

Introduction to Renal Pathology

VALUE OF RENAL BIOPSY

Provides Diagnosis

- Alters clinical diagnosis 24-47%

Guides Treatment

- Changes therapy 31-42%
- Determines reversibility and activity

Predicts Prognosis

- Specific pathologic features and extent of changes
- Changes prognosis 31-57%

Reveals Pathogenesis

- Molecular and cellular mechanisms

Validates Outcome

- Used as endpoint in clinical trials

INDICATIONS FOR RENAL BIOPSY

Elevated Cr or BUN (Acute or Chronic)

- Elevated with decreased renal filtration
- Measure creatinine clearance or estimated glomerular filtration rate (eGFR) based on gender, body weight, race, age

Proteinuria

- May be asymptomatic or symptomatic
- Usually a sign of increased permeability of glomerulus
 - Failure of reabsorption by tubules can lead to low-level proteinuria
- 1-3 g/d usually asymptomatic
- Higher levels lead to edema and nephrotic syndrome

Nephrotic Syndrome

- Proteinuria > 3.5 g/d, hypoalbuminemia, edema, hyperlipidemia, lipiduria
- Increased glomerular permeability to albumin and other plasma proteins

Hematuria (Microscopic or Gross)

- May be asymptomatic or symptomatic (gross hematuria)

- Usually a sign of glomerular inflammation and ruptured glomerular basement membrane (GBM), especially with red blood cell (RBC) casts
- When combined with acute renal failure and RBC casts, termed nephritic syndrome

Nephritic Syndrome

- Hematuria, proteinuria, elevated Cr, hypertension, edema
- Loss of function due to decreased glomerular blood flow, salt retention

BIOPSY TECHNIQUE AND SAFETY

Percutaneous (Needle) Biopsy

- Ultrasound guided, automated gun
 - Generally regarded as safe outpatient procedure
 - 14-16 gauge needle recommended for adults; 16-18 gauge for children < 8 years old
 - At least 2 cores if possible
- Complications varies with technique
 - Microscopic (~ 35%) or gross hematuria (4.5%)
 - Complications requiring intervention 6.6% (Korbet 2014)
 - Hematoma 3.5%
 - Transfusion 5.3%
 - Embolization 0.8%
 - Obstruction 0.2%
 - Mortality 0.09%
- Adequacy
 - Excellent diagnostic yield with two 14-g cores (99%; mean: 32 glomeruli)
 - 94% adequacy with 18-g needle (mean 9 glomeruli)

Open (Wedge) Biopsy

- Primarily samples outer cortex

Transjugular Vein Biopsy

- High-risk patients

PROCESSING OF TISSUE

Gross Examination

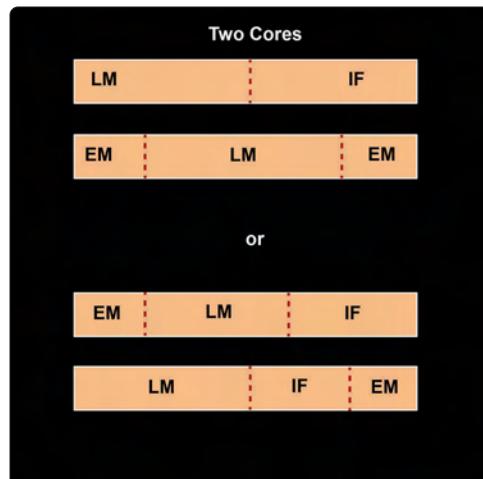
- Determine whether glomeruli in sample

Gross Appearance of Renal Biopsy Cores

(Left) Renal biopsy cores from 16-g needle show glomeruli appearing as pale or congested bulges and red cell casts as brown streaks or dots. (Right) Renal biopsy cores are divided into 3 portions for light microscopy (LM), immunofluorescence (IF), and electron microscopy (EM). Two cores are generally taken and divided transversely with effort to ensure that each of the 3 portions include cortex. Longitudinal division is not recommended.



Division of Renal Biopsy Cores



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- Dissecting microscope, loupe

Division of Sample

- Divide into 3 parts for light (LM), immunofluorescence (IF), and electron microscopy (EM)
 - Take LM portions from both cores, EM from ends

Light Microscopy

- Formalin-fixed, paraffin-embedded, 2-3 μm sections
 - Multiple levels
- H&E, PAS, silver and trichrome stains usual
 - Other stains as indicated

Immunofluorescence

- Quick freeze on cryostat chuck or liquid N₂
- Frozen sections cut at 3-4 μm
- Stain for IgG, IgA, IgM, kappa, lambda, C1q, C3, fibrinogen, albumin
 - C4d on transplant biopsies

Electron Microscopy

- 2% paraformaldehyde/2.5% glutaraldehyde in cacodylate or phosphate buffered fixative (Karnovsky half strength, "K2") and osmium post fix
- 1 μm toluidine blue-stained sections to screen for glomeruli
- Choose 1-2 blocks with glomeruli and trim for EM sectioning and staining (Pb/Ur)

Recording Results

- Digital cameras commonly used for IF and EM
- Whole slide scans for LM for clinical trials/teaching
- EM morphometry to measure GBM thickness

SYSTEMATIC APPROACH

Light Microscopy

- Examine each of 4 components
 - Glomeruli, tubules, interstitium, and vessels
 - Try to decide which component is primarily affected
- Describe and quantitate changes in each compartment
 - Distinguish acute and chronic changes
 - Examine each section
- Examine frozen and plastic section by light microscopy

Immunofluorescence

- Assess pattern, extent, and intensity of glomerular staining
- Assess presence and pattern of deposits in other sites (tubular basement membrane [TBM], vessels, interstitium)

Electron Microscopy

- GBM thickness and appearance
- Presence and location of electron dense deposits
 - Substructure and periodicity, if any
- Podocyte changes (effacement)
- Endothelial changes
- Mesangial features
- TBM, interstitium, peritubular capillaries

ISSUES IN INTERPRETATION

Sampling

- Adequacy of sample is dependent on nature of disease
 - Small samples are adequate for diffuse diseases

- Large samples are needed for focal diseases
- The rarer the lesion, the greater the sample needed
 - $S = 1 - (1 - p)^n$, where S = probability of obtaining at least 1 affected glomerulus, p = fraction of affected glomeruli in kidney, and n = number of glomeruli in sample (binomial distribution)
 - For example, if 10% of glomeruli are affected, need 30 glomeruli to have > 95% chance of sampling at least 1 affected glomerulus
- Estimation of % affected glomeruli in kidney is similarly subject to sampling error (e.g., distinction between > 50% and < 50%)
- Distribution of lesions is not random in some diseases (e.g., focal segmental glomerular sclerosis FSGS)
- Options when inadequate
 - Reprocess paraffin or frozen block for EM or frozen for paraffin
 - Immunohistochemistry for Ig in paraffin block

Scoring Systems and Definitions

- Described by several classification systems
 - Lupus (ISN/RPS), IgA (Oxford), transplants (Banff)
- Do not always agree on definitions or method of scoring for same features

Complex Biopsies

- > 1 disease may be present
 - Common in allografts
 - Residue from past disease persists

Functional Interrelationships

- Disease of 1 component affects others
 - Loss of glomeruli affects blood supply of tubules
 - Vascular disease affects tubules and glomeruli

REPORTING RECOMMENDATIONS

Diagnosis

- Use current classification system for particular disease (e.g., lupus, IgA, diabetes, vasculitis, transplant)
- Include severity and activity whenever possible

Description

- Indicate sample (number of cores, cortex, medulla, corticomedullary junction)
- Glomeruli
 - Count number in sample (can count section with greatest number)
 - Give % of globally and segmentally sclerotic glomeruli
 - Mesangial cellularity
 - Thickening of capillary wall/GBM
 - Presence or absence of inflammation, necrosis, crescents, thrombi, adhesions, hyaline, periglomerular fibrosis
 - Indicate fraction of glomeruli involved
 - Useful to give % of normal glomeruli
- Tubules
 - Acute injury, necrosis
 - Atrophy (give %)
 - Casts (RBC, protein, pigment, neutrophils)
 - Tubular reabsorption droplets
 - Vacuolization, nuclear inclusions, giant mitochondria

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- Interstitium
 - Inflammation, type of cells, granuloma
 - Fibrosis, pattern, extent (%)
- Vessels
 - Count arteries
 - Intimal fibrosis, arteries (% luminal occlusion)
 - Arteriolar hyalinization (extent)
 - Vasculitis
 - Peritubular capillaritis
- Immunofluorescence
 - Indicate number of glomeruli in sample
 - Give pattern and intensity of glomerular staining for each positive reactant and score 0-4(+)
 - Note other relevant staining: TBM, interstitium, vessels, reabsorption droplets
 - List all stains used, including negative
- Electron microscopy
 - Indicate number of glomeruli
 - Status of podocytes (effacement, hypertrophy, separation from GBM)
 - GBM (thickness, lamination, deposits)
 - Extent and position of deposits
 - Give substructure, if any, and dimensions
 - Mesangial features (fibrils, cells, deposits)

Summary

- Link to clinical information
- Compare with previous biopsy
- Discuss differential and basis of conclusion

DEFINITIONS FOR GLOMERULI

Adhesion

- Abnormal attachment of glomerular tuft to Bowman capsule; area of continuity between glomerular tuft and Bowman capsule separate from extracapillary lesion or from area of segmental sclerosis

Bowman Capsule

- Layer of basement membrane surrounding Bowman space on which parietal epithelial cells rest; continuous with GBM at base of glomerulus

Bowman Space

- Space between glomerular tuft and surrounding Bowman capsule, in continuity with lumen of proximal tubule

Capillary Wall Thickening

- Used for H&E sections in which GBM, deposits, and cellular elements all contribute to thickness

Collapsing Lesion

- Collapse of glomerular capillaries with overlying podocyte hypercellularity

Crescent

- Extracapillary proliferation of > 2 cell layers occupying 25% or more of glomerular capsular circumference or > 10%
 - Sometimes graded: < 10% (tiny focus), 10-25%, 25-50%, > 50% of glomerular capsular circumference

Crescent, Cellular

- Crescent with cells and no fibrosis; usually have fibrin and inflammatory cells

Crescent, Fibrocellular

- Crescent with mixture of cellular and fibrous components

Crescent, Fibrous

- Predominantly fibrous tissue in Bowman space; no fibrin or inflammatory cells

Diffuse

- Majority of glomeruli ($\geq 50\%$)

Disappearing Glomerulosclerosis

- Global glomerulosclerosis with some dissolution of Bowman capsule

Duplication of GBM

- Double layer of GBM separated by clear zone on silver or PAS stains; sometimes likened to tram tracks; sometimes redundantly called "reduplication"

Endocapillary Hypercellularity (Proliferation)

- Increased numbers of intracapillary cells causing narrowing of glomerular capillary lumina

Extracapillary Hypercellularity (Proliferation)

- Synonym for crescent

Fenestrations (Fenestrae)

- Openings through endothelial cells (~ 50 nm in diameter) that allow fluid passage but retain formed elements

Fibrinoid Necrosis

- Area of necrosis that stains brick red with eosin due to denatured proteins and fibrin

Filtration Slit Diaphragm

- Connection between podocyte foot processes consisting of nephrin and other components
- Thought to be responsible for macromolecular filtration
- a.k.a. "zipper" for its en face appearance

Focal

- Minority of glomeruli ($< 50\%$)

Global Glomerulosclerosis

- Sclerotic remnant of glomerulus largely consisting of extracellular material; sometimes subdivided into obsolescent, solidified, and disappearing types

Glomerular Basement Membrane

- Continuous layer of collagen type IV and matrix components on which podocytes and endothelial cells rest; does not include Bowman capsule

GBM Thickening

- Used for PAS and silver stains that distinguish GBM elements

Hyaline Deposits

- Homogeneous, dense eosinophilic deposits, often with clear fine lipid droplets; composition not well defined

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Hyaline Thrombi

- Synonym for pseudothrombi

Hypertrophy

- Increase in size (diameter) of glomerulus (normally < radius of a 40x field ≈ 440µm); typically accompanied by increased mesangium and thickened GBM

Inflammation

- Increased numbers of leukocytes (granulocytes, monocytes, lymphocytes) in capillaries (normally < 2 per glomerulus)

Global

- Entire glomerulus involved (> 50% in lupus)

Ischemic Collapse (Sclerosis)

- Glomerulus showing collapse of capillary tuft ± thickening of Bowman capsule and fibrosis in Bowman space

Karyorrhexis

- Pyknotic and fragmented nuclei

Mesangial Cell

- Normal resident of mesangium in glomerulus; has contractile and phagocytic properties

Mesangial Hypercellularity

- 3 or more mesangial nuclei in 1 mesangial area in a 3 µm section (lupus classification); 4 or more in IgA classification, subdivided into mild (4-5), moderate (6-7), and severe (8 or more)

Mesangial Matrix

- Extracellular component of normal mesangium, includes collagen IV alpha 1, 2 chains, fibronectin, and variety of glycosaminoglycans

Mesangial Matrix Expansion

- Width of mesangial interspace exceeds 2 mesangial cell nuclei in at least 2 glomerular lobules (IgA)

Mesangiolyisis

- Loss of integrity of mesangium so that glomerular capillary forms aneurysmal dilation

Necrosis

- Loss of integrity of glomerulus; typically manifested by fragmented nuclei (karyorrhexis), disruption of GBM, and deposition of fibrin; minimum requirement is extravascular fibrin (IgA)

