Disseminated fusariosis in a lymphoproliferative syndrome. A report of two cases

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Abstract

Disseminated fusariosis is an increasingly frequent fungal infection in immunodeficient patients, especially in those with severe and prolonged neutropenia receiving chemotherapy for a hematologic malignancy or having a bone marrow transplant. Cutaneous manifestations are more frequent than in other opportunistic mycoses. A bad response to systemic wide-spectrum antifungal drugs is the rule; high dose liposomal amphotericin B or voriconazole are suggested as therapeutic options.

We report 2 patients with invasive fusariosis, where appearance of dermatologic lesions was one of the clues leading to diagnosis (Dermatol Argent 2008;14(3):191-195).

Key words: Fusarium, disseminated fusariosis, febrile neutropenia, voriconazole.

Introduction

Fungi of Fusarium genus are filamentous, hyaline, septated, and produce infections of the hyalohyphomycosis group. This fungal genus of worldwide distribution is a soil saprophyte and a common plant pathogen.1 Occasionally, it may cause local infections in immunocompetent hosts (in nails, surgical wounds, burns, paranasal sinuses, eyes, and bones).2,3 In immunocompromised patients, mycosis behaves as opportunistic, comprising a group of entities known as emerging diseases. Disseminated infection appears almost exclusively in these patients, particularly those having a hematologic disease with long periods of severe neutropenia as a result of treatment with immunosuppressive/ssent drugs.

Clinical cases

Case 1

A 57-year-old female patient with history of breast cancer, parotid gland cancer, gastric ulcer, and hypertension, who was diagnosed with acute myeloid leukemia, and received chemotherapy with cytosine arabinoside, daunorubicine, and etoposide. Five months after starting treatment, she had an episode of febrile neutropenia and melena, and was admitted in the Clinical Department. Blood samples were cultured, resulting in isolations of Escherichia coli, and antibiotic therapy with imipenem 2 g/day for seven days was indicated. She remained febrile, and a thorax computed tomography was obtained, evidencing diffuse infiltrate in lower left lung. The patient developed dermatosis with papules and erythematous-purpuric nodules with vesicle-crusty core of 1 to 3 cm in diameter, later evolving to necrosis; lesions were located on the head, the trunk and limbs, and were associated to intense myalgia (Figure 1). Several days
later, the patient showed edema of both eyelids of left eye (Figure 2), conjunctival injection and loss of sight. Skin biopsies were obtained for histopathological study and cultures (mycological and bacteriological). The histopathological examination reported: preserved epidermis, dermis with diffuse hyalinosis, and with the PAS technique large septated hyphae and chlamydospores in one end were identified in the blood vessel walls and adjacent to the adnexal structures. Skin and vitreous humor cultures evidenced growth of *Fusarium solani*, with septated 3 to 8 μm thick branched hyphae, frequently in 45º angle and with a constriction area where branching emerged. An antimycotic scheme was indicated with intravenous liposomal amphotericin B 250 mg/day and intravenous voriconazole 400 mg/day, but the patient died with diagnosis of disseminated fusariosis with endophthalmitis.

**Case 2**

A 18-year-old male patient with history of localized mediastinum lymphoblastic lymphoma, with poor response to chemotherapy and radiotherapy, and who was subjected to bone marrow transplant. He was admitted two years later to the Clinical Department of the hospital with severe headache, vomiting, and general impairment due to progression of the underlying disease. During hospitalization, great bone marrow involvement was found, together with blast crisis with febrile neutropenia; thus, a joint scheme was indicated, with chemotherapy (mitoxantrone, cisplatin and cytosine arabinoside) and antibiotic treatment with vancomycin 2 g/day, amikacin 1 g/day, and imipenem 2 g/day for ten days. Blood cultures resulted in isolations of *Escherichia coli* and beta-hemolytic streptococcus. The patient evolved favorably. At 20 days of hospitalization, fever reappeared in the neutropenia context, associated with intense myalgia and skin lesions represented by papules, plaques and erythematous painful nodules in upper and lower limbs (Figure 3). Lesions evolved to the production of a central necrotic crust tending to ulceration. New cultures and skin biopsies were done, and they developed filamentous fungi of *Fusarium* spp. Histopathology of the skin reported preserved epidermis, dermis with follicular adnexa with septated elements and chlamydospores in the distal end, consistent with hyalohyphomycosis. PAS and Grocott stains were performed, and confirmed said findings (Figures 4 and 5). Antibiotic regimen with amphotericin B 60 mg/day during three days was indicated. The patient did not improve, and change/rotation to liposomal amphotericin B 300 mg/day was decided, but without the expected response. Oral itraconazole 400 mg/day was added, together with treatment with granulocyte-colony stimulating factor. The patient evolved unfavorably, his hematologic malignancy progressed, the disseminated mycosis persisted, and he died.
Infections caused by *Fusarium* genus are grouped as hyalohyphomycosis, a term adopted by Ajello and Mc. Ginnis to name the mycosis where the etiologic agent is represented by non-pigmented, septated, hyaline hyphae in the mycelial wall.4

*Fusarium* spp. have long been recognized by causing low-virulence, localized fungal infections, mainly in eyes, skin and nails in immunocompetent patients.2,6 In immunosuppressed patients, they behave as opportunistic pathogens causing severe disseminated infection. Although the first case was described in 1973 in a girl with acute leukemia,7 its incidence noticeably increased in the last two decades with the emergence of new immunosuppressive/antitumor drug therapies; therefore, it currently is included in the group of entities called emerging diseases.

