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Case Report

Disseminated *Penicillium marneffei* mimicking paradoxical response and relapse in a non-HIV patient with pulmonary tuberculosis

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Abstract

Clinical deterioration during the treatment of tuberculosis remains a diagnostic challenge. We describe the case of a 46-year-old man with a history of oral cancer status after a radical operation who had pulmonary tuberculosis with pleura and neck lymph node involvement. The clinical condition improved after antituberculosis therapy. However, the patient suffered from low-grade fever, progressive dyspnea, and cough after 7 weeks of the therapy. The findings of chest plain films were relapse and progression of left lung haziness. The deterioration was caused by disseminated *Penicillium marneffei* infection. Disseminated *P. marneffei* in a non-HIV patient with tuberculosis is rarely seen, and the manifestations are similar to a paradoxical response and relapse of pulmonary tuberculosis, thereby making it difficult to establish a diagnosis.

Keywords: human immunodeficiency virus; *Penicillium marneffei*; tuberculosis

1. Introduction

A paradoxical response is generally defined as the clinical or radiological worsening of preexisting tuberculous lesions or the development of new lesions in a patient who initially improves with antituberculosis therapy, and is diagnosed only after excluding any other possible diagnoses.[1] Even though *Penicillium marneffei* is the third most common opportunistic infection in human immunodeficiency virus (HIV)-infected patients in certain parts of Southeast Asia,[2] it is a very rare cause of paradoxical deterioration during antituberculosis therapy in non-HIV patients. The symptoms of *P. marneffei* infection are similar to those of pulmonary tuberculosis and a paradoxical response. The diagnosis may be delayed because of a low suspicion and similar symptoms, and such a delay can lead to worse outcomes. Herein, we present the case of a non-HIV patient who deteriorated during antituberculosis treatment and was later proven to have *P. marneffei* infection.

2. Case report

This 46-year-old man was a heavy smoker with a consumption of two packs of cigarettes per day for >30 years, and he also had the habit of betel nut chewing since adolescence. He had always lived in Taiwan and had never traveled abroad. His occupation was a street vendor selling fruits. He underwent a radical operation for left buccal cancer $pT_2N_0M_0$ in June 2001. The postoperative course was smooth, and no recurrence was found during regular follow-up. Except for the operation, no other systemic diseases were noted until 2006.

He was admitted to our hospital in May 2006 with manifestations of nonproductive cough for 2 months, progressive

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dyspnea, and a body weight loss of 8 kg in 2 months. He denied apparent fever and night sweating. Physically, multiple right supraclavicular lymphadenopathies were noted. The white blood cell count was 13,200, with an absolute lymphocyte count of 2033, and the hemoglobulin level was 12.2 g/dL. A chest plain film showed haziness in the left lower lung field, increased infiltrates in the right lower lung field, and suspicious upper mediastinal widening (Fig. 1A). Pleural effusion analysis showed lymphocyte predominant exudates with 93% lymphocytes. Acid-fast staining (AFS) and cytology of the pleural effusion were both negative. An incision biopsy of the right supraclavicular lymphadenopathies showed chronic caseating granulomatous inflammation with AFS bacilli. Anti- *Mycobacterium tuberculosis* (MTB) chemotherapy including isoniazid, rifampin, ethambutol, and pyrazinamide was prescribed. Ethambutol was stopped after 1 week because of optic neuritis. Sputum, pleural effusion, and tissue cultures all yielded MTB. Chest radiography 1 month later showed much improvement.

