

Allergic Fungal Sinusitis

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Abstract

Many common chronic inflammatory rhinosinusitis conditions (hypertrophic sinus disease [HSD]) have the histopathological profile of allergic or asthmatic inflammation. Allergic fungal sinusitis (AFS) is both a type of noninvasive fungal rhinosinusitis and a type of HSD. AFS has clinicopathological features that make it similar, but not identical, to allergic bronchopulmonary aspergillosis (ABPA). Allergic mucin is a defined pathological entity occurring in ABPA, AFS, and in the HSD "eosinophilic mucin rhinosinusitis (EMRS)." Diagnosis of AFS requires a careful review of surgical reports, histopathology, and culture results. Treatment includes surgery and aggressive postoperative medical management of allergic inflammatory disease. Prognosis is good with integrated medical-surgical follow-up, but recurrence remains problematic. The association of ABPA, AFS, and HSD with class II genes of the major histocompatibility complex places the initiation of these inflammatory diseases within the context of antigen presentation and the acquired immune response. Pathological immunomanipulation of this response by local microbial superantigens may be a common mechanism for disease pathogenesis. Future research into the molecular biology of these related conditions may offer insight into the pathogenesis of other chronic inflammatory diseases.

Index Entries

Allergic fungal sinusitis; chronic rhinosinusitis; allergic bronchopulmonary aspergillosis; *Bipolaris spicifera*; *Staphylococcus aureus*; aspirin triad; nasal polyp; allergic mucin; phaeohyphomycosis; superantigen; antigen-presenting cell; human leukocyte antigen; MHC class II; HLA-DQB1*03; immunoglobulin E; inflammation; fungal diseases treatment; corticosteroids.

Rhinosinusitis

In the past, it was common to ascribe the general term “sinusitis” to any infectious or inflammatory process involving the paranasal sinuses. More recent research over the last decade from numerous centers has led to the consensus that “sinusitis” actually represents a heterogeneity of inflammatory paranasal sinus conditions (1–3). Some of these are infectious, and some are noninfectious; some are acute in onset and some are chronic. Therefore, a modifier or descriptive term applied to “sinusitis” is now required to differentiate one type of “sinusitis” condition from another. There is also a growing trend to use the term “rhinosinusitis” (RS) rather than “sinusitis” in recognition of the contiguous and potential functional integration of the nose in infectious and inflammatory paranasal sinus processes (3). Chronic RS can develop as a continuation of unresolved acute RS, can represent a dysfunctional chronic inflammatory sinonasal mucositis, or can involve some combination of infection, anatomy, and other predisposing host factors (1–4). Our recognition of the pathophysiological and clinical heterogeneity of all of the RS disorders now necessitates a much more specific description of the “type” of RS being discussed. This is important for both current treatment and future research.

Chronic Inflammatory RS (Hypertrophic Sinus Disease)

Chronic inflammatory RS conditions (hypertrophic sinus disease [HSD]) can be compared by their variations in phenotypic presentations (1–5), such as those with or without sinonasal polyp formation, aspirin (ASA)/nonsteroidal anti-inflammatory drug (NSAID) hypersensitivity, asthma, presence or absence of inhalant atopy, inspissated allergic mucin formation (so-called “eosinophilic mucin rhinosinusitis” [EMRS], which is discussed later), cystic fibrosis or the related cystic fibrosis mutation het-

erozygotes, the ciliary dyskinesias, or those with sinus involvement of extramucosal fungi, such as fungal ball/mycetoma and allergic fungal RS (AFS; discussed later). The sinus mucosa in HSD becomes dysfunctional, hypertrophic, hyperplastic, and often forms polyps (1,3,5,6). The mucosal inflammation can be characterized as “allergic” or “asthmatic” because it is usually comprised of eosinophils, small lymphocytes, and plasma cells (1,5–7). The inflammatory cytokine profile from involved sinus mucosa recapitulates that found in the bronchial mucosa in allergic and nonallergic asthma, respectively (4). Extracellular eosinophil degranulation products within the mucosa—particularly major basic protein—likely play an important role in promoting sinonasal mucosal injury (8). Additionally, HSD with or without polyps may have differing *in situ* matrix metalloproteinase profiles (9) and cytokine profiles further differ in cystic fibrosis sinonasal polyps (10). Therefore, along with their associated clinical phenotypes, HSD conditions can be additionally characterized by their histopathological and cytokine profiles. A controversial hypothesis proposed by Ponikau et al. (11) stated that all HSD conditions should be renamed “eosinophilic fungal RS” because they felt that patients with any form of HSD actually have fungi in their sinus mucus as the primary inflammatory stimulus for disease. However, this hypothesis has been criticized because of the mucus-acquisition techniques and office-based transnasal fungal cultures in which control patients experienced similar results (12–16).

