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Cytomegalovirus and Acute Rejection in Kidney Transplantation

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Cytomegalovirus infection and disaese may represent a serious complication in renal transplant recipients, being potentially involved in the pathogenesis of acute vascular rejection. Evaluation of potential markers of subsequent risk of acute renal allograft vascular rejection, such as cytomegalovirus-induced anti-endothelial cell antibodies, could be useful in the clinical management.

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Cytomegalovirus (CMV) is a highly seroprevalent β-herpesvirus that, following primary infection, establishes a lifelong latent infection in several sites of the body and may reactivate in the presence of immunosuppression, such as in transplant recipients. In these patients, beside direct effects such as systemic and organ infection/disease, CMV has been associated to indirect effects, including increase in systemic immunosuppression (i.e. effect favoring opportunistic infections), increased risk of neoplasms (i.e. Epstein-Barr virus-related posttransplantation lymphoproliferative diseases) and the potential role in allograft rejection (1). In particular, the potential impact in terms of graft rejection and the underlying pathogenic mechanisms are still largely unknown. Among the pathogenic factors considered as potentially contributing to allograft injury, following hypotheses have been proposed: CMV could break graft acceptance via reactivation inside the transplanted organ; the quality of CMV-specific immune response (particularly, cellular response) could influence graft outcome; latent CMV infection is linked to immune senescence and vascular disease. The understanding of the mechanisms by which CMV plays a role in the development of allograft rejection is crucial in that, despite the recent advancements in the development of efficacious antiviral agents, the real impact of CMV, especially in kidney transplantation, may be misestimated because of many confounding factors and research on new therapeutic protocols could have an impact also on indirect effects. To better understand the association between CMV reactivation and acute rejection in renal transplantation, in addition to the amount of experimental data, clinical studies on large populations are fundamentals, in particular, randomized trials evaluating long-term graft survival in patients having received prophylaxis versus those treated with pre-emptive therapy (i.e. treatment of CMV infection as evidenced by laboratory data in the absence of signs and symptoms) (2). It seems that CMV disease, but not asymptomatic infection, is an independent risk factor for biopsy-proven acute rejection, particularly in the first 12 months following renal transplantation (3). Moreover, beside the fact that anti-CMV prophylaxis is effective in the prevention of CMV disease, it seems that it is associated with a significant reduction in the risk of onset of acute rejection.

Among the mechanism hypothesized for the onset of renal allograft rejection, an immune-mediated assault against endothelial cell lining the vasculature with the development of anti-endothelial cell antibodies (AECAs) has been proposed. In a study by histological

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and immunohistochemical analyses on 50 patients with tubulointerstitial graft rejection, vascular rejection or diffuse thrombosis (4), Kooijmans-Coutinho MF *et al.* found that positive AECA-dependent cellular cytotoxicity was associated with vascular rejection and thrombosis of the graft in all the cases, and with graft loss in 75%; CMV infection was associated with a higher percentage of graft loss. Moreover, the titres of AECAs were significantly higher in cases with vascular rejection and thrombosis in comparison to cases with interstitial nephritis, thus supporting a humorally mediated pathogenesis. The occurrence of high levels of AECAs in relation to CMV infection has been also demonstrated in 80% of renal and heart and in > 40% of liver transplant recipients (5-7) and several studies suggested their potential role in the development of antibody-mediated rejection (8-13).

In a study (13) on 30 renal transplant patients undergoing early acute rejection (type IA and IB according to the Banff 97 classification), 15 individuals experienced CMV or Epstein-Barr virus disease within the first year posttransplantation; in this group, acute rejection biopsies displayed plasma cell infiltrates and, in several cases, C4d deposition, a marker of antibody-mediated reactions. In a recent study (14), Ismail *et al.* evidenced the presence of a significant association between the occurrence of AECAs and multiple graft rejection episodes and inferior long-term graft survival in kidney allograft recipients, thus suggesting that testing for AECAs prior to kidney grafting could be indicative in identifying patients at risk of developing immune mediated graft loss. This hypothesis has been evaluated by Han *et al.* (15), that retrospectively examined the occurrence of AECA using cellular enzyme linked immunosorbent assay (ELISA) in pre-transplant sera from 392 renal transplant recipients and found a significant relation to the occurrence of acute rejection post-transplantation: AECA-positive patients had significantly higher rates of acute grade II T-cell mediated and antibody mediated rejection compared to AECA-negative individuals. As the vascular endothelial cell antigenic system is genetically linked to HLA antigens, some authors have hypothesized that AECA positivity rates decreased dramatically when sera were first incubated with platelets to absorb anti-HLA antibodies (16). Therefore, to avoid cross reaction with anti-HLA antibodies, Han *et al.* (15) evaluated the pre-transplantation context. The occurrence of AECAs and also non-organ-specific autoantibodies (including smooth muscle antibodies, anti-nuclear antibodies, anti-mitochondrial antibodies and liver-kidney microsome type 1 antibodies) was evaluated by us in 96 renal transplant patients (17), 48 CMV pp65-antigenemia-negative and 48 positive and evaluated before and after transplantation and in relation to the occurrence of acute rejection. No significant correlation was found between acute rejection and the occurrence of non-organ-specific antibodies, while 75% (three out of four) of the cases of vascular rejection was associated to CMV infection and AECA-positivity post-transplantation.

In this study, in contrast to previous studies, no case of AECA-positivity before transplantation was evidenced, thus suggesting the opportunity to better evaluate this issue in larger populations to assess the potential to predict the risk of episodes of immune mediated rejection post-transplantation. The vascular endothelium of transplanted organs is the first line between the allograft and the host as it forms an allogeneic barrier between the recipient's circulating lymphocytes and the graft and expresses alloantigens functioning as targets during rejection. Previous studies have shown that CMV infection induces vascular damage by several mechanisms, including endothelial cell procoagulant activity, induction of ICAM-1 expression on CMV-infected endothelial cells, increased neutrophil and mononuclear cell adherence to infected endothelial cells, increased alloantigen expression on these cells, augmented production of the C-X-C chemokine, interleukin-8 in endothelial cells leading to neutrophil recruitment and enhanced neutrophil transendothelial migration (5, 18-21).

Anti-endothelial cell antibodies represent an heterogeneous group of autoantibodies directed against a wide spectrum of antigenic epitopes on endothelial cells and have been detected in a variety of autoimmune diseases, including vasculitis, systemic sclerosis, and Wegener's granulomatosis. Different methods have been used to evaluate their occurrence in patients' sera, including indirect immunofluorescence of tissue substrates, ELISA, and western blotting, thus complicating the comparison between different studies. Pre-transplantation study of AECAs as a predictive marker of subsequent risk of acute renal allograft vascular rejection has to be evaluated in studies on large populations and taking into account other potentially influencing factors. This could be relevant also in consideration of the choice of the appropriate anti-rejection treatment.

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