Invasive Tracheobronchial Aspergillosis with Bronchial Ulcers Complicated by Nontuberculous Mycobacterial Disease: A Case Report

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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-
Table 1. Laboratory Findings of the Patient.

| Hematology | Biochemistry |
|------------|--------------|
| WBC 4,500 µL | AST 30 U/L |
| Neut 59.3 % | ALT 42 U/L |
| Lym 27.6 % | LDH 199 U/L |
| Mono 8.2 % | ALP 206 U/L |
| Eo 4.2 % | γ-GTP 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 x10^4/µL | BUN 11.1 mg/dL |
| BC 4,500/µL | Cre 0.76 mg/dL |
| CRP 1.64 mg/dL | Na 139 mEq/L |
| ANA <×20 | K 3.8 mEq/L |
| 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, Mc: 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.

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 ulcers, NTM was detected from all samples. Mycobacterium intracellulare was identified through the culture examination and through polymerase chain reaction of the biopsy specimen.

He was treated with voriconazole (VRCZ) from the 24th day, and his symptoms gradually improved. VRCZ was later changed to itraconazole as he lost appetite. On the 40th day, infiltrative and small nodular shadows in both lungs and ground-glass opacities mainly in the right lower lobe (Fig. 1B and 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-2C). 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.
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-2F). 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-2I).

**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 such as steroids and those suffering from acquired immu-
nodeficiency 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). Ivansick 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, before BAE because hemoptysis was recognized before BAE.

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 | Histological examination Culture | Bone marrow transplantation Steroid pulse therapy Methylprednisolone | AMPH-B | Dead | Respiratory failure | 3            |
| 91        | F   | Dyspnea | SPTS | Histological examination Culture | No | MCFG VRCZ | Alive | 4            |
| 69        | F   | Cough, Dyspnea | ML | Cytological examination Culture | Chemotherapy Radioimmunotherapy | L-AMB ITZ | Dead | ML | 5            |
| 44        | F   | Fever | EP | Histological examination Culture | Oral corticosteroid | L-AMB VRCZ CCFG | Death | ARDS | 6            |
| 45        | M   | Dyspnea, Polyarthritis | SLE, DM | Histological examination Culture | No | ITZC+VRCZ(oral) VRCZ+MCFG | Dead | SLE, DM | 7            |
| 61        | F   | Diarrhea | MG, CKD | Histological examination Culture | No | VRCZ | Alive | 8            |
| 57        | F   | Respiratory failure | Fulminant hepatitis HPS | Histological examination Culture | Steroid pulse therapy | VRCZ+CCFG | Dead | ARDS | 9            |
| 43        | F   | Dyspnea, Sputum | LAM | Histological examination Culture | Lung transplantation Deflazacort, TAC and MMF | AMPH-B VRCZ | Dead | Recurrent LAM | 10          |
| 23        | M   | Cough, Dyspnea | AA | Histological examination Culture | Allogeneic HSCT | L-AMB PSCZ+CCFG | Alive | 11          |
| 45        | M   | Cough, Rhinorrhea | AIDSc | Histological examination Culture | No | AMPH-B VRCZ | Dead | Respiratory failure | 12          |
| 42        | M   | Cough | Tuberculosis | Culture | No | AMPH-B ITZC | Alive | 13          |
| 60        | M   | Chiefly, Chest pain | Fever, Cough | Histological examination | No | VRCZ | Alive | 14          |

CML: chronic myelocytic leukemia, GVHD: graft versus host disease, SPTS: severe fever with thrombocytopenia syndrome, ML: malignant lymphoma, EP: eosinophilic pneumonia, SLE: systemic lupus erythematosus, DM: dermatomyositis, MG: monoclonal gamopathy, 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, ITZC: itraconazole, CCFG: caspofungin, MCFG: micafungin, ARDS: acute respiratory distress syndrome.
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). Chin-Chung 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). Oh-Kyung 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 VRAL, 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).**

