

***Burkholderia pseudomallei*: Public Health and Occupational Risk of Exposure due to an Imported Case of Melioidosis**

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Abstract We describe the case of a 47 years old Sri Lankan man living in Oman with melioidosis and the resultant occupational risk of exposure to 5 laboratory staff members to the causative agent, *Burkholderia pseudomallei*. Widely reported as an endemic disease in tropical and subtropical areas, *B. pseudomallei* was imported to Oman by our patient who had risk factors of diabetes mellitus and alcoholic cirrhotic liver disease. Microbiological and biochemical tests identified the gram negative bacillus, *B. pseudomallei*, in the patient's blood sample. Five laboratory workers had occupational exposure to *Burkholderia pseudomallei* and received post-exposure prophylaxis. Our report highlights the importance of early suspicion of the infection and managing the patient with the correct international protocols for melioidosis especially for patients with severe sepsis and septic shock in the Intensive Care Unit (ICU). Furthermore, the importance of increased awareness among laboratory personnel and the need for good laboratory practices is reported. Furthermore, improved surveillance is essential to guide early diagnosis and prompt treatment.

Keywords: *Burkholderia pseudomallei*, melioidosis, occupational risk

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1. Introduction

Melioidosis is an emerging infectious disease which is of public health importance. The disease is predominantly endemic in many tropical and sub-tropical countries particularly in Southeast Asia and Northern Australia [1,2,3,4]. Thailand has the highest reported number of cases [5]. Recent reports have documented melioidosis in south and north America [6]. The global burden of melioidosis and the potential to become established in non-endemic areas is not known [4]. There are several reports of melioidosis as imported cases in non-endemic areas however cases in Oman are rare [7]. Despite antibiotic therapy, melioidosis is a life-threatening infection, with fatality rates of up to 44% in endemic regions [8]. We report an imported case of melioidosis with occupational risk of exposure to laboratory staff members.

2. Case Report

A 47 years old man from Sri Lanka was admitted to Sinaw Hospital, Oman, on 21 February 2019, he presented

with a history of fever, jaundice and generalized body aches for 10 days. He was known to have diabetes mellitus with poor compliance to medications, alcohol cirrhotic liver disease and previous dengue infections in his homeland. His symptoms started in Sri Lanka a week before returning to Oman where he had spent his vacation with his family and consumed alcohol on a daily basis for almost 40 days. He was admitted to a secondary care hospital in Sinaw for further evaluation and management. On examination, he was dehydrated, jaundiced and was febrile with tachypnea and tachycardia and the following results were noted: body temperature, 38.3-38.5°C; blood pressure, 130/80 mmHg; pulse, 90-113 beats/min and respiratory rate, 20 breaths/min. Chest exam was normal and his abdomen was distended with hepatosplenomegaly but no ascites. Laboratory blood results shown in Table 1 reveal that the patient had a leukocytosis, neutrophilia and thrombocytopenia. CRP was abnormally raised, 114 mg/L. His LFTs were abnormal. Renal function tests were normal. Blood culture, urine culture, malaria screening, serology for HIV, HBV, HCV, *Brucella* and *Coxiella* serology were negative. PCR for viral hemorrhagic fever including CCHF, dengue and rift valley fever were negative. Chest X-ray showed bronchial shadows with reticulonodular pattern suggestive of airway disease and

pneumatic infiltration (Figure 1). Abdominal ultrasound showed chronic parenchymatous liver (nodular surface) disease with splenomegaly. The patient was treated for Community Acquired Pneumonia (CAP) with a short course of antibiotics (intravenous ceftioxone 1gm once daily and oral (po) clarithromycin 500 mg twice daily for 5 days) and he was discharged home when his clinical condition improved. He was readmitted to the same hospital few days later with high grade fever. His blood results shown in Table 1 revealed a further increase in his WCC and neutrophil count. His platelet counts were still low and his CRP had risen to 155mg/L. On this occasion, his septic work up revealed that a blood culture flagged positive for Gram negative bacilli. The initial impression was sepsis so the patient was treated with a broader spectrum antibiotic, intravenous meropenem 1gm three times a day. His general condition started to improve but his abdominal distension worsened. An abdominal computed tomography (CT) scan showed hepatosplenomegaly with signs of liver parenchymal disease and portal hypertension (Figure 2). Multiple splenic focal lesions, most likely splenic abscesses were observed. A few days later he developed massive melena and his Hb dropped so he was transferred to the intensive care unit. An emergency oesophago-gastro-duodenoscopy (OGD) showed esophageal varices grade 1 but not bleeding. The patient's stomach was full of altered blood with no varices. A duodenal ulcer with a visible vessel was a possible source of bleeding. After transfusion with packed red blood cells (PRBC), his condition stabilised and he was then transferred to the

