

Mepolizumab improved airway hyperresponsiveness in a patient with allergic bronchopulmonary aspergillosis

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Abstract

Background: Allergic bronchopulmonary aspergillosis (ABPA) is a severe type of asthma characterized by hypersensitivity to *Aspergillus fumigatus* and lung infiltration with eosinophilia. The central pathogenesis of asthma is airway hyperresponsiveness (AHR), with eosinophils playing a critical role. Anti-interleukin (IL)-5 antibody therapy has been recently introduced to treat severe asthma, which reportedly inactivates and reduces eosinophil count. A recent case series highlighted the improvement in asthmatic symptoms associated with ABPA, but previous reports failed to demonstrate any improvement in AHR.

Objective: Herein, we aimed to elucidate the efficacy of mepolizumab in a patient with ABPA who showed improvement in AHR.

Method: Case report.

Results: A 63-year-old Asian woman with ABPA showed improvement in asthmatic symptoms and AHR following mepolizumab therapy.

Conclusion: Our results suggest that IL-5 may serve in the pathogenesis of ABPA

Key words: *Aspergillus fumigatus*, ABPA, severe asthma, AHR, mepolizumab

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Introduction

Allergic bronchopulmonary aspergillosis (ABPA), a severe type of asthma, is characterized by hypersensitivity to *Aspergillus fumigatus* (AF) and lung infiltration with eosinophilia.¹ In addition, airway hyperresponsiveness (AHR) is a central abnormality in patients with allergic asthma, with inflammatory cytokines/chemokines demonstrating well-established pathological functions.² There are several methods to measure AHR, and a test using histamine is a well-known method. Type I and IV hypersensitivity play a pivotal role in the airway mucosal surface of ABPA.^{3,4} Inhaled and oral corticosteroids, as well as anti-fungal agents, are the mainstream treatment for ABPA, but adverse events, mainly attributed to oral corticosteroids, could cause serious outcomes, such as life-threatening infections.

Mepolizumab is a humanized monoclonal antibody used to treat severe eosinophilic asthma by neutralizing interleukin (IL)-5, a key cytokine that promotes eosinophil activation and proliferation. Efficacy has been proven in large-scale studies and long-term safety has also been established.⁵⁻⁷ A recent small study has revealed the efficacy of mepolizumab in patients with ABPA, but the underlying mechanism, other than eosinophil inactivation,

remains unclear.⁸ Herein, we report a case of ABPA successfully treated with mepolizumab, with improvement in AHR, which suggests the effectiveness of mepolizumab among patients with ABPA.

Case Report

A 63-year-old Asian woman was referred to our hospital due to uncontrolled asthmatic symptoms. Previously, ABPA was diagnosed using chest computed tomography (CT), and she fulfilled the diagnostic criteria presented by the International Society for Human and Animal Mycology in 2013.⁹ Although she was on high-dose fluticasone furoate/vilanterol (corticosteroid and long-acting beta-agonist) with tiotropium for the treatment of asthma, dyspnea and cough were poorly managed. Moreover, her symptoms necessitated the use of short-term oral corticosteroids at least once a month. Her laboratory data at initial visit showed marked eosinophilia (501 cells/ μ L; 11.4%), elevated total IgE level (10,694 IU/mL), and positive results for both *Aspergillus*-specific IgE (class 2) and IgG. Her total leukocyte count and lactate dehydrogenase and C-reactive protein levels were within the normal range. Her initial lung function showed a decline in forced expiratory volume in 1 second

(FEV₁) to 1.52 (L). Chest radiography revealed infiltration in the right upper lung field (**Figure 1A**), and chest CT demonstrated bronchial wall thickening, centrilobular nodules, and mosaic attenuation compatible with the diagnostic criteria of ABPA (**Figure 1B**). Before initiating any additional treatment, her AHR value was measured using histamine and was found to be 2,062.1 (μ g/mL), which was a strong positive value.

Based on these findings, including parenchymal radiological changes, we diagnosed ABPA with profound asthmatic symptoms (asthma control test [ACT] score of 16). Given her uncontrollable symptoms, mepolizumab (100 mg every 4 weeks) was initiated. As a result, her blood eosinophil count was decreased to 54 cells/ μ L (0.9%), FEV₁ value was increased to 2.31 (L), chest CT showed partial improvement regarding infiltration previously seen in the lung field (**Figure 1C**), AHR value improved from 2,062.1 to 23,201.78 (μ g/mL) (**Figure 2**), and finally resulted in a superior ACT score of 23 after 6 months of mepolizumab, without any adverse events. These results after mepolizumab initiation suggested that parenchymal radiological changes were, at least partially, caused by eosinophilic inflammation of asthma and ABPA, rather than AF infection.

