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Letter to the Editor

Allergic bronchopulmonary aspergillosis in succession to chronic eosinophilic pneumonia

Dear Editor,

Allergic bronchopulmonary aspergillosis (ABPA) is an immunological pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus*. Patients with asthma who present with ABPA typically report symptoms such as chronic mucus hypersecretion, and previous research has indicated that ABPA is a risk factor for accelerated loss of lung function.¹ However, the pathogenesis of ABPA is not fully understood.² In the present report, we discuss a case of ABPA occurring after eosinophilic pneumonia (CEP).

Case report

A 26-year-old woman who had had bronchial asthma since childhood presented with abnormal shadows on X-ray images. Her asthma was controlled by treatment with inhaled corticosteroid/long-acting beta-agonists (ICS/LABA) and she had no symptoms. Computer tomography (CT) revealed a mass (maximum diameter: 58 mm) in the left lower lobe accompanied by diffuse bronchial wall thickening. Laboratory findings were as follows: white blood cell count: 12,000/mm³ with 28.7% eosinophils, immunoglobulin E (IgE): 990 IU/ml. The patient tested negative for *Aspergillus*-specific IgE, precipitins against *A. fumigatus*, myeloperoxidase-antineutrophil cytoplasmic antibodies (MPO-ANCAs), and proteinase 3-ANCAs. Serum levels of tumor markers were as follows: carcinoembryonic antigen (CEA): 29.0 ng/ml, cytokeratin-19 fragments (CYFRA): 1.1 ng/ml, and pro-gastrin-releasing peptide (Pro-GRP): 35.1 pg/ml. To exclude lung cancer, we performed bronchial alveolar lavage (BAL) and transbronchial lung biopsy via bronchoscopy, as well as CT-guided lung needle biopsy. Although mucous plugs in airways were not observed via bronchoscopy, eosinophil infiltration into alveolar spaces in pathology and BAL fluid analysis revealed eosinophilic elevation (eosinophils 88.5%, lymphocytes 3.0%, neutrophils 3.0%, macrophages 4.5%, and basophils 1.0%). However, neither the BAL fluid nor biopsy specimens contained malignant cells, bacteria, or fungus. Based on these findings, the patient was diagnosed with CEP. Although we recommended systemic steroid therapy at this stage, the patient declined treatment.

Five years later, she returned to our hospital to receive treatment for CEP. She had continued ICS/LABA treatment for asthma at other hospitals, and had no symptoms. However, her lung function had been deteriorating in the 5 years since her CEP diagnosis (Table 1). Compared with CT images obtained 5 years earlier, the mass in her left lower lobe had disappeared (Fig. 1A, B), while

bronchiectasis and mucoid impaction had increased in severity (Fig. 1C, D). The patient tested positive for *Aspergillus*-specific IgE (1.01 UA/ml) and precipitins against *A. fumigatus*. Her *Aspergillus* skin test was also positive (Table 1). Based on these results, we diagnosed her as ABPA.

Treatment with oral prednisolone was initiated at 0.5 mg/kg body weight, after which the dose was tapered. Two months after the initiation of steroid therapy, her mucoid impaction had improved, although bronchiectasis remained (Fig. 1E). Her forced expiratory volume in 1 s (FEV1) had also increased to within the normal range (Table 1).

Discussion

To our knowledge, this is the first reported case of ABPA occurring in succession to CEP, making our findings invaluable for clinicians.

The global prevalence of ABPA has been estimated at 2.5%,³ and delays in the diagnosis of ABPA may lead to the deterioration of lung function due to pulmonary fibrosis and bronchiectasis. However, the pathogenesis of ABPA remains unclear. In the present case, ABPA developed following CEP. Ueki *et al.* reported that both activated human eosinophils and neutrophils can release extracellular chromatin to form DNA traps which cause extracellular trap cell death and that these traps may entrap certain fungi.⁴ We speculate that eosinophilic airway inflammation, such as that caused by CEP, may be the underlying cause of ABPA by means of eosinophil DNA traps. Nonetheless, further studies are required to elucidate the pathogenesis of ABPA.

