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Case report

Scedosporium apiospermum fungemia successfully treated with voriconazole and terbinafine

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ABSTRACT

Scedosporium apiospermum is ubiquitous in the environment and is considered an emerging infection. Immunocompromised hosts can have a wide spectrum of diseases ranging from cutaneous to disseminated disease that may involve pulmonary, central nervous system, or bone. Disseminated disease in immunocompetent hosts is uncommon. Treatment of deep-seated infections is challenging because of the limited susceptibility of the *Scedosporium* species to all current antifungal drugs. We report a case of *Scedosporidium apiospermum* fungemia with a presumed pulmonary involvement in an immunocompetent patient. The fungemia was successfully treated with oral voriconazole and terbinafine.

Introduction

Scedosporium apiospermum (S. apiospermun) is an environmental pathogen that can be found in soil, sewage, and polluted water [1]. Infections caused by this organism occur in the paranasal sinuses, lungs, skin, soft tissue, central nervous system, and bones. Disseminated disease is also common with usually hematogenous dissemination [1]. It is an emerging pathogen associated with the increase use of glucocorticosteroids, immunosuppressive therapy, and chemotherapy [2]. *S. apiospermun* is considered as a major cause of non-Aspergillus mold infections in organ transplant recipients and cystic fibrosis patients [3]. It is important to have an accurate and prompt diagnosis because *S. apiospermum* can be misidentified as other molds with different resistance profiles, such as *Aspergillus* species (spp).

Case report

A 72-year-old female patient was admitted to the hospital with fever, intermittent hemoptysis, and worsening shortness of breath of 2–3 weeks duration. Her past medical history is significant for severe primary pulmonary arterial hypertension on treprostinil infusion through a peripherally inserted central catheter (PICC). Physical examination was remarkable for temperature of 102 F, crackles on lungs examination, and tunneled right internal jugular catheter with no local signs of infection. Initial work up showed white blood cell count of 12,500/ul with normal differential. Her respiratory viral panel from nasal wash, urine legionella antigen, and Streptococcus urinary antigen were negative. Computer tomography (CT) of the chest showed scattered ill-defined airspace opacities in both lungs (Fig. 1). She was started on broad spectrum antibiotics for suspected community acquired pneumonia. On hospital day two, she was transferred to the ICU after an episode of massive hemoptysis and acute hypoxemic respiratory failure. Bronchoscopy showed normal appearance of the trachea and bronchial tree. Her automated blood cultures obtained on admission grew *S. apiospermum* (after 5 days of incubation). The patient was started on voriconazole and liposomal amphotericin B. The source of fungemia was thought to be secondary to PICC infection, and it was removed. The tip of the PICC and bronchoalveolar lavage fungal cultures remained negative. Her Aspergillus Galactomannan antigen index was 0.109 (reference value < 0.5) and HIV serology was negative. A repeat CT scan of the chest on day 14 after initiation of antifungal therapy showed worsening diffuse lung nodules (Fig. 2). She was clinically stable but remained hypoxic, her (1,3)-Beta-D-Glucan (Fungitel) decreased from 257 pg./mL to 164 pg./mL (normal < 60 pg./mL). susceptibility testing is summarized in Table 1, terbinafine susceptibility and antifungal synergy testing were not performed. Micafungin was added later during the hospital course. The patient expressed wishes to be transitioned to oral antifungals and to

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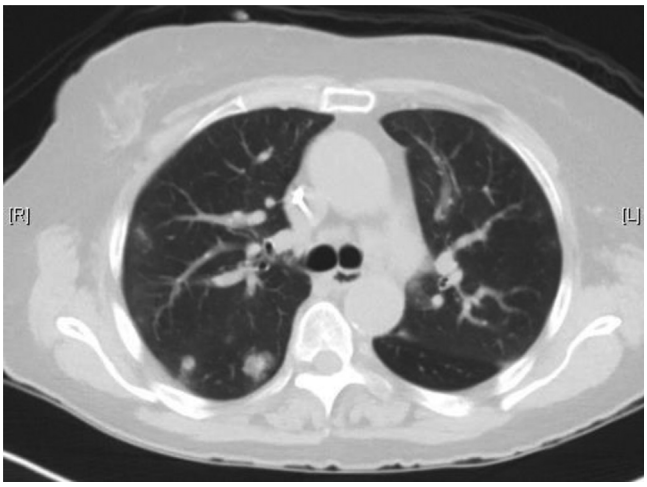

