Tuberculosis Associated Pancytopenia After Kidney Transplantation

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Citation

Abstract
A case of renal transplant patient with disseminated tuberculosis presented as pancytopenia is reported here confirming the diagnostic difficulties. A 36 year old male received the first kidney transplant from his father in February, 1988, after 8 months of regular hemodialysis treatment (unknown underlying renal disease). Triple immunosuppressive therapy (azathioprine, prednisolone and cyclosporine A) had been used until the outbreak of the Bosnian war in 1992 when he immigrated to Serbia. He has been living in a refugee camp, discontinued his regular check up and cyclosporine therapy. In March 1997, he was admitted for the first time to our Department with a two month history of fever (maximum body temperature 39°C), chest pain, 5-kg weight loss and malaise. Physical examination revealed a pale, malnourished man, with body temperature of 36.8°C, arterial blood pressure 140/100 mm Hg, regular pulse rate of 100/minute, right pleural effusion, pericardial friction rub, slight hepatomegaly without lymphadenopathy and slight pedal edema. Laboratory tests showed anemia, white blood cell count 4.1 x 10^4, erythrocyte sedimentation rate 80 mm/h, C-reactive protein 152 mg/l, fibrinogen 4.4 g/l, blood urea nitrogen 38.3 mmol/l, serum creatinine concentration 284 m mol/l, potassium 6.3 mmol/l, calcium 2.5 mmol/l, phosphate 2.4 mmol/l. His liver enzyme levels were normal. In addition to febrile status, a rapid deterioration of the graft function developed and hemodialyses were started on April, 4. Despite intensive investigation, the cause of fever could not be found: repeated viral serology test for CMV, HSV, EBV, HIV remained negative; sputum, urine and blood cultures were negative including stains for acid-fast bacilli. On April, 9th severe pancytopenia ensued and bone biopsy was done. The bone marrow biopsy revealed granuloma with giant cells, partially necrotized and tuberculous bacilli by acid-fast stain. It can be concluded that pancytopenia due to tuberculosis should be added to the differential diagnosis of pancytopenia in renal graft recipients. Therefore, early bone marrow biopsy is recommended if fever of unknown origin and pancytopenia develop in renal transplant patients.

INTRODUCTION
Mycobacterial infection remains an important health problem in graft recipients. Prolonged immunocompromised state promotes reactivation of latent tuberculosis or development of newly acquired disease in these patients (1, 2). Apart from the usual pulmonary manifestations, hematogenous dissemination of tuberculosis occurs in transplant patients more frequently (1) affecting the graft (3), CNS (4), joints or bone marrow (5). These extrapulmonary presentations may cause a delay in the diagnosis and therefore increase morbidity and mortality of immunocompromised patients.

A case of renal transplant patient with disseminated tuberculosis presented as pancytopenia is reported here confirming the diagnostic difficulties.

CASE REPORT
A 36 year old male received his first kidney transplant from his father in February, 1988, after 8 months of regular hemodialysis treatment (unknown underlying renal disease). Normal graft function was established after the transplantation. Triple immunosuppressive therapy (azathioprine, prednisolone and cyclosporine A) had been used until the outbreak of the Bosnian war in 1992 when he immigrated to Serbia. He has been living in a refugee camp, discontinued his regular check up and cyclosporine therapy. In March 1997, he was admitted for the first time to our Department with a two month history of fever (maximum body temperature 39°C), chest pain, 5-kg weight loss and malaise. He experienced massive skin hematoma (thoracic and abdominal) caused by trauma appearing three weeks before his admission. The immunosuppressants consisted of azathioprine 100 mg and prednisolone 20 mg. Physical examination revealed a pale, malnourished man, with body temperature of 36.8°C, arterial blood pressure 140/100 mm Hg, regular pulse rate of 100/minute, right pleural effusion.
(confirmed on chest X-ray), pericardial friction rub, slight hepatomegaly without lymphadenopathy (according to abdominal ultrasound and computed tomographic scan) and slight edema on the foot. Neurological examination revealed polynuropathy.

