CASE REPORT

Isolated tuberculosis of the calcaneum in a constitutionally well patient

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SUMMARY

A 66-year-old Caucasian man presented with a 9-month history of a painful left heel with associated soft tissue swelling. Pitting oedema was present to the upper shin. Plain radiograph showed a sclerotic calcaneum with lucent patches and the CT scan revealed bony destruction at the posterosuperior aspect of the calcaneus with a moth-eaten appearance. To obtain a more definitive diagnosis, the patient underwent a CT-guided biopsy, which showed caseating granulomatous inflammation strongly suggestive of *Mycobacterium* infection. A Ziehl-Neelsen stain did not show any microorganisms. Microbiology confirmed the presence of *Staphylococcus aureus*. A diagnosis of tuberculosis with concomitant *Staphylococcus* superinfection was made based on the histology and clinical context. The patient was treated with curettage and cementing of the lesion in order to debride the infected tissue and provide structural support to the bone. A 9-month course of quadruple antituberculous therapy was also initiated.

BACKGROUND

The incidence of tuberculosis (TB) in the UK is increasing with approximately 9000 new cases reported annually. Isolated TB infection of the bone, however, remains uncommon at 1–3%^{1 2} and, as a result, can lead to unnecessary delays in diagnosis and treatment. Often referred to as a 'great imitator',³ its clinical and radiological presentation can lack any obvious pathognomonic features, often resulting in differential diagnoses including sarcoma or bony metastases, multiple myeloma or lymphoma.

Differentiation between infective and neoplastic causes in such cases ultimately necessitates a biopsy with further histopathological and microbiological analysis. Difficulties can arise, however, with low yield of microorganisms with standard stains. Clinicians are often forced to balance the risks of starting the patient on antituberculous drugs with potential side effects without a definitive diagnosis or further delay treatment and risk more bone destruction and a worsening prognosis. Furthermore, where concomitant infection, such as *Staphylococcus aureus*, exists doubt is cast over the diagnosis.

To highlight these issues, we present a case of a destructive bony lesion of the calcaneus, which was referred to a specialist bone and soft tissue tumour service, arguably delaying the correct diagnosis in attempts to definitively rule out malignancy and prove TB. This case draws attention to the

'diagnostic dilemma'⁴ and should help raise awareness of atypical presentations of skeletal TB so that early management can help ensure a good prognosis.

CASE PRESENTATION

A previously well 66-year-old Caucasian man presented to his general practitioner initially with a 1-month history of a painful left heel with associated swelling and a limp. There was no history of trauma or previous similar symptoms. Non-steroidal anti-inflammatory drugs had no effect on the pain. He denied classical symptoms of weight loss, night sweats or fever. He was initially referred to his local hospital where plain radiographs were carried out before eventually being referred to a specialist bone and soft tissue tumour unit. The time from first presentation to diagnosis was 10 months.

On examination there was significant soft tissue swelling, erythema and hypersensitivity over the posterior calcaneum (figure 1). Bony tenderness in this area was also present. Stretching of the Achilles elicited pain but there was no evidence of tendon dysfunction. Pitting oedema was present up to the upper shin. There were two discharging wounds and the patient reported constant serosanguinous discharge. Examination of the ankle, hindfoot and mid-foot joints were unremarkable.

The patient was otherwise fit and well and had been very active. There was no past history or history of contact/exposure to TB or immunocompromise.

INVESTIGATIONS

Blood tests

The patient's initial C reactive protein (CRP) was within normal range at 4 mg/L. Similarly his white cell count was also normal. However, his erythrocyte sedimentation rate (ESR) was mildly elevated at 31 mm/h; the normal range being <20 mm/h. There were no other abnormalities noted.

Plain radiograph

Initial plain radiographs (figure 2) of the left ankle revealed a diffusely sclerotic calcaneum. There was diffuse lucency within the posterior aspect of the calcaneus measuring 3.6 cm×2.6 cm with more marked patchy lucency in the posterosuperior corner of the calcaneum measuring 2 cm×1 cm. There was no obvious periosteal reaction but there was swelling of the overlying soft tissue. The calcaneal erosion was suggestive of infection or neoplasia.

