CASE REPORT

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Brain Eating Amoeba: Cerebral Infarction Caused by a Naegleria fowleri Infection

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ABSTRACT Although encephalitis caused by amoebas is commonly known in the literature, ischemic stroke associated with these microorganisms is very rare. Contrasted neuroimaging is a key modality for the rapid identification of atypical strokes in immunosuppressed patients. In this paper, a fatal case of amoebic encephalitis caused by Naegleria fowleri is presented in an immunosuppressed patient, with the infection being revealed by cerebrospinal fluid microscopy, amoeba culture, and neuroimaging. This paper is significant being the first case report on N. fowleri in Turkey and showing the importance of neuroimaging in atypical stroke cases.

Keywords: Infection and stroke; brain eating amoeba; vasculitis

Free-living amoebae, such as *Naegleria*, *Acanthamoeba*, and *Balamuthia* are known as opportunistic and deadly protozoa in humans and animals. They are widely found in soil and water. They cause primary amoebic meningoencephalitis (PAM), which usually results in death.[1-3] Most cases are healthy young adults with a post-mortem diagnosis and a history of water contact.[4] Although encephalitis caused by amoebas is commonly known in the literature, ischemic stroke associated with these microorganisms is very rare.

It is known that opportunistic infections due to immune suppression lead to an increased risk of stroke.[5,6] Vasculitis associated with opportunistic infections, such as bacterial (syphilis, tuberculosis), viral (cytomegalovirus, herpes), fungal (cryptococcosis, aspergillosis, candidiasis), and parasitic (toxoplasmosis) infections can lead to stroke.[7] Although PAM and granulomatous amoebic encephalitis (GAE) are well defined in the literature, stroke cases caused by *Naegleria fowleri* are extremely rare. Its pathogenesis is the infiltration of intracranial arteries with lymphocytes, amoebic trophozoites, and cysts, resulting in the development of vasculitis.

Neuroimaging is the first step for any cerebrovascular disease. In atypical cases, contrast-enhanced imaging must be considered. It has been more than three decades since the publications of the first report on the computed tomography (CT) findings in PAM and GAE.[8,9]

CASE REPORT

A 68-year-old female patient was admitted to our hospital with altered mental state and generalized tonic-clonic seizure. Four days before her admission, she had developed nausea, vomiting, and fever. She had a history of idiopathic aortitis when she was on immunosuppressive and antiaggregant therapy. The pa-

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tient had been using azathioprine, anti-tumor necrosis factor-alpha agent, methotrexate and steroids for various periods for the last 8 years and dexametazone 4 mg/day and 100 mg acetyl salicylic acid for the past year. She had no contact with water but she had planted orchids about a week earlier, and amoebae (*Acanthamoeba* sp., *Naegleria* sp.) was found in the soil by examination at microbiology laboratory. It was considered that the patient's immune system might have been suppressed depending on the drugs she used, and that she might have been contaminated during contact with the soil. The neurological examination revealed lethargic consciousness, global aphasia, right hemiplegia, right homonymous hemianopia, and right central facial paralysis.

A complete blood count analysis identified mild neutrophilic leucocytosis. Cranial CT, diffusion weighted magnetic resonance imaging (DW-MRI), and non-enhanced MRI findings were normal. Multifocal ring-enhancing lesions (largest 2x2.5 cm) were seen in both hemispheres on the gadolinium-enhanced T1-weighted MRI image (Figure 1 and Figure 2). Cerebrospinal fluid (CSF) parameters were normal [glucose: 56 mg/dL, protein: 43.7 mg/dL, lactate dehydrogenase (LDH): 203 U/L]. Mobile amoeba trophozoites with two whips each were identified in CSF (Figure 3). The presence of amoeba footprints was detected in 48 hours in the non-nutritious agar medium with *Escherichia coli*. Amoebae were also present in the axenic medium and cell culture. Cyst formation tests were performed at 46 degrees in temperature. In addition to direct microscopic examination, same agents were also identified with electron microscopy. The patient was given trimethoprim sulfamethoxazole, metronidazole, amphotericin B, clarithromycin, albendazole, acetyl salicylic acid and low molecular weight heparin treatments. The patient's fever reduced and her consciousness improved, but MRI was repeated after two days due to the permanent focal neurological signs. The second DW-MRI showed a new middle cerebral artery infarction on the left side (Figure 4). Echocardiography, 24-hour Holter monitoring, CT angiography imaging were performed, but findings were normal.

