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Chronic allograft injury: Mechanisms and potential treatment targets

Leonardo V. Riella [a,*], Arjang Djamali [b], Julio Pascual [c]

[a] Renal Division, Brigham & Women's Hospital, Harvard Medical School, Boston, MA
[b] Renal Division, University of Wisconsin School of Medicine and Public Health, Madison, WI
[c] Servicio de Nefrología, Hospital del Mar, Barcelona, Spain

A B S T R A C T

Improving long-term graft survival remains one of the critical challenges facing kidney transplantation since a great portion of kidney grafts are lost by 10 years after transplantation. Understanding the causes of chronic allograft injury and providing timely therapeutic interventions are essential for improving these outcomes. In this review, we will discuss the recent data that emerged turning down calcineurin inhibitors as the primary cause of long-term graft injury and highlighting the increased importance of non-compliance, antibody-mediated injury, disease recurrence, and BK nephropathy as culprits. We suggest a number of different strategies to better manage kidney transplant recipients that, ultimately, may improve long-term graft survival.

1. Introduction

Despite the improved short-term outcomes of kidney transplantation, more than 50% of kidney allografts are lost by 10 years after transplant [1]. [2] Furthermore, death-censored attrition rates beyond the first year of transplant have remained relatively unchanged for the past 25 years, with 3%–5% per year for standard criteria donor kidneys and 2%–3% per year for living donor kidneys [3]. The causes of chronic allograft loss are multifactorial, including both immunological and non-immunological factors (Fig. 1). In the largest longitudinal surveillance biopsy study available, El-Zoghby et al. evaluated 1317 kidney transplant recipients with protocol biopsies at different time-points after transplantation including time 0, 4 months, 1, 2 and 5 years post-transplant [4]. With a mean follow-up of 50 months, they observed that death with a functioning graft was the most common cause of graft loss. For those patients that survived up to 5 years after transplant, the predominant findings on protocol biopsies were glomerular disease (37%), tubular atrophy/tubular atrophy (IFTA; 30.7%) and acute rejection (12% of cases). Among glomerular diseases, both recurrent glomerular disease and transplant glomerulopathy accounted for the majority of cases. Although IFTA is a non-specific finding, analyzing previous biopsies allowed them to identify specific culprits for the allograft scarring in most cases. Cellular and/or antibody-mediated rejection (ABMR) was the leading culprit of IFTA followed by BK nephropathy, recurrent pyelonephritis, poor quality donor kidney, ureteral stenosis and calcineurin inhibitor (CNI) nephrotoxicity. In the past, the term chronic allograft nephropathy (CAN) was used to encompass dysfunctional kidney grafts of unclear cause. However, the revised Banff 2005 classification system renamed CAN to IFTA, without evidence of any specific etiology [5]. This was done in attempt to encourage physicians to determine the underlying cause of the histologic lesions rather than labeling with the nonspecific term CAN. In this article, we will detail the pathogenesis and treatment strategies of chronic allograft injury.

2. Immunological causes

The persistent presence of allo-MHC molecules in the donor kidney leads to a life-long low-grade exposure to foreign antigens that may lead to chronic immunologically mediated injury. This process may take the form of cellular, antibody-mediated or a mix rejection. Furthermore, even kidney graft inflammation detected early on surveillance biopsies that do not fit the criteria of rejection has been associated with the development of tubular atrophy and/or graft loss [6–8]. However, it is unclear if this subclinical inflammation is related to a smoldering cellular-mediated rejection or other processes.

Although acute rejection is less common after the first year of transplant, the rate of late acute rejection is about 5% per year [1]. The most common type of rejection after the first year of transplant is chronic rejection, which is defined as a prolonged cellular and/or antibody-mediated immune response against the transplanted organ that may present with either a rise in creatinine and/or proteinuria. In particular, the role of donor-specific antibodies (DSA) as a major cause of graft dysfunction late after transplant in being increasingly recognized [9]. Among the risk factors, noncompliance may be a major culprit, affecting up to 40% of kidney recipients and associated with more than half of cases of late rejection leading to graft loss [9]. The pattern and reasoning for noncompliance is variable ranging from intentional due to significant side effects to accidental or deliberate due to other life stressing event or financial trouble [10]. Diagnosis of chronic ABMR requires a kidney biopsy to exclude other potential causes. The DeKAF study investigated kidney recipients with a for-cause biopsy in average

* Corresponding author at: 221 Longwood Ave, Boston, MA, 02115, USA. Tel.: +1 617 732 5252; fax: +1 617 732 5254.
E-mail address: lriella@bwh.harvard.edu (L.V. Riella).

