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EDUCATIONAL REVIEW

Histopathological diagnosis of acute and chronic rejection in pediatric kidney transplantation

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Abstract ABO-compatible as well as ABO-incompatible kidney transplantation are well established in the pediatric population. There are particularities in the histopathological evaluation of pediatric kidney transplant biopsies as for example the recurrence of certain diseases different from the adult population. Furthermore, the challenging transition of pediatric renal transplant recipients to adulthood is associated with an increased rate of non-adherence triggered rejection episodes. With modern immunosuppressive drugs, T-cell-mediated rejection of renal allografts is well controlled. In contrast, antibody-mediated rejection (AMR) is increasingly recognized as one of the major reasons for allograft loss. However, the 2001 diagnostic Banff criteria for antibody-mediated rejection require further refinement, as the morphological spectrum of AMR expands while effective therapeutic strategies are lacking. For example, endarteritis, which traditionally has been attributed to T-cell-mediated rejection, has recently been shown to be part of the AMR spectrum in some cases. Many findings in transplant renal biopsies are not specific for a certain disease but need consideration of differential diagnoses. To use the term "chronic allograft nephropathy" as a diagnostic entity is no longer appropriate. Therefore, the precise identification of specific diseases is paramount in the assessment of transplant renal biopsies in order to enable tailored therapeutic management.

Keywords Kidney transplantation · Acute rejection · Chronic rejection · Donor-specific antibodies · Endarteritis · Allograft loss · Banff classification

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Introduction

Since 1995, the 5-year kidney graft survival has not substantially increased and currently, estimated graft survival probabilities are reported to be approx. 84 and 78 % for the first transplant from a living or deceased donor, respectively [1]. These figures decrease in subsequent transplantations. The American data are comparable to European results and similar to the adult population younger than 65 years of age [2].

The most common cause of transplant failure in the pediatric population is reported to be chronic rejection with 35 % [1]. It has been shown recently that a high proportion of transplant losses in adults is attributable to antibody-mediated rejection (AMR) rather than T-cell-mediated cellular rejection and that non-adherence is a major risk factor for late AMR and graft loss [3]. Adolescents are especially susceptible to non-adherence with medication taking. A meta-analysis has shown that the mean prevalence of medication non-adherence is 32 % in pediatric renal transplant recipients but is presumably even higher in the adolescent subgroup [4].

Aplastic, -hypo and dysplastic kidneys together with obstructive uropathy account for approx. 30 % of the primary diagnoses leading to renal transplantation in the pediatric population [1]. Focal segmental glomerular sclerosis (FSGS) is the most common glomerular disease accounting for approx. 11 % of renal transplants [1]. Recurrent primary disease is the reason for graft failure in 6.9 % of cases, but increases in subsequent grafts [1]. However, the risk of recurrence and graft loss varies substantially between the individual diseases. Among the more common diseases with high recurrence rates and high risk of graft loss due to recurrence are primary FSGS, Membrano proliferative glomerulo nephritis (MPGN) type II (Dense deposit disease) and atypical Hemolytic uremic syndrome (HUS) (albeit variable depending on to the underlying genetic defect) [5]. The histological diagnosis of recurrent diseases in renal transplants is rendered by identical approaches as in native kidneys. As this is not in the focus of this article, we refer to respective comprehensive textbooks in this regard.

Historically, acute rejection was seen more frequently in children compared with adults. This was attributed to an increased immunologic responsiveness in young children [6, 7]. Altogether, the rejection rates in children have markedly decreased (as seen in adults) during the last decades from 70 % before 1990 to 13 % in the most recent observation period [1]. Current 1-year incidence of acute rejection is only slightly higher in children compared with adults (12.5 % versus 11 %) [8].

The average expected remaining lifetime of an individual between 0 and 19 years on dialysis is similar to a 45-year-old in the general population. However, the estimated gain in lifetime following renal transplantation is another 25 years [2]. This underscores the importance of improving the long-term graft survival in the pediatric population with such an enormous potential benefit from a functioning graft.

