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Case Report

Cerebral Aspergillosis on autopsy; masquerading clinically as Brain tumor in a young female

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E-mail: drshwetarana15@gmail.com**Abstract**

Cerebral aspergillosis is a rare pathology with fatal outcome. It is mostly a post-mortem diagnosis because the initial symptoms are mostly nonspecific and the existing diagnostic modalities are not sensitive to ensure early and definite diagnosis. The clinical manifestations and disease severity are dictated by the immunologic state of the patient. Cerebral aspergillosis can mimic tuberculous meningitis, pyogenic abscess, or brain tumor. Maxillary sinusitis of dental origin or the lungs are the most common sites of primary aspergillus infection. Infection reaches the brain directly from the nasal sinuses via vascular channels or is blood borne from the lungs and gastrointestinal tract. Dissemination of aspergillus is relatively common, with the central nervous system (CNS) being one of the most frequent sites of Invasive aspergillosis (IA) after the lungs. Aspergillosis should be considered in cases manifesting with acute onset of focal neurologic deficits resulting from a suspected vascular or space occupying lesion especially in immunocompromised hosts. Only a high index of suspicion, an aggressive approach to diagnosis, and rapid vigorous therapy can alter the clinical course in this group of patients.

Keywords: Autopsy, Aspergillosis, central nervous system, cerebral aspergillosis**1.Introduction**

Fungal infections of the central nervous system (CNS) are almost always a clinical surprise.[1] The antemortem diagnosis of fungal infection always poses a problem. The diagnosis of fungal infections relies on microscopy, culture and pathogen specific tests.[2] With the continuing rise in the number of immunocompromised patients, the incidence of invasive mycoses is on the rise. Because of the limitations in antemortem clinical diagnosis owing to lack of sensitive diagnostic tools, information regarding frequency and pathogenesis of fungal infections is largely dependent on autopsy studies.[3] Aspergillus is the most common fungus affecting CNS.[4] Aspergillus fumigatus is the most common human pathogen in the genus Aspergillus. Granulocytopenia, cellular and humoral mediated immune dysfunctions are predisposing factors to the development of CNS infections in immunocompromised patients. Intracranial spread of

Aspergillus infection occurs more frequently by hematogenous routes and less frequently through direct or contiguous spread. Intracranial infection can affect the parenchyma or the meninges. According to the site and nature of infection, the patient may present with features of meningitis, focal neurological signs, or symptoms of raised intracranial pressure.[1] In India, sinocranial aspergillosis accounts for a significant proportion of histologically verified cases reported in otherwise normal hosts in contrast to the disseminated forms that account for the majority of cases from Western countries.[5][6][7][8] Compromised sinus aeration, altered immune status could facilitate growth of the organism and eventual contiguous spread into the cranial cavity.[8] We report a case of cerebral aspergillosis diagnosed on post-mortem histopathological examination. Antemortem the patient was suspected of brain tumor and was

investigated accordingly and died due to lack of appropriate diagnosis and treatment.

2. Case Report

We received a post-mortem Brain (bilateral cerebral hemispheres) specimen of a 26 year's old female for histopathological examination. The deceased was a domestic help of Nepalese origin. She had undergone an elective caesarean section 9 months prior to presentation. There was history of sudden severe headache, vomiting, blurring of vision, high grade fever, dizziness only three days before her death. She took treatment from the local hospital where she was suspected of having ICSOL (Intra Cranial Space Occupying Lesion) and only supportive and symptomatic treatment was provided. No CSF examination, blood culture or serological tests were conducted. She was advised CT scan brain. She had another episode of severe headache, vomiting and unconsciousness after 2 days and this was fatal. Police report mentioned the diagnosis of brain tumor on CT scan. Bilateral cerebral

hemispheres were received for histopathological examination. Grossly, the cerebral hemispheres weighed 974g and measured 18x17x4cm. Cut surface of cerebral hemispheres and the attached meninges were unremarkable. Microscopic examination showed mixed inflammatory infiltrate comprising of lymphocytes, plasma cells, histiocytes and neutrophils in the meninges. Prominent fungal elements in hyphal forms showing septation and acute angle branching in the meningeal blood vessels and in occasional intracerebral vessels were seen (Fig.1a & 1b). Occasional vessels showing perivascular collections of inflammatory cells were present. No associated infarction was seen. There was no gross/ microscopic evidence of neoplasm in the bilateral cerebral hemispheres submitted for histopathology. Staining with Periodic acid Schiff (PAS) and Gomori methenamine silver (GMS) confirmed Aspergillosis (Fig 1c & 1d). Fungal infection was missed clinically and was diagnosed only at autopsy in the present case.

