Case report

Navigating Diagnostic and Therapeutic Challenges in SuspectedNeuromelioidosis: A Comprehensive Case-Report of a Post-Natal Mother

ABSTRACT

Neuromelioidosis, a severe neurological form of melioidosis caused by *Burkholderiapseudomallei*, presents significant diagnostic and therapeutic challenges. This case report describes a 28-year-old post-natal woman with progressive right-sided weakness, facial palsy, and respiratory distress. MRI findings, including the tunnel sign, and cerebrospinal fluid (CSF) analysis were crucial for diagnosis. Despite initial broad-spectrum antibiotics, targeted treatment with meropenem, ceftazidime, and trimethoprim-sulfamethoxazole led to significant clinical improvement. This case highlights the importance of early recognition and appropriate management of neuromelioidosis to improve patient outcomes.

Keywords: Melioidosis; neuromelioidosis; Diagnostic challenges; Therapeutic interventions.

1. INTRODUCTION

Neuromelioidosis is a severe neurological manifestation of melioidosis, an infectious disease caused by the gram-negative bacterium *Burkholderiapseudomallei*. The pathogen is predominantly found in soil and water in tropical and subtropical regions and can infect humans through inhalation, ingestion or direct contact. Neurological involvement occurs in approximately 4-5% of melioidosis cases, with a higher incidence reported in areas with endemic melioidosis. *B. pseudomallei* enters the body through skin abrasions, inhalation, or ingestion and can spread hematogenously to various organs, including the central nervous system (CNS). Neuromelioidosis occurs when the pathogen invades the CNS, causing brain abscesses, encephalomyelitis, or meningitis. Neuromelioidosis can present with a wide range of neurological symptoms, reflecting the diversity of CNS involvement. Magnetic Resonance Imaging (MRI) is crucial in diagnosing neuromelioidosis. Neuromelioidosis can lead to severe complications and death, if not promptly and adequately treated. Diagnosis of neuromelioidosis is challenging and relies on a combination of clinical suspicion, imaging studies, and microbiological testing. MRI is particularly valuable for identifying brain abscesses and other CNS abnormalities. Laboratory tests such as cerebrospinal fluid (CSF) analysis, blood cultures and serological tests may also help confirm the diagnosis. Treatment of neuromelioidosis involves prolonged antibiotic therapy, usually consisting of intravenous antibiotics such as ceftazidime or meropenem, followed by oral antibiotics like trimethoprim-sulfamethoxazole [1].

Supportive care and management of complications are also crucial. This case report details the clinical presentation, diagnostic approach, and management of neuromelioidosis, highlighting the importance of early recognition and targeted treatment in improving patient outcomes in a 28-year-old post-natal woman, who presented with progressive demyelination syndrome and respiratory distress.

2. PRESENTATION OF CASE:

The patient is a 28-year-old post-natal mother, who underwent a lower segment cesarean section (LSCS) 15 days prior to admission, delivering a full-term neonate. She presented to the hospital with:

- Inability to use her right upper and lower limbs
- Deviation of the angle of the mouth to the left side
- Slurring of speech for 5 days
- Respiratory distress and breathlessness for 2 days
- 11 days before admission, she has been having fever with chills and rigor, treated with antipyretics and amikacin for 3 days
- 5 days before admission, she had developed numbness and weakness over the right thumb, which gradually progressed to involve the entire right arm and leg
- She was transferred to our facility, while being treated for bacterial meningitis, urinary tract infection (UTI), and bilateral lower lobe pneumonia

Medical & medication history:
She was on Labetalol, for gestational HTN developed during the second pregnancy.

General examination:
The patient was conscious, oriented, afebrile, with mild dyspnea and tachypnea. Bilateral crackles were present during the respiratory examination. The blood pressure was elevated to 140/90 mmHg.

Examination of the central nervous system:

- Bilateral pupils were equal and reactive to light
- Right upper motor neuron (UMN) facial palsy
- Right hemiplegia
- Decreased tone and power in right upper (0/5) and lower limbs (0/5),
- Right plantar reflex: positive Babinski sign indicating an extensor plantar response.
- Left plantar reflex: negative Babinski sign indicating a flexor plantar response or absent plantar reflex.

Diagnostic work-up:
Cerebrospinal fluid (CSF) analysis: revealed a protein concentration of 74 mg/dl, lactate dehydrogenase (LDH) level of 358 IU/L, red blood cell (RBC) count of 184 cells/mm^3, and white blood cell (WBC) count of 1018 cells/mm^3, with a slightly turbid appearance.