Protocol biopsies in pediatric renal transplant patients

A protocol biopsy is defined as a renal biopsy sample from a stable graft at a pre-determined point of time after transplantation. The idea is to detect early potentially treatable diseases in the transplant before they cause graft impairment and come to clinical attention. Experiences from over a decade of protocol biopsies in the adult population have created doubts on their utility as a general diagnostic tool in an unselected approach, although the procedure itself has been shown to be relatively safe [9]. Their implementation in specialized centers, however, has created substantial insight into the natural course of allograft pathology [10–12]. Results from a small recent study in pediatric patients suggest potential benefit from protocol biopsy-driven intervention, which has not been unequivocally shown in adults [13]. In general, it has been proposed to confine the use of protocol biopsies to immunologically high-risk patients [11, 14]. Consensus recommendations on the use of protocol biopsies in the context of presence or absence of donor-specific antibodies have recently been published [15].

Cell-mediated rejection

Cell-mediated rejection (CMR) is conducted by effector T cells originating from the lymphoid organs and infiltrating the allograft, leading to an inflammatory response. Thus, the term "cell-mediated rejection" refers to T-cell-mediated rejection (TCMR). The T cells are thought to be reactive against donor alloantigen [16]. The interstitium is permeated by this cellular infiltrate, eventually leading to tubulitis lesions (i.e., the infiltration of T cells between tubular epithelial cells, Fig. 1a). Most of the cells in the interstitium are CD4+ and CD8+ T cells and CD68+ monocyte/macrophages. Eosinophils may also be present, possibly indicative of a worse outcome [17]. Although tubulitis is frequently considered as fairly specific for TCMR, recent data suggest that tubulitis is the consequence rather than the cause of epithelial injury [18]. Furthermore, tubulitis can be observed in other diseases of renal allograft, e.g., polyoma virus-associated nephritis, and also in native kidneys, e.g., interstitial nephritis.

Acute cell-mediated rejection

Acute tubulo-interstitial rejection consists of interstitial edema with a mononuclear infiltrate accompanied by tubulitis lesions. For a diagnosis of acute CMR under Banff criteria (Table 1), interstitial infiltrate ("i"-score) and tubulitis ("t"-score) are graded. Acute CMR, type IA, requires tubulitis reaching a threshold of "moderate" severity accompanied by a "significant" inflammatory infiltrate. If there is more intense tubulitis, a designation of acute CMR, type IB, can be made, which has been shown to be associated with a worse prognosis [19]. Such more severe tubulo-interstitial acute CMR is primarily characterized by multifocal rupture/destruction of tubular basement membranes, putatively indicating irreversible destruction of nephrons.

In the category of tubulointerstitial rejection, a "gray zone" exists in which either only tubulitis is present without a substantial interstitial infiltrate or an interstitial infiltrate is accompanied by only mild tubulitis. Such cases are termed "borderline"/"suspicious for acute CMR" [20]. However, the implications of such lesions are controversial, and it depends on the center and the type of biopsy (indication versus protocol biopsy) whether these "borderline" cases are regarded and treated as rejection or not. A recent study using gene expression analysis in borderline cases revealed that 1/3 of these cases presents with a molecular phenotype identical to 'true' TCMR cases, while 2/3 were similar to cases showing no evidence of rejection [21]. Previous studies indicate that withholding additional rejection therapy may be appropriate in some of these cases [22]. Additional clinical and histopathological features such as concomitant impairment of renal function and presence of interstitial edema and tubular injury, which are an integral part of a rejection diagnosis in the CCTT-classification of renal allograft rejection, may be helpful in guiding clinical decisions for further treatment in "borderline" cases [23]. However, no prospective clinical trials have ever been conducted to assess whether borderline rejection requires similar treatment as overt TCMR. It is hoped that further research will clarify the significance of the "borderline" category and eliminate this ambiguous "gray zone" [21].

Although tubulitis in the context of acute cellular rejection is caused by T-cells, B-cells are frequently found in renal allografts and their role is still a matter of debate.

B cells may play multiple roles in the immune responses to allografts: in production of high-affinity donor-specific antibody in the central lymphoid organs; as antigen-presenting cells (APCs) in secondary lymphoid organs; and in local inflammatory processes in the graft through interactions with T cells,

