Review Article

Surgical management of intracranial fungal masses

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Background: Intracranial fungal masses (IFMs, granulomas and abscesses) are uncommon lesions, infrequently encountered by neurosurgeons. There is no conclusive evidence on the ideal surgical management of these lesions.

Aims: To summarize the recent literature on the prevalence, presentation, surgical management and outcome of patients with IFMs. Materials and Methods: The recent published literature was searched using standard search engines (PubMed and Google) for articles reporting on the databases and surgical management of IFMs. A special effort was made to include publications from Indian centers. Results: Intracranial fungal masses were rarely seen even in major neurosurgical centers in India with a prevalence of around one to two per year. While most patients with IFM have immunosuppressed states, nearly 50% of patients with IFMs (especially in India) have no obvious predisposing causes and are apparently immunocompetent. The clinical presentation could be categorized into three groups: 1. Involvement of the cranial nerves 1 to 6 with orbital and nasal symptoms. 2. Focal neurological deficits due to involvement of any part of the neuraxis; and 3. “Stroke-like” presentation with sudden onset of hemiparesis. Based on the presence or absence of radiological evidence of paranasal sinus disease, IFMs were classified into two types: 1. Rhinocerebral type; 2. Purely intracranial type that was further divided into a. intracerebral or b. extracerebral forms. Aspergillus species was the commonest fungal organism causing IFMs but a number of other fungi have been reported to cause IFMs. Surgery for IFMs can be of different types, namely 1. Stereotactic procedures; 2. Craniotomy; 3. Shunt surgery; and 4. Treatment of fungal aneurysms. Generally, radical surgery is advocated for IFMs but there is no unanimity regarding the radicality of the excision especially for the rhinocerebral form of the disease. Surgery should always be followed by antifungal therapy for prolonged periods. Mortality and morbidity in patients with IFMs is very high and ranges from 40-92%. Immunosuppressed patients with IFMs and those in whom the diagnosis is delayed have the highest mortality rates, with immunocompetent patients with the rhinocerebral form of the disease having the best outcome. Conclusions: There should be a high index of suspicion for IFMs not only in patients with known risk factors for the development of fungal infections but also in immunocompetent patients in India. Intraoperative pathological diagnosis should be obtained in any patient suspected to have an IFM and tissue should be processed for fungal cultures. Prompt diagnosis, radical and safe surgery and aggressive and prolonged treatment with anti-fungal agents may lead to a better outcome especially in immunocompetent patients.

Key words: Brain, fungal abscess, fungal granuloma, outcome, stereotactic surgery, surgery

Intracranial fungal masses (IFMs, granulomas and abscesses) are uncommon entities, although, they are being increasingly recognized in recent years. The largest case series reported to date has 40 patients gathered over 22 years from two centers, one in India and the other in the United States.[1] It is speculated that their increasing incidence is attributable to the rising incidence of human immunodeficiency virus (HIV) infections, increased use of immunosuppressants, increased survival amongst patients undergoing organ transplants and cancer chemotherapy and the rising incidence of diabetes mellitus (DM) especially in India. Intracranial fungal infections including meningitis are quite commonly seen in the group of patients mentioned above but IFMs are relatively infrequently reported. The management of patients with IFM has not been standardized although it is agreed that medical management with antifungal agents is the mainstay of therapy. The role of surgery (biopsy versus partial excision versus radical excision) and the duration of antifungal antibiotic therapy have not been clearly elucidated in the literature. This article attempts to review the literature on the role of surgery in the management of patients with IFM and to determine prognostic factors if any reported in the literature. The recent published literature was searched using standard search engines (PubMed and Google) for articles reporting on the surgical management of IFMs.
A special effort was made to include publications from Indian centers.

