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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 imme-

diated hypersensitivity may cause an abnormal 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 meticulous 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, coagu-

lation parameters) were normal. White blood cell count showed a mild peripheral hypereosinophilia (percentage of eosinophils 18% and absolute value 0.8×10^3 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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A case of hereditary angioedema who presented with difficulty in urination and globe

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KEY WORDS

Hereditary angioedema; C1 inhibitor deficiency; difficulty in urination; globe

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Summary

Hereditary angioedema (HEA) is a disease characterized by decreased levels or function of C1 esterase inhibitor (C1-INH). The symptoms of HEA in pediatric age group generally consist of recurrent episodes of soft tissue swelling. These symptoms can be transient, subtle, and varied in severity. Genitourinary system is rarely affected in this disease. Here, a three-year-old girl who presented with angioedema on her hands, fingers, and face, and had difficulty in urination and globe is reported. The aim of this case is to focus on this rare disease, hereditary angioedema, which presented with difficulty in urination and urinary globe.

Introduction

C1-INH deficiency can be genetic or acquired. HAE is a rare, life-threatening condition manifested by acute attacks of facial, laryngeal, peripheral or genital edema. The estimated prevalence of HAE is between 1 in 10,000 and 1 in 150,000 people (1,2). The genetic HEA deficiency is due to mutations in one of the two alleles of the C1-INH gene that result in reduced protein levels in plasma (type I HEA) or in normal protein levels but always in reduced function (type II HEA). A third type has also been reported, occurring exclusively in women who have normal C1-INH levels and function (Type III HEA). It is estimated that 20% to 25% of HAE cases are caused by spontaneous mutations in patients with no family history of the disease (3,5). The development of angioedema in C1-INH-deficient patients involves the inappropriate generation of kinins (particularly bradykinin) that stimulate vascular smooth-muscle relaxation

and induce increased permeability. C1-INH is a serine protease inhibitor (serpin), also known as SERPING1, that blocks the activity of some complement components (e.g. C1r, C1s, Mannose binding lectin-associated serine protease; MASP-1 and MASP-2). C1-INH also controls contact-kinins, coagulation, and fibrinolytic cascades (6).

In this paper, we report a case with rarely manifested hereditary angioedema who presented with difficulty in urination and globe.

Case report

One day, a three-year-old girl with HEA was admitted to our emergency pediatric department with swelling of right forearm and urinary globe, and difficulty in urination (**figure 1**). She didn't have dysuria, fever or pelvic pain. Urinary globe, mild external genital swelling and right forearm angioedema were examined in her physical examination. Her urine analyses,

complete blood counts, biochemical tests, C reactive protein were normal. The patient was treated with C1 esterase inhibitor concentrate. Within a few hours, her difficulty in urination decreased, and urinary globe as well as right forearm angioedema resolved. She was being followed in pediatric allergy department. In her past life, the patient has experienced a lot of angioedema on her hands, fingers and face. When she was 1.5 year old she had experienced her first angioedema attack, which had been treated with intravenous corticosteroids and antihistamines without effect in a private hospital. At first, the symptoms usually subsided spontaneously within a few days. On the day of her first pediatric allergy clinic visit (she was 20 months old), on her physical examination blood tests [eosinophil counts (3.1%, 370/mm³), nephelometric IgE 70 (0-90 iU/mL)] and skin prick test were normal. C1 inhibitor [41.7 and 63 (210-345 mg/dL)] and C4 [2.9 and 2.7 (16-38 mg/dL)] levels were low for two times. There was no similar history in her family. Father's and mother's C4 and C1 inhibitor levels were normal. These laboratory data and clinical features were compatible with a diagnosis of type I HAE.

Discussion

Hereditary angioedema accounts for approximately 2% of all cases of angioedema. Three types of HAE have been described in the literature: type I HAE (approximately 85% of cases), type II HAE (approximately 15% of cases) and type III HAE (less than 1% of cases) without abnormalities of complement or C1 inhibitor characterized by a coagulation factor XII gene mutation and seen primarily in females. In 50% of patients with HAE, the initial symptoms appear during the first decade of life, in 35% symptoms appear during the second decade, and in the remaining 15% symptoms appear after 20 years of age. Almost 20-25% of patients lack a family history, which can make difficulty in diagnosis (4,5).

