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【 CASE REPORT 】

Invasive Tracheobronchial Aspergillosis with Bronchial Ulcers Complicated by Nontuberculous Mycobacterial Disease

Tomohiro Kanai[1], Yumiko Samejima[1], Yoshimi Noda[1], Sung-Ho Kim[1], Kanako Tamura[1], Taisei Umakoshi[1], Kazunori Shimizu[1], Yozo Kashiwa[1], Hiroshi Morishita[1], Kayo Ueda[2], Kunimitsu Kawahara[2], Takashi Yaguchi[3] and Hiroto Matsuoka[1]

Abstract:

Invasive tracheobronchial aspergillosis (ITBA) complicated by nontuberculous mycobacteria (NTM) is rare. An 88-year-old man was admitted for hemoptysis. Bronchoscopy revealed bronchial ulcers, and a tissue biopsy showed *Aspergillus fumigatus*. He was diagnosed with ITBA, which improved with voriconazole. During treatment, infiltrative shadows appeared in his lungs, and bronchoscopy was performed once again. A non-necrotic epithelioid granuloma and *Mycobacterium intracellulare* were detected in the biopsy specimen. He was diagnosed with NTM disease. It is important to note that tracheobronchial ulcers may cause hemoptysis and to identify the etiology and treat it appropriately when multiple bacteria are found.

Key words: invasive tracheobronchial aspergillosis, non-tuberculous mycobacteria, bronchial ulcer, hemoptysis

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Introduction

Pulmonary aspergillosis is classified into invasive pulmonary aspergillosis, pulmonary aspergilloma, chronic progressive pulmonary aspergillosis, and allergic bronchopulmonary aspergillosis. Pulmonary aspergillosis rarely but occasionally leads to ulcerative lesions in the trachea and bronchus, and when it does, it is considered to be invasive tracheobronchial aspergillosis (ITBA) (1). In addition, ITBA complicated by nontuberculous mycobacteria (NTM) is rare, although co-infection of Aspergillus and NTM is not uncommon (2). The use of therapeutic agents is limited due to drug interactions.

We herein report a case of ITBA with bronchial ulcers and NTM disease.

Case Report

An 88-year-old man visited our hospital due to hemoptysis. He had no history of respiratory diseases and had been admitted to another hospital for the treatment of duodenal ulcer and pyloric stenosis. After his condition improved, he had been discharged but presented with hemoptysis the next day. He was a non-smoker and had worked as a French horn player until 60 years of age.

His percutaneous oxygen saturation was 95% (under room air condition). He had no fever, and no abnormalities were detected on a physical examination. A peripheral blood test showed elevated C-reactive protein and proteinase-3 antineutrophil cytoplasmic antibody (PR3-ANCA) (Table 1). Chest X-ray showed small nodular shadows and ground-glass opacities in the right middle and lower lobes (Fig. 1A). High-resolution computed tomography (HRCT) revealed in-

[1]Department of Pulmonary and Critical Care Medicine, Osaka Habikino Medical Center, Japan, [2]Department of Pathology, Osaka Habikino Medical Center, Japan and [3]Medical Mycology Research Center, Chiba University, Japan
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Correspondence to Dr. Tomohiro Kanai, t.kanai777@gmail.com

Table 1. Laboratory Findings of the Patient.

Hematology		Biochemistry	
WBC	4,500 /μL	AST	30 U/L
Neut	59.3 %	ALT	42 U/L
Lymp	27.6 %	LDH	199 U/L
Mono	8.2 %	ALP	206 U/L
Eo	4.2 %	γGTP	22 U/L
Baso	0.7 %	CK	72 U/L
Hb	11.1 g/dL	TP	6.1 g/dL
HCT	32.8 %	ALB	3.0 g/dL
MCV	97 fl	T-Bil	0.57 mg/dL
PLT	20.5 ×10⁴/μL	BUN	11.1 mg/dL
		Cre	0.76 mg/dL
Serology		Na	139 mEq/L
CRP	1.64 mg/dL	K	3.8 mEq/L
ANA	<×20	BS	115 mg/dL
MPO-ANCA	1.6 U/mL	IgG	1,325 mg/dL
PR3-ANCA	21.3 U/mL	IgA	601 mg/dL
anti-GBM Ab	2.6 U/mL	IgM	64 mg/dL
β-D-glucan	13 pg/mL		
		anti-fungal Ab	
Coagulation		Candida	negative
PT-INR	1.27	Aspergillus	negative
APTT	35.7 sec		

