Renal Pathology and Kidney Biopsy Interpretation — Module 23

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Renal Pathology and Kidney Biopsy Interpretation

Advanced Nephrology Module 23 — Student Handout

Learning Objectives

By the end of this module, you will be able to:

1. **Determine appropriate indications and contraindications** for percutaneous kidney biopsy
2. **Interpret light microscopy patterns** using standardized classification systems (ISN/RPS, Oxford, Banff)
3. **Recognize immunofluorescence patterns** and their diagnostic significance
4. **Understand electron microscopy findings** including deposit location and podocyte changes
5. **Integrate findings from LM, IF, and EM** to formulate a unified pathologic diagnosis
6. **Apply pattern recognition approach** to optimize diagnostic accuracy in glomerulonephritis
7. **Counsel patients** on biopsy risks, benefits, and expected diagnostic yield

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Part I: Clinical Decision-Making for Kidney Biopsy

Indications for Kidney Biopsy

Absolute/Strong Indications: - Acute kidney injury of unclear etiology (especially if rapidly progressive or crescentic features on serologies) - New-onset nephrotic syndrome in adults (especially if age >40 or atypical presentation) - Hematuria + proteinuria + systemic features (suspect glomerulonephritis, vasculitis, lupus) - Suspected lupus nephritis (baseline and to assess activity for treatment decisions) - CKD of unknown etiology (biopsy may reveal unexpected diagnosis with treatment implications) - Suspected crescentic/rapidly progressive GN (ANCA-associated, anti-GBM disease, immune complex) - Evaluation of transplant dysfunction (acute rejection, calcineurin toxicity, recurrent disease)

Relative Indications: - Proteinuria >3–5 g/day with persistent hematuria (differential diagnosis of primary vs. secondary FSGS) - Suspected hereditary kidney disease (Alport syndrome, thin basement membrane, etc.) - Evaluation of suspected amyloidosis or monoclonal gammopathy - Persistent hematuria with normal renal function (rule out IgA nephropathy, thin basement disease) - Pre-transplant evaluation in living donors with hematuria or proteinuria

Contraindications (Relative, Not Absolute): - Severe uncontrolled hypertension (BP >180/110 mm Hg) - Thrombocytopenia <50,000/μL or uncontrolled bleeding disorder - Anticoagulation that cannot be safely held (balance risk vs. benefit) - Single kidney or solitary functioning kidney (increased morbidity risk) - Acute kidney injury with severe volume overload or pulmonary edema - Uncooperative patient or inability to comply with post-biopsy precautions - Infection over biopsy site

Biopsy Technique & Safety

- Native kidney: 16–18 gauge needle, ultrasound- or CT-guided
- Transplant kidney: often easier access, same needle gauge
- 2–4 glomeruli minimum for diagnostic adequacy (more if specialized staining needed)
- Complication rate 5–10% (most common: hematuria, usually self-limited)
- Major hemorrhage requiring intervention: <1%
- Post-biopsy monitoring: bed rest 4–6 hours, serial urine checks for gross hematuria, discharge if stable

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Part II: Light Microscopy Patterns

Overview of LM Classification

Light microscopy categorizes glomerular injury patterns based on predominant structural changes. The key patterns correlate with immunofluorescence findings and patient presentation.

Pattern 1: Proliferative GN

Definition: Increase in glomerular cellularity (endocapillary or extracapillary proliferation)

Subtypes: - **Endocapillary:** Glomerular luminal proliferation (foam cells, monocytes) - Classic appearance in post-infectious GN, lupus Class III - Preservation of capillary wall architecture initially - May progress to crescentic if untreated

- **Extracapillary (Crescentic):** Proliferation OUTSIDE Bowman's capsule
  - Parietal epithelial cells, monocytes, fibrin
  - **Cellular crescent:** Early, may be reversible if treated quickly
  - **Fibrocellular crescent:** Mixed cellular and fibrin
  - **Fibrous crescent:** Healed, irreversible sclerosis
  - Urgent treatment indicated (see RPGN below)

Associated IF: IgA-dominant (IgA nephropathy), IgG/IgM (post-infectious), full-house (lupus)

Prognosis: Depends on extent of crescentic involvement; cellular crescents have better prognosis than fibrous

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Pattern 2: Membranoproliferative GN (MPGN)

