Rhinocerebral Mucormycosis and Trichosporon asahii Fungemia in a patient with acute lymphoblastic leukemia: A rare co-infection and literature review

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Case Report

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Abstract

Background

We report one rare case of concomitant rhinocerebral mucormycosis and Trichosporon asahii (T. asahi) Fungemia secondary to Pseudomonas aeruginosa bloodstream infection (BSI) in a neutropenic patient with acute lymphoblastic leukemia. A review of the literature is included.

Case presentation:

A 1-year-old baby was diagnosed with B-line acute lymphoblastic leukemia and received regular chemotherapy which was admitted to hospital for vomiting, diarrhea, low fever and poor mental reaction. Carbapenem resistant-Pseudomonas aeruginosa was isolated via blood culture, and ceftazidime/ averbactam was administrated. The patient presented with necrotizing lesion on the right side of the nasal alar and the right corner of the eye. Later, necrosis rapidly expanded to almost his entire face on the 8th day, Rhizopus delemar and T. asahi was isolated from necrotic tissue. T. asahi was further recovered via blood culture. The anti-infection protocol was changed to treatment of Pseudomonas aeruginosa BSI with ceftazidime/ averbactam, amphotericin B cholesterol sulfate and voriconazole was administrated for Rhizopus delemar and T. asahi. Unfortunately, He deteriorated and died for multiple organ failure and rapid progress of infection.

Conclusions

For acute lymphoblastic leukemia patients, by maintaining a high level of clinical suspicion, promptly starting antifungal treatment, aggressively removing necrotic tissue through surgery, and addressing the underlying immunosuppression, it may be possible to decrease mortality rates.

Background

Mucor and trichosporidium are ubiquitous in nature and can cause acute fulminating infection in haematologic malignancy patients[1, 2]. The main risk factors of mucor and trichosporidium infections are immunocompromised host, hematological malignancies, neutropenia, solid organ transplantation, autoimmune diseases, multiple injuries, central venous catheters, cortisol use and surgery[3, 4]. Mucormycosis is a rare life-threatening opportunistic infection, of which rhinocerebral mucormycosis (ROCM) is the principal manifestation. T. asahi is the most common species isolated from invasive trichosporidiosis, and approximately 80% of cases are secondary to fungemia, which resulted in a high mortality rate (40%-90%)[5]. Accurate identification of mucor and T. asahi are essential to initiate pathogen specific therapy, due to their high drug resistance to certain antifungal drugs.

We report one rare case of concomitant ROCM and T. asahi Fungemia secondary to Pseudomonas aeruginosa bloodstream infection in a neutropenic patient with acute lymphoblastic leukemia.

