皮膚毛黴菌病

– 病例報告 –

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Cutaneous Mucormycosis

—A Case Report—

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Cutaneous mucormycosis is an uncommon fungal infection, occurring mainly in immunosuppressed and diabetic patients, leading to mortality if adequate treatment is delayed. It could also happen in normal healthy person after localized trauma. Here we report a case of cutaneous mucormycosis manifesting as a painful erythematous papule, rapidly progressing to necrotic ulcer with eschar formation. Treatment was initiated with extensive surgical debridement, intravenous amphotericin B, and oral itraconazole. No recurrence was found at 7 months follow-up. (Dermatol Sinica 22 : 53-58, 2004)

Key words: Mucormycosis, Amphotericin B, Itraconazole

皮膚毛黴菌病是一種少見的黴菌感染，主要發生在免疫功能不全及糖尿病患者，假如延遲治療的話會導致死亡。此病也可發生於健康患者在局部受傷之後。在此吾人報告一位皮膚毛黴菌感染病例，臨床表現爲一疼痛紅色丘疹並快速地進展成壞死性潰瘍合併焦痂形成。治療以廣泛外科清創、靜脈注射amphotericin B及口服itraconazole。經七個月追蹤後無再發現象。(中華皮誌22 : 53-58, 2004)

INTRODUCTION

Mucormycosis refers to fungal infection caused by members of the order Mucorales. The genera *Rhizopus*, *Absidia*, *Rhizomucor* and *Mucor* are the organisms most commonly isolated from patients suffering from mucormycosis.[1] The principle infections involve rhinocerebral, pulmonary, gastrointestinal, cutaneous, and disseminated mycosis.[1, 2] Conditions associated with an increasing risk of mucormycosis include

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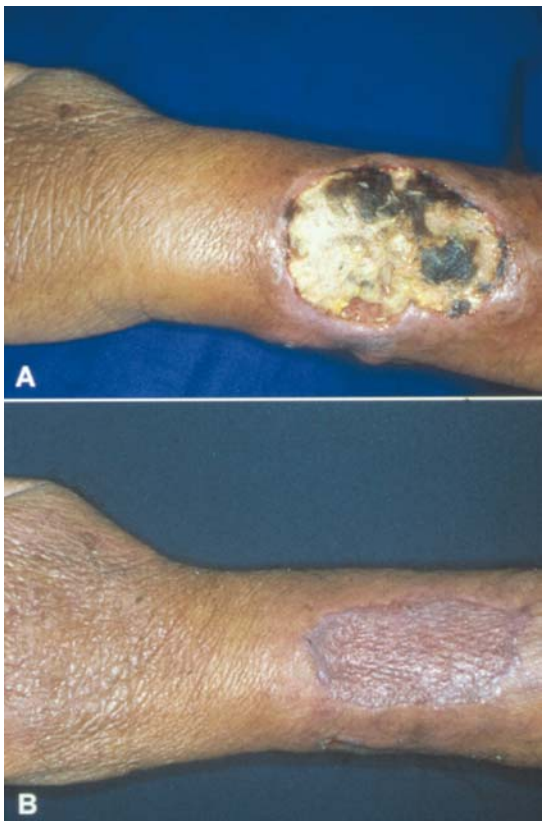

Fig. 1
(A) Necrotic ulcer with black eschar formation on his left forearm.
(B) 7 months post-treatment with extensive surgical debridement with split-thickness skin graft, intravenous amphotericin B and oral itraconazole.

