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CLINICAL REPORT

Chronic Infection Due to *Fusarium oxysporum* Mimicking Lupus Vulgaris: Case Report and Review of Cutaneous Involvement in Fusariosis

M. PEREIRO Jr.[1], M. T. ABALDE[1], A. ZULAICA[2], J. L. CAEIRO[2], A. FLÓREZ[1], C. PETEIRO[1] and J. TORIBIO[1]

Departments of Dermatology, [1]Faculty of Medicine, Complejo Hospitalario Universitario, Santiago de Compostela, Spain and [2]Hospital Xeral CiesVigo, Spain

A 67-year-old female presented with a 20-year-old lesion involving the right ear and preauricular area mimicking tuberculous lupus. *Fusarium oxysporum* infection was confirmed by biopsy studies and cultures. The biopsy specimen showed an unusually extensive dermal invasion with fungal hyphae. This is an uncommon clinical presentation for *Fusarium* infection in a healthy patient. When referred to us, the patient had received antifungal therapy with itraconazole without any benefit. Improvement was obtained with fluconazole therapy. The spectrum of cutaneous involvement related to *Fusarium* spp. includes toxic reactions, colonization, superficial indolent infection, deep cutaneous or subcutaneous infections and disseminated infection.

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Manuel Pereiro Jr., MD, PhD, Departamento de Dermatología, Facultad de Medicina, C/. San Francisco, s/n, 15705 Santiago de Compostela, Spain.
E-mail: manuelpe@usc.es

Fusarium spp. are soil and plant saprophytes commonly associated with human and animal myco-toxicosis. However, species in this genus play an emerging role as pathogens in human infections. *F. solani*, *F. oxysporum* and *F. verticilloides* are the species most frequently reported as human pathogens in localized and disseminated infections (1).

Reports on localized *Fusarium* infections have mainly described therapeutic and diagnostic difficulties in onycho-mycosis and keratitis and other extra-cutaneous involvement. There have been few reports of atypical cutaneous fusariosis. We report a well-documented case of long-standing localized cutaneous fusariosis mimicking lupus vulgaris that responded well to fluconazole therapy. Cutaneous diseases related to *Fusarium spp*. infections are reviewed.

CASE REPORT

A 67-year-old female with a history of type II diabetes, which had been treated orally, was referred to our hospital for diagnosis and management of a 20-year-old lesion in the right ear. The patient did not recall any previous traumatic injury in the affected area. In 1980 she was diagnosed with infectious granuloma caused by fungi or mycobacteria. At that time, all complementary tests for mycobacteriosis were negative. No mycological cultures were carried out. However, based on clinical and histological findings she then received treatment with rifampicin, isoniazid and ethambutol for 2 months, followed by rifampicin and isoniazid for 7 months. In 1982 she received tentative cryotherapy. In 1990, as a result of the presence of fungal elements in biopsy specimens, she was diagnosed with cutaneous mycosis and received treatment with itraconazole 200 mg/day for 6 months followed by terbinafine 250 mg/day for 2 months, without any benefit.

In January 2000 she was referred to us, presenting with an infiltrated, soft plaque involving the whole helix, slight pruriginous, resembling lupus vulgaris (Fig. 1). Routine tests, including blood cell count, biochemistry and X-ray examination were normal. A standard multi-test for cellular immunity (tetanus, diphtheria, Streptococci, proteus, tuberculin, glycerol, Candidin, trichophytin) gave normal results. All laboratory tests for mycobacteria, including cultures and PCR detection, were negative. A biopsy specimen was taken for histological examination. Hematoxylin–eosin staining showed a chronic inflammatory response produced by epithelioid cells, eosinophils and numerous giant foreign body cells. Inside the foreign

