

Current Concepts in the Management of Allergic Fungal Rhinosinusitis

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KEYWORDS

- Allergic fungal rhinosinusitis • Chronic rhinosinusitis • Nasal polyps
- Type 2 inflammation • Allergic sinusitis • Fungal sinusitis • Fungal allergy
- Eosinophilic mucin rhinosinusitis

KEY POINTS

- The Bent and Kuhn diagnostic criteria serve as the framework for diagnosis of allergic fungal rhinosinusitis (AFRS).
- The pathophysiology of AFRS is hypothesized to result from a combination of defective mucosal barrier function, altered innate immune signaling, and fungal overgrowth, which culminate in a localized, hyperallergic type 2 immune response.
- Standard therapy for AFRS includes complete surgery in combination with systemic and topical steroids.
- Adjunctive treatments like immunotherapy, antifungal therapy, and biologic therapy may have some benefit in recalcitrant cases of AFRS.

INTRODUCTION

Katzenstein and colleagues^{1,2} were among the first to describe a unique type of fungal sinusitis in 7 patients, characterized by the presence of thick, mucinous material with impacted fungal elements and termed it, “allergic *Aspergillus* sinusitis.” The investigators noted a striking similarity with allergic bronchopulmonary

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aspergillosis, where thick concretions of mucin lead to lower airway obstruction in the lung. Allergic fungal rhinosinusitis (AFRS) initially was conceptualized by many to represent a subtype of fungal sinusitis along with invasive fungal sinusitis and sinus fungus ball; now, it is instead thought to be a subtype of chronic rhinosinusitis (CRS). Subsequent investigations showed that a variety of fungal species could be associated with an identical clinical presentation, so the more encompassing term, *allergic fungal rhinosinusitis*, was adopted. In 1993, Bent and Kuhn³ established criteria for diagnosis of AFRS based on their prospective review of 15 patients. These 5 diagnostic criteria are

1. Type I hypersensitivity to fungi
2. Characteristic areas of hyperattenuation on computed tomography (CT)
3. Eosinophilic mucin
4. Nasal polyps
5. Presence of noninvasive fungus within sinus mucin³

EPIDEMIOLOGY AND RISK FACTORS IN ALLERGIC FUNGAL RHINOSINUSITIS

AFRS demonstrates a higher prevalence in South Central and Southeastern United States, where it is believed that higher mold counts lead to greater disease burden in these territories.⁴ It remains unclear, however, if mold counts truly correlate with the rate of AFRS in these regions. AFRS is more common in men and presents at a mean age range of 21 years to 33 years.^{5–9} Certain studies have identified patients with lower socioeconomic status as more prone to advanced presentation, including bone erosion and orbitocranial complications; however, these studies have been disputed by other investigators showing that socioeconomic status has no association with disease severity.^{7,10–12} Where early descriptions of AFRS cited a high rate of comorbid asthma, recent studies have found that the prevalence of asthma is approximately half that of patients with non-AFRS CRS with nasal polyps (CRSwNP), suggesting a unique underlying pathophysiology in AFRS.^{9,13–15}

DIAGNOSIS OF ALLERGIC FUNGAL RHINOSINUSITIS

Among otolaryngologists, the Bent and Kuhn diagnostic criteria still serve as the framework for diagnosis of AFRS. Sometimes, advanced presentation on physical examination is heralded by the presence of proptosis or extensive polyposis. The radiographic findings in patients with AFRS is remarkable; some investigators propose that these features are among the most clinically differentiating characteristics of AFRS (Fig. 1).¹⁶ The classic CT radiographic appearance includes unilateral diseased sinuses, bony expansion/erosion of the sinus walls, and areas of hyperattenuation. Imaging in AFRS may mimic that in inverted papilloma or, more worrisome, malignancy. AFRS typically, however, is an expansile process and does not exhibit features of bony or soft tissue invasion. Peripheral eosinophilia may not always be present; however, serum IgE levels often are elevated, many times more than 1000 U/mL. Fungal-specific hypersensitivity, by itself, is not specific for AFRS, because fungal-specific IgE and IgG are present in both non-AFRS CRS and AFRS.^{17–19} Similarly, positive fungal cultures can be recovered from both non-AFRS CRS and healthy controls.^{20,21} Intraoperatively, the thick, tenacious mucin should further alert a surgeon to the possibility of AFRS, and, along with the presence of noninvasive fungal elements on pathologic analysis, the diagnosis is more likely. The challenge of making a diagnosis of AFRS arises in cases of revision surgery, when polyposis and thick mucinous debris may not be as apparent as in the primary surgery.



