



Case report

Melioidosis of the central nervous system; A potentially lethal impersonator



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ABSTRACT

A 57-year-old Australian woman, with a history of hazardous alcohol consumption, presented with a seizure following 2 days of fever and headache. Initial imaging suggested the presence of an isolated brain abscess, however, a thorough physical examination, identified no additional septic focus. Five sets of blood cultures were sterile and serology for *Burkholderia pseudomallei* was negative. Other investigations including computed tomography of her chest, abdomen and pelvis and a trans-esophageal echocardiogram were normal. Despite the administration of intravenous vancomycin, ceftriaxone, and metronidazole, her condition deteriorated. At emergency craniotomy, the abscess was drained and *B. pseudomallei* was cultured, confirming a diagnosis of melioidosis. She received 8 weeks of intravenous meropenem, combined with oral trimethoprim/sulfamethoxazole; the trimethoprim/sulfamethoxazole was continued for a total of 12 months. She recovered completely and was able to return to full-time work. Melioidosis, is endemic to Australia and South East Asia and, globally, is estimated to kill 89,000 every year. It can affect almost any organ, but up to 5% have central nervous system (CNS) involvement, where it may present as an encephalomyelitis, brain abscess or meningitis. *B. pseudomallei* is resistant to many commonly used antibiotics and even in well-resourced settings the case-fatality rate of CNS infection may rise to 50%. This patient lived in a melioid-endemic region, and, with hazardous alcohol consumption, had a classical risk factor for the disease, but the sterile blood cultures and negative *B. pseudomallei* serology delayed definitive therapy. Despite the delayed diagnosis, definitive drainage and prolonged anti-bacterial therapy ensured a complete recovery.

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Case presentation

A fifty-seven-year-old woman, resident in tropical northern Australia, presented to a regional hospital with fever of 39.5 °C and a generalized seizure. She had experienced two days of subjective fevers and occipital headache, but otherwise had no localizing symptoms. She had an unremarkable medical history, although she had a hazardous alcohol intake, drinking up to eight standard drinks daily. Empirical treatment for bacterial meningitis was commenced with intravenous (IV) ceftriaxone and dexamethasone, she received IV phenytoin loading, and she was transferred to a tertiary hospital.

On arrival, her Glasgow Coma Scale (GCS) was 14, blood pressure 92/50 mmHg, heart rate 77 beats/minute, respiratory rate 19 breaths/minutes, oxygen saturation 95% on room air and she was afebrile. She had no meningism or localizing neurological signs and the remainder of her physical examination was unremarkable. Laboratory investigations revealed a white cell count of $17.8 \times 10^9/L$ (reference range: $4.0-11.0 \times 10^9/L$), neutrophil count of $10.5 \times 10^9/L$ (reference range: $2.0-8.0 \times 10^9/L$) and C-reactive protein of 19 mg/L (reference range <5.0 mg/L). Her urea, electrolytes, creatinine, and liver function tests were normal. Computed tomography (CT) of her head, performed with contrast (Fig. 1), showed an area of decreased attenuation in the right frontal lobe suggestive of a space-occupying lesion which was further characterised by Magnetic Resonance Imaging (MRI) (Fig. 2). Her IV ceftriaxone was continued with the addition of metronidazole [1]. A CT of her chest, abdomen and pelvis was normal, and blood and urine cultures were negative. She was transferred to a neurosurgical centre for ongoing management.

