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Allergic Fungal Sinusitis
Pathogenesis and Management Strategies

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Contents

Abstract

Allergic fungal sinusitis (AFS) is a noninvasive form of highly recurrent chronic allergic hypertrophic rhinosinusitis that can be distinguished clinically, histopathologically and prognostically from the other forms of chronic fungal rhinosinusitis. There are three invasive (acute necrotising, chronic invasive and granulomatous invasive) and two noninvasive (fungal ball and allergic fungal) forms of fungal rhinosinusitis currently recognised. Confusion in differentiating between the various forms of fungal rhinosinusitis and between other forms of chronic hypertrophic sinus disease (HSD) can be eliminated by adhering to strict diagnostic criteria. Although there are characteristic presenting clinical history and physical examination findings, laboratory test results, including elevated total serum IgE and positive inhalant allergy skin tests, and sinus computed tomography scans showing chronic rhinosinusitis (often with the presence of hyperattenuating sinus contents) diagnosis of AFS is essentially based on histopathology obtained from sinus surgery. Histopathology shows the presence of eosinophilic--lymphocytic sinus mucosal inflammation, extramucosal allergic mucin (that is also seen grossly at surgery as a characteristic 'peanut-buttery' material), and scattered silver stain positive fungal hyphae within the allergic mucin but not in the mucosa.

Treatment and follow up of AFS has been based on its immunopathological analogy to allergic bronchopulmonary aspergillosis, a similar noninvasive fungal hypersensitivity disorder of the lung, and its clinical and pathophysiological relationship to other forms of HSD and asthma. Treatment involves aggressive sinus surgery followed by medical management that includes allergen immunotherapy, topical and systemic corticosteroids, antihistamines and antileukotrienes. Total serum IgE levels should be followed postoperatively as they can be prognostic for recurrent disease. Close follow up and coordination of treatment by both medical and surgical physicians as a team leads to the best clinical outcomes. Ongoing studies are being directed at furthering our understanding of the pathophysiological relationships and treatment options for AFS, and other common forms of chronic hypertrophic rhinosinusitis disorders.

1. Fungal Rhinosinusitis

Five forms of fungal rhinosinusitis disorders are currently recognised, as clarified by deShazo et al.[1] (table I). Earlier medical literature did not differentiate between the various forms of fungal rhinosinusitis, leading to confusion in diagnosis, prognosis and treatment outcomes. Specific histopathological criteria are now applied to help differentiate the various forms of fungal rhinosinusitis, which have different clinical characteristics, treatment approaches and prognosis.[1,2] Three of the disorders are tissue-invasive, whereas the other two are nontissue–invasive. Both haematoxylin and eosin stains, and fungal stains such as periodic acid-Schiff and/or Gomori methenamine silver (GMS), of surgically resected tissue are required for proper diagnosis. Although fungal culture results may be helpful in planning treatment for invasive fungal rhinosinusitis, cultures are not usually required for diagnosis or treatment of the noninvasive forms as long as histopathological criteria are met. This review briefly discusses all of the forms of fungal rhinosinusitis, but focuses on allergic fungal sinusitis (AFS).

Table I. Currently recognised forms of fungal rhinosinusitis[1]

Invasive fungal rhinosinusitis
Acute necrotising fungal rhinosinusitis
Chronic invasive fungal rhinosinusitis
Granulomatous invasive fungal rhinosinusitis
Noninvasive fungal rhinosinusitis
Fungal ball (sinus mycetoma)
Allergic fungal rhinosinusitis

1.1 Invasive Fungal Rhinosinusitis

1.1.1 Acute Necrotising Fungal Sinusitis

Acute necrotising fungal sinusitis is the classic, clinically aggressive, tissue-invasive fungal infection of which most clinicians are aware. Patients are typically immunocompromised (cancer, immunosuppressive drugs, immune deficiency). Bone marrow transplant recipients have a reported incidence of any form of invasive fungal rhinosinusitis of up to 4%.[3] These patients may initially present with paranasal anaesthesia or fever.[4,5] A nasal, paranasal or palatal eschar spreads rapidly to involve paranasal sinuses, the face and orbit. *Rhizopus*, *Aspergillus* and *Mucor* spp. are common offending fungi, but many fungal species can be aetiological.[6] Histopathology shows tissue necrosis with invasion of fungal organisms into respiratory mucosa, often with the necrotising infection extending into juxtaposed soft tissues and bone. Treatment must be undertaken urgently and requires wide surgical debridement and intravenous antifungal drugs such as amphotericin B. Prognosis is poor without correction of the underlying predisposing immunocompromise.