Fig. 1. Imaging features characteristic of AFRS. This coronal image demonstrates predominately unilateral disease with expansion of the ethmoid cavity. There is demineralization of the lamina papyracea and ethmoid roof. Central hyperattenuation suggests the presence of inspissated, eosinophilic mucin with fungal elements.

PATHOPHYSIOLOGY OF ALLERGIC FUNGAL RHINOSINUSITIS

Alterations in Innate Immunity and Barrier Function

The sinonasal mucosa, its epithelium, and a diverse milieu of proteins and peptides make up a constitutive line of defense in the prevention of pathogen infiltration and immune stimulation in the sinonasal cavity. The immune barrier hypothesis in CRS hypothesizes that alterations in mucosal barrier function lead to chronic inflammation by (1) permitting over-colonization of sinonasal mucosa with pathogenic microbiota, which (2) acts as a source of antigenic stimulation and inflammation in the sinuses.²² Preliminary studies have indicated that defective barrier function may be a source of fungal over-colonization and overactive adaptive immune stimulation in AFRS. For example, in vitro studies have shown that AFRS epithelial resistance is lowered compared with controls, which may be the result of increased expression of type 2 inflammatory cytokines, like interleukin (IL)-4 and IL-13.^{23,24} Studies in AFRS also have shown reduced expression of antimicrobial peptides, including surfactant protein D, lactoferrin, and histatins.^{13,25,26}

Type 2 Inflammation and Adaptive Immunity

More recently, an emphasis has been placed on type 2 inflammation and eosinophilia in categorizing subtypes, or endotypes, of CRS, because this often is a marker of recalcitrant sinus inflammation in CRS. Certainly, AFRS represents an exaggerated type 2 inflammatory response characterized by allergic-type, eosinophilic inflammation. Underlying this profound type 2 inflammatory response seems to be an alteration in the local, sinonasal adaptive immune response. For instance, patients with AFRS demonstrates altered frequencies in HLA major histocompatibility complex class II (MHC II) DQB1*03 allelic variants.²⁷ Separate investigations have shown that local and circulating dendritic cells are elevated in AFRS, although this also has been observed in CRSwNP.^{28,29} Furthermore, Pant and Macardle³⁰ have shown that patients with AFRS exhibit defective CD8⁺ T-cell response to fungi, suggesting that this alteration may permit local fungal accumulation in these patients, and the resultant inflammatory response can be exacerbated by the

presence of fungal/allergic hypersensitivity. In a recent study performed by Tyler and colleagues,¹³ whole-genome analysis was performed using inflamed sinus mucosal specimen from AFRS and CRSwNP, in which approximately 3000 unique gene expression variations were identified in AFRS that differentiated it from CRSwNP. Many of these unique gene expression variations were associated with alterations in gene expression pathways associated with adaptive immunity, including antigen-sensing pathways, costimulatory signaling, and T-cell receptor signaling. Additional studies are needed to better understand the mechanisms leading to this profound over-activation of the adaptive immune system in AFRS; however, this appears to be a distinct feature that separates this subtype from other subtypes of CRS.

