Scedosporium prolificans: an emerging pathogen in France?

FREDERIC GRENOUILLET*, FRANÇOISE BOTTEREL§, JULIEN CROUZET*, FABRICE LAROSA†, YOSR HICHERI', JEAN-MARIE FOREL+/, PHILIPPE HELIAS†, STEPHANE RANQUES§ & LAURENCE DELHAES#

*Mycology-Parasitology and †Hematology Units, University Hospital J. Minjoz, Besançon, ‡UMR CNRS 6249, University of Franche-Comté, Besançon, §Mycology-Parasitology and ††Hematology Units, University Hospital H. Mondor, Créteil, +Medical Intensive Care Unit, Sainte Marguerite Hospital, AP-HM, and §Department of Mycology-Parasitology, La Timone Hospital, University of La Méditerranée, Marseille, and #Department of Mycology-Parasitology – Lille University Hospital, and EA3609 – Lille 2 University, France

For the last ten years, non-Aspergillus mold species have been increasingly involved in human invasive infections, probably as a consequence of more intense immunosuppression and prolonged patient survival, and of selective pressure since antifungal agents are currently used for prophylaxis or therapy. Scedosporium prolificans, one of these emerging fungi, has been isolated in a broad spectrum of clinical presentations in humans, including respiratory-tract colonization, superficial or locally invasive infections, and disseminated infections in immunocompromised patients. Here, we report the recent emergence of invasive infections due to S. prolificans in France, and describe four new cases diagnosed during the last six years. Only one disseminated scedosporiosis has been reported before this in France, in 1994. Three out of our four cases were breakthrough infections in immunocompromised patients receiving posaconazole or voriconazole therapy. The aims of the present review were thus to gain a better understanding of scedosporiosis epidemiology and clinical features, and to review recent advances in multimodal management of these infections, including surgery, recovery and/or enhancement of immunity, and antifungal combinations, especially voriconazole plus terbinafine.

Keywords Scedosporium prolificans, mold, emerging infectious diseases, antifungal agents, active immunotherapy, breakthrough infections
common cause of disseminated phaeohyphomycosis [1,4,6,7,9,10]. Infections due to *S. prolificans* are frequently refractory to treatment, and it is thus one of the most harmful opportunistic pathogens in highly immunosuppressed patients [5,11].

*S. prolificans* has been isolated predominantly from agricultural soils and potted plants [12]. Its worldwide distribution is heterogeneous: most of the environmental and clinical isolations described are from the Iberian Peninsula, Australia, and less frequently from California and the South of the United States [5].

In France, one case of *S. prolificans* invasive infection was reported in 1994 [13]. Here, we describe its emergence in France, with three disseminated scedosporiosis and one pulmonary invasive infection diagnosed during the last six years. Based on our experience and on a few reports of therapeutic success in the literature, proposals for optimal management of these infections are discussed; current epidemiological and clinical data are also reviewed.

**Case reports**

Scedosporiosis is usually described as a complication linked to hematological malignancies such as acute leukemia. Here we report the main characteristics of recent cases in France diagnosed with invasive infections due to *S. prolificans* (see specific details in Table 1). The patients originated from three different geographic areas: Eastern, Southern and Northern France (respectively, in Besançon, Marseille and Paris). These areas differ considerably from one another in climate and degree of urbanization. All patients presented with underlying hematological disorders, including three recipients of an allogeneic hematopoietic stem cell transplantation (alloHSCT), which is one of the highest risk factors for developing invasive mycosis (patients 2, 3 and 4 – Table 1).

**Case 1**

A 68-year-old man, with lymphocytic lymphoma associated with neutropenia, developed febrile pneumonia which deteriorated rapidly and became disseminated mycosis. *S. prolificans* was isolated from both sputum and blood culture. Despite implementation of an antifungal combination (Table 1), further invasion of the left cavernous sinus was shown on CT-scan. No response was observed, despite increased doses of amphotericin B of up to 1.8 mg/kg/day. The patient died 24 days after diagnosis.

