

Pseudomembranous *Aspergillus* Tracheobronchitis in an Immunocompetent Patient

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면역적격환자에서 발생한 위막성 아스페르길루스 기관기관지염 1예

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경북대학교 의학전문대학원 ¹내과학교실, ²영상의학교실, ³병리학교실

아스페르길루스 기관기관지염은 침습적 폐 아스페르길루스증의 일종으로 심한 기관기관지염과 위막형성을 특징으로 한다. 이 질환은 일반적으로 면역억제 환자에서 발생하며 치명률이 높은 질환이다. 저자들은 비교적 건강한 환자에서 발생하였고 항진균제에 잘 반응하였던 아스페르길루스 기관기관지염을 1예 경험하였기에 보고하는 바이다. (*Tuberc Respir Dis* 2008;65:400-404)

Key Words: *Aspergillus*, Bronchitis, Immunocompetence

Introduction

Aspergillus causes a variety of clinical syndromes in the lung, ranging from aspergilloma to invasive pulmonary aspergillosis (IPA), a severe and fatal disease which largely depends on the immune status of the host¹. *Aspergillus* tracheobronchitis (ATB), one form of IPA, is uniquely localized to the tracheobronchial tree and characterized by ulcers and pseudomembrane formation², although it can be accompanied by pneumonia. ATB usually occurs in neutropenic or severely immunocompromised hosts, including patients receiving cytotoxic chemotherapy^{3,5}, patients with AIDS⁵, or in patients following bone marrow transplantation^{6,7}. However, ATB has occasionally been reported in patients who are not fully immunocompetent, such as following influenza infection⁸, chronic obstructive pulmonary disease (COPD)^{9,10}, and diabetes^{9,11}. ATB has not heretofore

been reported in an immunocompetent patient. We report a case of ATB in a previously healthy patient, who was initially thought to have tuberculosis, and was subsequently diagnosed by bronchoscopy, and successfully treated with antifungal therapy.

Case Report

A 47-year-old male presented with a productive cough and fever over a period of 3 weeks. He had been previously healthy with no history of respiratory illnesses, such as tuberculosis. He was a former smoker with a smoking history of 40 pack-years. On admission, he had a mild fever of 37.7°C. The laboratory work-up revealed a leukocyte count of 19,110/mm³ (86.7% neutrophils), a C-reactive protein (CRP) level of 29.13 mg/dl, an erythrocyte sedimentation rate (ESR) of 10³ mm/h, and a lactate dehydrogenase (LDH) level of 644.9 IU/L. The other blood chemistries were normal and a HIV test was negative. A blood gas analysis on room air revealed mild hypoxemia (PaO₂, 73 mmHg; PaCO₂, 31.5 mmHg; pH, 7.48; and HCO₃⁻, 23.6 mmol/L). A chest radiograph showed peribronchial infiltrates in both lungs (Figure 1A). Empirical antibiotic therapy with cefotaxime plus clarithromycin was

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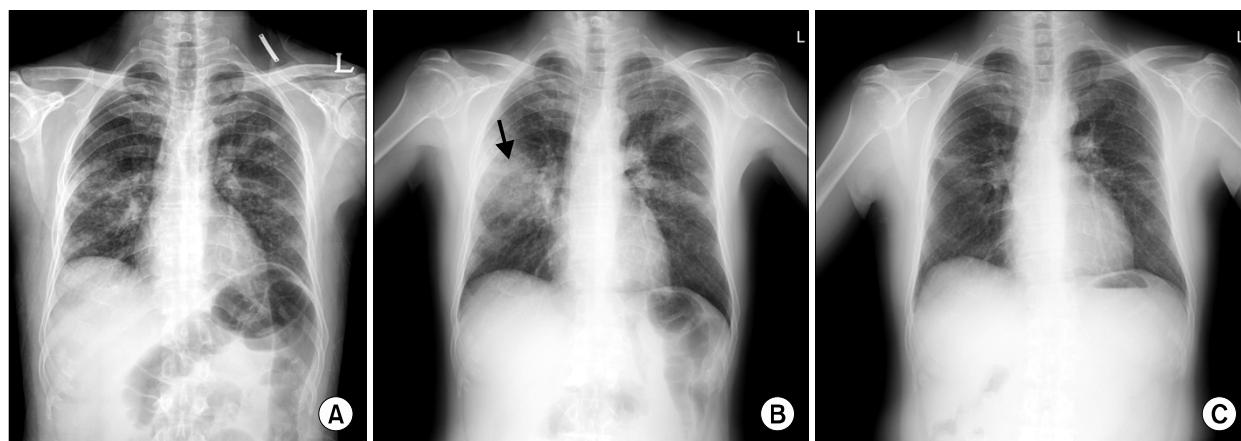


Figure 1. (A) Initial chest radiograph reveals peribronchial infiltrates in both lungs. (B) On the 4th day, the peribronchial infiltrates in the right middle lobe coalesce to a diffuse consolidation (arrow). (C) One month after discontinuing antifungal therapy, chest radiograph shows healed lesions in both lungs.

