Dear Editor,

Infectious diseases of the central nervous system (CNS) are a constant diagnostic challenge. We present a challenging case of a young immune-competent man with seizures, whose imaging was thought to be a tumor, histopathology review revealed the final diagnosis of granulomatous amebic encephalitis (GAE) and the patient is steadily improving.

A 34-year-old gentleman, presented with seizures during January 2018. The neurological examination was normal. Routine blood investigations including human immunodeficiency virus were unremarkable. Computed Tomography (CT) and magnetic resonance imaging (MRI) of the head showed left frontal ring-enhancing lesion [Figure 1a-f]. Differentials considered were tumor/ granuloma. Biopsy of the lesion was performed in April 2018, which revealed necrotizing granulomatous inflammation [Figure 2a-c]. The Grocott’s methenamine silver (GMS) and Periodic acid Schiff (PAS) stains for fungi and Ziehl-Neelsen stain for acid-fast bacilli (AFB) were negative. Since the most common cause for necrotizing chronic granulomatous inflammation is tuberculosis, he was empirically started on anti-tubercular therapy (ATT) with isoniazid 300 mg, rifampicin 450 mg, pyrazinamide 1500 mg, ethambutol 800 mg, pyridoxine 40 mg and phenytoin 200 mg per day in April 2018, followed by two drugs (isoniazid and rifampicin) after two months. After 11 months (March 2019), he had status epilepticus and repeat imaging showed [Figure 1g-j] new lesions in the right frontal, left temporal, right cerebellum with enhancement, and reduction of lesions in the left frontal lobe. Hence levetiracetam 1000 grams a day was added and alternate possibility of fungal or parasitic granuloma was considered.

A review of the previously performed biopsy was requested. Numerous deeper sections of the tissue blocks were taken. Detailed scrutiny revealed a very occasional amoebic trophozoite located near the perivascular inflammation [Figure 2d]. The trophozoite was rounded and had a well-delineated cell membrane and round nucleus with a central poorly made out karyosome [Figure 2d], whereas macrophages are more heterogeneous with a thin cell margin, and irregular nuclei [Figure 2c]. The diagnosis was revised to GAE. Further speciation on morphology (Acanthameba versus Balamuthia) could not be done due to scanty organisms and absence of cysts in the biopsy. Molecular testing was not possible.

In August 2019, treatment was changed to rifampicin 450 mg, fluconazole 150 mg, trimethoprim-sulfamethoxazole.

Figure 1: CT head in January 2018 shows left frontal hypodensity (arrow) (a) with enhancement (b). MRI-2018 February reveals T1- Left frontal iso-hypo intense (black arrow) (c), T2- heterogenous (d), T1 contrast enhancement with wavy margins (e), and blooming in susceptibility Weighted Imaging (SWI). MRI March 2019: (g) T1 shows hypointensity in right frontal peri-ventricular white matter (arrow), (h) T2- heterogenous lesion, (i) Multiple ring enhancing lesions- bilateral frontal, (j) Enhancing right cerebellar lesion.
There has been no further recurrence of seizures. The last follow-up was in June 2020 and he is stable.

**Discussion**

Our patient is a young, immune-competent man who presented with recurrent seizures. Imaging was initially thought to be tumor or granuloma. After biopsy which suggested granuloma, he was started on empirical ATT. After 11 months, he developed status epilepticus. Repeat MRI showed the appearance of lesions in new areas and disappearance of the old lesions. Biopsy review revealed scant amebic trophozoites establishing the diagnosis as GAE.

The GAE, described in 1965, is a neuro infection with a mortality rate of more than 90%.[3] Naegleria fowleri, Acanthamoeba, Balamuthia mandrillaris, and Sappinia diploidea are the free-living amoebae affecting CNS.[4] The factors favoring good outcome are immunocompetent status (50%), combination therapy (100%) and excision of brain lesion (37%).[5] In India, around 20 cases are published, most of which are postmortem.[6-8] Naegleria fowleri, called as “brain-eating ameba” causes Primary Amebic Encephalitis (PAE).[9] The clinical picture is of a fulminating meningoencephalitis. Acanthamoeba spp, Balamuthia mandrillaris, and Sappinia diploidea cause GAE. Acanthamoeba causes disease in debilitated, malnourished individuals.[10] Balamuthia mandrillaris affects both immune-competent and immune-compromised individuals.[11]

Patients with GAE can present with the mental status abnormality, (86%) seizures, (66%) headache, (53%) fever, (53%) meningismus, (40%) hemiplegia, (53%) visual disturbances, (26%) and ataxia (20%).[10]

The incubation period is a few weeks to months. Imaging differentials are tuberculoma, fungal granuloma, and toxoplasmosis. Multifocal parenchymal lesions in corticomedullary junction, tumor-like appearance, hemorrhagic infarcts, necrosis are suggestive of amebic encephalitis.[12] T2 sequence shows lesions isointense to gray, T1 contrast image shows a linear pattern of enhancement due to meningeal and underlying cortical inflammation. Intracerebral hemorrhage is characteristic of amebic encephalitis.[9] CNS tuberculomas show T1 isointense, T2 central hypointensity with surrounding hyperintensity (edema) and conglomerate enhancement.[12] Fungal granulomas show T2 hypointensity, with an irregular wall, T1 hypointensity and peripheral enhancement. In toxoplasmosis, T1 hypointensities, T2 hyperintensities with eccentric target sign is the characteristic feature.[11] In our patient, lesions are hypointense in T1, heterogenous in T2, with blooming and wavy enhancement which gives us a clue for amebic encephalitis.

