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# OVERVIEW OF SURGICAL MANAGEMENT OF INFECTIOUS NON-SUPPURATIVE BRAIN LESIONS (PART II)

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## ASPERGILLOSIS

Aspergillosis disseminating to the central nervous system (CNS) is amongst the most fearsome manifestations of opportunistic fungal infections.<sup>1</sup> Among the various disease causing subtypes in the genus *Aspergillus*, *A. fumigatus* is the most commonly identified human pathogen mostly affecting immunocompromised individuals. The incidence appears to be rising due to better means of diagnosis, better reporting and increase in immunocompromised patient population. The disease was once considered to be restricted to immunocompromised patients; however a recent increase has been observed in the immunocompetent population as well, especially in Pakistan and India, where more than half of all the affected patients did not have any evidence of immunosuppression, a population known as the "apparently immunocompetent".<sup>1-9</sup> Primary sites of aspergillus infection are the lungs in immunosuppressed and paranasal sinuses in immunocompetent individuals. CNS may also be involved as a primary site, but more commonly it is involved secondary to hematogenous spread from disease elsewhere or as a result of contiguous extension from adjacent structures.<sup>3,4</sup> The CNS is now the second commonest organ to be secondarily affected by invasive aspergillosis. Intracranial aspergillosis has been classified as extradural, intradural or a combination of both. Extradural disease is associated with the best outcome.<sup>4</sup>

The mechanism of damage at the cellular level in cerebral *Aspergillus* lesions has been shown to be due to secretion of various necrotizing factors with activity toward neurons and glial cells.<sup>10</sup> *Aspergillus* also has a tendency to invade blood vessels producing a necrotizing angiitis leading to secondary thrombosis with or without

hemorrhage.<sup>11</sup> Aspergillomas, reactive masses formed commonly in immunocompetent patients, are mainly present in the frontal or temporal lobes and rarely, in the posterior fossa as well.<sup>12</sup> Out of more than 40 cases managed at our institution over the past ten years, we have come across just two patients with aspergillomas involving the cerebellum. Aspergillomas may also co-exist with septic or vascular infarcts or with intracranial abscesses.

In our country where solid organ transplant and acquired immunodeficiency syndrome are not that common, the majority of immunocompromised patients are due to diabetes mellitus.<sup>4</sup> In nearly half of the patients suffering from aspergillosis, however, we did not find any predisposing underlying condition.

Multiple studies have described a variety of presenting features such as nasal stuffiness, headache, peri-orbital pain, vomiting, seizures, hemi paresis, cranial nerve palsies, impaired consciousness.<sup>5,3,14</sup> In patients with orbital involvement, proptosis, ophthalmoplegia and visual deterioration are usually the presenting features.<sup>13-15</sup> Patients with aspergillomas may also present with classical skull-base syndromes such as the orbital apex syndrome, cavernous sinus syndrome, polyneuritis cranialis and orbito-cranial syndromes, depending upon the site of lesion. In one study of patients suffering from CNS aspergillosis, 64 patients out of 89 presented with skull base syndromes.<sup>16</sup> The disease is usually slowly progressive and symptoms may persist for months before clinically apparent.

Cranio-cerebral aspergillosis is difficult to diagnose, as blood cultures and cerebrospinal fluid (CSF) cultures are frequently negative.<sup>17</sup> Other serologic tests such as

double diffusion counter immuno-electrophoresis, immuno- fluorescence, or enzyme-linked immuno-sorbent assay (ELISA) may be helpful in arriving at a diagnosis but are rarely performed.<sup>17,18</sup> CSF analysis findings are usually non-specific for fungal disease, cell counts are usually elevated, showing pleocytosis, proteins also are usually elevated and glucose may be decreased. Antibody detection in serum or CSF is also not shown to be useful. The yield of PCR is comparatively high in cases of disseminated invasive aspergillosis and cerebral abscesses, but not in patients with aspergillomas. We do not recommend the use of CSF in the diagnosis of cerebral aspergillosis as obtaining a CSF sample through lumbar puncture in such a patient may be dangerous.<sup>18</sup> A peri-operative squash smear or frozen section seems to us a much better means of identifying the pathology and we strongly recommend that it be carried out in all patients with suspected aspergillus infection.<sup>18</sup>

Cerebral aspergillosis presents with four principal neuroimaging findings. These include infarction, abscesses, infiltration originating from paranasal sinuses or orbits, and intracranial (intra or extra-axial) space occupying lesions. All of these may also co-exist in the same patient.<sup>18,19</sup> On CT scanning the lesions are characteristically hyper-dense with mass effect and may or may not show contrast enhancement.<sup>18</sup> Calcifications within the fungal mass may also be present. On MR imaging, the classical description is that of an irregular space occupying mass lesion having hypointense to isointense signals on T1 weighted images due to coagulative necrosis of brain tissue secondary to fungal involvement of vessels, a finding that has been histologically proven.<sup>20</sup> On T2 weighted images, hypointense signals when present are considered characteristic of aspergillus lesions. However, slightly less hypointense zones may also be present within the wall of these lesions. These have been attributed to the dense population of aspergillus hyphal elements or recent hemorrhage, and are not considered characteristic.<sup>21,22</sup> Presence of iron, manganese, and magnesium in the fungal concretions may also lead to hypointense signals on T2 weighted images.<sup>21-23</sup> On contrast administration, the lesion may show either bright homogenous enhancement, ring enhancement or no enhancement, although a thick perimeter of enhancement is the most characteristic feature of aspergillomas, especially in the presence of a competent host defense mechanism.

