

Melioidosis of the extremities in Brunei Darussalam

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ABSTRACT

Introduction: Melioidosis caused by *Burkholderia pseudomallei* is an infectious disease endemic to Southeast Asia and northern Australia. It has a broad spectrum of clinical manifestations and high mortality, and can mimic other infectious diseases. The aim of this study was to review cases of melioidosis of the extremities in Brunei Darussalam.

Methods: Culture-positive cases for *Burkholderia pseudomallei* in Raja Isteri Pengiran Anak Saleha Hospital were identified from records in the Microbiology Department. The case notes were reviewed to identify patients who were treated for problems affecting the extremities. 14 (13 males and one female) out of 48 patients were identified.

Results: The median age of the patients was 45 (range 14–55) years. Septicaemia was the most common presenting feature in 11 patients. Multisystem involvement was noted in eight patients, diabetes mellitus in nine patients and other risk factors in two patients. Blood culture was positive in ten patients and pus culture in 11 patients. The presentations noted were cellulitis of the limbs, abscess, osteomyelitis (three patients each) and septic arthritis (five patients). Orthopaedic intervention (joint washout/incision and drainage/curettage) was required in 11 patients. The median hospital stay was 27.5 (range 13–63) days; two patients required admission to intensive care. No mortality was reported.

Conclusion: Melioidosis of the extremities is not uncommon in Brunei Darussalam. It is associated with significant morbidity, and a large number of patients require surgical intervention. Thus, a high index of suspicion is required for early diagnosis and institution of appropriate antibiotic therapy.

Keywords: *Burkholderia pseudomallei*,

complications, diabetes mellitus, melioidosis, surgery

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INTRODUCTION

Melioidosis is an infectious disease endemic to Southeast Asia and northern Australia. It is caused by a gram-negative, soil-dwelling bacillus, *Burkholderia pseudomallei*. More reports are now available from other parts of the world.⁽¹⁻³⁾ Some authors have suggested that there is a re-emergence of melioidosis in endemic areas and that it is spreading to non-endemic areas.^(4,5) The clinical and radiological features of melioidosis can be similar to those of other bone and joint infections. In melioidosis patients, the systemic manifestations of the illness are often more prominent. Hence, a high index of suspicion is essential for early diagnosis, microbiological confirmation and effective treatment.⁽²⁾

The epidemiology, pathophysiology and management of melioidosis have been extensively reviewed by Cheng and Currie.⁽²⁾ Similarly, Jain et al have presented a review of its orthopaedic manifestations with clinical features, diagnosis and management.⁽⁶⁾ The aim of the present study was to review cases of melioidosis of the extremities in Brunei Darussalam, with particular reference to the demographics, identification of risk factors and clinical presentation.

METHODS

In this retrospective study, culture-positive cases for *Burkholderia pseudomallei* that were treated in Raja Isteri Pengiran Anak Saleha Hospital between August 2001 and November 2007 were identified from the records maintained in the Department of Microbiology. The records were retrieved and further data was collected on patients who were either treated at or referred to the Department of Orthopaedics for management. A total of 48 culture-positive patients were identified. 14 of these had melioidosis of the extremities. Data related to demographics, risk factors, duration of symptoms, hospital stay, the systems involved and details of musculoskeletal affection were recorded. In addition to the radiography, ultrasonography of the abdomen, computed tomography and magnetic resonance (MR)

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Table I. Summary of patients with melioidosis of the extremities in Brunei Darussalam.

