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Pathology of Calcineurin and Mammalian Target of Rapamycin Inhibitors in Kidney Transplantation

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The recent evolution in immunosuppression therapy has led to significant improvement in short-term kidney allograft outcomes; however, this progress did not translate into similar improvement in long-term graft survival. The latter, at least in part, is likely to be attributed to immunosuppressant side effects. In this review, we focus on the histologic manifestations of calcineurin inhibitor and mammalian target of rapamycin inhibitor toxicity. We discuss the pathologic features attributed to such toxicity and allude to the lack of highly specific pathognomonic lesions. Finally, we highlight the importance of clinicopathologic correlation to achieve a meaningful pathologic interpretation.

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Acute rejection is the major obstacle for allograft survival in nonimmunosuppressed animals. T-cell activation, which is the main step in initiating rejection following solid organ transplantation, needs 3 sequential signals.[1] Signal 1 requires interaction of a major histocompatibility complex molecule that carries an allopeptide on an antigen-presenting cell with a T-cell receptor on the recipient T cell. Signal 2 is provided by the binding of costimulatory molecules on an antigen-presenting cell (e.g., CD80/CD86) with their T-cell counterparts (e.g., CD28). Signals 1 and 2 activate the downstream pathways of calcium-calcineurin, RAS-mitogen-activated protein kinase, and nuclear factor-kappa B pathways, which trigger the expression of several cytokines, including interleukin (IL)-2. Signal 3 follows IL-2/IL-2 receptor binding, which activates mammalian target of rapamycin (mTOR) that leads to T-cell proliferation and clonal expansion. Fully activated T cells can then initiate T-cell–mediated rejection and/or activate B cells to trigger antibody-mediated rejection.[1,2] Disrupting T-cell activation has been the target for immunosuppressive medications in solid organ transplantation. The development of potent immunosuppressive medications has dramatically decreased the incidence of early acute rejection and improved short-term allograft survival.[3] Despite this significant improvement, long-term allograft survival remains suboptimal. This may be largely attributed to the limitations of the current immunosuppressive agents related to their toxic side effects and inability to control late smoldering rejection.[4]

Calcineurin Inhibitors

The introduction of cyclosporine and then tacrolimus has revolutionized the field of solid organ transplantation. Because cyclosporine has been used for a longer time, most data in this field pertain to cyclosporine. However, tacrolimus, which is the current first-line immunosuppressive agent in kidney transplant recipients,[5,6] causes similar functional and structural nephrotoxicity.[7–9] Priming T cells via signal 1 in the presence of signal 2 leads to an increase in intracellular calcium concentration and activates calcineurin. The latter moves to the nucleus and stimulates proinflammatory cytokines that are necessary for T-cell

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activation.[2] Calcineurin inhibitor (CNI) binds intracellular proteins called immunophilins (FK-binding proteins if tacrolimus) to form a complex that can bind and inhibit intracellular calcineurin and, thus, block further T-cell activation.[2]

Despite being the backbone of current immunosuppression, there is considerable concern that CNI use may lead to significant nephrotoxicity.[10] CNI can cause endothelial cell injury and vasoconstriction, which is mediated by production of endothelin, activation of renin-angiotensin II system, and inhibition of vasodilators (such as cyclooxygenase-2 and nitric oxide).[7] This vascular toxicity often manifests as hypertension and decreased glomerular filtration rate. CNI is also associated with acute tubular damage, which its mechanism is not completely understood. In addition to ischemia effects, tubular injury can be caused by direct toxicity probably affecting endoplasmic reticulum and mitochondria.[7,11]

Acute CNI Toxicity

Acute CNI nephrotoxicity typically occurs early after kidney transplantation, correlates with the period of high CNI exposure, and is often reversible with dose reduction or discontinuation of the drug.[12] There are 3 major clinico-pathologic manifestations of acute CNI toxicity: functional/acute arteriolopathy, thrombotic microangiopathy (TMA), and toxic tubulopathy.[7]

Acute arteriolopathy is a hemodynamically mediated phenomenon that leads to allograft dysfunction secondary to afferent arteriolar constriction and increased renal vascular resistance.[13,14] Sometimes, acute arteriolar toxicity can manifest as arteriolar wall vacuolization, which is a morphologic expression of arteriolar vasospasm (Figure 1a and b).[15] That said, arteriolar wall vacuolization is neither sensitive nor specific for CNI toxicity and can be even encountered in a subgroup of implantation biopsies.[16]