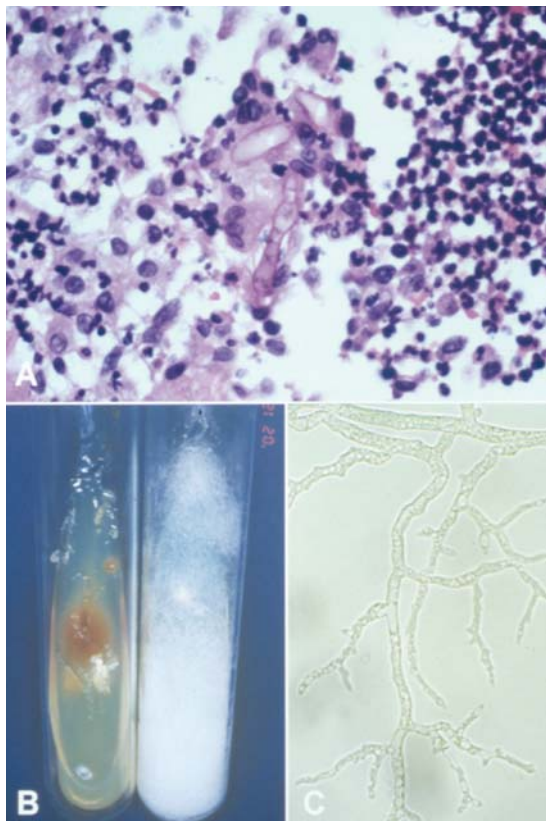

Fig. 2
(A) Suppurative granulomatous inflammation with broad nonseptate hyaline hyphae. (H & E, x400)
(B) Sabouraud's dextrose agar (right tube) at 25°C yields whitish fluffy colonies and Mycosel (left tube) yields no colony.
(C) Unstained Sabouraud's dextrose agar slide culture reveals broad aseptate hyphae. (H & E, x400)

immunosuppression, diabetes mellitus, hematologic malignancy, and renal failure.[3] We report a case of cutaneous mucormycosis manifesting as a painful erythematous papule. Good outcome was achieved by combination treatment with extensive surgical debridement, intravenous amphotericin B and oral itraconazole.

CASE REPORT

A 56-year-old male presented to our clinic with a 5 X 7 cm necrotic ulcer with partial black eschar formation and purulent discharge, surrounded by erythematous to violaceous elevated border, which had rapidly developed from a painful erythematous papule on his left forearm over the past 2 weeks (Fig. 1 A). There were two other erythematous suppurative nodules adjacent to the main necrotic ulcer. There was no known history of trauma or insect bite. Past history disclosed the uptake of some kind of "black herbal pills" for 2 months before clinical presentation for treatment of his hepatitis C. Oral antibiotics provided little clinical benefit. On admission, the patient was afebrile with normal vital signs in the absence of regional lymphadenopathy.

Significant laboratory findings included mildly elevated liver enzyme, positive anti-

HCV antibody, low serum cortisol levels of 0.113 μg/dL (normal, 6-28 μg/dL) in the morning and 0.297 μg/dL (normal, 3-16 μg/dL) in the afternoon. A biopsy from the purulent nodule showed suppurative granulomatous inflammation with broad nonseptate hyaline hyphae (Fig. 2A). Tissue culture on Sabouraud's dextrose agar at 25℃ yielded whitish fluffy colonies (Fig. 2B), which microscopically displayed broad nonseptate hyphae in unstained slide culture, identified to be a member of the Mucorales (Fig. 2C). The species of pathogen could not be further determined due to lack of sporangia and rhizoids. After extensive wound debridement, intravenous amphotericin B was initiated at dosage of 0.25 mg/kg/day and raised by 0.25 mg/kg/day until daily dose of 50 mg. Topical use of silver sulfadiazine cream dressings and oral levofloxacin 200 mg twice daily were administered to cover the secondary bacterial infection of *Citrobacter freundii*. One week later, a second debridement was done and no more active infection was found in histopathologic examination and fungal cultures of the specimens. A split-thickness skin graft was then placed. After a total dose of 340 mg given over 9 days, amphotericin B was discontinued due to the impaired renal function and drug intolerance of the patient accompanied by fever, chills and nausea. The therapy was then switched to oral itraconazole 100 mg twice daily and maintained for 3 months. The uptake of skin graft was good and no recurrent infection was found at 7 months follow-up (Fig. 1B).

