CASE REPORT

Bacille Calmette-Guérin osteomyelitis of the proximal femur

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All newborns in Hong Kong are given bacille Calmette-Guérin vaccinations. Reported complications include formation of regional and extra-regional localised abscesses, osteomyelitis, and lymphadenitis. Several cases of bacille Calmette-Guérin osteomyelitis have been reported in Europe, but there are few reports of this in Asia. To the author's knowledge, this is the first case report of bacille Calmette-Guérin osteomyelitis in Hong Kong. Bacille Calmette-Guérin osteomyelitis, although rare, should be kept in mind as a potential complication of bacille Calmette-Guérin vaccination. Clinical suspicion, early diagnosis using an image-guided tissue biopsy and polymerase chain reaction study, and early commencement of chemotherapy are key to the effective management of this problem.

Introduction

All newborn babies are given bacille Calmette-Guérin (BCG) vaccinations in Hong Kong. Such vaccination has a good safety profile[1] but complications have been reported, including formation of regional and extra-regional localised abscesses, osteomyelitis, and lymphadenitis.[2-4] Several cases of BCG osteomyelitis have been reported in Europe, but there are few reports of this in Asia. There has been one reported case of BCG osteomyelitis of the radius in Japan,[5] and reports of BCG osteomyelitis of the humerus and sternum in Taiwan.[6,7] A literature search found no reports of previous cases of BCG osteomyelitis in Hong Kong.

Case report

A 19-month-old boy with good past health presented to the Prince of Wales Hospital in September 2006 with a 4-week history of an intermittent right limp and nocturnal fever. There was no history of trauma before the onset of the limp. He was up to date with his immunisations, including a BCG inoculation over his right deltoid region given at birth in a private hospital. His most recent vaccination was a triple vaccination (DTaP-IPV vaccine–booster dose), given 1 week prior to the onset of his symptoms. He lived in the city and had no history of farm or zoo visits. He had no close contact history of pulmonary tuberculosis (TB), and no recent travel history. He was breastfed from birth then gradually weaned to formula milk several months afterwards. There was no history of feeding with unpasteurised cow's milk. He was afebrile on admission. A physical examination found him to be a playful child walking with a right limp with mild swelling and warmth over the right proximal thigh. His right hip range of movement was limited by pain. His chest X-ray was clear, and an X-ray of his pelvis showed a well-defined radiolucent lesion over the metaphysis of his right proximal femur (Fig 1a). He had a normal white blood cell count and C-reactive protein (CRP) level, but his erythrocyte sedimentation rate (ESR) was elevated (57 mm/h). An ultrasound of his right hip showed a right hip effusion and synovial thickening with probable metaphyseal involvement. Magnetic resonance imaging of his right hip (Fig 1b) showed a medium-sized (16 mm x 12 mm) defect in the proximal femoral metaphysis with inflammation around the proximal femur and within the medullary canal. The radiological findings were suggestive of chronic low-grade infection. Computed tomographic (CT) scanning (Fig 2a, b), and a CT-guided biopsy of the radiolucent lesion were performed under general anaesthesia (Fig 2c). Only a small volume (<1 mL) of bloodstained fluid was aspirated. The biopsy materials were sent for histological examination and microbiological studies.

Because the radiological signs suggested a chronic, low-grade infection, the biopsy material was specifically investigated for TB infection by using the polymerase chain reaction (PCR)–mediated direct DNA sequencing analysis. A Mantoux test (MT-2) was also performed, and was positive (15 mm in duration after 48 hours of injection). In view of the positive Mantoux test result and the radiological features suggesting TB infection, anti-TB medication was commenced after the biopsy (regimen: 2 months of

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出現於股骨的卡介苗近端骨髓炎

所有在香港的初生嬰兒都會接種卡介苗，曾有報告指出不良反應包括在接種位置及其他位置出現局部性膿腫、骨髓炎和淋巴結發炎。歐洲曾有數宗因接種卡介苗而引發骨髓炎的病例，但亞洲很少有類似病例。據我們所知，本報告為香港首宗卡介苗骨髓炎病例，雖然非常罕見，但必須緊記此病可以是卡介苗的一種併發。要有效處理此病，最重要是有高度警覺性、透過圖像引導的組織切片及聚合酶鏈反應得到早期診斷、以及為病人盡早施行化療。

isoniazid/rifampicin/pyrazinamide/ethambutol, 7 months of isoniazid/rifampicin). In order to prevent a pathological fracture, the patient was fitted with Hip-Knee-Ankle-Foot-Orthosis. The boy's right hip pain resolved soon after commencing chemotherapy and his ESR returned to normal. He was discharged from hospital and referred to a government outpatient chest clinic for direct observed therapy. The PCR (amplified *Mycobacterium tuberculosis* direct test) result, returned 1 week after the biopsy, turned out to be positive. A histological examination of the aspirate found caseating granulomatous inflammation with one acid-fast bacillus seen on Ziehl-Neelsen staining. The bacterium was cultured and subjected to PCR and identified as a strain of *Mycobacterium bovis*. The planned chemotherapy regimen was continued, which he tolerated well. He has been followed up for 3 years and has remained well with no relapses, and no complications such as pathological fracture, avascular necrosis of the femoral head, physeal arrest, leg length discrepancy or bony deformity in the proximal femur. His most recent right hip X-ray (Fig 2d) shows that the radiolucent lesion has almost resolved.

