Open Forum Infectious Diseases

BRIEF REPORT

Fulminant *Acanthamoeba castellanii* Encephalitis in an Ibrutinib-Treated Patient

Jessica W. Crothers,[1] Liangge Hsu,[2] and Francisco M. Marty[2]

[1]University of Vermont Medical Center, Burlington, Vermont, USA, and [2]Brigham and Women's Hospital, Boston, Massachusetts, USA

We report a case of fulminant *Acanthamoeba castellanii* encephalitis in a patient with chronic lymphocytic leukemia treated with ibrutinib. The unusually rapid neurologic decline and fatal outcome observed are probably related to alterations in immunologic function associated with inhibition of Bruton tyrosine kinase.

Keywords: *Acanthamoeba castellanii*; amoeba; *Naegleria*; encephalitis; ibrutinib.

A 70-year-old man on treatment with ibrutinib for chronic lymphocytic leukemia (CLL) presented to an outside hospital with fever (40.3°C), malaise, weakness, and confusion in August 2018. His medical history was notable for interstitial lung disease and splenectomy. He was treated with ceftriazone and azithromycin for presumed pneumonia but developed confusion followed by seizures a day later. Brain magnetic resonance imaging (MRI) demonstrated a 3.4-cm irregular enhancing lesion in the left occipital lobe. Empirical treatment was changed to vancomycin, cefepime, and metronidazole, and the patient was transferred to our institution 4 days later. Upon arrival, the patient was nonresponsive. Head computed tomography demonstrated vasogenic edema surrounding the occipital lesion, but no hemorrhages or midline shift to explain his coma (Figure 1). On physical exam, his heart rate was 92 bpm, blood pressure 126/60 mmHg, temperature 37.8°C, and oxygen saturation 93%. He was unable to answer questions or follow commands and had only minimal withdrawal from painful stimuli.

His family reported that he had been well until 4 days before presentation, when he developed drenching night sweats and confusion, followed by visual disturbances, including loss of color vision, and then he lost the ability to care for himself, becoming noninteractive and unable to recognize others. He previously worked as a carpenter and had not traveled recently. Of note, the patient had cats and had cleaned his Koi pond filters, spraying them with a hose 3 days before developing symptoms.

Upon admission, the patient's antimicrobial regimen included vancomycin, cefepime, metronidazole, and liposomal amphotericin B, which was later changed to isavuconazole. Laboratory testing included a leukocyte count of 16 200 cells/μL with 70.8% neutrophils; hematocrit, 40.2%; platelets, 124 K/μL; galactomannan, 0.04; 1-3-Beta D glucan, <31 pg/mL; serum cryptococcal antigen, negative; anaplasma, babesia, and Lyme polymerase chain reaction (PCR), negative; blood cultures, negative; HIV testing, negative; toxoplasma IgG and IgM, negative; toxoplasma PCR, negative; JC virus (John Cunningham or Human polyomavirus 2 virus), negative. Lumbar puncture was performed (opening pressure, 29 cm^2 H_20; glucose, 98; protein, 111; nucleated cells, 53; lymphocytes, 59%; monocytes, 18%; neutrophils, 16%; atypical lymphocytes, 5%). Initial cerebrospinal fluid (CSF) testing was extensive and unremarkable.

The patient declined, becoming comatose with decorticate posturing. Repeat MRI imaging in preparation for neurosurgical intervention revealed multiple new contiguous and noncontiguous areas of supra- and infratentorial involvement with hemorrhagic transformation. Surgery was not performed. The patient expired 10 days after initial presentation; autopsy was declined.

Given the patient's history of freshwater exposure from spraying Koi pond filters, a CSF sample was sent to the Centers for Disease Control and Prevention Free-Living and Intestinal Amebas Laboratory for molecular testing. The sample was initially reported as negative for *Naegleria fowleri*, *Balamuthia mandrillaris*, and *Acanthameoba* spp. by PCR, but retesting as part of the laboratory's internal assessment practices revealed inconsistent low-level positivity with atypical PCR products (2 sequences at 430 bp and 330 bp instead of 1 longer product). This prompted further evaluation by Sanger sequencing, which identified *Acanthamoeba castellanii* genotype I. No trophozoites were seen on CSF Gram stain or cytology.

Amebiasis of the CNS represents a critical yet often challenging clinical diagnosis. Caused by free-living amoebas, including *Acanthamoeba* spp., *Balamuthia mandrillaris*, and *Naegleria fowleri*, case fatality of amebic encephalitis approaches 100%. Primary amoebic meningoencephalitis (PAM) usually occurs when *N. fowleri* gains access to the brain via the olfactory bulb. Death is rapid, and patients, who are commonly young and healthy with a history of fresh water exposure in summer

Received 2 December 2019; editorial decision 16 January 2020; accepted 17 January 2020.

