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The Allo-Immunological Injury in Chronic Allograft Nephropathy

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1. Introduction

Progressive loss of renal allograft function after the first year of kidney transplant is often referred to as chronic rejection, transplant nephropathy, transplant glomerulopathy or chronic allograft nephropathy (CAN) and the use of these terms is often interchangeable. Clinically, it is usually diagnosed by a slowly rising serum creatinine level, increasing proteinuria and worsening hypertension (Zhang et al., 2004). CAN is the second most common cause of graft loss after the leading cause, death with a functioning graft (DWFG) (Zhang et al., 2004). According to estimates, 25-30% of patients currently awaiting kidney transplant have received a transplant before.

With the widespread usage of induction agents and the advancements in immunosuppressive medications, the first year outcomes after kidney transplant have shown steady improvement. In the United States, the incidence of acute rejection (AR) in the first year is below 10% (United States Renal Data System [USRDS]) while the unadjusted graft survival is 96%, 92% and 85% for living, deceased and extended criteria deceased donors respectively (Organ Procurement and Transplant Network/Scientific Registry of Transplant Recipients [OPTN/SRTR], 2008).

In the long term though, the survival of grafts has shown very little improvement over the past decade. The 5 year graft survival is reported at 81%, 71% and 55% for living, deceased and extended criteria deceased donors in the time interval of year 2000-2005. This, in comparison, is hardly different from the 79%, 68% and 51% reported in the interval of 1994-1999 (OPTN/SRTR, 2008). The median graft survival years for all kidney transplants, according to a report published in 2004 has changed little when comparing transplants performed in the years 1988 through 1995, ranging between 7.5 to 8.0 years. (Meier-Kriesche et al, 2004)

An overall shortage of organs and the high cost of providing any form of renal replacement therapy inclusive of a kidney transplant, calls for attention into making efforts for kidney transplants to last longer. This would entail looking into the pathological processes that result in the eventual failure of grafts, delineating as far as possible one process from the other, and examining immunological and non-immunological determinants that may be targeted with the eventual goal of adopting strategies that may help in prolonging the survival of renal allografts (Zhang et al, 2004). The non-immunological factors may include

poor graft quality, ischemia and reperfusion injury, delayed graft function, recurrent or de novo kidney disease, hypertension, diabetes, obstruction, infection, renal artery stenosis and calcineurin inhibitor toxicity. It has been recently suggested that the autoimmunity may also contribute to the post-transplant allograft injury (Dinavahi et al., 2011; Porcheray et al., 2010; Vendrame et al., 2010). Here, we will focus our discussion on the allo-immunological injury, as this mechanism has been well established and its importance has been increasingly recognized in the pathogenesis of CAN.

2. Pathological classification

The 8th Banff Conference on Allograft Pathology, held in 2005 (Solez et al, 2007) focused on removing the term CAN as a pathological entity. This term was first used in 1991 when it replaced the term 'chronic rejection'. While it was successful in removing the notion that an immunologically mediated mechanism was in all instances the reason for the graft to slowly deteriorate, its use as a generic term came in the way of ascertaining a specific diagnosis and identification of the actual pathological process at play.

While the pathological findings of 'interstitial fibrosis and tubular atrophy' (IF/TA) are common in most instances of chronic allograft injury, other features can sometimes point towards the actual disease process. For example, arterial fibrointimal thickening with duplication of internal elastica (fibroelastosis), arteriolar and small artery hyalinosis, glomerulosclerosis, along with IF/TA can be a manifestation of chronic hypertension (Olson et al, 1998); hyaline arteriolar changes, sometimes with peripheral hyaline nodules, and IF/TA either in 'striped' ischemic or diffuse form can be secondary to calcineurin inhibitor (CNI) toxicity (Morozumi et al, 2004, Basauschina et al, 2004 and Mihatsch et al, 1995); IF/TA with relative glomerular sparing, dilated tubules, atubular glomeruli and intratubular Tamm-Horsfall protein casts with extravasation into the interstitium may suggest chronic obstruction (Klahr et al, 2003); IF/TA with chronic inflammation, intranuclear inclusions highlighted on immunostaining for the SV40 large T antigen can be due to BK virus infection (Drachenberg et al, 2005), a polyoma virus that may infect the tubular cells in immune suppressed patients. In other instances, recurrent or de novo vascular or glomerular diseases may lead to glomerulosclerosis along with IF/TA.

