Melioidosis of the Musculoskeletal System

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Significance of the Study

- We aimed to describe the clinical presentation of *Burkholderia pseudomallei* infection of the musculoskeletal system as it is under-reported in the literature.
- Out of 342 (9.2%) patients with *B. pseudomallei* infection, 37 had musculoskeletal involvement in our series of melioidosis.
- We present the varied surgical treatment modalities used in addition to medical management that resulted in resolution of disease in all our patients.

Keywords
*Burkholderia pseudomallei* · Melioidosis · Musculoskeletal system

Abstract

**Objective:** Recent studies indicate that India is an endemic region for *Burkholderia pseudomallei* infection. We aimed to describe the clinical presentation of *B. pseudomallei* infection of the musculoskeletal system and summarise the various treatment modalities used in our clinical practice. **Subjects and Methods:** Patients with confirmed microbiological diagnosis of *B. pseudomallei* infection involving the musculoskeletal system treated from January 2007 to December 2016 with a minimum follow-up of 1 year were included. A retrospective review of medical records was carried out and patients’ demographic data, co-morbidities, clinical presentation, and details of medical and surgical treatment were documented. **Results:** Of 342 patients diagnosed with *B. pseudomallei* infection, 37 (9.2%) had musculoskeletal involvement; 26 patients (23 males) followed up for at least a year were included in the study. Four patients (15%) had multisystem involvement and 10 (37%) had multiple musculoskeletal foci of infection; 15 patients (58%) had osteomyelitis, 10 (38%) had septic arthritis with or without osteomyelitis, and 1 patient (4%) presented with only soft tissue abscess. All patients required surgical intervention in addition to medical management. Surgical treatment varied from soft tissue abscess drainage, arthrotomy for septic arthritis, decompression and curettage for osteomyelitis, and/or use of antibiotic (meropenem or ceftazidime)-loaded polymethylmethacrylate bone cement for local drug delivery. At final follow-up (average: 37 months, range: 12–120), all patients were disease free. **Conclusion:** We found the rate of musculoskeletal involvement in *B. pseudomallei* infection to be 9.2%. Appropriate surgical treatment in addition to medical management resulted in resolution of disease in all our patients.

Introduction

Melioidosis is caused by the Gram-negative bacterium *Burkholderia pseudomallei* [1]. It was first described by Whitmore and Krishnaswami [1] and is mainly present in southeast Asia and northern Australia [1, 2]. It was first reported in India in 1990, and India has been recently
recognition as an endemic zone [2, 3]. This infection is transmitted through direct contact, cutaneous inoculation, inhalation, or ingestion, and patients clinically exhibit abscesses in single or multiple organs [4, 5]. This infection is clinically under-reported due to a low index of suspicion, lack of diagnostic facilities, and misdiagnosis as tuberculosis [6]. An increase in reports from India has been noted since the beginning of this millennium because of increased awareness and improved diagnostic modalities [7]. Herein, we describe the clinical presentation of *B. pseudomallei* infection of the musculoskeletal system and summarise the varied surgical treatment modalities used in addition to medical management in our practice.

**Patients and Methods**

The inclusion criteria for our study were patients diagnosed with *B. pseudomallei* infection involving the musculoskeletal system treated at our institution between 2007 and 2016 and followed up for a minimum of 1 year. Patients with multisystem involvement were included in the study if the musculoskeletal system was also involved. Patients with less than a 1-year follow-up were excluded from the study. Patient information was collected from electronic outpatient records, inpatient records, discharge summaries, and medical reports. Patient demographic data, comorbidities, clinical manifestations, and medical and surgical treatment details were documented.

