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Epidemiology and outcome of *Scedosporium prolificans* infection, a review of 162 cases

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Scedosporium prolificans is a truly emerging fungal pathogen. It has only been recognized as a human pathogen for 22 years and has been related with numerous infections in immunocompromised and immunocompetent patients. A search for cases in the literature was performed and a database was constructed. Cases were reviewed in order to analyse the epidemiology and outcome of infection. A total of 162 cases were included. The median age of patients was 45 years (ranging from a few months to 81 years), and 102 (63%) infections were diagnosed in males. Risk factors for scedosporiosis were malignancy, 74/162 (45.7%), cystic fibrosis, 19/172 (11.7%), and solid organ transplantation 14/162 (8.6%). The most common clinical presentations were disseminated infection, 72/162 cases (44.4%), pulmonary mycosis, 47/162 (29%), and bone and joint infections, 17/162 (10.4%). All disseminated infections afflicted patents with underlying diseases, primarily haematological malignancies (57/72 [80%]). Blood cultures were positive in 70% of patients suffering from disseminated mycosis. Neutropenia, fever and cerebral symptoms were independently related to the development of disseminated infection whereas recovery from aplasia was associated with a reduced risk. The overall mortality was 46.9% but mortality rate was 87.5% in patients with disseminated disease. Survival was independently associated with surgical excision and recovery from aplasia. Antifungal treatments were not related to a reduced risk of death. Infections caused by *S. prolificans* are life threatening in susceptible patients, and can be considered a truly emerging disease. Infections are difficult to treat since it is a multi-resistant species. Multicenter studies are essential with the aim of developing and disseminating appropriate techniques and protocols to treat this mycosis.

Keywords *Scedosporium prolificans*, risk factors, treatment

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Introduction

'Scedosporiosis' is a clinical term used to describe infections caused by the two main species of the genus *Scedosporium*, *Scedosporium apiospermum* – the anamorph (asexual state) of the ascomycete *Pseudallescheria boydii* – and *Scedosporium prolificans*. Both are significant opportunists with very high levels of antifungal resistance.

Despite its rather frequent occurrence in clinical settings, the history of *S. prolificans* is remarkably short. In 1974, Hennebert and Desai [1] described this morphologically well-recognizable fungus (as *Lomentospora prolificans*) from greenhouse soil. Ten years later, this species was rediscovered by Malloch and Salkin (as *Scedosporium inflatum*) from disseminated infections in immunocompromised hosts [2]; the identity of these two taxa was recognized in 1991 by Guého and de Hoog [3] on molecular grounds. Since then, numerous strains have been recovered, nearly all from clinical cases with major immunosuppression, and because no older reports of cases in immunocompetent patients are known, the species is a truly emerging opportunist [4]. Infections by *S. prolificans* are more recent than those by *S. apiospermum*. Initially *S. prolificans* was found to cause mainly bone and soft tissue infections in immunocompetent individuals. The first disseminated and fatal cases were reported in Europe in 1992 [5,6]. *S. prolificans* seems to be more virulent than *S. apiospermum*. In addition it is more resistant to antifungals, tolerating virtually all systemically active antifungal agents including the new triazoles and echinocandins.

The present review analyses the epidemiology and the outcome of 162 cases caused by *S. prolificans*, including 153 cases published in English-language, Spanish-language and French-language literature and 9 additional unpublished cases reported here for the first time.

Material and methods

Literature search

A MEDLINE (National Library of Medicine, Bethesda, Maryland) search was undertaken using the following key words: *Scedosporium prolificans, Scedosporium inflatum, Lomentospora prolificans,* Scedosporiosis, as well as text word searching. In addition, the reference sections of the articles obtained by MEDLINE search were reviewed. All references identified were included in a database. In addition, 9 unpublished cases were also incorporated. Articles in English, Spanish and French were included.

Criteria for inclusion of case reports

Documentation of infection. All cases with a positive culture for *Scedosporium prolificans* were included in the database. In case of negative culture during the patients' life, the inclusion in the database required the demonstration of the infection at autopsy by culture of the causative agent from the affected organs.

Anatomical location of infection. Documentation of the primary site of the infection was required. The definitions employed were the following. (i) *Disseminated infections* were defined by the isolation of *S. prolificans* from two or more noncontiguous sites showing clinical or histological evidence of infection, and/or positive blood cultures; (ii) *Localized infections* were defined by the isolation of the fungus from a clinically infected site without positive blood cultures or evidence of dissemination to distant organs. Despite all cases having positive cultures for *S. prolificans,* there were several cases difficult to classify mainly because the only clinical data was a positive culture for *S. prolificans* associated with unspecific symptoms and/or signs.

