Combined Allergic Bronchopulmonary Aspergillosis and Eosinophilic Granulomatosis with Polyangiitis: Three Cases and a Review of the Literature

Takashi Ishiguro, Noboru Takayanagi, Yotaro Takaku, Naho Kagiyama, Kazuyoshi Kurashima and Yutaka Sugita

Abstract

Previous reports of combined allergic bronchopulmonary mycosis (ABPM) and eosinophilic granulomatosis with polyangiitis (EGPA) are limited; however, among 41 cases of ABPM and 18 cases of EGPA treated at our hospital, we experienced three cases of combined ABPM and EGPA. In two of these cases, the diagnosis of EGPA preceded that of ABPM, however, one of the two cases had already shown findings suggestive of ABPM, such as mucous plugs and central bronchiectasis, at the time of the diagnosis of EGPA. In six previously reported cases of combined ABPM and EGPA, ABPM preceded EGPA in four cases. In the other two cases in which EGPA was diagnosed before or simultaneously with ABPM, findings suggestive of ABPM had been detected when EGPA was diagnosed, which suggests that sensitization to fungi resulting in ABPM may play an important role in the development of EGPA. Careful attention should therefore be paid to the possibility that these diseases may coexist during the course of either disease.

Key words: allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome, Wegener’s granulomatosis, antineutrophil cytoplasmic antibody, vasculitis


Introduction

Allergic bronchopulmonary mycosis (ABPM), an immunologic disorder caused by a hyperimmune response to the endobronchial growth of certain fungi, occurs most commonly in atopic patients with asthma. Aspergillus spp. are regarded as the most common causative organism. Allergic bronchopulmonary aspergillosis (ABPA) is characterized by asthma, eosinophilia, and bronchopulmonary lesions with bronchiectasis.

In contrast, eosinophilic granulomatosis with polyangiitis (EGPA), formerly reported as Churg-Strauss syndrome, is a small-vessel vasculitis defined as an eosinophil-rich and granulomatous inflammation involving the respiratory tract and associated with asthma and eosinophilia. EGPA is included in the group of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), which also include microscopic polyangiitis and granulomatosis with polyangiitis (GPA, formerly reported as Wegener’s granulomatosis). Although both ABPM and EGPA are included in the category of eosinophilic lung diseases (1), to the best of our knowledge, only six cases of combined ABPM and EGPA have been reported (2-7), whereas we have experienced 3 cases of combined ABPA and EGPA up to March 2015. We herein report our 3 cases and review the pertinent literature associated with ABPM and EGPA.

Case Reports

We experienced 41 cases of ABPM and 18 cases of EGPA without cystic fibrosis from 1998 through 2014. Among them, 3 cases were of combined ABPA and EGPA (7.3% with ABPM and 16.7% with EGPA).
Case 1

A 47-year-old man with an initial presentation in February 1999.

The patient was diagnosed with bronchial asthma at 18 years of age. In February 1999, (47 years of age), he suffered a low-grade fever, and abnormal shadows were detected on a chest X-ray by a local physician, who referred him to our hospital. He had numbness of the extremities (polyneuropathy), and laboratory data showed an increased white blood cell (WBC) count of 11,700/mm$^3$ (eosinophils, 4,400/mm$^3$) and IgE of 1,115 IU/mL, however, Aspergillus-specific IgG antibody measured by the complement fixation method (8) and perinuclear (P)-ANCA were negative. Skin tests for Aspergillus antigen were positive for both the immediate and delayed types. Chest computed tomography did not show central bronchiectasis, however, structures suggestive of mucous plugs were observed (Figure a). Bronchoscopy revealed mucous plugs, and histology of the mucous plugs showed a picture of allergic mucin, but fungal hyphae were not detected. Bronchoalveolar lavage fluid testing showed an increased fraction of eosinophils (98%), and histology obtained via a transbronchial lung biopsy showed eosinophilic pneumonia without vasculitis. Sputum culture yielded no significant pathogens including fungi. We diagnosed the patient with chronic eosinophilic pneumonia, and prednisolone (PSL) 40 mg/day was administered, which improved his symptoms, the laboratory data, and radiologic findings. In November 2005 (53 years of age; PSL dose, 2.5 mg/day), the patient developed eosinophilic cardiomyositis, diagnosed by a myocardial biopsy, and congestive heart failure with a peripheral eosinophilia count of 600/mm$^3$. Implantation of a heart pacemaker was required for his arrhythmia. We retrospectively diagnosed the patient with EGPA according to the symptoms of asthma, polyneuropathy, eosinophilia, and pulmonary infiltration at the initial presentation in addition to cardiomyositis (9, 10). The PSL dose was increased to 30 mg/day and then tapered. Sputum culture at this time yielded A. niger, and his Aspergillus-specific IgG antibody was positive, at which point we diagnosed him with ABPA. As of March 2015, the patient is alive and continues to be followed.

