



Pseudomembranous *Aspergillus* Tracheobronchitis: Case Report of a Rare Manifestation of Airway Invasive Aspergillosis

거짓막성 아스페르길루스 기관-기관지염: 기도침습성 아스페르길루스증의 희귀한 발현에 대한 증례 보고

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Aspergillus tracheobronchitis, an uncommon form of invasive pulmonary aspergillosis, is characterized by the development of a pseudomembrane, ulcers, or an obstruction that is predominantly confined to the tracheobronchial tree. Pseudomembranous *Aspergillus* tracheobronchitis is the most severe form of *Aspergillus* tracheobronchitis, and only a few cases have been reported in Korea. We report the characteristic chest CT findings in a patient diagnosed with pseudomembranous *Aspergillus* tracheobronchitis after bronchoscopy and successfully treated by proper antifungal treatment.

Index terms Invasive Pulmonary Aspergillosis; Respiratory Tract Infections; *Aspergillus*

INTRODUCTION

The most common disease caused by *Aspergillus* species in the immunocompromised host is invasive pulmonary aspergillosis, which mainly involves the lung parenchyma, and, rarely, the tracheobronchial tree. *Aspergillus* tracheobronchitis is an infrequent (about 7%) but severe form of invasive pulmonary aspergillosis in which the fungal infection is predominantly confined to the tracheobronchial tree (1, 2). It typically affects immunocompromised patients who are neutropenic and have hematologic

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malignancies, acquired immunodeficiency syndrome (AIDS), or lung transplantation (1, 2). Pseudomembranous *Aspergillus* tracheobronchitis is a form of *Aspergillus* tracheobronchitis which is considered as the most severe and fatal condition. We describe a case of pseudomembranous *Aspergillus* tracheobronchitis in an immunocompromised patient with transient neutropenia due to chemotherapy along with recent influenza type A infection. We have emphasized the characteristic chest CT findings of the patient, which were well-correlated with the bronchoscopy findings of *Aspergillus* tracheobronchitis.

