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Soluble CD30 and Acute Renal Allograft Rejection

Koosha Kamali[1], Mohammad Amin Abbasi[2],
Ata Abbasi[3] and Alireza R. Rezaie[4]
*[1]Hasheminezhad hospital, Department of urology,
Tehran University of medical science, Tehran
[2]Department of Internal Medicine, Shahid Beheshti
University of Medical Sciences, Tehran
[3]Pathology department, Faculty of Medicine, Tehran University of medical science, Tehran
[4]Department of Biochemistry and Molecular Biology,
Saint Louis University School of Medicine, Saint Louis, MO
[1,2,3]Iran
[4]United States of America*

1. Introduction

1.1 Renal transplantation

Renal transplantation is the treatment of choice for most patients with end-stage renal diseases (ESRD). Patients usually undergo transplantation after a variable period of dialysis.

Recently, due to development of standard surgical techniques and improvement in post transplantation care such as organ preservation, immunosuppressive and antimicrobial agents graft and patient outcome has significantly improved. The recognition of anti-donor-HLA antibodies in a renal allograft recipient's serum, at the time of or after transplantation, is usually correlated with specific antibody-mediated clinical syndromes which can be categorized into three groups such as hyperacute rejection, acute humoral rejection and chronic humoral rejection. Allograft rejection is caused by several component of the immune system; consist of antibody, complement, T cells and other cell types. The mechanisms of pathways of acute rejection are being determined and the consequences of immune rejection are identified by graft dysfunction and classified by histological features of allograft biopsy specimens (Solez et al., 2008).

1.2 Hyperacute rejection

Hyperacute rejection occurs within 24 hours of reperfusion and is characterized by immediate loss of graft function resulting abrupt cessation of urine flow. Hyperacute rejection might be either diagnosed clinically by the surgeon with mottling cyanosis and reduced turgor in the graft or by a histopathologic feature of interstitial hemorrhage, microthrombosis and inflammation (neutrophils and fibrin infiltration) of the failed allografts which might be qualitatively similar to those seen in acute antibody mediated rejection (AMR). Hyperacute

rejection is generally considered to be mediated by humoral immutnity (Baid S e al., 2001). Immunofluorescence (IF) studies demonstrated IgG (but not IgM) in glomerular and peritubular capillaries The pathogenesis of hyperacute rejection depends on the activation of complement activated through any pathway (classical, alternative, or lectin) can initiate hyperacute rejection regardless of how complement is activated (Chang A.T and Platt J.L. 2009). Hyperacute rejection of clinical allografts is most often caused by anti-HLA antibodies which bind to blood vessels and activate the complement system in a newly transplanted organ. Hyperacute rejection is observed in up to 80% of the kidneys transplanted into recipients with cytotoxic antibodies detected by cytotoxic cross match (Patel R and Terasaki PI, 1969). Hyperacute rejection is more common in allogarfts with these antibodies compared with ABO-incompatible renal transplants. Hyperacute rejection can also occur independent of anti-donor antibodies and these cases may reflect activation of the alternative or lectin pathways as might occur with ischemic injury (Chang A.T and Platt J.L, 2009).

Hyperacute rejection may occur in some recipients appearing to lack anti-donor antibodies. In some cases antibody capable of binding to and injuring the graft may be present but is not detected by assays in which leukocytes are used as the target. Fortunately, with the serologic technologies and expertise now available, hyperacute rejection has become an extremely rare occurrence.

1.3 Acute rejection

Acute rejection episodes (ARE) typically develop after transplantation at any time after organ transplantation and are divided histopathologically in to two categories: interstitial and vascular (Fig 1). A key clinical sign of acute rejection is a baseline rise in serum creatinine of 25% in the asymptomatic patient with no other apparent explanation. Novel immunosuppressive drugs and regimens have decreased the incidence of acute rejection occurrence, however, acute rejection (AR) is still a major risk of early graft dysfunction and late kidney graft loss (kamali et al., 2009). Despite the introduction of successful immunosuppressive drug therapies, acute renal allograft rejection still occurs in 10–20% of patients after cadaveric renal transplantation and causes graft loss in up to 6% in the first year after transplantation (Magee, Pascual., 2004). The early phase of diagnosis of acute allograft rejection might help clinicians to perform required procedures to prevent undesirable posttransplant complications (kamali et al., 2009).

1.3.1 Acute interstitial allograft rejection

Also termed acute cellular rejection or acute reversible rejection is characterized by an infiltration of inflammatory cells (mainly of CD8 T lymphocytes) in the interstitium, and tubular epithelium involvement named tubulitis (Racusen LC et al. 1999). Tubulitis has been regarded as a reliable marker for acute rejection even though it can be seen in other forms of interstitial nephritis (Colvin., 1996). The infiltrate is more concentrated in the cortex than in the renal medulla. Rejection that is predominantly cellular is considered to be readily reversible with therapy.

1.3.2 Acute vascular rejection

Acute vascular rejection is called as acute humoral rejection contains the most severe changes in the small arteries, veins, and arterioles. Humoral antibodies may cause tissue

injury or organ dysfunction by themselves or in collaboration with immunocompotent cells (Fig2) (Lederer S.R et al, 2001). The diagnostic criteria for acute humoral rejection are given in Table 1.

1. Morphologic evidence of acute tissue injury acute tubular injury neutrophils and/or mononuclear cells in PTC and/or glomeruli and/or capillary thrombosis fibrinoid necrosis/intramural or transmural inflammation in arteries
2. Immunopathologic evidence for antibody action C4d and/or (rarely) immunoglobulin in PTC Ig and complement in arterial fibrinoid necrosis
3. Serologic evidence of circulating antibodies to donor HLA or other anti-donor endothelial antigen

*Cases that meet only two of the three numbered criteria are considered suspicious for acute humeral rejection (AHR). Acute cellular rejection may also be present.

