Cranial melioidosis presenting as a mass lesion or osteomyelitis

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Object. Melioidosis is caused by Burkholderia pseudomallei and causes multiple abscesses in different organs of the body. Cranial melioidosis, although uncommon, is sometimes confused with tuberculosis and is therefore underecognized. The authors report on 6 cases of cranial infections caused by Burkholderia pseudomallei, presenting as mass lesions or cranial osteomyelitis, and review the literature.

Methods. The authors performed a retrospective review of the records of patients with cranial melioidosis treated at their institution between 1998 and 2005 to determine the presentation, management, and outcome of patients with this infection.

Results. Of the 6 patients diagnosed with cranial melioidosis during this period, 4 had brain abscesses and 2 had cranial osteomyelitis. All patients were treated surgically, and a diagnosis was made on the basis of histopathological studies. All patients were started on antibiotic therapy following surgery and this was continued for 6 months. One patient died soon after stereotactic aspiration of a brain abscess, and the other 5 patients had good outcomes.

Conclusions. Cranial melioidosis is probably more prevalent than has been previously reported. A high index of suspicion, early diagnosis, initiation of appropriate antibiotic therapy and treatment for an adequate period are essential for assuring good outcome in patients with cranial melioidosis. The authors recommend surgery followed by intravenous ceftazidime treatment for 6 weeks and oral cotrimoxazole for 6 months thereafter in patients with cranial melioidosis. (DOI: 10.3171/JNS/2008/108/2/0243)

Key Words • brain abscess • Burkholderia pseudomallei • melioidosis • osteomyelitis • outcome • treatment

Burkholderia pseudomallei is a gram-negative bacillus that causes melioidosis, a disease that is associated with abscesses in multiple organs. The term melioidosis was coined by Stanton and Fletcher32 and is derived from the Greek word “melis,” meaning “a distemper of asses” and “eidos,” meaning resemblance, because the lesion resembles the glanders disease in equines that is caused by Pseudomonas mallei. Melioidosis is endemic to Southeast Asian countries and northern Australia. Neurological involvement in melioidosis, although rare, may manifest as peripheral neuropathy, stroke, meningitis, encephalitis, myelitis, discharging scalp sinuses, or brain abscesses. The mortality rate in patients without early and adequate treatment is very high. Cranial involvement is uncommon, with only a few reports in recent years. We report on a series of 6 cases of cranial melioidosis presenting as mass lesions or osteomyelitis.

Clinical Material and Methods

A summary of the clinical and imaging data, management, and outcome in these 6 patients is shown in Table 1. Four patients had brain abscesses and 2 had cranial osteomyelitis. None of the patients had systemic symptoms. The diagnosis of melioidosis was reached on the basis of a positive culture for B. pseudomallei, and appropriate treatment was instituted after the culture report had been obtained. In 4 patients the outcome was excellent, with complete resolution of their symptoms. Our first patient died before the culture report was available, and 1 patient was lost to follow-up.

Illustrative Case (Case 6)

This 35-year-old man presented with clinical features of raised intracranial pressure, aphasia, and weakness in his right arm. Magnetic resonance imaging of the brain revealed a left frontoparietal ring-enhancing lesion with edema and midline shift. There were also separate small ring-enhancing lesions extending into the corpus callosum (Fig. 1A and B). The patient underwent a left frontoparietal craniotomy with excision of the frontal abscess. The culture of a pus sample grew B. pseudomallei that was susceptible to cotrimoxazole, ciprofloxacin, and ceftazidime, and resistant to amikacin and gentamicin. Biopsy sampling revealed a chronic abscess. The patient received 2 g intravenous ceftazidime every 8 hours for 6 weeks, followed by an oral

Abbreviations used in this paper: CT = computed tomography; MIC = minimum inhibitory concentration; MR = magnetic resonance.
cotrimoxazole regimen for 6 months. At 8 months’ follow-up he had no headaches, and his aphasia and right arm weakness had recovered completely. He had had 4 episodes of generalized tonic–clonic seizures because he had discontinued the prescribed antiepileptic drugs. A contrast-enhanced CT scan of the brain (Fig. 1C) demonstrated volume loss with minimal enhancement of cortex in the left frontal region. Antiepileptic drugs were reinstated, and he was advised to continue cotrimoxazole therapy for 3 more months.