1.1.2 Chronic Invasive Fungal Sinusitis

Chronic invasive fungal sinusitis is much less aggressive than the acute necrotising form. A retrospective histopathological analysis of 789 cases of

inflammatory sinusitis from the Mayo Clinic (Rochester, MN, USA) reported an incidence of invasive fungal sinusitis of 0.004% which represented any form of invasive disease.[7] Patients often have diabetes mellitus as an underlying risk factor, and may present with extension of the fungal infection from the ethmoid sinus into the orbit, the orbital apex syndrome.[8,9] Histopathology shows fungal invasion into the mucosa with an element of tissue necrosis, and an associated chronic inflammatory infiltrate along with granulomas and giant cells. Treatment requires aggressive surgical debridement and systemic antifungal drugs. Prognosis tends to be poor as the infection is often difficult to control.[1]

1.1.3 Granulomatous Invasive Fungal Sinusitis

Granulomatous invasive fungal sinusitis typically occurs in the immunocompetent host, and is a more indolent form of invasive disease that generally has a good prognosis. There may be two types of granulomatous invasive fungal sinusitis. One form, also called primary paranasal granuloma, has been described most often from Sudan,[10,11] usually culturing positive for *Aspergillus flavus*. Histopathology shows tissue invasion by fungi which can be extensive, noncaseating granulomas that include giant cells, and fibrinoid necrosis.[12] Recurrence after surgical resection and antifungal drugs occurs commonly and it may be difficult to treat.[13] The other form may be found incidentally in resected sinus mucosa from patients who have hypertrophic sinus disease (HSD) [histologically characterised as chronic eosinophilic-lymphocytic inflammation within oedematous hypertrophic and hyperplastic sinonasal mucosa and associated nasal polyps] or other forms of chronic rhinosinusitis; they may occasionally concomitantly have AFS (see section 3).[14] It has been reported at an incidence of 1.4%.[14] Histopathology shows a more limited microinvasion through the mucosal epithelium into the submucosa harbouring well-formed granulomas that contain the majority of the fungal hyphae. It may represent a disorder analogous to bronchocentric granulomatosis.[2,14,15] Bronchocentric granulomatosis is an indolent bronchial/peribronchial infection with *A. fumigatus* and occurs as an associated condition to allergic bronchopulmonary aspergillosis (ABPA). Treatment of this second, more indolent form is often complete with surgical resection alone, but oral antifungal drugs are commonly used postoperatively to increase confidence that any residual invasive disease is eliminated,[2,15] although there have been no studies addressing this.

1.2 Non-invasive Fungal Rhinosinusitis

1.2.1 Fungal Ball

Fungal ball (or sinus mycetoma) is a noninvasive form of fungal rhinosinusitis, representing an accumulation of many fungal hyphae compressed into a mat or ball lying within the sinus lumen extrinsic to the mucosa.[16] The incidence of fungal ball has been estimated at 3.7% of all inflammatory sinusitis going to surgery.[7] There may be associated HSD, although only one sinus is usually involved. There are no histological signs of true fungal infection, for example, no granulomas, giant cells or mucosal tissue necrosis. A low-grade chronic inflammatory infiltrate with associated fibrosis is typically seen within the juxtaposed sinus mucosa. Possible risk factors for acquiring fungal balls are previous sinus surgery, oral-sinus fistulas, previous chemotherapy and atopy;[15,16] often no risk factors are evident.[1] Treatment with surgical resection appears to be curative.[16,17]

1.2.2 Allergic Fungal Sinusitis (AFS)

First reported in 1981 by Millar et al.,[18] AFS is a noninvasive fungal rhinosinusitis with associated HSD that represents an allergic and immunological response to the presence of fungal hyphae found within the sinus cavities. The remainder of this review focuses on this challenging new allergic disorder.

