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CASE REPORT

Severe uncontrolled asthma with biologic therapy in a pediatric patient. The role of fungal sensitization, a case report

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ABSTRACT

We present the case of M., a girl followed by our Center since 2020 for severe asthma. After an initial positive response to Mepolizumab, she experienced multiple asthma exacerbations with poor response to conventional therapies, increased IgE levels, peripheral eosinophilia, and new sensitization to *Aspergillus*, raising suspicion of Allergic Bronchopulmonary Aspergillosis (ABPA). Consequently, Mepolizumab was discontinued. However, due to insufficient diagnostic criteria to confirm ABPA, she was ultimately diagnosed with Severe Asthma with Fungal Sensitization (SAFS).

Her environmental history revealed significant mold exposure at home. Following environmental remediation and the initiation of Dupilumab therapy, she showed clinical improvement.

IMPACT STATEMENT

This case report underscores the diagnostic and therapeutic challenges of managing Severe Asthma with Fungal Sensitization (SAFS) in pediatric patients. By highlighting the role of environmental mold exposure and the clinical benefit of Dupilumab after Mepolizumab failure, the report emphasizes the importance of comprehensive environmental assessment and personalized biologic therapy. It contributes to the growing understanding of SAFS and supports the consideration of alternative biologics in children with uncontrolled asthma and fungal sensitization, even in the absence of clear ABPA criteria.

ABBREVIATIONS

ABPA: Allergic Bronchopulmonary Aspergillosis
SAFS: Severe Asthma with Fungal Sensitization
LABA: long acting beta-adrenoceptor agonists
ACT: Asthma Control Test
BAL: bronchoalveolar lavage

KEY WORDS

Severe Asthma; biologic therapy; Dupilumab; SAFS; ABPA.

INTRODUCTION

Severe Asthma with Fungal Sensitization (SAFS) is a complex and challenging subtype of asthma, characterized by an exaggerated immune response to fungal antigens, leading to exacerbations and poor symptom control. Although the association between asthma and fungal sensitization has long been recognized, its pathophysiology remains incompletely understood, and diagnosis is complicated by overlapping symptoms with other forms of severe asthma. The identification and management of SAFS are further hindered by the lack of standardized diagnostic criteria and variability in patient responses to treatment.

Severe asthma in pediatric patients presents a significant clinical challenge, as it is associated with frequent exacerbations and the need for intensive therapies. Allergic Bronchopulmonary Aspergillosis (ABPA) is a rare but potentially serious complication of allergic asthma, often linked to environmental mold exposure. However, not all diagnostic criteria for ABPA are always met, making it crucial to consider an alternative condition: Severe Asthma with Fungal Sensitization (SAFS). This clinical entity was first described in a 2006 publication, which explored the relationship between fungal sensitization and severe asthma symptoms, distinguishing SAFS as a separate clinical condition from ABPA (1-2). This case report aims to provide insight into the diagnostic challenges and management of SAFS by presenting a novel case that highlights its unique clinical features and treatment response. The significance of this case lies in its contribution to the growing body of literature on SAFS, offering new perspectives on patient management, diagnostic approaches, and therapeutic options. By discussing this case, we hope to enhance awareness of SAFS, improve its clinical recognition, and optimize diagnostic and treatment strategies for affected patients.

CLINICAL CASE

Asthma diagnosis and severe disease course

M. was born in 2013 at term via cesarean section. She has a family history of asthma and inhalant allergies. At the age of three, after entering preschool, she began experiencing frequent episodes of asthma-like bronchitis with significant bronchospasm, requiring repeated courses of oral corticosteroids and inhaled bronchodilators. These episodes had no clear seasonal pattern and were associated with both daytime and nighttime cough, limiting her daily activities.

In 2017, she was diagnosed with asthma and started on inhaled corticosteroids, with minimal benefit.

In 2018, skin prick tests were negative except for mild sensitization to cat epithelium.

In 2020, she was referred to our Pulmonology Department for further evaluation.

Despite escalating inhaled corticosteroids to high doses (fluticasone 500 mcg/day) combined with a long-acting β_2-agonist (LABA) as a second controller, she continued to require frequent courses of oral corticosteroids. Throughout the year, she experienced approximately five acute exacerbations requiring oral corticosteroids and one severe attack necessitating oxygen therapy in the emergency department. Following these episodes, leukotriene receptor antagonist therapy was introduced. However, even after six months, disease control remained poor, with an Asthma Control Test (ACT) score frequently around 16.

Spirometry could not be performed at the time due to pandemic-related restrictions in accordance with recommendations from the Italian Pediatric Respiratory Society (3).

