

## Non-neoplastic Kidney Pathology for the General Surgical Pathologist

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2/12/20

### 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

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## 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!**

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## 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.

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## 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

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

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

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### 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): \_\_\_\_\_

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## 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

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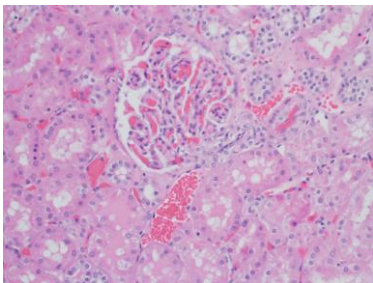
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## Normal Kidney



Four compartments: glomeruli, tubules, interstitium, vessels

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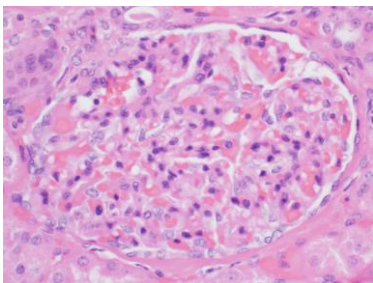
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## Normal Kidney (H+E)



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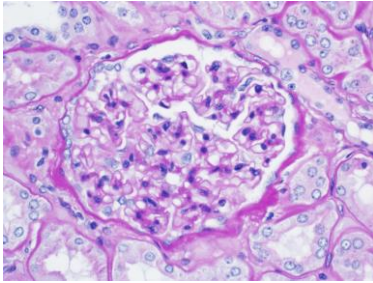
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## Normal Kidney (PAS)



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

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## 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

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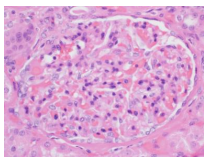
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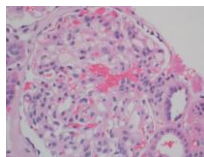
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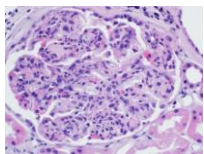
## Glomerular Proliferative Patterns



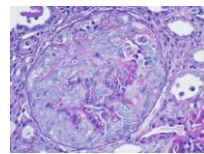
Normal



Mesangial Proliferation



Endocapillary Proliferation



Extracapillary Proliferation / Crescent

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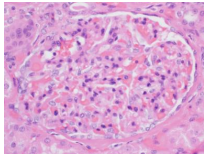
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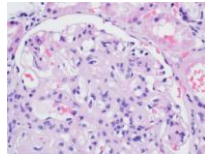
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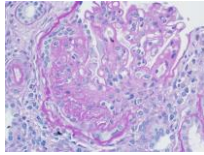
## Glomerular Sclerosing Patterns



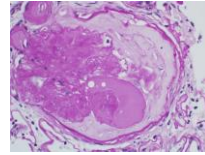
Normal



Diffuse mesangial sclerosis



Segmental sclerosis



Global sclerosis

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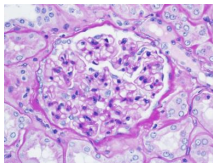
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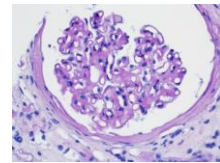
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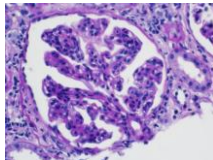
## Thickened Glomerular Basement Membranes



Normal



Membranous nephropathy



Membranoproliferative GN

Other Causes include:

Advanced Diabetic glomerulosclerosis  
Amyloidosis  
Chronic thrombotic microangiopathy

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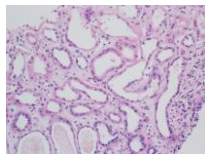
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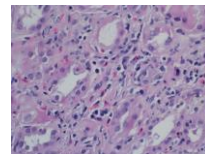
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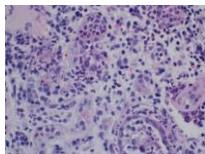
## Tubulo-interstitial patterns of injury



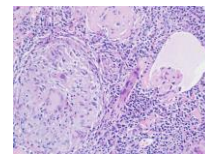
Acute Tubular Injury



Allergic Interstitial Nephritis (Eosinophils)



Acute pyelonephritis (neutrophils)



