

***Burkholderia pseudomallei* meningitis following inadequate treatment of melioidotic mycotic aneurysm**

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ABSTRACT

We report a 64-year-old man presenting with meningitis caused by *Burkholderia pseudomallei* predisposed by persistent aortic graft infection following inadequate treatment of a melioidotic mycotic aneurysm. The relapse of melioidosis presenting as acute meningitis is a unique event. Successful treatment of deep-seated melioidosis can only be achieved when robust antimicrobial therapy is combined with appropriate surgical debridement.

Keywords: aortic graft infection, *Burkholderia pseudomallei*, melioidosis, melioidotic meningitis, meningitis, mycotic aneurysm

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INTRODUCTION

Melioidosis is a potentially fatal infection, endemic in Southeast Asia and northern Australia. A characteristic feature of this disease is the formation of deep-seated abscesses, especially in the lung, liver, spleen and prostate.^(1,2) Meningitis is very rare, and only four cases of culture-positive meningitis caused by *Burkholderia pseudomallei* have been reported in the medical literature.⁽³⁻⁵⁾ The beta-lactam antibiotics, such as carbapenems or ceftazidime, constitute the backbone of the initial treatment, while other antibiotics (doxycycline, trimethoprim-sulfamethoxazole (TMP-SMX) and chloramphenicol) are less effective and are used only for maintenance therapy.^(1,2)

This case report involves a rare case of culture-positive meningitis caused by *Burkholderia pseudomallei* in a patient with persistent aortic graft infection, which complicated treatment of melioidosis mycotic aneurysm. It is probably the first case of relapse of melioidosis presenting as acute meningitis. This case underscores the challenges in achieving treatment success with deep-seated melioidosis, especially when the choice of the therapeutic agents is limited by severe, adverse drug reactions.

CASE REPORT

A 64-year-old-man with a past medical history of severe aortic regurgitation of unknown aetiology and

alcohol abuse was admitted with fever and confusion for one day.

He had been admitted 11 months earlier with fever and back pain of three weeks' duration. Initial blood cultures were negative and he did not respond to empirical ceftriaxone. Imaging studies revealed a large thoracoabdominal mycotic aneurysm and right pleural effusion. He underwent drainage of the right pleural effusion and thoracotomy with Dacron graft replacement of the distal descending aorta. Both pleural fluid and tissue from aortic aneurysm (collected intraoperatively) grew *Burkholderia pseudomallei* susceptible to all standard antibiotics used in therapy of melioidosis. The patient was then treated with a combination of intravenous ceftazidime and TMP-SMX, and he slowly improved. However, six weeks later, he developed severe exfoliative dermatitis. Both antibiotics were implicated and stopped. In view of the serious allergic reaction to the above antibiotics, maintenance therapy was continued with oral doxycycline alone.

Three months prior to the current admission, the patient developed back pain and haemoptysis. Work-up revealed leakage from the lower anastomosis of the aortic graft, which was contained by omentum. He was treated with endovascular stent placement, intravenous imipenem for five days (until all cultures proved to be negative) and discharged in stable clinical condition with maintenance doxycycline. When he presented with fever and confusion, physical examination revealed an elderly, cachectic and agitated man. He was febrile at 38.4°C. Blood pressure was 140/80 mmHg, heart rate 108/min and respiratory rate 20/min. He had terminal neck stiffness but no focal neurological deficit. Urgent computed tomography (CT) of the brain was unremarkable and lumbar puncture was performed. Cerebrospinal fluid (CSF) examination showed moderate pleocytosis (307 cells/mm³) with the predominance of mononuclear cells. Protein level in the CSF was 0.7 G/L and glucose level was 2.0 mmol/L (serum level 4.6 mmol/L).

Both blood and CSF cultures on admission yielded *Burkholderia pseudomallei*. These isolates were now resistant to tetracycline but otherwise had the same antibiotic susceptibility profile as those obtained

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11 months earlier. He was treated with intravenous imipenem, but remained febrile and bacteraemic ten days later. Oral chloramphenicol was added, and fever and bacteraemia resolved in several days. However, chloramphenicol had to be discontinued after 16 days due to myelosuppression. CT of the thorax showed a rim-enhancing, high-density collection of fluid with air locules around the aortic graft. The option of replacing the aortic graft in order to remove the nidus of infection was discussed with the cardiothoracic surgeon. However, the risk of an extensive cardiothoracic surgery was felt to be unacceptably high in this frail, elderly patient and hence conservative therapy was adopted. The patient slowly improved and completed six weeks of imipenem. He was also challenged with oral amoxicillin/clavulanate and tolerated it well. He was prescribed amoxicillin/clavulanate upon discharge for chronic, lifelong suppressive therapy. He remained stable and afebrile when seen five months later. Subsequently he was lost to further follow-up.