**Case 2**

A 44-year-old man with chronic myeloid leukemia underwent allogeneic bone marrow transplantation and developed chronic graft versus host disease (GVHD); immunosuppressive therapy was administered (Table 1).

After 70 days of hospital stay (admitted for pulmonary legionellosis) he developed disseminated scedosporiosis following primary gingival abscess (Table 1). A combination of voriconazole (800 mg/day) and terbinafine (750 mg/day) was implemented, and the immunosuppressive therapy prescribed for GVHD control was partially reduced. Unfortunately, a temporary national shortage of terbinafine during the summer of 2004 gave physicians no other choice but to prescribe voriconazole monotherapy. Concomitantly, patient status deteriorated rapidly, with progressive multivisceral failure and death on day 559 post-alloHSCT, despite a re-implementation of the bitherapy. Although scedosporiosis occurred about 70 days after hospital admittance, *S. prolificans* was not isolated from air and surface samples from the patient’s environment (*n* = 27), making it impossible to prove the nosocomial origin of this case of scedosporiosis.

**Case 3**

On day 300 post-alloHSCT, a 67-year-old man, on immunosuppressive therapy for chronic GVHD, developed febrile pneumonia which was diagnosed as possible pulmonary aspergillosis (*Aspergillus ustus* isolated from bronchoalveolar lavage (BAL), repeated positive galactomannan antigenemia with no concomitant typical CT-scan abnormalities). Curative therapy with voriconazole (800 mg/day) was implemented. Three weeks later, he developed disseminated scedosporiosis; *S. prolificans* was isolated from blood cultures, urine and BAL (Table 1). Six days after diagnosis, he developed multiple organ failures and died despite implementation of a voriconazole-caspofungin combination.

**Case 4**

A 41-year-old man developed clinical signs of pulmonary invasive aspergillosis one month before alloHSCT for Hodgkin’s disease. He was treated with voriconazole, followed by posaconazole (severe liver intolerance to voriconazole). Three months after transplantation, CT-scan showed multiple nodules. Pulmonary scedosporiosis was diagnosed after isolation of *S. prolificans* from respiratory samples (sputum, BAL). Infection remained localized, and there was no evi-
Table 1  Main characteristics of *Scedosporium prolificans* infection cases diagnosed in France since 2001.

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Sex, Age</th>
<th>Year of diagnosis/Geographic origin</th>
<th>Underlying disease, immunosuppression (Antifungal previous exposure)</th>
<th>Symptoms Site(s) of isolation (with respect to chronology of positivity)</th>
<th>Antifungal management of infection **** in chronologic order (Duration)</th>
<th>Outcome (Follow-up after diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 M*, 68 yrs</td>
<td>2001 Besançon (Eastern France)</td>
<td>Lymphocytic lymphoma, with neutropenia</td>
<td></td>
<td>Pneumonia then dissemination <em>Sputum</em>, <em>blood</em>²</td>
<td>1) AMB + ITC (21 days)</td>
<td>Death 24 days</td>
</tr>
<tr>
<td>2 M, 44 yrs</td>
<td>2004 Besançon</td>
<td>LMC AlloHSCT** (508 days post-HSCT) with chronic extensive GVHD*** treated with tacrolimus, corticoids, and mycophenolate mofetil Breakthrough during VRC “prophylaxis” (5 months)</td>
<td></td>
<td>Gingival abscess then dissemination <em>Gingival abscess, blood</em>³, <em>urine, trachea</em></td>
<td>1) VRC + TRB (18 days)  2) VRC (8 days)  3) VRC + TRB (12 days)</td>
<td>Death 40 days</td>
</tr>
<tr>
<td>3 M, 67 yrs</td>
<td>2005 Marseille (Southern France)</td>
<td>Hodgkin’s disease AlloHSCT (300 days post HSCT), with chronic extensive GVHD treated with corticoids and cyclosporine Breakthrough during VRC curative treatment (3 weeks)</td>
<td></td>
<td>Pneumonia then dissemination <em>BAL</em>**, blood*, <em>urine</em></td>
<td>1) VRC (1 day)  2) VRC + CAS (5 days)</td>
<td>Death 6 days</td>
</tr>
<tr>
<td>4 M, 41 yrs</td>
<td>2006 Créteil (Northern France, near Paris)</td>
<td>Hodgkin’s disease AlloHSCT (85 days post HSCT), GVHD prophylaxis with cyclosporine Breakthrough during VRC (3 months) then PSC curative treatment (1 month)</td>
<td></td>
<td>Pneumonia with no further dissemination <em>Sputum, BAL</em>⁵</td>
<td>1) PSC and stop cyclosporine (3 weeks)  2) PSC + L-AMB + IFN-γ + G-CSF (2 weeks)  3) L-AMB + G-CSF (2 weeks)  4) L-AMB + TRB + IFNγ (6 weeks)  5) TRB (17 months)</td>
<td>Survival 600 days</td>
</tr>
</tbody>
</table>

