Phaeohyphomycosis caused by *Exophiala* species has recently been reported with increasing frequency with wide-spread use of immunosuppressive agents and improved laboratory methods for making the diagnosis. However, no standard therapeutic regimens have been established to date. Often, treatment is frustratingly prolonged, especially for larger lesions when surgery is not feasible.

We report a case of cutaneous verrucous phaeohyphomycosis caused by *Exophiala jeanselmei* in a 75-year-old female. She was successfully treated as an outpatient with a combination of oral itraconazole and topical heat therapy with disposable pocket warmers, followed by cryotherapy. A complete resolution without complications or disfigurement was achieved. (Dermatol Sinica 22: 327-332, 2004)

**Key words**: Phaeohyphomycosis, *Exophiala jeanselmei*, Topical heat therapy

隨著免疫抑制劑的廣泛使用，以及診斷學的進步，*Exophiala*所引起的表皮暗色絲孢菌病在近年來有越多越多的病例報告。然而，至今仍然沒有一標準有效的治療方式。通常療程冗長結果令人沮喪，特別是無法切除的大片疣狀病塊。

吾人報告一例發生在七十五歲女性，由*Exophiala jeanselmei*所致的表皮疣狀暗色絲孢菌病。成功的以口服itraconazole加上熱敷包熱治療，再施予局部液態氮冷凍。達到臨床上治癒且無併發症或破壞性疤痕產生。（中華皮誌 22: 327-332, 2004）
INTRODUCTION

The term phaeohyphomycosis was first coined by Ajello et al. in 1974 to encompass a distinct, heterogenous group of mycotic infections. These are characterized by the appearance in tissue of dematiaceous, yeast-like cells, pseudohyphae-like or hyphal elements of all shapes, or any combination of these forms. With the number of iatrogenically immunocompromised patients increasing, fungi causing phaeohyphomycosis are receiving more and more attention. Exophiala species are among the most important genera involved.1, 6-7 Members of the genus Exophiala are widely distributed in nature, especially in soil, wood and other plant matter, but also in drainpipe sludge, polluted water, sewage, and agricultural warehouses. The most typical lesions according to the literature are subcutaneous phaeohyphomycotic cysts or abscesses at the site of trauma. Rarely, the infection presents as verrucous cutaneous plaques with nodularities.1, 3-5, 8 Lymph node involvement or hematogenous dissemination are rare but may occur in immunocompromised patients.1, 5-7 Therefore, prompt diagnosis and treatment with effective regimens are important to decrease morbidity and mortality.

CASE REPORT

A 75-year-old female had diabetes mellitus and iatrogenic Cushing syndrome due to prolonged use of systemic steroids for joint pain. She was seen in our clinic with a two-year history of an enlarging erythematous, brownish crusted verrucous plaque with several fluctuant nodules studded with pustules on her right forearm (Fig. 1A). She was unaware of any antecedent trauma. Initially, the lesion consisted of small nodules, but it gradually progressed in size and developed oozing and discharge. On her first visit, we performed a skin biopsy for histologic diagnosis as well as fungal, bacterial, mycobacterial and atypical mycobacterial cul-

Fig. 1
(A) An enlarging verrucous plaque with fluctuant nodulopustules on the right forearm.
(B) Lesions responded well within a month of the combination therapy with itraconazole plus topical heat. Some residual nodules were noted.
(C) A complete resolution was observed at the third month of the combined regimen. Two sessions of cryotherapy have been done on the recalcitrant nodules.

Fig. 2
(A) Histopathology showed suppurative granulomatous inflammation with focal microabscesses. (H & E, x20) Only a few hyaline fungal elements were found with hematoxylin and eosin stain. Inset showed a hyaline fungal element engulfed by a multinucleated giant cell.
(B) With melanin stain, abundant dematiaceous fungal elements were readily unveiled.
Histological examination revealed suppurative granulomatous inflammation with focal microabscesses (Fig. 2A). The infiltrate was characterized by polymorphonuclear leukocytes, histiocytes, lymphocytes, and numerous multinucleated giant cells. On careful examination, a few hyaline fungal elements were seen with hematoxylin and eosin stain (Fig. 2A, inset). However, both periodic acid-Schiff and Gomori’s methenamine-silver stains clearly demonstrated abundant fungal elements.

Fungal culture of minced specimen on Sabouraud dextrose agar (SDA) resulted in the growth of black yeast-like colonies. At 27°C, the growth was a moist-appearing, olive-brown to dark yeast-like colony with a raised center, which rapidly became velvety, covered with gray filamentous aerial mycelium. In the second week, the colony grew to a diameter of 2.0 cm (Fig. 3A). A microscopic morphology study with a slide culture revealed brown, septate, branching hyphae with conidiophores extending laterally (Fig. 3C). The characteristic conidiogenesis were clearly observed with the ellipsoidal conidia emerging form the tapered tip of the cylindrical or lageniform annellides. The patient was instructed to apply one disposable pocket warmer on the affected area and secure it with an elastic bandage everyday.