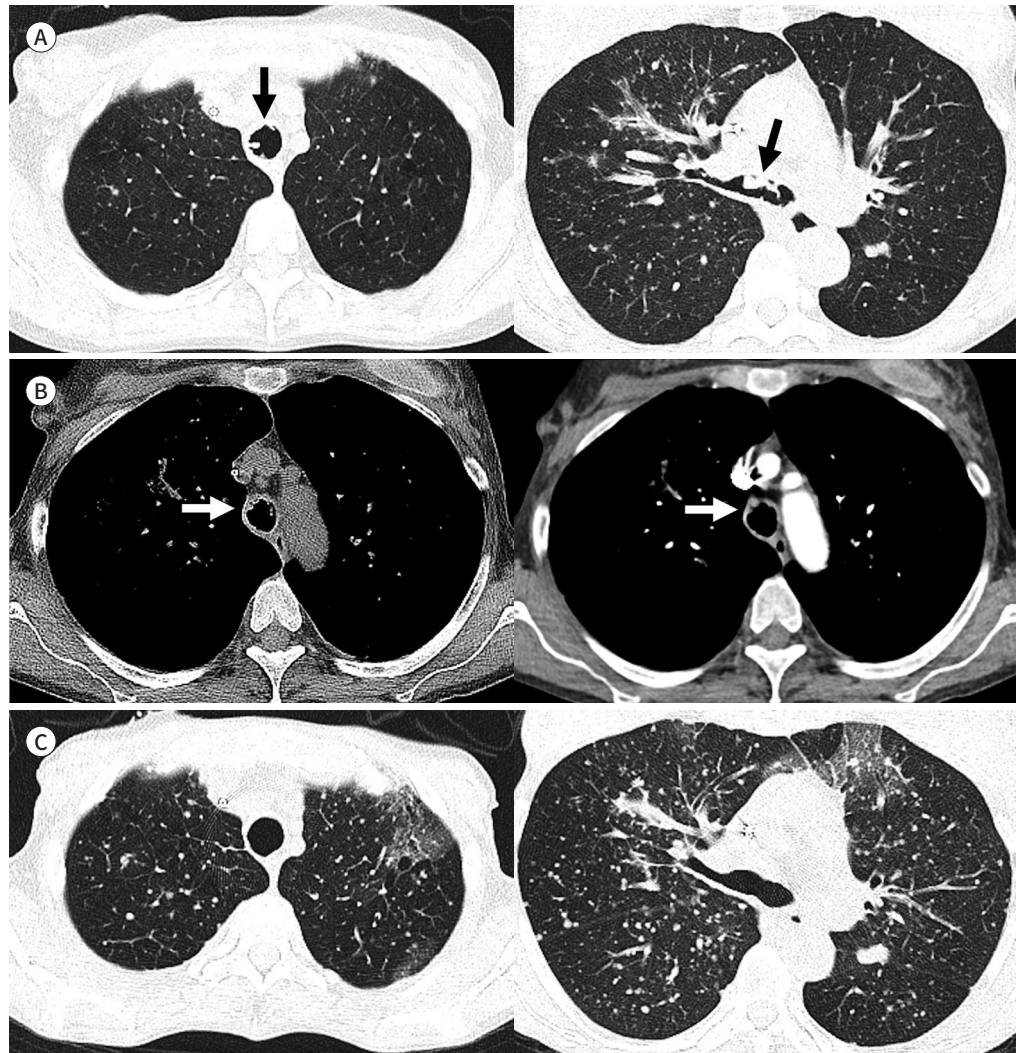
CASE REPORT

A 55-year-old female with a history of advanced colon cancer (stage IV) and multiple metastases in the lung and liver had been receiving palliative chemotherapy with bevacizumab (Avastin, Roche, Basel, Switzerland) - FOLFIRI regimen. She was admitted to the oncology center of our hospital with fever, sore throat, and myalgia for 1 day. Since she had received the last chemotherapy 5 days before admission, she demonstrated mild neutropenia on initial laboratory examination with a decreased absolute neutrophil count ($1070/\mu\text{L}$). She was diagnosed with influenza type A infection and was administered oral oseltamivir along with empirical antibiotics for opportunistic infection. There was no evidence of other 18 common respiratory pathogens, tuberculosis (TB), or nontuberculous mycobacteria infection based on the results of sputum and blood culture tests. She developed severe dyspnea with wheezing on day 5 of hospitalization. Because she had a history of asthma, her symptoms were considered to be an acute exacerbation of asthma. Despite inhaled bronchodilators and systemic corticosteroid treatment, cough, dyspnea, and stridor worsened with appearance of intermittent bloody sputum.

Consequently, on the 7th hospitalization day, a chest CT scan was performed to evaluate the airways and lung parenchyma. It demonstrated various-sized innumerable pleuropulmonary nodules, suggesting pleuropulmonary metastasis, as well as multifocal bronchial wall thickening with peribronchial and patchy mixed ground-glass attenuation, suggesting bronchiolitis and bronchopneumonia in both lungs. Additionally, the CT showed multifocal endoluminal irregular nodular lesions within the trachea, both main bronchi, bronchus intermedius, right upper, and middle lobar bronchi (Fig. 1A). This tracheobronchial finding was considered a tenacious secretion or pseudomembrane, which is associated with tracheobronchial infection, or a tumorous condition. In a follow-up contrast-enhanced chest CT scan after 8 days of antibiotic therapy, the multifocal dense peribronchial consolidation was increased in extent and interval along with development of bronchiectasis and some cavitation in the right lung. The previously noted endo-tracheobronchial lesions remained with circumferential tracheobronchial wall thickening and contrast enhancement (Fig. 1B). Interval increased extent of bronchial wall thickening was noted in the lobar and segmental bronchi of both lungs. Additionally, mucoid impaction within the right middle lobar bronchus was noted.

Bronchoscopy was performed for evaluation of the tracheobronchial lesions that were noted in the chest CT scans. Tracheal mucosa showed a diffuse edematous change with hyperemia, which extended to both the main bronchi, bronchus intermedius, and lobar bronchi of both lungs. It was covered with a confluent thick grayish plaque-like pseudomembrane,

Fig. 1. A 55-year-old female with pseudomembranous *Aspergillus* tracheobronchitis.
A. Lung window images of the initial chest CT (2.0-mm section thickness) at the level of the upper trachea and bronchus intermedius show multifocal irregular endoluminal nodular lesions (arrows). Note micronodules in both lungs, suggesting lung metastasis.
B. Mediastinal window images of the chest CT obtained after 8 days of initial chest CT show circumferential wall thickening with contrast enhancement of the trachea (arrows).
C. Lung window images of the follow-up chest CT obtained after 14 days of voriconazole administration show the decreased extent of the previously noted endoluminal nodular lesions. Micronodules in both lungs are increased, considered to be aggravation of lung metastasis.