Definition: Proliferation + membrane remodeling with capillary wall duplication

Morphologic Features: - Endocapillary and mesangial proliferation - Tram-track or double-contour capillary walls (duplication of GBM) - Mesangial expansion - May have crescent formation

MPGN Classification (Updated 2016): - **MPGN due to immune complex (IC-MPGN):** Granular IF pattern - Post-infectious MPGN (most common in this era) - Lupus - Viral (HCV, HBV)

- **MPGN due to monoclonal immunoglobulin (MGRS-type):** Single immunoglobulin dominant
  - IgG MPGN (often kappa or lambda monoclonal)
  - IgM MPGN
- **MPGN due to complement dysregulation (C3GN and C3-MPGN):** C3 dominant, weak or absent Ig
  - Post-infectious C3GN (most common)
  - Membranoproliferative C3GN (dysregulation)

Associated IF: Granular C3/IgG (post-infectious), monoclonal single heavy chain (MGRS), C3-dominant (C3GN)

Prognosis: Post-infectious has better outlook; C3GN more progressive; MGRS depends on clone

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Pattern 3: Membranous Nephropathy (MN)

Definition: Thickening of GBM with subepithelial immune deposits, WITHOUT proliferation

LM Features: - Thin capillary walls initially (may appear normal in stage 1) - Capillary wall thickening best seen with PAS or silver stain - Stage 1: Subepithelial deposits only (LM may appear normal; IF diagnostic) - Stage 2: Early basement membrane remodeling - Stage 3: Prominent spikes (true membrane thickening) - Stage 4: Sclerosis and hyalinosis

Classification (Modern): - **Primary MN:** Antibodies to PLA2R (70–80%), THSD7A (3–5%), other podocyte antigens - **Secondary MN:** Associated with malignancy, SLE, infection, drugs

IF Pattern: Granular IgG + C3 (most common), may have IgA or IgM co-dominance

EM Pattern: Subepithelial electron-dense deposits with foot process effacement

Prognosis: ~30% remit spontaneously; 30% progress to ESRD; 40% remain stable; poor prognostic factors: male sex, older age, high proteinuria at baseline

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Pattern 4: Focal Segmental Glomerulosclerosis (FSGS)

Definition: Sclerosis and hyalinosis involving <50% of glomeruli and affecting only segments of involved glomeruli

Subtypes (Columbia Classification): - **Not Otherwise Specified (NOS):** No specific distribution pattern - **Perihilar:** Segmental sclerosis at hilum (associated with APOL1 variants) - **Cellular:** Intracapillary cell proliferation/migration - **Tip lesion:** Sclerosis at tubular pole (better prognosis) - **Collapsing:** Podocyte injury/collapse (aggressive, often viral or drug-related)

LM Features: - Segmental areas of sclerosis and hyalinosis - Surrounding capillaries appear open - Mesangial proliferation may be present - FSGS collapsing variant: podocyte swelling, nuclei crowding, collapse of capillary wall

IF Pattern: Nonspecific (usually negative or mild IgM/C3 in sclerotic areas); full IF needed to exclude immune-complex disease

Associated Conditions: - Primary FSGS (mutation in podocyte genes: NPHS2, ACTN4, INF2, etc.) - Secondary FSGS (HIV, heroin, obesity, reflux, hyperfiltration) - APOL1-associated (African American ancestry, 2 copies = high risk) - Adaptive (obesity, solitary kidney)

Prognosis: Highly variable; collapsing FSGS poorest prognosis (50% ESRD in 5 years); tip lesion best prognosis

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Pattern 5: IgA Nephropathy (IgAN)

Definition: Dominant IgA deposits in glomerular mesangium

LM Findings: - Mesangial proliferation (variable degree) - Mild to moderate mesangial expansion - Segmental or global involvement - Crescent formation (10–50% depending on severity) - May see hypercellularity

Oxford Classification (MEST-C Score): - **M (Mesangial):** 0 = M0 (<25% glomeruli), 1 = ≥25% glomeruli - **E (Endocapillary):** 0 = absent, 1 = present - **S (Segmental sclerosis):** 0 = absent, 1 = present - **T (Tubular atrophy/interstitial fibrosis):** 0 = absent, 1 = 0–25%, 2 = >25% - **C (Crescent):** 0 = absent, 1 = cellular, 2 = fibrocellular/fibrous

