Short Report

# Spinal cord disease due to melioidosis

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**Keywords:** melioidosis, spinal cord, *Burkholderia pseudomallei*, case reports, Australia

Acute melioidosis typically presents as severe pneumonia or septicaemia. WOODS *et al.* (1992) have described neurological presentations of melioidosis affecting the brainstem and producing motor weakness. We describe a case of acute melioidosis which predominantly affected the spinal cord to produce paraplegia mimicking acute epidural abscess. The neurological lesions may have occurred in the setting of partially treated meningitis; however, the cerebrospinal fluid was sterile and no radiological evidence of abscess was identified. It is possible that immune or toxin-mediated mechanisms may have contributed to the neurological damage, perhaps in the context of partially treated central nervous system infection.

## Case report

A 23-year-old male Australian Aborigine from Arnhem Land, Northern Territory, developed mid-thoracic back pain, rhinorrhoea and a dry cough over 2 weeks and received doxycycline for several days. The pain increased in severity and 1 week prior to admission he developed progressive lower-limb weakness. He was unable to void or walk for 3 days before admission. There was no significant past medical history, allergies or family history.

On examination, his temperature was 39·3°C, blood pressure was 110/60 mmHg with regular relative bradycardia of 78/min. He had flaccid paraplegia with absent sphincter function and a sensory level at T5. There was bilateral mild generalized upper-limb weakness.

Cerebrospinal fluid (CSF) examination showed 380 leucocytes (59% lymphocytes, 6% monocytes, 35% neutrophils) and 20 red cells per $mm^3$, glucose 1·4 mmol/L, and protein 9360 mg/L (albumin 2640 mg/L, IgG 2440 mg/L). Gram stain and Giemsa stains of CSF revealed no bacteria. Bacterial culture of CSF was negative after 7 days. Cultures of CSF for viruses, mycobacteria, and fungi were also negative. A full blood count revealed leucocytosis [$14{\cdot}5 \times 10^9$/L (85% neutrophils)].

Serology was negative for mycoplasma, syphilis, hepatitis A, B and C, Japanese B encephalitis, equine morbillivirus, and dengue, Sindbis, Barmah Forest, and Ross River viruses. Cryptococcal antigen was not detected in CSF or serum. Hepatitis B surface antigen was negative. HIV and HTLV-I ELISA tests were negative. Serological tests for *Toxoplasma gondii*, cytomegalovirus, varicella zoster virus and Epstein–Barr virus were IgG positive and IgM negative.

Ceftazidime therapy was started after 2 sets of blood cultures were obtained because of the possibility of melioidosis, but was stopped when the blood cultures were sterile after 4 days.

A magnetic resonance imaging (MRI) scan of the brain and spinal cord performed on admission (Fig. 1) demonstrated an extensive high-signal lesion in the spinal cord, extending from the level of C4 to the conus on the T2-weighted images. There was no evidence of extrinsic compression, osteomyelitis, or epidural abscess. Further lesions were seen to extend from the right medulla to the right cerebral peduncle (Fig. 2).

On day 2, a provisional diagnosis of acute disseminated encephalomyelitis (ADEM) was made and treatment was commenced with intravenous methylprednisolone, 500 mg daily for 5 days.

On day 9 the patient became acutely confused with a

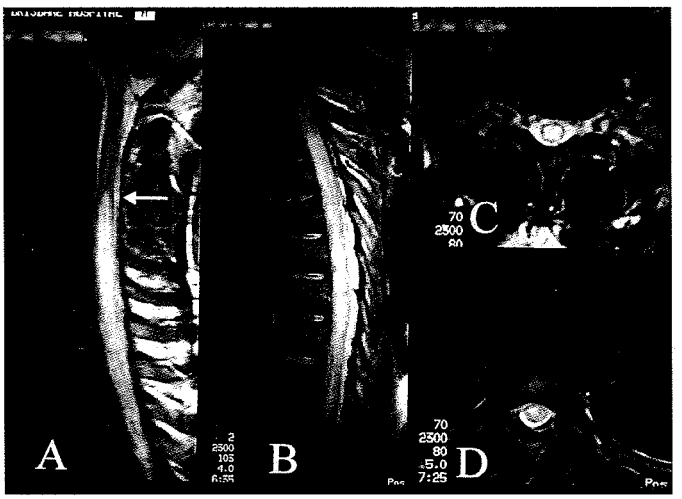


Fig. 1. Initial magnetic resonance imaging of the spine and spinal cord. Sagittal T2 weighted spin echo midline images of the cervical (A) and thoracic cord (B) demonstrate diffuse oedema producing swelling of the cord from the conus to C4 level (arrow). Axial T2 weighted gradient echo images of the cervical (C) and thoracic cord (D) show the extensive cord involvement.