Laboratory investigations revealed:

- WBC 9200/mm³;
- eosinophils 550/mm³;
- elevated total IgE at 2065 IU/ml;
- specific IgE for: Dermatophagoides pteronyssinus 1.34 IU/ml; Dermatophagoides farinae 1.24 IU/ml; Cat dander 2.44 IU/ml; for Dog dander >100 IU/ml;
- alpha-1-antitrypsin levels, sweat tests, serologies for major respiratory pathogens, and screening for celiac disease were normal.

Biological Treatment and Disease Progression

Due to a poor response to conventional therapy, the patient was diagnosed with severe asthma and started on biological therapy. In March 2021, Mepolizumab (40 mg subcutaneously every four weeks) was initiated alongside background therapy with fluticasone-salmeterol (25/125 mcg, two puffs twice daily) and a leukotriene antagonist. Symptoms improved rapidly within a month. Follow-up assessments showed a stable ACT score of 24, indicating good asthma control. No acute respiratory symptoms occurred, either at rest or during physical activity.

However, spirometry showed mild obstruction with a positive bronchodilation test even after three and six months of therapy:

Pre-B:

- FEV1: 1.35 L (89%);
- FVC: 1.62 L (95%);
- FEV1/FVC: 83.58 (93%);
- MEF: 75-25 (64%).

Post-B:

- FEV1: 1.53 L (101%);
- FVC: 1.73 L (102%);

- FEV1/FVC: 88.46 (98%);
- MEF: 75-25 (87%).

During monthly check-ups, laboratory parameters improved within three months: total IgE levels decreased to 1817 IU/ml, and eosinophils dropped to 50/mm³.

Given the stable clinical condition, the fluticasone-salmeterol dosage was reduced to one puff twice daily, while leukotriene antagonist therapy was continued.

Worsening asthma disease control

However, in December 2022, total IgE levels increased again to 3368 IU/ml, while eosinophils remained stable at 50/mm³.

In March 2023, M. experienced her first asthma exacerbation without clear signs of infection, requiring a course of oral corticosteroids. The ACT score dropped to 13, and she reported episodes of dyspnea requiring inhaled bronchodilators.

Spirometry revealed an obstructive pattern:

Pre-B:

- FEV1: 1.42 L (83%);
- FVC: 1.62 L (84%);
- FEV1/FVC: 87.76 (98%);
- MEF: 75-25 (67 %).

Post-B:

- FEV1: 1.68 L (99%);
- FVC: 1.71 L (89%);
- FEV1/FVC: 98.79 (110%);
- MEF: 75-25 (110%).

In June 2023, due to persistent symptoms and worsening lung function despite good compliance with maximal therapy and repeated courses of oral corticosteroids, a chest CT was performed but showed no abnormalities. Given the poor efficacy of Mepolizumab, biological therapy was discontinued in August 2023.

At reevaluation in October 2023, total IgE levels exceeded 5000 IU/ml, with eosinophilia (360/mm³) and an exhaled FENO of 75 ppb.

Skin prick tests revealed new sensitization to *Aspergillus*, with weakly positive specific IgE for *Aspergillus fumigatus* and *Alternaria*.

Blood tests evaluated specific IgE levels as follows:

- *Aspergillus fumigatus*: f2 0.14 kU/L, f4 0.24 kU/L, f6 0.11 kU/L;
- *Alternaria*: 0.15 kU/L.

Specific IgG antibodies for *Aspergillus fumigatus* were negative.

Environmental Exposure and SAFS Diagnosis

She underwent bronchoscopy with Bronchoalveolar Lavage (BAL) to detect fungal hyphae. The results were negative for bacterial and fungal cultures, bacterial PCR, and mycobacteria.

During hospitalization, the patient reported significant improvement in dyspnea and fatigue, raising suspicion of an environmental exposure at home. A further review of her history revealed that her home had been severely infested with mold for years, with visible growth covering the walls of her bedroom. While the specific mold species were not initially identified, the persistent dampness suggested the presence of *Aspergillus* and *Alternaria*, both commonly associated with allergic airway diseases. The family had attempted multiple remediation efforts, including commercial antifungal treatments, but structural issues in the home prevented complete resolution. Their residence, located in a historic building, suffered from severe rising dampness, making eradication of the mold nearly impossible.

The patient's clinical improvement during hospitalization and after relocating to a different sleeping area

***Table 1**. Comparison between ABPA and SAFS criteria with our clinical case.*

Criteria	ABPA	SAFS	Patient Findings
Central bronchiectasis	Present	Absent	Absent
Specific IgE for Aspergillus fumigatus	High	Low or absent	Low
Total IgE levels	>500 IU/mL	Elevated	>5000 IU/mL
Recurrent pulmonary infiltrates	Present	Absent	Absent
Asthma severity	Variable	Severe, steroid-dependent	Severe, steroid-dependent
Response to antifungal therapy	Often beneficial	Not always effective	Not tested

further supported the role of environmental exposure in her disease progression. Based on her clinical presentation and laboratory findings, allergic bronchopulmonary aspergillosis (ABPA) was suspected. However, due to the absence of full ABPA diagnostic criteria, she was instead diagnosed with Severe Asthma with Fungal Sensitization (SAFS) (**Table 1**).

