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【 CASE REPORT 】

Development of Allergic Bronchopulmonary Aspergillosis in a Patient with Crohn's Disease

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Abstract:
Allergic bronchopulmonary aspergillosis (ABPA) is an eosinophilic inflammatory condition characterized by exaggerated immune responses to the fungal genus *Aspergillus*. Pulmonary manifestations in patients with Crohn's disease (CD) are frequent comorbidities. A 66-year-old man with CD treated with an anti-tumor necrosis factor-α antibody presented with dyspnea. Laboratory findings of elevated blood eosinophils and total serum IgE and positive aspergillus-specific antibodies as well as imaging findings of central bronchiectasis and mucoid impaction indicated a diagnosis of ABPA. To our knowledge, this is the first report of ABPA arising in a patient with CD. We discuss the pathophysiological mechanism of this rare complication.

Key words: anti-tumor necrosis factor-α antibody, aspergillus, asthma, inflammatory bowel disease, pulmonary disorder

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Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is characterized by central bronchiectasis and recurrent pulmonary infiltrates. It manifests as poorly controlled asthma and affects an estimated four million patients worldwide (1). This condition is an established complication of asthma and cystic fibrosis. However, its pathophysiological mechanism remains unknown. Environmental factors might not be the sole cause of this pulmonary disorder because not all patients with asthma who are sensitive to aspergillus develop ABPA. This indicates the importance of genetic predispositions or multiple environmental factors.

We herein report a patient who developed ABPA during treatment with anti-tumor necrosis factor (TNF)-α antibody for Crohn's disease (CD).

Case Report

A 66-year-old man who had developed CD 33 years earlier was initially treated with mesalazine (3,000 mg/day), but the symptoms gradually worsened, and he underwent two surgical resections of inflamed intestinal lesions, where longitudinal ulcers with noncaseating epithelioid granuloma were observed. He had been started on systemic corticosteroids (40 mg/day) 3 years earlier to improve control of the CD, but the symptoms persisted. The corticosteroid was tapered to 30 mg/day after a few months, but the symptoms worsened. To avoid adverse reactions to corticosteroids, the patient had been started on anti-TNF-α antibody without modification of the steroid dosage two years earlier. This strategy suppressed his symptoms and enabled him to discontinue the corticosteroid.

After two years on maintenance doses of anti-TNF-α antibody, he presented with paroxysmal dyspnea and wheezing that worsened at night and during the early morning. These symptoms indicated asthma. Respiratory function tests revealed obstructive airway impairment. He had a history of acute myocardial infarction but had no symptoms or laboratory findings suggestive of heart failure. He did not have a history of childhood asthma, indicative of adult-onset asthma. There was the possibility of concomitant chronic obstructive pulmonary disease because he had smoked one pack of cigarettes per day until smoking cessation. Initial asthma therapy with an inhaled corticosteroid and long-

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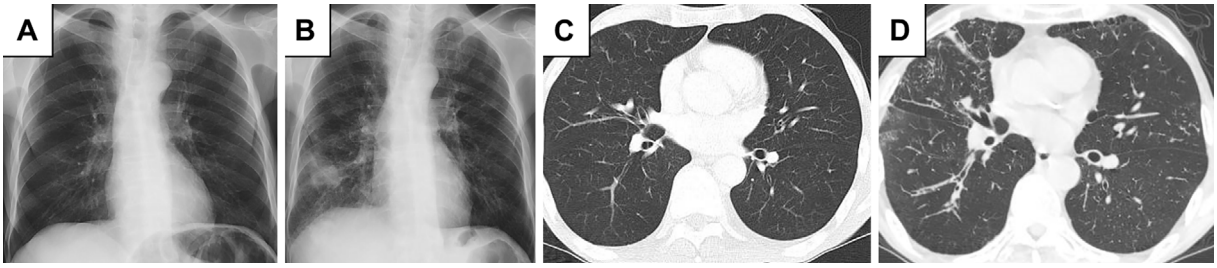

Figure 1. Imaging findings three years before ABPA development and after two years of anti-TNF-α antibody therapy. Imaging findings three years before ABPA development show no abnormalities (A, C) but support a diagnosis of ABPA two years later (B, D). Chest radiograph (B) shows consolidation in the middle and lower areas of the right lung. Chest computed tomography (D) shows airspace consolidation, ground glass opacity, and central bronchiectasis in the lower lobe of the right lung. ABPA: allergic bronchopulmonary aspergillosis

Table 1. Blood Findings upon Admission.

