Variable Presentation of Neurological Melioidosis in Northeast Thailand

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Abstract. We describe three instructive cases of neurologic melioidosis that demonstrate the variable nature of clinical manifestations and disease pathology. The appropriate duration and choice of parenteral and oral antimicrobial therapy for neurologic melioidosis are also discussed.

INTRODUCTION

Melioidosis, the infection caused by Burkholderia pseudomallei, is most commonly reported from Northeast Thailand and Northern Australia.1-2 Manifestations of disease are extremely broad-ranging.3 A specific syndrome of meningocerephalitis with flaccid paralysis or peripheral motor weakness occurs in 5% of cases in Northern Australia, and cerebral abscess is occasionally reported.4-6 We prospectively evaluated 191 melioidosis cases presenting to Sappasithiprasong Hospital, Ubon Ratchathani, Northeast Thailand, during 2005 to define the frequency and manifestations of neurologic melioidosis in this setting. Three adult cases were defined with variable presenting features and disease pathology. These cases provide a framework for the discussion of appropriate antimicrobial therapy of neurologic melioidosis.

CASE REPORTS

Patient 1, a 68-year-old male rice farmer with a history of chronic kidney disease associated with renal calculi and a left lithotomy 2 years previously, presented with a 7-day history of fever. Parenteral ceftriaxone was prescribed for suspected acute pyelonephritis, but on day 3 he developed a left hemiparesis (grade I) with a left upper motor neuron facial palsy; his Glasgow coma score (GCS) was 14. A random plasma glucose was 25 mmol/L. Three blood cultures were negative. Throat swab and urine were culture-negative for B. pseudomallei. Computer tomography (CT) showed hypodensity in the right frontal lobe area (Figure 1–1A). He was treated for acute pyelonephritis, acute ischemic stroke, and a new diagnosis of diabetes mellitus. Parenteral cefazidime was given for 9 days, during which his fever settled and the motor weakness improved (grade IV). He was discharged after 6 weeks; no oral antimicrobials were prescribed. He made a full neurologic recovery and remained well for 5 months, after which he presented with recurrent hemiparesis (grade IV). CT showed a ring-enhancing lesion in the right frontal lobe with surrounding edema (Figure 1–1C). He was treated with cefazidime for 3 months, followed by a 1-year course of oral eradicative treatment with trimethoprim–sulfamethoxazole (80 mg/400 mg, 6 tablets/day; body weight 55 kg). He has since regained full neurologic function.

Patient 2, a 51-year-old female rice farmer with a history of diabetes mellitus and chronic kidney disease associated with a right nephrectomy 10 years previously, presented with a 6-day history of fever and two generalized tonic–clonic convulsions. Neurologic examination on admission was normal with a GCS of 15. A blood culture grew B. pseudomallei with a typical susceptibility pattern (susceptible to cefazidime, meropenem, trimethoprim–sulfamethoxazole, doxycycline, and amoxicillin–clavulanic acid). He was treated with meropenem for 2 weeks followed by cefazidime for 6 weeks; no oral antimicrobials were prescribed. He made a full neurologic recovery and remained well for 5 months, after which he presented with recurrent hemiparesis (grade IV). CT showed a ring-enhancing lesion in the right frontal lobe with surrounding edema (Figure 1–1A). He was treated with cefazidime for 14 days, followed on discharge by trimethoprim–sulfamethoxazole (80 mg/400 mg, 6 tablets/day) plus doxycycline (100 mg, 2 tablets/day). At follow-up clinic 1 month later, she complained of nausea, vomiting, and anorexia. Oral antimicrobials were changed to amoxicillin–clavulanic acid (amoxicillin 3 g/day and clavulanic acid 750 mg/day). Two months subsequent to this, she developed a progressive left hemiparesis (grade I) over a period of 1 week and had four generalized seizures. CT showed an epidural collection in the right frontal lobe area with surrounding edema (Figure 1–2B). Blood and urine cultures were negative; she was treated with cefazidime for 2 weeks followed by meropenem for 2 weeks. Follow-up CT showed no improvement. Craniotomy was performed, and 5 mL of pus obtained from the epidural space was culture-positive for B. pseudomallei with a typical antimicrobial susceptibility pattern. Cefazidime was continued for a further 5 weeks before switching to oral trimethoprim–sulfamethoxazole (80 mg/400 mg, 8 tablets/day; body weight 64 kg). She completed 20 weeks of oral treatment and regained full neurologic function. Repeat CT showed almost complete resolution of the abnormalities (Figure 1–2C). B. pseudomallei obtained from the first and second episodes had an identical banding pattern on pulsed-field gel electrophoresis (data not shown).

