

CASE REPORT

Chronic pulmonary aspergillosis may cause eosinophilic granulomatosis with polyangiitis via allergic bronchopulmonary aspergillosis

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Abstract

An 84-year-old man visited our hospital with a prolonged productive cough. Chest computed tomography showed a thick wall cavity and bilateral consolidations. Laboratory findings revealed peripheral blood eosinophilia, increased total IgE and elevated myeloperoxidase anti-neutrophil cytoplasmic antibody. Specific IgE and IgG antibodies and an immediate skin reaction against *Aspergillus* showed positive results. The histological findings of the lung parenchyma were compatible with eosinophilic pneumonia and bronchial biopsy showed eosinophilic vasculitis. Bronchoalveolar lavage fluid culture yielded *Aspergillus fumigatus*. These results met the diagnosis criteria for both allergic bronchopulmonary aspergillosis (ABPA) and eosinophilic granulomatosis with polyangiitis (EGPA). This case thus suggests that *A. fumigatus* might be a pathogen common to both diseases, and prolonged exposure to *A. fumigatus* in some patients with ABPA may promote progression to EGPA.

INTRODUCTION

Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic disorder, related to eosinophilic necrotizing vasculitis, while allergic bronchopulmonary aspergillosis (ABPA) is an allergic disease involving hyper-reactivity to *Aspergillus*. Several diagnostic criteria are common to both diseases. Although several immune mechanisms have been reported, the precise pathogenesis of EGPA remains unclear [1, 2], and there have been few reports of the coexistence of ABPA and EGPA. Here, we present a patient who simultaneously met the diagnostic criteria for both eosinophilic vasculitis and ABPA.

CASE REPORT

An 84-year-old man visited our hospital with a 2-month history of productive cough and an abnormal chest X-ray. A lung computed tomography (CT) scan revealed a thick wall cavity in his left upper lung and diffuse consolidation in bilateral lungs (Fig. 1). He had been a smoker for many years. He was a former smoker but did not have a drinking habit or history of allergies. There was no other relevant social or family history, except for lung tuberculosis 7 years ago. His general condition was stable throughout his clinical course. A systemic physical examination was normal, except for bilateral coarse crackles.

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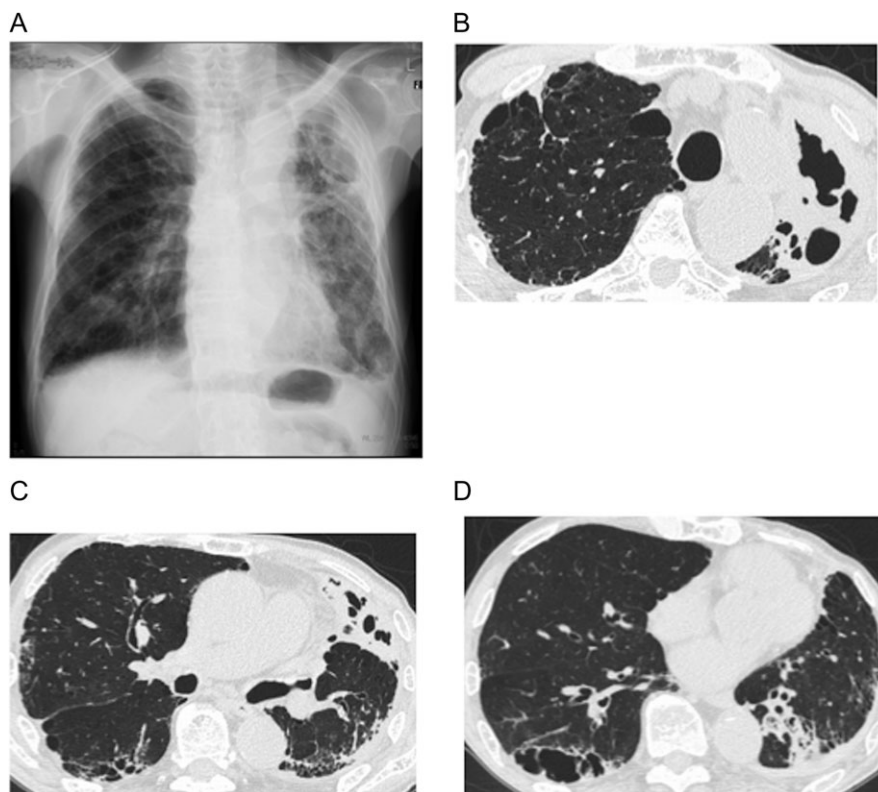


Figure 1: Chest radiogram (A). Thorax CT showing upper (B), middle (C) and lower (D) lobes.

