

Mixed Allergic Bronchopulmonary Aspergillosis and Candidiasis

Foula Vassilara¹,
Aikaterini Spyridaki¹,
Athanassia Deliveliotou¹,
Georgios Pothitos¹,
Stavros Anevlavis²,
Demosthenes Bouros²

¹Division of Internal Medicine, Hygeia General Hospital, Athens, Greece

²Department of Pneumology, Medical School, Democritus University of Thrace, Greece

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Correspondence:

Aikaterini Spyridaki,
Hygeia Hospital, Athens, Maroussi, GR-151 23,
4 Erithrou Stavrou Str. & Kifissias Ave., Greece
Tel.: 210-6867960
E-mail: kspyridaki@yahoo.gr

SUMMARY. A 67 year-old woman presented with dyspnea, fever and productive cough. She was a heavy smoker (80 pack/years), with history of hypertension and alcohol consumption. Chest CT revealed bilateral diffuse infiltrates and ground glass opacities. Sputum cultures revealed multiple colonies of *C. albicans* and cytology showed spores and hyphae of *Candida*. The patient had positive skin prick test for *Candida* and elevated IgE level (IgE= 543 IU/mL). Allergic bronchopulmonary candidiasis was diagnosed, the patient received corticosteroids and fluconazole and showed clinical improvement. After 20 days, her symptoms reappeared as she reported poor compliance to her medication. Sputum cultures revealed *A. niger* colonies, one sample yielded both *Aspergillus* and *Candida* colonies. Precipitating antibodies and specific IgG and IgE against *Aspergillus* were present in patient's serum. Diagnosis was revised to mixed allergic bronchopulmonary aspergillosis and candidiasis. The patient received corticosteroids and voriconazole and improved. *Pneumon* 2014, 27(2):152-156.

INTRODUCTION

Allergic bronchopulmonary mycosis (ABPM) is a clinical entity that was first defined in 1952 by Hinson et al¹. Since then, many fungi have been incriminated in the causation of ABPM. *A. fumigatus* is the most described and well studied etiologic agent. Other fungi include *Candida albicans*, *Schizophyllum commune*, *Altenaria*, *Bipolaris*, *Cladosporium*, *Fusarium*, *Penicillium*, *Pseudallescheria*, *Rhizopus* and others. There are a few reports that suggest concurrently more than one fungi with causative role^{2,3}. The diagnostic criteria of Allergic Bronchopulmonary Aspergillosis are commonly used for the identification of ABPM regardless of the presence of one or two fungi. Although new reports of ABPM increasingly appear, light needs to be shed on the underlying conditions that predispose to an immunological response against fungi. Our report aims to contribute to this purpose with a case of certain specificities.

CASE REPORT

A 67 year-old-woman presented to the emergency department because of increasing dyspnea, productive cough with purulent sputum, fever without chills, malaise and tachypnea. The symptoms had an acute onset and started 3 days ago. The patient was a heavy smoker (80 pack/years), but was never diagnosed with asthma or COPD. Her medical history included hypertension, right hip arthroplasty and chronic alcohol consumption. She also reported that she was currently renovating her home.

Physical examination revealed an overweight woman (BMI = 29 kg/m²) with a respiratory rate of 30 per minute, bilateral wheeze all over the chest and crackles at the middle lung fields. Hypoxemia was present with PaO₂= 48 mmHg and PaO₂/FiO₂= 240. Chest radiograph at admission (Figure 1) showed bilateral diffuse opacities and high dense patchy areas. Chest CT (Figures 2a, 2b) showed bilateral diffuse infiltrates mainly centrally and opacities with ground glass characteristics. Leukocytosis was present with 13.63x10³/μL absolute count and 92% neutrophils, 2% eosinophils, elevated CRP and hypoalbuminemia.

