Chapter 20

Advances in Antibody Mediated Rejection

Siddharth Sharma, Kimberley Oliver and
David W Mudge

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1. Introduction

Kidney transplantation is considered the treatment of choice for patients with end-stage renal disease, and is associated with improved survival, better quality of life and reduced costs when compared with dialysis.[1, 2] However, the renal transplantation waiting list is forever growing, out of proportion to the number of donors.[2, 3] Therefore it is all the more crucial to develop strategies to extend the life and functionality of every allograft.

Rejection is no longer considered as a primarily T-cell-mediated process. We are fast realising that inadequate control of the humoral arm of a recipient's immune system is the pathogenic factor primarily responsible for allograft dysfunction and loss. The destructive power of anti-Human Leucocyte Antigen (HLA) alloantibodies and their association with antibody-mediated rejection (ABMR) has been demonstrated and compelling evidence exists to show that donor-specific anti-HLA antibodies (DSAs) are largely responsible for the chronic deterioration of allografts, and may be a major contributor to the entity of chronic allograft nephropathy (CAN).

ABMR must now be considered to be a spectrum of diseases; which include indolent ABMR, C4d-negative ABMR, and transplant arteriopathy— in which DSAs have significant pathological effect. Also it has been shown that arteriosclerosis is accelerated in ABMR.[4-11]

A dynamic and progressive process of injury and repair that ultimately contributes to failure of the allograft is considered the hallmark of ABMR.[12]

It has been demonstrated that glomerular endothelial swelling, subendothelial widening, and early glomerular basement membrane duplication (precursor lesions) appear in the first weeks after transplantation in a substantial number of crossmatch-positive kidney transplant recipients.[13] Thus suggesting that the process of chronic antibody-mediated changes

(transplant glomerulopathy) may occur earlier than previously reported.[12, 13] In addition, DSAs can emerge at any time after transplantation and need not be present prior to transplantation.[14] Another important issue is that DSAs may differ in terms of their pathogenicity and so have varying prognosis. [14]

Currently, treatment options for ABMR are aimed at antibody reduction and the inhibition of complement activation and injury. These include plasma exchange with low-dose IVIG, high-dose IVIG and rituximab for antibody reduction, and high-dose IVIG for complement and C3 convertase inhibition and the absorption of complement activation fragments (such as C3a, C5a and C4b). Eculizumab (monoclonal anti-C5 antibody) and inhibitors of C1 are likely to show benefit in the prevention and treatment of ABMR.

Advances in B-cell-directed immunotherapeutics will have a considerable impact on DSA production, and consequently ABMR and allograft loss.

This chapter reviews the current understanding of antibody mediated rejection, and details its diagnosis, and treatments, both those established in current routine clinical practice and those on the horizon.

2. Rejection

Over the past two decades, our thinking has changed from considering rejection as a primarily T-cell-mediated process (one that is now increasingly better managed in the era of more potent calcineurin inhibitors and broader use of T-cell depleting therapies), to the realization that insufficient control of the humoral arm of a recipient's immune system by current immunosuppressive regimens is now the pathogenic factor primarily responsible for allograft dysfunction and loss.[13, 15, 16] This has changed our perception about allograft losses which were deemed to be caused by calcineurin inhibitor (CNI) toxicity and chronic allograft nephropathy (CAN).

Furthermore, the growing incidence of transplantation across HLA and ABO barriers by using desensitisation programs, but in the face of known DSAs, has led to increased incidence and a wider variety of ABMR. We are now exposed to a greater spectrum of antibody-mediated graft injury.

3. Donor Specific Antibodies (DSAs)

Great advances have occurred in solid organ transplantation since the pioneering observation of Kissmeyer et al.[17] in the 1960s, of the deleterious impact of allo-antibodies in kidney grafts. About three decades later, the team of Edmonton described rejection episodes following kidney transplantation related to the presence of anti-HLA donor specific antibodies (DSA) [18]. The presence of DSAs and positive crossmatches with donors has long been considered a contraindication to proceeding with transplantation as ABMR and graft loss is highly likely

to occur in such situations[4]. However, recent data by Montgomery *et al.*[19] demonstrated a significant reduction in the risk of mortality among highly sensitized patients who underwent desensitization and transplantation compared with a well-controlled group of patients who remained on dialysis. These authors concluded that desensitization followed by living-donor transplantation offered significant survival benefit and that the survival advantage more than doubled by 8 years.

In addition to DSAs existing prior to transplant, it has been realised that they can emerge at any time after transplant, thus mediating allograft injury [14]. These *de novo* DSAs are different in their pathogenicity. They are active against class II HLA and are associated with a worse prognosis than DSAs against Class I HLA [14].

DSAs can cause all types of ABMR, including chronic ABMR, otherwise known as transplant glomerulopathy.[4, 5, 7-10, 20]

4. ABMR

The pathophysiology of ABMR is not fully understood, but is an area of rapidly expanding research. Several different patterns of allograft injury have been realised. These are initiated by DSAs which bind to HLA antigens or to other targets on the allograft endothelium.

