Penicillium marneffei infection is characterized by disseminated and progressive clinical course and mainly involves the skin, blood, bone marrow and lymph nodes with fever, anemia and weight loss. Mycobacterial spindle cell pseudotumor (MSP) is a peculiar and very rare form of mycobacterial infection mainly caused by Mycobacterium avium-intracellulare (MAI), and most commonly affects lymph nodes. MSP resembles spindle cells neoplasm pathologically and may be easily misdiagnosed. Both infections mainly occur in immunocompromised hosts, especially in patients with AIDS, and are easily confused with each other or other opportunistic infections clinically or/and pathologically. We reported a very rare case of cutaneous P. marneffei infection on the anterior chest with a separate MSP on the right thigh caused by MAI infection in a HIV-negative immunocompromised woman with chronic rheumatoid arthritis. The P. marneffei infection manifested multiple ulcers while the MSP presented as an ulcerated nodule. Biopsy specimens revealed numerous oval-shaped yeasts, some two-celled with a central septum (binary fission) in the former, and a dense diffuse infiltrate of spindle cells with vacuolated cytoplasm containing numerous acid-fast bacilli in the latter. The former was confirmed by fungal culture while the latter was proved by bacterial culture followed by polymerase chain reaction study. The cutaneous MSP was preceded by a chronic osteomyelitis with draining fistulae in both big toes for 2 years. The diagnosis of mycobacterial osteomyelitis was made retrospectively after reviewing the bone curettage specimens that revealed numerous acid-fast bacilli. This case represents the first case with two such rare infections. Clinicians and pathologists should be aware of these rare types of infection in immunocompromised hosts, so that the diseases could be diagnosed and treated in a timely fashion.(Dermatol Sinica 22 : 338-344, 2004)
**Introduction**

*Penicillium marneffei* infection is an emerging infection in immunocompromised patients, especially in HIV-infected patients. The infection is usually disseminated and progressive, commonly involving the skin, blood, bone marrow, lymph nodes, liver and lung. Mycobacterial spindle cell pseudotumor (MSP) is a rare form of atypical mycobacterial infection in immunocompromised hosts. MSP resembles spindle cells neoplasm pathologically and may be easily misdiagnosed. MSP usually involved the lymph nodes and only three cases of cutaneous MSP are recorded. Both *P. marneffei* infection and MSP are rare but are important because of increasing population of immunocompromised hosts, especially HIV-infected patients. Here we reported a rare case with concurrent *P. marneffei* infection and MSP in a HIV-negative patient with rheumatoid arthritis.

**Case Report**

A 45-year-old Taiwanese woman presented with a 3-month history of painful enlarging ulcers on the left anterior chest in January 2003. She had rheumatoid arthritis with severe joint deformity for 10 years and was on long-term low-dose prednisolone, methotrexate and hydroxychloroquine treatment. She denied local trauma and foreign travel. Physical examination revealed 5 deep ulcers with violaceous undermining border (Fig. 1A). Bacterial cultures of the ulcers yielded negative findings. Under a presumptive diagnosis of pyoderma gangrenosum, vasculitis or unusual infection, a skin biopsy was performed for pathology as well as fungal and mycobacterial cultures. Histopathologic examination revealed a dense suppurative granulomatous dermatitis with extensive dermal...
fibrosis (Fig. 1B). Grocott's methenamine silver (GMS) stain showed numerous thin-walled, oval-shaped yeasts, some two-celled with a central septum in the suppurative areas (Fig. 1C). Fungal culture using Sabouraud's dextrose-agar (SDA) medium at 25˚C yielded dark red colonies with red pigment diffusing into the medium, and characteristic septate and branched hyphae and conidiophores microscopically (Fig. 2). P. marneffei infection was diagnosed. Other survey including hemogram, chest X-ray and liver enzymes were within normal limits. Immunity profiles were normal except for a high serum IgG (1.8 g/L) and a low IgM (0.427 g/L). Anti-HIV antibody was negative.

Oral itraconazole 100 mg daily was initiated. The ulcers healed within one month. Itraconazole was continued for 12 weeks. In January 2004, 8 months after discontinuing itraconazole treatment, two ulcers appeared on the left anterior chest (Fig. 1D) and arm and were proven to be recurrence of P. marneffei infection by fungal culture. Itraconazole 100 mg/day was reinitiated. The ulcers again healed in about one month. The treatment was maintained to prevent further relapse.

