CASE REPORT

CUTANEOUS MILIARY TUBERCULOSIS IN A RENAL TRANSPLANT PATIENT: A CASE REPORT AND LITERATURE REVIEW

Songadul Yodmalai[1], Siri Chiewchanvit[1] and Pongsak Mahanupab[2]

[1]Department of Internal Medicine, [2]Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Abstract. The incidence of tuberculosis in renal transplant recipients is higher than in the general population. However, the incidence of cutaneous miliary tuberculosis in these patients is very rare. We report a 56-year-old renal transplant Thai man admitted to the hospital with prolong fever, dry cough and multiple small erythematous papules on his extremities. A chest X-ray revealed diffuse miliary infiltration. *Mycobacterium tuberculosis* DNA was demonstrated in bronchoalveolar lavage fluid by polymerase chain reaction. Histopathology of a skin biopsy showed poorly formed noncaseating granulomatous inflammation in the lower dermis and was positive for many acid-fast bacilli. Miliary tuberculosis of the lung and skin were diagnosed. The respiratory symptom and the skin lesions improved after treatment with anti-tuberculous drugs.

Key words: *Mycobacterium tuberculosis*, cutaneous miliary, tuberculosis, renal transplant

INTRODUCTION

Tuberculosis (TB) infection has been present since prehistoric times. Recent data from the WHO (2009) indicates the global incidence of TB had increased to 139 per 100,000 people in 2007. Although TB prevalence is increasing in the era of HIV infection and the use of immunosuppressive agents, cutaneous TB is a rare manifestation of extrapulmonary TB. The incidence of cutaneous TB is about 1-2% of all cases of TB (Bravo and Gotuzzo, 2007), and about 0.2% of the patients in a dermatology outpatient clinic (Sehgal *et al*, 1987, 1989; Kakakhel and Fritsch, 1989). The most common manifestations of cutaneous TB from several studies are lupus vulgaris and scrofuloderma (Hamada *et al*, 2004) while other forms are quite rare.

Cutaneous miliary TB (tuberculosis cutis miliaris disseminata) is a very rare form of cutaneous TB, usually resulting from overwhelming pulmonary infection, which seeds the skin and other organs hematogenously, spreading in patients with immune dysfunction (Macgregor, 1995).

We report a case of disseminated cutaneous and pulmonary miliary TB in a renal transplant patient.

Correspondence: Dr Siri Chiewchanvit, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.
E-mail: schiewch@mail.med.cmu.ac.th

CASE REPORT

A 56-year-old Thai man with a history of a renal transplant presented with low grade fever, nonproductive cough and weight loss for 1 month. He had a history of diabetes mellitus with end stage renal disease for 10 years. He was on cyclosporin 100 mg/d. Physical examination revealed a temperature of 37.5°C, fine crepitations in both lungs, and about 20 discrete erythematous papules, 1-2 mm in diameter, on all extremities, but more particularly on both lower extremities (Fig 1). Laboratory findings showed a hemoglobin level of 9.8 g/dl, a white blood cell count of 6,130/mm^3 with 93.1% neutrophils, and a platelet count of 65,000/mm^3. Chest x-ray showed miliary infiltration of both lungs. An imprint of a skin biopsy from the left thigh was negative for acid-fast bacilli (AFB). Histopathology of the skin biopsy specimen showed noncaseating granulomatous inflammation in the lower dermis (Fig 2) and was positive for many AFB. Sputum examination was positive for AFB. Bronchoalveolar lavage (BAL) fluid revealed AFB and *M. tuberculosis* DNA was demonstrated by polymerase chain reaction. Sputum and BAL fluid cultures for TB were not done due to contamination of the specimens. Miliary tuberculosis of the lungs and skin was diagnosed. The patient was treated with INH 300 mg/d, rifampicin 600 mg/d, ethambutol 500 mg/d and pyrazinamide 1,500 mg every other day. Two weeks after the onset of treatment, his skin lesions and pulmonary symptoms were improved.

Fig 1–Multiple small erythematous papules on both lower extremities.

