Pathology of Renal Transplantation

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Renal Biopsy-Diagnostic Value

- **Gold standard for diagnosis of graft dysfunction**
  - **Occurring in up to 30% early post transplant & at a yearly rate of 2-4% after the 1st year**
- **Adequacy**
  - **At least 7 non-sclerotic glom & 1 artery (Banff)**
  - **Medulla alone is insufficient**
    - **If prominent monocyte infiltrate with tubulitis- rejection likely**
    - **Medulla can be used for C4d staining**
  - **Subcapsular bx often shows inflammation & fibrosis (not representative)**

Banff Classification

- 1. Normal
- 2. Antibody-mediated rejection (AMR)
  - Hyperacute
  - Acute
  - Chronic active
- 3. Borderline changes: suspicious for acute T-cell-mediated rejection
- 4. T-cell-mediated rejection (TCMR)
  - Acute (Types IA; IB; IIA; IIB; III)
  - Chronic active
- 5. Interstitial fibrosis & tubular atrophy, no evidence of any specific etiology
- 6. Others: changes not related to rejection

T-cell-mediated rejection (TCMR)

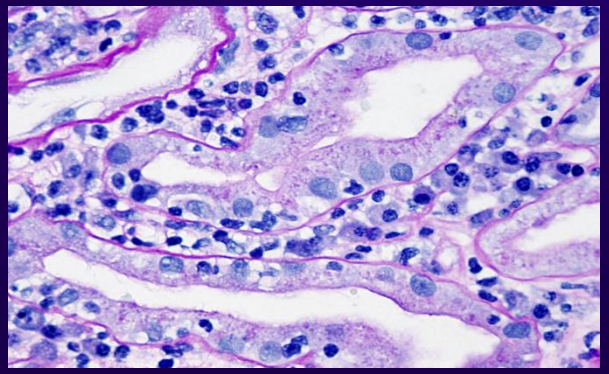
- **Acute**
  - IA: >25% parenchyma affected (i2 or i3) and focal moderate tubulitis (t2)
  - IB: >25% parenchyma affected (i2 or i3) and focal severe tubulitis (t3)
  - IIA: mild to moderate intimal arteritis (v1)
  - IIB: severe intimal arteritis comprising >25% of the luminal area (v2)
  - III: transmural arteritis/arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3)
- **Chronic active**
  - Obliterative transplant arteriopathy- intimal fibrosis with mononuclear cell infiltration in fibrosis, formation of neo-intima

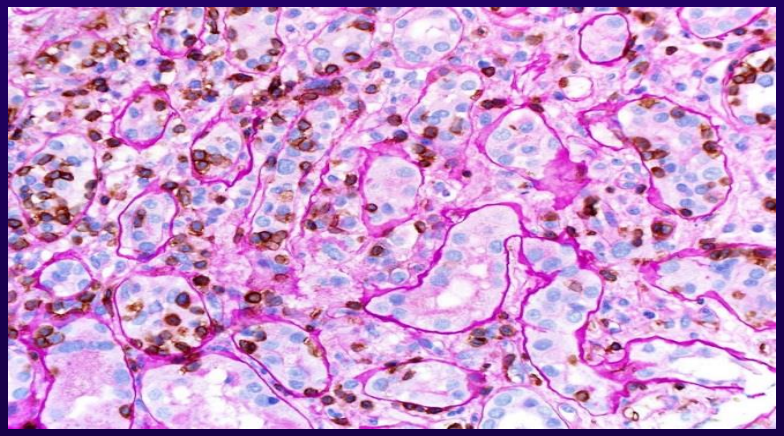
Acute TCMR-Clinical

- Most frequent type of rejection- abrupt rise in serum Cr
  - Most commonly seen in the first 4 wks after transplantation
  - Can occur any time (rare in compliant patient after the 1st month)
  - 20-30% are PTC C4d+; combined cellular/humoral rejection
- Mediated primarily by T cells reacting to donor histocompatibility antigens in the kidney and affects the tubules, interstitium, vessels and glomeruli, separately or in combination

Acute Cellular Rejection-Tubulitis

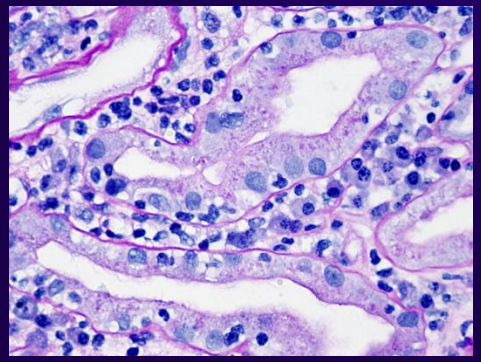
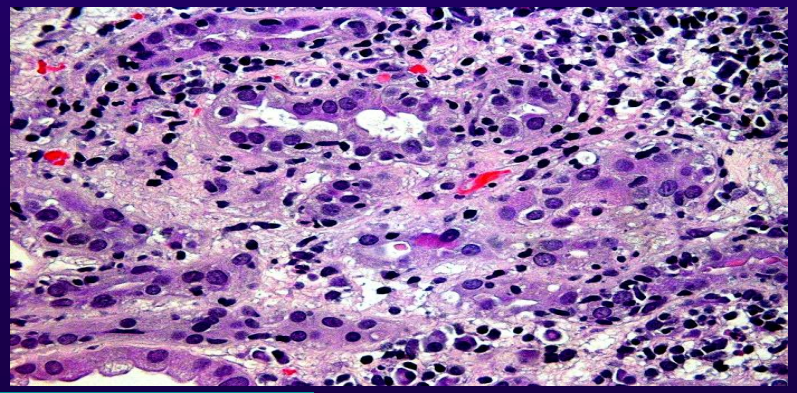
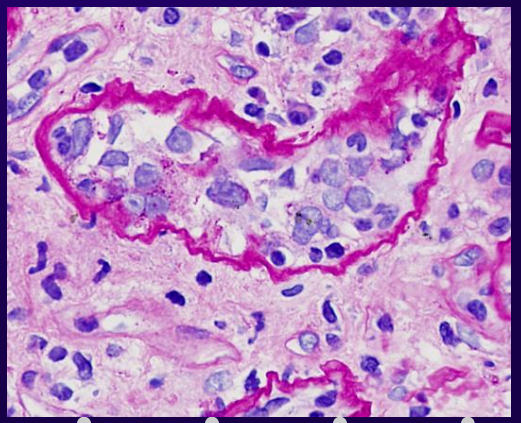
- **Tubulitis: infiltration of the tubular epithelium by inflammatory cells (mostly in distal tubules)**
- **Banff Grading**
  - **t0 – no tubulitis**
  - **t1 – 1~4 inflammatory cells in the most inflamed tubular cross-section**
  - **t2 – 5~10 inflammatory cells per tubular cross-section**
  - **t3 – > 10 inflammatory cells per tubular cross-section**





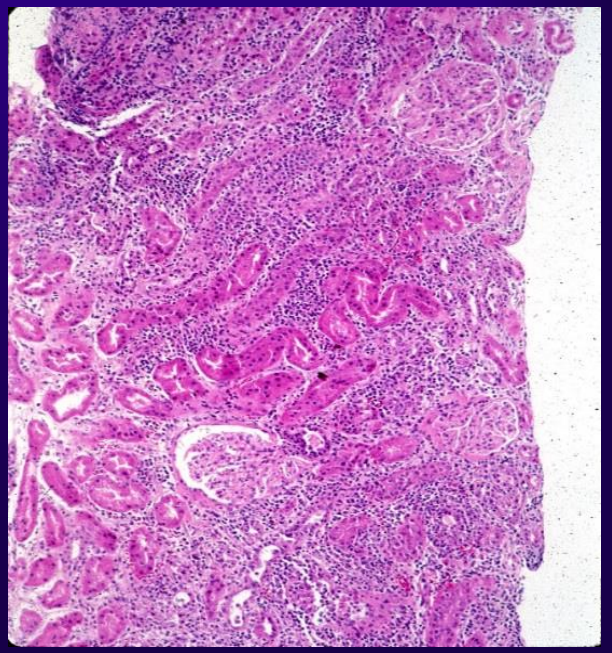
Acute Cellular Rejection-Pathology

- **Tubulitis: infiltration of the tubular epithelium by inflammatory cells (mostly in distal tubules)**
  - **Tubulitis in atrophic tubules is not a diagnostic feature of acute TCMR**
  - **Recent understanding: inflammatory cell infiltrate in fibrotic area with tubulitis in atrophic tubules is a feature of ongoing active inflammation**
  - **Newly introduced total inflammation score (ti)**
  - **Tubular degeneration and patchy tubular necrosis secondary to rejection are frequently seen**

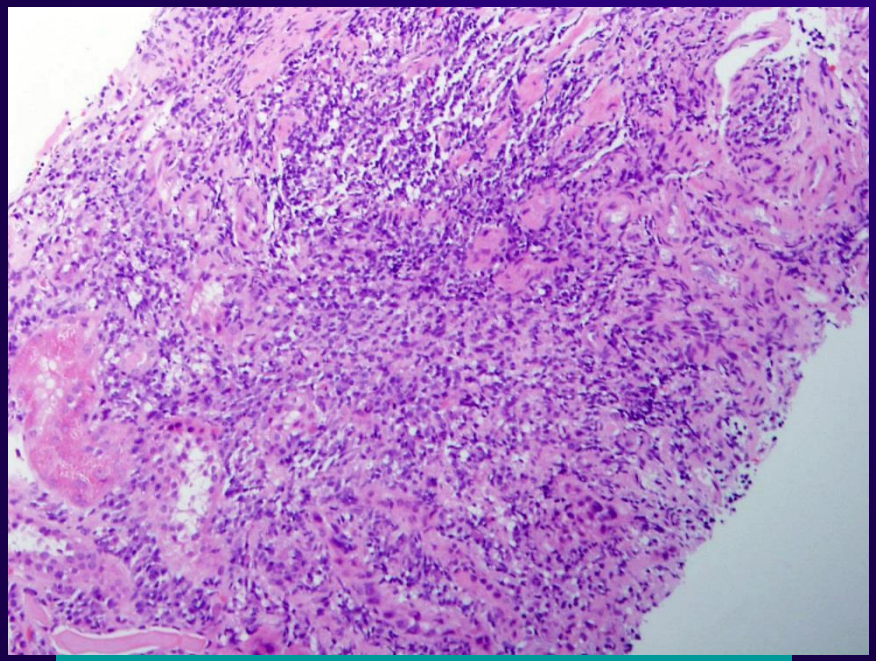
Acute Cellular Rejection-Pathology

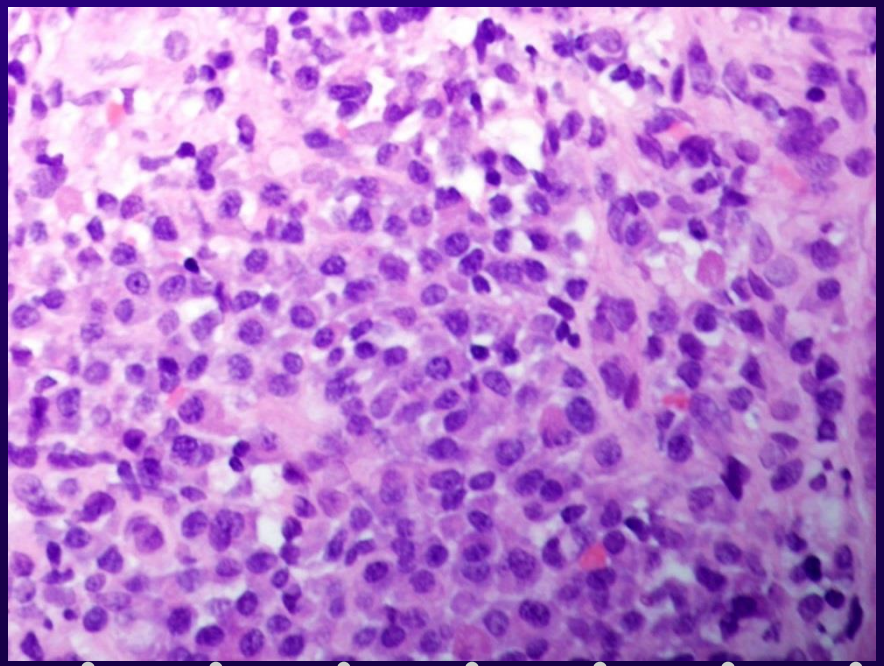
- **Interstitium:**
  - **Mononuclear cell infiltrate (largely T-cells and macrophages); scattered PMNs, plasma cells and eosinophils may be seen; occasionally large number of eosinophils present**
  - **Edema; hemorrhage is unusual, if present, consider more severe rejection process**
- **Banff Grading**
  - **i0- <10% cortex involved by inflammation**
  - **i1- 10~25% cortex involved by inflammation**
  - **i2- 26%~50% cortex involved by inflammation**
  - **i3- >50% cortex involved by inflammation**