Fungal RS Disorders

Fungal RS can occur as either invasive or noninvasive diseases (12,18). Invasive fungal RS diseases are true tissue-invasive infections, presenting in three different forms: acute necrotising, chronic invasive, and granulomatous invasive (indolent). Noninvasive fungal RS occurs as fungal ball (sinus mycetoma) and AFS.

In noninvasive fungal rhinosinusitis, fungal hyphae do not penetrate the mucosal barrier but reside within the sinus lumen. Each form of fungal RS can be differentiated histopathologically. Clinical presentations, comorbidities, and prognosis are also characteristic.

Acute necrotizing fungal RS is the classic fungal infection, occasionally referred to as "mucormycosis" (17,19). Its incidence has been reported at 4% of bone marrow transplant recipients (29). Although *Rhizopus* is a common offender, virtually any fungi can be causative (19,21). The infection often starts with fever, a nasal eschar, or paranasal anesthesia (19). It is seen most often in immunocompromised patients. Rapid spread of the fungal infection from sinonasal mucosa to surrounding soft tissues and bone must be dealt with by systemic antifungal drug treatment and wide surgical debridement of infected and devitalized tissues (18,19,22). Surgical histopathology shows necrosis, tissue-invasive fungal hyphae, and an inflammatory infiltrate that varies depending on the level of host immunocompetence (18). The prognosis is poor, particularly without correction of the predisposing host immunocompromise.

Chronic invasive fungal RS is less aggressive than acute necrotizing disease in its presentation and clinical course (17,18). It is observed most often in patients with diabetes mellitus or immunocompromise. Ethmoid fungal infection commonly causes the orbital apex syndrome (23,24). Histopathology shows tissue-invasive fungal hyphae, necrotizing granulomas, and a mixed acute and chronic inflammatory infiltrate. Treatment requires systemic antifungal drugs and surgical debridement. The infection often recurs and can be difficult to treat (18,19).

Granulomatous invasive (previously called "indolent") fungal RS is a limited "micro-invasion" of the sinus mucosa (12,17,25). Invading fungal hyphae are well-contained within necrotizing granulomas at the surface of the sinus mucosa. There is no significant tissue invasion by fungi outside of such granulo-

mas. In addition to granulomas and giant cells, a chronic inflammatory infiltrate with variable numbers of small lymphocytes, plasma cells, and occasional eosinophils is usually present (25). Patients are immunocompetent, and the most common predisposing risk factor is previous sinus surgery for some type of chronic recurring RS (25). Occasionally, granulomatous invasive fungal RS is observed within the context of another fungal RS disorder, such as AFS (25,26). Of the AFS cases from the southwestern United States, 1.5% of patients were reported to have concomitant granulomatous invasive fungal RS (26). The southwestern United States cases typically involved dematiaceous fungi. Other published cases include those from the Sudan (because of *Aspergillus flavus*) and St. Louis, MO (27,28). Treatment is complete if all diseased sinus mucosa is resected, but oral antifungal drugs are commonly administered for a period of time postoperatively to ensure that all potential fungal infection has been eradicated. Continued medical treatment for ongoing HSD is still required in many cases.

Fungal ball, or sinus mycetoma, is found in 3.7% of all sinus surgeries (29). It is a noninvasive condition in which many devitalized fungal hyphae are found compressed into a mat or ball within the sinus cavity (25,30). Histopathology of the juxtaposed hypertrophic sinus mucosa shows chronic inflammation and fibrosis, but no giant cells, granulomatous inflammation, or necrosis. Risk factors include oral-sinus fistula or previous sinus surgery, although no risk factors may be evident (25). Surgical resection is curative.

AFS is the other noninvasive fungal RS disorder. It has distinguishing clinical, histopathological, and immunological characteristics. The remainder of this article focuses on this challenging new sinus disease, including its relationship to other types of HSD.

