Case report

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Neurological melioidosis complicated by cerebral venous sinus thrombosis

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Abstract

Melioidosis is a systemic disease endemic in South-east Asia and Northern Australia. The spectrum of the disease varies from asymptomatic infection to severe systemic manifestations. Timely diagnosis and treatment of melioidosis is a challenge due to its atypical presentations. We report a case of melioidosis causing cerebral abscesses and cerebral venous sinus thrombosis. Occurrence of these neurological manifestations in melioidosis is rare and it is a difficult condition to diagnose and treat. Timely diagnosis was a challenge in this patient due to the atypical presentation and the use of empirical antibiotics in the primary care setting. Limited laboratory diagnostic capability also contributed to this delay.

Key words: melioidosis, cerebral abscess, cerebral venous sinus thrombosis

Introduction

Melioidosis is an infectious disease caused by a Gram-negative bacterium, *Burkholderia pseudomallei,* found in soil and water.[1] Three forms of infection have been documented; subclinical, acute and chronic.[2] Acute melioidosis is defined as an illness with symptoms lasting less than two months. In acute melioidosis, the spectrum of clinical presentations ranges from minor localized infection to severe fulminant disease. The clinical presentation may be influenced by the magnitude of exposure, mode of acquisition and host factors such as immune-compromised state[3]. Melioidosis may present as pneumonia, abscesses in skin or in internal organs, osteomyelitis, septic arthritis and rarely as encephalomyelitis.[3] Central nervous system (CNS) melioidosis accounts for only 3-5% of the cases but carries a high mortality of up to 25%, compared to the overall mortality of 7% for systemic melioidosis.[4] CNS melioidosis can present as meningitis, encephalitis, brain abscesses, subdural empyema, or skull osteomyelitis. Dural sinus thrombosis complicating CNS melioidosis is rare.

Case presentation

A 69-year-old businessman with poorly controlled type 2 diabetes mellitus presented with intermittent high-grade fever with chills for three weeks. He also noticed multiple painful lumps on his scalp, generalized headache, intractable vomiting, weight loss and poor appetite. He came from the North Western Province of Sri Lanka, which has a tropical climate throughout the year. Heavy rainfall and flooding were present during the onset of his illness although he denied any contact with muddy water. On admission he was febrile (101°F), apathetic, emaciated and pale. There were multiple tender fluctuant lumps with purulent discharge on the scalp which were 2-3 cm in diameter. There was no lymphadenopathy. Spleen was palpable 3 cm below the costal margin and soft in consistency. Neurological

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examination was unremarkable except for reduced visual acuity in the left eye attributable to a mature cataract. A differential diagnosis of disseminated *Staphylococcus aureus* infection, extra pulmonary-tuberculosis, melioidosis and disseminated malignancy was entertained.

Full blood count showed white blood cell count of $11.9x10^9$/L with neutrophil leucocytosis, hemoglobin of 10.4 g/dl and platelet count of $380x10^9$/L. Blood picture showed toxic changes in neutrophils and microcytic hypochromic anemia. An ESR of 90 mm 1st hour, and C reactive protein (CRP) of 267 mg/L were reported. HbA1c was 9% and random blood glucose on admission was 320 mg/dl. Three blood cultures and culture of pus from scalp abscesses were reported as negative. Sputum for acid fast bacilli, Mantoux test and retroviral screening were negative. Chest X-ray and transthoracic echo-cardiogram were normal. Ultra sound scan of the abdomen showed 16 cm splenomegaly. Non-contrast computerized tomography (CT) scan of brain was unremarkable. He had an initial clinical response for empirical treatment with intravenous meropenem 1 g 8 hourly and vancomycin 1 g 12 hourly. However, he later deteriorated and developed acute confusion and agitation without focal neurological signs. Cerebrospinal fluid (CSF) analysis showed an acellular smear with elevated proteins (66 mg/dl). CSF for pyogenic culture including melioidosis and polymerase chain reaction (PCR) for tuberculosis (TB) were negative. Bone marrow biopsy showed features of severe sepsis and TB-PCR and culture were negative. Contrast enhanced CT scan of the chest revealed multiple micro abscesses in both lungs suggestive of either melioidosis or septic embolization. Magnetic resonance imaging (MRI) of brain revealed multiple cerebral and cerebellar abscesses (the largest one in the left occipital lobe) and superior sagittal venous-sinus thrombosis (CVST) (Figure 1). Results of the indirect haemagglutination assay (IHA) for melioidosis which was available on the 17th day of the hospital stay showed a titer of 1:160. Repeat IHA carried out in the 3rd week of hospital stay showed a rising titer of 1:1200 confirming the diagnosis of acute melioidosis. Vancomycin was withheld. The intensive phase of antibiotic therapy was initiated with the dose of meropenem increased to 2g tid to cover neurological melioidosis and the addition oral trimethoprim-sulfamethoxazole 320/1600 mg 12 hourly. The patient showed a remarkable recovery by the end of two weeks. The intensive phase was continued only for two weeks since he had already been treated with intravenous meropenem 1g 8 hourly for four weeks prior to the diagnosis. He was switched to eradication phase of treatment with oral doxycycline 100 mg 12 hourly and trimethoprim-sulfamethoxazole 320/1600 mg 12 hourly which was continued for five months. The patient was treated with warfarin for 3 months maintaining a target international normalized ratio (INR) of 2-3. Treatment for diabetes was optimized using subcutaneous premixed insulin and metformin. Scalp abscesses were healed at three weeks and patient showed a complete recovery by the end of eradication phase. However, MRI brain was not performed to assess the resolution of the brain abscesses.

