



Review Article

Challenging cases in fungal asthma

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Abstract

Fungal asthma broadly encompasses the presence of fungal sensitization or fungal allergy in patients with asthma. The clinical presentation of fungal asthma can vary from fungal-sensitized asthma at one end to allergic bronchopulmonary mycosis at the other end of the spectrum. Here we present five cases that illustrate some of the most challenging aspects of the diagnosis and management of fungal asthma. The cases are aimed at elucidating complex clinical presentations in fungal asthma such as allergic bronchopulmonary mycosis presenting with normal immunoglobulin E (IgE) values, the role of several different fungi in causing allergic mycosis, newer treatments like omalizumab (and mepolizumab), and a complication of long-standing allergic bronchopulmonary aspergillosis, namely, chronic pulmonary aspergillosis.

Key words: allergic bronchopulmonary aspergillosis, ABPA, ABPM, fungal sensitization, allergic bronchopulmonary mycosis, *Aspergillus*.

Introduction

Asthma is a chronic inflammatory disorder of the airways characterized by bronchial hyperresponsiveness and variable airflow obstruction.¹ There is a close association between fungi and asthma, the so-called fungal asthma.² In contrast to other allergens, fungi are viable and can colonize the tracheobronchial tree of asthmatic patients, thus having a far greater impact on the patients' immune system. Fungal asthma can manifest itself either as fungal sensitization or fungal allergy.³ Fungal sensitization is an immune-mediated response to a fungus, without evidence of inflammation or tissue damage, clinically documented by an elevated fungal-specific immunoglobulin E (IgE) or a positive skin test. On the other hand, fungal allergy is an immune-mediated inflammatory response to a fungus manifesting as tissue damage. Although several fungi can cause fungal sensitization, fungal allergy is caused only by a small number of thermotolerant fungi,⁴ the most common being *Aspergillus fumigatus*.^{5,6}

The clinical presentation of fungal asthma can vary from isolated fungal sensitization at one end to allergic bronchopulmonary mycosis (ABPM) at the other end of the spectrum (Table 1). Severe asthma with fungal sensitization is a new entity defined by the presence of severe asthma, fungal sensitization, and exclusion of allergic bronchopulmonary aspergillosis (ABPA).^{2,5} Conventionally, allergic bronchopulmonary mycosis caused by *A. fumigatus* is alluded to as ABPA, while ABPM refers to an ABPA-like syndrome caused by fungi other than *A. fumigatus*.⁷ ABPA is the most well-characterized form of fungal asthma that manifests clinically as difficult-to-control asthma, recurrent pulmonary opacities, and bronchiectasis.⁸ The interest in ABPA and ABPM stems from the fact that if the disorder is recognized and treated adequately, the onset and progression of bronchiectasis can be arrested.

Although most cases can be diagnosed and managed straightforwardly (Fig. 1), on several occasions, challenges in diagnosis and treatment are encountered by clinicians caring for these

Table 1. Diagnosis and treatment of various types of fungal asthma.

Syndrome	Diagnostic features	Treatment
Fungal-IgE sensitized asthma	- Controlled asthma - Elevated <i>A. fumigatus</i>-specific IgE (>0.35 kUA/l) - Total IgE <500 IU/ml	No specific treatment required other than treatment for bronchial asthma
Severe asthma with fungal sensitization (SAFS)	- Severe asthma - Elevated <i>A. fumigatus</i>-specific IgE (>0.35 kUA/l) - Total IgE 500–1000 IU/ml - Normal <i>A. fumigatus</i>-specific IgG (<27 mgA/l)	Intensive treatment for asthma including use of high-dose inhaled corticosteroids and long-acting β_2 agonists, leukotriene-receptor antagonists, inhaled long-acting antimuscarinic agents and omalizumab. May consider oral itraconazole 200 mg twice a day for six months as it has been shown to improve the quality of life
Serologic allergic bronchopulmonary aspergillosis (ABPA-S)	- Asthma <i>A. fumigatus</i>-specific IgE >0.35 kUA/l - Total IgE >1000 IU/ml - Elevated <i>A. fumigatus</i>-specific IgG (>27 mgA/l) - Total eosinophil count >500 cells/μl - Total eosinophil count >500 cells/μl - Normal high-resolution computed tomography (HRCT) of the chest	Intensive treatment for asthma including use of high-dose inhaled corticosteroids and long-acting β_2 agonists, leukotriene-receptor antagonists, inhaled long-acting antimuscarinic agents and omalizumab. May consider oral itraconazole 200 mg twice a day for six months. The patient must be closely monitored as theoretically there is a higher possibility of developing bronchiectasis
ABPA with bronchiectasis (ABPA-B)	- Asthma <i>A. fumigatus</i>-specific IgE >0.35 kUA/l - Total IgE >1000 IU/ml - Elevated <i>A. fumigatus</i>-specific IgG (>27 mgA/l) - Transient or fixed pulmonary opacities - Total eosinophil count >500 cells/μl - Bronchiectasis on HRCT of the chest	Oral glucocorticoids are the most effective treatment. ⁴⁵ Oral itraconazole can also be used as primary therapy in acute stage especially in those at risk for steroid-related complications. ⁴⁴ In those with recurrent exacerbations, prolonged therapy with itraconazole, low-dose glucocorticoids, inhaled amphotericin and omalizumab may be tried. ^{27,28,33,37}