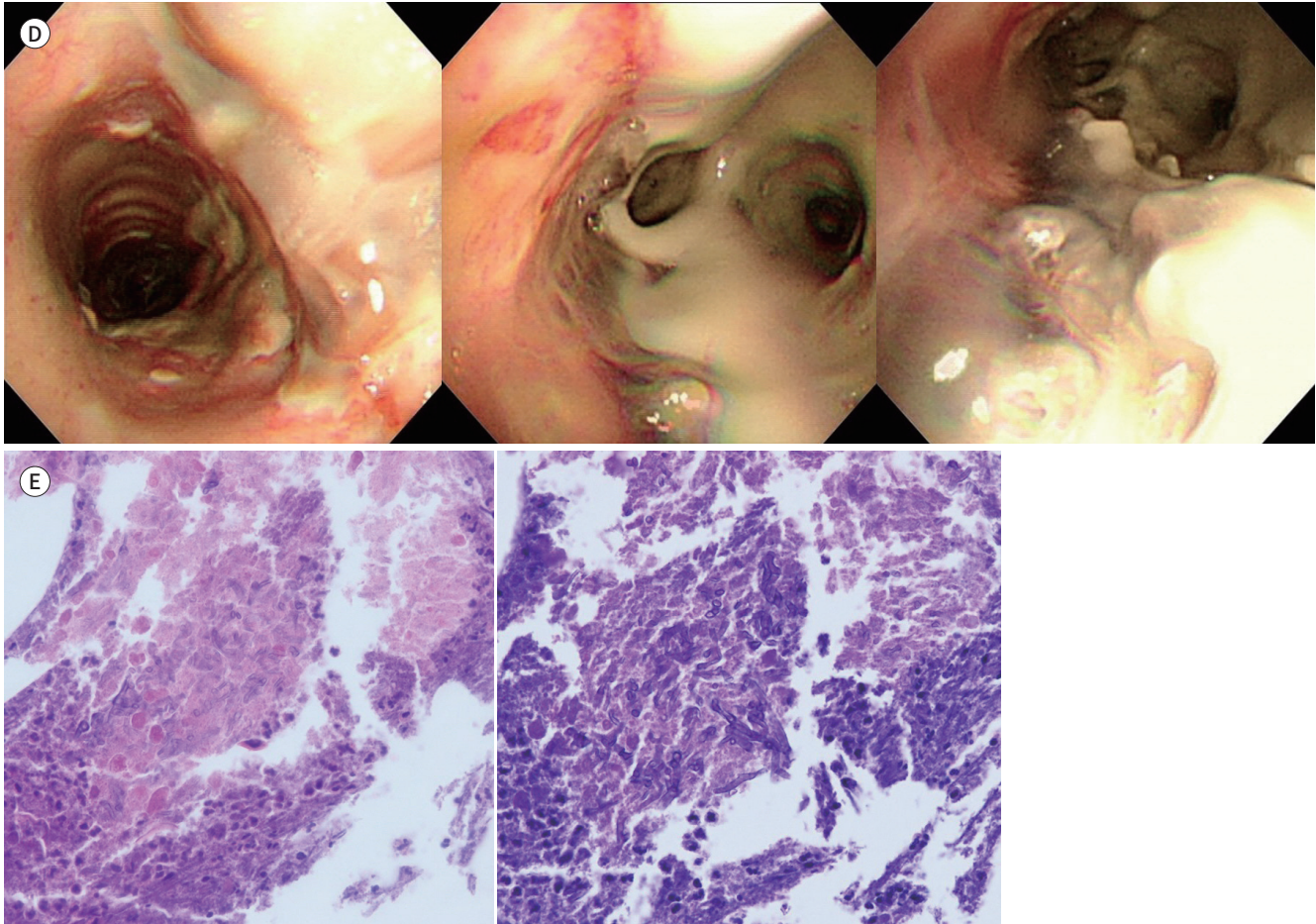
and multifocal nodular, necrotic lesions adhered firmly to the mucosa, causing mild tracheobronchial luminal narrowing (Fig. 1D). A bronchoscopy biopsy specimen was obtained from the right middle lobar bronchus.

