OSTEOMYELITIS IN THE DIABETIC FOOT

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INTRODUCTION

Osteomyelitis is potentially one of the most serious problems seen in the diabetic foot. In a classic review, Waldvogel (1) determined that approximately one-third of all patients with osteomyelitis were diabetic. Certainly, the podiatrist is frequently confronted with this condition in the diabetic. One must be able to properly identify the presence of osteomyelitis, differentiating it from diabetic osteoarthropathy, and must then develop a proper treatment plan. In many areas, the diagnostic and therapeutic process is still very controversial. This requires one to have a working knowledge of the pathophysiology of both diabetes mellitus and osteomyelitis as a basis for rational decisions in treatment.

DEFINITION

Osteomyelitis can be defined as an inflammation of bone marrow which most commonly presents as a pyogenic infection of marrow and/or bone (2). The term osteomyelitis has frequently been used interchangeably with the term osteitis which technically describes the inflammation of bone. However, one must be aware that osteitis like osteomyelitis can represent an inflammatory process due to pyogenic infection of bone. Buckholz (3) recently attempted to clarify the confusion by describing osteomyelitis as "an infection involving the marrow cavity or growth plate" and osteitis as "an infection of bone tissue that does not penetrate the medullary cavity or involve the growth plate." For practical purposes, this differentiation is only important in certain classification schemes with related treatment suggestions.

PATHOPHYSIOLOGY

Many frequently misunderstood terms are used when attempting to describe the pathogenic process and findings in osteomyelitis. Terms such as sequestrum, involucrum, and cloacae are distinctly defined osseous changes. When properly understood these findings can facilitate a more thorough understanding of the pathogenesis of the disease.

Osteomyelitis occurs when factors are present which favor the localization of bacteria. Obviously, circulatory compromise or diabetic angiopathy can create an environment suitable for the proliferation of bacteria via small areas of gangrene or skin ulceration with associated necrotic tissue. Other factors in the diabetic foot can also contribute to such localization, including sensory or autonomic changes frequently seen with diabetic neuropathy.

A decrease in sensation may be associated with repetitive mechanical, thermal, or chemical trauma to the foot resulting in local tissue necrosis or ulceration. This may even occur without local vascular insufficiency. Osteoarthropathy may also be associated with the sensory dysfunction creating new pressure areas for the repetitive trauma. Further, autonomic dysfunction may impair the vascular response to local tissue damage allowing pH changes which will be favorable to bacterial proliferation (4). Thus, angiopathy and neuropathy together or individually can contribute to the localization of bacteria and eventual development of osteomyelitis. The adage that vascular insufficiency is the only cause for diabetic osteomyelitis has certainly been disproven.

Once localization of bacteria has occurred, further destructive changes may become apparent. The bacteria and any associated inflammatory reaction and pH change may contribute to the breakdown of trabeculae and removal of matrix with calcium deposits. Therefore, the earliest radiographic change suggesting osteomyelitis is a loss of bone density or radiolucency (Fig. 1).

As the infection proliferates, it spreads to neighboring osseous structures through the Haversian and Volkman channels. This leads to the destruction of vascular channels and to additional necrosis and osteocyte death. As bone dies, it becomes sclerotic and will appear as such on radiographs. Large segments of devascularized dead bone can become separated to form sequestra (isolation of dead bone from living bone) (Fig. 2) (4). Radiographic identification of bone sequestration is highly suggestive of osteomyelitis (Fig. 3). However, in the diabetic foot it must be carefully differentiated from the sequestrum associated with osteoarthropathy.