Eosinophil cell counts (15.4%, 1401 cells/ μ l), C-reactive protein, and serum immunoglobulin (Ig) E (1510 IU/ml) and IgG (2494 mg/dl) were elevated. He was positive for specific IgE and IgG against *Aspergillus fumigatus*, anti-nuclear antibody ($\times 40$), rheumatoid factor (21 IU/ml), and myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) (14.0 IU/ml). There were no other specific antibodies related to collagen vascular disease or various anti-fungal antigens detected, and the beta-D glucan value was within normal range. Culture of bacteria and acid-fast bacilli from blood and sputum were all negative.

Rhinoscopy revealed a nasal polyp and CT of the paranasal sinus showed sinusitis (Fig. 2). Exhaled nitric oxide was elevated to 61 ppb (normal range: 15–37 ppb). Although airway hypersensitivity examination was normal, respiratory tract reversibility was shown. Precipitation antibody and scratch skin tests against *A. fumigatus* were also positive. These results suggested either ABPA or EGPA, and we therefore performed a bronchoscopy. Bronchoalveolar lavage fluid (BALF) revealed 37.3% eosinophils with an increased total cell count of 3.4×10^5 /ml. Grocott staining of a BALF smear showed a few fragments of fungal hyphae, and *A. fumigatus* was isolated from the BALF (Fig. 3). Histological examination of a transbronchial lung biopsy showed thickening of the alveolar septa due to mononuclear cell infiltration with eosinophils. The elevated FENO, bronchial hyper-reversibility test results, and this histological finding suggested bronchial asthma. A bronchial mucosal lesion of the second carina also showed eosinophilic inflammation accompanied by eosinophilic capillaritis (Fig. 4). The gastric mucosa was also infiltrated with eosinophils. According to these findings, our patient was diagnosed with EGPA with ABPA based on the ACR 1990 criteria for EGPA and Rosenberg's

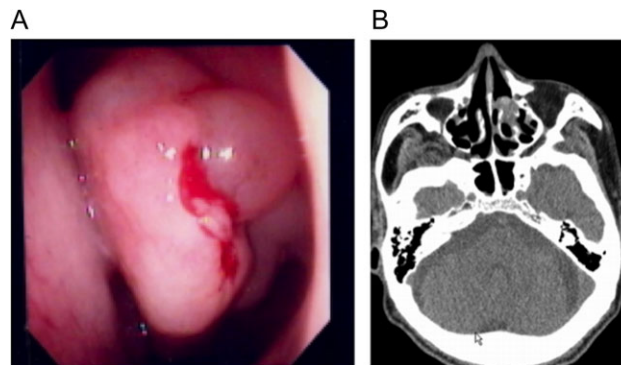


Figure 2: Nasal polyp in the upper airway (A). CT of the ethmoid sinus level (B)

criteria for ABPA. He was treated with itraconazole (200 mg/day) and steroids (prednisolone 0.5 mg/kg/day), with improvement of his symptoms and chest CT findings, and the beta-D glucan value was not increased. Predonisolone was gradually tapered to 15 mg and he remained well.

DISCUSSION

This case represents a rare example of a patient with simultaneous EGPA and ABPA. While ABPA is known to be a disease limited to the respiratory tract, EGPA is a systemic eosinophilic disease with vasculitis. However, these diseases share several diagnostic criteria, including asthma, peripheral blood eosinophilia, eosinophilic pneumonia and elevated serum IgE, suggesting that some antigens contribute to the development of

both diseases. A few previous studies have reported on the immunological networks related to *Aspergillus* [1, 2].

