Neuromelioidosis: A Single-Center Experience with Emphasis on Imaging

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Introduction Infection with Burkholderia pseudomallei, a gram-negative bacterium found in soil and surface water, is termed melioidosis and is commonly reported to occur in Southeast Asia and Northern Australia, where it is endemic. It is being increasingly reported in India, and transmission occurs through inhalation, inoculation, and ingestion. The neuroparenchyma, the adjacent soft tissue, and bone are known to be affected in both the acute and chronic disease forms. Involvement of these structures is rare but causes significant mortality and morbidity.

Material and Methods Eighteen culture-proven cases of neuromelioidosis were identified between January 2008 and December 2019. The patients were retrospectively identified via search of the hospital’s electronic database.

Results Cranial disease was in the form of parenchymal abscesses (n = 4), cerebritis/encephalitis (n = 5), and extradural (n = 4) and dural disease (n = 1). Acute myelitis (n = 1) and spondylodiscitis (n = 3) were seen in the spinal disease form. Neuroparenchymal involvement ranged from cerebritis/encephalitis to early and mature parenchymal abscesses. Extradural involvement was in the form of extradural abscesses and/or thick irregular enhancement in the extradural region. Early diagnosis and initiation of appropriate therapy had favorable outcomes in 15 out of 18 patients. Two patients with parenchymal abscesses and one with myelitis succumbed to the illness.

Conclusion Neuromelioidosis is a rare manifestation of melioidosis with significant morbidity and mortality, necessitating a high index of clinical suspicion, especially if there has been travel to endemic regions. Imaging plays a key role in facilitating early diagnosis and initiation of therapy.
Background

Melioidosis is an infection caused by the environmental saprophytic gram-negative bacillus *Burkholderia pseudomallei*. It is a well-recognized disease entity in Southeast Asia and Australia and has a high mortality. The organism has been classified as a class B bioterrorism agent by Centers for Disease Control and Prevention (CDC). Diabetics, alcoholics, and immunosuppressed individuals are at increased risk of acquiring the infection. The main mode of acquiring melioidosis is inhalation, the others being via ingestion of contaminated material, inoculation through abraded skin, and exposure to the pathogen in laboratories. *B. pseudomallei* can replicate in phagicytic and nonphagicytic cells, and this is crucial for disease pathogenesis. Humans are incidental hosts and person-to-person transmission is rare but has been reported to occur. The bacterium can evade the host's immune mechanisms for years, and has been reported in Vietnam War veterans, years after exposure. With increasing numbers of global travelers, melioidosis is likely to be increasingly recognized in nondendemic areas as well.

Melioidosis can be localized or disseminated and has protean manifestations ranging from acute bacteremic forms (<2-month symptom duration) with pneumonia, multiple disseminated abscesses, and septic arthritis to chronic forms with localized abscesses and osteomyelitis. Bacilli remain dormant in the host with reactivation occurring during downregulation of host immunity, resulting in chronic (>2-month symptom duration) disease. Commonly affected areas include, in decreasing order of frequency, the musculoskeletal system, lung, liver, spleen, and the genitourinary system. Septic arthritis and intramuscular abscesses occur in the musculoskeletal disease form, and lung involvement occurs as pneumonia and/or pleural effusions in the acute septicemic form and patchy consolidation with cavitation in the chronic granulomatous form. The spleen and liver are the most common sites of visceral abscesses.

Neuromelioidosis refers to central nervous system (CNS) involvement in melioidosis. Neuromelioidosis is rare but associated with higher rates of mortality. The radiologic findings in neuromelioidosis are varied and an awareness of this infection facilitates accurate diagnosis. In this article, we present the clinical and imaging features of neuromelioidosis in a series of 18 adult patients treated at a tertiary-care center in South India.

Material and Methods

This study was conducted in a single-center, tertiary-care institution in South India between January 2008 and August 2019. Adults with neurological symptoms and abnormal CNS imaging studies with culture proof of *B. pseudomallei* were retrospectively identified using the institution's electronic database. Patients were classified as having an acute or chronic presentation if the duration of symptoms was less or more than 2 months, respectively. Data regarding patient demographics, risk factors, clinical characteristics, laboratory and radiological data, and outcome were collected using a standard data abstraction form. Multifocal disease was defined as the presence of two or more organs of involvement or one organ involvement with a positive blood culture. Imaging of the CNS was undertaken when there were neurological symptoms such as altered sensorium, seizures, or focal neurological deficits.

