

Allergic fungal sinusitis: pathophysiology, diagnosis and management

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Allergic fungal sinusitis (AFS) is a noninvasive form of fungal rhinosinusitis with an incidence of between 6 and 9% of all rhinosinusitis requiring surgery. Regional variation in incidence has been reported, with the southern and southwestern US particularly endemic. Patients with AFS commonly present with chronic rhinosinusitis with nasal polyps, inhalant atopy, elevated total serum immunoglobulin E (IgE), and sinus-obstructing inspissates of a characteristic extramucosal 'peanut buttery' visco-elastic eosinophil-rich material called 'allergic mucin' that contains sparse numbers of fungal hyphae. Sinus CT is always abnormal, showing findings of chronic rhinosinusitis that often include central areas of increased contrast ('hyperattenuation') within abnormal paranasal sinuses that represent the presence of fungal-containing allergic mucin. AFS has been found to be analogous in several ways to allergic bronchopulmonary aspergillosis (ABPA). Both are chronic inflammatory respiratory tract disorders that are driven by hypersensitivity responses to the presence of small numbers of extramucosal fungi found growing within airway-impacting allergic mucin. AFS allergic mucin typically cultures positive for either dematiaceous fungi such as *Bipolaris spicifera* or *Curvularia lunata*, or *Aspergillus* species such as *A. fumigatus*, *A. flavus* or *A. niger*. As with ABPA, patients have type I immediate hypersensitivity to the etiologic mold in AFS. Further, both AFS and ABPA have been found to have association with specific class II major histocompatibility alleles. Proper diagnosis of AFS and differentiation from the other forms of both noninvasive and invasive fungal rhinosinusitis requires strict adherence to published diagnostic criteria. Medical treatment of AFS has been modeled to an extent after treatment approaches for ABPA that includes the use of postoperative oral corticosteroids and aggressive antiallergic inflammation therapy. The use of follow-up measurements of total serum IgE during treatment of both AFS and ABPA patients can help to monitor disease activity. Future AFS research will lead to further insights into pathogenesis, improved treatments, and ultimately decreases in surgical recurrence rates for this highly recurrent hypertrophic rhinosinusitis disorder.

Keywords Sinusitis, rhinosinusitis, nasal polyp, allergic fungal sinusitis, *Aspergillus*, *Bipolaris spicifera*, dematiaceous fungi, eosinophilic diseases, allergy, type I immediate hypersensitivity, superantigen, MHC class II, fungal diseases treatment

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Introduction

Sinusitis is the term representing inflammation of the paranasal sinus mucosa. The term 'rhinosinusitis' has become a common replacement for the term 'sinusitis' due to the contiguous nature of nasal and paranasal sinus mucosa, as well as their interactions and

potentially shared involvement in various inflammatory processes. Rhinosinusitis occurs in both acute and chronic forms, and represents a potential heterogeneity of pathophysiologies and prognosis. For example, acute rhinosinusitis is invariably due to an infection, and depending on the host's level of immunocompetence and type of microorganism involved, outcomes can range from self-limited rapid resolution to that of serious morbidity and mortality.

As a general rule, rhinosinusitis that lasts at least 12 weeks is termed chronic rhinosinusitis (CRS) [1]. CRS can represent a failure to properly resolve an infection, can represent a chronic inflammatory disorder, or can include some mix of persistent inflammation and infection [1–5]. Thus, there is heterogeneity in the pathophysiology of CRS disorders. Only recently have we begun research into chronic rhinosinusitis and noted potential distinctions in immunopathology between various phenotypic subgroups of CRS, such as those with or without nasal polyps, inhalant atopy (type I immediate hypersensitivity), aspirin (ASA)/nonsteroidal antiinflammatory drug (NSAID) hypersensitivity, or presence of comorbid predisposing conditions such as cystic fibrosis, ciliary dyskinesias, or immunodeficiencies [2].

Fungal rhinosinusitis disorders

Fungi can cause both acute and CRS disorders, and can occur as either tissue-invasive or noninvasive conditions as delineated by deShazo and colleagues [6] (Table 1). Specific fungal rhinosinusitis disorders each have distinguishing clinical and histopathologic features.