WBC: white blood cell, Neut: neutrophil, Ly: lymphocyte, Mo: monocyte, Eo: eosinophil, Ba: basophil, RBC: red blood cell, Hb: hemoglobin, Hct: hematocrit, MCV: mean corpuscular volume, PLT: platelets, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial clotting time, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, TP: total protein, ALB: albumin, T-Bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatinine, BS: blood sugar, CRP: C-reactive protein, ANA: antinuclear antibody, anti-dsDNA Ab: anti-double-stranded DNA antibody

filtrative and small nodular shadows in both lungs and ground-glass opacities mainly in the right lower lobe (Fig. 1B, C). Hemostatic agents were administered, and hemoptysis improved. However, he had a fever, and hemoptysis recurred on the 11th day of hospitalization.

Bronchial arteriography was performed on the 13th day. The bronchial arteries were dilated bilaterally, which indicated chronic airway infection. Bronchial artery embolization (BAE) was performed with gelatin sponges, and the hemoptysis improved. Bronchoscopy was performed on the 18th day to investigate the cause of hemoptysis, revealing multiple bronchial ulcers and flares of bronchial mucosa on both bronchi (Fig. 2A-C). Samples were collected from the aspiration sputum, followed by the bronchial lavage fluid and bronchial tissue around the ulcers (obtained by a biopsy). *Pseudomonas aeruginosa* and NTM were detected in all samples, and Aspergillus was detected only in the culture of the bronchial tissue around ulcers. NTM was detected from all samples. *Mycobacterium intracellulare* was identified through the culture examination and through polymerase chain reaction of the biopsy specimen.

Although a cytological examination revealed filamentous fungi, a histological examination of the biopsy specimen revealed neutrophil infiltration, necrotic tissue and epithelial defects without fungus. A histological examination revealed no granuloma that were suggestive of NTM disease. Since Aspergillus was detected in the culture of the bronchial tissue around the ulcers, he was diagnosed with ITBA.

He was treated with voriconazole (VRCZ) from the 24th day, and his symptoms gradually improved. VRCZ was later changed to itraconazole (ITCZ) as he lost appetite. On the

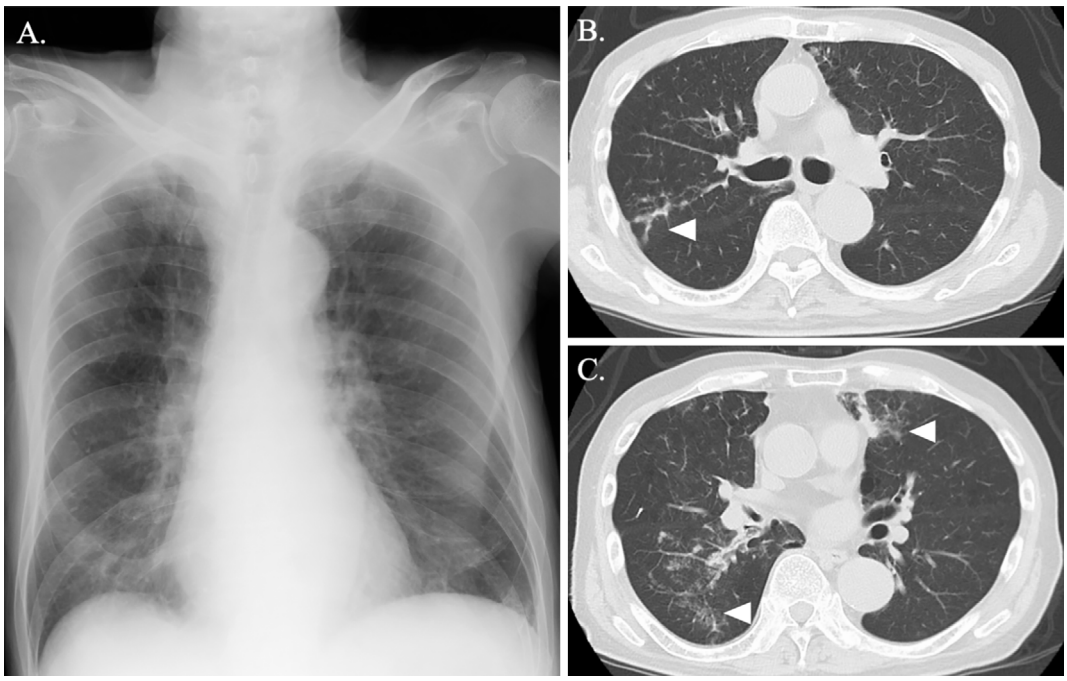

Figure 1. Chest X-ray showed small nodular shadows and ground-glass opacities in the right middle and lower lobes (A). High-resolution computed tomography revealed infiltrative and small nodular shadows in both lungs and ground-glass opacities in the right lower lobe (B and C) (arrowheads).