Plasma cell rich late cellular rejection

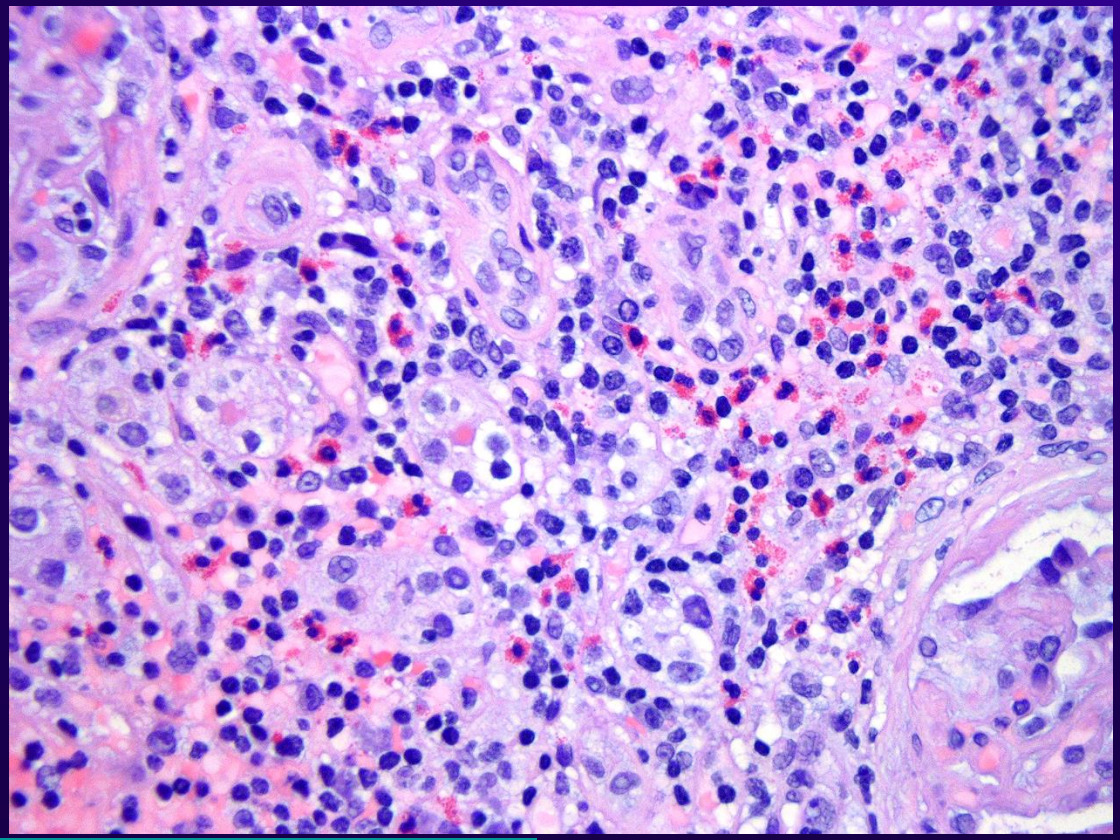
- Late acute rejection episodes (months or years posttransplant): large numbers of plasma cells (so called “plasma cell rich late acute rejection”)
- Many cases are PTC C4d+, representing a late mixed acute cellular and humoral rejection
- Often do not respond well to antirejection therapy





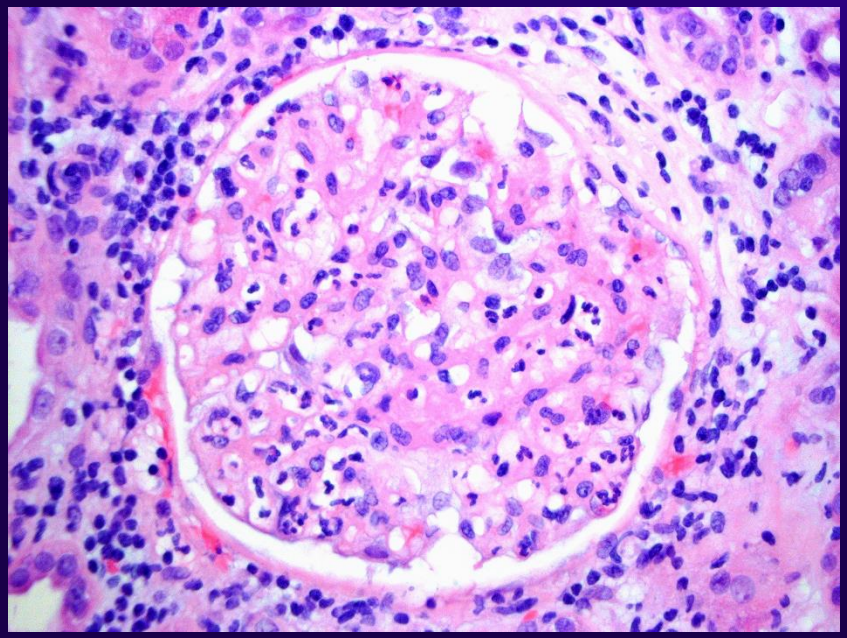
Late Acute cellular Rejection

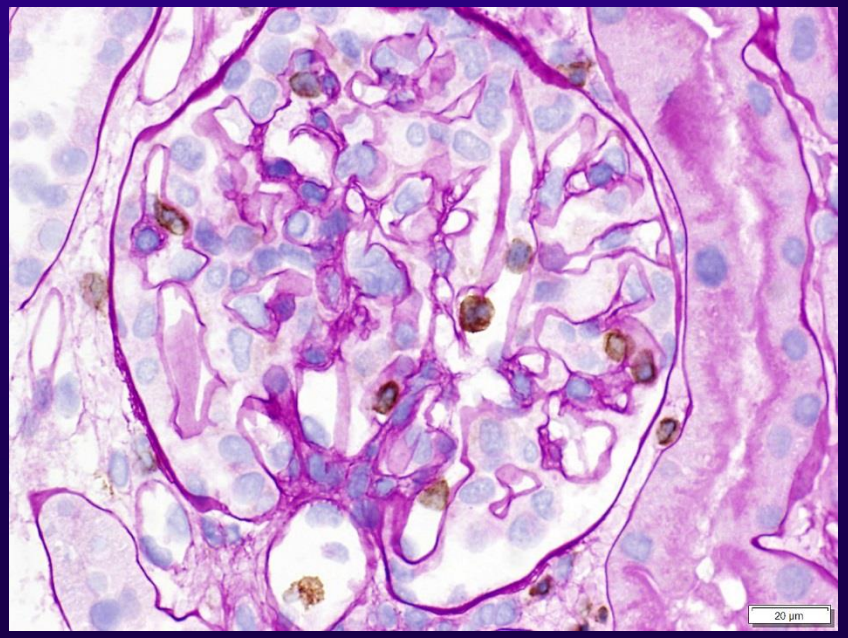
- **Numerous eosinophils**
- **Needs to rule out drug-induced interstitial nephritis**



Acute Cellular Rejection-Pathology

- **Glomeruli**
  - **Typically normal**
  - **Mild glomerulitis (increase in glomerular intracapillar mononuclear cells) may be noted; often focal/segmental**



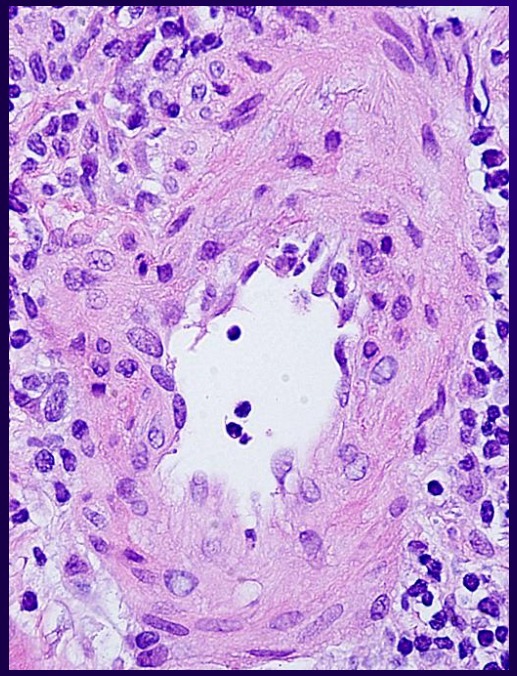


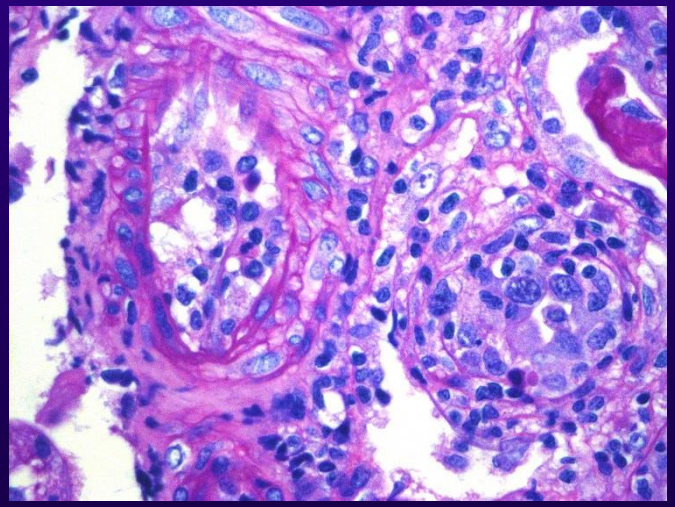
Acute Cellular Rejection-Pathology

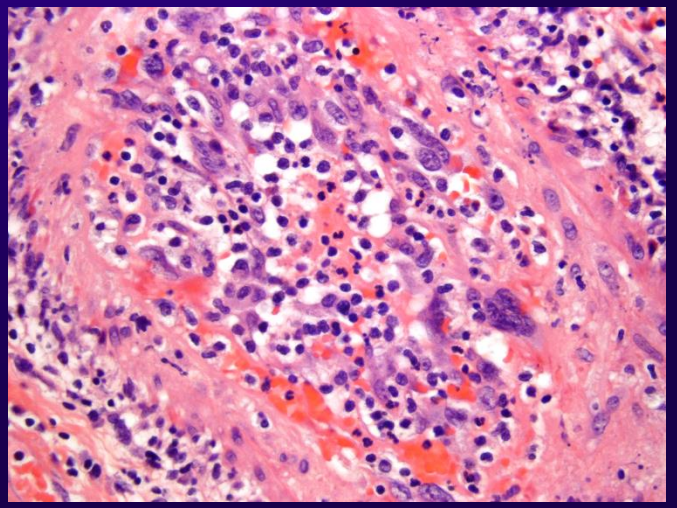
- **Vessels: infiltration of mononuclear cells under arterial and arteriolar epithelium is a typical lesion of acute cellular rejection (endothelialitis; intimal arteritis; endarteritis)**
  - **A considerable portion of acute TCMR with transplant endarteritis also has concurrent acute AMR**
  - **Tend to affect larger arteries (i.e. arcuate or large interlobular arteries)**
  - **One inflammatory cell under the arterial endothelium is sufficient for the diagnosis of endarteritis**
  - **Cells adherent to endothelium is insufficient for Dx**
  - **Transmural arteritis or fibrinoid necrosis can occur in severe acute TCMR, but more often seen in bxs with (concurrent) acute AMR and C4d+**
  - **PTC inflammation- peritubular capillaritis**

Arterial inflammation (vasculitis) - Banff grading

- v0 – no arterial inflammation
- v1 – intimal arteritis reducing lumen by <25%
- v2 – intimal arteritis reducing lumen by > 25%
- v3 – transmural inflammation or fibrinoid necrosis

