

Management of allergic fungal sinusitis with intracranial spread

Mubasher Ikram · Shabbir Akhtar ·
Shehzad Ghaffar · Syed Ather Enam

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Abstract Allergic fungal sinusitis (AFS) is a form of paranasal nasal disease if not managed early often involves bone destruction and extension into the orbit and anterior skull base. We present our study of patients with AFS with intracranial, extradural extension. This study includes our experience of 26 patients with the histological and immunological diagnosis of AFS based on findings of branching septate fungi interspersed with eosinophilic mucin and Charcot-Leyden crystals without fungal invasion of soft tissue, with intracranial extension. All had erosion of bone, which was observed on computerized tomography (CT) scans, extending intracranially and eight had disease that additionally involved the lamina papyracea. The average age of patients in this study was 25 years (range 9–46). There were 20 male and 6 female patients. All patients were immunocompetent. Skin test against aspergillin showed all patients had Type 1 hypersensitivity. All patients underwent transnasal and/or transmaxillary endoscopic approaches for debridement and eight underwent orbital decompression. No patient underwent craniotomy for removal of intracranial extradural disease. No patient had a cerebrospinal fluid leak. Postoperatively, all 26 were treated with a course of corticosteroids. The follow-up period ranged from 2 to 5 years. We conclude AFS is a unique form of fungal disease that might mimic anterior

skull base and paranasal sinus tumors. Most cases can be successfully managed with transnasal and/or transmaxillary endoscopic techniques.

Keywords Allergic fungal sinusitis · Intracranial · Intraorbital

Introduction

Allergic fungal sinusitis (AFS) is a disease of the nose and paranasal sinuses, characterized by immune hypersensitivity reaction to fungal antigens that produce allergic mucin, which accumulates within paranasal sinuses.

AFS was first described in the early 1980s by Miller et al. [1] in UK and by Katzenstein et al. [2] in USA. Members of the family of dematiaceous fungi and *Aspergillus* are responsible for most of the cases of this disease [3, 4]. Typically, patients are young and immune competent, with history of atopic disease. The disease starts with inhalation of fungal spores to which patient is allergic, the sinonasal mucosa produces copious amount of secretions (mucin), the mucociliary clearance of the nose fails to remove the spore, and then the fungal spore germinates in the mucin and continues to provide an antigenic stimulus. Polyps and hyperplastic mucosa forms as a result of the inflammatory stimulus. The diagnostic criteria for AFS includes presence of nasal polyposis, atopy to fungi, characteristic findings on CT/MRI and distinctive histopathologic picture, in which fungal hyphae are found in eosinophilic mucin, without evidence of tissue invasion [5, 6]. Schubert [7] proposed that for diagnosis of AFS, the allergic mucin must be positive for fungal hyphae, or fungal cultures must be positive in properly obtained surgical sinus content. Over time the mucin mass if not treated, expands and can potentially

M. Ikram · S. Akhtar (✉) · S. Ghaffar
Department of Otolaryngology Head and Neck Surgery,
Aga Khan University Hospital, Stadium Road,
PO Box 3500, Karachi 74800, Pakistan
e-mail: shabbir.akhtar@aku.edu

S. A. Enam
Department of Neurosurgery,
Aga Khan University Hospital, Karachi, Pakistan

cause pressure necrosis of bone. It then extends into intracranial or intraorbital cavities, often mimicking malignant skull base tumors. AFS may be easily mistaken for malignancy or invasive fungal disease, which could potentially lead to its overtly aggressive treatment [8].

The initial management of AFS is surgery [5, 8], post-operatively the use of steroids has also been recommended and practiced by different centers worldwide [9]. This recommendation is based on experience of managing allergic bronchopulmonary aspergillosis [8].

The mucin and polypoidal debris of AFS with intracranial extension because of its noninvasive nature can be surgically removed while leaving the mucosal lining intact, obviating radical resection or potentially toxic antifungal therapy.

We report our experience of management of patients with extensive AFS with intracranial, extradural spread, who had transnasal endoscopic surgery and were given post-operative oral and topical steroids.

Material and methods

A retrospective analysis was performed on patients who underwent removal of pathologically verified AFS. In this study, we have only included those patients who had intracranial spread of the disease. Out of 224 cases only 26 patients fulfilled our criteria. The histological diagnosis was based on evidence of branching septate fungi interspersed with eosinophilic mucin and Charcot-Leyden crystals without soft tissue fungal invasion of soft tissue. Patient charts, operative reports, pathology reports, microbiological studies, and radiographs were reviewed. On CT imaging studies, the lesions were classified as having paranasal sinus, intracranial, and/or intraorbital extension.