Besides P. marneffei infection, she noticed chronic inflammation of both big toes since mid 2001. The inflammation occurred about 5 years after a Swanson arthroplasty in 1996 to correct the deformity of the big toes. Small ulcers developed on the big toes in mid October 2001, and she was referred to us for further evaluation. Fistulae were found and an X-ray study of both

Fig. 1
(A) Cutaneous P. marneffei infection manifesting deep ulcers with violaceous undermining borders on the anterior chest.
(B) Histopathology shows an ulcer with a suppurative and granulomatous infiltrate (H & E, 20X).
(C) Numerous yeast forms are found in the infiltrate (H & E, 400X) and confirmed by GMS stain (inset).
(D) Recurrence of P. marneffei infection on the anterior chest.

Fig. 2
The colonies of P. marneffei at 25˚C SDA agar (A, left, day 14, middle, day 5) are dark red with red pigment diffusing into the medium. Septate and branched hyphae and conidiophores are found microscopically (B, 400X). At 37˚C, the colonies are white with smooth surface (A, right, day 3), consisting of yeast-like cells with central septum (C, 400X).

Fig. 3
(A) Chronic osteomyelitis with pus draining fistula on right big toe.
(B) Mycobacterial spindle cell pseudotumor manifested as an ulcerated nodule on the right thigh.
(C&D) Histopathology reveals a dense diffuse infiltrate of spindle cells with eosinophilic and vacuolated cytoplasm arranged in fascicles in the dermis and upper subcutaneous tissue (H & E, C, 40X, D, 200X). Numerous acid-fast bacilli are found in the spindle cells (inset, acid-fast stain).
big toes confirmed the presence of chronic osteomyelitis. The Swanson implants were removed in November 2001. In September 2003, about 8 months after the initial diagnosis of *P. marneffei* infection, the ulcers and inflammation of the big toes worsened with painful swelling and pus drainage (Fig. 3A). Bacterial culture showed coagulase-negative Staphylococcus. Despite cephalexin therapy, the lesions did not improve. Meanwhile, a painful ulcer appeared on the right thigh.

Intermittent fever was noted since the beginning of November 2003 and she was admitted to the rheumatology service in mid November due to high fevers up to 39°C, chills, poor appetite and body weight loss (4 kg in 3 weeks). Leukopenia (2700/mm³) with lymphopenia (11%) was found. A dermatology consultation in late November revealed an ulcerated indurated nodule on the right thigh (Fig. 3B). The patient was on prednisolone 10 mg/day and without itraconazole treatment. Reactivation of *P. marneffei* infection was suspected. However, fungal cultures yielded negative results. Biopsy of the lesion revealed a dense diffuse infiltrate of spindle cells with vacuolated cytoplasm arranged in long fascicles in the dermis and upper subcutaneous tissue (Fig. 3C & D). The infiltrate also contained many neutrophils and occasional multinucleated giant cells and Langhans giant cells. Acid-fast stain showed numerous acid-fast bacilli, mostly within the spindle cells. GMS stain failed to detect fungus. *Mycobacterium intracellulare* (MAI) was isolated from the skin specimen and confirmed by polymerase chain reaction (PCR) study. MSP was diagnosed.

Antimycobacterial therapy with clarithromycin 1000 mg/day, ethambutal 800 mg/day and rifampicin 600 mg/day was initiated at the end of December 2003. In early February 2004, the patient was admitted for further care. Worsening of leukopenia (1900/mm³) with lymphopenia (20%) were noted and the CD4/CD8 ratio was reversed (32%/48%) with CD4 125/mm³ and CD8 187/mm³. The fever and the ulcers of the right thigh resolved in about 7 weeks after initiation of antimycobacterial therapy. The big toe lesions also improved gradually. Review of the pathologic specimens obtained from the osteomyelitis lesion of the big toes in 2001 revealed presence of numerous acid-fast bacilli. Mycobacterial osteomyelitis was diagnosed retrospectively.

**DISCUSSION**

*P. marneffei* is present in the soil and naturally hosted by bamboo rats. Infection in humans is reported in patients with tuberculosis, lymphoproliferative disorders, lupus erythematosus and, most commonly, AIDS. Most cases of *P. marneffei* infection occurred in residents of or travelers to the endemic area in Southeast Asia (Thailand, Hong Kong and Vietnam) and Southern China (Guanxi and Canton). A study in Thailand reported *P. marneffei* infection in 3054 AIDS patients, occurring in 3% of the AIDS patients. In Taiwan, at least 27 cases had been reported, including 18 HIV-positive cases; had travel history to the endemic areas. Our patient was immunosuppressed, HIV-negative and had no foreign travel.

*P. marneffei* is a dimorphic fungus which exists in two different forms, mold at 25°C and yeast form at 37°C. The fungal culture from the anterior chest lesions showed typical dark red colonies with reddish pigment diffusing into the agar at 25°C (Fig. 2A) and characteristic septate and branched hyphae and conidiophores (Fig. 2B). At 37°C, the colonies were white, convoluted and smooth surfaced, and consisted of yeast-like cells with central septum as a result of fission (Fig. 2C).

