Transpl Int (1996) 9: 589–592


BRIEF REPORT

**Takashi Nishizaki**
**Katsuhiko Yanaga**
**Yuji Soejima**
**Keiji Kishikawa**
**Kiyoshi Kajiyama**
**Hideaki Uchiyama**
**Jun Yatsunami**
**Nobuyuki Hara**
**Keizo Sugimachi**

# Tuberculosis following liver transplantation: report of a case and review of the literature

Received: 28 February 1996
Received after revision: 10 May 1996
Accepted: 14 May 1996

T. Nishizaki (✉) · K. Yanaga
Y. Soejima · K. Kishikawa · K. Kajiyama
H. Uchiyama · K. Sugimachi
Department of Surgery II,
Faculty of Medicine,
Kyushu University,
Fukuoka 812, Japan
Fax: + 81 92 632 3001

J. Yatsunami · N. Hara
Department of Respiratory Medicine,
Faculty of Medicine,
Kyushu University,
Fukuoka 812, Japan

**Abstract** We report on a 44-year-old man who developed tuberculosis 4 months after liver transplantation. The diagnosis was confirmed using a polymerase chain reaction (PCR) technique in bronchial alveolar lavage (BAL) fluid, and the patient was successfully treated by reducing his immunosuppression and administering antituberculous drugs. The patient became afebrile 20 days after starting antituberculous therapy and remains well at home. A review of the literature revealed that tuberculosis after liver transplantation is a rare complication with a reported mortality rate of as high as 40 %. The mortality is highest for patients who become symptomatic within 3 months after transplantation (83 % vs 0 %, $P < 0.01$; Fisher's exact test) and for those with an interval between the initial symptom and diagnosis of more than 2 weeks (71 % vs 0 %, $P < 0.05$). Early diagnosis is, therefore, essential for successful resolution of tuberculosis after liver transplantation.

**Key words** Tuberculosis, liver transplantation · Liver transplantation, tuberculosis

## Introduction

The incidence of tuberculosis in liver transplant (LTx) recipients is largely unknown [4, 6–8]. In 1991, Higgins et al. [4] reported that 5 of 2380 patients (0.2 %) developed tuberculosis after LTx. In 1994, Meyers et al. [7] documented that 5 of 550 LTx recipients (0.9 %) suffered from tuberculosis. The reported mortality rate of tuberculosis following LTx is as high as 40 % [4, 7]. Organ recipients in endemic areas, such as South and Central America, Asia, the Middle East, and the Mediterranean area, seem especially susceptible. In Japan, tuberculosis remains a leading infectious disease with an incidence of 39.3 per 100,000 people in 1992, four times greater than that in the United States (10.5 per 100,000) [1, 3].

Herein we report a patient who developed miliary tuberculosis after LTx and we review the literature on this complication.

## Case report

A 44-year-old man, born and raised in Japan, underwent orthotopic LTx on 15 October 1994 in the United States for postnecrotic liver cirrhosis due to hepatitis C. He had a positive purified protein derivative (PPD) test (20 × 20 mm) preoperatively, but had no history of active tuberculous disease or prophylaxis for tuberculosis. His preoperative chest x-ray and computed tomogram (CT) revealed no abnormalities. The patient had an uneventful postoperative course and was discharged on FK 506 and prednisolone 2 months post-transplantation. He then returned to Japan. The patient had no obvious exposure to tuberculosis before or after surgery.

On postoperative day 112, the patient became febrile and complained of heartburn, which was attributed to esophageal candidiasis. At that time, a chest x-ray still showed no abnormalities. Although his heartburn disappeared after starting oral amphotericin B, fever persisted for a month, and miliary pulmonary lesions and an infiltrate in the left upper lobe developed on chest x-ray and CT (Fig. 1).

The patient was admitted to our hospital for suspected miliary tuberculosis on 6 March 1995. Three days later, the diagnosis was confirmed by a polymerase chain reaction (PCR) method for spe-

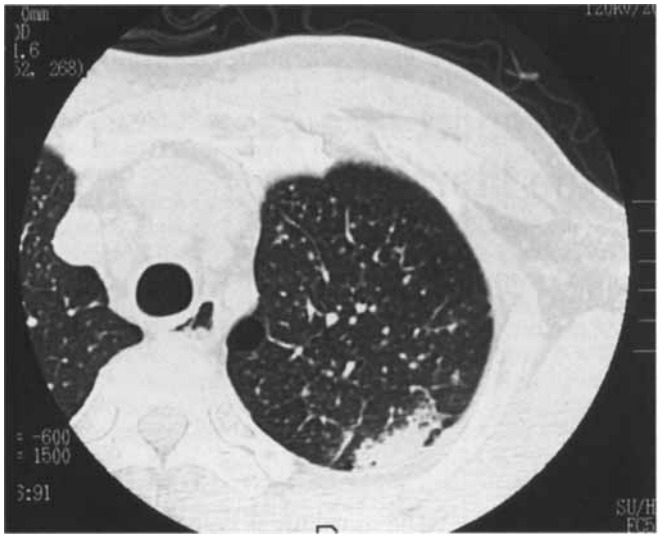

**Fig. 1** Computed tomogram of the chest demonstrating miliary lesions in both lungs and an infiltrate in the left upper lobe of the lung