As mentioned earlier, the pathogenicity of DSAs is influenced by the isotype of the heavy chain. Therefore, if DSAs are complement activating (IgG1 and IgG3), by binding IgG and activation of C1q the classic complement pathway is rapidly activated[21] resulting in rapid loss of graft. Alternatively, DSAs can bind to endothelial cell targets and stimulate cell proliferation (NK cells) or induce antibody-dependent cell- mediated cytotoxicity (ADCC) with interferon γ release.[4, 21]

Antibodies can also bind to HLA and other targets and incompletely activate the complement system (that is, no C5b-C9 membrane attack complex generation) without causing apparent injury. This process is referred to as accommodation.[22, 23] In addition, the long-term lack of ADCC may be related to IgG Fc polymorphisms that lead to the failure of activation of NK cells through FcγR (CD16)-dependent pathways[24] thus creating a greater degree of difficulty in assessing pathogenicity of DSAs.

Protocol biopsy studies have shown that substantial oscillations occur in a patient's humoral status during the first 12 months after kidney transplantation. These oscillations are characterized by fluctuations in DSAs, C4d deposition and scores for glomerulitis and/or capillaritis in a dynamic and multidirectional fashion.[12] Hence, the new concept that allograft injury is unlikely the result of a single episode of ABMR, but instead that it represents a dynamic process of injury and repair that begins early after transplantation and continues, unabated, at varying levels thereafter.[3, 12]

The most florid form of ABMR, hyperacute rejection, has been almost completely eliminated, owing to greatly improved crossmatching techniques between recipients and prospective

donors, particularly technologies such as flow-cytometry. These tests are much more sensitive for detecting a problem due to potential DSAs than older methods such as cell-dependent cytotocity (CDC). With the waning of hyperacute rejection, the different manifestations of ABMR that have emerged are indolent ABMR and C4d –negative ABMR.

4.1. Indolent ABMR

Modern therapies can efficiently reverse acute renal dysfunction from ABMR, but they usually fail to deplete antibody-secreting plasma cells from the spleen and bone marrow of allograft recipients.[25] Hence, after a clinical episode of acute ABMR, DSAs remain in circulation and cause slowly progressive microvascular abnormalities without acute compromise of graft function, at least initially. This truncated form of antibody-mediated injury is called subclinical or indolent ABMR. [26, 27]

4.2. C4d-negative disease

In 1991, Feucht and co-workers discovered peritubular capillary deposition of C4d, an inactive product of the classic complement pathway [28] in the histology of cases of ABMR. This greatly improved the understanding and diagnosis of ABMR. It was called the "footprint" of antibody mediated tissue injury. It soon became a requisite to test for C4d in all transplant allograft biopsies. However, it has been recognised over time that C4d may only be the tip of the iceberg of the humoral process and that it was neither completely specific nor sufficiently sensitive for the diagnosis of ABMR[12, 29, 30].

C4d negative ABMR usually occurs more than 12 months after transplantation, but can occur acutely in highly sensitised patients with persistent DSAs (even after desensitisation).

There have been many theories put forth to explain the presence of microvascular inflammation on biopsy and presence of DSAs in circulation, without any evidence of complement deposition. One is the technical issues related to type of fixative used and different methods of C4d detection. Another is that some DSAs are poor at fixing complement. Also, some believe the existence of a complement-independent pathway.[4] Furthermore, it is thought that as a result of treatment of high risk patients, the clinical and histological presentation of ABMR has changed.[3]

4.3. Acceleration of arteriosclerosis

This phenomenon has been recognised for many decades. It is evidenced by monocytic and lymphocytic inflammation of the intima, myofibroblast proliferation and extracellular matrix deposition causing mild to severe intimal arteritis and compromise of the lumen. It is a major component of graft rejection but thought to be cell mediated. However, in 2003 Banff criteria, the v^3 lesions have been classified to reflect probable ABMR. More and more, studies have shown that even v^1 and v^2 lesions occur in ABMR.[31]

Studies suggest that in DSA-positive patients there is significant acceleration of arteriosclerosis.[11] Pathological examination demonstrated that while there is active ABMR, the intima is

hypercellular, laying down new collagen over older (usually originating from donor). Once ABMR is brought under control, the myofibroblasts stop proliferating, and the intima is no longer hypercellular. What is left behind is a lesion no different from simple arteriosclerosis of aging. This is termed "transplant arteriopathy".[11, 32]

Chronic Antibody Mediated Rejection First described in 2001[33], the natural history of chronic humoral rejection is now well known.[12, 29, 34] The presence of DSAs activates the classical complement pathway causing peritubular multilamination and transplant glomerulopathy. These gradually become irreversible and cause permanent graft dysfunction. The main challenges are when to initiate treatment and how to treat it, as it may be too late to slow or halt the progress of this injury.[34, 35]

5. Pathology of antibody-mediated rejection

Antibody-mediated rejection (ABMR) was described in the early 1990s but was not incorporated into the Banff classification until 2001. Now, due to an expanding spectrum of clinical disease, two phenotypes of acute antibody-mediated rejection have been postulated and the chronic form of ABMR is recognized as a leading cause of late allograft failure. The histology of acute and chronic ABMR remains non-specific however.

5.1. Acute antibody-mediated rejection

Three patterns of tissue injury reflect acute antibody-mediated damage. These are acute tubular injury (Figure 1), inflammation of glomerular and/or peritubular capillaries (so-called microcirculation inflammation) (Figure 2 and 3), and fibrinoid necrosis of arteries (v3 lesion) (Figure 4). Microcirculation inflammation may include a TMA-like pattern as well. It is immediately obvious that all three types are not specific for ABMR and may be encountered in a variety of clinical settings in the transplanted kidney. For example, the acute tubular injury pattern is similar to that produced by ischaemia and capillaritis can be seen in the setting of acute tubular necrosis or acute cellular rejection.