Discussion

The BCG vaccine is used to protect recipients against TB. Because of the relatively high prevalence of TB infection in Hong Kong, universal BCG vaccination is practised here. Although BCG vaccination does not prevent TB infection, it helps to confine the

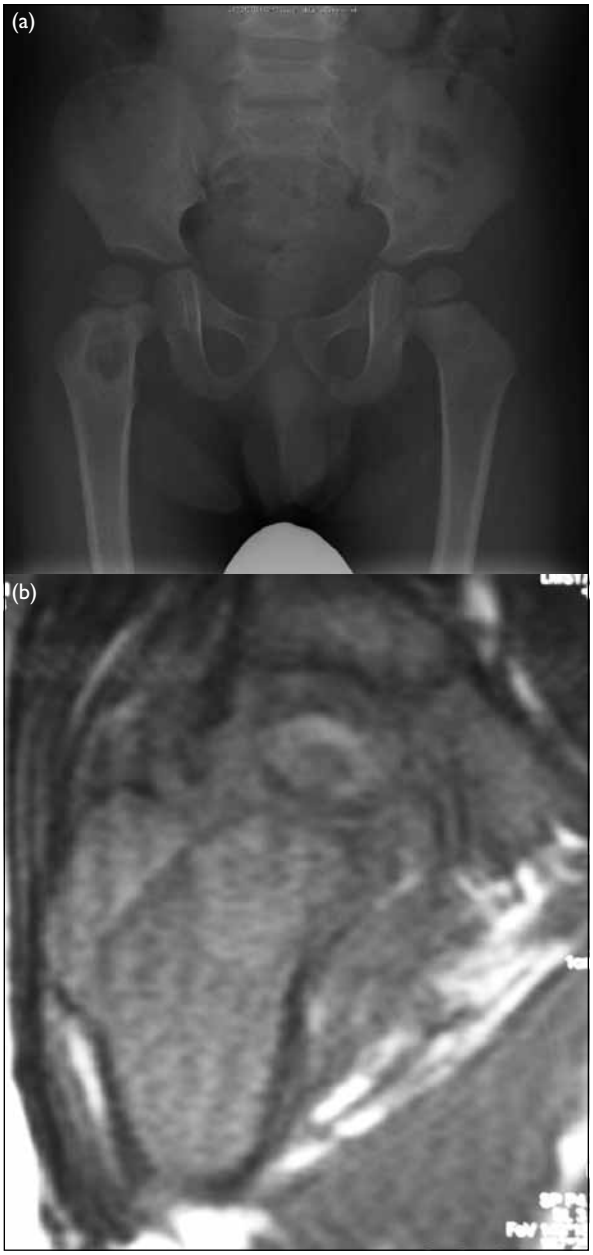

FIG 1. (a) Pelvis X-ray showing an osteolytic lesion over the metaphyseal region of the right proximal femur. (b) Magnetic resonance image of the right proximal femur showing inflammation around the proximal femur and within the medullary canal

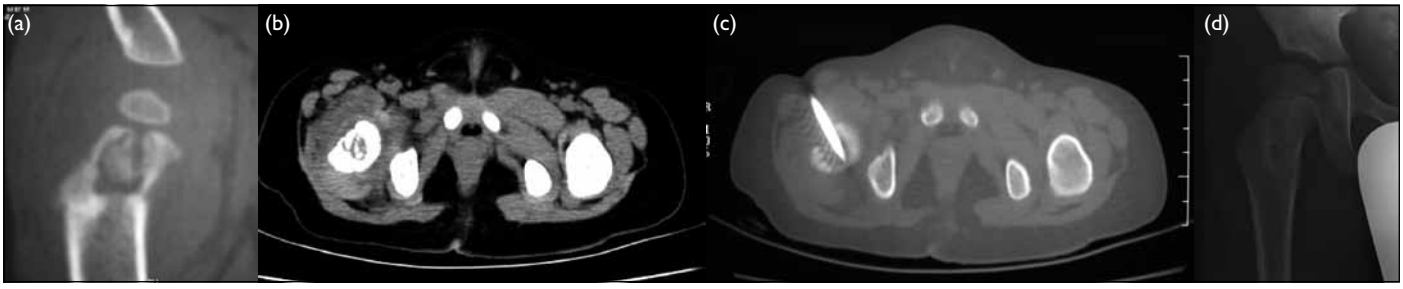

FIG 2. (a) Computed tomographic (CT) coronal reconstruction film showing an osteolytic lesion with a partially preserved bone matrix in the proximal femur metaphysis; (b) CT transverse cut of the right proximal femur showing the osteolytic lesion; (c) CT-guided biopsy of the osteolytic lesion; (d) X-ray of the right hip taken 3 years after the onset of the disease showing that the radiolucent lesion has almost resolved

