Neuromeliodosis: A Rare Case Report Highlighting, the Need of Long Intensive Phase Therapy

Samhita Ankala[1]*, Thomas John[2] and Binoj Varghese[3]

[1]Amala Institute of Medical Sciences

[2]Head of Department and Professor Department of Neurology

[3]Professor Department of Radiodiagnosis

Received: 17 May 2023

Accepted: 13 July 2023

*Corresponding author: ankalasamhita@gmail.com

DOI 10.5001/omj.2025.14

Abstract

Neuromeliodosis is a rare CNS manifestation of melioidosis, a multi-system involving disease, caused by Burkholederia pseudomallei. The disease is endemic to tropical regions with like Southeast Asian countries, and Indian subcontinent and has high mortality and morbidity. We report a case of a 37 year old man who had disseminated melioidosis with severe CNS involvement with radiological demomstration of spread along white matter tracts. We highlight the importance of a prolonged intensive phase therapy in order to achieve clinical remission and prevent relapses.

Keywords: Neuromeliodosis; Meliodosis; Burkholderia Pseudomallei.

Introduction

Melioidosis is an infectious disease caused by the soil saprophytic gram-negative bacillus Burkholderia pseudomallei. It is endemic to Southeast Asia and Northern Australia, with increasing reports of imported cases in non-endemic areas like the Middle East due to global travel[1]. Melioidosis commonly causes pneumonia, bacteremia, deep-seated abscesses, and skin infections but can affect any organ[2]. Diabetes mellitus and excessive alcohol consumption are reported as common risk factors for melioidosis [3]. Although uncommon, neurological manifestations have been reported in 3% to 5% of cases[3, 4, 7]. Neuromelioidosis carries a mortality rate of approximately 25% [3-7] with significant morbidity among survivors [6, 7].

Burkholderia pseudomallei is intrinsically resistant to several antibiotics [8, 9]. Unlike other bacterial infections, melioidosis requires an intensive phase of intravenous antibiotic treatment followed by a prolonged oral eradication phase to prevent relapse[10, 11]. Ceftazidime and meropenem are recommended for the intensive phase, while co-trimoxazole or amoxicillin/clavulanic acid combination is used for the eradication phase. However, the preferred antibiotic for the treatment of neuromelioidosis is meropenem [10, 11], along with oral co-trimoxazole for eradication treatment[10, 11]. CDC guidelines for neuromelioidosis treatment recommend an initial intensive phase of high-dose meropenem (2g intravenous every eight hours) for 4-8 weeks, followed by eradication therapy with co-trimoxazole 160 mg/800 mg tablets: 2 tablets every 12 hours for at least 6 months [10].

In this case report, we present a patient with disseminated melioidosis with neurological involvement who had multiple relapses despite receiving repeated courses of proper treatment as per the CDC guidelines. Neuroimaging during relapses demonstrated progressive dissemination along white matter tracts in spite of being on eradication treatment. However, with an extended period of intensive intravenous (IV) meropenem treatment, the patient eventually achieved recovery.

Case Report

A 37-year-old gentleman from a coastal area of Kerala, India, presented to the emergency services with a sudden onset of left hemiplegia and left focal motor seizures. He worked as an agricultural laborer in wet paddy fields. He had a history of alcohol addiction but was a non-smoker. He was a diabetic on irregular treatment but had no significant pre-existing illnesses such as chronic lung, kidney, or liver diseases or HIV infection. There was no history of steroid or other immunosuppressive drug use. Additionally, there was no history of recent injury or broken skin in the extremities. Physical examination revealed emaciation, with a body weight of 54 kg and a height of 165 cm, resulting in a body mass index (BMI) of 19.8 kg/m^2. He was also found to be febrile and had right knee joint arthritis. An immediate non-contrast-enhanced MRI brain showed areas of patchy diffusion restriction with corresponding low Apparent Diffusion Coefficient (ADC) values in the right fronto-parietal cortex. Surrounding T2 FLAIR hyperintensity suggestive of edema was present in the adjacent white matter with extension to the thalamocapsular region. Ultrasonography of the abdomen revealed hepatosplenomegaly, prostatomegaly with abscess formation, and multiple splenic microabscesses [Figure 1-A to G]. Culture of his right knee aspirate yielded Burkholderia pseudomallei. However, the blood culture was negative.