Table 1. Diagnostic criteria for acute antibody-mediated rejection (adapted from Lorraine et al., 2006)*

It is emphasized that humoral immune reactions soon after transplantation had a much stronger impact than alloreactivity during later periods. Occurrence of delayed graft function (DGF) was assumed as long-term consequences of alloreactivity events early after transplantation (Ojo et a.l, 1997). Humoral reactions late after transplantation that are clearly detectable in serum and biopsy samples obviously do not significantly reduce graft survival (Lederer et al., 2001). In renal allograft recipients who experienced acute humoral rejection, donor-specific circulating alloantibody showed a sensitivity and specificity of 95% and 96% respectively (Feucht HE et al, 1991). Crespo and colleagues reported an acute rejection prevalence of 6.3% among 232 transplanted patients, two thirds of whom were steroid resistant (Crespo et a.l, 1999). Acute humoral rejection refractory to steroids and polyclonal antibodies leads to a 70% to 80% rate of graft loss (Watschinger B, Pascual M, 2002). The earliest morphologic characteristics of acute vascular rejection are swelling and vacuolization of the endothelial cells with areas of ulceration. Graft survival among patients with acute humoral rejection and without specific therapy is poor but novel treatment modalities of acute humoral rejection has saved some grafts (Watschinger B, Pascual M, 2002). Acute humoral rejection therapy seeks to remove circulating antibodies through plasmapheresis or immunabsorption and to inhibit B-cell proliferation using mycophenolate. Acute humoral rejection requires different therapy than cell-mediated rejection. Therapy for Acute humoral rejection is plasmapheresis and intravenous Ig combined with intense immunosuppression (typically tacrolimus and mycophenolate mofetil). In analysis of 113 renal allograft recipients by Péfaur J. et al, the recipients received high doses of IVIG (2 g/kg in five doses; two also received plasmapheresis or thymoglobulin). Mycophenolate, tacrolimus, and steroids were used as maintenance immunosuppressive therapy. Patient and graft survivals were 100% (abapted from Péfaur J. et al, 2008).
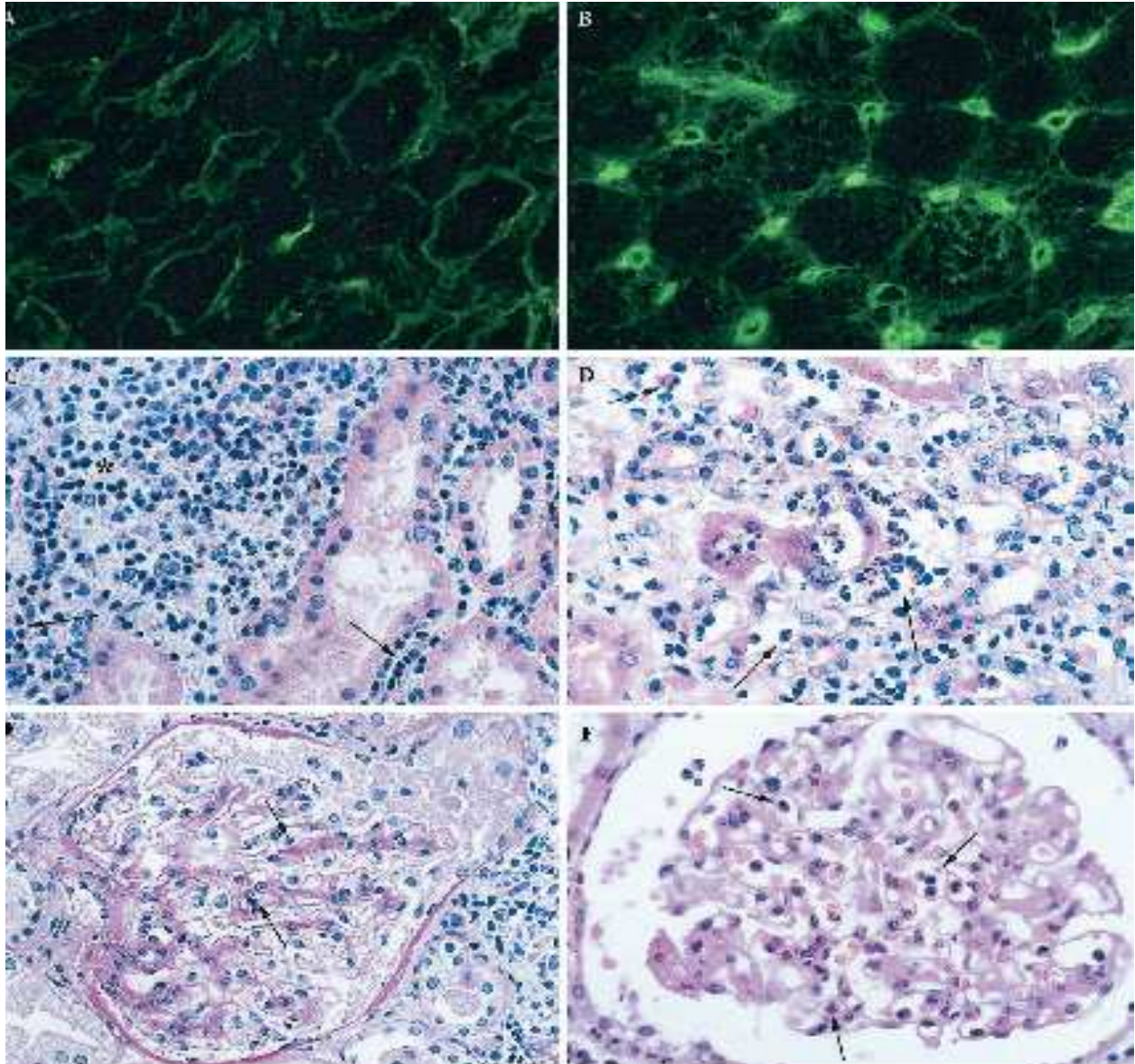
Fig. 1. (A) Acute cellular rejection (ACR): no staining for C4d is seen in peritubular capillaries. (B) Acute humoral rejection (AHR): widespread and bright staining for C4d is present in the peritubular capillaries that are interspersed in between the silhouettes of tubules. (C) ACR: mononuclear cells are present in the interstitium (*) and in peritubular capillaries (arrows). (D) AHR: abundant neutrophils are present in dilated peritubular capillaries (arrows). (E) ACR: scattered mononuclear cells are present in glomerular capillaries (arrows). (F) AHR: neutrophils are present in glomerular capillaries (arrows). Staining: C4d-FITC in A and B; Hematoxylin and eosin (H&E) in C, D, and F; and periodic acid-Schiff (PAS) in E. Magnifications: _400 in A through D; _450 in E and F. (adapted from Saadi et al. 2004)