Notes: M*: male, AlloHSCT**: allogeneic hematopoietic stem cell transplantation, GVHD***: graft versus host disease, BAL****: bronchoalveolar lavage.

**** Drug abbreviations: AMB, Amphotericin B; ITC, Itraconazole; VRC, Voriconazole; TRB, Terbinafine; CAS, Caspofungin; PSC, Posaconazole; L-AMB, Liposomal amphotericin B; IFN-γ, Interferon gamma; G-CSF, Granulocyte colony stimulating factor. Duration of each treatment was given in brackets.

Strains deposited at the BCCM™/IHEM, Scientific Institute of Public Health, Brussels, Belgium and the National Reference Center for Mycoses and Antifungals (CNRMA), Pasteur Institute, Paris, France: ¹IHEM 18756, ²IHEM 18755, ³IHEM 23387 (diagnosis), ⁴IHEM 23388 (death), ⁵CNRMA 2005/00693, ⁶CNRMA 2006/00707.
dence of dissemination. An antifungal combination, liposomal amphotericin B (3 mg/kg/day two weeks then 5 mg/kg/day) plus terbinafine (250 mg/day), was implemented, as no improvement with posaconazole (800 mg/day) was observed. Adjunct immune therapy including interferon gamma (IFN-γ), granulocyte colony stimulating factor (G-CSF) and immunoglobulin was added to antifungals.

The patient had clinically improved 3 months later, and he was given thereafter only terbinafine monotherapy (250 mg/day). Now, more than 20 months afterwards, still on terbinafine treatment, his condition is favorable.

Discussion

Update on the clinical features of S. prolificans infection

The main characteristics of S. prolificans disseminated infections, according to the definition by Husain et al. [14], have been reported in the recent literature [5,15]: sex ratio 1.2 males vs 1 female, hematological malignancies as underlying disease for 82% of the patients, neutropenia reported in 73% of cases, concomitant immunosuppressive therapy in 84% at time of scedosporiosis diagnosis. Three out of our four patients had developed GVHD, and were on immunosuppressive therapy. All our patients were male. Males seem to be at higher risk for S. prolificans infection, perhaps because underlying malignancies such as acute leukemia are more frequent in males than in females [6,16].

Primary clinical localizations were pulmonary and/or sinusal for two-thirds of the patients. In one-third of cases, skin lesions were observed. S. prolificans was isolated predominantly from respiratory sites of patients (Table 1), which is in agreement with most of the clinical manifestations reported and is the most frequently-suggested path of entry (aerogenous infection route) [5,6,11,15,17]. Blood cultures were positive for S. prolificans in 70–80% of patients, similar to Fusarium sp. blood isolation during disseminated fusariosis [2,5,8,15]. The lethality rate was over 90%.

