Case report

A case of recurrent and seronegative melioidosis with deep seated abscesses

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Abstract

Melioidosis has a varied clinical presentation. This is a case of recurrent melioidosis diagnosed in a 46 year old male with a prolonged febrile illness and multiple deep seated abscesses. He had intermittent fever since 2020 which was eventually diagnosed as melioidosis in 2021 following isolation of *Burkholderia pseudomallei* from a blood culture. Treatment was given and he was asymptomatic for seven months, but the fever recurred and needed reinvestigation. Inflammatory markers were high and contrast CT scan revealed multiple abscesses in the liver, spleen and lungs. Bacterial culture in blood and melioidosis antibodies were negative. As other causes were excluded, he was treated as recurrence of melioidosis with a prolonged course of antibiotics and remains well to date. The diagnosis of melioidosis is challenging and clinicians should be aware of the varied presentations. Following diagnosis, treatment with appropriate antibiotics for an adequate duration is vital to ensure complete cure and minimize chances of a recurrence.

Keywords: melioidosis, recurrent, seronegative

Introduction

Melioidosis is caused by a Gram-negative bacteria known as *Burkholderia pseudomallei*. Due to its varied presentation, clinical features mimicking other common tropical diseases and challenges in diagnosis such as misinterpretation of results and low sensitivity in detection in blood cultures, it is often diagnosed late or in some cases overlooked completely. The disease is primarily endemic to tropical regions, with 44% of the global disease estimated to be in South Asia.[1] *B. pseudomallei* is found in muddy soil and stagnated water on soil. It has also been frequently found in farmed lands, such as paddy fields.[2,3]

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Melioidosis occurs through exposure to contaminated soil or water leading to percutaneous inoculation of the organism from penetrating wounds or abrasions in the skin. The bacteria can exist in an aerosol form and inhalation of contaminated dust particles or water droplets is another route of infection, often leading to pneumonia or severe systemic disease.

Since the establishment of national surveillance in Sri Lanka in 2018, the disease has been recognized as endemic in Sri Lanka.[4] Recurrence of melioidosis may result from reinfection with a new strain of the organism or relapse due to inadequate clearance of the original infection.[5] Here we discuss a patient with fever spanning several years ultimately diagnosed with recurrent melioidosis.

Case presentation

A 46-year-old diabetic male was admitted to our unit in January 2023 with a history of fever for two months. He had a complicated past medical history. He first became unwell in 2020, when he developed a prolonged fever with constitutional symptoms. Despite several admissions where he was treated with broad spectrum antibiotics no cause was identified, and he remained unwell. Due to continuing symptoms, he was given a trial of anti-tuberculosis medication with category one drugs for six months which gave only temporary relief.

In early 2021 the fever recurred prompting further investigations. This time the blood cultures were positive for *Burkholderia pseudomallei* confirming a diagnosis of melioidosis. A contrast-enhanced CT scan of the abdomen revealed multiple hypoattenuating lesions in the spleen, indicative of splenic abscesses. IV meropenem was given for 21 days, followed by a course of oral cotrimoxazole and doxycycline for ten weeks. On follow-up, there was normalization of inflammatory markers, and the abdominal ultrasound showed complete resolution of the splenic abscesses therefore a decision was made to discontinue the oral antibiotics at end of ten weeks.

However, after seven months, the patient returned with fever, loss of appetite loss of weight and was admitted to our unit in January 2023. Our investigations revealed elevated inflammatory markers and a blood picture suggestive of bacterial infection. Of the three blood cultures collected, only one grew *Acinetobacter* species, which was interpreted as contamination. A contrast-enhanced CT scan revealed multiple abscesses in the lungs, liver, and spleen (Figure 1). Infective endocarditis and tuberculosis were ruled out. Serology for melioidosis and brucellosis was negative. A summary of the presentation and investigations is provided in Figure 2 and Table 3.

Based on the patient's history and radiological findings, a diagnosis of recurrence of melioidosis was made. We were unable to aspirate the abscesses as the ones that were accessible were too small. As there was multiple deep seated abscesses, we decided to give IV meropenem for 28 days and oral cotrimoxazole and doxycycline for 16 weeks. A bone scan performed during follow-up excluded osteomyelitis. One year after completing treatment, the patient remains well.