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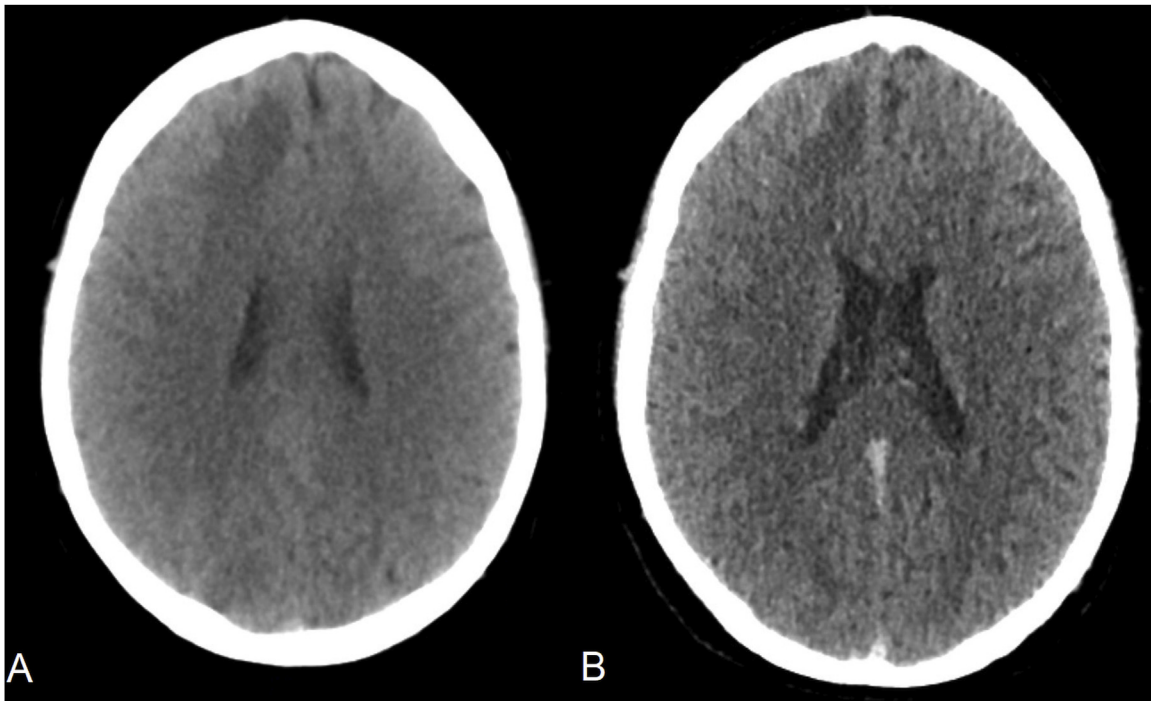


Fig. 1. A) Non contrast CT brain depicting an area of decreased attenuation in the right frontal lobe. B) Contrast CT brain demonstrating subtle peripheral enhancement with associated vasogenic edema.

Vancomycin was added to her antimicrobial regimen and her dexamethasone was ceased. Repeat blood cultures, serum cryptococcal antigen and *Burkholderia pseudomallei* serology (indirect hemagglutination test (IHA)) were all negative. A transesophageal echocardiogram was normal. Lumbar puncture was deferred. After initial resolution of her fevers, six days later her headaches returned, and her temperature rose to 37.8 °C. Repeat MRI demonstrated significant evolution of the lesion and she proceeded to craniotomy where a stereotactic system was used to localize the lesion. A curvilinear incision to dura revealed obvious abnormal yellow/grey discoloration to cortex with edematous brain. A corticotomy identified a thick yellow lesion, which was resected macroscopically using the ultrasonic aspirator (CUSA). Intraoperative histology (frozen section) was reported as consistent with a low-grade glioma.

Formal histopathology however, demonstrated abscess formation, and after three days *B. pseudomallei* was isolated, consistent with a diagnosis of melioidosis. IV meropenem (2 g IV three times daily) and trimethoprim/sulfamethoxazole (320/1600 mg orally twice daily) were commenced with folic acid. Meropenem was continued for eight weeks, and trimethoprim/sulfamethoxazole continued for ongoing eradication therapy. She made a slow recovery and was discharged home sixty-eight days after her initial presentation. She continued oral trimethoprim/sulfamethoxazole for twelve months, but now, fifteen months after completing treatment, she has returned to full-time work without residual neurological deficit.

Background

B. pseudomallei – the organism which causes the disease melioidosis – is an environmental, Gram-negative bacterium that lives in soil and fresh surface water [2]. It is endemic to tropical Australia and South East Asia, although it is known to have an even wider global distribution. Melioidosis is estimated to kill 89,000

people annually and cases in returning travelers from endemic regions are increasingly recognised [3–5].

Infection occurs predominantly by percutaneous inoculation, but the organism can also be inhaled or ingested. Most infections are subclinical, with only approximately 1 in 4600 antibody producing exposures resulting in disease [6]. However, in those with specific comorbidities – particularly diabetes mellitus, chronic lung disease, chronic kidney disease, immunosuppression and hazardous alcohol intake – the infection can lead to septic shock and be rapidly fatal [2].

Melioidosis can affect any organ system and most adults are bacteraemic at presentation [2]. Pneumonia, the most common clinical manifestation, is present in about half of adult cases, but the central nervous system (CNS) is involved in about 5%. CNS disease usually presents as a brainstem encephalomyelitis, although micro-abscesses of the brainstem and cerebellum may also be seen [7,8]. Larger abscesses are less common and are uncommonly seen without other organ involvement. Even in well-resourced settings, the case-fatality rate of CNS melioidosis is up to 50 %, with permanent disability common in survivors [7,9].