Only 11 patients, among the 119 cases identified in the literature and conference proceedings, survived disseminated scedosporiosis [7,10,14,18–22]. Survivor history analyses should help us in managing these infections, and in identifying several key points.

Advances in scedosporiosis management

We reviewed the disseminated scedosporiosis survivors reported in the literature (see Table 2), and summarized the recent advances in management of these refractory opportunistic fungal infections.

Briefly, a combinative approach using (i) surgery when the site of infection can be removed, (ii) immunoreconstitution, and (iii) combination of antifungal agents is recommended.

Four out of the 11 survivors underwent surgery (Table 2). Surgery should be considered for patient management when possible, although successful outcomes without surgery have been reported for locally invasive scedosporiosis [23,24]. In the four patients, debridement of spine or joint lesions was performed, and repeated in two cases. In one case, surgical decompression of sinus was also associated with laminectomy and repeated. A recent review of infections caused by S. prolificans or S. apiospermum in transplant patients underlined that surgery, as an adjunctive treatment, improves survival rates [14]. Patients with pulmonary lesions who underwent adjuvant surgery had a lower mortality rate than those who did not [14].

The enhancement of patients’ immune response is without a doubt a key point for a favorable outcome. Clinical as well as experimental data highlight not only the role of innate immunity, but also collaborative effects between immunoreconstitution and antifungal treatments. Neutrophil activity can be improved using granulocyte or granulocyte-macrophage growth factors (G-CSF, GM-CSF), granulocyte transfusion, or IFN-γ. These factors are known to be associated with enhanced activity of antifungal agents at the experimental level, and to a better outcome at the clinical level [20,25,26]. GM-CSF increased hyphal damage induced by posaconazole in ex vivo study [26]. All the neutropenic patients who survived disseminated scedosporiosis (n=5) received hematopoietic growth factor, administered to help them recover from their neutropenia. Granulocyte transfusions might be of interest when patients remain neutropenic, both to temporarily offset neutropenia and to induce potential collaborative effects, as in in vitro studies in which synergistic activity between granulocytes and antifungal agents (azoles, amphotericin lipid complex) has been observed [25,27,28]. In vitro studies have also demonstrated enhancement of polynuclear cell activity against S. prolificans by adjunction of IFN-γ, especially when combined with GM-CSF [29]. Cytokines and antifungal drugs have been combined to successfully treat invasive mold infection: IFN-γ, G-CSF and an antifungal combination was able to cure brain abscesses due to S. prolificans in a patient with chronic granulomatous disease [25]. IFN-γ therapy was also used in combination with G-CSF and antifungal drugs to treat the remaining living patient in our study (patient 4, Table 1). These data emphasize the benefit of immune
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Underlying disease, immunosuppression</th>
<th>Clinical symptoms</th>
<th>Surgery</th>
<th>Antifungal therapies used***</th>
<th>Adjunctive immunotherapy</th>
<th>Follow-up after diagnosis</th>
</tr>
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<tbody>
<tr>
<td>[18]</td>
<td>M, 30 yrs Intradavenous drug use</td>
<td>Endocarditis, hip arthritis</td>
<td>Arthroscopy (hip drainage)</td>
<td>AMB + 5FC 93 days</td>
