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Case Report

Long-term Follow-up of a Patient with Localized Bronchiectasis Complicated by Bronchial Aspergillosis After Bronchial Thermoplasty: A Case Report and Literature Review

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Clinical Question Box

What is the clinical course of a patient with postoperative bronchial aspergillosis after bronchial thermoplasty?

Allergic bronchopulmonary aspergillosis, chronic pulmonary aspergillosis, or an overlap of these conditions may arise, necessitating antifungal treatment, systemic corticosteroids, or both. Following these therapies, some patients may develop localized bronchiectasis, which can lead to chronic airway infections requiring further treatment strategies.

Abstract

Background: Bronchiectasis remains incompletely understood in terms of its causes, progression, and treatment strategies. It frequently arises as a secondary condition, underscoring the need to include it as a differential diagnosis during clinical evaluation. **Case Presentation:** A 35-year-old woman with type 2 severe bronchial asthma presented with persistent symptoms two weeks after bronchial thermoplasty (BT). Chest computed tomography revealed bronchial wall thickening and bronchiectasis in the left B8 bronchus. Bronchoscopy showed cultures positive for *Aspergillus fumigatus* from bronchial lavage fluid, and transbronchial biopsy revealed hyphae. The patient was diagnosed with bronchial aspergillosis localized to the left B8 bronchus as a postoperative complication of BT. Treatment with voriconazole for six months led to gradual improvement in bronchial aspergillosis, with imaging showing resolution of bronchial wall thickening and a trend toward improvement in bronchiectasis. Persistent yellow sputum prompted repeat bronchoscopy, revealing negative *Aspergillus fumigatus* cultures but positive *Staphylococcus aureus*, indicating localized bronchiectasis with chronic airway infection. Symptoms partially improved with low-dose erythromycin after limited response to repeated amoxicillin/clavulanic acid. Asthma control also improved post-BT. **Conclusions:** Bronchial aspergillosis is a rare complication of BT that can progress to localized bronchiectasis and chronic airway infections, necessitating careful long-term follow-up. The disease course appears similar to other types of bronchiectasis, even when it develops as a complication of BT.

Keywords: Bronchiectasis, bronchial thermoplasty, bronchial aspergillosis, bronchial asthma, *Aspergillus fumigatus*, case report.

Introduction

Despite advancements in the treatment of severe bronchial asthma (BA)[1,2] and allergic bronchopulmonary aspergillosis (ABPA),[3] some patients have reported secondary bronchiectasis.[4] The coexistence of bronchiectasis with these conditions poses significant challenges for disease management.[5] While the underlying mechanisms driving bronchiectasis progression and its treatment strategies are not fully understood, various clinical trials have proposed the vicious vortex model and introduced novel therapeutic approaches.[6–9] In this report, we present a rare case of bronchial aspergillosis following bronchial thermoplasty (BT), complicated by localized bronchiectasis and chronic airway infection. We review the existing literature on BT-related bronchial aspergillosis, including this case, and discuss potential treatment strategies for secondary localized bronchiectasis.

Case Presentation

A 35-year-old woman with a history of severe type 2 bronchial asthma (BA) was admitted to the hospital for persistent cough and purulent sputum, which worsened following the completion of BT. She had no significant medical history besides BA, including allergic bronchopulmonary mycosis, and was a non-smoker. Her home environment was observed to be humid, with occasional mold odors.

The patient's asthma, classified as Global Initiative for Asthma step 5, was treated with high-dose inhaled corticosteroids, long-acting β2 agonists, long-acting muscarinic antagonists, and leukotriene receptor antagonists. Despite this regimen, she occasionally required oral corticosteroids for exacerbations, occurring once or twice per year. Three weeks before admission, she had completed three

