

Neurological melioidosis in East Malaysia: Case series and review of the literature

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Abstract

Melioidosis is an infectious disease caused by an aerobic, non-spore forming gram negative bacillus, *Burkholderia pseudomallei*. It is known to be of high incidence in parts of rural South East Asia, and in Northern Australia. Pneumonia is the commonest manifestation. We report here three cases of neurological melioidosis from the registry of 169 cases of melioidosis in Bintulu Hospital, Sarawak, East Malaysia, with a review of neurological melioidosis in the literature. The annual incidence of melioidosis is estimated to be 8 per 100,000 populations in the Bintulu district. Neurological melioidosis accounts for 1.8% of our melioidosis cases. A review of 76 cases of neurological melioidosis reported in the literature inclusive of our 3 cases shows that localized brain or spinal inflammation or abscess is the most common manifestation occurring in 80% of patients. Close to half (53%) have intra axial abscess (brain or spinal cord), a quarter (27%) have extra axial lesions only (epidural or subdural collection, osteomyelitis or scalp abscess), and another quarter (27%) have both intra and extra axial lesions. Thus, *B. pseudomallei* appears to be unique among the bacterial central nervous system infection to be able to affect the brain and its contiguous tissues, crossing the tissue plane particularly resulting in osteomyelitis, scalp abscess and vice versa. Two thirds of the neurological melioidosis patients have only neurological disease with no evidence of disease elsewhere.

Key words: *Burkholderia pseudomallei*, neurological melioidosis, Bintulu, Sarawak, Malaysia

INTRODUCTION

Melioidosis is an infectious disease caused by an aerobic, non-spore forming gram negative bacillus, *Burkholderia pseudomallei*. This potentially fatal disease is transmitted by inhalation, ingestion or inoculation of microorganisms from the contaminated soil or water.¹ Farming, logging or outdoor recreational activities such as water rafting or jungle trekking increase the risk of infection.^{2,3} The common risk factors for melioidosis are diabetes mellitus, chronic renal disease, alcoholism, chronic liver disease and underlying malignancy.³ Melioidosis is known to be endemic in South East Asia, but it is also seen in parts of Australia, South Asia, China, Central and South America.^{2,4-6} Malaysia, North East Thailand and Northern Australia are recognized as “highly endemic” locations.² Melioidosis commonly manifest as pneumonia with prolonged fever. It can also manifests with abscesses in liver, spleen, skin and bone. Neurological melioidosis is uncommon, said to occur in less than 5% of patients.^{2,3} Bintulu Hospital in central Sarawak, East Malaysia serves

a population of around 250,000; covering the Bintulu and Belaga districts which are largely rural. Since January 2008, we have maintained a registry for melioidosis with 169 cases to date (July 2016) and have documented three cases of neurological melioidosis. We report here the three cases and present an updated literature review on the disease.

METHODS

Bintulu Hospital maintained a registry for all culture-confirmed melioidosis cases since January 2008. The main medical care facility in Bintulu district is the Bintulu Hospital. As the access to private health care facility particularly for an illness that require long term care such as melioidosis is limited, we believe that the hospital registry has captured majority of the cases of melioidosis in the area. However, as Bintulu Hospital also covers the rural population who has poor health care access in view of transport difficulties, some of these patients may not be diagnosed and captured into our registry. All patients admitted to Bintulu Hospital with fever or

sepsis will have bacterial cultures performed from all clinical specimens including asymptomatic sites for active search for melioidosis. Cultures for all clinical specimens are performed using routine culture medium (blood, chocolate, McConkey and Muller-Hinton agar). The existence of gentamicin-susceptible *B. pseudomallei* isolates in Sarawak, renders the use of selective medium such as Ashdown broth. We included patient's demography, risk factors, baseline investigations on admission, organ involvement, admission to intensive care unit with duration of intensive care, types of culture- confirmed clinical specimens, isolates' sensitivity results, ultrasonography findings, initial and eradication antibiotic therapy, follow up records and outcome of treatment into the registry.

In the search of literature, we found a total of 76 reported cases of neurological melioidosis over the past 50 years. Keywords such as melioidosis, neurological melioidosis and *B. pseudomallei* were searched in PubMed. We reviewed in detail all the case series of neurological melioidosis, where collection of cases was done systematically and imaging details were available. We excluded single case reports or reports based on a specific clinical presentation, or case series with incomplete clinical or imaging data. We tabulated the number of cases in each literature with patients' age, risk factors neuroimaging findings and outcome in this literature review.