1.4 Antibody-mediated rejection

As novel immunosuppressive protocols had effective control of T cell mediated acute rejection, antibody-mediated rejection (AMR) of renal allograft has re-emerged as an

important post-transplant complication.The complement system plays an important role in antibody mediated rejection (AMR) via classical pathway activation. Antibody-mediated rejection is characterized pathologically by focal ischemia, severe injury to the endothelial cells lining blood vessels in the graft and diffuse intravascular coagulation .

Expression of anticoagulant molecules (thrombomodulin and heparan sulfate) from normal endothelial cells inhibit coagulation process (Miyata Y and Platt JL). Activated endothelial cells promote coagulation and inflammation which induce expression of cell adhesion molecules and cytokines (Saadi et al. 2004)

1.5 Delayed graft function (DGF)

Delayed graft function (DGF) and acute rejection are the two main early adverse events in renal transplantation. Historically, DGF was defined by the requirement for dialysis within the first week of renal transplantation. The rate of DGF varies between among different centers from 20 to 40% (Koning OH et al ,1997). The incidence of DGF was 20% to 29% among deceased donor kidneys and 6% among living donor kidneys (Halloran and Hunsicker, 2001). Investigation of 689 allograft renal transplants form HLA-mismatched unrelated living donors revealed the incidence of DGF was 7.7%, which was higher than reports with HLA-matched living related donors (Ghods AJ et al, 2007). Many pathological findings are associated with DGF, the most common being acute tubular necrosis. Typical histological findings of DGF are dilatation of tubules, loss of proximal epithelial cell brush border, epithelial cell necrosis/apoptosis, and cellular casts (Smith KD et al , 2003). The impact of DGF on long-term graft survival is controversial. Some, though not all, evidence suggests that DGF may increase the frequency of acute rejection and thus reduce long-term survival. Univariate and multivariate analyses showed that DGF significantly reduced the survival rate and half-life of renal grafts. Troppmann et al. Found that only if DGF and early acute rejection co-existed would DGF be one of the risk factors that reduced the long-term survival rate of recipient kidney (Troppmann C et al. 1996). The early inflammatory response is initiated by ischemia/reperfusion, activation of innate immunity and subsequent alloantigen-primed T cell recruitment, activation and proliferative expansion. DGF is also thought to up-regulate MHC class II antigens, thus predisposing the transplanted graft to an increased incidence of acute rejection, which can be recognized histologically by the presence of tubulitis and infiltration of leukocytes into the tubular epithelium (Daily P et al, 2005). However, there are also reports showing that DGF played a greater role as a risk factor than acute rejection and HLA mismatch, and that DGF affected renal graft survival by increasing acute rejection and the chronic rejection rate, and decreased the survival rate of renal graft independent of acute rejection (Geddes CC et al. 2002). Aquino-Dias and associations have extended the diagnostic accuracy of mRNA profiles in recipients with DGF (Aquino-Dias EC. et al, 2008). Peripheral blood cell levels of TIM-3 mRNA are suspected to predict acute rejection in renal allograft recipients with DGF with a sensitivity of 100% and a specificity of 100% (Manfro RC et al, 2008). The main modality in management of DGF is to support the patient with dialysis and to monitor for rejection with serial biopsies.

At engraftment, ischemia-reperfusion injury occurs with activation of Toll-like receptors of the innate immune system and subsequent cytokine release. These pro-inflammatory mediators induce tubular epithelial cells to attract neutrophils and T cells by production of
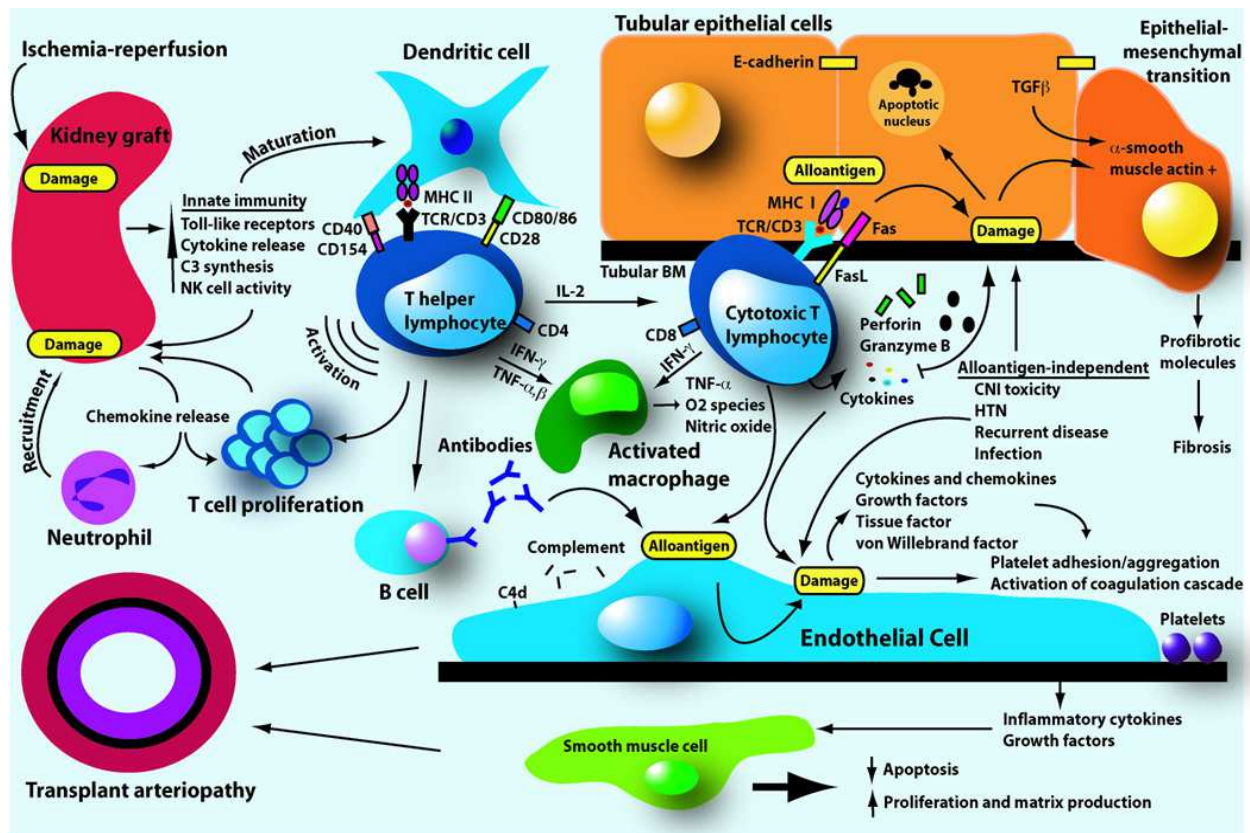
Fig. 2. Diagram of postulated events leading to graft damage during kidney transplantation (Adapted from Womer K.L. and Kaplan B, 2009).

