Successful Treatment of Granulomatous Amoebic Encephalitis with Combination Antimicrobial Therapy

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Abstract

Granulomatous amoebic encephalitis (GAE) is a rare but fatal infection. Due to its nonspecific symptoms and laboratory and neuroradiological findings, it is rarely diagnosed antemortem. We herein present the case of a 72-year-old Japanese woman who was diagnosed with GAE following the detection of a pathogen similar to Balamuthia mandrillaris under a microscopic examination of cerebrospinal fluid sediment and who achieved remission with combination antimicrobial therapy. There are no previous reports of pathogens similar to B. mandrillaris being detected in cerebrospinal fluid antemortem; therefore, this case may be used as a benchmark for further studies.

Key words: granulomatous amoebic encephalitis (GAE), antimicrobial therapy, free-living amoebae, cerebrospinal fluid (CSF)

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Introduction

Meningoencephalitis caused by free-living amoebae includes two clinical entities: primary amoebic meningoencephalitis (PAM) and granulomatous amoebic encephalitis (GAE). Both have a poor prognosis, usually resulting in death (1, 2). The pathogenic organism responsible for PAM is Naegleria fowleri. Infection with this organism generally progresses rapidly following the development of symptoms and leads to death within ten days. GAE, in contrast, is caused by Acanthamoeba species and Balamuthia mandrillaris and progresses from subacute to chronic over several weeks to two years, followed by death. Since B. mandrillaris was first isolated from the brain of a pregnant mandrill baboon in 1986, it has been found to cause GAE in humans (3), with almost 200 cases having been reported worldwide. Balamuthia encephalitis can develop in children and elderly individuals with normal immunity, while Acanthamoeba species usually cause encephalitis in immunocompromised hosts. The prognosis of patients with GAE caused by B. mandrillaris is very poor, with only eight reported cases of survival. Because GAE is a rare disease with nonspecific symptoms, making the diagnosis antemortem is difficult. Additionally, there are no reports in which the Balamuthia-like amoeba itself was found in cerebrospinal fluid (CSF) (4). The present report describes a case of GAE caused by amoebae with Balamuthia-like morphological characteristics detected in the CSF in which we administered antimicrobial therapy and were able to save the patient’s life.

Case Report

A 72-year-old right-handed Japanese woman presented to our emergency department complaining of disordered consciousness and left-sided paralysis. She had a history of hypertension when she had traveled to Guam 20 years earlier. Approximately six months prior to admission, she increasingly complained of sleepiness and lethargy. Starting approximately two months prior to admission, her appetite had also decreased, and she was diagnosed with depression and treated at a psychiatric clinic. Upon arrival to the emergency department, the patient exhibited slightly impaired con-
vomiting, a fever of 38°C, and nuchal rigidity. The initial blood pressure was 22 cmH₂O, and the CSF appeared yellowish-white and muddy. A CSF examination showed a cell count of 1,153 cells/mm³ (46% neutrophils), a protein level of 134 mg/dL, a sugar level of 40 mg/dL (the blood sugar level was 119 mg/dL in blood collected simultaneously) and an adenosine deaminase level of 5.5 IU/L. A microscopic examination with India ink staining, bacterial and tuberculosis bacillus cultures and cerebrospinal cytological diagnoses were all negative. Axial T1-weighted imaging with gadolinium of repeated head MRI revealed nodular pathological changes in the right insular cortex, meninges in the vicinity and left occipital lobe of the cerebrum (Fig. 1E, F). Because bacterial and/or fungal meningitis was suspected, ceftriaxone at a dose of 2 g/day and fluconazole at a dose of 200 mg/day were intravenously administered. Markers for several kinds of fungal antigens, viral antibodies and syphilis were all negative in both the serum and CSF. There were no abnormal findings on a random skin biopsy, and no malignant tumors were found in various tests. Anti-HIV antibodies were also negative. On day 32, a skull-opening brain biopsy was performed. A pure white, cheese-like, homogenous substance filled the right Sylvian fissure and adhered to the tissue so that the M1-M2 portion of the right MCA was covered. Although the external shape of the MCA was maintained, black discoloration characterized the middle of the M2 portion. The biopsied brain tissue manifested slight gliosis; however, there was no blood vessel inflammation or

Figure 1. Magnetic resonance imaging (MRI) and MRA of the brain performed on admission (A-D) and day 9 posthospitalization (E, F). An axial T2-weighted image shows a high signal in the right insular cortex and left occipital lobe of the cerebrum (A). MRA shows occlusion of the right middle cerebral artery (B). Diffusion-weighted MRI reveals a diffuse high signal in the right insular cortex and right parietal lobe (C, D). An axial T1-weighted image obtained following the administration of gadolinium shows nodular enhancement in the right insular cortex, meninges in the vicinity and left occipital lobe of the cerebrum (E, F).
granuloma or tumor formation. We therefore considered a diagnosis of amoebic meningoencephalitis, and on day 40, we observed a number of living amoebae on a direct microscopic examination of the centrifuged CSF. The amoebae had extended, branched pseudopodia, a specific characteristic of *B. mandrillaris* amongst trophozoites of known pathogenic amoebae (Fig. 2). To determine the species of amoeba, we performed a polymerase chain reaction (PCR) test of the CSF and indirect immunofluorescence (IIF) staining of the biopsy specimens for *B. mandrillaris, N. fowleri* and *Acanthamoeba* species; however, all tests were negative. Although we were unable to identify the type of amoeba, we diagnosed the patient with GAE based on the morphology and initiated treatment with fluconazole (400 mg/day p.o.), pentamidine isethionate (200 mg/day i.v.), clarithromycin (800 mg/day p.o) and albendazole (600 mg/day p.o). Pentamidine caused persistent low blood sugar, while clarithromycin resulted in obvious QT prolongation, and both were therefore stopped. Flucytosine (3,000 mg/day p.o) was added to fluconazole and albendazole, and the treatment was continued. The patient’s progress was good; there was no worsening of pathological changes on head MRI, and the number of cells in the CSF decreased. On day 90, the CSF was amoeba-free. Although the patient still had memory disturbance, impaired orientation and delusions, she left the hospital five months after admission. She was still taking fluconazole and albendazole 17 months after starting treatment, with no signs of recurrence.

