Isolated Orbital Aspergillosis in Immunocompetent Patients: A Multicenter Study

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- **OBJECTIVE**: To report clinicopathologic features, radiologic findings, and treatment outcomes of isolated, orbital aspergillosis.
- **DESIGN**: Multicenter, retrospective case series.
- **METHODS**: Setting: Multicenter. Participants: There were 8 lesions in 8 eyes of 8 patients with isolated, orbital aspergillosis. Procedure: Review of medical records and histopathology slides. Main outcome measures: Disease control.
- **RESULTS**: Of 34 patients with orbital aspergillosis, 8 (23.5%) had isolated orbital involvement at presentation. The mean age at presentation was 34.5 years (median, 43 years; range, 0.5–72 years). Gradually progressive proptosis and eyelid swelling were the most common presenting features (each 4/8). Proptosis ranged from 4 mm to 9 mm (median, 5.5 mm; mean, 5.75 mm). Restriction of ocular motility was seen in all 8 patients. Other examination findings included palpable mass (2/8), conjunctival chemosis (2/8), hyperglobus (1/8), hypoglobus (1/8), and resistance to retropulsion (1/8). Microbial culture results were available in 1 patient and showed Aspergillus fumigatus. Two patients were treated with complete surgical excision alone while 6 were treated with antifungal medications. Complete resolution of proptosis and restoration of ocular motility were seen in all patients following treatment. Visual disturbances present in 1 were corrected following treatment. Recurrence was observed in 1 patient.
- **CONCLUSION**: Isolated orbital aspergillosis, though rare, should be considered in the differential diagnosis of a patient presenting with a gradually progressive orbital mass, especially in Asian individuals. Early recognition will help reduce the morbidity and mortality associated with this disease. (Am J Ophthalmol 2016;165:125–132. © 2016 Elsevier Inc. All rights reserved.)

Aspergillosis is a multifaceted disease caused by fungi of the genus Aspergillus. Aspergillus spp. are ubiquitous, spore-forming, dichotomously branching fungi often found in dampened soil, humid areas, agricultural environments, and decaying or decomposing matter. The spectrum of aspergillosis is wide, ranging from mere colonization (Aspergilloma) to disseminated infection. Aspergillus spores are commensals of the respiratory tract and external auditory canal. Understandably, the lungs and paranasal sinuses are the most commonly affected sites in human beings. Orbital involvement is uncommon and often a result of contiguous spread from the oropharynx or paranasal sinuses. Isolated orbital aspergillosis is extremely rare. Equally rare is its occurrence in immunocompetent, otherwise healthy individuals. We report on 8 cases of isolated, orbital aspergillosis in immunocompetent patients and also review the literature on this disease.

**MATERIALS AND METHODS**

This was a retrospective, clinicopathologic study of 8 consecutive patients with isolated orbital aspergillosis treated at 6 centers; 5 of these were in India (Centre For Sight, Hyderabad, Delhi, and Jaipur, Vasan Eye Care Hospitals and Drishti Eye Care, Hyderabad) and 1 in Singapore (National University Health System, Singapore). This study was approved by the Institutional Review Board of each of the aforementioned institutes and was performed in accordance with the tenets of the 1964 Declaration of Helsinki. Informed consent was obtained from the patients. A retrospective chart review of all histopathologically or microbiologically proven cases of orbital aspergillosis was performed. Only those patients who had isolated orbital involvement at presentation and fungal elements with characteristics of aspergillosis on histopathologic examination of the orbital biopsy were included in the study. Exclusion criteria included incomplete data, unavailability of tissue material for histopathologic review, and follow-up less than 3 months. No cases were excluded. Patient folders were analyzed for demographic details, clinical features, imaging findings, treatment, and outcome. Patient survival with complete resolution of the lesion at 3 month follow-up was considered as treatment success. Histopathology slides were reviewed in all cases.
RESULTS

THIRTY-FOUR PATIENTS HAD HISTOLOGICALLY OR MICROBIOLOGICALLY PROVEN ORBITAL ASPERGILLOSIS AT THE 6 CENTERS IN THE PAST 33 MONTHS (JANUARY 2013 TO SEPTEMBER 2015). OF THESE, 8 (23.5%) HAD AN ISOLATED ORBITAL INVOLVEMENT AT PRESENTATION.

• CLINICAL FEATURES: Demographic details, clinical features, and imaging findings of all 8 patients with isolated orbital aspergillosis are shown in the Table. Common clinical and radiologic features are shown in Figures 1–3.