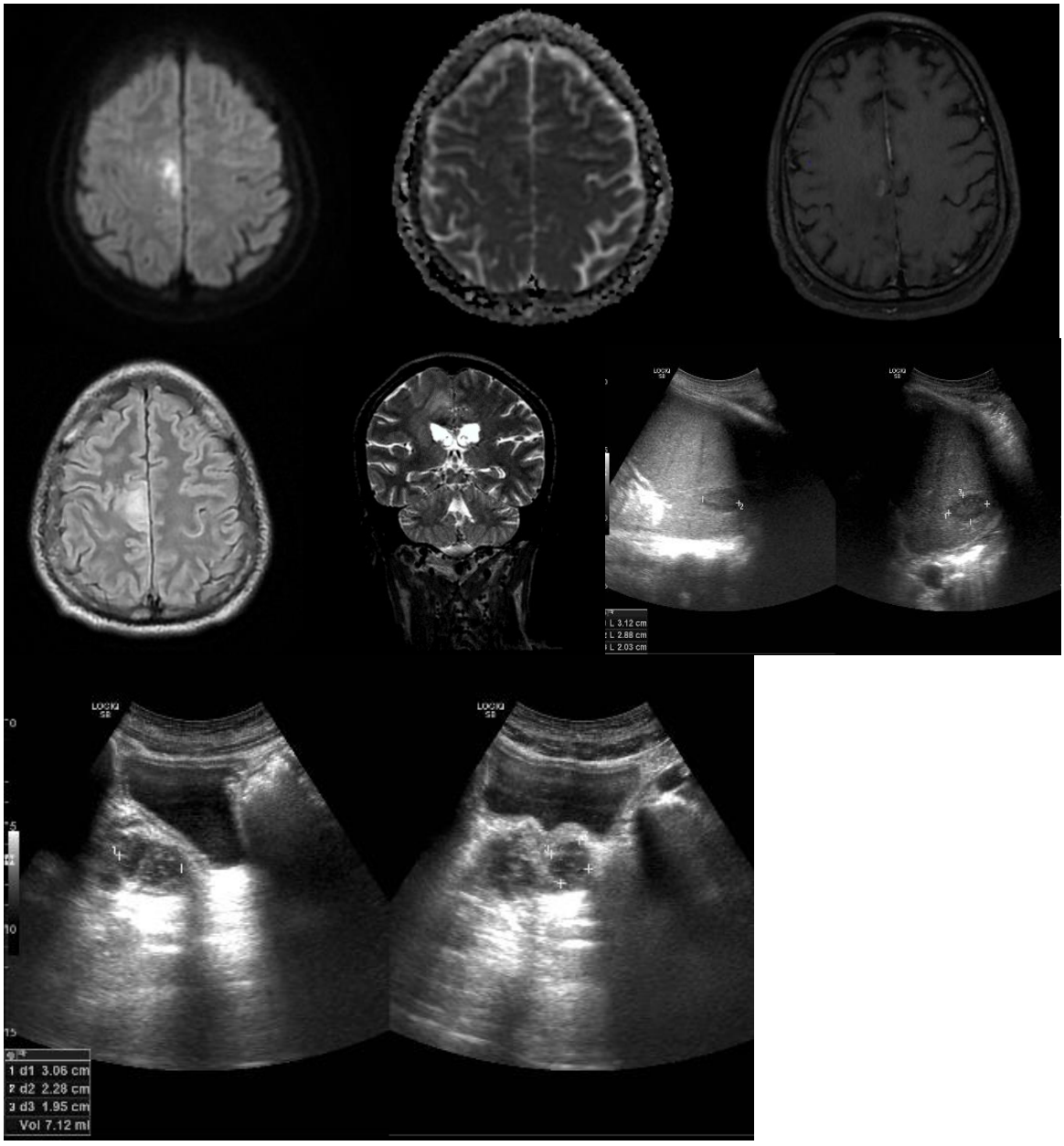

Figure 1: Ultrasonography of the abdomen revealed hepatosplenomegaly, prostatomegaly with abscess formation, and multiple splenic microabscesses.

