Trimethoprim/sulfamethoxazole Resistant *Burkholderia pseudomallei* in a Filipino Patient with Diabetes Mellitus: A Case Report

Princess Aurea L. Maderazo, MD,[1] Arthur Dessi E. Roman, MD,[2] and Karla Kristine S. Fernando, MD[3]

Abstract

Background: Melioidosis is an infectious disease caused by *Burkholderia pseudomallei*. It is endemic in the Philippines and is underreported. Of the reported cases, the most common comorbidity is diabetes mellitus. The increasing cases of antibiotic resistance and the relatively high mortality rate highlights the need for increased awareness among clinicians regarding this disease. We aim to report a case of *Burkholderia pseudomallei* resistant to trimethoprim/sulfamethoxazole (TMP-SMX), used in its eradication following initial intravenous therapy.

Case Presentation: A 51-year-old male Filipino with poor health-seeking behavior came with generalized body weakness, weight loss, dysarthria, fever, cough, difficulty breathing, bloatedness, dysuria, joint pains, and bilateral lower extremity hyperpigmented macules for four months. He has diabetes mellitus and hypertension and is a mechanic by trade. Initial workups revealed hemoglobin A1c (HbA1c) of 14.7%, and urinalysis with bacteriuria. Imaging revealed bilateral pneumonia on chest xray, hepatosplenomegaly on whole abdomen ultrasound, and old cerebral infarcts on cranial computed tomography scan (CT scan). Empiric antibiotics for the impression of sepsis from community-acquired pneumonia and urinary tract infection were ertapenem and azithromycin. Upon isolation of *Burkholderia pseudomallei* from blood cultures, the team shifted to TMP-SMX and ceftazidime for initial therapy of melioidosis. Sensitivity showed resistance to TMP-SMX; hence the team revised the antimicrobials to four weeks of levofloxacin and ceftazidime. After eleven hospital days, the team sent the patient home, clinically improved. The team continued levofloxacin for eradication therapy for three months and the patient responded well.

Conclusion: Fever with multi-system involvement in a Filipino patient with diabetes mellitus with significant environmental risk factors, poor glycemic control, splenomegaly, and treatment failure with appropriate empiric antibiotic therapy should raise suspicion for melioidosis. It is paramount that antimicrobial resistance be detected and documented upon isolation of *Burkholderia pseudomallei*, given the high relapse rates and the need for a prolonged duration of treatment.

Keywords: Melioidosis, Philippines, Diabetes Mellitus, *Burkholderia pseudomallei*, Trimethoprim/sulfamethoxazole

Introduction

Melioidosis, also called Whitmore's Disease, was first described by Whitmore and Krishnaswami in 1912 in Rangoon, Myanmar Burma. Melioidosis has become a global concern, and is predominantly found in the tropical and subtropical areas, including the Philippines.[1] The first reported case of melioidosis in the Philippines occurred in 1945.[2] Since then, there have been sporadic reports of melioidosis in the Philippine literature. Among these, the most common comorbidity is diabetes mellitus. A mean age of 50.2 years is seen, with males affected more than females. Blood cultures commonly yielded positive results. Despite mostly improved outcomes, there are still cases of relapse and death. The reported mortality rate of melioidosis in the Philippines is 14.6 %, with a case fatality rate suggested to be 50%.[1,3]

True resistance to Trimethoprim/sulfamethoxazole (TMP-SMX), a key antimicrobial in melioidosis, remains exceedingly rare.[4] The increasing cases of antibiotic

[1] Resident In-Training, Department of Internal Medicine, Manila Doctors Hospital
[2] Research Consultant, Section of Infectious Disease, Department of Internal Medicine, Manila Doctors Hospital
[3] Research Consultant, Section of Endocrinology, Department of Internal Medicine, Manila Doctors Hospital
Corresponding author: Princess Aurea L. Maderazo, MD eMail: maderazo.princess@yahoo.com