The C1NH gene maps onto chromosome 11q12-q13.1 and it is organized into 8 exons and 7 non introns, particularly rich in repetitive *Alu* sequences (7). Although the de novo mutation also made diagnosis difficult because of the lack of family history, this type of mutation seems not so rare. In the literature, more than 300 deficiency-causing mutations have been identified, and approximately 25% of them occur de novo. De novo mutations can belong to all types of deleterious changes (single nucleotide changes, microdeletions-insertions, and gross deletions) and their distribution according to these types is similar to that found for hereditary angioedema in general (8). In our patient's family, there was no similar history for HAE. Anamnesis and laboratory finding suggested that our patient most likely had de novo mutation.

In the literature, episodes affecting the urinary bladder were very rare (3:1000) (9). Hematuria association with HAE was rarely

Figure 1 - Angioedema on forearm



published in the literature (10,11). Our patient was admitted with forearm swelling, difficulty in urination and globe, without hematuria and dysuria, and her symptoms were decreased with the administration of C1 esterase inhibitor concentrate. Her laboratory tests (urine, blood) were normal for the other etiologies of urinary globe and difficulty in urination.

In summary, we have described a case of type I HAE with most likely de novo mutation. The patient had recurrent episodes of angioedema, urinary globe and difficulty in urination, which resembled manifestations of urinary infections and other etiologies of urinary globe. HAE should be taken into consideration for the differential diagnosis of urinary globe etiology.

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NSAIDs are the most frequent medicaments involved in hypersensitivity drug reactions

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Dear Sir

The editorial by Asero et al. in issue n° 1 of Vol. 45 of the European Annals of Allergy and Clinical Immunology (1) points out important data on cutaneous hypersensitivity to multiple non-steroidal anti-inflammatory drugs (NSAIDs) in the sense that a certain number of patients may also respond to selective COX-2 inhibitors. Although the cases of the two patients reported had good tolerance to paracetamol, the authors noted that tolerance to selective COX-2 inhibitors may vary according to previous tolerance to paracetamol. Comparing reactivity to different coxibs, figures lower than 10% could correspond to cases who had good tolerance to paracetamol, and higher figures could correspond to those who previously had skin problems after taking paracetamol, as reported by our group (2). However, a more detailed analysis (from the table) shows that tolerance to paracetamol was not tested in every patient (1).

It is important also to emphasize the relevance of NSAIDs in the induction of hypersensitivity reactions. Asero et al stated in the article that NSAIDs are one of the common causes inducing drug hypersensitivity. For this purpose, a detailed analysis of the manuscript published by Gomes et al. (3) indicates that NSAIDs were the second on the list of implicated drugs in hospital-based populations as well as in outpatients and general populations. However, a recent study published by our group (4) showed that after a detailed evaluation of 4460 patients

over a period of 6 years, 966 patients were finally confirmed as positive to NSAIDs, this representing the most frequent group of drugs involved and confirmed as causing allergy. A previous study focusing on the hypersensitivity patterns of responses to the NSAID group suggests that 60% were cross-intolerant (5). We believe that with the data now available, these references should be taken into account when referring to drugs involved in hypersensitive reactions.

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Reply

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Doña and co-workers' comments on our editorial (1) underline two aspects of NSAIDs hypersensitivity. The first one is paracetamol tolerance in NSAIDs-hypersensitive patients, particularly in those reacting to different NSAIDs, including selective COX-2 inhibitors (coxibs). As reported in the editorial, Doña and co-workers found that intolerance to paracetamol could represent a "marker" of reactivity to etoricoxib and to other coxibs (2). This was not the case in our two patients. On the other hand, reviewing the outcome of paracetamol tolerance in coxibs-reactive patients was out of scope of our article, dealing with challenge tests with coxibs in patients with cutaneous hypersensitivity to multiple NSAID. The two cases we presented underlined the need of checking tolerability of alternative NSAIDs (including selective COX2-inhibitors) in a proper setting. The same holds obviously true also for paracetamol, as highlighted by Doña et al. (2).

The second aspect is the prevalence of hypersensitivity reactions to NSAIDs: definitely this class of drugs is one of the most common causes of adverse reactions (3), and in some populations is the most frequent one, as recently reported by Doña et al. (4). Differences in the prevalence rate of drug hypersensitivity may

depend on study populations (ethnicities, inpatients or outpatients, adults or children), differences in methods for assessing offending drug, and different methods of data analyses (5). However, we believe that an exact ranking of prevalence doesn't appear very relevant in the evaluation of coxibs as alternative drug in cutaneous hypersensitivity to multiple NSAIDs.

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