Discussion

Melioidosis is a disease endemic to Southeast Asia and northern Australia that is caused by *B. pseudomallei*. Although there is known to be a high incidence of this disease in the tropics, it is probably underdiagnosed and underreported in other parts of the world, including India.

Microbiological Characteristics

*Burkholderia pseudomallei* is a motile, gram-negative, non–acid-fast, nonspore bearing rod that shows characteristic bipolar staining (“safety pin” appearance) on Gram staining. It grows readily on most laboratory media, but may take 48 hours or more to develop its characteristic colonial morphology. These colonies have a distinct “earthy” smell when the plate is opened. On blood agar, the colonies are opaque white, and on MacConkey agar they appear pink. This microorganism can be readily identified through a series of biochemical tests and observations of its other characteristics. It is the only pseudomonad that can grow at 42°C. It produces heat-stable phosphatase and is positive for oxidase, gelatinase, and arginine dihydrolase production. It does not produce a soluble pigment as *Pseudomonas aeruginosa* does.

Pathological Characteristics

This bacillus is a saprophyte found in the soil and surface waters of rice paddies and ponds and typically enters the host via inhalation, inoculation, or ingestion; person-to-person transmission is rare. After entering the host, the bacillus may cause local infection or spread to distant sites in the body via the blood. An infection with *B. pseudomallei* may remain latent for prolonged periods. Direct inoculation into the skin can cause subcutaneous abscesses that may later spread to the deeper tissues, resulting in osteomyelitis and discharging sinuses. Inhalation can cause pneumonia. Through the blood, the bacillus can reach distant organs such as the liver, spleen, and brain and cause abscesses in those locations. The infection can be acute or chronic, and may present as an asymptomatic pulmonary infection, acute pulmonary infection, acute localized suppurative skin infection with lymphadenitis, and an acute septicemic form with abscesses in multiple organs and chronic suppurative melioidosis..

Involvement of the nervous system is rare.

In some cases there is involvement of all layers starting from the scalp to the brain, similar to that seen in tuberculosis and fungal infections. On histopathological analysis, there is typically a chronic abscess with focal granulomatous reaction. Peripheral nervous system involvement can present as Guillain–Barré syndrome. Woods et al. reported cases of involvement of the brain without direct infection by the bacillus, which they attributed to an exotoxin. Diabetes mellitus, chronic renal failure, malignant tumors, alcohol abuse, liver disease, steroid use, and lymphoid or myeloid disorders are the usual predisposing factors to this disease. Melioidosis has been called the “Vietnamese time bomb” because of its frequent acquisition by United States soldiers during the Vietnam War and its recurrence after long periods of latency.

Chadwick and colleagues reported a high incidence of paranasal sinus inflammation in patients with cranial melioidosis.

Radiological Features

The radiological features in cranial melioidosis vary ac-
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### TABLE 1

