An unusual complication following Charcot neuroarthropathy

Robert Morley and Francis Webb

Charcot neuroarthropathy is a complication of diabetes mellitus and a potentially devastating condition sometimes resulting in ulceration and subsequent amputation. Recognising the condition can be challenging in the early stages and it is regularly misdiagnosed, thus increasing patient morbidity. Treatment, meanwhile, requires prolonged and specialist care primarily involving cast immobilisation while simultaneously optimising comorbidities. The authors demonstrate an unusual complication in a case of Charcot neuroarthropathy and how it was managed jointly between the community and acute care settings.

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Article points

1. Charcot neuroarthropathy is a devastating condition causing bone and joint destruction in which diabetes mellitus is the leading cause.
2. Diagnosis of Charcot neuroarthropathy is commonly delayed or missed altogether increasing the prospect of progression to deformity, ulceration and amputation.
3. Charcot neuroarthropathy can occur concomitantly with osteomyelitis where contiguous spread through a foot ulcer is the most common cause.
4. Differentiating Charcot neuroarthropathy from osteomyelitis can be challenging often requiring a multitude of diagnostic investigations and imaging modalities.

Key words

- Charcot neuroarthropathy
- Diabetic complications
- Infection
- Osteomyelitis

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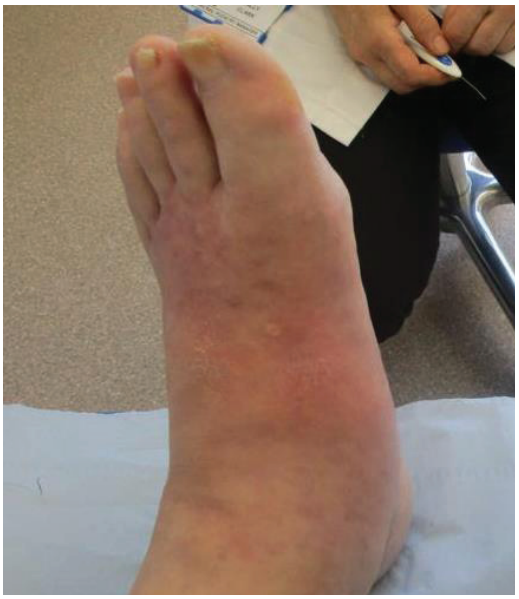
Charcot neuroarthropathy (CN) is a non-infectious condition of bone and joint destruction as a consequence of neuropathy, trauma and perturbations in bone metabolism (Guven et al, 2013). Diabetes mellitus is now the leading cause in which the foot is most commonly affected (Jones et al, 2000; Rogers et al, 2011; Guven et al, 2013). Diagnosis is commonly delayed or missed altogether with patients often progressing to deformity and ulceration (Rajbhandari et al, 2002) and a major cause of morbidity (Rajhbandari et al, 2002). With increased incidence of diabetes CN is only likely to increase in prevalence (Van der ven et al, 2009) heightening the need for early diagnosis and treatment.

The authors present an unusual complication following CN requiring multidisciplinary medical and surgical management with the aim of reaching a satisfactory outcome.

Case presentation

A 64-year-old male patient with type 1 diabetes presented with a five-week history of a warm, red, swollen, painless foot and loss of the medial longitudinal arch with no recollection of trauma and no improvement after five weeks of antibiotics prescribed by his GP (*Figure 1*). There was no evidence of ulceration and the foot was notably warmer with infrared temperature testing revealing an increase above two degrees on all areas tested compared to the contralateral foot.

A thorough medical and drug history were undertaken revealing a 45-year history of type 1 diabetes with other comorbidities, including peripheral neuropathy, retinopathy and anaemia. He was medicated with insulin, ferrous sulphate, atorvastatin and duloxetine for painful peripheral neuropathy. Neurological testing demonstrated an inability to appreciate a 10-g monofilament or vibration sensation within both feet consistent with profound peripheral neuropathy. Vascular testing revealed regular, palpable pedal pulses with biphasic Doppler signal audible for dorsalis pedis and posterior tibial pulses, and no evidence of ischaemia. The patient felt well in himself with all observations, including blood pressure, pulse, temperature, oxygen saturation and respiration within range and documented on