Patient no.	Age (yrs)	Gender	Nationality	Hospital stay (days)	Primary diagnosis	Organs involved	Risk factors	Isolate source: blood	Isolate source: pus/fluid	Orthopaedic manifestation	Surgical procedure
1	31	M	Bangladeshi	19	Septicaemia	Lung, liver, spleen		+	+	Septic arthritis: knee	Joint washout
2	43	M	Bruneian	14	Abscess		DM	+	+	Abscess: thigh	Incision & drainage
3	50	M	Filipino	16*	Septicaemia	Liver, spleen	DM	+	-	Cellulitis: foot	-
4	53	F	Bruneian	30	Septicaemia	Liver	DM, CRF	+	+	Septic arthritis: knee	Joint washout
5	55	M	Bruneian	45	Septicaemia	Spleen	DM	+	+	Osteomyelitis: tibia	Curettage
6	47	M	Bruneian	25	Septicaemia	Liver		+	-	Cellulitis: foot	-
7	54	M	Indian	13	Septicaemia		IMN	+	+	Septic arthritis: knee	Joint washout
8	41	M	Filipino	19*	Septicaemia	Lung, liver	DM	+	-	Cellulitis: leg	-
9	47	M	Bruneian	31	Septicaemia		DM	-	+	Abscess: forearm	Incision & drainage
10	42	M	Indian	43	Septicaemia	Liver	DM	+	+	Septic arthritis: elbow	Open joint washout
11	14	M	Bruneian	18	Abscess		G6PD deficiency	-	+	Abscess: forearm	Incision & drainage
12	41	M	Bruneian	41	Septicaemia		DM	+	+	Osteomyelitis: tibia	Curettage
13	34	M	Bruneian	37	Septic arthritis	Lung		-	+	Septic arthritis: knee	Joint washout
14	53	M	Bruneian	63	Septicaemia		DM, cirrhosis	+	+	Osteomyelitis: tibia	Curettage

* Patients requiring intensive care.

M: male; F: female; DM: diabetes mellitus; CRF: chronic renal failure; IMN: idiopathic membranous nephropathy; G6PD: glucose-6-phosphate dehydrogenase

imaging of the affected part were done, wherever appropriate.

Microbiological diagnosis was made by the isolation of *Burkholderia pseudomallei*, which was confirmed biochemically by the API20NE kit (bioMerieux, Marcy l'Etoile, France). As per the hospital guidelines, patients were treated with ceftazidime 40 mg/kg 8 hr (intravenous [IV]) and amoxicillin/clavulanic acid 1.2 gm 8 hr (IV) for 2–4 weeks. Patients requiring admission to intensive care were treated with meropenem 20 mg/kg 8 hr (IV) for 2–4 weeks. This was followed by amoxicillin/clavulanic acid 625 mg 12 hr or co-trimoxazole 1,440 mg 12 hr or doxycycline 100 mg 12 hr for six months. The patients were followed up every six weeks with clinical and haematological assessments.

RESULTS

A total of 14 out of 48 culture-positive patients (29%) were diagnosed with melioidosis of the extremities during the study period. The details of these cases are presented in Table I. There were 13 male patients and one female patient, with a median age of 45 (range 14–55) years. 64% (n = 9) of the patients were Bruneian, while the nationalities of the other patients were Indian (n =

2), Filipino (n = 2) and Bangladeshi (n = 1). Septicaemia was the most common presenting feature observed in 11 patients (78.5%), while the remaining three patients presented with abscess (n = 2) and septic arthritis (n = 1). Only one patient with abscess of the forearm was directly admitted under the care of orthopaedic surgeons, while the others were primarily treated under the care of physicians. The median time between the onset of symptoms and hospital admission was seven (range 2–30) days. Five patients were seeking treatment with general practitioners before being referred to the hospital. Multisystem involvement was noted in eight patients. Liver involvement was seen in six patients, while lung and spleen involvement was seen in three patients each. Diabetes mellitus was the most common risk factor noted in nine (64%) patients.

Septic arthritis (n = 5; [knee 4, elbow 1]) was the most common manifestation, followed by cellulitis, abscess of the limbs and osteomyelitis of the tibia (n = 3 for each manifestation). Eleven (78.5%) patients required surgical intervention to be performed by a senior orthopaedic surgeon, while no surgical procedure was indicated in three patients with cellulitis of the limbs.

