Pathology of Kidney Transplantation

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Contents

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Abstract

Kidney transplantation has been effectively used as therapy for end-stage kidney disease, thanks to advances in the surgical, immunologic, and therapeutic realms. Decreased mortality and improved quality of life are cited among reasons to continue to pursue transplantation in the growing number of patients with chronic kidney disease (Tonelli et al. Am J Transplant 11(10):2093–2109, 2011). Unfortunately, however, renal allografts are subject to a variety of injuries, including physical, ischemic, immunologic, infectious, therapy-induced, and neoplastic, in addition to the ever-present threat of recurrent and de novo disease. Renal biopsy remains a mainstay in diagnosing and categorizing the type of injury present, so as to best inform the clinical approach (Williams et al. Nat Rev Nephrol 8(2):110–121, 2012). Timely and accurate representation of the histopathologic features present in a representative sample of renal allograft tissue, combined with appropriate ancillary testing, such as immunohistochemical (IHC) stains and molecular-based tests, are necessary to facilitate the best clinical approach to an individual patient and support optimal survival of the graft. This chapter highlights key pathologic features of the common and significant types of injury to which renal allografts are subject, and discusses key diagnostic features of each.

Keywords

Renal allograft · Renal injury · Antibody-mediated rejection · Cell-mediated rejection · Renal infection · Drug-induced renal injury · Ischemic renal injury · Recurrent renal disease · De novo renal disease

Introduction

Renal allografts are vulnerable to a variety of injuries, beginning with the initial surgical procurement of the organ from the donor and continuing through transport and surgical implantation into the recipient. Moreover, once successfully implanted, the allograft, having been introduced into the foreign milieu of the recipient, is subject to further potential insults, including ischemic, immunologic, infectious, therapy-induced and neoplastic, as well as recurrent and de novo disease. Serum and urine laboratory evaluation are typically used to monitor for any hint of compromised renal function, since azotemia or abnormal urinalysis findings are often key indicators of such.

Whether used as part of a protocol, or when clinical suspicion warrants, renal biopsy with thorough and timely pathologic evaluation is key to categorizing the type of injury that may be present at a given time within a renal allograft. Furthermore, the use of ancillary studies on the allograft tissue specimen, including immunohistochemical stains, molecular-based tests, immunofluorescence stains, and electron microscopy can further amplify the information available through a single biopsy specimen. By promptly addressing the histopathologic findings with appropriate therapeutic intervention, a clinician can, in many circumstances, positively impact patient quality of life and graft survival.

This chapter discusses and illustrates key histopathologic findings of the most common and significant injuries encountered in renal allografts, so as to provide a succinct, comprehensive, and up-to-date review of renal transplant pathology. The role of the pathologist as a member of the patient care team is emphasized. Where

appropriate, discussions about ancillary tests are included to promote the best use of the renal biopsy in positively effecting clinical outcomes for patients.

Renal Biopsy: Pathologic Approach

Samples of renal tissue are routinely obtained, processed, and evaluated by a general surgical or renal pathologist in the setting of renal transplantation. A brief overview of the pathologic approach and intent of evaluation follows in this section.

Utility and Approach of Donor Kidney Biopsy

In some circumstances, prior to implantation of a harvested donor kidney, a transplant surgeon obtains a small wedge-shaped, capsular-based sample of the donor kidney and sends it to the pathology laboratory for urgent, on-site evaluation. A general surgical pathologist or renal pathologist can appropriately review the donor kidney sample in this context. In many pathology laboratories, this testing is achieved by means of performing an urgent frozen section of the renal tissue, with rapid, routine hematoxylin and eosin staining and light microscopic evaluation.

The primary intent of this on-site evaluation is to provide verification that the donor kidney is histologically viable and has no significant histopathologic findings that might preclude implantation into the recipient or significantly impact graft survival (Cockfield et al. 2010). Examples of such findings include a heavy burden of chronic damage (as manifest by high numbers of globally sclerosed or diseased glomeruli, significant tubular atrophy, or significant interstitial fibrosis), chronic vascular damage (such as severe arteriolar hyalinosis), heavy acute inflammation (that might suggest infection), nonviable parenchyma (necrosis), or unsuspected neoplasm, among others. The pathologist generally calls the surgeon in the surgical suite within minutes of reviewing the specimen, and reports on the viability of the renal tissue, as well as the status of glomeruli, tubules, interstitium, and blood vessels. Based upon the pathologist's report, the surgeon may either proceed with implanting the kidney or refuse to implant the organ, given a significant short- or long-term risk to the patient. It is worth noting that performance of on-site evaluation of donor samples varies across the globe, and a recent systematic literature review has called for a reexamination of this practice in the context of appropriate patient care (Wang et al. 2015).

Utility and Approach of Allograft Kidney Biopsy

Once a kidney is implanted into the recipient, allograft renal biopsy specimens may be obtained at regular intervals (protocol biopsies), or on an as-needed basis, depending on systemic findings, renal-specific signs and symptoms, or serum or urine laboratory test results. The specimens may be procured in the days immediately following transplantation, or in the months and years thereafter. The biopsy specimens may be procured by the transplant surgeon, a (transplant) nephrologist, or an interventional radiologist with on-site specimen adequacy evaluation performed by a pathologist or technician. Once obtained, renal tissue is often reserved for immunofluorescence and electron microscopic studies, if needed, and the majority of the sample is processed for light microscopic evaluation via paraffin-embedded sections, supplemented by special and immunohistochemial (IHC) stains (see below) (Walker et al. 2004). The primary intent of obtaining samples from the grafted kidney is to determine whether or not there is histopathologic evidence of injury, and if so, to determine the extent of the damage and most likely pathophysiologic mechanism for the injury.

Once obtained, allograft renal biopsy specimens are usually processed on an urgent basis, with the goal of evaluating the sample and determining the presence and extent of injury within hours. In many laboratories, stat processing is employed, with stained microscopic slides available for review within 4–6 hours. Most renal

pathologists advocate for obtaining multiple sections and stains of the specimen, to include a minimum of two hematoxylin and eosin (H&E), two periodic acid-Schiff (PAS), two Masson's trichrome (trichrome), and two Jones methenamine silver (silver) stains. The stains are typically used in a complementary fashion, with H&E stains providing a general overview of all structures, cytoplasmic and nuclear features, PAS stains serving to highlight tubular and glomerular basement membranes, trichrome stains accentuating fibrous tissue and fibrin, if present, and silver stains highlighting the glomerular and tubular basement membranes, as also sclerosis. An immunohistochemical or immunofluorescence stain for C4d is also routinely employed to evaluate for antibody-mediated rejection. Light microscopic review employing all stains is performed and results are typically reported directly by the pathologist to the surgeon or nephrologist.

Discussion with the clinician regarding the presence or absence of specific findings in the allograft may inform additional sections, stains, and ancillary studies, or prompt additional laboratory evaluation. As an example, in the absence of features of rejection, pursuit of immunofluorescence studies and/or electron microscopic studies may be warranted, so as to elucidate the cause of glomerular dysfunction, particularly if the suspicion of recurrent or de novo glomerular disease is high.