Of the invasive disorders, the acute fulminate necrotizing form is the classic fungal infection epitomized by 'mucormycosis'. Patients typically are immunosuppressed, and the infection leads to widespread facial and paranasal tissue necrosis that has high morbidity and mortality. Wide surgical debridement of infected tissue and concomitant antifungal drug therapy is required urgently. Prognosis is poor without correction of the underlying immunocompromise. A more chronic

form of tissue-invasive infection, chronic invasive fungal rhinosinusitis, has often been reported in diabetics and commonly leads to periorbital tissue invasion and the 'orbital apex syndrome' [7,8]. Surgical resection and systemic antifungal drugs are required, but the infection may recur and is difficult to treat. A more indolent form of invasive disease has been termed granulomatous invasive fungal sinusitis. Other terms for this condition have included 'indolent fungal sinusitis' and 'primary paranasal granuloma'. Published cases include those from the Sudan (due to *Aspergillus flavus*) and St. Louis, MO [9,10]. It may also occasionally be seen on mucosal histopathology from sinus surgery in otherwise uncomplicated CRS patients [6,11]. Here, the fungal infection is more localized to the superficial sinus mucosa and is well contained within a robust granulomatous inflammatory process. Sinus mucosal resection may be curative, but systemic antifungal drugs are commonly used postoperatively to assure complete resolution of fungal infection once the histopathological diagnosis is available.

Noninvasive fungal rhinosinusitis includes fungal ball ('sinus mycetoma') and allergic fungal sinusitis (AFS). In fungal ball, multitudes of fungal hyphae are compressed into a thick exudate within a sinus lumen. This may occur in patients with previous sinus surgery, oral-sinus fistula, history for cancer chemotherapy or those without any known predisposing factor [6,12,13]. AFS is the other form of noninvasive fungal rhinosinusitis. It represents more of a hypersensitivity response to the presence of extramucosal sinus fungal hyphae, with a prominent element of fungal-specific type I immediate hypersensitivity although the disease appears complex and likely involves the interplay of various inflammatory modalities [14,15]. AFS is the subject of the following review.

Diagnosis of AFS

The diagnosis of AFS is primarily histopathologic (Table 2) [16–22]. Surgically obtained characteristic inspissated allergic mucin must be seen histopathologically and/or grossly at surgery. The allergic mucin must be positive for fungal hyphae on fungal staining, and/or properly obtained surgical sinus fungal cultures must be positive in an otherwise characteristic patient. There should be no histopathologic evidence for mucosal fungal invasion, including commonly associated features of tissue invasion such as mucosal necrosis, granuloma formation, or giant cells. Other fungal rhinosinusitis disorders must also be excluded as the primary diagnosis.

Table 1 Clinicopathologic forms of fungal rhinosinusitis*

Invasive	Noninvasive
Acute fulminate invasive fungal sinusitis	Fungal ball ('sinus mycetoma')
Chronic invasive fungal sinusitis	Allergic fungal sinusitis
Granulomatous invasive ('indolent') fungal sinusitis	

*From: deShazo RD, *et al.* *N Engl J Med* 1997; **337**: 254–259.

Table 2 Diagnosis of AFS*

1. Surgically obtained characteristic inspissated allergic mucin must be seen histopathologically and/or grossly at surgery.
2. The allergic mucin must be positive for fungal hyphae on fungal staining, or properly obtained surgical sinus fungal cultures must be positive in an otherwise characteristic patient.
3. No histopathologic evidence for mucosal fungal invasion, mucosal necrosis, granulomas, or giant cells.
4. Other fungal rhinosinusitis disorders as the primary diagnosis must be excluded.

*From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998; **102**: 387–394.

