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Histopathological findings in transplanted kidneys

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Abstract

Improvements in immunosuppression have reduced acute kidney allograft rejection and clinicians are now seeking ways to prolong allograft survival to 20 years and beyond. The primary cause of kidney allograft loss is still chronic rejection, followed by death with a functioning allograft and primary kidney disease recurrence. Thus, overcoming kidney allograft rejection remains the most important issue. Kidney allograft rejection can be classified into two types: T cell- and antibody-mediated rejection. Both are diagnosed pathologically based on the Banff 2013 classification. Other important pathological features in addition to rejection include calcineurin inhibitor toxicity, polyomavirus nephropathy, and recurrence of the primary kidney disease. Here, we review the diagnosis and representative features of histopathological findings in transplanted kidneys.

Keywords: Transplant kidney pathology, Antibody-mediated rejection, T cell-mediated rejection, Calcineurin inhibitor (CNI) nephrotoxicity, Polyoma virus nephropathy, Recurrence of primary kidney disease

Background

Kidney transplantation enhances the quality of life and patient survival in end-stage renal disease (ESRD). The total number of kidney transplantations has increased 1.6-fold over the past decade in Japan. The Japanese Society for Clinical Renal Transplantation (JSCRT) reported that the total number of renal transplantations in 2015 was 1661 versus 994 in 2005. JSCRT data obtained since 2000 showed that the 10-year patient and graft survival times were 93.8 and 80.2%, respectively (http://www.asas.or.jp/jst/pdf/factbook/factbook/2015.pdf).

Reasons for graft loss were primarily chronic rejection (47%), followed by acute rejection (6.2%), and recurrence of the original kidney disease (1.8%) (http://www.asas.or.jp/jst/pdf/factbook/factbook2015.pdf). These data clearly suggest that the diagnosis and treatment of kidney allograft rejection remains the most important issue. Rates of acute rejection in the first year post-transplant have improved consistently since 2008 and remain similar for deceased- and living-donor recipients. For the period 2012–2013, only 8.5% of patients with deceased-donor kidneys and 8.1% with living-donor kidneys experienced acute rejection (T cell- or antibody-mediated) by 1 year after kidney transplantation [1]. Risk factors for acute rejection—T cell- and/or antibody-mediated—include the degree of histocompatibility between the donor and recipient, the level of presensitization [previous graft, pregnancy, blood transfusion], immunosuppressive drug regimens, and the level of patient adherence with daily therapy [2]. Current immunosuppressive drug protocols with calcineurin inhibitors (CNIs), steroids, and mycophenolate mofetil (MMF) have reduced the frequency of acute T cell-mediated rejection (TCMR) considerably [3].

Kidney allograft rejection can be classified into two types: T cell- and antibody-mediated rejection (ABMR). Both are diagnosed pathologically based on the Banff 2013 classification. The Banff meeting, firstly started in 1991 by Prof. Kim Solez of University of Alberta, is a consensus meeting regarding allograft pathology that has been held every 2 years. The latest version of the Banff classification was prepared in 2013. The Banff classification consists of the following six categories: (1) normal, (2) ABMR, (3) borderline changes, (4) TCMR, (5) interstitial fibrosis and tubular atrophy (IF/TA), and (6) other. It should be noted that not only rejection but also additional histopathological findings, such as CNI toxicity and polyomavirus nephropathy, may overlap [4]. Here, we introduce

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details of the classification and discuss representative histopathological findings from transplanted kidneys.

Kidney allograft rejection

ABMR

ABMR was first recognized in 1996 in the form of hyperacute rejection in patients with pre-transplant donor-specific antibodies (DSAs) [5]. DSAs, largely reactive to human leukocyte antigens (HLAs), are now recognized as a significant cause of ABMR [6]. In the Banff classification, ABMR is divided into two types: acute/active ABMR (acute ABMR) and chronic/active ABMR (chronic ABMR).

Acute ABMR occurs in patients who develop a threshold level of antidonor antibodies after transplantation or who were presensitized and transplanted after desensitization. Acute ABMR occurs most commonly 1–3 weeks after transplantation, particularly in desensitized patients, but can develop suddenly at any time. The primary risk factor for acute ABMR is presensitization [blood transfusion, pregnancy, prior transplant], as judged by a historical positive cross-match or high levels of panel-reactive antibody (PRA), flow cytometry cross-match, or LABScreen methods [6, 7].

In contrast, chronic ABMR typically presents insidiously, several years after transplantation. Chronic ABMR develops through a number of stages over many months to years [8]. The mechanism for the development of chronic ABMR consists of four steps:(1) de novo DSA production, (2) interaction of de novo DSA with the microvascular endothelium, resulting in C4d positivity, (3) specific histopathological changes, such as transplant glomerulopathy and peritubular capillary basement membrane multilayering accompanied by microvascular inflammation, and (4) increased serum creatinine. This sequence is based on several observations. For example, in non-presensitized patients, de novo DSA preceded the onset of proteinuria by an average of 9 months and the onset of elevated serum creatinine by 12 months [9]. Additionally, Regele et al. showed that, in the first year post-transplant, patients with $C4d^+$ biopsies had a higher frequency of transplant glomerulopathy (TG) and representative histopathology of chronic ABMR in later biopsies [10].

In the past decade, it has become clear that late-graft failure is often due to chronic ABMR [9, 11]. Indeed, ~60% of late-graft failure is due to chronic ABMR [12]. The histological features of acute ABMR are not absolutely specific and are thus insufficient alone for a definitive diagnosis. The Banff 2013 classification included a scheme for ABMR that required both pathological and clinical laboratory elements, as follows: (1) characteristic histological manifestations of both acute and chronic ABMR, (2) DSA-induced endothelial cell injury, represented by C4d positivity, microvascular inflammation (MVI), or the expression of activated endothelial gene transcripts (ENDATs), and (3) DSA positivity (Table 1).

Characteristic histological manifestations of acute ABMR

Histological evidence of acute ABMR has been divided into four types, based on light microscopy: (1) MVI with neutrophils and mononuclear cells in capillaries (i.e., transplant glomerulitis and peritubular capillaritis) (Fig. 1a, b), (2) intimal or transmural arteritis (Fig. 1c), (3) acute thrombotic microangiopathy (TMA) (Fig. 1d), and (4) acute tubular injury in the absence of any other cause. Transplant glomerulitis is characterized histologically by glomerular MVI and the enlargement of endothelial cells. Glomerular capillaries have neutrophils in 10–55% and mononuclear glomerulitis in 19–90% [13, 14] of cases (Fig. 1a). In the Banff 2013 classification, determination of the numerical transplant glomerulitis (g) score was still based on the percentage of glomeruli involved [15]: 1–25, 26–50, and >50% for g1, g2, and g3, respectively (Table 2). Indeed, the scoring of glomerulitis based on these fractions of involved glomeruli using the definition above was superior to scoring based on numbers of leukocytes per glomerulus, even when CD68 staining was added. In addition to these conventional criteria, endothelial swelling and capillary occlusion were adopted as a definition of transplant glomerulitis at the Banff 2013 meeting [16].

Peritubular capillaritis shows findings of dilated peritubular capillaries (PTCs) containing three to four more inflammatory cells per cross section in more than 10% of PTCs in non-atrophic cortex. Determination of the peritubular capillaritis (ptc) score is based on the number of inflammatory cells involved: 3–4, 5–10, and >10 for ptc1, ptc2, and ptc3, respectively (Fig. 1b). The scores refer to the highest number of cells in a single PTC (Table 2). Diffuse capillaritis in early protocol biopsies showed a significant negative prognostic impact in terms of glomerular filtration rate 2 years later. Subsequent work on the specificity and sensitivity of capillaritis, by Sis et al. in 329 indication biopsies [17], revealed peritubular capillaritis in not only 75% of acute and chronic ABMR biopsies but also in acute TCMR and acute tubular necrosis. The authors concluded that the g-score + the ptc-score sum, the MVI, was the best predictor of DSA, followed by time post-transplant in late-graft biopsies. We suggested that lymphatic vessels should be excluded by podoplanin staining to score ptc in confusing cases [18].

