CASE REPORT

Deep Skin Infection of Scedosporium *apiospermum* in a Patient with Refractory Idiopathic Thrombocytopenic Purpura

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Abstract

Infection of *Scedosporium apiospermum* is very rare but is now emerging as an important cause of both localized and disseminated infections in immunocompromised patients. A 62-year-old woman, who had undergone steroid therapy for refractory idiopathic thrombocytopenic purpura and had a history of diffuse large B cell lymphoma, developed a deep skin ulcer complicated with lymphangitis. After culture study demonstrated the presence of *S. apiospermum*, voriconazole (VRCZ) was administered and prompt improvement was observed. Because it is difficult to distinguish *S. apiospermum* from *Aspergillus* by histopathology and *S. apiospermum* is resistant to amphotericin B, VRCZ should be selected as the first choice of antifungal agent when mold is considered to be the causative organism.

Key words: *Scedosporium apiospermum*, deep skin infection, voriconazole, idiopathic thrombocytopenic purpura, steroid


Introduction

*Scedosporium apiospermum* is the asexual anamorph of the cosmopolitan fungus *Pseudallescheria boydii*. The organism is ubiquitous and has been isolated from a variety of natural substances such as farm soil and stream water (1). Although the incidence of infection of *S. apiospermum* is very low, it had been recognized as a pathogen of localized deep skin infection (mycetoma) after injury. Most reported patients were in an immunocompromised state but some cases that developed in immunocompetent patients have also been described (2, 3). Recently, the infection of *S. apiospermum* has emerged as an important cause of disseminated infection in severely immunocompromised patients, especially organ transplant recipients, and the prognosis of these invasive infections is poor (4-6). Furthermore, deep organ infections in immunologically normal patients have also been reported (7, 8), indicating that this organism should not be disregarded as a pathogen.

We report deep skin infection of *S. apiospermum* extending lymphangitis which developed in a patient with refractory idiopathic thrombocytopenic purpura (ITP) complicated with remission state of diffuse large B cell lymphoma (DLBCL). The infection developed after autologous peripheral blood stem cell transplantation (PBSCT) and was successfully treated with voriconazole (VRCZ) before the development of disseminated infection.

Case Report

A 62-year-old woman was admitted because of deteriorating bleeding tendency due to refractory and recurrent ITP in August 2009. She had a history of recurrent ITP and DLBCL. Her onset of ITP was in 1996. After the diagnosis of ITP, she underwent steroid therapy, resulting in remission. However, she experienced several relapses thereafter. In 2006, she underwent a splenectomy, which resulted in re-
mission. In November 2007, systemic lymphadenopathy developed. She was diagnosed as DLBCL stage III; IPI, high intermediate risk. She received 6 cycles of R-CHOP [Rituximab, cyclophosphamide, adriamycin, vincristine, prednisolone (PSL)] regimen followed by high-dose chemotherapy with autologous PBSCT in June 2008, resulting in complete remission.

In June 2009, ITP relapsed. Her platelet count was below \(1 \times 10^4/\mu L\). She received oral PSL (0.5 mg/kg daily), which resulted in no response. In August 2009, Rituximab was administered with a dose of 375 mg/m\(^2\) weekly 4 times. However, no response was observed. Furthermore, thrombocytopenia did not respond to high-dose gamma globulin therapy. Then, she was treated again with PSL (1 mg/m\(^2\)) and danazol. During the above period, she suffered from gastrointestinal bleeding and *Pneumocystis jiroveci* pneumonia and required insulin therapy owing to steroid-induced hyperglycemia.

In October, erythema with pustules was observed on the dorsal surface of her right first finger. Although she had a history of a slight injury at the site 4 months previously on a farm, the abnormality of the site was not recognized until then. This lesion deteriorated rapidly and deep ulceration developed in spite of antibiotics therapy (Fig. 1A, B). At that time, she did not have a fever. Her white blood cell count was 3,999/μL (neutrophil 72%, lymphocyte 19% and monocyte 9%), platelet count was 1.0×10⁷/μL and mild liver damage (asparate aminotransferase 55 IU/L, alanine aminotransferase 158 IU/L) was observed. C-reactive protein was 0.06 mg/dL and the titer of beta-D-glucan was 116 pg/mL. As mold was found in the smear of the exudate from the lesion, oral Itraconazol (ITCZ) (200 mg/day) was applied. However, the lesion worsened and a nodular lymphangitic pattern of spread was observed in the flexor side of the right upper limb, suggesting lymphangitic extension. Skin biopsy specimen demonstrated mold with separate and branching hyphae in the subcutaneous lesion (Fig. 2).

