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【 CASE REPORT 】

Bronchial Thermoplasty for Severe Asthma with Mucus Hypersecretion

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Abstract:
Bronchial thermoplasty (BT), which delivers thermal radiofrequency to the bronchial wall, is an effective therapy for patients with severe persistent uncontrolled asthma. We herein report the case of a 47-year-old man who underwent BT for uncontrolled severe asthma. After BT, his asthma control, asthma-related quality of life, and pulmonary function improved. Furthermore, a histologic examination of transbronchial biopsy specimens revealed a decrease in goblet cell hyperplasia and the smooth muscle mass as well as in the subepithelial basement membrane thickness. BT can be effective for patients with severe uncontrolled asthma and mucus hypersecretion.

Key words: bronchial thermoplasty, severe asthma, hypersecretion

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Introduction

Bronchial thermoplasty (BT) involves the delivery of thermal radiofrequency to the bronchial wall. It is an effective non-pharmacologic therapy for patients with severe persistent uncontrolled asthma (1). BT has been known to inhibit bronchoconstriction by reducing the airway smooth muscle mass (2, 3), subepithelial bronchial thickness, and number of bronchial nerve cells (4). However, the effect of BT on the bronchial epithelium has been unclear.

We herein report a patient whose asthma control, asthma-related quality of life, and pulmonary function improved along with the histologic confirmation of a decrease in goblet cell hyperplasia after BT.

Case Report

A 47-year-old non-smoking man was referred for severe persistent asthma. He had been diagnosed with asthma at 16 years of age. Since then, his symptoms had been poorly controlled, and he frequently experienced severe exacerbations that required unscheduled systemic steroid administration. One year prior to this consult, he suffered two instances of severe exacerbation that were treated by intravenous corticosteroids. His asthma remained poorly controlled despite maximal medical therapy with the subcutaneous injection of omalizumab 600 mg every 2 weeks; inhaled fluticasone furoate 100 μg/vilanterol 25 μg and tiotropium 5 μg; and oral theophylline 400 mg and montelukast 10 mg. Therefore, he was referred to our hospital to undergo BT.

He was allergic to house dust mites and moths. His comorbid conditions were atrial fibrillation and hyperuricemia. He had no remarkable family history. His occupation was a clerk in a lawyer's office. His physical findings were significant for wheezing in the bilateral lung fields.

Spirometry performed before BT showed a forced expiratory volume in 1 second (FEV_1) of 1.92 L (52.2% predicted) and a forced vital capacity (FVC) of 4.78 L (111.4% predicted). The FEV_1/FVC ratio was 40.2%, and the shape of the flow-volume curve suggested obstructive airway disease. Computed tomography (CT) of the chest showed bronchial wall thickness and air trapping in the expiratory phase.

Three BT procedures were completed without major adverse events. During the first BT procedure, an endobronchial inspection revealed significant findings of a large amount of yellow-white secretion that grew *Hemophilus influenzae* on culture. Cytology of the sputum revealed neutro-