Database development

A database in the software Statistical Package for the Social Sciences (SPSS, version 14.0) (SPSS S.L., Madrid, Spain) was developed with categorical and continuous variables. The categorical variables included sex, underlying disease, neutropenic status, administration of corticosteroids and/ore other immunosuppressive drugs, bone marrow transplantation (BMT), previous traumatism, previous surgery, existence of fever, symptoms related to involvement of central nervous system (CNS), skin lesions related to haematogenous spread, muscular pain, radiological findings, positive clinical samples for *S. prolificans,* concomitant isolation of other fungi, antifungal prophylaxis, antifungal chemotherapy, surgery, administration of colony stimulating factors, recovery from aplasia, localized or disseminated infection at necropsy and visualization of conidia in necropsy specimens. The continuous variables included year of publication, age of patient, number of positive cultures and number of organs involved at autopsy.

Statistical analysis

Descriptive statistical methodology was applied to the database. Univariate analyses were conducted to determine the association between potential risk factors and disseminated infection or death. Categorical

variables were compared with Chi-square or Fisher's exact test. All variables with a P value of <0.20 on univariate analysis were considered for inclusion in a multivariate model as were those variables noted to be confounders on stratified analysis. Multivariate analysis was performed using logistic regression methods. A 2-tailed P value of <0.05 was considered to be statistically significant. All statistical calculations were performed using SPSS 14.0 for windows (SPSS. Inc., Madrid, Spain).

Results

One hundred and sixty two cases were included in the database. The cases have been reported in references [4–60]. Nine of them are unpublished cases.

Demographic and epidemiological characteristics

The demographic characteristics and the underlying conditions are summarized in Table 1. The median age (range) of patients was 45 years (0 to 81 years). There were a total of 102 males (63%) and 50 females (37.2%). Sex was not reported in ten cases (6.2%). The overall mortality was 46.9%. Infections caused by *S. prolificans* occurred primarily in males (102 [63%] of 162 cases).

Malignancy was the most common underlying disease (45.7%) followed by cystic fibrosis (11.7%) and solid organ transplantation (8.6%). Thirty-four patients had not any underlying disease but 82% of them had suffered surgery or traumatism before the acquisition of the infection. Rest of underlying diseases is shown in Table 1.

Patterns and site of infection

Table 2 shows the patterns of infection caused by *S. prolificans* as well as the proportion of patients who died. The pattern of the infection varied as a function of the underlying disease (Table 3).

Disseminated infections. A total of 72 cases of disseminated infections were included. Disseminated infections were more frequent in patients with malignancies (81.9%). Fifty-seven out of 59 malignancies were haematological (96.6%). Forty-six patients (63.9%) were neutropenic and 12 (16.7%) had suffered a BMT. The most frequent symptoms were fever (90.3%), symptoms associated with involvement of central nervous system (40.3%), skin lesions related to haematogenous spread (30.6%) and muscular pain (12.5%). The most frequent radiological finding was lung lesions (38 cases; 52.7%). No lesions were reported in 10 cases (13.9%) and in 11 cases (15.3%), no radiological investigation was mentioned. In all cases, *S. prolificans* was isolated from clinical samples except in six patients where the samples were taken in the necropsy. In fifty-two patients (72.2%), blood cultures were positive. Only in one patient, *Aspergillus fumigatus* was isolated accompanying *S. prolificans*. There was information about the number of positive cultures in 69 cases of 72 (62.5% had ≥ 2 positive cultures: range 2–10). In addition, in 40 (55.5%) cases, there was

Table 1 Demographic and clinical characteristics of 162 patients infected or colonized by *Scedosporium prolificans*

Characteristics	Number of patients (%)	Number of patients who died (%)
Age, years		
Mean	41.9	
Median	45	—
Range	0–81	—
Gender		
Male	102 (63)	52 (51)
Female	50 (37.2)	27 (54)
Not-reported	10 (6.2)	1 (10)
No underlying condition at time of infection, cause of infection		
Trauma	18 (11.1)	0 (0)
Surgery	5 (3.1)	0 (0)
None	11 (6.8)	0 (0)
Underlying condition at time of infection		
Malignancy	74 (45.7)	63 (85.1)
Cystic fibrosis	19 (11.7)	0 (0)
Solid organ transplantation	14 (8.6)	7 (50)
AIDS	8 (4.9%)	3 (37.5)
Other[a]	13 (8%)	3 (23.1)

[a]Includes: immunological disorders (4); chronic obstructive pulmonary disease (COPD) (2); injection drug use (2); bronchiectasis (1); pulmonary fibrosis 81); diabetes (1); prematurity (1); and myocardial infarction (1).

