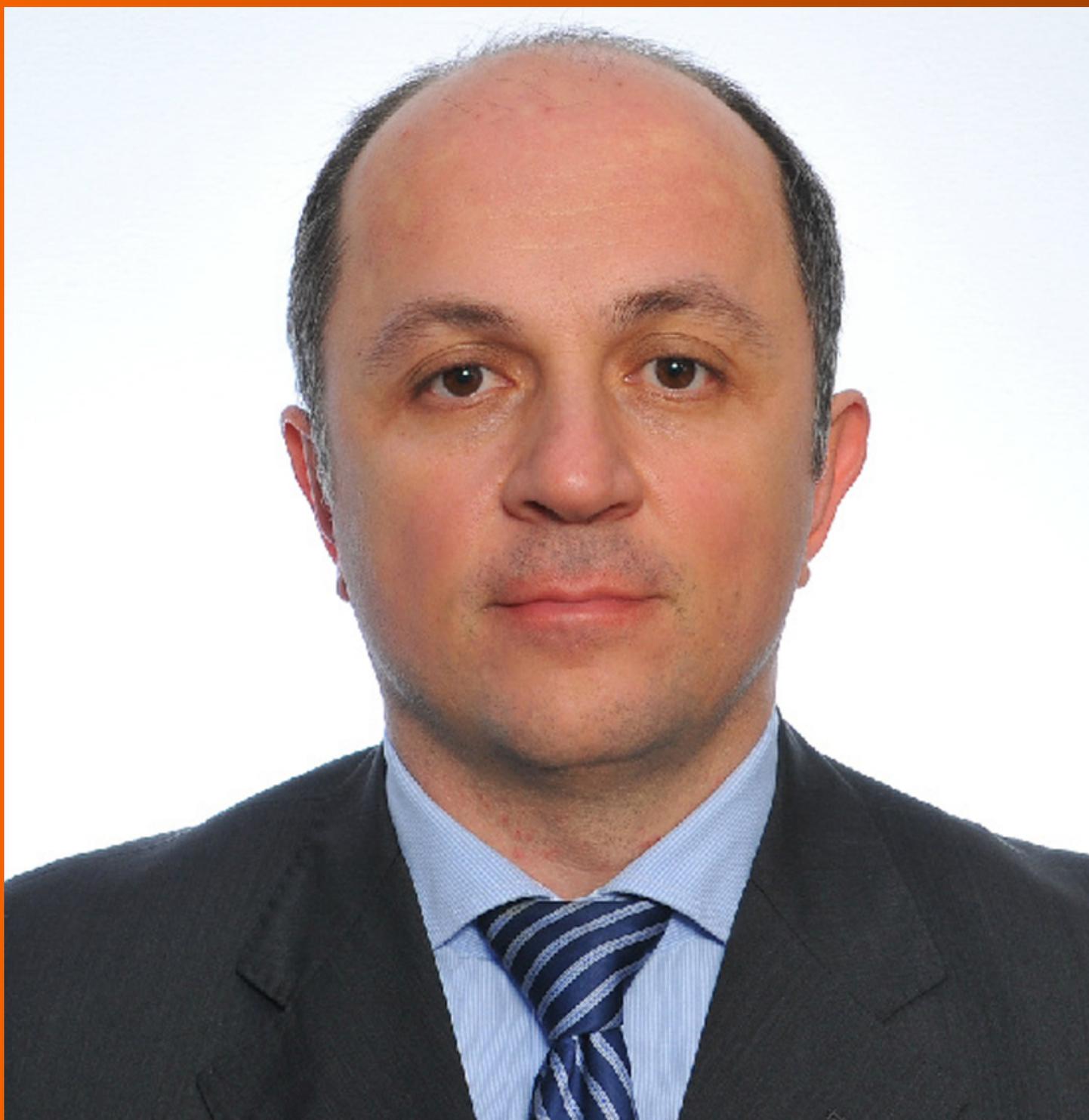


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Allergic fungal rhinosinusitis accompanied by allergic bronchopulmonary aspergillosis: A case report and literature review

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Abstract

BACKGROUND

Concomitant allergic fungal rhinosinusitis (AFRS) and allergic bronchopulmonary aspergillosis (ABPA) are extremely rare, with no more than 20 cases reported in the English literature.