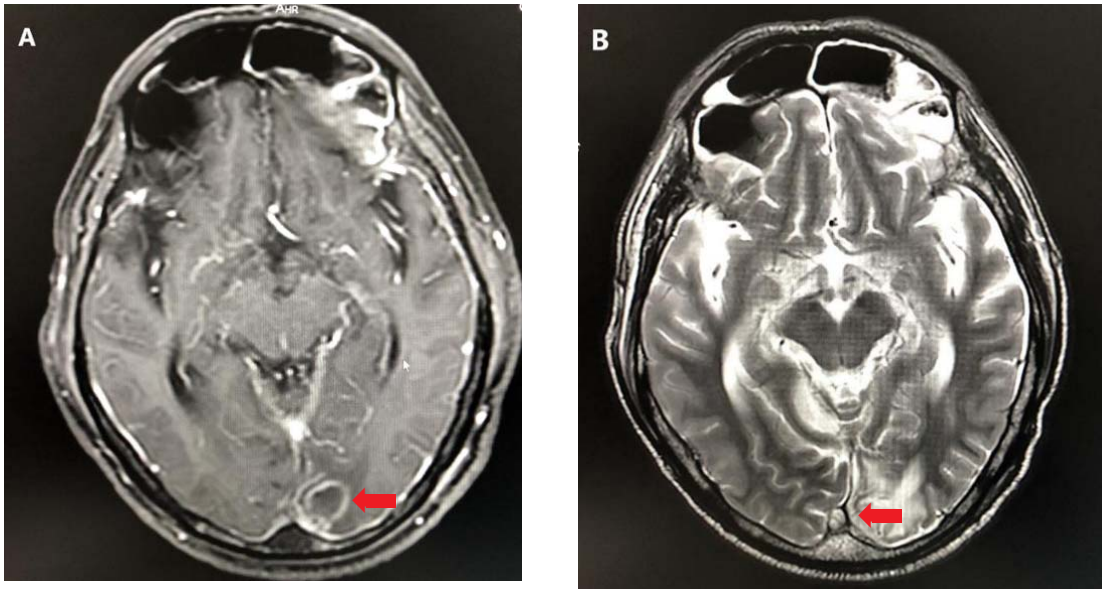

Figure 1. MRI brain with contrast: cystic lesion (1.2 × 1.5 cm) with ring enhancement located in left occipital lobe (A), diffuse meningeal enhancement and superior sagittal sinus thrombus (B).

Discussion

Melioidosis is increasingly recognized in Sri Lanka. The number of culture-positive cases has increased from year to year. Between 2006 and March 2017, 250 culture-positive cases were identified by a surveillance program.[5] Its prevalence in the island is not known. The symptoms and signs of the disease are nonspecific and, therefore, a high degree of suspicion is necessary to diagnose it early. The patient in this scenario presented with fever and discharging scalp abscesses. Negative pus and blood cultures hindered early diagnosis. Empirical treatment with co-amoxiclav may have resulted in negative cultures. CNS melioidosis is notorious because of difficulty in bacterial eradication and the destruction of brain structures which simulates a malignancy.[6] The patient had an initial recovery with empirical treatment with meropenem but later developed neurological manifestations suggestive of progression. This deterioration could have been due to occurrence of cerebral venous-sinus thrombosis, or inadequate dosage of meropenem required to penetrate the blood brain barrier.

Scalp abscesses may have been the infectious foci for brain abscesses. The scalp has a rich arterial supply and venous drainage. Emissary veins which connect the scalp and intracranial structures may have been the route for the dissemination of the organism to the brain. The initial unremarkable findings on the non-contrast CT of the brain may be due to poor sensitivity of the test to detect CVST and cerebral abscesses. Brain imaging with contrast enhanced MRI aided the diagnosis of cerebral abscess formation and CVST. Previous studies have also shown that, in the initial phase of neurological melioidosis brain CT scans are usually normal while the MRI shows dramatic changes.[7] The main diagnostic aid in this case was clinical suspicion and repetition of the antibody titer after two weeks. The confirmation of a diagnosis of melioidosis usually relies on isolation of the organism from biological specimens. However, when patients are treated with antibiotics prior to cultures, serological diagnostic methods are useful. Serological investigations are not widely available and are only performed in a single center in Sri Lanka as an in-house test.

CSF analysis usually reveals lymphocytic pleocytosis, high protein and normal glucose in neurological melioidosis.[8] Acellular CSF in this case may be due to the absence of meningeal inflammation in the early phase of the disease. Lumbar puncture was not repeated in the context of the MRI brain showing CVST and cerebral abscesses.

There are only a few case reports of melioidosis causing cerebral abscesses and CVST.[9,10] Furthermore, occurrence of CVST alone in association with melioidosis is uncommon. This may be due to the rarity of its occurrence with melioidosis or under-reporting. The pathological process causing CVST may be para-infectious immune-mediated vasospasm and secondary vasculitis or a hypercoagulable state in combination with endothelial dysfunction, due to activation of inflammatory and procoagulant cascades.[11] There are no studies to inform the optimum duration and therapeutic target of INR in CVST associated with melioidosis. Poor control of diabetes mellitus would have predisposed to disseminated acute melioidosis.[12]

Conclusion

Melioidosis is an increasingly recognized infectious disease in Sri Lanka. Knowledge about its varied clinical presentations would help to make an early diagnosis. Early diagnosis, which is important in prognosis, may be hindered by several factors such as false-negative culture reports due to prior use of antibiotics, lack of diagnostic facilities, and delayed time interval between specimen dispatch and report arrival. Therefore, national policy decisions such as promoting education about melioidosis and recognizing as a notifiable disease may improve the disease outcomes.

Consent

Consent for publication was obtained from the patient.

Competing interests

The authors declare that they have no competing interests.

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