If allowed to progress, the infection will eventually enter the subperiosteal area (Fig. 4). When the periosteum is elevated from the cortex by the suppurative process

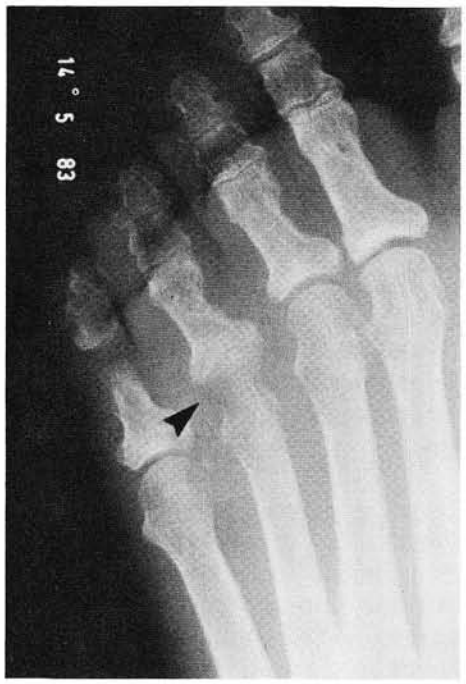

Fig. 1 Earliest radiographic sign of osteomyelitis: radiolucency. Notice changes in distal aspect of fourth metatarsal head.

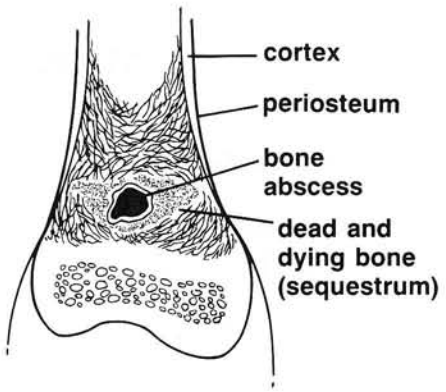

Fig. 2. Sequestrum: devascularized dead bone.

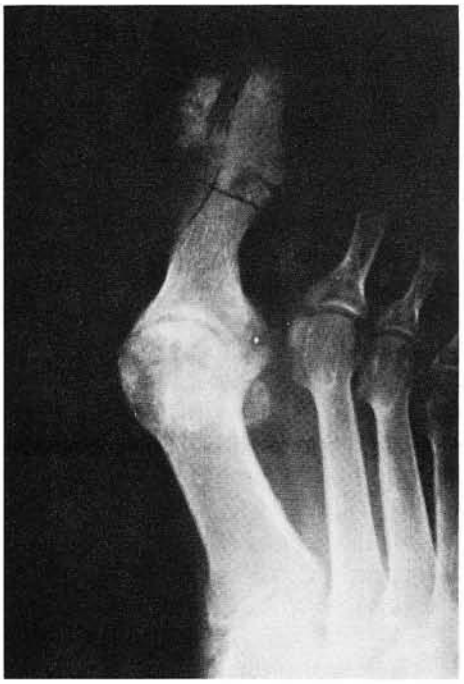

Fig. 3. Radiographic demonstration of sequestrum formation in distal hallux.

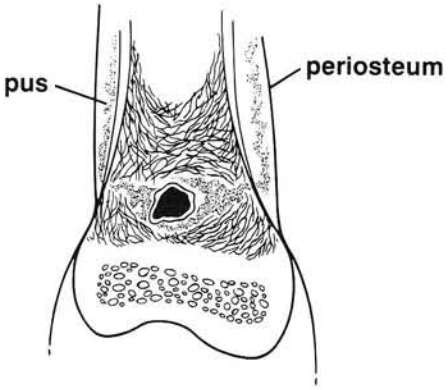

Fig. 4. Infection eventually reaches subperiosteal area. If close to joint or intracapsular, then septic arthritis occurs.

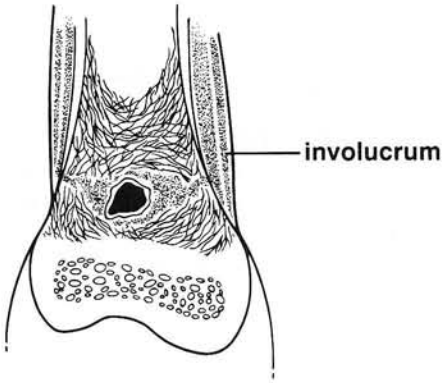

Fig. 5. Involucrum: new bone formation.