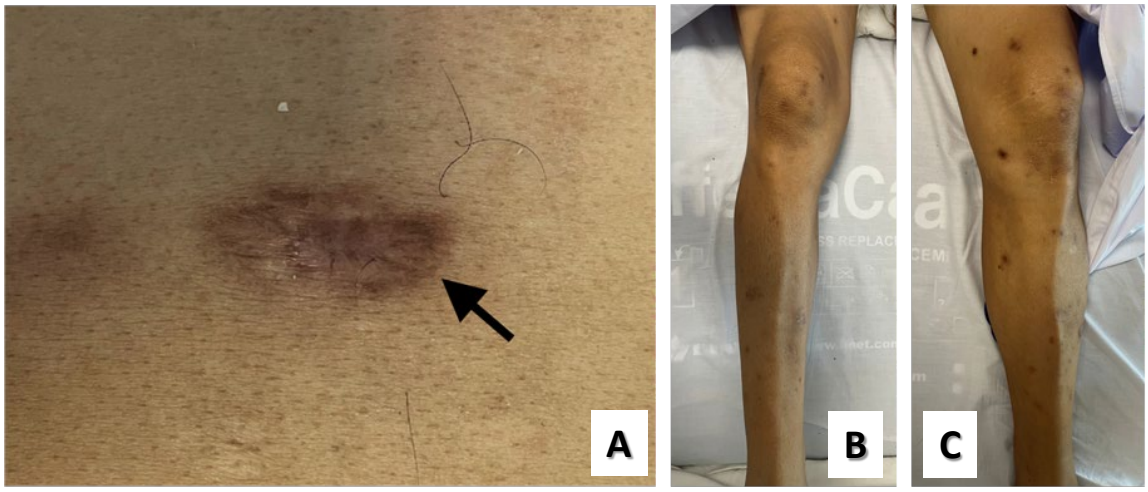

Figure 1. Lesions of the patient upon admission: multiple hyperpigmented circular ill-defined non-pruritic macules on the abdomen (A) and bilateral lower extremities (B, C) ~2-4 cm.

resistance and the relatively high mortality rate highlights the need for increased awareness among clinicians regarding this disease. Hopefully, this will lead to earlier clinical diagnosis, increased effort to develop a microbiologic diagnosis, better disease surveillance, antimicrobial resistance monitoring, and prompt initiation of appropriate antibiotics. This study aims to report a case of TMP-SMX-resistant *Burkholderia pseudomallei* in the Philippines, highlighting the urgent need for improved management strategies in response to evolving antibiotic resistance.

Case Presentation

A 51-year-old male Filipino power plant mechanic from Manila, with hypertension and poorly controlled type 2 diabetes mellitus, presented with generalized weakness. He had a history of non-compliance with medications and occasional alcohol consumption. Four months before admission, he had febrile episodes, reduced appetite, and hyperpigmented macules on both lower extremities. A week before admission, he had weakness, weight loss, dry cough, breathing difficulty, hiccups, bloatedness, dysarthria, and joint pains. Chest x-ray revealed bilateral pneumonia, and a complete blood count showed leukocytosis with neutrophilic predominance, leading to treatment for community-acquired pneumonia with amoxicillin/clavulanate 375 mg/tablet thrice daily. Hemoglobin A1c was 14.7%; hence, treatment with linagliptin and insulin glargine was started. A day before admission, he arrived at our institution due to worsening weakness, slow responses, dysuria, and urination difficulties.

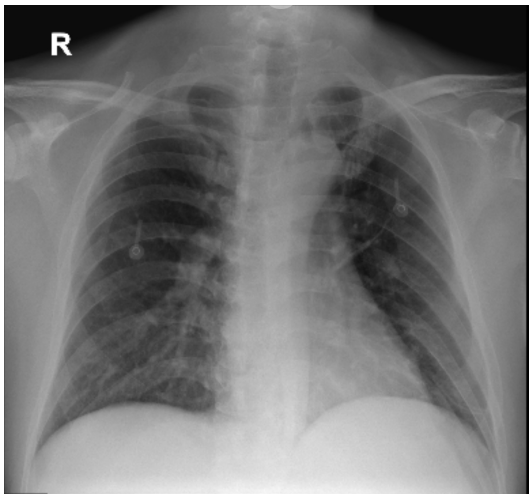

Figure 2. Chest x-ray of the patient showed bilateral lower lobe pneumonia.

Physical examination revealed tachycardia, tachypnea, fever, pallor, dehydration, drowsiness, left facial asymmetry, left uvula deviation, bilateral crackles, abdominal distension, hepatosplenomegaly, and hyperpigmented macules on the abdomen and bilateral lower extremities (*Figure 1*). Initial sepsis workup revealed chest x-ray with bilateral pneumonia (*Figure 2*), CBC with leukocytosis with neutrophilic predominance, elevated creatinine with an estimated glomerular filtration rate (eGFR) of 13 mL/min, and urinalysis with bacteriuria; hence, sepsis from community-acquired pneumonia and complicated urinary tract infection, and acute kidney injury were the primary impression. Initial antimicrobials include ertapenem 500 mg intravenously every 24 hours and azithromycin 500 mg/tablet once daily. The initial blood glucose level was 224 mg/dL. On urinalysis, there was glucosuria, but no ketonuria. The computed serum osmolality was 262 mOsm/kg, hence diabetic ketoacidosis and hyperosmolar hyperglycemic state was ruled out. Insulin glargine was started for elevated blood glucose levels.

