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Case report

Trichosporon asahii co-infection with *Pneumocystis jiroveci* in a renal transplant patient

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ABSTRACT

Trichosporon asahii is considered an opportunistic pathogen, capable of causing superficial infections in humans and invasive deep-seated infections in immunocompromised hosts. *Pneumocystis jirovecii* can cause life-threatening pneumonia in immunosuppressed patients. Both *Trichosporon* and *Pneumocystis jirovecii* are highly lethal in immunocompromised individuals. Here we present a case of invasive *Trichosporon asahii* co-infection with *Pneumocystis jiroveci* in a renal transplant patient.

Introduction

Trichosporon is an emerging basidiomycetous yeast-like fungus, typically a part of the human microbiota. These microorganisms occasionally appear in the gastrointestinal tract and oral cavity, and can briefly colonize the respiratory tract and skin [1]. *Trichosporon* is considered an opportunistic pathogen, capable of causing superficial infections in humans and invasive deep-seated infections in immunocompromised hosts [2]. Associated with a high mortality rate, Trichosporonosis is a fatal disseminated disease in patients with haematological malignancies, organ transplantation, AIDS, and deep burns [3]. Presently, 50 Trichosporon species are recognised, of which 16 are known to be pathogenic. *Trichosporon asahii* is an identified species within the filamentous yeast genus, and it is one of the most common pathogenic fungi in clinical invasive *Trichosporon* infections [4].

Pneumocystis jirovecii can cause life-threatening pneumonia in immunocompromised patients. *P. jirovecii* pneumonia (PJP)in patients without human immunodeficiency virus infection (non-HIV) is increasing and is the most common opportunistic fungal infection in renal transplant recipients who were not on PJP prophylaxis. PJP often occurs within 3–6 months after kidney transplantation, during which time the patient's immune function is severely compromised [5].

Although infections with *T. asahii* or *P. jirovecii* are common, simultaneous systemic co-infections with both are rare. We present a case of invasive *T. asahii* co-infection with *P. jirovecii* in a renal transplant patient. We describe the process of detecting fungus in the laboratory and the treatment administered for the infection after the patient's admission.

Case report

A 53-year-old man was hospitalized for kidney transplantation due to uremia on March 15th. Following successful surgery, he received mycophenolate mofetil, tacrolimus, and methylprednisolone as anti-rejection treatment and he was discharged home with appropriate care instructions.

Approximately five months later, the patient developed a cough and fever, leading to hospitalization on August 8th (day 0). An abdominal CT scan revealed mild dilatation of the renal pelvis and hydronephrosis. Meanwhile, a thoracic CT scan showed bilateral diffuse pulmonary infiltrates, slight pleural effusion, and pericardial effusion (Fig. 1). Blood samples were collected for laboratory examination during the hospitalization, and significant indicators during the treatment are displayed in Table 1.

On August 11th (day 3), blood metagenomics next-generation sequencing (mNGS) showed *P. jirovecii* infection. The patient was treated with dexamethasone for anti-inflammatory purposes Cefoperazone sulbactam sodium 6 g/day,Caspofungin 50 m/day and oral Sulfamethoxazole/Trimethoprim 250 mg/1250 mg for anti-infection purposes. Additionally, gastroprotection and blood sugar control treatments were administered.

On August 15th (day 7), microscopy of the Gram staining of the sputum smear revealed blastoconidia and arthroconidia (Fig. 2). The sputum was inoculated on various plates, including Blood plates, Chocolate plates, MacConkey plates, and Sabouraud plates at 37 °C with

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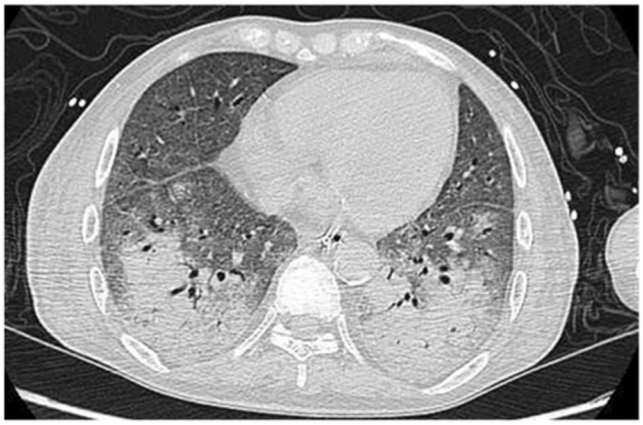

Fig. 1. The patient's thoracic CT scan showing bilateral diffuse pulmonary infiltrates, slight pleural effusion, and pericardial effusion.

Table 1
Part of the blood indicators during the treatment.

