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Pathology of the kidney allograft

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ABSTRACT

The kidney biopsy still represents the best approach to diagnose renal transplant complications. It is considered the gold standard in the diagnosis of rejection and non-rejection complications. Although invasive, it is a safe procedure with a very low complication rate. With adequate sampling, changes related to antibody-mediated rejection (ABMR) and T-cell mediated rejection (TCMR) can be identified. However, the pathologist needs to be aware of the many other complications, not related to rejection, that can affect the allograft function. Examples include viral infections, drug toxicity, systemic diseases such as hypertension and diabetes, and recurrent or de novo glomerulopathy, among others. In this article, we review the recent classification of pathology of the kidney allograft, with reference to recent consensus reached at the most recent Banff renal allograft classification meetings, and also highlight common non-rejection complications of the kidney transplant.

Introduction

The kidney transplant biopsy is still accepted as the gold standard for the diagnosis of kidney transplant dysfunction, and with advances in clinical kidney transplantation, biopsies are increasingly being used for:

1 surveillance of clinically stable transplants (i.e., protocol biopsies) for the diagnosis of subclinical acute and chronic rejection, and chronic antigen-independent injury;
2 evaluation of deceased donor organ quality and suitability for transplantation particularly in expanded criteria and donors after cardiac death;
3 guidance for therapy; and
4 assessment of immune tolerance through immunohistochemistry, genomic and transcriptomic analysis.

Indication biopsies are performed in the setting of kidney allograft dysfunction as defined by a 25% incremental change in serum creatinine above the steady-state level, proteinuria, and/or abnormal urinary sediment.

The most common histological diagnoses in transplant biopsy series vary according to the practices in immunosuppression and advances in transplant pathology understanding. Acute rejection, calcineurin inhibitor (CNI) toxicity, chronic allograft injury of immune or non-immune nature, recurrent/de-novo glomerular disease, and post-transplant lymphoproliferative disorders having been recognized since the early CNI era. With increasing use of potent induction agents and immunosuppressants, allograft viral infections – such as BK nephropathy – have been added to the spectrum of acute and chronic allograft dysfunction. Additionally, with increasing numbers of sensitized kidney transplant recipients and the use of C4d staining, antibody-mediated rejection (ABMR) has been identified as a common cause of dysfunction in acute and chronic stages of transplantation.

In this article we will review the pathology of the kidney allograft, including acute and chronic changes related to cellular rejection, antibody-mediated rejection and other common non-rejection related complications of the renal allograft.

Pathology of the kidney allograft

Depending on the series, graft dysfunction occurs in 30–60% of kidney transplants, and biopsy remains the gold standard for evaluation. Biopsies are particularly useful in separating rejection vs. non-rejection and to guide therapy.[1] On average, biopsy findings change the clinical diagnosis in 36% of cases and therapy in nearly 60%, while avoiding unnecessary immunosuppression in approximately 20% of cases.[1-6] The sensitivity of the kidney biopsy depends on the biopsy size, number of cores, and amount of cortex sampled. The reported sensitivity of two core biopsies is close to 99%,[7,8] and for specimen adequacy at least 7 non-globally sclerotic glomeruli and 2 cross sections of arteries must be present to evaluate. Arguably, the adequacy of the sample is relative to the underlying pathology. For instance, the finding

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Table 1
Pathologic classification of renal allograft diseases/conditions.

I- Immunologic Rejection
- Antibody-Mediated Rejection
- Hyperacute Rejection
- Acute Humoral Rejection
- Chronic Humoral Rejection
- T-cell Mediated Rejection
- Acute T-cell Mediated Rejection
- Chronic T-cell Mediated Rejection
II- Non-rejection injury
Acute Tubular Injury
Drug Toxicity (Calcineurin Inhibitors, OKT3, Rapamycin)
Infection (BK virus, CMV, Adenovirus, EBV)
Acute Tubulointerstitial Nephritis
Interstitial Fibrosis and Tubular Atrophy, no evidence of specific etiology
Post-Transplant Lymphoproliferative Disorder
Artery/Vein Thrombosis or stenosis
Obstruction, urine leak
III - Recurrent Primary Disease
Focal and Segmental Glomerulosclerosis (FSGS)
IgA Nephropathy
Membranoproliferative Glomerulonephritis (MPGN)
Membranous Nephropathy
Lupus Nephritis
Diabetes Mellitus
Amyloidosis
IV- Allo/Auto antibody-mediated diseases
De-novo Glomerulopathies
Anti-GBM in Alport Disease
Anti-TBM disease
Nephrotid syndrome in Nephrin-deficient recipients
V - "Pathology" of Allograft Tolerance