CASE SUMMARY

A 52-year-old female patient complained of right-sided nasal obstruction, rhinorrhea, sneezing, epistaxis, and hyposmia for a period of around 5 mo. Nasal examination detected paleness and edema of the nasal mucous membrane and a polyp in the right middle meatus. A computed tomography (CT) scan of the sinuses revealed a ground-glass opacity filling the right maxillary and ethmoid sinuses, along with bone absorption in the medial wall of the right maxillary sinus. Magnetic resonance images were obtained with T1-weighted, T2-weighted, and gadolinium-enhanced T1-weighted sequences. A well-defined mass, located in the right maxillary and ethmoid sinuses and displaying obvious hypointense features, was observed on both T1- and T2-weighted images, with peripheral enhancement on gadolinium-enhanced T1-weighted images. The patient also has a 20-year history of cough and dyspnea. Chest CT revealed columned and cystiform bronchiectasis in the bilateral bronchus, surrounded by a large number of spotted and funicular high-density lesions. The level of serum total IgE was > 5000 kU/L. Serum IgE levels related to house dust and aspergillus showed a positive result, with the values being 3.5 kU/L and 1.2 kU/L. We performed functional endoscopic sinus surgery under local anesthesia. After surgery, topical glucocorticoids and saline irrigation were applied in the nasal cavity until the present time. An oral glucocorticoid (methylprednisolone 16 mg/d) and antifungal agent (itraconazole 200 mg/d) were also used for a period of 4 wk. Montelukast was prescribed at 10 mg/d until the present time. An endoscopic examination showed that the patient was recovering well at 3 mo after surgery.

CONCLUSION

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Since different specialists treat ABPA and AFRS, their coexistence may be overlooked. AFRS accompanied by ABPA requires surgical therapy combined with medical control to improve the symptoms.

Key words: Allergic fungal rhinosinusitis; Allergic bronchopulmonary aspergillosis; Aspergillus; Clinical characteristics; Treatment; Surgery

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Core tip: Concomitant allergic fungal rhinosinusitis (AFRS) and allergic bronchopulmonary aspergillosis (ABPA) are extremely rare. We describe the clinical presentation and treatment in one patient with AFRS accompanied by ABPA and review the English literature from 1970 to 2016. The most common pulmonary symptom was dyspnea. Twelve patients underwent surgery on the sinuses, all patients received oral glucocorticoids for at least 2 wk, and 11 patients received topical glucocorticoids. All patients achieved a good prognosis. Since different specialists treat ABPA and AFRS, their coexistence may be overlooked. AFRS accompanied by ABPA requires surgical therapy combined with medical control to improve the symptoms.

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INTRODUCTION

Allergic fungal rhinosinusitis (AFRS) is a particular type of chronic rhinosinusitis associated with allergic reactions to fungal antigens. This disease was first described in 1983^[1]. AFRS affects around 1%–2% of the world's population, with the incidence differing among regions^[2,3]. Currently, patients are defined as having AFRS by meeting the following criteria: (1) Type I hypersensitivity; (2) Nasal polyposis; (3) Characteristic computed tomography (CT) findings; (4) Eosinophilic mucin without invasion; and (5) Positive fungal stain^[4]. AFRS usually requires endoscopic surgery and long-term postoperative medical treatment. Immunotherapy is also suggested for AFRS^[5].

Allergic bronchopulmonary aspergillosis (ABPA) is a type I hypersensitivity to the fungus *Aspergillus*, and presents as a necrotizing pneumonia^[6]. This entity was first described by Hinson *et al*^[7] in 1952. The pathological changes of ABPA are similar to those of AFRS. The major diagnostic criteria for ABPA are as follows: (1) Asthma; (2) Elevated total serum immunoglobulin E (IgE); (3) Elevated total serum immunoglobulin G (IgG); (4) Presence of transient pulmonary infiltrates; (5) Central/proximal bronchiectasis with normal tapering of the distal bronchi; and (6) Elevated serum IgE and IgG to *A. fumigatus*^[8]. ABPA usually accompanies asthma and requires oral antifungal and glucocorticoid treatment^[9]. AFRS has a close relationship with ABPA because of the location in the unified airway and the similarity in the pathogenesis. AFRS is an ENT equivalent of ABPA.

