CHAPTER **21**

ACUTE HEMATOGENOUS OSTEOMYELITIS: A "Once in a Lifetime Diagnosis"

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Osteomyelitis (OM) is a serious inflammatory condition with substantial morbidity. Differentiating between acute and chronic, hematogenous and contiguous, unifocal and multifocal osteomyelitis is essential for clinical decision making.[1] Acute hematogenous osteomyelitis (AHOM) is not a frequently diagnosed infection, therefore understanding the classic presentation is of utmost importance. It represents 20% of all OM cases.[2] Today in developed countries, children with AHOM rarely die, but preventable morbidity remains.[3] Prior to the advent of antibiotics in 1944, the mortality rate of AHOM reached as high as 20-40%.[3,4] Although diagnosis often proves difficult because the signs and symptoms mimic those of many everyday ailments and pathologies, recognition of the pathology is paramount.

Hematogenous OM is an infection of the bone and marrow cavity caused by bacterial seeding from the blood.[5] Acute HOM is characterized by an acute infection with absence of a penetrating wound adjacent to the site of disease.[1] Often in children, the etiology is due to an extra-skeletal focus (skin, ear, pharynx), yet in the majority of cases no source is clinically demonstrable.[4] It has been stated that in up to one third of cases, no causative organism can be isolated.[1] No specific classification system has been developed for AHOM, yet it is included in the Waldvogel Classification system (Table 1).[6]

AHOM occurs predominantly in children, accounting for >80% of all cases.[5,6] According to Mellors, it most commonly occurs in children prior to the age of epiphyseal closure (<21years).[4] The overall predominance is 1 per 5,000 children.[5] The male to female ratio is approximately 2:1.[6] It has been shown that daycare centers are a particularly good environment for transmission of many bacterial infections in toddlers that can result in AHOM. Through hematogenous dissemination, the bacteria can seed at remote sites that can be limb threatening. The origin of AHOM is generally located in the metaphysis of long tubular bones as it is the region of greatest vascularity and most rapid growth. The most commonly affected bones are, in order of frequency, the distal femur, proximal tibia and humerus, and the radius.[4] In a study by Bonhoeffer et al, 77% of the patients had AHOM in the lower extremity, with the most frequent sites being the femur (24%) and tibia (18%).[1]

DISSEMINATION

Hematogenous dissemination of infection is most commonly propagated via the diaphyseal and metaphyseal vessels.[7] In infants (0-1 year) and adults (>16 years), these vessels perforate the growth plate leading to rapid infection. At the distal metaphysis, the vessels make very sharp angles resulting in sludging or slowing of blood flow. This, in turn predisposes the vessels to thrombosis with resultant bacterial seeding and localized necrosis of the bone. In children (1-16 years) the diaphyseal and metaphyseal vessels do not penetrate the open growth plate. These vessels turn upon themselves and enter the adjacent venous sinusoids located just proximal to the growth plate.[4] This is one more reason that children are the most commonly affected patients with AHOM, as stated previously, accounting for >80% of AHOM cases. These venous sinusoids are larger than the arteries feeding them with slower blood flow, thus providing a better medium for bacterial growth.

Table 1

WALDVOGEL CLASSIFICATION SYSTEM FOR OSTEOMYELITIS

Hematogenous osteomyelitis
Osteomyelitis secondary to contiguous focus of infection
No generalized vascular disease
Generalized vascular disease
Chronic osteomyelitis (necrotic bone)

ADULT AHOM

In adults, osteomyelitis is generally a subacute or chronic infection. Although infrequent, hematogenous dissemination is possible. In the majority of adults with acute hematogenous osteomyelitis, *Staphylococcus aureus* is implicated.[6] In has been shown to be the causative organism in up to 55% of adult infections.[4] The majority of the remainder is due to gram negative bacilli and *Streptococcal* infections. AHOM most commonly affects the vertebrae as they are the most vascular region in the adult. The outcome can be debilitating with severe complications. These include extension into the adjacent disc space and into the retropharyngeal, mediastinal, peritoneal, and meningeal sites. Progression of neurological deficits and/or spinal-cord compression has been seen in up to 10-15% of patients with vertebral osteomyelitis.[1,5] Therefore, one can see that rapid dissemination to these sites with failure to achieve an early diagnosis can be paralyzing and even deadly. Tuberculoid osteomyelitis can also be seen as hematogenous dissemination is the main route of infection of the skeleton in patients with tuberculosis. Although, this is not a common diagnosis, it is very serious and requires careful consideration.