Granulomatous Interstitial Nephritis

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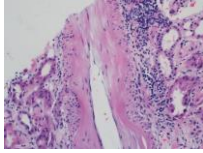
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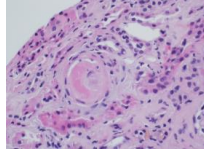
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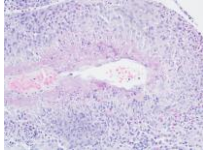
## Vascular patterns of injury



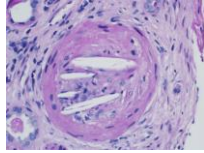
Vascular sclerosis



Thrombus



Vasculitis



Atheroembolism

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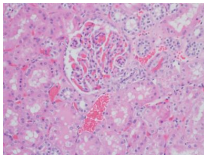
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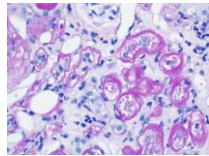
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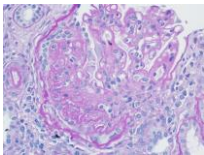
## Chronic Parenchymal Damage



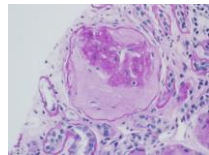
Normal kidney cortex



Interstitial fibrosis and tubular atrophy



(Secondary focal segmental sclerosis)



Global sclerosis

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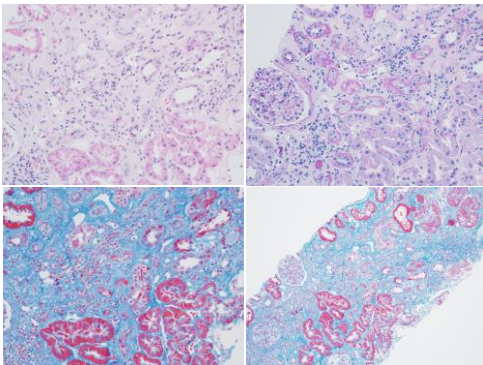
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## Interstitial fibrosis and tubular atrophy ("IFTA")




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## 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
  - Mucoïd change of intima
  - Hyperplastic change of small arteries/arterioles ("onion-skinning")
  - Thrombi

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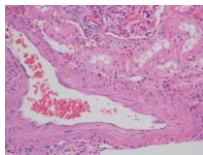
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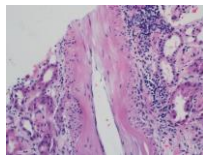
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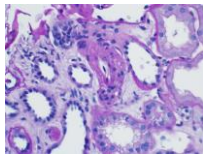
## Hypertensive Kidney Disease



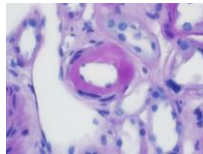
Arterial sclerosis, moderate



Arterial sclerosis, severe



Arteriolosclerosis



Arteriolar hyalinosis

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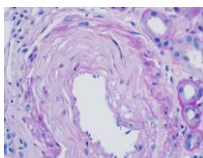
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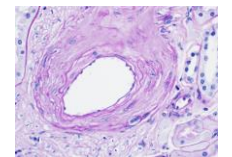
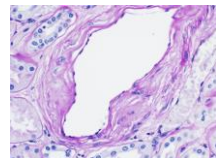
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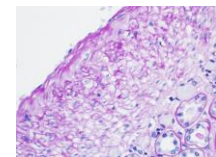
## Hypertensive Arterial Disease



Fibrosis of intima and thinning of media



Reduplication of internal elastic lamina



Hypertrophy of media

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## 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)

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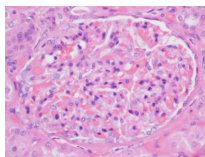
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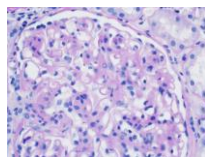
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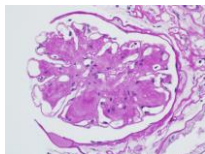
## Diabetic Glomerulosclerosis