*P. marneffei* infection is thought to be acquired via ingestion and inhalation. It usually manifests fever, anemia, weight loss, fungemia and generalized lymphadenopathy. Skin lesions, including necrotic, skin-colored or pigmented papules or nodules, ulcers or molluscum-like lesions, are found in over 50% of the cases. Histopathologically, the skin lesions usually show suppurative and granulomatous dermatitis. The diagnosis relies on identification of the characteristic two-celled yeast forms with a cen-
tral septum microscopically and by fungal culture.

Treatment for *P. marneffei* infection has not been optimized. An open-labeled, nonrandomized study HIV-infected Thai patients with disseminated *P. marneffei* infection showed that 97% of the infections responded to treatment with amphotericin B 0.6 mg/kg/day intravenously for 2 weeks, followed by oral itraconazole 400 mg/day for 10 weeks. However, a high recurrence rate (50%) was observed within 6 months after discontinuation of treatment. Prevention of relapse was achieved by a maintenance therapy with oral itraconazole 200 mg/day. In our patient, *P. marneffei* infection was limited to a localized area of the skin and responded rapidly to low dose itraconazole (100 mg/d) therapy. However, the relapse of infection 8 months after discontinuing itraconazole suggests that a maintenance treatment might be necessary. On the other hand, the relapse occurred 4 months after the appearance of MSP ulcer on the thigh. During that time period, she had lymphocytopenia with a low CD4 count of 125/mm^3^. Therefore, the relapse of *P. marneffei* infection was in part precipitated by the deterioration of her immunity, which might be attributable to the progression of mycobacterial infection.

MSP is first described by Wood et al. in a cardiac transplant recipient with MAI infection of the hand. Since then, more than 20 cases have been reported, including AIDS (about 80%), two organ transplant recipients, and one with sarcoidosis treated with prednisolone. MAI is the most common pathogen in MSP, although *M. tuberculosis* and *M. kansasii* and Bacille Calmette-Guerin (BCG) have also been reported. MSP typically manifests lymphadenopathy involving the axillary, paraaortic, mediastinal, and mesenteric nodes. Spleen, lung, brain and skin are also affected. Cutaneous MSP has only been reported in one heart transplant recipient and two AIDS patients, and manifests as tender nodules or a firm mass on the extremities. The pathogen was MAI in two cases and *M. kansasii* in the third case. The MSP in our patient presented as an ulcerated nodule on the right thigh. However, we suspect that the infection probably started in the big toe. Mycobacterial osteomyelitis was diagnosed retrospectively after the diagnosis of the cutaneous MSP was made.

Histopathologically, MSP is characterized by proliferation of spindle cells in sheets or storiform patterns. Capillary proliferation and infiltration of lymphocytes, plasma cells, histiocytes and neutrophils are also common features. The histology of MSP lesions mimic spindle cell neoplasms such as Kaposi’s sarcoma, leiomyoma, inflammatory myofibroblastic pseudotumor and dendritic cell tumor. However, some of the histiocytes have foamy cytoplasm and numerous acid-fast bacilli can be found inside or outside the spindle cells and histiocytes. PCR study is helpful for detection of the organism and identification species of mycobacteria. The spindle cells in MSP have been shown to express histiocytic markers such as CD68, MAC 387 and alpha-1-antichymotrypsin. However, another study found expression of smooth muscle actin, suggestive of smooth muscle differentiation.

In immunocompetent hosts, mycobacterial infection usually induces granulomatous reaction with or without caseous necrosis. Suppurative granulomatous inflammation may develop in MAI or atypical mycobacterial infection. In immunocompromised hosts, the extent of inflammation and granuloma formation is usually reduced. The histology of MSP is analogous to the histoid variant of lepromatous leprosy which is typified by diffuse infiltration of spindle cells loaded with acid-fast bacilli.

Anti-mycobacterial drugs in MSP may result in good disease control but mortality has been reported probably due to poor immune function of the patients. The cutaneous and osteomyelitis in our patient responded to antimycobacterial therapy. The patient remains afebrile on itraconazole and antimycobacterial therapy which has been continued for 6 months at the time of writing.

In summary, we report a very rare case of
concurrent cutaneous *P. marneffei* infection and mycobacterial spindle cell pseudotumor caused by MAI infection in a HIV-negative immunocompromised patient with rheumatoid arthritis. The cutaneous MSP was preceded by chronic osteomyelitis of the big toes that manifested draining fistulae for 2 years. Mycobacterial infection of the bone was identified retrospectively after cutaneous MSP was diagnosed. Clinicians and pathologists should be aware of these two rare types of infection in immunocompromised hosts, so the diseases could be diagnosed and treated in a timely fashion.

REFERENCES