

ALLERGIC FUNGAL RHINOSINUSITIS

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ABSTRACT

Allergic fungal rhinosinusitis is a distinct form of chronic rhinosinusitis characterised by the formation of nasal polyps, accumulation of eosinophilic mucin and possible bony erosion and mucocoele formation. A type I hypersensitivity to fungi is present. Management is both medical and surgical, with regular follow-up. Endoscopic sinus surgery and systemic and topical corticosteroids play key roles in management. Allergen-specific immunotherapy is an attractive additional treatment.

INTRODUCTION

Allergic fungal rhinosinusitis (AFRS), or allergic fungal sinusitis (AFS), is a distinct subtype of chronic rhinosinusitis (CRS).¹⁻⁴ The histopathological profile of many common chronic inflammatory rhinosinusitis conditions, or hypertrophic sinus disease (HSD), exhibits allergic inflammation. AFRS is both a type of non-invasive fungal rhinosinusitis and a type of HSD. It is characterised by the formation of nasal polyps, accumulation of eosinophilic mucin and fungal hyphae within the nasal cavity and sinuses, a Gell and Coombs type I hypersensitivity reaction to fungi and almost pathognomonic CT findings.^{1-3,5}

EPIDEMIOLOGY AND MICROBIOLOGY

AFRS may be the most common form of fungal sinusitis accounting for approximately 7-12% of CRS taken to surgery in the USA.^{3,4} Climate presumably accounts for varied distribution among regions and differences in microbiology.^{3,4}

The age group affected is predominantly young adults and adolescents, younger than most CRS patients, with a mean age at diagnosis of 21.9 years.³ Most studies demonstrate a fairly equal male-to-female ratio but there appears to be a male predominance in children and female predominance among adults.³⁻⁶ In the USA, the condition is more common in African Americans.³ Older patients who present with clinical features consistent with AFRS are more inclined to have some other eosinophilic mucin chronic rhinosinusitis syndrome (EMCRS).⁴ Patients are generally from a lower socioeconomic background, usually immunocompetent and with a history of atopy, though not all have a history of allergic rhinitis.⁴

Aspergillus fumigatus was initially implicated as the causative organism; however the dematiaceous fungal group have been shown to be present more commonly in eosinophilic mucus.¹⁻⁸ Identification of a fungus via histopathology or culture is more important for diagnosis than the specific fungal organism.

PATHOPHYSIOLOGY

In the past AFRS has been labelled as 'allergic aspergillosis' and its pathogenesis was thought to

mirror that of allergic bronchopulmonary aspergillosis (ABPA).^{3,4} Although fungal cultures were unavailable at that stage, histologically the mucin appeared identical to that found in ABPA. In ABPA, inspissated allergic mucin obstructs the bronchi, and histologically an inflammatory cell infiltrate of eosinophils and lymphocytes exists. A subgroup of patients with AFRS may present with concomitant allergic bronchopulmonary mycosis syndrome or sinobronchial allergic mycosis.

Fungal hypersensitivity is a central pathogenic component. As dematiaceous fungi and *Aspergillus* predominate, it is likely that they have important biological characteristics.⁹ Both atopy and environmental exposure to specific types of fungal spores are requirements. It is believed that a continuum may exist between HSD and AFRS, so AFRS may occur as a complication of, or in addition to, ongoing HSD, but may be the *de novo* cause for HSD in others.¹

There is an association of ABPA, AFRS and HSD with class II major histocompatibility (MHC) genes and thus an acquired immune response.^{1,2} Microbial superantigens may manipulate this response. A combination of a Gell and Coombs types I and III hypersensitivity reaction has been implicated.^{4,10} An atopic host typically inhales fungal allergens and an IgE-mediated response ensues with resultant sinonasal inflammation associated with oedema, sinus obstruction and stasis. The end stage of this chronic inflammation is nasal polyp formation and mucus accumulation. Trapped fungi continue to stimulate the immune system, and a vicious cycle is set up. In time, massive polyposis and mucocoeles may arise, causing bony erosion and expansion, distorting sinonasal anatomy.

