A Surgeons’ Guide to Renal Transplant Immunopathology, Immunology, and Immunosuppression

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KEYWORDS

• Immune suppression • Graft rejection • Biopsy • Adaptive immune responses

KEY POINTS

• The response to allografting involves both the adaptive and innate immune systems. In the adaptive immune system, T cells become activated upon recognition of alloantigens presented by donor and host antigen-presenting cells (APCs).

• Activated T cells can help B-cell differentiation to antibody producing plasma cells and memory cells. Antibody mediated rejection is triggered when enough circulating antibodies to allograft antigens are present or are produced.

• The innate immune system recognizes antigens and pathogens in a non-specific manner and its functions include removal of foreign substances and recruiting immune cells through the productions of chemotactic factors, and activation of cytokines and the complement cascade.

• In the kidney, Immune activation leads to targeting of the tubules and the endothelium by allo-stimulated cells. Based on the timing of its occurrence rejection was classified as hyperacute, accelerated acute, acute and chronic. These terminologies have been replaced by the Banff group with a more histological nomenclature.

• Immune suppressive medications are introduced during the induction phase and closely monitored in the adjustment phase to prevent early rejection. Following that the chronic maintenance phase of immune suppression is characterized by step wise decrease in medication doses and possibly by withdrawal of one or more of them.
The immune system response to allografting is a multistep process that involves both the adaptive and innate immune systems. In the adaptive immune system, T cells become activated on recognition of alloantigens presented by donor and host antigen-presenting cells (APCs).\(^1\) T-cell activation results in the activation and recruitment of other cell types, and in T-Cell maturation to effector cells, which induce tissue destruction and the production of cytokines.\(^2\)

The innate immune system comprises cells that recognize and respond to antigens and pathogens in a nonspecific manner, and without conferring long-lasting protective immunity. The major functions of the innate immune system include recruiting immune cells through the production of chemotactic factors and cytokines, activation of the complement cascade, identification and removal of foreign substances, and acting as a physical and chemical barrier to foreign agents. One of the most important functions of the innate immune system is the activation of the adaptive immune system through a process known as antigen presentation. In the allograft, ischemia reperfusion–induced oxidative allograft injury can lead to generation of damage-associated molecules, such as heat shock protein 72, high mobility group box 1, and a hyaluronan fragment. All of these molecules act as endogenous ligands of toll-like receptors and are recognized by intragraft toll-like receptor 4–bearing and toll-like receptor 2–bearing dendritic cells. Stimulated dendritic cells mature and initiate cytokine-driven development of the recipient’s adaptive alloimmune response. This same mechanism has been implicated in the development of accelerated atherosclerosis of the allograft and chronic rejection via injury-induced proliferation of smooth muscle cells.\(^3,4\) Recent evidence has shown that brain death is a powerful trigger of cytokine storms. Besides inducing organ damage, cytokines recruit inflammatory cells into organs that accentuate the damage and are instrumental in mediating the manifestations of ischemic damage. Allograft injury, induced by the reperfusion response, initiates an innate immune response by activating innate immune cells (such as donor-derived and recipient-derived toll-like receptor–bearing dendritic cells and innate lymphocytes natural killer cells, dendritic cells, and macrophages) as well as humoral factors (complement, natural IgM antibodies).\(^5\) These innate immune cells act as inflammatory cells promoting rejection by directly damaging the graft. Alternatively, the acute innate intragraft inflammatory response can initiate and expand the adaptive alloimmune system, because the innate inflammatory cells act as APCs to the different major histocompatibility complex (MHC) antigens. Innate immune cells can also regulate differentiation of T effector cells by the virtue of their cytokine production, thus affecting the nature and strength of the rejection response.\(^6\) The impact of innate immune system activation on tolerance development is also 2 sided, because some cell types promote tolerance induction by eliminating donor APCs.\(^7\) The cytokine milieu created by the activation of innate immune cells can be detrimental to the induction of Foxp3\(^+\) regulatory T cells, a key cell type involved in transplant tolerance.\(^8\)