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Figure 1 Photographs highlighting the swelling at the Achilles tendon insertion site.

CT scan

The CT scan (figures 3 and 4) showed discontinuity of the calcaneal cortex as a result of bone destruction in the posterosuperior aspect. The lesion contained areas of calcification. The posterior calcaneum had a moth eaten appearance.

The initial differential diagnosis for the destructive lesion included primary or secondary malignancy and osteomyelitis, perhaps related to chronic infection such as TB. Metal clips inserted as a result of a previous right ventricular brain tumour contraindicated the use of MRI for further imaging.

CT guided biopsy

A CT-guided biopsy of the left calcaneum was carried out and this showed lamellar bone with intervening necrotising epithelioid granulomatous inflammation suggestive of a mycobacterium infection. Ziehl-Neelson and PAS stain did not show any microorganisms. Confirmation with microbiology instead revealed *S. aureus* infection raising the possibility of contamination or superinfection.

Chest radiograph

The patient's chest radiograph was clear of any signs of active TB or previous infection.

DIFFERENTIAL DIAGNOSIS

- ▶ Extrapulmonary TB
- ▶ Acute bacterial or chronic osteomyelitis
- ▶ Bone metastases

Figure 2 Initial plain radiographs showing a diffusely sclerotic calcaneum.

TREATMENT

As a result of the extent of the initial infection and presence of *S. aureus*, the patient was treated with curettage and cementing of the lesion in order to debride the infected tissue and provide structural support to the bone. In addition, the patient was started on a 9-month course of quadruple anti-TB medication comprised of rifampicin, isoniazid, pyrazinamide and ethambutol.

OUTCOME AND FOLLOW-UP

Following the operation, the patient was immobilised in plaster for 2 weeks and then mobilised with crutches and a walking boot for a further 6 weeks. At the time of writing, the patient is nearing the end of his course of antibiotics. Since the operation and initiation of treatment, he has been attending the local fracture clinic monthly for radiograph examination (figures 5 and 6) as well as monitoring for any adverse drug reactions under the chest physicians. Blood test results from 2 months post-operatively showed a mildly elevated CRP of 11 and a normal ESR of 5. His most recent set of blood tests showed resolution with a CRP of 3 and an ESR of 5. White cell counts have remained normal throughout treatment. He is now fully mobile and pain-free and it is anticipated that on completion of his course of antibiotics, no further follow-up will be needed unless the patient reports any signs of recurrence.

DISCUSSION

TB is a leading cause of infection and death. The WHO estimates that there were 8.7 million new cases of TB worldwide in 2011, 13% of which were in patients co-infected with HIV.⁵

Figure 3 CT scans highlighting the moth eaten lesion on the posterior calcaneus.

Although more than 20–50 times more common in under developed and developing countries, it is becoming increasingly more prevalent in the UK. Cases tend to be clustered in large cities, particularly London. This is thought to be multifactorial: increased immigration from endemic areas, decreased socioeconomic conditions and the use of immunosuppressive drugs, such as for HIV, which can potentially lead to reactivation of latent TB.

Caused by *Mycobacterium tuberculosis*, the primary infection is often asymptomatic with symptomatic reactivation occurring years later, often due to declining immune status as a result of age or chronic ill health. While extra pulmonary TB accounts for 10–20% of cases,⁶ isolated TB affecting bone is rare in the Western world with few reported cases. The worldwide incidence of skeletal TB is reported as between 1% and 3% of cases. Where it does occur, common sites are the vertebral column, hip and knee. The presence of skeletal TB in immunocompetent patients is thought to be as a result of reactivation of latent TB in the lungs or gastrointestinal tract with haematogenous spread.

