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Case report

Fever in a returning traveler: A case and literature review of melioidosis

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ABSTRACT

Burkholderia pseudomallei is an aerobic, motile, non-spore-forming gram-negative bacillus found in tropical endemic environments that causes the disease melioidosis. Melioidosis displays a diversity of clinical presentations ranging from septic shock to chronic latent infection, often with characteristic abscesses in multiple organs. Melioidosis is an opportunistic infection, with risk factors, including diabetes, alcohol use, chronic lung disease, and chronic renal disease, and these risk factors increase the severity of disease (Wiersinga et al., 2006) [1]. In this case report, we illustrate a case of a 32 year old man with several risk factors and recent travel to an endemic region presenting with melioidosis. Our case demonstrates the challenges in obtaining a diagnosis in a non-endemic location, highlights a complex presentation of this disease, and describes the multifaceted clinical management required to care for this patient. As global travel increases, there is an increased need for clinician awareness of this disease in non-endemic regions.
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Introduction

Burkholderia pseudomallei is an aerobic, motile, non-spore-forming gram-negative bacillus found in the environment of endemic tropical areas [1]. While well-known to be present in Southeast Asia and Northern Australia, *Burkholderia pseudomallei* is also endemic in other tropical areas, including the Indian subcontinent, China, equatorial Africa, Central and South America. Though not endemic to the contiguous United States, endemic cases have been found in Puerto Rico [3] and cases associated with travel to Mexico have been found in the Southwestern US [4]. Recently, cases were described in the US for patients who had not traveled to endemic areas, although the source of these non-travel related cases has not been identified [4]. The majority cases of melioidosis in the United States have been found in patients with documented travel to endemic areas [6]. *Burkholderia pseudomallei* is classified as a Tier 1 biological select agent and toxin by the CDC [7].

Case

A 32-year-old male initially presented with two-week of generalized weakness, fever, and non-bloody diarrhea at an outside institution. Patient had past medical histories of type-2 diabetes, hyperlipidemia, non-alcoholic fatty liver disease, and SARS CoV-2 infection. He recently returned from Bangladesh. The laboratory results from outside institution were significant for severe hyponatremia (sodium 108 mEq/l), elevated D-dimer (11.9 mcg/ml), elevated ESR (109 mm/h), acute kidney injury, and thrombocytopenia. Subsequently, patient developed hypoxic respiratory failure for which he was intubated. CT chest showed development of extensive bilateral alveolar opacities with subpleural sparing. CT abdomen demonstrated hepatosplenomegaly with associated hepatic and splenic abscesses, splenic vein thrombosis, and multiple splenic infarcts. Preliminary blood cultures grew gram negative rods initially reported as *Acinetobacter baumannii*. Transthoracic echocardiogram was negative for vegetations. After receiving multiple doses of empiric antibiotics, patient was ultimately treated with meropenem, levofloxacin, and metronidazole and transferred to our institution due to a complex clinical course.

On admission to our hospital, patient was found to be hypotensive with BP of 80/40. Physical exam was significant for coarse breath sounds in bilateral lung fields; a hyperpigmented, desquamating lower extremity rash; and a 4.5 cm enlarged right axillary lymph node. Antibiotics were changed to meropenem and minocycline based on initial blood cultures from outside hospital. Repeat blood cultures were ordered which were positive, one with a Gram stain of Gram negative bacilli, and another bottle with a Gram stain of Gram positive cocci. The bottle with Gram negative bacilli was tested on a multiplex PCR assay for common organisms causing bloodstream infections which identified *Pseudomonas aeruginosa*. The blood culture with Gram positive cocci subsequently grew *Staphylococcus hominis,* most likely a blood culture contaminant. The identification

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of *Pseudomonas* by PCR was subsequently determined to be a false-positive result, related to residual organism DNA in sterilized but DNA contaminated blood culture media. A correction of the initial blood cultures was called from outside institution and identified as possible *Burkholderia pseudomallei*, which was eventually confirmed by PCR at the state laboratory. We informed our microbiology lab about this update from the outside hospital microbiology laboratory. Our microbiology lab used a rule out procedure to analyze cultures drawn at our institution and was not able to rule out *Burkholderia pseudomallei* – characteristic safety pin morphology on Gram stain, growth on MacConkey agar, oxidase positive and spot indole negative, no hemolysis on blood agar, non-pigmented – referring final identification to the state public health laboratory.

