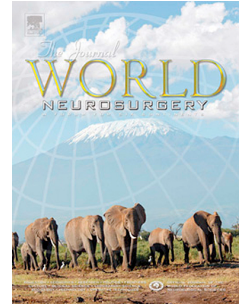


# Accepted Manuscript

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# CNS Melioidosis mimics malignancy: A case report and literature review

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CNS melioidosis, brain abscess, *Burkholderia pseudomallei*, MRS, intraventricular antibiotics

# Manuscript

## Introduction

Melioidosis is an infectious disease caused by the Gram-negative bacteria *Burkholderia pseudomallei*. Pneumonia is the most common presentation (51%), followed by genitourinary symptom (14%) and skin abscess (12%) (1, 2). Central nervous system (CNS) melioidosis accounts for only 3-5% of the cases but carries a high mortality up to 25%, in comparison with an overall mortality of 7% for systemic melioidosis (2, 3). CNS melioidosis can present as meningitis, encephalitis, brain abscess, subdural empyema, or skull osteomyelitis (4-7). Early diagnosis and initiation of appropriate treatment are crucial for survival. Although Melioidosis is endemic in Southeastern Asia and northern Australia, it may be more prevalent than estimated due to increasing global travel. We report a case of a patient who survived and recovered from a difficult-to-treat CNS melioidosis. Treatment details and images at different stages of the disease course are presented.

## Case Report

### *Presentation*

A 30-year-old healthy young man from middle of Taiwan presented with a sudden onset of left limb weakness and partial seizure lasting for a few seconds. On exam, he was alert, orientated and afebrile with stable vital signs, but with decreased muscle strength 1/5 over the left upper extremity and 2/5 over the left lower extremity without increased reflex of the left extremities. Laboratory data showed a normal complete blood count and basic metabolic panel.

### *Image Finding*

Computed tomography (CT) showed a low-density edematous lesion at right motor cortex. Ischemic stroke was initially suspected. Magnetic resonance image (MRI) showed a 2-cm lobulated enhancing lesion with prominent peri-lesional edema without diffusion

restriction on Diffusion Weighted Imaging (DWI)(Figure 1). MR spectroscopy (MRS) with single voxel technique showed increased choline and N-acetylaspartate (NAA) ratio and absence of a lactate peak, which was suggestive of malignancy (Figure 2).

### *Clinical Course and Management*

Navigation-guided craniotomy was performed for tissue biopsy and potential tumor removal. However, the pathology revealed only an accumulation of polymorphonuclear lymphocytes without evidence of malignancy. The patient remained alert and left hemiplegic after the first operation. Three days later, he suddenly developed fever of 39 °C, stupor (GCS E2V1M4) and dilatation of the right pupil. Brain CT showed severe swelling in the right hemisphere with midline shift, for which emergent decompression craniectomy and Intracranial pressure (ICP) sensor (Integra® Camino® Parenchymal Intracranial Pressure/Temperature Kit 110-4BT) placement was performed. During the procedure, we were astonished to see pus in the previous surgical field. Specimens for culture and cytology were collected. Vancomycin and Ceftriaxone were empirically initiated immediately. However, the patient continued to have persistent elevated intracranial pressure (ICP, ~ 30-40 mmHg), chill, and daily fever spikes of 38.5-40 °C. Laboratory data showed leukocytosis (WBC count 16,620/mm<sup>3</sup>, predominantly neutrophils), elevated C-reactive protein level and erythrocyte sedimentation rate. Both blood and pus cultures revealed abundant colonies of *Burkholderia pseudomallei* within one week. The antibiotic was changed to intravenous Meropenem (2g q8h). On further questioning about the patient's exposure history, he acknowledged playing MilSim (Military Simulation). He did not travel abroad but had just finished an outdoor survival game at a grassy and muddy ground in the middle of Taiwan 1 week prior to presentation. He had abrasion wounds on both legs, which could have been the possible invasion route. Despite high dose of Meropenem, the patient remained unconscious (GCS E2VeM3), and had increased ICP and intermittent fever during the following two weeks. MRI showed rapid enlargement of the abscess in the right frontal-parietal lobe, with extension to the thalamus, cerebral peduncle, and medial temporal lobe, crossing the midline via the corpus callosum to the subependymal area of the left lateral ventricle (Figure 3A). Additionally, a subcutaneous abscess was found in the left parietal region, where the

Mayfield 3-pin cranial fixation had been applied during surgery (Figure 3B).

