Ab Mediated Rejection and Renal Transplantation:Banff Classification Update And Challenges

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, 2022

The Banff Schema was first developed by a group of pathologists, nephrologists, and transplant surgeons at a meeting in Banff Canada August 2-4, 1991.

It has continued to evolve through meetings every two years and has become the worldwide standard for interpretation of transplant biopsies.

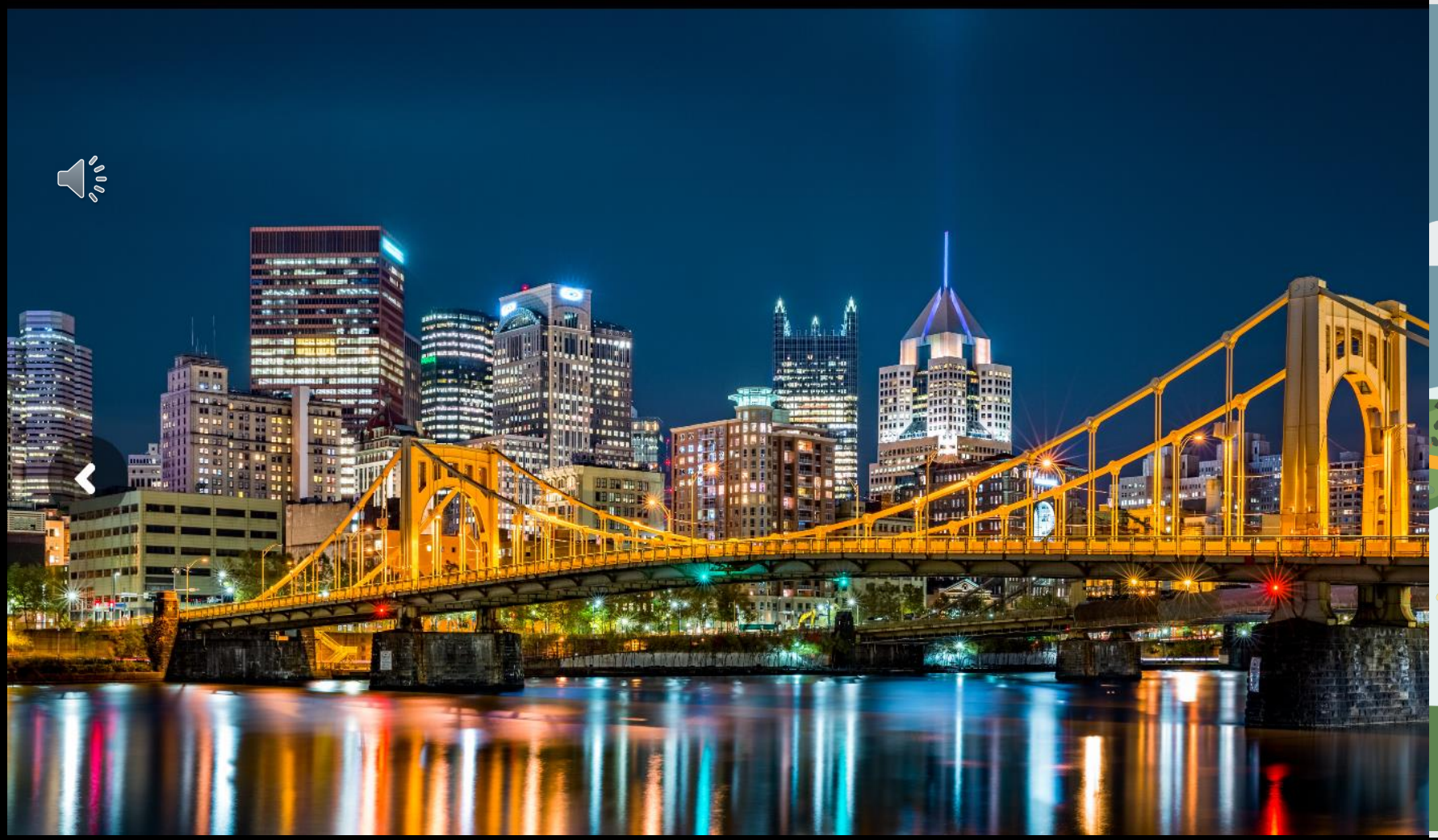
Courtesy of Dr. Solez

The Banff process has evolved from being a primarily pathology- driven group to a more comprehensive and multidisciplinary approach that includes relevant subject matter expertise from immunogeneticists, clinicians and pathologists with the goal to establish and refine

