Allergic Fungal Sinusitis

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Core Messages

- AFS is a form of noninvasive fungal sinusitis that causes nasal polyps
- Hypersensitivity to fungus is the basis for polyp formation in AFS
- *Aspergillus* and the dematiaceous fungi have been implicated in AFS
- AFS is overdiagnosed and often confused with other forms of polypoid CRS

15.1 Introduction/History

Allergic fungal sinusitis (AFS) is a well characterized, discrete clinicopathologic entity that is recognized as a cause of polypoid chronic rhinosinusitis (CRS). AFS was first recognized as a distinct pathologic entity when the thick, dark, inspissated mucus filling the paranasal sinuses of some patients was noticed to be similar both grossly and microscopically to that seen in the bronchial passages of patients with allergic bronchopulmonary aspergillosis (ABPA) [17, 30, 35]. The accurate diagnosis and appropriate treatment of AFS still generate controversy despite years of investigation.

One widely accepted criterion for the diagnosis of AFS has been the characteristic "allergic mucin" first responsible for the description of the disease. However, investigators soon noted that in some cases, the allergic mucin evacuated from the sinuses did not have identifiable fungal elements; these patients were labeled as having an "AFS-like syndrome" [1, 6]. Additionally, Ferguson [11] proposed the term "eosinophilic mucin rhinosinusitis" (EMRS) to describe cases in which fungus was not identified histologically. Some patients with clinical features of AFS may have demonstrable fungus within their allergic mucin, yet do not have allergy [32]. Some authors still report these AFS-like cases as AFS [16], and others have eliminated allergy as a requisite feature to make the diagnosis [41]. The report of Ponikau et al. [33] suggesting that most, if not all, CRS was a hypersensitivity response to fungi and that fungi could be universally cultured from nasal secretions also further clouded the distinction between AFS and AFS-like CRS. AFS has been overdiagnosed because of clinical similarity to other forms of CRS, and the problem of distinguishing AFS from other forms of CRS has fueled interest in the appropriate classification of polypoid rhinosinusitis.

A collateral benefit of these reports has been an increased interest in the pathogenesis of AFS and polypoid CRS in general. If patients with the clinical picture of AFS do not have allergy and/or do not have evidence of fungus in their eosinophilic mucin, how should these patients be classified? Is fungus really the stimulus for inflammation? Is allergy important in the pathogenesis of AFS? The clinicopathologic distinction of AFS from other forms of EMRS requires further investigation. Allergy is probably not the only

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cause of AFS, and other immunologic mechanisms, anatomic, and physical factors are required for explaining the clinical observations in AFS [26]. Investigations into the role that fungi play in CRS and eosinophilic mucin chronic rhinosinusitis (EMCRS) are discussed in greater detail in other chapters of this text. Questions regarding the proper diagnosis, classification, and pathogenesis of AFS are yet to be resolved and have important implications for treatment. The current controversies are not merely academic because refinement of our treatment approach will depend upon the development of better methods to differentiate AFS from other forms of chronic polypoid rhinosinusitis.

15.2 Epidemiology and Microbiology

AFS may be the most common form of fungal sinusitis. AFS accounts for about 7–12% of CRS cases taken to surgery in the United States [9, 15]. Perhaps because climate determines the exposure to fungi, the highest incidence in the USA is in the south and along the Mississippi basin [12]. The disease has a worldwide distribution, though there may be differences in the microbiology of the disease across continents. AFS develops primarily in young adults and adolescents [26]. Older patients with the clinical features of AFS may be more likely to have some other EMCRS syndrome. Affected patients are immunocompetent and have a history of atopy [9, 39]. Allergic rhinitis and asthma are common associated conditions. By definition, AFS patients have allergy that should be evident by skin or in vitro testing, but only about two-thirds of patients will give a history of allergic rhinitis [22].