For these reasons, it was recommended that histology be correlated with C4d immunomicroscopy and donor-specific antibodies (DSA) status. The former is an inactive fragment, split from its parent molecule C4b during activation of the classical complement pathway, but due to covalent binding with the endothelium, able to persist at sites of complement activation. This covalent binding can be demonstrated with immunoperoxidase or immunofluorescent (Figure 5 and 6) techniques and serves as a marker of complement activation. Neither method is sensitive enough to detect all cases of ABMR.

A positive C4d result on renal biopsy shows linear, circumferential endothelial reaction in peritubular capillaries by either method, although the immunoperoxidase signal may be less intense by one grade. Interrupted, granular deposition is considered non-specific. Diffuse and focal linear reaction in peritubular capillaries appears to correlate with glomerulitis and presensitization [36], however an important caveat is the ABO-incompatible renal allograft. In this situation, diffuse linear C4d may be seen in the absence of tissue injury and graft dysfunction.

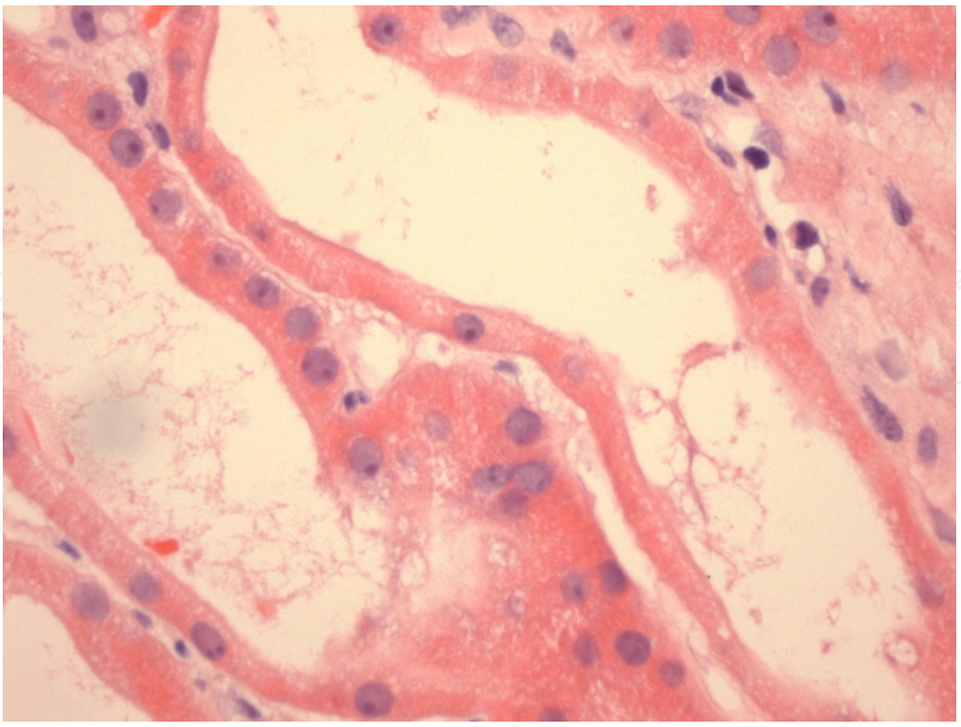

Figure 1. Acute tubular necrosis (ATN) in acute ABMR

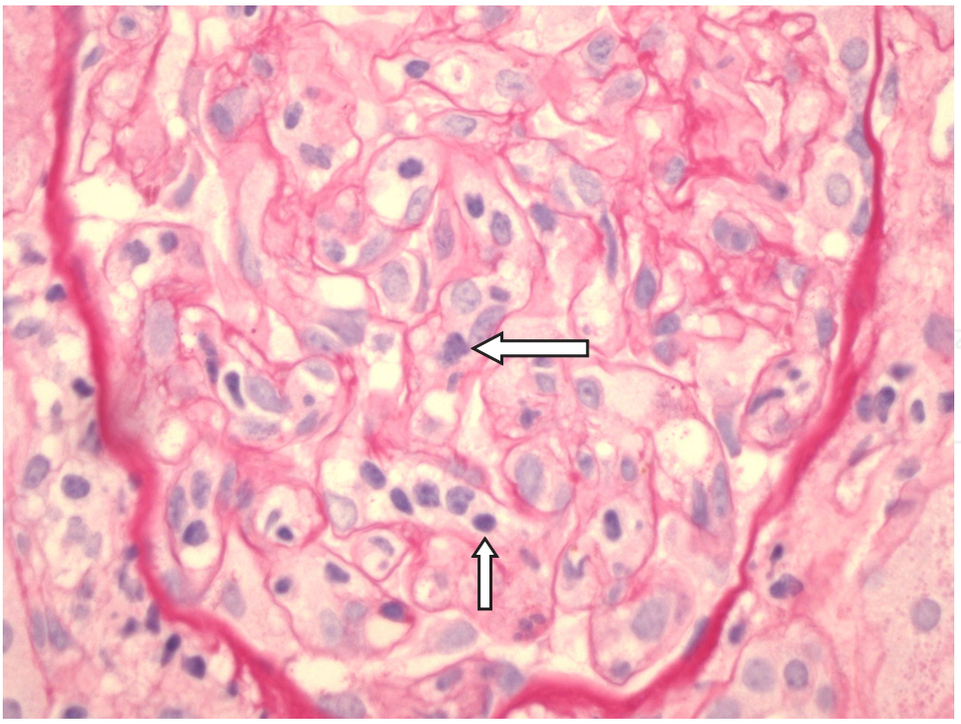

Figure 2. Glomerulitis (infiltration of capillary loops by monocytes [white arrows])

