

REVIEW

Severe Asthma with Fungal Sensitization: A Case Report and Review of Literature

YASSER MADANI, M.B.B.S., D.P.M.S.A.,^{1,*} ANDREW BARLOW, M.Sc., FRCP, M.B.Ch.B. HONS, B.Sc. HONS,¹
AND FURQAN TAHER, M.B.B.S.²

¹Department of Respiratory Medicine, Watford General Hospital, Watford, Hertfordshire, United Kingdom

²Royal London Hospital, Whitechapel, London, United Kingdom

There is a substantial body of evidence supporting an association between asthma severity and fungal exposure and sensitization. Fungal allergens are a recognized risk factor for severe asthma. We describe the case of a 44-year-old asthmatic whose asthma control deteriorated after moving to a new flat with walls covered in mould. Allergic bronchopulmonary aspergillosis was excluded. Although sensitization to *Candida* was demonstrated by a positive *Candida*-specific radioallergen sorbent test, the patient did not entirely satisfy the criteria for a diagnosis of allergic bronchopulmonary candidiasis. The patient's asthma control improved after engaging in a monthly washing regimen of the walls. This case further demonstrates the association between fungal sensitization and asthma severity. The term *severe asthma with fungal sensitization* has been recently coined to describe this phenomenon.

Keywords asthma; allergy; fungi; *Candida albicans*; allergic bronchopulmonary

A 44-year-old lifelong asthmatic presented to the respiratory clinic with a 6-month history of worsening asthma control, the beginning of which coincided with a move to a new flat, which was predominantly carpeted and damp. She complained of regular nighttime waking and multiple daily use of her salbutamol inhaler. She had presented eight times to the emergency department in the preceding year with acute asthma exacerbations and had required a short course of prednisolone almost each time. Her peak expiratory flow rates (PEFR) had decreased from 430 to 200 L per minute (46% predicted). Her PEFR diary showed more than 30% variability with lower morning scores. The main triggers of her asthma included dust, animals (primarily cats), oranges, cold air, perfumes, and smoke. She had pronounced upper respiratory tract symptoms, in particular sneezing and nasal congestion, consistent with seasonal allergic rhinitis. She was an ex-smoker with a 20-pack year history. She denied expectoration of thick mucus plugs. The patient reported that the walls of her flat appear to develop black mould if left unwashed for more than 4 weeks, as such she undertook a monthly washing regimen. Her past medical history included hiatus hernia, laparoscopic cholecystectomy, and tonsillectomy. At the time the patient was taking montelukast; 10 mg; once daily; symbicort 400/12, two puffs, twice daily; and salbutamol, as required. The physical examination was unremarkable.

Skin prick testing found evidence of significant sensitivity to dust mites and cats but was negative for *Aspergillus*. The initial plain chest radiograph did not show any evidence of pulmonary infiltrates (Figure 1). Pulmonary function tests were largely normal. Her eosinophil differential count was raised

at $0.8 \times 10^9/L$ during one of her acute asthma exacerbations. The total serum immunoglobulin (IgE) was raised at 1,312 ku/L and *Candida albicans*-specific radioallergen sorbent test (RAST) was significantly positive at 9.03 ku/L (grade 3), while the *Aspergillus*-specific RAST was negative. Precipitating antibodies against *Candida* species were negative. A high-resolution computed tomography (HRCT) scan showed evidence of collapse consolidation affecting the medial segment of the right middle lobe together with minor scattered bronchiectatic changes in the mid and lower zones but no central bronchiectasis (Figure 2). Bronchoscopy demonstrated no mucosal pathology to explain the right middle lobe collapse, therefore mucus plugging was assumed to be the aetiology. Bronchoalveolar lavage (BAL) did not yield *Candida* species but cytological analysis found scanty eosinophils. A subsequent plain chest radiograph showed resolution of the earlier pulmonary infiltrates identified on HRCT (Figure 3).

We performed wall scrapings from several areas in the patient's flat. The scrapings were cultured and grew unidentified "mixed environmental fungi," but *Candida* species were not isolated. The scrapings were sent to a specialist laboratory for further analysis together with a paired serum sample. Bespoke precipitins were positive for the mixed environmental fungi but negative for *Candida*. Bespoke *Candida*-specific RAST was significantly positive at 10.0 ku/L (grade 3). A strict mould removal cleaning regimen and fluticasone nasal spray lead to significant subjective and objective improvement in asthma control. The patient reported better asthma control and her PEFR increased to 89% predicted. A case was made to the local housing authority for the patient to be re-housed.

