

[ CASE REPORT ]

## Fulminant Tracheobronchial Aspergillosis in an Apparently Healthy Adult

Hayato Moribuchi<sup>1</sup>, Rumi Sato<sup>1,2</sup>, Shuntaro Matsushima<sup>3</sup>, Masaki Tominaga<sup>1</sup>, Jun Sasaki<sup>1</sup>, Masayuki Nakamura<sup>1</sup>, Yuki Sakazaki<sup>1</sup>, Mamoru Nishiyama<sup>1</sup>, Tomoaki Hoshino<sup>1</sup> and Tomotaka Kawayama<sup>1</sup>

### Abstract:

A 56-year-old healthy man who was a current smoker died from fulminant tracheobronchial aspergillosis despite a month of treatment with a combination of intravenous anti-fungal agents that had been started immediately after the diagnosis. This case report is important for understanding and managing fulminant *Aspergillus* infections in healthy subjects, although the pathogenesis and underlying pathways are still unknown.

**Key words:** fulminant, tracheobronchial aspergillosis, healthy individual

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### Introduction

Tracheobronchial aspergillosis is a well-recognized phenotype of rare invasive pulmonary aspergillosis (IPA); patients suspected of having tracheobronchial aspergillosis require admission to an intensive-care unit and prompt initiation of antifungal therapy (1-10). We encountered a fatal case of fulminant tracheobronchial aspergillosis in an apparently healthy adult, although most of the previously reported patients with tracheobronchial aspergillosis and IPA were immunocompromised (1-10).

### Case Report

A 56-year-old, healthy man who was a current smoker required emergency admission at Asakura Medical Hospital with chief complaints of a fever, cough, sputum, and dyspnea for 10 days. He had no history of medications or circumstances indicative of inhaled hyphal exposure before the onset of respiratory symptoms. His respiratory rate was 30 beats per min, and his oxygen saturation was 92% (87% at room air) with 4 L/min of nasal oxygen therapy. His blood test showed values almost within the normal range: neutro-

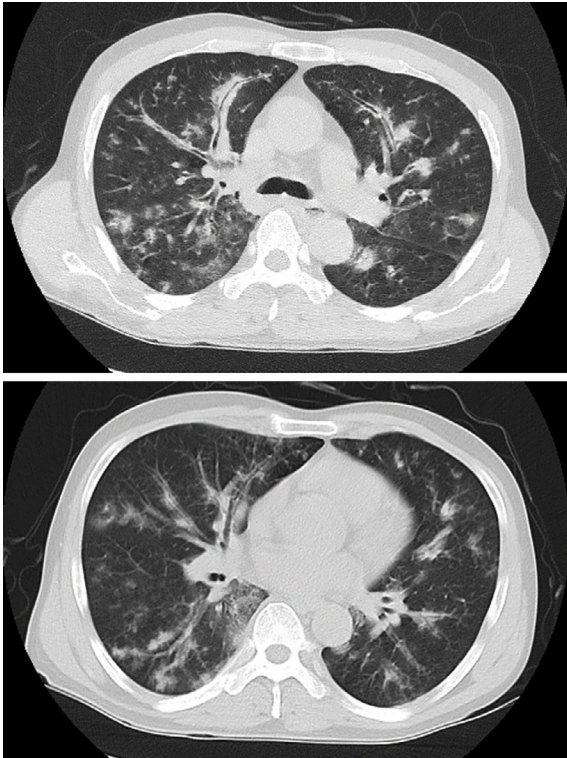
phil count ( $4,940 \times 10^3$  cells/mL), fasting glucose (10.8 mg/L), and hemoglobin A1c (6.2% of the value recommended by the National Glycohemoglobin Standardization Program). The 1-3-beta-D glucan level in blood was 488 pg/mL (cut-off value, 20 pg/mL). The serum galactomannan antigen level for *Aspergillus*, assessed by an enzyme-linked immunosorbent assay, was 3.8 according to the cut-off index. A complement fixation test (BML, Tokyo, Japan) indicated a less than four-fold increased level of anti-*Aspergillus* antibodies (negative results). Serum human immunodeficiency virus (HIV)-1 and HIV-2 antibodies and HIVp24 antigen were not detected by a chemiluminescent enzyme immunoassay (BML). Chest computed tomography (CT) revealed multiple regions of bronchial wall thickening with peribronchial infiltrations before treatment (Fig. 1). No evidence of rhinosinusitis was found on facial CT. Fiberoptic bronchoscopy showed multiple areas of ulceration and swelling, with geographical, moss-like white coats on the tracheobronchial mucosa (Fig. 2A).

