BRIEF REPORT

Disseminated Infection and Colonization by *Scedosporium prolificans:* A Review of 18 Cases, 1990–1999

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Scedosporium prolificans **infection was analyzed in 18 patients from whom the fungus was isolated during the period 1990–1999. Of these 18 patients, 12 had some predisposing factor and either unconfirmed infection or colonization, and 6 patients had confirmed disseminated infection: 4 patients with leukemia died, 1 patient with breast cancer who underwent autologous bone marrow transplantation survived, and 1 patient with advanced acquired immunodeficiency syndrome died, although the fungal infection did not seem to affect his clinical symptoms.**

Infection with *Scedosporium prolificans,* an uncommon filamentous fungus, was first described in humans in 1984 [1]. It has been associated with localized [1–14] as well as disseminated infections [2, 9, 13–32]. Epidemic outbreaks have also been described in hospital units where there were immunosuppressed patients [15]. Effective treatment is lacking and, as a result, most disseminated infections have a fatal outcome [2, 3, 13–15, 17–19, 21–26, 28–32]. Most infections have been described in Spain [2–4, 6, 15, 16, 20–23, 27, 31, 33–35], especially disseminated infections [2, 3, 15, 16, 20–23, 27, 31]. In our hospital, the first case was diagnosed in 1990, and it was associated with disseminated infection [22]. Since then, over the past decade, we have isolated the fungus from 18 patients. Because of the limited number of published reviews about this fungus [2, 12, 14] we thought our experience would be of interest.

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Materials and methods. Data obtained during 1990–1999 were reviewed retrospectively for patients who were admitted to Hospital Nuestra Señora de Aranzazu in San Sebastian (Gipuzkoa, Basque Country, Spain), a general university hospital with 800 beds that provides services for an average of 26,312 patients per year.

Strains of *S. prolificans* were identified on the basis of their macroscopic appearance (olive-green pigmentation, initial appearance of yeast, and scarce aerial mycelia) and microscopic appearance (septate hyphae and bottle-shaped annellide with oval conidia of truncated base). In addition, the lack of growth on Sabouraud's agar with cycloheximide was verified. In 15 cases, the strain was sent to a reference center (Unidad de Micología, Centro Nacional de Microbiología de Majadahonda, Spain) for confirmation and susceptibility study, which was performed according to the National Committee for Clinical Laboratory Standards reference micromethod, with minor modifications [36]. Susceptibility to the following antifungal drugs was tested: flucytosine, amphotericin B, itraconazole, fluconazole, ketoconazole, and miconazole.

Medline was searched for studies of *S. prolificans* infection published during the period 1966–2000, with use of the entries *"Scedosporium," "inflatum,"* and *"prolificans";* the Metacrawler search engine was also used, and the references of the citations consulted were reviewed.

Results. The patients were divided into 2 groups on the basis of microbiological confirmation of the signs of disseminated infection. The major characteristics of each case patient are shown in table 1.

The first 6 case patients had disseminated infection. Patient 1 was a 44-year-old woman with nonlymphoblastic acute leukemia who was admitted to the hospital with fever and rib pain. She also developed a cutaneous eruption with pruritus and conjunctival effusion. After reinstitution of chemotherapy, on day 10 of the hospital stay, lung condensation was observed on the left lower lobe, and broad-spectrum antibiotic treatment was initiated. No clinical response was observed. Therefore, 21 days after admission, amphotericin B treatment was introduced, and the patient died 3 days later. *S. prolificans* was isolated from cultures of blood samples performed on days 22 and 23 of admission. The patient had neutrophil counts of <500 cells/mm^3. The isolated strain was resistant to flucytosine (MIC >64 μg/mL), amphotericin B (MIC, 16 μg/mL), itraconazole (MIC >64 μg/mL), fluconazole (MIC >64 μg/mL), ketoconazole (MIC, 64 μg/mL), and miconazole (MIC, 64 μg/mL).

Patient 2 was a 55-year-old woman with breast neoplasia

Table 1. Demographic characteristics, clinical data, diagnosis, treatment, and outcome for 18 patients with *Scedosporium prolificans* infection in Gipuzkoa, Spain, 1990–1999.