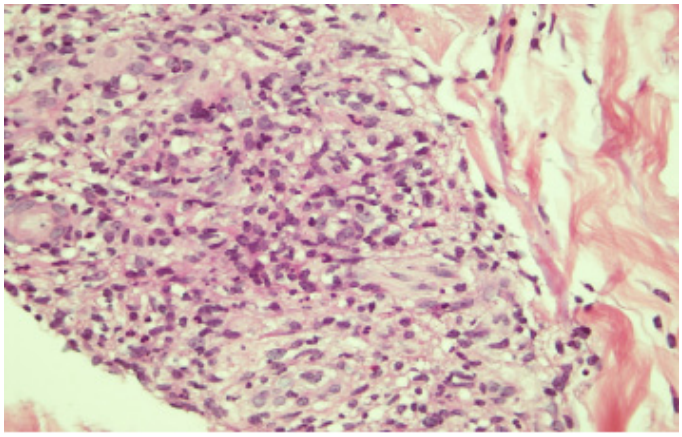

Fig 2–Histopathology of the skin biopsy showed poorly formed noncaseating granulomatous inflammation in the dermis (H&E, x400).

DISCUSSION

Cutaneous miliary tuberculosis (tuberculosis cutis miliaris disseminata) was first reported by Fox (1895). The lesions (Macgregor, 1995) usually begin with acute generalized discrete blue-red to brownish papules, 20-30 in number (Antinori *et al*, 1995), sometimes capped by vesicles that break and dry with crust or progress to form small round ulcers with

purulent exudate. Sometimes they appear as pustules, macules, or subcutaneous nodules. Diagnosis can be made by the clinical manifestations, identification of AFB on skin biopsy, and isolation of *M. tuberculosis* from PCR or culture of the tissue. Our patient presented with prolonged fever, miliary infiltration in the lungs, and multiple small discrete erythematous papules distributed on extremities. The differential diagnoses includs insect bites, folliculitis and disseminated infections caused by bacteria, herpes virus, fungus, and *M. avium-intracellulare*. The identification of AFB on skin biopsy and AFB or *M. tuberculosis* DNA from BAL fluid confirms the diagnosis of miliary tuberculosis of the lungs and skin.

In the literature from 1889 to 1991, only 18 cases of cutaneous miliary tuberculosis in patients older than 15 years old were found (Schermer *et al*, 1969; Reitbroek *et al*, 1991; Stein *et al*, 1999; del Giudice *et al*, 2000; Park *et al*, 2002). Cutaneous miliary tuberculosis in patients with HIV infection was first reported by Stack *et al* (1990). Since then, only 19 cutaneous miliary tuberculosis cases in HIV patients have been reported (Rohatgi *et al*, 1992; Bassiri *et al*, 1993; Inwald *et al*, 1994; Antinori *et al*, 1995; Corbett *et al*, 1995; Farina *et al*, 1995; Libraty and Byrd, 1996; Antinori *et al*, 1997; Hudson *et al*, 1997; Daikos *et al*, 1998; Chiewchanvit *et al*, 2000; High *et al*, 2004; Regnier *et al*, 2009). The incidence of tuberculosis in renal transplant recipients was reported as 0.5-1% in the United States, 1-4% in Europe, and about 10% in developing countries (Sakhuja *et al*, 1996; Naqvi *et al*, 1997). Although the incidence of tuberculosis in renal transplant recipients is 5 times higher than in the general population (Biz *et al*, 2000); the incidence of cutaneous miliary tuberculosis in these patients was very rare. A study of 36 cases of tuberculosis among 305 renal transplant recipients in India over an 8-year period found infections in the thoracic cavity in 41.7%, single extrapulmonary infection in 11.1%, disseminated infection in 27.8%, and pyrexia of unknown etiology in 19.4% (Sakhuja *et al*, 1996). In the disseminated patients, only 1 case presented with skin lesions (an ulcer on the left groin) and positive for AFB. There was only 1 reported case of cutaneous miliary tuberculosis in a kidney transplant recipient with immunosuppressive therapy from South Korea (Park *et al*, 2002). She presented with fever, pulmonary tuberculosis, respiratory failure and disseminated erythematous papules of the trunk and extremities.