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Presenting Symptoms</th>
<th>Imaging Finding (Modality)</th>
<th>Antibiotic Treatment</th>
<th>Surgical Treatment</th>
<th>Outcome (FU Duration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1†</td>
<td>35, M</td>
<td></td>
<td>rt hemiparesis &amp; seizures</td>
<td>lt parietal abscess (CT)</td>
<td>crystalline penicillin, chloramphenicol, &amp; metronidazole</td>
<td>CT-guided stereotactic aspiration</td>
<td>death on postop Day 4</td>
</tr>
<tr>
<td>2</td>
<td>41, F</td>
<td></td>
<td>scalp swelling &amp; raised ICP</td>
<td>rt temporal lobe abscess (CT)</td>
<td>ceftazidime &amp; cotrimoxazole</td>
<td>abscess excision</td>
<td>good (6 mos)</td>
</tr>
<tr>
<td>3</td>
<td>54, M</td>
<td></td>
<td>pus discharge from wound</td>
<td>lt parietal osteomyelitis (CT)</td>
<td>ceftazidime &amp; cotrimoxazole</td>
<td>bone flap removal</td>
<td>good (2 yrs)</td>
</tr>
<tr>
<td>4</td>
<td>50, M</td>
<td></td>
<td>scalp sinus discharge</td>
<td>lt frontal osteomyelitis (CT)</td>
<td>ceftazidime &amp; cotrimoxazole</td>
<td>osteomyelitic bone excision</td>
<td>unknown, (no FU)</td>
</tr>
<tr>
<td>5</td>
<td>40, M</td>
<td></td>
<td>headache &amp; lt hemiparesis</td>
<td>multiple abscesses (MR)</td>
<td>ceftazidime &amp; cotrimoxazole</td>
<td>frontal abscess excision</td>
<td>good (6 mos)</td>
</tr>
<tr>
<td>6</td>
<td>35, M</td>
<td></td>
<td>headache, aphasia, &amp; rt monoparesis</td>
<td>lt frontal abscess (MR)</td>
<td>ceftazidime &amp; cotrimoxazole</td>
<td>abscess excision</td>
<td>good (12 mos)</td>
</tr>
</tbody>
</table>

* In all cases, pus cultures were positive for *B. pseudomallei*. Abbreviations: FU = follow-up; ICP = intracranial pressure.
† Case reported on previously by Lath et al. This was the only patient in the present study with systemic disease, which had spread to the lungs.

According to the pathological characteristics of the disease, ranging from normal CT findings in the initial stages of cerebritis to well-defined macroabscess formation. Magnetic resonance imaging is more sensitive in the initial stages of the disease, with T2-weighted images detecting hyperintense changes in the brain parenchyma. There is a predilection for infection of the frontal lobes and brainstem.\(^{19}\) Other radiological features include microabscesses, osteomyelitis, encephalitis, and myelitis. Bergin and colleagues\(^4\) reported on 2 cases of cranial melioidosis in which there was involvement of the occipital lobes with extension across the midline via the splenium, an unusual radiological feature in infections. In 1 of our patients (Case 6), there was a similar radiological finding of small enhancing lesions extending into the corpus callosum (Fig. 1B). These imaging results can be confused with a malignant glioma and may lead to a nihilistic approach to management, especially in elderly patients. More commonly, because the imaging features of the intracranial abscesses caused by *B. pseudomallei* infection resemble those caused by other infective agents, the patient may be treated empirically with antibiotic or antituberculosis drug therapy, thus delaying appropriate treatment.