With a diagnosis of disseminated melioidosis with central nervous system (CNS) involvement, he was started on intensive treatment with intravenous (IV) meropenem 2g every eight hours, along with oral co-trimoxazole (800mg sulfamethoxazole and 160mg trimethoprim). By the second week, he improved and became afebrile, but left hemiplegia persisted. Intensive treatment with IV meropenem was discontinued after 4 weeks, and eradication treatment with co-trimoxazole was continued. The patient was discharged to a rehabilitation facility.

However, one month later, while still on oral co-trimoxazole, the patient presented with fever, headache, recurrent left focal motor seizures, and eventually fell into a coma, necessitating mechanical ventilation. Repeat contrast-enhanced MRI (CE-MRI) of the brain showed irregular streak-like enhancing areas with surrounding edema, starting in the precentral gyrus of the right frontal lobe and extending to the posterior limb of the internal capsule and to the midbrain via the cerebral crus. It was noted to cross the midline at the level of the red nucleus. This irregular enhancement was also noted to involve the superior cerebellar peduncle [Figure 2]. Blood culture was repeated but yielded no growth. Intensive treatment with IV meropenem and oral co-trimoxazole was resumed, resulting in gradual improvement, resolution of seizures, and extubation after four weeks. Since then, he remained fully conscious, but had residual left hemiplegia as his only deficit. After receiving a total of eight weeks of IV meropenem, it was stopped, but he continued on oral co-trimoxazole.

