Rapidly progressive *Aspergillus* meningitis successfully treated with voriconazole and corticosteroids

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Dear Editors,

Central nervous system (CNS) aspergillosis is a frequently fatal infection that mainly affects immunosuppressed patients. Mortality rates in patients receiving voriconazole (VRZ) treatment remain unacceptably high, and more efficacious therapies are needed [1]. Unlike bacterial or tuberculosis meningitis, corticosteroid treatment for CNS aspergillosis has not yet been established. We report the case of a young immunocompetent woman with acute *Aspergillus* meningitis presenting with rapidly progressive respiratory failure and successfully treated using VRZ and a corticosteroid.

Case report A 21-year-old immunocompetent woman with no medical history developed a frontal headache, followed by appetite loss and fever. Abdominal and chest computed tomography (CT) performed at a local hospital showed no abnormalities. She was referred to our hospital 8 days after the onset of headache. On admission, her body temperature was 38.4 °C, and she was alert and cooperative. She had neck stiffness. No cranial nerve palsies, motor paresis, or sensory disturbances were observed. Enzyme-linked immunosorbent assay was negative for human immunodeficiency virus. Her CD4 cell count was 470/ μ L, which was 39.9% of the total lymphocyte count. Cerebrospinal fluid (CSF) analysis revealed a white blood cell count of 96/ mm^3 (12% neutrophils and 88% lymphocytes) and a glucose level of 35 mg/dL

(simultaneous blood sugar, 102 mg/dL). CSF bacterial cultures were negative for pathogens and CSF cryptococcal antigen. The results of polymerase chain reaction (PCR) analysis of CSF were negative for tuberculosis. CSF viral titres were negative. Brain CT showed no abnormalities. Although the CSF glucose level was mildly lower than normal, the patient's clinical history of acute symptoms, physical examination findings, and elevated CSF lymphocyte levels were consistent with a diagnosis of aseptic meningitis; therefore, we chose conservative therapy. On day 2 of admission, her level of consciousness deteriorated that was incompatible with the diagnosis of aseptic meningitis. Brain magnetic resonance imaging (MRI) including the paranasal area showed no abnormalities. We suspected viral encephal meningitis and administered intravenous acyclovir. However, her symptoms did not improve, and she became comatose and developed respiratory failure on the following day. She was transferred to the intensive care unit and was intubated and placed on a ventilator. Thereafter, spontaneous respiration stopped, and brain CT showed bilateral cerebral oedema (Fig. 1). Intravenous methylprednisolone was administered (1 g/day for 3 days), followed by prednisolone via a nasogastric tube. The disturbance of consciousness, respiratory failure, and brain oedema improved after corticosteroid treatment (Fig. 1). Serum 1,3- β -D-glucan (BG) values obtained using the Fungitec G Test MKII (Nissui Pharmaceutical, Tokyo, Japan) were elevated to 230 pg/mL (normal, < 20 pg/mL), and a test for CSF *Aspergillus* galactomannan (GM) antigen performed using enzyme-linked immunosorbent assay (*Plateria Aspergillus*, Bio-Rad) showed an optical density of 0.6 (cut-off, < 0.5). PCR analysis of CSF was negative for *Aspergillus*, and CSF was negative for *Candida* antigen. Based on these findings, a diagnosis of acute *Aspergillus* meningitis was made. VRZ was intravenously administered beginning on day 10 of admission. The neurologic symptoms resolved and treatment

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Fig. 1 Serial brain computed tomography at (a) admission, (b) 3 days after admission (showing bilateral brain oedema) and (c) 9 days after admission (showing amelioration of brain oedema after corticosteroid therapy)

continued with oral VRZ and oral prednisolone. Blood cultures on both days 5 and 13 after admission were negative, and an ultracardiogram detected no vegetation. Post-contrast brain MRI showed no abnormally enhanced lesions. Whole-spine MRI showed no abnormalities and no sign of abscess or discitis. Her urine and sputum cultures were negative for *Aspergillus*. These findings indicated that the focus of infection of aspergillosis was uncertain. *Aspergillus* GM antigen in CSF was 0.0 on day 17 and persisted at 0.0 on days 28 and 38 after admission and serum BG values levels normalised. The patient showed good clinical recovery without residual signs or symptoms, and VRZ was discontinued 6 months after initiation. Relapse had not occurred at 12 months after onset.

