Pneumonia caused by Scedosporium in non-Transplant and non-HIV-infected adults:A case series and review of the literature

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Abstract

The lung is one of the most commonly encountered sites of Scedosporium infection. Due to its intrinsic resistance to all current antifungal agents, treatment of Scedosporium infections still remains a great challenge. Voriconazole has been recommended to the first-line systemic treatment of Scedosporium infections, but the duration is not well recommended, especially for immunocompetent patients. This case series presented our experience on diagnostic, manifestation, and treatment strategies of Scedosporium pneumonia. The case records of non-Transplanted non-HIV adults with Scedosporium pneumonia hospitalized in our Hospital from January 2020 to February 2022 were retrospectively analyzed, and their case characteristics, antifungal therapy drug selection and treatment course were summarized: All 3 patients had underlying lung disease, 2 female patients had a history of bronchiectasis, and 1 male patient had a history of emphysema. Both female patients had a mixed infection with Scedosporium and nontuberculous mycobacteria. In one female patients, Scedosporium was no longer detected after 2 months of treatment with voriconazole, and the clinical symptoms were improved than before, with no significant change in imaging. In one female patient, although Scedosporium was still isolated from sputum after 12 months with voriconazole treatment, the symptoms were improved than before, and antifungal therapy was discontinued after no significant improvement 1 and a half months after switching to Posaconazole. In one male patient, Scedosporium was no longer detected after 3 months treatment with voriconazole, and the clinical symptoms and imaging were significantly improved. Three patients had voriconazole concentrations between 1.1-2.8 μg/mL during treatment.

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Abstract The lung is one of the most commonly encountered sites of *Scedosporium* infection. Due to its intrinsic resistance to all current antifungal agents, treatment of *Scedosporium* infections still remains a great challenge. Voriconazole has been recommended to the first-line systemic treatment of *Scedosporium* infections, but the duration is not well recommended, especially for immunocompetent patients. This case series presented our experience on diagnostic, manifestation, and treatment strategies of *Scedosporium*pneumonia. The case records of non-Transplanted non-HIV adults with*Scedosporium* pneumonia hospitalized in our Hospital from January 2020 to February 2022 were retrospectively analyzed, and their case characteristics, antifungal therapy drug selection and treatment course were summarized: All 3 patients had underlying lung disease, 2 female patients had a history of bronchiectasis, and 1 male patient had a history of emphysema. Both female patients had a mixed infection with*Scedosporium* and nontuberculous mycobacteria. In one

female patients, *Scedosporium* was no longer detected after 2 months of treatment with voriconazole, and the clinical symptoms were improved than before, with no significant change in imaging. In one female patient, although *Scedosporium* was still isolated from sputum after 12 months with voriconazole treatment, the symptoms were improved than before, and antifungal therapy was discontinued after no significant improvement 1 and a half months after switching to Posaconazole. In one male patient, *Scedosporium* was no longer detected after 3 months treatment with voriconazole, and the clinical symptoms and imaging were significantly improved. Three patients had voriconazole concentrations between 1.1-2.8 μg/mL during treatment.

KEY WORDS: *Scedosporium* ; pneumonia; voriconazole

1 INTRODUCTION

The *Scedosporium* is a group of soil saprophytic moulds, which are widely distributed in the environment, particularly in soil, sewage and polluted waters. At least ten distinct *Scedosporium* species have been identified in molecular taxonomy. Five of them can cause human infections, namely *S apiospermum, P boydii, Saurantiacum, S dehoogii and S minutispora* [1-3]. And their environmental distribution and epidemiology is different worldwide[4-8]. As opportunistic pathogens, infections caused by *Scedosporium* genus will happen in not only immunosuppressed but immunocompetent hosts, but most infections are associated with compromised immune status[9]. The clinical manifestation of infections include respiratory colonization, cutaneous infections, and severe invasive localized or disseminated mycosis. There is even a risk of central nervous system infection after drowning in immunocompetent hosts[1], and the mortality rate of susceptible people exceeds 50%[2]. Immunosuppression may increase the prevalence of disseminated infections caused by *Scedosporium* , such as in patients with cancer, hematopoietic stem cells or solid organ transplant recipients, and those receiving immunosuppressive therapy[7]. To immunocompetent populations, *Scedosporium* infections frequently caused by trauma, drowning, and aspiration of conidia[1,9], mainly infecting the skin, lungs, soft tissues, central nervous system, and sinuses, among which pulmonary infections rank the second[10-11], and those with underlying lung diseases are more susceptible than other healthy people[12]. Treatment of *Scedosporium* infections still remains a great challenge because of their intrinsic resistance to all current antifungal agents, easy to relapse, and the mixed infection with tuberculosis or non-tuberculous mycobacteria or viruses occur frequently[14-16]. Voriconazole has been recommended to the first-line systemic treatment of *Scedosporium*infections[13], but the duration of therapy is not well recommended. Therefore, it is necessary to summarize the clinical cases and treatment experience of *Scedosporium* infections, especially the risk factors, infection routes, therapeutic strategies and duration of treatment in immunocompetent patients. In this paper, we retrospectively analyzed 3 cases of non-Transplant, non-HIV adults with*Scedosporium* pneumonia, and present our therapeutic experience and improved patient outcomes.