Aspergillus was initially believed to be the causative organism in AFS, but further experience with cases in the USA showed that the dematiaceous fungi were most commonly found in AFS mucus [9, 24]. The terminology for this condition subsequently changed from "allergic *Aspergillus* sinusitis" to "AFS." In the series of AFS and nonallergic eosinophilic fungal sinusitis from other parts of the world, *Aspergillus* is still found to be a common isolate [16, 36, 41]. The specific fungal organism has not been shown to be an important or predictive clinical characteristic, but the identification of fungus in allergic mucin either via histopathology or culture is still considered to be important to make the diagnosis of AFS.

- AFS develops slowly and disease is usually severe at diagnosis
- Severe nasal obstruction from nasal polyps is common
- Proptosis or telecanthus are frequently present
- Patients often have dramatically elevated total serum IgE

15.3 Clinical Presentation

Symptoms of AFS are insidious in onset. Patients with AFS usually present with rhinosinusitis symptoms lasting for months or years and they may not seek medical attention until complete nasal obstruction, headaches, visual disturbances, or facial dysmorphia are noticed. Symptoms are frequently unilateral. Patients may report dark, thick nasal mucus. Proptosis or telecanthus are not infrequently seen at presentation, especially in younger patients [16, 21, 23, 26]. Disease is often well advanced before a diagnosis is made.

The physical exam findings in AFS often reflect the advanced nature of disease at presentation. There may be proptosis or hypertelorism. Intranasal examination will reveal polyps that are either unilateral or bilateral. It is not uncommon for the bulk of polyp disease to be asymmetric. On nasal endoscopy inspissated yellowish mucus may be visualized among the polyps.

Testing is important to establish evidence of atopy, and demonstration of type 1 hypersensitivity is required for diagnosis. This may be accomplished with skin testing or in vitro testing for antigen-specific IgE. In addition to fungal antigens, patients should be tested against a region-specific panel of seasonal and perennial allergens. Possible laboratory abnormalities in AFS patients include peripheral eosinophilia and elevated total IgE levels. Skin testing or RAST testing will usually demonstrate IgE-mediated hypersensitivity to multiple fungal and nonfungal antigens [26].

Diagnostic Criteria for AFS

- Polypoid rhinosinusitis
- Fungal allergy
- Allergic mucin
- Fungus detected by stain or culture
- Characteristic imaging findings

15.4 Diagnostic Criteria

The diagnosis of AFS requires a combination of clinical, radiographic, microbiologic, and histopathologic information. Therefore, the diagnosis of AFS cannot be made reliably until after surgical intervention. There is no universally recognized set of diagnostic criteria for AFS, though there is a general agreement about what constitutes AFS. An important criterion is the presence of allergic mucin. Grossly, allergic mucin is thick, tenacious, and darkly colored; it may appear similar to a fungus ball but microscopically the two are quite different. Microscopically, allergic mucin consists of onion-skin laminations of necrotic and degranulating eosinophils in a background of mucin with occasional Charcot–Leyden crystals (Fig. 15.1). Fungal hyphae are present but scarce, and special fungal stains may be needed for identification (Fig. 15.2). Fungal hyphae do not invade tissue: the presence of fungal tissue invasion is incompatible with a diagnosis of AFS. Adjacent mucosa and polyps demonstrate a prominent eosinophilic inflammatory infiltrate. Many patients with polypoid CRS and allergic mucin lack other important clinical characteristics of AFS: demonstrable fungi and fungal allergy. These patients should not be classified as having AFS.

A variety of diagnostic criteria for AFS have been proposed by various authors and these criteria have been further refined by a recent consensus conference on definitions of rhinosinusitis [29]. The classic and still widely accepted diagnostic criteria for AFS were described by Bent and Kuhn, who proposed the following: type 1 hypersensitivity; nasal polyposis; characteristic CT scan findings; eosinophilic mucus without fungal invasion into sinus tissue; and a positive fungal stain of sinus contents removed at surgery [3]. In the absence of better defined immunologic parameters to distinguish AFS from other forms of EMCRS, the Bent and Kuhn criteria are still important. The debate about the value of these diagnostic criteria has contributed greatly to the level of interest in the disease and helped fuel further investigation.

