Disseminated *Scedosporium prolificans* Infection in a Patient with Acute Myeloid Leukemia and Prolonged Febrile Neutropenia

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ABSTRACT

Patients with hematologic malignancies and prolonged neutropenia are at high risk for life threatening infections including invasive and uncommon fungal infections. Here, we report a case of a 17-year-old man who developed a disseminated infection caused by *Scedosporium prolificans* following chemotherapy. The pathogen was isolated from the skin biopsy and blood. It was identified on the basis of its macroscopic and microscopic morphological features. Empirical antifungal treatment with amphotericin B showed no improvement. Combination of high-dose intravenous voriconazole and terbinafine was provided because of high minimal inhibitory concentration of *S. prolificans* to available antifungal agents. However, the patient was clinically deteriorated and eventually succumbed due to multi-organ failure. (*J Infect Dis Antimicrob Agents* 2014;31:101-5.)

INTRODUCTION

Aggressive chemotherapy and immunosuppressive treatment may prolong patients’ life. However, there are many life threatening infections in leukemic patients who have prolonged febrile neutropenia. Patients with hematologic malignancies are susceptible to invasive and uncommon fungal infections. *Scedosporium prolificans* is a ubiquitous filamentous fungus found in soil and water. Scedosporiosis has been related with numerous infections in immunocompromised and immuno-competent patients. This infection is one of the very difficult-to-treat and fatal fungal infections.¹ The clinical spectrum of invasive scedosporiosis varies from localized infections involving the bone and joint to disseminated infections.² We report here a case of disseminated *S. prolificans* infection in an acute myeloid leukemia patient with prolonged febrile neutropenia.

CASE REPORT

A 17-year-old high school man from Buriram Province was admitted to Ramathibodi Hospital due
to fever for 2 days. Five months prior to admission, he presented to a local hospital with fever and upper respiratory tract symptoms. His laboratory findings showed anemia and thrombocytopenia and he was diagnosed dengue hemorrhagic fever. He had improved after admission for 3 days. Two months prior to admission, he had dyspnea on exertion. He went to the same hospital and bicytopenia was still noted. He was referred to another hospital where bone marrow study was performed and he was diagnosed myelodysplastic syndrome. Bone marrow transplantation was planned but the patient was lost to follow-up. One month prior to admission, he had high grade fever and went to a tertiary care hospital. His complete blood count (CBC) showed WBC 3,100/mm³ (neutrophil 10%, lymphocyte 61%, monocyte 6%, atypical lymphocyte 3%, myeloblast 20%), hematocrit (Hct) 27.2%, platelets 65,000/mm³. He was given piperacillin-tazobactam for 14 days for empirical treatment of febrile neutropenia and the fever subsided after one week of treatment. He was discharged from the hospital and doing well for a few days. Two days prior to admission, he had a new onset of fever and came to Ramathibodi Hospital. He had weight loss of about 8 kilograms during these 5 months.

On physical examination, his temperature was 38.0°C, heart rate was 100 beats per minute, blood pressure was 100/60 mmHg, and respiratory rate was 28 per minute. Lymph nodes were impalpable. Hepatomegaly was noted but no splenomegaly. CBC showed pancytopenia; Hb 8.8 g/dL, Hct 26.2%, MCV 80.4 fL, WBC 3,100/mm³ (neutrophil 2%, lymphocyte 77%, monocyte 6%, eosinophil 1%, atypical lymphocyte 10%, immature cell 4%), and platelets 4,000/mm³.