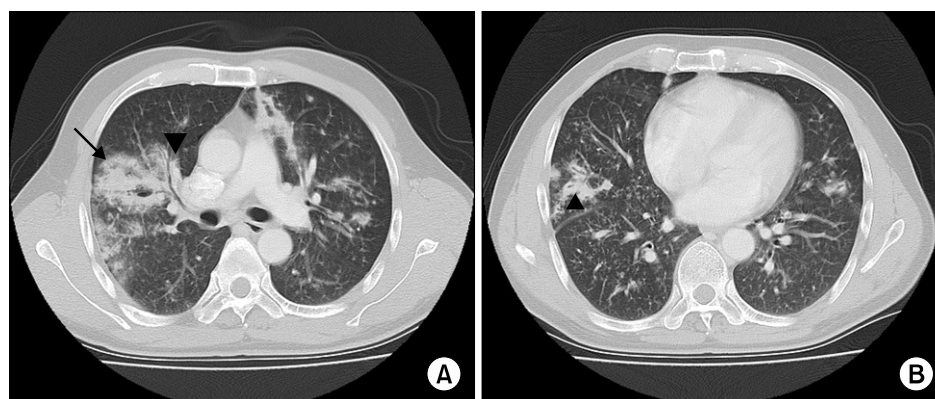


Figure 2. On CT scan, peribronchial consolidation (arrow) with bronchial wall thickening (arrowheads) in the right upper lobe and right middle lobe is noted.

started. On chest CT scan, peribronchial consolidations with bronchial wall thickenings were noted in the right middle and both upper lobes (Figure 2). Centrilobular nodules and tree-in-bud opacities were also present throughout both lungs. The following day, anti-tuberculous medication was added based on a suspicion of tuberculosis because of the tree-in-bud pattern on CT scan, although an acid-fast bacilli (AFB) smear of the sputum was negative.

On the 4th hospital day, the sputum culture obtained on the admission yielded *Aspergillus fumigatus*, and on the chest radiograph, peribronchial infiltrates in the right middle lobe had coalesced to form a diffuse consolidation (Figure 1B). The patient underwent a flexible bronchoscopy for bronchial washings, including an AFB smear and culture, and a bronchoscopic or trans-

bronchial biopsy. The bronchoscopic examination demonstrated hyperemic mucosa and white-to-yellowish, thick, adherent membranes throughout the trachea, main bronchi, and lobar and segmental bronchi of the right middle and lower lobes, left upper lobe, and lingula (Figure 3). A forceps biopsy of the pseudomembranes revealed fungal septate hyphae with dichotomous branching at 45° (Figure 4), and 3 days later, *Aspergillus fumigatus* was isolated from the bronchial washings. Intravenous amphotericin B (1 mg/kg/day) was started on the 5th hospital day. Serum *Aspergillus* IgG antibody was positive (40 U/ml; normal range, 0~8 U/ml), but the serum galactomannan antigen level (Bio-Rad Platelia *Aspergillus* EIA; Bio-Rad Laboratories, Hercules, CA, USA) was negative.