IF Pattern: IgA dominant (>IgG, >IgM), C3 co-dominant, usually weak IgG/IgM

Prognosis: 20–30% progress to ESRD over 10 years; poor prognostic factors: M1, E1, S1, T1-2, C1-2, high proteinuria, hypertension

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Pattern 6: Minimal Change Disease (MCD)

Definition: Glomerulonephritis presenting with nephrotic syndrome but NO visible changes on light microscopy

LM Features: - Normal-appearing glomeruli on routine LM - No proliferation, no deposits, no sclerosis - Glomeruli appear patent and open

IF Pattern: Negative for immunoglobulins and complement (diagnostic feature)

EM Pattern: Diffuse foot process effacement (essential for diagnosis; distinguishes MCD from other causes of podocyte injury)

Clinical Context: Young children predominantly; may occur in adults, especially if allergic triggers identified

Prognosis: Excellent with corticosteroid therapy; >90% respond; relapse common but generally steroid-responsive

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Pattern 7: Diabetic Nephropathy

Definition: Kidney changes due to prolonged hyperglycemia

Stages (Tervaert/Mogensen): 1. **Hyperfunctional Stage:** Enlarged kidneys, GFR increased, normal biopsy 2. **Silent Stage:** Structural changes begin; normal UA; normal GFR 3. **Incipient Diabetic Nephropathy:** Persistent microalbuminuria; GFR may be elevated or normal 4. **Overt Diabetic Nephropathy:** Macroalbuminuria; declining GFR

Characteristic LM Findings: - **Glomerular basement membrane thickening** (universal finding) - **Mesangial expansion** (early and progressive, dominated by matrix deposition) - **Nodular sclerosis (Kimmelstiel-Wilson lesions):** Round, eosinophilic nodules in mesangium - **Capillary wall thickening** - **Hyalinosis** of afferent and efferent arterioles - **Basement membrane duplication** (may mimic early MPGN)

IF Pattern: Nonspecific; may show IgG/IgM deposition similar to distribution of PAS-positive matrix

If atypical features present (rapid deterioration, active urinary sediment, systemic features), consider concurrent GN

Prognosis: Progressive over years to decades if glycemic control inadequate; glycemic and blood pressure control slow progression

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Part III: Immunofluorescence Patterns & Interpretation

IF Staining Technique

- Direct IF: Kidney tissue incubated with fluorescent antibodies against Ig, complement
- Standard panel: IgG, IgA, IgM, C3, C1q, and fibrin
- Extended panel: kappa/lambda (assess monoclonal vs. polyclonal), C4, factor H, factor B

Major IF Patterns

IF Pattern	Disease(s)	LM Findings	Comments
Linear IgG (GBM) + C3	Anti-GBM disease (Goodpasture)	Crescentic GN (often 80–100%)	Linear deposition along entire GBM; very specific

IF Pattern	Disease(s)	LM Findings	Comments
Granular IgG/IgM/IgA + C3	Post-infectious GN, IgAN, lupus, other IC GN	Proliferative ± crescent	Granular/lumpy pattern; indicates immune complex deposition
Full-house pattern	SLE (Lupus Nephritis)	Proliferative (Class III/IV usually)	IgG, IgA, IgM, C3, C1q all present and dominant
IgA-dominant	IgA Nephropathy	Mesangial proliferation ± crescent	IgA>IgG>IgM; C3 co-dominant
Pauci-immune (negative IF)	ANCA-associated (GPA, MPA, EGPA)	Crescentic GN (80–90%)	No Ig or C3; ANCA serology positive
C3-dominant	Post-infectious C3GN, C3 dysregulation	MPGN pattern or mixed	Weak or absent Ig; associated with complement dysregulation
Monoclonal IgG/IgM/IgA	Monoclonal Gammopathy-Related Kidney Disease	MPGN, nodular, light chain cast	Single heavy chain + single light chain (kappa or lambda)
IgM-dominant + C3	IgM nephropathy, some post-infectious	Mesangial proliferation	IgM>IgG>IgA (opposite of normal); C3 prominent

Special Immunofluorescence Findings

C1q Deposition: - Present in lupus (full-house), especially in Class III/IV - Indicates active immune complex disease - More specific for lupus than other markers - Absence of C1q in lupus should raise concern for alternate diagnosis

