Journal of
Medical Case Reports

CASE REPORT

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Melioidosis with venous thrombosis and cellulitis in the left lower limb: a case report

Anik Palit[1*], Mahmudur Rahman[2], Md. Mahfuzer Rahman[5], Zubair Akhtar[1,3], Mohammed Ziaur Rahman[1], Muntasir Alam[1], Arpita Shyama Deb[1], Sukanta Chowdhury[1], Md. Mahfuzur Rahman[1], Pritimoy Das[4], Fahmida Chowdhury[1] and Tanzir Ahmed Shuvo[1]

Abstract

Background Melioidosis, which is caused by *Burkholderia pseudomallei*, is a disease with a high case fatality rate and a wide variety of disease manifestations causing diagnostic dilemmas for medical professionals. Risk factors such as diabetes contribute to a worse prognosis if not treated with appropriate antibiotics during the course of management. This case report describes a diabetic melioidosis case with a rare presentation of venous thrombosis of the lower limb and a successful course of treatment.

Case presentation The patient was a 48-year-old Bangladeshi male who was admitted with gradually increasing left knee pain and intermittent high-grade fever for 7 days. On examination, he had a palpable spleen, high body temperature (102 °F), and pitting edema in the left lower limb during admission. He was treated with empiric meropenem on admission considering his serious illness. Doppler ultrasound of the left lower limb revealed superficial venous thrombosis and thrombophlebitis involving the long saphenous vein and superficial veins of saphenous territory below the knee. The patient was enrolled as an eligible case in a research study called the Acute Febrile Illness study. Blood culture confirmed the diagnosis as melioidosis. Doxycycline was added to his treatment regimen when the research study team informed the treating physician at the hospital about the diagnosis of melioidosis. He was discharged with cotrimoxazole, which was advised to be taken for 3 months.

Conclusion This case report shows us the lack of diagnostics to detect melioidosis in hospital settings in Bangladesh. The successful treatment outcome proved the importance of routine surveillance for rare or unusual diseases, in addition to endemic pathogens. In addition, training is essential to improve knowledge and raise awareness among clinicians about the clinical diagnosis and management of melioidosis.

Keywords *Burkholderia pseudomallei*, Melioidosis, Venous thrombosis, Bangladesh, Case report

Background

Melioidosis is a bacterial infection caused by *Burkholderia pseudomallei*, a bacterium that poses a public health threat. It is estimated to cause 165,000 cases and 89,000 deaths worldwide annually [1] with a high case fatality rate (10–50%) [2]. Meloidosis is endemic in Northeast Thailand and Northern Australia within 20° of the equator, with large numbers of cases detected in Vietnam, Malaysia, Singapore, and China [3, 4]. There are sporadic reports of the infection in Bangladesh as well, the first case being reported in 1961 [5].

*Correspondence:
Anik Palit
Anik.Palit@icddrb.org
[1] Infectious Diseases Division, International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), 68, Shaheed Tajuddin Ahmed Sarani, Mohakhali, Dhaka 1212, Bangladesh
[2] Global Health Development, EMPHNET, Dhaka, Bangladesh
[3] Kirby Institute, UNSW, Sydney, Australia
[4] Institute of Health and Wellbeing, Federation University, Ballarat, Australia
[5] Rangpur Medical College Hospital, Rangpur, Bangladesh

Melioidosis typically presents as a febrile illness with a wide variety of disease manifestations, which include pneumonia, septicemia, localized cutaneous infection, and chronic suppurative lesions [3, 6, 7]. Diabetes, chronic liver illness, chronic renal disease, thalassemia, cancer, and lung disorders are risk factors for melioidosis, as is exposure to contaminated soil or water and being an agricultural worker [8]. Evidence suggests *B. pseudomallei* affects individuals with diabetes three times more than individuals without diabetes [8].