chemokines. Innate immune system activation induces maturation of dendritic cells, leading the transition to the adaptive or antigen-specific phase of transplantation immunity. Dendritic cells activate CD4+ T helper cells through presentation of alloantigen in the context of major histocompatibility complex (MHC) molecules and ligation of appropriate T cell surface costimulatory molecules. After activation, CD4+ T helper cells induce further T cell proliferation, the production of alloantibodies from B cells, activation of macrophages, and differentiation of naïve CD8+ T cells into cytotoxic T lymphocytes. Mononuclear cells, especially cytotoxic T lymphocytes, enter between tubular cells and induce apoptosis by releasing cytolytic granules containing perforin and granzyme or by exposure to FasL on the T cell surface. Tubular cells chronically exposed to transforming growth factor β (TGFβ) may undergo epithelial-mesenchymal transition, an aberrant phenotype evidenced by epithelial cell expression of α-smooth muscle actin and loss of E-cadherin expression. These cells then may migrate to the interstitium and contribute to fibrosis. Both T cells and antibody likely recognize alloantigen on target endothelium. While T cells may cause cytotoxicity directly, alloantibody is usually directed against the MHC molecule, followed by activation of complement. Antigen recognition leads to endothelial secretion of factors that activate the immune and coagulation systems. These activities promote rejection and chronic changes of the endothelium and underlying smooth muscle layer, resulting in the characteristic histopathologic findings of transplant arteriopathy. Alloantigen-independent factors also contribute to tubular and endothelial cell damage.

2. HLA matching

The human leukocyte antigen system (HLA) is the name of the major histocompatibility complex (MHC) which contains a large number of genes related to immune system function in humans. This group of genes resides on chromosome 6 and encodes cell-surface antigen-presenting proteins and many other proteins. HLA antigens on the cell membrane play an important role in the immune response to foreign tissue (Muczynski KA et al. 2003). HLA complex is highly polymorphous (Marsh SG et al. 2002). Thus it is difficult to identify none-mismatched donors with only limited samples. In order to increase the matching rates, HLA typing has been recommended supported by the public epitope theory. MHC molecules are divided into 2 main classes: HLA class I antigens (HLA-A, HLA-B, HLA-C) are presented on the surface of all nucleated cells and platelets and HLA class II antigens (HLA-DR, HLA-DQ, HLA-DP, HLA-DM, HLA-DO) are expressed on professional antigen-presenting cells, but also on the surface of endothelial vascular cells and renal tubular epithelial cells (Muczynski KA et al. 2003). Human capillary endothelial cells, in contrast to rodents, express both human lymphocyte antigen (HLA) class I and class II molecules with high density even under normal physiological conditions (McDouall RM. et al, 1997). Cytotoxic antibodies (anti-HLA) are not detectable normally but after the blood/plasma transfusion, in pregnancy or after a previous transplant. When these antibodies are directed against HLA system of transplanted organ, their targets are represented by the graft endothelial cells which is followed by activation of complement, coagulation cascade and other inflammation factors. This mechanism mediated by anti-HLA antibodies is called humoral rejection (hyperacute rejection) that results in severe injury of endothelial cells and dysfunction of the transplanted organ (Moise A et al 2010). The first clinical importance of anti-HLA antibodies was demonstrated in 1969 (Patel R and Terasaki PI. 1969). Now it is known that the recipients who present preformed cytotoxic antibodies have a high rate of graft rejection. Production of antibodies after transplantation remains the main factor of acute and chronic rejections. Sometimes, antibody-mediated rejection (AMR) is still inevitable in human leukocyte antigen (HLA)-identical donor-recipient transplants (Zou Y and Stastny P, 2009). Antibody sensitization to alloantigens of the HLA system is one of the greatest barriers in successful renal transplantation (Zou YZ et al. 2007). Moise and colleagues reported that in both, compatible and incompatible subjects, post-renal transplantation could develop de novo anti-HLA antibodies especially those had an HLA mismatch with donor predictable for acute graft rejection (Moise A et al 2010). HLA-I antigens can be identified on nucleated cells, including on the endothelia of small renal vessels. Anti-HLA-I Ig G antibodies can injure the small vascular endothelia of the graft and induce serious rejections such as HR (Halloran PF et al 1990, 1992). HLA-II antigens are mainly expressed by immune cells. It is previously accepted that HLA-II antibodies have a relatively minor impact on the early graft outcome, despite a few cases reported with a higher rejection rate and humoral rejections occurrence due to HLA-II antibodies. A large-scale multi-center clinical study illustrated that graft survival rate at two or three years was decreased in recipients with both HLA-I and HLA-II antibodies, this was lower in recipients with more than three mismatched HLA alleles (Susal C and Opelz G. 2004). However, no significant difference was found in recipients with HLA-II antibodies compared with unsensitized patients. It is suggested that ELISA detected development of HLA antibodies, especially HLA-I antibodies, in the post-transplant period may provide a good predictor of acute rejection and of graft survival. Besides according to tissue inflammation and repair mechanisms inflicted by anti-HLA

antibodies results in exposure of self antigens which lead to post-transplant autoimmunity. Detection of immune responses to self-antigens will provide new strategies to monitor and prevent development of late graft dysfunction (Natha DS. et al, 2010).

