Chronic Allograft Dysfunction
Major Contributing Factors

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Chronic, progressive, and irreversible loss of a transplanted kidney function, previously named chronic allograft nephropathy, is the leading cause of chronic allograft failure among kidney transplant recipients. Chronic allograft dysfunction (CAD) is a multifactorial process associated with progressive interstitial fibrosis and tubular atrophy. Current Data confirms that an additive series of time-dependent immunological factors such as acute and chronic antibody- and/or cell-mediated rejection and nonimmunological factors are involved in development of interstitial fibrosis and tubular atrophy as the fundamental parts of CAD. The use of calcineurin inhibitors has produced a major impact on achieving successful organ transplantation; however, although this assumption has been doubted recently, calcineurin inhibitors are deemed to be associated with nephrotoxicity and subsequent interstitial fibrosis, tubular atrophy, and kidney dysfunction. The early fibrotic changes are due to implantation stress, T-cell–mediated rejection, and infection; however, usually they do not lead to progressive fibrosis and allograft dysfunction per se. In the setting of CAD, many factors occurring lately after 1 year, such as chronic antibody-mediated rejection, recurrent or de novo glomerulonephritis, and nonadherent adequately address the existence of ongoing injuries and progression to fibrosis. Identification of patients who are at risk, close clinical monitoring, and optimization and individualization of their maintenance immunosuppressive regimen are among the means that could help us to improve the long-term outcome of kidney transplantation.

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INTRODUCTION

The short-term outcome of kidney transplantation has significantly improved over the past 2 decades; however, there has been little progress in improving the longer-term survival of the allografts. The two major causes of graft loss include death and graft failure. Graft failure is the consequence of a series of pathological insults resulting in incremental damage to the nephrons within the transplanted kidney.[1] This process was formerly known as chronic allograft nephropathy, a nonspecific term that did not carry any information regarding the cause. In recent years, with better recognition of the pathogenic factors, we have seen a change in the terminology (Banff 2009).[2] When the cause of progressive fibrosis is unclear, *interstitial fibrosis and tubular atrophy* (IFTA), a not otherwise specified term, is used for description of the histological changes in the biopsy. The progressive process of nephron loss is due to immunological and nonimmunological factors. Among them, the major components leading to chronic allograft dysfunction (CAD) include chronic cellular and humoral injury and calcineurin inhibitor toxicity that cause progressive IFTA. Chronic allograft nephropathy is clinically defined as decline in kidney function, proteinuria, and hypertension.

ETIOLOGIES AND OUTCOMES

Is Calcineurin Inhibitor Toxicity Real?

Since the early 1980s when calcineurin inhibitors became the main component of the immunosuppressive regimen, their acute and chronic nephrotoxic effects have been recognized. The hallmark of chronic calcineurin inhibitor toxicity is de novo arterial hyalinosis, which starts eccentrically as a nodule and gradually extends to concentric thickening of the arteriolar wall. The systematic description of chronic calcineurin inhibitor toxicity was reported by Nankivell and colleagues.[3] They studied serial protocol biopsies in 120 simultaneous kidney and pancreas transplant recipients and described 2 phases of allograft injury, an early fibrogenic phase attributed to reperfusion injury and acute rejection, present in 66% of the patients, and a late phase injury attributed to calcineurin inhibitor toxicity. The late phase is characterized by fibrosis and arteriolar hyalinosis, found in 95% of the biopsies after 10 years. Despite the universal presence of chronic calcineurin inhibitor toxicity, with severe changes in 58.4% of patients, the long-term outcome was excellent, 10-year death-censored graft survival was 95%, and the mean serum creatinine was 1.6 ± 0.5 mg/dL. Although this study provided more information supporting the universal presence of calcineurin inhibitor toxicity, the results need to be cautiously interpreted. In this study, the majority of the patients were treated with cyclosporine, azathioprine, and prednisolone. They did not compare the results with the patients on the non-calcineurin inhibitor–based regimens. Indeed, they did not look for late long-term pathological changes. The histological findings attributed to the calcineurin inhibitor toxicity were generally nonspecific. It was likely that subclinical rejection, found in 19.5% and 12.3% of the biopsies during 2 to 5 years and 6 to 10 years, respectively, led to these chronic histological changes. In patients with combined pancreas and kidney transplantation, there are more surgical and renal complications compared to the patients with the only kidney transplant, and this might be a contributing factor in producing chronic histological changes.[4] In a subsequent study, the authors compared the chronic histological changes between those who received mycophenolate mofetil with those who took azathioprine as a part of their cyclosporine-based regimen.[5] They reported that mycophenolate mofetil-treated patients had reduced rates of arterial hyalinosis, striped fibrosis, and tubular microcalcification. One can assume that the lower rate of acute rejection in the former group was associated with less immunological injury.

