Cutaneous phaeohyphomycosis of the sole caused by *Exophiala jeanselmei* and its susceptibility to amphotericin B, 5-FC and ketaoconazole

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Abstract

Cutaneous phaeohyphomycosis due to *E. jeanselmei* developed on the sole of a 61 years old Japanese female who was receiving the corticoids therapy for nephrotic syndrome. Although the causative fungus was resistant to 5-fluorocytosine, amphotericin B and ketoconazole, the lesion was successfully treated by surgical excision.

Introduction

The genus *Exophiala* contains six or more species that are known as opportunistic pathogens of man and animals (1, 4, 5–10). Mycoses caused by members of this genus include keratitis, mycetoma, phaeohyphomycosis (chromoblastomycosis in part) and tinea nigra (Table 1). In Japan, two species of *Exophiala,* namely, *E. dermatitidis* (Kano) de Hoog and *E. jeanselmei* (Langeron) McGinnis et Padhye, have been occasionally recovered as causative agents of human deep mycoses (2).

Described herein is a case of cutaneous phaeohyphomycosis of the sole in a 61 years old female who was receiving the corticoids therapy for nephrotic syndrome which had begun five years earlier.

Table 1. Human pathogenic members of the genus *Exophiala.*

Species	Mycoses
E. dermatitidis	Phaeohyphomycosis, (Chromoblastomycosis in part)
E. jeanselmei	Keratitis, Phaeohyphomycosis, Mycetoma
E. moniliae	Phaeohyphomycosis
E. spinifera	Phaeohyphomycosis
E. werneckii	Tinea nigra

Materials and results

Case report

In December 1980, a 61 years old female farmer was admitted to the hospital. She had a history of long-term steroid therapy for nephrotic syndrome and of chronic hepatitis. Physical examination revealed a 2 × 3 cm, flatly elevated, erythematous plaque on the plantar aspect of her right foot. The lesion had begun approximately 3 months earlier as a small, slightly tender, erythematous papule, which gradually increasing in size. It scarcely fluctuated, but discharged a drop of yellowish pus. The direct microscopic examination of the pus revealed branching, septate hyphae that were pale yellowish-brown in colour. Regional lymph nodes were not enlarged and chest film revealed no abnormalities.

Laboratory studies on admission disclosed the following abnormal values: white blood cell count 10,200/mm^3 with 60% neutrophils, 28% lymphocytes, 11% monocytes, and 1% basophil; total protein 6.3 g/100 ml, urea nitrogen 25.2 mg/100 ml, cholesterol 325 mg/100 ml, alkaline phosphatase

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123 mU/100 ml, and lactic dehydrogenase 677 mU/100 ml. Intradermal PPD and sensitization to dinitrochlorobenzene (DNCB) produced positive delayed reactions. Immunoglobulin and complement concentrations were within normal limits.

Systemic administration of 5-fluorocytosine, 10 g/day by oral, was started on January 7, but discontinued on February 6, because of preexisting nephrotic syndrome and a high MIC of the causative fungus for the drug. Since the cutaneous lesion was almost unchanged in size at that time, it was excised totally on February 9. She was discharged from the hospital on February 28, after that no recurrence of the lesion was noted.

Histology

The cutaneous tissue excised at surgery was fixed in 10% formalin and H&E and PAS slides were prepared. The lesion was solitary, encapsulated by thin collagenous connective tissue, and confined to the dermis and subcutaneous fat. The dermis showed a polymorphous granulation tissue composed of lymphocytes, histiocytes, epithelioid cells, and multinucleated giant cells (Fig. 1). In the center of the granulation tissue, multiple foci of microabscesses were present. Short, branching, septate hyphae that were pale yellowish-brown in color and 2 to 5 μm in width were found within giant cells or as a liberated form in the tissue (Fig. 2).

Mycology

After four days of inoculation of the pus at 25 °C on Sabouraud dextrose agar, pure culture of *E. jeanselmei* developed on the isolation media. The colonies were at first yeast-like and black, and later covered with short aerial hyphae, becoming velvety and mouse grey to olive grey in colour. The reverse colour was olivaceous black. Microscopically, the colonies primarily consisted of globose or ellipsoidal yeastlike cells which were thin-walled, at first subhyaline, but later somewhat darker in colour, and 3 to 6 μm in diamater. Each yeast-like cell, after some inflation, produced similar shaped, smaller conidia from 1 to 3 loci; some of the conidiogenous loci appeared to be annellides (Fig. 3). The fungus grew well at 37 °C on several different agar media.

