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Fungemia due to *Scedosporium prolificans*: a description of two cases with fatal outcome

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Two cases, probably related, of fungemia due to *Scedosporium prolificans* are described in two patients with acute leukemia. Both were admitted to the hematological ward in nearby rooms, during building work in the hospital. After a previous bacterial sepsis in the neutropenic phase, which improved with antibiotic treatment, the respiratory status in both patients deteriorated presenting acute dyspnea, with a lung infiltrate in one of them. A few hours later both patients died. Blood cultures were positive for *S. prolificans*.

These two new cases of *S. prolificans* infection stress the importance of awareness of this emerging pathogen in patients who suffer a hematologic malignancy during the neutropenic phase, especially if building work is taking place in the hospital.

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In the last two decades, the use of aggressive treatment and techniques such as transplants, chemotherapy, catheter implants and others to prolong the lives of patients, and the existence of HIV, have created a new group of patients who are especially susceptible to fungal infections, and consequently the morbidity and mortality due to these organisms have witnessed notable increases.

In 1984, Malloch and Salkin described the first case of human infection due to *Scedosporium inflatum* [1]. Recent DNA analyses have demonstrated that this fungus is identical to *Lomentospora prolificans*, a species isolated in Belgium by Hennebert and Desai [2], and, according to the current rules of botanical nomenclature, it was renamed *Scedosporium prolificans*. The natural habitat of this fungus is not well known; it has been isolated in soil from flower pots and also from cats and horses [3,4]. In humans, the clinical spectrum of *S. prolificans* ranges from asymptomatic colonisation to severe disseminated infections. Most of these latter cases have been associated with immunocompromised patients, especially those with profound neutropenia. Contaminated air-conditioning systems and renovation inside hospitals have been related to nosocomial infections

produced by several opportunistic fungi such as *Aspergillus* spp. [5]; a report has recently been published on the first possible outbreak of nosocomial infection due to *S. prolificans* [6].

Our study describes two new cases of fatal *S. prolificans* infection in two leukemic patients coinciding with rebuilding work in the hospital.

PATIENTS AND METHODS

Two leukemic patients had fungemia due to *S. prolificans* during profound neutropenia. Both cases were detected in the same ward over a period of 20 days and coincided with reconstruction work at the hospital. Blood samples were inoculated into aerobic and anaerobic bottles (Bactec Plus/F* aerobic and anaerobic; Becton Dickinson, Sparks, MD, USA) and processed in the Bactec 9120 automatic system for 7 days. The bottles were subcultured on blood agar and Sabouraud dextrose agar (Difco, Detroit, MI, USA) when the system detected growth. Environmental samples were taken from each of the rooms to identify the reservoir. Saline-moistened sterile cotton swabs were used for collecting samples from walls, floors, the surfaces

of furniture and air-conditioning ducts, but no air volumetric samples were taken. The swabs were cultured on blood agar, Sabouraud dextrose agar without and with amphotericin B at a final concentration of 10 mg/L, and Mycobiotic agar (Difco). The plates were incubated at 30 °C for 10 days. The colonies of fungi which grew in the culture medium were identified according to standard methods. In vitro susceptibility testing of the strains isolated from both patients against amphotericin B, ketoconazole, itraconazole, flucytosine, fluconazole, miconazole and voriconazole was performed in the Centro Nacional de Microbiología in Majadahonda using a modification of the microdilution method proposed by the National Committee for Clinical Laboratory Standards (NCCLS) [7].

CASE REPORTS

Case 1

A 34-year-old woman had been treated for acute myeloblastic leukemia in October 1997. After complete remission, the patient was readmitted in December and was treated with a cycle of chemotherapy with idarubicin and cytarabine. Intravenous fluconazole (400 mg/day) was administered as prophylaxis. Nine days later, during profound neutropenia (leukocyte count $0.1 \times 10^9/L$ and thrombocyte count $20 \times 10^9/L$) and fever of 39 °C, the patient had diffuse abdominal pain. Blood cultures revealed *Pseudomonas aeruginosa*. Treatment with piperacillin-tazobactam plus amikacin was instituted. After 48 h of therapy, the patient's clinical condition improved but she continued to be febrile. *Candida albicans* (fluconazole MIC = 0.5 mg/L) was isolated in another blood culture. Faced with this episode of breakthrough candidemia during treatment with fluconazole, we substituted it with liposomal amphotericin B (3 mg/kg/day). Four days later, the patient presented dyspnea and hemoptysis. A chest radiograph revealed an infiltrate in the left lung. A further blood analysis revealed, among others, the following results: leukocyte count $0.1 \times 10^9/L$, PCO₂ 20.9 mmHg, PO₂ 88 mmHg, and 96% oxygen saturation. Several blood cultures were taken, and several hours later the patient's dyspnea worsened, the oxygen saturation fell to 54%, and she died. These last blood cultures were positive for *S. prolificans*. A postmortem study was not authorised by the family.