Physical Injury and Ischemia

Direct physical injury may occur during implantation of the renal allograft. The surgeon is likely immediately aware of the injury, and will repair the injury at that time (such as direct capsular injury, direct vascular injury). In these circumstances, the injurious effects may or may not have an impact on functioning of the graft postoperatively. If lingering effects of operative injury are suspected or if there is delayed allograft function, an allograft biopsy may be performed. Depending upon the nature of the injury, histopathologic findings may include fibroblastic capsular proliferation with acute inflammation, edema and/or hemorrhage, indicating previous capsular injury with subsequent repair.

Ischemic changes, such as those caused by direct vascular injury or ischemic reperfusion injury, may be manifest in the hours and days following transplantation. If an allograft renal biopsy is performed, the histopathologic changes may be subtle or profound. Subtle changes may include tubular epithelial cell blebbing, vacuolization, or epithelial cell attenuation. Accompanying interstitial edema may be seen. More profound changes may be manifest as overt acute tubular injury or necrosis (ATN). Tubular epithelial cell sloughing with necrotic and apoptotic cells filling or distending the tubular lumina may be present (Salvadori et al. 2015), and manifest in urine sediment as renal tubular epithelial (RTE) cell casts or individual RTEs. If significant vascular injury has occurred, changes may also be seen within the renal cortex proper, including overt necrosis of glomeruli. In some instances, depending upon the timing of the originating vascular insult, significant neutrophilic infiltration of the renal parenchyma can be seen, raising concern for acute bacterial infection. Correlation with urine microscopy and/or culture may be important in such cases to exclude acute pyelonephritis.

Rejection

Acute rejection, both cellular and antibody-mediated, has been shown to be a significant factor in diminished renal allograft survival in a number of studies (El Ters et al. 2013). Many risk factors for developing acute rejection, both cellular and antibody-mediated, have been evaluated, and efforts to identify those recipients of "high immunological risk" continue. In a recent study of multivariate analyses, Lebranchu et al. evaluated a number of recipient clinical and immunological characteristics as well as donor clinical characteristics and transplant-related factors in an attempt to definitively determine the relative contribution of these factors to development of acute rejection. Those risk factors with good quality of evidence and strong impact for developing acute rejection

included younger recipient age, HLA mismatch, presence of anti-HLA antibodies, presence of pre-transplant donor-specific antibodies (DSA), and delayed graft function (Lebranchu et al. 2013). Awareness of the characteristics of antibody-mediated and cellular rejection, as well as their clinical and histopathologic commonalities, is important to providing optimal care of the renal transplant patient.

Antibody-Mediated Rejection (ABMR)

Antibody-mediated rejection (ABMR) remains one of the key effectors of long-term adverse outcomes in kidney transplants (Sellarés et al. 2012; Wiebe et al. 2012). ABMR has been traditionally classified into hyperacute, acute, and chronic ABMR types.

Hyperacute Rejection

Hyperacute rejection, characterized by rejection within minutes to hours, caused by preexisting antibodies with a histopathologic picture of diffuse vascular thrombosis, hemorrhage and ischemic necrosis, and positive C4d staining in peritubular capillaries has become rare due to improved matching strategies (Colvin and Mauiyyedi 2008).

Acute and Chronic ABMR

Acute and chronic ABMR, however, have remained both a diagnostic and therapeutic challenge. Acute and chronic ABMR is initiated by B cell and plasma cell activation that generate donor-specific antibodies binding to HLA and other non-H antigens on the endothelium, initiating a cascade of complement dependent and independent pathways that eventually contribute to capillaritis (Farkash and Colvin 2012). Initial definitions of acute ABMR included neutrophils in peritubular capillaries (PTCs), de novo anti-donor HLA class I antibodies, and C4d endocapillary positivity as key markers. C4d detection can be performed on both fixed and frozen tissue using immunohistochemistry with peroxidase or fluorescent conjugated antibodies. The sensitivity of these tests is low and highly dependent on the density of PTCs in the biopsy, leading to the concept of C4d-negative acute and chronic ABMR. The 2013 Banff criteria acknowledge these limitations with the inclusion of modified diagnostic criteria for ABMR. These include (1) histologic evidence of acute tissue injury, (2) evidence of antibody interaction with vascular endothelium (may or may not have positive C4d staining), and (3) serologic evidence of donor-specific antibodies (Haas et al. 2014) (see Table 1). The threshold for C4d positivity was lowered with a score of greater than 0% staining noted to be positive by IHC (see Fig. 1). The current Banff scheme also standardizes definitions of capillaritis. Absence of peritubular capillaritis or PTC0 is defined as less than three luminal inflammatory cells in 10% or less of cortical PTC, PTC1 is defined as greater than 10% of cortical PTCs involved with 3–4 luminal inflammatory cells, PTC2 is defined as greater than 10% of PTCs with 5–10 luminal inflammatory cells, and PTC3 is defined as greater than 10% of cortical PTCs with greater than 10 inflammatory cells. The cellular

Table 1 Revised (Banff 2013) classification of antibody-mediated rejection (ABMR) in renal allografts

Acute/active ABMR; all three features must be present
1. Histologic evidence of acute tissue injury, including one or more of:
a. Microvascular inflammation, in the form of glomerulitis or peritubularcapillaritis
b. Intimal or transmural arteritis
c. Acute thrombotic microangiopathy (without other etiology)
d. Acute tubular injury (without other etiology)
2. Evidence of recent or ongoing antibody interaction with endothelium, including one or more of:
a. Linear C4d staining in peritubular capillaries
b. Moderate microvascular inflammation (at least)
c. Increased expression of gene transcripts supporting endothelial injury
3. Serologic evidence of donor-specific antibodies (DSAs)

Reference: Haas et al. (2014), p. 277

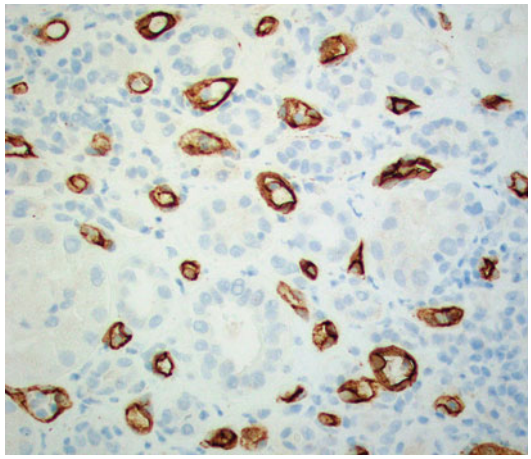

Fig. 1 C4d positive staining in setting of acute antibody-mediated rejection (*AMR*). Peritubular capillaries demonstrate intense positive staining with C4d by immunohistochemical staining (C4d immunostain x400)

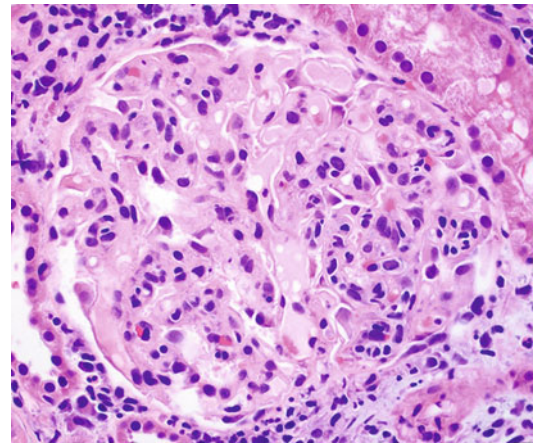

Fig. 2 Thrombotic microangiopathy. The glomerulus demonstrates neutrophilic and lymphocytic inflammation, as also a fibrin thrombus. In such cases, ABMR and acute TCMR may be concurrent (H&E x400)

composition with subsets of mononuclear cells versus polymorphonuclear cell components may also be important, as high monocyte to T cell ratios may be observed with C4d-negative ABMR. The minimum number of inflammatory cells within the glomerulus for a diagnosis of glomerulitis has not been similarly defined, though five or more mononuclear cells/glomerulus are considered to be adequate. Immunohistochemical stains for CD68 may be employed to highlight infiltrating glomerular macrophages.

