Acute and Chronic Antibody Mediated Graft Rejection in Renal Transplantation

Essay
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Introduction

Rejection has always been the major obstacle in transplantation of tissues or cells from a donor who differs genetically from the graft recipient induces an immune response in the recipient against alloantigens of the donor graft. If not controlled, this response will destroy the graft ***(Morris et al., 2004).***

Rejection can be classified according to duration: hyperacute occurring within minutes, acute occurring within days to weeks, late acute occurring after 3 months, or chronic occurring months to years after transplantation ***(Sis et al., 2010).***

Antibody-Mediated Rejection include antibodies against HLA molecules, endothelial-cell antigens, and ABO blood-group antigens on endothelial cells and red cells ***(Colvin et al., 2007).***

Hyperacute rejection of the renal graft that occurs almost immediately after release of the vascular cross clamps the kidney appears flaccid and mottled, reflecting the deposition of antibodies against HLA antigens expressed on the endothelium of the glomeruli and microvasculature. Due to activation of the classic complement cascade within the graft is followed by endothelial necrosis, platelet deposition, and local coagulation ***(Colvin et al., 2007).***

Acute Antibody-Mediated Rejection: Antibody-mediated rejection often begins within days after transplantation or within weeks if antilymphocyte antibody therapy was given. The main feature is rapid graft dysfunction due to inflammation ***(Terasaki et al., 2003).***

Acute antibody mediated rejection (ABMR) can also develop years after transplantation, often triggered by a decrease in immunosuppression iatrogenic, noncompliance, or malabsorption. Presensitization is the major risk factor but most of the patients with ABMR had a negative cross match. AHR has occurred with all immunosuppression regimens even profoundly depleting therapy ***(Lorenz et al., 2004).***

Chronic antibody mediated rejection (CAMR): ongoing immune injury to the graft is due to a failure to maintain sufficient immunosuppression to control residual antigraft lymphocytes or antibodies. Its features include a progressive decline in renal function, invasion of the renal parenchyma by T cells, and persistent infiltration of the interstitium by T cells and macrophages. Occasionally one also sees smooth-muscle proliferation and hyperplasia in vessels forming a neointima focal destruction of internal elastic lamina and finally vascular occlusion ***(Solez et al., 2008).***

The importance of antibody-mediated rejection has been fueled by advances in antibody detection solid-phase assays such as enzyme-linked immunosorbent assay and Luminex flow

beads the introduction of C4d staining of renal allograft biopsy specimens; and the implementation of new technologies directed against antibody, B lymphocytes, such as plasmapheresis, intravenous immune globulin, immunoabsorption with protein A, splenectomy, anti-B-cell agents (rituximab, alemtuzumab, rabbit antithymocyte globulin, bortezomib), and maintenance immunosuppressants, such as tacrolimus and mycophenolate ***(Lachmann et al., 2009).***

Although anti-HLA antibodies appear to be the most immunogenic, major histocompatibility complex class 1 chain-related gene A antigens and minor histocompatibility antigens may also play a role in causing chronic allograft damage. Despite the development of novel and more potent immunosuppressive agents, the long-term graft survival of transplanted organs has improved only marginally in the past 2 decades. This observation may be partly explained by the discovery of the importance of humoral immunity as newer ***(Lachmann et al., 2009).***

Aim of the Study

Aim of our essay:

1- To give an overview in recent methods in diagnosis of acute and chronic Ab mediated graft rejection.

2- To clarify the updates of treatment of acute and chronic Ab mediated graft rejection and their clinical outcome.

Chapter (1)

Immunology of Transplantation

The immunologic threat to the renal graft begins before transplantation and arises from the systemic effects of donor brain death or peri-operative ischemia reperfusion injury. Ischemia followed by reperfusion up-regulates the expression of HLA antigens by the graft and causes the release of a cascade of chemokines, pro inflammatory cytokines, and adhesion molecules within the graft. This increased display of HLA antigens intensifies the immune response and increases cellular infiltration of the graft, and both these responses increase the risk of rejection ***(Briscoe et al., 1998) and (Kim et al., 2008).***

The Innate Immune System:

Pathways of inflammation up-regulate innate injury molecules and aggravate the rejection process either directly or indirectly through the activation and recruitment of T lymphocytes. Injured tissues express ligands of the toll-like receptor system damage-associated molecular-pattern (DAMP) molecules and other innate danger molecules ***(Alegre et al., 2008).***

Toll-like receptors normally detect pathogens, but they can also sense the presence of foreign-tissue molecules and can

produce factors that cause the maturation and activation of dendritic cells. These cells have an important role in promoting acute rejection. Another element of innate immunity, the complement system, produces C3a and C5a, which directly activate intragraft T cells and antigen-presenting cells ***(Brown et al., 2006) and (Zhou et al., 2007).***