To control the infection, CSF extraventricular drainage (EVD) and abscess drainage were performed. CSF was turbid and its cultures rapidly grew colonies of *B. pseudomallei*. Intraventricular (IVT) Ceftazidime 100 mg per day was administered via the EVD for two weeks, until the CSF cultures turned negative.

The patient became afebrile and his BP stabilized gradually after EVD placement and 2 weeks of IVT and systemic antibiotic treatment. CT of the chest, abdomen and pelvis and cardiac sonography were negative for other foci of infection. Meropenem was administered for 12 weeks and followed with 3 months of oral trimethoprim-sulfamethoxazole.

During a 4-month hospital course, the patient received a total of 12 EVD revisions because due to septum formation and debris in the abscess and ventricles that obstructed the EVD. The brain abscess became restricted and shrunk gradually (Figure 3D). Eventually, shunt placement in the fourth month became inevitable due to long-term ventriculitis.

After completion of 3 months of oral form antibiotics, he was followed for 1 year and has remained free from relapse.

## Discussion

### *Epidemiology of Melioidosis*

Melioidosis is mainly endemic in Southeast Asia and Northern Australia. According to the largest prospective study by B.J. Currie et al, which enrolled 540 patients in the past 20 years in Northern Australia, 85% of cases happened in the monsoon season. Most of cases had recreational or occupational activities, such as gardener, farmer, or construction worker, that result in environmental exposure to *B. pseudomallei*. Pneumonia accounts for 65% of the cases at presentation, followed by genitourinary symptom and skin lesion. Septic shock is not uncommon (21%) associated with a high mortality rate as 50%. Pneumonia is the most common cause of septic shock. There is epidemiological evidence that aerosolized *B. pseudomallei* can be inhaled during severe weather, resulting in

pneumonia with a high mortality (2). According to Currie et al, neurological melioidosis accounts for only 3-5% of cases but results in 21% of mortality (3 out of 14 patients)(2, 3).

Taiwan is located in the subtropical area and offers favorable conditions for spread of this disease. Before 2005, there were only sporadic cases in Taiwan. The largest cluster, 40 cases, occurred during the typhoon season, July to September, in 2005 in south Taiwan. The monthly new cases were significantly correlated with the rainfall. Septicemia happened in 31 out of 40 patients (78%), while pneumonia was present in 26 out of 40 clusters (65%). There was no neurological melioidosis in this Taiwanese study. In spite of direct skin inoculation, inhalation is a reasonable invasion route because the pathogens in soil tend to be aerosolized and inhaled in the typhoon season (9, 10).

The patient we presented came from the middle of Taiwan (Taichung City) but not in the rainfall season. He was a construction worker who practiced MilSim (Military Simulation Game). He had finished one game on grassy and muddy ground in Taichung city 1 week prior to presentation. He had a high likelihood of pathogen exposure, both by inhalation or skin inoculation. Since 2000, Melioidosis has been designated as a notifiable infectious disease by the Taiwan Centers for Disease Control (CDC).

### *Clinical Features of CNS Melioidosis*

The clinical features of CNS Melioidosis vary in literature reports. Headache and fever are not uncommon but non-specific. Meningitis, encephalitis, brain abscess with focal neurological deficit, cranial nerve palsy, subdural empyema, spinal epidural abscess, or skull and vertebra osteomyelitis have been described (4-8).

Four percent of cases of Melioidosis in Australia, and rarely elsewhere, presented with brainstem encephalitis (11). In the review by Currie et al in 2000, in which 12 CNS Melioidosis cases were collected from Australia, most cases presented with brainstem encephalitis and resulted in unilateral hemiparesis and cranial nerve palsy. Respiratory failure that required prolonged ventilatory support developed in 5 out of 12 patients (1). *B. pseudomallei* penetrate the CNS through the blood stream or direct skull base invasion.