RESULTS

A total of 169 cases of melioidosis have been seen at our hospital over 8.5 years, suggesting an annual incidence of melioidosis in Bintulu of approximately 8 per 100,000 populations. We found 3 patients with neurological melioidosis among the 169 melioidosis cases (1.8%) in our registry.

B. pseudomallei isolate's sensitivity were captured in the registry in Bintulu Hospital, Sarawak. An unusual gentamicin- susceptible *B. pseudomallei* isolates were found in Sarawak. One of the three patients (Case 3)' isolates were gentamicin-susceptible. The other 2 patients' isolates did not have gentamicin susceptibility tested as this is not a routine antibiotic susceptibility test done in Bintulu Hospital before the year of 2013.

The followings are the clinical details of the three cases.

Patient 1

A 46 year-old farmer, an active smoker without past medical illness, presented in August 2011 with fever for 2 months associated with generalized headache, lethargy and frontal scalp swelling. On examination, there was no neurological deficit. Initial magnetic resonance imaging (MRI) of the brain showed a mass at mid frontal region which extended inferiorly and eroded the left frontallbone (Figure 1).

Incision and drainage of scalp abscess was performed, which grew *B. pseudomallei*. The abdomen ultrasonography showed multiple splenic abscesses measuring 4 -5 mm although she had no gastrointestinal symptoms. She was also found to have diabetes, and was commenced on metformin.

She was treated with intravenous (IV) ceftazidime 2 gram thrice daily for 14 day which was then escalated to meropenem 2g 8 hourly for 2 weeks, then IV ceftazidime 2 gram 6 hourly for 4 week and followed by oral trimethoprim-sulfamethoxazole (TMP- SMX) 240/ 1200mg twice daily for one year. Repeat MRI brain at 6 weeks, 4 months and 7 months showed gradual resolution of the lesions. There were no residual neurological symptoms.

Patient 2

A 16 year-old boy presented in February 2012 with three days of fever, associated with vomiting, diarrhea and one episode of generalized tonic-clonic seizure. He was diagnosed with diffuse B cell lymphoma in October 2011 and had completed 4 cycles of chemotherapy (R-CHOP regime) prior to his presentation. Chemotherapy was given one week prior to his symptom. His temperature was 39°C but he was haemodynamically stable. Neurological examination showed no meningism or focal neurological signs. He had pancytopenia: hemoglobin was 9.8g/dL, total white cell count was $1.68 \times 10^3/\text{mm}^3$ (absolute neutrophil count: $1.2 \times 10^3/\text{mm}^3$) and platelet was $147 \times 10^3/\text{mm}^3$. Erythrocyte sedimentation rate (ESR) was raised at 64 mm/ hour, renal profile and liver function test were normal. He was treated initially as neutropenic sepsis with IV piperacillin-tazobactam. MRI brain showed multiple abscesses of various sizes in the left temporal regions with surrounding white matter edema (Figure 2).

Blood culture grew *B. pseudomallei* and the antibiotics regime was escalated to IV meropenem gram 8 hourly. Ultrasonography of abdomen showed a solitary 2.3 x 2.1 cm liver abscess at