DISCUSSION

As with allergic bronchopulmonary aspergillosis (ABPA) there is no single diagnostic criteria for allergic bronchopulmonary candidiasis (ABPC), but several criteria have been

*Corresponding author: Yasser Madani, M.B.B.S., D.P.M.S.A., Department of Respiratory Medicine, Watford General Hospital, Vicarage Road, Watford, Hertfordshire, WD18 0HB, United Kingdom;
E-mail: yasser.madani@doctors.org.uk



FIGURE 1.—Plain chest radiograph showing no pulmonary infiltrates.

used (1, 2) and proposed (3). It is generally suggested that the diagnostic criteria for ABPC and other allergic bronchopulmonary mycoses (ABPM) are analogous to ABPA (1, 4), and this assumption will be continued forward in this discussion. The diagnosis of ABPC was initially considered because of the peripheral eosinophilia, elevated total serum IgE, positive *Candida*-specific RAST, lobar collapse with radiological consolidation secondary to a presumed mucus plug, together with peripheral bronchiectasis. However, there was no central bronchiectasis, serum *Candida* precipitins were negative (although positive for the mixed environmental fungi isolated from the wall scrapings), and colonization was not proven as BAL did not yield *Candida* species. As such, some of the diagnostic criteria as developed by Rosenberg et al. (5) and Ricketti et al. (6) were not met (Table 1). Furthermore, the minimum essential criteria that includes [1] asthma, [2] immediate skin reactivity, [3] total serum IgE > 1000 ng/mL,



FIGURE 2.—High-resolution computed tomography scan of the thorax showing collapse consolidation affecting the medial segment of the right middle lobe and minor peripherally scattered bronchiectatic changes in the mid zone.



FIGURE 3.—Plain chest radiograph showing resolution of the pulmonary infiltrates seen earlier on the high-resolution computed tomography scan.

[4] elevated serum antigen-specific IgE or IgG antibodies, and [5] central bronchiectasis (7) was not entirely met.

Some possible explanations can be offered for these negative findings. Firstly, not all criteria need to be met to establish a diagnosis of ABPA (8). Colonization of fungi in the sputum (8, 9) or from bronchial washings does not commonly appear in the diagnostic criteria for ABPA. In this case the patient's radiology series did demonstrate fleeting pulmonary infiltrates and early bronchiectasis, but not the characteristic central bronchiectasis. However, it is well recognized that central bronchiectasis may be absent in early disease (10). As such, patients have been classified into those with central bronchiectasis (ABPA-CB) and those without it, but in whom there is serological evidence of ABPA (ABPA-S, "S" denoting "seropositive") (10). The latter group represents an earlier stage of the disease and a possibly less aggressive form of it (11). There is still a minimal criteria required to diagnose ABPA-S and this includes [1] asthma, [2] immediate skin reactivity, [3] serum IgE > 1,000 ng/mL, [4] history of pulmonary infiltrates, and [5] elevated serum antigen-specific IgE and IgG antibodies (12). Even still, our case did not satisfy all of these criteria.

Although the diagnostic criteria for ABPM were not met entirely, there was a clear history of worsening asthma severity and proven fungal exposure and sensitization (positive

TABLE 1.—Diagnostic Criteria for ABPA ^[6,8] (and ABPM).

Asthma
Immediate skin reactivity to fungi
Radiological
Pulmonary infiltrates
Central bronchiectasis
Serological
Peripheral eosinophilia
Positive serum fungal precipitins
Elevated total serum IgE > 1000 IU·mL ⁻¹
Elevated serum IgE and IgG to fungi

TABLE 2.—Proposed Diagnostic Criteria for SAFS^[13]

Required
Severe asthma*
Positive fungal skin prick test, or positive fungal specific-RAST
Unknown
Airway fungal colonisation
Thick mucous plugs
Peripheral eosinophilia
Absent
Pulmonary infiltrates
Central bronchiectasis
Positive serum fungal precipitins
Elevated total serum IgE > 1000 IU·mL ⁻¹

*British Guideline on the Management of Asthma step 4 or equivalent.

Candida-specific RAST). It has recently been suggested that ABPA may represent the extreme end of a spectrum of bronchopulmonary fungal sensitivity, while at the less severe end is a recently described phenotype of severe asthma without all the radiological and serological hallmarks of ABPA, but in which there is evidence of fungal sensitization, proven by positive skin prick testing and/or fungal antigen-specific serum IgE testing. The term *severe asthma with fungal sensitization* (SAFS) has been recently coined to describe this phenomenon (13). It is thought that fungal colonization of the airways is not easily demonstrable in SAFS, unlike in ABPA, but fungal sensitization should be, by definition, demonstrable. Denning and O'Driscoll et al. have suggested a diagnostic criteria for SAFS (Table 2) (13). The patient described in this case had severe asthma and evidence of fungal sensitization, fulfilling the two inclusion criteria for a diagnosis of SAFS. However, she also had fleeting pulmonary infiltrates and a raised total serum IgE level > 1,000 IU·mL⁻¹, both of which should be absent in SAFS.

Fungal sensitization in asthmatics is most common in patients with severe asthma, who are thought to account for approximately 20% of adult asthmatics 20 to 44 years of age (14, 15). There are few agreed definitions of severe asthma. Currie et al. (16) have defined "difficult" asthma as the presence of persistent symptoms and frequent exacerbations, despite treatment at steps 4 or 5 of the British Guideline on the Management of Asthma (17). Based on the above definition, the patient presented in our case had severe asthma when referred to our clinic.