Prevalence

In a neurosurgical service, one would only rarely encounter IFMs. This is borne out by the sparse reports of IFMs from several large neurosurgical centers in India. There were 32 IFMs in a 14-year period in PGI, Chandigarh. In a study spanning 22 years, 40 patients with IFMs were seen in NIMHANS, Bangalore and another center in the United States. From NIMS, Hyderabad, 21 patients with aspergillomas were reported over a period of seven years. In our center, we encountered 13 patients with intracranial aspergillomas over a 12-year period. Mehta et al. from AIIMS, New Delhi, reported 14 patients with an IFM over a 17-year period. In a review of cerebral aspergillomas, Nadkarni et al. from KEM Hospital, Mumbai collected 18 patients over a 38-year period. It is, therefore, likely that even in large neurosurgical centers in India, the caseload of IFMs would not exceed two per year. Surgery for IFMs would constitute about one per 1000 neurosurgical procedures performed at these centers. With these prevalence rates, it is not surprising that IFMs are rarely suspected in patients with isolated intracranial masses.

One could conversely study the prevalence of IFMs in patients who undergo transplant procedures. During a three-year period, 17 cases of IFMs (abscesses) were diagnosed in a cohort of 1620 patients who had undergone liver, heart, lung, renal and stem cell transplants in a center in the United States. In another series from Pittsburgh, over a 14-year period, involving 2380 liver transplants, 1650 kidney transplants and 598 heart and heart-lung transplants, IFMs were diagnosed in 24 patients (0.5%). These were most often seen within the first 3 months of the transplant. Another series from a major center for bone marrow transplantation in the United States reported 53 patients with fungal brain abscess over an 8.5-year period. In a prospective study from our center, 1476 primary renal transplant recipients were evaluated for systemic mycoses and eight (0.5%) were diagnosed with IFMs. The cumulative prevalence of IFMs in transplant recipients thus varies between 0.5 and 1%.

Clinical Presentation

Intracranial fungal masses can be seen in any age group but most patients are in the third, fourth and fifth decades of life. They have been reported even in neonates, infants and young children. The duration of symptoms can vary from a few days to several months or even years. The illness generally has a shorter duration in patients with an IFM without sinus disease. The disease can be indolent especially in those in whom the disease spreads from the sinuses to the brain and such patients may present with symptoms of several years duration. The clinical presentation is not specific but can be divided into three distinct types depending on the nature of the disease. The three types of clinical presentation are: 1. Involvement of the cranial nerves 1 to 6 with orbital and nasal symptoms. These symptoms/signs are common in patients with fungal infections that originate in the paranasal sinuses (PNS) and spread to the intracranial compartment by the contiguous route; 2. Focal neurological deficits due to involvement of any part of the neuraxis; and 3. “Stroke-like” presentation with sudden onset of hemiparesis. Additionally, patients with any of these presentations might manifest features of raised intracranial pressure, seizures and altered sensorium. The altered sensorium can result from raised intracranial pressure, ischemia due to the vasculitis associated with the concomitant fungal meningitis and fungal meningoencephalitis. “Stroke-like” presentation is not common and has been reported in 6-10% of patients. It results from fungal arteritis involving the cerebral vessels in the cavernous sinus or the circle of Willis. Rarely, patients with fungal aneurysms present with subarachnoid hemorrhage. Interestingly, fever is an infrequent symptom in patients with IFM and is seen in only 10 - 31% of patients.

Predisposing Illnesses

DM is a frequent predisposing illness in patients with IFM especially that associated with PNS involvement. Several other diseases and conditions that are reported as risk factors in patients with IFM include, HIV infection organ transplantation, cancer chemotherapy, prolonged steroid therapy, autoimmune disorders such as systemic lupus erythromatosis and tuberculosis. In recent years there have been several reports of IFMs in large numbers of immunocompetent patients with no obvious focus of infection. Intracranial fungal masses in immunocompetent patients have been predominantly reported from India, Pakistan, Saudi Arabia, Africa and California in the United States. It is postulated that a hot, dry climate with a high content of aspergillus spores in the atmosphere due to agriculture dust may be a probable cause for the occurrence of IFMs in persons residing in these regions. Nearly 50% of patients with IFMs have no overt predisposing illness or evidence of immunosuppression. It is possible that in some of these patients, there might be subclinical impairment of cell-mediated immunity.