Histopathologic examination of the bronchoscopy biopsy specimen demonstrated chronic active inflammation with necrosis, and periodic acid-Schiff staining was positive for fungal organisms (Fig. 1E). The results of laboratory examination were positive for *Aspergillus* antigen (galactomannan) (0.52 index) and *Aspergillus* immunoglobulin G antibody (46), and negative for 1,3- β -D-Glucan (< 10.0). Fungal culture from bronchoalveolar lavage fluid confirmed

Fig. 1. A 55-year-old female with pseudomembranous *Aspergillus* tracheobronchitis.

D. Bronchoscopy findings of the patient show edematous mucosa with a confluent thick grayish pseudomembrane and ulcerative/necrotic lesions in the upper trachea (right), carina (middle), and bronchus intermedius (left).

E. Histopathological findings of the bronchoscopy biopsy specimen demonstrate extensive tissue necrosis associated with infiltration of the fungal hyphae on hematoxylin & eosin stain ($\times 100$, left) and periodic acid-Schiff stain ($\times 100$, right).



Aspergillus species. According to the Infectious Diseases Society and European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) guidelines, the host factors, clinical features, and mycological evidence satisfied the criteria for proven invasive pulmonary *Aspergillus* disease (3). Therefore, pseudomembranous *Aspergillus* tracheobronchitis was diagnosed. After administration of voriconazole (200 mg, bid), the clinical symptoms including dyspnea and cough resolved, and tracheobronchial findings on chest CT disappeared (Fig. 1C).

This case report was approved by relevant Institutional Review Board and the requirement for written informed consent was waived (IRB No. 2020-05-014).

DISCUSSION

Aspergillus are saprophytic filamentous fungi that are widespread in the environment, and cause a variety of diseases, ranging from simple colonization (e.g., aspergilloma) to life threat-

ening invasive infection. According to Kramer et al. (4), the behavior of *Aspergillus* can be divided into allergic, saprophytic, and invasive in the human respiratory tract based on the pathologic, bronchoscopy, and clinical findings (1, 4, 5). Among them, invasive pulmonary aspergillosis implies invasion of the lung tissue by fungal hyphae, and is characterized by opportunistic infections mostly in immunocompromised hosts. Defense mechanisms against *Aspergillus* infection include bronchial mucociliary reactions, phagocytosis by alveolar macrophages and polymorphonuclear leukocytes, innate T cell response, and the complement system. Neutrophils are the dominant host defense mechanism in the invasive hyphal stage. Clinically, predisposing conditions for invasive pulmonary aspergillosis can be broadly divided into local factors and systemic factors. Systemic factors includes neutropenic patients with defects in the immune function such as patients with leukemia, human immunodeficiency virus/AIDS (reduced number of helper T lymphocytes), recipients of hematopoietic stem cell transplant or solid organ transplantation, graft versus host disease, receiving antineoplastic treatment or chronic systemic high-dose corticosteroids, and those with chronic granulomatous diseases. However, about 25% of invasive aspergillosis patients are not apparently immunocompromised. According to Wu et al. (6) neutropenia was only 15.8% among 19 cases of isolated tracheobronchial aspergillosis. Impaired local defense functions of the airways, regardless of their systemic immune status might correspond to *Aspergillus* tracheobronchitis. It characteristically occurred at anastomosis site of lung transplant recipient and which is single most common predisposing factor (4, 6). Likewise, inhaled corticosteroid administration, prolonged use of endotracheal tubes, preexisting anatomic airway abnormalities including stricture/stenosis after bronchial TB, and radiotherapy can also important risk factor (6, 7). Recently, influenza A, which impairs cell-mediated immunity and mucociliary clearance function, has also been reported as an important local predisposing risk factor (8).