Table 2 Infection pattern among 162 patients with *Scedosporium prolificans* infection

Type of infection by site	Number of patients (%)	Number of patients who died (%r)
Disseminated infection	72 (44.4)	63 (87.5)
Pulmonary	47 (29.0)	10 (21.3)
Osteomyelitis & arthritis	17 (10.4)	0 (0)
Cutaneous & wound	7 (4.3)	0 (0)
Ocular	7 (4.3)	0 (0)
Otitis	6 (3.7)	0 (0)
Cerebral	2 (1.2)	2 (100%)
Sinusitis	2 (1.2)	0 (0)
Peritonitis	1 (0.6)	1 (100%)
Onychomycosis	1 (0.6)	0 (0)
All	162 (100)	76 (46.9)

Table 3 Pattern of infection by host population and site of disease among 162 patients with *Scedosporium prolificans* infection.

Pattern of infection	Underlying condition at time of infection[a]					No underlying condition/cause of infection[a]			Number of patients (%)
	Malignancy	Cystic fibrosis	SOT[b]	AIDS	Other[c]	Trauma	Surgery	None	
Disseminated	59 (81.9)	—	6 (8.3)	3 (4.2)	3 (4.2)	—	1 (1.4)	—	72 (44.4)
Pulmonary	11 (23.4)	19 (40.4)	4 (8.5)	5 (10.6)	7 (14.9)	—	—	1 (2.1)	47 (29)
Osteomyelitis and arthritis	—	—	1 (5.9)	—	—	16 (94.1)	—	—	17 (10.4)
Cutaneous and wound	2 (28.6)	—	2 (28.6)	—	1 (14.3)	1 (14.3)	—	1 (14.3)	7 (4.3)
Ocular	—	—	—	—	1 (14.3)	1 (14.3)	4 (57.1)	1 (14.3)	7 (4.3)
Otitis	—	—	—	—	—	—	—	6 (100)	6 (3.7)
Cerebral	2 (100)	—	—	—	—	—	—	—	2 (1.2)
Sinusitis	—	—	—	—	1(50)	—	—	1 (50)	2 (1.2)
Peritonitis	—	—	1 (100)	—	—	—	—	—	1 (0.6)
Onychomycosis	—	—	—	—	—	—	—	1 (100)	1 (0.6)
All	74 (45.6)	19 (11.7)	14 (8.6)	8 (4.9)	13 (8.0)	18 (11.1)	5 (3)	11 (6.7)	162

[a]Data that are presented correspond to the number of patients and the percentage of the total number of patients (162) in parentheses.
[b]Solid organ transplant.
[c]Includes: immunological disorders (4); COPD (2); injection drug use (2); bronchiectasis (1); pulmonary fibrosis (1); diabetes (1); prematurity (1); and myocardial infarction (1).

information about the time when the cultures became positive. In 33 cases (82.5%), they were positive a short time before the death of the patient.

Data about the use of antifungal prophylaxis was available in 69 patients out of 72 with disseminated infection. Only nine received antifungal prophylaxis (four fluconazole, three itraconazole and two amphotericin B). Only nine patients with disseminated infection survived (12.5%). Table 4 shows the treatments given to patients who survived. There was information about 29 necropsies. All of them confirmed that infection was caused by *S. prolificans.* In six cases, it was reported the visualization of conidiation in tissues.

Table 5 shows the results of multivariate regression analyses to develop a disseminated disease sorted by underlying diseases. In all cases, significant risk factors were neutropenic status, existence of fever and symptoms related to CNS involvement. For patients with haematological malignancy, recovery from aplasia was significantly associated with a reduced risk of disseminated disease.

Lung infections. Forty-seven patients had symptoms and signs compatible with lung infection (Table 2 and 3). However, in 39 (82.9%) patients, it was difficult to ascertain if they were colonized or infected. Underlying diseases are shown in Table 3. Eleven patients had malignancy as underlying disease. Eight patients (72.7%) with malignancies were neutropenic and one had suffered a BMT. Radiology detected lung lesions in 10 (90.0%) out of 11 cases. In all patients, respiratory samples were positive for *S. prolificans,* but in one case it grew together with *Candida albicans* and *Aspergillus terreus.* Eight patients (72.7%) received an antifungal drug (four amphotericin B, two itraconazole, one liposomal amphotericin B and one fluconazole). Seven patients (63.6%) died.