Clinical Presentation

While the onset of symptoms in AHOM is quite sudden in children, it is a more insidious course in adults. The course is also quite age-dependent. Infants present abruptly and are desperately ill with a hectic fever, rapid pulse, vomiting, and occasionally seizures.[8] Less frequently they are gradually ill with loss of appetite, lethargy, fretfullness, and variable fever.

Children present with the same symptoms, yet are less desperately ill than infants. The children usually present within several days to weeks after the onset of infection. Although the systemic signs of infection, fever, lethargy, irritability, are present, there is generally absence of any local signs. The clinical presentation is that of tenderness over the involved bone and decreased ROM in the adjacent joint, and limping. Often, the patient refuses to bear weight on the affected limb. Adults, on the other hand, do not appear as acutely ill. They present with global aches and pains, such as migrating arthralgias and myalgias, prior to the localization of pain. Due to the extreme variability in presentation the outcome varies significantly among different ages.

The presentation one might see in the podiatric office is that of the parent arriving with a child that is limping, often times crawling, significantly guarding the affected extremity. The child often has no open lesions and no significant current injuries related to the lower extremity. Determining the etiology can be challenging and is often unapparent. Searching deep into the patient's clinical history can help lead to the diagnosis, taking care to research for any previous common illnesses, such as colds and flu, and other risk factors that will be discussed below. These everyday illnesses have been shown to be responsible for a large portion of pediatric cases of AHOM. In adults, the presentation can be tricky making diagnosis much more difficult. These patients are commonly less ill and less symptomatic, but the risk of mortality is still a large concern. Correlating recent illnesses and injuries can help assist in the diagnosis. In any case, determining the etiology is imperative to aid in the identification of the causative organism and allow prompt diagnosis and treatment.

Risk Factors

Once the clinical presentation has been evaluated, the risk factors for AHOM must then be examined. These include recent illness (within the past few weeks), trauma, bacteremia, malnutrition, as well as immune system deficiency. It must be understood that the recent illnesses referred to are those of common day illnesses: cold, influenza, and ear infections. The trauma can be related to anything as simple as ordinary cuts, bruises, and bites, specifically human and animal bites. These trivial traumas and illnesses are the most common causative incidents, therefore day care centers represent the most common location for these to occur.[9] Recognizing that these risk factors can be associated with specific pathogens can aid in a more rapid diagnosis (Table 2).

Diagnosis

The diagnosis of acute hematogenous osteomyelitis, although proven difficult, can be established based on several specific findings, both clinical and diagnostic (Table 3).[6] Prompt diagnosis of acute hematogenous osteomyelitis in children is essential as long term sequelae and serious complications rise

at a dramatic rate if diagnosis is delayed.[1] Early diagnosis is imperative to prevent sepsis, chronic infection, growth arrest, and possible deformation of bone, however, diagnosis often proves difficult.[10]

Once the diagnosis has been made, identifying the microbe is the next key. At this point, one can begin to appreciate the enormous importance of a thorough history and physical exam. Next, a correlation must be made between the history and the current presentation. For example, if the patient had a recent cold, the possibility of an infection due to *Streptococcal* or *Kingella* species must be considered. The knowledge of likely pathogens related to specific etiologies or conditions is paramount (Table 2). This helps to narrow down the treatment options whether it be antibiotic therapy, surgical intervention, or otherwise.

Diagnostic studies can also be implemented. Magnetic resonance imaging (MRI), radiographs, and bone scans have all proven helpful. Plain film radiographs may demonstrate the typical radiographic changes of osteomyelitis including osteolysis and periosteal reactions. Bone scans although sensitive, are nonspecific. One cannot differentiate osteomyelitis from soft tissue infection, gout, degenerative joint disease, postsurgical changes, and any other inflammatory process.[6] Therefore, it cannot confirm osteomyelitis, but can assist in the diagnosis. MRI allows greater spatial resolution to allow determination of the anatomic boundaries of the infection, thus is more specific in comparison with bone scintigraphy. Computed tomography and ultrasound can help identify fluid collection, osteolysis with loose bone fragments, and gas collection. All of these modalities may be used to assist in diagnosis and management.

