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Case Report

Melioidotic septic arthritis: a case report and literature review

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Burkholderia pseudomallei, the causative agent of melioidosis, is endemic in southeast Asia and northern Australia. In recent years, the incidence of melioidosis has increased worldwide. Septic arthritis is a rare but well-recognized manifestation of melioidosis. Patients with underlying medical conditions, such as diabetes mellitus, renal impairment, cirrhosis, and malignancy are at greater risk. The presentations of melioidotic septic arthritis often mimic other disease processes and patients may not always be clinically septic. We present a case of septic arthritis due to *B. pseudomallei* in a 66-year-old male with diabetes mellitus presenting with a history of fever and ankle swelling. Follow-up ankle X-ray showed soft tissue swelling. Synovial fluid and blood samples grew *B. pseudomallei*. The patient improved gradually after parenteral administration of ceftazidime (2 g 8-hourly) and cotrimoxazole (1440 mg 8-hourly). He was discharged on oral cotrimoxazole (1440 mg 12-hourly), doxycycline (100 mg 12-hourly), and chloramphenicol (500 mg 6-hourly) for 6 months. This case highlights the possible occurrence of melioidotic septic arthritis, and the importance of prompt initiation of appropriate antimicrobials to achieve good outcomes.

Key words: Arthritis; *Burkholderia pseudomallei*; Melioidosis

Introduction

Most cases of septic arthritis are of hematogenous origin and are increasingly reported in the elderly or in patients who often have underlying medical conditions, such as diabetes mellitus, malignancy, acquired immunodeficiency syndrome, chronic renal failure, rheumatoid arthritis, alcoholism, degenerative joint disease, cirrhosis, and hypogammaglobulinemia [1,2]. It has previously been reported in patients on corticosteroid therapy as well as in stem cell transplant recipients [1-3]. The other possible causes of acute septic arthritis include direct introduction or extension from contiguous focus of infection and penetrating trauma [1]. It is the most serious cause of acute joint inflammation and if not diagnosed and treated promptly can be linked with severe morbidity [4].

In the absence of clear indication of the causative agent, the initial choice of empirical antimicrobial therapy is an educated guess [5]. The most commonly isolated organisms include S*taphylococcus aureus*, *Streptococcus* spp. (most common species include *Streptococcus pneumoniae*, groups B, G, C, or F beta (β)-hemolytic *Streptococcus*), followed by Gram-negative bacilli such as *Pseudomonas aeruginosa* and *Escherichia coli*, which account for approximately 10% to 20% of cases. *Haemophilus influenzae* was the most common cause of septic arthritis in children, but its incidence is decreasing due to the advent of *H. influenzae* type B vaccine for children. Other possible causative agents are *Kingella kingae*, *Neisseria gonorrhoeae*, *Shigella* spp., *Salmonella* spp., and *Streptobacillus moniliformis* [1,5]. *Burkholderia pseudomallei*, the causative agent of melioidosis, has rarely been reported as a causative agent of septic arthritis. Here, we report a patient with melioidotic septic arthritis of the ankle joint and a literature review.

Case Report

A 66-year-old male presented to the emergency room of the University of Malaya Medical Centre (UMMC),

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Kuala Lumpur, Malaysia, with a 1-month history of fever, chills, and left ankle swelling. The patient had a history of diabetes mellitus for 30 years, hypertension, severe retinopathy, glaucoma, retinal detachment, and paroxysmal atrial fibrillation. He also had an exercise-induced 2:1 atrioventricular block and an intermittent complete heart block. A permanent pace-maker had been implanted 2 years ago.

One month prior to the recent admission, there was a history of blunt trauma over the pacemaker site, which ultimately developed a small non-tender erythematous lump. It was later proven to be a superficial abscess, and incisional drainage was done at a private hospital. No communication between the abscess and the pace-maker system was noted. Pus and blood specimen grew *Acinetobacter* spp. and meropenem was administered. Meropenem was discontinued after 4 days, before the patient was referred. In view of persistent presumed *Acinetobacter* spp. bacteremia and ankle swelling, he was referred to UMMC. Vital signs on admission were temperature, 37°C; pulse rate, 70/min; and blood pressure, 120/60 mm Hg. On physical examination, he had a markedly edematous, tender, and hyperaemic left ankle with decreased range of movements. Laboratory investigations revealed hemoglobin of 9.9 g/dL, peripheral leukocyte count of 13.6×10^9/L with 84% polymorphonuclear leukocytes, and platelet count of 30,900/mm^3. The erythrocyte sedimentation rate (75 mm/h) and C-reactive protein (8.6 mg/dL; normal, 0-4 mg/dL) were elevated.

