

[CASE REPORT]

Pseudomembranous Invasive Tracheobronchial Aspergillosis with Fulminant Hepatitis and Hemophagocytic Syndrome

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Abstract:

Invasive tracheobronchial aspergillosis (ITBA), a rare form of invasive pulmonary *Aspergillus* infection (IPA), is predominantly confined to the tracheobronchial tree. We herein report a case of ITBA with severe necrotic pseudomembrane in a 57-year-old woman with fulminant hepatitis and hemophagocytic syndrome. Bronchoscopic findings revealed a widespread pseudomembranous formation of the trachea and bronchi. *Aspergillus fumigatus* was cultured from bronchial lavage fluid, and the histological findings of an endobronchial biopsy revealed necrosis and invasive hyphae. Although she responded to antifungal treatment, she ultimately died of a septic shock with *Burkholderia cepacia* 57 days after admission.

Key words: invasive tracheobronchial aspergillosis, fulminant hepatitis, hemophagocytic syndrome, bronchoscopy

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Introduction

Invasive tracheobronchial aspergillosis (ITBA), a rare form of invasive *Aspergillus* infection, is mainly restricted to tracheobronchial lesions (1). It primarily occurs in immunocompromised hosts, such as patients receiving solid organ transplant, patients with hematologic malignancies, or patients undergoing immunosuppressive therapy, including corticosteroid therapy (2-4). Three different forms of ITBA have been described on the basis of the bronchoscopic or pathologic appearance: *Aspergillus* tracheobronchitis, ulcerative *Aspergillus* tracheobronchitis, and pseudomembranous *Aspergillus* tracheobronchitis (5). Li et al. suggested that pseudomembranous ITBA potentially followed an aggressive course with the rapid progression of lung parenchymal involvement and a fatal outcome, even in immunocompetent patients (6).

We herein report a rare case of *whole-circumference* pseudomembranous ITBA with fulminant hepatitis (FH) and hemophagocytic syndrome (HPS).

Case Report

A 57-year-old woman with no significant medical history of the habitual use of alcohol, tobacco, or diet supplements suffered from a fever and diarrhea. Following the ingestion of tetracycline as prescribed by a family doctor, she felt fatigue and was admitted to a local general hospital. The laboratory findings revealed elevated transaminase levels [aspartate aminotransferase (AST), 5,255 IU/L; alanine aminotransferase (ALT), 2,435 IU/L], bicytopenia (leukocytes, 1,200/ μ L; polymorphonuclear neutrophils, 36.3%; atypical lymphocytes, 24%; and platelets, 5.0×10^4 / μ L), and a reduced prothrombin time (PT) activity, 36.3%. Her hepatitis A virus-specific IgM antibodies (HAV-IgM), hepatitis B surface (HBs) antigen, hepatitis C virus (HCV) antibody, viral capsid antigen (VCM)-IGM, cytomegalovirus (CMV) antigenemia, antimitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA), HTLV-1 antibody, and HIV antibody findings were negative. She subsequently demonstrated signs of encephalopathy in the form of confusion and slow

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Table. Laboratory Data on Admission.

[Hematology]		[Biochemistry]		[Infection marker]	
WBC	3,400 / μ L	TP	5.0 g/dL	PCT	0.4 ng/mL
Neu	69.2 %	alb	2.3 g/dL	HBVDNA	0 Logcp/mL
Lym	21.5 %	Na	134 mEq/L	HCV ab	0.1 S/CO
Aty-Lym	16 %	K	4.2 mEq/L	HIV ab	0.3 S/CO
RBC	404 \times 10 ⁴ / μ L	Cl	97 mEq/L	HTLV-1ab	0.1 S/CO
Hb	10.1 g/dL	BUN	21.3 mg/dL	β -D glucan	617 pg/mL
Plt	3.8 \times 10 ⁴ / μ L	Cr	0.78 mg/dL	Aspergillus Ag	(+)
		T-Bil	1.7 mg/dL	CMV ag	(-)
		D-Bil	1.1 mg/dL		
[Immunology]		AST	4,457 U/L	[Coagulation]	
CRP	2.52 mg/dL	ALT	1,417 U/L	PT%	42 %
IgA	267 mg/dL	LDH	4,692 U/L	APTT%	35.2 %
IgG	1,165 mg/dL	ALP	859 U/L		
IgM	112 mg/dL	γ -GTP	500 U/L	[Arterial blood gas (room air)]	
ANA(FA)	<40	Ferritin	13,990 ng/dL	pH	7.33
AMA(FA)	<20	NH ₃	105 μ g/dL	PaO ₂	89.4 mmHg
ASMA(FA)	<20			PaCO ₂	40.6 mmHg
				HCO ₃ ⁻	21 mmol/L
				BE	-4.4 mmol/L