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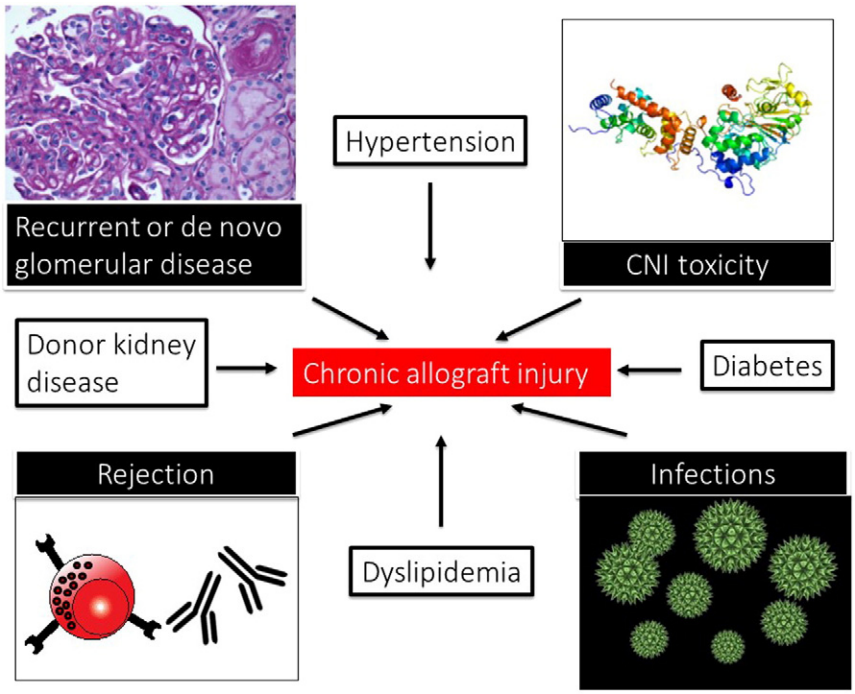

Fig. 1. Causes of chronic allograft injury.

7 years post-transplant. Risk of subsequent graft failure was significantly higher in patients with DSA, C4d staining or both, and the severity of clinical injury directly correlated with the intensity of the antibody response [11].

The recognition of alloantibodies as a major cause of chronic rejection has also been driven by the development of novel techniques that allowed better identification and quantification of anti-HLA DSA (such as the single-antigen bead assays) and the improvement in the

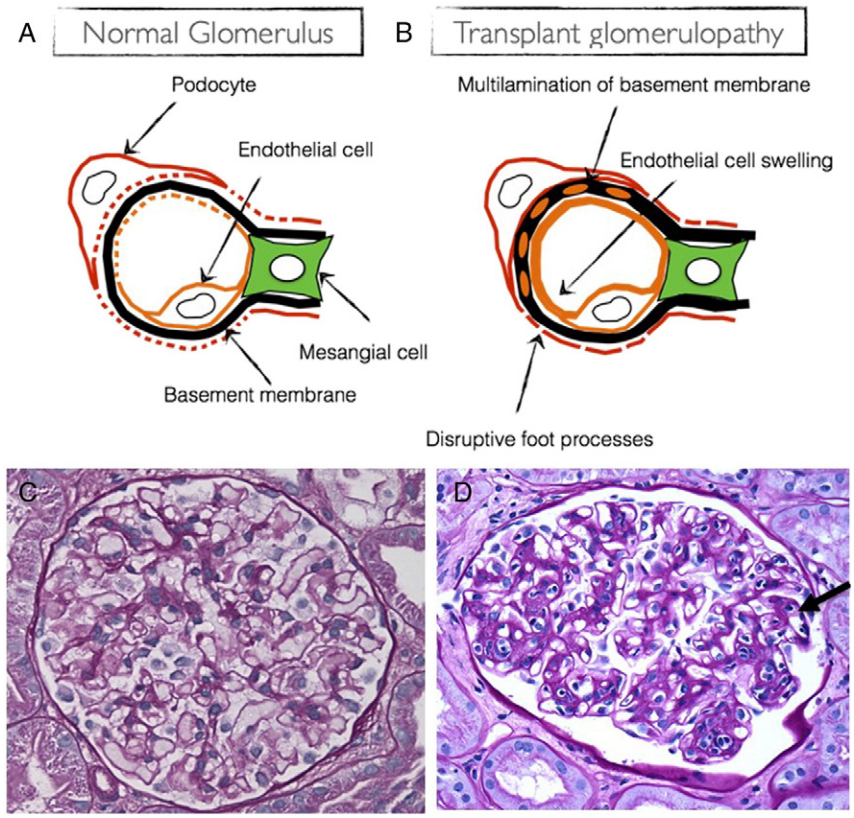

Fig. 2. Transplant glomerulopathy. Illustration of a normal glomerular capillary structure (A) next to one with changes characteristics of transplant glomerulopathy (B), including the endothelial swelling, the multilamination of the basement membrane and the disruptive foot processes. Representative light microscopy images of a normal glomerulus (C) and one with transplant glomerulopathy with thickened capillary walls (arrow). Adapted from [100].