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A Rare Case of Isolated Paediatric Central Nervous System Melioidosis: An Imaging Chameleon

***Nurdiyana Mohamed[1], Muhammad Zakwan Yahya[2], Muttaqillah Najihan Abdul Samat[3], Hamzaini Abdul Hamid[4]**

[1]Department of Pathology and Laboratory Medicine, Kulliyyah of Medicine, International Islamic University Malaysia,

[2]Radiology Department, Kulliyyah of Medicine, International Islamic University Malaysia,

[3]Department of Medical Microbiology and Immunology, Hospital Canselor Tuanku Muhriz

[4] Radiology Department, Hospital Canselor Tuanku Muhriz

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ABSTRACT

*Burkholderia pseudomallei***,** the agent of melioidosis, can cause multisystemic infections, including rare cases in the central nervous system (CNS). Isolated CNS melioidosis is particularly rare, with a 3% of cases in long-term study. In this region that is high endemicity, risk factors include direct contact with contaminated soil or water, particularly among individual with immunosuppressive condition. Without timely intervention, CNS melioidosis will lead to high mortality and morbidity rate.

Case Presentation: A 6-year-old boy with G6PD deficiency and acute lymphoblastic leukaemia (B cell ALL) presented with a persistent headache and intermittent fever for two months and vomiting for one day. CNS examination was unremarkable. CT and MRI revealed a right fronto-parietal rim-enhancing lesion with mass effect, suggesting meningeal tuberculoma, infection, or malignancy. Abdominal ultrasound and chest x-ray were negative for abscesses. Craniotomy and tumour excision were performed, and culture confirmed Burkholderia pseudomallei**.**

Conclusion: Imaging is essential for differentiating CNS melioidosis from malignancy and characterizing the infection. Diffusion-weighted imaging (DWI) on MRI can help distinguish pyogenic abscesses from cystic tumours. The involvement of white matter tracts and brainstem in CNS melioidosis aids differentiation from other infections, like tuberculosis. In endemic regions, CNS melioidosis should be considered in patients with relevant risk factors, clinical suspicion, and radiological evidence. Microbiological diagnosis is vital for early targeted therapy and improved recovery.

Keywords- Burkholderia pseudomallei**,** melioidosis, central nervous system, imaging, diffusion-weighted imaging, paediatrics

INTRODUCTION

Burkholderia pseudomallei that causes melioidosis is a Gram-negative bacterium, typically discovered in endemic geographical area such as Southeast Asia, and Australia. In the endemic localities, this organism is widely dispersed as an environmental saprophyte in freshwater and soil environments [1]. Serologic investigations indicate that the

majority of infections are either subclinical or asymptomatic. While commonly associated respiratory, soft tissue, and blood stream infection, central nervous system (CNS) involvement is exceedingly rare, particularly in paediatric population [2]-[4]. In these cases, early diagnosis is often hindered as CNS condition may mimic other condition like tuberculosis or malignancy of CNS, on imaging studies. This report underscores the

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importance of considering melioidosis in differential diagnoses, particularly in endemic region to facilitate prompt and targeted intervention.

Case Report

Patient history and examinations

We reported a 6-year-old boy with underlying G6PD deficiency and acute lymphoblastic leukaemia (B cell ALL) since past one year. He presented at our emergency and trauma facility for persistent headache in the past two month and vomiting for the past one day about three times at home with absence of seizure. Otherwise, patient had no fever, was active, and had no gastrointestinal symptoms, meningism or constitutional symptoms. During physical examination, he was clinically very well, vital signs was stable with blood pressure (BP) 90/50, cardiac rate of 107 beats per minute and temperature of 37.1˚C. The leukocyte count and c-reactive protein level were within the standard range. The central nervous system (CNS) examination revealed normal tone of lower limbs with a power of 4/5, no clonus and deep tendon reflexes. Other systems were unremarkable. Further history from his parents revealed an intermittent fever for two months.

Imaging findings

Contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) were done to rule out any space-occupying lesion (SOL) that can be caused by a meningeal tuberculoma, infection or malignancy. The CECT and MRI results are documented as in Fig. 1-3.

