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Case report

Allergic bronchopulmonary aspergillosis successfully treated with mepolizumab: Case report and review of the literature

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ABSTRACT

A 56-year-old woman was referred to our hospital for recurrent asthma of 20 years duration. She was diagnosed as having allergic bronchopulmonary aspergillosis on the basis of clinical symptoms, peripheral blood eosinophilia, elevated total serum immunoglobulin E value, positive results of specific IgE and precipitating antibodies against *Aspergillus* sp., central bronchiectasis, and mucoid impaction. Systemic corticosteroids and anti-fungal therapy improved her symptoms, but the cessation of these treatments led to frequent exacerbations. Omalizumab improved her asthmatic symptoms to the point that corticosteroids could be stopped; however, radiological findings were not improved, and coexisting eosinophilic sinusitis and otitis media worsened. After her treatment was changed from omalizumab to mepolizumab, not only her asthmatic symptoms but also her sinusitis and otitis media became well controlled, and chest radiological findings improved.

1. Introduction

Allergic bronchopulmonary aspergillosis (ABPA), an eosinophilic pulmonary disease resulting from a hypersensitivity response to *Aspergillus* spp., is characterized by recurrent asthma, peripheral blood eosinophilia, elevated total serum immunoglobulin E (IgE) value, central bronchiectasis, and mucoid impaction [1]. It is important to diagnose and treat ABPA as soon as possible because progression of the disease causes irreversible destruction of the airways and fibrosis that can lead to chronic respiratory failure. Systemic corticosteroids are recommended as the treatment of choice, and concomitant anti-fungal therapy is effective in reducing corticosteroid use and preventing recurrence [1–4].

Recently, various molecular targeted drugs have been used for refractory asthma. Omalizumab, a monoclonal antibody against IgE, and mepolizumab, a monoclonal antibody against interleukin-5, are similar Th 2 inflammatory cascade inhibitors, and both are considered to be effective in reducing rates of exacerbation, steroid requirement, controlling asthmatic symptoms, and improving pulmonary function [5,6]. However, which drug should be used as initial therapy for refractory asthma remains unclear [7,8]. Similarly, these drugs have the possibility to improve ABPA and issues related to selection criteria. Omalizumab has been reported to be effective for ABPA [9–11], but some patients with ABPA have not responded to omalizumab adequately [12]. The effects of mepolizumab on ABPA have also been reported. One case report showed that combination therapy with omalizumab and mepolizumab was effective for ABPA [13], and two case reports showed that ABPA was successfully treated with mepolizumab alone [14,15]. We report a case of ABPA in which switching from omalizumab to mepolizumab contributed to the patient's improvement.

2. Case presentation

A 56-year-old woman presented to our hospital with dyspnea on exertion (modified Medical Research Council dyspnea scale: 1) for a few days. She had experienced an asthma attack several times a year for 20 years. In 2011, she was referred to our hospital and hospitalized for further evaluation. She had a history of sinusitis treated surgically 30 years ago and a family history of asthma. She did not smoke or drink alcohol and had no history of dust exposure. On admission, chest auscultation revealed wheezes and rhonchi. Laboratory findings showed peripheral blood eosinophilia (1500/mm^3) and elevated total serum IgE value of 2421 IU/mL, and specific IgE and precipitation antibodies against *Aspergillus fumigatus* were positive. Pulmonary function testing (% predicted) showed a forced vital capacity (FVC) of 2.17 L (70.2%), forced expiratory volume in 1 s (FEV_1) of 1.42 L (62%), and FEV_1/FVC