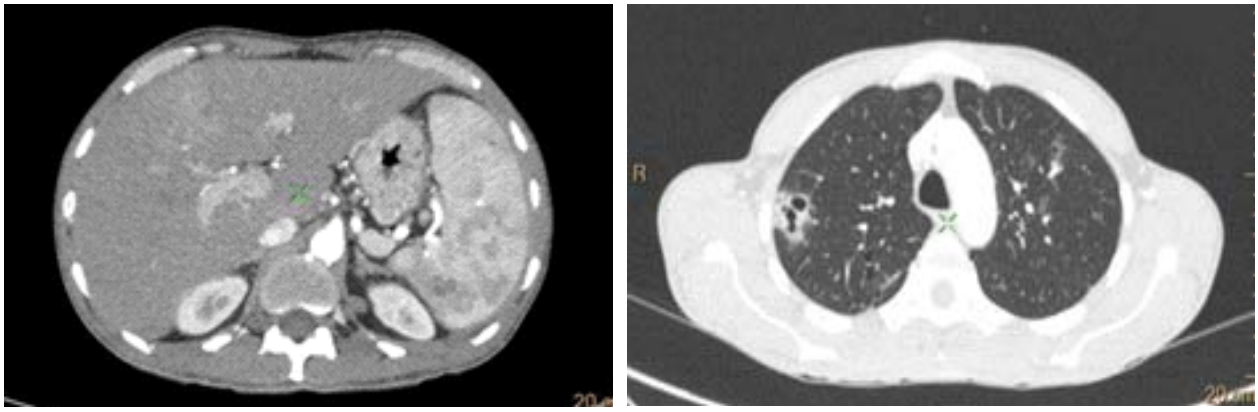

Figure 1. Contrast enhanced CT scan of chest and abdomen showing multiple abscesses in the lungs, liver and spleen.

Figure 2. Timeline of clinical presentation with summary of investigations.

Table 1. Summary of investigations done in admission to UHKDU

January - February 2023	FBC - WBC 3.51x 1000 u/L, Hb - 11.3g/dL, Plt 117000/uL Blood picture - Features of a bacterial infection CRP - 226 mg/dL, ESR - 100mm/1st hour Blood culture 1 - Acenetobacter sps Blood culture 2,3 - Negative CECT Chest Abdomen Pelvis - Multiple cavities/abcesses in both lungs, irregular enhancing areas with cystic clusters in the liver compatible with honeycomb abscesses. Cystic areas in the spleen likely representing abscesses. CSF full report- normal CECT Brain - Normal TransThoracicEcho-No evidence of endocarditis Stool AOC - Normal Weil Felix test - Negative, SAT- Negative Rheumatoid Factor -positive, Anti-ccp - Negative Retroviral Ab - Negative Hepatits B Surface Ag, Hepatitis C Antibodies - Negative Mantoux and sputum AFB - Negative Brucella antibodies - Negative VDRL- negative Ferritin- 3479 ng/ml LDH - 448 u/L ANA 1:80 positive titre C4- 6 (12-38), C3 103 (83-122) Bone Marrow - Reactive marrow with ongoing infection/inflammation Bone marrow culture (TB and Bacterial) - Negative Bone marrow TB PCR - negative Isotope bone scan: Normal (no evidence of osteomyelitis) Melioidosis antibody titre 1/80 (repeated 8 weeks apart)

Discussion

The presentation of melioidosis can vary from an acute sepsis to an indolent infection with prolonged fever and abscess formation in the internal organs also known as chronic melioidosis. In our case study, the diagnosis was not straightforward as the blood culture and melioidosis antibodies in serum were negative. However, the history of melioidosis infection and multiple abscesses in the visceral organs were important clues. The other differentials that were considered and excluded was disseminated tuberculosis, brucellosis, infective endocarditis and typhoid.

The gold standard to confirm the diagnosis remains to be the isolation of *Burkholderia pseudomallei* from bacterial culture of any specimens including blood, sputum, urine, cerebrospinal fluid (CSF), or pus aspirated from abscesses and other lesions.[5] *B. pseudomallei* grows in bacteriological culture media such as blood agar or MacConkey agar; however visual identification of the organism is challenging even in areas where the disease is prevalent. Misidentification of the pathogen as *Pseudomonas* spp[1,6,7] and under diagnosis due to low sensitivity of detection from bacterial cultures and lack of rapid molecular diagnostics are some of the diagnostic challenges. *B. pseudomallei* takes two to three days to grow in a blood culture. Hence it is vital to inform the laboratory and the microbiologist of any clinical suspicion of melioidosis in order to ensure the cultures are scrutinised properly.