Most of the immune targets in an allograft are the polymorphic HLA molecules. Class I HLA antigens are expressed in all nucleated cells, such as tubular cells, and interact with CD8\(^+\) T cells. HLA class II molecules are expressed on activated cells and on APCs. T cells are activated by graft antigens either directly through cross-linking with HLA molecules or more commonly indirectly via interacting with APCs that are processing donor antigen. This interaction requires engagement of the cell receptor and accessory activation molecules. T-cell activation results in expression of T-cell activation markers, secretion of cytokines such as interleukin 2 (IL-2), leading to activation and mobilization of CD4\(^+\) and CD8\(^+\) cells into the graft, and creates the conditions prompting graft infiltration.\(^9\)
Activated T cells can also help B cells, which in response to antigenic stimulation are triggered into differentiation to antibody-producing plasma cells and memory cells. Conversely, there is some evidence that T-cell depletion early after transplantation in patients receiving some of the depleting antibodies may cause increased levels of the B-cell cytokine BAFF. Calcineurin inhibitors (CNIs) may also hold B cells in a transitional state, and weaning of CNIs may release B cells to become fully activated and differentiate. Once B cells are activated, memory cells maintain the sensitization memory for the inciting HLA antigen, and plasma cell activation produces anti-HLA antibodies. Antibody-mediated rejection (ABMR) is triggered when enough circulating antibodies to allograft antigens are present or are produced. Antigen-antibody interaction and their deposition in the graft lead to complement activation and triggering of an inflammatory response centered on endothelial surfaces of the peritubular and glomerular capillaries.

In addition, T-cell activation induces activation of cytokines and other inflammatory mediators, both within the interstitium and around blood vessels. This activation results in upregulation of vascular endothelial adhesion molecules, which attract inflammatory cells into the vascular space. Graft infiltrating cells recognize class I alloantigens on donor tubular cells, whereas vascular endothelial cells express both class I and class II MHC antigens. Inflammatory activation of the endothelium increases the intensity of class II expression and may also accentuate the expression of other alloantigens, such as endothelial-monocyte antigens, and other polymorphic alloantigen systems, which can be particularly important in the evolution of vascular rejection.

**CLINICAL MANIFESTATIONS OF TRANSPLANT REJECTION**

The result of immune system activation is the targeting of the allograft tissue by allostimulated cells. In the kidney, the tubules, the endothelium, or both are the main targets for the inflammatory antigen-specific immune response. This immune injury is manifested clinically by reduction in excretory capacity of the kidney with decreased urine output and increase in serum creatinine level. Endothelial swelling and injury result in reduction in blood flow and development of manifestation of tubular necrosis. On examination, there is kidney swelling, tenderness, and possibly fever, proteinuria, and hematuria. These classic clinical manifestations of rejection have almost disappeared with the newer immune suppressants, leaving frequent monitoring of function and repeated biopsies as the only effective means to monitor for rejection besides changes in serum creatinine level.

**REJECTION CLASSIFICATION**

Based on the timing of its occurrence, rejection was classified as hyperacute, accelerated acute, acute, and chronic. Although these terminologies have been replaced by more histologic nomenclature, they still provide a useful guide to the cause and progression of rejection. Hyperacute rejection started immediately after perfusion and was related to the presence of high levels of antidonor antibodies, the deposition of which on the vascular endothelium led to complement activation and intravascular thrombosis. Advances in antibody detection by single antigen beads have almost eliminated this type of rejection. Accelerated acute rejection was usually diagnosed in patients with preexisting antibodies in whom antibody levels had decreased over time. Usually, the graft works for a few days, then an anamnestic immune response is mounted by the sensitized host. Immune activation leads to florid production of antibodies and endothelial cell injury. Acute rejection described the rejection occurring
usually early after the transplant and characterized by the lymphocytic infiltration whether in the tubules (acute cellular rejection) or the blood vessels (acute vascular rejection [AVR]). Chronic rejection was believed to be related to chronic slow antibody deposition, leading to progressive vascular sclerosis of the allograft.

**DESIGN OF IMMUNE SUPPRESSION PROTOCOLS**

Because all immune suppressants possess significant side effects, immunosuppression protocols are based on the simultaneous use of multiple drugs. This strategy achieves immune suppression efficacy without having to use any of the drugs in full, toxic doses. After transplantation, the induction phase of immunosuppression is achieved by administration of biological agents. Immune-suppressive medications are introduced during the induction phase and closely monitored in the adjustment phase to prevent early rejection. After that, the chronic maintenance phase of immune suppression is characterized by stepwise decrease in medication doses and possibly by withdrawal of 1 or more of them.

