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CASE REPORT

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Severe asthma remaining well-controlled after mepolizumab discontinuation: A case report and literature review

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Abstract

Mepolizumab, a humanized anti-IL-5 monoclonal antibody used for severe asthma, results in a reduced rate of asthma exacerbation, improved lung function, reduced oral corticosteroid use, and improved quality of life. A 62-year-old man using high-dose inhaled corticosteroid visited our hospital because of poorly-controlled asthma. He had eosinophilia in peripheral blood and sputum, and high levels of fraction of exhaled nitric oxide. Therefore, he was treated with mepolizumab for severe asthma. Mepolizumab treatment resulted in significantly improved pulmonary function and reduced frequencies of asthma exacerbations. Because of his good asthma control, mepolizumab treatment was discontinued after 3 years. Since discontinuing mepolizumab, his asthma control has remained without exacerbation. Previous studies suggest that mepolizumab should be continued to sustain clinical benefits. However, cases of long-term controlled asthma have not been reported after mepolizumab withdrawal, and our case may be instructive.

KEYWORDS
asthma control, eosinophil, mepolizumab, severe asthma

INTRODUCTION

Patients with severe asthma uncontrolled despite standard therapy may be considered candidates for biologic therapy. Currently, biologics targeting IgE, IL-5, IL-5 receptor (IL-5R), IL-4 receptor, and TSLP are available. Although these biologics have been shown to reduce asthma exacerbation rates and improve lung function and quality of life,[1] little is known about the effects of withdrawal after long-term biological treatments. Here, we report a case of asthma well-controlled without exacerbation after withdrawal of mepolizumab, an anti-IL-5 antibody.

CASE REPORT

A 62-year-old man presented with cough, wheezing, and dyspnea. He was a former smoker (111 pack years) and had a medical history of chronic sinusitis and allergy to theophylline and levofloxacin, which caused skin rash and itching. His chest computed tomography (CT) scans showed consolidation in the right lower lobe and emphysema and bronchial wall thickening in bilateral lung fields (Figure 1A). He was admitted to the community hospital with a diagnosis of pneumonia with asthma and/or chronic obstructive pulmonary disease (COPD). He was treated with antibiotics, ICS/long-acting β_2 agonist (LABA) (fluticasone/salmeterol 500/100 μg), and long-acting muscarinic antagonist (LAMA) (tiotropium 5 μg). His symptoms improved, and he was discharged. However, as wheezing and dyspnea flared up in a few days, he was readmitted to the hospital. Upon admission, he was reevaluated and diagnosed with severe asthma and COPD based on eosinophilia in peripheral blood and sputum, elevated serum IgE level, emphysema, and bronchial wall thickening on chest CT. Short-term oral corticosteroids (OCS) was administered due to an asthma attack. Furthermore, as a step-up therapy