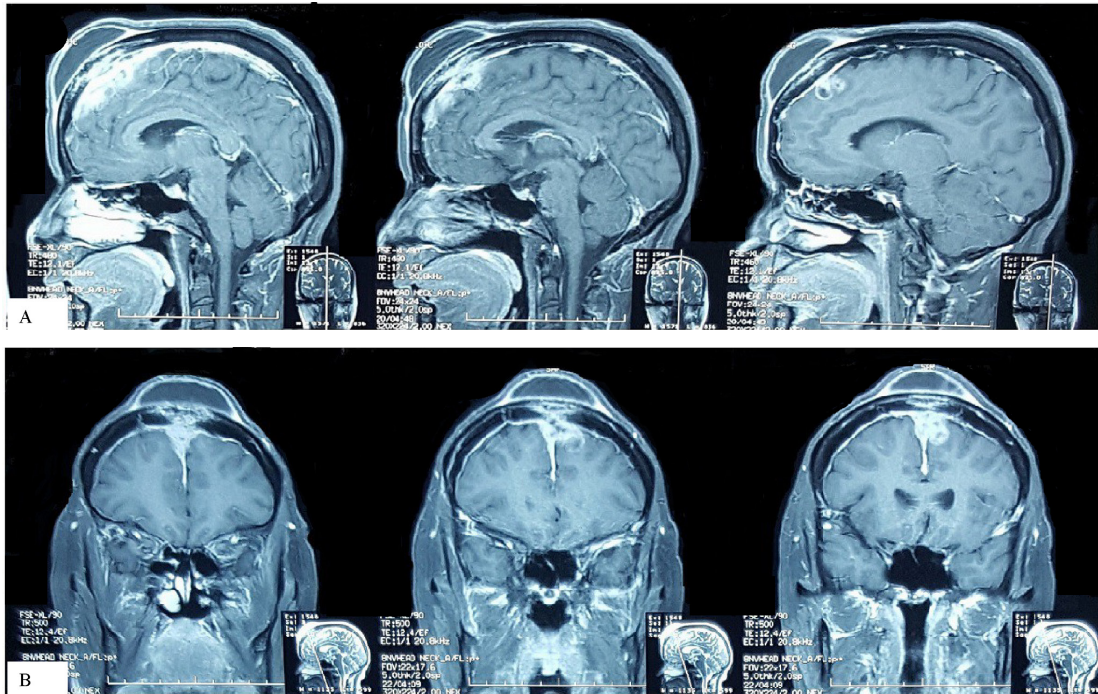


Figure 1. (A) Initial MRI brain sagittal T1-weighted image and (B) coronal T1-weighted image showed hypointense mass over mid frontal bone. The mass extends inferiorly to erode the left frontal bone with peripheral enhancement.

segment V and echocardiography did not show any evidence of vegetation. Repeat MRI brain 2 weeks after treatment showed improvement of left temporal lobe abscesses (Fig 3). He completed a total of 6 months eradication therapy, consisting of TMP-SMX 320/1600mg twice daily. He recovered well, and managed to complete the last 2 cycles of chemotherapy for lymphoma.

Patient 3

A 67 year-old lady presented in January 2016 with one week history of fever and cough. She had past history of diabetes mellitus and hypertension. On examination, she was febrile but was not in respiratory distress. Her initial blood investigations showed elevated white blood cell

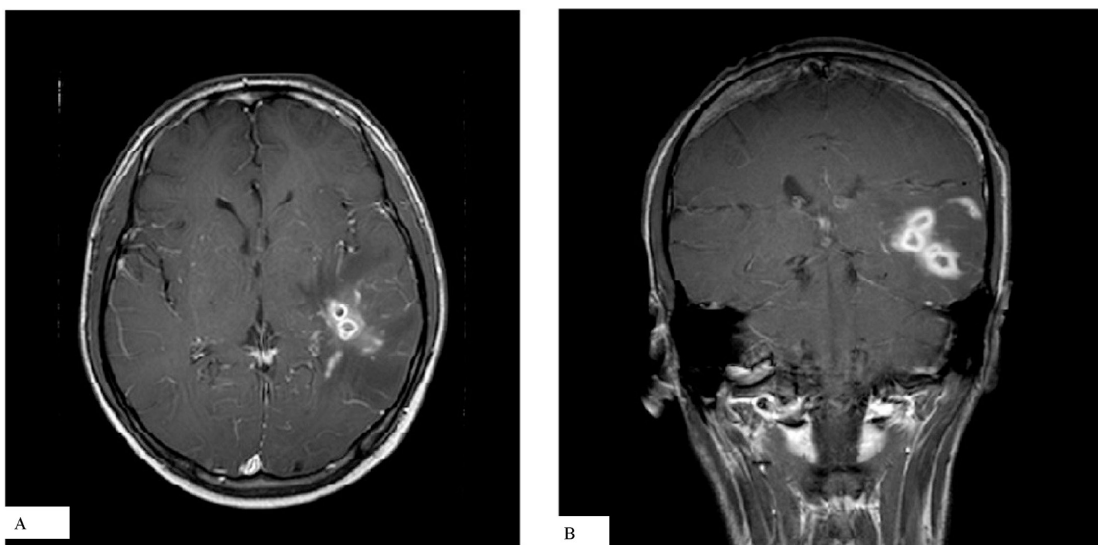


Figure 2. (A) Initial MRI brain axial T1-weighted image and (B) coronal T1-weighted image showed multiple abscesses in the left temporal lobe.