Case 2

A 45-year-old woman with initial presentation in November 2001.

The patient was diagnosed with asthma in December 1999 (41 years of age) and was treated with inhaled steroid therapy. Dyspnea and rales worsened in September 2001 (45 years of age), and she presented to our hospital in November 2001. Chest computed tomography showed bronchial wall thickening, and structures suggestive of mucous plugs were observed (Figure b). P-ANCA was negative, and systemic corticosteroid therapy was started combined with montelukast and an inhaled β2 stimulator. In December 2003 (47 years of age), the patient developed a fever and erup-
tologic findings of the mucous plugs showing allergic mucous plugs. Bronchoscopy revealed mucous plugs, with the histologic findings of the mucous plugs showing allergic mucous plugs, but no fungal hyphae were detected. Aspergillus fumigatus was repeatedly isolated from his sputum, but no fungal hyphae were detected. S. aureus was repeatedly isolated from his sputum, but no fungal hyphae were detected. Laboratory tests showed increased eosinophil counts of 1,000/mm³ and serum IgE, however, both Aspergillus-specific IgE and IgG antibodies measured by the complement fixation method (8) were negative. In February 2008 (58 years of age), we performed bronchoscopy, and A. fumigatus was isolated from the bronchial washings. Aspergillus-specific IgE and IgG antibodies turned positive, and we diagnosed him as having ABPA (10). P-ANCA was negative. PSL 30 mg/day was started and then tapered. In March 2014 (64 years of age; PSL 5 mg/day), he developed a fever, myalgia, and difficulty in hearing and presented to another hospital. Sinusitis and otitis media, which showed characteristic findings of AAV (11), were present, although a histologic examination was not performed. The patient then presented to our hospital, where MPO-ANCA turned positive, and EGPA developed 6 years after the diagnosis of ABPM.

Case 3

A 47-year-old man with initial presentation in July 1997. The patient was diagnosed as having asthma at 15 years of age. In July 1997 (47 years of age), chest abnormal shadows were found on a medical examination, and he presented to our hospital. Chest computed tomography showed structures suggestive of mucous plugs and central bronchiectasis (Figure c). From August 2000 (50 years of age), Staphylococcus aureus was repeatedly isolated from his sputum, but no fungi were isolated. Laboratory tests showed increased eosinophil counts of 1,000/mm³ and serum IgE, however, both Aspergillus-specific IgE and IgG antibodies measured by the complement fixation method (8) were negative. In February 2008 (58 years of age), we performed bronchoscopy, and A. fumigatus was isolated from the bronchial washings. Aspergillus-specific IgE and IgG antibodies turned positive, and we diagnosed him as having ABPA (10). P-ANCA was negative. PSL 30 mg/day was started and then tapered. In March 2014 (64 years of age; PSL 5 mg/day), he developed a fever, myalgia, and difficulty in hearing and presented to another hospital. Sinusitis and otitis media, which showed characteristic findings of AAV (11), were present, although a histologic examination was not performed. The patient then presented to our hospital, where MPO-ANCA turned positive, and EGPA developed 6 years after the diagnosis of ABPM.

Discussion

We experienced 3 cases of combined ABPM and EGPA. Case 3 developed sinusitis and otitis media, and S. aureus, which was related to the development and relapse of GPA (13), was repeatedly isolated. It was challenging to determine whether the patient had EGPA or GPA, but because he satisfied 4 of the classification criteria of EGPA, he was thus classified as having EGPA based on a previously established algorithm (9).

A review of the previously reported cases of combined ABPM and EGPA (2-7), including our 3 cases, is shown in Table. Among these 9 cases, causative fungi included Aspergillus spp. in 6, Candida spp. in 3, and Fusarium vasinfectum in 1 patient.

No clear causes of EGPA have been established, however, there are reports suggesting drugs, especially macrolides, vaccines, and fungal antigen (14), as a causal factor. Mechanisms for producing ANCA, which plays an important role in AAV, remain unknown, however, abnormal conformation