The controversy will continue as the boundaries between AFS and AFS-like chronic polypoid rhinosinusitis are explored. In one recent study, a considerable overlap in the findings between AFS and EMCRS groups was observed, but AFS subjects were more likely to have bony erosion, heterogeneous opacity, and sinus expansion on CT scan [36]. These findings are similar to those of Dhiwakar et al. who point out that the combination of nasal polyps, CT scan

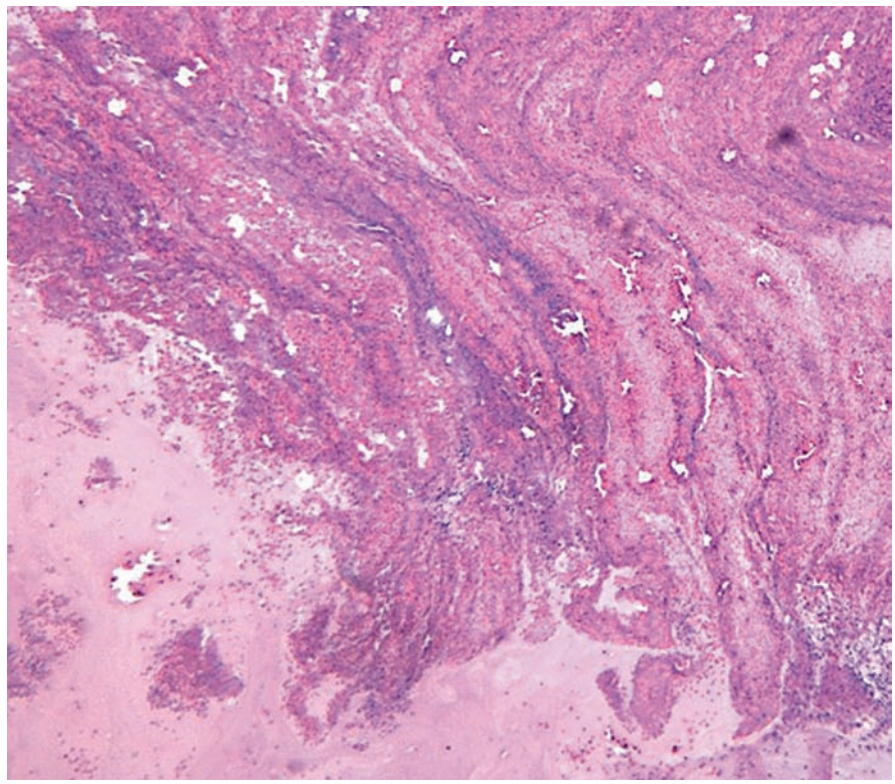

Fig. 15.1 Photomicrograph of an H&E-stained section of allergic mucin from a patient with AFS. There are layers of eosinophils in a background of mucin. No fungal hyphae can be seen (original magnification 40×)

