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CASE REPORT

Allergic Bronchopulmonary Mycosis with Eosinophilia Caused by Schizophyllum Infection

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SUMMARY

Background: **As an opportunistic pathogenic fungus, Schizophyllum has been rarely reported to infect humans. By reporting a case of definite diagnosis of Schizophyllum infection, we aim to improve clinicians' understanding of this bacterium.**
Methods: **By reporting a case with cough and sputum as the main manifestations, after empirical anti-infective chest CT suggesting a more progressive inflammatory lesion and a mass-like lesion in the paratracheal area of the main airways, a diagnosis of Schizophyllum infection was finally made by bronchoscopy with the delivery of metagenomic next-generation sequencing (mNGS).**
Results: **The patient was finally diagnosed with rare Schizophyllum infection. After antifungal treatment, the symptoms improved, and the patient was discharged.**
Conclusions: **Although Schizophyllum is a rare fungal infection, it should be taken seriously in patients with diabetes or who are immunocompromised. At the same time, mNGS plays a key role in the detection of rare and emerging pathogens, which is worthy of clinical interest.**
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KEYWORDS

schizophyllum, allergic bronchopulmonary mycosis, metagenomic next-generation sequencing

CASE REPORT

Schizophyllum is a widespread fungus in nature and is commonly found in decaying trees [1]. Schizophyllum was first reported as a human pathogen by Kligman in 1950 [2]. The most common pulmonary fungal infections are pulmonary Aspergillus species, non-Aspergillus species are generally rare, and Schizophyllum infections are rare pathogens. In recent years, intermittent case reports have shown that Schizophyllum is the causative agent of allergic bronchopulmonary mycosis (ABPM) and sinusitis [3]. ABPM can be formed when Schizophyllum colonizes hypersensitivity reactions occurring in the airways, manifested as irritating cough, wheezing, and other clinical symptoms [4]. However, there is currently no definitive treatment for Schizophyllum infection. In this paper, we describe a success-

ful case of effective antifungal therapy with oral itraconazole, combined with literature analysis to further improve the understanding of Schizophyllum.

A 64-year-old female presented with a 2-month history of episodic cough associated with exposure to irritating odors, predominantly at night. She had a history of diabetes for 19 years and was treated with metformin 5 mg orally twice daily and glibenclamide 2.5 mg orally twice daily (irregular medication and irregular monitoring of blood glucose) with poor glycemic control and complained of fasting blood glucose of about 18.6 mmol/L. She had a history of hypothyroidism and was controlled with Euthyrox half tablets orally once a day. The patient lived in an urban area and had no history of smoking or soot exposure, but had a large number of potted plants growing in his home. Physical examinations showed temperature (T) of 36.2℃, pulse (P) of 102 beats/minute, respiratory rate (R) of 21 beats/minute, blood pressure (BP) of 117/68 mmHg, clear consciousness, pharyngeal congestion, no rhonchi or crackles heard in either lungs, regular rhythm, and no pathological murmur heard. Abdomen was flat and soft without tenderness, liver, and spleen were not palpable, and lower limbs showed no edema. Blood routine showed normal absolute leukocyte and neutrophil count and percentage, eosinophil (EOS) 1.1 x 10^9/L, EOS% 14.9%. IgE 1,500 IU/mL, C-reactive protein 32.87 mg/L, G test, GM test, procalcitonin, rheumatism series, antinuclear antibody profile, and tumor markers were in the normal range, and glycosylated hemoglobin 9.8%. On November 10, 2023, a chest CT was performed suggesting an inflammatory lesion in the upper lobe of the right lung. Multiple inflammatory fibrosis was observed in the right middle lobe and left upper lobe. Considering the patient had community-acquired pneumonia, Moxifloxacin 0.4 g ivgtt qd was administered for anti-infection. Unfortunately, after 6 days of treatment, reexamination of chest CT showed that the inflammatory lesions had progressed more than before, and mass-like lesions appeared beside the main trachea (Figure 1). We performed bronchoscopy with the consent of the patient and her family on November 20, 2023, alveolar lavage was performed in the upper lobe of the right lung and sent for pathogenetic testing, and ultrasonic bronchoscopy was used to detect non-homogeneous hypoechoic echogenicity in the 4R area and the 3 o'clock direction of the paratracheal side of the main airway. Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed in the 4R area and paratracheal side of the main airway. Results of bronchoscopy: (4R area TBNA liquid base) A few ciliated columnar epithelial cells, neutrophils, and lymphocytes were found in the submitted samples; (3 points TBNA liquid base beside the bronchi) the submitted samples showed ciliated columnar epithelial cells and bar cells, and no tumor cells were found. Lavage fluid bacterial and fungal cultures and acid-fast stains showed no significant positive results, but metagenomic next-generation sequencing (mNGS) of lavage fluid revealed Schizophyllum with a sequence number of 1766. Therefore, it was considered to be allergic bronchopulmonary mycosis (Schizophyllum), and the patient was given Itraconazole 0.2 g PO bid for antifungal therapy, Budesonide 2 mg via aerosol inhalation bid for anti-inflammatory and anti-asthmatic therapy, and Ambroxol 30 mg PO tid for reducing phlegm. After treatment, the patient's cough and dyspnea symptoms were significantly relieved compared with the previous symptoms. The blood routine eosinophils and C-reactive protein returned to normal on December 26, 2023, and the chest CT suggested that the inflammatory lesions were significantly absorbed compared with the previous ones (Figure 2).