ABPA can accompany several types of rhinomycozosis, including invasive sinus aspergillosis^[10], aspergilloma^[11], and AFRS^[11]. However, concomitant AFRS and ABPA are extremely rare; this may be because the two different diseases might be overlooked by pulmonary physicians or otolaryngologists. Some articles mentioned the occurrence of concomitant AFRS and ABPA but provided no detailed information^[9]. No more than 20 cases of AFRS accompanied by ABPA have been reported in the English literature. Whether AFRS causes ABPA, ABPA causes AFRS, or AFRS occurs concurrently with ABPA is still open to debate. The treatment options for this disease are controversial and its prognosis is uncertain. In this article, we describe a case of AFRS accompanied by ABPA and review the literature. The clinical manifestation, management, and prognosis of the disease are also discussed.

CASE PRESENTATION

Chief complaints

Right-sided nasal obstruction, rhinorrhea, sneezing, epistaxis, and hyposmia.

History of present illness

Five months.

History of past illness

The patient had a 20-year history of asthma with poor pulmonary function. She manifested obvious dyspnea and cough on exertion and the symptoms were not fully relieved after the application of asthma medication.

Personal and family history

None.

Physical examination upon admission

Nasal examination detected paleness and edema of the nasal mucous membrane and a polyp in the right middle meatus.

Laboratory examinations

A blood test indicated an elevation of eosinophil level by 5.2%. The level of serum total IgE was > 5000 kU/L. Serum IgE levels related to house dust and aspergillus showed a positive result, with the values being 3.5 kU/L and 1.2 kU/L, respectively.

Imaging examinations

A CT scan of the sinuses revealed a ground-glass opacity filling the right maxillary and ethmoid sinuses, along with bone absorption in the medial wall of the right maxillary sinus (Figure 1A and B). The bones of the anterior skull base and lamina papyracea were unaffected. The other side of the sinuses also showed no involvement. Magnetic resonance images were obtained with T1-weighted, T2-weighted, and gadolinium-enhanced T1-weighted sequences. A well-defined mass, located in the right maxillary and ethmoid sinuses and displaying obvious hypointense features, was observed on both T1- and T2-weighted images, with peripheral enhancement on gadolinium-enhanced T1-weighted images (Figure 1C and D). A chest radiograph showed dilatation of the bilateral bronchus surrounded by a flocculent shadow and plaques. Chest CT revealed columned and cystiform bronchiectasis in the bilateral bronchus, surrounded by a large number of spotted and funicular high-density lesions (Figure 2A and B).

FINAL DIAGNOSIS

AFRS accompanied by ABPA.

TREATMENT

Because of the poor pulmonary function, the patient was unable to undergo surgery under general anesthesia. Therefore, we performed functional endoscopic sinus surgery under local anesthesia. We resected the polyp, opened the right maxillary and ethmoid sinus, and found a large amount of yellow, jam-like mucin in the right maxillary and ethmoid sinuses (Figure 3). We enlarged the ostium of the sinuses and cleared the mucin. The postoperative pathology found the aspergillus. The postoperative course was uneventful. After surgery, topical glucocorticoids and saline irrigation were applied in the nasal cavity until the present time. An oral glucocorticoid (methylprednisolone 16 mg/d) and antifungal agent (itraconazole 200 mg/d) were also used for a period of 4 wk. Montelukast was prescribed at 10 mg/d until the present time.