In her current presentation, an ischemic stroke caused by *N. fowleri* was present. The patient re-

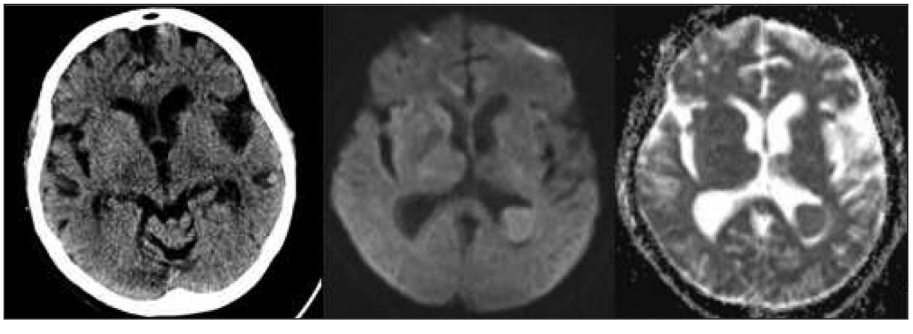

FIGURE 1: No acute changes were seen in computed tomography, diffusion weighted magnetic resonance imaging and apparent diffusion coefficient images.

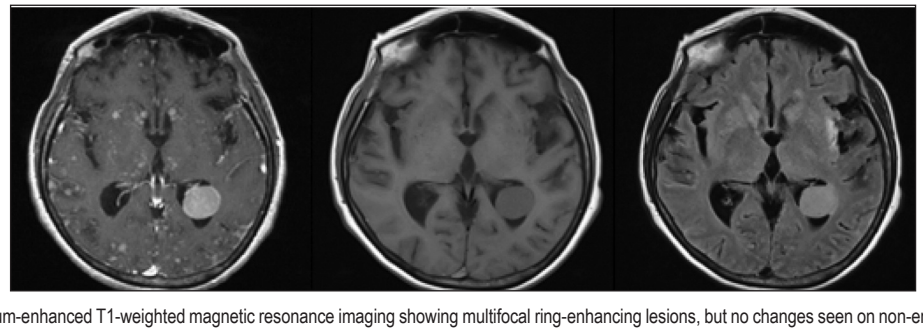

FIGURE 2: Gadolinium-enhanced T1-weighted magnetic resonance imaging showing multifocal ring-enhancing lesions, but no changes seen on non-enhanced T1-weighted magnetic resonance imaging and fluid attenuation recovery images.

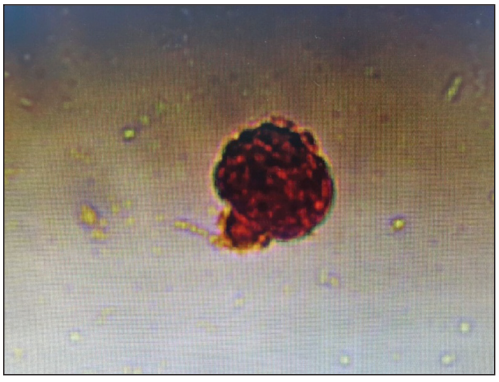

FIGURE 3: Fine morphology of trophozoites of Naegleria fowleri, direct microscopy.

ceived 97 days of treatment with a combination of amoebicidal, antifungal and antibiotic drugs in addition to anti-edema and antiaggregant treatment. Results of 2 time repeated CSF studies on days 15 to 30 all revealed positive results for trophozoites also normal glucose, protein, LDH levels. Multisystem organ failure developed and she died in the intensive care unit on the 97th day of hospitalization. Informed consent was obtained from the patient's daughter.