Nineteen (40.4%) patients had cystic fibrosis. Sixteen (84.2%) were receiving corticosteroids. All patients had positive cultures, but cultures were persistently positive in five cases only. Nine patients (47.4%) had respiratory symptoms. In eight patients, radiological findings were reported, but only one patient had pulmonary abnormalities. Four patients (21.1%) were receiving itraconazole prophylaxis and three (15.8%) were treated with fluconazole. No deaths happened in this group of patients.

Four patients had solid organ transplantation (SOT) as underlying disease. Three cases were considered as doubtful and one as a pulmonary infection. Radiology showed lesions in one case. Respiratory samples from all patients were positive for *S. prolificans,* but in one case *Aspergillus terreus* was also isolated. Three

Table 4 Treatment of patients who survived from disseminated infection

Case no.	Underlying disease	Antifungal prophylaxis	First antifungal course	Second antifungal course	Third antifungal course	Other measures	Recovery from aplasia
1	Acute leukemia	None	AB	FZ	—	Surgery*	Yes
2	Acute leukemia	ITZ	AB	L-AB	ITZ	Colony stimulating factors	Yes
3	Aplastic anemia	None	AB + 5FC	MZ	FZ	Colony stimulating factors	Yes
4	Multiple myeloma	None	IZ + TB	VZ + TB	—	Colony stimulating factors	Yes
5	Solid organ transplantation	None	VZ	—	—	Colony stimulating factors	NA
6	Solid organ cancer	ITZ	—	—	—	Colony stimulating factors	Yes
7	Valvulopathy	None	AB	FZ	—	None	NA
8	AIDS	None	—	—	—	None	NA
9	Injection drug use	None	AB+5FC	—	—	Surgery**	NA

AB: amphotericin B; L-AB: Liposomal amphotericin B; FZ: fluconazole; ITZ: itraconazole; 5FC: flucytosine; MZ: miconazole; VZ: voriconazole; TB: terbinafine; NA: not applicable.
*Surgery consisted of the excision of a rib lesion developed after the patient recovered from neutropenia.
**Surgery consisted of hip joint arthrotomy.

Table 5 Multivariate model of risk factors for disseminated disease among patients with *Scedosporium prolificans* infections

Variable	Odds Ratio	95% Confidence interval	*P*
All cases			
Neutropenia	18.6	6.7–51.6	0.000
Fever	3.16	1.6–6.2	0.001
Symptoms CNS	8.4	2.1–32.9	0.002
Any underlying condition at time of infection [a]			
Neutropenia	10.0	3.6–27.6	0.000
Fever	2.2	1.1–4.4	0.026
Symptoms CNS	5.0	1.3–18.5	0.016
Malignancy			
Neutropenia	29.8	2.1–412	0.011
Fever	55.3	2.7–1131	0.09
Symptoms CNS	21.1	1.5–285	0.022
Haematologic malignancy			
Neutropenia	17.3	1.1–269	0.041
Symptoms CNS	29.5	2.2–381	0.010
Recovery from aplasia	0.24	0.08–0.73	0.012

[a] Includes malignancy, solid organ transplantation, AIDS, and other conditions.

patients received antifungal treatment. Two received miconazole or voriconazole. Another patient was initially treated with miconazole, then with liposomal amphotericin B and then with itraconazole. Two patients died.

Five cases described in AIDS patients were considered doubtful. In two, other pathogens (*A. fumigatus* and *S. apiospermum*) were also recovered from clinical samples. Two patients received itraconazole as antifungal treatment. One patient died.

Seven patients had different underlying diseases (Table 3) but six were considered as doubtful. All patients had positive cultures, but in two other pathogens (*A. fumigatus, Candida* sp. plus *A. fumigatus*) were also detected. Three patients received itraconazole. One patient died.

Osteomyelitis and/or arthritis. Seventeen patients had osteomyelitis and/or arthritis. Sixteen suffered a previous traumatism and one had a SOT. All patients had bone lesions on radiology. Cultures were positive in all patients, permitting the recovery of *S. prolificans*, together with *A. fumigatus* in one culture. All cases except two were treated with antifungals (six amphotericin B, three itraconazole, three miconazole, two fluconazole, one voriconazole plus terbinafine) (Table 6). All patients underwent surgery. All patients survived. In two, amputation was required for cure.