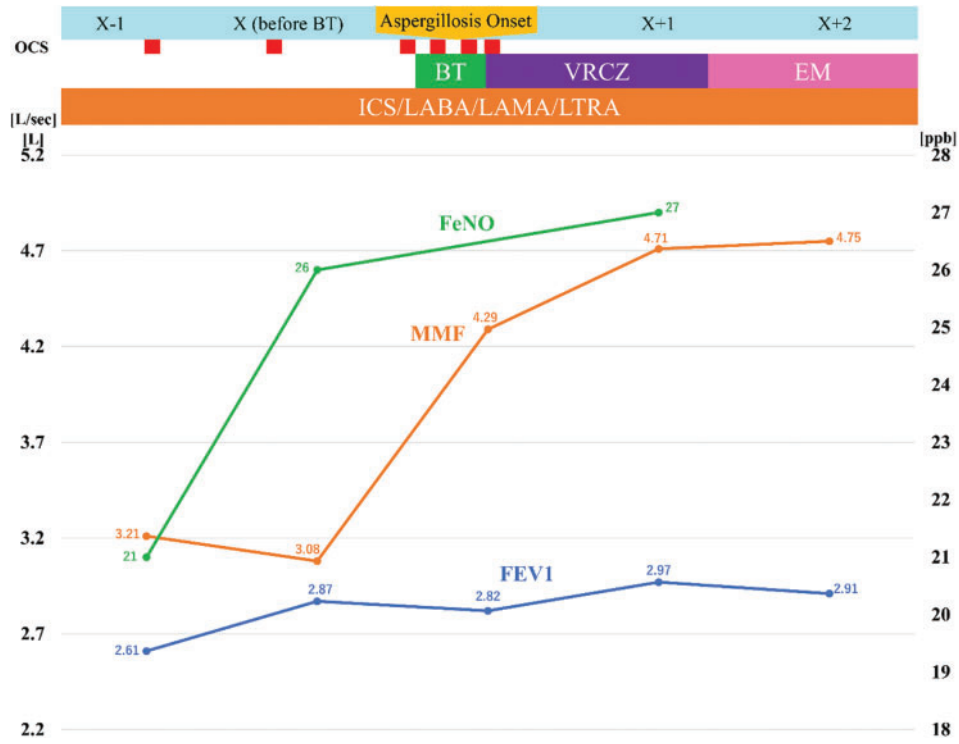

Figure 1. Clinical course and pulmonary function test findings. OCS; oral corticosteroid; BT, bronchial thermoplasty; EM, erythromycin; ICS, inhaled corticosteroids; LABA, long-acting β2 agonists; LAMA, long-acting muscarinic antagonists; LTRA, leukotriene receptor antagonists; FeNO, fractional exhaled nitric oxide; MMF, maximum mid-expiratory flow rate; FEV1, forced expiratory volume in one second.

Table 1. Clinical course of laboratory results for the patient undergoing bronchial thermoplasty

Items	Before BT	Aspergillosis onset	3 years after BT	Reference	Unit
White blood cell count	5010	10850	6220	3300–8600	/μL
Neutrophils	51.7	55.0	62.1	49.7–72.7	%
Lymphocytes	36.5	33.0	28.3	24.5–38.9	%
Monocytes	5.0	5.8	4.5	1.7–8.7	%
Eosinophils	5.4	5.8	4.5	0.0–5.0	%
Basophils	1.4	0.4	0.6	0.0–3.0	%
C-reactive protein	0.02	0.11	0.03	0.00–0.14	mg/dL
Aspergillus antigen	0	0.1	0.1	<0.5	
Serum total IgE	226	212	108	<3.5	IU/mL
Aspergillus-specific IgEclass (levels)	0 (0)	0 (0.18)	3 (4.76)	<0.35	U_A/mL
Alternaria-specific IgEclass (levels)	3 (4.65)	3 (11.6)	3 (6.35)	<0.35	U_A/mL

Note: BT, bronchial thermoplasty; IgE, immunoglobulin E.