Correspondence: Jessica Crothers, MD, Department of Pathology and Laboratory Medicine, University of Vermont Medical Center, 111 Colchester Ave, Burlington, VT 05401 (jessica.crothers@uvmhealth.org).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofaa025

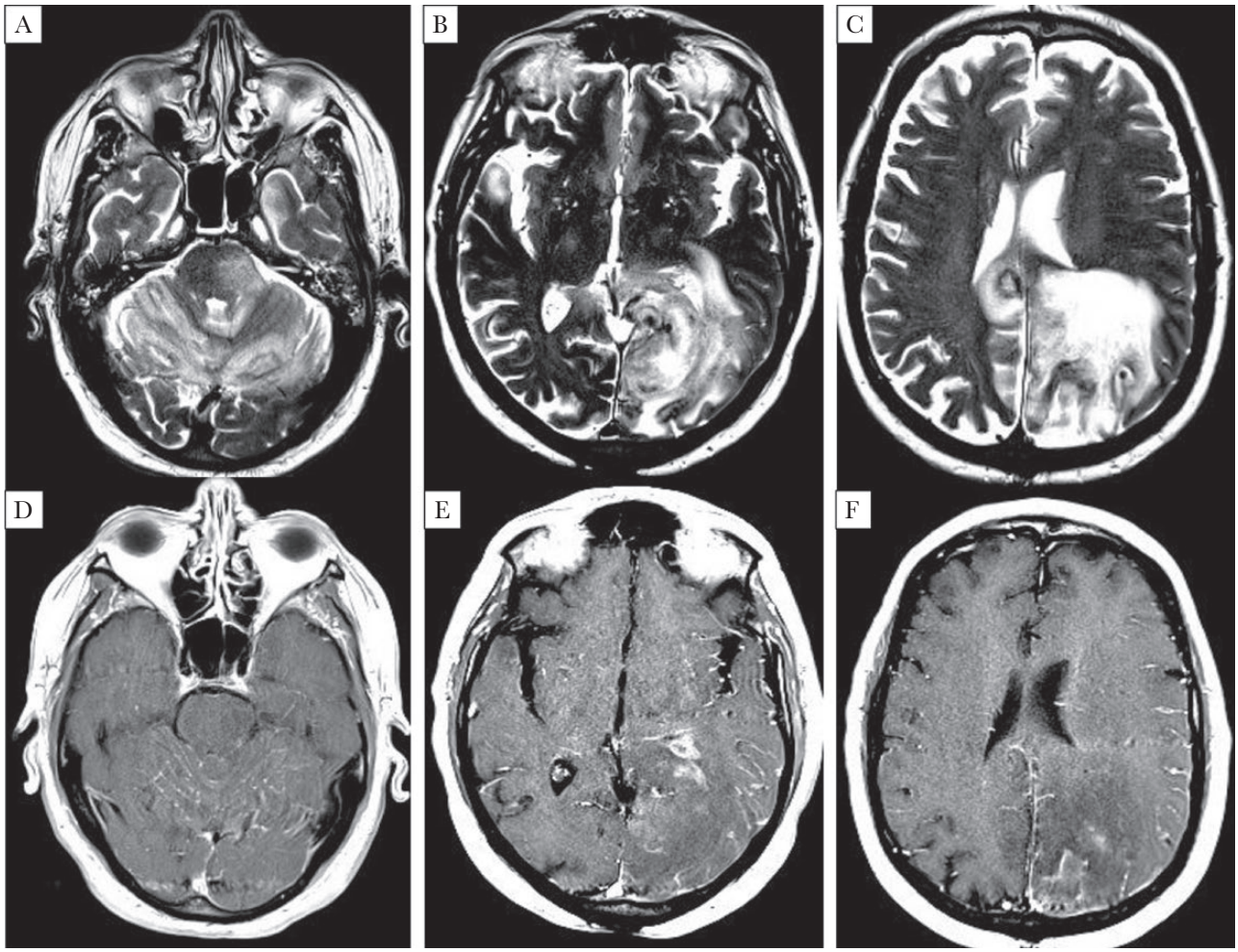

Figure 1. Multiple axial T2 (A, B, C) and postcontrast (D, E, F) images show numerous lesions at the left pons, bilateral cerebellum (A, D), right anterior temporal and left occipital lobes (B, E), and right splenium (C, F) associated with dark T2 rim, edema, and mild amorphous enhancement.

months, present with frontal lobe lesions and grossly abnormal CSF findings [1, 2]. *Acanthamoeba* spp. typically cause subacute infections, termed granulomatous amoebic encephalitis (GAE), in older, immunocompromised patients, who present with vague neurologic symptoms for weeks to months with progressive CNS disease and death. Free-living amoebas, including *Acanthamoeba*, are widely distributed in the environment, and many healthy individuals have serologic evidence of exposure [3, 4]. Exposure can occur by inhalation or by direct inoculation into the cornea, sinonasal mucosa, or skin. Ensuing disease varies according to host immunologic status, route of exposure, and strain virulence. CNS invasion occurs hematogenously or by direct extension through the nasal epithelium. Mucosal IgA antibodies appear to play an important role in initial host defense, followed by complement activation and antibody-mediated recognition of the organisms by phagocytic cells [5]. Well-developed granulomata are not observed in immunocompromised patients, who instead develop multifocal lesions with severe hemorrhagic necrosis filled by numerous trophozoites.

