

Ophthalmic Manifestations of Allergic Fungal Sinusitis

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Purposes: To study the ophthalmic manifestations of patients with allergic fungal sinusitis (AFS) and evaluate the importance of early diagnosis and management in preventing the possible future complications of AFS.

Methods: Retrospective chart review of 100 patients with the diagnosis of AFS from a single institution was performed. Age, gender, clinical presentation including ophthalmic and radiological findings, immune status, patterns of sinus involvement, medical and surgical intervention needed, laboratory results, and the course of the disease were evaluated.

Results: The mean age at presentation was 19.8 years (range, 10–42 years) with no clear gender predominance (52% of patients were female). The most common sinuses involved were ethmoid and maxillary sinuses. All patients underwent functional endoscopic sinus surgery and received systemic and topical steroids. There were no intervention-related complications. Thirty-four of 100 patients had ophthalmic consequences of AFS. The most common ophthalmic presentation was proptosis ($n = 21$, 61.7%), followed by epiphora ($n = 5$, 14.7%), visual loss ($n = 4$, 11.7%), diplopia ($n = 3$, 8.8%), and dystopia ($n = 1$, 2.9%) in addition to 1 patient having ptosis beside proptosis. CT scans of these 34 patients showed that 82.3% had nonhomogenous opacification of sinuses, 52% had erosion of lamina papyracea, 17.6% had intraorbital extension, and 8.8% had intracranial extension.

Conclusions: Ophthalmologists may be the first who encounter these patients which necessitates familiarity with AFS presentations and complications. In cases of sudden visual loss, early intervention may prevent permanent vision loss. Functional endoscopic sinus surgery and postoperative systemic and topical steroids resulted in dramatic improvement of ophthalmic symptoms and signs.

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Sinusitis is a common disorder affecting about 20% of the population at different stages of their lives. Fungal sinusitis is a rare form of sinusitis with increasing reported cases in the past 3 decades.^{1,2}

Fungal sinusitis is classified into 2 groups: 1) invasive, which may be granulomatous, acute fulminant or chronic invasive and 2) noninvasive, which includes allergic fungal sinusitis (AFS) and a localized type (mycetoma). The invasiveness is determined by histologic detection of mucosal invasion.¹

Allergic fungal sinusitis is a chronic noninvasive autoimmune reaction to a fungal element in immunocompetent patients. It is seen in highly atopic individuals with sinusitis and nasal polyposis. Serologic testing often shows elevated IgE and IgG levels that are frequently associated with eosinophilia. It accounts for about 7% of patients with sinus disease requiring surgery.^{2–4}

The pathophysiology of AFS is not fully understood. It is postulated that these fungi become deposited in the sinus and proliferate under anaerobic conditions induced by mucous impaction and obstruction of the ostiomeatal complex.² These patients develop an allergic reaction to the fungal elements with accumulation of eosinophil-rich allergic thick mucin containing sparse fungal elements.

Type I and type III hypersensitivity reactions to fungal antigen play a major role in AFS.⁵ This process was thought to be similar to that of allergic bronchopulmonary aspergillosis. Subsequently similar cases were reported in Dematiaceae molds and found to be a distinct entity; therefore, the name was changed to AFS.^{6,7}

About 17% of patients with AFS may experience ophthalmic manifestations.^{4,8} Previous case series of AFS found that ophthalmic symptoms and signs may present in varying degrees; the most common symptoms are proptosis, diplopia, blepharoptosis, epiphora, visual loss, and ophthalmoplegia which all may complicate AFS. In most of the cases, surgical intervention and oral steroids followed by intranasal steroid spray were the management choices.^{2–4,8–17}

These symptoms and signs are caused by the extension of inflammation associated with AFS beyond the sinus boundaries.^{2,4,10} The disease frequently affects multiple sinuses of which the maxillary and ethmoid sinuses are affected most often, with unilateral predominance.^{2,3,11}

Here, the authors present their experience with 100 patients diagnosed with AFS among which 34 patients presented with ophthalmic findings.

