Effectiveness of mepolizumab for eosinophilic pneumonia following bronchial thermoplasty

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Abstract
A 57-year-old woman with poorly controlled diabetes was admitted to our hospital for additional treatment of severe asthma. Although bronchial thermoplasty was performed in the both upper lobes, cough and dyspnoea gradually appeared 2 weeks later. High-resolution computed tomography revealed thickness of intralobular septa and a diffuse ground-glass attenuation in the lung fields. Laboratory examination revealed elevated levels of serum eosinophils and total immunoglobulin E. Bronchoalveolar lavage fluid showed a remarkable increase of eosinophils as high as 48.5%, then eosinophilic pneumonia was diagnosed. Although treatment with steroids resulted in an improvement of eosinophilic pneumonia, the treatment was discontinued after 4 days because it worsened her diabetic condition. Since eosinophilic pneumonia recurred after discontinuing steroid, mepolizumab was administered, which subsequently improved her disease condition. Clinicians should be aware that bronchial thermoplasty can lead to eosinophilic pneumonia and mepolizumab might be an effective treatment in this setting.

Introduction
Bronchial thermoplasty (BT) is a bronchoscopic procedure for treating severe asthma using thermal energy to reduce airway smooth muscle. It reportedly improves quality of life and exacerbation of asthma [1]. Although there are some reports of complications such as bronchitis and atelectasis due to transient inflammation and oedema, to the best of our knowledge, no studies have reported eosinophilic pneumonia (EP) due to BT [2,3]. Mepolizumab is an anti-interleukin (IL)-5 monoclonal antibody that is reportedly effective against eosinophilic inflammation such as bronchial asthma; however, only few studies have reported its use in treating EP [4,5]. Here, we report the effectiveness of mepolizumab in treating EP following BT.

Case Report
A 57-year-old woman with a history of type 1 diabetes, which was managed with insulin, was diagnosed with bronchial asthma by her primary care doctor in 2013. Despite undergoing step 5 treatment according to the guidelines of Global Initiative for Asthma for severe asthma with high-dose inhaled therapy (fluticasone furoate 200 μg/day, vilanterol 25 μg/day and tiotropium 18 μg/day) and montelukast sodium 10 mg/day, she experienced frequent asthma attacks at night and her peak expiratory flow was 230–270 L/min. Subsequently, she was referred to our hospital for additional treatment in January 2017 because her asthma was poorly controlled despite adequate pharmacological therapy. Chest radiography showed lung hyperinflation, and chest high-resolution computed tomography (HRCT) revealed thickened bronchial walls (Fig. 1A,B). Laboratory examination revealed elevated levels of serum eosinophils at 413/μL (8.1%) and total immunoglobulin E (IgE) at 195 U/mL. Her HbA1c level was high at 8.1% despite the use of insulin. Because her asthma did not improve despite a modification in inhaled medication and guidance on how to inhale and she refused a treatment with anti-IL-5 monoclonal antibody due to its inconvenient injection schedule, treatment with BT was initiated. BT was performed in the right lower lobe in March and in the left lower lobe in May 2017 without any complications. After first and second BT, her asthma was stable and she had
disappearance of night symptoms for the first time in several years. Although a third procedure of BT was performed in the both upper lobes in July 2017, cough and dyspnoea gradually appeared after two weeks of BT. Physical examination revealed wheezing in the entire lung field and peripheral capillary oxygen saturation was 94% in room air. Chest radiography showed a ground-glass attenuation (GGA) in both lower lung fields, and HRCT showed thickening of the interlobular septa and a diffuse GGA predominantly in the lower lobe, which was consistent with acute EP (Fig. 2A–C). Laboratory examination revealed elevated levels of eosinophil at 3780/μL (43.8%) and total IgE at 5453 U/mL. Anti-neutrophil cytoplasmic antibodies was negative. Bronchoalveolar lavage fluid (BALF) from the right middle lobe (B4) revealed a remarkable increase of eosinophils as high as 48.5%; no significant bacteria were detected. On the basis of these results, EP was diagnosed. After we started treatment with methylprednisolone (40 mg/day), her symptoms and GGA improved, and peripheral eosinophil count returned to normal. However, the treatment with steroids was discontinued after four days because of the worsening of diabetes. This resulted in relapsed symptoms of asthma and elevated levels of serum eosinophils; therefore, mepolizumab 100 mg/day was administered instead of steroids. Following single dose of mepolizumab, her symptom, GGA and elevated levels of eosinophils improved, and EP did not relapse after that.