Intimal or transmural arteritis, defined by the infiltration of mononuclear cells under enlarged and "activated" arterial endothelial cells (primarily arcuate caliber vessels or interlobular arteries, and less often arterioles), has been scored according to the degree of luminal narrowing: <25%, ≥25%, and transmural necrosis for v1, v2, and v3, respectively (Table 2) (Fig. 1c). Intimal or transmural arteritis has long been categorized as a typical lesion of acute TCMR;

Table 1 The Banff 2013 classification

1. Normal
2. Antibody-mediated

   Acute/active ABMR; all three features must be present for diagnosis

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

      Microvascular inflammation (g > 0 and/or ptc > 0)

      Intimal or transmural arteritis (v > 0)

      Acute thrombotic microangiopathy, in the absence of any other cause

   2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one 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] > 2)

      Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury if thoroughly validated

   3. Serologic evidence of donor-specific antibodies (DSAs) (HLAor other antigens)

   Chronic, active ABMR; all three features must be present for diagnosis

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

      Transplant glomerulopathy (TG) (eg > 0), if no evidence of chronic thrombotic microangiopathy Severe peritubular capillary basement membrane multilayering (requires EM)

      Arterial intimal fibrosis of new onset, excluding other causes

   2. Evidence of current/recent antibody interaction with vascular endothelium, including at least one 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] > 2)

      Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, if thoroughly valiated

   3. Serologic evidence of DSAs (HLA or other antigens)

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

   1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   2. g = 0, ptc = 0, eg = 0 (by light microscopy and by EM if available), v = 0; no TMA, no peritubular capillary basement membrane multilayering, no acute tubular injury (in the absence of another apparent cause for this)
   3. No acute cell-mediated rejection (Banff 97 type 1A or greater) or borderline changes

3. Borderline changes: 'Suspicious' for acute T-cell mediated rejection (may coincide with categories 2 and 5, and 6)

   This category is used when no intimal arteritis is present, but there are foci of tubulitis (t1, t2, or t3) with minor interstitial infiltration (i0, or i1) or interstitial infiltration (i2, i3) with mild (t1) tubulitis

4. T cell mediated rejection (TCMR, may coincide with categories 2 and 5 and 6)

   Acute T-cell mediated rejection (Type/Grade:)

   I A. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)

   I B. Cases with significant interstitial infiltration (>25% of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)

   II A. Cases with mild to moderate intimal arteritis (v1)

   II B. Cases with sever intimal arteritis comprising >25% of the luminal area (v2)

   III. Cases with 'transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)

   Chronic active T-cell mediated rejection

   'chronic allograft aiteriopathy' (arterial intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima)

5. Interstitial fibrosis and tubular atrophy, no evidence of any specific etiology

   (may include nonspecific vascular and glomerular sclerosis, but severity graded by tubulointerstitial features)

   I. Mild interstitial fibrosis and tubular atrophy (>25% of cortical area)

   II. Moderate interstitial fibrosis and tubular atrophy (26-50% of cortical area)

   III. Sever interstitial fibrosis and tubular atrophy/loss (>50% of cortical area)

6. Other: Changes not considered to be due to rejection-acute and/or chronic

   (For diagnoses see table 14 in (Banff 97 KI -1999:)[15]); may include isolated g, eg, or cv lesions and coincide with categories 2, 3,4, and 5)

Modified Table of ref. [16]

cg Banff chronic glomerulopathy score, *EM* electron microscopy, *ENDAT* endothelial activation and injury transcript, *g* Banff glomerulitis score, *GBM* glomerular basement membrane, *IF* immunofluorescence, *IHC* immunohistochemistry, *ptc* peritubular capillary, *TCMR* T cell-mediated rejection, *v* Banff arteritis score

however, recent observations showed that the occurrence of intimal or transmural arteritis was more often observed in cases with acute ABMR (21%) than TCMR (9%), and the grade of intimal arteritis in acute ABMR was 52% in v1, followed by 30% in v2, and 19% in v3. [19]. These pathological features correlated historically with increased graft loss in acute rejection with fibrinoid necrosis of the arteries (type III), with ~25% graft survival at 1 year [20, 21].

Recently, isolated endarteritis in kidney transplants has become an increasingly recognized and reported entity [22], but identification of the mechanisms underlying the arterial lesions remains problematic. Salazar ID et al. [23] suggested that after 1-year post-transplant, isolated v lesions usually indicate rejection. Many such cases are DSA-positive and have acute ABMR, but some may reflect TCMR, particularly at less than 5 years post-transplant. Although it has not yet been established about the need and the contents of the antirejection treatment to isolated v lesion, a recent report showed the efficacy of antirejection

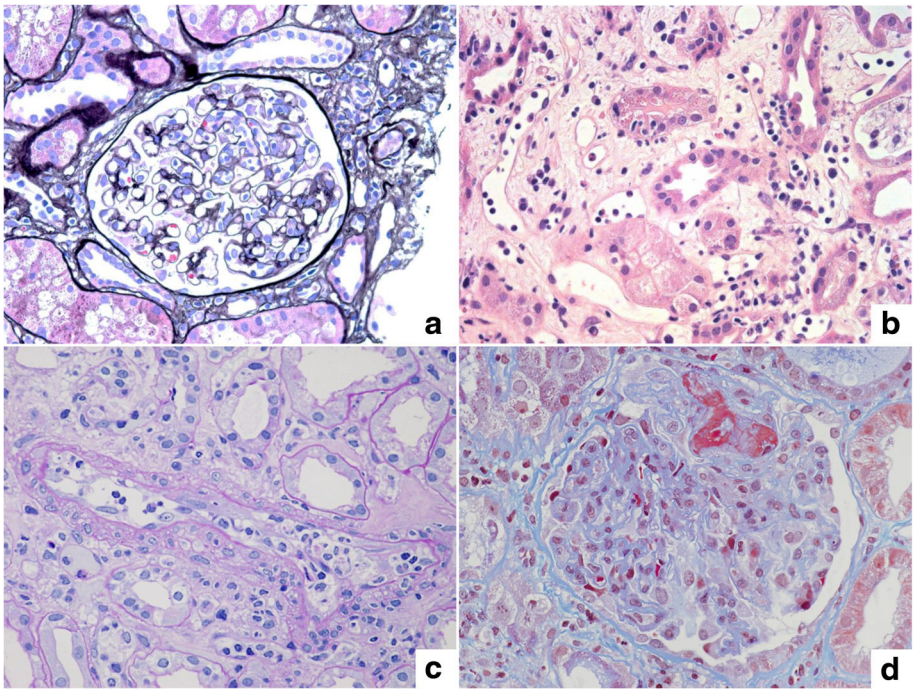

Fig. 1 Pathological findings of acute antibody-mediated rejection. **a** Transplant glomerulitis (Banff classification; g) in a patient with ABMR. Most of the endothelial cells were swelling and inflammatory cells including mononuclear cells and neutrophils were present with focal occlusion in glomerular capillaries. [PAM, ×400]. **b** Peritubular capillaritis (Banff classification; ptc) in a patient with antibody-mediated rejection (ABMR). Peritubular capillaries (PTCs) were markedly dilated, and inflammatory cells including mononuclear cells and neutrophils were present in PTCs [HE, ×400]. **c** Transplant endoarteritis (Banff classification; v) in a patient with ABMR. Endothelial cells of interlobular artery were swelling and marked inflammatory cells infiltration narrowed the lumen [PAS, ×400]. **d** Thrombotic microangiopathy in a patient with ABMR. The dilated capillary lumen was occluded by a fibrin thrombus in glomerulus focally, and the fragment red blood cells were present in mesangial lesion. Endothelial cells were swelling and capillary walls were dilated with subendothelial widening [Masson Trichrome, ×400]

Table 2 Pathological features and Banff score

Feature	Banff term	Banff Score			
		0	1	2	3
Interstitial inflammation (% of nonfibrotic cortex)	i	<10%	10–25%	26–50%	>50%
Total inflammation (% all cortex)	ti	<10%	10–25%	26–50%	>50%
Tubulitis (maximum mononuclear cells/tubule)	t	0	1–4	5–10	>10
Arterial inflammation (% lumen endarteritis)	V	None	<25%	>25%	Transmural or necrosis
Glomerulitis (% glomeruli involved)	g	None	<25%	26–50%	>50%
Capillaritis (cells per cortical PTC, requires >10% of PTC to be affected for scoring)	ptc	<10%	<5/PTC	5–10/PTC	>10/PTC
C4d deposition in PTC (% positive)	C4d	0%	l–9%	10–50%	>50%
Interstitial fibrosis (% of cortex)	ci	<5%	6–25%	26–50%	>50%
Tubular atrophy (% cortex)	ct	0%	<25%	26–50%	>50%
Arterial intimal thickening (% narrowing lumen of most severely affected glomerulus)	cv	0%	<25%	26–50%	>50%
Transplant glomerulopathy (% of capillaries with duplication in most severely affected glomerulus)	cg	0%	<25%	26–50%	>50%
Arteriolar hyalinosis (number with focal or circumferential hyaline)	ah	None	1 focal	>1 focal	1 circumferential >50%
Mesangial matrix increase (% affected glomeruli)	mm	0%	<25%	26–50%	>50%

treatment including high-dose steroids and sometimes followed by antithymocyte globulin [23].