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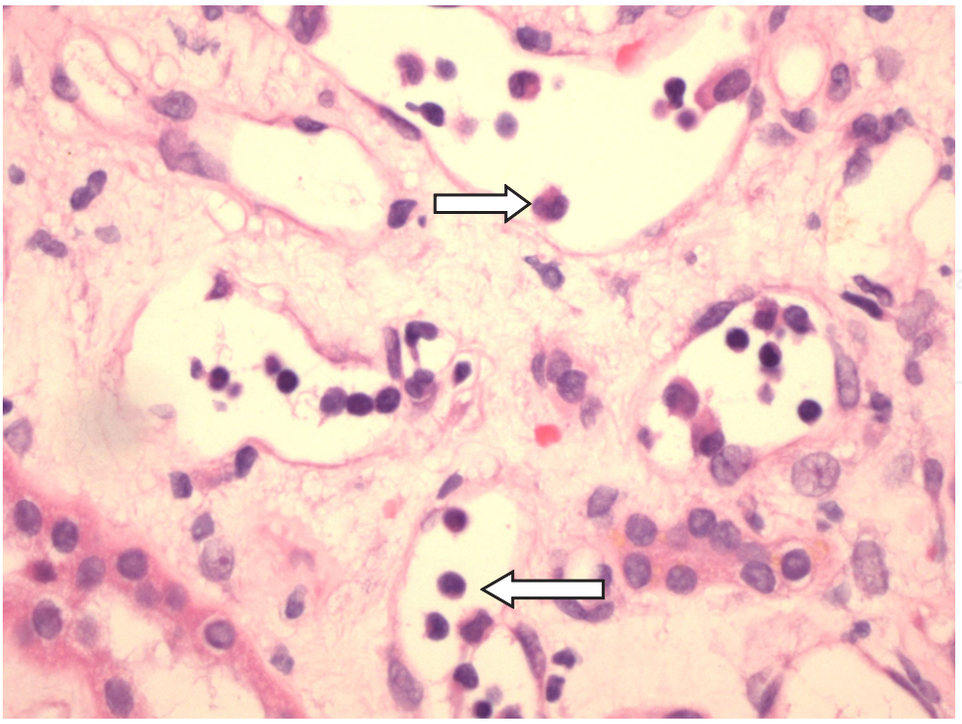

Figure 3. Peritubular Capillaritis (dilatation of capillaries and margination of monocytes [white arrows])

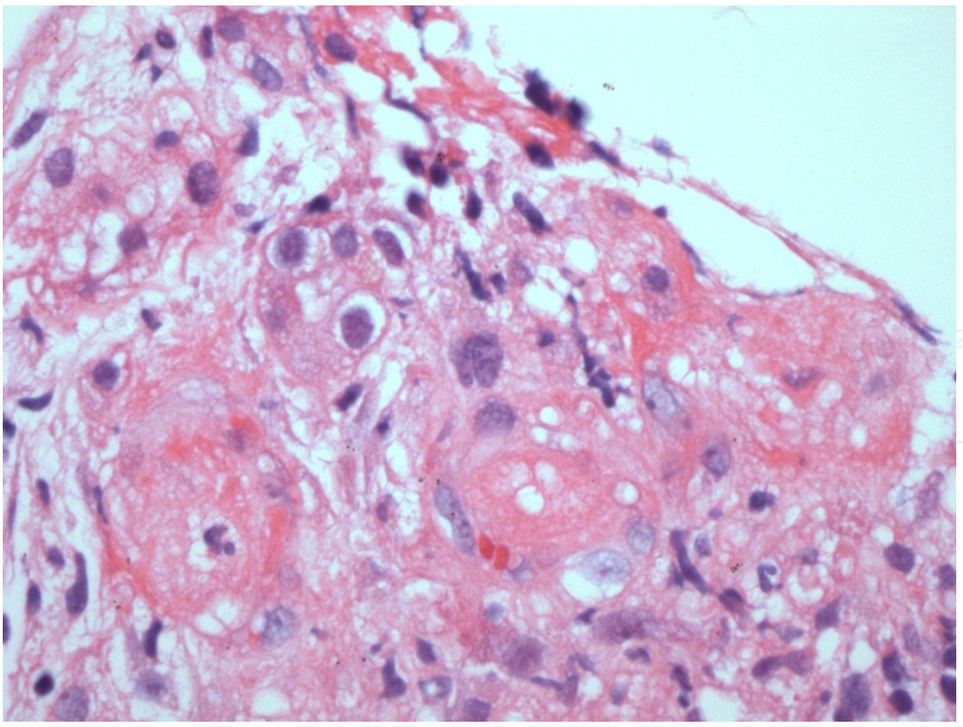

Figure 4. Fibrinoid necrosis of small arteries (v3 lesion)