Although the diagnosis of AFS is primarily histopathologic, there are many clinically presenting features that are always present [16,18–22]. For example, all patients present with CRS, nasal polyps, and abnormal sinus computed tomography (CT) scans [16,20,22] (Fig. 1). The sinus CT scan may show areas of hyperattenuation which are seen best on tissue window settings [13,16,18–22]. At surgery, a characteristic inspissated sinonasal inflammatory exudate called allergic mucin is encountered [5,16–22]. Allergic mucin is largely responsible for the sinus CT hyperattenuation [5,13,21,22]. Allergic mucin appears grossly at surgery as a peanut-buttery to viscoelastic material, and histopathologically on hematoxylin and eosin (H&E) stains as strongly staining laminated concretions of pyknotic and degranulated eosinophils surrounded by areas of lightly staining mucin sprinkled with Charcot-Leyden crystals [16,17,19]. Further staining of allergic mucin with fungal stains such as Gomori's methenamine silver (GMS) will show scattered fungal hyphae within the



Fig. 1 Sinus CT (bone window) of an AFS patient. Allergic mucin (arrow).

allergic mucin [16–22] (Fig. 2). Attempts at identification of specific fungal genus/species using fungal stains of allergic mucin are often unreliable. Fungal identification requires culture of allergic mucin obtained intraoperatively. Surgically obtained AFS allergic mucin commonly cultures positive for dematiaceous fungi (such as *Bipolaris spicifera* or *Curvularia lunata*), or *Aspergillus* species such as *A. fumigatus*, *A. niger*, or *A. flavus* [16,22]. Bacterial cultures or staining of this allergic mucin may detect the presence of *Staphylococcal aureus* [16,23]. A pitfall to avoid in diagnosing AFS is failure to recognize that the presence of classic allergic mucin, but without fungal involvement, can also be seen patients with the non-AFS disorder 'eosinophilic mucin rhinosinusitis' (EMRS) [24–26].

Additional associated clinical findings in AFS include the presence of inhalant atopy [15,16,27–29]. Patients with AFS are usually allergic to multiple aeroallergens as assessed by skin testing for type I immediate hypersensitivity, and can be shown to be allergic to the etiologic mold when it has been properly identified [15,16,27–29]. A review of 67 consecutive AFS patients from the southwestern United States found all patients to have inhalant atopy, skin test positivity to the AFS-etiological mold, and immunocompetence [16]. Other presenting features included reactive airway disease in 64% of patients and aspirin/nonsteroidal antiinflammatory drug hypersensitivity in 13%. 3% of AFS patients were also found to carry the diagnosis of allergic bronchopulmonary mycosis, subsequently termed the sinobronchial allergic mycosis (SAM) syndrome [30].

Diagnostic confusion can be minimized by avoiding the temptation to culture transnasal secretions in the office, the results of which include the presence of normal nasal flora. Such cultures might also be

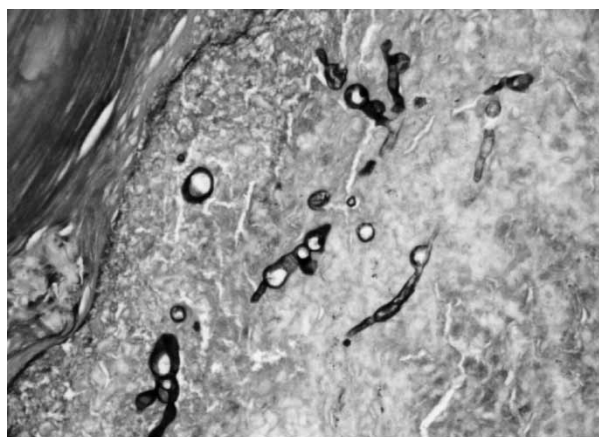


Fig. 2 AFS allergic mucin with fungal hyphae (GMS stain).

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expected to culture many different saprophytic organisms in any CRS patient who has had previous sinus surgery that usually leaves surgically enlarged sinonasal communications [5]. Intraoperatively obtained classic allergic mucin appears to be much more reliable for fungal culture [5]. A controversial hypothesis proposed by several researchers from the Mayo Clinic suggested that virtually all patients with any form of CRS have fungal immunopathogenesis for their disorder because they found that office based transnasal cultures grew many different fungi from all of their CRS patients, despite reporting identical culture results from their non-CRS controls [31]. They then suggested both abandoning AFS as a diagnostic category and using the term 'eosinophilic fungal rhinosinusitis' for virtually all CRS patients. Criticisms of their conclusions and suggestions have included the low specificity of their microbiology data [5,32–36]. In support of possible proinflammatory effects of specific fungi in CRS patients, subsequent work from the same group found their CRS patients' peripheral blood lymphocytes to have enhanced humoral and cellular immune parameters in vitro to *Alternaria* stimulation compared to controls [58]. However, similar work from others have no differences in measured in vitro cellular immune parameters between control and CRS patients' peripheral blood lymphocytes when co-cultured with either *Alternaria* or *Aspergillus* antigens [59]. More studies will be needed to help settle this CRS/fungal controversy.

