**Title Page**

**Invasive** ***Aspergillus*** **Pseudomembranous Tracheobronchitis Accompanied with Fever and Hemoptysis: A Case Report**

Xiaolong Li, MM1, Xin Wang, MD1, Shuhao Xu, SMM2, Yinhe Feng, MD1, Yuanyuan Liu, MM1, Chunfang Zeng, MM1,\*

# 1Pulmonary and Critical Care Medicine, People's Hospital of Deyang City, Deyang, Sichuan, China,2Department of stomatology, People's Hospital of Deyang City, Deyang, Sichuan, China.

# \*Correspondence: Chunfang Zeng, Pulmonary and Critical Care Medicine, People's Hospital of Deyang City, Deyang 618000, Sichuan, China, (e-mail: 717142334@qq.com).

**AUTHOR CONTRIBUTIONS**

**Xiaolong Li:** Validation; Writing - original draft; Writing - review and editing. **Xin Wang:** Writing - review and editing. **Shuhao Xu:** Data curation, Writing - review and editing. **Yinhe Feng:** Writing - review and editing. **Yuanyuan Liu:** Writing - review and editing. **Chunfang Zeng:** Writing - review and editing.

**FUNDING INFORMATION**

This case was supported by Deyang People's Hospital incubation project, Grant No.FHT202412.

**CONSENT**

The patient gave written informed consent for publication of medical information and images.

**CONFLICT OF INTEREST STATEMENT**

The authors have no conflicts of interest to disclose.

**ETHICS STATEMENT**

This case was approved The Ethics Committee of the People's Hospital of Deyang City(2024-04-059-K01).

**DATA AVAILABILITY STATEMENT**

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

**Abbreviations:**

**COPD** chronic obstructive pulmonary disease

**IPA** invasive pulmonary aspergillosis

**AIDS** acquired immune deficiency syndrome

**NOX** NADP oxidase

**ROS** reactive oxygen species

**HIF-1α** hypoxia-inducible factor-1α

**Key Clinical Message**

Pseudomembranous *Aspergillus* tracheobronchits is a relatively rare disease, and it is very easy for clinicians to misdiagnose. It is particularly necessary for the patient presenting with recurrent pyrexia and hemoptysis in the absence of clear-cut pulmonary radiological findings to receive a bronchoscopy.

**Abstract**

Pseudomembranous *Aspergillus* tracheobronchits is a sporadic invasive pulmonary aspergillosis. Owing to the lack of typical clinical manifestations, the diagnosis and treatment are usually delayed. Therefore, it is necessary to summarize and analyze the typical case in detail in order to improve diagnosis and treatment of this disease.

We reported a patient with pseudomembranous *Aspergillus* tracheobronchits with clinical findings, Thoracic computed tomography findings and bronchoscopic findings. The patient was diagnosed with pseudomembranous *Aspergillus* tracheobronchits by performed bronchoscopy and performed a biopsy of the bronchial mucosa.

**KEYWORDS:**pseudomembranous *Aspergillus* tracheobronchits, bronchoscopy, diagnosis, treatment

**1 INTRODUCTION**

Invasive aspergillosis tracheobronchitis represents a rare manifestation of *Aspergillus* infection limited entirely or predominantly to the tracheobronchial tree. posing significant therapeutic challenges[1]. Given its infrequency and the lack of pathognomonic clinical signs, diagnostic oversights or errors are common. Here, we present a rare case of invasive aspergillosis tracheobronchitis and, through a comprehensive review of relevant literature, encapsulate the diagnostic and therapeutic paradigms associated with this condition.

**2 CASE PRESENTATION**

**2.1 Case history**

A 63-year-old male was admitted to the hospital after experiencing a week of recurrent pyrexia and minimal hemoptysis. The patient had a documented history of chronic obstructive pulmonary disease (COPD) and was receiving long-term treatment with Fluticasone Furoate/Umeclidinium/Vilanterol. The patient has previously suffered from type 2 diabetes and has long-term oral administration of metformin tablets.

