

CORE CURRICULUM IN NEPHROLOGY

Approach to Renal Biopsy

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I. Tissue Sampling, Allocation, and Fixative

A. Sampling

1. Sample Size

An adequate sample size must be obtained for diagnosis. Needle gauge has dramatic impact on sample obtained. Eighteen- or 19-gauge needles give very small, narrow samples and often may have inadequate representation of vessels. For focal lesions involving a small number of glomeruli, 25 glomeruli may be needed for LM examination to have a greater than 95% chance of detecting those lesions. Minimum sample size for diagnosis varies greatly with the specific diagnosis; for instance, membranous glomerulonephritis can be diagnosed from a single glomerulus. Transplant diagnoses are most accurate when the sample includes a minimum of seven glomeruli. For most light microscopic assessment to adequately assess severity and distribution of lesions, 8 to 10 glomeruli are needed.

2. Sample Location—Juxtamedullary Versus Cortical

Subcapsular cortical samples have overrepresentation of global sclerosis related to aging/hypertension and non-specific 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.

B. Allocation and Fixatives

An adequate assessment of native renal biopsies includes light microscopy (LM), immunofluorescence microscopy (IF), and electron microscopy (EM). For transplant biopsy, LM and IF are considered the standard, with repeat biopsies only needing LM in many cases.

- LM: For most differential diagnoses, the largest portion of cortex should be placed in fixative for LM. These fixatives include formalin, paraformaldehyde, or less commonly used alcoholic Bouin's or Zenker's.
- IF: 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 media such as Michel's, and transported to the laboratory. Tissue is stable at room temperature for express mailing to central laboratories in this media.
- EM: Small, 1-mm tubes of cortex are allocated for EM, and optimally are placed directly in glutaraldehyde.

1. Dividing the Tissue

A dissecting microscope can be used or one can blindly remove 1-mm cubes from each end of each core and place in glutaraldehyde for EM, divide each remaining core into 2

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nearly equal pieces, placing the larger of each core in fixative for LM, and the smaller section of each core in tissue-transport media for IF.

2. *Handling of Tissue*

- No forceps, manipulate with thin wooden stick to avoid crush artifact.
- Avoid touching tissue with a fixative-contaminated scalpel or razor blade (this contaminates the tissue for IF).

If there is inadequate tissue in any of the media, sometimes results can still be obtained as follows:

IF tissue is frozen for IF stains—the remaining frozen tissue may be fixed in formalin and processed for LM.

EM study can be done by processing remaining tissue from the LM sample from the paraffin block.

Tissue that has not been in paraffin blocks too long can sometimes give satisfactory results for immunofluorescence done on fixed, paraffin-embedded tissue.

LM: Tissue for LM is processed, dehydrated, and placed in paraffin block, and multiple serial sections are obtained and stained. Usual stains include hematoxylin & eosin, 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.

IF: Tissue for IF is surrounded with OCT compound and frozen, and sections are produced and stained with fluorescein-tagged antibodies against IgG, IgA, IgM, complements C3 and C1q, κ and λ light chain. Complement product C4d may also be stained on frozen tissue, with more technical difficulty in staining on paraffin-block tissue. One to 2 hours of processing, sectioning, and staining time are needed for production of IF slides.

EM: EM tissue is processed and embedded in a plastic, hard media, 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 and produce EM sections for ultrastructural examination.

II. Tissue Examination

A. Injury Localization: Glomerular/Vascular/Tubulointerstitial

1. *Overview of slides assesses injury and localizes to the specific anatomic compartment*
2. *Assessment of type of injury (see below), extent of injury in each*

B. Category of Injury: Active Versus Fibrosing

1. *Active lesions*
 - a. Proliferation
 - b. Necrosis
 - c. Crescents
 - d. Edema
 - e. Active inflammation (eg, glomerulitis, tubulitis, vasculitis)
2. *Fibrosing*
 - a. Glomerulosclerosis
 - b. Fibrous crescents
 - c. Tubular atrophy
 - d. Interstitial fibrosis
 - e. Vascular sclerosis

C. Types of Lesions

1. *Determination of the nature and pathogenesis of lesions: examination by IF, EM and LM*

Note: Correlation of LM with IF and EM and clinical history is needed for optimal interpretation.