The olfactory or trigeminal nerve, given the absence of blood-brain-barrier (BBB) in these structures, provides direct access for bacteria inoculated in the nasal mucosa. The presence of microorganism has been found in the olfactory bulb and trigeminal nerve. The trigeminal route of CNS invasion may explain the prevalence of brainstem neurological Melioidosis (9, 10).

In contrast, cases reported from other areas presented differently. In 2007, Muthusamy et al reported 3 CNS melioidosis from Malaysia that consisted of an occipital lobe abscess, a subdural empyema, and a spinal epidural abscess (4). Another case series with 5 CNS melioidosis cases showed brain abscesses not located in the brainstem. However, four of these five cases had other foci of abscess, mostly in the abdomen (7). The dissemination route for these cases may have been the blood stream. Our patient had a brain abscess located far from the skull base, positive blood cultures for *B pseudomallei*, and negative lung findings. CNS melioidosis most likely spread from the blood stream rather from inhalation.

### *Investigation*

The diagnosis of Melioidosis depends on definitive microorganism culture. There can be a prolonged period, months to years, between pathogen exposure and clinical manifestation. Detailed history taking and awareness of this microbial infection is crucial for treatment. The mortality and morbidity rate have been decreased with the increased awareness and improved diagnostic ability. Most cases were initially approached by general infection survey. Positive culture from blood and abscess provides a definitive diagnosis. CSF study in these reported cases, if available, had a non-specific bacterial meningitis appearance. In the series of 12 patients by Currie et al, 11 CSF samples were analyzed but only one had a positive culture result (3). Serology testing for *B pseudomallei* antibody has been applied in endemic areas. It could provide a faster diagnosis, but 80% of the population in endemic area has antibodies to *B. pseudomallei* but these antibodies are not protective (11, 12).

The prostate is the most vulnerable organ as the other focus of abscess (20%), followed by the spleen (5%), kidney (3%), and liver (3%). Systemic survey for other foci of abscess is mandatory (2).

### *Radiology Features*

Brain CT is the first line of examination when a patient presents with change of consciousness and focal neurological sign. However, as in this patient, a non-conclusive appearance was initially detected. MRI with contrast enhancement can delineate the abscess foci and peri-lesional edema better than CT at an early stage.

According to Lai et al, combination of MRS and DWI increase the level of confidence in differentiating abscess and cystic tumor. The criteria for pyogenic abscess was hyperintensity on DWI, presence of lactate or amino acid at 0.9 ppm; for cystic tumor, hypointensity on DWI and presence of lactate and/or lipid (0.9-1.2 ppm) with choline at 3.2 ppm on MRS. This led to a 95% accuracy in diagnosis(13). Our patient did not show typical diffusion restriction of the brain abscess, but a low signal on DWI, increased choline to N-aspartate (NAA) ratio, and lack of lactate and amino acid peak on MRS. The finding was compatible with neuronal damage with increased cellular turnover that is usually observed in malignancy. A possible explanation could be the extremely early stage of the brain abscess with only localized inflammation without necrosis formation. However, this case presents the unique aspect of an early abscess that was misdiagnosed as malignancy due to the MRS and DWI findings. The criteria for differentiating tumor and abscess are applicable to organized abscess rather than to an early stage (13, 14).

### *Treatment*

Given the rarity of CNS melioidosis, no standard treatment protocol for CNS melioidosis is available. The choices of antibiotics include Ceftazidime (3<sup>rd</sup> generation cephalosporin, but not Ceftriaxone or Cefotaxime), Imipenem or Meropenem, or Amoxicillin-clavulanate (11). Meropenem was chosen because of its good CNS penetration. We also administered intraventricular (IVT) injection of 100 mg Ceftazidime once daily until the CSF culture turned negative due to the patient's dire clinical condition. No seizure occurred during the treatment course. The benefits of intraventricular antibiotic injection for CNS infection remain uncertain because their neurotoxicity, such as seizures, limited its IVT application (15, 16). Intraventricular colistin, gentamicin or



daptomycin for meningitis and ventriculitis caused by multi-drug-resistant Gram-negative rods or vancomycin-resistant enterococcus, respectively, have been reported with favorable outcomes (17-19). This case is the first reporting IVT administration of ceftazidime for the treatment of CNS melioidosis.