Distinguishing between SAFS and ABPA can be challenging, as can selecting the most appropriate treatment. Given the patient's condition, Dupilumab therapy was initiated, leading to sustained clinical improvement.

DISCUSSION

We presented a case of severe asthma under biological treatment with worsening disease control. Given the high total IgE levels, weakly positive specific IgE for *Aspergillus fumigatus*, and a positive skin prick test, an initial diagnosis of ABPA was suspected.

The diagnosis of ABPA requires a series of criteria, including:

- presence of high risk conditions such as persistent severe asthma or cystic fibrosis;
- elevated total IgE levels (>500 IU/ml);
- presence of specific IgE and IgG against Aspergillus fumigatus (M. only had weakly positive specific IgE but skin prick test were positive for Aspergillus fumigatus);
- eosinophilia (present in M.);
- chest X-ray or CT showing evidence of transient pulmonary infiltrates or central bronchiectasis (absent in M.);
- expectoration of mucus plugs with pulmonary eosinophilia (4) (absent in M.).

Although M. had elevated total IgE levels and sensitization to *Aspergillus fumigatus*, other key criteria for ABPA, such as structural lung alterations, infiltrates, or bronchiectasis, were absent.

Additionally, during hospitalization, her symptoms significantly improved simply by removing her from the mold-infested home environment an outcome more consistent with chronic allergenic exposure rather than an invasive lung disease like ABPA.

Since the diagnostic criteria for ABPA were not fully met, SAFS was considered the more appropriate diagnosis. Her clinical presentation aligned more closely with SAFS, characterized by severe asthma poorly controlled with standard therapy, high total IgE levels, and fungal sensitization without structural lung changes.

Currently, scientific literature lacks well-defined, evidence-based guidelines for SAFS treatment. Management typically involves minimizing environmental exposure to fungal allergens alongside optimized pharmacological therapy, such as corticosteroids or biologics when available (5).

While immediate relocation was not feasible, every effort was made to reduce mold exposure. Given M.'s prolonged corticosteroid use, alternative therapies were also considered.

During Mepolizumab treatment, she initially showed a good clinical response, with significant reductions in total IgE and eosinophils. However, despite nearly three years of therapy, full lung function recovery was not achieved an outcome previously noted in the literature (6). As disease control worsened and the response to Mepolizumab declined, the treatment was discontinued.

Although evidence on Dupilumab for SAFS is limited, studies have demonstrated its effectiveness in severe eosinophilic asthma, reducing corticosteroid dependence and improving quality of life (7-9).

Dupilumab targets the IL-4 and IL-13 pathways, which play a central role in Th2-driven inflammation in severe asthma and allergic diseases. Unlike other biologics, it has been shown to reduce corticosteroid dependence and improve lung function, particularly in patients with allergic sensitization.

Given the patient's high total IgE and fungal sensitization, it was deemed the most appropriate option compared to alternative biologics targeting eosinophils alone. Other options, such as Omalizumab, were considered but deemed less suitable due to the extreme IgE levels, which exceeded standard dosing recommendations.

Therefore, Dupilumab was chosen as an alternative biologic therapy.

CONCLUSIONS

The management of SAFS remains challenging due to the lack of standardized guidelines. Current recommendations emphasize environmental control, aggressive asthma management, and the use of biologics when appropriate. Studies suggest that Dupilumab may pro-

vide significant benefits for patients with severe allergic asthma, including those with fungal sensitization. However, the role of antifungal therapy in SAFS remains controversial, as its efficacy is not well established in the absence of ABPA.

This case highlights the importance of obtaining a thorough environmental history when asthma is poorly controlled, conventional therapy proves ineffective, or socio-economic and environmental risk factors are present. A precise evaluation of ABPA criteria in severe asthma is essential, as is considering SAFS in the differential diagnosis.

Future research is needed to establish definitive treatment protocols, but emerging evidence supports the use of targeted biologic therapy in cases like ours.

By presenting this case, we aim to contribute to the growing body of literature on SAFS, raise awareness of its clinical presentation, and improve diagnostic and treatment approaches for affected patients.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Ethical approval

Human studies and subjects

Not applicable for this case.

Data sharing and data accessibility

The respiratory sound database is not available for researchers.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

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