infection to the lungs, effectively protecting against serious illness, especially TB meningitis.[8,9] The BCG vaccination programme in Hong Kong has kept the incidence of childhood TB meningitis low here. The reported complications of BCG vaccination include local ulceration, scarring, local injection site abscesses, and lymphadenitis. Systemic BCGosis is a recognised but rare consequence of BCG vaccination that has traditionally been seen in children with severe immune deficiencies. Osteitis/osteomyelitis is another of the rare and severe consequences of BCG vaccination. The reported frequency of BCG osteomyelitis ranges from 1 in 80 000 to 1 in 100 000 vaccinations.[10,11] Several cases of BCG osteomyelitis have been reported, in particular in Scandinavia and Eastern Europe, and it is typically associated with changes in the BCG vaccine strain. Local reactogenicity differs between vaccines, varying with both the strain and the number of viable bacilli. The Hong Kong Department of Health uses the BCG vaccine produced by Glaxo, because, despite having lower efficacy, it has a better safety record.[5,9]

The pathogenesis of BCG osteomyelitis remains obscure. Possible risk factors include the strain used for the BCG vaccine and the method of vaccination, but no single cause has been established.[12,13] In one case report the authors postulated that the disorder was caused by direct BCG inoculation.[7] In our case, haematogenous spread is the likely cause as the radiolucent lesion is located in the metaphysis of the proximal femur and is remote from the site of the vaccination (in the right deltoid region).

The clinical presentation of BCG osteomyelitis is non-specific. Patients may present with a limp, as in our case. Several previous reports of BCG osteomyelitis found the symptoms generally appeared approximately 1 year after BCG vaccination (range, 3-26 months).[12] Our patient also had a significant time delay between the BCG vaccination and the onset of BCG osteomyelitis.

Bacille Calmette-Guérin osteomyelitis usually involves the peripheral skeleton. Less common sites include the bones of the axial skeleton such as the vertebrae, ribs, sternum, and clavicle.[14] Approximately 80% of long bone lesions are in the epiphysis or the metaphysis.[12] It is difficult to diagnose BCG osteomyelitis, principally because it is a rare disease with a long latency period between the vaccination and the onset of symptoms. The symptoms may evolve insidiously and be deceptively benign. Moreover, preliminary investigations are often unhelpful. Inflammatory markers, such as the ESR and the CRP level, are only mildly elevated. Radiographic changes are also non-specific. The differential diagnosis for an osteolytic lesion in the metaphysis includes infective causes such as pyogenic, TB, syphilitic, and fungal osteomyelitis, or neoplastic causes like a simple bone cyst or an eosinophilic granuloma. A tissue biopsy is necessary to make a definitive diagnosis. We adopted a minimally invasive technique, using CT to guide the biopsy, whereas most of the reported cases adopted an open biopsy approach.[6,7] Our CT-guided biopsy was free of complications, whereas use of an open biopsy may lead to wound infection and bleeding. Apart from the routine microbiological and histological investigations, the biopsy material was also subjected to a PCR enabling diagnosis of TB infection within 1 week, and subsequent differentiation between mycobacterium species (*M tuberculosis*, *M bovis*, and *M bovis* BCG), permitting use of the correct treatment regimens. Chemotherapy was commenced immediately after the biopsy in order to avoid further bone destruction and abscess collection while waiting for the laboratory result. Early treatment permitted this patient to make an uneventful recovery with chemotherapy alone. He has developed no complications in the 3 years since the onset of his illness.

The most effective chemotherapy regimen for the treatment of *M bovis* BCG osteomyelitis is yet to be determined. Pyrazinamide is generally considered ineffective for BCG osteomyelitis as all strains of *M bovis* are resistant to it. Kröger et al[2] suggested the regimen should include streptomycin combined with ethionamide and isoniazid for 1 month, isoniazid combined with ethionamide or rifampicin for 4 more months, and isoniazid alone for 12 months. In our case, the favourable clinical, radiological, and serological response to our initial anti-TB drug regimen, which included isoniazid, rifampicin, pyrazinamide and ethambutol, and the absence of side-effects persuaded us to continue this drug regimen for a total of 2 months. This was followed by 7 months of isoniazid and rifampicin. By the time the bacterium was proven to be a BCG strain of *M bovis* (2.5 months post-chemotherapy), the patient had finished his quadruple therapy so he was kept on isoniazid and rifampicin. If the BCG strain of *M bovis* had been identified earlier, the chemotherapy would have been changed.

Conclusion

Bacille Calmette-Guérin osteomyelitis, although rare, should be kept in mind when assessing a child presenting with a limp after BCG vaccination. Clinical suspicion, early diagnosis using an image-guided tissue biopsy and PCR studies, and early commencement of chemotherapy are key to the effective management of this disease. Early use of a CT-guided tissue biopsy and PCR study along with commencement of chemotherapy soon after the biopsy enabled this child to enjoy a satisfactory clinical outcome with chemotherapy alone.

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