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Case report

Balamuthia mandrillaris encephalitis in an uncontrolled diabetic patient

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ABSTRACT

Balamuthia mandrillaris is a free-living amoeba that may result in a disseminated infection of the central nervous system called granulomatous amoebic encephalitis. We present a case of balamuthiasis in a Hispanic male with poorly controlled type 2 diabetes mellitus (hemoglobin A1C of 12.2 %) who did not have access to healthcare. He initially presented with the non-specific symptoms of blurry vision, headache and imbalance which rapidly progressed to altered mental status over two months. Imaging revealed multiple peripherally enhancing lesions throughout the cerebellum and cortical regions which corresponded to the patient's deficits. Brain biopsy showed amoebic forms consistent with *Balamuthia mandrillaris* and later confirmed with cerebrospinal fluid PCR. Our patient was treated with a combination of various antimicrobials, including azithromycin, fluconazole, flucytosine, sulfadiazine, and miltefosine. Unfortunately, his prognosis continued to worsen and he ultimately died after being placed on comfort care.

Introduction

Balamuthia mandrillaris is a free-living amoeba found in soil, water and dust that can cause granulomatous amoebic encephalitis (GAE) in immunocompetent and immunocompromised patients. *Balamuthia encephalitis* is very rare, and has a high fatality rate of more than 95 % with only 10 reported cases of patients surviving this CNS infection, despite various combinations of antimicrobials [1]. We report a case of *Balamuthia encephalitis* in a patient who presented initially with blurry vision and headache.

Case report

A 51 year old Hispanic male with a past medical history of diabetes presented to the emergency department in Reading, Pennsylvania complaining of vision changes and headache. He reported acute onset of worsening blurry vision bilaterally one week prior, associated with a dull 4/10 occipital headache and unsteadiness (swaying to his left side), denying fever, photophobia, focal weakness or sensory changes. The patient had a 10 year history of diabetes on metformin 100 mg twice daily and glyburide 5 mg daily; however, he did not check glucose regularly at home and had not seen a physician in years. He denied intravenous drug use or smoking. The patient immigrated from Mexico 23 years ago and had not traveled outside of the United States since then. He worked in landscaping and gardening.

Upon examination, he was afebrile and well-appearing, alert and oriented to person, place and time. Cranial nerves 2–12 were intact, as well as strength and sensation in his extremities. Significant laboratory values included hyperglycemia 175 mg/dL and hemoglobin A1C of 12.2 %. Computerized tomography (CT) of the head showed numerous foci of decreased attenuation throughout the cerebral hemispheres. Follow up magnetic resonance imaging (MRI) after admission showed numerous peripheral enhancing lesions throughout the brain, demonstrating central liquefaction and surrounding edema (Fig. 1). The largest was one 2 cm lesion in the right occipital region and other lesions were in the left occipital, right frontal parietal, left cerebellum, and left temporal regions. Lesions were surrounded by extensive cerebral edema (Fig. 2). Differential diagnoses at this point included cerebral abscesses and multiple metastasis. CT of chest/abdomen/pelvis showed no metastatic disease. For empiric brain abscess coverage, the patient was started on IV vancomycin 1250 mg q8hrs, cefepime 2 g q8hrs and metronidazole 500 mg q6hrs and a right frontal brain biopsy was performed on day 2. HIV testing and toxoplasmosis IgM titers were negative.

The patient underwent a stereotactic biopsy of the right frontal lesion using the pre-operative fine-cut MRI brain that was

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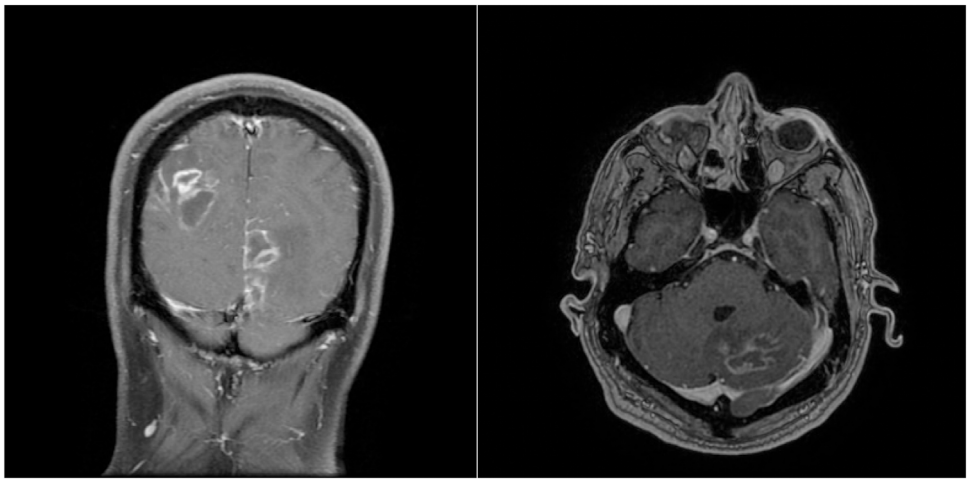

