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REVIEW ARTICLE

Osteomyelitis of the lower extremity: pathophysiology, imaging, and classification, with an emphasis on diabetic foot infection

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Abstract Osteomyelitis is inflammation of the bone caused by an infectious organism, and is a difficult clinical problem. The pathophysiology, imaging, and classification of osteomyelitis are challenging, varying with the age of the patient (child versus adult), the chronicity of the infection (acute versus chronic), and the route of spread (hematogenous versus contiguous focus), as well as the immune and vascular status of the patient and affected region. The two most common classification schemes are those of Lew and Waldvogel, and Cierny and Mader. Brodie's abscess is seen in subacute osteomyelitis, while sequestrum, involucrum, and cloaca are interrelated entities of chronic osteomyelitis. Imaging workup of suspected osteomyelitis should begin with radiographs, although MRI is the most accurate imaging test. Three patterns of T1 signal change have been described in the setting of suspected osteomyelitis including confluent intramedullary, hazy reticular, and subcortical. The confluent intramedullary pattern is most associated with osteomyelitis, while hazy reticular is rarely associated with hematogenous osteomyelitis, and subcortical is not associated with osteomyelitis. It can be challenging to differentiate neuropathic arthropathy from osteomyelitis. Osteomyelitis tends to involve a single bone subjacent to an ulcer or sinus tract. In contrast, neuropathic arthropathy tends to involve multiple bones of the midfoot. Subchondral cystic change, thin rim enhancement of a joint effusion, and the presence of intra-articular bodies are more indicative of a neuropathic joint without infection. Biopsy can play an important role in diagnosis and treatment of osteomyelitis.

Keywords Osteomyelitis · Lower extremity · Foot and ankle · Neuropathic arthropathy · Diabetic foot infection

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Introduction

Osteomyelitis, defined as inflammation of the bone caused by an infectious organism, is a difficult clinical problem to diagnose, treat, and classify, often requiring a multidisciplinary approach [1]. Patients commonly present to the emergency department with either signs or symptoms related to underlying osteomyelitis, or with clinical concern for possible osteomyelitis. It is therefore important for the emergency radiologist to have a thorough understanding of the imaging and pathophysiology of this challenging problem. Osteomyelitis has afflicted humanity since the earliest recorded history, with the oldest recorded account in the Edwin Smith papyrus dating from the seventeenth century BC, although signs of chronic osteomyelitis have also been identified in hominid fossils from far earlier [2]. In modern times, the incidence of osteomyelitis has nearly tripled among older adults in the past 30 years, driven predominantly by an increase in diabetes-related pedal osteomyelitis [3]. Post-traumatic osteomyelitis, most commonly due to open fractures, has also increased in prevalence in the past century, thought to be due to improved survival following traumatic injury [4].

The pathophysiology, imaging, and classification of osteomyelitis is challenging, varying with the age of the patient (child versus adult), the chronicity of the infection (acute versus chronic), and the route of spread (hematogenous versus contiguous focus), as well as the immune and vascular status of the patient and affected region. To further complicate matters, common clinical scenarios such as diabetic pedal osteomyelitis have unique anatomic, imaging, and treatment considerations. In this review, we will describe the pathophysiology and imaging of osteomyelitis of the lower extremity in adults, present an overview of the classification of osteomyelitis, and provide a focused discussion on diabetic pedal osteomyelitis.

Pathophysiology of osteomyelitis

Osteomyelitis can be acute, subacute, or chronic in duration (Fig. 1), although the differentiation between these designations is variably described. In general, acute osteomyelitis is defined as either less than 10-day [5] or 2-week [6] duration, while subacute osteomyelitis describes the phase of disease lasting less than 3-month duration [6] but lacking acute symptoms. However, this distinction between acute and subacute phases is arbitrary [7], and the chronicity of osteomyelitis can also be divided into acute and non-acute (encompassing both subacute and chronic) phases. The hallmark of chronic osteomyelitis is the development of bone necrosis, which is usually surrounded by sclerotic, hypovascular bone, thickened periosteum, and compromised surrounding soft tissues [1].

Bone may become infected through contiguous spread, such as extension of an adjacent soft-tissue infection or direct inoculation from trauma, or by hematogenous dissemination. Non-spinal hematogenous osteomyelitis is predominantly a disease of childhood due to its predilection to involve the highly vascularized metaphyseal region of growing bone [6]. Although pediatric osteomyelitis is not the focus of this review, it is helpful to understand the role of osseous blood supply in the etiology of hematogenous osteomyelitis. Specifically, the metaphysis is the primary site of infection in older children and adults due to sluggish flow in terminal capillaries at the junction between the physis and the metaphysis [6]. This is in contrast to the pattern of infection typically seen in young children under 18 months of age, where direct vascular communication between the epiphyseal and metaphyseal vessels contributes to early extension of infection into the epiphysis and resultant greater incidence of septic arthritis in this young age group [8]. In adults, hematogenous osteomyelitis predominantly involves the spine, with the vertebral body endplate the most common nidus of infection. Non-spinal hematogenous osteomyelitis (Fig. 2) in adults is rare [9].

The terminology of various entities seen in non-acute osteomyelitis can be confusing. There are four named lesions that deserve clarification, which include Brodie's abscess, sequestrum, involucrum, and cloaca. Brodie's abscess is a localized manifestation of subacute osteomyelitis, while sequestrum, involucrum, and cloaca are inter-related entities of chronic osteomyelitis.

Brodie's abscess, first described by Sir Benjamin Brodie in 1832, represents an intra-osseous abscess (Fig. 3). It is considered a form of subacute osteomyelitis, although Brodie's abscess has been reported to develop within a variable time period ranging from 1 week to 1 year after the first acute symptoms [10]. The signs and symptoms of acute osteomyelitis, such as fever and recent onset pain, are typically absent. The Roberts classification of Brodie's abscesses, which is beyond the scope of this article, defines six types depending on the anatomic location, with the most classic case a metaphyseal lucent lesion with sclerotic borders [10]. On MRI, the classic appearance of a Brodie's abscess is a fluid signal intensity lesion, sometimes with a peripheral "penumbra" sign. The "penumbra" sign represents a thin rim of vascularized granulation tissue and is reflected as hyperintense signal on T1-weighted images at the periphery of the intra-osseous abscess [11]. The "penumbra" sign is reported to have a specificity of 96% for the presence of infection (although a sensitivity of only 27%) and has been advocated as being a reliable sign to differentiate between subacute osteomyelitis ("penumbra" sign present) and neoplasm [11].

A *sequestrum* is a segment of devascularized bone that becomes separated ("sequestered") from host bone due to surrounding necrosis, thereby providing a safe harbor for bacteria that is inaccessible to antibiotics [5]. A sequestrum is a lesion of chronic osteomyelitis. The definitive treatment of a sequestrum is surgical resection. A sequestrum is best imaged with CT (Fig. 4), where it will appear as a mineralized segment of bone with circumferential surrounding lucency. However, the imaging appearance of an apparent sequestrum is not pathognomonic for chronic osteomyelitis. Several primary bone tumors may produce a mineralized matrix that can simulate a sequestrum, most notably osteoid tumors such as osteoid osteoma or osteoblastoma [12]. In contrast to a sequestrum, which typically features an irregular margin, the calcification at the center of an osteoid osteoma nidus (Fig. 5) is smooth and round [13].

Involucrum describes reactive bone sclerosis that surrounds the sequestrum [12], and which functions to isolate the sequestrum from the bloodstream similar to a walled-off abscess [14].