3. Immunologic factors in renal transplantation

A major challenge for the field of transplantation is the lack of understanding of molecular mechanisms of immune response early after transplantation. The association between the presence of donor specific antibodies (DSA) and acute rejection has been noted in the late 1970s (Hartono C et al. 2010). Complement proteins have been described to play a significant role in organ damage following transplantation both in the process of ischemia reperfusion and in modulating the activation of the adaptive immune response. Based on the knowledge alloreactive T cells are key mediators of transplant injury (Dinavahi R. et al, 2008). It has become clear that the type of specific immune response to offending agents is largely dependent on the preferential activation of peculiar $CD4_1$ T helper (Th) cells able to secrete defined patterns of cytokines. Two distinct $CD4_1$ T helper cell subsets, coded as Th_1 and Th_2, showing distinct and mutually exclusive patterns of cytokine secretion, have been identified in both mice and humans (Romagnani S. et al, 1995). Significant efforts have been carried out to demonstrate methodologies that reliably measure cellular alloimmunity, and in determining the utility of these approaches as biomarkers for acute rejection, biopsy proven fibrosis and impaired allograft function. Traditional methods of measuring T cell alloreactivity include proliferation and cytotoxicity assays, performed either on bulk cultures (mixed lymphocyte responses) or as limiting dilution assays. While these methods are accepted as useful research tools, their intensive labor requirements and limited reproducibility have prevented them from becoming standardized clinical tests (Dinavahi R. et al, 2008).

4. Serum markers of allograft dysfunction

Identification of serum markers or parameters before and after transplantation of recipients assuming increased risk of allograft rejection helps clinicians for a successful performance in individualization of immunosuppression therapeutic regimens and ensures a more adequate follow-up of these patients (Rouschop KM et al, 2005). High dose immunosuppression should be avoided at least for low-risk recipients due to the massive side effects such as cancer development, infection and toxicity. For example, Aggressive immunosuppression may reactivate polyoma BK virus, which is usually latent in the urinary tract. Few biologic assays that might be potentially useful for monitoring the immune status of renal graft recipients have been reported (Susal C et al. 2003). Some reports have elucidated that a number of acute-phase reactants, such as C-reactive protein (Oyen O et al, 2001) and pro-inflammatory cytokinesn (IL-6), have been associated with allograft rejection (Waiser J et al, 1997), although their usefulness also has been debated (Cueto-Manzano et al, 2005). It is noted that IL-17 may be involved early alloimmune response during the course of acute rejection. IL-17 may play the role of an early initiator of the T cell-dependent inflammatory reaction. Human IL-17, a new cytokine secreted from CD4+ activated memory T cells, can stimulate the production of proinflammatory and haematopoietic cytokines by macrophages and stromal cells (Fossiez F et al, 1996). Immunofluorescence has shown the expression of IL-17 in kidney biopsies from patients suffering from graft rejection, while pretransplant biopsies and normal kidneys were

negative. Recently, monocyte-associated IL-18 has been suggested to be a pertinent biomarker in keeping with growing interest in monocyte infiltration during rejection. Striz *et al*. also observed a significant increase in serum IL-18 levels in patients with acute renal allograft rejection, compared with patients with uncomplicated transplantation, and further showed that IL-18 mRNA was released in response to increased TNF-_ and IFN-_ production (Striz I et al, 2005). Another complement component which has important role in organ transplantation is CD55, which is also called Decay Accelerating Factor (DAF). This molecule is present on the cell surface e where it accelerates the decay of C3 and C5 convertases from the classic and alternative pathway of complement to prevent their amplification and self-damaging effect on cells (Medof ME. et al, 1984).   Early post-transplant acute rejection and infection are major causes of morbidity and mortality, whereas, lack of full rehabilitation, drug toxicity, chronic rejection and malignancies constitute debilitating the long-term complications. All problems described above may be (directly or indirectly) related to the lack of easy and feasible immunological tests for predicting the risk of rejection and recognizing ongoing rejections after transplantation as early as possible. (Truong DQ. et al, 2007). It has long been a goal of transplant immunologists to develop tests for assessing the pretransplant risk of patients for immunologic rejection and for recognizing impending rejections after transplantation as early as possible (Susal C. al, 2004).

5. Soluble CD30 (sCD30)

In addition to cytokines, other relevant proteins have been studied. Soluble CD30 (sCD30), a member of the TNF receptor superfamily that is a 120 kD membrane glycoprotein and expressed on Th2 cells, may be useful. (Serum levels of sCD30 are associated with disease activity of Th2-type cells and with disease remission in Th1-mediated disease states. Although the role of Th1 versus Th2 responses in allograft rejection has been strongly debated, CD30_ T cells are implicated in the alloimmune response (Martinez OM et al, 1998).

