JCM Accepts, published online ahead of print on 10 March 2010
J. Clin. Microbiol. doi:10.1128/JCM.01840-09

Disseminated *Scedosporium/Pseudallescheria* infection after double-lung transplantation in patients with cystic fibrosis: case report and review of the literature

Running title: *P. boydii* infection after lung transplantation

Florent Morio,[1,2*] Delphine Horeau-Langlard,[3] Françoise Gay-Andrieu,[1,2] Jean-Philippe Talarmin,[4] Alain Haloun,[3] Michelle Treilhaud,[3] Philippe Despins,[3] Frédérique Jossic,[5] Laurence Nourry,[3] Isabelle Danner-Boucher,[3] Sabine Pattier,[3] Jean-Philippe Bouchara,[6] Patrice Le Pape,[1,2] and Michel Miegeville[1,2]

Laboratoire de Parasitologie-Mycologie, CHU de Nantes, France[1] ; Département de Parasitologie et Mycologie Médicale, Université de Nantes, Nantes Atlantique Universités, EA 1155 – IICiMed, Faculté de Pharmacie, Nantes, France[2] ; Unité de Transplantation Thoracique, CHU de Nantes, France[3] ; Services des Maladies Infectieuses et Tropicales, CHU de Nantes, France[4] ; Laboratoire d'anatomo-pathologie, CHU de Nantes, France[5] ; Laboratoire de Parasitologie-Mycologie, CHU d'Angers, France[6]

***Corresponding author.** Mailing Address : Laboratoire de Parasitologie-Mycologie, CHU de Nantes, Hôtel Dieu, 9 quai Moncousu, 44093 Nantes cedex 1, France. Tel.: +33-2-40-08-40-79; fax: +33-2-40-08-42-49. Email:florent.morio@chu-nantes.fr

Abstract

We report a case of disseminated *Scedosporium*/*Pseudallescheria* infection due to *P. boydii sensu stricto* after lung transplantation in a patient with cystic fibrosis. Dissemination occurred under voriconazole. Despite surgery and combination therapy with voriconazole, caspofungin and terbinafine, the patient died 8 months after transplantation. Previously reported cases are reviewed.

Case report

A 37-year-old woman suffering from cystic fibrosis (CF) was admitted to our institution in April 2008 for double-lung transplantation. Her medical history included diabetes mellitus since 2002, and more than 10 years of airway colonization with *Aspergillus fumigatus* and *Scedosporium/Pseudallescheria*. Since 2006, and while awaiting transplantation, she received oral voriconazole (250 mg, twice a day). Her post-operative course was relatively uncomplicated except for cytomegalovirus infection (CMV) due to a mismatch at the time of transplantation in spite of valganciclovir prophylactic treatment (900 mg/day). The immunosuppressive regimen included tacrolimus (therapeutic range 12-13.5 ng/mL), mycophenolate mophetil (750 mg/day) and prednisone (37.5 mg/day). Oral voriconazole was continued as long-term post-transplantation prophylaxis (250 mg twice a day). Fungal culture of a bronchial secretion performed the day after transplantation was positive for a filamentous fungus routinely identified as *S. apiospermum/P. boydii* (isolate I) but several other respiratory specimens performed over the following weeks were negative. The patient was discharged from hospital on day 45 after transplantation, still taking voriconazole. Voriconazole serum level, checked regularly (1.06, 1.96, 1.69, on days 26, 36 and 50 mg/L respectively) was within therapeutic limits (1-2.5 mg/L) except for two occasions (0.16 and 0.35 mg/L on days 18 and 64 respectively).

In June (day 70), she presented at our hospital with nodules on her legs that had appeared 2 weeks previously. On examination the nodules were fibrous, dermo-hypodermic, measuring 1–2 cm in diameter, and slightly pigmented on the surface. A biopsy was performed. Histopathological microscopic examination (Gomori-Grocott and Periodic Acid-Schiff stainings) revealed an inflammatory infiltrate along with several branched and septate hyaline hyphae (fungal cultures were not performed). Continuation of voriconazole in association

with a reduced dose of corticosteroid was associated with clinical improvement. However, 3 weeks later, a new biopsy was performed and septate hyphae were again seen on direct examination. Fungal culture of this biopsy was positive for *S. apiospermum/P. boydii* (isolate II). At this time, chest computed tomography (CT) was unremarkable and no sign of dissemination was noted on brain CT and the nodules disappeared over the following weeks.