CMV: cytomegalovirus, EBV: Epstein-Barr virus, GBM: glomerular basement membrane, TBM: tubular basement membrane.

of only one artery with intimal arteritis is sufficient for the diagnosis of acute vascular rejection. Similarly, the finding of acute crescentic glomerulonephritis in a biopsy with only 2 non-sclerotic glomeruli present would be sufficient for a diagnosis.

Kidney allografts can suffer immune damage, both cellular and antibody-mediated, and therefore show signs of acute or chronic rejection (Table 1). Additionally, there are a number of non-rejection related causes of allograft injury that may affect the allograft at any time point. Immunosuppressive drugs, especially calcineurin inhibitors, can cause acute or chronic changes as well. Viruses, including polyoma (BK) virus, cytomegalovirus, adenovirus, or Epstein-Barr may infect the allograft under appropriate conditions. The kidney allograft may also exhibit changes related to recurrence of the primary glomerulopathy (ie. focal and segmental glomerulosclerosis, IgA nephropathy, membranous glomerulopathy, membranoproliferative glomerulonephritis), or the primary disease process (lupus nephritis, diabetes mellitus), but the glomerulopathy can also appear as a “de-novo” process without any prior history. It has been recognized that some allograft leukocytic infiltrates develop a level of tolerance and are not necessarily related to rejection. [9-11] Products of these infiltrates may be detected in the urine of patents with normal renal function and graft tolerance.[12] Hence, these unique cases could be regarded as a category of allograft tolerance.[9,10,13]

Traditionally, three major forms of rejection are recognized: hyperacute rejection, acute rejection, and chronic rejection. Acute rejection, either cellular or antibody-mediated, can happen in the allograft either separately or concurrently. These can occur even with changes of chronic allograft injury or findings not related to rejection. In order to standardize diagnoses and reporting on allograft kidney biopsies, a classification system known as “Banff” classification was developed through a combined effort between pathologists, transplant physicians, and researchers in Banff, Canada [14]. This system has undergone a number of significant revisions and modification since it was first published in 1993, the most recent revisions happening in 2017 in Barcelona, Spain that led to the current revised Banff’17 classification (Table 2).[15] A meeting was held in 2019, but the revisions/consensus have yet to be published.

Table 2
Banff diagnostic categories for renal allograft biopsies - Banff’17 updates.

1- Normal biopsy or non-specific changes
2- Antibody-mediated changes
Active ABMR; all 3 criteria must met for diagnosis
Histologic evidence of acute tissue injury, including 1 or more of the following:
Microvascular inflammation ($g > 0$ and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute
TCMR, borderline infiltrate, or infection, ptc ≥ 1 alone is not sufficient and g must be ≥ 1
Intimal or transmural arteritis ($v > 0$)1
Acute thrombotic microangiopathy, in the absence of any other cause
Acute tubular injury, in the absence of any other apparent cause
Evidence of current/recent antibody interaction with vascular endothelium, including 1 or more of the following:
Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
At least moderate microvascular inflammation ([g + ptc] ≥ 2) in the absence of recurrent or de novo glomerulonephritis, although in the presence
of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥ 1
Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated
Serologic evidence of donor-specific antibodies (DSA to HLA or other antigens)
Chronic active ABMR; all 3 criteria must be met for diagnosis
Morphologic evidence of chronic tissue injury, including 1 or more of the following:
Transplant glomerulopathy (cg >0) if no evidence of chronic TMA or chronic recurrent/de novo glomerulonephritis; includes changes evident by electron microscopy (EM) alone (cg1a)
Severe peritubular capillary basement membrane multilayering (requires EM)3
Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of TCMR, but are not required
Identical to criterion 2 for active ABMR
Identical to criterion 3 for active ABM
3- Suspicious (Borderline) changes for acute TCMR
Biopsies without intimal or transmural arteritis, and with foci of tubulitis ($t > 0$) with minor interstitial inflammation (i0 or i1), or moderate-severe interstitial inflammation (i2 or i3) with mild (t1) tubulitis; retaining the i1 threshold for borderline with $t > 0$ is permitted although this must be made transparent in reports and publications
4- T-cell-mediated rejection
Acute T-cell-mediated rejection (Type/Grade)
IA. Significant interstitial inflammation ($>25\%$ of parenchyma) and foci of moderate tubulitis
IB. Significant interstitial inflammation ($>25\%$ of parenchyma) and foci of severe tubulitis
IIA. Mild to moderate intimal arteritis
IIB. Severe intimal arteritis comprising more than 25% of the luminal area
III. Transmural arteritis and/or arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation
Chronic Active T-cell mediated-rejection
Grade IA
Interstitial inflammation involving $>25\%$ of the total cortex (ti score 2 or 3) and $>25\%$ of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with moderate tubulitis (t2) involving 1 or more tubules, not including severely atrophic tubules5; other known causes of i-IFTA should be ruled out
Grade IB
Interstitial inflammation involving $>25\%$ of the total cortex (ti score 2 or 3) and $>25\%$ of the sclerotic cortical parenchyma (i-IFTA score 2 or 3) with severe tubulitis (t3) involving 1 or more tubules, not including severely atrophic tubules5; other known causes of i-IFTA should be ruled out
Grade II
Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima)
5- Interstitial fibrosis and tubular atrophy, no evidence of any specific etiology
Grade I. Mild interstitial fibrosis and tubular atrophy ($<25\%$ of cortical area)
Grade II Moderate interstitial fibrosis and tubular atrophy (26–50% of cortical area)
Grade III Severe interstitial fibrosis and tubular atrophy ($>50\%$ of cortical area)
6- Other.
Changes not considered to be due to rejection, acute or chronic