In patients with ABPM, the specific IgE and IgG against the fungus in question (e.g., *A. flavus*) is used, instead of *A. fumigatus*.

patients. We illustrate these difficulties using the subsequent case presentations.

Case 1

A 22-year old lady with history of asthma for the preceding 5 years presented with complaints of worsening asthma control in the past year. She denied any history of fever, hemoptysis, or weight loss. The patient was being treated with a combination of inhaled corticosteroids (ICS, budesonide 400 μ g/day), long-acting β_2 agonists (LABA; formoterol 24 μ g/day), and montelukast (10 mg/day). She had been treated for pneumonia twice in the past. A review of her chest radiographs revealed fleeting pulmonary opacities. She was investigated for ABPA. The *A. fumigatus*-specific IgE was 0.1 kUA/l, total IgE 84 IU/ml, *A. fumigatus*-specific immunoglobulin G (IgG) 10 mgA/l, *Aspergillus* precipitins were negative, and *Aspergillus* skin test was negative. Peripheral blood eosinophil count was elevated (840 cells/ μ l). Sputum culture grew *A. fumigatus*. High-resolution computed tomography (HRCT) of the chest revealed high-attenuation mucus (Fig. 2). Flexible bronchoscopy was performed. Bronchoalveolar lavage fluid grew *A. fumigatus*, and so did the post-bronchoscopy sputum. A diagnosis of ABPA was made given the presence of eosinophilia, persistent growth of

A. fumigatus and high-attenuation mucus. There was a good response to oral glucocorticoids.

Case 2

A 60-year old lady, a known asthmatic for the last 26 years, presented with complaints of fever and hemoptysis of 2 weeks duration. Her asthma was being treated with ICS (budesonide 800 μ g/day), LABA (formoterol 24 μ g/day), and montelukast (10 mg/day). Chest radiograph and HRCT chest (Fig. 3) revealed left lower lobe consolidation. There was no response with oral antibiotics, and she was referred to our center. Sputum culture did not grow any organism. For the diagnosis of nonresolving pneumonia, a CT-guided transthoracic aspiration was performed. Cytological examination revealed the presence of acute inflammation with numerous eosinophils. Cultures were sterile. In view of asthma and tissue eosinophilia, she was further investigated. Anti-neutrophil cytoplasmic antibodies were negative. The *A. fumigatus*-specific IgE was 89 kUA/l, total IgE 201 IU/ml, *A. fumigatus*-specific IgG 18 mgA/l, peripheral blood eosinophil count was 280 cells/ μ l, *Aspergillus* precipitins and *Aspergillus* skin test was negative. She was treated with itraconazole 400 mg/day for 4 months with which she demonstrated a good response. The *A. fumigatus*-specific IgE decreased over

