We describe an immunocompromised patient who developed a large frontal brain abscess caused by *Legionella micdadei*. This is, to our knowledge, a rare case of culture-proven *Legionella* central nervous system infection.

**CASE REPORT**

We present an uncommon case of an immunocompromised patient who developed a brain abscess caused by *Legionella micdadei* without any evident source.

The patient, a 59-year-old gentleman, presented with fever, weakness, dizziness, presyncope, and an intermittent nonproductive cough over the preceding 2 months. On history, he denied any headache, nausea, vomiting, or significant recent travel. He was empirically treated for an undefined infectious process with 1 g of intravenous (i.v.) ceftriaxone daily.

The patient had known Waldenstrom’s macroglobulinemia, an indolent B-cell lymphoma. Six weeks prior to his initial presentation, he had completed a 6-month course of chemotherapy with an anti-CD20 agent (rituximab) and a DNA synthesis inhibitor (fludarabine). Five days after initiation of empirical ceftriaxone, the patient presented again to an emergency department with recurrent fevers, aphasia, confusion, and hallucinations. He had a decreased level of consciousness and new gastrointestinal symptoms in the form of nausea and vomiting. On examination, the patient was afebrile, with a Glasgow coma score of 14/15, and displayed mild left-sided weakness involving upper and lower extremities. The initial investigation included a computerized tomography (CT) scan of the head that showed a large right frontal lobe mass with significant mass effect. At that time, neoplasms were high on the differential, and the patient was started on dexamethasone 24 mg/day i.v. and dilantin 200 mg/day i.v. He was then transferred to a tertiary care center.

An urgent magnetic resonance image (MRI) scanning report noted the presence of a solitary, cystic/necrotic, right frontal lobe lesion suggestive of a brain abscess. The lesion had approximate dimensions of 6.4 by 5 by 5 cm and was associated with significant vasogenic edema (Fig. 1A). Eight days after his first visit to the emergency department, the patient underwent craniotomy with partial excision and drainage of an early encapsulated, frankly purulent abscess. Empirical antibiotic therapy was initiated and included 2 g/day i.v. ceftriaxone, 4.5 g/day i.v. vancomycin, and 1 g/day i.v. metronidazole with 24 mg/day i.v. adjuvant dexamethasone. On initial Gram stain of the abscess fluid, only polymorphonuclear cells and lymphocytes were noted. The abscess fluid was culture negative for bacteria after 7 days of incubation on sheep blood agar, chocolate agar (CO2 incubation at 37°C), brain heart infusion broth, and phenylethyl alcohol blood agar (anaerobic incubation at 37°C). An aliquot of the direct specimen, abscess fluid, was sent for universal 16S rRNA PCR and amplicon sequencing. Pending the results of the PCR, ciprofloxacin, 800 mg i.v. daily, was added to broaden the antimicrobial coverage. Investigations also included multiple blood culture sets (BD Bactec FX, paired aerobic and anaerobic bottles), with all reported as “No growth after 5 days of incubation.” Serology for histoplasmosis, blastomycosis, toxoplasmosis, amoebiasis, and cryptococcal antigen were reported negative. Despite empirical antibiotics, steroids, and surgical intervention, the patient continued to deteriorate and died of an axial herniation 10 days after admission.

On the day of the patient’s death, the results of the 16S rRNA of the brain abscess fluid were reported as positive for *Legionella micdadei* (100% identity with ATCC 33218, NR_041791) comparison made on EMBL-GenBank. Primers 27F (5′-AGAGTTTGATCMTGGCTCAG-3′) and DG74 (5′-AAGGAGGTGATCACCACGCA-3′) were used to amplify a 16S PCR product of 1,420 bp. Given the environmental distribution of the unusual organism identified, and the direct method used, confirmation of the pathogenic role of this organism was needed. A subsequent review of the initial abscess fluid Gram stain, after extended counterstaining time with safranin, demonstrated faintly staining intra- and extracellular Gram-negative bacilli.