There have been three previous cases of co-existing EGPA and ABPA [3-5], and allergic bronchopulmonary candidiasis has also been reported to co-exist with EGPA [6] (Table 1). In two of these three cases, ABPA was diagnosed prior to EGPA, though the interval varied. Ren et al. reported a patient with ABPA whose radiographic condition had worsened 7 years later, with eosinophilia, paranasal sinusitis, peripheral neuropathy, and positive MPO-ANCA [3], and who was subsequently diagnosed with EGPA. Stephanes et al. reported a patient who developed EGPA 17 years after the diagnosis of ABPA [4]. Although ABPA only occurs in the respiratory tract, prolonged exposure to *Aspergillus* or long duration of ABPA might lead to systemic lesions. In contrast, Lee et al reported a case of EGPA diagnosed 4 years before ABPA [5]. In this case, EGPA was treated with steroids and oral cyclophosphamide, which might have suppressed the ABPA (Table 1). ABPA and EGPA were diagnosed concomitantly in the current case, but it was unclear which

came first because the patient had no further medical check-ups. He had tuberculosis 7 years previously, and there was a thick wall cavity in his left upper lung. Because *Aspergillus* species can usually colonize this location easily, *Aspergillus* might have been colonized there for a long time; if so, ABPA could have occurred earlier than EGPA in our case, as in previous cases [3, 4].

Eosinophils induce tissue damage because they include granules containing cationic proteins, cytokines, growth factors and enzymes [7]. If released into the vessel wall or perivascular tissues, these proteins may cause eosinophilic vasculitis [8], fibrogenesis, thrombosis and allergic inflammation [7], promoting systemic progression of the disease from the respiratory tract. We therefore speculate that continuous exposure to *A. fumigatus* may have played a role in the common aetiology of both ABPA and EGPA in our case. There are two established theories regarding the coexistence of ABPA and EGPA. One holds that the ABPA precedes the EGPA [3, 4, 6, 9]. In this case, *Aspergillus* that has been colonized within the airway or cavity for a long time leads to the eosinophilia that is a common pathogenesis of ABPA and EGPA. The other theory claims that the EGPA precedes the ABPA [5, 9]. In this case, under the compromised condition created by treatment for EGPA, *Aspergillus* are easily able to colonize on the airway with type-1 allergy.

Eosinophils differentiate from the bone marrow through interleukin (IL)-5 mediation induced from long-lived type 2 innate lymphoid cells (ILC2) [10]. IL-5 also supports a complicated network of eosinophil proliferation via various chemokines and soluble mediators [7]. The current patient demonstrated not only *Aspergillus* infection, but also allergic reactions. He had been infected with *A. fumigatus* for a prolonged period, leading to eosinophilic vasculitis via an activated Th2 reaction. All previously reported cases had a previous lung disease (Table 1), such that the fungus could attach to the respiratory tract easily and promote the development of cytokine networks. Although we

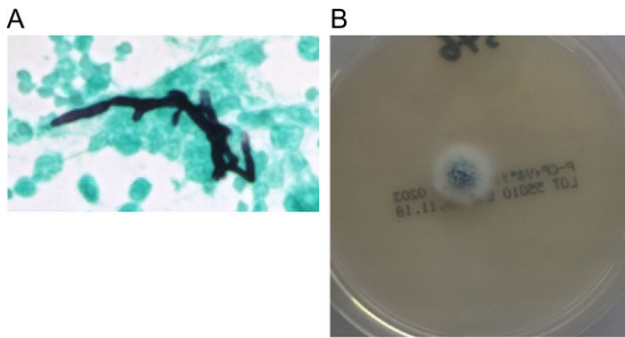


Figure 3: Grocott stain (A) and fungus culture (potato dextrose agar with chloramphenicol) (B) of BALF.