DISCUSSION

Recently, there has been a significant increase in the reporting of infections due to free-living amoeba. These organisms increase worldwide due to global warming and pollution. Due to their thermophilic and polymorphic structures, amoebae are expected to become even more dangerous in the future with their easy adaptation ability and resistant cyst walls.[10] To the best of our knowledge, this is the first case to survive for such a long time with a diagnosis of PAM and suffer a stroke due to *N. fowleri* in Turkey. This case highlights the importance of imaging in the diagnosis of atypical stroke cases. Although CT and DW-MRI did not provide diagnostic findings, contrast-enhanced MRI was consistent with an amoebic infection. In such cases, a CSF analysis is also as important as imaging since a CSF examination with direct microscopy can easily reveal amoebic trophozoites.[11]

GAE is typically a subacute or chronic disease characterized by the insidious onset of neurologic change, resulting in death occurring within eight days to several months.[12] Pathologically, GAE is characterized by multifocal areas of brain softening, edema, and abscess formation. Angiitis is invariably present secondary to amoebic invasion into vascular walls and lumens and results in fibrinoid necrosis and variable degrees of vessel thrombosis.[12-14] Our patient also had middle cerebral artery infarction that developed as a result of vascular invasion caused by amoeba. By the examination of the rheumatologist; the fact that the patient's values indicating inflammation such as sedimentation and C-reactive protein were normal demonstrated that there was no aortitis activation; therefore we thought that the infarction developed secondary to amoeba infection. Although GAE is usually seen with *Balamuthia mandrillaris*, clinical presentation, neuroimaging, CSF examination and amoeba culture findings in our case indicated the presence of GAE caused by an *N. fowleri* infection.

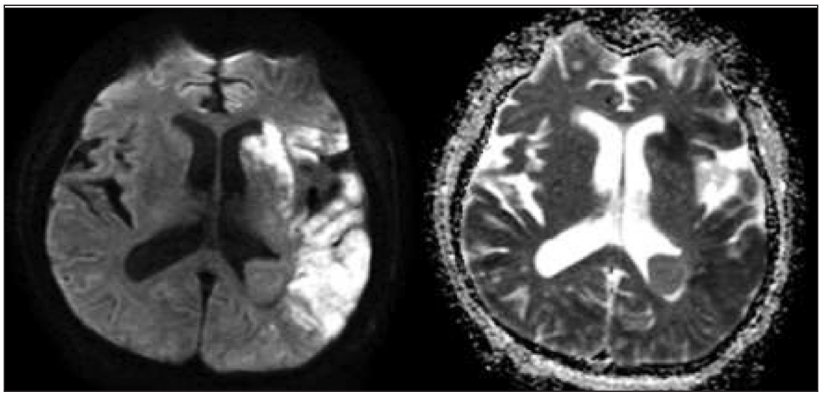

FIGURE 4: Diffusion weighted magnetic resonance imaging, taken due to the persistence of focal neurological deficit, showing acute middle cerebral artery infarction.

In this infection, the most common findings on CT (seen in 50%) are interpreted as cerebral oedema, but it is also not surprising to see normal appearance on the brain CT in the early course of the disease, as described in 40% of cases reported in the literature.[12] In our patient, there was no acute change on CT, and multiple ring-enhancing lesions were observed in both hemispheres on the gadolinium-enhanced T1-weighted MRI image. In the literature, the typical MRI findings of the disease are reported to be multifocal lesions showing T2 hyperintensity and a heterogeneous or ring-like pattern of enhancement, with a predilection for the cerebral hemispheres, diencephalon, thalamus, brain stem, and posterior fossa structures.[15]

