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CASE REPORT

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Development of allergic bronchopulmonary aspergillosis in a patient with nontuberculous mycobacterial-pulmonary disease successfully treated with dupilumab: A case report and literature review

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Abstract

Pulmonary manifestations in patients with allergic bronchopulmonary aspergillosis (ABPA) and nontuberculous mycobacterial-pulmonary disease (NTM-PD) include bronchiectasis and mucus plugging. A 68-year-old woman, treated with antibiotics and inhaled corticosteroids for NTM-PD and asthma, presented with fever and wheezing. ABPA was diagnosed based on laboratory findings (elevated peripheral blood eosinophil counts and serum total IgE levels and positive *Aspergillus*-specific IgE and IgG) and imaging observation of a high-attenuation mucus plug. Systemic prednisolone was avoided to prevent NTM-PD progression. Dupilumab, a monoclonal antibody that blocks IL-4/13, was introduced to improve the clinical findings. Herein, we discuss the pathophysiological mechanisms underlying this rare comorbidity.

KEYWORDS

allergic bronchopulmonary aspergillosis, bronchiectasis, dupilumab, mucus plug, nontuberculous mycobacterial-pulmonary disease

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is characterized by central bronchiectasis and recurrent pulmonary infiltrates and manifests as poorly controlled asthma, affecting an estimated 4 million patients worldwide.[1,2] It is a well-recognized complication of asthma and cystic fibrosis. Therapeutic strategies include using systemic corticosteroids and antifungal agents during the initiation. Although multiple environmental factors play an important role, their pathophysiological mechanisms remain unclear.

The incidence and prevalence of nontuberculous mycobacterial-pulmonary disease (NTM-PD) are increasing worldwide.[3] Pulmonary manifestations include bronchiectasis and mucus plugging, similar to those observed in ABPA. Neutrophilic inflammation occurs in NTM-PD, whereas ABPA is characterized by eosinophilic inflammation.[4,5] Patients with NTM-PD often present with secondary infections by various microorganisms, including *Aspergillus* species.[6] Herein, we describe a patient who developed ABPA during NTM-PD and was successfully treated with dupilumab.

CASE REPORT

A 68-year-old woman has been allergic to Japanese cedar and house dust mite since reaching adulthood. The patient

