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Case report

Immune-based guidance of foscarnet treatment duration in a transplant recipient with ganciclovir-resistant cytomegalovirus infection

Janine Mihm[a], Sarah Leyking[a], Jan Dirks[b,1], Sigrun Smola[c], Danilo Fliser[a], Urban Sester[a], Martina Sester[b,*], Heinrike Wilkens[d], Jürgen Rissland[c]

[a] Department of Internal Medicine IV, Saarland University, D-66421 Homburg, Germany
[b] Department of Transplant and Infection Immunology, Saarland University, D-66421 Homburg, Germany
[c] Institute of Virology, Saarland University, D-66421 Homburg, Germany
[d] Department of Internal Medicine V, Saarland University, D-66421 Homburg, Germany

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ABSTRACT

A lung and kidney transplant recipient underwent cytomegalovirus (CMV) primary infection with a UL97 mutation. Combined monitoring of viral load and CMV-specific CD4 T-cells allowed reduction of treatment duration with foscarnet, and illustrates how knowledge on the individual immunocompetence towards CMV may be used to individualize duration of antiviral treatment.

1. Why this case is important

After solid organ transplantation even asymptomatic cytomegalovirus (CMV) infections may indirectly contribute to reduced graft survival [1] and increased patient mortality [2]. The treatment of ganciclovir-resistant CMV-infection and defining optimal treatment duration still remain challenging [2]. Management of resistance is further aggravated in patients with impaired kidney function due to drug-mediated nephrotoxicity. Therefore, duration of antiviral therapy should be kept as short as possible to avoid side effects. The present case of a lung and kidney transplant recipient with a CMV-UL97-mutation outlines the relevance of combining standard viral load testing with immunological monitoring of CMV-specific CD4 T-cells to optimize and individualize antiviral treatment. This combined monitoring approach allowed reduction of treatment duration with foscarnet to a necessary minimum. This case highlights CMV-specific T-cell monitoring as an adjunct diagnostic tool to assess individual immunocompetence towards CMV. Its use in guiding treatment duration illustrates a novel area of application in patients after solid organ transplantation.

2. Case description

In August 1999, a 27 year-old CMV-seronegative woman underwent double lung transplantation because of cystic fibrosis. Maintenance immunosuppression consisted of cyclosporine, prednisolone and azathioprine. To prevent active herpes simplex virus infection the patient was treated continuously with aciclovir, and was regularly monitored for evidence of CMV viremia. Due to calcineurin-inhibitor mediated toxicity the patient reached end-stage renal disease in July 2005 and hemodialysis was initiated. After 19 months of dialysis the patient received a kidney from her CMV-seropositive mother in February 2007. Maintenance immunosuppression was changed to tacrolimus, prednisolone and mycophenolate mofetil. Valganciclovir prophylaxis was given for 3 months to prevent CMV primary infection, and aciclovir therapy was administered thereafter. The characteristics of the recipient and the lung and kidney donors are summarized in Table 1. CMV-seronegative recipients of a CMV-seropositive graft are at risk to develop CMV primary infection[2], that is generally followed by the

* Corresponding author.
E-mail address: martina.sester@uks.eu (M. Sester).
[1] Present address: University Hospital Basel, CH 4031 Basel, Switzerland.

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Table 1
Demographic characteristics of transplant recipient and her donors.

	Patient	Donor lung	Donor kidney
Age (years)[a]	27	44	57
Sex	female	female	female
Blood group (ABO, rhesus)	0 positive	0 positive	0 positive
HLA-alleles	A2, A3, B12, B16, DR6, DR12	A2, B5, B41, DR2, DR5	A1, A2, B8, B12, DR3, DR6
CMV-serostatus[a]	negative	positive	positive
Type of donor	n.a.	Deceased (cerebrovascular insult)	Living (mother)
Organ		Double lung	Left kidney

[a] at the time of lung transplantation; HLA, human leukocyte antigen; CMV, cytomegalovirus.