Patient	Date of presentation	Sex, age in years	Primary disease or preexisting medical conditions; previous treatment	Clinical manifestations	Radiological findings	Culture specimen (no. of cultures yielding *S. prolificans*)	Neutrophil count,[a] cells/mm^3	Treatment		Outcome
								G-CSF	Antifungal agent(s)	
1	1/90	F, 44	ANLL; chemotherapy	Fever, rib pain, cutaneous eruption, conjunctival effusion	Condensation on LL lobe	Blood (3)	500	No	AmB	Died
2	2/96	F, 55	Breast cancer; chemotherapy, autotransfusion stem cells	Fever	Normal	Blood (1)	110	Yes	Itr	Survived
3	8/96	M, 28	AIDS; injection drug abuse	Diarrhea, cough with exp	Bilateral interstitial pattern	Blood (2), sputum (5), BAL (1), urine (1), feces (1)	4270	No	None	Survived (died 11/96)
4	1/99	M, 65	ANLL; chemotherapy	Fever, dyspnea, cough with exp, nodular cutaneous lesions	Condensation on LL lobe	Blood (2), sputum (2)	0	Yes	Flu, Itr, AmB	Died
5	6/99	F, 56	ANLL; chemotherapy	Fever	Bilateral interstitial pattern	Blood (2)	0	Yes	Flu	Died
6	11/99	M, 28	ANLL; chemotherapy	Spondylodiskitis (L1–L2), fever, cholecystitis, abd abscess, nodular cutaneous lesions	Retrocardiac condensation	Blood (1), abd wound (1), abd abscess (1)	3600	Yes	Flu, AmB, Itr, Ter, Vor	Died[b]
7	8/92	M, 61	COPD; corticosteroid therapy	Dyspnea, exp	Lesions, prior tuberculosis	Sputum (1)	16,640	No	Itr	Survived
8	10/92	F, 46	ANLL; chemotherapy	Fever, cough	Condensation, cavitary formation on RU lobe	BAL (1)	100	No	AmB	Survived (died 11/93)
9	3/96	M, 30	AIDS; injection drug abuse	Fever, cough, exp, rhinitis, HIV encephalopathy	Normal	Sputum (1)	1720	No	Itr	Died
10	11/96	M, 34	AIDS; injection drug abuse	Fever, dyspnea, myalgia	Normal	Bronchial asp (2), BAL (1)	1610	No	None	Survived (died 5/97)
11	3/97	M, 69	Intravascular lymphoma B, pulmonary fibrosis; IS therapy	Multiorgan failure (hepatic, pulmonary, cerebral)	Reticulonodular interstitial pattern	Sputum (1)	2430	No	Itr	Died[c]
12	2/98	M, 64	Chronic lymphoblastic leukemia type B, pancytopenia; chemotherapy, corticosteroid therapy	Fever, cough with exp, pneumonia	Node on RU lobe, bilateral alveolar condensation	Sputum (1)	111	Yes	AmB	Died
13	3/99	F, 70	Diabetes mellitus and systemic pulmonary, renal, and peripheral vascular disease; IS therapy	Diarrhea, cough with exp	Lung condensation	Sputum (4)	4010	No	Itr, Flu	Died
14	4/99	M, 31	Acute lymphoblastic leukemia	Cough with exp	Normal	Sputum (3)	100	Yes	Itr	Survived
15	9/99	F, 54	Chronic renal failure, pancytopenia, bronchiectasis; IS therapy	Asthenia, cough with exp	Normal	Sputum (7)	4200	Yes	No	Survived
16	10/99	M, 59	COPD, pulmonary carcinoma; pneumonectomy and radiotherapy	Fever, dyspnea, cough with exp, chest pain	Condensation on RU lobe	Sputum (1)	5670	No	No	Survived
17	11/99	M, 81	COPD, diabetes mellitus, pancytopenia; corticosteroid therapy	Dyspnea, cough with exp, hemoptysis	Lung condensation	Sputum (1)	410	No	No	Died
18	12/99	F, 76	COPD	Fever, dyspnea, cough with exp	Normal	Sputum (1)	12,000	No	No	Survived

NOTE. Abd, abdominal; AmB, amphotericin B; ANLL, acute nonlymphoblastic leukemia; asp, aspirate; BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; exp, expectoration; F, female; Flu, fluconazole; G-CSF, granulocyte colony-stimulating factor; IS, immunosuppressive; Itr, itroconazole; LL, left lower; M, male; RU, right upper; Ter, terbinafine; Vor, voriconazole.