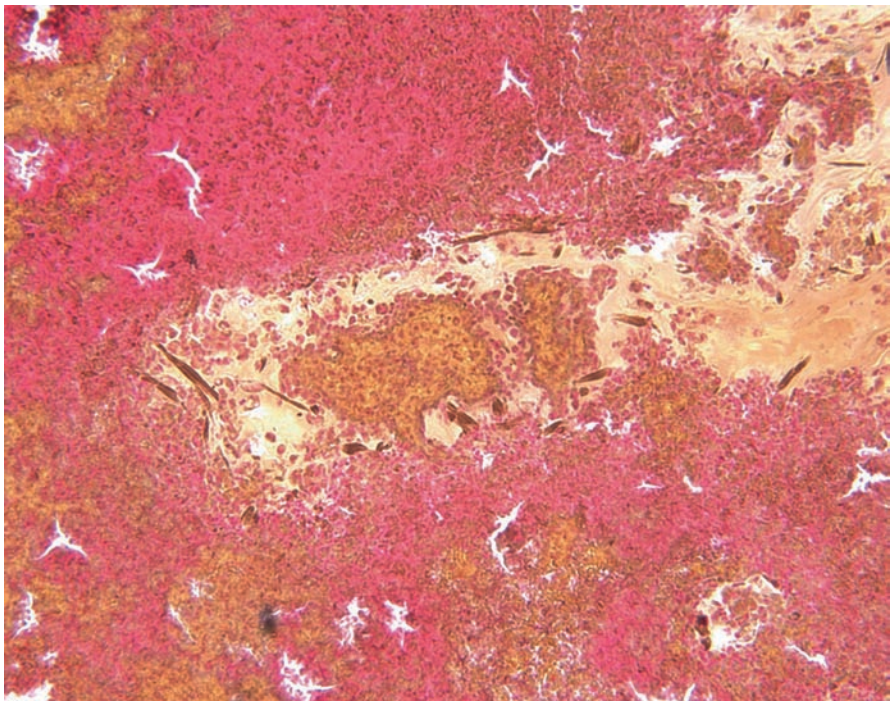

Fig. 15.2 Fontana-Mason stain of allergic mucin. The Fontana-Mason stains the melanin pigment of dematiaceous fungi. In this image, clusters of eosinophils as well as a few scattered, dark brown fungal hyphae are seen

hyperattenuation, and elevated titers of anti-*Aspergillus* IgE have a high predictive value for AFS, though considered in isolation they are not specific [8]. Clearly, considerable overlap exists between AFS, EMCRS, and CRS from other causes, and the Bent and Kuhn criteria are still helpful to distinguish between these.

Imaging Findings in AFS

- Hyperattenuation of sinus contents on CT imaging
- Bone erosion, sinus expansion, and mucocele formation
- MRI: low signal intensity of sinus contents on T1- and T2-weighted images

15.5 Radiologic Features

AFS has characteristic features on CT or MR imaging. The characteristic imaging findings of AFS cases are still considered extremely important for diagnosis. CT is the initial study of choice for evaluating these patients. CT imaging shows multiple opacified sinuses with central hyperattenuation, sinus mucocele formation, and erosion of the lamina papyracea or skull base with a pushing border (Figs. 15.3–15.5). AFS causes more bone erosion than other forms of CRS. Ghegan et al. showed that 56% of AFS cases presented with radiographic evidence of skull base erosion or intraorbital extension, while similar findings were noticed only in 5% of other cases of inflammatory sinusitis (mostly from mucoceles) [14]. Campbell et al. [5] reported that 50% of children with AFS had proptosis with orbital erosion, consistent with previous reports [21]. Bony erosion in the setting of polypoid sinusitis clearly is an important feature which should raise suspicions of AFS.

Magnetic resonance imaging is not usually clinically necessary, but may be indicated with CNS or orbital complications. Nevertheless, AFS has characteristic MR findings. On MR imaging, the sinuses have a central low signal on T1- and T2-imaging, corresponding to areas of allergic mucin, with peripheral high signal intensity corresponding to inflamed mucosa (Figs. 15.6 and 15.7) [2, 25, 45]. Sometimes the sinus contents have an isointense T1-signal. The low signal intensity of areas filled with allergic mucin

