

Approach to Kidney Biopsy: Core Curriculum 2022

Behzad Najafian, Mark A. Lusco, Charles E. Alpers, and Agnes B. Fogo



The kidney biopsy is an essential tool for diagnosis of many kidney diseases. Obtaining an adequate biopsy sample with appropriate allocation for various studies is essential. Nephrologists should understand key lesions and their interpretation because these are essential elements underlying optimal approaches for interventions. This installment in the *AJKD* Core Curriculum in Nephrology will review these topics. We will first briefly discuss considerations for allocation and processing of kidney biopsies. We will then present in outline form the differential diagnoses of a spectrum of patterns of injury and consideration for interpretation of specific lesions. Lesions are presented according to anatomic site as glomerular, vascular, or tubulointerstitial. Native and transplant kidney biopsy lesions are included. These lesions and differential diagnoses and specific diseases are then linked to detailed clinicopathologic discussion of specific diseases presented in the *AJKD* Atlas of Kidney Pathology II. Correlation with immunofluorescence, electron microscopy, and clinical findings are emphasized to reach a differential diagnosis and the final diagnosis.

Complete author and article information provided at end of article.

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Introduction

This installment of *AJKD*'s Core Curriculum in Nephrology consists of 2 parts, which together constitute an update and extension to a 2003 Core Curriculum installment, "Approach to Renal Biopsy." The first part is in the form of a brief narrative description of approaches to allocate and process kidney biopsies. The second part presents in outline form the differential diagnoses of a spectrum of patterns of injury and consideration for interpretation of specific lesions. These lesions and specific diseases are then linked to detailed clinicopathologic discussion of specific disease presented in the *Atlas of Renal Pathology II*.

Tissue Sampling, Allocation, and Processing

Sampling

Sample Size

An adequate sample size must be obtained for diagnosis. Considerations regarding biopsy indications, procedure, and relative and absolute contraindications are discussed in detail in Core Curriculum "Update on the Native Kidney Biopsy." Needle gauge has dramatic impact on the sample obtained. Although 18- or 19-gauge needles are commonly used and usually provide samples that are diagnostic, they provide very small, narrow samples and may have inadequate representation of vessels. For focal lesions involving a small number of glomeruli, 25 glomeruli may be needed for light microscopy (LM) examination to have a greater than 95% chance of detecting those

lesions. For lesions that are segmental, preparing serial sections and levels is critical to increase the likelihood that any such lesions represented in the biopsy core will be identified in the histologic sections, especially when the number of available glomeruli is limited. The minimum sample size for diagnosis varies greatly with the specific diagnosis; for instance, membranous nephropathy can be diagnosed from a single glomerulus although even this disorder requires a greater number of glomeruli to fully characterize the lesion and the extent of chronicity or scarring that may be present. Transplant diagnoses are most accurate when the sample includes a minimum of 7 glomeruli from 2 separate sites of cortex. For most LM assessments to adequately assess the severity and distribution of lesions, 8 to 10 glomeruli are needed.

Sample Location

Subcapsular cortical samples have overrepresentation of global sclerosis related to aging/hypertension and nonspecific scarring. Juxtamedullary glomeruli are the earliest to be involved with segmental sclerosis in focal segmental glomerulosclerosis (FSGS). This region should be included in the sample for optimal detection. Some processes are better represented in the corticomedullary or medullary regions (eg, polyomavirus nephropathy).

Dividing the Tissue

A dissecting microscope can be used to identify cortical parenchyma containing glomeruli,

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or without any visual guidance one can remove 1-mm cubes from each end of each core and place them in glutaraldehyde for electron microscopy (EM). The remaining cores can then be divided into 2 pieces, placing the larger of each core, about two-thirds of the core length, in fixative for LM, and the smaller section of each core in tissue-transport media for immunofluorescence (IF). If immunohistochemistry (IHC) on formalin-fixed tissue is used in place of IF, then the remaining tissue after EM allocation is allocated in toto for combined LM and IHC. Allocation should be done on a clean surface (such as a wax cutting board) with a sharp razor or blade to avoid crushing parts of the biopsy sample.

Handling of Tissue

To avoid crush artifacts, forceps should not be used. The tissue can be manipulated by allowing it to adhere to a thin wooden stick that then is placed in the fixative or transport medium, respectively. Avoid touching the tissue with a fixative-contaminated scalpel or razor blade (this contaminates the tissue for IF and could result in false-negative IF results).

Allocation and Fixatives

An adequate assessment of native kidney biopsies includes LM, IF or IHC, and EM. For transplant biopsy, LM and IF or IHC are considered the standard, with repeat biopsies only needing LM in many cases and C4d staining, best done from frozen tissue by IF. However, we recommend that transplant biopsies include allocation of tissue for EM in first biopsies because often the primary disease process is unknown and EM may provide unexpected value in assessment of kidney graft dysfunction. In follow-up transplant biopsies, allocation for EM may depend on the clinical situation (eg, proteinuria, concern for recurrent or de novo deposit-related disease). When possible, allocation of small pieces for EM (which can be saved and processed later as clinically indicated) provides the best opportunities for diagnosis in complex cases.

Light Microscopy

For most differential diagnoses, the largest portion of cortex should be placed in fixative for LM. These fixatives include formalin, paraformaldehyde, or, less commonly, alcoholic Bouin or Zenker fixative. Although formalin may not allow some morphologic details to be as defined as with Zenker fixative, the use of formalin allows much greater IHC ancillary testing to be done, as indicated in individual cases. If observation of urate crystals is intended, ethanol is preferred.

Immunofluorescence Microscopy

IF tissue should include a small piece of cortex, usually 3 to 4 mm. Tissue for IF can be directly frozen or placed in tissue transport medium (such as Michel) and transported

to the laboratory. Tissue is stable at room temperature for express mailing to central laboratories in this medium.

Immunohistochemistry

In some laboratories, IHC on formalin-fixed tissue, instead of IF on frozen tissue, is used with good results for identification of deposited immunoglobulins and complement. Success with this technique requires expert histotechnologists and may not work optimally if tissue has been in fixative or paraffin-embedded for a long period of time.

Electron Microscopy

Small, 1-mm cubes of cortex are allocated for EM and optimally are placed directly in glutaraldehyde.

Tissue Processing

Light Microscopy

Tissue for LM is processed, dehydrated, and embedded in a paraffin block, and multiple serial sections at 2.5-3 μm thickness are obtained and stained. Usual stains include hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), silver methenamine (Jones), and Masson trichrome. Additional unstained slides are produced to allow additional special studies as needed. Five hours of processing, sectioning, and staining time are typically needed to produce LM slides.

Immunofluorescence Microscopy

Tissue for IF is surrounded with optimal cutting temperature (OCT) compound and frozen in a cryomicrotome (if not directly frozen after biopsy). Sections are produced, fixed with acetone and stained with fluorescein-tagged antibodies against IgG, IgA, IgM, complement pathway components C3 (junction of all 3 complement pathways) and C1q and/or C4 (classical pathway), κ and λ light chain, fibrinogen, and albumin. Some laboratories use properdin as a marker for alternative complement pathway activation. Complement product C4d, a marker of classical and mannose-binding lectin pathways, optimally is stained on frozen tissue, with less sensitivity if staining is performed on paraffin-block tissue. One to 2 hours of processing, sectioning, and staining time are needed for production of IF slides.

