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CASE STUDY

Allergic bronchopulmonary aspergillosis in lung allograft recipients

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Allergic bronchopulmonary aspergillosis in lung allograft recipients. J.J. Egan, N. Yonan, K.B. Carroll, A.K. Deiraniya, A.K. Webb, A.A. Woodcock. ©ERS Journals Ltd 1996.
ABSTRACT: Following lung transplantation for end-stage cystic fibrosis, two male patients presented with shortness of breath, peripheral blood eosinophilia and segmental lung collapse.

At bronchoscopy, each had bronchial mucous plugging containing *Aspergillus fumigatus*. This finding was associated with a systemic eosinophilia and skin test positivity to Aspergillus. Augmented steroid therapy resulted in the successful resolution of the symptoms.

We believe that these are the first reported cases of allergic bronchopulmonary aspergillosis in lung allograft recipients.
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Aspergillus fumigatus (*Asp f*) infection is associated with high morbidity and mortality following lung transplantation [1]. A spectrum of infection has been described ranging from colonization to invasive disease [1], but to date this has not included Aspergillus-induced allergy-mediated pulmonary dysfunction in lung transplant recipients. We describe two cases of allergic bronchopulmonary aspergillosis (ABPA) following lung transplantation for cystic fibrosis (CF). They provide insights into the pathogenesis of allergy-mediated airways disease.

Case Reports

Patient No. 1

A 20 year old, 42 kg male patient received a double sequential lung transplantation for CF. The 15 year old donor had mild asthma requiring salbutamol on a *p.r.n.* basis and had previously been prescribed oral antihistamines for allergic rhinitis. The recipient was atopic with positive skin tests to *Dermatophagoides pteronyssinus*, grass pollen and *Asp f* extracts (8 mm weal, as an immediate type reaction). Prior to transplant, Aspergillus was not isolated from his sputum and he was Aspergillus precipitins negative. Four months following transplantation, the recipient underwent a routine surveillance transbronchial biopsy (TBB) which demonstrated moderate (A3a) rejection. He received 500 mg of methylprednisolone on three consecutive days. Twelve days later, he presented in respiratory failure (arterial oxygen tension (P_{a,O_2}) 4.6 kPa, arterial carbon dioxide tension (P_{a,CO_2}) 4.2 kPa) with collapse of the left lower lobe, which progressed over 24 h to show complete collapse of the left lung (fig. 1). Flexible bronchoscopy (FB) revealed mucous plugging of the left bronchial tree, and histological examination of the plugs revealed eosinophils and fungal hyphae. Bronchial biopsies demonstrated

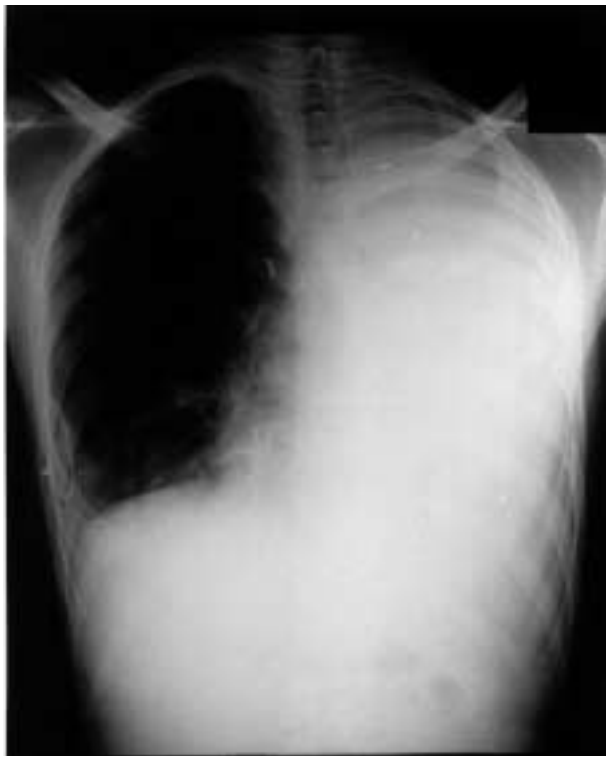

Fig. 1. – The chest radiograph of patient No. 1 (prior to treatment with steroids and ventilatory support) which demonstrates complete collapse of the left lung.