Monoclonal vs. Polyclonal Light Chains: - **Polyclonal (both kappa and lambda):** Typical of primary immune complex GN - **Monoclonal (kappa OR lambda only):** Indicates clonal population (monoclonal gammopathy, myeloma, MGRS) - Ratio of involved to uninvolved light chain helps establish pathologic relevance

C3-Only (Pauci-Immune C3): - Unusual pattern; suggests membranoproliferative C3GN (dysregulation) or post-infectious - Investigate complement dysregulation (factor H mutation, C3 mutation, factor B, etc.) - Differentiate from typical post-infectious where IgG/IgM also present

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Part IV: Electron Microscopy (EM) Findings

EM Deposit Location & Disease Association

Deposit Location	Electron Density	Associated Diseases	LM/IF Correlation
Subepithelial (podocyte side)	Dense, discrete	Membranous nephropathy, lupus Class V, post-infectious	LM: spikes; IF: granular
Subendothelial (endothelial side)	Dense, large	Lupus (Class III/IV), post-infectious, other IC GN	LM: proliferative; IF: full-house or granular
Intramembranous	Dense	Membranous, MPGN, IgAN	LM: membrane thickening; IF: granular
Mesangial	Dense, variable size	IgAN, lupus Class II, other IC GN	LM: mesangial proliferation; IF: mesangial-dominant
No deposits (Pauci-immune)	Absent	ANCA-associated GN, anti-GBM	LM: crescentic; IF: negative or minimal C3

Glomerular Basement Membrane Changes

Normal GBM: Thin, 300–350 nm, three layers (endothelial, intermediate, epithelial)

Thickening (>400 nm): - Membranous nephropathy - Diabetic nephropathy - Post-infectious GN - Some lupus

Thinning (<250 nm): - Thin basement membrane disease (benign familial hematuria) - Some IgAN - Alport syndrome (initially thin, then irregular)

Splitting (GBM Splitting): - **Basket-weave appearance (Alport):** Characteristic splitting and multilayering of GBM - Genetic mutation in α3(IV) or α4(IV) collagen - Progressive; associated with sensorineural hearing loss - Males more severely affected

Irregular Architecture (Alport Syndrome): - Splitting with basket-weave pattern - Rupture of GBM with microaneurysms - Progressive thinning and splitting

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Podocyte/Foot Process Changes

Foot Process Effacement (Fusion): - Fusion of podocyte foot processes, widening of filtration slit - Universal in nephrotic syndrome (MCD, FSGS, MN, diabetic) - Indicates podocyte injury/dysfunction - May be reversible (MCD, some FSGS) or progressive (many others)

Podocyte Detachment/Collapse (Collapsing FSGS): - Podocyte swelling, nuclear crowding - Actual collapse of glomerular capillary - Associated with viral infection, drugs, genetic mutations - Very poor prognosis

Focal Foot Process Loss: - Incomplete effacement; variably affected areas - Less severe than global effacement - Seen in segmental sclerotic lesions of FSGS

Key EM Patterns by Disease

Disease	EM Findings	Prognostic Value
Membranous Nephropathy	Subepithelial deposits, spikes, foot process effacement	Stage of disease (1–4) predicts progression
IgA Nephropathy	Mesangial electron-dense deposits, variable size	Large or numerous deposits = worse prognosis
Lupus Nephritis	Subendothelial + subepithelial deposits (tubuloreticular inclusions in endothelium)	Type of deposits correlates with activity
Diabetes	GBM thickening, mesangial expansion	Progressive thinning indicates advanced disease
FSGS Collapsing	Podocyte collapse, microvillous transformation	Very poor prognosis
Post-Infectious	Subepithelial "hump" deposits, mesangial deposits	Usually temporary; resolve with recovery
Thin Basement Membrane	GBM thinning (<250 nm), usually uniform	Benign; excellent prognosis
Alport Syndrome	GBM splitting, basket-weave, irregular thickening	Progressive to ESRD; acoustic dysfunction

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Part V: Classification Systems for Standardized Reporting

ISN/RPS Classification for Lupus Nephritis

Class I: Minimal mesangial LN - Mesangial immune deposits only - LM: Normal or mild mesangial proliferation - Good prognosis

Class II: Mesangial proliferative LN - Mesangial proliferation with deposits - LM: Mesangial proliferation - Good prognosis with treatment

