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Musculoskeletal melioidosis masquerading as diabetic amyotrophy

A W C Kow, K B L Lee, Y S Wong

ABSTRACT

A patient with musculoskeletal melioidosis masquerading as diabetic amyotrophy is described. A 43-year-old man presented with left thigh pain, fever, malaise and loss of weight. He had diabetes mellitus for six years. He was initially diagnosed with diabetic amyotrophy and was treated conservatively. Recurrence of symptoms prompted further investigations which revealed melioidosis of the left femur. Magnetic resonance imaging showed an enhancing subperiosteal collection. The diagnosis was confirmed by open biopsy and tissue culture. Acute treatment consisted of intravenous ceftazidime for 24 days and oral cotrimoxazole. The patient showed marked improvement clinically and biochemically. He was discharged with oral doxycycline and cotrimoxazole for three months. This disease is eminently treatable, but can be a diagnostic challenge when it presents in an uncommon site.

Keywords: Diabetes amyotrophy, diabetes mellitus, melioidosis, musculoskeletal infection

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INTRODUCTION

Melioidosis, also known as soil disease, is caused by the bacteria, *Burkholderia pseudomallei*. It was first described by Whitmore and Krishnaswami in Burma in 1912[1]. Stanton and Fletcher subsequently introduced the term "melioidosis" in 1925 when this organism was isolated from a patient's blood in Malaysia[2]. Singapore reported its first case in 1920[3]. Melioidosis has a myriad of presentations. Thus, a high index of suspicion is required to diagnose the disease.

CASE REPORT

A 43-year-old man with type II diabetes mellitus of six years duration, complained of left thigh pain associated with muscle cramps one month prior to admission. He had been diagnosed with diabetic amyotrophy in December 2002, based on the symptoms of muscle wasting, absent knee reflexes and poor blood sugar control. He was treated conservatively with analgesia and diabetic control. The pain recurred two weeks later. He had associated malaise and weight loss of 4kg over two weeks, with occasional fever which was worse at night. There were no respiratory or other systemic symptoms.

On examination, his vital signs were stable. He was afebrile and systemic review was unremarkable. However, his left thigh was tender on palpation, especially at the medial aspect. No lump or solid lesion was found. Range of motion for the left hip and knee was full. Proximal muscles on the left thigh appeared weaker compared to the right, but sensation was intact. Initial radiograph of the left femur showed no bony changes suggestive of osteomyelitis or fracture. There was no evidence of a lytic lesion or periosteal elevation. An endocrine consultation was initiated to rule out possible muscular endocrinopathy, in view of the left proximal muscular weakness. Thyroid function test and cortisol level were normal. A myeloma screen was also unremarkable.

The patient developed a spiking fever on the third day after admission. A septic work-up was carried out, but blood cultures were negative. Magnetic resonance (MR) imaging of the left thigh performed on day 11 showed possible periosteal abscess or neoplasm, with associated marrow and adjacent soft tissue oedema. There was uplifting of the overlying femoral periosteum and an enhancing rim that suggest an infective focus (Fig. 1).

The patient underwent an open biopsy of the left femur. Intraoperatively, a 5cm subperiosteal collection with a surrounding capsule was found at the medial aspect of the mid-shaft of the femur. There was no extension into bone. Histology of the friable tissues revealed large amounts of inflammatory cells representing reactive changes secondary to infection. No malignant cells were seen.

The tissue culture grew *Burkholderia pseudomallei* that was sensitive to ceftazidime, cotrimoxazole and doxycycline. The patient was treated with intravenous ceftazidime and oral cotrimoxazole for 24 days followed by oral cotrimoxazole and doxycycline.