2. Diagnosis of AFS

Patients with AFS tend to be young (average age early 30s), immunocompetent, atopic and initially present with HSD and associated nasal polyps.[1,14,19-21] Although many cases have been reported from the southern and southwestern states of America, AFS occurs throughout the US and

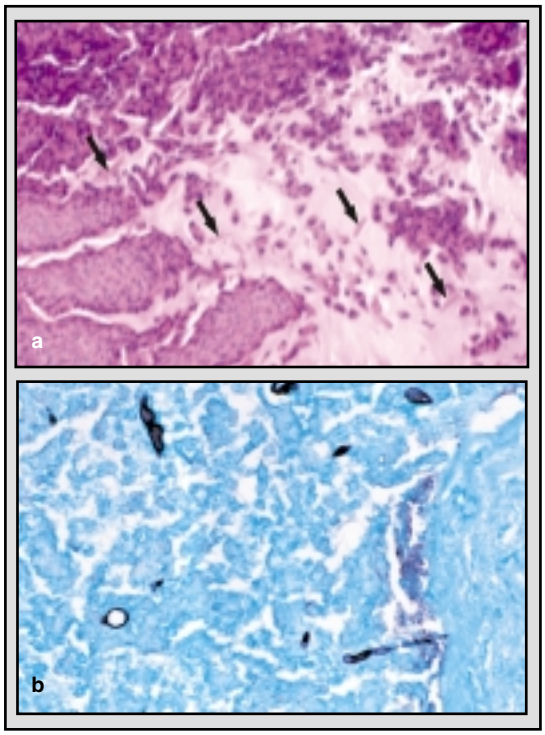

Fig. 1. Histopathology of allergic fungal sinusitis. (**a**) Inspissated allergic mucin; Charcot-Leyden crystals (arrows); haematoxylin and eosin × 40 (original magnification); and (**b**) Gomori methenamine silver stain of allergic mucin showing *Bipolaris spicifera* hyphae; × 100 original magnification.

worldwide (reviewed in Ferguson et al.[22]). The incidence of AFS has been estimated to be about 6% of all chronic sinusitis going to surgery;[7,23,24] a recent report from Southern Australia found the incidence there to be 9%.[25] AFS patients often give a history for nasal cast production,[14] 'green to blackish rubbery formed elements' expelled from the nose. These casts are made of allergic mucin, a thick 'peanut-buttery' inspissate seen grossly at sinus surgery that is comprised primarily of concreted masses of eosinophils with associated mucus and Charcot-Leyden crystals[14,19,21,24] (figure 1a). Allergic mucin is histologically identical to the inspissated bronchial mucus plugs seen in allergic bronchopulmonary aspergillosis (ABPA). Scattered fungal hyphae are seen within the allergic mucin when stained with the GMS fungal stain[14,19-21,23,24,26] (figure 1b); they may be hard to find.

Diagnostic criteria for AFS are primarily histopathological and obtained from sinus surgery specimens[2,14,19-21,23,24,26-29] (table II). The sinus mucosa shows a typical HSD inflammatory infiltrate comprised of eosinophils, small lymphocytes and plasma cells, the mucosa is hypertrophic and hyperplastic, and the extramucosal allergic mucin that is present contains small numbers of fungal hyphae. There is no mucosal necrosis, nor evidence for giant cells or granulomas within the mucosa. Tissue invasion by fungi does not occur unless an invasive fungal rhinosinusitis form is present. Rarely, the indolent form of granulomatous invasive fungal sinusitis has been seen in concert with AFS[14] (see section 1.3).

Dematiaceous fungi, most commonly *Bipolaris spicifera*, but including *Curvularia*, *Exserohilum* and *Alternaria* species, are cultured from AFS surgical sinus cultures most often, followed by *Aspergillus* spp.[14,19-21] *B. spicifera* may predominate in the southwest of the US and *Curvularia lunata* in the southern US.[14,21,27] *B. spicifera* spores are found in the ambient outdoor air in significant amounts in the autumn in Phoenix, Arizona, USA, a 'hot spot' for AFS.[14] A recent paper that concluded *A. fumigatus* was the primary AFS aetiological microbe from the southern US was based on an attempt to histologically identify the fungus found within *in situ* allergic mucin by GMS stain, but was not supported by surgical sinus culture results that showed 14 of 18 AFS patients described actually grew dematiaceous fungi and not *A. fumigatus*.[27] This underscores the potential inaccuracy of attempted *in situ* fungal speciation in AFS by histological fungal stains in the

Table II. Histopathological diagnostic criteria for allergic fungal sinusitis (all criteria must be met) [adapted from Schubert and Goetz[14]]

