Medical Mycology Case Reports 11 (2016) 53–56

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

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

Bárbara Balandin [a,*], Miriam Aguilar [b], Isabel Sánchez [c], Araceli Monzón [d], Isabel Rivera [e], Clara Salas [f], Miguel Valdivia [a], Sara Alcántara [a], Aris Pérez [a], Piedad Ussetti [b]

[a] Intensive Care Unit, Hospital Universitario Puerta de Hierro Majadahonda, Spain
[b] Department of Pneumology and Lung Transplant Unit, Hospital Universitario Puerta de Hierro Majadahonda, Spain
[c] Department of Microbiology, Hospital Universitario Puerta de Hierro Majadahonda, Spain
[d] Department of Mycology, Instituto de Salud Carlos III, Majadahonda, Spain
[e] Department of Radiology, Hospital Universitario Puerta de Hierro Majadahonda, Spain
[f] Department of Pathology, Hospital Universitario Puerta de Hierro Majadahonda, Spain

ARTICLE INFO

Article history:
Received 21 February 2016
Received in revised form
12 April 2016
Accepted 25 April 2016
Available online 30 April 2016

Keywords:
Scedosporium spp
Disseminated infection
Lung transplant recipient
Long-term survival
Local antifungal therapy
Synergy test

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

* Corresponding author.

http://dx.doi.org/10.1016/j.mmcr.2016.04.006

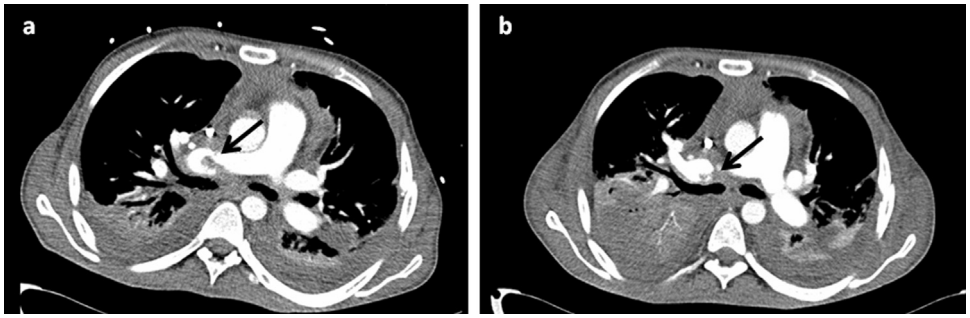

Fig. 1. Axial image from contrast-enhanced computed tomography scan of the chest showing a filling defect compatible with thrombus in the anastomosis of right pulmonary artery (arrows). The diameter of lesions shown are (a) 17 × 10 mm and (b) 11 × 8 mm observed after intensive antifungal therapy.

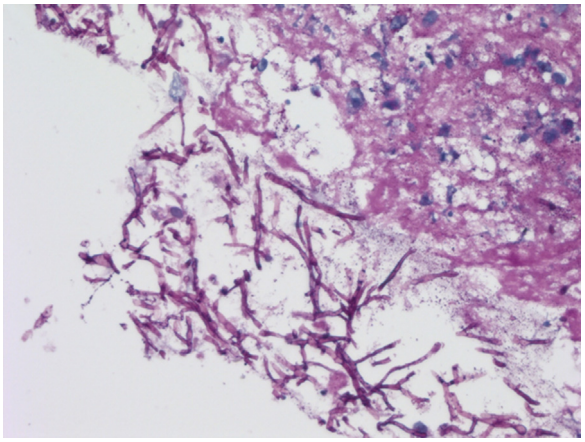

Fig. 2. Histopathology demonstrating organized hematic material that includes fungal organism with narrow-angle branching septate hyphae (periodic – acid Schiff [PAS] stain X 400).

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

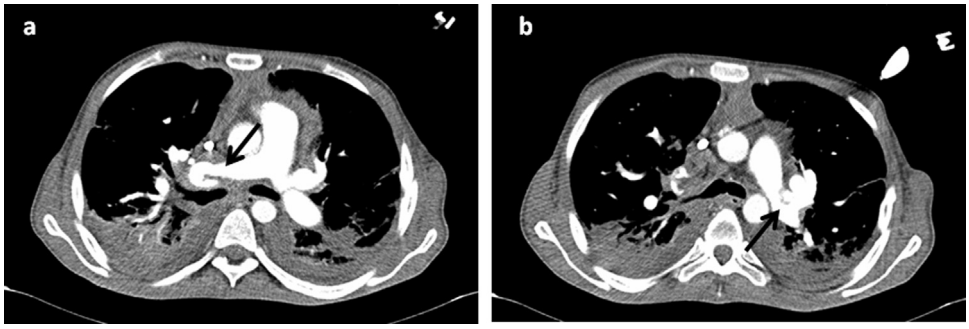

Fig. 3. Axial image from contrast-enhanced computed tomography scan of the chest showing a filling defect compatible with thrombus (arrows). The size of lesions shown are (a) 7 × 10 mm in right pulmonary artery and (b) 14 × 5 mm in the anastomosis of left pulmonary artery.

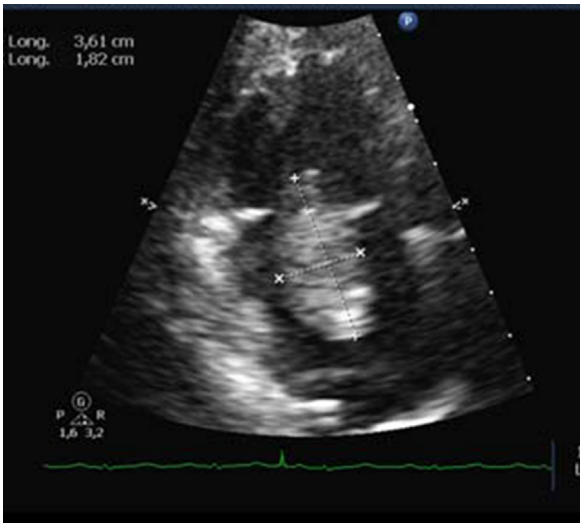

Fig. 4. Transthoracic echocardiography of right heart structures showing tricuspid valve with a large vegetation (36 × 18 mm) suggestive fungal endocarditis.