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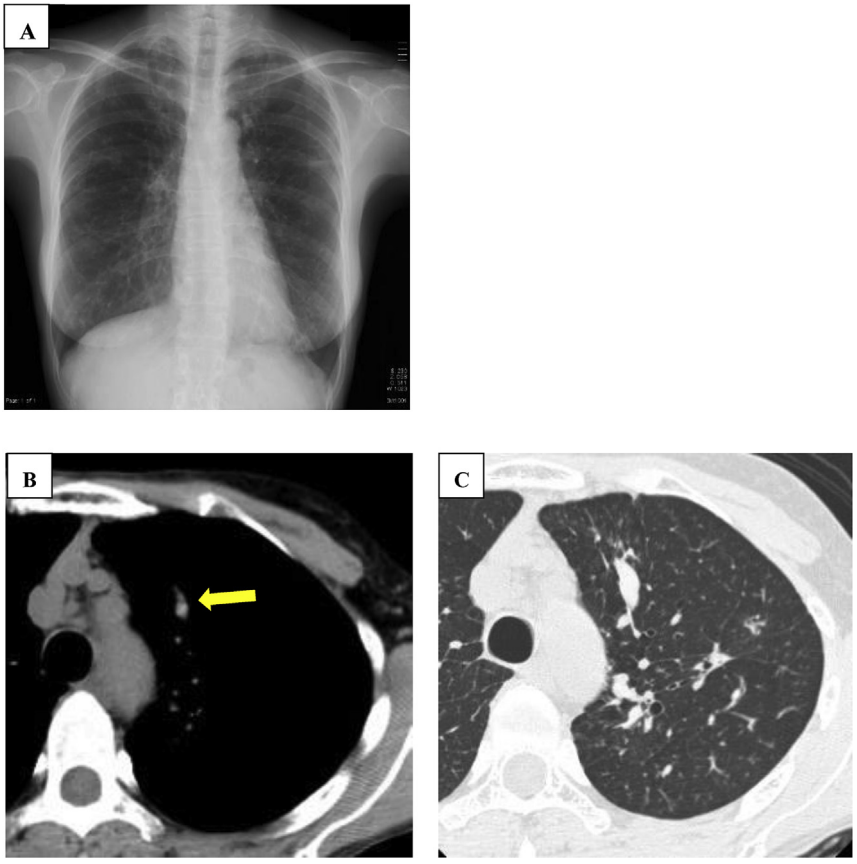

Fig. 1. Radiological findings on admission. Chest X-ray showed bilateral bronchial wall thickening (A), and CT showed central bronchiectasis, high-attenuation mucoid impaction (arrow) (B), and centrilobular opacities and nodules (C).

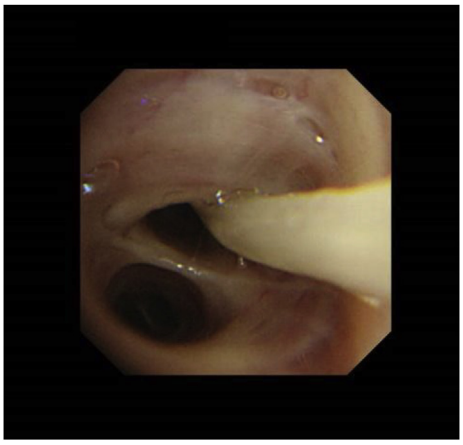

Fig. 2. Bronchoscopy findings. Mucoid plugs were found in several bronchi.

of 65.4%. Chest X-ray showed bilateral bronchial wall thickening, and chest computed tomography (CT) revealed central bronchiectasis, mucoid impaction, and diffuse bronchial wall thickening (Fig. 1). Bronchoscopy showed mucous plugs (Fig. 2), and Fig. 3A shows the mucus plugs aspirated by bronchial washing. Histopathological findings showed eosinophilic infiltrates and Charcot-Leyden crystals, but we could find no fungal hyphae. Eight days after admission, she was diagnosed as having ABPA on the basis of clinical symptoms, elevated total serum IgE value, positive *Aspergillus*-specific IgE and precipitation antibodies against *A. fumigatus*, and radiological findings (mucoid impaction and central bronchiectasis). She was treated with a high-dose inhaled corticosteroid combined with a long-acting beta agonist and systemic corticosteroid (prednisolone 30 mg/day). Itraconazole (200 mg/day) was also added, and her symptoms improved. The corticosteroids were then gradually tapered and discontinued in March 2012. However, 3 months later, clinical symptoms recurred, and CT showed exacerbations of bronchial wall thickness and infiltration, and systemic corticosteroids and itraconazole were restarted. Reducing the dose of corticosteroids resulted in recurrent asthma attacks, and her coexisting eosinophilic sinusitis and otitis media were not well controlled. In May 2014, omalizumab (600 mg/2 weeks) was started, which improved her symptoms by 6 weeks after treatment and maintained her FEV_1, but her radiological findings did not improve, and her coexisting eosinophilic sinusitis and otitis media also became worse. In January 2018, 94 weeks after starting omalizumab, it was switched to mepolizumab (100 mg/4 weeks), which kept her asthma in remission, led to the remission of her sinusitis and otitis media, and improved her radiological findings (Fig. 4). At the final follow-up visit, she had been receiving mepolizumab for 56 weeks and showed no asthmatic symptoms with normal peripheral blood eosinophils (0/mm^3) and serum IgE value of 362 IU/mL.