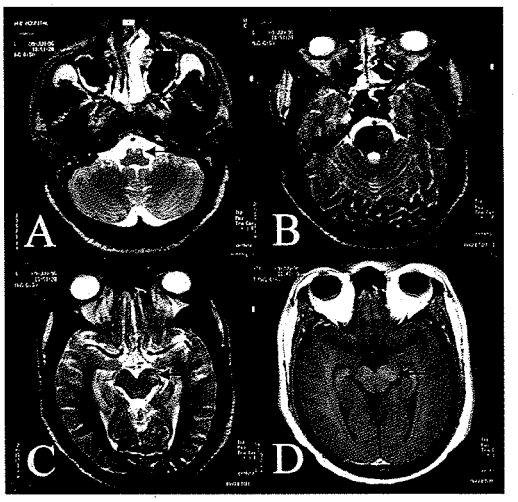


Fig. 2. Initial intracranial magnetic resonance imaging. (A), (B) and (C) Axial T2 weighted turbo spin echo images show focal high signal extending from the right medulla to the right cerebral peduncle (arrows). (D) Axial T1 weighted post contrast image of the cerebral peduncles shows swelling of the right peduncle with only minimal enhancement (arrow).

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new fever to 41°C with relative bradycardia (pulse, 100/min) and blood pressure 120/70 mmHg. He developed neck extension and extensor spasms of the upper limbs. No septic focus was found. The blood leucocyte count increased to $24{\cdot}0 \times 10^9$/L (90% neutrophils). Of 3 blood cultures taken at this time, 1 grew *Burkholderia pseudomallei* in <48 h, sensitive to ceftazidime and trimethoprim–sulphamethoxazole. Results of melioidosis serology, available on day 17, were positive [day 1, indirect haemagglutination assay (IHA) 640; day 10, IHA 160, IgM enzyme immunoassay (EIA) positive, IgG EIA positive]. Treatment with ceftazidime and oral trimethoprim–sulphamethoxazole was commenced. A second MRI study demonstrated new lesions in the cerebellum and centrum semi-ovale as well as symmetrical evolution of the original brainstem lesions which now extended into the supratentorial white matter (not shown). After 7 days of therapy, the patient's fever resolved and his leucocyte count became normal.

The patient completed 6 weeks of intravenous ceftazidime and oral trimethoprim–sulphamethoxazole, followed by 6 months of oral trimethoprim–sulphamethoxazole. His residual neurological deficits included paraplegia, extensor plantar responses, and sensory loss to all modalities below the mid-thoracic level, and he required intermittent self-catheterization.

## Discussion

Spinal cord involvement is an unusual neurological manifestation of melioidosis. Our previous series of neurological melioidosis cases demonstrated brainstem involvement predominantly, in the context of CSF pleocytosis, with elevated protein and variable glucose and negative CSF cultures in 4 of 5 patients. Neurological involvement continues to be associated with 10 (6%) of 180 cases of melioidosis in the prospective study at Royal Darwin Hospital since 1989 (HOWE *et al.*, 1997; B. J. Currie, unpublished) with most reported neurological melioidosis cases acquiring infection in northern Australia.

Whereas it is possible that this patient's neurological illness was unrelated to melioidosis, and that high-dose prednisolone unmasked a latent subclinical infection, the clinical presentation of fever, leucocytosis, neurological involvement and high-titre IHA tests for melioidosis on admission in a patient from this region is consistent with the diagnosis of melioidosis.

High-dose intravenous methylprednisolone was administered to this patient to treat presumed ADEM, a syndrome related to increased immune reactivity to myelin basic protein triggered by antecedent viral, mycoplasma or bacterial infection or vaccination (PENDER, 1995). T-cell proliferation assays performed on the patient's peripheral blood lymphocytes during convalescence, after methylprednisolone therapy, failed to show increased autoreactivity against myelin basic protein but may have missed the peak reactivity. An adverse outcome of immunosuppressive therapy is the acceleration of growth of intracellular pathogens kept static by macrophages, which almost certainly occurred in our patient.

This patient had none of the prior typical risk factors for developing melioidosis which include alcoholism, corticosteroid use, or diabetes mellitus. We speculate that the initial respiratory illness was caused by *B. pseudomallei* which was partially treated with tetracycline. Positive IHA test on admission supports a diagnosis of melioidosis on presentation which was eventually culture positive after high-dose methylprednisolone therapy.

The pathogenesis of neurological melioidosis is unclear. It is possible that this patient developed the neurological syndrome from a partially treated infection of the central nervous system (CNS). CSF cell counts and glucose support that possibility; however, no antibacterial substances were detected in the CSF at the time CSF cultures were negative. *B. pseudomallei* can reside in phagocytic cells and thus CSF cultures for this organism may have lower sensitivity than culture for other agents of meningitis. Other possibilities for the CNS pathology include immune-induced lesions, e.g., ADEM, or exotoxin-mediated pathology perhaps in the context of a sequestered focus of the pathogen in the CNS. We previously hypothesized that an exotoxin, which produced hind-limb paralysis in mice, could be responsible for at least some of the neurological manifestations of melioidosis. The *B. pseudomallei* isolate from our patient produced an exotoxin with cytotoxicity for HeLa cells as did each of the isolates tested in our previous series. Insufficient CSF was available to test for local production of exotoxin antibody. To clarify the pathogenesis of neurological melioidosis, future investigations should include assays of CSF for evidence of direct infection by *B. pseudomallei* by culture and polymerase chain reaction (DHARAKUL *et al.*, 1996), assay of CSF for evidence of antibody production against the exotoxins of *B. pseudomallei*, and evaluation of lymphocytes for increased autoreactivity to myelin antigens. Antigen detection in CSF may be a sensitive diagnostic test for future studies (ANUNTAGOOL *et al.*, 1996).

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*Received 3 September 1998; revised 23 November 1998; accepted for publication 15 December 1998*