The gold standard for diagnosis is bone biopsy. This allows identification of the organism, but may be limited due lack of uniform specimen collection and prior antibiotic use.[6] Sinus tract cultures may or may not provide the causative organism, reiterating the importance of a bone biopsy. Studies have shown that blood cultures indicate the organism in up to 50% of children with AHOM.[1,9] Routine lab studies can also assist in the diagnosis often demonstrating elevated WBC, ESR, and CRP values.

COMMON AND UNCOMMON OGANISMS IN CHILDREN

As previously stated, specific organisms can be associated with certain etiologies or insults and these are often age related or related to a particular clinical scenario (Table 2).[6,11] The most common organism seen in children is *Staph aureus*. It has been found to be responsible for 50-90% of AHOM cases in children.[1,6,7,9] Other common organisms must be considered, as a large portion of children with AHOM are children that attend daycare centers. Many pathogens linger in daycare centers and many trivial injuries can cause raging infections that can prove difficult to diagnose. *Eikonella corrodens* from human bites, Streptococcus, and Pseudomonas from trauma are common causative organisms. It has been proposed that fastidious organisms such as *Kingella kingae* might be responsible for a large number of cases with negative routine cultures.[1]

Kingella kingae is now recognized with greater frequency than Haemophilus influenzae for causing gram-negative infections in children, more

Table 2

Condition	Pathogen
Trauma	*S. aureus*
	Streptococcus
	Pseudomonas
SCA	Salmonella
	S. pneumoniae
Sexual activity	*N. gonorrheae*
IVDU*	Pseudomonas
	Serratia
	S. aureus
Dog / Cat bite	*P. multocida*
Human bite	*E. corrodens*
Marine life	*M. marinum*
Tick bite	*B. burgdorferi*

*IVDU = intravenous drug use

Table 3

DIAGNOSIS OF ACUTE OSTEOMYELITIS

1. Pus on aspiration
2. (+) bacterial cxs from bone or blood
3. Presence of classic signs and symptoms of AHOM
4. Typical radiographic changes

specifically children in daycare centers. Due to routine immunizations against *H. influenzae,* this new pathogen has been peaking the interest of many healthcare organizations. *K. kingae* is a fastidious gram-negative organism that is part of the normal respiratory flora in children. The bacteria is transmitted through salivary secretions and is aerobic in nature. Although this coccobacillus normally colonizes the respiratory and oropharyngeal tract, any small disruption in the membrane can result in invasive disease, including AHOM.[12]

Due to the fastidious nature of the organism, which includes complicated nutritional requirements as well as specific medium for growth, the diagnosis is frequently missed. According to the CDC in 2004, recovery of the organism often requires the lab to hold the specimen for up to 7 days, which is longer than most routine laboratory protocols.[12] It was also suggested that inoculating the synovial or bone biopsies directly into the blood-culture bottles with a continuous monitoring system, in contrast to direct plating on solid media, increases the rate of *K. kingae* recovery considerably. In a study performed by Yagupsky et al in 2002, a vancomycin-containing medium was specially designed to aid in detection of the organism that proved satisfactory.[13] Also in the study, more than half of the children identified with *K. kingae* infections, upper respiratory tract infections (URI), stomatitis, or diarrhea were found on admission.

In a similar study, the Minnesota Department of Health (MDH) investigated a daycare center that had two reportable and one probable case of AHOM secondary to *K. kingae.*[12] All of the children investigated were from the same daycare center and between the ages of 17-21 months. All of the children presented within the same week with the same symptoms fever: preceding or current URI, and refusal to bear weight on the affected limb. Relatively normal to slightly elevated lab values (WBC, CRP, ESR, CRP) were found in all the patients initially, which were previously healthy children. Almost all of the patients had intra-operative cultures performed that initially precipitated negative gram stains. A brief synopsis of each patient is listed below:

Patient 1 presented with 6 days of a worsening limp. He underwent radiographic imaging studies and was diagnosed with a possible fracture of the proximal femur. He continued to have pain and deteriorated from a limp to a crawl with total refusal to bear weight on the affected limb. Seven days later he underwent surgery on the right hip. Synovial fluid and bone cultures demonstrated *K. kingae* after 5 days.