DISCUSSION

Melioidosis can occasionally affect the central nervous system, causing brain abscesses and encephalitis. Neurological melioidosis usually is characterised by various combinations of unilateral limb weakness, cerebellar and brainstem signs, cranial nerve palsies and peripheral weakness. CT is usually initially normal but magnetic resonance imaging may show significant changes.^(5,6) Meningitis is exceedingly rare. In the prospective investigation of more than 2,000 patients with melioidosis in Thailand, no cases of primary meningitis were noted.⁽¹⁾ Our search of the available medical literature revealed four cases (three adults and one infant) of culture-positive primary meningitis caused by *Burkholderia pseudomallei*.⁽³⁻⁵⁾ The clinical presentation of our patient (as well as that of all four previously-reported cases) was strongly suggestive of acute bacterial meningitis. The duration of symptoms in our patient was only one day. It was shorter than in previously-reported patients who had been symptomatic variably from two to ten days prior to the diagnosis.

The meningitis in this patient (as well as in previously-reported cases) was probably caused by a haematogeneous spread of *Burkholderia pseudomallei* from a remote infective focus. Our patient and three out of four previously-reported cases had positive blood cultures. Most patients (except one who was probably severely immunocompromised as evidenced by concomitant cryptococcal meningitis) had an obvious infection elsewhere in the body. In our patient, it was infection of the prosthetic aortic graft. Previously-

reported patients had pneumonia, prostate abscess or cellulitis.

The microscopical examination of cerebrospinal fluid in our patient revealed pleocytosis with lymphocytic predominance. The similar microscopical findings were also observed in one of four formerly-described cases.⁽³⁾ In the case series of neurological melioidosis published by Woods et al, four of seven reported patients were noted to have mononuclear pleocytosis.⁽⁵⁾ However, all these four patients had documented focal neurological deficit and negative CSF culture.

Melioidosis presenting as mycotic aneurysm is very rare, and is associated with significant morbidity and high relapse rates.⁽⁷⁾ Our knowledge about the optimal maintenance therapy for mycotic aneurysm caused by *Burkholderia pseudomallei* is very limited. Elliott and Currie summarised outcomes of 18 reported episodes of maintenance therapy among 14 patients with mycotic aneurysm.⁽⁸⁾ Regimens containing TMP-SMX were effective in all nine reported episodes of maintenance therapy. In contrast, monotherapy with doxycycline failed in all three reported cases. The relapse of melioidosis in our patient underscores difficulties in the management of melioidosis. First of all, no effort should be spared to remove a focus of infection. All suppurative collections should be drained or debrided in order to facilitate treatment and prevent recurrence.⁽¹⁾ Ideally, our patient should have undergone replacement of the infected aortic graft. An alternative would have been extra-anatomical bypass and resection of infected prosthesis with suturing of the arterial stumps.⁽⁷⁾ However, the risk of performing these complicated procedures was unacceptably high in this frail, elderly patient. The inability to remove the focus of infection was probably the most important reason for the relapse.

Furthermore, this case illustrates that doxycycline monotherapy should never be used for oral maintenance treatment of melioidosis. Its use may have also contributed to the relapse in this patient. In a recent study, Chaowagul et al compared doxycycline monotherapy with a combination of chloramphenicol, TMP-SMX and doxycycline for maintenance therapy for melioidosis. The rates of culture-confirmed relapse and treatment failure were significantly higher among patients randomised to the doxycycline regimen.⁽⁹⁾ Our patient previously developed severe exfoliative dermatitis while receiving a combination of ceftazidime and TMP-SMX. This precluded the use of beta-lactam antibiotics and TMP-SMX, which have much better track records for successful chronic suppressive therapy. Desensitisation and re-challenge of these

drugs should be considered in similar situations in the future. In summary, this case report highlights that melioidosis can relapse as acute meningitis. It also emphasises that therapy of melioidosis may be very difficult whenever the choice of the therapeutic agents is limited by severe adverse drug reactions and when the source of infection cannot be eradicated.

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