This case report describes the clinical presentation and management of a patient who is diabetic and has melioidosis with lower limb venous thrombosis with cellulitis. The patient was enrolled as part of an ongoing research study called the Acute Febrile Illness (AFI) study [9]. The AFI study aims to identify circulating pathogens (bacteria, viruses, and protozoa) causing acute febrile illness in Bangladesh using different diagnostic techniques, that is, rapid diagnostic test (RDT), blood culture, urine culture, and real-time-polymerase chain reaction (RT-PCR) assay. This study enrolled eligible febrile cases admitted to the medicine and pediatric department on the basis of randomization.

Case presentation

On 13 November 2021, a 48-year-old Bangladeshi male patient with diabetes (type-2) was admitted to a public tertiary hospital in Rangpur district in Bangladesh. On admission, his chief complaints were gradually increasing left knee pain and intermittent high-grade fever for 7 days with a history of weight loss (5 kg in 3 months). He had a dry cough for 5 days but denied respiratory distress or chest pain (Fig. 1).

Upon further examination, his body temperature was recorded as 102 °F (oral) with pitting edema in the left lower limb, which was swollen, shiny, warm, and tender from mid-thigh to foot. The spleen was enlarged and palpable. The remainder of the physical examination was unremarkable.

After 2 days he developed skin lesions (Fig. 2) in the left lower limb, which was suggestive of cellulitis with further swelling of the left knee.

The patient had worked at Cox's Bazar's Forcibly Displaced Myanmar Nationals Camp for 3 years. He was assigned to visit the camps and worked during the rain and in muddy water. He quit in September 2020 owing to recurring febrile episodes. He recalled an additional exacerbation for 10–15 days in March 2021 with no history of hospitalization. He consulted with a private physician and was diagnosed with cystitis, pyelonephritis, and a perinephric abscess, which improved after antibiotic treatment (oral cefuroxime and clavulanic acid twice daily for 14 days). He became very ill in mid-November