Mean age at the time of first presentation to the clinic was 34.5 years (median, 43 years; range, 6 months to 72 years). One patient presented during infancy. No sex predilection was observed. There were 4 male and 4 female patients. Six patients were of Indian origin; 1 was a Myanmarese, and 1 was from the Middle East, both residing in Singapore for a considerable period. Orbital involvement was unilateral in all patients (8/8) with no predilection for any side (right, 4/8; left, 4/8). The mean duration of symptoms was 5.7 months (median, 3.5 months; range, 0.5–18 months). Gradually increasing proptosis (Figure 1, Top left, and Figure 2, Top left) and eyelid fullness (Figure 2, Middle left and Bottom left, and Figure 3, Top left) each occurred in 4 of 8 patients. Other symptoms included mass (2/8), diplopia (2/8), and intermittent and transient blurring of vision (1/8).

Proptosis ranged from 4 to 9 mm (median, 5.5 mm; mean, 5.75 mm). While variable degree (mild to severe) of ocular movement restriction (Figure 1, Middle and Bottom panels) was seen in all patients, a nontender, nonreducible, and noncompressible mass (Figure 3, Top left) was palpable in 2 patients (Cases 1 and 4). Visual acuity, colored vision, and papillary reactions (both direct and consensual) were normal in all patients. Fungal granuloma was suspected in only 1 patient (Case 7) at the time of clinical examination. Differential diagnoses on clinical examination included idiopathic orbital inflammation (5/8), ocular adnexal lymphoma (3/8), rhabdomyosarcoma (1/8), and lacrimal gland tumor (1/7). Intraoperatively, the mass was firm to gritty in all cases.

• IMAGING FEATURES: Computed tomography (CT) and magnetic resonance imaging (MRI) were performed in 6 and 2 patients, respectively. CT scan showed an ill-defined, infiltrative, homogenous, and hyperdense mass limited to the orbit in 4 patients (Cases 1, 6, 7, and 8) and was well-defined, homogenous, and hyperdense in 2 (Cases 2 and 4). MRI in 2 patients (Cases 3 and 5) showed the mass to be isointense to the extraocular muscle on T1-weighted images and hypointense to the muscle on T2-weighted images. Contrast enhancement was mild to moderate and patchy in 7 patients (Cases 1, 2, and 4–8). In the infant (Case 3), a diffuse, intense, and homogenous enhancement with gadolinium was observed. The mass was extraconal in 6 (Cases 1–5 and 8) and both intra- and extraconal in 2 (Cases 6 and 7). In 3 patients (Cases 6, 7, and 8), the disease extended posteriorly to involve the apex (Figure 2, Top right). Bone remodeling secondary to pressure effect (Figure 2, Middle right) was seen in 3 patients (Cases 1, 6, and 8). In 1 patient (Case 6), the mass was inseparable from the medial rectus and closely approximated to the optic nerve (Figure 2, Top right). The paranasal sinuses and nasal cavity were normal in all.

• HISTOPATHOLOGIC AND MICROBIOLOGIC FINDINGS: An incision biopsy was performed in 5 patients (Cases 1 and 5–8), complete excision in 2 (Cases 2 and 4), and debulking in 1 (Case 3). Light microscopy, in all cases, showed noncaseating, epithelioid cell granulomas with multinucleate giant cells and lymphoplasmacytic infiltrate in a densely fibrotic stroma (Figure 4, Top panel). Thin-walled, septate fungal hyphae that were relatively uniform in size and branching dichotomously at 45 degrees were identified in all (Figure 4, Bottom panel). These were characteristic of Aspergillus and stained positively with Gomori methanamine silver (Figure 4, Bottom left) and periodic acid–Schiff stains (Figure 4, Bottom right). Variable numbers of eosinophils were present in all patients. A fungal etiology was suspected in only 1 case (Case 7) on clinical examination. The tissue in this case grew Aspergillus fumigatus on Sabouraud dextrose agar. In the remaining 7, fungal granuloma not being an initial suspicion, tissue was not preserved for microbiologic examination.

Complete blood count was normal and human immunodeficiency virus (HIV) serology negative in all patients.

• TREATMENT AND OUTCOME: Six patients were treated with antifungal drugs (Table): 2 of these (Cases 1 and 7) with oral itraconazole, 1 (Case 3) with a combination of intravenous (IV) amphotericin B and voriconazole followed by oral voriconazole, and 3 (Cases 5, 6, and 8) with a combination of IV and oral voriconazole. Two patients (Cases 2 and 4) underwent a complete excision of the mass and had no systemic lesion, as a result of which they did not receive any further treatment. Post-treatment, a complete resolution of proptosis and restoration of ocular motility was observed in all. Visual disturbances observed in 1 (Case 5) were also corrected after completion of treatment. Follow-up duration ranged from 6 to 28 months (mean, 12.5 months). One patient (Case 1) developed recurrence 6 months after surgery, this time with involvement of the ethmoid sinus, and was lost to follow-up before any further treatment could be initiated. The remaining 7 patients were disease-free at the time of last follow-up.