Class III: Focal proliferative LN - Endocapillary or extracapillary proliferation in <50% of glomeruli - LM: Focal proliferative changes - Moderate prognosis; requires treatment

Class IV: Diffuse proliferative LN - Proliferation in ≥50% of glomeruli (subdivided into IV-S "segmental" or IV-G "global") - LM: Extensive proliferation ± crescent - Poorest prognosis; aggressive treatment necessary

Class V: Membranous LN - Subepithelial deposits ± proliferative changes - LM: Membranous pattern ± Class III/IV features - Variable prognosis; may have nephrotic syndrome

Class VI: Advanced sclerotic LN - ≥90% of glomeruli globally sclerosed - Represents end-stage disease - Very poor prognosis; supportive care only

Activity vs. Chronicity Index: - Activity Index: Scores proliferative lesions (0–24) - Chronicity Index: Scores sclerotic/fibrotic changes (0–12) - Higher activity: more reversible; guides aggressive immunosuppression - Higher chronicity: less reversible; consider if aggressive therapy still beneficial

Oxford Classification for IgA Nephropathy (MEST-C)

Variable	Score	Prognostic Impact
M (Mesangial)	0: <25% glomeruli involved	M1 associated with worse renal outcomes
	1: ≥25% glomeruli involved	
E (Endocapillary)	0: Absent	E1 indicates active endocapillary inflammation
	1: Present	E1 predicts worse outcomes; targets for therapy
S (Segmental sclerosis)	0: Absent	S1 indicates chronic injury; less reversible
	1: Present	S1 = worse prognosis
T (Tubular atrophy/IF)	0: 0%	T2 = most advanced chronic changes
	1: 0–25%	Correlates with declining GFR
	2: >25%	T score strongest predictor of progression
C (Crescent)	0: Absent	C1/C2 indicate active crescentic disease
	1: Cellular/Fibrocellular	Risk of rapid deterioration if untreated
	2: Fibrous	C2 = irreversible damage; poor prognosis

Prognostic Algorithm: MEST-C scoring predicts renal survival; highest risk if M1, E1, S1, T2, C2

Banff Classification for Kidney Transplant Pathology

Acute Rejection: - **T cell-mediated (TCMR):** Tubulitis and/or intimal arteritis - **Antibody-mediated (ABMR):** C4d staining + microvascular inflammation + endothelial injury

Chronic Changes: - **Chronic active TCMR:** Chronic arterial changes (intimal fibrosis) - **Chronic active ABMR:** Chronic arterial changes + C4d + glomerular/peritubular capillary multilayering

Recurrent Disease: - Biopsy must distinguish between transplant rejection and recurrent glomerular disease (IgAN, FSGS, lupus, etc.)

CNI (Calcineurin Inhibitor) Toxicity: - Acute: Vacuolization of tubular epithelium, arteriolar changes - Chronic: Irreversible arterial intimal fibrosis, tubular atrophy

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Part VI: Pattern Recognition Approach to Diagnosis

The 5-Step Integration Strategy

Step 1: Clinical Presentation - **Nephrotic syndrome** (☐proteinuria, ☐albumin, edema, ☐lipids)? - Favors: MN, FSGS, MCD, amyloidosis - **Nephritic syndrome** (hematuria, proteinuria, hypertension, AKI)? - Favors: Post-infectious, IgAN, crescentic GN, lupus - **RPGN** (rapid AKI, active urinary sediment)? - Favors: ANCA-associated, anti-GBM, immune complex crescentic

Step 2: Immunofluorescence Pattern (Most Specific) - **Linear IgG:** Think anti-GBM ☐ crescentic GN on LM, check anti-GBM serology - **Granular IgG/IgM/IgA with C3:** Immune complex ☐ look for post-infectious, lupus, secondary causes - **IgA-dominant:** IgAN ☐ check Oxford score, prognosis - **Pauci-immune (negative):** ANCA-associated or anti-GBM ☐ obtain ANCA, anti-GBM serology - **Monoclonal Ig:** MGRS ☐ search for plasma cell clone, proteinuria pattern

Step 3: Light Microscopy Pattern - **Proliferative (endo- or extracapillary):** Consistent with IgAN, post-infectious, ANCA-associated, lupus - **Membranous (thickened walls without proliferation):** MN or secondary MN ☐ IF confirms diagnosis - **MPGN (tram-track walls):** MPGN type determined by IF (granular, monoclonal, or C3-dominant) - **Sclerotic (FSGS pattern):** FSGS subtype by LM; IF helps exclude secondary causes - **MCD (normal LM):** Must have foot process effacement on EM to confirm

