Non-neoplastic Kidney Pathology for the General Surgical Pathologist

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Learning Objectives

- To appreciate the most common pathologic findings in the non-neoplastic component of a nephrectomy or partial nephrectomy specimen (a component which is part of the CAP kidney tumor template), and to understand the potential clinical significance of these findings.

- To understand the role of pathology in the workup of the donor kidney for transplantation, and to appreciate common findings at frozen section, and the clinical significance of these findings.

- To appreciate common pathologic findings in the autopsy kidney, and to be able to differentiate between acute tubular injury and tubular autolytic artifact.

Tumor Nephrectomy Specimens

- Renal cell carcinoma:
  - 74,000 new cases per year in the US currently
  - SEER Registry (2005-11)
    - Localized: 65% (most stage 1)
  - Steady decrease in tumor size at presentation likely due to incidental detection on CT/MRI (stage migration)
  - 5 year survival has greatly improved over 50 years, especially good for stage 1 (95-100%)
- We are seeing more nephrectomy/partial nephrectomy specimens!

End stage renal disease

- Despite dialysis, mortality from ESRD is high
- Medicare patients >65 yo, on dialysis:
  - Substantially higher mortality than similar patients with cancer, diabetes, cardiovascular disease
- Kidney cancer and chronic kidney disease share risk factors (hypertension, diabetes, smoking…)
  - 25% of patients have CKD → risk for ESRD → risk of death
- Implications for the importance of the assessment of the non-neoplastic component of the kidney:

- In some patients the medical kidney disease may be the most consequential finding…may allow earlier intervention/preventive measures

Pathology assessment of non-neoplastic kidney

- 1. Diagnosis of specific pathologic entities
  - Bijol (2006): pathologic abnormalities in 60% of tumor nephrectomies
    - Mostly **vascular** sclerosing disease with parenchymal scarring, **diabetic** renal disease
    - Salvatore (2013) found similar prevalence
  - Henriksen (2007): 24/246 tumor nephrectomies had non-neoplastic disease
    - Mostly **diabetic** renal disease and **vascular** pathology (including thrombotic microangiopathy, atheroembolism)
    - **88% of these diagnoses were initially missed!**

Pathology assessment of non-neoplastic kidney

Spectrum of findings:

- Hypertensive kidney disease (30%)
- Diabetic kidney disease (20%)
- Thrombotic microangiopathy
- Focal segmental glomerulosclerosis
- IgA nephropathy
- Amyloidosis
- Etc.

Pathology assessment of non-neoplastic kidney

- 2. Help predict risk of progressive renal failure
  - >20% Global glomerulosclerosis or advanced diffuse diabetic glomerulosclerosis predict significant decline in kidney function at six months Bijol (2006)
  - For each 10% increase in glomerulosclerosis, estimated GFR decreased by 9% from baseline Gautam (2010)
- →NB implications for preventive measures

Progression of kidney disease

- Concept of structural and functional adaptations to loss of kidney mass
- Once enough damage has been done, kidney will progress to failure even if the initial disease is no longer active – a final common pathway to chronic injury
- Kidney injures itself trying to compensate
- Nephron loss→hyperfiltration of remaining nephrons→segmental/global glomerulosclerosis
- Secondary focal segmental glomerulosclerosis
- Particular issue for neprectomy is patient with CKD

- Motivates: nephron sparing surgery, ablation etc (remember 25% with RCC already have CKD)

CAP Cancer protocols: renal cancer, and ureter and renal pelvis cancers

Pathologic Findings in Nonneoplastic Kidney (select all that apply)

___ Insufficient tissue
___ None identified
___ Glomerular disease (specify type): _____
___ Tubulointerstitial disease (specify type): _____
___ Vascular disease (specify type): _____
___ Other (specify): _____

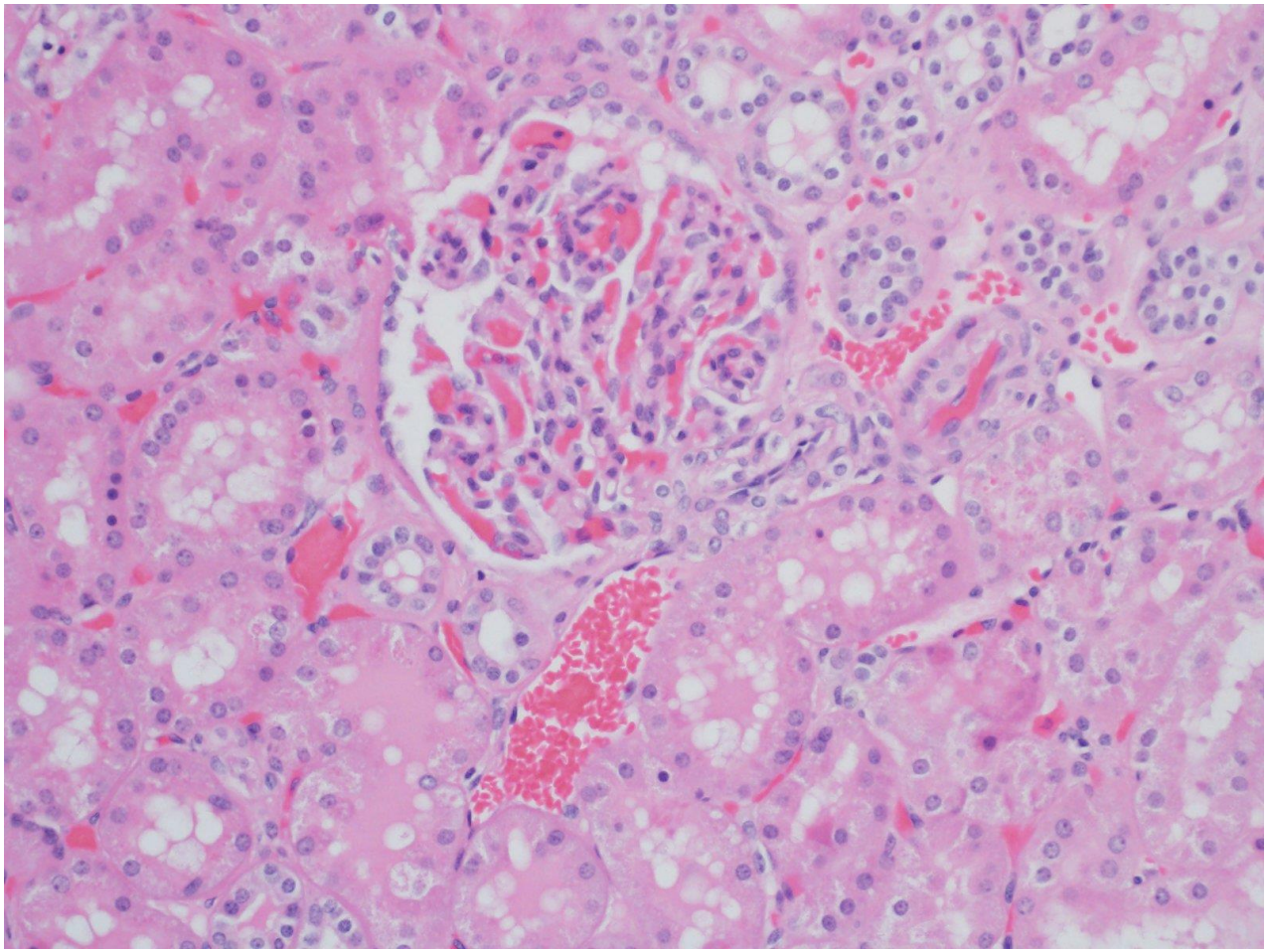
Quick Tour of Renal Pathology!

- Kidney pathology is esoteric
- Terminologically difficult
- Various special stains used routinely
- Specific modalities (IF, EM) used routinely
- Clinical-pathologic correlation is very important

But remember:

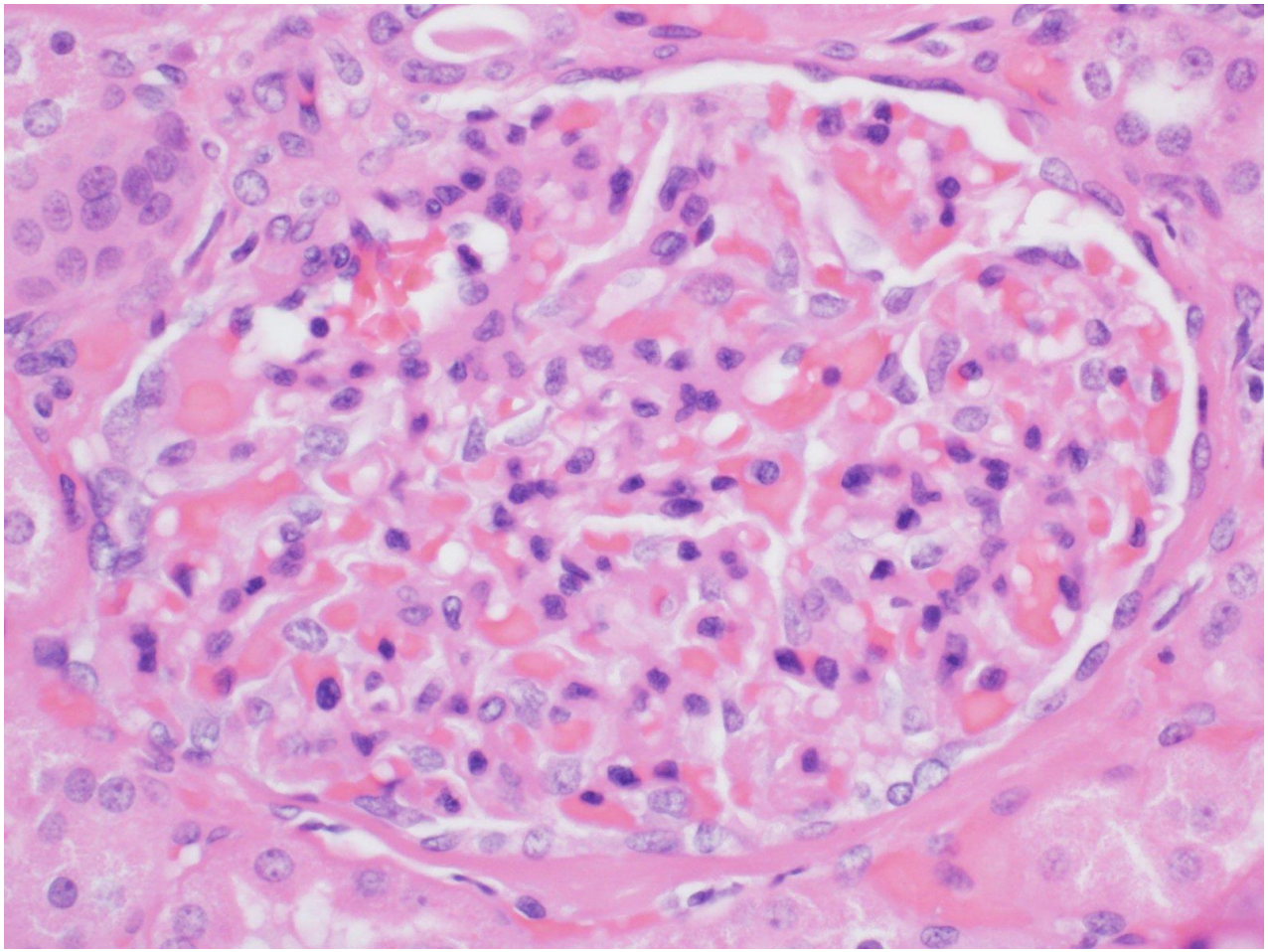
- Common things are common (esp. HTN, DM)
- In this session I try to approach from the H&E (maybe PAS…) vantage point
- Cover some of the most common patterns

Normal Kidney

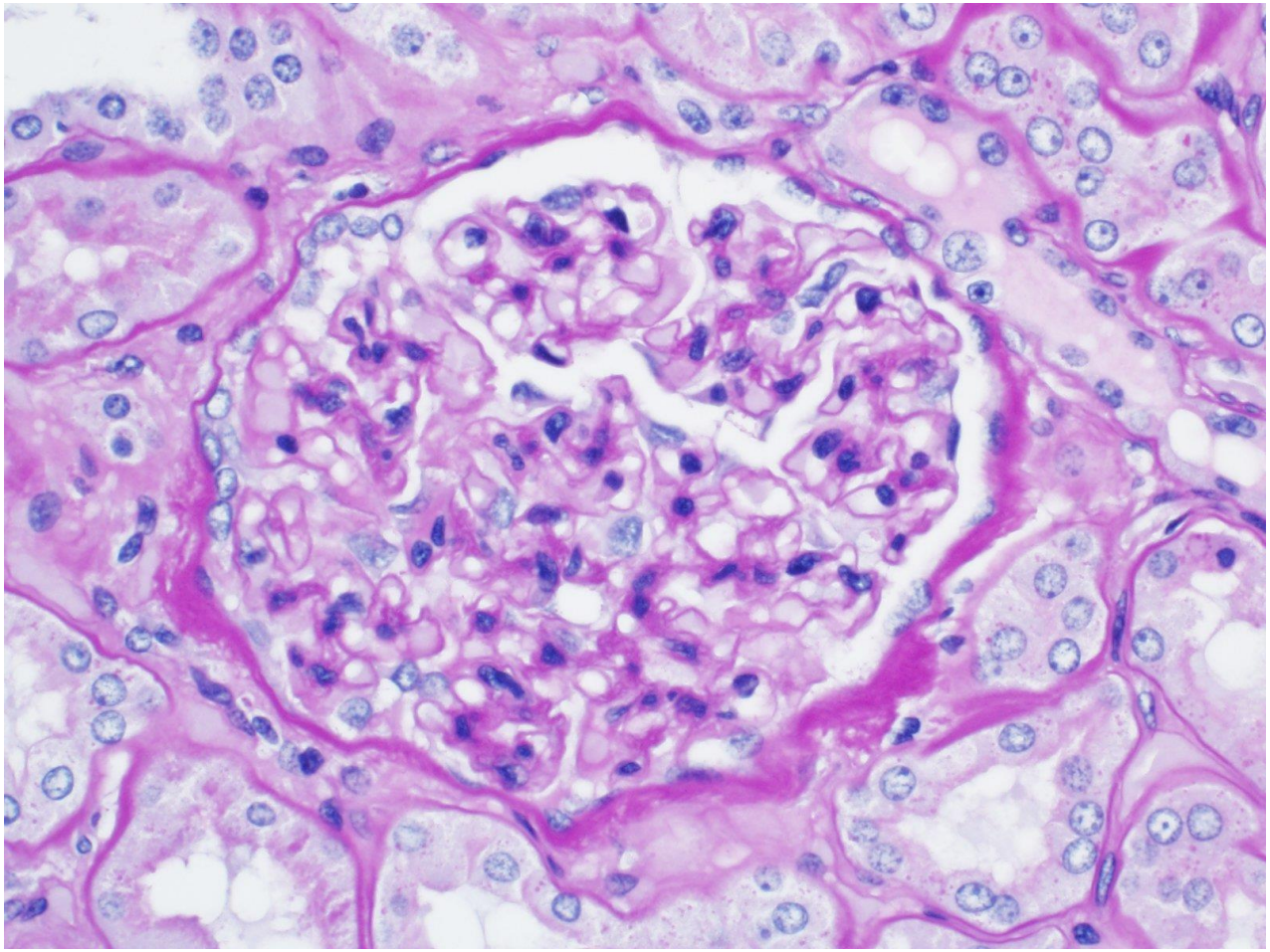


Four compartments: glomeruli, tubules, interstitium, vessels

Normal Kidney (H+E)



Normal Kidney (PAS)



The most helpful stain for assessing glomerular basement membranes and mesangium (stains glycoproteins particularly well)

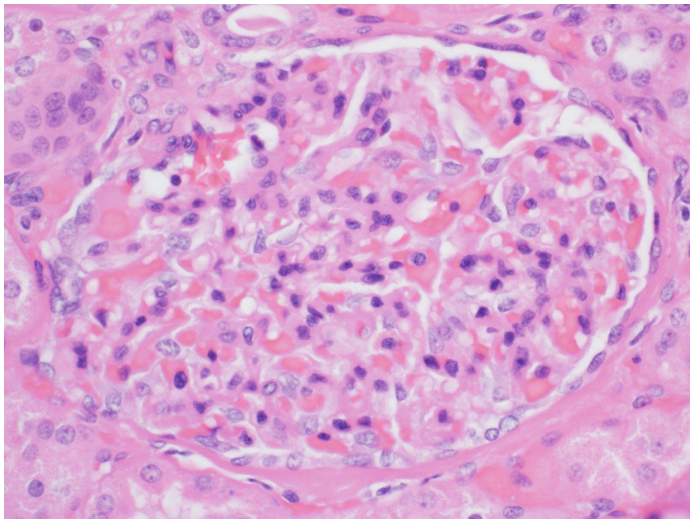
Terminology

Glomerular:

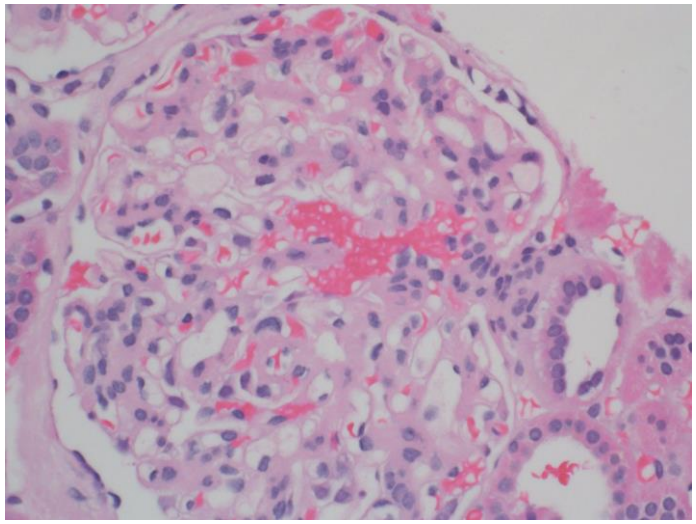
- Segmental, Global: @ glomerulus level
- Focal, Diffuse: @ biopsy level

- Endocapillary proliferation: glomerular capillary loops filled with cells
- Mesangial proliferation: too many cells in the little mesangial areas (>3 cells on a nice section)
- Extracapillary proliferation: Crescent formation

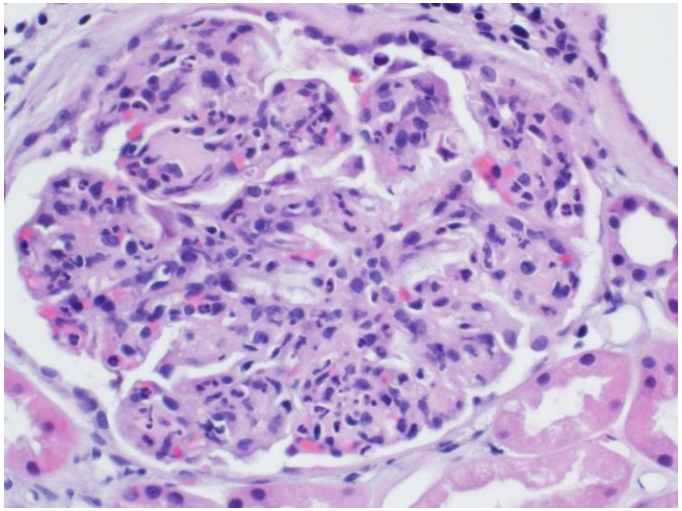
Glomerular Proliferative Patterns



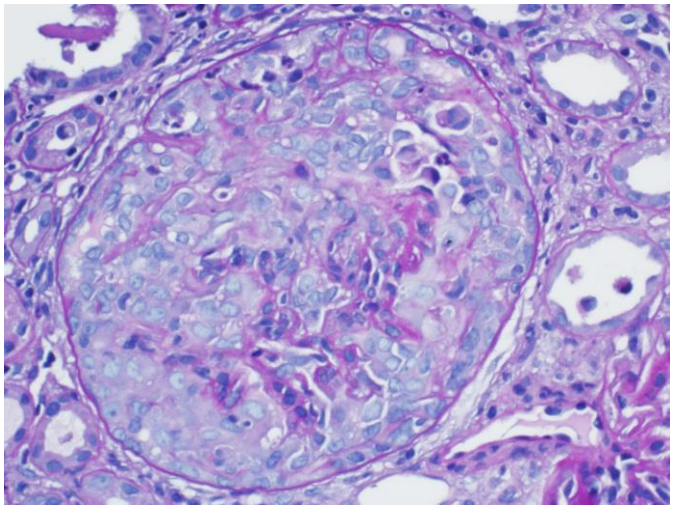
Normal



Mesangial Proliferation

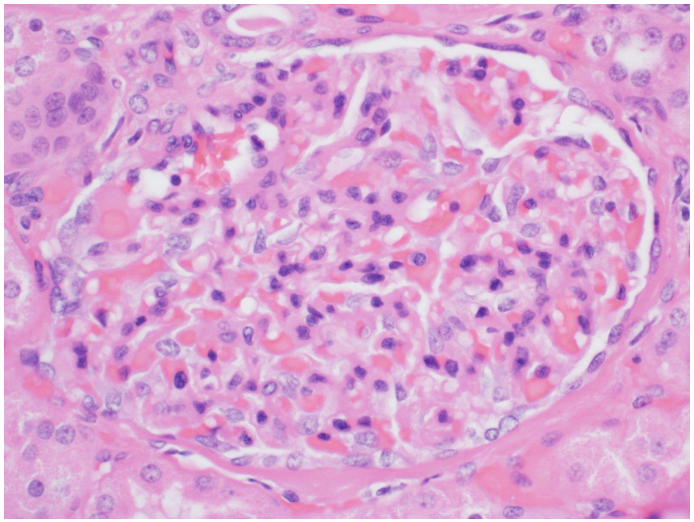


Endocapillary Proliferation



Extracapillary Proliferation / Crescent

Glomerular Sclerosing Patterns



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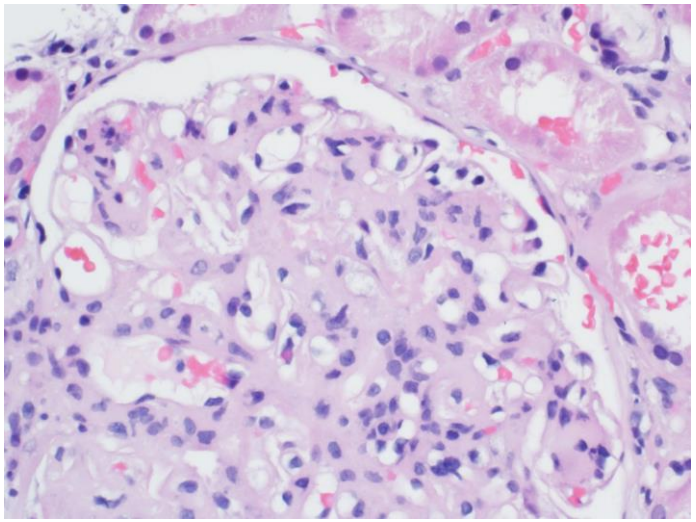
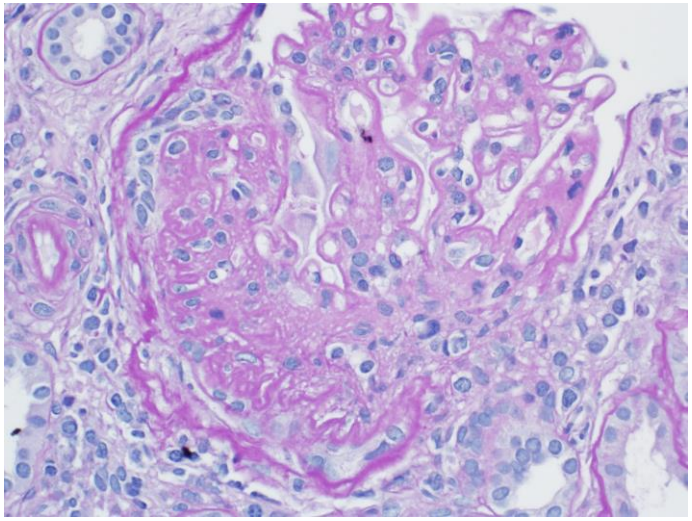
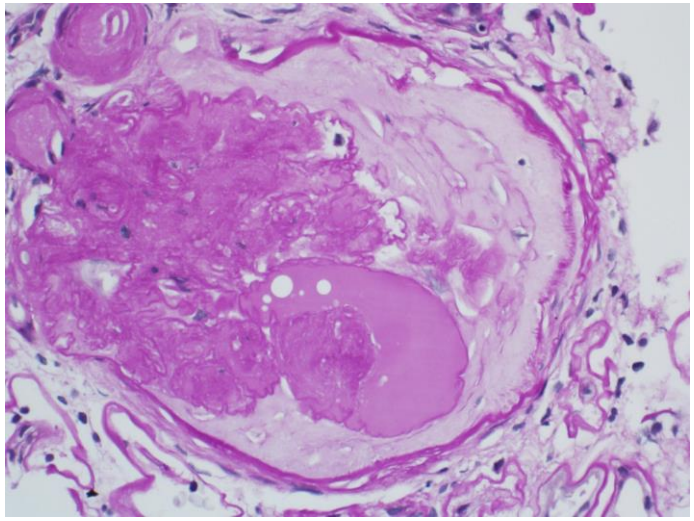


