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CASE REPORT

Phialemonium curvatum INFECTION AFTER BONE MARROW TRANSPLANTATION

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SUMMARY

We report a case of cutaneous infection caused by *Phialemonium curvatum* GAMS et COOKE, 1983, after bone marrow transplantation. The genus *Phialemonium* was created by GAMS & MCGINNIS in 1983 including three new species: *Ph. obovatum*, *Ph. curvatum* and *Ph. dimorphosporum*, and represents an intermediate genus between *Acremonium* and *Phialophora*. Nowadays, the genus *Phialemonium* is considered to be a pheoid fungus which may cause the eventual lesions observed in pheo- and hyalohyphomycosis. Species of this genus have been described as opportunistic agents in humans and animals, mainly as a result of immunosuppression. In the present case, the patient had multiple myeloma and received an allogenic bone marrow transplant from his HLA-compatible brother. Two months after transplantation, he developed purplish and painful nodular lesions on the right ankle. Some of these lesions drained spontaneously and apparently hyaline mycelial filaments were observed, whose culture was initially identified as *Acremonium sp*. Subsequent studies showed that the fungus was *Phialemonium curvatum*. The infection was treated with amphotericin B, followed by ketoconazole. The patient was submitted to surgical debridement followed by two skin grafts to repair the bloody area. The duration of the treatment was 4 months and secondary prophylaxis with ketoconazole alone was maintained for one additional month. No recurrence was observed after discontinuation of treatment. The authors comment on the pathogenicity of the genus *Phialemonium*.

KEYWORDS: *Phialemonium curvatum;* Bone marrow transplantation; Phaeohyphomycosis; Hyalohyphomycosis.

INTRODUCTION

Phaeohyphomycosis is an infection caused by a large number of genera and species of dematiaceous fungi, which can affect cutaneous and subcutaneous tissues, the ocular region, frontal and maxillary sinuses, lungs, bones and the nervous system. Although the fungal elements observed in the tissue have been described as dematiaceous, melanin is not always easily visualized.

In some cases, it is necessary to carefully examine various histological sections before the dematiaceous nature can be established. In phaeohyphomycotic infections caused by *Alternaria alternata*, *Bipolaris spicifera*, *Exophiala jeanselmei* or *E. spinifera*, most fungal elements are found to be hyaline. The presence of melanin in the fungal cell wall is determined by Fontana-Masson staining.

Factors predisposing to fungal infection are antibiotic therapy for the treatment of chronic bacterial infections, post-transplant immunosuppressive therapy and HIV infections.

The genus *Phialemonium*, an intermediate genus between *Acremonium* and *Phialophora*, created by GAMS & McGINNIS in 1983, comprises three species according to these authors: *Ph. obovatum*; *Ph. curvatum* and *Ph. dimorphosporum*. HOOG & GUARRO (1995) accepted the species *Ph. curvatum* and *Ph. obovatum*.

AJELLO (1986), MATSUMOTO *et al*. (1994), MATSUMOTO & AJELLO (1998), KWON-CHUNG & BENNETT (1992) and MISHRA *et al*. (1992) consider the genus *Phialemonium* to be an agent causing phaeohyphomycosis. This genus was also considered to be an agent of hyalohyphomycosis by MATSUMOTO *et al.* (1994) and MISHRA *et al.* (1992).

The colonies of this phaeoid hyphomycete are expanding, presenting scarce white mycelium which sometimes turns yellow-greyish. Phialoconidia are produced from inconspicuous collarettes or from discrete, lateral, tapering phialides, often without basal septa. Conidia are hyaline, smooth and thin-walled, cylindrical to allantoid, grouped in slimy heads.

KING *et al.* (1993), when describing one case of a phaeohyphomycotic cyst and another of peritonitis caused by species of the genus *Phialemonium*, believed that *Ph. curvatum* and *Ph. dimorphosporum* form a complex, with strong evidence indicating that the latter species resembles more intimately to *Ph. curvatum*.