3. Discussion

We successfully treated a patient with ABPA with mepolizumab. Omalizumab therapy in our patient had also improved her asthmatic symptoms and led to a reduction in the rate of exacerbations, but the effect was only partial as the symptoms of her sinusitis and otitis media and her radiological findings did not improve. Mepolizumab not only kept her asthma in remission but also improved her sinusitis and otitis media and radiological findings.

The research so far shows that systemic corticosteroids are recommended as a treatment of choice for ABPA, especially in the acute stage [2,3]. However, ABPA frequently relapses, and it is frequently

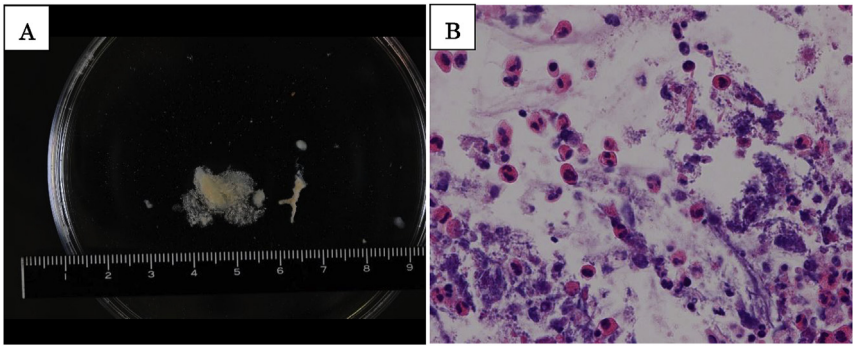

Fig. 3. Histopathological findings. Photograph shows mucus plugs (A). Mucus plugs contained many eosinophils and Charcot-Leyden crystals (B).

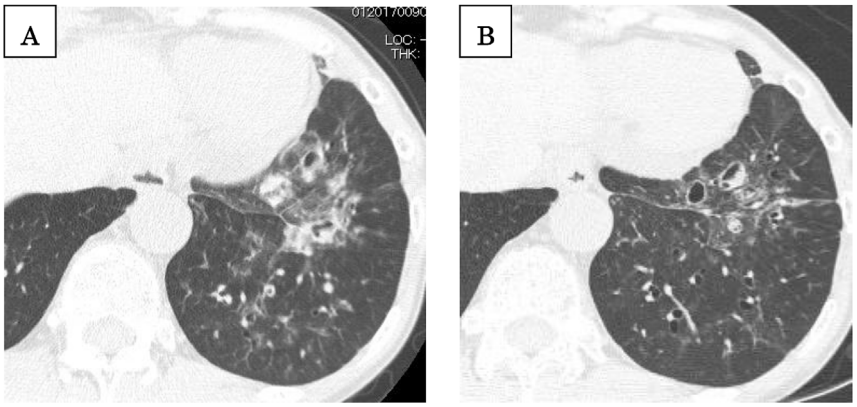

Fig. 4. Radiological findings over the clinical course showed improvement (A: before mepolizumab, B: after mepolizumab).

difficult to stop systemic corticosteroids. A medium dose of oral corticosteroids has been reported to be effective and safer than a high dose of oral corticosteroids [16], but considering their adverse effects, it is better to reduce them. The combination of antifungal agents such as itraconazole, voriconazole, or nebulized amphotericin is considered to be helpful in treating ABPA as these drugs decrease the fungal load in the airways, contribute to reducing corticosteroids, and inhibit recurrence after the cessation of corticosteroids [3,4,17,18]. Itraconazole monotherapy has also been reported to be effective in the acute stage of ABPA [19]; however, our patient experienced relapses when corticosteroids were decreased during combination therapy with itraconazole. Inhaled corticosteroids are expected to control asthmatic symptoms to some degree, but they is not effective in treating and preventing the recurrence of ABPM and halting the progression of pulmonary dysfunction [3].