Acute TMA, characterized by endothelial swelling and subendothelial widening, fibrin thrombi in capillary lumens, mesangiolysis, and fragmented red blood cells in the subendothelium and mesangium, occurs in several diseases (Fig. 1d). Acute ABMR has emerged as a significant cause of TMA, based on the occurrence of TMA being higher in cases that were PTC C4d$^+$ (13.6%) versus PTC C4d$^-$ (3.6%). Moreover, plasma exchange was effective in TMA cases with PTC C4d positivity [24]. An acute tubular necrosis-like histology with minimal inflammation can also occur in cases with acute ABMR.

Characteristic histological manifestations of chronic ABMR

Histological evidence of chronic ABMR includes three types: (1) TG type, (2) severe PTC basement membrane multilayering type, and (3) arterial intimal fibrosis of new onset type. The most characteristic feature of chronic ABMR is TG, defined as the widespread duplication or multilayering of glomerular basement membrane (GBM) in the absence of specific de novo or recurrent glomerular disease or evidence of TMA (Fig. 2a). TG develops in stages, best seen by electron microscopy (EM), and these stages have been related to chronic ABMR recently [25].

In addition to these chronic features, signs of activity are often present, with prominent mononuclear cells in capillary loops with endothelial swelling (transplant glomerulitis) [26]. The cells are primarily monocytes, with few T cells. There is no known specific tubular or interstitial lesion in chronic ABMR. The median time of diagnosis for TG by indication biopsies is 5–8 years [27, 28]. The risk of TG is increased by the presence of higher levels of class II DSA [29], particularly those reactive to HLA-DQ which was refractory to conventional therapy [30, 31]. A history of acute ABMR and presensitization also increases the risk [29].

TG has a poor prognosis, particularly when accompanied by PTC C4d deposition [29, 32]. Lesage et al. showed recently that TG was associated with a poor prognosis, independent of the level of graft dysfunction and other chronic histological changes [33]. Notably, the early diagnosis of, and therapy for, TG within 3 months may be important for graft survival [25]. Based on these observations, the Banff 2013 meeting focused on the early diagnosis of TG. The Banff cg0 was defined as no double contours by light microscopy

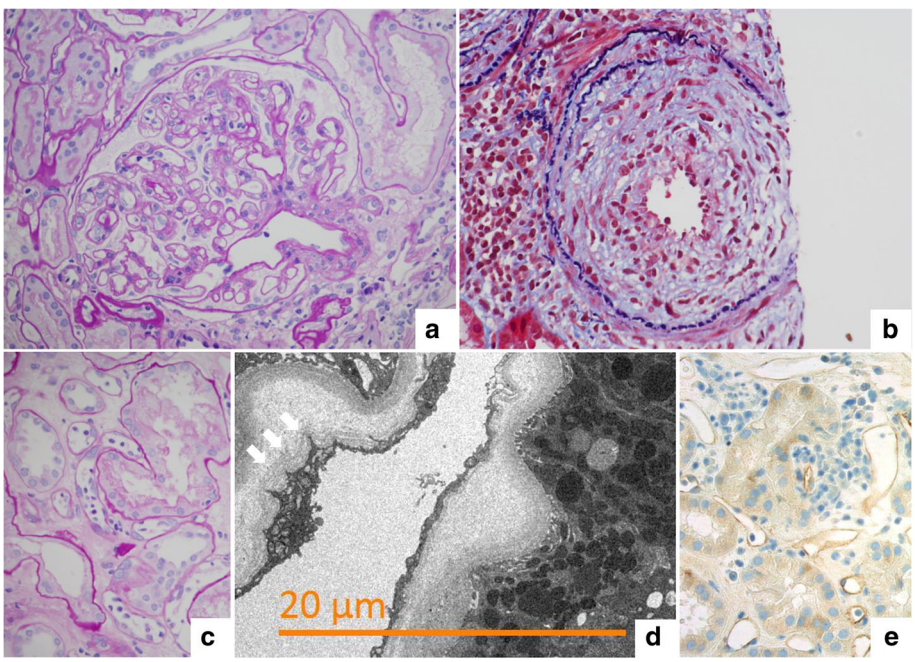

Fig. 2 Pathological findings of chronic antibody-mediated rejection. **a** Transplant glomerulopathy (Banff classification; cg). Glomerular capillary walls were duplicated diffusely and narrowed capillary lumens were markedly present with endothelial cell swelling and few inflammatory cells [PAS, ×400]. **b** Transplant arteriopathy (Banff classification;cv) The intima in interlobular arteries showed a neointima formation without prominent elastic fibers, in which a few mononuclear inflammatory cells were included [Masson Trichrome, ×400]. **c** Transplant capillaropathy, multilayering of the basement membrane in PTCs (*arrow*). Light microscopic findings showed PTCs in chronic ABMR. Basement membranes of PTCs were thick as same as tubular basement membranes [PAS, ×400]. **d** Electron microscopy findings showed multilayering of the PTCs basement membrane outside (*arrow*). Mononuclear cells were present in PTCs and endothelial cell was swelling. **e** Positive C4d immunostaining in PTCs of ABMR. C4d immunostaining in dilated PTCs was linearly positive with inflammatory cells presentation in the capillary lumens

or EM. Regarding cg1, two subcategories were newly defined: cg1a indicates double contours associated with subendothelial widening detected only by EM, whereas cg1b corresponds to one or more glomerular capillaries with double contours in non-sclerotic glomeruli, observed by light microscopy [16]. The duplicated GBM, best seen with periodic acid–Schiff (PAS) or silver staining in light microscopy, is involved segmentally or globally and may show mesangial cell interposition. The TG (cg) score is still based on the most severely affected glomeruli: 1–25, 26–50, and >50% for cg1, cg2, and cg3, respectively (Table 2).

Multilayering of the basement membrane in PTCs has been associated with chronic ABMR [10]. Each ring of basement membrane surrounding a PTC probably represents the residue of one previous episode of endothelial injury, from oldest (outer) to most recent (inner) (Fig. 2d). Ivanyi found that biopsies with three or more PTCs with seven or more circumferential layers were found only in patients with other features of chronic rejection [34]. A subsequent comprehensive study by Liapis et al. compared native and transplanted kidneys [35]. In this study, higher threshold levels were set to define severe PTC lamination (15 PTCs examined, with the three most-affected used for scoring: severe PTC lamination defined as ≥7 layers in one capillary and ≥5 layers in the remaining two capillaries). Based on these observations, severe peritubular basement membrane multilayering was defined by seven or more layers in one cortical PTC and five or more in two additional PTCs using EM. Aita et al. demonstrated that thickening and lamination of the basement membrane may be seen by light microscopy in favorable PAS- or silver-stained sections. When the thickness is similar to or thicker than non-atrophic tubular basement membrane (TBM), it correlates well with multilayering on EM [36]. Although these light microscopic observations of peritubular basement membrane multilayering might be useful, it is not incorporated in the current Banff criteria.