Integrative diagnostic standards in transplantation

BANFF FOUNDATION
FOR ALLOGRAFT PATHOLOGY

Banff Meeting Sep 2019



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MEETING REPORT

AJT

The Banff 2019 Kidney Meeting Report (I): Updates on and clarification of criteria for T cell– and antibody-mediated rejection

Alexandre Loupy[1*] | Mark Haas[2*] | Candice Roufosse[3] | Maarten Naesens[4,5] | Benjamin Adam[6] | Marjan Afrouzian[7] | Enver Akalin[8] | Nada Alachkar[9] | Serena Bagnasco[10] | Jan U. Becker[11] | Lynn D. Cornell[12] | Marian C. Clahsen-van Groningen[13] | Anthony J. Demetris[14] | Duska Dragun[15] | Jean-Paul Duong van Huyen[1] | Alton B. Farris[16] | Agnes B. Fogo[17] | Ian W. Gibson[18] | Denis Glotz[19] | Juliette Gueguen[1] | Zeljko Kikic[20] | Nicolas Kozakowski[20] | Edward Kraus[9] | Carmen Lefaucheur[19] | Helen Liapis[21] | Roslyn B. Mannon[22] | Robert A. Montgomery[23] | Brian J. Nankivell[24] | Volker Nickeleit[25] | Peter Nickerson[26] | Marion Rabant[1] | Lorraine Racusen[10] | Parmjeet Randhawa[14] | Blaise Robin[1] | Ivy A. Rosales[27] | Ruth Sapir-Pichhadze[28] | Carrie A. Schinstock[29] | Daniel Seron[30] | Harsharan K. Singh[25] | Rex N. Smith[27] | Mark D. Stegall[31] | Adriana Zeevi[14] | Kim Solez[6] | Robert B. Colvin[27] | Michael Mengel[6]

Antibody Mediated Effects on Allografts

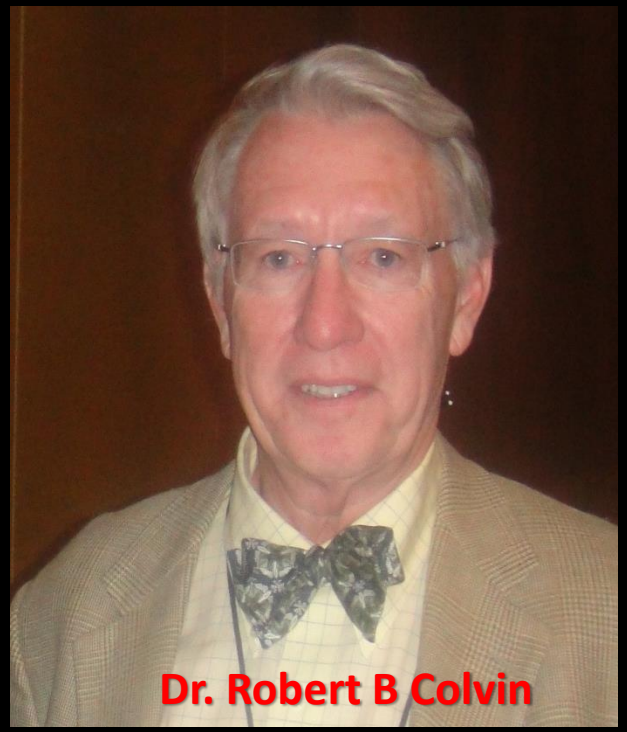
- Hyperacute rejection
- Acute humoral rejection
- Chronic humoral rejection
- Accommodation

Diagnostic Criteria for Acute ABMR

- **Characteristic histologic features including:**
  1) glomerulitis
  2) margination of neutrophils in the PTC
  3) fibrin thrombi
  4) interstitial hemorrhage
  5) severe or necrotizing vasculitis

- **Diffuse, linear C4d staining in the PTC**

- **Identification of DSA**



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Updates of 2019 Banff classification

