**Original Article**

**Intracranial Aspergillus Fungal Granuloma: Local Experience**

**Tariq Elemam Awad* and Khaled Elsayed Mohamed**

Department of Neurosurgery – Faculty of Medicine - Suez Canal University, Ismailia, Egypt

**ABSTRACT**

**Background:** Fungal infections of the brain are almost always a surprising finding. Their presentation is usually subtle, often without any diagnostic characteristics, and they are frequently mistaken for pyogenic abscesses, or brain tumors. Aspergillosis of the brain is an uncommon infection, mainly occurring in immunocompromised patients. **Objective:** The aim of this study was to present our local experience with eight consecutive patients with rare intracranial granuloma due to aspergillus fungus infection. **Patients and Methods:** The authors reviewed their clinic data archive from 2004 through 2016, and eight patients who harbored intracranial aspergillus fungal granuloma were enrolled. Patients' symptoms, radiographs, intraoperative findings, and clinical results were evaluated. All patients underwent surgical debridement. **Results:** There were four men and four women included in the study, with a mean age of 24 years (range 17–34 years). Headache, fever and symptoms of increased intracranial pressure were the predominant symptoms. Predisposing factors were diabetes in three patients and immunocompromise related to non-Hodgkin’s lymphoma in one patient. Location was primarily frontal with anterior cranial fossa involved in all cases. Six patients had parasinal sinus involvement. All the patients underwent craniotomy for resection. Mortality was in three patients (37.5%). **Conclusion:** Our small series highlights the clinical features of aspergillus fungal granuloma of the brain. Surgical debridement augments antifungal drugs by removal of necrotic debris.

**INTRODUCTION**

Aspergillosis is a fungal infection caused by fungi of the genus Aspergillus. Aspergillus fumigatus is the most common human pathogen in the Aspergillus genus, but Aspergillus flavus and Aspergillus niger are also frequently found.1 Aspergillus fungal spores are commensal in the respiratory tract and external auditory canal. The primary route of entry foraspergillosis pathogens is the respiratory tract. In the nervous system, this type of infection can be found in the cerebral parenchyma, the meninges or the vascular system.2,3

The central nervous system fungal infection with the Aspergillus species is a fatal infection that mainly involves immunocompromised patients.4 The most common presenting symptoms are nonspecific neurologic manifestations, including headache, cranial or somatic nerve weakness or paraesthesia, altered mental status, and seizures. Neutropenia, hematologic malignancies, autoimmune diseases, and bone marrow or solid organ transplantation were the most predominant predisposing conditions.5-6 In these cases, the primary focus of aspergillosis was the lung or parasanal sinus; however, in few cases, no obvious primary organ involvement was found.4,6-7 In patients with parasanal fungal infection, the disease originates in the nasal or sinus mucosa after inhalation of fungal spores, colonizes and extends to the nearby organs including orbit and brain. 7 In aggressive forms, the angioinvasive property of the fungi causes vascular thrombosis with extensive tissue necrosis.7,8 In patients with better immunity, chronic invasive granulomatous fungal sinusitis is developed.5-8

**PATIENTS AND METHODS**

A total of eight consecutive patients (four males and four females) with symptomatic intracranial fungal mass were surgically treated in Suez Canal University Hospital in the Neurosurgery Department between June 2004 and January 2016. The mean patient age was 24 years (range 17 to 34 years).

Only mass-forming lesions with pathologically proven fungal involvement were included. We followed only patients with proven CNS aspergillosis according to the criteria of the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) for deep tissue mold infections.11 These criteria divide patients into proven, probable, and possible cases according to symptoms, culture, and serologic criteria. To diagnose a proven deep tissue mold infection, EORTC/MSG criteria state that histopathologic or cytopathologic evidence of hyphae
from needle aspiration or biopsy specimen with evidence of associated tissue damage (either microscopically or unequivocally by imaging) is needed; otherwise, a positive culture result for a sample obtained by sterile procedure from a normally sterile and clinically or radiologically abnormal site consistent with infection, excluding urine and mucous membranes, is sufficient.

Patients were reviewed, with respect to the following: presenting features (including neurological deficits and features of raised intracranial pressure), predisposing factors, intracranial location of lesions, identification of organisms, involvement of paranasal sinuses, extension into intracranial cavity, and outcome after treatment. Diagnostic studies, including blood and urine cultures, plain x-rays of chest, skull, computed tomography (CT), and/or magnetic resonance imaging (MRI), were performed in all cases. All patients underwent surgical treatment with either biopsy or resection being performed; acquired specimens underwent both histopathologic and microbiological analyses.

After surgical treatment, all patients were treated with itraconazole and/or fluconazole. Follow-up varied from one month to four years and was largely contingent upon survival for patients. The literature on this topic available in PubMed was also reviewed.