cific DNA fragments of *Mycobacterium tuberculosis* (Amplicor, Roche Molecular Systems, Branchburg, N.J., USA) in bronchial alveolar lavage (BAL) fluid. The acid-fast bacilli (AFB) stain of BAL was negative. At this point, the patient's FK 506 whole blood trough level was 23 ng/ml. Because an infectious complication was suspected, his FK 506 dose was decreased from 8 mg to 4 mg/day and prednisolone from 10 mg to 5 mg/day. He was started on isoniazid (INH), 400 mg/day, ethambutol (EB), 750 mg/day, streptomycin (SM), 1 g i.m./day, and rifampicin (RFP), 450 mg/day (Fig. 2).

The patient's blood FK 506 level decreased to 2.3 ng/ml within 10 days, and serum transaminases started to increase after 20 days of under-immunosuppression. A percutaneous liver biopsy on 23 March 1995 showed mild acute cellular rejection and granulomas. RFP, which enhances the metabolism of FK 506, was therefore discontinued and sparfloxacin (SPFX), a neuquinolone, was added. A mini-recycle of steroids was initiated on 27 March 1995, and the FK 506 dose was increased from 4 mg to 12 mg/day. The rejection responded well to the therapy. A percutaneous liver biopsy on 5 April 1995 showed granulomatous hepatitis and resolution of the rejection. In the meantime, the patient became afebrile, and miliary lesions on chest X-ray and CT improved while the C-reactive protein normalized by the end of April 1995. The patient was discharged on 1 May 1995 and remains afebrile and doing well at home.

## Discussion

To our knowledge, 12 patients with tuberculosis after liver transplantation have been reported in the literature. Clinical data on these 12 patients, as well as our patient, are presented in Table 1 [4, 6–8]. There were 10 men and 3 women, ranging in age from 20 to 66 (mean 45) years. The underlying liver diseases were chronic viral hepatitis ($n = 6$), sclerosing cholangitis ($n = 2$), primary biliary cirrhosis ($n = 2$), cryptogenic cirrhosis ($n = 2$), and fulminant hepatitis ($n = 1$).

Eight of the 13 patients received immunosuppression consisting of cyclosporin A (CyA), azathioprine, and steroids, while two others received CyA and steroids and the other three FK 506 and steroids. Six patients were treated for rejection before developing tuberculosis. Three patients received OKT3 to treat rejection. Four of the six patients with rejection before tuberculosis died, while five of six patients without rejection before tuberculosis survived.

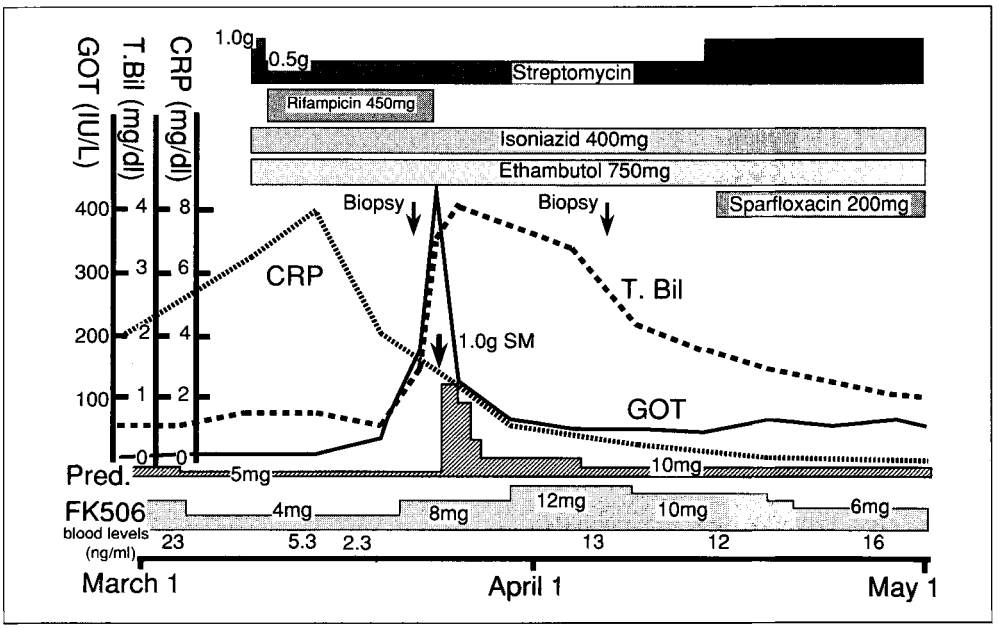


**Fig. 2** Clinical course of the patient (*CRP*, C-reactive protein; *T. Bil*, total bilirubin; *GOT*, glutamic oxaloacetic transaminase; *SM*, Solu-Medrol)