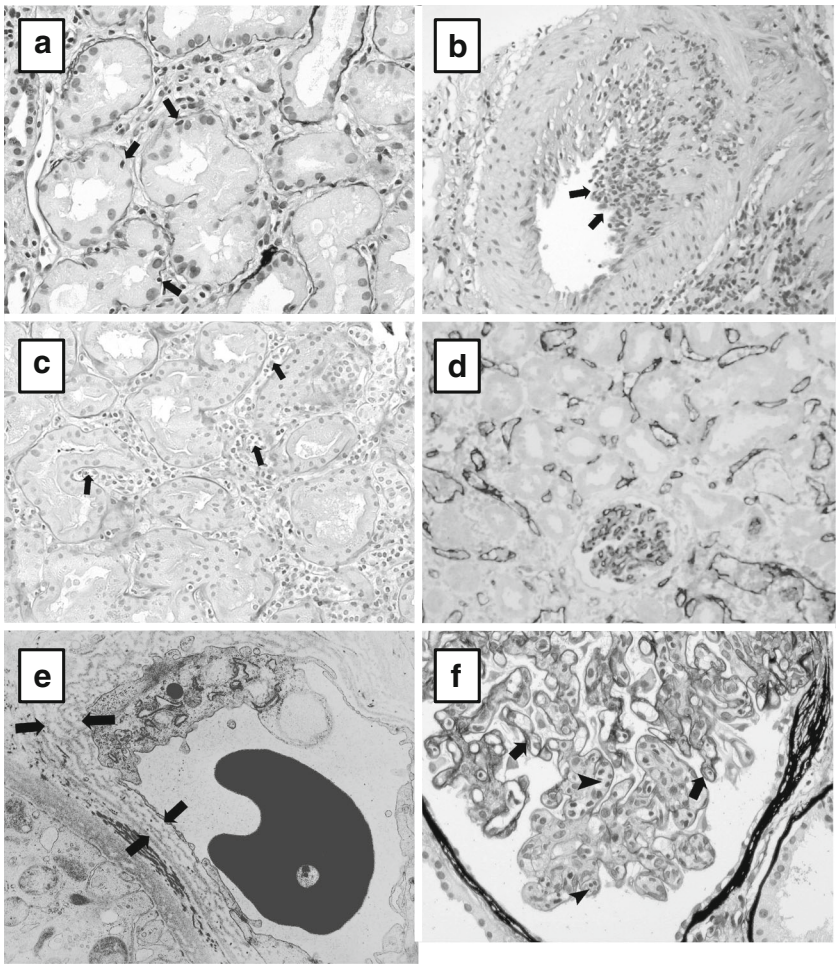

Fig. 1 **a** Tubulitis: Lymphocytes (*arrows*) infiltrate the tubules (Banff "t"-lesion), which is suspicious of acute cellular rejection. **b** Endothelialitis: Inflammatory cells are seen below the arterial endothelium (*arrows*, Banff "v"-lesion), which can be associated with donor-specific anti-HLA antibodies. **c** Peritubular capillaritis: Accumulation of inflammatory cells in peritubular capillaries (*arrows*) of a renal allograft (Banff "ptc"-lesion) as one of the morphological features of microcirculation injury in antibody-mediated rejection. **d** C4d positivity: Diffuse, linear, and circumferential C4d deposition in peritubular capillaries as a biomarker for complement activation in the microcirculation of the allograft. **e** Peritubular capillary basement membrane multilayering: Electron microscopy picture showing multilayering (*between arrows*) of the basement membrane of a peritubular capillary, indicating chronic antibody-mediated rejection. **f** Glomerulitis and initial transplant glomerulopathy: Mononuclear inflammatory cells are present within glomerular capillaries (*arrowheads*, Banff "g"-lesion). In addition, segmental double contours are seen in some glomerular loops (*arrows*, Banff "cg"-lesion). This is suspicious of chronic-active antibody-mediated rejection

dendritic cells, and macrophages. Recent reports have focused on the significance of $CD20^+$ B cells infiltrates in kidney allografts, suggesting that these infiltrates are associated with poor graft survival [24–27]. However, this association is complex and still controversial [28–32]. Gene expression studies revealed that B cells are features of late biopsies and associated with inflammation in areas of fibrosis, and the mere fact of having a late biopsy itself is associated with a poor prognosis. While the significance of B cell infiltrates remains unclear, it is relevant because of potential consequences for therapy, since highly effective anti-B cell drugs are available [33].

