



Review Article

Are allergic fungal rhinosinusitis and allergic bronchopulmonary aspergillosis lifelong conditions?

Ritesh Agarwal^{1,*}, Sandeep Bansal² and Arunaloke Chakrabarti³

¹Department of Pulmonary Medicine, ²Department of Otorhinolaryngology and ³Department of Medical Microbiology, Post Graduate Institute of Medical Education and Research, Sector-12, Chandigarh, India

*To whom correspondence should be addressed. Dr. Ritesh Agarwal, Additional Professor, Department of Pulmonary Medicine, Post Graduate Institute of Medical Education and Research, Sector-12, Chandigarh-160012 (India). Tel: +(91, 172) 2756825; Fax: (91, 172) 2748215; E-mail: agarwal.ritesh@outlook.in

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Abstract

Aspergillus fumigatus can cause several allergic disorders including *Aspergillus*-sensitized asthma, allergic bronchopulmonary aspergillosis (ABPA), and allergic fungal rhinosinusitis (AFRS). ABPA is an immunological pulmonary disorder caused by allergic reactions mounted against antigens of *A. fumigatus* colonizing the airways of patients with asthma (and cystic fibrosis). Allergic bronchopulmonary mycosis is an allergic fungal airway disease caused by thermotolerant fungi other than *A. fumigatus*. On the other hand, AFRS is a type of chronic rhinosinusitis that is also a result of hypersensitivity reactions to the presence of fungi that become resident in the sinuses. The pathogenesis of ABPA and AFRS share several common features, and in fact, AFRS can be considered as the upper airway counterpart of ABPA. Despite sharing similar immunopathogenetic features, the simultaneous occurrence of the two disorders is uncommon. Due to the lacuna in understanding of the causative mechanisms, and deficiencies in the diagnosis and treatment, these disorders unfortunately are lifelong illnesses. This review provides an overview of the pathogenesis, diagnosis, and long-term outcomes of both these disorders.

Key words: ABPA, AFRS, aspergillus, allergy, asthma, sinusitis.

Introduction

In general, illnesses are chronic either because the pathogenesis is unclear or the diagnosis is difficult or when there is no effective treatment. Unfortunately, all three are true of two allergic fungal airway disorders namely allergic bronchopulmonary aspergillosis (ABPA) and allergic fungal rhinosinusitis (AFRS).

The most common pathogenic fungi causing a variety of upper and lower airway disorders is *Aspergillus fumigatus*.¹ Airway disorders caused by fungi can be broadly classified as saprophytic, invasive (acute, subacute, and chronic) and allergic, depending on the extent of mycelial colonization or invasion, both of which are determined primarily by the immune status of the host.² Allergic

bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disorder caused by hypersensitivity reactions mounted against *A. fumigatus* colonizing the tracheo-bronchial tree of patients with asthma and cystic fibrosis.^{1,3} A similar disorder, allergic bronchopulmonary mycosis (ABPM), is an ABPA-like syndrome caused by fungi other than *A. fumigatus*.⁴ On the other hand, allergic fungal rhinosinusitis (AFRS) is a distinct type of chronic rhinosinusitis that again occurs as a result of immunological reactions to noninvasive fungal presence in the sinuses.⁵ In fact, AFRS can be considered as the upper airway analogue of ABPA.⁶ Both disorders incite an intense inflammation causing accumulation of eosinophilic mucin containing fungal hyphae. This article provides an overview of the pathogenesis, diagnosis and long-term outcomes of both these disorders.