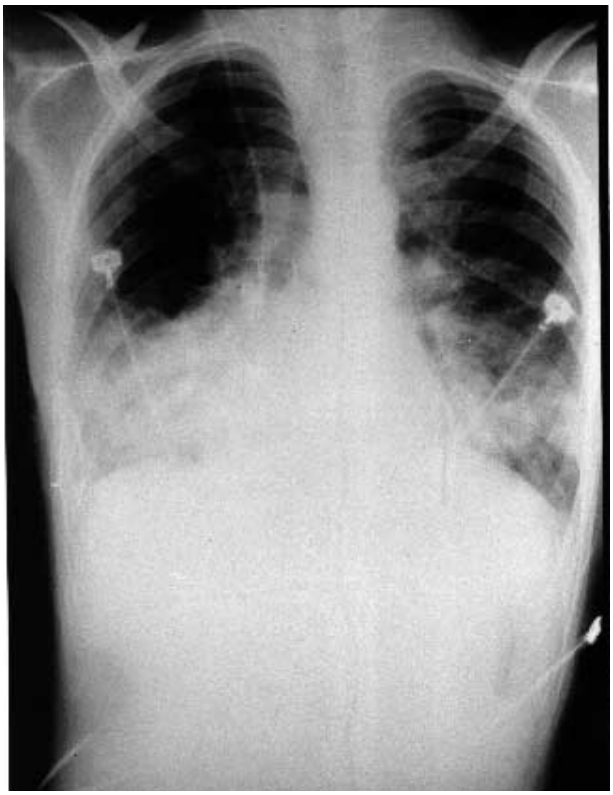

Fig. 2. – The chest radiograph of patient No. 1 (following initiation of treatment with steroids) demonstrating resolution of the changes in the left lung with a new " migratory" infiltrate in the right lower zone.

eosinophilic bronchitis without any indication of invasive Aspergillus. TBB showed an eosinophilic pulmonary interstitial infiltrate but no evidence of eosinophilic pneumonia. The serum total immunoglobin E (IgE) was 1,500 $kU \cdot L^{-1}$ (normal <200 $kU \cdot L^{-1}$), radioallergosorbent test (RAST) to Aspergillus was 55 Phadebas RAST Units (PRU) (normal <0.35 PRU), and *Aspergillus fumigatus* precipitins was positive. The patient required ventilatory support, and was given methylprednisolone 500 mg on 3 days and nebulized budesonide 3 mg daily. This resulted in a rapid improvement of the radiological and bronchoscopic findings and he was extubated after 36 h, but migratory infiltrates were observed radiologically (fig. 2). The patient additionally received liposomal amphotericin (amphotericin encapsulated in liposomes, Zeneca Pharmaceuticals, Cheshire, UK) and itraconazole (Janssen Pharmaceutical Ltd, Oxfordshire, UK) as prophylaxis, but effective control of his respiratory failure required 60 mg prednisolone daily for 7 days followed by 30 mg prednisolone daily. On the reduction of the steroid therapy to 15 $mg \cdot day^{-1}$, persistent airflow obstruction was seen without histological evidence of obliterative bronchiolitis.

Patient No. 2

A 37 year old 53 kg male patient received a heart/lung transplant for CF. The donor was an 18 year old male with no history of atopy or asthma. The recipient was *Aspergillus fumigatus* precipitins negative prior to transplantation and Aspergillus had not been isolated from his sputum. One year after surgery, he was weaned off steroids and maintained on cyclosporin A and azathioprine. Three years following transplantation, he presented with a 25% reduction in forced expiratory volume in one second (FEV_1) (predicted 3.1 L) associated with a cough and wheeze. A peripheral eosinophilia of $2 \times 10^9 \cdot L^{-1}$ (normal $<0.4 \times 10^9 \cdot L^{-1}$) was observed, and skin-prick tests were positive for *Aspergillus fumigatus* (6 mm weal as an immediate type reaction) but negative for all other common allergens. Total IgE was 70 $kU \cdot L^{-1}$ (normal <200 $kU \cdot L^{-1}$), Aspergillus precipitins remained negative but RAST to *Aspergillus fumigatus* was positive at 4 PRU (normal <0.35 PRU). High resolution computed tomography (HRCT) demonstrated areas of collapse and consolidation but no hyperinflation or bronchiectasis. At FB, purulent, thick, tenacious mucous plugs were aspirated with difficulty from the right lower lobe and Aspergillus was cultured from the aspirate. TBB showed a single obliterated bronchiole. Treatment with itraconazole resulted in the pulmonary function initially returning to normal (FEV_1 2.9 L); however, 4 weeks later the patient relapsed with a cough, wheeze and a 30% fall in FEV_1. Repeated FB demonstrated thick tenacious mucus plugs that were sterile on culture and TBB was normal. Treatment with prednisolone and inhaled fluticasone propionate resulted in a continuing remission of symptoms and a further improvement in FEV_1 by 25% from what was considered to be the patients normal baseline FEV_1.