**2.2 Differential diagnosis, investigations, and treatment**

Upon admission, laboratory tests upon admission revealed leukocytosis with a count of 12.4×109/L, neutrophilia at 9.6×109/L, and a hemoglobin level of 117 g/L. The highly sensitive C-reactive protein level was notably elevated at 182 mg/L. Thoracic computed tomography showed findings consistent with pulmonary emphysema and bullae. Additionally, the patient displayed febrile symptoms and a pharyngeal swab tested positive for Influenza A nucleic acids. The initial diagnoses included an acute exacerbation of COPD and Influenza A infection. Despite the administration of intravenous Ceftriaxone for the patient's continued pyrexia and production of yellow, purulent sputum, along with the initiation of antiviral therapy using Oseltamivir Phosphate capsules and hemostatic intervention with intravenous Tranexamic Acid, the patient continued to experience persistent minor hemoptysis. Subsequently, bronchoscopy was performed, revealing the presence of a yellow-white pseudomembrane on the tracheal and bronchial surfaces, which appeared friable and bled upon contact (Figs. 1A-E). Tracheal lavage and mucosal biopsy of the tracheal lesions were then carried out. Examination of the lavage fluid at high magnification identified fungal spores and *Aspergillus* hyphae (Fig. 2). Furthermore, histopathological analysis of the tracheal mucosal biopsy confirmed the presence of *Aspergillus* hyphae (Fig. 3). The patient was finally diagnosed with pseudomembranous *Aspergillus* tracheobronchits. During the hospitalization, the patient was initiated on intravenous Voriconazole treatment(200 mg every 12 h), complemented by inhalation of Voriconazole, resulting in the cessation of febrile episodes and a significant reduction in hemoptysis.

**3 Outcome and follow-up**

Post-discharge, the patient continued oral Voriconazole. A follow-up bronchoscopy after two months showed significant recovery of the tracheal and bronchial mucosa (Figs. 4A-E).

**4 DISCUSSION**

Invasive pulmonary aspergillosis stands out as the most prevalent fungal infection affecting the lungs in immunocompromised individuals, typically centered on the lung parenchyma, while tracheal and bronchial involvement remains an infrequent occurrence. Specifically, *Aspergillus* tracheobronchitis denotes an *Aspergillus* infection localized within the trachea and bronchi, presenting as a rare subset of invasive pulmonary aspergillosis (IPA)[2] .

In this case, the patient was diagnosed with pseudomembranous *Aspergillus* tracheobronchitis mainly relying on the presence of *Aspergillus* hyphae by mucosal biopsy and yellow-white pseudomembrane on the tracheal and bronchial surfaces by bronchoscopy. Pseudomembranous *Aspergillus* tracheobronchitis is a type of tracheobronchial aspergillosis. Pseudomembranous *Aspergillus* tracheobronchitis is relatively rare, which is easy for doctors to misdiagnose as endobronchial tuberculosis. Therefore, we wish to raise clinicians' awareness by reporting this case. Tracheobronchial aspergillosis is presently classified into three distinct clinical patterns: obstructive tracheobronchitis, characterized by thick secretions and mycelial masses with minimal *Aspergillus* mucosal infiltration; ulcerative tracheobronchitis, where fungal hyphae aggressively invade the tracheobronchial mucosa, resulting in ulcerative lesions; and pseudomembranous or necrotizing tracheobronchitis, characterized by a pseudomembrane composed of *Aspergillus* hyphae and necrotic debris[3,4] .

Pseudomembranous *Aspergillus* tracheobronchitis commonly afflicts patients with compromised immune function, including those undergoing prolonged corticosteroid therapy, organ transplant recipients, individuals with malignancies, AIDS patients, or those experiencing malnutrition post-major surgery. Nonetheless, instances also sporadically manifest in patients with mild immunosuppression stemming from conditions like diabetes and COPD[5-7] . Furthermore, the patient was diagnosed with influenza A after admission. Studies have shown that influenza has emerged as an independent risk factor for invasive aspergillosis. Recent investigations have underscored the pivotal role of airway epithelium damage and disruption of the tracheal epithelial barrier in the development of invasive *Aspergillus* tracheobronchitis among influenza patients[1]. Additionally, the influenza virus may disrupt host immune regulation by impeding the NADP oxidase (NOX) complex, thereby compromising tracheal defenses against *Aspergillus*[8]. In the context of this case involving a patient with type 2 diabetes, susceptibility to *Aspergillus* in diabetic individuals may be linked to intra- and extracellular levels of reactive oxygen species (ROS). Studies have indicated that heightened intracellular ROS levels correlate closely with neutrophil and lung tissue damage, while reduced extracellular ROS levels diminish the bactericidal capacity of neutrophils[9]. Moreover, hyperglycemia could impede the expression of HIF-1α, an anti-inflammatory hypoxia-inducible factor-1α, thereby disrupting the NLRP3/IL-1β signaling pathway and influencing T lymphocyte differentiation, thereby compromising the body's anti-inflammatory response against *Aspergillus*[10]. The patient’s blood sugar was not well controlled and always in a state of high blood sugar before admitted to the hospital. Therefore, the recent hyperglycemia may also be an important factor leading to his pseudomembranous *Aspergillus* tracheobronchitis.

