NEUROASPERGILLOSIS IN AN IMMUNOCOMPETENT PATIENT

*S Sood, R Sharma, S Gupta, D Pathak, S Rishi

Abstract

Aspergillosis of the central nervous system (CNS) is an uncommon infection, mainly occurring in immunocompromised patients. We report a case of neuroaspergillosis caused by Aspergillus flavus in an immunocompetent patient presenting as a space-occupying lesion of the CNS. The patient was responding favorably to voriconazole at the time of this report.

Key words: Aspergillus flavus, immunocompetent patient, neuroaspergillosis

Aspergillus is a common fungus that lives in soil and decaying vegetation and is ubiquitous throughout the world. Invasive aspergillosis has emerged as an increasing cause of mortality and morbidity in immunocompromised patients. Extension of invasive aspergillosis to the central nervous system (CNS) is associated with an exceedingly high mortality which approaches 100.

Primary sites of infection are the lungs in immunosuppressed and paranasal sinuses in the immunocompetent individuals. Less frequently, gastrointestinal and skin infection preceding CNS infection can occur and even more rarely a CNS primary infection can occur without an extra cranial source.

Risk factors for invasive CNS aspergillosis include major or prolonged neutropenia, hematologic malignancies, prolonged corticosteroid treatment, bone marrow or solid organ transplant, AIDS, cytotoxic agents, thermal burns, hepatic failure, diabetes mellitus, intravenous drug abuse, head trauma, postoperative nosocomial infections complicating neurosurgical operations and alcoholism.

There was no past history of hypertension, diabetes, tuberculosis, jaundice, asthma and allergy. Patient had undergone an uneventful appendicectomy 15 years back. On examination, there was difficulty in mouth opening with fifth and sixth cranial nerve paresis.

The patient’s routine hematological investigations were within normal limits. He was seronegative for HIV antibodies and no anomaly was detected in his X-ray chest. CT features were suggestive of right parasellar mass showing heterogeneous enhancement, involving brainstem, right cerebellar peduncle and extending up to the right temporal lobe. The MRI findings revealed an ill-defined lesion appearing hyper intense on T2 and flair weighted images and intermediate on T1 weighted images. It was seen involving the brainstem, right cerebellar peduncle and right temporoparietal region. Rest of the cerebral and cerebellar hemispheres were normal. Mucosal thickening in bilateral maxillary sinuses appearing hyper intense on T2 weighted images were also seen. The patient was diagnosed as a case of right temporal space occupying lesion and referred to the Neurosurgery Department for admission.

Right temporo-parietal craniotomy and near total removal of right temporal mass was performed. During the operative procedure biopsies of mass tissue were taken and sent to the Pathology Department for histopathological examination and to the Microbiology Department for mycological culture and microscopy.

In the Mycology section of our department, the excised brain tissue was ground in sterile saline in a tissue grinder. A direct wet mount and a KOH mount were examined under low and high power of microscope. Both the preparations showed hyaline septate hyphae with dichotomous branching (Fig. 1).

The ground tissue was also inoculated on two sets of Sabouraud dextrose agar (with and without antibiotics) and incubated at 25°C and 37°C. On the third day of incubation, all the four culture bottles revealed identical pure growths of a yellowish-green granular colony covering the entire surface of the agar slants. Lactophenol cotton blue mount of the
fungal colonies revealed typical picture of *Aspergillus* vesicles borne on conidiophores and covered entirely on their surfaces by sterigmata and conidia (Fig. 2). The growths were identified as those of *Aspergillus flavus*. Our findings were further supported by the histopathology report, which was also in favour of a fungal granuloma.

The patient was kept in the neurosurgical ICU for seven days postoperatively. On the basis of the laboratory report intravenous voriconazole was started. The condition of the patient improved neurologically and he was shifted to the neurosurgery ward. At the time of writing of this report (20 days after the operation) the patient was still recovering in the ward.

**Discussion**

Aspergillosis of the CNS is an uncommon infection mainly occurring in the immunocompromised. It accounts for 5% of all intracranial fungal infections. Neuroaspergillosis may result from two different mechanisms - hematogenous dissemination and direct extension from an area anatomically adjacent to the brain (i.e., sinuses, ear and orbit). In comparison with the cerebrum, the cerebellum and brainstem are less commonly affected.

Neuroaspergillosis may present in several forms such as aseptic and persistent meningitis, encephalitis, meningoencephalitis, mycotic aneurysm, ischaemic and hemorrhagic infarcts, stroke like syndrome, intracranial space occupying lesion, skull base syndrome, brain abscess, intraorbital space occupying lesion and tumoural form (aspergilloma).

Our patient was an immunologically competent individual as there were no underlying risk factors. There was no evidence of systemic fungal infection. His routine X-ray chest was normal. Despite the clinical evidences of immune competence, this patient developed locally invasive CNS aspergillosis. The MRI revealed a space-occupying lesion in the brain and mucosal thickening of both the maxillary sinuses. The mucosal thickening might have been a result of chronic fungal rhino-sinusitis, the clinical symptoms of which were probably ignored by the patient. Thus the probable mode of transmission of the disease in our patient was via a sinocranial route. In fact, this is the commonest form of CNS aspergillosis reported from India. Intracranial extension of the *Aspergillus* from the sinuses occurs by erosion of the base of skull and along the blood vessels. Distinct intracranial perineural extension of *Aspergillus* rhino-sinusitis has also been described.

The mechanism causing invasiveness of aspergillosis in immunocompetent hosts remains unclear. It is possibly caused by qualitative cellular or sub cellular immunodeficiency that is either unrecognized or poorly characterized. Regarding a mechanism of damage at the cellular level in cerebral *Aspergillus* lesions, recent *in vitro* studies have implicated secretion of various necrotizing factors with toxic and lytic activity towards neurons and glial cells.

![Figure 1a: Direct wet mount of the brain tissue demonstrating hyaline septate hyphae with dichotomous branching (x400)](image1a)

![Figure 1b: KOH mount of the brain tissue demonstrating hyaline septate hyphae with dichotomous branching (x400)](image1b)

![Figure 2: LCB mount demonstrating typical *Aspergillus* vesicles borne on conidiophores and covered on their entire surfaces by sterigmata and conidia (x100)](image2)
The findings of hyaline, septate hyphae with dichotomous branching in the direct wet mount and KOH mount and isolation of *Aspergillus flavus* colonies as pure growths on culture implicates *Aspergillus flavus* as the causative agent of neuroaspergillosis in this patient. *Aspergillus flavus* has been reported as the most frequent species isolated in cultures of invasive CNS aspergillosis of nasal and paranasal origin. However, *Aspergillus fumigatus* is more frequently implicated as a cause of invasive aspergillosis in immunocompromised patients.

CNS aspergillosis is favored by working in agriculture, craftwork and by a tropical climate. This patient gives no significant occupational exposure history; it is most likely that he inhaled the fungal spores from his environment. The patient is a resident of the state of Rajasthan, which has very hot and dry climatic conditions all round the year. *Aspergillus flavus* has a peculiar propensity to grow and flourish in the microaerophilic environment of nasal and paranasal sinuses in hot and dry climates such as those of Africa, Saudi-Arabia and Indian subcontinent.

Voriconazole treatment together with neurosurgical management, whenever feasible, is currently the best approach to treat patients with CNS aspergillosis. Factors such as nonspecific clinical presentation, low sensitivity of conventional diagnostic techniques and long time taken for diagnosis, contribute to the difficulty encountered in detecting fungal infection of the CNS.

References


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