METHODOLOGY

Retrospective chart review of all consecutive patients with the diagnosis of AFS presenting to the Department of Otolaryngology, Head and Neck surgery or the Department of Ophthalmology at King Abdulaziz University Hospital, Riyadh, Saudi Arabia between January 2004 and June 2016 was done. All patients underwent functional endoscopic sinus surgery which was conducted at least 1 year ago. In this study, the authors looked for age, gender, clinical presentation, immune status, sinus involvement, radiological findings, operative results, laboratory results, ophthalmic findings, management, and outcome. The authors used the diagnostic criteria proposed by Bent and Kuhn⁶ which were modified by Houser and Corey¹⁸ in diagnosing patients with AFS. These diagnostic criteria include patients having type I hypersensitivity, asthma, nasal polyps, characteristic CT scan findings such as bone erosion, often positive fungal stain or culture, and allergic mucin with fungal elements with no sinus mucosal invasion. All included patients were

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TABLE 1. Clinical data summary for patients having allergic fungus sinusitis with and without ophthalmic manifestations

Characteristics	Patients with ophthalmic manifestations	Patients without ophthalmic manifestations
No.	34	66
Age	10–42	10–40
Sex	F: 18, M: 16	F: 35, M: 31
History of allergy	20	38
History of asthma	16	31
Nasal polyposis	34	66
High total IgE	31	50
Peripheral eosinophilia	30	60
Allergic mucin in biopsy specimen	32	62
Positive fungal stain in biopsy specimen	14	20
CT finding		
Bilateral sinus disease	20	41
Unilateral sinus disease	14	25
Multiple sinuses affected	31	60
Heterogeneous opacity	28	55
Sinus wall expansion	26	51
Lamina papyracea erosion	18	27
Intraorbital extension	6	0
Intracranial extension	3	0

checked for total eosinophil count, skin tests, total serum IgE levels, and Charcot-Leyden crystals. The study was approved by the institutional review board of King Saud University, College of Medicine, adhered to the tenets of the Declaration of Helsinki and an informed consent was obtained from the patients.

RESULTS

Thirty-four of 100 AFS cases were found to have ophthalmic manifestations (Table 1). The age ranged from 10 to 42 years with a mean of 19.8 years. 53% were female and 47% were male. All patients were Saudi and the majority lived in the central region. The most common ophthalmic presentations were proptosis ($n = 21$, 61.7%), followed by epiphora ($n = 5$, 14.7%), visual loss ($n = 4$, 11.7%), diplopia ($n = 3$, 8.8%), and globe dystopia ($n = 1$, 2.9%) with 1 patient had ptosis in addition to proptosis. It took 3 to 12 months for AFS in the sinus to develop ophthalmic signs or symptoms. Five patients presented with epiphora. In 4 of them, partial nasolacrimal obstruction was found and complete obstruction was found in 1 patient. Complete resolution of the obstruction was observed among all the 5 patients after only functional endoscopic sinus surgery. All patients had nasal polyposis at presentation or previously reported. Allergies were seen in 58.8% of cases and 47% had a history of bronchial asthma.

Serologic testing disclosed an increased IgE level in 31 patients and increased IgG level in 3 patients. Peripheral eosinophilia was present in 30 patients. Allergic mucin was found in 32 patients and fungal hyphae in 18 patients. The most common fungus grown from the culture was *Aspergillus fumigatus* in 8 cases and *Aspergillus flavus* in 6 cases.

Imaging studies revealed that 58.8% were bilateral disease and 41.2% were unilateral disease with right-sided predominance. CT scan showed that 82.3% of cases had nonhomogenous opacification of sinuses (Fig.). The lamina papyracea was eroded in 52.8% of cases. The intraorbital extension was seen in 17.6% of cases and intracranial extension in 8.8% of cases. The most common sinus involved was ethmoid and maxillary sinuses.

The treatment regimen included functional endoscopic sinus surgery, postoperative antibiotics, steroid nasal spray, and systemic steroids. All patients had dramatic improvement in ophthalmic symptoms and signs after only 1 sinus surgery. Twenty of the 100 patients with AFS needed surgical revision for their sinus disease, but none of them developed recurrence of ophthalmic manifestations.

The follow up of these patients ranged from 12 months to 3 years and all of them were free of ophthalmic symptoms except 2 patients with permanent visual loss due to permanent optic nerve damage.

