

Case Report

The Difficulty of Diagnosing Invasive Aspergillosis Initially Manifesting as Optic Neuropathy

Sotaro Mori^a Takuji Kurimoto^a Kana Kawara^a Kaori Ueda^a
Mari Sakamoto^a Yukako Keshi^a Yuko Yamada-Nakanishi^a
Hisatsugu Tachibana^b Makoto Nakamura^a

^aDivision of Ophthalmology, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Japan; ^bDivision of Neurology, Kobe University Graduate School of Medicine, Kobe, Japan

Keywords

Invasive aspergillosis · Optic neuropathy · Autopsy · Steroid pulse therapy · Fungal infections

Abstract

Background: Invasive aspergillosis is often fatal. Here, we report a patient with invasive aspergillosis primarily involving the optic nerve diagnosed on autopsy. **Case Presentation:** A 77-year-old female with underlying diabetes mellitus, hyperlipidemia, and hypertension presented with disc swelling of the left eye. Although mini-pulse steroid therapy improved visual acuity (VA) of the left eye, it abruptly decreased to no light perception within a month, followed by a decrease in VA of the right eye to 0.5. At referral, VA was 0.3 in the right eye, and there was no light perception in the left eye. **Results:** Fundus examination revealed optic disc swelling of both eyes. Goldmann perimetry showed irregular visual field defects, whereas magnetic resonance imaging (MRI), general, and cerebrospinal fluid (CSF) examinations revealed no distinct abnormalities. We suspected anterior ischemic optic neuropathy and invasive optic neuropathy. As with the left eye, steroid pulse therapy temporarily improved VA of the right eye and then decreased to 0.2. Additional anticoagulant therapy did not improve VA. Concurrent to therapy, the patient became febrile with depressed consciousness. Repeat MRI identified suspected midbrain infarction, and CSF examination indicated cerebral meningitis. In spite of administering transfusions and antibiotics, she died on hospital day 40. Autopsy revealed large

amounts of *Aspergillus hyphae* mainly localized in the dura mater of the optic nerve and destruction of the cerebral artery wall, suggesting an etiology of subarachnoid hemorrhage. **Conclusions:** When examining refractory and persistent disc swelling, we should rule out fungal infections of the optic nerve.

© 2019 The Author(s)
Published by S. Karger AG, Basel

Background

Patients who are immunocompromized due to cancer, infections, organ transplantation, diabetes mellitus, steroid use, or chemotherapy are at risk of developing invasive aspergillosis arising from noninvasive aspergillosis. Invasive aspergillosis commonly involves the lungs and paranasal sinus, but at low rates, other organs including the skin, adrenal glands, heart, central nervous system (CNS), liver, spleen, and the gastrointestinal tract are affected. Of these disease types, CNS aspergillosis frequently is fatal [1, 2]. The primary route of CNS aspergillosis is hematogenous dissemination from the lung or contiguous spread from an adjacent focus such as the orbit or paranasal sinuses. Optic nerve involvement typically occurs secondary to paranasal sinus aspergillosis [3]. However, localized aspergillosis at the orbital apex or optic nerve can make diagnosis difficult because it mimics other optic neuropathies including optic neuritis and other inflammatory and vascular conditions and demonstrates temporary visual improvement with steroid therapy [4–9]. Here, we report a patient with invasive aspergillosis in whom optic nerve involvement initially manifested as ischemic or invasive optic neuropathy, showed temporary improvement of visual acuity (VA) and visual field impairment with steroid therapy, and autopsy confirmed *Aspergillus hyphae* invading multiple areas of the brain.