Recently, various molecular targeted drugs have been widely used for refractory asthma and ABPA. Previous studies reported that omalizumab decreased the frequency of recurrence of asthma and reduced corticosteroids, which thereby decreased their adverse events [9–11,20]. However, Aydin and Sözener reported that omalizumab was perfectly effective in 78.6% of ABPA patients, but only partially so in 21.4% [12]. Most patients with ABPA can be treated with omalizumab, but some require additional or other treatment.

Mepolizumab, which is a monoclonal antibody against interleukin-5 (IL-5), inhibits the binding of IL-5 to its receptor, which leads to eosinophilic activation [5]. Therefore, it is expected to be efficacious in the treatment of eosinophilic pulmonary diseases. To our knowledge, three cases of ABPA treated with mepolizumab have been reported (Table 1). Altman et al. reported that combination therapy with omalizumab and mepolizumab improved ABPA, and together, they might have a potential synergistic effect [13]. In their report, omalizumab led to a reduction in corticosteroids, inhibited the recurrence of ABPA, and improved respiratory symptoms, but the patient still required oxygen therapy. Adding mepolizumab led to stopping the oxygen therapy and corticosteroids. Terashima et al. [14] and Oda et al. [15] reported that only mepolizumab improved clinical symptoms, pulmonary function, and radiological findings of ABPA in their patients with steroid-dependent asthma. None of these patients have experienced adverse events with mepolizumab, and all have been controlled for more than 8 months.

Several studies of asthma have not shown any differences in the effects of omalizumab and mepolizumab. Some studies showed that total IgE and blood eosinophil levels could be a predictor for both omalizumab and mepolizumab use [6]. The comparison of these two drugs in ABPA has been inadequate, but this remains an important issue. Our patient differed from the three patients treated with mepolizumab in that we switched her omalizumab to mepolizumab. Our case shows that mepolizumab may be a better choice for steroid-dependent ABPA if eosinophilic sinusitis and otitis media coexist or mucoid impactions have remained because the formation of mucoid impactions is considered to be a main pathologic feature of ABPA. Eosinophil extracellular DNA trap cell death (EETosis), which is a special form of cell death, has been reported to contribute to the formation of mucoid impaction [21]. Activation of eosinophils results in trapping of fungi, i.e., EETosis, which forms mucoid impaction by releasing chromatin in the cytoplasm into the extracellular space. Omokawa et al. reported that EETosis occurred in ABPA and that corticosteroid therapy improved it [22]. We considered the inhibition of eosinophilic activation by mepolizumab to have contributed to inhibiting the formation of mucoid impaction, which resulted in the improvement of ABPA in our patient.

Molecular targeted drugs are expensive, and we will need to address when they should be used and in which cases they are needed in a future study.

Table 1
Reported cases of allergic bronchopulmonary aspergillosis treated with mepolizumab.

Author and Year	Age	Sex	Treatment	Laboratory data				Clinical symptoms	FEV_1	Radiological findings
				Eosinophils (/mm^3)		IgE (IU/mL)				
				Before mepolizumab	After mepolizumab	Before mepolizumab	After mepolizumab			
Altman et al. [13] 2017	58	F	Mepolizumab added to omalizumab	1100	0	1730	298	Improved	No change	N.A.
Terashima et al. [14] 2018	64	F	Mepolizumab alone	3017	174	3400	N.A.	Improved	Improved	Improved
Oda et al. [15] 2018	33	M	Mepolizumab alone	6370	64	182	N.A.	Improved	Improved	Improved
Our case	56	F	Switched omalizumab to mepolizumab	800	0	1121	362	Improved	No change	Improved

CB, central bronchiectasis; FEV1, forced expiratory volume in 1 s; ICS/LABA, inhaled corticosteroids/long-acting beta agonists; PSL, prednisolone; N.A., not available.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2018.11.013.

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