Rarely, fungal infection may follow direct inoculation of the brain during intracranial or transsphenoidal surgery or following trauma. Sharma et al. reported...
two patients who developed IFMs following intracranial surgery.

Associated systemic fungal infections

Intracranial fungal masses usually develop by the spread of fungal infection to the intracranial compartment from a systemic source of infection. The commonest focus of such infection is the PNS and the mastoid sinuses. The other systemic sources of infection include the lungs and heart especially in the presence of artificial heart valves. The disease is usually spread through the hematogenous route but invasion of contiguous tissues and spread into the intracranial compartment is also common in the case of PNS and mastoid infections. In a proportion of patients with IFM, however, no obvious systemic source for the fungal infection is discernible in spite of an extensive search for the same.

Causative Organisms

The fungi that cause IFMs are dealt with in detail in other articles in this issue. Only the common organisms will be mentioned here. The commonest fungus that produces an IFM is the Aspergillus spp. Aspergillus flavus is generally implicated as the causative organism in patients who are immunocompetent whereas A. fumigatus is more frequently reported in immunocompromised individuals.[6,12] The other fungi causing IFMs include Cryptococcus, mucormycosis, Candida, cladosporium and dematiaceous fungi.[1,2,5,7-9,10,17-20] Reports of several other fungi producing IFMs are available in the literature but most are individual case reports.[21,22] Fungal aneurysms are caused usually by Aspergillus or mucormycosis. The angioinvasive nature of these organisms leads to the digestion of the elastic lamina of the vessels by the production of the enzyme elastase.[14]

Imaging Diagnosis

Imaging diagnosis of IFMs is dealt with in another article in this issue and only some salient features will be mentioned here. Contrast enhanced computerized tomography (CT) and magnetic resonance imaging (MRI) of the head are the investigations of choice. Unfortunately, neither of these tests provides a definitive diagnosis of an IFM. CT and MRI only reveal intracranial mass or masses that enhance with contrast and can also provide evidence of involvement of the paranasal sinuses and the mastoid sinus. Careful attention should be paid to the sinuses in any patient suspected to have an IFM. The masses are contrast enhancing with perilesional edema.[1,2,4,6] It has been postulated that MR appearances are characteristic for IFMs caused by different fungal agents. Cryptococcomas appear as hypointense masses on T2W images whereas aspergillomas have an intermediate signal intensity on T2W sequences.[1] Siddiqui et al.[12] reported that IFMs caused by aspergillus were extremely hypointense on T2-weighted MR images and were hypointense to isointense on T1-weighted sequences and suggested that MR features of an intracranial aspergilloma are characteristic enough to initiate empiric anti-fungal therapy without microbiological confirmation of the diagnosis, prior to definitive surgery. While this strategy might be acceptable as an interim measure prior to surgery, imaging diagnosis should not be considered as a replacement for pathological or microbiological diagnosis as anti-fungal agents are generally toxic and should not be administered on a long-term basis to any patient without definitive diagnosis of a fungal infection.

As the imaging features of IFM are non-specific, several differential diagnoses are generally considered prior to surgery except in patients with easily identifiable risk factors. The commonly considered imaging differential diagnoses are tuberculomas, metastasis, lymphoma, glioma and meningioma if the mass is dural based. In the case of rhino-cerebral disease a common differential diagnosis would be sinonasal malignancy.

Classification of IFMs

Based on the presence or absence of the involvement of the paranasal sinuses (PNS), IFMs can be classified into 1. Rhinocerebral or sinocranial group (when PNS disease is identifiable on the CT/MR imaging); or 2. Primary intracranial group (when PNS disease is absent). Primary intracranial IFMs can be further classified as a. Extracerebral (extra-axial); or b. intracerebral (intra-axial) group based on the relationship of the IFM to the brain parenchyma.[2] The rhino-cerebral form of the disease is the most common presentation of IFMs and accounts for 40 to 80% of most large series of IFMs from India.[1,6] Although in patients with the extracerebral form of the disease, no PNS involvement is evident on initial imaging, this may become manifest later in the course of the disease.[1,2,4] It is therefore possible that even at initial presentation PNS involvement was present but occult.