Pathogenesis of ABPA/AFRS remains unclear

Despite several decades of research, the pathogenesis of ABPA and AFRS still remains unclear.⁷ The putative steps in the pathogenesis are shown in Figure 1, the sequence of events remains largely theoretical. The conidia of *A. fumigatus* are omnipresent, but they are immunologically inert due to the presence of a hydrophobic layer on the conidial surface comprised of Rod A hydrophobin. This prevents the recognition of the immunogenic components of the fungal conidia by the host.^{8,9} In patients with ABPA and AFRS, defective clearance of conidia in the airway or sinus mucus allows them to germinate into hyphae. The innate immune cells recognize the fungal products (pathogen-

associated molecular patterns; β glucan, galactomannan, and others) through pattern recognition receptors (such as Toll-like receptors, nucleotide-binding oligomerization domain [NOD]-like receptors and, C-type lectin receptors) present on airway epithelium and airway macrophages,¹⁰ or a complement receptor 3 (CR-3) pathway in mononuclear cells.¹¹ Subsequently, there is release of chemokines and cytokines that lead to adaptive immune response mediated by T-helper cells.¹² In normal individuals, a Th1 CD4+ T cell response against *Aspergillus* leads to clearance of *Aspergillus* secondary to macrophage and neutrophil-mediated phagocytosis.¹³ In contrast, the immune response in AFRS and ABPA is a Th2 CD4+ T cell response.^{14–16} In ABPA and AFRS, the host susceptibility (due to several defects in innate and adaptive immunity) causes persistence of *A. fumigatus*.¹⁷ The subsequent fungal growth then leads to the release of several proteins that not only activate the airway epithelium but also directly damage the pulmonary epithelium.^{18–21} This coupled with activation of pattern recognition receptors prime group 2 innate lymphoid cells towards Th2 differentiation.²² Recently, it has been shown that *Aspergillus* inhibited interferon- β signaling in human bronchial epithelium by activation of protease-activated receptor-2 (PAR-2) and tyrosine-protein phosphatase non-receptor type 11 (PTPN11), and inhibition of the phosphorylation of signal transducer and activator of transcription 1 (STAT1) pathway; all of these changes led to the reduction of the chemokine CXCL10, thus polarizing epithelial responses towards Th2.^{23,24}

The Th2 response triggers release of Th2 chemokines and cytokines (CCL17, 1L-4, IL-5, IL-9, IL-13, and others); however, they do not clear the fungi²⁵ but lead to profound inflammatory reaction with mast cell degranulation, influx of large number of neutrophils and eosinophils,²⁶ and IgE (total and *A. fumigatus* specific) synthesis.²⁷ Eosinophils and neutrophils attack the fungal hyphae, degranulate, and further release inflammatory mediators, cytokines, and growth factors. This causes the characteristic pathological findings of AFRS and ABPA namely eosinophilic mucin formation in the former; and, eosinophilic pneumonia, bronchocentric granulomatosis, and mucus plugging in the latter. Persistent inflammation leads to nasal polyp formation and bony demineralization in AFRS and bronchiectasis in ABPA. While the immunopathogenesis is believed to be common for both of these entities, the simultaneous occurrence of these disorders is uncommon. In fact, most patients with ABPA do not develop AFRS or vice versa. In one study that specifically investigated patients with ABPA for AFRS at a tertiary care referral center, only about 21% of patients with ABPA were found to have AFRS.²⁸

Although any fungi can be allergenic, only the thermo-tolerant fungi that can survive both in the environment and

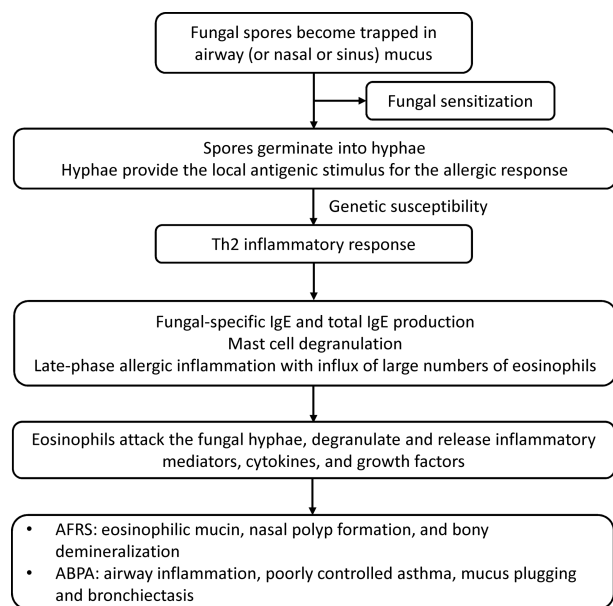


Figure 1. Model for the pathogenesis of allergic bronchopulmonary aspergillosis (ABPA) and allergic fungal rhinosinusitis (AFRS).

