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CASE REPORT

Two different diseases in two adolescent girls with the same clinic: Allergic bronchopulmonary aspergillosis

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ABSTRACT

Two different diseases in two adolescent girls with the same clinic: Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction observed in asthma as well as cystic fibrosis (CF) patients due to the colonization of the airways by *Aspergillus fumigatus*. While ABPA is most commonly observed in CF patients (2-9%), it is seen at a rate of 1-2% in patients diagnosed with asthma. ABPA is mostly seen in steroid dependent adult asthma patients and has rarely been reported in pediatric asthma patients. The aim of our study was to provide the clinical, laboratory, and radiological characteristics of two patients under our follow-up care who were also diagnosed with ABPA. In the pediatric population, ABPA is often seen in patients with cystic fibrosis and rarely as a complication of childhood asthma. However, it is not clear whether this is because ABPA is really rare or because there is low level of suspicion for this disease. Furthermore, diagnostic criteria and staging systems are created by taking adults into consideration and not having different diagnostic criteria or staging systems for pediatric patients makes the diagnosis even more difficult.

Key words: Asthma; cystic fibrosis; allergic bronchopulmonary aspergillosis

ÖZ

İki farklı hastalık, aynı klinik: İki adolesan hastada alerjik bronkopulmoner aspergilloz

Alerjik bronkopulmoner aspergilloz (ABPA), hava yollarının *Aspergillus fumigatus* tarafından kolonizasyonu sonucu astım ve kistik fibrozis (KF) hastalarında görülen kompleks bir aşırı duyarlılık reaksiyonudur. Alerjik bronkopulmoner aspergilloz en sık KF hastalarında görülürken (%2-9), astım tanısı almış hastalarda da %1-2 oranında görülmektedir. Alerjik bronkopulmoner aspergilloz çoğunlukla steroid bağımlısı erişkin astım hastalarında görülürken, nadiren çocuk astım hastalarında da bildirilmiştir. Bu yazının amacı, takibimiz altında olan ve farklı hastalıklara sahip olup; ABPA tanısı da konulan iki hastanın klinik, laboratuvar ve radyolojik özelliklerini sunmaktır.

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Pediyatrik popülasyonda ABPA sıklıkla KF'li hastalarda ve nadiren çocukluk çağı astımının bir komplikasyonu olarak görülmektedir. Ancak, bu durumun ABPA'nın gerçekten nadir olmasından mı yoksa bu hastalık için düşük şüphe düzeyinden mi kaynaklandığı açık değildir. Ayrıca, tanı kriterleri ve evreleme sistemleri yetişkinler göz önünde bulundurularak oluşturulmuştur ve çocuk hastalar için farklı tanı kriterleri veya evreleme sistemlerinin olmaması tanıyı daha da zorlaştırmaktadır.

Anahtar kelimeler: Astım; kistik fibrozis; alerjik bronkopulmoner aspergilloz

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is a complex hypersensitivity reaction observed in asthma as well as cystic fibrosis (CF) patients due to the colonization of the airways by *Aspergillus fumigatus* (1). Genetic tendency for ABPA initiates the inflammatory process and results in the development of atopy. The etiology of the disease is explained by the predominance of the Th2 response, the release of IL-4, IL-15, IgE synthesis, the eosinophil response to inflammation, increased mucus formation, and airway hypersensitivity.

A. fumigatus is the fungus species most commonly causing this condition; however, other species can cause ABPA as well (Figure 1) (2). While ABPA is most commonly observed in CF patients (2-9%), it is seen at a rate of 1-2% in patients diagnosed as asthma (2). ABPA is mostly seen in steroid dependent adult asthma patients and has rarely been reported in pediatric asthma patients. Clinical signs are unresponsiveness to inhaled bronchodilators,

temporary response to oral corticosteroids, productive cough (brownish sputum), wheezing, fatigue, fever, hemoptysis and pleuritic chest pain. As establishing a diagnosis is very difficult, diagnostic criteria including clinical, laboratory and radiological findings have been developed (Table 1). The aim of the treatment is to prevent acute inflammation, limit the progression of the damage, and control the development of new episodes. Systemic steroids and antifungal agents are used for this purpose, while biological agents like anti-IgE and anti-IL5 are available for selected cases (1,2).

