomyelitis of the Lower Extremity: Comparison of Magnetic Resonance Imaging and Combined Bone Scintigraphy/ Immunoscintigraphy with Radiolabelled Monoclonal Antigranulocyte Antibodies. *Skeletal Radiol* 2000;29:378-86.

Lipsky BA. Osteomyelitis of the Foot in Diabetic Patients. CID. December 1997; 25. p1318-1326.

Milgram JW. Radiographic and Histologic pathology of NonTumorous *Diseases of Bone and Joints.* Lea& Febiger.Volume 1-2.

Rosai J. Ackerman's Surgical Pathology. Mosby. Eight Edition. p1917-2019.

Schauwecker DS, et al. Combined Bone Scintigraphy and Indium-111 Leukocyte Scans in Neuropathic Foot Disease. *J Nuclear Med* 1988;29:1651-5.

Schauwecker DS. Osteomyelitis: Diagnosis with In-111-labeled Leukocytes. *Radiology* 1989;4:141-6.

Tehranzadeh J, et al. imaging of Osteomyelitis in the Mature Skeleton. *Radiologic Clin N Am* 2001;39:223-50.

Walvogel FA, et al. Treatment of Osteomyelitis. *N Engl J Med* 1970;8:283.

Yu GV, Hudson JR. Evaluation and Treatment of Stage 0 Charcot's Neuroarthropathy of the Foot and Ankle. *JAPMA* 2002;92:210-20.