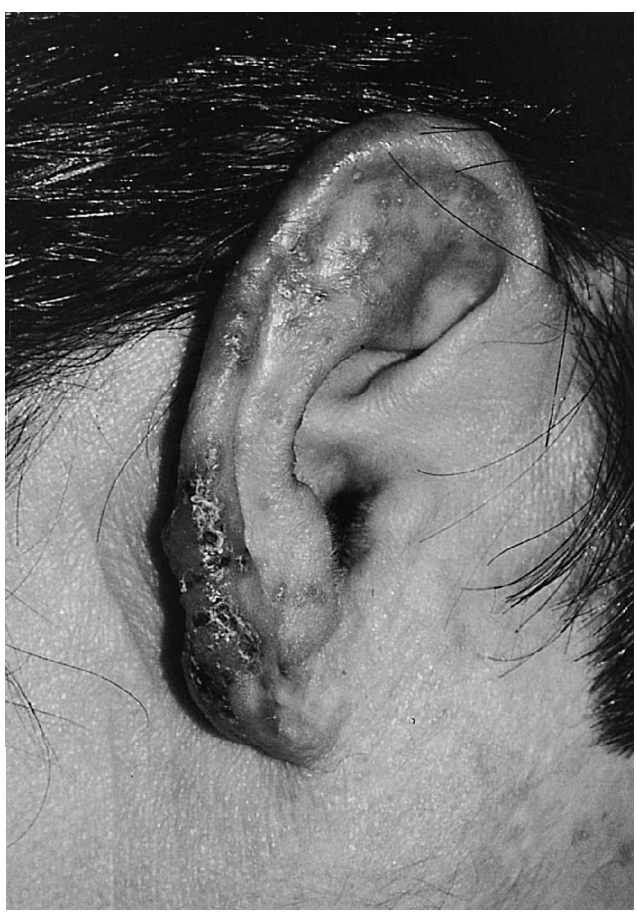

Fig. 1. Infiltrated plaque with erythematous areas, covered by slight scaling and scars and with badly defined margin in the right ear.

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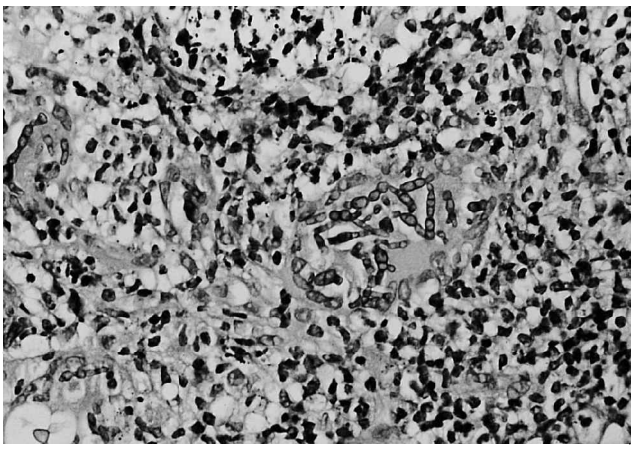

Fig. 2. PAS-positive hyphae sparsely distributed in the dermis (original magnification ×400).

body cells, pale structures resembling fungal hyphae were observed. Periodic acid–Schiff (PAS) staining showed numerous hyphae sparsely distributed in the dermis and also inside giant cells (Fig. 2).

A new biopsy specimen for mycological identification was sampled onto chloramphenicol–gentamicin–Sabouraud's agar and cyclohexamide–Sabouraud's agar at 25°C and 37°C. Chloramphenicol–gentamicin–Sabouraud's agar cultures yielded velvety colonies, white to pale gray in color at 25°C and orange at 37°C. Old cultures developed violet areas at both 25°C and 37°C. Subcultures and slide cultures were prepared for species identification onto oatmeal agar, potato sucrose and potato dextrose agar. Microscopic examination revealed wide vegetative aerial mycelium with septate, branched hyphae, scarce fusiform, 3–5-celled, slightly curved, macroconidia, pointed at the tip, numerous, single-celled, oval/ellipsoid, non-chain microconidia developed on short lateral conidiophores and intercalary, single or paired, hyaline, smooth-walled chlamydospores (Fig. 3).

On the basis of these data we identified the colony as *F. oxysporum* Schlecht.:Fr. (2), and started treatment with oral fluconazole 150 mg/day. After 3 months the patient showed a marked improvement.