The aim this study was to present the clinical, laboratory and radiological features of two adolescent patients who were diagnosed with ABPA in the background of asthma and cystic fibrosis.

CASE 1

A 13-year-old girl patient who did not have any previously known disease was admitted to another center six months ago with the complaints of nasal

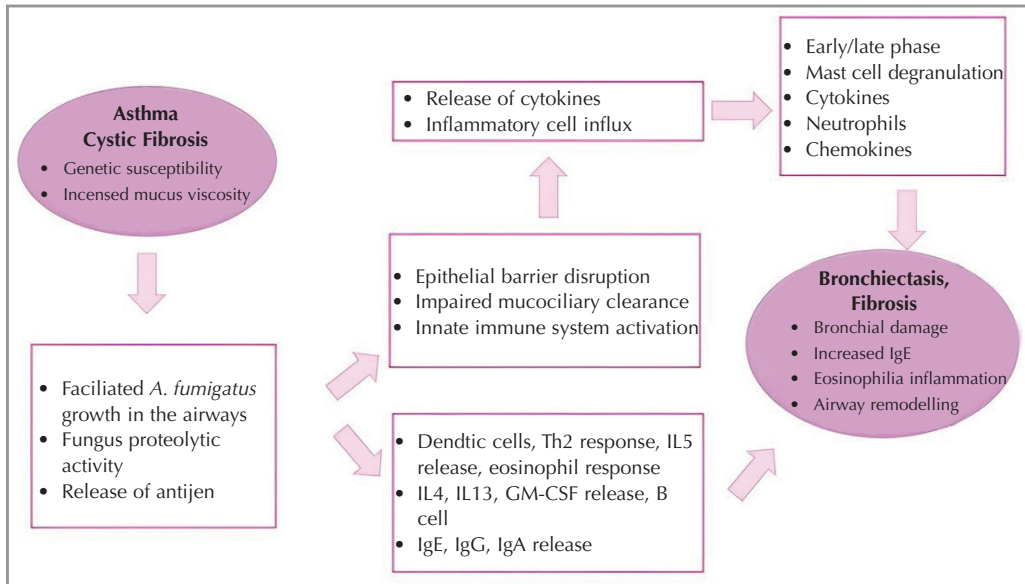


Figure 1. The pathogenesis of allergic bronchopulmonary aspergillosis.

Ig: Immunglobulin, IL: Interleukin, GM- CSF: Granulocyte-macrophage colony-stimulating factor (2).

Table 1. ISHAM ABPA diagnostic criteria (obtained from reference no 3)/Clinical and laboratory features of Case 1 and 2		
ISHAM criteria	Case 1: 13-year-old girl	Case 2: 13-year-old girl
Asthma, cystic fibrosis	Cystic fibrosis Bronchodilator response in spirometric evaluation: (+) Sweat chloride test: Normal CFTR gene analysis: Compound heterozygous	Asthma Bronchodilator response in spirometric evaluation: (+) Sweat chloride test: Two suspicious results CFTR gene analysis: Negative
Serum eosinophil count (>500 mm ³)	1600/mm ³	730/mm ³
Aspergillus skin test positivity	Negative	Negative
Elevated IgE (1000 IU/mL)	719 IU/mL	4501 IU/mL
Radiological presence of lung opacities correlating with ABPA	Infiltrates stemming from fungi, tree-in-bud appearance and the presence of central bronchiectasis	Mucus impaction, accompanying air entrapment, wall thickening of segmentary bronchi and the presence of central bronchiectasis
Central bronchiectasis	+	+
Aspergillus serum specific IgE elevation	Aspergillus specific IgE= 5.45 kU/L (3+++)	Aspergillus specific IgE= 13.1 kU/mL (3+++)
Secondary		
Aspergillus growth in sputum	Not identified	Not identified
Brownish sputum	+	+
Treatment	Systemic steroids, voriconazole	Systemic steroids, itraconazole
Stage	Acute/Remission after treatment	Acute/Remission after treatment
Radiological stage	ABPA-B	ABPA-B
Prognosis	IgE levels decreased at the end of two weeks of treatment, the dose of systemic steroids was tapered according to the treatment scheme	IgE levels decreased at the end of two weeks of treatment, the dose of systemic steroids was tapered according to the treatment scheme
ISHAM: International society of human and animal mycology, ABPA: Allergic bronchopulmonary aspergillosis, CFTR: Cystic fibrosis transmembrane conductance regulator (3).		

