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Disseminated tuberculosis after renal transplantation

A report of two cases

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Abstract. Disseminated mycobacterial infections occurred in two female renal graft recipients late after transplantation. In the first patient, initially presenting with fever, diagnosis was made at autopsy. Temporary defervescence following antibiotic therapy with ofloxacin possibly contributed to the fatal diagnostic delay. In the second case, body temperature was normal throughout the protracted course of the patient's illness. Her presenting symptom was rapidly increasing ascites, attributed initially to chronic liver disease. These cases demonstrate that tuberculosis remains a serious complication after renal transplantation, in particular due to its sometimes atypical clinical manifestations. Response to antibacterial therapy has to be critically evaluated in order to avoid fatal diagnostic delay.

Key words: Tuberculosis, in renal transplantation – Renal transplantation, tuberculosis

In this report we describe two renal transplant recipients with disseminated mycobacterial infections presenting 5 and 7 years after transplantation. In the first case, a fatal diagnostic delay occurred because fever, being the only presenting symptom of disseminated tuberculosis, temporarily responded to therapy with ofloxacin. In the second case, diagnosis was delayed because, in the absence of fever, ascites was wrongly attributed to chronic liver disease.

Case reports

Case 1

A 34-year-old Caucasian woman was started on chronic hemodialysis in June 1978 because of renal failure due to hemolytic-uremic syndrome. While on hemodialysis she received multiple blood transfusions for severe renal anemia. Subsequently, she developed hemosiderosis and porphyria cutanea tarda. On 8 June 1980 a cadaveric renal transplantation was performed. The postoperative course was uneventful and the patient was discharged with excellent graft function. Maintenance immunosuppression consisted of 10 mg/day methylprednisolone and 100 mg/day azathioprine. In August 1982 she developed acute nonoliguric renal failure following *E. coli* urosepsis. Subsequently, graft function remained impaired with a serum creatinine between 250 and 300 µmol/l. One year later insulin therapy was started because of diabetes mellitus not controlled by diet. In February 1985 she underwent splenectomy because of severe thrombocytopenia due to hypersplenism.

In December 1985 the patient developed recurrent fever to 39°C without other constitutional symptoms. Since empirical antibiotic therapy with amoxicillin and cephadroxil failed, she was admitted to our hospital for a further work-up on 21 December 1985. On admission hemoglobin was 9.1 g/dl, which was about 1 g/dl lower than previously. Leukocytes were 14200/µl, on control 9100/µl. Differential blood count was normal. Platelet count was 269000/µl. Prothrombin time was normal. Liver function studies showed a borderline elevated GOT (17 IU/l), a normal GPT (12 IU/l), and a markedly decreased activity of cholinesterase (1290 IU/l), thought to be due to chronic liver failure secondary to iron overload. Initial blood and urine cultures were negative. Screening serology showed no evidence of hepatitis A or B infection, HIV-I (ELISA), cytomegalovirus, herpes simplex, Epstein-Barr virus, or *Toxoplasma gondii*. A tine test was negative. A chest x-ray showed clear lung fields without evidence of old granulomatous disease. On computer tomogram liver, gallbladder, pancreas, and renal allograft appeared normal. Retroperitoneal lymph nodes were not enlarged. There was no ascites. There were no vegetations detectable on echocardiogram.

Despite broad-spectrum antibiotic therapy with azlocillin, oxacillin, and cefatoxime, the patient continued to have fever up to 39°C. On the 7th day, all antibiotics were discontinued. Repeat blood cultures showed growth of coagulase-negative staphylococcus in one bottle. Four days after the start of ofloxacin and fosfomycin, body temperature returned to normal and the patient felt generally improved. On 7 January 1986 she was discharged on oral ofloxacin (400 mg/day), which she took for 4 more weeks. While on ofloxacin she only had low-grade temperatures and otherwise felt well.

On 16 March 1986 the patient was readmitted to another hospital because of the recurrence of spiking temperatures to 39°C. Treatment for suspected toxoplasmosis was started with pyrimethamine and spiramycin.

