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Disseminated Infection Caused by *Scedosporium prolificans* in a Patient with Acute Multilineal Leukemia

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In this report, we describe a case of disseminated infection caused by *Scedosporium prolificans* (*S. inflatum*) in a patient affected by chemotherapy-induced acute multilineal leukemia and neutropenia. For the fungus isolated in four blood cultures, high MICs of currently available antifungal agents were found. Postmortem examination revealed multiorgan involvement.

In 1984, Malloch and Salkin described a dematiaceous fungus, *Scedosporium inflatum*, as a new human pathogen (12). Although the first infections described were located in the joints (11, 21), other cases have since been reported with endocarditis (20), meningoencephalitis (10), corneal infection (14), and even sinusitis of dental origin (3). Colonies of the fungus have also been identified in the external auditory conduct (21) and in the respiratory tract (8). Certain invasive techniques and prosthetic implants, as well as treatments with immunosuppressive chemotherapeutic agents, appear to have contributed to the increase in severe disseminated mycosis, often with fatal results (1, 6, 7, 9, 13, 15, 17, 19, 22; J. Garland, E. Stool, Jr., J. Gathe, G. Micheletti, J. Oliphant, and M. Rinaldi, VIII Int. Conf. AIDS, abstr. 7196).

A 45-year-old male, a smoker with no significant pathological antecedents, was admitted to our hospital on 16 December 1996 with a toxic syndrome and bone pain that had evolved over 4 months. At the time of admission, blood tests showed the following: hemoglobin, 94 g/liter; hematocrit, 26%; platelets, 21×10^9/liter; leukocytes, 3.3×10^9/liter (15% neutrophils, 69% lymphocytes, 1% monocytes, 1% eosinophils, 9% blasts, 3% myelocytes, and 2% bands). Following an immunophenotypic study, a diagnosis of acute multilineal leukemia was made with a predominant lymphoblastic and myelomonocytic component and, to a minor degree, an erythroblastic and megakaryocytic component. Genetic study proved the bone marrow to be normal. The patient was transferred to the hematology unit, where for 1 week he was given the standard treatment of vincristine (2 mg/day), daunorubicin (50 mg/day), prednisone (90 mg/day), and two doses of cytarabine, methotrexate, and hydrocortisone administered inthrathecally. After the immunophenotypic study, this was changed for 1 week to idarubicin (15 mg/3 days), etoposide (150 mg/3 days), and cytarabine (150 mg/day). The patient developed intense postchemotherapeutic aplasia (leukocytes, 0.5×10^9/liter; neutrophils, $<0.1 \times 10^9$/liter). The day after chemotherapy ended, his temperature rose to 38°C, no infectious focus was identified, and microbiological cultures were negative. Empirical treatment with piperacillin-tazobactam and amikacin (4 g/6 h intravenously [i.v.] and 1 g/24 h i.v., respectively) was administered. The fever initially diminished but rose again after 5 days of treatment; once again, there was no infectious focus and microbiological cultures were negative. The antibiotics were changed to imipenem (500 mg/6 h i.v.), aztreonam (2 g/8 h i.v.), and vancomycin (500 mg/6 h i.v.). After 4 days, and owing to the presence of a persistent fever, a lipid complex amphotericin B (Abelcet)—150 mg on the first day and 300 mg/day afterwards—was added. From then onward, the patient was without fever. He did, however, complain of headache and intense lumbar pain. He showed slight facial paresis, had a skin rash, and experienced dizziness. A cerebral computerized axial tomography scan was normal. The following day, the patient's clinical condition worsened considerably, with acute respiratory distress, hypotension, and oliguria, and he was transferred to the intensive care unit (ICU).