Immunopathology

Much remains unknown about the biology of AFS. The largest AFS case series reported from the southwestern United States found that all patients with AFS had inhalant atopy, including type I immediate hypersensitivity to the AFS etiologic mold [16]. Other features of AFS were also always present, including an intense mucosal inflammatory response best characterized as eosinophilic-lymphocytic/atopic/allergic and even asthmatic [16]. The extramucosal inspissate of allergic mucin and eosinophil degranulation products further characterize the eosinophilic component of the disorder [16,37]. All of these immunopathological features occur in AFS and appear to be necessary constituents of AFS immunopathogenesis. However, atopy by itself is clearly not sufficient to cause AFS because inhalant atopy to common AFS etiologic molds is seen commonly in the absence of AFS [5,13].

IgE also appears to be important in AFS pathogenesis. Elevated total serum IgE in AFS is common, and changes in total serum IgE over time were reported

to reflect the patient's clinical status [38]. IgG may also have significant roles in AFS immunopathogenesis, because changes in antigen specific-IgG to the AFS-etiologic mold also predicted clinical status [38]. Presence of specific IgE to *Staphylococcal aureus* superantigens and their correlation with total serum IgE levels in AFS also suggests a role for these superantigens in the immunobiology of AFS [39]. Superantigens may even be required as a cofactor in AFS immunopathogenesis [23,40], and *S. aureus* superantigens have already been strongly implicated in the immunopathogenesis of common forms of chronic rhinosinusitis with nasal polyps [40–44]. *S. aureus*, a prodigious superantigen-producer, is commonly cultured from AFS sinus surgeries, and can be seen extramucosally in many forms of chronic rhinosinusitis [16,23,40]. *S. aureus* superantigens are also known to have an important role in the pathogenesis of atopic dermatitis in most patients [45,46].

Other aspects of AFS immunobiology include the finding of a class II major histocompatibility (MHC) association with the beta chains human leukocyte antigen (HLA)-DQB1*0301 and DQB1*0302 [14]. The analogous disorder ABPA was reported to have association with the MHC class II beta chains HLA-DRB1*1501 and *1503 [47]. This implicates acquired immunity involving professional antigen presenting cells and T cell responses in both AFS and ABPA, similar to that seen with other common chronic inflammatory diseases [14]. Ferguson's group recently reported on the patterns of gene activity *in situ* within sinonasal polyp tissue, and compared AFS with EMRS disorders [48]. Gene activation patterns for AFS and EMRS showed differences from the pooled control, with AFS and EMRS showing both similarities and differences between themselves. Of interest was the finding that several genes differentially expressed in EMRS, and to some extent AFS, have been previously implicated to be involved in autoimmune and neoplastic diseases.

A comparison of features of the two analogous disorders, AFS and ABPA, is shown in Table 3.

Treatment

There are no published prospectively controlled studies for the treatment of AFS. Current treatment recommendations derive from retrospective and case series analysis, and modeling after the analogous disorder, ABPA. In ABPA, bronchial suctioning of an allergic mucin inspissate to relieve obstructive atelectasis, together with systemic corticosteroids, represent established primary treatment modalities [49]. An add-on

Table 3 ABPA and AFS

	ABPA	AFS
Allergic mucin with noninvasive fungal hyphae	Yes	Yes
Respiratory atopy	Yes	Yes
Allergy skin test positive to etiologic fungal organism	Yes	Yes
Total serum IgE elevated	Yes	Yes
Fungal-specific IgG elevated	Yes	Yes
Fungal-specific IgE elevated beyond common atopy	Yes	No
Serum precipitins to fungal organism	Yes	No
Peripheral eosinophilia	Yes	Yes/no
Change in total serum IgE prognostic	Yes	Yes
MHC class II association	Yes ^a	Yes ^b
Favorable clinical response to systemic corticosteroids	Yes	Yes ^c

^a HLA-DR2 and DR5; DQ2 was found to be protective. From: Chauhan B, Santiago L, Hutcheson PS, *et al. J Allergy Clin Immunol* 2000; **106**: 723–729.