On the 17th hospital day, the patient's general con-

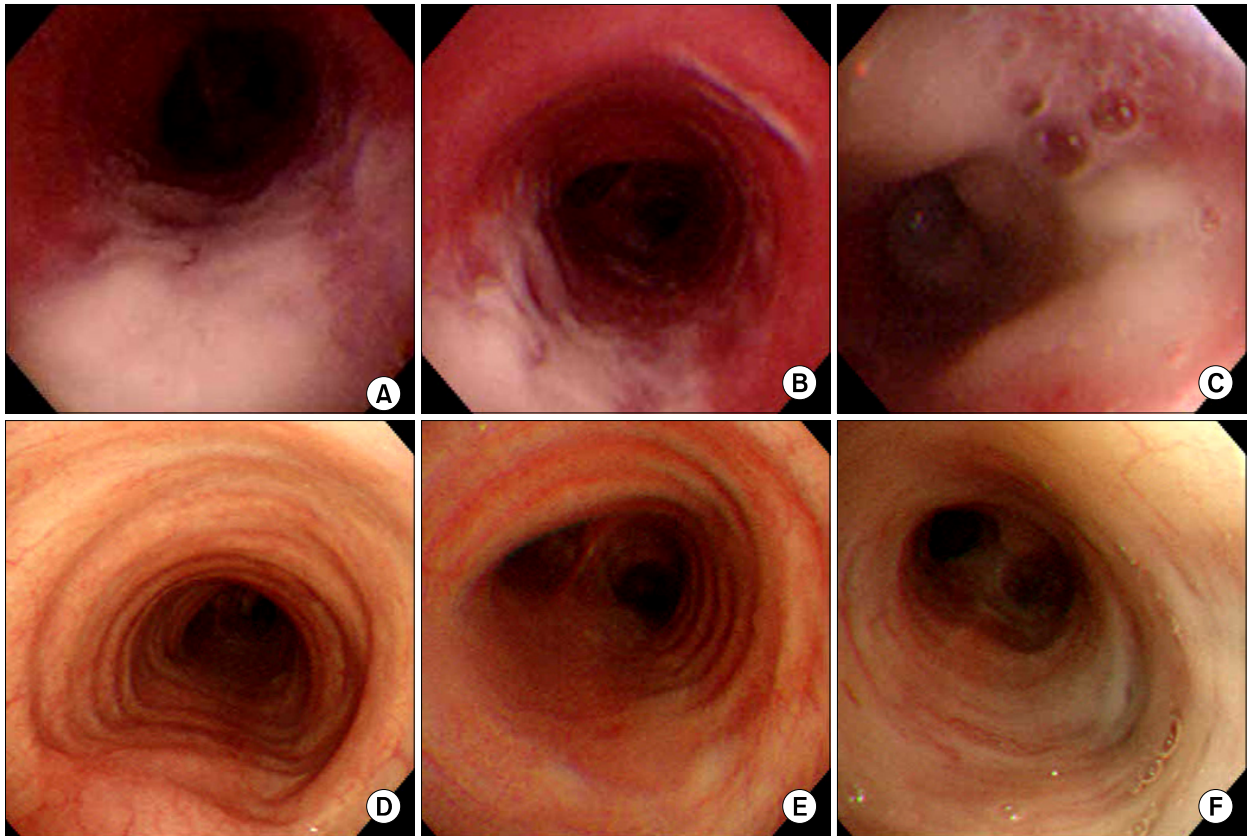


Figure 3. Initial bronchoscopic examination reveals extensive tracheobronchitis and white-to-yellowish thick pseudomembrane throughout the trachea (A, B) and right middle lobe (C). Repeat bronchoscopy shows a remarkable improvement of previous lesions in the trachea (D, E) and right middle lobe (F).

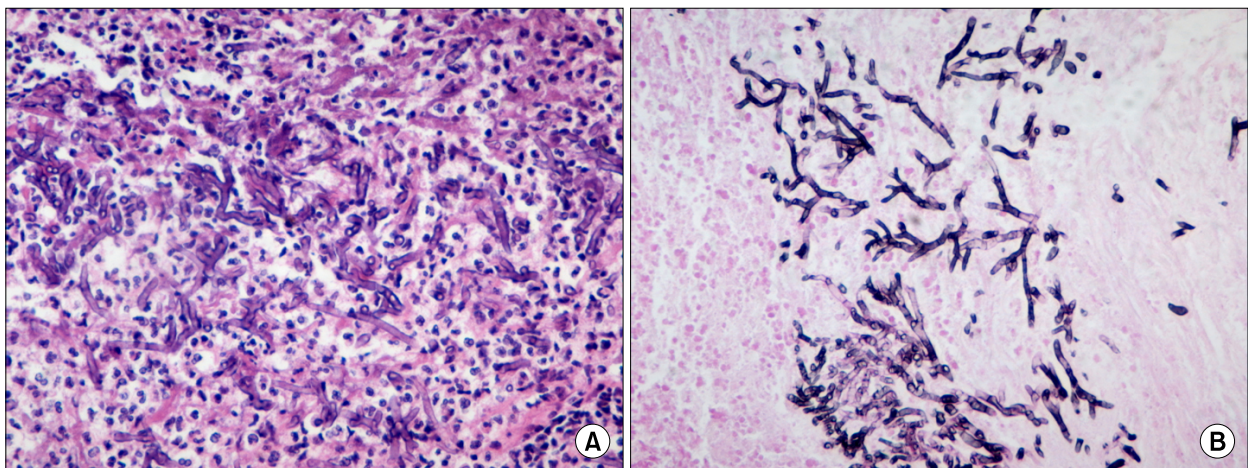


Figure 4. Bronchoscopic biopsy demonstrated septate hyphae with branching at 45° (A: H&E stain, $\times 400$; B: methenamine silver stain, $\times 400$).