Diffuse mesangial sclerosis

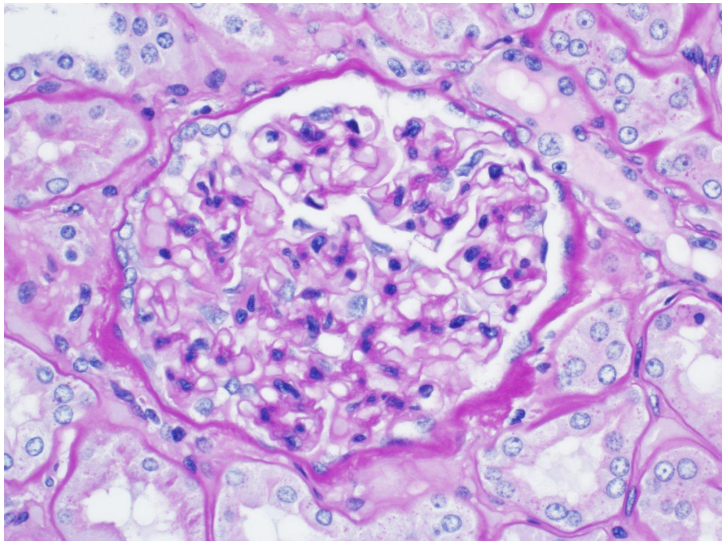


Segmental sclerosis



Global sclerosis

Thickened Glomerular Basement Membranes



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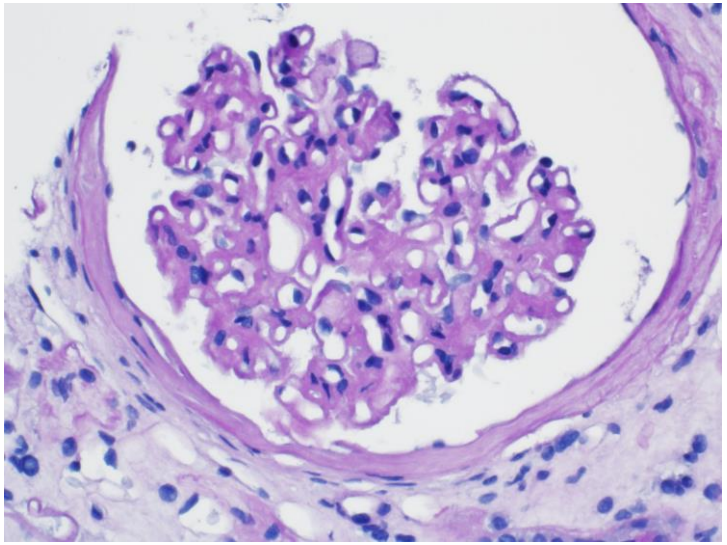
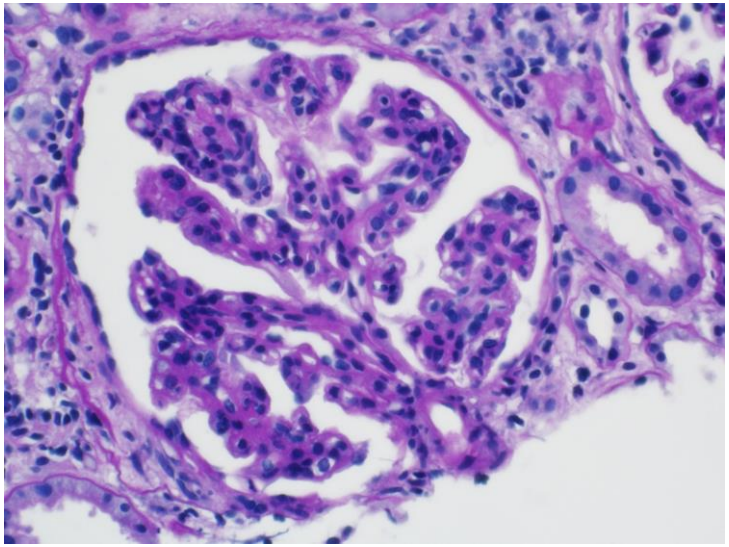


Membranous nephropathy

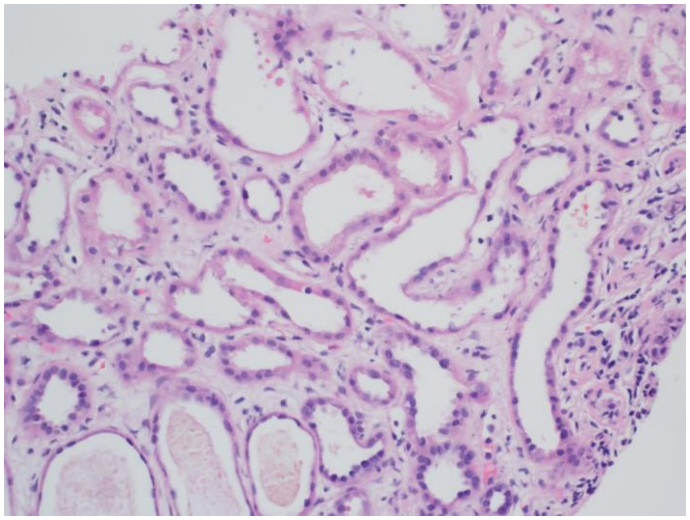


Membranoproliferative GN

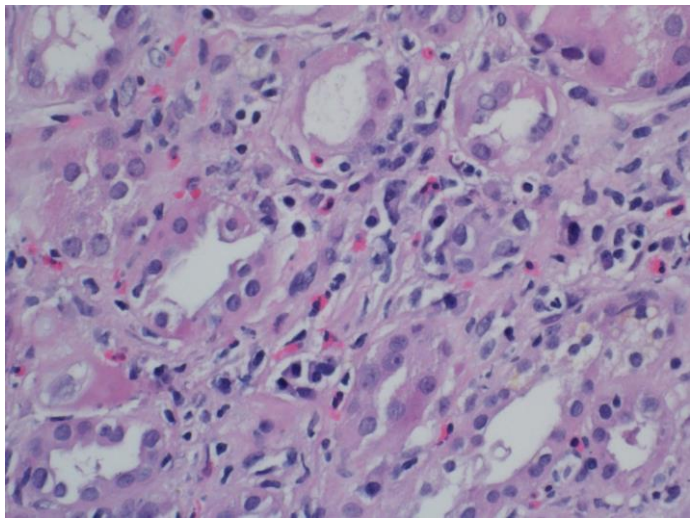
Other Causes include:

Advanced Diabetic glomerulosclerosis
Amyloidosis
Chronic thrombotic microangiopathy

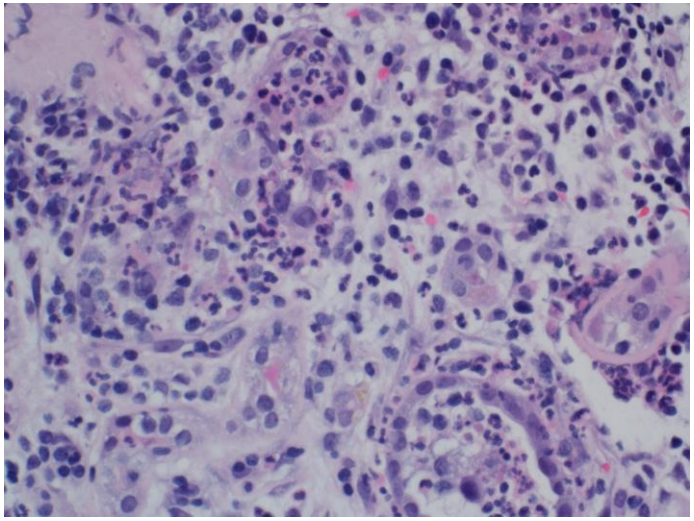
Tubulo-interstitial patterns of injury



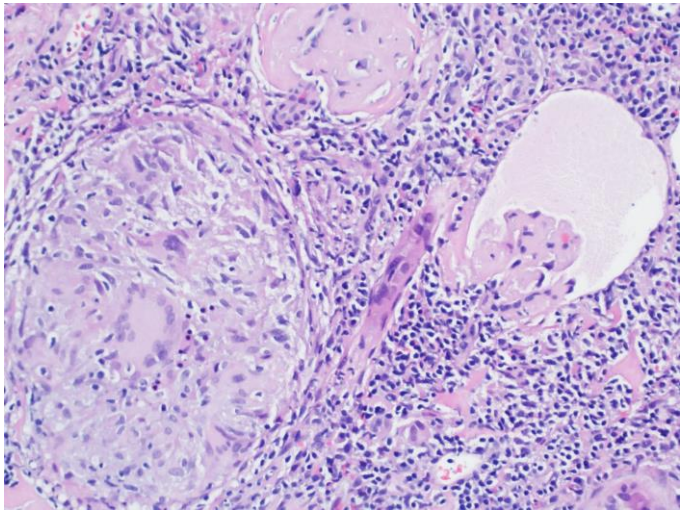
Acute Tubular Injury



Allergic Interstitial Nephritis (Eosinophils)

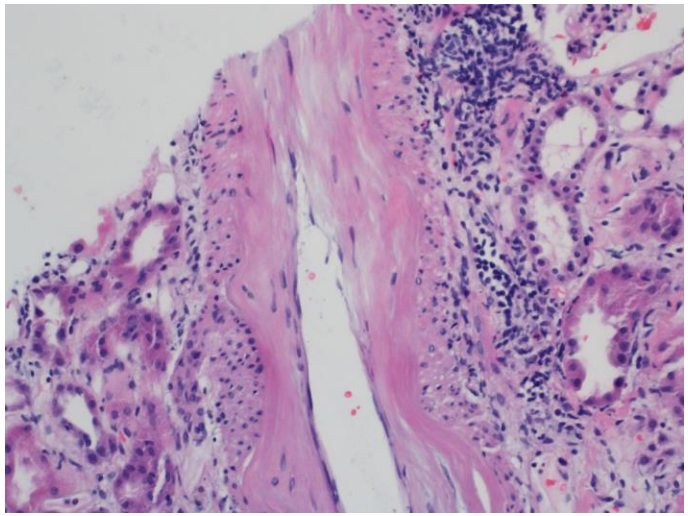


Acute pyelonephritis (neutrophils)

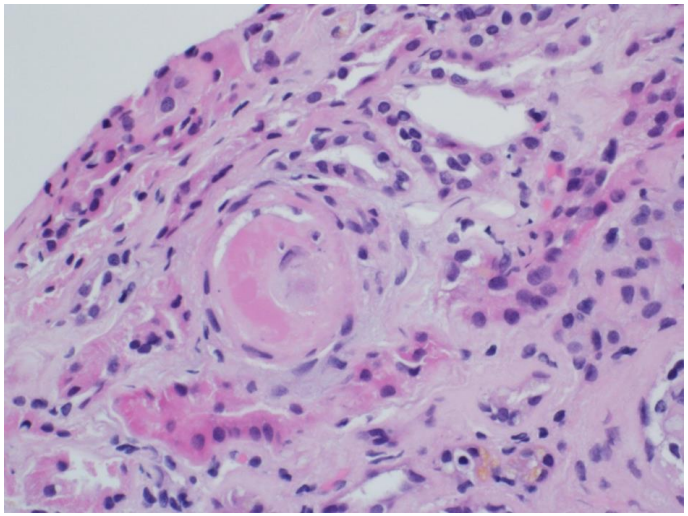


Granulomatous Interstitial Nephritis

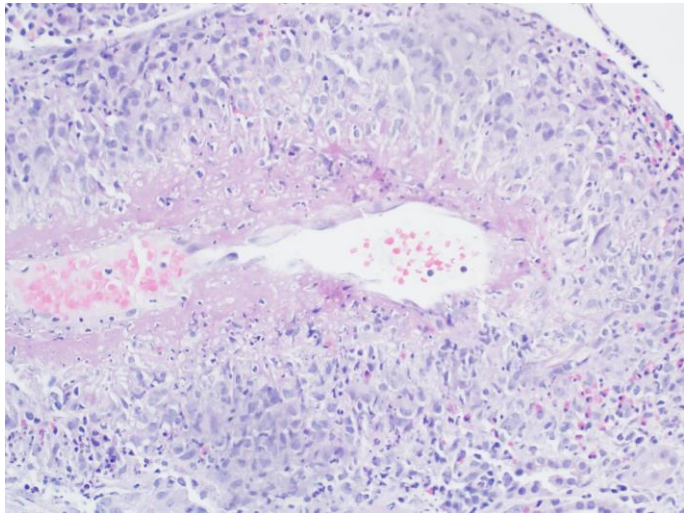
Vascular patterns of injury



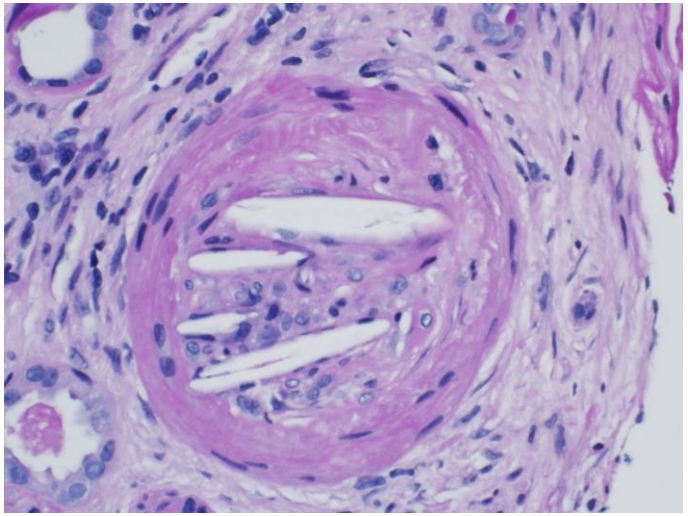
Vascular sclerosis



Thrombus

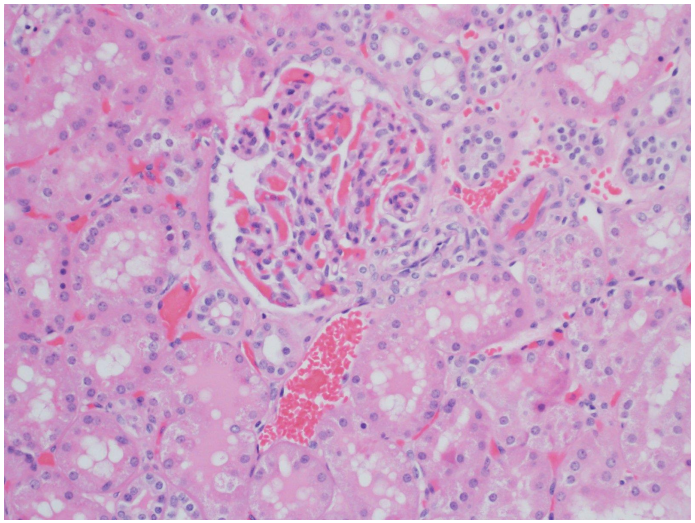


Vasculitis

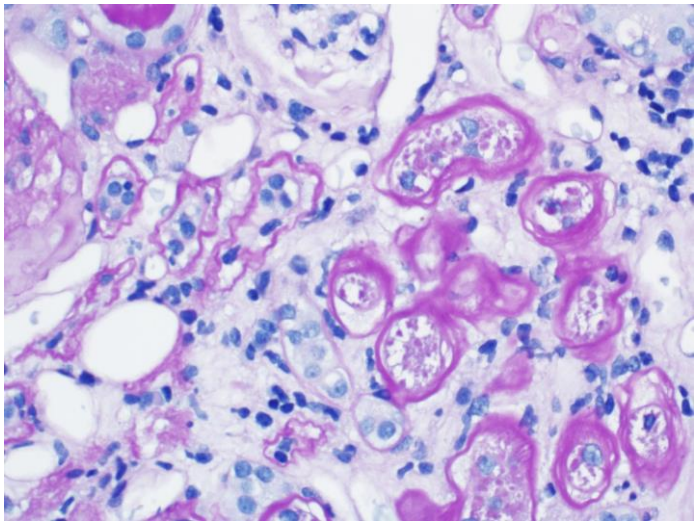


Atheroembolism

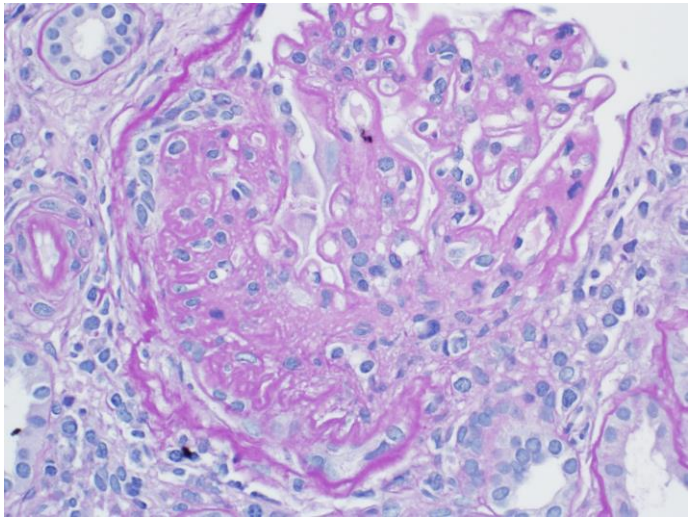
Chronic Parenchymal Damage



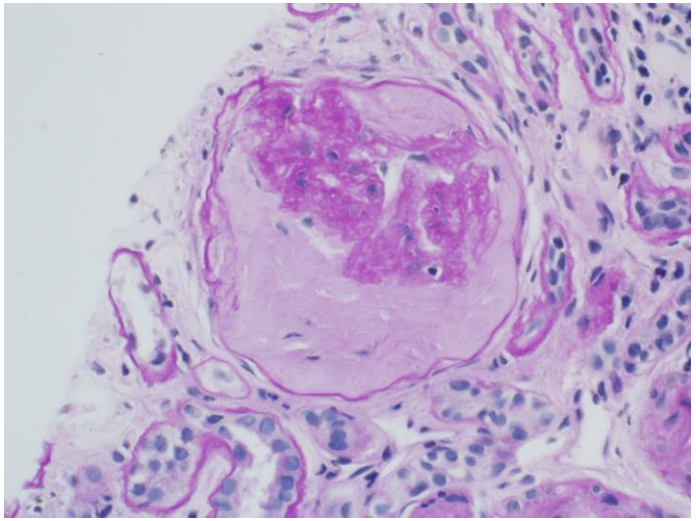
Normal kidney cortex



Interstitial fibrosis and tubular atrophy

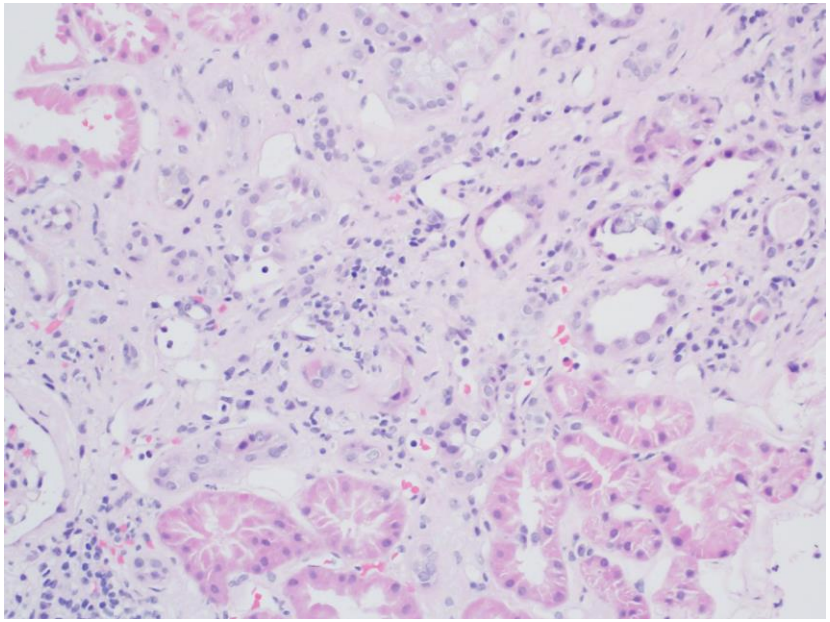
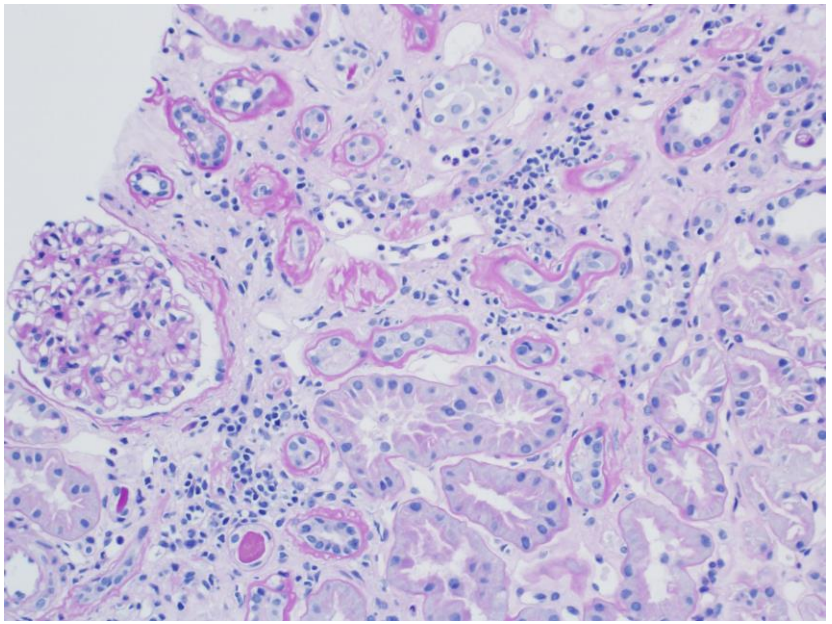
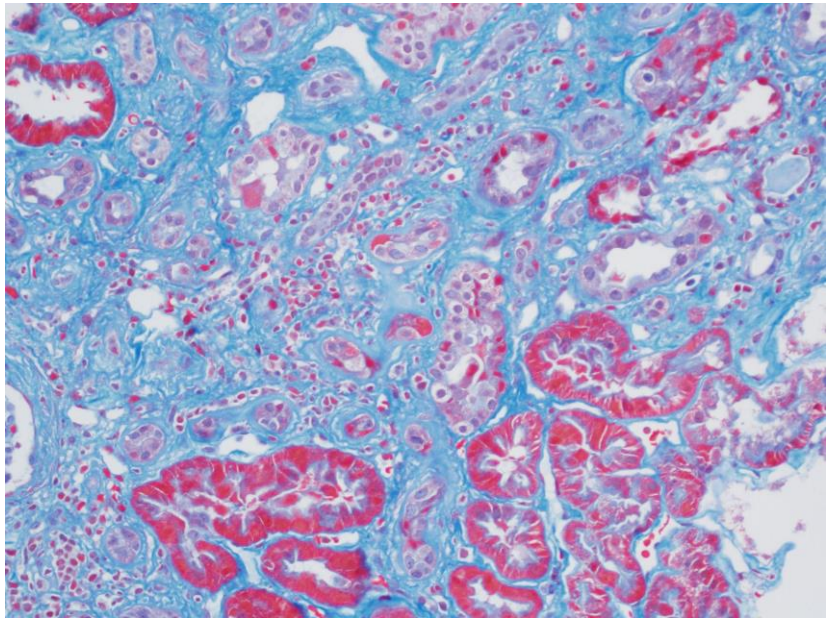
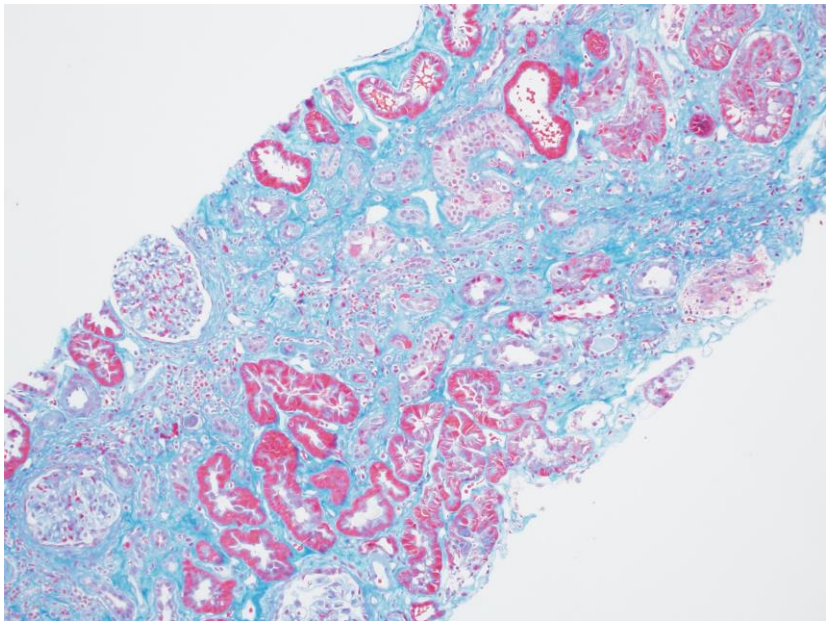