CRP: C-reactive protein, Aty-Lym: atypical lymphocytes, AMA: anti-mitochondrial antibody, ASMA: anti-smooth muscle antibody, ANA: anti-nuclear antibody, PCT: procalcitonin, ab: antibody, ag: antigen, CMV: cytomegalovirus, BE: base excess

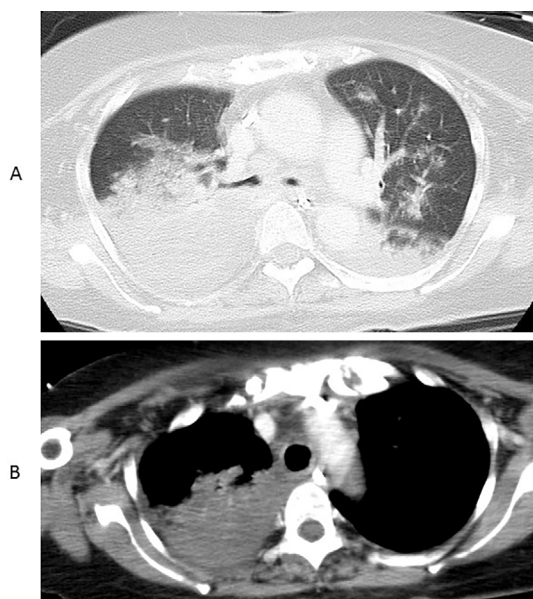


Figure 1. Computed tomography (CT) of the chest revealed a diffuse infiltration shadow of the lungs (A) and bronchial wall thickening (B).

movement. A bone marrow biopsy revealed increased numbers of maturity histiocytes with significant hemophagocytosis. She was subsequently diagnosed with FH and HPS. Although she underwent steroid pulse therapy and continuous hemodiafiltration (CHDF), her condition did not improve. Therefore, she was transferred to our hospital for treatment, including liver transplantation.

Three days after admission, she developed severe respira-

tory failure and underwent tracheal intubation for mechanical ventilation. Computed tomography (CT) of the chest revealed bronchial wall thickening and bilateral diffuse infiltration shadow of lungs (Fig. 1). The bronchoscopic findings revealed a widespread pseudomembranous formation covering the entire circumference of the trachea and bronchi (Fig. 2). In addition, the β -D-glucan level was significantly increased to 617 pg/dL, and the *Aspergillus* galactomannan antigen level (ELISA) was >5.0. Other laboratory findings revealed C-reactive protein (CRP) at 2.52 mg/dl and procalcitonin (PCT) at 0.4 ng/mL (Table). The findings from a blood gas test were as follows: pH 7.32; PaO₂, 89.4 mmHg; PaCO₂, 53.9 mmHg; HCO₃⁻, 19.3 mmol/L; and PaO₂/FiO₂, 149. Furthermore, an endobronchial biopsy under bronchoscopy revealed active inflammation with necrotic tissue and numerous filamentous fungal hyphae infiltration in all layers (except for some parts of the gland duct structure and cartilage tissue) (Fig. 3). *Aspergillus fumigatus* and *Burkholderia cepacia* were isolated from bronchial lavage fluid cultures. She was therefore diagnosed with pseudomembranous ITBA and acute respiratory distress syndrome (ARDS). Possible causes of the diffuse infiltration shadow of the lungs included bacterial pneumonia, invasive pulmonary aspergillosis (IPA), and pulmonary edema; however, we were unable to perform bronchoalveolar lavage (BAL) because of severe respiratory failure.

