Eur Ann Allergy Clin Immunol Vol 47, N 6, 228-231, 2015

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Eosinophilic Granulomatosis with Polyangiitis preceding allergic bronchopulmonary aspergillosis

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Keywords
Churg Strauss Syndrome, Asthma, Obstructive lung physiology, Allergic Bronchopulmonary Aspergillosis

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Summary
A 61-year-old Chinese man with long-standing, stable Eosinophilic Granulomatosis with Polyangiitis (EGPA) and asthma, presented with acute hypoxemia and declining obstructive pulmonary function. Elevated serum IgE levels, positive Aspergillus fumigatus specific IgE and CT findings of central bronchiectasis with small airway mucoid impaction confirmed new development of Allergic Bronchopulmonary Aspergillosis (ABPA). The maintenance therapy for EGPA, azathioprine, was discontinued. Prednisolone 0.5mg/kg/day and Itraconazole improved his symptoms and IgE levels. To our knowledge, ABPA occurring in a patient with EGPA has not been reported. Differentiation of EGPA with asthmatic flare vs ABPA vs asthma with aspergillus hypersensitivity is discussed. Heightened Th2 immunity where eosinophils play a central role may link these conditions.

Manuscript

Introduction

Eosinophilic Granulomatosis with Polyangiitis (EGPA) is a small-vessel vasculitis which was first described as "allergic granulomatosis and angiitis" in patients with asthma and eosinophilia (1). There exist many overlapping features between EGPA and ABPA. ABPA is an allergic pulmonary disorder characterized by chronic asthma, recurrent pulmonary infiltrates, and bronchiectasis caused by hypersensitivity to *Aspergillus fumigatus*. Coexistence of EGPA and ABPA is extremely rare and to our knowledge, ABPA occurring in a patient with EGPA has not been reported. Differentiation between EGPA, ABPA and asthma exacerbation is crucial in directing subsequent management, as illustrated by our case.

Case Description

A 61-year-old Chinese man with mild intermittent bronchial asthma and rhino-sinusitis since the age of 30 years and chronic hepatitis B, was evaluated eight years ago for hypereosinophilia. He presented with anorexia and weight loss, lethargy and fever. Besides intermittent nasal congestion and post-nasal drip, he had no facial fullness, hyposmia, diplopia or severe headache. He denied any new cough or dyspnea, weakness, numbness, diarrhea or rashes and had not been taking any new medications. Examination was unremarkable, he had no focal neurologic or cutaneous signs, his lungs were clear and there was no organomegaly. Investigations revealed leucocytosis with absolute eosinophil count (AEC) 22.9 x 10^9/L (0.00 - 0.60 x 10^9/L). Work-up ruled out parasitic infection and lymphoproliferative diseases. Bone marrow biopsy showed eosinophilic hyperplasia without clonality. Immunoglobulin E (IgE) were highly elevated at 7610

(0 - 87 IU/mL). Anti-neutrophil cytoplasmic antibody (ANCA) was negative. High Resolution Computed tomography (HRCT) thorax and abdomen and echocardiography were normal. CT sinuses showed mild mucosal thickening of the maxillary and frontal sinuses with good aeration, absence of polyposis or abscess, confirming uncomplicated chronic rhinosinusitis. There were no recent symptoms suggestive of asthma exacerbations and no other organ-systems involvement. He was treated with prednisolone for hypereosinophilic syndrome, concurrent with lamivudine. However, the patient did not return for follow-up visits and stopped taking his medications.

Four years later, he developed skin rash and neuropathies affecting the left common peroneal and right median nerves. His AEC was 14.67 x 10^9/L and erythrocyte sedimentation rate 87 mm/hr. He had palpable purpura mixed with hyperpigmented macules scattered on both lower limbs up to the thighs, as well as some petechial rash on the dorsum of his right hand. Skin biopsy showed fibrinoid necrosis of small vessels with surrounding neutrophils, nuclear dust and extravasated red blood cells, consistent with leucocytoclastic vasculitis (**figure 1**). Anti-proteinase-3 and myeloperoxidase antibodies were negative. Based on the progression of clinical findings, he was diagnosed with EGPA, despite stable asthma and normal chest radiograph. In addition to prednisolone, he received oral cyclophosphamide 50 mg/day for a year for the indication of peripheral neuropathy as an organ-threatening manifestation (2) and steroid sparing effect, he recovered with no residual neurological deficit and treatment was maintained with azathioprine.