 - a. IF → immune complex or not
 - b. EM → immune complex or not;

localization of injury;
 nature of any deposits;
 GBM abnormalities;
 foot process effacement

- c. LM: special stains → deposits or not;
 character of lesions

2. *Native kidney-specific lesions*

a. Glomerular lesions

1) Thickened GBM

● **Negative IF:**

- No splitting or double contour by silver stain, thick lamina densa by EM → **diabetic nephropathy**
- Splitting by silver stain → chronic **thrombotic microangiopathy**
 OR
transplant glomerulopathy (see Transplant)
- Irregular by silver stain, basket weaving by EM → hereditary nephritis (**Alport**)

● **Positive IF:**

- Granular capillary loop staining by IF, spikes by Jones' stain, subepithelial deposits by EM → **membranous glomerulonephritis**
- Molded, sausage-shaped contour of deposits along capillary loop, mesangial granular deposits, GBM splitting by silver stain, subendothelial deposits by EM → **membranoproliferative glomerulonephritis**
- GBM variable splitting by silver stain, fibrils by EM, negative Congo Red → **fibrillary glomerulonephritis**
- **Variable IF:**
Note: May have positive IF for AL amyloid, negative, or non-specific IF for other amyloid.
- Feathery spikes by Jones', fibrils by EM, positive Congo Red → **amyloid**

2) **Thin GBM by EM**

- Benign familial hematuria
- Alport syndrome: early lesion in X-linked affected male, or male or female autosomal, or female X-linked carrier.

Note: Mosaic GBM staining pattern for $\alpha 5$ type IV collagen indicates female X-linked carrier of Alport.

Note: The GBM thickness increases normally with age, and thickness must be compared with age-matched control.

Note: More specific diagnosis of type of abnormality causing thin GBM may be made by special immunostaining for subtypes of type IV collagen. Total absence of $\alpha 5$ type IV collagen indicates X-linked Alport.

3) Proliferation

i) Mesangial proliferation with nodules

Note: Nodular sclerosis may be seen in the below conditions. Correlation with IF and/or EM allows distinction of these possibilities.

(a) **Diabetic nephropathy**

nodular sclerosis + thick GBM + arteriolar hyalinization (afferent and efferent), no deposits

(b) **Light chain deposition disease**

nodular sclerosis + κ or λ staining of glomerulus + TBM + amorphous deposits by EM.