The Role of Fungus in the Immunopathogenesis of Allergic Fungal Rhinosinusitis

Mechanistic studies have demonstrated a direct role of fungal elements in the pathogenesis of allergic airway inflammation. Much of this research has been proliferated in the field of asthma and allergy. These studies have provided insight in regard to fungal immunopathogenesis in AFRS. Important proinflammatory fungal molecules, either secreted or present in the cell wall, include β -glucan, chitin, glycosidases, and fungal proteases. Fungal proteases are among the most studied disease mediators in allergy, asthma and AFRS. Proteases from *Aspergillus* species have been shown to induce classic molecular signatures of type 2 inflammation, including IL-4, IL-5, and IL-13 production; eosinophilia; and airway goblet hyperplasia.^{31–33} This has been shown to be mediated partially by cleavage of fibrinogen, which signals through pattern recognition receptors, such as Toll-like receptor 4 (TLR4), to induce antifungal and allergic airway inflammation.³² Fungal elements also promote innate immune cells to secrete cytokines that promote type 2 inflammation. Patel and colleagues³⁴ have shown that fungal extracts promote solitary chemosensory cells isolated from AFRS patient polyps to expand and increase secretion of the innate inflammatory mediator, IL-25. Other studies have demonstrated that fungal extracts promote the release of innate inflammatory mediators, like IL-33, a potent effector of type 2 helper T cell (T_H2) polarization and type 2 inflammation, from airway epithelial cells.³⁵ Increasing emphasis also has been placed on the importance of the group 2 innate lymphoid cells in fungal-mediated allergic airway inflammation.³⁶ This relatively recently described population of cells is responsive to IL-25 and IL-33 and represents an important effector cell type responsible for T_H2 polarization in response to fungal stimulation.^{36–38}

To summarize, the observed phenotype in AFRS may be the result of innate barrier dysfunction and a dysfunctional antifungal response. As a result, fungal conidia accumulate in the sinuses, germinating to fungal hyphae, and promote the over-activation of local innate and adaptive type 2 immune responses. A diagram summarizing proposed mechanisms of the pathophysiology in AFRS is presented in **Fig. 2**.

TREATMENT OF ALLERGIC FUNGAL RHINOSINUSITIS

Surgery

Endoscopic sinus surgery (ESS) represents a standard of care in the management of AFRS. Complete evacuation of fungus and eosinophilic mucin from involved sinuses is of paramount importance. Leaving residual fungi and eosinophilic debris can lead to a rapid recurrence in fungal colonization, inflammation, and patient symptoms. Infrequently, erosion and expansion of the bony walls of the sinuses occur to the extent