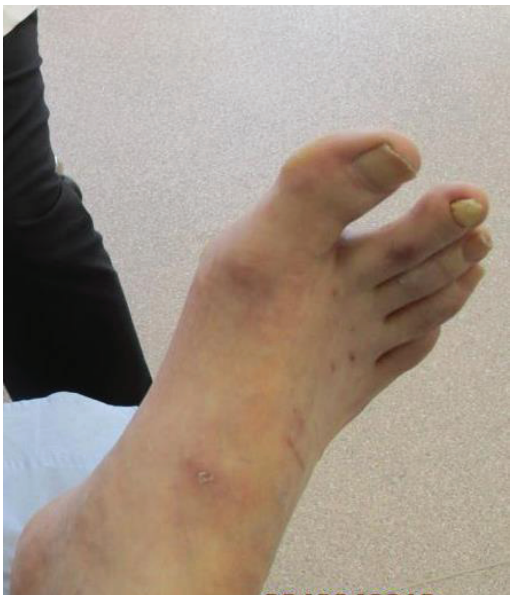


Figure 1. (a) A warm, erythemic and oedematous left foot with loss of the medial longitudinal arch and (b) contralateral foot.

the national early warning score (NEWS). His previous blood glucose level was checked and found to be elevated with an HbA_{1c} at 78 mmol/mol (9.3%) taken 3 months previously.

The patient was sent for X-rays, which confirmed Charcot neuroarthropathy affecting the talo-navicular, naviculo-cuneiform and tarso-metatarsal joints (*Figure 2*). Infection was not suspected due to there being no breach in the skin and, therefore, no portal of entry for bacteria and radiographic confirmation of CN.

The patient was subsequently counselled on the nature of this devastating condition and the associated prolonged recovery time of approximately 6–12 months of cast immobilisation. A treatment plan was put in place recommending non weight-bearing total contact casting to immobilise, prevent further damage and enable osseous consolidation. In addition, the patient was referred to physiotherapy as he initially appeared unsteady on his crutches and was referred to the diabetes specialist nurse to optimise glycaemic control.

The patient was reviewed back after 72 hours to ensure he was tolerating the cast and crutches. There were no iatrogenic abrasions or ulcerations as a consequence of the cast and was subsequently seen weekly for cast change, infra-red thermometer measurement and regular X-rays to ensure he was progressing from the active towards the inactive phase of Charcot.

For the first 10 weeks of treatment the patient tolerated the cast well and was fully compliant. However, the clinical signs and symptoms were not settling with the patient appearing to remain in the active phase with erythema, swelling and heat remaining elevated. A second opinion was sought with other podiatric colleagues who fully agreed with the diagnosis and treatment strategy.

After 15 weeks of treatment, however, the clinical picture deteriorated with ulceration appearing on the medial and lateral aspects of the foot both of which probed to bone and discharged a small amount of yellow pus (*Figure 3*).

Osteomyelitis was immediately suspected. The patient remained systemically well, which was documented in the NEWS. Diagnostic investigations ensued, including charcoal swabs for culture and sensitivity and blood work to determine white cell count and differential, inflammatory markers and liver and renal function tests as it was anticipated the patient would be prescribed a long course of antibiotics and, therefore, baselines were required. A bone biopsy was also arranged for the following day in the operating theatre for diagnostic accuracy with antimicrobial therapy delayed until after the biopsy had been conducted.

The following day the patient attended the community hospital for a bone biopsy as a day case procedure under local anaesthetic (*Figure 4*). Two incisions were created adjacent to the ulcerations through clean skin to prevent

contaminated samples. Multiple bone samples and deep swabs were taken and sent to microbiology and histopathology. Following the biopsy, the incisions and ulcerations were thoroughly irrigated with a povidone iodine and saline 50/50 mix and 5 cm^3 of calcium sulphate (Stimulan®, Biocomposites) impregnated with 120 mgs of gentamicin and 1 g of vancomycin were administered into the biopsy sites and ulceration (*Figure 5*). On microbiological advice, the patient was also commenced on intravenous teicoplanin until the bone biopsy results were made available and a joint consultation arranged at the local acute hospital diabetic multidisciplinary team (MDT) for a second opinion.

Six days following the procedure biopsy results had demonstrated *Staphylococcus aureus* sensitive to flucloxacillin and fucidin amongst other antibiotics. Histopathology results meanwhile showed no evidence of acute inflammation. In line with local guidelines and microbiological results, the teicoplanin was discontinued and the patient commenced on oral flucloxacillin 1 g four times daily and sodium fusidate 500 mgs three times daily. He was followed up twice weekly initially for assessment, redressing's and total contact casting.

The joint consultation with the local acute diabetic foot MDT corroborated our diagnosis that the patient had initially presented with Charcot neuroarthropathy and went on to develop osteomyelitis. The cause of the infection, however, was initially not clear, but following a prolonged discussion with the patient it appeared he had an insect bite at the back of the neck requiring a course of antibiotics along with a cat scratch affecting the contralateral foot within a few weeks of developing his symptoms. It was thought that either of these events may have given rise to haematogenous osteomyelitis with bacteria naturally gravitating towards the closed foot fractures and inflamed tissue within the foot.

