Balamuthia mandrillaris brain infection: a rare cause of a ring-enhancing central nervous system lesion. Illustrative case

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BACKGROUND An 80-year-old man presented with subacute mental status change, dizziness, and left-sided vision loss. Magnetic resonance imaging demonstrated a ring-enhancing right parietooccipital lesion.

OBSERVATIONS Biopsy and laboratory testing demonstrated an amoebic Balamuthia mandrillaris infection. Fewer than 200 cases of this infection have been recognized in the United States, and no standardized treatment regimen currently exists.

LESSONS Rapid antimicrobial therapy with miltefosine, azithromycin, fluconazole, flucytosine, sulfadiazine, and albendazole was initiated. The pathophysiology, diagnosis, and management of this infection and the patient’s course were reviewed. The importance of biopsy for pathologic and laboratory diagnosis and rapid treatment initiation with a multidisciplinary team was reinforced.

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KEYWORDS brain infection; amoeba; Balamuthia mandrillaris; granulomatous amoebic encephalitis; ring-enhancing lesion

Central nervous system (CNS) infection from amoebic species is an important but infrequent cause of encephalitis worldwide. These ubiquitous organisms colonize the soil and water supply of a wide range of natural environments, yet only few of the thousands of known amoebic species (Naegleria fowleri, Acanthamoeba spp., Balamuthia mandrillaris, and, very rarely, Sappinia pedata) cause infection in humans.1–4

Balamuthia mandrillaris can cause infection of the mammalian CNS. It is relatively novel, having only been discovered in 1986 during an autopsy of a mandrill monkey at the San Diego Zoo. Since then, this organism, which can cause cutaneous, CNS, and disseminated infections in immunocompromised or immunocompetent hosts, has been associated with at least 200 cases of human infection worldwide. Infection of the CNS manifests as granulomatous amoebic encephalitis (GAE), which has a reported fatality rate of >90%.5 Although few treatments exist, early diagnosis, however challenging, is thought to increase chances for survival.

Illustrative Case

An 80-year-old immunocompetent man with a history of epilepsy secondary to an amygdaloid cyst well controlled on phenytoin for many years presented to his neurologist for 2 weeks of mental status changes. Over the course of 2 days, he developed a feeling of disorientation and fatigue followed by balance and coordination issues. He was still able to perform activities of daily living and household chores. His neurologist, concerned about possible stroke, sent the patient to the emergency department, where magnetic resonance imaging (MRI) demonstrated a focal area of cortical restricted diffusion and hemosiderin staining involving the right posterior parietooccipital lobe with peripheral enhancement as well as prominent surrounding vasogenic edema with resultant mild effacement of right ventricular atria (Fig. 1). The left amygdaloid cyst was unchanged compared to results on MRI from 4 years earlier. On initial presentation, his neurological examination was intact except for left inferior quadrantanopia, mild gait imbalance, and left-sided peripheral vision loss.
Extensive history revealed that the patient was initially born in Germany and then emigrated to the United States as a teenager, where he lived briefly in New Hampshire before moving to California. He lived in Northern California at the time of presentation. He has recently traveled to Arizona to visit family but had no recent international travel. He enjoys gardening and has noticed bat droppings around his house, and he does have a koi pond in his backyard but does not swim in it or have contact with the pond water. He has a dog and cat. He does not use nasal irrigation of any kind.

Examination
A full neurological examination was undertaken. Initially, the leading differential was cerebral amyloid angiopathy/angiitis or new malignancy. Intravascular lymphoma was considered, but biopsy of a cherry hemangioma of the left shoulder was unrevealing. Chest, abdomen, and pelvis computed tomography performed to assess for a primary tumor showed similarly negative results for acute findings or masses. A lumbar puncture was then performed with an opening pressure of 20 mm H₂O, and cerebrospinal fluid (CSF) sample revealed 82 white blood cells (66% lymphocytes, 17% monocytes, 17% atypical mononuclear cells, and 0% neutrophils), protein level of 97 mg/dL, and glucose level of 71 mg/dL (serum glucose 104 mg/dL). CSF cytology and flow cytometry were negative for malignancy. Viral and fungal CSF studies also had negative results.

Diagnosis
The patient then received a stereotactic brain biopsy of the parietal lesion. Histopathological review showed abundant necrosis and brain parenchyma with mixed inflammation (Fig. 2). Focal nonnecrotizing, perivascular granulomas were present. Some regions also demonstrated histiocyte-like cells with small nuclei, foamy cytoplasm, and glassy, undulating rims, predominately in regions of necrosis. The histological appearance raised suspicion for ameba, initiating laboratory-developed multiplex real-time polymerase chain reaction (PCR) testing of CSF and formalin-fixed paraffin-embedded tissue using primers/probes targeting the 18S rRNA gene and cycling conditions as previously described. Both CSF and tissue tested positive for B. mandrillaris.

Treatment
After discussions with experts at the Centers for Disease Control and Prevention, the patient was started on six antimicrobial medications: miltefosine, azithromycin, fluconazole, flucytosine, sulfadiazine, and albendazole. He was also continued on phenytoin. Local public health authorities were also notified.

The patient presented 2 weeks after being discharged with significantly increased lethargy, poor food and water intake, severe anxiety, nausea, and vomiting. Physical examination demonstrated nystagmus. Laboratory testing revealed supratherapeutic phenytoin levels thought most likely secondary to poor oral intake and drug-drug interactions with antimicrobials. Phenytoin was switched to lacosamide. A lower-extremity deep venous thrombus was also discovered, for which the patient was started on Lovenox. Albendazole was stopped to limit side effects. He improved significantly after these adjustments and was discharged to home with family to continue medical therapy.