Based on culture results and clinical presentation, antibiotics were changed to meropenem and trimethroprim-sulfamethoxazole. Patient's course in the ICU was complicated by acute respiratory distress syndrome, and diffuse alveolar hemorrhage, which later resolved. Splenic vein thrombus was treated with anticoagulation, and thrombocytopenia was assessed to be secondary to splenic sequestration. Splenic and hepatic abscesses were evaluated by interventional radiology and were assessed to be too small to drain. Patient's clinical course improved, repeat blood cultures were negative, and patient was able to be downgraded from the ICU. Three members of the microbiology lab staff were exposed to the blood or respiratory *B. pseudomallei* cultures outside of a biosafety cabinet (BSC) and were offered trimethroprim-sulfamethoxazole prophylaxis. Of note, one of the three technologists was subsequently hospitalized, not due to infection, but rather severe allergic reaction to trimethroprim-sulfamethoxazole. None of the three technologists sero-converted to produce antibodies to *B. pseudomallei*. The patient was later discharged with a tracheostomy, a PEG tube, and close follow up. On discharge, patient continued meropenem for an intensive phase of four weeks and trimethroprim-sulfamethoxazole for an eradication phase of four months after getting sensitivities back from CDC and the isolate was susceptible to Ceftazidime, Meropenem and Trimethoprim-Sulfamethoxazole. Repeat CT abdomen/pelvis one and half months after presentation showed resolution of lung infiltrates, improvement in splenic abscesses, improvement in previously seen left hepatic lobe abscesses, and development of new right hepatic lobe lesions concerning for ongoing infection. However, during this follow up visit, patient's tracheostomy and PEG tube had been removed. Patient continued taking his Trimethroprim-Sulfamethoxazole and a CT scan 3 months later showed resolution of all hepato-splenic abscesses and the patient was stable without any reported symptoms.

Discussion

This case highlights the importance of provider awareness and clinical suspicion of melioidosis when treating traveling patients with disseminated gram negative bacterial infections. Because *Burkholderia pseudomallei* is not endemic to the US, preliminary laboratory analysis may misidentify this pathogen in cultures. Sepsis, pneumonia, skin infections, and disseminated internal organ abscesses in a patient who has traveled from the tropics should raise clinician suspicion for melioidosis and prompt collaboration with microbiology laboratory to ensure an appropriate diagnosis.

Infection in this patient who recently traveled from Bangladesh should raise suspicion for an emerging infection. Though melioidosis is classically associated with Southeast Asia and northern Australia, it is also endemic to Bangladesh. Similar to our patient, cases in Bangladesh have been young in men with a median age of 45. While most cases are seen in the rainy season of June-October, some cases have been seen in the winter months, around the time this patient traveled [8]. The pathogen is harbored in contaminated dust and water, and is transmitted through inhalation, ingestion, or contact with skin abrasions. Person-to-person transmission is rare [9]. Incubation period generally ranges from one to twenty-one days, however, an incubation period as long as 62 years have been identified in one case [10,11]. Route of transmission can impact severity of disease, with inhalation associated with pneumonia and more severe disease compared to other modes of transmission [10]. However, the greatest predictor for severe disease and mortality in patients with melioidosis is presence of risk factors. The largest risk factor for mortality from melioidosis is diabetes, followed by alcohol use, chronic lung disease, and chronic renal disease [13]. Diabetes was our patient's greatest risk factor and likely contributed to his severe disease.

Though an unusual presentation for regularly found gram-negative infections in the US, our patient's presentation was classic for severe melioidosis. Melioidosis is characterized by internal organ abscesses, and can include sepsis, pneumonia, skin infection, and neurological presentation [13]. Though initially with a nonspecific presentation, our patient quickly developed pneumonia, sepsis and skin lesions. Abscesses in liver and spleen initially raised suspicion for endocarditis, however, TTE was negative. These later were determined to be the characteristic internal organ abscesses seen in melioidosis.