Electron Microscopy

EM tissue is processed and embedded in a plastic, hard medium, and scout sections (so-called thick sections) are stained with toluidine blue to identify the specific area to be cut for thin sections to be placed on a grid for EM examination. Typically, 2 working days are needed to process the specimen and produce thin sections for ultrastructural examination. Microwave processing can hasten polymerization and cut down this processing time, but morphology may be suboptimal.

Salvage Techniques

If there is inadequate tissue in any of the media, sometimes results can still be obtained as described in the following.

Salvage LM from frozen tissue. The remaining frozen tissue after IF may be retrieved and fixed in formalin and processed for LM. This approach, while associated with some freezing artifacts and some loss of morphologic detail, can provide invaluable information when the original LM sample is inadequate.

Salvage EM from paraffin-embedded tissue. EM study can be done by processing remaining tissue from the LM sample from the paraffin block for EM. Of note, glomerular basement membranes (GBM) are artefactually thinner with such processing, precluding accurate GBM measures. Reprocessing the frozen tissue (for IF) for EM is possible; however, the outcome quality is variable and may be associated with significant artifacts. Salvage EM from frozen tissue has major artefacts and is not recommended.

Salvage IF from paraffin tissue. Immunofluorescence done on fixed, paraffin-embedded tissue sections after pronase or proteinase K digestion can yield diagnostic information when glomeruli are not present in the original IF sample. Sensitivity for detection of deposits varies. IgA deposits are robustly detected by this method, whereas anti-GBM staining is not detected, and the results for membranous nephropathy are variable. Crystalline light chain deposits are not reliably detected by frozen section IF and by contrast are robustly detected after pronase/proteinase digestion of formalin-fixed paraffin-embedded (FFPE) sections. Some deposits that are masked (the epitopes targeted by the antibodies are hidden due to conformational changes) and not detectable by routine IF on frozen tissue can become detectable after pronase digestion. This technique is of use in assessment of C3 glomerulopathies and to assess possible clonality of deposits (see the separate sections).

Additional Readings

- Corwin HL, Schwartz MM, Lewis EJ. The importance of sample size in the interpretation of the renal biopsy. *Am J Nephrol.* 1988;8:85-89. ★**ESSENTIAL READING**
- Luciano RL, Moeckel GW. Update on the native kidney biopsy: core curriculum 2019. *Am J Kidney Dis.* 2019;73:404-415. ★**ESSENTIAL READING**
- Messias NC, Walker PD, Larsen CP. Paraffin immunofluorescence in the renal pathology laboratory: more than a salvage technique. *Mod Pathol.* 2015;28:854-860. ★**ESSENTIAL READING**
- Hou J, Markowitz GS, Bombach AS, et al. Toward a working definition of C3 glomerulopathy by immunofluorescence. *Kidney Int.* 2014;85(2):450-456.
- Larsen CP, Messias NC, Walker PD, et al. Membranoproliferative glomerulonephritis with masked

monotypic immunoglobulin deposits. *Kidney Int.* 2015;88: 867-873.

- Nankivell BJ, Renthawa J, Shingde M, Khan A. The importance of kidney medullary tissue for the accurate diagnosis of BK virus allograft nephropathy. *Clin J Am Soc Nephrol.* 2020;15(7):1015-1023.
- Nasr SH, Galgano SJ, Markowitz GS, et al. Immunofluorescence on pronase-digested paraffin sections: a valuable salvage technique for renal biopsies. *Kidney Int.* 2006;70:2148-2151.
- Seemayer CA, Gaspert A, Nিকেleit V, Mihatsch MJ. C4d staining of renal allograft biopsies: a comparative analysis of different staining techniques. *Nephrol Dial Transplant.* 2007;22(2):568-576.

Tissue Examination

We will now provide an overview of approaches to assess injury and localize pathologic alterations to the specific anatomic compartment. Injuries are categorized as active versus chronic lesions. In addition, injuries are categorized as involving predominantly glomeruli, vessels, or the tubulointerstitium, recognizing that eventually injury in any one of these anatomical compartments may affect other anatomical sites. We have organized discussion of specific lesions according to these anatomical compartments.

Active Versus Chronic Lesions

Active lesions of glomeruli include hypercellularity (either mesangial or endocapillary, the latter including influx of leukocytes), fibrinoid necrosis with destruction of architecture, rupture of GBMs, and karyorrhexis. Crescents are a response to injury that breaks the capillary wall. The early lesion consists predominantly of proliferation of parietal epithelial cells with later influx of inflammatory cells and fibrous organization. Crescents are classified as cellular (active), fibrocellular (both active and chronic), or fibrous (chronic). Tubulointerstitial active lesions are characterized by edema, inflammatory infiltrates, often with tubulitis, with variable lymphocytes, plasma cells, and/or polymorphonuclear leukocytes. Active lesions of vessels include intimal swelling necrosis, thrombosis, and inflammation (vasculitis).

Chronic lesions of glomeruli include sclerosis, either segmental or global, and fibrous crescents. The pattern of sclerosis gives hints to the underlying etiology, in conjunction with IF and EM examination, integrated with clinical findings. Chronic changes of the GBMs include thickening and duplication of the basement membrane matrices. Fibrous crescents are chronic lesions whereas fibrocellular crescentic lesions are a mixture of active and chronic. Chronic tubulointerstitial lesions are interstitial fibrosis and tubular atrophy, which usually develop in parallel. Lymphocytic infiltration occurs in fibrosed areas

as part of the scarring process. Neutrophils within these areas suggest additional or other etiologies. Chronic lesions of vessels include medial thickening, hyalinosis, and intimal or medial fibrosis. Concentric intimal proliferation (“onion-skin” lesion) indicates injury related to chronic endothelial injury seen in for example scleroderma or severe hypertension.

Types of Lesions

Examination by IF (or IHC), EM, and LM is essential to determine the nature and pathogenesis of lesions. A group of pathologists from the Renal Pathology Society has recently proposed precise definitions for use of a spectrum of morphologic lesion descriptions, aimed to provide uniformity in reporting.

Special stains are useful for determining if thickened GBMs are likely due to immune-complex deposits or not because deposits and cells do not stain with Jones silver stain. Some stains such as PAS can highlight large confluent deposits or intracapillary accumulations of immune complexes such as those that may be encountered in lupus nephritis or cryoglobulinemic glomerulonephritis (GN). Assessment by IF then determines whether lesions are mediated by immune complexes or other deposits or not. EM aids in determination of specific localization of any deposits, nature of any deposits, GBM abnormalities, foot process effacement, and other specific abnormalities of, for example, tubules or interstitium. Correlation of LM with IF and EM and clinical history is needed for optimal interpretation.

In the remainder of this Core Curriculum, we give integrated differential diagnosis for a spectrum of lesions/patterns of injury, with illustrations provided in the hyperlinked disease-specific installments of the [AJKD Atlas of Renal Pathology II](#).

Additional Readings

- Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/ Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. *Kidney Int.* 2018;93(4):789-796.
- Haas M, Seshan SV, Barisoni L, et al. Consensus definitions for glomerular lesions by light and electron microscopy: recommendations from a working group of the Renal Pathology Society. *Kidney Int.* 2020;98(5):1120-1134. **★ESSENTIAL READING**
- Sethi S, D’Agati VD, Nast CC, et al. A proposal for standardized grading of chronic changes in native kidney biopsy specimens. *Kidney Int.* 2017;91(4):787-789.
- Sethi S, Haas M, Markowitz GS, et al. Mayo Clinic/ Renal Pathology Society consensus report on pathologic classification, diagnosis, and reporting of GN. *J Am Soc Nephrol.* 2016;27:1278-1287.