DISCUSSION

Schizophyllum, an opportunistic pathogen, has weak pathogenic ability and generally rarely infects the human body [5]. Sinuses and bronchopulmonary diseases account for 94% of the 71 patients reported worldwide, indicating that the respiratory tract is the main focus of the disease [6]. The pathogenic process may be that inhaled spores colonize the lungs, germinate to form hyphae and stimulate the body to produce cytokines such as interleukins and colony-stimulating factors, which promote the secretion of IgE as well as the increase of eosinophils [7]. Therefore, the increased eosinophil and IgE levels in this patient were also explained. As opportunistic pathogens, Schizophyllum occurs mostly in patients with hematological diseases, tumors, and various immunodeficiencies. Some patients with diabetes, especially poorly controlled diabetes, are also susceptible to the fungus [8]. This patient is diabetic. Although oral metformin hypoglycemic therapy is used, blood glucose is not regularly monitored. The increase in glycosylated hemoglobin level also suggests that the patient has poor previous blood glucose control. Poor glycemic control can reduce immunity in patients. The basal body environment underlying hyperglycemia is more conducive to the growth and reproduction of pulmonary fungi. At the same time, a large amount of vegetation grows all year round in the patient's home, which is a very favorable living environment for Schizophyllum and eventually leads to the invasion and infection of Schizophyllum.

Patients infected with Schizophyllum do not have characteristic clinical manifestations. They mainly have cough and sputum, and some patients may show increased levels of eosinophils and IgE, but this is not specific. In terms of imaging, chest CT of pneumonia caused by Schizophyllum often shows abnormal lung imaging such as bronchial wall thickening, pulmonary fungal spheres, pulmonary consolidation, and atelectasis [9]. The most common findings are fungal spheres or evenly dense bands and mass-like consolidation in the lungs, which may be the result of Schizophyllum growth in the pulmonary lumen; atelectasis may be