[a] At the time when *S. prolificans* was first isolated.

[b] Autopsy revealed disseminated fungal infection.

[c] Autopsy revealed *Aspergillus fumigatus* pneumonia.

treated previously with surgery and chemotherapy who was admitted to the hospital for autologous peripheral blood stem cell transfusion after intensification chemotherapy. The patient underwent prophylaxis with itraconazole after admission. Beginning on day 6 after the initiation of chemotherapy, her neutrophil count was 110 cells/mm^3. On day 9, treatment with granulocyte colony-stimulating factor (G-CSF) was introduced. On day 14, the patient had a neutrophil count of 1 cell/mm^3 and a febrile peak without focal signs of infection. The *S. prolificans* isolated from blood culture was resistant to flucytosine (MIC >128 μg/mL), amphotericin B (MIC >16 μg/mL), itraconazole (MIC >8 μg/mL), fluconazole (MIC >128 μg/mL), ketoconazole (MIC, 128 μg/mL), and miconazole (MIC >128 μg/mL). On day 18, the neutrophil count had already reached 1490 cells/mm^3. When the results of the blood culture were reported, her general condition was satisfactory and the neutrophil counts were within the normal range of values. Therefore, no additional antifungal treatment was instituted, and the patient was discharged.

Patient 3 was a 28-year-old man with HIV infection who was admitted to the hospital with diarrhea, cough with expectoration, and general progressive deterioration. The chest radiograph showed a bilateral interstitial pattern. Pneumonia due to *Pneumocystis carinii* and diarrhea due to *Clostridium difficile* were confirmed. Moreover, cytomegalovirus was isolated from a biopsy specimen of the colon. All of these infections were treated with specific drugs. On day 4 of the hospital stay, *S. prolificans* was isolated from a bronchoalveolar lavage specimen; on day 6, it was isolated from 2 blood specimens (from 1 of those 2, in association with *Aspergillus fumigatus*). Both *S. prolificans* and *A. fumigatus* were also isolated from samples of feces and urine and from 5 sputum specimens. The isolated strain was resistant to flucytosine (MIC, 128 μg/mL), amphotericin B (MIC, 4 μg/mL), and itraconazole (MIC, 8 μg/mL). The fungal infection was not treated because there was an initial favorable evolution with the specific treatment administered to clear the other pathogens. Three months later, the patient was admitted to the hospital in a terminal condition. No samples for culture were obtained before death.

Patient 4 was a 65-year-old man with acute nonlymphoblastic leukemia who was admitted to the hospital with general malaise, fever, cough with expectoration of 2 months' duration that showed no response to antibiotics. The patient was treated with cranial radiotherapy and chemotherapy. Ten days after the initiation of treatment, G-CSF treatment was introduced. At day 16, he developed cough, hemoptysis, and cutaneous nodular lesions. Because of the suspected pulmonary aspergillosis, the fluconazole initiated 15 days before was replaced with itraconazole; 48 h later the patient developed respiratory insufficiency, and lung condensation was observed on the left lower lobe. Treatment with amphotericin B was introduced, and the patient died the next day. *S. prolificans* was isolated from 2 blood samples (obtained 2 and 3 days before death) and from 2 sputum samples (obtained 2 days before and on the same day as death). At the time of isolation, the neutrophil count was 0 cells/mm^3. The isolated strain was resistant to flucytosine (MIC, 128 μg/mL), amphotericin B (MIC, 8 μg/mL), itraconazole (MIC, 8 μg/mL), fluconazole (MIC, 128 μg/mL), and ketoconazole (MIC, 128 μg/mL).

Patient 5 was a 56-year-old woman with acute nonlymphoblastic leukemia who was admitted to the hospital with relapse of disease. Beginning on day 10 of the hospital stay, her neutrophil counts were <1500 cells/mm^3. On day 14, her neutrophil count was 410 cells/mm^3, and chemotherapy was initiated in conjunction with treatment with G-CSF. No response was obtained (neutrophil count, 0 since day 19). On day 24, the patient developed febrile syndrome, but a chest radiograph appeared normal. Broad-spectrum antibiotic therapy and fluconazole therapy were introduced. *S. prolificans* was isolated from 2 blood samples on the same and the next days. The strain was resistant to flucytosine (MIC, 128 μg/mL), amphotericin B (MIC, 4 μg/mL), and itraconazole (MIC, 8 μg/mL). On day 26, the patient developed shock symptoms, and a bilateral interstitial pattern was visible on a chest radiograph. She died the next day.