Finally, a *cloaca* is an opening or rupture of the involucrum that allows granulation tissue to be discharged [14], and which can give rise to a subperiosteal abscess [15]. Eventually, a sinus tract may result if the cloaca communicates with the skin surface through the soft tissues [16]. Longstanding sinus tracts

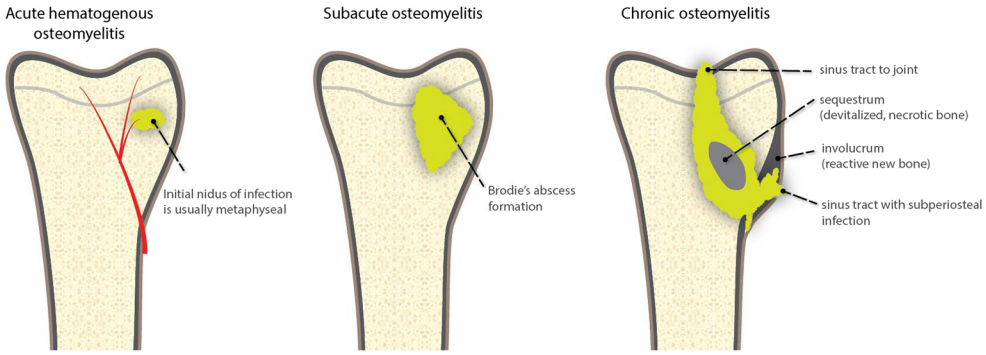

Fig. 1 Illustration demonstrates the findings in acute, subacute, and chronic osteomyelitis. The initial infection in acute hematogenous osteomyelitis is usually metaphyseal. In subacute osteomyelitis, a Brodie's abscess may develop, which is an intra-osseous abscess that is typically seen in young adults. Chronic osteomyelitis features characteristic bony lesions including sequestrum (devitalized, necrotic bone surrounded by osteomyelitis) and involucrum (reactive new bone through which sinus tracts may form)

from chronic osteomyelitis may lead to malignant transformation, with squamous cell carcinoma the most frequent malignancy [1, 17].

Imaging of osteomyelitis

Imaging workup of suspected osteomyelitis should begin with radiographs [15, 18], which are often negative but can provide a helpful anatomic overview and allow one to evaluate for possible alternative diagnoses such as fracture. The radiographic findings of osteomyelitis may differ depending on the route of spread, although the imaging findings mirror the pathophysiology in both hematogenous and contiguous focus osteomyelitis. The earliest radiographic changes of hematogenous osteomyelitis occur in the soft tissues, with soft tissue swelling evident within 2–3 days of symptom onset [19, 20]. Bony changes of hematogenous osteomyelitis are not typically seen until 10–12 days [19] and begin in the medullary cavity and extend outward. In general, at least 30% of the bone matrix must be destroyed for changes to be evident on conventional radiography [20]. Early bone changes include focal osteopenia and periosteal new bone formation. It typically takes 2–3 weeks for a cortical erosion to develop [6], and bony destruction may be evident in the late stage of disease.

In contiguous focus osteomyelitis, the radiologist should carefully search for an ulcer tract, which can be seen on radiographs as a lucent soft tissue defect at the skin surface, often with foci of gas extending to the underlying bone [21]. Radiographic findings of contiguous focus osteomyelitis include ill-defined cortical erosion contiguous with the ulcer tract and focal osteopenia [22], corresponding to trabecular lysis. Bony destruction and soft tissue or intra-osseous gas can be present in advanced cases.

CT is able to image a large anatomic region rapidly and is therefore commonly used in the assessment of infection in the emergency department [23]. While CT is less sensitive than MR and nuclear medicine studies for detecting early intramedullary changes of osteomyelitis, CT is an excellent modality to evaluate for soft-tissue infection in the emergency department, due to its ability to reliably detect soft tissue abscess and soft tissue gas [23]. CT can also detect small foreign bodies that may serve as a nidus of infection [24]. Similar to radiography, the CT findings of osteomyelitis depend on the

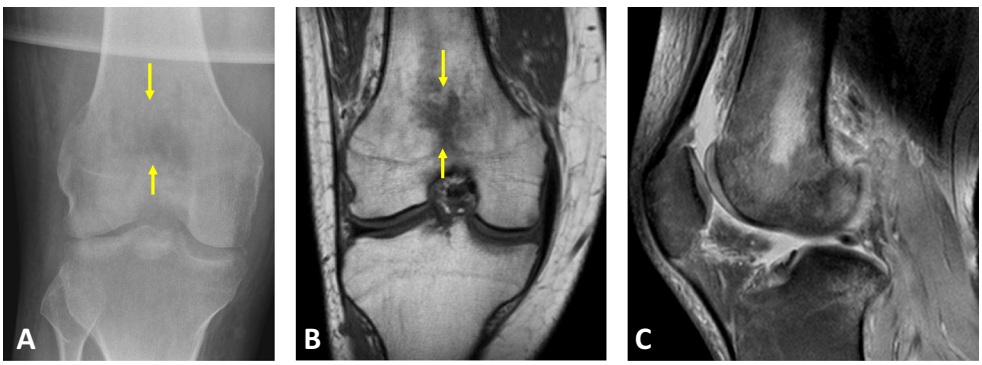

Fig. 2 A 31-year-old male with a history of intravenous drug abuse and biopsy-proven acute hematogenous osteomyelitis. Frontal radiograph of the knee (**a**) demonstrates a lytic lesion of the distal femoral metaphysis (arrows) with a wide zone of transition. Coronal T1-weighted image (**b**) and sagittal proton-density-weighted image with fat suppression (**c**) show heterogeneous bone marrow edema-like signal in the central femoral metaphysis, which appears confluent on the T1-weighted sequence (arrows)

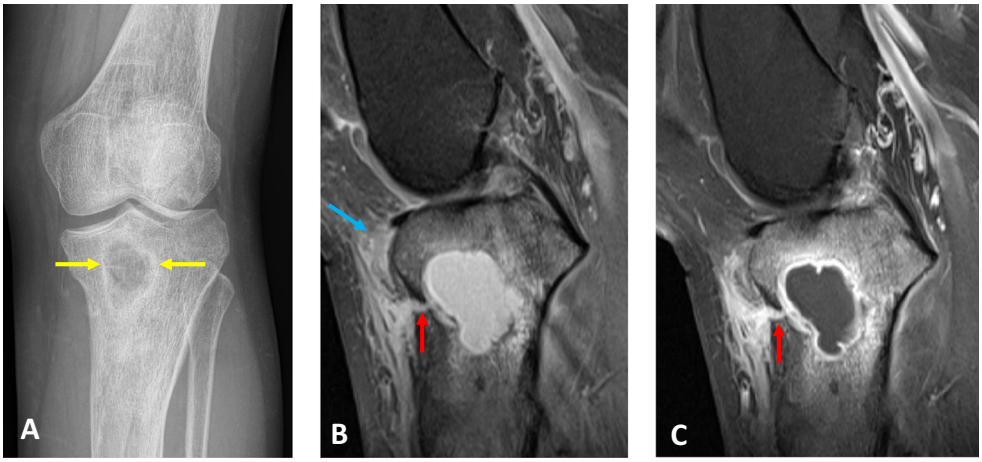

Fig. 3 A 34-year-old female with Brodie's abscess. Frontal knee radiograph (**a**) demonstrates a lucent lesion in the proximal tibial metaphysis with a sclerotic margin (yellow arrows). Sagittal proton-density weighted MR (**b**) and T1-weighted post-contrast MR (**c**), both with fat suppression, demonstrate a peripherally enhancing intra-osseous abscess of the proximal tibial metaphysis, consistent with a Brodie's abscess. There is disruption of the anterior cortex and the periosteum, and formation of a sinus tract (red arrows) into the pretibial soft tissues. Edema-like signal tracks superiorly into the inferior margin of Hoffa's fat pad (blue arrow), raising concern for developing septic arthritis

route of spread but generally include soft tissue swelling, periosteal reaction, decreased attenuation of the medullary space, and cortical erosions [23]. Additionally, CT is the best modality to assess characteristic bony changes of chronic osteomyelitis including sequestrum, involucrum, and cloaca [15, 24].

Ultrasound can visualize superficial fluid collections, joint effusions, or subperiosteal abscesses in pediatric patients [15]; however, ultrasound is not a first-line modality for assessment of suspected osteomyelitis [18].