Blood picture: showed a predominance of polymorphonuclear cells at 93%, with a total leukocyte count of 19,200 cells/mm^3. The gamma-glutamyl transferase (GGT) level was 129 IU/L, alkaline phosphatase (ALP) was 545 IU/L, and C-reactive protein (CRP) was elevated at 242 mg/dl. The serum albumin level was 2.8 g/dl, D-dimer was markedly increased at 1965 ng/ml, and the erythrocyte sedimentation rate (ESR) was 82 mm/hr. HIV serology was negative.

Urine analysis: revealed a slightly turbid appearance with a high presence of pus cells (45-50 per high power field) and leukocytes (75 per high power field), along with mucus threads, multi-drug resistant *Escherichia coli* sensitive to colistin.

MRI Brain with Whole Spine Screening Contrast: revealed an ill-defined area of T2/FLAIR and diffusion hyper-intensity in the left corona radiata, centrum semiovale, and pre-frontal gyrus involving the posterior internal capsule (Figure 1). There was no evidence of post-contrast enhancement or diffusion restriction. The differential diagnosis included demyelination or subacute infarct.

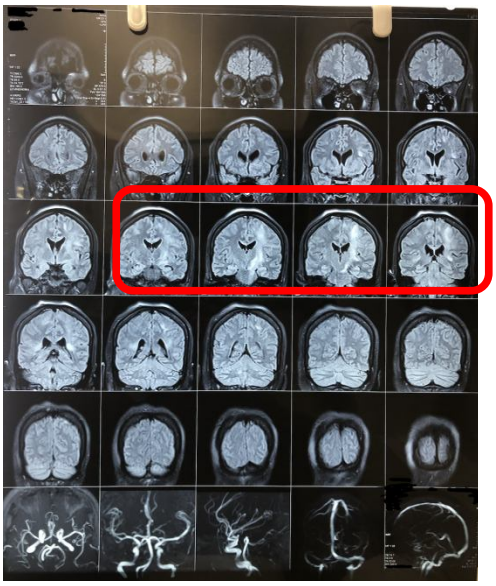

Figure.1: MRI Brain with Whole Spine Screening Contrast revealing an ill-defined area of T2/FLAIR and diffusion hyper-intensity in the left corona radiata, centrum semiovale, and pre-frontal gyrus involving the posterior internal capsule. MRI Tunnel sign highlighted.

Chest X-ray: revealed bilateral lower lobe consolidation with patchy and ground-glass opacities, bilateral subpleural atelectasis.

Echocardiogram: showed dilated pulmonary arteries, trace pericardial effusion near the right atrium and ventricle.

Course in the hospital:

- The patient had episode(s) of focal seizures, Broca's aphasia, fever, acute pulmonary edema, invasive candidemia, chest pain, SSTI, right ear pain.
- Antibiotics such as Ceftriaxone, Vancomycin, Linezolid, Doxycycline were used in the initial days, for suspected bacterial infections.
- After suspicion for Neuromelioidosis arose with respect to the MRI Tunnel sign, clinical presentations and CSF analysis, antibiotics such as Meropenem, Ceftazidime and Trimethoprim-Sulfamethoxazole were used as mainstay of treatment.
- IV Fluconazole was started for invasive candidemia for the isolated non-albicanscandida.
- Supportive medications were used to manage the complications, such as Levetiracetam and fosphenytoin were used for management of seizures, Mannitol was used to reduce Intra-cranial pressure, Furosemide was used for Acute pulmonary edema, Steroids such as Dexamethasone and Methyl prednisolone were used to reduce inflammation. Nifedipine and Labetalol were used to reduce High BP. Atropine, Midazolam and Atracurium were also used when needed.
- The patient required tracheostomy for mechanical ventilation and the duration of intensive care unit stay was 48 days.

Challenges in diagnosis:

Since a biopsy is required to confirm the presence of *BurkholderiaPseudomallei*, in consideration of the risk-benefit ratio and accessibility, the organism was not microbiologically confirmed.

Outcome of therapy:

- In spite of the prevailing diagnostic challenges, significant clinical improvement was noted with targeted therapy with Ceftazidime and Trimethoprim-Sulfamethoxazole.
- The patient returned to normalcy, she was discharged on Oral Trimethoprim-Sulfamethoxazole and physiotherapy plan.