**Treatment and Outcome**

A high index of suspicion for this infection, early diagnosis, and early initiation of high doses of appropriate intravenous antibiotics continued for a long duration are important because the mortality rates in infected individuals are otherwise very high. Melioidosis can mimic tuberculosis in clinical presentation, imaging characteristics, and histopathology, and, therefore, patients with melioidosis might be inappropriately treated with antituberculous therapy. Before the use of antibiotics, the mortality rate for melioidosis was 95%. Treatment usually consists of intravenous antibiotics for 2–6 weeks, followed by oral maintenance therapy with cotrimoxazole, doxycycline, or quinolones for 6–8 months. The antibiotic medication used should have a good penetration into the brain tissue as well as activity against *B. pseudomallei*. The drug of choice for the treatment of melioidosis is ceftazidime, and the mortality rate has been halved with its use.\(^{37}\) Although there is a tendency to use multiple antibiotic drugs in the acute stage of the disease, available evidence based on in vitro studies and previously reported cases shows that use of monotherapy in the acute stage results in good outcome.\(^{12,30}\) These studies have shown antagonism between bacteriostatic (chloramphenicol) and bactericidal antibiotics. The MIC of ceftazidime for *B. pseudomallei* is up to 4 mg/L, and it attains an MIC of 2.7–27 mg/L in brain abscesses.\(^{15}\) Other antibiotics that are recommended are trimethoprim–sulfamethoxazole, imipenem, cefoperazone–sultabactam, cefotaxime, doxycycline, and amoxycillin/clavulanate.\(^{15,19,23}\) In their study of in vitro susceptibility of strains of *B. pseudomallei* from Southeast Asia, Chau et al.\(^4\) have recommended ceftazidime, piperacillin, and carumonam based on the MICs of these drugs. These authors suggested that the in vitro activity of cephalosporins against *B. pseudomallei* in decreasing order is ceftazidime, ceftriaxone, cefotaxime, cefoperazone, moxalactam, and cefuroxime. Chetchotisakd et al.\(^5\) showed in their randomized, double-blind, controlled study that cefoperazone–sultabactam plus cotrimoxazole might be an alternative to the use of ceftazidime and cotrimoxazole. Angus and colleagues\(^4\) suggested continuous infusion of ceftazidime (12 mg/kg priming dose followed by 4 mg/kg/hour) in patients with septicemic melioidosis. The treatment is for a period of 6–12 months, initially with a cephalosporin and followed by ofloxacin, cotrimoxazole, or doxycycline.\(^7,26,28\) Jenney et al.\(^11\) recommend prolonged eradication therapy with regular clinical and microbiological monitoring so that the emergence of bacterial resistance can be detected early and appropriate modifications in drug therapy made. These authors have demonstrated acquired resistance in 4 of 17 patients who had a relapse in their study. The infection in our patients responded well to an initial course of intravenous ceftazidime for 6 weeks followed by oral trimethoprim–sulfamethoxazole therapy for 6 months.

The cases of cranial melioidosis presenting as mass lesions or osteomyelitis reported in the literature are summarized in Table 2.\(^4,6,19–22,25–27,29\) (cases of meningitis and encephalitis due to *B. pseudomallei* are not included in our literature review). The mortality rate in these cases was high, with nearly a quarter of the reported patients succumbing to the disease. Recurrence was seen in 2 patients, both of whom had initially received antibiotic therapy for less than 12 weeks, due to noncompliance. This underlines the importance of prolonged antibiotic therapy in these patients.
TABLE 2