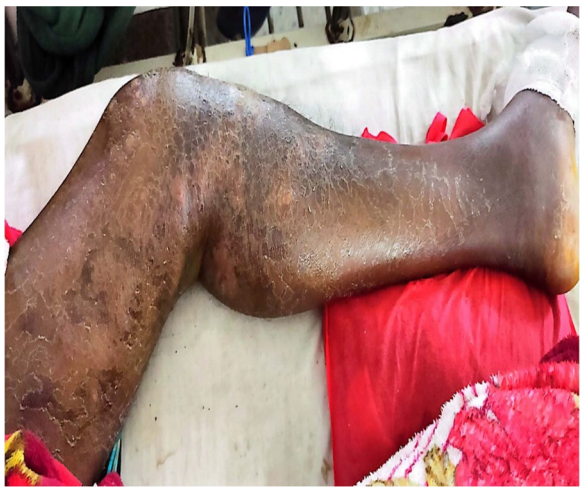

Fig. 2 Skin lesion from mid-thigh to foot

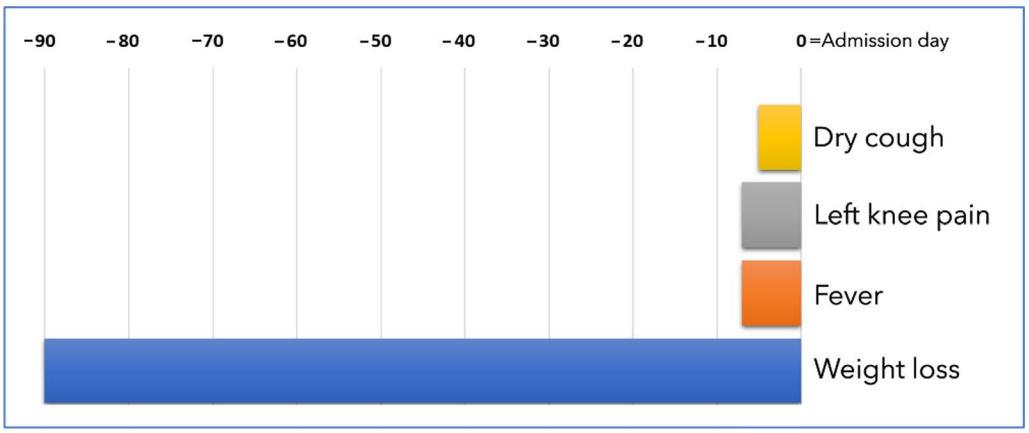

Fig. 1 Reported symptoms on admission

Table 1 Results of laboratory tests at hospital

Lists of investigation	Values	Reference values
Erythrocyte Sedimentation Rate (ESR) (mm in first hour: Westergren)	94	< 15
Hemoglobin (g/dL)	8.50	13–18
Total count: WBC (×10^9/L)	6.5	3.6–11
Neutrophil (%)	88	40–60
Lymphocyte (%)	9	20–40
C-reactive protein (mg/L)	190	< 5
Creatinine (mg/dL)	1.2	0.6–1.4
Urine Routine Examination	6–8 RBC/HPF	0–2
	Albumin (+)	Negative

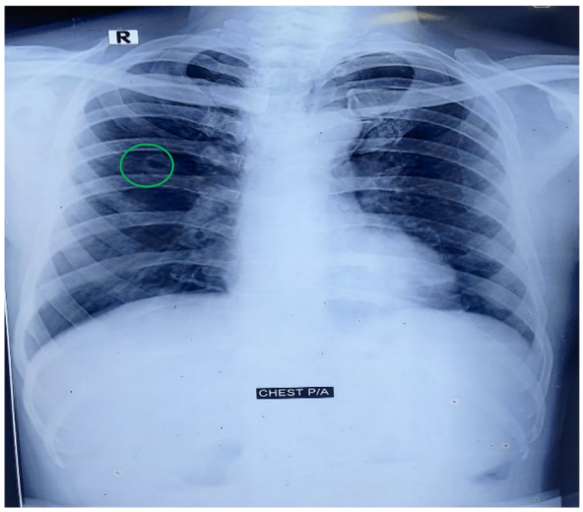

Fig. 3 Green circle in chest X-ray showing suspected cavitary lesion on right lung

2021 and was hospitalized as per the suggestion of a private physician.

After admission, complete blood count revealed high erythrocyte sedimentation rate (94 mm in the first hour) with moderate anemia (hemoglobin: 8.50 g/dL), and relative neutrophilia (total white blood cell (WBC) count: 6.5×10^9/L; neutrophils: 88%) with elevated C-reactive protein (CRP) (190 mg/L). Routine urinalysis revealed 6–8 red blood cells (RBC) per high power field (HPF) and the presence of albumin (+) (Table 1).

Chest X-ray revealed a cavitary lesion on the right lung (Fig. 3). Doppler ultrasound of the left lower limb reported superficial venous thrombosis and thrombophlebitis involving the long saphenous vein and superficial veins of saphenous territory below the knee (Fig. 4), and abdominal ultrasound revealed mild splenomegaly (15 cm) (Fig. 5). Other investigations were found to be unremarkable. The research team performed bedside RDT testing of dengue (NS1), malaria (*Plasmodium falciparum* and *Plasmodium vivax*), chikungunya (IgM and IgG), and *Leptospira* (IgM)—all were negative.

Microbiological and other investigations at icddr,b: The study team collected clinical samples on day 3 of admission, and the samples were sent to the icddr,b One Health Laboratory in Dhaka for subsequent testing. Blood culture showed growth after 5 days of incubation. Following subculture on blood agar, VITEK-2 (BioMerieux) identified the isolate as *Burkholderia pseudomallei* on day 16 of hospitalization. This considerable delay was owing to some administrative and interdepartmental procedures at icddr,b. Clinical and Laboratory Standards Institute (CLSI)-recommended Kirby-Bauer disk susceptibility testing determined antibiotic susceptibility. The isolate was sensitive to cefoperazone/sulbactam, ceftazidime, imipenem, meropenem, piperacillin/tazobactam, and