The presence of CD20+ B cells in renal allografts is often associated with the aggregation of infiltrates into lymphoid clusters (LC), although some B cells can also be found in diffuse interstitial infiltrates [34, 35]. Lymphoid clusters in renal allografts represent a mixed aggregate of $CD20^+$ cells with T cells and macrophages in the immediate vicinity and can comprise between 5 and 90 % $CD20^+$ cells [31]. The prevalence of LC varies considerably between studies (between 15 and 59 % in indication biopsies, 30 % in protocol biopsies [34]. The variability of these results is influenced by the lack of uniform criteria for the definition of lymphoid clusters. Although B-cell nodular infiltrates resemble ectopic germinal centers in grafts that were explanted because of terminal rejection inducing graft failure [36], it is not clear if the nodular infiltrates observed in transplant biopsies share similar features with these end-stage organs. The key question that yet needs to be answered is whether the dense B cell nodular infiltrates observed in some renal allografts are functioning in generation of effector T cells or of high-affinity

Table 1 Banff classification for renal allograft pathology: diagnostic categories summarized with updates (adapted from [20], used with permission)

Cat.	Features
1	Normal
2	Ab-mediated changes (± Cat. 3, 4, 5, 6)
	Circulating antidonor Ab, C4d+, and allograft pathology
	• C4d deposition without morphologic evidence of active rejection
	C4d+, circulating antidonor Ab, no signs of acute or chronic TCMR or AMR (i.e., g0, cg0, ptc0, no ptc lamination [<5 layers by EM], no ATN-like minimal inflammation) [Considered indeterminate if simultaneous borderline changes]
	• Acute antibody-mediated rejection
	C4d+, circulating antidonor Ab, morphologic evidence of acute tissue injury
	I. ATN-like minimal inflammation
	II. Capillary and/or glomerular inflammation (ptc/g >0) and/or thrombosis
	III. Arterial—v3
	• Chronic active antibody-mediated rejection
	C4d+, circulating antidonor Ab, morphologic evidence of chronic tissue injury [glomerular double contours and/or ptc lamination and/or interstitial fibrosis/tubular atrophy and/or fibrous intimal thickening in arteries]
3	Borderline changes: 'Suspicious' for acute T-cell-mediated rejection [± Cat. 2, 5, 6]
	No arteritis but present are tubulitis (t1, t2, or t3) with minor interstitial infiltration (i0 or i1) or interstitial infiltration (i2, i3) with mild tubulitis (t1)
4	T-cell-mediated rejection (TCMR) [± Cat. 2, 5, 6]
	• Acute TCMR
	IA. Significant interstitial infiltration
	(>25 % of parenchyma affected, i2 or i3) and foci of moderate tubulitis (t2)
	IB. Significant interstitial infiltration
	(>25 % of parenchyma affected, i2 or i3) and foci of severe tubulitis (t3)
	IIA. Mild to moderate intimal arteritis (v1)
	IIB. Severe intimal arteritis comprising >25 % of the luminal area (v2)
	III. 'Transmural' arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle with accompanying lymphocytic inflammation
	• Chronic active T-cell-mediated rejection
	'Chronic allograft arteriopathy' (arterial intimal fibrosis with mononuclear infiltration of fibrosis, formation of neo-intima)
5	Interstitial fibrosis and tubular atrophy (IFTA), no evidence of specific etiology
	[Graded according to IFTA; may also have nonspecific vascular and glomerular sclerosis]
	I. Mild IFTA (<25 % of cortical area)
	II. Moderate IFTA (25–50 % of cortical area)
	III. Severe IFTA/loss (>25 % of cortical area)
6	Other
	Changes not due to rejection—acute or chronic—ay include cg or cv lesions, ± Cat. 2, 3, 4, 5

antibody, via their acquired structural and functional properties of tertiary lymphoid organs. Recent evidence emerged that B cells can in addition to present antigen and enhance T cell activation also regulated and inhibit immune responses. A subset of B cells, co-called "regulatory B cells" (Bregs) act independently from antibody production and antigen presentation, and are generally IL-10 dependent [37]. Key future directions in this regard include finding more specific markers for Bregs and through this find ways to inhibit antibody-producing B cells without depleting Bregs.

The presence of subendothelial inflammatory cells in the arteries is referred to as "endothelialitis", "vascular rejection", or more accurately "endarteritis" (Fig. 1b). Mild to moderate endarteritis is diagnosed as acute CMR, type IIA according to Banff criteria. If severe endarteritis is present, a designation of type IIB acute CMR can be rendered [20]. These cases have been shown to be associated with a worse prognosis compared to Banff type IIA cases [38]. Cases with transmural arteritis and/or arterial fibrinoid changes are diagnosed as acute CMR, type III. However, it is recognized that such lesions may often have an antibody-mediated component [20]. Studies have indicated a worse prognosis of cases with endarteritis, but it needs to be taken into consideration that most of these studies were done prior to sensitive antibody testing and thus may represent AMR instead of CMR [39].