This leads to a new category of "interstitial fibrosis and tubular atrophy, no evidence of any specific etiology" to replace "CAN". There is further sub-categorization within the category of "IF/TA, no evidence of any specific etiology" and this is based on amount of interstitial fibrosis, and the degree of atrophy and loss of tubules. It is described as mild (Grade I), moderate (Grade II) and severe (Grade III) determined by <25%, 25-50% and >50% of the cortical area involved respectively (Salez et al, 2007). The pitfall to this classification is that the degree of IF/TA in a renal graft is yet to be shown to correlate with the prognosis and overall graft survival. This is therefore an area where protocol biopsies done at previously determined time intervals, and the correlation of these results with graft survival in the long term, will provide invaluable prognostic information.

In the same revision of the Banff criteria, there was also the introduction of the subcategories of 'chronic active antibody mediated rejection' and 'chronic active T-cell mediated rejection' within the categories of antibody mediated rejection (AMR) and T-cell mediated rejection respectively. These were introduced to highlight the features of arterial and capillary

changes, believed to be pathognomonic of an immunologically mediated chronic allograft injury which would also have IF/TA, in other words identifying true chronic rejection. The need for introducing the subcategory of chronic antibody mediated rejection (CAMR) was based on the abundantly available literature that highlighted the presence of complement fragments (C4d) positivity (explained in more detail in Role of B cells and DSA) and the presence of anti-HLA antibodies in transplant patients correlating with the chronic failing of the allografts. When these are seen in the presence of pathological changes specific to an active process of AMR taking place, that subset of patients could be safely assumed to be undergoing an immunologically mediated, in specific humorally mediated reaction. The diagnostic criteria therefore for 'CAMR' are as follows;

Morphological features of duplication or 'double contours' in glomerular basement membranes, and/or peri-tubular capillary basement membrane multi-layering (PTCBMML) and/or IF/TA with or without PTC loss, and/or fibrous intimal thickening in arteries without duplication of the internal elastica

1. C4d deposition in the peri-tubular capillaries (PTC)
2. The presence of donor specific antibodies (DSA)

The pathological significance of these findings and their role in causing deterioration in graft function will be highlighted in the section "Role of B-cells and DSA" below. Transplant glomerulopathy of membrano-proliferative glomerular nephritis (MPGN) pattern should be distinguished from the immune complex-mediated MPGN that is frequently associated with hepatitis C infection or due to recurrent or de novo glomerular disease. They appear similar (MPGN) on light microscopy, but their distinction can be made by electron microscopy, as transplant glomerulopathy does not have immune-complex deposits on the glomerular basement membrane.

'Chronic active T-cell mediated rejection' is described as a subcategory of "T-cell mediated rejection" and it denotes the presence of chronic allograft arteriopathy with arterial intimal fibrosis along with mononuclear cell infiltration and fibrosis and the formation of neo-intima. These changes and their role will also be described in more detail in the section "Role of T-cell" below.

3. Role of T cells

The introduction of an "allograft" into an immunocompetent individual would typically result in a process of recognizing the graft tissue as foreign "allorecognition" and the initiation of what is known as an "alloresponse", invariably resulting in tissue inflammation, architectural distortion and infiltration by T-cells that are responsive to the graft resulting in loss of function and eventual failure of the graft, a process we call acute cellular rejection. This occurs after a number of steps taking place at the molecular and cellular level, steps that have been recognized and become the target of therapy in order to prevent rejection.

Allorecognition can occur by three well-described mechanisms referred to as direct, indirect and the semi direct pathways. (Safinia et al, 2010). In the direct pathway recipient T cells recognize intact allogeneic major histocompatibility complex or MHC-peptide complexes expressed by foreign cells, while in the indirect pathway T cells recognize peptides derived from allogeneic MHC proteins presented by antigen-presenting cell and finally the semi

direct pathway where recipient dendritic cells acquire intact allogeneic MHC-peptide complexes from donor cells and present them to recipient T cells. (Harrera et al., 2004; Lechlar and Batchelar, 1982; Warrens et al., 1994). In the context of transplantation, while the direct and the indirect pathways are well recognized and understood, the semi-direct pathway is not known to be of clinical importance in allograft rejection. (Figure 1)