Involvement of the foot and ankle is rare, accounting for only 1% of all TB infections.^{1 2} There are several case reports of calcaneal TB^{7–9} but this appears to be the first reported case of isolated calcaneal TB in a patient with no signs of constitutional illness, originating from a non-TB-endemic country. All reported cases appear to involve patients originally from India who displayed constitutional symptoms. Common presenting symptoms are pain, swelling and loss of function. Delays in presentation or treatment can lead to formation of discharging sinuses or palpable abscesses. Emphasis was placed on the need for a high index of clinical suspicion when diagnosing calcaneal TB.

Numerous commentators cite delays in diagnosis and initiation treatment as the biggest obstacles in successful management of TB confined to bone.^{1 2} This is fuelled by a lack of awareness of the signs and symptoms which are often less

dramatic than that of long bones and without constitutional involvement.¹⁰ It is estimated that 70–90% of patients may have a positive skin test. This was not carried out in this patient. Fewer than 50% have chest X-ray abnormalities consistent with previous or currently active TB.¹¹ An elevated ESR appears to be more sensitive compared with CRP.

Radiological parallels with malignancy are a further hindrance.^{12 13} Radiographic signs of TB bone infection include diffuse lucency in the area of infection, bony erosion and a soft tissue shadow, often suggestive of an abscess. The presence of osteopenia in the surrounding bone is also a common finding. Lytic and sclerotic areas can also be present in bone metastases from several primary tumours, including breast, prostate and renal cell carcinoma. In addition to X-ray, MRIs are often used to evaluate soft tissue involvement and abscess formation. Imaging is rarely enough to diagnose skeletal TB and fine-needle aspiration or bone biopsy is usually needed for histopathological analysis.

Although definitive diagnosis is achieved with culture of *M. tuberculosis* from the affected bone with accompanying histopathology confirmation, in practice 10–15% of cases of extra-pulmonary TB diagnoses are based on clinical grounds.¹⁴ This is often as a result of the time taken to receive back microbiology results and the fact that acid-fast bacilli smears are unlikely to be positive, as in this case, as a result of low bacillary loads. Diagnosis is often confirmed on finding granulomatous tissue and caseating necrosis on biopsy with histology giving rise to a higher positive diagnosis compared with microbiological culture.¹⁵ In support of this, current National Institute for Health and Care Excellence (NICE) guidelines¹⁶ state that the appropriate treatment regime can be started without waiting for culture results provided that the histological and clinical picture is consistent. Dhillon *et al*,¹⁷ however, advocate exhausting the full selection of available tests first. This is particularly pertinent in cases such as this one, which is in a non-endemic country

Figure 4 Multiplanar three-dimensional CT scans demonstrating the calcaneal lesion.

Figure 5 CT scans showing the cemented lesion at 2 weeks postoperatively.

with a somewhat atypical presentation. The finding of *S. aureus*, as in this case, can cast doubt over the diagnosis, leading to further delays in starting initial treatment.¹⁸

Where histology comes back negative or uncertainty persists, more sensitive PCR testing is able to detect tubercular bacilli at low quantities and results are obtainable within 24 h. A recent study¹⁹ reported overall sensitivity of 70.83% for skeletal TB with lower sensitivity for non-spinal samples due to dilution of bacilli. Specificity was high at 93.75%.

Interferon Gamma Ray Assays (IGRAs) are also of potential use in the diagnosis of TB. The two assays available for use in the UK are QuantiFERON-TB Gold (QFT-G) and T-SPOT.TB. They measure the amount of interferon γ released from T cells that have previously been in contact with *M. tuberculosis*. They specifically detect the response to proteins made specifically by *M. tuberculosis*, which are not present in BCG vaccines or environmental TB, thereby reducing the number of false-positive results that can occur with tuberculin skin tests.