The molecular mechanisms involving the endothelium of the GC and PTC in patients with chronic ABMR are not fully understood. We previously reported that PV-1 and caveolin-1 expression were a distinct feature of chronic rejection-induced transplant glomerulopathy and capillaropathy, respectively [37–39]. More recent data showed that three markers of endothelial-to-mesenchymal transition (EndMT), fascin1, vimentin, and heat shock protein 47 provide a sensitive and reliable diagnostic tool for detecting endothelial activation during ABMR [40].

Arterial intimal fibrosis is a typical feature of rejection in late grafts. These lesions are thought to be caused by antibodies, T cells, or both. Intimal changes are most prominent in the larger arteries, but extend from the main renal artery to the interlobular arteries. The intima shows pronounced fibrous thickening without prominent elastic fiber accumulation, in contrast to the multilayering of elastic typical of hypertensive and involutive arteriosclerosis (Fig. 2b) Arterial intimal thickening (cv) scores are still based on the most severely affected artery: 1–25, 26–50, and > 50% for cv1, cv2, and cv3, respectively. The elastic interna generally remains intact. The media generally shows no obvious abnormality, aside from the focal loss of smooth muscle.

Arterial lesions are common in allografts caused by chronic rejection (including ABMR and TCMR), hypertension, and donor disease. Transplant arteriopathy is associated with DSA in kidney transplants. DSA may also promote arteriosclerosis, as judged by progression of severity in allografts from patients with DSA. Loupy et al. recently suggested that circulating antibodies are major determinants of severe arteriosclerosis and major adverse cardiovascular events, independent of traditional cardiovascular risk factors [41].

C4d positivity, MVI, and ENDAT

To determine DSA-induced endothelial cell injury, the clinician must confirm one of the following: (1) C4d positivity in PTC, (2) MVI, or (3) expression of activated ENDATs. C4d positivity in PTCs has been a cardinal feature for the diagnosis of both acute and chronic ABMR since its adoption into the Banff 2005 classification [42]. However, previous report showed the evidence of ABMR without complement activation demonstrated by transcriptome analysis using ENDATs [43], and now C4d staining has been considered as one of the criteria to suggest evidence of endothelial activation triggered by DSA interaction. Of note, positive C4d deposition in PTCs without graft dysfunction in ABO-incompatible kidney transplantation may present accommodation since they do not appear to be injurious to the renal allografts [44, 45].

In the 2013 Banff classification [16], the threshold for C4d positivity was modified. In a four-tiered grading system that ranged from 0 to 3+ (1–9, 10–50, and > 50% for c4d1, c4d2, and c4d3, respectively; Table 2), C4d positivity was defined originally as 3+ in both frozen (immunofluorescence, IF) and paraffin (immunohistochemistry, IHC) sections [46]. The criteria for C4d positivity were revised to 2+ or 3+ in frozen sections (IF) and > 0 in paraffin wax sections (IHC) [16] (Fig. 2e) However, 1+ in frozen sections was not approved unanimously as a criterion for C4d positivity. The pattern tends to be linear and circumferential, similar to that in acute ABMR; however, fewer positive capillaries are found and the “widespread” pattern is not common. In chronic ABMR, PTC C4d deposition was found in ~50% of the grafts with transplant arteriopathy or glomerulopathy [27, 47]. Cases with little or no C4d (C4d0-1) but demonstrating other features of chronic ABMR

(e.g., DSA, capillaritis, TG) are referred to as C4d-negative chronic ABMR [48] according to the Banff 2013 classification [16].

The MVI score was defined as the total of the Banff g + ptc scores. Recent data showed that the threshold for moderate MVI (g + ptc ≥ 2) was associated with the development of overt TG in the presence of DSA, even in $C4d^-$ cases [17, 49]. Gupta et al. showed that MVI scores of 2 or more were significantly associated with a histological diagnosis of acute and chronic ABMR using microarrays [50], confirming the validity of the MVI score.

The Alberta Transplant Applied Genomics Center (ATAGC) team at the University of Alberta developed a "molecular microscope" approach to kidney transplant biopsies and has provided a system for distinguishing TCMR from ABMR 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 [51, 52]. Reeve et al. showed that histological assessments can be improved by placing more emphasis on i and t lesions and incorporating new algorithms for diagnosis [53]. Halloran et al. recently showed that ABMR presented distinct subphenotypes—early "pg (peritubular capillaries and/or glomerulitis lesion)-dominant," late "cg (GBM double contour)-dominant," and combined "pgcg phenotype"—differing in time, molecular features, accompanying TCMR, HLA antibodies, and the probability of non-adherence, using a microarray assessment [54]. This combined approach will help in developing new diagnostic tools and will lead to new disease classifications. But it has not yet been prevailing in clinical setting in the present time.

DSA positivity

DSAs may be directed against HLAs or other endothelial cell antigens, and their presence is required for the diagnosis of acute and chronic, active ABMR [55]. DSAs bind to HLAs on endothelium and complement activation is accelerated through the C1 complex. The complement cascade proceeds through C4, C2, C3, and C5, finally leading to the membrane-attack complex (MAC) resulting in endothelial cell lysis.

There is growing evidence supporting risk stratification according to anti-HLA DSA phenotypes, as follows: (1) preformed/de novo, (2) mean fluorescence intensity (MFI), (3) C1q/C3d binding, and (4) immunoglobulin G (IgG) subclass. Preformed and de novo DSAs are independent risk factors for acute and chronic ABMR and graft loss [56–58]. Wiebe et al. [9] followed 365 non-presensitized patients prospectively with protocol biopsies and serum samples for DSAs. Overall, 15% developed de novo DSAs, at a mean time of 4.6 years post-transplant. Most patients developed DSAs to HLA class II (94%); only 6% had antibodies to donor HLA class I alone.

Most of the graft loss in the DSA-positive patients was due to chronic ABMR (84%). Wiebe also showed in a subsequent study [58] that, in recipients with de novo DSAs, the rate of estimated glomerular filtration rate (eGFR) decline increased significantly prior to de novo DSA onset and accelerated post-de novo DSAs, suggesting that de novo DSAs were both a marker and contributor to ongoing alloimmunity. Another report supported the evidence that the risk of acute ABMR and poor outcome were correlated with the level of MFI of the DSAs in Luminex assays [59]. Importantly, not all DSAs fix complement or cause ABMR and, conversely, not all episodes of acute graft injury with capillary inflammation and C4d deposition are associated with DSAs detectable with standard assays. For example, Loupy et al. demonstrated that C1q-binding DSAs showed worse graft survival than non-C1q-binding DSA (HR = 9.23, 95% CI: 5.99–14.23, $p < 0.001$). Moreover, the existence of C1q-binding DSA correlated with MVI, PTC C4d deposition, TG, and IF/TA [60]. Sicard et al. demonstrated that C3d-binding DSAs showed worse graft survival than non-C3d-binding DSA [log-rank test, $p = 0.0003$]. Additionally, the existence of C3d-binding DSAs showed better sensitivity (84.7%) and specificity (73.3%) than C1q-binding DSAs or PTC C4d positivity [61]. Lefaucheur et al. suggested the clinical relevance of IgG DSA subclasses and their association with the phenotype of antibody-mediated injury [62].

Recent studies have focused on DSA other than anti-HLA antibodies: i.e., non-HLA antibodies. Non-HLA antibodies existed in 2.3% of ABMR cases occurring within 7 days after kidney transplantation [63, 64]. Representative non-HLA antibodies included MICA, MICB, and angiotensin type 1 receptor [AT1R] antibodies [65–68]. Among these, AT1R antibodies were the most investigated. Banasik et al. reported that 27 of 117 (23%) patients were positive for anti-AT1R antibodies prior to surgery and 4 (3.4%) developed acute rejection [67]. Importantly, Dragun et al. found that 11 of 16 patients with acute rejection resulting from anti-AT1R antibodies were $C4d^-$ [65]. Beyond this observation, Reinsmoen et al. evaluated 63 patients with acute rejection; six cases resulted from anti-AT1R antibodies and four of them were PTC $C4d^-$ [69]. Additionally, Scornik et al. found no correlation between antibodies to HLA-DP, MICA, or AT1R and $C4d^+$ rejection [69]. Recently, antivascular endothelial cell antibodies (AECAs: XM-ONE) [70], and reagents for identification of non-HLAs, non-MICA antibodies, have become available. Moreover, Jackson et al. discovered four new non-HLA antibodies: endoglin, Fms-like tyrosine kinase-3 ligand, EGF-like repeats and discoidin I-like domains 3, and intercellular adhesion molecule 4. All

four AECAs were detected in 24% of pre-transplant sera, and they were associated with post-transplant DSA, ABMR, and early TG [71].