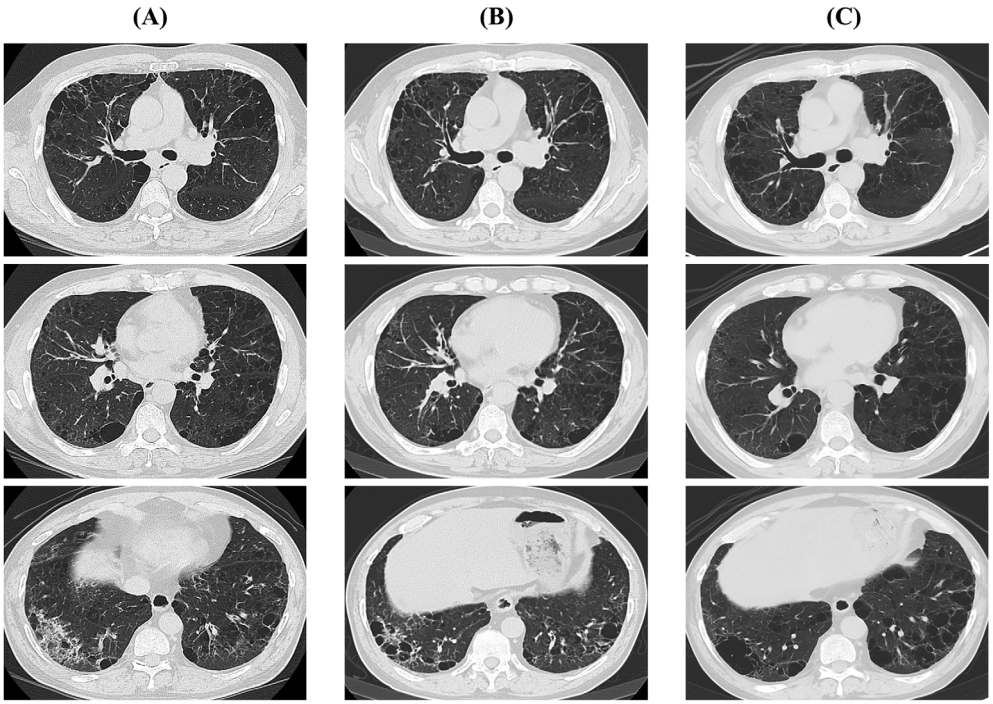

FIGURE 1 The findings of chest computed tomography (CT). (A) In the community hospital, his chest CT showed consolidation in the right lower lobe and emphysema and bronchial wall thickening in bilateral lung field. (B) Before mepolizumab treatment, while consolidation in the right lower lobe improved, bronchial wall thickening in bilateral lung field remained. (C) After mepolizumab treatment, bronchial wall thickening improved.

for asthma, his inhaler medication was switched to high-dose ICS/LABA (budesonide/formoterol 1280/36 μg) in addition to tiotropium, and montelukast 10 mg/day was added. However, wheezing and dyspnea were exacerbated by exposure to cold air during an overnight stay at home, and he was treated with systemic corticosteroids under respiratory control with non-invasive positive pressure ventilation for a severe asthma attack. After discharge from the hospital, frequent short-term administration of OCS for asthma control was necessary. Therefore, he was referred to our hospital for asthma control.

Physical examination revealed wheezes on chest auscultation bilaterally. Laboratory examination revealed increased peripheral blood eosinophil numbers (698 /μL) and elevated serum IgE level (1077 IU/mL). Serum-specific IgE was positive for house dust mites (*Dermatophagoides* species) and fungus (*Alternaria*, *Candida*, and *Aspergillus*) (Figure 2A). Pulmonary function test showed obstructive pulmonary dysfunction (FEV1: 1.17 L, FEV1% (FEV1/FVC): 40.63%) and the absence of bronchodilator reversibility (<12% or <200 mL change in FEV1). The fraction of exhaled nitric oxide (FeNO) was elevated (108 ppb) (Figure 2B). Chest CT scans showed that consolidation in the right lower lobe improved, but that bronchial wall thickening in bilateral lung field remained (Figure 1B). Because he had refractory asthma, we listed allergic bronchopulmonary mycosis (ABPM) as a differential diagnosis. In the new clinical diagnostic criteria for ABPM,[2] he met four criteria: asthma diagnosis, peripheral blood eosinophil numbers (≥500 cells/mm^3), serum IgE levels (≥417 IU/mL), and specific IgE for *Aspergillus*. However, he did not have central bronchiectasis and high-attenuation mucus in his chest CT findings, and filamentous fungal growth in sputum cultures was not detected. Based on these findings, we ruled out ABPM and diagnosed severe asthma.

Despite inhaler instruction and confirmation of inhaler adherence, he had repeated hospitalizations for asthma attacks. Therefore, he was treated with mepolizumab (100 mg/4 weeks). After initiation of mepolizumab, his condition gradually improved; increased levels of FEV1, better score on the asthma control test (ACT), decreased levels of FeNO, and decreased frequencies of asthma exacerbations were recorded. Bronchial wall thickening in bilateral lung fields was improved, but emphysema remained unchanged (Figure 1C). His mepolizumab administration was discontinued of 3 years. After the withdrawal of mepolizumab treatment, the number of eosinophils in peripheral blood increased, but asthma has remained under control without hospitalization or short-term OCS use; levels of FEV1 and ACT was well maintained. Furthermore, he was able to step down to a moderate-dose ICS/LABA+LAMA as controller medication (Figure 3).

DISCUSSION

Mepolizumab prevents IL-5 from binding to its receptors on eosinophils, leading to reduced eosinophil count in peripheral blood and sputum.[1] In clinical studies, mepolizumab shows reduced asthma exacerbation rates, improved lung

(A)

【Laboratory test】

<Hematology>

WBC	8120 /μl
Neu.	64.2%
Lym.	22.0%
Mon.	4.6%
Eos.	8.6%
Bas.	0.6%
RBC	489 × 10^4 /μl
Hb	14.9 g/dl
Ht	45.3%
PLT	20.4 × 10^4 /μl

<Arterial blood gas>

Room air, RR 24 /min

pH	7.422
PaO_2	78.3 Torr
$PaCO_2$	39.0 Torr
HCO_3^-	24.9 mEq/l
A-aDO_2	23.0 Torr

<Biochemistry>

TP	6.7 g/dl
Alb	4.1 g/dl
AST	30 IU/l
ALT	56 IU/l
LDH	228 IU/l
ALP	419 IU/l
CK	44 IU/l
γ-GTP	67 IU/l
BUN	13.2 mg/dl
Cr	0.69 mg/dl
CK	44 IU/l
Na	140 mEq/l
K	4.0 mEq/l
Cl	107 mEq/l

