

## Cytomegalovirus infection of the renal graft

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Received for publication: 18/07/2006

Accepted in revised form: 27/11/2006

### ■ ABSTRACT

Presented here is a clinical case of a 45-year-old patient with cytomegalovirus (CMV) infection three months post renal transplant (Tx). The cadaver kidney transplant was carried out without complications. HLA compatibilities were: 1-DR, o-A and o-B, with a PRA of 0%; cold ischemic time was 17 hours. Immunosuppression was initiated with mycophenolate mofetil (MMF), cyclosporine (CsA), and methylprednisolone. Initial functioning of the graft was observed. He continued to be followed post-Tx, remaining clinically stable with average creatinine levels of 1.5 mg/dL and average cyclosporine (C<sub>2</sub>) blood levels of 1500 ng/mL. Acute CMV infection and disease manifested itself after 3 months, with gastrointestinal, hepatic, and renal graft involvement. Diagnosis was made based on serological exams, detection of viral DNA in the blood by PCR, and by renal biopsy, which showed extra-capillary proliferative glomerular nephritis with CMV nuclear inclusion bodies in the glomeruli. Treatment consisted of reducing immunosuppression and administering ganciclovir IV and hyperimmune immunoglobulin, with good systemic response, although the renal graft did develop lesions that led to chronic dysfunction.

Renal graft dysfunction due to CMV infection is a well-known but infrequent complication. Histologically, inclusion bodies are found in different types of cells, with the tubular and interstitial cells the most

affected. Occasionally the peritubular cells are affected and very rarely the capillary glomeruli. Proliferative glomerulonephritis associated with CMV is an unusual situation, this being one of the few cases described to date.

### Key-Words:

Cytomegalovirus; glomerulonephritis; immunosuppression; renal transplantation.

### ■ INTRODUCTION

CMV is a member of the human Herpes-virus family and constitutes one of the most important causes of post renal Tx infection, most often occurring within the first 3 months<sup>1</sup>.

Between 20 and 60% of patients who do not receive prophylactic treatment develop symptomatic infections, which contribute significantly to increased morbidity and mortality<sup>1</sup>.

The virus may trigger acute effects, such as pneumonitis, hepatitis, gastroenteritis, retinitis, loss of the graft or even death (in most cases caused by opportunistic infections, such as *pneumocystis carinii*); and may present other long term effects, such as chronic graft dysfunction and the development of neoplastic processes, such as lymphoproliferative diseases<sup>2,3</sup>.

## ■ CASE REPORT

The patient is a 45-year-old Caucasian male from Castelo Branco, married, senior civil service employee.

In 2001 the patient was diagnosed with end stage chronic renal disease of unknown aetiology. A programme of peritoneal dialysis (CAPD) was begun in October of that year. Two years later (December 2003) the patient underwent renal Tx with a cadaver kidney, without complications. HLA compatibilities were: 1-DR, o-A and o-B, with a PRA of 0%; cold ischemic time was 17 hours. Immunosuppression was initiated with mycophenolate mofetil (MMF) 2g per day, CsA 8 mg/kg/day, and methylprednisolone 8 mg/kg. Initial functioning of the graft was observed, with gradual recovery of renal function, and the patient was discharged 7 days later with a creatinine level of 2.1 mg/dL, on MMF 2 g/day, CsA 500 mg/day, prednisone 20 mg/day and cotrimoxazole 480 mg/day. For three months he maintained renal function with average creatinine levels of 1.5 mg/dL and average cyclosporine (C2) levels of 1500 ng/mL.

The patient's known medical history included arterial hypertension controlled with medication, highlighted by the fact that he had positive IgG serum markers for CMV and serology was negative for hepatitis B and C and HIV.

Three months later (March 2004), after missing his scheduled appointments for a week, the patient presented with a fever (38-39°C) of 2 days' duration, worsening of renal function (serum creatinine: 1.8 – 3.5 mg/dl), leucopenia (total leucocytes 2.1 G/L) with neutropenia (30%), and oesophageal candidiasis diagnosed by upper GI endoscopy. For these reasons, he was admitted to the Transplant Unit.

