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Melioidosis Case Series: Various Clinical Presentations and Risk Factors

Ibrahim Azlina[1]* and Wan Zakaria Wan Helmi[2]

[1]Department of Medicine, Hospital Bentong, Pahang, Malaysia

2Radiology Unit, Hospital Bentong, Pahang, Malaysia

Abstract

Melioidosis is an infectious disease caused primarily in countries with tropical climates, especially Southeast Asia and Northern Australia, by the bacterium *Burkholderia Pseudomallei*. The bacteria can be found in contaminated water and soil and it is spread to humans and animals by direct contact with the contaminated source. Melioidosis can involve multiple system which can lead to severe infections and fatal. We report on three cases of melioidosis in the Bentong district of Malaysia over a 12-month period; a 61-year-old man with a right elbow abscess; a 69-year-old man with a recurrent admission and splenic abscess; and a 24-year-old young man with a splenic abscess. The first two patients had poorly controlled diabetes mellitus, while the third patient did not have any comorbidities, but operated on oil palm plantations. All these patients remained in Bentong, Pahang. Pahang is the largest state in the Peninsular of Malaysia, with the production of rubber and oil palms as its key economic source. This case series highlights differences in presentation of melioidosis and occupational exposure as a risk factor for melioidosis in addition to poorly controlled diabetes mellitus.

Keywords: Melioidosis • Clinical presentation • Risk factors

Introduction

Melioidosis is an endemic disease in Malaysia [1-3]. It is a tropical bacterial infection caused by *Burkholderia Pseudomallei*, a Gram-negative bacillus usually found from fresh water and soil saprophyte [1]. Most cases of melioidosis have occurred in person with regular contact with contaminated soil or water through penetrating wounds or skin abrasion [1]. Other modes of transmission include inhalation through contaminated dust and aspiration of contaminated water from swimming or near drowning. Melioidosis is an acute febrile illness ranging from acute pneumonia, localized infection or septicemia [4]. It can occur at any age with a peak occurrence in the Malaysian case series between the ages of 40 years and 60 years [3]. Type 2 diabetes mellitus is the most common co-morbid associated with melioidosis [3]. States that are involved in agriculture have recorded a higher incidence of melioidosis, with workers in agriculture and construction being considered to be at high risk due to their contact with polluted soil and water [3]. Common clinical manifestations are fever and abscess formation in multiple distant site organs. Melioidosis can resemble other infections, and therefore clinical diagnosis can be difficult. Delays in clinical diagnosis and lack of access to critical care services lead to higher risk of death [5]. We present case series of patients with different clinical presentations and occupational exposures are presented as a single risk factor for melioidosis, particularly for individuals from endemic regions

Case 1

61-year-old man, poorly managed diabetes mellitus presented with right elbow swelling and fever for 4 days. He had minimal mobility of his right elbow due to pain and swelling. He denies history of trauma or fall. He denied any other symptoms. On physical examination, his right elbow was swollen, erythematous, warm and tender to touch over the olecranon, medial and lateral epicondyle. Patient had a limited range of passive movements over his right elbow. His peripheral circulation was intact with normal sensation. Right elbow x-ray did not indicate a fracture. Blood investigations showed that the number of leukocytes was 11.1x103/UL with predominately neutrophils; 84.4% and the platelet was 404x103/UL. Serum uric acid was normal. ESR was elevated (71 mm/hr). The blood sugar profile was 10 mmol/L to15 mmol/L. He was initiated with basal bolus insulin therapy and strict diabetic diet in ward. His Hba1c was 8.9%. Ultrasound of the right elbow showed intramuscular collection at the medial part of the distal right arm suggestive abscess (Figure 1). His initial diagnosis was right elbow abscess with possible septic arthritis. Patient had a wound debridement and arthrotomy washout of the right elbow. Tissue and pus were sent for culture and sensitivity testing, then showed *Burkholderia Pseudomallei* sensitive to ceftazidime. Melioidosis was diagnosed with a clinical presentation of joint infection with soft tissue abscess and was then given intravenous ceftazidime for 6 weeks. The patient was treated successfully with eradication therapy and discharged well.

