Short Report

Angio-invasive Cerebral Aspergillosis Resulting in Hemispheric Infarct in an Immunocompetent Man

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ABSTRACT

Background: Cerebral aspergillosis usually affects immunocompromised hosts and may rarely occur in immunocompetent individuals. Due to its angio-invasive nature, Aspergillus may cause various vascular complications, particularly mycotic aneurysms and infarcts. Case presentation: A 22-year-old immunocompetent male with diagnosed case of sino-cerebral aspergillosis was taking voriconazole for two months. His headache worsened and repeat imaging showed an increase in the size of the lesion. The patient was managed with right frontal craniotomy and surgical debridement, and voriconazole was continued. After ten days of uneventful post-operative course, the patient developed left-sided hemispheric infarct. The patient is doing well at nine months’ follow-up, and he is off voriconazole for three months after the follow-up imaging showed complete resolution of disease. Conclusion: Treatment of choice for cerebral aspergillosis is voriconazole. Surgical debridement may be a useful adjunct in patients not responding to voriconazole alone.

Key words: angio-invasive, anti-fungal treatment, cerebral aspergillosis, debridement, hemispheric infarct, immunocompetent, vascular complications

Introduction

Cerebral aspergillosis (CA) is an opportunistic fungal infection that usually affects immunocompromised hosts. Rarely, it has been reported to occur in immunocompetent individuals1, 2. Due to the angio-invasive nature of Aspergillus, it has been shown to cause various vascular complications, particularly mycotic aneurysms and infarcts3. We report the case of an intracranial angio-invasive aspergillosis in a young immunocompetent man who developed a hemispheric infarct. The pathogenesis of vascular complications of Aspergillus in immunocompetent individuals is also discussed.

Case report

A 22-year-old man was brought to our clinic with extremely severe bifrontal headache for the last four months. There was no history of fever, vomiting, diminution of vision, or seizure. An otorhinolaryngologist had previously done a biopsy from mass in the ethmoidal sinus, which was suggestive of aspergillosis. The patient was taking voriconazole 200 milligrams (mg) twice a day for the last two months as per the advice of the otorhinolaryngologist. There was no history of chemotherapy or immunosuppressive treatment. His nervous system, including visual acuity, was within normal limits. His blood sugar was within normal limits, and HIV status was negative. Apart from these, his complete blood counts, hemoglobin, prothrombin time, kidney and liver function test, done as a part of pre-operative investigations, were normal.

His previous non-contrast computed tomography (NCCT) and contrast-enhanced magnetic resonance imaging (MRI) of the brain and paranasal sinuses done two months back revealed a soft tissue mass in the ethmoidal sinus extending into the bifrontal bases (Fig. 1). A repeat contrast-enhanced...
MRI of the brain was advised, which revealed the mass to have grown in size and the intracranial component appeared to have become significantly large in size. The intracranial component was located in the bilateral frontal bases, was ring-enhancing and appeared to have a necrotic center (Fig. 2). This increase in size of the lesion was in spite of two months of voriconazole treatment. The chest radiograph revealed no abnormality.

Fig. 1. Axial images of plain computed tomography (CT) showing mass lesion around the cribriform plate extending through the medial orbital wall on the left side (a). Axial (b), sagittal (c), and coronal (d) images of contrast-enhanced MRI of brain and paranasal sinuses showing homogenously contrast-enhancing lesion in the ethmoid sinuses extending into the frontal base bilaterally and breaching the medial orbital wall on the left side.

Fig. 2. Axial (a), coronal (b), and sagittal (c) images of repeat contrast-enhanced MRI of brain revealing the mass to have grown in size as compared to the previous imaging (Fig 1). The intracranial component located in the bilateral frontal base has become significantly large in size, is now ring-enhancing, and has developed a necrotic center.

The patient underwent a right frontal craniotomy and debridement of the bilateral frontal Aspergillus granulation tissue. Intra-operatively, the mass was greyish in color, firm in consistency, and moderately vascular. No obvious pus was drained, and no major vessels were injured. In the immediate post-operative period, his headache resolved completely. A CT scan of the head done on the day of surgery revealed good operative cavity and no evidence of hematoma/infarct. However, he developed meningitis, which was managed with culture-sensitive antibiotics (piperacillin-tazobactam) along with amikacin and metrogyl. On the third post-operative day, he developed cerebrospinal fluid (CSF) rhinorrhea. A lumbar drain was inserted and kept for 5 days, following which the CSF rhinorrhea improved.

On the seventh post-operative day, he developed sudden-onset right-sided hemiplegia (power 0/5) and aphasia. A plain CT scan of the head revealed left-sided hemispheric infarct with significant mass effect and midline shift. At discharge, one month after the surgery, the patient was E4V1M6 and was able to fix gaze. His right-sided hemiparesis had gradually improved to 4-/5. He was continued on voriconazole (200 mg twice a day) throughout the hospital course and was advised to continue voriconazole at discharge for another 4 months. The tissue sample was sent to microbiology laboratory for diagnosis of fungal species. The KOH wet mount of the sample showed narrow, septate hyaline hyphae with dichotomous branching. On Sabouraud Dextrose agar (SDA), the fungus was rapidly growing, yellow-green in color, with white reverse. Lactophe-
Lactophenol cotton blue wet mount of the vesicle showed septate hyphae with globular vesicle and conidia arising from the entire vesicle suggestive of *Aspergillus flavus*. Confirmation of species was done using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (Bruker) (Fig. 4). Minimum inhibitory concentration (MIC) of the isolate to voriconazole could not be tested due to unavailability of anti-fungal susceptibility testing for molds at our center (Fig. 4).

