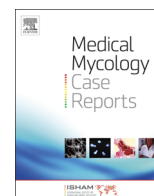




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## Successful prevention of scedosporiosis after lung transplantation in a cystic fibrosis patient by combined local and systemic triazole therapy<sup>☆</sup>

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### ABSTRACT

A persistent colonization with *Scedosporium apiospermum* (*S. apiospermum*) often results in disseminated infection with a high mortality rate in immunosuppressed patients. We present the first case of successful prevention of scedosporiosis in an adolescent female cystic fibrosis patient post double lung transplant, with a combination of local and systemic voriconazole therapy and surgical intervention.

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### 1. Introduction

*Scedosporium apiospermum* (*S. apiospermum*), one of the main species within the newly defined *Pseudallescheria boydii* complex [1], is a common, clinically important filamentous mold responsible for numerous opportunistic infections in immunocompromised patients or individuals after near-drowning accidents. It is ubiquitously found in polluted water or soil and is not transmitted from person to person. The clinical presentation of *S. apiospermum* colonization varies and depends on the underlying immune status of its host [2]. In patients with cystic fibrosis (CF), persistent colonization and infection with *S. apiospermum* is a major though still underestimated problem. Additionally to allergic bronchopulmonary aspergillosis-like manifestations [3], there is an increased risk for scedosporiosis in lung and heart-lung transplant recipients [4]. Without effective eradication, colonization often results in disseminating infections with a high mortality [4]. Due to the intrinsic resistance pattern of *Scedosporium* spp. against commonly used

antifungal compounds, treatment options are often limited. Surgical excision (where possible) and combined antifungal therapy are considered for invasive infections [2].

We present the first case of an adolescent female double lung transplant recipient, colonized with *S. apiospermum* within the lung and paranasal sinuses, and the successful prevention of an invasive infection by a combination of voriconazole treatment and surgical intervention.

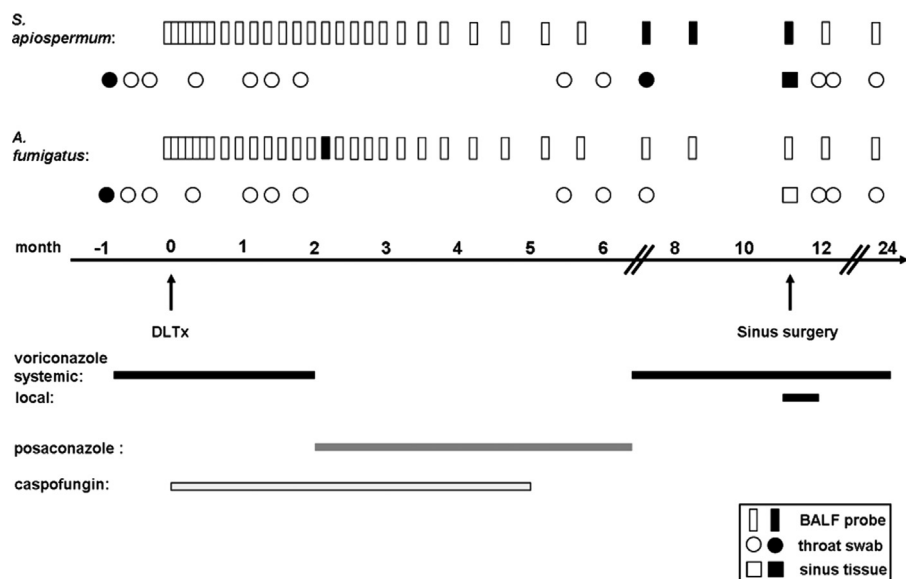
### 2. Case

A 17 year old girl suffering from CF (by mutation D-F 508) presented to our pediatric lung transplantation center with acute pulmonary exacerbation with severe hypercapnia (pCO<sub>2</sub> = 85 mmHg) and atelectasis of the left lung. Two weeks before double lung transplantation (DLTx) *Aspergillus fumigatus* and *S. apiospermum* were detected in throat swabs for the first time. Serum IgE levels before and even after DLTxs were in normal range (1–3 IU/ml). An antifungal therapy with voriconazole (2 mg/kg, twice daily (b.i.d.), intravenously (i.v.)) was immediately started according to susceptibility testing (microdilution test and minimal inhibitory concentration (MIC) 1 µg/ml). DLTx was performed with cardiopulmonary bypass (day 0). Due to mismatch between donor and patient lung size the right lower lobe had to be resected anatomically. Immunosuppressive therapy