The rhinocerebral form of the disease presents most often in the anterior skull base or the sellar and parasellar regions. If the focus of infection is in the mastoid air cells then the spread of the disease is to the petrous bone and subsequently to the middle or posterior fossa. The commonest location for a primary intracranial IFM is the supratentorial compartment with the majority of lesions being present in the frontal lobes. There are two reasons for the predilection of the frontal lobes for IFMs. First, the frontal lobes account for nearly a third of the cerebral hemispheres and hence receive a major portion of the blood supply to the brain and second, the frontal lobes being in close proximity to the frontal and
ethmoidal PNS present an obvious target for the spread of infection from the sinuses. The other common location for an IFM is the temporal lobe. Because of its proximity to the petrous temporal bone fungal infections from the mastoid air cells can spread to the temporal lobe. Kumar et al.\(^\text{[23]}\) reported one patient with an IFM in the lateral ventricle, this location being extremely rare.

The posterior fossa structures are very infrequently involved especially by isolated infections and may only be occasionally involved when there are several IFMs. Mastoid sinus fungal infections can, however, spread to the cerebellar hemispheres through contiguous spread. In their series of 25 patients with craniocerebral aspergillomas, Siddiqui et al.\(^\text{[12]}\) did not have a single patient with a posterior fossa lesion. Dubey et al.\(^\text{[1]}\) who reported one of the largest series of IFMs with 40 patients, did not have a single patient with a posterior fossa lesion. In the series of IFMs reported by Sharma et al.,\(^\text{[2]}\) five of the 32 patients had posterior fossa lesions (three in the cerebellopontine angle and two in the cerebellum) but all of these lesions were in association with either parasellar or temporal lobe fungal masses and were not seen in isolation. Therefore, isolated cerebellar fungal masses are rare and may not be suspected pre-operatively.

The consistency of the IFMs differs based on the type of cerebral involvement.\(^\text{[2]}\) In the rhinocerebral form, the IFMs are firm to hard in consistency and are difficult to cut into. On the other hand, the IFMs in the intracerebral form of the disease are soft and suckable and may have pockets of pus within them. This difference is also evident in the pathological examination with marked fibrosis being a prominent feature of the rhinocerebral form of the disease.\(^\text{[3]}\)

Fungal aneurysms are rare entities with only about 15 cases reported till 2001.\(^\text{[14]}\) Most of these aneurysms involve the proximal intracranial vessels typically involving the intradural portion of the internal carotid artery. They are fusiform and involve longer segments of the artery when compared with bacterial aneurysms which are globular and small.\(^\text{[14]}\) They result from invasion of the vessel wall either from hematogenous spread of infection or direct invasion of the vessel wall from outside.

**Surgical management**

Surgical management of IFMs is primarily directed at achieving a definitive diagnosis but may involve other objectives as detailed below. Whatever surgical approach is used, there should be a high index of intra-operative suspicion of a fungal etiology for an inflammatory mass. Only with this approach will the tissue be sent for fungal cultures. If this opportunity is missed then the diagnosis might become doubtful and exact speciation will be impossible even if fungal hyphae are recognized in the histopathological samples.

**Stereotactic procedures**

Stereotactic biopsy/aspiration is resorted to when the IFM is deep seated (e.g. ganglionic, brain stem, thalamus), located in an eloquent region of the brain (e.g. motor regions) or when the masses are multiple and the object of surgery is to arrive at a diagnosis and obtain pus/tissue for culture studies. Although the procedure only achieves a diagnosis and obtains tissue/pus for microbiological studies, there are reports of successful management of patients with IFMs using stereotactic biopsy/aspiration along with appropriate medical therapy.\(^\text{[24-26]}\) It is suggested that both the periphery and the center of the mass be targeted as the fungal hyphae may only be present in the periphery of the mass.\(^\text{[12]}\) Stereotactic procedures are, attractive as they are minimally invasive procedures and are especially appropriate in those patients with IFMs whose general condition precludes major cranial surgery. Stereotactic biopsy/aspiration can be performed under local analgesia in most adults and thus helps avoid the additional morbidity of general anaesthesia in moribund patients.\(^\text{[27]}\) Stereotactic craniotomies might also be done in patients with IFMs to reduce the morbidity of a craniotomy procedure and shorten the duration of the surgery.\(^\text{[29]}\)