Peripheral blood		Biochemistry	
White blood cells	9,400 /uL	Total bilirubin	0.36 mg/dL
Neutrophil	45.1 %	Aspartate transaminase	22 U/L
Lymphocyte	16.5 %	Alanine transaminase	15 U/L
Basophil	0.4 %	Lactate dehydrogenase	246 U/L
Eosinophil	28.9 %	Alkaline phophatase	485 U/L
Monocyte	9.1 %	γ-glutamyl transpeptidase	27 U/L
Hemoglobin	10.5 g/dL	Total protein	7.7 g/dL
Hematocrit	32.0 %	Albumin	3.9 g/dL
Platelets	24.4 /uL	Urea nitrogen	29 mg/dL
		Creatinine	1.12 mg/dL
IgE-RIST	1,200 IU/mL	Sodium	132 mEq/L
IgE-RAST		Potassium	5.0 mEq/L
Aspergillus	29.9 UA/mL	Chloride	96 mEq/L
		Calcium	9.6 mEq/L
		C-reactive protein	1.3 mEq/L

IgE: immunoglobulin-E, RIST: radioimmunosorbent test, RAST: radioallergosorbent test

acting beta-agonist controlled his respiratory symptoms well. However, radiography findings revealed consolidation in the middle and lower areas of the right lung (Fig. 1A and B), and chest computed tomography revealed central bronchiectasis in the bilateral lungs with mixed consolidation and ground-glass opacity (Fig. 1C and D). Emphysema and/or interstitial opacities were not observed in this examination.

Laboratory data showed an excessive proportion of eosinophils (2,717 cells/mL) among leukocytes from peripheral blood and a serum total immunoglobulin E (IgE) value of 1,200 IU/mL (Table 1). Specific IgE antibody to *Aspergillus fumigatus*, specific IgG antibody, and a rapid cutaneous reaction to *A. fumigatus* extract were all positive. A bronchoscopic examination did not reveal mucoid impaction in the airway. However, eosinophil infiltration and myxoid organization with no filamentous fungus were identified in the peripheral airway mucosa of a transbronchial lung biopsy specimen (Fig. 2). A clinical diagnosis of ABPA was established based on the above findings, in accordance with the diagnostic criteria described by Greenberger-Patterson (2) and Agarwal (3).

Systemic prednisolone (30 mg/day) and itraconazole (100 mg/day) were initiated because of inadequate symptomatic improvement. The patient responded well to these agents, and his symptoms improved substantially. Serum total IgE and eosinophil counts simultaneously decreased (650 IU/mL and 76 cells/mL, respectively) with reduced radiographic abnormalities. Fig. 3 shows the clinical course of this patient.

Discussion

To our knowledge, this is the first case report to describe ABPA developing in a patient with CD. Airway disorders are the most frequently described pulmonary manifestations of inflammatory bowel disease (IBD). Epidemiological studies have uncovered associations with bronchiectasis, chronic bronchitis, chronic obstructive pulmonary disease and asthma during the course of IBD (4). In addition, the incidence of CD is increased in patients with asthma (5), indicating complex interplay between both pathologies.

Genome-wide association studies have revealed a genetic linkage between asthma and CD, and nucleotide binding oli-

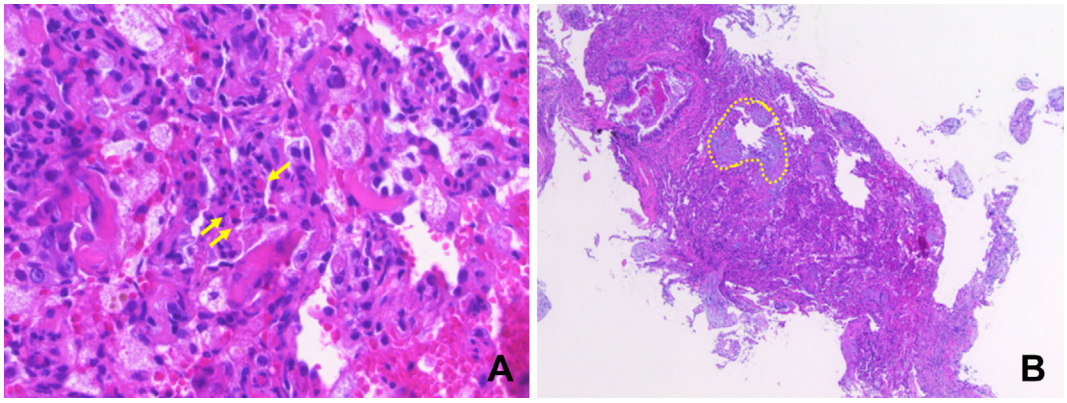

Figure 2. **A pathological analysis of the transbronchial lung biopsy specimen using Hematoxylin and Eosin staining. Eosinophil infiltration (arrow) (A) and myxoid organization (area surrounded by dotted lines) (B) are evident. A: magnification ×400, B: magnification ×40.**