ABPA and CEP share similar clinical features, such as comorbid asthma and peripheral blood eosinophilia. However, the treatment

Table 1
Changes in clinical data.

Diagnosis	CEP	ABPA	
		Before treatment	After treatment
<i>Aspergillus</i> -specific IgE	negative	positive	not checked
precipitins against <i>A. fumigatus</i>	negative	positive	not checked
<i>Aspergillus</i> skin test	not checked	positive	not checked
serum total IgE (IU/ml)	990	710	97
CEA (ng/ml)	29.0	38.3	0.9
White blood cell count (mm ³)	12,000	8200	8400
Eosinophil (%)	28.7	24.5	0.7
Creatinine (mg/dl)	0.64	0.84	0.81
Lactate dehydrogenase (U/L)	221	181	177
VC (L)	3.27	3.04	3.28
FEV1 (L)	2.55	1.76	2.72
FEV1% (%)	78.0	60.5	84.7

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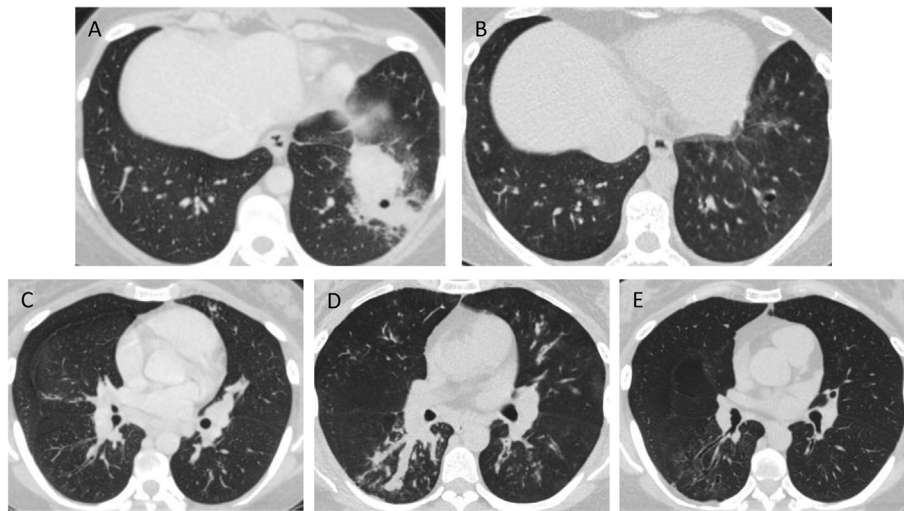


Fig. 1. (A) CT scan showed a mass (maximum size 58 mm in diameter) in the left lower lobe (B) Five years later, lung mass at left lower lobe was disappeared. These slides show the result of CT scan at the time of diagnosis of CEP (C), of ABPA (D), and after steroid treatment against ABPA (E).

differs for each disease. Although initial therapy with systemic steroids is common, antifungal therapy is preferable for ABPA.^{5–7} Previous studies have demonstrated that itraconazole reduces total serum IgE, symptom severity, and the need for oral steroids.⁵ Agarwal *et al.* further reported that itraconazole is associated with fewer side effects than prednisolone.⁶ Additional studies have reported that voriconazole and posaconazole are also effective against ABPA.⁷ We initially assumed that our patient experienced a CEP relapse. Clinicians should remain aware of the potential for ABPA to avoid misdiagnosis and the delay of appropriate treatment.

In general, CEA is a marker of malignant disease. Noguchi *et al.* reported that serum concentrations of CEA are elevated in some patients with ABPA.⁸ Other eosinophilic airway diseases such as bronchial asthma and CEP have also been associated with higher serum concentrations of CEA.^{9,10} In the present case, serum CEA concentration improved to within the normal range following steroid treatment. Thus, CEA may not only be elevated in serum of CEP and ABPA patients but may also be a marker of ABPA activity.

Overall, the present case highlights several important points for clinicians: 1) ABPA may occur in succession to CEP; 2) clinicians should first exclude ABPA when diagnosing CEP relapse; and 3) CEA may represent a marker of ABPA activity.

Conflict of interest

The authors have no conflict of interest to declare.

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