at body temperature are associated with human disease.²⁹ The most common fungus involved in causation of allergic bronchopulmonary disease is *A. fumigatus*. The occurrence of ABPM is far less common, and most reports are in the form of individual cases or brief series.⁴ Unlike ABPA, there are significant differences in the mycology of AFRS. AFRS was first recognized as an upper airway analog of ABPA and was termed as allergic aspergillus sinusitis.^{30,31} Subsequently, in a study of 22 cases of culture-positive AFRS, dematiaceous fungi (*Bipolaris*, *Curvularia*, *Alternaria*, and others) were found to be the most common fungi, whereas *Aspergillus* was found in only one case.³² In the Indian subcontinent and the Middle East, *A. flavus* is the most common agent causing AFRS.^{33–35} To add to the confusion, patients with AFRS may not be allergic to the same fungal species identified in their surgical specimen.³⁶

Diagnosis of ABPA/AFRS remains difficult

The diagnosis of ABPA is made on a combination of clinical, radiological, and immunological findings. The diagnostic criteria are far from perfect, primarily due to the lack of a reference standard. Also, there is no clear consensus on the diagnostic criteria for ABPA, and the criteria have been revised on several occasions since the disorder was first recognized.^{37–40} Recently, the International Society for Human and Animal Mycology (ISHAM) had convened a Working Group on ABPA complicating asthma to resolve some of these controversies. The diagnostic criteria proposed by this working group are the latest evidence-based guidelines on the diagnosis of this disease (Table 1).⁴⁰ The criteria are now clearly defined, offer more importance to certain components (*A. fumigatus* specific IgE and total IgE) and provide specific cutoff limits for various immunological components. Despite the availability of these diagnostic criteria, about 25–30% of patients with ABPA are still

Table 1. Diagnostic criteria for allergic bronchopulmonary aspergillosis (ABPA).

Predisposing conditions
Bronchial asthma, cystic fibrosis
Obligatory criteria (both must be present)
<i>A. fumigatus</i> -specific IgE > 0.35 kUA/l
Serum total IgE levels > 1000 IU/ml*
Other criteria (at least two of three)
Elevated <i>A. fumigatus</i> -specific IgG antibodies in serum
Thoracic imaging findings consistent with ABPA†
Peripheral blood eosinophil count > 500 cells/μl

*An IgE value < 1000 IU/ml may be acceptable, if all other criteria are met.
†The features on thoracic imaging consistent with ABPA include fleeting opacities, gloved finger opacities, tram-track opacities and bronchiectasis.
Adapted from reference⁴⁰.

Table 2. Bent and Kuhn diagnostic criteria for allergic fungal rhinosinusitis.⁴⁵

Major
Eosinophilic mucin in sinuses without invasion
Positive fungal smear in eosinophilic mucin
Computed tomography findings of hyperattenuated mucus
Type 1 hypersensitivity to the causative fungus
Nasal polyps
Minor
Positive fungal cultures from mucus removed from sinuses
Charcot-Leyden crystals in mucus from sinuses
Unilateral disease
Bony erosion
Asthma
Peripheral blood eosinophilia

misdiagnosed as pulmonary tuberculosis in the developing countries.^{41,42} Further, several patients do not fulfill all the criteria for diagnosis and require categorization as “ABPA-at risk.” Recent evidence suggests that investigations like *A. fumigatus* specific IgE and IgG (performed with automated immunoassays) are more sensitive than traditional tests like *Aspergillus* skin test and *Aspergillus* precipitins, respectively.^{43,44} Thus, these older tests need to be replaced by the newer ones, and the diagnostic criteria needs to be updated. ABPM is diagnosed in a manner similar to ABPA, except documenting immune responses to a particular fungus.