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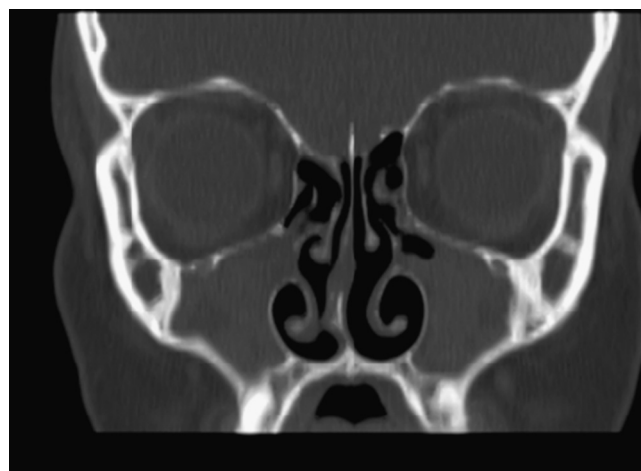
**Fig. 1.** Fungal isolation in the respiratory tract and antifungal therapy. Each symbol represents one single specimen of microbiological examination: rectangles represent BALF cultures, circles symbolize throat swab cultures while squares represent intraoperative sinus tissue (filled=positive culture result, open=negative culture result). DLTx (double lung transplantation).

consisted of tacrolimus (trough level 10–14 ng/ml), prednisolone and mycophenolat mofetil (1.2 g/m<sup>2</sup>/day, orally (p.o.)). Her initial post-transplant course was complicated by recurrent bacterial empyema with a need for multiple surgical revisions, pleural effusion and atelectasis of the middle lobe due to a bronchial stenosis with unsuccessful stenting.

Antimycotic treatment was continued with voriconazole (2 mg/kg, b.i.d, i.v.) and caspofungin (0.7 mg/kg/day, i.v.) over 2 months (Fig. 1). Subsequently, bronchoalveolar lavage fluid (BALF) cultures and throat swabs proved negative for *S. apiospermum*. Besides ongoing therapy, two months after DLTx, BALF and pleural fluid cultures were positive for *Aspergillus fumigatus*. Therefore we changed the antifungal triazole therapy to posaconazole (12 mg/kg, every 8 h, p.o.) for 5 months with continuation of caspofungin therapy over 3 months (Fig. 1).

*S. apiospermum* was detected again in BALF and a throat swab 7 months after DLTx. Since susceptibility testing proved the fungus to be nonsusceptible to caspofungin (minimal effective concentration (MEC) > 16 µg/ml), intermediately susceptible against posaconazole (MIC 2–4 µg/ml) but unchanged susceptible to voriconazole (MIC 1 µg/ml), we changed antifungal treatment back to voriconazole (4 mg/kg, b.i.d, p.o.) (Fig. 1). However, positive BALF cultures persisted. Further investigations in search of the focus site revealed radiological signs of chronic sinusitis one month thereafter (Fig. 2). Due to a subtotal occlusion of all paranasal sinuses we opted for a surgical intervention.

Eleven months after DLTx, extensive surgical debridement with removal of tough mucoid material in all paranasal sinuses was performed. Intraoperative tissue cultures of sinuses and BALF again grew *S. apiospermum* confirming the sinuses as probable colonization and drip-off origin. Intraoperatively, local voriconazole lavage was performed (100 mg voriconazole dissolved in 200 ml saline) and external drainages within each frontal sinus were inserted. We repeated local voriconazole lavages (1 mg/ml, 25 ml in total, each side) on days 2, 7 and 16 postoperatively via the external drainages. Patient has been continued on prophylactic systematic voriconazole therapy (4 mg/kg, b.i.d, p.o.), with serum level voriconazole of 1.3 µg/ml. This combined local and systemic treatment finally led to a persistent negative microbiological examination of *S. apiospermum* in BALF and throat swab cultures over a 24 months post debridement period. Routine monitoring on echocardiographic and dermatologic irregularities and liver enzymes under long-term



**Fig. 2.** Contrast-enhanced (bone-algorithm) computed tomography scan of paranasal sinuses, 10 months post-transplant. Ethmoid sinuses showing extensive circular soft tissue thickening with subtotal occlusion. Both maxillary sinuses with (sub) total occlusion, increased sclerosis and thickening of bony limitations as sign of chronic sinusitis.

voriconazole therapy revealed a distinct photosensitivity without any further adverse effects.