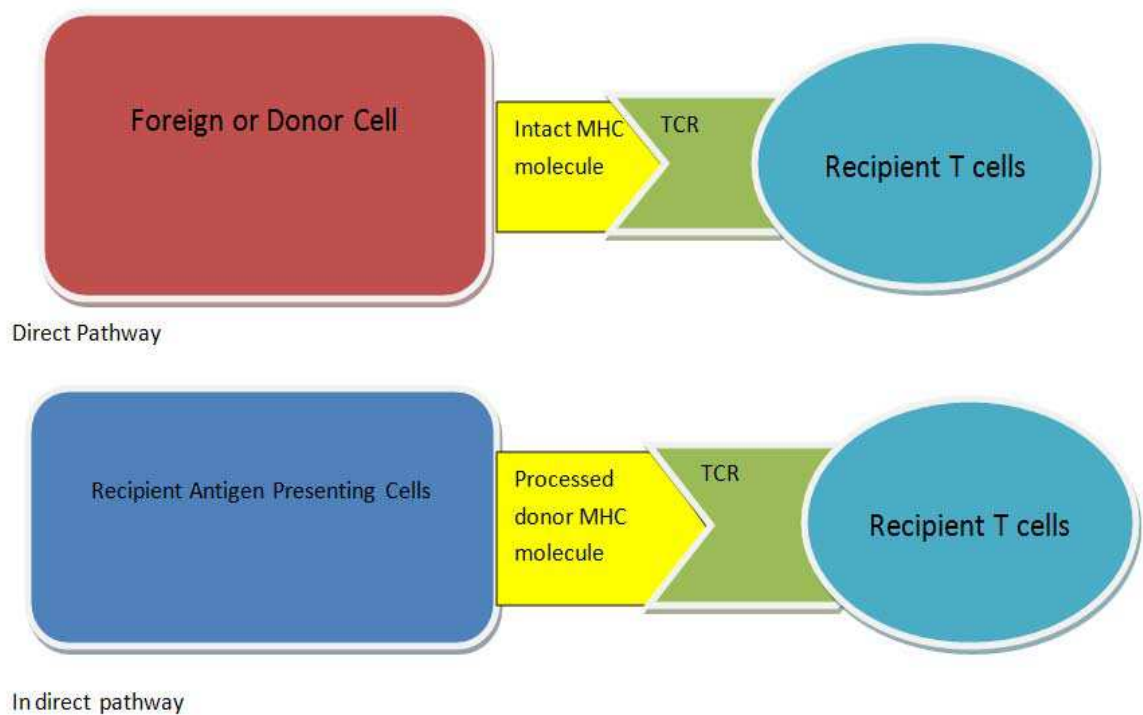


Fig. 1. Mechanism of antigen presentation in the direct and indirect pathways.

As far as the direct pathway is concerned, if the immunological milieu is left unaltered, a strong and effective alloresponse would follow primarily due to the very high number of recipient T-cells that will recognize the transplant tissue as foreign. Due to the nature of this mechanism, this pathway is of primary importance in the immediate post transplant period. T-cell depletion using various immunosuppressive regimens, including induction protocols, severely compromises this process. Another phenomenon observed is depletion of donor derived dendritic cells through apoptosis and elimination by recipient immune reactivity. This is also accompanied by a decline in the number of recipient T cells with direct antidonor allospecificity with time, most pronounced in the CD4+ CD45RO+ (memory) subset (Hornick et al, 1998). However, this decline in direct pathway responses with time is as pronounced in patients with chronic rejection as in those with stable graft function and this supports the view that the direct pathway of allorecognition is of little importance in the context of chronic graft failure.

As the direct pathway declines with time, recipient dendritic and other antigen presenting cells travel through the graft, picking up soluble MHC alloantigens or antigens derived from donor cells and present them to T-cells activating CD4 + and CD 8+ cells (the indirect pathway) (Auchincloss et al. , 1993; Kievits et al.,1991). The predominant antigen presentation is done through MHC-Class II cells which have an affinity towards the CD4+

T-cell subtype. The indirect alloresponse, while less rapid compared with the direct pathway, dominates reactivity to transplanted antigens in the long term. This is the main reason why, despite tolerance afforded by the direct pathway, immune suppression is required for as long as the graft remains viable. Any inflammation induces the expression of MHC class II molecules on endothelial and epithelial cells in the graft, conferring the ability to present antigen to CD4⁺ T cells (Bal et al., 1990).