OUTCOME AND FOLLOW-UP

An endoscopic examination showed that the patient was recovering well at 3 mo after surgery. The ostium of the sinuses had opened well, and the mucin had disappeared. Sinus CT indicated a good recovery, with secretions in the right maxillary sinus after surgery (Figure 4). Moreover, after surgery the discomfort in the nasal cavity

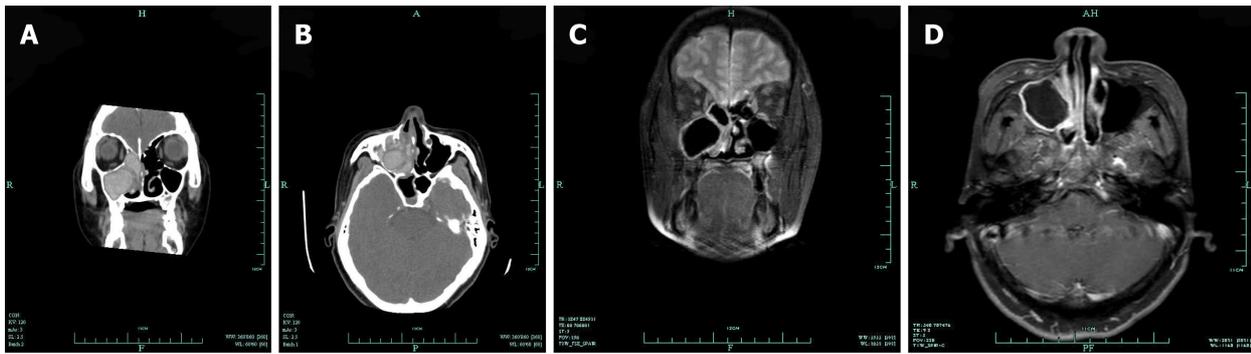


Figure 1 Images of our patient with allergic fungal rhinosinusitis accompanied by allergic bronchopulmonary aspergillosis. A: Coronal CT scan of the sinuses revealed a ground-glass opacity filling the right maxillary and ethmoid sinuses, along with bone absorption in the medial wall of the right maxillary sinus; B: Axial CT scan of the sinuses; C: A well-defined mass, located in the right maxillary and ethmoid sinuses and displaying obvious hypointense features, was observed on coronal T2-weighted image; D: There was a peripheral enhancement of the mass on gadolinium-enhanced axial T1-weighted image.

disappeared immediately and the patient felt that the dyspnea had also improved. A 25-month period of follow-up revealed no recurrence.

REVIEW OF THE LITERATURE AND DISCUSSION

Fungi are almost ubiquitous and can be found in the nasal cavity and sinuses of healthy people. However, fungal infections of the airway are uncommon and may occur both in immunocompromised and immunocompetent individuals^[12]. Fungal rhinosinusitis is the main type of fungal infection and inflammation of the upper airway, and can be divided into non-invasive and invasive forms^[13]. The non-invasive types include localized fungal colonization, fungal ball, and AFRS^[14]. AFRS is usually caused by *Aspergillus* spp., which is termed allergic aspergillus sinusitis. Fungal infections and inflammation of the lower airway are also mainly caused by *Aspergillus* spp., including ABPA, aspergilloma, chronic necrotizing pneumonia, and invasive pulmonary aspergillosis^[15]. Other fungi can also lead to diseases such as ABPA, which is termed allergic bronchopulmonary mycosis (ABPM)^[16]. ABPA belongs to ABPM. Recently, the morbidity of this allergic disease has increased perceptibly, in line with the increased prevalence of AFRS and ABPA. However, coexistence of AFRS and ABPA is still uncommon. Some authors have defined this type of disease as sinobronchial allergic mycosis^[17]. We searched the PubMed database for reports of coexisting AFRS and ABPA for the period from 1970 to 2016 (keywords: allergic fungal rhinosinusitis, allergic bronchopulmonary aspergillosis; or allergic aspergillus sinusitis, allergic bronchopulmonary aspergillosis) and found 20 patients in 13 English articles (including the present case) that included clinical and imaging details (Tables 1 and 2)^[18-28]. Until now, only one article recorded a case of coexisting AFRS and ABPM that did not originate with *Aspergillus* spp.^[29]. Some articles mentioned the coexistence of AFRS and ABPA but did not include details (or the reports were written in other languages)^[30-33].