Allergic Fungal Sinusitis

AFS was first described in 1981 as "allergic aspergillosis" (31). A subsequent study from

Chicago in 1983 by Katzenstein et al. significantly expanded the number of reported cases and confirmed the definitive histopathological description of this condition (32). They found that 6% of 113 retrospective, but consecutive, surgical sinusitis cases had a characteristic histopathology. This included the presence of an extramucosal inspissate of *allergic mucin*—so named in deference to the previously accepted pathological term for the same material that was known to obstruct bronchi in allergic bronchopulmonary aspergillosis (ABPA) (33). The use of the modifier “allergic” denoted a histologically defined inflammatory process variably comprised of two basic cell types—eosinophils and lymphocytes. Hematoxylin and eosin staining of the allergic mucin showed it to be comprised of masses of many pyknotic eosinophils (eosinophil concretions) with surrounding areas of thin, pink-stained mucus where Charcot–Leyden crystals were observed; sparse numbers of fungal hyphae were found within this when stained with the Gomori methenamine silver (GMS) fungal stain. The sinus mucosa demonstrated eosinophilic–lymphocytic inflammation characteristic of allergic asthma; no tissue invasion by fungi was found. They named the condition allergic aspergillus sinusitis, although fungal cultures had not been available. In 1990, Gorley and colleagues reported *Bipolaris spicifera* as a common etiological agent from the southern United States (34). They also found *B. spicifera* serologies to be analogous to those seen with *Aspergillus fumigatus* serologies in ABPA. Many more cases have been published, and the condition is now named AFS.

AFS Clinical and Histopathological Presentation

AFS has an incidence of 6 to 9% of all the HSD cases that require surgery (32,35). Patients present with nasal polyps, which can be unilateral (25,36–38). The sinus CT scan always shows evidence for extensive rhinosinusitis,

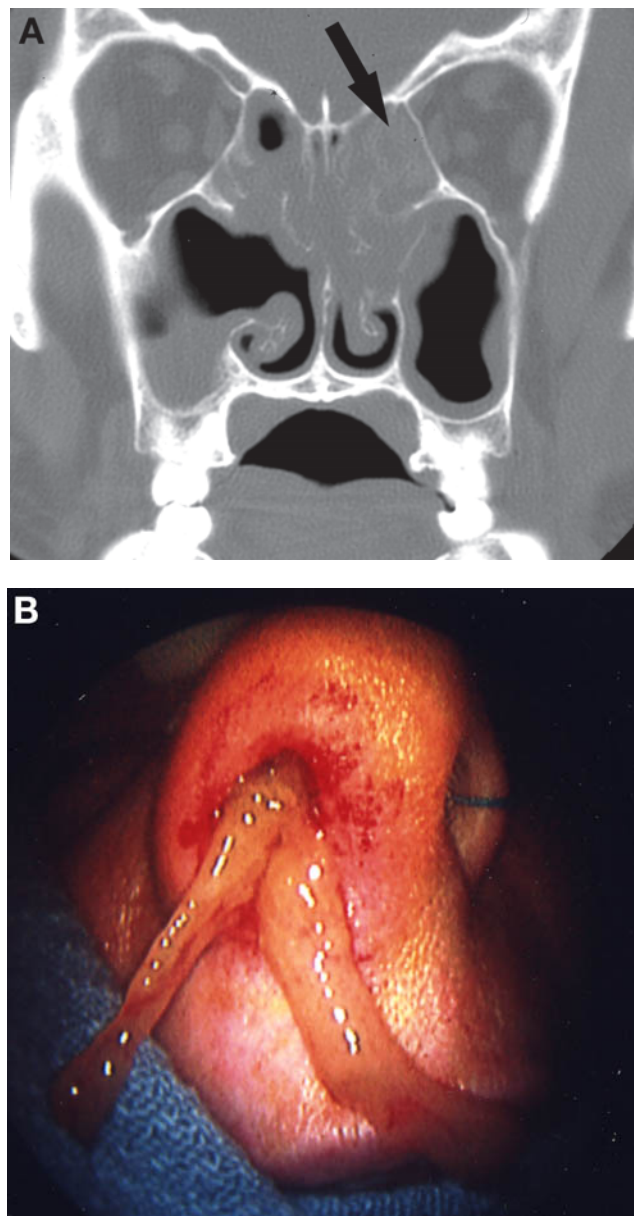


Fig. 1. (A) Sinus CT of a 17-yr-old male with *Bipolaris spicifera* allergic fungal sinusitis (AFS); allergic mucin (arrow). (B) Allergic mucin in a 23-yr-old female with *B. spicifera* AFS. (Photo courtesy of David Hecht, MD.)