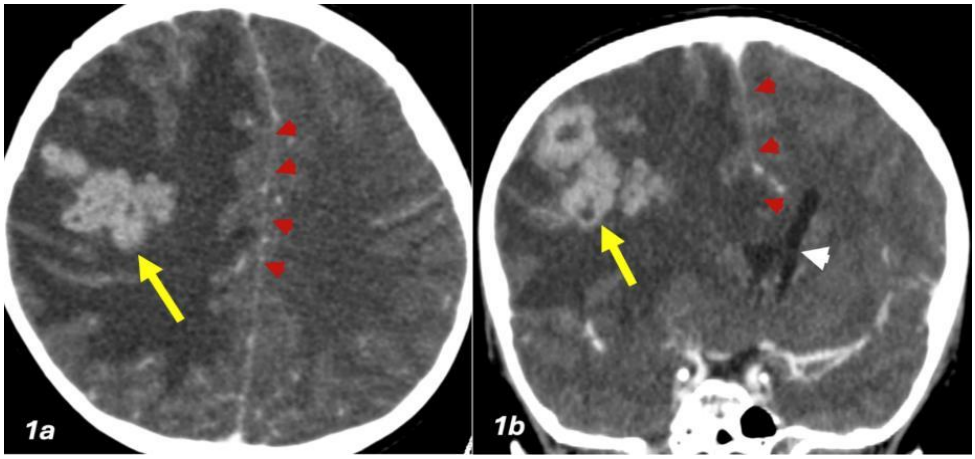

Fig. 1(a) and 1 (b) Contrast- enhanced computed-tomography scan (CECT) brain axial and coronal planes show a cluster of rim enhancing lesions (yellow arrow) at the right frontal lobe with significant midline shifts (red arrow heads) and effacement of the bilateral lateral ventricles (white arrow head).

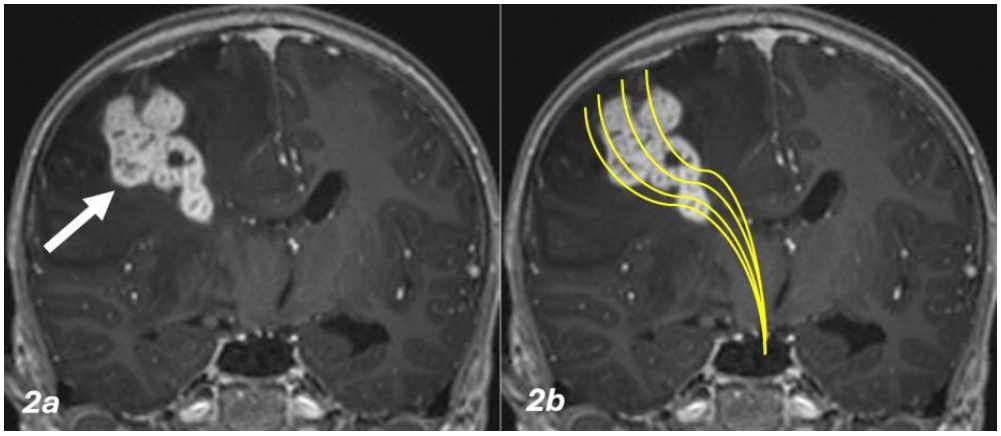

Fig. 2(a) Gadolinium-enhanced MRI brain T1-weighted image in coronal view shows the cluster of rim-enhancing lesions (white arrow) spreading along the right corticospinal tract (CST) which further illustrated in Fig. 2 (b).