DISCUSSION

Allergic fungal sinusitis is a type of colonization of paranasal sinuses caused by various saprophytic fungi.¹⁴ It is a chronic noninvasive form of sinusitis seen commonly in young atopic immunocompetent patients. Most patients have nasal polyposis,^{1,2,6,18} and it accounts for approximately 7% of patients with sinus disease requiring surgery.¹⁹ The disease is characterized by the formation of allergic mucin-containing numerous eosinophils and Charcot-Leyden crystals.¹⁸ It is more common in warm, humid climates.⁶ Patients referred to the hospital were from the central part of Saudi Arabia. This part of the country is mainly a deserted area where the weather in most part of the year is dry and hot for many centuries. Ophthalmic manifestations among our patients was found to be 34% which is higher than a previously published percentage of 17%. Interestingly, the authors found the sinuses were involved bilaterally in 59%. Due to lack of major studies about AFS in the area, it is difficult to know whether the higher percentage is secondary to the disease behavior in the area or due to a referral bias as the hospital is one of the major referral centers for ophthalmology and otolaryngology in the area.

Aspergillus and *Dematiaceae* fungi are the most common etiologic agents reported to be involved with AFS. Waxman et al.²⁰ provided serological evidence of immune hypersensitivity to *Aspergillus* species as an etiological factor and they found increased total IgE levels in 85% of patients. Manning et al.²¹ found positive results in their series of 16 patients with AFS. Carter et al.² found increased total IgE levels in 5 of 6 patients. In our study, 91% of patients had increased total IgE levels.

The radiologic finding of AFS usually involves multiple sinuses of the affected side. CT scan reveals nonhomogenous opacification of the affected sinuses that produce heterodense signal intensities which was found in the most patients. The most common sinuses involved were ethmoid and maxillary sinuses. Allergic fungal sinusitis is characterized by not invading the nasal mucosa. However, patients with AFS develop an allergic reaction to the fungal elements and produce a thick mucoid material. This can be associated with bony erosion secondary to pressure effect, pushing of surrounding structures, demineralization of bone, or expansion of a fungal allergic mass to the orbit and subsequent brain involvement.^{22,23} Fifty-two percentage of cases had erosion of the lamina papyracea. Intraorbital extension was seen in 17.6% of cases and intracranial extension in 8.8% of cases.

Allergic fungal mucin was seen in 32 of 34 patients. It serves as a hallmark of the disease which is characterized by thick, tenacious, and highly viscous consistency. Histopathological techniques provide the only means of determining whether a fungus is invading host tissue or not. A combination of histologic stains, Periodic acid-Schiff and Gomori's methenamine silver, was used to visualize both the tissue reaction and the fungal etiology. Culture of sinus content may be performed also but may take a number of weeks. Mycological evaluation of the fungal mucin of the patients revealed the growth of *A. fumigatus* in 8 cases and *A. flavus* in 6 cases.

TABLE 2. Ophthalmic signs and symptoms of patients with allergic fungus sinusitis in comparison with the previous published literature

Signs	No. of cases	References	No. of cases in current series
Proptosis	31	Carter et al., ² Klapper et al., ⁴ Daghistani et al., ⁹ Chang et al., ¹¹ Bartynski et al., ⁵ Waxman et al., ²⁰ Manning et al., ²⁴ Jacobson et al., ²⁵ Young et al., ²⁶ Goldstein et al., ²⁷ Aviv et al., ²⁸ De Juan et al., ²⁹ Jay et al., ³⁰ Dunlop and Billson, ³¹ Roth, ³² Berry et al. ³³	21
Diplopia	9	Carter et al., ² Klapper et al., ⁴ Bartynski et al., ⁵ Jacobson et al., ²⁵ Young et al., ²⁶ Dunlop and Billson, ³¹ Brummund et al. ³⁴	3
Blepharoptosis	6	Carter et al., ² Klapper et al., ⁴ Jacobson et al., ²⁵ Goldstein et al., ²⁷ De Juan et al., ²⁹ Berry et al., ³³ Brummund et al. ³⁴	1
Epiphora	5	Klapper et al., ⁴ Bartynski et al., ⁵ De Juan et al., ²⁹ Brummund et al. ³⁴	5
Visual loss	8	Carter et al., ² Gupta et al., ¹⁶ Manning et al., ²⁴ Jay et al., ³⁰ Dunlop and Billson ³¹	4
Ophthalmoplegia	2	Klapper et al., ⁴ Jacobson et al. ²⁵	0
Dystopia	0		1