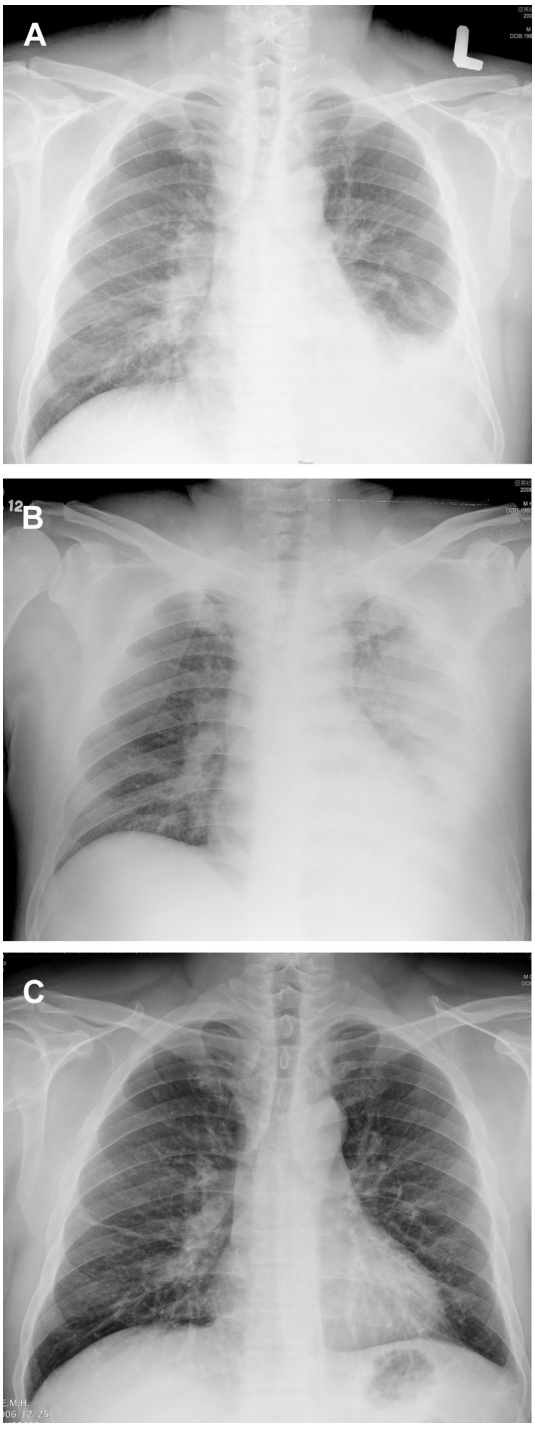

Fig. 1. (A) Chest plain film in May 2006 shows haziness in the left lower lung field, increased infiltrates in the right lower lung field, near the right hilum, and suspicious upper mediastinal widening. (B) Chest plain film in September 2006 reveals a relapse of the left lung haziness after 7 weeks of antituberculosis therapy. (C) Chest radiograph in October 2008 shows no apparent lung lesions.

However, similar symptoms including progressive dyspnea and cough recurred in September 2006, after about 7 weeks of anti-MTB therapy. Low-grade fever was noted, and breath sounds were decreased, with crackles in the left lower chest. The patient's liver and spleen were impalpable. Chest radiography showed left lung haziness (Fig. 1B), and chest computed tomography (CT) revealed consolidation in the left lower lobe with pleural effusion and pleural thickening. The pleural effusion still revealed exudates, with 67% lymphocytes, and the cytology was negative for malignancy. No recurrence of buccal cancer was found by the dentist. Drug compliance was confirmed by directly observed therapy. Initially, treatment failure of MTB or paradoxical response was suspected. We prescribed kanamycin and moxifloxacin from hospital Day 4 and maintained the previous anti-MTB regimen. Prednisolone 20 mg per day was used from hospital Day 7 because of a progression of the symptoms. In addition to the antecedent manifestations, multiple skin nodules were noted in the left anterior chest, left shoulder, and knees on hospital Day 9. These skin nodules became enlarged under these medications. A skin biopsy was done on hospital Day 13, and the pathologic report revealed small-sized yeasts, with endospore-like arrangements within giant cells and macrophages (Fig. 2). Amphotericin B 0.6 mg/kg/d was substituted for moxifloxacin and kanamycin, and systemic steroids were stopped on hospital Day 16. A subsequent culture confirmed *P. marneffei*, and

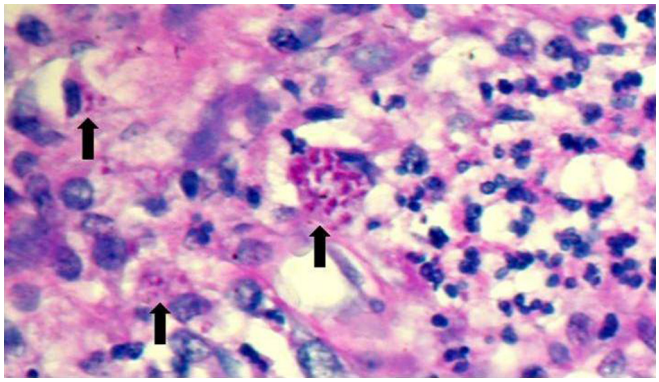

Fig. 2. The skin biopsy microscopically reveals small-sized yeasts, with endospore-like arrangements, demonstrated by periodic acid-Schiff staining (arrows) and surrounded by giant cells and macrophages (magnification × 800).

the serology for HIV was negative. Liposomal amphotericin B was substituted for amphotericin B because of a renal injury after 7 days. Itraconazole 200 mg twice per day was given for 3 months after completion of 14-day amphotericin B therapy. The patient recovered well after 3 months of antifungal and 6 months of anti-MTB therapies. The chest plain film in December 2006 showed no apparent lung lesion (Fig. 1C).

3. Discussion

In this article, we present a non-HIV patient with disseminated *P. marneffei* infection during pulmonary tuberculosis treatment. Disseminated *P. marneffei* infection is seldom seen in immunocompetent patients, even in endemic areas. It is very rare for a non-HIV patient to have disseminated *P. marneffei* infection. Some investigators have demonstrated that non-HIV hosts without any immunosuppressant may have impaired cell-mediated immunity, resulting from the derangement of cytokine cascades, including overproduction of suppressive cytokine, interleukin (IL)-10, and cytokine deficiency in the IL-12/interferon-γ pathway.[3−6] This patient did not undergo specific studies of cellular immunity defects because of a lack of laboratory resources. However, concerns about cellular immunity abnormalities of such a patient should be kept in mind in spite of negative HIV serology and no immunosuppressive therapy.