(Secondary focal segmental sclerosis)



Global sclerosis

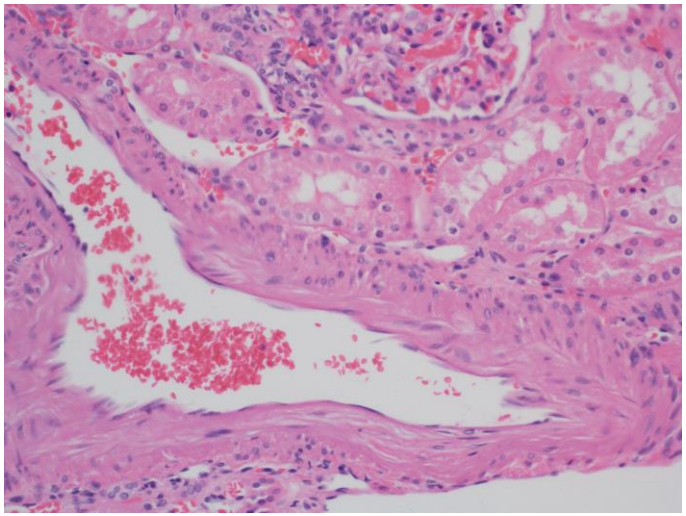
Interstitial fibrosis and tubular atrophy ("IFTA")

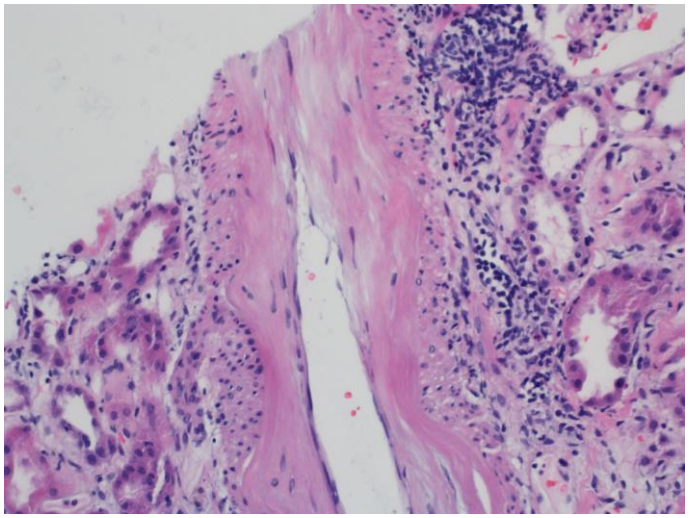
Hypertension and the kidney

- Commonest disease in tumor nephrectomies (30%)
  - Areas of subcapsular scarring (grossly granular)
  - Fibrosis of intima
  - Thinning or hypertrophy of media
  - Hyalinosis of arterioles
- Accelerated/malignant hypertension
  - Fibrinoid necrosis of vessel walls
  - Mucoid change of intima
  - Hyperplastic change of small arteries/arterioles (“onion-skinning”)
  - Thrombi

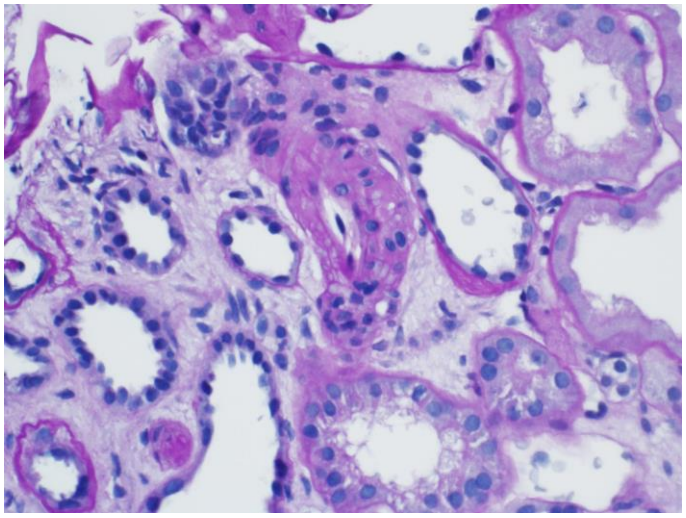
Hypertensive Kidney Disease



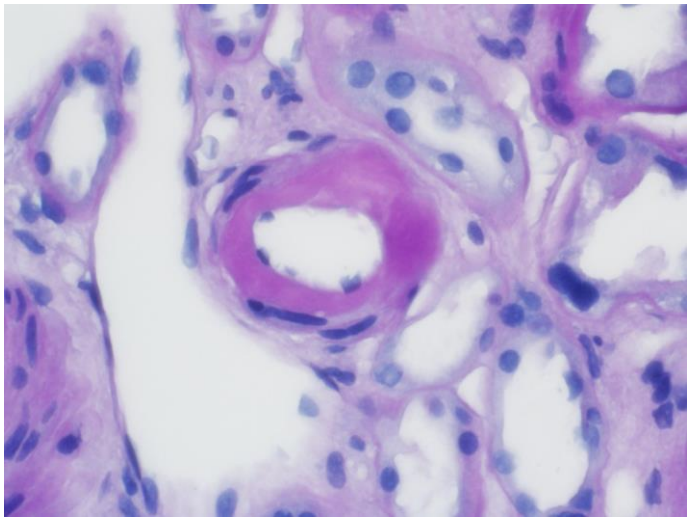
Arterial sclerosis, moderate



Arterial sclerosis, severe

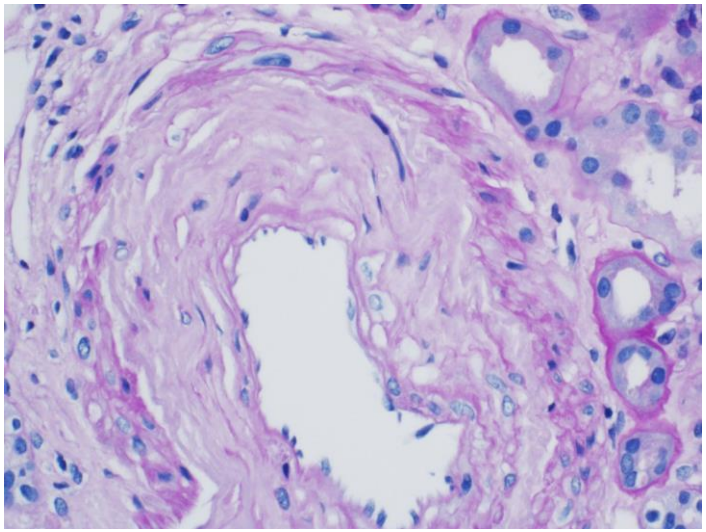


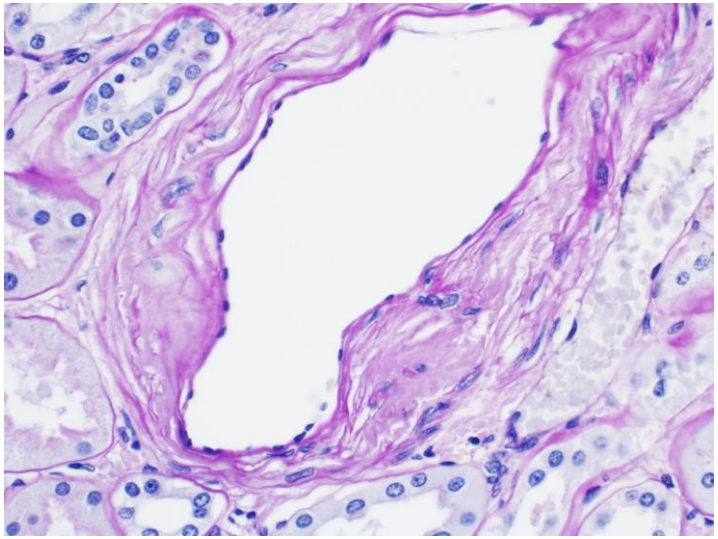
Arteriolosclerosis



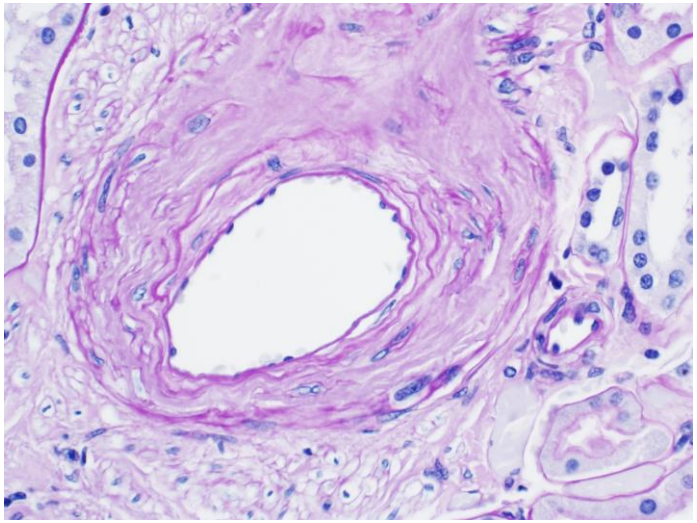
Arteriolar hyalinosis

Hypertensive Arterial Disease

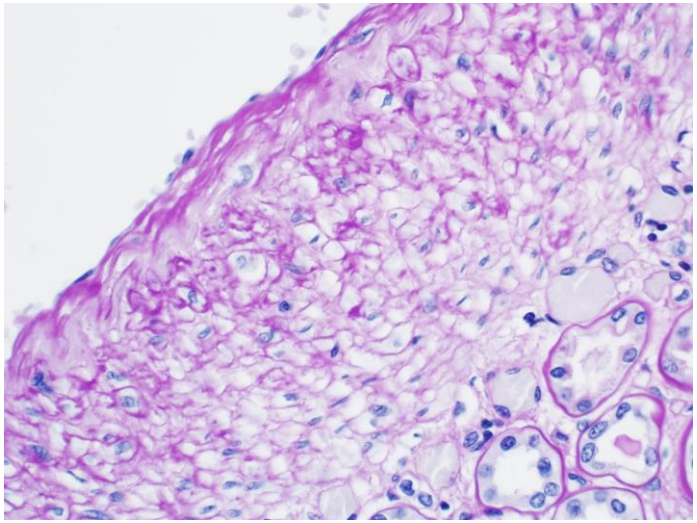




Fibrosis of intima and thinning of media



Reduplication of internal elastic lamina

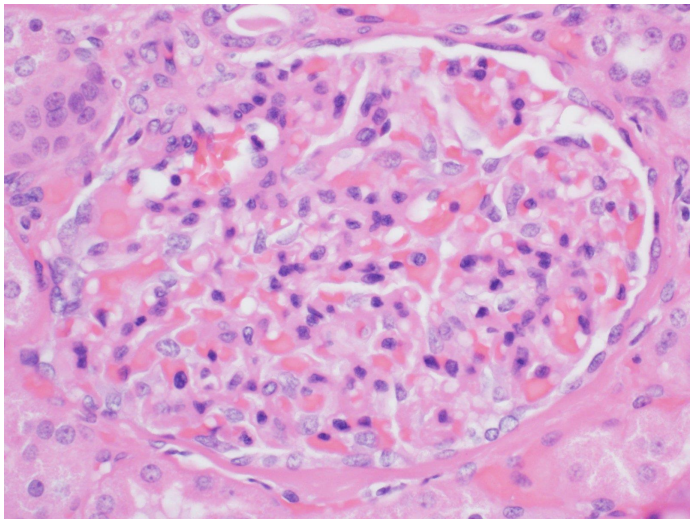


Hypertrophy of media

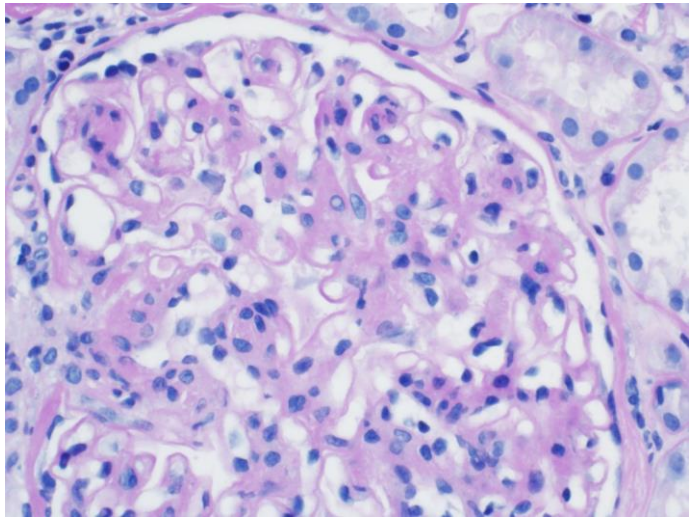
Diabetes and the kidney

- Second commonest disease in tumor nephrectomies
- All compartments involved
- Most characteristic (but not completely specific): glomerular findings
  - Diffuse mesangial sclerosis
  - Nodular sclerosis (Kimmelstiel-Wilson nodules)
- Associated with prominent arteriolar hyalinosis (esp. involvement of both afferent and efferent arterioles)
- Increased risk for arterial sclerosis
- Chronic parenchymal damage (IFTA)

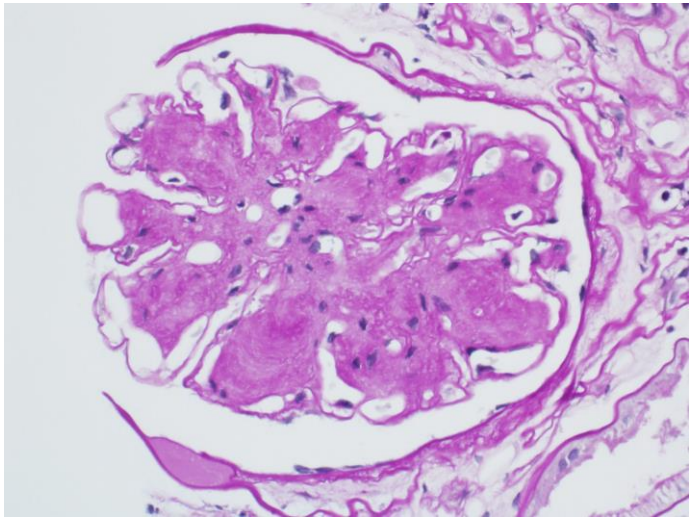
Diabetic Glomerulosclerosis



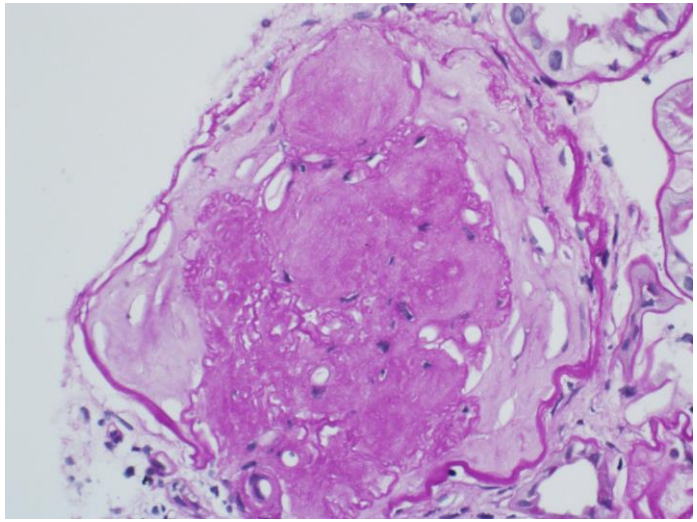
Normal



Diffuse mesangial sclerosis

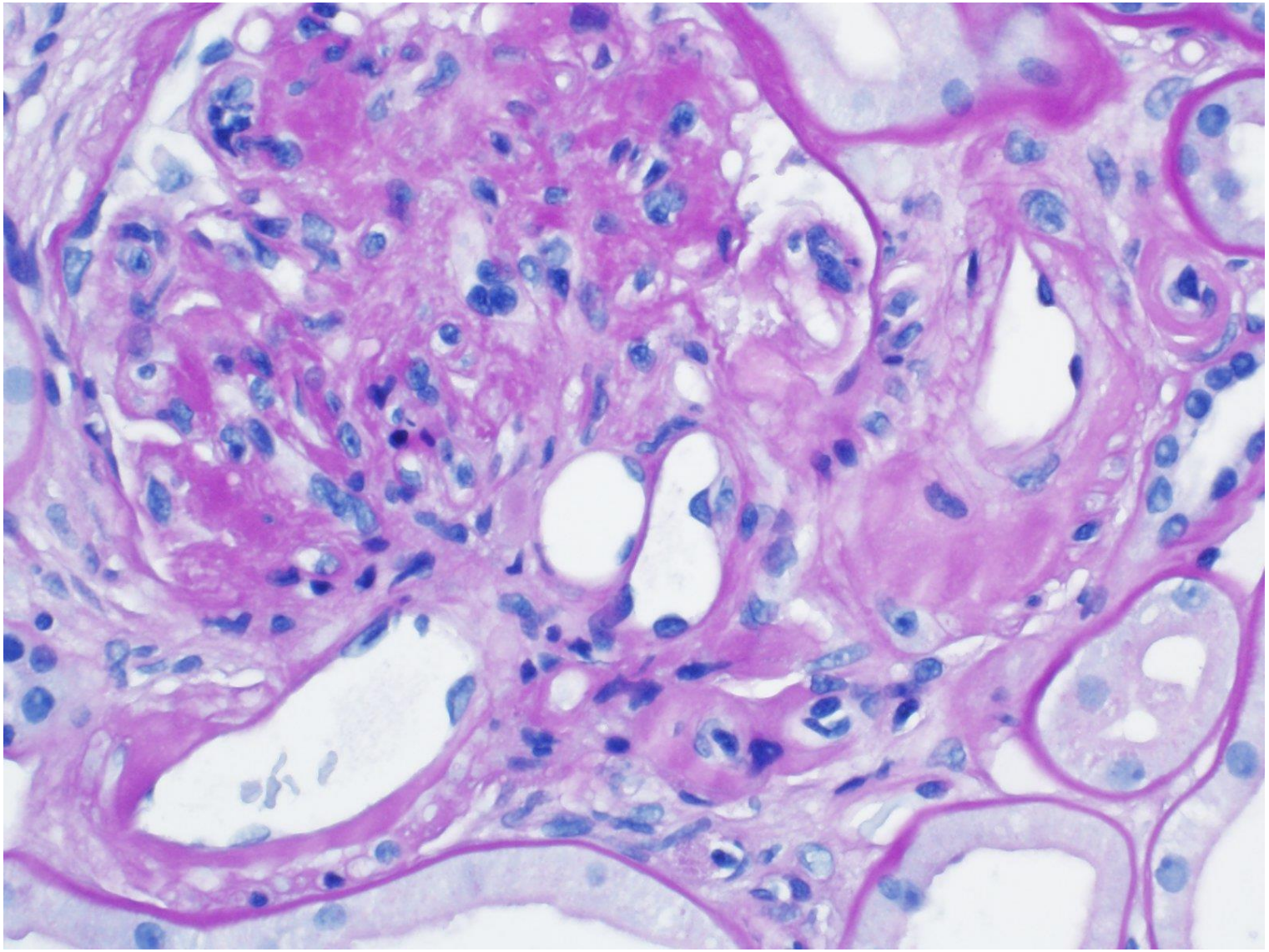


Nodular Glomerulosclerosis



Global sclerosis

Diabetic Kidney Disease

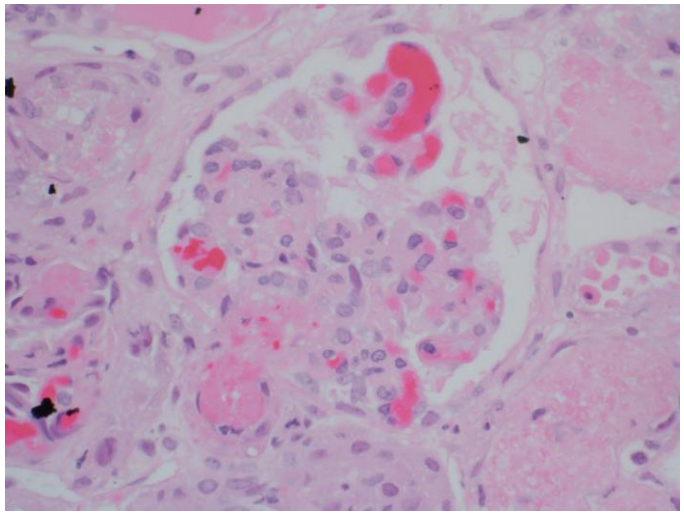


Hyalinosis of afferent and efferent arterioles

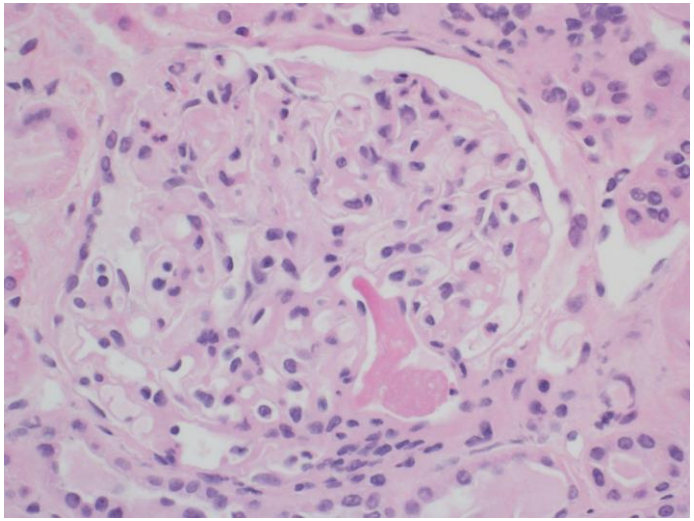
Thrombotic Microangiopathy (TMA)

- Microvascular endothelial injury and thrombosis
- May have important systemic implications
- Many causes (HUS, TTP, DIC, APLA, scleroderma, malignant hypertension, drug etc)
- Acute TMA:
  - “Bloodless glomeruli”, endothelial swelling, mesangiolysis, thrombi, intimal mucoid change, fragmented red cells
- Chronic TMA:
  - Glomerular basement membrane reduplication (double contours/tram-tracking)
  - Concentric intimal fibrosis (“onion-skinning” of arteries)

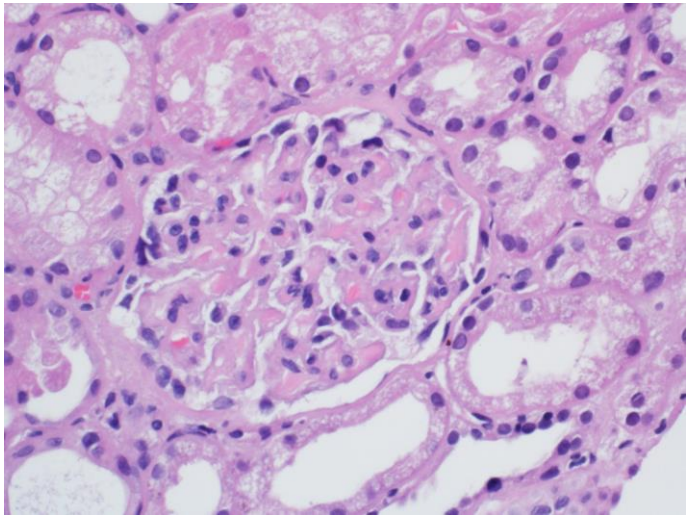
Acute Thrombotic Microangiopathy



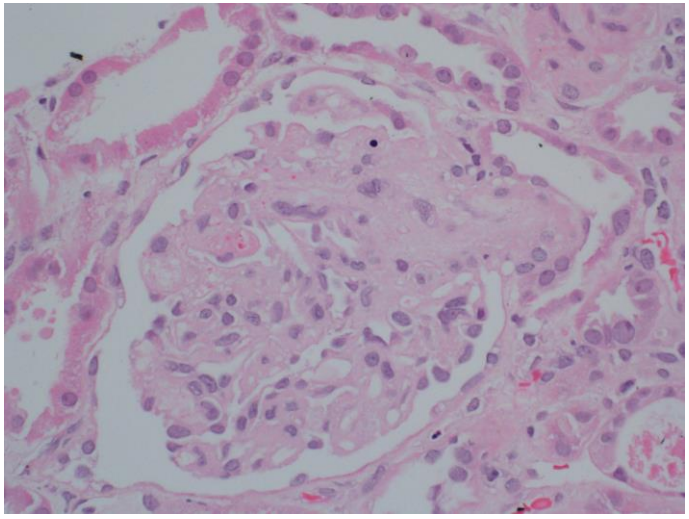
Thrombus at vascular pole, fragmented RBCs



