**Scedosporium apiospermum** and **S. prolificans** mixed disseminated infection in a lung transplant recipient: An unusual case of long-term survival with combined systemic and local antifungal therapy in intensive care unit

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**Abstract**

Infections due *Scedosporium* spp. in lung transplant recipients are associated with disseminated disease with high mortality rates. The adjunctive local antifungal therapy may be a useful option when systemic treatment is insufficient and/or surgery is not feasible. We present a case of mixed disseminated infection due *Scedosporium apiospermum* and *S. prolificans* in a lung transplant recipient. Combined local and systemic antifungal therapy provided an unusual long-term survival in the intensive care unit.

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**1. Introduction**

*Scedosporium* species are opportunistic fungal pathogens recognized as a cause of infection in patients with solid organ transplant (SOT). In lung transplant (LT) recipients the invasive pulmonary infection and disseminated disease are the predominant manifestations and carry high mortality rates [1]. Voriconazole (VRC) is recommended as first line of therapy for *Scedosporium* spp. infections however, treatment options are often limited due to resistance/less susceptibility to current antifungal drugs [2]. Several antifungal combinations have been employed but nowadays, no solid recommendations have been made, remaining still a concern.

We present a case of mixed disseminated infection due *S. apiospermum* and *S. prolificans* in a LT recipient. He was treated with a very broad combination of systemic and local antifungal agents achieving an outstanding prolonged survival in the Intensive Care Unit (ICU).

**2. Case**

A 27-years-old man with cystic fibrosis (CF) underwent bilateral lung transplant on May 2014 (day 0). He was chronically colonized with *S. apiospermum* and received long-term suppressive therapy with VRC. Anti-infective prophylaxis included broad-spectrum antibiotics, intravenous VRC 200 mg twice daily, intravenous liposomal amphotericin B (L-AMB) 350 mg daily and nebulized L-AMB 25 mg (L-AMB 50 mg diluted in 12 cc of sterile water and remove 6 cc from the mixture) daily. Maintenance immunosuppressive therapy consisted in tacrolimus and prednisone. His immediate post-transplant course was complicated by an urgent surgery for massive left hemothorax. On day +7, the patient developed multifactorial acute kidney injury and renal replacement therapy (RRT) was started. On day +30, he required surgical intervention for left pleural empyema. Cultures from respiratory tract samples and pleural fluid revealed *S. prolificans* and *S. apiospermum*. The antifungal treatment was intensified; intravenous VRC was associated with terbinafine (TRB) 250 mg daily, caspofungin (CAS) 50 mg daily, nebulized VRC...
40 mg (VRC 200 mg diluted in 20 cc of sterile water and remove 4 cc from the mixture) three times daily and intrapleural instillations with VRC (400 mg in 100 ml of normal saline) twice daily. Intravenous L-AMB was discontinued. Serum VRC levels were monitored twice monthly resulting in subtherapeutic levels (o 1 mg/L) in all samples but antifungals dose was not increased due to a progressive increase in liver enzyme levels and renal failure. The patient recovered clinically and maintained an acceptable lung function with minimal oxygen requirements. He was discharged to general ward on day +87. However, on day +90 the patient was readmitted to ICU due severe respiratory failure requiring continuous mechanical ventilation. A bronchoscopy was performed and cultures from bronchoalveolar lavages and pleural fluid remained positive for S. prolificans and S. apiospermum. A chest computed tomography (CT) evidenced a thrombus in the anastomosis of right pulmonary artery and bibasilar pulmonary consolidations (Fig. 1a). Thrombus sample was taken through an intravascular catheter with embolic protection device. Histopathological evaluation revealed organized hematic material with visible fungal elements (Fig. 2).

The patient received a new combination of antifungal therapy with intravenous posaconazole (POS) 300 mg once daily, miltefosine (MTF) 50 mg twice daily and anidulafungin (ANF) 100 mg daily. Intrapleural VRC, nebulated VRC and nebulated L-AMB were maintained. Intravenous VRC, TRB and CAS were discontinued. Surgery was ruled out due to progressive disseminated infection.

Fungal strains isolated from respiratory, pleural fluid and thrombus samples were sent to the Mycology Reference Laboratory. Definitive identification was performed by macro-microscopic morphological characteristics and by real time PCR assay specific for the detection of S. apiospermum and S. prolificans [3]. Antifungal activity of VRC, POS, CAS and MTF were tested and a synergy test was also performed by checkerboard microdilution method [4]. S. apiospermum was susceptible to VRC, POS and MTF, while S. prolificans was resistant to all antifungals tested. In addition, neither synergy between VRC–MTF nor POS–MTF was present (Table 1) [5].

Progressive improvement was observed, and on day +160 a reduction of the thrombus size was seen in a control chest CT (Fig. 1b). Cultures from respiratory tract and pleural fluid samples became negative consequently, intrapleural VRC was discontinued and POS switched to oral therapy (200 mg four times daily). POS concentration was also monitored twice monthly with levels ranged between 0.31 and 1.17 mg/L. Nevertheless, the patient remained in ICU due to critical illness polyneuropathy with difficult weaning from mechanical ventilation.

On day +230 the patient started with new-onset dyspnea and fever. A new chest CT revealed a big mass in the tricuspid valve, an increase in the size of the thrombus of the right pulmonary artery with distal progression, and a new thrombus in the anastomosis of left pulmonary artery, suggesting mycotic emboli (Fig. 3). Trans-thoracic echocardiography confirmed a large vegetation on tricuspid valve (Fig. 4).

S. prolificans and S. apiospermum were identified on respiratory samples and the patient died on day +245 due multiorgan failure.