The diagnosis of AFRS is also shrouded with controversy. In fact, there is no uniformity even in the terminology for AFRS, and a working group under ISHAM has proposed a categorization and definition scheme for AFRS.⁵ The most widely used criteria for the diagnosis of AFRS are the Bent and Kuhn criteria, which are based on histopathologic, radiologic and immunologic characteristics of the disease (Table 2).⁴⁵ Unlike ABPA, in AFRS the diagnostic role of total IgE and fungal-specific IgE is limited.⁴⁶ The most important and mandatory diagnostic feature in AFRS is demonstration of eosinophilic mucin from one or more sinus cavities obtained during sinus surgery. Demonstration of fungus by traditional methods has low sensitivity, however fluorescein-labeled chitinase stain that stains the chitin layer of the fungal organism has been demonstrated to have good sensitivity.⁴⁷

Clinical course of ABPA

The natural history of ABPA is not well characterized. Moreover, it is difficult to predict as spontaneous improvement of symptoms and pulmonary opacities characterizes an important aspect of the disease.⁴⁸ Although there is no

Table 3. Clinical staging of allergic bronchopulmonary aspergillosis.⁴⁰

Stage	Definition	Features
0	Asymptomatic	• Asthma well controlled with step 1–3 GINA therapy • Fulfills the diagnostic criteria of ABPA (Table 1) • Not been previously diagnosed as ABPA
1	Acute	• Uncontrolled asthma/constitutional symptoms • Fulfills diagnostic criteria for ABPA • Not previously diagnosed as ABPA
1a	with mucoid impaction	ABPA with mucoid impaction on chest radiograph, CT chest or bronchoscopy
1b	without mucoid impaction	ABPA without mucoid impaction on CT chest or bronchoscopy
2	Response	• Clinical improvement (resolution of constitutional symptoms, improving asthma control) • Major radiological improvement* • Decline in IgE by $\geq 25\%$ of baseline at eight weeks
3	Exacerbation	Clinical and/or radiological deterioration associated with an increase in IgE by $\geq 50\%$ of the post-treatment values
4	Remission	Sustained clinicoradiological improvement with IgE levels remaining at or below the post-treatment values (or increase by $< 50\%$) for ≥ 6 months off therapy
5a	Treatment-dependent ABPA	Exacerbation on two or more consecutive occasions within six months of stopping treatment or worsening of clinical, radiological or immunological parameters on tapering oral glucocorticoids/azoles
5b	Glucocorticoid-dependent asthma	Patient requiring oral or parenteral glucocorticoids for control of asthma while the activity of ABPA is controlled (indicated by IgE levels and chest radiograph)
6	Advanced ABPA	Presence of chronic hypercapnic respiratory failure and/or cor pulmonale with extensive bronchiectasis and/or fibrosis on HRCT of the chest after excluding reversible causes of acute respiratory failure

Stages are not sequential. * Permanent damage should not be considered in radiological response.

Abbreviations: CT, computed tomography; HRCT, high resolution CT; GINA, global initiative for asthma.

particular age predilection, most patients present in the third decade.⁴⁸ The clinical course is marked by recurrent episodes of remission and exacerbation. Importantly, if the disease is not recognized and treated adequately, the inflammatory process can progress and result in irreversible lung destruction in the form of bronchiectasis. The understanding of the natural history becomes easy if we appreciate the clinical stages of ABPA (Table 3). Importantly, these are not sequential stages, and a patient does not always progress from one stage to the other serially.

Although most patients with ABPA are symptomatic, occasionally ABPA may manifest in an asthmatic patient whose asthma is well controlled with minimal therapy (“stage 0”). This is especially true for asthma clinics where there is a policy for routinely screening all asthmatic patients for ABPA.^{49–51} Patients meeting all the criteria for ABPA and who present either with typical symptoms (fever, malaise, weight loss, hemoptysis) or have difficult-to-control asthma are said to be “stage 1.” Following treatment with glucocorticoids,⁵² there is improvement in symptoms, clearing of radiographic opacities and decline in IgE levels by at least 25% after eight weeks; and this

