Eur Respir Rev 2010; 19: 118, 261–263
DOI: 10.1183/09059180.00009010

EDITORIAL

Concurrent allergic bronchopulmonary aspergillosis and aspergilloma: is it a more severe form of the disease?

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The mould *Aspergillus*, a genus of spore forming fungi, affects the respiratory system in more ways than one. The clinical spectrum of *Aspergillus* involvement of the lungs ranges from various hypersensitivity manifestations to invasive disease which can be fatal. The inhaled spores hardly affect healthy persons but in asthmatic subjects these spores are trapped in the viscid secretions found in the airways. Repeated inhalation of *Aspergillus* antigens triggers allergic reactions in atopic individuals, which may manifest as *Aspergillus*-induced asthma, allergic bronchopulmonary aspergillosis (ABPA) and allergic *Aspergillus* sinusitis (AAS) [1]. Saprobic colonisation of airways, cavities and necrotic tissue leads to the development of aspergillomas.

Although ABPA is predominantly a disease of asthmatics, only a few asthmatics actually suffer from it. Contemporary reports suggest that ABPA occurs in up to 11% of patients with asthma [2–6]. The variable prevalence rates of ABPA in asthma may be attributable to the lack of a single diagnostic criterion and standardised tests [7]. A set of eight major and three minor criteria for the diagnosis of ABPA has evolved over time but minimal essential criteria have been identified: 1) asthma; 2) immediate cutaneous reactivity to *A. fumigatus*; 3) total serum immunoglobulin (Ig)E $>1{,}000$ ng·mL^{-1}; 4) elevated specific IgE-*Af*/IgG-*Af*; and 5) central bronchiectasis in the absence of distal bronchiectasis [8].

This 'picturesque' disease causes a wide spectrum of chest radiographic appearances, which could be either transient or permanent [9]. The most characteristic transient changes are ''fleeting opacities'' or transient pulmonary infiltrates while the most pathognomonic permanent feature is the occurrence of central bronchiectasis with normal peripheral bronchi [10]. Cavitation, though not a common feature of ABPA, has been reported in 3–14% of patients [11–13].

Aspergillomas or fungal balls, due to *Aspergillus* species, form in pre-existing cavities and are most commonly found in healed tuberculous cavities [14]. Other cystic and cavitating lung diseases in which aspergilloma formation has been reported include sarcoidosis [15], hydatidosis [16], pneumatocoele caused by *Pneumocystis* pneumonia [17], bronchiectasis, emphysematous bullae, and sites of prior lobectomies or pneumonectomies. The time required for the development of fungal balls ranges from a few months to more than 10 yrs [18].

The clinical categories of *Aspergillus*-related respiratory disorders, for reasons unknown, usually remain mutually exclusive. In spite of similar immunopathological responses, concomitant occurrence of ABPA and AAS is infrequently reported [19–22]. In this issue of the *European Respiratory Review*, MONTANI *et al.* [23] describe a 50-yr-old female with concomitant ABPA and aspergilloma. Even though chronic lung damage appears to provide a favourable milieu for aspergilloma formation, the concomitant occurrence of aspergillomas is rather uncommon in patients with ABPA, even in the presence of cavitation [24, 25].

From 1956 to 1980, JEWKES *et al.* [26] analysed 85 patients with pulmonary aspergilloma and showed that type 1 hypersensitivity to *A. fumigatus* skin testing was positive in 39 (70%) of the 56 patients tested, but symptoms of asthma were present in 22 and pre-existing ABPA was evident in only 10 patients. In a study of 28 patients with pulmonary aspergilloma described by MCCARTHY and PEPYS [27], immediate hypersensitivity to *A. fumigatus* was demonstrated in 21 subjects, 12 of whom had asthma. 10 of these 12 subjects had ABPA. This is the only study that has demonstrated such a high occurrence of ABPA and aspergilloma.