Treatment of ABMR

The treatment of acute ABMR is still evolving; however, randomized controlled trials of therapies are rare [72]. The most common strategies are based on the quick reduction of antibody titers with plasmapheresis (PE), intravenous immunoglobulin (IVIG), and thymoglobulin to treat any concurrent TCMR. The best evidence supporting the use of PE and IVIG shows various immunomodulatory effects, especially on B cells, antibodies, and complement. Rituximab, an anti-CD20 monoclonal antibody, reacts with CD20 on pre- and mature B cells and leads to transient B-cell depletion, with B-cell recovery after 6–9 months. Bortezomib, a proteasome inhibitor used in the treatment of multiple myeloma for plasma cell depletion, has been tried in a small cohort with acute ABMR, with some evidence of success [73, 74]. Eculizumab, an antibody to C5 that blocks the terminal complement pathway, has shown some efficacy in non-randomized pilot trials and isolated cases. The efficacy of eculizumab in the prevention of ABMR was also assessed in renal transplant recipients with a positive cross-match [75]. In this study, the authors concluded that despite decreasing acute clinical ABMR rates, eculizumab-treated (EC)-positive cross-match kidney transplants did not prevent chronic ABMR in recipients with persistently high B flow cytometric cross-matches [76].

Treatment of chronic ABMR remains to be established. Strategies have included IVIG and rituximab [77] and bortezomib [78]. Whether complement inhibition will be useful remains to be determined. Regular monitoring of DSAs and appropriate surveillance biopsies are recommended [6, 79]. The best intervention is prevention, which remains elusive.

TCMR

TCMR was long believed to be the central process in allograft rejection. Consequently, therapies to prevent and treat allograft rejection were directed primarily against T cells before ABMR was recognized. In the Banff 2013 classification, T cell-mediated rejection (TCMR) included categories 3 (borderline changes) and 4 (acute/chronic TCMR) (Table 1). TCMR can be divided into two types: acute TCMR and chronic TCMR. Acute TMCR (Banff category 4, types I–III) is the form of rejection that develops most commonly in the first several months after transplantation. TCMR can occur as early as 6 days, and as late as decades, post-transplantation [1]. The clinical manifestations of severe acute TCMR include an abrupt increase in serum creatinine, a decline in urine output, fever, graft tenderness, and swelling, but these symptoms are often absent in patients under modern immunosuppression.

Characteristic histological manifestations of acute TCMR

Acute TCMR is characterized by tubulitis with interstitial inflammatory cells infiltration and arteritis in more severe form. In the former, the infiltration of activated T lymphocytes and macrophages occurs into a mildly edematous interstitial lesion and into the tubules, so-called tubulointerstitial cellular rejection (Banff category 4, type I) (Fig. 3a, b). In the latter, another major finding is the infiltration of mononuclear cells in the enlarged and activated arterial endothelial cells, so-called transplant endarteritis (Banff category 4, type II or III). The approximate frequencies of the different patterns of acute TCMR are 45–70% tubulointerstitial, 30–55% arteritis, and 2–4% glomerular (not used specifically for the categorization of rejection in the Banff 2013 classification). Notably, ~20–40% of acute TCMR cases show C4d positivity along with PTC; that is, evidence of concurrent antibody-mediated injury [80]. Mixed ABMR and acute TCMR episodes are more severe and constitute an independent risk factor for graft failure [19, 81].

Regarding the detailed morphological features of tubulointerstitial cellular rejection, T cells and macrophages invade tubules and insinuate between tubular epithelial cells inside the basement membrane, a process termed “tubulitis” (Fig. 3a, b). Tubulitis is usually recognized by increased numbers of small, dark nuclei, often arranged along the inner aspect of the TBM and occasionally surrounded by small clear spaces/halos. In the Banff 2013 classification, determination of the numerical tubulitis (t) score is based on the maximum number of mononuclear cells in the most affected tubuli: 1–4, 5–10, and >10 for t1, t2, and t3, respectively (Table 2). Tubulitis affects mostly distal tubular segments in the cortex; proximal tubules are often spared and collecting ducts in the medulla are hardly involved [82]. Tubulitis in distal segment should be excluded infection which are commonly extended from proximal site. Contrary to this, tubulitis in proximal segments means extended inflammation from distal by rejection. Tubulitis in atrophic tubules (<50% of the original diameter and markedly thickened TBMs) is currently considered to be a non-diagnostic sign of parenchymal scarring; presently, this feature is not used to establish a diagnosis of acute TCMR. However, this view may change in the future because there is increasing evidence that all tubulitis (in atrophic and non-atrophic tubules) and all interstitial inflammation (in scarred and non-scarred regions) is a sign of TCMR [83].

Mononuclear cell interstitial inflammation was defined by a pleomorphic interstitial infiltrate of mononuclear cells

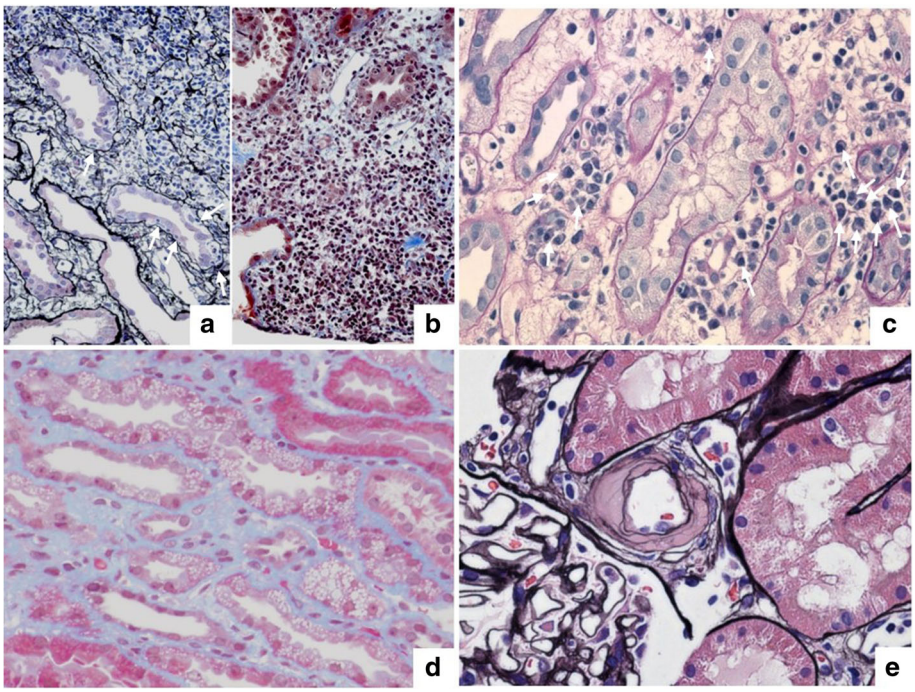

Fig. 3 Pathological findings of T cell-mediated rejection, plasma cell-rich rejection, and acute and chronic CNI nephrotoxicity. **a** Focal aggressive tubulointerstitial rejection with moderate tubulitis. (Banff classification; i and t) Inflammatory cells were present in the edematous interstitial lesions and inside of tubular basement membrane staying between tubular epithelial cells (*arrow*). **b** Diffuse aggressive tubulointerstitial rejection with severe tubulitis. (Banff classification; i and t) Massive inflammatory cells were occupied in the interstitium. Partial dissolution and rupture of the tubular basement membrane were evident (*arrow*) [Masson Trichrome, ×400]. **c** Plasma cell-rich acute rejection (PCAR). Tubulointerstitial inflammatory cells infiltration, which are predominantly plasma cells (*arrow*) [PAS, ×400]. **d** Acute CNI nephrotoxicity. The straight portion of proximal tubular epithelial cells showed isometric vacuolization. **e** Chronic CNI nephrotoxicity. Arteriole were surrounded by the amorphous materials substitute for the medial smooth muscle cells

(lymphocytes, macrophages) and occasionally scattered polymorphonuclear leukocytes in areas of severe tubular injury. In the Banff 2013 classification, determination of the numerical interstitial inflammation (i) score is based on the parenchymal area affected by inflammatory cells: <10–25, 25–50, and >50% for i1, i2, and i3, respectively (Table 2). Using these t and i scores, tubulointerstitial cellular rejection includes type IA (i2, 3 with t2) and type IB (i2, 3 with t3 or at least two areas of TBM destruction and moderate tubulitis elsewhere).