Case Presentation

A 77-year-old female with a history of diabetes mellitus, hyperlipidemia, and hypertension presented with visual loss in the left eye. Ophthalmic examination revealed best-corrected decimal VA (BCVA) of 1.0 and 0.3. Light reflex of the left eye was weakened with a relative afferent pupillary defect. Fundus examination showed optic disc swelling of the left eye (Fig. 1a). Goldmann perimetry (GP) revealed lower altitudinal hemianopia in the left eye (Fig. 1b). Magnetic resonance imaging (MRI) on fat-suppressed T2-weighted imaging (T2WI) and short-T1 inversion recovery (STIR) showed no optic nerve or paranasal sinus abnormalities without gadolinium (Gd) enhancement due to renal dysfunction (Fig. 2a, b). Thus, the previous ophthalmologist suspected her as having anterior ischemic optic neuropathy and administered mini-pulse steroid therapy and 500 mg methylprednisolone to relieve the disc swelling. After mini-pulse therapy, which was not followed by the administration of oral prednisolone, BCVA in the left eye increased to 0.8 within 3 days. However, 2 days later, VA in the left eye abruptly decreased to 0.1, and although additional mini-pulse therapy was performed, BCVA in the left eye further decreased to no light perception within a month. Two months later, BCVA in the right eye also decreased to 0.5, the right optic disc began to swell, and swelling of the left optic disc persisted and became more severe (Fig. 1c, d). Fluorescein angiography exhibited marked hyperfluorescence of the optic disc with filling defect in the choroidal circulation in the left eye and slight hyperfluorescence of the optic disc in the right eye (Fig. 1e, f). Finally, she was referred to our hospital for further treatment.

Our initial examination showed that BCVA was 0.3 in the right eye and no light perception in the left eye. GP in the right eye showed irregular visual defect in both the superior and inferior visual field (Fig. 1g). There was no pain with eye movement, and there were no abnormal signs on general neurological examination. Laboratory data showed increased creatinine (1.24 mg/dL) and decreased estimated glomerular filtration rate (32.6 mL/min/1.73 m²), indicating renal dysfunction, and slightly increased soluble interleukin-2 receptor (sIL2-R, 670 U/mL). Other routine blood and metabolic laboratory studies were unremarkable, and erythrocyte sedimentation rate and C-reactive protein were not elevated. Antibodies for anti-aquaporin 4 and anti-myelin oligodendrocyte glycoprotein were also negative. No abnormalities were seen on chest X-ray. Cerebrospinal fluid (CSF) analysis showed no elevation of CSF pressure, no significant infectious changes, and no tumor cells (initial pressure 10 mm Hg, colorless and transparent, cells <1/μL, proteins 47 mg/dL, glucose 71 mg/dL, sIL2-R <50 U/mL, myelin basic protein <31.3 ng/mL, and positive oligoclonal IgG bands). Cytologic examination of CSF was performed 3 times throughout the course, but no tumor or atypical cells were detected.

MRI of the brain and orbits revealed no obvious optic nerve swelling without any apparent parenchymal hyperintensity on STIR images (Fig. 2c). There were no other findings of nasal sinusitis or space-occupying lesion. Echocardiography of the temporal artery showed negative signs of giant-cell arteritis. Bilateral arteritic anterior ischemic optic neuropathy and invasive optic neuropathy were suspected because of the lack of significant findings on MRI and the occurrence of bilateral disc swelling. Because oral prednisolone was not given following mini-pulse therapy at the first hospital, we again initiated intravenous methylprednisolone pulse therapy (1,000 mg/day for 3 days), followed by prednisolone 0.5 mg/kg of body weight. BCVA of the right eye improved to 0.7 after two courses of steroid pulse therapy, but the left eye had not improved on hospital day 15. However, BCVA of the right eye suddenly decreased to 0.2 following the third course of steroid pulse therapy. We rechecked CSF for further examination including cytology, but no abnormalities were seen (colorless and transparent cells <1/μL, proteins 49 mg/dL, glucose 65 mg/dL, and sIL2-R <50 U/mL). We initiated anticoagulant and antiplatelet therapy consisting of warfarin 2 mg and clopidogrel sulfate 75 mg taken orally. On hospital day 34, VA in the right eye further decreased to hand motions, and the patient's body temperature elevated to 38° with depressed consciousness. On the same day, repeat MRI showed suspected midbrain infarction (Fig. 2d–f), and CSF findings indicated cerebral meningitis (cells 303/μL, proteins 63 mg/dL, glucose 89 mg/dL, and negative cryptococcal antigen). Arterial and venous blood and CSF culture demonstrated no bacterial or fungal growth. Despite transfusions, antibiotic therapy, and anticoagulant therapy, the patient died on hospital day 40. After we obtained informed consent from her family, the autopsy was conducted. The autopsy findings revealed a primary cause of death of subarachnoid hemorrhage. No apparent paranasal sinus inflammatory changes were observed. Histological examination showed a significant amount of *Aspergillus hyphae*, inflammatory cells, and fibrous formation mainly localized in the dura mater, whereas cellular infiltration into the parenchyma of the optic nerve was less observed (Fig. 3a–d). Fungal ball formation was observed surrounding the mesencephalic aqueduct with massive invasion of *A. hyphae* and further destroyed the wall of the cerebral artery, suggesting a primary cause of midbrain and subarachnoid hemorrhage.