**BIOLOGICAL AGENTS**

Biological agents include both monoclonal and polyclonal antibodies. A monoclonal antibody is derived from a single cell line that is reactive with a single epitope. The most commonly used monoclonal antibody in clinical transplantation is basiliximab, a chimeric mouse-human monoclonal antibody to the \( \alpha \) chain (CD25) of the IL-2 receptor of T cells. A polyclonal antibody is made up of a combination of immunoglobulin molecules that identify different epitopes on the same cells or different antigenic determinants on multiple cells. Thymoglobulin, a rabbit antithymocyte globulin, is the most widely used polyclonal antibody. Thymoglobulin and some monoclonal antibodies such as alemtuzumab remove lymphocytes from the peripheral circulation and are thus classified as depleting antibodies. The cells may be removed by several different mechanisms, including complement-mediated lysis or reticuloendothelial-dependent phagocytosis. The effects of depleting antibodies tend to be long lasting. In the case of thymoglobulin and alemtuzumab, it takes several months for the peripheral T-cell count to return to normal after treatment. Conversely, nondepleting antibodies inactivate the target cell but do not remove it from the circulation. An example of a nondepleting antibody is basiliximab. By binding to the IL-2 receptor, it effectively inhibits the cell from responding to IL-2, but the T cell remains in the peripheral circulation.

These 3 biological agents (basiliximab, alemtuzumab, and thymoglobulin) are all used in induction of immune suppression. Thymoglobulin is also used for the treatment of acute rejection. The success of thymoglobulin has been attributed to the large number of antibodies and targets that it recognizes, including immune response antigens, adhesion and cell trafficking epitopes, and multiple heterogeneous pathway antigens. Thymoglobulin is the preferred induction agent in recipients at high immunologic risk and in patients with delayed graft function, in whom the introduction of nephrotoxic immunosuppressants has to be delayed until kidney function recovers. Alemtuzumab is a humanized depleting antibody that targets both T and B cells by binding to the CD-52 receptor on the surface of lymphocytes. Alemtuzumab is used also as an induction agent, generally in patients with a similar profile to those requiring thymoglobulin.

Rituximab is another depleting humanized antibody that binds to the CD-20 receptor on B cells. It is used for desensitization of recipients with preformed HLA antibodies before transplantation, as part of multimodality treatment of antibody-mediated acute
rejection, and as a therapy for recurrent glomerular disease after transplantation. Recently, there have been trials to use rituximab in induction of sensitized patients, and the results seem encouraging.20

Another newly introduced biological agent, eculizumab, is a humanized monoclonal antibody that is unique among biological agents used in transplantation. Eculizumab does not bind to lymphocytes but acts on the complement system through binding to complement component C5, resulting in effective inhibition of the complement cascade. Based on its mechanism of action, it has predictably been considered a potential adjunctive agent for the prevention or treatment of antibody-mediated acute rejection. A recent preliminary study of its use in induction therapy for patients with flow crossmatch-positive kidney transplants has stimulated the conduct of a phase 3 randomized trial for that same indication.12

MAINTENANCE IMMunosUPPRESSION

Maintenance immunosuppressive agents have traditionally been pharmacologic agents used for long-term immunosuppression. Pharmacologic immunosuppression is divided into 4 groups: corticosteroids, CNIs (such as cyclosporine and tacrolimus), mammalian target of rapamycin (mTOR) inhibitors (including sirolimus and everolimus), and the antimetabolites (including mycophenolate mofetil and azathioprine). These drugs are used to prevent T-cell–mediated acute rejection. A useful way to understand their function is to consider these agents as lymphocyte cell cycle inhibitors.

THE LYMPHOCYTE CELL CYCLE

G0 is the resting stage of the cell. T lymphocytes exist for most of their life span in this state. In order to proliferate, cells must reenter the G1 phase, in which a variety of proteins, including cytokines, are synthesized in preparation for DNA synthesis.21 In the S phase, DNA synthesis and replication result in each chromosome producing 2 identical chromatids. A second gap or G2 phase allows the final cytoplasmic reorganizations required for cellular division to occur. The M (mitotic) phase then involves chromosomal condensation, breakdown of the nuclear membrane, separation of the sister chromatids, generation of 2 new nuclei, and division of the cytoplasm to form 2 daughter cells. A typical lymphocyte cell cycle may take 12 to 16 hours to complete, with several additional hours initially required to take the cell from G0 to G1.22,23