In acute TCMR, MHC class II/HLA-DR antigens and intercellular adhesion molecules are expressed, stimulated by the release of interferon-γ in inflamed regions [84, 85]. The detection of MHC class II in the cytoplasm of tubular epithelial cells by IF in frozen tissue samples may be used as an adjunct marker to establish a diagnosis of acute TCMR.

Regarding the detailed morphological features of transplant endarteritis, infiltration of mononuclear cells under enlarged and activated arterial endothelial cells, mainly arcuate-caliber vessels or interlobular arteries, and less often arterioles, is often observed [endarteritis figure IIA(v1), IIB(v2), II(v3)] (Table 2). The importance of this lesion has been emphasized for many years and is accepted widely as a feature of acute TCMR, particularly if transplant endarteritis is accompanied by tubulointerstitial cellular rejection. However, a considerable proportion of acute TCMR with transplant endarteritis also shows concurrent acute ABMR [19]. Endarteritis has been reported in 18–56% of renal biopsies with acute TCMR [20, 21, 86]. The prevalence of endarteritis in biopsies is affected by the sample size, timing of the biopsy, HLA matching, and the level of immunosuppression. Endarteritis tends to affect larger arteries preferentially [87]. If biopsy samples are small and do not contain arcuate arteries or interlobular arteries, such transplant endarteritis may remain undetected. In cases of endarteritis, endothelial cells are usually activated, with basophilic cytoplasms, and show lifting from the supporting elastic intern by infiltrating inflammatory cells. One inflammatory cell under the arterial endothelium is considered to be sufficient for the diagnosis of transplant endarteritis. Mononuclear inflammatory cells that are solely adherent to the lumina surface of endothelial cells are insufficient for making a diagnosis of transplant endarteritis.

Usually, elastic tissue staining allows for easy detection because hypertension-induced arterial intimal fibroelastosis gives an intense staining reaction that is lacking in cases of chronic vascular rejection. In transplant endarteritis, inflammation is typically limited to the intima/subendothelial zone, sparing the medial smooth muscle layer. Transmural inflammation, involving all layers of the arterial walls, including segmental fibrinoid necrosis, can occur in severe cases of acute TCMR (Banff category 4, type III rejection). However, this feature is more often seen in biopsies with concurrent acute AMR and C4d positivity [88]. Infiltration of mononuclear cells into the wall of the veins or lymphatics is found in ~10% of biopsies with acute TCMR. This is a sign of inflammatory cell trafficking in areas of inflammation with no direct diagnostic significance [89].

The so-called isolated v lesion is characterized by endarteritis with minimal interstitial inflammation ($i \leq 1$) and tubulitis ($t \leq 1$) [22]. The Banff working group reported that the risk for renal allograft failure was 3.51-fold higher in patients with isolated v lesions versus a patient having no diagnostic rejection, concluding that isolated v lesions should be diagnosed and treated as acute rejection to prevent long-term kidney transplant failure [90].

Characteristic histological manifestations of chronic TCMR

In the Banff 2013 classification, chronic TCMR was defined by sclerosing transplant arteriopathy. This lesion is characterized by intimal widening due to the de novo accumulation of collagens I and III, lack of elastosis, and varying degrees of intimal inflammation with mononuclear inflammatory cells. In sclerosing transplant arteriopathy, the intima usually contains varying numbers of myofibroblasts, occasional foam cells, and, in active disease stages, scattered, often clustered mononuclear inflammatory cells that may be most prominent along the inner elastic lamina. Endothelial cells are often enlarged with reactive nuclei sometimes overlying an ill-defined ring of smooth muscle cells: that is, so-called neomedia formation.

Treatment of TCMR

The first-line treatment for acute cellular rejection (i.e., rejection in the absence of C4d staining and/or circulating DSA) is bolus steroids for up to 3 days. This therapeutic approach works well in patients with T cell-mediated tubulointerstitial rejection (i.e., Banff category 4, type I). In patients who do not respond, primarily those with transplant endarteritis and glomerulitis, the standard rescue therapy is thymoglobulin. Certain pathological features of acute cellular rejection have prognostic significance. The most important predictors of outcome are arterial lesions. Endarteritis, which defines type II rejection, has an adverse effect on prognosis compared with tubulointerstitial rejection with no arterial involvement [21]. The intensity of the interstitial infiltrate, or tubulitis, for that matter, has no correlation with the severity of the rejection episode [86, 91]. Many, but not all, "borderline" cases are, indeed, rejection. Untreated borderline cases can progress to frank rejection during follow-up [92]. If there is any evidence that favors rejection, a diagnosis of rejection should be made and therapy initiated.

Subclinical rejection

Rejection episodes detected in allografts with stable function are referred to as "subclinical". Subclinical rejection is defined as the presence of histological evidence of acute rejection on a protocol or surveillance biopsy with no elevation in the serum creatinine level. Most previous reports of subclinical rejection involved cellular rejection [93–95]. However, there are reports of allografts with histological manifestations of ABMR in the absence of functional deterioration of kidney function [30, 96–99]. Loupy et al. suggested that subclinical TCMR was not associated with a significant effect on allograft outcome but triggered the appearance of de novo DSAs and progression to TG in a subset of patients. They also showed that subclinical ABMR detected at the 1-year screening biopsy carried prognostic value independent of initial DSA status, previous immunological events, current eGFR, and proteinuria [100]. Further studies with longer follow-up are required to determine whether surveillance biopsies, combined with enhanced immunosuppression, administered for the treatment of subclinical rejection, improve long-term outcomes.

Plasma cell-rich acute rejection (PCAR)

PCAR is a morphological type of acute rejection with prominent plasma cells, which normally account for >10% of interstitial mononuclear cells [101–104] (Fig. 3c). The histological diagnosis of PCAR requires consideration of post-transplant lymphoproliferative disorder (PTLD), viral infection, and drug toxicity. In previous studies, the response to antirejection therapy in PCAR, such as steroids, was less than satisfactory, with poor graft survival rates [105]. Some reports support the hypothesis that an antibody-mediated component participates in the graft injury of PCAR because it can be associated with both C4d staining and DSAs [99, 103, 106]. If there appears to be rapid progression of allograft dysfunction in the setting of significant plasma cell infiltration, then treatment modalities targeting both cellular and antibody-mediated pathways can be considered, although there are no data to support this line of

treatment. In the setting of a significant plasma cell infiltrate with slow progression of allograft dysfunction, it is unclear whether therapies used in the setting of ABMR are of any benefit, and augmentation of the maintenance immunosuppressive regimen may be the best approach. Abbas et al. reported that PCAR occurs late after transplantation and in many cases associated with DSAs. Graft outcome was poor when PCAR was associated with DSAs [107]. Due to the rarity of PCAR, its incorporation into the Banff classification is still awaited. Recognition of this entity, description of more cases in the literature, and further molecular approaches would help in determining its clinical features and appropriate therapeutic approaches. The differential diagnosis of PCAR includes polyomavirus allograft nephropathy (PVN), PTLD, and cytomegalovirus infection. Therefore, SV40 staining, light chain (kappa and lambda) staining, and EBER (Epstein-Barr encoded early RNAs) were useful to diagnose PCAR.