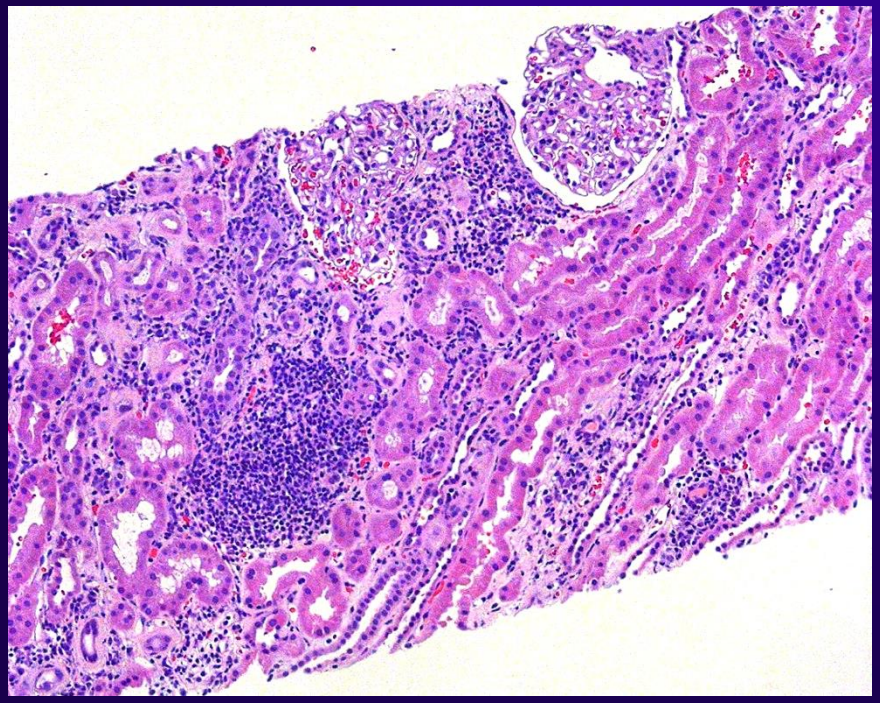


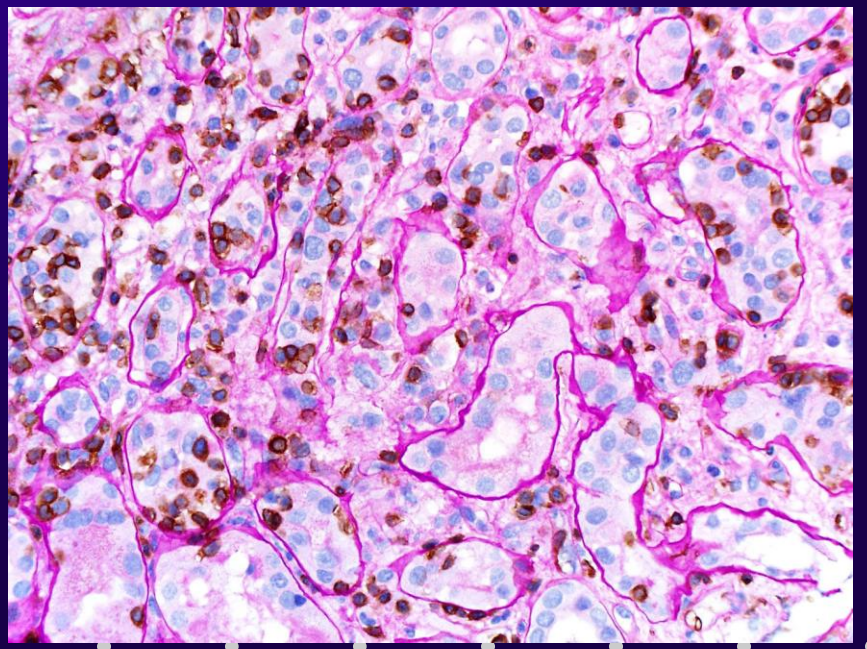




Acute TCMR-Banff IA

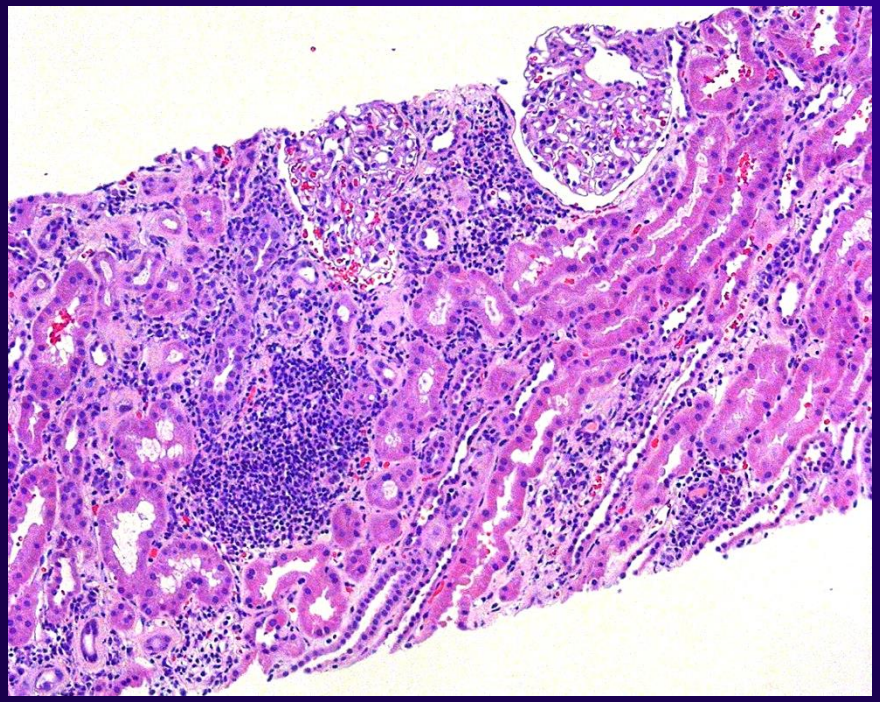
IA: >25% parenchyma affected (i2 or i3) and focal moderate Tubulitis (t2)

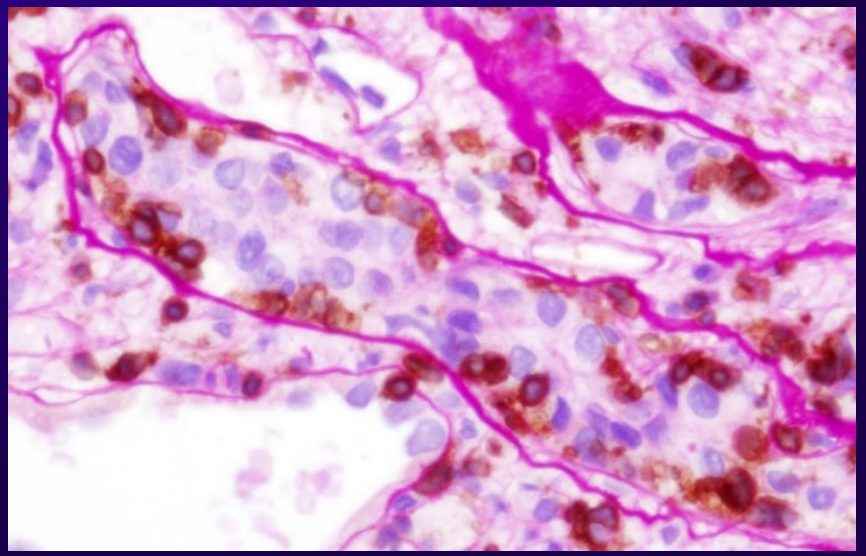




Acute TCMR-Banff IB

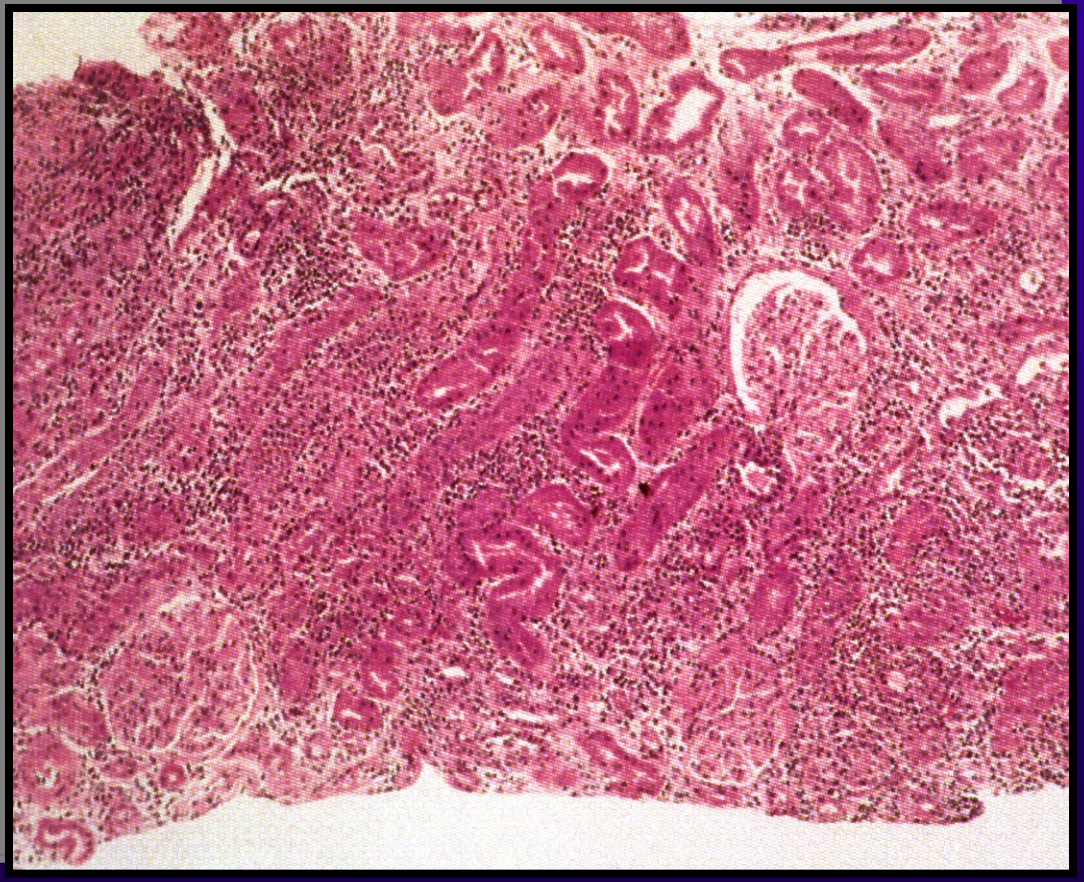
Ib >25% parenchyma affected (i2 or i3) and focal severe tubulitis (t3)