A year into his remission of vasculitis, he presented with more frequent symptoms of dyspnea, productive cough and wheezing, from once monthly to weekly. He was started on Formoterol/Budesonide (4.5/160 units) inhaler and theophylline, with prompt improvement. In the following year, however, he developed acute asthmatic exacerbations with hypoxemia. His white cell count was 11.97 x 10^9/L and AEC 0.52 - 1.88 x 10^9/L. Serial pulmonary function tests (**table 1**) showed significant deterioration with obstructive physiology. Lung volume and diffusion capacity remained normal. CT thorax (**figure 2**) showed predominantly upper lobe central bronchiectasis.

Bronchoscopic lavage revealed 8470 nucleated cells with neutrophil predominance. Microbiological investigations were negative. Transbronchial biopsy showed no evidence of infection, granuloma or vasculitis. A skin prick test (SPT) was conducted on the volar aspect of the patient's forearm. Histamine (1 mg/ml) served as positive control, while physiological saline served as negative control (both from Allergopharma®); the SPT was considered to be positive if the wheal diameter was larger than 3 mm. SPT showed a small wheal diameter (< 3mm) to several tested allergens, including *Aspergillus* and *Penicillium* (10000 U/ml, both from Allergopharma®). We therefore proceeded with an intradermal test to *Aspergillus* and *Penicillium* (both intradermal test solutions at 2500 U/ml from Allergopharma®, undiluted), which was positive to *Aspergillus* (6 mm wheal) but negative to *Penicillium* (0 mm wheal). *Aspergillus fumigatus* specific IgE level was raised at 1.85 kU/L. On a clinical diagnosis of Allergic Bronchopulmonary Aspergillosis (ABPA), azathioprine was discontinued and prednisolone was increased to 0.5 mg/kg daily for 3 weeks, with improvement in clinical symptoms and laboratory parameters. Prednisolone was decreased over 5 months based on symptoms, IgE and eosinophil levels, then maintained between 7.5 - 10 mg daily thereafter. Serum IgE levels declined by more than 50%, but remained at high levels (538 - 1889 IU/mL) over the next two years. Itraconazole was subsequently initiated to allow further tapering of prednisolone. CT evidence of bronchiectasis remained largely stable, with decreased mucus plugging.

Figure 1 - *Hematoxylin and eosin (H&E) stained sections showed (**A**) perivascular and interstitial inflammatory cellular infiltrate within the dermis at 10x magnification; and (**B**) neutrophils and nuclear dust (long arrows) and extravasated red blood cells (short arrow) at 40x magnification.*