CNI nephrotoxicity

CNIs are fundamental maintenance immunosuppressants but, ironically, these drugs can cause renal toxicity by several mechanisms. The histological features can be divided into two types, acute and chronic nephrotoxicity, and the target lesions involve the glomeruli, arterioles, and tubulo-interstitium. Acute CNI nephrotoxicity include TMA, afferent arteriolar vasoconstriction, and isometric vacuolization of tubules, whereas chronic CNI nephrotoxicity includes glomerulosclerosis, arteriolar hyaline thickening, and IF/TA [108]. CNI nephrotoxicity also affects recipients with non-renal organ transplantation. Indeed, the risk of chronic renal failure at 10 years after transplantation of a non-renal organ was reported to be ~20% [107]. However, end-stage renal failure caused by CNIs is uncommon, at 3.2–4.8% [109, 110]. For kidney transplantation, the actual occurrence rates at 5 and 10 years after kidney transplantation were 66 and 100%, respectively [111].

Characteristic histological manifestations of acute CNI nephrotoxicity

Early histopathological changes in glomerular capillaries include fibrin thrombi and endothelial cell swelling. These TMA-like changes range from mild to severe, and mild changes occur sometimes with no clinical sign. Afferent arterioles are likely to be affected by CNI nephrotoxicity and the histopathology shows smooth muscle cell swelling and ballooning in early changes. Regarding tubular injury, the straight portions of proximal tubules are likely to be affected. An isometric vacuolization, characterized by small vacuoles filled to normal-size tubular epithelial cells, is an early change in CNI nephrotoxicity [112] (Fig. 3d).

Characteristic histological manifestations of chronic CNI nephrotoxicity

Late histopathological changes in glomerular capillaries include the thickening and duplication GBM. These changes are believed to result from the remodeling action induced by chronic CNI endothelial cell injury [113]. The nodular hyaline deposits, which are replaced by the necrotic smooth muscle cells of the media, are distinct features of late changes in CNI nephrotoxicity (Fig. 3e) [114]. In chronic tubular injury, IF/TA may occur but such changes are non-specific.

Therapy for CNI nephrotoxicity

To reduce CNI nephrotoxicity, the clinician should try to control serum CNI concentrations to lower levels, but such methodologies may induce rejection episodes. Recent data from CTOT-9 (Clinical Trial of Transplantation) investigated a CNI withdrawal regimen in cases with an immunologically low risk of rejection. However, 6 of 14 cases of CNI withdrawal experienced acute rejection [115]. Also, ZEUS study reported by Budde et al. demonstrated the development of de novo DSA production after conversion from cyclosporine to everolimus [116]. Additionally, Gallon et al. investigated the conversion from CNI to sirolimus. It was concluded that renal function was equal between the groups but the sirolimus group showed activation of IL6 and IFN-γ, suggesting indirect alloreactive T cell activation [117].

Polyomavirus infection

Polyomavirus allograft nephropathy (PVN), typically associated with BK virus, is caused by re-activation of latent intragraft polyomaviruses under immunosuppression. PVN was first described by Mackenzie in 1978 [118], and subsequent reports described the importance of PVN in patients with kidney transplantation. Approximately 30–50% of recipients demonstrate viruria by cytology or polymerase chain reaction within the first 3 months after kidney transplantation and PVN can occur at the average time of 10–14 months, but as early as 6 days and as late as 6 years, after kidney transplantation [119]. The prevalence of PVN was reportedly 1–10 and 20% of PVN cases showed graft failure [120].

The key to diagnosing PVN is the histological features of the epithelial cells: the so-called ground-glass intranuclear inclusion body, cell lysis, necrosis, shedding into the tubular lumen, denudation of tubular basement membrane, interstitial inflammation, tubulitis, IF/TA, and the positivity of these cells for SV40

staining [121]. Clinicopathological features of PVN include a high rate of false-negative biopsies, difficulties in distinguishing TCMR, the presence of CMV infection, and persistence, for months to years [122–126].

Characteristic histological manifestations of polyomavirus infection

The target lesions in PVN are epithelial cells of the collecting duct, tubules, and Bowman's capsule (parietal epithelial cells). PVN may spread from the urothelium and medulla to the ascending parts of the tubules and Bowman's capsule. Thus, if the foci of parenchymal involvement are smaller, there may be a higher rate of false-negative biopsies. To diagnose early PVN, it is important to pay attention to the depth zones of the kidney samples (medullary ray and medulla). The distinctive histological findings of PVN consist of four types. The most common type is (1) the ground-glass intranuclear inclusion body, followed by (2) a central intranuclear inclusion body surrounded by a halo, (3) nuclear enlargement and fine granular and vesicular changes, and (4) clumped changes [122] (Fig. 4a). The positivity of SV40 T antigen staining is also helpful and indicates polyomavirus replication [124] (Fig. 4b). Banff Polyomavirus Working Group has performed multicenter retrospective study to develop the histological staging system of this disease. AST (American Society of Transplantation) staging system focuses on interstitial inflammation and fibrosis [127], and Banff Working Proposal 2009 focused on tubular cell shedding and fibrosis [22]. Both systems did not show significant predictive value in a single center study [121]. In 2013, Banff Working Group proposed a new staging system consists of in situ viral load (pvl score) and interstitial fibrosis and now under consideration to incorporate official Banff criteria [128].

Treatment of polyomavirus infection

Specific antiviral drugs for polyomavirus infections are not yet available; thus, patient screening and early diagnosis remain important. Therapeutic methods consist primarily of reduced maintenance immunosuppression proposed in AST guideline [127]. However, clinicians should be aware that about one-quarter of patients experience acute rejection during such a reduction in immunosuppressive therapy [126]. Beyond serum CNI concentrations, mycophenolic acid monitoring is also useful in the clinical setting [129]. In terms of a preventive protocol, low-dose maintenance tacrolimus showed decreased PVN [130]. Of note, Johnston et al. reported the effect of cidofovir and leflunomide for PVN in meta-analysis [131].

Recurrent disease

Graft loss due to recurrent native kidney disease had been thought to be rare and the prevalence was estimated at 1.8% in Japan (http://www.asas.or.jp/jst/pdf/factbook/factbook2015.pdf). However, several recent reports suggest that recurrent kidney disease could contribute more than had been estimated previously. To

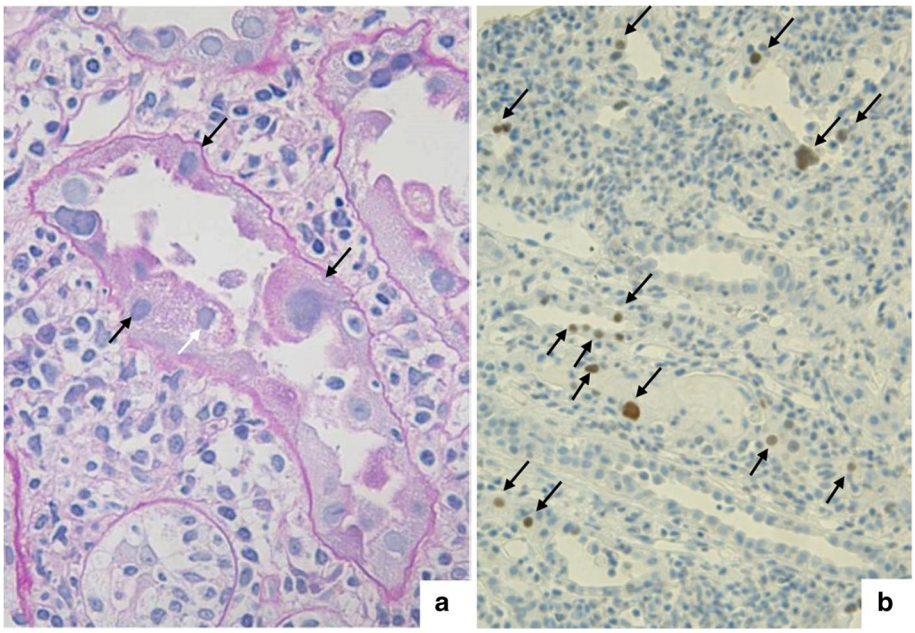

Fig. 4 Pathological findings of BK virus nephropathy. **a** Tubular epithelial cells were swelling and showed ground-glass intranuclear inclusion body (*black arrow*) or intranuclear inclusion body surrounded by a halo (*white arrow*) in a patient with BK virus nephropathy. **b** SV40 immunostaining in a patient with BK virus nephropathy. Distal tubular epithelial cells showed scattered nuclear SV 40 positivity (*arrow*)

diagnose recurrent disease, we should confirm the diagnosis of the native kidney biopsy together with the kidney allograft biopsy. Importantly, the timing or criteria for episode or protocol biopsies differ by institution; these differences can affect the rate and period of the recurrent disease. In most cases, estimations of the recurrence rate for native kidney disease based on protocol biopsies showed higher recurrence rates (Table 3).

