EARLY ONSET TRANSPLANT GLOMERULOPATHY IS ASSOCIATED WITH ANTIBODY MEDIATED REJECTION AND ACCELERATED GRAFT LOSS

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Objectives: Transplant glomerulopathy (TG), as per the current Banff classification, is considered to be a chronic feature. Recently TG has been designated as a defining feature of chronic antibody mediated rejection (C-AMR). Upon observing TG in an early post-transplant setting, we investigated its clinicopathological correlates.

Methods: All cases of acute rejection (within 6 months post transplantation) in patients transplanted during a one year period from May 1, 2005- April 30, 2006 at the University of Iowa Hospitals, Iowa City were identified. Clinical charts were reviewed for age, sex, donor type, primary renal disease, human leukocyte antigen (HLA) profile, donor specific anti-HLA antibodies (DSA), renal function (serum creatinine and creatinine clearance), proteinuria, and clinical course. AMR was diagnosed if serial biopsies contained peritubular capillaries (PTC) showing diffuse margination of inflammatory cells and C4d staining (focal or diffuse). TG was defined as glomeruli showing endotheliosis (occlusive endothelial swelling) and/or double contours of capillary loops. Early transplant glomerulopathy was defined as TG occurring within six months of transplantation. Immunohistochemical stains for CD45, CD3, CD20, CD68 and myeloperoxidase were done on selected biopsies in which TG was identified.

Results: During the 1 year period of the study 90 transplants were done (52-deceased donor, 31-living related and 7-combined kidney/pancreas). 9(10%) patients had acute rejection (ACR 4 and AMR 5). Three patients, all recipients from deceased donors had features of AMR and developed TG by 3 months (30-93 days). Although two of these three patients were highly sensitized, none of the patients had detectable DSA. All three patients developed glomerular endotheliosis (30-93 days) followed by the appearance of capillary loop double contours in later biopsies (170-280 days). One patient developed endotheliosis by day 30 before other classic features of AMR developed. C4d stain was focal and weak, and the presence of CD68 positive monocytes marginating in peritubular and glomerular capillaries in all three patients was a common feature. All patients with TG developed proteinuria rapidly (detected in 1-7 months) and two had accelerated allograft loss (return to dialysis at 6 and 12 months). The third patient at one year follow up has marginal renal function with a creatinine clearance of 30 ml/min/1.73 m^2.

Conclusions: 1) TG can develop early (as early as 30 days). 2) Early onset TG is associated with AMR. 3) Minor HLA or non-HLA antibodies may possibly be involved in the pathogenesis of AMR with TG. 4) TG can develop prior to other classic features of AMR. 5) Endotheliosis precedes capillary loop double contours suggesting that the endothelium is the primary pathogenic target in TG. 6) CD68 positive monocyte margination in glomerular and peritubular capillaries is a common feature. 7) TG leads to proteinuria and accelerated loss of allograft. The findings provide insights into the pathogenesis of TG and AMR. Current classification schemes do not include TG as a feature of acute AMR. Investigations to explore pathogenic mechanisms of early onset TG are warranted.