DISCUSSION

ASPERGILLUS SPP. BELONG TO THE ASCOMYCETE moulds and, together with penicillium, form the family
TABLE. Clinical Features in Patients With Isolated Orbital Aspergillosis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Laterality</th>
<th>Duration of Symptoms (mo)</th>
<th>Presenting Features</th>
<th>Examination Findings</th>
<th>Primary Management</th>
<th>Medical Management</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>Male</td>
<td>Left</td>
<td>2</td>
<td>Lower eyelid swelling</td>
<td>Hypoglobus mass, proptosis, ROM (vertical gaze)</td>
<td>Incision biopsy</td>
<td>Itraconazole (200 mg BD orally for 3 months)</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>Female</td>
<td>Right</td>
<td>3</td>
<td>Upper eyelid swelling</td>
<td>ROM (vertical gaze), erythema and tenderness of upper eyelid</td>
<td>Complete excision</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>Male</td>
<td>Right</td>
<td>0.5</td>
<td>Upper and lower eyelid swelling</td>
<td>ROM (all gazes), hyperglobus, chemosis</td>
<td>Incision biopsy</td>
<td>IV amphotericin B (0.25 mg/kg for 3 weeks) followed by voriconazole (50 mg BD orally for 6 weeks)</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>Female</td>
<td>Right</td>
<td>6</td>
<td>Lower eyelid swelling, anterior orbital mass, diplopia</td>
<td>ROM (vertical gaze); firm, noncompressible mass</td>
<td>Complete excision</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>Female</td>
<td>Left</td>
<td>4</td>
<td>Gradually progressive proptosis, transient blurring of vision</td>
<td>ROM (vertical gaze), proptosis, resistance to retropulsion</td>
<td>Incision biopsy</td>
<td>Voriconazole (4 mg/kg IV for 6 weeks followed by 200 mg orally for 3 months)</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>42</td>
<td>Male</td>
<td>Left</td>
<td>18</td>
<td>Gradually progressive proptosis, diplopia, ptosis</td>
<td>ROM (all gazes), proptosis</td>
<td>Incision biopsy</td>
<td>Voriconazole (oral; 400 mg BD for 3 days followed by bolus 400 mg IV and then 200 mg orally BD for 6 months)</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>Female</td>
<td>Right</td>
<td>9</td>
<td>Gradually progressive proptosis</td>
<td>ROM (all gazes), chemosis, proptosis, periocular swelling</td>
<td>Incision biopsy</td>
<td>Itraconazole (200 mg TID for 3 days followed by 200 mg BD for 2 months)</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>45</td>
<td>Male</td>
<td>Left</td>
<td>3</td>
<td>Gradually progressive proptosis</td>
<td>ROM (all gazes), proptosis</td>
<td>Incision biopsy</td>
<td>Voriconazole (200 mg TID for 3 days followed by 200 mg BD for 2 months)</td>
<td>No</td>
</tr>
</tbody>
</table>

BD = twice daily; IV = intravenous; ROM = restricted ocular motility; TID = thrice daily.
Aspergillaceae. Although Aspergillus fumigatus is the most common pathogen in this genus to affect human beings, A niger, A flavus, and A oxyzae may also be seen. The first mention of aspergillosis as an opportunistic infection dates back to 1953. Row-Jones and Moore-Gillon, in 1994, classified aspergillosis into 3 types: (1) noninvasive, either an aspergilloma or allergic type; (2) destructive, noninvasive; and (3) invasive. While the noninvasive form may cause local tissue destruction including mucosal or bony destruction, it does not cause tissue invasion or necrosis. The invasive form is often aggressive and associated with high morbidity and mortality. It may result in invasion of adjacent tissues, necrosis, vascular invasion, or thrombosis. This form, although common in immunocompromised patients, may be seen in healthy individuals as well. Predisposing factors include neutrophil disorders, corticosteroid usage, HIV infection, diabetes mellitus, organ transplants, trauma, use of prosthetic devices, and advanced age. All patients in this study were otherwise immunocompetent, healthy individuals at the time of diagnosis. None were exposed to drugs or had diseases that compromise immunity.

Orbital aspergillosis is uncommon worldwide. It is considered to be endemic in Sudan. Interestingly, a significantly large number of reports come from India. Secondary involvement of the orbit may be a result of contiguous spread from the paranasal sinuses or central nervous system or as a sequela of a disseminated systemic disease. A concomitant sinus disease is present in 60%–90% of patients. Primary orbital aspergillosis is rare, and it may remain localized or at times extend to involve adjacent tissues such as infratemporal fossa and cheek. In all our patients, the disease remained localized to the orbit. This could possibly be a result of spread of a latent, subclinical focus of infection in the sinuses through the fissures, which later, by itself, was cleared owing to the aeration process.

