PHAEOHYPHOMYCOSIS CAUSED BY *EXOPHIALA* SPECIES IN IMMUNOCOMPROMISED HOSTS

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Abstract: *Exophiala* species are rarely implicated in clinical diseases. In the past 2 years, we have treated phaeohyphomycosis caused by *Exophiala* species in three immunocompromised patients. Two of these patients presented with subcutaneous abscess or cutaneous verrucous lesions due to *Exophiala jeanselmei*. The former, an 81-year-old woman, had pulmonary tuberculosis and the latter, a 62-year-old man, had undergone heart transplantation and was receiving immunosuppressive treatment. The third patient, a 62-year-old woman, had acute lymphoblastic leukemia and developed lymphadenitis due to *Wangiella (Exophiala) dermatitidis*. In each case, the fungus was discovered on a Gram stain of the aspirated material and was identified by conventional tests. One patient died of bacterial pneumonia with acute respiratory distress syndrome and the other two were treated successfully with surgical excision and antifungal agents. With the more frequent and widespread use of immunosuppressive agents, the incidence of *Exophiala* infection will certainly increase. Surgical excision or debridement with or without antifungal agents may offer the possibility of cure for phaeohyphomycosis due to *Exophiala* species.

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Wangiella dermatitidis

Exophiala species were first identified on the island of Martinique (West Indies) by Jeanselme in 1928 [1]. They belong to the dematiaceous group of fungi and are widely distributed in the environment, especially in soil, wood, and other plant matter [1, 2]. The dematiaceous fungi produce three kinds of disease: phaeohyphomycosis, chromoblastomycosis, and mycetoma. Phaeohyphomycosis is a broad term describing a heterogeneous group of superficial, cutaneous and corneal, subcutaneous, and systemic mycoses that contain dematiaceous yeast-like cells or hyphal elements of the dematiaceous fungi. *Exophiala* species have been reported to cause both subcutaneous phaeohyphomycosis and mycetomas with increasing frequency, especially among patients with immune deficiency [3, 4]. Experimental studies using animal models suggest that immune suppression may be the most important predisposing factor in systemic phaeohyphomycosis [5], which has been reported in patients with diabetes [6], recipients of organ transplantation [7], patients with pulmonary tuberculosis [8], patients treated with steroids [9], and healthy individuals [10]. Nosocomial *Exophiala jeanselmei* pseudoinfection involving 16 patients after sonography-guided aspiration of thoracic lesions has also been reported [11].

Exophiala species are distributed worldwide but are more common in tropical and subtropical regions [12, 13]. Here we report three cases of phaeohyphomycosis caused by *Exophiala* species. All three patients were immunocompromised. With the increasing use of immunosuppressive therapies for organ transplant recipients and improved microbiologic techniques, the incidence of *Exophiala* infection is likely to increase.

Case Reports

Case 1

An 81-year-old woman developed a prolonged cough and low-grade fever in August 1999. Pulmonary tuberculosis was

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Table. Clinical characteristics of three patients with *Exophiala* infection

Case No.	Age (yr) / Sex	Organism	Site	Underlying condition	Treatment	Outcome (period of follow-up)
1	81 / F	*E. jeanselmei*	Foot	Pulmonary tuberculosis	Amphotericin B	Died
2	62 / M	*E. jeanselmei*	Hand	Heart transplantation recipient	Itraconazole, debridement	Survived (3 yr) No recurrence
3	62 / F	*W. dermatitidis*	Axillary lymph node	ALL (before C/T)	Itraconazole, excision	Survived (2 yr) No recurrence

ALL = acute lymphoblastic leukemia ; C/T = chemotherapy

diagnosed from characteristic chest roentgenogram findings and a sputum culture positive for *Mycobacterium tuberculosis*. A soft nodule over the medial aspect of the left foot developed 5 months after the start of anti-tuberculosis chemotherapy. The nodule enlarged gradually without obvious symptoms. She was admitted to the hospital because of low-grade fever and jaundice in February 2000. Gram stain of the pus aspirated from the lesion revealed septated hyphae with branches at acute angles. Amphotericin B was administered and her fever gradually improved. At the same time, multiple retroperitoneal lymphadenopathy was found on abdominal sonography and computerized tomography. Lymphoma was suspected, but the patient refused further invasive study. On the 28th hospital day, she died of bacterial pneumonia with acute respiratory distress syndrome.