Thrombus

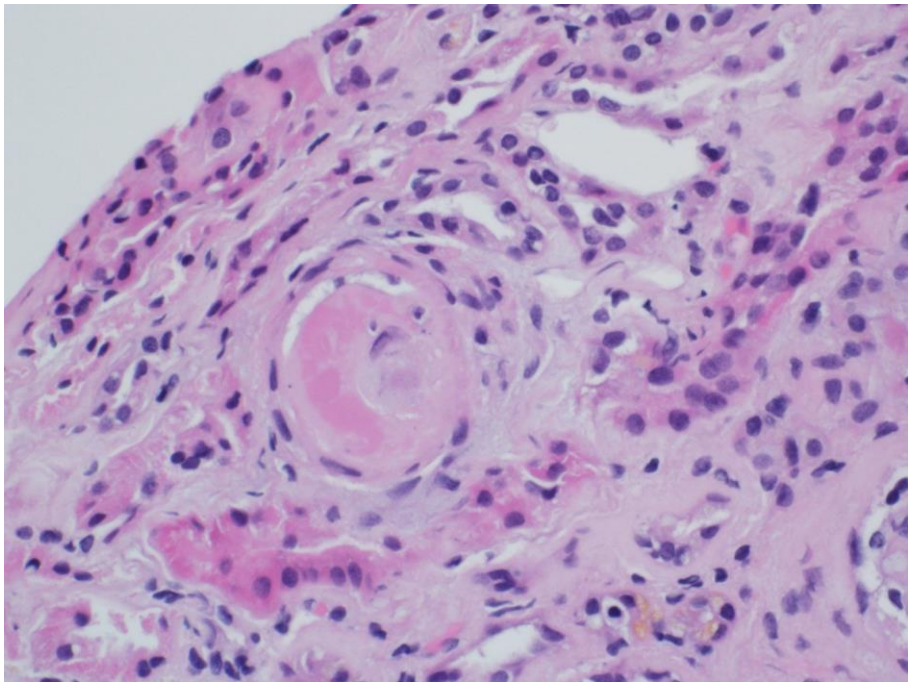


Subtle intracapillary thrombi

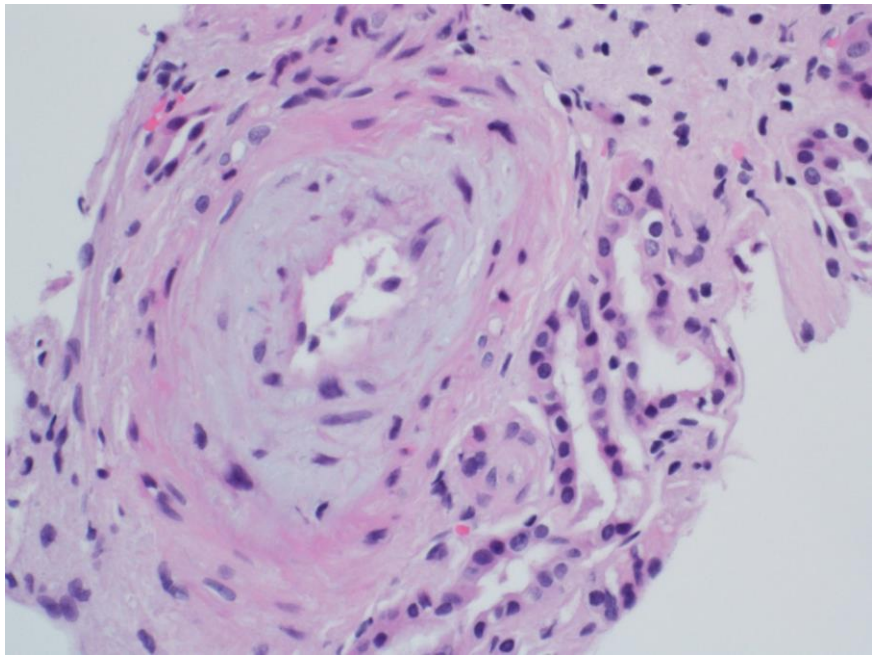


“Bloodless” appearance, fragmented RBCs

Acute Thrombotic Microangiopathy

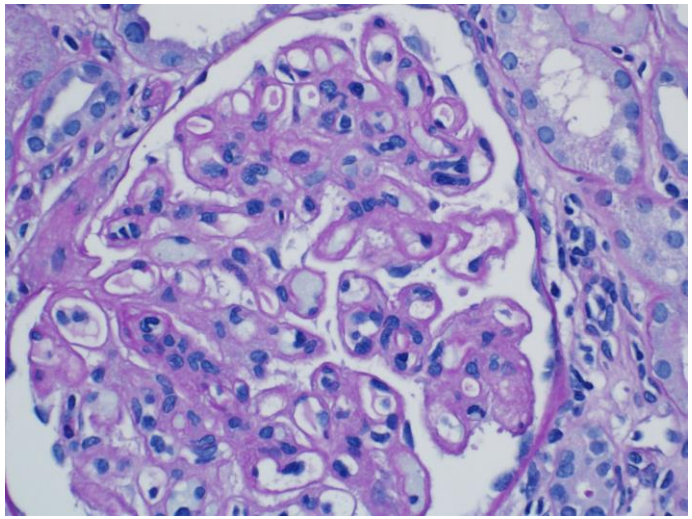


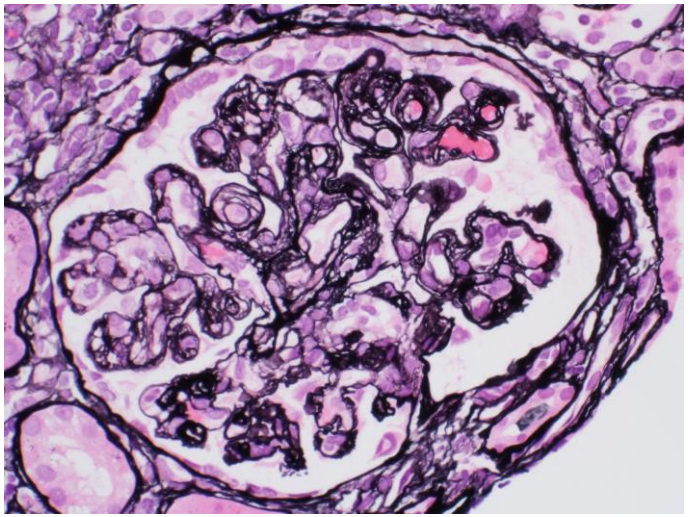
Arterial/arteriolar thrombus



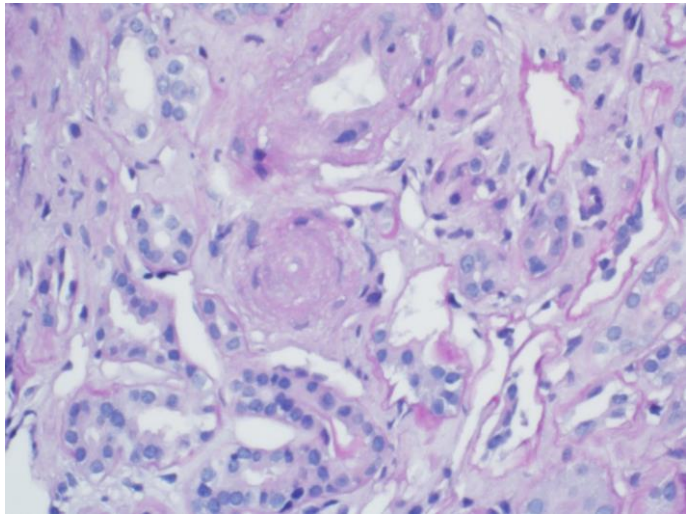
Mucoid intimal change of artery

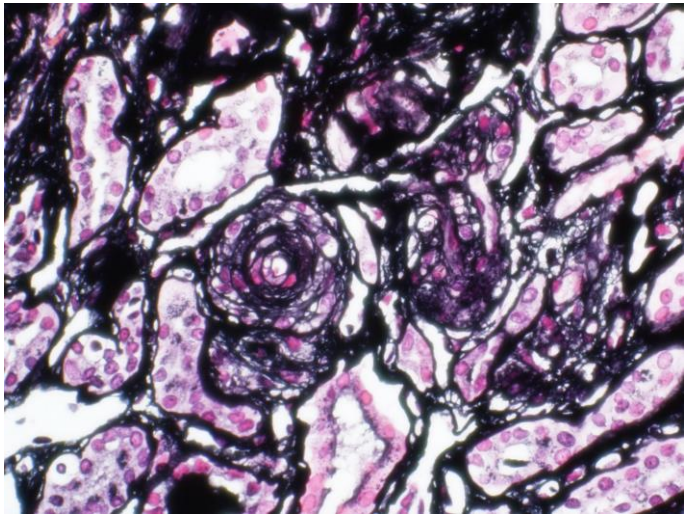
Chronic Thrombotic Microangiopathy





Glomerular basement membrane reduplication: aka peripheral capillary loop “double contouring” or “tram-tracking”



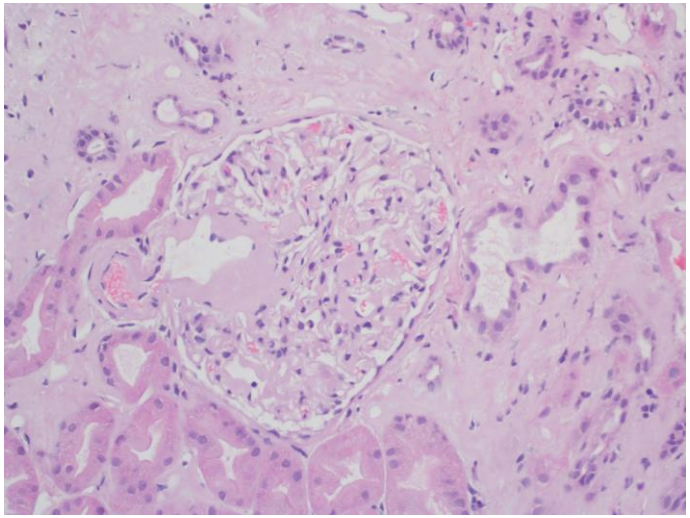


Hyperplastic arteriolosclerosis / “onion skinning”

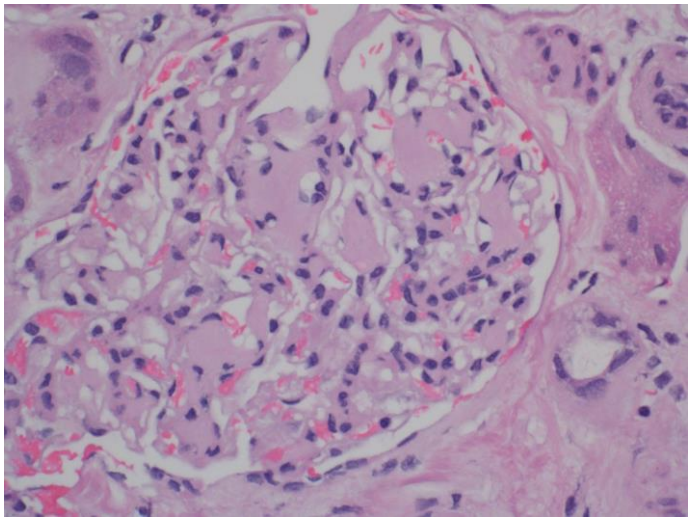
Amyloidosis

- May have important systemic implications also (e.g. myeloma, chronic inflammatory disease etc)
- Many causes: AL, AA, ALECT2, etc
- May deposit in glomeruli, vessels, interstitium and tubular basement membranes
- H&E: eosinophilic, PAS: pale, Congo Red positive (with green birefringence on polarized microscopy)
- Can send for typing by Mass Spectrometry (FFPE)

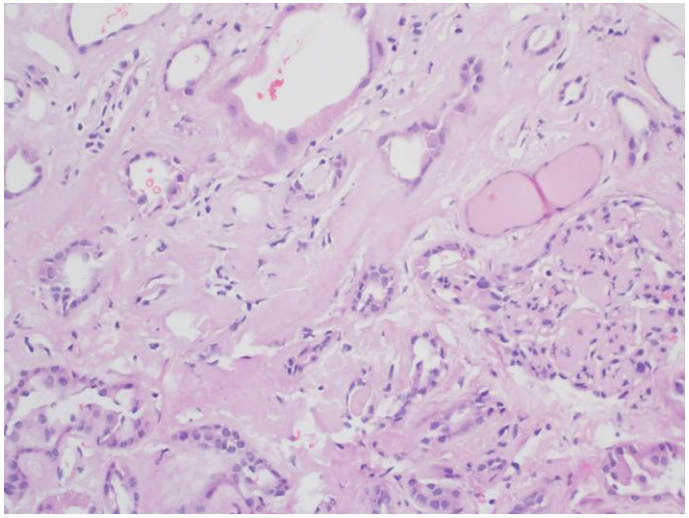
Amyloidosis



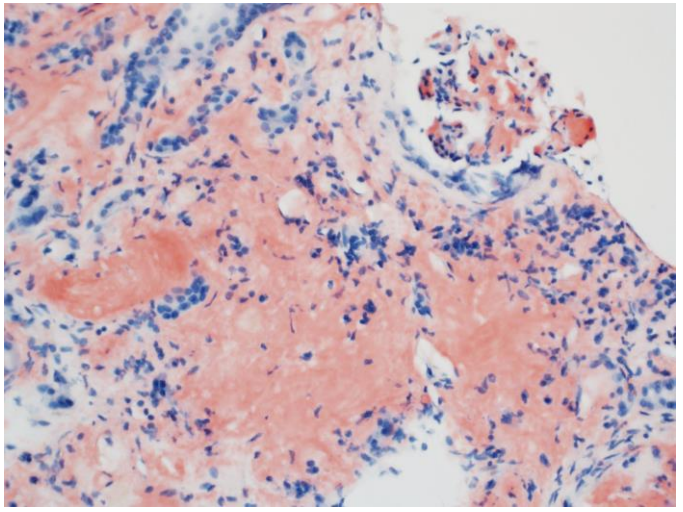
Amyloid involving glomerulus and interstitium



Amyloid involving glomerulus, simulating nodular diabetic GS

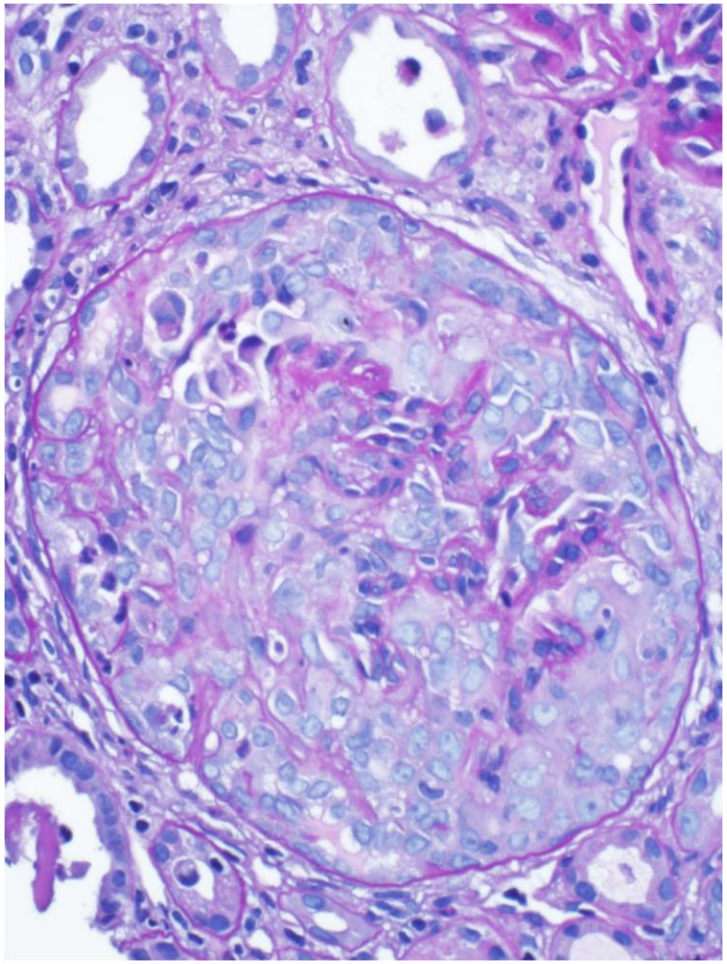


Amyloid involving interstitium



Don’t forget Congo Red stain if suspicious!

Crescentic Glomerulonephritis



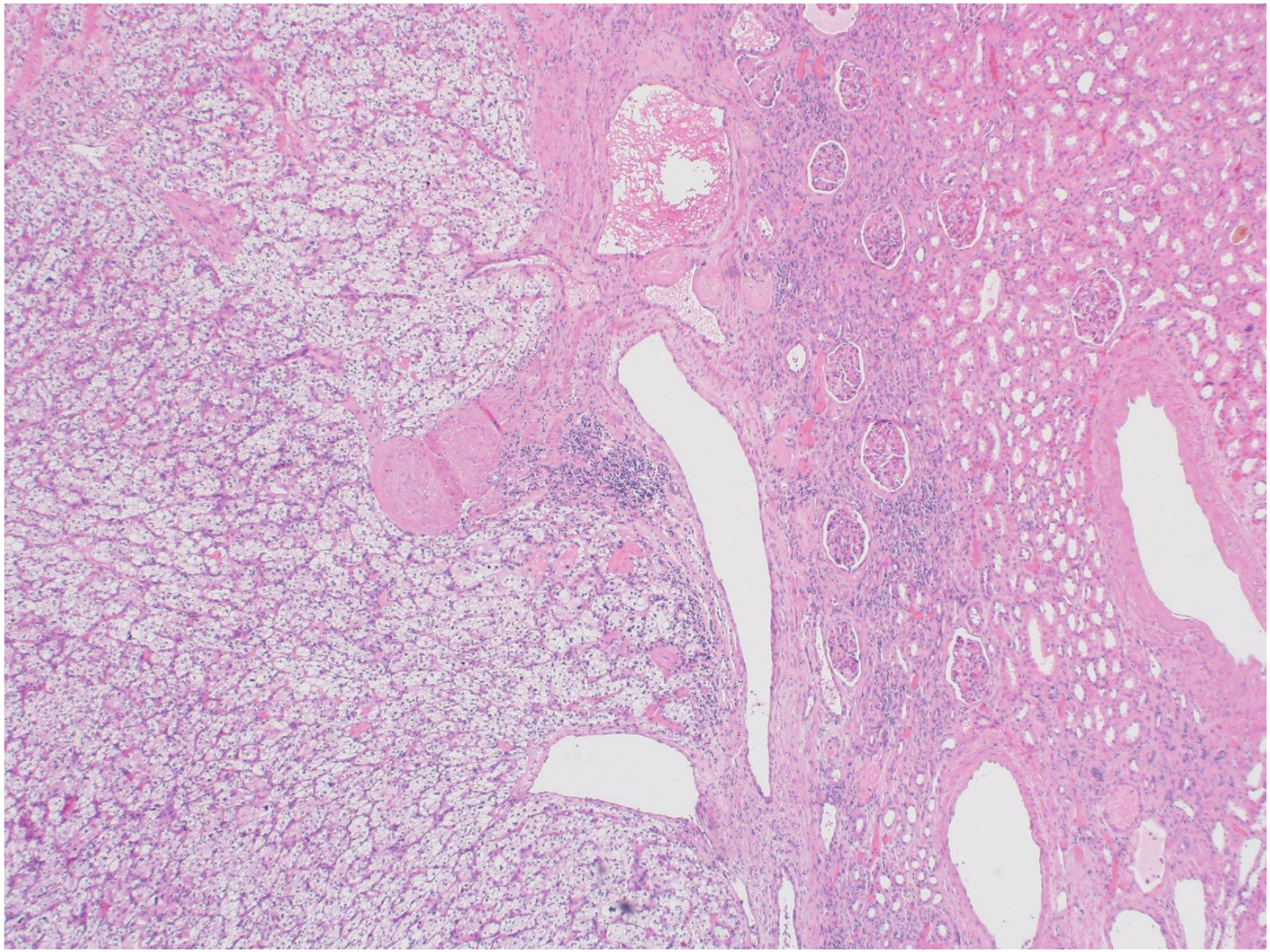
- The most severe manifestation of glomerular disease
  - Anti-GBM disease
  - Pauci-immune (ANCA-associated)
  - Associated with immune complex deposition
- IF and EM are key in diagnosis (can do on FFPE material)

Direct Tumor Effects

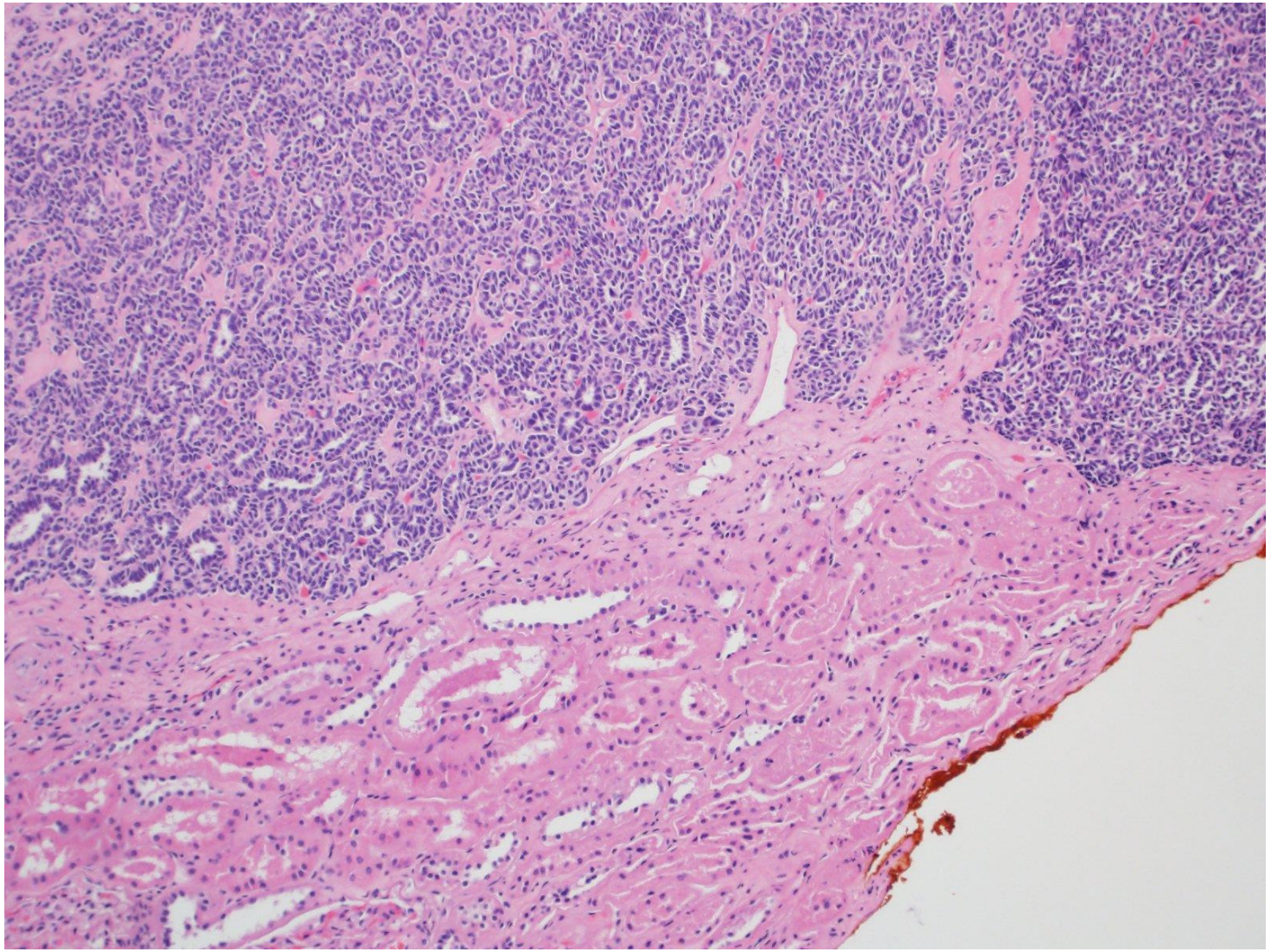
- 1. Tumor capsule/pseudocapsule formation
  - Underlies the recommendation to sample away from tumor
  - Localized chronic parenchymal damage
  - May have surrounding zone of acute tubular injury
- 2. Consequences of obstruction due to tumor
  - Chronic pyelonephritis
  - May be significant chronic parenchymal damage associated specifically with this (rather than other intrinsic kidney disease)

