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Antibody Mediated Rejection in Kidney Transplant Recipients

Nika Kojc and Željka Večerić Haler

Abstract

Antibody mediated rejection (ABMR) presents a significant challenge for long term graft survival in kidney transplantation. New technologies, including genomic studies and assays to detect and define donor-specific antibodies, have provided important insights into the pathophysiology and diagnosis of ABMR. Unfortunately, this progress has not yet translated into better outcomes for patients, as in the absence of a drug able to suppress antibody generation by plasma cells, available therapies can only slow down graft destruction. This chapter reviews the current understanding of ABMR, and details its diagnosis, and treatments, both those established in current routine clinical practice and those on the horizon.

Keywords: antibody mediated rejection, humoral rejection, kidney rejection, kidney transplantation, kidney transplant rejection, donor specific antibodies

1. Introduction

Antibody-mediated rejection (ABMR), also termed humoral rejection, is one of the most important causes of allograft dysfunction and loss accounting for up to 76% of death-censored graft failures beyond the first year of transplantation [1, 2]. According to current evidence, B cell and plasma cell activation results in the generation of donor-specific antibodies (DSAs), which bind to human leukocyte antigen (HLA) or non-HLA molecules expressed on endothelial cells within the renal allograft [3].

ABMR often represents a pathological spectrum that co-exists with T-cell-mediated rejection [3]. Active (acute) ABMR is characterized by serological evidence of DSA, peritubular capillaritis, glomerulitis, cellular necrosis, thrombotic microangiopathy, and a relatively rapid decline in allograft function. The response to currently available therapies is often favorable. Chronic ABMR, on the other hand, is characterized by transplant glomerulopathy, a distinct pathophysiological process resulting from a repetitive pattern of thrombotic events and inflammatory changes that lead to endothelial cell injury and allograft matrix remodeling. It usually results in a slow and progressive decline in renal function, unlikely to be reversed by current therapeutic strategies [3, 4].

2. Pathogenesis

In the 1960 Kissmeyer et al. [5] were the first to observe the deleterious impact of allo-antibodies in kidney grafts. Since then great advances have

occurred in solid organ transplantation. Nowadays, it is believed that immunologic reactions associated with ABMR can be triggered by circulating antibodies against donor HLA, non-HLA or ABO antigens, i.e. donor specific antibodies (DSAs) [6].

DSAs are most commonly directed against human leukocyte antigen (HLA)/major-histocompatibility-complex (MHC) class I and II antigens [7]. HLA class I antigens are expressed on all nucleated cells, whereas HLA class II antigens are restricted to antigen-presenting cells (B lymphocytes, dendritic cells) and endothelial cells [8]. In addition to DSAs existing prior to transplant due to recipient sensitization (pregnancy, blood transfusions, and previous transplantation), it has been realized that they can emerge at any time after transplant, thus mediating allograft injury [9, 10]. These *de novo* DSAs are different in their pathogenicity. Those directed against class II HLA are associated with a worse prognosis than DSAs against class I HLA [10].

However, the antibodies can also be directed against other donor specific antigens such as MHC-class I-related chain A (MICA) antigens, MHC-class I-related chain B (MICB) antigens, platelet-specific antigens, molecules of the renin-angiotensin pathway, and polymorphisms involving chemokines and their receptors [11–13]. MICA antigens are expressed on endothelial cells, dendritic cells, fibroblasts, epithelial cells, and many tumors, but not on peripheral-blood lymphocytes [12].

The major mechanism involved in antibody-mediated kidney injury is activation of the classical complement pathway by the binding of DSA to HLA and subsequent binding of the C1 complex, which ultimately leads to formation of the membrane attack complex (C5b-C9) (Figure 1) [14, 15].

This leads to activation of polymorphonuclear inflammatory cells, NK cell and monocyte recruitment and inflammation, as well as activation of the coagulation cascade, which in turn leads to widespread microvascular injury evident as peritubular capillaritis, glomerulitis and microvascular thrombosis. B-cell responses against MHC antigens are T-cell dependent and require the involvement of antigen-presenting cells and costimulatory molecules such as CD40 ligand or soluble interleukins. These responses take 2–3 weeks to develop and lead to immunologic memory, allowing a more efficient antibody response upon repeat stimulation. Eventually transplant glomerulopathy develops (chronic phase) due to recurrent injury and repair with glomerular basement

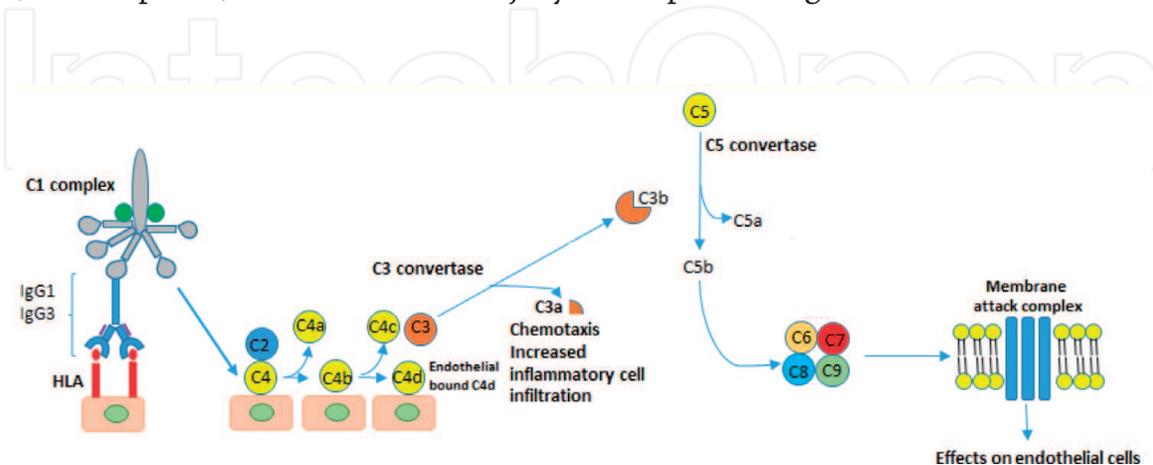


Figure 1.

Activation of classical complement pathway in ABMR in renal transplant recipients. Following binding of DSA to the vascular endothelium of kidney allograft, the C1 complex activates the serine esterases C1s and C1r, resulting in the cleavage of C4, deposition of C4d, and the assembly of the classical pathway C3 convertase. C3 convertase cleaves C3 into C3a, a potent pro-inflammatory mediator, and C3b, which propagates the complement cascade and leads to the formation of the pro-inflammatory mediator C5a and the membrane attack complex (C5b-C9). For more details, see Stegall et al. [15] ABMR-antibody-mediated rejection; DSA-donor-specific antibody; HLA-human leukocyte antigen.

membrane remodeling, mesangial matrix expansion, capillary obliteration, foot process effacement [15]. Microcirculation remodeling at the level of peritubular capillaries progresses to interstitial fibrosis and tubular atrophy causing allograft failure.

3. Diagnostic criteria for antibody mediated rejection

3.1 Histopathological features

By light microscopy, active antibody mediated rejection is characterized by 3 types of tissue injury: acute tubular injury, microcirculation inflammation with neutrophils and mononuclear cells in glomeruli and peritubular capillaries, and fibrinoid necrosis of arteries (**Figure 2**) [14].

Acute tubular injury includes loss of brush borders, thinning of tubular epithelial cells cytoplasm, shedding of tubular epithelium, and focal loss of nuclei (**Figure 3**). Focal necrosis of tubules can be found in minority of cases. In addition to oedema without significant interstitial infiltrate, proximal tubules express HLA-DR (**Figure 4**). Microcirculation inflammation with neutrophils and mononuclear cells in glomeruli and peritubular capillaries appears as glomerulitis and peritubular capillaritis. Glomerular capillaries are dilated and filled with swollen endothelial cells and inflammatory cells (**Figure 5**). In severe cases, glomerular capillary thrombosis can be detected (**Figure 6**). In glomerular injury due to ABMR usually predominates macrophages which express CD68 and neutrophils.