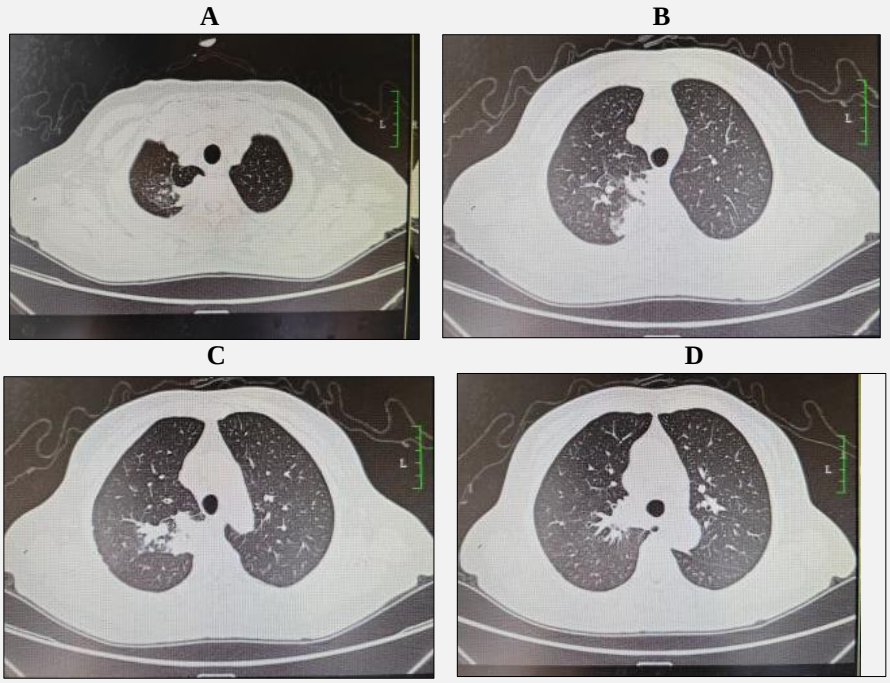

Figure 1. Repeat chest CT after initial treatment suggested an increase in the number of upper lobe-like hyperdense shadows in the right lung compared with that on admission, with well-defined borders, which was considered to be an inflammatory lesion.

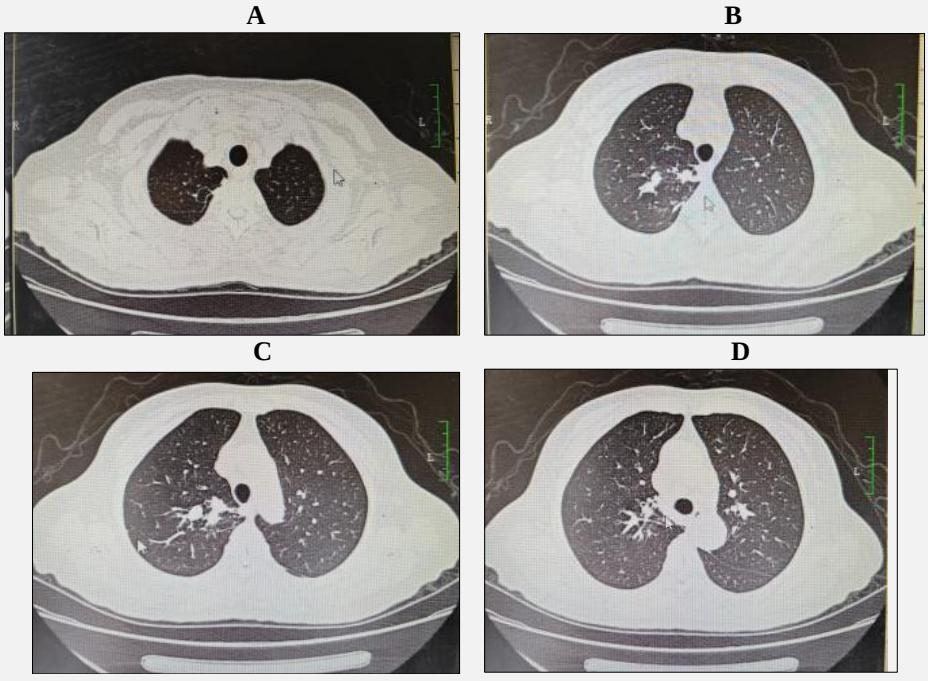

Figure 2. After antifungal treatment on December 26, 2023, a repeat chest CT showed a decrease in the upper lobe-like hyperdense shadow in the right lung compared to the previous one.