Fig. 1. Multiple diffuse contrast enhancing lesions with central cavitation. Large lesion in the right occipital lobe and left cerebellum on T1 MRI.

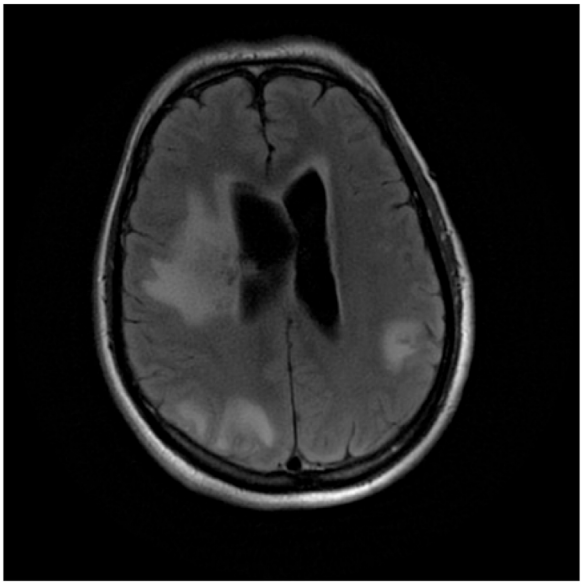

Fig. 2. Diffuse cerebral edema on MRI FLAIR.

co-registered to the patient's skull using Medtronic Stealth ® intraoperative navigation. Several core biopsy samples were collected and sent for evaluation by microbiology and pathology. Brain tissue biopsy was sent to the University of Michigan. Pathology report described necrosis with multiple amoebic forms consistent with trophozoites of *Balamuthia mandrillaris* (Fig. 3). Slides were sent to the Center for Disease Control for confirmation and Polymerase chain reaction (PCR) analysis; however, the submitted tissue was depleted and could not be assessed. Antimicrobials were discontinued, and patient was started on a recommended multi-drug treatment based on the limited literature available: azithromycin 500 mg daily, fluconazole 400 mg daily, flucytosine 25 mg/kg q6hrs, sulfadiazine 1000 mg q6hrs, and miltefosine 50 mg q8hr. On Day 14, the patient was discharged to rehab. During his time there, he was not oriented to date or day of week. He had difficulty performing multi step commands and required increased assistance in tasks such as dressing and bathing. After two weeks, he was discharged home, one month after his initial presentation.

One week later, the patient was brought to the ED again for worsening altered mental status by his wife. She noted that he was

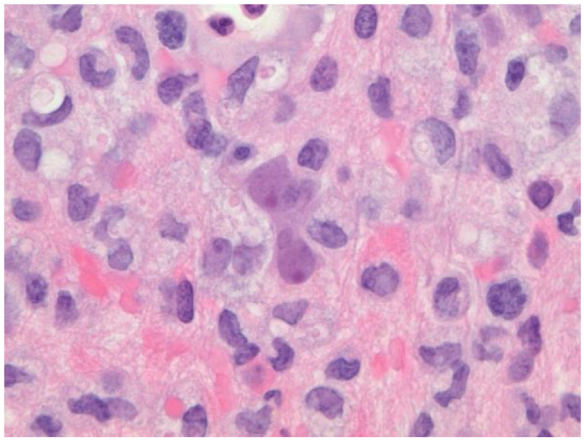

Fig. 3. Right occipital lobe histopathology showing amoebic trophozoites. Basophilic cytoplasm, large nucleus, and prominent nucleolus.

lethargic and not answering questions as usual. His vitals were significant for a temperature 101.4 F and heart rate 110. On examination, he was nonverbal and disoriented with GCS of 8. CT scan showed hydrocephalus and a left frontal extraventricular drain was placed emergently. A cerebrospinal fluid sample was sent to the CDC at this time. Multiplex free living amoeba real time PCR was performed on the cerebrospinal fluid (CSF) and confirmed *Balamuthia mandrillaris* organisms were present in the CSF. The case was discussed with the CDC as to the possibility of intrathecal treatment; however, it was not recommended. The patient remained in the ICU for the next week, where he was unresponsive and lethargic, with no significant neurological improvement despite drain placement. He developed respiratory distress from aspiration after an episode of emesis. After extensive discussion with the family, they decided to pursue comfort care, rather than mechanical ventilation, and our patient transitioned to inpatient hospice. He ultimately died within a few days.