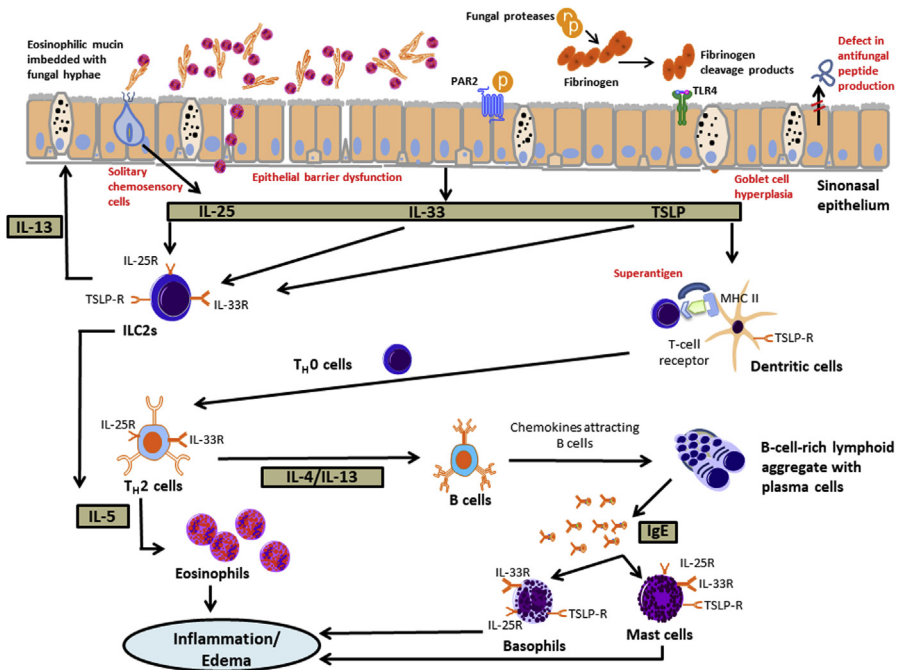


Fig. 2. Summary of proposed pathophysiology in AFRS. There are several mechanisms that may contribute to the overactive type 2 inflammatory response observed in AFRS. Loss of antifungal peptides, changes in epithelial permeability, fungal proteases, and other fungal elements together contribute to production of innate inflammatory cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Innate lymphoid cells, which are IL-25 responsive and IL-33 responsive, are capable of producing IL-5, which promotes eosinophil recruitment and activation. Dendritic cells respond to the presence of innate inflammatory mediators, like TSLP, and antigenic stimulation by fungal (and other) microbiota, which then promotes T_H2 cell development. In addition, T-cell activation can be activated further by superantigens. T_H2 activation affects B-cell isotype switching and differentiation to IgE-producing and IgG-producing plasma cells, further promoting a hyperallergic inflammation within the sinuses. TSLP-R, thymic stromal lymphopoietin receptor; ILC2, type 2 innate lymphoid cell.

that there is a risk of orbital and/or cranial complications.^{39,40} These complications can occur in severe cases that are left untreated. Despite a significant expansion of the sinus boundaries causing cranial compression, dural invasion and CSF fistulae usually are not present. Not only can surgery be undertaken to prevent, and many times reverse, complication but also a thorough and complete evacuation of inflammatory mucin and fungal elements can be performed in the same setting, such that staging of surgery is not necessary. Given that distortion of normal anatomic landmarks is commonplace in AFRS, computerized image guidance is an indispensable tool in these endeavors.

The expansion of the sinuses often makes complete evacuation of fungal elements and inflammatory mucin challenging. The authors have found specialized instrumentation, including the Hydrodebrider (Medtronic, Minneapolis, Minnesota), a valuable tool that allows for complete removal of inflammatory debris and fungus. This powered irrigation system includes a flexible and rotatable instrument tip that aids with clearing of tenacious inflammatory debris residing within deep recesses of expanded sinuses.

Uniquely, AFRS frequently can present as a unilateral disease. Still, delayed, contralateral involvement can occur in 30.8% of cases.⁴¹ Although its mechanism is unclear, progression to contralateral disease may be the result of seeding of fungal and inflammatory material into nondiseased mucosa that is susceptible to hyperallergic inflammatory response. For this reason, in the authors' practice, instrumentation of the contralateral side typically is limited during primary surgery in cases of unilateral disease; and ESS for AFRS is not combined with other procedures, such as septoplasty and/or contralateral turbinate submucous resection.

Medical Management

Steroid therapy

Systemic steroids used immediately postoperatively are important in reducing early disease recurrence and achieving stable sinonasal mucosa, at which point, a transition to topical steroid therapy can be initiated. Studies evaluating the efficacy of systemic steroids in AFRS have demonstrated benefits in improving endoscopic scores and patient symptoms, reducing markers of inflammation, and eliminating radiographic evidence of disease postoperatively.^{42–45} The duration of postoperative systemic steroid therapy reported by controlled studies conducted in AFRS varies widely. Some investigations reported acceptable outcomes with only preoperative administration, whereas studies conducted in the early 2000s reported good outcomes when steroid maintenance therapy was extended for 4 months postoperatively.^{42–45} In the authors' personal experience, disease stabilization can be achieved when oral prednisone is started at 30 mg to 40 mg immediately postoperatively and tapered 7 days to 14 days after surgery, when topical steroid therapy can be initiated.