- →These findings do not generalize to the contralateral kidney

Tumor capsule

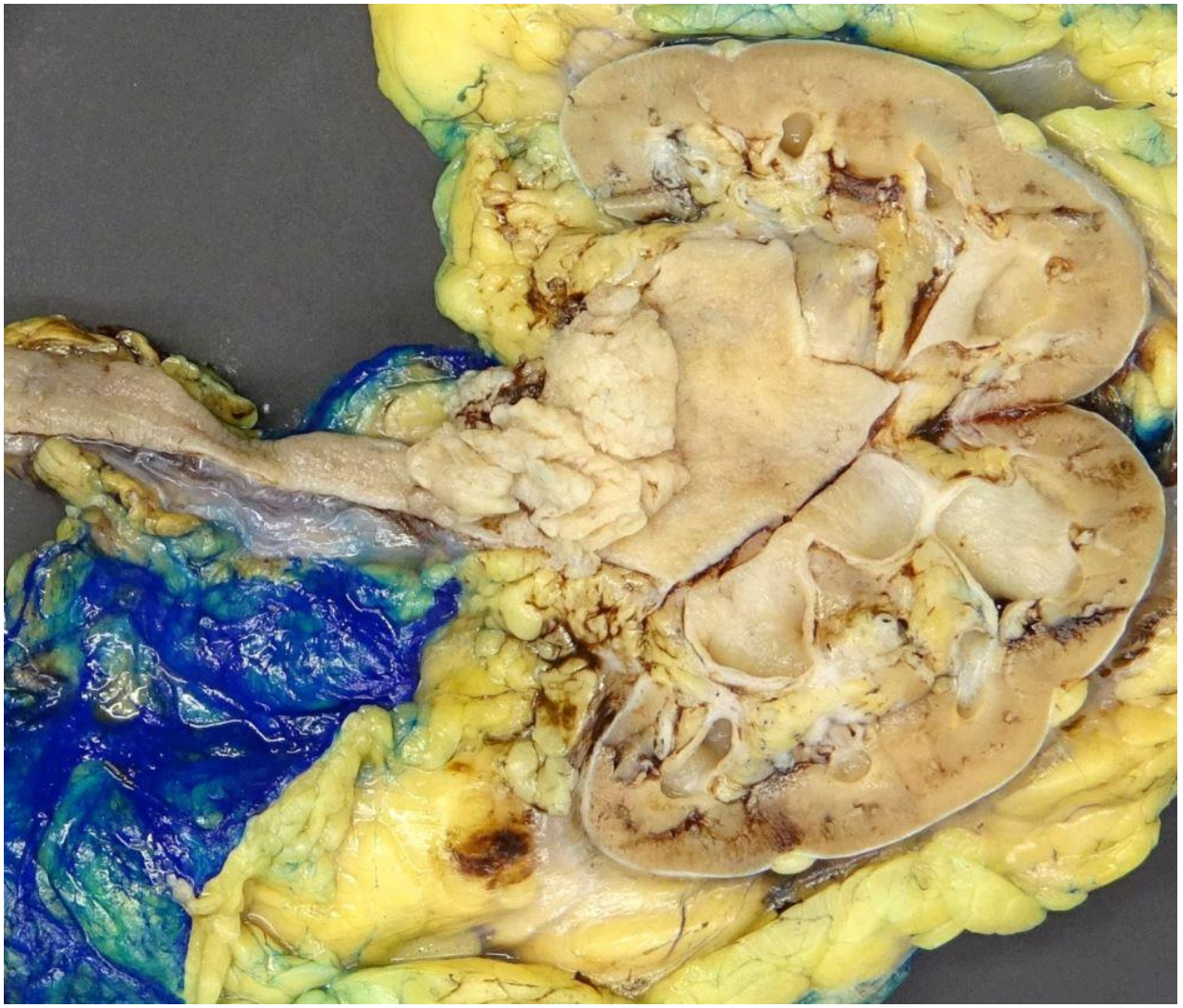


Benign tumors may lack capsule

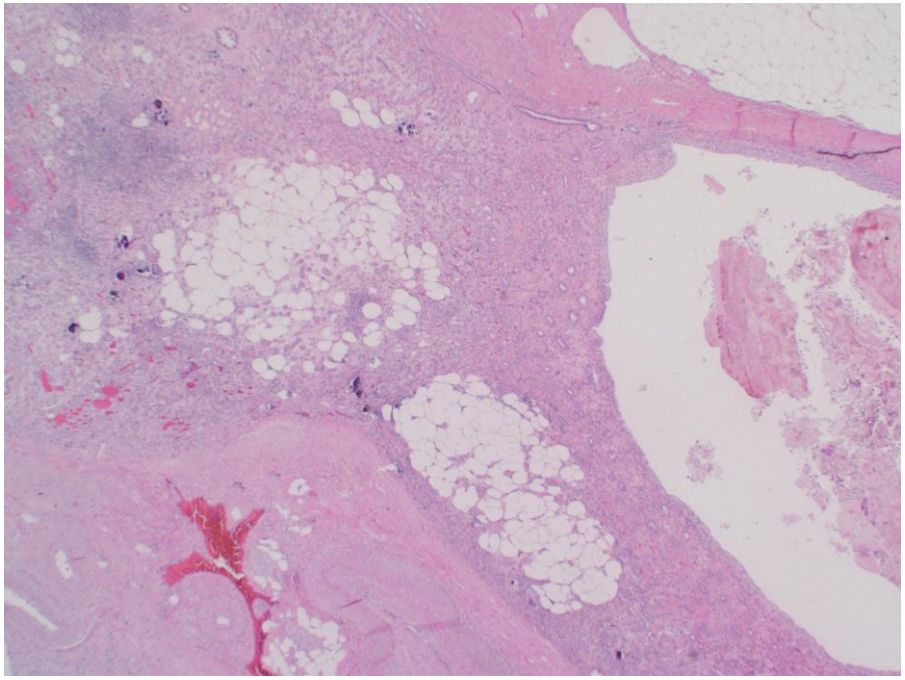


Above: metanephric adenoma
Another characteristic example is oncocytoma

Obstruction due to tumor

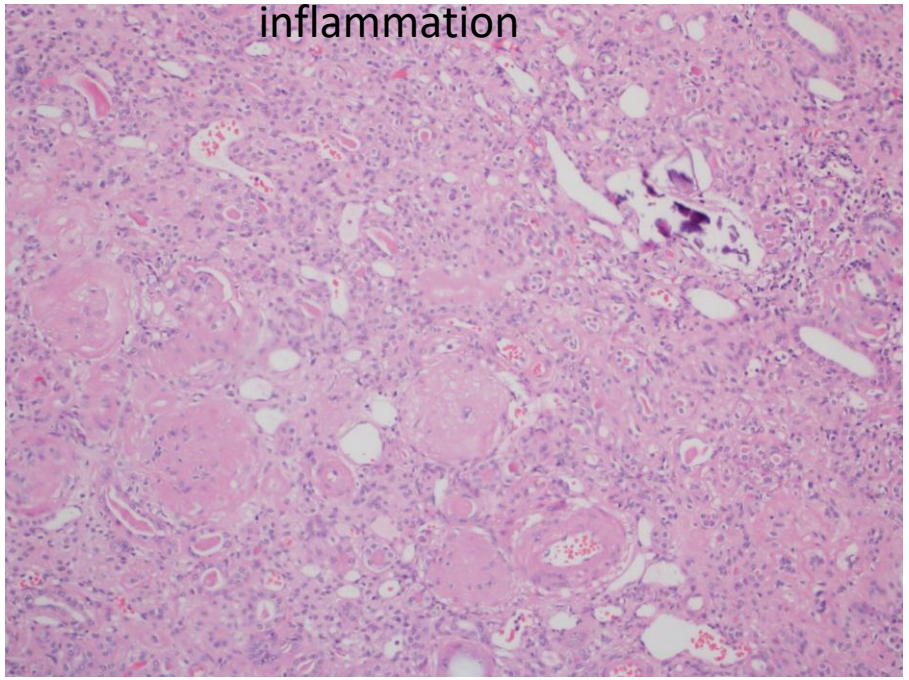


Obstruction due to tumor



Hydronephrosis with calyceal dilatation, and parenchymal atrophy and inflammation

Parenchymal chronic damage: global glomerulosclerosis, and marked interstitial fibrosis and tubular atrophy
Interstitial chronic inflammation



Reporting

Pathologic Findings in Nonneoplastic Kidney (select all that apply)

___ Insufficient tissue
___ None identified
___ Glomerular disease (specify type): _____
___ Tubulointerstitial disease (specify type): _____
___ Vascular disease (specify type): _____
___ Other (specify): _____

Tumor Nephrectomy Summary

- Take section of non-neoplastic kidney **at least 1 cm** away from tumor if possible
- Consider ordering **PAS** (or Jones silver) up front
- **Systematically** approach pathology (4 compartments)
- Use **synoptic** reports
- Don’t forget to assess in **benign** tumor specimens!
- Use **PAS**, **Congo Red**, other stains as needed
- Remember, IF and EM can be performed on **FFPE** tissue

- The pathologist can be a **conduit** between urologist and nephrology

Donor Kidney Assessment

- Previous donor criteria
  - SCD: “standard criteria donor”
  - ECD: “expanded criteria donor”
- Currently “KDPI” (Kidney Donor Profile Index)
  - Score based on multiple clinical and some laboratory values
  - Low score: shorter graft survival
- Consequence: seeing more donor biopsies!

Initial Approach to Specimen

- Wedge (usually) or needle biopsy
- For frozen section (usually) or rapid processing

- Gently blot tissue dry
- Freeze all tissue
- Try to embed perpendicular to capsule
- Multiple levels (donor services request some)
- Adequate:
  - 25 or more glomeruli
  - 2 or more vessels
- Donor services provide form to fill out

General Approach to Assessment

- Assessment of degree of chronic damage
  - Percentage global glomerulosclerosis (excluding subcapsular scarring)
  - Amount of IFTA
- Assessment of vessels for sclerosis, hyalinosis
- ?Glomerular thrombi
- ?Acute tubular injury
- Other features (if seen)

Remember:

- Degree of chronic damage and vascular sclerosis may help predict graft survival
- Acute diseases less common, may not impact graft survival (may have delayed function)

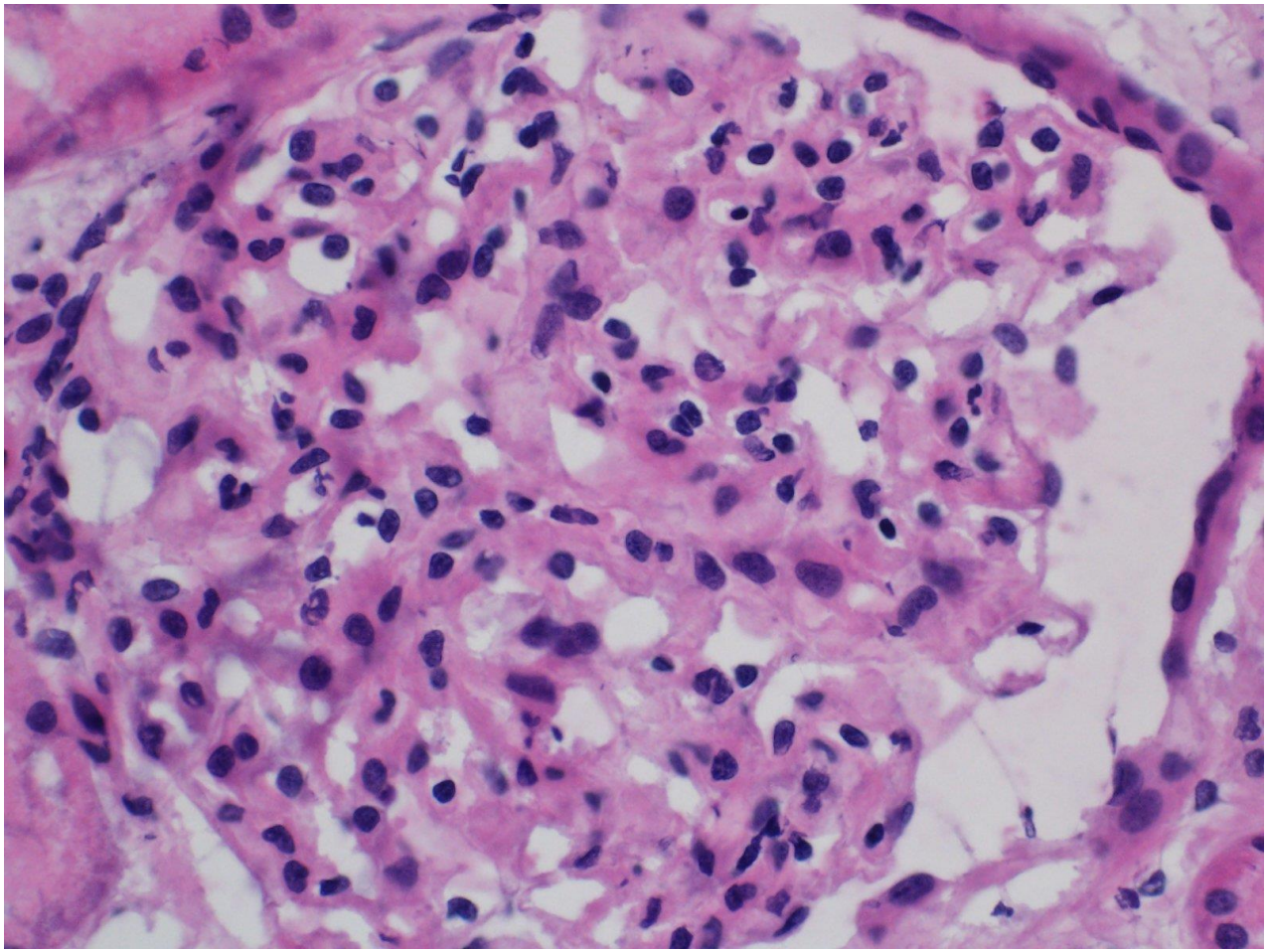
BUT

- **"Histopathologic assessment of preimplantation biopsies is one component of donor organ assessment and is not an exclusive determinant… . Rigidly defined cutoffs…should not be used in isolation…"** Banff consensus (Liapis 2017)

Frozen Section Artifacts

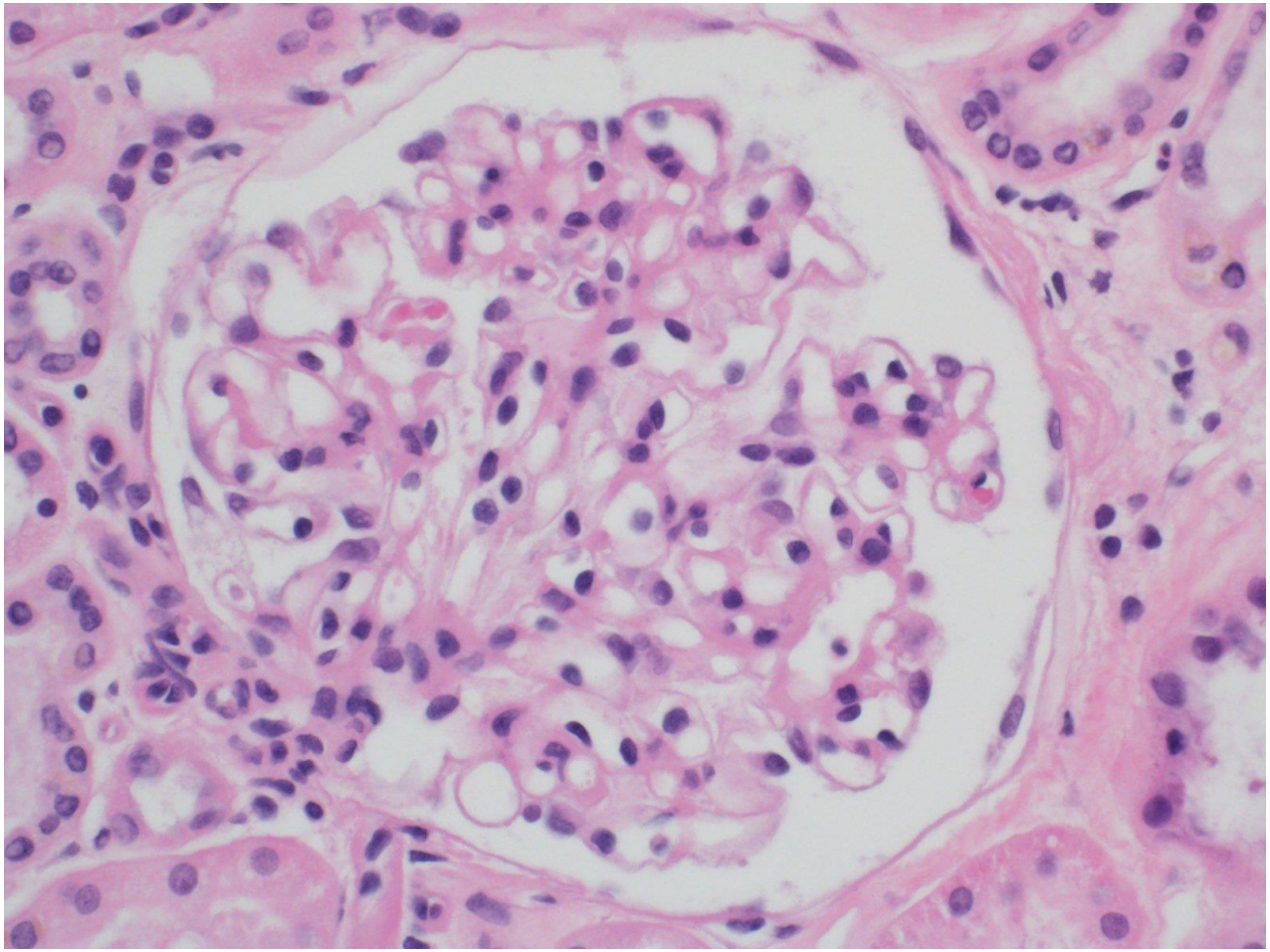
- Glomeruli:
  - Normal may appear hypercellular, pathology may be difficult to assess (e.g. diabetic glomerulosclerosis)
- Tubules:
  - Retraction – normal may appear like acute injury or atrophy
- Interstitium:
  - Can look “edematous”, “atrophic”
- Vessels:
  - Arteriolar hyalinosis may be difficult to see

Glomerulus: Frozen Section

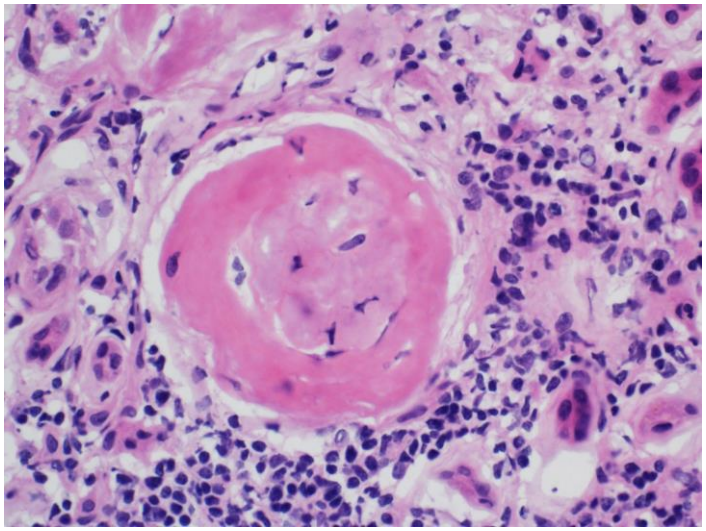


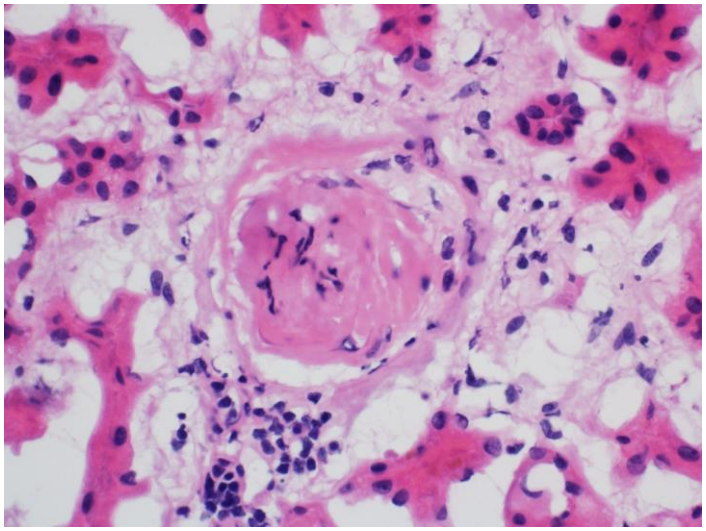
Is it hypercellular?

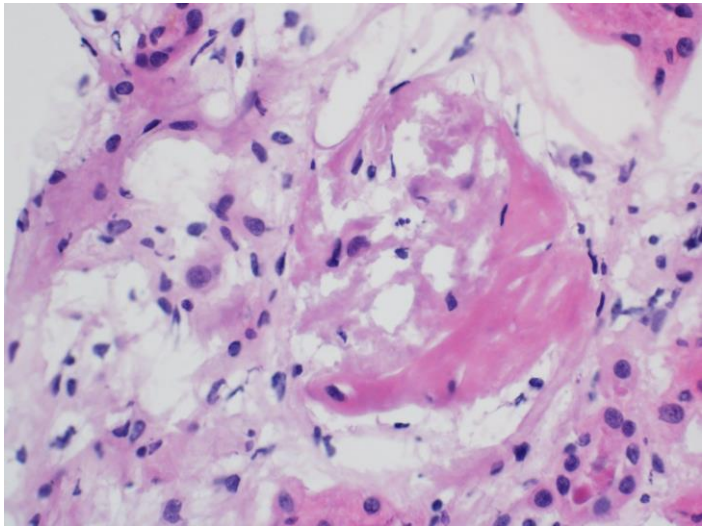
Glomerulus: Permanent (same case)