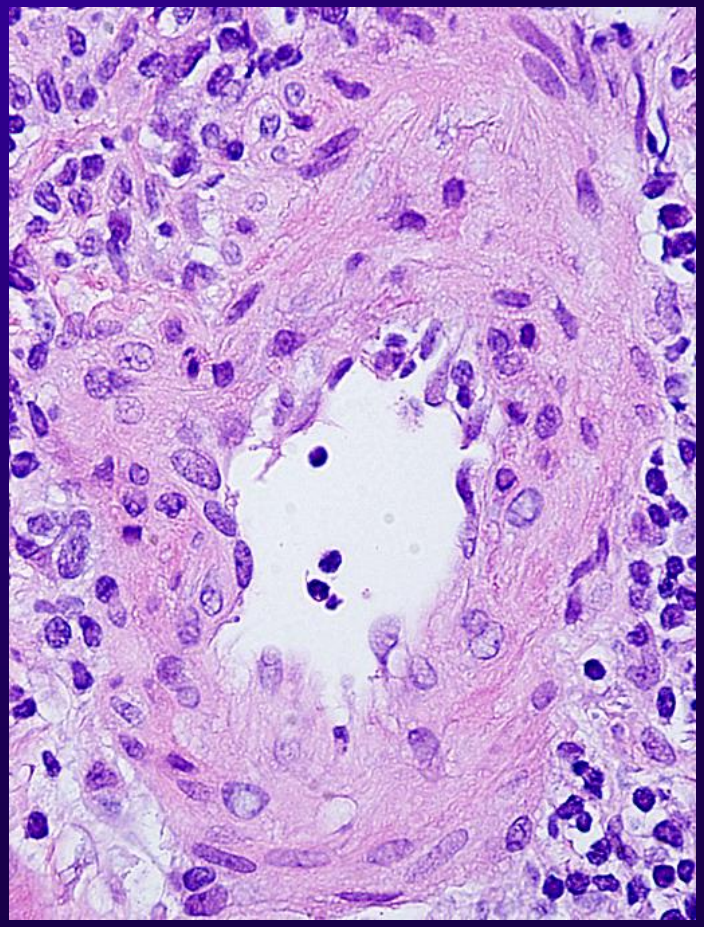




Acute TCMR-IIA

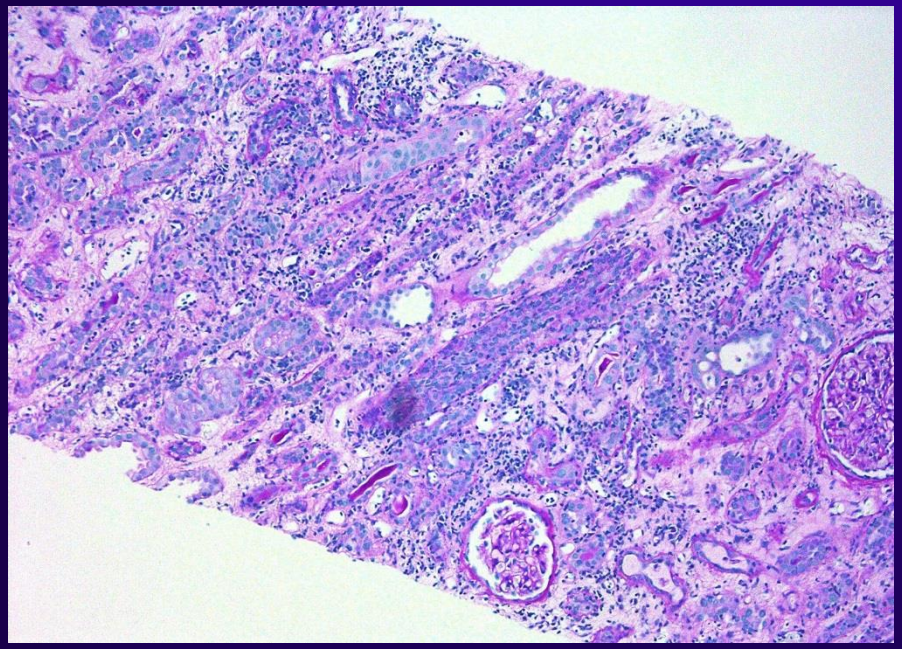
- **IIA: mild to moderate intimal arteritis (v1)**

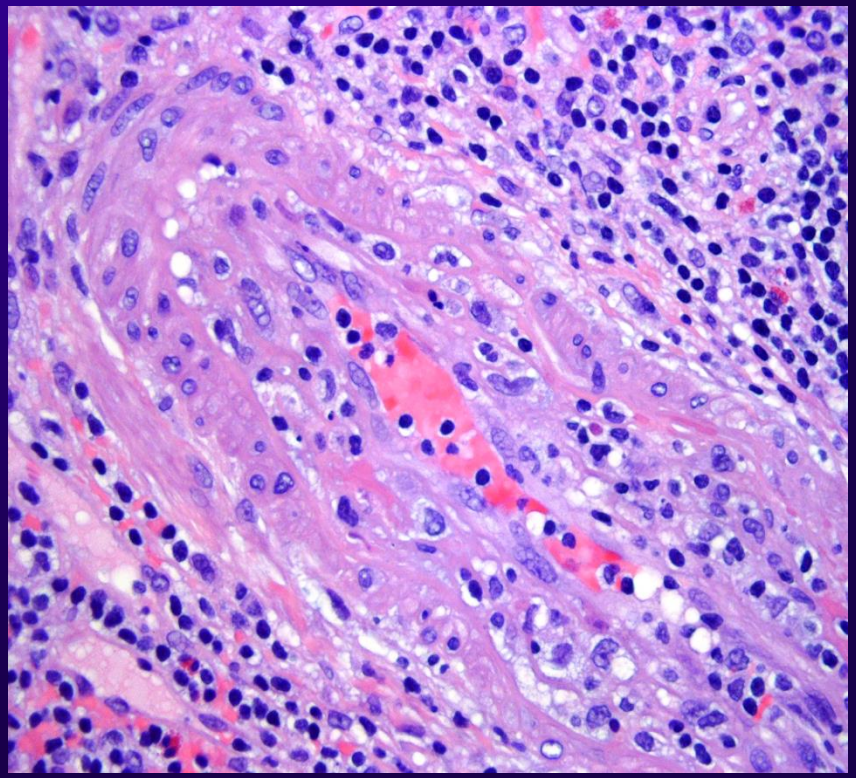




Acute TCMR-IIB

- **IIB: severe intimal arteritis comprising >25% of the luminal area (v2)**

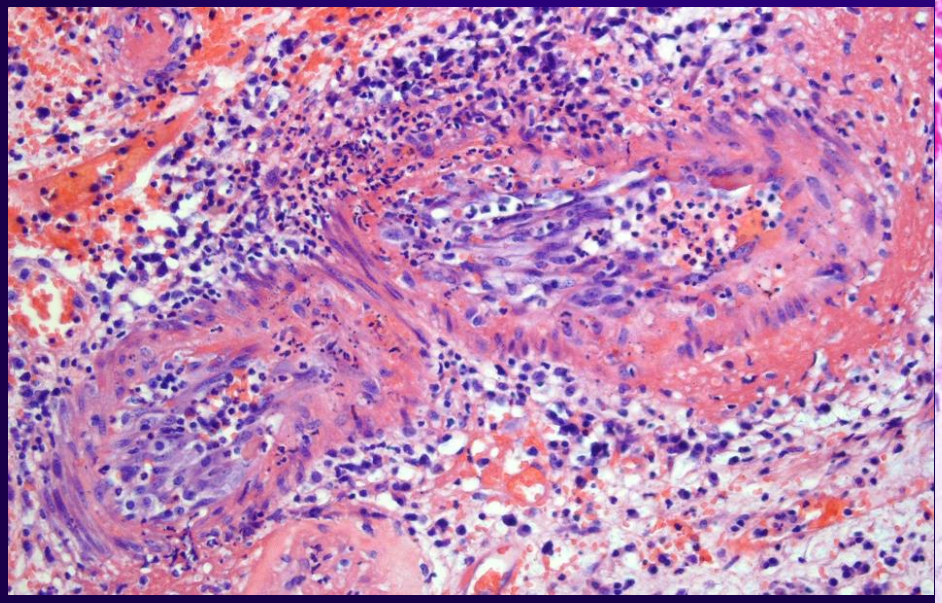


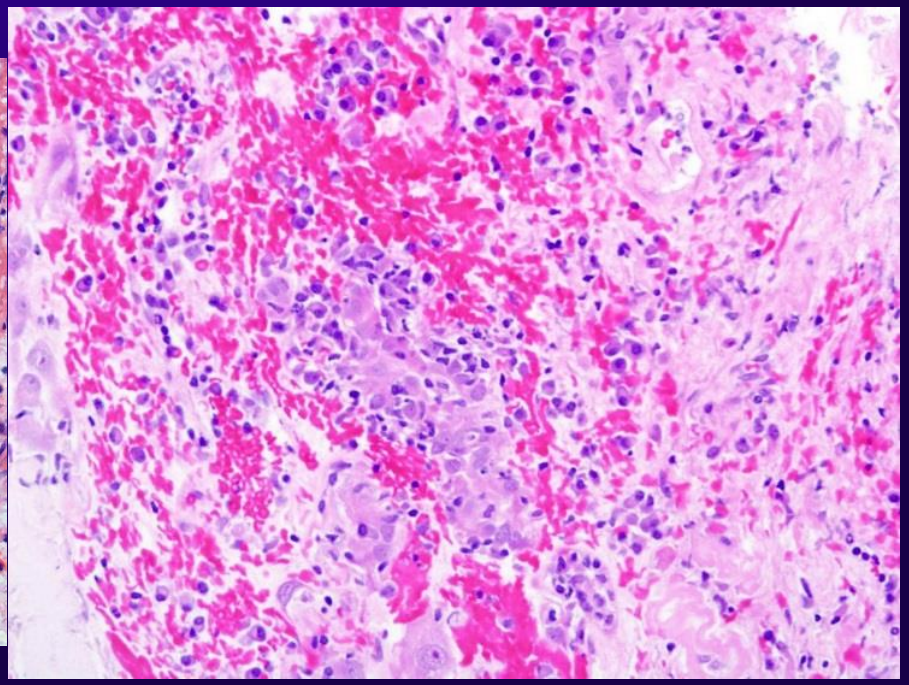


Acute TCMR-III

III: transmural arteritis/arterial fibrinoid change and necrosis of medial smooth muscle cells with accompanying lymphocytic inflammation (v3).

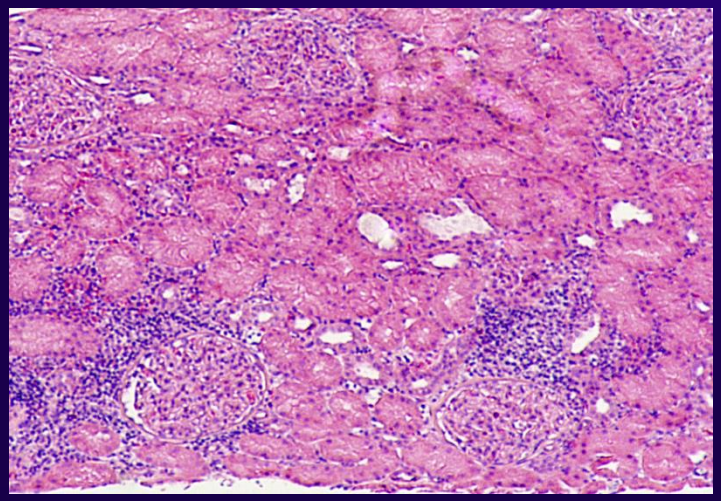
PTC C4d (-).

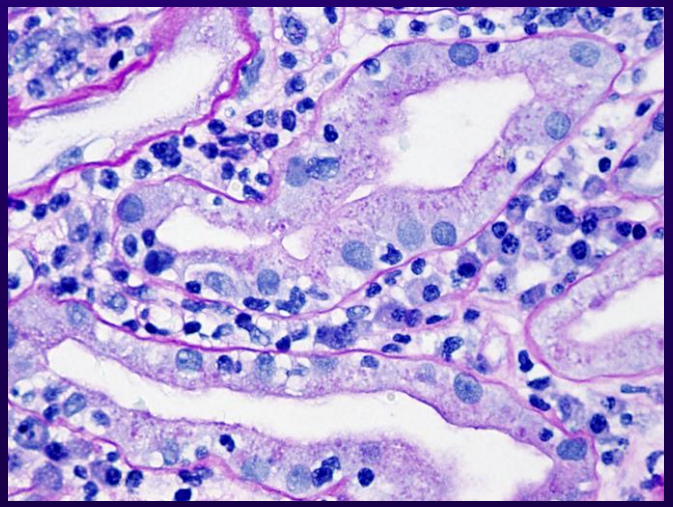




Suspicious for Acute Cellular (Borderline) Rejection

- Foci of mild tubulitis: 1-4 mononuclear cells/tubular cross section
- At least 10-25% of parenchyma inflamed
- No intimal arteritis
- Borderline rejection should be interpreted in the context of clinical situation; if there is any other evidence favoring rejection, the diagnosis of acute rejection (rather than borderline) is preferred.