B. pseudomallei is intrinsically resistant to many antibiotics, including those in empirical regimens for sepsis and CNS infection [2]. It is therefore important – in the appropriate clinical context – to consider the diagnosis, preventing delays in effective therapy and the risk of death and permanent disability. Meropenem is recommended for the initial intensive therapy and is usually continued for at least eight weeks. Adjunctive oral trimethoprim/sulfamethoxazole is also recommended in Australia [10]. Disease recrudescence and relapse is common, necessitating a minimum of six months eradication antibiotic therapy – ideally with trimethoprim/sulfamethoxazole – following the initial intensive phase of therapy [10]. Appropriate source control is an essential part of management [2].

In this case report we illustrate the challenges in diagnosing CNS melioidosis even for clinicians familiar with the disease.

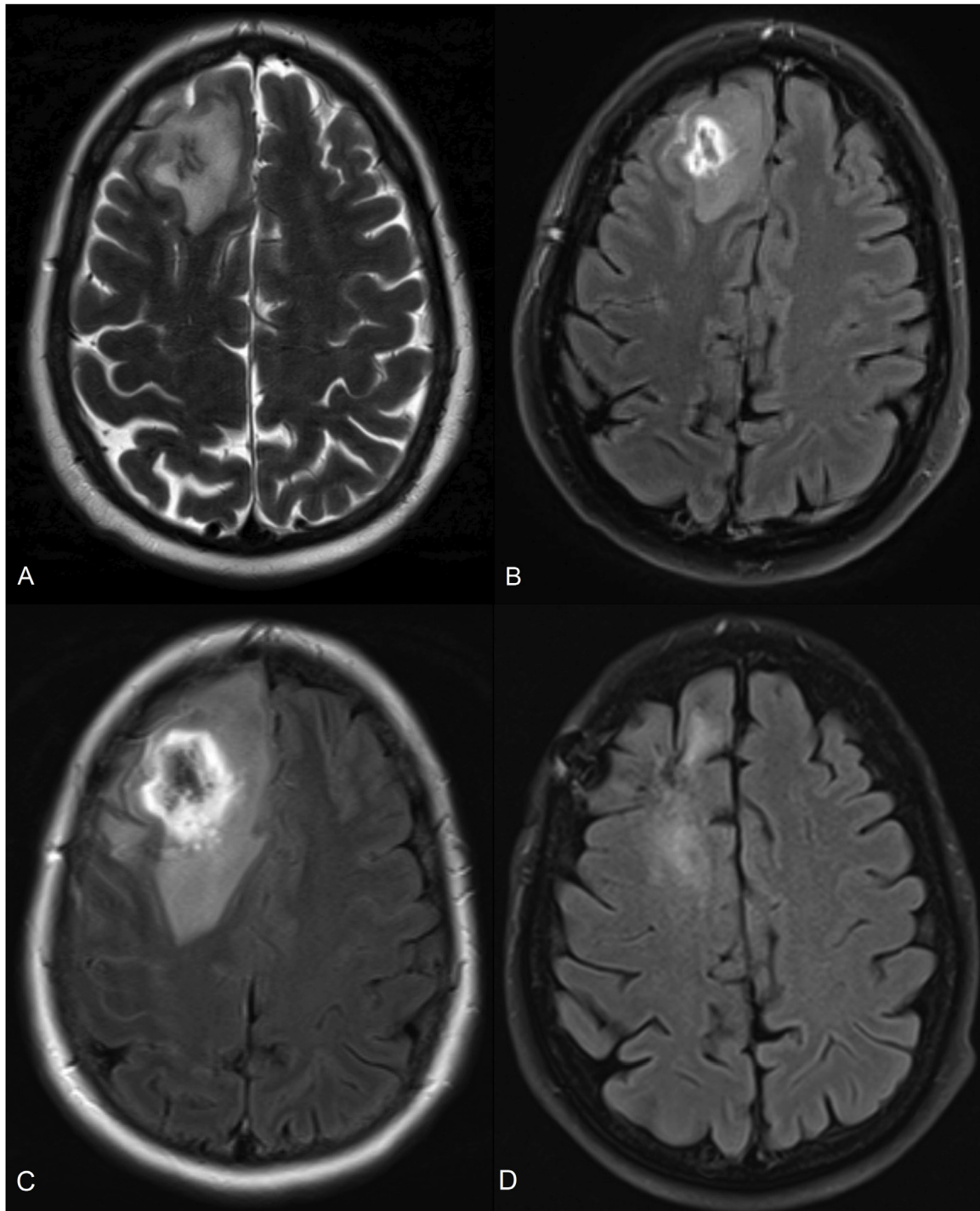


Fig. 2. MRI imaging depicting pre and post treatment appearances of the abscess. A) Initial T2 weighted MRI demonstrating the heterogenous right frontal lobe mass without any meningeal or ventricular involvement. B) Initial T2 FLAIR sequence. C) T2 FLAIR MRI performed seven days after initial presentation depicting rapid interval growth. D) T2 FLAIR weighted MRI eight months following operative intervention, demonstrating significant improvement.

