Neurosurgical implications of allergic fungal sinusitis

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Object. Allergic fungal sinusitis (AFS) is a form of paranasal mycosis that often involves bone destruction and extension into the orbit and anterior skull base. Treatment consists of surgical extirpation and a course of corticosteroids. Despite frequent intracranial involvement, AFS is rarely reported in the neurosurgical literature.

Methods. The records of 21 patients with the histological diagnosis of AFS were reviewed. The histological diagnosis was based on findings of branching septated fungi interspersed with eosinophilic mucin and Charcot–Leyden crystals without fungal invasion of soft tissue.

The average age of the 21 patients in this study was 25 years (range 9–46) and the male/female ratio was 3.75:1. All patients were immunocompetent. All had a history of chronic sinusitis and imaging findings of expansile disease involving multiple sinuses. Fifteen patients had nasal polyposis, eight had erosion of bone, which was observed on computerized tomography (CT) scans, eight had disease extending intracranially, and six had disease that involved the lamina papyracea. All patients underwent transnasal and/or transmaxillary endoscopic approaches for debridement and irrigation, six underwent orbital decompression, and three underwent a bifrontal craniotomy for removal of intracranial extradural disease. No patient had a cerebrospinal fluid leak. Postoperatively, one patient was treated with amphotericin B and the other 20 were treated with a short course of corticosteroids. The follow-up period ranged from 2 to 19 years.

Conclusions. Allergic fungal sinusitis is a unique form of fungal disease that may mimic anterior skull base and paranasal sinus tumors. A cranial base team approach of neurosurgeons and otolaryngologists is recommended. Most cases can be successfully managed with transnasal and/or transmaxillary endoscopic techniques. A craniotomy is rarely indicated unless there is the suspicion of dural invasion or extensive intracranial and/or intraorbital involvement that is inaccessible from below.

Key Words • allergic fungal sinusitis • anterior skull base • endoscope • paranasal sinus

Allergic fungal sinusitis is a disease of the paranasal sinuses that is most commonly managed by otolaryngologists. Although there is still some debate regarding its exact pathogenesis, AFS is typically characterized by an immune hypersensitivity reaction to fungal antigens that produces allergic mucin, which accumulates within the paranasal sinuses. Over time the mucin mass expands and can potentially erode through bone into the intracranial or intraorbital cavities, often mimicking malignant skull base tumors. Neurosurgeons usually encounter patients with AFS at this stage of the disease. If not diagnosed properly, AFS may be easily mistaken for malignancy or invasive fungal disease, which could potentially lead to its overly aggressive treatment. Because AFS is a noninvasive disease, the allergic fungal mucin can be surgically removed while leaving the mucosal lining intact, obviating radical resection or potentially toxic antifungal therapy. We present our surgical experience of 21 patients with AFS. The clinical presentation of the disease as well as its pathogenesis, neuroimaging features, histopathological characteristics, and surgical management are reviewed.

Clinical Material and Methods

Patient Population

A retrospective analysis was performed in 21 patients who underwent resection of pathologically verified AFS. The histological diagnosis was based on evidence of branching septated fungi interspersed with eosinophilic mucin and Charcot–Leyden crystals without fungal invasion of soft tissue. Patient charts, operative reports, pathology reports, microbiological studies, and radiographs were reviewed. On neuroimaging studies, the lesions were classified as having paranasal sinus, intracranial, and/or intraorbital extension.

Surgical Management

The patients were treated by a multidisciplinary cranial base team composed of neurosurgeons and otolaryngologists. All patients underwent minimally invasive transnasal
endoscopic resections and some of them underwent direct transmaxillary (Caldwell–Luc) endoscopic resections. The transmaxillary approaches were performed through a sublabial maxillotomy. If indicated, a bifrontal transbasal approach was performed to remove intracranial and/or intraorbital disease. None of the patients underwent a traditional craniofacial resection (bifrontal craniotomy combined with a Weber–Fergusson transfacial approach). Among the patients in whom intracranial disease was removed, the anterior skull base was reconstructed with a vascularized pericranial flap and a fat and fascia lata graft. Temporary lumbar drainage was used in these cases.