Antibody-mediated rejection (AMR)

- Hyperacute
- Acute
- Chronic active

Acute Antibody-mediated Rejection

Criteria for Acute/active AMR

1. Histologic evidence of acute renal injury, including at least one of the following:
   (a) Microvascular inflammation (g>0 and/or PTC>0)
   (b) Intimal or transmural arteritis (v>0)
   (c) Acute TMA, in the absence of any other cause
   (d) acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent Ab interaction with vascular endothelium, including at least one of the following:
   (a) Linear C4d staining in PTCs (IF- C4d2 or C4d3; IHC C4d>0).
   (b) At least moderate microvascular inflammation [(g+PTC)=/>2)
   (c) Increased expression of gene transcripts indicative of endothelial injury
3. Serologic evidence of DSAs (to donor HLA or other anti-donor endothelial antigens)

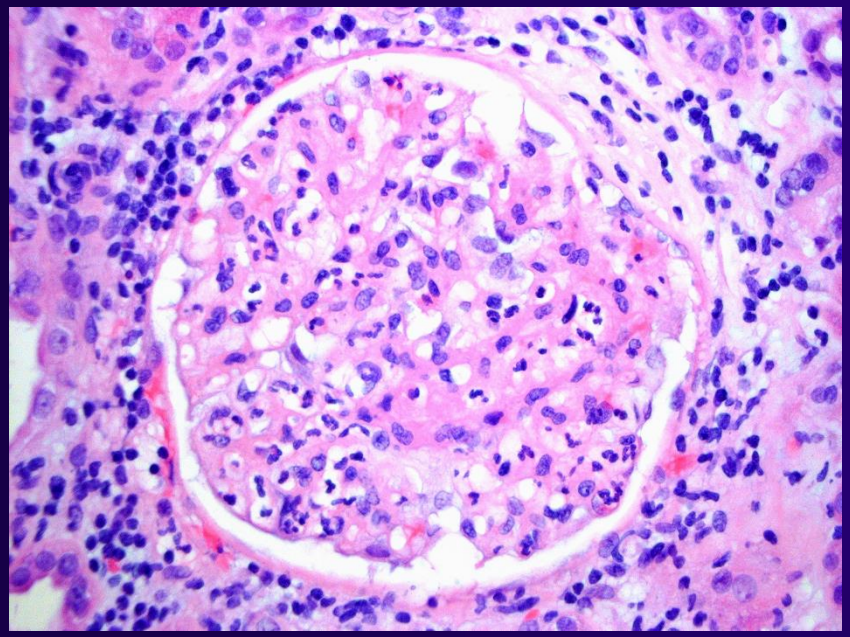
Acute AMR- clinical

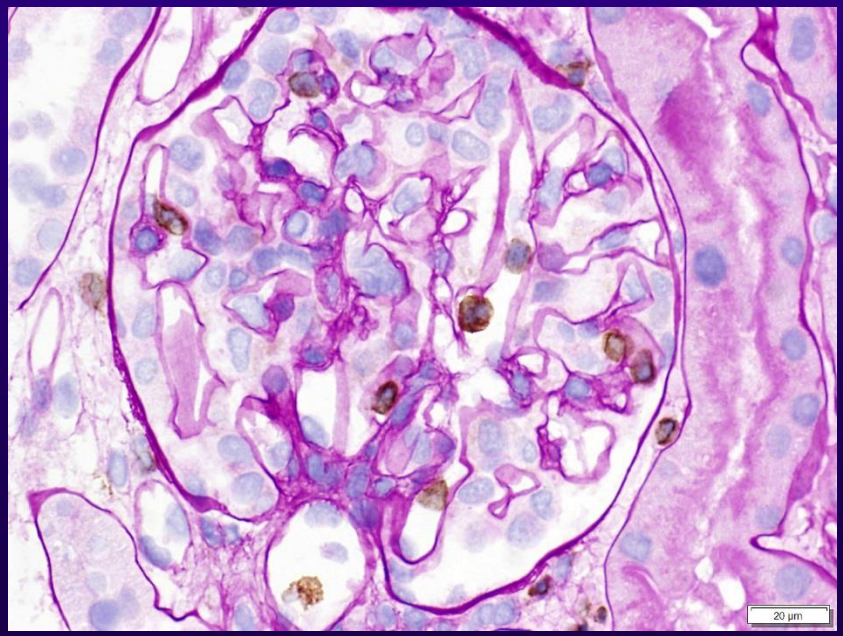
- **Clinical presentation:**
  - **Manifestations of severe rejection**
  - **No clinical features allow to separate acute AMR from TCMR**
  - **Occurs from 3 d to yrs post transplant (most common in the 1st mo)**
  - **Risk factors: presensitization**
  - **~24% bxs for acute rejection meet the criteria for acute AMR**
- **Outcome:**
  - **Acute AMR is considerably worse than acute TCMR**
  - **Mixed acute TCMR/AMR is worse than acute AMR**

Acute AMR-LM

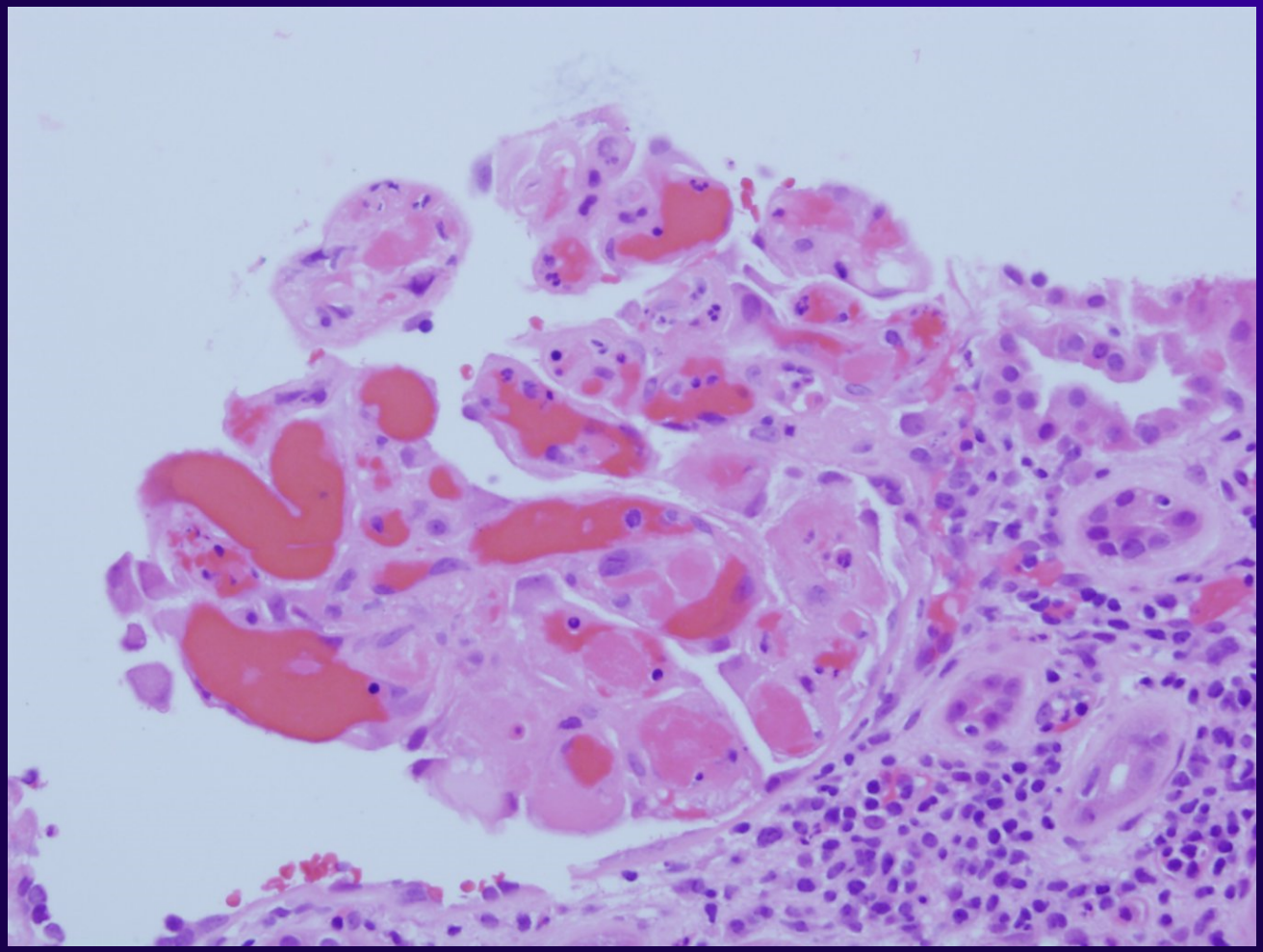
- Changes are nonspecific
- Most characteristic finding- margination of inflammatory cells in PTCs
  - Early stages: PNMs + mononuclear cells
  - Later stages: monocyts + lymphocytes
- Glomeruli: glomerulitis
- TI: little tubulitis; focal necrosis, patchy infarction; interstitial hemorrhage
- Vessels: fibrinoid necrosis and/or transmural arteritis may occur
- TMA may occur