Kandaswamy and coworkers reported long-term survival of 1263 patients who remained on calcineurin inhibitors after the first 10 years posttransplant.[6] In this group, the mean serum creatinine level and calculated creatinine clearance were stable during the following years. Recently, Stegall and colleagues[7] reported the results of kidney allograft biopsies at 1 and 5 years posttransplant. The overall prevalence of moderate to severe fibrosis was 13% (60 of 447) at 1 year and 17% (60 of 343) at 5 years. In a subgroup of 296 patients who underwent allograft biopsy, 23% showed mild fibrosis after 1 year, which progressed to more severe forms after 5 years. The prevalence of moderate or severe arteriolar hyalinosis was similar in tacrolimus and calcineurin inhibitor-free regimens. In a study by Humar and colleagues,[8] the actuarial 10 year graft survival with calcineurin inhibitor-based regimen in kidney transplant recipients with no rejection was 91% compared with 45% for those with 1 or more episodes of rejection ($P = .001$). Calcineurin inhibitor toxicity was reported as a rare cause of graft loss in both groups.

As described, the importance of calcineurin inhibitor toxicity as a major pathogenic factor in progression of CAD and nephron loss has been challenged in recent reports. However, one should be careful with regard to the adverse role of calcineurin inhibitors on long-term graft outcome. It is important to note that in these studies, the effect of nonimmunological factors such as hypertension, antihypertensive drugs, and diabetes mellitus has not generally been considered. Moreover, in many centers over the past 3 decades, the immunosuppressive protocols have been changed by replacement of cyclosporine with tacrolimus or rapamycin, decreasing the targeted drug levels for both calcineurin inhibitors, and changing the adjunctive agent from azathioprine to mycophenolate mofetil. Moreover, induction with anti-T-cell antibody has become a regular component of the immunosuppressive regimen. In the light of these considerations, we suggest that calcineurin inhibitor toxicity with the modern immunosuppressive regimens may play a smaller role in progression of chronic histological changes in kidney allografts, but it still contributes to deterioration of graft function and outcome.

Association of Graft Fibrosis With Allograft Function and Loss

An important question is whether the presence of IFTA on biopsy results is necessarily predictive of poor graft function or survival. In the study reported by Rush and coworkers, 240 patients were randomized into a biopsy protocol at 1, 2, 3, and 6 months or biopsy only at 6 months posttransplantation. All the patients were on a combination of tacrolimus, mycophenolate mofetil, and prednisolone. Although repeated biopsy revealed that IFTA increased from 3% at baseline to the 40% to 50% of biopsies after 2 years, the graft function was excellent with a mean estimated glomerular filtration rate of 74 mL/min.[9] This suggests that presence of fibrosis in the biopsy does not necessarily point to poor graft function at least in short term. In the DeKAF study, 337 patients underwent indication biopsy due to recent graft dysfunction. Poor graft survival in patients with IFTA was seen only in those who had inflammation in the area of fibrosis.[10] Mengel and colleagues[11] assessed the molecular phenotypes by microarray analysis and histopathological findings in six weeks protocol biopsy series. They showed that up to 60% to 80% of kidney allografts had some degrees of IFTA, associated with inflammation, which were remained stable in subsequent biopsies. The early inflammation with later mild IFTA is often the natural history of the injury-repair response to the implantation stress such as delayed graft function, viral infections, and other complications. This process is like wound healing in which the wound will be stabilized after a while; however, when repeated injuries occur, this could lead to a permanent damage. Persistent inflammation on sequential early protocol biopsies was associated with the molecular phenotype of injury-repair inflammation rather than acute T-cell-mediated rejection. A good correlation was found between subclinical molecular phenotype and pathological findings characterized by interstitial inflammation and tubulitis, which does not translate to the future episodes of T-cell-mediated rejection or loss of graft function. Despite persistence of some degrees of inflammation and progression of IFTA, allograft function did not change within the first 2 years.[11]

Is There Any Need for Protocol Biopsies?