- Category 1: Normal biopsy or nonspecific changes
- Category 2: Antibody-mediated changes

1- *Active ABMR; all 3 criteria must be met for diagnosis*

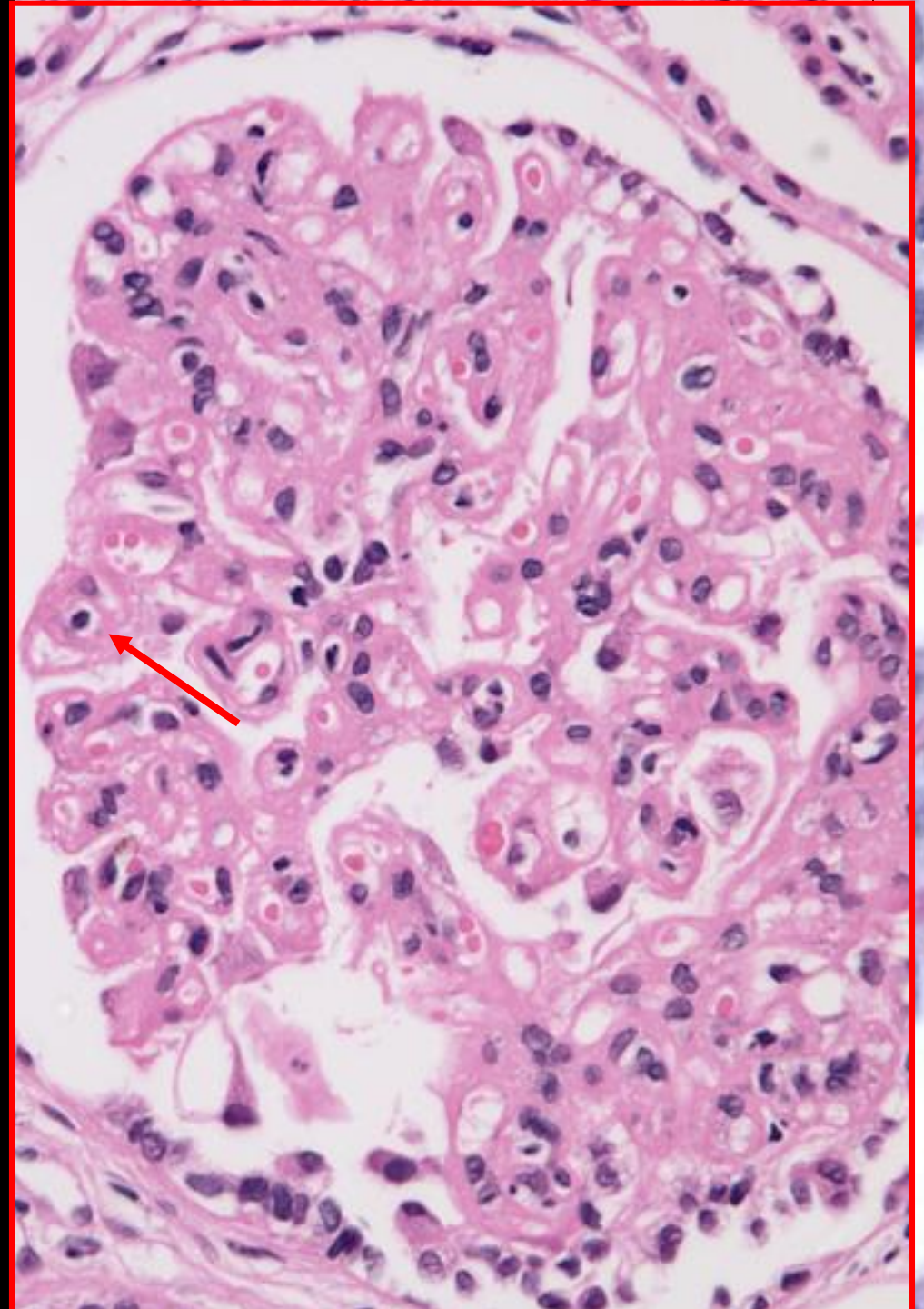
1. Histologic evidence of acute tissue injury
2. Evidence of current/recent antibody interaction with vascular endothelium
3. Serologic evidence of circulating donor-specific antibodies(DSA to HLA or other antigens).

