LATE ONSET OPPORTUNISTIC INFECTIONS IN A RENAL ALLOGRAFT RECIPIENT: A CASE REPORT

Infezioni opportunistiche ad esordio tardivo in un trapiantato renale: descrizione di un caso clinico

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INTRODUCTION

In renal allograft recipients, infectious disease complications remain an important cause of morbidity and mortality during the post-transplant period. This complication occurs more frequently from 1 to 6 months after transplant [1], although the risk of serious infection never disappears [2]. Approximately 80% of solid organ transplant recipients suffer at least one significant episode of infection during the first year after transplant [2]. The epidemiology of infection during the postoperative period is not well characterized, because recipients routinely reside at home [2].

CASE REPORT

We report a case of a 67-year-old man, who was admitted to our hospital in November 2001 with an 11-day history of persistent fever and dysphagia. He had suffered from membranoproliferative glomerulonephritis since 1967. He had been treated with haemodialysis from 1986 to 1993 for renal failure. In 1993 he received a cadaveric kidney transplant, followed by immunosuppressive therapy with methylprednisolone, azathioprine and cyclosporin A. In July 2001 he had biliary colic due to choledoch and cholecystis lithiasis. Two ERCPs (endoscopic retrograde cholangio-pancreatography) were performed with placement of an internal stent. In August 2001 azathioprine was stopped and mycophenolate mofetil started (1 g twice daily os), since cholestasis is a side effect of the first agent. At the beginning of November 2001, he suffered fever (39°C), dysphagia and diarrhoea. Physical examination revealed jaundice, dyscrasic edema of the extremities, bilateral basal rales at thorax auscultation, and mild hepatomegaly. The laboratory findings revealed severe lymphocytopenia and hypogammaglobulinaemia (IgG 309 mg/dl, IgA 62 mg/dl, and IgM 91 mg/dl). The white cell count was 6550/mm³ (87.6% neutrophils and 10% lymphocytes), with haemoglobin 7.4 g/dl, and haematocrit 21.7%. Urea nitrogen was 66 mg/dl, creatinine 0.83 mg/dl, and creatinine clearance 35 ml/min. Aspartate transaminase (AST) was 94 mU/ml, alanine transaminase (ALT) 78 mU/ml, γ-glutamil transpeptidase (GTT) 674 mU/ml, alkaline phosphatase (ALP) 1536 mU/ml, and LDH was normal. Pseudomonas aeruginosa septicemia was diagnosed with blood cultures. Gastrointestinal endoscopy examination showed esophagitis attributable by standard histological and microbiological investigation to HSV1 and Candida albicans. An ELISA test for HIV infection proved negative. Treatment was started with ciprofloxacin (500 mg x 2 daily os) and imipenem (500 mg x 3 daily intravenous) with partial temperature reduction. The mycophenolate mofetil treatment was stopped and prednisone started (15 mg daily po).

As the febricula persisted, he was admitted to the Infectious Disease Department. On admission his temperature was 37.8°C, blood pressure 100/60, pulse 92 beats/min, and respira-
tion 24. On physical examination he was jaundiced, dehydrated, with dyscrasic edema of the extremities, bilateral and basal rales at thorax auscultation, and mild hepatomegaly. There were no other abnormal findings. The laboratory tests were stable; the blood cultures were negative. T-helper count (CD4) was 77 cells/mm$^3$ (14%), and T-suppressor count (CD8) 459 cells/mm$^3$. An X-ray of the chest revealed minimal bilateral pleural effusion. A sample of arterial blood was normal. The patient underwent a treatment course with fluconazole (200 mg x 2 daily os) and ganciclovir (200 mg x 2 daily os), for the esophagitis. The temperature went down in a few days and the patient’s condition remained stationary.