In all patients, an intradermal skin test was performed using 0.1 ml of antigen (1,000 protein nitrogen units/ml aspergillin; Hollister Stier, Spokane, Washington DC). The same volume of sterile phosphate-buffered saline (pH, 7.2) was injected intradermally on the other arm to serve as a control. Type 1 (erythema and wheal of any size within 1 h) hypersensitivity reaction was considered positive only when there was no reaction in the control arm.

Pre-operative neurosurgical opinion was obtained. All the patients were treated by otolaryngologists using minimally invasive transnasal endoscopic resections except in two patients, who also underwent direct transmaxillary (Caldwell-Luc) resection performed through a sub-labial maxillotomy along with endoscopic resection. None of the patients had to undergo a traditional craniofacial resection (bifrontal craniotomy combined with a Weber-Fergusson transfacial approach).

Results

Clinical characteristics of the patients are listed in Table 1. The mean age of the patients at presentation was 25 years (range 9–46 years). There were 20 male and 6 female patients. The most common presentation of the disease was sinusitis, which was associated with nasal polyps, obstruction and/or proptosis.

A skin test against aspergillin antigen was performed on all 26 patients, and type 1 hypersensitivity was found positive in all. On CT imaging studies, all patients were found to have fungal disease in their paranasal sinuses (Figs. 1 and 2). In all patients the disease had intracranial extension and in 8, it also extended intra-orbitally as well. All intracranial fungal diseases were entirely extradural without evidence of dural invasion.

All patients underwent transnasal debridement of fungal debris without the need for a craniotomy. The transnasal procedure was performed either using an endoscopic or transmaxillary approach. In 24 patients, minimally invasive transnasal endoscopic resections were adequate enough to clear the disease while in 2 patients who had pathology at endoscopically inaccessible sites additional external procedures were done to remove the disease. In those patients in whom the disease extended into the orbits resulting in proptosis, orbital decompression was done through a transnasal approach. In all of these patients, the intracranial and intra-orbital disease was adequately cleared with this approach and none of the patients had any post-operative CSF leaks.

All intraoperative fungal specimens were sent for microbiological analysis. The most common organism identified in the cultured was from the genus *Aspergillus*. All these patients received post-operative oral steroid therapy for 1 month (0.5 mg/kg). All patients remained disease free for a period of up to 5 years (range 2–5 years).

Illustrative cases

Case 1

A 30-year-old man was presented with chronic sinusitis, headache, nasal congestion, and proptosis of both the eyes. On physical examination, the patient had obvious proptosis of both eyes. His visual acuity and fields were intact. Motor and sensory examinations yielded normal findings. Computerized tomography images revealed polypoid tissue in the nasal cavity and extensive fungal pan sinusitis with bone erosion through the anterior skull base and both the orbits (Fig. 1).

The fungal debris was entirely extradural, it was brown and appeared cheese like. An endoscopic transnasal approach was used to remove nasal polyps and fungal

Table 1 Surgical treatment of 26 patients with AFS

Case No.	Age (years), Sex	Presentation	Location	Type of surgery	Followup (years)
1	20, M	Sinusitis, polyps, proptosis	PNS,IC,IO	Endoscopic/transnasal	2
2	24, M	Sinusitis, nasal obstruction, polyps, proptosis	PNS,IC,	Endoscopic/transnasal	2
3	37, M	Sinusitis, nasal obstruction, polyps	PNS,IC,	Endoscopic/transnasal	2
4	42, M	Sinusitis, nasal obstruction, polyps	PNS,IC,IO	Endoscopic/transnasal	2
5	46, F	Sinusitis, nasal obstruction, polyps	PNS,IC	Endoscopic/transnasal	2.5
6	25, M	Sinusitis, nasal obstruction, polyps	PNS,IC	Endoscopic/transnasal	3
7	31, F	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	3
8	16, M	Sinusitis, proptosis	PNS,IO/IC	Endoscopic/transnasal	3
9	24, F	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	3
10	36, M	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	3
11	19, M	Sinusitis, polyps	PNS,IC,IO	Endoscopic/transnasal	3
12	32, F	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	3.5
13	9, M	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	3.5
14	10, F	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	4
15	22, M	Sinusitis, polyps, proptosis	PNS,IC,IO	Endoscopic/transnasal	4
16	26, M	Sinusitis, nasal, obstruction, proptosis	PNS,IC,IO	Endoscopic/transnasal	4
17	16, M	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	4
18	36, M	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	4
19	18, F	Sinusitis, polyps	PNS,IC,IO	Endoscopic/transnasal	5
20	29, M	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	5
21	34, M	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	5
22	40, M	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	5
23	26, M	Sinusitis, polyps	PNS,IC,IO	Endoscopic/transnasal	5
24	34, M	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal	5
25	26, M	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal CWL/Exp.thmoid	5
26	41, M	Sinusitis, polyps	PNS,IC	Endoscopic/transnasal CWL/Exp.thmoid	5

PNS paranasal sinus; IC intra-cranial; IO intraorbital

material from all the paranasal sinuses. The sinuses were copiously irrigated. The orbital lateral walls were decompressed to relieve the proptosis. There was no evidence of dural invasion or CSF leak.