CALCINEURIN INHIBITORS (CNIs)

The CNIs are cyclosporine and tacrolimus, which, although structurally distinct, act to block the synthesis of proinflammatory cytokines through the inhibition of calcineurin. The activity of tacrolimus in vitro is 10 to 100 times greater than that of cyclosporine. Both cyclosporine A (CsA) and tacrolimus are prodrugs; in order to gain pharmacologic activity they must bind to cytoplasmic components termed immunophilins. The immunophilins are cytoplasmic enzymes; cyclophilin, which binds to CsA, and FK-binding protein 12 (FKBP12), which binds to tacrolimus.

T-CELL SIGNALING AND CALCINEURIN INHIBITION

The T-cell receptor recognizes foreign antigen in combination with an APC. This recognition event is transferred from the cell membrane to the cell interior via the CD3 membrane complex. This signal initiates a programmed series of
phosphorylations of membrane-associated and cytoplasmic kinases. These events cause a rapid and sustained increase in cytosolic calcium via influx through surface channels and release from intracellular membrane stores. Increases in intracellular calcium concentration stimulate the catalytic activity of the phosphatase calcineurin. The best-defined target of calcineurin activity is the nuclear factor of activated T cells (NF-AT). Calcineurin causes dephosphorylation of NF-AT and carries the product through the nuclear membrane. Once in the nucleus, NF-AT serves as the primary regulatory protein that promotes the transcription of IL-2 (Fig. 1).24

Thus, the CsA-cyclophilin and the tacrolimus-FK binding complexes block T-cell activation by binding to the phosphatase calcineurin, forming an inhibitory association, which thereby dampens the dephosphorylation, transport, and release of NF-AT in the nucleus. As a consequence of these events, entry in to the cell cycle is arrested at the G0 or G1 phase, synthesis of DNA, RNA, is inhibited, and cytokine production is abrogated. This is not the only mechanism of action of the CNIs. Both CsA and tacrolimus also enhance the expression of transforming growth factor β, a cytokine that has not only immunosuppressive effects but causes renal allograft fibrosis.

mTOR INHIBITORS

Like the CNIs, sirolimus is a prodrug and binds to the same protein as tacrolimus, FKBP12, but at a different site. The enzyme target of this complex is mTOR, a 289-kDa serine-threonine kinase. Whereas the calcineurin inhibitors act early at the G0 to G1 phase to block IL-2 transcription, sirolimus acts later at the G1 stage of the cell cycle to block the T-cell response to IL-2, resulting in inhibition of protein synthesis.

Fig. 1. Cyclosporine (CsA) and tacrolimus (TAC) are prodrugs that bind to cytoplasmic immunophilins: cyclophilin binds to CsA, and FKBP12 (FK binding protein) binds to tacrolimus. The drug-immunophilin complexes block the phosphatase activity of calcineurin; the best-defined target of calcineurin activity is Nuclear factor of activated T cells (NF-AT). Calcineurin causes dephosphorylation of NF-AT, affecting the transcription of interleukin -2(IL-2). Thus, the calcineurin inhibitors interfere with T-cell cycle progression from G0 to G1. DAG, diacylglycerol; IP3, Inositol trisphosphate; PIP2, Phosphatidylinositol 4,5-bisphosphate; PKC, protein kinase C; TcR, T-cell receptor; ZAP 70, Zeta-chain-associated protein kinase 70.
T-CELL SIGNALING AND mTOR INHIBITION

First, IL-2 binding to the IL-2 receptor (CD25) on T cells results in activation of phosphoinositide-3-OH kinase to generate phosphatidylinositol 3,4,5 triphosphate. This molecule, in turn, activates the serine-threonine protein kinase Akt. Once activated, Akt relieves the inhibitory effect of the tuberous sclerosis complex proteins TSC1 and TSC2 on mTOR. This event permits mTOR to activate 2 p70S6 kinases known as S6 kinase 1 and 2, which, in turn, catalyze phosphorylation of S6, a 40S ribosomal protein required to drive messenger RNA (mRNA) translation and protein synthesis. In addition, through a separate pathway, mTOR activates the eukaryotic initiation factor 4E, which is also necessary for mRNA translation and ribosomal biosynthesis. Thus, mTOR plays a critical role in regulation of protein synthesis and cell cycle progression from late G1 into S phase. Logically, then, blockade of mTOR by sirolimus inhibits mRNA translation and protein synthesis and arrests T-cell cycle progression to S phase. Everolimus has the same mechanism of action but has a shorter half-life.25–27