**References**

1. Krenke R, Grabczak EM. Tracheobronchial manifestations of Aspergillus infections. ScientificWorldJournal 11: 2310-2329, 2011.
2. Takeda K, Inamura Y. Takazono T, et al. The risk factors for developing of chronic pulmonary aspergillosis in nontuberculous mycobacteria patients and clinical characteristics and outcomes in chronic pulmonary aspergillosis patients coinfected with nontuberculous mycobacteria. Med Mycol 54: 120-127, 2016.
3. Machida U, Kami M, Kanda Y, et al. Aspergillus tracheobronchitis after allogeneic bone marrow transplantation. Bone Marrow Transplant 24: 1145-1149, 1999.
4. Sakaguchi K, Koga Y, Yagi T, et al. Severe Fever with Thrombocytopenia Syndrome Complicated with Pseudomonas Aeruginosa Aspergillus Tracheobronchitis in a Patient without Apparent Risk Factors for Invasive Aspergillosis: A Case Report. Intern Med 2019.
5. Sato S, Tamai Y, Sugimoto H, et al. Invasive tracheobronchial aspergillosis developed during radioimmunotherapy for malignant lymphoma. Clin Case Rep 6: 745-749, 2018.
6. Kushima H, Tokimatsu I, Ishii H, Kadota J. Invasive Pulmonary Aspergillosis Presenting with Tracheobronchial Involvement. Intern Med 55: 1679, 2016.
7. Sada M, Saraya T, Tanaka Y, et al. Invasive tracheobronchial aspergillosis in a patient with systemic lupus erythematosus-dermatomyositis overlap syndrome. Intern Med 52: 2149-2153, 2013.
8. Ohtaa H, Yamazaki S, Miura Y, Kanazawa M, Sakai F, Nagata M. Invasive tracheobronchial aspergillosis progressing from bronchial to diffuse lung parenchymal lesions. Respir Prod Case Rep 4: 32-34, 2016.
9. Majima S, Okachi S, Asano M, et al. Pseudomembranous Invasive Tracheobronchial Aspergillosis with Fulminant Hepatitis and Hemophagocytic Syndrome. Intern Med 57: 2371-2375, 2018.
10. Cho WH, Kim JE, Jeon DS, Kim YS, Shin HW, Shin DH. Tracheobronchial aspergillosis following primary cutaneous aspergillosis in a lung-transplant recipient. Intern Med 50: 131-134, 2011.
11. Tao T, Zhang YH, Xue SL, Wu DP, Chen F. Fulminant Laryngeal-tracheobronchial-pulmonary Aspergillosis: A Rare and Fatal Complication in Allogeneic Hematopoietic Stem Cell Transplantation Recipients. Intern Med 56: 347-351, 2017.
12. Lee J-Y, Joo E-J, Yeom J-S, et al. Aspergillus Tracheobronchitis and Influenza A Co-infection in a Patient with AIDS and Neutropenia. Infection & chemotherapy 46: 209-215, 2014.
13. Cho BH, Oh Y, Kang ES, et al. Aspergillus tracheobronchitis in a mild immunocompromised host. Tuberculosis and respiratory diseases 77: 223-226, 2014.
14. Kwon OK, Lee MG, Kim HS, Park MS, Kwak KM, Park SY. Invasive pulmonary aspergillosis after influenza infection in an immunocompetent patient. Tuberculosis and respiratory diseases 75.
21. Mohan A, Guleria R, Mukhopadhyaya S, Das C, Nayak A, Sharma SK. Invasive tracheobronchial aspergillosis in an immunocompetent person. Am J Med Sci 329: 107-109, 2005.

22. King I, Richardson M, Quinn AM, Holme I, Chaudhuri N. Bagpipe lung: a new type of interstitial lung disease? Thorax 72: 380-382, 2017.

23. Vankayalapati R, Wizel B, Samten B, et al. Cytokine profiles in immunocompetent persons infected with Mycobacterium avium complex. J Infect Dis 183: 478-484, 2001.

24. Shu CC, Wang JY, Wu MF, et al. Attenuation of lymphocyte immune responses during Mycobacterium avium complex-induced lung disease due to increasing expression of programmed death-1 on lymphocytes. Sci Rep 7: 42004, 2017.

25. Wu N, Huang Y, Li Q, Bai C, Huang HD, Yao XP. Isolated invasive Aspergillus tracheobronchitis: a clinical study of 19 cases. Clin Microbiol Infect 16: 689-695, 2010.

26. Miwa S, Shirai M, Toyoshima M, et al. Efficacy of clarithromycin and ethambutol for Mycobacterium avium complex pulmonary disease. A preliminary study. Ann Am Thorac Soc 11: 23-29, 2014.

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