The pathological specimen revealed AFS and microbiological cultures displayed growth of *Aspergillus* species. The patient was discharged on post-operative day 2 and was given a course of systemic corticosteroids. He has not shown any evidence of disease recurrence at 2 years followup after surgery.

Case 2

A 25-year-old man was presented with chronic sinusitis, nasal polyposis, and nasal obstruction. His neurological

examination yielded normal findings. CT scan revealed a soft tissue mass in the paranasal sinuses with extension into the anterior cranial fossa due erosion of the posterior wall of frontal sinus (Fig. 2).

The patient underwent a transnasal endoscopic approach to remove the allergic fungal mucin. The fungal mass had eroded the posterior wall of frontal sinus. Because of the bony remodeling secondary to this disease, frontal sinus opening was already wide and was readily accessible from the transnasal endoscopic approach and a craniotomy was avoided. The lesion was also entirely extradural and there was no evidence of a dural invasion or a CSF leak.

The pathological examination demonstrated AFS and microbiological cultures exhibited growth of *Aspergillus* species. Patient was discharged on post-operative day 1 and



Fig. 1 Computerized tomographic image Case 1



Fig. 2 Computerized tomographic image Case 2

was given a course of systemic corticosteroids. Subsequent followups revealed well-healed mucous membranes of the ethmoid and frontal sinuses. The patient remained disease free at his last follow-up which was 3 years after the surgery.

Discussion

Allergic *Aspergillus*-induced sinusitis was first described in 1983 by Katzenstein et al. [2, 10]. They reported a series of immunocompetent patients who harbored a noninvasive fungal sinusitis that was histologically identical to allergic bronchopulmonary aspergillosis. The condition was initially thought to be an allergic reaction to *Aspergillus*, but since then other causative fungal species have been identified. Thus, the disease is now referred to as AFS [11]. AFS is the most recently described and the most common form

of fungal sinusitis. In our series, all patients were immunocompetent and there was no histological evidence of tissue invasion. It is imperative to differentiate AFS from invasive forms of fungal sinusitis because allergic disease does not need to be treated with radical craniofacial surgery or potentially toxic antifungal medications [8].

Allergic fungal sinusitis most commonly affects adolescents and young adults [13–16]. The mean age in our series was 25 years. Patients typically present with nasal obstruction and chronic allergic rhino sinusitis that has been refractory to medical management and to multiple sinus surgeries. They may also have a history of asthma, atopic disease, or nasal polyposis. In 90% of patients there are elevated levels of an IgE specific to one or more fungal antigens [17]. When the lesions become extensive, they occupy the entire paranasal sinuses and erode through the anterior skull base and lamina papyracea, mimicking malignant sinonasal tumors [8, 18]. Intracranial and orbital extension can produce headache, frontal lobe compression, facial deformity, diplopia, proptosis, and/or visual loss [11, 16, 18–22]. In the present series, in all patients the disease displayed intracranial extension and 8 had the disease extension intraorbitally. Proptosis was present in 5 of the 8 patients in whom there was intraorbital extension of the disease. Our patients had a higher rate of intracranial and intraorbital extension of disease then reported in literature. The high incidence could be attributed to late presentation. AFS should be suspected in any immunocompetent patient who has chronic sinusitis that is refractory to medical management. If proptosis is present, AFS should be considered in the differential diagnosis [11]. The diagnostic criteria of AFS include type 1 (IgE-mediated) hypersensitivity, nasal polyposis, characteristic neuroimaging findings, and histological data demonstrating characteristic allergic mucin with fungus but without tissue invasion [23–25]. All patients in our series demonstrated histologically confirmed fungus and culture-positive AFS.

Although the exact pathogenesis of AFS remains unknown, it has been characterized as similar to the pathogenesis of allergic bronchopulmonary aspergillosis [4, 8, 25]. It is postulated that ubiquitous fungi become deposited in the sinus and produce type I (IgE)- and type II (immune complex)- mediated reactions that trigger an intense eosinophilic inflammatory response. The inflammation leads to sinus obstruction and subsequent stasis and inspissations of allergic mucin. This environment is ideal for proliferation of the fungus, which promotes further antigenic exposure and a host response, producing nasal obstruction and allergic mucin. This result in a vicious cycle of increased sinus mucosal inflammation with drainage obstruction, reduced ventilation, and further increased antigen contact. As the “fungocele” expands with time, bone erosion can lead to intracranial or intraorbital extension without tissue invasion

[17]. Initially, *Aspergillus* species was presumed to be only the suspected organism because of its morphologic similarities on histological examination [10]. It is now known, however, that the Dematiaceae family of fungi, including the genera of *Bipolaris*, *Curvularia*, *Exserohilum*, *Alternaria*, *Fusarium*, *Helminthosporium*, and *Drechslera*, are more commonly associated with AFS [8, 17, 20, 25]. Certain geographic locations have been implicated in the incidence of AFS [12, 26]. The majority of reported cases of AFS have been in temperate regions with relatively high humidity, such as the southeastern portion of the US and the Mississippi basin.