Table. Cases Previously Reported in the Literature and in the Present Report.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/Sex</th>
<th>Causative fungi of ABPM</th>
<th>Order of diagnosis</th>
<th>Comments on timing of diagnosis of ABPM and EGPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>61/male</td>
<td>Candida albicans</td>
<td>ABPM→EGPA</td>
<td>EGPA developed 15 months after diagnosis of ABPM.</td>
</tr>
<tr>
<td>3</td>
<td>41/female</td>
<td>Aspergillus fumigatus</td>
<td>EGPA→ABPM</td>
<td>ABPM and EGPA were diagnosed simultaneously, but central bronchiectasis had been already detected before. The patient developed mononeuritis multiplex a few months before the diagnosis of ABPM was made, but central bronchiectasis was also detected.</td>
</tr>
<tr>
<td>4</td>
<td>46/male</td>
<td>Fusarium vasinfectum</td>
<td>ABPM→EGPA</td>
<td>ABM was diagnosed based on histological findings 17 years before developing EGPA.</td>
</tr>
<tr>
<td>5</td>
<td>67/female</td>
<td>Aspergillus fumigatus</td>
<td>ABPM→EGPA</td>
<td>Pulmonary consolidation suggesting a pulmonary lesion of ABPM had been already detected 5 years before developing EGPA. Diagnosis of EGPA preceded the diagnosis of ABPM, but mucous plugs suggesting ABPM had been already detected 3 years before developing EGPA.</td>
</tr>
<tr>
<td>6</td>
<td>64/female</td>
<td>Aspergillus sp. and Candida sp.</td>
<td>ABPM→EGPA</td>
<td>Diagnosis of EGPA preceded the diagnosis of ABPM. Eosinophilic pneumonia with polyneuropathy and mucous plugs had been already detected 6 years before diagnosing EGPA.</td>
</tr>
<tr>
<td>7</td>
<td>56/female</td>
<td>Candida albicans</td>
<td>EGPA→ABPM</td>
<td>EGPA developed 6 years after the diagnosis of ABPM.</td>
</tr>
</tbody>
</table>

ABPM: allergic bronchopulmonary mycosis, ABPM→EGPA: ABPM diagnosed before EGPA, EGPA: eosinophilic granulomatosis with polyangiitis, EGPA = ABPM: EGPA diagnosed simultaneously with ABPM, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody
and degradation of neutrophil extracellular traps, which have antibacterial and antifungal functions, are included in the production of MPO-ANCA (15, 16). Among the 9 cases with combined ABPM and EGPA, the diagnosis of ABPM preceded the development of EGPA in 5 cases. In the other 3 cases, except for our Case 1, the diagnosis of EGPA preceded the diagnosis of ABPM or the diagnosis of EGPA was established simultaneously with ABPM, however, mucous plugs and/or central bronchiectasis suggestive of ABPM had already been detected before these patients developed EGPA. These results imply that findings suggestive of ABPM had already been found in most patients with combined ABPM and EGPA and further suggest the involvement of chronic exposure to fungal antigen and immune complex in the mechanisms of the development of EGPA in patients with underlying ABPM. However, in our Case 1, eosinophilic pneumonia with polyneuropathy was a presenting feature, which suggests that EGPA preceded ABPM (17). Although the detailed mechanisms remain unknown, whether patients with EGPA have hypersensitivity to fungi and are more subject to ABPM than normal controls should be investigated in future studies.

From 1998 through 2014, 41 patients were diagnosed as having ABPM and treated at our hospital, and ABPM coexisted with EGPA in 3 (7.3%) of these patients. The prevalence of EGPA in Japan is 17.8/1,000,000 in the general population and 1/5,000 in patients with asthma (18). Although the reported prevalence of ABPA without cystic fibrosis is as high as 1 to 3% (19, 20) of patients with persistent asthma, ABPM combined with EGPA was present in 16.7% of the EGPA patients in our hospital. Previous reports of patients with combined ABPM and EGPA are limited, however, the prevalence of EGPA in patients with ABPM and that of ABPM in patients with EGPA does not appear to be uncommon.

It is problematic that patients with EGPA are occasionally functionally handicapped due to the sequelae (21) and prognosis of this disease. ABPM also causes irreversible structural destruction in the lung, suggesting the necessity for early diagnosis and treatment. However, previous use of corticosteroids for predisposing asthma, or predisposing ABPM or EGPA, may delay the manifestation of symptoms and laboratory findings characteristic of ABPM or EGPA (11, 22). In addition, ANCA is present in nearly 40% of the patients with EGPA. In ABPA, sputum cultures for Aspergillus spp. are often negative (10), and Aspergillus-specific IgG occasionally turns positive several years after the development of the characteristic pathological mucous plugs seen with ABPA (23), suggesting that the diagnostic criteria are not necessarily complete for the early stage of ABPA. Careful investigation and follow-up of patients with ABPM or EGPA in order to identify the development of the other disease is therefore needed.

We herein reported three cases of combined ABPA and EGPA. Previous reports of the combination of ABPM and EGPA are limited; our results suggest that the prevalence of the combination ABPM and EGPA is not as low as previously reported. During the follow-up of patients with ABPM or EGPA, a careful investigation to determine the development of the other condition is therefore required.

The authors state that they have no Conflict of Interest (COI).

References