1.	Characteristic allergic mucin is seen histopathologically and/or grossly
2.	Fungal stain is positive for hyphae within the allergic mucin but not in the mucosa, or the surgical sinus fungal culture is positive in an otherwise characteristic patient
3.	The sinus mucosa demonstrates eosinophilic-lymphocytic inflammation without evidence for tissue necrosis, granulomas or fungal invasion
4.	Other fungal diseases are excluded

absence of surgical sinus culture data. A controversial report from Ponikau et al.[28] concluding that all patients with HSD have AFS has been criticised because of its reliance on nasal culture where even control patients without HSD were positive.[30-32]

Sinus computed tomography (CT) is always abnormal, often showing chronic sinusitis throughout multiple sinuses (figure 2a), although AFS may often present with unilateral findings.[2,14,20,21,25] A high density or hyperattenuating region within the abnormal sinus(s) on CT is often seen[2,15,19] (figure 2b). Such CT hyperattenuation may also be seen in other fungal rhinosinusitis forms, particularly fungal ball.[16] It may also be seen in the presence of HSD with associated inspissated allergic mucin but without the presence of fungi, currently termed eosinophilic mucin rhinosinusitis.[2,15,33-35]

3. Immunopathology of AFS

Much of what we know about the immunopathogenesis of AFS draws a strong analogy to allergic bronchopulmonary aspergillosis. In ABPA, *A. fumigatus* is found within inspissated bronchial allergic mucin in a patient with severe asthma; very high titres of fungal-specific IgG and IgE are found in serum along with peripheral eosinophilia.[36,37] In *B. spicifera* AFS, *B. spicifera* is found within inspissated sinus allergic mucin in a patient with HSD; high titres of fungal-specific IgG are found in serum, but not as high as in ABPA.[14] Although such patients are uniformly skin test positive for type I immediate hypersensitivity to *B. spicifera*, fungal-specific IgE in serum is no higher than that found in common *B. spicifera* inhalant atopy.[14] As in ABPA, the vast majority of patients with AFS are allergic to multiple aeroallergens,[14,19-21] with an 100% incidence of inhalant atopy reported in patients with AFS from the southwest of the US.[14] Total serum IgE levels are often elevated in AFS, but not as high as in ABPA.[14] Peripheral eosinophilia does not occur uniformly in AFS, and erythrocyte sedimentation rates are generally not elevated.[14] AFS has even occasionally been seen concomitantly with the analogous bronchial disorder, usually involving the same fungal organism in both the upper (sinonasal) and lower (bronchial) airways, with the suggested term being sinobronchial allergic mycosis syndrome.[38] Taken together, the immunopathology of AFS and ABPA appears similar but not identical (table III), suggesting a magni-