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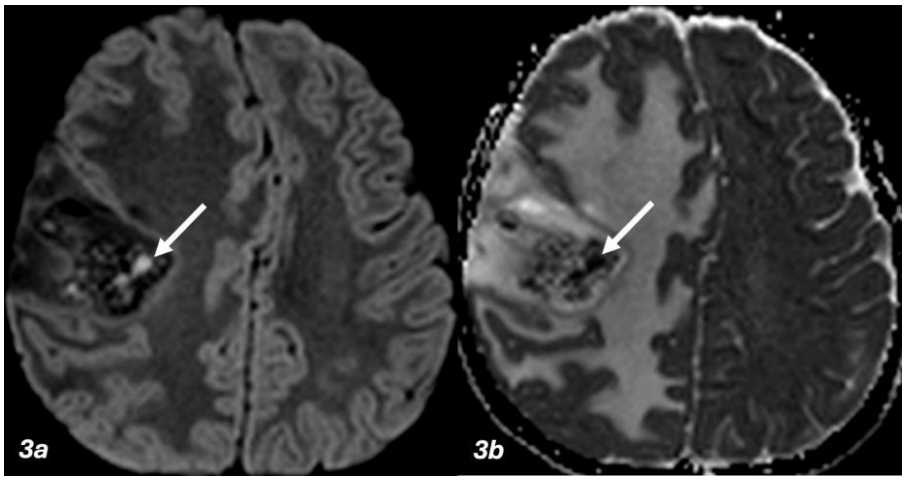

Fig. 3a and 3b. MRI brain DWI/ADC[1] mapping of the lesions show central restricted diffusion (white arrow); central hyperintensity on DWI (3a) and hypointensity on ADC (3b). [1]DWI/ ADC; diffusion weighted imaging/apparent diffusion coefficient.

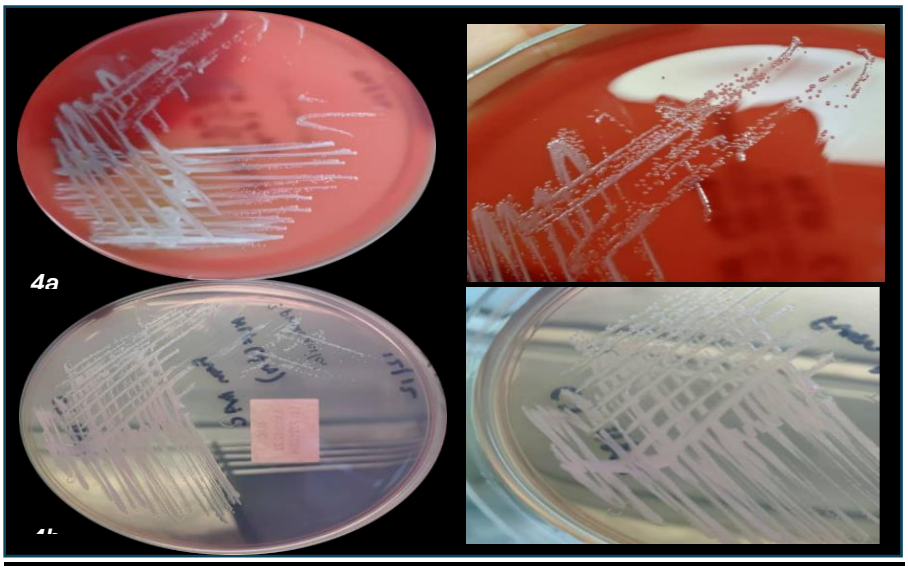

Fig. 4(a) On blood agar, *B. pseudomallei* colonies are cream coloured, and produced a metallic sheen at 24 hours incubation. The colonies will become more pinkish, dry, and wrinkled after 24 hours incubation. 4(b) On MacConkey agar, *B. pseudomallei* colonies grow as tiny, non-lactose fermenters seen as opaque, colourless with a metallic sheen initially, but after 48 hours, will become more pinkish as it takes dyes from the medium. Ultrasonography of the abdomen and chest x-ray were also performed to rule out any deep-seated or localised abscess, but they were negative.