An increase in major-histocompatibility-complex (MHC) class I peptide‑related sequence A (MICA) antigens on endothelial surfaces can activate natural killer cells and CD8 T cells. Moreover, there is an association between poor graft outcomes and sensitization to the highly polymorphic MICA antigens in HLA-matched transplants ***(Sumitran, 2008).***

The Donor:

Certain features of the donor − older age, presence of hypotension or hypertension, diabetes, renal impairment, donation after cardiac death, and prolonged ischemia of the graft due to a delay in shipping − influence the decision about whether to accept an organ from a deceased donor or to discard it ***(Danovitch and Cecka, 2003) and (Stratta et al., 2006).***

As compared with transplants from deceased donors, transplants obtained from a spouse, friend, or altruistic donor under optimal physiological conditions and with shorter ischemia times lead to excellent results, even when genetic and HLA differences are greater ***(Terasaki et al., 1995).***

Antibody-Mediated Rejection:

Antibodies that can mediate rejection include those against HLA molecules, endothelial-cell antigens, and ABO blood-group antigens on endothelial cells and red cells. Most recipients do not have antibodies against HLA molecules before transplantation unless they were sensitized by exposure to alloantigens through pregnancy, blood transfusion, or previous transplantation. Antibodies against Blood-Group Antigens Kidneys selected for transplantation are routinely assigned to recipients with a compatible blood group; however, ABO-incompatible kidneys have been successfully transplanted with the use of an experimental protocol that entails peri-operative removal of antibodies from the recipient by means of plasmapheresis or immunoadsorption. After they have been removed, anti‑blood-group antibodies can rise to pretreatment levels after transplantation, adhere to the microvasculature, and activate complement, yet they generally do not injure the endothelium. This anomaly has been attributed to "accommodation" within the kidney, but the mechanism responsible for this benign response is unknown ***(Lynch and Platt, 2008).***

In contrast, injury to the graft by anti-HLA antibodies is frequently insidious, and accommodation is uncommon ***(Johnvella et al., 2008).***

Hyperacute Rejection:

Rejection of the renal graft that occurs almost immediately after release of the vascular crossclamps is classified as hyperacute. Instead of "pinking up" as a result of normal reperfusion, the kidney appears flaccid and mottled, reflecting the deposition of antibodies against HLA antigens expressed on the endothelium of the glomeruli and microvasculature. Activation of the classic complement cascade within the graft is followed by endothelial necrosis, platelet deposition, and local coagulation ***(Colvin, 2007).***

In these cases, the initial organ transplantation procedure usually ends with removal of the graft. Improvements in crossmatching techniques that can better detect donorspecific antibodies before surgery have largely eliminated this problem ***(Terasaki, 2003).***

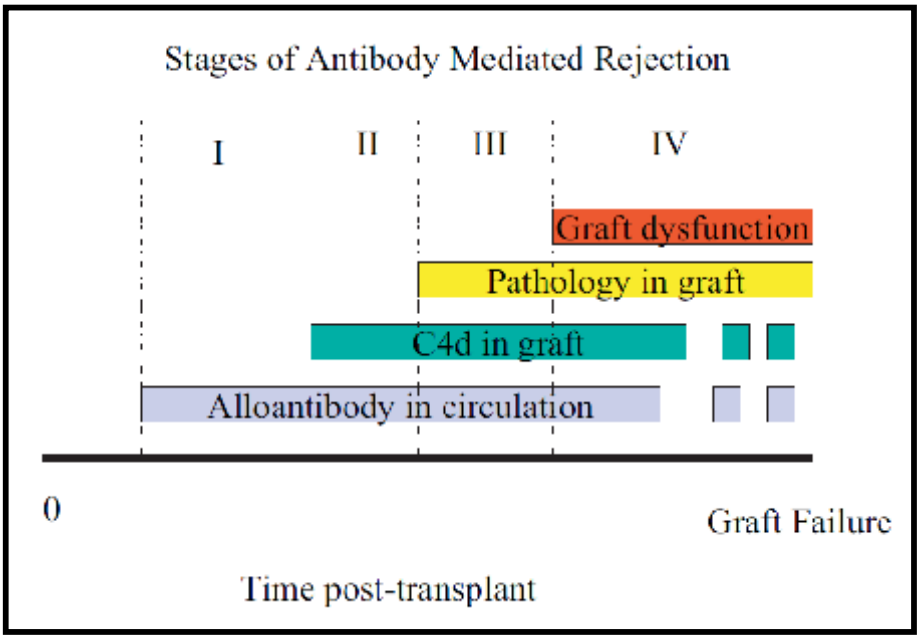

Fig. (1): Postulated stages of antibody-mediated rejection. Stages I to II represent accommodation, stage III represents subclinical humoral rejection, and stage IV represents CHR. The dashed lines for antibody and C4d deposition are meant to reflect the possibility of intermittent positivity over time. Inevitability of progression is not meant to be implied by the term "stages." The rate of progression is likely to be variable, and the early stages, I and II, are reversible. At any stage, the antibody/ C4d may become negative, in which case the process is inactive.