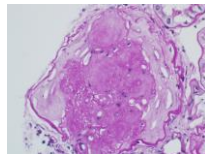
Normal



Diffuse mesangial sclerosis



Nodular Glomerulosclerosis



Global sclerosis

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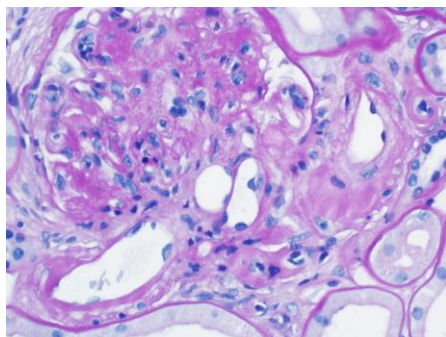
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## Diabetic Kidney Disease



Hyalinosis of afferent and efferent arterioles

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## 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)

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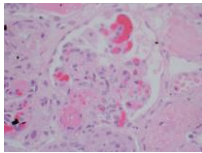
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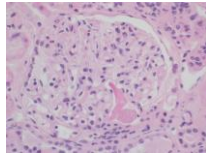
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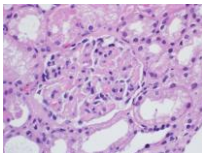
## Acute Thrombotic Microangiopathy



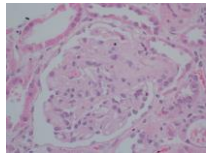
Thrombus at vascular pole, fragmented RBCs



Thrombus



Subtle intracapillary thrombi



“Bloodless” appearance, fragmented RBCs

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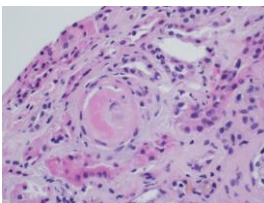
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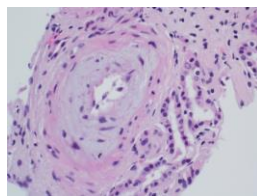
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## Acute Thrombotic Microangiopathy



Arterial/arteriolar thrombus



Mucoid intimal change of artery

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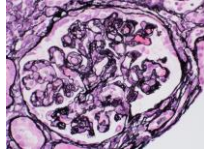
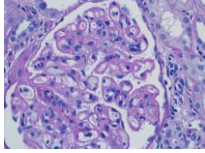
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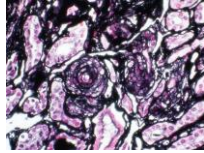
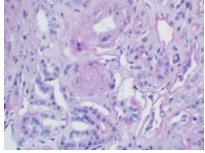
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## Chronic Thrombotic Microangiopathy



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



Hyperplastic arteriosclerosis / "onion skinning"

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## 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)

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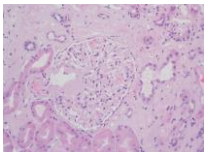
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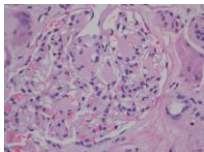
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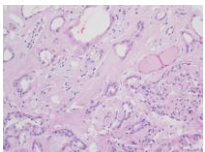
## Amyloidosis



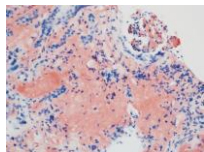
Amyloid involving glomerulus and interstitium



Amyloid involving glomerulus, simulating nodular diabetic GS



Amyloid involving interstitium



Don't forget Congo Red stain if suspicious!

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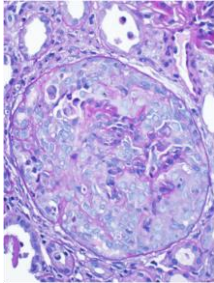
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## Crescentic Glomerulonephritis



- 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)

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## 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

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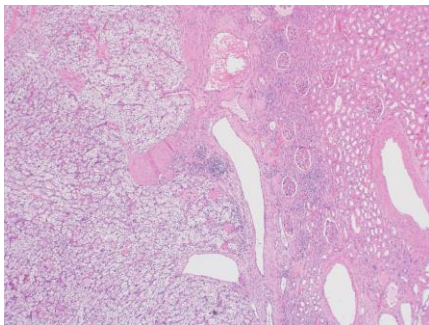
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## Tumor capsule