discharge and cough. She began taking systemic steroids, clarithromycin, inhaled salbutamol, and inhaled corticosteroids as her cough worsened despite receiving symptomatic therapy. Her therapy was changed to a combination of inhaled corticosteroid (ICS) and long acting beta agonist (LABA) when her symptoms worsened. She received intravenous antibiotics (piperacillin, tazobactam/teicoplanin) for 10 days, but there was no improvement in the symptoms. Her purified protein derivative (ppd) test was anergic. A computed tomography (CT) scan of the thorax revealed bronchiectatic alterations in both lungs along with the existence of soft tissues within bilaterally expanded bronchi (Figure 2). In complete blood count, total eosinophil count was= 2340/mm³. Therefore, she was referred to our center with a preliminary diagnosis of ABPA. Her physical examination was normal other than the presence of clubbed fingers. Sweat chloride tests were= 37

mmol/L and 23.7 mmol/L (0-30 mmol/L: normal, 30-60 mmol/L: intermediate value). In spirometric evaluation, bronchodilator response was identified. Flexible bronchoscopy examination demonstrated mucoid type secretions within both bronchi that

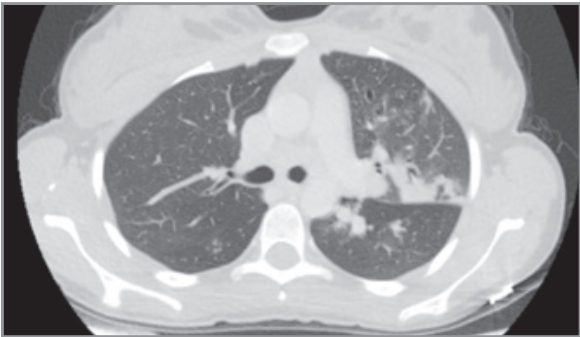


Figure 2. Thorax CT image for Case 1: Bronchiectatic changes in both lungs, soft tissues inside of the bilaterally dilated bronchi, findings favoring allergic bronchopulmonary aspergillosis.

were difficult to remove. Serum total IgE level was= 719 IU/mL, Aspergillus specific IgE was= 5.45 kU/L (3+), and peripheral blood total eosinophil count was= 1600/mm³. Based on International Society of Human and Animal Mycology (ISHAM) radiological staging, the patient was diagnosed as ABPA-B (with bronchiectasis); 2 mg/kg/day systemic steroid was given and voriconazole was administered as an antifungal agent. Two weeks later, during the follow-up, total IgE levels were found to be decreased by 30% (more than 25%); the patient was regarded as treatment responsive ABPA and steroids started to be tapered. In the follow-up of the patient who was diagnosed as ABPA on the basis of asthma clinic due to positive response to inhaled salbutamol on spirometry and responded to ABPA treatment, c.2052del mutation in exon 14 and c.3454G>C compound heterozygous mutation in exon 21 were found in CFTR gene analysis. She continues to receive steroid and antifungal treatment at our center.