Adapted from [15, 24, 41].

Antibody-mediated rejection

In the recent decades, with new techniques to detect donor-specific antibodies (DSA) and the development of C4d immunolabeling, three forms of antibody-mediated rejection and graft injury have been defined: Hyper-acute rejection, active antibody- mediated rejection (Active ABMR), and chronic active antibody-mediated rejection (Chronic Active ABMR). [15–19]

Hyper-acute rejection

Hyper-acute rejection occurs within minutes to hours in the post-transplant period. It occurs in pre-sensitized patients who have circulating HLA, ABO, or other alloantibody-to-donor endothelial surface antigen and is usually irreversible.[20] At implantation, the graft rapidly becomes dark and cyanotic following renal artery anastomosis. If several hours, or even days, have passed before the graft is removed, a biopsy would find hemorrhagic infarction of the kidney parenchyma. The earliest light microscopic changes are swelling of vascular endothelial cells accompanied by neutrophil margination in glomerular and interstitial capillaries. Fibrin thrombi within glomerular capillaries and within arterioles follow, with subsequent hemorrhage, necrosis, and infarction. In these circumstances, C4d immunolabeling shows diffuse positive staining within peritubular capillaries. Early in the process, however, C4d may be negative.[21]

Active antibody mediated rejection (Active ABMR)

Patients with Active ABMR present with acute allograft dysfunction, elevated serum creatinine, and occasionally by reduced urine output and/or tenderness of the graft. Active ABMR occurs most often within the first few weeks post transplantation, but can happen at any time, particularly when immunosuppression is decreased due to non-compliance or dose reduction. Pre-sensitization via pregnancies, blood transfusions, or prior transplants are major risk factors. By light microscopy, the earliest finding is neutrophil or leukocyte margination in dilated peritubular capillaries (Fig 1). Peritubular capillaritis is followed by endothelial injury and thrombosis of glomerular and interstitial capillaries. The interstitium typically shows variable degrees of edema and in some cases hemorrhage. Macrophages are recognized as a common intracapillary cell in ABMR.[22] Because of the short half-life of immunoglobulins and complement components, immunofluorescence studies don't reveal specific antibody or complement deposition. However, C4d, a stable degradation product of the C4, binds covalently to tissue proteins and can remain for 7–10 days, thus serving as a surrogate marker for active antibody-mediated damage.[16-19] The diagnostic pattern of C4d immunolabeling in ABMR is strong, linear, smooth, and circumferential staining of peritubular capillaries (Fig 1). It is recommended to perform C4d immunolabeling on frozen preparations due to an associated higher sensitivity. Immunohistochemistry on formalin-fixed paraffin embedded tissue may be an option when frozen tissue is unavailable.[21,23,24] C4d, however, may not be a reliable marker of acute antibody-mediated rejection in ABO incompatible allograft, as over 80% of protocol biopsies, without evidence of histologic injury, in this setting have shown diffuse staining of peritubular capillaries.[25] C3d, a stable degradation product of C3, may act as a marker of antibody-mediated rejection in ABO incompatible grafts.[25] It has been reported that more severe forms of antibody-mediated rejection can happen in biopsies positive for C3d.[26,27] As explained below, it is not required to have C4d staining to diagnose ABMR.[24]