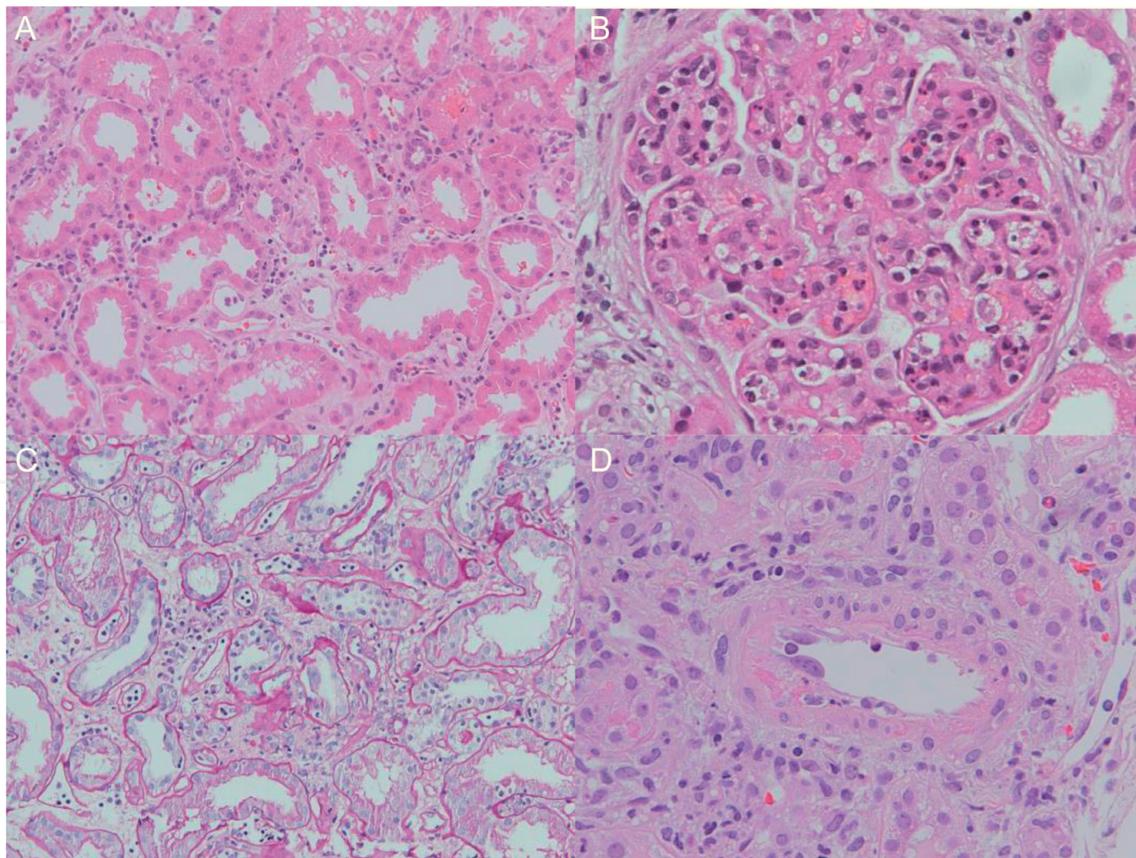


Figure 2. Features of active antibody mediated rejection: Acute tubular injury [(A) hematoxylin-eosin stain (HE), 200×], microcirculation inflammation with neutrophils and mononuclear cells in glomeruli-glomerulitis [(B) HE, 400×] and peritubular capillaries-peritubular capillaritis [(C) HE, 200×], and fibrinoid necrosis of artery [(D) HE, 200×].

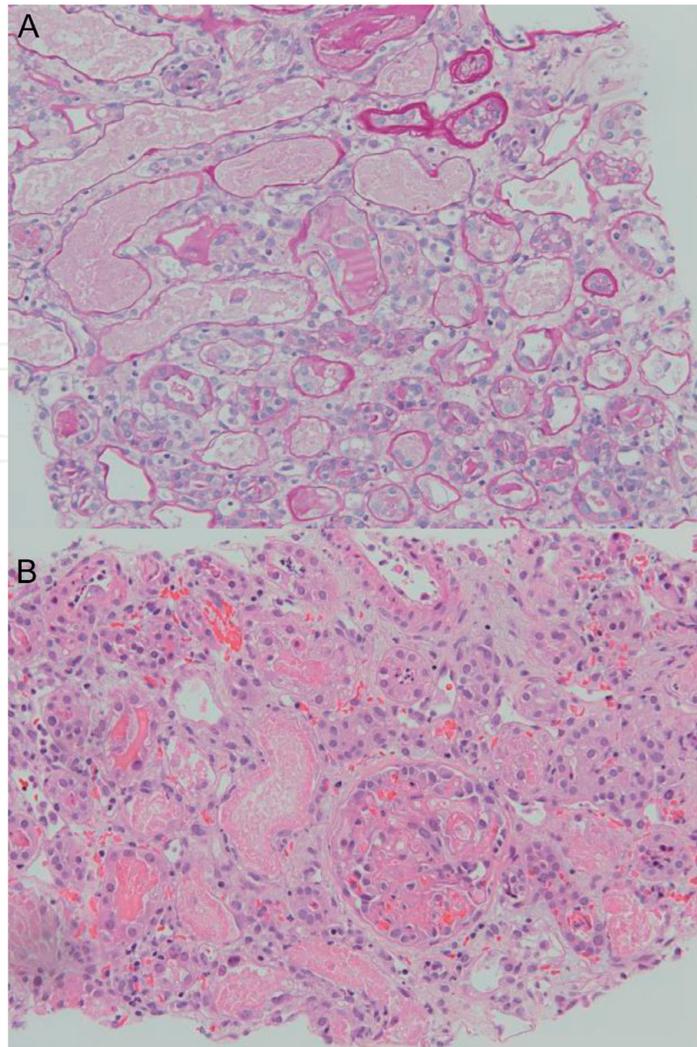


Figure 3. Acute tubular injury/necrosis accompanied by interstitial edema in active antibody mediated rejection [(A) periodic-acid Schiff (PAS), 100 \times]. Acute tubular injury/necrosis and glomerular capillary necrosis [(B) HE, 100 \times].

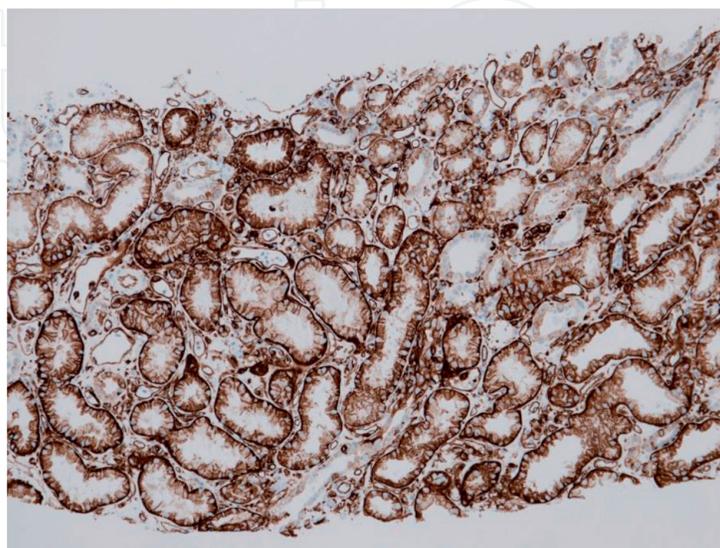


Figure 4. Diffuse HLA-DR positivity in proximal tubules in active antibody mediated rejection (immunohistochemistry, HLA-DR, 100 \times).

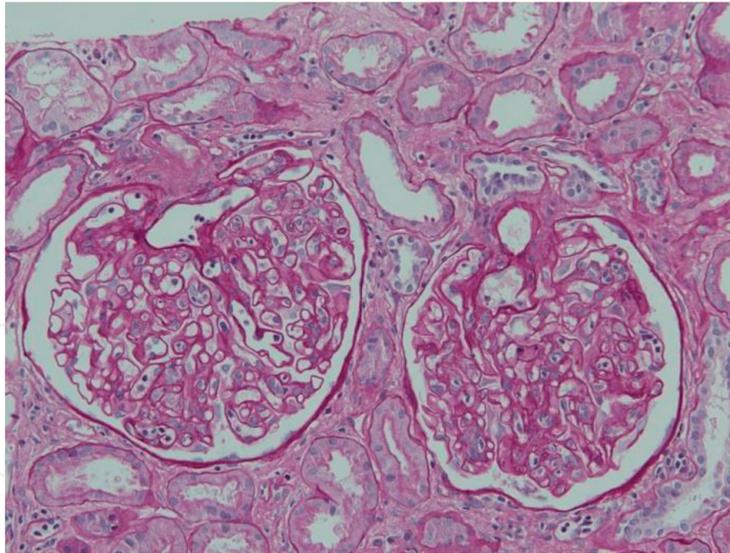


Figure 5.
Focal glomerulitis in active antibody mediated rejection-Banff score g3. Dilated glomerular capillaries are filled with swollen endothelial cells and inflammatory cells (PAS, 200×).