However, we also demonstrate that neurosurgical intervention and effective antibiotic therapy can result in an excellent functional outcome.

Discussion

The case is noteworthy for several reasons. Although the patient was generally well, her hazardous alcohol intake increased her risk for melioidosis. Most of the comorbidities that predispose patients to developing the disease – including excessive alcohol intake,

diabetes mellitus and chronic kidney disease – are associated with impaired neutrophil function, and melioidosis should be considered in patients with these conditions.

Though the possibility of melioidosis was entertained in her case, establishing the diagnosis was challenging. Five sets of blood cultures were collected, all of which were sterile; an unusual finding in a location where 74 % patients are bacteraemic at presentation [2,11]. In one series from the Northern Territory of Australia every one of eight cases of brain abscess were bacteraemic, although a systematic review – that included series from resource-limited

settings where there may be less access to sophisticated microbiological support - reported that only 58 % of patients with brain abscesses were bacteremic [8,12]. In this systemic review it was reported that 67 % of patients had involvement of at least one extra-neurological organ - and 37 % of cases in this series included cases of encephalomyelitis where direct CNS invasion is believed to play a role - the normal findings on the patient's CT chest, abdomen and pelvis are therefore also noteworthy [8,13].

Experimental animal models have demonstrated spread of *B. pseudomallei* from the nasal epithelium via the olfactory or trigeminal nerve into the brain. As the trigeminal nerve nucleus lies in the brainstem this may explain the predilection for microabscess formation and encephalitis within the brainstem [14]. Conversely, macroscopic abscess formation is more likely through hematogenous spread and we hypothesize that given the absence of brainstem disease this was the likely mechanism in this case. The sterile blood cultures may be explained by the fact that ceftriaxone has some *in vitro* activity against *B. pseudomallei*, although its use in management of cases is associated with increased mortality and it is therefore not recommended [2].

The case demonstrates the limited diagnostic utility of serology. Seropositivity can be delayed or absent - as in this case - but background seropositivity - which has little clinical significance is also seen in regions endemic for melioidosis [15]. In another series from Northern Australia serology was also unhelpful with only 2/10 (20 %) of CNS melioidosis cases had a positive IHA result in the first 7 days of their care [9]. Polymerase chain reaction (PCR) and lateral flow assays for *B. pseudomallei* show promise but have yet to be incorporated into diagnostic algorithms [16,17]. The case therefore emphasises the importance of promptly obtaining serial samples from a range of tissues to increase the likelihood of a diagnostic culture. It is also crucial to ensure that the laboratory - particularly in non-endemic regions - is aware that *B. pseudomallei* is being considered as a potential pathogen so as to avoid misidentification.

The patient's imaging findings were critical in expediting referral for assessment and definitive neurosurgical management. CT imaging in CNS melioidosis may be normal if performed early, particularly in cases of encephalomyelitis, although MRI changes are usually grossly abnormal [7-9]. As the patient in this case had a brain abscess - rather than encephalomyelitis - the CT was abnormal at presentation, despite only forty-eight hours of preceding symptoms. However, MRI imaging taken only hours later demonstrated far greater parenchymal involvement. The MRI changes showed impressive evolution over the course of 7 days, despite the absence of fever and only modest symptomatology.

While in Australia, patients usually receive adjunctive trimethoprim/sulfamethoxazole during initial intensive therapy for complicated cases, a clear benefit of this strategy has not demonstrated. However, the importance of eradication therapy is emphasized by recrudescence if the duration of this therapy is inadequate [2,3]. In this case the course was conservatively extended to 12 months due to persisting changes on sequential MRI imaging and concerns about relapse.

Conclusions

Melioidosis of the CNS can be rapidly fatal even in well-resourced settings. Although it is endemic in tropical regions, clinicians in temperate regions need to consider this life-threatening diagnosis, particularly in returning travelers with specific comorbidities. The key tenets of management are early recognition, specific antibiotic therapy and - where necessary - definitive neurosurgical intervention.

Author contribution

WO wrote the first draft of the manuscript. SS, SK, DA, JH were all involved in the care of the patient and reviewed and revised the manuscript.

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Consent

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

CRedit authorship contribution statement

William Owen: Data curation, Investigation, Methodology, Visualization, Writing - original draft. **Simon Smith:** Conceptualization, Data curation, Project administration, Validation, Visualization, Writing - review & editing. **Sarin Kuruvath:** Writing - review & editing. **David Anderson:** Writing - review & editing. **Josh Hanson:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

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