Case 2

69-year-old man with diabetes mellitus and chronic hepatitis B initially had fever and suprapubic pain accompanied by acute urinary retention for two days. The patient reported pus in the urine and was given tablet amoxicillin for urinary tract infection but symptoms deteriorated. Onexamination, noted that the patient was septic and ill, dehydrated and temperature was 40°C. Blood pressure was 162/70 mmHg and pulse rate was 100 beats per minute. Abdominal examination revealed tenderness in the suprapubic region. Blood tests showed leukocyte counts of 23.3x103/UL with predominant neutrophils; 81.6% and platelet count of 223x103/UL. He had hyponatremia with sodium of 125 mmol/L and creatinine of 129 µmol/L. ESR was 2 mm/hr. His renal ureter and bladder ultrasound showed only prostatomegaly but no hypoechoic lesion to indicate abscess. There was no evidence of intraabdominal collection from the abdominal ultrasound either. Blood culture and sensitivity test showed isolated *Burkholderia Pseudomallei* susceptible to ceftazidime. Patient was diagnosed with melioidosis with unknown primary site, hence intravenous ceftazidime was administered for two weeks. He was discharged with tablet sulfamethoxazole and trimethoprim (400/80) four tablet twice daily. After two weeks, the patient was readmitted due to high-grade fever, vomiting and abdominal pain. He was clinically ill with a temperature of 39°C, compensated shock with a blood pressure of 110/50 mmHg and a heart rate of 110 beats per minute. He had metabolic acidosis with venous blood gas revealed a blood pH of 7.26 and a HCO_3 of 19 mmol/L. He elicited generalized tenderness with voluntary guarding on abdominal palpation. Blood investigation found that leucocyte counts were 10.1x10³/UL with predominantly neutrophils; 95.9% and

***Address for Correspondence:** Ibrahim Azlina, Department of Medicine, Hospital Bentong, Pahang, Malaysia, Tel: 60142216970, E-mail: azlina1984@yahoo.com*

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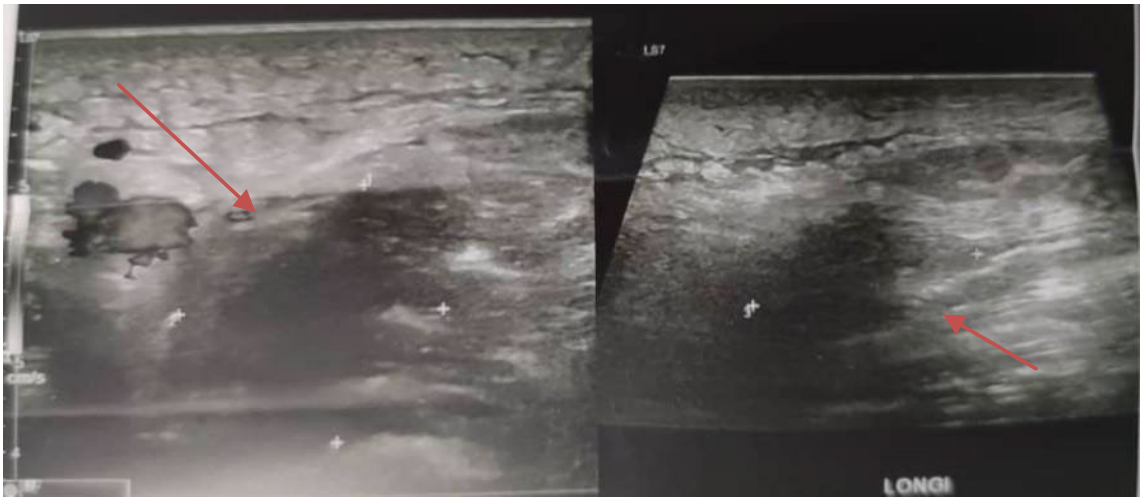

Figure 1. Ultrasound of the right medial elbow showed an intramuscular collection indicating abscess.