Histopathology is the key to the diagnosis of GAE. The PAE caused by Naegleria fowleri species is characterized by necrosis with predominant neutrophils. The trophozoites are smaller, (10 microns) than Acanthamoeba and Balamuthia (14-40 microns). The tissue cysts of Balamuthia contain two to three nucleoli whereas Acanthameba has one nucleolus. Ultrastructurally, the Balamuthia cyst wall has three layers and Acanthameba has two. Naegleria and Acanthamoeba grow in non-nutrient agar with *Escherichia coli*. Balamuthia grows in mammalian cell culture.[11] A triplex real-time PCR developed by the center for disease control and prevention helps in specific diagnosis.

In our case, the histopathology showed chronic granulomatous inflammation. As there were new lesions and recurrent seizures while on ATT, a detailed review was necessitated that identified the scarce amebic trophozoites, indicating a diagnosis of GAE. Hence, it is important to have a high index of suspicion in all CNS granulomas, and while on treatment, repeat imaging is helpful. The clinical stability and disappearance of a few lesions in the latest MRI in our patient may be due to rifampicin.

The drugs that can be tried are fluconazole, sulfadiazine, rifampicin, voriconazole, miltefosine,[13,14] clarithromycin, pentamidine, flucytosine, azithromycin, albendazole.[6] Our patient was started on fluconazole (150 mg), trimethoprim-sulphamethoxazole (320/1600 mg), rifampicin (450 mg), and anti-epileptics. He is seizure-free since September 2019 and is on regular follow-up.
Our patient is unique in the following ways- 1) No systemic lesions, 2) Prolonged survivor, 3) Rifampicin (ATT) might be the drug restricting the infection to a limited extent.

**Conclusions**

Granulomatous amebic encephalitis is a rare and fatal illness. A high index of suspicion is required for diagnosis. Brain biopsy is crucial for diagnosis. If there is no clinical and radiological resolution, histopathology must be reviewed.

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**Conflicts of interest**

There are no conflicts of interest.

**References**

1. da Rocha AJ, Maia AC Jr, Ferreira NP, do Amaral LL. Granulomatous diseases of the central nervous system. Top Magn Reson Imaging 2005;16:155-87.
2. Jumla A, James D. Granulomatous infections: Etiology and classification. Clin Infect Dis 1996;23:146-58.
3. Silva RA, de Almeida Araujo S, de Freitas E Avellar IF, Pittella JE, de Oliveira JT, Christo PP. Granulomatous amoebic meningoencephalitis in an immunocompetent patient. Arch Neurol 2010;67:1516-20.
4. Zamora A, Henderson H, Swiatlo E. Acanthamoeba encephalitis: A case report and review of therapy. Surg Neurol Int 2014;5:68.
5. Das S, Gunasekaran K, Ajampur SS, Abraham D, George T, Janela MA, et al. Acanthamoeba encephalitis in immunocompetent hosts: A report of two cases. J Family Med Prim Care 2020;9:1240-3.
6. Hamide A, Sarkar E, Kumar N, Das AK, Narayan SK, Parija SC. Acanthameba meningoencephalitis: A case report. Neurol India 2002;50:484-6.
7. Thamtam V, Uppin M, Pyal A, Kaul S, Rani J, Sundaram C. Fatal granulomatous amoebic encephalitis caused by Acanthamoeba in a newly diagnosed patient with systemic lupus erythematosus. Neurol India 2016;64:101-4.
8. Chandra SR, Adwani S, Mahadevan A. Acanthamoeba meningoencephalitis. Ann Indian Acad Neurol 2014;17:108-12.
9. Gupta R, Parashar MK, Kale A. Primary amoebic meningoencephalitis. J Assoc Physicians India 2015;63:64-71.
10. Maritschnegg P, Sovinz P, Lackner H, Benesch M, Nebi A, Schwinger W, et al. Granulomatous amebic encephalitis in a child with acute lymphoblastic leukemia successfully treated with multimodal antimicrobial therapy and hyperbaric oxygen. J Clin Microbiol 2011;49:446-8.
11. Shehab KW, Aboul‑Nasr K, Elliott SP. Balamuthia mandrillaris granulomatous amebic encephalitis with renal dissemination in a previously healthy child: Case report and review of the pediatric literature. J Pediatric Infect Dis Soc 2018;7:e163-8.
12. Singh P, Kochhar R, Vashishta RK, Khandelwal N, Prabhakar S, Mohindra S, et al. Amebic meningoencephalitis: Spectrum of imaging findings. AJNR Am J Neuroradiol 2006;27:1217-21.
13. Singhal T, Bajpai A, Kalra V, Kabra SK, Samantaray JC, Satpathy G, et al. Successful treatment of Acanthamoeba meningitis with combination oral antimicrobials. Pediatr Infect Dis J 2001;20:623‑7.
14. Umar I, Kolyvas G, Visvesvara GS, Bilbao J, Guiot M‑C, Duplisea K, et al. Treatment of granulomatous amoebic encephalitis with voriconazole and miltefosine in an immunocompetent soldier. Am J Trop Med Hyg 2012;87:715-8.

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