Results from a retrospective multicenter case cohort study presented at the 2011 Banff meeting indicated that cases with so-called "isolated v-lesions" (i.e., endarteritis in the absence of significant tubulointerstitial inflammation or capillaritis) might represent a heterogeneous group of disease processes [11]. After the exclusion of AMR cases, two types of isolated v-lesion cases were identified: Those associated with TCMR and those with delayed graft function. More recently, Lefaucheur et al. found that one-third of all vascular rejections were antibody mediated, half of which showed v1 lesions only [40]. Thus, this distinct group of antibody-mediated vascular rejection is not yet represented in the current Banff classification. Furthermore, the same group from Paris recently reported that donor-specific antibodies (DSAs) very likely contribute to the severity and progression of arteriosclerosis in renal transplants [41]. Comparing protocol biopsies from patients with and without DSA showed that arteriosclerosis significantly progressed between month 3 and month 12 after transplant in DSA-positive patients while among DSA-negative patients no statistically significant progression was observed during the same timeframe. Available biopsies at later time points in some of the patients supported a rate of progression of arteriosclerosis in DSA-negative patients that was approximately one-third of that observed in DSA-positive patients. Accelerated arteriosclerosis was also significantly associated with peritubular capillaritis and glomerulitis, i.e., features of AMR. These observations strongly support the hypothesis that DSA accelerate post-transplant progression of

arteriosclerosis. Therefore, a more differentiated diagnostic and therapeutic approach towards cases with endarteritis and transplant vasculopathy seems warranted.

Chronic cell-mediated rejection

Interstitial fibrosis and tubular atrophy (IFTA) is the non-specific final common pathway in both chronic CMR and AMR as well as in other forms of graft deterioration, e.g., PVAN and recurrent disease [42]. However, the only accepted diagnostic feature for chronic CMR under Banff criteria is the presence of intimal inflammation in the setting of chronic allograft arteriopathy consisting of arterial intimal fibrosis with mononuclear infiltration and formation of a neo-intima [20]. However, as discussed above, recent data suggest that DSA play a major role in accelerated arteriosclerosis in renal allografts [41].

With progressing IFTA, the renal tubules shrink, acquire wrinkled, thickened tubular basement membranes, and are infiltrated by inflammatory cells. Currently, inflammation in areas of IFTA is not considered for the Banff i score for the diagnosis of CMR. However, recent studies have shown the importance of inflammation in areas of fibrosis, suggesting a role in chronic rejection and ultimate graft deterioration, at least as a robust prognostic marker [43–45]. A scoring system has been proposed to address "total interstitial inflammation" and is currently under review for its inter-observer reproducibility and clinical utility by the Banff Working Group [46, 47].

Antibody-mediated rejection

Antibody-mediated rejection (AMR) has emerged as a major clinical challenge and has recently been identified as the most frequent cause for renal allograft failure in adults [48, 49]. Donor-specific anti HLA-antibodies (DSA) are identified in the vast majority of AMR and patients with DSA are at increased risk for allograft failure. The primary target of DSA is the endothelium of the microcirculation in the allograft. Clinical management of AMR differs significantly from TCMR. Therefore, accurate diagnosis of AMR is crucial. However, the morphological spectrum of AMR is heterogeneous and comprises a set of non-specific morphological lesions which are nevertheless an essential part of current diagnostic criteria for AMR along with C4d deposition on the endothelium, presence of DSA, and graft dysfunction [24]. Chronic AMR has been widely recognized in kidney transplants, but needs yet to be defined in other organ transplants. Despite being a significant contributor to late graft loss, it is often missed due to limitations of current diagnostic criteria. In particular the lack of sensitivity of C4d and the limited specificity of DSA account for most missed AMR cases.

Acute antibody-mediated rejection

With the exception of hyper-acute AMR mediated by pre-existing unrecognized DSA [50, 51], T cells were thought to be the major determinant in graft rejection. However, over the past decade, it has become clear that significant graft injury occurs through AMR-mediated primarily by donor-specific anti-HLA antibodies [52]. Consequently, in 2001 AMR was introduced as a diagnostic category into the Banff classification [24]. AMR contributes to both early and in particular late graft loss [48, 49]. Antibodies can cause tissue injury through three main pathways: the classical activation of complement, via direct activation of the antigen-expressing target endothelial cell, and through cell-mediated cytotoxicity after binding to Fc receptors of neutrophils, macrophages, and NK cells [52–54]. Since donor HLA is widely expressed in the microcirculation of the allograft, these pathways can all culminate in endothelial injury.