The antituberculosis regimen for cutaneous miliary tuberculosis does not differ from that used for tuberculosis in the general population (Biz *et al*, 2000), but the possibility of hepatotoxicity increases when combined with immunosuppressive drugs (McAllister *et al*, 1983; Hebert *et al*, 1992; Koselj *et al*, 1994; Di Peri *et al*, 1998). The use of rifampicin can lower blood levels of prednisolone and cyclosporin, which increases the risk of graft rejection (Sakhuja *et al*, 1996). Disseminated tuberculosis in the immunosuppressed patients has a higher mortality rate. In a study of 30 renal transplant recipients with tuberculosis, 7 patients died (23.3%), of which 5 had disseminated tuberculosis (Biz *et al*, 2000).

Since the incidence of worldwide tuberculosis is increasing but the incidence of cutaneous miliary tuberculosis remains quite rare, it is possible that there have been missed diagnoses and/or skin lesions are easily overlooked. Cutaneous miliary tuberculosis should be in the differential diagnosis of discrete small erythematous papules in HIV-infected or immunosuppressed patients.

REFERENCES

Antinori S, Bini T, Galimberti L, Meroni L, Esposito R. Cutaneous miliary tuberculosis in a patient infected with human immunodeficiency virus [Letter]. *Clin Infect Dis* 1997; 25: 1484-6.

Antinori S, Galimberti L, Tadini GL, *et al*. Tuberculosis cutis miliaris disseminata due to multidrug-resistant *Mycobacterium tuberculosis* in AIDS patients. *Eur J Clin Microbiol Infect Dis* 1995; 14: 911-4.

Bassiri A, Chan NB, McLeod A, Rossi S, Phillips P. Disseminated cutaneous infection due to *Mycobacterium tuberculosis* in a person with AIDS. *CMAJ* 1993; 148: 577-8.

Biz E, Pereira CA, Moura LA, *et al*. The use of cyclosporine modifies the clinical and histopathological presentation of tuberculosis after renal transplantation. *Rev Inst Med trop Sao Paulo* 2000; 42: 225-30.

Bravo FG, Gotuzzo E. Cutaneous tuberculosis. *Clin Dermatol* 2007; 25: 173-80.

Chiewchanvit S, Mahanupab P, Walker PF. Cutaneous tuberculosis in three HIV-infected patients. *J Med Assoc Thai* 2000; 83: 1550-4.

Corbett EL, Crossley I, De Cock KM, Miller RF. Disseminated cutaneous *Mycobacterium tuberculosis* infection in a patient with AIDS. *Genitourin Med* 1995; 71: 308-10.

Daikos GL, Uttamchandani RB, Tuda C, *et al*. Disseminated miliary tuberculosis of the skin in patients with AIDS: report of four cases. *Clin Infect Dis* 1998; 27: 205-8.

del Giudice P, Bernard E, Perrin C, *et al*. Unusual cutaneous manifestations of miliary tuberculosis. *Clin Infect Dis* 2000; 30: 201-4.

Di Peri G, Luzzati R, Forni A, *et al*. Fatal primary multidrug-resistant tuberculosis in a heart transplant recipient. *Transpl Int* 1998; 11: 305-7.

Farina MC, Gegundez MI, Pique E, *et al*. Cutaneous tuberculosis: a clinical, histopathologic, and bacteriologic study. *J Am Acad Dermatol* 1995; 33: 433-40.

Fox TC. On acne scrofulosorum in infants. *Br J Dermatol* 1895; 7: 340-8.

Hamada M, Urabe K, Moroi Y, Miyazaki M, Furue M. Epidemiology of cutaneous tuberculosis in Japan: a retrospective study from 1906 to 2002. *Int J Dermatol* 2004; 43: 727-31.

Hebert MF, Roberts JP, Prueksaritanont T, Benet LZ. Bioavailability of cyclosporine with concomitant rifampin administration is markedly less than predicted by hepatic enzyme induction. *Clin Pharmacol Ther* 1992; 52: 453-7.