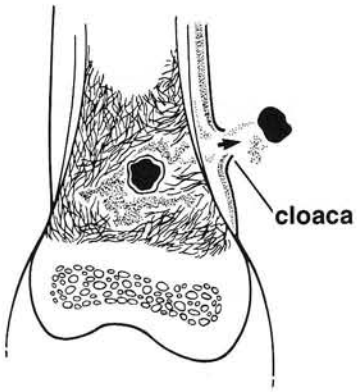

Fig. 7. Cloaca: Opening for extrusion of sequestrum and necrotic products.

exuberant growth of new bone (involucrum) will be initiated (Fig. 5). The radiographic identification of subperiosteal involucrum formation is highly indicative of osteomyelitis (Fig. 6).

Finally, a cloaca may form at the bone-periosteal interface and this represents an opening in the region for the extrusion of sequestered bone (Fig. 7) (5).

Identification and an understanding of the pathophysiology and etiological causes of osteomyelitis are paramount in its proper treatment and in the prevention of recurrence.

CLASSIFICATION

Osteomyelitis has been classified in numerous ways. Each classification has offered some assistance in understanding the disease process, but no system has yet been developed nor accepted which adequately describes the disease process and its relation to preferred treatment. Perhaps this is why so many classification and treatment systems exist.

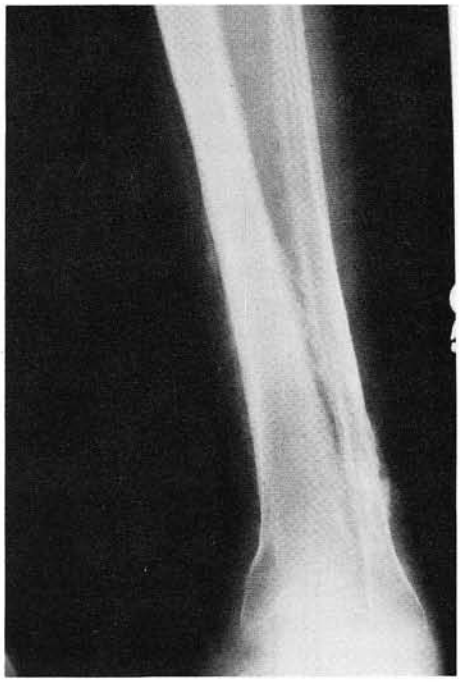

Fig. 6. Subperiosteal involucrum formation along fibula secondary to osteomyelitis.

Traditionally, osteomyelitis has been classified as an acute, subacute, or chronic infection based upon the clinical course of the disease and the histological findings (6). This classification has always suffered from debate over the strict definitions for acute, subacute, and chronic osteomyelitis.

In 1970, Waldvogel (7) described a classification based loosely upon the pathogenesis of the disease. He divided osteomyelitis into three types:

1. hematogenous osteomyelitis,
2. osteomyelitis secondary to a contiguous focus of infection, and
3. osteomyelitis associated with peripheral vascular disease.

This classification may permit some suggestion of possible causative organisms and recommended therapy. However, there are certainly too many variables which this classification does not address (e.g., what is the contiguous focus of infection, an ulcer?, a puncture wound?) and, thus it is of limited usefulness. This is particularly true in the diabetic where osteomyelitis may be due to contiguous spread, vascular insufficiency, or both.

Cierny and associates (8) described a somewhat useful clinical staging system for osteomyelitis in adults utilizing both a physiological classification (A-host: good systemic defenses, good local vascularity; B-host: local compromise, systemic compromise; C-host: minimal disability, not a surgical candidate, treatment worse than

disease) and an anatomic classification (type I: medullary; type II: superficial; type III: localized, and type IV: diffuse). Thus, by taking the three physiological types and mixing them with each anatomic type, twelve different clinical stages or types of osteomyelitis are described. Treatment is then varied based upon these twelve stages. This staging system has been used at the University of Texas Medical Center and the report described the results of treatment in 189 patients. Although not yet widely accepted, this system is a solid attempt at a practical classification scheme.

Buckholz (3) recently described yet another classification system based upon the strict definitions of osteitis and osteomyelitis. He described seven types of bone infection:

1. wound induced,
2. mechanogenic infection,
3. physeal osteomyelitis,
4. ischemic limb disease,
5. combinations of 1-4,
6. osteitis with septic arthritis, and
7. chronic osteitis/osteomyelitis.