Radionuclide imaging can play a role in problem solving extremity infection. Notably, radionuclide imaging may be helpful in the setting of suspected osteomyelitis with extensive hardware present [18], and also in differentiating osteomyelitis from neuropathic arthropathy [25]. A three-phase bone scan is sensitive, although not specific in differentiating osteomyelitis from a neuropathic foot due to the increased osteoblastic activity seen in both infection and arthropathy, and is therefore rarely a helpful test in isolation [25]. In contrast, a radiolabeled leuokocyte scan is both sensitive and specific, and is considered the radionuclide test of choice for evaluation of osteomyelitis, with an accuracy of approximately 90% when combined with sulfur colloid imaging [26]. A recent systematic review of imaging tests to evaluate for diabetic foot infection found that a radiolabeled leukocyte scan with ^{99m}Tc-hexamethylpropyleneamineoxime (HMPAO) had a sensitivity of 91% and specificity of 92%, in contrast to MR with a sensitivity of 93% and specificity of 75% for this specific clinical scenario [27]. However, MRI remains the preferred modality for comprehensive assessment of suspected extremity infection in most cases [18].

MRI is the most accurate imaging test for assessment of suspected osteomyelitis, with a meta-analysis showing a sensitivity of 90% and specificity of 79% [28]. Intravenous contrast is preferred for assessment of suspected osteomyelitis,

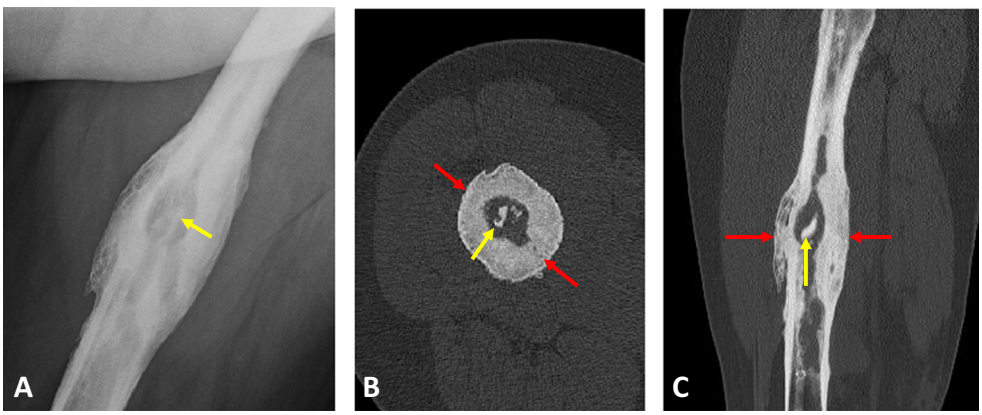

Fig. 4 A 27-year-old male with chronic osteomyelitis, sequestrum, and involucrum. Lateral radiograph of the femur (**a**) demonstrates extensive cortical thickening, and an intramedullary lucency with central sclerosis (yellow arrow). Axial (**b**) and sagittal (**c**) noncontrast CT through the femur demonstrates a central lucent lesion, completely surrounding a sclerotic and irregular segment of bone. The central sclerotic segment (yellow arrows) represents a sequestrum. There is surrounding reactive bone formation (red arrows), also known as involucrum

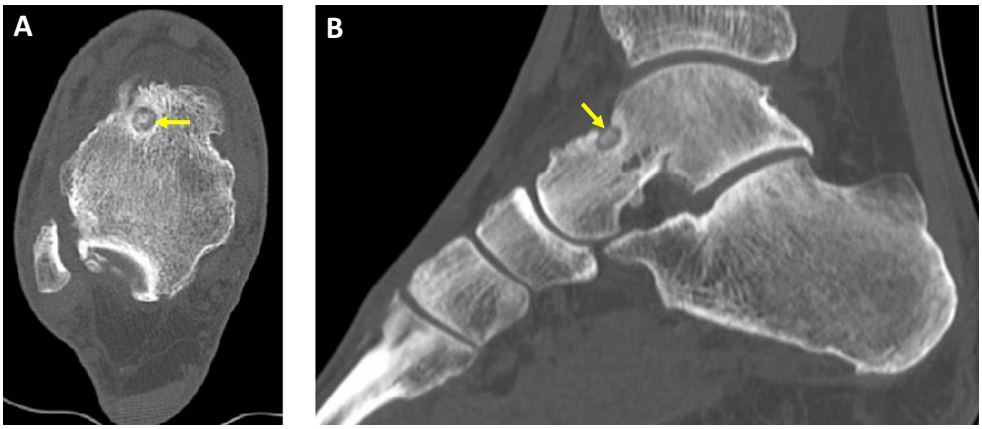

Fig. 5 A 55-year-old male with osteoid osteoma of the talus. Axial (**a**) and sagittal (**b**) non-contrast CT images of the ankle demonstrate a lucent lesion of the anterior aspect of the talar neck with a round calcified central nidus (yellow arrows). In contrast to a sequestrum, which features a central calcification with irregular margins and irregular shape, the central mineralization of an osteoid osteoma has smooth margins and round shape

but is not necessary for its diagnosis. Specifically, soft-tissue abscesses may not be apparent without the presence of contrast to delineate the typical peripheral enhancement pattern. Additionally, the presence of non-enhancing necrotic bone with preserved T1 signal intensity may be masked in the absence of intravenous contrast. Intravenous contrast can help to guide surgical management, as the preferred treatment of necrotic tissues is surgical resection [29], and contrast assists in identification and demarcation of areas of necrotic, non-enhancing bone or soft tissue [30].

The imaging assessment of suspected osteomyelitis should begin with a fluid sensitive sequence (T2-weighted/PD-weighted with fat suppression or STIR), which is the most sensitive sequence type to evaluate for osteomyelitis. If the fluid sensitive sequence is normal, osteomyelitis is exceedingly unlikely to be present. However, bone marrow edema-like signal is a non-specific finding and its presence only alerts one to the *possible* presence of osteomyelitis. If bone marrow edema is present, the T1-weighted sequence is critical to further characterize the signal abnormality and increase specificity. Although rare false negatives have been reported (as will be subsequently discussed), it is generally considered necessary to demonstrate decreased signal intensity on T1-weighted images to diagnose osteomyelitis.

When bone marrow edema is evident on T2-weighted images but the T1-weighted images are normal, radiologists may describe this phenomenon as osteitis, rather than osteomyelitis, implying that infection is thought to be not present. This terminology may lead to confusion, as *osteitis* means "inflammation of the bone" and has been used to imply inflammation of the cortex only [31]. In contrast, *osteomyelitis* means "inflammation of the medullary cavity of bone." Neither term strictly describes the presence or absence of infection, although osteomyelitis is universally understood to mean infection of the bone. To avoid this potential confusion, the authors suggest using terminology such as "bone marrow edema-like signal, thought to be most likely reactive" or simply "reactive osteitis" when describing bone marrow edema with normal T1-weighted images.

Not all signal alterations evident on T1-weighted images correspond to osteomyelitis, however. Three discrete patterns of decreased (iso- or hypointense relative to muscle) signal on T1-weighted imaging performed for suspected pedal osteomyelitis were initially described by Collins et al. [32], including *confluent intramedullary*, *subcortical*, and *hazy reticular* (Fig. 6). Collins reported that all confirmed cases of osteomyelitis demonstrated the confluent intramedullary pattern (Fig. 7) of decreased signal intensity on T1-weighted images, although this pattern was not specific. The hazy reticular (Fig. 8) and subcortical (Fig. 9) patterns did not represent osteomyelitis in any case. A follow-up study of pedal osteomyelitis by Johnson et al. [33] confirmed that the confluent intramedullary pattern of decreased signal on T1-weighted images corresponded to a sensitivity of 95% and specificity of 91% for detection of osteomyelitis; however, this pattern was also present in 9% of cases proven not to represent osteomyelitis. Johnson also confirmed that none of the cases of subcortical or hazy reticular pattern of decreased signal on T1-weighted images represented osteomyelitis. Howe et al. [34] applied these patterns of T1-weighted imaging seen in pedal osteomyelitis by Collins and Johnson to both contiguous focus and hematogenous non-pedal osteomyelitis and found that non-pedal osteomyelitis largely followed the T1-weighted imaging features of pedal osteomyelitis, demonstrating confluent intramedullary decreased signal intensity. However, Howe also described five cases of osteomyelitis with "atypical" imaging findings, where confluent intramedullary decreased signal intensity was absent; four of which were hematological in etiology.