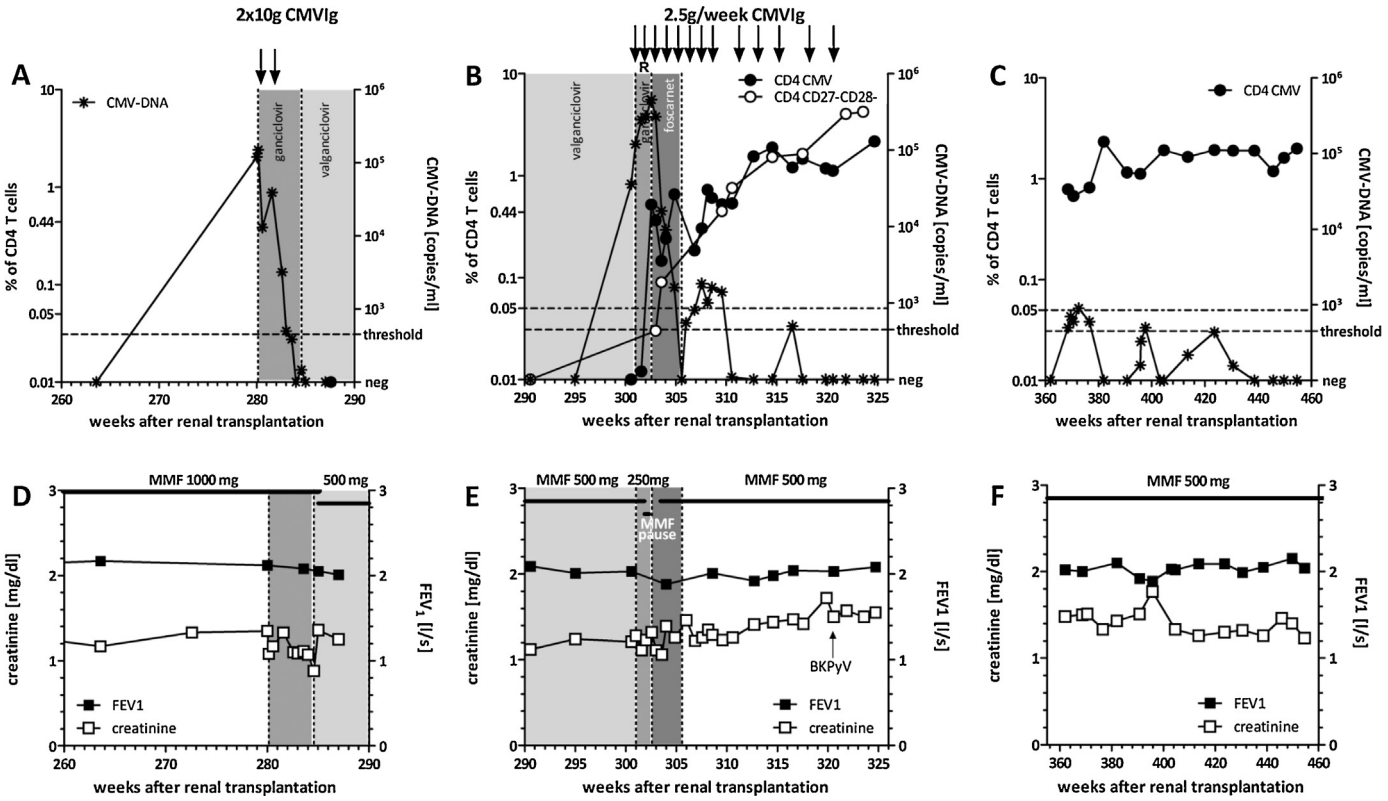

Fig. 1. Viral load, CMV-specific CD4 T-cells and organ function during primary infection and reactivation. (A) Course of CMV primary infection with maximum CMV-load of 150.000 copies/ml. Antiviral therapy was carried out with ganciclovir (gray shading) and CMV-specific immunoglobulins (CMVIg, 2 × 10 g, indicated by arrows); secondary prophylaxis was carried out with valganciclovir (light shading). CMV-specific T-cells were not detectable. (B) Following viral reactivation with viral load of 120.000 copies/ml, therapy with i.v. ganciclovir and immunoglobulins (2,5 g, once weekly, arrows) was initiated. As viral load increased further (maximum 460.000 copies/ml) and as a UL97-mutation was identified (week 302, denoted by an "R"), therapy was switched to foscarnet and continued for three weeks (dark shading). Foscarnet duration was guided by CMV-specific CD4 T-cells and CD27-CD28- CD4 T-cells that became detectable for the first time and remained stable thereafter. Although viral load increased again (maximum 1.800 copies/ml) no antiviral drugs were administered. (C) CMV-specific CD4 T-cell frequencies were stable in the long-term despite intermittently positive CMV-load. No further antiviral therapy was given. Kidney and lung function is shown (D) during primary infection, (E) during reactivation with the ganciclovir resistant strain, and (F) during long-term follow-up. Two rises in creatinine were due to a self-limited BK-polyomavirus (BKPyV) nephropathy (arrow in panel E) without evidence of rejection or further involvement of CMV, and a temporarily high calcineurin inhibitor level (panel F), respectively. CMV-DNA is given in copies/ml with a clinically relevant threshold of 450 copies/ml indicated by a stippled line; copies/ml correlated well with IU/ml obtained by the WHO reference standard ($r^2 = 0.873$, $p < 0.0001$), and peak viral loads during primary infection and reactivation correspond to 150.000 and 810.000 U/ml, respectively. Detection limits for CMV-specific CD4 T-cells and $CD27^-CD28^-$ CD4 T-cells that are associated with CMV-seropositivity are 0.05% and 0.44%, respectively. $CD27^-CD28^-$ CD4 T-cells were determined throughout the first half year after their induction only (panel B). Mycophenolate mofetil (MMF) dosages per day are displayed in panels D-F; FEV1, forced expiratory volume at 1 s.; The x-axes depict weeks after kidney transplantation.

induction of both CMV-specific antibodies and cellular immunity [3–5]. The time of antibody and T-cell induction after primary viremia may be variable, and their stable induction may contribute to long-term control of viral replication in the absence of antiviral drugs [5–8]. Although the recipient was CMV-seronegative and both donors were CMV-seropositive, the patient did not acquire primary infection directly after the two transplantations. As expected, she remained CMV-seronegative, and did not develop any CMV-specific T-cell immunity, whereas cells readily reacted after polyclonal stimulation with *Staphylococcus aureus* enterotoxin B (data not shown). In June 2012 (13 years after lung and five years after kidney transplantation, respectively), the patient was admitted to hospital with temperatures between 36.5 °C and 39.5 °C, dyspnea and aching joints. Fever was unresponsive to antibiotic therapy. The patient underwent complete physical examination including an eye exam, abdominal sonography, renal function tests and serial chest x-rays. All examinations did not reveal any signs of CMV associated organ damage and no focus for bacterial infection. CMV primary infection was diagnosed based on detection of 120.000 copies/ml CMV DNA one day thereafter (week 280 after renal transplantation, Fig. 1A). During acute CMV-infection, lung and kidney function, viral load and CMV-specific cellular immu-