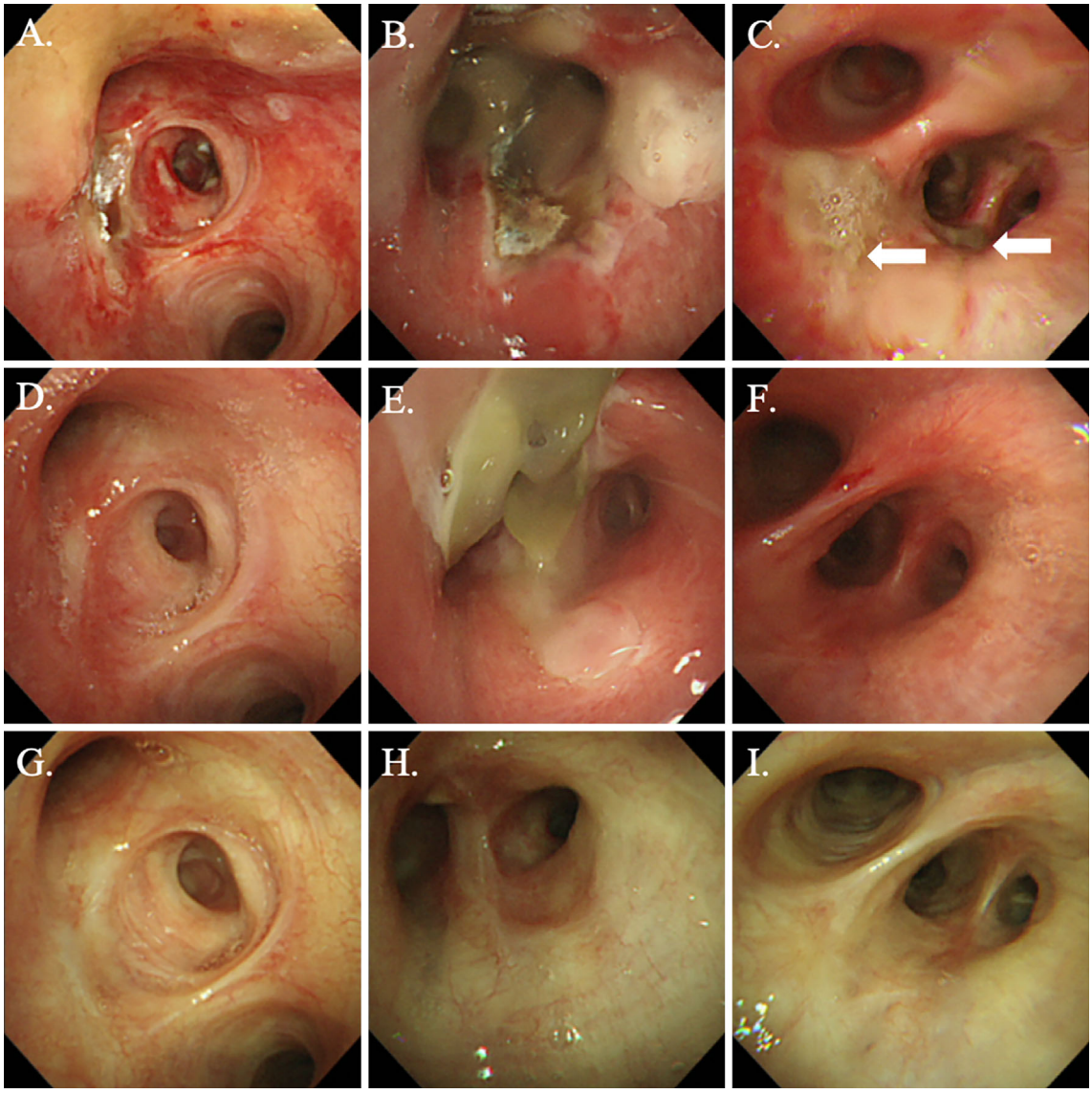

Figure 2. **Bronchoscopy on the 18th hospital day revealed multiple bronchial ulcers and bronchitis (A-C). A biopsy was performed on the ulcerative lesions (arrows). Bronchoscopy on the 46th day showed partial improvement of bronchial ulcers and flares (D-F). On the 46th day, the ulcerative lesions and flares had improved (G-I). (A), (D), and (G): Left superior bronchus, (B), (E) and (H): right superior bronchus, (C), (F), and (I): right middle and lower bronchus.**

