The Basics of Renal Allograft Pathology

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KEYWORDS

• Kidney • Transplant • T-cell–mediated rejection • Antibody-mediated rejection • C4d • Polyomavirus

ABSTRACT

Renal allograft biopsy provides critical information in the management of renal transplant patients, and must be analyzed in close collaboration with the clinical team. The histologic correlates of acute T-cell mediated rejection are interstitial inflammation, tubulitis, and endothelialitis; polyomavirus nephropathy is a potential mimic. Evidence of antibody-mediated rejection includes C4d deposition; morphologic acute tissue injury; and donor specific antibodies. Acute tubular injury/necrosis is a reversible cause of impaired graft function, especially in the immediate post-transplant period. Drug toxicity, recurrent disease, chronic injury, and other entities affecting both native and transplant kidneys must also be evaluated.

OVERVIEW

Renal transplantation greatly enhances quality of life and survival of patients with end-stage renal failure, as compared with dialysis. Patients may receive a living donor kidney, or a deceased donor allograft through the United Network of Organ Sharing paradigm. ABO blood group compatibility is an important factor in kidney transplantation; however, a few centers perform ABO-incompatible transplants after desensitization protocols. Pretransplantation HLA crossmatching is a critical component of transplant evaluation, as preexisting antibodies to the kidney graft can result in immediate (hyperacute) rejection. Crossmatching technology has evolved considerably over the past 50 years; potential recipients are typed for HLA antigen expression, and have their serum tested for preformed anti-HLA antibodies as an important part of the pretransplant workup. Large studies have shown that the fewer the HLA mismatches between donor and recipient, the better the long-term allograft survival.[1] Once the HLA type of an available organ is characterized, a "virtual" crossmatch can be computed with potential recipients, usually but not always followed by tissue studies (such as cytotoxic, B-cell and T-cell crossmatches, **Table 1**).[1] Recipients also may develop antibodies to their kidney allograft after transplantation, which can be elucidated with so-called "donor-specific antibody" (DSA) testing: testing patient serum for HLA antibodies, and comparison with the donor HLA type or archived blood.[1]

Renal allograft biopsies are performed primarily for graft dysfunction, as measured by serum creatinine ("indication" or "for-cause" biopsies). In addition, many centers also perform so-called surveillance or protocol biopsies at defined post-transplantation intervals to assess for subclinical rejection and other pathology. Careful histopathologic evaluation of tissue sections, including special studies, is necessary to distinguish rejection from potential mimics; further, clinicopathologic correlation, including drug levels, medication compliance, clinical history, viral studies, DSAs, imaging, and so forth, is key to appropriate diagnosis and, thus, therapy.

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Surgical Pathology 7 (2014) 367–387
http://dx.doi.org/10.1016/j.path.2014.04.009

Table 1
HLA testing vocabulary

Cell based	
National Institutes of Health standard crossmatch	"Classic assay": most specific, least sensitive; complement-dependent cytotoxicity. Donor lymphocytes are incubated with dilutions of recipient serum in the presence of complement; cell death is assayed
Antiglobulin-enhanced cross match	Detects non–complement binding antibodies and lower-titer antibodies (more sensitive due to addition of antihuman globulin)
B-cell crossmatch	Detects both anti-Class I and II antibodies; detects anti-Class I even when standard crossmatch negative (tests lymphocyte population enriched for B cells)
T-cell crossmatch	Detects only anti-Class I antibodies (T cells do not express Class II HLA)
Flow crossmatch	Most sensitive current assay; does not require viable donor cells. Donor lymphocytes are mixed with recipient serum then with fluorochrome-tagged antihuman immunoglobulin; cells with bound antibody are detected by a flow cytometer
Bead based (Luminex)	
Flow panel reactive antibodies (PRA)	Detects HLA antigen (coated beads) that react with antibodies in patient serum (expressed as a % of antibodies in a pool)
Donor-specific antibody (DSA)	Detects HLA antigens that react with antibodies in patient serum (single antigen–coated beads)
Mean fluorescence intensity (MFI)	A measure of the strength/amount of antibody in a bead-based assay; thresholds are set by individual HLA laboratory tests.

Data from Delos Santos R, Langewisch E, Norman DJ. Immunologic assessment of the transplant patient. In: Kidney transplantation: a practical guide to medical management. Springer Science+Business Media, LLC; 2014.

ALLOGRAFT BIOPSY LABORATORY PREPARATION

Several excellent references outline methods for kidney biopsy tissue handling and reporting.[2–4] Briefly, for allograft biopsies, at least 2 cores of renal parenchyma containing generous proportions of kidney cortex (10 or preferably more glomeruli) for light microscopy are necessary to adequately assess allograft rejection, as inflammatory cell infiltrates and other abnormalities may be patchy. Depending on local practice, tissue also may be needed for immunofluorescence microscopy (IF; usually in Michels or Zeus solution, see C4d Staining in Antibody-Mediated Rejection section), or electron microscopy (EM; usually in glutaraldehyde). If there is proteinuria, hematuria, or any concern for glomerular disease, tissue containing glomeruli should be handled similarly to a native biopsy, and sent for all 3 studies (light microscopy, IF, EM).

For light microscopy, attention to handling and processing is necessary to prevent artifacts and tissue loss.[2,3] Renal biopsies require thin sections (2–3 μm), multiple levels, hematoxylin-eosin (H&E), and additional histochemical stains to fully assess various facets of allograft pathology. Periodic acid-Schiff (PAS) stains are particularly useful in evaluating hyaline (as described in detail later in this article); PAS and other basement membrane stains (such as silver or Jones silver) help to reveal tubulitis.[2,3] As in native renal biopsies, trichrome staining is useful in assessing fibrosis.[2,3] Special immunostains, such as stains for C4d and polyomavirus, are essential in many scenarios, and are described in detail later in this article. Consensus guidelines for renal allograft reporting were recently published.[4]

ACUTE REJECTION: T-CELL MEDIATED

OVERVIEW

Acute T-cell–mediated rejection (acute cellular rejection) occurs most commonly within the first months after transplantation, but can arise at any time point. Interstitial inflammation, tubulitis, and endothelialitis are the hallmarks of acute T-cell–mediated rejection in the renal allograft, although these histopathologic findings are not entirely specific for rejection. Classification schemes have evolved for the assessment and grading of allograft rejection; the Banff classification system is used in many centers and is undergoing continual evaluation and revision as data emerge (**Box 1**).[5–8] Acute rejection is illustrated in the framework