Following advice from the consultant diabetologist it was decided that Magnetic Resonance Imaging (MRI) should be arranged to determine the extent of osteomyelitis in addition to continuing with the cast immobilisation and to extend the two oral antibiotics for a total duration of 3 months.

Three weeks following the intervention it was evident that erythema and swelling were settling down considerably and the patient was tolerating the antibiotics with no adverse effects (*Figure 6*). The MRI, meanwhile, confirmed clinical and X-ray findings, which concluded there was background neuropathic arthropathy with superimposed osteomyelitis although the reporting radiologist conceded that it was difficult to differentiate the two pathologies.

As the patient was showing signs of entering a quiescent state weekly appointments were arranged for dressing and cast changes in addition to blood

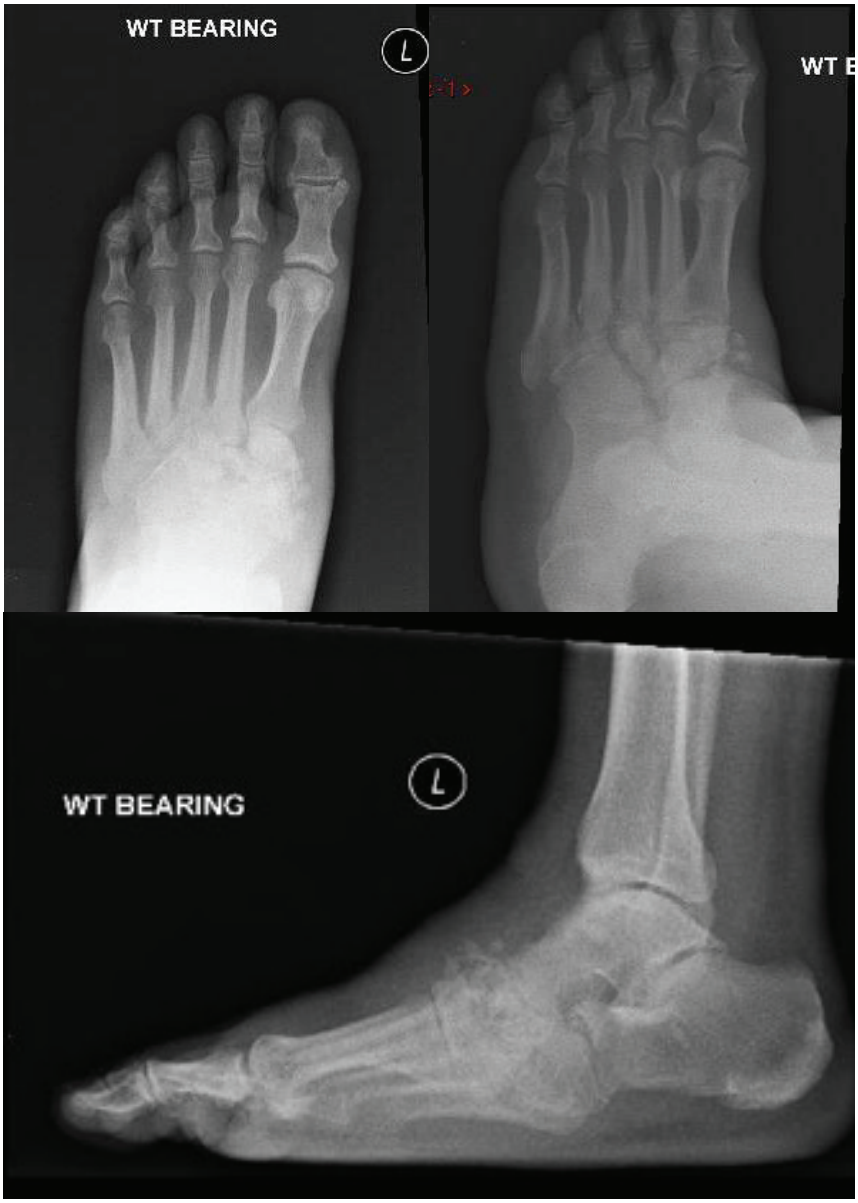


Figure 2. X-ray of the left foot demonstrating mid foot joint destruction in (a) dorsoplantar (b) medial oblique (c) and lateral.