Treatment with a combination of empirical intravenous anti-fungal agents [250 mg twice daily (total 500 mg/body/day) of voriconazole and 150 mg twice daily (total 300 mg/body/day) of micafungin] was initiated after confirming the presence of fungal hyphae in bronchial lavage samples

<sup>1</sup>Division of Respiriology, Neurology, and Rheumatology, Department of Medicine, Kurume University School of Medicine, Japan, <sup>2</sup>Respiratory Medicine, Asakura Medical Association Hospital, Japan and <sup>3</sup>Kurume Medical Resident Center, Kurume University Hospital, Japan

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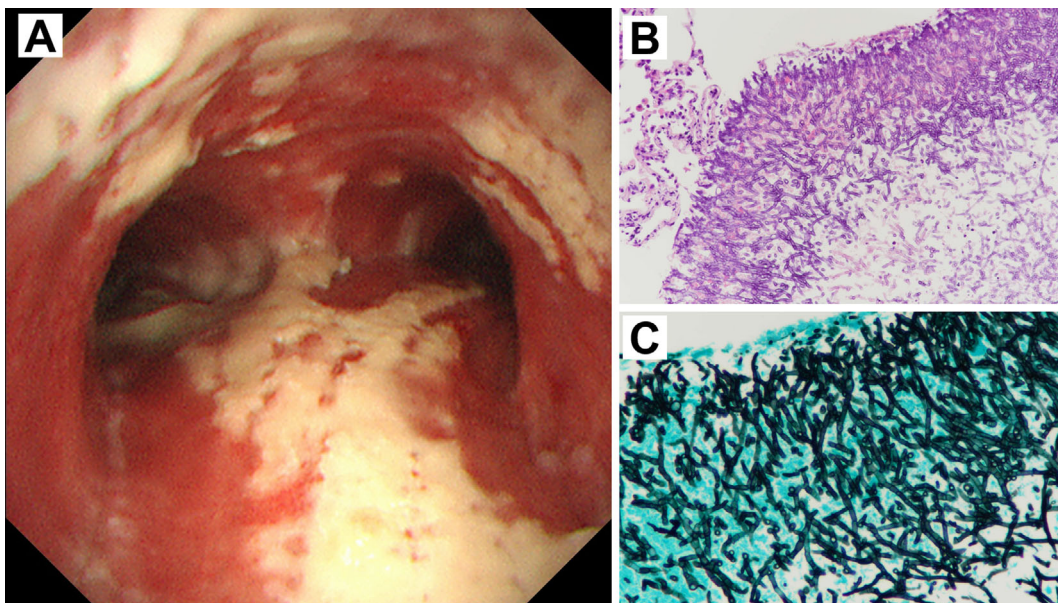
Correspondence to Dr. Tomotaka Kawayama, kawayama\_tomotaka@med.kurume-u.ac.jp



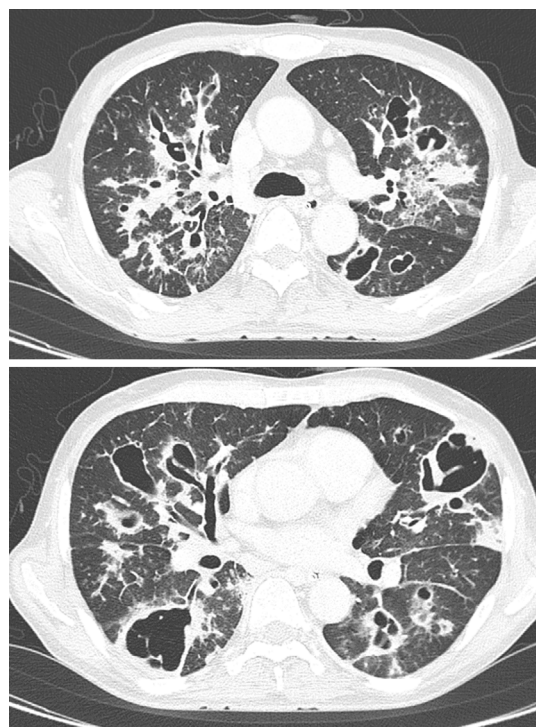
**Figure 1.** Chest CT findings before treatment. An examination of the carina (upper) and lower lobe (bottom) revealed bronchial wall thickening with para-bronchi infiltration in almost all large bronchi. CT: computed tomography

(eighth day of hospitalization). Evidence of bacterial and mycobacterial infections in the sputum, bronchial lavage, and blood and tests for urinary antigens of *Legionella* and pneumococcus were negative; nevertheless, intravenous administration of 500 mg thrice daily (total 1,500 mg/body/day) of doripenem and 200 mg twice daily (total 400 mg/body/day) of minocycline was added to the treatment regimen for suspected mixed typical and/or atypical pneumonia with fungal infections from day 1 to 10 after hospitalization. *Pneumocystis jirovecii* DNA was not detected in the bronchial lavage samples by a polymerase chain reaction assay.