Chronic stage thrombotic microangiopathy (TMA) is not specific to the ABMR process. The differential diagnosis includes TMA secondary to calcineurin inhibitors or viral infections and can be diagnostically challenging (Nadasdy 2014). Chronic stage TMA and transplant glomerulopathy share morphologic similarities, including light microscopic features of thickened glomerular capillaries with double contours, widening of the subendothelial space, endothelial cell vacuolation and thickening (see Fig. 2). Thickened glomerular capillaries and double contours are typically highlighted on silver stains and electron microscopy. Banff 2013 definitions include cg1 with mild remodeling of the glomerular tufts in 10–25% of glomerular capillaries, cg2 to 25–50% of glomerular capillaries, and cg3 greater than 50% of glomerular capillaries. Of interest is the concept of subclinical ABMR which can also be C4d positive or negative and is defined by the identification of peritubular capillaritis and glomerulitis greater than 0. Identification of subclinical rejection is strongly associated with subsequent interstitial fibrosis, tubular atrophy, and chronic allograft nephropathy (Moreso et al. 2006). Additionally, a recent study has shown that patients with subclinical ABMR experience long-term effects distinct from those patients with subclinical TCMR (Loupy et al. 2015). Banff 2013 guidelines include molecular tests for antibody interaction with vascular endothelium such as measuring of endothelial activation and injury transcripts (ENDATs). In addition, the noninvasive blood test "diagnosing acute rejection in kidney transplant recipients" (DART) prospective multisite study examining the levels of donor-derived cell-free DNA levels using a commercial test (AlloSure) (Bloom et al. 2017) has recently shown that elevation of cell-free DNA levels greater than 1% was associated with acute and chronic ABMR. However, two cases of BK virus injury were also associated with elevated cell-free DNA, indicating that elevated levels may still need to be explored using traditional biopsies.

T Cell-Mediated Rejection (TCMR)

Acute T Cell-Mediated Rejection (TCMR)

Acute T cell-mediated rejection (TCMR) is a relatively common cause of renal allograft dysfunction, particularly in the days to months following transplantation. While less common, acute TCMR can be seen years following transplantation (Rao et al. 1989).

Clinically, acute TCMR may manifest as fatigue, fever, weight gain, or swelling, with accompanying decreased urine output and graft tenderness. Patients may experience an elevation in serum creatinine to varying degrees (Nankivell and Alexander 2010). Accompanying urinalysis findings are usually subtle to nonexistent, but may include hematuria, proteinuria, or inflammation. Sometimes, subclinical acute TCMR may be present, and only is discovered upon a routine allograft biopsy for other reasons or as part of a protocol (Nankivell and Alexander 2010). In many cases, the transplant nephrologist or surgeon will perform an allograft renal biopsy and serologic evaluation for donor-specific antibodies (DSAs) simultaneously. In this way, histopathologic findings in the allograft biopsy specimen can be interpreted in the context of new serologic findings, if any (Haas et al. 2014).

Molecular Diagnostics of Rejection

Given concerns with intraobserver agreement on histopathologic diagnoses for renal allograft biopsy specimens using rejection classification schema (Joh et al. 2006), molecular diagnostic tests may prove beneficial in the near future, offering more specific and sensitive markers for acute TCMR. As molecular diagnostics and mRNA microarray data are gathered, increasing evidence is mounting to support a specific signature or molecular phenotype in the setting of acute TCMR. Further, combining clinical, histopathologic, and molecular-based diagnostic tests may serve to additionally increase the diagnostic power in settings of acute TCMR (Reeve et al. 2009, 2013).

Gross Features of Acute TCMR

Gross changes may be seen within the kidney in acute TCMR some of which may be visualized with appropriate radiologic evaluation (O'Neill and Baumgarten 2002; O'Neill 2014). In cases of severe disease, renal function may be significantly impaired to the point of necessitating graft removal. In such cases, gross findings of organ swelling, significant parenchymal hemorrhage and segmental necrosis consistent with cortical and sometimes medullary infarcts may be seen in the resected graft. In cases of severe vascular injury (such as fibrinoid necrosis) imparted by T cell infiltration, or if accompanying antibody-mediated rejection (ABMR) is present, grossly visible intravascular thrombi may also be noted upon sectioning of the resected organ (Nickeleit et al. 2015).

Light Microscopic Features of Acute TCMR

In acute TCMR, activated T cells infiltrate various renal structures, thereby negatively impacting overall renal function. The degree of cellular infiltration and the structures affected ultimately determine the grade or degree of acute cellular rejection (Solez et al. 2008) (see Table 2). While activated T cells are typically the predominant infiltrating inflammatory cells, accompanying macrophages, neutrophils, plasma cells, and even B cells and eosinophils may be seen. As expected, with cytokine generation, vascular dilation with endothelial cell prominence and interstitial edema are seen, particularly in more severe cases. Careful

Table 2 Banff 97 diagnostic categories for T cell-mediated rejection (TCMR) – Banff'07 update

Type/ grade	Criteria
IA	Significant interstitial inflammation (i2 or i3) and foci of moderate tubulitis (t2)
IB	Significant interstitial inflammation (i2 or i3) and foci of severe tubulitis (t3)
IIA	Mild to moderate intimal arteritis (v1)
IIB	Severe intimal arteritis (v2)
III	Transmural arteritis with or without fibrinoid change and necrosis (v3)

Reference: (Solez et al. 2008), p. 758

evaluation of multiple tissue sections and special stains is warranted, since acute TCMR may be focal. If necessary, immunohistochemical stains such as CD3 for T cells and CD68 for macrophages can be employed to distinctly determine the origin of a specific infiltrating mononuclear cell.

Tubular and Interstitial Changes

Most commonly in acute TCMR, T cells infiltrate cortical tubules, often with associated reactive tubular epithelial and interstitial changes. In some cases, tubulitis may be widespread within a renal allograft sample and easily detected on H&E stains (see Fig. 3a). In other cases, tubulitis may be more difficult to ascertain. PAS stains can be used to highlight tubular basement membranes, thereby accentuating and delineating the location of inflammatory cells (either within tubules or the interstitium) (see Fig. 3b). As mentioned, an immunohistochemical stain for CD3 will also highlight tubulitis (see Fig. 3c).