The classification system is rather confusing and as Buckholz states "Unfortunately, familiarity with all seven types is not common to medical or surgical specialities. Each specialty encounters certain types of infection, and as a result misunderstanding may arise between surgeon and clinician as to correct treatment." The classification may be useful if it becomes more widely understood and accepted.

In conclusion, although no specific classification exists that is universally accepted, certain findings are common to the disease and will be discussed in relation to osteomyelitis in the diabetic foot. Any classification system may be helpful if it allows more accurate description and communication between the various medical disciplines involved in the patient's care.

Diagnosis

The diagnosis of osteomyelitis in the diabetic foot can be a challenging and perplexing problem. Indeed, the diagnosis is frequently more difficult than the treatment itself. The clinician must always be alert to the possibility of osteomyelitis. Frequently, the disease is overlooked if the cardinal signs of infection are absent, if leukocytosis is absent, or if soft tissue cultures are misleading or negative. The diagnosis of osteomyelitis depends on an accurate evaluation of clinical findings combined as necessary with radiographs, nuclear medicine studies, laboratory studies, and bone biopsies and cultures.

Clinical Evaluation

Clinical evaluation includes a thorough history and physical examination. Examination for systemic and local signs of infection must be done. Any examination where infection is a possibility should begin with the taking of the patient's vital signs including body temperature. Locally, the cardinal signs which one should evaluate and monitor are edema, erythema, and increased temperature in the area. Most importantly, one must remember that in diabetes immunopathy is frequently present impairing the patient's response to inflammation and/or infection (9).

Radiographic Examination

As stated earlier, classic radiographic changes associated with osteomyelitis include initial radiolucency followed by sclerosis, sequestrum formation, and involucrum formation. It is commonly believed that 10-14 days must pass before the initial radiolucency associated with osteomyelitis can be visualized radiographically. However, with careful observation, particularly when baseline or previous radiographs have been taken, radiolucency may be visualized within 5-7 days after the onset of infection.

Nuclear Medicine Studies

Nuclear medicine studies may be particularly helpful in the diagnosis of osteomyelitis. In some cases, they may be particularly helpful in differentiating osteomyelitis from osteoarthropathy. Technitium-99m methylene diphosphonate (Tc-99), gallium-67 citrate (Ga-67), and indium-111 oxine (In-111) are frequently used as imaging agents to aid in the diagnosis of osteomyelitis. Each has specific properties, advantages, and limitations.

The technitium-99 bone scan is the most widely used study to document the evidence of osteomyelitis. However, Tc-99 is known for its sensitivity, but not for its specificity. It is very important to use a three or even four-phase bone scan to differentiate infections of the soft tissues around bone from infection within bone. The three-phase bone scan is composed of a radionuclide angiogram (first phase), an immediate post-injection blood pool image (second phase), and a 2 to 4 hour delayed image (third phase). Recent evidence suggests that a fourth phase, another delayed image taken 24 hours post-injection, may be helpful (10).

The first phase consists of several images taken in rapid sequence 1 to 3 seconds apart as the isotope approaches the extremity. This affords a dynamic visualization of blood flow to the extremity and functions much like an angiogram. The second phase is also a vascular phase and is taken only minutes after injection of the isotope.

After the first several minutes, an equilibrium is reached throughout the blood volume and a series of images can be taken to demonstrate the "blood pool." This term accurately describes the quantity of blood "pooling" present in the capillary beds and veins. Thus, the first two phases demonstrate the vascularity to the region and will be "hot" whether the infectious process is soft tissue or bone.

The delayed image phases (third and fourth phases) take advantage of the Tc-99 as a "bone-seeking" isotope or an isotope which demonstrates the amount of osteoblastic activity. By taking an image 2 to 4 hours after injection, one has allowed osteoblasts to use the isotope in the production of new bone, whether for repair or maintenance. One has also allowed the excretion of most of the unused isotope since the half-life of Tc-99 is about 6 hours. The greater the delay, the more the bone activity and the less the soft tissue activity.