All the while, positive CMV DNAemia was still detected in spite of successive curative treatments with per os valganciclovir (1800 mg/day from day 63 to 80), intravenous ganciclovir (from day 80 to 97) and finally foscarnet (from day 97 to 115 and 138 to 151). Cytomegalovirus infection was associated with fever, leucopenia and digestive symptoms. In August (day 138), a CMV strain resistant to both ganciclovir (L595F mutation on UL97 gene) and foscarnet (E756D mutation on UL54 gene) was detected. Since then CMV infection could not be controlled by antiviral therapy, leading to high viral loads ranging from 5 to 6.7 log10cop/10^6 cells.

At the beginning of November (day 213), while still taking voriconazole, she was referred to our hospital for acute vestibular syndrome, dizziness, and dysarthria. On examination, the patient presented with left complete hemiplegia. Cerebral magnetic resonance imaging revealed a large ischemic region located in the right sylvian area (Figure 1). A few days later, a blood culture (BACTEC Mycosis IC/F, Becton Dickinson, Sparks, Md.) performed on admission was positive on direct examination for branched and septate hyaline hyphae, with terminal conidial cells suggestive of *Scedosporium*/*Pseudallescheria* (Figure 2A). At the same time, a large vegetation was observed on the mitral valve by transesophageal echography. No evidence of dissemination to the kidneys, liver or spleen was detected by CT. Subcultures of the blood culture grew *S. apiospermum*/*P. boydii* (Figure 2B, isolate III). MICs against voriconazole, posaconazole and caspofungin were determined with the E-test (0.002, 3 and >32 µg/mL, respectively) and the isolate was sent to the French National Reference

Center for Mycoses and Antifungals (CNRMA, Institut Pasteur, Paris, France) for antifungal susceptibility testing according to European Committee on Antimicrobial Susceptibility Testing standardized methodology (EUCAST) (27). The antifungal susceptibility profile was in agreement with previous results, with a low MIC to voriconazole (0.5 µg/mL) but higher MICs to posaconazole (≥8 µg/mL) and caspofungin (2 µg/mL).

In light of probable fungal endocarditis emerging while on voriconazole therapy, caspofungin was added on day 220 (70 mg/kg/day as a loading dose followed by 50 mg/kg/day). Three days later, the combination therapy was reinforced with terbinafine (250 mg/day) and caspofungin was increased to 150 mg/day. This combination therapy was associated with clinical improvement allowing valve replacement and excision of the vegetation on day 228. Several septate hyphae and conidial formation typical of *Scedosporium/Pseudallescheria* were observed on direct examination of the vegetation (Figure 2C). Fungal cultures yielded *S. apiospermum/P.boydii* confirming the diagnosis of fungal endocarditis (isolate IV). The day after surgery, a bronchial specimen was also positive for *S. apiospermum/P. boydii* (isolate V). The patient's condition improved slightly in the following days but neurological deterioration with headache was observed on day 240. Death occurred the day after due to a massive cerebral hemorrhage.

Molecular identification of each of the five isolates was performed by amplification and sequencing of a region within the β-tubulin gene (519-bp), calmodulin gene (633-bp), internal transcribed spacer (575-bp) and D1-D2 region of 28S ribosomal DNA (568-bp), and yielded 100%, 99.5%, 99.3 % and 100% homology, respectively, with the sequences (nucleotide accession numbers AJ890121, AJ890207, AY213680 and AY213623) of the type strain of *P. boydii sensu stricto* (CBS 101.22)(14). Random amplified polymorphic DNA (RAPD) genotyping performed using GC70, UBC-701 and UBC-703 primers as described previously revealed a unique RAPD pattern for the five *P. boydii* isolates (9).

Nucleotide sequences have been deposited in GenBank database under accession numbers GU180097 to GU180101, GU186103 to GU186107, GU192438 to GU192442 and GU213261 to GU213265.