- (c) **Membranoproliferative glomerulonephritis**
can be nodular, with splitting by LM, capillary loop and mesangial deposits by IF, subendothelial and mesangial deposits by EM.
- (d) **Amyloid**
relatively acellular, may have feathery spikes of GBM by LM, has fibrils by EM, Congo Red positive.
- (e) Idiopathic nodular sclerosis
- ii) Mesangial proliferation without nodules
Note: Distinction of cause of mesangial proliferation relies heavily on immunofluorescence findings:
- (a) **Mesangial lupus nephritis**
IF and EM, and clinical history, distinguish 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 (footprints of high interferon levels, found in endothelial cells throughout the body).
- (b) **IgA nephropathy**
Diagnosis is made by IF. Dominant or co-dominant IgA with mesangial deposits by EM is diagnostic of IgA nephropathy
- (c) Chronic infection-related glomerulonephritis
May be IgG or IgM predominant. The presence of any subepithelial hump-shaped deposits in addition to the mesangial deposits strongly suggests an infection-related etiology (see **Post-infectious glomerulonephritis**).
- iii) Nonspecific mesangial proliferation (no immune complexes)—could be, eg, variant of minimal change disease/FSGS, early diabetic nephropathy, nonspecific
- iv) No deposits by IF/EM. EM can show extensive FP effacement in MCD or FSGS or GBM thickening in early diabetic nephropathy.
- v) Mesangial plus endocapillary proliferation
Note: Many diseases may cause endocapillary proliferation with mesangial proliferation. IF and EM are crucial for distinction as follows:
- (a) **Membranoproliferative glomerulonephritis (MPGN) type I**
- MPGN type I has predominant IgG, splitting by LM and subendothelial deposits and mesangial deposits.
- (b) **Proliferative lupus nephritis**
- Lupus nephritis is characterized by IF positivity often with all 3 immunoglobulins and both complements (full house), reticular aggregates in endothelial cells (footprints of high interferon levels, found in endothelial cells throughout the body).
- (c) **Cryoglobulinemic glomerulonephritis**
- Cryoglobulinemic GN may have predominant IgM, substructure of deposits by EM, and sometimes strongly positive PAS plugs (cryopugs) in capillary lumens.
- (d) **Post-infectious glomerulonephritis**
- Post-infectious (often post-streptococcal) GN most commonly has prominent PMN infiltrate in the glomerular tuft, with starry sky appearance of IgG+C3 deposits by IF, and hump-shaped subepithelial deposits by EM.
- (e) **Fibrillary glomerulonephritis**
- Fibrillary glomerulonephritis has IgG predominance, deposits with fibrillary substructure by EM, Congo Red-negative.
- (f) **Immunotactoid glomerulopathy**
- Immunotactoid glomerulopathy has IgG predominance, deposits with

microtubular or parallel array substructure by EM, is associated with paraprotein. Similar morphology may be caused by cryoglobulin deposits.

(g) **Dense deposit disease** (DDD; aka MPGN type II)

- Dense deposit disease has C3 only + dense transformation of GBM, mesangial nodules by EM

4. 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. Comparison of glomerular size must be made to age-matched normal.

i) Usual type sclerosis

Localized anywhere, defined by obliteration of capillary lumen and increased matrix, extensive foot process effacement by EM, typical of **focal segmental glomerulosclerosis** (FSGS)

ii) **Collapsing glomerulosclerosis**

Defined by collapse and retraction of glomerular tuft, segmental (involving part of the tuft) or global (involving all of the tuft), with proliferation of overlying podocytes, may be idiopathic or **HIV associated**

Note: Worse prognosis than usual FSGS. If HIV-associated → reticular aggregates by EM.

iii) **Tip lesion 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.

Note: Absence of sclerosis in an adequate sample (greater than 25 glomeruli, including juxtamedullary area), no immune complexes and complete foot process effacement → consistent with **minimal change disease** in a nephrotic patient.

iv) Secondary sclerosis

May have positive immune complexes, retracted tuft with adhesion and fibrous crescent, periglomerular fibrosis, or other morphologic signs of underlying injury (eg, advanced lupus nephritis, severe **IgA nephropathy**).

5. Crescents

Note: Crescents are classified as cellular, fibrocellular, or fibrous, depending upon degree of fibrous tissue, with less responsiveness to therapy the more fibrosis there is.

Note: Crescents are composed of proliferating parietal epithelial cells and occur with any injury that breaks the capillary wall. Injury may be categorized as follows:

i) Immune etiology

- Linear IgG stain of GBM → **anti-GBM antibody-mediated glomerulonephritis**
- Other immune complex positivity → other immune complex disease (eg, **lupus nephritis, post-infectious glomerulonephritis, IgA nephropathy**, etc)

ii) Pauci-immune (eg, minimal or no deposits by IF and/or EM)

- **Wegener's granulomatosis or microscopic polyangiitis**

Note: Wegener's granulomatosis and microscopic polyangiitis cannot be distinguished from each other in a renal biopsy. They both have glomerular necrotizing lesions with crescents.