Outline of Native Kidney–Specific Lesions

I. Glomerular lesions

A. Thickened GBM appearance by LM

i. Thick appearance of GBM by LM with negative IF.

- a. No double contour by silver stain, thick lamina densa by EM:
 1. [Diabetic nephropathy](#).
 2. [Idiopathic nodular glomerulosclerosis](#).

b. Double contour by silver stain:

1. Chronic (thrombotic) microangiopathy.
Note: Microangiopathy may or may not have thrombosis detected at this stage; when thrombosis is absent, it is better termed “chronic microangiopathy.”
Note: In some cases of chronic thrombotic microangiopathy (TMA), some endocapillary/mesangial hypercellularity may be present, and the differential diagnosis of membranoproliferative glomerulonephritis (MPGN) pattern is then considered (see section on MPGN pattern).

2. Transplant glomerulopathy (see “Outline of Transplant Kidney Lesions” section and [Chronic Antibody-Mediated Rejection Atlas](#) installment).

c. Irregular by silver stain, basketweaving by EM: hereditary nephritis ([Alport syndrome](#)).

- ##### d. Variable spikes or double contour by silver stain: may be due to masked deposits on standard frozen tissue IF, with subsequent IF on paraffin-embedded tissue after pronase digestion positive after this unmasking of deposits (deposits also visualized by EM, see specific sections according to findings).

ii. Thick appearance of GBM by LM with positive IF:

- a. Granular capillary loop IgG polyclonal and C3 staining by IF, spikes by Jones stain, subepithelial deposits by EM: [membranous nephropathy](#).

Note: Diagnosis of specific etiology is aided by integration with IF, EM, and clinical history and staining for novel antigens found in membranous nephropathy (eg, PLA₂R [phospholipase A₂ receptor], THSD7A [thrombospondin type 1 domain-containing 7A], EXT1/2 [exostosin 1/2], NELL-1 [neuroepidermal growth factor-like 1], and others).

- b. Molded, sausage-shaped contour of deposits along capillary loop, mesangial granular deposits, GBM double contour by silver stain, subendothelial deposits by EM: MPGN due to deposits.

The nature of the deposits must then be defined, whether C3 dominant or immunoglobulin (either monoclonal or polyclonal). MPGN pattern can be due to, for example,

immune complexes (see [MPGN](#) and [Focal and Diffuse Lupus Nephritis \(ISN/RPS Class III and IV\)](#)), other deposits ([fibrillary GN](#)) or clonal deposits ([proliferative GN with monoclonal immunoglobulin deposits](#)), or C3 glomerulopathy (including C3 GN and [dense deposit disease \[DDD\]](#)).

- c. Polyclonal IgG with full house staining (ie, all immunoglobulins [IgG, IgA, IgM], C3, and C1q) suggests [lupus nephritis class III focal or IV diffuse](#), depending on whether <50% or ≥50% of glomeruli involved.
- d. Polyclonal IgG and strong IgM component, often with clonal shift (ie, 1 light chain significantly dominant); may have strong PAS-positive deposits in capillary lumens (cryoplug) and short fibrillary substructure by EM: [cryoglobulinemic GN](#).
- e. Polyclonal IgG with lesser C3; GBM variable double contours by silver stain, randomly arranged fibrils by EM, negative Congo Red, positive DNAJB9 staining by IHC: [fibrillary GN](#). Note: Rarely, fibrillary GN has been described with apparent clonal deposits. Studies with newer antibodies against combined heavy and light chain regions and mass spectrometry support the deposits are polyclonal in nearly all cases.

- iii. Thickened appearance of GBMs by LM with variable IF.

Amyloid deposits can result in thickened GBM with long feathery spikes on silver stain, Congo red positive (see [AL Amyloidosis](#)).

AL amyloid shows positive IF for 1 light chain, with smudgy mesangial and capillary wall pattern, often also in vessels (most often λ but κ can also form amyloid; rare cases of heavy chain amyloid exist).

Note: IF is negative or shows only nonspecific trapping in other types of amyloid, with specific type defined by IHC and/or mass spectrometry (see [Hereditary and Other Non-AL Amyloidoses](#)).

B. Thin GBM by EM

Collagen IV abnormalities, such as Alport syndrome, have thin GBM as an early lesion in X-linked affected male, male or female autosomal recessive heterozygotes, or female X-linked heterozygotes (see [Thin Glomerular Basement Membrane Lesion](#) and [Alport Syndrome](#)).

Note: Thin GBMs cannot reliably be detected by LM. GBM should be extensively thin to diagnose thin GBM lesion, as very segmental thinning may occur in healthy individuals.

Note: GBM thickness increases normally with age, so thickness must be compared with age-matched control (~100 vs 200 nm in age 1 year vs age 8

years; 325 vs 375 nm average in female vs male adults).

Note: More specific morphologic diagnosis of type of abnormality causing thin GBM may be made by special immunostaining for subtypes of type IV collagen. Total absence of collagen IV $\alpha 5$ chain indicates male with X-linked Alport. Mosaic GBM staining pattern for collagen IV $\alpha 5$ indicates female X-linked heterozygote. Preserved collagen IV $\alpha 5$ staining in Bowman capsule but not in GBM indicates autosomal form of Alport due to mutation in $\alpha 3$ or $\alpha 4$ chain.

C. Mesangial hypercellularity

- i. Variable mesangial hypercellularity with nodules: nodular sclerosis may be seen in the following conditions. Correlation with IF and/or EM allows distinction of these possibilities:

- a. [Diabetic nephropathy](#): nodular sclerosis, with increased matrix more than cells, thick GBM, arteriolar hyalinosis (afferent and efferent), no deposits.

- b. Monoclonal immunoglobulin deposition disease: most common type is light chain deposition disease (see [Light Chain Deposition Disease](#), [Light and Heavy Chain Deposition Disease](#), and [Heavy Chain Deposition Disease](#)). Nodular sclerosis with monoclonal light chain staining of GBM and tubular basement membrane (TBM) with corresponding amorphous powdery deposits by EM.

- c. [Idiopathic nodular glomerulosclerosis](#): appears morphologically like diabetic glomerulosclerosis but patients do not have diabetes.

- d. Amyloid (see [AL Amyloidosis](#) and [Hereditary and Other Non-AL Amyloidoses](#)): relatively acellular expansion of mesangial areas, may be nodular, may have feathery spikes of GBM by LM, has randomly arranged 9-11 nm fibrils by EM, Congo Red positive.

- e. MPGN pattern: can be nodular—various causes (see below), diagnosed by IF, EM, IHC (see [MPGN](#)).