Gray colonies of mould grew upon the culture examination of the exudate and we identified the pathogen as *Scedosporium apiospermum* by morphological characterization (Fig. 3). Then, we administered oral VRCZ with a daily dose of 400 mg with a loading dose of 600 mg on the initial day and performed pus drainage by finger compression twice every day. Promptly, decreased discharge was noted. Formation of regenerating epidermis was observed after 2 weeks of VRCZ administration. Normal epidermis recovered within 2 months (Fig. 1C, D). Furthermore, probably because of the effect of danazol, her platelet counts were elevated to a normal level. VRCZ was continued for 2 months and her skin lesion became covered with normal epidermis.
Discussion

In a surveillance study in Australia (9), 180 identified cases of *Scedosporium* were collected. Among them, 41% were *S. prolificans* and 59% were *S. apiospermum*, and 65.6% were colonization and 34.4% were infection. Predisposing factors included chronic lung disease (37.8%) and malignancies (21.7%). Hematopoietic stem cell transplantation (HSCT), leukemia and diabetes mellitus were the predictors of invasive disease. In another survey of 80 scedosporiosis cases in transplant recipients, disseminated extension was observed in 69% of the infections in HCST recipients and 53% of the infections in organ transplant recipients (10).

Concerning the incidence of scedosporiosis among a certain disease status, Caira et al (11) reported the incidence of *Scedosporium* infections in patients with acute leukemia in Italy. They collected a total of 542 proven/probable mold infections among 8,633 patients with acute leukemia. Among all mold infections, only 5 cases (0.9%) of proven scedosporiosis were diagnosed, with an incidence of 0.08% in all acute leukemia patients. *S. apiospermum* was responsible for all 5 cases. All patients had chemotherapy-induced severe neutropenia at the onset of the infection. Disseminated disease was the most common clinical presentation. The lung, sinuses, skin and orbit were the affected sites. All of these patients died within a short period.

In the diagnosis of this infection, it is important to recognize that *S. apiospermum* resembles *Aspergillus* spp. clinically and histopathologically. Both fungi display thin, delicate, septate hyphae branching at acute angles. It should be emphasized that they cannot be differentiated except on fungal cultures (12). Rapid identification is essential because this organism is resistant to amphotericin B. Diagnostic confusion with *Aspergillus* spp. and uncertain therapy complicate the management of this rare entity (13, 14).
Amphotericin B has historically been proven to be ineffective in the treatment of S. apiospermum infection, and most isolates exhibit resistance in vitro (15-17). Intravenous miconazole has been used despite limited efficacy. In addition, in spite of some case reports demonstrating successful outcomes for localized infections, there are fewer published reports describing successful outcomes with ITZC for the treatment of disseminated disease in immunocompromised hosts (2, 18). VRZC has a broad spectrum of antifungal activity in vitro, including S. apiospermum, Aspergillus spp. and Fusarium spp., but generally shows poor activity against the class Zygomycetes (15, 17, 19, 20). The successful use of VRZC has been reported in localized subcutaneous infections (21), deep organ infections and disseminated diseases in immunocompromised adults (22-25) and children (26, 27).

Troke et al (28) analyzed 107 cases of Scedosporium infections including S. apiospermum (65%) and S. prolificans (35%), treated with voriconazole. Solid organ transplantation (22%), hematological malignancy (21%), surgery/trauma (15%), HSCT (9%) and high-dose steroid use (9%) were the predominant underlying conditions. Principal infection sites were the lungs/sinuses (24%), central nervous system (CNS) (20%) and bone (18%), while 21% of patients had disseminated infection. A successful therapeutic response was achieved in 57% of patients treated with VRZC. Differences of response rate among infection sites were seen for skin/subcutaneous (91%) and bone (79%) infections, and the lowest was for CNS infections (43%). In all, 43 (40%) patients died, 73% due to scedosporiosis. In addition, in transplant recipients, VRZC has been reported to have a superior clinical effect for scedosporiosis over other antifungal agents (10).

The present case is considered as an immunocompromised patient because she had received high-dose steroid therapy, had been in the state of hyperglycemia due to high-dose ITP 3 months before the onset of this infection and had received chemotherapy and autologous PBSCT 12 months before the onset of this infection. Also, our patient had an episode of a slight injury on a farm 4 months before the onset of the skin lesion. In addition to potential exposure due to injury, the impact of the patient’s augmented immunosuppression is thought to be that the pathogenesis contributed to the development of deep skin infection and lymphangitic extension. Although ITZC was ineffective, VRZC showed a striking effect on this infection. The skin lesion had almost healed within 2 months and dissemination was stopped.

Because Aspergillus spp. and S. apiospermum are often difficult to distinguish by histopathology, the fact that most isolates of S. apiospermum are resistant to amphotericin B is a critical consideration to select an antifungal agent prior to final species identification. We emphasize the importance of avoiding mistaken assumptions regarding the identity of fungal isolates on the basis of the histopathology or early cultures, especially in an acutely ill patient. VRZC should be selected as the first choice of antifungal agent when mold is considered to be the causative organism.

The authors state that they have no Conflict of Interest (COI).

References