TMA is a rare manifestation of a more severe form of acute CNI-induced vascular damage.[17–19] Extensive endothelial injury causes endothelial leaking, necrosis, or sloughing that consequently leads to antifibrinolysis, platelet aggregation, and activation of coagulation cascades.[18,20] Accordingly, the biopsy usually shows fibrinoid necrosis and/or thrombi affecting the afferent arterioles, and to a lesser extent, the glomeruli (Figure 1c). The differential diagnosis of CNI-induced TMA should include other forms of TMA, such as accelerated antibody-mediated rejection, anti-phospholipid syndrome, procoagulant states, and recurrent hemolytic–uremic syndrome.[20] Therefore,

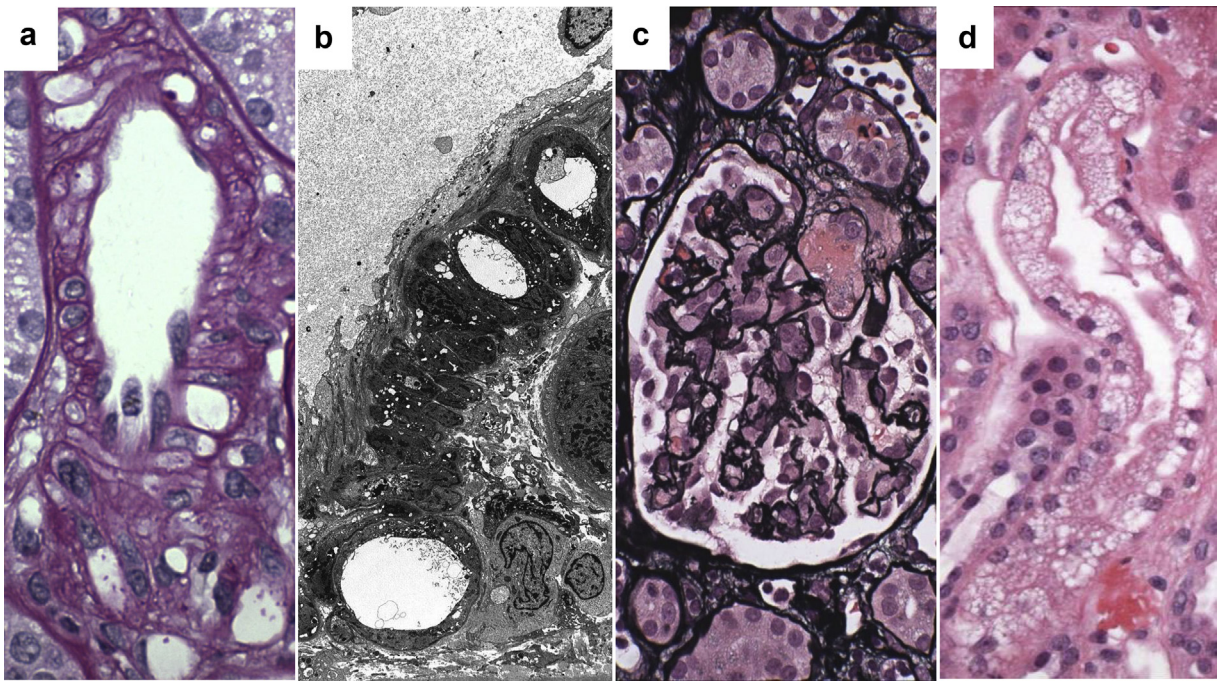

Figure 1. Acute calcineurin inhibitor toxicity. (a) Light microscopy from a kidney allograft recipient with acute calcineurin inhibitor toxicity reveals arteriolar vacuolization (periodic acid–Schiff, original magnification ×600). (b) Ultrastructural view of coarse large vacuoles in the muscularis of an arteriole from the same patient as in (a) (electron microscopy, original magnification ×3000). (c) Afferent arteriolar thrombosis leading to glomerular wrinkling in a kidney allograft recipient with acute calcineurin inhibitor toxicity. This finding is the most severe form of acute calcineurin inhibitor toxicity (Jones methenamine silver stain, original magnification ×400). (d) Isometric tubular vacuolization in the biopsy from the same patient illustrated in (a,b). Note the small clear cytoplasmic vacuolization, which is referred to as "isometric vacuolization" (hematoxylin and eosin, original magnification ×600).