More recently, studies have focused on humoral immune responses in EMRS and AFRS patients, and have shown that fungal-specific IgG was increased without regard to the presence of allergy or fungal elements in eosinophilic mucin.⁴ Fungal species present in the eosinophilic mucin correlate poorly with the specific fungal allergy, but elevated fungal-specific IgG3 appears to be a distinguishing factor between those patients with EMRS and AFRS and those with other forms of CRS and allergic rhinitis. Fungal antigens have also been shown to stimulate the secretion of T-helper cell 2 (Th2)-type cytokines by peripheral blood mononuclear cells (PBMC) in AFRS. The cell walls of fungi contain a polysaccharide polymer, chitin, recognised by pattern recognition receptors in airway epithelia, inducing an innate immune response (Th2 immune response) as well as acid mammalian chitinase (AMCase), which acts to degrade chitin as a defence mechanism (downregulates Th2 response).⁹ The role of chitin and AMCase remains unclear.

Type I hypersensitivity and dysregulated IgE metabolism occur locally in AFRS.¹¹ The majority have detectable fungal-specific IgE in their eosinophilic mucin whereas those with other forms of EMRS do not, and mucosal total and specific IgE to fungal and non-fungal antigens are raised.¹²

Controversy still exists as to whether or not fungal allergy can be implicated as the primary inflammatory stimulus in AFRS.^{4,9} The similarity between EMRS and AFRS is uncanny. Studies have revealed similar polyp histology, inflammatory cell infiltrate, tissue eosinophilia

and fungal-specific PBMC proliferation, suggesting that both allergic and non-allergic fungal hypersensitivity may play an important role in the underlying pathophysiology of both AFRS and EMCRS.⁴ The initial enthusiasm of a fungal hypothesis as the basis of all chronic sinus disease has died down as a result of lack of evidence and failure of clinical trials with amphotericin, thus making the central role of fungi in CRS unlikely.⁹ An argument has also been made for the possible role of environmental and local anatomical factors in the development of AFRS.

It is clear that a complex combination of pathophysiological mechanisms exist, and that some are yet to be elucidated. The outstanding feature, it seems, is the presence of type I hypersensitivity to fungi in AFRS, an important distinguishing feature from other types of EMRS.

IMMUNOPATHOLOGY¹⁻³

Antigen presentation to T cells represents the first step in an acquired immune response. This occurs by means of antigen-presenting cells (APCs). The human leukocyte antigen (HLA) genes within the MHC class II gene complex, located on chromosome 6, code for the polymorphic HLA-DR, DQ and DP antigen-presenting molecules found on APCs. Foreign peptides are bound by the MHC class II genes and then presented to antigen-specific T-cell receptors (TCRs). About 0.01% of resting T cells have TCRs capable of recognising any given MHC-peptide complex. A link exists between certain MHC class II alleles and the aetiology-specific inflammatory diseases. These genes also play a role in microbial superantigen-induced disease. Superantigens are microbial toxins capable of activating up to 30% of all T cells by simultaneously binding to the MHC class II molecule on the APC and to the TCR at its V_B region, away from their respective peptide-binding sites, so creating a molecular bridge bypassing normal antigen-specific interaction. Specific TCR V_B motifs bind specific superantigens; however some MHC class II molecules are better at binding and presenting specific superantigens. *Staphylococcus*, *Streptococcus*, *Mycoplasma*, *Yersinia* and certain retroviruses all produce superantigens. They have been shown to play an important role in atopic dermatitis, chronic severe asthma, type I diabetes mellitus, multiple sclerosis, rheumatoid arthritis, Kawasaki's disease, psoriasis and now HSD, with patients exhibiting oligoclonal T-cell expansion, characteristic of superantigen activity and serological positivity to staphylococcal superantigens. ABPA has been linked to HLA-DR2 and DR5, with DQ2 found to be protective. AFRS has been found to be linked to HLA-DQB1*0301 and *0302 alleles, while other HSD disorders may be associated with HLA-DQ3.^{2,13} It has been hypothesised that *A. fumigatus* and other dematiaceous fungi may also produce or induce superantigens, so defining their role in AFRS.

CLINICAL PRESENTATION

Symptomatology is much the same as those of patients suffering from CRS.⁴ Patients may present with an unrelenting history of rhinosinusitis and seek medical attention only with an increase in the severity of the symptoms such as complete nasal obstruction, intractable headaches, visual disturbances, facial pain, visual disturbances or facial distortion.^{3,4,6} Generally speaking symptoms are unilateral; however bilateral cases do occur.⁴ The ethmoid and maxillary sinuses are most commonly affected. A history of allergic rhinitis is common (66%) and about 50% of cases have associated asthma.³⁻⁵

Children may present subtly or more typically present with nasal obstruction, intermittent purulent nasal discharge, anosmia/ageusia and headaches.^{3,6,14} As is the case with adults, the onset is insidious and pain may indicate a concomitant bacterial infection.