The modalities used to image such patients included computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain, MRI scan of the spine, and CT of the abdomen for assessment of paraspinal soft tissue. The scans were independently assessed by two neuroradiologists (P. M. and S. M. E., with 6 and 12 years of experience, respectively). MRI scans were performed on 1.5T (Magnetom Avanto; Siemens, Erlangen, Germany) or 3T (Philips Intera Achieva; Philips Medical Systems, Netherlands) scanners, while CT scans were performed on 6-slice (Brilliance 6; Philips Medical Systems, the Netherlands) or 64-slice (Discovery 750 HD; GE Healthcare, Milwaukee, Wisconsin, United States) scanners.

Results

Eighteen patients (14 cranial and 4 spinal) with culture-confirmed neuromelioidosis were included during the 11-year study period. The patients were predominantly male, with a male:female ratio of 5:1. The mean age of the patients was 41.83 years (range, 21–61 years). Eleven of the patients (61%) has diabetes mellitus, and poor glycemic control (mean HbA1C, 10.1) was identified in 44.4% of patients (n = 8). One patient had received high-dose immunosuppression, which appeared to adversely affect the disease course. Seven patients (38.8%) had no identifiable risk factors. Two patients had history of scalp injuries prior to onset of CNS symptoms, with the subsequent illness likely to have resulted from inoculation of the wound with contaminated material. There was no noticeable seasonal variation in the presentation of the illness. Table 1 summarizes the clinical profile of the patients who were eventually diagnosed with craniospinal melioidosis.

Fever was the most common presenting symptom (83.3%). In addition to the common presenting complaints of patients with cranial disease mentioned in Table 2, additional presenting complaints included cerebellar symptoms (n = 1), visual deficits (n = 1), and monoparesis (n = 1).

Diagnosis

The diagnosis was established by positive blood cultures (n = 6), cerebrospinal fluid (CSF) culture (n = 1), pus cultures from brain/epidural abscesses (n = 5), dural tissue cultures (n = 2), and pus cultures from extra-CNS regions (n = 6). Two patients with dural site cultures also had positive pus cultures from extra-CNS region. CSF examination was characterized by lymphocytic pleocytosis with elevated protein and low glucose in two patients.
Imaging in Cranial Disease (14 Patients)
Cranial disease was seen in 14 patients in the form of brain parenchymal disease \((n = 9)\), cranial nerve involvement \((n = 3)\), epidural disease \((n = 5)\), calvarial disease \((8)\), and scalp changes \((n = 5)\) in various combinations.

- **Brain parenchymal disease:**
  
  - **Intracranial macroabscesses** were seen in four \((40\%)\) patients, out of which three were multiple. The multiple abscesses were 2 to 4 cm in size and were predominantly located in parieto-occipital regions, while the solitary abscess was located in the left frontal region. The abscesses were seen as multiple/solitary, moderate-to-intensely enhancing ring lesions with central diffusion restriction, low apparent diffusion coefficient (ADC) values, and perilesional edema. The abscesses were accompanied by leptomeningeal and pachymeningeal enhancement in three patients.
Intracranial microabscesses with cerebritis: Cerebritis and indistinct, near-contiguous foci of diffusion restriction which are microabscesses were seen in five (50%) patients with intracranial disease and were seen on MRI scans as ill-defined areas of T2 hyperintensity with irregular areas of diffusion restriction, low ADC values, irregular, multiple incomplete rings, and linear streaks of enhancement in the involved brain parenchyma. There was no clear demarcation of the diffusion-restricting areas from the surrounding edema. Encephalitis and microabscesses were seen in the brainstem and cerebellar hemispheres in two patients, and in the occipital and frontal lobes in three patients. Additional leptomeningeal and dural enhancement was seen in two of these patients.

- Cranial nerve involvement: Thickening and enhancement of the trigeminal nerves was seen in 3 of the 14 (21.4%) patients and was associated with leptomeningeal (n = 2) or pachymeningeal disease (n = 1).

- Extradural and dural disease: Extradural disease without brain parenchymal involvement occurred in five patients but was invariably accompanied by overlying bony calvarial changes, again in a predominantly parieto-occipital location. Diffusion-restricted and/or enhancing material was identified in frontal and parieto-occipital extradural spaces in four of five patients. Isolated dural disease was seen in one patient in the form of thickening and moderate enhancement of left temporal, tentorial, and cavernous sinus dura.

- Calvarial changes: Calvarial signal changes such as marrow edema, excessive marrow enhancement (MRI), erosions, destruction, and endosteal reaction (CT) were seen in 8/14 patients with cranial disease (57%).

- Scalp changes: Scalp edema and/or collections were seen in four patients and discharging scalp sinuses in one patient.

- Other cranial findings: Venous sinus thrombosis (n = 2) and features of elevated intracranial pressure (n = 4) were seen in different, mutually exclusive sets of patients. Extraconal orbital collection (n = 1), otomastoiditis (n = 3), nasopharyngeal mucosal thickening, and collections in the longus colli muscle were additional features seen with cranial disease.