- ii. Mesangial hypercellularity with positive IF without nodules—distinction of cause relies heavily on IF findings:

- a. Mesangial lupus nephritis (see [Minimal Mesangial and Mesangial Proliferative Lupus Nephritis \(ISN/RPS Class I and II\)](#)): IF and EM, and clinical history distinguish mesangial lupus nephritis from other causes of mesangial immune complexes. Lupus nephritis is characterized by IF positivity often with all 3 immunoglobulins and both complements (full house), reticular aggregates in endothelial cells by EM (footprints of high interferon

levels, found in endothelial cells throughout the body).

b. **IgA nephropathy (IgAN)**: diagnosis made by IF. Dominant or co-dominant (with other immunoglobulins) IgA mesangial deposits, with mesangial deposits most often detected by EM, are typical. Deposits may extend to subendothelial areas of adjacent GBMs, often eliciting a focal endocapillary hypercellular reaction.

c. **Chronic infection-related GN**: deposits may be IgG or IgM predominant. The presence of any subepithelial hump-shaped deposits, seen by EM, in addition to the mesangial deposits, strongly suggests an infection-related etiology (see **Post-Infectious Glomerulonephritis**). **C3-dominant GN** due to complement dysregulation can also have hump-shaped deposits.

iii. **Mesangial hypercellularity without immune complexes**—the differential diagnosis includes:

a. Variant of **minimal change disease (MCD)/FSGS** (EM shows extensive foot process effacement in untreated MCD or primary FSGS (due to initial podocyte injury)).

b. Early **diabetic nephropathy** (GBM thickening by EM).

c. A nonspecific finding.

D. Endocapillary hypercellularity

The MPGN pattern is characterized by mesangial and endocapillary hypercellularity, a term denoting a combination of both endothelial cell prominence and influx of leukocytes in glomerular capillaries, with double contours of the GBM by LM. Glomeruli may show a nodular pattern. IF, EM, and/or IHC are needed for specific diagnosis. If the MPGN pattern is caused by deposits, IF or IHC will show the causative deposits along capillary loop and in mesangial areas, with subendothelial and mesangial deposits by EM. This pattern can be caused by immune complexes (ie, with immunoglobulin[s] and complement [see **Membranoproliferative Glomerulonephritis**]), **C3-dominant deposits** in C3 glomerulopathies, monoclonal proteins (see **Light Chain Deposition Disease**, **Light and Heavy Chain Deposition Disease**, and **Heavy Chain Deposition Disease**), and other deposits or chronic microangiopathies, with or without thrombosis (see **Thrombotic Microangiopathy**):

i. **MPGN pattern due to immune complex deposits**: has predominant IgG, double contours of GBM by LM, and subendothelial and mesangial deposits.

ii. **Lupus nephritis class III focal or IV diffuse**: is characterized by IF positivity, often with all 3 immunoglobulins and both complement components C3 and either C4 or C1q (full house), reticular aggregates in endothelial cells (footprints of high interferon levels,

found in endothelial cells throughout the body).

iii. **Cryoglobulinemic GN**: may have predominant IgM, substructure of deposits by EM, and sometimes strongly positive PAS plugs (cryoplugs) in capillary lumens.

iv. **Postinfectious GN**: most commonly has prominent PMN (polymorphonuclear leukocyte) infiltrate in the glomerular tuft, with starry sky appearance of IgG and strong C3 deposits by IF, and hump-shaped subepithelial deposits by EM. In the chronic phase, seen more often in adults, the term “infection-related GN” should be used as the infection often is ongoing. The active lesions seen in classic poststreptococcal GN may not be present, with only mild hypercellularity, few if any neutrophils in the glomerular capillaries, and rare hump-typed deposits, often in the hinge region where the GBM reflects over the mesangium.

v. **Fibrillary GN**: has IgG polyclonal predominance, randomly arranged deposits with fibrillary substructure 11–24 nm by EM, Congo red–negative, DNAJB9 positive by IHC.

vi. **Immunotactoid glomerulopathy**: has IgG predominance, deposits are often clonal, with microtubular and/or parallel array substructure by EM and is usually associated with a paraprotein. Similar morphology may be caused by cryoglobulin deposits, particularly monoclonal cryoglobulin.

vii. **DDD**: has C3 only or C3 dominant staining, at least 2 intensity steps greater than IgG, with limited immunoglobulin, dense transformation of GBM, with dense mesangial nodules by EM.

viii. **C3-dominant GN**: has C3 only or dominant staining, at least 2 intensity steps greater than IgG, limited or no immunoglobulin, with deposits of varying density, which may be subendothelial, mesangial, and often intramembranous permeating the GBM, and can also have hump-type subepithelial deposits by EM.

E. Sclerosis

Glomerulosclerosis must be assessed in terms of its location within the glomerular tuft and its quality. Glomerulomegaly may be present in cases of FSGS even before sclerosis is evident. Comparisons of glomerular size must be age matched.

i. **Usual type sclerosis**: localized anywhere within the glomerular tuft, defined by obliteration of capillary lumens by increased matrix and/or hyalin, extensive foot process effacement by EM, typical of FSGS (see **FSGS, NOS**).

ii. **Collapsing glomerulosclerosis** (see **Collapsing Glomerulopathy** and **HIV-Associated Nephropathy**): defined by collapse and

retraction of glomerular tuft that can be segmental (involving part of the tuft) or global (involving all of the tuft), with proliferation of overlying visceral epithelial cells, may be idiopathic (most often seen in patients with high-risk alleles of *APOL1*) or linked to a variety of etiologies, such as viral infections (eg, HIV, parvovirus, SARS-CoV-2), medications (eg, bisphosphonates, tumor necrosis factor α agonists, anabolic steroids) or severe ischemia (nephrotoxicity due to [calcineurin inhibitor](#) or cocaine) and rarely in combination with diffuse lupus nephritis.

Note: This lesion has worse prognosis than other types of FSGS. Collapsing glomerulopathy due to HIV or SARS-CoV-2 can show reticular aggregates by EM.

- iii. **Tip lesion variant of FSGS:** defined by sclerosis involving the proximal tubular pole of the glomerulus, with adhesion to the proximal tubule, often with intracapillary foam cells, extensive foot process effacement by EM, may have better prognosis than usual FSGS. This lesion is not specific for primary FSGS.

Note: Absence of segmental sclerosis in an adequate sample (>25 glomeruli, including juxtamedullary area), no immune complexes, and complete foot process effacement is consistent with MCD in a nephrotic patient.

- iv. **Hilar variant of FSGS:** the sclerosis is at the vascular pole, often with hyalinosis, and typically is associated with a maladaptive reaction to nephron loss or low nephron number or other overload (as, eg, with obesity-related glomerulopathy).
- v. **Secondary sclerosis:** can occur with any injury. In diseases due to immune deposits, sclerosis can occur. Sclerosis due to healing of past aggressive necrotizing injuries, whether immune complex-related or pauci-immune, will often show broad-based adhesion, fibrous crescent, and/or periglomerular fibrosis (see [Pauci-immune Necrotizing Crescentic GN](#), [Arterionephrosclerosis](#), and [Chronic Pyelonephritis](#)). Globally sclerosed glomeruli due to such aggressive injury show a fractionated appearance of the tuft, surrounded by fibrous matrix.

F. Crescents

Crescents are classified as cellular, fibrocellular, or fibrous, depending on degree of fibrous tissue, with less responsiveness to therapy corresponding to greater degrees of fibrosis. Crescents are composed of proliferating parietal epithelial cells and variable inflammatory cells and matrix and occur with any injury that breaks the capillary wall. Injury may be categorized as in the following.