often with areas of increased contrast (“hyperattenuation”) resulting from fungal-containing allergic mucin (25,36–38) (Fig. 1A). The allergic mucin and associated hypertrophic sinus mucosa may occasionally expand and extend through the sinus wall into the orbit or intracranium, but no tissue invasion by fungi is

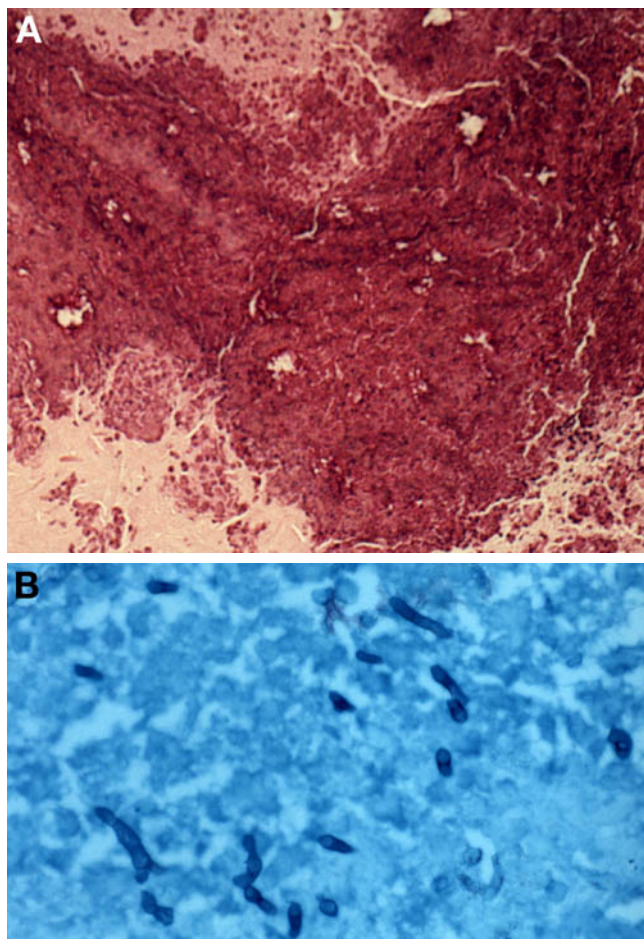


Fig. 2. (A) Allergic mucin (H&E $\times 40$). (B) Scattered fungal hyphae within allergic mucin (GMS $\times 100$).

observed on histopathology (12,18,25). Such extra-sinus extension presumably results from bone resorption under pressure from the expanding allergic mucin mass.

Allergic mucin has the appearance of “peanut butter” at surgery (25,26,34,36–38) (Fig. 1B). The allergic mucin (Fig. 2A) contains sparse numbers of fungal hyphae when visualized by GMS staining (Fig. 2B) (25,26). Occasionally, no hyphae can be found because of issues with surgical sampling or pathology sectioning, but in such cases, the surgically obtained allergic mucin fungal culture should be positive in an otherwise characteristic patient (25,26). Causative organisms include the dematiaceous fungi (“phaeohyphomycosis”) and *Aspergillus* spp. (26). The most common dematiaceous fungi

found by AFS surgical sinus fungal culture in the southwestern United States include *B. spicifera*, *Curvularia lunata*, *Exserohilum rostratum*, and *Alternaria alternata*. *Bipolaris* spp. have been reported more frequently than *Aspergillus* spp. (67% vs 9%, respectively [26]).