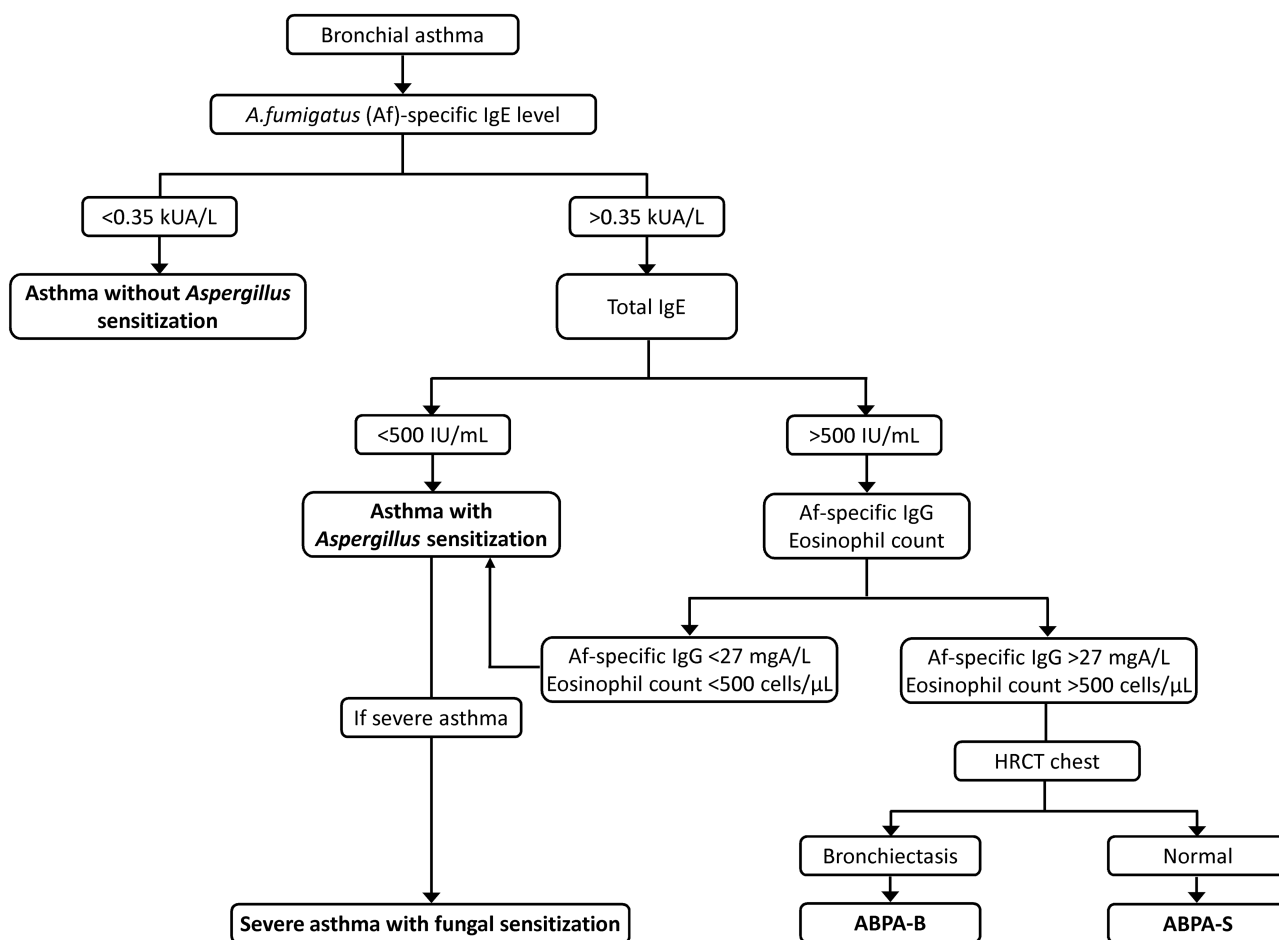


Figure 1. Algorithmic approach to the diagnosis of various manifestations of fungal asthma. The *A. fumigatus* IgE and IgG are assayed using the fluorescent enzyme immunoassay method (Phadia). In patients with ABPM, the specific IgE and IgG against the fungus in question (e.g., *A. flavus*) is used, instead of *A. fumigatus*.

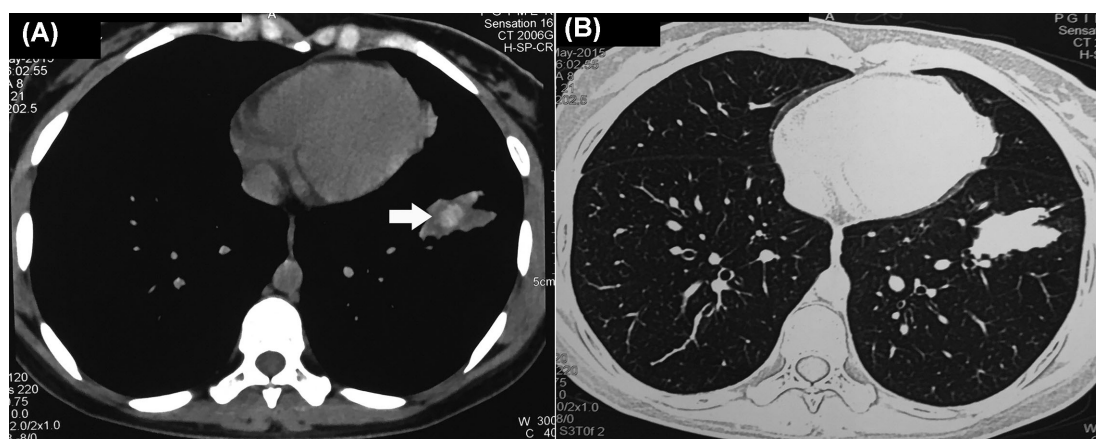


Figure 2. Computed tomography (mediastinal window, panel A) showing high-attenuation mucus (arrow). The corresponding lung window section is shown as panel B.