Discussion

Following lung transplantation, a range of Aspergillus-related disease has been described and classified [1]. This has included, aspergillus bronchitis [1], ulcerative tracheobronchitis [1], pseudomembranous bronchitis [1], and bronchocentric granulomatosis [2]. Within the spectrum of Aspergillus disease, in lung allograft recipients we believe this is the first report of ABPA. Neither of our patients had evidence of invasive Aspergillus disease on TBB or bronchial biopsies. Both responded to steroid therapy but, in view of the risk of invasive disease in an immunosuppressed patient, both patients were given specific antifungal therapy as prophylaxis.

There is a high incidence of hypersensitivity to Aspergillus in CF but controversy exists as to its importance [3, 4]. Prior to transplantation, because of the confounding influence of co-existing *Pseudomonas aeruginosa* (*P. aeruginosa*) infection, it is often not clear whether an immune response to Aspergillus in CF patients contributes to the decline in lung function [3]. In the absence of *P. aeruginosa* related pulmonary disease in these transplanted CF patients, the immune response to Aspergillus resulted in pulmonary dysfunction. This supports the suggestion that Aspergillus-induced immune injury is important in nontransplanted CF patients [5], with classic ABPA occurring in up to 10% of CF patients [5], and an additional 13% of patients demonstrating a variant of ABPA characterized by showing a normal IgE level [5].

As neither patient was recognized as having asthma at the time of presentation, it may be considered that these patients did not closely fulfil the recognized criteria

required for the diagnosis of ABPA [6]. In particular, the second case had a normal total IgE in the presence of a negative serum precipitins to, Aspergillus, and neither case had central bronchiectasis. However, we believe the absence of these criteria does not detract from the diagnosis of ABPA in these cases, as both were receiving immunosuppressive therapy which may have modified the natural history of ABPA. Indeed, the first patient was later shown to have airflow obstruction, thus fulfilling all the criteria for the diagnosis of ABPA. In addition, the second case although having a normal IgE in the presence of the other positive criteria (skin test positivity, positive RAST, peripheral eosinophilia, pulmonary collapse) was subsequently seen to have a 25% improvement in his FEV_1 from baseline following the institution of steroid therapy. In view of the normal IgE, it is possible that this second patient represents a variant of ABPA seen in CF patients, which is thought to represent immunoregulatory imbalances preventing the expression of an elevated serum IgE [5].

We are not aware that ABPA has previously been described in immunocompromised patients. A syndrome of bronchial obstructive mucous plugging in association with Aspergillus but without an associated eosinophilia has been described in acquired immune deficiency syndrome (AIDS) patients [7]. Aspergillus hypersensitivity data was not available on these AIDS patients [7]. One might speculate that the AIDS patients were unable to mount an eosinophilic reaction to Aspergillus, suggesting that Aspergillus hypersensitivity can result in a spectrum of clinical pulmonary disease whose expression is determined by an individuals immune status [5].

The clinical expression of ABPA in lung allograft recipients may be dependent on the donors atopic status. This is suggested by the clinical severity of ABPA in patient No. 1, where the donor had mild asthma and the recipient was also atopic. In contrast, in patient No. 2, where the clinical syndrome was mild, the recipient had isolated hypersensitivity to Aspergillus and the donor had no known history of atopic disease. In this latter case, despite treatment with itraconazole alone the patient had recurrence of the mucous plugging. Symptom control was only achieved when itraconazole was used as an adjunctive treatment with steroids [9].

We believe these are the first reported cases of ABPA in lung allograft recipients. These cases suggest that systemic factors are important in the pathogenesis and clinical expression of ABPA and that allergy mediated airflow obstruction is not just a local phenomenon [8].

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