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# Practice of Kidney Biopsy Pathology

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Renal biopsies are essential for diagnosis of cause of proteinuria and impaired renal function in a variety of medical renal diseases that affect the kidneys, and also for assessment of etiology of deranged renal function in the kidney transplant setting. Adequate assessment of diagnosis requires integrated analysis of light microscopy, including various special stains, immunofluorescence microscopy, electron microscopy and additional morphometric and immunohistochemical stains as indicated. In this brief session, we will review the current use of various techniques to accomplish these objectives.

## Approach to Kidney Biopsy: Light Microscopy

The standard workup of a renal biopsy involves serial sectioning through the tissue. This approach is necessary as many renal diseases have an irregular, i.e. focal distribution affecting only some glomeruli, and are even segmental, i.e. affecting only portions of glomeruli. Thus, limited sectioning will not allow adequate recognition of lesions. Although the hematoxylin and eosin stain is the mainstay for routine surgical pathology, it is of limited use for diagnosis and recognition of medical renal diseases. Its usefulness is mainly in recognizing tubular injury and interstitial infiltrates, including specifically eosinophils and crystals, which tend to be dissolved by the longer processing used for other special stains.

Additional standard stains used include a periodic acid Schiff and a stain to distinguish basement membrane, such as a Jones silver stain. Glomerular basement membrane remodeling occurs in response to deposition of immune complexes or other material. Thus, small excrescences of glomerular basement membranes, so-called spikes, are indicators of subepithelial deposits, whereas so-called splitting or tram-tracking, is an indication of a response to subendothelial deposits or chronic endothelial injury. In addition, stains to define the amount of fibrosis, a key indicator of progressive chronic kidney disease, are often used, including sirius red or Masson trichrome stain. For particular unusual vascular lesions, such as some of the vasculitides, elastic stains may also be used.

## Approach to the Renal Biopsy: Immunofluorescence

Detection of immune or other abnormal deposits is an essential part of diagnosis in renal biopsies. The most sensitive method relies on frozen sections incubated with fluorescein- tagged antibodies. An alternative approach is to do antigen retrieval with digestion and immunohistochemistry from formalin-fixed, paraffin-embedded tissue, but this has more problems with potential background and less sensitivity. Routine workup of renal biopsy includes staining for IgG, IgA, IgM, both classic and alternate pathways of complement and kappa and lambda light chains. This allows diagnosis of specific immune complex disease processes such as membranous glomerulopathy, lupus nephritis, hepatitis C-related cryoglobulinemic glomerulonephritis or IgA nephropathy. In addition, transplant biopsies are now routinely worked up with immunostaining for the complement breakdown product C4d, which covalently binds to tissue. When this is present staining peritubular capillaries, it correlates highly with antibody-mediated rejection.

Approach to Renal Biopsy: Electron Microscopy

Electron microscopy is essential for the workup of renal biopsies. Relying only on light microscopy and immunofluorescence is estimated to result in missed diagnosis in as much as 15% of cases. Special recognition of location of deposits, of ultrastructural features correlating with high interferon levels, such as reticular aggregates (seen in HIV infection and in SLE) and recognition of unusual substructure of deposits or abnormalities of glomerular or tubular basement membrane components are all possible by electron microscopy, but not by other techniques. Morphometry of the glomerular basement membrane allows specific diagnosis of hereditary conditions with mutation of the type IV collagen components of the glomerular basement membrane, so-called Alport Syndrome. The glomerular basement membrane increases normally in thickness with maturational growth, and such measures must therefore be compared to normal for age. Recognition of the abnormal basket-weaving appearance in advanced Alport Syndrome is also only possible by electron microscopy. An unusual cause of proteinuria, hematuria and chronic kidney disease is fibrillary glomerulopathy. The pattern by light microscopy is one of proliferation, but by EM the distinct fibrillary nature of the deposits can be recognized. Distinction from amyloid, which has similar but slightly smaller fibrillary deposits, is made by Congo red stain and other special immunostaining.

Renal Biopsy Approach: Special Studies

In addition to the above routinely applied studies, special staining for, for instance, subtypes of type IV collagen, immunohistochemistry for specific viral antigens, and research studies to examine expression of specifically mutated molecules are in the forefront of investigative work and specialized diagnostic work in renal pathology. Some of these studies include immunostaining for dystroglycan, a glomerular basement membrane protein that allows communication of the GBM to the podocyte, and is decreased in minimal change disease but perhaps not in focal segmental glomerulosclerosis. Immunophenotyping of infiltrating cells allows distinction of involvement of the kidney by malignant hematopoietic lymphoid neoplasms. New proteomic approaches, when paired with careful analysis of morphologic abnormalities, will likely result in further insights and progress in both diagnostic and mechanistic aspects of kidney diseases.

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