The treatment protocol for systemic Melioidosis should be parental antibiotics for at least 10-14 days until the infection process is controlled, and followed by oral combination of four antibiotics (Doxycycline, Chloramphenicol, Trimethoprim-sulfamethoxazole) for at least 3 months (11). As in other CNS melioidosis reports, we administered systemic parental antibiotics for 12 weeks, followed by oral Trimethoprim-sulfamethoxazole for 3 months. The patient had been followed for more than 1 year and has no evidence of recurrence.

In addition to long-term systemic antibiotics, the favorable outcome of this patient should be attributed to adequate ventricle and abscess drainage. Ventricular drainage has been known to help symptom relief and infection control (16), but reference to surgical debridement in CNS melioidosis is limited. During the disease course, the abscess continued enlarging and invaded the lateral ventricle in spite of systemic Meropenem. Prolonged ventriculitis led to hydrocephalus and septated ventricles. Repeated EVD revisions were needed and stereotactic technique and intraventricular endoscopy were sometimes necessary to ensure proper drainage tube placement. His vital signs, consciousness, and bacterial load improved gradually after a series of surgical debridement and continuous extraventricular drainage. Similar to the treatment melioidosis with internal organ abscess, debridement and adequate drainage improved the outcome (11).

## Conclusions

We report a case of CNS melioidosis who survived and recovered from this difficult-to-treat disease. Long-term antibiotic treatment is mandatory for bacteria eradication and relapse prevention. Debridement and adequate drainage provide better infection control and outcome.

## Figures

### Figure 1.

(A) Pre-operative non-contrast CT. A low-density lesion is observed in the right motor cortex. (B) Coronal T1WI MRI. A enhancing 2-cm lesion with prominent peri-lesional edema. (C) Diffusion-weighted image

### Figure 2.

Single voxel MR spectroscopy (MRS) showed an increased Choline to NAA ratio ( $>1$ ), which is a common sign of malignancy. No lactate spectrum peak (1.3 ppm) was detectable.

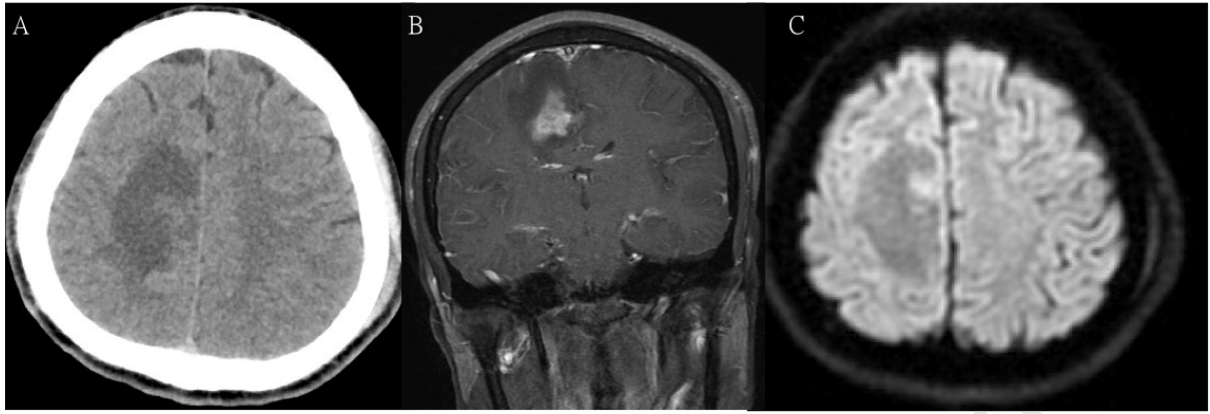
### Figure 3.