Tracheobronchial aspergillosis is classified as an invasive pulmonary aspergillosis, which is diagnosed according to the EORTC/MSG definition (3). Kramer et al. (4) proposed three entities or different forms of the disease, mainly differentiable by the level of underlying immunosuppression and progression of the disease: 1) *Aspergillus* tracheobronchitis, 2) ulcerative *Aspergillus* tracheobronchitis, 3) pseudomembranous *Aspergillus* tracheobronchitis. Pseudomembranous *Aspergillus* tracheobronchitis refers to extensive invasion of the entire tracheobronchial tree, which is covered by a combined grayish plaque-like membrane and has the highest mortality rate (4). Histologically, *Aspergillus* tracheobronchitis begins with intraluminal proliferation of the *Aspergillus* hyphae on the surface of the bronchial mucosa, followed by development of bronchial and/or tracheal inflammation with mucus production. Focal intense submucosal pyogranulomatous inflammation leads to ulceration of the surface respiratory epithelium. Fungal hyphae, purulent exudates, viscous mucus, and necrotic tissue with fibrin form an extensive plaque-like pseudomembrane or multiple partly fibrinous nodular plaques, resulting in luminal narrowing, and often causing obstruction (4, 5). If diagnosis is delayed, full-layer airway invasion may progress into the adjacent tissue, leading to bronchoesophageal fistulation or broncho-arterial fistulation, which can cause fatal hemorrhage.

Clinical presentation of *Aspergillus* tracheobronchitis is nonspecific, including cough, dyspnea, bloody sputum, hemoptysis, wheezing, and stridor. Due to the high prevalence of pulmonary TB in Korea, along with an increasing number of critically ill patents, thoracic surgery,

and increasing antineoplastic or immunosuppressive medication usage, *Aspergillus* tracheobronchitis may be increasingly diagnosed domestically (9).

Fiberoptic bronchoscopy is a useful investigation for diagnosis of *Aspergillus* tracheobronchitis that allows detection of various abnormalities, such as inflammatory infiltration, mucosa hyperemia, edematous mucosa, endobronchial nodules, ulcerative/necrotic lesions, pseudomembrane, and luminal narrowing (7).

Chest CT findings of isolated *Aspergillus* tracheobronchitis can include endoluminal irregular nodular lesions, nodular or circumferential thickening, and enhancement of the tracheobronchial tree. However, CT may be normal, especially in the early stage of the disease (10). Consequently, an accurate diagnosis of isolated *Aspergillus* tracheobronchitis based on only chest CT findings is often difficult. Because delayed diagnosis of *Aspergillus* tracheobronchitis can cause fatal complications and increasing mortality, it is important to detect the minor changes along the tracheobronchial tree in the chest CT, especially in clinically suspected patients.

We experienced a rare case of histologically confirmed pseudomembranous pulmonary aspergillosis that was suspected on the basis of the chest CT findings. Detection of minor changes in the tracheobronchial tree in the chest CT by a radiologist can help in the early diagnosis and proper management of patients with *Aspergillus* tracheobronchitis. We propose that if the characteristic imaging findings such as endoluminal irregular nodular lesions, nodular or circumferential thickening, and enhancement of the tracheobronchial tree are observed in a CT scan, *Aspergillus* tracheobronchitis should be included in the differential diagnoses on the basis of variable clinical predisposing factors.

Author Contributions

Conceptualization, K.J.J., J.S.Y.; data curation, C.J.S.; formal analysis, K.J.J.; investigation, C.J.S., P.S.J., L.Y.S., K.M.; methodology, K.M.J.; project administration, K.M.J.; resources, C.J.S., P.S.J., L.Y.S., K.M.; supervision, K.J.J.; validation, K.J.J.; visualization, C.J.S.; writing—original draft, C.J.S.; and writing—review & editing, K.J.J., C.J.S.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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거짓막성 아스페르길루스 기관-기관지염: 기도침습성 아스페르길루스증의 희귀한 발현에 대한 증례 보고

조재성¹ · 김정재^{1*} · 정선영² · 이연수³ · 김미옥³ · 박성준⁴ · 고명주¹

아스페르길루스 기관-기관지염은 침습성 폐 아스페르길루스의 매우 드문 형태 중 하나로 주로 기관-기관지에 국한되어 거짓막이나 궤양을 형성하거나 폐쇄를 유발하는 질환이다. 거짓막성 아스페르길루스 기관-기관지염은 아스페르길루스 기관-기관지염 중 가장 심한 형태로 대개는 면역저하자에서 발병하고 예후가 좋지 않다. 현재까지 이 질환에 대해 몇 개의 국내 보고가 있으나 영상 소견에 대한 보고는 드물다. 이에 저자들은 기관지경 검사상 거짓막성 아스페르길루스 기관-기관지염으로 진단되고 적절한 항진균제 투여로 성공적으로 치료된 환자의 증례를 특징적인 영상 소견과 함께 보고하고자 한다.

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