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We report a case of *Phialemonium curvatum* infection in a patient submitted to bone marrow transplantation. The authors also alert mycologists about the rarity of the case and the increasing occurrence of emerging fungi in immunocompromised patients.

CASE REPORT

F. F. de S., a 30-year-old male, an Elementary School teacher from Ceará, Brazil, with multiple myeloma received an allogenic bone marrow transplant from his HLA-compatible brother. The patient received busulfan and melphalan for transplantation conditioning and cyclosporin A and methotrexate for graft-versus-host disease (GVHD) prophylaxis. On the 32nd day post-transplantation, acute GVHD was diagnosed, which was controlled with solumedrol (2 mg/kg/day) pulse therapy. One month later, a new episode of acute GVHD led to the introduction of pulse therapy using high doses of solumedrol (5 mg/kg/day). The patient improved slowly and developed a gastrointestinal disease caused by cytomegalovirus on the 98th day, responding to treatment with ganciclovir. Cyclosporine

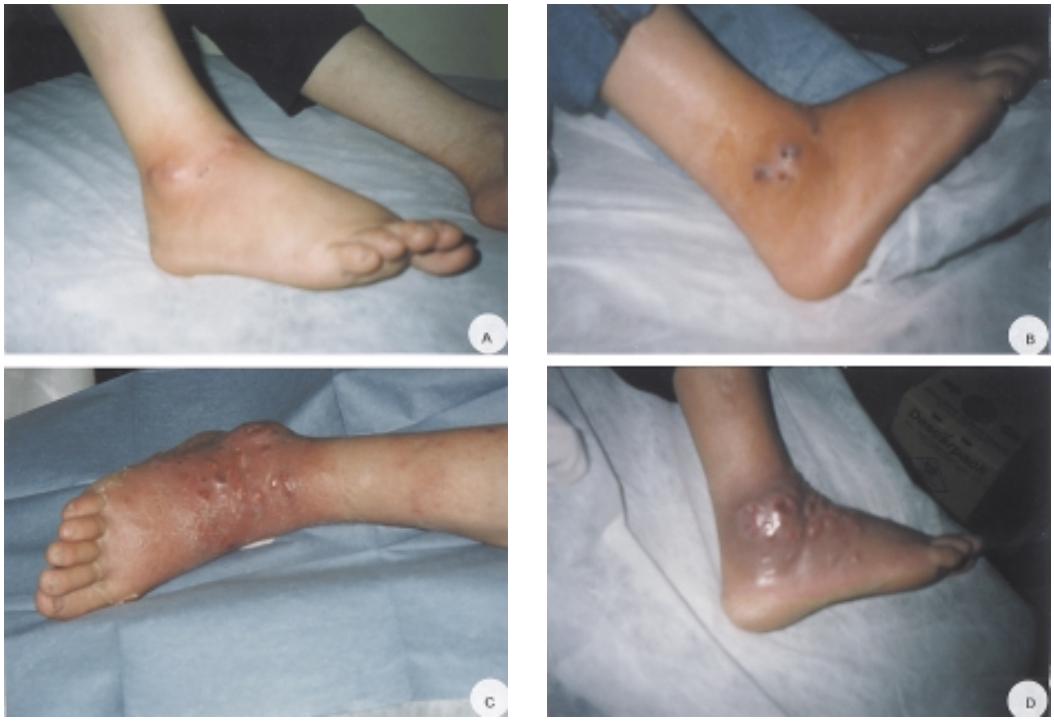

Fig. 1 - Evolution of the fungal infection. Aspect of the nodular lesions on the right ankle. A) On 28 August 1996; B) on 30 August; C) on 20 September, and D) on 4 October 1996.