Taiwan is an endemic area of *P. marneffei*. Details of the ecological reservoir of human *P. marneffei* remain unknown.[7] There is a significantly seasonal variation in infection rates, with an increased incidence in the rainy season.[8] Some investigators have suggested that soil exposure, especially during the rainy season, is a critical risk factor associated with infection by *P. marneffei*.[8] One typhoon in July 2006 and two typhoons in August 2006 hit Taiwan, bringing substantial rain and mudslides. In addition, our patient was a street vendor selling fruits, durian in particular. He also had the habit of betel nut chewing, and it is possible that both fruits and betel nut may be contaminated by *P. marneffei* during rainy periods. These conditions may increase the opportunity for *P. marneffei* infection.

The presence of clinical deterioration is a great challenge in the treatment course of anti-MTB chemotherapy. A paradoxical response is diagnosed only after other possible diagnoses have been excluded. It is not a rare phenomenon, occurring in 6−30% of patients receiving antituberculosis therapy.[9,10] The onset of a paradoxical response from initiation of antituberculosis therapy ranges from weeks to months.[10,11] Some investigators have suggested a number of risk factors for a paradoxical response.[10] However, these factors are not crucial for a diagnosis of paradoxical response. For our patient, the tentative diagnosis was treatment failure or paradoxical response after a series of initial work-ups because of the relatively subacute clinical course and lymphocyte predominant effusion. Nevertheless, the skin nodules hinted at a differential diagnosis. Pulmonary tuberculosis and *P. marneffei* share a similar symptomology and geographical distribution,[12] however, two-thirds of disseminated *P. marneffei* infections are characterized by skin lesions. The septate yeast-like organism seen in skin biopsy specimens is diagnostic of *P. marneffei*,[2] and the skin is the most common culture-positive site.[12]

In conclusion, a paradoxical response can only be diagnosed after all other possibilities have been excluded. Fungal infections such as *P. marneffei* should be considered as a differential diagnosis, especially in endemic areas. Our case had *M. tuberculosis* and *P. marneffei* infections sequentially, which is very rare in a non-HIV patient. Such patients may have unidentified defects of cellular immunity, or the cause may be related to particular geographical or occupational factors.

References

1. Cheng VC, Ho PL, Lee RA, Chan KS, Chan KK, Woo PC, et al. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 2002;**21**:803−9.
2. Supparatpinyo K, Khamwan C, Baosoung V, Nelson KE, Sirisanthana T. Disseminated *Penicillium marneffei* infection in Southeast Asia. *Lancet* 1994;**344**:110−3.
3. Chen YP, Yen YS, Chen TY, Yen CL, Shien CC, Chang KC. Systemic *Mycobacterium kansasii* infection mimicking peripheral T-cell lymphoma. *APMIS* 2008;**116**:850−8.
4. Arend SM, Janssen R, Gosen JJ, Waanders H, de Boer T, Ottenhoff TH, et al. Multifocal osteomylitis caused by nontuberculous mycobacteria in patients with a genetic defect of the interferon-gamma receptor. *Neth J Med* 2001;**59**:140−51.
5. Lillo M, Orengo S, Cemoch P, Harris RL. Pulmonary and disseminated infection due to *Mycobacterium kansasii*: a decade of experience. *Rev Infect Dis* 1990;**12**:760−7.
6. Browne SK, Burbelo PD, Chetchotisakd P, Suputtamongkol Y, Kiertiburanakul S, Shaw PA, et al. Adult-onset immunodeficiency in Thailand and Taiwan. *N Engl J Med* 2012;**367**:725−34.
7. Vanittanakom N, Cooper Jr CR, Fisher MC, Sirisanthana T. *Penicillium marneffei* infections and recent advances in epidemiology and molecular biology aspects. *Clin Microb Rev* 2006;**19**:95−110.
8. Chariyalertsak S, Sirisanthana T, Supparatpinyo K, Nelson KE. Seasonal variation of disseminated *Penicillium marneffei* infections in northern Thailand: a clue to the reservoir? *J Infect Dis* 1996;**173**:1490−3.
9. AL-Majed SA. Study of paradoxical response to chemotherapy in tuberculous pleural effusion. *Respir Med* 1996;**90**:211−4.
10. Cheng VC, Yam WC, Woo PCY, Lau SKP, Hung IFN, Wong SPY, et al. Risk factors for development of paradoxical response during antituberculosis therapy in HIV-negative patients. *Eur J Clin Microbiol Infect Dis* 2003;**22**:597−602.
11. Gupta RC, Dixit R, Purhit SD, Saxena A. Development of pleural effusion in patients during antituberculous chemotherapy: analysis of twenty-nine cases with review of literature. *Indian J Chest Dis Allied Sci* 2000;**42**:161−6.
12. Duong TA. Infection due to *Penicillium marneffei*, an emerging pathogen: review of 155 reported cases. *Clin Infect Dis* 1996;**23**:125−30.