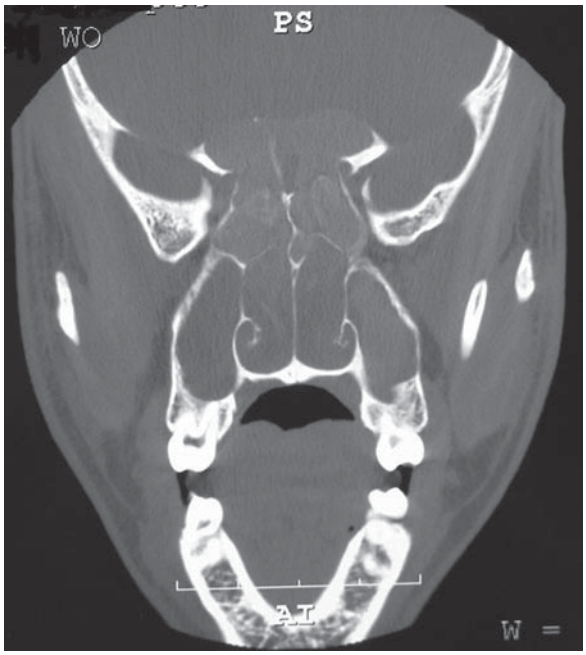

Fig. 15.3 Coronal noncontrasted CT image with intermediate windowing from a patient with AFS. Faint hyperattenuation of sinus contents are seen within the left maxillary sinus and bilateral posterior ethmoid cells. The planum sphenoidale has been eroded. Also note that the nasal cavity is occluded with polyps

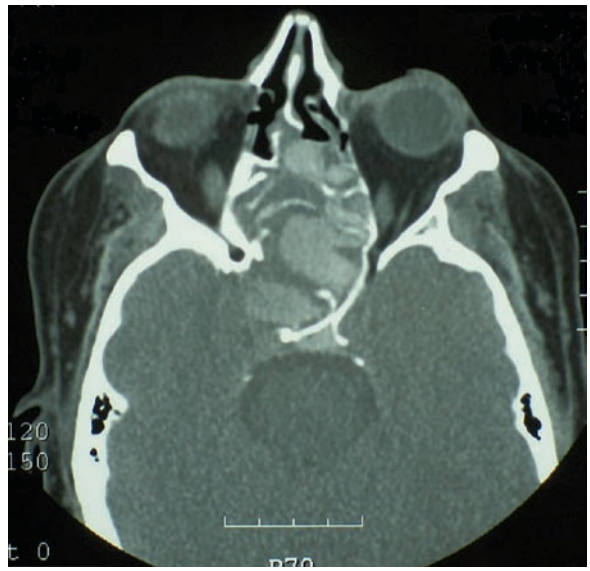

Fig. 15.5 Axial noncontrasted CT image with soft tissue windowing. Hyperdense sinus contents can be easily seen with this windowing. There has been distortion of the ethmoidal labyrinth and erosion of the posterolateral wall of the right sphenoid sinus. This patient had AFS

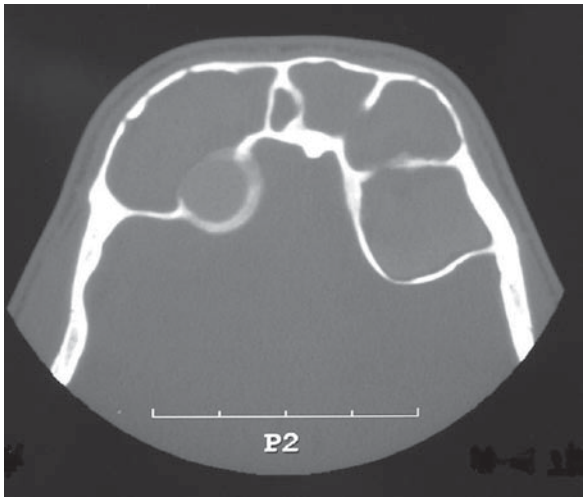

Fig. 15.4 Axial noncontrasted CT image of the frontal region in bone windows. There has been expansion of bilateral frontal sinuses with extension of supraorbital ethmoid cells intracranially. Note that the hyperdense sinus contents are not seen in this image. This patient had AFS