general medical ward. While in ICU he was started on po cotrimoxazole as a combination with IV meropenem for probable *Burkholderia pseudomallei* isolate on blood culture. An initial finding in the blood culture showed gram negative bacilli with safety pin appearance (Figure 3A). Colonies were subcultured on blood, chocolate and MacConkey agars. Colonies appeared initially as dry but on prolonged incubation were wrinkled in appearance (Figure 3B). Disc susceptibility testing performed in Sinaw Hospital laboratory showed sensitivity to coamoxiclave, caftazidime, cefepime, piperacillin-tazobactam, meropenem, imipenem, cotrimoxazole and ciprofloxacin and resistance to ampicillin, cefuroxime, amikacina, gentamicin and colistin (Table 2). Initial identification attempts were not successful. The isolate was sent to the Central Public Health Laboratories (CPHL) for confirmation where API 20 NE (bioMerieux, France), Vitek 2 (bioMerieux) and MALDI TOF (Bruker typer) identified the isolate as *Burkholderia pseudomallei* with good identification scores in all methods. API 20 NE identified *Burkholderia pseudomallei* with a 92.5% match and Vitek with 87% probability. MALDI TOF could not ID up to species level, however 16s PCR confirmed the identification. Biochemical tests revealed oxidase and catalase positive tests and targeted treatment could be given to the patient (Table 2). The patient improved after 14 days of IV meropenem and cotrimoxazole and was discharged home with po cotrimoxazole for 2 more months along with regular outpatient visits for follow up.

Table 1. Laboratory investigations performed on the patient

| | WCC | Neutrophil | Platelet | CRP | Bilirubin | ALT | AST | AlkPhos |
|------------|-----|------------|----------|-----|-----------|-----|-----|---------|
| 21/02/2019 | 7.4 | 4.4 | 91.16 | 114 | 275 | 129 | 102 | 101 |
| 09/03/2019 | 9.9 | 7.4 | 136 | 155 | 34.4 | 72 | 61 | 300 |

WCC: $10^3/uL$, Neutrophil: $10^3/uL$, Platelets: $10^3/uL$, CRP:mg/L, Billirubin: umol/L, ALT: U/L, AST: U/L, AlkPhos: U/L.

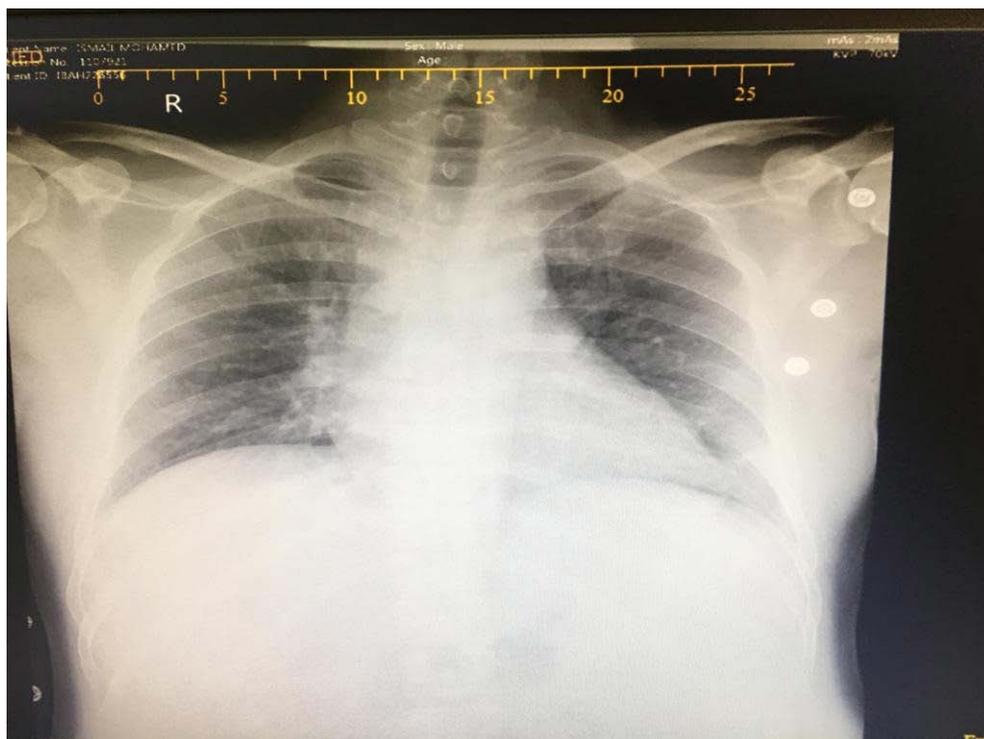


Figure 1. Chest X-ray showed bronchial shadows with reticulonodular pattern suggestive of airway disease and pneumonic infiltration