2 CASE DESCRIPTIONS

2.1 Case 1

A 43-year-old woman was admitted to the hospital with cough and expectoration of sputum with hemoptysis for more than a year and a half. She was previously diagnosed with bronchiectasis and hemoptysis and was hospitalized several times. Ten months ago, she underwent left pulmonary bullectomy, but the symptoms of cough and sputum still existed. Her symptoms worsened two month prior and bronchoscopy examination was performed. Next-generation sequencing (NGS) of bronchoalveolar lavage (BAL) revealed 87 copies of *S. apiospermum* and 1 copy of Aspergillus. Oral treatment with voriconazole was initiated at a dose of 350mg twice daily. The patient was still coughing and expectorating sputum repeatedly during the treatment. Computed tomography (CT) of the chest revealed the lesions progressed after one month therapy and he was admitted to hospitalization with the diagnosis of bronchiectasis and infection, pulmonary fungal infection (*Sedosporium*), and left pulmonary bullectomy, continuing oral voriconazole after admission. Physical examination revealed her body temperature was 36.3, heart rate was 82 times per minute, breathing rate was 14 times per minute, her blood pressure was 96/58mmHg and her body weight was 45kg. The breath sounds of both side lungs were slightly coarse, and no obvious wet or dry rales were heard. Bronchoscopy

examination was performed after admission. Mycobacterium tuberculosis smear examination found acid-fast bacilli. NGS of BAL presented 45 sequences of Mycobacterium abscessus, and no *Sedosporium* was detected again. Therapeutic drug monitoring (TDM) of voriconazole revealed 2.8 μg·mL^{-1}. The patient was then suggested to treat in department of Infectious Diseases and discharged. Four days later, he was seen in the Department of Infectious Diseases and started anti-Mycobacterium abscessus treatment. Voriconazole was discontinued meantime with a treatment course of 2-months. No *Sedosporium* was detected in 8 months following. Her symptoms were improved after treatment, but there was no obvious change in imaging.

2.2 Case 2

A-36-year-old woman was admitted to the hospital due to repeated coughing and expectoration for 11 years and aggravating for half a year. 11 years ago, she was diagnosed with bronchiectasis, and Mycobacterium intracellulare was found by sputum culture. She visited the local hospital for many times. 5-month ago, she found the sputum was thick and wire drawing. Fluconazole was added and the anti-mycobacterial treatment strategies were adjusted without clinical improvement. She was seen in the outpatient clinic 10 days prior for hemoptysis and viscous sputum. A moderate amount of *S. apiospermum* was found by sputum culture, then antifungal drug was switched to oral voriconazole (200mg, twice daily). This treatment resulted into clinical improvement, and the sputum was easy to cough up and the amount decreased. A moderate amount of *S. apiospermum* were still detected from sputum samples after 4-month treatment. TDM of voriconazole was performed and the outcome revealed 2.7 μg·mL^{-1}. There was no fungi detected again in the next 3 months. However, a large amount of *S. apiospermum* were still detected from sputum samples after treating with voriconazole for 12-month. Then voriconazole was replaced by posaconazole and continuing therapy for a month and a half, *S. apiospermum* was not detected again and posaconazole was discontinued. In the next 6 months, *S. apiospermum* was still founded intermittently from sputum culture, but her clinical symptoms and radiological findings did not significantly worsen and no antifungal therapy was performed again.