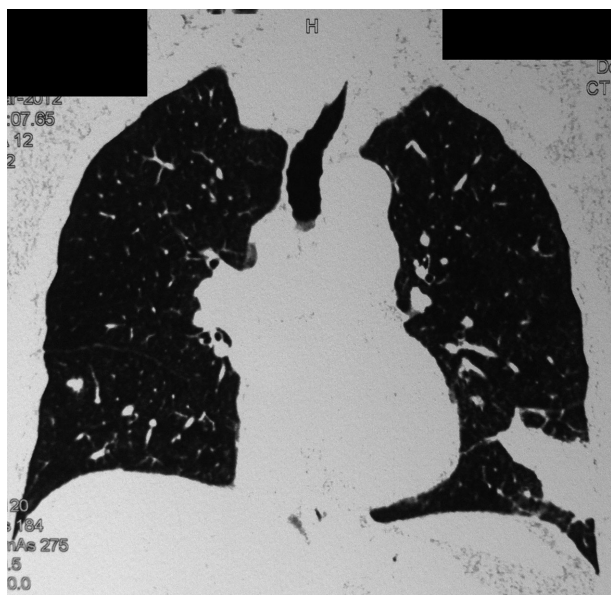


Figure 3. Computed tomography (lung window, coronal section) showing left lower lobe consolidation.

time (89 to 15.6 to 0.6 kUA/l). CT thorax performed after 6 months was normal.

Discussion

The diagnosis of ABPA in cases 1 and 2 is unusual in that they do not fulfill the minimum criteria proposed for ABPA (Table 1).⁹ Most importantly, both the cases had a normal serum total IgE, which is accepted as a major criterion in the diagnosis of disease activity and exacerbations.^{10–12} Although uncommon, there are several clinical situations where serum total IgE can be normal in patients with ABPA, the most common being the setting where the patient has received glucocorticoid therapy before the diagnosis.¹³ It might also be encountered when the patient has low IgE before the onset of florid disease, as in case 2.^{14–16} For example, if the patient's IgE value is 10–20 IU/ml, to begin with;

despite a 10- to 20-fold rise it would remain less than 500 IU/ml (200–400 IU/ml). Another instance where the total IgE can be normal is when the patient has received rituximab, a monoclonal antibody against CD20, which can completely suppress the humoral immune responses.¹⁷ Finally, any criteria or range for a population would generally cover only 95% of the population.¹⁸ It is expected that several individuals would not meet a particular level or criteria. The low serum IgE can lead to challenges in diagnosis, as seen in both the cases. The diagnosis in the first case was made by the presence of high-attenuation mucus,¹⁹ which is a pathognomonic finding in the diagnosis of ABPA.²⁰ Another highly specific investigation in the diagnosis of ABPA is *A. fumigatus*-specific IgG, which was shown to have high specificity (cutoff, 27 mgA/l, fluorescent enzyme immunoassay, Phadia) in the diagnosis of ABPA.²¹ In the second case, the diagnosis of ABPA was suspected on the presence of numerous eosinophils in the transthoracic needle aspirate sample. We made a diagnosis of ABPA given the raised *A. fumigatus*-specific IgE, the absence of other causes, and response to itraconazole.

Case 3

A 56-year old lady with a history of asthma for the last 22 years was referred to our chest clinic for the investigation of fleeting pulmonary opacities. She denied any history of fever, hemoptysis, or weight loss. She was currently receiving ICS (budesonide 800 µg/day), and LABA (formoterol 24 µg/day) for asthma control. Chest radiograph revealed fleeting pulmonary opacities, *A. fumigatus*-specific IgE was 60.3 kUA/l, total IgE 12,546 IU/ml, *A. fumigatus* skin test was positive, *A. fumigatus*-specific IgG was 92 mgA/l, *A. fumigatus* precipitins were positive, and eosinophil count was 240 cells/µl. HRCT chest revealed the presence of bronchiectasis and high-attenuation mucus (Fig. 4). A diagnosis of ABPA was made; however, sputum culture grew *A. flavus*. *A. flavus*-specific IgE done subsequently was 75.7 kUA/l; *A. flavus* skin test and *A. flavus* precipitins were positive.