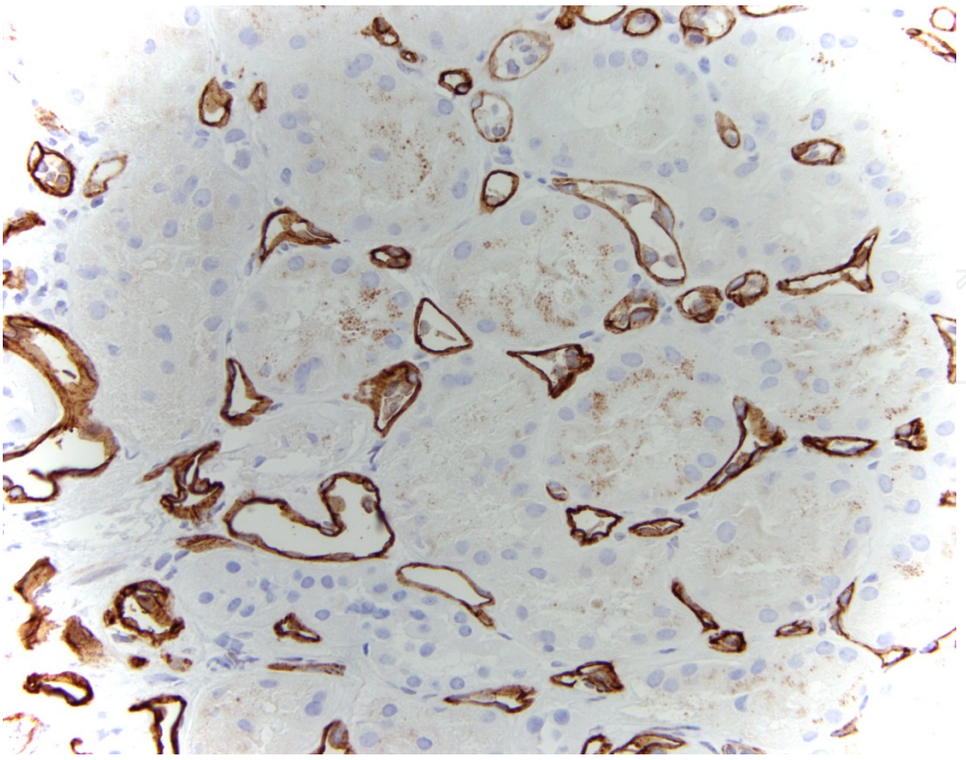

Figure 5. Diffuse C4d staining (immunoperoxidase method)

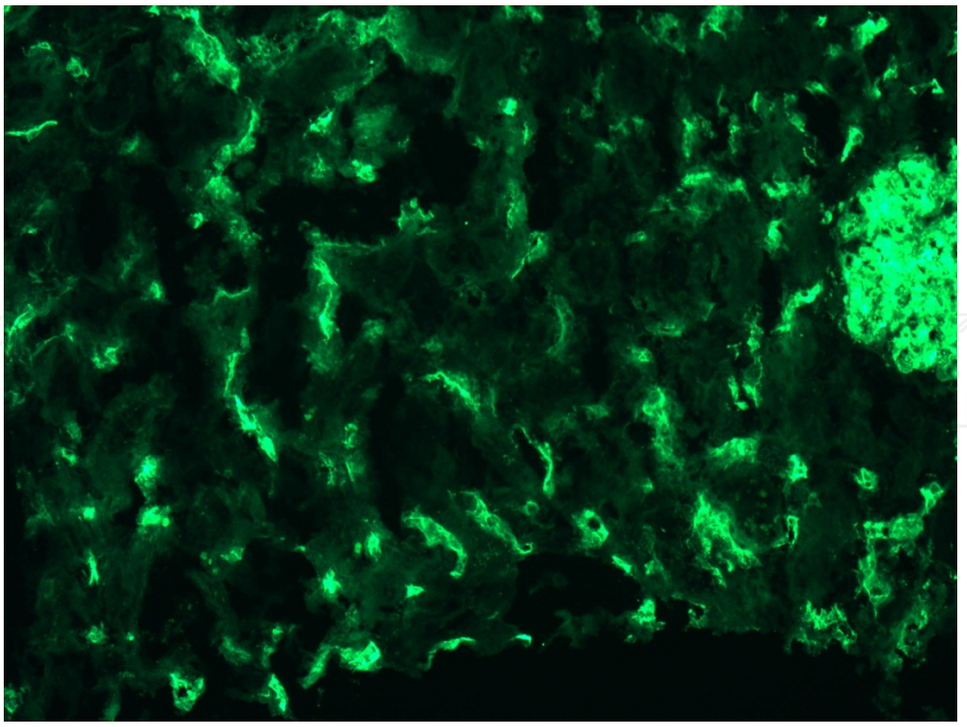

Figure 6. Diffuse C4d staining (immunofluorescence method)

The most recent Banff meeting update highlights two major phenotypes of ABMR. The first type appears early in the post-transplant period in a presensitized patient and is more likely to be C4d-positive. The second type develops late post-transplant, is due to de novo DSA development and is likely to be C4d-negative [36]. The second phenotype is an important factor in late graft loss[37]. It appears that Class II HLA molecules may be responsible and that much of the endothelial damage is mediated by NK cells and, to a lesser extent, monocytes and neutrophils (antibody-dependent cell-mediated cytotoxicity (ADCC) [38].

