Breakthrough lung *Scedosporium prolificans* infection with multiple cavity lesions in a patient receiving voriconazole for probable invasive aspergillosis associated with monoclonal gammopathy of undetermined significance (MGUS)

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ABSTRACT

Breakthrough non-*Aspergillus* mold infections among patients receiving the anti-mold azole antifungal agents like voriconazole or posaconazole have been increasingly reported. We report a case of lung *Scedosporium prolificans* infection with multiple cavities in a 58-year-old man with monoclonal gammopathy of undetermined significance (MGUS) during voriconazole treatment for probable invasive aspergillosis. Cultures of repeated sputum specimens yielded the same fungus until his death 83 days after diagnosis. *S. prolificans* should be considered in patients with breakthrough infections receiving voriconazole.

Key words: *Scedosporium prolificans*, breakthrough infection, multiple cavities, voriconazole

Introduction

*Scedosporium* is a ubiquitous fungus in human impacted environments such as agricultural and garden soils, sewers, polluted ponds and sediments¹. Two species of *Scedosporium, Scedosporium apiospermum* (anamorph, *Pseudoallescheria boydii* as teleomorph) and *S. prolificans* (anamorph, teleomorph unknown) have been known to be human opportunistic pathogens¹. *S. prolificans* was first described by Hennebert² as *Lomentospora prolificans* from greenhouse soil and has caused life-threatening and disseminated infections as an emerging fungus infection¹.³ After introduction of anti-mold azole antifungal agents like voriconazole or posaconazole, breakthrough invasive fungal infections by Zygomy- cete or *Scedosporium* in patients have receiving such azole agents for treatment of aspergillosis or prophylactic use in hematological malignancies has been increased⁴,⁵. We report a case of pulmonary *S. prolificans* infection which emerged in a patient with monoclonal gammopathy of undetermined significance (MGUS) during voriconazole treatment for probable invasive aspergillosis.

Case Report

A 58-year-old man, with monoclonal gammopathy of undetermined significance (MGUS), was admitted to our hospital due to uncontrollable nephrotic syndrome on November 12th, 2008. Following treatment with 30 mg of prednisolone daily and introduction of hemodialysis, he had a fever (> 38.5°C) when prednisolone was attenu-
ated to 15 mg daily on December 10, 2008. There were no isolates detected from any of the consecutive blood cultures or when the intravenous hemodialysis catheter was removed. Although receiving 1 g daily of each vancomycin and meropenem, his fever still remained and bilateral pulmonary infiltrative changes appeared in a chest radiograph (Fig. 1B) on December 26th, 2009. Parenteral itraconazole was begun of 200 mg daily, but acute respiratory failure occurred. He was intubated and controlled under mechanical ventilation on January 3rd, 2009. Laboratory studies showed a white blood cell count of 11,900/mm$^3$, platelets 166,000/mm$^3$, creatinine 2.4 mg/dl, C-reactive protein 4.0 mg/dl, 1,3-β-D-glucan 61 pg/ml (Fungitec-MK$^R$, Seikagaku Bio Business, Co., Tokyo, Japan, using a cut-off value of 20 pg/ml). Chest computed tomography (CT) scan revealed multiple well-circumscribed nodular lesions with a halo sign in both lungs (Fig. 2B). No significant bacteria including Mycobacterium and fungi were isolated from sputum. Treatment was switched to liposomal amphotericin B (3 mg/kg daily), and then changed to micafungin (50 mg daily) because pancytopenia developed, sulfamethoxazole/trimethoprim (4,800/960 mg daily) was added with 3-day methylprednisolone (500 mg daily) pulse therapy, but no clinical response was obtained. At that time, probable invasive aspergillosis was diagnosed based on fulfilled criteria of host factor (prolonged use of corticosteroids), clinical criteria (the presence of dense, well-circumscribed lesions with halo sign by chest CT) and mycological criteria (positive Aspergillus galactomannan antigen with elevated 1,3-β-D-glucan: 138 pg/ml. Voriconazole (loading dose 300 mg, and maintenance dose 200 mg daily, 4 mg/kg) was implemented intravenously, and clinical manifestation was improved and galactomannan and 1,3-β-D-glucan became
negative. However, multiple nodular lesions of both lungs still remained and these changed to multiple cavities on a CT scan on February 20, 2009 (Fig. 3). Hyphal element was observed by Gram-staining of aspirated sputum and blood and chocolate agar plates grew white mold after 3-day incubation at 35℃ (Fig. 4A, B). This fungus grew as white colonies at first, then turned to dark green on Sabouraud dextrose agar after 5 days of incubation at 25℃ (Fig. 4C). On potato dextrose agar slide culture stained with lactophenol cotton blue, septate hyphae with conidiogenous cells having swollen base and elongated neck.

Fig. 3. Chest radiograph (A) and CT scan (B) on onset of pulmonary *S. prolificans* infection (February 20, 2009). Multiple cavity lesions appeared on both lungs.