Table I. Taxonomy of the Agent of Zygomycosis*

Kingdom fungi
Phyllum Zygomycota
Class Zygomycetes
Order Mucorales
Family Mucoraceae
Absidia corymbifera
Apophysomyces elegans
Mucor insidous
Mucor racemosus
Mucor circinelloides
Rhizomucor pusillus
Rhizopus arrhizus
Rhizopus azygosporus
Rhizopus microsporus var. microsporus
Rhizopus microsporus var. rhizopodiformis
Family Cunninghamellaceae
Cunninghamella bertholletiae
Family Saksenaea
Saksenaea vasiformis

**Adapted from* Dromer F, McGinnis MR: Zygomycosis. In: Anaissie EJ, McGinnis MR, Pfaller MA, *et al*., eds. Clinical Mycology. 1st ed. Philadelphia: Churchill Livingstone, 297, 2003.

DISCUSSION

Mucormycosis is a saprophytic fungal opportunistic infection of the order Mucorales under the class Zygomycetes (Table I).[2] The order Mucorales is composed of a main family Mucoraceae and other minor families such as the Cunninghamellaceae, Saksenaea, etc. The common pathogens belonging to the family Mucoraceae are *Rhizopus*, *Mucor*, *Rhizomucor* and *Absidia*, and have a wide geographic distribution and are found in decaying vegetables, foodstuffs, fruits, soil, and animal excreta. The mode of entry of the organism is through the respiratory tract or by direct inoculation of traumatized skin. After inhalation or inoculation, the spores germinate and grow in susceptible host tissues, turning into invasive hyphae. Pathogenesis results chiefly from invasion of blood vessels by hyphae, leading to tissue infarction in various organs.[1, 2] While rhinocerebral mucormycosis is the most common form,[2, 4] cutaneous mucormycosis becomes an increasingly prevalent presentation.[5] The clinical features are characterized by rapidly progressive course with eschar formation, usually resulting to fatality.[1] The initial clinical appearance of cutaneous mucormycosis is generally non-specific and may present as a painful erythematous induration of skin resembling common phlebitis, pyoderma gangrenosum, ecthyma-like lesions or non-healing ulcer.[1, 6-8] The lesions may progress to a necrotic ulcer with black eschar formation surrounded by indurated erythema.

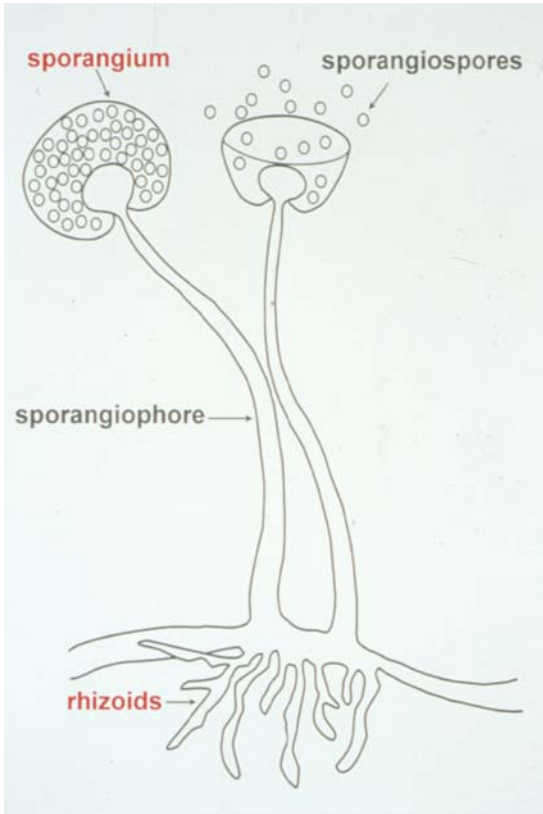

Fig. 3
The sporangium (plural: sporangia) and rhizoids.

