Unusual presentation of more common disease/injury

Unusual presentations of osteoarticular tuberculosis in two paediatric patients

Jason Pui Yin Cheung,¹ Kenneth Wai Yip Ho,¹ Ying Lee Lam,¹ Tony Wai Hung Shek²¹Department of Orthopaedics and Traumatology, Queen Mary Hospital, Hong Kong, Hong Kong²Department of Pathology, Queen Mary Hospital, Hong Kong, Hong Kong

Correspondence to Dr Jason Pui Yin Cheung, jcheung98@hotmail.com

Summary

Tuberculosis is a universal mimicker and thus could be a differential diagnosis of any osteolytic lesion. Bone biopsy is crucial in these cases for culture and histological proof of tuberculous infection. This is a case report of two paediatric patients with unusual presentations of tuberculosis. One patient presented with knee pain and had imaged findings of an osteolytic lesion at the epiphysis. Interval scan showed spread of the lesion through the physis to the metaphyseal region. The second patient presented with hip pain and an osteolytic lesion of the acetabulum. He was subsequently found to have involvement of the brain and spine as well. Both patients were diagnosed with tuberculosis by bone biopsy for culture and pathological examination. They were treated successfully with antituberculous medications without chronic sequelae. These two patients showed that early recognition and prompt treatment are critical for management of tuberculosis to avoid chronic sequelae.

BACKGROUND

Extrapulmonary tuberculosis (TB) was estimated to occur in 20% of patients with TB.¹ Furthermore, osteoarticular TB accounted for 1–5% of all TB cases and 10–18% of extrapulmonary TB cases.² These osteoarticular TB may not have lung involvement and thus are commonly misdiagnosed as having other osteoarticular diseases such as tumours.³ The frequently involved areas besides the spine include the knee (44.4%), the hip (22.2%) and the ankle (33.3%).^{3–6} We present two paediatric patients with unusual presentations of TB. Both patients were admitted to our orthopaedic ward because of joint pain and finding of an osteolytic lesion on imaging. Both patients were being investigated for malignancy and required biopsies for diagnosis. It came as a surprise that the biopsies yielded positive results for TB. This case report discusses these two unusual presentations of TB and identifies some management pearls for these difficult conditions.

CASE PRESENTATION

Case 1: epiphyseal osteolytic lesion

A 24-month-old female baby born full-term, normal vaginal delivery and uneventful antenatal and postnatal history presented with left knee pain. The knee pain was sudden in onset and she refused to walk. The painful episode only lasted for two days during which she had a limping gait and painful swelling in the left knee. There was a low-grade fever (38°C) and coryzal symptoms at the time. Since then, she was able to walk normally and had no definite effusion or knee swelling. She presented to us 2 weeks after the symptom onset and on examination there was no focal tenderness at the knee and no limb length discrepancy. The range of motion of the knees was full.

INVESTIGATIONS

Blood tests showed C reactive protein (CRP) of <0.35 mg/dl, white cell count (WCC) elevated to 13.6×10^9 and erythrocyte sedimentation rate (ESR) of 20 mm/h. Radiographs (figure 1A,B) showed an osteolytic lesion at the epiphysis of the left knee without periosteal reaction or significant soft tissue swelling. MRI (figure 2A,B) showed a $1.6 \times 2.7 \times 1.6$ cm size mass lesion surrounded by a sclerotic rim and irregular thickness. There were strands and dots of hypodensity within the lesion suggestive of fibrous tissue

Figure 1 Anteroposterior (A) and lateral (B) radiographs of the left knee at 2 weeks after onset of symptoms showing an epiphyseal osteolytic lesion which appears benign in nature. There was no periosteal reaction or physeal involvement.

Figure 2 Coronal (A) and sagittal (B) cuts of postgadolinium MRI of the left knee at 2 weeks after onset of symptoms showing a heterogeneous mass at the epiphysis with no cortical erosion or periosteal reaction. The most likely diagnosis from the MRI findings was a chondroblastoma.

and calcifications. There was no cortical erosion or periosteal reaction. The postgadolinium scan showed dense inhomogeneous enhancement of the lesion.