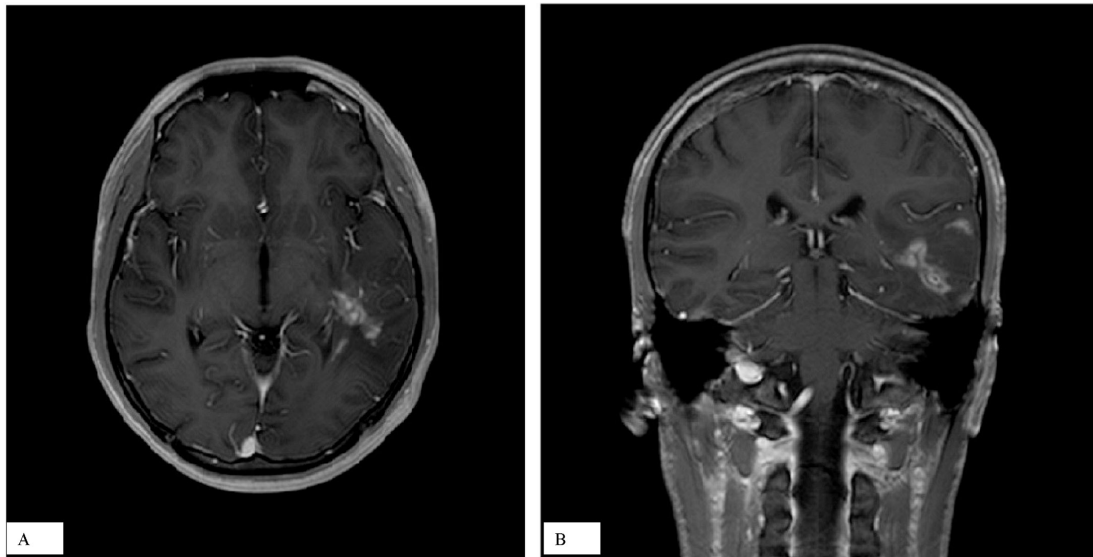


Figure 3. MRI brain after 3 weeks of treatment. (A) Axial T1-weighted image and (B) coronal T1-weighted image 3 weeks after IV meropenem showed reduction in size of left temporal lobe abscesses.

count of $3.5 \times 10^3/\text{mm}^3$ with normal haemoglobin and platelet count. Her liver enzymes were mildly elevated with ESR raised at 58 mm/hour, and C reactive protein (CRP) was positive. Her initial chest radiograph showed right lower zone opacity. She was diagnosed as lobar pneumonia and was started with IV ceftazidime 2 gram 8 hourly. Despite parenteral antibiotic, she continued to be febrile for the next 12 days with persistent leukocytosis.

On day twelve of admission, she developed confusion with left hemiplegia. The Glasgow Coma Scale (GCS) was E4V1M5. Urgent contrasted MRI brain showed two large enhancing lesions within the right parietal lobe with perilesional edema, meningeal enhancement, adjacent subdural collection and an overlying scalp abscess with periosteum erosion (Figure 4). Lumbar puncture showed clear cerebrospinal fluid (CSF), mild lymphocyte pleocytosis (lymphocyte