Nodules

- Rounded expansion of mesangial matrix &/or cells with peripheral necklace of capillaries

Nuclear Dust

- Fragments of neutrophil nuclei (karyorrhexis) in site of inflammation

Obsolescent Glomeruli

- Retracted, globally sclerotic glomeruli with Bowman space filled with matrix

Parietal Epithelium

- Cells that line Bowman capsule

Pseudothrombi

- Eosinophilic, rounded aggregates in glomerular capillaries due to immune complex precipitates rather than fibrin (typically due to cryoglobulins with IgG, IgM, and C3); a.k.a. hyaline thrombi

Podocyte

- Cell on outside of GBM with extensive foot processes connected with filtration slit diaphragms; terminally differentiated

Sclerosis

- Obliteration of capillary lumen by increased extracellular matrix ± hyalinosis or foam cells

Segmental

- Part of glomerulus involved; definitions varies from any amount to < 50%

Solidified Glomerulosclerosis

- Globally sclerotic glomeruli filling Bowman space

Spikes

- "Hair on end" pattern of subepithelial GBM on silver or PAS stain; need 40-100x to appreciate

Visceral Epithelium

- Normally synonymous with podocyte. Preferred term when nature of cell on the GBM is uncertain, as in collapsing glomerulopathy

DEFINITIONS FOR TUBULES

Acute Tubular Injury

- Loss of brush border on PAS stain, thin cytoplasm, loss of nuclei; simplification of epithelium without TBM thickening

Acute Tubular Necrosis

- Epithelial cell death, as manifested by loss of or pale-staining nuclei and eosinophilic cytoplasm; usually not conspicuous unless toxin or vessel occlusion; sometimes used as synonym for acute tubular injury

Apoptosis

- Programmed cell death, as manifested by pyknosis and fragmentation of nuclei

Casts

- Presence of protein or cells in tubular lumen taking shape of tubule

Casts, Red Cell

- Presence of compacted red cells in tubular lumen; may be hemolyzed or fragmented; need to distinguish loose red cells from biopsy artifact

Casts, Tamm-Horsfall Protein (Uromodulin)

- Cast of protein normally produced in distal tubule; pale on H&E, strongly PAS positive

Dystrophic Calcification

- Calcification of necrotic cells or debris; typically in casts as variably sized basophilic granules

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Fatty Change

- Tubules with clear cytoplasm containing lipid (demonstrable in Oil red O-stained frozen sections), a feature of nephrotic syndrome

Intranuclear Inclusions

- Homogeneous dense or pale transformation of nucleus
 - Indicative of active viral replication

Isometric Vacuolization

- Abundant clear cytoplasmic vacuoles of about same size

Nephrocalcinosis

- Accumulation of calcium salts, typically in TBM as basophilic, linear deposit; also present in casts

Osmotic Nephrosis

- Fine, clear vacuolization in tubules

Thyroidization

- Dilated tubular segments with eosinophilic proteinaceous casts and thin epithelial lining

Tubular Atrophy

- Loss of cytoplasmic organelles (pale cytoplasm) accompanied by shrinkage of tubular diameter and often thickened TBM

Tubular Hypertrophy

- Increased diameter of tubules with increased size of epithelial cells

Tubular Reabsorption Droplets (Hyaline Droplets)

- PAS(+) small round granules in tubular cells; contain albumin and often other plasma proteins and indicate glomerular proteinuria

Tubular Rupture

- Disruption of TBM with localized inflammatory response; may have granulomatous reaction and spilling of Tamm-Horsfall protein into interstitium (piss granuloma)

Tubulitis

- Mononuclear leukocytes within epithelial layer of tubules

DEFINITIONS FOR INTERSTITIUM

Abscess

- Localized collection of neutrophils in area of destruction of normal tissue components

Interstitial Fibrosis

- Expansion of normal interstitial connective tissue by increased collagen (I and III, typically); may or may not be accompanied by tubular atrophy; may be diffuse or focal
 - Scored by % of cortex involved or area of fibrosis

Interstitial Inflammation

- Increased numbers of leukocytes between tubules; may be focal or diffuse, nodular, perivascular, subcapsular
- Should be noted whether or not inflammation is confined to areas of interstitial fibrosis

Granuloma

- Nodular collection of epithelioid macrophages, sometimes with multinucleated macrophages (a.k.a histiocytes), usually with lymphocytes

DEFINITIONS FOR VESSELS

Arteriolar Hyalinosis

- Accumulation of eosinophilic, amorphous material (usually containing plasma proteins) in arteriolar wall; may be subendothelial, peripheral nodular, or transmural; focal or circumferential

Capillaritis

- Accumulation of leukocytes in peritubular capillaries

Endarteritis

- Mononuclear inflammatory cells under endothelium of arteries and arterioles

Fibrinoid Necrosis

- Brick red staining of vessel wall on H&E with loss of smooth muscle nuclei; may have inflammatory component

Intimal Fibroelastosis

- Thickening of arterial intima with multiple layers of elastic fibers and collagen; usually not very cellular

Intimal Fibrosis

- Accumulation of fibrous tissue in intima, usually concentric, causing stenosis of lumen

Mucoid Intimal Thickening

- Accumulation of edematous extracellular matrix in intima resembling mucus; pale blue on H&E, Alcian blue positive

Onion Skinning

- Multilayered cells and matrix in intima of small arteries and arterioles

Vasculitis

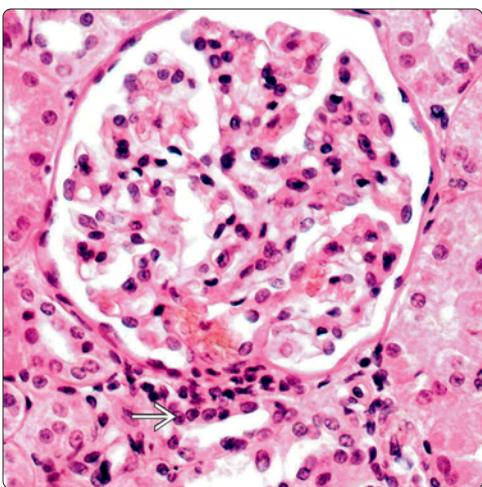
- Inflammation in wall of vessel, as manifested by neutrophil karyorrhexis, fibrinoid necrosis of media; may occur in any sized vessel, artery, capillary, or vein

SELECTED REFERENCES

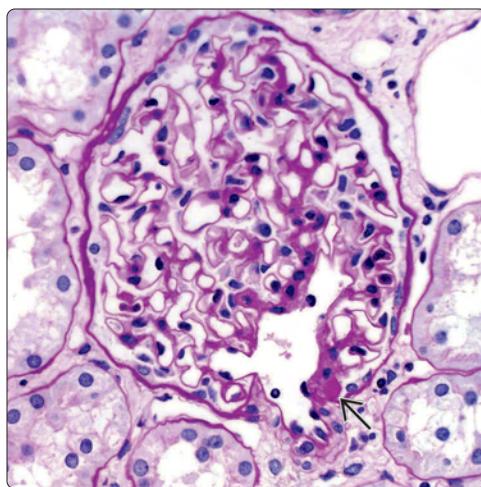
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Normal Glomerulus

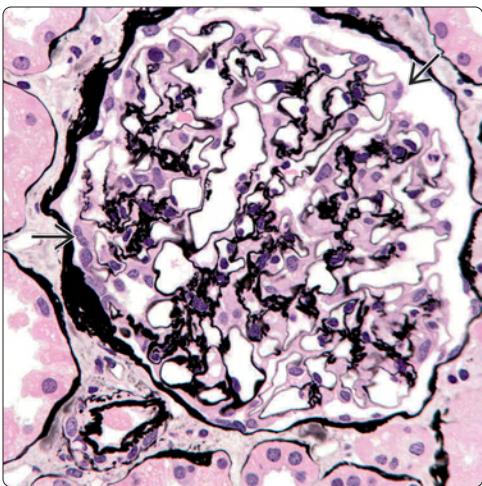


Normal Glomerulus

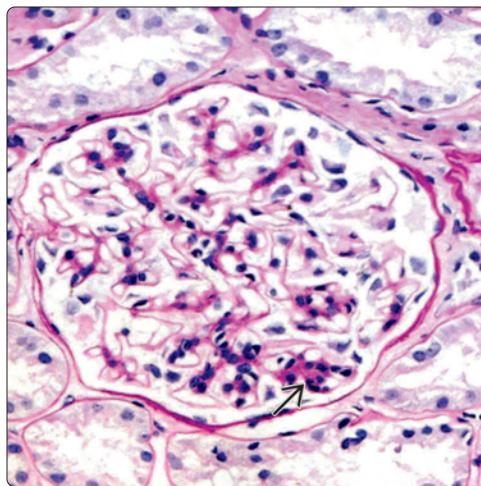


(Left) H&E shows a normal glomerulus from a biopsy for asymptomatic microhematuria. The juxtaglomerular apparatus is at the base . The capillaries are open, and the cellularity is normal although it is difficult to define the mesangium. (Right) Glomerulus in a donor biopsy stained with PAS reveals a thin GBM, open capillaries, an inconspicuous mesangium, and normal podocytes. A small hyaline deposit is present at the hilum but it is otherwise normal.

Normal Glomerulus

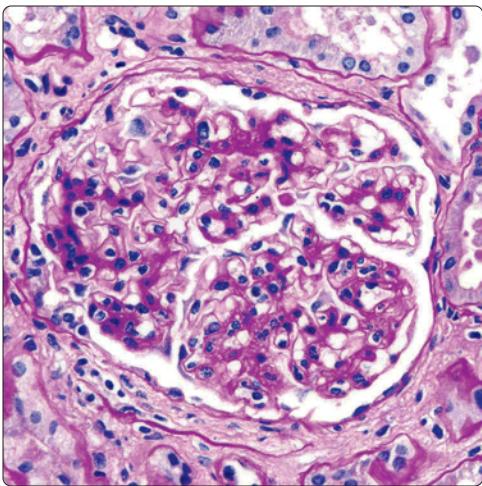


Minimal Mesangial Hypercellularity

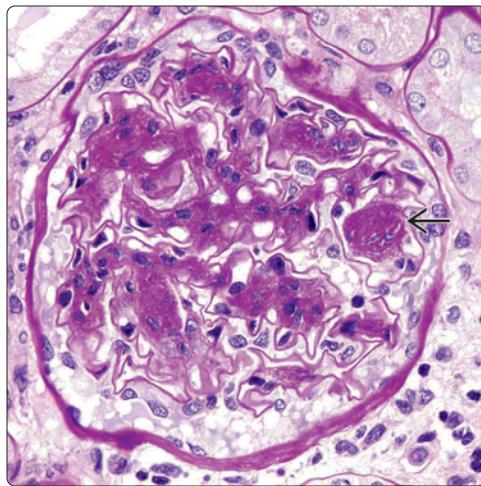


(Left) Donor biopsy stained with Jones silver stain highlights the normal GBM. The podocytes are well seen, but the mesangial cells are lost in the densely stained mesangial matrix. This and the PAS stain are most valuable for appreciating the LM glomerular anatomy. (Right) PAS stain shows minimal mesangial hypercellularity in a patient with lupus nephritis. The threshold for mesangial hypercellularity is 3-4 mesangial cells per mesangial area in a 2-3 μm section.

Moderate Mesangial Hypercellularity



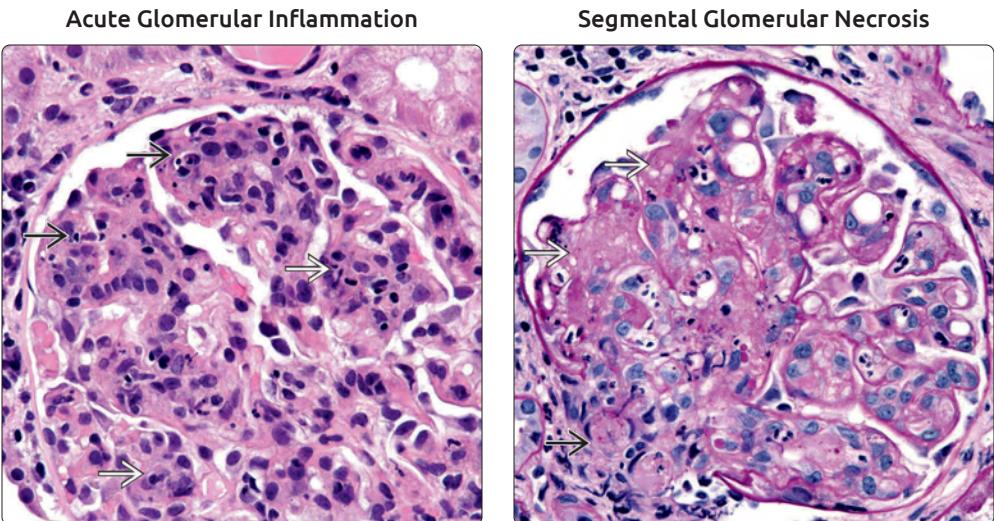
Mesangial Hypercellularity and Nodules



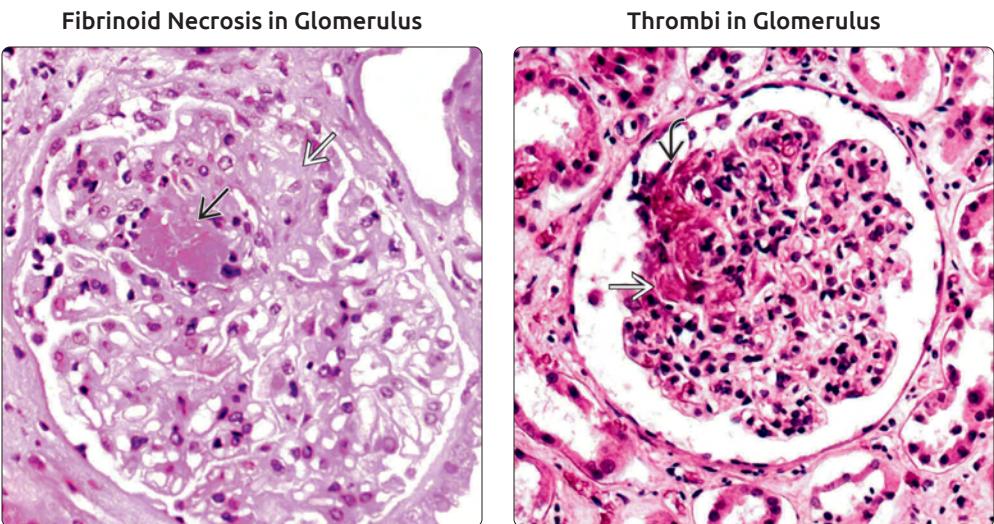
(Left) PAS stain shows moderate global mesangial hypercellularity in a patient with IgA nephropathy. All segments of the glomerulus have increased mesangial cells and matrix. (Right) Marked global expansion of the mesangial matrix and cellularity with a segmental nodular pattern is evident in this PAS-stained glomerulus with diabetic glomerulosclerosis.