A chest X-ray showed bilateral alveolar condensations and bilateral pleuritic effusion. After two episodes of hypotension, and in spite of the hemodynamic support, the patient suffered heart failure and died the day after ICU admission. During his stay in the ICU, *S. prolificans* (*S. inflatum*) was isolated in four blood cultures. Postmortem examination confirmed a generalized fungal infection caused by *S. prolificans* with multiple intravascular mycotic thromboses with lung, liver, spleen, renal, cardiac, gastrointestinal, brain, thyroid, and bone marrow involvement.

Each blood culture specimen taken was injected into BACTEC Plus Aerobic/F (enriched soybean-casein digest broth with CO_2) and BACTEC Plus Anaerobic/F (prereduced enriched soybean-casein digest broth with CO_2) culture vials for aerobic and anaerobic cultures, respectively, and processed in a blood culture system (BACTEC 9240 fluorescent series instruments; Becton Dickinson Diagnostic Instrument Systems, Cockeysville, Md.). In the last four positive blood cultures, taken on the day of death, growth was detected after 44, 43, 45, and 44 h, respectively. While the aerobic test bottles showed positive growth, the anaerobic test bottles showed none, in spite of a prolonged incubation period of 1 month. Subcultures in blood agar and blood agar with IsoVitaleX showed growth at 24 h. The colonies developed aerial hyphae at 72 h. The fungus grew well in Saboraud dextrose agar, although more slowly than in blood agar with 5% sheep blood. Initially, the colony was blackish gray, becoming much darker with time, and with whitish cotton-like stains appearing and spreading over the surface. Observation of this fungus under a microscope revealed hyaline conidiophores without ramifications, the apex of which showed inflated annellides with rounded extremes. No chlamydospores were observed. The fungus, initially classified as *S. prolificans*, was sent to the Centro Nacional de Microbiologia del Instituto Carlos III

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TABLE 1. Comparative MICs obtained for *S. prolificans*

Antifungal agent	MIC (μg/ml) determined in:			
	This study	Reference 9	Reference 7	Reference 5
Amphotericin B	32	16	40	12.5
5-Flucytosine	256	>64	40	50
Ketoconazole	128	64		
Fluconazole	256	>64		50
Itraconazole	16	>64	40	25
Miconazole	256	64	5	25

(Carlos III National Institute of Microbiology) for confirmation and for antifungal susceptibility studies as described by Cuenca-Estrella et al. (4) (Table 1).

Exhaustive studies on the susceptibility of these species have not been done (1, 5, 7, 8, 9, 15, 17, 21, 22). The lack of universally accepted standardized methods makes it difficult to compare susceptibility data of a given case with the results obtained by other authors, most of whom report high-level resistance to 5-flucytosine, amphotericin B, ketoconazole, miconazole, and fluconazole, and that some strains are susceptible to itraconazole (21, 23). In our case, we stress the considerable resistance (MIC, 256 μg/ml) to 5-flucytosine, fluconazole, and miconazole shown by the fungus. On the other hand, when tested in vitro, itraconazole (MIC, 16 μg/ml) proved to be the drug to which it was more susceptible. The identification of *S. prolificans* in blood explains the rapid spread of the infection, with multiorgan involvement and a fatal outcome, in our patient.

In the published cases, the majority of the recoveries correspond to localized infections in immunocompetent patients. The severe neutropenia (absolute neutrophil count of <100/μl) of long duration which usually affects hematological patients after intensive chemotherapy provides favorable conditions for opportunistic infections. Neutropenia often remains a constant factor in patients who have not been cured of their hematological malignancy, and the possibility of a disseminated mycosis in this type of patient should be taken seriously. *S. prolificans* is one of the saprophytic fungi that should be considered a causative agent. In our case, the infection developed very quickly, which led us initially to consider a bacterial origin.

It is very important to take every possible measure to prevent infection in neutropenic hematological patients and not to discount the presence of saprophytic fungi whenever the number of leukocytes falls below 0.5×10^9/liter (6, 23). It should be noted that some authors have pointed out the utility of treatment with stimulating granulocytic factors and macrophages (2) in preventing invasive mycosis in this type of patient.

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