Discussion

Scedosporium/Pseudallescheria species are ubiquitous, saprophytic, filamentous fungi found widely in the environment, but are also increasingly recognized as opportunistic pathogens. The clinical spectrum of these infections ranges from localized disease to disseminated infection, with a poor prognosis in solid-organ or Hematopoietic Stem Cell Transplant Recipients (HSCT) transplant recipients and patients with haematological malignancies especially when dissemination or fungemia occur (7, 18, 26). Colonization of the respiratory tract by *Scedosporium/Pseudallescheria* is common in patients with CF, where it is the second most frequent filamentous fungus after *A. fumigatus* with a prevalence ranging from 5.7–10% (6, 21, 31). Despite this high prevalence, disseminated *Scedosporium/Pseudallescheria* infections remain rare in patients with CF, even in highly immunosuppressed patients such as those undergoing lung transplantation (1, 5, 24, 25, 28). Here we present a case involving a patient who had several years of known airway colonization with *S. apiospermum*/*P. boydii* and was admitted to our institution for double-lung transplantation. The patient subsequently developed a fatal disseminated infection due to *P. boydii sensu stricto*.

To the best of our knowledge, only 5 patients with CF who developed invasive scedosporiosis after lung transplantation have been reported in the literature since 1996 (reviewed in Table 1). Most of them had a history of airway colonization with *Scedosporium/Pseudallescheria* before transplantation. All but one were treated with antifungal combinations but the mortality was 100%. The median time from transplantation to the onset of infection was 5

weeks (range, 2 weeks–7,5 months). According to Husain et al., the median time to infection in solid-organ transplant recipients was 4 months in the case of *S. apiospermum* infection and earlier when *S. prolificans* was involved (18). The colonization with *Scedosporium/Pseudallescheria* at the time of transplantation could explain the shorter time to infection in patients with CF. Apart from the present case, dissemination to the skin was noted in two other patients (patients 4 and 5). This highlights that the recovery of filamentous fungi from cutaneous lesions in patients with CF who undergo lung transplantation, even without other clinical manifestations, requires complementary investigations.

In the present case, a fatal outcome occurred despite valve replacement and salvage therapy based on a combination of voriconazole, caspofungin and terbinafine. Regarding the pre-transplantation period, it is interesting to note that *Scedosporium/Pseudallescheria* was isolated repeatedly from respiratory tract specimens from our patient despite long-term voriconazole prophylaxis. Clearly, the fungemia and central nervous system involvement were poor prognostic factors in our patient. Indeed, fungemia has been clearly associated with a higher mortality rate in transplant recipients (18). However, the underlying, rampant and multi-resistant CMV infection in our patient must also be considered. Indeed, CMV infection has been associated with an increased risk of invasive aspergillosis in solid-organ transplant recipients, but data are still lacking for scedosporiosis (10, 19). Finally, the difficulty encountered in maintaining voriconazole plasma levels within therapeutic limits must also be considered. The pharmacokinetic variability of voriconazole levels in patients with CF, that can be responsible to underdosage and therefore inefficacy of antifungal therapy has been described in a previous study showing that voriconazole levels is often undetectable in such patients (3). In our patient cutaneous nodules appeared when the voriconazole serum level was low, despite any discontinuation of voriconazole therapy (day 64, 0.35 mg/L). However,