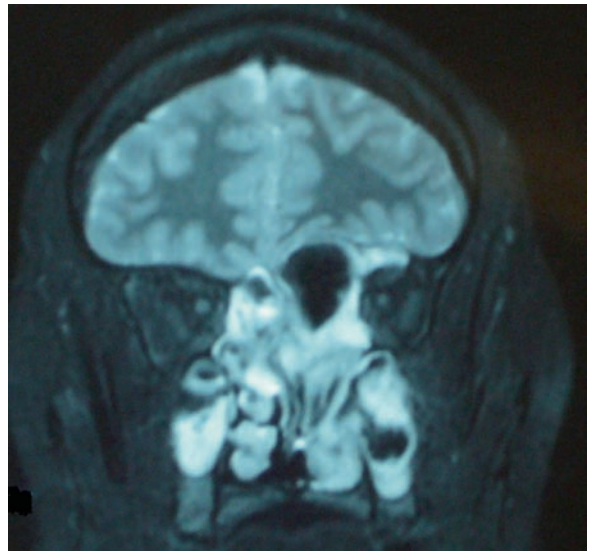

Fig. 15.6 T2-weighted coronal MR image with STIR fat suppression in a patient with AFS. Note the signal void in the left maxillary sinus and the expanded left posterior ethmoid cell with intracranial expansion. The signal void in this ethmoid cell is caused by allergic mucin with high protein and low water content

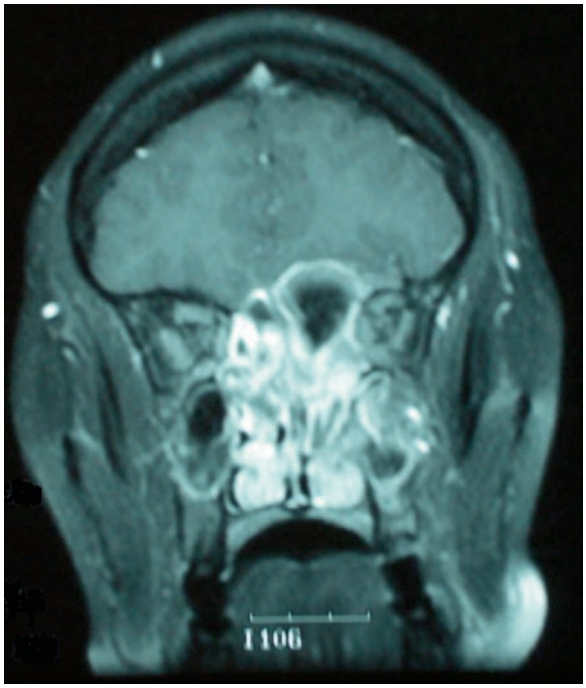

Fig. 15.7 Contrast-enhanced T1 coronal MR image from the same patient as Fig. 15.6 shows signal void in an expanded left posterior ethmoid cell, and peripheral mucosal enhancement

has been attributed to high protein and low water content within the mucin. While the CT and MR imaging findings in AFS are considered important in diagnosis, definitive diagnosis requires histologic verification and other clinical information.

15.6 Pathophysiology

A hypersensitivity to fungus is believed to underlie the pathogenesis of AFS, but the nature of this hypersensitivity is still debated. The dominant theory to explain the pathogenesis of AFS was adopted from the model of ABPA pathogenesis [26]: a combination of Gell and Coombs type 1 and type 3 hypersensitivity to fungal allergens causes sinonasal inflammation [39]. This paradigm was reinforced by the clinical association of AFS with allergy and the detection of elevated serum levels of total and fungal antigen-specific IgE and IgG in AFS patients [22, 43]. Most patients with AFS also have detectable fungal-specific IgE in their allergic mucin [7]. Elevated levels of fungal-specific IgG3 are a consistent finding in patients with AFS and AFS-like disease. A recent study of patients with EMCRS including AFS cases found that elevated fungal-specific IgG3 was a distinguishing serologic feature of both EMCRS and AFS patients, and IgE levels could be used to distinguish EMCRS from AFS [31]. Type 1 hypersensitivity to fungal antigens thus helps distinguish AFS from other forms of EMCRS.