Discussion

Invasive aspergillosis typically exhibits nonspecific findings on imaging, and blood and CSF cultures are frequently negative until the disease has progressed considerably. In the case of invasive aspergillosis with optic nerve involvement around the orbital apex, autopsy is often the only definitive way to make a definitive diagnosis. In our case, subtle changes on MRI, blood, and CSF examinations and temporary improvement of visual function early after steroid pulse therapy could further complicate making a diagnosis.

MRI analysis of 28 immunocompetent patients associated with *Aspergillus* infection demonstrated that 90% of the patients had lesions with a low-signal intensity on T2WI and hypo-intensity to isointensity on T1WI in the brain parenchyma [10]. In vitro studies, a low-signal intensity on T2WI in *Aspergillus* colonies reflected on the accumulation of paramagnetic elements; iron and manganese produced by fungal hyphae [11]. Furthermore, CT and MRI analysis in 18 patients with CNS aspergillosis revealed that leptomeningeal lesions were not enhanced by Gd and iodinated contrast material in all patients, although leptomeningeal inflammation was confirmed by autopsy or biopsy. They presumed this phenomenon might be related to the immunocompromized state of the patients [12]. In our patient, no significant abnormalities were seen on T2WI and STIR of the optic nerve, but autopsy revealed massive *A. hyphae* invasion mainly into the dura mater, which is similar to previous reports and may indicate the difficulty of detecting invasion of *A. hyphae* into the dura mater of the optic nerve. Given that the high-intensity area surrounding the optic nerve includes not only spinal fluid but also invasive aspergillosis, MRI without Gd enhancement could make it impossible to distinguish the high-intensity area of *Aspergillus* lesions from spinal fluid.

Kourkoumpetis et al. [1] documented that in 14 consecutive cases of CNS aspergillosis, 11 out of 14 had invasive pulmonary involvement, 2 had primary paranasal sinus involvement, and 1 had primary spinal involvement. Of note, most patients had undergone either chronic steroid therapy or cancer chemotherapy for underlying diseases. Coleman et al. [13] conducted a detailed review of the literature and reported that invasive CNS aspergillosis is a fatal disease with a mortality rate of >90% in most series, and often a definitive diagnosis of invasive aspergillosis cannot be made until autopsy, especially in the immunocompromized host. Our case had underlying diabetes mellitus and had already received steroid pulse therapy early after the onset of optic neuropathy at the first hospital, which possibly changed her condition to the compromised host.

Because no significant lung or paranasal sinus lesion was identified at autopsy, the invasive route of aspergillosis remains inconclusive; however, when she was febrile with depressed consciousness, invasive aspergillosis might have already spread hematogenously from the optic nerve to other areas in the brain. Furthermore, additional CT should have been performed to eliminate the possibility of the presence of inflammatory changes or bone destruction in the paranasal sinuses.