The diagnostic criteria for active antibody-mediated rejection requires the demonstration of the following: 1- Morphologic evidence of acute microvascular injury, 2- Evidence of antibody interaction with vascular endothelium or increased expression of genes transcripts in the biopsy validated for ABMR, and 3- Serologic evidence of circulating donor-specific HLA or other anti-donor endothelial antigen. (Table 2, category 2).[15] All three criteria must be present for an ABMR diagnosis.

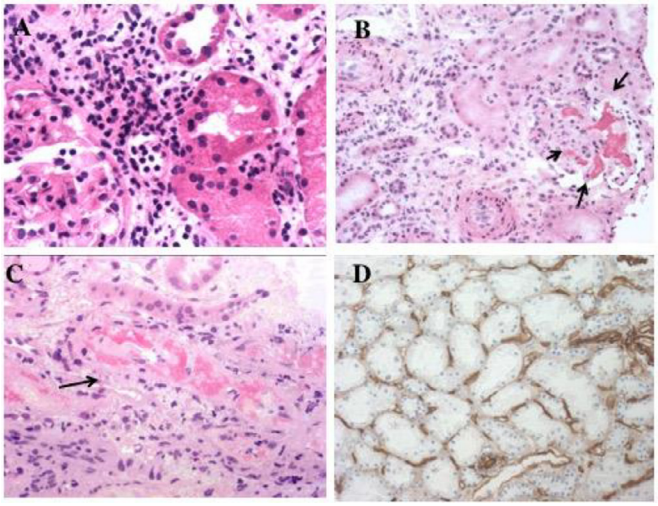

Fig. 1. Active Antibody-Mediated Rejection. A- Dilated peritubular capillaries and moderate leukocyte margination, representing peritubular capillaritis (H/E, 200X); B- Glomerulus with intracapillary fibrin thrombi (arrows), normal mesangial matrix and cellularity and normal capillary wall thickness (H/E, 100X); C- Acute vascular rejection with transmural arterial fibrinoid necrosis (arrow, H/E, 200X); D- C4d immunolabeling of paraffin section preparation depicts diffusely positive peritubular capillaries with a strong, smooth, and linear pattern of staining (C4d Immunohistochemistry, 100X).

Chronic active antibody mediated rejection (Chronic active ABMR)

After the elimination of chronic allograft nephropathy (CAN) by the Banff'05 meeting,[28] it is recommended that pathologists identify the specific etiology when reporting biopsies with chronic allograft injury. The chronic injury may be rejection-related (antibody or cellular) or non-rejection related. When no etiology is identified the biopsy could be classified as "interstitial fibrosis and tubular atrophy without evidence of any specific etiology" (Table 2, category 5).

Several groups have demonstrated that circulating anti-HLA class I/II antibodies, either donor or non-donor specific, have been found in a significant number of renal allograft recipients with subsequent chronic allograft loss.[29-31] Pathologic findings associated with chronic allo-immune injury are transplant arteriopathy and transplant glomerulopathy. Transplant arteriopathy histologically presents as progressive narrowing/occlusion of medium to large caliber arteries by a dense fibro-intimal proliferation (Fig.2). Transplant glomerulopathy is characterized by global duplication of glomerular basement membranes, accompanied by mesangial expansion and intracapillary mononuclear cells, resembling a membranoproliferative pattern of glomerular injury (Fig. 2). Patients with this pattern often have significant proteinuria. These findings have been shown to be significantly associated with diffuse C4d labeling of peritubular capillaries.[16,32-35] Transplant glomerulopathy is strongly associated with circulating donor-specific HLA antibodies and a history of prior ABMR and is associated with a 3-year graft survival of approximately 50%.[17,36] Similar to Active ABMR, the diagnostic criteria for chronic ABMR (Table 2, category 2) has been defined.[28,37] Three elements should be present, which include both criteria 2 and 3 from the active ABMR criteria in addition to histologic evidence of chronic injury. Evidence of chronic injury can manifest as arterial intimal fibrosis without elastosis, duplication of glomerular basement membrane, multi-lamination of peritubular capillaries basement membrane and/or interstitial fibrosis with tubular atrophy.[15]