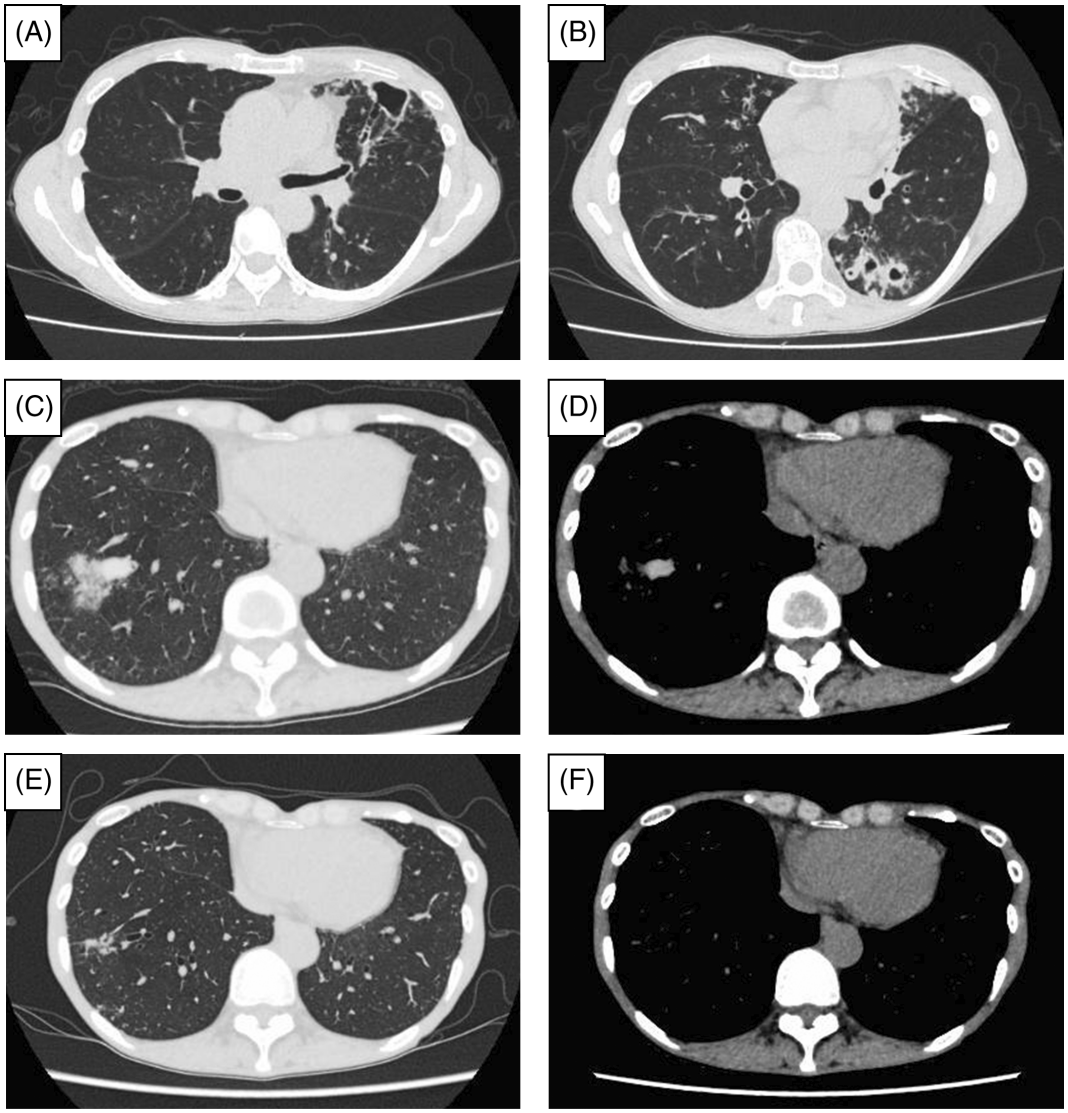

FIGURE 1 Imaging findings of chest CT at the diagnosis of NTM-PD, at the diagnosis of ABPA, and after the initiation of dupilumab. CT showed cavities with their wall thickness and bronchiectasis in the upper and lower lobe of the left lung (A, B). At the diagnosis of ABPA, CT showed a high attenuation mucus plug in the lower lobe of the right lung (C, D). After initiating dupilumab, mucus plugging improved, and bronchiectasis was observed in the same lesion (E, F). ABPA, allergic bronchopulmonary aspergillosis; CT, computed tomography; NTM-PD, nontuberculous mycobacterial-pulmonary disease.

was diagnosed with bullous pemphigoid 16 years ago, and treatment with systemic corticosteroids was initiated 13 years ago. Serum *Aspergillus*-specific IgE antibody was positive 12 years ago. Asthma was diagnosed 10 years ago based on the findings of cough and rhinitis that improve with inhaled corticosteroids/long-acting β2-agonist. A bacteriological examination of the sputum revealed *Mycobacterium avium* 8 years ago, and a diagnosis of NTM-PD was made. Imaging findings of NTM-PD on chest radiography and computed tomography (CT) worsened 6 years ago (Figure 1A,B), and treatment with antibiotics combined with clarithromycin (800 mg/day), ethambutol (500 mg/day), and rifampicin (600 mg/day) was initiated. However, NTM-PD was difficult to treat despite the use of multidrug therapy with the addition of amikacin and sitafloxacin to this treatment.

Serum *Aspergillus*-specific IgG antibody became positive 3 years ago. Sputum culture revealed the presence of filamentous fungi in the previous year. This patient presented with wheezing and fever. Respiratory function test showed normal vital capacity (VC, 2.04 L; %VC, 80.3%) and forced expiratory volume in 1 s (FEV1, 1.78 L; %FEV1, 93.7%; FEV1%, 87.3%) with a high level of fractional exhaled nitric oxide (FeNO, 42 ppb). The laboratory findings are summarized in Table 1. Serum total IgE levels and peripheral blood eosinophil counts were high. Chest CT revealed a high-attenuation mucus plug (HAM) (Figure 1C,D). Based on these findings, ABPA was diagnosed according to its diagnostic criteria.[7]

The use of systemic corticosteroids was avoided to prevent the exacerbation of NTM-PD. Antifungal agents were

TABLE 1 Results of blood test.