An autopsy was conducted to clarify the cause of death and attempt to identify the source of infection. Specimens were sampled from lungs, heart valves, kidney, liver, and central nervous system (CNS; cerebrospinal fluid [CSF], brain tissue, and abscess fluid). Correlating with the MRI findings, examination of the brain at autopsy disclosed an abscess cavity deep in the right frontal white matter (Fig. 1B). Microscopic examination of the abscess revealed rudimentary formation of a capsule, consisting of rows of proliferating blood vessels and scattered macrophages along the interface with the fibrinopurulent exudate. Tissue Gram stain failed to demonstrate microorganisms, but Warthin-Starry stains showed an abundance of rod-shaped bacteria in the extrudate (Fig. 1C and D).

Considering the 16S rRNA results, premortem abscess fluid and autopsy specimens were planted on in-house-prepared buffered charcoal yeast extract (BCYE-α; ketoglutarate supple-
mented) agar. *L. micdadei (>100 colonies) was isolated by culture after 72 h of incubation (O2, high humidity) from premortem abscess fluid and from brain abscess tissue, abscess fluid, and cerebrospinal fluid taken at the autopsy. The identification was confirmed by fatty acid analysis (MIDI) and 16S rRNA. Autopsy specimens from the lungs, heart valves, urine, and kidney were negative for *Legionella* by culture. Blood cultures were not available for subculture on BCYE. A single serologic test for *Legionella* (CDC in-house-derived protocol) was negative from serum taken the day following the craniotomy. Of note, *Mycobacterium avium* complex (MAC) was also isolated from postmortem lung tissue.

*Legionellaceae* species are fastidious, facultatively intracellular Gram-negative bacilli which fail to grow on the majority of standard media routinely used in clinical laboratories (1). Culture on specialized charcoal agar medium remains the gold standard for diagnosis of any form of *Legionella* infection. Clinical laboratories often rely on antigenuria, direct fluorescence antibody staining (DFA), serology, and molecular amplification to make the diagnosis. Except for the latter, these tests are somewhat more specific for *L. pneumophila* serotype 1 (2).

*Legionella* infections are generally associated with pneumonia or other respiratory tract infection. Extrapulmonary infections without lung involvement are rare (3). Systemic involvement, exhibited as renal impairment, cardiac manifestations, as well as gastrointestinal or neurological symptoms, can also occur (4). Early after the description of Legionnaires’ disease, several case reports, as reviewed by Johnson et al. (4), documented a greater-than-expected associated frequency of neurological signs and symptoms in an estimated 40 to 50% of patients. The described neurological disorders ranged from nonspecific alterations in the sensorium, including coma, to specific cerebellar dysfunction and an assortment of focal signs. However, an infective etiology for these associated neurologic conditions has evaded detection. In an autopsy-neuropathology study of 40 patients dying with *Legionella* pneumonia, 40% of whom had a neurologic disorder; Pendlebury et al. (5) were unable to attribute the cause to direct infection of the CNS. Therefore, it has been proposed that these neurological disturbances are due to either the effect of neurotoxins or immune-mediated mechanisms (5, 6). In regard to the latter mechanism, rare case reports of acute disseminated encephalomyelitis have been documented in the setting of Legionnaires’ disease (4, 7–9). Problematic in assessment are cases reported in the literature (4, 9–11), in which *Legionella* has been identified in CNS tissue or CSF by means other than culture (specific staining techniques, DFA, PCR) and for which there has been no clinical, radiological, or pathological correlation of infection. This difficulty

**FIG 1** (A) Preoperative MRI scan, T2 coronal window, showing a large abscess in the right frontal lobe surrounded by extensive vasogenic edema (L, left; R, right). (B) Corresponding coronal section of frontal lobes at autopsy demonstrating tracking of the abscess (asterisk) from the cortectomy site (arrow) deep into the white matter to undermine the orbital cortex. Wall of abscess is highlighted by rim of hyperemia. (C) Microscopic section of abscess wall showing the fibrinopurulent exudate (asterisk) bordered by a zone of engorged proliferating blood vessels between which are interspersed macrophages and acute inflammatory cells. Hematoxylin and eosin. (D) Warthin-Starry stain reveals within the fibrinopurulent exudate numerous rod-shaped bacteria (arrows) among acute inflammatory cells and less often within cells (top right arrow).
may reflect the sensitivity of the diagnostic tools employed and the fastidious requirements of the organism for culture. Table 1 summarizes the reported cases of confirmed *Legionella* sp. central nervous system infection.