Immunoglobulin A neuropathy/immunoglobulin A (IgAN/IgA) vasculitis

The reported recurrence rates of IgAN after transplantation vary between 30 and 35%. The diagnosis of IgAN recurrence requires the presence of mesangial deposits and hyperplasia in the graft, as well as known primary IgAN. IgAN recurrence occurs typically more than 3 years after transplantation. The risk of graft loss due to IgAN recurrence ranged from 3 to 5% [132]. Compared with IgAN, relatively little is known about recurrent IgA vasculitis in renal allografts. The recurrence rate ranges from 15 to 53%, and graft loss due to recurrent IgA vasculitis was 7.5–28.6% in different observation periods [133–135]. A large case-controlled study of 318 patients from one center showed no difference in 10-year graft survival between patients with IgAN recurrence and non-IgAN matched controls: 75% versus 82% [136]. However, it is possible that IgAN recurrence represents a risk factor for graft loss over the long term.

Predictors of active IgAN recurrence include young age, rapid progression of the original disease, and high serum levels of galactose-deficient IgA1 and IgA-IgG complexes [137–139]. Risk factors associated with recurrent IgA vasculitis include shorter duration of the original disease, a living related donor, and necrotizing/crescent glomerulonephritis of the native kidneys [140]. No specific therapy for IgAN and IgA vasculitis recurrence is available; guidelines recommend using angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) [141]. No immunosuppressive regimen has been shown to be superior [142]. There are some reports that a tonsillectomy followed by steroid pulse therapy resulted in decreased proteinuria and improved renal function and pathological findings of recurrent IgAN and IgA vasculitis in a renal allograft [143–146].

Table 3 Recurrence rate and consequent graft loss risk of glomerular disease

	Recurrence rate	Graft loss risk
IgAN	30–35%	3–5%
IgA vasculitis (HSPN)	15–53%	7.5–21%
FSGS	30–60%	~50%
MN	30–45%	10–50%
MPGN type I	30–50%	~15%
MPGN type II (DDD)	66–100%	34–66%

IgAN IgA nephroathy, *HSPN* Henoch Schonlein purpura nephritis, *FSGS* focal segmental glomerulosclerosis, *MN* membranous nephropathy, *MPGN* membranoproliferative glomerulonephritis, *DDD* dense deposit disease

FSGS

The reported risk of recurrence of focal segmental glomerulosclerosis (FSGS) in the first graft ranges from 30 to 60%, whereas the rate approaches 100% in subsequent grafts [147]. Clinical features of FSGS recurrence include the early and acute onset of massive proteinuria (hours to days after transplantation). Risk factors for recurrence include childhood onset, age <15 years, progression to ESRD within 3 years of onset, diffuse increases in mesangial cells in the native kidney, development of recurrent FSGS in a previous allograft kidney, white race, and receiving a kidney from an elderly donor [148, 149].

The existence of circulating permeability factors, proposed by Savin's group, may be a notable predictor of FSGS recurrence [150]. Circulating urokinase receptor (suPAR), which has been reported as a cause of FSGS, may also be a predictor of FSGS recurrence [151]. However, the significance of suPAR is still controversial [152]. In addition, novel candidates such as CLC-1, anti-CD40 Ab, and vasodilator-stimulated phosphoprotein are proposed [153]. The pathological significance of variant transition remains unknown. IJpelaar et al. [154] evaluated variants of primary and recurrent FSGS for both native and transplanted kidneys and found that 81% of patients showed variant consistency between native and allograft kidneys. They also found collapsing variant and cellular variant (CELL) to be distinct disease entities that did not change after transplantation [154]. In contrast, Canaud et al. [155] reported several transitions between variants in recurrent FSGS after transplantation. PE and immunoadsorption (IA) are effective treatments for recurrent FSGS [148]. Ponticelli reported that partial or complete remission was achievable using PE or IA in 63% of adult patients [148]. Rituximab is also known to be an effective treatment for FSGS and was more effective with PE [156, 157]. However, other reports have noted that rituximab showed an intermediate, or no, response [158].

MN

Recurrence rates of membranous nephropathy (MN) after kidney transplantation have been reported to be 30–45%. The disease usually occurs 2–3 years after transplantation, negatively impacting graft survival with a 10–50% rate of graft loss at 10 years [159]. Determination of the IgG subtypes within the immune deposits in MN may be helpful in the differential diagnosis. IgG4 is the predominant subtype in idiopathic MN and recurrent MN, which did not change over time in recurrent MN [160]. Phospholipase A2 receptor (PLA2R) staining

in kidney biopsy specimens is useful to distinguish between recurrent and de novo MN. Larsen and Walker reported that recurrent MN was correlated closely with PLA2R positivity, with a sensitivity of 83% and a specificity of 92% for recurrent MN [161]. Circulating anti-PLA2R antibodies at the time of transplantation seems to be a potential risk factor for MN recurrence [162]. Symptomatic treatment with diuretics, ACEI/ARBs, and anticoagulants may be useful in recurrent MN with nephritic syndrome. Some cases of complete responses to therapy with steroids and cyclophosphamide have been reported [163, 164]. Rituximab showed responses more frequently in several, but not all, cases of MN recurrence [165, 166].

MPGN

The traditional classification of membranoproliferative glomerulonephritis (MPGN) was based on the location and type of electron-dense deposits: type I was characterized by subendothelial deposits, type II by intramembranous electron-dense deposits, and type III by subendothelial and subepithelial deposits. The current classification recognizes the importance of IF microscopy in further dividing MPGN into immune complex-mediated MPGN, with glomerular immunoglobulins and complement deposition, and MPGN with abnormalities in alternative complement pathway regulation, resulting in isolated C3 deposits with little or no immunoglobulin by IF(C3 glomerulopathy). MPGN type II is currently designated as dense deposit disease (DDD) and is recognized as a variant of C3 glomerulopathy. C3 glomerulonephritis (C3GN) refers to cases of C3 glomerulopathy in which the electron-dense deposits do not have classic appearance like DDD. The recurrence rate of DDD is 66–100% and has the worst prognosis in MPGN. The rates of graft loss due to recurrence ranges between 34 and 66% [167, 168]. A few patients may respond to plasma exchange [169]. Good results have been reported with eculizumab in DDD patients [170, 171]. Fourteen of 21 (66.7%) patients with C3GN developed recurrence at 28 months (median) after transplantation. Graft failure occurred in 50% of patients with recurrent C3GN after 77 months (median). The remaining 50% of patients had functioning grafts, with a median follow-up of 73.9 months [172]. MPGN type I shows a high recurrence rate, of ~30–50% after transplantation. Risk factors for recurrence include young recipient age, aggressive disease in the native kidneys, and persistently low complement levels. Recurrence occurs early, usually in the first year post-transplantation. The risk for graft loss is ~15% at 10 years [132].

Information on recurrence rates for MPGN type III is limited. Little et al. [167] showed recurrence of MPGN type III in 4 of 12 patients [33%]. Risk factors for recurrent MPGN type III were younger age at initial diagnosis and the presence of crescents on the original biopsy [167].

Conclusions

The combination of molecular and conventional data will provide new diagnostic criteria in the near future, but conventional histopathology remains the gold standard for the specific diagnosis of allograft dysfunction. Because kidney allografts show considerable diversity, understanding the basics of rejection, CNI nephrotoxicity, PVN, and native kidney disease recurrence is essential for better kidney allograft survival.

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Authors' contributions

AK designed and wrote the manuscript. TY designed and wrote the manuscript. YN designed and helped to draft the manuscript. IY designed and wrote the manuscript and performed the manuscript review. TY performed manuscript review. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

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