Patients are immunocompetent, and all are atopic (26). They all are positive for type I immediate hypersensitivity to many common aero-allergens, including the causative mold found growing from the surgical sinus fungal culture (26). Analogous to ABPA, total serum IgE and fungal-specific IgG are usually elevated and subsequently rise and fall with disease recurrence and remission, respectively (26). However, the total serum IgE is usually not as high as that found with ABPA, typically ranging between normal values and 3000 IU/mL, with mean values around 500 IU/mL (25,26). Some patients with AFS present with a concomitant allergic bronchopulmonary mycosis syndrome resulting from the same mold involved in their AFS (26,39–43), termed sino-bronchial allergic mycosis (43). Two of 67 (3%) AFS cases presented with sinobronchial allergic mycosis in a series of cases in Phoenix, AZ (26). In that series, 64% of patients with AFS also had reactive airways disease, and 13% had hypersensitivity to ASA/nonsteroidal anti-inflammatory drugs.

Diagnosis of AFS

The diagnosis of AFS is primarily histopathological (25,26,34,36–38,44). Both hematoxylin and eosin and GMS stains of surgical pathology are required. The following diagnostic criteria must be met (25,26):

1. Surgically obtained characteristic inspissated allergic mucin must be observed histopathologically and/or grossly at surgery.
2. 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.

3. There is no histopathological evidence for mucosal fungal invasion, mucosal necrosis, granulomas, or giant cells.
4. Other fungal rhinosinusitis disorders are excluded.

If the histopathological criteria are met, all other features of AFS will be present, such as a pre-operative sinus CT scan showing chronic sinusitis, presence of inhalant atopy (including a positive type I immediate hypersensitivity skin test or RAST to the fungus cultured from surgery), and, usually, an elevated total serum IgE. If GMS stains of the allergic mucin are negative because of subtotal surgical sampling for histopathology in an otherwise characteristic patient, a positive surgical sinus fungal culture is required for diagnosis of AFS. However, 13% of AFS surgical fungal cultures are negative, despite histopathological confirmation of AFS (26). A misconception occasionally encountered in operative reports is the belief that characteristic allergic mucin, a dense extramucosal inspissate of many pyknotic eosinophils (Figs. 1B and 2A), is “fungal debris.” Fungal hyphae represent an extremely small component of the total allergic mucin mass. Additionally, the same characteristic inspissated allergic mucin can be found in other non-AFS subgroups of HSD, such as aspirin triad (Samter’s syndrome) and EMRS (Fig 3) (18,25,45–47), without involvement or presence of fungi. Such allergic mucin without fungal hyphae also “hyperattenuates” on sinus CT scans and can create confusion in the differential diagnosis of AFS.

Immunopathology of Allergic Fungal Sinusitis

We do not know why patients get AFS. We do know that inhalant atopy, including type I immediate hypersensitivity to the etiological fungus, is essential (25,26). Dematiaceous fungi are the most common cause of AFS—particularly *B. spicifera*. *Aspergillus* spp. are also etiological. Because dematiaceous fungi and *Aspergillus* spp. predominate in AFS, it is likely that these

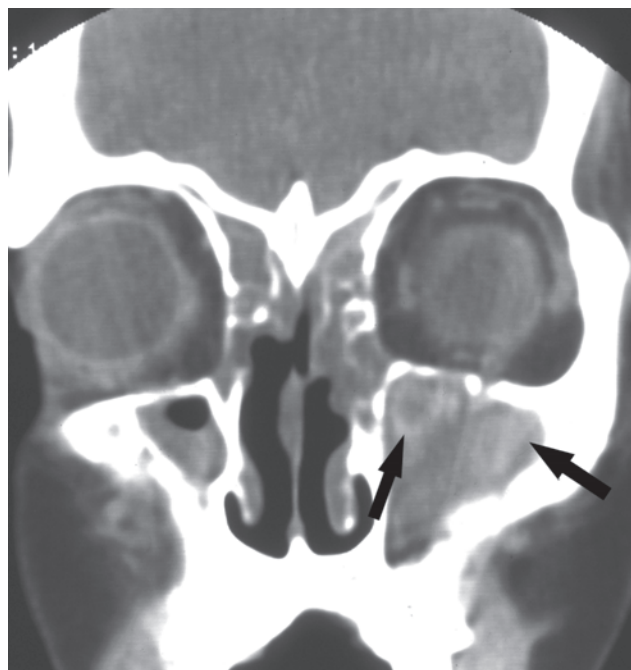


Fig. 3. Sinus CT of 31-yr-old female with Samter’s syndrome (ASA triad) and “eosinophilic mucin rhinosinusitis;” hyperattenuating allergic mucin (arrows). This patient had multiple sinus surgeries for recurrent hypertrophic sinus disease, and, despite the presence of allergic mucin, was negative for fungi by both culture and histopathology on all surgeries.