The temporal relationship between ABPA and aspergilloma is not clearly defined. The appearance of aspergilloma prior to or consequent to ABPA has been documented. In six of the 10 patients with ABPA described earlier [27], aspergilloma formation happened many years after the diagnosis of ABPA was established. In the six patients of ABPA with aspergilloma documented by us [20, 24, 25, 28, 29], aspergillomas formed in pre-existing cavities in patients with ABPA. The manifestation of ABPA subsequent to aspergilloma formation has also been recorded [27, 30]. It was postulated that an aspergilloma may function as a nidus for antigenic stimulation in a genetically predisposed individual, thus leading to ABPA [30]. In four of the 10 patients studied by MCCARTHY and PEPYS [27], fungal balls were present a number of years before ABPA could be diagnosed. The authors speculated that these patients could

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Received: Sept 22 2010; Accepted: Sept 27 2010

PROVENANCE: Submitted article, peer reviewed.

possibly have been sensitised to *Aspergillus* antigens released from the aspergilloma.

In a background of cavitary lung disease occurring due to ABPA, formation of an aspergilloma might be accelerated by corticosteroid therapy [24, 28]. All of the 10 patients with ABPA and aspergilloma described by JEWKES *et al.* [26] were treated with corticosteroids and the size of the aspergilloma increased in two patients. It has been postulated that the use of corticosteroids in patients with ABPA with cavitary disease may predispose them to aspergilloma formation and invasive aspergillosis. In two of the six patients with coexistent ABPA and aspergilloma reported by us, evolution of aspergilloma occurred after initiation of corticosteroids [24, 28]. One of them, a 42-yr-old male, developed an ovoid density in the inferior margin of the pre-existing cavity after starting corticosteroid therapy, with which remission was achieved. The patient suffered an exacerbation after 3 yrs in remission state although he had radiological evidence of the fungal ball [31]. The second patient, a 20-yr-old female, developed an aspergilloma 2 yrs after receiving corticosteroid therapy for ABPA [28]. Rapid development of an aspergilloma within a 2-month period was reported in a 47-yr-old female who had cavitary disease for 7 yrs due to tuberculosis. This occurred after she was prescribed corticosteroids for pulmonary–renal syndrome due to systemic vasculitis [32].

The association of ABPA, AAS and aspergilloma in the same patient has been documented only twice to date [20, 29]. The first patient initially developed an aspergilloma in a bronchiectatic cavity, for which she underwent left lower lobectomy in view of severe haemoptysis [20]. The diagnosis of ABPA and AAS was made subsequently when she presented with collapse of the left lung and associated pleural effusion. In our second patient, all the three clinical entities, ABPA, AAS and aspergilloma, were diagnosed concurrently when he presented to us for evaluation of progressive respiratory symptoms [29]. In this patient, the fungal ball was no longer visible on a follow-up computed tomography scan at 3.5 yrs, after maintenance therapy with repeated courses of prednisolone.

Management of coexistent ABPA and aspergilloma could pose a dilemma due to the constant risk of aggravation with corticosteroids. Antifungal agents, especially itraconazole could possibly be offered as an adjunct therapy to oral corticosteroids. A reduction in *Aspergillus* colonisation of the airways in ABPA has been noted with itraconazole. The patient reported in this issue of the *European Respiratory Review* responded well to wedge resection of the aspergilloma and itraconazole post-operatively [23]. A significant reduction in the total IgE level was noted at 5 months and itraconazole was discontinued after 1.5 yrs. The patient continued to remain asymptomatic at 2 yrs. However, itraconazole is yet to emerge as the mainstay of therapy.

When ABPA and aspergilloma ensue together, the severity of the disease is likely to increase. Not only will this cause loss of control of asthma, but also increases the risk of life-threatening complications like haemoptysis and invasive disease. It would be prudent to closely monitor all patients with ABPA with cavitation, when initiated on systemic corticosteroids.

STATEMENT OF INTEREST

None declared.

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