Fig. 1. Computed tomography of the chest on admission showing scattered ill-defined airspace opacities in both lungs.

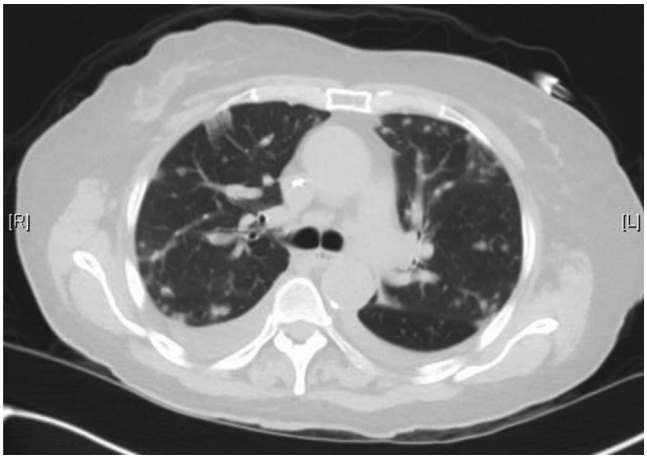

Fig. 2. Repeat CT scan of the chest 14 days after starting voriconazole and liposomal amphotericin B showing worsening lungs findings with innombrable nodules.

Table 1
Antifungal Susceptibility testing for *Scedosporidium apiospermum.*

Antifungal Agent	MIC (mcg/mL)
Itraconazole	2
Voriconazole	1
Posaconazole	1
Amphotericin B	> 8
Micafungin	0.25
Caspufungin	> 8

MIC: minimal inhibitory concentration. Testing performed at University of Texas Health Science Center according to CLSI M38-A2 (broth dilution).There are no established breakpoints for *S. apiospermum* antifungal susceptibility.

consider hospice care if any further deterioration. She was discharged on oral voriconazole and terbinafine. Repeat blood cultures were negative. She had a gradual resolution of her symptoms. A CT scan of the chest, done 12 days after discharge (2 weeks after changing antifungal therapy to voriconazole and terbinafine), showed significant improvement, and a repeat CT scan 6 months after discharge showed almost resolution of pulmonary infiltrates and nodules. The patient was treated for a total of 7 months with voriconazole and terbinafine with no evidence of relapse after 7 years of follow up.

Discussion

Scedosporium/Lomentospora spp is a major cause of infection in immunocompromised patients. It has been recognized that *Scedosporium* spp. can also cause severe infection in immunocompetent hosts (in victims of near-drowning or after penetrating trauma). *Scedosporium* spp. was identified as the second most common filamentous fungi after *Aspergillus* spp. in a study done in Spain [4]. It causes broad spectrum of diseases, including skin and soft tissue infections, septic arthritis, osteomyelitis, sinusitis, pneumonia, meningitis, brain abscesses, endocarditis, keratitis, chorioretinitis, endophthalmitis, and disseminated infection.

S. apiospermum was initially considered the anamorph of *Scedosporium boydii* (formerly known as *Pseudallescheria boydii*). In 2005, it was found that they are two distinct species based on molecular, physiological, and biochemical data [5]. *S. apiospermum* complex has been recognized to encompass five distinct species: *S. apiospermum*, *S.aurantiacum*, *S. boydii*, *S.minutisporum*, and *S. dehoogii* [6]. Out of these five species, *S. apiospermum*, *S. aurantiacum* and *S. boydii*, are causing human infections [6].