The patient was readmitted for hypercalcemia with calcium level of 13.1 mg/dL, acute kidney injury (AKI) with creatinine level of 1.9 mg/dL, and decreased oral intake. Kidney biopsy showed primary acute tubular necrosis and mild acute interstitial nephritis (AIN) as the cause of AKI. Flucytosine was stopped because of toxic serum levels, and sulfadiazine was held in the setting of AKI and AIN. The patient was discharged home and instructed to continue miltefosine, azithromycin, and fluconazole after improvement of calcium and creatinine levels.

As of the time of publication, approximately 7 months from diagnosis, the patient was generally doing well. He was living at home with family, ambulating with assistance of a walker, stable on the above-mentioned medication regimen, and being closely monitored by his treatment team.
Discussion

CNS infection from free-living amoeba can result in either primary amoebic meningoencephalitis (PAM) or GAE. PAM is caused by *N. fowleri* and presents most often as a rapidly progressing and usually fatal infection with a time course of days to weeks. GAE conversely has a more subacute presentation and usually, although not always, occurs in immunocompromised individuals. The median length of time from symptom onset to death from GAE is 24 days.2

We present a case of laboratory-confirmed *B. mandrillaris* infection in an otherwise immunocompetent individual that resulted in GAE.

Observations

In investigating the cause of this infection, the only significant environmental risk factor was gardening. Mechanisms of infection by *B. mandrillaris* include entry through an open skin wound exposed to colonized soil and respiratory exposure through aerosolized soil or water sources, most commonly in areas with high levels of farming, excavation, or construction.2,8 Improper sterilization of nasal irrigation has also been reported as an infectious source.9 Rare cases of transmission via solid organ transplantation have occurred.10

Cutaneous disease is often seen to precede CNS infection; however, a full dermatologic examination in this patient did not reveal any lesions. In some case series, the cutaneous lesions precede encephalitis by nearly 4 years and carry a far more favorable prognosis.6,11

Multiple theories on the mechanism of CNS spread have been proposed. While retrograde transport through cranial nerves has been investigated (as shown to be the case in *N. fowleri* infection), more recent studies have proposed hematogenous spread from an initial cutaneous lesion or lower respiratory tract.2,3,5,7,8 There can be findings of necrosis and hemorrhagic infarcts as well.14

Lessons

Although rare and quite serious, rapid diagnosis and initiation of appropriate treatment of amoebic CNS infections caused by *B. mandrillaris* are key to survival.15 The far more common causes of newly discovered ring-enhancing brain lesions (gliomas, metastatic cancer, and bacterial abscesses) should always be considered, yet having a clinical suspicion for this uncommon, but potentially fatal, cause is important.

Given a low prevalence and nonspecific findings, clinical or radiographic diagnosis of *Balamuthia* is extremely difficult. When considering the differential of CNS infections, if the history or clinical presentation is not consistent with *N. fowleri* infection, it is tempting to rule out all other free-living amoeba infections due to their low incidence. However, because *Balamuthia* and other amoeba have different epidemiological risk factors and infectious routes, this is an important pitfall to avoid. One notable feature of *B. mandrillaris* infection is that it can rapidly progress with initiation of corticosteroid therapy, which can be a heralding sign if steroids are initiated for a presumed neoplastic process.9,16,17

Biopsy and subsequent histopathology and laboratory testing are essential for diagnosis. Whereas histopathology traditionally was the gold standard, new rapid PCR testing can rapidly provide a definitive diagnosis from a tissue (or CSF) sample. The assay used to diagnose in this case has been reported to be highly analytically sensitive and specific.6

Once confirmed, treatment should be initiated rapidly. Various regimens have been reported in GAE survivors, including pentamidine, fluconazole, sulfadiazine, and fluconazole or itraconazole, plus one or more of the following drugs: a macrolide, thioldiazine/trifluoperazine, liposomal amphotericin, and/or miltefosine.5 Given the lack of clinical experience and unfavorable prognosis, the patient was started on six antimicrobials: miltefosine, azithromycin, fluconazole, fluclotyline, sulfadiazine, and albendazole. Because of the side effect profiles, fluconazole and albendazole were discontinued.

New agents for treatment of GAE caused by *B. mandrillaris*, namely plicamycin, TG02, panobinostat, lestaurtinib, GDC-0084, and nitroxoline, are under investigation with promising in vitro results.10,19 No human studies for treatment of GAE have been published.

Beyond antimicrobial therapy, there have been reports of successful treatment of *B. mandrillaris* CNS infection with resection of the entire lesion.11,16 Given the general poor prognosis and lack of a clinically proven and standardized antimicrobial regimen, it may be reasonable to consider this approach in good surgical candidates and those who fail medical management.

Conclusions

It is highly likely that, given challenges with diagnosis, there are many more cases of *B. mandrillaris* CNS infection than have been reported. For a patient who presents with new ring-enhancing brain lesions, once the more common causes have been excluded, consideration for *B. mandrillaris* and other amoeba species should be pursued, especially considering that failure to diagnose early can limit the effectiveness of any treatment.

We present a rare case of CNS *B. mandrillaris* infection that was diagnosed via brain biopsy. *B. mandrillaris* is an emerging free-living amoeba that should be included in the differential in the appropriate clinical setting because early diagnosis and rapid initiation of treatment portend the best prognosis for this often fatal infection.

References


Disclosures
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