Determination of the number of infiltrating lymphocytes per tubule cross section is key to classifying the degree of tubulitis as nonexistent (t0, no lymphocytes present), mild (t1, 1–4 cells per tubule cross section), moderate (t2, 5–10 cells per tubule cross section), or severe (t3, greater than 10 cells per tubule cross section) (Racusen et al. 1999). Associated tubular epithelial changes

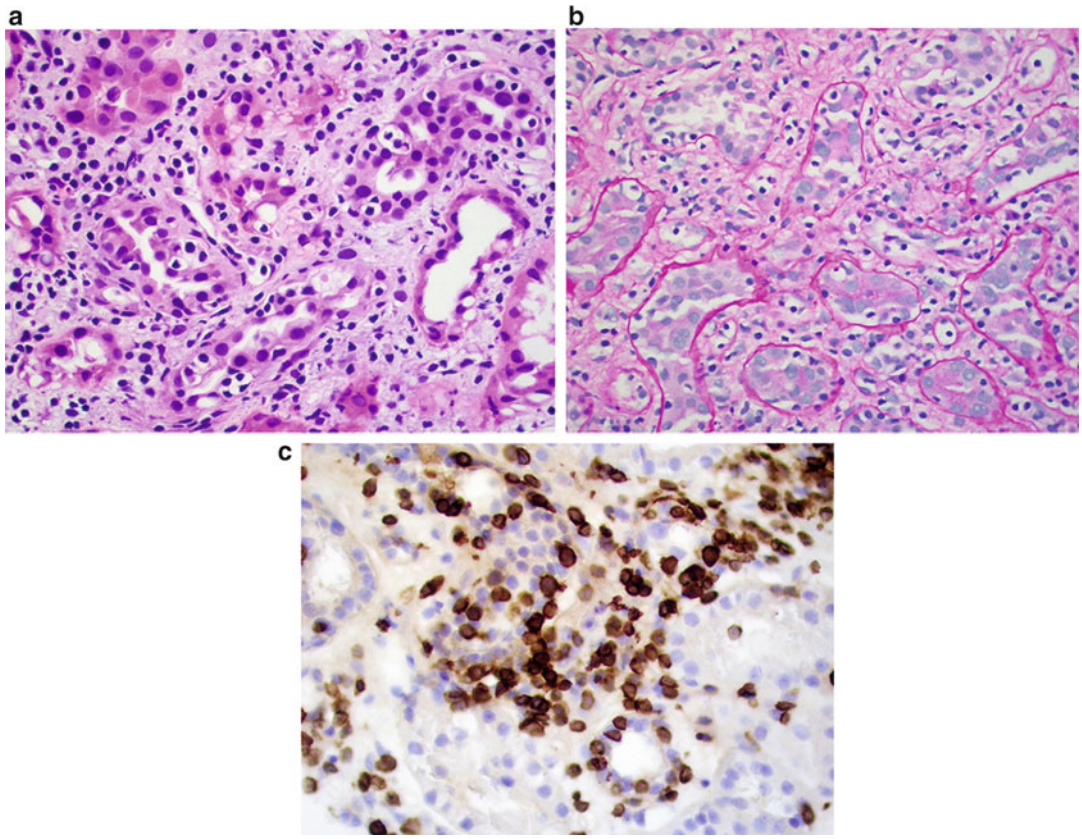

Fig. 3 (**a**) Acute cellular rejection, tubulitis. Cortical parenchyma demonstrates interstitial lymphocytic inflammation and lymphocytes infiltrating tubules, consistent with tubulitis. Note the halos surrounding infiltrating lymphocytes (H&E x400). (**b**) Acute cellular rejection, tubulitis, PAS stain. Use of PAS stain highlights basement membranes, which allows for detection of lymphocytes infiltrating tubules (PAS x400). (**c**) Acute cellular rejection, tubulitis, CD3 stain. Use of immunohistochemical stain for CD3 highlights T cells infiltrating tubules (CD3 immunostain x400)

may include nuclear enlargement, presence of visible nucleoli, and tubular epithelial cell mitoses. In severe cases, overt tubular epithelial cell necrosis may be present. Of note, there is some debate regarding whether a diagnosis of tubulitis should be rendered if inflammation is seen only within atrophic tubules. At this time, most renal pathologists score tubulitis within nonatrophic tubules (Mannon et al. 2010). Detailed review of multiple tissue sections is necessary, given the focal nature of tubulitis that is seen in some cases.

Accompanying interstitial inflammation plays a role in grading rejection, depending upon the percentage of sampled parenchyma that is involved. If less than 10% of the parenchyma is occupied by inflammation, the case is scored as i0; if 10–25% of the parenchyma is involved, a score of i1 is rendered; if from 26–50% of the parenchyma is inflamed, a score of i2 is given, and inflammation occupying greater than 50% of the tissue is scored as i3 (Racusen et al. 1999). In severe cases of acute TCMR, aggregates of interstitial inflammatory cells are typically easy to detect on low-power microscopic evaluation of the renal allograft biopsy specimen.

If accompanying neutrophils demonstrate margination along the endothelium, particularly of peritubular capillaries, acute antibody-mediated rejection or pyelonephritis should be suspected (Solez et al. 2008). Acute TCMR and ABMR or pyelonephritis can be present in the same specimen and may be difficult to delineate.

Glomerular Changes

While not frequent, some cases of acute TCMR may demonstrate mononuclear inflammatory cell infiltration of glomeruli, consistent with glomerulitis. In such instances, reactive glomerular changes, including endothelial cell swelling and occlusion of glomerular capillaries, may be seen (see Fig. 4a). These findings are often segmental but may be global in nature. Use of immunohistochemical stains to delineate glomerular infiltrating CD3-positive T cells can be employed to highlight acute TCMR (see Fig. 4b). Immunohistochemical stains for CD68 may also be used to highlight accompanying infiltrating macrophages.

Less often, infiltrating glomerular neutrophils may be present. If significant numbers of neutrophils are noted, accompanied by intraluminal thrombi or fibrinoid necrosis, ABMR should be considered, and a careful search for arteritis should be undertaken. Additionally, infiltrating glomerular neutrophils may be a manifestation of thrombotic microangiopathy (Racusen et al. 1999). As with tubulitis and interstitial