40th day, however, he had a fever once again, and HRCT revealed multiple patchy infiltrative shadows. In order to observe the bronchial ulcers and investigate the etiology of the fever and the new shadows, bronchoscopy was performed again on the 46th day. It showed partial improvement of the bronchial ulcers and flares (Fig. 2D-F). A biopsy was performed on the lung field, and a histological examination of the biopsy specimen revealed non-necrotizing epithelioid granuloma with fibrin deposition, swelling of alveolar epithelium and lymphocyte infiltration. Polymerase chain reaction of the biopsy specimen for *M. intracellulare* was positive, so the new infiltrative shadows were diagnosed as NTM disease. On the 53rd day, in addition to ITCZ, he was treated with clarithromycin (CAM) and ethambutol (EB) without rifampicin (RFP) due to drug interactions. The infiltrative shadows and fever improved after addition of CAM and EB. On the 88th day, bronchoscopy was performed, which showed the complete healing of the bronchial ulcers (Fig. 2G-I.)

Discussion

We encountered a case of ITBA with bronchial ulcers followed by NTM disease (1). To our knowledge, seven cases of ITBA have been published in Japan (3-9); these cases were identified using the keywords “invasive tracheobronchial aspergillosis” or “aspergillus tracheobronchitis” in the PubMed database (Table 2).

ITBA is a rare form of invasive pulmonary aspergillosis. In previous reports, immunocompromised patients, such as those who had received organ or bone marrow transplantation, those being treated with immunosuppressive agents

Table 2. Summary of the Published Cases of Invasive Tracheobronchial Aspergillosis.

Age, years	Sex	Symptoms	Complications	Diagnosis	Pre-immunosuppressive therapy	Treatment	Outcome	Cause of death	Reference No.
44	F	Cough, Fever	CML GVHD	Histrogical examination Culture	Bone marrow transplantation Steroid pulse therapy Metylprednisolone	AMPH-B	Dead	Respiratory failure	3
91	F	Dyspnea	SFTS	Histrogical examination Culture	No	MCFG VRCZ	Alive		4
69	F	Cough, Dyspnea	ML	Cytological examination Culture	Chemotherapy Radioimmunotherapy	L-AMB ITCZ	Dead	ML	5
44	F	Fever	EP	Histological examination Culture	Oral corticosteroid	L-AMB VRCZ CPFG	Dead	ARDS	6
45	M	Dyspnea, Polyarthralgia Fever, weight loss	SLE, DM	Histrogical examination Culture	No	ITCZ+VRCZ(oral) VRCZ+MCFG	Dead	SLE, DM	7
61	F	Diarrhea	MG, CKD	Histrogical examination Culture	No	VRCZ	Alive		8
57	F	Respiratory failure	Fulminant hepatitis HPS	Histrogical examination Culture	Steroid pulse therapy	VRCZ+CPFG	Dead	ARDS	9
43	F	Dyspnea, Sputum	LAM	Histrogical examination Culture	Lung transplantation Deflazacort, TAC and MMF	AMPH-B VRCZ	Dead	Recurrent LAM	10
23	M	Cough, Dyspnea	AA	Histological examination	Allogeneic HSCT	L-AMB PSCZ+CPFG	Alive		11
45	M	Cough, Rhinorrhea Headache	AIDS with HARRT Neutropenia DLBCL (CR)	Histlogical examination Culture	No	AMPH-B VRCZ	Dead	Respiratory failure	12
42	M	Cough	Tuberculosis scar Diabetes mellitus	Culture	No	AMPH-B ITCZ	Alive		13
60	M	Chiefly, Chest pain Fever, Cough	Influenzae	Histological examination	No	VRCZ	Alive		14

CML: chronic myelocytic leukemia, GVHD: graft versus host disease, SFTS: severe fever with thrombocytopenia syndrome, ML: malignant lymphoma, EP: eosinophilic pneumonia, SLE: systemic lupus erythematosus, DM: dermatomyositis, MG: monoclonal gammopathy, CKD: chronic kidney disease, HPS: hemophagocytic syndrome, LAM: lymphangioleiomyomatosis, AA: aplastic anemia, AIDS: acquired immunodeficiency syndrome, DLBCL: diffuse large B-cell lymphoma, CR: complete remission, TAC: tacrolimus., MMF: mycophenolate Mofetil, HSCT: hematopoietic stem cell transplantation, AMPH-B: amphotericin B, L-AMB: liposomal amphotericin B, VRCZ: voriconazole, PSCZ: posaconazole, ITCZ: itraconazole, CPFG: caspofungin, MCFG: micafungin, ARDS: acute respiratory distress syndrome

such as steroids and those suffering from acquired immunodeficiency syndrome, were diagnosed with ITBA (6, 10-12). The symptoms are usually non-specific, such as cough, dyspnea and respiratory failure (9, 13, 14). Although we were unable to identify cases in which the main symptom was hemoptysis, hemoptysis is also a non-specific symptom.