Lomentospora prolificans (formerly *Scedosporium prolificans*) was named as *Scedosporium inflatum* when first isolated due to its basally swollen, flask-shaped cells but was later named *S. prolificans* [7]. Based on ultrastructure studies and DNA-DNA hybridization analysis, this organism was subsequently assigned to the genus *Lomentospora* and reclassified as *Lomentospora prolificans* [8]. There is no available active antifungal therapy for *Lomentospora prolificans.*

One case series and review of literature of S. *apiospermum and L. prolificans* infections in transplant recipients revealed 80 cases, the majority were *S. apiospermum* (58 patients) [10]. Fungemia reported in 40 % (4/10) of organ transplant recipients with *L. prolificans*, compared with 4.7 % (2/43) of those with *S. apiospermum* infections [9]. Another review of the literature showed that 12 out of 204 cases had fungemia (5.8 %) (compared to 46.4 % in *L. prolificans*). Among the 12 patients with S. *apiospermum* fungemia, seven were immunosuppressed (six of them are solid organ transplant recipients), five were immunocompetent [10]. All 12 patients with fungemia died and death was mostly attributed to the infection with overall attributable mortality of 76 %. In this case series, the authors performed an electronic literature search for case reports in PubMed and the FungiScope registry.

Voriconazole is the antifungal agent of choice for treatment of *S. apiospermum* given efficacy and good tolerance [11]. *In vitro* data suggest that micafungin is the second most active antifungal agent against *S. apiospermum* [12]. The combination of micafungin and voriconazole *in vitro* has been demonstrated to have a synergistic effect against several fungi including *Scedosporium spp* [13]. Studies have shown that terbinafine monotherapy has poor potency against *Scedosporium* species (MIC90, >16 ug/mL) but the addition of terbinafine to voriconazole has a potential synergistic role based on case reports [14–17]. Henao-Martínez et al. reported two cases of *S. apiospermum* CNS infections treated successfully with the combination of voriconazole and terbinafine [14]. Musk et al. reported two cases of successful treatment of post-lung transplant *S. apiospermum* infection with same combination therapy [15]. Rolfe et al. reported a case of *S. apiospermum pulmonary infections in a* cystic fibrosis that was treated with voriconazole and terbinafine prior to lung transplantation two months after staring the therapy [16]. Following lung transplant, multiple bronchoscopes were performed and remained negative for the growth of bacterial or fungal organisms. Voriconazole was discontinued after six months; and terbinafine discontinued after nine months (from transplant). Goldman et al. reported a 77-year-old man on high dose steroids for presumed temporal arteritis who has cutaneous *S. apiospermum* infection that disseminated on

voriconazole [17]. The addition of micafungin and granulocyte macrophage colony-stimulating factor (GM-CSF) provided partial recovery.

Our patient didn't have evidence of immunosuppression, we presumed that the source of her fungemia and pneumonia was her PICC. She had a clear radiological worsening 14 days after starting voriconazole and liposomal amphotericin B. We postulated that the combination of voriconazole and terbinafine was likely synergistic and cured this patient, she had significant radiological and clinical improvement after 14 days of this therapy and subsequent complete resolution of her infection. To our knowledge, this is the first reported case of presumed *S. apiospermum* PICC infection with secondary pulmonary dissemination.

Invasive *S. apiospermun* infection is associated with a very high mortality rate, the optimal therapy remains unknown and data on treatment is anectodal. The most promising therapy seems to be the combination of voriconazole and terbinafine but more data is needed about its efficacy.

Author statement

This case is unique due the rarity of *Scedosporium apiospermum* fungemia especially in immunocompetent patients. In addition, we believe this is the first reported case of fungemia associated with central line infection with secondary pulmonary dissemination. This case also adds to the anecdotal evidence that the combination therapy with voriconazole and terbinafine may be synergistic and effective for the treatment of *S. apiopermum* invasive infection.

Declaration of Competing Interest

The authors report no declarations of interest.

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