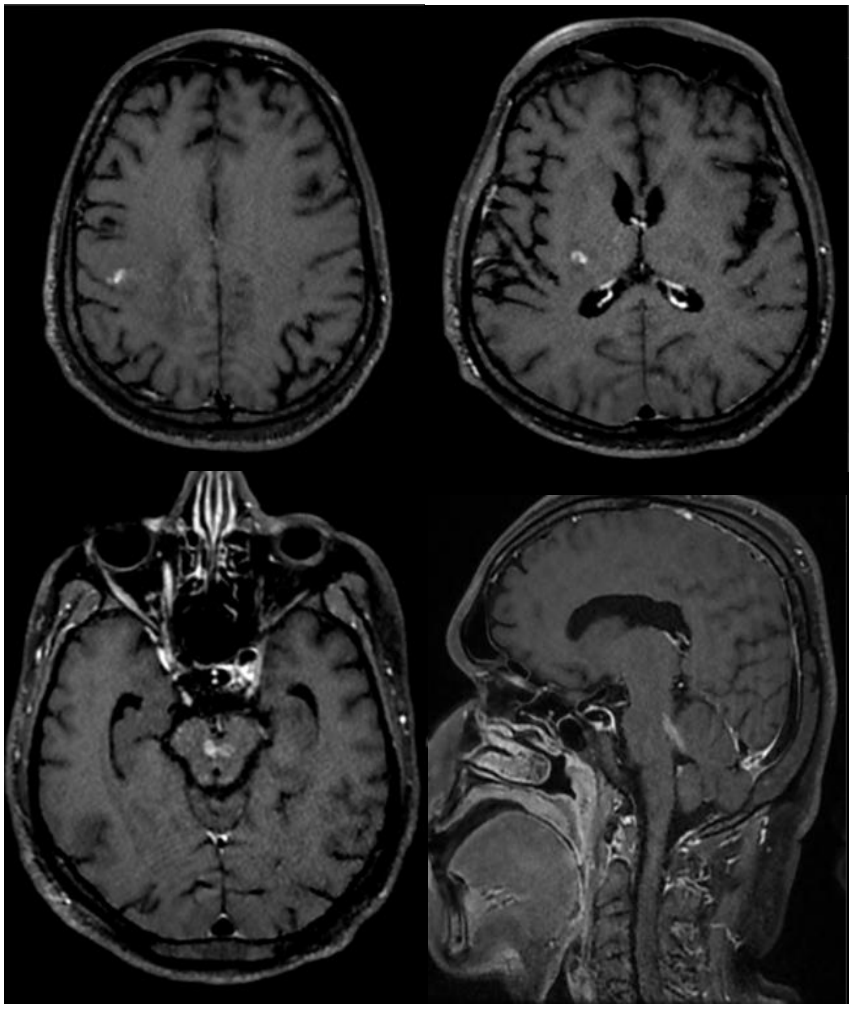

Figure 2: Contrast enhance MRI of the brain.

Despite being on eradication treatment, the patient encountered another relapse two months later, presenting with headache and left focal motor seizures. A repeat CE-MRI of the brain showed similar findings to the previous study, with additional edema in the ventral aspect of the medulla (more affected on the right side), which extended to the upper cervical cord, affecting the right spinothalamic and left lateral corticospinal tracts [Figure 3]. A third course of intensive treatment with IV meropenem, along with co-trimoxazole, was initiated, eventually leading to

good recovery. IV meropenem was continued for another 8 weeks. At 18 months from symptom onset (10 months after stopping the third course of intensive IV meropenem treatment), the patient demonstrated only slight disability (modified Rankin scale: 2) and was able to walk with minimal support. Although unable to return to his previous job due to residual left hemiparesis, the patient remains symptom-free and is on regular outpatient follow-up. Financial constraints prevented a repeat MRI imaging.

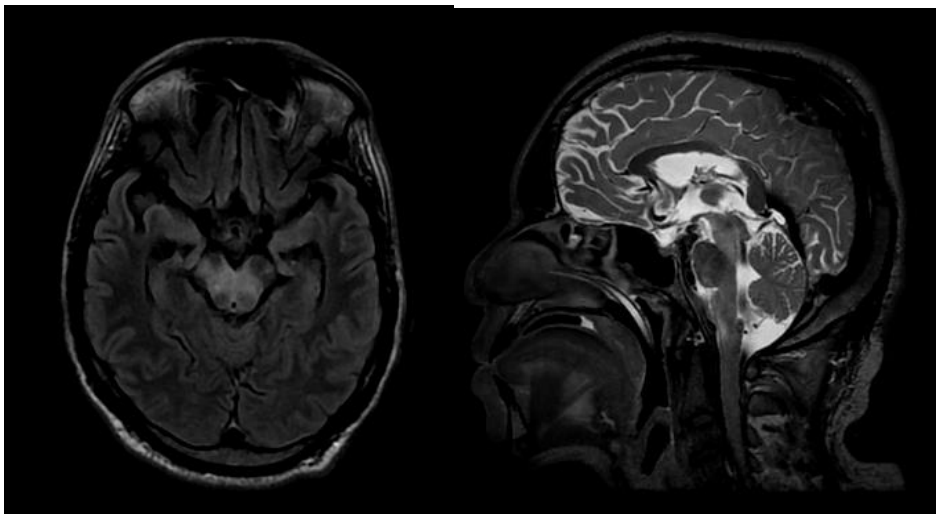

Figure 3: Repeated contrast enhance MRI.

Discussion

Our patient had culture-proven Burkholderia pseudomallei infection with dissemination into the central nervous system (CNS). The spread of CNS infection is believed to occur through either bacteremia or retrograde axonal transmission along the olfactory and trigeminal nerves [12, 13]. In our case, the patient exhibited a stroke-like presentation with diffusion restriction in the right perirolandic regions, likely due to hematogenous dissemination via the middle cerebral artery. Subsequent MRI evaluations revealed dissemination along the descending corticospinal and cerebellar tracts to the brainstem and upper spinal cord.