Morphologically, acute AMR presents with three main patterns of injury, which are reflected in the Banff classification [46]. Type/Grade I: An acute tubular necrosis (ATN)-like minimal inflammation pattern; Type/Grade II: A pattern including peritubular capillary (PTC) and/or glomerular capillary inflammation (=microcirculation inflammation: Fig. 1c and f), sometimes accompanied by microthrombi. Type/Grade III: Presence of vascular fibrinoid necrosis. According to current Banff consensus criteria, two or more criteria are required for the diagnosis of AMR in addition to one of the injury patterns described above: evidence of DSA and the deposition of the complement split product component C4d on the endothelium of PTCs (Fig. 1d) [20]. Ultrastructurally, peritubular and glomerular capillary endothelium show signs of injury with cell enlargement, loss of fenestration, detachment from basement membranes with lamina rara interna widening, lysis, and apoptosis [55].

Chronic antibody-mediated rejection

Chronic antibody-mediated rejection (CAMR) is characterized by structural remodeling of the allograft microvasculature but also larger arteries (intimal hyperplasia) with secondary IFTA and eventual decline in renal allograft function. As a consequence of chronic antibody-mediated injury to the microcirculation, structural remodeling of glomerular basement membranes takes place with lamellation and duplication, resulting in so-called transplant glomerulopathy with double contours appreciable by light microscopy (Fig. 1f). Similar changes take place in peritubular capillaries (PTC), leading to basement membrane multilayering (Fig. 1e) [40]. According to Banff criteria, prerequisites for a diagnosis of CAMR are the evidence of chronic tissue injury, the presence of C4d and a documented DSA [20]. Chronic tissue injury includes glomerular double contours, PTC basement membrane multilayering, IFTA, and fibrous thickening in arteries [20].

At least two of four of these criteria are typically required for a diagnosis of CAMR. Glomerular and PTC basement membrane multilayering are considered the most valuable evidence of chronic antibody-mediated injury [56]. Similar to acute AMR, at least some degree of glomerulitis and/or peritubular capillaritis is typically present in most biopsies with CAMR. This can be interpreted as ongoing disease activity and thus risk for progression. The glomerular inflammatory infiltrate is mostly composed of CD68+ monocytes with fewer numbers of CD3+ T cells and occasional neutrophils. PTCs may be positive for C4d in CAMR, and C4d staining can also be seen in glomeruli with double contours. C4d and DSA may be intermittently present throughout this process. AMR may proceed to allograft failure within months or may be procrastinated over years, depending on the compliance and immunosuppressive status of the patient [3].

Attention has recently been drawn to so-called "C4d-negative AMR". These cases have DSA and morphological evidence of microcirculation injury but lack C4d positivity in PTC endothelium. Negativity for C4d in AMR can be explained by various mechanisms: complement independent antibody-mediated injury, lack of sensitivity and reproducibility of the staining methods, arbitrary criteria for defining positivity, and time-dependent degradation of C4d-deposits in the microcirculation. Inter-institutional reproducibility of C4d staining has recently been shown to be poor [57]. Molecular studies identified a subset of cases with DSA and morphological features of antibody-mediated injury showing increased expression of endothelial cell-associated transcripts as a sign of endothelial cell activation and stress [58]. These data suggest that 50–60 % of AMR cases are missed by current Banff criteria due to C4d-negativity. Eventually, this will be added to the Banff diagnostic armamentarium as a distinct category of AMR. However, data is still being reviewed by a respective Banff Working Group regarding the significance of this entity in attempt to provide valid diagnostic criteria, a task on the agenda for the 2013 Banff meeting [11, 59].

Particularities in ABO-incompatible transplantation

A peculiar scenario occurs in ABO-incompatible transplantation, related to the presence of PTC C4d deposition in the absence of other evidence of antibody-mediated injury, a phenomenon called "accommodation". Anti-blood group antibodies may be detectable in these cases. Signs of acute or chronic TCMR or AMR are absent. More specifically, there is no ATN-like minimal inflammation, no glomerulitis, no transplant glomerulopathy, no peritubular capillaritis, and no PTC basement membrane multilayering. These cases are considered to represent "C4d deposition without evidence of active rejection" under current Banff criteria [20]. Accommodation is often described in the setting of ABO-incompatible transplantation, where non-HLA anti-blood group antibodies are present. The long-term significance of this observation is still under investigation [60, 61]. In contrast, those cases in which anti-HLA DSA occur de novo have been described to develop typical AMR and thus are associated with an inferior prognosis [62].