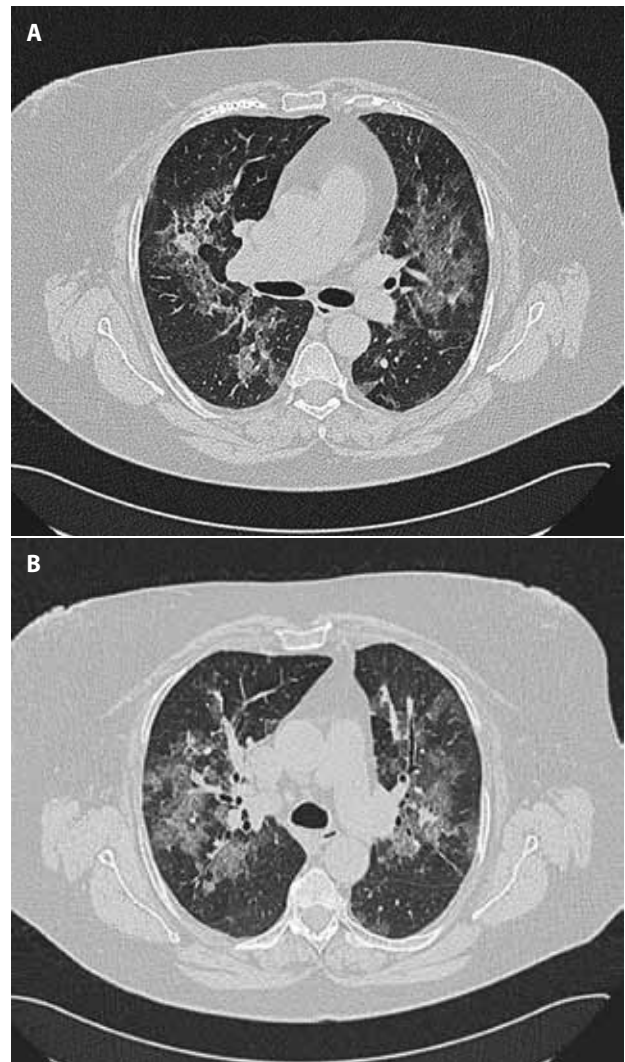
The patient was initially empirically treated with ceftriaxone, azithromycin and oseltamivir and nebulization with salbutamol and budesonide. PCR for Influenza A, B, H1N1, RSV, Adenovirus, Coxsackie, TB, Quantiferon, blood cultures and Grocott stain on sputum cytology were negative.

On the 4th hospital day, the patient reported worsen-



FIGURE 1. Chest X-ray at admission.

ing of her symptoms. ARDS was diagnosed with a PaO₂/FiO₂= 130. Antimicrobial treatment was escalated to meropenem, linezolid and caspofungin and methylprednisolone 1mg/kg/d was added. The patient expectorated thick brownish sputum which was further investigated. Sputum cultures revealed multiple colonies of *Candida albicans*, Gram stain was negative and cytology showed spores and hyphae of *Candida*. A new chest CT revealed expanded opacities and bilateral new infiltrates. Total serum IgE level was elevated (IgE= 543 IU/mL), skin prick test was positive for *Candida albicans*, β-D glucan was positive and serum IgE antibodies for *Aspergillus* were negative (Figures 3, 4a and 4b).



FIGURES 2A and 2B. Chest CT at admission showing bilateral diffuse infiltrates mainly centrally and opacities with ground glass characteristics.