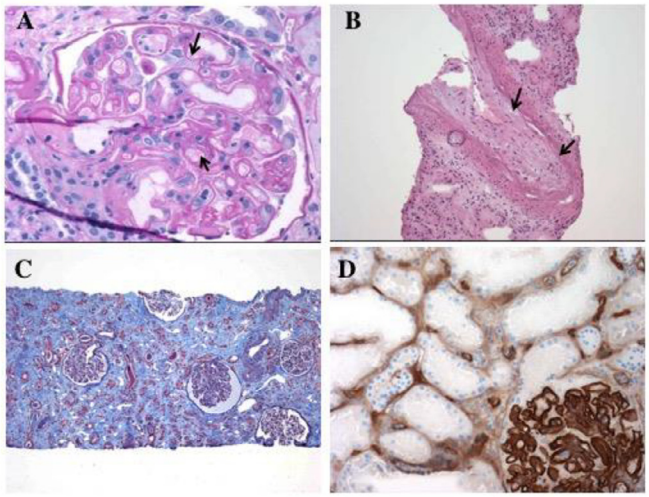

Fig. 2. Chronic Active ABMR. A- Transplant Glomerulopathy. Glomerulus shows global duplication of capillary walls (arrows) with segmental intracapillary hypercellularity and cellular interposition, 400X, PAS. B- Transplant arteriopathy. The artery depicted reveals severe fibrointimal thickening (arrows) and luminal narrowing (100X, HE). C- Core kidney biopsy with severe interstitial fibrosis and tubular atrophy (Trichrome, 100X). D. C4d Immunoperoxidase labeled biopsy shows round, smooth staining of peritubular capillaries (200X).

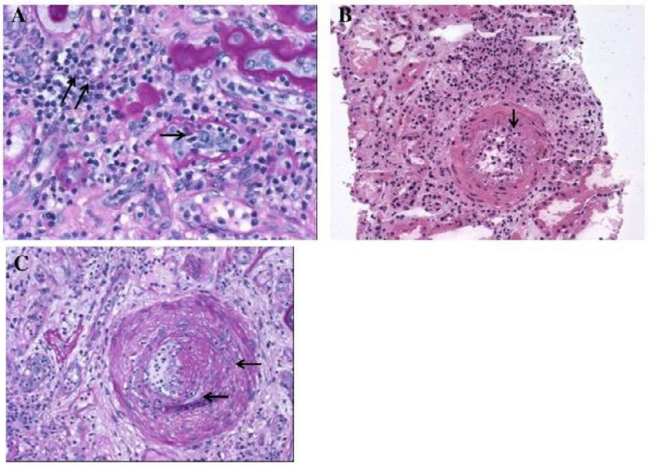

Fig. 3. T-cell Mediated Rejection. A- Tubulointerstitial acute T-cell mediated rejection with severe tubulitis (arrow) and severe interstitial mononuclear inflammation (double arrows), PAS, 400X. B- Endarteritis, mild to moderate. The artery depicted in the center of the biopsy reveals mild to moderate intimal mononuclear inflammatory infiltrate (arrow). Associated interstitial inflammation and tubulitis are also noted (H/E, 100X). C- This artery reveals severe fibrointimal proliferation with luminal narrowing along with intimal mononuclaer inflammation (arrows), representing an example of chronic active T-cell mediated rejection grade II. Interstitial fibrosis and chronic inflammation are also present (PAS, 200X).