**Table 1** Summary of clinical data in patients with tuberculosis following liver transplantation (*PPD*, purified protein derivative; *Tx*, transplantation; *Symp*, symptom; *AFB*, acid-fast bacilli; *PNC*, postnecrotic cirrhosis; *PBC*, primary biliary cirrhosis; *ND*, not done; *LA*, lymphadenopathy; *LN*, lymph node; *CXR*, chest x-ray; *LUL*, left upper lobe; *Inf*, pulmonary infiltrates; *Bil*, bilateral; *Cerv*, cervical; *Rt*, right; *RUL*, right upper lobe; *CSF*, cerebrospinal fluid; *BAL*, bronchoalveolar lavage; *SM*, streptomycin; *EB*, ethambutol; *INH*, isoniazid; *RFP*, rifampicin; *AMK*, amikacin; *PZA*, pyrazinamide; *OFLX*, ofloxacin; *SPFX*, sparfloxacin)

| Author(s) | Age/Sex Ethnicity | Underlying disease | PPD pre-transplant | Symptoms | Signs | Tx to Symp (months) | AFB stain | Culture | Pathology | Treatment | Out-come |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 Lie et al. (1988) [6] | 55/M ? | PNC-B | ? | Fever Cough | CXR; LUL Inf | 7 | ? | Sputum | ? | SM/EB/INH | Alive |
| 2 Higgins et al. (1991) [4] | 20/M Black | Fulminant hepatitis | ND | Fever | CXR; Bil Inf Cerv LA | 1.2 | (+) BAL, LN | ? | Granulomas Liver | INH/RFP/ EB | Dead |
| 3 Higgins et al. (1991) [4] | 58/F White | Cryptogenic Cirrhosis | ND | Fever | CXR; Bil Inf | 2 | (+) Sputum | ? | Granulomas Liver | INH/EB/ RFP/AMK | Dead |
| 4 Higgins et al. (1991) [4] | 61/M White | Sclerosing Cholangitis | (+) | Fever | CXR; Bil Inf Axillary LA | 4 | (+) | ? | Granulomas Liver, LN, lung | INH/EB/RFP/ PZA/AMK | Alive |
| 5 Higgins et al. (1991) [4] | 34/M Oriental | PNC-B | ND | Fever | Cerv LA | 3 | (+) LN | ? | Granulomas LN | INH/EB/ RFP | Alive |
| 6 Higgins et al. (1991) [4] | 40/M Arabic | Cryptogenic Cirrhosis | ND | Fever | Cerv LA | 1.5 | (+) LN | ? | Granulomas LN | INH/RFP/ PZA | Alive |
| 7 Salizzoni et al. (1992) [8] | ? | PNC-B | ? | Fever | CXR; Rt Inf Ascites | 0.4 | (+) BAL | Intestine Lung | Granulomas Liver | INH/RFP/ PZA | Dead |
| 8 Meyers et al. (1994) [7] | 57/F White | PBC | Anergic | Fever Cough | CXR; Inf | 2.0 | (+) Liver, Sputum | Liver | Granulomas Liver | INH/RFP/ PZA | Dead |
| 9 Meyers et al. (1994) [7] | 47/F White | PBC | Anergic | Fever | CXR; Inf | 1.0 | (–) | Pleural fluid | ND | ND | Dead |
| 10 Meyers et al. (1994) [7] | 51/M White | PNC-B & C | (+) | Fever Neck pain | CXR; RUL Inf | 12 | (+) BAL | BAL CSF | Granulomas Liver | INH/RFP/ AMK | Alive |
| 11 Meyers et al. (1994) [7] | 66/M White | PNC-C | ND | (–) | ? | ? | (+) Peritoneum | Small bowel Peritoneum | Granulomas Small bowel Peritoneum | INH/RFP/ AMK/EB | Alive |
| 12 Meyers et al. (1994) [7] | 25/M Black | Sclerosing cholangitis | ? | Fever, Headache | Stiff neck | 57 | (–) | CSF | ? | INH/RFP/EB/ PZA/OFLX | Alive |
| 13 Present case | 44/M Oriental | PNC-C | (+) | Fever | CXR; miliary nodules LUL Inf | 4 | (–) | BAL | Granulomas Liver | INH/RFP/EB/ SM/SPFX | Alive |

All but one patient (Patient 11) presented with fever. Other stigmata of tuberculosis consisted of pulmonary lesions ($n = 9$), meningitis ($n = 2$), and lymphadenopathy ($n = 4$). In Patient 11, miliary tuberculous lesions in the peritoneum and the intestine were identified at surgery. All but one patient had extrapulmonary lesions.