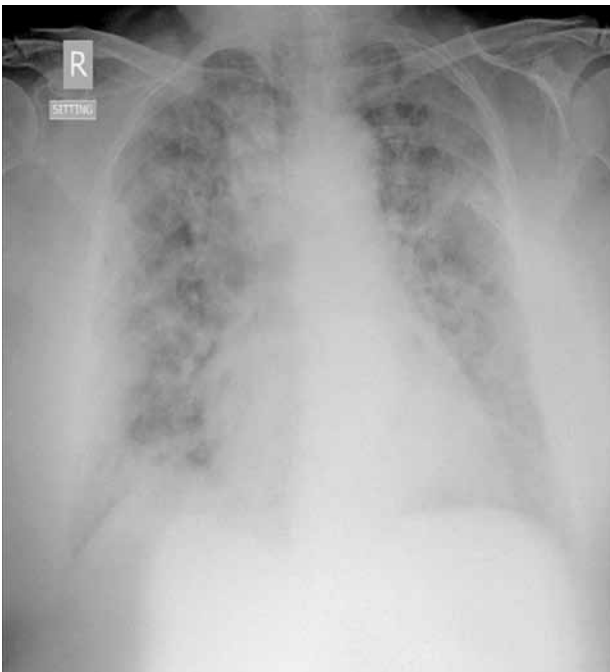


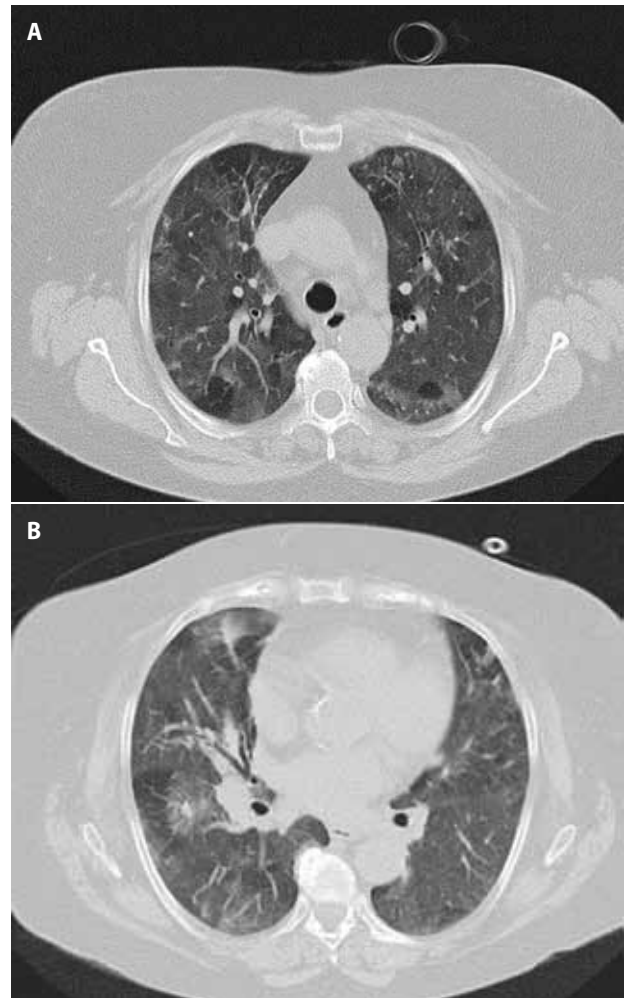
FIGURE 3. Chest X-ray at the 4th day: worsening new infiltrates.

The patient was diagnosed as a case of Allergic Bronchopulmonary Candidiasis and the administration of antifungal and corticosteroid treatment was continued with a view to last for 16 weeks. The patient's cough and dyspnea decreased within one week of treatment. Her total serum IgE levels decreased gradually and she was discharged from the hospital with instructions to continue per os with the regimen of prednisolone 0.5mg/kg daily for the next 6 weeks and fluconazole.

Twenty-days after her hospital discharge, the patient experienced acute worsening of her symptoms. This exacerbation was a result of poor compliance to prescribed medications. She was hospitalized and received corticosteroids iv and caspofungin. The patient's CT demonstrated new bilateral pulmonary infiltrates and ground glass opacities. Chest examination revealed decrease in breath sounds and inspiratory rales over the upper and middle chest bilaterally.

Repeated bacterial and fungal cultures of the thick brownish sputum yielded *Aspergillus niger*, one sputum sample yielded both *Aspergillus spp.* and few colonies of *Candida spp.* (Figure 5).

Total serum IgE was obtained which was raised, specific IgG and IgE against *Aspergillus spp.* revealed high titers and precipitating antibodies to *Aspergillus* were present. The diagnosis was revised to Allergic Bronchopulmonary



FIGURES 4A and 4B. Chest CT at the 9th day: ground glass opacities.



FIGURE 5. *A. niger* white colonies cultured in growth medium.

Aspergillosis and Candidiasis. The patient was discharged with instructions to carry on with prednisolone 0.5 mg/kg daily and voriconazole (Figure 6, Table 1).