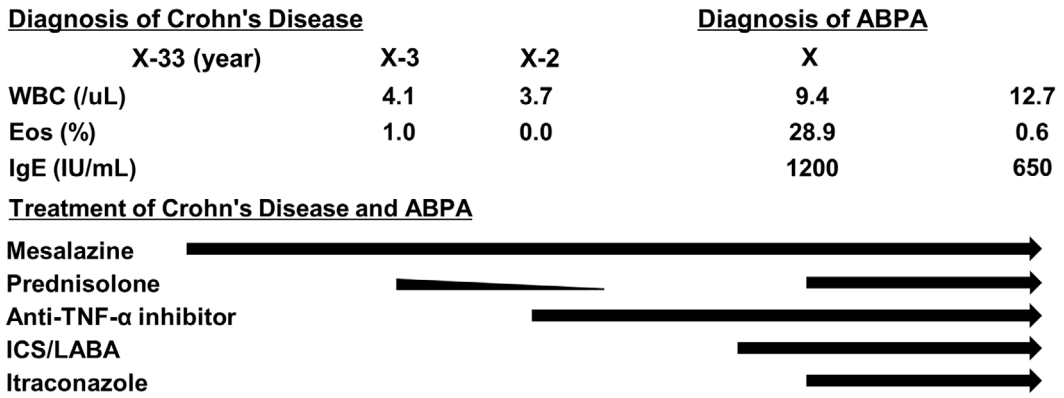

Figure 3. **Clinical course of the disease. ABPA: allergic bronchopulmonary aspergillosis, Eos: eosinophils, ICS/LABA: inhaled corticosteroid/long-acting beta agonist, WBC: white blood cells**

gomerization domain (NOD)-like receptor-related gene variants are evident in both asthma and CD (6, 7). For example, a genetic deficiency of NOD2 has been associated with CD (7) and resistance to *Aspergillus* infection (8). An immunological overreaction to *Aspergillus* induced by a NOD2 deficiency might be one factor that triggers ABPA onset. However, further investigations should be performed to confirm any premature speculation regarding genetic relationships.

The gut microbiome is considered to be one element involved in the development of CD, and its contents are associated with the disease severity (9). The intestinal microbiota is involved in the pathogenesis of not only IBD but also allergic airway inflammation (9). Fungal microbiota in the gut might be particularly important to the regulation of inflammation in both CD and asthma (9-11). The overgrowth of fungal species in the gut promotes M2 macrophage activation, which leads to pulmonary allergic airway inflammatory states, such as asthma (10). Furthermore, *Candida albicans* increased in the inflamed colon expanded Th17 cells that could also respond to *A. fumigatus* eliciting pulmonary inflammation in patients with ABPA (12). Controlling dysbiosis is a potential therapeutic strategy for preventing CD and the subsequent onset of asthma.

TNF-α plays a key role in the immunopathology of IBD and autoimmune disorders that are frequently treated with anti-TNF-α antibody. Because TNF-α plays a key role in the recruitment of neutrophils into the lungs in response to pathogens such as *A. fumigatus* (13), anti-TNF-α antibody might induce intratracheal expansion or colonization with this pathogen. This concept is supported by the finding of an association between invasive pulmonary aspergillosis and infliximab therapy (14).

Previous reports have described patients with rheumatoid arthritis (RA) and sarcoidosis in whom ABPA developed while under therapy with anti-TNF-α antibody (Table 2) (15-17). In addition, patients with RA treated with anti-TNF-α-antibody presented with acute exacerbation of asthma (18). These findings suggest that impaired TNF-α-mediated immune responses are involved in the subsequent development of asthma and ABPA. Because TNF-α is thought to be involved in the development of type 1 inflammation, the inhibition of TNF-α might result in disrupting the immune balance to augment the type 2 inflammation that is dominant in the inflamed airways of patients with asthma. A dysregulated immune balance under anti-TNF-α-

Table 2. Summary of Patients who Developed ABPA under Therapy with Antibodies.

Reference	Age	Sex	Underlying pathology	Antibody	Duration (m)	ABPA therapy
(15)	47	F	Sarcoidosis	Infliximab	15	Prednisolone
(16)	68	F	Rheumatoid arthritis	Etanercept, tocilizumab, infliximab	15	Itraconazole
(17)	77	F	Rheumatoid arthritis	Adalimumab, etanercept	30	Prednisolone, itraconazole
Present report	66	M	Crohn disease	Infliximab	24	Prednisolone, itraconazole

ABPA: allergic bronchopulmonary aspergillosis, F: female, M: male

antibody treatment may therefore conceivably exert an additive effect on allergic responses to colonized *A. fumigatus* in the airway. However, CD and RA have been associated with asthma, regardless of the type of antibody therapy (4, 5, 19), suggesting the involvement of multiple pathogenic factors in the development of asthma and ABPA in patients with CD or RA. Of note, CD is often treated with corticosteroid that suppresses type 2 inflammation. Systemic steroid therapy for CD with occult ABPA comorbidity may attenuate the disease activity.

Our experience with this patient led us to speculate that the pathogenesis of CD is intimately associated with the development of ABPA along with asthma. Genetic factors, dysbiosis, and anti-TNF-α antibody might be potential causes of asthma and ABPA. Clinical practitioners should be aware of these associations before selecting strategies for managing CD accompanied by pulmonary manifestations.

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

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