<td>Not performed</td>
<td>1 year</td>
</tr>
<tr>
<td>[10]</td>
<td>M, 4 yrs Aplastic anemia, neutropenia</td>
<td>Severe esophagitis, liver and spleen microabscesses</td>
<td>Not performed</td>
<td>1) AMB + 5FC 8 weeks 2) Miconazole IV 6 weeks 3) Fluconazole</td>
<td>GM-CSF****</td>
<td>&gt; 100 days</td>
</tr>
<tr>
<td>[20]</td>
<td>F, 74 yrs Acute leukemia, neutropenia</td>
<td>Skin &amp; multiple lung infiltrates</td>
<td>No data</td>
<td>1) AMB 12 days 2) L-AMB + ITC</td>
<td>G-CSF</td>
<td>No data</td>
</tr>
<tr>
<td>[20]</td>
<td>M, 48 yrs Acute leukemia, neutropenia</td>
<td>Skin, bone involvement-later lung infiltrates</td>
<td>Excision of infected rib</td>
<td>1) AMB 2 weeks 2) Fluconazole</td>
<td>Not performed (recovery from neutropenia)</td>
<td>No data</td>
</tr>
<tr>
<td>[7]</td>
<td>F, 55 yrs Breast cancer, autoHSCT**</td>
<td>Fever without focal signs of infection</td>
<td>Not performed</td>
<td>ITR</td>
<td>GM-CSF (implemented before scedosporiosis diagnosis)</td>
<td>No data</td>
</tr>
<tr>
<td>[7]</td>
<td>H, 28 yrs Intradavenous drug use, VIH</td>
<td>Diarrhea, interstitial pneumonia</td>
<td>Not performed</td>
<td>No antifungals (antibiotics and antiviral for cytomegalovirus, Pneumocystis jiroveci and Clostridium difficile infections)</td>
<td>Not performed (death not related to infection)</td>
<td>3 months</td>
</tr>
<tr>
<td>[19]</td>
<td>F, 53 yrs Multiple myeloma, autoHSCT</td>
<td>Extensive sinusitis 4 months later discitis and osteomyelitis L2, L3 &amp; L5, S1</td>
<td>1) Surgical decompression of sinusitis (three times) 2) Laminectomy and discectomy of L5, S1 3) Laminectomy and debriement of L2, L3 4) Excision of hepatic artery mycotic aneurysm</td>
<td>1) ITC 2 months 2) No antifungals 2 months 3) ITC + TRB 2 weeks 4) VRC + TRB 15 months</td>
<td>GM-CSF</td>
<td>18 months</td>
</tr>
<tr>
<td>[14]</td>
<td>M, 40 yr Kidney/pancreas transplant with tacrolimus therapy</td>
<td>Brain and pulmonary abscesses</td>
<td>No data</td>
<td>VRC</td>
<td>No data</td>
<td>20 months</td>
</tr>
<tr>
<td>[22]</td>
<td>F, 8 yr Acute leukemia, chemotherapy</td>
<td>Multiple pulmonary lesions, arthritis (knee, elbow, shoulder), L2 osteomyelitis and L2/L3 discitis</td>
<td>Repeated open surgical washout of infected joints L2/L3 laminectomy and disc debriement</td>
<td>1) AMB 2) VRC + TRB</td>
<td>G-CSF</td>
<td>No data</td>
</tr>
<tr>
<td>[25]</td>
<td>M, 23 yr Chronic granulomatous disease</td>
<td>Brain abscesses</td>
<td>Not performed</td>
<td>No data</td>
<td>No antifungals (antibiotics and antiviral for cytomegalovirus, Pneumocystis jiroveci and Clostridium difficile infections)</td>
<td>No data</td>
</tr>
<tr>
<td>[21]</td>
<td>M, 61 yr Myeloid acute leukemia, alloHSCT, GVHD treated by mycophenolate and corticosteroids</td>
<td>Isolated fever One month later endophtalmatitis</td>
<td>Not performed</td>
<td>1) ABLC +/- CAS 11 weeks 2) ITC +/- CAS 8 weeks 3) L-AMB + CAS 8 weeks 4) L-AMB + VRC + CAS 12 weeks 5) L-AMB + PSC 10 weeks 6) VRC + TRB 10 months</td>
<td>Granulocyte transfusions IFN-γ G-CSF</td>
<td>22 months</td>
</tr>
</tbody>
</table>

Notes: *Ref: Reference; **autoHSCT: autologous hematopoietic stem cell transplantation; *** Drug abbreviations: 5FC, 5-fluorocytosine, **** GM-CSF: Granulocyte-macrophage colony stimulating factor.
enhancement strategies for the management of refractory invasive mycosis, particularly *S. prolificans* infections, in immunocompromised patients [30–33]. Immunosuppressive therapies need to be decreased or stopped when possible [19], but this may not be a possibility for patients with severe GVH disease, as in the case of patient 2 in our study.