In these studies, fungal disease usually had a regional susceptibility. Ferguson *et al*^[34] found an increased prevalence of AFRS in the southeastern United States, where mold counts are notably high. Other studies suggested that AFRS was associated with lower income, rural counties, poor housing quality, and reduced access to healthcare^[35,36]. In this review, 14 patients lived in India, 5 in the United States, and 1 in China. We inferred that the high prevalence of coexisting AFRS and ABPA might be due to the high temperature and humid climate in India. In this review, 10 female and 10 male patients had coexisting AFRS and ABPM, with no gender difference. The patients ranged in age from 9 to 57 years, with a mean age of 36.1 years, implying that this disease is very rare in older people.

The most common nasal symptom in our review was rhinorrhea, followed by nasal block, sneezing, and postnasal discharge; thus there was no difference in symptoms compared to the more common disease of chronic rhinosinusitis. The most common pulmonary symptom was dyspnea, followed by wheeze, cough, and chest pain. The duration of nasal symptoms ranged from 5 mo to 57 years, as did the duration of pulmonary symptoms. In this review, seven patients initially presented with nasal symptoms, four first showed pulmonary manifestations, seven showed concurrent nasal and pulmonary symptoms, and the symptoms were unknown in two cases. The upper airway is closely related to the lower airway. Based on the concept of “one

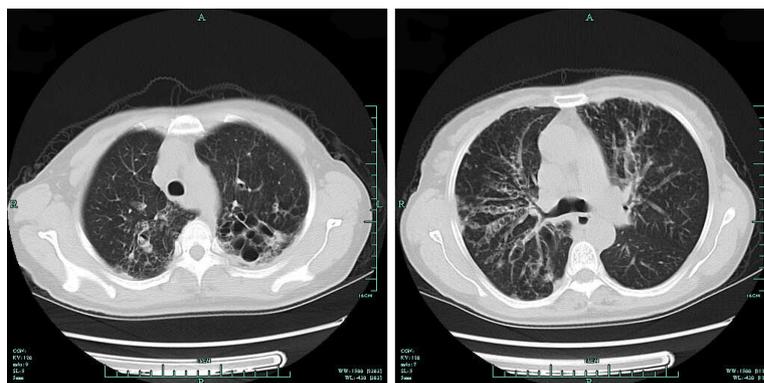


Figure 2 Chest CT revealed columned and cystiform bronchiectasis in the bilateral bronchus, surrounded by a large number of spotted and funicular high-density lesions.

airway one disease” in fungal allergy, one fungal antigen may therefore cause both AFRS and ABPA^[37]. AFRS may lead to ABPA, and *vice versa*. Because of the lack of a convenient system for identifying fungi, diagnosis of coexisting AFRS and ABPA is usually difficult. Since different specialists treat ABPA and AFRS, their coexistence may be overlooked^[38]. AFRS is a relatively common disease and with increasing focus on multi-disciplinary care, there should be more simultaneous cases. Moreover, the use of oral glucocorticoids and/or antifungal agents in either disorder may mask the manifestation of the other disorder^[38]. We suggest that patients with AFRS should undergo pulmonary CT if they exhibit pulmonary symptoms. Conversely, patients with ABPA should undergo sinus CT if they show nasal symptoms. If this disease is recognized and treated appropriately, the inflammation process can be inhibited and irreversible lung destruction can be avoided.

ABPA usually accompanies asthma and cystic fibrosis (CF). Although rare, ABPA without asthma or CF can still occur^[39]. In our review, 16 (80%) patients had asthma, but none had CF. This result implies that the coexistence of AFRS and ABPA might have nothing to do with CF. The CT findings of AFRS often demonstrate unilateral involvement of the sinuses^[40], with the ethmoid sinus being the most commonly involved sinus^[41]. In this review, the disease affected the bilateral sinuses in 11 patients. The most commonly affected sinus was the maxillary sinus, followed by the ethmoid, frontal, and sphenoid sinuses. The main manifestation of sinus CT was opacification, with two cases of destruction of bone.