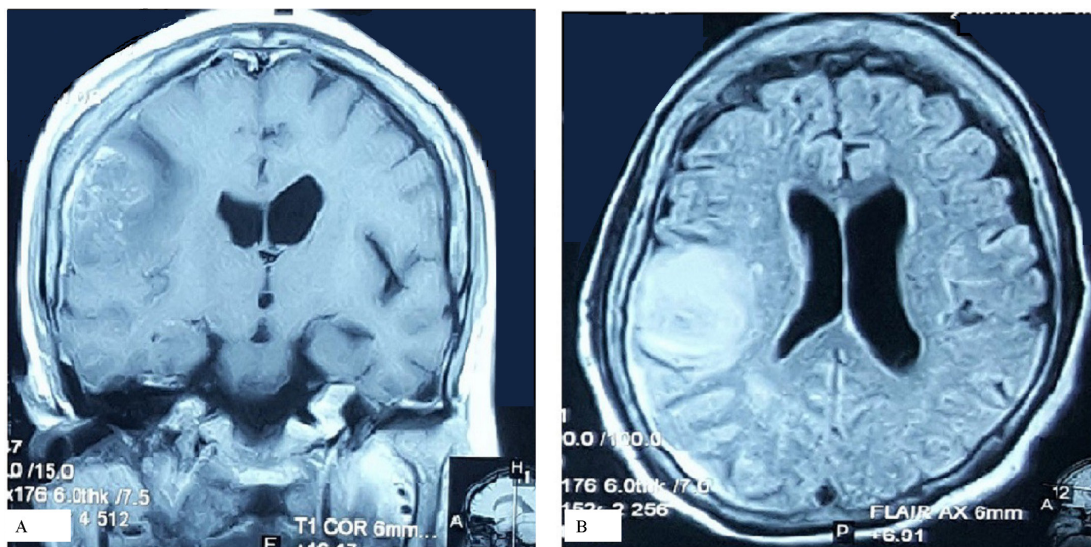


Figure 4. Initial MRI brain. (A) Coronal T1-weighted image and (B) axial T2-FLAIR image showed 2 lesions within right parietal lobe, the large lesions measuring about 3.5 x 3.5 x 3.0 cm (Width x AP x CC length) and the smaller lesion 1.3cm in diameter which is immediately posterior to the larger lesions which appears homogenous.

count 20 cells/mm), raised protein at 0.81g/L; glucose of 5.1mmol/L and no growth on cultures. CT scan of thorax, abdomen and pelvis showed consolidation of the right lower lobe and splenic abscess. Blood cultures grew *B. pseudomallei* and the diagnosis of disseminated melioidosis was made. She was treated with IV meropenem 2 grams 8 hourly for 10 days, followed by IV ceftazidime 2 grams 6 hourly for another 4 weeks and oral TMP-SMX 320/ 1600mg twice daily for 6months.

After 2 weeks of intravenous antibiotics, she responded well and showed slight neurological recovery (power left upper limb 0/5, left lower limb 2/5, and she was able to vocalize incomprehensible words). Her symptoms gradually improved with physiotherapy and occupational therapy. After 6 weeks of IV antibiotics, repeat MRI brain showed improvement in the right parietal lobes abscess with resolution of the scalp abscess and subdural collection (Figure 5). She recovered fully with no neurological deficit after a total of 6 weeks of IV antibiotics.

DISCUSSION

As mentioned above, a total of 169 cases of melioidosis have been seen at our hospital over 8.5 years, suggesting an annual incidence of melioidosis in Bintulu of approximately 8 per 100,000 populations. This is similar to the annual incidence reported in Alor Setar, Kedah state in Peninsular Malaysia (16.4 per 100,000)⁷, NorthEast Thailand (12.7 per 100,000)⁸ and

Northern Territory of Australia (19.6/100,000).³

We found 3 patients with neurological melioidosis among the 169 melioidosis cases (1.8%) in our registry. Such a low prevalence of nervous system involvement is consistent with previous reports from elsewhere. Currie *et al.* reported 3% of neurological melioidosis in 540 patients seen over 20 years in the Royal Darwin Hospital, Northern Territory Australia, while Limmathurotsakul *et al.* reported 1.5% of neurological melioidosis in North East Thailand.^{3,9} Similarly, the proportion of melioidosis cases with neurological involvement in other states of Malaysia was previously reported to be between 1.8% to 5.7%.^{7,10,13}

We found a total of 42 cases (from 7 case series including our own) that fulfilled the criteria mentioned above in the literature review. Prevalence, age and risk factors of the patients with neurological melioidosis are shown in Table 1. The risk factors in our patients were similar to the risk factors of other neurological melioidosis in other case series, i.e., diabetes mellitus, malignancy and farming. The mortality rate for neurological melioidosis is 7/42 (16.6%). Twenty patients (47.6%) who survived have full neurological recovery without neurological deficit, with the remaining 12 patients (28.6%) having residual neurological deficit (Table 1), showing that neurological melioidosis has significant mortality and morbidity.