6. 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 by EM in various cells, especially podocytes
- ii) Intraglomerular foamy macrophages—often with secondary sclerosis—consider lipid storage disease—eg, **LCAT deficiency**
- iii) Abundant type III banded collagen by EM—consider **type III collagen glomerulopathy**

b. Vascular lesions

1. Sclerosis

Intimal fibrosis/medial hypertrophy → **hypertensive changes**

2. Thrombotic lesions

- Arteriolar/glomerular predominance: typical of **thrombotic microangiopathy** due to hemolytic uremic syndrome.
- Arteriolar/interlobular artery predominance: more typical of **progressive systemic sclerosis**. This may overlap completely with **malignant hypertension**.

3. Necrosis

“Fibrinoid” necrosis (lesion in, eg, **progressive systemic sclerosis/malignant hypertension**)—term used to describe necrosis of wall with chunky, eosinophilic appearance, often containing fibrin and karyorrhectic debris

4. Vasculitis

Vasculitis is defined as transmural inflammation with lymphocytes/PMNs. Positive IF may be seen in lupus vasculitis or **cryoglobulinemic vasculitis**. Pauci-immune conditions may also have vasculitis lesions.

5. Embolic lesions

Cholesterol emboli lodge in interlobular arteries, seen as clear cleft-shaped space with surrounding mononuclear cell reaction (cholesterol per se is extracted during processing).

6. Endothelial lesions

Swollen endothelial cells are a feature of the endotheliosis lesion of **pre-eclampsia/eclampsia**.

c. Tubulointerstitial lesions

1. **Necrosis**

- a) Frank necrosis: sloughing off of cells
- b) Flattened, regenerating epithelium

Note: Tubular necrosis can occur in isolation, or with associated glomerular necrosis (the combination is called **cortical necrosis**)

Note: Ischemic versus toxic etiologies—ischemia often zones of injury; toxic often with individual cell injury/blebbing/degeneration/apoptosis.

2. Edema

Increased interstitial space with loose appearance and normal thickness tubular basement membranes is generally due to edema. This is in contrast to interstitial fibrosis (see below), where tubules are widely spaced with intervening dense, fibrotic tissue, and TBMs are thick and fibrotic.

3. Interstitial inflammation

- a) PMNs—intratubular PMNs forming plugs are diagnostic of **acute pyelonephritis**
- b) Interstitial or peritubular capillary PMNs may be nonspecific, due to renal vein thrombosis, or **humoral rejection** (see Transplant)
- c) Lymphocytes + edema → **acute interstitial nephritis**

Note: There is often associated tubulitis, even in native kidneys.

- d) Lymphocytes + interstitial fibrosis → chronic interstitial nephritis
Note: This is a nonspecific diagnosis and an underlying cause should be diligently sought, eg, myeloma cast nephropathy (see Intratubular casts below).
- e) Eosinophils in the interstitium: consider **hypersensitivity reaction**.
- f) Granulomas: the most common cause for non-necrotizing granulomas is a hypersensitivity reaction. Confluent granulomas → possible **sarcoidosis**.
- g) Necrotizing granulomas are indicative of infection, particularly TB or fungus
- h) Interstitial inflammation with positive tubular BM IF staining:
 - Linear → anti-TBM disease
 - Granular, discrete, immune complex deposits along TBM by IF and EM → most often associated with lupus nephritis
4. Intratubular casts
- a) Pigmented
 - Bilirubin casts in, eg, acute liver failure
 - Myoglobin casts in rhabdomyolysis (special stains can differentiate)
 - Numerous tubules with iron pigment → consider **sickle cell nephropathy**
- b) Polarizable casts
Most common is calcium oxalate **in oxalosis**
Note: Could be secondary or primary oxalosis; scattered calcium oxalate crystals commonly occur secondary to scarring. 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.
- c) Nonpolarizable casts
 - Drugs, such as **indinavir** with surrounding granulomatous reaction
 - **Urate:** feathery crystals with surrounding tophus reaction
 - Fractured, brittle appearing with surrounding syncytial giant cell reaction, highly indicative of **light chain cast nephropathy** (aka myeloma cast nephropathy)
Note: Only about half of cases with light chain cast nephropathy show monoclonal staining of casts with light chain.
5. Interstitial fibrosis
Note: Interstitial fibrosis and tubular atrophy generally correlate better with renal function than extent of glomerular lesions, which often are focal and segmental. The pattern gives hints to the etiology:
- a) Diffuse pattern: nonspecific
- b) Striped, along medullary rays: related to ischemia along medullary rays, seen with, eg, **cyclosporine toxicity**
- c) Patchy/geographic, “jigsaw puzzle” pattern: suggestive of **chronic pyelonephritis**
3. *Transplant kidney lesions*
Note: Many diseases can recur in the transplant, including immune complex (eg, IgA nephropathy, lupus nephritis, MPGN type I, dense deposit disease) 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 Native kidney lesion discussion.)
- a. Glomerular lesions
- 1) **Glomerulitis**
Glomerulitis with increased mononuclear cells/PMNs: consider virus, renal vein thrombosis, or humoral rejection
 - 2) Enlarged cells with smudgy nuclei: possible virus, particularly **CMV**
 - 3) Intraglomerular fibrin thrombi (**thrombotic microangiopathy**)