Clinically, the activity of T-cells in renal allografts is represented by cellular rejection. The diagnosis is made by detecting tubulitis, interstitial infiltration and edema, and sometimes intimal arteritis. A grade is assigned depending on the severity of these lesions. The inflammatory activity of T-cells results in renal injury resulting in architectural distortion of the renal parenchyma. The Banff Classification for T-cell mediated rejection along with histological description of each category and sub category is described below.

3.1 T-cell mediated rejection

Acute T-cell mediated rejection (Type/Grade)

- i. Significant tubular and interstitial infiltration (Figure 2)
- ii. Intimal arteritis (vascular rejection) (Figure 3)
- iii. Transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (Figure 4)

Chronic T-cell mediated rejection

‘Chronic allograft arteriopathy’ (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)

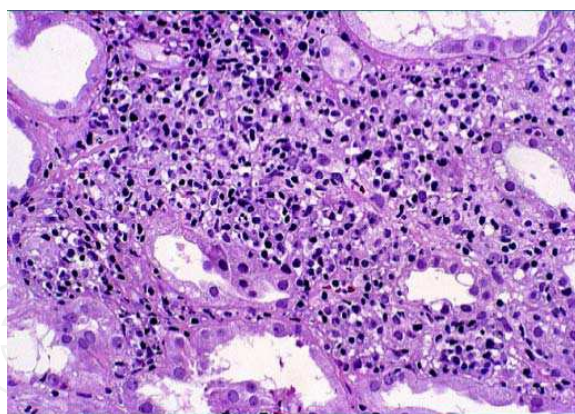


Fig. 2. Infiltration of tubules and interstitium with T cells (Courtesy of Suzanne Meleg-Smith, MD.)

4. Role of B cells and DSA

Based on the principles of immunology, B cells are known to play vital roles, from antigen presentation, immune regulation, to their most characteristic role of differentiating into plasma cells that secrete antibodies. The secretion of antibodies and their role in the pathogenesis of CAN is what makes B cells of great clinical significance in the long term survival of the renal graft.

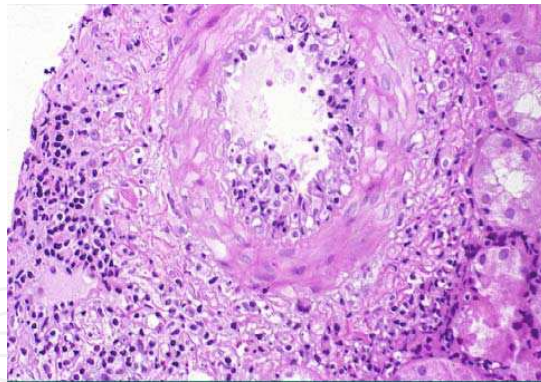


Fig. 3. Infiltration of arterial intima with T cells (*Courtesy of Suzanne Meleg-Smith, MD.*)

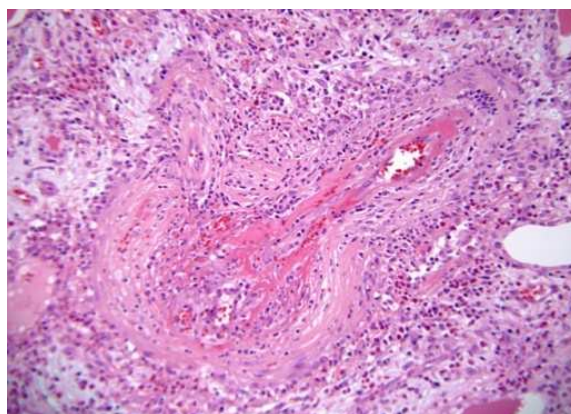


Fig. 4. Fibrinoid necrosis of arterial wall and transmural infiltration of T cells (*Courtesy of Suzanne Meleg-Smith, MD.*)

The association between graft dysfunction with antibodies produced against donor human leukocyte antigens (HLA) has long been recognized (Jeannet et al., 1970; Terasaki et al. 2007). Their role in acute AMR is well defined and they have been popularly referred to as DSA. Their pathogenesis became evident with the discovery of deposition of complement fragments (C4d) along peritubular capillaries (PTC) in grafts of patients suffering from graft dysfunction and known to have circulating DSAs (Feuch et al., 1991). (Figure 5)