These findings suggest that both "allergic" and "nonallergic" fungal hypersensitivity are important components of the underlying pathophysiology of AFS. However, the pathophysiologic mechanisms in AFS are likely more complicated. It appears that AFS develops in susceptible patients with a convergence of local anatomic as well as environmental factors [26]. Fungi enter the nose and sinuses and trigger an inflammatory response. This inflammation induces polyp formation and the accumulation of allergic mucin. Trapped fungi continue to stimulate the adaptive immune system in a vicious cycle. Over time, massive polyposis develops and fungal mucoceles distort the sinonasal anatomy.

Treatment of AFS

- Endoscopic sinus surgery
- Saline irrigations
- Topical nasal steroid
- Systemic corticosteroids
- Leukotriene modifiers
- Immunotherapy
- Antifungals

15.7 Treatment

The medical and surgical treatment of AFS advanced after widespread recognition that AFS is not a form of invasive fungal sinusitis. Aggressive surgery and toxic antifungal medications have been replaced by endoscopic surgery and medical therapy directed at suppressing inflammation and reducing the burden of fungal antigen in the nose. AFS is now considered, by definition, to be a noninvasive, immunologically mediated hypersensitivity to fungi, and treatment approaches have been altered accordingly.

Surgery is required initially in almost all cases of AFS. An aggressive surgical approach utilizing external approaches and stripping of sinus mucosa was often used in the past before the true nature of AFS was understood [18, 44]. But surgery today relies on endoscopic tissue preserving approaches that are sufficient to remove obstructing polypoid mucosa, evacuate sinus contents, and facilitate sinus drainage [26]. External surgeries are not necessary except in rare circumstances. The sinonasal expansion from massive polyposis and fungal mucoceles actually facilitates surgery by improving surgical access. However, this disease may distort the normal intranasal landmarks and erode the important bony barriers to the orbit or brain, potentially increasing the risk of surgery. Image guidance is helpful for orientation and to facilitate more complete surgery. Incomplete surgery, with retention of cells filled with allergic mucin appears to be a risk factor for early recurrence [27]. Surgical treatment for recurrences is indicated when intense medical management fails to clear an exacerbation. Intense medical therapy can reduce polyp volume, but massive polyposis and outflow tract obstruction may not respond to medical management if there is a significant polyp burden or allergic mucin within the sinuses. The goals of surgical treatment for recurrence are the same as for primary surgery.

Medical treatment for AFS is absolutely essential to prevent or delay recurrence of disease. A variety of medical therapies are now employed to suppress inflammation, prevent reaccumulation of allergic mucin, and maintain sinus drainage. Systemic anti-inflammatory agents are usually required in the treatment of AFS. Systemic steroids have the best substantiation in the literature [19, 38]. A brief course of preoperative systemic corticosteroids will shrink polyps and decrease bleeding during surgery [26]. Systemic corticosteroids given in the immediate post op period will prevent early recurrence of polypoid inflammation [42]. Prolonged treatment with systemic steroids may abrogate the vicious cycle of mucosal inflammation in AFS, but the ideal dosing and treatment course are yet to be defined. Long-term treatment with systemic corticosteroids entails considerable risk; therefore, short bursts are usually employed to keep sinonasal inflammation controlled. Leukotriene receptor antagonists are sometimes employed, and while strong evidence for efficacy is lacking, these antileukotriene agents are attractive because of their safety and possible steroid-sparing effect [37]. Other anti-inflammatory agents such as macrolide antibiotics may have a role, though again data are lacking [40]. Unfortunately there is no regimen of systemic anti-inflammatory medication that has proven superior to another for improving patient outcome or reducing the need for revision surgery.