	DAY1	DAY4	DAY5	DAY9	DAY14	Reference Range
1,3-β-D-glucan(pg/ml)	246.15	399.71	426.45	/	154.31	0.00-60.00
CRP(mg/L)	66.94	32.33	71.96	84.36	255.23	0.00-8.00
PCT (ng/ml)	1.87	0.5	1.76	0.84	5.23	0.00-0.50
Creatinine (μmol/L)	382	394	638	85	80	57.00-97.00

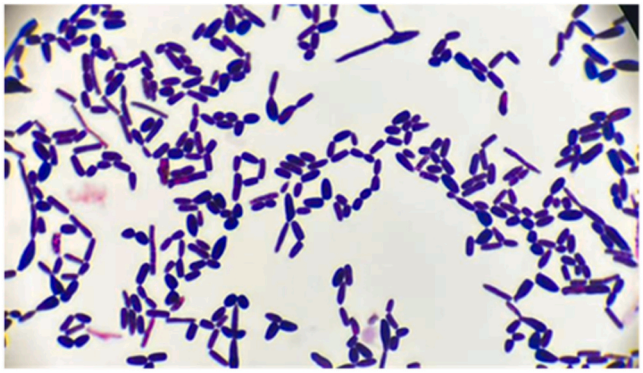

Fig. 2. Gram stain of the colonies showing septate hyphae with arthrospores.

5% CO2. After 48 h of incubation, white, wrinkled velvety colonies with mycelial fringe were observed on the plates. Similar colonies were also cultured from the patient's mid-stage urine and blood cultures that indicated bloodstream infection on the same day (Fig. 3). All these fungus strains were identified using the VITEK-2 Compact YST identification card as *T. asahii.* Subsequently, mass spectrometry using the Bruker MALDI-TOF identified it as *T. asahii*. Antimicrobial susceptibility analysis was performed with ATB FUNGUS3, and the results are shown in Table 2. The antifungal treatment transferred from Caspofungin 50 m/day to Voriconazole 400 mg /day.

On August 19th (day 11), the patient's infection continued to worsen, and in order to better assess the infection in the patient's lungs, we performed mNGS on the bronchoalveolar lavage fluid(BALF). The result revealed *E.faecium, P. jirovecii,* and *T. asahii*. The patient's condition was discussed during a multi-disciplinary team (MDT) meeting, and it was determined that the patient had septic shock. Finally, the

Fig. 3. After 48 h of incubation at 37 °C, showing white, wrinkled velvety colonies with mycelial fringe.

Table 2
The antifungal susceptibility results of *T. asahii*.

	MIC (mg/L)
5-Fluorocytosine	4
Amphotericin B	0.5
Fluconazole	1
Itraconazole	0.25
Voriconazole	0.125

patient was treated with Voriconazole 400 mg /day,Cefepime 13.5 g/day and oral Sulfamethoxazole/Trimethoprim 250 mg/1250 mg for anti-infection purposes.

On August 22nd (day 14), the patient's condition deteriorated further, requiring high-dose vasopressor support, mechanical ventilation, and continuous renal replacement therapy (CRRT) from August 16th (day 8). Despite these measures, the patient's vital signs could not be maintained, and blood pressure continued to decline while lactate and carbon dioxide pressure increased progressively. Finally, the patient was declared clinically deceased. (Fig. 4).

Discussion

The reporting of disseminated Trichosporonosis is increasing worldwide, posing challenges for both diagnosis and species identification. Over the past two decades, there has been a significant rise in the incidence of Trichosporonosis, primarily affecting immunosuppressed patients with haematological disorders [2]. The standard first-line treatment is voriconazole, which has been shown to improve the prognosis of haematological patients and demonstrated successful clearance in research after the failure of amphotericin B treatment [6]. The main issue lies in its resistance to antifungal drugs, including echinocandins and amphotericin B [7]. Although combination therapy with amphotericin B and 5-fluorocytosine has been proposed, there is limited available data. There are currently no specific treatment recommendations for infections caused by *T. asahii* due to the lack of CLSI breakpoints. The best antifungal regimen and treatment plan can be determined based on data on drug sensitivity in vitro and clinical experience. For detailed information on options for dealing with *T. asahii* infections, refer to the 2021 edition of the Global Guidelines for the Diagnosis and Management of Rare Yeast Infections.In recent decades, Trimethoprim/sulfamethoxazole has been the first-line drug for the treatment and prevention of Pneumocystis. We had been using Trimethoprim/sulfamethoxazole since we first found it, but the patient's condition has not improved.