Patient 3, a 45-year-old female rice farmer with a history of diabetes mellitus, presented with a splenic abscess. She was...
treated for suspected melioidosis with parenteral amoxicillin–
clavulanic acid for 9 days followed by oral amoxicillin–
clavulanic acid for 4 months (amoxicillin 3 g/day and clavu-
lanic acid 750 mg/day), and trimethoprim–sulfamethoxazole
(80 mg/400 mg, 4 tablets/day; body weight 35 kg) for a month
after the development of a rash. Follow-up abdominal ultra-
sound showed complete resolution of the splenic lesion.

Eleven months after the first admission, she presented with a
1-month history of fever, chills, and a progressively enlarging
skull mass. On examination, there was an 8-cm soft fluctuant
parietal skull mass (Figure 1-3A). No neurologic deficit was
present. Blood cultures were negative, but urine culture grew
*B. pseudomallei*. Skull x-ray revealed two “punched-out”
bone lesions in the affected area (Figure 1-3B). CT showed a
cystic lesion in the scalp and an epidural abscess with bone
changes consistent with osteomyelitis (Figure 1-3C). Cefazidi-
dime was commenced 4 days prior to a craniotomy, during
which the infectious process was found to involve the scalp
muscle, bone, and epidural space. Craniectomy was per-
formed, and 30 mL of yellowish pus was evacuated, which was
culture-negative. Ceftazidime was continued for 16 days, followed by oral trimethoprim–sulfamethoxazole (80 mg/400 mg, 6 tablets/day; body weight 35 kg) for 20 weeks.

DISCUSSION

Patients presenting with fever together with seizures and/or a neurologic deficit in melioidosis-endemic regions should be investigated by brain CT. The initial scan, however, may show few or no abnormalities in cases of melioidosis with cerebral involvement. Individuals with suspected melioidosis affecting any site should have cultures of blood, urine, throat swab, respiratory secretions, pus, or swabs from skin lesions as available. Patient 3 demonstrates the utility of culturing from disseminated sites, because urine culture alone was positive in this case. On the basis of this study, 1.5% of melioidosis patients in Thailand appear to have neurologic melioidosis with intracranial involvement, while the syndrome of meningoencephalitis was not found.

Antimicrobial therapy for melioidosis generally requires parenteral therapy for 10–14 days, followed by oral antimicrobials for 12–20 weeks. Recommended drugs are cefazidime or a carbapenem drug for parenteral therapy, followed by trimethoprim–sulfamethoxazole with or without doxycycline for oral eradication therapy. Therapy for intracerebral melioidosis requires special consideration because not all drugs used for the treatment of melioidosis achieve therapeutic concentrations in the brain. Ceftazidime or a carbapenem are appropriate because they both achieve high levels in CSF. The addition of parenteral trimethoprim–sulfamethoxazole to ceftazidime is not associated with a survival advantage in the treatment of melioidosis in general, but dual therapy should be considered for the treatment of neurologic infection in view of its excellent CNS penetration. Doxycycline concentrations in CSF are not higher than their minimal inhibitory concentration (MIC) to B. pseudomallei but may be important for the treatment of extracerebral sites. We recommend parenteral treatment of neurologic melioidosis for a minimum of 4 weeks, followed by oral eradication therapy for a minimum of 6 months. This mirrors treatment recommendations at the Royal Darwin Hospital in Northern Australia (Professor Bart Currie, personal communication). Choice and duration of oral eradication treatment are determinants of relapse. Amoxicillin–clavulanic acid has been shown to be associated with a higher rate of relapse, but the combination remains an alternative oral agent in Thailand. This is not an acceptable option, however, for treatment of neurologic melioidosis because the concentration of amoxicillin–clavulanic acid in CSF is < 10% relative to blood, which falls below the MIC for B. pseudomallei. Patient 2 had relapse while being treated with amoxicillin–clavulanic acid, and patient 3 had relapse 5 months after completing 20 weeks of oral treatment, 16 weeks of which was with amoxicillin–clavulanic acid. Options for treatment of patients with intolerance to trimethoprim–sulfamethoxazole or infected with strains resistant to trimethoprim–sulfamethoxazole are limited. Prolonged parenteral therapy is impossible in resource-poor regions, where probably the best option is chloramphenicol plus doxycycline.

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