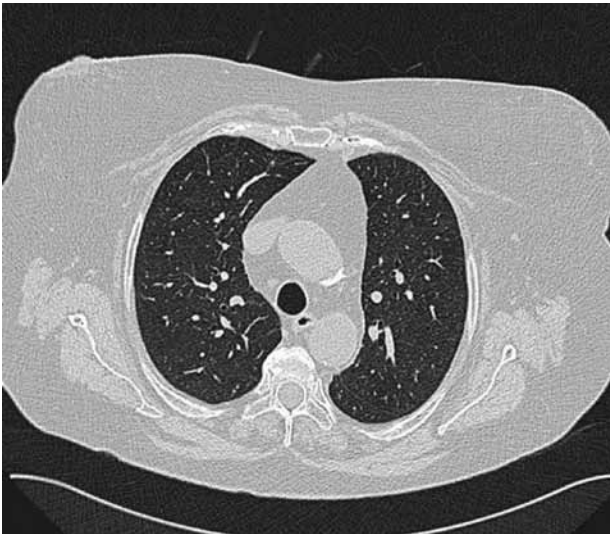


FIGURE 6. Chest CT at patients discharge, showing diminished opacities.

TABLE 1. Decline of IgE values during the first and second hospitalization of the patient.

Total serum IgE	
1st Hospitalization	
Day 8	543 IU/ml
Day 18	311 IU/ml
2nd Hospitalization	
Day 1	295 IU/ml
Day 11	233 IU/ml
Day 31	133 IU/ml

She was monitored for the next 6 months as an out-patient. At this time interval the patient stopped smoking and continued to receive voriconazole and prednisolone with gradual lowering of the dose. No exacerbations or new symptoms were reported and the medications were well tolerated.

DISCUSSION

A recent review estimates that in 9% of all cases, more than one fungi has been implicated in the diagnosis of ABPM⁴. The combination of clinical, radiological and serologic manifestations indicate the diagnosis of ABPM, as only a minority of patients fulfill all the suggested diagnostic criteria^{5,6}.

The presence of immediate cutaneous hyperreactivity of our patient with positive skin prick test suggests

sensitization of the host to the antigen of *C. albicans*. Fungi act as allergens and activate both type I and III hypersensitivity response⁷. Additionally, IgE levels have been high and decreased gradually after the initiation of the therapy regimen. IgE values are taken as a marker of disease activity⁸.

Although ABPA was first described in asthmatics, many cases of ABPM proved in patients with no history of allergic disorders. It is notable that asthma was absent in 70% of ABPM cases in a recent review⁴. Our patient was a heavy smoker who had never manifested any allergic reaction. Heavy smokers have defective mucociliary clearance, probably predisposing the colonization of their bronchial airways, since *C. albicans* presumably enters the lower respiratory tract by direct extension from the oropharynx⁹.

An important implement in the diagnosis of ABPM are central bronchiectasis and transient non-specific opacities that are revealed in consecutive radiological images¹⁰ and represent an inflammatory response in the lung. Central bronchiectasis was not present in our patient's CT examination, which might be attributed to the early immunosuppressing therapy with corticosteroids. ABPM is a disease of diverse histopathological manifestations and it is not uncommon to find exudative or granulomatous bronchiolitis in the peribronchial and pulmonary tissue, that might present with ground glass opacities in CT¹¹.

Our patient experienced acute exacerbation of her symptoms after the discontinuation of her medication. New infiltrates in chest radiology indicated reactivation of the local inflammatory process. The appearance of *A. niger* in serial sputum cultures expanded the diagnosed etiologic fungi stimulus. The described patient was probably exposed to inhaled spores of *A. niger* in her renovating home. *A. niger* is ubiquitous in soil and is commonly reported from indoor environments¹². Her immune system reacted both against the foreign antigenic stimulus of *A. niger* and the colonized spores of *C. albicans* in her bronchi. The presence of cross-reacting antigens and the potential absence of detectable antibody has been described previously in another case report¹³.

Treatment with caspofungin and corticosteroids led to clinical improvement. When discharged from the hospital the patient received fluconazole, with the aim to control and eradicate *C. albicans* colonization in her airways. As a result exposure to fluconazole-resistant *A. niger* was revealed. Additionally, the cessation of her corticosteroid treatment amplified the occasion of a new immune response against fungal antigens.

This case highlights the need to further investigate

possible association between heavy smokers and ABPM. It still remains unclear and we need to elucidate the possible host factors which contribute to ABPM.

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