The cornerstone of management of intracranial aspergilloma remains surgical excision, a standard based on reports, personal experiences and on the basis of a recent multifactorial risk analysis.<sup>18,24,25</sup> Surgical excision must always be followed by aggressive antifungal

chemotherapy to achieve best response.<sup>26-29</sup> Radical surgery done early and as a first procedure has been considered superior to repeated sub radical resections but it has also been suggested that radical excision of fungal mass does not seem to be necessary.<sup>4,30</sup> The risk of morbidity seem excessive for an infective process and therefore, sub radical excision aimed at establishing diagnosis and reducing disease burden followed by systemic antifungal therapy seems to be a better course of action. However, when a lesion in a non-eloquent area is encountered that can be safely and totally excised, the best plan would be to eradicate the lesion completely. Sub-radical resection may be reserved for lesions which are only partially resectable. In a lesion occupying an eloquent area a biopsy would suffice.

Whenever the nasal passages are suspected to be involved, a thorough debridement of nasal passages should be simultaneously carried out by otorhinolaryngologists.<sup>18</sup> When the globe is involved the patient mostly does not have vision in that eye and enucleation should be considered.

Peri-operative management of these patients is challenging. The aspergillus at times shows a peculiar response to surgery and seems to flare up post-operatively assuming a rapidly fulminant course if not dealt with aggressively. The response is characterized by high grade fever, tachycardia and malignant cerebral edema refractory to medical management, presumed to be due to iatrogenic acute aspergillus meningo-encephalitis. Whenever such a response is encountered, patient should be managed on principles of malignant cerebral swelling with consideration for mannitol, steroids, decompressive craniotomy, and if ever necessary, decompressive lobectomies, along with other aspects of neuro-intensive care such as intracranial pressure monitoring and propofol sedation. Based on anecdotal experience, it is suggested that pre-operative use of itraconazole may be associated with better outcome.<sup>31</sup> Special attention should also be given to patient's metabolic profile, as the patient is under the influence of a number of factors which may lead to metabolic derangements. Such caution is not required in patients have extradural disease alone. It is only when the fungus involves brain parenchyma, and during surgery the dura is breached that we see series of events referred to as "forest fire phenomenon".<sup>18</sup>

Until recently, cerebral aspergillosis was treated routinely with intravenous amphotericin B combined with flucytosine or itraconazole.<sup>4,27-29,32</sup> But with the introduction of itraconazole, the paradigm has shifted as many multicenter clinical trials have proven its efficacy

over the previous drug regimens.<sup>4,27-29,32</sup> In addition to efficacy, other advantages of itraconazole therapy are that it is less toxic and thus better tolerated although it shows variable and inconsistent absorption in some patients. Two newer parenteral antifungal medications (echinocandins) caspofungin and micafungin are also under scrutiny and a newer triazole, voriconazole, is also becoming increasingly popular.<sup>33-35</sup> Several studies suggest voriconazole is more effective and less toxic than amphotericin B, and has been proposed as the first line treatment of aspergillosis.<sup>33-35</sup> There is also the debate over monotherapy and combination therapy and animal models have suggested that combination of liposomal amphotericin B and voriconazole given concurrently are significantly efficacious in comparison with any other combination, even when administered in sub-optimal doses.<sup>33,34</sup> There may also be some advantage in the administration of granulocyte monocyte colony stimulating factors (GM-CSF) and recombinant-IFN, although evidence is lacking.<sup>36,37</sup>

Unlike intracranial tuberculomas and intracranial hydatid cysts, intracranial aspergillomas do not carry the same favourable prognosis and initial literature suggested a mortality of nearly 100%.<sup>38</sup> Beside the adverse effects of antifungal medications, some specific complications reported for these patients include vascular invasion leading to infarcts, intracerebral hemorrhage, fungal dissemination, massive anaphylaxis, meningitis, formation of mycotic aneurysm, subarachnoid hemorrhage and hydrocephalus. Patients who are immunocompetent or who have only extradural disease have the best outcomes, with reported mortality rates ranging from 40-80%. The mortality rate is reduced to less than 20% if the disease is entirely extradural.<sup>3,4,18</sup> Patients with underlying malignancies or who have intraparenchymal disease have the worst outcomes.<sup>38</sup> Presence of vascular invasion nearly always indicates a poor prognosis.

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