The diagnosis can usually be made histologically by identifying broad, nonseptate or sparsely septate hyphae, ranging from 7 to 30 μm in diameter in the tissue. Vascular invasion with thrombosis is commonly seen.[2, 4, 9]

Further species identification of our case was difficult because of the absence of taxonomically important structures such as sporangia or other specific structures such as rhizoids (Fig. 3). In addition to aforementioned common isolates of cutaneous mucormycosis, *Saksenaea vasiformis* or *Apophysomyces elegans* has been isolated from the tissues of patients with cutaneous mucormycosis and such cases are mounting.[10-16] Determination of *Saksenaea vasiformis* and *Apophysomyces elegans* is sometimes difficult because of the lack of sporulation on routine mycological media.[14, 17] Further methods, such as corn meal agar, Czapek Dox or Czapek solution agar, hay infusion agar, saline agar or a technique recommended by Padhye and Ajello have been successfully used to stimulate sporulation.[13, 14, 17]

The prognosis of cutaneous infections is much better than those of the other forms of mucormycosis. The mortality rate is 16% for cutaneous mucormycosis as compared to 67% for rhinocerebral infections and 100% for disseminated or gastrointestinal infections.[10] Early diagnosis and prompt treatment can improve the prognosis. The major management consists of extensive surgical debridement with concomitant intravenous amphotericin B and control of the predisposing factors.[2] Surgical debridement with adequate free margin is needed, while the extent of debridement remains poorly defined.[18] Successful results have been described in two reported cases with 1 cm free margin and in one reported case with 2 mm free margin, respectively.[18, 19] Amphotericin B remains one of the most potent and rapidly acting antifungal agents available today.[2] In addition to the major side effect of nephrotoxicity, amphotericin B can cause infusion-related adverse events like nausea, vomiting, fever, chills, hypotension, local thrombophlebitis, and cardiac arrhythmia.[2, 20] For rhinocerebral mucormycosis, a total dose of at least 2 g was recommended by most authors.[21] For cutaneous mucormycosis, however, the exact duration and total dose for adequate treatment remains to be determined.[2, 4] An optimal treatment may depend on the resolution of symptoms and infection. Due to intolerance to the adverse effects of amphotericin B, our patient had only received an accumulated dose of 340 mg. The new lipid formulations of amphotericin B such as liposomal amphotericin B, amphotericin B colloidal dispersion and amphotericin B lipid complex could represent promising alternative drugs in the treatment of mucormycosis due to their relatively little nephrotoxicity.[20] The effectiveness of itraconazole is controversial; while some authors suspect its effectiveness in the treatment of cutaneous mucormycosis,[2, 22] others consider it has some potential benefit. In a case of acute non-

lymphocytic leukemia with cutaneous mucormycosis developing around a central venous catheter after bone marrow transplantation, successful treatment was achieved with wide excision, intravenous amphotericin B and oral itraconazole, and there was no any evidence of recurrence at 2 years follow-up.[23] In another immunocompromised female patient with abdominal wall mucormycosis, treatment with amphotericin B followed by oral itraconazole 200 mg twice daily for 3 months seemed to eradicate the fungal infection.[24] The therapeutic response in these two cases and our case suggested that surgical debridement combined with amphotericin B and itraconazole can be effective in cutaneous mucormycosis.

In conclusion, cutaneous mucormycosis should be considered in patients with rapidly progressive necrotic ulcer covered with eschar and surrounding erythematous swelling, especially under the circumstances of immunosuppression and poor response to antibiotic treatment. Histologic examination and fungal culture are required for a quick and definitive diagnosis. Early aggressive extensive surgical debridement with adjunctive antifungal therapy are essential for an optimal outcome. For those patients intolerant to conventional intravenous amphotericin B, oral itraconazole might be considered as an alternative option, although more evidences are needed to confirm its efficacy.

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