fungi have important biological characteristics that distinguish them in this regard. Therefore, both atopy and environmental exposure to specific types of fungal spores are necessary components of AFS. The “AFS rhinosinusitis cycle” was proposed to describe the steps likely to be important in producing the final disorder (12). It has been suggested that atopic patients can either develop HSD from AFS or can develop AFS as a complication of their pre-existing HSD. In the former case, the patient’s HSD is entirely contingent on the presence and activity of AFS, whereas in the latter case the patient may have recurrences of HSD without involvement of AFS at every surgery. Therefore, AFS can occur as a complication of, or addition to, ongoing HSD in some patients but is the *de novo* cause for the HSD in others.

Both the histopathology and the immunopathology of AFS strongly resembles ABPA. In ABPA, patients have very elevated levels of total serum IgE (commonly 1000–10,000 IU/mL) and *A. fumigatus*-specific IgE and IgG with precipitins (48). The total serum IgE is also elevated in AFS but is not as high as with ABPA (26). Conversely to ABPA, serum levels of *B. spicifera* fungal-specific IgE were no higher in patients with *B. spicifera* AFS than in those who had common atopy to *B. spicifera* (26). Additionally, *B. spicifera*-specific IgG was present in all patients with *B. spicifera* AFS but was not high enough to develop serum precipitins in most cases. *B. spicifera* fungal-specific IgG was found to fluctuate during follow-up similar to fungal-specific IgE, rising with exacerbations and falling with remissions. Together with the lower incidence and magnitude of peripheral eosinophilia in AFS compared with ABPA (26), it appears that there is less intensity of immunological hypersensitivity in AFS compared to ABPA. This may result from differences in the target organ for disease and/or the etiological fungus.

Antigen presentation to T-cells by antigen-presenting cells (APCs) represents the first step in the generation of an acquired immune response. The human leukocyte antigen (HLA) genes within the major histocompatibility (MHC) class II gene complex on chromosome 6 code for these polymorphic HLA-DR, DQ, and DP antigen-presenting molecules on APCs. The MHC class II molecules bind and present foreign peptides to the antigen-specific T-cell receptors (TCRs) on responding T-cells. The genetically determined peptide-binding specificities of the class II molecules on the APCs determine the “universe” of peptides capable of being bound and presented to T-cells. Approximately 0.01% of resting T-cells have TCRs that are capable of recognizing any given MHC-peptide complex. Many inflammatory diseases depend on early events in antigen presentation and response, including the genetics of the

MHC class II molecules. Linkage of specific MHC class II alleles to specific inflammatory diseases suggests that certain peptides presented by certain inherited MHC class II molecules are critically involved in the etiology of inflammatory diseases (49).

A second role for specific MHC class II alleles in inflammatory pathology relates to microbial superantigen-induced disease (5). Superantigens are microbial toxins that can activate up to 30% of all T-cells (50,51). They accomplish this activation by simultaneously binding to the side of the MHC class II molecule on the APC and to the side of the TCR at its V_B region (motif), away from each of their peptide-binding areas. This creates a molecular bridge that bypasses the normal antigen-specific MHC–TCR interaction (50,51). Specific inherited TCR V_B motifs bind to specific superantigens. This common mechanism of microbial virulence causes a number of clinical syndromes, including toxic shock, tissue necrosis, and food poisoning (50–52). Some MHC class II molecules are better at binding and presenting a specific superantigen (52,53). This leads to an MHC class II association of superantigen action, with its clinical effects resulting from high T-cell cytokine responses. Microorganisms that produce superantigens include staphylococcus, streptococcus, mycoplasma, yersinia, and certain retroviruses, including endogenous retroviruses. Superantigens have an important role in atopic dermatitis and, possibly, chronic severe asthma, type I diabetes, multiple sclerosis, rheumatoid arthritis, Kawasaki’s disease, and psoriasis (5,54–66). Studies recently demonstrated that many patients with HSD have serological positivity (particularly antigen-specific IgE) to staphylococcal superantigens as well as oligoclonal T-cell expansion *in situ* that is characteristic of superantigen activity (67,68), suggesting a role for superantigens in HSD.