Neuromelioidosis is often described as an infective tractopathy, and the affinity of B. pseudomallei for white matter tracts, specifically the corticospinal tract, through the formation of multiple microabscesses, is well-documented [3, 14]. A wide range of imaging presentations has been reported in neuromelioidosis [5,14,15]. Solitary or multiple intracranial macroabscesses, frequently with cerebritis, are commonly seen, and they appear on MRI as ring-enhancing lesions with diffusion restriction and low ADC values. Extradural/dural disease with overlying calvarial involvement and scalp-based collections, marrow edema with enhancement, and leptomeningeal disease presenting as leptomeningeal thickening and enhancement are also rarely reported[5,14,15].

Despite receiving repeated courses of intensive treatment with IV meropenem following CDC guidelines [14], our patient suffered multiple clinical relapses. Radiological evidence of white matter dissemination was demonstrated even during proper oral eradication treatment. Currently, meropenem is the preferred drug for neuromelioidosis due to its rapid bactericidal effect, longer post-antibiotic effects, lower toxicity compared to ceftazidime, and lower incidence of treatment failure[16]. There have been no reports of primary or acquired resistance to meropenem in B. pseudomallei [9]. However, our patient required a total of 20 weeks of intensive meropenem treatment to achieve a complete cure.

As a facultative intracellular pathogen, B. pseudomallei can evade the host's immune response, particularly in immunocompromised patients. The suppressed immune activation associated with diabetes mellitus and alcoholism in our patient may have allowed the bacteria to persist in intracellular locations and disseminate through white matter tracts[17-19]. Such patients may require an extended period of intensive-phase antibiotic therapy, as in our case, to prevent relapses. Researchers from Darwin, Australia, have stressed the importance of the intensive phase treatment, recommending at least 8 weeks of IV meropenem and suggesting the possibility of extension based on disease severity and clinical course [11]. Previous studies have emphasized the intensive phase for preventing mortality and the importance of oral eradication treatment to prevent relapse [20, 21]. However, our

case highlights the need for a more extended intensive therapy period to achieve recovery and prevent relapses, raising questions about the efficacy and necessity of oral eradication treatment.

Conclusion

Our patient encountered multiple relapses despite receiving repeated courses of the recommended intensive treatment with meropenem. However, eventual recovery was achieved through an extended period of intensive treatment using the same antibiotic. This case highlights the critical need for a more prolonged intensive phase treatment with meropenem in cases of protracted neuromelioidosis, which has not been adequately addressed in previous studies. Furthermore, we observed multiple relapses with radiological deterioration despite the administration of eradication treatment, raising concerns regarding the effectiveness and necessity of oral eradication therapy. Further research is needed to determine the optimal duration of the intensive phase and assess the necessity of the eradication phase. Our case demonstrates the potential for good functional recovery and cure with prolonged intensive-phase meropenem treatment.

References

1. Tamtami NA, Al et al. Imported case of melioidosis in Oman: case report. Oman Med J. 2017;32(1):62-65. doi:10.5001/omj.2017.11

2. White NJ. Melioidosis. Lancet. 2003;361(9370):1715-1722.

3. Currie BJ, et al. The epidemiology and clinical spectrum of melioidosis: 540 cases from the 20-year Darwin prospective study. PLoS Negl Trop Dis. 2010;4(11):e900. doi:10.1371/journal.pntd.0000900

4. Kingsley PV, et al. Melioidosis in Malaysia: a review of case reports. PLoS Negl Trop Dis. 2016;10(12):e0005182. doi:10.1371/journal.pntd.0005182

5. Mannam P, et al. Neuromelioidosis: a single-center experience with emphasis on imaging. Indian J Radiol Imaging. 2021;31(1):57-64. doi:10.1055/s-0041-1729125