Table 6 Therapy of 17 cases of bone infections

Case no.	First antifungal course	Second antifungal course	Third antifungal course	Fourth antifungal course	Fifth antifungal course	Secondary consequences
1	AB	KZ	MZ	AB + KZ	KZ	Amputation
2	AB	ITZ	—	—	—	None
3	Topical MZ	KZ	FZ	Topical AB	AB	Amputation
4	MZ	Topical AB	KZ	—	—	None
5	AB	Topical AB	—	—	—	None
6	AB	KZ	MZ	—	—	None
7	None	—	—	—	—	None
8	AB	KZ	—	—	—	None
9	FZ	—	—	—	—	Ankylosis
10	None	—	—	—	—	None
11	MZ	AB	—	—	—	None
12	AB	FZ	NY	ITZ	—	None
13	VZ + TB	—	—	—	—	None
14	ITZ	VZ	VZ + CP	—	—	None
15	FZ	AB + ITZ	—	—	—	None
16	ITZ	—	—	—	—	Unknown
17	ITZ	ITZ + TB	VZ	—	—	None

AB: amphotericin B; L-AB: Liposomal amphotericin B; FZ: fluconazole; ITZ: itraconazole; 5FC: flucytosine; MZ: miconazole; VZ: voriconazole; TB: terbinafine; CP: caspofungin; NY: nystatin.

Cutaneous and/or wound infections. Seven patients had cutaneous and/or wound infections (Table 3). Six were considered as infections and one doubtful. All cultures were positive, but in one *A. fumigatus* and *Fusarium solani* were also recovered. Six (85.7%) were treated with antifungals (3 amphotericin B, 2 fluconazole and 1 voriconazole). Six patients (85.7%) underwent surgery. All were cured.

Ocular infections. There were seven ocular infections, four patients underwent previously pterygium surgery followed by beta-irradiation or mitomycin C, one had a penetrating trauma, one a foreign body and one was an injection drug abuser. Patients underwent pterygium surgery more than seven years before *S. prolificans* ocular infection happened, and one of them referred a traumatism in his eye ten days before the symptoms. In all cases, clinical picture was corneoscleritis that required surgery and a variety of antifungal drugs. In two cases, enucleation of the eye was performed. Patients experienced some kind of visual loss in the affected eye. The endophthalmitis case related to a penetrating trauma with a wood chip was treated initially with intravenous and intravitreally amphotericin B, but required eye enucleation. A further case of keratouveitis was related to a contact lens retained for a long time intraocularly. Removal of the contact lens and local debridement were sufficient to cure this. Finally, an intravenous drug user presented a clinical picture of endophthalmitis that was resolved by means of enucleation of the eye. All cases were documented with positive cultures of *S. prolificans* from the ocular clinical samples obtained from these patients.

External otitis. Six patients had symptoms compatible with external otitis. None of the patients had any underlying disease. In five cases, mixed isolation of *S. prolificans* and *Staphylococcus aureus* (two cases) or *Pseudomonas aeruginosa* (three cases) was obtained. In one unpublished case, *S. prolificans* was isolated in pure culture. All cases were resolved with ear cleansing with or without topical antibiotic treatment.

Miscellaneous infections. In Table 2, the outcomes of patients with miscellaneous infections are shown. Two patients with acute leukemia as underlying disease had meningoencephalitis. Only cultures from cerebrospinal fluid (CSF) were positive. Both patients were treated with itraconazole, but died. Analysis of necropsy specimens confirmed that cerebral lesions were caused by *S. prolificans* and in one of them conidias were seen in cerebral tissue.

Two cases of fungal sinusitis were resolved after local debridement. One of them was related to a fragment of a dental filling inside the maxillary sinus. The other happened in a patient with atopic rhinitis who developed a fungus ball in the sphenoid sinus.

One SOT patient with peritonitis was treated with amphotericin B, but died.

A case of onychomycosis was resolved by nail excision and 2% tincture of miconazole until the nail bed healed.

