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Review

Chronic alloantibody mediated rejection

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ABSTRACT

Alloantibodies clearly cause acute antibody mediated rejection, and all available evidence supports their pathogenic etiology in the development of chronic alloantibody mediated rejection (CAMR). But the slow evolution of this disease, the on-going immunosuppression, the variations in titer of alloantibodies, and variation in antigenic targets all complicate identifying which dynamic factors are most important clinically and pathologically. This review highlights the pathological factors related to the diagnosis of CAMR, the time course and natural history of this disease. What is known about CAMR pathogenesis is discussed including alloantibodies, the role of complement, gene activation, and Fc effector cell function. Therapy, which is problematic for this disease, is also discussed, including on-going and potential therapies and their limitations.

1. Introduction

Alloantibodies were first associated with the chronic rejection of human renal allografts when chronic allograft arteriopathy developed in patients with de novo anti-donor antibodies (HLA) [1]. Subsequent studies showed an association of circulating HLA antibodies with an increased risk of long term graft loss [2–4]. Acute renal allograft rejection in patients with donor specific anti class I HLA antibodies showed some identifying characteristic pathological features (e.g., neutrophils in capillaries) [5,6], but these studies did not identify a direct or indirect link to alloantibodies. This linkage was provided by showing that the complement fragment C4d was present in peritubular capillaries (PTCs) in some patients with acute rejection [7]. This finding was then associated with circulating donor specific antibodies and graft pathology [8,9] and confirmed by many others, leading to the introduction of the diagnosis of acute antibody mediated rejection (acute humoral rejection) in the Banff classification [10]. These findings were then extended to show that glomerulopathy and arteriopathy in chronic rejection were linked to C4d deposition in peritubular capillaries (PTC) and donor specific alloantibody (DSA) [11]. A new term, chronic antibody mediated rejection (CAMR) or chronic humoral rejection, was created for this diagnosis [12]. These observations were confirmed and then extended also to include capillaritis and basement membrane multilaminations of the PTC [13]. About 30–50% of patients with chronic rejection and transplant glomerulopathy or arteriopathy have C4d deposition in PTC, but the frequency varied considerably by center [9,14–17]. Most if not all cases with C4d positive antibody mediated rejection, even if it is subclinical, have detectable circulating antibodies [18]. The presence of donor specific de novo anti-HLA antibodies (DSA) associates with a poorer kidney graft survival as compared to subjects without de novo anti-HLA antibodies [19–23].

2. Chronic antibody mediated rejection

CAMR is common in some indication biopsies, found in one 10-year series in 9.3% of 771 cases [24]. Typically the onset is after the first year with the prevalence rising to about 20% in the 5th year. Proteinuria is common but not invariable (~50% of patients with CAMR have >1 g/day proteinuria). Renal function is often abnormal but can remain stable for considerable time (years) [25]. The strongest risk factor is pre-transplant donor specific antibodies [26], but most cases arise in patients without a history of presensitization or even a single episode of acute antibody mediated rejection. Serologically, CAMR shows a strong correlation with Class II DSA [16,26], as compared with acute antibody mediated rejection. Chronic antibody mediated rejection (CAMR) is characterized by chronic glomerular and capillary endothelial injury [10,11,27], is usually associated with proteinuria [25,28–30] and pathological markers including transplant glomerulopathy (duplication and laminations of the glomerular basement membrane) plus excess laminations of the peritubular capillaries. CAMR correlates with alloantibodies [11,13,16,25,26,31,32] but less well with C4d [16]. The infiltrating inflammatory cells in glomerular and peritubular capillaries are primarily macrophages (CD68+) [33], which express the Fc gamma RIII receptor. Some leukocytes in glomeruli also express T-bet, a transcription factor related associated with interferon gamma [34]. Glomerular endothelial

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cells display increased plasmalemmal vesicle-associated protein-1, indicating altered vesicle physiology [35]. In addition to multilamination of basement membranes, loss of PTCs is seen in some patients with chronic graft injury, and this correlates inversely with serum creatinine [32]. Loss of PTCs can affect the extent of C4d positivity and contribute to the lower density of C4d positive PTC often observed in CAMR [36], although other factors including C4d assay sensitivity may contribute to variable staining. Confident diagnosis of CAMR is problematic because not all diagnostic components may be present. For example, while PTC multilamination is almost always present (91%) in patients with transplant glomerulopathy, detectable DSA in the circulation and C4d deposition in the graft are less common (70% and 32%, respectively) [16]. Overall, about 26% of patients with transplant glomerulopathy have no DSA or C4d. The frequency of transplant glomerulopathy is seen in excess of alloantibodies or C4d staining, suggesting an additional etiology of transplant glomerulopathy such as thrombotic microangiopathy (TMA), complement independent injury, or immune complex glomerulonephritis. Alternatively, the transplant glomerulopathy represents the sequela of prior antibody mediated injury with alloantibodies no longer present at the time of transplant glomerulopathy diagnosis. Subclass variation of IgG alloantibodies with variation of the efficacy of complement activation or microchimerism of endothelial cells may confound or create additional C4d staining variation. Transplant glomerulopathy with DSA but without C4d may be due to complement independent antibody mediated injury.