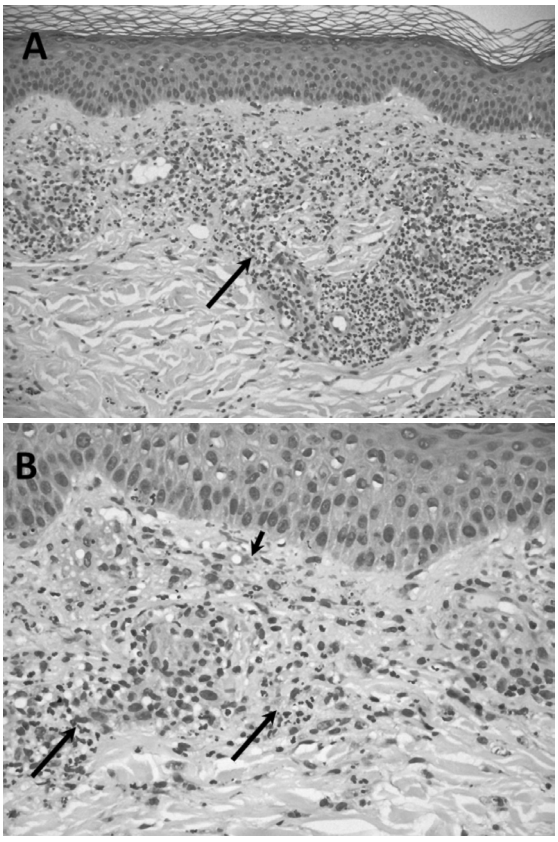
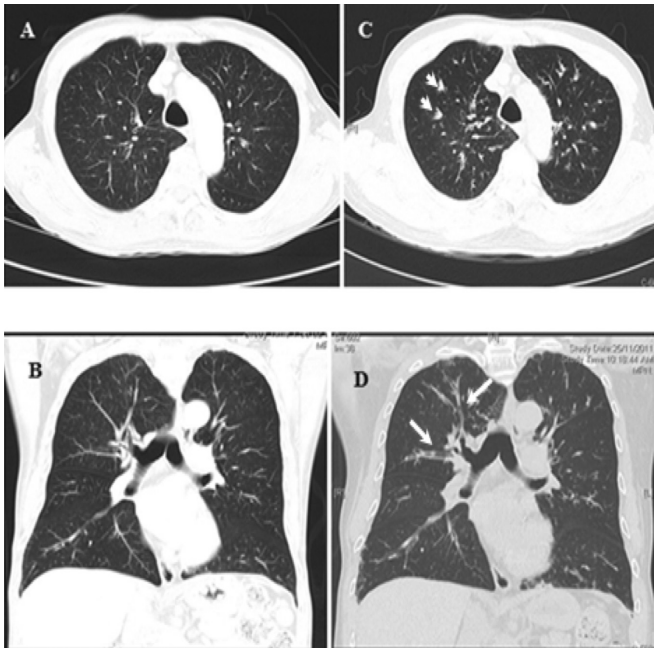


Table 1 - *Results of spirometry at clinical remission of Eosinophilic Granulomatosis with Polyangiitis (EGPA) and at diagnosis of Allergic bronchopulmonary aspergillosis (ABPA).*

	Jan 2011 (EGPA remission)		Dec 2011 (ABPA diagnosis)	
	Pre-Bronchodilator	**Post-Bronchodilator**	**Pre-Bronchodilator**	**Post-Bronchodilator**
FVC (L) (% of predicted)	2.85 (102%)	3.11 (111%)	2.52 (91%)	2.35 (85%)
FEV1 (L) (% of predicted)	1.34 (64%)	1.70 (81%)	0.83 (40%)	0.83 (40%)
FEV1/FVC	47	55	33	35

FVC: Forced vital capacity; FEV1: Forced expiratory volume in one second.

Figure 2 - *Computed tomography of the lung with high resolution cuts showing normal lung fields (**A** and **B**) compared with lung parenchymal changes after two years (**C** and **D**). There is interval development of predominantly central bronchiectasis (long arrows), with evidence of small airway mucoid impaction (short arrows), consistent with a diagnosis of allergic bronchopulmonary aspergillosis.*



Discussion

This patient has EGPA but developed ABPA many years later. A diagnostic concern in a patient with sensitization to *Aspergillus* is whether a proportion of asthmatic patients merely have asymptomatic *Aspergillus* sensitization rather than true ABPA, which can be difficult to differentiate from each other. Patients with sensitization only typically have a positive SPT to *Aspergillus* antigens without other accompanying laboratory indices associated with ABPA, specifically excessively elevated serum IgE levels (> 1000 IU/mL) and a positive *Aspergillus* specific antibody (> 0.35 kUA) (3). Sensitization to recombinant *Asp f 4* and *Asp f 6* allergens are more specific for the diagnosis of ABPA (4); however, these tests are not readily available in our center.