Patient 2 had completed a 14 day course of Augmentin for a diagnosis of otitis media. A few weeks later she returned with a warm right ankle refusing to bear weight on her right foot. Symptoms continued to progress with increasing temperatures. An MRI was performed, demonstrating fluid in her ankle. She underwent surgery 3 days later with synovial fluid biopsies revealing *K. kingae* after 5 days.

Patient 3 was seen by the ER with irritability, fever, and a limp for 2 days. His ankle was moderately swollen and warm. Radiographs were negative. He was discharged with a diagnosis of right ankle synovitis and otitis media, and given a 7 day course of oral Amoxicillin. His clinical status improved, yet he continued to limp. An MRI was performed 16 days later, and demonstrated distal tibial osteomyelitis. No specimens were collected, but *K. kingae* infection should be suspected and listed in the differential diagnosis.

This data indicated the importance of a thorough examination as well as clinical correlation. These reports also suggest that toddlers should be under specific clinical suspicion for invasive bacterial infections, such as *K. kingae.* These infections should be diagnosed rapidly utilizing the correct modalities as they can disseminate hematogenously and infect remote sites. These sequelae can be debilitating and limb threatening. Although the clinical and diagnostic criteria for *K. kingae* infections are advancing, the epidemiology of the organism is still not entirely clear. These factors have made treatment a challenge.

DIFFERENTIAL DIAGNOSES

In children, the differential diagnoses vary from adults. Synovitis, Perthes' disease, and acute rheumatic fever can be excluded by a thorough history and diagnostic testing.[14] In adults the differential diagnoses of Ewing's sarcoma as well as arthropathies including rheumatoid, osteo, septic, and crystalline must be ruled-out.[14]

GENERAL COMPLICATIONS

The complications of undiagnosed AHOM can lead to substantial mortality. A septic joint is a serious complication and is considered a surgical emergency. Secondary involvement of adjacent joints can also be encountered. Chronic infection is inevitable if not recognized in an expedient manner. Recurrence is also possible, yet uncommon. The rate of recurrence has been shown to be higher in the lower extremity, demonstrating approximately 50% when located in the metatarsals and 25% in the tibia and femur.[14] Overall the rate is quite low and infrequent.

MANAGEMENT

The proper treatment of patients with AHOM is controversial.[15] Different opinions exist regarding antibiotic therapy, duration of treatment, surgical intervention (when and which type), and the overall effect of these factors on eradication of infection.[15] Antibiotic therapy is an important step in the management of AHOM as well as treatment of constitutional symptomatology, such as fever and pain.[11] It should be noted that during the acute stage, antibiotics should be initiated as early as possible to prevent progression of infection.[16] Empiric therapy can be initiated until cultures have identified the organism. Once identified, the appropriate antibiotic regimen should be administered. Although the disease is treatable, remissions are possible.[11]

CASE PRESENTATION OF AN UNUSUAL CASE OF AHOM

A 62-year-old male presented with a chief complaint of exquisite pain on the dorsolateral right foot that has been present for 2 years. He related having a fever on and off with progressive erythema and edema of the foot for the past month. He could not recall any history of trauma or a wound in the area. He had previously seen another physician and was diagnosed with an upper respiratory tract infection and a cuboid fracture. He was treated conservatively with a below the knee cast and was non-weight-bearing. He continued to have pain and the symptoms stated above and followed-up with a podiatrist.

Ancillary tests were performed including radiographs, CT, and MRI. The radiography report revealed a well defined focal osteolytic process in the cuboid (Figures 1, 2). The report also noted it was uncertain whether it was a postsurgical residual or due to an intraosseous ganglion cyst. The CT demonstrated a destructive lesion involving the cuboid suggesting a differential diagnosis including osteomyelitis and metastasis (Figure 3). It was stated that post-traumatic fracture was less likely, given the permeative margins and the cortical destructions. A bone scan revealed significant increased radiotracer

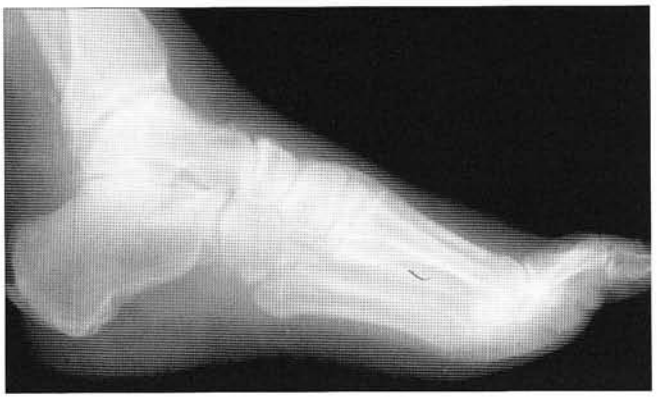

Figure 1. Focal osteolytic process of the cuboid.