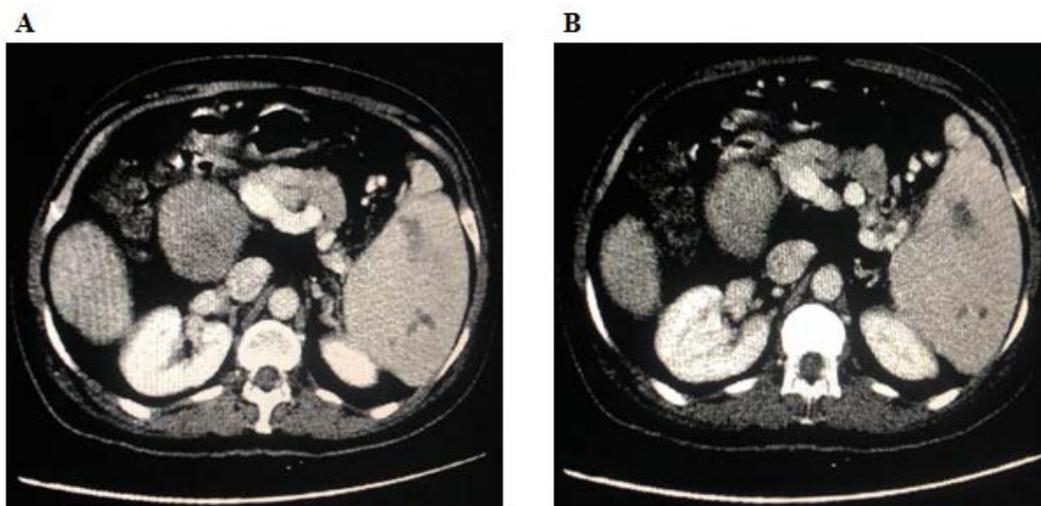


Figure 2. Abdominal computed tomography scans showing multiple splenic focal lesions were observed with contrast enhancement during arterial phase (splenic abscess)

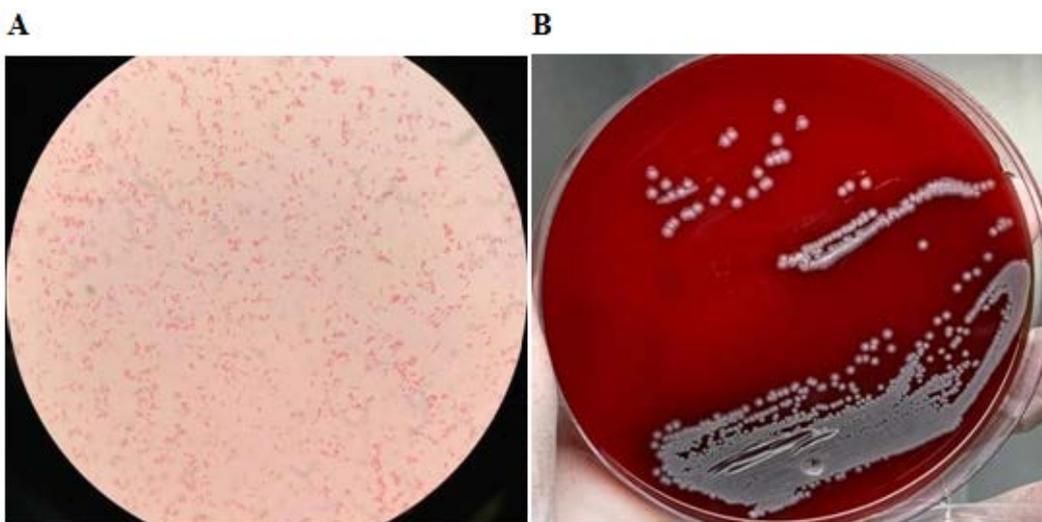


Figure 3. A. An initial finding in the blood culture showed gram negative bacilli with safety pin appearance. **B.** Colonies were subcultured on blood, chocolate and MacConkey agars. Colonies appeared initially as dry but on prolonged incubation were wrinkled in appearance

Table 2. Antibiotic susceptibility & biochemical tests of the isolate

| Test | Results | Antibiotic | Susceptibility results |
|--------------------------|----------|---------------|------------------------|
| Oxidase and catalase | Positive | Co-amoxiclave | S |
| Growth on MacConkey agar | Positive | Cefuroxime | R |
| Nitrate reduction | Positive | Ceftazidime | S |
| Motility | Motile | Cefepime | S |
| Citrate | Negative | Pip/Taz | S |
| Arginine dihydrogenase | Positive | Gentamicine | R |
| Urea | Negative | Amikacin | R |
| Gelatin | Negative | Cotrimoxazole | S |
| Esculin | Negative | Ciprofloxacin | S |
| Indole | Negative | Colistin | R |
| | | Meropenem | S |
| | | Imipenem | S |