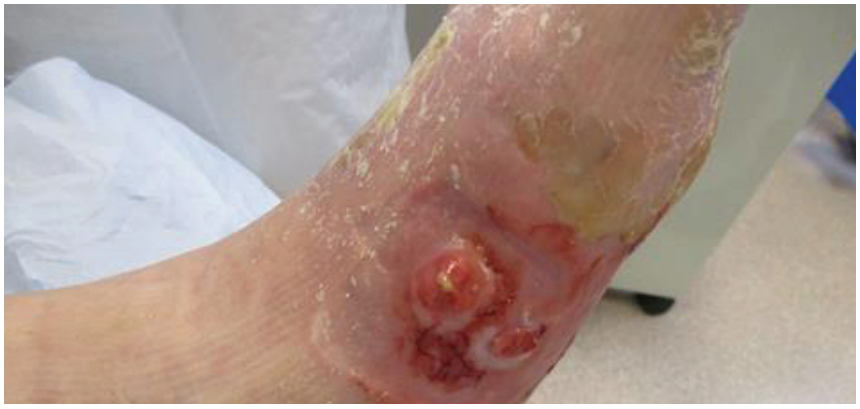


Figure 3. Foot ulceration.

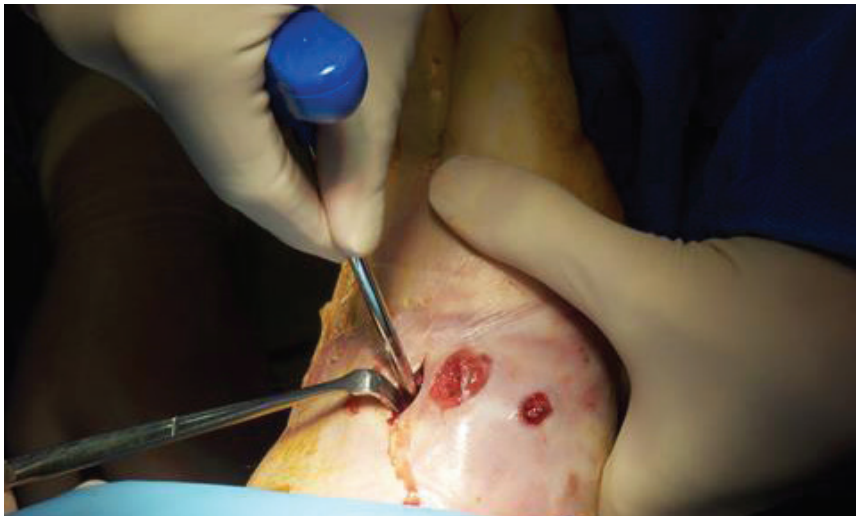


Figure 4. Trephine biopsy of bone.

work to ensure inflammatory markers were reducing and liver and renal function were not adversely affected by the antibiotics. X-rays meanwhile were taken monthly which demonstrated no further loss of alignment with gradual consolidation of bone across the mid foot.

At 3 months post bone biopsy and 6 months post initial presentation, the antibiotics were discontinued. All wounds had healed, erythema and swelling had settled, foot temperatures had normalised and inflammatory markers, including CRP and ESR, had been within normal reference range for the previous 6 weeks suggesting the CN had reached the inactive phase and the infection had resolved. There was also rigidity on manipulation of the mid foot suggesting fracture consolidation and corroborated by X-ray findings and he was subsequently stepped down from a non-weight bearing total contact cast to a partial weight bearing aircast boot until bespoke footwear and total contact insoles were in place.

At 12 months post initial presentation, the foot remains infection and ulceration free with only moderate deformity (*Figure 7*) with X-rays showing minimal loss of alignment between the time of initial presentation and at final discharge (*Figure 8*), which was a consequence medical and surgical management of the infection, total contact casting and patient adherence.

Discussion

Diabetic foot osteomyelitis (DFO) almost always occurs through contiguous spread where bacteria infect bone through the adjacent soft tissues as a consequence of foot ulceration (Jeffcoate and Lipsky, 2004; Donovan and Schweitzer, 2010; Ertugrul et al, 2013). This can occur following CN where foot deformity results in abnormally excessive pressures in what would normally be non-weight bearing areas sometimes leading to ulceration, soft tissue infection and subsequent osteomyelitis.

DFO, however, can be blood borne (Donegan et al, 2013; Ertugrul et al, 2013) where it is also known as haematogenous osteomyelitis (HO). This condition is a rare event following a closed fracture with only 18 cases found following a medline literature search between 1976 and 2015 (Kokutar et al, 2016). The authors were unable to find any previous documented cases of HO following CN of the foot during a thorough medline search.