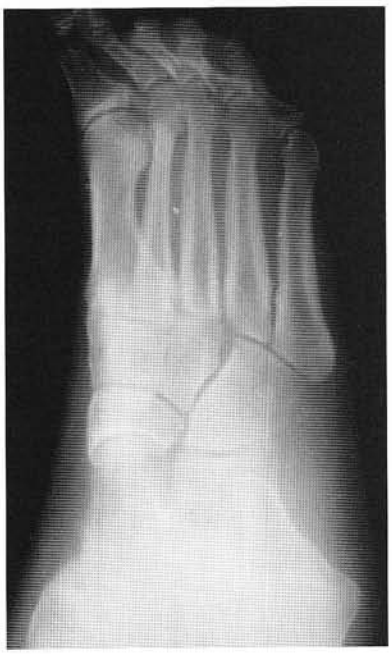

Figure 2.

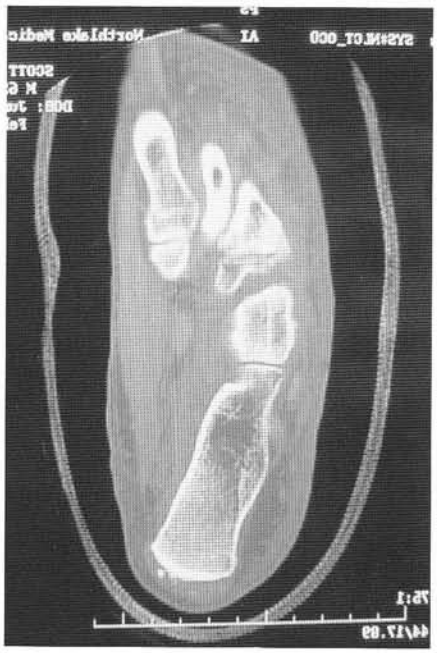

Figure 3. Destructive lesion with a differential diagnosis of OM and metastasis.

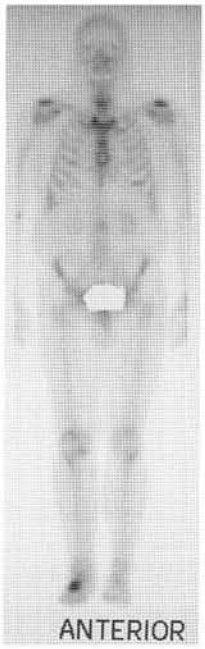

Figure 4. Increased radiotracer activity in the cuboid.

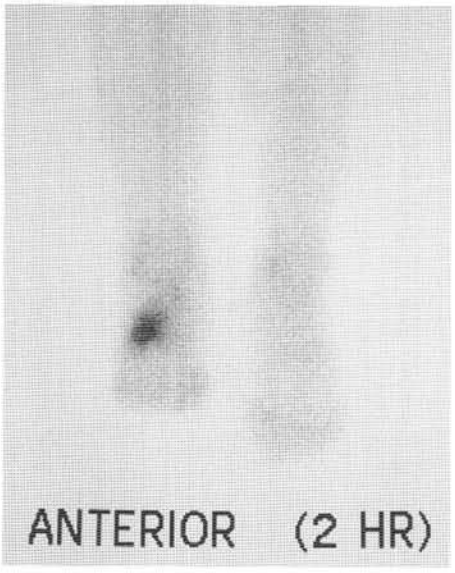

Figure 5.