Our patient was diagnosed with rapidly progressing acute *Aspergillus* meningitis with respiratory failure. In managing this patient, we identified two key clinical issues. First, young immunocompetent patients may present acute meningitis mimicking aseptic meningitis, without a focus of aspergillosis, such as the lungs or paranasal sinuses, and testing for CSF *Aspergillus* GM antigen is diagnostically useful in such cases. Second, corticosteroid treatment combined with VRZ was effective for our patient with CNS aspergillosis.

Aspergillus meningitis is an infrequently encountered clinical entity, and its diagnosis is extremely challenging. Its diagnosis during life is observed only in 55.9% of patients, and the overall mortality rate is 72.1% [2]. Potential sites of primary infection in CNS aspergillosis include the paranasal sinuses, lungs, and other sites; however, similar to our patient, 22% of patients have no apparent primary site of infection [1]. Brain biopsy or low-signal-intensity T2-weighted MRI is a diagnostic tool for fungal infection; however, it is difficult to diagnose *Aspergillus* meningitis when brain abscesses and primal organ involvement are absent in immunocompetent

patients. CSF cultures are usually negative, and the cell count and glucose and protein concentrations are non-specific in CNS aspergillosis. Moreover, the results of a CSF PCR analysis may be negative for the fungal agent in CNS aspergillosis, because the number of fungal cells present in a CSF specimen obtained via lumbar puncture is extremely low. Therefore, the detection of the CSF *Aspergillus* GM antigen might be the earliest indicator of the condition and be useful for monitoring treatment response [3]. Indeed, previous reports comparing CSF PCR analysis and CSF antigen assays for CNS aspergillosis showed that in some patients, assays are positive for *Aspergillus* GM antigen, but PCR results are negative [3].

In our patient, corticosteroid treatment dramatically reduced brain oedema and improved clinical symptoms. In the Infectious Disease Society of America treatment guidelines for CNS aspergillosis, corticosteroids are considered to be deleterious and should be avoided [4]. However, we have previously reported the successful treatment of CNS aspergillosis in an immunocompetent patient with VRZ and corticosteroids [5]. Unlike the present patient, the previous patient was characterised by gadolinium-enhanced extramedullary lesions (presenting aspergilloma) with intramedullary pontine and cerebellar T2 hyperintense lesions. The extramedullary lesions were ameliorated by VRZ, and the intramedullary lesions, which worsened during treatment with VRZ alone, were resolved by corticosteroid treatment. The cases of these two patients indicate that both direct ongoing infectious damage and secondary inflammation are present in CNS aspergillosis. These cases also raise the possibility that advanced treatment of secondary inflammation with corticosteroids combined with anti-fungal drugs is effective in this condition. Immunosuppressed patients with CNS aspergillosis might be unable to tolerate corticosteroid treatment; however, patients

with CNS aspergillosis with secondary inflammation may be candidates for combined corticosteroid and VRZ therapy if there are no indications of immunosuppression.

The limitation of this case report is that we did not perform fungal culture, and GM antigen level in CSF is lower than that reported in a previous systematic review (range, 2.2–578) [2], suggesting that other causes of meningoencephalitis cannot be completely excluded. If the patient had viral or autoimmune meningoencephalitis, the patient probably improved by corticosteroid. Actually, some virus could not be identified by usual testing. Although the appropriate cutoff value of GM antigen level in CSF has not been established till date, the decline in GM antigen level in CSF, which corresponded with the clinical response to treatment with VRZ in the present case, indicates that the diagnosis of *Aspergillus* meningitis might be appropriate and was managed successfully. Factors that cause false-positive results of BG or *Aspergillus* GM antigen, such as albumin, intravenous immune globulin, gauze packing, cellulose depth filters, beta-lactam antimicrobials, or soybean proteins were excluded in this case. However, cross-reactivity of other fungi was not completely excluded.

In conclusion, combination therapy with VRZ and corticosteroid may be effective for the treatment of certain patients with CNS aspergillosis. The diagnosis of acute *Aspergillus* meningitis without a primary focus, such as the paranasal

sinuses or lungs, in immunocompetent patient is still challenging. Testing for CSF GM antigen is probably a useful diagnostic tool.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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