With the current immunosuppressive regimens in "low risk" transplant patients, the prevalence and progression of early inflammation and chronic histological changes is low, with the little impact on future function of the graft, at least in medium-term follow-up. Therefore, it has been suggested that protocol biopsies lack significant clinical benefit in patients who receive induction therapy and are maintained on tacrolimus and mycophenolate mofetil. This does not apply to those who are presensitized, patients with prolonged delayed graft function, or those taking high doses of calcineurin inhibitors or have developed drug toxicity and infection.[12] It seems that the long-term aggravation of histopathological changes in these patients is more due to a new specific disease or graft rejection, which may be due to nonadherence, rather than chronic calcineurin inhibitor toxicity. However, by increasing the use of kidneys from extended criteria donors—living donors who are older, and have mild hypertension or dysglycemia—the utility of protocol biopsies after transplantation needs to be re-addressed. Preliminary data from the protocol biopsies in overall high-risk patients from the University of Maryland Transplant Center has shown significant subclinical changes that could lead to progression of graft fibrosis and loss of function, if untreated (personal communication).[12]

Chronic Antibody-Mediated Rejection

Advanced IFTA is the common histological feature of deterioration of graft function and loss regardless of the pathogenic cause. The causes and phenotypes of late graft failure are not well understood. Meanwhile, nephrologists' willingness to perform a biopsy is often low and many patients do not agree with the procedure. Histopathological findings of IFTA cannot lead us to the etiology, and still the specific causes need to be found.

Terasaki and coworkers[13] showed in both deceased and living kidney transplants that the presence of anti-human leukocyte antigen (HLA) antibodies led to 5% allograft loss every year; therefore, after 4 years, 20% of the grafts will be lost. Donor-specific antibodies (DSAs) against HLA antigens increase the risk of late graft loss, supporting a major role for antibody-mediated rejection (ABMR).[14] Histological findings in chronic ABMR include peritubular capillary (PTC) deposition of C4d, transplant glomerulopathy characterized by the glomerular basement membrane double contours, PTC membrane multilayering, fibrous intimal thickening, and IFTA.[15] The Banff criteria require PTC C4d positivity for diagnosis of ABMR as well as microcirculation injury. However, C4d is not a sensitive marker of chronic ABMR, and in many patients with transplant glomerulopathy C4d staining is negative in the presence of anti-HLA DSA. Therefore, the recent update of the Banff classification introduced the diagnostic category of "suspicious for ABMR." It is defined with the presence of morphologic evidence of antibody-mediated tissue injury and positive anti-HLA antibody with negative C4d, or PTC C4d positivity in the absence of alloantibody.[16] Moreover, gene microarray studies in C4d-negative patients with graft loss showed increased expression of endothelial activation transcripts with a positive antidonor antibody. In the study by the Edmonton group,[17] patients with indicated graft biopsies in the early posttransplant period rarely progressed to the graft failure, whereas those patients with late grafts biopsies often progressed to graft failure within 3 years. Patients who underwent indicated graft biopsies (> 1 year) frequently showed donor-specific HLA antibody (particularly anti-class II) and microcirculation changes. Hence, the problem of progressive graft dysfunction cannot be explained by biopsy findings in an early period after transplantation, which is expected to reveal an injury-repair response in kidney transplants during the first months. The majority of these changes reflect the resolution and stabilization of the injuries which correlate with donation factors and implantation stress such as delayed graft function, T-cell mediated damage, or viral and bacterial infections, considering that active injury-repair response will usually leave at least some permanent damage secondary to the injury and inflammation. These changes are not usually progressive in nature and do not result in kidney graft loss, unless repeated additive events of injury happens over time. In this time, some injured nephrons cannot be repaired, leading to atrophy and fibrosis after 6 to 12 months.[18] Occurrence of T-cell-mediated rejection is more prevalent in the early posttransplant period and uncommonly happens after six months in compliant patients. Treated T-cell mediated acute rejection in first 6 months with a good response to treatment has no significant impact on long-term graft survival.[19] Therefore, late deterioration of graft function should not be explained as the result of early injuries. Time influences the probability of development of de novo DSA.[20] The Edmonton group has suggested that kidneys that present with late onset (> 1 year) dysfunction usually have a new disease such as ABMR or recurrent glomerulonephritis, which initiate a new injury-repair response with more pathological changes, tubular atrophy, and interstitial fibrosis. In this cohort, the etiologies of graft loss among those patients who underwent late biopsies included: DSA-positive ABMR (particularly anti-class II antibody), associated with microcirculation changes and scarring in 63% of patients, while many of them were C4d negative, glomerulonephritis in 22%, and the remainder were due to nonadherence, T-cell-mediated rejection, or drug toxicity.[18] Haririan and colleagues[21] showed that up to one-third of patients who required indication biopsy had circulating DSA and a similar portion showed C4d positivity in the biopsy. Presence of these markers of ABMR was associated with a more than 4-fold increase in the risk of graft failure.