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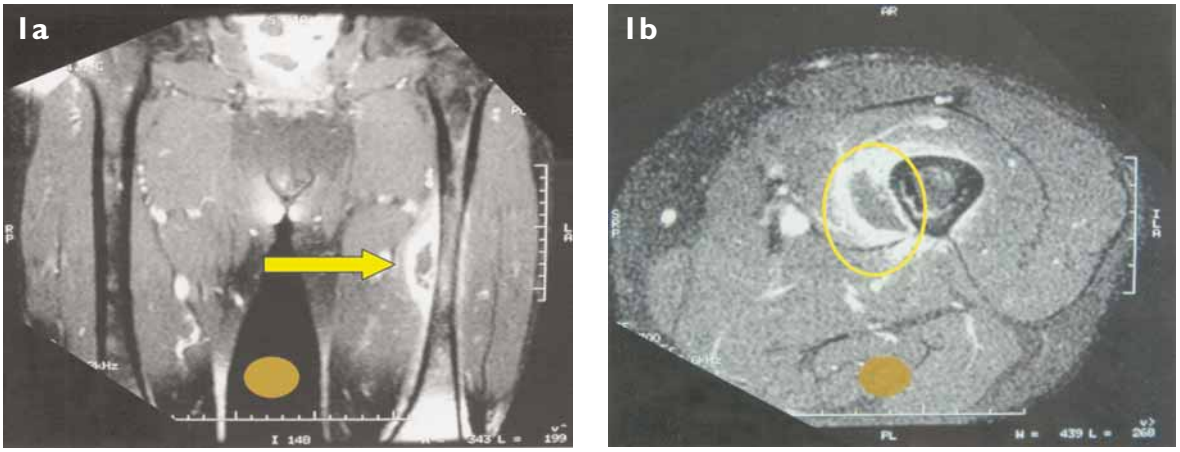

Fig. 1 Enhanced (a) coronal and (b) axial fat-suppressed T1-W MR images show marrow and adjacent soft tissue oedema of the mid-shaft of the left femur, with lifting of overlying periosteum and enhancing rim, consistent with abscess (labelled).

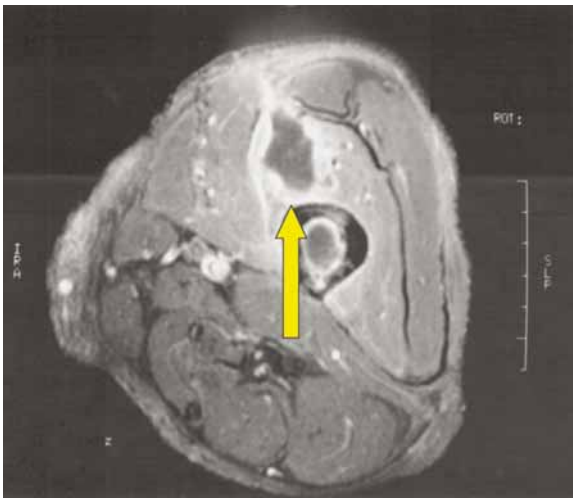

Fig. 2 Repeat enhanced axial fat-suppressed T1-W MR image shows a small abscess (arrow) in left vastus intermedius muscle. This was subsequently drained under ultrasonographical guidance.

His fever settled with this treatment, and his appetite improved markedly. His inflammatory markers also normalised with treatment.

Repeat MR imaging of the left thigh three weeks later revealed a small abscess in the left vastus intermedius muscle (Fig. 2). Ultrasonographical-guided drainage was carried out and approximately 5ml of serous fluid was collected, but there was no pus. Cultures were negative. The patient recovered well and was discharged with three months of oral doxycycline and cotrimoxazole. He was followed-up at regular six-month intervals and has no signs of relapse to date.

DISCUSSION

Burkholderia pseudomallei is a gram-negative aerobic organism. It is a saprophyte found mainly in soil and ponds from endemic areas in Southeast Asia and Northern Australia. In Thailand, the incidence of melioidosis is as high as 5.5 cases per 100,000 population (1994)[4]. In Singapore, it has a mean annual incidence of 1.7 per 100,000 population between 1989 and 1996. The disease has a preponderance for males, with a male to female ratio of 4.5:1[5].