The fourth phase may actually prove to be the most valuable although dropping activity may make imaging more difficult. In the diabetic with severe vascular disease, the isotope may localize in bone very slowly and be excreted very slowly as well. An image 5-24 hours after injection may be more helpful in diagnosing osteomyelitis in such instances (11).

The most reliable evaluation of an osteomyelitic process comes from the evaluation of all of the phases simultaneously. The earlier phases will be "hot" in the face of soft tissue and/or bone infection. However, if a soft tissue infection alone is present the third and fourth phases should demonstrate comparatively less activity. A Tc-99 bone scan that does not demonstrate appreciable activity in the third and fourth phases significantly decreases the likelihood of osteomyelitis. If the third and fourth phases seem to demonstrate similar or greater activity, then osteomyelitis may be suspected.

Difficulty arises in the diabetic with osteoarthropathy in that the bone scan may be "hot" in all phases due to the bone activity associated with this hyperemic pathogenic process. One must recognize this limitation, but with skill and experience one can utilize Tc-99 bone scans and specific diagnostic patterns to occasionally establish the presence or absence of osteomyelitis even with concomitant osteoarthropathy.

Gallium-67 scanning is used predominantly for the detection of acute inflammation or infection as the isotope binds to white blood cells and plasma proteins. Ga-67 alone is not indicated for the detection of osteomyelitis in the diabetic foot. The concurrent use of Tc-99 bone scans and Ga-67 may have some practical use in the diagnosis of osteomyelitis. Acute osteomyelitis can be more intensely "hot" on Ga-67 scanning compared to simultaneous Tc-99 bone scans. In more chronic cases of osteomyelitis the Ga-67 scan theoretically should be negative while the Tc-99 bone scan should be "hot". However, in practice the Ga-67 scan demonstrates variable activity in cases of chronic osteomyelitis.

Many investigators have reported that Ga-67 scanning may be useful in following the success of therapy oriented at the sterilization of osteomyelitis (12-15). Tc-99 bone scans may be positive for months or years, while Ga-67 scans will generally become negative as the infection is arrested. However, the use of Ga-67 scans for this purpose is still controversial and clinical studies have reported positive Ga-67 scans following the complete clinical resolution of the osteomyelitis (16).

The Indium-111 white blood cell scan may be the most helpful in the diabetic foot. Early evidence suggests that it may be of use in differentiating osteomyelitis from osteoarthropathy. To perform this study neutrophils isolated from blood taken from the patient are labelled with In-111. The tagged In-111 white blood cells are then injected back into the patient and the scan performed approximately 24 hours later. The neutrophils localize in the inflammatory area, whether bone or soft tissue. The scan is both highly sensitive and highly specific for acute soft tissue and osseous infection. Thus, it can be used to differentiate acute osteomyelitis from osteoarthropathy in the diabetic foot. The In-111 scan should be negative in osteoarthropathy and "hot" (positive) in the presence of acute osteomyelitis (Figs. 8, 9). Indium-111 scanning may not be beneficial in chronic osteomyelitis due to a predominately lymphocytic pattern that will not cause localization of the In-111 labeled neutrophil (17).

Laboratory studies

Laboratory studies are more useful for following the treatment of osteomyelitis than in diagnosing osteomyelitis. The complete blood count (CBC) may be normal as previously mentioned. The Westergren erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) may be positive, but are only a general indication of inflammation. They may also be positive in osteoarthropathy.

Most of the laboratory studies are helpful in following the therapeutic course of osteomyelitis. If the CBC demonstrated an elevated white blood cell count and differential shift, it should demonstrate a marked decrease in the white blood cell count and band cell count after initiation of appropriate treatment. The ESR and CRP have also been reported to be helpful in monitoring the clinical improvement in the treatment of osteomyelitis,