dition and chest radiograph began to improve and the CRP level continued to decline. On the 32nd hospital day, he underwent a repeat bronchoscopic examination,

which revealed a remarkable improvement of the previously observed pseudomembranous lesions and hyperemic mucosa, despite persistence of a residual lesion

in the segmental bronchi of the right middle lobe (Figure 3). On the 40th hospital day, a mild fever persisted, the CRP remained >4 mg/dl, and no further improvement on the chest radiograph was noted. Thus, amphotericin B was changed to intravenous voriconazole (6 mg/kg every 12 h for 1 day, followed by 4 mg/kg every 12 h). Three days later, the fever resolved and the chest radiograph showed further improvement. On the 55th hospital day, the patient was discharged on oral voriconazole (400 mg/day), which was continued for an additional 6 weeks. One month after discontinuing antifungal therapy, a follow-up chest radiograph showed haziness in both middle lung fields, suggesting healed lesions (Figure 1C).

Discussion

This case demonstrated that ATB can develop in a previously healthy patient who has no recognizable medical illnesses. *Aspergillus fumigatus* cultured from the sputum and the bronchopneumonia pattern on the CT scan provided a clue to the diagnosis of ATB. Early diagnosis and prompt antifungal therapy may lead to success in the treatment of ATB in immunocompetent patients, in contrast to the high fatality rate in immunocompromised patients.

ATB is a rare and less well-recognized variant of IPA, which is limited entirely or predominantly to the tracheobronchial tree³. Similar to IPA in severely immunocompromised patients, ATB carries a very high mortality rate, especially when fungal growth obstructing the lumen leads to acute respiratory failure^{3,4}. According to the proposed classification by Denning¹², ATB is classified into three forms: obstructive, pseudomembranous, and ulcerative types. Obstructive and pseudomembranous ATBs are considered to be refractory to therapy and to have a fatal outcome, whereas up to 82% of patients with ulcerative ATB respond to antifungal therapy and/or surgical treatment⁵. In 20 patients with pseudomembranous ATB, the overall mortality rate was 80%, and significantly higher in ventilated patients than in non-ventilated patients⁵. IPA develops not only in im-

munocompromised patients, but is also increasingly recognized in ICU patients with COPD¹³, suggesting that ATB patients are usually less immunocompromised compared to those with IPA⁶. Until now, ATB has been reported in less immunocompromised patients, such as after influenza⁸, COPD⁹ and diabetes^{9,11}. However, no predisposing condition was recognized for IPA and no flu-like symptoms were noted in the case described herein, although the patient did not undergo serological examination for viral illnesses, such as influenza.

In immunocompetent patients, what should lead to a clinician suspecting ATB and performing a bronchoscopy for the diagnosis of ATB? Although this case was initially suspected to be tuberculosis, two features served as important clues for the diagnosis of ATB: 1) isolation of *Aspergillus* from the sputum culture; and 2) CT findings suggestive of bronchopneumonia, including peribronchial consolidation with bronchial wall thickening and a tree-in-bud appearance, mimicking a radiographic finding of active pulmonary tuberculosis with a rapid deterioration. The confirmatory diagnosis of ATB depends mainly on bronchoscopy, which can enable a pathologic diagnosis of fungal hyphae with a microbiologic diagnosis of *Aspergillus*.

If ATB is suspected or diagnosed by bronchoscopy, an immediate antifungal therapy should be started. The patient described herein showed a favorable response to antifungal therapy, as opposed to severely immunocompromised patients. This corresponds with previous reports^{8,9,11} in which ATB patients with modest immune impairment improved with prompt antifungal therapy. These findings suggest that the outcome of antifungal therapy against ATB depends largely on the immune status of the patient.

In conclusion, ATB may occur, although very rarely, in immunocompetent patients, as well as immunocompromised patients. Early diagnosis and prompt institution of antifungal therapies can lead to a good result in immunocompetent patients in contrast to immunocompromised patients.

Summary

Aspergillus tracheobronchitis (ATB), a variant of invasive pulmonary aspergillosis, is characterized by extensive tracheobronchitis and pseudomembrane formation. ATB usually occurs in immunocompromised patients with a high fatality rate. We report a case of ATB in a previously healthy patient who responded well to antifungal therapy.

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