Although it is difficult to establish the exact timing of this patient's infection, his lack of previous symptoms and potential exposure to contaminated water via spraying of Koi pond filters suggest inhalation of amoebae, with a fulminant clinical course in the spectrum of PAM despite the identification of *Acanthamoeba castellanii*. The use of molecular sequencing in this case highlights the need for multimodal approaches in the diagnosis of CNS infections. Likely due to a low level of potentially degraded DNA in the CSF, this case was initially negative by targeted multiplex TaqMan real-time PCR, a technique that requires 180 bp of nonamplified DNA [6]. Sanger sequencing, however, was able to provide species-level identification of the causative organisms. Sanger sequencing is based on the selective incorporation of chain-termination dideoxynucleotides by DNA polymerase and does not rely on primer binding, making it a more sensitive technique capable of picking up small fragments of DNA that might not bind strongly and consistently to a particular PCR primer. Sanger sequencing also has the advantage over newer, next-generation short-read technologies of

creating longer sequence reads (>500 bp) for improved species identification.

To our knowledge, this is the second case of amebic encephalitis reported in the literature in a patient taking ibrutinib, highlighting the potentially unique risk of infection in patients taking Bruton kinase inhibitors [7]. We hypothesize that ibrutinib-mediated alterations of immunologic function resulted in uncontrolled amoebic proliferation, CNS invasion, and unusually rapid clinical deterioration [8, 9] There have been several reports of fungal diseases in patients receiving ibrutinib, including invasive aspergillosis, cryptococcosis, and pneumocystosis [10], suggesting that off-target effects of ibrutinib may be additive, altering the T cell–macrophage axis in addition to B-cell function. The propensity of these invasive diseases to be neurotropic in patients receiving ibrutinib [11, 12] remains to be elucidated.

Acknowledgments

We have no formal acknowledgments for the completion of this work.

Financial support. This work was not supported by extramural funding.

Potential conflicts of interest. J.W.C., no conflict; L.H., no conflict; F.M.M., no conflict. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Ong TYY, Khan NA, Siddiqui R. Brain-eating amoebae: predilection sites in the brain and disease outcome. J Clin Microbiol **2017**; 55:1989–97.
2. Visvesvara GS, Moura H, Schuster FL. Pathogenic and opportunistic free-living amoebae: *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappinia diploidea*. FEMS Immunol Med Microbiol **2007**; 50:1–26.
3. Cursons RT, Brown TJ, Keys EA, et al. Immunity to pathogenic free-living amoebae: role of humoral antibody. Infect Immun **1980**; 29:401–7.
4. Lares-Jiménez LF, Borquez-Román MA, Alfaro-Sifuentes R, et al. Detection of serum antibodies in children and adolescents against *Balamuthia mandrillaris*, *Naegleria fowleri* and *Acanthamoeba* T4. Exp Parasitol **2018**; 189:28–33.
5. Alizadeh H, Apte S, El-Agha MS, et al. Tear IgA and serum IgG antibodies against *Acanthamoeba* in patients with *Acanthamoeba keratitis*. Cornea **2001**; 20:622–7.
6. Qvarnstrom Y, Visvesvara GS, Sriram R, da Silva AJ. Multiplex real-time PCR assay for simultaneous detection of *Acanthamoeba* spp., *Balamuthia mandrillaris*, and *Naegleria fowleri*. J Clin Microbiol **2006**; 44:3589–95.
7. Voshtina E, Huang H, Raj R, Atallah E. Amebic encephalitis in a patient with chronic lymphocytic leukemia on ibrutinib therapy. Case Rep Hematol **2018**; 2018:6514604.
8. Łanocha-Arendarczyk N, Kolasa-Wołosiuk A, Wojciechowska-Koszko I, et al. Changes in the immune system in experimental acanthamoebiasis in immunocompetent and immunosuppressed hosts. Parasit Vectors **2018**; 11:517.
9. Marciano-Cabral F, Cabral GA. The immune response to *Naegleria fowleri* amebae and pathogenesis of infection. FEMS Immunol Med Microbiol **2007**; 51:243–59.
10. Chamilos G, Lionakis MS, Kontoyiannis DP. Call for action: invasive fungal infections associated with ibrutinib and other small molecule kinase inhibitors targeting immune signaling pathways. Clin Infect Dis **2018**; 66:140–8.
11. Ghez D, Calleja A, Protin C, et al; French Innovative Leukemia Organization (FILO) CLL group. Early-onset invasive aspergillosis and other fungal infections in patients treated with ibrutinib. Blood **2018**; 131:1955–9.
12. Lionakis MS, Dunleavy K, Roschewski M, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. Cancer Cell **2017**; 31:833–843.e5.