DIFFERENTIAL DIAGNOSIS

The list of differential diagnoses included aneurysmal bone cyst, chondroblastoma, Langerhans cell histiocytosis, haematological malignancies and infection.

OUTCOME AND FOLLOW-UP

Bone biopsy was performed to confirm the diagnosis. The bone biopsy sample unexpectedly yielded positive PCR for TB. The histology (figure 3A,B) showed granulomatous inflammation and visible acid-fast bacilli (AFB). Repeated radiographs (figure 4A,B) and MRI (figure 5A,B) performed 1 month after the onset of symptoms showed that the epiphysial lesion has progressed through the physeal plate to the metaphyseal region. After discussion with the microbiologist, daily oral isoniazid 120 mg, rifampicin 180 mg, pyrazinamide 300 mg and ethambutol 150 mg were prescribed for 1 year duration.

Figure 4 Anteroposterior (A) and lateral (B) radiographs 1 month after onset of symptoms showing the epiphysial lesion has progressed to the metaphysis of the left distal femur.

At 14 months follow-up, examination and imaging showed that the patient had no bone bar formation. Follow-up blood tests were normalised.

CASE PRESENTATION

Case 2: miliary TB presenting as hip pain

A boy of 15 years of age with complete immunisations including BCG for TB presented with insidious onset of left hip pain for 5 months. He had no history of trauma or signs or symptoms suggesting infection. There was persistent hip pain but was partially controlled by non-steroidal anti-inflammatory medications. He was able to continue sport activities such as basketball and soccer without any problems. On physical examination, there was no hip tenderness and he was able to perform single leg hopping without problem. There was a slight reduction of the hip range of motion as compared with the

Figure 3 (A) A granuloma with Langhans giant cells (H&E staining $\times 200$ magnification). (B) An acid-fast bacilli (Ziehl-Neelsen stain $\times 400$ magnification).

Figure 5 Coronal (A) and sagittal (B) cuts of postgadolinium MRI of the left knee at 1 month after onset of symptoms showing the transphyseal canal in which the epiphyseal lesion has spread to the metaphysis.

normal side. There was also some tenderness over the lower back but no pain found at the knee joint.

INVESTIGATIONS

Blood tests yielded normal WCC but elevated alkaline phosphatase to 112 U/l, CRP to 3.47 mg/dl and ESR to 68 mm/h. Pelvis radiograph (figure 6) and CT (figure 7) showed a 2×1.1 cm defect at the left acetabulum with joint space narrowing. There was also marrow infiltration at the acetabulum. Lumbosacral radiograph (figure 8) also showed collapse of the anterior aspect of the L3 upper endplate.

DIFFERENTIAL DIAGNOSIS

The list of differential diagnoses included haematological malignancy and multiple eosinophilic granulomas.

OUTCOME AND FOLLOW-UP

Positron emission tomography (PET) CT scan was ordered to look for other sites of involvement and to aid the

Figure 7 Axial CT slide of the pelvis showing an osteolytic lesion at the left acetabulum.

diagnosis. The PET-CT showed hypermetabolic disease involving the lungs, bones and lymph nodes, typical for eosinophilic granuloma-type Langerhans cell histiocytosis. Ultrasound-guided aspiration of a right cervical lymph node was performed and the cytology showed reactive changes only. CT-guided biopsy of the acetabular lesion was also performed and subsequently yielded positive PCR for TB and histology showed presence of AFB. Following discussion with the microbiologist, the diagnosis of miliary TB was made due to multiple sites of involvement. Subsequent investigations such as lumbar puncture and MRI of brain (figure 9) and spine confirmed TB meningitis, L2/3 spondylodiscitis and also myelitis distally. Sputum AFB smear was positive but TB-PCR from the sputum and urine were negative.

Figure 6 Anteroposterior radiograph of the pelvis showing a cortical discontinuity at the left acetabulum.

Figure 8 Lateral radiograph of the lumbar-sacral spine showing collapse of the anterior upper endplate of the L3 vertebrae.

Figure 9 Axial MRI slide showing multiple tuberculomas in the brain.