Patient 6 was a 28-year-old man with acute nonlymphoblastic leukemia admitted to the hospital for a third cycle of chemotherapy. During a previous hospital stay, he had developed spondylodiskitis in vertebrae L1–L2 that was associated with infection with *Staphylococcus epidermidis,* which was isolated from several blood samples. During this hospitalization, antifungal prophylaxis with fluconazole was initiated. Beginning day 12 of the hospital stay, G-CSF was added. From that point until day 22, neutrophil counts were <100 cells/mm^3. On day 20, the patient showed febrile symptoms that persisted despite broad-spectrum antibiotic therapy. Surgical intervention was done 4 days later because of acute cholecystitis. At 48 h, the patient was febrile, with tachypnea, stupor, and nodular cutaneous lesions suggestive of septic emboli. Retrocardiac condensation was visible on a chest radiograph. Fluconazole was replaced with amphotericin B. An abscess in the surgical wound was drained, and *S. prolificans* was isolated from pure culture of a specimen of the dermal exudate of the wound and from culture of specimens of the abscess fluid and of blood. The strain was resistant to flucytosine (MIC, 128 μg/mL), amphotericin B (MIC, 16 μg/mL), and itraconazole (MIC, 8 μg/mL). At that time, the neutrophil count was 3600 cells/mm^3. The patient was transferred to another room. *S. prolificans* was isolated from an air specimen of the first room, obtained 5 days after the change. Treatment with itraconazole and terbinafine was introduced. In response to the unsatisfactory evolution of the patient, voriconazole was administered for 5 days until

death. At autopsy, multiple fungal septic foci were observed in the lungs, liver, heart, diaphragm, and right kidney.

The remainder of the case patients had either unconfirmed disseminated infection or colonization. Patient 7 was a 61-year-old man with pleuropulmonary sequelae of tuberculosis and chronic obstructive pulmonary disease (COPD) who was admitted to the hospital with respiratory infection with dyspnea, cough with expectoration and had leukocytosis. Sputum cultures performed while this patient was in the hospital were positive for *Haemophilus influenzae, Alcaligenes* species, *Pseudomonas aeruginosa, A. fumigatus,* and *S. prolificans* (1 positive culture result obtained 23 days after admission). The isolated strain of *S. prolificans* was resistant to flucytosine (MIC >16 μg/mL), amphotericin B (MIC >16 μg/mL), itraconazole (MIC >16 μg/mL), fluconazole (MIC >16 μg/mL), ketoconazole (MIC >16 μg/mL), and miconazole (MIC >16 μg/mL). Blood cultures were negative for *S. prolificans.* The patient was treated with high-dose corticosteroids, broad-spectrum antibiotics, and itraconazole (for 25 days, beginning on day 10). He was discharged in satisfactory clinical condition, and *S. prolificans* was not isolated sputum specimens obtained thereafter.

Patient 8 was a 46-year-old woman with a diagnosis of acute nonlymphoblastic leukemia, who developed fever and productive cough 10 days before admission. An image of condensation on the right hemithorax was observed on the chest radiograph. Broad-spectrum antibiotic therapy was instituted, and evolution of her symptoms was favorable. The patient began complete remission with the first cycle of chemotherapy, and her neutrophil count remained <100 cells/mm^3 for 5 days. On day 16 of the hospital stay, *S. prolificans* was isolated from bronchoalveolar lavage fluid. An infiltrate on the left upper lobe and a cavitary nodular formation on the right upper lobe were visible on a chest radiograph. In a puncture-biopsy specimen of the nodular lesion, abundant septate hyphae were observed. Therefore, treatment with amphotericin B was initiated. The patient was discharged in satisfactory general condition. Months later she developed pancytopenia and died with a pulmonary pathology of probable fungal etiology.

Patient 9 was a 30-year-old man infected with HIV who was admitted to the hospital with a history of 20 days of fever, cough with expectoration, and rhinitis that failed to respond to treatment with antibiotic agents. His neutrophil count was 1720 cells/mm^3 and CD4 cell count was 8 cells/mm^3. Gram staining of a sputum specimen revealed abundant hyphae, and *S. prolificans* was isolated from culture. Treatment with itraconazole was initiated. The chest radiograph appeared normal at all times. The patient was discharged 5 days later with a diagnosis of respiratory infection of probable fungal origin. Treatment with itraconazole continued and no further cultures were performed. Eighteen days after discharge, the patient was readmitted because of deterioration of his general condition, and he died 24 h later.