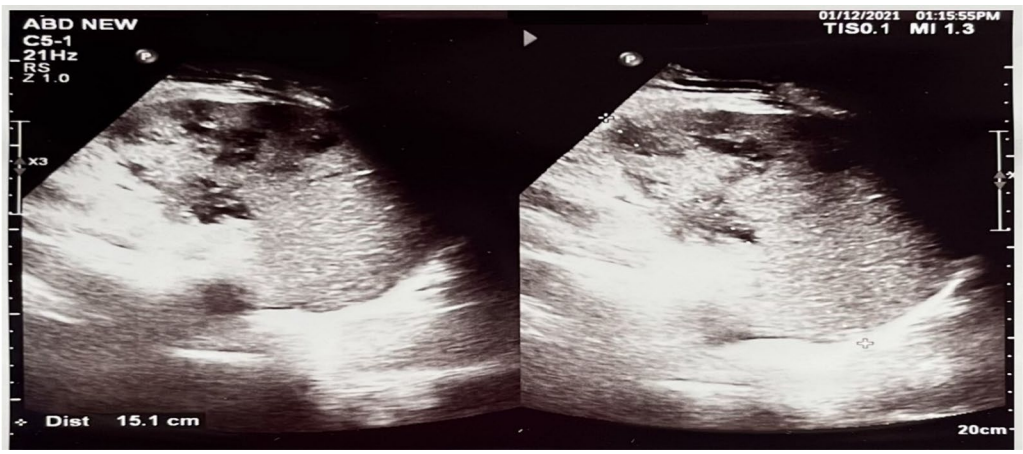

Fig. 4 Positive compressibility test denoting the presence of thrombus

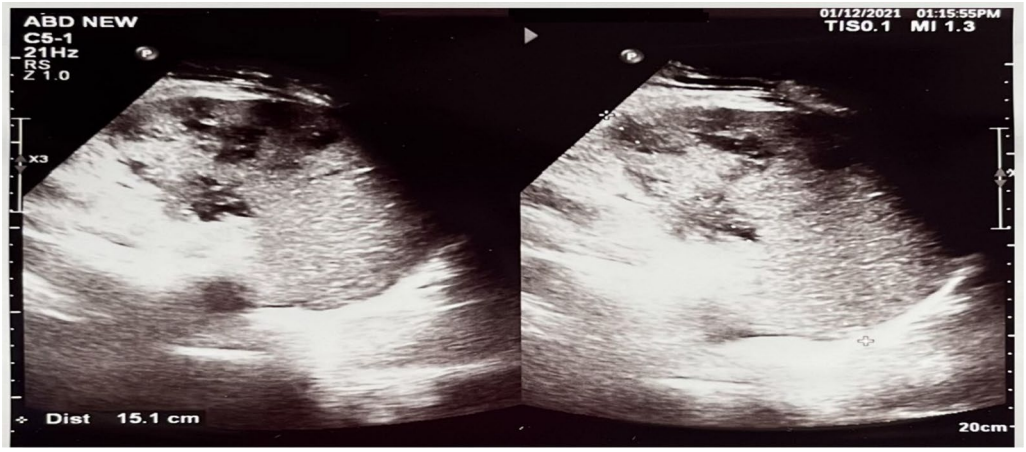

Fig. 5 Ultrasonography showing mildly enlarged spleen (15 cm)

tigecycline and resistant to amikacin, cefepime, colistin, and gentamicin. An automated ABI 3500 XL genetic analyzer (Applied Biosystems, Foster City, USA) sequenced 16S ribosomal RNA (rRNA) using separate forward and reverse primers to confirm the identification of *B. pseudomallei*. The generated sequence demonstrated an identity of 100% with the reference sequence *B. pseudomallei* K96243 (NZ_CP009538.1). The 16S-rRNA sequence of the isolate is available in the GenBank database (accession no. OR344787).