Serum *Aspergillus* antigen, *Aspergillus* polymerase chain reaction, and beta-D-glucan are thought to be helpful for diagnosing invasive aspergillosis. Serum beta-D-glucan has a high sensitivity and specificity for diagnosing invasive aspergillosis, but CSF culture is not considered useful for detecting fungal infections in invasive aspergillosis [14]. Kourkoumpetis et al. [1] reported that 7 out of 14 patients with a CSF culture were negative for aspergillosis, and blood culture also has a poor ability for detecting CNS aspergillosis [15]. We regret that beta-D-glucan was not examined early in our case. In retrospect, given that serum *Aspergillus* antigen or beta-D-glucan was positive in the early phase, it might be difficult to diagnose aspergillosis, but antifungal agents should be applied prophylactically.

In conclusion, the present case indicates that the diagnosis of optic nerve aspergillosis is extremely difficult. However, when examining the persistent swelling of the optic disc together with steroid resistance and anticoagulant therapy without significant general examinations or when using steroid to the point of immunocompromisation, we should rule out fungal infection of the optic nerve by testing for beta-D-glucan or antigen in the blood or CSF several times.

Acknowledgement

We are grateful to Enago (www.enago.jp) for the English language review.

Statement of Ethics

This report was published with the permission and informed consent of the patient.

Disclosure Statement

None of the authors have any conflicts of interest.

References

- 1 Kourkoumpetis TK, Desalermos A, Muhammed M, Mylonakis E. Central nervous system aspergillosis: a series of 14 cases from a general hospital and review of 123 cases from the literature. *Medicine (Baltimore)*. 2012 Nov;91(6):328–36.
- 2 Sivak-Callcott JA, Livesley N, Nugent RA, Rasmussen SL, Saeed P, Rootman J. Localised invasive sino-orbital aspergillosis: characteristic features. *Br J Ophthalmol*. 2004 May;88(5):681–7.
- 3 Fernando SS, Lauer CS. Aspergillus fumigatus infection of the optic nerve with mycotic arteritis of cerebral vessels. *Histopathology*. 1982 Mar;6(2):227–34.
- 4 Choi MY, Bae JH, Lee JH, Lee SJ. Aspergillosis presenting as an optic neuritis. *Korean J Ophthalmol*. 2002 Dec;16(2):119–23.
- 5 Matsuo T, Notohara K, Yamadori I. Aspergillosis causing bilateral optic neuritis and later orbital apex syndrome. *Jpn J Ophthalmol*. 2005 Sep-Oct;49(5):430–1.
- 6 Subramanian S, Kandpal H, Sharma R, Pushkar N, Sen S, Gamanagatti S, et al. Invasive sinus aspergillosis with perineural spread in an immunocompetent patient. *Australas Radiol*. 2007 Dec;51 Suppl:B189–92.
- 7 Weinstein JM, Morris GL, ZuRhein GM, Gentry LR. Posterior ischemic optic neuropathy due to Aspergillus fumigatus. *J Clin Neuroophthalmol*. 1989 Mar;9(1):7–13.
- 8 Yuan L, Prayson RA. Optic nerve aspergillosis. *J Clin Neurosci*. 2015 Jul;22(7):1191–3.
- 9 Spoor TC, Hartel WC, Harding S, Kocher G. Aspergillosis presenting as a corticosteroid-responsive optic neuropathy. *J Clin Neuroophthalmol*. 1982 Jun;2(2):103–7.
- 10 Siddiqui AA, Shah AA, Bashir SH. Craniocerebral aspergillosis of sinonasal origin in immunocompetent patients: clinical spectrum and outcome in 25 cases. *Neurosurgery*. 2004 Sep;55(3):602–11;discussion 611–3.
- 11 Fellows DW, King VD, Conturo T, Bryan RN, Merz WG, Zinreich SJ. In vitro evaluation of MR hypointensity in Aspergillus colonies. *AJNR Am J Neuroradiol*. 1994 Jun;15(6):1139–44.
- 12 DeLone DR, Goldstein RA, Petermann G, Salamat MS, Miles JM, Knechtle SJ, et al. Disseminated aspergillosis involving the brain: distribution and imaging characteristics. *AJNR Am J Neuroradiol*. 1999 Oct;20(9):1597–604.
- 13 Coleman JM, Hogg GG, Rosenfeld JV, Waters KD. Invasive central nervous system aspergillosis: cure with liposomal amphotericin B, itraconazole, and radical surgery—case report and review of the literature. *Neurosurgery*. 1995 Apr;36(4):858–63.