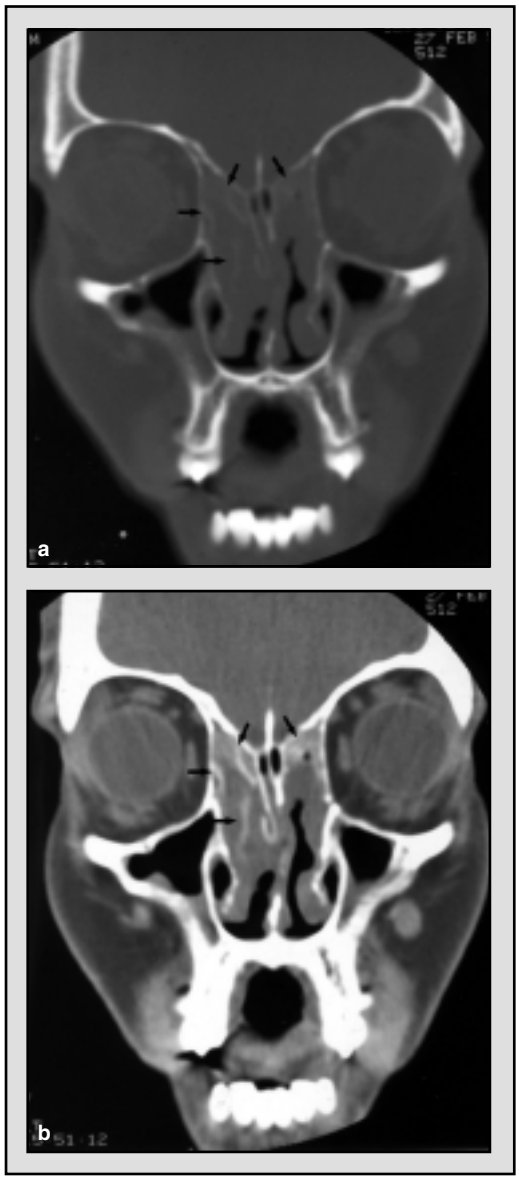

Fig. 2. Representative allergic fungal sinusitis patient sinus computed tomography scan. (**a**) Arrows point to suspected areas of allergic mucin; and (**b**) photography at soft tissue windows to accentuate hyperattenuating allergic mucin (arrows).

Table III. Immunopathology of allergic bronchopulmonary aspergillosis and allergic fungal sinusitis (adapted from Schubert and Goetz[14])

Feature	ABPA	AFS
Characteristic extramucosal allergic mucin containing fungal hyphae	Yes	Yes
Eosinophilic-lymphocytic respiratory mucosal inflammation	Yes	Yes
Common inhalant atopy	Yes	Yes
Positive allergy skin test to aetiological fungus	Yes	Yes
Elevated total serum IgE	Yes	Yes
Elevated fungal-specific IgG	Yes	Yes
Change in total serum IgE and fungal-specific IgG mirrors clinical status	Yes	Yes
Fungal-specific IgE elevated above that found in common atopy to aetiological fungus	Yes	No
Fungal-specific precipitins	Yes	No
Peripheral eosinophilia	Yes	No

ABPA = allergic bronchopulmonary aspergillosis; **AFS** = allergic fungal sinusitis; **Ig** = immunoglobulin.

fied immunological response in ABPA as compared with AFS. The reason(s) for this are unknown, but may relate to target organ and/or aetiological microbial differences between the two disorders.

The allergic mucin in AFS contains prominent amounts of extracellular eosinophil-derived major basic protein[39] which is known to be proinflammatory,[40] and is believed to play an important role in the inflammatory pathology of AFS. Additionally, AFS patient sera recognised by IgE immunoblotting an 18kD fungal protein within surgically obtained AFS allergic mucin, and IgE from all tested AFS patient sera recognised the same 18kD protein in all commercial fungal extracts selected, suggesting a potential 18kD fungal panallergen in AFS.[41]

Total serum IgE levels during ABPA follow up are prognostic, acting as an allergic acute phase reactant.[39,42] Similar results have been found in AFS, where a falling total serum IgE levels correlated with clinical improvement, a rising IgE with clinical worsening and the absolute total serum IgE level correlated with rhinosinusitis clinical severity.[43]

Interest in the pathogenesis of AFS, as well as other forms of HSD, has also focused on the early steps in the immunological recognition and response to foreign antigens. Genes for the human leucocyte antigen (HLA)-associated major histocompatibility complex (MHC) class II molecules that bind and display foreign peptides on antigen presenting cells are inherited. Such HLA MHC class II genetics place constraints on an individual's ability to immunologically present and to subsequently recognise, via T cells, specific foreign peptides that effect the final immune response generated. It was recently reported that patients with AFS primarily carry HLA MHC class II genes for *HLA DQ3*.[44] In contrast, patients with ABPA carry *HLA DR2* and *HLA DR5* genes as a risk factor for disease; *HLA DQ2* appears to be protective.[45]

It has recently been theorised that common chronic eosinophilic-lymphocytic respiratory mucosal inflammatory disorders, such as AFS, other forms of HSD, ABPA and chronic severe asthma, are all interrelated immunopathologically and may be microbial T-cell superantigen-driven disorders.[46] T-cell superantigens are microbial toxins that activate T cells through the T-cell receptor but bypass antigen specificity.[47] T-cell receptors for foreign antigens dictate the specificity of antigen recognition by T cells; they also have heritable elements, including the V beta component of the T-cell receptor that carries the superantigen binding motif.[47,48] Superantigens bind the side of the HLA class II molecule on the antigen-presenting cell, and the side of the T-cell receptor at the V beta motif on the responding T cell simultaneously, bridging the two and activating the T cell inappropriately. Whereas antigen-specific T cells have a baseline (preimmunised) frequency of about 0.01%, a given superantigen is potentially capable of activating up to 30% of all T cells.[49] If locally present in the respiratory mucosa, microbial T-cell superantigens are theoretically capable of amplifying T-cell activity inappropriately into a chronic severe inflammatory process, in patients who carry the proper T-cell receptor V beta motifs for the relevant superantigen(s).[46]