153 we are not sure that the breakthrough in our patient is the result of voriconazole underdosage,
154 all other dosages, performed monthly, being within the therapeutic range.
155 *Scedosporium/Pseudallescheria* species are generally considered to have a low *in vitro*
156 susceptibility to antifungal drugs that can also differ between species (12). According to both
157 *in vitro* and *in vivo* studies voriconazole could be the most effective antifungal agent, but no
158 recommendations regarding the optimal antifungal therapy for scedosporiosis have yet
159 emerged (12, 29). In particular, the benefit of antifungal combination therapy has not been
160 clearly established despite the increasing number of reports describing a favorable outcome
161 with voriconazole in combination with terbinafine and/or caspofungin (15–17, 22). The *in*
162 *vitro* study of 35 antifungal combinations against *S. apiospermum* and *S. prolificans*
163 describing a potent synergy between azole drugs and echinocandins will probably reopen the
164 debate on combination therapy (8, 23). Promising results obtained with new antifungal agents
165 such as miltefosine remain to be confirmed (20, 30). In the present case, it is interesting to
166 note the reliability of the E-test for MIC determination against *Scedosporium* species, as
167 MICs obtained by E-test were generally correlated with those obtained by the EUCAST
168 method, especially for voriconazole. The moderately high MIC to caspofungin found in this
169 has also been reported by others (8). Despite these high *in vitro* MICs, both caspofungin and
170 terbinafine have been associated with a favorable outcome in clinical practice highlighting
171 that the results of antifungal susceptibility testing must be considered with caution since no
172 correlation between MIC data and clinical success has been described to date for
173 *Scedosporium/Pseudallescheria* (16, 17, 22).
174 Recent advances in molecular methods have led to a revision of *Pseudallescheria* taxonomy,
175 revealing that *Pseudallescheria boydii* is a species complex. Importantly, *P. boydii,* formerly
176 considered as the sexual state of *Scedosporium apiospermum* (i.e. teleomorph), must now be
177 considered as a distinct species and new species have also recently been identified (11, 14).

Despite being difficult and time-consuming in routine practice, identification of *Scedosporium/Pseudallescheria* to the species level is important because virulence and antifungal susceptibility can differ significantly between species (2, 12, 13). Here, molecular typing performed using DNA sequencing at four loci revealed that the five isolates belonged to *P. boydii sensu stricto*. Finally, RAPD genotyping revealed that the five *P. boydii* isolates recovered over a 7.5-month period and from different anatomic sites had the same RAPD pattern, suggesting that a single strain of *P. boydii* was responsible for the breakthrough infection in our patient. Unfortunately, the *Scedosporium/Pseudallescheria* strains isolated before transplantation were not available for analysis.

This report demonstrates again, the rare but mostly fatal, risk of invasive *Scedosporium/Pseudallescheria* infections in patients with CF. In this setting, the utility of a screening of fungal airway colonization to detect patients having a risk of infection need to be discuss. According to a recent article, the choice of media used for culture specimens could influence the rate of recovery of *Scedosporium* species, a better recovery rate being described with SceSel+ media (4). Importantly, without any guidelines, the management of patients colonized with *Scedosporium/Pseudallescheria* remains, at present, mainly based on the own experience of each center and there is probably variations in practice between center/country. In Nantes, France, CF patients are regularly screened for fungal colonization of their respiratory tract. Those being colonized with *Scedosporium/Pseudallescheria* and having a deterioration of lung function are given voriconazole that is in our experience, generally associated with a clinical improvement. Regarding the time to infection, we suggest that both clinical and microbiological surveillance using blood cultures as well as respiratory tract specimens, focused mainly on the first weeks after transplantation, could be beneficial for the early diagnosis of these life-threatening infections. Finally, in light of this and previously

reported cases, several questions must be raised: (1) does *Scedosporium/Pseudallescheria* airway colonization represent a risk factor for invasive infection after transplantation in patients with CF and should it be a contraindication to transplantation ? (2) Is antifungal prophylaxis before and after transplantation really effective in this setting and which antifungal(s) should be administered ? (3) Regarding antifungal therapy, is voriconazole really the most effective drug and what will be the role of new agents such as miltefosine ? Larger studies are now warranted to answer to these questions and establish guidelines for the management of *Scedosporium/Pseudallescheria* in patients with CF.

Aknowledgments

We acknowledge Olivier Lortholary (CNRMA, Institut Pasteur, Paris) for helpful discussion concerning the management of our patient, Eric Dannaoui (CNRMA, Institut Pasteur, Paris) for performing *in vitro* antifungal susceptibility testing of the isolates and Celine Bressollette-Bodin (Laboratoire de Virologie, CHU de Nantes) for interesting comments on CMV disease. We acknowledge Adeline Maitte, Tiphaine Robert and Bernard Besse for their technical assistance.

References

1. **Albernaz, V., B. Huston, M. Castillo, S. Mukherji, and T. Bouldin.** 1996. *Pseudallescheria boydii* infection of the brain: imaging with pathologic confirmation. Am J Neuroradiol.**17:**589-592.

