HISTOLOGICAL MARKERS OF HUMORAL REJECTION AND VIRAL INFECTIONS IN RENAL TRANSPLANTED PATIENTS.

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Objective: “Suspicious humoral rejection” is diagnosed in the presence of peritubular capillary (PTC) C4d deposition and one of the following tissue changes: 1) acute tubular necrosis, 2) glomerulitis or presence of polymophonuclear leukocytes and/or monocytes in PTC, 3) arteritis. Humoral alloreactivity results in endothelial damage and vascular obliteration that could play an important role in the development of chronic allograft nephropathy (CAN). In transplanted patients, viral infections can trigger the formation of anti-endothelial cell antibodies, which have been proposed to play a role in antibody-mediated rejections. The aim of this study was to evaluate viral infections in renal transplanted patients undergone to renal biopsy with and without evidence of C4d deposition in PTC.

Methods: From January 2004 to October 2006 54 renal biopsies from 39 renal transplanted patients were performed and immunohistochemically stained with anti-C4d antibody. In 25 biopsies diffuse (n = 13) or focal (n = 12) C4d deposition was observed. Based on C4d-positivity patients were divided in 3 groups, Group 1 (19 C4d negative patients), Group 2 (10 patients with diffuse Cd4-positivity) and Group 3 (10 patients with focal Cd4-positivity). Pre-transplant detection of panel reactive circulating antibodies (PRA test) ≥ 25% was considered positive. CMV infection was assessed by measurement of pp65 antigenemia and real time PCR for detection of viral DNA sequences. EBV infection was assessed by serological analysis (detection of Ig G to EBV early antigen associated to a four-fold or greater rise of in the titer of IgG to viral capsid antigen) and real time PCR and polyoma virus infection by real time PCR.

Results: PRA-positive test was associated with diffuse C4d-positivity, as 50% of the patients of group 2 had a positive test while no patients of group 1 and 3 had a positive test ($P < 0.001$). Glomerulitis was observed in 6 biopsies and was present only in association with diffuse C4d staining. Mean serum creatinine levels at six months were not significantly different among the 3 groups. Graft loss occurred in 6 cases: 3/10 patients of group 2 (30%) 3/19 patients of group 1 (15.7%) and 1/10 patients of group 3 (10%). In three patients (50%) it was due to acute vascular rejection. Viral infections in the year of the biopsy were experienced by 50% of patients of group 1, 80% of patients of group 2 and 100% of patients of group 3 ($P< 0.025$) indicating a significantly higher number of infections in patients with C4d positive biopsies.

Conclusions: Patients with C4d positive biopsies experienced a significantly higher number of viral infections than patients with C4d negative biopsies. This could be one of the factors that increase the risk of development of CAN in these patients. Focal C4d-positivity was not associated with severe glomerulitis and patients with biopsies with focal C4d-positivity exhibited a number of graft loss similar to that of patients with Cd4-negative biopsies suggesting that the presence of focal Cd4-positivity is not associated to a poor prognosis.