Of our 3 patients, two presented with brain abscess with involvement of the adjacent

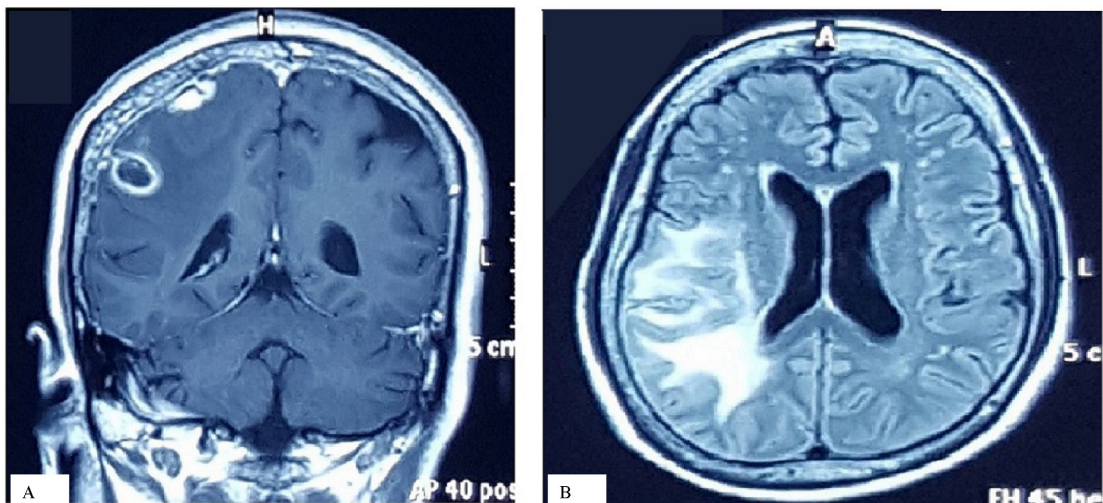


Figure 5. MRI brain after 6 weeks of treatment. (A) Coronal T1-weighted image and (B) axial T2-FLAIR image showed 2 right parietal lobe abscess with reducing size. Larger lesion measures 1.3 x 1.2 x 1.0 cm and smaller lesions measure 1.0x0.7x1.0cm. Subdural collection has reduced in size, measured 0.5x0.6x2cm. There were persistent right parietal marrow signal changes and scalp abscess has resolved.

Table 1: Prevalence, age and risk factors of neurological melioidosis patients

	Currie 2000 ¹¹	Chadwick 2002 ¹²	Muthusamy 2007 ¹³	Limmathuro t-sakul 2007 ⁹	Kumar 2008 ¹⁴	Hsu 2015 ¹⁵	Fong 2017	Total
Country	Northern Australia	Singapore	Malaysia	Thailand	India	Northern Australia	Malaysia	
Number of cases of neurological melioidosis (%)	12 (5%)	5	3/ 160 (1.8%)	3/191 (1.6%)	6	10	3/169 (1.8%)	
Age range	20-68	29-74	17-45	45-68	35-54	13-69	16-67	
Risk factors	Diabetes, chronic renal disease, farmer	Diabetes, alcoholism, farmer	Diabetes,	Diabetes, chronic renal disease, farmer	Not mentioned	Diabetes, alcoholism	Diabetes farmer malignancy	
Outcome								
Death	3	0	0	0	1	3	0	7/42
Partial neurological recovery	6	2	-	-	-	4	-	12/42
Neurological deficit (if partial recovery)	2 (Residual hemiplegia), 2 (Residual paraplegia), 2 (Residual cerebellar ataxia)	2 (Residual hemiparesis)	-	-			-	
Full neurological recovery	3	2	3	3	4	2	3	20/42
Relapse/ Other complications		2	-	1	2	1 (Requires long term antibiotic)	-	5/42

leptomeninges, osteomyelitis and scalp (Cases 1 and 3), and one with focal brain abscesses (Case 2). Table 2 shows the neuroimaging findings of the 30 patients from the 6 case series including our own, and whether there are foci of infection elsewhere. As shown, localized brain or spinal cord infection including abscess formation is the predominant manifestation occurring in 24/30 (80%) of patients. More than half (53.3%, 16/30) have intra axial lesions only (single or multiple abscesses in cerebrum, cerebellum, brainstem or spinal cord), as in our Case 2. The predominant neurological manifestations as localized brain

or spinal cord infection as described above, is consistent with findings from post-mortem pathology studies by Koszyca *et al*, where micro- and macro-abscesses with central necrosis are the main pathologic findings.¹⁶