Blood chemistry results showed slightly increased total bilirubin (4 mmol/L; normal range, 0-3 mmol/L) and alkaline phosphatase (154 IU/L; normal range, 50-136 IU/L), while serum aspartate aminotransferase and alanine aminotransferase levels were within normal limits. Serum levels of sodium and chloride were disturbed, while urea and creatinine levels were normal. Chest X-ray and abdominal ultrasonography were normal. Echocardiogram showed no vegetation in the heart.

Left ankle radiograph showed soft tissue swelling. Synovial fluid of affected joint had a leukocyte count of 25,800/μL with 95% polymorphs and 5% lymphocytes. The aspirated fluid and blood specimens were processed using standard laboratory procedures and susceptibility testing was performed in accordance with disc diffusion methods of the National Committee of Clinical Laboratory Standards [6]. Gram stain of synovial fluid showed Gram-negative bacilli. Empirical therapy with intravenous ampicillin-sulbactam (1.5 g 8-hourly) was initiated. The blood agar culture of aspirated fluid revealed colonies with a metallic sheen, which were confirmed to be *B. pseudomallei* by bipolar appearance under microscope, conventional biochemical test, API 20NE biochemical identification system (bioMérieux, Marcy l'Etoile, France), and by a positive reaction to latex agglutination test (All Eights Sdn. Bhd., Kuala Lumpur, Malaysia). Blood sample also yielded *B. pseudomallei*. Antimicrobial susceptibility tests of *B. pseudomallei* isolates showed resistance to ampicillin, aminoglycosides, and susceptibility to cotrimoxazole, tetracycline, chloramphenicol, piperacillin, piperacillin-tazobactam, amoxicillin-clavulanic acid, ceftazidime, and carbapenems.

The patient responded well to intravenous ceftazidime (2 g 8-hourly) administered for 2 weeks in combination with intravenous amoxicillin-clavulanic acid (1.2 g 8-hourly) for 4 days, and then with oral cotrimoxazole (1440 mg 8-hourly) for 8 days. The patient had diminished pain and joint swelling and was discharged on maintenance therapy of cotrimoxazole (1440 mg 12-hourly), chloramphenicol (500 mg 6-hourly), and doxycycline (100 mg 12-hourly) for 6 months.

Discussion

B. pseudomallei, a Gram-negative aerobic bacillus, was first described by Whitmore and Krishnaswami from Burma in 1911. It is endemic in regions that typically border 20° north and 20° south of the equator. Some reports of meloidotic septic arthritis from around the world are summarised in Table 1 [4,7-11]. The incidence of melioidosis is especially high in southeast Asia and northern Australia. However, sporadic cases have been reported worldwide [12-14]. The spectrum of disease ranges from localized suppurative skin infection to septicemia with abscess formation in any organ, and it is associated with a high mortality rate. Septic arthritis and oesteomyelitis are rare but well recognized forms of the disease [10,13]. A 10-year prospective study and review of literature reported that septic arthritis and osteomyelitis were recorded in 9 of 252 confirmed cases of melioidosis [10].

In a more recent study of 77 patients with culture-confirmed septic arthritis in Thailand, 25 had melioidotic septic arthritis [11]. Jesudason et al reported 3 cases of melioidotic septic arthritis from south India [15], and 3 cases imported from the Indian subcontinent have been reported in UK [9]. Very few cases of melioidotic

Table 1. Summary of melioidotic septic arthritis cases in endemic and non-endemic areas

Reference	Country	Patients with arthritis/total number of patients	Mean age (years)	Risk factors	Involved Joint	Isolate source involvement	Treatment
Saengnipanthkul et al 1991 [7]	Thailand	9/160	-	DM, CRF	Knee, ankle, upper extremity joints	Pus, blood	Ceftazidime, cotrimoxazole, OR doxycycline, chloramphenicol, cotrimoxazole
Puthucheary et al 1992 [8]	Malaysia	6/50	>30	DM, CRF, malignancy, SLE	-	Synovial fluid, blood	Ceftazidime, cotrimoxazole, OR doxycycline, chloramphenicol, cotrimoxazole
Morgan et al 1996 [4]	Australia	3/191	30.2	Alcohol, DM, corticosteroids	Knee (54%), hip (13%)	Synovial fluid, blood	-
Hoque et al 1999 [9]	United Kingdom	3/3	51.7	DM	Elbow, knee, wrist	Synovial fluid, blood	-
Currie et al 2000 [10]	Australia	5/252	47	Alcoholism, DM, CRF, CLD	-	Synovial fluid, blood	Ceftazidime, cotrimoxazole, OR doxycycline, chloramphenicol, cotrimoxazole
Kosuwon et al 2003 [11]	Thailand	25/104	53.7	DM, CRF, SLE, farmers	Mostly upper extremity joints	Synovial fluid, blood	Ceftazidime, cotrimoxazole, OR doxycycline, chloramphenicol, cotrimoxazole