Clinical examination may reveal advanced disease with proptosis, telecanthus and facial dysmorphism, especially in younger patients.^{3,4,6} Nasal polyps may be unilateral or bilateral, with the bulk of disease asymmetrically distributed.⁴ The characteristic dark yellow-brown inspissated mucus may also be encountered on endoscopy.^{4,8}

As type I hypersensitivity is a requirement for diagnosis, testing for atopy is necessary. This may be achieved either by means of skin tests, which should include fungal antigens as well as a region-specific panel, or *in vitro* testing for antigen-specific IgE. Hypersensitivity to multiple fungal and non-fungal antigens will usually be revealed.¹⁻⁵ A peripheral eosinophilia and dramatically elevated IgE levels may be present.^{2,5,15}

DIAGNOSIS

A multifaceted approach is required for diagnosis which encompasses a combination of clinical, radiographic, microbiological and histopathological information. Currently no universally accepted criteria exist.⁴ Various investigators have proposed diagnostic criteria and these have been refined further as definitions of rhinosinusitis evolve. Bent and Kuhn¹⁶ pioneered the criteria which are most often used (Table I).¹⁶ However, although widely used, many of these criteria are not unique to patients with AFRS.⁹ All patients with CRS with nasal polyps have nasal polyposis and a large proportion also have eosinophilic mucin without fungal invasion.⁹ Type I hypersensitivity to fungi and characteristic computed tomography (CT) findings are the only unique factors in Bent and Kuhn's criteria for AFRS that allow it be distinguished from other forms of sinus disease. Minor diagnostic criteria that have been proposed include the presence of asthma, Charcot-Leyden crystals, eosinophilia, unilateral disease, osseous erosion and positive sinonasal fungal culture.^{3,16}

Table I. Bent and Kuhn criteria

Type I hypersensitivity to fungi
Elevated total serum IgE
Nasal polyposis
Characteristic CT scan findings
Eosinophilic mucus without fungal tissue invasion, mucosal necrosis, granulomas or giant cells
Positive fungal stain of sinus contents removed at surgery
Exclusion of other fungal rhinosinusitis disorders

The allergic or eosinophilic mucin is a hallmark of the disease. It is a thick, tenacious material with the consistency of peanut butter and a dark, greenish colour.^{1,2,4,5} Histologically it consists of onion-skin laminations of necrotic and degranulating eosinophils in a background of mucin (Figures 1 and 2).^{2,4,8} Characteristically, 'tide lines', 'tree rings', waves or ripples created by an alternating pattern of mucinous material and inflammatory debris, which appear blue and pink with haematoxylin and eosin staining, are found. Charcot-Leyden crystals, as well as fungal hyphae, which are usually sparsely distributed, may be present. Fungal stains such as the Gomori methenamine silver or a PAS light-green staining may be necessary for identification (Figure 3).² Fungal invasion is not a feature.² The surrounding nasal mucosa and polyps demonstrate an eosinophilic inflammatory infiltrate.

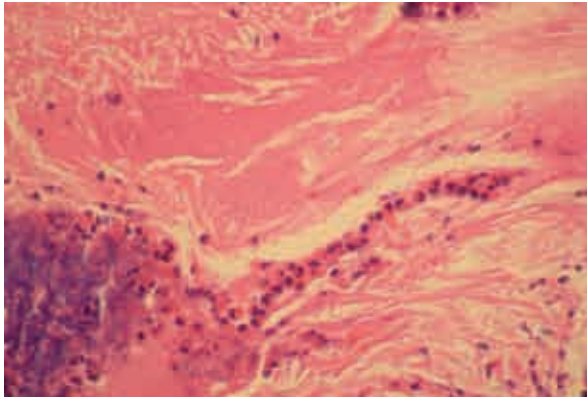


Fig. 1. Allergic mucin (high power magnification).

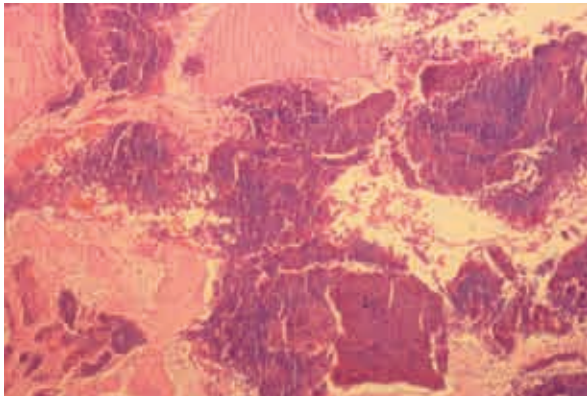


Fig. 2. Allergic mucin (low power magnification)



Fig. 3. Gomori stain.