Like systemic steroids, topical nasal steroids are a mainstay in the management of AFRS. Regular topical nasal steroids delivered via standard spray device have demonstrated efficacy in reducing symptoms and polyp size in the setting of CRSwNP.^{46–48} There have been limited studies conducted in the context of AFRS; however, expert opinion indicates that the use of long-term topical nasal steroids is indicated in AFRS. In the authors' personal experience, the use of nonstandard, or off-label, topical nasal steroids, like high-volume budesonide irrigations (0.25-mg/2 mL or 0.5-mg/2 mL respules in 240 mL of nasal saline solution), is effective in reducing inflammation in the sinonasal cavity early postoperatively, especially in cases of severe disease. When indicated, high-volume steroid irrigations can be continued long term, because studies have demonstrated that use for 1 year or longer can be safe. Regular testing of cortisol levels to ensure no HPA axis suppression occurs, however, may be necessary.^{49,50}

Antifungal therapy

The use of antifungal therapy typically is limited to the azole class of antifungals (ie, posaconazole, itraconazole, and others), because this drug class targets the genus of fungi commonly associated with AFRS. There currently is a paucity of high-quality evidence that supports the use of oral antifungals in the setting of AFRS; however, the available studies performed in AFRS suggest that there may be some benefit. Rojita and colleagues⁵¹ conducted a prospective randomized clinical trial in 60 patients with AFRS diagnosed by the Bent and Kuhn criteria, in which they compared systemic steroids (given for 1 month postoperatively) plus nasal steroid spray versus oral itraconazole (100 mg twice a day, given for 6 months postoperatively). The study found no difference between the 2 groups using mean 20-item Sino-Nasal Outcome Test (SNOT-20), serum IgE level, and eosinophil

count as outcomes. The investigators conclude that itraconazole used postoperatively may be a safe and effective alternative to systemic steroid therapy in AFRS patients.

A handful of retrospective studies have evaluated the efficacy of systemic antifungal therapies in AFRS. The largest was performed by Rains and Mineck,⁵² including 139 patients diagnosed with AFRS using the Bent and Kuhn criteria. The investigators describe a regimen of high-dose itraconazole (400 mg/d for 1 month, 300 mg/d for 1 month, 200 mg/d for 1 month, or until clear by endoscopy) along with routine steroid taper and topical nasal steroid postoperatively. They reported a recurrence rate of 50.3% and reoperation rate of 20.5% during an average follow-up of 31.4 months. The use of itraconazole also has been studied in cases of recalcitrant disease, when standard therapy fails. Chan and colleagues⁵³ performed a pilot study in 32 patients with AFRS who had disease refractory to prednisone, nasal steroids, and amphotericin B nasal sprays. The investigators treated with oral itraconazole for a minimum of 3 months. They found endoscopic improvement in 12 cases and no improvement or worse endoscopic appearance in 20 patients; 56% of patients reported moderate to significant symptom improvement, whereas 44% reported little or no change in symptoms. Seiberling and Wormald⁵⁴ also performed a retrospective chart review in 23 patients with AFRS and nonallergic eosinophilic fungal rhinosinusitis who failed maximal medical and surgical therapy. All patients were treated with oral itraconazole (100 mg twice a day) for 6 months when recurrence developed after surgery. The investigators found that 19 patients had a decrease in symptoms and endoscopic scores. Sixteen patients required a decreased amount of oral steroids, and a significant portion of the patients remained disease-free at a mean of 15.7 months of follow-up.

Although the cumulative evidence does not strongly support the use of antifungals for AFRS, they may be considered an option in cases of disease recurrence when standard maximum medical therapy and/or surgery has failed. Serious toxicities have not been reported in the available published studies; however, transaminitis has been reported to occur in 4% to 19% of patients, so liver function should be monitored closely.^{53,54} A summary of these selected studies evaluating oral antifungal therapy in AFRS is presented in [Table 1](#).