Microbiology findings

All patients except 6 (3.7%) had positive cultures for *S. prolificans*. Autopsy data from all six patients showing negative cultures were available, indicating one cerebral infection and five disseminated infections respectively. Blood cultures were positive in 52 patients (32%) and all of them had disseminated infection. The mean $\pm$ SD of the number of positive blood cultures was 2.76 $\pm$ 1.82 (range 1–10). There was available information about the time when the blood cultures became positive in 39 patients. In 33 cases (63.5%), blood cultures were positive around death of the patients. In 6 patients (11.5%), blood cultures were positive in the mid phase of the disease, but only one survived. In twenty two patients, *S. prolificans* was isolated in blood cultures plus other clinical samples including respiratory tract (12), CSF (4), brain (2), skin (4), endocardium (1), catheter (1), peritoneum (1), ocular (1), surgical wound (1) abscess (1) urine (1) and faeces (1). Respiratory samples were positive in 49 patients (30.2%). Clinical samples taken from joints and/or bones were positive in all 17 patients with osteomyelitis and/or arthritis. In addition, the ocular samples taken from the 7 patients suffering *S. prolificans* eye infections were positive as well as ear swabs from the 6 patients with otitis. Finally, a miscellaneous of clinical samples was positive for *S. prolificans* including skin (5), wounds (5), vascular (2), sinus (2), catheter (1), peritoneum (1), and nails (1). In six cases (3.7%), the clinical sample which allowed the recovery of the mould was not specified.

Treatment

Of the 162 patients included in this review, 113 (69.8%) received an antifungal therapy (Table 7). In this group, there were 72 disseminated infections and 38 localized. The group, who not received antifungal chemotherapy, had a high survival rate (72.7%). This figure deserved an in-depth analysis. Sixteen patients survived while six died. The patients who died, were neutropenic, suffered from a disseminated infection, and or had an haematologic malignancy in five of them. None underwent

Table 7 Treatment administered to 109 patients with *Scedosporium prolificans* infection and some underlying condition at time of infection

Treatment	Any underlying condition at time of infection[a]	
	Number of patients (%)	Number of patients who survived (%)
None	15 (13.7)	10 (66.7)
No antifungal chemotherapy	22 (20.2)	16 (72.7)
Any antifungal	87 (79.8)	17 (19.5)
Polyene	52 (59.8)	4 (7.7)
Azole	22 (25.3)	10 (45.5)
Combination	7 (8.1)	3 (42.9)
Unknown	6 (6.8)	0 (0)
Surgery and antifungal chemotherapy	8 (7.3)	6 (75)
Colony stimulating factor	20 (18.3)	6 (30)

[a] Includes malignancy, solid organ transplantation, AIDS, and other conditions.

surgery or recovered from the aplasia. On the other hand, 15 out of the 16 patients who survived had non-hematological underlying diseases. In 11 cases, a lung infection was suspected, but ten remained as doubtful. The patient with the confirmed infection underwent surgery. In addition, there were a cutaneous and/or wound infection, an ocular infection and a sinusitis. All of them underwent surgery. Two patients, one with solid organ cancer and the other with AIDS, had a disseminated infection. Solid organ cancer patient was neutropenic due to a BMT and recovered from the aplasia. Finally, the results showed that patients on antifungal chemotherapy had more disseminated infections than those who did not receive any antifungals (63 vs 8; $P = 0.002$). In any case, the administration of antifungal chemotherapy did not improve the survival rate in patients with underlying disease.

Outcome

The rate of mortality sorted by underlying diseases is shown in Table 1. Mortality was very high (85.1%) in patients with malignancy.

Table 8 summarizes the results of the univariate analysis and Table 9 shows the results of the multivariate regression analysis of risk factors for mortality stratified by underlying disease at time of infection. Significant risk factors for mortality included disseminated disease as well as symptoms related with involvement of CNS. On the other hand, surgery and recovery from aplasia were independently associated with a reduced risk of death. Antifungal treatment was included in the model, but it was not associated with a reduced risk of death.

Discussion

Scedosporium prolificans can be considered as a truly emerging pathogen. It was discovered in greenhouse soil in 1974 [1], but it was not associated with human infections until 1984 [2]. Therefore, this mould was only recognized as a human pathogen 22 years ago. Since then, 153 cases have been reported in the English-, French-, or Spanish-language literature. In this review, 162 cases are analyzed; nine of them are described here for the first time.

Scedosporium prolificans produces infections in immunocompromised patients as well as in other populations (Table 1). However, the pattern of diseases was different. Thus, in patients with malignancies, disseminated infection was the most frequent (81.9%) and it was associated with a high mortality rate (Table 2). Most of the patients had a haematological malignancy (96.6%). A multivariate analysis by means of logistic regression was performed in order to find out if there were risk factors associated with the development of disseminated disease (Table 5). The risk factors found were evident, stressing the importance of neutropenia. On the other hand, recovery from aplasia was obviously associated with a reduced risk of disseminated disease.

