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CASE REPORT

A Case of Invasive Pulmonary Aspergillosis

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SUMMARY

Background: **Invasive pulmonary aspergillosis (IPA) is a deep fungal infection caused by invasion of Aspergillus mycelium into the lung parenchyma resulting in tissue destruction and necrosis, which occurs more often in immunosuppressed populations. The severity of the disease and the rapid progression of the lung lesions puts patients at high risk of death and poor prognosis if the correct therapeutic intervention is not given as early as possible.**

Methods: **Here we report a case of IPA, which was initially diagnosed as community-acquired pneumonia in a local hospital. The symptoms did not improve after receiving anti-infective treatment. The patient was diagnosed with IPA after completing a chest CT examination and an electronic bronchoscopy, as well as pathogenetic examination of the bronchoalveolar lavage fluid and pathological examination of the left bronchial mass in the respiratory department of our hospital, which was finally diagnosed as IPA. After one week of administration of voriconazole for anti-fungal infection treatment, the patient's symptoms improved significantly, and a repeat chest CT suggested that the lung lesions were better than before. In order to raise clinicians' awareness of this disease, we also conducted a literature analysis.**

Results: **The final diagnosis of IPA was made by analyzing the patient's history, symptoms, signs, and relevant findings.**

Conclusions: **When the patient's clinical symptoms and imaging manifestations are consistent with IPA, electronic bronchoscopy and pathogenetic and pathological examinations may be appropriately performed to clarify the nature of the lesion. More consideration should be given to the possibility of disease diagnosis to avoid misdiagnosis and underdiagnosis. Appropriate treatment should be given at an early stage.**

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KEYWORDS

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INTRODUCTION

Aspergillus is a conditionally pathogenic bacteria, widely distributed in nature, commonly found in soil, feed, and moldy grains. Aspergillus spores can enter the human body through the respiratory tract and thus colonize the body [1]. Aspergillus has more pathological types, clinically common are Aspergillus fumigatus, Aspergillus flavus, Aspergillus niger, soil mold, and so on [2]. Aspergillus is generally not pathogenic, because most immunologically normal people can clear Aspergillus through the anatomical structure and natural bar-

rier of the trachea and bronchus, but when the body inhales a large number of Aspergillus conidia at one time, when the lung infrastructure is destroyed, or when the human body has an abnormal immune status, Aspergillus can invade the human body, resulting in Aspergillosis, which is most prominent in lung infection [3]. Lung diseases caused by Aspergillosis are called pulmonary aspergillosis, including invasive pulmonary aspergillosis (IPA), allergic bronchopulmonary aspergillosis (ABPA), and chronic pulmonary aspergillosis (CPA) [4]. IPA is an infectious disease triggered by invasion of the lung parenchyma by the mycelia of Aspergillus. It is the most common and harmful type of pulmonary aspergillosis. We recently saw a patient diagnosed with IPA, and by reviewing the case report and related literature, we aimed to raise clinicians' awareness of this disease. When encountering patients with clinical manifestations and imaging consistent with the diagnosis of IPA, we should improve bronchoscopy and pathogenetic and histopathological examinations as soon as possible, and give timely and appropriate treatment to reduce the risk of death and improve the prognosis.

CASE REPORT

The patient was a 60-year-old male with blood in sputum for 1 month. One month before admission, the patient had a cough and sputum with blood in sputum after catching a cold, accompanied by retrosternal pain when coughing, chest tightness, and shortness of breath after activity. He was admitted to a local hospital for chest CT, which showed an enlarged left hilar, narrowing of the left main bronchus, inflammatory lesions in the left upper lobe, and thickening of the left pleura. The symptoms did not improve significantly after 3 weeks of treatment with various anti-infective drugs such as azithromycin, levofloxacin, penicillin, moxifloxacin, and a repeat chest CT suggested that there was no improvement in the lung lesions. The patient came to our respiratory department on April 24, 2023. Physical examination revealed that the patient's left tactile speech fibrillation was weakened, the respiratory sounds of the left lung were low, and the rest of the examination showed no obvious abnormalities. The patient had a history of chronic lymphocytic leukemia for more than 10 years and had been treated with zebrutinib 160 mg orally 2/day for the past year.

