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Case Report

Successful management of post-COVID-19 acanthamoebic encephalitis

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ABSTRACT

Acanthamoebic encephalitis is a rare and highly fatal disease that has no standard management protocol. Coronavirus disease 2019 (COVID-19) causes immune dysfunction and may predispose patients to this infection.

The present study describes successful management of acanthamoebic encephalitis in a young male who recently recovered from COVID-19 using a combination of medical and surgical approaches.

A combination of miltefosine with other agents with trophicidal and cysticidal activities should be used in the regimen. Surgical excision of the abscess should be undertaken whenever feasible.

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Background

Acanthamoebae are free living amoebae ubiquitously present in the environment. Human exposure to this organism is quite frequent, as reflected by its high seroprevalence of more than 80% in the general population (Brindley et al., 2009). Both trophozoites and cysts can enter the body via contact lens use, skin wounds, or inhalation and can hematogenously disseminate to the central nervous system (Acanthamoeba - Granulomatous Amebic Encephalitis (GAE); Keratitis | Acanthamoeba | Parasites | CDC, n.d.). Dissemination occurs in individuals with immune dysfunction; however, coronavirus disease 2019 (COVID-19)-induced predisposition of individuals to acanthamoebic encephalitis has not been reported previously.

Acanthamoebic encephalitis rapidly progresses over days and has a mortality rate of 97% – 98% (Kot et al., 2018). Optimal approach to the treatment of this disease is uncertain. Only a few reports of successful treatment with combination drug therapy are available in the literature; the following drugs were used in various combinations for variable durations ranging from two weeks to several months: miltefosine, fluconazole, ketoconazole, trimethoprim-sulfamethoxazole, sulfadiazine, metronidazole, rifampicin, vancomycin, ceftriaxone, dexamethasone, albendazole, carbamazepine, pentamidine, liposomal amphotericin B, flucytosine, and voriconazole (Kot et al., 2021).

The present study reports a case of acanthamoebic encephalitis in a patient after recovery from COVID-19 that was successfully managed with a combination of the medical and surgical approaches.

Case Report

A 32-year-old man with no previously known comorbidities was diagnosed with moderate COVID-19 and received a five-day course of methylprednisolone and oxygen supplementation along with other supportive measures; the patient remained asymptomatic for six weeks. One day, the patient nearly got into an accident while driving because he was unable to correctly estimate the distance to a nearby vehicle. Three days after the incident, the patient developed a weakness of the right side of the body and facial deviation to the left, which rapidly progressed to a maximum within four days. Magnetic resonance imaging (MRI) of the brain showed a multifocal variable-sized ring and enhancing nodular lesions in the bilateral hemispheres (Figure 1A).

Cerebrospinal fluid (CSF) analysis showed 4 lymphocytes per microliter and normal levels of the protein and sugar. The tests for bacterial, fungal, and tubercular infections were negative. The patient had a family history of diabetes mellitus, and HbA1c at admission was 8.61 g/dL. The tests for HIV-1 and -2 were negative.

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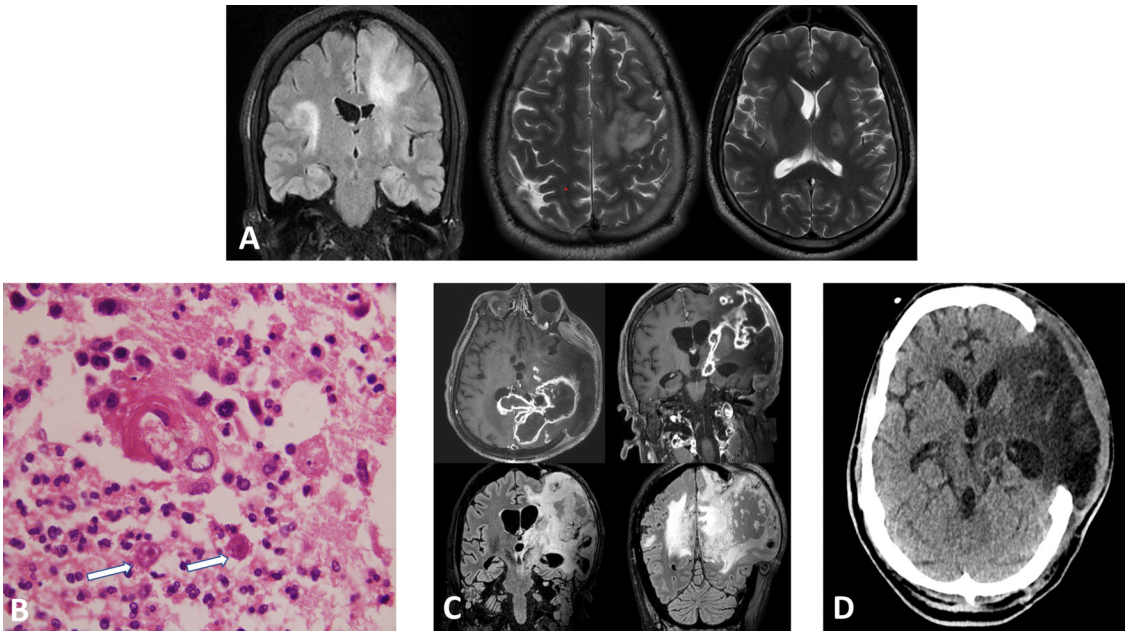

Figure 1. A. The brain-axial T2 and coronal fluid attenuated inversion recovery (FLAIR) MRI images showing a multifocal variable-sized ring and nodular enhancing lesions in the bilateral hemispheres. **B.** Histopathological examination showing acanthamoeba trophozoites in the brain tissue (arrows). **C.** MRI images prior to excision of the abscess **D.** Noncontrast computed tomography image after surgical debridement.