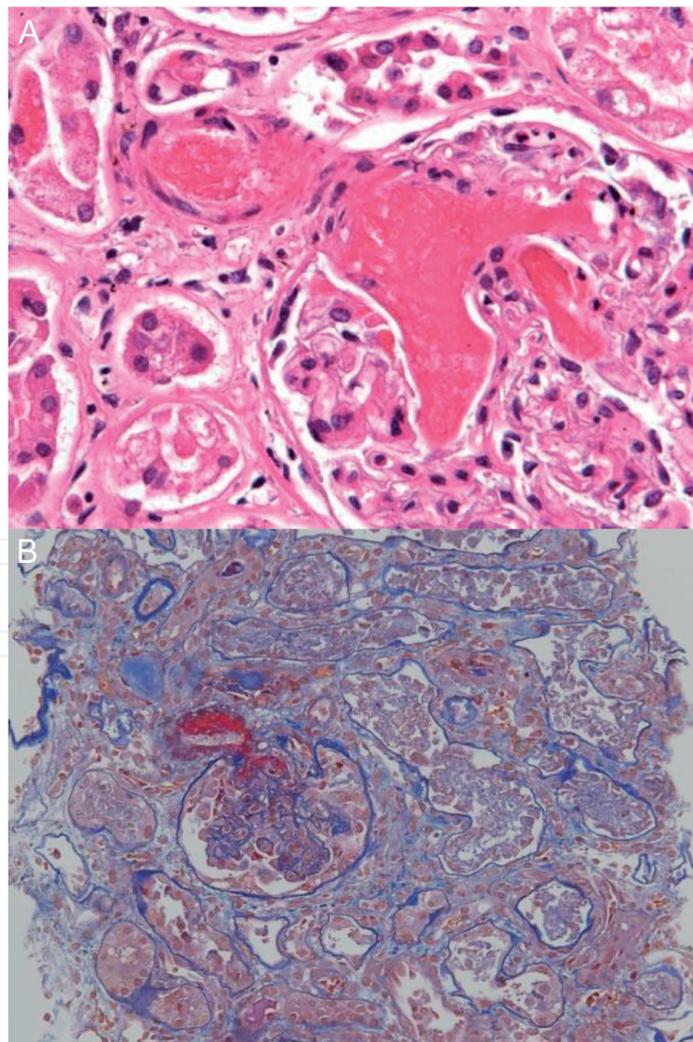


Figure 6.
Glomerular capillary thrombosis [(A) HE, 400×] and fibrinoid necrosis of hilar arteriole [(B) trichrome stain, 200×] in severe active antibody mediated rejection.

Cortical peritubular capillaries are dilated and filled with numerous inflammatory cells and sometimes focal interstitial hemorrhages are found (**Figure 7**). Presence of neutrophils in dilated peritubular capillaries may be associated with class I DSA and hyperacute rejection. Immunohistochemistry and immunofluorescence revealed diffuse linear positivity of C4d along peritubular capillaries in the

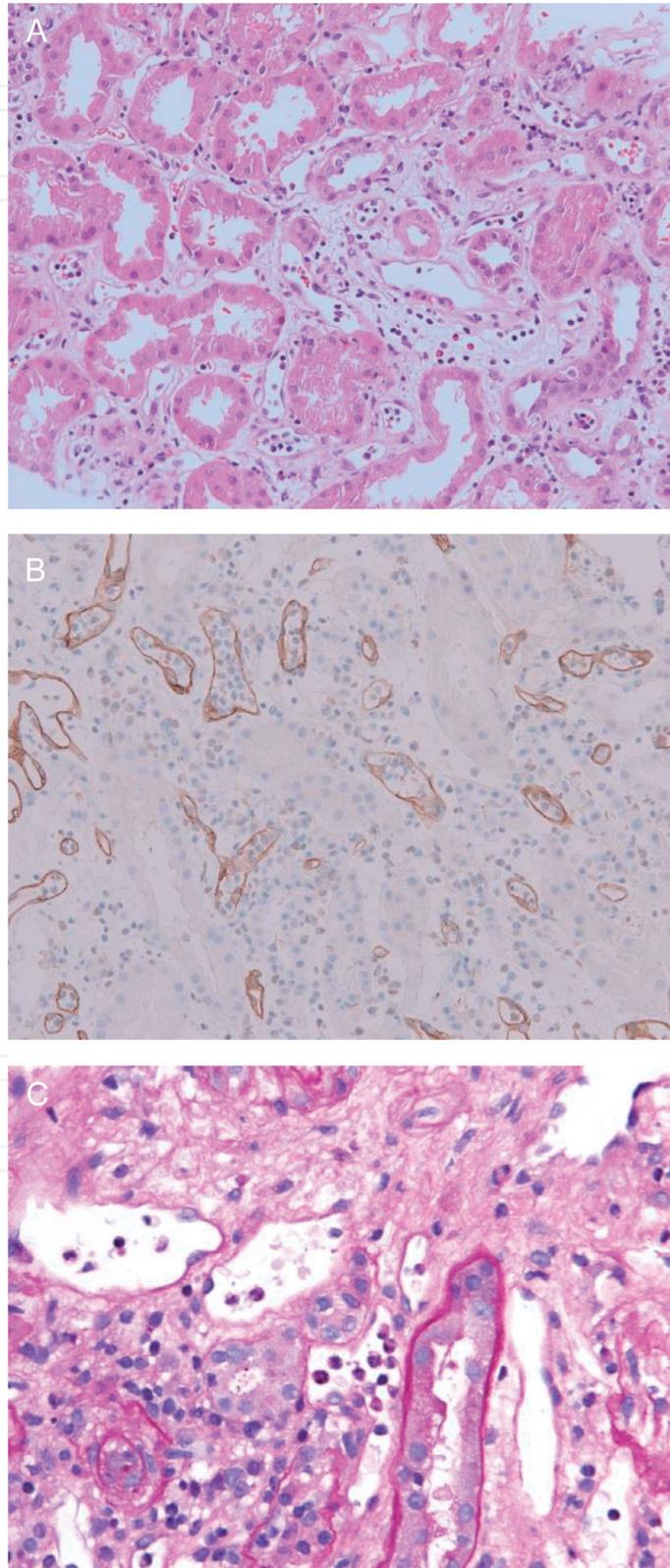


Figure 7. Diffuse peritubular capillaritis in active antibody mediated rejection-Banff score ptc3 [(A and B) HE and immunohistochemistry, C4d, 200×]. Neutrophils in peritubular capillaries in severe active antibody mediated rejection [(C) HE, 400×].

cortex and medulla (**Figure 8**). Dilated vascular spaces in the area between cortex and medulla should not be assessed as peritubular capillaritis, since those vascular spaces represent increased turnover between cortex and medulla not related to

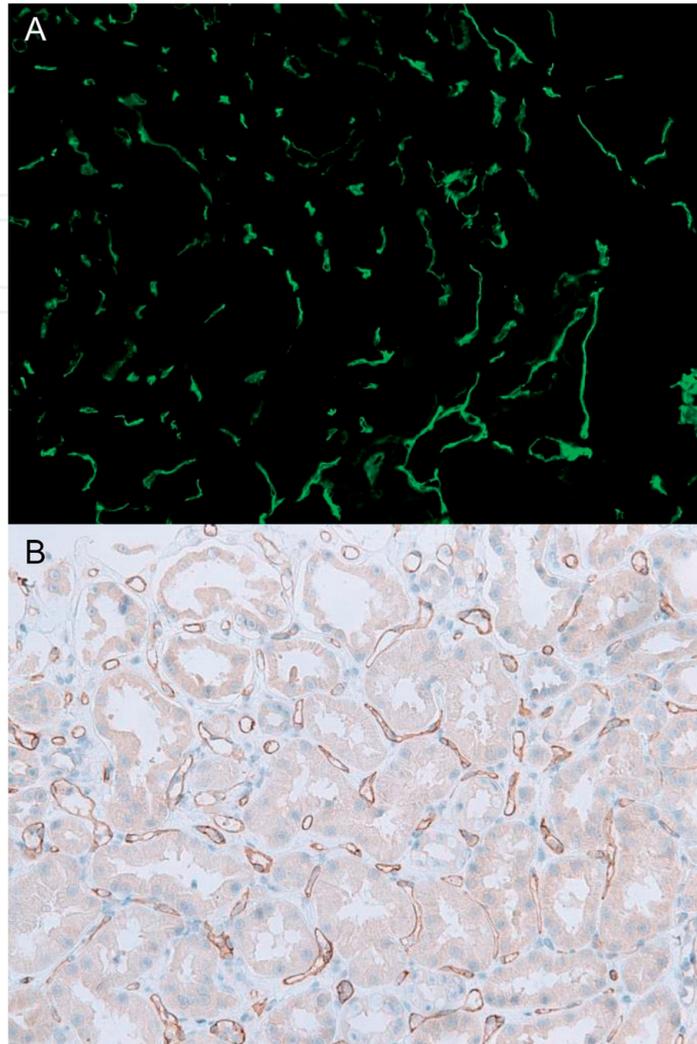


Figure 8. Diffuse C4d positivity in active antibody mediated rejection (Banff score C4d 3) by immunofluorescence [(A) 200 \times] and immunohistochemistry [(B) 200 \times].