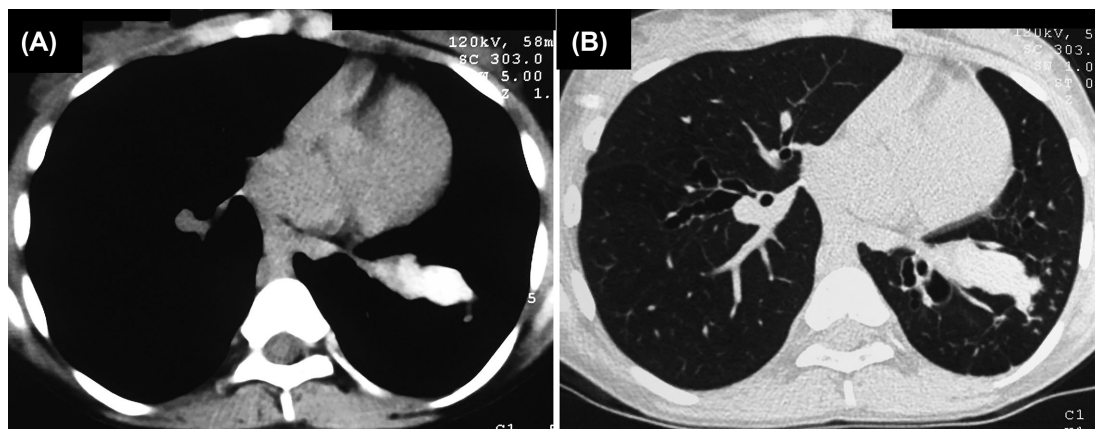


Figure 4. Multi-detector computed tomography showing the presence of high attenuation mucus (panel A). The corresponding lung window shows the presence of bronchiectasis in the right lung and mucus-filled dilated bronchi (corresponding to the high-attenuation mucus) in the left lung.

Discussion

The patient in case 3 demonstrated the classic immunologic findings of ABPA (raised *A. fumigatus*-specific IgE and IgG, positive *A. fumigatus* skin test, and *A. fumigatus* precipitins). However, sputum culture grew *A. flavus* and *A. flavus*-specific IgE was quantitatively greater than *A. fumigatus*-specific IgE. In patients with allergic mycoses, multiple fungi can colonize the airways with frequent dissociation between the colonizing and the sensitizing species.²² Several allergens (fungi) can contribute to allergy either due to co-sensitization or cross-reactivity. Cross-reactivity is a phenomenon where the IgE antibody recognizes, binds, and induces an immune response to similar allergenic molecules. The IgE cross-reactivity can occur between allergens in closely related species or between molecules with similar function present in widely different species belonging to the same protein family.²³ For example, asthmatics with *Alternaria* allergy may cross-react with *Aspergillus* due to the homologous allergen namely manganese superoxide dismutase. A sequence identity of at least 50% seems to be required in order to exhibit cross-reactivity.²⁴ On the other hand, co-sensitization is genuine sensitization to more than one allergen source, where the sensitization is not due to cross-reactivity. The presence of cross-reactivity can be discerned by performing qualitative IgE inhibition tests or by identifying the amino-acid sequence responsible for cross-reactivity. In a recent study, 53 subjects with a diagnosis of ABPA were evaluated for sensitization to *A. flavus*.²⁵ Sensitization to *A. flavus* was seen in 51 (96.2%) subjects; 49 (92.5%), 21 (39.6%), and 12 (22.6%) instances on fungal-specific IgE, skin prick test, and precipitins, respectively. Sputum culture was positive in 18 (33.9%; *A. flavus* [*n* = 12], *A. fumigatus* [*n* = 6]) subjects. Allergic bronchopulmonary mycosis due to *A. flavus* was diagnosed in 16 of the 51 (30.2%) subjects.²⁵ This study did not investigate whether sensitization to *A. flavus* was due to cross-reactivity or co-sensitization. Future work should evaluate the role of component-resolved diagnostics in differentiating between allergic bronchopulmonary mycosis caused by *A. fumigatus* and *A. flavus*.

Case 4

A 32-year old gentleman, a diagnosed case of ABPA for the last 8 years, was referred to our chest clinic for recurrent asthma and ABPA exacerbations and glucocorticoid-dependent ABPA. Chest radiograph revealed fleeting pulmonary opacities, *A. fumigatus*-specific IgE was 98 kUA/l, total IgE was 4300 IU/ml, *A. fumigatus* skin test and *A. fumigatus* precipitins were positive, *A. fumigatus*-specific IgG was 42 mgA/l, and eosinophil count was 986 cells/ μ l. HRCT chest revealed the presence of bronchiectasis involving all the lobes (Fig. 5). Spirometry revealed severe obstruction with a forced expiratory volume in the first second (FEV1) of 1.1 liters (42% predicted) and forced vital capacity of 2.62 liters. He was being treated with pred-