3. DISCUSSION

Epidemiology: Burkholderiapseudomallei, a soil-dwelling gram-negative bacillus, causes melioidosis. The disease typically presents with abscesses, particularly in the lungs, liver, spleen, skin, and skeletal muscle. Although central nervous system involvement is rare (1–5%), it is linked to a higher mortality rate, reaching up to 25% [2].B. pseudomallei can enter the body through skin cuts, inhalation, or ingestion, spreading via the bloodstream to various organs, including the central nervous system (CNS). In our patient, potential routes of infection entry, such as inadequate protection of the surgery site or other skin cuts during the LSCS procedure, could have facilitated the entry of *B. pseudomallei* into her system. A similar mode of entry was also observed in the case-report of a 57 year-old man who developed neuromelioidosis, sustaining a penetrating injury to the foot [3]. The bacterium's ability to avoid the immune system and persist within host cells results in chronic and relapsing infections. Neuromelioidosis occurs when the pathogen reaches the CNS, leading to brain abscesses, encephalomyelitis, or meningitis. The bacteria are found in soil, untreated water, and undercooked food, with a very low risk of person-to-person transmission. Melioidosis is often underreported or unrecognized in tropical and subtropical regions, with over 165,000 cases estimated annually, primarily in Southeast Asia and northern Australia. Risk factors for developing melioidosis include diabetes, excessive alcohol use, chronic lung diseases (such as COPD or cystic fibrosis), chronic kidney disease, thalassemia, and cancer or other non-HIV-related immune suppression.

Signs & symptoms: The incubation period ranges from 1 to 21 days, with a median of 4 days, although symptoms can appear within hours if the inoculum is high. Melioidosis can also remain dormant for months or years before symptoms emerge. It can manifest as a localized infection, pneumonia, bacteremia, or a disseminated infection affecting any organ, including the brain [4]. Symptoms are nonspecific and vary depending on the infection route, including abdominal pain, abscesses or ulcers, chest pain, cough, respiratory distress, disorientation, headache, seizures, fever, localized pain and swelling, muscle or joint pain, and weight loss. Patients typically present with acute illnesses, but about 9% have symptoms lasting two months or more. Chronic melioidosis often resembles a Mycobacterium tuberculosis infection clinically. Prompt diagnosis and treatment are crucial. Neuromelioidosis can present with a wide range of neurological symptoms, reflecting the diversity of CNS involvement. Common clinical features including fever and headache (often severe and persistent), focal or generalized seizures reflecting underlying brain abscesses or inflammation, Focal neurological deficits manifesting as limb weakness, hemiparesis, or cranial nerve palsies may occur depending on the location of the infection within the brain or spinal cord, Altered mental status may present with confusion, lethargy, or coma. Signs of meningitis such as neck stiffness, photophobia, and other meningeal signs may be present, particularly in cases of meningitis. In case of myelitis and encephalomyelitis, inflammation of the spinal cord or both the brain and spinal cord can lead to additional symptoms such as paraplegia or quadriplegia. Raj et al., in their case-report comprising of 3 cases of neuromelioidosis, described presentations of fever, neck stiffness, limb weakness, leucocytosis similar to ours, and two cases also had cranial nerve palsies [5]. Our case had bilateral pneumonia, but Burkholderiapseudomallei was not isolated. However, Rosie. et al., in their case-report of vagal nerve neuritis associated with pulmonary melioidosis, described an image-proven cranial neuropathy due to Burkholderiapseudomallei, without intracranial involvement [6]. Zhan et al. reported pulmonary involvement as the most common manifestation in five out of the seven patients with neuromelioidosis included in their case-series [7]. The features of MRI in our case were coherent with the study of Agarwal et al., and other literature [8].

Diagnosis: Magnetic Resonance Imaging (MRI) is crucial in diagnosing neuromelioidosis. MRI findings may include brain abscesses (multiple ring-enhancing lesions are commonly seen, often in the cerebral hemispheres, cerebellum, or brainstem, cerebral edema (swelling around the abscesses or diffuse cerebral edema), myelitis (hyperintense lesions in the spinal cord on T2-weighted images, indicating inflammation) and meningeal enhancement (contrast enhancement of the meninges may indicate meningitis). Neuromelioidosis can lead to severe complications if not promptly and adequately treated. These include cerebral abscesses which may rupture, causing secondary infections or increased intracranial pressure, Accumulation of cerebrospinal fluid within the brain's ventricles, leading to increased intracranial pressure and potential brain herniation causing hydrocephalus, chronic neurological deficits manifesting as persistent neurological impairments such as motor deficits, sensory loss, or cognitive dysfunction, Dissemination of the infection into the bloodstream, leading to septic shock and multi-organ failure. The Diagnosis of neuromelioidosis is challenging and relies on a combination of clinical suspicion, imaging studies, and microbiological testing. MRI is particularly valuable for identifying brain abscesses and other CNS abnormalities. Laboratory tests include cerebrospinal fluid (CSF) analysis, which typically reveals elevated protein, increased white blood cells, and sometimes bacteria on Gram stain or culture. Blood cultures and serological tests may also help confirm the diagnosis. Our patient had non-specific symptoms such as

