특별강연 III

Late Allograft Loss – Why does it Happen?

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Since the first successful kidney transplant was carried out in 1954 at the Brigham and Women's Hospital, transplantation has become a routine procedure extending and saving many lives. Over the years with improvements in immunosuppression and lower rates of acute cellular rejection, there has been a gradual increase in the short-term allograft survival. Despite this short term improvement the improvement in long-term survival has been more disappointing. This has always been somewhat surprising as a major driver of late allograft loss was thought to be related to injury caused by acute cellular rejection.

However, in reality one of the major reasons that we have not been able to significantly improve longer term outcomes is related to a lack of understanding of the mechanisms that contribute to the allograft survival. Many different factors have been shown to contribute to late graft dysfunction. In this presentation the current thinking on the causes of late allograft dysfunction will be discussed, including recurrent disease, drug nephrotoxicity and antibody mediated rejection.

Recurrent disease is a significant contributor to late allograft loss, but has been difficult to quantify its real impact, partially because many of the immunologically medicated diseases would be expected to be modified by the use of immunosuppressive medications post transplantation.

Nephrotoxicity as caused by calcineurin inhibitors was once thought to be the major cause for late allograft loss. This was particularly true when cyclosporin was the main calcineurin inhibitor being used. With the introduction of tacrolimus (thought to be less nephrotoxic) and mycophenolate (a more potent immunosuppressive drug allowing the use of lower doses of tacrolimus) concern about nephrotoxicity has receded. Some experts even believe that calcimeurin inhibitor toxicity is not a significant contributor to late allograft loss.

Over the last several years the impact of antibody mediated injury has been increasingly recognized, initially as a cause of acute allograft rejection and more recently as a contributing factor to later allograft loss. As we have become better at detectingan antibody response and recognizing the associated antibody mediated injury patterns, the relationship between a circulating humoral response and allograft damage have become more apparent. The triggering factors, the tempo and causative link between development of circulating anti HLA antibodies and allograft dysfunction has left much still to be explained. The risks associated with anti HLA antibodies, such as the timing of appearance of antibodies, whether directed against HLA class I or II, the strength of the antibody response, whether the antibody is complement bindingor not have all still to be fully appreciated. In addition a number of other factors such as the age/gender of the recipient as well as the use of induction therapy and types of maintenance immunosuppression used have been shown to influence the antibody response.