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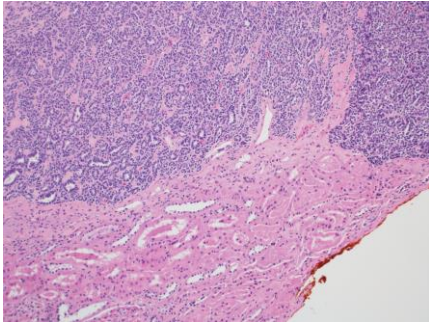
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## Benign tumors may lack capsule



Above: metanephric adenoma  
Another characteristic example is oncocytoma

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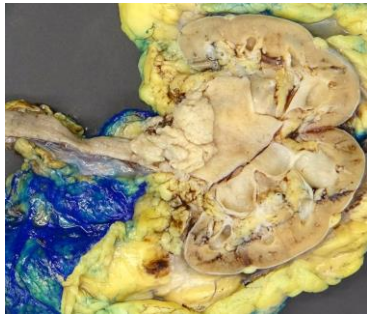
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## Obstruction due to tumor



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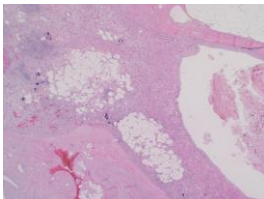
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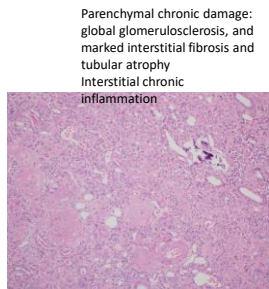
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## Obstruction due to tumor



Hydronephrosis with calyceal dilatation, and parenchymal atrophy and inflammation



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

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## 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

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## 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)

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## 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)

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## 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

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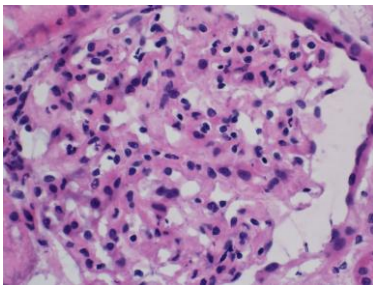
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## Glomerulus: Frozen Section



Is it hypercellular?

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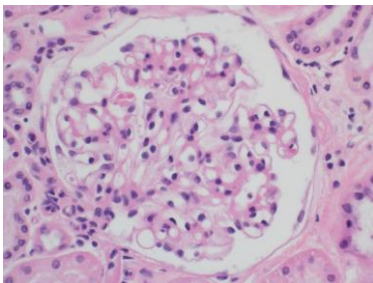
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## Glomerulus: Permanent (same case)



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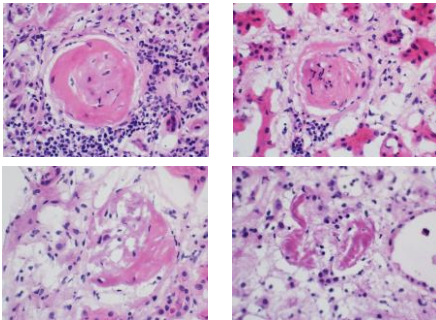
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## Global Glomerulosclerosis



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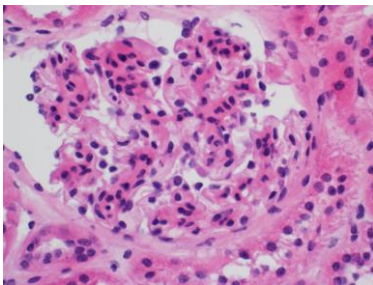
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## Diabetic Glomerulosclerosis



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

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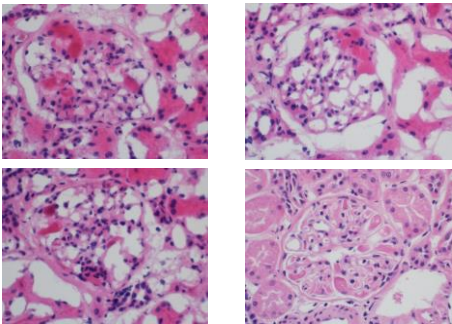
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## Glomerular Thrombi