RESULTS

A total of eight consecutive patients (four males and four females) with intracranial aspergillus fungal mass were surgically and medically treated in Suez Canal University Hospital in the Neurosurgery Department between 2004 and 2016. The mean patient age was 24 years (range 17 to 34 years). Patient characteristics and clinical findings are presented in Table 1 & 2.

Table 1: Patient characteristics and clinical findings in the study series

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Main Symptom</th>
<th>Duration of Symptoms</th>
<th>Predisposing factors</th>
<th>Surgical intervention</th>
<th>Follow Up (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22, F</td>
<td>headache, nasal obstruction, nausea</td>
<td>2m</td>
<td>Diabetes mellitus</td>
<td>2 nasal endoscopic approach, craniotomy, nasal endoscopy</td>
<td>4</td>
<td>Improving</td>
</tr>
<tr>
<td>2</td>
<td>19, M</td>
<td>headache, diplopia, vomiting, behavior changes</td>
<td>1m</td>
<td></td>
<td>Surgical excision</td>
<td>4</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>27, M</td>
<td>headache, fever, confusion</td>
<td>3m</td>
<td>Diabetes mellitus</td>
<td>Tapping then frontal lobectomy</td>
<td>6</td>
<td>Improving</td>
</tr>
<tr>
<td>4</td>
<td>17, F</td>
<td>headache, fever</td>
<td>2m</td>
<td>Diabetes mellitus</td>
<td>Surgical excision</td>
<td>48</td>
<td>Improving</td>
</tr>
<tr>
<td>5</td>
<td>34, M</td>
<td>headache, nasal obstruction, convulsions</td>
<td>3 m</td>
<td></td>
<td>Endoscopic nasal then craniotomy</td>
<td>12</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>25, F</td>
<td>headache, fever, decreased level of consciousness, convulsions</td>
<td>2m</td>
<td>Diabetes mellitus</td>
<td>Surgical excision</td>
<td>30</td>
<td>Improving</td>
</tr>
<tr>
<td>7</td>
<td>29, F</td>
<td>headache, fever</td>
<td>1m</td>
<td>Non-Hodgkin's lymphoma &amp; chemotherapy</td>
<td>Frontal lobectomy</td>
<td>1</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>19, M</td>
<td>headache</td>
<td>6m</td>
<td></td>
<td>Surgical excision</td>
<td>30</td>
<td>Improving</td>
</tr>
</tbody>
</table>

The clinical presentation of patients with brain Aspergillosis was variable and nonspecific. Headache was the predominant symptom, noted in all patients (100%). Fever was noted in four patients (50%). Other signs and symptoms included increased intracranial pressure in four patients (50%), nasal obstruction in four patients (50%), seizures in two patients (25%), and anosmia in two patients (25%).

Common signs included papilledema in four patients (50%), cranial neuropathy (I, III/IV/VI, and V in two, one, and two patients, respectively), hemiparesis in two patients, and meningismus in two patients. Predisposing factors were diabetes in three patients (37.5%), and immunocompromised related to non-Hodgkin's lymphoma in one patient. Radiologic imaging is useful for diagnosing brain aspergillosis; however, there were no unique characteristics that could differentiate an infection from other types of space-occupying lesions. Location was primarily frontal with...
anterior cranial fossa involved in all cases. Six patients had paranasal sinus involvement.

All the patients underwent craniotomy for resection, with two undergoing transnasal endoscopic biopsy. Histopathology revealed aspergilloma in all of our cases. Microbiological analysis of the specimen was positive in four (50%) patients. All patients were treated with itraconazole and/or fluconazole for six months. Mortality was in three patients (37.5%), most commonly due to meningoencephalitis. Poor neurologic status before surgery and severe brain edema with mass effect during surgery were associated with poor outcome (Figure 1 & 2).

Table 2: Clinical data in the study group

<table>
<thead>
<tr>
<th></th>
<th>No of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>24, range 17-34</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
</tr>
<tr>
<td>Male</td>
<td>4</td>
</tr>
<tr>
<td><strong>Symptoms and signs</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Symptoms of increased ICP</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Nasal blockage and discharge</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>papilledema</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Proptosis</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>3rd nerve palsy</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td><strong>Duration of symptoms</strong></td>
<td>1m – 6m</td>
</tr>
</tbody>
</table>

Fig. 1 a-d: Case No 1. 22 years old female patient presented with headache and nasal obstruction. a: preoperative contrasted CT showing left frontal mass. b: preoperative bone window CT showing left ethmoidal and frontal sinus involvement. c: preoperative MRI with gadolinium showing enhanced left frontal mass with ethmoidal sinus involvement and d: postoperative CT after mass excision.
Fig. 2 a-d: Case No 3. 27 years old male patient presented with fever, headache and confusion. a: preoperative contrasted CT showing right frontal mass. b & c: preoperative MRI T2, T1 of the right frontal granuloma with mass effect d: preoperative MRI with gadolinium showing enhanced right frontal mass.