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 15 male and six female patients. The most common presentation of the disease was sinusitis (100% of patients), which was associated with nasal polyps (76% of patients), nasal obstruction (29% of patients), and/or proptosis (24% of patients). On neuroimaging studies, all patients were found to have fungal disease in their paranasal sinuses (Figs. 1 and 2). In eight patients the disease extended intracranially and in six it extended intraorbitally. All intracranial fungal diseases were entirely extradural without evidence of dural invasion.

All patients underwent endoscopic resection of fungal debris, which was performed using a transnasal and/or a transmaxillary approach. Eighteen patients (86%) underwent endoscopic treatment alone without the need for a craniotomy. In five of these patients there was intracranial disease, which was adequately treated with an endoscopic resection. Three patients (14%) required an additional bifrontal craniotomy to remove intracranial and intraorbital disease, which was inaccessible from below. Two of these patients, in whom the disease involved the superior orbit resulting in proptosis, underwent orbital decompression through the transcranial approach (Fig. 1). Cranial base reconstruction was performed in the three patients who underwent a bifrontal craniotomy; this was accomplished using a fat and fascia lata graft supplemented by a vascularized pericranial flap. There were no postoperative CSF leaks.

All intraoperative fungal specimens were sent for microbiological analysis. The most common organism that was cultured was from the Bipolaris genus (57%) followed by those from the Dreschslera (14%) and Curvularia (10%) genera. In all patients there was an elevated serum level of IgE. Only one patient received antifungal therapy. All patients remained free from disease after a mean follow-up period of 9 years (range 2–19 years).

Illustrative Cases

Case 1

This 30-year-old man presented with chronic sinusitis,
headache, nasal congestion, and diplopia and proptosis of the right eye that had worsened during the previous 2 months. On physical examination, the patient had obvious diplopia and proptosis of the right eye. His visual acuity and visual fields were intact. Motor and sensory examinations yielded normal findings. Computerized tomography and MR images revealed polypoid tissue in the nasal cavity and extensive fungal pansinusitis with bone erosion through the anterior skull base and the right orbit (Fig. 1).

The patient underwent an endoscope-assisted craniofacial approach. First, a bifrontal transbasal craniotomy was performed to remove the intracranial portion of the mass. The fungal debris was entirely extradural; it was green and appeared cheeselike. The frontal sinuses were removed and cranialized, and the right orbital roof was decompressed to relieve the proptosis. From below, an endoscopic transnasal and bilateral transmaxillary (Caldwell–Luc) approach was used to remove nasal polyps and fungal material from all the paranasal sinuses. The sinuses were copiously irrigated and a pericranial flap was fashioned and sutured into the
base of the dura mater along the anterior skull base. There was no evidence of dural invasion or CSF leak. A lumbar drain placed at the time of operation was removed the next day.

The pathological specimen revealed AFS and microbiological cultures displayed growth of *Aspergillus* species. The patient was discharged on postoperative Day 4 and was given a short course of systemic corticosteroids. He has not shown any evidence of disease recurrence at 2 years after surgery. This case was briefly described in another publication.18

**Case 4**

This 42-year-old man presented with chronic sinusitis, nasal polyposis, and nasal obstruction. His neurological examination yielded normal findings. An endoscopic nasal examination revealed a greenish slime that raised suspicions for fungal debris. A CT scan revealed an expansile mass in the paranasal sinuses with extension into the frontal sinuses and erosion of the anterior skull base (Fig. 2).

The patient underwent a transnasal endoscopic approach to remove the allergic fungal mucin. The fungal mass had eroded through the anterior skull base and created a large opening from the frontal sinuses into the nasal cavity. Because of this large opening, the fungal mass was entirely 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 *Bipolaris* spp. The patient was discharged on postoperative Day 1 and was given a short course of systemic corticosteroids. At the 6-month follow up, an endoscopic nasal examination revealed well-healed mucous membranes of the ethmoid and frontal sinuses. There was no evidence of recurrent fungal disease at the 3-year follow-up review.

**Discussion**

Allergic *Aspergillus*-induced sinusitis was first described

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**Fig. 2.** Case 4. Coronal (left) and axial (right) CT scans obtained in a 42-year-old man who presented with sinusitis, polyps, and nasal obstruction. The images reveal AFS with extensive paranasal sinus involvement extending into the frontal sinus and the adjacent epidural space. Fungal debris was removed entirely through a transnasal endoscopic approach.
Allergic fungal sinusitis

in 1983 by Katzenstein and coworkers. They reported a series of immunocompetent patients who harbored a non-invasive fungal sinusitis that was histologically identical to allergic bronchopulmonary aspergillosis. The condition was initially thought to be an allergic reaction to Aspergillus spp., but since then other causative fungal species have been identified. Thus, the disease is now referred to as AFS.