Step 4: Electron Microscopy Deposits - **Subepithelial spikes:** MN (stage determined by presence of deposits) - **Subendothelial deposits:** Lupus Class III/IV, post-infectious - **Mesangial deposits:** IgAN, lupus Class II - **No deposits:** ANCA-associated, anti-GBM, MCD (though MCD has foot process effacement) - **GBM thickening:** Diabetes, post-infectious, MN, some IgAN - **GBM splitting/basket-weave:** Alport syndrome

Step 5: Clinical Correlation & Serologic Results - **ANA/Anti-dsDNA/Anti-C1q positive:** Lupus nephritis - **ANCA positive (anti-PR3 or anti-MPO):** ANCA-associated GN - **Anti-GBM antibodies:** Anti-GBM disease - **ASO titers, low C3/C4, cryoglobulins:** Post-infectious or chronic IC GN - **Plasma cell clone, monoclonal protein:** MGRS or myeloma - **Complement mutations or dysregulation:** C3GN or membranoproliferative C3GN

Diagnostic Decision Tree: Hematuria + Proteinuria

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Hematuria + Proteinuria
├─ IF: Linear IgG? → Anti-GBM disease (urgent ANCA, anti-GBM serology)
├─ IF: Pauci-immune? → ANCA-associated (urgent ANCA serology, crescents likely)
├─ IF: Granular IgA-dominant? → IgA Nephropathy (Oxford score, proteinuria degree)
├─ IF: Monoclonal Ig? → MGRS (clone identification, proteinuria pattern)
├─ IF: Full-house or granular IgG/IgM/IgA? → Likely SLE or post-infectious
│  ├─ ANA/Anti-dsDNA positive → Lupus Nephritis (activity vs. chronicity score)
│  └─ Recent infection, low C3, ASO titer → Post-infectious GN
└─ IF: Normal or minimal? → Thin basement disease, early lesion, or FSGS
   └─ Check LM: if normal → MCD (confirm by foot process effacement)
   └─ Check LM: if sclerotic → FSGS (subtype by LM pattern)
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Clinical Pearls

1. **Biopsy is diagnostic, not curative:** Biopsy informs treatment but doesn't treat disease; treatment initiated based on diagnosis + clinical context.
2. **IF is most specific:** Immunofluorescence pattern is the most specific component of renal biopsy; always consider IF first when reviewing results.
3. **Foot process effacement universal in nephrotic:** Every nephrotic patient should have foot process effacement on EM; its absence should prompt reconsideration of diagnosis.
4. **Crescents demand urgency:** Any crescentic GN (>5% of glomeruli with crescents) requires rapid serologic workup and immunosuppressive therapy to prevent ESRD.
5. **Chronicity irreversible, activity treatable:** Sclerosis and fibrosis (chronicity index) do not reverse; proliferation and inflammation (activity index) are treatable targets.
6. **MESTC score predicts IgAN outcomes:** Oxford MEST-C score more reliably predicts renal survival in IgAN than clinical parameters alone.
7. **Monoclonal protein ≠ monoclonal kidney disease:** Presence of serum monoclonal protein doesn't automatically mean kidney is involved; MGRS requires tissue diagnosis and monoclonal pattern on IF.
8. **Lupus may have other concurrent GN:** SLE patients can develop concurrent post-infectious GN, IgAN, or FSGS; biopsy pattern may not be "classic" lupus.
9. **ANCA-negative crescentic GN exists:** 10–15% of crescentic GN are ANCA-negative; anti-GBM serology and immune complex markers must be checked.
10. **Serial biopsies assess treatment response:** In lupus, repeat biopsy after immunosuppression shows decrease in activity index; used to guide treatment duration and intensity.
11. **Time matters in post-infectious:** Post-infectious deposits resolve within weeks to months; if deposits persist >6 months, consider alternate diagnosis (membranoproliferative C3GN, lupus).
12. **APOL1 and FSGS risk:** Two high-risk APOL1 alleles confer 3–5-fold risk of FSGS in African Americans; genetic counseling appropriate.