On potato dextrose agar plates at 25 °C, the colonies were initially smooth, becoming velvety with age. The colonies were 3 cm in diameter and mouse grey to olive grey in color after 30 days. The conidiogenous cells were annellides having typical characteristics of those of *E. jeanselmei* (Fig. 4) (9). The annelloconidia were one-celled, subglobose or ellipsoidal, smooth-walled, almost hyaline, and 1.2–2.6 × 1.0–4.0 μm in size. They accumulated in balls that tended to slide down the annellides and along hyphae.

The organism had a MIC of 100 μg/ml for amphotericin B, 50 μg/ml for 5-fluorocytosine, and 12.0 μg/ml for ketoconazole when tested according to the methods of Shadomy & Espinel-Ingroff (12).

Discussion

The genus *Exophiala* includes seven or more species (1, 4, 5, 6–10), five of which have caused documented infections of man (Table 1). Some mycologists (3) would place *E. spinefera* in the genus *Rhinocladiella,* while McGinnis (5) claimed that the langeniform annellide arising at the apices of spine-like conidiophores of *E. spinifera* justifies its placement in the genus *Exophiala* rather than *Rhinocladiella.* Also McGinnis (5) placed *E. dermatitidis* in the new genus *Wangiella* elected by himself. According to McGinnis, *W. dermatitidis* forms conidia predominantly from phialides without collarettes, but in contrast *Exophiala* produces annellides. However, de Hoog (3) disagreed and placed the fungus in the genus *Exophiala* because he regarded its mode of conidium production as annellidic. Nishimura *et al.* (11) have also confirmed by scanning electron microscopy that the conidia of *E. dermatitidis* arise predominantly from annellides. Therefore, *E. dermatitidis* is best classified in *Exophiala* than *Wangiella.*

In Japan, phaeohyphomycoses due to *E. jeanselmei* have been occasionally reported. Recently Fukushiro (2) reviewed 16 such cases which appeared in the literature before 1977. Among the 16 cases, the patients were predominant in female and in middleaged to senile adults. Although the site of the lesion was exclusively restricted to the exposed areas, their clinical pictures varied among cases from cutaneous or subcutaneous abscesses, often with ulceration or fistula, and subcutaneous nodules, to flat or verrucous plaques resembling to chromoblastomycosis. The predisposing factors were found in 5 cases; i.e., diabetes 2, systemic lupus

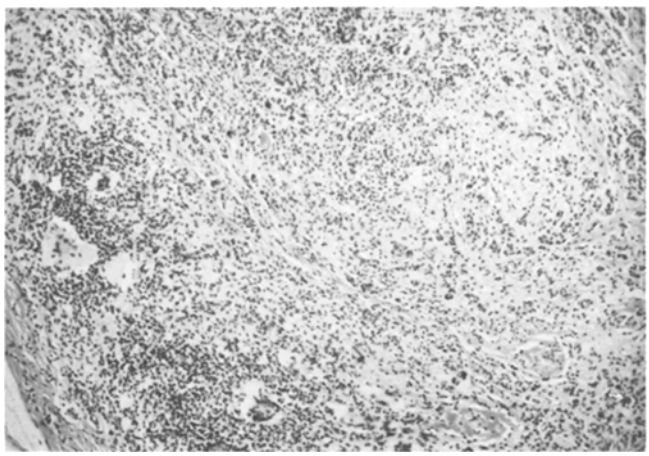

Fig. 1. Granulomatous lesion in the dermis. H&E, × 60.