Case presentation

A 1-year-old baby was diagnosed with B-line acute lymphoblastic leukemia and received regular chemotherapy. On August 17, 2022, he admitted to People's Hospital of Guangxi Zhuang Autonomous Region (Nanning, China) for vomiting, diarrhea, low fever and poor mental reaction. Physical examination revealed he had fever (39.2 °C),
tachycardiac (180 beats/min), and hypotension. Abnormal laboratory findings included leukopenia (0.48×10^9/L), anemia (Hemoglobin: 73g / L), thrombocytopenia (41×10^9/L), impaired liver function (ALT 154U/L; AST 102U/L), hyponatremia (Na + 165mmol/L), and high C-reactive protein (149.63mg/L), procalcitonin (> 100.00ng/mL), and IL-6 (> 5000.00pg/mL). He received supportive circulation, large dose vasoactive drugs and multiple transfusions of platelet, cryoprecipitate, fresh frozen plasma and granulocyte colony-stimulating factor (G-CSF). On the 2nd day, Extracorporeal Membrane Oxygenation (ECMO) was used to provide continuous extracorporeal respiration and circulation. Carbapenem resistant-Pseudomonas aeruginosa (ceftazidime/ averbactam sensitive) was isolated via blood culture, and ceftazidime/ averbactam was administrated. On the 3rd day, he was noticed with symmetrical large purpura gradually on his limbs and trunk (Fig. 1A). On the 4rd day, the child received continuous renal replacement therapy (CRRT) at the bedside due to hyponatremia and anuria. On the 7rd day, he developed worsening jaundice, and his liver was significantly enlarged to 9 cm below the rib. On the 8th day, T. asahi was further recovered via blood culture with a minimum inhibitory concentration (MIC) of 2 µg/mL for amphotericin B, 0.03 µg/mL for voriconazole, 0.5 µg/mL for itraconazole, 2 µg/mL for fluconazole. Thus, voriconazole was then added for antifungal treatment. The patient presented with necrotizing lesion on the right side of the nasal alar and the right corner of the eye. Later, necrosis rapidly expanded to almost his entire face (Fig. 1B). Necrotic tissue culture recovered two kinds of fungi on blood agar, and identified as T. asahi by MALDI-TOF and Rhizopus delemar by Internal transcribed spacer (ITS) sequencing (94.99% nucleotide identity), respectively (Fig. 1C). Rhizopus delemar MICs were 0.5 µg/mL for posaconazole, 1 µg/mL for amphotericin B. Computed tomography of the brain revealed new multiple infarcts in the right frontal lobe (Fig. 1D). The anti-infection protocol was changed to treatment of Pseudomonas aeruginosa fungemia with ceftazidime/ averbactam, amphotericin B cholesterol sulfate and voriconazole was administrated for Rhizopus delemar and T. asahi. Unfortunately, he deteriorated and died for multiple organ failure and rapid progress of infection.

**Discussion and conclusion**

In recent decades, the incidence of ROCM in patients with hematological malignancies were increasing, which caused high mortality. ROCM requires early clinical suspicion and accurate identification, as the mucormycosis invade to the vessels advances rapidly. Early diagnosis, prompt medical drug treatment combined with active surgical treatment and improve patient's basic diseases as much as possible, such as restoring the number of white blood cells, and adjusting the use of immunosuppressants, will significantly improve the survival rate of patients with hematological diseases complicated by mucormycosis[6].

The most common symptoms for ROCM were eyeball protrusion, ophthalmoplegia, and decreased vision, which were not specific[7]. The only specific finding of ROCM described in the relevant reports is the necrotic eschar with blackened nasal mucosa. However, facial necrosis remains a late sign, with only 2% of patients presenting with this sign[7]. It is reported that the orbital involvement rate of nose brain mucormycosis ranges from 66–100%, orbital involvement leads to increased mortality, and the survival rate of patients with fungal encephalopathy is very low[8]. A combined surgical and medical management was associated with better survival. Surgical debridement of necrotic tissue may enable better penetration of antifungal agents, thereby improving outcomes. Unfortunately, surgical debridement is not feasible for patients with intracranial extension. Despite appropriate antifungal treatment, the mortality rate of patients who were unable to undergo surgery was high, indicating the need for early diagnosis and better treatment strategies[9]. Thus, surgical debridement may be considered in patients with malignant hematological disease even if they had leukopenia and thrombocytopenia[10]. Liposome amphotericin B should be used as a first-line treatment drug and given early in the course of the disease. Delayed initiation of liposome amphotericin B therapy (> 6 days after diagnosis) has been reported to be associated with a doubling mortality at 3
Itraconazole has recently become a first-line alternative for patients who are either intolerant to amphotericin B or do not respond favorably to it[12]. Some cases of successful treatment of mucormycosis with posaconazole have been reported, thus posaconazole was considered as salvage treatment for mucormycosis[13].