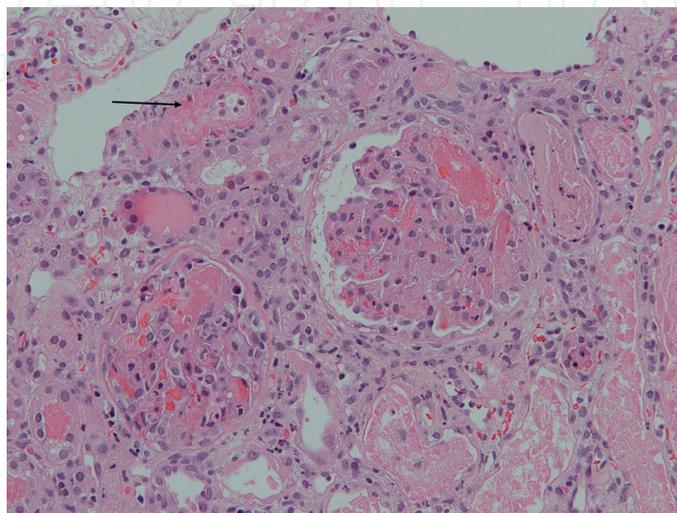


Figure 9. Fibrinoid necrosis in small interlobular artery-Banff score v3 in severe active antibody mediated rejection (arrow). Glomerular capillary thrombosis and acute tubular necrosis are also seen (HE, 200 \times).

rejection. Interstitial oedema and hemorrhage may be prominent. B cells can be found in aggregates, and plasma cells can be detected, but interstitial infiltrate does not fulfill criteria for T-cell mediated rejection.

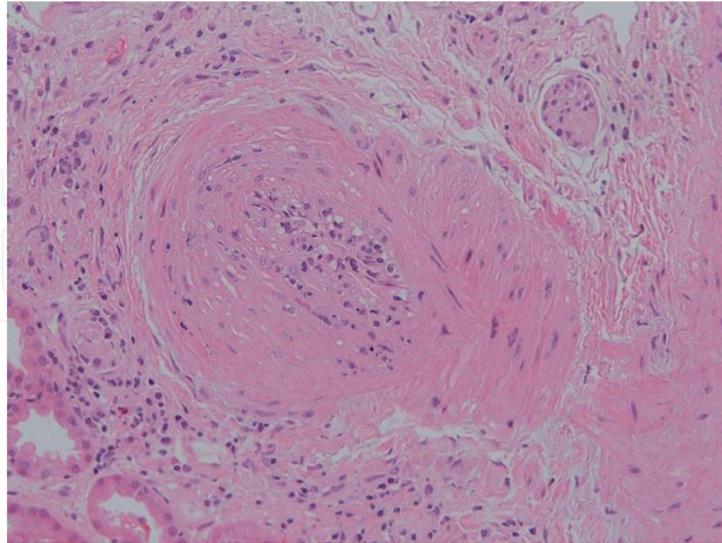


Figure 10.
Chronic active vascular rejection with intimal endarteritis and intimal fibrosis. HE, 200 \times .

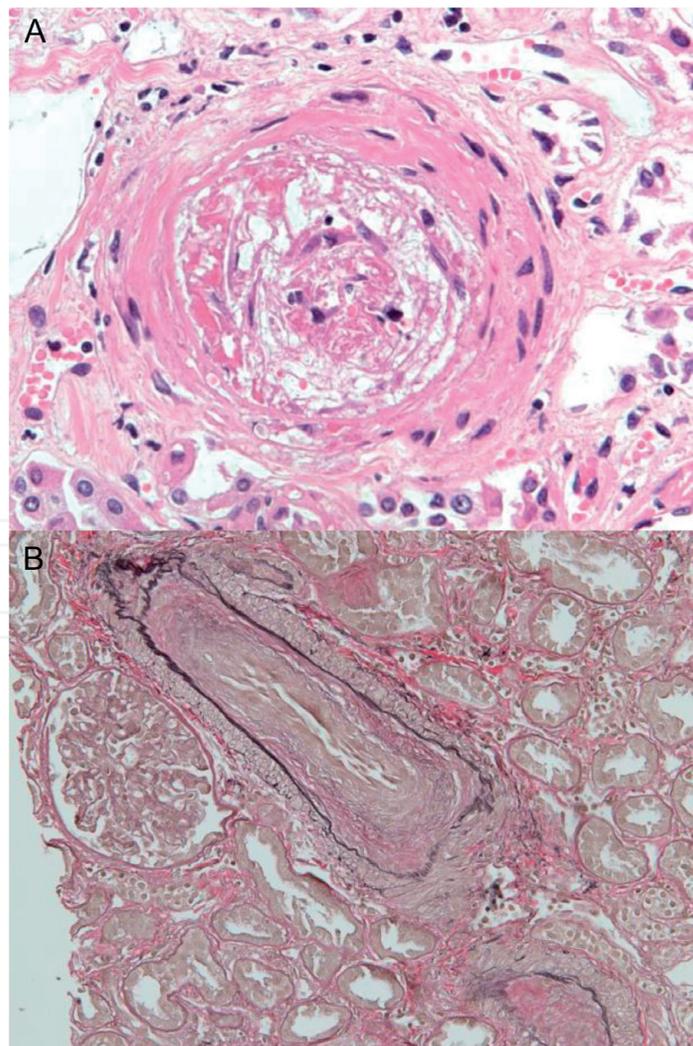


Figure 11.
*Acute vascular thrombotic microangiopathy in active antibody mediated rejection [(A) HE, 200 \times].
Chronic glomerular and vascular thrombotic microangiopathy in chronic active antibody mediated rejection [(B) Weigert stain (W), 100 \times].*

In about 25% of cases with ABMR, small interlobular arteries show myocyte necrosis, fragmentation of elastica, and accumulation of eosinophilic material termed fibrinoid necrosis (**Figure 9**). There is usually only scant mononuclear infiltrate in the intima and adventitia. Some arteries may show transmural arterial inflammation without fibrinoid necrosis reminiscent of T-cell mediated vascular rejection (**Figure 10**). Whether the cellular component of