fever, respiratory distress, chest pain and ear pain along with specific manifestations of neuromelioidosis such as dysrthria, Broca's apasia, facial palsy, focal seizures, focal neurological deficits such as right-sided hemiparesis that lead to right-sided hemiplegia. These manifestations, coupled with the MRI Brain and Whole Spine Screening Contrast of the patient (Figure.1), revealing an ill-defined area of T2/FLAIR and diffusion hyper-intensity in the left corona radiata, centrum semiovale, and pre-frontal gyrus involving the posterior internal capsule, led to the suspicion of neuromelioidosis. However, when neuromelioidosis was suspected based on MRI findings (Tunnel sign), coherent with the systematic review of Zamzuri et al and the case-series by Govindappa, S.K.G. et al., along with the clinical presentations, targeted therapy with, Ceftazidime, was initiated [9] [10]. Although a biopsy was not performed to confirm Burkholderiapseudomallei, the patient showed significant clinical improvement with the targeted therapy.

Treatment: Treating melioidosis requires long-term antibiotic therapy, consisting of an acute phase followed by an eradication phase. Initial treatment typically involves intravenous Ceftazidime (2 g thrice daily), or Meropenem (50 mg/kg up to 2 g every 8 hours) for severe cases of sepsis for at least 14 days.Depending on the patient's response, intravenous treatment may be extended up to 8 weeks in severe cases. After the initial treatment, a 3–6 month course of eradication therapy with oral Trimethoprim-Sulfamethoxazole (TMP-SMX) or amoxicillin-clavulanic acid (for those who cannot tolerate TMP-SMX) should be provided [11]. Relapses can occur, particularly in patients who do not complete the recommended duration of therapy. In our patient, Ceftazidime was started on day 19. However, the patient has recieved Meropenem since day 3 of hospital admission, in view of other infections present. A 29 day course of intravenous Ceftazidime was provided for the patient, after which, the patient was discharged on oral Trimethoprim- Sulfamethoxazole.
Sahathevan. et al., in their case-report of two patients presenting with long segment myelitis secondary to melioidosis, concluded that delayed diagnosis and extensive involvement of the spinal cord and brain can make the prognosis poor in this condition, in their first case, and an early diagnosis with the initiation of appropriate therapy may result in a favorable outcome. In spite of the availability of culture-confirmed *Burkholderiapseudomallei*, they proposed that neuro-melioidosis should be considered an important differential when evaluating long segment myelitis, especially in endemic areas. However, in our report, we conclude the need to suspect and initiate empiric therapy for neuromelioidosis with antibiotics such as Meropenem, Ceftazidime and/or Trimethoprim-Sulfamethoxazole in patients with un-resolving neurological symptoms and other non-specific symptoms, supported by imaging studies with findings favorable to neuromelioidosis, despite the lack of microbiological evidence due to potential concerns in accessibility or availability, especially in endemic regions, considering the impact of initiating empiric therapy at earlier stages to ensure a desirable prognosis of the condition.

4. CONCLUSION

Neuromelioidosis, a rare but serious neurological manifestation of melioidosis, poses significant diagnostic and therapeutic challenges. This case report underscores the complexity of neuromelioidosis diagnosis, which often requires a multifaceted approach encompassing clinical suspicion, advanced imaging like MRI, and microbiological testing. The challenges of invasive biopsies and the need for multidisciplinary collaboration are evident in the management of this condition, especially when accessibility to confirmatory tests is limited.

The presented case of a 28-year-old post-natal mother highlights the diverse clinical manifestations of neuromelioidosis, ranging from focal neurological deficits to respiratory distress. The utilization of MRI, particularly the identification of the tunnel sign, along with the clinical manifestations, were pivotal in guiding targeted antibiotic therapy despite the absence of microbiological confirmation. This emphasizes the crucial role of imaging in facilitating early diagnosis and initiating appropriate treatment, ultimately leading to significant clinical improvement and patient recovery.

In conclusion, this case report underscores the importance of a comprehensive approach to tackling neuromelioidosis, integrating clinical, imaging, and microbiological findings to optimize patient outcomes. Continued research and awareness are essential in enhancing our understanding and management of this challenging neurological condition, especially in endemic regions and resource-limited settings.

CONSENT

The participation was on voluntary basis and
written consent was obtained from the individual who participated in this case report.

Ethical Approval:

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

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1.

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