2. **Alastruey-Izquierdo, A., M. Cuenca-Estrella, A. Monzon, and J. L. Rodriguez-Tudela.** 2007. Prevalence and susceptibility testing of new species of *Pseudallescheria* and *Scedosporium* in a collection of clinical mold isolates. Antimicrob. Agents Chemother. **51:**748-751.

3. **Berge M., R. Guillemain, V. Boussaud, M. H. Pham, P. Chevalier, A. Batisse, C. Amrein, E. Dannaoui, M. A. Loriot, A. Lillo-Le Louet, and E. M. Billaud.** 2009. Voriconazole pharmacokinetic variability in cystic fibrosis lung transplant patients. Transpl. Infect. Dis.**11**:211-219.

4. **Blyth C.C., A. Harun, P.G. Middleton, S. Sleiman, O. Lee, T.C. Sorrell, W. Meyer, and S.C Chen.** 2009. Detection of occult *Scedosporium* species in respiratory tract specimens from patients with cystic fibrosis (CF) by use of selective media. J. Clin. Microbiol. Nov 11 [Epub ahead of print]

5. **Castiglioni, B., D. A. Sutton, M. G. Rinaldi, J. Fung, and S. Kusne.** 2002. *Pseudallescheria boydii* (anamorph *Scedosporium apiospermum*). Infection in solid organ transplant recipients in a tertiary medical center and review of the literature. Medicine (Baltimore). **81:**333-348.

6. **Cimon, B., J. Carrere, J. F. Vinatier, J. P. Chazalette, D. Chabasse, and J. P. Bouchara.** 2000. Clinical significance of *Scedosporium apiospermum* in patients with cystic fibrosis. Eur. J. Clin. Microbiol. Infect. Dis. **19:**53-56.

7. **Cortez, K. J., E. Roilides, F. Quiroz-Telles, J. Meletiadis, C. Antachopoulos, T. Knudsen, W. Buchanan, J. Milanovich, D. A. Sutton, A. Fothergill, M. G. Rinaldi,**

Y. R. Shea, T. Zaoutis, S. Kottilil, and T. J. Walsh. 2008. Infections caused by *Scedosporium* spp. Clin. Microbiol. Rev. **21:**157-197.

8. **Cuenca-Estrella, M., A. Alastruey-Izquierdo, L. Alcazar-Fuoli, L. Bernal-Martinez, A. Gomez-Lopez, M. J. Buitrago, E. Mellado, and J. L. Rodriguez-Tudela.** 2008. In vitro activities of 35 double combinations of antifungal agents against *Scedosporium apiospermum* and *Scedosporium prolificans*. Antimicrob. Agents Chemother. **52:**1136-1139.

9. **Defontaine, A., R. Zouhair, B. Cimon, J. Carrere, E. Bailly, F. Symoens, M. Diouri, J. N. Hallet, and J. P. Bouchara.** 2002. Genotyping study of *Scedosporium apiospermum* isolates from patients with cystic fibrosis. J. Clin. Microbiol. **40:**2108-2114.

10. **Gavalda, J., O. Len, R. San Juan, J. M. Aguado, J. Fortun, C. Lumbreras, A. Moreno, P. Munoz, M. Blanes, A. Ramos, G. Rufi, M. Gurgui, J. Torre-Cisneros, M. Montejo, M. Cuenca-Estrella, J. L. Rodriguez-Tudela, A. Pahissa; RESITRA (Spanish Network for Research on Infection in Transplantation).** 2005. Risk factors for invasive aspergillosis in solid-organ transplant recipients: a case-control study. Clin. Infect. Dis. **41:**52-59.

11. **Gilgado, F., J. Cano, J. Gene, and J. Guarro.** 2005. Molecular phylogeny of the *Pseudallescheria boydii* species complex: proposal of two new species. J. Clin. Microbiol. **43:**4930-4942.

12. **Gilgado, F., C. Serena, J. Cano, J. Gene, and J. Guarro.** 2006. Antifungal susceptibilities of the species of the *Pseudallescheria boydii* complex. Antimicrob. Agents Chemother. **50:**4211-4213

13. **Gilgado, F., J. Cano, J. Gene, C. Serena, and J. Guarro.** 2008. Different virulence of the species of the *Pseudallescheria boydii* complex. Med. Mycol. **47**:371-374.