Daily oral isoniazid 200 mg, rifampicin 600 mg, ethambutol 600 mg and pyrazinamide 1 g were prescribed. Dexamethasone was also prescribed for 2 weeks before stepping down to prednisolone for another 4 weeks. The anti-TB medication was given for 1 year.

On follow-up, the back became non-tender and there were no complications of neurological deficit. In addition, the range of motion of the left hip improved with some residual limitation in internal rotation on examination. Radiographs showed stable L3 endplate erosion and mild reduction of joint space at the left hip. The patient remained asymptomatic at 1 year follow-up with normalised blood tests.

DISCUSSION

This case report described two patients with unusual presentations of TB as osteolytic lesions. For the first patient with an osteolytic lesion at the distal femur, good clinical practice dictates comprehensive investigations to rule out malignancies as the management plan is vastly different. There are multiple differential diagnoses for an epiphyseal osteolytic lesion in such a paediatric patient. In one study, 18% of enchondromas occur in the distal femur while metaphyseal extension is seen in 61% of patients.⁷ Unicameral bone cysts can also be found and there have been reports of growth plate invasion.⁸ This leads to direct physeal damage and subsequent growth arrest.⁸ Other differential diagnoses of epiphyseal lesions include chondroblastoma, Langerhans cell histiocytosis, aneurysmal bone cyst, eosinophilic granuloma, osteoid osteoma and epiphyseal osteomyelitis.⁷⁻¹⁴ Aneurysmal bone cysts are usually found (28% of cases) concomitantly with chondroblastoma and are reported to be at risk of local recurrence.¹³ Giant cell tumours are rarely found in young patients and have only been reported in case reports.^{10 15} In this group of patients, the tibia (26%) is the most commonly affected site.¹⁰

In the first patient, interval radiographs showed spread of the lesion into the metaphyseal region. This finding vaulted osteomyelitis to the top of the list of differential diagnoses since it is highly unlikely for epiphyseal tumours to traverse the physis due to the inherent resistance of cartilage to tumour invasion.¹⁶ A unique collagenase inhibitor of physeal cartilage resists both tumour

angiogenesis and tumour cell invasion.¹⁶ Nevertheless, tumour invasion can still be possible if vascular compromise of the epiphysis occurs, leading to physeal damage and reduced growth.^{17 18} For infections, the microorganism usually adheres to the transphyseal blood vessels which are channels that could allow spread through the physis to the metaphyseal region.¹⁹ This phenomenon would undoubtedly only occur in skeletally immature patients. Transphyseal spread may have significant sequelae on functional prognosis as physeal growth from the distal femur accounts for 70% of the growth of the limb.^{20 21} One study showed that 17% of patients with physeal damage had bone bar formation.²² Fortunately for our patient, she did not develop any complications despite the transphyseal spread of the infection.

For the second patient, the diagnosis of TB was a surprise as he only presented with hip pain and an osteolytic lesion of the acetabulum. What was further unusual about this case was the absence of symptoms suggestive of miliary TB. The incidence of miliary TB has been quoted to be 1% of all cases of TB.²³ Fever is the most common symptom (94%) followed by malnutrition (84.1%), adenopathy (79.3%), cough (68%), weight loss (57%), respiratory complaints (57%) and hepatosplenomegaly (44.4%).^{3 24-26} Other presentations that were also found in our patient include multiple brain and spinal tuberculomas that are shown as ring-enhancing lesions on contrast MRI.^{27 28} One major pitfall in managing these patients is the misconception that immunisation with BCG can completely eradicate miliary disease and TB meningitis. Miliary TB had been shown to occur in patients with complete immunisation including BCG.^{24 29} In addition, a meta-analysis reported that the efficacy was only 73% for TB meningitis and 77% for miliary TB.³⁰ Although the efficacy reported is not optimal but it is more important for endemic countries such as Asia where even a 70% reduction of severe TB manifestations could have improved the prognosis for many patients. As such, there is adequate evidence supporting the development of TB meningitis and miliary TB in our patient despite previous BCG immunisation. Owing to the multiple bony involvement of our patient, a prolonged duration of anti-TB medications for 1 year was provided. Corticosteroids were also given to him, which has been shown to be beneficial in the setting of severe disease including TB meningitis and miliary TB.^{22 31}