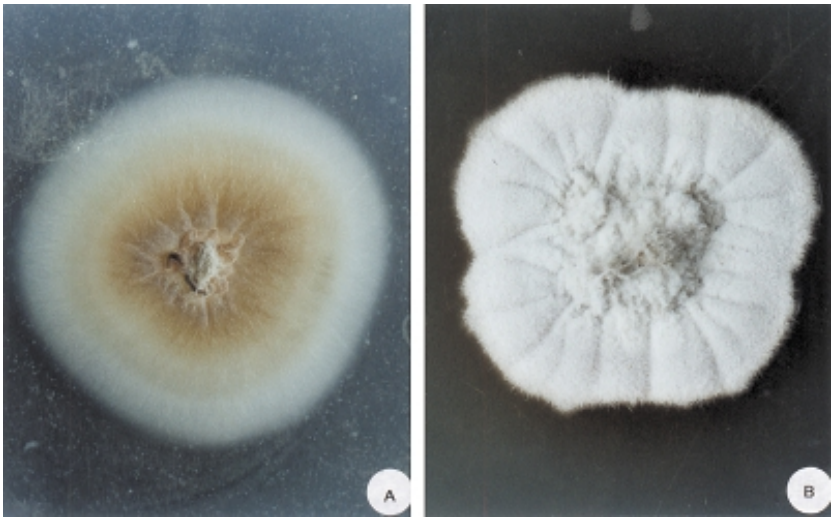

Fig. 2 - *Phialemonium curvatum*. A) Colony on potato-agar and B) colony on Sabouraud agar after 14-day incubation at room temperature.

treatment was discontinued on the 143rd day due to a uremic-hemolytic syndrome and GVHD prophylaxis was only maintained with prednisone. Two months later, purplish and painful nodular lesions occurred on the right ankle, without concurrent fever or other signs of systemic infection. Some lesions drained spontaneously, while others developed a fluctuation or necrotic point. Direct examination of the secretion obtained by lesion puncture showed the presence of hyphae but the biopsy of adjacent normal skin failed to demonstrate fungal infection. One mg/kg/day amphotericin B was introduced for the treatment of a supposed *Fusarium* infection due to the characteristic of the lesions. After discontinuation of corticoid therapy and despite the introduction of antifungal drugs, new lesions continued to arise, reaching confluence and infiltrating the skin, leading to a "mycetoma-like" aspect. Conventional amphotericin B was replaced with a liposomal formulation in an attempt to use a higher dose (3 mg/kg/day) with lower toxicity. Ten days after the material was seeded, the microscopic aspect of the conidia suggested the presence of *Acremonium sp*. The lesions evolved, draining spontaneously without response to the clinical treatment with amphotericin B. On day +233, darkening of the colonies led us to suspect that the fungus was not *Acremonium* and *Phialemonium* was subsequently identified. Amphotericin B was discontinued and ketoconazole (600 mg/day) was introduced. RX of the right foot and CT scan of the foot, thorax and abdomen were performed to rule out osteomyelitis and/or organ involvement. These exams were repeated during and at the end of follow-up and persisted negative. Ten days later, as a gradual worsening of the lesions was observed, surgical debridement of the lesions was performed and amphotericin B was restarted in combination with ketoconazole. All skin and subcutaneous tissue was removed in various surgical debridement sessions until the macro and microscopic aspect of the bloody area no longer showed the presence of the fungus. The patient received two skin grafts to repair the bloody area. During this period, secondary *Enterobacter cloacae* infection occurred and the patient had several episodes of fever and bacteremia controlled with systemic antibiotic therapy, Hickman catheter removal and surgical debridement of the lesions followed by a second skin graft on day +289. Thirty-two days later, direct examination and cultures of both secretion and skin tested negative for *Phialemonium* as well as histopathology. Since a great improvement of the lesion was observed, amphotericin B was discontinued on day +338 after a total dose of 6,050 mg. Secondary prophylaxis with ketoconazole was maintained for one additional month. No recurrence of the lesions was observed up to one year after the end of treatment.