One month after the discharge (two months post-operative), the patient was brought to the clinic with complaints of decreased oral intake and increased sleepiness. A CT scan revealed communicating hydrocephalus with evidence of old infarct in the left ICA territory (Fig. 3d). A medium pressure ventriculoperitoneal shunt was inserted, following which the patient showed improvement in his symptoms.

A follow-up MRI done at 6 months after the definitive surgery showed no evidence of disease (Fig. 5) and therefore, voriconazole was stopped. He is doing well at 9 months’ follow-up. His present GCS is E4V1M6, and power in the right side upper and right lower limb is 4/5. He is able to ambulate without support and is able to take care of himself.

The shunt was removed at six months in view of leakage from the abdominal end, after which he did well and did not require re-insertion of the shunt.

**Discussion**

*Aspergillus* is a common fungus that lives in soil and decaying vegetation and is ubiquitous throughout the world. Aspergillosis of the central nervous system (CNS) is an uncommon infection that mainly affects immunocompromised individuals. It accounts for 5% of all intracranial fungal infections.

There are two mechanisms for the spread of *Aspergillus* to the CNS: hematogenous dissemination from the lungs and direct extension from paranasal sinuses, ear, and orbit, i.e. adjacent areas. In immunosuppressed individuals, the primary route of infection is from the lungs via hematogenous dissemination, while in immunocompetent individuals, it is by contiguous spread from the paranasal sinuses. The mode of transmission of disease in our patient was sinocranial route as the chest X-ray was normal, and there was a direct extension of the mass lesion from the ethmoid sinuses. Intracranial extension of the *Aspergillus* from the sinuses occurs secondary to erosion of the skull base and along the blood vessels.

Neuro-aspergillosis may present as aseptic and persistent meningitis, encephalitis, or meningoencephalitis (like other infections of the brain) or may present as a space-occupying...
lesion or brain abscess. In addition, aspergillosis has a pathophysiology unique from other infectious organisms. It results in an infective vasculopathy leading to acute infarction or hemorrhage, then extending into surrounding tissue as infectious cerebritis which may evolve into an abscess. Aspergillus typically causes infarcts and petechial hemorrhages in the cortico-medullary junction, basal nuclei and thalami due to its special affinity for the perforating arteries. This angio-invasive nature of Aspergillus is due to its ability to produce elastase, which results in digestion of elastic tissue. Due to their narrower lumen, the perforating arteries tend to get affected more commonly. The fungal hyphae may grow through the vessel wall, thus making them weak and leading to the formation of mycotic aneurysms of the larger vessels, leading in turn to rupture and massive hemorrhage. Sometimes, the hyphal elements may completely occlude the vessel lumen leading to ischemic stroke. This is the most likely explanation for development of ischemic infarct of the complete hemisphere on left side in our patient, while the frontal craniotomy was done on the right side. The surgery might have resulted in exposure of the larger vessels at the anterior cranial base to the fungal hyphae, thereby aiding in occlusion of the larger vessels by the hyphal elements. This resulted in the appearance of the infarct on CT scan. The disappearance of the infarct in the later CT scan can possibly be explained by the clearance of the hyphal elements after breaking off from the vessel walls (Fig. 3).

Without proper treatment, patients of cerebral aspergillosis have poor prognosis. The mortality rate in immunocompetent patients without systemic involvement is 10-20% as compared to 90-100% in immunocompromised patients. The drug of choice for CA is voriconazole, whose use has led to profound improvement in the survival rates for patients. Other medical alternatives are liposomal amphotericin B, caspofungin, or posaconazole, which can be used in patients refractory to, or intolerant of, voriconazole. Generally, anti-fungal treatment should be continued until the clinical manifestations have completely resolved or until residual scarring can be demonstrated on imaging, which usually takes up to 12 weeks. Surgical excision or drainage has been described as an important adjunct to anti-fungal therapy and may help by decreasing fungal load, allowing better anti-fungal penetration, relieving mass effect, and decreasing the local neurotoxic and inflammatory effects of the fungal infection. Neurosurgical debridement along with anti-fungal therapy has provided better survival rates than pharmacologic treatment alone. In our patient, the fungal lesion continued to grow despite being on anti-fungal treatment for two months and was resolved only when surgical debridement was done along with voriconazole administration, thereby stressing the role of surgical excision.

Conclusion

Cerebral aspergillosis is a fungal infection rarely seen in the immunocompetent. Due to the angio-invasive nature of Aspergillus, the patients may develop various vascular complications. In addition to anti-fungal drugs, surgical debridement is useful for treatment.

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Conflicts of interest

None.
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