A fifth of (20%, 6/30) patients have extra axial lesions only (epidural or subdural collection, scalp abscesses or skull osteomyelitis) while 8 patients (26.6%, 8/30) have both intra and extra axial lesions, as seen in our Case 1 and 3. When the abscess involve the brain, bone, and scalp, it is interesting to speculate which come first. It would be more likely to start in the bone or the brain,

Table 2: Neuroimaging findings based on location and distribution of the lesions^a

	Chadwick 2002 ¹²	Muthusamy 2007 ¹³	Limmathurot- sakul 2007 ⁹	Kumar 2008 ¹⁴	Hsu 2015 ¹⁵	Fong 2017	Total
Cerebrum	5	2	1	4	3	2	17 ^b
Cerebellum	-	-	-	-	5	-	5
Brainstem	1	-	-	-	6	-	7
Spinal cord	-	-	-	-	4	-	4
Leptomeninges	1	-	-	-	4	1	6
Subdural/ Epidural	1	2	2	-	2	1	6
Skull/Vertebrae	1	2	1	2	1	2	9
Scalp	-	-	1	-	1	1	3
Intra- axial only	3	-	1	4	7	1	16/30
Extra- axial only	-	1	2	2	2	1	6/30
Both intra and extra-axial	2	2	-	-	1	1	8/30
Other foci of infection	4(Lungs, prostate, spleen, scrotum, obturator internus	None	1(Spleen)	None	2 (Lungs)	3 (Lungs, spleen, liver)	10/30

^a Twelve cases from Currie *et al.* were excluded as there were no detail description of the neuroimaging findings in the case series.¹¹

^bLocation of cerebral abscesses: 6 cases of frontal lobe, 4 cases of parietal lobe, 2 cases each for temporal lobe and occipital lobe. Location is not specified for 5 cases.

rather than the scalp, as patient with initial skin symptom would be expected to present early. Thus, *B. pseudomallei* appear to be able to affect the brain and its contiguous tissues across tissue planes, resulting in osteomyelitis and scalp abscess. Such contiguous involvement is more commonly seen in fungi infection (mucormycosis) as compared to bacterial infection, except for melioidosis.^{17,18}

Of the 30 patients from the various series including our own (Table 2), only one third (10/30) of the patients had other organ involvement, with majority of the patients (20/30) not having other foci of abscesses outside the nervous system.

There have been reports of neurological melioidosis mimicking Guillian Barré syndrome, mainly from Northern Australia, which are likely due to brainstem encephalitis or abscess.¹⁹

The disparate location of cerebritis or abscess is consistent with systemic embolic spread of infection. Hsu *et al.* have drawn attention to

propensity of *B. pseudomallei* to spread over long distances along commissural and projection white matter tract, including the corpus callosum, corticospinal tract and cerebellar peduncle.¹⁵ Hsu *et al.* also reported 3 cases of neurological melioidosis with evidence of trigeminal nerve enhancement.^{11,15} Studies in mice have supported the hypothesis that melioidosis may invade the brain via movement along olfactory or trigeminal nerve roots.^{20,21} However, there was no evidence of orbitobasal frontal lobe brain abscesses in the case series reviewed to support the mechanism of spread via the nasal mucosa and olfactory nerve route.

A standard regime for the treatment of melioidosis consists of an intensive phase of at least 10 to 14 days of intravenous ceftazidime, meropenem, or imipenem, followed by oral eradication therapy, usually with trimethoprim-sulfamethoxazole (TMP-SMX) for 3 to 6 months.¹³

Podin *et al.* have reported that up to 86% of clinical isolates from all melioidosis patients in district hospitals in Sarawak, Malaysia were gentamicin-susceptible. Further studies need to be done to determine the clinical implications of these isolates especially in neurological melioidosis.²²

In conclusion, melioidosis can present as a primary or isolated nervous system infection. Cerebral abscesses are the most common presentation. Concomitant extra-axial involvement such as adjacent osteomyelitis or scalp abscess should raise further suspicion for neurological melioidosis.

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DISCLOSURE

Conflict of interest: None

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