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On 2 April 1986 the patient's family urged that she be transferred to a third hospital where, on admission, blood cultures showed growth of coagulase-negative staphylococcus. On echocardiogram a large pericardial effusion was now apparent. Upper and lower endoscopic studies for recurrent intestinal bleeding were negative. A leukocyte scan was performed, which demonstrated increased activity in the right lower abdomen. A subsequent computer tomogram showed a small amount of ascites and a thickened cecal wall compatible with colitis. On 18 April 1986 exploratory surgery of the lower abdomen revealed extensive necrosis of the whole right transverse abdominal muscle. There was no evidence of intraperitoneal abscess formation. Postoperatively, the patient developed generalized organ failure. She eventually died on 23 April 1986, at the age of 41.

Autopsy showed cirrhosis of the liver and disseminated and exudative tuberculosis with involvement of pericardium, meninges, lungs, liver, ileum, and peritoneum.

Case 2

A 48-year-old Caucasian female renal transplant recipient was transferred from another hospital because of ascites. In April 1969, at age 30, renal replacement therapy was begun because of chronic renal failure due to polycystic kidney disease. In October 1969 she received 6 months of triple drug therapy for tuberculosis of cervical lymph nodes. In 1974 she developed uncomplicated postransfusion hepatitis B. In September 1979 cadaveric renal transplantation was performed. An early rejection crisis was successfully treated with steroid pulses. Subsequently, graft function was excellent on 75–125 mg/day azathioprine and 10 mg/day prednisolone. After 1982 liver enzymes were mildly elevated. On 15 April 1986 the patient was admitted to another hospital because her waist size had been increasing for 3 months. Computer tomogram showed massive ascites, hepatosplenomegaly with portal collateral vessels, and lower abdominal masses suggestive of ovarian tumors. Sonography confirmed parenchymatous liver changes.

On 28 April 1986 the patient was transferred to our hospital for a further work-up. She denied fever, night sweats, abdominal pain, shortness of breath, or leg edema. On examination body temperature was 36.5°C. Apart from a firm walnut-sized right submandibular mass, which had developed a few days prior to transfer, examination showed splenomegaly and ascites.

Hemoglobin was 12.8 g/dl, leukocytes 2400, 6% monocytes. Normal values were found for coagulation parameters, GOT, GPT, alkaline phosphatase, protein, and creatinine. Hepatitis B-surface antigen was negative. A chest x-ray revealed nothing unusual. Ascites showed 4.2 g/dl protein; routine bacteriology and cytology were negative.

Initially, ascites responded to mild diuretic therapy. On the 10th day, excision of the submandibular mass yielded a lymph node abscess draining whitish pus. A smear showed the presence of acid-fast bacilli. On the 15th day, laparoscopy revealed the whole peritoneum covered with greyish-white nodules highly suggestive of tuberculous peritonitis. There were no ovarian tumors and the liver appeared almost normal. Biopsy showed mild chronic fatty liver without granulomatous changes. Isoniazid (300 mg/day), rifampicin (600 mg/day), and ethambutol (1200 mg/day) were begun. Because of progressive leukopenia, azathioprine was discontinued. Recurrent crampy abdominal pain caused frequent interruption of oral tuberculostatic therapy. Small bowel study showed inflammatory changes in the terminal ileum, suggestive of nonobstructive tuberculous ileitis. The patient's condition continued to deteriorate. She developed a cervical fistula and progressive pulmonary infiltrates. On the 71st day, ethambutol was stopped and pyrazinamide (1200 mg/day) and streptomycin (1 g/day) for 4 weeks were added. Subsequently, the patient started to gain weight. The neck fistula and the pulmonary infiltrates began to shrink. Cultures of urine, lymph node, and ascites became positive for growth of mycobacterium hominis sensitive to all tested tuberculostatic agents. Mycobacterial cultures of bronchial aspirates and bone marrow remained negative.