ABPA has strong linkage with HLA-DR2 and DR5; DQ2 was found to be protective (69). AFS was recently found to have linkage

to HLA-DQB1*0301 and *0302 alleles (70). Researchers also found that other HSD disorders had HLA-DQ3 association, although not as high as with AFS. However, other HSDs were associated with any of the DQB1*03 allelic variants, DQB1*0301, *0302, *0303, *0304, and *0305. It was concluded that specific DQB1*03 allelic variants were involved in AFS but any DQB1*03 allelic variant could be involved in other HSD disorders. Therefore, the role for HLA-DQ3 in AFS and other HSDs may include both antigen-specific peptide presentation (i.e., specific DQB1*03 alleles) and an additional function of the DQ3 molecule that uses all DQ3 molecules without regard for peptide-presentation specificities (i.e., any DQB1*03 allele).

The presence of both antigen specificity issues and preferential DQ3 molecule binding and presentation of a putative superantigen were suggested as a possible explanation for this finding. The "superantigen hypothesis" has been proposed as a fundamental immunopathogenic mechanism for AFS and other common HSDs, as well as a pathogenic mechanism for numerous other chronic inflammatory diseases (5). Dematiaceous fungi and *A. fumigatus* were suggested to be putative superantigen producers, inducers, or both, thereby explaining their associations with AFS; however, this hypothesis has not yet been tested.

Treatment of AFS

Treatment of AFS requires the surgical clearing of current disease and then prevention of recurrence (12,18,25,71,72). All inspissated fungal-containing allergic mucin and diseased hypertrophic/hyperplastic sinonasal mucosa should be removed at surgery. Long-term follow-up and medical-surgical integration is required. Postoperative surgical management requires close follow-up for recurrent disease and proper in-office debridement. Postoperative medical management centers on treatment for allergic inflammatory disease (12,18,25,71–73). Antibiotics (particularly for *Staphylococcus aureus*) may have a role in inter-

current episodes of acute purulent rhinosinusitis, along with an oral corticosteroid (OCS) "burst" (12,25,72,73). Similar to ABPA, longer-term use of OCS as a form of postoperative chemotherapy is often required for AFS (12,18,25,72,73).

There are no published placebo-controlled trials of any treatment for AFS. The closest available to such a study is the large retrospective series from Phoenix, AZ in which 67 consecutive patients with AFS were treated and followed for up to 8 yr (73). In this series, roughly half elected to take up to 1 yr of postoperative OCS. OCSs were dosed according to a modified ABPA protocol, and the other half of the patients were not administered OCS. Patients were otherwise treated similarly regarding the use of traditional allergy treatment, including antihistamines, topical anti-inflammatories, and allergen immunotherapy to all relevant aero-allergens as determined by skin testing for type I immediate hypersensitivity. Statistically significant improvements in clinical assessments at various time-points and in the time to recurrent sinus surgery were noted in the group treated with OCS compared with those not treated with OCS. Additionally, increases of 10% or more in the total serum IgE between follow-up time-points were strongly associated with recurrent surgery. A decrease in total serum IgE was even more predictive of resolving disease. Therefore, postoperative OCS using this modified ABPA protocol led to better overall outcomes for AFS and measuring total serum IgE was effective as a follow-up tool. Importantly, no tissue-invasive fungal infections or long-term side effects from OCS were noted using this dosing regimen.

There have been several other published cases that were treated with either oral or topical corticosteroids (12,25,72,78). One case report described success with montelukast (74). A large retrospective case series from Texas found that allergen immunotherapy was beneficial in AFS during the first 3 yr of postoperative treatment (75). Their longer-term follow-up study found that some patients with AFS did just as

well, even without immunotherapy (76). The rationale for currently recommending allergen immunotherapy in AFS is that these patients are uniformly atopic to multiple aero-allergens and that any reasonable treatment should be considered that could realistically reduce allergic inflammatory sinonasal disease. Such inflammation is felt to be conducive to AFS relapse with subsequent need for additional OCS and repeat surgery (12).