Patient 10 was a 34-year-old man infected with HIV who had previously had episodes of neutropenia associated with drug treatment. The patient was admitted to the hospital with fever, myalgia, and dyspnea. He did not have chest pain, cough, or expectoration. Broad-spectrum antibiotic therapy was instituted, and the clinical symptoms subsided quickly. His neutrophil count was 1610 cells/mm^3, and a CD4 lymphocyte count of 35 cells/mm^3 had been recorded 8 months before. Gram staining of bronchial aspirate and bronchoalveolar lavage fluid revealed abundant hyphae (some with an appearance characteristic of *S. prolificans*). *A. fumigatus* and *S. prolificans* were isolated from culture of bronshial aspirates and bronchoalveolar lavage specimens. Four days later, the patient was discharged in satisfactory general condition. Antifungal treatment was not administered. He died 6 months after discharge from progressive multifocal leukoencephalopathy. The fungus was not isolated from any other clinical specimen during this time.

Patient 11 was a 69-year-old man with idiopathic pulmonary fibrosis who was undergoing treatment with high-dose corticosteroids and who was admitted to the hospital with dyspnea on exertion with cyanosis. The patient was treated with broad-spectrum antibiotic therapy, corticosteroids, azathioprine, and cyclophosphamide. The neutrophil counts remained within the normal range of values at all times. During weeks 4 and 5 of the hospital stay, he received empirical treatment with itraconazole. During weeks 6 and 7, several cultures of sputum samples were positive for *Candida albicans, A. fumigatus, Aspergillus terreus* and *Aspergillus flavus.* During weeks 8 through 13, treatment with itraconazole was reinitiated. At week 10, *S. prolificans* was isolated from a culture of a sputum specimen. This strain was resistant to flucytosine (MIC, 256 μg/mL), amphotericin B (MIC, 32 μg/mL), itraconazole (MIC, 8 μg/mL), fluconazole (MIC, 256 μg/mL), ketoconazole (MIC, 64 μg/mL), and miconazole (MIC, 16 μg/mL). During the hospital stay, the patient had multiorgan failure (hepatic, pulmonary, and cerebral) of unknown etiology and died. At autopsy, intravascular lymphoma B and pneumonia due to *A. fumigatus* were diagnosed.

Patient 12 was a 64-year-old man with chronic lymphoid leukemia that was refractory to treatment who was admitted to the hospital with autoimmune hemolytic anemia and a neutrophil count of 1800 cells/mm^3. Treatment with high-dose corticosteroids and chemotherapy was initiated. At 6 days after chemotherapy, treatment with G-CSF was begun. Nine days after discharge, the patient was readmitted with febrile syndrome, cough, and expectoration. Broad-spectrum antibiotic treatment was instituted. One week later, a right parahilar condensation was shown on the chest radiograph, and treatment with amphotericin B was introduced. Later, radiography revealed a node on the right upper lobe that had an appearance

compatible with pulmonary aspergillosis. Subsequently, bilateral alveolar condensation developed, and the patient died despite treatment with broad-spectrum antibiotics and amphotericin B. Abundant colonies of *C. albicans, A. terreus,* and *S. prolificans* were isolated from sputum samples obtained 10 days before death. The isolated strain of *S. prolificans* was resistant to flucytosine (MIC, 128 μg/mL), amphotericin B (MIC, 16 μg/mL), itraconazole (MIC, 8 μg/mL), and fluconazole (MIC, 64 μg/mL). Blood cultures were negative for *S. prolificans* at all times. The neutrophil count remained <100 cells/mm^3 during at least the 1 month before death.