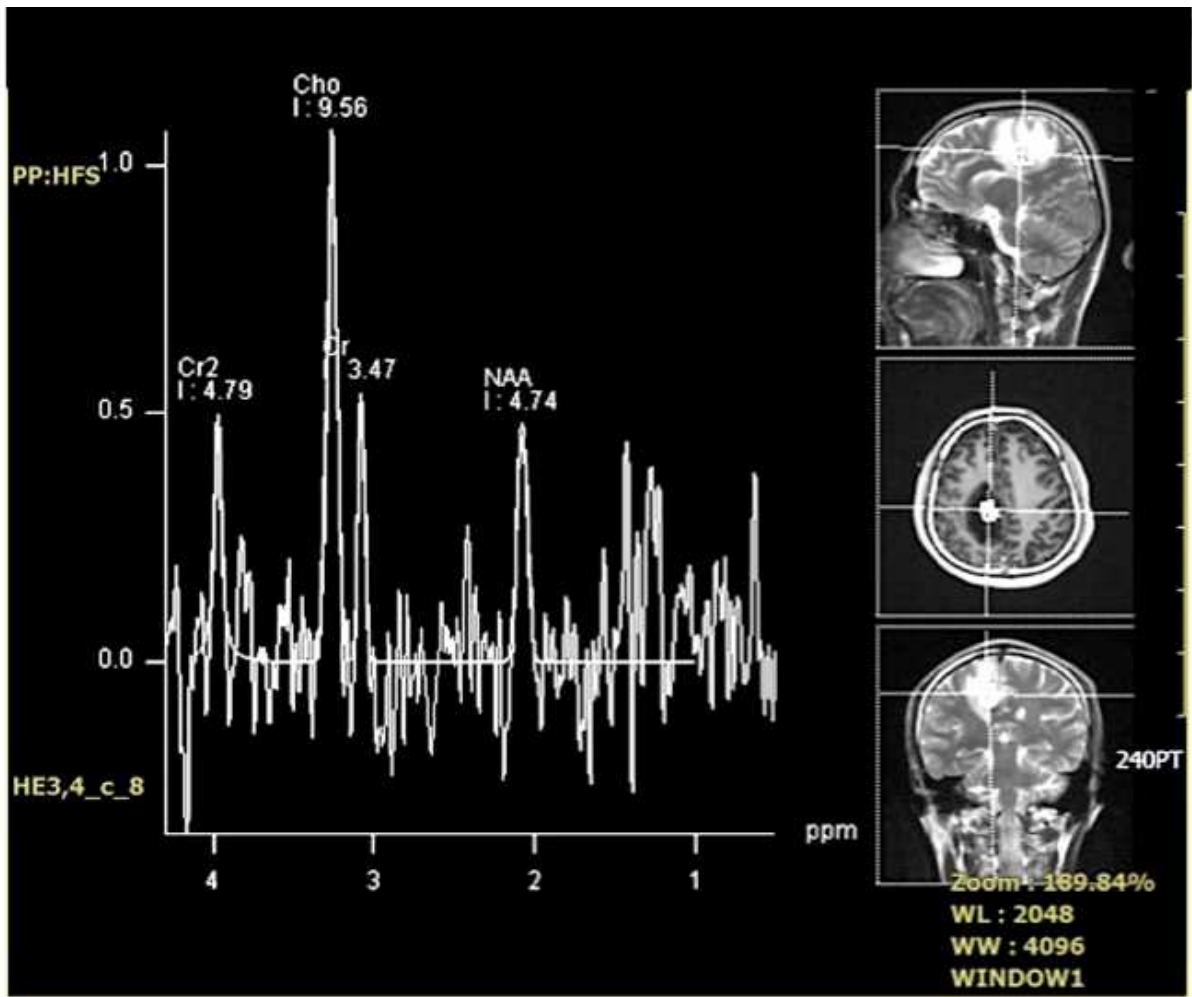
A and B were taken 1 week after the abscess was identified. (A) Coronal T1WI MRI. Enhancing abscess wall with rapid progression, compared with Figure 1B. The abscess enlarged and invaded along the corticospinal tract and crossed the midline at the corpus callosum. Abscess drainage and EVD were performed at this time. (B) A subgaleal abscess (white arrow), away from the surgical field, developed at the 3-pin holder location. (C) Coronal T1WI MRI, 2 weeks after the abscess was found. The abscess was better organized and its content more liquefied than the previous week (Fig. 3A). (D) Coronal MRI at 6 month.