^b HLA-DQB1*0301 and *0302 for *B. spicifera* AFS. From: Schubert MS, Hutcheson PS, Graff RJ, *et al. J Allergy Clin Immunol* 2004; **114**: 1376–1383.

^c From: Schubert MS, Goetz DW. *J Allergy Clin Immunol* 1998; **102**: 395–402.

treatment option with oral itraconazole has been shown to be effective in steroid-dependent cases [50–52].

The first step in treatment for any AFS patient is paranasal sinus surgery to both remove all obstructing inspissated allergic mucin and resect all diseased hypertrophic sinus mucosa [5,13,16,34]. Failure to adequately surgically remove all sinus disease leads to higher AFS relapse rates [5,13,16,38,34]. The addition of postoperative oral corticosteroids (OCS) in AFS, as

has been shown with ABPA, further reduces overall disease activity, including decreasing both symptoms and surgical recurrence rates (Fig. 3) [34,38]. Most experts now agree that adding OCS to sinus surgery gives the best outcomes [11,34,38,53,54]. Systemic antifungal drugs have not been shown to be effective in treatment of AFS [11,34,54–56]. Topical antifungals have not been adequately studied in AFS, but such treatment might be eventually shown to act in concert with OCS as has been shown in ABPA – we await the studies.

A retrospective analysis showed that AFS patients fared better on allergen immunotherapy to aeroallergens [55,56]. We have advocated allergen immunotherapy to all relevant aeroallergens, including the etiologic mold if known, in an attempt to reduce sinonasal allergic reactivity to the lowest possible levels [5,11,13]. The rationale is that any treatment that can realistically reduce the allergic inflammatory milieu felt to be conducive to AFS relapse and need for continued OCS and sinus surgery should be considered. Topical nasal steroids, antihistamines, and even antileukotrienes should be considered [5,11,15,53–57].

Conclusion

AFS is now recognized to be a distinct subgroup of the common hypertrophic rhinosinusitis disorders. Diagnosis is relatively straightforward when following proper published diagnostic criteria. Treatment remains challenging, with persistent or recurrent disease a common finding. The best outcomes are a product of coordinated medical-surgical care. The study of the immunopathogenesis of AFS continues to lead to insights into the pathophysiology of other forms of chronic rhinosinusitis, and may additionally lead to insights into other types of chronic inflammatory disorders.

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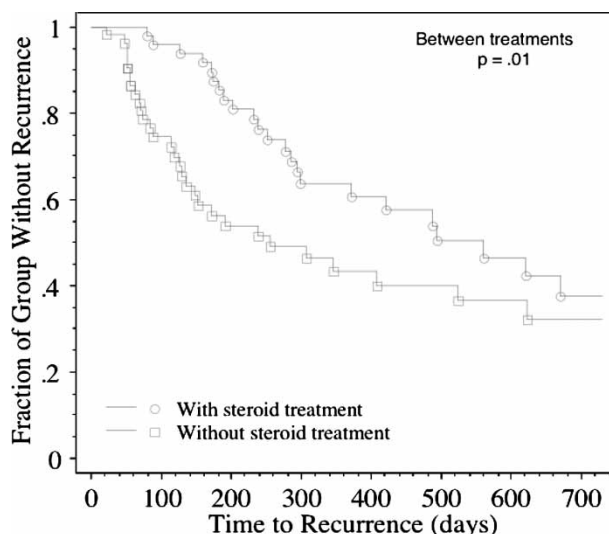


Fig. 3 Comparison of AFS recurrence rates between those treated with vs. without postoperative OCS. From reference 38 with permission.

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