After admission to the hospital to improve the relevant auxiliary examination was done: blood routine: red blood cells 3.86 x 10^{12}/L, hemoglobin 122 g/L, platelets 115 x 10^{9}/L, lymphocytes 4.63 x 10^{9}/L, lymphocyte percentage of 85.3%, neutrophils 0.44 x 10^{9}/L, neutrophil percentage of 8.1%, serum c-reactive protein (CRP) 18.0 mg/L, erythrocyte sedimentation rate (ESR) 27 mm/h. April 24, 2023 Chest CT examination: left lung hilar enlargement, local bronchial narrowing in the left lung, surrounding soft tissue density foci, consider occupying lesions, multiple nodular foci in the right lung and the upper lobe of the left lung, pleural hypertrophy on the left side, and pleural adhesions on both sides. April 27, 2023 Under general anesthesia, electronic bronchoscopy was performed, and was visible microscopically: The proximal lumen of the left main bronchus shows neoplasm nearly blocking the lumen, stenosis of about 95%, peripheral mucosal infiltration-like changes. Due to the presence of the mass, the bronchoscope was unable to enter the official lumen of the left main bronchus and could only observe that the surface of the mass was not smooth and bled easily when touched, NBI can be seen in the mass of the local mucosal staining, neoplasm is rich in hematopoiesis, where the line of forceps, electric coil lassoing, freezing freeze-cutting of the neoplastic tissue and a local brush inspection, local bleeding, the application of argon knife coagulation to stop the hemorrhage, no active bleeding. The neoplastic tissue was subjected to ROSE, suggesting good sampling, large nucleated cells were seen, the tissue and brush test were sent to pathology, no active hemorrhage was observed, and it was retired from the microscope. Bronchoalveolar lavage fluid macrogene sequencing results suggestive of the aflatoxin complex group. Pathology of the left main bronchial mass on clamp examination was suggestive of chronic granulomatous inflammation with visible caseous necrosis. Ultimately, the patient was diagnosed with IPA.

May 4, 2023 voriconazole 200 mg oral 2/day antifungal treatment was given, because voriconazole and zerbutinib both affect the CYP3A4 pathway, zerbutinib was reduced to 80 mg oral 2/day after consulting with a hematologist. May 7, 2023 review of the chest CT suggests that the left lung hilar is enlarged and the local bronchioles in the lower lobe of the left lung are narrowed, with foci of density in the surrounding soft tissues, and consideration is given to occupational lesions, left lung upper lobe atelectasis, bronchial opacity, left main bronchus and left lung lower lobe bronchial intrabronchial high-density shadow, consider sputum, left lung upper lobe nodular foci show unclear, right lung upper lobe apical segment nodular foci show unclear, the remaining right lung multiple nodular foci compared to the previous did not see obvious changes, the left side of the pleural hypertrophy, the two sides of the pleural adherence compared to the previous did not see obvious changes. Based on the patient's left lung upper lobe atelectasis and bronchial opacity, he was given methylprednisolone 40 mg intravenous infusion 1/day for anti-inflammation and promotion of airway inflammation absorption. May 11, 2023 review chest CT suggested that the narrowing of the local bronchus of the left lower lobe of the lung was relieved compared with the previous one, and the density of the surrounding soft tissue foci was narrowed compared with the previous one; the atelectasis of the left upper lobe of the lung and bronchial opacity were relieved compared with the previous one; the hyper density of the left main bronchus and bronchus in the left lower lobe of the lung was reduced compared with the previous one. The high density in the

left main bronchus and bronchioles of the left lower lobe of the lung was reduced. After treatment, the patient's cough was better than before, sputum volume was less than before, there was no blood in sputum, no chest tightness, chest pain and other uncomfortable symptoms. He was discharged from the hospital to continue oral voriconazole, methylprednisolone, and other medications.