In our two patients, TB osteomyelitis likely developed as a result of haematogenous spread from a primary lung focus. In fact, epiphyseal involvement was reported to be less common in the literature. TB osteomyelitis usually occurs in the metaphysis of long bones and one study quoted only 4% of all haematogenous bone infections involved in the epiphyses of long bones.³² This condition is more commonly found in children than adults and especially so in those younger than 6 years of age.³³ The seeded granulomatous lesion enlarges, leading to caseous and liquefaction necrosis along with bone resorption. Although *Mycobacterium tuberculosis* is a slow-growing organism, if untreated early, disease progression would cause bone destruction, transphyseal spread of disease and joint involvement.³⁴

Prompt diagnosis and early treatment remain the most critical steps for proper management of TB and

preventing secondary joint destruction and deformity. Radiographs are usually not reliable for diagnosis of TB osteomyelitis. Formation of new subperiosteal bone and lytic lesions were only seen in 8.1% of cases and concomitant evidence of pulmonary TB in chest x-rays was only reported in 31.1% of patients.³ MRI is generally more helpful for assessment where diffuse heterogeneous marrow signal changes may be seen.³⁵ TB collections are best seen on postcontrast T1-weighted images where the abscess cavity would appear hypointense due to caseous necrosis.³⁶ The appearance of the abscess wall is also characteristic being thinner and more regular than pyogenic infections.³⁶ Diagnosis of TB requires confirmation by histology or positive culture of tubercle bacillus.^{22 37} There is a wide array of investigations such as serological and microbiological (AFB culture and staining) tests that can help clinicians initiate the appropriate treatment earlier. However, there are limitations to the above tests. Serological tests such as ESR, immunoglobulin (Ig) M, and IgG have no diagnostic value.³⁸ ESR is always high in all inflammatory conditions and has been quoted to be 48–84.5 mm/h for TB.³ AFB staining has sensitivity of only 25–75% and AFB culture has sensitivity of only 48.6–80%.³⁹ Other drawbacks to AFB culture and sensitivity are the requirement of live specimens and a long incubation period. A large number of organisms are also required for detection of *M tuberculosis*. PCR has become a key component of the diagnostic armamentarium for TB. There are many advantages to the PCR including the ability to amplify the genome from a single organism so that even very low levels of AFB in the clinical specimen can be detected. It is also a highly efficient and rapid method for diagnosis (results within 24 h) and can differentiate typical and atypical mycobacteria. PCR does have some limitations such as difficulty in differentiating between living and dead organisms and easy contamination as small amount of contaminating DNA may become amplified. In general, the sensitivity and specificity of PCR have been reported to be 78.6–100% and 71.4–87.1%, respectively.³⁸ Biopsy is the gold standard as it could provide a tissue diagnosis of granulomatous inflammation and caseous necrosis. It could also be used to identify AFB and also to exclude malignancy.⁹

Unlike pulmonary TB, there are no standard guidelines for duration of chemotherapy for extrapulmonary TB. In a recent review of 28 studies, only three reported 6-month treatment regimens and 25 studies reported longer regimens extending over more than 12 months.⁴⁰ Generally speaking, regimens shorter than 6 months were deemed inadequate while those longer than 12 months, except for drug-resistant TB, were too long. In our two patients, we adopted the recommendation of 1 year treatment as our usual practice.

TB is notorious for being a universal mimicker. Clinicians must treat TB as a possible differential diagnosis for any patient presenting with an osteolytic bony lesion. The diagnosis of these two cases presented here was a surprise as all the investigations including imaging and serological tests prior to the biopsy were indicative of a tumour condition. Hence, it is a general rule that biopsies must be taken in all cases during work-up for orthopaedic malignancies. Biopsies can provide confirmation of diagnosis by obtaining tissues for culture of organism and

for pathological examination for AFB or malignancy. PCR can also be performed for the biopsy specimens to obtain early results. Diagnosis of TB can be challenging but if identified early, treatment is effective and severe consequences can be avoided.