Recent reports have proposed sCD30 as a noninvasive serological marker to predict immunological risk and graft failure among kidney transplant recipients (Pelzl S. et al, 2003). Both CD4 and CD8 T cells expressed CD30 after primary alloantigenic stimulation (Martinez OM. et al, 1998). Th_1 cytokines including IL-2, TNF-α, and IFN-γ mediate cellular immune responses and are pro-inflammatory, whereas, Th2-type cytokines IL-4 and IL-10 have been shown to inhibit the development and function of Th1-cells, to suppress inflammation, and to enhance humoral pathways of the immune response (Warle Mc. et al, 2001). Some studies suggested that CD30 may serve as a marker for human T lymphocytes that produce Th_2 cytokines (Manetti R. et al, 2007), while others demonstrated a strict association between CD30 expression and Th_1 cytokine production (Martinez OM. et al, 1998). However, Pellegrini et al. found that CD30 may be an important co-stimulatory molecule and marker for the physiological balance between Th_1/Th_2 immune response (Pellegrini P. et al, 2003). After activation of CD30+ T cells, a soluble form of CD30 (sCD30) is released proteolytically, however, the biological significance of this process is still not clearly defined (Dong W. et al, 2006). Th_1-cytokines are mainly involved in allograft rejection, while Th2-type immune response may be graft protective by blocking the graft damaging Th1-type anti-donor response (Reding R. et al, 2006). A soluble form of CD30 (sCD30) is released into the bloodstream after activation of CD30+ T cells (Romagnani S. et al, 1995).

5.1 Pre transplant CD30

Several reports from the Collaborative Transplant Study (CTS) have suggested that elevated pre and post-transplantation levels of the soluble CD30 (sCD30) molecule might be predictive for an increased incidence of rejection and worse kidney graft prognosis (Sengul S et al 2006).

Many reports have supported a role for sCD30 in the immune response associated with renal allograft rejection. The presence of increased pretransplantation concentrations of sCD30 has been associated with the development of acute rejection (Langan LL et al. 2007) and with humoral rejection and graft loss. While some reports demonstrated that T-cell activation marker soluble CD30 (sCD30) was an independent predictor of immunologic risk in renal transplant recipients without preformed alloantibodies (Vaidya S et al. 2006). It was reported that high sCD30 levels measured before transplantation, which might be a sign of activation of Th2 responses and, consequently, antibody production, could correlate with the risk of vascular rejection and production of DSA (Weimer R. et al, 2006). However lower levels of sCD30 was determined to be a helpful marker to distinguish patients with a low risk for development of DSA and antibody-mediated rejection (Slavcev A. et al, 2007). Study by Vaidya et al. recognized that estimation of sCD30 before transplantation might be a better predictive factor than PRA for the evaluation of the risk for occurrence of DSA and development of vascular rejection (Vaidya S et al. 2006). Some authors described an increased sCD30 level only during a rejection episode of the vascular type, while the more common tubulointerstitial type showed decreased sCD30 levels even lower than those of healthy volunteers (Rajakariar R. et al, 2005). According to some studies the sCD30 concentration was also high in both groups of patients before transplantation and levels of sCD30 decreased during the first 3 to 5 posttransplant days, increasing significantly between 5 and 15 days following transplantation among recipients who developed acute rejection episodes (Ayed K et al. 2006). Measurements of serial changes in soluble CD30 levels after transplantation have revealed a decrease of sCD30 in stable transplant recipients (Sengul S et al 2006). Kamali and colleagues have measured Pre and post-operative sCD30 levels of 3 groups (acute rejection, delayed graft function, and uncomplicated course group). It has been described significant decreases in sCD30 plasma levels on 14th day after transplant. Despite a significant decrease, groups of patients with acute rejection had higher CD30 concentrations on the 14th day after the transplants, compared with delayed graft function and uncomplicated course groups (Kamali K. et al, 2009). Based on published results pre-transplant sCD30 serum levels higher than 100 U/ml have been classified as a risk factor for the survival of kidney allografts (Cinti P. et al, 2005). In a large series of nearly 3900 kidney transplants performed at 29 centers in 15 countries, it was demonstrated that pretransplant determination of the Th2-type activation marker sCD30 is a powerful indicator for estimating the risk of graft rejection not only in presensitized but also in nonsensitized recipients (Susal et al. 2002). Patients with history of renal transplantation had higher levels of s CD30 than first kidney graft recipients (Susal et al. 2002). Investigation of pretransplant serum sCD30 content in 2998 recipients with a low sCD30 of <100 U/ml demonstrated a higher a 5-yr graft survival rate compared with 901 recipients with a high sCD30 of >100 U/ml. Determination of the sensitivity and specifity sCD30 testing based on positive (≥100U/ml) and negative (<100 U/ml) levels has revealed that with a specificity of sCD30 >80%, negative sCD30 levels might be a useful marker for identifying patients with a low risk for development of donor specific antibody (DSA) and antibody-mediated rejection

(Slavcev A. et al, 2007). Spiridon C and associates found no statistically significant difference among patients with 3–6 HLA-A, B, DR mismatches and 0–2 HLA-A, B, DR mismatches when pre-transplant level of sCD30 was below 90 U/mL. It is indicated that the effect of HLA mismatches can only be seen among patients with high level of sCD30 (Spiridon C. et al, 2008). Correlation between serum levels of sCD30 and Neopterin, which is a known activation marker of the T-cell/monocyte system and plays an important role in the chronic allograft nephropathy (CAN) process, demonstrated that up-regulation of 1-year sCD30 levels was associated with decreased 2-year GFR (. It was observed that increased 1-year sCD30 as well as Neopterin/CR are significantly associated with impaired 2-year graft function and serve as indicators of graft deterioration by chronic allograft nephropathy (Weimer R. et al, 2006). Association of sCD30 levels and immunosuppressive regimen has also been investigated. Pretransplant sCD30 assessment may serve as a useful parameter because high pretransplant sCD30 levels were shown to be associated with impaired kidney graft survival in Cyclosporine-A treated recipients (Susal C. et al, 2002). The current prospective randomized study shows that both cyclosporine-A and Tacrolimus based immunosuppressive regimens, used either in combination with Azathioprine or mycophenolate mofetil (CellCept), were associated with down-regulation of pretransplant sCD30 levels 4 months post-transplant, without a further significant change from 4 months to 1 and 2 years. It was demonstrated that Tacrolimus based regimens are more effective in suppressing sCD30 levels and thus might be the appropriate treatment in patients with pretransplant elevated sCD30. It was found an association between CD4 helper function and sCD30 2 years post-transplant, both in Cyclosporine-A and Tacrolimus treated patients, which might be the result of diminished suppression of CD4 helper activity due to reduced Calcineurin inhibitor drug exposure (Weimer R. et al, 2000). This evidence suggests that the measurement of sCD30 levels offers relevant clinical information regarding rejection risk and can contribute to the selection of the appropriate immunosuppressive regimen in high-risk recipients for the prevention of acute rejection and chronic allograft nephropathy (Kim MS et al. 2006).