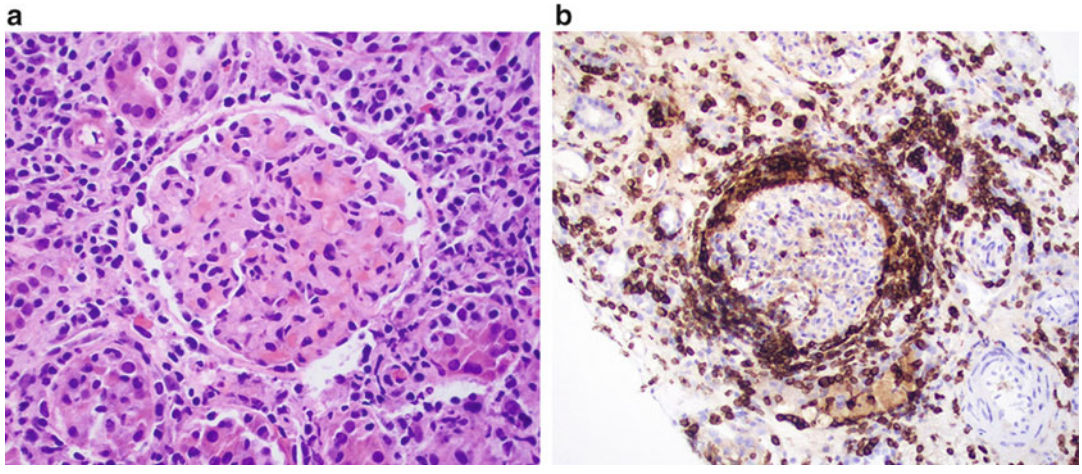

Fig. 4 (**a**) Acute cellular rejection, glomerulitis. Cortical tissue shows a relatively dense lymphocytic inflammatory infiltrate with focal infiltration of a congested glomerulus by mononuclear cells (H&E x400). (**b**) Acute cellular rejection, glomerulitis, CD3 stain. An immunohistochemical stain for CD3 shows T cells surrounding and focally infiltrating a glomerulus with focal infiltration of adjacent tubules as well (CD3 immunostain x200)

inflammation, the degree of glomerulitis should be appropriately documented, and is graded based upon the percentage of glomeruli involved by the inflammatory process (Racusen et al. 1999).

Vascular Changes

Infiltration of arteries by T cells, as demonstrated by histopathologic evaluation, should trigger a diagnosis of at least grade II cellular rejection by the Banff criteria. Such inflammatory cell infiltration is usually accompanied by endothelial cell changes, including swelling and apparent activation. Detection of focal arteritis may be challenging, and as with tubulitis, requires careful review of multiple sections with the aid of special stains. Grading of arteritis is dependent upon a determination of how much luminal area is involved by inflammation in a given artery. For a designation of v1, mild to moderate intimal arteritis must be present in at least a cross section of one artery. A designation of v2 requires inflammation involving at least 25% of the luminal area of one arterial cross section. Changes such as significant transmural inflammation, necrosis of the media, or fibrinoid change warrant a diagnosis of a higher grade of arteritis (v3) and thus, of acute TCMR. Similarly, such changes may also raise suspicion of synchronous ABMR. Notably, in cases of at least moderate acute TCMR with arteritis, associated tubulitis and significant interstitial inflammation will be present. However, some cases may manifest at least mild arteritis (v1), with only minimal to mild tubulitis (t0 or t1) and mild interstitial inflammation (i1) (Racusen et al. 1999; Solez et al. 2008). Changes of acute TCMR may also be present in a background of chronic rejection (see Fig. 5a, b).

Grading of Acute TCMR

Currently, for acute TCMR, the 2007 update to the Banff 97 classification is used by pathologists, nephrologists, and transplant surgeons (Solez et al. 2008). Utilizing a common language for the findings in renal allograft biopsy specimens allows for effective communication and optimal patient care. Additional studies to evaluate criteria for inclusion in the Banff classification are ongoing, with published updates occurring on a relatively regular basis (Haas et al. 2014).

Acute TCMR may occur synchronously with antibody-mediated rejection (ABMR) and with chronic changes in the renal allograft (Racusen et al. 2003). Careful determination of the presence and degree of tubulitis, interstitial inflammation,

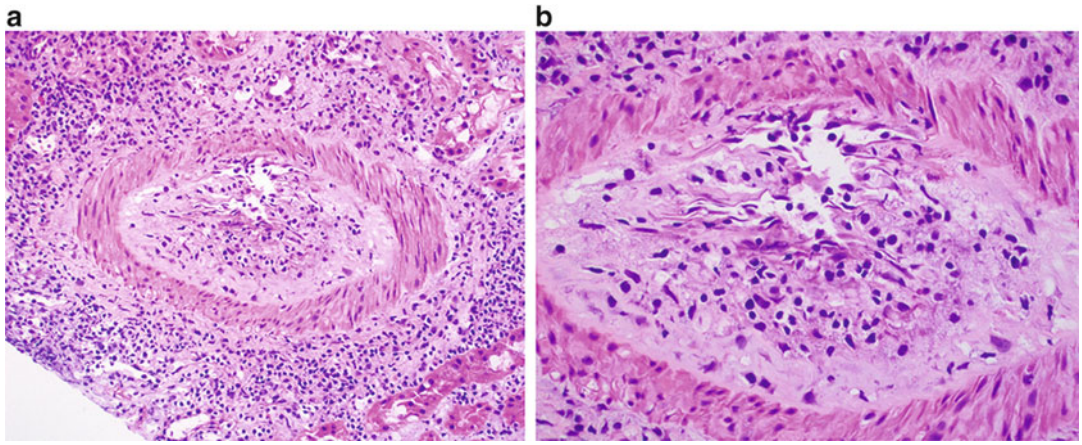

Fig. 5 (**a**) Acute cellular rejection in setting of chronic rejection. This muscular artery shows infiltration of the wall by mononuclear cells, consistent with cellular rejection, as well as significant intimal thickening and marked luminal narrowing, consistent with chronic rejection (H&E x200). (**b**) Acute cellular rejection in setting of chronic rejection, high power. This muscular artery shows infiltration of the wall by mononuclear cells, consistent with cellular rejection, as well as significant intimal thickening and marked luminal narrowing, consistent with chronic rejection (H&E x400)

and arteritis are all essential to determining the overall category or grade of acute TCMR. Allograft biopsy specimens that are categorized as borderline or "suspicious" may demonstrate tubulitis with only minor interstitial inflammation or significant interstitial inflammation with only mild tubulitis and no evidence of arteritis (Solez et al. 2008). In such cases, additional sampling may reveal diagnostic findings that are more definitive for acute TCMR, suggest resolving injury, or indicate sampling errors (Solez et al. 1993). For acute TCMR, cases are graded from I to III, with types I and II being subdivided into A and B subtypes (see Table 2). As mentioned, if at least some degree of arteritis is present, then a diagnosis of at least type II acute TCMR is warranted. A diagnosis of type III acute TCMR rejection is reserved for cases with severe transmural arteritis with or without fibrinoid change and necrosis of the arterial smooth muscle cells (Racusen et al. 2003; Solez et al. 2008). As noted previously, these changes can occur in concert with features of chronic rejection and ABMR.

Immunofluorescence Studies

Immunofluorescence (IF) microscopy utilizing antibodies against immunoglobulin components, light chains, complement components, and fibrinogen can be employed on fresh renal allograft biopsy tissue. If the light microscopic features are diagnostic for acute TCMR, IF may not be performed. However, if IF is pursued in cases of acute TCMR (or even ABMR), fibrinogen may be deposited within blood vessels, particularly if significant vascular injury is present. In the setting of thrombotic microangiopathy, fibrin thrombi can also be easily highlighted. If light microscopic findings are not definitive for acute TCMR or ABMR, immunofluorescence studies can be used to help evaluate for the presence of a recurrent or de novo glomerular disorder, which may be immune complex-mediated (Walker et al. 2004). As noted previously, some institutions perform an immunofluorescence stain for C4d as an alternative to traditional immunohistochemistry to support a diagnosis of ABMR (Solez et al. 2008; Haas et al. 2014).