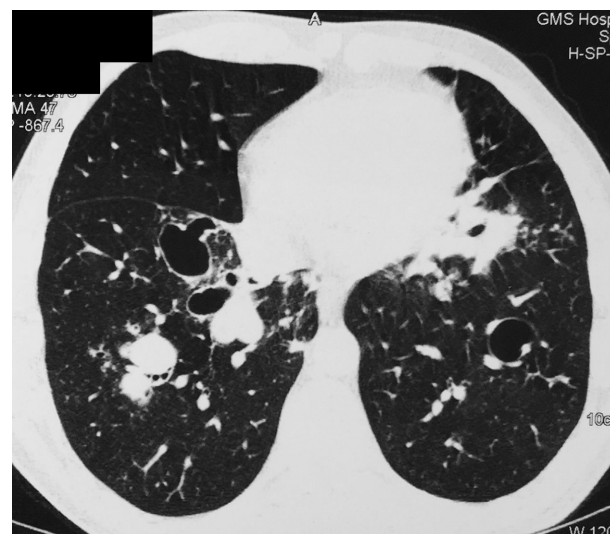


Figure 5. High-resolution computed tomography (lung window) showing mosaic attenuation and extensive bronchiectasis.

nisolone (20 mg/day), itraconazole (400 mg/day), ICS (budesonide 1600 μ g/day), LABA (formoterol 24 μ g/day), theophylline (400 mg/day), and montelukast (10 mg/day). The patient had significant steroid-related adverse effects (weight gain, cushingoid facies, acne, skin striae). Due to recurrent exacerbations, we increased the dose of prednisolone to 50 mg/day and changed itraconazole to voriconazole (400 mg/day for 6 months) as he had significant anorexia and fatigue. Despite this, the patient experienced two asthma exacerbations over the next 2 months. Also, the IgE decreased to only 3900 IU/ml (10%) after 2 months with no significant improvement in symptoms. Subsequently, the patient received intravenous methylprednisolone pulse 1 gm/day for 3 days. All other therapies were continued. The patient again presented in the emergency department with another asthma exacerbation. Prednisolone was increased to 60 mg/day. In view of treatment-refractory ABPA, omalizumab 375 mg every 2 weeks subcutaneously was initiated. The patient had another mild asthma exacerbation in the next month which was managed with nebulized bronchodilators at home. There was only mild improvement in symptoms initially. However, there was no exacerbation over the subsequent 4 months and over another 4 months, we could taper his steroids and voriconazole. After 8 months of omalizumab therapy, the patient was off prednisolone, montelukast, voriconazole, and theophylline. For the first time in 8 years, the patient was off any oral medication. He continues to remain on omalizumab and ICS/LABA.

Discussion

Glucocorticoids are the most effective treatment in ABPA.²⁶ In a recent study, lower doses of glucocorticoids were found to be as effective as higher doses. However, about 12% of cases do not respond to lower doses and may require an

increase in the glucocorticoid dose. This was the rationale for increasing the dose of prednisolone in case 4. In patients with glucocorticoid-dependent ABPA, the use of itraconazole has been shown to cause a decline in the inflammatory markers in sputum, reduction in serum IgE, a decrease in the usage of glucocorticoid, and improvement in exercise capacity.^{27,28} Unfortunately, the patient had a poor response to itraconazole and developed itraconazole-related side effects (fatigue). Itraconazole was changed to voriconazole, which has also been shown to be effective in ABPA.²⁹ The patient continued to experience exacerbations despite glucocorticoids and azole therapy. Hence, the patient was treated with intravenous pulse doses of methylprednisolone, which has been used in refractory ABPA exacerbations.³⁰ Despite all treatments, the patient experienced recurrent exacerbations. Finally, the patient was started on omalizumab.

Omalizumab is a monoclonal antibody against IgE that binds to free serum IgE and prevents the binding of IgE to the high-affinity FcεRI receptor on the surface of mast cells and basophils. Omalizumab therapy has been associated with reduced frequency of exacerbations and increased likelihood of complete withdrawal of ICS in patients with severe asthma.³¹ The goal of treatment with omalizumab is to decrease the serum total IgE to less than 21 IU/ml, and a dose of 0.016 mg/kg/IU of IgE/ml of omalizumab is required.³² An upper limit of IgE of 700 IU/ml and a maximum dose of omalizumab 750 mg monthly is prescribed. In ABPA, the total IgE is markedly elevated (in thousands); thus, the dosing according to the standard calculation would be impossible to administer. Recently, in a randomized, placebo-controlled, cross-over trial, Voskamp et al. randomized 13 patients with chronic ABPA complicating asthma to 4-month treatment with subcutaneous omalizumab (750 mg monthly) or placebo followed by a three-month washout period.³³ The use of omalizumab was associated with a significant reduction in exacerbations during the active treatment phase. Moreover, treatment with omalizumab was associated with reduction in exhaled nitric oxide levels, reduction in basophil sensitivity to *A. fumigatus* and decrease in basophil FcεRI and surface-bound IgE levels, suggesting an anti-inflammatory activity.³³ Even in the index case 4, the use of omalizumab led to significant improvement in the patient's condition and we could withdraw all-oral treatments for ABPA including glucocorticoids and azoles. Mepolizumab, a monoclonal antibody against interleukin 5 is another additional and effective treatment option for severe ABPA resistant to glucocorticoids, antifungal therapy, and omalizumab.^{34–36}