The mortality rate among these 13 patients was 38 % (5/13). We examined risks related to mortality in patients with tuberculosis and identified early infection as a detrimental factor. The mortality rate in patients who developed symptoms less than 3 months after transplantation was 83 % (5/6), while all those who had symptoms after 3 months survived ($P < 0.01$; Fisher's exact test). In the early period following liver transplantation, when patients are under heavy immunosuppression, disturbed cellular immunity seems responsible for the high mortality of tuberculosis.

Early diagnosis is the key to better prognosis for tuberculosis. All five patients whose tuberculosis was diagnosed within 2 weeks after the initial symptom survived, while the mortality rate of those whose diagnosis was established over 2 weeks after symptoms was as high as 71 % (5/7) ($P < 0.05$; Fisher's exact test). Patient 6 survived after an early diagnosis of tuberculosis that developed 1.5 months after LTx.

As for the diagnosis of tuberculosis, the AFB stain was positive in 9 of 12 patients (75 %). Three patients had a positive culture but a negative AFB stain. Granulomas were found in the biopsy specimens of ten patients. We established early diagnosis using PCR of BAL, which takes only 5.5 h [2].

As for the treatment of tuberculosis, four antituberculous drugs are standard treatment for patients with suspected tuberculosis until drug sensitivity is known [9]. All patients reported received INH. RFP was given to 11, EB to 8, and pyrazinamide (PZA) to 5 patients. Amikacin (AMK) and SM were given to four and two patients, respectively. Ofloxacin (OFLX) and SPFX were each given to one patient. Each patient received more than three antituberculous drugs. If drugs are effective, symptoms usually resolve after a few weeks of therapy. Repeat tissue specimens, such as liver biopsies, seem useful for judging the effectiveness of therapy [4].

Although we intended to maintain minimal immunosuppression for our patient in order to resuscitate cellular immunity until evidence of acute cellular rejection developed, the dose-blood level relationship of FK 506 was significantly disturbed by RFP. Higgins et al. [4] reported that three of their five patients required discontinuation of RFP for hepatotoxicity. RFP should, therefore, be given with special care to LTx recipients.

The duration of treatment for tuberculosis has not yet been established in liver recipients. Meyers et al. [7] recommended 12–18 months of therapy for sensitive isolates. Others [5] have suggested that therapy for multiresistant tuberculous strains can be continued for 18–24 months.

As for prophylaxis for tuberculosis, none of the 13 patients received such a treatment pretransplantation. A PPD test was performed before LTx in five patients; two were anergic and the other three had a positive reaction. Some tuberculosis occurred in liver recipients who were PPD test-negative, anergic, or whose results were unknown. Cutaneous anergy is a well-known phenomenon in patients with protein malnutrition or intercurrent viral infections who are also on corticosteroids [4]. All potential LTx recipients in endemic areas should have a PPD test to identify previous exposure to the infection [4, 7].

## References


1. Anonymous (1993) Tuberculosis morbidity – United States, 1992. Morb Mortal Wkly Rep 42: 696–697
2. Aoki M, Katayama T, Yamagishi F, et al (1994) Efficacy of PCR-microwell plate hybridization method (Amplicor™ Mycobacterium) for detection of M. tuberculosis, M. avium and/or M. intracellulare in clinical specimen. Kekkaku 69: 593–605
3. Health and Welfare Statistics Association (1994) Annual statistical report of nation health conditions (in Japanese). 41st edn. Kousaido, Tokyo p 160
4. Higgins RSD, Kusne S, Reyes J, et al (1992) Mycobacterium tuberculosis after liver transplantation: management and guidelines for prevention. Clin Transplant 6: 81–90
5. Iseman MD (1993) Treatment of multidrug-resistant tuberculosis. N Engl J Med 329: 784–791
6. Lie TS, Möfer M (1988) Tuberculosis after liver transplantation. Dtsch Med Wochenschr 113: 731–734
7. Meyers BR, Halpern M, Sheiner P, Hendelson MH, Neibart E, Miller C (1994) Tuberculosis in liver transplant patients. Transplantation 58: 301–306
8. Salizzoni JL, Tiruviluamala P, Reichman LB (1992) Liver transplantation: an unheralded probable risk for tuberculosis. Tuber Lung Dis 73: 232–238
9. Sinnott JT, Emmanuel PJ (1990) Mycobacterial infections in the transplant patient. Semin Respir Infect 5: 65–73