3. Discussion

Scedosporium spp. accounts for to 25% of all non-Aspergillus mold infections in SOT [6], being the second most frequently filamentous fungi recovered in patient with LT [7]. Disseminated
Scedosporium spp. infection has been reported in 18–55% amongst SOT with Scedosporium spp. infection, and it usually carries an ominous prognosis, with mortality rates around 80% [6–8].

Time to onset Scedosporium spp. disease varies greatly, from first month after transplant to several years later. Increased mortality with early-onset infection is expected during the pre-engraftment period, and most patients die during the first month following the diagnosis [7,8]. Scedosporium spp. disseminated infections with intravascular involvement is usually a fulminant process in an immunocompromised patient [7,9]. We present a LT patient with an early-onset Scedosporium spp. disseminated disease with lung, intravascular and endocardial involvement. Regardless the poor prognosis, the patient presented an exceptionally long-term survival in ICU, nearly 9 months, probably attributed to a broad antifungal combination therapy.

The genus Scedosporium show decreased susceptibility to the majority of current antifungal agents. VRC is recommended as first-line treatment for Scedosporium spp. infections. S. apiospermum demonstrates variable susceptibility to azoles and echinocandins. S. prolificans is generally resistant to most antifungal drugs [2]. The usefulness of combination therapy for Scedosporium spp. infections is controversial and in most cases applied as salvage therapy. Several in vitro studies have demonstrated successful growth inhibition of Scedosporium spp. when combining antifungals [10,11]. Several cases reported successful treatment with azole plus terbinafine or azole plus echinocandins, nevertheless these combinations are moderately or marginally recommended respectively, for the treatment of Scedosporium spp. infections [2].

The experience of MTF combined in Scedosporium spp. infections is anecdotal, and only one case report with successful outcome is available [12].

We started an intensive systemic therapy with VRC, TRB and CAS combined with intrapleural and nebulized VRC obtaining transient clinical improvement. An increase in liver enzymes attributed to the antifungal therapy occurred and he was kept on RRT during all ICU admission. These inconveniences compelled us to a change systemic therapy to POS, MTF and ANF. At that time, our patient was in a critical condition, and oral intake was decreased. The new intravenous formulation of POS provides an option for the same indications in patients who are unable to receive oral formulations [13]. A case report has shown that intravenous POS may be used in critically ill patient undergoing RRT without significant risk of cyclodextrin accumulation [14]. We started with intravenous POS with the aim of achieving a through concentration at least $\geq 1\, \text{mg/L}$ as literature recommended [15]. A significant clinical improvement was observed, with a reduction in the size of thrombus, and negative cultures were obtained in respiratory samples.

In our patient, therapeutic levels of VRC never were achieved and POS levels varied greatly. Data from real world studies in CF patients indicate a high inter-subject variability inazole pharmacokinetics, achieving appropriate levels can be challenging in these patients [16].

The susceptibility patterns of Scedosporium spp. to current antifungal agents is difficult to predict and synergy tests may be useful to choose the more appropriate treatment [10]. The checkerboard test provides a two-dimensional arrangement of different concentrations of antimicrobials and allows the calculation of the fractional inhibitory concentration index (FIC), assessing the additivity, indifference or antagonism between antimicrobials [4]. Unfortunately, the results obtained in our patient samples showed that S. apiospermum was susceptible to VRC, POS and MTF, while S. prolificans was resistant to all antifungal agents used. Besides, each antifungal combination showed indifference interaction for both strains.

Systemic antifungal therapy in Scedosporium spp. infection is not always effective. Surgical removal of the affected tissue has been a component of the standard of care and should be considered whenever possible [2,7]. Surgery was ruled out in our patient due to critical situation and disseminated infection. On this issue, local (nebulized plus intrapleural) antifungals may provide higher concentrations at the site of infection without increasing the risk of systemic side-effects and may be a promising option to not-candidate patients. Some studies reports successful treatments in invasive pulmonary aspergillosis and Aspergillus pleural empyema with local antifungal therapy [17,18] and at present time only one case describes successful treatment with nebulized VRC in S. apiospermum pulmonary infection in CF patient, highlighting the therapeutic potential and the safety of these alternative antifungals.

**Fig. 3.** Axial image from contrast-enhanced computed tomography scan of the chest showing a filling defect compatible with thrombus (arrows). The size of lesions shown are (a) $7 \times 10$ mm in right pulmonary artery and (b) $14 \times 5$ mm in the Anastomosis of left pulmonary artery.

**Fig. 4.** Transthoracic echocardiography of right heart structures showing tricuspid valve with a large vegetation (36 $\times$ 18 mm) suggestive fungal endocarditis.
administration routes [19].

Despite the hopelessness of the case, we assume that the patient could have a realistic chance of survival. Therefore, treatment was aimed to suppress the progression of the infection and open the possibility of a surgical approach.

We report an early onset disseminated infection due to *S. apiospermum* and *S. prolificans* in a CF patient with LT. The patient survived nearly 9 months in ICU, an unusually survival time much greater than described in the literature. In addition, this is the first report describing a combination of systemic, intrapleural and nebulized antifungal therapy in *Scedosporium* spp. mixed disseminated infection in LT recipient.

We must acknowledge some limitations as antifungals agents failed to show in vitro synergy and besides, we could not determine the most effective antifungal drug used. Nevertheless, we assume that the antifungals combination described here was effective in slowing the progression of the disease and prolonging the patient’s survival.

The relevance of this report is highlighted by the fact that a very broad combination of systemic and local antifungals in *Scedosporium* spp. invasive infections as described may be an option in severely ill patients with surgical chance awaiting definitive treatment.

Conflict of interest

There are none.

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