The patient had no respiratory, genital-urinary or gastrointestinal complaints but he complained of generalised myalgia and pain upon swallowing associated with the oesophageal candidiasis, for which he had been receiving fluconazole for 2 days. Chest x-ray revealed no pleural-pulmonary changes, and an abdominal ultrasound and Doppler of the renal graft were normal.

Blood and urine cultures were taken, along with viral serologies (CMV, HBV, HVC, EBV, and HIV), CMV

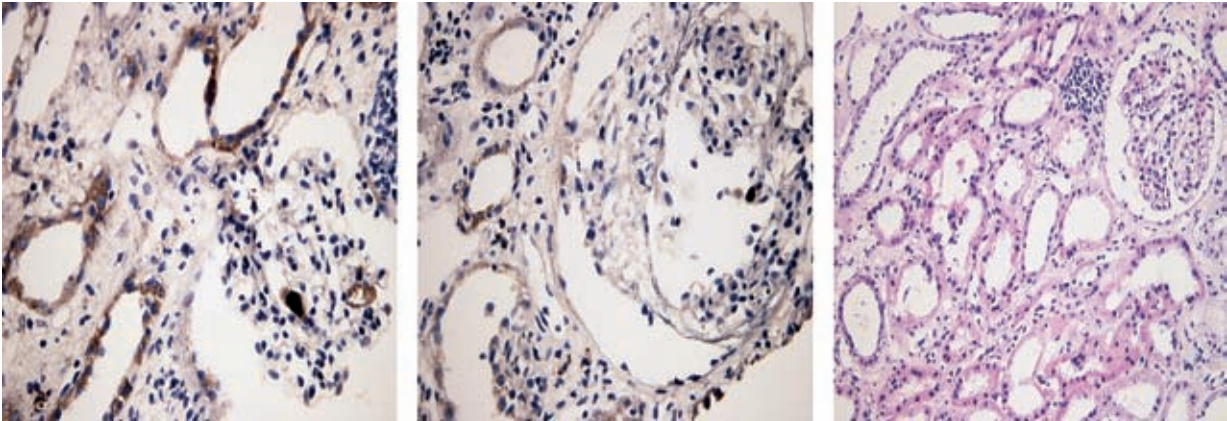
shell vial method blood and urine cultures, and PCR-mediated screening for virus DNA.

The patient began empirical treatment with valganciclovir and continued the fluconazole. Immunosuppression was reduced by suspending the MMF dose, maintaining only the CsA 250 mg/day and prednisone 20 mg/day.

On the third day of hospitalization, after fever had subsided, a renal graft biopsy was performed, which revealed "Acute tubular necrosis lesions with mild focal interstitial infiltrate with mild tubulitis (borderline AR) and extra-capillary proliferation in 2 out of 7 glomeruli, without vascular lesions." Based on these results, the patient was treated with IV boluses of methylprednisolone 500 mg/day for 3 days.

On the tenth day of hospitalization, the patient remained afebrile, and his cultures were negative. On that day he began to experience diarrhoea, with no loss of blood, mucous or pus, accompanied by worsening azotemia (creatinine of 6 mg/dL) and leucopenia (total leucocytes <2 G/L) requiring treatment with leucocyte growth factor. An increase in transaminases (SGOT-62 U/L, SGTP-152 U/L) and the appearance of sustained macroscopic haematuria along with proteinuria of 4.3 g/24 hours were also observed. At this time serum IgM markers for CMV were elevated (1.51 IU/mL), and the DNA blood screening came back positive as well. In the light of the patient's worsening renal function, a second renal biopsy was done, which showed "Worsening of the ATN lesions, without signs of AR; extra-capillary proliferation in 2 out of 8 glomeruli; nuclear inclusions positive for CMV in 2 glomeruli. Screening for polyoma virus (PMV) (SV40) was negative." (fig. 1). Treatment with ganciclovir IV and Megalotec® was then given for 3 weeks. Immunosuppression was changed to sirolimus 2 mg/day and prednisone 20 mg/day.

