Neuroaspergillosis in an Immunocompetent Patient Successfully Treated with Voriconazole and a Corticosteroid

Akiyuki Hiraga¹, Akiyuki Uzawa¹, Mariko Shibuya², Tsutomu Numata²,
Shigeko Sunami³ and Ikuo Kamitsukasa¹

Abstract

Aspergillosis of the central nervous system (CNS) is an uncommon infection, mainly occurring in immunocompromised patients. We report a case of nasocerebral aspergillosis in an immunocompetent patient successfully treated with voriconazole and a corticosteroid. Magnetic resonance imaging (MRI) showed contrast enhancement surrounding the brainstem and cerebellum with intramedullary pontine and cerebellar T2-hyperintense lesions. The patient's symptoms and MRI abnormalities improved after voriconazole and corticosteroid treatment; however, discontinuation of the corticosteroid caused a worsening of the T2-hyperintense lesions, whereas resuming it resulted in its improvement. This suggested that these T2-hyperintense lesions may be due to secondary inflammation caused by aspergillosis and not the aspergillosis itself. We conclude that treatment with a combination of voriconazole and a corticosteroid appears to be effective for the treatment of some patients with CNS aspergillosis.

Key words: neuroaspergillosis, MRI, voriconazole

(Inter Med 48: 1225-1229, 2009)

(DOI: 10.2169/internalmedicine.48.2165)

Introduction

Although central nervous system (CNS) aspergillosis is a rare condition that occurs mainly in immunocompromised patients (1), it has been reported in immunocompetent patients (2-6), especially in cases in which there is direct extension from the paranasal sinus. Because of the high mortality rate associated with this infection, early diagnosis and prompt initiation of treatment is crucial (5). In tuberculous meningitis and acute bacterial meningitis, early adjunctive treatment with dexamethasone improves the disease outcome (7, 8), and a previous study showed that corticosteroid treatment was effective in a patient with cryptococcus meningitis presenting with late deterioration (9). However, the effects of corticosteroids on CNS aspergillosis is not well known. We report the case of an immunocompetent patient who developed nasocerebral aspergillosis and was successfully

treated by a combination of voriconazole and a corticosteroid.

Case Report

In February 2006, a 74-year-old non-diabetic man with hypertension and a history of cerebellar infarction developed a headache and low-grade fever, which lasted for 3 months. He was admitted to another hospital in May 2006. Upon admission, a neurological examination showed no abnormalities, and examination of the cerebrospinal fluid (CSF) showed elevated WBC count and protein concentrations and a low glucose concentration. Tuberculous meningitis was suspected, and he was treated with oral ethambutol hydrochloride, rifampicin and isoniazid (anti-tuberculosis treatment); however, no improvement was observed. Notably, MRI performed in that hospital showed enhanced lesions surrounding the basilar artery (Fig. 1), which were ignored.

¹Department of Neurology, Chiba Rosai Hospital, Chiba, ²Department of Otolaryngology, National Hospital Organization Chiba Medical Center, Chiba and ³Department of Otolaryngology, Chiba Rosai Hospital, Chiba

Received for publication February 14, 2009; Accepted for publication April 6, 2009

Correspondence to Dr. Akiyuki Hiraga, hiragaa@yahoo.co.jp

Figure 1. Contrast-enhanced axial MRI scans taken in May 2006 from another hospital showed enhanced lesions surrounding the basilar artery. T2-weighted imaging showed no intramedullary lesions.

At the time of discharge, the patient was able to walk, but he developed a gait disturbance two months later. He was referred to another neurosurgery clinic, where MRI showed abnormalities in mid-July 2006, following which he was introduced to our department and admitted on the same day.

A physical examination showed a temperature of 36.9°C, isocoric pupils and a mild limitation of the abductor of the right eye during movement. He had no facial nerve palsy, and his speech, muscle strength in his four extremities and results of a sensory examination were normal. Limb ataxia was not evident. A slight gait disturbance was noted, but he could walk unassisted.