There are about 50 species of *Fusarium*, whereof the most commonly affecting humans are: *F. solani*, *F. oxysporum* and *F. moniliforme*. In most described cases, the involved agent in the disseminated infection is *F. solani*.8 The most often found species in onychomycosis is *F. oxysporum*.6 Portals of entry may be the respiratory airways and gastrointestinal tract, paranasal sinus, skin (ulcers, burns, foreign bodies, and intravenous catheters) and nails.9-12 A further infection source is by contact with contaminated waters in the hospital setting; therefore, it is advisable not to use shower water for personal hygiene of neutropenic patients.13

Main risk factors of localized infection are trauma and presence of a foreign body colonized by this filamentous fungus (e.g., keratitis secondary to the use of contact lenses).

Predisposing factors in disseminated disease are prolonged and severe neutropenia, and T-cell immunodeficiency, as well as graft-versus-host disease, and immunosuppressors therapies in general.1,3,9,14

Clinical manifestations of disseminated fusariosis usually appear on the skin (60-90 percent), respiratory airways and paranasal sinuses (70-80 percent), although any organ may be involved.9,11,14,15

The high frequency of fusariosis cutaneous involvement contrasts with other opportunistic mycosis such as candidiasis and aspergillosis, where skin involvement is rare.16,17

Dermatologic lesions are often found as papules and painful necrotizing violaceous erythema nodules (similar to ecthyma gangrenosum), or necrotic eschars with peripheral erythematous ring, as target lesions; less commonly, blisters, pustules and purpura may appear.15,17-19 Lesions may be localized at any area, especially in limbs.11 They may occur in different developmental stages, thus giving a polymorphic aspect. High fever and intense myalgia complete the presentation. Our two patients showed necrotic skin lesions, intense myalgia and fever in the neutropenia context. Therefore, we suggest that disseminated fusariosis should be suspected in any patient with underlying hematologic disease, and severe neutropenia, persistent fever, intense myalgia, and respiratory and cutaneous involvement (particularly rapidly necrotizing nodules) (Table 1).

In order to reach a diagnosis, skin biopsy, blood cultures, and chest and paranasal sinus image studies are the most important tools.
Histopathology of skin lesions disclose septated hyaline hyphae 3 to 8 μm thick, in closed angle, more or less branching, invading intermediate and deep layers of the skin, and extending to the blood vessels, where they cause thrombosis and later necrosis. These findings are indistinguishable from those seen in aspergillosis, an infection from which it must be differentiated, due to the very good response of *Aspergillus* to antifungal treatments.16 (Table 2). Blood cultures are useful to reach a final diagnosis, where *Fusarium* genus isolation is much easier from disseminated disease than other opportunistic fungi. According to the authors, blood culture sensitivity is 40 to 70 percent.4,9,11 Diagnosis of species of *Fusarium* genus is difficult to reach, due to the rapid morphologic change of colonies.20

Disseminated fusariosis mortality rate is 80 to 100 percent,9,14 because of the immunocompromised status of the host and the poor response of fusariosis to antifungal treatments. The therapeutic options include high-dose amphotericin B, 1mg/kg/day, or as liposome 5mg/kg/day; though resolution of the persistent neutropenia is crucial for patient recovery.12,21 Therefore, use of granulocyte-macrophage colony-stimulating factors is necessary for therapeutic success.11,24

On the other hand, the newer antifungals of the triazole group, especially voriconazole (6 mg/kg loading dose every 12 hours on the first day and then 4 mg/kg/day every 12 hours) are an alternative in resistant disseminated fusariosis.25,26

Prognosis of disseminated fusariosis is very poor, due to the patient’s general conditions upon the mycosis diagnosis, and since there is no specific antifungal therapy against *Fusarium* spp. Prevention is the management clue in these patients. Prevent contact with stemmed waters, or the use of showers in high-risk patients. Search and try to prevent areas of injured skin when using catheters or adhesive bands on these patients. Perionyxis or onychomycosis by *Fusarium* must be ruled out in patients prior to any intended neutropenia or bone marrow transplant; adequate treatment must be carried out if diagnosis is confirmed.

**References**