It also demonstrates a potentially synergistic effect with omalizumab.³⁴ Recently, inhaled amphotericin B has also been shown to maintain response in patients with recurrent exacerbations of ABPA. However, in the index case, the patient was not able to attain response with any treatment; hence inhaled amphotericin was not used.³⁷

Case 5

A 21 year-old gentleman previously treated twice for tuberculosis with empiric anti-tuberculosis treatment presented with cough, recurrent hemoptysis, low grade fever and wheezing for eight months. Six months prior to presentation, he had a history of spontaneous pneumothorax requiring placement of intercostal tube (Fig. 6A). HRCT chest revealed bronchiectasis and fungal ball in both the upper lobes (Fig. 6B). *A. fumigatus*-specific IgE was 61.7 kUA/l, total IgE 19366 IU/ml, *A. fumigatus* skin test and *A. fumigatus* precipitins were positive, *A. fumigatus*-specific IgG was 182 mgA/l, and eosinophil count was 350 cells/μl. Sputum culture grew *A. fumigatus*. In view of the persistent presence of a fungal ball, he was diagnosed as chronic pulmonary aspergillosis (CPA) complicating ABPA and started on oral itraconazole (400 mg/day). The level of itraconazole in the serum after 2 weeks was 1.24 μg/ml. After 6 months of itraconazole therapy, he had clinical and serological response (total IgE 6911 IU/ml, *A. fumigatus*-IgG 26 mgA/l), and itraconazole was stopped. Six months later, he again presented with low grade fever, hemoptysis and worsening breathlessness. The total IgE was 19,994 IU/ml, and *A. fumigatus*-specific IgG was 84 mgA/l. He was again started on itraconazole; there was partial response, fever and breathlessness persisted (serum itraconazole levels, 1.4 μg/ml). IgE had declined to 15,441 IU/ml after 2 months (Fig. 6C). At this time, oral glucocorticoids were added. At 6-month follow up, the patient was symptomatically better (Fig. 6D), and the total IgE was 8720 IU/ml.

Discussion

The patient was diagnosed as CPA complicating ABPA, a complication that is recognized worldwide. Recently, a global case burden of CPA complicating ABPA (at a 10% rate with 15% annual attrition) of 411,000 (range, 206,300–589,400) was estimated.³⁸ The identification of CPA complicating ABPA is difficult. The diagnostic hallmark for CPA is elevated *A. fumigatus*-specific IgG,³⁹ which is also seen in ABPA.²¹ Detection of *Aspergillus* species by culture, antigen or molecular testing is seen in both the conditions. Occasionally, patients with CPA can also demonstrate raised serum total IgE and *A. fumigatus*-specific IgE.⁴⁰ Thus, a firm diagnosis of CPA complicating ABPA is based on clinical features, serial radiological investigations, and immunological findings. Clinically, the presence of persistent fever, significant weight loss, and incessant hemoptysis may be clues to the presence of CPA. Although these symptoms may occur in ABPA, they are in general, more severe in CPA. The CT findings of bronchiectasis, mucus impaction, fleeting consolidation and transient segmental atelectasis is typical of ABPA.⁴¹ However, the occurrence of persistent cavitation, pleural thickening, and volume loss are highly suggestive of CPA complicating ABPA.⁴² Although the presence of a fungal ball is definitive,⁴² it is not very frequent.⁴³ In the index case, the patient had a persistent