- i. Immune etiology:

- a. Linear IgG stain along capillary wall, polyclonal, with discontinuous or even granular C3, of GBM in [anti-GBM antibody-mediated GN](#). No deposits are visualized by EM. No extraglomerular kidney lesions are present, unless the patient also has microscopic polyangiitis (see [Pauci-immune Necrotizing Crescentic Glomerulonephritis](#)).
- b. Immune complex disease (eg, [lupus nephritis class III focal or IV diffuse](#), [postinfectious GN](#), [IgAN](#)).
- c. [Pauci-immune necrotizing crescentic GN](#): minimal or no deposits by IF and/or EM.
- d. Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), or eosinophilic polyangiitis (EPA).
Note: GPA, MPA, and EPA cannot be distinguished from each other in a kidney biopsy. They all can have glomerular necrotizing lesions with crescents and may also involve small vessels with vasculitis.

G. Unusual Lesions—Rare Diseases

Note: EM and/or LM may reveal abnormal accumulations that are diagnostic of specific diseases.

- i. Foamy podocytes: most common cause is Fabry disease. Myelin-body type inclusions seen by EM in various cells, especially podocytes. Other storage diseases can also cause this lesion (see [Fabry Nephropathy](#)).
- ii. Intraglomerular foamy macrophages, often with secondary sclerosis: consider lipid storage disease (eg, [LCAT deficiency](#)). This lesion can also be seen in diabetic nephropathy and with sclerosis and marked proteinuria.
- iii. Abundant type III banded collagen in glomeruli in mesangial, subendothelial areas by EM: consider [type III collagen glomerulopathy](#).

Additional Readings

- Bridoux F, Hugue V, Coldefy O, et al. Fibrillary glomerulonephritis and immunotactoid (microtubular) glomerulopathy are associated with distinct immunologic features. *Kidney Int.* 2002;62:1764-1775.
- D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis.* 2004;43(2):368-382. **★ESSENTIAL READING**
- D'Agati VD, Kaskel FD, Falk RJ. Focal segmental glomerulosclerosis. *N Engl J Med.* 2011;365:2398-2411.
- Fogo AB. Causes and pathogenesis of focal segmental glomerulosclerosis. *Nat Rev Nephrol.* 2015;11(2):76-87.
- Geetha D, Jefferson JA. ANCA-associated vasculitis: core curriculum 2020. *Am J Kidney Dis.* 2020;75(1):124-137.

- Glasscock RJ, Alvarado A, Prosek J, et al. Staphylococcus-related glomerulonephritis and poststreptococcal glomerulonephritis: why defining “post” is important in understanding and treating infection-related glomerulonephritis. *Am J Kidney Dis*. 2015;65(6):826-832.
 - Goodship TH, Cook HT, Fakhouri F, et al. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a “Kidney Disease: Improving Global Outcomes” (KDIGO) Controversies Conference. *Kidney Int*. 2017;91(3):539-551. **★ESSENTIAL READING**
 - Haas M. Alport syndrome and thin glomerular basement membrane nephropathy: a practical approach to diagnosis. *Arch Pathol Lab Med*. 2009;133(2):224-232. **★ESSENTIAL READING**
 - Lusco MA, Fogo AB. Hereditary nephritis and thin basement membrane lesion. *Glomerular Dis*. 2021;1:135-144.
 - Markowitz GS, Lin J, Valeri AM, et al. Idiopathic nodular glomerulosclerosis is a distinct clinicopathologic entity linked to hypertension and smoking. *Hum Pathol*. 2002;33(8):826-835.
 - Najafian B, Alpers CE, Fogo AB. Pathology of human diabetic nephropathy. *Contrib Nephrol*. 2011;170:36-47.
 - Nasr S, Fogo AB. New developments in the diagnosis of fibrillary glomerulonephritis. *Kidney Int*. 2019;96:581-592.
 - Nasr SH, Fidler ME, Said SM, et al. Immunofluorescence staining for immunoglobulin heavy chain/light chain on kidney biopsies is a valuable ancillary technique for the diagnosis of monoclonal gammopathy-associated kidney diseases. *Kidney Int*. 2021;100(1):155-170.
 - Picken MM. Diagnosis of amyloid beyond Congo red. *Curr Opin Nephrol Hypertens*. 2021;30(3):303-309.
 - Renwick N, Nasr SH, Chung WK, et al. Foamy podocytes. *Am J Kidney Dis*. 2003;41(4):891-896.
 - Rossini M, Fogo AB. Interpreting segmental glomerular sclerosis. *Curr Diag Pathol*. 2004;10:1-10.
 - Said SM, Leung N, Alexander MP, et al. DNAJB9-positive monotypic fibrillary glomerulonephritis is not associated with monoclonal gammopathy in the vast majority of patients. *Kidney Int*. 2020;98:498-504.
 - Sethi S. New ‘antigens’ in membranous nephropathy. *J Am Soc Nephrol*. 2021;32(2):268-278.
 - Sethi S, Rajkumar SV, D’Agati VD. The complexity and heterogeneity of monoclonal immunoglobulin-associated renal diseases. *J Am Soc Nephrol*. 2018;29(7):1810-1823.
 - Smith RJH, Appel GB, Blom AM, et al. C3 glomerulopathy—understanding a rare complement-driven renal disease. *Nat Rev Nephrol*. 2019;15(3):129-143.
 - Swanepoel CR, Atta MG, D’Agati VD, et al. Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2018;93(3):545-559.
 - Trimarchi H, Barratt J, Cattran DC, et al. IgAN Classification Working Group of the International IgA Nephropathy Network and the Renal Pathology Society; Conference Participants. Oxford classification of IgA nephropathy 2016: an update from the IgA Nephropathy Classification Working Group. *Kidney Int*. 2017;91(5):1014-1021.
- II. Vascular Lesions
- A. Sclerosis/Intimal fibrosis/medial hypertrophy represent common hypertension-associated changes (see [Arterionephrosclerosis](#)).
 - B. Thrombotic lesions
 - i. Arteriolar/glomerular predominance: typical of [TMA](#) due to hemolytic uremic syndrome. Microangiopathy lesions without thrombosis include necrosis within the wall, red blood cell fragments within the vascular wall, and mucoid expansion of the intima.
 - ii. Arteriolar/interlobular artery predominance of microangiopathy lesions: more typical of [systemic sclerosis](#). This may overlap morphologically completely with lesions seen with severe hypertension (see [Arterionephrosclerosis](#)).
 - C. Necrosis
 - “Fibrinoid” necrosis (lesion in, eg, [systemic sclerosis](#) and severe hypertension [see [Arterionephrosclerosis](#)]): term used to describe necrosis of wall with chunky, eosinophilic appearance, often containing fibrin and karyorrhectic debris.
 - D. Vasculitis
 - Defined as vascular inflammation with lymphocytes/PMNs and may be transmural or just intimal. Positive IF may be seen in lupus vasculitis or cryoglobulinemic vasculitis. Pauci-immune conditions may also have vasculitis lesions (see [Focal or Diffuse Lupus Nephritis, ISN/RPS Class III and IV](#), and [Cryoglobulinemic GN](#)).
 - E. Embolic lesions
 - [Cholesterol emboli](#) lodge in interlobular arteries, and sometimes also in smaller vessels downstream (rarely in glomeruli) and appear as clear cleft-shaped space with surrounding mononuclear cell reaction (cholesterol per se is extracted during processing for LM).
 - F. Endothelial lesion
 - Swollen endothelial cells are a feature of the endotheliosis lesion of pre-eclampsia/eclampsia (see [Thrombotic Microangiopathy](#)).
- Additional Readings**
- Butler EA, Baron M, Fogo AB, et al. Generation of a core set of items to develop classification criteria for scleroderma renal crisis using consensus methodology. *Arthritis Rheumatol*. 2019;71(6):964-971.