MYCOLOGIC STUDY

Direct examination of the material obtained from the lesion showed few branched, septate hyphae and some apparently hyaline dilated cells. We first believed that this was a case of hyalohyphomycosis but the initially white colony later becoming ochraceous with whitish borders forming moist and plane colonies on potato-agar.

The colony became grayish on Sabouraud agar with sparse white mycelium, reaching a diameter of 33 mm after 14 days of incubation at room temperature.

Phialoconidia formed in tapering phialides similar to those of *Acremonium* were generally located in short branches of the superficial and submersed hyphae. These short prolongations were cylindric, thin and lacking the collarette. Adelophialides and some well-developed phialides frequently without basal septum were observed. The conidia were unicellular, hyaline, cylindric and most of them allantoid.

Based on these observations, the diagnosis was *Phialemonium curvatum*.

DISCUSSION

The genus *Phialemonium* has now been accepted to be an agent of phaeohyphomycosis (AJELLO, 1986; MATSUMOTO *et al*., 1994; MATSUMOTO & AJELLO, 1998; KWON-CHUNG & BENNETT, 1992) or of hyalohyphomycosis (MATSUMOTO *et al*., 1994; MISHRA *et al*., 1992), and is therefore currently considered to be a phaeoid fungus.

McGINNIS *et al*. (1986) described a secondary *Ph. obovatum* infection in a burned child. LOMAX *et al*. (1986) reported a case of osteolytic lesions in the left tibia of a dog caused by *Ph. obovatum*.

KING *et al*. (1993) described two cases of phaeohyphomycosis, one in the form of a cyst and the other as peritonitis, caused by *Ph. curvatum* and *Ph. obovatum*, respectively. MAGNON *et al*. (1993) observed an osteolytic lesion caused by *Ph. obovatum* in humans and SCHONHEYDER *et al*. (1996) reported a case of valvular endocarditis. GUARRO *et al*. (1999) isolated *Ph. curvatum* from the circulating blood of two immunosuppressed patients hospitalized due to neoplasias, and proposed that *Ph. dimorphosporum* is a synonym for this species. The cited authors showed that seven *Phialemonium sp*. samples were sensitive to the inhibitory action of amphotericin B, itraconazole, ketoconazole, miconazole and fluconazole *in vitro*.

The medical literature has been reporting an increasing number of cases of disseminated or non-disseminated infection in immunocompromised patients, as shown, for example, by the study of SMITH *et al*. (2000) who observed a disseminated infection with *Ph. obovatum* in a dog.

Different fungi present in the environment or part of the indigenous or human microbiota may, in certain "opportunities", change from a saprobic or saprophytic organism to a pathogenic one, causing variable clinical pictures ranging from febrile benign processes to septicemia, which, in some cases, may be fatal if not diagnosed and treated early. In the present case, mycetoma-like aspect was the clinical manifestation of *Phialemonium curvatum* localized infection and systemic disease was ruled out after extensive investigation. Although the presence of the fungus had never been demonstrated on the three skin biopsies that were performed during follow-up, the diagnosis of mycetoma caused by *Phialemonium curvatum* was assumed since no other agent was identified while clinical symptoms evolved. *Enterobacter cloacae* colonized the bloody area and caused secondary systemic infection after the mycetoma-like lesion was established and the surgical debridements were started.

The present case also stresses the decisive role of the surgical debridements in the control of the infection as reported in the other cases in the literature (KING *et al*., 1993), as well the need of skin grafts to repair the bloody area and accelerate healing.

The sample isolated in the present study was identified as *Ph. curvatum* due to the presence of allantoid conidia. The authors intend to alert mycologists and clinicians about the rarity of the case and the increasing occurrence of opportunistic fungi in immunocompromised patients.