THE ANTIMETABOLIC AGENTS

Mechanistically, mycophenolic acid (MPA) is an antimetabolite and acts at the S phase of cell cycle progression by interfering with purine synthesis. MPA interferes with the de novo pathway of purine biosynthesis by preventing the conversion of inosine monophosphate to xanthine monophosphate. MPA is a selective, reversibly noncompetitive inhibitor of inosine monophosphate dehydrogenase, the rate-limiting enzyme in de novo purine synthesis. This inhibition results in intracellular depletion of guanosine nucleotides, thereby halting the progression of activated T and B cells during the S phase of the cell cycle.26,29

Two major cellular pathways are involved in purine synthesis: the de novo pathway and the salvage pathway. Because T and B lymphocytes are critically dependent for their proliferation on de novo synthesis of purines, whereas other cell types can use salvage pathways, MPA has a potent cytostatic effect on lymphocytes.

CORTICOSTEROIDS

Corticosteroids exert a variety of actions, but those most important to transplantation include the disruption of APC functions and inhibition of proinflammatory cytokine synthesis. Corticosteroids also cause a profound but transient lymphopenia, particularly of the T-cell population. This situation is because of a redistribution of cells out of the intravascular and into the extravascular lymphoid compartment. This particular effect is typically observed with high-dose administration of steroids used for induction immunotherapy or treatment of acute rejection and is not expected with maintenance doses of steroids. Glucocorticoids have an immunosuppressive effect on proinflammatory T cells, whereas they stimulate regulatory T-cell activity Fig. 2.30,31

BELATACEPT

Belatacept is the most recent addition to the maintenance immunosuppression regimens and differs from traditional maintenance drugs in that it is a fusion protein composed of the Fc fragment of a human IgG1 immunoglobulin linked to the extracellular domain of CTLA-4.32 Because CTLA-4 is a molecule crucial for T-cell costimulation, belatacept can selectively block the process of T-cell activation. Belatacept is
administered intravenously and is intended to maintain graft function and limit the toxicity generated by standard immune-suppressing regimens, such as CNIs.33,34

THE HISTOLOGY OF GRAFT REJECTION

The pathology of transplant rejection reflects the immune mechanisms that mediate kidney allograft graft injury. Posttransplant rejection disease is now being classified based on the 2 major effector pathways; cytotoxic cells (cellular rejection) and antibodies (ABMR).

Acute Cell-mediated Rejection

The features of acute cell-mediated rejection are dominated by the presence of lymphocyte infiltrates in the interstitium with varying degrees of tubulitis and tubular infiltration (tubulointerstitial rejection). More severe cases can be associated with infiltration of the blood vessels and the appearance of intimal arteritis (vascular rejection). In its most advanced form, vascular changes are associated with transmural arterial changes and extensive endothelial injury. Up to one third of allografts biopsied during clinical quiescence show some degree of interstitial inflammation and even some scattered focal tubulitis.35 The significance of this subclinical inflammation has been debated, with conflicting evidence that these changes contribute to long-term allograft deterioration36 and evidence that, at least in the short-term, this mild form of inflammation imparts no significant negative consequence on the allograft.37 The histologic changes of rejection are graded by the Banff classification. In the Banff classification, tubulitis is the hallmark of the diagnosis of grade I rejection, and is graded based on the number of tubules within the most inflamed area of the biopsy (Fig. 3).38
Acute Vascular Rejection

AVR most commonly occurs in the first few months after transplantation. The detection of vascular lesions in an episode of rejection usually denotes worse prognosis and an increased chance of being resistant to standard antirejection therapy. AVR can be a manifestation of both cellular and ABMR.\(^{39}\)

The histologic changes include intimal arteritis, in which lymphocytes, and monocytes (Fig. 4) infiltrate the vascular intima and the resulting inflammation causes intimal thickening with inflammatory cells. Besides classifying the severity of these lesions, the Banff 09 classification also added acute ABMR, which has similar vascular lesions but with associated circulatory antidonor antibody and C4d positivity in peritubular capillaries.\(^{40}\)

Inflammation of the blood vessels in renal glomeruli (acute glomerulitis) can also be seen in rejection. Acute glomerulitis is characterized by the presence of mononuclear cell infiltrates and endothelial injury and swelling. Less common with acute cell mediated rejection, acute glomerulitis should always lead to the suspicion of ABMR.

