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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.

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 colonizated 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 antimycotic treatment was intensified; intravenous VRC was associated with terbinafine (TRB) 250 mg daily, caspofungin (CAS) 50 mg daily, nebulized VRC

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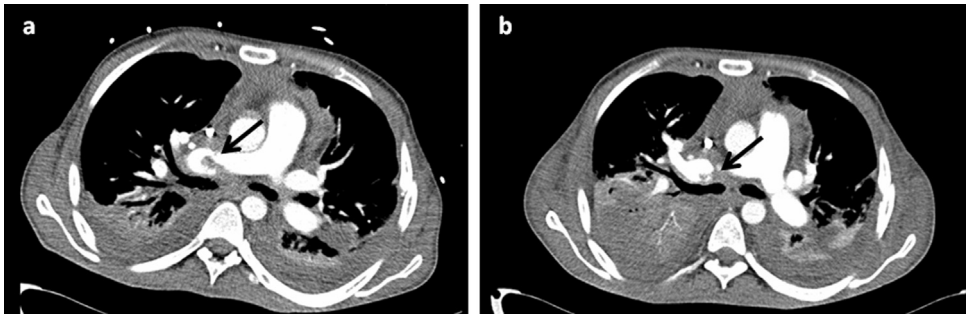

Fig. 1. Axial image from contrast-enhanced computed tomography scan of the chest showing a filling defect compatible with thrombus in the anastomosis of right pulmonary artery (arrows). The diameter of lesions shown are (a) 17 × 10 mm and (b) 11 × 8 mm observed after intensive antifungal therapy.

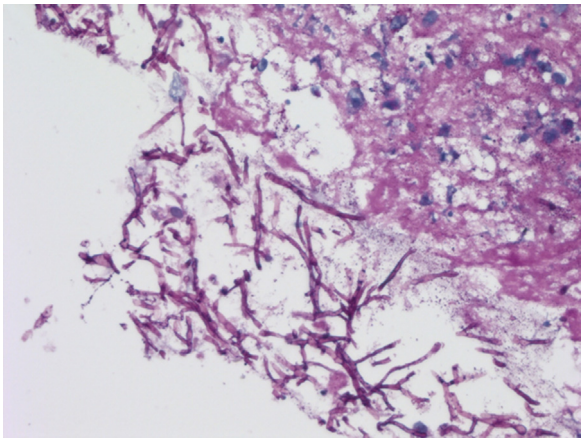

Fig. 2. Histopathology demonstrating organized hematic material that includes fungal organism with narrow-angle branching septate hyphae (periodic – acid Schiff [PAS] stain X 400).

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 (< 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, nebulized VRC and nebulized 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 to be confirmed. 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].

Table 1
Results of individual and combined antifungal activity in *S. apiospermum* and *S. prolificans* isolates sent to the Mycology Reference Laboratory.

Organism	MIC [a]					FIC [b]	
	VRC	POS	CAS	TRB	MTF	VRC–MTF	POS–MTF
Scedosporium apiospermum	0.12	≤ 12	NT	NT	0.12	2	2
Scedosporium prolificans	> 16	> 16	4	> 16	16	2	2.5

Abbreviations: *MIC* minimal inhibitory concentration (mg/L), *FIC* fractional inhibitory concentration index, *VOR* voriconazole, *POS* posaconazole, *CAS* caspofungin, *TRB* terbinafine *MTF* miltefosine, *NT* not tested.

[a] Individual MICs were determined following the broth microdilution method recommended by EUCAST.

[b] MIC of VOR and POS in combination with MTF was performed by using a two-dimensional *checkerboard microdilution* method. The final concentration assayed ranged from 16 to 0.12 mg/L for VOR, 16–0.12 mg/L for POS and 32–0.06 mg/L for MTF. The interaction between drugs was quantitatively evaluated by means of the FIC. The interaction was defined as synergistic if the FIC index was 0.5, additive if FIC was > 0.5 and < 1, indifferent if 1 < FIC > 4, and antagonistic if FIC was > 4.

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). Transthoracic 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

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