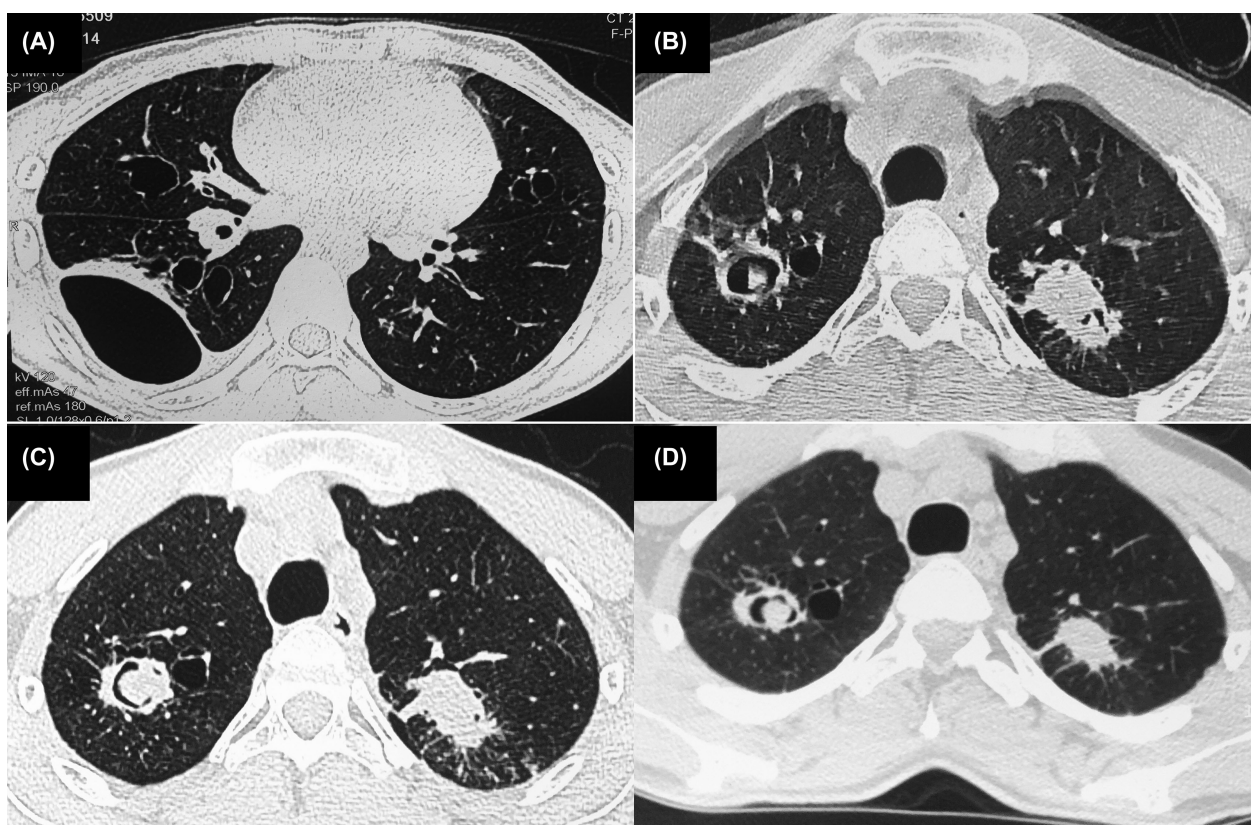


Figure 6. Computed tomography (lung window, panel A) showing bilateral bronchiectasis and loculated pneumothorax. Panel B showing the presence of a fungal ball inside a cavity with surrounding linear tags suggesting fibrosis in the right lung. The left lung shows a cavity filled with a fungal ball. Panel C is the CT done after treatment with itraconazole when the patient documented a partial response. Panel D shows the CT image after treatment with glucocorticoids (see case 5 for details).

cavity with a fungal ball apart from ‘central’ bronchiectasis and was thus considered as CPA with ABPA.

The treatment of these patients is also fraught with difficulties. Oral triazoles are the treatment of choice for CPA while glucocorticoids are generally contraindicated. On the other hand, oral glucocorticoids are the treatment of choice for ABPA although itraconazole monotherapy is also beneficial in about 88% of cases.⁴⁴ Thus, in CPA complicating ABPA, itraconazole can control the disease activity of both ABPA and CPA. Hence, if in doubt, whether the patient has ABPA or CPA, it is better to initiate treatment with itraconazole alone. Occasionally, patients with CPA complicating ABPA may demonstrate incomplete responses to itraconazole therapy. Clinically, most patients tend to have diffuse wheeze on auscultation of the chest. In such instances, glucocorticoids might be required, and they are not contraindicated in CPA complicating ABPA.⁴³ In other patients with CPA and ABPA, asthma goes into remission, the total IgE does not increase when the patient has worsening symptoms while the levels of *A. fumigatus*-specific IgG tend to increase. These findings suggest that ABPA (i.e., the allergic component) is in remission in such patients, while the semi-invasive form of the disease (CPA) is active. In these patients, glucocorticoids may be potentially harmful.

In conclusion, the complex cases presented suggest that fungal asthma can present with varied manifestations, which can challenge even the most astute physician. Although most patients with fungal asthma present with typical manifestations, some do not. The diagnosis in such instances is made in the presence of other immunological and radiological findings and exclusion of other common causes of similar presentation. Multiple fungi can colonize the airways in patients with fungal asthma, the significance of which may sometimes be unclear. Newer therapies like omalizumab and mepolizumab may be required in patients with fungal asthma refractory to conventional treatment. Finally, patients with allergic bronchopulmonary mycosis can develop chronic pulmonary aspergillosis, which can pose difficulties in both diagnosis and management.

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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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