Immunotherapy

Several studies have demonstrated that immunotherapy (IT) is a safe adjunct in the management of AFRS; however, because of limitations in study design, limited conclusions can be made regarding its efficacy. Mabry and colleagues^{55–58} reported results from case series following AFRS patients receiving IT for 3 years, which demonstrated improved endoscopic examinations and reduced need for corticosteroids; however, these observational studies were limited by lack of a defined control group. Bassichis and colleagues⁵⁹ and Folker and colleagues⁶⁰ have conducted case-control studies in patients with AFRS and compared outcomes in those receiving IT with those not receiving IT. Together, these studies demonstrated improved endoscopic examinations and symptom scores and reduced need for systemic steroids and revision surgery when IT was used. Taken together, the available evidence indicates that IT for AFRS is a safe adjunct with unclear benefit (given few studies with design limitations); however, it remains an option in the management of AFRS.⁶¹

Biologic therapy

Biologic therapy includes antibody-based therapies that target mediators of type 2 inflammation. A majority of biologic therapies investigated in CRS were developed

Table 1
Summary of selected studies evaluating oral antifungal therapy in allergic fungal rhinosinusitis

Study, Year	Design (n)	Intervention Group	Control Group	Outcomes	Results
Rojita et al, ⁵¹ 2017	Prospective, randomized (60 pts)	Oral itraconazole, 100 mg bid for 6 mo	Oral prednisolone for 1 mo, then topical nasal steroids for 6 mo postoperatively	SNOT-20; Kupferberg endoscopic staging; AEC; total serum IgE	No significant difference in outcomes between groups
Seiberling & Wormald, ⁵⁴ 2009	Retrospective chart review in recalcitrant AFRS and nonallergic eosinophilic fungal sinusitis (23 pts)	Oral itraconazole, 100 mg bid for 6 mo	None	Time to recurrence; endoscopic examination; oral steroid use; liver function tests	19 pts with clinical response 16 pts with decrease in oral steroid use 11 pts disease-free at mean 15.7 mo 3 pts stopped tx for elevated liver enzymes
Chan et al, ⁵³ 2008	Prospective, pilot study in recalcitrant AFRS (32 pts)	Oral itraconazole for minimum of 3 mo	None	Endoscopic score; serum IgE; RSOM-31; liver function testing	Endoscopic improvement: 12 cases No improvement/worse on endoscopy: 20 patients Mean increase in serum IgE post-treatment (581 → 766 µg/L) Moderate-significant symptom improvement: 56% Little or no change in symptoms: 44%

Rains & Mineck, ⁵² 2003	Retrospective (139 pts)	Postoperative regimen Itraconazole: 400 mg/d for 1 mo, 300 mg/d for 1 mo, 200 mg/d for 1 mo, or until clear by endoscopy. PLUS postoperative steroid taper and nasal steroid spray	None	Recurrence; revision surgery; serious adverse events	Recurrence: 50.3% Revision: 20.5% No serious adverse events
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Abbreviations: AEC, absolute eosinophil count; pts, patients; RSOM-31, 31-item rhinosinusitis outcome measure; tx, treatment.

for the management of asthma and other atopic diseases.⁶² Recently, the Food and Drug Administration (FDA) approved the use of dupilumab—an antibody that binds the IL-4R α subunit of the IL-4 and IL-13 receptors and prevents IL-4-mediated and IL-13-mediated signaling—for use in patients with nasal polyposis. The approval came after 2 phase 3 studies (24-week outcomes [Liberty NP SINUS-24], and 52-week outcomes [Liberty NP SINUS-52]) enrolling a total of 724 subjects were completed. Collectively, the studies found that patients previously treated with surgery and systemic corticosteroids receiving dupilumab (300 mg, every 2 weeks for the first 24 weeks, and then every 4 weeks for the subsequent 28 weeks) had significant improvements in olfaction (measured by University of Pennsylvania Smell Identification Test), nasal polyp score, CT Lund-Mackay score, and 22-item SNOT (SNOT-22) and reduced the need for systemic corticosteroid and surgery. Additionally, patients with comorbid asthma (59.6% of cohort) had improved lung function (forced expiratory volume in the first second of expiration) and asthma control (Asthma Control Questionnaire 6).^{63,64} These studies, however, specifically excluded AFRS patients despite the shared type 2 immune response with other CRSwNP subtypes.