Perm

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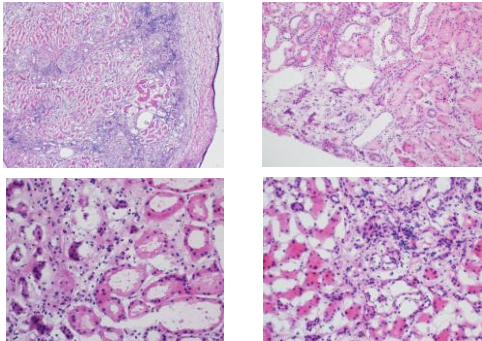
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## Interstitial Fibrosis and Tubular Atrophy



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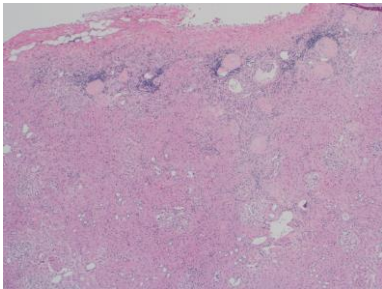
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## Pitfall for assessment of chronic damage: subcapsular scarring with hypertension



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

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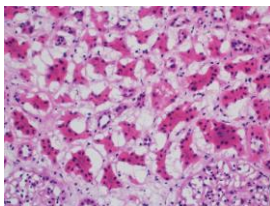
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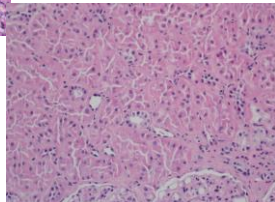
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## Tubular Frozen Section Artifact



Frozen section

Same case - permanent section



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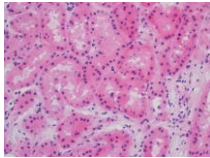
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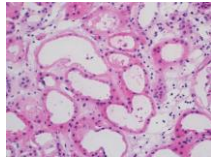
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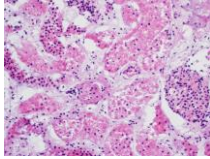
## Acute Tubular Injury/Necrosis/Infarction



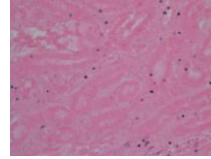
Normal (very good frozen section!)



Acute tubular injury (not usually this easy!)



Acute tubular necrosis



Infarction or cortical necrosis

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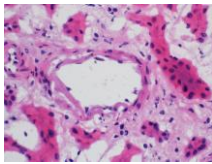
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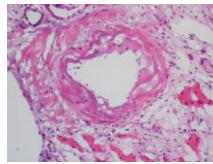
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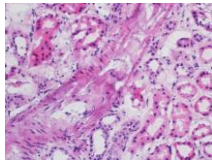
## Arterial Sclerosis and Arteriolar Hyalinosis



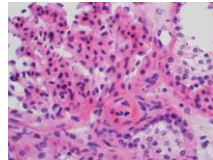
Mild arterial sclerosis <25%



Moderate arterial sclerosis 25-50%



Severe arterial sclerosis >50%



Arteriolar hyalinosis: may be difficult to see

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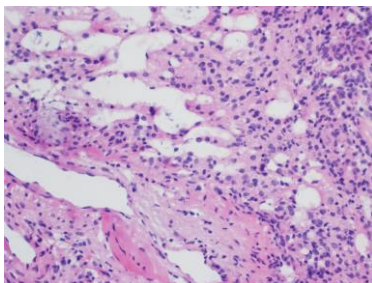
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## May receive "Lesion" biopsies for frozen



Angiolymphoma

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## 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

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## Reporting

<b>Interstitial fibrosis</b>	None <5%	Mild 6-25%	Moderate 26-50%	Severe >50% of cortex involved
<b>Tubular atrophy</b>	None 0%	Mild <25%	Moderate 26-50%	Severe >50% of cortical tubules involved
<b>Interstitial inflammation</b>	None <10%	Mild 10-25%	Moderate 26-50%	Severe >50% of cortex involved
<b>Arterial intimal fibrosis</b>	None 0%	Mild <25%	Moderate 26-50%	Severe >50% vascular narrowing
<b>Arteriolar hyalinosis</b> 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)

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<b>Glomerular thrombi</b>	None	Mild *	Moderate*	Severe*
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\*mild <10% of capillaries occluded; moderate: 10-25% occlusion; severe: >25% occlusion  
evaluate in the most severely affected glomerulus