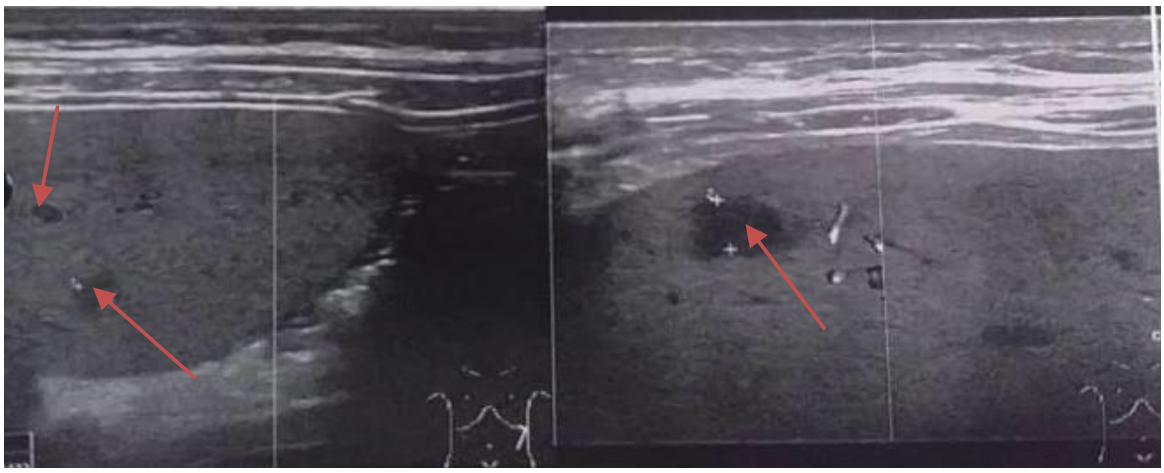

Figure 2. Ultrasound of the spleen revealed multiple sub centimeter hypoechoic lesions scattered throughout the spleen represent splenic abscess.

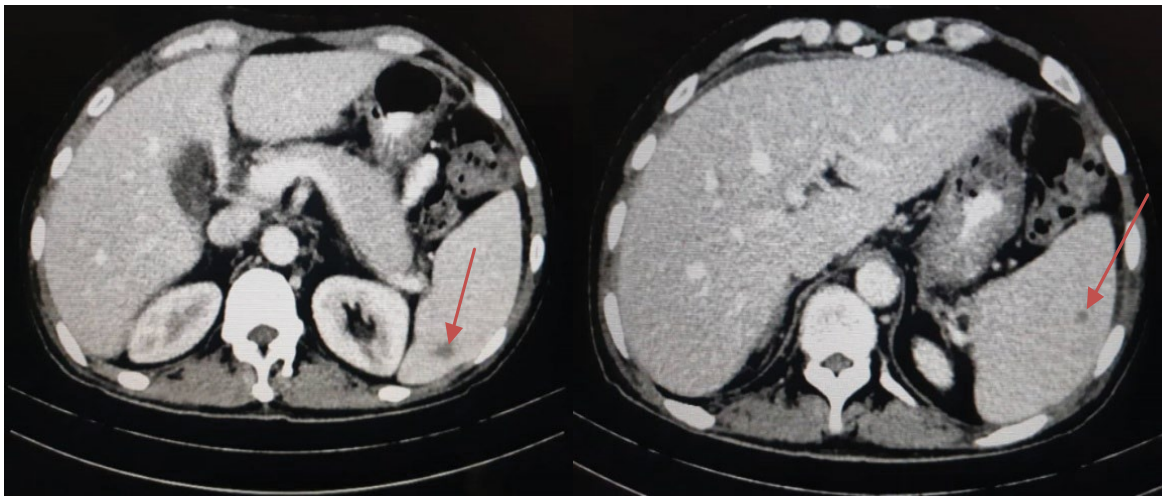

Figure 3. Abdominal CT scan showed multifocal splenic abscess.

platelet counts of 193x 10^3/UL. Liver function test showed mild transaminitis with ALT of 58 U/L and AST of 116 U/L. Total bilirubin and alkaline phosphatase were normal. A repeated abdominal ultrasound showed a mildly enlarged spleen with multiple scattered subcentimeter hypoechoic lesions representing splenic abscess (Figure 2). Multifocal splenic abscess with perisplenic fluids was shown by abdominal CT scans (Figure 3). The blood culture and sensitivity test showed isolated *Burkholderia Pseudomallei* sensitive to ceftazidime. Patient treated for persistent melioidosis with multiple splenic abscess secondary to non-compliance to eradication therapy. He underwent intravenous ceftazidime for six weeks followed by eradication therapy with doxycycline tablet and amoxicillin/clavulanic acid as he had allergies to trimethoprim-sulfamethoxazole. A repeated abdominal ultrasound revealed smaller residual tiny multifocal splenic abscess with resolved perisplenic and perihepatic fluid at 4 weeks of ceftazidime.