In some cases, however, fungal elements may be lacking. This may be due to issues with surgical sampling or pathology sections, but the surgically obtained mucin usually yields a positive fungal culture in an otherwise characteristic patient. Up to 13% of AFRS surgical cultures are negative despite histopathological confirmation of AFRS.⁵ In some, fungal elements are truly lacking and Ferguson¹⁷ proposed the term 'eosinophilic mucin rhinosinusitis' (EMRS) for this subset of patients.¹⁷ The spectrum of AFRS-like conditions include those in which fungi are present within the eosinophilic mucin, but without allergy, and others with eosinophilic mucin, but no evidence of fungi or allergy. The presence or absence of fungal allergy or gross fungal elements in eosinophilic mucin has no effect on histology, inflammatory cell infiltrate, tissue eosinophilia or fungal-specific PBMC proliferation.¹⁸ These overlapping clinicopathological features may pose diagnostic dilemmas. Owing to the clinical similarity between EMCRS and AFRS, it is often difficult to distinguish one from the other, though AFRS patients are reported to have more severe bony erosion and expansion with heterogeneous sinus opacification on CT scan.

Clinically, AFRS is also associated with elevated serum total IgE as well as fungal antigen-specific IgE and IgG concentrations that subsequently rise and fall with disease recurrence and remission, respectively.^{1,2} Total serum IgE levels are not as high as those found with ABPA (commonly 1 000-10 000 IU/ml), typically ranging between normal and 3 000 IU/ml, with mean values around 500 IU/ml.^{1,5,15} Various authors have investigated the inter-relationship between elevated serum total IgE, fungal-specific IgE and fungal-specific IgG in different chronic rhinosinusitis subgroups and found that in AFRS and AFRS-like groups, fungus-specific IgE and IgG (especially anti-*Alternaria*-specific antibodies) were significantly raised.^{5,15,19}

RADIOLOGICAL FEATURES

While characteristic CT findings are frequently the earliest documented signs of disease, patients often fail to exhibit these findings at any point in their disease course.³ Both magnetic resonance imaging (MRI) and CT exhibit characteristic findings.

A CT scan is the initial study of choice and shows multiple opacified sinuses with central hyperattenuation ('double-density')(Figure 4); mucocoele formation may be present, as well as erosion of the lamina papyracea or skull base (pushing borders).^{2,4,8} AFRS displays significantly more osseous expansion and thinning of the bony confines of the sinonasal cavities than other forms of CRS, with 56% of cases presenting with radiographic evidence of skull base erosion or intraorbital extension as compared to 5% of other causes of CRS (Figure 5).^{3,4} The paediatric population presents with asymmetric/unilateral disease more often than adults.³

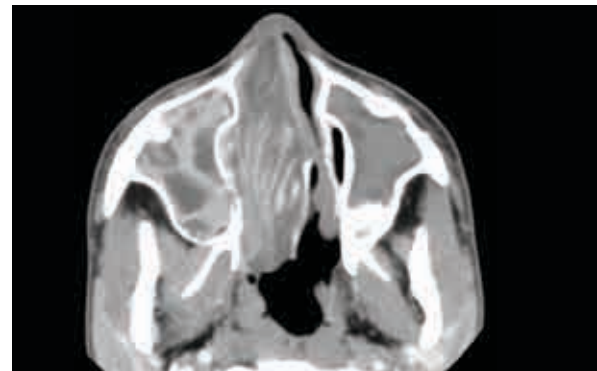


Fig. 4. Axial CT demonstrating double densities in the maxillary sinus.

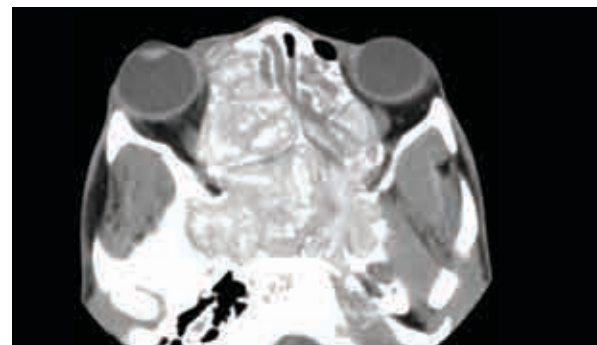


Fig. 5. Axial cut at the level of ethmoid sinuses demonstrating bony erosion and expansion into the orbits.