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>CNS Involvement</th>
<th>Systemic Involvement</th>
<th>Imaging Finding (Modality)</th>
<th>Positive Culture Source</th>
<th>Antibiotics Used</th>
<th>Surgical Management</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee &amp; Chua, 1986</td>
<td>18, M</td>
<td>aphasia, rt hemiparesis, rt CN VI &amp; VII palsy</td>
<td>none</td>
<td>It occipital abscess (CT)</td>
<td>pus</td>
<td>crystalline penicillin &amp; chloramphenicol</td>
<td>bur hole &amp; drainage</td>
<td>good</td>
</tr>
<tr>
<td>Pit et al., 1988</td>
<td>48, M</td>
<td>scalp abscess &amp; altered sensorium</td>
<td>septicemia</td>
<td>rt parietal abscess (CT)</td>
<td>pus &amp; blood</td>
<td>ampicillin, cloxacillin, chloramphenicol &amp; cephalothin</td>
<td>needle aspiration &amp; later craniotomy</td>
<td>death</td>
</tr>
<tr>
<td>Pelekanos &amp; Appleton, 1989</td>
<td>12, F</td>
<td>It hemiparesis &amp; CN palsy</td>
<td>none</td>
<td>multiple abscesses (CT)</td>
<td>no culture</td>
<td>none</td>
<td>none</td>
<td>good</td>
</tr>
<tr>
<td>Kasanitkul et al., 1992</td>
<td>51, F</td>
<td>rt hemiparesis</td>
<td>lung &amp; liver</td>
<td>It frontal &amp; parietal abscesses (CT)</td>
<td>blood</td>
<td>none (was considered small-cell carcinoma of lung)</td>
<td>none</td>
<td>death</td>
</tr>
<tr>
<td>Kong et al., 1993</td>
<td>9, M</td>
<td>It lateral gaze palsy, rt CN VII palsy, &amp; lt hemiparesis</td>
<td>none</td>
<td>multiple abscesses (CT)</td>
<td>brain tissue</td>
<td>cefazidime</td>
<td>CT-guided biopsy</td>
<td>good</td>
</tr>
<tr>
<td>Padiglione et al., 1998</td>
<td>20, M</td>
<td>diplopia, dysphasia, &amp; difficulty walking</td>
<td>none</td>
<td>normal (CT), enhancement around the 4th ventricle (MR) &amp; CSF &amp; CSF &amp; CSF &amp; CSF &amp; CSF</td>
<td>blood, multiple</td>
<td>cefazidime &amp; chloramphenicol multiple</td>
<td>none</td>
<td>death on 21st day post-admission</td>
</tr>
<tr>
<td>Peetermans et al., 1999</td>
<td>66, M</td>
<td>altered sensorium</td>
<td>lung</td>
<td>frontal lesion (CT)</td>
<td>lung aspirate</td>
<td>cefazidime &amp; long-term oral ofloxacin</td>
<td>cefazidime (56 days) &amp; ofloxacin (8 mos)</td>
<td>good</td>
</tr>
<tr>
<td>Chadwick et al., 2002</td>
<td>52, M</td>
<td>altered sensorium &amp; rt hemiparesis</td>
<td>lung &amp; sinusesis</td>
<td>multiple abscesses lt cerebrum (CT &amp; MR)</td>
<td>pus</td>
<td>cefazidime, then oral doxycycline &amp; cotrimoxazol</td>
<td>drainage of abscess</td>
<td>good</td>
</tr>
<tr>
<td>60, M altered sensorium &amp; seizures</td>
<td>lung, prostate, &amp; sinusesis</td>
<td>rt frontal abscess (CT)</td>
<td>no culture</td>
<td>imipenem, then doxycycline &amp; cotrimoxazol</td>
<td>drainage of abscess</td>
<td>good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29, M seizures</td>
<td>liver, spleen, &amp; scrotum</td>
<td>rt frontal abscess (CT)</td>
<td>pus</td>
<td>cefazidime, chloro- &amp; doxycycline, followed by cotrimoxazol</td>
<td>drainage of abscess</td>
<td>recurrence w/ osteomyelitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46, M rt leg &amp; facial weakness</td>
<td>muscle &amp; sinusesis</td>
<td>lt cerebral &amp; midbrain abscess (MR)</td>
<td>pus</td>
<td>cefazidime, imipenem, followed by doxycycline &amp; cotrimoxazol</td>
<td>drainage of abscess</td>
<td>good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>74, F meningitis</td>
<td>sinusitis</td>
<td>rt parietal osteomyelitis &amp; empyema (MR)</td>
<td>blood</td>
<td>multiple including cefazidime, doxycycline, &amp; cotrimoxazol</td>
<td>none</td>
<td>recurrence, recovered after 2nd tx day 16 days post-admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bergin et al., 2005</td>
<td>69, M</td>
<td>fever, confusion, &amp; headache</td>
<td>kidney</td>
<td>abscesses, lt parietooccip (MR)</td>
<td>brain tissue</td>
<td>gentamicin &amp; ceftriaxone</td>
<td>none</td>
<td>death 16 days post-admission</td>
</tr>
<tr>
<td>30, F headache, fever, &amp; seizures</td>
<td>bones &amp; spleen</td>
<td>lt parietooccip cerebritis (CT)</td>
<td>brain tissue</td>
<td>cefazidime, then meropenem &amp; cotrimoxazol</td>
<td>CT-guided stereotactic biopsy</td>
<td>good</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* CN = cranial nerve; CNS = central nervous system; CSF = cerebrospinal fluid; parietooccip = parietooccipital; tx = treatment.
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Conclusions

Cranial melioidosis can mimic cranial and intracranial tuberculosis in several ways, and it is possible that the scarcity of reports of this disease is partly due to misdiagnosis of patients with melioidosis. An increased awareness of this pathological entity among physicians and surgeons, especially in view of the increased prevalence of HIV, is therefore necessary. Early detection, initiation of appropriate antibiotic therapy, and treatment for an adequate time period are essential for good recovery.

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