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Efficacy of omalizumab in severe asthma with fungal sensitisation: a case report

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Key words

Severe asthma with fungal sensitisation; omalizumab

Summary

Severe asthma with fungal sensitisation (SAFS) is characterized by poor symptoms control and frequent hospital admissions for exacerbations despite treatment with high dose inhaled steroids, long-acting beta-2 agonists and leukotriene receptor antagonists. Treatment with oral steroids is usually necessary and courses of antifungal therapy may improve asthma symptoms. We report a case refractory to conventional inhaled therapies, continuous oral steroids and antifungal therapy courses, who was effectively treated with omalizumab.

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The link between fungi and severe asthma is complex and not fully understood. Both allergy to fungi (spores, hyphae) and the effects of cell wall constituents (glucan, volatile organic compounds) on bronchi are involved in asthma (1,2).

Distinct pathways of exposure to fungal allergens may be associated with asthma, mainly inhalation of airborne fungal allergens (spores or hyphae) with symptoms due to both persistent indoor exposure (in particular in mouldy and damp houses) or to outdoor acute exposure to very high concentration of these allergens (3,4). Fungal infection outside the respiratory tract, most often dermatophyte infection of the skin or nails may also be associated with immediate hypersensitivity, and in these patients courses of antifungal therapy may improve asthma symptoms (5).

Chronic or intermittent colonization of the airways by the ubiquitous fungus *Aspergillus Fumigatus* in conjunction with immediate hypersensitivity may cause an abnorm allergic response leading to allergic bronchopulmonary aspergillosis (ABPA). However, many other species of fungi, including *Cladosporium, Alternaria, Penicillium, Trichophyton and Candida*, may be involved leading to a less specific disease named allergic bronchopulmonary mycosis (ABPM) (1,2,6). Criteria for diagnosis of ABPA and ABPM include presence of severe asthma, peripheral blood eosinophilia, elevated total serum IgE level (> 1000 IU/ml), migrant chest radiographic infiltrates and central bronchiectasis easily detected by chest CT scan. Additional criteria are usually considered mucus plugs production, *Aspergillus* or other fungi species immediate skin prick test reactivity, and/or elevated specific IgE antibodies.

Many patients with severe asthma do not have the diagnostic criteria of ABPA and ABPM and are not demonstrably colonized

by fungi in the respiratory tract, yet are sensitized to fungi such as *Aspergillus, Cladosporium, Alternaria, Penicillium, Trichophyton, Candida* and other species (1,2). In these patients direct external exposure to fungi ubiquitous in air or limited airways colonization for saprophytic fungi may enhance the specific allergic response, and consequently the pulmonary inflammation in a persistent severe asthma condition.

The severe asthma with fungal sensitization (SAFS) is a particular phenotype of severe asthma, in which a therapeutic effect of antifungal therapy was documented (1,7). In SAFS fungal colonization is not easily demonstrable as it is limited and intermittent. Moreover the airborne fungi implicated are barely capable of growth at 37°C and inept at establishing themselves within the human host, whereas saprophytic fungi are not isolated from respiratory biologic samples if meticolous procedures for processing the materials are not used (7).

The antifungal therapy impact on asthma may be explained by the reduction of allergen exposure due to the direct killing of viable filamentous fungi. However, daily interactions between fungi and humans and their effects on asthma remain to be better understood, as within SAFS patients nearly 40% of non-responders to antifungal therapy with symptoms unchanged or relatively worse were documented (7).

We report the case of a 57 year-old female, former smoker (about 10 cigarettes a day for 20 years), who complained for almost 5 years of poorly productive cough, progressive fatigue and dyspnea after moderate exertion. The patient was initially diagnosed with COPD on the basis of a spirometry flow volume curve which showed moderate obstructive ventilatory defect. She remained severely symptomatic despite inhaled therapy with long-acting anticholinergic (tiotropium 18 ug once daily) and combination of topical steroid with long-acting B2 agonist (fluticasone 500 ug - salmeterol 50 ug twice daily). She was diagnosed also of a hiatal hernia with minimum gastroesophageal reflux, treated with proton pump inhibitors in high doses, with no improvement in respiratory symptoms. Despite the maximal inhalation therapy, the patient frequently had to use inhaled short acting B2 agonist (salbutamol 100-200 ug) as needed, with side effects such as tremors and tachycardia, as well as several cycles of oral steroid (prednisone 25 mg). In the last 12 months she experienced four significant exacerbations and two hospitalizations for acute respiratory failure. The patient was referred to our attention for further investigations and to evaluate a more effective therapeutic strategy. Spirometry (**table 1**) showed a very severe obstructive ventilatory defect with hyperinflation; the bronchodilation test with salbutamol 400 ug was positive, with partial reversibility of the obstruction. The Asthma Control Test (ACT score 12) was indicative of poor control of symptoms. Routine blood tests (erythrocyte sedimentation rate, C-reactive protein, liver and renal function indices, coagulation parameters) were normal. White blood cell count showed a mild peripheral hypereosinophilia (percentage of eosinophils 18% and absolute value 0.8x10^3 ul). Total serum IgE level was 279 KU/L. Skin prick test with the most important allergens of the mediterranean area, along with *Aspergillus sp, Alternaria sp, Cladosporium sp and Penicillium sp* were negative (Lofarma Allergeni, Milano, Italy). Serum specific IgE were positive for *Candida albicans* (4.31 KUA/L), *Aspergillus fumigatus* (2.53 KUA/L), *Cladosporium herbarum* (1.14 KUA/L), *Penicillium notatum* (0.6 KUA/L) and negative for *Saccaromices Cerevisiae* (0.10 KUA/L) (Immunocap Termofisher, Uppsala, Sweden). A microarray-based immunoassay (ISAC 112, Termofisher, Uppsala, Sweden) was positive for Fel d1 (10 ISU-E), Der f 1 (03 ISU-E), Der f 2 (06 ISU-E) and Der p 2 (04 ISU-E). Serum immunoglobulins were normal and there was not any IgG subclass deficiency. Paranasal sinuses CT scan and rhinoscopy were normal. High-resolution chest CT scan showed only bronchial wall thickening and areas of pulmonary hyperinflation. Bronchoalveolar lavages obtained from a previous bronchoscopy and sputum culture, performed several times during phases of productive cough, were negative for bacterial and fungal growth.