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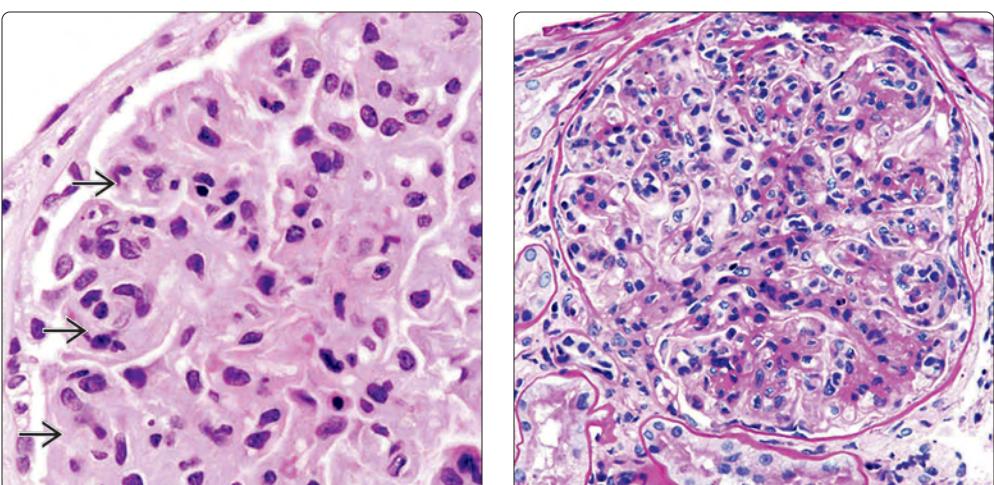
(Left) Neutrophils can be seen in glomerular capillaries → with swollen endothelial cells that occlude the capillary lumina in a lupus nephritis case. Fragments of nuclei (nuclear dust) or karyorrhexis are present ↗. (Right) Necrosis of a glomerulus is shown with loss of nuclei and obliteration of the normal architecture of the glomerulus →. Thrombi are evident in arterioles → in this case of thrombotic microangiopathy.



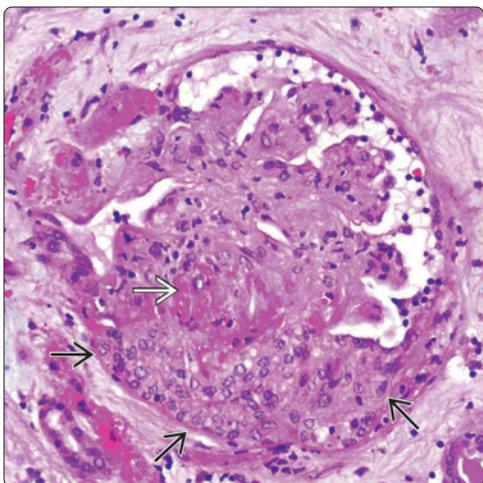
(Left) Fibrinoid necrosis is best seen on H&E-stained sections in which the fibrin and denatured protein stain brick red → with nearby nuclear dust. An area of old necrosis → with loss of the normal architecture but without fibrin is also present. Patient has ANCA-related glomerulonephritis. (Right) Thrombi in capillaries → and fibrinoid necrosis → are shown in a glomerular tuft from a patient with endocarditis.



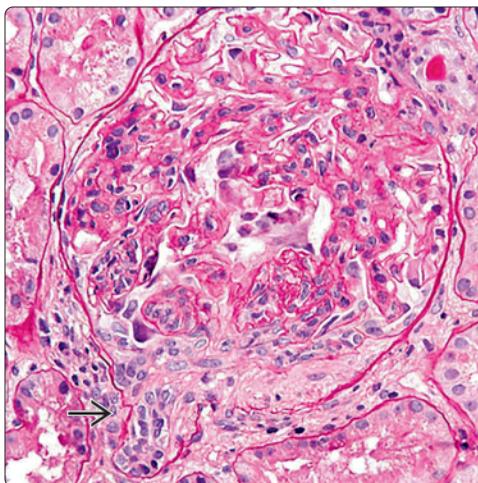
(Left) Endocapillary hypercellularity → illustrated in this glomerulus from a patient with lupus nephritis is defined as leukocytes or other cells filling the capillary loops. Here there are both mononuclear and polymorphonuclear cells. The capillary walls are also thickened, but this is better appreciated in PAS or silver stains. (Right) This glomerulus has an infiltrate of monocytes in the capillaries, occluding the lumina. Patient has mixed cryoglobulinemia.



Cellular Crescent

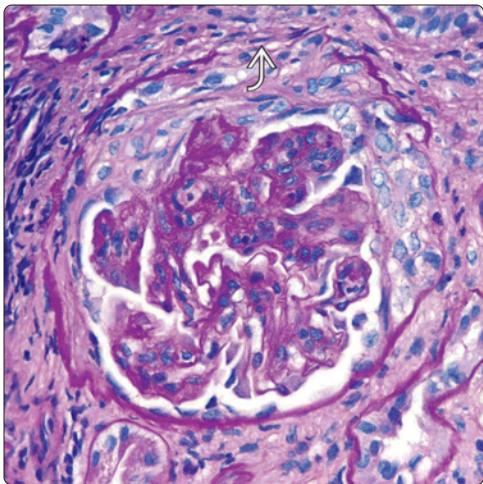


Cellular Crescent Blocking Tubule

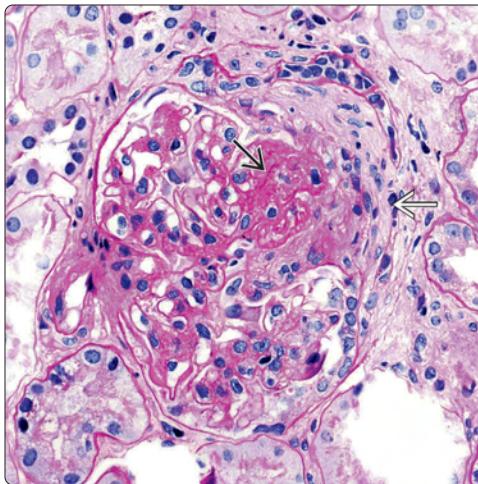


(Left) H&E shows a cellular crescent occupying 1/3 of the circumference of Bowman capsule with associated fibrinoid necrosis . A crescent is defined as a layer of > 2 cells in Bowman space occupying ≥ 25% of the circumference of Bowman capsule. Crescents are also known as extracapillary proliferation. (Right) Crescents interfere with glomerular function by compressing the tuft and blocking the outlet of Bowman space into the proximal tubule .

Fibrocellular Crescent

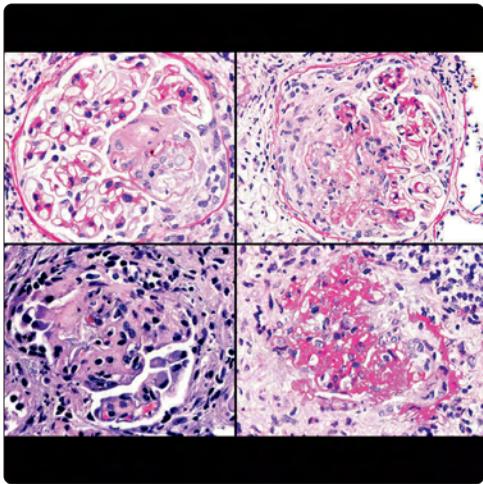


Fibrous Crescent

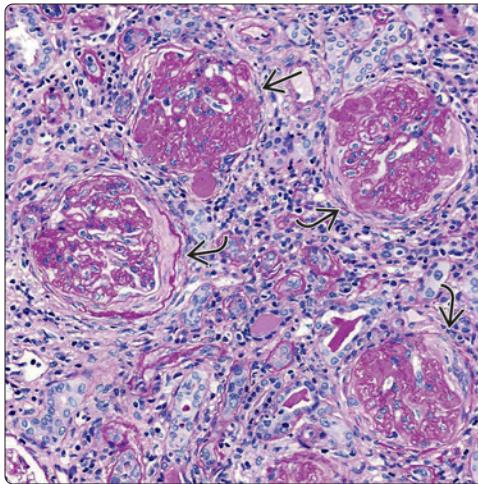


(Left) Crescents start as a cellular proliferation of parietal epithelial cells and evolve into fibrocellular crescents (shown here), which have less cellularity and more collagen deposition. Disruption of Bowman capsule is present, a typical feature of crescents. (Right) A fibrous crescent remains in this glomerulus with associated adherent segmental sclerosis of the tuft due to prior necrosis. Bowman capsule is disrupted .

Evolution of Crescents



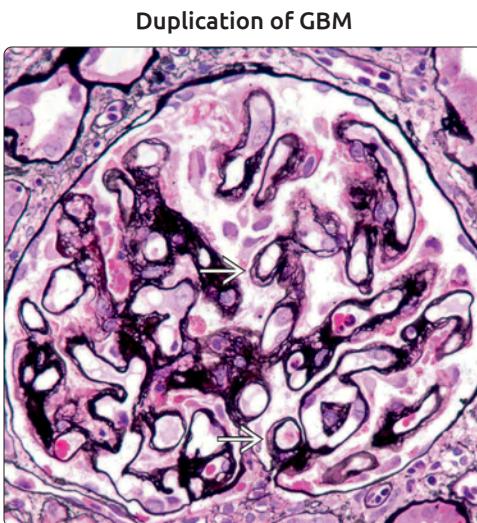
Global Glomerulosclerosis



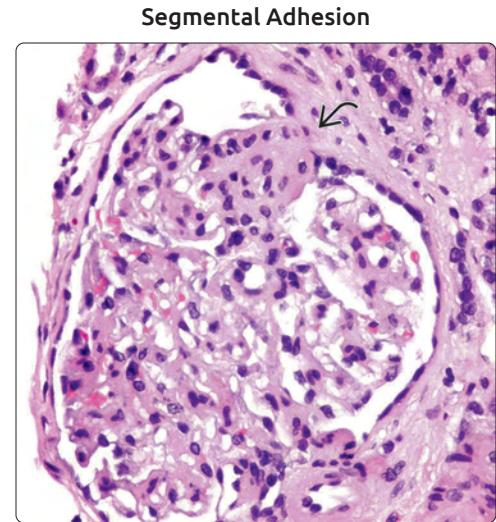
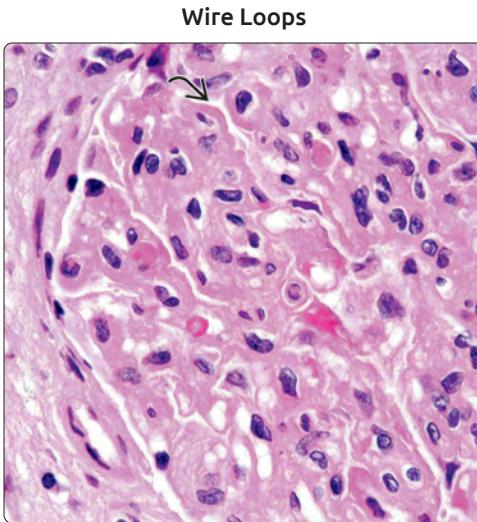
(Left) Evolution of crescents is shown from cellular (upper left) to partial destruction of tuft (upper right), to global destruction of architecture (lower left), to "dissolving" global glomerulosclerosis with remnants of GBM and disrupted Bowman capsule (lower right). (Right) Global glomerulosclerosis is best appreciated in PAS stains because of the definition of the GBM and Bowman capsule. Three are "obsolescent" with matrix filling Bowman space and one is "solidified" filling Bowman capsule .