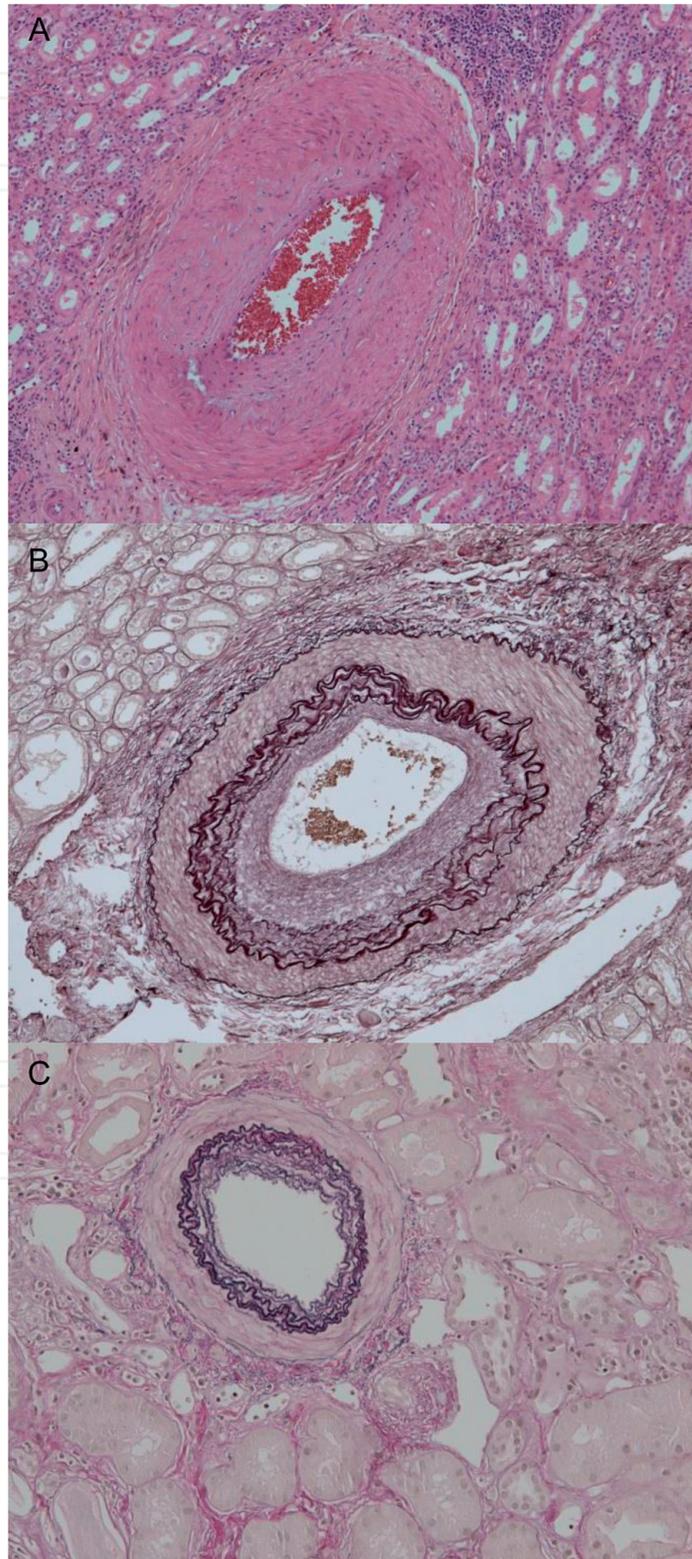


Figure 12. Chronic burn out vascular rejection without intimal infiltrate in arcuate artery-Banff score cv3 [(A) HE, 100 \times]. Intimal fibrosis due to chronic rejection is superimposed on fibroelastic lamellation associated with arterial hypertension [(B) W, 100 \times]. Artery with elastic duplication due to arterial hypertension without rejection [(C) W, 100 \times].

transplant endarteritis in ABMR is different from that due to T-cell mediated rejection is not apparent. Arterial thrombosis is uncommon. However, acute ABMR may also manifest as TMA affecting glomerular and vascular endothelium (**Figure 11**). TMA is characterized by bloodless glomeruli with swollen endothelium and mucoid intimal thickening and trapped red cells in the vessel walls.

Over time, active ABMR usually transform to chronic ABMR with different levels of activity. Arterial lesions progress to intimal fibrosis with neointima formation and progressive narrowing of vascular lumen (**Figure 12**) leading to chronic transplant changes—widespread interstitial fibrosis and tubular atrophy. In addition, chronic microvasculature changes appeared, including glomerular and peritubular capillaries. At the beginning, chronic glomerular lesions are visible only by EM as neolamina in glomerular capillary loops (**Figure 13**), which may progress to double contour formation and mesangial interposition seen by light microscopy (**Figure 14**). Peritubular capillaries electron micrograph revealed basement membrane multilamellation consistent with chronic ABMR (**Figure 15**) [14].

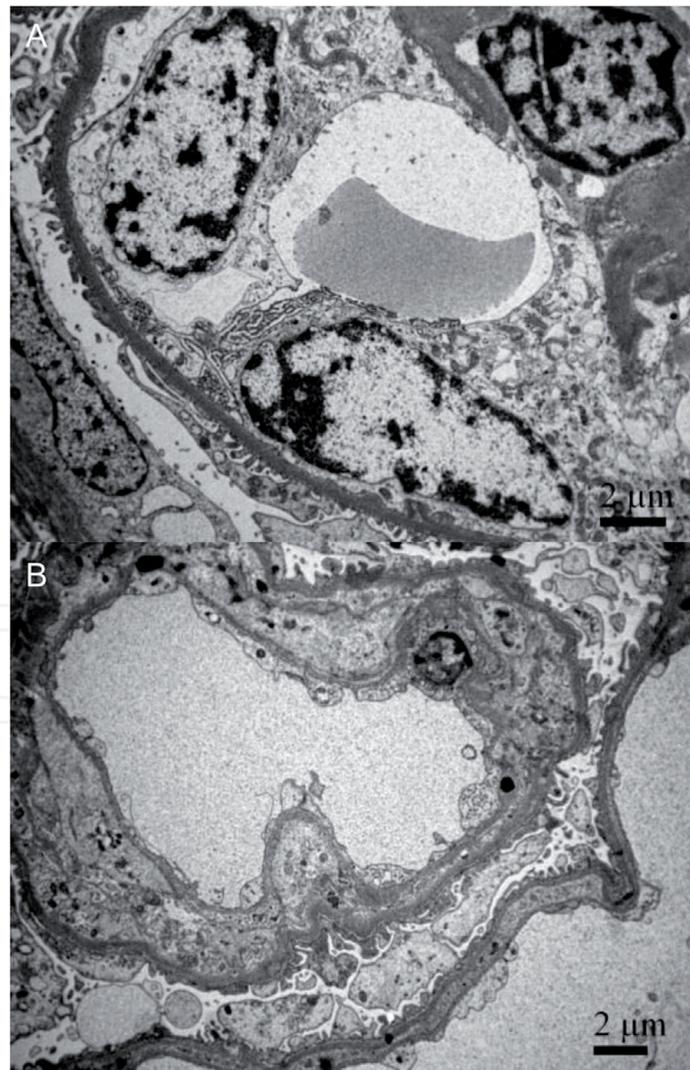


Figure 13. Swollen endothelial cells in early glomerular thrombotic microangiopathy due to severe active antibody mediated rejection. Glomerular basement membrane appears normal (A). Subendothelial widening with oedema and neolamina formation in early chronic active antibody mediated rejection seen only by electron microscopy-Banff score cg1a [(B), all electron micrographs].

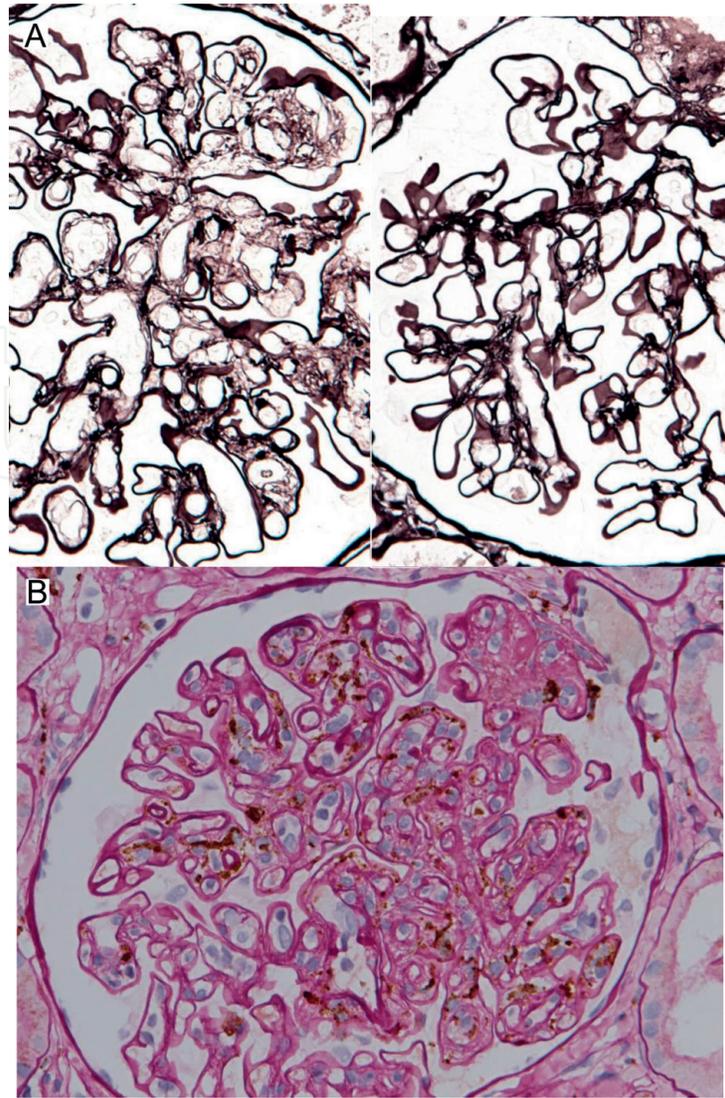


Figure 14.