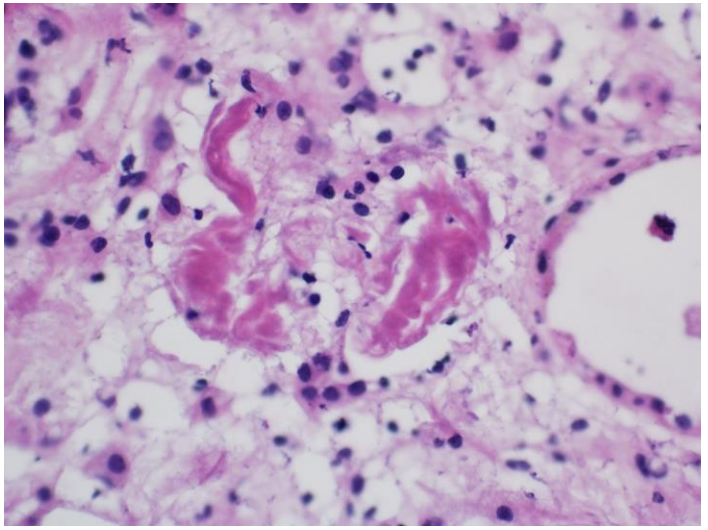


Global Glomerulosclerosis

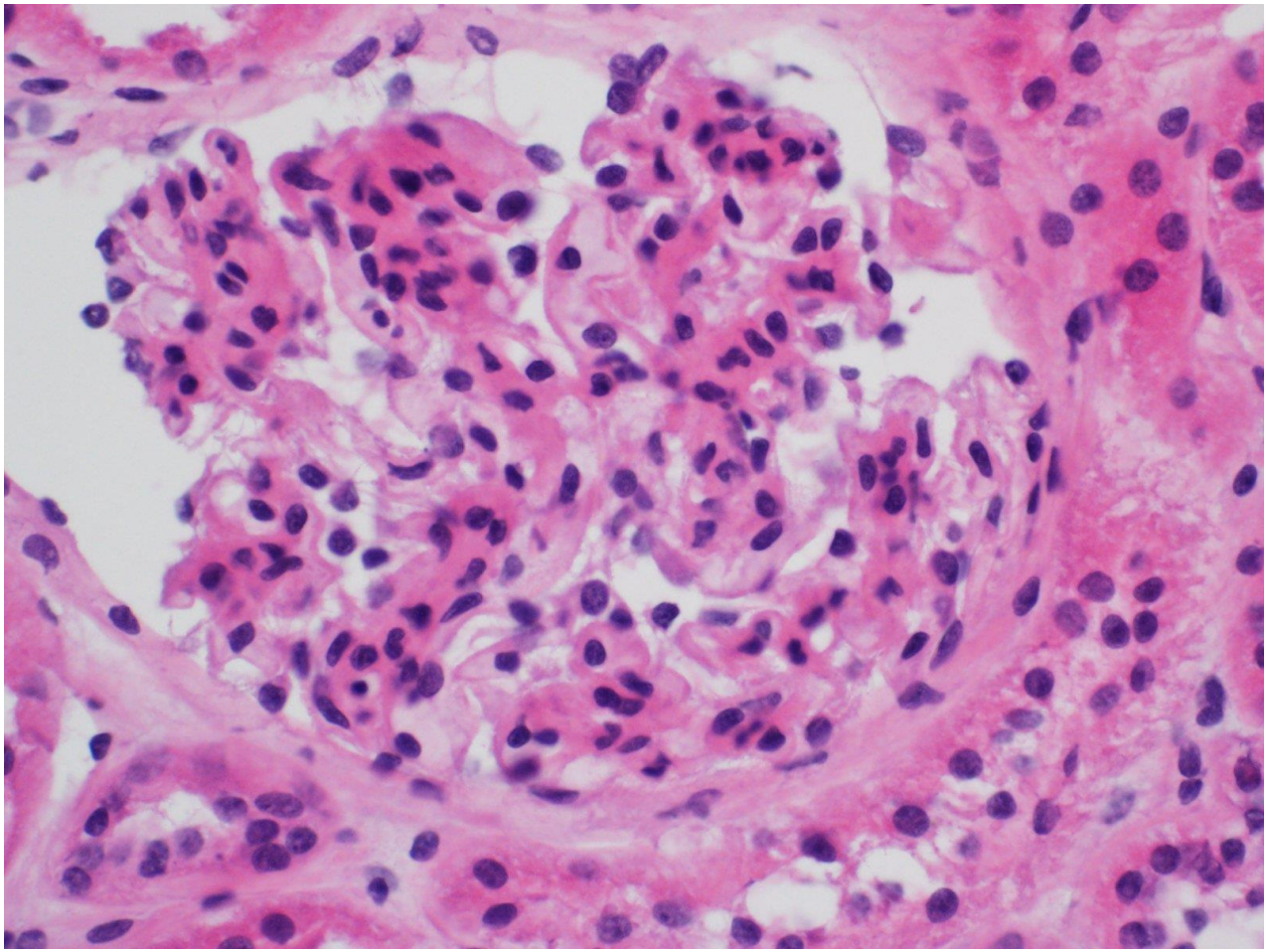






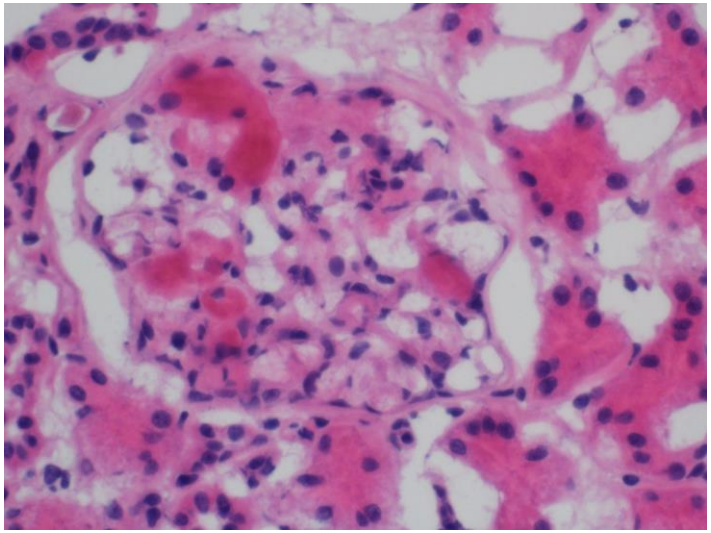


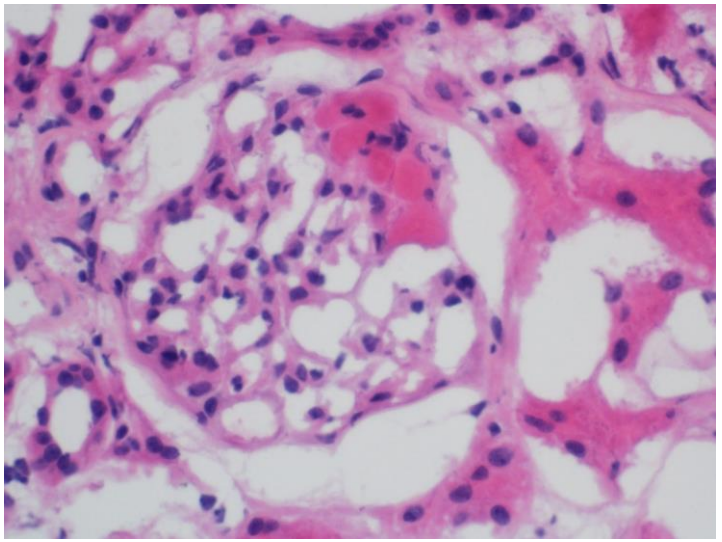
Diabetic Glomerulosclerosis

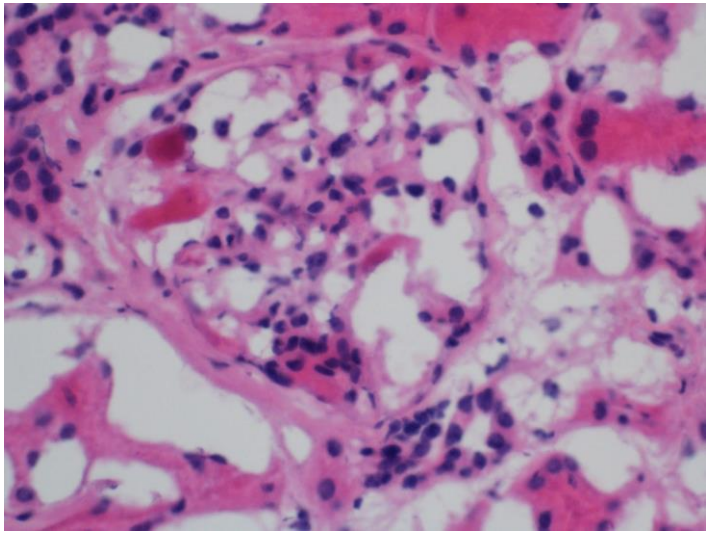


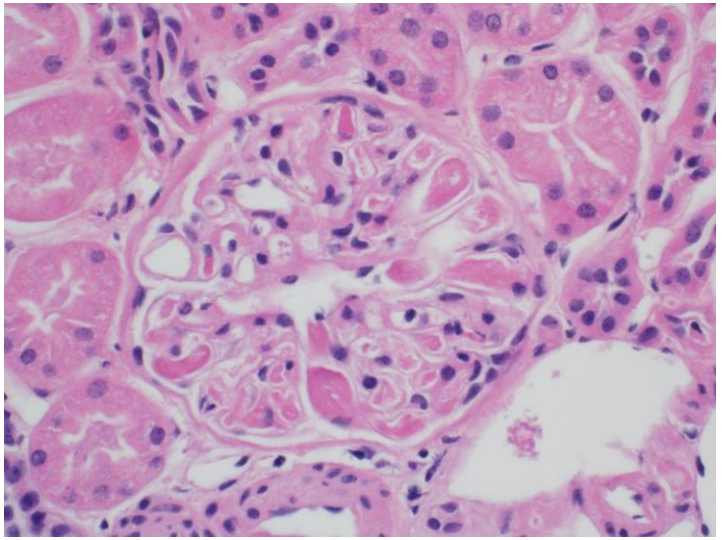
May not always be easy to appreciate, esp. earlier stage

Glomerular Thrombi



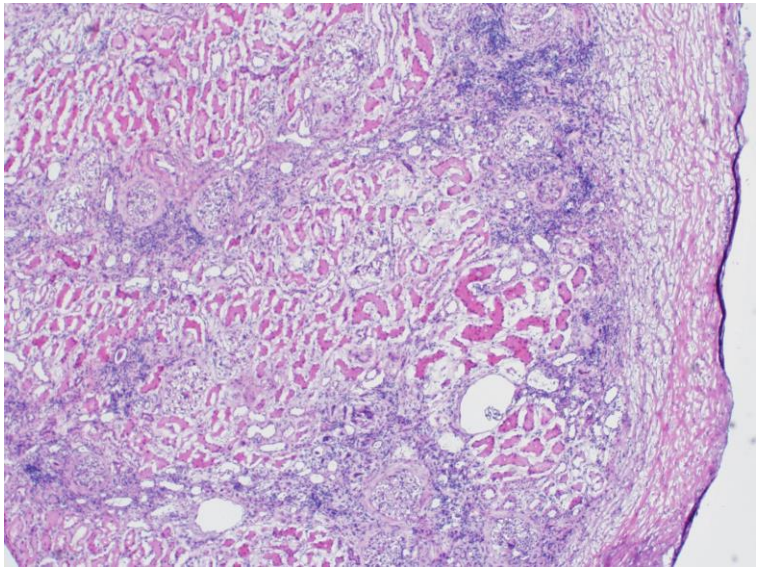


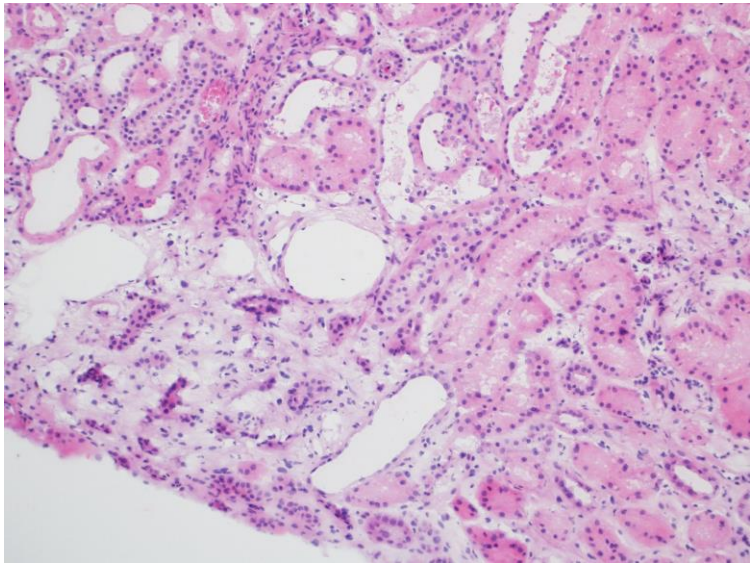


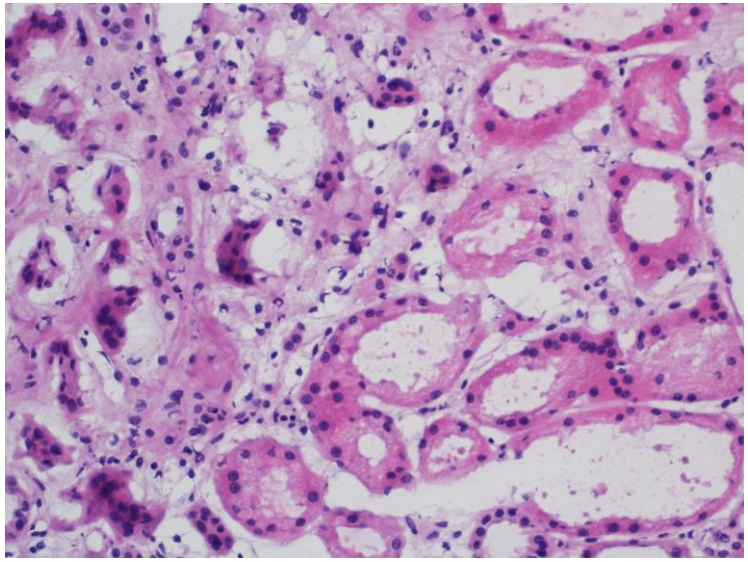


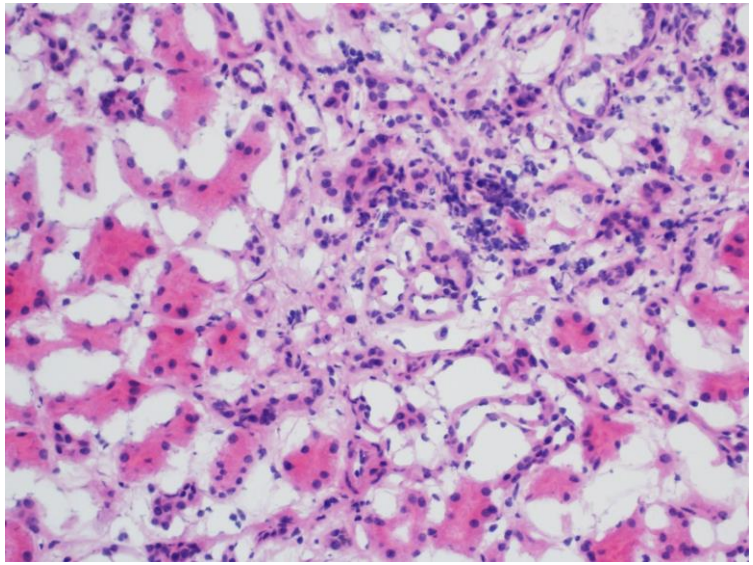
Perm

Interstitial Fibrosis and Tubular Atrophy

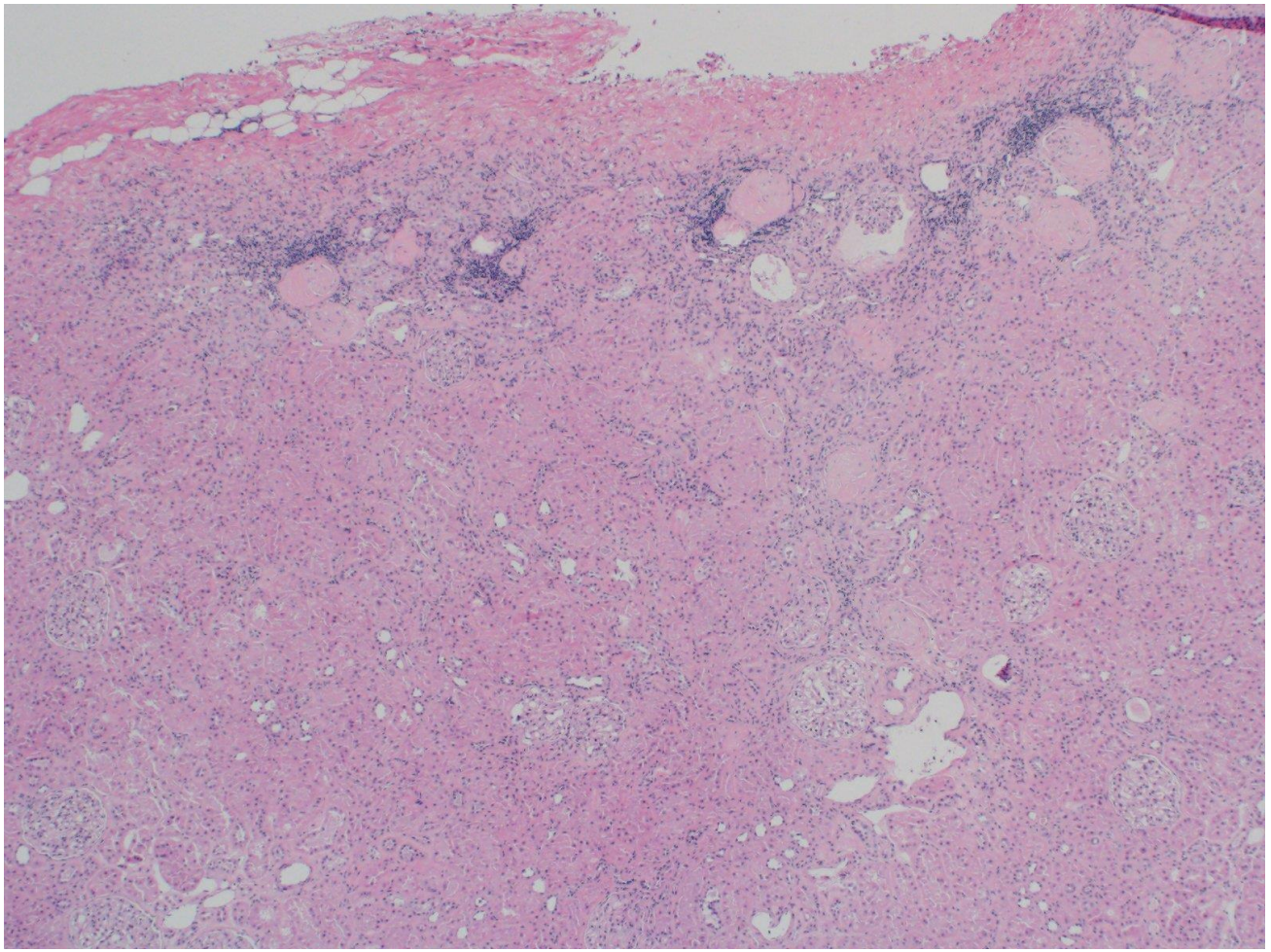






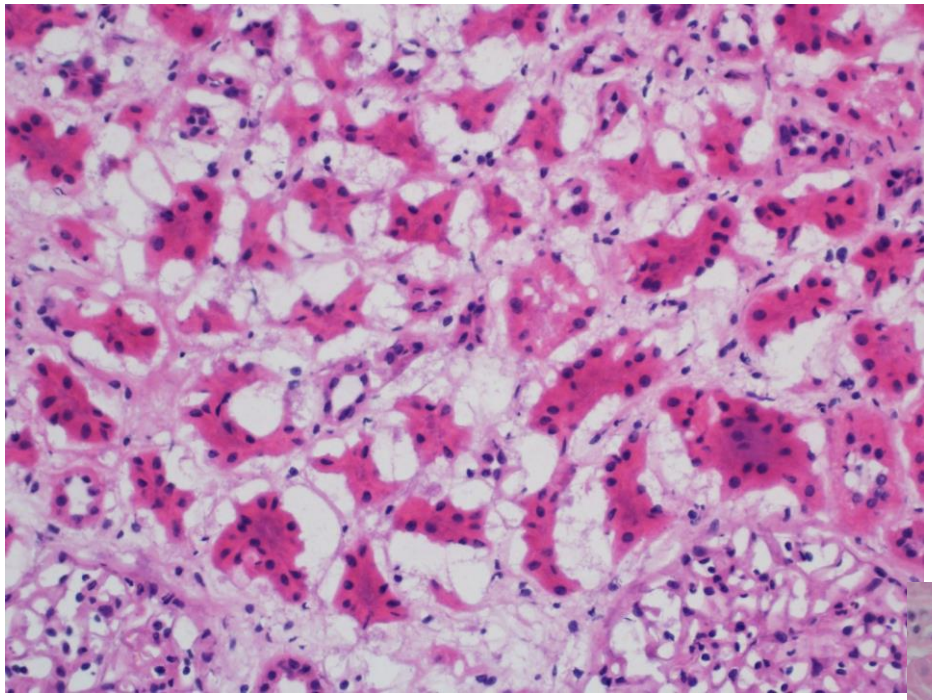


Pitfall for assessment of chronic damage: subcapsular scarring with hypertension



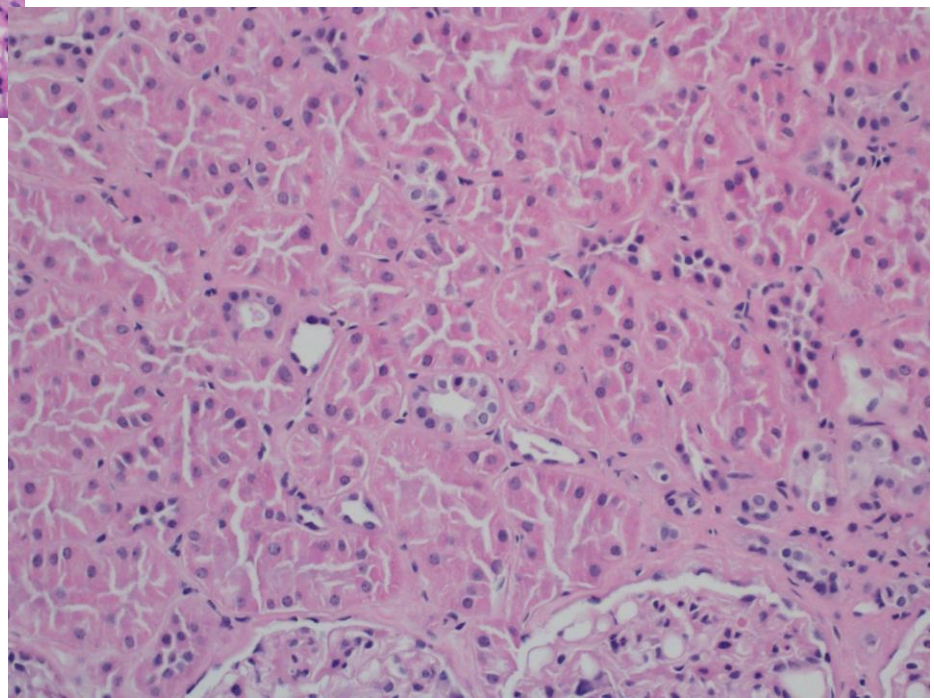
Subcapsular scarring seen in hypertension may not be representative of IFTA in the sample, and is excluded from IFTA quantification (it is noted separately)

Tubular Frozen Section Artifact

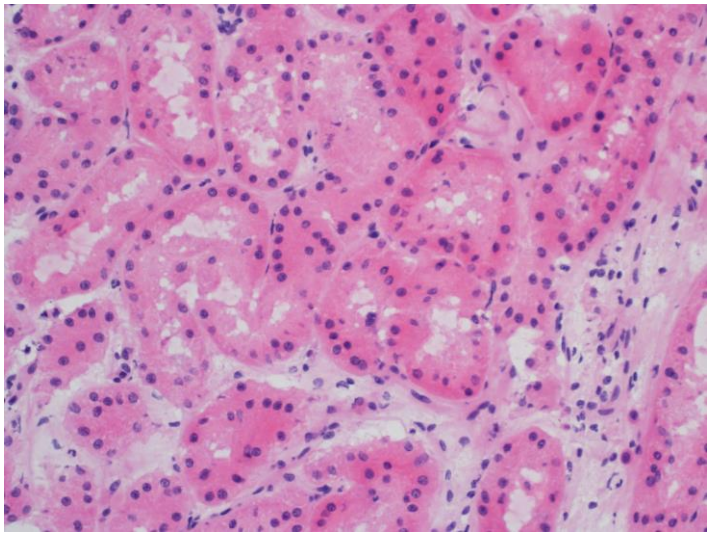


Frozen section

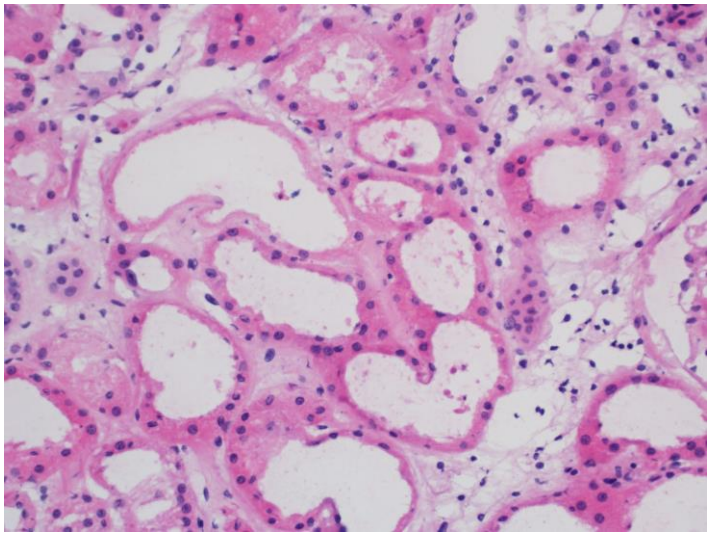
Same case - permanent section



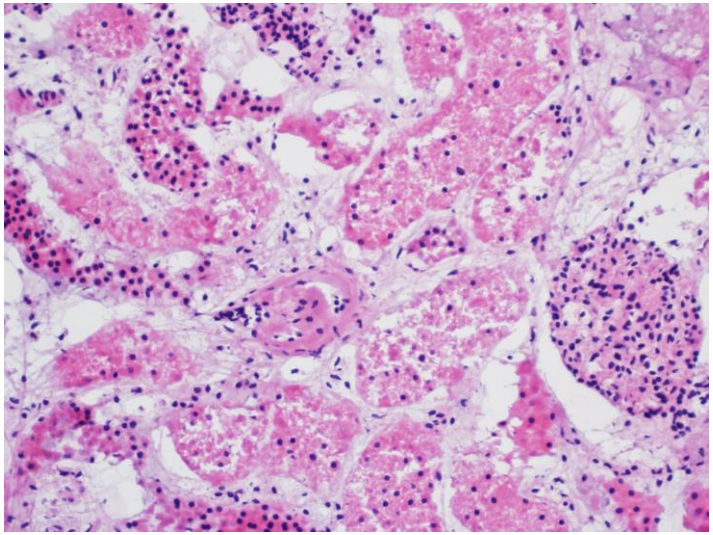
Acute Tubular Injury/Necrosis/Infarction



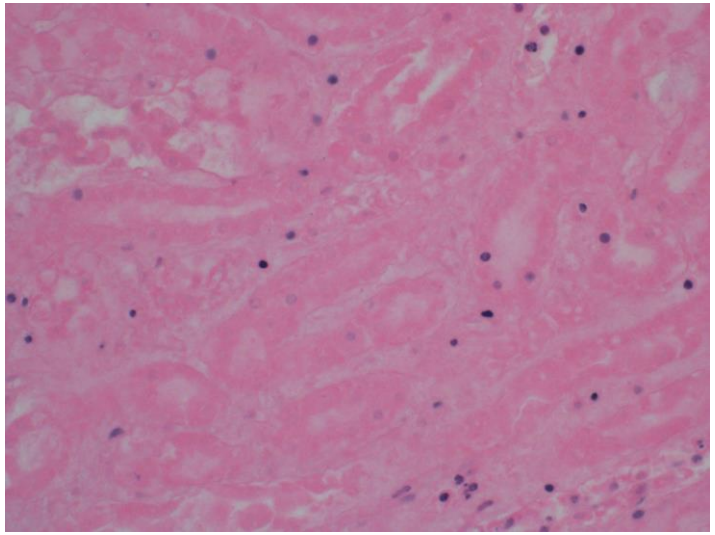
Normal (very good frozen section!)