HO more readily affects children due to the vulnerable and highly vascular metaphysis, which is susceptible to trauma (Kokutar et al, 2016), where, in adults, the patient is more likely to be immunocompromised through underlying disease, including diabetes mellitus (Nather et al, 2005), cancer, renal disease (Hatzenbuehler and Pulling, 2011), HIV and IV drug abuse, with a history of trauma occurring in most adult cases (Kankate and Slevan, 2000). Similarly, our patient was immunocompromised with mild anaemia and type 1 diabetes mellitus with poor glycaemic control rendering him at risk of infection and had undergone significant trauma through his CN.

Presentation of HO includes an insidious onset with a dull ache or pain, restricted joint mobility, erythema, swelling and tenderness with or without

signs of fever (Erza and Wientroub, 1997; Bonhoeffer et al, 2001). Location is varied with the upper and lower limbs, pelvis, clavicle and spine all having been previously implicated with or without multifocal involvement (Bonhoeffer et al, 2001; Kokutar et al, 2016).

It is paramount to diagnose HO early as if left untreated can be fatal (Kokutar et al, 2016), but differentiating osteomyelitis from CN in the foot can be clinically and radiologically challenging (Ertugrul et al 2013; Kokutar et al 2016). A full history and physical examination, including vascular and neurological assessment, is crucial in determining the correct diagnosis bearing they are often clinically indistinguishable presenting as a warm, oedematous and erythemic foot (Jones et al, 2000; Hatzenbuehler and Pulling, 2011; Donegan et al 2013)

Assessing for peripheral neuropathy can help to rule out CN with no reported cases developing in the absence of peripheral neuropathy. During the inactive phase of CN, meanwhile, any signs or symptoms of infection are strongly suggestive of osteomyelitis (Donovan and Schweitzer, 2010). Other indicative features of osteomyelitis in the foot include ulceration with dimensions greater than $2cm^2$ along with a positive probe to bone test (Ertugrul et al, 2013), but these are features associated with contiguous spread and are of no value in HO.

Laboratory tests, meanwhile, are far from conclusive but may help build up the clinical picture. CN is not usually associated with elevated systemic inflammatory markers except in the acute stage (Ertugrul et al, 2013), while leukocytosis, elevated CRP and unexplained hyperglycaemia can all indicate infection but their absence does not exclude it (Donegan et al, 2013). Of greater value for DFO is an elevated ESR (>70 mm/hr) which has been shown to increase the probability of diagnosis where infection is suspected (Jeffcoate and Lipsky, 2004; Butalia et al, 2008) with subsequent slow reduction in appropriate antimicrobial therapy (Ertugrul et al, 2013). Interestingly, this case demonstrated an ESR of 66 mm/hr at initial suspicion of osteomyelitis gradually normalising to 10 mm/hr after 6 weeks, while CRP was elevated at 17 mg/L and normalised to below 10 mg/L after two weeks of treatment. Leukocyte count remained

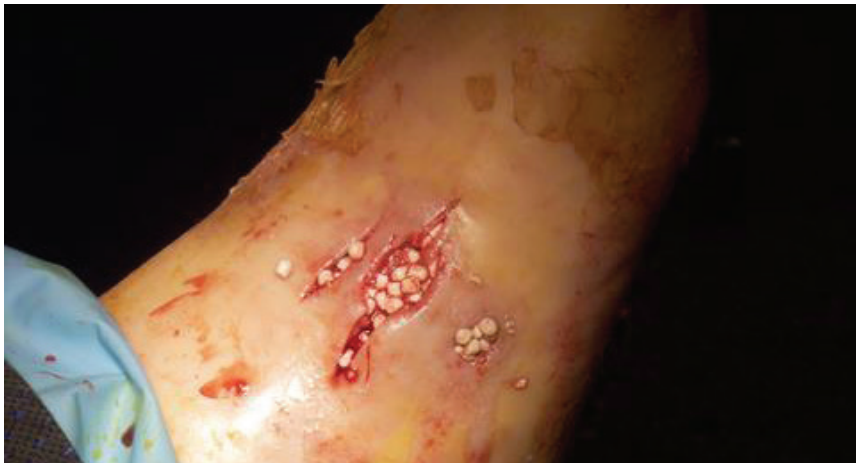


Figure 5. Packing the foot with antibiotic loaded calcium sulphate beads.