Regarding therapeutic strategies, Voriconazole stands as the principal antifungal agent for managing *Aspergillus* tracheobronchitis. In this case, the patient began the treatment of voliconazole after diagnosis of pseudomembranous *Aspergillus* tracheobronchitis, and the trachea and bronchial recovered significantly after two months of treatment. This shows the importance of voliconazole in the first-line treatment of pseudomembranous *Aspergillus* tracheobronchitis. In cases where Voriconazole is contraindicated, alternatives such as liposomal Amphotericin B and other triazole antifungals can be considered[11]. Noteworthy expert opinions suggest that intratracheal administration of Voriconazole may yield beneficial effects in managing *Aspergillus* tracheobronchitis in patients unable to receive intravenous formulations[3,11,12].

**5 CONCLUSION**

Given the elusive nature of pseudomembranous *Aspergillus* tracheobronchitis in diagnosis, maintaining a vigilant bronchoscopic approach becomes paramount. This becomes especially crucial in patients presenting with recurrent pyrexia and hemoptysis in the absence of clear-cut pulmonary radiological findings, necessitating heightened surveillance for potential tracheobronchial abnormalities. Currently, the preferred therapeutic approach for *Aspergillus* tracheobronchitis involves the use of Voriconazole, administered either intravenously or orally. Additionally, the potential benefits of intratracheal Voriconazole instillation in managing *Aspergillus* tracheobronchitis warrant consideration.

**REFERENCES**

1. van de Veerdonk FL, Brüggemann RJM, Vos S, et al. COVID-19-associated Aspergillus tracheobronchitis: the interplay between viral tropism, host defence, and fungal invasion. *Lancet Respiratory Medicine.* 2021;9(7):795-802.

2. Fukuda Y, Homma T, Suzuki S, et al. High burden of Aspergillus fumigatus infection among chronic respiratory diseases. *Chronic respiratory disease.* 2018;15(3):279-285.

3. Carboni Bisso I, Las Heras M, Valencia L, Villarroel S, Dalurzo L, San Román E. [Necrotizing tracheobronchitis due to invasive aspergillosis in an immunocompetent patient]. *Medicina-buenos aires.* 2020;80(4):397-400.

4. Singh S, Moore LSP. Novel inhaled antifungal for pseudomembranous Aspergillus tracheobronchitis complicating connective tissue disease. 2023;78(1):110-111.

5. Argüder E, Şentürk A, Hasanoğlu HC, Hasanoğlu İ, Kanbay A, Doğan HT. Unique Case of Pseudomembranous Aspergillus Tracheobronchitis: Tracheal Perforation and Horner's Syndrome. *Mycopathologia.* 2016;181(11-12):885-889.

6. Zhang R, Zhang Y. Primary Cutaneous Aspergillosis Due to Aspergillus fumigatus in an Immunocompetent Patient with Diabetes Mellitus After Tattooing: A Case Report and Review of Literature. 2023;16:791-797.

7. So C, Izumi S, Kusaba Y. Melting cheese-like appearance in the bronchi: Aspergillus tracheobronchitis. *Qjm-an international journal of medicine.* 2022;115(3):173-174.

8. van de Veerdonk FL, Wauters J. Invasive Aspergillus Tracheobronchitis Emerging as a Highly Lethal Complication of Severe Influenza. 2020;202(5):646-648.

9. Xu X, Xia C, Huang Y. Different roles of intracellular and extracellular reactive oxygen species of neutrophils in type 2 diabetic mice with invasive aspergillosis. *Immunobiology.* 2020;225(5):151996.

10. Ye Y, Chen Y, Sun J, et al. Hyperglycemia suppresses the regulatory effect of hypoxia-inducible factor-1α in pulmonary Aspergillus fumigatus infection. *Pathogens and disease.* 2020;78(5).

11. Wu H, Xiong X, Han Q, Zhuo K, Wang K, Cheng D. Instillation of Amphotericin B by bronchoscopy combined with systemic voriconazole in advanced non-small cell lung cancer patients with chronic cavitary pulmonary aspergillosis: A case series and literature review. *Journal of Medical Mycology.* 2023;33(3):101385.

12. Arora S, Haghi M, Young PM, Kappl M, Traini D, Jain S. Highly respirable dry powder inhalable formulation of voriconazole with enhanced pulmonary bioavailability. *Expert opinion on drug delivery.* 2016;13(2):183-193.

**Figure Legends**

**Figs 1A-E.** Yellow-white pseudomembrane on the tracheal and bronchial surfaces, friable and bled upon contact.

**Fig 2.** Fungal spores and *Aspergillus* hyphae were identified in lavage fluid by high magnification.

**Fig 3.** Histopathological by tracheal mucosal biopsy showed *Aspergillus* hyphae.

**Fig 4A-E.** A follow-up bronchoscopy after two months showed significant recovery of the tracheal and bronchial mucosa.