<Serology>

CRP	0.27 mg/dl
KL-6	447 U/ml
IgE	1077 IU/ml
ANA	< × 40
β-D glucan	<5 pg/ml
MPO-ANCA	(-)
PR3-ANCA	(-)

Specific IgE antibody

House dust	class 2
Dermatophagoides farina	class 2
Dermatophagoides pteronyssinus	class 2
Dactylis	class 2
Alternaria	class 3
Candida	class 3
Aspergillus	class 3

<Sputum>

Eosinophil	(3+)

(B)

【Pulmonary function test】

VC	3.10	L	(91.2%)
FVC	2.88	L	(86.2%)
FEV_1	1.17	L	(42.5%)
FEV_1/FVC	40.63	%	
%DLco	57.9	%	
Bronchodilator reversibility test	FEV_1 +130 mL (+11.1%)		
FeNO	108	ppb	

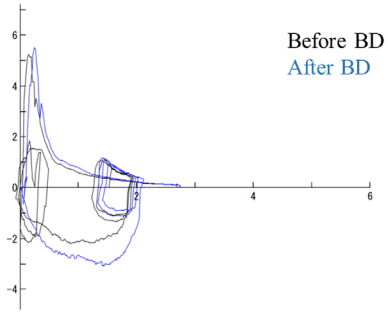

FIGURE 2 (A) Laboratory findings on first visit. (B) The findings of pulmonary function test and fraction of exhaled nitric oxide (FeNO) on first visit. BD, bronchodilator.

function and OCS-sparing effect.[3,4] However, the effects of mepolizumab withdrawal are not understood enough. In the follow-up study discontinuing mepolizumab after 12-month treatment, eosinophil numbers in peripheral blood and sputum increased within 3 months, and the frequencies of asthma exacerbation also significantly increased.[5] Further, in the recent study evaluated the effects of withdrawal after long-term (>3 years) mepolizumab therapy, a higher proportion of patients who discontinued mepolizumab had increased frequencies of asthma exacerbation, worsened asthma control and increased eosinophil numbers in peripheral blood compared with those who continued.[6] To date, cases of long-term controlled asthma have not been reported after mepolizumab withdrawal. These studies suggest that mepolizumab should be continued to sustain clinical benefits. While our case showed a slightly increased peripheral blood eosinophil counts after mepolizumab withdrawal, the frequencies of asthma exacerbation and asthma control did not worsen for 2 years, and he has achieved good asthma control even after step-down to a moderate-dose ICS/LABA and LAMA.

Asthma remission is defined as a high level of disease control, such as sustained absence of signs and symptoms, and normalization and/or optimization of lung function with or without ongoing treatment. Actually, the addition of biologics achieves multiple criteria for asthma remission on treatment.[7] The percentage of remissions has been shown to reach approximately 30% after 1 year in patients treated with mepolizumab.[8,9] The characteristics of patients successfully discontinuing mepolizumab have been shown to have fewer asthma symptoms, well-controlled asthma comorbidities and suppressed type 2 inflammation, such as lower blood eosinophil counts and/or FeNO levels, during the treatment of mepolizumab.[10] Further, Hamada K et al. present two cases of severe eosinophilic asthma withdrawing the treatment of benralizumab, anti-IL-5R antibody. Asthma in one case sustained well-controlled, while asthma in the other was deteriorated in 6 months. The differences between these two cases were a smoking history and the presence of asthma comorbidities.[10] Our case had a smoking history and a history of chronic sinusitis as well as the latter case.