Fungal sinusitis is generally classified into one of five distinct clinical entities based on the host’s immune status and the presence or absence of tissue invasion (Table 2). Two are found in patients whose immune systems are compromised: acute fulminant invasive fungal sinusitis, characterized by vascular invasion and tissue necrosis; and chronic invasive fungal sinusitis, characterized by tissue necrosis and a low-grade inflammatory reaction. Three types of fungal sinusitis are found in immunocompetent patients: granulomatous invasive fungal sinusitis, characterized by a chronic granulomatous reaction with fungal invasion limited to the superficial mucosa; fungus ball (sinus mycetoma), characterized by a tangled mass of fungal hyphae with a minimal mucosal reaction; and AFS, characterized by a noninvasive immune hypersensitivity reaction to fungal elements. Allergic fungal sinusitis 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.

Clinical Presentation

Allergic fungal sinusitis most commonly affects adolescents and young adults. The mean age in our series was 25 years. Patients typically present with nasal obstruction and chronic allergic rhinosinusitis 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. 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.

Pathophysiology of AFS

Although the exact pathogenesis of AFS remains unknown, it has been characterized as similar to the pathogenesis of allergic bronchopulmonary aspergillosis. It is postulated that ubiquitous fungi become deposited in the sinus and produce Type I (IgE-mediated) hypersensitivity, nasal polyposis, characteristic neuroimaging findings, and histological data demonstrating characteristic allergic mucin with fungal forms but without tissue invasion.

All patients in our series demonstrated histologically confirmed fungus and culture-positive AFS. There are some cases in which the histological findings are similar to AFS but lack evidence of fungal hyphae; in these cases the disease has been referred to as EMRS. There is some evidence that supports EMRS as a clinicopathological entity that is distinct from AFS. Patients with EMRS have a higher association with asthma, an increased incidence of aspirin sensitivity, an increased incidence of IgG1 deficiency, and are generally older than patients with AFS. Although two patients in our series were older than 40 years of age, in both there was a positive fungal culture supporting the diagnosis of AFS.

Differential diagnosis. The diagnostic criteria of AFS include Type I (IgE-mediated) hypersensitivity, nasal polyposis, characteristic neuroimaging findings, and histological data demonstrating characteristic allergic mucin with fungal forms but without tissue invasion.
Helminthosporium, and Drechslera, are more commonly associated with AFS. In our series of AFS, the Bipolaris spp. were the predominant fungi cultured. In all but one patient (95%) there was a positive culture from the Dematiaceae family. There was only one case of allergic aspergillosin sinusitis. Certain geographic locations have been implicated in the incidence of AFS. 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 warm and moist climate in these regions may provide an optimal environment for fungal proliferation.

**Imaging Characteristics**

The imaging findings of AFS are well recognized. Computed tomography scans commonly demonstrate irregular hyperdense expansive masses involving multiple sinuses (Figs. 1 and 2). With the expansile nature of the accumulating allergic mucin, bone erosion through the anterior skull base and orbital walls can sometimes mimic malignant paranasal sinus tumors. 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 MR images, the high protein and low water concentrations of the allergic fungal mucin result in decreased intensities on T1- and T2-weighted images with peripheral enhancement in the surrounding edematous paranasal sinus mucosa (Fig. 1). A signal void on T2-weighted MR images is highly suggestive of fungal debris and is helpful in differentiating a malignant neoplasm from fungal disease.

**Histopathological Characteristics**

On gross examination, the allergic fungal mucin is brown or dark green and often appears thick and caseous. Microscopically, the histological findings of AFS are identical to those in allergic bronchopulmonary aspergillosis. Fungal hyphae are present within the allergic mucin and consist of degenerated inflammatory cells, lamellated aggregates of eosinophils, calcifications, and Charcot–Leyden crystals (Fig. 4). The hyphae, characterized by septae and acute angle branching, are morphologically similar to Aspergillus spp. The fungal hyphae are poorly seen on hematoxylin and eosin preparations and require the application of Gomori methenamine–silver stains for adequate visualization. Unlike the acute fulminant form of fungal sinusitis, there is no histological evidence of vascular or tissue invasion in cases of AFS.