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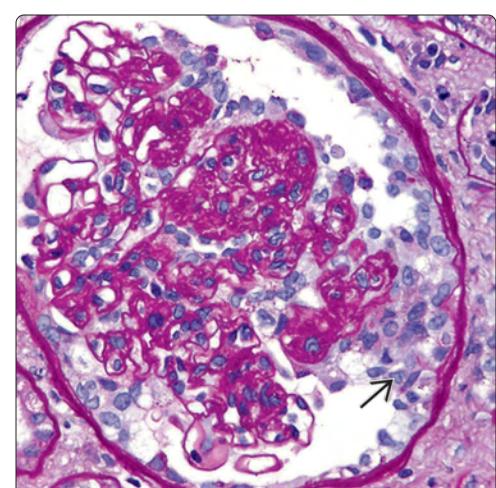
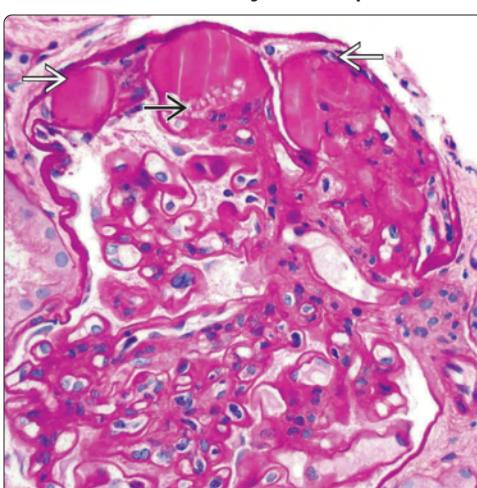
(Left) Silver stain is useful to demonstrate abnormalities of the GBM in this patient with an allograft with transplant glomerulopathy, as shown here in a glomerulus with prominent duplication of the GBM (tram tracks) ➤. (Right) GBM "spikes" can be appreciated in membranous glomerulonephritis ➡ on a thin (2 µm) silver-stained section. These protrusions of the GBM surround the silver-negative immune complex deposits.



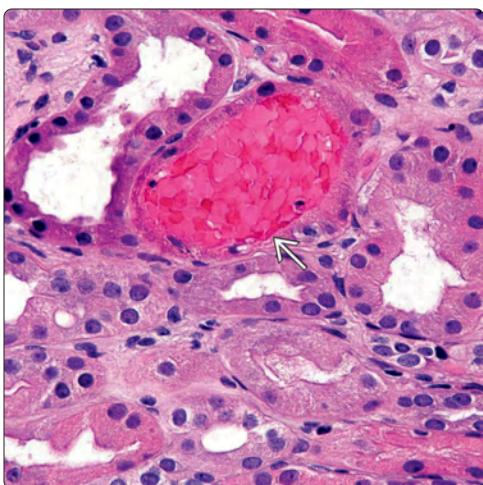
(Left) Wire loops ➡ are eosinophilic thickening of the glomerular capillary wall due to subendothelial deposits, shown here in a case of active lupus nephritis, class IV. (Right) Adhesion of a sclerotic glomerular segment to Bowman capsule is shown in a patient with idiopathic focal segmental glomerulosclerosis (FSGS). A useful feature to distinguish an adhesion from artifactual compression of the tuft against the Bowman capsule ➡ toward the glomerulus.



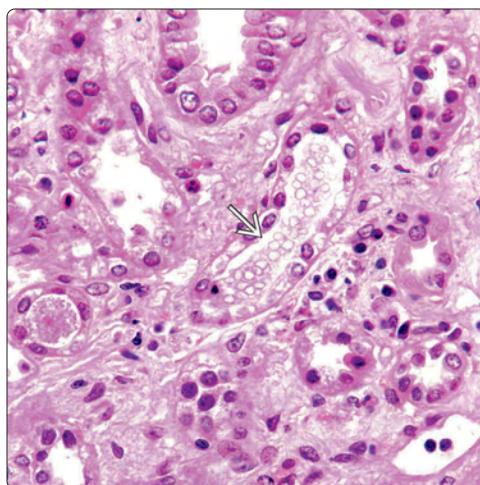
(Left) Abundant hyaline deposition ➡ in an adhesion with scarred segment of the glomerulus is shown. Lipid droplets ➡ (unstained) help distinguish this from fibrin. (Right) PAS shows a pseudocrescent ➡ caused by bridging of parietal (or visceral) epithelial cells from Bowman capsule to the GBM in a patient with collapsing glomerulopathy. The cellular proliferation in Bowman space can mimic a crescent, but does not usually contain fibrin or inflammatory cells.



Red Cell Cast

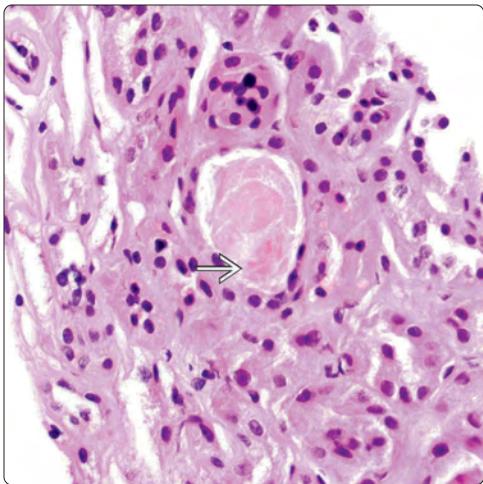


Hemolyzed Red Cell Cast

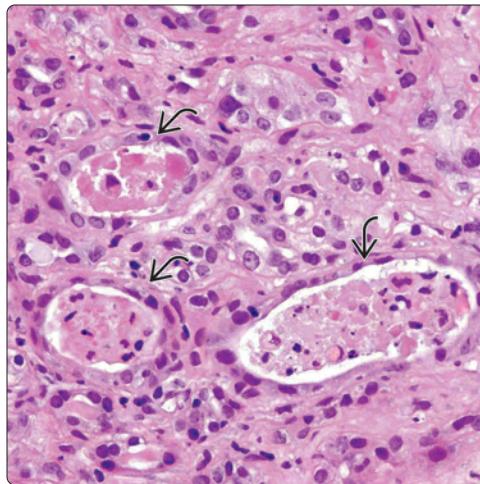


(Left) Red cell cast in a tubule is shown. The compaction of the erythrocytes and complete filling of the tubule indicate that this is not an artifact of the biopsy procedure. (Right) Hemolyzed red cell cast in a tubule is shown . The ghost cells can still be recognized on H&E. Hemolysis indicates that these are not artifacts of the biopsy. Patient has Henoch-Schönlein purpura.

Pigmented Cast

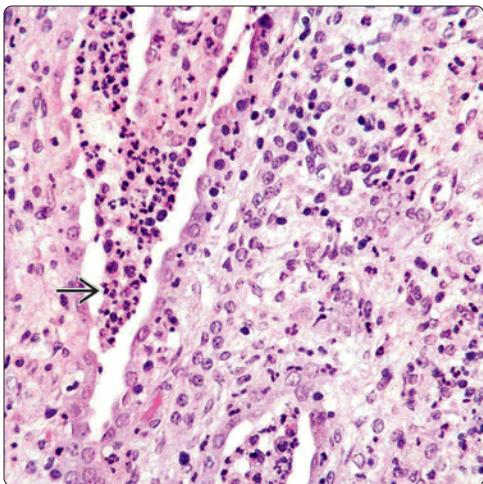


Cellular Cast

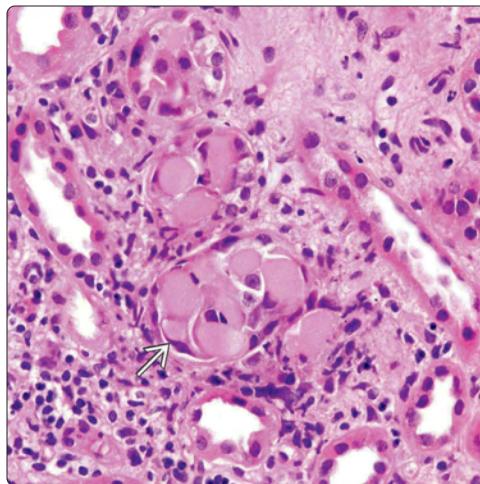


(Left) A pigmented cast was all that remained as evidence of prior glomerular bleeding in a patient with IgA nephropathy. (Right) Casts in acute tubular necrosis typically contain nuclear fragments and eosinophilic cytoplasmic debris derived from necrotic tubular epithelial cells.

Neutrophil Cast



Myeloma Casts

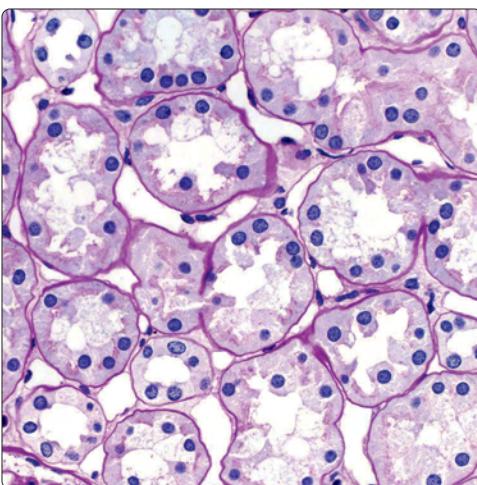


(Left) In acute pyelonephritis (not often diagnosed in biopsy), prominent neutrophil casts can be seen in a collecting duct identifiable by its branching. (Right) Eosinophilic casts with attached mononuclear cells should raise suspicion of myeloma cast nephropathy, as illustrated in this case.

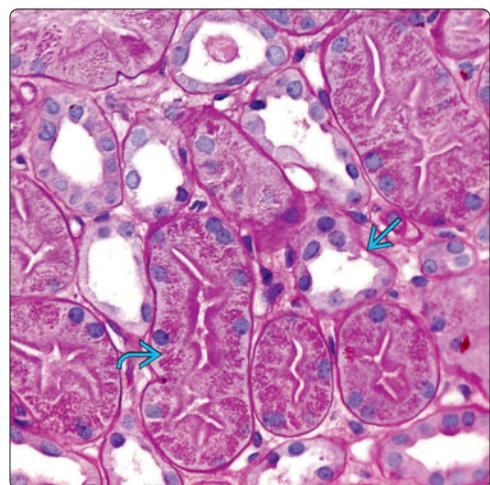
Introduction to Renal Pathology

(Left) Normal tubules and interstitium in a donor biopsy stained with PAS are shown. Tubules are separated by peritubular capillaries, and there is minimal fibrous tissue. **(Right)** Tubular reabsorption droplets in the cytoplasm of proximal tubular cells are round granules that are positive with PAS stain. The distal tubules are negative . Patient had minimal change disease.

Normal Cortical Tubules and Capillaries



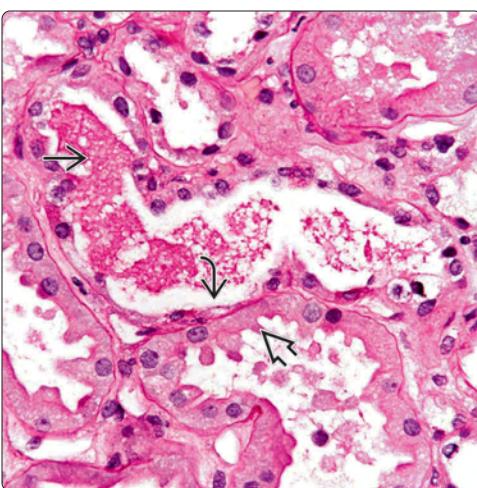
Tubular Reabsorption Droplets



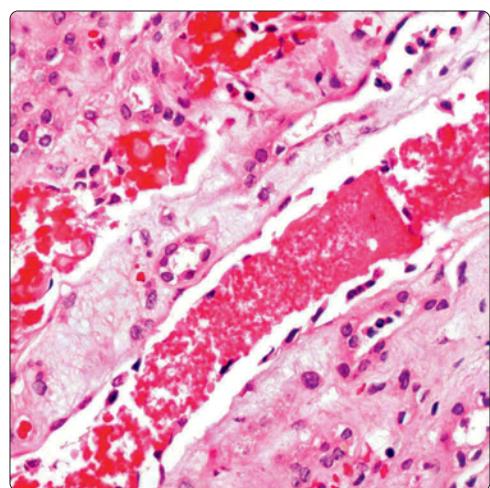
Acute Tubular Injury

(Left) PAS shows acute tubular injury with thinned cytoplasm with loss of brush border, decreased numbers of nuclei , and granular casts .

(Right) Myoglobin casts are typically strongly eosinophilic and granular. They can be identified with antimyoglobin immunohistochemistry.



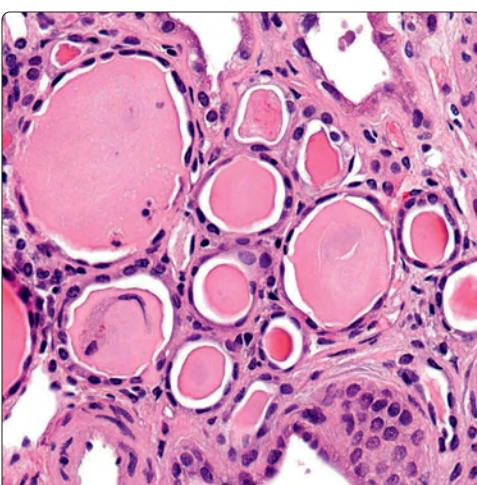
Myoglobin Casts



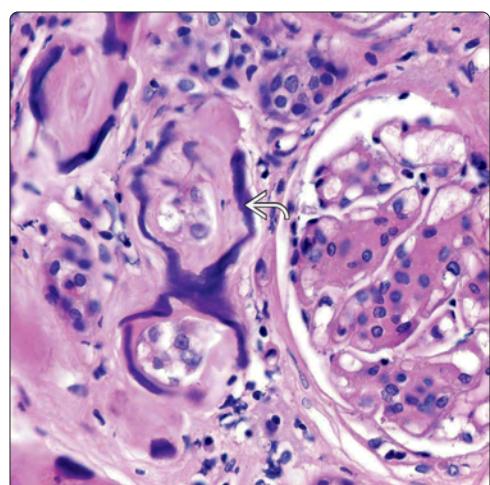
Atrophic Tubules in Thyroidization Pattern

(Left) Thyroidization is a term applied to the eosinophilic casts in atrophic, microcystic tubules. These are generally associated with chronic pyelonephritis but are not specific. They are caused by disruption of the tubules by scar and retention of Tamm-Horsfall protein. **(Right)** Nephrocalcinosis is manifested by TBM deposits of basophilic calcium salts .