The serological diagnosis of melioidosis is also challenging. There is no international standardization of the antibody assays and as several antigens are evaluated there is a varied sensitivity and specificity among the different assays. Also, high rate of seropositivity in healthy individuals from endemic areas have been reported.[8] When there is a seropositive patient it is difficult to differentiate if this is an acute infection, chronic infection, a resolved past infection or just exposure without infection. Furthermore, the positivity of anti-Burkholderia pseudomallei (Bp) antibody in infected sera relies on several factors, such as age and comorbidities.[8] Studies have shown the proportion of negative serology among acutely infected patients is as high as 27.5%.[8] The negative antibody titre therefore does not exclude the possibility of melioidosis being the diagnosis.

Imaging is very useful in reaching a probable diagnosis of melioidosis. In our case study, imaging revealed multiple splenic, lung and liver abscesses, characteristic of the disease.

Our patient had been diagnosed and treated for melioidosis few months ago, remained asymptomatic for seven months before becoming unwell again. Recurrent melioidosis is defined as culture positive melioidosis diagnosed in a patient who once again develops symptoms following completion of their recommended antibiotic regime.[9,10] This could occur due to reactivation from a latent focus or reinfection with the same or new strain. Darwin Prospective Melioidosis Study studied a large number of patients with melioidosis spanning 23 years. They found recurrence of melioidosis occurred in 5.7% patients who survived the initial infection. Of those 29 patients suffered relapse of the original strain of melioidosis, and 10 presented with a new strain.[11] Due to increased awareness and improved therapeutic options relapses have become rare in the recent years.

In this patient, *B pseudomallei* was not found in the blood culture in the current presentation and the diagnosis of recurrent infection was based on the previous blood culture positivity, recurrence of fever and presence of abscesses in multiple internal organs. Strain identification has not been performed on the initial blood culture isolate due to a lack of sequencing facilities. Therefore, it is not possible to confirm that the recurrence is due to relapse or reinfection. With the absence of continued exposure history and considering the short duration of treatment of the previous episode, the possibility of a relapse is likely in this patient.

Risk factors for relapse/ recurrence include: the presence of deep-seated abscesses, and multifocal disease, inappropriate choice of antimicrobial agents during the intensive and eradication phases of treatment; sub-therapeutic doses, inadequate duration of treatment and poor compliance of patients.[8] Relapse or a recurrence may occur in patients despite appropriate microbial therapy as well. The organism may lie dormant and then become clinically evident when host defence is compromised such as if the patient develops diabetes mellitus or chronic kidney disease. Therefore, particular attention must be paid to the duration of the eradication phase and cannot be guided by purely by clinical condition, radiological resolution of the abscesses or normalisation of the inflammatory markers.

Current guidance advises treatment in two phases. An intensive phase where intravenous antibiotics are given for a minimum of 10 to 14 days and the eradication phase in which three to six months of oral antibiotics are given.[1,12,13] Antibiotics that can be used for the intensive phase include ceftazidime or a carbapenem.[13] The duration of intensive phase is should be extended to four to six weeks in cases of septic shock or where there has been deep-seated or organ abscesses, extensive lung involvement, septic arthritis, osteomyelitis, or neurological melioidosis.[10] Antibiotics useful in the eradication phase include trimethoprim-sulfamethoxazole (TMP-SMX),

doxycycline or amoxicillin-clavulanate.[13] The minimum duration of the eradication phase found to be associated with low relapse rates is three months. However, if there were deep-seated abscesses, osteomyelitis, neurological or endovascular involvement the eradication phase may be extended to six months.[10]

Conclusion

The diagnosis of melioidosis is challenging and high level of clinical suspicion is warranted in an endemic country such as Sri Lanka. Following clinical diagnosis collection of blood and other appropriate specimens for culture is vital for confirmation of diagnosis. Treatment with appropriate antibiotics for the recommended duration is key to ensure complete cure and minimise the chances of a recurrence.

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