**Surgical Management**

Successful treatment of AFS requires complete removal of all fungal antigens and a course of systemic corticosteroids for long-term prevention of disease recurrence. Complete extirpation of allergic mucin and fungal debris eliminates the antigen-inciting factor of the inflammatory response. Surgery also achieves adequate drainage and ventilation of the sinuses. Inadequate sinus drainage allows further exposure to fungal antigens and an ongoing inflammatory response.
Allergic fungal sinusitis

It is important to remember that, although on neuroimages 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–Ferguson transfacial approaches, and extensive mucosal exenteration. 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. Maxillary sinus disease can be removed via an intranasal antrostomy; however, in rare situations, a sublabial transmaxillary approach (Caldwell–Luc procedure) may be needed to remove the allergic mucin in the maxillary sinus. The majority of the patients in this series (86%) were treated through endoscopic approaches alone, obviating the need for a craniotomy. A transnasal endoscopic approach alone was feasible in five of the eight patients in whom there was intracranial disease because the lesion was extradural and remained in the midline field of endoscopic visualization. Three of the six patients with intraorbital disease were treatable endoscopically because these lesions had eroded through the medial orbital wall and were accessible through the transnasal or transmaxillary routes.

If the intracranial and/or intraorbital extension of AFS are inaccessible from below, a bifrontal transbasal approach may be necessary to achieve total removal of fungal disease and to perform an orbital roof decompression. The three patients in this series who required a craniotomy in addition to an endoscopic approach all harbored intracranial disease that extended laterally across the anterior cranial fossa and intracranial disease that occupied the superior orbit. These locations were inaccessible through endoscopic transnasal and/or transmaxillary approaches, thus necessitating a transcranial approach from above to remove fungal debris and decompress the orbital roofs.

Our strategy of surgical management allows successful debridement of allergic mucin and fungus without requiring disfiguring facial incisions or extensive facial osteotomies. Because AFS is primarily a disease of the paranasal sinuses, most patients will initially present to an otolaryngologist. If AFS is diagnosed at an early stage before extensive intracranial and/or intraorbital involvement, the majority of patients can be surgically treated endoscopically. Only a few patients will require a craniotomy for complete fungal exirpation.

Adjuvant Medical Therapy

The concomitant use of systemic corticosteroid medications has been advocated as a means of suppressing the immunological reaction to the persisting fungal antigen as well as a means of controlling the underlying allergic rhinitis.6,10,21,26,28,29 The optimal dosing regimen and duration of therapy have yet to be determined. Twenty patients in our series received a short course of corticosteroids postoperatively. There have been no cases of disease recurrence after a mean follow-up period of 9 years. The postoperative administration of intranasal corticosteroids and nasal saline irrigations may also be beneficial.6,29 Our patients have been followed up by their otolaryngologists for periodic examinations and nasal irrigations.

Long-term systemic or local antifungal therapy can produce toxic and deleterious side effects and is not recommended in the absence of histological evidence of tissue invasion.3,14,24 One patient (Case 7) in our series received a short course of intravenous amphotericin B without any systemic complications. This was the first patient in our surgical experience who was treated before we gained a better knowledge of the disease. We now routinely treat patients with a short course of corticosteroids. The use of immunotherapy to downregulate the production of fungus-specific IgE and to decrease the inflammatory response appears promising.16,21,22

Although some physicians have argued against the use of adjunctive antifungal therapy in patients with AFS,4,21,24 there are some reports that support its use in severe cases of recurrent AFS after surgical debridement and corticosteroid therapy.1,26 Postoperative recurrences usually appear after the patient has been weaned from corticosteroid therapy. Topical or systemic antifungal medications may reduce the rate of recurrence by theoretically decreasing the fungal antigen loads and, thereby, preventing subsequent hypersensitivity reactions. The use of itraconazole has been reported to treat recurrent AFS successfully with minimal side effects.1,33

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 neuroimages, there is no histological evidence of tissue invasion. A cranial base team approach of neurosurgeons and otolaryngologists 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.

References

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