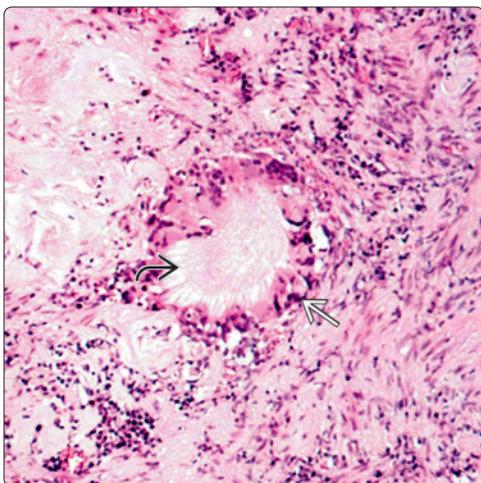
Nephrocalcinosis can be seen in a variety of conditions with hypercalcemia and in nephrogenic systemic sclerosis related to gadolinium scans.



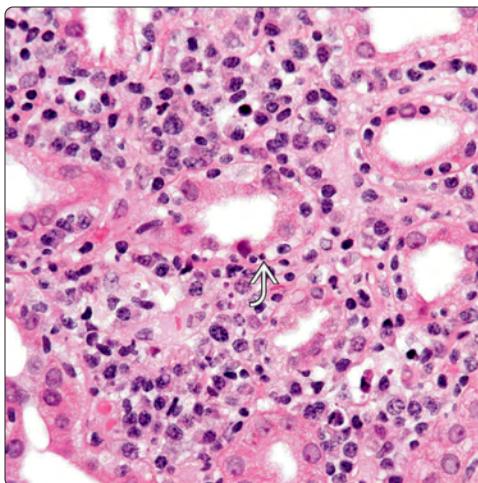
Nephrocalcinosis



Urate Deposition With Giant Cells



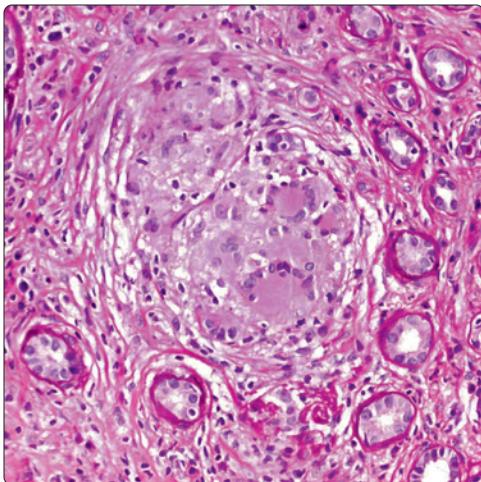
Acute Interstitial Inflammation



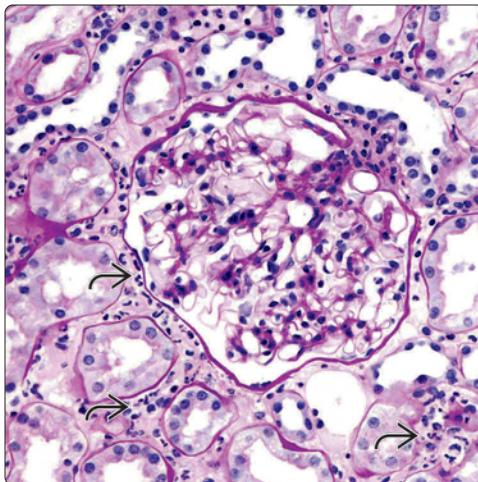
(Left) H&E shows a urate deposit ↗ with a giant cell reaction ↘ in the medulla of kidney from a patient with gout. The crystals dissolve, in contrast to oxalates, but can be seen in frozen tissue.

(Right) Acute interstitial inflammation with mononuclear cells separates and invades the tubules (tubulitis) ↗. This pattern can be seen in acute rejection (as in this case) or in drug allergy and other conditions.

Granuloma Interstitium



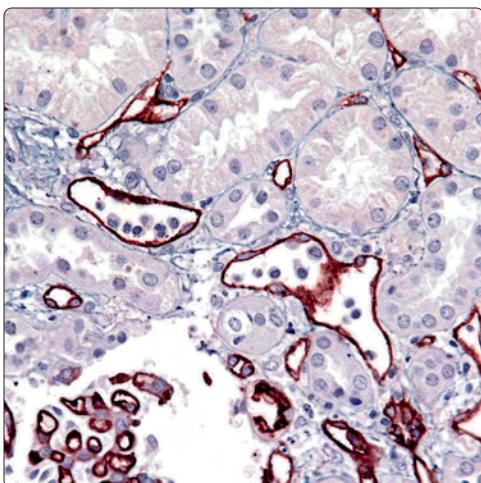
Neutrophils in Peritubular Capillaries



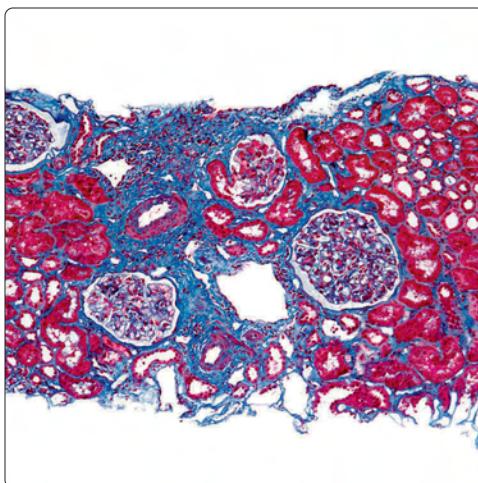
(Left) Interstitial granuloma with multinucleated giant cells is shown. Granulomatous interstitial nephritis has a broad differential, including infection (mycobacteria, adenovirus), sarcoidosis, Crohn disease, and drug allergy.

(Right) Neutrophils in peritubular capillaries (capillaritis) ↗ are a sign of acute antibody-mediated rejection. Neutrophils can be relatively inconspicuous.

Mononuclear Cells and C4d in Peritubular Capillaries



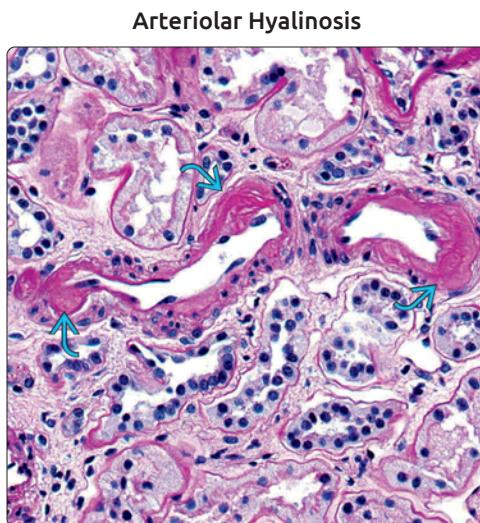
Focal Cortical Fibrosis



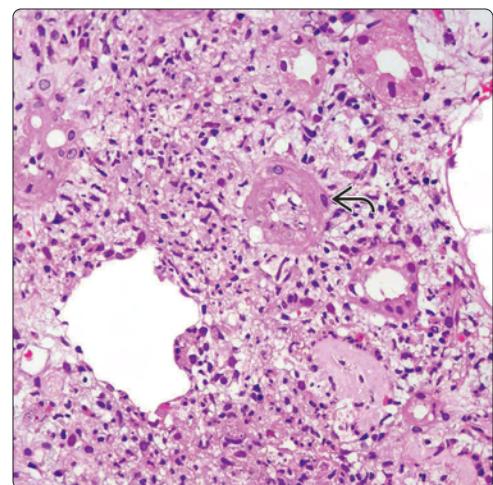
(Left) Intracapillary mononuclear cells and positive staining for C4d in peritubular capillaries are defining characteristics of chronic humoral rejection. (Right) Trichrome stain allows more accurate assessment of interstitial fibrosis; illustrated here is focal fibrosis that is typical of vascular disease, with loss of tubules and relative preservation of glomeruli.

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(Left) Arteriolar hyalinosis is PAS positive and may be focal, circumferential, or nodular . This case is a donor biopsy. Arteriolar hyalinosis is caused by hypertension, diabetes, aging, and calcineurin inhibitors. **(Right)** Leukocytoclastic vasculitis with nuclear dust and fibrinoid necrosis is evident in a small artery . Microscopic polyangiitis in a renal biopsy is associated with ANCA(+), cryoglobulinemia, and Henoch-Schönlein purpura.

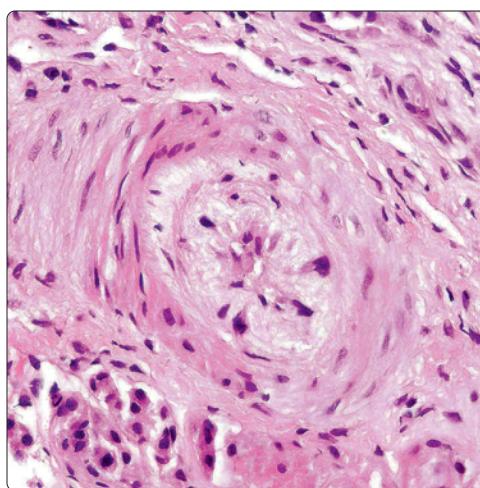


Leukocytoclastic Vasculitis

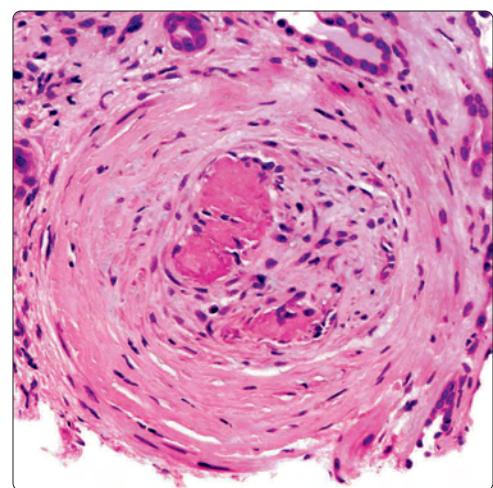


Mucoid Intimal Thickening in TMA

(Left) Mucoid intimal thickening appears as a loose, slightly basophilic accumulation of matrix in the intima, a sign of thrombotic microangiopathy (TMA). In this case, it was related to a factor H mutation. **(Right)** Organized thrombus in an arcuate-sized artery in a patient with TMA is shown.

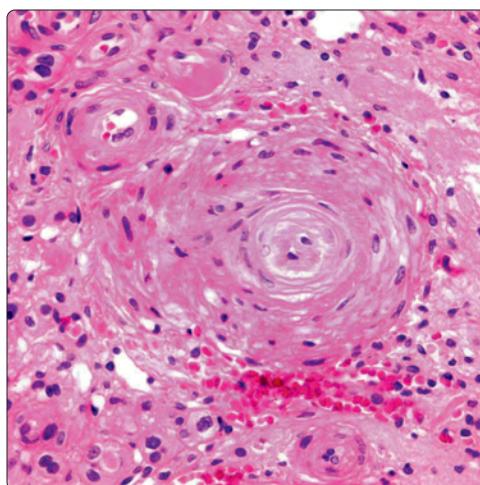


Organized Arterial Thrombus in TMA

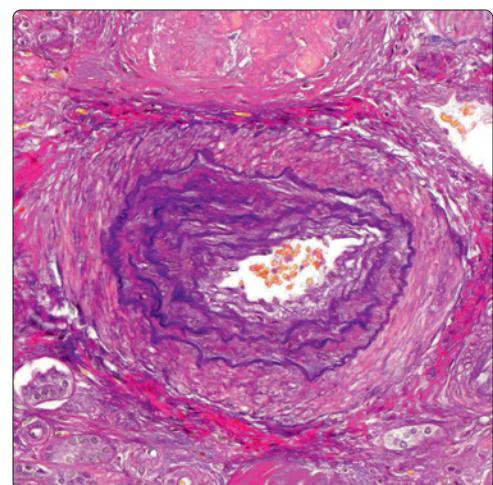


Onion Skin Thickening of Arteriole

(Left) Onion skin pattern of intimal thickening in a small artery in a patient with severe hypertension is shown. **(Right)** Elastic fiber stain highlights the fibroelastosis of the intima that occurs in longstanding hypertension.