Case 3

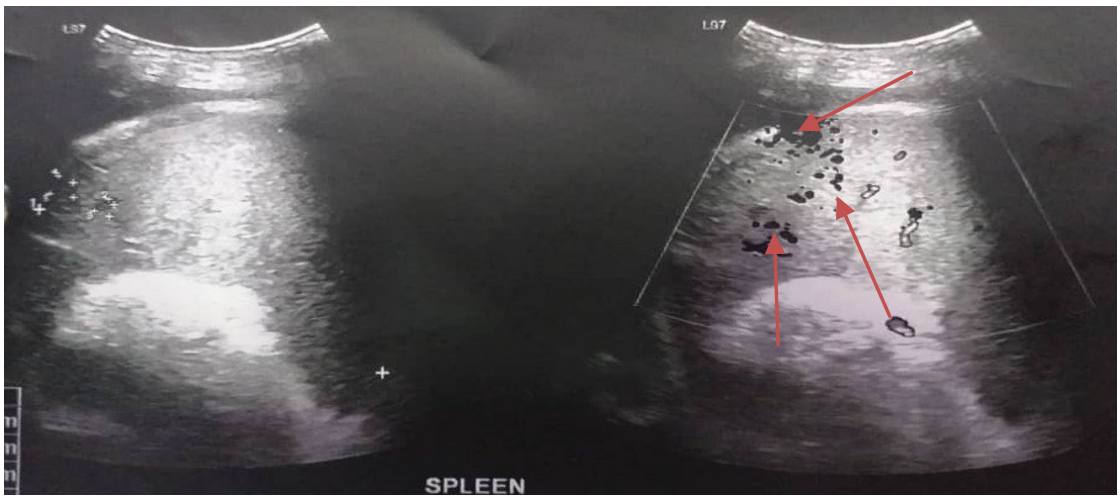

Figure 4. Abdominal ultrasound showed splenic microabscess.

24-year-old young man, no known illness presented for one-week fever and vomiting accompanied by stomach pain and diarrhea for one day. He denies travelling, jungle tracking or swimming in the river. Patient worked at the oil palm plantation in Pahang. On inspection, patient was septic and lethargic looking, dehydrated, febrile with 40°C temperature. His blood pressure was 122/67 mmHg. He was tachycardic and tachypneic with pulse rate of 150 beats per minute and oxygenation saturation of 90% on room air. He was given fluid boluses and was electively intubated due to respiratory failure. Full blood counts showed leucocyte counts with mainly neutrophils of 9.9x103/UL; 68.3%. Hishaemoglobin level was 8.7xG/dL with platelet counts of 340x103/UL. His kidney and liver function test were normal. His LDH was 329 U/L with ESR level of 90 mm/h. Splenic micro abscess was seen by abdominal ultrasound (Figure 4). The patient was empirically treated for probable melioidosis with splenic abscess in view of his risk factor as a palmoil plantation worker. Blood culture and sensitivity test later showed *Burhkolderia Pseudomallei*. Intravenous ceftazidime for a total period of six weeks was administered to the patient, followed by sulfamethoxazole and trimethoprim (400/80) 4 tablets twice daily as eradication therapy for a total duration of five months. He discharged well.

Discussion

Melioidosis is an endemic disease in Malaysia. It was first reported in 1913 following an outbreak involving guinea pigs and rabbits at one of the Kuala Lumpur research centers [5]. Multiple case reports and reviews were published at the end of the 1980s hence led Malaysian clinicians to increase their research interest in melioidosis [3]. The true incidence of melioidosis is uncertain, but data have shown that the higher incidence of melioidosis is reported to be involved in agriculture [3]. Pahang as the largest state in the peninsular of Malaysia with its main economic activity is agriculture, recorded incidence of culture-confirmed adult melioidosis of 6.1 per 100,000 population per year from 2000 to 2003 [3]. We reported 3 cases of culture-confirmed adult melioidosis in Bentong, Pahang with different clinical presentations and risk factors. The first case is a diabetic patient with soft tissue abscess. The second case is a diabetic patient with a chronic episode of splenic abscess due to inadequate antimicrobial therapy. The third case is a young patient with no comorbidities with acute bacteremia and splenic abscess. The only risk factor for him is his profession as an oil palm plantation worker.

