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Review

The aetiology and pathogenesis of chronic allograft nephropathy

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Abstract

Renal transplantation is the ultimate form of renal replacement therapy, and is the treatment of choice for many patients with end-stage renal failure. The advent of calcineurin inhibitor based immunosuppression resulted in the 1-year renal allograft failure rate dropping from around 50% twenty years ago to less than 10% in more recent times. Despite a massive improvement in renal allograft survival in the first year following transplantation 10-year graft survival can be as low as 50%. Chronic allograft nephropathy (CAN) is recognised as the main cause of renal allograft failure following the first year after transplantation.

The diagnosis of CAN can only be made histologically. Typically biopsy specimens in grafts with CAN demonstrate an overall fibrotic appearance effecting the vascular endothelium, renal tubules, interstitium, and glomerulus.

The risk factors for CAN are divided into alloimmune and alloimmune independent. Alloimmune dependent factors include acute cellular rejection, severity of rejection, subclinical rejection and HLA mismatch. Alloimmune independent factors such as delayed graft function, donor age, Cytomegalovirus infection, donor/recipient co-morbidity and of course calcineurin inhibitor toxicity are important in the development of CAN.

The pathogenesis of CAN is complex, multifactorial, and unfortunately incompletely understood. There are a number of pivotal steps in the initiation and propagation of the fibrosis seen in biopsy specimens from kidneys with CAN. Endothelial activation in response to one or more of the aforementioned risk factors stimulates leukocyte activation and recruitment. Recruited leukocytes subsequently infiltrate through the endothelium and induce key effector cells to secrete excessive and abnormal extracellular matrix (ECM). Enhanced deposition of ECM is a histological hallmark of CAN.

This paper aims to present a concise yet accurate and up-to-date review of the literature concerning the aetiological factors and pathological processes which are present in the generation of CAN.

Keywords: Chronic allograft nephropathy; Renal transplantation; Chronic rejection

Contents

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1. Introduction

Renal transplantation is the treatment of choice for many patients with end-stage renal failure and is universally accepted as the ultimate form of renal replacement therapy.

The past two decades have seen 1-year renal allograft survival increase from 50% to nearly 90% in cadaveric donors, and 95% in living related donors [1–3]. The increase in graft survival rates is largely due to the use of calcineurin inhibitor (CNI) based immunosuppression [2]. In addition to the use of CNI immunosuppressants a better understanding and treatment of acute rejection, improved tissue typing, and improved organ preservation techniques have undoubtedly contributed to the improvement in early graft survival. Unfortunately, despite massively improved 1-year graft survival, 10-year survival rates falls dramatically to 51% and 68% respectively, of which 50–80% are attributable to chronic allograft nephropathy (CAN) [1,4,5]. CAN is the most important cause of renal graft failure after the first year following transplantation.

2. Clinical presentation

Clinically CAN manifests as a progressive deterioration in renal function with associated proteinuria in the absence of another specific pathology [6]. In 80% of patients following the histological diagnosis of CAN declining renal function follows a linear relationship between the reciprocal of serum creatinine and time [7]. A frequent sequelae of CAN is *de novo* or accelerated hypertension [8]. Despite these strong clinical indicators, the diagnosis of CAN is made purely upon histological findings.

3. Histology

The histological features of CAN were first described in 1953 by Hume et al. in a review of outcome in nine renal transplants [9]. The main histopathological features of CAN involve the vascular endothelium, renal tubules, interstitium, and glomerulus. The vascular endothelium displays a spectrum of changes ranging from subendothelial inflammation, so called endothelialitis, through mild to moderate intimal hyperplasia, and ultimately atherosclerosis [10–12]. These intimal changes are associated with a mononuclear cell and T lymphocyte infiltrate [13,14]. Glomerular lesions, often described together as transplant glomerulopathy, may demonstrate mesangial cellular and matrix expansion, thickening and duplication of the basement membrane, and glomerulosclerosis associated with ischaemia [15–17]. Tubular atrophy and interstitial fibrosis of varying degrees are classically observed CAN.

The dominant process in intimal hyperplasia, interstitial fibrosis, and mesangial expansion is an over-accumulation of abnormal extracellular matrix (ECM). Extracellular matrix is secreted due to a phenotypic switch of smooth muscle cells (SMCs) in the endothelial media, myofibroblasts in the interstitium, and mesangial cells in the glomerulus, in response to endothelial injury [3,11,12].

The severity of CAN is most often graded using the 1997 Banff schema. The Banff schema categorises lesions as interstitial fibrosis, glomerulopathy, mesangial matrix increase, vascular fibrous intimal thickening and arteriolar hyaline thickening. The lesions are then scored according to severity on a scale of 0, 1, 2 or 3, with 0 representing no change and 3 representing severe pathology. Freese et al., reported that despite a low Banff score indicating better graft survival, for singular histopathologic components of the schema only interstitial fibrosis was a statistically significant predictor for graft survival [18].

In 2004 Nankivell et al. published a series of 961 renal transplant biopsies performed on 119 consecutive recipients from the period 1987 to 2000. These data showed 2 distinct histological phases of CAN. CAN within the first year after transplant demonstrated rapidly increasing Banff scores for interstitial fibrosis and tubular atrophy. These histological appearances were found in 94.2% of recipients at one-year post-transplant [19]. This early phase of CAN has also been described in other smaller studies [18,20]. After the first year post-transplant the pattern of CAN showed an increased prevalence of arteriolar hyalinisation, vascular narrowing and progressive glomerular sclerosis, with sclerosed glomeruli in 37.3% of biopsies by 10 years [19]. The two distinct phases of CAN represent a shift in aetiology from immunological causes, such as SCR, to calcineurin inhibitor nephrotoxicity [19].

4. Alloimmune dependent factors

Acute rejection is predictive for CAN with late acute rejection, greater than three months after transplantation, being