Case 2

A 62-year-old man had undergone an orthotopic heart transplant in 1997 due to ischemic cardiomyopathy. Afterwards, he received immunosuppressant therapy with cyclosporin, prednisolone, and azathioprine. A 4 x 6-cm plaque with a rough surface developed on the dorsum of his right hand (Fig. 1) 10 months after the heart transplant. Filamentous hyphae (Fig. 2) were found on the gram-stained smear of the pus aspirated from the lesion. Histopathologic examination of the skin biopsy showed budding yeast-like cells. Initially, the patient was treated daily with 200 mg itraconazole and topical liquid nitrogen therapy. Six weeks later, the skin lesion had progressed despite medical treatment. Magnetic resonance image of his right hand revealed nodular lesions involving the subcutaneous fat and extensor tendon. He underwent surgery, and a 9 x 6-cm multinodular mass with pus was excised. He received itraconazole for another 6 weeks after the operation, and the skin lesions resolved. During 3 years of follow-up, there was no recurrence of phaeohyphomycosis.

Case 3

A 62-year-old woman had two palpable lymph nodes (2 x 2 cm and 1.5 x 1 cm) in the left axilla when acute lymphoblastic leukemia was diagnosed. Histopathologic examination of the excised lymph node revealed budding yeast-like cells, soli-

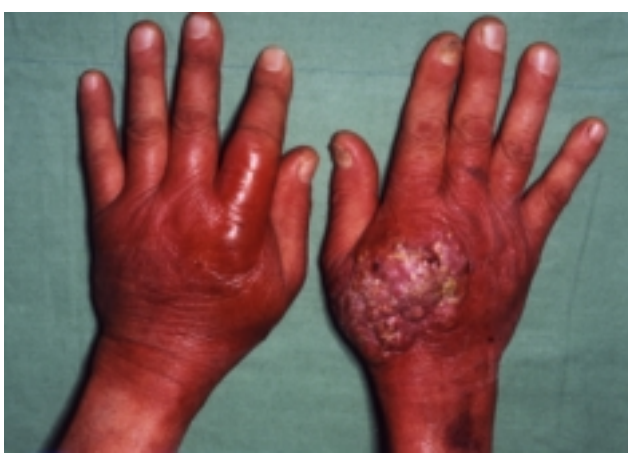

Fig. 1. *Case 2: 4 x 6-cm verrucous plaque with a rough surface on the dorsum of the right hand of a patient who had undergone heart transplantation.*

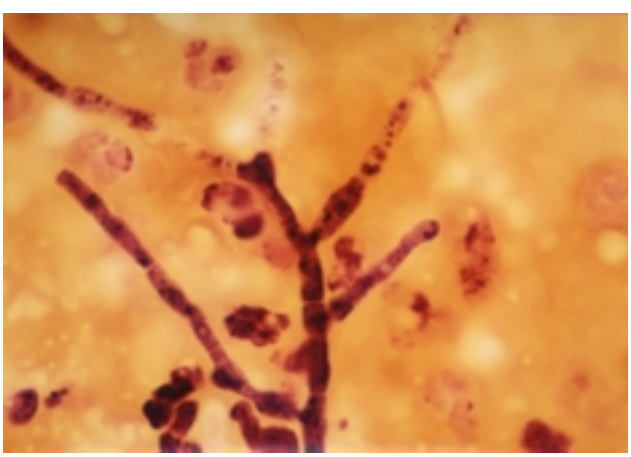

Fig. 2. *Case 2: Gram-stained smear of aspirated pus from the verrucous lesion of the same patient showing gram-positive and branching hyphae surrounded by abundant polymorphonuclear cells (x 1,000).*

tary or in chains, within the granulomatous tissue. She took itraconazole for 4 months, and amphotericin B was administered during the neutropenic stage after chemotherapy. The disease did not recur during the 2-year follow-up period.