2.3 Case 3

A 45-year-old man was admitted to the hospital with fever of unknown origin. He had high fever 5 days ago and the maximum body temperature was 40.5 accompanied by headache, dizziness, body aches, fatigue and sore throat. He went to other medical institution and completed some examinations. The lung CT showed inflammation of the upper lobes of both lungs. The C-reactive protein (CRP) was 52.02mg*L^{-1}. He was treated with piperacillin-tazobactam and levofloxacin for 2 days without clinical improvement, and his body temperature was still high. Then he came to our hospital for further diagnosis and treatment. The laboratory findings showed the white blood cell count was 5.75x10^{9}*L^{-1} and the neutrophils(%) was 83.2%, the CRP was 140.7 mg*L^{-1},the procalcitonin(PCT) was 0.65 ng*mL^{-1}. Then he was admitted to the hospital diagnosed with pulmonary infection. The patient was in good health in the past with no smoking and drinking habits, no history of food and drug allergies, no history of living in a humid environment, and no history of contacting with poultry and animals. His occupation was a building worker and he had a history of second-hand smoke exposure. Physical examination revealed body temperature was 38.3 , the pulse was 77 times per minute, the respiratory rate was 20 times per minute, the blood pressure was 126/86 mmHg, and his body weight was 69 kg. Breath sounds were clear in both lungs, and no dry or wet rales were heard. Lung CT was conducted again and revealed pneumonia and scattered lung air sacs in both lungs, and local thickening of the pleura on both sides. He still had fever after anti-infection therapy with moxifloxacin, cefoperazone sodium and sulbactam sodium and oseltamivir. The highest temperature was 39.8degC, and the routine etiological screening was negative. The bronchoscopy was performed in the third day and founded the both bronchi were unobstructed, and no new creatures. Moderate amount of septate hyphae were founded by immunofluorescence staining (fungi). Moderate amount of *S. apiospermum* were founded with BAL culture and the NGS of BAL also founded *Scedosporium* (sequence number 238), *Scedosporiumboydii* (sequence number 179). Treatment was performed with voriconazole intravenously (400mg daily) for 10 days. This treatment resulted into remission of the radiological findings and clinical improvement. The laboratory findings including white blood cell count (8.94x10^{9}*L^{-1}), CRP (6.56 mg*L^{-1}) and PCT (0.13ng*mL^{-1}) were all normal. TDM of voriconazole was 1.1μg·mL^{-1}. He was discharged from the hospital on the 12th day.

Oral voriconazole (400mg daily) was continued for 3 months, complete remission of the pneumonia and improvement of the clinical situation was received, and voriconazole was discontinued.

3 DISCUSSION

Although *Scedosporium* infection is more common in immunocompromised patients, it can also cause infection in immunocompetent hosts[8,17,18]. And the lung is one of the most common sites of *Scedosporium* infections. Patients with underlying lung diseases are more likely to develop infections. According to present knowledge of *Scedosporium* lung infection in immunocompetent adult patients[3,19], the infection rate of males and females is similar, and their age ranges from 26 to 84-year-old (mean 56.4 years). The most common underlying lung disease is the cavitary lesion caused by pulmonary tuberculosis, followed by bronchiectasis. Asthma, pleural tuberculosis, and chronic restrictive or obstructive pulmonary disease have also been reported. Here we reported a case series including a 43-year-old female, a 36-year-old female and a 45-year-old male, all of them were non-Transplant, non-HIV-infected hosts, and without a history of long-term high-dose glucocorticoid use, so they were considered the immunocompetent adult hosts. Among them, 2 female patients had a history of bronchiectasis. The left pulmonary bullectomy was also performed for the first female. And another was infected with pulmonary nontuberculous mycobacteria for many years. Both of them were mixed infection cases. Until now, only three mixed pulmonary infection cases of *Scedosporium* and nontuberculous mycobacteria was reported[15,20,21]. Two patients had a history of pulmonary tuberculosis and one had a 15-year history of nontuberculous mycobacteria (NTM) pneumonia. Although the reason for the rareness of coinfection with NTM and *Scedosporium* is unclear, some investigators considered it might be related to the lower frequency of cavitations in individuals with NTM than in those with tuberculosis[15]. Another male patient in our case had a history of emphysema. He was in good health before this thick and had no habit of smoking. However, he had been working on a construction site for a long time and had a history of exposure to second-hand smoke, which may be the important incentive caused him to develop*Sedosporium* infection.

There are many similarities between the clinical and imaging features of*Sedosporium* and Aspergillus infection. But their antifungal drug resistance is much different. The susceptibility to antifungal drugs among different species for *Sedosporium* is also quite different. Therefore, the differential diagnosis of microorganisms timely and accurately is crucial for conducting precise treatment[13]. In the reported cases[3,22], etiological culture of sputum, bronchoalveolar lavage fluid and lung biopsy specimens, NGS and polymerase chain reaction are the main methods to diagnose*Sedosporium* infection. Among them, the positive rate of biopsy tissue samples are higher than that of bronchoalveolar lavage fluid and sputum samples, and even multiple tests may be required to obtain positive results for bronchoalveolar lavage fluid and sputum samples. In our case, the first patient used NGS of bronchoalveolar lavage fluid to assist in the diagnosis of *Sedosporium* . The second patient was diagnosed the *Sedosporium* infection by continuous sputum cultures. The NGS and cultures of sputum and bronchoalveolar lavage fluid were all performed in the third patient to diagnose the*Sedosporium* . And NGS combined with traditional microbial culture could make diagnosis more accurate and efficient.