Amphotericin can be injected directly into the IFM and has been reported to provide a better outcome in isolated cases.\(^\text{[30]}\) Ommaya reservoirs may be placed stereotactically into IFMs and amphotericin B can be injected directly into the IFM.\(^\text{[31]}\) This has been reported to yield good outcomes in isolated cases. The rationale for local therapy with amphotericin B is that it avoids the high systemic toxicity of the drug and also bypasses the blood brain barrier.\(^\text{[12,13]}\)

**Craniotomy**

Open craniotomy is performed for suspected IFMs that are in relatively accessible regions of the brain and when it is perceived that a radical excision is feasible and safe. Open surgery is also done often when the diagnosis of IFM is not suspected eg. when the mass is present in the subfrontal region and an imaging diagnosis of an olfactory groove meningioma is made. Radical excision of the IFM can rapidly reduce the mass effect and might improve penetration of the antifungal agents into the infected tissue.\(^\text{[2]}\) While it is generally agreed that aggressive surgical management of IFMs leads to a better outcome,\(^\text{[1,2,4,6,13,28,29,31,32]}\) radical surgery might not be feasible due to the location of IFMs in eloquent regions of the brain or not advisable in some patients due to their poor general condition. Siddiqui et al.\(^\text{[12]}\) suggested that a less than radical approach should be taken in the surgical management of IFMs. The author would not advocate the use of radical approaches such as skull base approaches to excise IFMs as these procedures are associated with higher morbidity.
even in otherwise well-preserved patients. From the literature, there is no conclusive evidence that radical and aggressive surgery improves outcome in patients with IFMs but a reasonably radical approach would be advisable whenever it is feasible without severe morbidity or additional neurological deficits. In some patients, repeated craniotomies are required to eradicate residual or recurrent disease.\[2\] Local antifungal therapy with amphotericin B soaked in gelatin sponge has been used successfully in a patient with an IFM, following open surgical debridement.\[33\]

**Shunt surgery**

Hydrocephalus that develops in some patients with IFMs requires the placement of a ventriculoperitoneal (VP) shunt. Several authors have documented the need for VP shunts in patients with IFMs either as primary procedures or as a secondary procedure when patients with IFMs on medical therapy develop hydrocephalus.\[1,2,5,12,13,31\] It is presumed that hydrocephalus in these patients is the result of arachnoiditis of the basal cisterns producing a communicating type of hydrocephalus.

**Management of fungal aneurysms**

There are reports of clipping of fungal aneurysms.\[1,2\] More recently endovascular techniques have been used to obliterate these aneurysms.\[14\] However, the ultimate outcome for patients with fungal aneurysms is poor and almost uniformly fatal.\[14\]

**Surgery for PNS disease**

Whenever IFMs are associated with PNS disease, surgical eradication of the PNS disease should be attempted. In recent years, functional endoscopic sinus surgery (FESS) has been the mainstay of PNS surgery and is used frequently in the radical excision of fungal disease in the PNS.\[12\] Besides removal of the diseased mucosal tissues, FESS also restores the aeration of the sinuses which in itself prevents re-establishment of the fungal infection in the PNS.