Patient 13 was a 70-year-old woman with diabetes who had been hospitalized repeatedly for multiple-system vasculitis and who was receiving treatment with high-dose corticosteroids, cyclophosphamide, and azathioprine. During the 6 months before admission she had had a pretibial abscess and pulmonary infection associated with *Nocardia farcinica,* disseminated herpes zoster, urinary infection associated with *Candida* species (treated with fluconazole), and vasculitis with necrosis in her toes. During the days before the most recent admission, she had diarrhea, increased cough, and expectoration. *Candida* species was isolated from specimens of feces, urine, and sputum. One month after admission, *Burkholderia cepacia, Candida* species, *A. fumigatus,* and *S. prolificans* were isolated from 3 sputum cultures, and at this time, lung condensation was visible on radiological images. The neutrophil counts always remained within the normal range of values. The patient was treated with high-dose corticosteroids, broad-spectrum antibiotics, and antifungal drugs (fluconazole before isolation of *S. prolificans* and subsequently itraconazole). Clinical symptoms improved. The patient was readmitted to the hospital 6 days after discharge because of multiorgan failure, renal failure, and respiratory infection. Sputum culture was positive for *B. cepacia* and *S. prolificans.* The isolated strain of *S. prolificans* was resistant to flucytosine (MIC, 128 μg/mL), amphotericin B (MIC, 16 μg/mL), and itraconazole (MIC, 8 μg/mL). The patient died on day 5 of hospitalization.

Patient 14 was a 31-year-old man admitted to the hospital with acute lymphoblastic leukemia, who had cough and expectoration but no fever. During the first week of hospitalization, the patient received treatment with corticosteroids and ciprofloxacin. Chemotherapy was initiated on day 7 of the hospital stay. Neutropenia (neutrophil count <500 cells/mm^3) remained for 14 days. On day 7 of the cylce of chemotherapy, treatment with G-CSF was introduced. On day 10, the patient developed fever without focal signs of infection. The chest radiograph was normal and cultures were negative for *S. prolificans.* The patient was treated with broad-spectrum antibiotic therapy and fluconazole, but he did not recover from the symptoms of infection until the neutrophil count normalized. On days 14 and 16 of the cycle of chemotherapy, *S. prolificans* was isolated from 2 sputum cultures but not from cultures of blood samples. Treatment with itraconazole was introduced. *S. prolificans* was isolated once again from culture of sputum samples obtained on week 7 of the hospital stay. The isolated strain was resistant to flucytosine (MIC >16 μg/mL), amphotericin B (MIC, 8 μg/mL), itraconazole (MIC >16 μg/mL), fluconazole (MIC >16 μg/mL), ketoconazole (MIC >16 μg/mL), and miconazole (MIC >16 μg/mL). The patient was discharged in satisfactory general condition. During the successive cycles of chemotherapy, blood and sputum cultures were negative for *S. prolificans.*

Patient 15 was a 54-year-old woman who was undergoing hemodialysis because of renal insufficiency secondary to pulmonary-renal vasculitis. The patient had bronchiectasis and pulmonary infection associated with *N. farcinica* and was receiving treatment with high-dose corticosteroids and cyclophosphamide. She was admitted to the hospital with progressive pancytopenia (neutrophil count, 300 cells/mm^3). On days 2 and 3 of hospitalization, she G-CSF was administered, and neutrophil values determined on day 4 and after were normal. On days 19 and 20, *S. prolificans* was isolated from 4 sputum cultures. The patient was discharged in satisfactory general condition. Antifungal prophylaxis was not administered. *S. prolificans* was isolated on 7 additional occasions from follow-up sputum cultures. The isolated strain was resistant to flucytosine (MIC, 128 μg/mL), amphotericin B (MIC, 16 μg/mL), and itraconazole (MIC, 8 μg/mL). The patient is presently waiting for a renal transplant, and colonization with *S. prolificans* persists despite normal neutrophil counts.

Patient 16 was a 59-year-old man with COPD and squamous cell lung carcinoma who, 6 months previously, had undergone pneumonectomy and had received radiotherapy. The patient was admitted to the hospital with dyspnea, fever, cough, expectoration, and pain in the right hemithorax; neutrophil counts were normal. A chest radiograph revealed condensation in the right upper lobe. The patient responded well to treatment with high-dose corticosteroids and broad-spectrum antibiotics. At the time of admission, cultures were negative for *S. prolificans.* On day 6 of the hospital stay, *S. prolificans* was isolated from culture of sputum. The isolated strain was resistant to flucytosine (MIC, 128 μg/mL), amphotericin B (MIC, 4 μg/mL), and itraconazole (MIC, 8 μg/mL). The patient was discharged in satisfactory general condition. He did not receive antifungal treatment, and the subsequent cultures of blood and sputum samples were negative for *S. prolificans.*