- a) **Hyperacute rejection** in the immediate posttransplant period
 - b) Idiopathic
 - c) Recurrence of familial HUS
 - d) Drug-induced (cyclosporin, FK506)
 - e) Shiga toxin
- 4) GBM splitting
- a) **Transplant glomerulopathy** (TGP) (increased lucency of lamina rara interna by EM, no immune deposits)
 - b) Chronic, organizing phase of **thrombotic microangiopathy**
 - c) Recurrent or de novo **MPGN**, such as **cryoglobulin-related glomerulonephritis** (IF and EM differentiate immune complex etiology from other causes of split GBM, see above)
Note: Chronic thrombotic microangiopathy has the same appearance as TGP by EM; one can differentiate by clinical correlation, or concurrent acute thrombotic microangiopathy lesions.
- 5) Segmental sclerosis
- a) Recurrent **FSGS** (no GBM splitting in nonsclerotic areas, foot processes extensively effaced by EM)
 - b) **Transplant glomerulopathy** (GBM splitting in nonsclerotic areas, increased lamina rara interna by EM, less foot processes effacement than in recurrent FSGS)
 - c) Sclerosis with **collapsing features**
 - Cyclosporin toxicity
 - Pamidronate-associated
 - Parvovirus
 - Possible recurrence of collapsing FSGS
 - Severe ischemia**Note:** Many native glomerular disease may recur in the transplant. Full work-up with immunofluorescence and light microscopy (and EM as needed) is recommended.
- b. Vascular lesions
- 1) Hyaline
 - a) Eccentric
 - Pre-existing in the donor
 - **Hypertension-associated**
 - **Diabetic nephropathy**-associated
 - b) Concentric pattern, extending to media: more suggestive of **cyclosporine toxicity**
 - 2) Endothelialitis: Lymphocytes → **acute vascular rejection**, Cooperative Clinical Trials in Transplantation (CCTT) type 2
 - 3) Endothelialitis with PMNs → **hyperacute rejection**
Note: C4d positivity by IF in peritubular capillaries correlates with humoral rejection.
 - 4) Thrombi:
 - a) Glomeruli/smaller arteries: consider hyperacute rejection or **thrombotic microangiopathy** due to drug or other (see above)
 - b) Larger arteries: consider, eg, surgical technical difficulties; anti-phospholipid antibody (APL)
 - 5) Necrosis
Fibrinoid necrosis → most consistent with type 3 CCTT **acute vascular rejection**, associated with humoral rejection and C4d positivity in peritubular capillaries by IF

Note: Necrotic vessels in the middle of an area of cortical necrosis do not have specific diagnostic sensitivity for diagnosis of acute vascular rejection type 3.