DISCUSSION

The rarity of brain fungal infection, with nonspecific clinical picture, and progression to a fatal outcome provide considerable challenges for both diagnosis and management. In the large majority of the cases, paranasal fungal sinusitis and hematogenous dissemination from lung were the most common primary foci of infection; however, no obvious primary organ involvement was detected in few cases. Although the immunosuppression was the most common predisposing factor, there were a high number of reports on immunocompetent persons. In these cases, neurosurgical procedures might introduce fungus into the brain. In our series only one case of immunosuppression was evident due to Non-Hodgkin's lymphoma & chemotherapy.

The clinical presentation was variable. Headache was the predominant symptom, and after that focal neurological deficit, seizures, fever, and mental status changes were recorded. Radiologic imaging is in favor of space-occupying lesions, and in cases of fungal sinusitis, expansion of infection from the paranasal sinuses were detected. According to the criteria of the European Organization for Research and Treatment of Cancer/Mycoses Study Group for deep tissue mold infections, the patients were divided into proven, probable, and possible cases according to clinical symptoms, culture, and serologic findings. In proven cases, the histopathologic evidence of hyphae with tissue damage (either microscopically or by imaging) or a positive culture result from a normally sterile site is needed. In our series headache was the predominant symptom, noted in all patients (100%). Fever was noted in four patients (50%). Other signs and symptoms included increased intracranial pressure in four patients (50%), nasal obstruction in four patients (50%), seizures in two patients (25%), and anosmia in two patients (25%).

Kourkoumpetis and colleagues recently reported fourteen cases of brain aspergillosis. All patients were immunosuppressed. The lung (11 of 14) and paranasal sinus (2 of 14) were the primary foci of aspergillosis. In immunocompetent patients, the Aspergillus commonly causes a chronic noninvasive inflammation. An aggressive variant of the indolent form with invasion to the surrounding bony structures and tissue destruction has been reported in Turkey, Sudan, India, and the United States. In these reports, the sphenoid sinus represented the primary site for intracranial or orbital invasion.

Aspergillus is present in both air and soil and, after inhalation and entry to the respiratory system; it directly spreads from the nose to the sphenoid sinus. Gardeners and farmers have more chances for chronic inhalation of spores. Patients with occlusion of the natural ostia of sinuses and chronic hyperglycemia are more in
susceptible individuals. Three patients in our series got diabetes mellitus.

Cockrell et al. reported that there was a possible relationship between fungal granuloma and snuff abuse. They found twelve fungi and especially characterized as Aspergillus fumigatus, an organism that was frequently found in sinus fungal granulomas. Verweij et al. reported the possibility of fungal contamination of tobacco and marijuana with secondary risk for hypersensitivity and colonization of the respiratory system. In immunocompetent patients, inhalation and snuffing opium is considered a predisposing factor.

The rhino cerebral mycosis is usually associated with high-residual morbidity and mortality. The major causes were the insufficient delivery of antifungal drugs to the site of infection because of thrombotic blood vessel. And also because of the complex anatomy of the rhinoorbitocerebral regions, surgery is difficult.

Kourkoumpetis and colleagues suggested that patients who underwent the neurosurgical operation with mass resection had better survival than those who received only medical treatment. Therefore, early diagnosis and aggressive management in these patients are very important to reduce mortality. Our cases were managed with both surgical intervention for mass resection and after that received antifungal treatment.

The gold standard of systemic antifungal treatment is voriconazole, which has proven significantly superior to conventional amphotericin B and has led to a profound improvement of survival rates in patients with cerebral aspergillosis. Liposomal amphotericin B at standard dosages appears to be a suitable alternative for primary treatment, while caspofungin, amphotericin B lipid complex and posaconazole have given partial or complete cure in patients who are refractory to or intolerant of primary antifungal therapy. Combination therapies with two antifungal compounds could be a promising future strategy for first-line treatment. All patients in our series were treated with itraconazole and/or fluconazole for six months.

In summary, fungal granuloma should be considered in the differential diagnosis of brain mass, even in immunocompetent patients, and because of possible invasive behavior of aspergillosis, early diagnosis with surgery and medical treatment is important to prevent an unfavorable outcome.

CONCLUSION

Our small series highlights the clinical features of aspergillus fungal granuloma of the brain. Surgical debridement augments antifungal drugs by removal of necrotic debris.

Declaration

The author(s) declare no conflict of interest or any financial support and confirm the approval of the submitted article by the concerned ethical committee.

REFERENCES