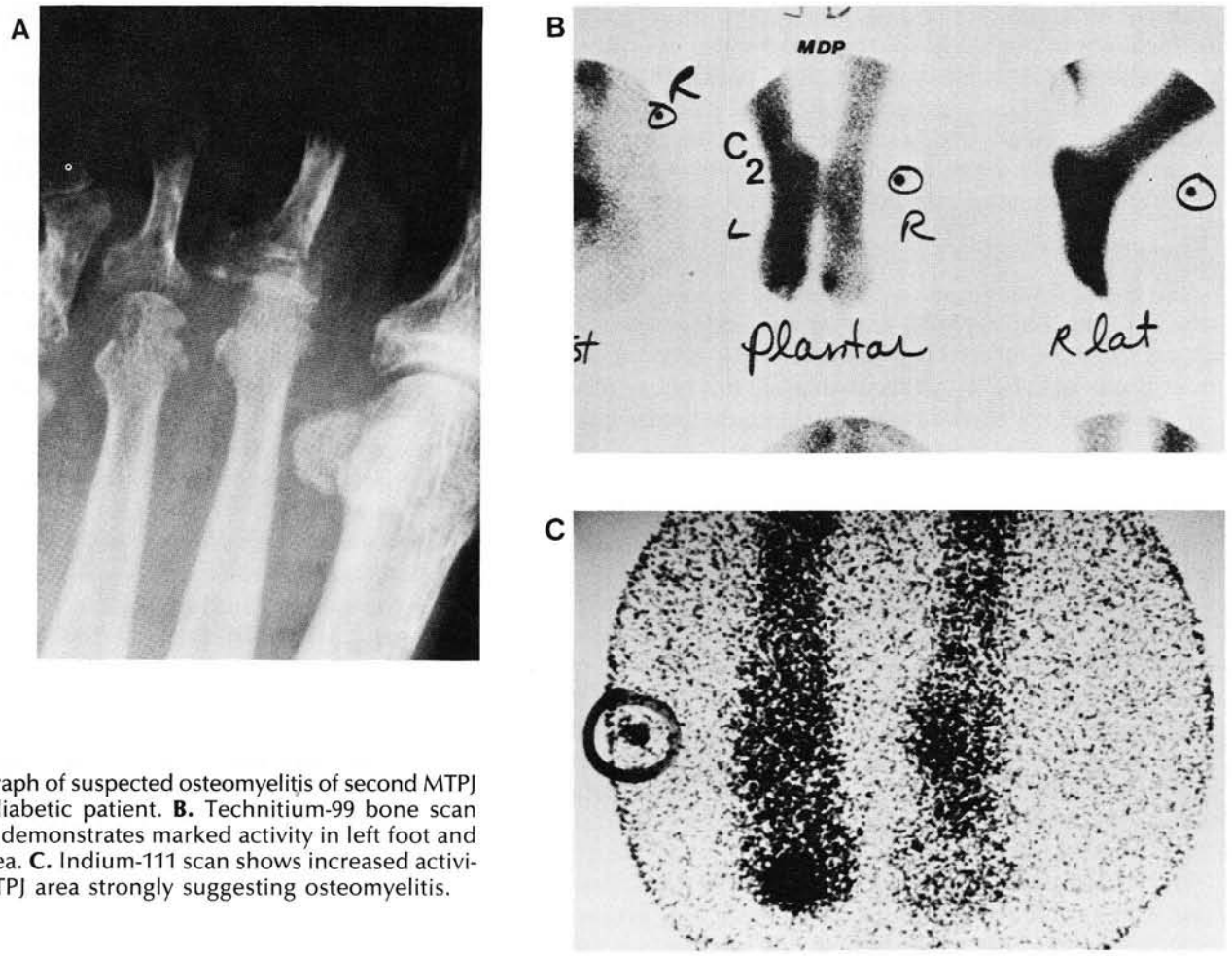

Fig. 8. A. Radiograph of suspected osteomyelitis of second MTPJ in left foot of diabetic patient. **B.** Technitium-99 bone scan (delayed image) demonstrates marked activity in left foot and second MTPJ area. **C.** Indium-111 scan shows increased activity in second MTPJ area strongly suggesting osteomyelitis.

particularly pseudomonas osteomyelitis. If the ESR was elevated, it should decrease with treatment, and if the CRP was positive it should become negative with treatment (18,19).