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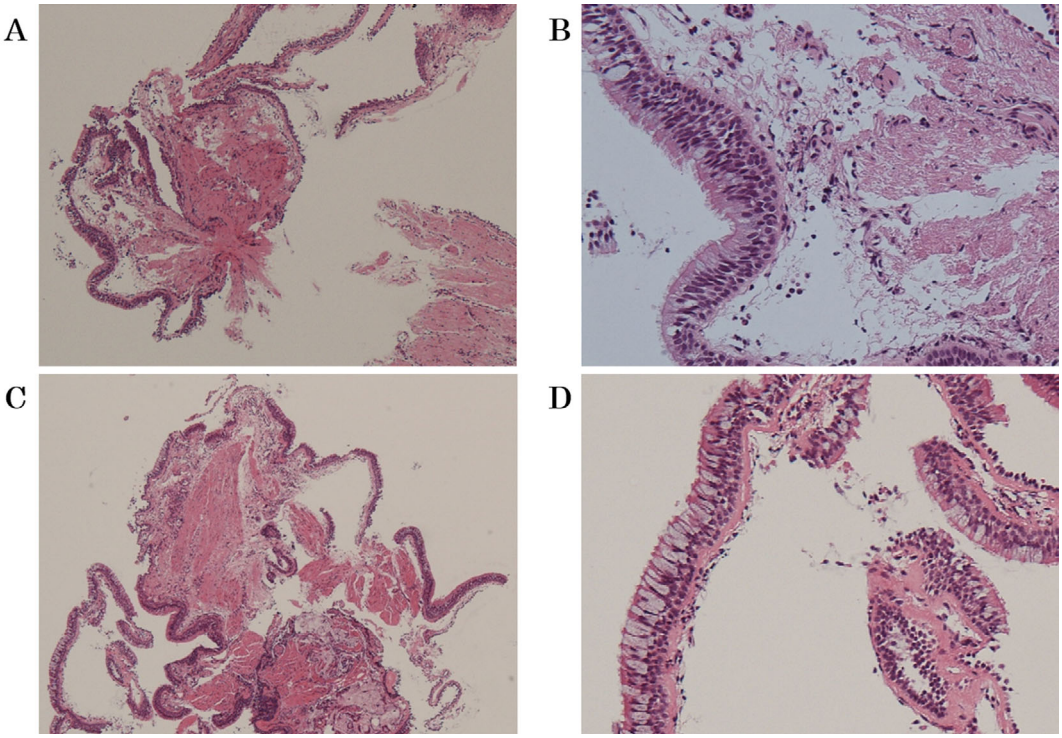

Figure 1. Photomicrograph of the TBB specimens during the third bronchial thermoplasty treatment. A pathologic examination of the TBB specimens revealed goblet cell hyperplasia and lower bronchial smooth muscle mass with a thinner subepithelial basement membrane in the right lower lobe bronchus B8 specimen [Hematoxylin and Eosin (H&E) staining; A: ×40 and B: ×400] than in the right middle lobe bronchus B4 specimen (H&E staining; C: ×40 and D: ×200). TBB: transbronchial biopsy

phil 2+, lymphocyte 1+, and no eosinophils. Clarithromycin 200 mg daily was added to treat the endobronchial secretions. However, during the second and third BT procedures, yellow-white secretion was still detected, growing *Pseudomonas aeruginosa* and *Acinetobacter baumanii*, respectively.

Six weeks after the first BT treatment, a transbronchial biopsy (TBB) through the right lower lobar bronchus (B8) and the right middle bronchus (B4) was performed using fiberoptic bronchoscopy. A pathologic examination of the TBB specimen of B8 demonstrated less severe goblet cell hyperplasia than that of the B4 specimen (Fig. 1), to which thermal energy had not been applied. In addition, the bronchial smooth muscle mass was smaller and the subepithelial basement membrane thinner in the B8 specimen than in the B4 specimen (Fig. 1).

One month after the third BT treatment, improvements were noted in the Asthma Control Questionnaire 5 (1.8 to 0.2) and the Asthma Quality of Life Questionnaire (AQLQ; 4.1 to 6.8). The patient claimed that his sputum had decreased in amount, and he no longer coughed when taking deep breaths and inhaling cold air. On spirometry, there were increases in the values of FEV_1 (1.92 L to 3.55 L) and $\%FEV_1$ (52.2% to 98.3%). The shape of the flow-volume curve at this time was normal. Chest CT after BT showed significant improvement in the bronchial wall thickness and air trapping (Fig. 2).

Discussion

In this patient with severe persistent asthma, BT improved his symptoms, quality of life (QOL) score, respiratory function, chest imaging findings, and histologic components. Previous studies have reported that BT reduced the number of exacerbations and improved the QOL of patients with severe refractory asthma (1). The major mechanism of action of BT is the reduction of the airway smooth muscle mass (2, 3).

This patient showed a decrease in goblet cell hyperplasia at the site of BT (i.e., B8) and its adjacent bronchus B9. Goblet cell hyperplasia was present in almost the entire epithelial area, but the area that received BT showed a decrease in hyperplasia. Because we performed only one biopsy sampling from B4, further pathologic investigation could not be performed. Nevertheless, after BT, there was obvious residual goblet cell hyperplasia in B4 compared with B8 and B9.