5.2 Post transplant CD30

To prevent irreversible graft damage, it is important to diagnose and treat acute rejection in its earliest phase. Serial measurement of sCD30 levels after transplantation could become a feasible and non invasive method to predict acute graft rejection and might allow identifying patients prone to acute rejection during the first days after transplantation; before an acute rejection was occurred and diagnosed by conventional methods. Importantly, at this early time point, detection of acute rejection in the kidney with DGF is made difficult because conventional noninvasive rejection parameters, such as rising serum creatinine and oliguria cannot be used to make the diagnosis, however, sCD30 allowed a differentiation of group acute rejection from group DGF patients (Dong W. et al, 2006). In contrast to patients with an uncomplicated course or acute tubular necrosis (ATN) in the absence of rejection, plasma sCD30 levels remained high during the first 3 to 5 posttransplant days in recipients who subsequently developed acute allograft rejection (Susal C. et al, 2004). Now it is clear that the sCD30 levels decrease significantly after renal transplantation. It was reported that even in patients developed kidney rejection sCD30 levels decreased up to 55% at day 7 post-transplantation (Truong DQ. et al, 2007). In a similar study, showed that an important decrease of sCD30 was detected 2 weeks after renal transplantation and patients without rejection had lower sCD30 value compared to patient

who experienced rejection episodes (Slavcev A. et al, 2005). Comparison of CD30 concentrations on the 14th day after transplantation, within acute rejection, delayed graft function (DGF) and uncomplicated course groups revealed that a higher soluble CD30 concentration on day 14 after transplant is associated with acute rejection (Kamali K. et al, 2009). In sera of 231 patients average sCD30 level before transplantation was much higher than that of healthy individuals. Most important, the decrease of sCD30 levels after transplantation varied in different groups. Compared with Group UC and DGF, patients of Group acute rejection had higher sCD30 levels on day 5 posttransplantation. Data also show that there was no association between rejection time and sCD30 levels (Dong W. et al, 2007). It is demonstrated that patients free of rejection in the first month post-transplant had lower sCD30 concentrations 2 weeks after transplantation compared to rejecting patients (Slavcev A. et al, 2005). Thus, an integration of the individualized evaluation of posttransplant sCD30 serum level as one biomarker, together with accompanying diseases which affect the immunological reactivity post-transplantation, may be a feasible approach for the non-invasive post-transplant prediction of acute kidney allograft rejection.

6. Panel-reactive antibody (PRA)

Renal transplantation in sensitized patients remains a highly significant challenge worldwide. However, highly sensitized candidates should not be eliminated from transplant waiting lists, as post-transplant survival rate and life quality can be greatly improved with transplantation, despite the risks. The level of sensitization in a kidney transplant recipient can be monitored before and after renal transplantation via PRA (panel-reactive antibody) test. Highly sensitized recipients usually refer to those with antibodies against HLA, who are defined as panel reactive antibody (PRA) >10%, or >20%. The humoral immune system is an important determinant of outcome: hypersensitized patients show reduced long term graft survival and 10% panel reactive antibodies (PRA) is a risk factor (Davis CL, 2004 and Opelz G, 2001). Thus elevated panel reactive antibody (PRA) levels, produced against HLA and induced by transfusions, pregnancies and prior transplants for HLA allo-immunization are linked to hyper-acute rejections, delayed graft functions and poor graft survival rates. Measurement of anti-HLA antibodies before and after transplantation is important, as their presence increases the risk and severity of rejection episodes and is a significant risk factor for allograft loss (Zhou YC. et al, 1996). During past years, transplant surgeons usually focused on the results of PRA levels and lymphocyte toxicity test in the treatment of sensitized patients, but sometimes serious antibody mediated rejections also happened in HLA-identical donor-recipient transplants. Although we have not yet confirmed whether there are any anti-HLA antibodies not well detected with existing technologies, the concept of non-HLA antibodies bring the transplant surgeons and researchers with great inspiration. Following the more recent development of ELISA methodology for detecting HLA antibodies, several reports showed that patients with pretransplant HLA-I antibodies (>10% PRA) had greater risk for acute or chronic rejection, or an increase in post-transplant reactivity (Van Kampen CA. et al, 2001). It was observed a higher incidence of post-transplant donor specific HLA antibodies in patients having 3–50% PRA compared with patients having 0% PRA at the time of transplantation (Supon P. et al, 2001). The determination of panel reactive antibodies, which at present are exclusively used as indicators for an increased risk of graft rejection, is currently being critically discussed. It is illustrated that combination of positive PRA and elevated sCD30

levels have an additional diagnostic value, as well as independent factors, to predict acute rejection risk and subsequent graft outcome (Langan L L. et al, 2007). For this reason novel markers are recommended for proper monitoring of pre- and post-transplant risks. Using the modalities described, immunosuppressive therapies in transplant recipients can now be selected on the basis of individual demand, with anti-B-cell directed immunosuppression being most promising during the early postoperative period.