MRI is usually not indicated unless central nervous system or orbital complications exist. In AFRS, the sinuses have a central low signal on T1 and T2 corresponding to areas of eosinophilic mucin with peripheral high-signal intensity corresponding to

inflamed mucosa.^{4,8} An iso-intense or hypo-intense T1 signal may also occur.

A study at two tertiary rhinology centres aimed to determine a more objective means of assessing radiological bony erosion and develop a novel CT scan staging system.²⁰ Each paranasal sinus is scored 1 point with a maximum of 3 points for each frontal sinus, 2 for each ethmoid complex, 3 for each sphenoid sinus and 3 for each maxillary sinus, and 1 point each for the frontal and intersphenoid sinus septae, with a maximum of 24 points. Males scored significantly higher than females and African-Americans scored significantly higher than Caucasians. Bony abnormalities were present in the following order: ethmoids 77%, maxillary sinuses 68%, sphenoids 58% and frontal sinuses 53%.

TREATMENT

Management typically involves a combination of both medical and surgical intervention. In all but the mildest cases of AFRS, medical therapy alone without surgical intervention is unlikely to be effective in the long term.⁹ A paradigm shift has resulted in less aggressive surgery being performed and less reliance on toxic antifungal medications.^{3,4} Endoscopic surgery combined with anti-inflammatory medication is now considered the gold standard.

Surgery is inevitable, but while earlier external approaches with stripping of sinus mucosa were the norm, they have now been superseded by endoscopic, tissue-preserving techniques, the aim being removal of obstructing polyps, evacuation of sinus contents and facilitation of sinus drainage.^{4,21,22} Massive polyposis and mucocoele formation often facilitate surgery; however, landmarks are similarly eroded and so may complicate surgery and increase possible risk. Image-guidance, if available, is invaluable for orientation, thus allowing for more complete surgery. Incomplete surgery may result in early recurrence and limit effectiveness of topical medication.^{2,3} Surgical treatment for recurrences is indicated in the face of failure of intense medical management for exacerbations, high polyp burden, or stubborn accumulation of eosinophilic mucin despite medical management. The goals of both primary and revision surgery are removal of mechanical obstruction, clearance of sinus contents and establishing adequate outflow tracts while maintaining mucociliary function.³ Optimal outcomes depend finally on prolonged and comprehensive medical therapy postoperatively.

Medical therapy plays a pivotal role in obtaining long-term symptom control, retarding further polyp growth and delaying or preventing revision surgery. Systemic corticosteroids appear most effective. Systemic corticosteroids given pre-operatively help to shrink polyps and decrease bleeding intra-operatively.^{4,21} Postoperative systemic corticosteroids lead to improvement in symptoms and on endoscopy, but can have significant side-effects.^{1,2,9,22,23} Prolonged treatment may be required in severe cases, but the risk of both acute and long-term toxicities must be weighed up against potential benefit.⁴ Best clinical practice would condone systemic steroid use in the peri-operative period and in short bursts, as required, for polyp recurrence or acute exacerbations.

Topical intranasal corticosteroids are important in long-term medical management.^{4,9} Topical delivery is advantageous as the risk of corticosteroid toxicity is minimised and inflammation is successfully suppressed for extended periods. A dose-response effect appears to exist.⁴ Some investigators recommend using three times the usual dosage to boost efficacy. The use of budesonide in the form of drops, atomised spray or low-volume irrigant in order to deliver a larger total dosage

of steroid compared to conventional intranasal steroid sprays is an emerging therapy.^{3,4}

Non-steroidal treatments are attractive alternatives and include the use of leukotriene receptor antagonists or synthesis inhibitors, monoclonal antibody selectively binding IgE, as well as macrolide antibiotics and steroid-impregnated antibiotic gels, though further investigation is required as data are lacking.^{1-4,24,25} Antihistamines may also be used in conjunction with the above.