Peripheral blood		Biochemistry	
White blood cells	6900/uL	Total bilirubin	0.7 mg/dL
Neutrophil	60.0%	Aspartate transaminase	25 U/L
Lymphocyte	13.0%	Alanine transaminase	11 U/L
Basophil	2.0%	Lactate dehydrogenase	177 U/L
Eosinophil	18.0%	Alkaline phophatase	63 U/L
Monocyte	7.0%	γ-glutamyl transpeptidase	19 U/L
Eosinophil count	1242/uL	Total protein	7.7 g/dL
Haemoglobin	13.2 g/dL	Albumin	3.8 g/dL
Haematocrit	41.5%	Urea nitrogen	13.8 mg/dL
Platelets	24.3×10^4/uL	Creatinine	0.58 mg/dL
		Sodium	138.6 mEq/L
IgE-RIST	2933 IU/mL	Potassium	4.3 mEq/L
IgE-RAST		Chloride	101 mEq/L
Aspergillus	25.00 UA/mL	Calcium	9.3 mEq/L
Asp f1	0.11 UA/mL	C-reactive protein	0.36 mEq/L
Aspergillus-specific IgG antibody	21 AU/mL	1,3 beta-D glucan	14.7 pg/mL
		Galactomannan antigen (ELISA)	0.2
		GPL core antibody	7.56 U/L