Although decreased signal intensity on T1-weighted images is almost always present in osteomyelitis, there have been rare reports of pathologically or culture-proven osteomyelitis corresponding to regions of normal T1 signal [33, 35], possibly reflecting necrotic bone with fatty marrow signal [30]. Additionally, if bone marrow edema is evident on T2-weighted sequences subjacent to an ulcer, then normal T1-weighted images should be interpreted with caution. Duryea et al. [36] recently demonstrated that 61% of patients with suspected pedal osteomyelitis and isolated T2 signal

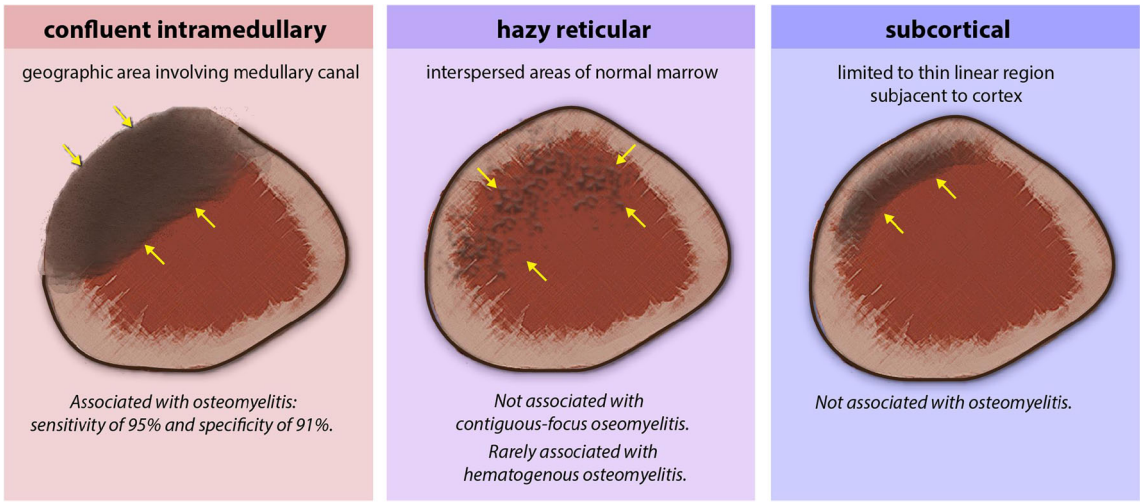

Fig. 6 Illustration demonstrates three described patterns of T1 signal alteration. The confluent medullary pattern is highly associated with osteomyelitis. The hazy reticular pattern of decreased signal intensity on T1-weighted images is not associated with contiguous focus osteomyelitis, but it has rarely been reported to represent hematogenous osteomyelitis. Subcortical T1 signal changes are not associated with osteomyelitis

abnormality deep to an ulcer with corresponding normal T1-weighted imaging ultimately developed osteomyelitis, and therefore these patients should be carefully followed clinically even if treated empirically.

Classification of osteomyelitis

In 1970, Lew and Waldvogel described three fundamental types of osteomyelitis as hematogenous, contiguous focus, and contiguous focus with vascular insufficiency [37–39]. Additionally, any of these categories may be acute or chronic. These basic concepts are still in wide use today; however, no guidance is provided as to the severity of each type of infection or treatment implications.

In 1985, Cierny and Mader developed a classification of osteomyelitis that combined four anatomic types with three host physiologic classes (Table 1) [40]. The Cierny-Mader classification can be helpful to guide treatment options, although this classification scheme is most useful in large or long bones with large marrow spaces and is less helpful in the digits or small bones, such as the foot [5]. Anatomic type 1 represents infection of the medullary space, with the primary lesion endosteal in location, typically due to early hematogenous spread. Type 2 represents early contiguous focus osteomyelitis involving either the periosteum or the cortex. Type 3 is a full thickness cortical disruption, most commonly following trauma but possibly resulting from extension of medullary osteomyelitis. Type 4 is circumferential or "through-and-through" involvement of the bone and surrounding soft tissue. Of these four primary anatomic types of osteomyelitis, type 4

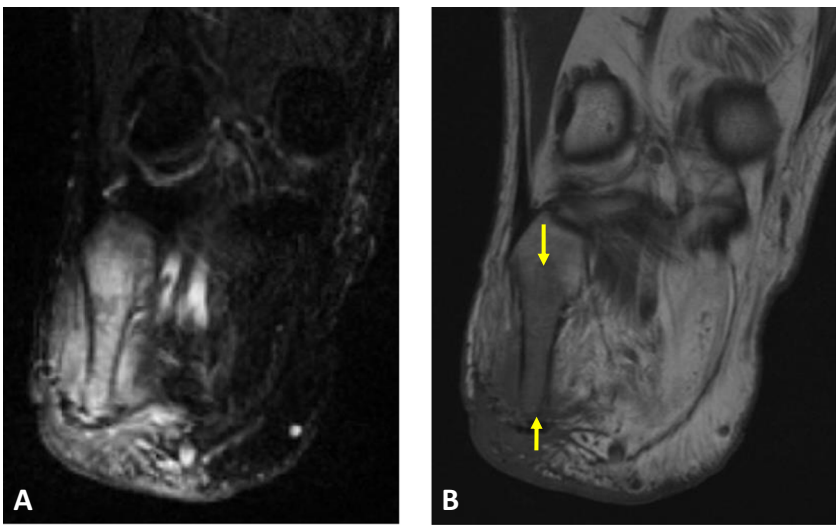

Fig. 7 A 61-year-old woman with osteomyelitis of the fibular stump after below-the-knee amputation, demonstrating typical confluent intramedullary pattern of decreased signal intensity on T1-weighted images. Coronal STIR (**a**) and coronal T1-weighted (**b**) images demonstrates extensive bone marrow edema within the residual fibular stump, corresponding to diffusely decreased signal intensity on T1-weighted images extending through the intramedullary space (arrows), consistent with a confluent intramedullary pattern

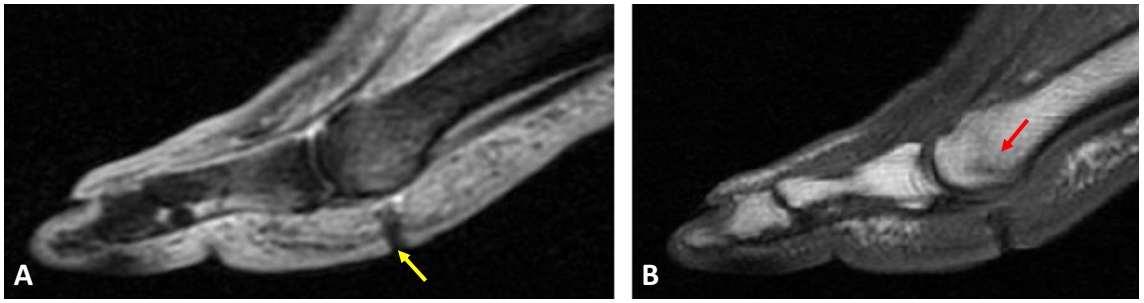

Fig. 8 A 58-year-old man with an ulcer (yellow arrow) subjacent to the great toe MTP, demonstrating the hazy reticular pattern of T1 signal change, which is not associated with osteomyelitis. There is mild bone marrow edema of the head of the first metatarsal evident on the sagittal STIR image (**a**). The corresponding T1-weighted image (**b**) demonstrates hazy reticular decreased signal (red arrow), with intervening fat present between the intact cortex and the regions of signal change. Given the presence of the ulcer directly subjacent to the area of signal change, a CT-guided biopsy was performed, which was negative for osteomyelitis. Although the hazy reticular pattern is not associated with contiguous focus osteomyelitis, this pattern has rarely been associated with hematogenous osteomyelitis

is the most severe and difficult to treat, with aggressive debridement necessary to lower the treatment failure rate, but with surgery inevitably causing unstable bone and soft tissue defects [41]. The host physiology is divided into three classes, including normal immunity (A-host), local or systemically compromised immunity (B-host), and hosts in whom treatment is worse than disease (C-host).