Currie et al found that risk factors commonly associated with melioidosis include diabetes mellitus (37%), alcohol abuse (39%), chronic lung disease (27%) and chronic renal disease (10%)[6]. Heng et al reported that 57.5% of their patients had diabetes mellitus[5]. Insulin markedly inhibits the growth of this pathogen *in-vitro* and *in-vivo*. It grows significantly better in insulin-depleted human serum than in control human serum. Our patient has diabetes mellitus, which predisposed him to the infection.

Melioidosis has a wide spectrum of presentations, ranging from chronic constitutional symptoms to acute fulminant septicaemia that is highly fatal. Heng et al showed that the main clinical presentations in Singapore were fever and respiratory symptoms such as cough, dyspnoea and chest discomfort[5]. Other clinical presentations include gastrointestinal, cutaneous and urinary symptoms[5]. Melioidosis presenting as prostatic abscesses is also widely reported in the literature[4]. Encephalomyelitis is also not uncommonly seen in endemic regions. Musculoskeletal melioidosis is rare.

Melioidosis that affects unusual sites can mimic various other conditions. Our patient had a history of diabetes mellitus, chronic thigh pain, significant weight loss and unilateral proximal muscular weakness with absence of sensory involvement, features that were highly suggestive of diabetic amyotrophy. In addition, his blood glucose levels were poorly controlled. Therefore, it was difficult to exclude diabetic amyotrophy clinically. Painful diabetic neuropathy accounts for 11% to 20% of all cases of diabetic neuropathy. Most of them are painless.

Loss or change of sensation may be detected only by clinical tests[7]. Elevated glucose levels have been implicated in the pathogenesis of pain in diabetic neuropathy. However, this seems to be more significant in type I diabetics[8].

The current gold standard for a definitive diagnosis of melioidosis is isolation and identification of the causative agent *(Burkholderia pseudomallei)* from various specimens. Research on serology and genetic testing are currently being carried out to hasten diagnosis. However, most of the tests lack sensitivity and specificity. Presence of subclinical infection in healthy individuals and possible cross-sensitivity of gram-negative organism with melioidosis antibody have limited the use of these assays[9].

Two decades ago, conventional treatment for acute melioidosis was a quadruple-drug regimen comprising of intravenous chloramphenicol, doxycycline and trimethoprim-sulphamethoxazole. Failure rate was high as these drugs are bacteriostatic and are thus ineffective in the management of acute melioidosis which usually presents as septicaemia[10]. High-dose intravenous ceftazidime is currently the treatment of choice in acute infection. A randomised controlled trial of the quadruple-drug regimen versus ceftazidime in Thailand showed that the latter was more effective and reduced mortality of up to 50%[10]. Further trials concluded that a combination of ceftazidime and cotrimoxazole can also achieve a similar reduction in mortality. Ceftadizime, with or without cotrimoxazole, has since become the gold standard in therapy. The mean duration of treatment is 10 to 14 days[10].

Cotrimoxazole with doxycycline is the most commonly-used combination in maintenance therapy. Derived from the original quadruple-drug therapy (cotrimoxazole, doxycycline and chloramphenicol), studies are underway to comparing this treatment regime with the conventional quadruple-drug therapy. Maintenance therapy should be prolonged to reduce the likelihood of relapse; it usually lasts from 12 to 20 weeks. Surgical intervention, such as drainage of abscesses, can be offered in cases of solid organ abscesses to treat melioidosis[10]. Our patient underwent surgical biopsy and curettage, which may have contributed to the improvement in his clinical condition.

A high index of suspicion is important, especially in endemic areas, when a patient presents with pyrexia of unknown origin. A prolonged course of high-dose intravenous ceftazidime, with or without cotrimoxazole, is the recommended therapy in the management of melioidosis. Maintenance therapy usually employs oral cotrimoxazole with doxycycline. Other options include co-amoxiclav and fluoroquinolones. Mortality was high previously as patients often develop septicaemia shortly after an acute infection. Thus, effective antibiotic therapy is essential to the reduction of mortality.

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