The patient received broad-spectrum antibiotics (imipenem) and antifungal therapy with intravenous voriconazole (200 mg/day) and caspofungin (35 mg/day). The β -D-glucan level decreased over time, and the tracheobronchial pseudomembrane showed scarring on reexamination

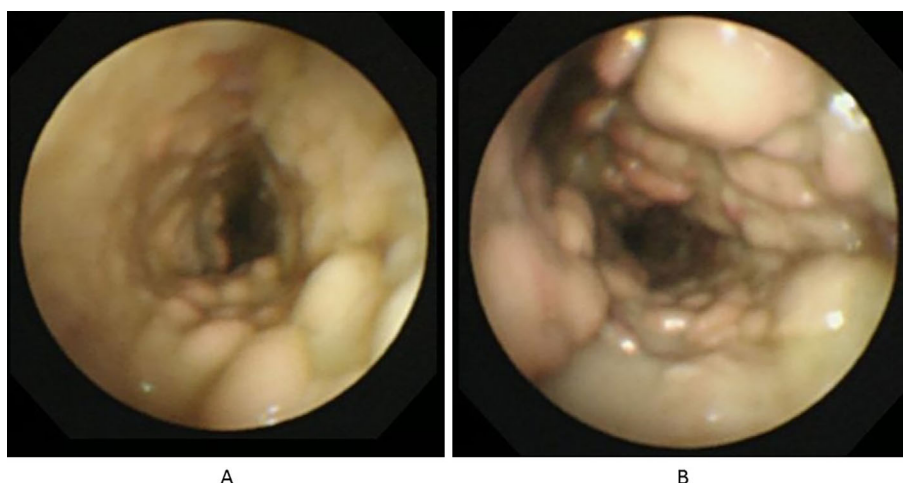


Figure 2. Bronchoscopic findings revealed a widespread pseudomembranous formation covering the entire circumference of the trachea (A) and right main bronchus (B).

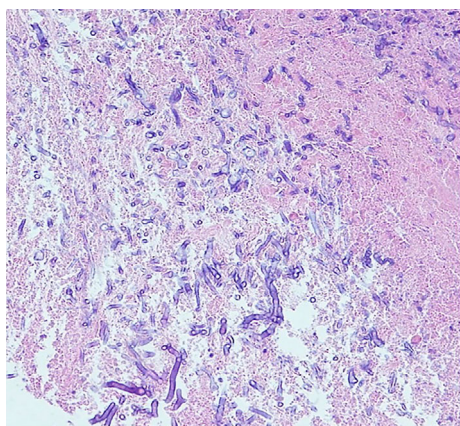


Figure 3. Photomicrograph of the biopsy specimen from the trachea showed active inflammation with necrotic tissue and numerous filamentous fungal hyphae infiltration at all layers of tissue (Hematoxylin and Eosin staining $\times 100$).

via bronchoscopy. However, she developed septic shock with *Burkholderia cepacia* that was further complicated with ARDS. Despite antibiotic therapy and intensive care, she died 57 days after admission.

Discussion

ITBA is relatively rare and is seen in less than 10% of IPA cases (7). Reported comorbidities with ITBA include solid organ transplantation, hematologic malignancies, or HIV infection. In a case series and review, most patients (86.5%) had some degree of immunosuppression, including long-term corticosteroid therapy (71.8%), active chemotherapy (25.0%), or neutropenia (18.7%) (7). However, the patient in the present case had no chronic immunosuppressive disease as described above. One case report describes a patient who developed ITBA following infection of influenza without a chronic immunosuppressive state (8). Although previous reports of ITBA with liver disease mainly describe patients undergoing liver transplantation, Marco et al. re-

ported that patients with advanced or acute liver disease had an increased susceptibility to fungal infections due to the impairment of neutrophil immune mechanisms, the frequent use of corticosteroids, and malnutrition. The report also revealed that the mortality rate for invasive aspergillosis in patients with severe liver disease was as high as 70% (9). Lawrence et al. reported a case of IPA complicated with HPS (10).