DISCUSSION

IPA is a fungal infectious disease that occurs mostly in patients with severely compromised immune systems, including organ transplant recipients, patients with malignant blood diseases, etc. It can also be seen in immunocompromised populations, such as patients with diabetes mellitus, chronic obstructive pulmonary disease (COPD), systemic lupus erythematosus (SLE), and AIDS, etc., or in patients without immune compromised status but with long-term application of large quantities of antibiotics and high doses of hormones, and also in hypoalbuminemia, anemia, and other populations [5]. Previous studies have shown that both neutrophils and macrophages appear to be important in the defense against Aspergillus *in vitro* and *in vivo* [6]. Macrophages are effective against conidia and neutrophils against mycelia. Therefore, when patients have a combination of diseases that inhibit the number or function of one or both of these cells, it results in a dysfunctional defense system and a greater susceptibility to IPA [7]. In IPA patients with severely compromised immune systems, Aspergillus infection may complicate the course of the underlying disease, further leading to poor prognosis and high case fatality rate, in which the prognosis of IPA patients with combined hematological malignancy is even less optimistic compared to organ transplant patients [8]. Therefore, early and correct diagnosis and appropriate antifungal therapy are crucial. IPA patients tend to present with symptoms such as fever, cough, hemoptysis, dyspnea, etc., and pulmonary atelectasis. Severe respiratory failure can occur when airway obstruction is present [9]. These symptoms lack specificity, so they are very easy to misdiagnose as lung infections, bronchial asthma and other common respiratory diseases, and thus incorrectly treated with broad-spectrum antibiotics and hormones. When antibiotics and hormones are applied for a long period of time, the growth of Aspergillus will be accelerated, further invading the airway mucosa and lung parenchyma, leading to respiratory failure. Aspergillus can spread to the heart, brain, gastrointestinal tract and other organs through the bloodstream, which ultimately leads to death of the patient with multi-organ dysfunction [10]. Therefore, timely and clear diagnosis is crucial for the treatment of IPA patients.

Imaging examinations can provide an important basis for the early diagnosis of IPA. When the patient is in a state of impaired immune function and the clinical manifestations are consistent with IPA, chest CT is important for diagnosis. Previous studies have shown that the halo sign can be observed in the parenchymal window of chest CT images in patients with IPA combined with hematological malignancies [11]. The pathophysiology of the halo sign is characterized by discrete nodules of vascular infiltrative aspergillosis with infarcts and coagulative necrosis surrounded by alveolar hemorrhage, and although this imaging manifestation is not characteristic of IPA, it may be associated with herpes simplex, cytomegalovirus, Legionella pneumophila, tuberculosis and a number of non-infectious diseases as well. IPA is, by far, the most common cause of CT imaging of patients with high risk of developing a halo sign in those at high risk of fungal infection [12,13]. In addition, another study found that the hypodense sign can be observed in the chest CT images of some patients with IPA, due to vascular obstruction caused by vascular invasive pulmonary aspergillosis secondary to pulmonary infarcts and pulmonary segregation, resulting finally in cavitation or lesion regression. Although the hypodense sign can also be found in other diseases, such as bacterial bronchopneumonia, it is not usually seen in patients with combined severe neutropenia. Therefore, in severely neutropenic cases, the differentiation of IPA from abscesses caused by bacterial infection or other pathogenic infections seems to be highly reliable [14]. This imaging feature has a low sensitivity but high specificity for the diagnosis of IPA. Future studies with more samples are needed to confirm this conclusion.

Due to the ubiquitous presence of Aspergillus in the air and on the ground, if there is a high suspicion that a patient has an Aspergillus infection, biospecimen sampling from a sterile site is usually required to differentiate between a true infection and a simple colonization of the upper respiratory tract. In recent years, with the development of electronic bronchoscopy and alveolar lavage macrogene second-generation sequencing, more precise diagnosis and treatment of clinical lung infections have been provided. For patients with suspected pulmonary Aspergillus infection, electronic bronchoscopy should be routinely improved when the patient's underlying condition permits. Aggressive electronic bronchoscopy is essential for early confirmation of the diagnosis, removal of secretions from the airways, and retention of specimens for testing.