**Spinal Disease**

Spinal disease was seen as infective spondylodiscitis with altered signal intensity of vertebrae and intervertebral discs along with epidural and/or paravertebral collections (n = 3) or longitudinally extensive transverse myelitis (n = 1) (►Fig. 1). All patients with spinal disease had multifocal involvement.

### Table 2 Summary of frequently seen clinical features (original table)

|                            | Fever | Altered sensorium | Seizures | Cranial nerve palsy | Hemiparesis | Paraparesis | Bulbar weakness |
|-----------------------------|-------|-------------------|----------|---------------------|-------------|-------------|-----------------|
| Cranial disease (n = 14)    | 11    | 4                 | 4        | 5                   | 5           | –           | –               |
| Spinal disease (n = 4)      | 4     | –                 | –        | –                   | –           | 1           | 1               |

**Fig. 1 (a)** Postcontrast T1-weighted (T1W) coronal and **(b)** axial scans with thickening and moderate enhancement of the tentorial and middle cranial fossa dura, respectively.

### Extra-CNS Disease

An additional extracranial disease focus was seen in 7 of the 14 patients with cranial disease and included septic arthritis, intramuscular collections, prostatic abscesses, splenic abscesses, and hepatitis. The imaging and key clinical characteristics of the cranial disease form are summarized in ►Table 3 and are compared with those in the published literature.

### Outcomes

Five patients underwent craniotomy: abscess drainage with wall excision (n = 3) and dural biopsy and/or epidural abscess drainage (n = 2). Eight patients underwent a nonneurosurgical diagnostic procedure. Most patients were treated successfully with intravenous ceftazidime or meropenem for 2 to 6 weeks, followed by eradicative therapy with trimethoprim–sulfamethoxazole and doxycycline. There were four (28.6%) fatalities. The remainder of patients recovered and were discharged with favorable outcomes. At follow-up (3 months to 2 years), these patients were doing well. One patient was lost to follow-up.

### Discussion

Neuromelioidosis is a unique infectious disease entity with acute and chronic disease forms. This condition can be a differential for both common acute neurological infections and chronic neurological infections such as tuberculosis and fungal infections. As the treatment regimen is considerably different from treatment regimens for other pathogens implicated in CNS infections, it is important for this...
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Table 3  Summary of location-specific involvement in neuromelioidosis of current study compared with those in published literature

| Parenchymal disease | Calvarial, scalp, dural, and extradural disease | Leptomeningeal disease | Others |
|---------------------|-----------------------------------------------|-----------------------|--------|
| Mannam et al (more than one site of involvement in 13 patients) | Early and late abscess, multiple lesions (5) | Scalp collections, calvarial osteomyelitis (8), dural and epidural (6) | Leptomeningeal enhancement (8) | Otomastoiditis (3), nasopharynx (1), musculoskeletal collections, splenic and prostatic abscesses |
| Wongwanee et al (April 2019) (n = 120) | Encephalomyelitis and brain abscesses (83) | Calvarial, scalp, and epidural disease (15) | Leptomeningeal enhancement (22) | No information |
| Hsu et al (February 2016) (n = 10) | Microabscesses along white matter tracts, brain (6), spinal cord (1) | Cranial extradural collection (1), spinal extradural collection (1) | Leptomeningeal enhancement (1) | No information |
| Prasad et al (April 2017) (n=27) | Meningoencephalitis (16), brain abscess (8) | None | None | Craniospinal, not otherwise specified, n = 2 |

Infection to be considered among the differentials, especially in endemic areas such as India. Systemic, multiorgan involvement, and, in the craniospinal region, a propensity to involve contiguous structures are some features that neuromelioidosis shares with tuberculosis, fungal, and other chronic bacterial infections. To the best of our knowledge, this is the largest single-center cohort of adult patients with neuromelioidosis. Most of the patients in our series were middle-aged working males and a large proportion were diabetics (►Table 1). Interestingly, approximately two-fifths of the patients in this series had no underlying comorbidities, which underlines the importance of considering this disease even in the absence of conventional risk factors.

Brain parenchymal involvement was characterized by multiple macroabscesses or a combination of encephalitis and microabscesses as described in the literature. The macroabscesses were in a parieto-occipital location and had central diffusion restriction, and the encephalitis and microabscesses were seen in the parieto-occipital/cerebellum-brainstem regions and had tiny indistinct areas of diffusion restriction and incomplete rings of peripheral enhancement (►Fig. 2). The ratio of supratentorial to brainstem–cerebellar lesion distribution in this series is 3.5:1, whereas that quoted in the literature is approximately 2:1. One patient had microabscesses and linear, near-continuous streaks of enhancement along white matter tracts similar to that described in the literature (►Fig. 2).