Urine culture showed no growth, and real-time RT-PCR assay for the detection of *Rickettsia* spp, *Orientia tsutsugamushi*, *Brucella*, *Coxiella burnetii*, Crimean–Congo hemorrhagic fever, hepatitis E, *Leptospira*, Zika, West Nile, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), influenza A, and influenza B was performed and all results were negative.

Treatment: Upon admission, meropenem (1 gm intravenous, 8-hourly) was administered for 21 days as empirical broad-spectrum treatment. Following *B. pseudomallei* detection on hospital day 17, doxycycline (100 mg twice daily) was added for 21 days. The fever subsided 3 days after doxycycline was started, and meropenem was discontinued. Subcutaneous human insulin (fast-acting) controlled the blood glucose.

Venous thrombi were treated with oral rivaroxaban (10 mg, twice daily). On hospital day 11, the patient developed compartment syndrome and had a fasciotomy on the dorsal left foot.

Outcome and follow-up: The fever subsided on hospital day 20 following the introduction of doxycycline. The swelling and pain in the leg subsided after 30 days. After considerable improvement, the patient was discharged after 36 days of admission. Cotrimoxazole was advised to be taken orally for 3 months during discharge. An illustration of the timeline of the current illness is shown in Fig. 6.

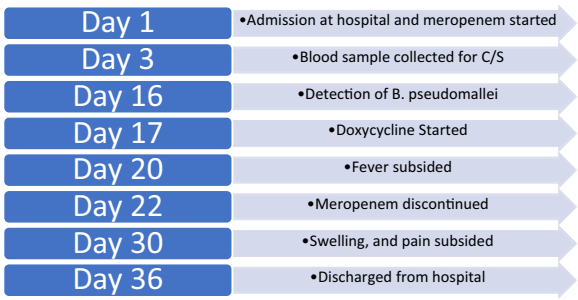

Fig. 6 Case timeline of major events

Following the discharge, periodic follow-up of the patient was performed by phone every 3 months for 1 year. The patient did not report any further serious illness or complications during this period.

Discussion

B. pseudomallei is nicknamed as "the great mimicker" because of its wide variety of nonspecific symptoms and clinical manifestations that can be mistaken for tuberculosis or other febrile illnesses prevalent in South Asia [4, 10]. Venous thrombosis is a seldom-reported manifestation of melioidosis. In 2012, Wu, Hua *et al.* [11] reported the earliest fatal known case of melioidosis-related deep vein thrombosis with pulmonary embolism in China. Globally, eight other thrombosis cases secondary to melioidosis have been reported: two dural venous sinus thrombosis [12, 13], two superior sagittal sinus thrombosis [14, 15], one transverse sinus thrombosis [16], one of both splenic and portal vein thrombosis [17], and one of each [18, 19] All these eight cases recovered well, except for one in which the patient passed away. All above

reported cases were male and four patients reported having diabetes.

Sepsis occurs in the majority of melioidosis cases [20]. Sepsis subsequently triggers the release of cytokines (TNF-alpha, interleukin-1, and interleukin-6), leading to endothelial injury and reduction of natural endothelial modulators (protein C, protein S, and antithrombin), causing microvascular thrombosis, organ failure, and death [21]. Diabetes also contributes to the formation of thrombi, because hyperglycemia impairs antithrombin secretion [22]. The patient was both diabetic and septic, which may have contributed to the development of thrombosis. Early detection of melioidosis-associated thrombosis with timely initiation of anticoagulant therapy and glycemic control can be lifesaving. It was interesting to see that despite the pathogen being sensitive to meropenem as per antimicrobial susceptibility testing (AST), the patient's condition did not improve with meropenem administration.

Despite having the most cases in South Asia, Bangladeshi physicians and microbiologists lack knowledge and awareness of melioidosis, which may lead to underdiagnosis [10]. The present case was diagnosed after 16 days of hospitalization and on day 23 from symptom onset. Chowdhury, Fazle Rabbi, *et al.* [5] reported that the median period between symptom onset and the diagnosis was 36 days (interquartile range (IQR): 18.75–79.5 days) among the 38 *B. pseudomallei* cases confirmed by culture in Bangladesh. Delay in diagnosis is also associated with poor outcomes.