Acute T-cell mediated rejection (Acute TCMR)

Acute TCMR is defined as the rapid loss (within days) of allograft function due to a T-cell mediated rejection. Acute TCMR can happen at any time post-transplantation, even years after the transplant if the immunosuppression is reduced or stopped. T cells recognize donor histocompatibility antigens in the kidney, affecting tubules, interstitium, and vessels, separately or in combination. Acute TCMR is characterized by interstitial infiltration by mononuclear cells, including lymphocytes and monocytes, accompanied by interstitial edema, acute tubular injury, and tubulitis. Histologically, tubulitis presents as invasion of tubules by mononuclear cells (lymphocytes or macrophages) across the tubular basement membrane (Fig. 3). Tubulitis should not be diagnosed on atrophic tubules. Grade IA cellular rejection requires the presence of inflammation in >25% of intact cortical interstitium accompanied by moderate tubulitis (t2) (Table 2, category 4). Interstitial inflammation or tubulitis of lesser degree shall be classified as "suspicious" for acute T-cell mediated rejection (Table 2, category 3). Grade IB has identical requirements as IA but with severe tubulitis (t3). Vascular (type II) acute T-cell mediated rejection is defined by the presence of mononuclear cells beneath the vascular endothelium ($v>0$, Fig. 3). Grade II is further divided into IIA, requiring mild to moderate intimal arteritis (v1) and IIB, requiring severe intimal arteritis (v2). [15] The finding of lymphocytes adherent to the endothelium or in the adventitia alone is not considered diagnostic of vascular cellular rejection. Likewise, venulitis is not included in the definition of vascular rejection.[20] One mononuclear cell beneath the arterial endothelium is sufficient for the diagnosis of endarteritis.[7,38] In severe cases, the intima of the vessels may be expanded by edema and fibrin deposition with endothelial swelling, proliferation, and degeneration. Transmural mononuclear infiltrates can be found affecting the media with focal myocyte necrosis, features that constitute type III vascular rejection (Table 2, category 4).

Regarding isolated "V" lesions, this scenario refers to endarteritis with little or no associated tubulointerstitial inflammation, usually classified as v1. These lesions have been seen associated with different circumstances, including ABMR, TCMR, and ischemic changes.[39] In Banff 2013 it was reported that patients with these lesions had a 3.51-fold change to lose the allograft. Therefore, these lesions should be treated as acute rejection in order to prevent long term kidney transplant damage/failure.[24,40]

Chronic active T-cell mediated rejection (Chronic active TCMR)

Chronic active TCMR is a form of chronic graft injury due to ongoing T-cell mediated immunologic reaction to donor antigens. This process is active and progresses slowly, over months to years. Two concepts are important in defining this category, total inflammation score of the cortical parenchyma (ti) and inflammation in areas of interstitial fibrosis and tubular atrophy (i-IFTA).[15,41] Chronic active TCMR grade I requires inflammation involving >25% of the total cortex (ti score 2 or 3), and >25% inflammation of the sclerotic kidney parenchyma (i-IFTA score 2 or 3) >25%, as well as tubulitis. The degree of tubulitis separates grade I into IA (t2) and Grade IB (t3). Grade II is defined by the presence of chronic allograft arteriopathy.[15] This may be seen concurrently with ABMR, both chronic and active, which would be a separate diagnosis. However, in the setting of concurrent findings meeting criteria for active TCMR, only chronic active TCMR should be diagnosed.

Other complications

BK-virus nephritis

BK virus, is a member of the polyomavirus family and is related to both the JC virus and simian virus 40 (SV40). It is an important cause of tubulointerstitial inflammation of the kidney allograft due to reactivation of a latent infection in the immunosuppressed. The condition is characterized by a prominent interstitial mononuclear infiltrate and tubulitis. Given its resemblance to acute cellular rejection, it is crucial to accurately make the diagnosis to guide appropriate treatment, ie. reduction of immunosuppression in BK-virus positive biopsies vs. increase of immunosuppression in cases of rejection. The main histologic findings are the presence of enlarged, atypical nuclei with smudgy, ground glass, basophilic inclusions within tubular epithelial cells. Confirmation by immunolabeling with antibodies for SV40 is available.

Banff classifications of BK-virus separate cases into class I, II, and III depending on the number of tubules involved. Tubules are considered involved if they either demonstrate viral histologic changes on light microscopy or positive immunohistochemical staining.[42,43]

