Disseminated *Scedosporium apiospermum* central nervous system infection after lung transplantation: A case report with successful recovery

Juuso Paajanena,*, Maija Halmea, Maarit Palomäkib, Veli-Jukka Anttila

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**ABSTRACT**

*Scedosporium* species are fungal opportunistic pathogens frequently seen in chronic lung diseases such as in cystic fibrosis (CF). They can cause a wide spectrum of diseases mainly in immunodeficient patients. Invasive, disseminated infections with poor prognosis have been described after lung transplantation. We present a CF-patient with disseminated *Scedosporium apiospermum* infection after lung transplantation. The patient had skin, surgical wound, spinal cord, and brain involvements. She recovered fully after prolonged course of voriconazole treatment.

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1. Introduction

Cystic fibrosis (CF) is an inherited disease due to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene [1]. Defective CFTR protein causes abnormal ion transport across the apical surfaces of epithelia in multiple organ systems. One consequence of abnormal ion transport in the lung is dehydration and thickening of airway secretions. The disease is characterized by recurrent bacterial and fungal infections and progressive respiratory failure. Lung transplantation (LT) is a therapeutic option for patients with end-stage lung disease.

*Scedosporium* is a saprophytic fungus isolated from soil, polluted water and plant residues worldwide. The genus *Scedosporium* consists of three medically important species: *Scedosporium apiospermum* (*S. apiospermum*), *Scedosporium boydii* (formerly *Pseudallescheria boydii*) and *Scedosporium aurantiacum* [2]. *Scedosporium* spp. is the second most prevalent opportunistic fungus after *Aspergillus* spp. found to colonize chronic lung diseases such as CF [3]. The role and pathogenicity of *S. apiospermum* in lung diseases is controversial, but either local or disseminated infections are described in immunodeficient patients [4]. Especially after organ transplant, the colonization may develop into invasive, disseminated infection with central nervous system (CNS) involvement leading to dismal outcome [5]. Thus, *Scedosporium* colonization prior to LT is considered as a contra-indication in some transplantation centers [3]. Unlike *Aspergillus*, *Scedosporium* spp. is inherently resistant to many antifungals such as amphotericin B and echinocandins. Voriconazole used alone or in combination is reported to be the most active agent against *Scedosporium* [6]. Also, a reduction in immunosuppression or surgical drainage should be considered when suitable.

Here, we present the first successfully treated disseminated *S. apiospermum* CNS infection after a lung transplantation.

2. Case

An 18-year-old woman with CF was considered as a candidate for bilateral LT. Her respiratory failure had advanced, so that a supplemental oxygen therapy and night-time non-invasive ventilation were initiated. Bilateral pneumothoraces with subcutaneous emphysema were detected on an elective control in March 2015. At that time, her FEV1 had decreased to 1.35 L (34% of predicted). She was referred to the respiratory department where her ventilatory failure acutely progressed. After a short resuscitation she was connected to ventilator and subsequently to extracorporeal membrane oxygenation (ECMO). She was listed for a Scandinavian emergency LT. *S. apiospermum* was detected in fungal culture of the tracheal aspirate with susceptibility testing showing minimal inhibitory concentrations of: voriconazole 0.125mg/L, itraconazole 6mg/L, posaconazole 6mg/L and amphotericin B 12mg/L. After five days on ECMO, she underwent a bilateral LT (defined as day 0). *Pseudomonas aeruginosa* and *S. apiospermum* colonizations were detected in the extracted native lungs. The peri-operative course was complicated by *pseudomonas* septicemia which was
treated with intravenous (IV) tazobactam/piperacillin, tobramycin, and oral ciprofloxacin with a good clinical outcome. IV caspofungin was started postoperatively for antifungal prophylaxis with a single loading dose of 70mg, followed by 50mg daily for 17 days.

Her baseline immunosuppression regimen consisted of tacrolimus, mycophenolate mofetil, and prednisolone. Prophylactic valganciclovir, a dose of 70mg, followed by 50mg daily for 17 days, started postoperatively for antifungal prophylaxis with a single loading dose of 300mg twice daily. Therapeutic serum levels were confirmed by repeated measurements (target therapeutic limits 2–5.5mg/l). At a control visit in June 2018 three years after LT and 35 months of treatment, the voriconazole treatment was terminated. After the discontinuation of antifungal treatment, the patient has visited our clinic for two controls with no signs of fungal re-infection. The last visit was in January 2019, nearly four years after the LT and eight months after the termination of voriconazole. She was symptomless with preserved lung allograft function: Her FEV1 was 2.7L (77% predicted). Brain MRI revealed only few residual lesions (Fig. 2d), which had been stable and inactive for months.

3. Discussion

To the best of our knowledge, the presented case is the first published S. apiospermum disseminated infection with brain and spinal cord abscesses after LT leading to a full recovery. Previous reports have shown a good response to antifungals with or without surgical drainage in patients with S. apiospermum local spondylodiscitis, osteomyelitis, septic arthritis, or lung infections in LT recipients [7,8]. However, the case reports after LT on both disseminated and CNS involvement have been disappointing [5,9–14]. Previously reported disseminated S. apiospermum infections after LT are reviewed in Table 1.

Careful balance in immunosuppression is needed to successfully manage patients after LT to prevent and treat both the rejection of the lung allograft and bacterial, viral, and fungal infections. Although less frequent than bacterial and viral infections, invasive fungal infection is associated with higher morbidity and mortality after LT [15]. The depth of immunosuppression is associated with both increased incidence and worse outcome of invasive fungal infections [5,15].

