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BRIEF REPORT

Olivier Mat
Daniel Abramowicz
Marie-Odile Peny
Marc Struelens
Jean-Marc Doutrelepont
Michael Adler
Luc De Pauw
Jean-Louis Vanherweghem
Paul Kinnaert
Pierre Vereerstraeten

Tuberculosis presenting as acute hepatitis in a renal transplant recipient

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O. Mat · D. Abramowicz (✉)
J.-M. Doutrelepont · L. De Pauw
J.-L. Vanherweghem · P. Kinnaert
P. Vereerstraeten
Department of Nephrology,
Dialysis and Transplantation,
Hôpital Erasme, Route de Lennik 808,
B-1070 Brussels, Belgium

M.-O. Peny
Department of Pathology, Hôpital Erasme,
Route de Lennik 808, B-1070 Brussels,
Belgium

M. Struelens
Department of Microbiology,
Hôpital Erasme, Route de Lennik 808,
B-1070 Brussels, Belgium

M. Adler
Department of Gastroenterology,
Hôpital Erasme, Route de Lennik 808,
B-1070 Brussels, Belgium

Abstract We observed a kidney transplant recipient in whom acute hepatitis was the initial manifestation of tuberculosis, preceding radiological lung involvement by several weeks. The diagnosis was suspected and treatment initiated based on the finding of a granulomatous hepatitis on liver biopsy. Mycobacterial tuberulosis was grown and identified first in liver samples and only later in sputum and bone marrow. This case illustrates the protean manifestations of tuberculosis in immunosuppressed patients.

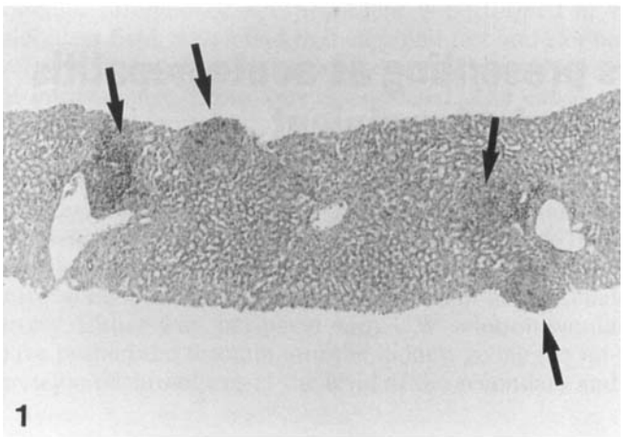
Key word Kidney transplantation tuberculosis

Introduction

Mycobacterial infections remain a significant complication in renal transplant recipients. Indeed, tuberculosis is thought to occur in 1%–4% of all patients after kidney transplantation [3]. A recent review of this patient population revealed that mycobacertial infection is already disseminated at the time of diagnosis in about 40% of the cases [8]. Isolated involvement of the lung occurs in 40% of the cases, while skin is the only site affected in 10% of the patients [8]. Mycobacterial infection of the liver has been documented in the context of disseminated tuberculosis [2], but we could not find a single case presenting as acute hepatitis in any of three large reviews reporting on a total of 146 cases [3, 6, 8] or in the additional 26 cases found by screening the National Library of Medicine's Medline system. We report here on a patient in whom acute hepatitis was, for several weeks, the only manifestation of disseminated tuberculosis.

Case report

A 42-year-old man with chronic renal failure of unknown cause started hemodialysis in 1979. He received multiple blood transfusions and became positive for HBsAg and, subsequently, for HCV



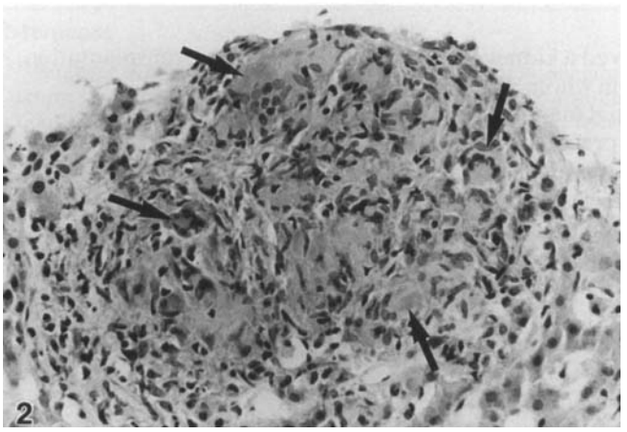


Fig. 1 Liver biopsy showing miliary granulomas *(arrows)* located in the portal tracts and in the parenchyma. H & E, × 100

Fig. 2 High magnification of a granuloma consisting of epithelioid cells, lymphocytes, and Langhans' giant cells *(arrows)*, without caseating necrosis. H & E, × 400