5.2. Chronic antibody-mediated rejection

Microcirculation Injury

The term "chronic ABMR" does not relate to a particular time post-transplantation, but rather to architectural remodelling which can affect all compartments of the biopsy. In addition, active ABMR may be superimposed on these changes. (Figure 7)

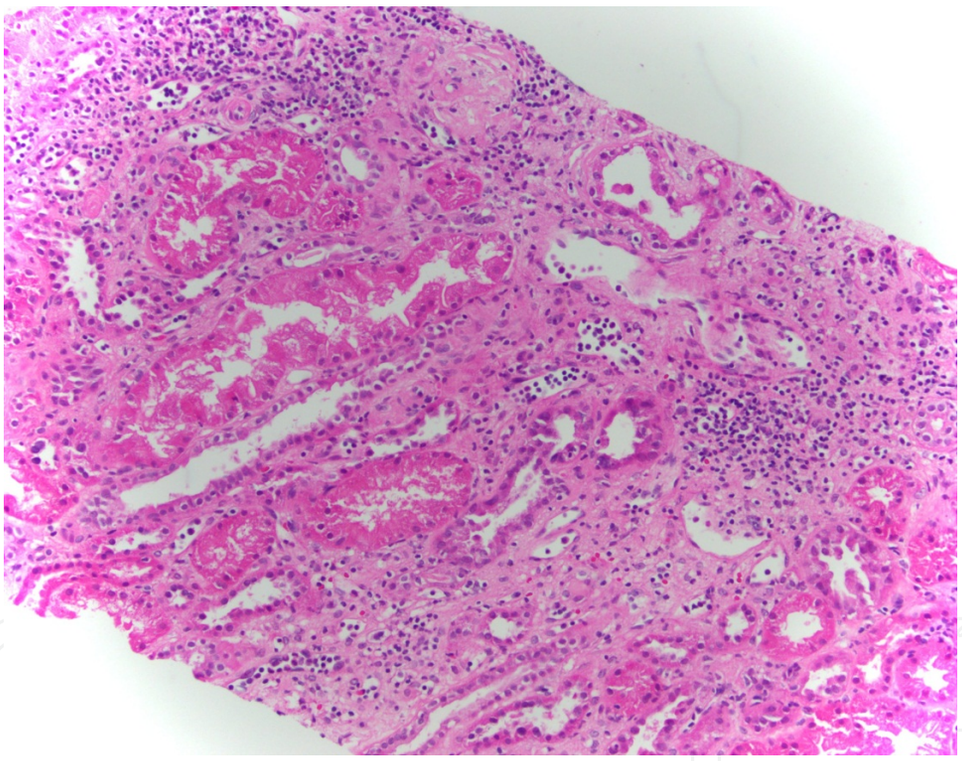

Figure 7. Active chronic ABMR. Severe peritubular capillaritis is seen in the setting of interstitial fibrosis (ci) and tubular atrophy (ct)

The hallmarks of chronic ABMR are transplant glomerulopathy (TG) and multilayering of peritubular capillary basement membranes, with or without transplant arteriopathy (TA) and interstitial fibrosis and tubular atrophy, indicating that the microcirculation is the main target of humoral attack. Transplant glomerulopathy manifests as double contours in silver-stained sections and is well demonstrated by electron microscopy (figure 8). There is widening of the subendothelial space by flocculent material and eventual duplication of the glomerular

basement membrane. It has been shown in protocol biopsies that ultrastructural changes of endothelial cell injury such as cell activation and loss, can be detected within weeks of transplantation [39], pre-dating more permanent changes like mesangial matrix expansion and glomerular basement membrane duplication.

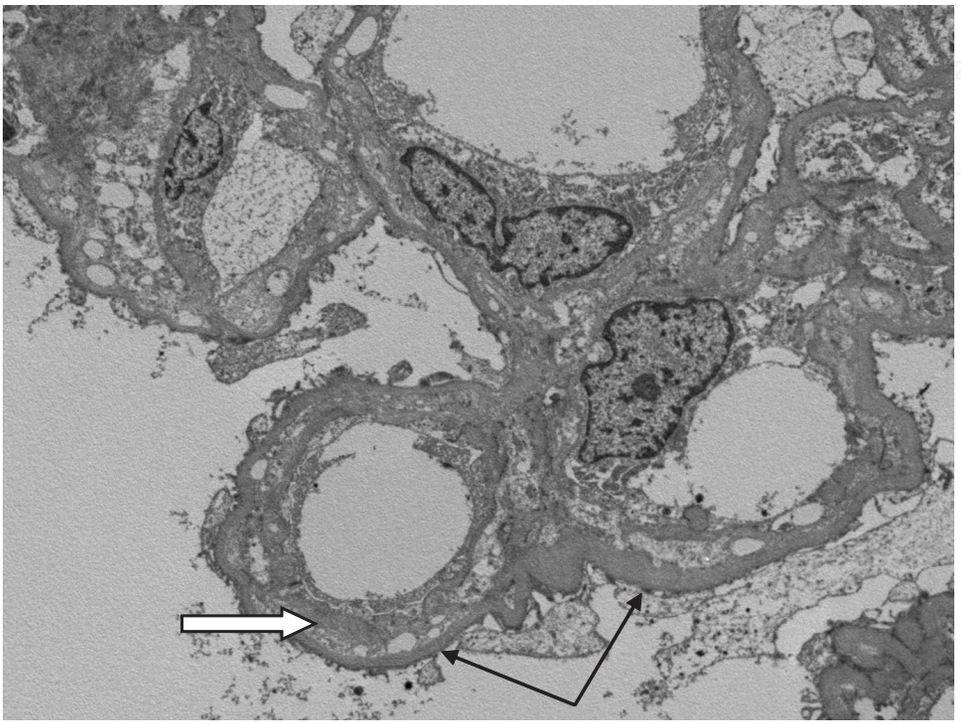

Figure 8. Electron microscopy showing a widened subendothelial space containing flocculent material (thick arrow). Duplication of the glomerular basement membrane is present (thin arrows).