**Discussion**

This case is an example of GAE with the onset of mental symptoms (decreased spontaneity, depression) actualized by a cerebral infarction. In the present case, we diagnosed the patient with GAE after observing free-living amoebae in the CSF on optical microscopy, although we were unable to determine the species. Combination therapy with albendazole, flucytosine and fluconazole effectively treated the GAE, resulting in remission.

PCR analyses of the CSF and IIF staining of biopsy sections are usually used to diagnose GAE (4, 5). Recently, high-sensitivity real-time PCR targeting the RNase P gene has been developed (6). In the current case, however, the PCR test was negative for amoebae, including *B. mandrillaris, N. fowleri* and *Acanthamoeba* species. One possible reason for the negative PCR results is an insufficient number of amoebic cells in the CSF sample. A report by the California Encephalitis Project demonstrated that the rate of positive findings on PCR tests using CSF samples obtained from patients with presumptive *Balamuthia* amoebic encephalitis was only 25% (7). In the current case, IIF staining was also negative. This may have been due to the fact that the tissue biopsy specimen was almost necrotic and did not include the inflammatory site or blood vessels. However, we visualized a number of living amoebae with extending, branched, pseudopodia on a direct microscopic examination of the centrifuged CSF antemortem. Based on the available information, including the specific morphological characteristics and the patient’s chronic clinical course, we considered the GAE to be due to *B. mandrillaris* rather than *Acanthamoeba* species or *N. fowleri*, although we were unable to determine the species using PCR tests of the CSF or IIF staining of biopsy specimens.

There have been four reports of meningoencephalitis caused by *B. mandrillaris* in Japan. Although brain biopsies were performed antemortem in these cases, the biopsy findings did not lead to a diagnosis (8-10). Unlike *N. fowleri* (11), *Acanthamoeba* species and *B. mandrillaris* are usually not visible in the CSF on microscopic examinations antemortem. To our knowledge, only one case involving culture isolation of *B. mandrillaris* in the CSF postmortem has been reported (12). Unlike *N. fowleri*, neither *Acanthamoeba* species nor *B. mandrillaris* multiply rapidly, which is presumably why they are rarely detected in CSF. When a diagnosis of amoebic meningoencephalitis is suspected, as in this case, careful analyses of the CSF may lead to detection.

In the current case, the disease itself was actualized by occlusion of the right MCA. Although an inflammatory mechanism was presumed based on the macroscopic findings of the tissue around the right MCA and the results of the skull biopsy, we did not perform a biopsy of the blood vessel itself, and the exact pathological changes in blood vessel invasion are unknown. However, occlusion of the blood vessels and bleeding have been reported in the brain tissue of patients with GAE, with vasculitis assumed to be the cause. Although there is usually invasion of small vessels, and necrosis is often observed over a small region, cases resulting in large vessel arterial infarction, as observed in this case, have also been reported (10, 13). The same mechanism has been reported to occur in cases of fungal meningitis, such as that involving aspergillosis, toxoplasma encephalitis, tuberculous meningitis and bacterial meningitis. Therefore, in cases in which psychological symptoms and cerebrovascular disorders proceed gradually, a diagnosis of
GAE should be considered, and the evidence should be carefully examined.

The optimal therapy for GAE has not been determined. In this case, we treated the patient with the antimicrobial drugs used in reported surviving cases of GAE caused by B. mandrillaris or Acanthamoeba species. There are nine cases of survivors of meningoencephalitis caused by B. mandrillaris (7, 14-19), and in most of these cases, combinations of drugs including fluconazole, flucytosine, pentamidine, amphotericin B, sulfadiazine, clarithromycin, albendazole and miltefosine were used (Table). Recently, a case of a complication of a brain abscess treated with a combination of antibiotics and surgical removal was reported (14, 19).

In the present case, clarithromycin, pentamidine, albendazole and flucytosine were added to fluconazole, which was administered in the first stage of treatment. Although pentamidine and clarithromycin were suspended due to side effects, the combination of the remaining drugs enabled the patient to achieve remission. We had assumed a diagnosis of fungal meningitis at an early stage and administered fluconazole, which may have suppressed the proliferation of the amoebeae, ultimately resulting in remission. The development of new antimicrobial drugs is needed, and confirming the efficacy and safety of antimicrobials when used continuously for long periods, especially in combination with each other, is required.

The authors state that they have no Conflict of Interest (COI).

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References