Case 2

A 20-year-old woman was diagnosed in March 1996 with acute lymphoblastic leukemia and treated with chemotherapy. In January 1998 she was readmitted due to a fever of several days' duration. There was a bone marrow relapse with a white blood cell count of $0.5 \times 10^9/L$. A few hours later, the patient developed septic shock and renal function deterioration.

Escherichia coli and *P. aeruginosa* were isolated in blood cultures, and treatment with piperacillin-tazobactam plus amikacin was initiated, with some improvement in her condition. In the following week chemotherapy was commenced, and, due to the persistence of the fever, amphotericin B (1 mg/kg/day) was added to the treatment and piperacillin-tazobactam was replaced by imipenem. Two days later, the patient suffered intense dyspnea with severe hypoxemia. Chest roentgenographic findings were normal. She died a few hours later due to respiratory failure. Two blood cultures (Bactec) obtained 24 h before death were positive for *S. prolificans*. A postmortem study was not authorised by the family.

RESULTS AND DISCUSSION

The three blood cultures taken from the first patient were positive between 59 and 67 h, and the two from the second patient between 48 and 60 h. On subculture, *S. prolificans* grew on blood agar and Sabouraud dextrose after 24–48 h. The colonies were greenish-brown in color with a woolly appearance. Microscopic examination using lactophenol-cotton blue revealed thin-walled hyphae with ovoid conidia spread throughout the hyphae and in clusters at the apex of conidiophores with the distinctive swollen base characteristic of *S. prolificans*. The environmental surface cultures were negative for *S. prolificans*, although there was growth of other environmental fungi, such as aspergilli.

Susceptibility tests revealed the same MICs (mg/L) for both strains for amphotericin B (16), ketoconazole (32), itraconazole (16), flucytosine (128), fluconazole (128) and miconazole (128). A dilution difference existed between the MICs (32 and 64) of voriconazole.

Although infections caused by *S. prolificans* are not frequently seen, they are extremely serious and, to our knowledge, only one patient in whom this fungus was isolated in the blood has survived the infection when granulocytopenia subsided [8]. Spain is the country in which most cases have been published, most of them appearing in the excellent review by Berenguer et al. [7], in which 16 patients from different hospitals and with very serious infections are described. The main predisposing factor for acquiring the infection is the presence of neutropenia, usually associated with serious blood disorders and chemotherapy treatment, although cases with different underlying illnesses, such as renal transplant [9], lung transplant [10] and AIDS [11], have been described. Our two cases presented with the triad of leukemia, chemotherapy and neutropenia with fatal outcome. Infection usually starts during or after treatment with broad-spectrum antibiotics and amphotericin B, as happened in our two patients. The most frequent clinical manifestations are fever and dyspnea with pulmonary infiltrates in the chest X-ray. These three conditions were fulfilled in our first patient, while the second one had fever and dyspnea and a normal chest X-ray,

as in the case described by Nenoff et al. [11]. In other less frequent cases, alterations of the central nervous system and skin lesions have been reported. Our two infections occurred over a short period of time, with the patients in nearby rooms, and during rebuilding work near the hematologic ward. These facts would suggest an epidemic context, although the fungus was not isolated from the environmental samples, perhaps due to a lack of sensitivity in the methods used, since no air samples were taken and materials and soil used in the reconstruction work at the hospital were not investigated. This same situation occurred in another possible outbreak of infection due to *S. prolificans* [6] and in a nosocomial infection reported in 1996 [12]. The isolation of the fungus from air samples taken in rooms where patients infected by *S. prolificans* were admitted has been documented by Durán et al. [13]. *S. prolificans* is detected in blood, unlike *Aspergillus* spp. infections. With use of the Bactec system, the detection time in Berenguer's series [7] ranged from 9 to 15 days. Thus, on many occasions, the diagnosis occurred after the death of the patient. Our two cases differ notably with regard to detection time, since the blood cultures were positive between 48 and 67 h, which is a similar time to that described for the Isolator system [6].

The two strains of *S. prolificans*, like others described previously, were resistant to all the antifungal agents tested, and this makes prognosis even bleaker. Recently, a case has been described of favorable outcome in a neutropenic patient with pneumonia, treated with liposomal amphotericin, although the strain was also resistant in vitro to the latter [14]. However, the first of our patients died in spite of treatment with 3 mg/kg per day of liposomal amphotericin 4 days before the appearance of her respiratory problems and pulmonary infiltrate.

These two new cases of infection due to *S. prolificans* stress the importance of the awareness of this emerging pathogen in patients who suffer a hematologic malignancy during the neutropenic phase, especially if rebuilding work is taking place in the hospital.

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