7. Immunosuppressive therapy

The influence of immunosuppressive regimens on sCD30 levels was provoked in many studies. Presensitized (PRA >5%) patients had a higher serum sCD30 content than nonsensitized (5% >PRA) patients. whereas, as shown in Figure 3, the effects of the two parameters on graft outcome were additive. Therefore presensitized patients are preferentially transplanted with HLA well-matched kidneys and receive stronger posttransplant immunosuppression, including prophylactic treatment with antilymphocyte antibodies (susal et at. 2002). Immunosuppressive treatment in recipients usually contains either with a triple drug regimen (Cyclosporine, Steroids and Azathioprine) or, in Presensitized patients with immunologic risk factors (presence of panel-reactive antibodies or history of graft rejection), a quadruple regimen, including polyvalent or monoclonal antilymphocyte antibodies. When patients were divided into well-matched group (with three or less mismatches) and poor-matched group (with more than three mismatches), no significant difference of sCD30 levels was shown between two groups. Soluble CD30 levels
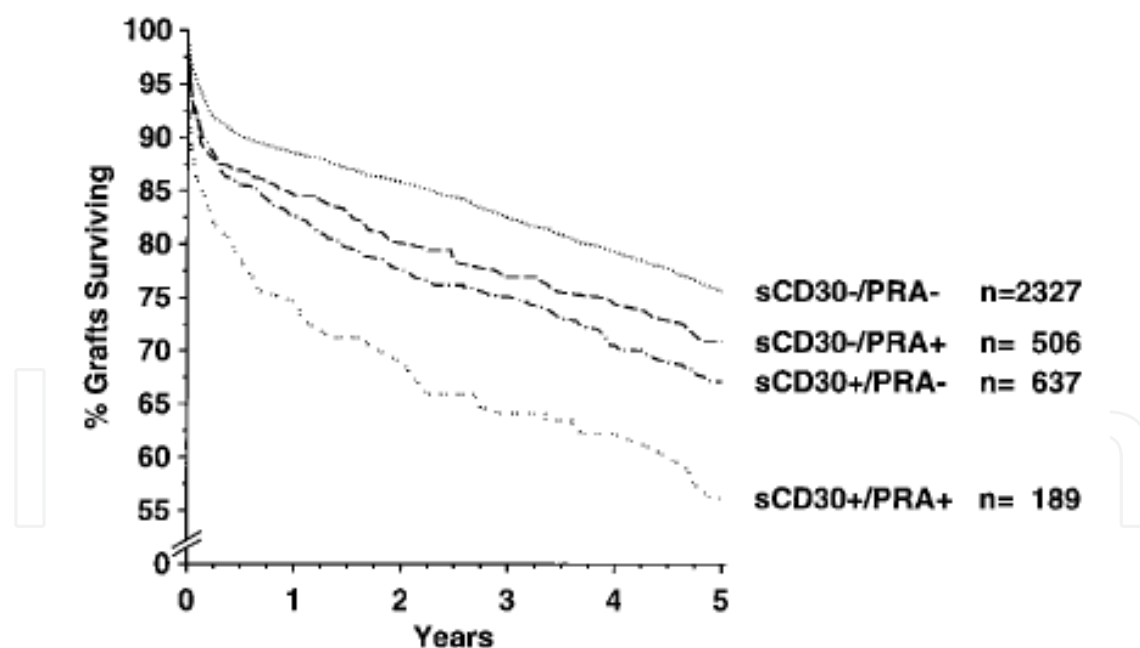
(Adapted from susal et at. 2002)

Fig. 3. Combined effect of serum sCD30 content and lymphocytotoxic panel reactivity (PRA) on kidney graft survival. sCD30- positive and PRA-positive recipients (sCD30+/PRA+) had a significantly impaired graft outcome, compared with sCD30-negative and PRA-negative (sCD30_/PRA_), sCD30-negative and PRA-positive (sCD30_/PRA+), or sCD30-positive and PRA negative recipients (sCD30+/PRA_) ($P < 0.0001$, $P = 0.0003$, and $P = 0.0048$, respectively).

were also independently evaluated in patients receiving cyclosporine A and FK506. There was also no significant difference of sCD30 levels between two groups. Significant difference of sCD30 levels was only observed between patients with acute rejection episodes and those without acute rejection on day 5 post-transplantation (Dong W. et al, 2006). Antithymocyte globulin (ATG) is recommended for desensitization of kidney transplant recipients with high panel-reactive antibody (PRA) and ABO-incompatibility as main modality for the treatment of AMR (Akalin E. et al, 2003 and Gloor JM. et al, 2003). But antilymphocyte antibodies did not improve graft outcome in patients with high sCD30. Graft survival of recipients with a high pretransplant sCD30 treated with prophylactic antilymphocyte antibodies (ATG, ALG, or OKT3), was significantly worse than the rate in recipients with low sCD30 levels. It is suggested that a single dose of Rituximab (50 mg/m² BSA) is as effective as higher doses (150 and 375 mg/m² BSA) in depleting Bcells and reducing PRA levels, While the standard dose of Rituximab in AMR is 375 mg/m2 BSA (Vieira CA. et al, 2004). Thus, to improve graft outcome in patients with high sCD30 levels, other strategies seem to be necessary, possibly immunosuppressive regimens that specifically inhibit CD30⁺ T cells.

8. Conclusion

It is illustrated that combination of positive PRA and elevated sCD30 levels have an additional diagnostic value, as well as independent factors, to predict acute rejection risk and subsequent graft outcome. For this reason novel markers are recommended for proper monitoring of pre- and post-transplant risks. This evidence suggests that the measurement of sCD30 levels offers relevant clinical information regarding rejection risk and can contribute to the selection of the appropriate immunosuppressive regimen in high-risk recipients for the prevention of acute rejection and also chronic allograft nephropathy.

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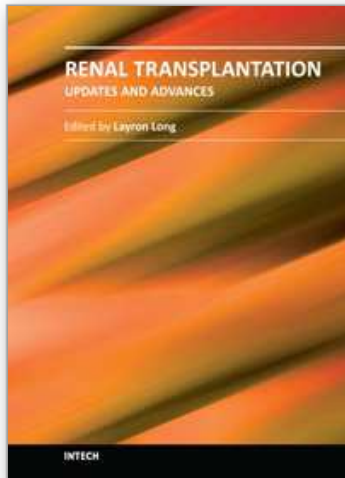
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Edited by Dr. Layron Long

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