Acute tubular necrosis

Acute tubular necrosis of the allograft is a common complication, presenting in the immediate postoperative period and it is usually the result of prolonged warm or cold ischemia, and is particularly common in cadaveric transplants.[44] If transient dialysis is required during the first week post-transplantation, the term delayed graft function (DGF) is used. If the graft never produces urine the allograft is considered a "primary nonfunction" (PNF). DGF has been reported to occur in 20–25% of deceased donor allograft recipients and is more common in those kidneys from asystolic donors (40–80%).[45,46] The average duration of DGF is 10–15 days. DGF is a clinical term that encompasses several possible pathologic processes, including acute ischemic injury related to cold and warm ischemia time, and other causes that may affect the allograft, alone or in conjunction with acute ischemia, such as drug toxicity (especially calcineurin inhibitors), acute cellular or antibody-mediated rejection, glomerular endothelial injury and surgical complications at the anastomotic site. In the immediate post-transplant period, a biopsy is indicated if renal function does not recover and/or remains marginal. The biopsy is useful in this scenario to rule out rejection, drug toxicity, or other non-ischemic related injuries. In one series, 18% of patients with DGF had acute rejection in biopsies taken within a week post-transplant.[47] As in native kidneys, ATN is characterized by flattening of tubular epithelial cells, loss of the brush border, focal epithelial coagulation necrosis and apoptosis, cytoplasmic basophilia, and evidence of epithelial regeneration. There may be interstitial edema, but interstitial inflammatory cells are usually sparse. Tubulitis and neutrophilic margination of peritubular capillaries are not findings consistent with ATN. Peritubular capillaries will negative for C4d. The finding of diffusely positive peritubular capillaries for C4d in the setting of ATN is consistent with type I acute antibody-mediated rejection in the Banff 2017 revised criteria (Table 2, category 2). Patients are maintained on dialysis as needed and calcineurin inhibitors are withheld until renal function recovers. Approximately 95–98% of grafts with DGF recover; 50% within 10 days and 83% within 20 days post-transplantation.[48]

Recurrent glomerular diseases

Recurrent glomerular disease is a small but significant problem in kidney transplants, affecting 1–8% of allografts. The diagnosis of recurrent disease requires that the primary kidney disease had been appropriately identified and that the allograft biopsy undergoes adequate microscopic evaluation. Most recurrences occur within 6 months. The most common glomerular disease that recurs in the allograft (95–100% recurrence) is membranoproliferative glomerulonephritis with dense deposit disease (formerly type II), followed by immune-complex related membranoproliferative glomerulonephritis (formerly type I (40–70%), IgA nephropathy/Henoch-Schoenlein purpura (30–50%), focal segmental glomerulosclerosis (30–40%), and hemolytic uremic syndrome (30%, non-epidemic form). Lower rates are reported for membranous glomerulopathy (10%), anti-GBM disease (5–10%), and lupus nephritis (less than 5%).[49] Systemic diseases that commonly recur in the allograft include diabetic nephropathy, amyloidosis, oxalosis, and Fabry's disease.

De novo glomerular disease

A "de novo" glomerulopathy is diagnosed when the allograft develops a glomerular disease that is different from the original disease of the native kidney. Therefore, documentation of the original disease is necessary required. As is the case in the majority of "recurrent glomerulopathies," "de novo glomerulopathies" are diagnosed incidentally in biopsies obtained during rejection episodes or in the evaluation of newly diagnosed proteinuria and/or active urinary sediment.

Membranous glomerulopathy is the most common de novo glomerular disease to occur in the allograft with a reported incidence of 2–5%.[49] The average presentation occurs 2 years after transplantation with proteinuria (sometime in the nephrotic range). De novo anti-glomerular basement membrane disease occurs in up to 15% of kidneys transplanted for end-stage hereditary nephritis.[50] Alport's kidneys fail to express the autoantigen of Goodpasture's syndrome, and therefore patients with Alport's may lack self-tolerance to certain alpha chains of type-4 collagen. These can be recognized as foreign antigens after transplantation, initiating an immune response. Some patients develop only linear IgG deposits in the allograft without evidence of nephritis. Others develop severe crescentic glomerulonephritis with identical morphology of anti-GBM disease in native kidneys, a condition that can lead to allograft failure.

De novo focal and segmental glomerulosclerosis (FSGS) in the allograft can occur in different settings, such as: (1) the result of hyperfiltration due to loss of nephrons and fibrosis or in adult recipients of pediatric kidneys; (2) in grafts with severe vascular disease with glomerular hypoperfusion and secondary collapsing FSGS; (3) in kidney transplants with other glomerulopathies (i.e. transplant glomerulopathy), or (4) as a new onset primary disease. The outcome is especially poor in those patients who develop collapsing variants of FSGS.[20]

Summary

Kidney allograft biopsies have proven to be a valuable tool and gold standard when managing renal transplant patients and, therefore, their accurate classification is paramount in guiding the appropriate treatment.

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