is “stage 2” (response). Essentially, the treatment objective is not normalization of IgE values but a decline in IgE that is commensurate with the clinical and radiological improvement.^{51,53} Usually within one year, about 40–50% of the patients experience an exacerbation (“stage 3”) of the disease,^{49,52,54,55} which is associated with clinicoradiological worsening and increase in serum total IgE by at least 50% of the post-treatment values. Certain radiological features have been shown to be associated with heightened risk for developing recurrent exacerbations namely extensive bronchiectasis, aspergilloma, and high-attenuation mucus.^{50,51,56,57} If there are no ABPA exacerbations over the next six months after stopping therapy, the patient has entered a state of prolonged response, and this stage is termed remission (“stage 4”). The IgE levels usually do not return to normal values even in those with remission.⁵⁸ Although some patients in stage 4 may enter into prolonged remission, it does not imply a permanent cure as exacerbations of the disease can occur several years after remission.⁵⁹ Patients with difficult-to-treat ABPA and/or asthma (“stage 5”) can be classified into two groups. The first group (treatment-dependent ABPA) is defined by those who

develop exacerbation on two or more consecutive occasions within six months of stopping treatment or require continuous treatment with glucocorticoids or azoles for the control of ABPA activity. The other category (glucocorticoid-dependent asthma) requires glucocorticoids for control of asthma, however the activity of ABPA (radiologically and immunologically) is under control. Patients in “stage 6” are those with complications due to advanced disease (extensive bronchiectasis and/or fibrosis) such as chronic hypercapnic respiratory failure and/or cor pulmonale. Sadly, unlike chronic renal failure where the underlying illness becomes quiescent, in patients with chronic respiratory failure due to ABPA, the disease can be clinically as well as immunologically active.^{60,61}

Clinical course of AFRS

The natural history of AFRS is poorly understood even compared to ABPA, and few studies have reported long-term follow up of patients with AFRS. Most patients with AFRS are adolescents and young adults (mean age, 21 years).⁶² Although there is a dramatic initial response to surgical therapy, the disease invariably recurs if there is no ongoing medical therapy.^{45,63} Thus, most patients would require some form of medical intervention for control of the disease. In one study, 17 patients with AFRS were followed up for 46 to 138 (mean, 82) months. The number of endoscopic sinus surgery ranged from 0 to 4 (mean, 2). After surgery, almost three-fourths of the patients demonstrated normal sinus mucosae but aggressive medical management was required for control of AFRS relapses over the first 1–4 years.⁶⁴ Depending on the length of follow up, the recurrence rates range from 10% to 100%, with a trend toward the higher end of the range.^{65,66} In another study, endoscopic evidence of disease preceded the recrudescence of symptoms.⁶³

Treatment for ABPA/AFRS is not satisfactory

Treatment of ABPA

The treatment protocol for the management of ABPA is shown in Figure 2. The cornerstone of managing ABPA includes initiation of anti-inflammatory therapy (systemic glucocorticoids) to restrain the immunological hyperactivity. Another option is to use antifungal agents (azoles, nebulized amphotericin B) to attenuate the fungal burden in the tracheobronchial tree thereby decreasing the antigen load. The goals of treatment include: (a) control of asthma; (b) prevention and treatment of acute exacerbations of ABPA; and (c) preventing the development or impeding the progression of bronchiectasis.

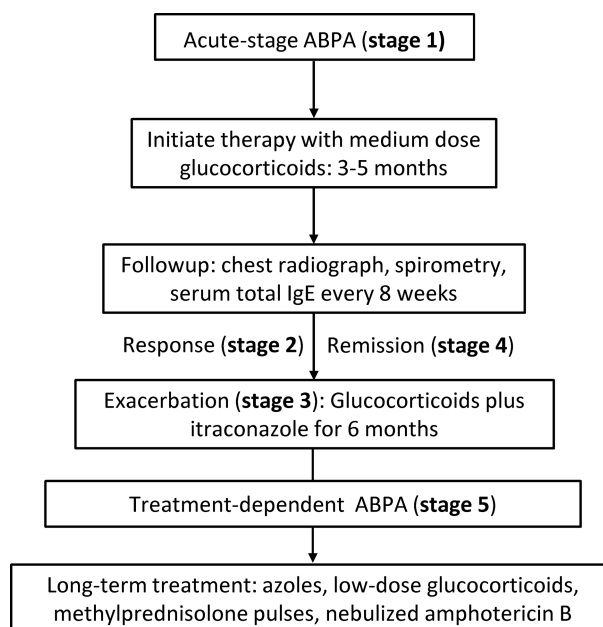


Figure 2. Treatment protocol for allergic bronchopulmonary aspergillosis (ABPA) followed at the author's institute.