There is a substantial body of evidence supporting an association between asthma severity and fungal exposure and sensitization. An international multi-center cross-sectional study of 1,132 patients found that sensitization to the fungi *A. alternata* and *C. herbarium* was a significant risk factor for severe asthma (OR 2.02 and 3.2, respectively) (14). A recent study in Manchester found that fungal sensitization is more common among patients with severe asthma who required multiple hospital admissions (15). In fact, the authors of this study argue that sensitization to fungi has a causative role in severe asthma and is a recognized risk factor for severe asthma, and several reasons have been postulated to explain this causative link (15). Furthermore, sensitization and exposure to fungi have been linked to hospital admissions (18) and emergency department visits (19) for asthma, life-threatening asthma (20, 21), admission to ITU (22), and asthma-related mortality (23). The evidence has been well summarized in a comprehensive review of the link between severe asthma and fungi (13).

In addition to outdoor fungi, indoor fungal exposure has also been shown to be associated with worsening asthma severity. In a review of nine cross-sectional studies on the relationship between domestic fungal exposure and allergic health effects, seven of the nine studies found one or more positive associations between fungal levels and health outcomes (24). Damp conditions, which greatly aid the proliferation of fungi, are also associated with worsening asthma (25–27), although it is argued that personal assessment of the degree of dampness is an unreliable measure (13). However, another study has shown a correlation between asthma severity and the presence of fungi and damp conditions in the home, assessed more objectively by a qualified surveyor. Patients living in damp homes were shown to have greater air-flow obstruction demonstrated by FEV₁ (28). A recent study found that patients whose indoor exposure to *Cladosporium* had doubled over 2 years were more likely to report asthma attacks in the previous 12 months (29). Damp conditions at home and at school have been shown to be associated with bronchial hyper-reactivity and worsening respiratory symptoms and asthma in children (30–34).

Despite this large body of evidence establishing a link between asthma severity and fungal sensitization, the effect of fungal exposure and its implications on management has not received the attention it merits (35). The presence of this substantial amount of evidence (13–15) suggests that testing for fungal sensitivity in asthmatics may identify those at risk of severe asthma (15). As such, it is suggested that fungal skin testing and/or fungal-specific RAST should be included in the workup of severe asthma (16). Zureik et al. suggest that patients who are sensitized to fungi should be educated to comply with treatment and to monitor their symptoms especially during seasons with high airborne fungal spore counts. They also propose that patients should be encouraged to decrease indoor fungal exposure by maintaining good ventilation and decreasing damp conditions (14). Two recent trials that have important implications on management should not go unmentioned.

The first is a randomized-controlled trial (RCT) conducted in Wales on the effect of eradication of indoor fungi on asthma severity (36). In the intervention group, indoor fungi was removed, fungicide was applied, and a fan was placed in the loft to aid ventilation. At the end of the 12 months there was less humidity and visible mould in the intervention group. However, there was no objective evidence of benefit (PEFR), although there were significant improvements in symptoms of asthma and medication use declined. Although an important trial, it is not without its weaknesses. There are several confounding factors including exposure to house dust mite and reduction in passive smoking (35). The follow-up rate at 6 months was low, therefore the data are open to selection bias (36). Finally, participants were not blinded, as this was understandably not possible. The findings of this study are consistent with our case; our patient's asthma control improved after she embarked on a monthly regimen involving removal of indoor mould from the walls of her residence.

The second is a recently published double-blind RCT conducted across four UK hospitals to evaluate the response of SAFS to oral itraconazole (37). Patients were screened for fungal sensitization using skin prick tests and fungal-specific RAST. A significant improvement in quality of life in 61%

of patients in the intervention group (compared to 17% in the placebo group) was observed. A modest effect on morning PEFr was also seen. However, the sample size in this study was small (38).

Asthma control is primarily pharmacotherapy based. Besides smoking cessation and house dust mite avoidance, little attention has been paid to environmental measures for other allergens, including visible indoor fungi. It is argued that this should receive as much attention since fungal sensitivity is such a significant risk factor for severe asthma (36).

CONCLUSION

There is ample evidence linking asthma severity to both indoor and outdoor fungal exposure and sensitization. Several explanations have even been postulated to argue for a causative role for fungal sensitization in severe asthma. This phenomenon should receive more attention than it has thus far given its impact on asthma-related morbidity and mortality.

We have reported a case of a patient with worsening asthma severity, the beginning of which coincided with a move to a damp and mouldy flat. This case further strengthens the association between fungal exposure and sensitization, in this case *indoor* fungal exposure specifically, and asthma severity. This case also demonstrates the impact of damp conditions on asthma severity. Although colonization was not proven in this case, it remains to be clear whether the association between severity of asthma and fungal sensitization is due to colonization of the airways by fungi or an allergic response to exogenous fungi (13).

SAFS is a recently-described phenomenon. Further research is required to ascertain the precise diagnostic criteria for SAFS. Only two other cases of SAFS have been described (38, 39), making comparison difficult. Although this case posed a diagnostic uncertainty, it further supports the suggestion that there is a disease spectrum of bronchopulmonary fungal sensitivity in asthmatics and that certain entities and phenotypes may be closer to one another along this spectrum than previously thought.

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DECLARATION OF INTEREST

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

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