Another option is the use of antifungal agents. Again, convincing data have not been forthcoming and the side-effect profile is unfavourable, as is the cost.⁴ Uncontrolled, cohort studies have shown some promise for itraconazole therapy, probably because of its anti-inflammatory properties and inhibition of prednisone metabolism.²⁶

Topical delivery of antifungals has also been investigated. The use of topical fluconazole solution in the form of a spray or irrigant may significantly reduce the recurrence rate.^{27,28} No synergistic or additive benefit is gained by adding oral itraconazole to topical fluconazole.²⁸ Antibiotics, mainly aimed at eradication of *Staphylococcus aureus*, may be necessary for intercurrent episodes of acute infection.¹ Manuka honey placed intranasally has also been investigated in a randomised, prospective, single-blind study in a group of AFRS patients failing surgery and maximal medical therapy but did not demonstrate any improvement.²⁹

Immunotherapy may be a potentially beneficial treatment option.^{2,4,7,9,10,25} Immunotherapy is commenced after the fungal load in the paranasal sinuses has been reduced by surgery as the allergen-specific IgG produced by immunotherapy could theoretically incite an immune-complex-mediated reaction.¹⁰ However, no systemic, severe local, or immune-complex reactions have been reported in studies on subcutaneous immunotherapy (SCIT) for AFRS.^{7,10} The anti-inflammatory effect may decrease reliance on systemic steroids and decrease the need for revision surgery. It may help to control concomitant allergic inflammation, though data for AFRS are lacking. Folker and colleagues³⁰ demonstrated better endoscopic mucosal appearance, lower CRS survey scores, fewer courses of systemic steroids and less reliance on nasal steroids in AFRS patients treated with immunotherapy, and highlight the possibility of its role in the overall management of AFRS.³⁰ SCIT for fungal allergens poses a risk no greater than that for pollens, and is usually initiated 4-6 weeks after surgery to prevent immunotherapy-induced exacerbation of symptoms in patients with active AFRS. Optimal duration of therapy is unclear at this stage.⁷ A 3-4-year course of SCIT demonstrated benefit 12-26 months after discontinuation and less need for prolonged courses of steroids.⁷ A smaller subset of this study group were followed up for 46-138 months and failed to demonstrate any benefit. Approximately 60% of the SCIT group had normal mucosa or mild oedema on endoscopy while 100% of the non-SCIT group had normal mucosa or mild oedema. As patients were not randomised, bias is a possibility.

Treatment is aimed at reducing inflammation and fungal antigen exposure while immunotherapy targets the IgE-mediated component. Ideal treatment approaches await the results of randomised controlled trials, which are lacking at this time. Overall goals of treatment include elimination of existing disease and prevention of recurrence while minimising side-effects. Aggressive, co-ordinated surgical and medical management are required.

NATURAL COURSE

Unfortunately, recurrence is a common finding,

reported to range between 10% and 100%, with varying severity.^{21,22} Marple *et al.*¹⁵ found that patients required an average of two surgical procedures and three courses of systemic steroids per year.¹⁵ Even asymptomatic patients had persistent polypoid mucosal oedema and elevated total serum IgE.

Measuring of total IgE levels may be useful for follow-up.²² Increases in total serum IgE of 10% or more between follow-up visits are strongly associated with recurrent surgery, while a decrease was strongly predictive of resolution.²² Close follow-up is recommended with regular nasal endoscopy and patients should be advised to return early if symptoms return or worsen. Postoperatively, patients are graded according to the Kupferberg endoscopic staging system (Table II).⁸ A potential problem with this staging system is that although patients may improve clinically, they may remain in the same stage as a result of persistence in one sinus cavity.³¹ A more recently proposed endoscopic staging system scores each sinus (maxillary, ethmoid, frontal, sphenoid) from 0 to 9 for increasing mucosal oedema with an extra 1 point for the presence of fungal mucin, giving a maximum score of 40 for each side of the nose (Table III).³¹ Patients may be ranked as: mild (1-20), moderate (21-40), severe (41-60), or extreme (61-80).

Table II. Kupferberg staging system

Stage	Endoscopic findings
0 (A/B)	No mucosal oedema
I (A/B)	Mucosal oedema
II (A/B)	Polypoid oedema
III (A/B)	Sinus polyps
A – without allergic mucin, B – allergic mucin present	

Table III. Modified staging system (Philpott-Javer)

Grading (each sinus, right and left, out of 40)	State of mucosa
0	No oedema
1-3	Mucosal oedema (mild/moderate/severe)
4-6	Polypoid oedema (mild/moderate/severe)
7-9	Frank polyps (mild/moderate/severe)
Mucin: plus 1 for each sinus	

CONCLUSION

AFRS is a distinct form of CRS characterised by the formation of nasal polyps, accumulation of eosinophilic mucin and possible bony erosion and mucocoele formation caused by an allergic response to fungi. Management is by a combination of medical and surgical treatment.

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Declaration of conflict of interest

The author declares no conflict of interest.

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