We considered ANCA-related vasculitis, NTM disease and adverse effects of BAE as potential causes of the bronchial ulcers in addition to ITBA. We rejected ANCA-related vasculitis and NTM disease because the patient had no abnormalities in any part of the body except the bronchus and there was no epithelioid granuloma in the biopsy specimen of the bronchial ulcers (15, 16). BAE is a treatment of hemoptysis that may rarely cause bronchial necrosis, stenosis or ischemia (17-19). Ivanick et al. reported a case of bronchial necrosis after BAE with alcohol as an embolic material. They considered that bronchial necrosis occurred due to obstruction of bronchopulmonary anastomoses because alcohol has a low viscosity (20). However, in the present case, gelatin sponges were used, and their diameter was not considered so small as to obstruct the bronchopulmonary anastomoses. We suspected that the bronchial ulcers had existed before BAE because hemoptysis was recognized before BAE, and HRCT revealed no shadows that might have caused hemoptysis. Aspergillus was detected only in culture,

and the ulcerative lesions improved despite being treated only with antifungal therapy until the second bronchoscopy procedures. Based on these findings, we diagnosed the patient with ITBA.

Not only severely immunocompromised but also mildly immunocompromised patients, such as those with malignancies, chronic obstructive pulmonary disease, chronic kidney disease and diabetes mellitus, can also develop ITBA (1, 5, 13, 21). In addition to *A. fumigatus*, *P. aeruginosa* and NTM were detected in the respiratory tract despite the patient not being immunosuppressed. Co-infection with Aspergillus and NTM is not rare, but the patient had no underlying diseases with structural changes in the lung, such as bronchiectasis, pulmonary emphysema or interstitial pneumonia, and no history of the long-term administration of antibiotics. King et al. reported that a bagpipe player died of hypersensitivity pneumonitis and found a large number of bacteria in the instrument he had used (22). In our case, the patient had worked as a French horn player until 60 years of age. Although roughly 30 years had passed since he retired and the pathophysiology differed from hypersensitivity pneumonitis, constant inhalation of the bacteria in the instrument may have resulted in the co-infection of Aspergillus and NTM.

In patients with mycobacterium avium complex (MAC) infections, the cytokine profiles in peripheral blood, programmed death-1 (PD-1) expression and apoptosis of lymphocytes are different from those of controls (23, 24). Shu et al. reported that the PD-1 and PD-ligand 1 expression and apoptosis of lymphocytes in patients with MAC were higher than in those without MAC (24). Kwon et al. reported a case of ITBA after influenza infection and the possibility of cell-mediated defect, disruption of normal ciliary clearance and leukopenia as a cause of ITBA in an immunocompetent patient (14). Co-infection with other infectious diseases may affect the host immunity. In this case, NTM may have suppressed the patient's immune system, which could have induced ITBA. He was also diagnosed with gastric cancer when examined due to a loss of appetite after his discharge from our hospital, so malignancy may also have affected ITBA.

Wu et al. reported that the average duration of treatment for ITBA was 25 days (25). There is no evidence suggesting whether or not monotherapy is adequate for ITBA. Although combination therapy of anti-fungal agents has been reported (7), ITBA has also been completely cured by monotherapy alone (4, 8, 21). In the present case, we treated him with antifungal drugs for 56 days and changed the antifungal drugs several times due to his loss of appetite. We completed treatment with monotherapy after confirming the improvement of bronchial ulcers and disappearance of Aspergillus. In addition to Aspergillus, we needed to treat NTM disease. Although it is difficult to use RFP due to its interaction with VRCZ, Miwa et al. reported that a two-drug regimen (CAM and EB) for the treatment of NTM disease was not inferior to a three-drug regimen (CAM, EB, and RFP), and the occurrence of adverse events in the two-drug regimen tended to be lower than that in the three-drug regimen (26).

Conclusion

We reported a case of ITBA with bronchial ulcers complicated by NTM disease. Tracheobronchial ulcers must be considered as a cause of hemoptysis. It is important to identify the etiology based on pathological and bacteriological examinations in order to treat overlapping chronic respiratory tract infection appropriately.

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

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