Learning points

- ▶ Tuberculosis (TB) may have unusual presentations.
- ▶ Any patient presenting with a tumour-like condition must have a biopsy done with the specimen sent for microbiological investigations. Likewise, any infection should have histological investigations to rule out tumours.
- ▶ PCR is a useful tool for rapid diagnosis of TB.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Westall J. Tuberculosis levelling off worldwide. *BMJ* 1997;**314**:921.
2. Ruiz G, Garcia Rodriguez J, et al. Osteoarticular tuberculosis in a general hospital during the last decade. *Clin Microbiol Infect* 2003;**9**:919–23.
3. Hadadi A, Rasoulinejad M, Khashayar P, et al. Osteoarticular tuberculosis in Tehran, Iran: a 2-year study. *Clin Microbiol Infect* 2010;**16**:1270–3.
4. Akgun U, Erol B, Cimsit C, et al. Tuberculosis of the knee joint: a case report. *Acta Orthop Traumatol Turc* 2008;**42**:214–18.
5. Evanchick CC, Davis DE, Harrington TM. Tuberculosis of peripheral joints: an often missed diagnosis. *J Rheumatol* 1986;**13**:187–9.
6. Rodrigo C, Atukorala I. Delay in diagnosis of generalized miliary tuberculosis with osseous-articular involvement: a case report. *J Med Case Rep* 2011;**5**:512.
7. Potter BK, Freedman BA, Lehman RA Jr, et al. Solitary epiphyseal enchondromas. *J Bone Joint Surg Am* 2005;**87**:1551–60.
8. Ovadia D, Ezra E, Segev E, et al. Epiphyseal involvement of simple bone cysts. *J Pediatr Orthop* 2003;**23**:222–9.
9. Ezra E, Cohen N, Segev E, et al. Primary subacute epiphyseal osteomyelitis: role of conservative treatment. *J Pediatr Orthop* 2002;**22**:333–7.
10. Gandhe A, Sankhe A, Aeron G, et al. Epiphyseal giant cell tumour in an immature skeleton. *Br J Radiol* 2008;**81**:e75–8.
11. Hamdy RC, Lawton L, Carey T, et al. Subacute hematogenous osteomyelitis: are biopsy and surgery always indicated? *J Pediatr Orthop* 1996;**16**:220–3.
12. Kandel SN, Mankin HJ. Pyogenic abscess of the long bones in children. *Clin Orthop Relat Res* 1973:108–17.
13. Sailhan F, Chotel F, Parot R. Chondroblastoma of bone in a pediatric population. *J Bone Joint Surg Am* 2009;**91**:2159–68.
14. Sorensen TS, Hedeboe J, Christensen ER. Primary epiphyseal osteomyelitis in children. Report of three cases and review of the literature. *J Bone Joint Surg Br* 1988;**70**:818–20.
15. Picci P, Manfrini M, Zucchi V, et al. Giant-cell tumor of bone in skeletally immature patients. *J Bone Joint Surg Am* 1983;**65**:486–90.
16. Kuettner KE, Pauli BU, Soble L. Morphological studies on the resistance of cartilage to invasion by osteosarcoma cells in vitro and in vivo. *Cancer Res* 1978;**38**:277–87.
17. Malawer MM, Markle B. Unicameral bone cyst with epiphyseal involvement: clinicoanatomic analysis. *J Pediatr Orthop* 1982;**2**:71–9.
18. Neer CS, Francis KC, Johnston AD, et al. Current concepts on the treatment of solitary unicameral bone cyst. *Clin Orthop Relat Res* 1973:40–51.
19. Alderson M, Speers D, Emslie K, et al. Acute haematogenous osteomyelitis and septic arthritis—a single disease. An hypothesis based upon the presence of transphyseal blood vessels. *J Bone Joint Surg Br* 1986;**68**:268–74.
20. Pritchett JW. Longitudinal growth and growth-plate activity in the lower extremity. *Clin Orthop Relat Res* 1992:274–9.
21. Pritchett JW. Growth plate activity in the upper extremity. *Clin Orthop Relat Res* 1991:235–42.
22. Chen SC, Huang SC, Wu CT. Nonspinal tuberculous osteomyelitis in children. *J Formos Med Assoc* 1998;**97**:26–31.