The mean time between onset of joint symptoms and orthopaedic referral was 6.2 (range 4–10) days. The surgical procedure was carried out with a mean delay of 3.2 (range 2–7) days. In cases where the knee joint was affected, a bedside aspiration was initially carried out and the specimen was sent for microbiological examination. After a positive identification of *Burkholderia pseudomallei*, percutaneous joint washout with saline using a wide bore cannula was performed in the four patients with septic arthritis of the knee, while the single patient with septic arthritis of the elbow underwent open drainage. In all cases, a drain was kept *in situ* for 2–3 days until the drainage was minimal and local signs of inflammation had settled.

All the three patients with osteomyelitis were admitted into the medical ward. The mean duration between the onset of symptoms and referral to the Orthopaedics Department was 12.3 (range 5–25) days. Surgery was performed at a mean of 4.6 (range 1–8) days after diagnosis. The delay in one patient was due to the necessity to perform MR imaging. In all the cases, a cortical window was made at the site of the osteomyelitis and the tibia was curetted off the infected material. The wound was closed primarily over a drain that was removed after 48 hours. The mean duration between the onset of symptoms and diagnosis in patients with cellulitis and abscess was 12.5 (range 3–30) days. Once the diagnosis of abscess was made, an incision and drainage was performed within 1–2 days. The wound was left open and allowed to heal by secondary intention.

Blood culture was positive in ten patients, while pus/fluid culture was positive in 11 patients. Both blood and pus cultures were positive in seven patients. Plain radiographic changes of osteomyelitis were noted in two patients, but they were not specific. In one patient, MR imaging of the leg was required to confirm the diagnosis, as plain radiographs did not reveal any changes. None of the patients with septic arthritis showed any radiographic changes. The median hospital stay was 27.5 (range 13–63) days, and two patients required admission to the intensive care unit. One patient with osteomyelitis of the tibia had a recurrence of symptoms and signs, and required further curettage and a course of antibiotics one year after the initial treatment. No mortality was reported in the present study.

DISCUSSION

Manifestations affecting the extremities were seen in 29% of melioidosis patients in the present study. These ranged from cellulitis and abscess formation to septic arthritis and osteomyelitis. In large case series

of melioidosis, the incidence of skin and soft tissue infections is reported to be 13%–24%, while that of bone and joint infections is 4%–12%.^(7–10) Most previous reports of musculoskeletal manifestations are in the form of case reports. These include septic arthritis^(9,11–15) or osteomyelitis, affecting either a single bone or multiple bones.^(16–20) Few larger series of patients are available in the literature.^(9,10,21–25) We also noted a male preponderance and an average age of around 40 years, a finding that is consistent with that reported in epidemiological studies and studies on musculoskeletal manifestations of melioidosis.^(9,10,21–23,25–27)

Associated risk factors are seen in a large number of patients with melioidosis, the most common being diabetes mellitus, which is seen in 37%–60% of patients.⁽²⁾ Other risk factors identified are chronic renal failure, high alcohol consumption, chronic granulomatous disease, splenectomy, aplastic anaemia, AIDS, cystic fibrosis, glucose-6-phosphate dehydrogenase (G6PD) deficiency, systemic lupus erythematosus (SLE), steroid use and renal transplantation.⁽²⁾ Kosuwon et al have shown that the odds of having melioidotic septic arthritis are 5.7 times greater in the presence of concurrent diabetes mellitus, chronic renal failure or SLE.⁽²⁴⁾ 64% of patients in the present study were diabetic. Other risk factors noted were chronic renal failure ($n = 1$) and G6PD deficiency ($n = 1$). One patient each had an associated co-morbid condition of hepatitis B infection, idiopathic membranous nephropathy and cirrhosis of the liver. 78.5% of the patients were admitted with a primary diagnosis of septicaemia, while in the remaining cases, affection of the extremities was the presenting complaint. Pneumonia was the most common clinical presentation, seen in approximately 50% of the patients.⁽²⁾ Pulmonary involvement was observed in only three out of 14 (21.4%) patients in the present series.