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Fig. 3. Acute cellular rejection, Banff type IB. Interstitial inflammation and severe tubulitis define this type of rejection. The photomicrograph shows all grades of tubulitis.

Fig. 4. AVR; the micrograph shows CD68-positive monocytes in the superficial vascular intima characteristic of mild intimal arteritis (i.e., mild vascular rejection).
particularly in cases with minimal vascular involvement, or those with polymorphonuclear leukocyte within the glomerular capillaries. The presence of donor-specific antibody and of C4d staining can usually differentiate cellular AVR and acute ABMR.

**Antibody-Mediated Rejection**

The immunologic mechanisms driving the development of acute ABMR occur in response to donor class I or class II alloantigens, which are particularly well expressed on activated endothelial cells. Antigens or antigenic determinants are carried by APCs to peripheral lymphoid organs where they are recognized by β cells. B cells differentiate into naive plasma cells that can secret antidonor-specific antibodies. Alternatively, antigens may be presented locally in the allograft and induce antibody production independent of lymphoid tissue. Although the latter has not been confirmed, it seems like the result is secretion of immunoglobulin with T-cell help.

Antibody deposition on vascular endothelial cells leads to in situ antigen-antibody interaction, with activation of the complement cascade. Deposition of activated complement results in activation of complement receptor-mediated neutrophil and macrophage chemotaxis, cytolysis, and apoptosis of target cells, including endothelial cells. Other changes include vasospasm through the release of prostaglandin from macrophages, edema through histamine release, and intravascular thrombosis through the triggering of endothelial synthesis of procoagulants and tissue factors. Several renal changes are characteristic for ABMR but none is pathognomonic. The 2003 Banff classification defined the criteria for diagnosing ABMR by 3 essential aspects, including (1) the presence of morphologic evidence of acute tissue injury, such as acute tubular injury, neutrophils, and/or mononuclear cells within the peritubular capillaries or glomerulus, and/or glomerular thrombosis, intimal arteritis, fibrinoid necrosis with or without transmural inflammation in the arteries; (2) the presence of immunopathologic evidence of antibody activity such as intense C4d in peritubular capillaries (>50% of capillaries) (Fig. 5); and (3) serologic evidence of circulating antibodies against HLA antigen or other donor-specific antigens. The C4d deposition should be diffuse and intense to diagnose ABMR (>50% of the peritubular capillaries). The presence and margination of inflammatory cells, particularly polymorphonuclear neutrophils, and mononuclear cells.

![Fig. 5. Diffuse deposition of complement protein C4d along the peritubular capillaries shown by direct immunofluorescence testing. Deposition of C4d is one of the diagnostic criteria used to establish ABMR.](https://via.placeholder.com/150)
**Immunosuppressant Nephrotoxicity**

Although there are a variety of protocols for calcineurin minimization, conversion, and elimination, most immune suppression protocols still use a CNI. Acute calcineurin renal toxicity is related to afferent arteriolar vasoconstriction, leading to reduced renal blood flow and tubular ischemia. In addition, FK506 (Prograf) has direct glomerular constrictive effect. Although toxicity of both calcineurins is dose dependent, nephrotoxicity can occur in 15% to 20% of patients receiving lower doses of these drugs, particularly in those receiving FK506. Acute nephrotoxicity is uncommon in modern kidney transplant cases because of the introduction of these drugs in lower doses. Lesions of acute toxicity are seen more often in native kidney biopsies of recipients of other organ transplants. The earliest feature in these biopsies is reversible isometric tubular epithelial vacuolization and acute tubular injury, and/or arteriolar hyalinosis. Less commonly, biopsies may have features of thrombotic microangiopathy, which has also been reported with the mTOR inhibitor sirolimus. Sirolimus tubulopathy is associated with induction of tubular and podocyte apoptosis, particularly in grafts with delayed graft function, and presents with obstructive intratubular casts surrounded by regenerating tubular epithelium and tubular dilatations.