It has been suggested that the aetiological fungus (AFS, ABPA) with or without the contribution of *Staphylococcus aureus* (AFS, HSD, asthma), human

endogenous retroviruses (AFS, ABPA, HSD, asthma) or other specific microbes are the source of such putative superantigens.[46] Some of the evidence consistent with the superantigen hypothesis in HSD and asthma includes: the finding of anti-*S. aureus* enterotoxin superantigen IgE in HSD nasal polyps, that correlates with *in situ* total and allergen-specific IgE levels, interleukin 5 and eotaxin;[50] an association between serum anti-*S. aureus* enterotoxin superantigen IgE and chronic severe asthma;[51] and the finding of a restricted heterogeneity of T-cell receptor V beta motifs of the type that bind common microbial superantigens on T cells from bronchoalveolar lavage in patients with chronic severe asthma.[52] More research will be required in the future to prove whether or not the superantigen theory for AFS, HSD, ABPA and chronic severe asthma pathogenesis is correct, thus leading to new treatment strategies for these related disorders.

4. Treatment of AFS

Postoperative medical treatment of AFS is usually required because AFS is a highly recurrent disease.[30,43] Unfortunately, there are no published double-blind, placebo-controlled studies of any therapeutic modality for AFS. However, it is important to note that AFS is a noninvasive fungal rhinosinusitis and does not represent a fungal infection *per se*, but rather an inflammatory/hypersensitivity-related disorder. Any approach to treatment of AFS should be designed to take this into consideration. Previous attempts at treatment of AFS with systemic antifungal drugs have generally met with failure,[53-58] presumably because AFS is not a tissue-invasive fungal infection; our experience has been similar. A recent case report described clinical improvement in one AFS case treated with oral itraconazole, although the patient was already being treated with oral corticosteroids.[59] A recent paper showed oral corticosteroid requirements in chronic ABPA, the disorder analogous to AFS, could be reduced in some patients with the addition of itraconazole.[60]

The use of topical antifungal drugs such as nasal amphotericin B or itraconazole in AFS have been suggested but not adequately studied. However, the anatomical constraints that present with any form of HSD, including AFS, presents difficulty in assuring adequate exposure of the deep sinuses with any drug via nasal application. Recent limited published experiences with nasal nebulised or lavaged antimicrobials for various chronic rhinosinusitis disorders have not been compared with saline control treatments[61-63] and it is currently unknown whether such an approach will prove to be efficacious in AFS or any other forms of HSD. A recent controlled study in patients with HSD comparing nebulised nasal tobramycin with saline showed some symptomatic improvement with saline but no benefit from the addition of tobramycin.[64] One study suggested that chronic pseudomonas sinusitis in patients with cystic fibrosis responded to aminoglycoside topical treatment when administered by surgically placed and fixed indwelling deep sinus catheters.[65]

It is clear that medical treatment for AFS is unlikely to be successful without adequate initial sinus surgery.[2] Failure to remove all fungal-containing allergic mucin and obstructing inflammatory hypertrophic/hyperplastic sinus mucosa renders the patient much less responsive to medical management by fostering persistent and recurrent disease.[2,14,15] Recurrence of AFS is not unusual, even with seemingly adequate surgical and postoperative medical treatment.[14] Initial surgery should be undertaken both as soon and as thoroughly as possible. It is also important that both medical and surgical management be coordinated for an optimal outcome.[2]

In ABPA, use of oral corticosteroids have proved to be the most effective medical treatment and are considered standard therapy.[37] Bronchoscopy can be considered the surgical equivalent. Evidence that AFS is an analogous disorder led to the use of oral corticosteroids.[24,29,30,43,66-73] The largest published series is a retrospective comparison of 67 AFS cases over 8 years treated with or without a postoperative oral corticosteroid protocol modelled after that used for ABPA but modified for AFS.[43] Patients were given an oral corticosteroid protocol immediately postoperatively, prednisone 0.5 mg/kg every morn-