Fig. 4. Detection and mycological identification of *S. prolificans*.
(A): Hyphal element detected from aspirated sputum by Gram-staining on February 20, 2009. (B): *S. prolificans* colonies on blood (left) and chocolate (right) agar plates after 72 h culture at 35℃ aerobically from the same specimen as A. (C): Giant single colony on Sabouraud dextrose agar after 5-day culture at 25℃. (D): Microscopic findings of a slide culture of the *S. prolificans* strain stained with lactophenol cotton blue. Septate hyphae with conidiogenous cells having swollen base and elongated neck.
ribosomal DNA D1/D2 region\(^7\)\(^-\)\(^9\). The MICs of various antifungal agents were determined by the broth microdilution method according to the methods of the National Committee of Clinical Laboratory Standards\(^10\). The results are shown in Table 1, and according to them, indicated that, this patient would be difficult to treat even using antifungal agents. Although the MIC of amphotericin B was the lowest of the antifungal agents tested, we could not use liposomal amphotericin B due to his previous history of pancytopenia with this drug. As the serum concentration of voriconazole was 2.87 μg/ml which did not achieve MIC and the clinical response was insufficient, the dose was escalated to 400 mg daily. However, consecutive sputum specimens still yielded *S. prolificans* and 1,3-β-D-glucan was elevated. He died on May 12th, 2009 (the 83rd day after diagnosis of *S. prolificans* infection) of respiratory failure. Schematic representation of his clinical course is shown in Fig. 5. No autopsy could be performed.

### Discussion

Since the first description of *S. prolificans* as the causative agent of osteomyelitis in 1984\(^11\), it has been recognized as an opportunistic pathogen that causes invasive, disseminated, and life-threatening disease in immunocompromised hosts. *S. prolificans* is resistant to most clinically available antifungal agents and seems to be more virulent than *S. apiospermum*, another *Scedosporium* species that can cause human infections\(^3\). *Scedosporium* has been common in a human-dominated environment including hospitals\(^3\). As *S. prolificans* has predominantly been isolated from respiratory sites, the most frequent entry might be

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\text{Antifungal agent} & \text{MIC (mg/ml)} \\
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\text{amphotericin B} & 4 \\
\text{5-fluorocytosine} & > 64 \\
\text{fluconazole} & > 64 \\
\text{miconazole} & > 16 \\
\text{itraconazole} & > 8 \\
\text{voriconazole} & 8 \\
\text{micafungin} & > 16 \\
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Fig. 5. Clinical course of this case. Abbreviations are followings, mPSL: methylprednisolone, PSL: prednisolone, ST: sulfamethoxazole/trimethoprim, ITCZ: itraconazole, MCFG: micafungin, VRCZ: voriconazole, L-AMB: liposomal amphotericin B, CRP: C-reactive protein.
The transmission route of S. prolificans in this case was uncertain, since there were no scedosporiosis patients or any S. prolificans strains yielded from specimens of other patients during this period. S. prolificans has also been colonized in the lungs of patients with cystic fibrosis. Recently, new azole antifungal agents with an extended spectrum to Aspergillus, like voriconazole or posaconazole, have been developed. However, even though these agents showed less activities to develop. However, even though these agents have triggered selective growth of colonized S. prolificans in patients receiving these agents have been reported. In addition to underlying MGUS, which is well known to harbor a risk of various infections, corticosteroid use and voriconazole treatment for aspergillosis might have triggered selective growth of colonized S. prolificans in his lung. Two similar breakthrough cases were described by Grenouillet et al.

Diagnosis of scedosporiosis is mainly based on fungal culture and pathological confirmation and its serodiagnosis has not been available in clinical settings. Detection of 1, 3-β-D-glucan in serum or plasma is a new useful method for diagnosis of invasive fungal infections except zygomycosis and cryptococcosis. This assay was also useful for diagnosis of scedosporiosis. In our case, although Aspergillus galactomannan antigen became negative, the elevated level of 1, 3-β-D-glucan strongly suggested infection of S. prolificans. Amphotericin B has been considered the first line treatment of life-threatening invasive fungal infections. However, in-vitro susceptibility of S. prolificans against amphotericin B was higher than voriconazole in the previous reports, and treatments of invasive S. prolificans infections by amphotericin B were commonly unsuccessful. There have been few reports about the efficacy of a high dose of liposomal amphotericin B for invasive S. prolificans infections. For treatments of such infections, antifungal combinations, especially voriconazole and terbinafine, showed synergy in vitro, in vivo and in clinical cases, but their usefulness has still been controversial. Although the mechanism of synergy of voriconazole and terbinafine is uncertain, its interaction can be explained as different inhibitory steps of the ergosterol synthetic pathway like the antibacterials trimethoprim and sulfamethoxazole. We could not add terbinafine to voriconazole because an oral prescription must not be used when there is gastrointestinal bleeding and intubation. Voriconazole is the most potent antifungal against S. prolificans of the clinically available agents. Troke et al. reported that responses to single voriconazole therapy including dose escalation were successful in 16/36 (44%) of S. prolificans infections. These facts forced us to select higher voriconazole, not a combination with terbinafine, but unfortunately the patient died. S. prolificans infection has not been reported in Japan. To our knowledge, this is the first report of breakthrough S. prolificans infection. Clinicians and microbiological laboratories should remain vigilant for the emergent breakthrough fungi such as S. prolificans in patients receiving long-term voriconazole treatment.

References