Among the most common clinical forms, pulmonary infection ranked second. However, despite all patients having positive cultures, in many of them (82.9%) it was difficult to ascertain if they were colonized or infected by this mould. In those with malignancy as underlying disease, the mortality was 63.6% suggesting that a positive culture should be seriously taken into consideration in this group of patients. On the contrary, this mould seems to be more a colonizer than a real pathogen in patients with cystic fibrosis. Finally, the data are limited for patients with other underlying diseases (Table 3) making the interpretation of a respiratory sample with a positive culture for *S. prolificans* very difficult.

Another frequent disease was osteomyelitis and/or arthritis, usually related to a previous trauma. All patients were operated on, and this seems the basic therapeutic approach. In addition, they received many antifungal treatments, as Table 6 shows, but any clear conclusion can be achieved.

Ocular infections have also been described. In addition to traumatisms or foreign bodies, pterygium surgery was a well-identified risk factor [32,37,38,48,53]. Enucleation of the eye was required in four out of seven

Table 8 Univariate analysis for mortality among patients with infections caused by *Scedosporium prolificans*

	All patients (n = 162)			Any underlying condition at time of infection [a] (n = 109)		
	n	Number of patients who died (%)	P	n	Number of patients who died (%)	P
Female	50	23 (54.0)	0.007	36	27 (75.0)	0.238
Disseminated infection	72	63 (87.5)	0.000	72	63 (88.7)	0.000
Malignancy	74	63 (85.1)	0.000	74	63 (85.1)	0.000
Haematologic malignancy	70	62 (88.6)	0.000	70	62 (88.6)	0.000
Solid organ transplantation	14	7 (50.0)	0.809	14	7 (50.0)	0.118
AIDS	8	3 (37.5)	0.724	8	3 (37.5)	0.053
Other underlying condition	13	3 (23.1)	0.073	13	3 (23.1)	0.000
Neutropenia	69	59 (85.5)	0.000	69	59 (85.5)	0.000
Immunosuppressive drugs	35	9 (25.7)	0.005	18	9 (50.0)	0.046
Bone marrow transplantation	14	11 (78.6)	0.013	14	11 (78.6)	0.545
Fever	88	68 (77.3)	0.000	81	68 (84.0)	0.000
CNS symptoms	33	30 (90.9)	0.000	32	30 (93.8)	0.000
Skin lesions	23	22 (95.7)	0.000	23	22 (95.7)	0.009
Muscular pain	10	8 (80.0)	0.053	9	8 (88.9)	0.425
Any treatment	130	71 (54.6)	0.000	94	71 (75.5)	0.002
Antifungal prophylaxis	11	6 (54.5)	0.519	11	6 (54.5)	0.496
Antifungal drugs	113	70 (61.9)	0.000	87	70 (80.5)	0.000
Surgery	38	2 (5.3)	0.000	12	2 (16.7)	0.000
Colony stimulating factor	20	14 (70.0)	0.027	20	14 (70.0)	0.976
Recovery from aplasia	15	7 (46.7)	0.000	15	7 (46.7)	0.000

[a] Includes malignancy, solid organ transplantation, AIDS, and other conditions.

Table 9 Multivariate model of risk factors for mortality among patients with *Scedosporium prolificans* infections

Variable	Odds ratio	95% Confidence interval	P
All cases			
Disseminated infection	7.9	2.1–29.4	0.002
Symptoms CNS	9.1	1.8–46.2	0.008
Surgery	0.042	0.004–0.39	0.006
Recovery aplasia	0.118	0.04–0.315	0.000
Any underlying condition at time of infection[a]			
Disseminated infection	5.6	1.4–21.8	0.012
Symptoms CNS	9.7	1.6–58.6	0.013
Surgery	0.05	0.04–0.58	0.017
Recovery from aplasia	0.17	0.07–0.44	0.000
Malignancy			
Recovery from aplasia	0.18	0.07–0.46	0.000
Haematologic malignancy			
Surgery	0.10	0.01–0.8	0.032
Recovery from aplasia	0.25	0.08–0.75	0.014
SOT, AIDS, other conditions			
Disseminated infection	13.7	2.5–75.4	0.03

[a] Includes malignancy, solid organ transplantation (SOT), AIDS, and other conditions.

cases (57.1%). Other localized cases as cutaneous and/or wound infection, sinusitis and onychomycosis were resolved with surgery plus antifungals. In summary, surgery seems to play an important role in the therapy of ocular infections caused by *S. prolificans* [32,37,38,48].