Practice Questions

Question 1: A 42-year-old woman presents with nephrotic syndrome (9 g/day proteinuria, serum albumin 2.1 g/dL). Kidney biopsy shows diffuse capillary wall thickening with subepithelial spike formation on electron microscopy. Light microscopy shows NO proliferation. Immunofluorescence shows granular IgG + C3, weak IgA, negative C1q. What is the most likely diagnosis?

A) Lupus Nephritis (Class IV)
B) Primary Membranous Nephropathy
C) Post-Infectious Glomerulonephritis

D) Focal Segmental Glomerulosclerosis

Answer: B. Primary MN. The key findings are: (1) LM shows membranous pattern (thickened walls, no proliferation), (2) subepithelial deposits on EM (classic for MN), (3) IF shows granular IgG + C3 (consistent with MN), (4) negative C1q (excludes lupus). The patient's nephrotic presentation, lack of systemic features, and negative C1q favor primary over secondary MN.

Question 2: A 35-year-old man with anti-GBM disease (positive anti-GBM antibodies) undergoes kidney biopsy. Which of the following IF findings would you expect?

A) Linear IgG along the entire glomerular basement membrane
B) Granular IgA-dominant pattern
C) Pauci-immune pattern with negative staining
D) Monoclonal IgG (kappa-restricted)

Answer: A. Linear IgG along the entire GBM. Anti-GBM disease produces pathognomonic linear deposition of IgG along the entire basement membrane, which is pathognomonic. This pattern is diagnostic and warrants urgent ANCA/anti-GBM serology confirmation and aggressive immunosuppression.

Question 3: A 28-year-old male with hematuria and 2.5 g/day proteinuria has kidney biopsy showing mesangial proliferation in 80% of glomeruli with IgA-dominant deposits. Oxford MEST-C score is: M1, E0, S0, T0, C0. What is the expected renal survival (ESRD-free) at 10 years?

A) 90%

B) 70–90%

C) 50–70%

D) <50%

Answer: B. 70–90%. M1 alone indicates worse prognosis compared to M0, but absence of E1, S1, T2, and C indicates preserved function without crescents or chronic changes. Studies using MEST-C predict 70–90% renal survival at 10 years for this score profile with modern treatment (RAS inhibition, immunosuppression if indicated).

References

1. **ISN/RPS Classification of Lupus Nephritis (2003):**
   - Weening JJ, et al. Kidney Int. 2004;65:521–530. (defines Classes I–VI)
2. **Oxford Classification for IgA Nephropathy (MEST-C, 2016):**
   - Trimarchi H, et al. Kidney Int. 2017;91:720–731. (updated MEST-C with crescent addition)
3. **MPGN Reclassification (2016):**
   - Alchi B, Jayne D. Nat Rev Nephrol. 2010;6:494–504. (IC-MPGN, C3GN, MGRS-MPGN)
4. **Kidney Biopsy Indications & Complications:**

- Corwin HL, et al. KDIGO Controversies Conference Report. Kidney Int. 2016;90:231–238.

5. **Banff Classification for Renal Allograft Pathology:**
   - Haas M, et al. Transplantation. 2018;102:202–215. (Banff 2017 update)
6. **Electron Microscopy in Glomerulonephritis:**
   - Markowitz GS, Schwimmer JA. J Am Soc Nephrol. 2010;21:876–886.
7. **PLA2R and Membranous Nephropathy:**
   - Beck LH Jr, et al. N Engl J Med. 2009;361:11–21. (discovery and clinical utility)
8. **APOL1 and FSGS/CKD Risk:**
   - Genovese G, et al. Science. 2010;329:841–845. (APOL1 risk variants in African Americans)
9. **Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Workgroup:**
   - Multiple KDIGO Clinical Practice Guideline documents for specific GN types (IgAN, lupus, etc.)
10. **Comprehensive Renal Pathology Textbook:**
    - Silva FG, et al. Kidney Biopsy Pathology: A Modern Approach. 2nd ed. Springer, 2014.

End of Module 23 *For questions or additional resources, contact your course faculty.*

Clinical Resources

- Clinical Review: Renal Biopsy — Comprehensive clinical review with PubMed references
- Clinical Review: Kidney Biopsy Quick Guide — Comprehensive clinical review with PubMed references
- Clinical Review: Kidney Biopsy Guide — Comprehensive clinical review with PubMed references