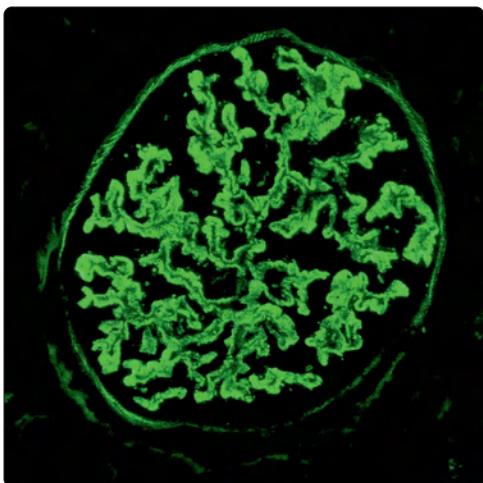


Fibroelastosis of Arterial Intima

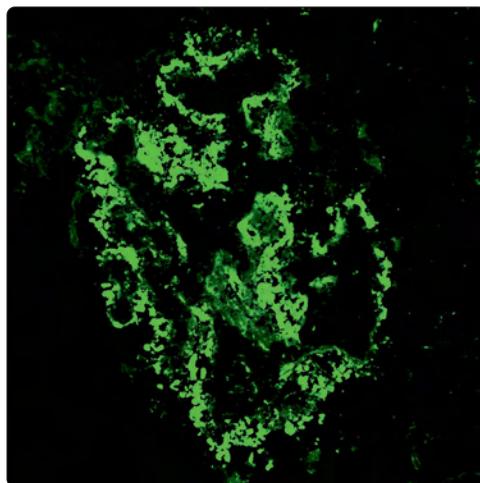


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Finely Granular GBM Deposits (IgG)

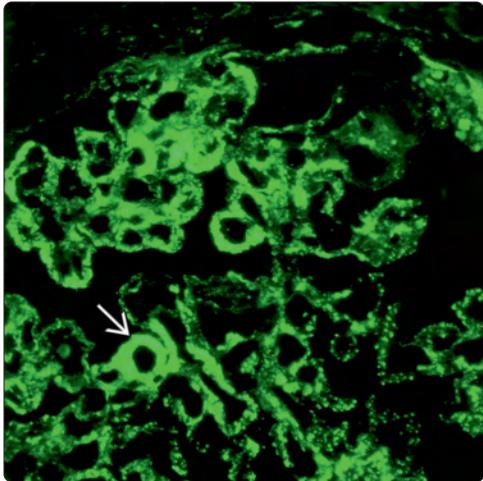


Coarse Granular GBM Deposits ("Humps") (IgG)

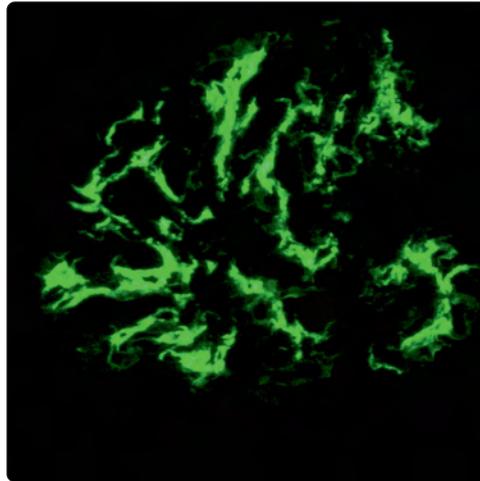


(Left) Fine, uniform, granular deposits all along the GBM are typical of subepithelial deposits in membranous glomerulonephritis, here stained for IgG. Some appear to be in the mesangium, but these may be tangential cuts of the GBM. (Right) Rounded granular deposits of IgG along the GBM are typical of the "humps" of post-infectious glomerulonephritis (GN), as in this case of post-streptococcal GN.

Broad Segmental GBM Deposits (IgG)

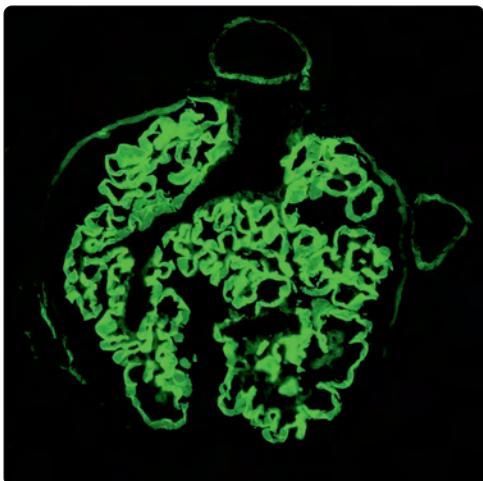


Mesangial Deposits

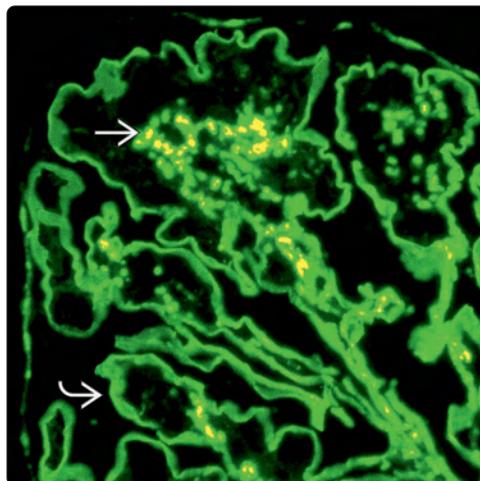


(Left) Broad, granular, and elongated deposits along the GBM (sometimes referred to as "wire loop" lesions) are typical of subendothelial deposits, as in this case of lupus nephritis. (Right) Classical mesangial deposition pattern in glomerulus resembles the branches of a tree, as in this IgA stain in IgA nephropathy.

Linear GBM Deposits



Coarse Granular Mesangial Deposits

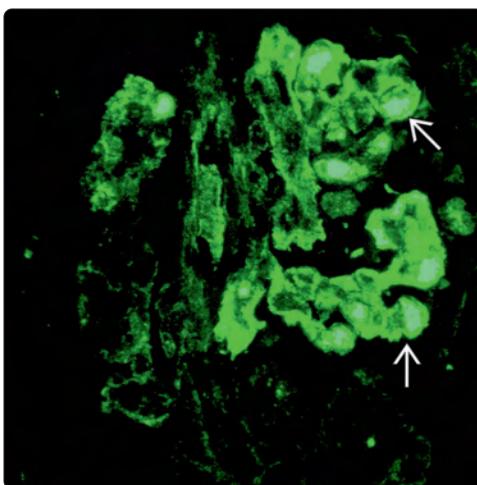


(Left) Linear IgG in the GBM is characteristic of anti-GBM disease, as shown in this case. Diabetes can also have prominent linear IgG, but in that case, albumin is similarly present. (Right) Dense deposit disease has a unique IF pattern. C3 is deposited in coarse, brightly staining granules in the mesangium, sometimes with a dark center. Linear GBM staining is also present.

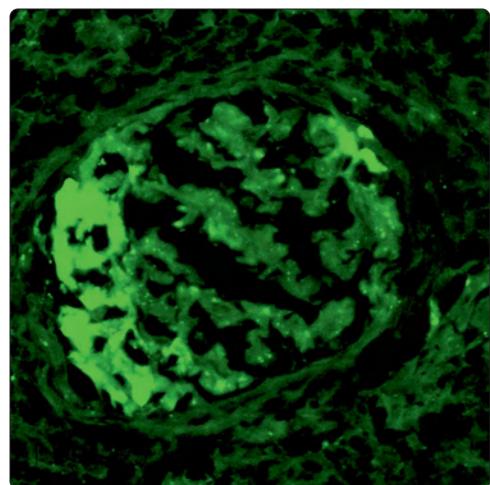
Introduction to Renal Pathology

(Left) Glomerular pseudothrombi (hyaline thrombi) of mixed cryoglobulinemia appear as rounded, brightly stained deposits in glomerular capillaries when stained for IgM. These are not fibrin thrombi but rather are precipitates of immune complexes. (Right) IgM and C3 commonly are present in segments of glomeruli that are sclerotic, as shown here in a case of FSGS stained for IgM.

Pseudothrombi

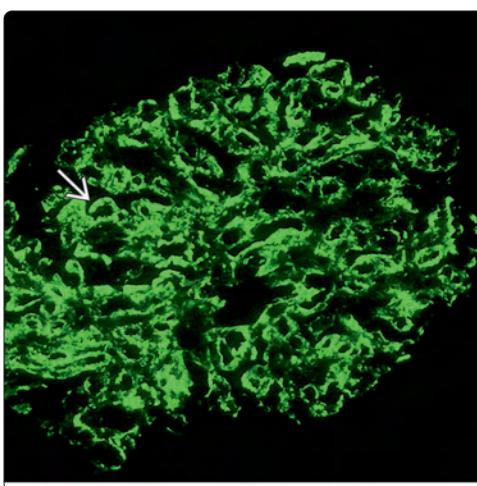


Segmental Glomerulosclerosis

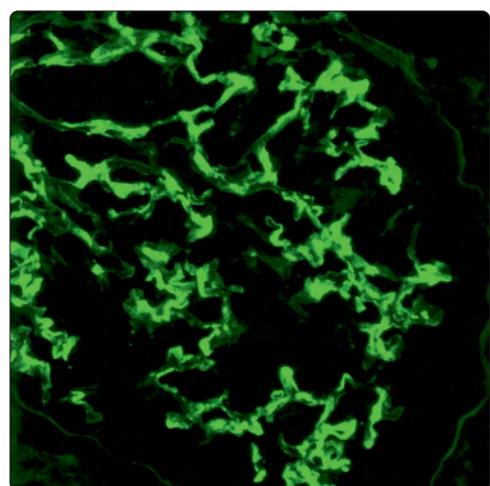


Coarse Granular GBM and Mesangial Deposits

(Left) Coarse granular C3 deposits in the mesangium and along the GBM are seen in diseases with mesangial and subendothelial deposits, as in this case of C3 glomerulopathy (or membranoproliferative glomerulonephritis, type I). (Right) Fibrillary GN has a distinctive pattern with deposits of IgG in the mesangium and segmentally along the GBM in a broad linear distribution.

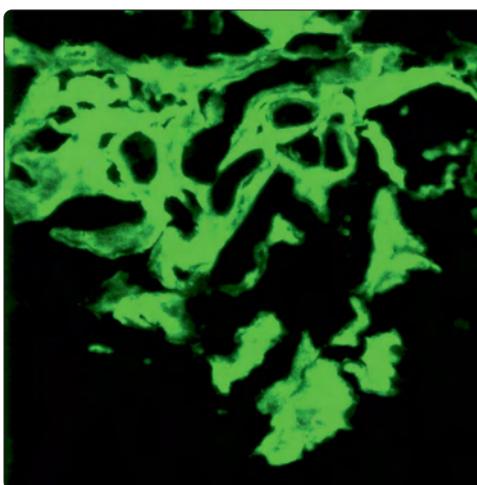


Broad Linear GBM Deposits

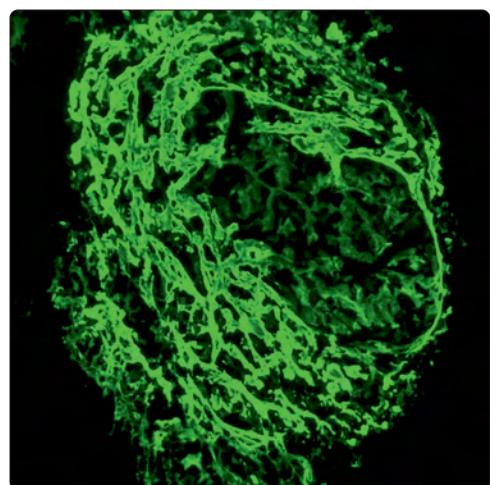


Broad Global Deposits (AA Protein)

(Left) Amyloid deposits in the glomeruli have broad, fairly homogeneous staining in the mesangium and GBM for the components of the amyloid (light chains, amyloid A protein, fibrinogen, etc.). This case is stained for amyloid A protein. (Right) Crescents typically have deposition of fibrin among the proliferating parietal epithelial cells. Activation of the clotting system in Bowman space is a general mechanism of formation of crescents, whatever the underlying glomerular disease.