Pretolani et al. analyzed the histopathologic changes in patients who underwent BT (4) and showed that 6 of 15 patients exhibited a decrease in goblet cell hypertrophy/hyperplasia. In the middle lobe, there may be transient ground glass opacities after BT (3), but in general, there was no pathologic confirmation of a decrease in goblet cell hyperplasia. Although the present case was similar to other cases previously reported to have a decrease in goblet cell hyper-

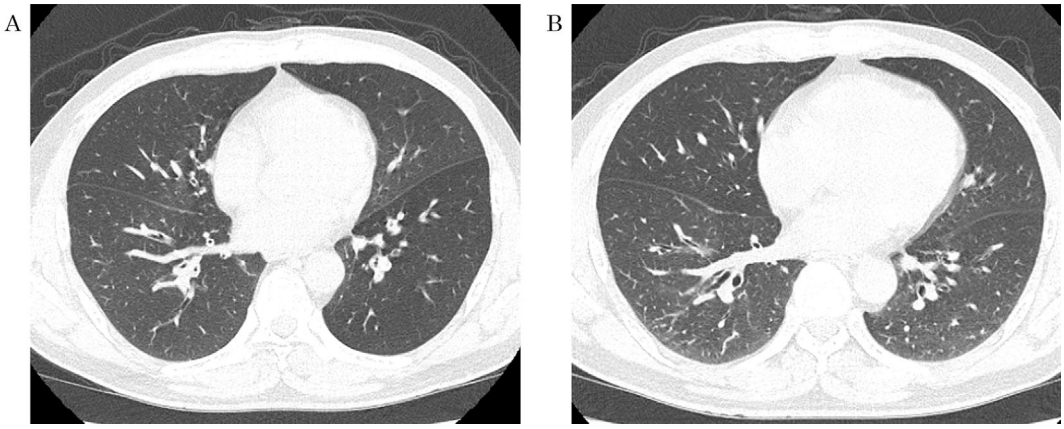

Figure 2. Chest CT scans in a patient with severe persistent asthma. Before BT, there was substantial bronchial wall thickness and air trapping in the expiratory phase (A). After BT, there was significant improvement in these findings (B). CT: computed tomography, BT: bronchial thermoplasty

plasia after BT (4), we were able to perform pathologic comparisons between treated and untreated regions in a single patient. In our patient, the subjective decrease in sputum after BT may have been brought about by the decrease in goblet cell hyperplasia. However, we did not objectively prove a decrease in the amount of sputum production.

The severity of airway inflammation can sometimes vary according to the involved bronchi. Therefore, there may be heterogeneity in the cells that comprise the airway mucosa. In this patient, CT in the expiratory phase before BT exhibited a similar degree of air trapping between S4 and S8. However, on CT after BT, only S8 showed ground-glass opacity; this may have represented the improvement of air trapping brought about by the BT intervention. Therefore, the pathological differences between B4 and B8/B9 were likely due not to the pre-existing heterogeneity but to the efficacy of BT.

Clarithromycin, which was prescribed after the first BT procedure, is an optional medication for asthma treatment. Previous studies have shown that clarithromycin was effective in improving the symptom scores (5), AQLQ scores (6), and airway hyperresponsiveness (7). Therefore, the addition of clarithromycin may have contributed to the improvement of asthma in this patient. In addition, clarithromycin has been known to inhibit goblet cell hyperplasia in human airway cells (8). Although the administration of clarithromycin may have influenced the histologic changes in goblet cell hyperplasia in this patient, it does not fully explain the localized changes in the lower bronchus. In hindsight, the three different bacteria detected in the secretions collected during each BT procedure were probably airway colonizers, not true pathogens, based on the absence of signs of airway infection, such as a fever and elevation of inflammatory markers, as well as changes in his chest imaging findings throughout the three BT sessions. Furthermore, his clinical findings improved despite the fact that the two bacteria detected in the secretions were innately resistant to clarithromycin.

In conclusion, we pathologically proved the effect of BT on the airway mucosa in a patient with severe uncontrolled asthma with mucus hypersecretion. Further studies will be required to confirm the mechanism underlying the effects of BT treatment on the airway epithelium.

The authors state that they have no Conflict of Interest (COI).

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