

# Allergic Bronchopulmonary Aspergillosis due to *Aspergillus niger*

## Report of two cases in Greece and review of the literature

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### Key words

- Allergic bronchopulmonary aspergillosis (ABPA)
- Bronchial asthma
- *Aspergillus niger*
- Greece
- Central bronchiectasis

### Abbreviations

Ab: Antibodies

*A. niger*: *Aspergillus niger*

DLC<sub>0.5</sub>: Diffusing capacity of the lung for carbon monoxide Single breath technique

HCO<sub>3</sub>: Bicarbonate

*A. fumigatus*: *Aspergillus fumigatus*

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**ABSTRACT.** Two cases of allergic bronchopulmonary aspergillosis (ABPA) are reported. Both patients presented severe asthma, central bronchiectasis and fleeting infiltrates on computed tomography of the chest, immediate cutaneous reactivity to *Aspergillus* spp, elevated total serum IgE and elevated IgG and/or IgM *Aspergillus* antibodies. Bronchoalveolar lavage culture documented *A. niger*, a very rarely encountered fungus species in this entity. Although the incidence and rate of hospitalization for asthma have increased the last decades in Greece and skin sensitization to *Aspergillus* is described in 5% of greek atopic patients, ABPA is scarcely reported. Untreated ABPA results in recurrent exacerbations of airway inflammation, persistent asthma and can progress to advanced fibrotic changes. Therefore high clinical suspicion, early diagnosis and timely treatment and follow-up are considered significant in the course of this rare and underdiagnosed entity. *Pneumon 2014, 27(4):336-339.*

## INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) represents an immunological fungal lung disease caused by type I and III hypersensitivity reactions to antigens of *Aspergillus* species.<sup>1</sup> This clinical entity is identified in 1%-2% of patients with bronchial asthma, in 2%-15% of patients with cystic fibrosis and very rarely in patients with allergic fungal sinusitis, hyper-IgE syndrome and chronic granulomatous disease.<sup>2-5</sup> The aim of the present study is to report the first two cases of *A. niger* ABPA in asthmatics described in Greece. Special consideration is given on the antigenic profile and the different immunopathogenic properties of *A. niger* especially in comparison to *A. fumigatus*, considered to be the most frequent pathogen in this clinical entity.

## CASE REPORT I

A 33 year old woman, never smoker, with a history of allergic rhinitis since childhood, and bronchial asthma for the last few years presented with a febrile exacerbation. The patient reported extensive construction works next to her residence during the last few months. On admission, she complained for dyspnea and on chest auscultation bilateral wheezing was present. The rest of the physical examination was unremarkable. Serial CXR revealed bilateral fleeting peripheral infiltrates and hyperinflation of both lungs. CT of the chest confirmed pulmonary infiltrates, and additionally disclosed central bronchiectasis some of which were obstructed by mucus (Figure 1a).

Arterial blood gases on room air at rest were as follows: PaO<sub>2</sub> 90mmHg, PaCO<sub>2</sub> 33mmHg, pH 7.47, HCO<sub>3</sub> 24.7mmol/L. Spirometry revealed moderate obstruction with significant response to bronchodilation. DLCO<sub>SB</sub> was 57% of predicted. Fiberoptic bronchoscopy revealed sparse mucous plugs. In BAL fluid macrophages accounted for 36%, lymphocytes for 12%, and eosinophils for 52%. BAL culture on Sabouraud medium for fungal culture was positive for *A. niger*. Laboratory investigations revealed peripheral eosinophilia (10.8%) and serology disclosed an increased total IgE titer (5078 IU/ml), *Aspergillus* IgG antibodies (Ab) titer 1/2560 on ELISA quantitative assay and positive *Aspergillus* IgM Abs. Skin prick test for *Aspergillus* was also positive.

## CASE REPORT II

A 55 year old asthmatic woman presented with a three months history of dyspnea and wheezing not responding to everyday treatment with inhaled β<sub>2</sub> agonists, inhaled corticosteroids and low doses of oral steroids. She mostly complained of productive cough with great difficulty in expectorating sputum and low fever. On admission to the hospital she was dyspneic and had a temperature of 37.4°C. The CXR revealed bilateral infiltrates and chest CT showed extensive thickening of the bronchial walls as well as central bronchiectasis especially of the right middle and both lower lobes. Signs of mucus impaction of several bronchi were also present (Figure 1b). Spirometry was compatible with obstructive pattern with significant response to bronchodilation. DLCO<sub>SB</sub> was not performed due to lack of collaboration. During bronchoscopy viscous mucus was detected in the bronchial tree and was removed with difficulty. In BAL fluid, polymorphonuclear cells accounted for 42%, macrophages for 55% and lymphocytes for 2%. BAL culture on Sabouraud medium was positive for *A. niger*. Further blood investigations revealed leukocytosis (WBC: 13,85 x 10<sup>6</sup>/μl) with marked eosinophilia (24%), an increased total IgE titer (1560 IU/ml), *Aspergillus* IgM Ab titer was positive and skin prick test was positive.