Trichosporon species have emerged as important opportunistic fungal pathogens, with T. asahii being the leading cause of disseminated infections and result in significant morbidity and death among those with a hematologic malignancy. 75% T. asahii was isolated from blood in pediatric cases and invasive T. asahii was frequently observed cutaneous involvement, which is helpful for high index of suspicion, early determine the etiology and initiate appropriate treatment[14]. Clinicians should highly suspicious of trichosporonosis in pediatric patients with a hematologic malignancy who present with persistent fever and neutropenia, especially when echinocandins are given for antifungal prophylaxis[15]. It is well known that Trichosporon is inherently resistant to echinocandins and has poor sensitivity to polyene drugs. Moreover, breakthrough trichosporosis may occur in patients receiving echinocandin as an empirical antifungal treatment[16]. In the past decade, amphotericin B and fluconazole have also been reported as antifungal drugs with high risk of breakthrough trichosporosis, including prophylactic joint use of fluconazole plus amphotericin B[16]. A number of studies have shown that the recommended first-line therapy for T. asahii is voriconazole, and likely superior to amphotericin B, fluconazole, and itraconazole for the treatment, but successful outcome depends largely on the underlying immune status of the host[17]. The mortality rate of was exceeding 80%, in patients with hematologic malignancy survival is thought to be primarily related to bone marrow recovery. Reported cured patients did not have neutropenia at the time of diagnosis or quickly recovered from neutropenia[17]. Clinicians should maintain a high level of clinical suspicion in patients with aforementioned risk factors, particularly in those with hematologic malignancies who have catheters in place. Remove central venous catheter and address the underlying immunosuppression may be possible to decrease mortality rates[17].

According to our investigation, this case is the third case of Mucormycosis and T. asahii co-infection. The clinical characterizations of Mucormycosis and T. asahii co-infection previously reported were listed in Table 1[18, 19].

### Table 1
Summary of reported cases of Mucormycosis and T. asahii co-infection

<table>
<thead>
<tr>
<th>Number</th>
<th>Year</th>
<th>Author</th>
<th>Age/sex</th>
<th>Presenting symptoms</th>
<th>Primary lesion</th>
<th>Underlying conditions</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2006</td>
<td>De Decker, K et al.[18]</td>
<td>12/F</td>
<td>Skin and muscles necrosis</td>
<td>Leg necrotizing fasciitis</td>
<td>Traffic accident</td>
<td>Amphotericin B, Posaconazole, surgery, Hyperbaric oxygen</td>
<td>Live</td>
</tr>
<tr>
<td>2</td>
<td>2016</td>
<td>Ozkaya-Parlakay, A et al. [19]</td>
<td>16/M</td>
<td>cutaneous necrosis, nasal bone necrosis</td>
<td>Paranasal Ewing sarcoma</td>
<td></td>
<td>Caspofungin, liposomal amphotericin B</td>
<td>Dead</td>
</tr>
</tbody>
</table>

In our case, P. aeruginosa BSI occurred in this immunocompromised children further worsened his immunity, and later a rare co-infection with Rhinocerebral Mucormycosis and T. asahii Fungemia associated with mortality. A acute lymphoblastic leukemia patient presented with necrotic eschar should maintain high level of clinical suspicion Mucor
and Trichosporon, reversal of risk factors, early diagnosis together with prompt and appropriate antifungal therapy and surgical debridement are essential for a favorable outcome.

**Abbreviations**

BSI: bloodstream infection; T. asahi: Trichosporon asahii; ROCM: rhinocerebral mucormycosis; G-CSF: granulocyte colony-stimulating factor; ECMO: Extracorporeal Membrane Oxygenation; MIC: minimum inhibitory concentration; Internal transcribed spacer: ITS.

**Declarations**

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Not applicable.

**Authors’ contributions**

Liuyang Hu contributed to the data collection, wrote the manuscript. Guiliang Liu and Xiuri Wang contributed to the data collection. Xingchun Chen contributed to critical revision and gave final approval of the clinical picture. All authors have read and agreed to the published version of the manuscript.

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**Availability of data and materials**

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval not applicable and consent to participate Ethics approval and patient parents performed informed consent.

Consent for publication

Patient parents provided written informed consent including consent to publish. Patient parents gave written consent for their relative's personal and clinical details along with any identifying images to be published in this study.

**Competing interests**

The authors have no conflicts of interest to declare.

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**Figures**

**Figure 1**

A: Symmetrical large purpura on his limbs. B: Necrotic lesion rapidly expanded to entire face. C: Necrotic tissue culture recovered two kinds of fungi on blood agar. D: Computed tomography of the brain revealed new multiple infarcts in the right frontal lobe.