The imaging findings of AFS are well recognized. CT scans commonly demonstrate irregular hyperdense expansible masses involving multiple sinuses (Figs. 1 and 2) [27]. With the expansible nature of the accumulating allergic mucin, bone erosion through the anterior skull base and orbital walls can sometimes mimic malignant paranasal sinus tumors [20, 28, 29]. Although the appearance of this intracranial or intraorbital extension can be quite remarkable, there is usually no histological evidence of tissue invasion. The fungal elements can also act as a foreign body to induce precipitation of calcium salts, giving the lesion a heterogeneous appearance.

On gross examination, the allergic fungal mucin is brown or dark green and often appears thick and caseous. Fungal hyphae are present within the allergic mucin and along with degenerated inflammatory cells, lamellated aggregates of eosinophils, calcifications, and Charcot–Leyden crystals. The hyphae are characterized by septae and acute angle branching.

Successful treatment of AFS requires complete removal of all fungal antigens and a course of systemic corticosteroids for long-term prevention of disease recurrence [17, 30]. Surgery also achieves adequate drainage and ventilation of the sinuses. It is important to remember that although on images AFS can exhibit dramatic bone erosion through adjacent anatomical spaces, it is not an invasive fungal disease. In the past, patients were unnecessarily treated with aggressive lateral rhinotomies, facial-degloving approaches, Weber–Fergusson transfacial approaches, and extensive mucosal exenteration. The salient features that can differentiate AFS from invasive fungal infections include type 1 (IgE-mediated) hypersensitivity and nasal polyposis. The characteristic neuroimaging findings, such as computerized tomography demonstrates irregular hyperdense expansible masses involving multiple sinuses and in addition fungal elements can also act as a foreign body to induce precipitation of substance like calcium and magnesium salts, which form radio opaque shadows on scan giving the lesion a heterogeneous appearance. AFS can also be differentiated from invasive fungus by the presence of edema in brain parenchyma in invasive fungal disease iden-

tified on MRI and the presence of mucin and fungal material at surgery. Finally, confirmation is on histological picture demonstrating characteristic allergic mucin with presence of fungus but without tissue invasion.

Because AFS is a noninvasive disease, the allergic fungal mucin occupying the sinus cavity can be removed in a blunt fashion while leaving the mucosal lining intact. This can be achieved in most cases by performing minimally invasive endoscopic transnasal approaches. All the patients in this series were operated by transnasal endoscopic approach alone, while two patients also required transmaxillary open surgery, thus obviating the need for a craniotomy. A transnasal approach alone was feasible in our patients in whom there was intracranial disease because the disease was extradural and access to intracranial extension of the disease was facilitated by already eroded bone. The bone erosion into the intracranial cavity is usually large enough to provide adequate window to the anterior fossa of cranium for debridement. All the 8 patients with intraorbital disease were treated endoscopically. Although these lesions had eroded through the medial orbital wall they were accessible through the transnasal or transmaxillary routes.

Our strategy of surgical management allows successful debridement of allergic mucin and fungus without requiring disfiguring facial incisions or extensive facial osteotomies.

The concomitant use of systemic corticosteroid medications has been advocated as means of suppressing the immunological reaction to the persisting fungal antigen as well as a means of controlling the underlying allergic rhinitis [4, 8, 31–33]. The optimal dosing regimen and duration of therapy have yet to be determined. All the patients in our series received a course of corticosteroids postoperatively. There has been no case of disease recurrence after a followup ranging between 2 and 5 years. The postoperative administration of intranasal corticosteroids and nasal saline irrigations may also be beneficial [25, 31].

Long-term systemic or local antifungal therapies can produce toxic and deleterious side effects and is not recommended in the absence of histological evidence of tissue invasion [8, 11, 20].

We now routinely treat patients with a course of corticosteroids (oral/nasal). The use of immunotherapy to down-regulate the production of fungus specific IgE and to decrease the inflammatory response appears promising [33–35]. Postoperative recurrences usually appear after the patient has been weaned from corticosteroid therapy.

Conclusions

Allergic fungal sinusitis is a unique form of fungal disease that may mimic anterior skull base and paranasal sinus tumors. Although AFS can appear “invasive” on images,

there is no histological evidence of tissue invasion. A trans-nasal approach is recommended. Most cases can be successfully managed with minimally invasive endoscopic techniques, a craniotomy may be indicated if there is extensive intracranial involvement that is inaccessible from below.

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