Seven days after admission there was a fever increase with a daily peak of 38.5 - 39°C. The laboratory tests were stable except for the LDH, that increased to 1263 mU/ml. Imipenem and ciprofloxacin were stopped and piperacillin/tazobactam (4.5 g x 3 daily iv) and teicoplanin (400 mg daily iv) started, but no improvement was noted. The serologic test was repeated for HIV infection and detection of HIV-RNA in the blood, both proving negative. A new lymphocyte subset demonstrated a further reduction in T-cells: CD4+ was 29 cells/mm$^3$ (13%), and CD8+ was 182 cells/mm$^3$ (69%). Repeated chest X-ray revealed a diffuse opacity in the left medium and lower lobe with diffuse reticular nodular densities in the right lobe. The patient became dyspnoic and hypoxic. A sample of arterial blood (with oxygen flow rate of 35%) revealed PaO$_2$ of 50 mmHg (with SaO$_2$ 87.6%), PaCO$_2$ of 26.8%, and pH 7.43. Seven days after fever increased, bronchoscopy with bronchoalveolar lavage were performed: the cytology of the aspirate showed epithelial and bronchial cells, polymorphonuclear leukocytes, and no bacterial forms. The immunofluorescence stain was positive for *Pneumocystis carinii*. The standard therapy for *P. carinii* pneumonia (PCP) was started. After three days the patient’s temperature became normal; the clinical condition and arterial blood gases improved (PaO$_2$ 66.9 mmHg, with SaO$_2$ 94 %, PaCO$_2$ 26.2 %). No deterioration of renal function was noted. After eight days, he died of heart failure.

## DISCUSSION

Renal transplantation has significantly improved with the advent of more potent immunosuppressive drugs. However, the incidence of side effects of immunosuppression has dramatically increased [3]. Our patient had a severe T-CD4 lymphocytopenia with hypogammaglobulinaemia. Various factors could compromise cellular immunity in this patient: immunosuppressive drugs, recent *Pseudomonas aeruginosa* septicemia, malnutrition, and transplant duration. But none of these can fully explain the selective CD4 deficit (CD4/CD8 was <1) in the absence of HIV infection, as a condition of idiopathic CD4+ T lymphocytopenia (ICL) was present. Moreover immunosuppressive therapy does not usually cause a selective CD4 deficit, with also hypogammaglobulinaemia [3]. Usually all the lymphocyte subpopulations decreased markedly in the first day after transplant, but they increased progressively to reach pretransplant values one year after transplant [3].

Our patient had recently modified his immunosuppressive therapy, substituting for azathioprine mycophenolate mofetil, the 2-4 morfolino ethyl ester of mycophenolic acid, an inhibitor of the Inosine Monophosphate Dehydrogenase, which inhibits proliferation of T and B cells [4]. This change can partially explain the severe immuno deficit which developed. Some trials demonstrated that the substitution of mycophenolate mofetil for azathioprine may reduce mortality and rejection in the first year after transplantation, but most adverse events have been reported concerned the gastrointestinal tract, the emic system (such as leucopenia) and opportunistic infections [5]. Before the documented CD4 lymphocytopenia, our patient also experienced *P. aeruginosa* septicæmia. Some cases of lymphocytopenia due to a systemic bacterial infection have been reported, even though not to *P. aeruginosa* [6]. Moreover, in all of these reported cases, unlike ours, the lymphocytic subpopulation went back to normal values, once the appropriated antibiotic therapy was implemented [7]. This report seeks to underline the need to monitor the lymphocyte subset in renal transplant recipients. There are still no absolute criteria that enable the clinician to predict the actual risk of overimmunosuppression in long-term renal transplant recipients. CD4 cell count can be one of these [3, 9, 10]. Some authors try to identify the patients who need a reduction in overimmunosuppression. A study underlines the possibility to reduce the immunosuppressive therapy in patients with opportunistic infections [8]. This re-
In renal allograft recipients, infection disease complications remain an important cause of morbidity and mortality during the post-transplant period. This complication occurs more frequently from 1 to 6 months after transplant. The epidemiology of infection during the postoperative period is less well characterized, because recipients routinely reside at home. We describe a case of late onset Candida albicans and HSV-1 esophagitis, and Pneumocystis carinii pneumonia, that occurs 9 years after renal transplantation in a patient with severe CD4+ T-lymphocytopenia and hypogammaglobulinaemia. We underline the importance of monitoring immunosuppressive therapy in these patients and the usefulness of prophylaxis against P. carinii pneumonia.

**Key Words:** renal allograft, opportunistic infections, lymphocytopeny.

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**REFERENCES**