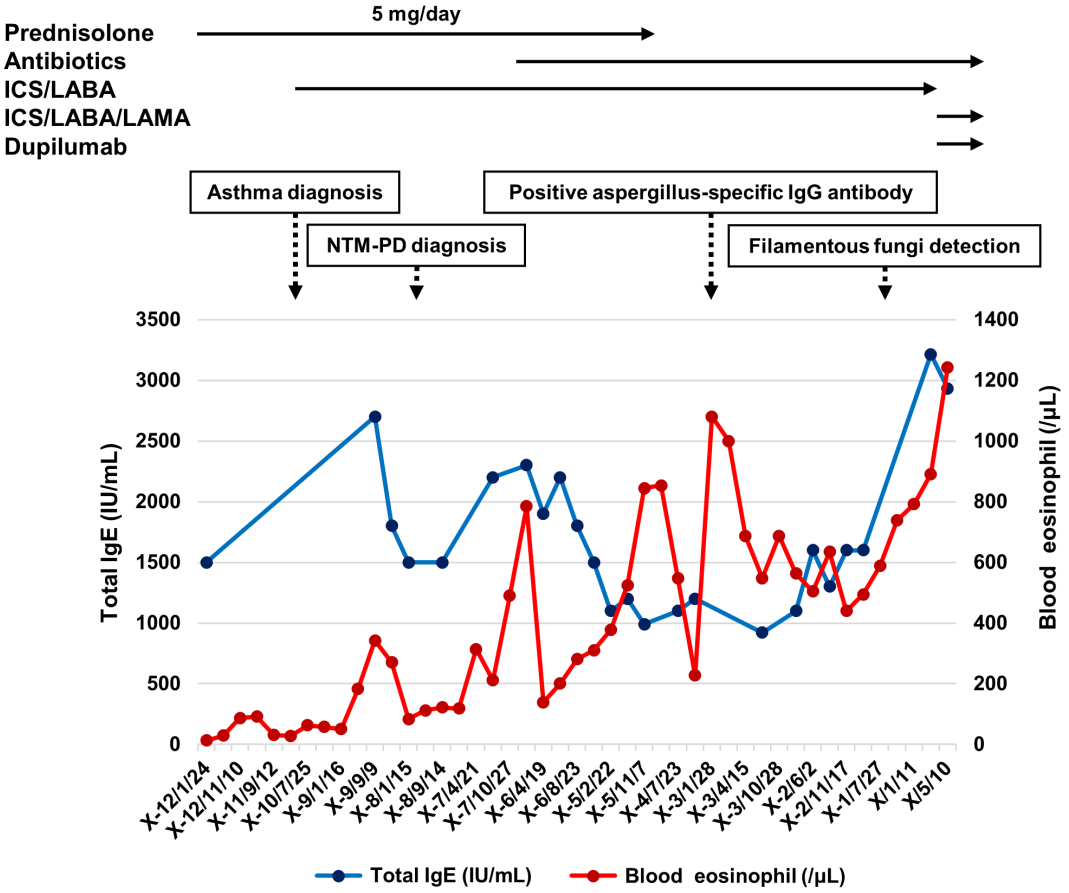

FIGURE 2 Clinical course of NTM-PD and ABPA in the present patient. ABPA, allergic bronchopulmonary aspergillosis; ICS/LABA, inhaled corticosteroid/long-acting β2-agonist; ICS/LABA/LAMA, inhaled corticosteroid/long-acting β2-agonist/long-acting muscarinic antagonist; IgE, immunoglobulin E; NTM-PD, nontuberculous mycobacterial-pulmonary disease.

TABLE 2 Summary of the cases with ABPA successfully treated with dupilumab.

Age	Sex	Comorbid disease	Treatment of ABPA	Previous treatment using biologics	References
81	F	Asthma	OCS (prednisolone)	Mepolizumab	[16]
63	F	Asthma	Itraconazole	Benralizumab	[17]
45	M	Asthma	OCS (prednisolone)	Mepolizumab	[18]
49	F	Asthma	Itraconazole, OCS (prednisolone)	Benralizumab, omalizumab	[19]
60	F	Asthma	OCS (unknown)	Omalizumab, mepolizumab	[20]
51	F	Asthma	Itraconazole, OCS (unknown)	Mepolizumab	[20]
33	M	Asthma, Klinefelter syndrome	Voriconazole	–	[20]
72	F	Asthma, NTM-PD	–	–	[21]
54	F	Asthma	itraconazole, OCS(prednisolone)	–	[4]
68	F	Asthma	–	-	Present case

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; NTM-PD, non-tuberculous mycobacterial-pulmonary disease; OCS, oral corticosteroid.

also excluded because of their pharmacological interactions with rifampicin. Single inhaler triple therapy using inhaled corticosteroid/long-acting β2-agonist/long-acting muscarinic antagonist (ICS/LABA/LAMA, fluticasone furoate (200 μg/day)/umeclidinium (62.5 μg/day)/vilanterol (25 μg/day)) and dupilumab, an anti-IL-4 receptor α monoclonal antibody, were initiated to treat comorbid severe eosinophilic asthma. The clinical symptoms and imaging findings improved after treatment initiation (Figure 1E,F), while serum total IgE levels and peripheral blood eosinophil counts slightly decreased (2236 IU/mL and 977/μL, respectively). Of note, there was no transient eosinophilia. No worsening of NTM-PD has been observed following treatment with dupilumab; however, residual shadows, including bronchiectasis, remain visible on the chest CT. Figure 2 summarizes the clinical course of the disease.

DISCUSSION

This is a valuable case report of ABPA in a patient with NTM-PD that describes the long-term follow-up period involving the onset of both diseases. Previous reports have shown that NTM-PD is associated with a higher frequency of ABPA.[8,9] Among patients with cystic fibrosis, the incidence of ABPA is higher in those with NTM-PD than in those without.[8] Patients with bronchiectasis also have a higher incidence of ABPA than those without NTM-PD.[9] In contrast, the cumulative incidence of NTM-PD increased over time in patients with ABPA and allergic bronchopulmonary mycosis (ABPM) who received oral corticosteroids as a risk factor for this complication.[10]