In the context of CAN, arteriopathy or glomerulopathy in the transplanted kidney is also linked to C4d deposition in the PTCs and to DSAs (Mauiyyedi et al., 2001). The pattern of renal injury in these circumstances was further elaborated with the evidence that when chronic failure occurs in the renal allograft and circulating DSAs are present along with C4d deposition in the PTCs, capillaritis and basement membrane multi-lamination was seen (Regele et al., 2002). Other features described and attributed to this pathology include duplication of the glomerular basement membrane, mononuclear cell infiltration in the glomeruli and the PTCs along with loss of normal glomerular capillary endothelial fenestrations (Colvin et al. 2006). With well-described morphological features, along with association of DSA and C4d deposition, “chronic antibody mediated rejection (CAMR)” gained its place in the revision of the BANFF classification in 2005 (Solez et al., 2007). The presence of proteinuria is not pathognomonic but can be seen and graft function may seem quite stable for years. While the pathogenesis is strongly linked to circulating DSAs, prior sensitization or an episode of acute AMR are not essential pre-requisites. Instead, DSAs may

develop slowly and sub clinically, and eventually lead to the dysfunction of the allograft mediated by a slow inflammatory process.

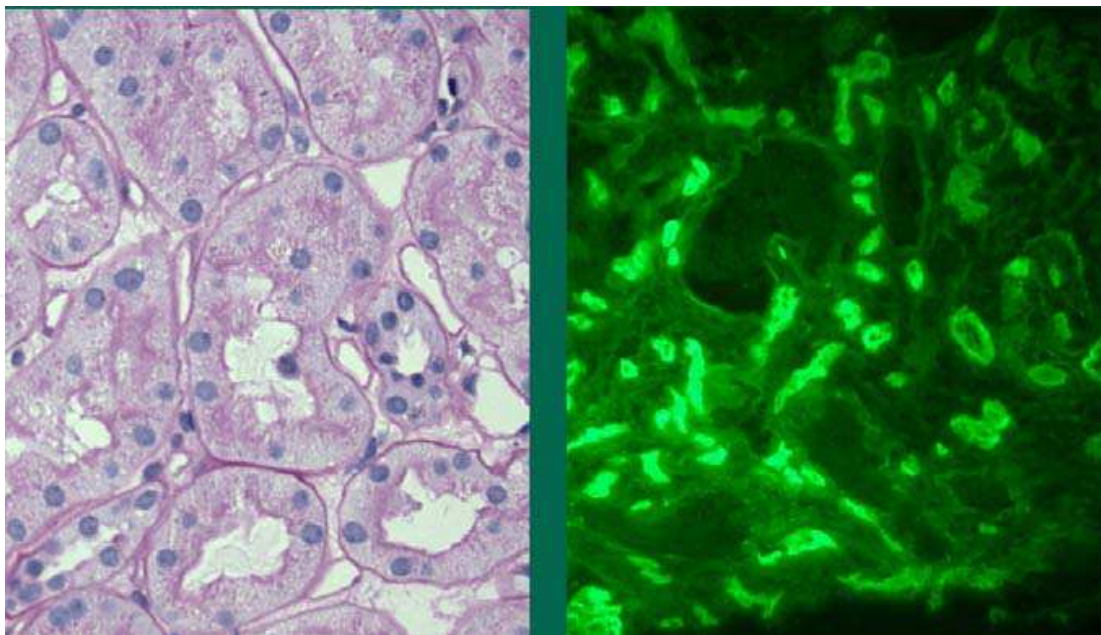


Fig. 5. Peritubular capillary deposition of C4d (right) in acute antibody mediated rejection. (Courtesy of Suzanne Meleg-Smith, MD.)

With the development of a diagnostic criterion for CAMR, many of the pathological findings that had known to exist have been tied in and explain the underlying mechanism of renal injury. However, there are few caveats that still make the accurate recognition of this clinical entity challenging.