Transbronchial lung biopsies (TBLBs) of the right B1, B3, B5, and B8 lung segments were performed. Each TBLB specimen stained with hematoxylin and eosin showed similar findings of the presence of extensive fungal hyphae, although the presence of hyphal invasion into the lung parenchyma and surrounding blood vessels could not be verified (Fig. 2B). Grocott staining revealed multiple septate hyphae, branched at acute angles, and the hyphae were grouped in typical *Aspergillus* conidial heads (Fig. 2C). Chest CT 14 days after treatment initiation revealed cylindrical bronchiectatic changes with peribronchial infiltration (Fig. 3). The patient died on the 29th day of hospitalization due to multiple organ failure with disseminated intravascular coagulation despite being transferred from the intensive-care unit to the high-care unit of Kurume University Hospital (16th day of hospitalization). *Aspergillus fumigatus* was repeatedly isolated from the bronchial washings and sputum, and the minimum inhibitory concentration (MIC) for micafungin and



**Figure 2.** Findings of fiberoptic bronchoscopy and histopathological examination of transbronchial lung biopsy (TBLB) specimens. A) An examination of the mucosa from the trachea to the bilateral distal bronchi showed ulceration and swelling with geographical moss-like white coats. B) A TBLB specimen stained with Hematoxylin and Eosin staining showed the presence of extensive fungal hyphae and lung parenchymal regions with inflammation. Hyphal invasion into the lung parenchyma and surrounding blood vessels from the right B4 lung segment was not observed ( $\times 200$ ). C) Grocott-stained specimens of the lung tissues ( $\times 400$ ).



**Figure 3.** Chest CT findings 14 days after initiation of anti-fungal treatment. Findings of the carina (upper) and lower lobe (bottom) revealed cylindrical bronchiectatic changes in almost all large bronchi. CT: computed tomography

voriconazole, calculated based on the isolated strains by the modified broth dilution method (BML), were found to be  $\leq 0.015$  and  $0.25 \mu\text{g/mL}$ , respectively (11, 12).

## Discussion

We herein report a rare case of fulminant tracheobronchial aspergillosis in an apparently healthy adult (9, 10). The TBLB findings were different from those observed in IPA cases. Our patient was healthy and had no history of diseases or medication use, such as corticosteroids and immunosuppressants, before this episode. Laboratory examinations did not indicate an immunocompromised status due to HIV infection, severe diabetes mellitus, liver and renal failure, or malignancy as a risk factor for fulminant or invasive fungal infections. The hyphae were suspected to have invaded the airway through the mouth and nose because the primary site of infection was the airway mucosa. The patient did not recall any instance of exposure to fungal hypha, and the CT findings for rhinosinusitis were insignificant. However, exposure might have been possible, given his occupation as a long-distance truck driver.

The pathogenesis of tracheobronchial aspergillosis in healthy subjects remains unclear (3, 9, 10). Pathologically, a diagnosis of IPA could not be established based on the results of a TBLB and bronchial biopsy in the present study. Empirical combination therapy with anti-fungal agents was started immediately, even before the diagnosis was confirmed, and the anti-fungal susceptibility of the isolated *As-*

*pergillus* strains was identified. The isolated strains were susceptible to micafungin and voriconazole. Combination therapy rather than monotherapy was initiated on the first day of hospitalization because the patient showed signs of severe infection with hypoxia, although the involvement of other comorbid fungal infections with *Aspergillus* could not be confirmed.

Despite the estimated synergistic or additive effects of micafungin and voriconazole based on previous studies (13, 14), the patient ultimately died; however, there is little clinical evidence supporting combination therapy (15). The minimal effective concentration (MEC) for the strain could not be obtained, although a previous study reported that the MEC, but not the MIC, of micafungin was more critical for treating infections caused by *Aspergillus* strains (16). An endobronchial approach with anti-fungal treatments may be combined with intravenous infusions for targeting tracheobronchial aspergillosis (17), or amphotericin B may be added to the regimen (2). However, the endobronchial approach and triple therapy including amphotericin B administration were not selected in the present patient, as those therapies have insufficient evidence supporting their efficacy and safety for *Aspergillus* infections in Japan.

Surprisingly, the structure of the large and small bronchi underwent a pathological transformation to cylindrical bronchiectasis several days after *Aspergillus* infection. Some strains of *A. fumigatus* are known to produce putative virulence factors, such as proteases and toxins (18), although our laboratory tests did not provide any evidence suggesting the presence of these factors. These factors may have led to the structural changes in the bronchi.

We believe that the present case report provides clinical information important to the understanding and management of fulminant *Aspergillus* infections in healthy subjects.

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

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