Double contour formation in glomerulus with chronic glomerulitis in chronic active antibody mediated rejection-Banff score cg3 [(A) Jones, 400×] and normal glomerulus [(B) Jones, 400×]. Glomerulitis in chronic active antibody mediated rejection (Banff score g3, cg3) with diffuse double contour formation (glomerular capillaries with double contours are filled with swollen endothelial cells and inflammatory cells, among them macrophages predominate (CD68 and PAS, ×400).

3.2 Classification of antibody mediated rejection

According to Banff 2017 two types of ABMR were proposed-active ABMR (previously referred as acute ABMR) and chronic active ABMR [16].

The 2017 Banff meeting report noted the confusion generated by reports on acute and chronic ABMR, and emphasized the importance of correctly defining ABMR, including additional characteristics, like the nature of the antibody; the significance of C4d; the severity of microcapillary injury, gene transcripts, molecular and cellular signatures. As the previously used term acute ABMR was found to be misleading by the majority of the working group, the term active was elected to simply refer to lesions of ABMR with microvascular injury and evidence of current or recent antibody interaction with graft endothelium but without morphologic evidence of chronic vascular injury (transplant glomerulopathy, peritubular capillary basement membrane multilayering, new-onset arterial intimal fibrosis).

Two principal phenotypes defined in association of previously termed acute ABMR (1) ABMR phenotype 1 in the presensitized patient, occurring early post-transplant; and (2) ABMR phenotype 2, which develops from the emergence of

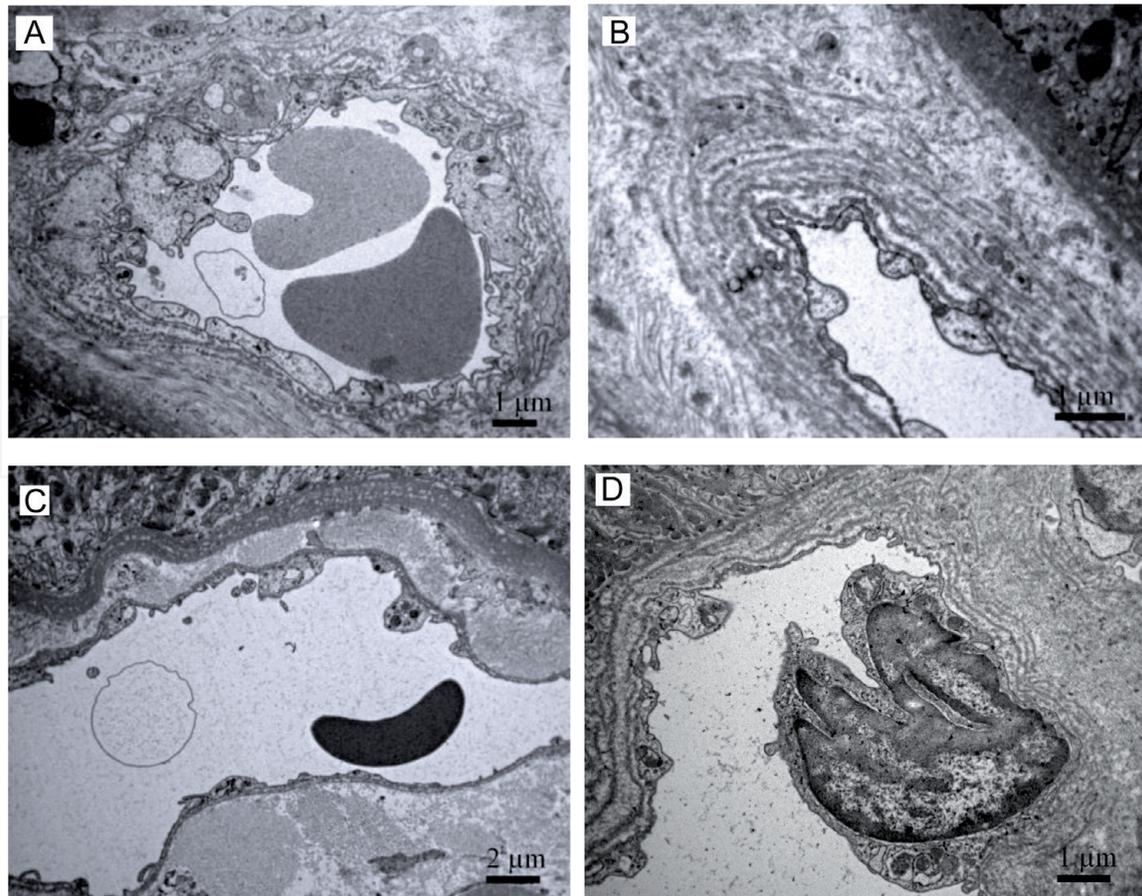


Figure 15. Chronic active antibody mediated rejection: mild basement membrane multilamellation with swollen endothelium (A) and significant basement membrane multilamellation (B, D). Normal peritubular capillary (C, all electron micrographs).

According to revised Banff 2017 classification of antibody-mediated rejection (ABMR) in renal allografts antibody-mediated changes are classified in *Category 2*, consisting of:

Active ABMR; all 3 criteria must be met for diagnosis

1. Histologic evidence of acute tissue injury, including 1 or more of the following:

- Microvascular inflammation ($g > 0$ and/or $ptc > 0$), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, $ptc \geq 1$ alone is not sufficient and g must be ≥ 1
- Intimal or transmural arteritis ($v > 0$)
- Acute thrombotic microangiopathy, in the absence of any other cause
- Acute tubular injury, in the absence of any other apparent cause

2. Evidence of current/recent antibody interaction with vascular endothelium, including 1 or more of the following:

- Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
- At least moderate microvascular inflammation ($[g + ptc] \geq 2$) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, $ptc \geq 2$ alone is not sufficient and g must be ≥ 1
- Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated

3. Serologic evidence of donor-specific antibodies (DSA to HLA or other antigens). C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA; however thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met.

Chronic active ABMR; all 3 criteria must be met for diagnosis

4. Morphologic evidence of chronic tissue injury, including 1 or more of the following:

- Transplant glomerulopathy (cg > 0) if no evidence of chronic TMA or chronic recurrent/de novo glomerulonephritis; includes changes evident by electron microscopy (EM) alone (cg1a)
- Severe peritubular capillary basement membrane multilayering (requires EM)
- Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of TCMR, but are not required

5. Identical to criterion 2 for active ABMR, above

6. Identical to criterion 3 for active ABMR, above, including strong recommendation for DSA testing whenever criteria 1 and 2 are met

C4d staining without evidence of rejection; all 4 features must be present for diagnosis

7. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)

8. Criterion 1 for active or chronic, active ABMR not met

9. No molecular evidence for ABMR as in criterion 2 for active and chronic, active ABMR

10. No acute or chronic active TCMR, or borderline changes

Table 1.

Classification of antibody mediated rejection according to Banff 2017 [16].

de novo DSA in the late posttransplant period and is thought to be mostly related to nonadherence or inadequate immunosuppression) are not positioned in Banff 2017 classification.

In accordance with major advances in molecular biology and gene rearrangement, the diagnosis of ABMR is now dependent on histologic, serologic and transcriptomics findings (see **Table 1**) [16]. For detailed scoring explanations of histological lesions for antibody mediated rejection according to Banff 2017, please see **Table 2**.