More than 90% of infectious *Legionella* isolates are *L. pneumophila*, while 60% of the remaining are attributed to *L. micdadei* and often affect immunocompromised patients (15). A PubMed search with the keywords "*L. micdadei*" and "brain abscess" produced only one case report. Fukuta et al. described a prosthetic valve endocarditis in a patient on immunosuppressive therapy for systemic lupus erythematosus complicated by *L. micdadei* brain abscess (14). As in our case, *L. micdadei* was detected with 16S rRNA PCR, and the organism was also visualized in the brain abscess exudate with a Warthin-Starry stain. Fukuta et al. however, did not isolate the organism by any culture method. Brain infection attributed to other *Legionella* species, specifically *L. pneumophila* and *L. cincinnatiensis*, have also been reported, although, again, the organism was never grown in culture (4, 10, 12, 13). *L. micdadei* has been identified in other infections, including prosthetic joint infections, lung abscesses, and necrotizing cellulis (3), as well as in soft tissue abscesses, often in association with acquired or congenital immunosuppression (12, 16, 17).

The wide distribution of *Legionella* spp. in the environment complicates its identification as a pathogen, because the source and transmission route may be difficult to define. Our patient was immunocompromised and thus at risk for non-*pneumophila* legionellosis. It is possible that the patient’s initial respiratory symptoms may have been due to *L. micdadei* pneumonia ("Pittsburgh pneumonia") or MAC infection, although the admission chest X ray had no evidence of pneumonia. The low prevalence of legionellosis in Alberta, Canada; the ubiquitous nature of this organism; and the paucity of literature describing this agent as a cause of brain abscess led us to question the 16S rRNA results. Furthermore, recent reports have described *Legionella* spp. as possible contaminants of DNA extraction columns (18). The autopsy failed to identify any specific focus of infection aside from the brain. We were unable to identify, on history, the origin of the infection, as the patient’s family denied risk factors such as recent whirlpool use or travel.

Despite diagnostic and pharmacological advances, bacterial brain abscesses remain associated with a high morbidity and significant mortality (19–21). Detection and identification of causal agents is critical to direct therapy, although approximately two-thirds of brain abscesses have “negative” cultures. 16S rRNA gene sequencing may serve as an important identification tool when pathological findings and Gram stains suggest bacterial abscess, but attempts to isolate the organism by culture have failed (22, 23). As illustrated by this case, culture-negative brain abscess represents a clinical management challenge and, in such circumstances, 16S rRNA gene sequencing can be a useful adjunct test. It may also help identify agents not typically considered causes of brain abscess. Nonetheless, as with all new technologies, caution is required when interpreting the clinical significance of 16S rRNA results.

In summary, we describe the first case to our knowledge of an isolated brain abscess due to *L. micdadei* in an immunocompromised patient, diagnosed by culture and 16S rRNA sequencing of a direct specimen. This adds to the scant literature regarding this manifestation of *Legionella* infection and demonstrates how recent technologies can assist the clinician to better direct antimicrobial therapy.

**ACKNOWLEDGMENTS**

We thank Tom Turner for assembling the composite photomicrograph.

All authors have declared no conflicts of interest in relation to this submission.

This work did not receive funding.

George Zahariadis is the senior author.

**REFERENCES**


---

**TABLE 1** Summary of case reports of *Legionella* sp. confirmed central nervous system infection described in the literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age, sex</th>
<th>Underlying illness</th>
<th>CNS lesion</th>
<th>Detection method</th>
<th>Identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>5 mo, male</td>
<td>SCID, respiratory failure</td>
<td>Microabscess; midbrain</td>
<td>DFA, brain/liver; culture, lung</td>
<td><em>L. pneumophila</em></td>
</tr>
<tr>
<td>13</td>
<td>33 yrs, male</td>
<td>None</td>
<td>Temporoparietal abscess (CT)</td>
<td>Serology</td>
<td><em>L. jordanis</em></td>
</tr>
<tr>
<td>14</td>
<td>57 yrs, female</td>
<td>SLE</td>
<td>Frontal brain abscess (MRI)</td>
<td>16S RNA, prosthetic valve</td>
<td><em>L. micdadei</em></td>
</tr>
</tbody>
</table>

SCID, severe combined immunodeficiency; DFA, direct fluorescent antibody; MRI, magnetic resonance image; CT, computed tomography; SLE, systemic lupus erythematosus.