Differential diagnoses

Many of the findings in transplant kidney biopsies are neither specific nor unique to the transplant setting, but may be seen in various diseases in transplant as well as native kidney biopsies (Table 2). Interstitial inflammation and tubulitis, for example, are not specific for acute allograft rejection, but may indicate bacterial or viral infection, allergic drug reaction, or PTLD. Often, a correct diagnosis can not be made without careful clinico-pathological correlation. Some of the findings that are typically problematic in terms of possible differential diagnoses are discussed in the following sections.

Differential diagnosis: polyoma virus-associated nephritis (PVAN)

The regimen of immunosuppression is one of the main risk factors for the development of polyoma virus nephropathy in kidney allografts [63]. The prevalence of PVAN varies between 1 and 10 % in the literature and the risk of graft failure from established PVAN is high [64]. However, it is likely that the prevalence of PVAN and subsequent graft failure will decline due to sufficient PCR screening of blood and urine and early reduction of immunosuppression [65]. PVAN infects the renal tubular epithelium and results in a tubulointerstitial nephritis with often typical cytopathic nuclear changes with nuclear inclusions. The inflammatory infiltrate is frequently rich in plasma cells. The prognosis of late-stage cases with advanced IFTA is poor [64, 66, 67]. It has been postulated that acute CMR and polyoma virus may coexist. However, as long as there is no endarteritis, the differential diagnosis between these two entities is notoriously difficult [68]. Immunohistochemistry directed against the polyoma virus SV40 large T antigen or in situ hybridization is crucial to detect virally infected cells to confirm the diagnosis.

A histopathological grading system for PVAN has been proposed, but its prognostic significance is debatable [11, 69].

Differential diagnosis: calcineurin inhibitor toxicity

Calcineurin inhibitors (e.g., ciclosporin and tacrolimus) are highly effective in preventing rejection in renal allografts [16]. However, calcineurin inhibitors can cause both acute and chronic nephrotoxicity [70]. Acute toxicity is characterized by tubular injury with isometric cytoplasmic vacuolization.

Table 2 Histopathological findings in transplant kidney biopsies and their potential differential diagnoses

Histopathological finding	Differential diagnosis	Helpful tool
Interstitial inflammation	Acute/chronic rejection	History of rejections?
	Pyelonephritis	Urine culture
	Drug reaction	Drug history
	PVAN[a]	Special stains[b]
		Blood virus PCR
	PTLD[c]	Immunohistochemistry
Tubulitis	Acute/chronic rejection	History of rejections?
	Pyelonephritis	Urine culture
	Drug reaction	Drug history
	PVAN[a]	Special stains[b]
		Blood virus PCR
Arteriolar hyalinosis	CNI[d] toxicity	CNI[d] levels/duration
	Diabetes	Medical history
	Hypertension	
	Donor related	Zero time/pre-implantation biopsy
Glomerular double contours	Transplant glomerulopathy in chronic AMR[e]	Presence of DSA[f]
		Previous biopsies with AMR[e]?
	Recurrent/de novo mesangiocapillary GN	Special stains
		Electron microscopy
	Chronic TMA[g]	Medical history
Focal segmental glomerulosclerosis	Recurrent disease	Medical history
	De novo glomerular disease	Special stains
		Electron microscopy
	CNI[d] toxicity	
	Unknown/non-specific	
	Donor related	Zero time/pre-implantation biopsy
Acute tubular injury	CNI[d] toxicity	CNI[d] levels
	Drug toxicity, other than CNI[d]	Drug history
	Pre-renal cause	Medical history
	Delayed recovery from CIT[h]	Zero time/pre-implantation biopsy
Thrombotic microangiopathy	CNI[d] toxicity	CNI[d] levels
	AMR[e]	Presence of DSA[f]
	Recurrent disease	Medical history
	De novo HUS	Genetic testing
Interstitial fibrosis/tubular atrophy	Chronic/repeated rejection	Previous biopsies
		DSA[f]
	Pyelonephritis	Urine culture
	Recurrent glomerular disease	Electron microscopy/special stains
	De novo glomerular disease	
	CNI[d] toxicity	CNI[d] levels/duration
	PVAN[a]	Special stains[b]
		Blood virus PCR
	Reno-vascular disease	Medical history