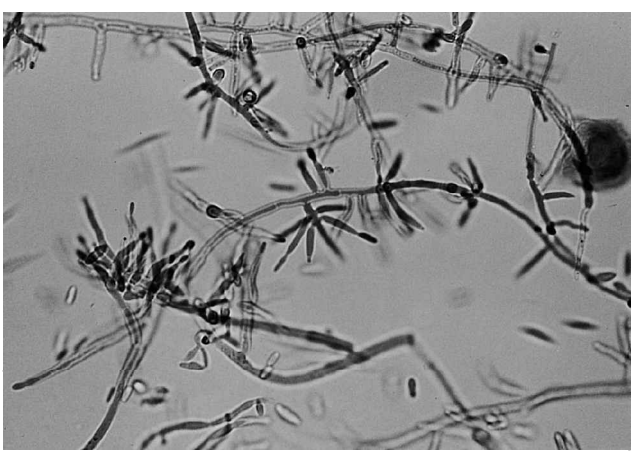

Fig. 3. Slide cultures on Sabouraud's agar reveal the presence of well-ramified, septate, hyaline hyphae, with lateral, short, simple, sometimes branched, conidiophores and sparse, ellipsoid, single-celled microconidia.

DISCUSSION

Cutaneous diseases related to *Fusarium* spp. can appear in both immunocompromised and healthy hosts and include toxic reactions, colonization, superficial infection, deep cutaneous or subcutaneous infections and disseminated infection.

Exposure to the toxin deoxynivalemol caused lesions of the skin and mucous membranes, suggesting a toxic reaction, in grass planters in The Netherlands (3). Chronic indolent superficial fusariosis limited to the skin appendages or corneal layer, namely onychomycosis and intertrigo, is frequent (4). *F. oxysporum* was reported as causing distal subungual, proximal subungual (5) and superficial white toenail mycosis in a patient who presented with a low extremity temperature after cranial trauma (6). Colonization in surgical wounds, severe burns, venous and arterial leg ulcers is a common finding (1, 7, 8) and was related to diabetes in one case (7). However, *F. oxysporum* was also reported as being the only causative agent of a large foot ulcer (9). When fungal hyphae reach the dermis and subcutaneous tissue, subcutaneous nodules (10, 11), sporotrichoid nodules (12), panniculitis (13), mycetoma (14, 15) or chronic granuloma (16, 17) can be observed in both immunocompromised and healthy hosts.

In healthy hosts, localized papular and pustular lesions that developed after trauma were reported (18, 19). A case presenting with extensive chronic granulomatous lesions involving the 2 arms, in which the authors could not demonstrate any known immune defect, was caused by *F. oxysporum* (20). Our case report described a diabetic patient who denied any trauma at the onset of the process. However, over the years she had received several treatments, including tentative cryotherapy. This cryotherapy injury possibly facilitated the deep invasion and later clinical appearance, as well as further antifungal resistance.

Host responses in localized cutaneous chronic *Fusarium* infections have included granuloma (16), pseudocarcinomatous hyperplasia (15), sometimes with carcinomatous changes (21), and eccrine syringofibroadenomatous hyperplasia (22). Despite the long evolution time, granuloma without carcinomatous changes was observed in the present case.

The first case of systemic infection by *Fusarium* spp. was published in 1973 (23). Since then, a number of systemic infections caused by *Fusarium* spp. alone (24, 25) or in association with other agents (26) have been published. Neutropenia is probably the most important predisposing factor for disseminated infections in immunocompromised hosts. The clinical picture is characterized by fever and muscular pain refractory to treatment. Cutaneous involvement is common, including painful erythematous maculae, palpable or non-palpable purpura, flaccid pustules and necrosis on the trunk, face, scalp, extremities, palms and soles (1, 23–26).

There is no agreement between the *in vitro* and *in vivo* results in the reports describing the management of *Fusarium* infections and therefore none of the therapeutic regimens reported can be considered ideal (1). The gold standard for the treatment of disseminated infection continues to be amphotericin B, either alone or in combination with 5-fluorocytosine, rifampicin or azole derivatives (1, 23–26). In deeply located infections, good results were obtained by

combining surgical excision with antifungal treatment (27). However, reported treatments have produced contradictory results depending on the patient's condition (3, 6–27). In the case reported here the patient's history, which revealed itraconazole resistance, and the benign condition of a 20-year-old infection caused us to reject the use of a more aggressive therapy. Fluconazole has little activity on intracellular fungi (28), but does enhance the killing activity of neutrophils, monocytes and macrophages (29). In our case clinical improvement was obtained after 3 months of fluconazole therapy.

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