Patient 17 was an 81-year-old man with diabetes and COPD who was receiving treatment with low-dose corticosteroids and had been admitted to the hospital 1 month previously with respiratory infection and atrial fibrillation. The patient was admitted because of worsening of respiratory symptoms; a radiograph revealed lung condensation. Anemia, thrombopenia,

and neutropenia (neutrophil count, 320 cells/mm^3) related to a probable myelodysplastic syndrome were observed at admission. The patient was treated with high-dose corticosteroids and broad-spectrum antibiotic therapy and died on day 5 after admission. *S. prolificans* was isolated from a culture of a sputum sample obtained on day 2. The strain was resistant to flucytosine (MIC, 128 μg/mL), amphotericin B (MIC, 4 μg/mL), and itraconazole (MIC, 128 μg/mL).

Patient 18 was a 76-year-old woman with COPD who was admitted to the hospital with fever, dyspnea, cough, and expectoration. The patient showed no improvement after he had received antibiotic treatment. Hypoventilation on the lower third of the left hemithorax was evident on auscultation. Neutrophil counts of 12,000 cells/mm^3 were recorded. *H. influenzae* and *S. prolificans* were isolated from culture of a sputum sample obtained the day after admission. The patient was treated with amoxicillin/clavulanate and corticosteroids and was discharged on day 8 in satisfactory general condition. No antifungal treatment was given. The isolated strain of *S. prolificans* was resistant to flucytosine (MIC, 128 μg/mL), amphotericin B (MIC, 16 μg/mL), and itraconazole (MIC, 8 μg/mL).

Discussion. *S. prolificans* was first described as a human pathogen by Malloch and Salkin [1] in 1984 and given the name *Scedosporium inflatum.* A subsequent taxonomic review [37, 38] verified that it had already been described by Hennebert and Dessai [39] in 1974. At that time, it was found in the soil of a greenhouse in Belgium and was referred to as *Lomentospora prolificans.* Therefore, the name *Scedosporium prolificans* was proposed.

With regard to its recent description, some authors have suggested that in previous years it was confused with the species *Scedosporium apiospermum* [21]. It is differentiated from the latter primarily by the bottle-shaped annellides and the lack of growth on Sabouraud's agar with cycloheximide. Laboratories that conserve collections of fungi of the *S. apiospermum* species isolated before 1984 could probably reclassify a significant number of these as *S. prolificans.*

During the 10 years of this review, *S. prolificans* was the filamentous fungus isolated most frequently from blood cultures performed for patients at our hospital. During 1999 it comprised 5.2% of all of the filamentous fungi isolated in our laboratory. Knowledge of its characteristic microscopic appearance in direct stains of blood cultures, as a pyriform or truncated-base yeast, has been useful for detection and rapid presumptive identification, preventing the need to wait for growth of the subcultures.

S. prolificans grows well in 2–4 days at 37°C in culture media that are specific for fungi, as well as in nonselective media (blood agar and chocolate agar). Its characteristic macroscopic appearance facilitates identification. The fungus was initially isolated from a patient with disseminated infection (patient 3) and colonized patients (patients 15–17) by use of culture media specific for mycobacteria (Middlebrook 7H11 agar, Mycobacteria Growth Indicator Tube, Lowenstein-Jensen, and Coletsos media). It was isolated from these patients despite the decontamination that is used regularly when performing mycobacterial cultures (with use of N-acetylcysteine-NaOH). In patient 18, the fungus was isolated only in a selective medium with amphotericin B during a prevalence study begun in November 1999. *Aspergillus* species are often associated with *S. prolificans* in clinical specimens (patients 3, 7, and 10–13). Therefore, the use of selective media that contain active antifungal agents to combat *Aspergillus* species may be useful. This fungus can mask the colonies of *S. prolificans,* which grow more slowly and have scarce aerial mycelia [40].