Infection with *P. jirovecii* was first indicated in mNGS two days after admission. However, in vitro, growth of Pneumocystis in lung epithelial cell layers is not suitable for routine microbiological diagnosis [8]. In

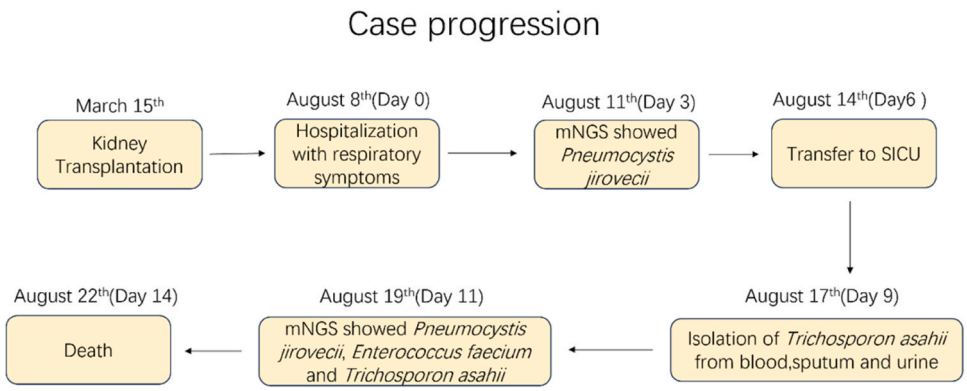

Fig. 4. Timeline of the case presented, showing progression from the onset of his symptoms to his fatal outcome.

our laboratory, we used hexamine silver staining to detect lung spore infections but did not find the pathogen in the patient's BALF and sputum, which correlated with the detection rate of lung spores. In contrast, we found articular spores in the first sputum smear after the patient was admitted to the hospital, and the laboratory cultured *T. asahii* the day after the specimen was delivered. In laboratory examinations, we were able to isolate *T. asahii* from sputum, lavage fluid, blood, and urine cultures. *T. asahii* grows rapidly, leading to a higher detection rate.

In recent years, metagenomic next-generation sequencing (mNGS) has become a new laboratory diagnostic tool. It has significantly reduced the time required for pathogen detection and provides valuable support for clinical treatment. mNGS offers several benefits such as high-throughput, broad coverage, and excellent accuracy [9,10]. It's worth noting that mNGS of BALF is a more accurate method in diagnosing HIV-negative PJP as compared to traditional techniques. [11] According to a meta-analysis, the pooled sensitivity of mNGS in diagnosing PJP in non-HIV patients was 99.2%, while the summary specificity was 91.0% [12]. However, we were unable to detect its sequence in the patient's first blood mNGS test. *T. asahii* is often found in the environment as a colonizing organism. This could be due to various factors such as sample or methodological variability. On the other hand, it is also possible that at the time of admission, *T. asahii* had not yet caused a systemic invasive infection.In this case, we report for the first time a kidney transplant patient who was simultaneously co-infected with *T. asahii*, *P. jirovecii* and *E.faecium*. Trichosporon fungaemia (TF) and has a mortality rate exceeding 50%– 90% [3]. Early detection and empirical treatment for patients is crucial for survival. 1,3-β-D-glucan (BG) assay is helpful for early detection of invasive fungal disease [13]. As we see, the BG levels of the patient are consistently high. The Serum BG assay is a useful diagnostic tool for detecting PJP and invasive fungal infections (IFI). The BG assay has a high accuracy rate for diagnosing PJP and moderate accuracy for diagnosing IFI. Due to its high sensitivity to PJP, the BG method can also be used as a screening tool for this type of pneumonia [14].

Clinical empirical treatment involved using caspofungin to combat fungal infections, but caspofungin is not appropriate for *Trichosporon*. After the laboratory reported confirmed *T. asahii*, the antibiotics were adjusted to voriconazole immediately, but the patient's infection was getting worse. Pneumocystis infection, even after treatment, is associated with a high mortality rate among people living with HIV, with a higher rate of non-HIV mortality (20–50%) than among people living with HIV (10–30%) [15].

This patient, a kidney transplant recipient, belonged to the immunosuppressed population, which has always been at high risk of infection. Unfortunately, the patient eventually succumbed. In managing such patients' infection issues, in addition to rapidly and accurately identifying the source of infection and providing effective clinical treatment, we must also consider the dual management of long-term immunosuppression and infection after transplantation to improve the patient's quality of life and control the occurrence of infections.

Ethical approval statement

Written informed consent was obtained from the patient or legal guardian(s)for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Consent

Ethical approval was obtained from the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University for this case report..

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Author statement

TingtingYang : Responsible for case collection and analysis,manuscript writing. YajieFu: Responsible for the culture and identification of samples and was responsible for patient follow-up.

CRediT authorship contribution statement

Tingting Yang: Data curation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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