c. Tubulointerstitial lesions

1) Edema

- Without any infiltrate: renal vein thrombosis, obstruction, non-specific injury
- With infiltrate: consider acute rejection, viral infection, other infection, or reaction to tissue necrosis

2) PMNs

- a) In tubular lumen → **acute pyelonephritis**
- b) In peritubular capillaries:
 - Numerous → suspicious for humoral rejection in peritubular capillaries
 - Less numerous → possible renal vein thrombosis

3) Interstitial lymphocytes

- a) In scarred areas → nonspecific
- b) In nonscarred areas → consider acute rejection, look for tubulitis
- c) Tubulitis:

- Lymphocytes invading atrophic tubules → nonspecific
- Lymphocytes invading intact tubules → lesion of **acute rejection**

Note: Two classification systems are widely used for acute rejection, Banff and CCTT. The classifications are similar:

Type 1 acute cellular rejection with tubulitis, type 2 acute vascular rejection with endothelialitis (lymphocytes underneath endothelium of arteries or arterioles), and type 3 acute vascular rejection with fibrinoid necrosis, indicative of antibody-mediated mechanisms. However, thresholds for minimum criteria for extent of tubulitis and lymphocytic infiltrate for type 1 differ, with lower threshold for CCTT versus Banff diagnosis of type 1 acute rejection. Recently, a change to mechanistic-based classification of lesions in transplant rejection is being pursued, dividing into cell-mediated versus humoral-mediated mechanisms. The use of C4d staining in peritubular capillaries as a marker for humoral rejection is a key part of this proposed new classification.

4) **Interstitial eosinophils**

- Possible hypersensitivity reaction due to, eg, drug
- Can be part of acute cellular rejection

Note: No evidence that eosinophils per se in rejection impacts prognosis

5) Interstitial plasma cells

- In scarred areas → nonspecific
- In nonscarred areas → can be part of acute cellular rejection (plasma cell-rich acute rejection, possibly worse prognosis)
- Expansile/dysplastic → consider posttransplant lymphoproliferative disease (PTLD)

Note: Features suggesting PTLN are expansile mass, dysplastic cells, monomorphism, serpiginous necrosis.

Note: Staining for Epstein-Barr (EB) virus is a useful adjunct for diagnosis of PTLN. Most PTLN, but not all, are EB virus positive and clonal. Additional staining studies and clinical investigation can confirm the diagnosis.

6) Mixed interstitial infiltrate

Pleomorphic infiltrate with lymphocytes, plasma cells and PMNs → suspicious for viral infection, particularly BK (**polyoma**) virus nephropathy.

Note: Look for viral changes (eg, inclusions, smudgy, enlarged tubular nuclei). Specific diagnosis made by immunostaining.

- 7) Interstitial fibrosis
 - a) **Diffuse** → nonspecific
 - b) Striped → consider possible **cyclosporine** or FK506 toxicity
 - c) Patchy → nonspecific or possible **chronic pyelonephritis**
- 8) **Tubular atrophy**: usually proportional to fibrosis (see above)
- 9) Enlarged tubular nuclei
 - May be reactive after injury
 - Virus: enlarged, smudgy cells, may have inclusions
 - BK (polyoma) virus**
 - CMV (cytomegalovirus)**
- 10) Necrosis
 - a) Frank **necrosis**, sloughing off of cells
Flattened, regenerating epithelium
Note: Tubular necrosis can occur in isolation, or with associated glomerular necrosis (the combination is called **cortical necrosis**)
Note: Ischemic versus toxic etiologies- ischemia often zones of injury; toxic often with individual cell injury/blebbing/degeneration/apoptosis
- 11) Tubular atrophy
 - Flattened tubular epithelium and thick tubular basement membrane, widely spaced tubules with intervening fibrosis (**chronic allograft nephropathy**)
 - Flattened tubular epithelium, normal tubular basement membranes, intervening edema → consider acute tubular necrosis (see above).

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