Initial blood cultures grew *Burkholderia pseudomallei*, and whole abdomen ultrasound showed splenomegaly. Ertapenem and azithromycin were shifted to trimethoprim/sulfamethoxazole 800/160 mg/tablet two tablets twice daily and ceftazidime 2 g intravenously

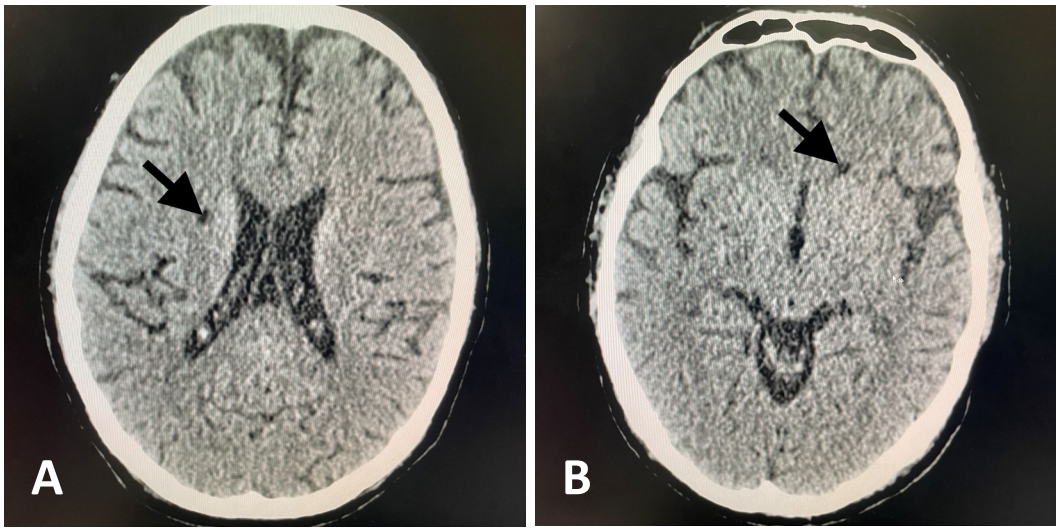

Figure 3. Cranial computed tomography scan showed old infarcts in the right corona radiata (A) and lentiform nucleus (B).

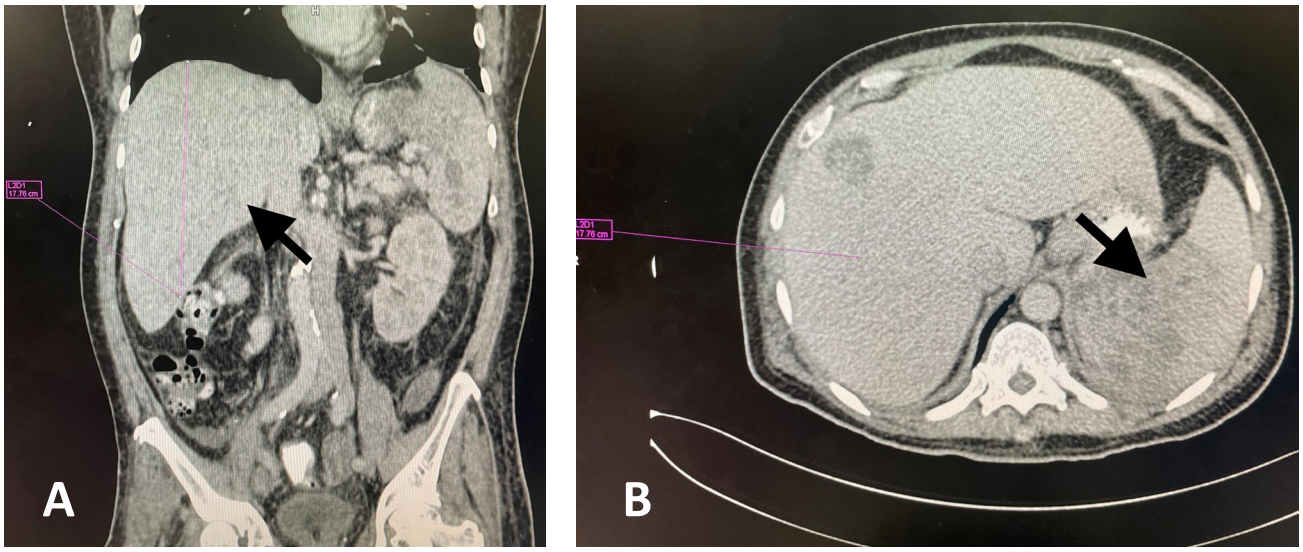

Figure 4. Whole abdomen computed tomography scan with oral, rectal, and intravenous contrast showing hepatomegaly (A) and splenomegaly (B).

every twelve hours for melioidosis. The patient remained drowsy, but with sustained eye opening, and acute cerebrovascular disease had to be ruled out. Accordingly, a cranial computed tomography scan (CT scan) revealed chronic infarcts (*Figure 3*). With increased creatinine trends and decreased urine output, hemodialysis for acute kidney injury was performed.