3. Time course and outcome

Regele observed that patients with C4d positive biopsies in the first post-transplant year have a greatly increased risk of transplant glomerulopathy after one year (6% vs 46%) [17]. This was the first clear demonstration that CAMR evolves over time. Subsequently we documented a sequence of four stages of CAMR in non-human primates: (1) production of DSA, (2) deposition of C4d in PTC, (3) development of transplant glomerulopathy and (4) loss of graft function [37,38]. In these animal studies, monkeys with kidney allografts and alloantibodies but off immunosuppression have identical pathology to humans and universally progress to kidney allograft failure [37,38]. These stages evolved over 3–4 months to more than 2 years in recipients that had no immunosuppressive drug therapy, indicating that CAMR is a slow process. Presumably, progression would be slower in patients on maintenance immunosuppressive therapy. More studies are needed in clinical transplantation to determine the natural history of CAMR and define features that predict outcome. Most studies have shown an adverse outcome for grafts with CAMR. In a study from the Mayo Clinic, transplant glomerulopathy increased the risk of graft loss by 6-fold [26]. Others have shown the combination of glomerulopathy and C4d deposition in late grafts has a markedly worse prognosis than either alone [25]. Even without glomerulopathy, C4d positive PTC is an adverse risk factor for graft loss over 3 years (40% vs 10%). In our cohort of 66 patients with CAMR, the one year graft survival was 54% and only 8% of the graft survived 5 years [24]. One contributing factor to the poor prognosis is that the diagnosis is too often made late, after considerable functional impairment. Clearly early markers are needed to diagnose CAMR before functional impairment develops. The only current method is to monitor patients for DSA and biopsy when these appear. Even with this procedure, diagnosis can only be made only when the disease is histologically obvious. Even with an ideal early detection system, better methods of treatment are needed. Therapies to mitigate the B cells response or reduce alloantibody production.

4. Accommodation

Initial observations in recipients of ABO-incompatible (ABOi) grafts identified that the ABO antibodies can return in patients without precipitating rejection. The grafts commonly (50–80%) have C4d positive PTC without an inflammatory response or evidence of graft injury pathologically [14]. Stable HLA-incompatible grafts have C4d positive PTC at a much lower frequency (2–4%) [39], although presensitized patients have been reported to show C4d positive in 17–26% of protocol biopsies [14,40]. This condition is called accommodation and is defined as stable allograft function without evidence of pathological injury with the simultaneous presence of alloantibodies and graft deposition of C4d. The molecular basis remains unknown but is of great interest, especially if it could be mimicked therapeutically. The mechanisms of accommodation are unknown but are associated with the expression of endothelial protective genes. In accommodated xenografts, expressions of A20 and bcl-2, as well as heme oxygenase (HO-1) are up-regulated and are important to both the development and maintenance of accommodation [41,42]. In another xenograft model of accommodation, the expression of complement regulatory proteins is thought important [43]. Some features detected in accommodated grafts are an increase in endothelial bcl-xL (anti-apoptotic) in renal allografts [44], an increase in CD55 (DAF) in stable heart grafts with C4d [45], and an increase in muc-1 expression in glomerular endothelium in ABOi grafts [46]. Graft accommodation can occur with antibodies that recognize carbohydrates on the graft endothelium, including anti-ABO as well as anti-Gal antibodies [43,47] in xenotransplantation [41]. Although anti-MHC antibodies can be associated with temporary accommodation [48], clinical data suggests that this state of accommodation is not enduringly stable and ultimately results in late graft deterioration. The long term stability of accommodation is unknown. In ABOi allografts, graft stability is present for a year or more. In the HLA allografts, some develop rejection but others seem stable for years [25].

5. Pathogenesis – antibodies

Although the primary targets of antibody mediated rejections are the conventional HLA class I and II antigens [22,49], other MHC related alloantigens (MICA) [50,51], autoantigens [52], parenchymal cell antigens, or unknown endothelial antigens [53] are considered potentially relevant. It is unclear when and if antibodies against the graft are pathogenic. Alloantibodies against the angiotensin type II receptor [54] are clearly pathogenic by inducing malignant hypertension. In many circumstances anti-class I and/or class II clearly are pathogenic. For other autoantibodies, there is little or contradictory evidence for pathogenicity. IgG subclasses and their efficacy to fix complement may be very relevant. C1q and C4d (complement fixing) alloantibodies are associated with the transplant glomerulopathy of CAMR [55], but low levels of C4d complement fixing are not, at least acutely [56]. Patients with kidney allografts have a pre-transplant mix of subclasses in their DSAs; IgG1 > IgG2 > IgG3 > IgG4, forming three groups: strong complement fixing with IgG1 and IgG3 (28%), weak complement fixing with IgG2 and IgG4 (5%), and the majority with a mix of all subclasses (62%) [57]. The patient group with the weakest complement fixation showed a lower incidence of acute antibody mediated rejections [57]. Anti-donor antibodies of the strongest complement fixing subclass, IgG3, were present in patients with acute rejection, but not in stable patients, whereas the latter had an increase in the non-complement fixing, IgG4 subclass [58]. Non-complement fixing anti donor antibodies of the IgG2 and IgG4 subclasses can be eluted from a minority of rejected renal allografts, and they may