### 3. Discussion

Persistent *S. apiospermum* colonization is found in 5.7–10% of CF patients ranking second after *Aspergillus fumigatus* among all hyaline molds [5]. The detection rate of these molds can be increased by the use of selective media. Nevertheless, despite the use of an additional semi selective medium (SceSel+) [6] at our hospital the prevalence of *S. apiospermum* and related species is below 3% among all CF patients.

*In vitro* and *in vivo* data show that voriconazole is the most active drug for the treatment of scedosporiosis, and systemic application has proved to be a successful and well tolerated antifungal therapy in solid organ transplant recipients [7]. However, recommendations

regarding the specific treatment of scedosporiosis remain yet to be defined [7].

A retrospective review among solid organ transplant recipients between 1976 and 1999 identified 23 patients with *S. apiospermum* infection (total incidence of one in 1000 patients) with a trend towards even higher numbers among lung transplant recipients [4]. 13/23 (57%) recipients presented with sinopulmonary disease and 11/23 (48%) recipients with invasive pneumonia, the latter showing an increased mortality rate up to 91% [4]. In a retrospective review by Tamm et al., BALF cultures of 7 out of 330 lung and heart-lung transplant recipients (2.3%) were either colonized by *S. apiospermum* or *S. prolificans*, four of which died within 3–35 months after diagnosis due to advanced bronchiolitis obliterans syndrome (BOS) [8]. Our patient has remained BOS-free for 36 months.

In general, episodes of sinus disease in CF patients are common due to the poor sinopulmonary drainage and may lead to persistent colonization, fungus ball formation and pulmonary exacerbation [2]. In addition, so far several case reports deal with disseminated *S. apiospermum*/*Pseudallescheria* spp. infections in CF patients after DLTx [9]. Four of those showed previous airway colonization with *S. apiospermum* like in our case. Dissemination of this colonization led to an overall mortality rate of 100% despite combined antifungal treatment [9]. In order to prevent dissemination of scedosporiosis after transplantation, we opted for a broad antifungal therapy. Treatment consisted of a triazole (voriconazole/posaconazole) in combination with an echinocandin (caspofungin) over 5 months to benefit from their previously described synergistic effect [10]. Systemic monotherapy by posaconazole for another 2 months was not able to control colonization effectively, since *S. apiospermum* was isolated subsequently from BALF. Chronic sinusitis, as identified in our patient, is an important source for persistent fungal colonization and/or reinfection [11]. In our patient, multilocus sequence typing of four *Scedosporium* isolates before and after DLTx (including one of the sinuses) showed an identical genotype.

Being aware of the high mortality associated with *S. apiospermum* in patients after DLTx and the poor penetration of paranasal sinuses with systemic antifungal therapy, we opted for a more aggressive therapeutical approach. Surgical intervention had previously shown good curative effects in *S. apiospermum* sinusitis [12]. However, even with combined surgery and systemic antifungal treatment the overall prognosis after invasive fungal sinusitis in immunocompromised hosts is still poor, with a mortality rate of 84% [12]. Therefore, we performed simultaneous intraoperative lavages with voriconazole, continuing for 2 weeks postoperatively via external drainages. The prompt response might be supported by the fact that frontal sinuses were almost entirely missing in our patient. The approach has led to persistently negative microbiological samples for this pathogen over two years of follow up. Effective local voriconazole therapy for *Scedosporium* has earlier been described for a keratitis and a surgical wound in immunocompetent hosts without any local or systemic side effects [13,14].

Despite its high mortality in immunocompromised hosts, we describe the first successful control of *S. apiospermum* colonization in an adolescent CF patient after DLTx with combined local and systemic voriconazole treatment and surgical intervention. In our case, the recurrence of *S. apiospermum* in the transplanted lungs was

most probably caused by a colonization of the patient's sinuses. Therefore, we consider a thorough investigation of common colonization sites together with an aggressive treatment strategy even before invasive dissemination crucial for patient and transplant survival.

Additional investigations are needed to further characterize eradication procedures of *Scedosporium* spp. in CF patients prior or post lung transplantation. In addition, the role of prophylactic voriconazole for lifetime in those patients might be further evaluated.

## Conflict of interest

There are none.

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