Over the next 15 days, the patient also developed left hemiparesis, followed by severe diffuse headache, vomiting, and a sensorial decline. Urgent decompressive craniectomy was performed.

Histopathological examination of the brain biopsy revealed the presence of necrotic tissue with inflammation and numerous amoebic trophozoites (Figure 1B). The tests for serum anti-Toxoplasma IgG and anti-herpes simplex virus (HSV) IgM were positive. However, Toxoplasma cysts or tachyzoites were not detected by histopathological examination, and the polymerase chain reaction (PCR) test for HSV in the CSF was negative.

The patient did not have any previous history of amoebic keratitis, use of contact lenses, or fresh-water swimming. A test for immunodeficiency revealed normal activities of NK, T, and B cells and slightly reduced neutrophil oxidative index (*i.e.,* 75). The absolute count of CD4-positive T cells was decreased (299/μL). Pending the confirmation of the presence of specific free-living amoeba, the patient was empirically administered a six-drug regimen, including liposomal amphotericin B (3 mg/kg/day), trimethoprim-sulfamethoxazole (TMP-SMX) (160 mg/800 mg per day), fluconazole (800 mg/day), albendazole (400 mg/day), azithromycin (500 mg/day), and rifampicin (600 mg/day). However, the patient developed Stevens-Johnson syndrome due to TMP-SMX, and the drug treatment was thus stopped. Flucytosine was added at a dose of 40 mg/kg/day. Continuous electroencephalogram showed features consistent with nonconvulsive status epilepticus. The condition was managed by intravenous infusion of midazolam for 24 hours and up-titration of anti-epileptics.

Aspiration of the scalp swelling revealed acanthamoeba cysts detected by lactophenol cotton blue staining. PCR for 18S ribosomal deoxyribonucleic acid (DNA) with the JDP primer confirmed the diagnosis. DNA was extracted using a QIAGEN test kit.

Miltefosine was added to the regimen at a dose of 50 mg thrice daily and was continued for four weeks.

The patient did not show any further improvement over the next four weeks; contrast-enhanced MRI of the brain was repeated, and the images showed an organizing abscess within central necrotic tissue and a surrounding enhancing rim (Figure 1C). A surgical procedure was performed to excise the abscess.

Another histopathological examination of the brain biopsy revealed multiple acanthamoeba trophozoites, as confirmed by PCR.

After debridement, the sensorium of the patient gradually improved, and repeated imaging of the brain revealed a significant decrease in the mass effect (Figure 1D).

After 15 weeks of hospital stay, the patient was finally discharged in a hemodynamically stable tracheostomized state with a Glasgow coma score of E4VtM6 on five anti-amoebic drugs, including flucytosine, fluconazole, rifampicin, azithromycin, and albendazole. The patient is being followed up by telephone due to the current COVID-19 surge. The patient is doing well at home eight weeks after discharge from the hospital.

Discussion

Infection with severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) predisposes patients to secondary infections in a number of ways, including immune dysregulation and treatment-related factors, such as the use of corticosteroids. SARS CoV-2 inhibits the type I interferon signaling pathway and attenuates the innate immune response (Li et al., 2020; Schreiber, 2020). COVID-19 is also characterized by the presence of dysfunctional mature neutrophils and neutrophil precursors and exhaustion of CD4- and CD8-positive T cells (Caserta et al., 2019; Schulte-Schrepping et al., 2020). In the patient described in the present study, both absolute CD4 count and neutrophil oxidative index were reduced on the seventh week of the illness. These effects can be a mechanism by which the patient developed acanthamoebic encephalitis following COVID-19 illness, in addition to diabetes mellitus, which was newly detected.

The treatment regimen used to treat the patient consisted of a combination of trophicidal agents (miltefosine, fluconazole, flucytosine, and azithromycin), cysticidal agents (miltefosine and fluconazole), and other agents that have been previously used to treat the survivors of acanthamoebic encephalitis (Alli et al., 2021; Elsheikha et al., 2020; Fischman et al., 1993; Id et al., 2020).

Caspofungin at a maintenance dose of 50 mg/day was administered to the patient for 34 days to treat candidaemia caused by

Candida auris. This agent has also been shown to have trophicidal and cysticidal activities against acanthamoebae in vitro (Bouyer et al., 2007).

Amphotericin B is the cornerstone therapy against Naegleria in primary amoebic meningoencephalitis; however, there is little evidence for the use of this drug in acanthamoebic encephalitis. The drug has been discontinued after the presence of the etiological agent in the patient was confirmed by PCR.

Considering the changes detected by MRI of the brain before and after the treatment with miltefosine, the drug apparently had the maximum effect in the studied case. *Acanthamoeba castellani* is highly sensitive to miltefosine in vitro, whereas *Acanthamoeba lugdunensis* and other species have low sensitivity to the drug even at higher concentrations (Mrva et al., 2011). The concentration of miltefosine achieved in the human brain parenchyma is yet to be determined.

The lesions began to organize following the combination medical therapy with miltefosine; however, the patient's sensorium further improved only after surgical excision of the abscess. This approach has been rarely used previously in the survivors but should be considered whenever feasible.

Conclusion

Acanthamoebic encephalitis should be considered when patients present with neurological deficits and brain lesions, which rapidly progress and cause mass effects. The best approach to the management involves a combination of medical and surgical interventions. Randomized clinical trials are needed to standardize the treatment for acanthamoebic encephalitis, and the role of COVID-19 in predisposition of the patients to this infection needs to be evaluated.

Competing interests

The authors declare that they have no known competing interests that influenced the work reported in this paper.

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Ethical approval

Next of kin of the patient described in the study gave consent to publish the history and images of the investigation anonymously.

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