Case Report

Severe cytomegalovirus ureteritis in a renal allograft recipient with negative CMV monitoring

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Introduction

Cytomegalovirus (CMV) is a significant opportunistic pathogen in immunocompromised patients. Virus circulating in the donors or the recipients of solid organ transplants places the latter group at risk of developing CMV disease. The prevention of serious complications in them relies on defining potential risk factors and on the early detection of the presence and replication of CMV.

We report a case of isolated CMV ureteritis, which developed into ureteric necrosis despite meticulous polymerase chain reaction (PCR)-based CMV monitoring.

Case

A 62-year-old man seropositive for CMV (R⁺) was transplanted with a kidney from a seronegative cadaveric donor (D⁻). The ureterocystostomy was routinely protected by a double-J stent. Cold and warm ischaemia times were 16 h and 40 min, respectively. Induction therapy by anti-lymphocyte globulins (Lymphoglobulines, Fresenius AG, Germany) was followed by a double sequential therapy with cyclosporin A (cyclosporin trough level: 150–200 ng/ml) and mycophenolate mofetil (1 g b.i.d), with a significant decrease in the CD4 lymphocyte count (pre-transplant and day 21 counts: 1.054 and 0.04 \times 10^9/l, respectively). On day 10, immunosuppression was intensified by the addition of pulse prednisone, for biopsy-proven acute rejection of the kidney. On day 21, the patient was discharged with a stable serum creatinine level [1.8 mg/dl (158 \, \text{mmol/l})].

On day 41 after transplantation, the patient was admitted because of acute ipsilateral leg oedema. He did not have fever; further physical examination and the biological parameters analysed, including serum creatinine level (1.9 mg/dl), white blood cell count (5600/mm³), polymorphonuclear cell count (3900/mm³) and alanine aminotransferase level (25 IU/l), were unremarkable. An ultrasound scan revealed considerable perirenal fluid of urinary origin (with an elevated creatinine content). Routine whole blood PCR-based CMV monitoring, performed weekly since transplantation, now had turned positive. Real-time quantitative PCR revealed a massive viral load, with up to \(1.8 \times 10^6\) copies/ml (detection limit 500 copies/ml). Donor ureter necrosis was confirmed at surgery. A re-implantation of the native ureter in the bladder and a renal biopsy were performed. At the same time, i.v. ganciclovir treatment (300 mg b.i.d., days 50–81) resulted in the rapid decrease of circulating copies of CMV, with none detected by day 76 (Figure 1). Mycophenolate mofetil was discontinued on day 60. The patient was discharged on the 81st post-transplantation day with improved renal function [serum creatinine 1.1 mg/dl (97 \, \text{mmol/l})].

The pathological examination of the surgical specimen revealed extensive submucosal ureteral necrosis with large intranuclear inclusions in the endothelial and vascular smooth muscle cells evocative of CMV infection, which was then confirmed by double labelling with anti-CMV and anti-CD31 antibodies (Figure 2). The renal biopsy examination, including immunohistochemistry for CMV, was unremarkable.
Discussion

Although viral monitoring still is advocated to detect the early development of CMV reactivation in order to prevent severe organ involvement by early antiviral treatment, CMV disease can develop in the absence of detectable viraemia [1]. Various biological methods of widely different sensitivities have been proposed for monitoring CMV presence and activity. We resorted to real-time PCR of whole blood samples [2,3], which we had recently demonstrated to be more sensitive than pp65 antigenaemia [4] or PCR in peripheral blood leukocytes [3] (detection limits of 500 copies/ml, one positive polymorphonuclear leukocyte/200,000 cells and 140 copies/200,000 leukocytes, respectively). In spite of that higher sensitivity, we had failed to identify CMV disease early enough to resort to antiviral therapy prior to the development of a severe complication.

The risk of CMV disease is highly dependent on the CMV statuses of both donor and recipient, the D+/R− group being at high risk, with up to 55% of patients developing the disease within the first 3 months of transplantation [5]. However, even in the lower risk group of positive recipients receiving negative grafts, D−/R+, as in our patient, CMV disease occurs in a significant minority of 16%. This risk is increased further by antilymphocyte therapy, use of mycophenolate mofetil administration or the treatment of acute rejection with corticosteroid pulses or antilymphocyte globulins [2,6].

In the present case, the initial low risk of CMV disease was increased by all three of the above noted risk factors. In addition, the patient’s CD4 T-lymphocyte count was low (0.04 x 10^9/l), indicating intense immune depression, a known risk factor for CMV disease both in AIDS [7] and in renal transplantation [8]. Finally, it was reported recently that in the CMV D+/R− group, a CMV surveillance strategy, although more cost effective, might be less efficient than prophylaxis in terms of preventing renal damage [1]. We suggest, therefore, that prophylactic anti-CMV therapy be extended to CMV-positive recipients presenting with additional risk factors such as intense immune depression, acute rejection or a low CD4 count.

Although prophylactic therapy has been shown to reduce the incidence of CMV disease in high-risk transplant recipients [9], the recommended use of iterative
ganciclovir infusions has some limitations in terms of related cost and impact on quality of life [2]. Using oral ganciclovir and its prodrug, valganciclovir, might be an attractive alternative strategy [2,6]. In a previous report by Moudgil et al. [11], prophylactic anti-CMV therapy failed to prevent CMV ureteritis. However, in that patient, prophylaxis consisted of oral acyclovir, a less efficient anti-CMV prophylactic drug than ganciclovir or its prodrug [2,10].

While graft involvement has been amply documented in all solid organ transplantations, until recently ureteritis has been reported rarely, and never as the sole manifestation of CMV disease in the absence of viraemia [11–14]. The widespread use of double-J stents might play a part in this new pattern of expression of CMV disease. Indeed, the inflammation induced by the endoluminal stent and the local expression of tumour necrosis factor-α, interleukin (IL)-1β and IL-6 may promote the selective homing of CMV-infected macrophages and the local activation and replication of CMV in target cells such as endothelial and smooth muscle cells [13]. In addition, the endoluminal catheter may delay the expression of initial signs of urinary obstruction, leaving ample time for ureteric inflammation to develop into severe stenosis or necrosis.

In our patient, meticulous CMV monitoring failed to identify isolated CMV ureteritis, an emerging complication of CMV disease. Therefore, we feel justified to suggest that, pending the development of even more sensitive means of CMV monitoring, prophylactic treatment should be considered liberally in all high-risk patients. Further large cohort studies are required to determine the need for anti-CMV prophylaxis in seropositive renal transplant recipients.

Conflict of interest statement. None declared.

References


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