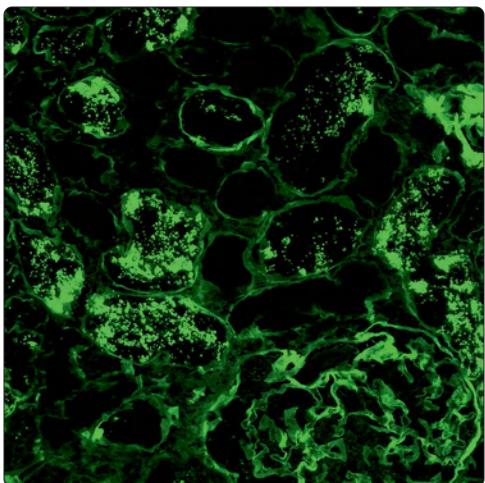


Fibrin in Crescent

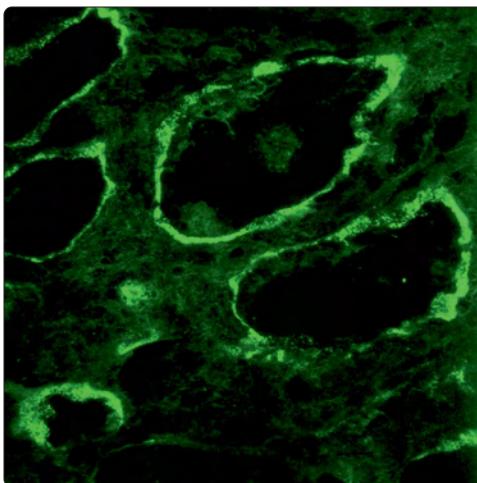


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Tubular Reabsorption Droplets

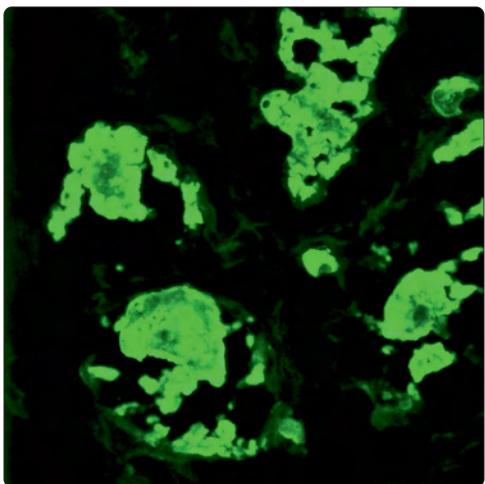


Granular TBM Deposits

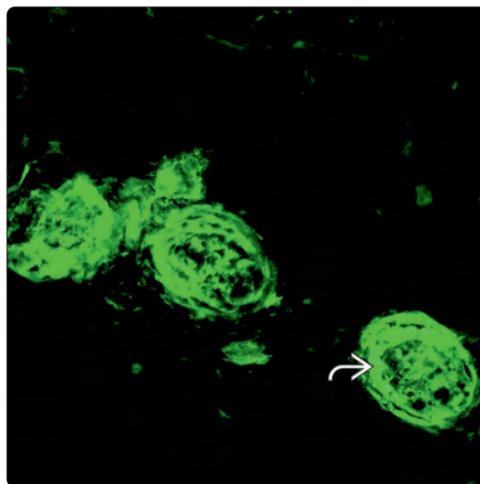


(Left) Tubular reabsorption droplets stain for albumin (as in this image) and other plasma proteins (IgG, C3, fibrinogen, etc.). This is an indication of glomerular proteinuria in this case of minimal change disease. (Right) Granular deposits of IgG along the TBM can be seen in lupus nephritis and occasionally in other diseases, such as polyoma infections. In contrast, C3 deposits segmentally in the TBM are common and should not be taken as evidence of immune complex deposition.

Myeloma Casts

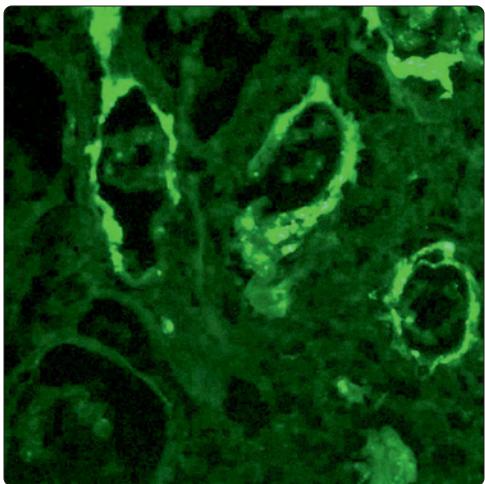


Fibrin in Arteriole in TMA

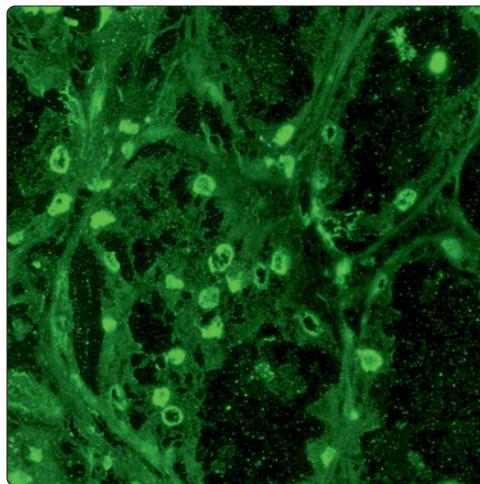


(Left) Light chain staining is essential for the diagnosis of monoclonal gammopathies. In this patient with myeloma cast nephropathy, kappa, but not lambda, was detected in the casts in the tubules. (Right) Fibrin is detected in the arterioles in this case of thrombotic microangiopathy due to Avastin therapy. Fibrin also permeates the wall, a reflection of fibrinoid necrosis of the vessels.

Broad Deposits in TBM



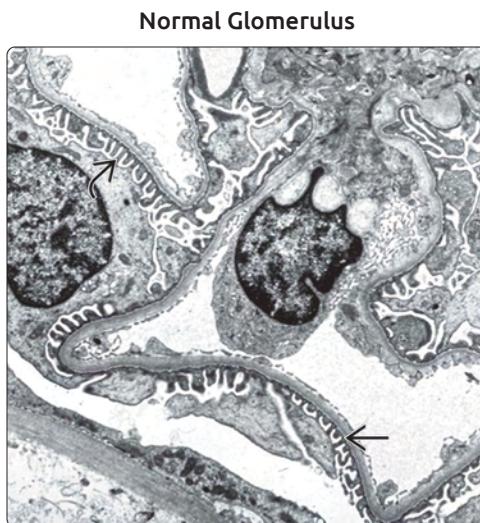
Tissue ANA



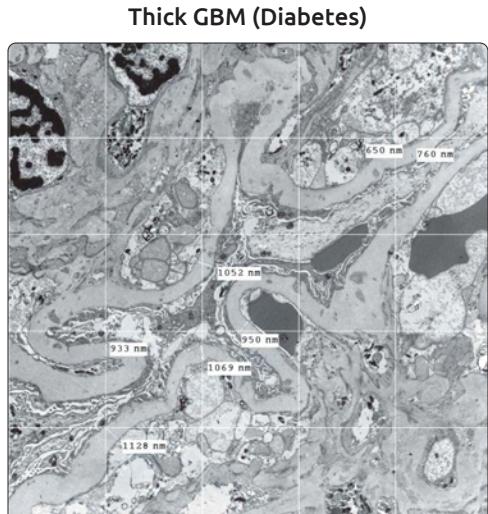
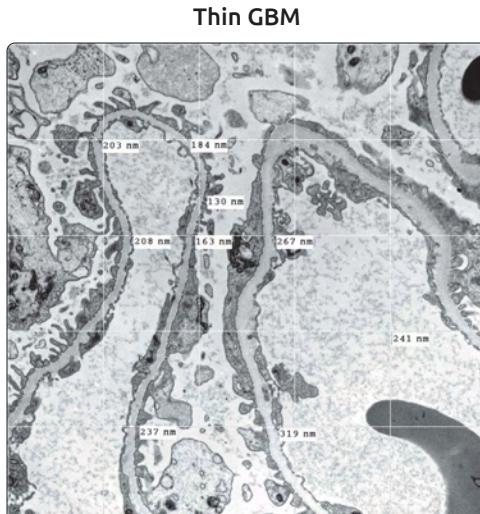
(Left) C3 is not uncommonly detected in the tubular basement membrane, as in this case of calcineurin inhibitor toxicity in an allograft. Tubular cells activate the alternative complement pathway, and this is probably a manifestation of tubular injury. (Right) Lupus biopsies sometimes show antinuclear antibody (ANA) in tubular cells, here stained with anti-IgM. These are probably due to plasma ANA artificially depositing during the IF staining procedure in permeabilized cells.

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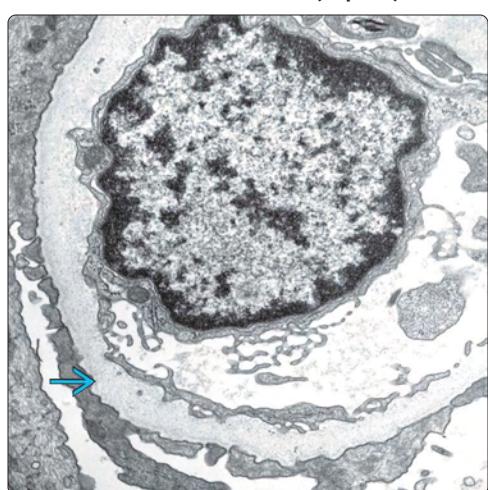
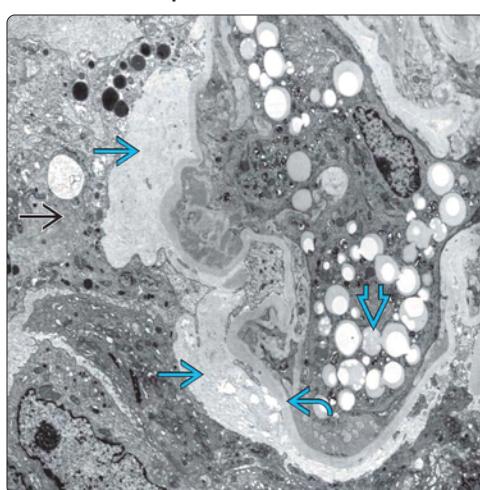
(Left) EM shows normal glomerulus with podocyte foot processes and a normal GBM . The normal GBM is thicker than a typical foot process. **(Right)** Widespread effacement of foot processes is a feature of minimal change disease and, to some degree, of other diseases with glomerular proteinuria.



(Left) Thin basement membrane disease has thin but otherwise normal GBM. The measurements are taken using a grid overlay. The distance is measured where the grid crosses the GBM, and the harmonic mean is calculated. Normal mean \pm 2 s.d. is 373 ± 84 nm for men, 326 ± 90 nm for women. **(Right)** Diabetes has a uniformly thickened but otherwise normal GBM. The thickness has been measured using a grid overlay. Normal mean \pm 2 s.d. is 373 ± 84 nm for men, 326 ± 90 nm for women.

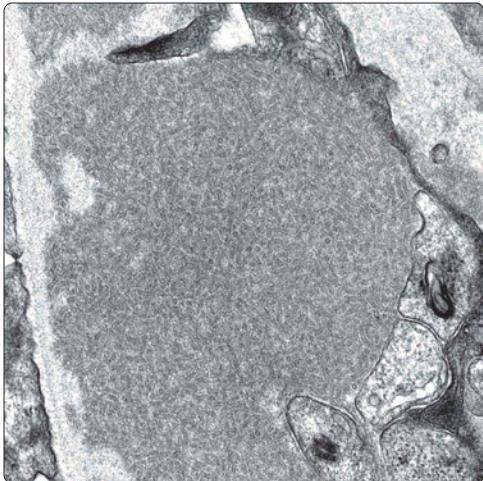


(Left) Podocyte injury is sometimes reflected by new subepithelial layers of basement membrane matrix between the podocyte and original GBM . This is a characteristic feature of collapsing glomerulopathy. Intracapillary endothelial cells or macrophages contain lipid (foam cells) . **(Right)** Fine reticulated lamination of a thickened GBM with scalloping of the subepithelial surface is a characteristic feature of Alport syndrome.

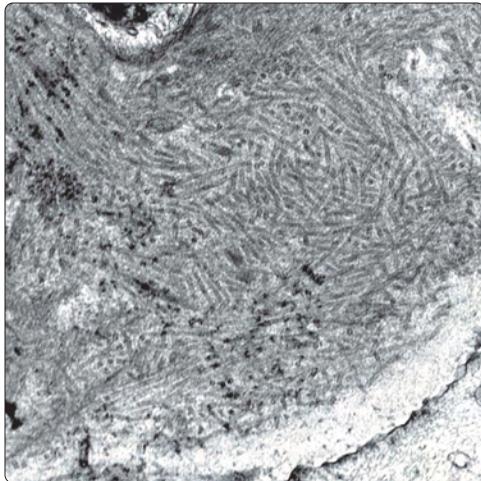


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Microtubular Deposits (Cryoglobulinemia)



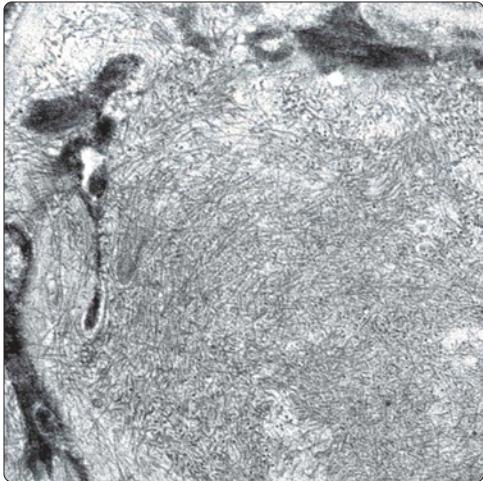
Microtubular Deposits (Immunotactoid Glomerulopathy)



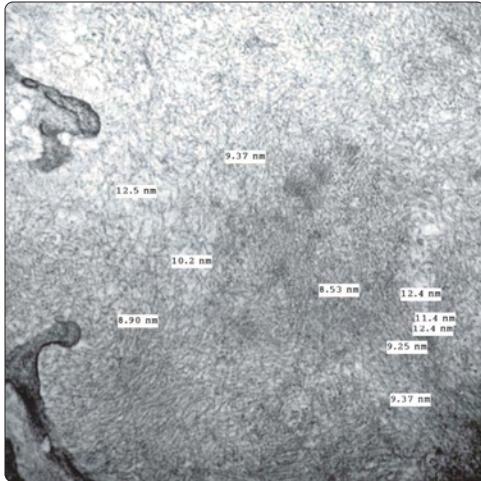
(Left) EM shows an organized mesangial deposit in a patient with mixed cryoglobulinemia.