Laboratory tests showed anemia (Hb 6.5 g/dl, Hct 19%, reticulocytes 0.026%, normal bilirubin, LDH 328), white blood cell count 4.1 x 104 with 65% segmented leukocytes, 5% monocytes, 26% lymphocytes, 4% eosinophiles, erythrocyte sedimentation rate 80 mm/h, C- reactive protein 152 mg/l, fibrinogen 4.4 g/l, blood urea nitrogen 38.3 mmol/l, serum creatinine concentration 284 m mol/l, alkaline phosphatase 53 U/l, potassium 6.3 mmol/l, calcium 2.5 mmol/l, phosphate 2.4 mmol/l. His liver enzyme levels were normal as well as immunoglobulin and complement levels. Urine analysis showed unremarkable findings and proteinuria of 1.0 g/ day.

In addition to febrile status, a rapid deterioration of the graft function developed and he became oliguric. Ultrasound showed normal sized unobstructed graft with thin (1.2 cm) and echogenous parenchyma. High doses of methylprednisolone (250 mg during 3 days) were applied without histological confirmation of graft rejection. The graft function was not stabilized and hemodialyses were started on April, 4.

Having taken the samples of sputum, blood and urine for microbiological analysis we started an empirical antibiotic therapy (ceftazidime). Although the initial sputum culture was negative, the next one was positive for Pseudomonas aeruginosa and Candida albicans. Combination of antibiotics: ofloxacin, and amikacin adjusted to the graft function and fluconazole were continued. Repeated viral serology test for CMV, HSV, EBV, HIV remained negative. Urine and blood cultures were sterile including negative smears of acid-fast bacilli. On April, 9th severe pancytopenia ensued (Hb 5.6 g/dl, leukocyte 2.5 and platelets 43), azathioprine and ranitidine were discontinued without histological confirmation of graft rejection. The bone marrow biopsy was done. The bone marrow biopsy revealed necrotizing granulomas with giant cells and positive acid-fast bacilli stain. Antituberculosis treatment (isoniazid, ethambutol, rifampicin) was initiated. In the following days, the patient's condition was complicated with purpura, melena and coma and he died on May, 2nd. No autopsy was performed. Mycobacterial culture of sputum in Loewenstein media was positive for MB and the results were obtained after his death.

DISCUSSION

The patient described here had a disseminated form of tuberculosis developing eight years after kidney transplantation and manifesting with prolonged fever, pleural effusion, pericarditis, hepatomegaly, rapid deterioration of kidney graft function and pancytopenia. Many nonmedical circumstances might contribute to such severe clinical tuberculosis course. After immigration to Serbia when the Bosnian war began our patient stopped his regular medical check up and cyclosporin therapy when his supplies ran out. Apart from cyclosporin, he had continued with his immunosuppressives in stable doses. However, the steroid dose was rather high. At the same time poor diet and lack of hygiene, poor living conditions may have promoted his tuberculous infection. Moreover, when the symptoms appeared he delayed his visit to doctor.

Different agents i.e. bacteria, viruses and fungi are taken into consideration as the possible causes of deteriorating patient's condition resembling life-threatening sepsis. Having in mind that the increased incidence of tuberculosis in our renal transplant patient population has already been observed (9), the highest awareness of possible tuberculosis should be maintained in the diagnostic procedure, more so in the light of the fact that clinical manifestation of tuberculosis in these patients is not typical. In recent years advances in molecular biology have permitted the development of new technologies that allow more sensitive and specific diagnosis to be made in a short period of time (10). Unfortunately, we did not have such a possibility. In addition, urine and sputum smear cultures were negative for acid-fast bacilli. At the end, the diagnosis of tuberculosis was confirmed by histological analysis of the bone marrow.

Although hematological abnormalities in disseminated tuberculosis are well recognized, only few reports have focused the occurrence of pancytopenia in general population and immunocompromised or hemodialysis patients (9-11). However, this complication appears to be extremely rare and if present, it is a poor prognosis factor with mortality rate of 30-40% (9, 11, 12). According to already published reports pancytopenia was caused by hemophagocytic syndrome or bone marrow gelatinous transformation (11, 13). Although, an immune-mediated mechanism of bone-marrow suppression has been presumed, the extensive necrotizing granulomata of the bone marrow was most likely the cause of the pancytopenia in our patient.

Pancytopenia due to tuberculosis should be added to the
differential diagnosis of pancytopenia in renal graft recipients. Therefore, we agree with Yang et al. that early bone marrow biopsy is recommended if fever of unknown origin and pancytopenia develop in renal transplant patients.

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References
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