In this case, the patient developed asthma with sensitization to *Aspergillus fumigatus* prior to the diagnosis of NTM-PD. IgE-mediated *A. fumigatus* sensitization aggravates respiratory conditions in patients with asthma who do not meet ABPA diagnostic criteria. Patients with *A. fumigatus* sensitization frequently exhibit impaired pulmonary function, mucus plugging, and bronchiectasis.[11] The positivity rate of *A. fumigatus*-specific IgE increases over time in patients with asthma, and risk factors include the use of medium-to high-dose inhaled corticosteroids and high serum levels of total IgE.[12] Inhaled or systemic steroids are known risk factors for the development of NTM-PD.[13,14] *A. fumigatus* may induce a Th2-mediated immune response and reduce cytokines involved in NTM eradication.[15] These findings suggest that airway inflammation, therapeutic agents used in asthma, and sensitization to *A. fumigatus* may trigger the development of NTM-PD.

Bronchiectasis often coexists with severe asthma, and *A. fumigatus* is frequently isolated from cultured microorganisms in such cases.[16] Bronchiectasis in NTM-PD is associated with enhanced airway inflammation and increased cytokine levels, including IL-1 and GM-CSF.[17,18] Animal studies have demonstrated that these cytokines induce sensitization to allergens.[19] Based on these findings, NTM-PD and bronchiectasis may promote further sensitization to Aspergillus in the airways.

A. fumigatus-specific IgG is frequently detected in patients with NTM-PD. A previous report showed that *Aspergillus* precipitating antibody-positive patients presented with a longer duration, more severe bronchiectasis, and lower pulmonary function, and 5 of 109 patients developed ABPA.[20] Another study demonstrated that *Aspergillus* precipitating antibody-positive cases were characterized by male sex, emphysema, and interstitial pneumonia, and 3 of 109 cases developed ABPA.[21] Additionally, the accumulation of neutrophils in the airways due to NTM-PD may enhance the migratory response of eosinophils.[4,22] It has been reported that some patients with bronchiectasis exhibit a mixed phenotype of neutrophilic and eosinophilic inflammation.[23] These findings indicate that *Aspergillus* sensitization aggravates the pathogenesis of NTM-PD and may trigger the development of ABPA.

Biologics are not currently available for ABPM cases. Case reports and series have reported that the use of biologics targeting IgE,[24] IL-5,[25] IL-4/IL-13,[26–32] and TSLP[33] improves the disease status of ABPA complicated by severe asthma. Monoclonal antibodies against IgE have therapeutic efficacy in patients with ABPA and severe asthma, including 12 of the 25 patients with NTM-PD.[24] Anti-IL-5/IL-5 receptor

antibodies are highly effective in patients with ABPA, especially for improving mucus plugging.[25] Previous case reports suggested that dupilumab is effective when switching from other biologics to this drug.[26–30] Similar to the present case, the therapeutic efficacy of dupilumab in patients with NTM-PD[31] and the discontinuation of oral steroids during the use of dupilumab[32] were also observed in patients with ABPA. Of note, dupilumab treatment was associated with a reduced incidence of respiratory infections in patients with moderate-to-severe asthma or severe CRSwNP.[34] Since IL-4 suppresses Th1 cells, this inhibition by dupilumab may contribute to the eradication of NTM in the lung by normalizing type 1 inflammation.[35–37] These findings suggestive of its usefulness in patients with infectious diseases. ABPA cases that were successfully treated with dupilumab are summarized in Table 2. It may be necessary to consider the phenotype of ABPA when selecting a specific biologic.[38]

Based on our experience with this patient, we speculated that the pathogenesis of NTM-PD is associated with the development of ABPA in asthma. Bronchiectasis and/or inhaled/systemic corticosteroid use may be the potential causes of this comorbidity. Clinical practitioners should know about this association to decide the appropriate therapeutic management for both conditions, including biologics.

AUTHOR CONTRIBUTIONS

Ryuta Onozato and Jun Miyata conceived the idea. Koichi Fukunaga overviewed the project. Ryuta Onozato and Jun Miyata wrote the paper. Takanori Asakura, Ho Namkoong, Koichiro Asano, Naoki Hasegawa critically contributed to the accomplishment of this report.

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CONFLICT OF INTEREST STATEMENT

Jun Miyata received lecture fees from Sanofi S.A..

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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