For simplification, the authors suggest thinking of anatomic types 1 and 2 as early disease (type 1 is early hematogenous and type 2 is early contiguous focus). Types 3 and 4 are simply more advanced disease, which may be from progression of contiguous focus or hematogenous osteomyelitis. Since types 1 and 2 are not progressive, it may be more intuitive to emphasize the descriptive name of each anatomic type rather than the number (Fig. 10).

Differential diagnosis of non-pedal osteomyelitis

The differential diagnosis of greatest clinical concern when evaluating a case of non-pedal osteomyelitis is malignancy. In particular, the imaging appearance of Ewing sarcoma (Fig. 11) often overlaps with osteomyelitis, especially in the younger patient population. Ewing sarcoma is the second most common primary bone neoplasm in children and young adults, typically occurring in the long bones of the lower extremities and pelvis in patients between 1 and 30 years of age [42]. The clinical presentation of Ewing sarcoma may mimic osteomyelitis, commonly presenting with pain, swelling, and fever from tumor necrosis. Additionally, it is often difficult to differentiate osteomyelitis from Ewing sarcoma on radiographs and MRI. One study showed that the most reliable MR imaging feature to differentiate between these two entities

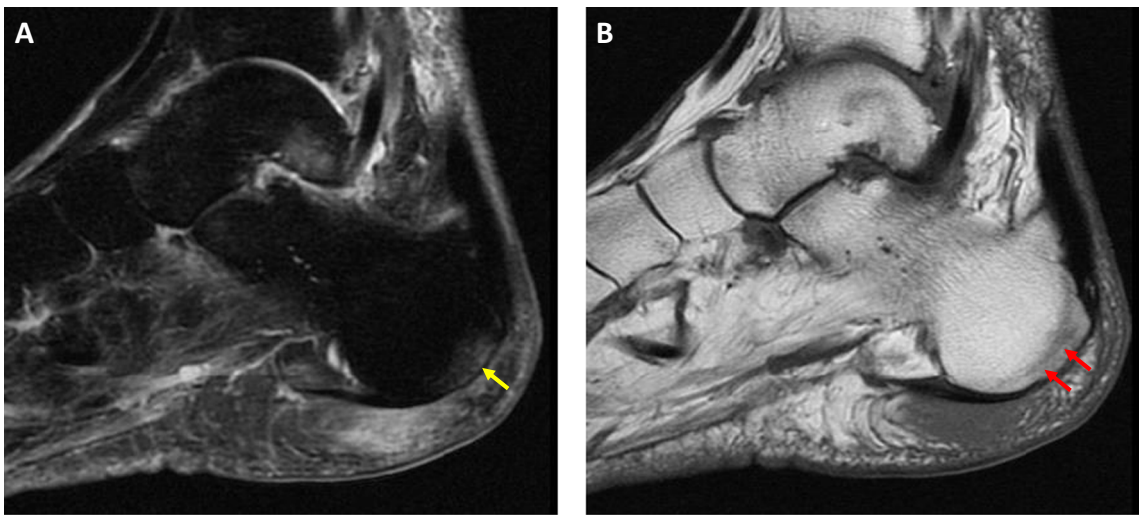

Fig. 9 A 61-year-old woman with mild signal changes of the plantar calcaneus demonstrating the subcortical pattern of decreased signal on T1-weighted images, which is not associated with osteomyelitis. Sagittal STIR MR (**a**) demonstrates edema of the plantar fat pad and mild bone marrow edema of the calcaneus more posteriorly (yellow arrow). The sagittal T1-weighted image (**b**) demonstrates corresponding decreased signal intensity confined to the subcortical region (red arrows). A biopsy was not performed in this case; however, the patient recovered fully with conservative management only

Table 1 The Cierny-Mader combined anatomic and physiologic classification of osteomyelitis

Anatomic type	
Type 1	Medullary osteomyelitis (early hematogenous)
Type 2	Superficial osteomyelitis (early contiguous focus)
Type 3	Localized osteomyelitis
Type 4	Diffuse osteomyelitis
Physiologic class	
A-host	Normal physiologic response to infection
B-host	Immunity compromised locally or systematically
C-host	Treatment worse than disease

is the presence of a sharp and well-defined margin of the bone lesion on T1-weighted and STIR sequences, seen in all patients with Ewing sarcoma but in no patients with osteomyelitis in a study of 28 patients [43]. However, a larger and more recent study of 63 patients (32 with osteomyelitis and 31 with Ewing sarcoma) [44] found no single distinguishing feature, although permeative cortical involvement and soft-tissue mass were more likely in subjects with Ewing sarcoma, while a serpiginous tract was more likely in osteomyelitis. Additionally, as previously mentioned, the "penumbra" sign of a Brodie's abscess, representing vascular, T1-hyperintense granulation tissue, is highly specific for infectious etiology, although to our knowledge, there is a single case report where a diffuse large B cell lymphoma mimicked Brodie's abscess with an apparent penumbra sign [45].

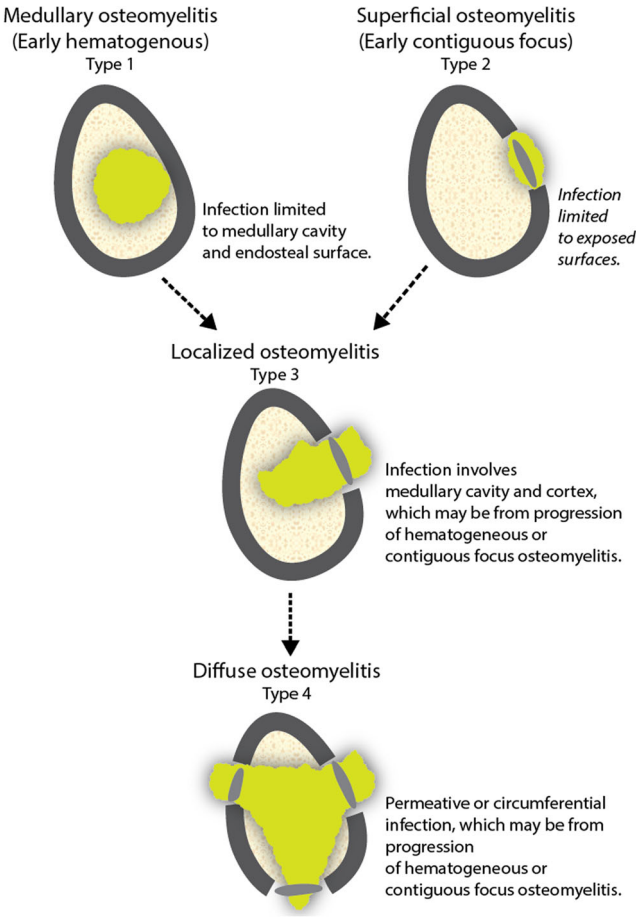

Fig. 10 The Cierny-Mader classification of osteomyelitis. Medullary osteomyelitis (type 1) and superficial osteomyelitis (type 2) can be thought of as early hematogenous and early contiguous focus, respectively. Note that types 1 and 2 are not sequential. Localized osteomyelitis (type 3) is from progression of contiguous focus or hematogenous osteomyelitis, and diffuse osteomyelitis (type 4) is "through-and-through" disease of the bone and surrounding soft tissues

Diabetic pedal osteomyelitis

Over one million cases of diabetic foot complications presented to United States emergency departments from 2006 to 2010, with serious adverse outcomes in 22.1% including mortality (2%), sepsis (9.6%), and amputation (10.5%) [46]. Foot ulcers are a common complication of diabetes, seen in 5.8% of diabetic patients over a 3-year period of observation, and greatly contribute to health care spending with the average cost per patient reaching nearly $28,000 in 1999 [47]. Fifteen percent of diabetic patients with ulcers also develop osteomyelitis [47]; however, the imaging assessment of suspected osteomyelitis in diabetic patients is made more difficult by the often-concomitant presence of neuropathic arthropathy and other bony changes in the feet including infarct, avascular necrosis, osteochondritis, and occult fracture [48].