Kosuwon et al studied 21 patients with musculoskeletal melioidosis, comprising 14 male and seven female patients with a mean age of 39 years. Septic arthritis was the most common presentation ($n = 10$), followed by soft tissue abscesses ($n = 8$) and osteomyelitis ($n = 3$). The knee was the most common site for septic arthritis ($n = 6$).⁽²¹⁾ In a retrospective analysis of the clinical and imaging features of 26 patients with musculoskeletal melioidosis, Pui and Tan found that septic arthritis was more common than soft tissue abscess and osteomyelitis. The knee was the most commonly affected joint, followed by the ankle, foot, shoulder, spine and pelvis.⁽²²⁾

Subhadrabandhu et al reviewed ten patients with localised melioidotic osteomyelitis. The average age at presentation was 46.8 years, and 70% of patients

had underlying or associated comorbid conditions. There were four cases each involving the vertebrae and proximal humerus, and one each of proximal femur and tibia. All patients were treated surgically by curettage and debridement.⁽²³⁾

In a previous study from Brunei Darussalam, 24 patients with melioidosis were analysed. About 80% of these had an underlying predisposing illness such as diabetes mellitus. The mean age of the patients was 49.8 years, and the male to female ratio was 3.8:1. Musculoskeletal involvement was noted in 41.6% of patients, which was second only to pulmonary involvement seen in 50% of patients.⁽²⁷⁾ Soft tissue abscesses, osteomyelitis and/or septic arthritis were noted in 4% of patients each, in one large epidemiologic study from northern Australia consisting of 252 patients. There were more male than female patients, and the average age of the patients was 47 years, with 80% of patients having one or more associated risk factors.⁽¹⁰⁾

In a study reported by Kosuwon et al, 11 of the 25 patients with melioidotic septic arthritis showed involvement of the upper limb joints, the shoulder being the most commonly involved.⁽²⁴⁾ This is in contrast to the findings in our study and the studies reviewed by Raja, where the knee joint was the most commonly involved joint.⁽¹⁵⁾ Ahmad et al presented a review of 33 patients with melioidosis, 11 of whom showed musculoskeletal involvement. Abscesses were noted in 64% of patients, septic arthritis in 23% and cellulitis in the rest. Nine patients had diabetes mellitus. Surgery was required in 81% of patients, and two patients died due to sepsis.⁽²⁵⁾

In the present study, we have noted that although the patients presented to the hospital within seven days of the onset of symptoms, there was a considerable delay in diagnosis, particularly in patients with osteomyelitis, cellulitis and abscess. This was due to the fact that all except one patient were admitted under the care of physicians, and there was a delay in their referral due to some other problems. Once the diagnosis was made, surgical procedure was carried out within a reasonable amount of time. We found that septic arthritis of the knee can be managed successfully by percutaneous drainage and washout, while septic arthritis of the elbow, soft tissue abscesses and osteomyelitis of the tibia are best treated by formal open drainage under standard surgical principles. Radiological changes in musculoskeletal melioidosis on plain radiographs or MR images are not specific and can mimic other infectious conditions.^(22,28) Our observations about the radiological features are similar to those reported in the above studies.

A number of techniques have been used to

diagnose melioidosis, but the isolation of *Burkholderia pseudomallei* from patients' blood or other body fluids remains the gold standard in the diagnosis of melioidosis.^(2,4) In the present study, positive blood or pus/fluid culture identified using the API 20NE kit was the mainstay of diagnosis. Serological tests were not performed in our hospital. In the present series, although there was a delay in the management of orthopaedic complications, the lack of mortality is likely due to the early diagnosis of melioidosis and the initiation of appropriate antibiotic treatment. One of the limitations of our study was its retrospective design. Also, we could not ascertain the history of soil exposure as well as assess the clinical outcome in individual cases.

Melioidosis is not uncommon in Brunei Darussalam. Melioidosis of the extremities accounts for 29% of the total cases of melioidosis, and a large number of these cases require surgical intervention. In our study, diabetes mellitus was the most common risk factor and septic arthritis of the knee, the most common musculoskeletal affection. Melioidosis should be suspected when one of the manifestations described in this study is observed in a systemically ill patient, with diabetes mellitus being the most common risk factor, particularly in an endemic area. A high index of suspicion is thus required for early referral and diagnosis of various manifestations noted in the extremities.

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