➤ Freedman BI, Cohen AH. Hypertension-attributed nephropathy: what's in a name? *Nat Rev Nephrol.* 2016;12:27-36. ★**ESSENTIAL READING**

III. Tubulointerstitial Lesions

A. Necrosis vs acute tubular injury (ATI)

- i. Frank necrosis: sloughing off of cells (see [Toxic Acute Tubular Injury](#)).
- ii. ATI: shows flattened, regenerating epithelium, often with vacuolization, may see sloughing of cells, without thickened tubular basement membranes.

Note: Acute tubular necrosis can occur in isolation or with associated glomerular necrosis (the combination is called [cortical necrosis](#) and can involve broad regions of the cortex).

Note: [Ischemic etiology](#) often results in zones of injury; [toxic etiology](#) often results in individual cell injury/blebbing/degeneration/apoptosis.

B. Edema

Increased interstitial space with loose appearance and normal thickness TBMs is generally due to edema. This is in contrast to interstitial fibrosis (see below), where tubules are widely spaced and TBMs are thickened, with intervening dense, fibrotic tissue with increased collagenous matrix (see [Acute Interstitial Nephritis](#), [Chronic Interstitial Nephritis](#), and [Tubular Atrophy](#)).

C. Interstitial inflammation

- i. Intratubular PMNs forming plugs are diagnostic of [acute pyelonephritis](#).
- ii. Interstitial or peritubular capillary PMNs may be nonspecific, due to renal vein thrombosis, or acute [antibody-mediated rejection](#) (see Transplant section). Medullary angiitis with increased PMNs in vasa recta can be due to ANCA-associated vasculitis or drug hypersensitivity reaction (see [Acute Interstitial Nephritis](#) and [Pauciimmune Necrotizing Crescentic Glomerulonephritis](#)).
- iii. Lymphocytes in the interstitium with edema are diagnostic of [acute interstitial nephritis](#), a lesion with varying etiology (see [Tubulointerstitial Nephritis With Uveitis](#) and [Kidney Disease in Primary Sjögren Syndrome](#)). Note: There is often associated tubulitis, even in native kidneys.
- iv. Lymphocytes and interstitial fibrosis are more characteristic of chronic interstitial nephritis. Note: This is a nonspecific diagnosis, and an underlying cause should be diligently sought, such as light chain cast nephropathy (see "Intratubular casts" section and [Chronic Interstitial Nephritis](#), [Light Cast Nephropathy](#), [Tubulointerstitial Nephritis with Uveitis](#), and [Kidney Disease in Primary Sjögren Syndrome](#)). Note: Kidney involvement by hematopoietic

neoplasms can manifest by infiltration of the malignant cells, which may be lymphocytes, blasts, or other cells. Monomorphic sheets of such cells, infiltration into surrounding fat, blast appearance, cytologic atypia, and clinical history of such neoplasms can then lead to diagnosis with additional IHC studies to define clonality of the process.

- v. Eosinophils clustered in the interstitium: consider hypersensitivity reaction (see [Acute Interstitial Nephritis](#)).

Note: In [diabetic nephropathy](#), eosinophils may be seen in areas of scarring and non-scarred areas and do not imply a hypersensitivity reaction.

- vi. Granulomas: the most common cause for non-necrotizing granulomas is a hypersensitivity reaction. Confluent granulomas suggest possible sarcoidosis (see [Acute Interstitial Nephritis](#) and [Sarcoidosis](#)).
- vii. Necrotizing granulomas are indicative of infection, particularly TB, fungus, or [adenovirus](#).
- viii. Interstitial inflammation with positive TBM IF staining:
 - a. Linear staining for IgG is diagnostic of [anti-TBM antibody disease](#).
 - b. Granular, discrete, immune complex deposits along TBM by IF and EM: staining pattern is most often associated with [lupus nephritis](#) but can also be seen ~25% of polyoma virus nephropathy cases and in most cases of [IgG4-related disease](#).

D. Intratubular casts

- i. Pigmented:
 - a. Bilirubin casts (eg, in acute liver failure [positive with Hall stain])(see [Bile Nephrosis](#)).
 - b. [Myoglobin casts](#) in rhabdomyolysis (positive with antimyoglobin IHC) and characteristic appearance by EM.
 - c. Numerous tubules with iron pigment: consider [sickle cell nephropathy](#); hemolysis, consider anticoagulant nephropathy if mostly intact RBCs and extending to Bowman spaces and peritubular capillaries. Note: Iron in degraded hemoglobin (eg, in interstitium or tubules) can be detected by Prussian blue stain; hemoglobin is best detected by antihemoglobin IHC.
- ii. Other casts:
 - a. Tamm-Horsfall protein stains pink and may elicit a local granulomatous reaction when leaked into the interstitium.
 - b. Fractured, brittle appearing with surrounding syncytial giant cell reaction: highly indicative of [light chain cast nephropathy](#) (also known

as myeloma cast nephropathy).

Note: Not all cases of light chain cast nephropathy show monoclonal staining of casts with light chain. Consider IF after pronase digestion on paraffin-embedded tissue.

E. Crystals

i. Polarizable:

- a. Calcium oxalate are the most commonly detected polarizable crystals, appearing relatively clear on LM and with birefringent fan-shaped morphology when polarized.

Note: **Oxalosis** can be secondary (eg, enteric hyperoxaluria) or primary due to genetic defects in key enzymes of oxalate metabolism; scattered calcium oxalate crystals commonly occur secondary to scarring and low glomerular filtration rate. In primary oxalosis or oxalosis due to ethylene glycol ingestion or secondary to jejunal intestinal bypass, the crystals are extremely numerous and associated with tubular injury.

- b. 2,8-Dihydroxyadenine (2,8-DHA) crystals appear similar to calcium oxalate when polarized but are muddy brown (vs clear and colorless) on H&E stain (see **2,8-Dihydroxyadeninuria**).

ii. Nonpolarizable:

- a. Calcium phosphate crystals: nonpolarizable, bluish purple on H&E stain (see **Nephrocalcinosis** and **Acute Phosphate Nephropathy**).
- b. Indinavir: rectangular intratubular crystalline material with surrounding granulomatous reaction (see **Indinavir Nephropathy**).
- c. Urate: feathery crystals with surrounding tophus reaction (see **Gouty Nephropathy**).

F. Interstitial fibrosis and tubular atrophy (IFTA)

IFTA generally correlates better with kidney function than extent of glomerular lesions, which often are focal and segmental, with the notable exception of early diabetic nephropathy where diffuse lesions are common with mild glomerulomegaly and mesangial expansion. The pattern gives hints to the etiology:

- i. Diffuse pattern: nonspecific.
- ii. Striped, along medullary rays: related to ischemia along medullary rays; cyclosporine toxicity is an example (see **Calcineurin Inhibitor Nephrotoxicity**).
- iii. Patchy/geographic, “jigsaw puzzle” pattern: suggestive of **chronic pyelonephritis**, often with thyroidization appearance of the intratubular casts (resembling thyroid colloid).
- iv. Endocrine change of tubules: seen with prolonged ischemia, with less surrounding interstitial matrix (see **Ischemic Acute Tubular Injury**).