Electron Microscopy

Electron microscopic (EM) evaluation of glutaraldehyde-preserved renal allograft biopsy tissue may be performed in some cases. If the light microscopic features are diagnostic for acute TCMR or other acute injury, EM may not be performed. Typically, if EM is done in the setting of acute TCMR, glomerular inflammatory cell infiltration (glomerulitis) may be demonstrated, along with interstitial inflammation, tubulitis, and arteritis. Previously suspected or unsuspected chronic changes, such as allograft glomerulopathy and multilayering of the peritubular capillary basement membranes, may be found, as well as evidence of an immune complex-mediated disorder with deposition of characteristic electron dense deposits (Racusen et al. 1999; Haas et al. 2014).

Chronic T Cell-Mediated Rejection (TCMR)

Some features of chronic TCMR may be difficult to distinguish histologically from other forms of allograft injury, such as chronic ABMR, hypertension, and therapy-related injury (Racusen et al. 1999). Changes of chronic TCMR and declining graft function may be expected if the patient has experienced any type of TCMR, particularly if late, or if the episodes of acute TCMR have been more severe with vasculitis (v) with or without accompanying ABMR (Wu et al. 2014). Light microscopic features are used to determine the presence and extent of chronic allograft injury, with the aid of special stains.

Vascular Changes

As might be predicted, vascular changes are a prominent histopathologic feature of chronic TCMR. Significant intimal fibrosis usually associated with varying degrees of luminal compromise and neo-intima formation (chronic allograft arteriopathy) is often seen. Such arterial lesions often show disruption of elastic lamina. Associated foam cells may be present along the intima beneath endothelial cells. Also, mononuclear cells may be seen within the wall,

particularly along the internal elastic lamina (Racusen et al. 1999; Solez et al. 2007).

Glomerular Changes

Glomerular changes of chronic TCMR may not be easy to distinguish from those seen in chronic ABMR, since these injurious mechanisms may occur concurrently in the same allograft. Transplant glomerulopathy is more often associated with chronic ABMR, and is manifest by reduplication of glomerular basement membranes and proliferative changes, often with a membranoproliferative pattern. Glomerular mononuclear cell infiltration may also be seen. These changes may be difficult to distinguish from chronic thrombotic microangiopathy. Glomerular basement membrane reduplication is most easily highlighted with PAS or silver stains (see Fig. 6). Confirmation of characteristic circumferential reduplication of glomerular basement membranes around glomerular capillary loops can be easily detected by electron microscopy (Solez et al. 2008; Haas et al. 2014).

Tubulointerstitial Changes

Chronic TCMR may result in tubular atrophy and interstitial fibrosis, although these findings are not specific. Tubular atrophy is highlighted with PAS stains, and interstitial fibrosis is accentuated with trichrome stains. Accompanying mononuclear cells, including lymphocytes and plasma cells, may also be present within the interstitium, along with mast cells.

Over the years, Banff classifications have relied on estimates of the percentage of parenchyma occupied by interstitial fibrosis and tubular atrophy. Grade I implies that less than 25% of the sampled cortex is involved; grade II is diagnosed when 26–50% of the cortex is involved; and grade III is diagnosed when greater than 50% of the cortical area is involved with interstitial fibrosis and tubular atrophy. Furthermore, these designations are ascribed only when no other etiology for the chronic features is determined (Solez et al. 2007). A recent study attempted to delineate a standardized method for evaluating chronic tubulointerstitial changes, given the interobserver variability in visually assessing tubular atrophy and interstitial fibrosis. Computer-assisted determination of collagen III staining by immunohistochemistry did show promise in this study (Farris et al. 2014). Of note, when evaluating the tubulointerstitial compartment, if significant numbers or clusters of plasma cells are seen, then acute ABMR should also be considered in the differential diagnosis, along with BK virus infection.

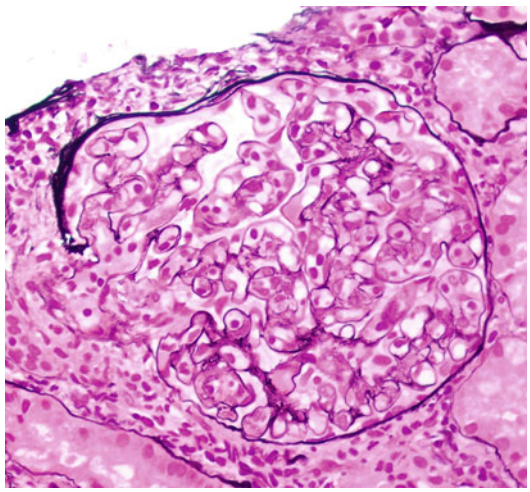

Fig. 6 Chronic transplant glomerulopathy. Focal splitting of the glomerular basement membranes is highlighted on this silver stain (PAM x400)

Infections

Immunosuppressed renal transplant patients are susceptible to both systemic and organ-limited infections of viral, bacterial, or fungal etiology. Viral pathogens, including polyoma virus, cytomegalovirus (CMV), and Epstein-Barr virus (EBV), can cause renal dysfunctions as also graft failure. Virus-induced allograft nephropathy and cellular, as also ABMR, rejection can coexist, giving rise to not only diagnostic, but also therapeutic challenges (Nickeleit and Mihatsch 2004; Celik et al. 2003).

Polyoma virus nephropathy (PVAN), a mainly iatrogenic complication resulting from use of high-dose immunosuppressive drugs, has seen a reduction in incidence from 10.5% to 2.5% with low-dose maintenance immunosuppression

(Cosio et al. 2007). Polyoma BK and JC viruses are associated with transplant nephropathy, with BK virus being the predominant virus. Morphological changes caused by these viruses include nuclear changes with inclusion bodies, cell injury, and rare granulomatous inflammation, commonly affecting ductal and tubular epithelium as also glomerular endothelial cells (see Fig. 7). The viral changes can be noted in both the cortex and medulla, but may be focal and missed on small biopsies. Diagnosis can be established by the presence of characteristic morphologic features or by using ancillary tests including immunohistochemistry, in situ hybridization, or polymerase chain reaction (PCR) (see Fig. 8). The BIFQUIT (Banff Initiative for Quality Assurance in Transplantation) multicentric trial evaluated the reproducibility of BK immunohistochemistry (IHC) at 60 institutions using central review adjudication as well as real-time BK virus PCR estimated loads as standards. Though PCR demonstrated superior sensitivity to IHC as expected, increasing concentrations of viral nucleic acid correlated well with staining intensity in the study, suggesting that BK virus IHC using heat retrieval, citrate or EDTA buffers, and monoclonal PAb416 antibody from Calbiochem (San Diego, CA) at a dilution of less than 1:100 for 25–35 min is a reproducible method for BK virus identification. Accurate viral load estimation in differentiation between BK and JC virus may still need additional PCR analysis (Adam et al. 2014).