Involvement of adjacent calvarium (erosions, destruction, marrow edema) and/or scalp (edema or collections) was also seen in a larger proportion in this cohort compared with those quoted in the literature—19 and 16%, respectively. The smaller patient numbers in the current study may account for this difference. Temporal bone and skull base disease was seen in one additional patient.

A feature that deserves special mention is that at least two contiguous anatomical structures (►Figs. 3 and 4) are often involved in conjunction (parenchyma + extradural + calvarium and extradural + calvarium). Presence of imaging features such as involvement of contiguous anatomical sites should alert the radiologist and the clinician to consider the possibility of infection with *B. pseudomallei* in addition to other commonly considered differentials in endemic regions such as tuberculosis and fungal infections.
Cranial nerve involvement is another important feature seen commonly in neuromelioidosis and occurs in conjunction with skull base/temporal bone disease and may be accompanied by leptomeningeal and/or pachymeningeal disease. Involvement of the cranial nerves seems to be a unique feature and was also reported by Hsu et al, although a larger group of patients need to be studied to establish the statistical significance of the same. Isolated pachymeningeal disease is rare and indistinguishable from other noninfectious granulomatous and infiltrative pachymeningeal diseases, which have essentially similar imaging characteristics (►Fig. 1).

Final diagnosis relies on obtaining positive bacterial cultures.

Sinonasal, skull base, and mastoid diseases were seen in combination or in isolation in most patients with cranial disease. The predominant posterior fossa and parieto-occipital involvement lends credence to the theory of bacterial seeding via the emissary and interneural veins accompanying the lower cranial nerves. These structures may serve as conduits for intracranial disease spread. Special caution is recommended in patients with extensive myelitis (►Fig. 5) where the differentials include infectious and parainfectious causes and demyelination. These are indistinguishable on imaging, and a CSF analysis is recommended prior to initiating therapy. The line of treatment must be directed by the results of the CSF analysis, as immunosuppressive therapy can prove detrimental.

Neuromelioidosis is almost always a systemic disease, with sepsis (positive blood cultures) and/or other organ involvement (abscesses in other regions). A significantly higher proportion of this patient cohort had systemic disease, more than the 33% quoted in the literature.

The importance of a detailed examination of the musculoskeletal system cannot be emphasized enough. Involvement of the musculoskeletal system has been variably documented to be 14 to 33% and, if involved, can provide easy access to sample material for culture.

Imaging work-up of patients with suspected neuromelioidosis must include abdominal ultrasound and chest radiograph and detailed clinical examination. Identification of other system involvement may reveal potentially more accessible locations from where pus samples can be percutaneously aspirated (►Fig. 6), especially in clinical settings where resources and expertise (neurosurgical intervention) are limited. Mandatory blood cultures are recommended in all patients with features of craniospinal infection on imaging, as blood was the most common specimen to grow B. pseudomallei. Mortality in this patient cohort is similar to those in the literature, i.e., approximately 20%, and is significantly higher than the overall mortality of melioidosis.

Brain parenchymal involvement is associated with poorer prognosis with higher mortality rates. The mortality rates were higher than that observed with melioidosis affecting other systems (musculoskeletal, respiratory, liver, spleen, etc.).
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and genitourinary systems) in our center. The lung was the other most common site of involvement associated with poor outcome.

Recurrence of disease was not reported in any of the followed-up patients. This is less than that quoted in the literature (16%), and may in part be related to the extended eradicator phase of therapy with oral cotrimoxazole that was used in all patients treated at this center.

Limitations

The study was retrospective; the cases spanned a decade and hence some temporal differences in work-up and management were inevitable. Additionally, the work-up was incomplete by current standards in the initial few patients.

Conclusion

Neuromelioidosis is a unique disease entity that can occur in the absence of risk factors and poses a diagnostic challenge. Imaging is an important tool for establishing the sites and extent of pathological involvement in systemic infection with B. pseudomallei. Imaging features of neuromelioidosis are not specific, and tuberculous and fungal infections can present with similar, indistinguishable imaging findings. Neuromelioidosis must be considered among the differentials in endemic locations like India. Imaging of the CNS is essential for the purpose of locating lesions and identifying lesions amenable to surgery or biopsy in order that appropriate management can be initiated in a timely manner.

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Nil.

Conflict of Interest

The authors declare conflict of interest.

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Fig. 6 (a) Axial CT sections of the pelvis with a prostatic abscess and (b) axial CT sections of the upper abdomen with a few splenic microabscesses.
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