Oral glucocorticoids are considered as the treatment of choice. In a randomized controlled trial (RCT) of 92 patients, it was found that medium dose of glucocorticoids were as effective as high doses in patients with acute-stage ABPA complicating asthma.⁵² The medium-dose regime used in ABPA includes oral prednisolone (or equivalent) at a dose of 0.5 mg/kg/day for two weeks followed by 0.5 mg/kg/day on alternate days for eight weeks. Then, the drug is tapered by 5 mg every two weeks and discontinued over 3–5 months. In this trial, the exacerbation rate at 1-year was 46%, while the prevalence of glucocorticoid-dependent ABPA was 13%. This suggests that the primary therapy for ABPA is inadequate.

Two randomized trials have evaluated the efficacy of azoles in ABPA.^{67,68} In the first RCT, 55 glucocorticoid-dependent patients were randomized to receive either itraconazole 400 mg/day or placebo for 16 weeks. While the difference between two groups was significant in composite outcome (reduction in glucocorticoid dose by $\geq 50\%$; and decline in total IgE by $\geq 25\%$; and at least one of the following: increment in exercise capacity by $\geq 25\%$, improvement in spirometric parameters by at least 25%, clearing of pulmonary opacities); however, it did not attain statistical significance when each outcome was examined separately.⁶⁷ Another RCT randomized 29 “clinically stable” ABPA patients to either itraconazole or placebo. There was significant decline in sputum inflammatory markers and serum IgE levels, however the study was not designed to evaluate exacerbation rates.⁶⁸ Apart from the small sample size, a major limitation was that neither study reported

outcomes longer than eight months in terms of relapses of ABPA. Also, the efficacy rate is about 60%. Currently, itraconazole is used at a dose of 200 mg twice daily for at least 16–20 weeks in patients with first exacerbation of ABPA or in those with glucocorticoid-dependent ABPA. An attractive proposition is monotherapy with azoles as this would altogether avoid the adverse effects of glucocorticoids. Two RCTs comparing monotherapy of itraconazole (and voriconazole) versus oral glucocorticoids alone have completed patient recruitment. The results of these trials are likely to clarify the place of azole monotherapy in ABPA (clinicaltrials.gov; NCT01321827, NCT01621321).

Newer azoles (voriconazole, posaconazole) are reserved in patients who experience inadequate response or develop side effects with itraconazole treatment.^{69,70} Pulse doses of methylprednisolone have been used in patients with refractory ABPA exacerbations or as an alternate to reduce the adverse effects associated with daily oral prednisolone.^{71,72} Omalizumab, a monoclonal antibody against IgE, has been tried in ABPA on a compassionate basis in cases refractory to standard therapy or in those experiencing adverse reactions with standard treatment.⁷³ Aerosolized amphotericin B can be used along with oral steroids or azoles.⁷⁴ Its primary role is likely to be in the maintenance of remission in ABPA given the fact that only a minority of patients either in acute-stage or exacerbation show response to nebulized amphotericin B.⁷⁵ In a recent RCT, 21 patients with recurrent (≥ 2) exacerbations but currently stable (stage 2) were randomized to receive either nebulized amphotericin B deoxycholate (20 mg thrice a week) plus nebulized budesonide vs. nebulized budesonide alone for four months. Although the time-to-first exacerbation was similar in the two groups, the numbers of patients experiencing exacerbation at one year were significantly lower in the amphotericin B arm (8.3% vs. 66.7%; $P = .016$).⁷⁶