On 13 August 1986 the patient was discharged to be readmitted 3 weeks later because of acute bowel obstruction. Laparotomy showed mechanical ileus due to adhesions in the low ileum, which was subsequently partially resected. Histology revealed scar tissue without florid tuberculous changes. Isoniazid and rifampicin were continued for 18 months without side effects. The patient has continued to do well with excellent graft function on 10 mg/day prednisolone alone after follow-up for 3 years. During her entire hospital stay, her temperature was normal, except for the evening after laparoscopy when her temperature rose to 37.6°C.

Discussion

In northern Europe and the United States tuberculosis has been reported to occur infrequently after renal transplantation [3, 9, 13, 15]. However, in a survey that included 35 American transplantation centers, Lichtenstein and Macgregor found an annual incidence of 313–340/100000 [8]. This was 24 times the incidence of tuberculosis in the general population of the United States in 1978. Based on these data, tuberculosis in renal transplant recipients seems to be at least as common as in patients on chronic hemodialysis, where the incidence of tuberculosis was reported to be 12 times higher than in the general community [1]. As expected, a much higher incidence of tuberculosis in renal transplant recipients has been reported from centers where tuberculosis is endemic [6, 10].

Fever was presumably the presenting symptom of disseminated tuberculosis in case 1, while in case 2, despite extensive and progressive disease, fever never developed. Clinical features are not mentioned in all reports and, therefore, it is difficult to know how often disseminated tuberculosis in renal transplant recipients occurs without fever. In any case, our second patient shows that fever is not an obligatory feature of miliary tuberculosis after renal transplantation. In fact, her completely afebrile course and imaging studies compatible with chronic liver disease initially suggested liver failure as the cause of her ascites. In retrospect, initial analysis of ascites for tuberculous disease might have led to the correct diagnosis earlier, although smear studies are often negative despite the presence of extensive tuberculous peritonitis [4].

Case 1 also demonstrates that one must be careful when judging clinical response to antibiotic therapy. It is not widely known that the new quinolones, in addition to their broad antibacterial action against gram-positive and gram-negative bacteria, have antituberculous activity [16, 17]. After the start of treatment with ofloxacin, the patient's body temperature rapidly normalized and she was, therefore, discharged. Use of oxfloxacin in this patient clearly led to a fatal delay in possible diagnostic procedures such as bone marrow biopsy or bronchoscopy.

Tuberculosis is disseminated in almost half of all renal transplant recipients [8]. The high percentage of miliary spread in the transplant population is generally explained by their continued treatment with immunosuppressive agents that depress T-cell immunity, which is the major defense mechanism against tuberculosis. As in our second case, other unusual sites of mycobacterial infections, such

as colon, joints, or mediastinum, are not rare and frequently cause diagnostic confusion [2, 5, 7, 18].

In case 2 tuberculosis most likely reactivated from the neck as the previous site of disease. In case 1 tuberculosis probably also reactivated, although there was no apparent primary focus. New infection after transplantation cannot completely be ruled out. Transmission of tuberculosis by the transplant to the graft recipient has been described, but in all reported cases clinical infection developed within months after transplantation [11, 12]. In both of our patients, mycobacterial infection was probably due to the prolonged state of immunosuppression from antirejection medication and conceivably from significant liver disease in the first case [14].

Tuberculosis in renal transplant recipients seems to have a poor outcome, with an estimated mortality of 25% when the lung is the primary disease site [15]. Because of this and the considerable risk of relapse, most authors recommend prolonged therapy for mycobacterial infections for a minimum of 18 months with a least two effective drugs [3, 9, 15].

In sum, tuberculosis after renal transplantation seems to be an infrequent complication in nonendemic areas. However, because of its high mortality, all renal graft recipients have to be carefully monitored for development of the sometimes atypical manifestations of mycobacterial disease. Clinical response to antibacterial therapy has to be critically evaluated in order to avoid fatal diagnostic delay. In cases of active tuberculosis, multidrug therapy should be given for at least 18 months.

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