Acute AMR-Transplant Glomerulitis



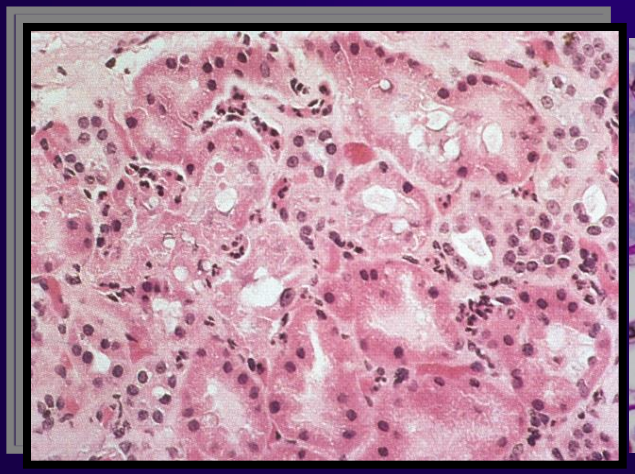


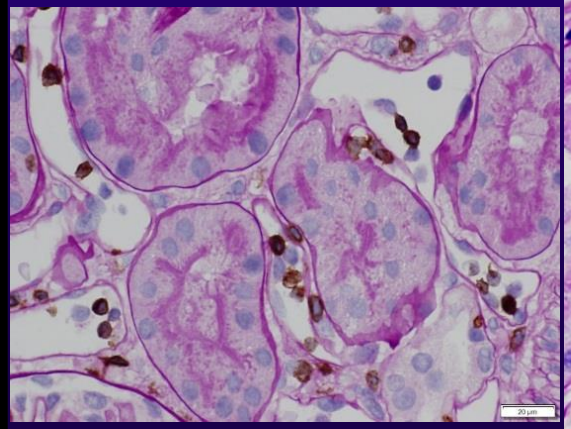
Acute AMR-TMA

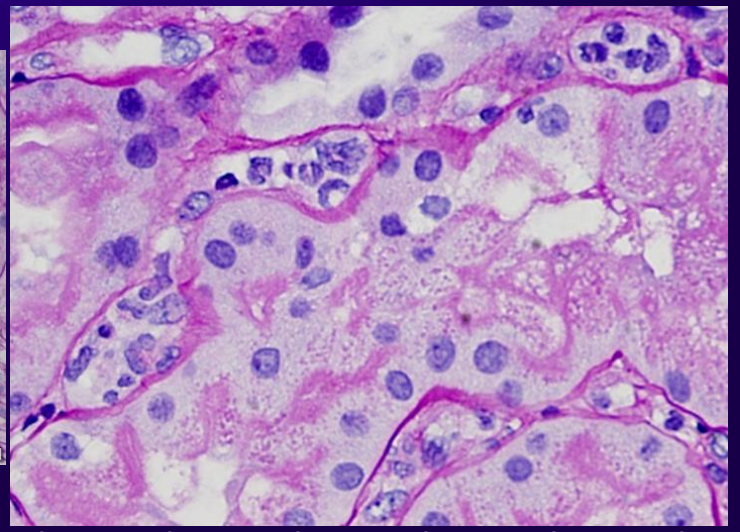


Peritubular capillaritis - Banff grading

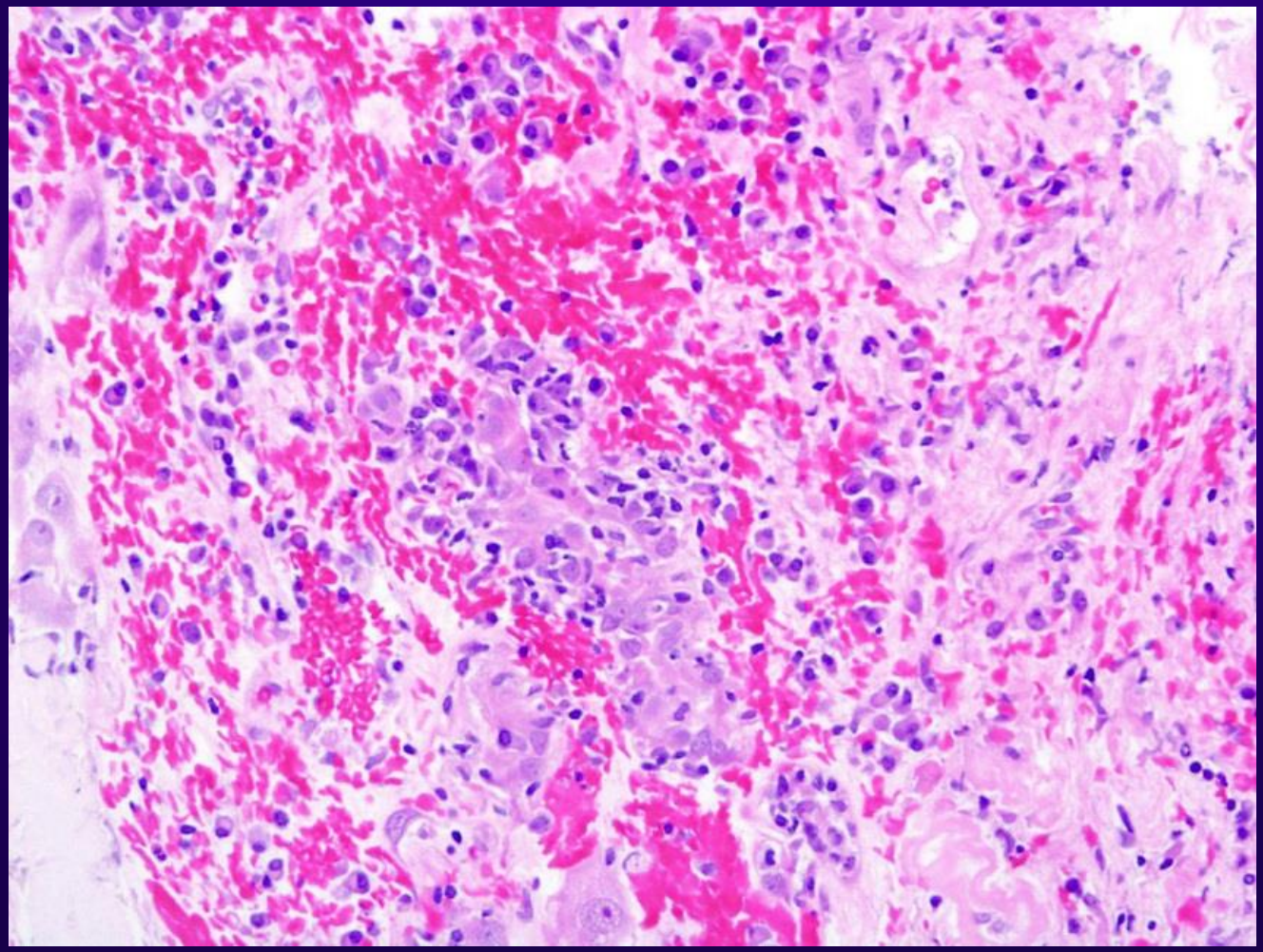
- ptc0: <10% cortical ptc with inflammation
- ptc1: >/=10% cortical ptc with capillaritis, with max 3-4 luminal inflammatory cells
- ptc2: >/=10% cortical ptc with capillaritis, with max 5-10 luminal inflammatory cells
- ptc3: >/=10% cortical ptc with capillaritis, with max >10 luminal inflammatory cells







Acute AMR-Interstitial Hemorrhage

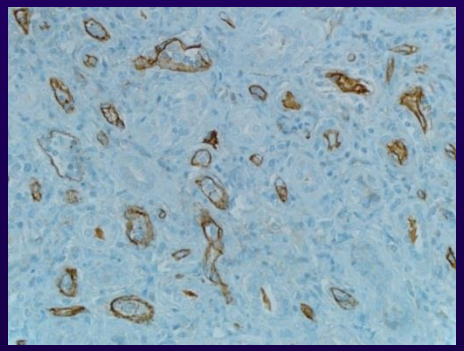


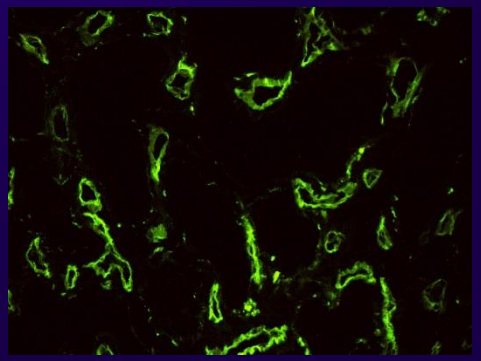
C4d

- Classical complement pathway activation (antibody mediated)

(binds covalently to capillary walls at local site)

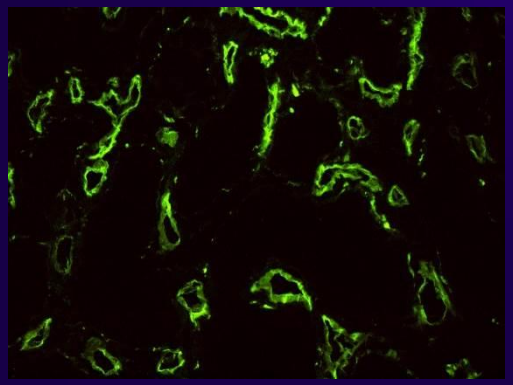
- 95% sensitive and 96% specific for anti-donor antibodies
- IF method: high sensitivity & quick turnaround time
- IHC method: slightly less sensitive than IF; longer time; background of nonspecific staining (of plasma)

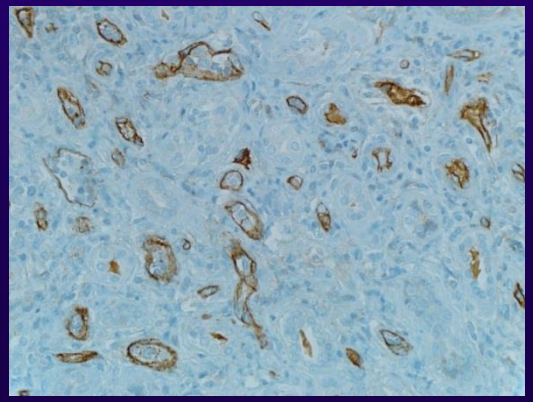


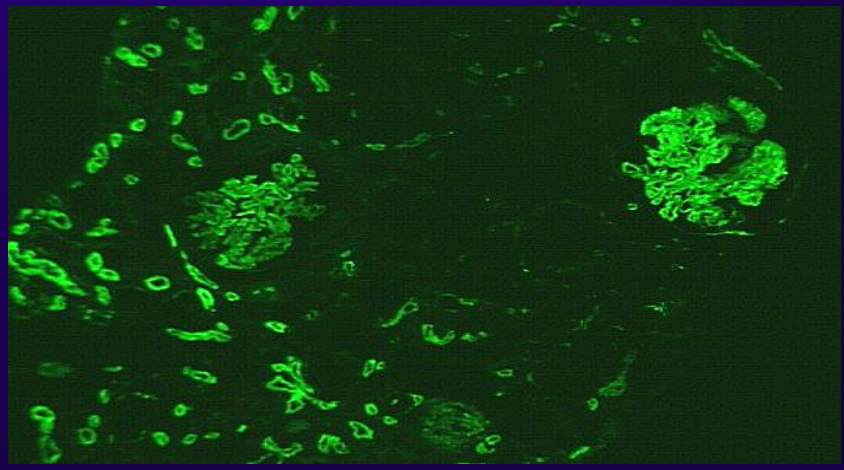


How to interpret C4d staining (1)

- PTC C4d staining should be diffuse, linear & circumferential
- Focal PTC C4d staining (10-50%); Minimal staining (<10%)
  - Focal staining- generally considered as positive; may be indicate early or resolving acute AMR; or persistent ongoing “chronic” AMR;
  - Focal staining is an indicator of potentially poor graft outcome
- Scarred/necrotic areas do not stain well; carefully look at the H&E section of the frozen tissue to determine that nonscarred viable renal cortex is available.

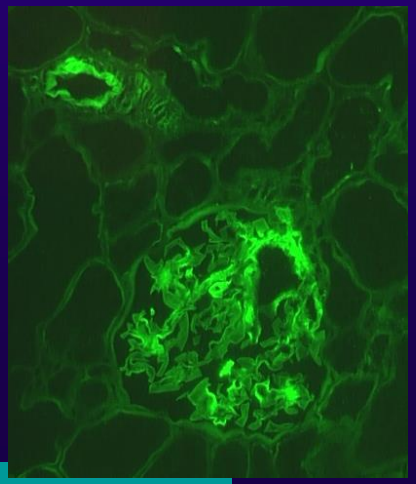


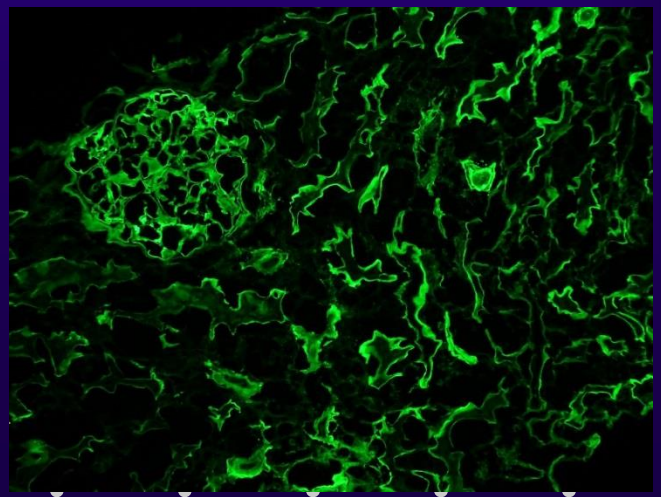




How to interpret C4d staining (2)

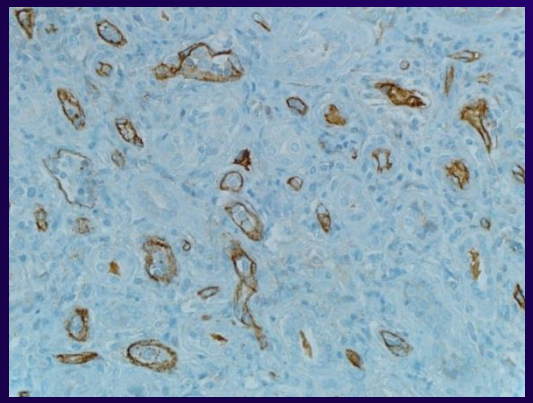
- If only medulla available & vasa recta are diffusely/strongly positive for C4d, should consider the bx as C4d positive
- The mesangium/arterioles normally stain for C4d. Thus, if negative, technical error need to be considered
- Glomerular capillary staining without PTC C4d is not diagnostic of AMR
- Atrophic TBMs are frequently C4d+, do not interpret TBM staining as PTC staining