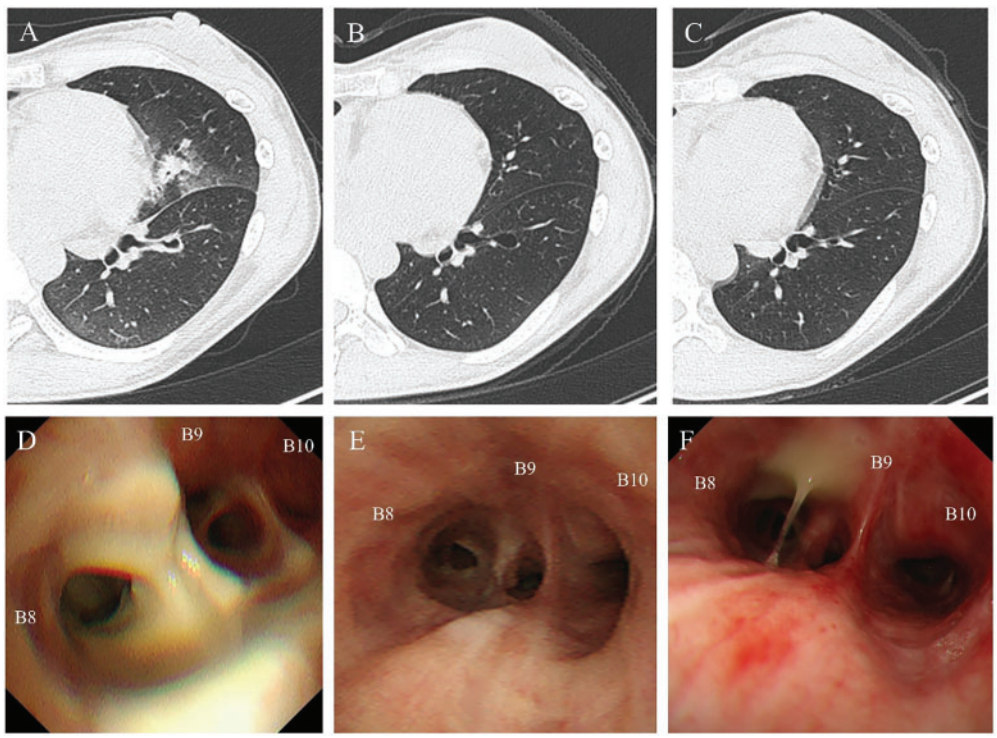

Figure 2. Patient's computed tomography and bronchoscopy images. (A) Diagnosis: CT shows bronchial wall thickening, bronchiectasis, consolidation, opacities, and upper lobe changes; (B) Six months: CT shows improvement in all parameters except bronchiectasis; (C) Three years: CT shows near-complete resolution; (D) Diagnosis: Bronchoscopy shows necrotic tissue and purulent mucus in the left B8 bronchus; (E) Six months: Bronchoscopy shows resolved necrosis and bronchial scarring; (F) Three years: Bronchoscopy shows improved scarring; purulent sputum persists.

BT procedures, each accompanied by systemic steroid administration (prednisolone, 50 mg daily for 5 days) (Fig. 1). The first BT procedure was performed on the right lower lobe, the second on the left lower lobe, and the third on the bilateral upper lobes. During the third BT treatment, the left lower lobe was observed to reveal only airway mucosal changes that could be attributed to activation during the second BT treatment. Serum-specific immunoglobulin E (IgE) testing before BT revealed sensitization to *Alternaria* but was negative for *Aspergillus* (Table 1, Table S1). Physical examination at admission showed no abnormalities. Blood tests indicated an elevated white blood cell count and a slight increase in CRP compared to pre-BT levels.

Chest computed tomography (CT) revealed focal thickening of the left lower bronchial wall, bronchiectasis, consolidation, opacities, and changes consistent with prior BT (Fig. 2A). On suspicion of BT-related complication, a bronchoscopy was performed and revealed necrotic tissue and purulent mucus within the lumen, predominantly in B8 of the left lung along the treated areas in the lower lobe (Fig. 2D). Transbronchial biopsy reveals necrotic material containing fungal hyphae, which stain black with Grocott's stain and display sharply branching structures (Figs. 3A–3C). Bronchial lavage fluid cultures confirmed the presence of *Aspergillus fumigatus*, prompting a diagnosis of bronchial aspergillosis. Treatment with voriconazole was initiated.

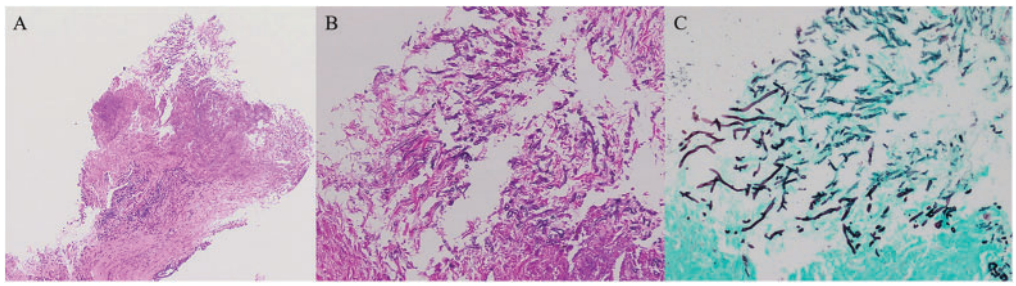

Figure 3. Patient's pathological findings. Hematoxylin and eosin staining revealed necrotic material with inflammatory cell infiltration (A, ×40; B, ×200). The Grocott-stained specimen (C, ×200) demonstrates fungal hyphae with consistent width and black.