The diagnosis was microbiologically confirmed in all patients. *B. pseudomallei* is a non-fermenting Gram-negative bacillus showing bipolar staining on Gram stain. It produces non-haemolytic greyish-white colonies on blood agar plates and non-lactose fermenting colonies on MacConkey agar. The organism is motile, oxidase positive, resistant to gentamicin and colistin, indole negative, and citrate negative. Alkaline slant/alkaline butt with no gas production is seen on triple sugar iron agar [8]. Colonies on culture plates with the above-mentioned characteristics were tested in our laboratory using *B. pseudomallei*-specific antisera raised in rabbits and agglutination of the suspected colonies with antisera aids in presumptive identification of the organism. Biochemical confirmation of the same was performed using the nitrate reduction test, gelatine liquefaction, and arginine dihydrolase activity which showed positive results, and the arabinose assimilation test which showed a negative result [8]. Antimicrobial susceptibility testing was performed as per guidelines of the Clinical Laboratory Standards Institute (CLSI) [9].

Descriptive statistics were used to analyse the results. Categorical variables were presented as raw values and percentages of study sample whereas continuous variables were presented as averages and ranges.

**Results**

A review of medical records revealed that 342 patients were diagnosed with *B. pseudomallei* infection between January 2007 and December 2016. Of these 342 patients, 37 (9.2%) had musculoskeletal infection. One patient with septic arthritis of the knee and multisystemic involvement (parotid abscess and pulmonary infection) died in the hospital due to septicemic shock. A total of 26 patients (70%), 23 males and 3 females, followed up for at least 1 year were included in this study. The average age of the patients was 47 years (range: 21–69). The duration of symptoms was less than 6 weeks in 10 patients (38%) and more than 6 weeks in 16 (62%).

At least one comorbidity was present in 20 patients (77%) and multiple comorbidities in 6 patients (23%) (Fig. 1). Diabetes was the most common comorbidity (20 patients, 77%). HbA1c levels were documented for 20 patients (77%), of whom 14 (70%) had HbA1c levels of more than 6.5 [10].

Blood cultures were performed for 13 patients (50%) and were positive for *B. pseudomallei* infection in 6 patients (23%). Three patients (11.5%) had evidence of *B. pseudomallei* infection in other systems (pulmonary infection, hepatic abscess, and splenic abscess).

The most common musculoskeletal site of infection was the femur (12 patients, 46%) (Table 1). Multiple musculoskeletal foci of infection was seen in 8 patients (30%). Osteomyelitis was seen in 15 patients (58%), septic arthritis with or without osteomyelitis in 10 patients (38%), and soft tissue abscess in 1 patient (4%).

The average follow-up duration was 41 months (range: 12–120). All patients received a course of injectable ceftazidime, followed by a course of oral doxycycline and/or co-trimoxazole. The exact duration of injectable and oral therapy was based on the clinical resolution of symptoms and was decided by the treating physicians.
Table 1. Clinical details of patients with musculoskeletal *Burkholderia pseudomallei* infection (melioidosis) included in the study

| Patient No. | Age, years | Sex | Multisystemic involvement | MSK foci | Duration, days | Blood culture | Surgical treatment | Antibiotic treatment | Antibiotic duration | Follow-up, months |
|-------------|------------|-----|---------------------------|----------|---------------|---------------|-------------------|---------------------|------------------|------------------|
| 1           | 60         | M   | –                         | Femur    | 30            | –             | 1. Decompression and curettage 2. Antibiotic PMMA beads | 3 1. Ceftazidime 2. Co-trimoxazole 3. Doxycycline | 11 days          | 10 weeks         | 48               |
| 2           | 52         | M   | –                         | Tibia    | 45            | –             | 1. Decompression and curettage 2. Antibiotic PMMA beads | 2 1. Ceftazidime 2. Co-trimoxazole | 8 days           | 18 weeks         | 20               |
| 3           | 37         | M   | –                         | Femur, Tibia | 90         | –             | 1. Soft tissue abscess drainage, arthrotomy, and drainage 2. Decompression and curettage | 1 1. Ceftazidime 2. Doxycycline | 6 weeks          | 30 weeks         | 12               |
| 4           | 58         | M   | –                         | Femur    | 30            | –             | Decompression and curettage | 1 1. Ceftazidime 2. Doxycycline | 10 days          | 26 weeks         | 60               |
| 5           | 29         | F   | –                         | Thigh, Knee | 45         | –             | Soft tissue abscess drainage, arthrotomy, and drainage | 1 1. Ceftazidime 2. Co-trimoxazole 3. Doxycycline | Details not available | 84               |
| 6           | 69         | M   | –                         | Knee, Leg | 15           | –             | Soft tissue abscess drainage, arthrotomy, and drainage | 1 1. Ceftazidime 2. Doxycycline | 19 days          | 37 weeks         | 36               |
| 7           | 62         | M   | –                         | Ankle    | 30            | –             | Arthrotomy, drainage, and soft tissue abscess drainage | 1 1. Ceftazidime 2. Co-trimoxazole 3. Doxycycline | 7 days           | 14 weeks 27 weeks | 26               |
| 8           | 38         | M   | –                         | Femur    | 16            | Positive      | Decompression and curettage | 1 1. Ceftazidime 2. Co-trimoxazole 3. Doxycycline | 6 weeks          | 25 weeks         | 26               |
| 9           | 40         | M   | –                         | Tibia    | 2,555         | –             | Decompression and curettage | 1 1. Ceftazidime 2. Co-trimoxazole | Details not available | 26               |
| 10          | 62         | F   | –                         | Knee     | 14            | Negative      | Arthrotomy and drainage | 2 1. Ceftazidime | 13 days          | 16               |
| 11          | 47         | M   | –                         | Humerus  | 45            | Negative      | Decompression and curettage | 1 1. Ceftazidime 2. Doxycycline 3. Co-trimoxazole | 15 days          | 24 weeks 40 weeks | 12               |
| 12          | 45         | M   | –                         | Knee, Leg | 60           | Negative      | Arthrotomy and drainage | 1 1. Ceftazidime 2. Co-trimoxazole | 25 days          | 30 weeks         | 12               |
| 13          | 38         | M   | –                         | Femur    | 21            | –             | 1. Soft tissue abscess drainage, arthrotomy, and drainage 2. Decompression and curettage 3. Antibiotic beads | 3 1. Ceftazidime 2. Co-trimoxazole 3. Doxycycline | 6 weeks          | 22 weeks 10 days | 24               |
| 14          | 40         | M   | –                         | Shoulder | 30            | –             | Arthrotomy and drainage | 1 1. Ceftazidime 2. Doxycycline | 4 weeks          | 12 weeks         | 30               |
| 15          | 33         | M   | –                         | Femur, Hip | 60           | Positive      | 1. Soft tissue abscess drainage, arthrotomy, and drainage 2. Decompression and curettage | 2 1. Meropenem 2. Ceftazidime 3. Doxycycline | 10 days          | 22 weeks 23 weeks | 24               |
| 16          | 36         | M   | –                         | Femur, Tibia, Ankle | 30         | Negative      | 1. Soft tissue abscess drainage 2. Arthrotomy and drainage 3. Decompression and curettage 4. Antibiotic beads | 3 1. Ceftazidime 2. Doxycycline 3. Co-trimoxazole | 6 weeks          | 3 weeks 21 weeks | 30               |
| 17          | 57         | M   | –                         | Tibia    | 150           | –             | 1. Decompression and curettage 2. Antibiotic beads | 1 1. Ceftazidime 2. Co-trimoxazole | 6 weeks          | 27 weeks         | 12               |
| 18          | 53         | F   | –                         | Femur    | 60            | –             | Soft tissue abscess drainage, arthrotomy, and drainage | 1 1. Ceftazidime 2. Co-trimoxazole | 4 weeks          | 140 weeks        | 12               |
| 19          | 42         | M   | –                         | Tibia    | 45            | Positive      | Decompression and curettage | 2 1. Ceftazidime 2. Co-trimoxazole 3. Doxycycline | 7 weeks          | 13 weeks 3 days | 12               |
| 20          | 42         | M   | –                         | Femur    | 120           | Positive      | Antibiotic beads | 2 1. Ceftazidime 2. Doxycycline 3. Co-trimoxazole | 8 weeks          | 33 weeks 48 weeks | 39               |
In addition to medical management with antibiotics, all patients required surgical intervention. Deep intraoperative cultures were performed for all patients, and these cultures confirmed *B. pseudomallei* infection. Histopathological evaluation of the operative surgical specimen was performed for 15 patients (58%). In 12 patients (46%), the microscopic lesion was acute inflammatory suppuration, consistent with pyogenic infection. A granulomatous microscopic lesion resembling the lesion in tuberculosis was noted in 3 patients (20%). A range of orthopaedic surgical procedures were performed to treat the infection (Table 1).

![Fig. 2. Preoperative anteroposterior (a) and lateral (b) radiographs and STIR sagittal MRI (c) of the right femur of a 38-year-old man (patient 13, Table 1) with right proximal thigh pain and swelling for 3 weeks associated with low-grade intermittent fever. He was diagnosed with acute chronic osteomyelitis, which was microbiologically confirmed as *Burkholderia pseudomallei* infection. A year prior to presentation, he was diagnosed and treated elsewhere for *Pseudomonas osteomyelitis.*](image)

### Table 1 (continued)

| Patient No. | Age, years | Sex | Multisystemic involvement | MSK foci | Duration, days | Blood culture | Surgical treatment | Surgeries, n | Antibiotic treatment | Antibiotic duration | Follow-up, months |
|-------------|------------|-----|---------------------------|----------|---------------|---------------|-------------------|--------------|---------------------|------------------|-----------------|
| 21          | 50         | M   | –                         | Femur    | 45            | Negative      | Decompression and curettage | 1            | 1. Ceftazidime 2. Doxycycline 3. Co-trimoxazole | 6 weeks 20 weeks 20 weeks | 84 |
| 22          | 54         | M   | –                         | Femur    | 19            | Negative      | Decompression and curettage | 2            | 1. Ceftazidime 2. Doxycycline 3. Co-trimoxazole | 7 weeks 44 weeks 87 weeks | 60 |
| 23          | 53         | M   | Liver Spleen              | Tibia    | 15            | Negative      | Decompression and curettage | 1            | 1. Ceftazidime 2. Co-trimoxazole 3. Doxycycline | 3 weeks 5 months 5 months | 84 |
| 24          | 25         | M   | Lungs Hepatosplenomegaly | Knee Ankle | 60     | Positive      | Arthrotomy and drainage | 1            | 1. Ceftazidime 2. Doxycycline 3. Co-trimoxazole | 6 weeks 20 weeks 39 weeks | 48 |
| 25          | 45         | M   | –                         | Knee     | 14            | –             | Arthrotomy and drainage | 1            | 1. Ceftazidime 2. Co-trimoxazole | 6 weeks 12 weeks | 120 |
| 26          | 45         | M   | Spleen Lungs              | Femur Spleen | 180    | Negative      | Decompression and curettage | 3             | 1. Ceftazidime 2. Doxycycline 3. Co-trimoxazole | 12 weeks 27 weeks 24 weeks | 20 |

MSK, musculoskeletal; PMMA, polymethylmethacrylate.

In addition to medical management with antibiotics, all patients required surgical intervention. Deep intraoperative cultures were performed for all patients, and these cultures confirmed *B. pseudomallei* infection. Histopathological evaluation of the operative surgical specimen was performed for 15 patients (58%). In 12 patients (46%), the microscopic lesion was acute inflammatory suppuration, consistent with pyogenic infection. A granulomatous microscopic lesion resembling the lesion in tuberculosis was noted in 3 patients (20%). A range of orthopaedic surgical procedures were performed to treat the infection (Table 1). Soft tissue abscesses were incised and drained. Septic arthritis was surgically managed by arthrotomy and drainage. Patients with osteomyelitis underwent debridement and curettage of the bone. In addition, 6 patients (23%) were also treated with meropenem- or ceftazidime-loaded bone cement for local drug delivery (Fig. 2, 3). Multiple surgical procedures (a maximum of three procedures) were performed in 11 patients (42%) (Fig. 4, 5). Pathological fractures that required additional operative intervention were seen in 3 patients (11%). At the final follow-up, all study patients were found to be free of the disease.
Though musculoskeletal melioidosis is a well-recognised entity, it is rare even in endemic areas [7]. In our study of 26 patients with musculoskeletal melioidosis, 30 and 11.5% of patients had multifocal musculoskeletal and multisystemic involvement, respectively. Punyagupta et al. [11] classified melioidosis based on clinical assessment. According to their classification, 19, 2, and 5 of our patients had localised, disseminated, and septicaemic melioidosis, respectively.

Discussion

The majority of our patients (60%) presented with symptoms for more than 6 weeks. Nonspecific clinical, radiological, and histopathological features were considered to be reasons for the delay in diagnosis. The biopsy reports of 5 patients were inconclusive and were suggestive of tuberculosis; however, their wound culture was positive for B. pseudomallei. With tuberculosis being common in India, some patients undergo empirical treatment for tuberculosis because of lack of definitive diagnosis [12]. Three of our patients had received prior empirical anti-tubercular therapy emphasising...
the need to consider *B. pseudomallei* as a differential diagnosis in a setting that mimics skeletal tuberculosis [12].

More than three quarters of our patients had medical comorbidities, with diabetes being the most common. Shetty et al. [13] in their review of 50 patients with musculoskeletal melioidosis also reported that 80% of their patients had one or more comorbidities with diabetes being the most common. Kosuwon et al. [14] in their retrospective review on 25 patients with melioidotic septic arthritis also highlighted the increased association of melioidosis with diabetes. Diabetes impairs neutrophil functions, such as mobilisation, delivery, adherence, and ingestion, and is known to be associated with melioidosis [15, 16]. Microscopically, the histopathological lesion in melioidosis has been reported to form a spectrum from suppurative inflammation in acute illness to caseous granulomatous inflammation, similar to chronic tuberculosis [6, 17]. Although most of our patients presented with symptoms of duration greater than 6 weeks, granuloma formation was noted in only 3 patients. The histopathological findings of the remaining patients were suggestive of inflammatory suppuration, with no evidence of granuloma formation. Therefore, a granulomatous histological appearance cannot be relied upon to confirm the diagnosis, even in chronic cases of melioidosis.

Musculoskeletal melioidosis may present as septic arthritis, osteomyelitis, or soft tissue abscess [13, 18]. The varied clinical presentation necessitated a range of orthopaedic procedures (Table 1). All 26 patients required surgical treatment along with a full course of antibiotics. The use of local antibiotic delivery with antibiotic-loaded bone cement beads or calcium hydroxyapatite for the treatment of musculoskeletal infections has been well described [19]. We used meropenem- or ceftazidime-loaded polymethylmethacrylate bone cement as a local drug delivery agent to successfully treat musculoskeletal melioidosis in 6 of our patients. Prolonged treatment and the need for multiple surgical interventions observed in our series highlight the clinical burden of treating this infection. Morse et al. [18] reviewed 20 patients with musculoskeletal melioidosis and noted that while appropriate intravenous antibiotics are important, adequate surgical drainage and debridement are vital. Subhadrabandhu et al. [20] and more recently Pandey et al. [21] have published their series of 10 and 5 patients, respectively, highlighting their treatment strategy of surgical debridement in addition to antibiotics to successfully treat all their patients. Shetty et al. [13] noted that most patients with musculoskeletal melioidosis needed operative intervention and those with multifocal bone and joint involvement needed significantly longer hospital stay and more operations.

Our study, being retrospective in nature, has limitations inherent to an observational clinical series, such as misclassification bias and medical record abstraction errors [22]. However, melioidosis is a rare disease, and the importance of retrospective observational studies conducted using pre-existing data for studying rare medical disorders is well established [22].

**Conclusion**

The rate of musculoskeletal involvement in *B. pseudomallei* infection was 9.2%. Varied clinical presentation and multifocal involvement necessitated a range of surgical procedures which, in combination with antibiotic therapy, was successful in the resolution of the infection.
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Disclosure Statement

The authors have no conflict of interest to declare.

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Author Contributions

Rajamani Perumal: data collection, manuscript writing, and patient care. Abel Livingston: data collection and manuscript writing. Sumant Samuel: manuscript writing, editing, and patient care. Santhosh Kumar Govindaraju: data collection and patient care.

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