An immediate investigation was initiated to investigate the risk of potential exposure to the isolate, any precautions taken while working with the isolate as well as the presence of any risk factors that might mitigate or exacerbate due to exposure. There were 4 laboratory technicians who worked with the isolate on an open bench in the Sinaw hospital laboratory and one technician in

CPHL. These workers were counseled and referred to Infectious Disease consultants (ID) for evaluation and management as required. A baseline blood sample (CBC, RFT, CRP, LFT) for all exposed Health Care Workers (HCWs) were obtained. Exposed HCWs were given post-exposure prophylactic an oral cotrimoxazole for 21 days with regular clinic follow up and very close

monitoring of vitals and signs and symptoms. None of them reported any symptoms during the follow up period.

3. Discussion

Burkholderia pseudomallei which is the causative agent of melioidosis, inhabits moist soil and stagnant water [3]. Although our patient did not recall any accidental or occupational exposure, the incubation period has been reported to be upto 26 years before clinical manifestations of melioidosis occurs, generally due to an alteration in immune status [9]. The primary route of *B. pseudomallei* infection is percutaneous inoculation however recent evidence suggests that inhalation during severe weather conditions and ingestion of contaminated water are also important routes of infection [2,8,10]. Several risk factors are associated with melioidosis; diabetes mellitus is the most common risk factor and has been reported to increase the relative risk to 20-fold [11]. Excessive alcohol intake is also an independent risk factor [12]. Our patient was very high risk as he was diabetic with poor compliance to medications and had alcoholic cirrhotic liver disease.

Melioidosis, also known as Whitmore's disease, has a wide range of clinical presentations from acute to chronic infection and has been reported to include diverse clinical manifestations such as a chronic low grade localized infection to an acute fulminant septicemia with dissemination to multiple organs characterized by abscesses [13]. As seen in our patient, pneumonia is the most common primary clinical presentation and has been reported in 32.1% of Indian patients [14], 45% of Thai patients [11] and 51% of northern Australian patients [15]. Abscesses due to melioidosis may be a source of systemic infection and can cause hematogenous spread [15], this was evident in our patient.

Confirmation of diagnosis of melioidosis relies on good practices for specimen collection, laboratory culture and isolation of *B. pseudomallei*. The organism is a motile gram negative bacillus with a safety pin appearance in culture and can readily grow in any standard culture media. The colonies were dry and wrinkled on prolonged incubation as shown in Figure 2. *B. pseudomallei* is known to be a category 3 pathogen requiring that all lab work be carried out in a biosafety cabinet [16]. Infections with *B. pseudomallei* may occur after laboratory exposure when enhanced precautions such as those used in biosafety level 3 facilities are not used during testing of isolates from infected patients or animals [16]. In our study, five laboratory staff members were unwittingly exposed to *B. pseudomallei* before it was identified, therefore, increased awareness among laboratory personnel and good laboratory practices are important.

Treatment for melioidosis consists of an initial intravenous intensive phase that lasts for 10–14 days (or longer when clinically indicated) and an oral eradication phase [17]. The oral antimicrobial eradication phase substantially lowers the risk for relapse that can occur with intravenous antimicrobial drugs only. In accordance with USA CDC Atlanta guidelines 23, our patient was treated with IV meropenem and cotrimoxazole for 14 days

and was discharged home with oral cotrimoxazole for another 2 months. Although there is little data on postexposure prophylaxis in the context of laboratory exposure, consensus guidance on postexposure prophylaxis (PEP) recommendations have changed little since the 2008 [18]. The recommended antimicrobial drugs include TMP/SMX and co-amoxiclav. Recommended duration of PEP is 21 days, based on the premise that this regimen would provide prophylaxis covering the common range of incubation periods [19].

Although prevention of infection via vaccination represents a more effective way to protect susceptible populations than antibiotics, there are currently no approved vaccines for any *Burkholderia* species to date. Several candidates for subunit vaccines against *B. pseudomallei* have also been tested, however pre-clinical studies indicate that protective immunity against *B. pseudomallei* may be induced by live attenuated immunogens [20]. Due to the concerns about the possible reversion to virulence of live vaccines, these vaccine candidates are unlikely to be approved for use in humans [21].

As the importation of *B. pseudomallei* into Oman is rare, increased clinical vigilance with good microbial work up would help with improved, accurate and rapid diagnosis. We hope this case study increases awareness among clinicians of its presence and have low index of suspicion especially with compatible travel history to an endemic country. The need to consider the risk of infection to other healthcare personnel with possible occupational exposure such as laboratory staff is highlighted in this case study. This risk is underscored by the importance of laboratory diagnosis which remains the gold standard for accurate diagnosis of melioidosis.

Disclosure

The authors declared no conflict of interest.

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