The etiology of diabetic foot infection is complex, with sensory, autonomic, and motor neuropathy thought to be the primary factors, and vascular insufficiency and relative immunodeficiency the secondary factors [40]. The sensory neuropathy predisposes to mechanical trauma without awareness. The autonomic neuropathy decreases sweat production, leading to a buildup of abnormal dry callus that is prone to cracking and ulcer formation, thereby allowing entry of microorganisms into the soft tissues. The motor neuropathy affecting the intrinsic muscles of the foot leads to gait disturbances, including hammer toes and claw toes, which result in maldistribution of weight-bearing and elevated focal skin pressure. Additionally, diabetic patients often develop an Achilles contracture, which leads to increased plantar forefoot pressures that contribute to forefoot callus and ulceration [49, 50]. Finally, when microorganism entry occurs, the secondary factors of vascular insufficiency and relative immunodeficiency of diabetes hinder proper healing. Successful healing requires an increase in local perfusion, which the ischemic lower extremity cannot adequately supply since its microcirculation is already maximally or near-maximally vasodilated to provide rest perfusion [51].

By the Lew and Waldvogel classification, nearly all diabetic patients with pedal osteomyelitis have chronic contiguous focus infections [31], typically associated with

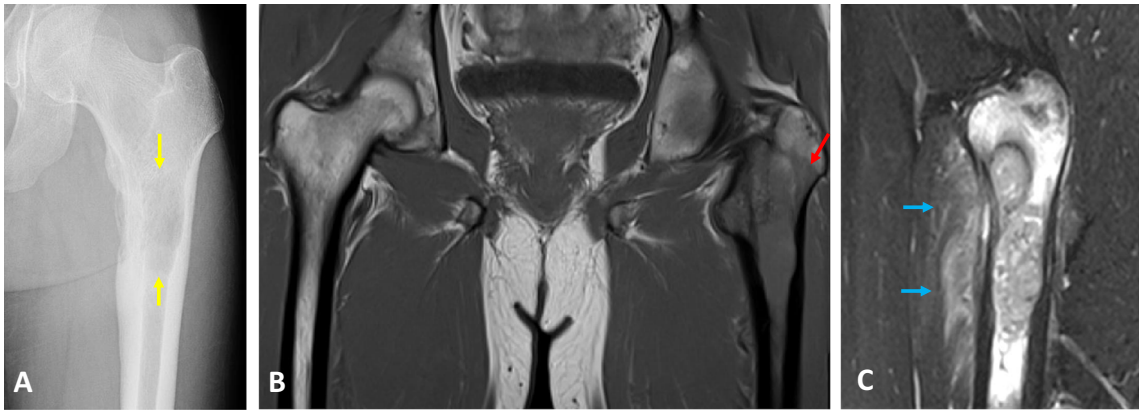

Fig. 11 A 21-year-old male with Ewing sarcoma. Radiograph (**a**) demonstrates a subtle lucency (yellow arrows) of the left proximal femoral diaphysis with associated endosteal scalloping laterally and cortical thickening medially. This appearance can mimic osteomyelitis. Coronal T1-weighted STIR image of both hips (**b**) demonstrates diffusely decreased signal intensity of the proximal femur. Note the sharp transition (red arrow) between the lesion and normal marrow at the greater trochanter, a feature that is suggestive of tumor rather than infection. Sagittal PD-weighted image with fat suppression (**c**) shows diffuse bone marrow edema of the proximal femur with an associated soft-tissue mass (blue arrows), an additional feature that is seen in Ewing sarcoma rather than infection

vasculopathy [40]. By the Cierny and Mader classifications, the majority of diabetic pedal osteomyelitis would be classified as superficial (type 2) in a physiologically compromised host with local and systemic compromise (B-host), while more severe or chronic infections may progress to localized (type 3) or diffuse (type 4) osteomyelitis [31]. The Cierny-Mader classification is not especially useful in the evaluation of pedal osteomyelitis, and to our knowledge, this classification system is not used in the radiology literature of pedal osteomyelitis.

The fifth metatarsal, first metatarsal (Fig. 12), calcaneus (Fig. 13), and great toe distal phalanx are the four most frequently involved anatomic sites of pedal osteomyelitis [52]. Septic arthritis is commonly seen, reportedly in 33% of all feet imaged for suspected osteomyelitis, most frequently involving the fifth and first metatarsophalangeal joints and manifesting on MR as synovial enhancement and adjacent cellulitis [52].

Primary and secondary signs have been described in the MR imaging of pedal osteomyelitis. As previously discussed, a confluent intramedullary pattern of decreased signal intensity on T1-weighted images is the most accurate primary imaging finding of osteomyelitis in the foot or elsewhere in the skeleton. Secondary signs of osteomyelitis can greatly increase the confidence of diagnosis, especially if there are alterations in bone marrow signal due to concomitant non-infectious processes, and include the presence of cutaneous ulcer, sinus tract, and cortical disruption [53]. Early infection may begin with periostitis [31], manifesting on imaging as fluid signal overlying the cortex. Cortical lesions are common, reflecting the contiguous focus etiology of spread [54].

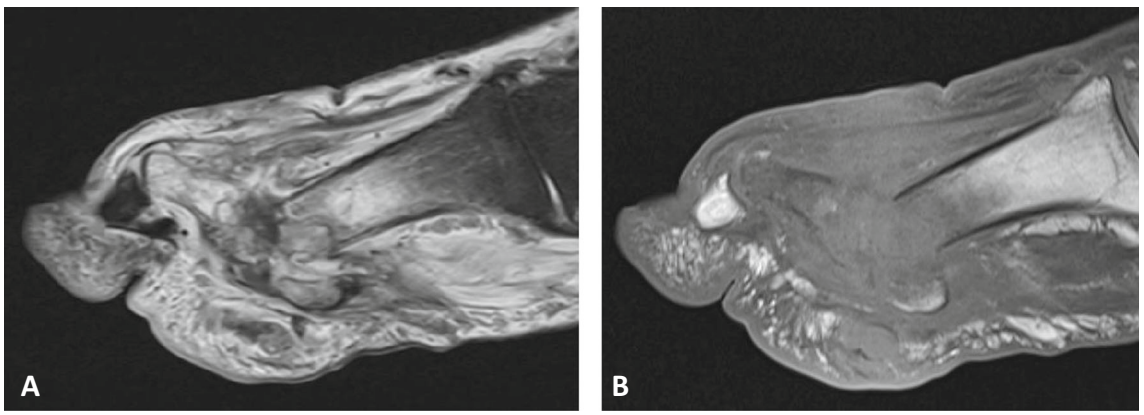

Fig. 12 A 61-year-old male with osteomyelitis of the great toe involving the distal aspect of the first metatarsal and the entire proximal phalanx. Sagittal STIR MR (**a**) demonstrates extensive bone marrow edema-like signal throughout the metatarsal and proximal phalanx, corresponding to a confluent intramedullary pattern of decreased signal intensity on the T1-weighted image (**b**). There is also septic arthritis of the great toe MTP with destruction of the joint