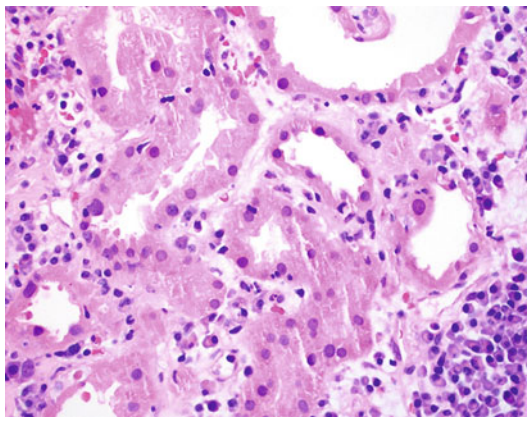

Fig. 7 Polyoma virus (BK) effect. Tubular epithelial cells demonstrate focal nuclear enlargement and atypia. The interstitium is occupied by a focally dense plasma cell infiltrate (H&E x400)

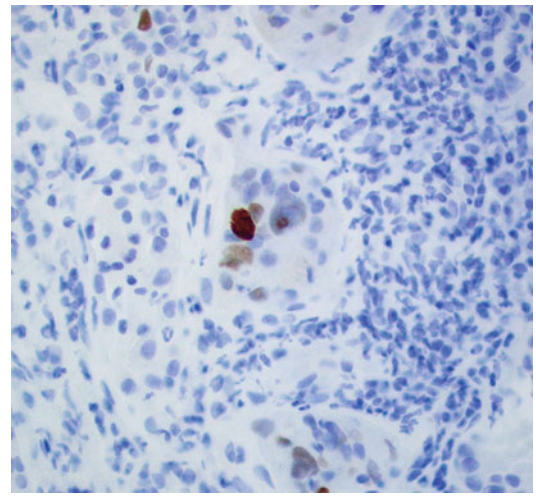

Fig. 8 Immunohistochemistry for SV40T antigen. Immunohistochemical stain for SV40T antigen shows strong nuclear staining within some tubular epithelial cell nuclei, consistent with BK virus infection (SV40T immunostain x400)

Cytomegalovirus (CMV) and adenovirus can cause symptomatic renal infections with defined pathologic features, including characteristic inclusions. CMV is more prevalent and pathological changes include cytopathic effects in nuclei and cytoplasm of tubular epithelial cells, endothelial cells, and also inflammatory cells. CMV-infected cells have a characteristic “owl’s eye” nuclear appearance, with occasional cytoplasmic inclusions identified as well. Techniques including IHC, in situ hybridization, and PCR can be used to detect CMV.

EBV is most commonly associated with post-transplant lymphoproliferative disorders (PTLD) in renal transplants. EBV-associated PTLD is commonly seen in patients on high-dose immunosuppression and in recipients with EBV seronegative status (Allen et al. 2013). The spectrum of PTLD can range from early reactive lymphocytic hyperplasia to monoclonal populations, eventually transforming into lymphomas of B cell, T cell, or Hodgkin’s type. Characteristic expansile infiltrates of activated lymphocytes can occasionally be mistaken for acute rejection.

However, PTLD infiltrates have a monotonous appearance with a paucity of other inflammatory cell types and may involve the capsule or perirenal tissue. IHC for B cell lineage and lack of CD3 and/or CD68 cells can help differentiate this infiltrate from that of rejection. ISH for EBV-encoded small nuclear RNA (EBER) is diagnostic on tissue biopsy sections (Allen et al. 2013).

Invasive fungal infections account for 5% of all infections in renal transplant patients and infections with *Aspergillus* species, *Mucorales* species, *Candida* species, and *Cryptococcus neoformans* are reported to cause most infections (Badiee and Alborzi 2011). Though these are usually systemic diseases, fungal or mycobacterial infection should be ruled out when granulomas are identified in renal allograft tissue.

Therapy-Induced Injury

As with native kidneys, renal allografts are susceptible to drug-induced injury. Injury due to immunosuppressive therapy is common and well-documented in the literature, although injury due to drugs, such as antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDS), is also encountered in renal transplant recipients.

Calcineurin Inhibitor (CNI) Toxicity

Use of calcineurin inhibitors (CNIs), such as cyclosporine and tacrolimus, has afforded significant benefits to patients by impacting overall renal allograft survival. CNIs are used widely throughout the United States to suppress the immune response to renal allografts and reduce the number of episodes of acute rejection that patients experience. These immunosuppressive agents are not without toxic effects that can impact graft function and structure in significant ways. The most common pathologic manifestations of such toxicity are seen within the blood vessels, including glomeruli, and the tubulointerstitial compartment, and may be acute or chronic (Naesens et al. 2009).

Vascular Changes of CNI Toxicity

Vascular changes of CNI toxicity may be minor or clinically significant, and CNIs may impart acute or chronic effects. Subtle endothelial injury can be a minor acute vascular effect, while overt thrombotic microangiopathic injury with glomerular capillary and arteriolar fibrin deposition may be significant. In cases of severe acute vascular injury due to CNIs, histopathologic changes may be indistinguishable from other thrombotic microangiopathies and even ABMR (Williams et al. 2012). These vascular changes may have significant consequences to glomeruli, including membranoproliferative changes and necrosis (in the setting of thrombotic microangiopathy), capsular fibrosis, as well as segmental or global sclerosis. Significant chronic vascular changes may include hyaline deposition within arteriolar walls (hyalinosis), which often appears nodular, and can cause significant luminal narrowing (Naesens et al. 2009). Such arteriolar changes are easily highlighted on PAS stains (see Fig. 9).

Tubulointerstitial Changes of CNI Toxicity

As with vascular changes, tubular and interstitial changes due to CNIs may be acute or chronic. In the acute setting, isometric vacuoles can be seen within tubular epithelial cell cytoplasm (see Fig. 10). These represent dilated endoplasmic reticulum as viewed by electron microscopy. Typically, the proximal tubular epithelial cell brush borders remain intact, as highlighted on PAS stain. Occasionally, microcalcifications may be seen within tubule lumens in cases of longstanding CNI use, but this is not a specific finding. Within the interstitium, chronic changes are typically not specific either, but are an expected consequence of chronic vascular injury due to CNIs. Interstitial (striped) fibrosis is commonly seen, highlighted with trichrome stains. This name has been coined since the fibrosis is zonal, with more normal-appearing tubules alternating with fibrotic zones (Naesens et al. 2009).