In conclusion, in immunosuppressed patients presenting with a stroke, contrast-enhanced imaging with DW-MRI should be performed. It should be remembered that atypical causes of stroke due to vasculopathies and opportunistic infections can be shown in contrast-enhanced imaging.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Fatma Ger Akarsu, Nihal Doğan, Atilla Özcan Özdemir;* ***Design:*** *Nihal Doğan;* ***Control/Supervision:*** *Demet Funda Baş Sökmez, Atilla Özcan Özdemir, Nurettin Erben;* ***Data Collection and/or Processing:*** *Fatma Ger Akarsu, Nihal Doğan;* ***Analysis and/or Interpretation:*** *Fatma Ger Akarsu, Atilla Özcan Özdemir;* ***Literature Review:*** *Fatma Ger Akarsu, Nihal Doğan, Atilla Özcan Özdemir;* ***Writing the Article:*** *Fatma Ger Akarsu, Nihal Doğan, Demet Funda Baş Sökmez;* ***Critical Review:*** *Nurettin Erben, Atilla Özcan Özdemir;* ***References and Fundings:*** *Atilla Özcan Özdemir, Demet Funda Baş Sökmez;* ***Materials:*** *Fatma Ger Akarsu, Nihal Doğan, Nurettin Erben.*

REFERENCES

1. Yoder JS, Eddy BA, Visvesvara GS, Capewell L, Beach MJ. The epidemiology of primary amoebic meningoencephalitis in the USA, 1962-2008. Epidemiol Infect. 2010;138(7): 968-75. [Crossref] [PubMed]
2. Siddiqui R, Khan NA. Primary amoebic meningoencephalitis caused by Naegleria fowleri: an old enemy presenting new challenges. PLoS Negl Trop Dis. 2014;8(8):e3017. [Crossref] [PubMed] [PMC]
3. Güémez A, García E. Primary Amoebic Meningoencephalitis by Naegleria fowleri: Pathogenesis and Treatments. Biomolecules. 2021;11(9):1320. [Crossref] [PubMed] [PMC]
4. Visvesvara GS. Infections with free-living amebae. Handb Clin Neurol. 2013;114:153-68. [Crossref] [PubMed]
5. Gorczyca I, Stanek M, Podlasin B, Furmanek M, Pniewski J. Recurrent cerebral infarcts as the first manifestation of infection with the HIV virus. Folia Neuropathol. 2005;43(1):45-9. [PubMed]
6. Bowen LN, Smith B, Reich D, Quezado M, Nath A. HIV-associated opportunistic CNS infections: pathophysiology, diagnosis and treatment. Nat Rev Neurol. 2016;12(11):662-74. [Crossref] [PubMed]
7. Gerber O, Roque C, Coyle PK. Vasculitis owing to infection. Neurol Clin. 1997;15(4): 903-25. [Crossref] [PubMed]
8. Benson RL, Ansbacher L, Hutchison RE, Rogers W. Cerebrospinal fluid centrifuge analysis in primary amebic meningoencephalitis due to Naegleria fowleri. Arch Pathol Lab Med. 1985;109(7):668-71. [PubMed]
9. Siddiqui R, Khan NA. Balamuthia amoebic encephalitis: an emerging disease with fatal consequences. Microb Pathog. 2008;44(2):89-97. [Crossref] [PubMed]
10. Maciver SK, Pi-ero JE, Lorenzo-Morales J. Is Naegleria fowleri an emerging parasite? Trends Parasitol. 2020;36(1):19-28. [Crossref] [PubMed]
11. Schumacher DJ, Tien RD, Lane K. Neuroimaging findings in rare amebic infections of the central nervous system. AJNR Am J Neuroradiol. 1995;16(4 Suppl):930-5. [PubMed]
12. Pindyck TN, Dvorscak LE, Hart BL, Palestine MD, Gallant JE, Allen SE, SantaCruz KS. Fatal granulomatous amebic encephalitis due to Balamuthia mandrillaris in New Mexico: a case report. Open Forum Infect Dis. 2014;1(2):ofu062. [Crossref] [PubMed] [PMC]
13. Healy JF. Balamuthia amebic encephalitis: radiographic and pathologic findings. AJNR Am J Neuroradiol. 2002;23(3):486-9. [PubMed] [PMC]
14. 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(6): 1217-21. [PubMed] [PMC]
15. Kidney DD, Kim SH. CNS infections with free-living amebas: neuroimaging findings. AJR Am J Roentgenol. 1998;171(3):809-12. [Crossref] [PubMed]