- 14 Son HJ, Sung H, Park SY, Kim T, Lee HJ, Kim SM, et al. Diagnostic performance of the (1-3)- β -D-glucan assay in patients with *Pneumocystis jirovecii* compared with those with candidiasis, aspergillosis, mucormycosis, and tuberculosis, and healthy volunteers. *PLoS One*. 2017 Nov;12(11):e0188860.
- 15 Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 Update by the infectious diseases society of America. *Clin Infect Dis*. 2016 Aug;63(4):e1–60.

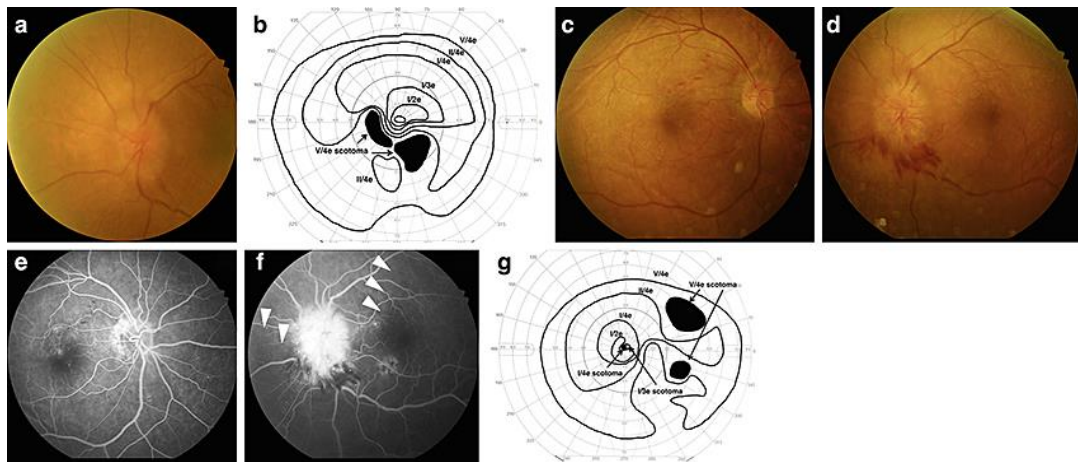


Fig. 1. Ophthalmic examination findings. Fundus photograph (a) and GP (b) of the left eye at initial onset. The optic disc was reddish and mildly swollen. GP showed lower horizontal hemianopia. Fundus photograph of the right eye (c) and the left eye (d), fluorescein angiography of the right eye (e) and left eye (f), and GP of the right eye (g) with onset in the right eye. The optic disc was reddish and mildly swollen with splinter hemorrhage, and the optic disc of the left eye was markedly swollen with mild retinal hemorrhage. Hyperfluorescence in the left eye was much more intense than in the right eye. Delay of choroidal circulation was detected in the lower retina (arrowheads). Time after initiation of the right eye and left eye was 113 and 65 s, respectively.

