Research Article

Rare cause of sepsis in an immunocompromised child with acute lymphocytic leukaemia - A Case Report

H Thabrew[1], LSM Sigera[1], MN Jayawardena[1], J Galappaththi[2], P Egodawela[2], SP Gunasekera[2], DS Gunasekera[3], PI Jayasekera[2]

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Abstract

Haematological malignancies are at a high risk of fungal infection and subsequent high mortality. A patient with a relapsed acute lymphocytic leukaemia (ALL) and a rare fungal infection is presented.

A four-year-old patient with ALL relapsed after 3 years of remission. He presented with a papular, erythematous rash mainly on the limbs and trunk, accompanied with high intermittent fever which did not respond to broad spectrum antibiotics.

Histopathological examination of a skin biopsy revealed yeast cells. *Trichosporon* species was isolated on culture. Voriconazole was started according to sensitivity test results and a brief response was demonstrated. Clinical deterioration was seen with worsening of the underlying malignancy. Amphotericin B was added with poor response. Unfortunately, he succumbed to his disease process without recovery from fever, skin rash or the malignancy.

Trichosporon species is a rare infection even in patients with haematological malignancies. Recovery from neutropenia is an important prognostic factor in the treatment of trichosporonosis.

Keywords: Trichosporonosis, Acute Lymphocytic Leukaemia, Sri Lanka

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[1] *Department of Mycology, Medical Research institute, Colombo 8, Sri Lanka*
[2] *Microbiology Laboratory, Apeksha Hospital, Maharagama, Sri Lanka*
[3] *Paediatric Oncology Unit, Apeksha Hospital, Maharagama, Sri Lanka*

Address for correspondence: Dr H Thabrew, Department of Mycology, Medical Research Institute, Colombo 8, Sri Lanka, Telephone+94 718 411697, email: harshanipj@gmail.com https://orcid.org/0000-0002-3049-3585

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Introduction

Trichosporonosis is an uncommon fungal infection that causes pulmonary and skin lesions in immunocompromised patients, especially in patients with haematological malignancies.[1] Timely treatment with correct antifungal is paramount, as the mortality rate is high, with a reported 30-day mortality of 51% and 38% fatality despite voriconazole therapy.[2] Resistance to first line antifungals is especially problematic with reported resistance to echinocandins, fluconazole and amphotericin B.[3] Twenty invasive *Trichosporon* infections in cancer patients have been reported in Sri Lanka over a 4 year retrospective study period, indicating the significance of this infection for the Sri Lankan patients.[4] Here we present the case of a 4-year-old child who presented with ALL relapses in severe neutropaenia with this rare fungal infection.

Case report

A four-year-old patient with CD 10 positive B cell ALL relapsed after 3 years of remission. He was started on standard ALL relapse therapy. During the first month of treatment, he developed fever and back pain of 3 days duration. He was given broad spectrum antibiotics at the onset of fever. Two weeks into treatment he developed a papular, erythematous rash, mainly on the limbs and trunk, accompanied by high spiking fever and respiratory distress which did not respond to broad spectrum antibiotic therapy. Blood cultures failed to isolate any organism in bacterial or fungal cultures.

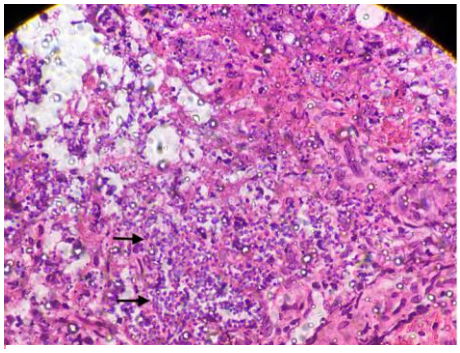

Figure 1: Periodic acid-Schiff stain of skin biopsy showing clumps of yeast cells (black arrow)

Skin biopsy was done on the lesions, which showed fungal filaments on direct microscopic examination with KOH. On culture, *Trichosporon asahii* was isolated. Histopathology of the skin biopsy also revealed fungal elements which were suggestive of fungal invasion of the skin (Figure 1).

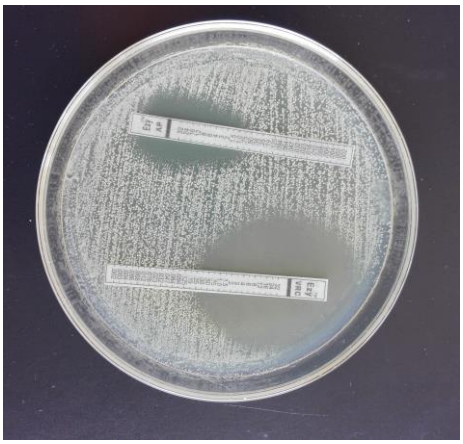

Figure 2: Antifungal sensitivity using E strips for voriconazole and amphotericin B