ing for 2 weeks, followed by 0.5 mg/kg every other morning for two more weeks, with a gradual taper of the dose to prednisone 5–7.5mg every other morning by 3 months. The dose at 5mg every other morning was then maintained over the remainder of one year. Short bursts of prednisone to 20mg daily for 4–7 days, followed by rapid taper to the baseline 5mg alternate day dose, were used for intercurrent acute viral rhinosinusitis episodes to prevent AFS recurrence which is common under these circumstances.[43] All patients were also treated with relevant allergen immunotherapy, anti-inflammatory nasal sprays and antihistamines. Those who took the oral corticosteroid protocol maintained significantly decreased rhinosinusitis scores and surgical recurrence rates postoperatively. At least 2 months of postoperative oral corticosteroids gave significant clinical improvement even at 1 year of follow up, but 1 year of oral corticosteroid treatment yielded the best results. No significant complications of oral corticosteroid treatment were seen with this protocol, including no cases of subsequent fungal tissue invasion.

Specific allergen immunotherapy has been recommended as adjunctive therapy for AFS[2,43,74] but there are no controlled studies. A recent noncontrolled study of immunotherapy directed against the multiplicity of allergens to which the AFS patients were allergic, concluded clinical benefit in the first 3 years of postoperative treatment, but the AFS aetiological fungal spores were generally not available for treatment.[74] One case report of *B. spicifera* immunotherapy for *B. spicifera* AFS suggested clinical improvement.[75] Many other cases of immunotherapy use in AFS have been published.[43,76] Use of the aetiological mould in the immunotherapy mix has not been felt to be contraindicated because precipitating antibody was generally not found in *B. spicifera* AFS, a presumed risk factor for possible immunotherapy-induced Arthus reactions.[2,14] The rationale behind recommending immunotherapy is that inhalant atopy is part of the pathognomy of AFS and any treatment that could realistically reduce the sinonasal allergic milieu felt to be conducive to AFS relapse and its subsequent requirement for repeat sinus surgery and continued oral corticosteroids, would be desired.

The inflammatory histopathology of AFS, as well as HSD in general, closely resembles that of asthma.[14,46] This suggests that systemic anti-inflammatory drugs used for the treatment of asthma, in addition to oral corticosteroids, might be beneficial in AFS and other forms of HSD. Clinical improvement in HSD by cysteinyl leukotriene antagonism with zafirlukast and inhibition of production of cysteinyl leukotrienes by 5-lipoxygenase inhibition with zileuton (drugs used for the treatment of asthma) have been reported.[77,78] A case report describing successful use of the antileukotriene drug montelukast in AFS was also recently published.[79] Other suggested and commonly used adjunctive medical treatments for AFS include nasal corticosteroids, antihistamines and sinonasal saline lavage.[2,15,25,43,80]

5. A Practical Approach to Managing AFS

A practical approach to managing AFS is shown in table IV. Proper diagnosis and differentiation of AFS from the other forms of fungal rhinosinusitis is required before planning any treatment strategy. A diagnosis of fungal sinusitis is inadequate, often leads to confusion and is potentially dangerous.[2,15] Also, although the presence of allergic mucin is necessary for the diagnosis of AFS (table II), it is not sufficient. Allergic mucin that is associated with common forms of non-AFS HSD, such as Samter's syndrome (aspirin triad) and other forms of eosinophilic mucin rhinosinusitis, can mistakenly be called fungal debris in operative reports without appreciating that allergic mucin is a specific histopathological entity which has a characteristic intraoperative 'peanut-buttery' appearance that can also occur in the absence of fungi.[2,15,33-35] AFS should also not be diagnosed by nasal fungal culture.[2]

After the diagnosis of AFS is made and a physical examination completed, patients should be skin tested for inhalant allergy (including the aetiological fungus, if available) and should have screening laboratory tests, including: total serum IgE, com-

Table IV. Practical management of allergic fungal sinusitis

Review the preoperative sinus computed tomography scan, surgical pathology and microbiology
Physical examination, laboratory testing to include inhalant allergy skin testing and screening laboratory tests
Use allergy medications to include corticosteroid nasal sprays and antihistamines; consider antileukotrienes if not contraindicated
Use allergen immunotherapy to all relevant inhalants as determined by skin testing; the aetiological mould should be included if available
Start oral corticosteroids as soon as possible postoperatively if not contraindicated
Follow up closely and routinely with medical and surgical specialists; use the total serum IgE as a follow-up diagnostic tool; obtain total serum IgE monthly for 6 months postoperatively, then intermittently as indicated
If the total serum IgE rises in the context of worsening rhinosinusitis, temporarily increase the oral corticosteroid dose and obtain surgical evaluation
For intercurrent acute rhinosinusitis episodes use a short burst of higher dose oral corticosteroids; add antibacterials if indicated
If AFS recurs, re-operate and restart the oral corticosteroid protocol from the beginning; review all surgical findings including histopathology
Avoid significant oral corticosteroid-related adverse effects
Discontinue oral corticosteroids after 1 year, or sooner/later as indicated