Additional Readings

- Bracamonte E, Leca N, Smith KD, et al. Tubular basement membrane immune deposits in association with BK polyomavirus nephropathy. *Am J Transplant.* 2007;7(6):1552-1560.
 - Brodsky SV, Satoskar A, Hemminger J, et al. Anticoagulant-related nephropathy in kidney biopsy: a single-center report of 41 cases. *Kidney Med.* 2019;1(2):51-56.
 - Cornell LD. IgG4-related kidney disease. *Semin Diagn Pathol.* 2012;29(4):245-250.
 - Dai DF, Sasaki K, Lin MY, et al. Interstitial eosinophilic aggregates in diabetic nephropathy: allergy or not? *Nephrol Dial Transplant.* 2015;30(8):1370-1376.
 - Drummond K, Mauer M. The early natural history of nephropathy in type 1 diabetes: II. Early renal structural changes in type I diabetes. *Diabetes.* 2002;51:1580-1587.
 - Dvanajscak Z, Cossey LN, Larsen CP. A practical approach to the pathology of renal intratubular casts. *Semin Diagn Pathol.* 2020;37(3):127-134.
- ★**ESSENTIAL READING**
- Markowitz GS, Perazella MA. Acute phosphate nephropathy. *Kidney Int.* 2009;76(10):1027-1034.
 - Nasr SH, Sethi S, Cornell LD et al. Crystalline nephropathy due to 2,8-dihydroxyadeninuria: an under-recognized cause of irreversible renal failure. *Nephrol Dial Transplant.* 2010;25(6):1909-1915.
 - Stokes MB, Valeri AM, Herlitz L, et al. Light chain proximal tubulopathy: clinical and pathologic characteristics in the modern treatment era. *J Am Soc Nephrol.* 2016;27(5):1555-1565. ★**ESSENTIAL READING**

Outline of Transplant Kidney Lesions

Many diseases can recur in the transplant, including immune complex and complement related (eg, IgAN, lupus nephritis, MPGN, DDD) and nonimmune disease (eg, diabetic nephropathy, FSGS). IF should be done for complete evaluation on the first biopsy of a transplant, with EM done as needed to evaluate the findings, depending on the clinical setting (see “Outline of Native Kidney-Specific Lesions” section).

I. Glomerular Lesions

A. Glomerulitis with increased mononuclear cells/PMNs

Consider antibody-mediated rejection, virus, or recurrent or de novo GN (see **Acute Antibody-Mediated Rejection** and **Chronic Antibody-Mediated Rejection** and various glomerular diseases discussed under “Endocapillary hypercellularity” section).

B. Enlarged cells with smudgy nuclei

Possible virus, particularly **cytomegalovirus** (CMV); rarely **polyoma virus** can infect glomerular epithelial cells.

C. Intraglomerular fibrin thrombi

This lesion can be due to antibody-mediated rejection, a drug-induced toxicity causing TMA, disseminated intravascular coagulation (DIC) that is donor-derived, or any of the causes that affect native kidneys:

- i. Antibody-mediated rejection: most often with glomerulitis and peritubular capillaritis (see [Acute Antibody-Mediated Rejection](#)).
- ii. Recurrence of atypical hemolytic uremic syndrome (HUS) (see [Thrombotic Microangiopathy](#)).
- iii. Drug-induced (eg, calcineurin inhibitor toxicity) (see [Thrombotic Microangiopathy](#)).
- iv. Shiga toxin (see [Thrombotic Microangiopathy](#)).

D. GBM double contours

- i. Transplant glomerulopathy (expansion of the lamina rara interna by lucent material, seen by EM, no immune deposits): usually chronic sequela of acute antibody-mediated rejection (see [Chronic Antibody-Mediated Rejection](#)).
- ii. Chronic, organizing phase of TMA.
- iii. Recurrent or de novo MPGN type disease (eg, cryoglobulin-related GN, C3 glomerulopathies): IF and EM differentiate immune complex etiology from other causes of double contour GBM (see section above on MPGN pattern).

Note: Chronic TMA has the same appearance as transplant glomerulopathy by EM; one can differentiate by clinical correlation.

E. Segmental sclerosis

- i. Recurrent FSGS: no GBM double contour in nonsclerotic areas, foot processes extensively effaced by EM (see [FSGS, NOS](#)).
- ii. Transplant glomerulopathy: GBM double contour in nonsclerotic areas, increased lamina rara interna by EM, less foot processes effacement than in recurrent FSGS (see [Chronic Antibody-Mediated Rejection](#)).
- iii. Sclerosis with collapsing features:
 - a. Cyclosporin toxicity (see [Calcineurin Inhibitor Nephrotoxicity](#)).
 - b. Pamidronate-associated (see [FSGS, Collapsing Variant](#)).
 - c. Parvovirus (see [FSGS, Collapsing Variant](#)).
 - d. Possible recurrence of collapsing FSGS (see also [FSGS, NOS](#)).
 - e. Severe ischemia (see [FSGS, Collapsing Variant](#)).

II. Vascular lesions

A. Hyaline

- i. Eccentric:
 - a. Pre-existing in the donor.
 - b. Hypertension-associated (see [Arterionephrosclerosis](#)).
 - c. [Diabetic nephropathy](#)-associated.

- ii. Concentric pattern, extending to media: more suggestive of cyclosporine toxicity (see [Calcineurin Inhibitor Nephrotoxicity](#)).

B. Endothelialitis

Defined as intimal infiltration by mononuclear cells underneath the endothelium of arteries or arterioles. Endothelialitis is indicative of acute vascular rejection, Cooperative Clinical Trials in Transplantation (CCTT) type 2; Banff T-cell mediated rejection type II (see [Acute T-Cell-Mediated Cellular Rejection](#)).

C. Peritubular capillaritis

Leukocytes within peritubular capillaries may be indicative of [acute antibody-mediated rejection](#) or may be present within areas with [acute T-cell mediated rejection](#).

Note: C4d positivity by IF in peritubular capillaries >10% on frozen tissue correlates with donor-specific antibody, and along with significant glomerulitis and peritubular capillaritis is diagnostic of acute antibody-mediated rejection.

D. Transmural vascular inflammation

This lesion is suspicious for [acute antibody-mediated rejection](#).

E. Thrombi

- i. Glomeruli/smaller arteries: consider hyperacute rejection or TMA due to antibody-mediated rejection, drug, or other (see above and [Acute Antibody-Mediated Rejection](#)).
- ii. Larger arteries: consider, for example, surgical technical difficulties, antiphospholipid antibody (see [Thrombotic Microangiopathy](#)).

F. Necrosis

Fibrinoid necrosis is most consistent with active antibody-mediated rejection (type 3 CCTT, acute vascular rejection, or Banff grade III T-cell mediated rejection, the latter with concomitant tubulointerstitial lymphocytic inflammation), often associated with C4d positivity in peritubular capillaries by IF (see [Acute Antibody-Mediated Rejection](#)).

Note: Necrotic vessels in the middle of an area of cortical necrosis do not have specific diagnostic sensitivity for etiology of this lesion.