A whole abdomen CT scan excluded intra-abdominal abscess but showed hepatosplenomegaly (figure 4 A). Final blood cultures showed resistance of *Burkholderia pseudomallei* to TMP-SMX, leading to a switch to levofloxacin 750 mg intravenously every forty-eight hours and ceftazidime. A lumbar tap revealed elevated protein and normal glucose in cerebrospinal fluid, but no growth in culture.

After eleven days of hospitalization and improved condition, the patient was discharged with a diagnosis of sepsis due to melioidosis pneumonia and acute kidney injury. He was advised to complete four weeks of levofloxacin 750 mg/tablet once every forty-eight hours and ceftazidime 2 g intravenously every twenty-four hours as outpatient antibiotic therapy, followed by continuation of levofloxacin for another three months.

Ten months post-discharge, upon follow up and completion of the prescribed antimicrobials, the patient is doing well.

Discussion

Burkholderia pseudomallei, a gram-negative aerobic bacillus with a distinctive "safety pin" staining pattern, is responsible for melioidosis. This bacterium thrives in soil and surface water, particularly in tropical regions like the Philippines.[5] Our patient, a mechanic at a power plant, may have contracted melioidosis through

occupational exposure to soil and water or inhalation during monsoonal rainfall.

Diabetes mellitus is a leading cause of death in the Philippines.[6] It weakens the immune system and thus increases susceptibility to infectious diseases. Patients with HbA1c > 8.5% have significant phagocytosis impairment and less efficient killing or inactivation of *Burkholderia pseudomallei*.[7] Our patient's uncontrolled diabetes, reflected in an HbA1c of 14.7%, heightened his risk for severe infections and complications. Compliance with treatment and glycemic control are crucial in reducing infection risks.

Melioidosis, as the great mimicker, can manifest in various organs, with pneumonia being the most common presentation.[5] The spleen and liver are frequently affected, presenting as abscesses.[8] Our patient exhibited hepatosplenomegaly with no abscess on whole abdomen CT scan. Melioidosis can also present as skin ulcers or abscesses, septic arthritis, or osteomyelitis. Our patient presented with skin lesions, which suggests a potential inoculation site.

A definitive melioidosis diagnosis requires a positive *Burkholderia pseudomallei* culture. Disk diffusion testing, despite its affordability, may overestimate TMP-SMX resistance, necessitating verification with the Epsilometer test (E-test) because of its ability to estimate the minimum inhibitory concentration (MIC). Thus, true resistance to TMP-SMX in *Burkholderia pseudomallei* is extremely rare.[4] The microbiology laboratory at our institution used both the disk diffusion and E-test for antibiotic sensitivity and yielded TMP-SMX resistance for *Burkholderia pseudomallei* on the final blood cultures. Therefore, our patient has true resistance to TMP-SMX.

Ceftazidime for ten to fourteen days is the preferred initial treatment for melioidosis, which can be supplemented with TMP-SMX for tissue penetration. Eradication therapy involves TMP-SMX monotherapy or alternatives such as amoxicillin/clavulanate, quinolones, doxycycline, or chloramphenicol.[5] Our patient initially received TMP-SMX and ceftazidime, subsequently switched to levofloxacin and ceftazidime due to TMP-SMX resistance. Treatment duration, per the 2020 Revised Darwin Melioidosis Guidelines, typically spans three to eight months, with longer intravenous therapy for extensive cases.[9] Our patient received four weeks of initial therapy with levofloxacin and ceftazidime, and three months of eradication therapy with levofloxacin.

Conclusion

Melioidosis is endemic in the Philippines and is underreported. Fever with multisystem involvement in a patient with diabetes mellitus with significant environmental risk factors should raise suspicion for melioidosis, especially when there is splenomegaly and treatment failure with appropriate empiric antibiotics. Detection and monitoring of resistance among antimicrobials used against *Burkholderia pseudomallei* are important given the high relapse rates and a need for prolonged antimicrobial treatment in melioidosis.

Conflict of Interest. The authors declare no conflict of interest.

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Ethical Statement. The patient gave his informed consent before he participated in our study. This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Manila Doctors Hospital Institutional Review Board (IRB).

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