There are currently three major classes of antifungal drugs used to treat Aspergillus infections: Azoles, polyenes and echinocandins [15]. In the last two decades, voriconazole has been recommended as the first-line treatment for Aspergillus infections [16]. However, it has been found that azoles interact severely with important immunosuppressants such as tacrolimus, sirolimus, and cyclosporine, for which drug dosage needs to be adjusted, and therefore affects the efficacy of the disease treatment and may lead to significant immunosuppression or toxicity [17]. Currently, there are a variety of novel antifungal drugs under development, but these drugs have not yet reached the final clinical trial stage

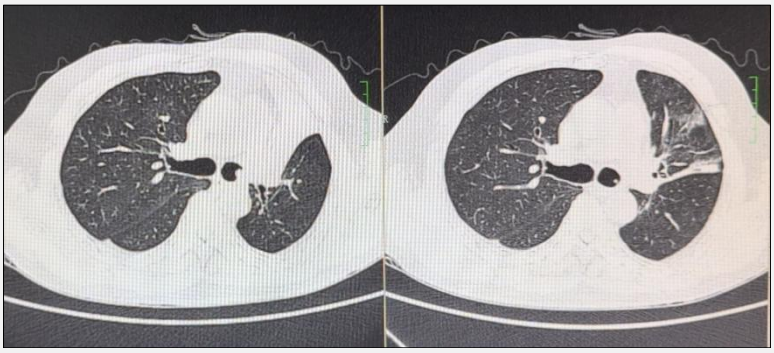

Figure 1. Chest CT changes.

May 7, 2023 Chest CT (A) showed enlarged left hilar, local bronchial narrowing in the lower lobe of the left lung, surrounding soft tissue density foci, left upper lobe atelectasis, bronchial opacity, and high-density shadows in the left main bronchus and the bronchi in the left lower lobe of the left lung.
May 11, 2023 Chest CT (B) showed local narrowing of the left lower lobe of the left lung was relieved compared with the previous, and the surrounding soft tissue density foci are narrower than before, atelectasis and bronchial opacification in the upper lobe of the left lung are significantly relieved compared to before, and the left main bronchus and endobronchial hyperdense shadows in the lower lobe of the left lung are reduced compared to before.

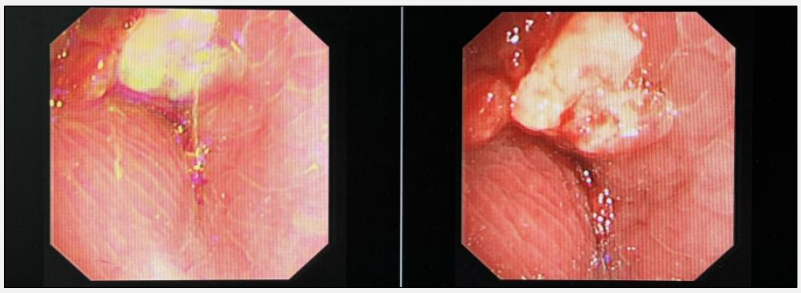

Figure 2. The picture shows an electron bronchoscopy that revealed neoplastic organisms nearly occluding the proximal lumen of the left main bronchus, with a stenosis of about 95%.

for practical application in the treatment of IPA patients [18]. However, it is undeniable that significant changes in the treatment of IPA are likely to occur in the coming years, and it is hoped that these changes will increase patient survival and improve quality of life.

CONCLUSION

Pulmonary aspergillosis, a relatively common and highly lethal fungal infectious disease in the clinic, still needs more clinical studies with large samples to find the early diagnostic features of imaging. With the emergence of azole-resistant strains, the research and development of new anti-Aspergillus drugs are also imminent. There is still a need to continue to increase the attention on Aspergillus infections in the future, in order to save more patients with IPA.

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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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