There is no widely accepted optimal recommendation for antifungal prophylaxis after LT [15]. The standard regimen used in our institute is trimethoprim/sulfamethoxazole for Pneumocystis jirovecii. In selected high-risk patients for Aspergillus infection, we have used nebulized amphotericin B and short-term systemic caspofungin prophylaxis with low invasive Aspergillus infection incidence [16]. However, this regimen has no effect in S. apiospermum. Several positive reports with either itraconazole, posaconazole or voriconazole prophylaxis have been reported in S. apiospermum colonization, even if the optimal dose or length of treatment are not well known [3,13]. In contrast, there are also reports with fatal invasive Scedosporium infections in spite of long-term voriconazole prophylaxis [13,14]. In our case, we didn’t use any prophylactic antifungal targeted to Scedosporium before LT. After LT, the patient received inhaled amphotericin B among other prophylactic agents without measurable prophylactic effects. The use of prophylactic triazole should be considered for the first months after LT or in the event of temporary additional immunosuppression in high-risk patients for Scedosporium infections.
**Fig. 2.** a–d: MRI T2 weighted imaging revealed multiple lesions with perifocal oedema (arrows) (a). Most of the lesions had ring-enhancement with gadolinium compatible with abscess (arrows). There were also nodular enhancing lesions (arrowheads) (b). Spinal cord MRI shows multiple ring-enhancing lesions (arrows) (c). The latest control image shows only small residual T2-lesions (arrows) that had remained stable over 8 months after completion of 35 months of voriconazole treatment (d).

| Table 1 |
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| Clinical characteristics of previously reported patients of disseminated Scedosporium apiospermum infections after lung transplantation. |

| Age, years | Sex | Antifungal prophylaxis | Time to diagnosis after LT | Infection sites | Antifungal therapy | Outcome (Survival time after diagnosis) | Reference |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 43 | M | ITC | 18 months | Pulmonary, mediastinum, joint, vertebra | ITC, CAS, AMB | Death (13 months) | [13] |
| 57 | F | ITC | 14 months | Pulmonary, brain, breast implant, skin | VRC, TRB, POS | Death (shortly after diagnosis) | [13] |
| 19 | F | VRC | 1 month | Eye, skin, mediastinum, chest wall, pulmonary, sinus, joint, vertebra | VRC, CAS, TRB, POS, AMB, PEN | Death (14 months) | [13] |
| 20 | F | None | 11 months | Kidneys, eye, pulmonary, vertebra | NA | Death (5 months) | [3] |
| 37 | F | None | 2 months | Pulmonary, brain, heart, eye | ITC, AMB | Death (1 month) | [3] |
| 64 | F | None | 3 years | Pulmonary, septicemia, heart | AMB, ITC | Death (18 days) | [11] |
| 37 | F | VRC | 2 months | Skin, brain, septicemia, heart | VRC, CAS, TRB | Death (6 months) | [14] |
| 24 | F | None | 7.5 months | Heart, spleen, kidneys, brain | ITC, MIC | Death (1 month) | [14] |
| 30 | M | None | 2 weeks | Pulmonary, heart | AMB, MIC | Death (7 days) | [10] |
| 26 | F | ITC, AMB | 3 weeks | Skin, eye, brain | VRC, MIC | Death (6 months) | [9] |
| 33 | F | AMB, ITC, CAS | 3 months | Joint, pulmonary | VRC | Alive | [8] |
| 27 | M | None | 6 weeks | Brain, pulmonary | AMB | Death (shortly after diagnosis) | [8] |
| 27 | M | VRC, AMB | 1 month | Pulmonary, heart, septic thrombus | VRC, TRB, CAS, POS, ANF, MTF | Death (7 months) | [12] |

LT, lung transplantation; M, male; ITC, itraconazole; CAS, caspofungin; AMB, amphotericin B; F, female; VRC, voriconazole; TRB, terbinafine; POS, posaconazole; PEN, pentamidine; NA, Not available; MIC, miconazole; ANF, anidulafungin; MTF, miltefosine.
The exact dosage, duration or combination of antifungal therapies in Scedosporium infections are not well known due to the lack of prospective studies. A successful therapeutic response in 57% of patients and a median survival time of 133 days were reported in a retrospective study of 107 patients with Scedosporium infections treated with voriconazole [17]. The median duration of the treatment was 103 days (range 1–802 days), while 21% of patients received treatment for a year or more. The initial treatment was similar to our case: intravenous 6mg/kg twice a day for one day, followed by 4mg/kg twice a day after switching to oral therapy. In another report of an LT patient, an initial response was seen in a disseminated S. apiospermum infection with ocular, skin and cerebrospinal fluid involvement [9]. However, a fatal relapse was seen only two days after the discontinuation of a six-month treatment period. In our case, we think that the immediate initiation of voriconazole was important for the good outcome. We used prolonged intravenous voriconazole regimen for ten months. The main reasons for that were slow recovery seen in MRI images, lack of side effects, and fear of inadequate therapeutic levels due to CF-related malabsorption. Mild photosensitivity reaction was the only adverse event reported by the patient. In hindsight, an earlier switch to oral treatment with voriconazole and repeated concentration controls could have been possible. We added miltefosine as combination therapy based on previously published in vitro susceptibility testing, but the treatment was terminated due to unwanted side effects and good clinical response to voriconazole [18].

In conclusion, we reported a lung transplant patient with disseminated S. apiospermum infection with CNS manifestation leading to a good and rapid response to voriconazole. Considering the preceding evidence in the literature, we think that prior colonization of Scedosporium should not be an absolute contraindication for a lung transplant. However, in the absence of prospective clinical trials, a careful case-by-case evaluation is needed to prevent and treat disseminated diseases. Especially the role of prophylactic antifungal therapy, preoperative clearance of potential reservoirs (e.g. sinuses), use of surgical drainage, and reduced immunotherapy will be needed to consider when treating LT patients with Scedosporium spp. colonization and infection.

Conflict of interest

There are none.

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