All of the patients in this review demonstrated elevated total IgE and eosinophil counts in peripheral blood tests, which agrees with previous research^[42,43]. The main manifestation of pulmonary CT was bronchiectasis, in agreement with another article^[44]. According to conventional staging, ABPA can be divided into five stages: Acute, remission, exacerbation, corticosteroid-dependent asthma, and fibrotic lung disease^[45]. In this review, six patients belonged to the exacerbation stage, three to the acute stage, three to the remission stage, and one to the corticosteroid-dependent asthma stage; the stage was unknown in seven cases.

AFRS usually requires surgical therapy combined with medical control^[40]. Surgery can remove the inciting fungal allergic mucin and enlarge the ostium of the involved sinuses. Medical therapy comprises corticosteroids, immunotherapy, and antifungal medications. However, there is limited evidence to support the use of topical or oral antifungal agents in patients with AFRS^[46]. Oral corticosteroids and antifungal medications are the main treatments for ABPA^[47]. In this review, 12 patients underwent surgery on the sinuses, all patients received oral glucocorticoids for at least 2 wk, and 11 patients received topical glucocorticoids. Seven patients received oral antifungal medications, and no patient was prescribed topical antifungal agents. All patients achieved a good prognosis, with 19 with an improved or resolved status and one case of recurrence after oral glucocorticoids were stopped.

In our opinion, surgery should be performed for sinusitis in patients with coexisting AFRS and ABPA to clear the fungal allergens and reduce the stimulation of allergic inflammation. Oral glucocorticoid and antifungal medications should be applied for a short time and then tapered off, due to the obvious side effects of these medicines. Topical glucocorticoids for the nasal cavity should be applied for longer periods. Until now, there has been no evidence of use of topical antifungal medications and immunotherapy to treat this disease.



Figure 3 A large amount of yellow, jam-like mucin in the right maxillary and ethmoid sinuses during the surgery.

CONCLUSION

Based on the concept of “one airway one disease” in fungal allergy, one fungal antigen may therefore cause both AFRS and ABPA. Since different specialists treat ABPA and AFRS, their coexistence may be overlooked. The patients with AFRS should undergo pulmonary CT if they exhibit pulmonary symptoms. Conversely, patients with ABPA should undergo sinus CT if they show nasal symptoms. AFRS accompanied by ABPA usually requires surgical therapy combined with medical control to improve the symptoms.

Table 1 Clinical presentation of allergic fungal rhinosinusitis accompanied by allergic bronchopulmonary aspergillosis