One factor is that under certain circumstances, C4d deposition might not be seen. This could happen when the DSAs induce damage via a non-complement fixing mechanism (Collins et al., 2008). Further, in advanced stages of CAMR, when tubular atrophy has already developed, it may well be hard to recognize positive C4d staining. Conversely, when typical changes such as PTC multi-lamination are seen in the absence of C4d deposition and circulating DSA, there could be a possibility of another diagnosis such as chronic or resolving thrombotic micro-angiopathy or these lesions could be assumed to be from a previous episode of acute antibody-mediated injury. Laboratory studies have demonstrated that complement, although relied on in order to make a clinical diagnosis, is not necessary in the pathogenesis of CAMR. Induction of DSAs that are non-complement fixing can have the same pathological changes as DSA that fix complement. Also, in animals that are selectively deficient in C3 (RAG1 -/-), introduction of complement fixing antibodies results in similar pathological changes and poor outcomes of the graft (Jin et al. 2005). What has been found to have a more pronounced role in the development of allograft arteriopathy characteristic of CAMR, is a host of changes in the endothelium brought about by the infiltration of natural killer (NK) cells that express FcγRIII, which is a receptor for the Fc (Fragment crystallizable) or the constant region of antibodies. Hence it is believed that in the pathogenesis of CAN mediated by circulating DSAs, NK cells have much more of a role than complement (Hirohashi et al., 2008).

Yet another phenomenon observed in the context of circulating antibodies is that sometimes, there may be no evidence of graft destruction at all, even with varying degree of C4d deposition. This process, termed accommodation, has been the focus of research in recent years, with a wealth of insight provided by transplantation of organs across the barrier of ABO incompatibility. Though anti-A or B isoagglutinin reappear after transplant, they can co-exist without precipitating rejection (Gonzalez-Strawinski et al., 2008). Interestingly, C4d deposition can be observed but, compatible with other observations, does not necessarily mean that CAMR is taking place. Understanding the mechanism by which the graft attains this ability to remain “non-reactive” despite the presence of antibodies circulating against it is of great interest as it can be therapeutically mimicked when DSAs are known to exist that would otherwise lead to an immunologically mediated rejection of the graft. Accommodated grafts have been found to have changes in the cells of the endothelium and that are believed to help in the adaptation to the presence of antibodies. These changes include increased expression of bcl-xL, (Salama et al. 2001), increased muc-1 expression (Park et al. 2003) and increase in the expression of indolamine-2,3-dioxygenase (Minnei et al., 2008) in the glomerular and PTC endothelium.

In conclusion, CAMR occurs slowly, with the first step being the development of DSA, followed by an immunological reaction that *may* result in the deposition of C4d, the resultant development of visible pathological changes characteristic of CAMR and then eventual graft loss. The speed at which these events occur is variable and the challenge is not just limited to the difficulty in diagnosis, but also in terms of therapy. In the future, the main strategies to counteract the risk for CAMR will be focused on screening for the development of new DSA, following the titers of known DSAs and correlating them with the function of the transplanted kidney. Also, as we learn more about the adaptive capabilities that lead to accommodation, strategies will likely be developed to mimic them in vivo to prolong the renal graft survival.

5. Acute and sub-acute rejection

Many studies have pointed out that the long term outcomes of transplanted kidneys that underwent episodes of AR are inferior compared to those that did not. The long term outcomes are even worse if the episodes of rejection have been multiple or if the acute rejection occurs late, usually meaning more than 6 months after the transplant. The obvious correlation here is that many times, non-compliance with immunosuppressive medications would be a confounding factor. What is also an obvious factor is that each episode of rejection leaves the transplanted organ with progressively increasing amounts of interstitial fibrosis and tubular atrophy with a cumulative effect of functional decline, eventually resulting in organ failure.

However, the incidence of AR has markedly declined, with the actual incidence within the first year being less than 10% (USRDS, 2008). This decrease has not translated into an improvement in the overall graft survival or the median survival time of renal allografts. An explanation to this phenomenon may be that even when there is no acute allograft dysfunction in terms of worsening creatinine clearance, proteinuria or hypertension, there is an ongoing inflammatory infiltration that leads to structural damage and eventual scarring of the renal parenchyma, termed as subclinical rejection. This entity is usually discovered by protocol biopsies, which are not performed in a cross-sectional manner. This means that an