The patient's peripheral WBC count was 4,400/ μ L, 16.2% of which were lymphocytes, and the hemoglobin concentration was 12.2 g/dL. The results of the blood chemistry analysis were as follows: 23 IU/L aspartate aminotransferase, 24 IU/L alanine aminotransferase, 3.8 g/dL albumin, 0.8 mg/dL creatinine, and 0.2 mg/dL serum C-reactive protein. His plasma blood sugar was 103 mg/dL and glycated haemoglobin was 4.7%. Chest radiography and chest computed tomography (CT) scans were normal. A CSF analysis showed a WBC count of 188/ μ L (70% neutrophils and 30% lymphocytes), a glucose concentration of 39 mg/dL, and a protein concentration of 207 mg/dL. The results of a polymerase chain reaction and cytological analysis of the CSF were negative for tuberculosis. CSF cultures showed no pathogens and were negative for the CSF cryptococcal antigen. The results of an enzyme-linked immunosorbent assay were negative for serum antibodies of the human immunodeficiency virus, and the CD4 cell count was 325/ μ L.

The T2-weighted brain MRI performed at the other neurosurgery clinic (just prior to admission, July 2006) showed high-signal-intensity areas in the pons and cerebellum (Fig. 2). Brain contrast-enhanced T1-weighted images showed enhanced lesions surrounding the pons and cerebellum (Fig. 2). A sinus CT scan showed soft tissue density with calcification in the right sphenoid sinus (Fig. 3B). The results of a brain MR angiography were normal.

Retrospectively, an MRI had been performed in mid-February 2005 during follow-up for a cerebellar infarction, 1 year before the onset of headache and fever. This cranial T2-weighted image notably showed hypointense signals of his sphenoid sinus (Fig. 3A); however, the patient received no treatment at that time.

Sphenoidotomy performed in early August 2006 revealed cheesy material in the sphenoid sinus. This material was removed and sent for pathological examination, and the patient was diagnosed as having nasocerebral aspergillosis. The patient's headache resolved after 3 weeks of treatment with intravenous amphotericin B, followed by treatment with oral fluconazole. After 21 days of treatment with amphotericin B, an MRI showed stable disease. The patient was discharged in early September 2006. However, in early October 2006, an MRI showed progression of the disease (Fig. 2). The patient developed a gait disturbance, anisocoria with a larger left pupil, and left proptosis. The patient was readmitted to our institution the following week (October 2006). His symptoms worsened after admission; he developed a mild consciousness disturbance. Therefore, we began treatment with intravenous voriconazole (600 mg/day) followed by intravenous dexamethasone (16 mg/day). The consciousness disturbance was ameliorated, and treatment continued with 400 mg/day of oral voriconazole and oral dexamethasone. A follow-up MRI at the end of October 2006 showed further improvement (Fig. 2). However, despite continuation of voriconazole treatment, the tapering and discontinuation of dexamethasone resulted in a recurrence of T2-hyperintense lesions, as evidenced by an MRI in mid-November 2006 (Fig. 2). Therefore, we resumed treatment with oral dexamethasone (8 mg/day). An MRI performed in mid-December 2006 (Fig. 2) showed improvement in the lesions, but residual lesions were still present. The patient was therefore maintained on oral voriconazole and dexamethasone (decreased to 2 mg/day on December 2006). The patient has shown good clinical recovery, which has been sustained for 2 years. Because the patient's neurological symp-

Figure 2. Serial axial MRI findings shown as T2-weighted and contrast-enhanced T1 images. MRI in mid-July 2006 showed T2-hyperintense lesions in the pons and cerebellum, and the following day, contrast-enhanced MRI before treatment showed contrast enhancement surrounding the pons and cerebellum presenting as aspergilloma, with no enhancement in the intramedullary lesions. MRI showed progressive disease in early October 2006. Follow-up MRI at the end of October 2006, after voriconazole and dexamethasone treatment had been started, showed marked improvement. Following the discontinuation of dexamethasone, the T2 hyperintensity of the lesions increased in mid-November 2006. Resumption of dexamethasone resulted in re-improvement of the T2-hyperintense lesions, as evidenced by MRI in mid-December 2006.

Figure 3. (A) Axial T2-weighted imaging in mid-February 2005 showed low and high signal intensities in the sphenoid sinus. (B) Axial CT scan in July 2006 showed soft tissue density with calcification in the right sphenoid sinus.

toms and MRI findings were stable, the dosage of dexamethasone was reduced to 1 mg/day in mid-January 2007 and further reduced to 0.5 mg/day in June 2007.

Discussion

This case was characterized by CNS aspergillosis originating in the sphenoid sinus. MRI findings showed T2-weighted hypointense lesions in the sphenoid sinus 1 year before and a small gadolinium-enhancement around the basilar artery 2 months before being referred to our institution. Serial MRI findings showed enhanced extramedullary lesions (presenting aspergilloma) and intramedullary T2-hypointense lesions. The patient's clinical and MRI findings improved after combination therapy with voriconazole and a corticosteroid.