After six months of voriconazole treatment, intermittent purulent sputum persisted. Chest CT demonstrated improvement in bronchial wall thickening, consolidation, and opacities; however, bronchiectasis remained (Fig. 2B). Bronchoscopy showed bronchial wall scarring and the absence of necrotic tissue (Fig. 2E). Sputum cultures were negative for *Aspergillus fumigatus* but revealed *Staphylococcus aureus*. The patient was treated with amoxicillin/clavulanic acid several times due to infectious exacerbation of bronchiectasis. Consequently, the patient was switched to low-dose erythromycin (400 mg daily). After starting erythromycin, the purulent sputum significantly improved but still intermittently persisted. Chest CT revealed further improvement in bronchial wall thickening and bronchiectasis (Fig. 2C). Bronchoscopy showed ongoing improvement in bronchial wall scarring, although purulent sputum was still present (Fig. 2F). Sputum culture remained positive for *Staphylococcus aureus*. The patient's asthma remained stable, including her pulmonary function (Fig. 1), but she required ongoing treatment for localized bronchiectasis.

Discussion

The patient developed aspergillosis as a postoperative complication following BT, which improved with voriconazole; however, localized bronchiectasis persisted. Subsequently, the patient experienced chronic lower respiratory tract infection caused by staphylococci. Bronchial aspergillosis has been reported as a postoperative complication in approximately 5% of BT cases.[10,11] Including the present case, five patients with bronchial aspergillosis have been reported, none of whom were suspected to have ABPA before treatment.[10,12–15] Separately, one additional case involved a patient in whom ABPA was suspected before treatment.[16] We analyzed five cases (Table 2),[10,12–15] excluding one where ABPA was suspected before BT.[16] All patients were female. Each patient received 30–50 mg of prednisolone

Table 2. Literature review of bronchial aspergillosis after bronchial thermoplasty

Author	Year	Age (years)	Sex	Symptom	Pre-BT steroid dose	Onset	Primary lesion	*Aspergillus*-specific IgE[a]	*Aspergillus* antigen[a]	Therapy	Follow-Up	Secondary bronchiectasis
Matsubayashi et al.[15]	2019	35	F	N.S.	m-PSL 32 mg/day	4w	right B9	20.9 UA/mL	N.S.	VRCZ	12m	N.S.
Kashizaki and Sekido[10]	2020	30	F	Cough, sputum	PSL 50 mg/day	3w	left B8, 9	55.6 UA/mL	2.5	VRCZ	76m	No
da Costa and Hsia[13]	2020	73	F	N.S.	PSL 50 mg/day	3w	right B8, 9	4.4 IU/mL[b]	N.S.	VRCZ to AMPH-B	2m	N.S.
Sasada et al.[14]	2020	19	F	Cough, sputum	PSL 30 mg/day	3w	left B9, 10	N.S.	N.S.	ITCZ	N.S.	N.S.
Present case	2024	35	F	Cough, sputum	PSL 50 mg/day	6w	left B8	4.76 UA/mL	0.1	VRCZ	38m	Yes

Note: BT, bronchial thermoplasty; F, female; N.S., not specified; IgE, immunoglobulin E; m-PSL, methylprednisolone; w, week; VRCZ, voriconazole; m, month; AMPH-B, amphotericin B; ITCZ, itraconazole.
a: Post-BT Measurement, b: Pre-BT Measurement.