Acute tubular injury (not usually this easy!)

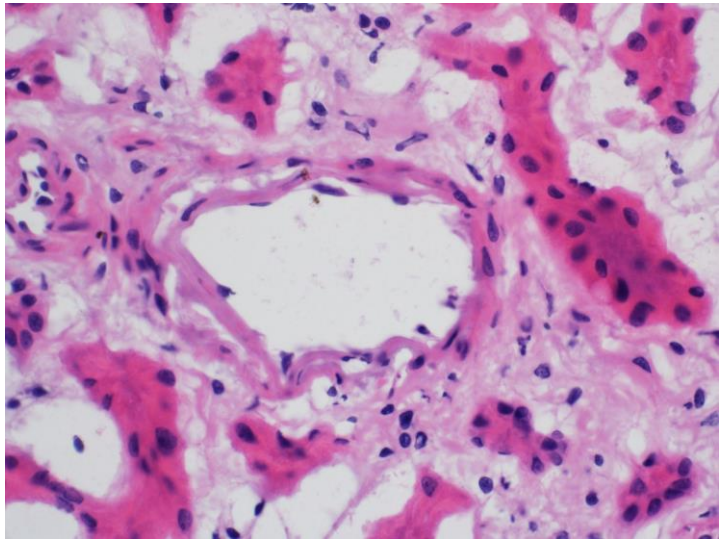


Acute tubular necrosis

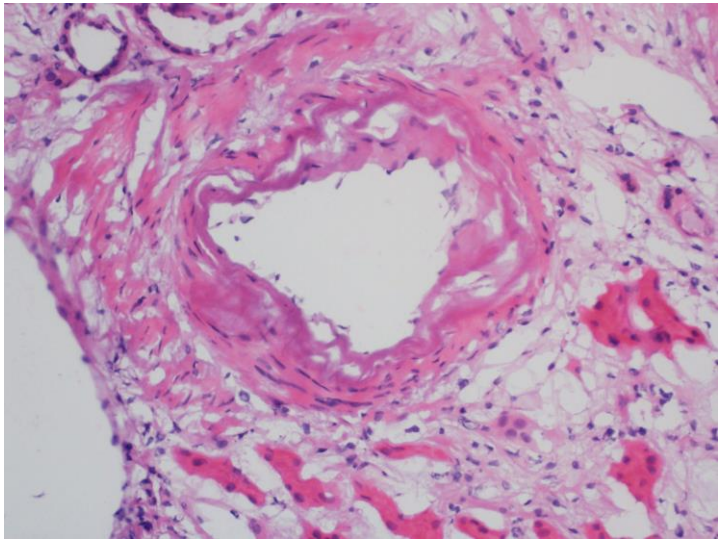


Infarction or cortical necrosis

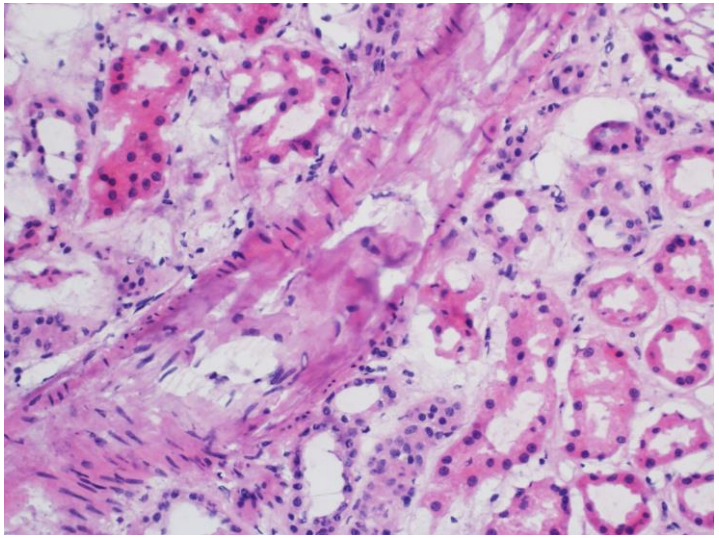
Arterial Sclerosis and Arteriolar Hyalinosis



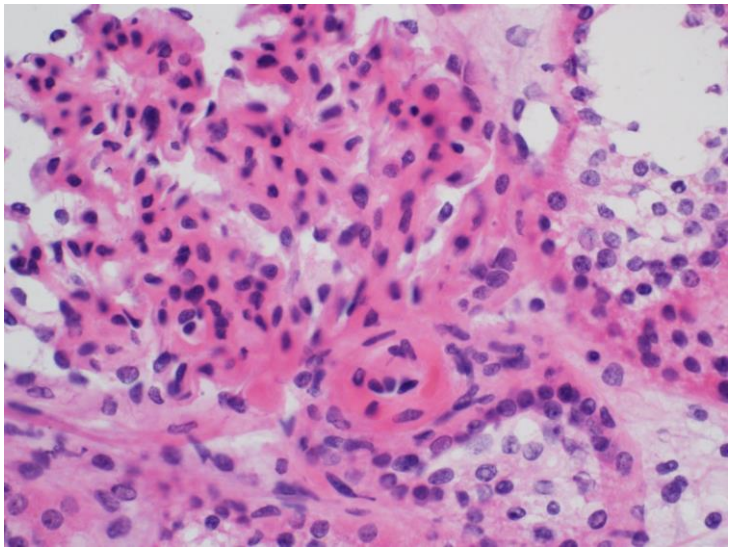
Mild arterial sclerosis <25%



Moderate arterial sclerosis 25-50%

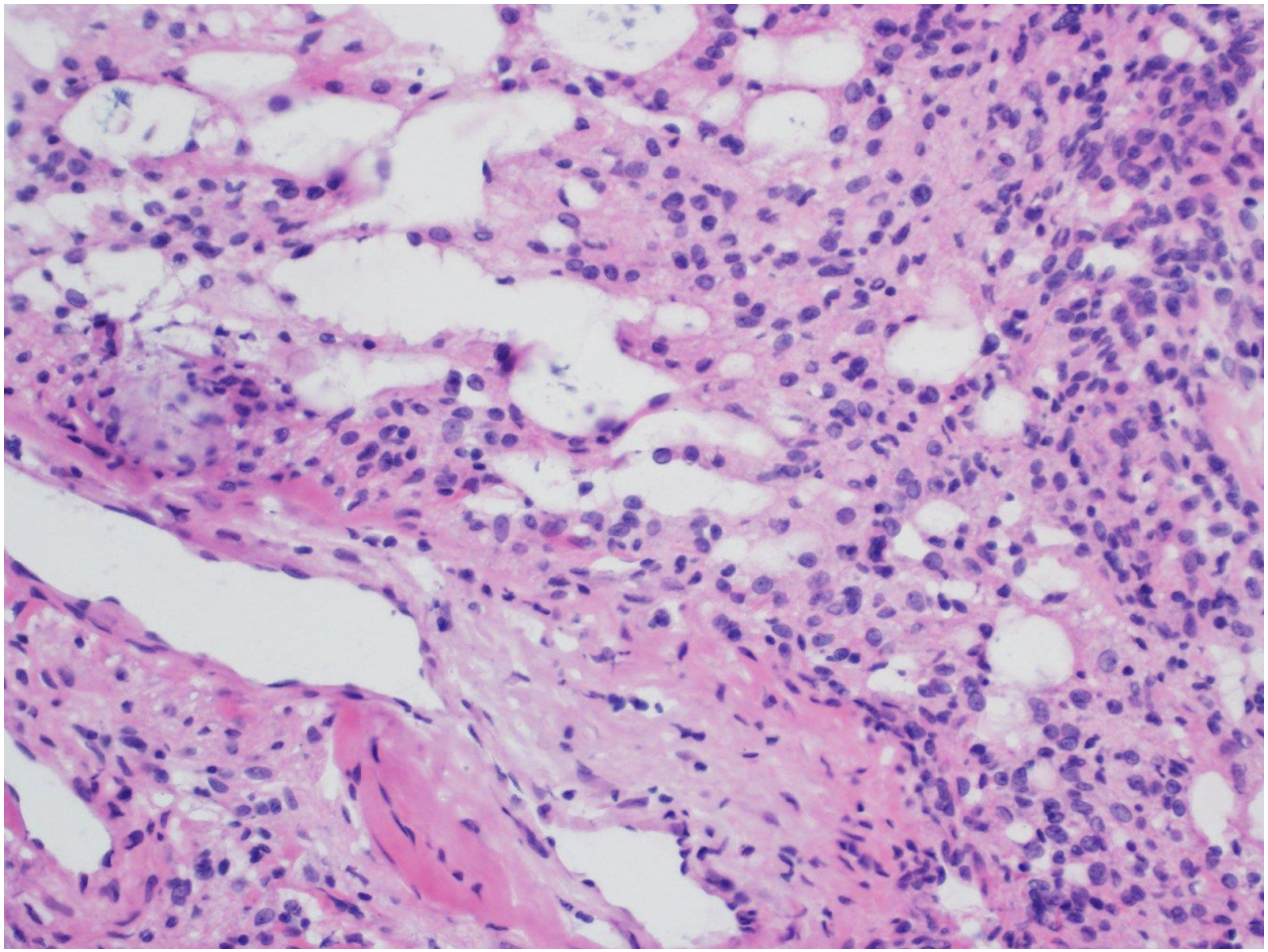


Severe arterial sclerosis >50%



Arteriolar hyalinosis: may be difficult to see

May receive “Lesion” biopsies for frozen



Angiomyolipoma

How do we do?

- Banff consensus (Liapis 2017), included study of pathologist interobserver variability
- Good-to-fair reproducibility for scoring of
  - Percentage glomerulosclerosis
  - Arterial intimal fibrosis
  - Interstitial fibrosis
- Arteriolar hyalinosis: poor reproducibility
- Acute tubular injury: poorer reproducibility
- Wedge biopsy: associated with better reproducibility for scoring of #glomeruli, glomerulosclerosis, interstitial fibrosis and tubular atrophy

Reporting

Interstitial fibrosis	None <5%;	Mild 6-25%	Moderate 26-50%	Severe >50% of cortex involved
Tubular atrophy	None 0%;	Mild <25%	Moderate 26-50%	Severe >50% of cortical tubules involved
Interstitial inflammation	None <10%;	Mild 10-25%	Moderate 26-50%	Severe >50% of cortex involved
Arterial intimal fibrosis	None 0%;	Mild <25%	Moderate 26-50%	Severe >50% vascular narrowing
Arteriolar hyalinosis hyalin restricted to subendothelial layer	None	Mild *	Moderate *	Severe *

*Mild: at least one arteriole
Moderate: more than one arteriole
Severe: multiple arterioles affected, circumferential

Banff Consensus (Liapis 2017)

Glomerular thrombi	None Mild * Moderate* Severe*
*mild <10% of capillaries occluded; moderate: 10-25% occlusion; severe: >25% occlusion evaluate in the most severely affected glomerulus	
Acute tubular injury/necrosis	None† Mild† Moderate † Severe†
†Mild: ATI – epithelial flattening, tubule dilation, nuclear dropout, loss of brush border; Moderate – focal COAGULATIVE TYPE necrosis; Severe – infarction.	
Other findings: (FSGS, nodular glomerulosclerosis, tumor, etc.)	

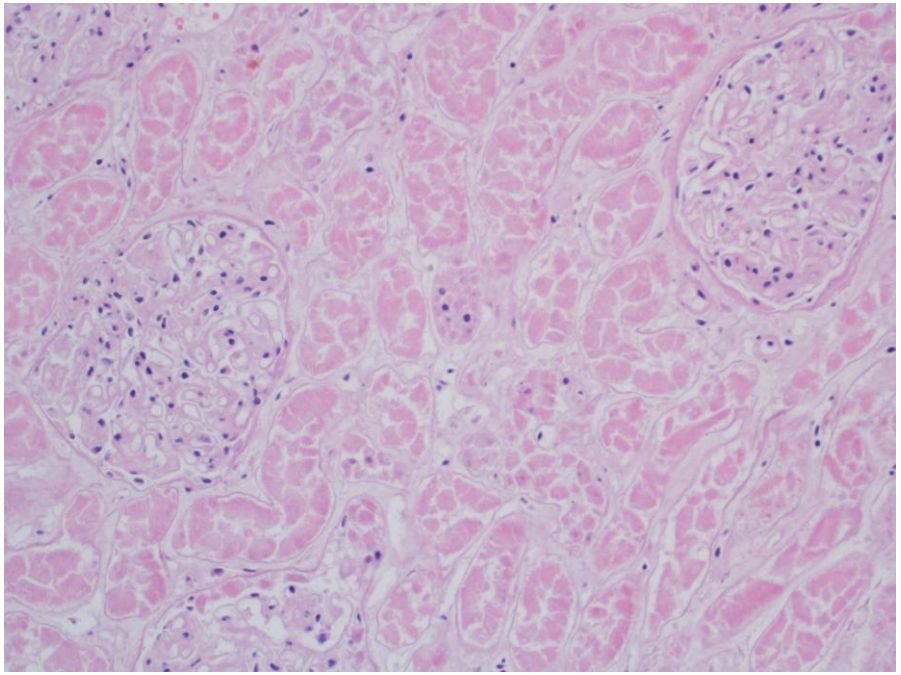
Banff Consensus (Liapis 2017)

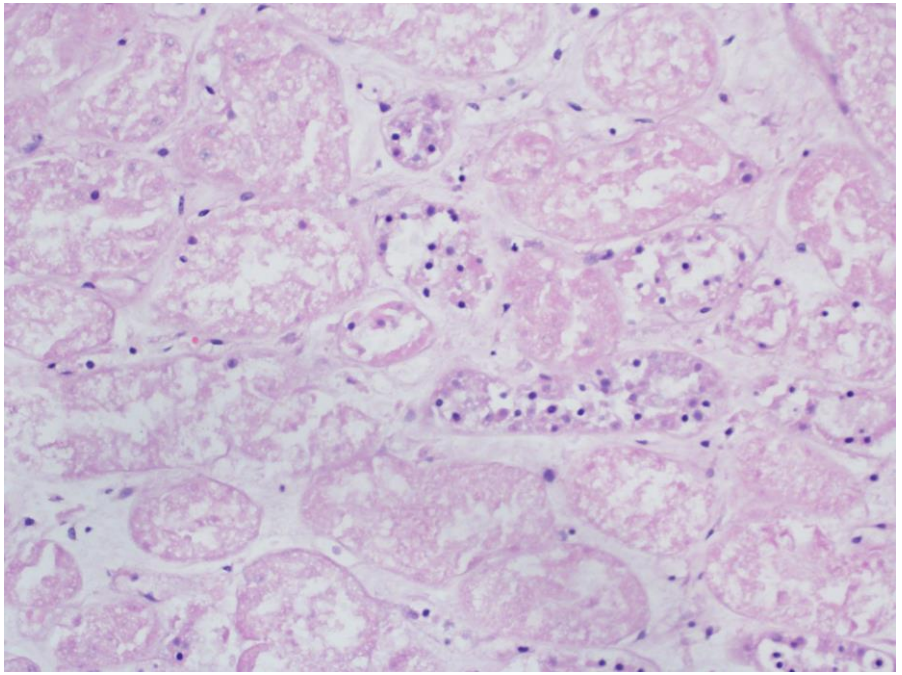
Autopsy Kidney

- More than 90,000 die of kidney disease in US per year
- Kidney findings are common at autopsy (Perrone 2018)
  - ~31% in 140 autopsies over 2 years at UChicago)
  - 60% of these had been missed at initial review
- Commonest findings in that series:
  - Diabetic nephropathy, bile cast nephropathy, thrombotic microangiopathy, infection-related GN, focal necrotizing/crescentic GN, LCCN etc (long tail of rarer cases)
  - Missed: Diabetic nephropathy (11/22), TMA (3/5), infection–related GN (3/4), LCCN (2/2)
- A key issue in pathology assessment is autolysis

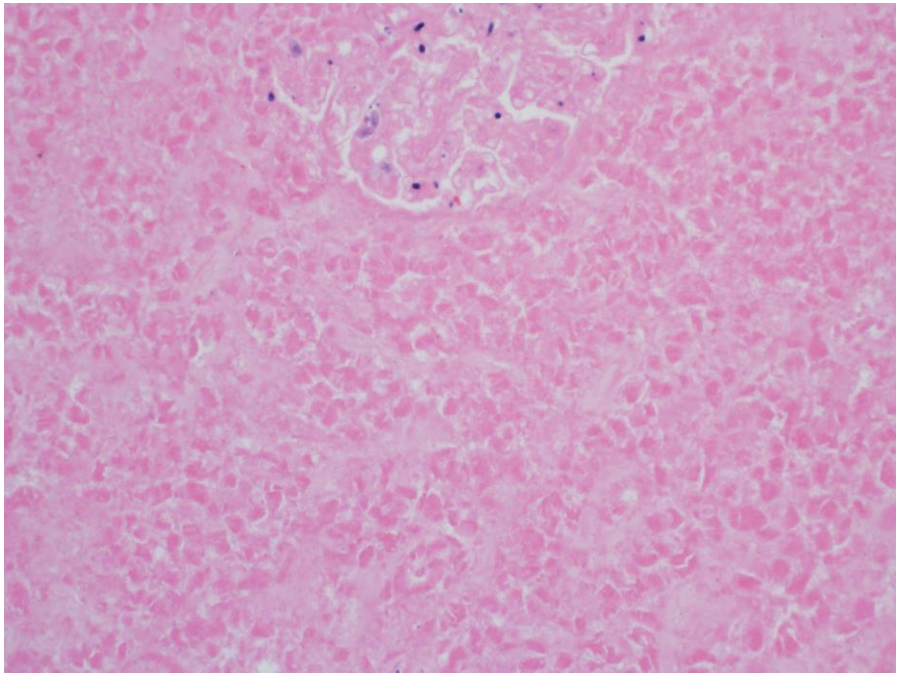
Autolysis versus Acute Tubular Injury

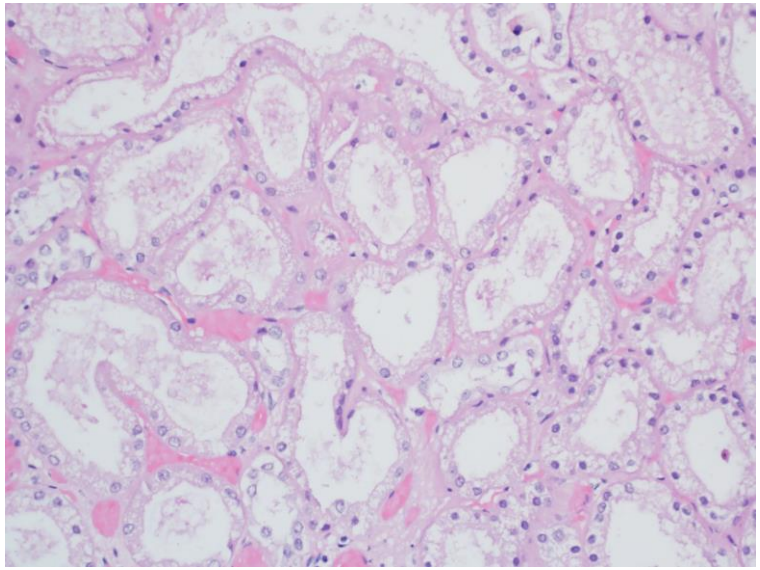
- Autolysis
  - Nuclear pyknosis (tubules and other compartments)
  - Degenerative changes of tubular cells (prox and distal)
  - Detachment of tubular cells from basement membranes
- Acute tubular injury
  - Proximal tubules particularly affected, distal tubules may be relatively preserved
  - Luminal dilatation, signs of regeneration