**Antifungal Therapy**

As antifungal therapy including the dose and duration of antifungal therapy will be discussed in a separate article, only some relevant aspects of the medical management of IFMs will be discussed here. Amphotericin B remains the mainstay of therapy in patients with IFMs. Due to its high systemic toxicity, patients undergoing therapy with amphotericin B require careful monitoring. Liposomal amphotericin B is a safer alternative with lower toxicity but is very expensive and many patients in our country might not be able to afford the drug. Oral antifungal agents such as flucytosine and itraconazole might be used in the long-term maintenance therapy. It has been suggested that itraconazole administered pre-operatively for a week might improve outcome in patients with IFMs.\[12\] Patients undergoing transplant procedures who are at high risk for developing IFMs might be given a trial of prophylactic amphotericin B but whether this strategy is effective in preventing IFMs is still unclear.\[8\]

**Prognosis and Outcome**

High mortality and morbidity have been uniformly reported in almost all series of patients with IFMs. The mortality rates range from around 40% in immunocompetent patients to 92% in transplant recipients. Unfortunately, newer drugs and more aggressive surgical procedures have not made a significant dent in the mortality and morbidity rates of patients with IFMs. Young et al.\[31\] reported a mortality rate of 43.6%; it was higher when the diagnosis was delayed (64%) and lower if the diagnosis was made early and treatment initiated promptly (39%). A mortality rate of 63% was reported by Dubey et al.\[1\] in their series of 40 patients with IFMs. Two-thirds of their patients had predisposing illnesses (diabetes, tuberculosis, renal transplant, lymphoma and HIV infection). Mortality in immunocompetent patients with intracerebral aspergillosis was 66.7% in the series reported by Siddiqui et al.\[12\] Jamjoom et al.\[13\] and Sharma et al.\[2\] reported a mortality of 41% and 50% respectively. Rhinocerebral mucormycosis has a high mortality associated with it. In immunocompromised patients, the survival is 75% but it decreases to 60% in patients with diabetes mellitus and to only 20% in those with other systemic disorders.\[34\]

Prognosis for IFMs is better in patients who are immunocompetent as opposed to those who are immunocompromized. In immunocompromized patients, the prognosis depends largely on the control of the underlying condition and not on the IFM alone. Patients with the rhinocerebral form of the disease have a better survival than those with the primary intracranial form. The longer survival, however, is associated with significant morbidity.

The other major cause of mortality and morbidity is the involvement of major cerebral blood vessels by the fungi leading to major strokes. Vasculitis seems to be a frequent sequel to surgery for IFMs in the skull base region and several authors have recorded mortality due to stroke following surgery for such lesions.\[2,6,12,13\] For some reason, patients who undergo surgery for IFMs, even distant from the skull base, seem to be at risk for the development of arteritis and subsequently develop morbidity due to the cerebral ischemia.

One of the major reasons for poor outcome in immunocompetent patients with IFMs is the delay in diagnosis. Several patients with primary intracranial IFMs in India are treated with empiric anti-tuberculous
therapy (ATT) on the basis of an imaging diagnosis.\[1,2\] This causes a delay of eight to 12 weeks in most patients as a repeat imaging is performed only after this interval and a possibility of a misdiagnosis recognized when the intracranial mass is not responding to ATT. Hydrocephalus due to a fungal infection can be misdiagnosed as being due to tuberculous meningitis and treated with empiric ATT after a VP shunt. Mehta et al.\[3\] reported such a patient in whom the diagnosis of a fungal meningitis was only made post-mortem. Finally, some of the mortality and morbidity in patients with IFMs is also attributable to the antifungal agents. Amphotericin B is notorious for causing renal and liver failure and has other serious side effects.

**Conclusions**

Intracranial fungal masses are uncommon lesions in most neurosurgical centers but are being increasingly diagnosed in not only immunocompromized but also immunocompetent patients especially in India. There should be a high index of suspicion for these lesions and whenever an inflammatory mass is encountered at surgery, the tissue from the intracranial mass should be subjected to fungal cultures in addition to cultures for bacteria. Stereotactic procedures might yield a good outcome in selected patients but whenever feasible safe radical excision of the IFM along with normal nervous tissue around it should be done. Medical therapy with antifungal agents is required for prolonged periods following surgery in patients with IFM. In spite of several advances in imaging and surgical techniques and the advent of some newer antifungal agents, the prognosis for patients with IFM continues to remain grim and mortality rates range between 40 and 90%. In immunocompromized patients with IFM the mortality rates are very high and the control of the underlying condition usually determines the outcome in these patients.

**References**

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