Culture and sensitivity

Given the MRI finding, a craniotomy and excision of the lesion were performed, and the tissue specimen was submitted for culture and histopathology evaluation (HPE). The surgical procedure was uneventful. The culture as seen in Fig. 4 revealed pure growth of *Burkholderia pseudomallei* confirmed with matrix-Assisted Laser Desorption/Ionization of Flight (MALDI-TOF). The organism showed in-vitro susceptibility to ceftazidime (MIC 4 ug/ml), amoxicillin-clavulanate (MIC 3 ug/ml), and imipenem (MIC 4ug/ml), but was resistant to trimethoprim-sulfamethoxazole (MIC 16 ug/ml). A combination of meropenem and ceftazidime was initiated in the induction phase, given the contraindication of SXT in G6PD deficiency. Intravenous meropenem 8-hourly and ceftazidime 6-hourly were administered for 3 weeks. Subsequently, the repeated brain drainage culture could still grow *B. pseudomallei,* hence, the IV ceftazidime was further continued for another six weeks. Subsequently, the patient no longer required intensive care unit care. He was completing maintenance therapy using the AMC for 6 months, and the repeated culture was negative, and imaging showed abscess resolution as shown in Fig. 5.

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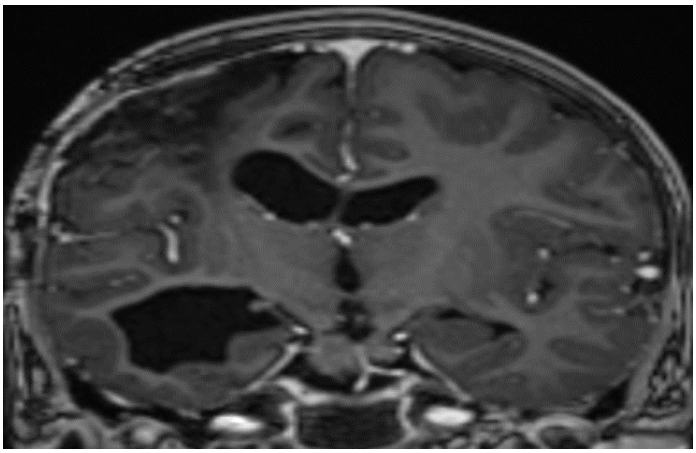

Fig 5. Follow up gadolinium-enhanced MRI brain T1-weighted image in coronal view after treatment completion shows right frontal encephalomalacia with cystic ex-vacuo dilatation of the right lateral ventricles as well as resolved right frontal rim enhancing lesions and mass effect.

DISCUSSION

Clinical presentations

Central nervous system (CNS) melioidosis is rare but potentially fatal especially in paediatric population. In twenty-seven cases analysed from paediatric group of melioidosis, meningoencephalitis was reported as the major manifestation and usually presented as cranial nerve palsies and fever with mean age was 6.7 years [4]. When reported, CNS melioidosis was mainly manifested as pyemic like brain abscess, subdural empyema, and epidural abscess [5]. The clinical and radiological features often mimic other common bacterial infection like tuberculosis, pyogenic abscess, or malignancy making early diagnosis challenging. In an Australian study, it was found that the rate of children affected by CNS melioidosis patients were higher compared to adults (23% and 5%), despite the fact that the majority of cases were observed in adult, with primary CNS melioidosis in the absence of bacteraemia being the most commonly described presentation [6]. Another 20 year-period study documented the paucity of CNS melioidosis in only 14 of the 540 cases (3%) with three being brain abscess cases, which were reported as secondary to bacteraemia [7]. The remaining 11 cases were reported as primary CNS melioidosis presenting as brainstem encephalitis or myelitis.

Epidemiology and risk factors

Diabetes mellitus is a well-documented risk factor for melioidosis, with 45.68% of cases reported in diabetic individuals. Other significant risk factors include exposure to soil and water, advanced age, chronic kidney disease, cardiorespiratory disease, and thalassemia [8]. Immunocompromised states, such as those in paediatric patients undergoing leukaemia therapy, further heighten susceptibility due to an increased risk of Gram-negative bacterial infections, including *B. pseudomallei* [9]. The relationship between G6PD deficiency and melioidosis remains unclear. However, G6PD deficiency compromises red blood cell integrity and increase vulnerability to infections, even in absence of environmental exposure. It has been identified as a potential risk factor for severe infection, as reported in a case study [10]. Together, immunosuppression and genetic vulnerabilities, caused by G6PD deficiency, may predispose individuals to melioidosis through alternative mechanisms, including nosocomial transmission or reactivation of latent infections [11].