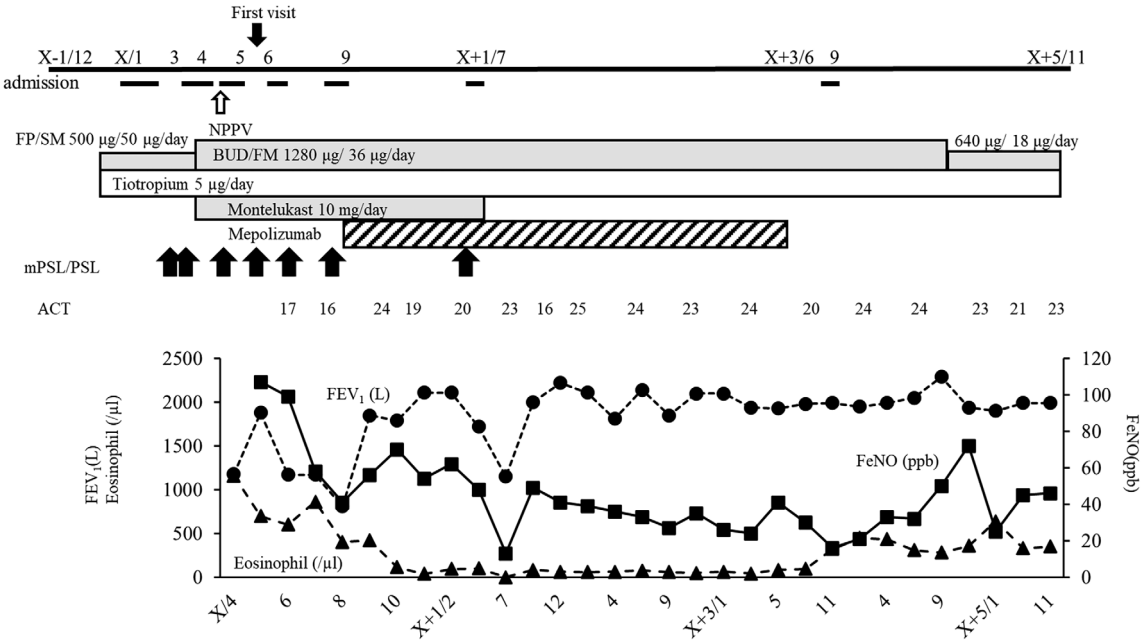

FIGURE 3 Clinical course. ACT, asthma control test; BUD/FM, budesonide/formoterol; FeNO, fraction of exhaled nitric oxide; FP/SM, formoterol/budesonide; NPPV, non-invasive positive pressure ventilation.

However, as his current chronic sinusitis was asymptomatic, his clinical characteristics were different from the deteriorated case. Thus, controlled comorbidities may be one of the factors contributing to the successful withdrawal of biologics.

Mesnil et al. have revealed that there are two different subtypes of eosinophils in a study using mice: "inflammatory eosinophils (iEOS)" as proinflammatory effector cells and "resident eosinophils (rEOS)'' as immunosuppressive cells via immune regulation and homeostasis.[11] Another report has also shown that long-term mepolizumab treatment restores the kinetics of eosinophils as normally found in homeostasis.[12] Thus, mepolizumab may induce rEOS dominance. However, there is no evidence that anti-IL-5 antibody increase the numbers or frequencies of rEOS, which has suppressive activity in our case, so far. On the other hand, antigen-specific regulatory T cells (Tregs) express IL-5R, and IL-5 may promote antigen-specific Tregs to induce immune tolerance in a murine model.[13] In peripheral blood of severe eosinophilic asthmatics, the frequencies of Tregs have been shown to be increased by mepolizumab treatment.[14] Thus, mepolizumab may suppress airway inflammation by increasing the frequencies of Tregs. In contrast, the treatment of benralizumab decreased the frequencies of Tregs in peripheral blood.[15] Furthermore, decreased response of basophils and mast cells to allergens was observed in patients with well-controlled asthma after withdrawal of omalizumab, an anti-IgE antibody.[16] These findings suggest that biologics may alter the natural course of severe asthma and achieve clinical remission by affecting the function of inflammatory cells.

We experienced a case of severe asthma well-controlled even after mepolizumab withdrawal. Currently, the difference between patients with and without asthma exacerbated after the withdrawal of mepolizumab has not been clear. The analysis of eosinophil subsets before and after mepolizumab administration may provide clues to solve this problem.

AUTHOR CONTRIBUTIONS

Takahiro Matsuyama, Kentaro Machida, and Hiromasa Inoue conceived, designed, and drafted the article. Takahiro Matsuyama, Yuya Tomioka, Hiromi Matsuyama, Yusuke Kamenohara, Kengo Tanigawa, Yoichi Dotake, Yoko Hagihara, Koichi Takagi and Hiromasa Inoue are attending physicians, and were involved in the data collection. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

Hiromasa Inoue reports grants from Boehringer-Ingelheim, GlaxoSmithKline, Kyorin and Ono with all payments going to his affiliated institution, and personal fees from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Kyorin, Novartis and Sanofi. Hiromasa Inoue reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events to AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Kyorin, Novartis and Sanofi. Hiromasa Inoue has participation on a data safety monitoring advisory

board to AstraZeneca, GlaxoSmithKline, Novartis and Sanofi. Hiromasa Inoue reports leadership or fiduciary role in Board of Directors in Japanese Respiratory Society, unpaid.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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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