Over the next 2 months the patient remained clinically stable, without diarrhoea; diuresis continued with macroscopic haematuria; elevated levels of azotemia continued, which required haemodialysis. Liver function tests returned to normal; the leucopenia improved, and blood became negative for viral DNA. Given the persistent renal failure, the patient underwent 3 more 500 mg IV boluses of methylprednisolone



**Figure 1**

ATN lesions, without signs of AR. Glomeruli with extra-capillary proliferation. Nuclear inclusion bodies positive for CMV in 2 glomeruli.

with no response. A third biopsy of the graft was then done, revealing “Severe tubular lesions with areas of interstitial fibrosis, extra-capillary proliferation in 50% of the glomeruli, vessels without significant changes. CMV and PMV screens were negative. Immunofluorescence revealed scarce C3, C1q, fibrinogen, and C4d deposits in the mesangium and in the capillary walls, but not in the peritubular capillaries.” Anti-HLA antibody screens were consistently negative.

This patient remained on haemodialysis (2 sessions per week) for 3 more months, with partial recovery of renal function, having been transferred to another unit in the meantime. At this time he is no longer on haemodialysis, but continues to suffer from chronic graft dysfunction (serum creatinine: 3-3.5 mg/dL) and is being followed as a post-Tx outpatient at another hospital.

## ■ DISCUSSION

CMV is one of the more frequent viral infections post renal transplant, occurring mainly after the first month<sup>4</sup>.

This clinical case is presented because of its unusual nature. The patient was 3 months post Tx, CMV seropositive, with no history of AR, receiving triple immunosuppression therapy (MMF, CsA, and corticosteroids), with cyclosporine blood levels (C2) within the

intended limits. There was no formal indication for prophylactic therapy. This is a rare instance of secondary infection where renal lesions with CMV glomerulopathy are observed evolving into glomerular sclerosis and interstitial fibrosis, which were responsible for the RI picture observed and the patient’s current chronic dysfunction. The initial lack of clinical specificity and the difficulty of diagnosis and consequent delay in starting treatment must be highlighted here. The first biopsy showed signs of borderline AR (the principal cause of graft dysfunction during the first few months post transplant), in a patient who was non-compliant with his required follow-up monitoring, which led us to treat him initially with IV boluses of methylprednisolone. Treatment with ganciclovir and hyperimmune immunoglobulin was instituted shortly thereafter, and immunosuppression was cut back. Two months later the clinical picture had improved and virus screening was negative, but the renal graft suffered irreversible sequelae.

A causal relationship between CMV infection and renal graft glomerular disease is still controversial<sup>5</sup>. Some studies have suggested that viral infection may damage the glomerulus indirectly, with immunological mediation, and that CMV may not be necessary or sufficient to provoke lesions<sup>6</sup>. However, a case of immunotactoid glomerulopathy resolved with treatment for CMV has been described<sup>7</sup>, as well as other glomerular lesions occurring in infected renal transplants that subside after reducing immunosuppression and treating the infection<sup>5</sup>. The first case of cres-

centic necrotizing glomerulonephritis associated with CMV inclusions in the glomerulus that responded to treatment directed at the virus was described in 1998<sup>8</sup>.

The case presented here is also one of extra-capillary glomerulonephritis associated with glomerular CMV inclusions that disappeared once treatment was instituted, although persistent lesions led to chronic dysfunction of the graft.

Thus, this case history, along with others described in the literature, suggests that, although it is rare, glomerular cells may be infected by the virus. We believe that the infection leads to cellular lesions and intraglomerular proliferation followed by sclerosis if immediate anti-viral treatment is not given. More studies are needed, however, to confirm the causal relationship.

**Conflict of interest statement.** None declared.

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