inflammatory response, which is not very severe, but in most cases chronic does occur and over time results in graft loss. There has been a clear demonstration that subclinical rejection leads to an early development of CAN and graft loss particularly if there is coexisting interstitial fibrosis and tubular atrophy (Cosio et al, 2005; Nankivell et al., 2004, Moreso et al., 2006; Shishido et al., 2003; Veronese et al. 2004). It is also important to stress that while there may not be a significant functional deterioration at the time sub-clinical rejection is diagnosed, many times the actual injury as demonstrated by protocol biopsies may be of high grade. One study categorized the results of a cohort of protocol biopsies and revealed that 1 out of 3 of these cases has interstitial acute rejection Grade 1 and 2 out of 3 were classified as borderline changes (Nankivell et al., 2004). There has also been a repeated demonstration that the degree of infiltration seen in protocol biopsies revealing subclinical rejection has correlated to the degree of HLA incompatibility further proving that this infiltration is driven by an immunological phenomenon. There are instances when there is clear histological demonstration of infiltration in the renal parenchyma with no rise in serum creatinine implying that there is no functional decline. This further elaborates the unreliability and underestimation of renal dysfunction offered by measuring serum creatinine level (Kaplan et al., 2003; Levey et al., 1999).

This raises the question of whether protocol biopsies should be performed on a regular interval. While some studies have demonstrated a clear benefit in terms of a decreased incidence of AR and lower serum creatinine at two years after the kidney transplant (Rush et al., 1998), there have been other studies that indicate that treatment of subclinical infiltration on the basis of a protocol biopsy may not have significant improvement in the long term and may further expose the patient to increased amounts of immunosuppression and further the risk of CNI toxicity. Therefore, with the currently existing data, most centers do not perform protocol biopsies on all patients; however, experts do recommend performing protocol biopsies on at least some of the patients that are considered high risk where an inflammatory infiltrate likely means a clinical rejection. If left untreated, it will likely result in an accelerated course towards CAN and the eventual loss of function of the allograft.

6. Degree of HLA mismatch

Three pairs of human leukocyte antigens (HLA) loci A, B and DR are traditionally used for organ allocation. They exist on chromosome 6 with both alleles inherited from either parent are co-expressed, resulting in any individual having 6 antigens. There is tremendous amount of variation in the actual antigen that is coded by each of these loci among individuals as this gene exhibits what is known as polymorphism. With advances in molecular biology more than 230 polymorphisms have been identified for HLA-A, more than 470 for HLA-B and more than 380 for HLA-DR. Their relevance stems from the fact that these antigens are expressed on the surface of all cells and are the major barrier to transplantation. Because of the way our immunological system is designed, the recognition of self versus foreign antigens is mediated through these HLA antigens. Hence when foreign tissue is introduced to the immune system of a host and it is recognized as foreign, it is due to lack of tolerance that the host has developed towards its own variety of HLA antigens.

As these antigens are carried on fixed loci, their inheritance follows a Mendelian pattern, and a combination of HLA-A, B and DR is inherited by an individual from both parents.

Hence, when identical twins or siblings, who have the same HLA antigens donate to each other, the survival is superior compared to randomly matched cadaveric donors, with an intermediate level of graft survival seen when parents or genetically non-identical siblings donate where one of the haplotypes are matched. In population based programs, which rely predominantly on cadaveric donation, finding single or double haplotype match is obviously not very common. The goal is to find a donor and recipient combination that has zero to minimum mismatches, meaning the least amount of HLA antigens expressed on the surface of donor cells that are not present in the recipient. There has also been recognition of the fact that there are some HLA mismatches that are more significant than others, for example having a DR mismatch is now known to be much more detrimental to graft survival than having a mismatch of the A and B antigens (Coupel et al., 2003; Opelz 1985).

In the earlier years of transplantation, having HLA mismatches led to a high incidence of early rejection and eventual graft failure. With the modern and more potent immunosuppressive agents used today, such episodes are rare in the first year. However, despite the immune suppression and the low incidence of AR in the first year, the long term survival of grafts from well matched (6 antigen match or zero mismatch) donors have a longer survival than from those who are not as well matched and according to recent analysis of the national database in the United States (OPTN/SRTR, 2008) this effect is seen in living donors and deceased donors of both extended and non-extended criteria. Despite the above stated evidence pointing towards better survival among well matched organ allocation, only 13% of the organs allocated in the US are well matched. (Takemoto et al., 2000). The main reasons are that despite the large numbers of people on the waiting list, well matched organs are difficult to find. When they are found, the absolute match may be in a different part of the country. If organ allocation is done by HLA only, not considering geographical location, the cold-ischemia time increases as the organ is transported. As the cold-ischemia time increases, chances of delayed graft function increase and overall it negatively affects outcomes and costs. According to an analysis, the added advantage of a zero mismatch is lost once the cold-ischemia time exceeds 36 hours (Lee et al., 2000).