High WA, Evans CC, Hoang MP. Cutaneous miliary tuberculosis in two patients with HIV infection. *J Am Acad Dermatol* 2004; 50: S110-3.

Hudson CP, Wood R, O'Keefe EA. Cutaneous miliary tuberculosis in the AIDS era [Letter]. *Clin Infect Dis* 1997; 25: 1484.

Inwald D, Nelson M, Cramp M, Francis N, Gazzard B. Cutaneous manifestations of mycobacterial infection in patients with AIDS. *Br J Dermatol* 1994; 130: 111-4.

Kakakhel KU, Fritsch P. Cutaneous tuberculosis. *Int J Dermatol* 1989; 28: 355-62.

Koselj M, Kandus A, Kovac D. Drug interactions between cyclosporine and rifampicin, erythromycin, and azoles in kidney recipients with opportunistic infections. *Transplant Proc* 1994; 26: 2823-4.

Libraty DH, Byrd TF. Cutaneous miliary tuberculosis in the AIDS era: case report and review. *Clin Infect Dis* 1996; 23: 706-10.

Macgregor RR. Cutaneous tuberculosis. *Clin Dermatol* 1995; 13: 245-55.

McAllister WA, Thompson PJ, Al-Habet SM, Rogers HJ. Rifampicin reduces effectiveness and bioavailability of prednisolone. *Br Med J* (*Clin Res Ed*) 1983; 286: 923-5.

Naqvi A, Akhtar F, Naqvi R, *et al*. Problems of diagnosis and treatment of tuberculosis following renal transplantation. *Transplant Proc* 1997; 29: 3051-2.

Park KW, Kim US, Shin JW, Yoo CG, Oh MD, Choe K. Disseminated erythematous

papules in a renal transplant recipient: a case of disseminated tuberculosis. *Scand J Infect Dis* 2002; 34: 775-7.

Regnier S, Ouagari Z, Perez ZL, Veziris N, Bricaire F, Caumes E. Cutaneous miliary tuberculosis in a patient infected with human immunodeficiency virus: case report and literature review. *Clin Exp Dermatol* 2009; 34: e690-2.

Reitbroek RC, Dahlmans RP, Smedts F, Frantzen PJ, Koopman RJ, van der Meer JW. Tuberculosis cutis miliaris disseminata as a manifestation of miliary tuberculosis: literature review and report of a case of recurrent skin lesions. *Rev Infect Dis* 1991; 13: 265-9.

Rohatgi PK, Palazzolo JV, Saini NB. Acute miliary tuberculosis of the skin in acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1992; 26: 356-9.

Sakhuja V, Jha V, Varma PP, Joshi K, Chugh KS. The high incidence of tuberculosis among renal transplant recipients in India. *Transplantation* 1996; 61: 211-5.

Schermer DR, Simpson CG, Haserick JR, Van Ordstrand HS. Tuberculosis cutis miliaris acuta generalisata. *Arch Dermatol* 1969; 99: 64-9.

Sehgal VN, Jain MK, Srivastava G. Changing pattern of cutaneous tuberculosis. A prospective study. *Int J Dermatol* 1989; 28: 231-6.

Sehgal VN, Srivastava G, Khurana VK, Sharma VK, Bhalla P, Beohar PC. An appraisal of epidemiologic, clinical, bacteriologic, histopathologic, and immunologic parameters in cutaneous tuberculosis. *Int J Dermatol* 1987; 26: 521-6.

Stack RJ, Bickley LK, Coppel IG. Miliary tuberculosis presenting as skin lesions in a patient with acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1990; 23: 1031-5.

Stein A, Purgus R, Drancourt M, Olmer M. Photo quiz: cutaneous miliary tuberculosis. *Clin Infect Dis* 1999; 29: 1126-7.

World Health Organization (WHO). Global tuberculosis control: surveillance planning, financing. WHO report 2009. *WHO/HTM/TB/2009.411*. 2009.