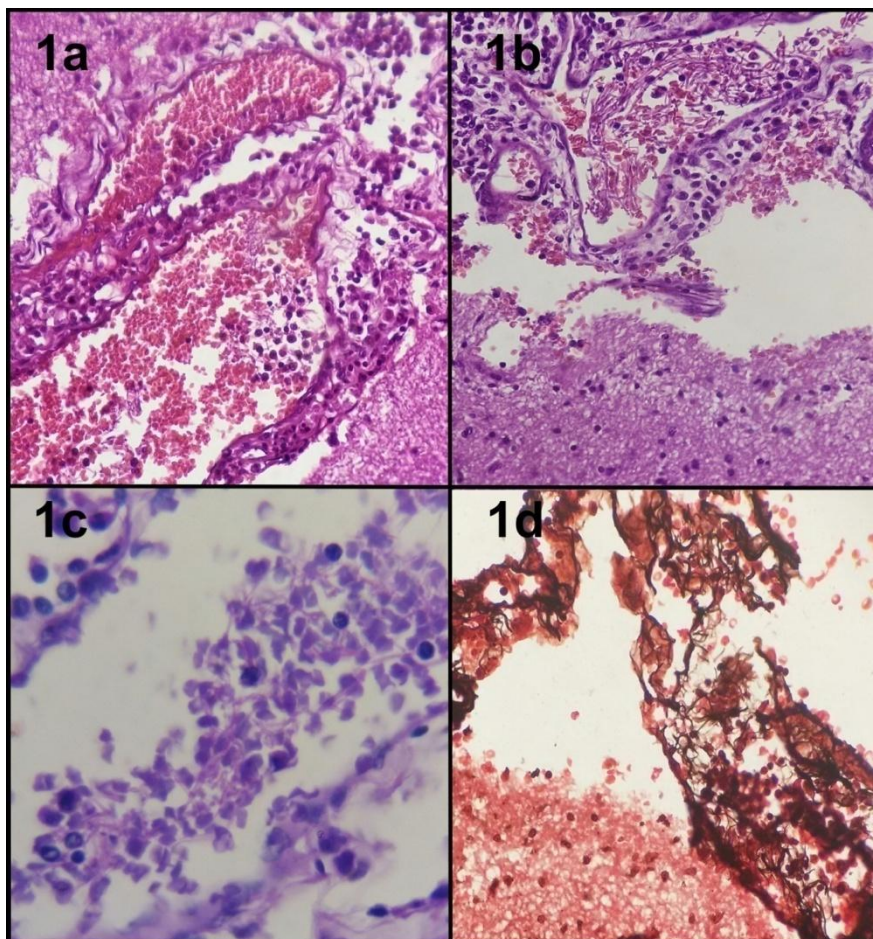


Fig. 1a and Fig. 1b- Microphotographs show prominent fungal elements in hyphal forms in meningeal blood vessels (H&E; 400x). **Fig. 1c-** Microphotograph shows fungal elements in hyphal forms in meningeal blood vessels (PAS; 400x). **Fig. 1d-** Microphotograph shows fungal elements in hyphal forms in meningeal blood vessels (GMS; 400x)