Other biologic therapies that target type 2 inflammation in CRS include mepolizumab and reslizumab, monoclonal antibodies that bind IL-5; benralizumab, a monoclonal antibody directed against the IL-5 α -chain receptor; and omalizumab, an antibody that binds free and membrane-bound IgE. None of these biologic therapies is FDA approved for use in CRS; however, they have demonstrated some utility in studies performed in patients with CRSwNP. Bachert and colleagues⁶⁵ conducted a randomized, double-blind, placebo-controlled clinical trial in 105 patients with CRSwNP, testing the efficacy of mepolizumab. This study found patients receiving mepolizumab ($n = 54$) had reduced need for surgery and demonstrated a significant improvement in nasal polyp score and SNOT-22 symptoms scores compared with a placebo group. Rivero completed a meta-analysis of 5 studies that evaluated the efficacy of biologics (mepolizumab, reslizumab, and omalizumab) for the treatment of CRSwNP and found a significant improvement in patients' nasal polyp scores.⁶⁶ Bidder and colleagues⁶⁷ prospectively evaluated the efficacy of omalizumab in patients with allergic asthma who also had comorbid CRSwNP. The investigators found a similar improvement in SNOT-22 scores in patients receiving omalizumab ($n = 13$) without surgery compared with a control group of patients ($n = 24$) with asthma/CRSwNP undergoing surgery.

Although these studies do not specify the subtype of CRSwNP included and in some cases excluded AFRS disease in their patient cohort, it seems that given the profound local type 2 inflammation observed in AFRS, biologic therapy may have a role in AFRS patients who fail standard therapy.

Prognosis After Treatment

Patients with AFRS undergoing ESS have significant improvements in quality of life after surgery.^{68,69} Like patients with CRSwNP, the recurrence and revision rate for AFRS can be high. Younis and Ahmed⁷⁰ conducted a retrospective study in 117 patients with AFRS and eosinophilic mucin CRS, and they found that 22% of patients required a revision surgery an average of 2.6 years after the initial surgery. Data from the CRS epidemiology study performed in the United Kingdom reported a median interval to revision surgery of 2 years in patients with AFRS.⁷¹ Reasons for disease recurrence and need for revision surgery likely are multifactorial and difficult to identify in these studies; however, these observations highlight the challenge in controlling inflammation in AFRS.

SUMMARY AND FUTURE CONSIDERATIONS

AFRS is a subtype of CRS characterized by an exaggerated, localized, type 2 inflammatory response within the paranasal sinuses and a characteristic clinical presentation. When good surgical techniques are combined with adequate steroid therapy, AFRS patients often obtain durable disease control with overall improvements in their quality of life. Certainly, the challenge lies in cases of recalcitrant disease. Future clinical studies will need to address the efficacy of antifungals, biologics, and IT in AFRS, especially those with difficult-to-treat disease. From a basic science viewpoint, a greater understanding of the molecular signatures that differentiate AFRS from other subtypes of CRS (altered barrier function, overactive adaptive immune signaling, and defective antifungal immunity) has been arrived at; however, a better understanding of the mechanisms that lead up to these stages of diseases is greatly needed. These studies would identify new disease targets for the development of novel therapies.

DISCLOSURE

A.U. Luong serves as a consultant for Aerin Medical (Sunnyvale, California), Arrinex (Redwood City, California), Lyra Therapeutics (Watertown, Massachusetts), and Stryker (Kalamazoo, Michigan). She is on the advisory board for ENTvantage (Austin, Texas), Sanofi (Paris, France), and Novartis (Basel, Switzerland).

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