6. Wongwandee M, Linasmita P. Central nervous system melioidosis: a systematic review of individual participant data of case reports and case series. PLoS Negl Trop Dis. 2019;13(4):e0007320. doi:10.1371/journal.pntd.0007320

7. Currie BJ, et al. Neurological melioidosis. Acta Trop. 2000;74(2-3):145-151. doi:10.1016/s0001-706x(99)00064-9

8. Wiersinga WJ, et al. Melioidosis. Nat Rev Dis Primers. 2018;4:17107. doi:10.1038/nrdp.2017.107

9. Schweizer HP. Mechanisms of antibiotic resistance in Burkholderia pseudomallei: implications for treatment of melioidosis. Future Microbiol. 2012;7(12):1389-1399. doi:10.2217/fmb.12.116

10. Lipsitz R, et al. Workshop on treatment of and postexposure prophylaxis for Burkholderia pseudomallei and B. mallei infection, 2010. Emerg Infect Dis. 2012;18(12):e2. doi:10.3201/eid1812.120638

11. Pitman MC, et al. Intravenous therapy duration and outcomes in melioidosis: a new treatment paradigm. PLoS Negl Trop Dis. 2015;9(3):e0003586. doi:10.1371/journal.pntd.0003586

12. John JA, et al. Burkholderia pseudomallei penetrates the brain via destruction of the olfactory and trigeminal nerves: implications for the pathogenesis of neurological melioidosis. MBio. 2014;5(1):e00025. doi:10.1128/mBio.00025-14

13. Liu PJ, Chen YS, Lin HH, et al. Induction of mouse melioidosis with meningitis by CD11b+ phagocytic cells harboring intracellular B. pseudomallei as a Trojan horse. PLoS Negl Trop Dis. 2013;7:e2363. doi: 10.1371/journal.pntd.0002363

14. Hsu CC, Singh D, Kwan G, Deuble M, Aquilina C, et al. Neuromelioidosis: craniospinal MRI findings in Burkholderia pseudomallei infection. J Neuroimaging. 2016;26(1):75-82. doi: 10.1111/jon.12282

15. Hsu CC-T, Singh D, Watkins TW, Kwan GNC, Skalski M, et al. Serial magnetic resonance imaging findings of intracerebral spread of listeria utilising subcortical U-fibres and the extreme capsule. Neuroradiolo J. 2016;29(6):425-430. doi: 10.1177/1971400916665384

16. Cheng AC, et al. Outcomes of patients with melioidosis treated with meropenem. Antimicrob Agents Chemother. 2004;48(5):1763-1765. doi: 10.1128/AAC.48.5.1763-1765.2004

17. Willcocks SJ, Denman CC, Atkins HS, Wren BW. Intracellular replication of the well-armed pathogen Burkholderia pseudomallei. Curr Opin Microbiol. 2016;29:94-103. doi: 10.1016/j.mib.2015.10.015

18. Currie BJ. Melioidosis: evolving concepts in epidemiology, pathogenesis, and treatment. Semin Respir Crit Care Med. 2015;36(1):111-125. doi: 10.1055/s-0034-1398387

19. Gan YH. Interaction between Burkholderia pseudomallei and the host immune response: sleeping with the enemy? J Infect Dis. 2005;192(10):1845-1850. doi: 10.1086/497173

20. Limmathurotsakul D, Chaowagul W, Chierakul W, Stepniewska K, Maharjan B, et al. Risk factors for recurrent melioidosis in northeast Thailand. Clin Infect Dis. 2006;43(7):979-986. doi: 10.1086/507631

21. Chaowagul W, Chierakul W, Simpson AJ, Short JM, Stepniewska K, et al. Open-label randomized trial of oral trimethoprim-sulfamethoxazole, doxycycline, and chloramphenicol compared with trimethoprim-sulfamethoxazole and doxycycline for maintenance therapy of melioidosis. Antimicrob Agents Chemother. 2005;49(10):4020-4025. doi: 10.1128/AAC.49.10.4020-4025.2005