Ref.	Sex / Age	Region	Nasal symptoms/ duration	Pulmonary symptoms/ duration	Asthmas/ cystic fibrosis	Total IgE	Eosinophil count	Affected sinuses	Pulmonary imaging
Safirstein ^[20]	F/24	United States	Rhinorrhea, blood-tinged casts	No obvious symptom	N/N	-	12%, 1650/mm ³	-	Infiltration
Sher and Schwartz ^[19]	F/42	United States	Symptoms of allergic rhinosinusitis /since childhood	Dyspnea, wheeze/2 yr	Y/N	13084 ng/mL	1355/mm ³	Left maxillary sinus	Bronchiectasis , interstitial scarring
Travis <i>et al</i> ^[26]	F/48	United States	Nasal block	No obvious symptom	N/N	794 IU/mL	1350/mm ³	Bilateral frontal and ethmoid sinuses	Nodule
	M/16	United States	Nasal block/ 7 yr, right proptosis, and periorbital edema	Asthma-like symptoms/ 11 yr	Y/N	785 IU/mL	Normal	Right maxillary sinus	Infiltration, bronchiolitis
Bhagat <i>et al</i> ^[18]	F/38	India	Rhinorrhea, nasal block, and discharge/ 5 yr	Pain, cough, wheezing, dyspnea/9 yr	Y/N	280 IU/L	12%	Bilateral maxillary sinuses	Pleural effusion, bronchiectasis , collapsed left lung
Shah <i>et al</i> ^[22]	M/55	India	Rhinorrhea, nasal block, brownish plugs/12 yr	Dyspnea, wheeze, brownish plugs/2 yr	Y/N	-	26%	Bilateral maxillary sinuses	Bronchiectasis , right lower zone opacity, transient infiltration
Shah <i>et al</i> ^[28]	M/24	India	Rhinorrhea, sneeze, nasal block, postnasal discharge, plugs, headache/ 12 yr	Chest pain, dyspnea, wheeze, cough, plugs/6 yr	Y/N	5600 IU/mL	9%	Right maxillary sinus	Central bronchiectasis
	M/45	India	Rhinorrhea, sneeze, nasal block, postnasal discharge/ 1 yr	Cough, chest pain, dyspnea, haemoptysis/ 1 yr	Y/N	680 IU/mL	3%	Bilateral maxillary sinuses	Central bronchiectasis
	M/55	India	Rhinorrhea, sneeze, nasal block, headache/ 12 yr	Chest pain, dyspnea, wheeze, cough, plugs/2 yr	Y/N	540 IU/mL	26%	Bilateral maxillary sinuses	Central bronchiectasis
	F/38	India	Rhinorrhea, sneeze, nasal block, plugs/5 yr	Chest pain, dyspnea, wheeze, cough, plugs, haemoptysis/ 37 yr	Y/N	280 IU/mL	24%	Bilateral maxillary sinuses	Central bronchiectasis
	F/29	India	Rhinorrhea, sneeze, nasal block, plugs, headache/ 5 yr	Dyspnea, wheeze, cough, plugs, haemoptysis/ 5 yr	Y/N	590 IU/mL	16%	Bilateral maxillary and frontal sinuses	Central bronchiectasis
	M/30	India	Rhinorrhea, sneeze, nasal block, headache/ 1 yr	Chest pain, cough/1 yr	Y/N	4560 IU/mL	8%	Bilateral maxillary and frontal sinuses	Central bronchiectasis
	F/14	India	Rhinorrhea, sneeze, nasal block/1.5 yr	Dyspnea, wheeze, cough, chest pain/1.5 yr	Y/N	25216 IU/mL	11%	Bilateral maxillary sinuses	Central bronchiectasis

Shah <i>et al</i> ^[28]	M/26	India	Rhinorrhea, nasal block, sneeze, postnasal discharge, brownish plugs/since childhood	Dyspnea, wheeze, cough, brownish plugs/since childhood	Y/N	34132 IU/mL	24%	Left maxillary sinus	Bronchiectasis transient infiltration
Prasad <i>et al</i> ^[21]	M/52	India	Rhinorrhea/ 25 yr	Hemoptysis/ 6 yr,	N/N	5652 IU/mL	12%, 1296/mm ³	Left maxillary, ethmoid sinuses	Bronchiectasis
Erwin and Fitzgerald ^[25]	M/57	United States	Nasal block/since childhood	Tightness, wheeze, cough, brownish plugs/ since childhood	Y/N	1987 IU/mL	6.50%	Bilateral frontal and left sphenoid sinuses	Bronchiectasis with mucus plugging
Das <i>et al</i> ^[27]	M/9	India	Brownish nasal discharge/ 6 yr	Chest pain, dyspnea, brownish sputum/5 yr	Y/N	4838.5 IU/mL	8%	Frontal and maxillary sinuses	-
Ghosh <i>et al</i> ^[24]	F/30	India	Rhinorrhea, sneeze/6 yr	Dry cough/ 5 mo	N/N	2500 ng/mL	36%	Right maxillary sinus	Bilateral central bronchiectasis with mucus plugging
Upadhyay <i>et al</i> ^[23]	F/35	India	Rhinorrhea, pain, tenderness/ 8 yr	Dyspnea, cough/8 yr	Y/N	1000 IU/mL	16%, 2240/mm ³	Bilateral maxillary sinuses	Bilateral central cystic bronchiectasis
Current case	F/52	China	Rhinorrhea, sneeze, nasal block, epistaxis, hyposmia/ 5 mo	Dyspnea, cough/20 yr	Y/N	> 5000 U/mL	5.20%	Right maxillary and ethmoid sinuses	Bronchiectasis with mucus plugging

F: Female; M: Male; Y: Yes; N: No.