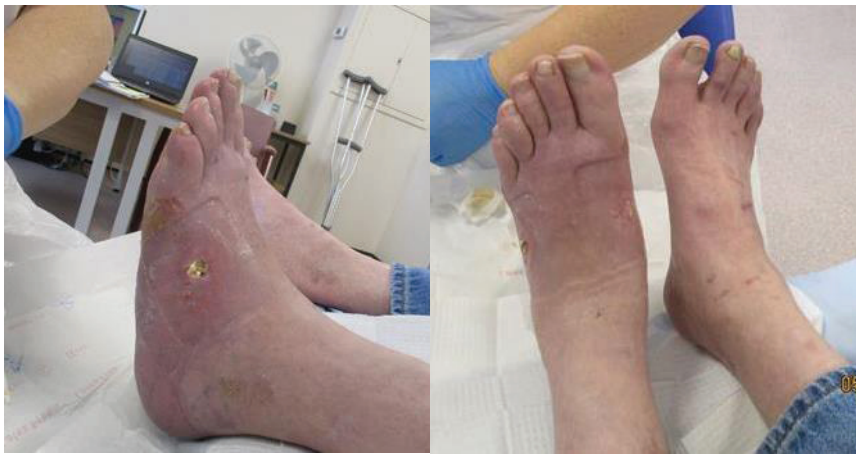


Figure 6. 3 weeks postoperatively the foot shows signs of quiescence.

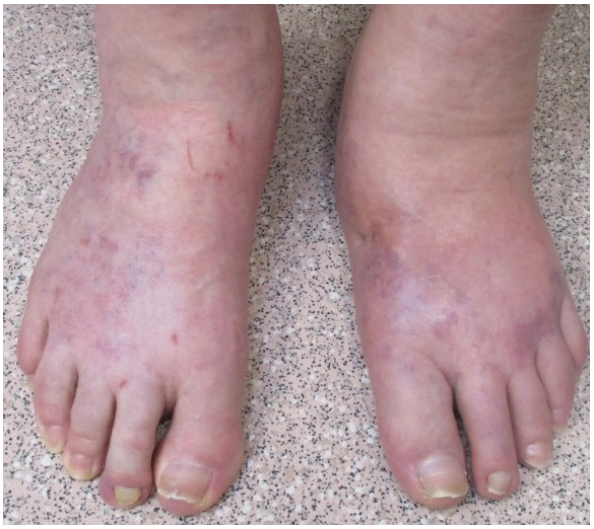


Figure 7. 12 months post initial presentation of Charcot neuroarthropathy complicated by haematogenous osteomyelitis.

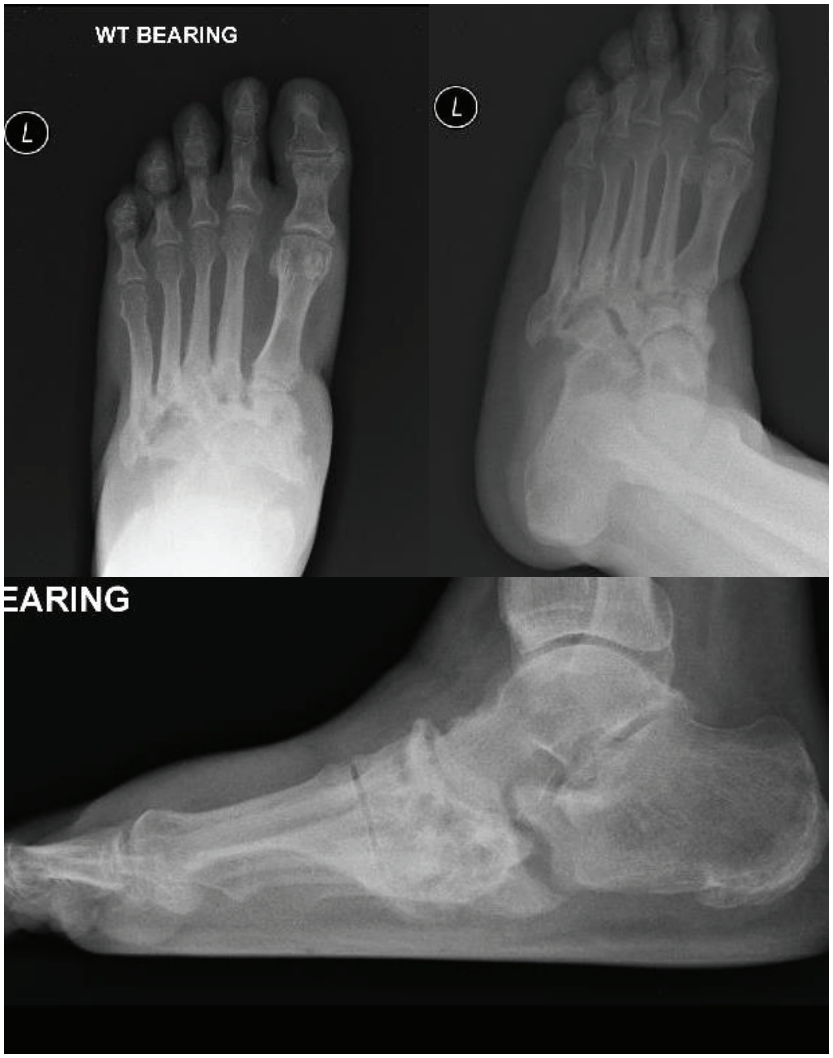


Figure 8. X-rays at 16 months post op demonstrating osseous consolidation with moderate loss of alignment in dorsoplantar (a), medial oblique (b) and lateral views.

within normal range and hence a poor marker for infection in our case.