Recent meta-analyses of QFT-G report high sensitivity ranging from 80 to 85% and specificity from 79 to 84%.^{20 21} Looking specifically at its use in extrapulmonary TB, one evaluation of the T-SPOT.TB test found overall sensitivity of 94.7% with little difference between the pulmonary and extrapulmonary groups but with a marked difference in specificity. Overall, it was 84.10% but was significantly lower in the pulmonary TB group (69.2% vs 88.9%, $p=0.02$).²² UK guidelines^{16 23} suggest, however, that the IGRAs should be used primarily in the diagnosis of latent TB, for example, in contact tracing, new migrants, healthcare workers and patients about to start

immunosuppressive medication. It is a more expensive option compared with the skin test, but higher sensitivity and specificity may mean that fewer patients will receive unnecessary treatment with concomitant side effects.

While routine use in suspected active TB is not recommended with diagnosis through culture remaining the 'gold standard', the HPA²³ concedes that IGRAs may be considered in cases where diagnosis proves difficult and where treatment options rely heavily on a diagnosis. In this case, where it was not possible to isolate *M. tuberculosis* from specimens, a positive IGRA would have increased confidence in the diagnosis and potentially reduced further delay. Larger studies are required to further assess the efficacy of IGRAs as well as their cost-effectiveness.

Isolated TB of bone can, in the early stages, be treated effectively with antituberculous chemotherapy. There remains much debate as to the length of treatment but research conducted agrees that it should be longer than for pulmonary TB. Dhillon *et al*¹⁷ assert that this is required because osteoarticular TB is a paucibacillary infection with many organisms lying dormant, resulting in an increased risk of resistance. They suggest a minimum of 12 months treatment. Mittal *et al*² suggest treatment of 9 months minimum but preferably up to 18 months. Longer courses help reduce the risk of recurrence. Treatment response is usually monitored with ESR measurements and plain radiographs,²⁴ although it is worth noting that radiological resolution can lag behind and cavities may persist for many years after the infection has been cleared.¹

With early initiation of treatment, radiographic changes can resolve and function can be completely restored. If bone

Figure 6 Plain radiographs taken at 4 months postoperatively highlighting the cementing of the initial lesion.

destruction is extensive and affecting neighbouring joints then surgery may be necessary; arthrodesis or joint replacement may be considered if disease persists. Repeat scans can highlight poor responders to medication, perhaps as a result of multidrug resistant disease. None of the reported cases of calcaneal TB had to resort to surgery. This patient appears to have been an exception as a result of the superinfection on top of the TB, necessitating surgery. Dhillon *et al*¹⁷ suggest that the size of the bone and preferential starting point of disease at the tuberosity means that early diagnosis can stop spread to other bones.

To conclude, this case highlights the need for a high degree of clinical suspicion when patients present with pain, swelling and reduced mobility in the presence of a destructive lesion of the calcaneus. Skeletal TB should be considered as a key differential even in the absence of other symptoms and a clear chest X-ray. This is particularly true in populations with high numbers of patients from countries where TB is endemic, but should also be borne in mind for those with no obvious connection or recent travel. Early diagnosis allows prompt medical treatment and encourages a more positive prognosis, with the avoidance of surgical intervention.

Learning points

- ▶ Although rare, a debilitating, destructive bone lesion of the heel with accompanying discharging sinus should lead clinicians to consider tuberculosis (TB) as a potential differential and investigate accordingly.
- ▶ This applies equally to Caucasian patients from non-TB-endemic countries with no obvious signs of immunocompromise or TB exposure.
- ▶ A lack of pulmonary involvement, constitutional symptoms or normal erythrocyte sedimentation rate (ESR) does not rule a diagnosis of skeletal TB.
- ▶ The clinical context and positive histopathology may be sufficient to start antituberculous treatment so as to prevent further joint destruction while waiting for culture confirmation.
- ▶ Where it is difficult to isolate *Mycobacterium tuberculosis* in clinical specimens, the use of Interferon Gamma Ray Assays or PCR may increase confidence in the diagnosis. ESR should be measured and consideration given to HIV testing. Tuberculin skin testing may also be useful.
- ▶ Initial treatment with antituberculous drugs for 6 months is in line with National Institute for Health and Care Excellence (NICE) guidelines but a minimum course of 9 months may be more beneficial in preventing recurrence.

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