Diabetes mellitus is the most common co-morbid disorder associated with melioidosis [3,6]. Almost more than half of patients with melioidosis were either newly diagnosed or pre-existing type 2 diabetes mellitus [3, 6]. This is followed by chronic renal disease, tuberculosis, immunosuppressive treatment, malignancies, chronic heart disease and social risk factors such as chronic alcoholism and smoking [3,6]. Studies have reported that diabetes has a 12-fold increase in the incidence of melioidosis and is by far the highest risk association for infectious disease [6,7].This is attributable to differences in immune response patterns in patients with diabetes relative to non-diabetic patients [8]. Several research in endemic areas have describe the association of environmental factors such as occupational and recreational exposure to melioidosis infection. Staff in the agricultural sector are considered to be at high risk due to their contact with polluted soil or water [4]. Darwin prospective study stated that melioidosis is a possible significant occupational hazard, with the most frequent mechanism of inoculation being contaminated wound by soil and water aerosolization [6]. This is well illustrated in case 3; a young patient with no comorbidity. He was diagnosed with melioidosis infection and the only risk factor was his occupation as an oil palm plantation worker. The risk of mortality for both workers with inoculating events is similar compared to those with non-work-related melioidosis [6].

Melioidosis most often present with acute onset of fever, with less than 10% of cases chronic onset [9]. The most common clinical presentation of primary infection is acute pulmonary infection, acute bacteremia, extreme soft tissue infection, or pyrexia ofunknown origin [9]. In case 1 patient presented with septic arthritis which is uncommon for melioidosis infection. Several reported case series and studies revealed 6% to 13% of cases of melioidosis presented with bone and joint infections; mainly septic arthritis [3]. The most frequently affected joints include knee, ankle, wrist and elbow joints [3]. However, osteomyelitis was less common [3]. Melioidotic bone and joint infections are difficult to differentiate from other causative agents unless microbiologically proven in cultures [10]. *Burkholderia Pseudomallei* could be isolated from aspiration of abscesses, skin pustules or skin biopsies [3]. A prospective study from Northern Australia reported that septic arthritis can be the primary manifestation of melioidosis or secondary to dissemination from infection elsewhere inthebody such as pneumonia or septicemia [11].

Septic arthritis from Burkholderia Pseudomallei infection can resemble other types of septic arthritis, osteomyelitis and rheumatic disorders [10]. The typical presentation of melioidotic septic arthritis is redness, swelling, tenderness and warmth around the joints [12]. These symptoms are similar to the clinical presentation in case 1 and the antimicrobial therapy provided on the basis of microbiological evidence. Beside primary infection, patient may present with secondary foci of infection as illustrated in case 2 and case 3. In both cases patients had acute bacteremia accompanied by splenic abscess. Abscesses in internal organs are well known, particularly in the prostate, spleen, kidney and liver [6]. Liver and splenic abscess are more commonly found in bacteremia cases [3]. In less than 25% of cases, isolated splenic abscesses can occur in endemic areas [13]. The presence of splenic abscess with poor treatment response in diabetic patients in non-endemic areas should also increase the suspicion of melioidosis [14]. The typical imaging appearance of the abdominal CT scan is the appearance of 'honeycomb' and 'swiss cheese' of the liver and spleen which is not seen in our case. However, a series in Thailand reported that multiple splenic lesions were also common in melioidosis infections, which is close to cases 2 and 3 [15].