One of the most remarkable characteristics of the infections caused by this mould is the high rate of positive blood cultures, especially in patients with disseminated infections. However, most of the blood cultures became positive close to the death of the patient, thus limiting their diagnostic utility. In addition, *S. prolificans* grew in many other clinical samples, showing that isolation of this mould is not a complicated process as happen with other filamentous fungi. Despite this apparent diagnostic ease, the mortality of disseminated infections is so high that new procedures allowing a more rapid diagnosis are required. Furthermore, in many cases, *S. prolificans* grew only from respiratory specimens. The interpretation of these positive cultures is very difficult and may lead to misinterpretation. However, the mortality in patients with malignancy reached 63.6% indicating that most of the patients with this underlying disease were infected by this mould. Recently, Troke *et al*. have found similar results [61]

Treatment of disseminated infections caused by *S. prolificans* is discouraging highlighted by the absence of reduced risk of mortality in patients who received antifungal chemotherapy. Sixty four (88.9%) out of 72 patients received antifungal chemotherapy and mortality in this group was 87.5%. Besides, surgery was performed in 76.5% of the patients cured without underlying diseases. The *in vitro* resistance of *S. prolificans* to antifungals supports this lack of response to antifungal treatment [62]. Therefore, new therapeutic approaches should be designed for this infection in order to improve the outcome of the patients. Pharmaceutical laboratories have explored new alternatives for treating these patients [62–65] Thus, new antifungals are being tested against this mould. Pneumocandin L-743,872 and Syn-2869 a novel triazole agent did not show activity against *S. prolificans* whereas albaconazole, another triazole, showed MICs between 0.5 and 4 μg/ml [66,67]. Meletiadis *et al.* [66,68] tested the combination of itraconazole plus terbinafine against 20 clinical isolates of *S. prolificans.* The combination was synergistic against 95% of the isolates and antagonism was not observed. The same authors [69] revealed synergism of terbinafine and voriconazole. In a recent work, the most active *in vitro* combination against this mould was ravuconazole plus caspofungin [70]. Other authors revealed additive or synergistic effects between amphotericin B, antifungal triazoles and polymorphonuclear leukocytes [71,72]. Experimental studies using different animal models of disseminated infection have demonstrated that high doses of liposomal amphotericin B [73,74] and the novel drugs albaconazole [75] and caspofungin are potentially significant for treatment of these infections. However, further studies are needed to confirm these results. Although G-CSF was used in addition to antifungal drugs in several of the resolved human disseminated infections [10,27,31,60], animal studies establishing the efficacy of cytokines yielded controversial results. While GM-CSF tended to prolong survival of mice infected with *S. prolificans* [76], G-CSF exhibited a detrimental effect on survival time [73,74].

Conclusion

In conclusion, infections caused by *S. prolificans* are life threatening in susceptible patient groups, and can be considered a truly emerging disease. Infections are difficult to diagnose and to treat. This review describes the groups of patients at risk of developing *S. prolificans* infections. Of all of them, patients with malignancy, especially those with haematological malignancy, are at high risk. In any case, the growth of *S. prolificans* from any clinical sample of a patient with malignancy must be taken into consideration. In other groups of patients, the mortality is lower and sometimes a positive culture may suggest colonization rather than infection, but we have to recommend an extensive investigation before to dismiss an infection. Due to the multi-resistant nature of *S. prolificans,* no antifungal chemotherapy seems to improve the outcome of these patients. Logistic regression showed that the most useful therapeutic measures are related with the recovery of a normal status of immunity and the use of surgery when this is possible. In other groups of patients without underlying disease, the use of surgery was basic for achieving a cure.

Given the recent clinical history of the species, research on the diagnostics, detection, and therapy is still in its infancy. The European Confederation of Medical Mycology (ECMM) has recently founded a Working Group (now also approved by the International Society for Human and Animal Mycology), with the aim to develop and disseminate appropriate techniques and protocols. Its website, (www.Scedosporium-ECMM.com), provides recent information on *Scedosporium* infections. The network currently involves participants from 22 countries and stimulates and co-ordinates research on all aspects of these significant environmental pathogens.

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