Antifungal sensitivity testing (AFST) is not routinely done for yeasts other than *Candida* spp. due to unavailability of a standardized testing method. AFST was done in this patient due to the severity of the infection which required optimal treatment as early as possible to prevent mortality. The epidemiology of Sri Lankan *Trichosporon* isolates was not known at the time of treatment of the patient. Sensitivity was done using E

test strips (Himedia) on Muller Hinton agar with the organism suspended in normal saline to McFarland turbidity of 0.5 according to the manufacturer's instructions. Clinical Laboratory Standards Institute (CLSI) M60 guidelines with quality control in parallel with *Candida parapsilosis* ATCC 22019 was also followed to ensure proper performance. Minimum inhibitory concentration (MIC) of voriconazole was 0.38µg/ml, amphotericin B was 0.75µg/ml and fluconazole resistance was demonstrated with MIC >256µg/ml (Figure 2). Intensive care was given, and he was started on oral voriconazole 9mg/ kg/ day. Therapeutic monitoring of voriconazole was not done due to unavailability. Fever responded after 10 days of antifungal therapy. This corresponded with a brief recovery from the neutropenic phase.

A subsequent bone marrow biopsy showed heavy residual disease of ALL and chemotherapy was further intensified while he was continued on voriconazole. This resulted in profound neutropenia and reappearance of the skin rash and fever indicating breakthrough fungaemia. Intravenous liposomal amphotericin B 3mg/kg/day was added to his treatment as salvage therapy for the infection to broaden the spectrum of antifungal therapy as well as to add synergistic effect with voriconazole. Blood culture obtained after 10 days of combination therapy grew *Trichosporon asahii.* The MIC was similar to the skin isolate which was 0.25µg/ml for voriconazole, 0.75µg/ml for amphotericin B and >256 µg/ml for fluconazole. Treatment was continued but unfortunately, he succumbed to his disease process without recovery from fever, skin rash or the malignancy.

Discussion

Trichosporon is a yeast found as a commensal in the gastrointestinal tract and skin in humans.[5] Disruption of the mucosal barrier with chemotherapy along with neutropaenia attribute to higher rate of infection in patients with haematological malignancies. However, other factors such as presence of invasive central lines and administration of total parenteral nutrition are also risk factors for *Trichosporon* infection similarly to *Candida* which is the commonest cause of fungaemia.[6].

Trichosporonosis was found to be the second most common fungal infection in patients with haematological malignancy.[1] However, the epidemiology of yeast infections has changed with the use of antifungal prophylaxis around the world. Prophylaxis with azoles led to significant reductions of *Trichosporon* infections. However, this uncommon yeast re-emerged with echinocandin prophylaxis in recent decades.[7] Echinocandins are not frequently used as antifungal prophylaxis in Sri Lanka.

Skin lesions are the second most common tissue involved in trichosporonosis and are present in 30% of patients with invasive disease. The skin lesions are mainly on the extremities but also involve the trunk and face which was similar to the pattern in our patient. Lesions are typically haemorrhagic macular or macular papular which differs from the skin lesions in infections with *Candida* spp. which are punctate, pseudopustular with a rim of erythema.[6]

T. asahii is the commonest species causing invasive infection. Lowest MICs were observed for voriconazole similar to our patient's isolate.[2,3] Other newer azoles such as posaconazole and

isavuconazole have good activity against *Trichosporon* sp. but best activity is reported for voriconazole in Sri Lanka as well as in other parts of the world.[4,8] However, voriconazole is fungistatic and not fungicidal and requires the support of neutrophils to clear the infection from the blood stream.[9] The poor response in our patient may also be due to undetected resistance of voriconazole as clinical breakpoints for interpretation are not available and voriconazole was selected on the best available MIC levels and evidence from the literature.[9] Therapeutic drug level monitoring was not done in this patient which would have ensured achievement of adequate drug levels.[10] This is a requirement in the use of voriconazole in treatment and is unfortunately not available in Sri Lanka. These may have been the reasons for the death of our patient as well as contributing to high mortality in patients with haematological malignancy.[11]

The limitation of our study is that broth microdilution, the recommended method for performance of antifungal sensitivity for other yeasts was not performed in this case due to unavailability. Moreover, there is no recommended standardized method for performing antifungal sensitivity testing for *Trichosporon*.[8]

Conclusion

Trichosporonosis is an infection that should be suspected in patients undergoing chemotherapy, with neutropenic fever not responding to first line antifungals such as fluconazole. Presence of haemorrhagic macular skin lesions could be a significant feature pointing to the diagnosis of *Trichosporon* fungaemia in patients at risk of this infection. Timely treatment with voriconazole, ideally with therapeutic drug level monitoring, should be started to prevent the high mortality associated with the condition.

Declaration

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- Ethics statement: All the details of the patient have been included respecting the patient's privacy and anonymity of the content has been maintained throughout the case. Consent for publication for this case was not obtained due to practical problems of collecting signatures from the patient's parents following the untimely death of their child
- Author contributions
  All authors contributed to the patient management and diagnostics as well as writing the manuscript

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