Orbital aspergillosis is generally considered as a disease of the elderly age group (mean 62.48 years). However, Indian patients are affected at a significantly younger age.
Two of the previously largest series on orbital aspergillosis in the Indian population have reported a mean age of 36.8 years at the time of first presentation. Our study (mean age: 34.5 years) had similar observations. As explained by Pushkar and associates, this difference may be a result of climatic conditions in India, which are conducive to fungal growth, or occupation-related (agriculture and construction) exposure of younger individuals to these pathogens. Six patients (Cases 1–3 and 6–8) in this study were from India, a dust-polluted region. However, none had any specific occupation-related exposure. Only 2 cases of orbital aspergillosis have been previously reported in infants. Ours was the third such case.

Clinical presentation in orbital aspergillosis is nonspecific and may mimic several non-neoplastic and neoplastic conditions. Idiopathic orbital inflammation and ocular adnexal lymphoma are the commonest clinical suspicions. As it is a chronic disease, patients tend to present late in the disease, often with a gradually progressive proptosis. Our results were in concordance with these observations. Orbital involvement is usually unilateral but may be bilateral. All our patients had a unilateral orbital involvement. A variable amount of ocular motility restriction is seen in these patients. Visual disturbances, sometimes to the extent of visual loss, are not uncommon and may be a result of inappropriate management, aggressive disease with sinus involvement, or compression of optic nerve. Blood culture is almost always negative in patients with invasive aspergillosis. Imaging features, similar to clinical ones, are not always helpful and need careful assessment of the paranasal sinuses, whose involvement may help suspect fungal infection in such patients. Sivak-Callcott and associates suggest assessment of sphenoid sinus on MRI scans to be particularly helpful. Presence of calcifications on CT scan, especially when their density is >2000 Hounsfield units, is suggestive of aspergillosis. Although fine-needle aspiration cytology has been used for the diagnosis of these lesions, its...
role remains unclear. Biopsy is necessary for diagnosis. Sivak-Callcott and associates suggest that biopsies be performed from hypodense areas to improve efficacy and accuracy. However, the organisms may be harbored deep in the mass, rendering the initial superficial biopsy noncontributory. A second, deeper biopsy is required in such cases.
There exist instances where the diagnosis was missed at the time of biopsy only to be picked up on autopsy. \textsuperscript{25,26} Suspicion at the time of initial clinical and radiologic examination helps to plan microbiologic examination of these lesions. A positive culture result may obviate a repeat biopsy. \textit{Aspergillus fumigatus} is the commonest pathogen encountered, followed by \textit{A. fumigatus}.\textsuperscript{3,10,11} \textit{Aspergillus} terrigas is rarely encountered.\textsuperscript{27} In our study, a culture result was available in only 1 case; it grew \textit{A. fumigatus} on Sabouraud dextrose agar.

The mortality associated with invasive aspergillosis remains high but has greatly reduced in the past 2 decades. No definite treatment protocols exist for orbital aspergillosis. Complete surgical debridement is advocated as the primary treatment in patients with orbital aspergillosis. However, involvement of bone, blood vessels, and other vital orbital structures limit this approach. In our study, all patients with an ill-defined and/or extensive disease were subjected to an incision biopsy, while those with a well-defined lesion (except the patient in Case 1, who preferred an incision biopsy) underwent complete excision. An extensive disease may at times necessitate exenteration, especially in those with apical and retrobulbar involvement\textsuperscript{13-18}; however, it does not guarantee eradication of the disease process. Although 2 of our patients had apical involvement, none underwent exenteration. They continue to be disease-free after treatment with antifungal medication. While some authors choose to treat patients medically even after complete excision of the lesions, others report complete surgical excision to suffice and yield favorable clinical outcomes.\textsuperscript{10,11} Two patients in our study were treated with surgical excision alone and continue to be disease-free. Amphotericin B (0.5 mg/kg/day) used to be the preferred drug for orbital aspergillosis.\textsuperscript{10,28} However, its use is limited because of the associated complications, such as nephrotoxicity. Voriconazole and posaconazole have now replaced amphotericin B. A large clinical trial showed voriconazole to have a better response rate and higher survival.\textsuperscript{28} Voriconazole has been successfully used in patients with orbital aspergillosis\textsuperscript{10,11,29} Three patients in our study were successfully treated with voriconazole.

To conclude, orbital involvement in aspergillosis usually occurs in association with a sinonasal disease. Its diagnosis relies heavily on the clinical circumstances of the infection and microscopic findings. A careful radiologic evaluation of sinus involvement will help suspect this disease. Isolated orbital aspergillosis is extremely rare, often with misleading presentations. Yet, it should be considered in the differential diagnosis of all patients presenting with gradually progressive orbital mass. Early recognition is of utmost importance to reduce the morbidity and mortality associated with this disease.

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REFERENCES