The implementation of antifungal combinations would seem to be mandatory for treatment of invasive scedosporiosis.

Antifungal combinations were used in eight out of the 11 survivors (Table 2). *S. prolificans* is known to be naturally resistant to almost all antifungal drugs; available systemic antifungals exhibit high levels of MICs against *S. prolificans* isolates [34–36]. Voriconazole plus terbinafine is probably the most effective combination and has been recently recommended by several authors [22,37]. Experimental studies and case reports have demonstrated the in *vitro* synergy of this association [19,21,36]; however, a recent study was not able to provide total confirmation of this data [35]. *In vivo*, this combination has been successfully used to manage three disseminated infections due to *S. prolificans* in the past six years [19,21,22], and to treat locally invasive scedosporiosis [23–25]. Patient 2 in our study was stable when we were able to use this combination, and deteriorated rapidly when it had to be interrupted. The development of new antifungal agents which are effective against *S. prolificans* could provide an alternative. Albaconazole (UR-9825) has shown promising in *vitro* activity against *S. prolificans* in animal models [38]. However, no phase 3 data are currently available for this new triazole [39]. As for treatments of other opportunistic fungi, the use of monotherapy, even based on the newer triazole agents such as voriconazole and posaconazole, are recommended less and less for management of disseminated infections [35–37,40].

*Scedosporium* and scedosporiosis epidemiology: what’s new?

We report four new cases of infection due to *S. prolificans* which have occurred in France within the past six years: only one similar case was described in France before 2001 [13]. We hypothesized that there is a probable emergence of this fungus in France. While the heterogeneous geographic distribution of *S. prolificans* infections has been solidly documented in more than 80% of cases occurring in Spain and Australia [5,15], the existence of specific environmental niches for this species, perhaps climatically and/or geographically restricted, is still under debate. Under-diagnosis in other geographical areas should not be excluded [5]. Our four patients originated from three different French areas, which differ greatly in climate, urbanization and flora. This probably reflects a wide geographical distribution of *S. prolificans* infections. Twelve cases of scedosporiosis due to *S. prolificans*, including six disseminated infections, have been recently documented in Germany [41].

The emergence of rare mold infections, reported primarily in severely immunocompromised patients, is probably multifactorial [40]. This trend could be related to more intense immunosuppression associated with the prolonged survival of patients, and to the selective pressure of antifungal agents used for prophylaxis or therapy [40]. Of our four patients, three can be considered as breakthrough infections during prophylactic or curative therapy with the new broad-spectrum azole antifungal drugs, i.e. posaconazole and voriconazole. Patient 2 received a 5-month voriconazole prophylaxis (400 mg/d) for invasive fungal infections. Curative therapy with voriconazole had been administered to patient 3 for three weeks before scedosporiosis was diagnosed. Aspergillosis curative treatment using voriconazole followed by posaconazole had been given to patient 4 for four months when scedosporiosis was diagnosed (Table 1). Our observations are in agreement with recent published case reports of breakthrough scedosporiosis during azole therapy [4,21,25,42,43], which could indicate a potential increase of the incidence of *S. prolificans* infections in the near future.

Conclusion

In conclusion, we have reported the emergence of invasive infections due to *S. prolificans* in France, with the descriptions of four new cases within the past six years. The occurrence of these uncommon infections could be related to an increased use of broad-spectrum antifungal azoles, for prophylaxis or therapy, as three out of these four scedosporiosis cases were breakthrough infections during posaconazole or voriconazole monotherapy. We also reviewed the current data on optimization of complex management of scedosporiosis, including surgery, recovery and/or enhancement of immunity, and antifungal combinations, especially voriconazole plus terbinafine.

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