Exposure to foreign antigens whether in the form of organ donation, blood transfusion and in the case of women, through child birth, leads to development of antibodies that are reactive towards these antigens, a process referred to as "sensitization". A measure known as the Panel Reactive Antibodies (PRA) estimates the degree of sensitization that a potential recipient has and this reflects the likelihood of having difficulty finding an organ to which the recipient does not have preformed antibodies against. Pre-existing DSA or developing de-novo DSA in the post-transplant period predisposes the recipient to develop AMR. Even if there is no overt episode of AMR clinically, the graft survival is still poor, which is explained by development of transplant glomerulopathy from CAMR.

Strategies to prevent CAN due to HLA incompatibility include matching donors and recipients with minimal mismatches, cross matching to ensure that there is no DSA. If DSA are present, various desensitization protocols utilizing intravenous immunoglobulin and plasmapheresis can be used to decrease the likelihood of AMR. In the post transplant period, a watchful evaluation of kidney function with close monitoring of serum markers as well as urinalysis should be kept to recognize early development of AMR and CAMR. The threshold to evaluate renal dysfunction with kidney biopsy should be low in patients at increased risk of rejection due to HLA incompatibility. In the outset, patients who are likely

to be in need of kidney transplantation should be transfused with caution during their course of CKD as well as when they are on renal replacement therapy to keep sensitization at minimum.

7. Gender

Due to lack of the Y chromosome in women, antigens coded for by the Y chromosome are recognized as foreign when organ transplantation occurs from a male donor to a female recipient (McGee et al., 2010, 2011). While this does not manifest immunologically as strongly as HLA incompatibility, it does have an effect of having shorter graft survival when an organ is taken from a male donor and transplanted to a female recipient (McGee et al., 2010). This effect is more strongly noted among bone marrow transplants, but is also present to some degree in solid organ transplants such as the kidney (Gratwohl et al., 2008). The decreased survival of male to female donation compared to female to male donation is seen despite the fact that in most instances a higher nephron mass of a male donor kidney is transplanted into a smaller body of a female recipient.

8. Summary

The significant improvement in the short-term graft survival has not transformed into a much better long-term graft survival. CAN is an important cause of graft loss and it represents a complex process culminating immunological and non-immunological injuries. The occurrences of overt acute rejections, either cellular, humoral or both, in the early stage driven by allo-immunity can have an important bearing on the long term immunological milieu that prevails and hence influences the graft survival. Sub-clinical rejection and/ or chronic rejection from inadequate immunosuppression are frequently undiagnosed and untreated. Persistent DSA or de novo development of DSA after kidney transplant is increasingly recognized as an independent and detrimental factor for transplant glomerulopathy. Other than allo-reactivity, there are emerging data suggesting that the pre-existing or de novo developing autoimmunity, mediated by either auto-antibodies and/or autoreactive T cells, may also cause post-transplant allograft injury (Dinavahi et al., 2011; Porcheray et al., 2010; Vendrame et al., 2010). Therefore, to appropriately identify and address the actual disease process, knowledge of the ongoing pathogenesis is needed in order to improve the long-term graft survival. From allo-immunological standpoint, it may include optimizing HLA match, avoiding sensitization, timely detecting and treating AR episodes, and maintaining adequate levels of immunosuppression to prevent the development of DSA, sub clinical rejection and chronic rejection of allografts.

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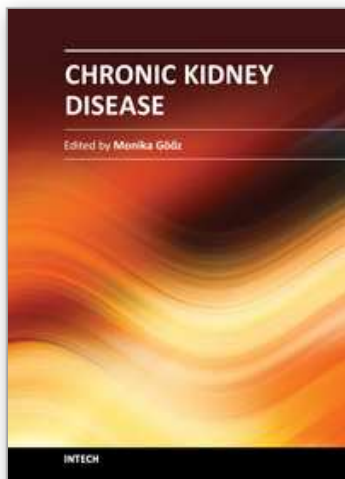
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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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