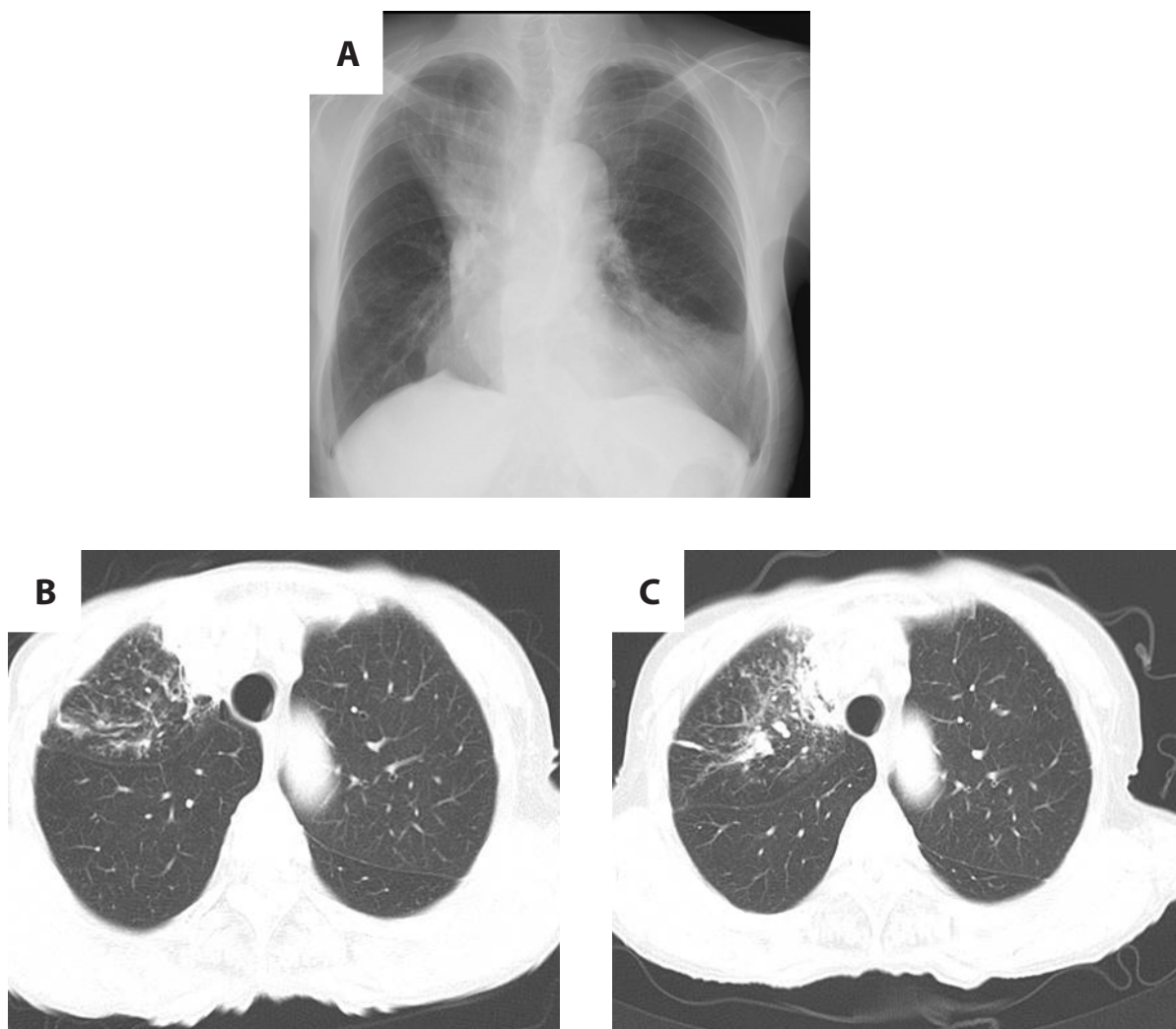


Figure 1. Clinical images of current case. Initial (A) chest X-ray and (B) chest CT images. (C) Chest CT image after treatment with mepolizumab.