**BK Nephropathy**

BK virus was first described in immune-suppressed kidney transplant recipients in the early 1970s. The early reports documented that the virus resided within the transitional urothelium and was shed by more than 65% of immune-suppressed transplant recipients. Almost 2 decades later, infection of the renal parenchyma by BK virus was reported and polyoma virus–associated nephropathy (PVAN) has become one of the major challenges of clinical transplantation. The rapid increase in number of cases in the early 2000s has been attributed to increased potency of immune suppression and to the increased rates of transplantation of diabetics and older patients. The inability to expand BK-specific T cells in heavily immune-suppressed patients is believed to precipitate active infection. Viral replication in the renal parenchyma results in cytopathic changes that cause tubular apoptosis and inflammatory infiltration and lead to tubular cell injury. Alternatively, viral replication may activate adaptive immunity to perpetuate injury and cause tubular cell injury and cell death. Tubular destruction is usually followed by fibrosis and scarring, loss of kidney function, and kidney loss.

The diagnosis of BK nephropathy is based on the presence of characteristic interstitial inflammation in the deep cortex and medulla, which spares the superficial cortex. Distinguishing features include the presence of various viral inclusions in the tubules, mostly large inclusions with enlarged coarsely vesicular nuclei, and by the less frequent presence of decoy cells, which are large intranuclear acidophilic inclusions rimmed by a ring of dense chromatin at the nuclear membrane. Tubular injury is manifested by the presence of acute tubular necrosis, with sloughing cells and accumulation of coarsely granular debris in tubular lumens. There is no known treatment of BK viral nephropathy, except for withdrawal or reduction of immunosuppression. Other antiviral agents are usually attempted in cases without rapid response to immunosuppression reduction; these include treatment with cidofovir and leflunomide. Follow-up biopsies are usually required for patient follow-up because fluctuations in renal function as immune suppression is being reduced raise the possibility of acute rejection. Another reason is to follow the resolution of BK nephropathy in response to immune-suppression reduction and to prevent unnecessary further withdrawal of immune suppression when the nephropathy is already resolving. Our observation in series of patients with repeat renal biopsies has indicated that
regardless of the PVAN status, there is almost always an increase in the Banff chronic score, and progression of interstitial fibrosis. This finding has stimulated our team to adopt prospective monitoring to diagnose early the viral infection and intervene before the onset of tubulointerstitial nephritis and renal fibrosis.45,46

**Chronic Allograft Changes**

Renal allografts undergo gradual, cumulative, and incremental damage to the nephron from time-dependent immunologic and nonimmunologic causes.47 In early classifications, the chronic pathologic changes were called chronic rejection,48 chronic transplant nephropathy,49 and chronic allograft nephropathy (CAN).50 The constellation of histologic findings of arteriosclerosis and arteriosclerosis, glomerulosclerosis, tubular atrophy, and interstitial fibrosis with chronic inflammation are seen in most allografts with chronic injury and are largely similar to chronic kidney disease (CKD) in the native kidney, regardless of the cause.51 Because most of the histopathologic features of CKD in the allograft could not be specifically attributed to an allospecific response (chronic rejection, CAN) was adopted for the Banff working classification.50 Chronic allograft injury is clinically characterized by progressive deterioration of graft function, proteinuria, and hypertension.52

Chronic ABMR is diagnosed when interstitial fibrosis and tubular atrophy are associated with 1 or more of these features: chronic transplant glomerulopathy, chronic microvascular injury, intragraft deposition of C4d, and the presence of donor-specific antibody.40 Chronic T-cell–mediated rejection is suspected in grafts that show tubulitis along with thickening of the elastic layer of the blood vessels, fibrous intimal hyperplasia, and variable inflammation in the intima, which are all features of chronic transplant vasculopathy. A long list of non–immune-mediated conditions can also cause chronic allograft injury or exacerbate an immune injury. Causes of nonimmune chronic allograft injury include donor factors such as senescence, nephrosclerosis, donor vasculopathy, or recipient diseases such as hypertension, diabetes, and hyperlipidemia (the metabolic syndrome). Other nonimmune causes include exposure to nephrotoxins, viral infections, and reflux nephropathy.52–54 A subset of allografts show chronic transplant glomerulopathy, possibly a form of allograft rejection.55,56

**REFERENCES**