Discussion

We herein report a case of the effectiveness of mepolizumab in treating EP following BT. Two prospective multi-centre studies have reported several respiratory adverse events following BT; however, to the best of our knowledge, no study has reported EP as a complication of BT [2,3]. In our case, although it is difficult to clearly demonstrate the implication between BT and eosinophilia, severe and acute eosinophilia and high IgE just after third BT procedure suggested that BT may trigger the eosinophilic inflammation. Importantly, lung involvement spread to not only upper lobes in which BT was directly performed but also the whole lung field. In addition, she had no history of EP before this event, and recurrence of EP has not occurred until now. It suggested that BT may cause systemic eosinophilic inflammation and pulmonary infiltration of eosinophilia, resulting in acute EP. Thus, we suppose the causative relationship between BT and EP is acceptable. Our results could provide the following two clinical implications.

First, BT potentially causes EP. Some complications due to BT such as atelectasis, organized pneumonia and necrosis, which are regional lesions, have been reported [2,3]. In reports with pathological examinations, these lesions were considered to reflect local inflammation and oedema in response to the thermal energy applied [6,7]. In the present case, the lesions extended to the whole lung field other than upper lobes in which BT was directly performed. The extended lesions and elevated levels of serum eosinophil and total IgE suggest that systemic eosinophilic inflammation is induced due to any stress of BT. We have proposed two hypotheses about this reaction. First, airway epithelial cells were damaged by physical stimulation of BT, and the cells became sensitive to allergens. These cells play an important role in the defence mechanism against environmental factors. In case of asthma, there is evidence in vivo.
and in vitro that the barrier function of airway epithelial cells is impaired [8]. In the present case, additional damage caused to the impaired airways epithelial cells by BT allowed an easy invasion of environmental factors which trigger allergic eosinophilic inflammation. Second, another hypothesis is that allergic eosinophilic inflammation would be induced by physical stimulation of BT. In general, it has been considered that in allergic eosinophilic inflammation, allergens stimulate airway epithelial cells, subsequently activating eosinophils and B cells. However, this reaction may not occur in cases involving non-allergic substances such as contaminants, microorganisms, and physical stimulation [9]. Conversely, recent studies have reported that cytokines such as thymic stromal lymphopoietin, IL-25 and IL-33, which are produced by epithelial cells damaged by stimulating factors other than allergens, induce allergic eosinophilic inflammation [10]. Based on these findings, the cytokines activated by BT-induced physical stimulation against airway epithelial cells might induce both non-allergic and allergic inflammation.

The second clinical implication of this case report is that mepolizumab would have an effect on EP. Mepolizumab is an anti-IL-5 monoclonal antibody and is reportedly effective in treating severe bronchial asthma [4]. In addition, the efficacy of mepolizumab in treating several other eosinophilic diseases, including eosinophilic granulomatosis with polyangiitis, has been reported [5,11]. Although there are a few reports suggesting the effectiveness of mepolizumab in treating EP, it still remains unclear [12,13]. But, it has been reported that blood IL-5 and BALF IL-5 levels are elevated in EP and IL-5 seems play an important role in the pathogenesis of EP [14]. Therefore, it is reasonable that mepolizumab suppresses levels of IL-5 and infiltration of eosinophils, resulting in the resolution of CT findings and decreased eosinophilia and symptoms [15]. Although mepolizumab has not been approved for treating EP, it may be a treatment option for patients with severe asthmatic symptoms and difficulty in using corticosteroid owing to their side effect.

In conclusion, we presented the effectiveness of mepolizumab for EP following BT. It was suggested that BT would occur with EP and mepolizumab may be effective against EP. Accumulation of case series will confirm our results.

Disclosure Statements
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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