Bone Biopsy and Culture

Bone biopsies and cultures provide the best and only definitive evidence of osteomyelitis. They are also the only definitive method to differentiate osteomyelitis from osteoarthropathy. The "key" to the appropriate treatment and antibiotic selection in any infection, including osteomyelitis, is reliable cultures. Soft tissue cultures and those obtained from sinus tracts are notoriously poor and very unreliable (20). Bone cultures from the involved bone should be obtained whenever possible in cases of osteomyelitis. Care must be taken to obtain these cultures without passing through infected soft tissue. Also the patient should be withdrawn from any antibiotics for at least 48 hours prior to culture. Biopsies and cultures are best obtained through open exposure as blind biopsies with a needle or trephine can lead to false-negative cultures and pathology reports.

Treatment

Norden (21) experimentally demonstrated that osteomyelitis is difficult to induce. but once established is even more difficult to eradicate. The treatment of osteomyelitis is still controversial in many areas. However, it is now generally accepted that surgical excision of the osteomyelitic bone combined with intravenous antibiotics should be instituted whenever possible. Only in very early cases of acute osteomyelitis or in chronic hematogenous osteomyelitis should antibiotic therapy alone be considered.

Once osteomyelitis is diagnosed, its surgical excision should be planned. In the diabetic with profound vascular insufficiency appropriate evaluation must be undertaken to determine the potential for healing prior to the surgical procedure. For the podiatric surgeon, this may involve referral to a vascular surgeon for evaluation and possibly revascularization procedures. Once the area demonstrates satisfactory vascularity, the surgical procedure may be performed. If severe infection and necrosis occurs prior to such revascularization, then am-