In addition to systemic treatment, topical treatments are important medical adjuncts. Topical nasal corticosteroids, saline irrigations, and antifungal agents [4, 34], are all utilized, though saline irrigations and topical steroid sprays are the mainstays of treatment. Nasal steroids have a minimal side effect profile, and are effective at decreasing sinonasal inflammation or even shrinking nasal polyps. Some authors have recommended that nasal steroid sprays be used up to three times the usual dosage to boost their efficacy [19]. However, unfortunately, local treatments are often not sufficient to dampen the brisk inflammatory reaction of AFS and prevent recurrence.

Antifungal treatments are sometimes employed for AFS in an attempt to decrease the fungal antigenic burden within the sinonasal cavities [10, 19], but convincing data of their effectiveness in AFS are still lacking. Antifungal therapy has not been widely adopted because of a lack of evidence that it adds benefit beyond that achieved with corticosteroids or that it decreases reliance on systemic steroids. The fungi in AFS are not invasive and are present in scant numbers. Antifungal drugs have many serious toxicities that limit their usefulness. Though newer antifungal agents have an appropriate spectrum and lower incidence of significant toxicities, prolonged treatment is extremely expensive and may not be justified in the absence of data that demonstrate benefit. The anecdotally observed efficacy of agents like itraconazole [34] may not be due to a reduced fungal burden in the nose, but rather due to the anti-inflammatory properties of the molecule or its inhibition of prednisone metabolism. Should antifungal therapy be employed, topical delivery seems preferable because of the lower risk of systemic side effects and the benefit of delivering higher doses directly to the site of disease. Even agents like amphotericin B which have excellent activity against the usual fungi may be administered without the significant toxicities associated with systemic administration. However, antifungal therapies need further investigation to establish their efficacy before their use is widely adopted.

Immunotherapy (IT) is another treatment modality that has been proposed to decrease the reliance on systemic steroids in the treatment of AFS. The rationale for IT presupposes that AFS is an IgE-mediated process. Folker et al. reported their experience with IT in AFS

patients and made a comparison to nonimmunotherapy-treated historical controls. After an average 33 months of follow-up, they showed that the IT-treated patients had better endoscopic mucosal appearance, lower CRS survey scores, required fewer courses of oral steroids (2 vs. 0), and showed less reliance on nasal steroids (73 vs. 27%) [13]. While this was not a randomized double blind study, these results suggest an important role for IT in the management of AFS. In summary, the ideal medical regimen for AFS is unknown and clinical decisions must be made based on the patient's age, concomitant medical conditions, and response to treatment.

15.8 Natural Course

After AFS was distinguished as a clinicopathologic entity, clinical experience soon revealed that the recurrence of the disease was extremely common. Kupferberg et al. reported universal recurrence in patients treated surgically without vigorous postoperative medical treatment [20]. The reported recurrence rates for AFS range from 10 to 100% [26]. One longitudinal study showed that over a period averaging almost 7 years of follow-up, patients required an average of two surgical procedures and three courses of systemic steroids per year. After many years, even asymptomatic patients had persistent polypoid mucosal edema and elevated total serum IgE [28]. So, while the disease may become quiescent over a period of years, a significant number of patients will have persistent sinonasal inflammation. Recurrent disease may silently progress until massive intranasal polyposis again creates significant nasal obstruction. If discovered at this point, revision surgery may be required. Endoscopy is the best way to follow the activity of disease, but some have found IgE levels to be helpful in monitoring patients for recurrence. Because of the chronic and recurring nature of this condition, patients should be closely followed for extended periods.

Take Home Pearls

- AFS is a disease of teenagers and young adults. Mucocele formation with sinus expansion is a specific sign that distinguishes AFS from other forms of polypoid CRS.
- Topical and systemic steroids are the most effective medications for AFS. Most patients with AFS will require multiple surgeries

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