III. Tubulointerstitial lesions

A. Edema

- i. Without any leukocyte infiltrate: renal vein thrombosis, obstruction, nonspecific injury.
- ii. With leukocyte infiltrate: consider [acute T-cell-mediated rejection](#), viral infection, other infection, or reaction to tissue necrosis (see [Polyoma Virus Nephropathy](#), [Acute Pyelonephritis](#), and [Cortical Necrosis](#)).

B. PMNs

- i. In tubular lumen: if forming plug of PMNs in tubules, diagnostic of [acute pyelonephritis](#).
- ii. In peritubular capillaries:

- a. Numerous: suspect [antibody-mediated rejection](#).
 - b. Less numerous: consider possible renal vein thrombosis.
- C. Interstitial lymphocytes
- i. In scarred areas: nonspecific. If associated with significant tubulitis in nonseverely atrophic tubules, consider chronic active T-cell-mediated rejection (see [Acute T-Cell-Mediated Cellular Rejection](#)).
 - ii. In nonscarred areas: consider [acute T-cell-mediated rejection](#), look for tubulitis.
 - iii. Tubulitis:
 - a. Lymphocytes invading severely atrophic tubules: nonspecific.
 - b. Lymphocytes invading nonseverely atrophic tubules: see above. Consider chronic active T-cell-mediated rejection (see [Acute T-Cell-Mediated Cellular Rejection](#)).
 - c. Lymphocytes invading intact tubules: lesion of [acute T-cell-mediated rejection](#); not pathognomonic for rejection, can also be seen with viral infection, hypersensitivity reaction (see [Polyoma Virus Nephropathy](#) and [Acute Interstitial Nephritis](#)).
 Note: The Banff classification system is widely used for diagnosis of transplant lesions. The CCTT classification (see below) may also be useful, with lower threshold specifically for diagnosis of T-cell-mediated rejection.
 CCTT types: type 1, acute T-cell rejection with tubulitis; type 2, acute vascular rejection with endothelialitis (lymphocytes underneath endothelium of arteries or arterioles); type 3, acute vascular rejection with fibrinoid necrosis, indicative of antibody-mediated mechanisms.
 The thresholds for minimum criteria for extent of tubulitis and lymphocytic infiltrate for diagnosing type 1 T-cell-mediated rejection differ by CCTT and Banff criteria. Current evidence-based studies by Banff working groups likely will lead to lowering of the Banff threshold (now >25% of cortex with inflammation required, with extensive tubulitis).
- D. Interstitial eosinophils
- i. Possible hypersensitivity reaction due to, for example, a drug (see [Acute Interstitial Nephritis](#)).
 - ii. Can be part of [acute T-cell-mediated rejection](#).
 Note: No evidence that eosinophils per se in rejection impacts prognosis.
- E. Interstitial plasma cells
- i. In scarred areas: nonspecific.
 - ii. In nonscarred areas: can be part of [acute T-cell-mediated rejection](#) (plasma cell-rich acute rejection, possibly worse prognosis).
 - iii. Expansile/dysplastic: consider posttransplant lymphoproliferative disease (PTLD).
 Note: Features suggesting PTLD are expansile mass, dysplastic cells, monomorphism, serpiginous necrosis.
 Note: Staining for Epstein-Barr (EB) virus is a useful adjunct for diagnosis of PTLD. Most PTLD, but not all, are EB virus positive and clonal. Additional staining studies and clinical investigation can confirm the diagnosis.
- F. Mixed interstitial infiltrate
- Pleomorphic infiltrate with lymphocytes, plasma cells, and PMNs raises suspicion of viral infection, particularly [polyoma virus](#). [CMV infection](#) is much more rare in transplant biopsies but also can cause interstitial inflammation and viral cytopathic change.
 Note: Look for viral changes (eg, inclusions, smudgy, enlarged tubular nuclei). Diagnosis of polyoma virus nephropathy is made by immunostaining for SV40 (detects all 3 polyoma viruses: BK, JC, and SV). In situ hybridization can be done with probes specific for BK versus JC to distinguish these 2 viruses. Tissue-based polymerase chain reaction has also been used to diagnose rare cases of SV40 infection. [CMV infection](#) and [adenovirus infection](#) can be diagnosed by IHC. EM appearances are also characteristic and differ for these viruses versus polyoma viruses.
- G. IFTA
- [Tubular atrophy](#) is characterized by flattened tubular epithelium and thick TBM, widely spaced tubules with intervening fibrosis (chronic allograft nephropathy, also designated as IFTA).
- i. Diffuse IFTA: nonspecific.
 - ii. Striped pattern IFTA, along medullary rays: consider possible [calcineurin inhibitor toxicity](#) with ischemia along medullary rays.
 - iii. Patchy, geographic IFTA: possible [chronic pyelonephritis](#).
- H. Enlarged tubular nuclei
- i. May be reactive after injury (see [Toxic Acute Tubular Injury](#) and [Ischemic Acute Tubular Injury](#)).
 - ii. Virus: enlarged, smudgy cells, may have inclusions.
 - a. [Polyoma virus](#) infection.
 - b. [CMV](#) infection.
 - c. [Adenovirus](#) infection.
- I. Acute tubular necrosis

- i. Frank necrosis, sloughing off of cells (see [Toxic Acute Tubular Injury](#) and [Ischemic Acute Tubular Injury](#)).
- ii. Flattened, regenerating epithelium: typical of ischemic tubular injury.

Note: Tubular necrosis can occur in isolation or with associated glomerular necrosis (the combination is called [cortical necrosis](#)).

J. ATI

Flattened simplified tubular epithelium.

Note: [Ischemic etiology](#) often results in zones of injury; [toxic etiology](#) often results in individual cell injury/blebbing/degeneration/apoptosis.

Additional Readings

- Cosio FG, Cattran DC. Recent advances in our understanding of recurrent primary glomerulonephritis after kidney transplantation. *Kidney Int.* 2017;91(2):304-314.
- Gaut JP, Liapis H. Acute kidney injury pathology and pathophysiology: a retrospective review. *Clin Kidney J.* 2020;14(2):526-536. **★ESSENTIAL READING**
- Farouk SS, Rein JL. The many faces of calcineurin inhibitor toxicity-what the FK? *Adv Chronic Kidney Dis.* 2020;27(1):56-66.
- Loupy A, Haas M, Roufousse C, et al. The Banff 2019 Kidney Meeting Report (I): updates on and clarification of criteria for T cell- and antibody-mediated rejection. *Am J Transplant.* 2020;20(9):2318-2331.

★ESSENTIAL READING

- Nickeleit V, Singh HK, Randhawa P, et al. The Banff Working Group classification of definitive polyomavirus nephropathy: morphologic definitions and clinical correlations. *J Am Soc Nephrol.* 2018;29(2):680-693.
- Roufousse C, Simmonds N, Clahsen-van Groningen M, et al. A 2018 reference guide to the Banff Classification of Renal Allograft Pathology. *Transplantation.* 2018;102(11):1795-1814. **★ESSENTIAL READING**

Article Information

Authors' Full Names and Academic Degrees: Behzad Najafian, Mark A. Lusco, Charles E. Alpers, and Agnes B. Fogo.

Authors' Affiliations: Department of Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee (MAL, ABF); and Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington (BN, CEA).

Address for Correspondence: Agnes B. Fogo, MD, Department of Pathology, Microbiology and Immunology, MCN C3310, Vanderbilt University Medical Center, Nashville, TN 37232. Email: agnes.fogo@vanderbilt.edu

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