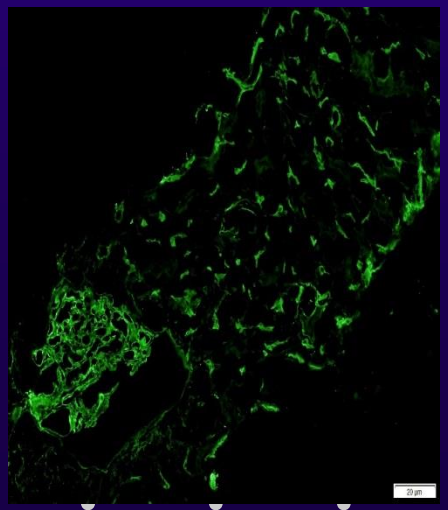




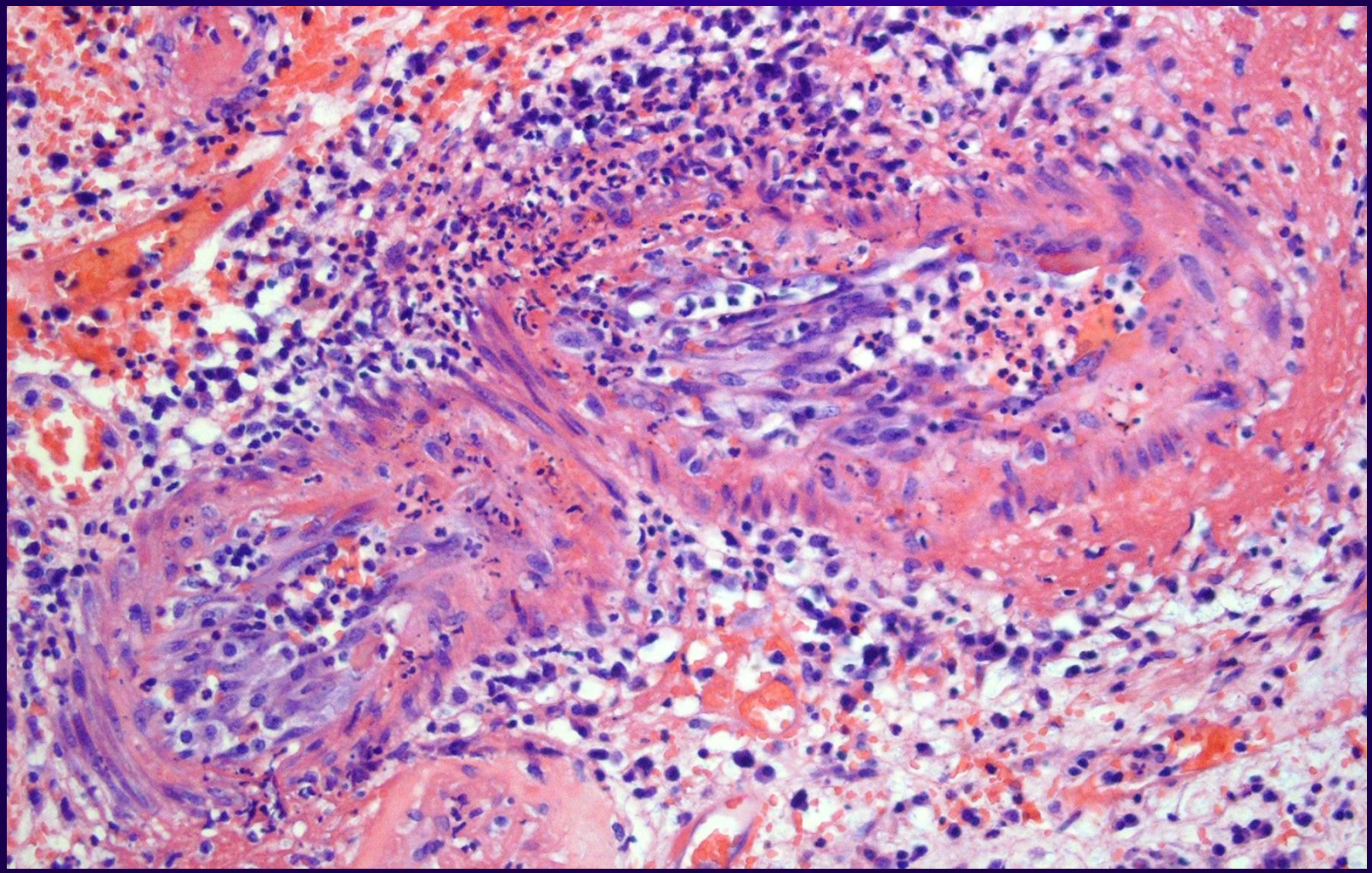
C4d-Banff grading

- % of bx or 5 high-power fields
  - C4d0: 0% Negative
  - C4d1: 1-10% Minimal C4d stain
  - C4d2: 10-50% Focal C4d stain/positive
  - C4d3: >50% Diffuse C4d stain/positive
- IHC on paraffin section is usually less sensitive by ~1 grade level



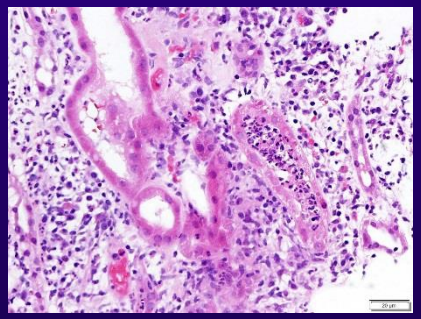


Acute AMR-Transmural Vasculitis



Acute AMR- Differential Dx

- **Acute Tubular Necrosis**
  - **May show PTC margination of inflammatory cells including PMNs, but PTC C4d (-)**
- **Acute Pyelonephritis**
  - **May show PTC margination of inflammatory cells including PMNs**
  - **Microabscesses; neutrophilic tubulitis**
  - **PTC C4d (-)**



- **Thrombotic Microangiopathy**
  - **TMA with diffuse positive PTC C4d: strongly suggestive of AMR**
  - **TMA with negative PTC C4d: Recurrent? Drug-induced?**

Chronic, active AMR-Criteria

- 1) Histologic evidence of chronic tissue injury, including at least one of the following:
  - transplant glomerulopathy (cg>0), if no evidence of chronic TMA
  - Severe PTC basement membrane multilayering (EM)
  - Arterial intimal fibrosis of new onset, excluding other causes
- 2) Evidence of current/recent Ab interaction with endothelium, including at least one of the following:
  - Linear PTC C4d (IF: C4d=2 or 3; IHC: C4d>0)
  - At least moderate microvascular inflammation [(g+PTC)=/>2]
  - Increased expression of gene transcripts indicative of endothelial injury
- 3) Serologic evidence of DSAs (anti-HLA or other antigens)

Chronic AMR- clinical

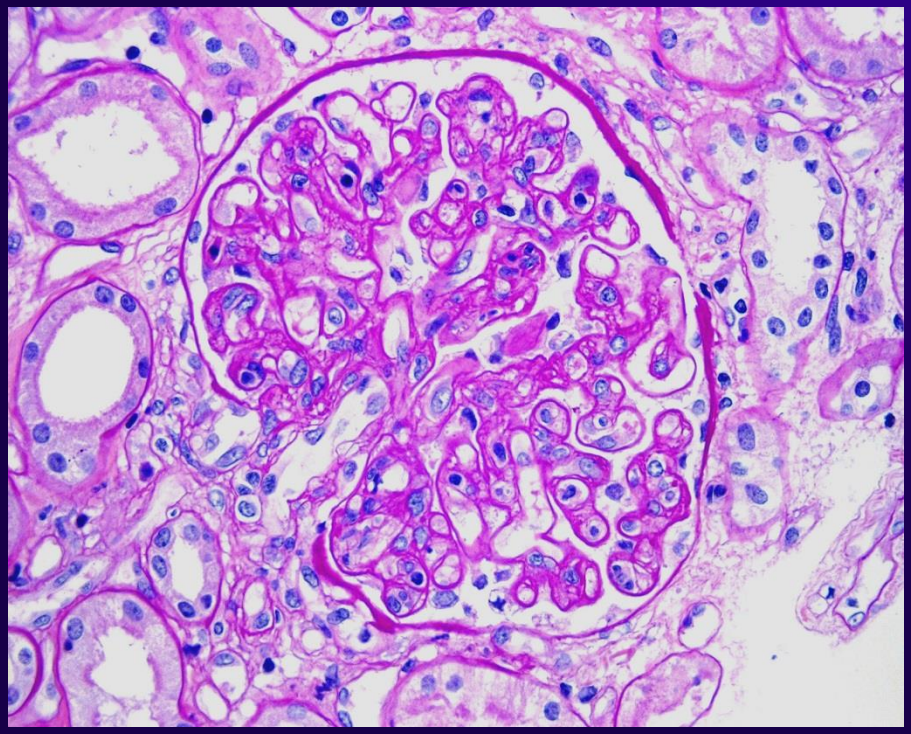
- ~60% of late graft failure is due to chronic AMR
- Typically presents insidiously several yrs post transplant
  - 1/3 indolent dysfunction; 1/3 acute dysfunction; 1/3 stable function
- Risk factors for developing DSAs:
  - Pretransplant: younger age & high number of HLA mismatches
  - Post transplant: non-adherence

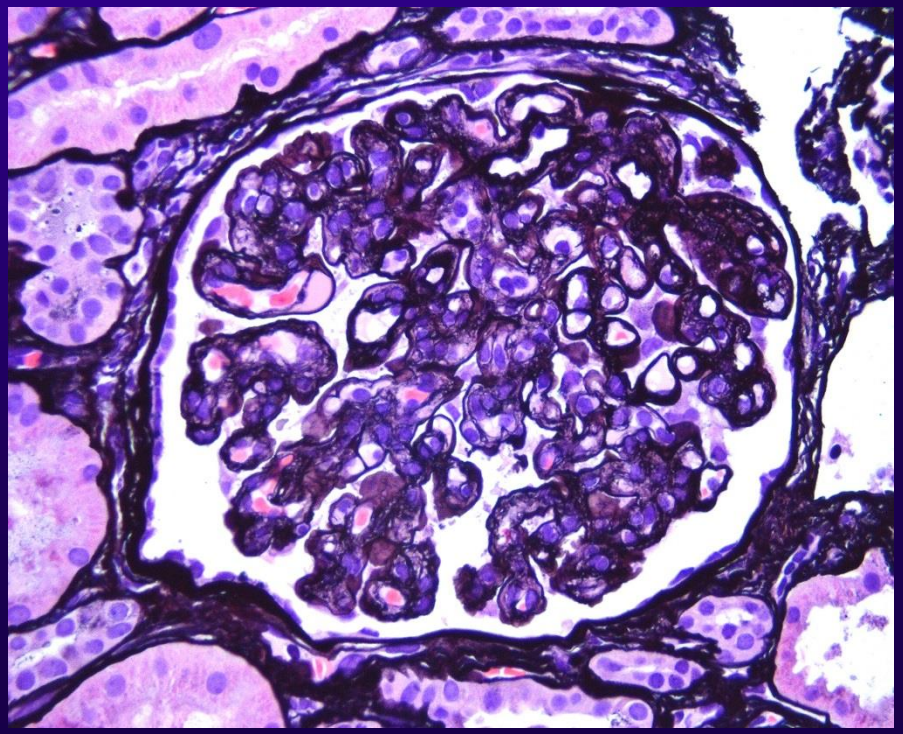
Chronic Antibody-mediated Rejection-LM

- Glomeruli: most characteristic feature is transplant glomerulopathy (TG)
- Tubules: nonspecific; focal/diffuse atrophy caused by ischemia due to loss of PTC and glomerular lesions
- Interstitium: nonspecific; fibrosis with mononuclear infiltrate
- PTC: 1). Capillaritis, 2) multilamination of PTC basement membrane
- Vessels: chronic transplant arteriopathy

Transplant glomerulopathy-LM

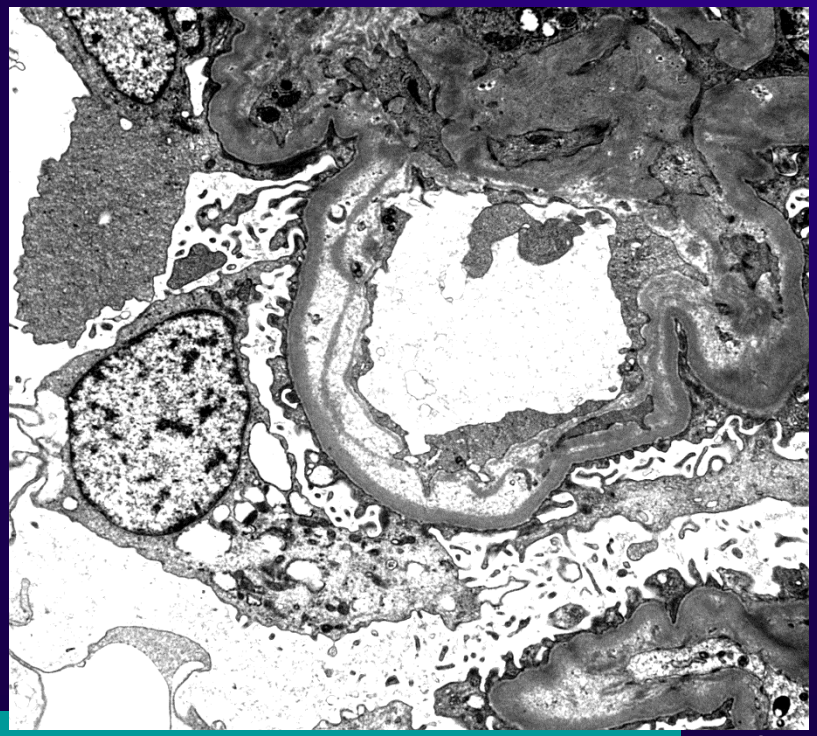
- Thickened capillary walls with frequent double contours; mesangial expansion with mild mesangial hypercellularity; may have endocapillary hypercellularity