AFS = allergic fungal sinusitis; **Ig** = immunoglobulin.

plete blood count, comprehensive metabolic panel (SMAC-20), erythrocyte sedimentation rate, quantitative immunoglobulins, urinalysis, delayed hypersensitivity skin tests to T-cell recall antigens (including the tuberculous purified protein derivative), chest radiograph and spirometry.[2,14]

If the patient is being considered for postoperative oral corticosteroid use, eye examination for cataracts and glaucoma, and bone densitometry (if indicated) should be obtained. These screening tests will help to rule out medical conditions that would tend to contraindicate the use of oral corticosteroids (such as diabetes mellitus, positive PPD), and will confirm that the patient is otherwise healthy, immunocompetent and not at unusual risk for complications such as serious infection or significant oral corticosteroid-related adverse effects.

The patient should start postoperative medical treatment as soon as possible. Undue delay in starting medical treatment, particularly oral corticosteroids, may lead to early AFS recurrence.[2] Postoperative oral corticosteroids using either the modified ABPA protocol[43] (as described in section 5), or a similar protocol, should be considered after fully explaining the potential risks and benefits. Relevant allergen immunotherapy based on complete inhalant skin testing, and the aetiological AFS mould if available, and medications such as nasal corticosteroids, antihistamines and antileukotrienes should be started if not contraindicated.

The total serum IgE should be followed postoperatively at intervals.[14] Oral corticosteroids should be continually tapered toward the 5mg alternate day maintenance dose in conjunction with a falling and stabilising total serum IgE value. If the total serum IgE rises 10% or more in the context of worsening rhinosinusitis, the prednisone should be temporarily raised and tapered again. If the total serum IgE continues to rise with subsequent oral corticosteroid tapering, surgical re-evaluation should be obtained. Coordinated postoperative surgical follow up should also be routinely obtained at regular intervals along with medical follow-up evaluations with oral corticosteroid dose administration instructions. If AFS has recurred, surgery should be performed to remove all disease, histopathological examination of all resected sinus material should be reviewed with the pathologist and surgical fungal/bacterial cultures should also be reviewed. The oral corticosteroid protocol should be restarted postoperatively from the beginning and tapered as before. Oral corticosteroids have been given for up to 1 year of treatment using the modified ABPA protocol as published,[14] but can be discontinued sooner or continued longer as the circumstances warrant. The role of oral corticosteroids (as well as the other medical management) is to reduce AFS recurrence rates and symptoms of recurrent rhinosinusitis. A further goal of therapy is to avoid significant oral corticosteroid-related adverse effects.

6. Conclusion

Fungal rhinosinusitis presents in three invasive and two noninvasive forms. Each form has different clinical presentations, treatment options and poten-

tial outcomes. AFS represents a noninvasive form of fungal rhinosinusitis with recognisable clinical and histopathological findings that have led us to specific therapeutic approaches. The immunopathophysiology appears somewhat similar to ABPA, the analogous disorder in the lung. Postoperative follow up of total serum IgE levels is prognostic. Treatment has been modelled after ABPA, with physical removal (sinus surgery for AFS, bronchoscopy for ABPA, if necessary) and chronic anti-inflammatory treatment postoperatively that may include oral corticosteroids administered by published protocols. Treatment with oral corticosteroids, along with other medical management that includes relevant allergen immunotherapy, reduces rhinosinusitis activity and forestalls the need for recurrent sinus surgery in this highly recurrent disease. New anti-inflammatory medications, such as antileukotrienes, have shown promise and are being further studied. Future research in AFS, as well as related chronic eosinophilic-lymphocytic respiratory mucositis disorders, such as other common forms of HSD and chronic severe asthma, will further refine our understanding of their pathogenesis, potential interrelatedness and attendant management strategies.

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