Despite its close correlation with DSA, TG may not be specific for chronic ABMR, with significant numbers of TG cases reportedly due to hepatitis C and thrombotic microangiopathy [40]. Superimposed active antibody-mediated injury produces endocapillary proliferation and, together with double contour formation, a mesangiocapillary-like pattern in glomeruli (Figure 9). This is not accompanied by immunofluorescence findings typical of that type of glomerulonephritis and no diagnostic deposits are seen by electron microscopy.

The endothelium of peritubular capillaries can also display early ultrastructural evidence of damage before remodelling of the basement membrane occurs. Moderate to severe lamination (>5 layers of basement membrane) is seen in chronic ABMR whereas mild lamination (2-5 layers) may be due to causes other than antibody-mediated rejection in the transplant kidney and is also seen in native renal disease [39].

A study by Sis and co-workers [41] found that approximately 40% of cases with transplant glomerulopathy were C4d negative despite having circulating antibodies and showing high endothelial cell-associated transcript (ENDAT) expression. ENDATs represent altered gene expression due to the effects of alloantibody and are thought to be a sensitive indicator of ABMR. This same study reported a high percentage of graft loss when both antibodies and

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high ENDAT expression were present; graft loss was even higher when the biopsies showed diffuse C4d positivity as well. Although currently experimental, the detection of high ENDAT expression may prove useful in cases with circulation DSA and C4d-positivity on biopsy but lacking histologic evidence of tissue damage.

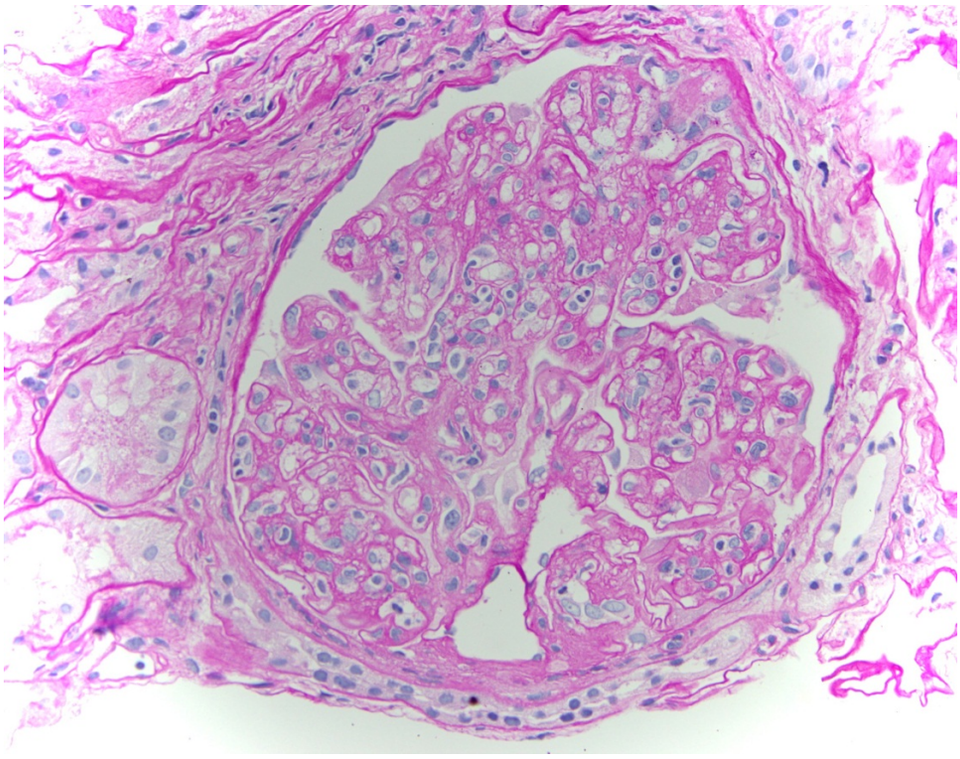

Figure 9. Active chronic ABMR. Glomerulitis is superimposed on changes of transplant glomerulopathy.

Vascular lesions

The lesion of Transplant Arteriopathy TA is characterized by expansion of the arterial intima by fibrous tissue and a variable amount of inflammation. Originally, TA was attributed to chronic T-cell mediated rejection (TCMR) but it more likely reflects generalized scarring seen in the aging kidney allograft, the causes of which include ABMR. A percentage of v1 and v2 lesions, also previously thought to be result of TCMR, may also be associated with DSA and microcirculation injury [31].

Scarring and hyalinosis

A cluster analysis of 234 indicated renal allograft biopsies by Sis and co-workers [31] revealed an association amongst arteriolar hyalinosis (ah), interstitial fibrosis (ci), tubular atrophy (ct) and transplant arteriopathy (cv). In the past, these features were thought to be the result of chronic calcineurin inhibitor use but it appears that they are non-specific and may be encountered in a variety of settings in the renal allograft, including ABMR. Arteriolar hyalinosis, in particular, is commonly encountered in the aging kidney, hypertensive nephrosclerosis and diabetic nephropathy.