mainly caused by complete blockage of the bronchi by mucus plugs [10] while some patients with normal chest CT mainly present with airway hyperreactivity. It is difficult to confirm the diagnosis based on clinical symptoms and imaging. The patient presented with paroxysmal cough and sputum, which were not specific; eosinophils, IgE, and imaging findings had some clinical significance, but still could not be diagnosed. Therefore, the etiological examination is the key to the diagnosis of this disease. At present, there are many methods used for the detection of pathogenic microorganisms in clinical practice, including traditional microbial culture such as sputum culture, bronchoalveolar lavage fluid culture, bacterial and fungal smear, serological detection, PCR, etc. However, the above detection methods show different degrees of disadvantages: Microbial culture is only used for the detection of bacteria and fungi, which is time-consuming, and the detection results are easily interfered by the external environment, so the sensitivity is low; PCR has a high detection rate for specific pathogens such as viruses, but specific primers are required, and the detection range is narrow; X-pert only recognizes Mycobacterium tuberculosis; GM test/G test only identifies fungi. In recent years, advances in genome sequencing technology and bioinformatics methods have provided useful tools for clinical diagnosis, such as mNGS has been widely used in etiological detection, especially in rare, unknown, and emerging pathogen detection showing greater advantages than traditional pathogen detection [11]. Traditional microbial cultures of this patient failed to yield ideal results, but macrogene sequencing of the lavage fluid only detected Schizophyllum sequences, thus clarifying the diagnosis of Schizophyllum. The positive rate and sensitivity of mNGS for the detection of pathogenic microorganisms in lower respiratory tract infections are higher than those in conventional microbiological testing methods. The combination of mNGS and traditional detection methods help to improve the level of clinical diagnosis and treatment. It is worthy of being widely popularized in clinical applications and further improves the discovery of rare pathogens including Schizophyllum [12].

Regarding the treatment of Schizophyllum, there is no clear treatment regimen, and the treatment of ABPM patients in previous reports includes antifungal, inhaled corticosteroids, systemic corticosteroids therapy, expectorant drugs, etc. Anti-infective efficacy such as itraconazole, voriconazole, fluconazole, and amphotericin B have been reported to suggest efficacy, and the majority of patients with allergic pulmonary mycosis who also received itraconazole showed no recurrence during 6 to 24 months of follow-up [11,13,14]. Eventually, the patient chose itraconazole for antifungal therapy. Glucocorticoids have a variety of effects such as systemic anti-inflammatory, relieving bronchospasm, and reducing eosinophil levels in the lungs and peripheral blood, but there are no guideline recommendations for the combined use of antifungal drugs with systemic or inhaled corticosteroids. According to previous literature, combined systemic medication or inhaled corticosteroids are recommended if symptoms such as shortness of breath, wheezing, dyspnea, elevated blood eosinophils, and serum total IgE occur. After hospitalization, the patient applied inhaled corticosteroids improving the cough, expectoration, and other symptoms compared to before, and the patient was diabetic. To avoid systemic hormone-induced increased blood glucose difficult to control, inhaled corticosteroids were finally selected for treatment. Finally, the patient was treated with itraconazole antifungal, inhaled corticosteroids, anti-inflammatory, anti-asthmatic, and ambroxol expectorant therapy. The clinical symptoms were significantly relieved, and the lung images were significantly absorbed compared to before, confirming the effective clinical effect of this treatment regimen. Therefore, we suggest that further attention should be paid to the possibility of infection with Schizophyllum species in the diagnosis of associated allergy-related lung diseases.

CONCLUSION

We reported a case of ABPM with eosinophilia caused by Schizophylla infection. We suggested that Schizophyllum infection should not be excluded in the diagnosis of allergy-associated lung disease, especially in diabetic or immunocompromised patients. The clinical application of mNGS can help early accurate diagnosis, reduce the misdiagnosis rate, and help patients get accurate treatment.

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Ethical Approval:
This study was approved by the ethics committee of North China University of Science and Technology Affiliated Hospital. All procedures performed in studies were in accordance with the ethical standards. Informed consent was obtained.

Declaration of Interest:
No conflicts of interest.

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