S. prolificans has been isolated from plants [10, 41], chicken manure [42], and some animals, such as horses, dogs, and cats [10, 43]. In humans, it has been reported in association with 3 different clinical conditions: (1) colonization, particularly of the respiratory system, in patients with cystic fibrosis [4, 35] or AIDS [44] and subjects who have undergone liver [34] or lung [32, 35] transplantation; (2) superficial and deep localized infections in immunocompetent and immunosuppressed patients, including cutaneous [5], ungual [14], ocular [8, 14], pulmonary [2, 4], and osteoarticular infections [1, 7, 9–11, 14], endocarditis [2, 11], peritonitis [10, 13, 14], and meningoencephalitis [6]; and (3) disseminated infections in immunosuppressed patients [2, 3, 9, 13–32]. *S. prolificans* infection has been described in patients with leukemia [2, 3, 9, 14–17, 19, 21–23, 25, 27, 29, 31, 32] and lymphoma [13, 14, 18], and, in some cases, it has been associated with HIV infection [20, 24]. This fungus has also been isolated from a patient who underwent lung transplantation [26] and from a patient who underwent autologous bone marrow transplantation because of breast cancer [30].

In our review, which is the largest reported from a single hospital, both colonization and disseminated infection were detected. All patients colonized by this fungus had some factor that predisposed them to fungal infections (e.g., leukemia, lymphoma, COPD, systemic autoimmune disease that is being treated with immunosuppressants, AIDS). In some patients (9, 12, 13, and 17) who were classified as having probable colonization, the presence of localized or even disseminated infection could not be ruled out because the nature of the infection could not be confirmed; other culture results were not positive for *S. prolificans* and necroscopic studies were not performed. Disseminated infections with this fungus have been reported in several countries, including Australia [9, 13, 14, 18, 32], the United States [25, 29, 30], Canada [17], Germany [24], France [26], and the Netherlands [19]. However, it has clearly been reported most frequently in Spain [2, 3, 15, 16, 20–23, 27, 31], especially in the north. This may be due to climatic factors,

such as the level of humidity, that favor the growth of this fungus in the environment or other factors that are presently unknown. In most of the cases that have described, the respiratory tract is suggested as the path of entry; this symptomatology also predominated in our review. *S. prolificans* has been isolated from samples taken from the ground and plants [10, 39] and from the flowerpots at a hospital [41]. *S. prolificans* was isolated from a specimen of air obtained from the hospital room of patient 6 [40].

Two clusters of cases were observed over time. Four cases occurred in 1996, and another group of 9 cases occurred in 1999. In the latter, 5 patients were in the hematology unit, and 4 of them had been admitted to simple isolation rooms with positive pressure.

A susceptibility study was conducted on 15 strains of *S. prolificans* and, as observed previously [2, 14, 36], *S. prolificans* was resistant to all drugs tested. Of the drugs, itraconazole had the lowest MICs (8 strains had MICs of 8 μg/mL). Some patients were receiving antifungal treatment when the fungus was isolated. In some in vitro studies, it has been verified that terbinafine in conjunction with itraconazole showed synergic activity in combating the fungus [45]. In our review, lipid-associated amphotericin B, itraconazole, and terbinafine were administered concomitantly to a patient with advanced disseminated infection (patient 6), and there was no clinical improvement. New drugs, such as voriconazole, have in vitro activity slightly greater than that of the traditional antifungal drugs and may be useful in treating these infections [46], although some authors question their efficacy in such treatment [36]. Patient 6 was treated with voriconazole for 5 days, with no apparent improvement.

Because of the multidrug resistance of the fungus, a patient's ability to overcome immunosuppression is an essential factor for resolution of the disseminated infection. The phagocytes modify the structure of the hyphae of *S. prolificans* [47]. Some studies have suggested the efficacy of treatment with G-CSF in association with antifungal drugs [14, 16]. In other cases, the use of these factors was not sufficient to overcome the infection [19, 20, 25]. Patient 2, who had breast cancer and had undergone autologous bone marrow transplantation, was treated with G-CSF and her neutropenia resolved. This was the most probable cause of the cure of the infection, because the fungus was resistant to the itraconazole treatment administered to the patient. Patient 3, who had advanced AIDS, was not treated with antifungal drugs or G-CSF, and no apparent impairment of his clinical condition was observed. Patients 4–6 received G-CSF and no noticeable effect was observed.

In our environment, *S. prolificans* infection is relatively frequent, especially among immunosuppressed patients. Therefore, we should be on alert for early diagnosis of this infection. Because the fungus can be observed directly in positive blood cultures, typically as a pyriform or truncated-base yeast, a preliminary report can be made. Unfortunately, at present there is no effective treatment for disseminated infections. There are limited therapeutic options, although treatment with G-CSF will result in rapid recovery from neutropenia. Control of the microbiological environment of the rooms where the patients neutropenia are admitted to the hospital may be determinant in prevention of these infections [40].

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