Recurrent melioidosis is characterized as the clinical features of melioidosis in conjunction with one or more positive cultures for *B. Pseudomallei* in a patient with a history of previous episodes [16]. This include patients who had recurrent symptoms when receiving oral antibiotics following initial clinical and microbiological responses to antibiotic therapy or patients who had undergone treatment during previous melioidosis episode [16]. Recurrent disease patients can be either relapse or re-infection [6]. Insufficient intravenous antibiotics, inadequate length of treatment, weak adherence to antimicrobial therapy and the severity of the disease itself, such as multifocal infection, bacteremia and disseminated melioidosis during the primary episode, are associated with recurrence. It is the responsibility of the clinician to educate patients on the importance of adherence to antimicrobial therapy to prevent life-threatening recurrence. Inadequate intravenous antibiotics and poor adherence to antimicrobial therapy contribute to persistent melioidosis in case 2. Diagnosis of melioidosis infection may be challenging due to absence of clinical pathognomonic and lack of knowledge on the disease among clinicians and laboratory personnel attending [3]. The gold standard diagnostic test for melioidosis is the isolation of *B. Pseudomallei* from clinical specimens. The use of selective media for processing samples helps to suppress the commensal organisms. Ashdown's Agar is the most widely used media for the isolation of *B. Pseudomallei* in endemic countries [3]. Serological test to detect the presence of anti-*B. Pseudomallei* antibody titers either the Indirect Hemagglutination Assay (IHA) or Enzyme- Linked Immunosorbent Assay (ELISA) may be helpful in cases of culture negative results. However, it should be interpreted with caution in endemic areas with high history seroprevalence rates [17]. Melioidosis has a potentially high mortality rate. It is estimated that over 2,000 patients die of melioidosis every year in Malaysia with higher mortality rate among bacteremia cases [3]. Septic shock is the strongest predictor for mortality in patient with melioidosis infection [18].

The mainstay treatment for melioidosis is divided into two phases: acute phase and eradication phase. Ceftazidime is the choice of agent during the acute phase, while Trimethoprim-Sulfamethoxazole (TMP-SMX) is recommended for the eradication phase. Carbapenems is reserved for serious infections or treatment failures and amoxicillin/clavulanic acid is used as second-line therapy [19]. The length of the intensive and eradication phase of antibiotics depends on the clinical foci of the infection. Patients with deep-seated or complicated infections need intravenous antibiotics for 4 weeks to 8 weeks, followed by oral antibiotics for at least 12 weeks. Our cases received intravenous antimicrobials for a minimum of 6 weeks for intensive therapy in view of the present of deep-seated tissue collection, followed by a minimum of 3 months eradication therapy.TMP-SMX plus doxycycline has been used for eradication therapy in some parts of the world, but numerous literatures indicated that this regimen is associated with side effects and poor patient adherence. A research in Southern Thailand comparing the efficacy and side-effects of TMP-SMX with TMP-SMX plus doxycycline in the oral phase of melioidosis therapy found that the addition of doxycycline to the co-trimoxazole does not confer additional therapeutic benefits on co-trimoxazole alone. The use of doxycycline leads to further adverse reactions and can predispose to drug non-compliance, incomplete treatment or fatal premature termination of eradication therapy [20]. A multicenter, double-blind, randomized controlled trial in Northeast Thailand also confirmed that TMP-SMX is not inferior to TMP-SMX plus doxycycline for the oral phase of melioidosis therapy and is preferable based on safety profile and tolerance [21]. Acquired doxycycline resistance was also reported in the past [22]. Doxycycline can be an alternative agent when TMP-SMX cannot be used but tends to be less efficient than TMP-SMX. Amoxicillin-clavulanate is indicated for eradication therapy during pregnancy in Thailand and in younger children if TMP-SMX resistance or intolerance occurs but the recommended dose is higher than the normal dose used for common conditions [23]. However, it is less effective in preventing relapse of melioidosis [24].

Conclusion

Melioidosis can be presented with different clinical presentations. The disease may resemble other infections. *B. Pseudomallei* should be considered as one of the causative agents of infections in an endemic area. Patients with comorbidities and immunocompromise are at greater risk for melioidosis infection. Environmental factors, such as occupational and recreational exposure, should also be considered as significant risk factors for melioidosis infection in the endemic area. Restricted laboratory resources to isolate the organism and lack of knowledge of the disease can contribute to misdiagnosis of melioidosis.Early detection of the disease on the basis of clinical, laboratory and radiological findings could prevent complications and death.

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