CASE 2

A 13-year-old girl, who was first admitted at the age of eight due to recurrent respiratory problems and pneumonia attacks, had a history of antibiotic and inhaler treatment. Her serum total IgE level was= 2097 IU/mL, and skin prick test and immunological evaluation were normal. Her ppd test was anergic. She was not cooperative during the spirometry test. The flexible bronchoscopic evaluation showed mucoid secretions in all lobar and segmental bronchi. Bronchoalveolar lavage culture grew 100.000 cfu/mL Haemophilus influenzae and 50.000 cfu/mL Pseudomonas aeruginosa. Thorax CT examination demonstrated bronchial wall thickening of the lower lobe posterior and lateral basal segments of the left lung together with accompanying air entrapment. She was diagnosed with asthma and following the completion of IV antibiotic treatment, ICS were given. She was discharged with recommendations for lung physiotherapy. In her admission to the hospital a year later, despite having normal spirometric test results, she reported to have experienced episodes following every viral upper respiratory tract infection, therefore her ICS dose was increased. During the COVID-19 pandemic, she did not show up for follow-up visits for about a year. During her first spirometric evaluation afterwards, inhaled steroid

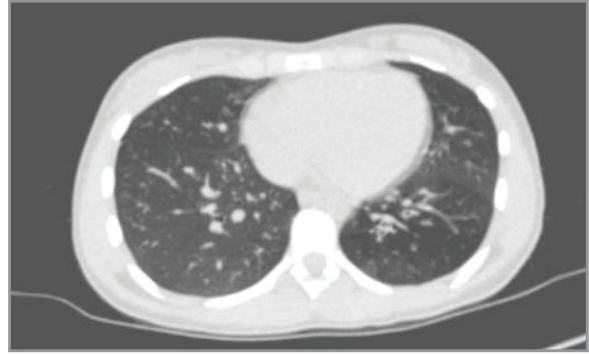


Figure 3. Thorax CT image for Case 2 (wall thickening of the segmentary bronchi in the left lower lobe, bronchiectasis and bronchiolectasis, mucus impaction and accompanying air entrapment).

treatment was switched to LABA and ICS upon identifying bronchodilator response. As the patient continued to have recurrent pneumonia and asthma attacks, sweat chloride test was performed yielding a result of 34 mmol/L. Serum total IgE measured during that time was= 5000 IU/mL and inhaler prick test identified Alternaria 3(+). Throughout the following two years, she only had cough during periods of upper respiratory tract infections (URTE) and the frequency of her attacks decreased, so her treatment was reduced to intermittent treatment. In the evaluation made six months after, serum total IgE was= 4501 IU/mL, Aspergillus specific IgE was= 13.1 ku/mL (3+), sweat chloride test was= 30.7 mmol/L and peripheral blood eosinophil count was= 730/mm³. In her sputum culture, there was abundant growth of Candida albicans, in thorax CT there was segmentary bronchial wall thickening of the left lower lobe, bronchiectasis/bronchiolectasis, mucoid impaction and accompanying air entrapment (Figure 3). As threshold values were found in two of the previously performed sweat chloride tests of the patient, CFTR sequence analysis and MLPA analysis were performed yielding negative results. In the light of these findings and based on ISHAM diagnostic and radiological criteria, the patient was regarded as ABPA-B (bronchiectasis) due to asthma and 2 mg/kg/day systemic steroid and itraconazole was administered. Two weeks later, total IgE levels of the patient have dropped by 30% (more than 25%) and she is being followed up as treatment responsive ABPA and her systemic steroids are to be tapered according to the treatment scheme.

DISCUSSION

ABPA was first described in 1970 by Slavin et al. in a child diagnosed with asthma (4). Especially in patients with asthma and CF, the disease presents as a progressive airway disease developing due to *A. fumigatus* hypersensitivity. Genetic predisposition and ensuing inflammation are closely associated with atopy. Fungal spores can be found anywhere, but *Aspergillus* colonization and infection is only seen in certain patients because some predisposing factors need to be in play to bring the growth of *Aspergillus* to a level that would result in a high antigen load. Clinical presentation varies depending on the immunity status of the patient (2).