Banff scoring for antibody mediated rejection	
v—vascular inflammation: the most severely affected artery dictates the score; an asterisk is added to the v score if interstitial hemorrhage or infarct present	v0: no arteritis v1: intimal arteritis with <25% luminal area lost (minimum = 1 cell, 1 artery) v2: intimal arteritis with ≥25% of luminal area lost in 1+ arteries v3: transmural arteritis or fibrinoid necrosis (medial smooth muscle necrosis) with lymphocyte infiltrate in vessels
g—glomerulitis: percentage of glomerular capillaries partially or completely occluded by inflammatory cells (polymorphonuclear leucocytes and mononuclear cells) and endothelial cell enlargement	g0: no glomerulitis g1: <25% of glomeruli involved (mostly segmental) g2: 25–75% of glomeruli involved (segmental to global) g3: >75% of glomeruli involved (mostly global)
ptc—peritubular capillaritis: the most severely affected peritubular capillary (PTC) dictates the score; an asterisk is added to the ptc score if neutrophils are lacking/only mononuclear cells are present	ptc0: <3 cells/PTC ptc1: 1+ inflammatory cells in >10% of cortical PTCs with 3–4 cells in most severely involved PTC ptc2: 1+ inflammatory cells in >10% of cortical PTCs with 5–10 cells in most severely involved PTC ptc3: 1+ inflammatory cells in >10% of cortical PTCs with >10 cells in most severely involved PTC

Banff scoring for antibody mediated rejection	
C4d—percentage of PTC (or vasa recta in the medulla) that has linear circumferential staining, scored in at least 5 high powered fields of cortex or medulla without scarring or infarct	C4d0: no staining of PTC and medullary vasa recta C4d1: <10% of PTC and medullary vasa recta C4d2: 10–50% of PTC and medullary vasa recta C4d3: >50% of PTC and medullary vasa recta
cg—transplant glomerulopathy: percentage of glomerular capillary loops with duplication of glomerular basement membrane in most affected nonsclerotic glomerulus	cg0: none by light microscopy (LM) and electron microscopy cg1a: only by electron microscopy in 3 glomerular capillaries cg1b: ≤25% by LM (1+ glomerular capillaries with glomerular basement membrane double contours by LM) cg2: 26–50% by LM cg3: >50% by LM
cv—transplant arteriopathy: arterial fibrointimal thickening; percentage of narrowing of lumen of most severely affected artery	cv0: none cv1: ≤25% of the luminal area cv2: 26–50% of the luminal area cv3: >50% of the luminal area

Table 2.
Detailed scoring explanations of histological lesions for antibody mediated rejection according to Banff 2017 [16].

3.3 Essential differences in comparison to previous classification

3.3.1 C4d in antibody mediated rejection

C4d is a split product of C4 activation and has no known biological action. It may be activated by the classical and lectin complement pathways. C4d staining is a specific marker of ABMR when the stain is deposited in the capillaries of kidney allograft and is now considered an alternative for DSA criterion in cases where DSA testing is not available or potentially false negative [17–19]. However, C4d staining has been shown to have significant limitations for diagnosis of ABMR due to low sensitivity, with negative results in up to 50% of patients with antibody-mediated rejection [4, 20]. Furthermore, C4d positivity has been reported in the absence of other evidence of graft injury as its expression depends on the density of PTCs and also may not be associated with measurable DSA in the case of non-HLA antibodies or antibodies absorbed by the allograft [21]. In studies comparing the risk of allograft loss among patients with consistently C4d negative ABMR vs. patients with C4d positive ABMR at a single center, both phenotypes were associated with statistically comparable increased graft loss compared with ABMR free matched controls. No clinical characteristics that reliably differentiated C4d negative and C4d positive ABMR were identified [22].

3.3.2 Expression of endothelium associated transcripts (ENDATs) in antibody mediated rejection

In patients with negative C4d staining, the diagnosis of ABMR may be confirmed on the basis of increased expression of gene transcripts or classifiers in the biopsy tissue that are strongly associated with ABMR [16].

Molecular markers associated with endothelial injury were first introduced into criteria of the ABMR classification in Banff 2013 [23]. Since that time, combinations of transcripts have been introduced and ABMR specific sets of transcripts proposed by different authors [16]. Data from Loupy et al. [4] showed that adding

the results of the ABMR classifier to histologic findings significantly improved their ability to diagnose ABMR, independently from C4d and DSA.

However, it should be noted that at this point no specific Banff recommendations are given regarding which molecular transcript sets should be tested to assess gene expression. This includes the decision whether to perform molecular studies on freshly sampled tissue or FFPE. An advanced molecular approach using machine learning and classifiers has been done in recent years and has provided valuable information for improvement of rejection assessment [24]. The Alberta Transplant Applied Genomics Center team at the University of Alberta developed a “molecular microscope” approach to kidney transplant biopsies and has provided a system for distinguishing ABMR from other allograft pathologies by the expression of activated ENDATs. They proposed new rules to integrate molecular tests and histology into a precise diagnostic system that can reduce errors, ambiguity, and inter-pathologist disagreement [25].

4. Clinical features

In clinical setting ABMR can present as hyperacute (occurring within minutes after the vascular anastomosis), acute (occurring days to weeks after transplantation), late acute (occurring 3 months after transplantation), or chronic (occurring months to years after transplantation) [26–28].

4.1 Acute antibody mediated rejection

Acute ABMR almost always presents with an increase in serum creatinine, which is sometimes severe and accompanied with oligo-/anuria necessitating dialysis treatment. It is usually seen during the first few weeks after transplantation but can occur later, in which case it is usually associated with decreased immunosuppression or noncompliance [29]. The incidence varies with the amount of DSA present at the time of transplantation. In patients with high levels of DSA (i.e. sufficient to cause strongly positive crossmatch) the incidence may be as high as 40% in the first month after transplantation, while the incidence is less than 10% in patients with a negative crossmatch and DSA demonstrated only by solid phase assay [30, 31]. According to Banff 2017 scoring system [16], histopathology in these patients is related to characteristics of *active ABMR*.

4.2 Chronic antibody mediated rejection

The diagnosis of chronic humoral rejection is usually, but not always, made in patients who are more than 6 months post transplantation [32]. The rise in serum creatinine is usually gradual and often accompanied by stepwise increase of proteinuria. Patients with chronic rejection are often hypertensive, sometimes nephrotic range proteinuria or even nephrotic syndrome can be observed. However, patients often have no clinical symptoms associated with chronic rejection, unless renal function is decreased enough that the patient has signs and symptoms of uremia. Except for proteinuria, urinalysis is usually unremarkable in chronic rejection. Contrary, in rare instances progression can be fairly rapid, especially with ongoing active lesions (chronic active ABMR), resulting in graft failure within months [33]. Chronic allograft injury is characteristically seen as transplant glomerulopathy on kidney biopsies. In addition to chronic features, signs of activity are often present, with prominent mononuclear cells in capillary loops with endothelial swelling (transplant glomerulitis) [34].

4.3 Subclinical antibody mediated rejection

A certain amount of kidney transplant recipients present with stable kidney graft function, but histological evidence of smoldering active ABMR on protocol biopsies [35]. These patients often have low-level DSAs (de novo or persistent/recurrent). Evidence suggests that untreated subclinical ABMR is an important predictor of poor renal allograft outcomes [36]. However, the lack of long-term follow-up data has prevented the development of strong guidelines for effective therapeutic interventions.

4.4 Hyperacute antibody mediated rejection

Nowadays, hyperacute rejection is a rare event in kidney transplantation affecting mostly presensitized patients (previous transplantation, blood transfusions, or pregnancy) [37]. It occurs due to preformed DSA present in high titers and presents as graft failure that can occur within minutes (but sometimes may be delayed for a few days) after transplantation [38]. The occurrence of this type of rejection is extremely rare, as preformed antibodies can usually be excluded by CDC crossmatch. However, there is growing evidence that there may exist hyperacute rejections mediated by endothelial, non-HLA antibodies that cannot be detected in standard T and B lymphocyte crossmatch techniques [39].

5. Treatment

Treatment for ABMR is not standardized, and there is still no evidence-based treatment guidelines. A recent therapy of ABMR in renal allografts is systematically reviewed by Wan et al. [2]. In addition to plasma exchange and intravenous immunoglobulin, which still present a backbone of treatment, a number of other therapies have been tried in small studies without consistent benefit, including anti-CD20, proteasome inhibitors, complement inhibitors, anti-interleukin-6 receptor blockers, and immunoglobulin G-degrading enzyme of *Streptococcus pyogenes* (IdeS).

5.1 IVIG

Intravenous immunoglobulin (IVIG) is used for treatment of ABMR, and it is used as an element of desensitizing protocols for ABO- and HLA-incompatible renal transplantation [40].

IVIG is prepared by human plasma from approximately 50,000–100,000 of healthy donors, composed of 90% intact IgG, a few dimers, Fabs (fragment antigen-binding) and traces of IgM and IgA [41].

There are many postulated immunomodulatory mechanisms of IVIG. Investigations in the early 1990s suggested the therapeutic potential of IVIG was due primarily to anti-idiotypic interactions with HLA antibodies [42]. Apart from its effects on B cells and phagocytes via Fc-gamma receptors, IVIG also functions as a scavenger of activated complement [43, 44].

Two general treatment protocols have been developed utilizing IVIG. The first is the use of high dose IVIG (2 g/kg) alone and the second is to combine lower dose IVIG with other modalities, usually plasmapheresis [45]. After the first successful report of Jordan et al. in 1998 [46] who treated acute ABMR in kidney and heart allografts by high-dose IVIG and methylprednisolone, there were more studies with usage of IVIG alone or in combination with plasmapheresis to show effectiveness in treatment of ABMR [47, 48].