23. **Rieder HL**, Snider DE Jr, Cauthen GM. Extrapulmonary tuberculosis in the United States. *Am Rev Respir Dis* 1990;**141**:347–51.
24. **Fernandes SR**, Homa MN, Igarashi A, *et al*. Miliary tuberculosis with positive acid-fast bacilli in a pediatric patient. *Sao Paulo Med J* 2003;**121**:125–7.
25. **Mert A**, Bilir M, Tabak F, *et al*. Miliary tuberculosis: clinical manifestations, diagnosis and outcome in 38 adults. *Respirology* 2001;**6**:217–24.
26. **Neonakis IK**, Alexandrakis MG, Gitti Z, *et al*. Miliary tuberculosis with no pulmonary involvement in myelodysplastic syndromes: a curable, yet rarely diagnosed, disease: case report and review of the literature. *Ann Clin Microbiol Antimicrob* 2008;**7**:8.
27. **Shen WC**, Cheng TY, Lee SK, *et al*. Disseminated tuberculomas in spinal cord and brain demonstrated by MRI with gadolinium-DTPA. *Neuroradiology* 1993;**35**:213–15.
28. **Yen HL**, Lee RJ, Lin JW, *et al*. Multiple tuberculomas in the brain and spinal cord: a case report. *Spine (Phila Pa 1976)* 2003;**28**:E499–502.
29. **Schaaf HS**, Donald PR. Radiological case of the month. Multiple-bone tuberculosis and dactylitis. *Arch Pediatr Adolesc Med* 2000;**154**:1059–60.
30. **Trunz BB**, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet* 2006;**367**:1173–80.
31. **Alzeer AH**, Fitzgerald JM. Corticosteroids and tuberculosis: risks and use as adjunct therapy. *Tuberc Lung Dis* 1993;**74**:6–11.
32. **Rosenbaum DM**, Blumhagen JD. Acute epiphyseal osteomyelitis in children. *Radiology* 1985;**156**:89–92.
33. **Agarwal S**, Caplivski D, Bottone EJ. Disseminated tuberculosis presenting with finger swelling in a patient with tuberculous osteomyelitis: a case report. *Ann Clin Microbiol Antimicrob* 2005;**4**:18.
34. **De Vuyst D**, Vanhoenacker F, Gielen J, *et al*. Imaging features of musculoskeletal tuberculosis. *Eur Radiol* 2003;**13**:1809–19.
35. **Sanghvi DA**, Iyer VR, Deshmukh T, *et al*. MRI features of tuberculosis of the knee. *Skeletal Radiol* 2009;**38**:267–73.
36. **Hong SH**, Kim SM, Ahn JM, *et al*. Tuberculous versus pyogenic arthritis: MR imaging evaluation. *Radiology* 2001;**218**:848–53.
37. **Martini M**, Adjrad A, Boudjemaa A. Tuberculous osteomyelitis. A review of 125 cases. *Int Orthop* 1986;**10**:201–7.
38. **Jain AK**, Jena SK, Singh MP, *et al*. Evaluation of clinico-radiological, bacteriological, serological, molecular and histological diagnosis of osteoarticular tuberculosis. *Indian J Orthop* 2008;**42**:173–7.
39. **Lakhanpal VP**, Tuli SM, Singh H, *et al*. The value of histology, culture and guinea pig inoculation examination in osteo-articular tuberculosis. *Acta Orthop Scand* 1974;**45**:36–42.
40. **Donald PR**. The chemotherapy of osteo-articular tuberculosis with recommendations for treatment of children. *J Infect* 2011;**62**:411–39.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Cheung JPY, Ho KKY, Lam YL, Shek TWH. Unusual presentations of osteoarticular tuberculosis in two paediatric patients. *BMJ Case Reports* 2012;10.1136/bcr-2012-006714, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow