RHEUMATOLOGICAL MANIFESTATIONS IN PATIENTS WITH MELIOIDOSIS

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Abstract. Melioidosis, an infection caused by the bacterium *Burkholderia pseudomallei*, has a wide range of clinical manifestations. Here, we describe rheumatological melioidosis (involving one or more of joint, bone or muscle), and compare features and outcome with patients without rheumatological involvement. A retrospective study of patients with culture-confirmed melioidosis admitted to Sappasithiprasong Hospital, Ubon Ratchathani during 2002 and 2005 identified 679 patients with melioidosis, of whom 98 (14.4%) had rheumatological melioidosis involving joint (*n*=52), bone (*n* = 5), or muscle (*n* = 12), or a combination of these (*n*=29). Females were over-represented in the rheumatological group, and diabetes and thalassemia were independent risk factors for rheumatological involvement (OR; 2.49 and 9.56, respectively). Patients with rheumatological involvement had a more chronic course, as reflected by a longer fever clearance time (13 *vs* 7 days, p = 0.06) and hospitalization (22 *vs* 14 days, p < 0.001), but lower mortality (28% *vs* 44%, p = 0.005). Patients with signs and symptoms of septic arthritis for longer than 2 weeks were more likely to have extensive infection of adjacent bone and muscle, particularly in diabetic patients. Surgical intervention was associated with a survival benefit, bur not a shortening of the course of infection.

INTRODUCTION

Melioidosis, a serious disease caused by the gram-negative saprophyte *Burkholderia pseudomallei*, is endemic across much of Southeast Asia and in northern Australia. *B. pseudomallei* accounts for up to 20% of community-acquired bacteremia in Northeast Thailand (Chaowagul *et al*, 1989), and is the most common cause of fatal community-acquired bacteremic pneumonia at the Royal Darwin Hospital, Australia (Douglas *et al*, 2004). The associated mortality rate is around 50% in Ubon Ratchathani, Northeast Thailand (White, 2003), and 20% in Australia (Currie *et al*, 2004). The clinical manifestations of melioidosis are extremely variable, can affect any organ, and may be disseminated or localized. The most common organ involved is the lung,

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while rheumatological involvement occurs in 5-27% of patients (Punyagupta, 1989; Simpson *et al*, 1999; Chetchotisakd *et al*, 2001). Several reports describe unusual rheumatological manifestations such as infection of the sternomanubrial joint (Borgmeier and Kalovidouris, 1980) and vertebral spondylitis that may mimic tuberculosis (Wilairatana and Wilairatana, 1994), some of which have affected people who were younger than the median age for melioidosis (Popoff *et al*, 1997). Melioidosis has been extensively studied in Thailand over the past twenty years, but there is limited description in the literature of infection involving bone, joints and soft tissues. The aims of this study were to determine the prevalence of rheumatological involvement in melioidosis patients presenting to a single center in Northeast Thailand, describe the characteristics of rheumatological involvement, and to compare non-rheumatological with rheumatological melioidosis in terms of demographic and clinical profiles, laboratory results, treatment and outcomes.

PATIENTS AND METHODS

A retrospective review was undertaken of patients with culture proven melioidosis presenting to Sappasithiprasong Hospital, a 1,000-bed, regional referral center in Ubon Ratchathani, Northeast Thailand, between February 2002 and May 2005. Melioidosis was defined on the basis of *B. pseudomallei* isolation from at least one clinical specimen (blood, sputum, throat swab, synovial fluid, pleural effusion, urine or pus). *B. pseudomallei* was identified as described previously (Walsh and Wuthiekanun, 1996). Patients were defined as having rheumatological involvement if they had clinical features consistent with septic arthritis, pyomyositis or osteomyelitis, supported by radiographic and microbiological evidence.

Statistical analysis

Statistical tests were performed using the statistical program STATA/SE, version 9.0 (College Station, Texas, United States). Comparisons of continuous data were performed using Student's *t* test or the Mann Whitney *U* test and proportions were compared using χ^2 test or Fisher's exact test, as appropriate. Length of hospitalization and fever clearance time were examined using Kaplan-Meier survival analysis. Multiple logistic regression analysis was performed to determine independent contributing factors for rheumatological infection.

RESULTS

A total of 679 patients were admitted with culture-confirmed melioidosis during the study period. The median [interquartile range (IQR) age was 49 (38-59)] years, and 410 (60%) were male. Ninety-eight (14.4%) patients had rheumatological melioidosis involving joint (*n* = 52), bone (*n* = 5), or muscle (*n* = 12), or a combination of joint and bone (*n* = 17), joint and muscle (*n* = 9), or joint and bone and muscle (*n* = 3).

A comparison of clinical manifestations and admission laboratory test results in patients with and without rheumatological melioidosis is shown in Table 1. Females were over-represented in the group with rheumatological involvement (49% *vs* 38%, p = 0.004), while median (IQR) age was not different [49 (37-60) *vs* 50 (41-57), p = 0.95] in the two groups. Overall, 553 (77%) patients had one or more underlying diseases that are risk factors for melioidosis (diabetes mellitus, renal insufficiency, liver disease, thalassemia, malignancy or steroid therapy). Patients with rheumatological melioidosis were more likely to have one of these underlying diseases than patients without rheumatological involvement [89/98 (91%) *vs* 434/581 (75%), p <0.001]. This was particularly marked for diabetes mellitus and thalassemia, which were independent risk factors for rheumatological melioidosis [OR,

Table 1
Demographic data, organ involvement and laboratory data for patients with or without rheumatological melioidosis.

Characteristic	Median (IQR)		p-value
	Rheumatologic (*n*=98)	Non-rheumatologic (*n*=581)	
Age	49 (37-60)	50 (41-57)	0.95
One or more risk factors[a], No. (%)	89 (91)	434 (75)	<0.001
Days of symptoms before presentation	14 (7-28)	7 (4-19)	0.002
Pulmonary involvement, No. (%)	20 (20)	222 (38)	<0.001
Skin and/or soft tissue involvement, No. (%)	37 (38)	81 (14)	<0.001
Liver abscess, No. (%)	9 (10)	59 (10)	ns
Splenic abscess, No. (%)	11 (12)	61 (11)	ns
Bacteremia, No. (%)	57 (58)	323 (56)	ns
Hemoglobin (g/dl)	9.8 (8.5-10.9)	10.1 (8.4-11.7)	ns
WBC (cell x10^9/l)	14.4 (10.6-20.1)	11.8 (0.79-14.9)	0.05
Platelets (cell x10^9/l)	293 (152-347)	200 (112-296)	0.003
Serum bicarbonate (mmol/l)	19 (13-24)	18 (12-23)	0.007
Creatinine (mg/dl)	2.2 (1.1-3.6)	1.7 (1.1-4.0)	0.04
Alanine aminotransferase (U/l)	58 (31-80)	60 (39-99)	ns
Albumin (g/l)	22 (18-27)	24 (19-28)	ns

[a]risk factors for melioidosis: diabetes mellitus, renal insufficiency, liver disease, thalassemia, malignancy or steroid therapy

Table 2
Severity, treatment and outcomes comparing patients with or without rheumatological melioidosis.

Characteristic	Number of cases (%)		p-value
	Rheumatologic (*n*=98)	Non-rheumatologic (*n*=581)	
Hypotension	24 (24)	216 (37)	0.02
Respiratory failure	20 (20)	189 (33)	0.02
Ceftazidime treatment	72 (81%)	360 (82%)	ns
Imipenem treatment	0	10 (2%)	ns
In-hospital mortality	27 (28)	258 (44)	0.002
In-hospital survivors	*n*=71	*n*=323	
Median (IQR) fever clearance time among survivors (days)	15 (10-21)	9 (5-14)	0.007[a]
Median (IQR) hospital stay among survivors (days)	20 (13-26)	12 (7-18)	<0.001[a]
Recurrent melioidosis	13 (18)	17 (5)	<0.001

[a]Kaplan-Meier survival analysis with log-rank test

95% confidence interval (CI) 2.49, 1.4-4.4, p = 0.002, and 9.56, 2.5-37.1, p = 0.001, respectively]. No patients had a recorded history of pre-existing rheumatoid arthritis, and the proportions of patients with pre-existing gout or systemic lupus erythematosus were not different between the two groups [2/98 (2%) *vs* 2/581 (0.3%), p = 0.10, and 1/98 (1%)

vs 6/581 (1%), p = 1.00, respectively]. A documented history of trauma was not associated with rheumatological melioidosis (OR, 95%CI 2.7, 0.69-9.85, p = 0.10).

Patients with rheumatological melioidosis had a longer duration of symptoms prior to hospital presentation compared with the non-rheumatological group [median (IQR) days 14 (7-28) *vs* 7 (4-19) respectively, p = 0.002]. Skin and/or soft tissue involvement were associated with rheumatological melioidosis (p <0.001), while pneumonia was more common in patients without rheumatological involvement (p <0.001). There were no significant differences in the presence of bacteremia or liver and/or splenic abscesses in the two groups (p > 0.05).

Features of severe melioidosis were more common in patients who did not have rheumatological involvement (Table 2). This included hypotension (defined as blood pressure less than 90/60 mmHg) (p = 0.02) and respiratory failure (defined as the need for mechanical ventilation) (p = 0.02). The mortality rate was significantly lower in patients with rheumatological melioidosis compared with the non-rheumatological group (28% *vs* 44%, p = 0.002). Among patients who survived to discharge, patients with rheumatological involvement had a longer hospital stay (p = 0.06), and had a longer median fever clearance time (p <0.001) (Table 2). Despite this, the median (IQR) duration of parenteral treatment and oral treatment were not significantly different between the two groups [13 (9-18) and 127 (50-145) days in rheumatological group *vs* 12 (8-15) and 135 (100-145) days in non-rheumatological group, p = 0.19 and 0.10, respectively].

The proportion of patients who developed recurrence during follow-up to May 2006 was higher in patients with rheumatological melioidosis (p <0.001). Duration of parenteral treatment was not associated with the recurrence while patients who received less than 12-weeks of oral eradication treatment had a significanlty higher rate of recurrent infection [OR, (95%CI) 6.63, 2.90-15.32, p < 0.001].

Rheumatological manifestations

Mono-arthritis occurred in 61 (75%) patients with septic arthritis. Of the remainder, 14 patients (17%), 5 patients (6%) and 1 patient had two, three and four joints involved, respectively. Arthralgia and/or joint swelling were recorded in only 41/81 (51%) patients with septic arthritis. Patients with these symptoms for more than two weeks had a higher chance of adjacent bone infection compared with patients with less than 2 weeks symptoms [8/12 (67%) *vs* 7/29 (24%), p = 0.02].

Sites of musculoskeletal involvement are shown in Table 3. The lower extremities were more often affected than the upper extremities. Knee, ankle and hip joints were the three most frequently affected joints, while the shoulder was the most frequently affected site in the upper extremities.

Diabetes mellitus was an independent risk factor for having multiple-site rheumatological involvement (OR; 8.64, 95%CI; 1.51-49.6, p = 0.015). Eighteen patients with diabetes mellitus had severe extensive infections involved joint, adjacent bones, muscle and soft tissues. These patients presented with a significantly longer median (IQR) duration of symptoms than diabetic patients without extensive infection [21 (14-30) *vs* 14 (7-15) days, p = 0.007].

Surgical interventions including needle aspiration, arthrotomy or incision and drainage were performed in 64 (65%) patients, and 17 (19%) patients underwent interventions more than once. Patients who had at least one intervention had a significant lower mortality than patients who had no intervention [9/64 (14%) *vs* 16/34 (47%), p < 0.001]. Among patients who survived, the length of hospital stay, duration of parenteral treatment and fever clearance time were not significantly different between patients who had an intervention versus those

Table 3
Sites of musculoskeletal involvement.

Sites	Number of cases (%)		
	Joint (*N*=81)	Bone (*N*=25)	Muscle (*N*=24)
Lower extremity	65 (76)	19 (76)	17 (71)
	Knee 41 (41)	Femur12 (48)	Leg 9 (38)
	Ankle 20 (20)	Tibia 9 (36)	Thigh 7 (29)
	Hip 15 (15)	Foot 2 (8)	Calf 2 (8)
	Foot 3 (3)		Buttock 1 (4)
Upper extremity	18 (21)	4 (16)	4 (17)
	Shoulder 10 (10)	Humerus 2 (8)	Elbow 3 (13)
	Elbow 4 (4)	Radius 1 (4)	Forearm 2 (8)
	Wrist 4 (4)	Hand 2 (8)	
	Hand 1 (1)		
Others	3 (3)	3 (12)	3 (13)
	Sacroiliac 2 (2)	T 10 spine 1 (4)	Psoas muscle 3 (13)
	Sternoclavicular 1 (1)	L 4-5 spines 1 (4)	
		Skull 1 (4)	

who did not (p >0.05). Rheumatological complications included limited range of motion, sinus tract formation and deformities which were recorded in 35.6%, 8.9% and 4.4%, respectively.

DISCUSSION

Rheumatological involvement occurs in one sixth of adult patients with melioidosis in Ubon Ratchathani, Northeast Thailand. This is higher than the frequency reported in Australia (Currie *et al*, 2000), but lower than that previously reported from Khon Kaen, Northeast Thailand (27%), another major center for the treatment of patients with melioidosis (Chetchotisakd *et al*, 2001). Melioidosis affects males more than females overall, but females are over-represented in the patient group with rheumatological involvement.

Underlying conditions such as diabetes mellitus, renal failure and thalassemia are established risk factors for melioidosis (Suputtamongkol *et al*, 1994). A previous study comparing patients with septic arthritis caused by *B. pseudomallei* versus other pathogens reported that patients with any concomitant disease were 12 times more likely to be infected with *B. pseudomallei* (Kosuwon *et al*, 1993). The same author reported that diabetes mellitus was an independent risk factor for septic arthritis caused by *B. pseudomallei* (Kosuwon *et al*, 2003). Our findings further emphasize that among patients with melioidosis, those with underlying illnesses such as diabetes mellitus and thalassemia were more likely to have rheumatological involvement. This may be due to the presence of an arthropathy that may accompany both diseases. These findings could not be confirmed in other pre-existing arthropathies including gout, rheumatoid arthritis and SLE may due to the limited number of those cases in our reviews. Delay in appropriate treatment for more than 2 weeks in diabetic patients with melioidosis associated with septic arthritis may lead to extensive infection affecting adjacent bone, muscle and soft tissue.

Septic arthritis involving the upper extremity joints has been reported to be 4.5 times more likely to be due to *B. pseudomallei* than other causes in this geographical setting (Kosuwon *et al*, 2003). In this study, involvement of lower extremities was more frequent than upper extremities. Large joints, especially the weight-bearing joints such as knee, ankle and hip joints, were more commonly affected than small joints. Infections of unusual sites such as sternoclavicular joint, sacroiliac joint, skull and spine were found to occur but were uncommon.

Patients with rheumatological melioidosis had several features consistent with a more chronic course compared with patients with non-rheumatological melioidosis. Patients were less likely to have shock and respiratory failure and had a lower mortality, but had a longer fever clearance time and hospitalization together with a higher rate of recurrent melioidosis.

Surgical intervention is known to be an important part of the management of rheumatological infection, since removal of pus and infected material can reduce time to resolution and reduces long-term morbidity from joint damage. Intervention was associated with a lower mortality in this study, although this did not appear to be associated with reduced fever clearance time, length of hospital stay or duration of parenteral treatment. Although a reduction in mortality may be due to a direct result of the intervention, this is potentially confounded by the fact that people who are severely ill may have died before an intevention could be carried out or may be considered high risk and not fit for an anesthetic and surgical procedure.

In conclusion, patients with melioidosis who are diabetic or have thalassemia have a higher risk for rheumatological involvement. Patients with melioidosis who present with features of arthritis for more than 2 weeks are at increased risk of complicated disease, and a delay in treatment may lead to extensive disease involving joint, adjacent bone, muscle and soft tissues.

ACKNOWLEDGEMENTS

The authors are grateful to the directors, medical and nursing staff of the Medical Department at Sappasithiprasong Hospital. We thank Vanaporn Wuthiekanun, Nongluk Getchalarat, Premjit Amornchai, Gumphol Wongsuvan, Sayan Langla and Jintana Suwannapruk for laboratory support. This study was funded by the Wellcome Trust of Great Britain.

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