6. Treatment

There has been significant development of newer and more specific therapies for ABMR. These are aimed at depleting B cells, antibodies and inhibiting complement, owing to the unique role of antibody and effector molecules in the process of ABMR. The therapeutic options include intensification of maintenance immunosuppression (e.g. tacrolimus and mycophenolate), plasmapheresis/plasma exchange, intravenous immunoglobulin (IVIg), corticosteroids and antilymphocyte antibodies. Rituximab, splenectomy, bortezomib, and eculizumab have also emerged as adjunctive or experimental therapies.

6.1. IVIg

The mechanism of action and the optimal dose of IVIg that should be administered in ABMR are poorly understood.[42], but it is thought to have an immunomodulatory effect. The proposed beneficial properties include compliment inhibition, suppression of immunoglobulin synthesis.[43, 44] High dose IVIg inhibits C3 convertase and the ability to absorb complement activation fragments (e.g. C3a,C5a and C4b).[45]

There have been retrospective studies reporting improved one year graft survival in cases of steroid and antithymocyte resistant ABMR treated with protocols incorporating IVIg and plasmapheresis/ plasma exchange.[46-49] The need to combine plasma exchange is however, unclear.[42]

6.2. Plasma exchange/plasmapheresis

Plasma exchange removes antibodies from the circulation. In the case of ABMR it is thought to be efficacious through the removal of DSAs. However, it does not suppress further production. In fact, it may stimulate rebound immunoglobulin production if used on its own. It is hence necessary to use it in conjunction with strategies which target antibody production (for example, the anti-CD20 monoclonal antibody rituximab). ABMR treatment protocols may utilise plasma exchange depending upon the antibody titre, the affinity of the antibody for the antigen, the dose of IVIg and use of other agents.[42]

6.3. Rituximab

This is a humanised mouse monoclonal antibody that targets CD20, which is expressed on the majority of B cells. However, most plasma cells lack CD20 and are unaffected by Rituximab. Hence, its role will be as an adjunctive treatment. A recent single centre study compared outcomes in 24 cases of ABMR treated with either high dose IVIg (2g/kg for four doses) versus plasmapheresis plus IVIg (100mg/kg) for four treatments followed by IVIg (2g/kg for four doses) and two doses of rituximab (375mg/m2). Improved 3-year survival (92% vs. 50%) and significantly reduced DSA at 3 months was observed in the plasmapheresis/IVIg/rituximab group.[6] It has also been seen to be effective when used as part of desensitization protocol in ABO- incompatible (ABOI) transplants, although there is concern over the cost of increased infections in recipients of such transplants. One study reported \patients who received B-cell

depletion with rituximab as an induction agent had significant reductions in DSA generation and rates of chronic transplant glomerulopathy over 5 years compared with ABO-compatible low-risk transplant recipients who did not receive rituximab.[50]

6.4. Eculizumab

Drugs that inhibit compliment and C1 are likely to show benefit in the prevention and treatment of ABMR and currently they are many human trials being conducted to evaluate their effect.[3, 51]

Eculizumab is an antibody against complement protein C5, and hence, inhibits the formation of the membrane attack complex (MAC). It is approved for use in paroxysmal nocturnal hemoglobinuria (PNH) and has had promising results in treatment and ongoing management of atypical haemolytic uraemic syndrome, for which it has also recently been approved for use. It is, however, and extremely expensive therapy. A single case reported the use of eculizumab in combination with plasmapheresis/IVIg to rescue a renal allograft undergoing severe ABMR, and showed significant reduction in C5b-C9 (MAC) complex deposition in the kidney.[52]

6.5. Splenectomy

The role of splenectomy in treating ABMR is not yet known. Case reports have demonstrated that it may be useful as a rescue treatment in severe ABMR.[53] Majority of its use has been in preventing hyperacute rejection in ABOI transplants [54, 55]. There remains concern over the increased infection risk in splenectomised patients, particularly due to encapsulated organisms, and vaccination against Meningococcus and Pneumococcus is warranted where possible prior to splenectomy to mitigate this risk.

7. Conclusion

Significant progress has occurred in the understanding of ABMR. Diagnosis, classification and treatment of this process have evolved greatly. However, standardisation of diagnostic tests (DSA-testing), and development of evidence-based treatment guidelines is still lacking. Currently, protocols are individualised among different centres and based largely on anecdotal and/or local experience. ABOI and HLA desensitisation protocols (not detailed in this chapter) also need to gain excellent long term results to justify the tremendous cost involved in order to reduce the growing number of sensitised potential recipients on the waiting list. Paired donor exchange programs, although fraught with major logistic as well as some ethical and occasionally legal concerns, may be part of the solution to provide allografts to some of these difficult-to-transplant individuals in order to improve their quality and quantity of life. Such recipients, after successful transplantation, will be at increased risk of ABMR and will need good monitoring and treatment strategies to enable successful long-term outcomes.

Author details

Siddharth Sharma[1], Kimberley Oliver[2] and David W Mudge[1]

*Address all correspondence to: siddharth_sharma@health.qld.gov.au

1 University of Queensland at Princess Alexandra Hospital, Queensland, Australia

2 Department of Anatomical Pathology, Princess Alexandra Hospital, Queensland, Australia

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