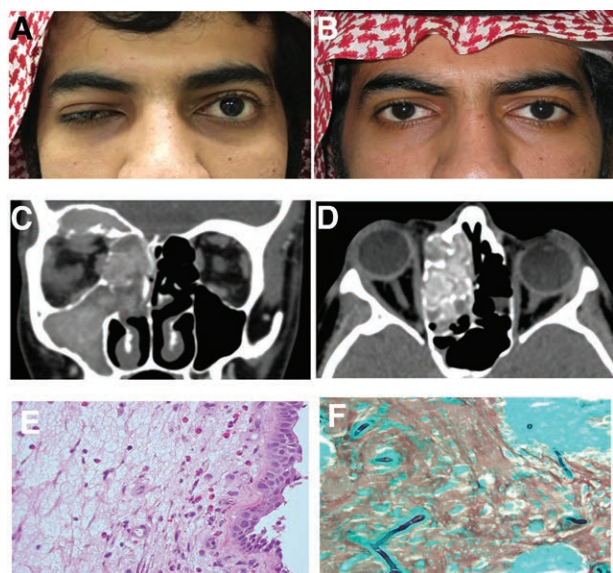


FIG. External photo for a 35-year-old male with allergic fungal sinusitis showing proptosis with ptosis at presentation (**A**) and 1 month after functional endoscopic sinus surgery and steroid therapy (**B**). Coronal (**C**) and axial (**D**) CT scan of the same patient at presentation showing diffuse opacification of the right ethmoid, maxillary and frontal sinuses with cystic extension in the right orbit and erosion of right orbital roof. Adjacent sinus mucosa with edematous submucosa and numerous eosinophils but no evidence of fungal invasion (**E**) (original magnification, $\times 400$, hematoxylin and eosin). Fungal septated hyphae within mucous debris in the same case (**F**) (original magnification, $\times 1000$, Gomori's methenamine silver oil).

Ophthalmic symptoms or signs can be the leading cause for seeking a treatment in patients with AFS. The most common reported sign of AFS presenting to the ophthalmologist is proptosis,² with diplopia, blepharoptosis, epiphora, visual loss, and ophthalmoplegia also reported (Table 2). In this study, the most common ophthalmic presentation was proptosis ($n = 21$) followed by epiphora ($n = 5$), visual loss ($n = 4$), diplopia ($n = 3$), and dystopia ($n = 1$). Carter et al.² found in their series of 6 patients that proptosis was seen in all cases, 1 with diplopia and 1 with visual loss. Although AFS is a benign disease, the resulting nasal polyposis and fungal mass can become so massive that bony landmarks are destroyed and surrounding structures are gradually displaced in addition to pressure necrosis of respective orbital wall.⁶ Because of the chronic nature of AFS, patients

may not be aware of proptosis when it is axial.² In this study, the proptosis ranged from 2 mm to 4 mm; all were axial. Two patients in addition had downward and lateral displacement. Regression of proptosis usually occurs after surgical evacuation of the sinuses and appropriate medical treatment without any need for orbital reconstruction.

The most hazardous complication of AFS lies in the visual loss. The proposed mechanism of vision loss is assumed to be secondary to direct compression or direct inflammation of the optic nerve. Gupta et al.¹⁶ proposed in addition a local immunologic reaction to fungal antigen. Four of our patients suffered visual loss due to optic neuropathy. All had increased IgE levels with positive fungal serology. All underwent functional endoscopic sinus surgery with postoperative systemic steroids. Two patients presented within days of onset of visual loss but they regained vision after the surgery. The other 2 had a permanent visual loss due to a delay in seeking proper medical care (patients presented a few weeks after starting to suffer visual loss) with chronic disease and significant optic disc pallor. Two had bony erosion of sphenoid sinus and 2 had bony erosion of the frontal and posterior ethmoid sinus on CT scan. Carter et al.² reported 1 case of temporary visual loss who regained vision rapidly after surgical evacuation and medical therapy. Gupta et al.¹⁶ reported 4 cases of visual loss where 3 recovered completely and 1 partially. Graham and Carter¹⁷ reported 1 case of visual loss who responded only to oral steroids because the general health of the patient did not allow them to be taken to the operating room immediately. This would support the local immunologic hypothesis and reinforce the role of steroids in the treatment of this condition.

Treatment of AFS is usually a combination of sinus surgery in addition to a postoperative oral steroids and steroid nasal spray. In most cases, this regimen works well. After reestablishment of sinus ventilation, temporary relief of symptoms occurs. Itraconazole was found to be effective in steroid potentiation, although no controlled study confirmed this.¹⁷

In conclusion, the diagnosis of AFS requires a high index of suspicion and should be considered in the differential diagnosis of patients with proptosis and sinusitis. Ophthalmologists may be the first who encounter these patients which necessitates familiarity with AFS presentations and complications. Early diagnosis and management may help in reaching a favorable outcome.

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