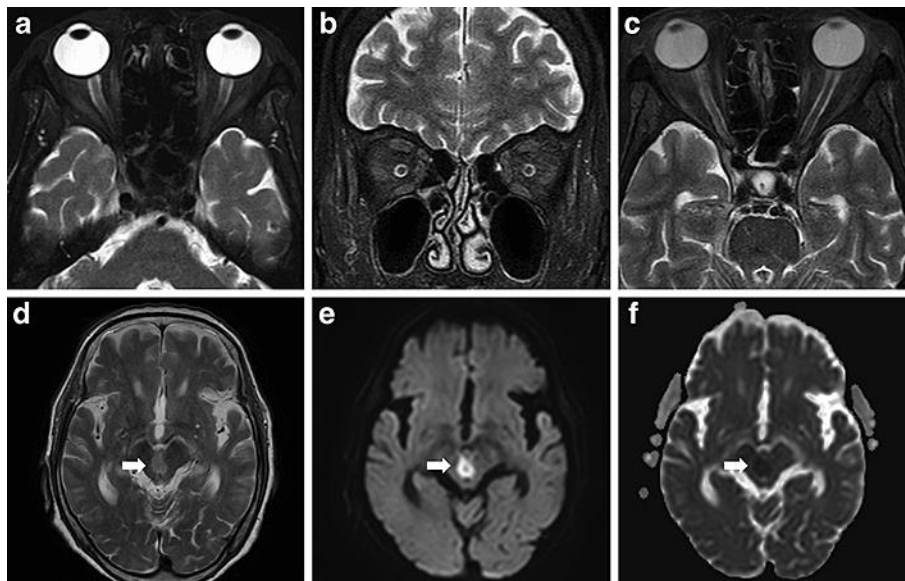


Fig. 2. Brain MRI STIR image (a) at the initial onset when the left eye was affected, T1WI (WI) at the onset when the right eye was affected (b), and STIR image at the onset when the right eye was affected (c). There was no the apparent swelling or high-intensity area in the optic nerve at the occurrence of disc swelling in both eyes. d T2WI of the brain at the time when the patient was febrile with depressed consciousness; e DWI; f ADC map. There was a high-intensity area around the cerebral aqueduct in the midbrain on T2WI, representing a high-intensity area on DWI and a low-intensity area on the ADC map (arrows in d–f). DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.

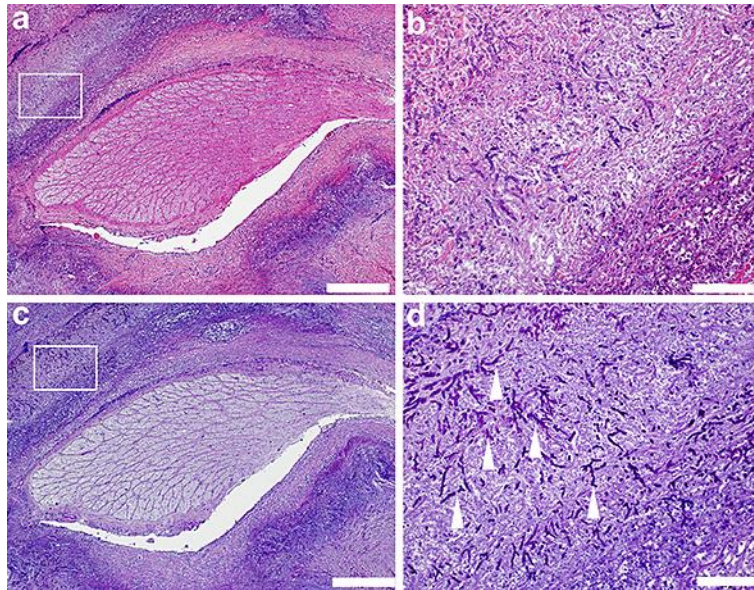


Fig. 3. Microphotograph of optic nerve sections. The transverse section of the optic nerve was stained with H&E (**a** low magnification image, **b** high magnification image). **c, d** The transverse section of the optic nerve stained with PAS. Scale bar indicates 500 μm in **a** and **c** and 100 μm in **b** and **d**. A large amount of PAS-positive *A. hyphae* and inflammatory cells densely accumulated in the dura mater (arrowheads). PAS, periodic acid-Schiff.