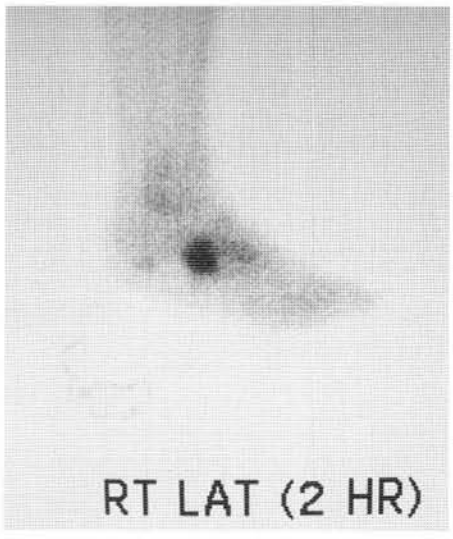

Figure 6.

activity in the cuboid. The findings were nonspecific and could not exclude osteomyelitis and metastasis (Figures 4-6). Finally, the MRI showed abnormal signal intensity with a focal nature involving the entire bone suggesting the possibility of metastasis, also including a differential diagnosis of osteomyelitis (Figures 7-9).

Once all the test results were examined, a bone biopsy and culture was performed. A trephine was used to remove a through and through specimen from the central portion of the cuboid. Histologic slides revealed increased number of plasma cells. The microscopic exam revealed a final diagnosis of chronic osteomyelitis with the final wound culture growing *Staphylococcus aureus*. At this point, infectious disease was consulted. The patient was given a 6-week course of intravenous Rocephin. A C-reactive protein series was performed during the treatment to monitor the therapy. At the end of therapy, a follow-up MRI was performed indicating resolving osteomyelitis of the cuboid.

CONCLUSION

Acute hematogenous osteomyelitis is a complex disease state. If a patient presents with the signs and symptoms suggestive of AHOM, serious consideration should be taken to either diagnosis or rule-out the condition. The increased awareness to common and not-so-common organisms as well as advanced technology of the laboratories to isolate difficult organisms aids in accurate and expedient diagnosis and treatment.[12] Once the diagnosis is made, swift action should be taken to prevent progression. During treatment, the patient should be monitored closely for the signs and symptoms of an infection that may be resistant and/or worsening.[6] Follow-up evaluation should be determined by the severity of disease, response to therapy, and the patient's overall health paying close attention to associated diseases.

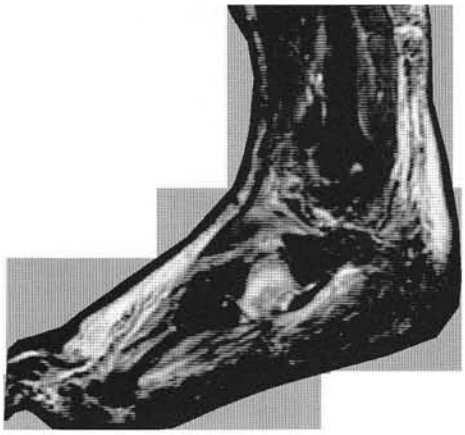

Figure 7. Abnormal signal intensity throughout the cuboid with a focal nature involving the entire bone.

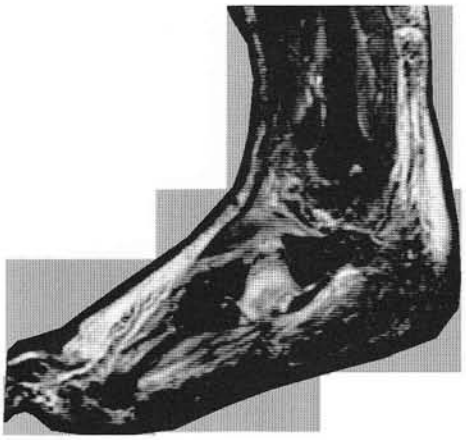

Figure 8.

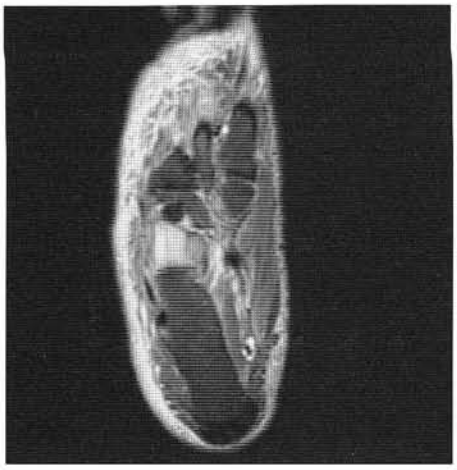

Figure 9.

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