Pathogenesis has been schematized in Figure 1. Fungal hyphae typically enter the body via inhalation and start multiplying without causing any tissue invasion. This continuous antigen exposure leads to a local and systemic inflammatory response triggering bronchospasm. Healthy individuals can wipe out these organisms, yet in individuals where non-specific immunity like mucociliary clearance mechanisms is hindered, spores can easily adhere to the airway epithelium. Locally, *Aspergillus* spores secrete proteolytic enzymes like elastase, collagenase and trypsin. By damaging the matrix through these products, they lead to further inflammation and to the secretion of proinflammatory cytokines aggravating the inflammatory response. IgE mediated type I hypersensitivity reaction (HSR) causes degranulation of mast cells and eosinophils. The cationic proteins histamine and matrix metalloproteinase 9 that cause tissue damage are secreted with the help of major basic protein (MBP). IgG and complement activation-mediated tissue damage are also inherent components of the inflammatory process, and type 3 HSR enters the picture as it goes on.

In time, bronchial wall thickens with the influence of growth factors and cytokines, there is remodeling of the airways leading to the development of bronchiectasis and eventually fibrosis. Systemic response involves activation of *Aspergillus* specific T and B lymphocytes. Here, Th2 type CD 4+ cells play an important role. CD4+ Th2 cells interact with IL 4, 5, 13 and interferon gamma and stimulate B cells which increases IgE synthesis. Atopic individuals have an already existing exaggerated Th2 response. IL-4 plays a central role in this process guiding the

Th2 response in an autocrine manner, stimulating the eosinophils and encouraging the non-specific IgE production. Humoral response also plays an important role in the pathogenesis. B lymphocytes produce polyclonal *Aspergillus* specific IgE, IgA and IgG that is not only seen in patients sensitive to *Aspergillus* (5).

ABPA can be observed in 1-2% of asthma patients and 1-9% of CF patients (2). The risk of ABPA has been linked to a number of factors, including long-term azithromycin treatment, bacterial colonization of the airways, high-dose inhaled corticosteroids, genetic factors such CFTR gene mutations, and the presence of atopy and eosinophilia (6). Clinically, there is unresponsiveness to bronchodilators, temporary response to oral corticosteroids, brownish productive cough, wheezing, fatigue, fever, hemoptysis and pleuritic chest pain. As concerns laboratory tests, there is elevated total eosinophil in peripheral blood samples (generally $>500/\text{mm}^3$), elevated serum total IgE (generally $>1000 \text{ IU/mL}$), elevated *Aspergillus* specific IgE and IgG levels. Serum galactomannan levels do not have a role to play in the diagnosis of ABPA. Bronchiectasis is commonly observed on thorax CTs. Pulmonary nodules, mucoid impaction, tree-in-bud appearance, atelectasis, peripheric parenchymal infiltration, ground glass opacities, and air entrapment are other findings observed on CT scans. ISHAM diagnostic criteria are used to establish a diagnosis (1).

In addition to diagnostic criteria, radiological staging based on clinical staging and radiological findings is used for evaluating the treatment response and disease stage. Radiological staging is as follows: Patients who do not have central bronchiectasis but satisfy all ABPA criteria -ABPA-serologic (ABPA-S), patients who have accompanying central bronchiectasis- ABPA-central bronchiectasis (ABPA-SB), patients who have other radiological findings in addition to central bronchiectasis ABPA/Central bronchiectasis/Other radiologic features (ABPA-SB-ORF) (3). Shah et al. retrospectively evaluated 349 ABPA patients due to asthma, 42 patients were in the pediatric age group with a mean diagnostic age of 12.9 years, which was similar to ours. In 32 patients, there was central bronchiectasis like the case in our patients, and 10 patients were diagnosed as ABPA serologically (7).