Both patients fulfilled criteria for ABPA<sup>10,11</sup> due to *A. niger*. Treatment with oral corticosteroids at a dose of



**FIGURE 1. a.** Computed tomography of the chest of the patient No 1, showing bilateral infiltrates, central bronchiectasis and mucus impaction. **b.** Computed tomography of the chest of the patient No 2, showing an infiltrate, central bronchiectasis, thickening of the bronchial walls and mucus impaction.

0.5 mg/kg/d and of inhaled formoterol 160 mcg and budesonide 4.5 mcg 2 puffs bd was initiated. Follow-up one month later revealed significant response to treatment. IgE titer subsided to 900 IU/ml for the first patient and to 600 IU/ml for the second one.

## DISCUSSION

For a diagnosis of ABPA there should be a minimum of five criteria that were all fulfilled in our cases: (1) asthma, (2) proximal bronchiectasis, (3) immediate cutaneous reactivity to *Aspergillus* species or *A. fumigatus*, (4) a total serum IgE that is elevated (>400 IU/ml), and (5) elevated serum IgE-*A. fumigatus* and/or serum IgG-*A. fumigatus*. Such patients can be designated as ABPA-central bronchiectasis.<sup>6,7</sup> In patients with asthma, ABPA is sometimes diagnosed in the absence of the typical proximal bronchiectasis and is then designated as ABPA-seropositive.<sup>7</sup> Findings helpful to diagnosis further include pulmonary infiltrates, blood eosinophilia, precipitating antibodies to *Aspergillus* spp, production of viscous mucus plugs and sputum or BAL cultures positive for *Aspergillus* spp.<sup>7</sup> Corticosteroids are the mainstay of treatment and proved very effective in both our patients. In case of patients who become steroid dependent or for those who have relapse after steroid treatment, addition of antifungal therapy—mostly itraconazole— is recommended.<sup>2,6</sup>

To our knowledge, these are the first two cases of allergic bronchopulmonary aspergillosis related to *A. niger* concerning Greek patients described in the literature. Microbiological work up documented *A. niger* as the etiologic agent, a very rarely encountered fungus species in this entity. *A. niger* consists along with *A. fumigatus*, *A. flavus* and *A. terreus* the commonest species of *Aspergillus* causing disease. *Aspergillus* species are spore-forming saprophytic fungi found everywhere in the world. The primary ecologic niche is decomposing vegetables and the soil in farms.<sup>8</sup> Environmental surveillance studies performed in Greece have demonstrated that *A. niger* is the most prevalent species in the air followed by *Aspergillus flavus* and *A. fumigatus*.<sup>9,10</sup> As far as pathogenicity is concerned, the growth rate of each species, the spore size which enables the fungus to penetrate deep into the lung, as well as the protein coat layer of conidia which help protect them from host defenses are considered to be the major determinants.<sup>11</sup> Studies focusing on the effect of *Aspergillus* spp on human respiratory ciliated

epithelium conclude that, apart from immunological mechanisms, bronchial damage in ABPA may be directly mediated by *Aspergillus*-derived products, including a chymotrypsin-like proteinase.<sup>12</sup> *A. niger* is less rapidly growing than *A. fumigatus* and does not reduce ciliary beat frequency but causes mild to moderate epithelial disruption. Proteases released by *A. fumigatus* on the other hand are very potent, even with few organisms present, explaining why *A. fumigatus* causes ciliary dyskinesia very early<sup>12,13</sup> and why it is implicated in most cases of ABPA reported worldwide. The size of the inoculum of spores necessary for the development of any manifestation of aspergillosis is not known but is considered to play a significant role. The higher air concentrations are encountered in areas located close to renovation works.<sup>10</sup> In the case of our patients, the high prevalence of *A. niger* in the Greek atmosphere in association with the increased exposure to soil in both cases, either through construction work in the first case or through farm work in the second could multiply the risk of disease from this *Aspergillus* species.

Although bronchial asthma is included in the major criteria of ABPA, there are data supporting that ABPA could be developed either in patients without it or in patients who develop asthma later in the course of the disease.<sup>14</sup> Two cases of ABPA due to *A. niger* found in the literature were not followed by bronchial asthma.<sup>14,15</sup> The most important issue in cases of ABPA without bronchial asthma is the difficulty in diagnosis and the delay in appropriate regimen, since most patients are initially treated for bronchogenic carcinoma or tuberculosis.<sup>14,16</sup> In this study both patients presented clinical and physiologic parameters characteristic of bronchial hyperreactivity. According to the ISAAC study, Greece belongs to the countries with the lowest prevalences of bronchial asthma reported worldwide (less than 5%).<sup>17</sup> It is important to note though that in Greece the prevalence of asthma has increased during the last decade to almost 6.5% as well as the hospitalizations for it.<sup>18,19</sup> ABPA is nevertheless scarcely reported, although the skin sensitization to *Aspergillus* spp is detected in Greek atopic patients in 5% of cases.<sup>20</sup> Untreated ABPA results in recurrent exacerbations of airway inflammation, persistent asthma and can progress to advanced fibrotic changes.<sup>3</sup> Therefore high clinical suspicion, early diagnosis and timely treatment and follow-up are considered significant in the course of this rare and underdiagnosed entity.

## COMPETING INTERESTS

All the authors declare that they do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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