<b>Acute tubular injury/necrosis</b>	None†	Mild†	Moderate †	Severe†
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†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)

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## 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

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## 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

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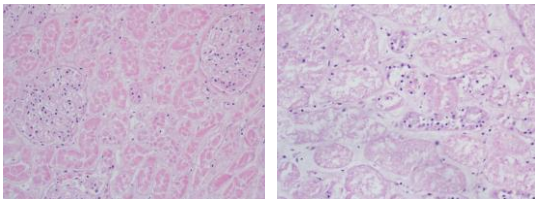
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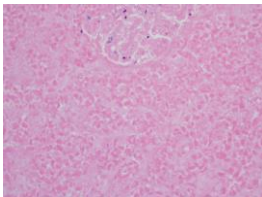
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Autolysis



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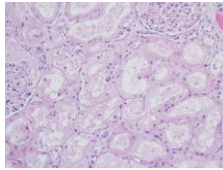
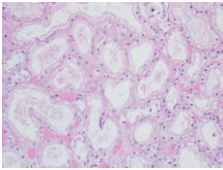
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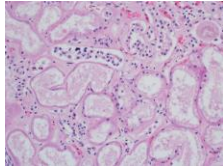
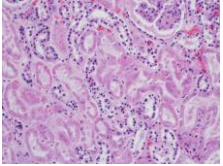
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Acute tubular injury



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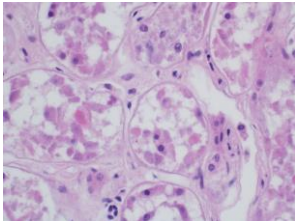
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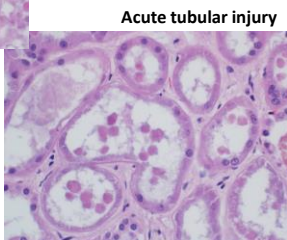
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Autolysis



Acute tubular injury

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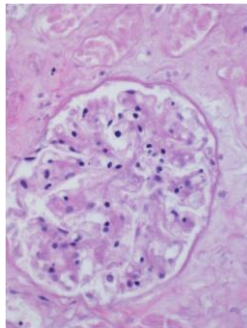
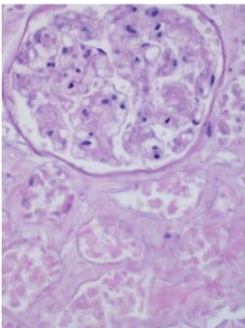
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## Diabetic Glomerulosclerosis



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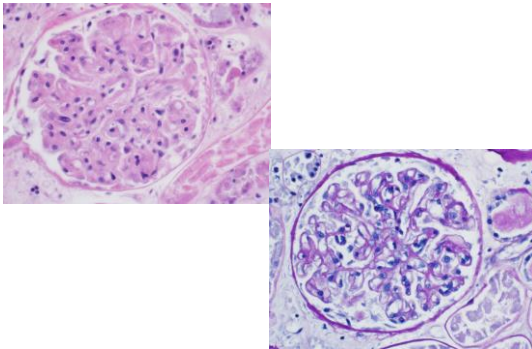
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### TMA (Chronic in this case)



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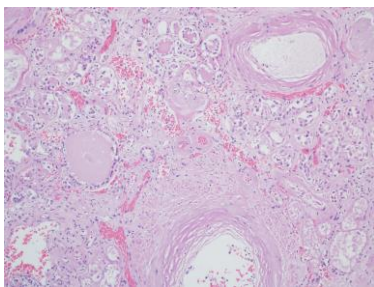
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### IFTA and Vascular Sclerosis



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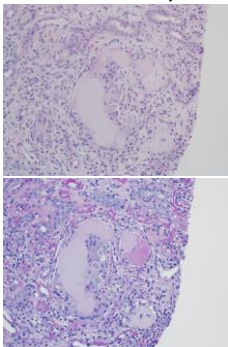
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### Monoclonal Immunoglobulin (Light Chain) Cast Nephropathy



- 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)

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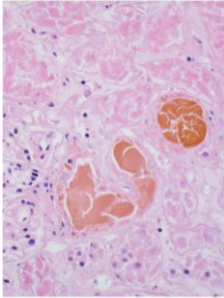
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## Bile Cast Nephropathy



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

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## 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)

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Thank you!