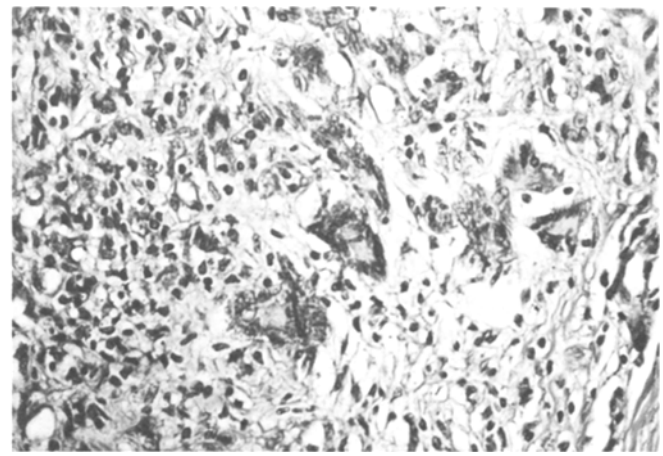

Fig. 2. Fungal elements in the granulation tissue. PAS, × 250.

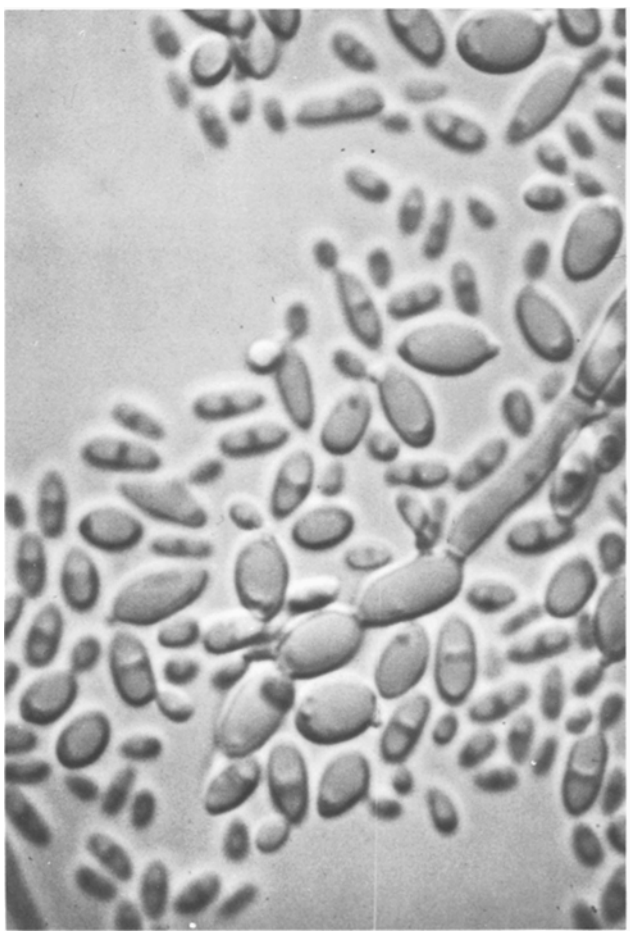

Fig. 3. E. jeanselmei (SM 1527). Yeast-like cells producing conidia. × 2 000, by Nomarski differential interference contrast microscopy (NDICM).

Fig. 4. SM 1527. An annellide with annelloconidia. × 2 000, by NDICM.

erythematodus 2, and leukemia 1. An interesting case is a 14 years old male who had concurrent infection due to *E. dermatitidis* of the several visceral organs including the central nervous system.

The mechanism by which an opportunistic fungus, like *E. jeanselmei,* establishes chronic, slowly spreading infection in man has not satisfactorily known. Some cases have been attributed to depressed cellular immunity, however most patients with the fungal infection were in good health and showed no depressed cellular immunity (2). Immunological tests in our patient also revealed no remarkable abnormalities, although she was receiving continuously the corticoids therapy for nephrotic syndrome.

Recently many successful cases of treatment of deep or systemic fungal infections with 5-fluorocytosine or imidazole derivatives, as ketoconazole, have been reported. Our present patient was also given at first a systemic administration of 5-fluorocytosine, but one month later it was discontinued because the causative fungus proved to be resistant to the drug in vitro as well as in vivo. Also the fungus was resistant to amphotericin B and ketoconazole in vitro, however the lesion was successfully treated by surgical excision. There was no question that the therapy of discrete cutaneous phaeohyphomycosis, as our present case, should be simple excision whenever the causative fungus proved to be resistant to antifungal agents as mentioned above.

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