Owing to a lack of diagnostic facilities, colonies of *B. pseudomallei* are often misidentified as "*Pseudomonas* spp" and discarded as environmental contaminants in South Asia, including Bangladesh [4, 10]. Among various selective media for the isolation of *B. pseudomallei*, Ashdown's medium is best in terms of sensitivity and specificity [23]. Gupta, Abhishek Prakash, *et al.* also suggested the use of Ashdown's medium for improved isolation, and in resource-poor settings, microbiologists can consider biochemical reaction techniques described in this case report to both confirm melioidosis and avoid misidentification [7]. In Bangladesh, most diagnosed melioidosis cases have been detected and treated at BIRDEM, a tertiary-level private hospital [5].

When melioidosis is suspected, appropriate antibiotics may be life-saving. The 2020 Revised Darwin melioidosis guideline recommends intravenous antibiotics (ceftazidime, meropenem, or imipenem) for 3–4 weeks during the intensive phase, followed by oral trimethoprim-sulfamethoxazole for a minimum of 3 months in the eradication phase [24]. In the present case, meropenem was started on the day of admission and continued for 3 weeks, but owing to limited resources in the hospital setting, the accurate diagnosis occurred 16 days later. Late diagnosis, delayed antibiotic treatment, and lack of intensive care may increase mortality by 40% in resource-poor endemic regions [6]. A recent study tested the CRISPR-BP34 diagnostic test assay in a resource-limited setting in northeast Thailand. It achieved a diagnostic sensitivity of 93% and specificity of 96·8%, with the result being obtained within 4 h to 1 day from different types of specimens. [25]. Another study based on the 4-plex dipstick assay achieved 92% sensitivity and up to 100% specificity [26]. Both studies are based on rapid tests, and early diagnosis is possible, which will ultimately aid in the early initiation of antibiotic treatment and will finally contribute to preventing mortality and reducing hospital stays in endemic regions.

Conclusion

This case of melioidosis was detected as a part of a research study. The treating hospital did not have the laboratory capacity to diagnose melioidosis in the clinical setting. This case illustrates the importance of exploratory research studies of infectious diseases and calls for the expansion of such studies at a larger scale, enabling the health system to identify conditions caused by rare or unusual pathogens in addition to what is already considered locally endemic. Physician training is essential to improve knowledge and awareness about the clinical diagnosis and management of melioidosis. In addition, appropriate diagnostic tools for a low-resource setting should be made available to aid early management of the infection.

Abbreviations

WBC	White blood cell
RBC	Red blood cell
CRP	C-reactive protein
HPF	High power field
TNF	Tumor necrosis factor
IQR	Interquartile range
BIRDEM	Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders
icddr,b	International Centre for Diarrhoeal Disease Research, Bangladesh
AST	Antimicrobial susceptibility testing

Acknowledgements

We express our gratitude to the patient, who kindly gave consent for his case to be presented in this paper. In addition, icddr,b is grateful to the Governments of Bangladesh and Canada for providing core support.

Author contributions

MR, ZA, and TAS made substantial contributions to the conception and design of the manuscript, and AP drafted the manuscript. MZR and MA supervised the laboratory activities during the identification process through blood culture and sequencing. ASD isolated the bacteria from the culture, and MMR performed the 16S ribosomal RNA sequencing. MMR from Rangpur Medical College Hospital was involved in patient care. SC, PD, FC, and TAS were involved in the extensive review of the manuscript. All authors contributed to the case report and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
This case report is produced from an ongoing research study by icddr,b. The protocol was approved by both the Ethics Review Committee and Research Review Committee of icddr,b. Before enrollment into the study, written informed consent was obtained.

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

Competing interests
The authors declare that they have no competing interests.

Received: 22 May 2024 Accepted: 12 March 2025
Published online: 09 April 2025

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