(Right) Immunotactoid glomerulopathy has tubular deposits typically > 25 nm in diameter; in this case they measured ~ 35 nm.

Fibrillar Deposits (Fibrillary GN)



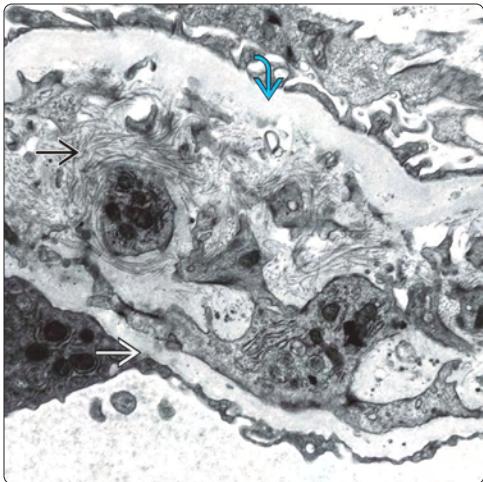
Amyloid Fibrils



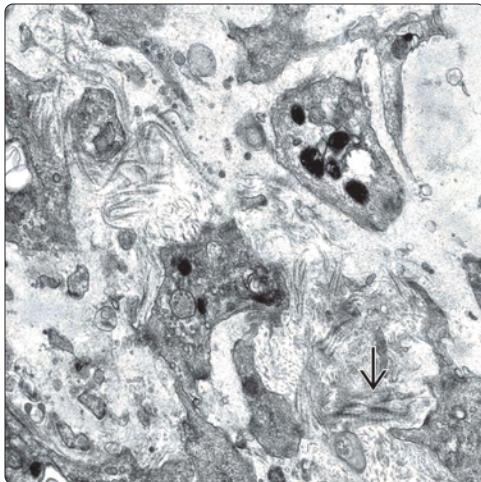
(Left) Fibrillary glomerulonephritis has nonperiodic fibrils that are typically 10-20 nm in diameter; in this case they were ~ 13 nm in diameter.

(Right) Amyloid fibrils are typically 8-12 nm in diameter without periodicity. These averaged ~ 10 nm. The appearance is similar to fibrillary glomerulonephritis, and a Congo red stain is necessary to confirm their identity.

Type III Collagen Deposits



Fibrillar Collagen in Mesangium

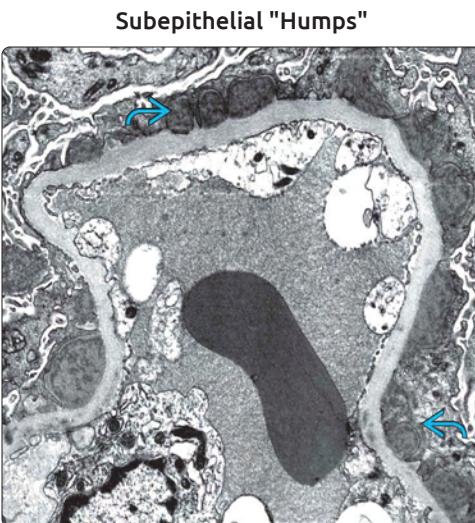


(Left) Type III collagen glomerulopathy (collagenofibrotic glomerulopathy) has deposits of fibrillar collagen with a periodicity of 62 nm. The GBM is duplicated; original and new subendothelial layers are indicated.

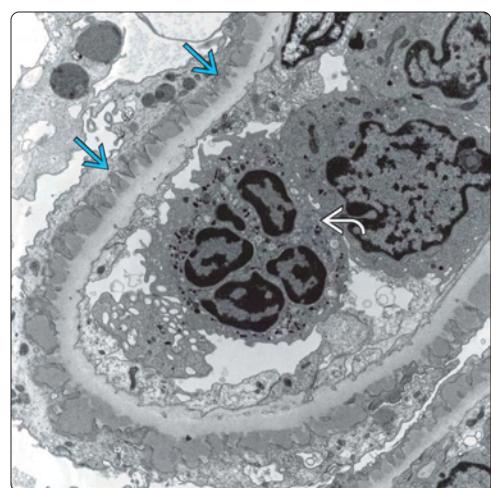
(Right) Fibrillar collagen is sometimes detected in the mesangium as part of a pathologic process of sclerosis. Here the fibrils are seen in a case of IgA nephropathy. This should not be confused with type III collagen glomerulopathy.

Introduction to Renal Pathology

(Left) EM of a glomerulus from a patient with poststreptococcal GN shows the characteristic humps located along the GBM in the subepithelial space (blue arrow). These do not elicit a GBM response of spikes in contrast to membranous GN. (Right) A glomerular capillary has subepithelial deposits with spikes of GBM between them (black arrow). This is a typical feature of membranous GN in contrast to postinfectious GN. The neutrophil (black arrowhead) in the capillary may be a sign of renal vein thrombosis.

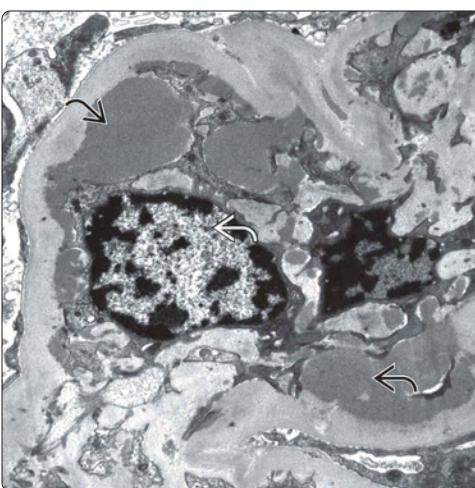


Subepithelial Deposits and GBM Spikes

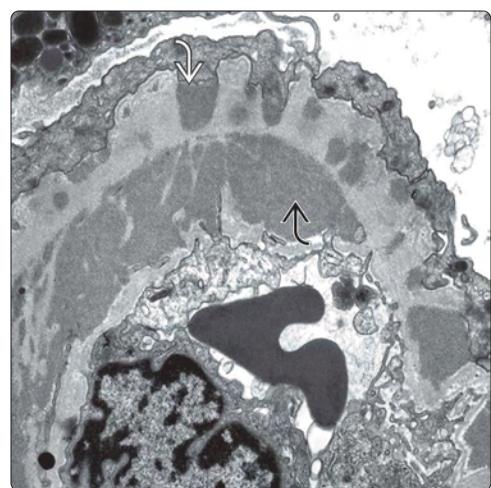


Mesangial Deposits

(Left) Mesangial deposits (black arrow) in IgA nephropathy typically hug the mesangial cells (black arrowhead) and are amorphous. (Right) Subendothelial deposits (black arrow) are present in many glomerular diseases and usually elicit a new layer of GBM over their surface, as in this case from a patient with lupus nephritis. Subepithelial deposits are also present and penetrate the GBM (black arrowhead).



Subendothelial and Subepithelial Deposits

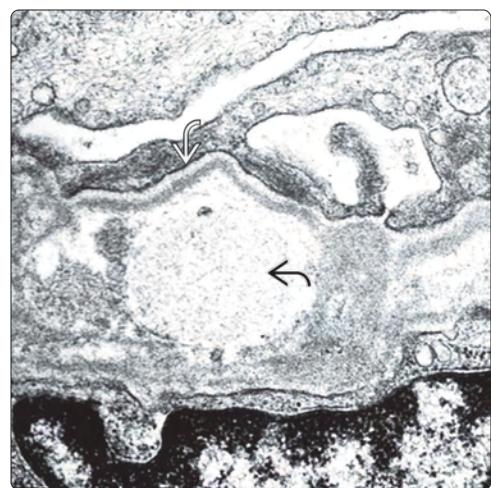


Partial Reabsorption of Deposits

(Left) Immune complex deposits can be reabsorbed or dissolved with time, in which case they begin to lose their electron density (blue arrow), as in this case of membranous GN. (Right) The reabsorption of deposits occurs with time in most diseases; here, a subepithelial deposit in membranous GN is almost completely removed (black arrow) and resurfaced with a new layer of subepithelial GBM (black arrowhead).

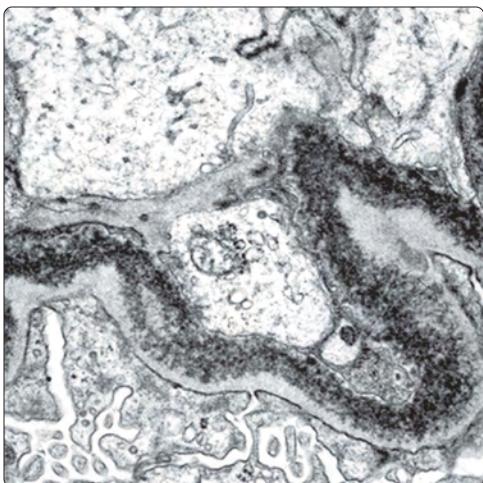


Reabsorbed Deposit



Introduction to Renal Pathology

Granular GBM Dense Deposits

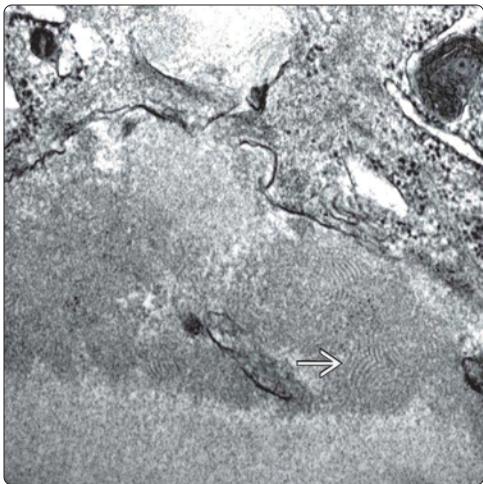


Dense Deposit Disease

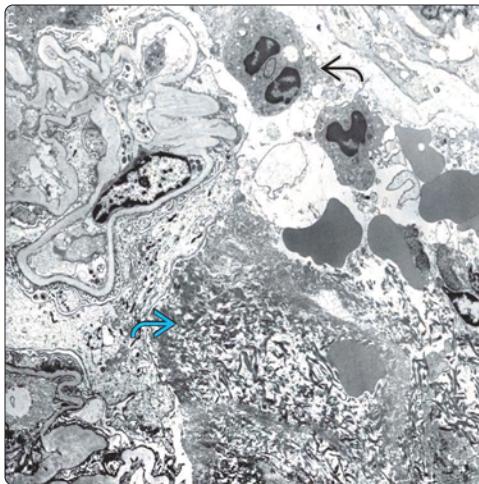


(Left) Granular dense deposits in the GBM, mesangium, TBM, and vascular basement membrane characterize systemic light chain deposition, here shown in a glomerular capillary in a patient with κ light chain deposition by IF. (Right) The densest deposit in renal pathology by EM is that in dense deposit disease (DDD), here shown replacing the GBM in a glomerular capillary in a child with DDD. The deposits contain C3 and factor H.

Fingerprint Deposits

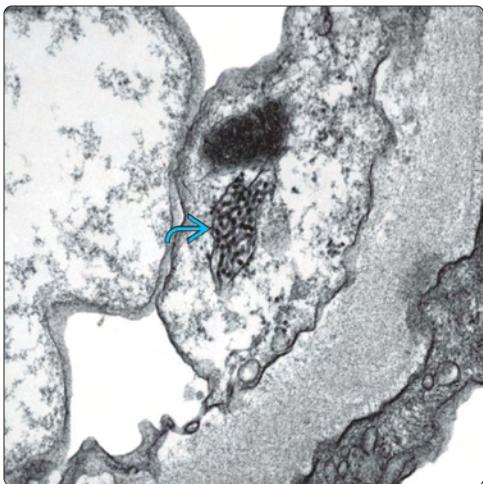


Fibrin in Bowman Space

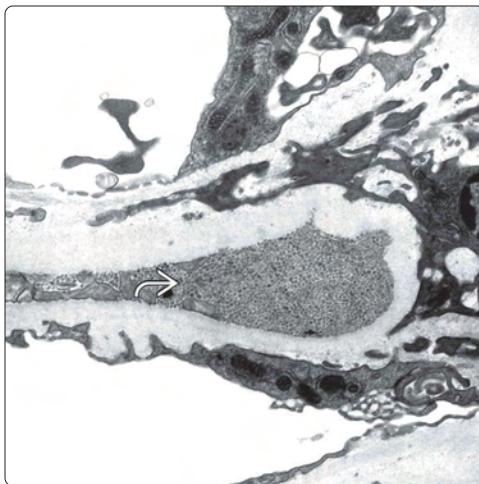


(Left) Deposits with periodicity are sometimes evident in lupus nephritis, where they have been called "Churg's thumbprints" ↗ for the renal pathologist who 1st described them. (Right) Fibrin by EM appears denser than the usual immune complex deposit and has a fibrillar tactoid pattern; sometimes the 22 nm periodicity is evident. Shown here are fibrin ↗ and neutrophils ↗ in Bowman space in a patient with ANCA-related GN and crescents.

Tubuloreticular Structure



Particulate Subepithelial Deposit



(Left) Once thought to be a virus, this intracellular tubular aggregate in a glomerular endothelial cell is known as a "tubuloreticular structure" ↗. This is a cellular response to interferons and is most often found in lupus and in patients treated with interferons. (Right) A particulate subepithelial deposit ↗ of unknown nature is sometimes found without clear explanation. This is almost certainly not a virus; theories include lipoproteins or components of the podocyte.