Ashdown et al (10) reported three different neuroimaging patterns of cerebral aspergillosis in immunosuppressed patients: 1) multiple areas of hypodensity on CT scan or hyperintensity on T2-weighted imaging consistent with embolic infarctions (with or without hemorrhage); 2) multiple intracerebral ring-enhancing lesions consistent with abscesses; and 3) dural enhancement associated with enhanced lesions in the adjacent paranasal sinus structure or calvaria or dural enhancement of the optic sheath with associated optic nerve and intraorbital fat enhancement. A recent MRI study showed patterns similar to the above-mentioned patterns, which had areas consistent with infarction, ring lesions consistent with abscess formation following infarction, and dural or vascular infiltration originating from paranasal sinusitis or orbital infiltration (11). MRI findings vary depending on the immune status of patients and the stage of the lesions (4, 12) and different clinical pictures can be observed in the same patient (13). In the present case, enhanced extramedullary lesions surrounding the brainstem and cerebellum were similar to previous dural or vascular infiltration originating from the paranasal sinusitis. Early MRI findings (February 2006) in our case showed enhancement surrounding the basilar artery, which suggested an affinity of aspergillosis for the arterial wall. It is well known that aspergillosis commonly invades vessel walls, which leads to thrombosis and infarction or arteritis and arterial

rupture (14). However, early-stage enhancement restricted to the vessel wall is rare. Thus, it was difficult to make an early diagnosis of CNS aspergillosis in our case.

Paranasal sinus imaging is useful for detecting aspergillosis of sinonasal origin, such as in the present case. Characteristics such as high levels of calcification evident on CT scans (15, 16) and T2-weighted images with an extremely low signal (15), as evident in our case, are helpful for diagnosing paranasal sinus aspergillosis. A recent report of 20 immunocompetent patients with craniocerebral aspergillosis of sinonasal origin indicated that mass lesions producing hypo- to isointense signals on T1-weighted imaging, extremely low signals (hypointense) on T2-weighted imaging and bright homogenous enhancement on post-gadolinium T1-weighted imaging are typical (6). In addition, our case had T2-hypointense lesions in the paranasal sinus and lesions surrounding the brainstem; however, the lesions in the brainstem and cerebellum were T2-hyperintense. Nasal aspergillosis was present 1 year before the development of CNS aspergillosis in our case, which indicated that at least several months are required for sinus aspergillosis to become invasive in immunocompetent patients.

Despite voriconazole treatment, the T2-hyperintense lesions worsened in our case after corticosteroid therapy was discontinued, but were ameliorated after treatment was resumed. This finding suggests that this T2-hyperintense lesion was not directly due to aspergillosis, but rather to the secondary inflammation caused by aspergillosis. Our case raises the possibility of the effectiveness of advanced treatment of secondary inflammation with corticosteroids in combination with anti-fungal drugs. A previously reported case of cryptococcus meningitis responded well to corticosteroid therapy (9). That case showed late deterioration, as evidenced by an elevated CSF WBC count, despite a good clinical response to anti-fungal treatment and despite a decrease in the CSF cryptococcal antigen titer. This late deterioration improved with dexamethasone treatment, worsened after steroid therapy was discontinued, and promptly improved after steroid therapy was reinitiated. This finding suggests that this late deterioration was caused by sterile arachnoiditis rather than by the ongoing infection. Similarly, our case showed a re-worsening of symptoms after corti-

costeroid therapy was discontinued and prompt improvement after corticosteroid therapy was resumed. Voriconazole is a new and effective therapeutic drug for CNS aspergillosis (17, 18), and the present case responded to it well and had a good clinical recovery. However, when the corticosteroid dosage was tapered off, secondary inflammation of the brainstem worsened. We therefore suggest that a combination of voriconazole and an adjunctive corticosteroid be used to treat some patients with CNS aspergillosis.

In conclusion, CNS aspergillosis in an immunocompetent patient was successfully treated with a combination of voriconazole and a corticosteroid. The MRI findings in this patient showed aspergilloma surrounding the brainstem and cerebellum with intramedullary T2-hyperintense patterns, which may have been due to secondary inflammation caused by aspergillosis. Combination therapy with voriconazole and a corticosteroid appears to be effective for the treatment of some patients with CNS aspergillosis.

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