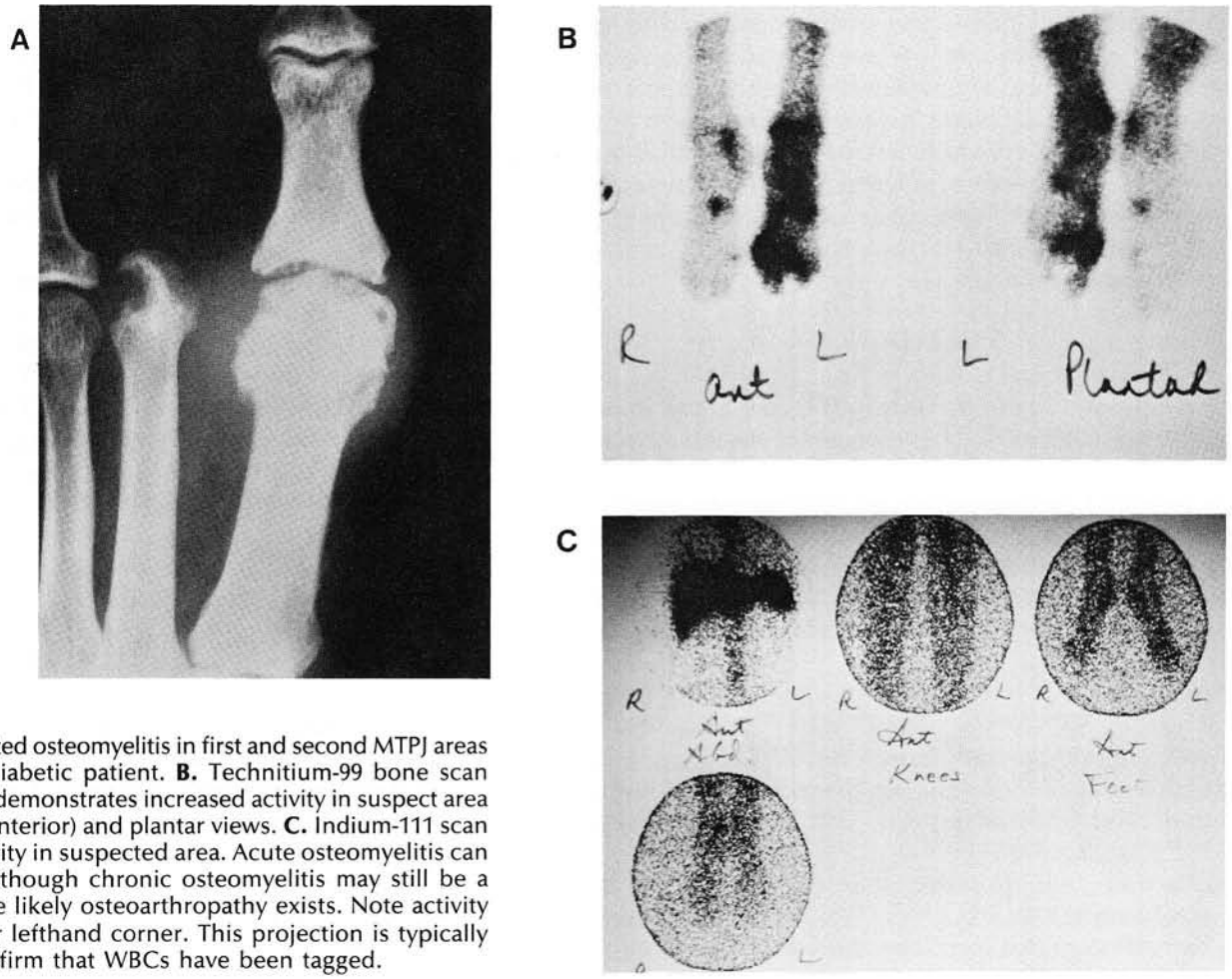

Fig. 9. A. Suspected osteomyelitis in first and second MTPJ areas in left foot of diabetic patient. **B.** Technitium-99 bone scan (delayed image) demonstrates increased activity in suspect area in both dorsal (anterior) and plantar views. **C.** Indium-111 scan shows little activity in suspected area. Acute osteomyelitis can be ruled out, although chronic osteomyelitis may still be a possibility. More likely osteoarthropathy exists. Note activity in liver in upper lefthand corner. This projection is typically obtained to confirm that WBCs have been tagged.

putation may need to be considered at a more proximal level where the healing potential has been determined to be satisfactory.

Whenever possible, all of the osteomyelitic bone should be excised. Surgical approaches can be done through a previous area of infection or through clean incisional areas. All necrotic bone, soft tissues, and devascularized structures should be excised and wound revision performed to accommodate appropriate closure at a later date. Debate continues as to how much bone should be excised. Certainly, all infected bone and a small portion of apparently uninvolved bone should be removed. This uninvolved bone may be sent for separate microscopic evaluation. If the infected bone exhibits microscopic evidence of osteomyelitis and the uninvolved bone is reported as noninfected, then one has documented the excision of the diseased bone.

Further debate continues as to the advantages and disadvantages of disarticulation versus transcortical resection in areas of joint involvement. Disarticulation maintains the subchondral bone and cartilage as a natural barrier to the spread of the infection into the remaining osseous structure. Transcortical amputation permits the microorganisms access to the Haversian and Volkman channels but excises the cartilage which will certainly become necrotic if left for several days in the open wound. A possible compromise is to perform a disarticulation and then gently currette the cartilage from the remaining portion of bone. The subchondral bone will provide a better barrier than that of transcortical resection.

Once surgical excision of osteomyelitic bone has been performed a method of wound care must be chosen. Closed suction irrigation systems and open packing are both acceptable alternatives. If open packing is chosen, the wound may be closed after subsequent wound cultures have documented the eradication of the infection.

All treatment regimens should include the use of intravenous antibiotics. The appropriate antibiotic should be chosen and oriented towards the pathogenic organism(s) identified by the reliable culture (22). Today,

appropriate antibiotic therapy is still considered to be 6 weeks of parenteral antibiotic administration. Frequent relapse and chronic osteomyelitis can be anticipated with short-term or oral antibiotic therapy (23). The patient may be discharged and continued on intravenous antibiotics at home if the services of a home health care team or nurse are available. This approach lowers cost significantly and drastically improves the patient's overall acceptance of lengthy therapy (24).

SUMMARY

Osteomyelitis in the diabetic foot is one of the more challenging diagnostic and treatment problems encountered by the podiatric physician and surgeon. Differentiation of the disease process from diabetic osteoarthropathy can be particularly difficult. An appreciation of the pathogenesis of the disease of diabetes and osteomyelitis is critical in aiding the diagnosis and in the development of an appropriate treatment plan.

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