antibodies but remained free of liver enzyme abnormalities. There was no history of tuberculosis. In June 1991 a cadaveric renal transplantation was performed under OKT3 prophylaxis. The postoperative course was uneventful and the serum creatinine at discharge was 1.3 mg/dl. Maintenance immunosuppression consisted of 12.5 mg methylprednisolone, 75 mg azathioprine, and 200 mg cyclosporin A daily. In September 1991 he experienced an episode of acute rejection that was treated with steroid pulses. In December 1991, liver function tests showed, for the first time, moderate elevations of ASAT (40 IU/l-N < 35), ALAT (81 IU/l-N < 35), GGT (78 IU/l-N < 40), and total bilirubin (1.4 mg/dl), thought to be due to HBV/HCV carriage. In January 1992, the patient was admitted to the hospital because of recurrent fever up to 39 °C, weight loss, and night sweats. Aside from fever, physical examination revealed nothing remarkable. On admission, hematocrit was 38 %, leukocytes 2800 × 10^3/l (62 % neutrophils, 32 % lymphocytes), platelet count 120 × 10^6/l, urea 126 mg/dl, serum creatinine 3.1 mg/dl, GOT 62 IU/l, GPT 81 IU/l, GGT 98 IU/l, LDH 562 IU/l (N < 350 IU/l), and total bilirubin 1.3 mg/dl. Chest X-ray was normal with no lesions suggestive of past tuberculosis infection. Assays for acute viral infection were negative, as were routine bacteriology and direct examination with auramine of blood, sputum, urine, stool, alveolar lavage fluid, and bone marrow aspiration. A purified protein derivate (PPD) skin test was also negative. An abdominal echography revealed moderate homogenous hepatosplenomegaly. Three days after admission, a transparietal liver biopsy was performed and showed severe granulomatous hepatitis without caseating necrosis or acid-fast bacilli. There was no histological evidence of acute viral involvement (Figs. 1, 2). There was no history of overt tuberculosis in the family, and previous tuberculin skin reactivity of the patient was unknown. Treatment for suspected tuberculosis was started with isoniazid (300 mg/day), rifampicin (600 mg/day), and ethambutol (600 mg/ day). Azathioprine was withdrawn and cyclosporin doses were adjusted to maintain trough blood levels between 150 and 250 ng/ml. A chest roentgenogram performed 9 days after admission revealed for the first time a bilateral reticular infiltrate compatible with miliary tuberculosis. Small bowel X-ray series showed no inflammatory changes in the terminal ileum. Ocular examination was negative for choroidal tubercles.

On day 26, cultures of hepatic biopsy samples in the Bactec 12 B medium (Becton-Dickinson, Erembodegem, Belgium) grew acid-fast bacilli that were presumptively identified as *Mycobacterium tuberculosis* complex by DNA-rRNA hybridization (Accuprobe, Gen-Probe, San Diego, Calif., USA) and confirmed later as tuberculosis on the basis of production of niacin. Four days later, cultures of sputum and bone marrow aspiration became positive for the same mycobacterium sensitive to all tuberculostatic agents tested. Cultures of urine, alveolar fluid lavage, blood (Isolator DuPont, Merck, Darmstadt, Germany) and stool remained negative. After the initiation of antituberculous therapy, fever resolved, weight increased, chest infiltrates disappeared, and hepatic enzymes returned to normal. Unfortunately, worsening graft function required dialysis and allograft removal 3 months after admission. There was neither pathological nor bacteriological evidence of tuberculous infection in the explanted kidney. The patient is in good condition 7 months after allograft removal.

Discussion

Mycobacterial infections still represent a serious threat in transplant recipients because diagnosis is sometimes delayed as a result of unusual clinical presentation. Indeed, isolated lesions involving the skin or joints are not rare in such patients. While miliary involvement of the liver has been found on biopsy [2] or postmortem examination [8], no report mentions hepatitis as the initial manifestation of tuberculosis. In the present case, abnormal liver enzymes and fever were the first manifestations of disseminated tuberculosis, preceding pulmonary infiltrates by several weeks. Furthermore, the diagnosis was suspected and treatment initiated on the basis of a liver biopsy showing granulomatous hepatitis. The interest of liver biopsy for the diagnosis of disseminated tuberculosis has been well described [1]. The absence of histological signs of viral hepatitis, together with a rapid normalization of liver enzymes after initiation of antituberculous therapy, suggests that mycobacterial infection was the only cause of liver enzyme abnormalities. Definitive diagnosis was achieved by microbiological techniques combining Bactec cultures with a DNA probe test, which proved useful for rapid detection and identification of the responsible mycobacteria [4].

The absence of lesions on initial chest X-rays and the lack of a pretransplantation tuberculin skin test make it unclear whether infection was due to reactivation of endogenous tuberculous bacilli or whether it was acquired after transplantation. Furthermore, a negative pretransplantation tuberculin skin test would not have excluded previous contact with mycobacteria, as cutaneous anergy is common in dialysis patients [7]. Recommending antituberculous prophylaxis after transplantation remains a matter of debate. Some authors advocate a 6-months course of isoniazid for patients with a positive tuberculin skin test, a history of tuberculosis, or a chest X-ray suggestive of previous granulomatous disease prior to transplantation [7, 8]. However, it is not known whether the small, but definite, risk of severe hepatic injury with isoniazid outweighs the benefits of tuberculosis prophylaxis in these patients [2, 7]. As a consequence, careful observation without prophylaxis represents a valid option in selected cases.

It is, of course, possible that mycobacterial dissemination in this patient was triggered by the recent steroid pulse therapy [2]. The reasons for eventual graft loss could have been smoldering rejection related to a reduction in immunosuppression. First, azathioprine was withdrawn from therapy. Second, rifampicin and isoniazid upregulate hepatic cytochrome P450 enzyme function, resulting in increased metabolism of both cyclosporin and prednisone [5]. While the cyclosporin dose was adjusted to maintain therapeutic levels, the steroid dose was left unchanged.

This case underscores the variety of clinical presentations of mycobacterial infections, as well as the need for prompt and, if needed, invasive diagnostic procedures in transplant recipients.

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