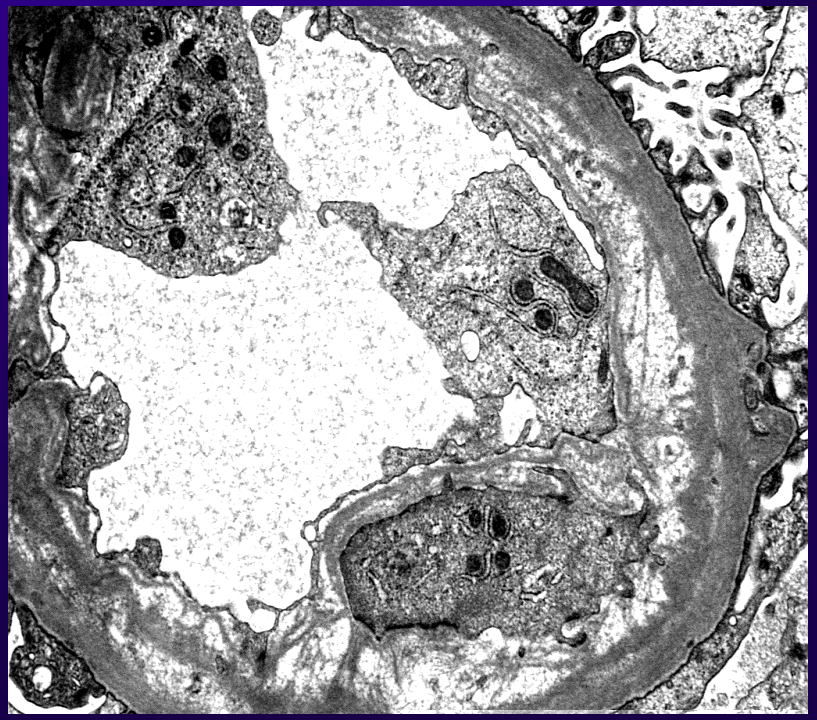




Transplant glomerulopathy-EM

- Subendothelial widening with electron lucent “fluffy” material, may have less electron lucent amorphous material, indistinct fibrillary material or even electron dense material (not true discrete immune-type deposits)
- Mesangial interposition

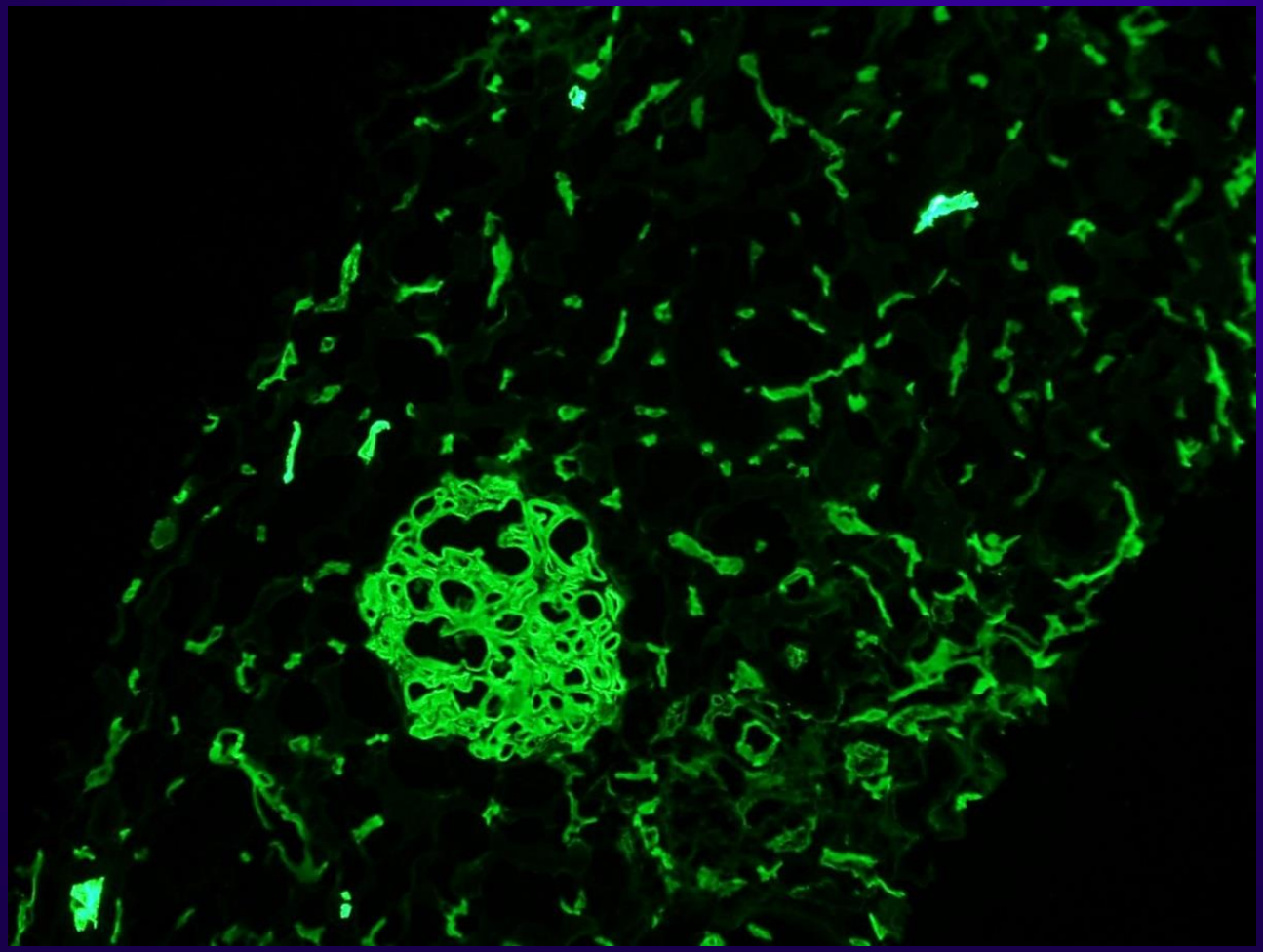




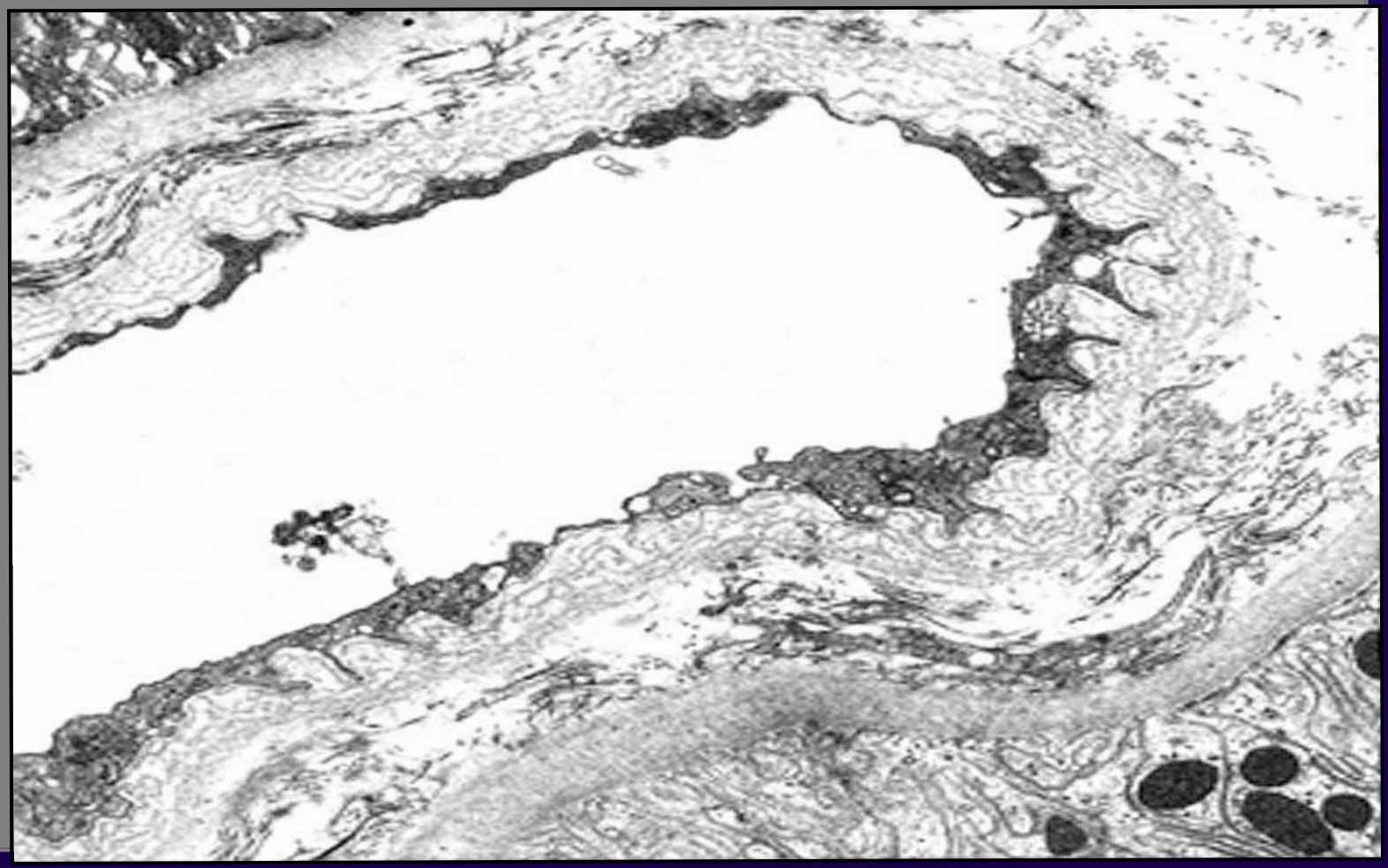
Transplant Glomerulopathy - Banff grading

- cg0 – <10% of peripheral glomerular capillaries with double contours on Jones stain
- cg1 – up to 25% glomerular capillaries with double contours in most affected glomeruli
- cg2 – 26-50% of glomerular capillaries with double contours in the most affected glomeruli
- cg3 – >50% of glomerular capillaries with double contours in the most affected glomeruli

Transplant Glomerulopathy-IF (C4d)



Peritubular capillary-EM



AMR Variants

- **Diffuse PTC C4d staining *DOES NOT* equal to acute AMR**
  - **C4d deposition without evidence of acute rejection**
    - **Can appear in ABO incompatible renal transplantation without any renal pathology with normal renal function- graft accommodation**
    - **PTC C4d can persist for months**
- **Negative PTC C4d staining *DOES NOT* rule out acute AMR**
  - **C4d-negative AMR: microvascular injury (i.e. glomerulitis, peritubular capillaritis, TMA) in the presence of DSA**
- **Smoldering/indolent AMR**
  - **DSA + Capillaritis (g + ptc) with/without C4d**
  - **No features of acute (neutrophils, necrosis, thrombosis) or chronic (increased matrix) AMR**
  - **Has shown to be the precursor of chronic AMR**

Changes unrelated to rejection

- Changes associated with immunosuppressive medications
  - Calcineurin inhibitor nephrotoxicity
  - Other immunosuppressive medications
- Infections
  - Virals:
    - polyomavirus
    - adenovirus
    - EB virus infection and PTLD
  - Bacterial infection (pyelonephritis)
- Recurrent & de novo diseases

General References

- T. Nadasdy, A. Satoskar, G. Nadasdy. Pathology of renal transplantation. In Zhou XJ et al (Eds). *Silva's Diagnostic Renal Pathology,* Cambridge University Press, 2009; pp 522-567.

- V. Nickeleit, M. Mengel, R.B. Colvin. Renal Transplant Pathology. In Jennette JC et (Eds). *Heptinstall's Pathology of the Kidney*. 7th edition, Wolters Kluwer, 2015; pp 1321-1459.