Melioidosis is often underdiagnosed due to lack of clinician awareness and lack of laboratory technology in rural communities in endemic areas. In non-endemic areas, laboratories can accidentally misidentify the pathogen or mischaracterize it as a contaminant [15]. Laboratory misidentification occurred in our case, with preliminary laboratory reports reporting *Acinetobacter baumannii* (admission hospital blood culture) and *Pseudomonas aeruginosa* (at our institution). Abnormal presentation, poor response to antibiotics targeting preliminarily reported pathogens, and reporting of varied pathogens appropriately prompted follow up with the laboratory. The state public health laboratory correctly identified *Burkholderia pseudomallei* and cultures were sent to the CDC for sensitivity testing. As non-culture based methods to diagnose melioidosis are not well established, clinical suspicion and laboratory rule-out procedures and subsequent referral to appropriate public health labs for final identification remains key to making the diagnosis. *Burkholderia pseudomallei* is not a part of normal human flora, and isolation on any culture is diagnostic. Taking multiple samples, including blood, throat, rectal, urine, abscess, and sputum, increases the rate of success in making the diagnosis. *Burkholderia pseudomallei* grows more slowly than most organisms, so agar plates with samples from suspected patients should be incubated and examined daily for up to four days [3]. CT imaging is also highly recommended due to high incidence of multiple organ abscesses. Early diagnosis and treatment is key to reducing mortality.

Antibiotic therapy for melioidosis comprises an initial intensive phase and then a longer eradication phase. Initial intensive phase should last a minimum of 10–14 days and longer in patients with more severe disease, such as this patient [3]. Intensive phase therapy should be with ceftazidime or meropenem. Ceftazidime is often the initial antibiotic chosen for most patients, however, meropenem has been shown to have better outcomes in patients with severe sepsis and is recommended for more severe disease [18]. Due to our patient's severe presentation, he was treated with meropenem for four weeks. Singular large abscesses should be drained if possible. However, often abscesses are too numerous and small to be drained, as was the case for this patient. The eradication phase with oral antibiotics is done to prevent recrudescence or relapse. Trimethoprim-sulfamethoxazole is the preferred agent because of excellent tissue penetration, and therapy is recommended for 3–6 weeks. Recrudescence can be seen with noncompliance with antibiotics, a shortened intensive or eradication phase, or incomplete drainage of abscesses [3]. As this patient's abscesses were not drainable, he is at risk for recrudescence. New lesions seen on follow up in this patient

increase concern for continued active infection, and this patient will require prolonged treatment and monitoring.

Of note, while *B. pseudomallei* has important biosafety considerations to prevent infections in laboratory staff due to exposure from handling the organism outside of biocontainment before the organism is suspected or identified, a recent study found that the risk of lab acquired infection with *B. pseudomallei* following standard diagnostic procedures may be relatively low [20]. In our case none of the technologists seroconverted, and one had a considerable adverse reaction to the prophylactic antibiotics.

In summary, melioidosis is an emerging infection that should be considered in patients that have traveled to endemic areas, present with abnormal gram-negative infection, and display typical clinical signs of disease including internal organ abscesses, pneumonia, and sepsis. Clinical suspicion and accurate laboratory identification is critical for early diagnosis and treatment. Severe disease and varied abscesses increase the challenge of management, and patients with complex and severe disease require prolonged antibiotic therapy and monitoring. As global travel increases, melioidosis cases can be expected to increase in the US, requiring a need for increased clinician awareness of this disease.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Akanksha Arya: first author, wrote most of the case report. **Hamadullah Shaikh:** saw the patient and helped out with details about the patient on presentation and initial work up obtained. Also obtained information from the transferring hospital. **Sean Moss and Devin Weber**: attending physicians on the case. Also helped with final drafting of the case report. **Sean Moss:** obtained verbal consent. **Matthew Pettengill:** helped with diagnostics and helped uswrite the diagnosing part of the case report.

Ethical approval

Not applicable

Consent

Verbal consent obtained by patient.

Author statement

The case report has been written and reviewed and amended by all the mentioned authors in the publication.

Conflicts of interest

No conflicts of interest.

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