Additional benefit of IVIG is its ability to replenish gamma globulin lost during therapeutic apheresis, decreasing infection risk [49].

5.2 Plasmapheresis

Both immunoabsorption (IA) and plasmapheresis (PP) are known to lower HLA-specific antibody levels in a variety of clinical settings [49]. Despite the substantial reductions in the titer of donor-specific anti-HLA antibodies achieved by IA and PP, the graft survival in these patients is significantly reduced, due to rebound synthesis of de novo alloantibodies.

PP is the most frequent modality applied and generally involves 1.0–1.5 volume exchange, using albumin as replacement. It is usually performed daily or every other day for an average of six sessions (up to 14 days). The initial treatment is typically a one-and-one-half-volume exchange with albumin, and subsequent treatments are a one-volume exchange with albumin. To avoid fresh frozen plasma administration, most clinicians prefer an every-other-day PP schedule as albumin alone can often be administered for replacement with interval recovery of the prothrombin time, partial thromboplastin time, and fibrinogen to acceptable levels. This avoids the risk of antigen sensitization. IA is a more selective modality that uses adsorbent membranes for antibody elimination [49, 50].

Few studies have been published where PP modalities are the sole or primary form of antibody reducing therapy [51–54]. However, PP alone has limited success in the treatment of ABMR, and this finding has led to the addition of therapies to prevent immunoglobulin resynthesis and B-cell proliferation. Therefore, PP is often used in combination with other antibody blocking (IVIG), suppression (rituximab, mycophenolate, calcineurin inhibitors), or depleting (bortezomib) modalities [2].

5.3 Rituximab and proteasome inhibitors

Rituximab is a chimeric monoclonal antibody directed against CD20, which is found on immature and mature B cells but not on plasma cells. Following treatment with rituximab, B cells undergo apoptosis and lysis [55]. Most adverse events are first infusion effects of generally mild severity. Additionally, an increased incidence of infections has been described including cases of progressive multifocal leukoencephalopathy [56], late onset *Pneumocystis pneumonia* [57] and fatal pneumococcus sepsis [58].

In renal transplantation rituximab is used for desensitization of highly sensitized patients or awaiting ABO-incompatible renal transplantation [59].

In case of ABMR, rituximab is used for the treatment of ABMR as a solo agent adjuncted to standard of care therapy [60, 61] or in some instances combined with bortezomib, a proteasome inhibitor causing apoptosis of mature plasma cells [62]. Treatment of ABMR with rituximab or bortezomib or combination in addition to standard therapy was in most instances partially effective on the short term, whereas treatment did not result in sufficient long-term graft survival [59–62].

The potential role of the anti-CD20 monoclonal antibody rituximab and the proteasome inhibitor bortezomib in decreasing the production of donor-specific anti-HLA antibodies and improving allograft survival in patients with antibody-mediated rejection was recently evaluated in two randomized, controlled trials RITUX ERAH [63] and BORTEJECT [64], but neither trial showed clinical benefits.

5.4 Complement inhibition

5.4.1 C5 inhibitors

Activation of the complement cascade in acute ABMR rejection has been identified as a major pathophysiological mechanism leading to allograft damage and dysfunction [65]. As a consequence, it has been proposed that specific inhibition of the recipient's complement system of limited duration may be useful to prevent acute ABMR.

The anti-C5 monoclonal antibody eculizumab, which inhibits terminal complement activation, was reported to decrease the incidence of early antibody-mediated rejection in HLA-sensitized renal-transplant recipients [66], although it failed to prevent chronic antibody-mediated rejection in recipients with persistently high levels of donor-specific anti-HLA antibodies [67]. It was also shown that preemptive usage of eculizumab following positive B-cell flow cytometric crossmatch transplant resulted in a reduced incidence of early ABMR from 41.0% in historical controls to 7.7% in eculizumab-treated patients [68].

5.4.2 C1 inhibitors

Binding of anti-HLA DSAs to complement fraction C1q, the first component in the activation of the complement cascade, has been associated with poor graft outcomes and severe phenotypes of ABMR [69]. These findings have provided the rationale for the use of proximal complement inhibition using C1 inhibitors (C1 INHs) in the treatment of ABMR. C1-INH is a serine protease inhibitor that inactivates both C1r and C1s and has multiple effects. Following antibody/immune complex activation of C1qrs, C1-INH dissociates C1r and C1s from the activated C1 macromolecule. This prevents proteolytic activation of C4 and C2 that form C3 convertase, which is important in the context of C4d deposition in AMR [70]. The use of a plasma-derived C1 INH in the treatment of active ABMR was evaluated in trial of 18 kidney transplant recipients with biopsy-proven, active ABMR [71], who were randomly assigned to receive C1 INH or placebo as adjunct therapy to standard-of-care treatment with PP, IVIG, and rituximab. Although there was no significant difference between the groups in posttreatment renal histopathology or graft survival on day 20, a trend toward sustained improvement in graft function at day 90 was observed in the C1 INH group.

Similar findings were reported in six kidney transplant recipients with active ABMR that were unresponsive to treatment with PP, IVIG, and rituximab [72]. All patients received the C1 INH Berinert (20 units/kg on days 1, 2, and 3 and then twice weekly) and high-dose IVIG (2 g/kg once per month) for 6 months. At 6 months, all patients showed an improvement in eGFR compared with baseline at the time of inclusion in the study. Renal allograft biopsies at 6 months revealed no significant change in histologic features; however, C4d deposition was observed in only one of six patients compared with five of six patients at baseline. In addition, of the six patients who were positive for a C1q-binding circulating DSA at the start of the study, only one had a positive DSA at 6 months.

5.5 IL-6 inhibition

The potential of proinflammatory cytokine blockade in kidney-transplant recipients with chronic ABMR has recently been highlighted [73]. Tocilizumab is a monoclonal antibody directed against the interleukin IL-6 receptor that has

been used for the treatment of rheumatic diseases, such as rheumatoid arthritis and systemic juvenile idiopathic arthritis. Recently, tocilizumab was also evaluated as rescue therapy in 36 kidney transplant patients with chronic ABMR who failed standard-of-care treatment with IVIG and rituximab, with or without plasma exchange [74]. Tocilizumab was administered as 8 mg/kg monthly for 6 to 25 months. Significant reductions in DSAs and stabilization of renal allograft function were observed at 2 years. No significant adverse events or severe adverse events were reported.

5.6 IdeS

IgG-degrading enzyme of *Streptococcus pyogenes* (IdeS) cleaves at a very specific amino acid sequence in the hinge region of human IgG and essentially neutralizes all of the IgG in the body within 4 hours of administration. There is a period of about 7 days during which both soluble IgG and the B cell receptor are not detectable, after which it begins to rebound and can reconstitute fully by day 14 [75]. In clinical trials ideS was used in attempting to evaluate the efficacy to desensitize transplant patients with a positive crossmatch, where it showed efficacy in reduction of anti-HLA antibodies before kidney transplantation in patients who were HLA-incompatible with their donors [76, 77]. Further studies are necessary to evaluate IdeS treatment as a therapeutic strategy for ABMR.

5.7 Splenectomy

A desensitization protocol may be required to avoid ABMR in patients that are highly sensitized, have positive crossmatch or ABO incompatibility, however current protocols are not always effective to prevent ABMR and in some cases fail to convert subjects to a negative crossmatch before transplantation. Studies have shown that splenectomy can be successfully performed alone or in association with other treatments like bortezomib, rituximab or eculizumab to overcome severe ABMR, resistant to standard treatment [78–82].

In an effort to spare recipients the morbidity of a splenectomy, splenic irradiation in addition to other therapy may provide an effective intervention for rescuing and preserving allograft function [81].

6. Conclusions

Antibody-mediated rejection is an important cause of acute and chronic graft failure. Diagnosis of acute and chronic ABMR is based on typical histological hallmarks, positive C4d in peritubular capillaries and presence of donor-specific antibodies (DSA). Among standard of care treatment based on PP and IVIG, new treatment options have become available: B cell depletion (rituximab), plasma cell depletion (bortezomib), complement activation inhibition (c1 and c5 inhibitors), recently also IL-6 inhibitors and ideS. However, the high cost of novel medications and a lack of prospective studies evaluating their efficacy and safety limit the routine use of these agents in the treatment of ABMR in kidney transplant recipients.

Conflict of interest

Authors declare no conflicts of interest.

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