14. **Gilgado, F., J. Cano, J. Gene, D. A. Sutton, and J. Guarro.** 2008. Molecular and phenotypic data supporting distinct species statuses for *Scedosporium apiospermum* and *Pseudallescheria boydii* and the proposed new species *Scedosporium dehoogii*. J. Clin. Microbiol. **46:**766-771.

15. **Grenouillet, F., F. Botterel, J. Crouzet, F. Larosa, Y. Hicheri, J.M. Forel, P. Helias, S. Ranque, and L. Delhaes.** 2008. *Scedosporium prolificans*: an emerging pathogen in France? Med. Mycol. **47:**343-350.

16. **Guignard, S., D. Hubert, B. Dupont, P. Anract, D. Alioua, H. Guerini, A. Paugam, and M. Dougados.** 2008. Multifocal *Scedosporium apiospermum* spondylitis in a cystic fibrosis patient. J. Cyst. Fibros. **7:**89-91.

17. **Howden, B. P., M. A. Slavin, A. P. Schwarer, and A. M. Mijch.** 2003. Successful control of disseminated *Scedosporium prolificans* infection with a combination of voriconazole and terbinafine. Eur. J. Clin. Microbiol. Infect. Dis. **22:**111-1113.

18. **Husain S., P. Munoz, G. Forrest, B. D. Alexander, J. Somani, K. Brennan, M. M. Wagener, and N. Singh.** 2005. Infections due to *Scedosporium apiospermum* and *Scedosporium prolificans* in transplant recipients: clinical characteristics and impact of antifungal agent therapy on outcome. Clin. Infect. Dis. **40:**89-99.

19. **Husni, R.N., S. M. Gordon, D. L. Longworth, A. Arroliga, P. C. Stillwell, R. K. Avery, J. R. Maurer, A. Mehta, and T. Kirby.** 1998. Cytomegalovirus infection is a risk factor for invasive aspergillosis in lung transplant recipients. Clin. Infect. Dis. **26:**753-755.

20. **Kesson, A.M., M. C. Bellemore, T. J. O'Mara, D. H. Ellis, and T. C. Sorrell.** 2009. 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:**1257-1261.

21. **L'Hirondel, J., A. Espern, V. David, D. Horeau-Langlard, M. Besse, and F. Morio.** 2008. Prévalence de la colonisation fongique au cours de la mucoviscidose: étude rétrospective sur 30 mois au CHU de Nantes, abstr. 522/80A, p. 235. Abstr. 28è Réunion interdisciplinaire de chimiothérapie anti-infectieuse, Paris, France.

22. **Li, J.Y., T. Y. Yong, D. I. Grove, and P. T. Coates.** 2008. Successful control of *Scedosporium prolificans* septic arthritis and probable osteomyelitis without radical surgery in a long-term renal transplant recipient Transpl. Infect. Dis. **10:**63-65.

23. **Montoya, J.G., and F. Rosso**. 2006. Is combination therapy indicated for invasive fungal infections? Yes and no. Curr. Opin. Infect. Dis. **19:**357-359.

24. **Morin, O., A. Haloun, M. Treilhaud, C. Sagan, and P. Boiron.** 1999. Systemic mycosis due *Pseudallescheria boydii* in a double transplant patient with a cystic fibrosis. Study of isolated strains with RAPD (Random Amplification of Polymorphic DNA). J Med Mycol. **9:**119-123.

25. **Sahi, H., R. K. Avery, O. A. Minai, G. Hall, A. C. Mehta, P. Raina, and M. Budev.** 2007. *Scedosporium apiospermum* (*Pseudallescheria boydii*) infection in lung transplant recipients. J. Heart Lung Transplant. **26:**350-356.

26. **Solé, A., and M. Salavert.** 2008. Fungal infections after lung transplantation Transplant. Rev. **22:**89-104.