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 a 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 inable 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 ≥ 1 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 in azole 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

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 *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.

Acknowledgments

MA. Romera, B. Lobo and P. Galdos for reviewing the manuscript.

References

[1] A. Bhaskaran, S.M. Hosseini-Moghaddam, C. Rotstein, S. Husain, Molds infections in lung transplant recipients, Semin. Respir. Crit. Care Med. 34 (2013) 371–379.
[2] A.M. Tortorano, M. Richardson, E. Roilides, A. van Diepeningen, M. Caira, P. Muñoz, et al., ESCMID and ECMM joint guidelines on diagnosis and management of hyalohyphomycosis: *Fusarium* spp., *Scedosporium* spp. and others, Clin. Microbiol. Infect. 20 (2014) 27–46.
[3] M.V. Castelli, M.J. Buitrago, L. Bernal-Martínez, A. Gómez-López, J.L. Rodriguez-Tudela, M. Cuenca-Estrella, Development and validation of a quantitative PCR assay for diagnosis of scedosporiosis, J. Clin. Microbiol. 46 (2008) 3412–3416.
[4] F.C. Odds, Synergy, antagonism, and what the chequerboard puts between them, J. Antimicrob. Chemother. 52 (2003) 1.
[5] EUCAST definitive document E.DEF 9.1: EUCAST Technical Note on the method for the determination of broth dilution minimum inhibitory concentration of antifungal agents for conidia-forming moulds. Clin Microbiol Infect, vol. 14, 2008, pp. 982–984.
[6] A. Solé, M. Salavert, Fungal infections after lung transplantation, Curr. Opin. Pulm. Med. 15 (2009) 243–253.
[7] K.J. Cortez, E. Roilides, F. Quiroz–Tellez, J. Meletiadis, C. Antachopoulos, T. Knudsen, et al., Infections caused by *Scedosporium* spp, Clin. Microbiol. Rev. 21 (2008) 157–197.
[8] L.S. Johnson, R.K. Shields, C.J. Clancy, Epidemiology, clinical manifestations, and outcomes of *Scedosporium* infections among solid organ transplant recipients, Transpl. Infect. Dis. 16 (2013) 578–587.
[9] M.L. Fernández-Guerrero, E. Askari, E. Prieto, I. Gadea, A. Román, Emerging infectious endocarditis due to *Scedosporium prolificans*: a model of therapeutic complexity, Eur. J. Clin. Microbiol. Infect. Dis. 30 (2011) 1321–1324.
[10] R. Araujo, M. Oliveira, A. Amorim, B. Sampaio-Maia, Unpredictable susceptibility of emerging clinical moulds to tri-azoles: review of the literature and upcoming challenges for mould identification, Eur. J. Clin. Microbiol. Infect. Dis. 34 (2015) 1289–1301.
[11] C. Biswas, T.C. Sorrell, J.T. Djordjevic, X. Zuo, K.A. Jolliffe, S.C. Chen, In vitro activity of miltefosine as a single agent and in combination with voriconazole or posaconazole against uncommon filamentous fungal pathogens, J. Antimicrob. Chemother. 68 (2013) 2842–2846.
[12] A.M. Kesson, M.C. Bellemore, T.J. O´Mara, D.H. Ellis, T.C. Sorrell, Scedosporium prolificans osteomyelitis in an immunocompetent child treated with a novel agent, hexadecylphospocholine (miltefosine), in combination with terbinafine and voriconazole: a case report, Clin. Infect. Dis. 48 (2009) 1257–1261.
[13] McKeage, K. Posaconazole, A review of the gastro-resistant tablet and intravenous solution in invasive fungal infections, Drugs 75 (2015) 397–406.
[14] A.A. Morris, S.W. Mueller, J.E. Rower, T. Washburn, T.H. Kiser, Evaluation of sulfobutylether-β-cyclodextrin in exposure in a critically ill patient receiving intravenous posaconazole while undergoing continuous venovenous hemofiltration, Antimicrob. Agents Chemother. 59 (2015) 6653–6656.
[15] H.R. Ashbee, R.A. Barnes, E.M. Johnson, M.D. Richardson, R. Gorton, W. W. Hope, Therapeutic drug monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology, J. Antimicrob Chemother. 69 (2014) 1162–1176.
[16] F.M. C Müller, M. Seidler, Characteristic of pathogenic fungi and antifungal therapy in cystic fibrosis, Expert Rev. Anti-Infect. Ther. 69 (2010) 957–964.
[17] S.C. Ko, K.Y. Chen, P.R. Hsueh, K.T. Luh, P.C. Yang, Fungal empyema thoracis. An emerging clinical entity, Chest 117 (2000) 1672–1678.
[18] O. Hilberg, C.U. Andersen, O. Henning, T. Lundy, J. Mortensen, Bendstrup, Remarkably efficient inhaled antifungal monotherapy for invasive pulmonary aspergillosis, Eur. Respire. J. 40 (2012) 271–273.
[19] J. Holle, M. Leichsenring, P.E. Meissner, Nebulized voriconazole in infections with *Scedosporium apiospermum* – case report and review of literature, J. Cyst. Fibros. 13 (2014) 400–402.