There are many causes of FH, including viral infection, autoimmune hepatitis, and drug-related hepatitis (11). The etiology in the present case was likely drug-related (tetracycline), as almost all of the virological tests (HAV, HBV, HCV, CMV, or EBV) and immunological tests (ANA, AMA, or ASMA) were negative. In addition, there have been some reports of drug-induced acute hepatic failure associated with tetracycline (12-14).

Bronchoscopic procedures, such as BAL and transbronchial biopsies, are very useful for the diagnosis of IPA (15). Moçin et al. reported that the sensitivity, specificity, and positive and negative predictive values of BAL for the diagnosis of tracheobronchial fungal infection were 85.1%, 81.4%, 66.3%, and 92.7%, respectively, and 35% of patients who underwent biopsies were confirmed to have fungal elements (16). *Aspergillus fumigatus* is the most common species in patients with tracheobronchial involvement. Karnak et al. reviewed 121 cases of endobronchial aspergillosis and found that 63% of patients with tracheobronchial infections had *Aspergillus fumigatus*, just as in this case (17).

ITBA is classified into three subtypes based on the bronchoscopic and/or pathologic features: *Aspergillus* tracheobronchitis, ulcerative *Aspergillus* tracheobronchitis, and pseudomembranous *Aspergillus* tracheobronchitis (5). Pseudomembranous *Aspergillus* tracheobronchitis is characterized by pseudomembranes coating the mucosal surface of the tracheobronchial tree. The present case in particular showed a significant pseudomembranous mucosal surface with whitish plaques covering the entire circumference from the trachea to bronchi. This case is also rare in terms of the severe en-

doscopic findings compared with previous reports of ITBA (18). Although *Staphylococcus aureus*, *Bacillus cereus*, *Streptococcus pyogenes*, and *nondiphtherial corynebacteria* have also been reported as differential causative pathogens of pseudomembranous tracheobronchitis, *Aspergillus* spp. is the most common organism inducing pseudomembranous tracheobronchitis (19-23).

In lung transplant patients, the mortality ratio of ITBA reportedly ranges from 14-23.7% (24-26). The prognosis in severely immunocompromised patients with hematological malignancies and ITBA is significantly worse than that of ITBA with other diseases. Tasci et al. reported that no patients with hematological malignancies with ITBA survived (18). Krenke et al. conducted a review and reported that the mortality rate related to *Aspergillus* infection with hematological malignancies was as high as 72.2% (27), although several reports have suggested a better prognosis in patients with ITBA without malignant disease, with only 1 in 5 reported patients dying (mortality rate 20%) (28, 29). In their multivariate logistic regression analysis, Fernández et al. found that the presence of neutropenia [odds ratio (OR), 20.47; 95% confidence interval (CI), 3.92-106.94; $p < 0.001$] and acute respiratory distress at presentation (OR, 9.54; 95% CI, 2.27-40.05; $p = 0.002$) were independent prognostic factors for the in-hospital mortality rate of *Aspergillus* tracheobronchitis (7). In the present case, both acute respiratory distress and neutropenia were applicable as prognostic factors.

The latest Infectious Diseases Society of America (IDSA) guidelines recommend voriconazole for the primary treatment of IPA (30). Alternative therapies include liposomal amphotericin (AmB), isavuconazole, or other lipid formulations of AmB. The combination of antifungal therapy with voriconazole and echinocandin may be considered in select patients with documented IPA. Fernández et al. reported combination therapy with triazole or AmB plus nebulized AmB (n-AmB) as the initial treatment for ITBA (7). The IDSA guidelines recommend the use of an inhaled AmB as well as a systemic triazole for antifungal prophylaxis in lung transplant recipients, however, the effectiveness of inhaled antifungal therapy for ITBA in immunosuppressed patients remains to be elucidated (30).

We administered combination therapy with voriconazole and caspofungin in the present patient because of her severe status. While the antifungal therapy was deemed effective, resulting in reduced β -D-glucan levels and positive changes in the tracheal bronchus mucosa on follow-up bronchoscopy, the patient ultimately died of septic shock and respiratory failure.

In conclusion, we reported a unique case of whole-circumference pseudomembranous ITBA without organ transplantation or malignancy that followed a fatal clinical course.

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

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