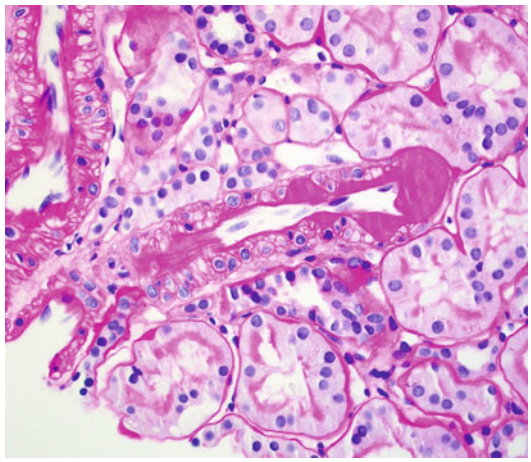

Fig. 9 Calcineurin inhibitor toxicity in arteriole. A PAS stain highlights the nodular aggregates of hyaline material within the wall of an arteriole, causing some luminal compromise (PAS x400)

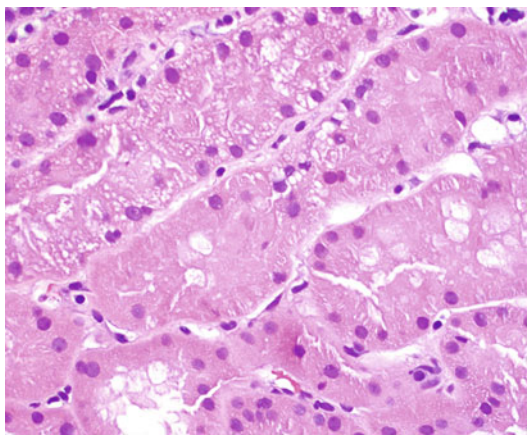

Fig. 10 Calcineurin inhibitor toxicity in tubules. Isometric vacuoles can be seen within tubules, consistent with calcineurin inhibitor toxicity. Note the prominent vacuoles in the *upper left hand corner* of the figure (H&E x400)

Other Therapy-Induced Injury

As with native kidneys, renal allografts are susceptible to acute interstitial nephritis induced by agents such as NSAIDS and antibiotics. In such cases, findings similar to those seen in native renal specimens can be seen, including lymphocytic and plasma cell interstitial infiltrates accompanied by eosinophils and neutrophils. However, these histopathologic findings may overlap with those seen in acute TCMR and ABMR. For that reason, careful histologic evaluation of the allograft specimen and appropriate clinical correlation are required, so as not to overlook acute rejection. The finding of non-necrotizing granulomas may be a clue that favors a diagnosis of drug-associated injury over acute TCMR, but associated infection should also be excluded (Hotta et al. 2012).

Neoplasia

Renal allograft recipients are at risk for developing malignancies at a rate higher than that of the general population, and this can be associated with increased morbidity and mortality. Means whereby these malignancies develop include those that are present in the recipient prior to organ transplantation, those that are donor-derived and are transplanted into the patient, and those malignancies that develop de novo in the recipient after transplantation (Stallone et al. 2015). A recent study by Farrugia et al. in England found that the most common cancer deaths in kidney transplant patients were attributable to lymphoproliferative disease, lung cancers, and kidney cancers, although a significant number of cancer deaths (18.6%) were due to unspecified malignancies. More studies are needed to determine the most appropriate immunosuppressive regimens that might ameliorate the risk of malignancy in renal transplant patients. Targeted surveillance for malignancies by transplant nephrologists and surgeons is strongly recommended (Farrugia et al. 2014).

As mentioned above, cases of PTLD include EBV-associated B cell (or less often T cell) proliferations, which may contain polyclonal or monoclonal lymphocytic populations. Common sites of PTLD in renal transplant patients include abdominal and pelvic lymph nodes, the renal allograft itself, and lymph nodes in the chest, as also the gastrointestinal tract and retroperitoneum. Clinical symptoms vary and PTLD can be difficult to diagnose. Histopathologic features, immunohistochemistry, flow cytometric studies, and molecular tests, as noted above, remain essential

to the diagnosis, and in differentiating neoplasia from acute TCMR (Morgans et al. 2010).

Recurrent and De Novo Disease

In addition to ischemic, immune, infectious, and therapy-associated insults, renal allografts are subject to both recurrent and de novo disease, both primarily affecting glomeruli. Recurrent and de novo disease may be seen simultaneously with any number of the aforementioned renal insults. For both recurrent and de novo disease, retransplantation may or may not be pursued, depending upon the disorder present (Ponticelli et al. 2014).

Recurrent Disease

Recurrent disease represents a significant number of graft failures over time, which might be expected, given the nature of many glomerular disorders and the fact that renal allograft transplantation replaces the target but does not impact the cause of many glomerular disorders. It seems obvious, but recurrent disease can only be recognized when the original disorder causing renal failure was diagnosed and characterized prior to renal transplantation. Furthermore, documentation of recurrence in the renal allograft typically requires thorough investigation with the aid of special stains, immunofluorescence and electron microscopy, and differentiation from other injuries suffered by the graft (Marinaki et al. 2013).

Common recurring disorders in renal allografts include focal and segmental glomerulosclerosis (FSGS), C3 nephropathies (including dense deposit disease/membranoproliferative glomerulonephritis (MPGN)), IgA nephropathy, and idiopathic membranous nephropathy, although other primary glomerular disorders can also recur, such as antiglomerular basement membrane (GBM) glomerulonephritis, antineutrophil cytoplasmic antibody (ANCA)-mediated disease, lupus nephritis, and diabetic nephropathy. Depending upon the disorder, recurrence may occur soon after transplantation or late (Marinaki et al. 2013). When recurrent, these disorders demonstrate histopathologic features very similar to those seen in the original manifestation of the disease. However, the course of the recurrent disorder may be altered, due to the use of immunosuppression in renal allograft recipients.

De Novo Disease

Any number of glomerular disorders can occur de novo within the renal allograft, and diagnosis thereof relies on evaluation of the renal allograft biopsy specimen with appropriate studies. More frequent de novo glomerular disorders encountered include minimal change disease, FSGS, membranous nephropathy, MPGN, and IgA nephropathy. De novo focal and segmental glomerular sclerosis (FSGS) may occur as a result of hyperfiltration injury or hypoperfusion, resulting in secondary type glomerular scarring. Interestingly, patients with de novo membranous nephropathy often lack autoantibodies to phospholipase A2 receptor (PLA2R), which is in contrast to patients with primary membranous nephropathy. Other de novo disorders might be expected to occur in specific patient populations, given the pathogenesis of the disorder. For example, patients with Alport syndrome, given their lack of specific α chains in type IV collagen, may manifest autoantibodies against the glomerular basement membrane, which can prompt antiglomerular basement membrane antibody-mediated disease. De novo diabetic nephropathy has been documented to occur in patients who develop diabetes mellitus after renal allograft transplantation. Other de novo disease of most types has been reported in the literature (Ponticelli et al. 2014).

Conclusion

Significant clinical improvements in the outcome of patients with chronic kidney disease have been made with the advent of renal allograft transplantation. Such allografts may experience a variety of insults, which may have

inconsequential or significant impact on graft function and patient morbidity and mortality. These insults range from ischemia to immunologic, infectious, therapy-induced, and neoplastic, and include recurrent and de novo disease. Patients must be closely monitored clinically, with the aid of laboratory evaluation, so as to detect even slight changes in allograft function. When warranted, procurement and appropriate interpretation of a renal allograft biopsy specimen can yield very helpful insights into the pathophysiologic mechanisms underlying allograft dysfunction. Use of special studies in the pathology laboratory can further augment histopathologic findings and direct the most appropriate therapeutic interventions, in efforts to assure optimal graft survival.

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Cross-References

- Immunology of Kidney Transplantation
- Infection in Kidney Transplantation
- Medical Complications After Kidney Transplantation: Early
- Medical Complications After Kidney Transplantation: Late
- Transplant Immunosuppression

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