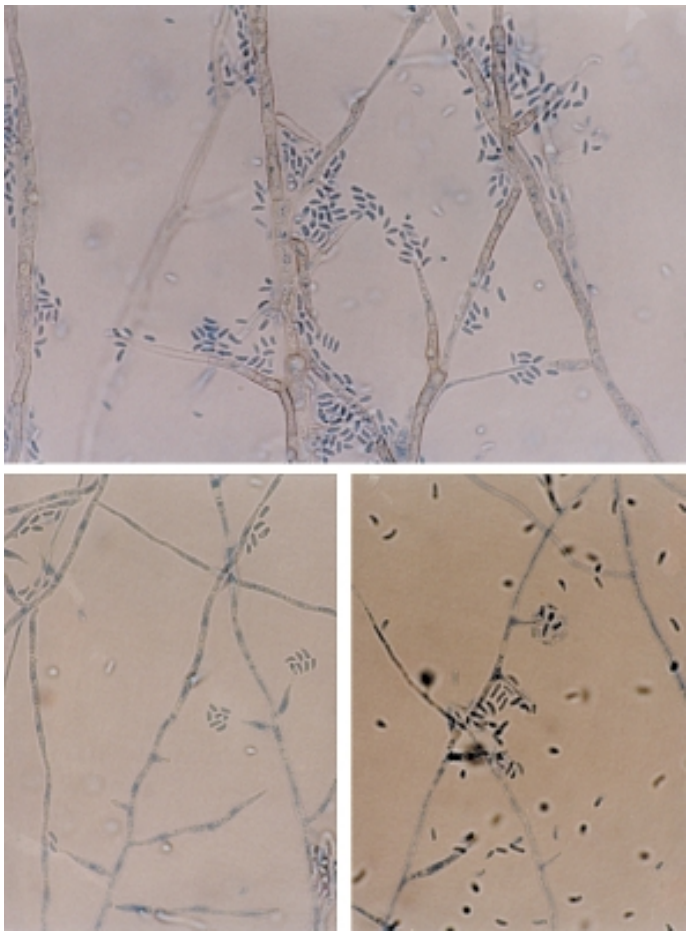

Fig. 3 - *Phialemonium curvatum*. A) Hyaline and dematiaceous hyphae with lateral phialides, frequently without a basal septum. Accumulation of hyaline conidia was observed at the apex, most of them allantoid. B) and C) Hyaline hyphae, phialides and adelophialides (1000X).

RESUMO

Infecção por *Phialemonium curvatum* pós-transplante de medula óssea.

Os autores registram caso de infecção cutânea em transplantado de medula óssea provocada por *Phialemonium curvatum* Gams et Cooke, 1983. O gênero *Phialemonium* foi criado em 1983 por Gams & McGinnis, com três novas espécies: *Ph. obovatum*, *Ph. curvatum e Ph. dimorphosporum*, sendo intermediário entre *Acremonium* e *Phialophora*. Atualmente este fungo é considerado como feóide, podendo provocar eventuais lesões de feo ou hialo-hifomicose. Espécies deste gênero vêm sendo descritas como agentes oportunistas em seres humanos e em outros animais, principalmente na vigência de imunossupressão. No caso que registramos, o paciente era portador de mieloma múltiplo, tendo recebido transplante halogênico sendo doador seu irmão, HLA-compatível. Dois meses após o transplante, lesões nodulares, arroxeadas e dolorosas surgiram no tornozelo direito. Algumas dessas lesões drenaram espontaneamente, com a demonstração de filamentos micelianos aparentemente hialinos, cultivando-se *Ph. curvatum* inicialmente identificado como *Acremonium* sp. Foi instituido tratamento com anfotericina B e, posteriormente, itraconazol. Debridamento cirúrgico das lesões foi instituido com dois enxertos cutâneos para fechamento da área cruenta. Profilaxia secundária com cetoconazol, mantida por mais de um mês e depois suspenso, sem recidiva do processo. Os autores fazem comentários sobre a patogenicidade do gênero *Phialemonium*.

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