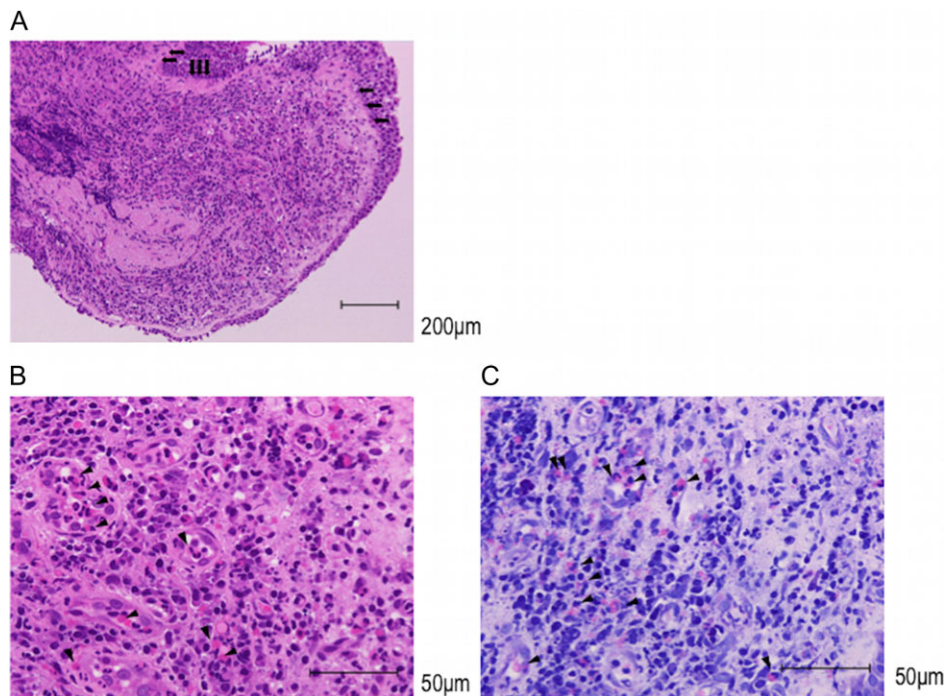


Figure 4: Airway mucosal biopsy on secondary carina, Hematoxylin-Eosin (HE) stain at low power (bar = 200 μm) (A) and high power (bar = 50 μm) (B) and Giemsa stain at high power (bar = 50 μm) (C). Arrow indicates subepithelial basement membrane, and arrow head indicates eosinophils.

Table 1: Clinical appearances of previous and current cases

Case reports	Ren [3]	Stephens et al. [4]	Lee et al. [5]	This case
Age/sex	41/F	67/F	61/M	84/M
Former-lung disease	+	+	+	+
IgE RIST (mg/dl)	1326	≥1000	≥1889	1510
Eos(/mm ³)	1633	21797	1880	1401
ANCA	+	NA	–	+
Disease organ	L, N, SD	L, M, S, C, K	L	L, G, SD
Length to EGPA (years)	7	20	–4	≤1
Treatment	GS, AZA, ITCZ	GS	GS, ITCZ	ITCZ, GS
Prognosis	Alive	Alive	Alive	Alive

AZA, azathioprine; C, cardiovascular system; G, gastrointestinal tract; GS, glucocorticosterone; ITCZ, itraconazole; K, kidney; L, lung; M, muscle; N, nervous system; NA, not available; S, skin; SD, sinus disease.

could not measure the key cytokines such as IL-5, ILC2, and IL-25 in this patient, it is still possible that his course may have involved complex immune networks. In most reported cases, the diagnosis of ABPA preceded the development of EGPA [3, 4, 6, 9]. The possibility that treatments for ABPA mask the symptoms or laboratory findings of EGPA poses an important problem because it can lead to delays in EGPA diagnosis and treatment. It is very important to consider the existence of ABPA or EGPA.

These results suggest that prolonged *Aspergillus* exposure may trigger ABPA and EGPA, while an aberrant Th2 reaction may lead to systemic eosinophilia and eosinophilic vasculitis. Although the pathogenesis of EGPA is complicated, ABPA and EGPA share several immune cascades, which might help to inform the choice of EGPA therapy. Previous lung deformities may also promote the development of eosinophil-related immune networks by *Aspergillus* infections.

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CONFLICT OF INTEREST STATEMENT

None declared.

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ETHICAL APPROVAL

Not required as the events described were part of routine patient care

CONSENT

Written consent from the patient has been uploaded.

GUARANTOR

Shiro Imokawa is a guarantor of this study.

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