At Ramathibodi Hospital, bone marrow study was repeated, which showed diffusely infiltrated with myeloblast. He was diagnosed acute myeloid leukemia. Induction chemotherapy with idarubicin and cytarabine was commenced. Piperacillin-tazobactam had been continued since the first day of admission but the fever had not subsided. Antibiotic was changed to imipenem on day 7 after chemotherapy. Fluconazole was started on day 9 after chemotherapy and changed to amphotericin B on day 11 post chemotherapy. However, he was still febrile and his symptoms were deteriorated. He was intubated on day 13 after chemotherapy. On day 15 post chemotherapy, he had a new hemorrhagic bleb on his left forearm and the lesion turned to a central necrotic lesion the next day. Skin biopsy was done and septate hyphae were demonstrated by Grocott-Gomorimethenamine-silver nitrate (GMS) stain. Skin culture grew a black mold on blood agar two days later. The fungus was later identified by morphology and biochemistry as *Scedosporium prolificans* (Fig 1-3). Further investigation revealed a few small bilateral pulmonary nodules and pansinusitis from computed tomography (CT) scan. Additional cultures were performed in which *S. prolificans* was isolated from sinus culture and tracheal suction culture. Antifungal therapy with high dose (trough level 5-10 μg/mL) intravenous voriconazole was started. The minimal inhibitory concentrations (MIC) of amphotericin B, voriconazole and posaconazole to *S. prolificans* were more than 32 μg/mL. Terbinafine was added for synergistic effect. However, the patient was deteriorating and passed away on day 14 after treatment due to multi-organ failure.

**DISCUSSION**

The genus *Scedosporium* consists of 4 important species: *Scedosporium boydii* (teleomorphic state, *Pseudallescheria boydii*), *Scedosporium apiospermum*
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S. prolificans is a ubiquitous filamentous fungus. It can be found in soil, sewage and polluted water. In 1984, Malloch and Salkin described a new species of Scedosporium (S. inflatum) isolated from a bone biopsy specimen from an immunocompetent child.

The common risk factors of scedosporiosis were prolonged neutropenia, receiving chemotherapy or immunosuppressive treatment, recipients of solid organ or bone marrow transplantation, patients with advanced human immunodeficiency virus infection, graft-versus-host disease, CMV infection and cystic fibrosis. There are 4 different clinical conditions of scedosporiosis including mycetoma, saprobic involvement of the airways, localized sinopulmonary or extrapulmonary, and disseminated infections. Disseminated form was
found in 44-86% of patients. Mortality rate was as high as 76.8-87.5%.\textsuperscript{5,6}

The diagnosis of \textit{S. prolificans} infection is often difficult. The clinical symptoms and radiographic finding are non-specific. There are currently no commercially available tests which would be helpful for diagnosis of scedosporiosis.\textsuperscript{7} The definitive diagnosis of filamentous fungal infection can only be made on histological evidence of fungal hyphae in the biopsy specimens. In our patient, the diagnosis was made on the basis of the presence of invasive septate fungal hyphae in dilated thrombosed vascular lumen and positive cultures of blood, skin tissue, sinus tissue and tracheal secretion. \textit{S. prolificans} was identified by its macroscopic and microscopic appearance.

Several in vitro studies demonstrated that \textit{S. prolificans} is generally resistant to many conventional and new antifungal agents. The resistance is inherent for amphotericin B, ketoconazole, miconazole, itraconazole, nystatin and 5-fluorocystosine.\textsuperscript{8,9} Therefore, it has a poor clinical response and high mortality.\textsuperscript{10} Some studies demonstrated that voriconazole exhibited a lower MIC than conventional antifungals.\textsuperscript{8,11,12} A new antifungal agent, posaconazole, showed moderate in vitro activity against \textit{Scedosporium} spp.\textsuperscript{13} There were several studies of combination antifungal agents that exhibited in vitro activity against \textit{S. prolificans} such as amphotericin B plus pentamidine,\textsuperscript{14} voriconazole plus micafungin,\textsuperscript{15} voriconazole plus mitel fosine\textsuperscript{16} and azoles plus terbinafine.\textsuperscript{17} They all showed synergic effect but in vivo study was lacking. Unfortunately, the fungus isolated from our patient was resistant to many antifungal agents and synergic test was not available at that time. There was evidence suggesting that a combination of growth factors (e.g. G-CSF) and purified polymorphonuclear leukocytes (PMNs) with aggressive therapy may increase the efficacy of the treatment.\textsuperscript{18,19}

In summary, disseminated infections due to \textit{S. prolificans} are rare. Efficient treatment was not well defined and prognosis was very poor. Early diagnosis and proper prophylaxis of invasive fungal infections in immunocompromised patients should be practiced.

References
8. Meletiadis J, Meis JF, Mouton JW, Rodriguez-