Route of invasion and genetic predispositions

Primary CNS melioidosis, without systemic involvement, as seen in this case is particularly uncommon. One previous study proposed route of infection in primary CNS melioidosis was described in a mice model showing direct extension of *B. pseudomallei* down the olfactory and/or trigeminal nerve root pathway subsequent to inhalation and colonisation in the nasal mucosa leading to microabscess formation and encephalitis within the brainstem [12],[4]. The $bimA_{Bm}$ variant which is the most common in Australia, has a substantially increase capacity to cause CNS disease, possibly due to heightened bacteria's motility through the

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olfactory pathway [13]. In contrast, disease involving macroabscess formation was always precipitated by hematogenous route as hypothesized by Owen et al., given that an absence of brain stem disease that might suggest this to be the potential route [14]. While direct neural invasion is the possible mechanism for our case, the imaging result was contradicting. Yet, the data on such genetic predispositions in Malaysia strains are limited, highlights the need for further molecular study.

Role of diagnostic imaging

This case demonstrates the critical role of advanced imaging modalities, particularly diffusion-weighted imaging (DWI), in differentiating CNS melioidosis from other pathologies. But, as we saw in this case, the imaging differentiation of CNS melioidosis is already challenging due to the heterogenicity of CNS melioidosis result. An extensive systemic review shows that the rim-enhancing pattern is the greatest commonly observed, while the brainstem being the area furthermost impacted [15]. Another systematic review of CNS melioidosis in the Asia-Pacific region was conducted in 2021, emphasizing the rim-enhancing cerebral microbscesses from MRI findings, which may overlap with other CNS infection like neurocysticercosis and toxoplasmosis, thus necessitates a careful differential diagnosis particularly in endemic region [16]. The imaging findings may include cranial osteomyelitis, encephalitis, cerebral abscess, and myelitis [17]. Another author proposed that the microabscesses in CNS melioidosis tended to occur in cluster and has the capacity to extend across the commissural and white matter tracts projections [18]. Central nervous system melioidosis can be hard to tell apart from brain cancer on standard imaging. But with diffusion-weighted imaging (DWI), the diagnostic accuracy can reach 95%, greatly increasing the confidence in distinguishing abscesses from cystic tumours. On DWI, a pyogenic abscess would show up as a diffuse hyperintensity, while the pathognomonic feature of cystic tumour is hypointensity [17]. Melioidosis can greatly mimics tuberculosis in clinical presentation, imaging characteristics and histopathology; therefore, propensity of the white matter tract spread as well as brainstem involvement would be helpful to discriminate and suspect CNS melioidosis from other CNS infection before definitive confirmatory culture and sensitivity results are available.

Antibiotic susceptibility pattern and its impact

Intravenous meropenem or imipenem in combination with oral trimethoprim/suphamethoxazole (SXT) for 8 weeks is the preferred method of treatment in intensive phase for CNS melioidosis and could be de-escalated to ceftazidime once symptoms improve. In eradication or maintenance phase, oral SXT is suggested for 24 weeks. Our patient's therapy was complicated by having G6PD deficiency which contraindicated SXT use. Maintenance therapy with AMC, though associated with higher relapse rates than SXT, was necessary in this case due to patient's underlying condition [19]. The resistance of *B. pseudomallei* against SXT poses future challenges in treatment regimens, highlighting the need for concise research to understand the genetic and molecular mechanisms driving to SXT resistance. Study on genetic variant like *bimABm*, which increase bacteria's ability to effect CNS should be encouraged, as this may lead to the exploration of new treatments alternative.

CONCLUSION

This unique case of a subtle clinical presentation may lead to a delay in diagnosis. Propensity of the commissural and white matter tract spread as well as brainstem involvement as observed in our patient, that also aligned with other reports, suggesting it may be a distinguished factor of CNS melioidosis. This case reinforces the importance of a high index of suspicion for CNS melioidosis in highly prevalent areas even in absence of systemic manifestations. There is also a need to increase awareness of such patterns among clinicians and encourage the usage of advanced imaging techniques and microbiological confirmation in directing treatment and improving patients' outcomes.

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