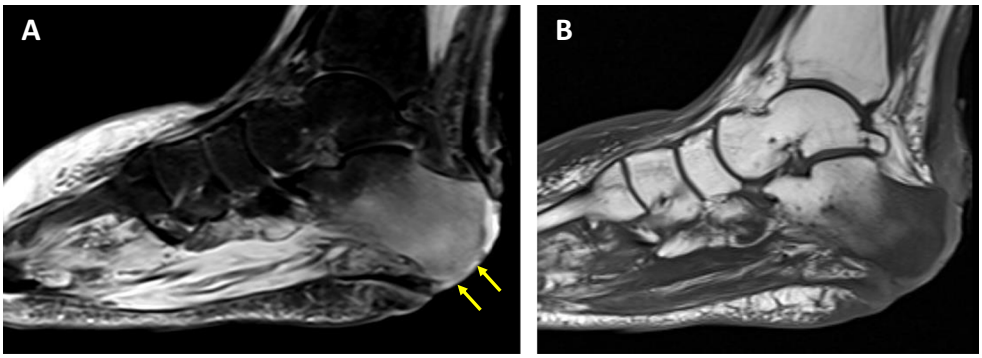

Fig. 13 A 45-year-old male with calcaneal osteomyelitis. Sagittal STIR MR (**a**) of the foot demonstrates extensive bone marrow edema throughout the posterior aspect of the calcaneus, contiguous with a posterior heel ulcer (arrows). The T1-weighted sagittal MR (**b**) demonstrates corresponding confluent intramedullary pattern of decreased signal intensity.

Distinguishing between neuropathic arthropathy and osteomyelitis

A common and challenging task for the radiologist is to differentiate between osteomyelitis and neuropathic arthropathy, otherwise known as Charcot arthropathy. The eminent neurologist Jean-Martin Charcot first described *arthropathy of ataxic patients* in 1868 as being caused by neurosyphilis [55]. Interestingly, although diabetes is now by far the most common cause of peripheral neuropathy leading to neuropathic arthropathy, it was not until 1959 that diabetes was recognized as an important cause of neuropathic arthropathy of the foot [56].

Table 2 Imaging findings to aid in the differentiation between osteomyelitis and neuropathic arthropathy

Imaging finding	Osteomyelitis	Non-infected Charcot arthropathy
Direct imaging findings suggestive of osteomyelitis		
Confluent, medullary decreased signal intensity on T1-weighted imaging	Common	Less common
Metatarsal, phalangeal, or calcaneal location	Very common	Rare
"Ghost sign" (disappearance of cortices on T1-weighted imaging)	Suggests infected neuropathic arthropathy	Not reported to date
Indirect imaging findings suggestive of osteomyelitis		
Single bone involved	Common	Rare
Cortical disruption	Common	Rare
Replacement of soft-tissue fat	Common	Less common
Sinus tract	Exclusive	Never
Imaging findings suggesting absence of infection		
Midfoot location	Uncommon, unless weight-bearing bone due to midfoot collapse	Common
Normal marrow signal on T1-weighted images	Very rare (may represent focal necrosis)	Uncommon
Cystic change	Very rare	Common
Thin rim enhancement of joints	Uncommon	Common
Intra-articular bodies	Uncommon	Common

Several imaging features have been described to help differentiate between neuropathic arthropathy and osteomyelitis [57, 58], as summarized in Table 2. However, it can often be very difficult to distinguish between these two entities, especially if a patient has an underlying neuropathic foot with a clinical question of superimposed infection. In general, osteomyelitis tends to involve a single weight-bearing bone subjacent to an ulcer, with the calcaneus, fifth metatarsal, first metatarsal, and first distal phalanx the most common sites (Fig. 14). In contrast, neuropathic arthropathy (Fig. 15) tends to involve multiple bones of the midfoot [59]. However, the altered gait of neuropathic arthropathy can cause typically non-weight-bearing bones, such as the cuboid, to become weight-bearing and predispose to subjacent callus and ulceration with subsequent development of osteomyelitis and septic arthritis of the midfoot [58, 59]. Bone marrow edema-like signal is almost invariably present in both osteomyelitis and non-infected neuropathic arthropathy and is not helpful to differentiate between the two entities.

The only imaging feature of conventional MRI that has been shown to be exclusive to osteomyelitis is a sinus tract extending from the ulcer to the infected bone [57]. Interestingly, the presence of an ulcer alone is seen equally commonly in patients with neuropathic joints with and without superimposed infection. Therefore, the presence of an ulcer does not help to differentiate between neuropathic arthropathy and osteomyelitis, unless a sinus tract to bone is present. However, the absence of an ulcer is a helpful ancillary finding to exclude osteomyelitis, as pedal osteomyelitis is considerably less likely to be present in the absence of ulceration. Imaging features seen more commonly in infection include replacement of soft-tissue fat, soft-tissue fluid collection, and extensive marrow abnormality. Subchondral cystic change, thin rim enhancement of a joint effusion, and the presence of intra-articular bodies are more indicative of a neuropathic joint without infection. The "ghost sign" (Fig. 16) may also be helpful to differentiate non-infected neuropathic arthropathy from superimposed infection [60]. The "ghost sign" is said to

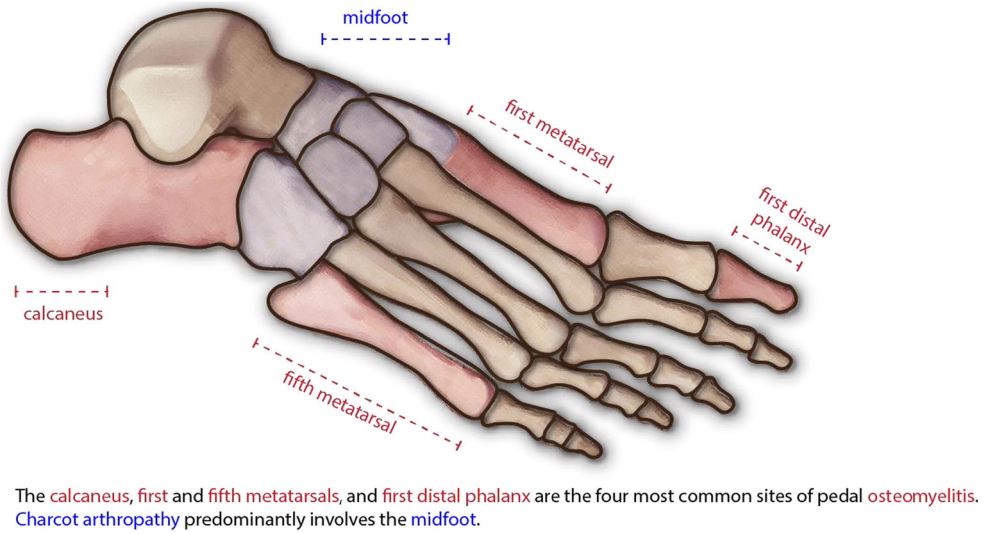

Fig. 14 Illustration demonstrates the typical location of neuropathic arthropathy (blue), which predominantly involves the midfoot, and osteomyelitis (red), which occurs most commonly in the calcaneus, the fifth and first metatarsals, and the first distal phalanx

be indicative of superinfection and is present when the cortical margins "disappear" on T1-weighted images and "reappear" on T2-weighted or contrast-enhanced T1-weighted images. The absence of the "ghost sign" is said to be due to true destruction of the bones by advanced neuropathic arthropathy; however, this sign has not been clinically validated.

Recently, diffusion-weighted imaging has been suggested as allowing accurate differentiation between neuropathic arthropathy and osteomyelitis [61]. Additional advanced MRI techniques include dynamic contrast-enhanced MR, MR angiography, and MR neurography [62], although these techniques are not in widespread clinical use.