Abbreviations: DM = diabetes mellitus; CRF = chronic renal failure; SLE = systemic lupus erythematosus; CLD = chronic lung disease

septic arthritis were reported from our hospital in 1992 [8]. Large joints, such as knee, ankle, elbow, or shoulder, are usually involved in this disease. The most commonly affected joints are the knee and shoulder [4,7,11], while in our patient, the ankle joint was involved.

Melioidotic septic arthritis is often linked with underlying diseases, such as diabetes mellitus, chronic renal failure, cirrhosis, systemic lupus erythematosus, and malignancies [11,13,15]. Kosuwon et al revealed that diabetes mellitus was a predisposing factor in the majority of patients with septic arthritis [11]. In this study, diabetes mellitus was identified as the chronic underlying illness. The common portals of entry of *B. pseudomallei* are inoculation through minor skin abrasions, inhalation, and ingestion.

Generally, septic arthritis results from hematogenous dissemination of the organism, but it may follow direct spread from other organs or soft tissue infections over joints. In 4 reported cases, lung and psoas muscle abscesses were the evident sites of infections [16]. We could not ascertain the source of transmission of *B. pseudomallei* infection in our patient. We assume that melioidotic septic arthritis occurred as a result of hematogenous seeding in our patient, since diabetic patients were susceptible to hematogenous seeding [1].

The clinical manifestations of melioidotic septic arthritis alone are not diagnostic, and such a diagnosis requires a high degree of suspicion, especially in residents or travelers from endemic areas [16]. The affected joint is usually tender, hot, red, and swollen. In addition, it can mimic acute or chronic forms of other infections or rheumatic disorder [11]. Occasionally, infections may not become evident for several years after exposure to *B. pseudomallei*. The latency period in one case has been presumed to be as long as 26 years [17]. The diagnosis is ultimately confirmed by culturing the pathogen on ordinary media; however, selective media can be used.

Gram stain of synovial fluids is a quick approach, but the identification of Gram-negative bacilli with bipolar staining is infrequent [7]. Latex agglutination test based on polyclonal or specific monoclonal antibodies to lipopolysacchride or exopolysacchride

can therefore be undertaken for definitive identification [14]. Serological tests, such as enzyme-linked immunosorbent assay, to detect immunoglobulin M and immunoglobulin G antibodies, and molecular methods (for instance, polymerase chain reaction) are also used for definitive diagnosis of disease [13,14].

B. pseudomallei is resistant to many aminoglycosides, rifampicin, penicillins, first- and second-generation cephalosporins, and macrolides [13,14]. It is notably susceptible to ceftazidime, chloramphenicol, tetracycline, cotrimoxazole, flouroquinolones, and β-lactam/β-lactamase inhibitor combinations [18]. Intravenous ceftazidime, imipenem, and cotrimoxazole for 10 days to 4 weeks have been recommended in severe melioidosis cases [13,19]. The emergence of ceftazidime resistance during treatment has been reported [20]. Nevertheless, carbapenems have shown greater activity against *B. pseudomallei* strains, which have reduced susceptibility to ceftazidime or amoxicillin-clavulanic acid [19].

Our patient respond-ed well to intravenous ceftazidime and showed marked clinical improvement. Surgical drainage of the affected joint has also been recommended, if indicated [11]. Despite advances in treatment, relapse is common. To prevent relapse, oral maintenance therapy is recommended with a combination of chloramphenicol, tetracycline, cotrimoxazole, or amoxicillin-clavulanic acid for 20 weeks [14]. It is important to note that relapse was less common (10%) in patients who completed a full course of antibiotic than those who received therapy for 8 weeks or less (30%) [14,21]. A previous study reported relapse in 3 out of 4 cases due to non-compliance with treatment [16].

Although septic arthritis is uncommon, it has on occasion been a major clinical manifestation of melioidosis. Melioidotic septic arthritis usually occurs in well-recognized risk groups, particularly patients with diabetes mellitus, renal impairment, chronic lung disease, systemic lupus erythematosus, and alcoholics. This requires early awareness and better understanding of melioidosis, as well as prompt and definitive diagnosis and administration of accurate antimicrobial drugs for treating melioidosis in order to achieve a desirable outcome.

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