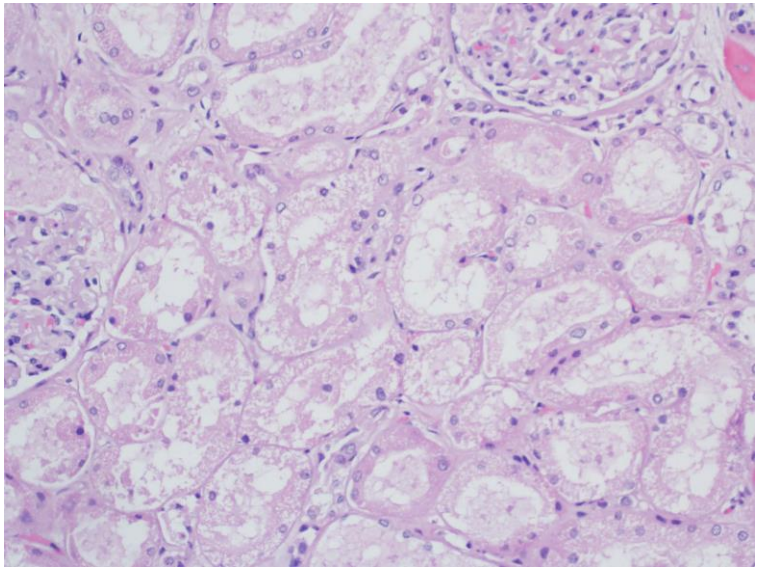




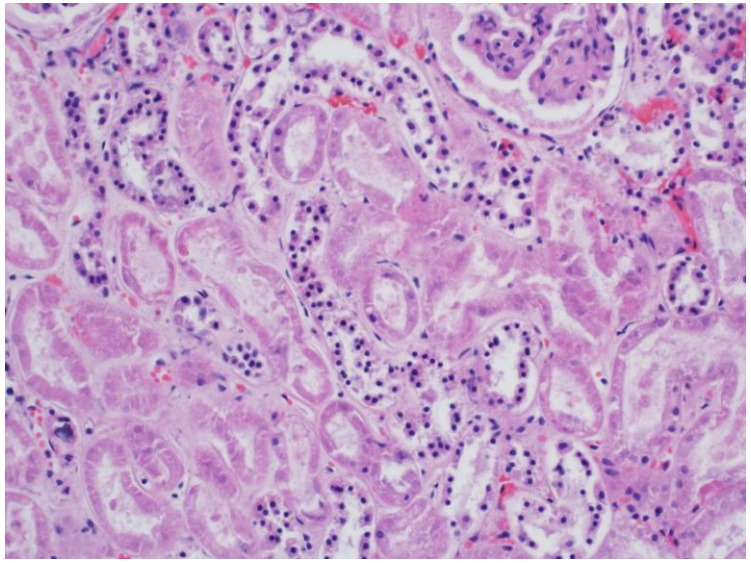
Autolysis

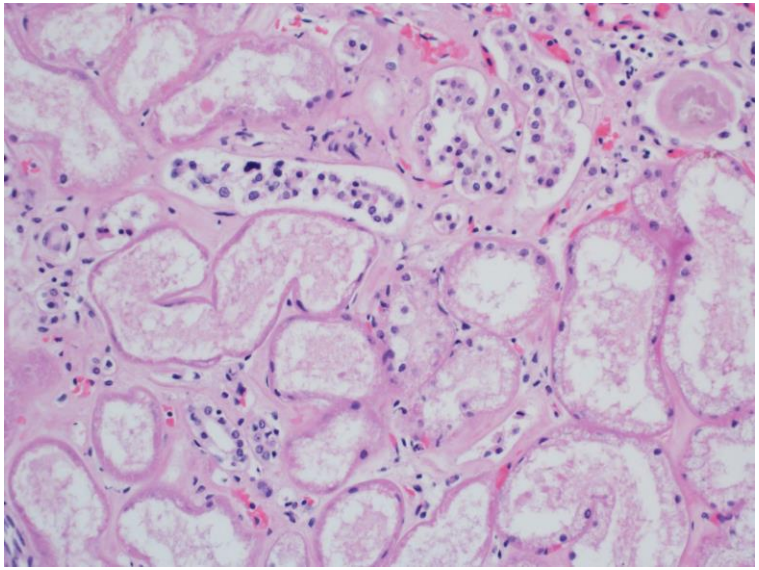


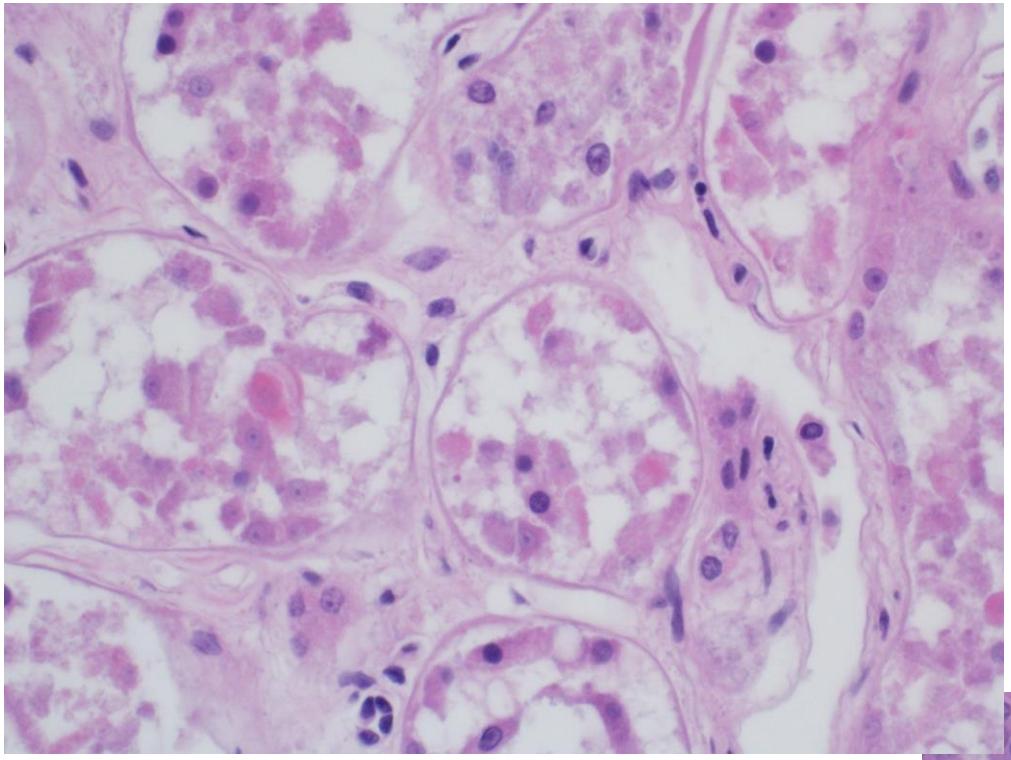




Acute tubular injury

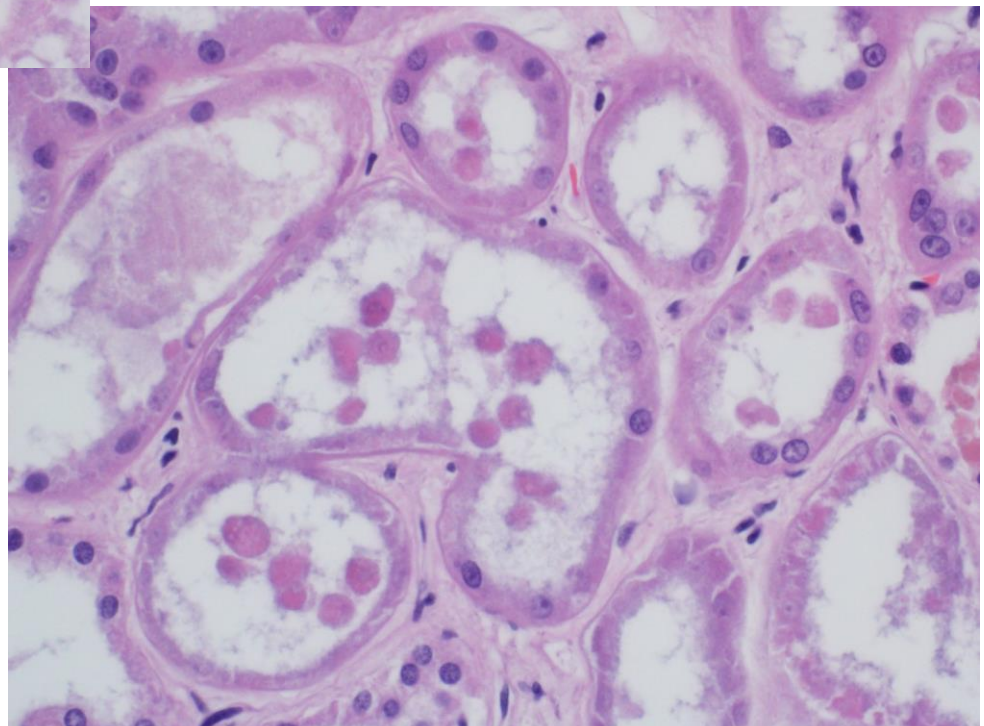




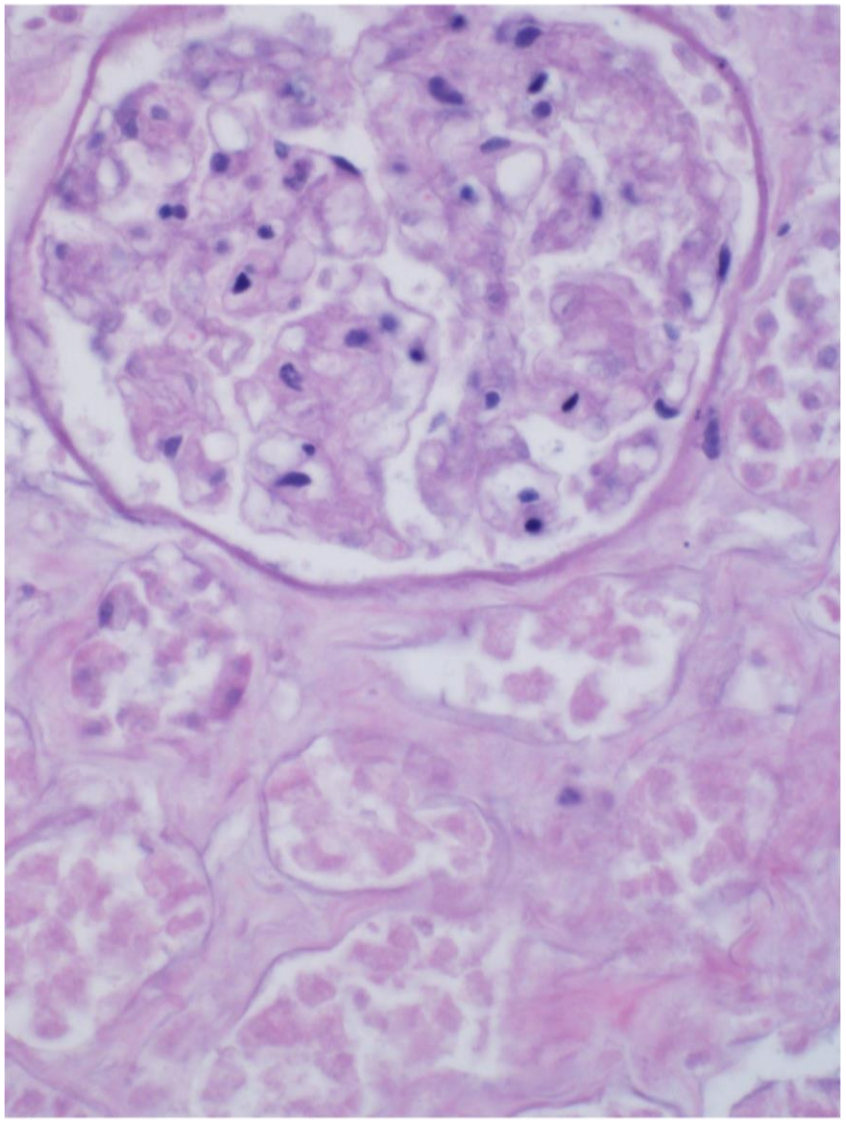


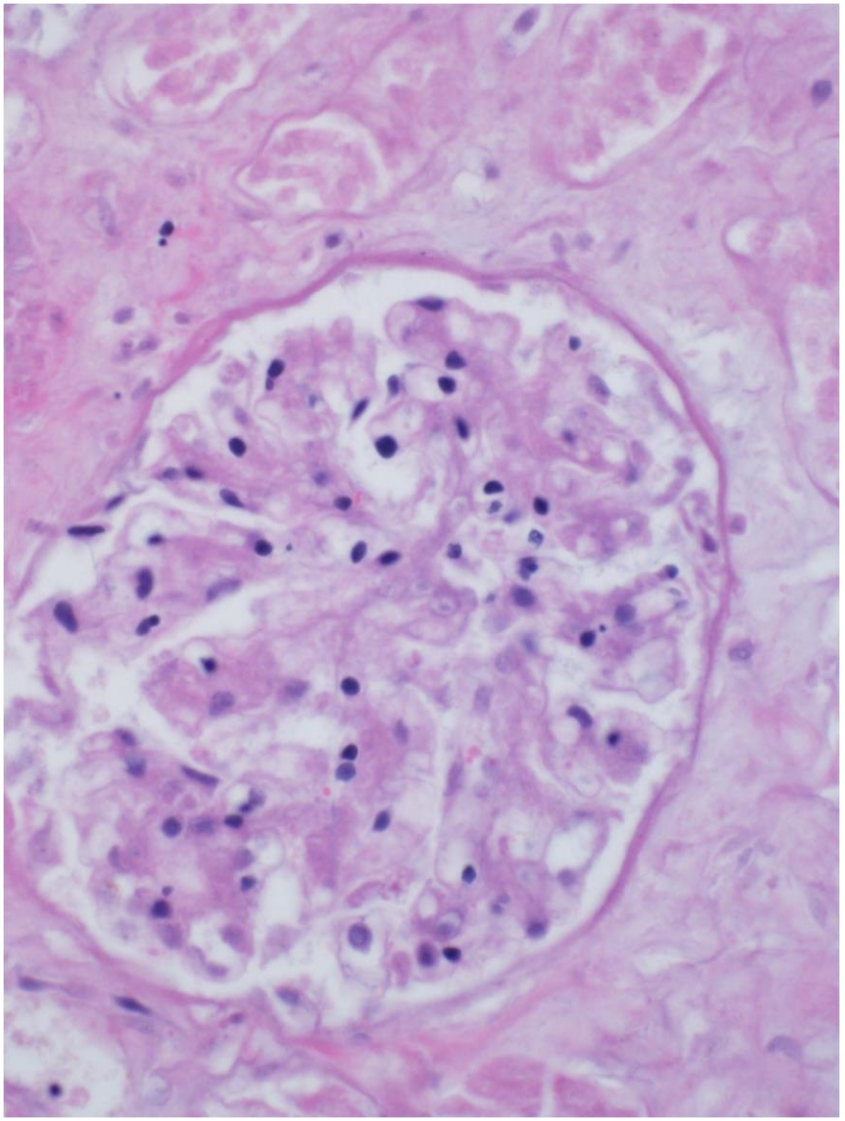
Autolysis

Acute tubular injury

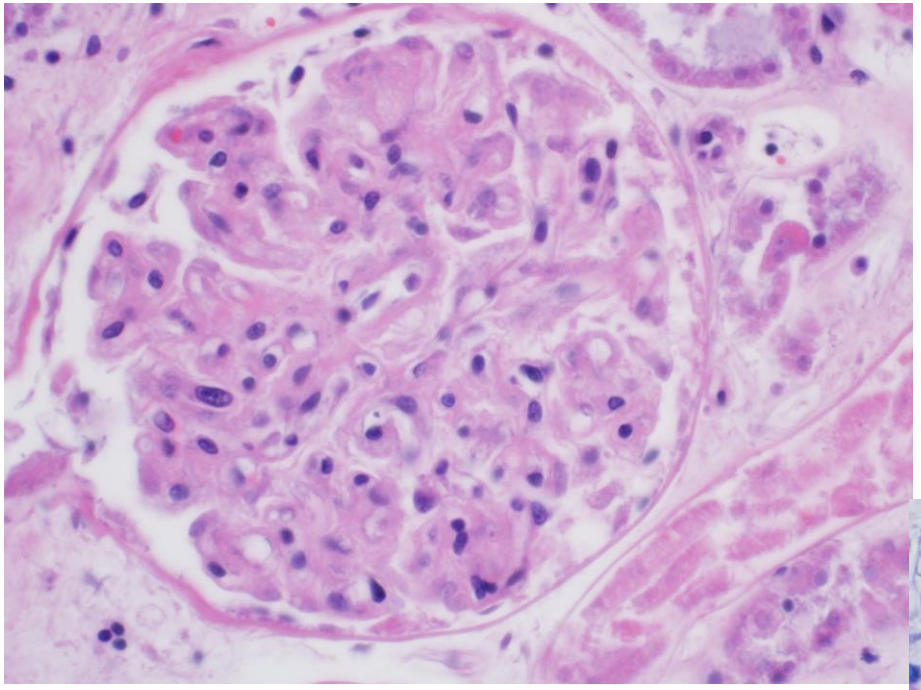


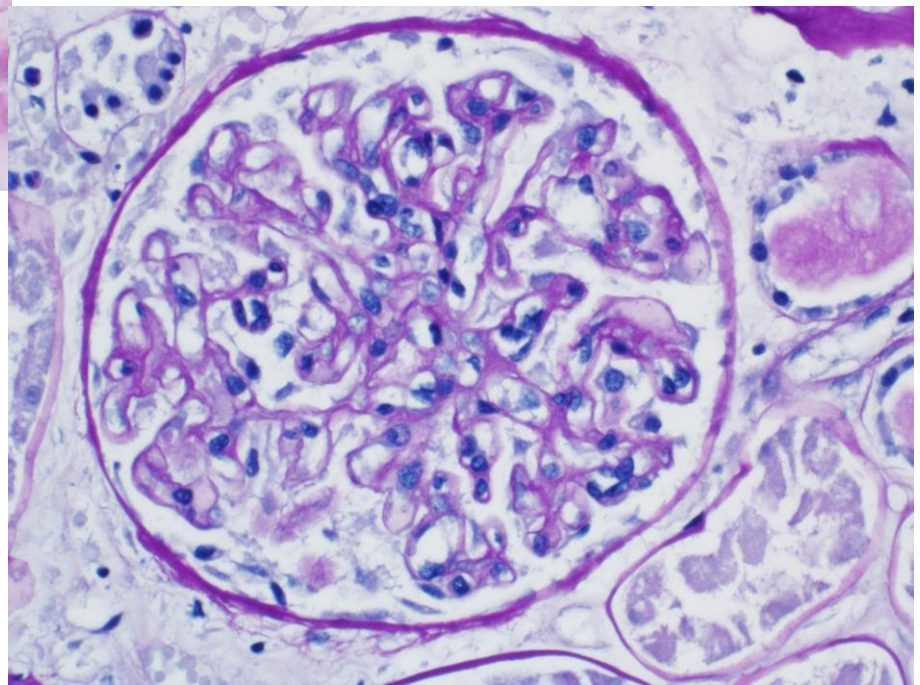
Diabetic Glomerulosclerosis



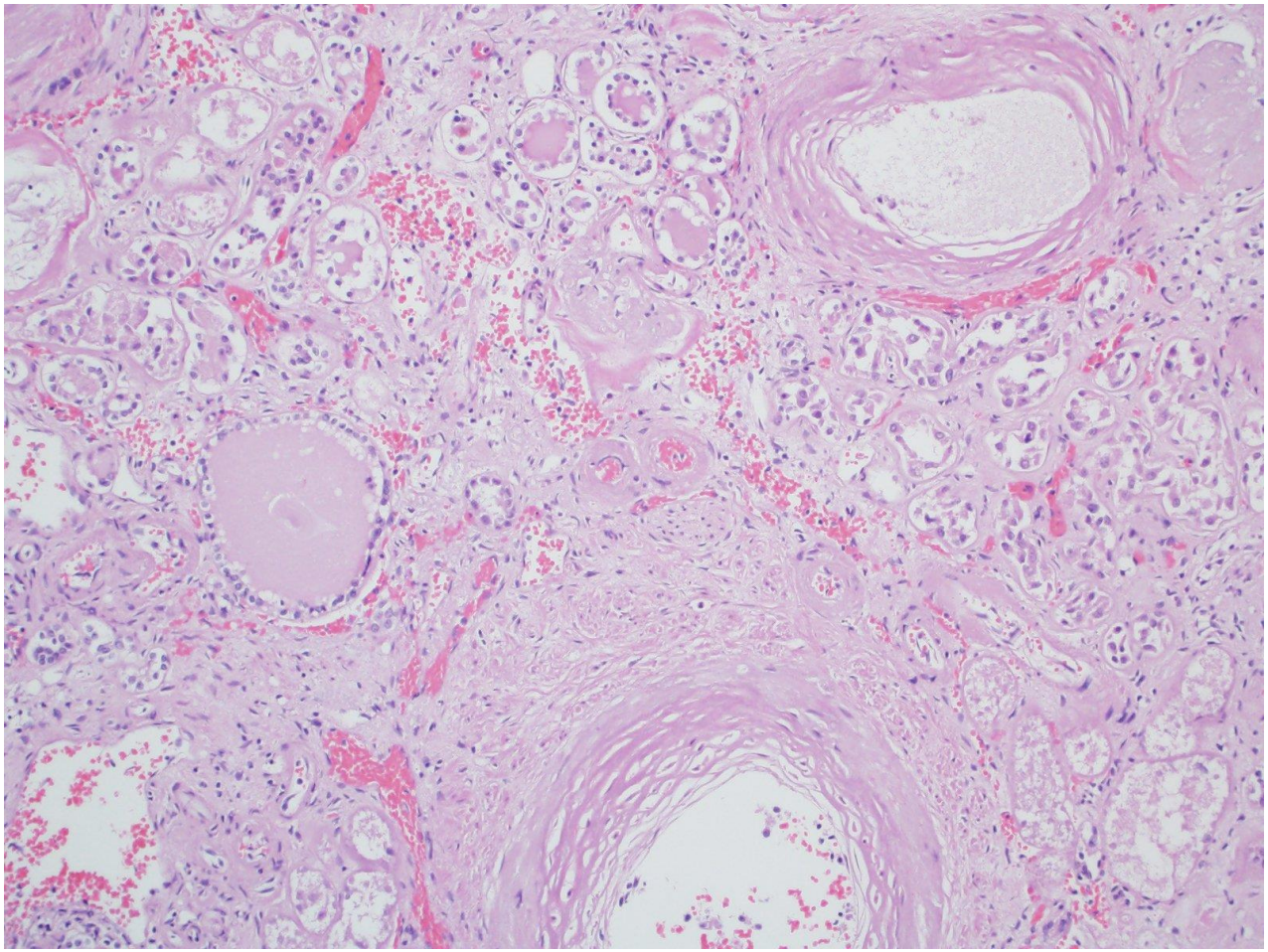


TMA (Chronic in this case)

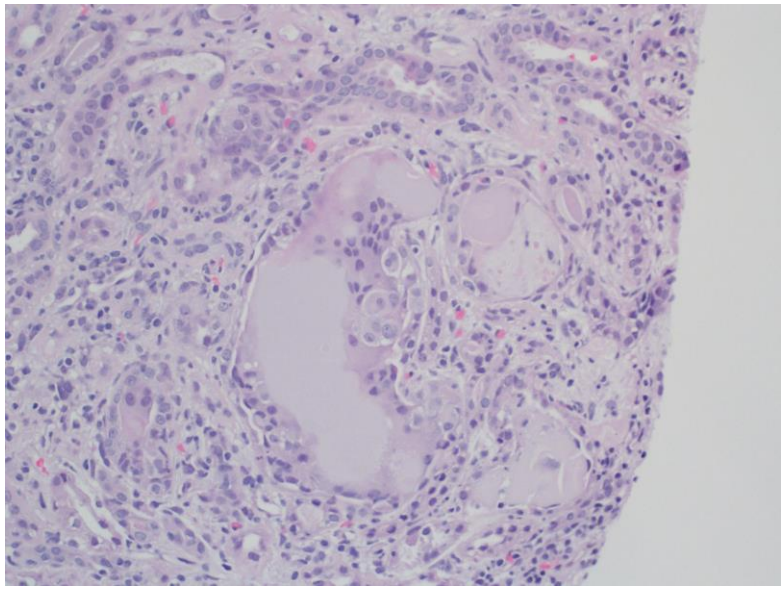


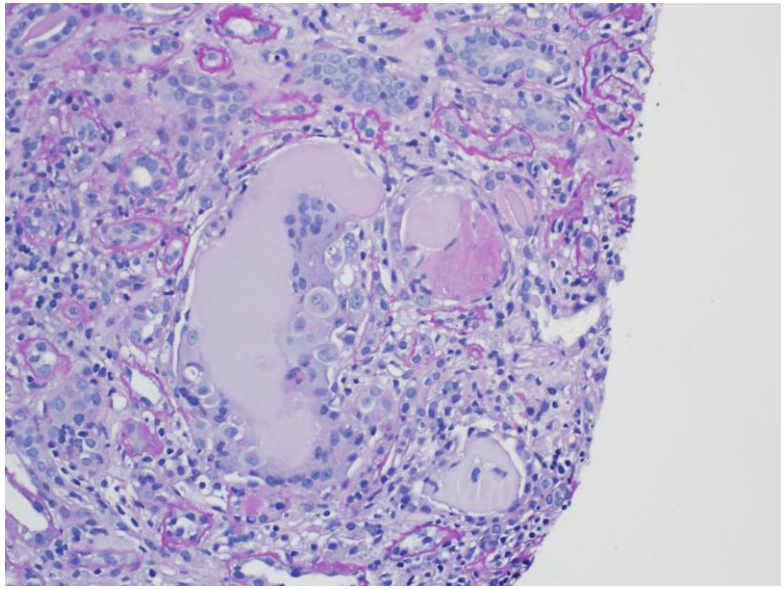


IFTA and Vascular Sclerosis



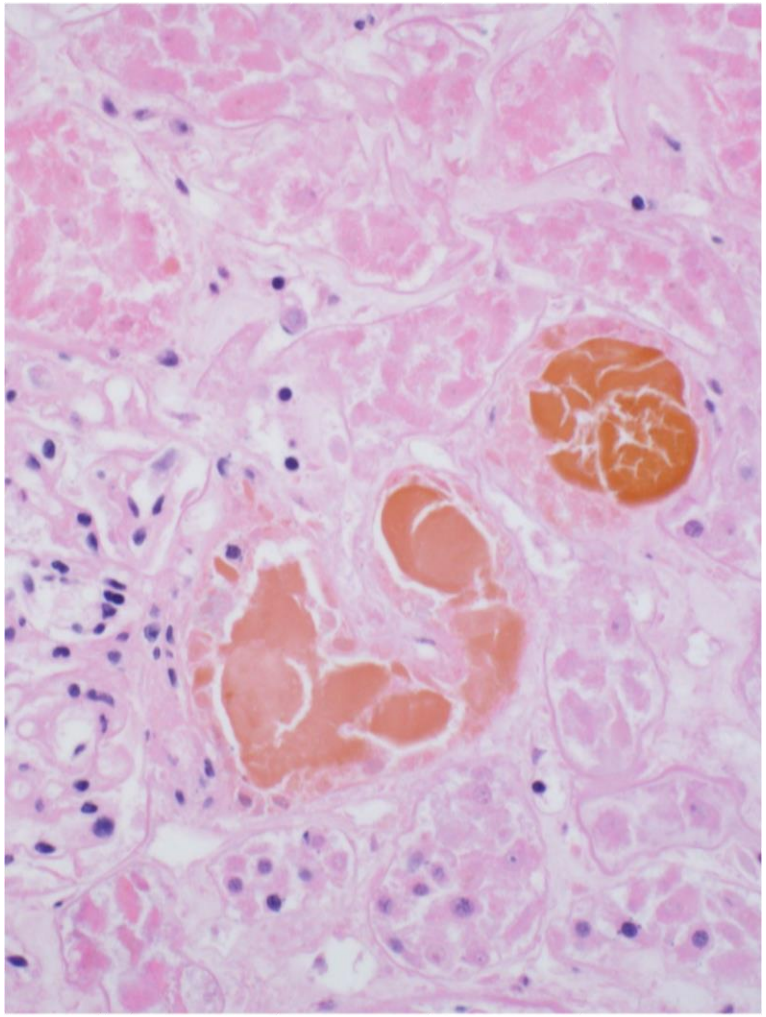
Monoclonal Immunoglobulin (Light Chain) Cast Nephropathy





- PAS pale (vs typical tubular casts)
- May be associated with giant cell and neutrophilic reaction
- “Shatter artifact”
- Associated acute tubular injury
- (Light chain restriction on IF)

Bile Cast Nephropathy



- Associated with severe liver dysfunction
- Causes acute tubular injury
- Red/yellow/green tubular casts
- Differential diagnosis for pigmented casts:
  - Hemoglobin
  - Myoglobin
  - LCCN
  - Hemosiderin

Autopsy Kidney Summary

- Many autopsy cases have kidney disease
- Most disease can be at least suspected on H&E
- IF and EM can be performed on FFPE tissue (but consider triaging fresh tissue if there is a suspicious clinical history)

Thank you!