In differential diagnosis, pulmonary eosinophilia should be considered when eosinophilia accompanies radiological findings but when *Aspergillus* specific IgE test and skin prick tests are negative. Differential diagnosis should also include other conditions presenting with eosinophilia like eosinophilic pneumonia due to drugs or toxins, hypereosinophilic syndromes, tropical eosinophilic pneumonia, Loeffler pneumonia and eosinophilic granulomatous polyangiitis (8). None of our patients had findings that would necessitate covering these conditions in differential diagnosis.

Özdemir published a case report in 2017 about a 12-year-old patient who experienced symptoms for the previous two years, was treated for recurrent pneumonia episodes, and eventually got worse. The patient was given a diagnosis of tuberculosis as a follow-up to the initial diagnostic of ABPA, which was not taken into consideration at that time (9). As stated by Özdemir, the prevalence of ABPA being low and associating the symptoms of the patient with exacerbations of asthma were the main factors contributing to a delay in the diagnosis.

Case 1 was evaluated for treatment-refractory persistent cough, asthma, pneumonia, and central bronchiectasis. She had no prior medical history and her growth was consistent with that of her age-matched peers. Following CFTR gene testing at the age of 13, the patient was diagnosed with CF. Ig E specific to *Aspergillus* and total Ig E were positive, whereas the sweat chloride test yielded an inconclusive results.

As evidenced by one of our patients, having asthma symptoms that worsen despite treatment, thoracic CT scans that specifically reveal central bronchiectasis, and total IgE levels greater than 1000 IU/mL should unquestionably be considered for ABPA.

Antifungal medications and systemic steroids are the mainstays of treatment. Voriconazole is an effective antifungal medication that can be administered in conjunction with systemic steroids, even though itraconazole is the preferred option.

If remission cannot be achieved with these treatments, biological agents like Anti-IgE and Anti-IL5 can be

tried (2). Although this practice is an adaptation from adult ABPA patients and there are not enough studies performed for the treatment of ABPA in pediatric asthma patients, we used systemic steroids and antifungal agents in both of our patients obtaining favorable responses.

Atay et al. presented six pediatric ABPA cases in their study, half of them were diagnosed as asthma associated ABPA and the other half of them were diagnosed as cystic fibrosis associated ABPA. One but all patients had central bronchiectasis on thorax CT scans. All three asthma patients received itraconazole together with inhaled steroids. Although their choice of antifungal agent was itraconazole like our study, they preferred inhaled steroids over systemic ones as they were concerned about possible side effects (6). Since the response to inhaled steroids was inadequate in both of our patients, systemic steroid treatment was initiated by considering the benefit-loss ratio. Clinical response to systemic steroids was achieved in both patients and no side effects were observed.

CONCLUSION

In conclusion, as ABPA is more common in adults than in children, diagnosis and treatment protocols are generally tailored to adults. In the pediatric population, ABPA is often seen in patients with CF and rarely as a complication of childhood asthma. However, it is not clear whether this is because ABPA is really rare or because there is low level of suspicion for this disease. Furthermore, diagnostic criteria and staging systems are created by taking adults into consideration and not having different diagnostic criteria or staging systems for pediatric patients makes the diagnosis even more difficult. Early and appropriate treatment of ABPA is of essential importance to prevent the development of sequelae like central bronchiectasis, pulmonary fibrosis, severe deterioration of pulmonary functions and cor pulmonale. Therefore, if pediatric patients being followed up for asthma or cystic fibrosis do not respond to treatment, they should definitely be evaluated for ABPA.

CONFLICT of INTEREST

The authors have no conflict of interest to declare.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: GÖ, ŞH, EGO, SS

Analysis/Interpretation: GÖ, ŞH, EGO

Data acquisition: GÖ, ŞH, EGO, SS, Cİ, FZ, MT

Writing: GÖ, EGO

Clinical Revision: EÇ, FD, Aİ, NÇ

Final Approval: ŞH, FD, Aİ, NÇ

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