Table 2 Treatment and prognosis of allergic fungal rhinosinusitis accompanied by allergic bronchopulmonary aspergillosis

Ref.	Clinical stage of ABPA	Treatment	Outcome
Bhagat <i>et al</i> ^[18]	Acute	Oral glucocorticoid/2 wk	Improvement/1 mo
Sher and Schwartz ^[19]	Acute	Surgery for sinuses, oral glucocorticoid	Improvement
Safirstein ^[20]	Acute	Surgery for sinuses, oral glucocorticoid/6 mo	Improvement, recurrence after stopping oral glucocorticoid
Prasad <i>et al</i> ^[21]	Exacerbation	Surgery for sinuses, oral and topical glucocorticoid, montelukast sodium	Resolution
Shah <i>et al</i> ^[18]	Exacerbation	Oral glucocorticoid/2 wk	Resolution/1 mo
Shah and Panjabi ^[11]	Exacerbation	Oral glucocorticoid/tapered off	Resolution/3.5 yr
Upadhyay <i>et al</i> ^[23]	Exacerbation	Oral glucocorticoid, oral itraconazole/6 wk, then tapered off, omalizumab/6 wk	Improvement
Ghosh <i>et al</i> ^[24]	Remission	Oral glucocorticoid, oral itraconazole	Resolution
Erwin and Fitzgerald ^[25]	Corticosteroid dependent asthma	Surgery for sinuses, oral glucocorticoid/tapered off, topical glucocorticoid, oral itraconazole/2 mo, oral voriconazole/2 mo	Improvement/2 yr
Travis <i>et al</i> ^[26]	Remission	Surgery for sinuses, oral ketoconazole, surgery for lung	Improvement
	Remission	Surgery for sinuses, lung biopsy	Improvement
Das <i>et al</i> ^[27]	Exacerbation	Oral itraconazole/4 mo, oral glucocorticoid/tapered off 8 mo	Improvement
Shah <i>et al</i> ^[28]	-	Polypectomy, septoplasty, oral glucocorticoid/ tapered off 2 yr, topical glucocorticoid	Improvement

	-	Oral glucocorticoid/tapered off 6 mo, topical glucocorticoid	Improvement
	-	Septoplasty, oral glucocorticoid/irregular, topical glucocorticoid	Improvement
	-	Polypectomy, oral glucocorticoid/tapered off 6 mo, topical glucocorticoid	Improvement
	-	Polypectomy, oral glucocorticoid/1-3 yr, topical glucocorticoid	Improvement
	-	Polypectomy, oral glucocorticoid/1-3 yr, topical glucocorticoid	Improvement
	-	Oral glucocorticoid/1-3 yr, topical glucocorticoid	Improvement
Current case	Exacerbation	Surgery for sinuses, oral glucocorticoid, oral itraconazol/4 wk, montelukast, topical glucocorticoid	AFRS/resolution, ABPA/ improvement

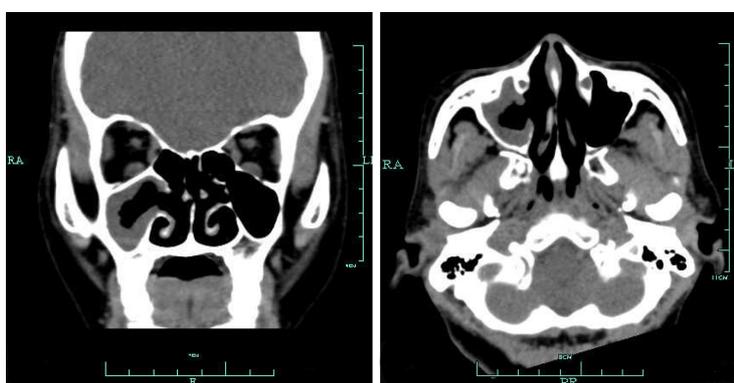


Figure 4 Sinus CT images indicating a good recovery, with secretions in the right maxillary sinus after surgery.

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