Role of image-guided biopsy in diabetic foot infection

Evaluation of a bone specimen is considered the gold standard to diagnose osteomyelitis and to determine the responsible organism and its antibiotic susceptibility [63, 64]. Wound swabs are not considered a reliable method to identify the causative organism, as wound culture results are only concordant with bone cultures in a minority of cases [65]. While the traditional management of diabetic foot infection is surgical resection of the infected bone and soft tissues, there is an emerging trend to perform non-surgical management with prolonged, targeted antibiotic therapy [66]. Bone biopsy is considered especially helpful in patients treated conservatively, as the patients who received targeted therapy based on biopsy culture results have greater therapeutic success compared to those patients who did not receive bone biopsy [67].

Image guidance of percutaneous bone biopsy has the advantage of precisely localizing even small target areas, to document that the targeted area was actually biopsied and to triangulate the needle path to the target area from the skin entry site. The specimen should be obtained by going through intact skin, and pre-procedure imaging should be carefully reviewed to ensure that a deep fluid collection or phlegmon is not traversed by the needle. The highest diagnostic yield is obtained by performing the biopsy before antibiotic therapy is initiated, or by imposing an antibiotic vacation for 14 days [66] if the patient is able, although a shorter antibiotic-free period may also be acceptable [66]. Complications such as bleeding, introduction of bacteria into bone, or fracture are rare [64]. The bone specimen should be sent for both histology and culture,

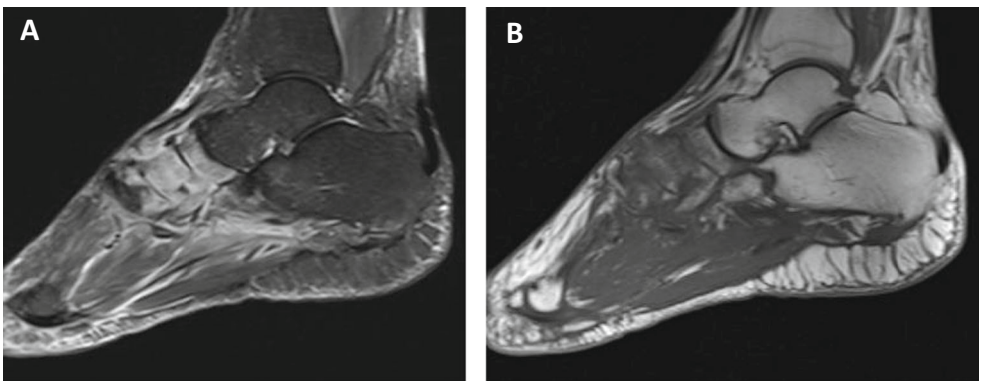

Fig. 15 A 60-year-old female with neuropathic arthropathy, without superimposed infection. Sagittal STIR (**a**) and T1-weighted image (**b**) demonstrate diffuse bone marrow edema involving multiple bones of the midfoot including the navicular and the cuneiforms. There is no plantar ulcer and the subcutaneous fat is preserved

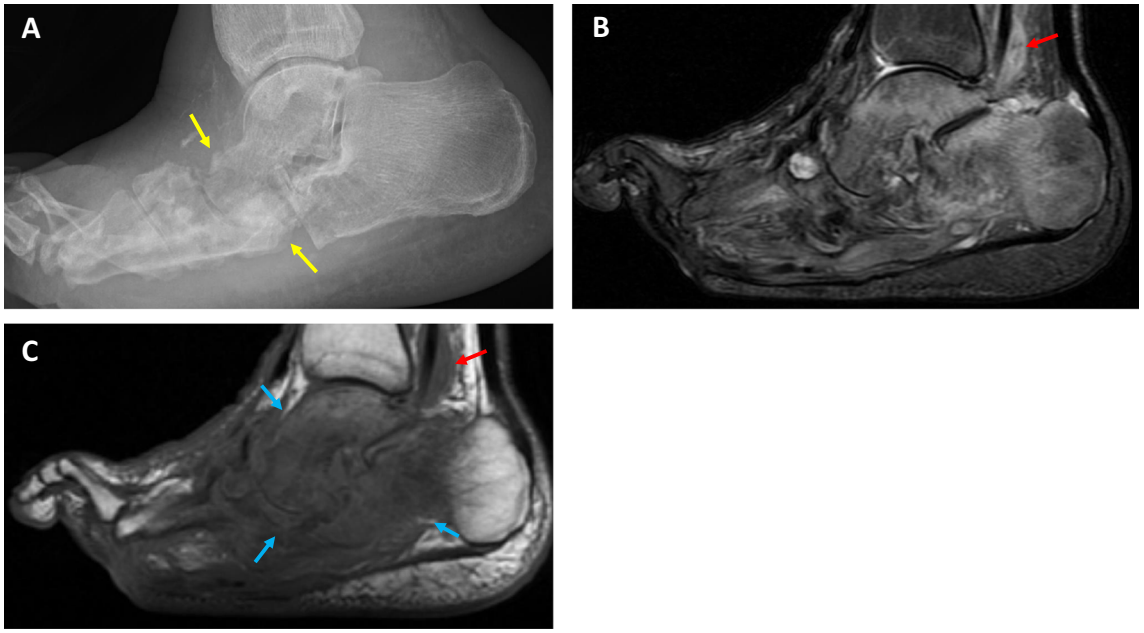

Fig. 16 "Ghost" sign of osteomyelitis superimposed upon neuropathic arthropathy. Lateral radiograph of the foot (**a**) demonstrates extensive destruction and debris formation of the midfoot with marked plantarflexion of the talus and fragmentation of the cuboid (yellow arrows), consistent with neuropathic joint. Sagittal STIR (**b**) and T1-weighted (**c**) MR images demonstrate severe extensive edema of the midfoot. The margins of the bones appear to disappear on the T1-weighted image (blue arrows), suggestive of the "ghost" sign, which has been reported to be indicative of osteomyelitis. There is also tenosynovitis of the peroneus longus tendon (red arrows), which may be infectious

which maximizes the chance of an accurate diagnosis of osteomyelitis as well as specifically identifying the pathogenic organism(s).

Treatment of lower extremity osteomyelitis varies depending upon the extent of infection and patient-specific factors such as co-morbidities and vascular status. While antibiotic therapy alone can be successful, often patients with pedal osteomyelitis present with chronic osteomyelitis adjacent to an ulcer. In these patients, an operative debridement of the ulcer and infected bone may be required, followed by culture-specific antibiotic therapy. Pressure-offloading operative techniques are also critical to prevent ulcer persistence or recurrence [25]. Common offloading techniques include claw toe or hammertoe correction and Achilles tendon lengthening procedures. If removal of all devitalized bone will render the extremity unstable or dysfunctional, amputation may be the most appropriate course. Many different amputation levels exist, including digit, trans-metatarsal, Chopart joint, and below knee—with the decision dependent upon the specific clinical scenario.

Conclusion

Osteomyelitis is a common clinical problem with increasing incidence, driven primarily by the increased prevalence of diabetes-related foot infection. The vast majority of cases of adult osteomyelitis are caused by spread of contiguous focus of infection, and non-spinal hematogenous osteomyelitis in adults is rare. Radiographs are often negative in the early stage of osteomyelitis, with bony changes evident after 10–12 days including focal osteopenia, periosteal reaction, and cortical erosion, dependent on the route of spread. MRI is the best non-invasive imaging modality to evaluate for osteomyelitis, and the confluent intramedullary pattern of decreased signal intensity on T1-weighted images is the single most reliable sign to diagnose osteomyelitis. In children and young adults, a primary differential consideration of osteomyelitis is Ewing sarcoma. In the adult diabetic patient, differentiation between neuropathic arthropathy and osteomyelitis can be challenging, although there are helpful MR imaging features to aid in the distinction. Additionally, a radiolabeled leukocyte scan is a sensitive and specific test and may be helpful to differentiate pedal osteomyelitis from neuropathic arthropathy. Biopsy is the gold standard to diagnose osteomyelitis and determine the optimal antibiotic therapy, which can lead to greater therapeutic success.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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