Discussion

Balamuthia mandrillaris is among three amoeba that cause encephalitis, along with *Acanthamoeba* and *Naegleria fowleri*. *Acanthamoeba* and *Balamuthia* cause an insidious, subacute disease course over weeks to months, as seen in this patient [2]. However, *Balamuthia* is particularly concerning because it affects not only

the immunocompromised, but also may evade host responses in immunocompetent individuals [2] Although our patient tested negative for HIV, he had poorly controlled diabetes with a HA1C of 12.2, making him somewhat immunocompromised.

There are two stages in the life cycle of *Balamuthia* – the dormant cyst and infective trophozoite [2]. It is thought to enter the body when contaminated soil comes into contact with skin wounds or through inhalation of dust [3]. The man worked in landscaping, and this could have been a risk factor for exposure to the organism. It can then invade the central nervous system through hematogenous dissemination causing encephalitis, most likely gaining access through the blood brain barrier (BBB) [4]. A recent study showed that the amoeba induces human brain microvascular endothelial cells to release the cytokine IL-6, playing a role in early inflammation and possible breakdown of the BBB [5]. A disproportionate number of Hispanic Americans have been affected by *Balamuthia* infection compared with other ethnicities. In a retrospective analysis of GAE cases in California, 73 % occurred in Hispanic Americans. On a national level, Hispanic Americans comprise 50 % of all cases of balamuthiasis, although they constitute only 12.5 % of the overall population [6]. One explanation could be the increased proportion of Hispanic workers in the landscape and lawn care service industry. There are also significant health care disparities in this population, including decreased health insurance coverage as well as delayed diagnosis and treatment of immunocompromising diseases, such as HIV/AIDS and diabetes [7]. Another possible explanation is a genetic predisposition; however, this mechanism has not been clearly defined.

Clinical symptoms of *Balamuthia* amoebic encephalitis are similar to viral or bacterial meningitis, including stiff neck, fever and photophobia. As the infection progresses, other signs include nausea, vomiting, confusion, and lethargy secondary to increased intracranial pressure [2]. This patient's presentation on assessment was nonspecific with symptoms of headache, blurry vision and gait imbalance, indicative of possible mass lesion. These findings correlated with lesions in the occipital lobe and cerebellum on MRI. Lesions on MRI for amoebic encephalitis showed peripheral enhancement with cavitation with surrounding edema likely from extensive damage to the brain parenchyma. Therefore, when edema is seen, clinicians should have a higher suspicion for underlying infection. There is no consistently effective treatment available to manage this lethal condition. Most cases of *Balamuthia* GAE were treated empirically with steroids, antibacterial, antifungal and antivirals, with no effect on the course of infection. One case series presented two patients who survived after treatment with pentamidine, sulfadiazine, clarithromycin, fluconazole, flucytosine [8]. Another patient was successfully treated with fluconazole, albendazole, and miltefosine [9]. Miltefosine is an investigational drug that has shown in vitro activity against free living amoebas and a survival advantage for those with fatal infections [10]. It is not widely available for treatment in the U.S. and was added to this patient's therapy later in its course. It may have been more efficacious if administered earlier. The use of multiple antimicrobials in treatment makes it difficult to identify a single drug for optimal therapy.

Conclusion

Balamuthia mandrillaris is an amoebic infection causing dissemination throughout the central nervous system. Because this disease is rare and there are no distinctive initial symptoms, diagnosis of *Balamuthia* is difficult. For this reason, it is important to increase clinical suspicion for certain populations–those exposed to dirt or soil for occupational or recreational purposes, people with less access to healthcare or immunocompromising conditions, and Hispanic patients. Earlier identification and treatment may result in better outcomes. Many antibiotics have not been effective in the treatment of this disease because they do not penetrate the blood brain barrier. Thus, the possibility of intrathecal treatment should be explored further. Additional research is clearly needed to develop empiric antibiotic selection and standardized pharmacotherapy regimen to treat balamuthiasis.

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None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Valli Mani (medical student) – wrote the case report.

Eric Hudgins, MD – neurosurgeon on case, received consents and images.

Declaration of Competing Interest

The authors report no declarations of interest.

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