Treatment of AFRS

The mainstay of treatment for AFRS is surgical debridement of the sinuses with endoscopic sinus surgery.⁶² During surgery, the sinuses are cleared of eosinophilic mucin, thus providing drainage and aeration to the sinuses. Patients usually receive preoperative glucocorticoids (prednisolone 0.5 mg/kg/day) for two weeks. Surgery is followed by aggressive medical therapy with post-operative glucocorticoids (prednisolone 0.5 mg/kg for 4 weeks, tapered over the next 2–5 months) to achieve a satisfactory long-term outcome.⁷⁷ Medical management with intranasal steroids and nasal irrigation with saline is required for indefinite period in most patients. Short bursts of oral steroids may be required in patients who experience worsening of symptoms despite medical management. The role of immunotherapy in management of AFRS is not clear because of the ab-

sence of RCTs.^{78,79} The role of antifungal agents in the treatment of AFRS remains unproven because of paucity of good quality studies. Older studies used topical fluconazole or low doses of itraconazole (100 mg/day).^{80,81} Recent data suggests that the use of itraconazole in appropriate doses (400 mg/day) or the use of voriconazole may lead to clinical improvement and reduction of oral glucocorticoid requirement in glucocorticoid-dependent patients.^{82–86} In a recent study, the use of preoperative itraconazole when added to glucocorticoids was associated with improvements in clinical, radiologic, and endoscopic parameters in patients with AFRS.⁸⁷ However, more data are required for adequately defining the role of antifungal agents in AFRS. Finally, the use of antifungal agents in AFRS should ideally be guided by the fungus isolated from sinus specimen, and susceptibility of various fungi to different agents. In fact, some of the confusion in AFRS regarding antifungal agents might be due to the lack of tailoring the treatment to presumptive pathogen identification and susceptibility.

ABPA and AFRS can coexist

The simultaneous occurrence of ABPA and AFRS is known as sinobronchial allergic mycosis (SAM) syndrome (Figure 3).^{6,28} Because different specialists treat ABPA and AFRS, their coexistence may be overlooked. Moreover, the use of oral glucocorticoids and/or antifungal agents in either disorder may mask the manifestation of the other disorder. In one study of 95 patients with ABPA, a diagnosis of definite and probable AFRS was made in 7 and 13 patients, respectively.²⁸ Thus, it may be prudent to enquire for troublesome and persistent upper and lower respiratory tract symptoms in ABPA and AFRS patients, respectively for diagnosing coexistent AFRS and ABPA, as it may decrease the

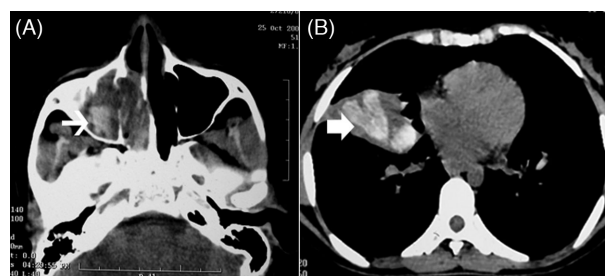


Figure 3. Radiology of a patient with simultaneous allergic bronchopulmonary aspergillosis (ABPA) and allergic fungal rhinosinusitis (AFRS). The patient presented with ABPA and was diagnosed as AFRS a year later when the patient manifested with upper respiratory tract symptoms. Noncontrast computed tomography (CT) of the paranasal sinuses showing soft tissue opacity within the right maxillary sinus (panel A). The soft tissue represents mucus impaction and the mucus is hyperattenuating (thin arrow). Mediastinal sections of the high resolution CT of the chest (panel B) showing hyperattenuating mucus impaction in the lateral segment of the right middle lobe (thick arrow).

morbidity of these disorders. In the authors' experience, the simultaneous occurrence of the two disorders is associated with poorer outcomes.

Conclusions

In conclusion, it appears that ABPA and AFRS are lifelong illnesses due to fungal allergy. Although response to initial treatment is excellent, there is a high propensity for recurrent exacerbations in both ABPA and AFRS. Judicious use of glucocorticoids and long-term use of antifungal agents is required in patients with recurrent exacerbations of ABPA. Surgical debridement and short course of glucocorticoids followed by long-term use of intranasal steroids and saline irrigation remains the mainstay of therapy in AFRS.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

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