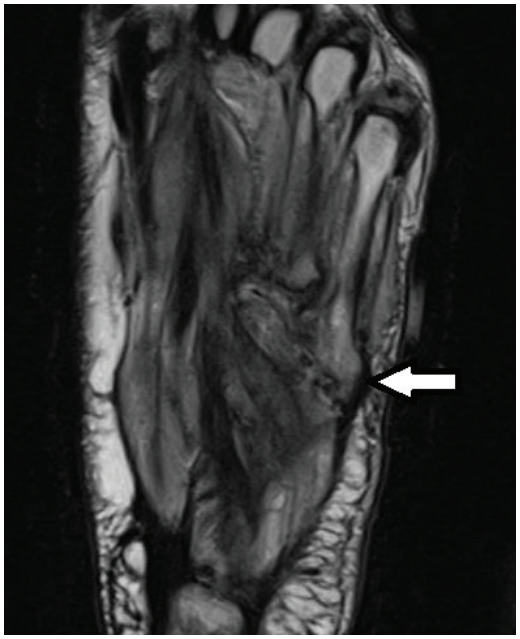
Plain radiographs should be the primary imaging modality (Rogers et al, 2011; Ertugrul et al, 2013; Hatzenbuehler and Pulling, 2011), but can be inconclusive for both CN and DFO in the early stages (Jeffcoate and Lipsky, 2004; Rogers et al, 2011) with DFO demonstrating low sensitivity and X-ray changes delayed by up to 4 weeks (Jeffcoate and Lipsky, 2004). CN can exhibit a hypertrophic appearance including joint destruction, sclerosis and osteophyte formation or an atrophic appearance with osseous resorption. Both forms, however, may show joint disorganisation more severe than that seen in other forms of arthropathy (Jones et al, 2000). DFO, meanwhile, demonstrates periosteal reaction, osteolysis (Hatzenbuehler and Pulling, 2011), cortical destruction and periosteal elevation (Jeffcoate and Lipsky, 2004)

Where plain radiographs are equivocal particularly in the early stages of disease MRI is the modality of choice (Rogers et al, 2011) enabling evaluation of osseous and soft tissue structures (Jeffcoate and Lipsky, 2004; Rogers et al 2011; Ertugrul et al, 2013). CN will often show periarticular bone marrow oedema with low signal intensity in T1 and T2 weighted images along with cysts, cortical fragmentation and joint subluxation and dislocation (Ertugrul et al, 2013). The diagnosis of DFO, however, relies on the presence of an overlying foot ulcer where the radiologist can then follow the path down to bone with subsequent evaluation of signal intensity of bone marrow (Donovan and Schweitzer, 2010). Low signal intensity on T1 and high on T2 and contrast enhancement are indicative of DFO (Jeffcoate and Lipsky, 2004) as are secondary signs including periosteal reaction, skin ulcer, sinus tracts, abscess and tenosynovitis (Donovan and Schweitzer, 2010).

Where both pathologies occur concomitantly specificity of MRI is limited and more useful to determine extent of disease as opposed to diagnosis (Ertugrul et al, 2013). The presence of 'Ghost sign' however, is a feature that can help determine CN with super-imposed infection and occurs when osseous tissue is apparent on T2-weighted images or after contrast administration, but seemingly disappears on T1. This is a consequence of bone destruction causing the images to appear less distinct (Donovan and Schweitzer, 2010) and was noted as a distinguishing feature in our case (*Figure 9*).

Other imaging modalities that have been shown to of been of benefit include nuclear imaging studies, such as three phase bone scans and labelled white cell scanning (Rogers et al, 2011), which are highly sensitive for active bone pathology (Rogers et al, 2011), but lack specificity (Ertugrul et al 2013). More recent developments in the form of positron emission tomography and single-photon emission computed tomography/computed tomography (SPECT/CT) has shown potential to aid future diagnosis (Rogers et al, 2011; Ertugrul et al, 2013).