Sedosporium species are highly resistant to many available antifungals, including amphotericin B, echinocandins, flucytosine and the first-generation azoles. Currently, voriconazole is still preferred for the first-line drug therapy, and the recommend adult dosage was 6 $mg{\cdot}kg^{-1}$, q12h on the first day, followed by 4 $mg{\cdot}kg^{-1}$, bid with intravenous administration, or 200 mg bid with oral administration[13], but its duration of therapy is uncertain. In 10 cases of *Sedosporium* pulmonary infections in immunocompetent hosts treated with voriconazole[3,19], the treatment dosage was adjusted according to a combination of recommended dosage and TDM results, and the therapy duration ranged from 1 to 10 months. Among them, one was recovered, eight was improved in clinical symptoms or images, and one was died. The maximum follow-up time of them was 18 months. And there was no recurrence case reported. The cured case was a 51-year-old female with no underlying lung diseases, but with surgery history. And she was continuously treated with voriconazole for 3 months. All three patients in this case received no operation but voriconazole alone with a recommended dose or above. The TDM results of their voriconazole were all reached the standard between 0.5-5$mg{\cdot}L^{-1}$. There was no *Sedosporium*detected in the first patient with 2-month treatment. The third patient was treated

for 3-month with complete improvement in symptoms and imaging. The second patient responded poorly to the recommended dose of voriconazole and failed to achieve pathogenic clearance even after 12-month of continuous treatment, but her symptoms improved slightly. Research[23] found voriconazole therapy may have a better effect when MIC was below 2 g·mL^{-1}, but a limited effect to treatment at MIC of 4 g·mL^{-1} and may lead to treatment failure. No guideline recommendation could be given because no antifungal susceptibility testing results were available for the second patient. In the cases of pulmonary nontuberculous mycobacterial and *Sedosporium*coinfection[15,20,21], only one patient who had no indication for surgery was treated with voriconazole alone for 6-month with initial dose of 400 mg daily, then increased to 500 mg daily based on TDM results. The symptoms and imaging improved after 6 months, but no follow-up records were reported. Another patient was followed up for 2 years after discontinuation of methylprednisolone and no deterioration was found with pulmonary imaging. Therefore, patients without indications for surgery could be treated with voriconazole alone with the recommended dose or above and treatment outcomes such as pathogens clearance or clinical and imaging improvement in most patients could be received. TDM would be required for dose adjustment and continuous treatment for at least 2 months also would be required. To patients with long duration of pulmonary nontuberculous mycobacterial infection and mixed infection with *Sedosporium* with no indication for surgery, voriconazole monotherapy could be less effective in clearing the pathogenic, and real-time drug sensitivity may be an important option to guide treatment. Current treatment experience needs to be confirmed with more clinical practices. Besides, posaconazole has been shown effective against *Sedosporium* in animal models, but was less active than voriconazole[24-26]. In this case, patient 2 failed to achieve clearance of pathogenic even after switching to posaconazole treatment for more than 1 month. It suggests that posaconazole only have limited effect to those patients *Sedosporium* is not cleared with voriconazole.

Considering the experience of *Sedosporium* clearance from patients with cystic fibrosis, combination therapy may be a good option, such as voriconazole or posaconazole was synergistic with echinocandins in a double combination[27], and a combination of voriconazole, caspofungin and amphotericin B aerosol was recommended in a triple combination[28]. Besides, novel drug studies found that Manogepix (APX001A), Olorofim (F901318), and fosmanogepix (APX001) showed good antifungal activity, and vitro activity of the first two kinds were higher than voriconazole against*Sedosporium* [29-31]. The antirheumatic drug Auranofin[32] was also found effective against a variety of fungus, including *Sedosporium* . And the *Sedosporium*evading host immunity is associated with thioredoxin reductase[33]. The appearance of the above new drugs, new applications and new targets will provide new basis and options for the treatment of *Sedosporium* infections.

4 CONCLUSION

In summary, for non-Transplanted and non-HIV young adult patients, altered lung structure may be an important cause of *Sedosporium*lung infections. Voriconazole is effective against the*Sedosporium* infections, but treatment duration often over several months. Individualized therapeutic decisions are always required according to the patients' clinical symptoms and imaging. For patients who suffered a long course of pulmonary nontuberculous mycobacterial disease and mixed infection with *Sedosporium* and no indication for surgery, the pathogenic clearance is difficult though voriconazole is added.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTIONS

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