3. Discussion

Fungi can be either 'pathogenic' to cause infection in a normal host or 'opportunistic' infecting patients with compromised host defences. With the continuing rise in the number of immunocompromised patients, the incidence of invasive mycoses is on the rise.[9] *Aspergillus fumigatus* is the most common human pathogen in the genus *Aspergillus*. *Aspergillus* is a saprophytic opportunistic ubiquitous fungi found in soil and on plants. It grows as a mould on decaying vegetable matter. It has branching septate hyphae which shows dichotomous branching and produces numerous spores on the tips of long conidiophores.[1] The asexually produced conidia on aerial hyphal stalk are the infective form of the organism that is inhaled through the respiratory route. Its germination into filamentous forms results in tissue destruction and disease.[8] *Aspergillus* spores are commensal in the respiratory tract and external auditory canal. Maxillary sinusitis of dental origin or the lungs are the most common sites of primary *aspergillus* infection.[10]

Infection of the CNS by *Aspergillus* follows hematogenous seedings or direct inoculation into the CNS during surgical procedures or spread from contiguous structures like paranasal sinuses, mastoid and middle ear. The morphological changes observed depend on the mode of acquisition, whether by hematogenous dissemination or local spread from contiguous anatomical structures. The former leads to multiple lesions involving the middle or anterior cerebral arterial territory with acute necrotizing and purulent lesions (cerebrovascular aspergillosis). In the latter event, the resultant lesions are chronic granulomas eliciting dense fibrosis. The infection in the nervous system can be found in the cerebral parenchyma, meninges or the vascular system.[8]

Aspergillus tends to invade arteries and veins because of its angiotropism, leading to necrotizing vasculitis, secondary thrombosis and hemorrhage.[11] Extension of fungal invasion in the neighbouring neuronal tissues and in blood vessels provoke hemorrhage, thrombosis, infarcts, necrosis, meningitis and ventriculitis.[12] The ability of *Aspergillus* to produce enzyme elastase confers direct angioinvasive property to this fungus leading to cerebral hemorrhage or aneurysm formation.[13] The neuropathological findings also depend on the extent of immunosuppression. In case of extreme immunosuppression as in bone marrow transplantation or prolonged severe neutropenia, strands are found associated with ill circumscribed

inflammation, comprising of some mononuclear and polymorphonuclear cells. In case of less severe immunosuppression, inflammation is frank with frequent granulomas composed of lymphocytes, plasma cells, and rare mycelia strands. Necrotic damage is frequent, whatever be the severity of immunodeficiency, confirming the vascular tropism of the pathogen.[12] True mycotic aneurysms caused by direct invasion of *aspergillus* hyphae into vessel wall and rupture causing subarachnoid hemorrhage are also reported.[14] The possibility of iatrogenic fungal meningitis with fungi being introduced into the subarachnoid space during spinal anaesthesia is suggested in some of the cases.[15]

The diagnosis of cerebral aspergillosis is difficult because the inaugural symptoms are mostly non specific comprising of headache, fever, paralysis of cranial nerves, paraesthesias, hemiparesis, mental confusion, and/ or epileptic seizures.[16] The symptoms are usually those of a cerebral mass lesion, although the propensity of the fungus to invade blood vessels may lead to extensive necrosis and sometimes to intracranial bleeding.[1] The diagnosis of fungal infections relies on microscopy, culture and pathologic specific tests. However CSF examination, neuroradiology, culture and serologic tests are not always reliable. Newer rapid and non culture based methods like Polymerase chain reaction (PCR), galactomannan antigenemia, Western blot and detection of fungal metabolites like D- arabinitol are being developed.[2]

The most effective treatment of cerebral aspergillosis is medical and surgical. Now a days, antifungal first line treatment of invasive aspergillosis is Voriconazole, whose efficacy and tolerance is superior to Amphotericin B; its good intracerebral distribution justifies its first use as the first line drug in Cerebral aspergillosis. Cerebral aspergillosis entails an unfavourable prognosis. A high index of clinical suspicion with vigilant laboratory help and use of antifungal agents as empirical therapy in suspected cases will definitely improve the outcome and reduce the mortality associated with invasive aspergillosis.[17]

4. Conclusion

The present case highlights the fact that existing diagnostic modalities may not be sensitive enough to ensure antemortem diagnosis of fungal infections. There is a definite need to develop the newer techniques for early and definite diagnosis of these infections along with a reasonably high index of clinical suspicion.

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