Bone biopsy is recognised as the gold standard for diagnosing osteomyelitis (Jeffcoate and



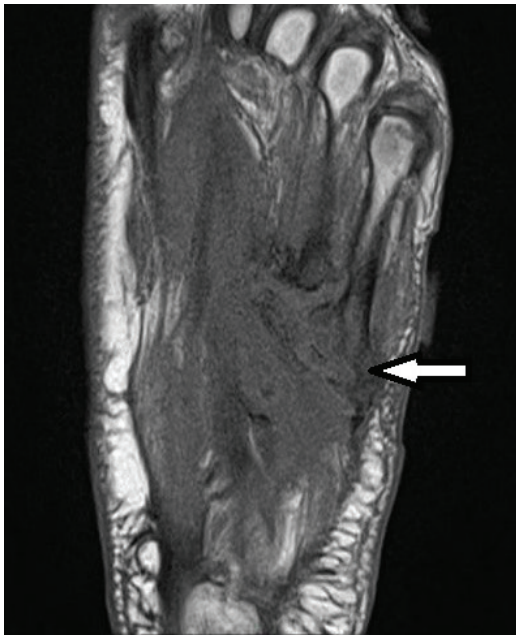


Figure 9. (a) T2 weighted MR image demonstrating the clearly visible fifth metatarsal base and (b) T1 image showing loss of clarity of the same bone.

Lipsky, 2004; Butalia et al, 2008; Ertugrul et al, 2013) and has been reported to have a sensitivity and specificity of 92% and 60% respectively (Ertugrul et al, 2013) with *Staphylococcus aureu*s found to be the most commonly cultured isolate in reported cases of haematogenous osteomyelitis following closed fractures (Kokutar et al, 2016). This isolate was also cultured in our case and treated as the offending organism. Biopsy is not only beneficial in diagnosis but has the huge advantage of helping to guide antimicrobial treatment through sensitivity testing (Donegan et al 2013).

However, false negatives may ensue where treatment has already commenced (Hatzenbuehler and Pulling, 2011) and so delaying treatment where appropriate should be considered. Simultaneous histology testing should also be performed to determine evidence of bone fragmentation with associated active inflammatory cells, including leukocytes (Jeffcoate and Lipsky, 2004).

Treatment strategies for CN vary from centre to centre but where possible the affected foot should be immobilised in a non-weight bearing, non-removable total contact cast with regular cast changes (Cavanagh and Bus, 2010; Rogers et al, 2011) until clinical symptoms have normalised and following radiological consolidation. This is endorsed at our hospital with subsequent step down to bespoke footwear and total contact insoles to help prevent re-ulceration. Surgery for CN is indicated in certain circumstances usually in the form of Achilles tendon lengthening for equinus contracture, exostectomy for recurrent ulceration of bony prominences and arthrodesis to help correct deformity (Rogers et al, 2011; Guven et al, 2013). This is usually performed where conservative management has failed, but can be considered as a primary treatment in severe deformity using internal or external fixation devices. (Guven et al, 2013)

Treatment for HO should ideally be preventative through management of skin and soft tissue wounds which may predispose to local and systemic infection particularly in immunocompromised patients (Kokutar et al, 2016). Following a positive diagnosis, most authors agree that it should be treated with a combination of antimicrocbial therapy and surgical intervention (Kankate and Selvan, 2000; Bonhoeffer et al, 2001; Jeffcoate and Lipsky, 2004; Hatzenbuehler and Pulling, 2011). However, there is no agreed consensus on antibiotic agents, route of administration or duration of treatment. Similarly, there is no agreement as to whether surgery should involve excision of all infected tissue or merely isolated to the tissue which is non-viable or necrotic (Jeffcoate and Lipsky, 2004).

At the authors' centre, multidisciplinary working is strongly endorsed and a strategy of

targeted medical management is adhered to through culture and sensitivity testing with highly bioavailable oral agents where appropriate and early surgical management through lavage and drainage, excision of only non-viable tissue and local administration of antimicrobials. This enables a high concentration to be delivered locally helping to preserve tissue that may be infective, but still viable and aid early discontinuation of systemic antibiotics when clinically, haematologically and radiologically stable.

Conclusion

Haematogenous osteomyelitis occurring in Charcot neuroarthropathy is a rare event, but should be considered as a differential diagnosis in a neuropathic patient with CN that is not settling.

Education of the patient and the healthcare professional is essential to enable early recognition of these devastating conditions. Future research should therefore focus on education programmes and diagnostic investigations including imaging to help differentiate these different pathologies to aid diagnosis and drive treatment to ultimately help minimise deformity and subsequent amputation. ■

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