[a] *PVAN* Polyoma virus-associated nephropathy

[b] Special stains: In situ hybridization/immunohistochemistry/immunofluorescence

[c] *PTLD* Post-transplant lymphoproliferative disease

[d] *CNI* Calcineurin inhibitor

[e] *AMR* Antibody-mediated rejection

[f] *DSA* Donor-specific antibodies

[g] *TMA* Thrombotic microangiopathy

[h] *CIT* Cold ischemia time

Afferent arterioles can display smooth muscle cell necrosis with vacuolization. Uncommonly, thrombotic microangiopathy can develop. Chronic CNI-mediated toxicity leads to deposition of hyaline material in the media of arterioles with a pearl necklace-like appearance. The interstitium may also display striped fibrosis and tubular atrophy.

However, none of these histological features, which have been described during the first decade of calcineurin inhibitors when higher doses where administered, is specific for calcineurin inhibitor toxicity and can be observed in kidneys from patients who never received calcineurin inhibitors [71]. Thus, the actual contribution of calcineurin inhibitors to renal

allograft loss as well as a reliable risk–benefit analysis of calcineurin inhibitors is still a matter of ongoing debate [72].

Differential diagnosis: interstitial fibrosis/tubular atrophy (IF/TA)

In the past, the term "chronic allograft nephropathy (CAN)" has been widely used in the literature to describe a final common fade of kidney allografts. Unfortunately, this term more and more became a waste basket for a variety of poorly understood conditions in fact representing different disease entities. However, it is obvious that the key to deciphering the reasons for allograft failure is the understanding of individual diseases rather than interpreting CAN as an entity [3, 72]. Therefore, the term CAN has been eliminated from the Banff classification and the use of IF/TA is reserved for those cases only in which no specific disease entity can be identified as the cause of chronic allograft damage after taking into consideration all available clinical, serological, and histological information [73].

Key summary points

While T-cell-mediated rejection is well controlled with modern immunosuppressive drugs, antibody-mediated rejection is increasingly recognized as a major contributor to renal allograft loss. As it should be the paramount aim to uncover specific diseases in kidney allograft biopsies, the use of the unspecific term "chronic allograft nephropathy" is discouraged.

Key research points

The histopathological diagnostic criteria for antibody-mediated kidney allograft rejection are currently under review, as the morphological spectrum of this disease is expanding. The utility of complement split product C4d is limited because of its lack of sensitivity. "C4d-negative antibody-mediated rejection" is now widely recognized.

Questions (answers are provided following the reference list)

1. Antibody-mediated (humoral) rejection—What is correct?
   a. Is exceedingly rare later than 1 year after transplantation
   b. Presents with tubulitis in the kidney biopsy
   c. Is one important contributor to allograft loss
   d. Only affects ABO-incompatible transplant recipients
2. Chronic antibody-mediated rejection—What is wrong?
   a. Is characterized by structural remodeling of the kidney microvasculature
   b. By definition requires detection of a donor-specific antibody
   c. Is synonymous to "chronic allograft nephropathy"
   d. Electron microscopy is a helpful diagnostic tool in this context
3. Endarteritis/Endothelialitis—What is wrong?
   a. Is considered a sign of T-cell-mediated rejection according to the current Banff classification
   b. Is currently disregarded for the diagnosis of acute rejection if not accompanied by an interstitial inflammatory infiltrate or tubulitis
   c. May be antibody mediated in some cases
   d. Affects small as well as larger intrarenal arteries
4. ABO-incompatible transplantation—What is wrong?
   a. Diagnosis of antibody-mediated rejection in these cases is based upon presence or absence of C4d-staining in peritubular capillaries
   b. The outcome is comparable to ABO-compatible kidney transplantation
   c. Is performed in children as well as in adults
   d. May represent one of the scenarios in which accommodation occurs.
5. Borderline acute cellular rejection—What is correct?
   a. Designates cases in which a diagnosis of acute cellular rejection can not be made because of insufficient material
   b. Designates cases that are "borderline" between acute cellular and acute humoral rejection
   c. Designates cases in which either the amount of interstitial infiltrate or the degree of tubulitis is not sufficient to make a diagnosis of acute cellular rejection
   d. Is always treated as an acute cellular rejection

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Correct answers to questions:

1 C
2 C
3 B
4 A
5 C