These investigations allowed us to rule out diseases such as ABPA or ABPM and the Churg Strauss syndrome. We established instead the diagnosis of severe asthma with fungal sensitization (SAFS) also considering inadequate control and instability of the disease despite the maximal inhalation and systemic therapy. Patient's house indoor walls, which were very damp and probably contaminated by ubiquitous moulds, were repainted. However, there was not any symptoms improvement despite the environmental sanitation. The patient was then started with a course of oral itraconazole (200 mg twice daily) for a scheduled period of 32 weeks. Antifungal therapy was suspended at 24 weeks due to lack of clinical response with symptoms and respiratory functional parameters unchanged. Peripheral blood eosinophils and serum total IgE were also unchanged. Therefore, we decided to start a course of treatment with the anti-IgE recombinant humanized monoclonal antibody omalizumab. According to the level of circulating total IgE (279 KU/L) and body weight (54 kg), we decided to administer a subcutaneous dose of 300 mg (2 pre-filled syringes of 150 mg) every 4 weeks. After 12-14 weeks the patient already reported an improvement in her respiratory symptoms as documented by the significant increase in ACT score (from 12 to 21). The oral steroid was reduced gradually and then suspended. Symptoms control persisted (ACT score 21) and in this time there was not any asthma exacerbation. Spirometry was performed after 16 weeks of treatment and showed a significant improvement of the functional parameters compared to the values obtained before therapy with omalizumab (**table 2**). The patient has never accused any side effects during treatment with omalizumab, has continued to

Table 1 *- Spirometry parameters and reversibility before omalizumab treatment*

	Pred	Pre Meas	Pre % Pred	Post Meas	Post % Pred	Post % Chg
FVC (L)	2.00	1.94	97	2.42	121	25
FEV1 (L)	1.63	0.54	33	0.73	45	35
FEV1/ FVC %	76	28	37	30	40	8
RV (L)	1.89	3.02	160	/	/	/

Reversibility with 400 µg salbutamol

Table 2 *- Spirometry parameters and reversibility after omalizumab treatment*

	Pred	Pre Meas	Pre % Pred	Post Meas	Post % Pred	Post % Chg
FVC (L)	2.00	2.12	106	2,44	122	15
FEV1 (L)	1.63	1.12	69	1.48	91	32
FEV1/ FVC %	76	53	70	61	75	7
RV (L)	1.89	2.15	114	/	/	/

Reversibility with 400 µg salbutamol

show good asthma control without the use of oral steroids and her quality of life has much improved.

This case report provides two important recommendations for clinical practice. Firstly, it shows the persistent unreliability of the diagnostic tools for fungal allergy, and secondly confirms the efficacy of omalizumab in severe asthma refractory to conventional therapies.

We found negative results of fungal skin test and allergen microarray in comparison with several positive results of fungal allergens serological test. This is consistent with previous findings, and suggests the need to perform both cutaneous and serological test in patient with severe asthma (8). The presence of relatively high levels of serum IgE against *Candida sp* seems common in severe asthma with fungal sensitization (7), but their pathological role remains poorly understood. Sensitisation to saprophytic fungi such as *Candida sp* may be undoubtedly elicited by frequent and transient airways colonizations favored by systemic steroidal treatments used in severe asthmatic patients. It is possible that these fungi, having the ability to actively germinate and colonise the host skin or the respiratory tract, may produce toxins and enzymes that have an accessory role in triggering allergy (1).

The clinical course of this case clearly demonstrates the effectiveness of omalizumab treatment in severe allergic asthma despite high level of allergen exposure (9,10). The antifungal treatment therapeutic failure and its lack of any effect on total serum IgE (11), suggest that the severity of symptoms was not consequent to an hidden fungal colonization, but rather to a consistent and prolonged environmental fungal allergens indoor exposure. The insignificant clinical effect of the indoor environment sanitation may be explained by several reasons. Probably the indoor quality of air was still unhealthy. Many fungi are present in great numbers also in the outdoor environment if some climatic conditions occur. Finally there are evidences that some fungal antigens may generate cross-reactive responses and induce a self-perpetuating allergic inflammation (1,12)

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