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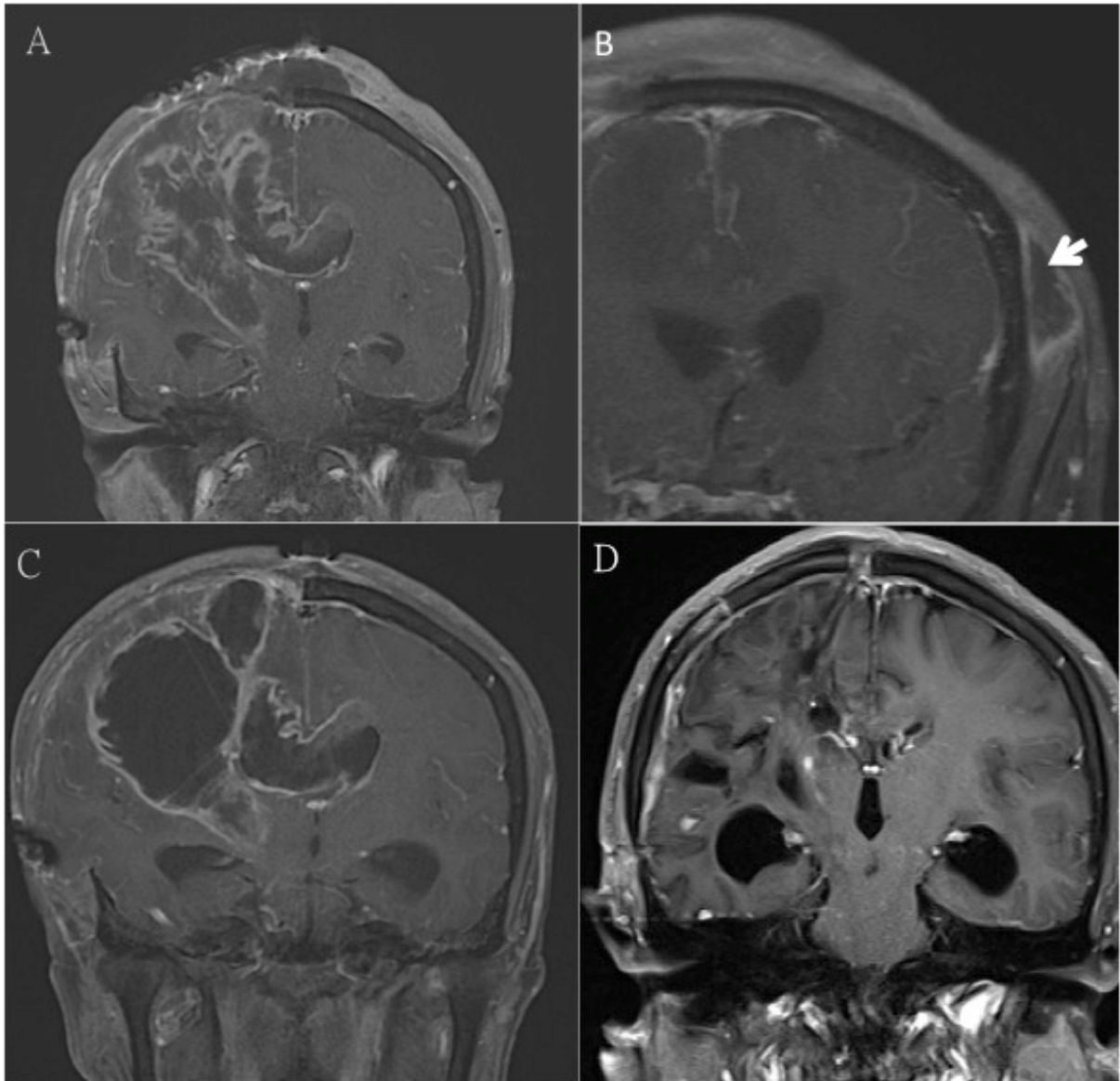
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**Abbreviations**

CNS : Central nervous system

CSF : Cerebrospinal fluid

CT : Computed tomography

DWI : Diffusion weighted image

GCS : Glasgow coma scale

ICP : Intracranial pressure

IVT : Intraventricular

MRI : Magnetic resonance image

MRS : Magnetic resonance spectroscopy

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### Highlights

1. Long-term systemic antibiotic is crucial for CNS melioidosis.
2. Debridement and adequate drainage contributed to infection control.
3. Intraventricular antibiotic helped in bacteria clearance.

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