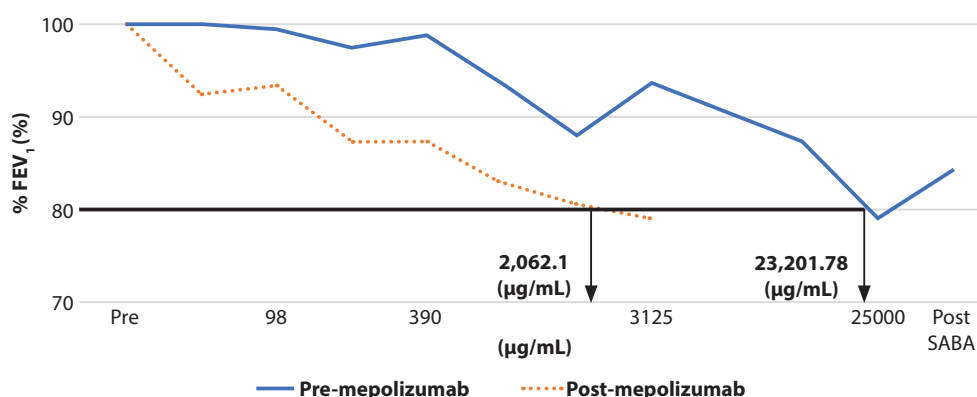


Figure 2. AHR value of pre- and post-administration of mepolizumab.

Discussion

Herein, we report a case of ABPA with improvement in AHR following additional monthly mepolizumab therapy. The patient showed improvements in terms of pulmonary function, chest CT, AHR, and ACT score after peripheral blood eosinophil counts were reduced with mepolizumab therapy.

Mepolizumab is a monoclonal antibody against IL-5, the key cytokine that activates eosinophils.¹⁰ Mepolizumab reportedly reduces the frequency of asthma exacerbations and exhibits a corticosteroid-sparing effect in patients with eosinophilic asthma and systemic corticosteroid-dependent severe asthma.^{5,6} Furthermore, mepolizumab is recommended for patients with asthma presenting both a high peripheral eosinophil count and total IgE > 1,500 IU/mL. A case series of patients with ABPA has demonstrated the effectiveness of mepolizumab, but the degree of AHR improvement was unknown.^{8,11}

AHR is orchestrated by the number of inflammatory cells within the tissue and lumen of asthmatic airways.¹² Among the proteins released by eosinophils, major basic protein (MBP) is related to AHR.¹³ In a study using an *Alternaria*-induced asthma mouse model, IL-5, IL-13, and IL-33 were shown to be sufficient to drive airway eosinophilia with AHR.¹⁴ Additionally, a recent study has demonstrated that patients with asthma show improvements in AHR following treatment with either mepolizumab or benralizumab, an anti-IL-5 receptor antibody.¹⁵ Therefore, eosinophils and related inflammatory cytokines are suggested to play a crucial role in AHR in asthmatic airways. Other than eosinophils, T helper 2 (Th2) cells, type 2 innate lymphoid cells (ILC2s), and natural killer T (NKT) cells are known to modulate AHR. In our current case, mepolizumab treatment reduced AHR but did not completely eliminate the reactivity. This observation suggests that eosinophils are likely to play a pivotal role in AHR but are not the only cells involved in this reaction.

Recent reports described the efficacy of omalizumab, a humanized anti-IgE antibody, for treating ABPA.¹⁶ As clinical trials assessing mepolizumab excluded patients with ABPA, therefore the true efficacy of mepolizumab among subjects with ABPA is not clear.^{5,6} In the present case, the serum IgE level was suppressed with oral corticosteroid, but the blood eosinophil count stayed elevated. Accordingly, we considered that oral corticosteroids did not suppress IL-5-induced eosinophilic inflammation, thus initiating mepolizumab treatment. In addition, a previous case study of ABPA treated with combined mepolizumab and omalizumab has been reported.¹⁷ To the best of our knowledge, this is the first report to demonstrate the efficacy of mepolizumab as a treatment for ABPA by improving AHR.

Conclusion

Double-blind, placebo-controlled trials are necessary to determine the efficacy and safety of newly developed treatment for ABPA.

Conflict of interest

The authors have none to declare.

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Authors' contributions

- All authors have read, approved, and showed significant contribution toward this manuscript.
- Conception and design: CO, TH, HS
- Manuscript writing: CO, TH, TKa
- Correction: TKi, YM
- Final approval of manuscript: CO, TH, HS
- Also, all authors approved the final version of the manuscript.

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