daily for approximately five days and developed bronchial aspergillosis localized to the lower lobe bronchus within six weeks of undergoing BT. Among the five cases, this case had the longest time to disease onset. However, it is possible that the bronchial aspergillosis was mild at the time of the third procedure BT, being regarded as post-BT airway mucosal changes during observation. Most cases are likely to develop within four weeks. In three of these cases,[10,12,13,15] elevated *Aspergillus*-specific IgE levels were observed after the onset of aspergillosis, although none reported the presence of a clear mucus plug. In our two cases where *Aspergillus* antigen levels were measured before and after BT, the previously reported case[10] showed a significant increase, while in the present case, the levels remained within the normal range. This pattern may suggest a combination of localized *Aspergillus* infection and ABPA-like conditions,[17] potentially influenced by individual allergic predispositions and airway-destructive factors.[18–20] While da Costa et al. described this condition as *Aspergillus* tracheobronchitis,[13] we refer to it as bronchial aspergillosis to account for individual immune conditions and its diverse clinical presentations. Factors contributing to the development of bronchial aspergillosis following BT possibly include the short-term use of moderate to high doses of systemic corticosteroids, mucosal damage to the central airways (an environment favorable to *Aspergillus* growth), the lower lobe's susceptibility to mucociliary impairment, and the patient's home environment.[12] Antifungal treatment was administered in all five reported cases, with one treated with itraconazole,[14] three with voriconazole,[10,12,15] and one transitioning from voriconazole to amphotericin B inhalation.[13] In all cases, aspergillosis improved within one year, possibly due to the infection being localized. However, the long-term outcomes of bronchial aspergillosis after BT remain unknown.

In a prior report, a six-year follow-up of a patient treated for aspergillosis revealed only mild bronchiectasis on CT, with no significant increase in sputum production.[10] In contrast, the present case showed persistent localized bronchiectasis and purulent sputum following bronchial aspergillosis. Additionally, a chronic lower respiratory tract infection caused by staphylococci emerged during the disease course, requiring ongoing treatment with erythromycin. This progression is similar to that of bronchiectasis secondary to ABPA in patients without a history of BT.[21]

Bronchiectasis is a chronic disease characterized by permanent dilation of the bronchi and various clinical manifestations, including cough and sputum production.[4,22] In the EMBARC cohort, 61.9% of bronchiectasis cases were reported to be associated with secondary causes, with BA accounting for 6.9% and ABPA for 2.8%.[4] Though it was once believed that bronchiectasis progressed continuously due to infection, recent research has introduced the widely accepted "vicious vortex" model.[23] This model highlights the interplay of four factors contributing to disease progression, viz., chronic infection, lung destruction and dysfunction, neutrophilic inflammation, and impaired mucociliary clearance.[5,23,24] The differences between the two cases we encountered suggest that the development of bronchiectasis may have been influenced by lung damage, impaired function, and chronic infection caused by BT, along with patient-specific factors such as neutrophilic inflammation and reduced mucociliary clearance.[5,23]

Advances in treatment strategies for bronchiectasis have improved management options. Long-term macrolide therapy has gained worldwide attention for managing frequent exacerbations unresponsive to short-term antimicrobial treatment. Studies such as EMBRACE,[6] BLESS,[8] and BAT[7] have demonstrated the efficacy of macrolides in reducing exacerbations, particularly in patients with persistent *P. aeruginosa* infections. Additionally, meta-analyses have shown similar benefits in subgroups without *P. aeruginosa* infections,[25] further supporting this approach. In fact, administering low-dose, long-term macrolide therapy reduced the frequency of exacerbations compared to pre-treatment levels. Recently, emerging therapies such as brensocatib, which targets neutrophil reprogramming by inhibiting dipeptidyl peptidase 1 (DPP1),[9,26] have shown promise in improving outcomes for patients with bronchiectasis. These advancements provide hope for more effective management strategies in this challenging condition.

Conclusions

Bronchial aspergillosis, a rare complication following BT, is typically treated with antifungal agents; however, long-term follow-up is crucial as some cases may progress to bronchiectasis. While no

standard treatment exists for these cases, recent strategies for managing bronchiectasis, such as long-term macrolide therapy and DPP1 inhibitors, may mitigate disease progression.

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Author Contributions

F.K. and Y.S. were responsible for data curation. F.K. interpreted the data and drafted the original manuscript. Both authors have read the manuscript and agree with the content, data, and the revision process.

Data Availability Statement

The datasets used in the current study are available from the corresponding author upon reasonable request.

Ethical Statement

The article does not involve the participation of any animals. The patient provided written informed consent for the publication of this report and accompanying images.

Conflicts of Interest

The authors declare no conflicts of interest related to this study.

Supplemental Information

Supplemental information for this article can be found online at https://sup.jclinque.com/api/articles/57/download-suppl.

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