Systemic antifungal drugs have not been effective for AFS, presumably because AFS is not tissue-invasive (12,25,72,77,78). One randomized controlled trial found benefit with the addition of oral itraconazole to OCS in ABPA (79). The several published cases using topical antifungal drugs to treat AFS via sinonasal lavage or nebulizer have produced questionable results (80,81). However, anatomic constraints in delivering adequate drug transnasally to the paranasal sinuses continue to be problematic (25,72). A recent study showed a small but significant improvement in sinus mucosal thickening in a potentially heterogeneous group of patients with HSD treated with nasal amphotericin B compared with placebo, but it is unclear whether any of these patients actually had AFS (82). The authors of this study had tested efficacy of topical amphotericin B for HSD because of their theory that virtually all patients with any form of HSD have sinonasal extramucosal fungi as the etiology of their disease (11; see following section). Despite the use of amphotericin B, they found no change in the levels of alternaria antigens in sinonasal mucus. Because amphotericin B also has immunomodulatory and toxic potential (83–85), it is possible that it had an effect on the respiratory mucosa not resulting from its antimicrobial spectrum. Conversely, a similar study from another institution found no effect of topical sinonasal amphotericin B over placebo in treating HSD (86).

The overall goals of treatment are to eliminate existing disease and prevent recurrence

without causing treatment side effects. Although AFS recurrence remains problematic, prognosis is generally good with aggressive coordinated surgical and medical treatments with close follow-up.

Controversy and Pitfalls

There is no real controversy regarding the existence of AFS as a distinct clinicopathological entity. Diagnostic criteria are well known and accepted. The clinical, histopathological, and immunological analogy of AFS to ABPA has been developed by a number of researchers over the last 20 yr.

“Allergic inflammation” is a histological term describing an inflammatory process involving variable numbers of eosinophils and lymphocytes, often with associated tissue edema. It can be confused with the term “atopy,” which is also called “type 1 immediate hypersensitivity.” Atopy is often, but not always, the underlying cause of histologically defined allergic inflammation (5).

Ponikau et al. (11,82) hypothesized virtually all HSD to result from fungi. They felt that AFS does not exist as a clinicopathological entity partly because not all patients with HSD are atopic. Their suggestion that all HSDs should be renamed “eosinophilic fungal rhinosinusitis” has not been met with wide acceptance and remains “controversial.” Their hypothesis was based on office-obtained transnasal fungal cultures in which control patients experienced similar results. It is well known that nasal cultures are often positive for various microorganisms, even in normal control patients. Cultures from office-based sinonasal washes in patients who have had previous sinus surgeries are particularly prone to positivity because of incidental nosocomial colonization with various microbes—particularly bacteria and fungi. Such culturing techniques have been discouraged and are a pitfall in the diagnosis of AFS (12,25). Intra-operatively directed deep-sinus culturing—particularly of inspissated allergic

mucin-appears to be more reliable for such fungal culturing (25).

Diagnostic error can be reduced by reviewing the pre-operative sinus CT scan, surgical sinus histopathology and culture, operative reports, and medical work-up, including total serum IgE and skin testing for type I immediate hypersensitivity. It should be noted that allergic mucin is not mucus with scattered eosinophils. Allergic mucin is a defined pathological entity with histopathological features that include massive concretions of pyknotic eosinophils and the gross intra-operative appearance of a peanut-buttery material (Fig. 1B) that "hyperattenuates" on sinus CT (12,25). It can occur without the presence or involvement of fungal hyphae (Fig. 3) (18,45–47). Therefore, AFS cannot be diagnosed by the presence of allergic mucin alone. EMRS may be diagnostically confused with AFS because both involve the presence of allergic mucin (18,45–47). Therefore, EMRS as a diagnostic term is potentially confusing and could be termed *allergic mucin rhinosinusitis* or AMRS.

Conclusion

AFS represents a distinct type of fungal RS. Adherence to strict diagnostic criteria is required because it can be confused with other forms of fungal RS and other types of HSD. Proper diagnosis is essential for planning treatment and follow-up. Similarities and differences between AFS and other forms of HSD and ABPA have been described. Recent advances in our understanding of the immunopathology of AFS have drawn comparisons to other chronic inflammatory diseases. Future AFS, HSD, and ABPA research may provide additional insight into mechanisms of not only other common chronic inflammatory respiratory tract diseases but of those of other organ systems as well.

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