27 **Subcommittee on Antifungal Susceptibility Testing (AFST) of the ESCMID European Committee for Antimicrobial Susceptibility Testing (EUCAST), J. L. Rodriguez-Tudela, M. C. Arendrup, S. Arikan, F. Barchiesi, J. Bille, E. Chryssanthou, M. Cuenca-Estrella, E. Dannaoui, D. W. Denning, J. P. Donnelly, W. Fegeler, C. Lass-Flörl, C. Moore, M. Richardson, P. Gaustad, A. Schmalreck, A. Velegraki, and P. Verweij.** 2008. EUCAST Technical Note on the method for the

determination of broth dilution minimum inhibitory concentrations of antifungal agents for conidia-forming moulds. Clin. Microbiol. Infect. **14**:982-984.

28. **Symoens, F., C. Knoop, M. Schrooyen, O. Denis, M. Estenne, N. Nolard, and F. Jacobs.** 2006. Disseminated *Scedosporium apiospermum* infection in a cystic fibrosis patient after double-lung transplantation. J. Heart Lung Transplant. **25:**603-607.

29. **Troke, P., K. Aguirrebengoa, C. Arteaga, D. Ellis, C. H. Heath, I. Lutsar, M. Rovira, Q. Nguyen, M. Slavin, and S. C. Chen.** 2008. Treatment of scedosporiosis with voriconazole: clinical experience with 107 patients. Antimicrob. Agents Chemother. **52:**1743-1750.

30. **Widmer, F., L. C. Wright, D. Obando, R. Handke, R. Ganendren, D. H. Ellis, and T. C. Sorrell.** 2006. Hexadecylphosphocholine (miltefosine) has broad-spectrum fungicidal activity and is efficacious in a mouse model of cryptococcosis. Antimicrob. Agents Chemother. **50:**414-421.

31. **Williamson, E. C., D. Speers, I. H. Arthur, G. Harnett, G. Ryan, and T. J. Inglis.** 2001. Molecular epidemiology of *Scedosporium apiospermum* infection determined by PCR amplification of ribosomal intergenic spacer sequences in patients with chronic lung disease. J. Clin. Microbiol. **39:**47-50.

Figure legends

Table 1. Clinical characteristics of reported cases of invasive scedosporiosis in patients with cystic fibrosis after lung transplantation

NA: not available; ITC: itraconazole; MIC: miconazole; VRC: voriconazole; POS: posaconazole; AMB: amphotericin B; CAS: caspofungin; TRB: terbinafine; LTx: lung transplantation; CNS: central nervous system.

[1]Diagnosis was made on brain biopsy.

[2]Intraocular miconazole.

Figure 1. Cerebral magnetic resonance imaging showing a large ischemic region located in the right area.

Figure 2. (A) Direct microscopic examination of the blood culture showing hyphae and conidia (x 500). (B) Lactophenol cotton blue stain of the fungal culture from blood showing septate hyphae and sessile conidia (x 1000). (C) Direct examination of the cardiac vegetation showing several septate hyphae along with conidial formation (x 400).

Patient	Age	Sex	Colonization before LTx	Antifungal prophylaxis after LTx	Time to diagnosis after LTx	Mycological identification	Antifungal therapy	Sites / clinical manifestations	Survival after the diagnosis	Outcome	Reference
1	27	M	NA	NO	6 weeks[1]	*S. apiospermum/P. boydii*	AMB	CNS	NA	death	(1)
2	24	F	NO	NO	7,5 months	*S. apiospermum/P. boydii*	ITC+MIC	Heart, spleen, kidneys, CNS	4 weeks	death	(24)
3	30	M	YES	NO	2 weeks	*S. apiospermum/P. boydii*	AMB+MIC	Pneumonia, pleuritis, pericarditis	1 week	death	(5)
4	26	F	YES	YES (ITC, AMB)	3 weeks	*S. apiospermum/P. boydii*	VRC+MIC[2]	Skin nodules, endophtalmitis, meningitis	6 months	death	(23)
5	19	F	YES	YES (VRC)	4 weeks	*S. apiospermum/P. boydii*	VRC+CAS−TRB followed by POS	Skin nodules, endophtalmitis, pansinusitis, chest wall cellulitis, mediastinis, vertebral osteomyelitis, septic arthritis	14 months	death	(25)
6	37	F	YES	YES (VRC)	3 weeks	*P. boydii*	VRC+CAS−TRB	Skin nodules, endocarditis, CNS	6 months	death	This article