Arguably, chronic persistent asthma symptoms (with or without EGPA) may have led to airway remodelling in our patient, with irreversible obstructive physiology and even central bronchiectasis. However, the dramatic fall in FEV1 with radiologic evolution of bronchiectasis over one year, together with serological evidence of significant immuno-reactivity to *Aspergillus fumigatus*, favours a diagnosis of ABPA over Aspergillus hypersensitivity (AH) with chronic asthma. By the Rosenberg-Patterson criteria, our patient fulfils 6 out of 8 major criteria, namely asthma, positive intradermal test (type 1), elevated serum IgE, elevated serum *Aspergillus*-specific IgE, hyper-eosinophilia and central bronchiectasis.

EGPA has recently replaced the eponym Churg Strauss Syndrome (CSS) (5). The patient's background diagnosis was consistent with EGPA despite the patient's normal CXR and stable asthma, because it is well-recognized that one-third of patients may have normal chest radiographs and attenuation of asthma during the vasculitic phase (6,7). Although the characteristic granulomatous reaction associated with eosinophilic infiltration of tissues was absent in our patient, the cutaneous and subcutaneous lesions in EGPA often lack diagnostic specificity, with biopsies revealing only nonspecific inflammatory features of leukocytoclastic vasculitis (7,8). At least two other cases of ABPA and EGPA have been reported (9,10). A 67 year-old woman with intermittent wheeze with histological diagnosis of ABPA developed EGPA 17 years later (10). Another woman with long-standing bronchiectasis and asthma who was first diagnosed with anti-MPO positive EGPA with peripheral neuropathy was found to have ABPA during the same hospitalization

(9). The authors concluded that radiographic evidence of ABPA was present seven years prior (9). This patient responded to systemic glucocorticoid but was given itraconazole subsequently. ANCA became negative after 2 weeks (9). Other fungi, including *C. albicans* (11) and *Fusarium* (12) may produce clinical presentations similar to ABPA and have been reported to predate the onset of EGPA. To our knowledge, our case may be the first of EGPA antecedent to ABPA.

EGPA and ABPA share many common features, such as asthma, rhinosinus involvement, eosinophilia, raised IgE levels and radiographic evidence of pulmonary involvement. An antigenic stimulus drives the Th2 immunity (driven by interleukin (IL)-5, IL-4 and IL-13), leading to increased production and activation of eosinophils (7,13) in EGPA. However, the extrapulmonary manifestations as well as the additional mechanisms, which trigger leucocyte infiltration into vessel walls and tissues to cause systemic vasculitis are not found in ABPA. In our patient, it is possible that fungal sensitization occurred during the period of more intense immunosuppression, which may have masked the manifestations of ABPA until the steroid doses were tapered. On the other hand, Aspergillus colonization as the etiologic factor of EGPA may be hypothesized. However, a study showed that a minority of EGPA was linked to specific allergic responses to common allergens and even then, *Aspergillus* was not one of the identified allergens (14), suggesting that *Aspergillus* exposure is an unlikely trigger of EGPA.

Our case report highlights that a change in asthma control in a patient with EGPA may not merely be attributable to a flare of asthma or pulmonary vasculitis. Once remission of the systemic vasculitic phase of EGPA is achieved with treatment, asthma exacerbation constitutes the majority (70%) of first flares in a large prospective cohort (2). Therefore, other etiologies for asthma may sometimes be overlooked. Due to the significant immunosuppressive burden inherent to the treatment of vasculitis, physicians treating EGPA must be cognizant of possible intercurrent infective processes.

Long term oral glucocorticoid therapy is often required for ABPA and its dose and duration is guided by IgE levels. As long term glucocorticoid use is associated with significant side effects, itraconazole or voriconazole may be used in steroid dependent cases to reduce fungal burden. Biologics such as anti-IgE (omalizumab) and anti-IL5 (mepolizumab) may have a role in the future management of refractory cases of ABPA, but their use is best reserved for exceptional cases (13,15).

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