Exophiala jeanselmei

Initially, itraconazole (200 mg/day) was continued as monotherapy for four months, but the lesion showed little response. The patient was then placed on the regimen with the combination of itraconazole plus topical hyperthermia. As a source of heat, a regular sized (13.5cm x 10cm) disposable chemical pocket warmer that covered the entire lesion was used for each daily treatment (Fig. 4). The pocket warmer can provide a sustained average temperature of 45°C for twenty hours to raise the skin surface to the desired temperature of 42°C to 43°C. The patient was instructed to apply one pocket warmer to the affected area above layers of gauze and secure it with an elastic bandage. Each daily treatment was set for 10 hours. To avoid thermal burns, the patient was told not to keep the warmer on the skin during sleep, to take it off whenever unbearable heat sensation, and to keep it away for one or two days if there was still any pain in the area.
The combination of itraconazole and topical heat therapy yielded marked improvement within a month, although there were some residual nodules (Fig. 1B). In addition to the combined therapy, a monthly cryotherapy was then performed on these recalcitrant lesions using an open spray, two-freeze-thaw-cycle method. The freeze time was about fifteen seconds on each lesion with a 2 mm peripheral frozen rim, and the thaw time was about one minute until the white color faded away. The procedure was then repeated.

With two sessions of cryotherapy, a satisfactory clinical resolution was obtained at the end of the third month of the combination therapy with itraconazole plus topical heat (Fig. 1C). The regimen was discontinued. No signs of relapse were noted after two months' follow up.

DISCUSSION

Phaeohyphomycosis includes a wide spectra of mycotic infections caused by dematiaceous fungi. These organisms, by definition, have melanin or melanin-like pigments in their vegetative cell walls, which impart a golden brown color under light microscopy. However, this feature is not demonstrated in all cases. In our patient, only a few hyaline hyphae were demonstrated with hematoxylin and eosin, which delayed the diagnosis of phaeohyphomycosis. A melanin stain was later performed and numerous fungal elements were readily unveiled (Fig. 2B).

Treatment of phaeohyphomycosis has been frustrating. Approaches include surgery and chemotherapy. Although resection of a single cystic lesion may offer the best hope of cure, surgery is not always possible, especially for larger plaques or when the patients are in poor conditions for surgical intervention. Besides, risks of re-implantation or contamination after surgery were reported. Many drugs have been used in the treatment of phaeohyphomycosis, including systemic amphotericin B, ketoconazole, 5-fluorocytosine, griseofulvin, fluconazole, miconazole, as well as various combinations of them. However, there has been a high rate of failure and frequent relapses. Itraconazole, a triazole agent, has shown great promise and is now considered first-line chemotherapy for phaeohyphomycosis. It is less toxic than many other antifungal agents, easily administered orally, and fungi are less resistant to it. In our patient, itraconazole did not seem to be effective as a single agent, but it worked well as part of a combined regimen.

Topical heat therapy was first introduced for the treatment of sporotrichosis and other dermal fungal infections by Romero et al. and Conti-Diaz et al. in the 1960s. Recently, there are increasing reports of its effectiveness, particularly since its first successful trial in chromoblastomycosis by Yanase et al. which resulted in a complete cure in 9 weeks. Our patient had significant improvement as early as the second week when topical heat was added to itraconazole.

As a source of heat, many modalities have been reported, including electric pads, infrared frames, etc. We chose disposable pocket warmers for our patient for several reasons. They are readily and inexpensively available from any pharmacy in Taiwan, and provide a sustained and safe heat source to maintain the skin surface at the desired temperature of 42°C to 43°C for at least twenty hours. They are flexible enough to closely conform to the contours of the body, and they are light enough to be worn under a bandage without hindering daily activity. It is easy to instruct the patient on how to apply the pocket warmers at home.

The mechanisms underlying the effect of topical heat therapy are not completely clear. On culture, the Exophiala jeanselmei infecting our patient was not able to grow at above 40°C, which may explain the direct fungicidal or fungistatic action of topical heat on the organisms. Additionally, Nishimura and Miyaji have demonstrated that cellular immunity plays an important role in deep fungal infection, with a local relative immunodeficiency of cellular immunity of the skin that may be due to its lower temperature as compared to visceral...
organs.\textsuperscript{18, 19} Therefore, local heating may enhance cellular immune reactions.\textsuperscript{15, 17, 19} Topical heat also increases local circulation, which may deliver more itraconazole to the area. Shortening the treatment period may also be of benefit in reducing undesirable side effects and perhaps in preventing drug resistance. This type of combined therapy has been reported be safe and effective.\textsuperscript{15, 17, 19}

After maximal reduction of lesions was achieved, we used cryotherapy in addition to eliminate residual nodules. We used the open-spray technique in order to produce a deeper freezing depth.\textsuperscript{20, 21} No prophylactic antibiotics were given. Our experience demonstrated several advantages of cryotherapy. It is a simple, easily accepted procedure with low cost, requiring no anesthesia, which can be carried out in the outpatient clinic. It also yields a good cosmetic result.\textsuperscript{20-22} We therefore recommend cryotherapy for residual lesions in non-flexion areas without underlying vital structures.

Based on our experience in this patient, we recommend outpatient treatment of cutaneous phaeohyphomycosis with the combination of itraconazole and topical heat therapy, followed by cryotherapy as needed.

REFERENCES