In the Mayo clinic study, among 1317 transplanted patients, overall 330 grafts were lost within 50.3 months posttransplant during a 10-year period. Among those with the identifiable causes of graft failure, primary glomerular disease was found in 37%, IFTA in 31%, and acute rejection in 12% of the patients. Interestingly, in the IFTA group, one-fourth did have a history of acute rejection. Pure calcineurin inhibitor toxicity was rare and found only in 1 case. Among the glomerular causes, transplant glomerulopathy associated with HLA-antibody was found in 40%, de novo glomerulonephritis in 20%, and recurrent glomerulonephritis in 40%. Overall, one-third of graft losses were, directly or indirectly, due to immunological injury.[22] These recent reports and the others suggest that despite nonspecific histological finding of IFTA, specific disease entities, particularly ABMR and glomerular diseases are the major causes of late allograft failure, and in contrast to the old belief, calcineurin inhibitor toxicity probably plays a minor role.[23]

MANAGEMENT

Considering the variety of the causes of CAD, individualization of its management is very important. The general approach should be attempting to minimize the risk of acute rejection by choosing an appropriate regimen, considering patient and transplant-related characteristics. Studies such as the Symphony trial[24] suggested that a combination of tacrolimus and mycophenolate mofetil as maintenance agents provide lower risk of rejection, while considering their limitations could help choosing the appropriate maintenance regime. Screening for BK virus reactivation and preemptive reduction in immunosuppression could reduce the chance of chronic changes. Close screening of high-risk patients for cytomegalovirus infection and using preemptive treatment, or universal prophylaxis to reduce the risk of cytomegalovirus infection could reduce the risk of direct or indirect injury and subsequent irreversible fibrosis. Patients should be educated about the importance of biopsy, and nephrologists need to realize the value of performing biopsies in patients with increased serum creatinine or proteinuria. Although protocol biopsies may not provide information that could impact the management in low-risk compliant patients, they could be valuable in high-risk patients by helping adjustment of the immunosuppressive regimen. Optimal control of hyperglycemia and hypertension are essential in reducing the risk of CAD. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are safe in kidney transplant recipients and should be considered for blood pressure control, particularly in the presence of proteinuria. Although there is no strong data supporting their beneficial effect on improving graft survival, patient survival may improve.[25] Aggressive treatment of traditional risk factors for cardiovascular disease, which is the major cause of death in patients with functioning graft, is strongly recommended. Early calcineurin inhibitor conversion to sirolimus has been shown to improve the graft function in short-medium term and should be considered in properly chosen patients. Late conversion in patients with an estimated glomerular filtration rate more than 40 mL/min and minimal proteinuria is also advisable.[26]

Posttransplant monitoring for development of DSA could identify patients at risk for the adverse long-term outcome. Although we are currently unable to identify the characteristics of the antibodies that cause chronic ABMR and do not have specific therapeutic agents for its treatment, by identifying these at-risk patients, closer clinical monitoring and optimizing their maintenance immunosuppressive regimen could help to improve the long-term outcome.

CONCLUSIONS

Chronic allograft dysfunction is a multifactorial process that leads to progressive glomerular sclerosis, interstitial fibrosis, and tubular atrophy. Recent studies suggest that calcineurin inhibitor nephrotoxicity may not play a major role in late allograft deterioration and dysfunction; rather processes like chronic ABMR and recurrent glomerular disease are major contributors.. Since CAD is irreversible and there is no specific treatment for it, preventive measures using individualized approach are essential. Calcineurin inhibitor-free therapy may be helpful in patients with low to moderate immunological risk factors.

CONFLICT OF INTEREST

None declared.

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