Microbiology

Cultures of the aspirated pus from Cases 1 and 2 on Sabouraud dextrose agar (BBL Microbiology Systems, Cockeyville, MD, USA) yielded a black mold after 14 days of incubation at 27°C. The slide culture revealed annelloconidia aggregating at the apex of the annellides and conidiophores. Biochemical tests showed hydrolysis of tyrosine but were negative for casein, hypoxan-thine, and xanthine. The organisms grew slowly (more than 3 weeks) at 37°C but were unable to grow at 42°C. Based on the mycologic findings, *E. jeanselmei* was identified. The culture on Sabouraud dextrose agar of a specimen from an excised lymph node from Case 3 grew a black, moist, shiny, and yeast-like colony after 20 days of incubation at 27°C. Microscopically, sparse conidia had accumulated at the apex of the phialide and down the sides of the conidiophore. The isolate had a positive hydrolysis reaction for tyrosine but was negative for casein, hypoxanthine, and xanthine. It grew well at both 37°C and 42°C. Based on the mycologic findings, *Wangiella* (*Exophiala*) *dermatitidis* was identified.

Using the E test (AB Biodisk, Solna, Sweden), performed as previously described [11], identical minimum inhibitory concentrations (MICs) of the three isolates were determined: 0.032 mg/mL for amphotericin B, 0.25 mg/mL for itraconazole, and 16 mg/mL for fluconazole.

Discussion

Infection due to *Exophiala* species is rarely reported in Taiwan [11]. In our university hospital with 2,000 beds in northern Taiwan, the first isolate of *Exophiala* species was found in 1994 [11]. Since then, a total of 19 isolates of *Exophiala* species have been recovered from clinical samples from 19 patients (including the three patients in this report). Among these isolates, 16 were collected during a pseudo-outbreak between 1994 and 1998 [11]. The three cases in the present study all acquired the infection in the last 3 years, indicating the emerging nature of this disease entity in Taiwan.

The reported risk factors for *Exophiala* species infection include systemic or topical steroid therapy [7, 9], malignancy [14], diabetes mellitus [6], and prolonged administration of broad-spectrum antibiotics [15]. The three patients in this report were all immunocompromised. The first patient had recurrent pulmonary tuberculosis and possible retroperitoneal malignancy. The second patient had received immunosuppressants after heart transplantation. The third patient had newly diagnosed acute lymphoblastic leukemia. None of the three patients were HIV positive. This is similar to findings in other reports [12]. Since T-cells are affected predominantly in patients infected with HIV, the predominant mycoses in AIDS are those normally controlled by T-lymphocytes. Granulocytes are involved primarily in the control of phaeohyphomycosis. This explains why there are so few cases of phaeohyphomycosis in patients who are HIV positive.

Traumatic inoculation has been reported in about half of patients with subcutaneous phaeohyphomycosis [9]. However, the patients in our report could not recall any recent trauma in the affected area. *Exophiala* species are the most common etiologic agents in subcutaneous phaeohyphomycosis [12]. Clinical infections due to *Exophiala* species include mycetoma, subcutaneous phaeohyphomycosis, endocarditis, pneumonia, lung abscess, synovitis, arthritis, peritonitis, esophagitis, and keratitis [12, 13, 16]. The clinical presentations of skin infection caused by *Exophiala* species include cysts in 57%, plaque type in 22%, nodular lesions in 13%, impetigo in 4%, and crust in 4% of cases [9]. The first two of our patients presented with a nodular lesion and plaque type, respectively. The third patient presented with lymphadenopathy.

Exophiala dermatitidis has been transferred to the genus *Wangiella* [17]. The morphologic distinction between *E. jeanselmei* and *W. dermatitidis* is very difficult to make. Physiologic and biochemical tests can facilitate the process of identification [18]. Both culture and biochemical tests were used for fungus identification in our patients.

Amphotericin B, 5-fluorocytosine, and azoles such as itraconazole, ketoconazole, and clotrimazole have been reported to be effective in the treatment of phaeohyphomycosis [19], but surgical excision or surgery combined with medical treatment is usually required [20]. Sudduth et al reviewed 11 cases of phaeohyphomycosis caused by *Exophiala* species [16]. Four were treated successfully with surgical excision alone. Another four were treated successfully with a combination of surgical excision and antifungal agents. One patient was treated with amphotericin B, but she died before *E. jeanselmei was* identified. Another two patients were treated successfully with a combination of surgical excision and itraconazole.

In conclusion, with the more frequent and widespread use of immunosuppressive agents, the incidence of *Exophiala* infection will certainly increase. When an immunosuppressed patient presents with subcutaneous or cutaneous nodules, phaeohyphomycosis due to *Exophiala* species should be suspected and included in the differential diagnosis. Surgical excision or debridement with or without antifungal agents may offer the possibility of a cure for phaeohypho-mycosis due to *Exophiala* species.

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