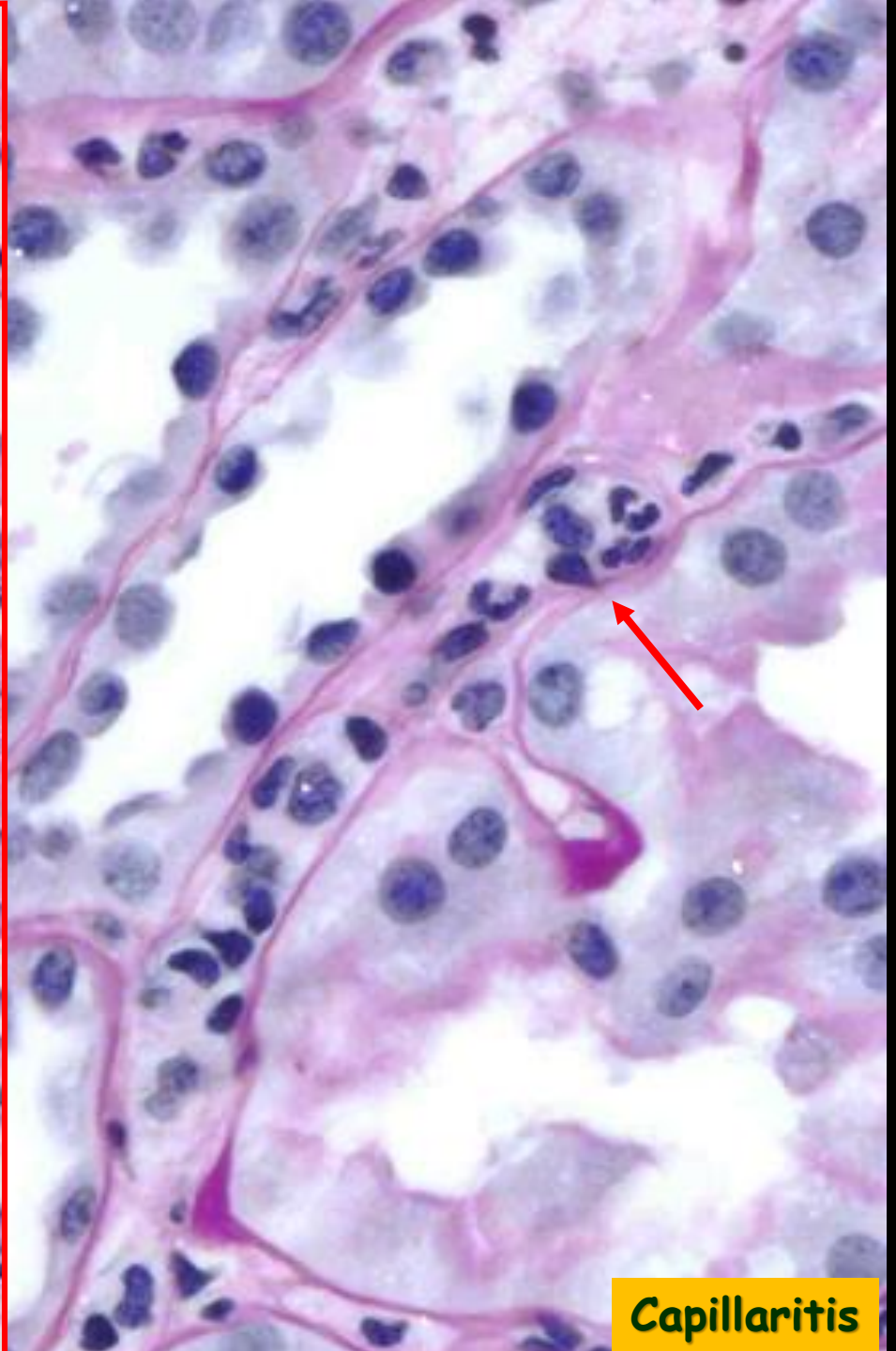
C4d staining or expression of validated transcripts/ classifiers as noted above in criterion 2 may substitute for DSA

TABLE 4 Updates of 2019 Banff classification for ABMR, borderline changes, TCMR, and polyomavirus nephropathy. All updates in boldface type[a]

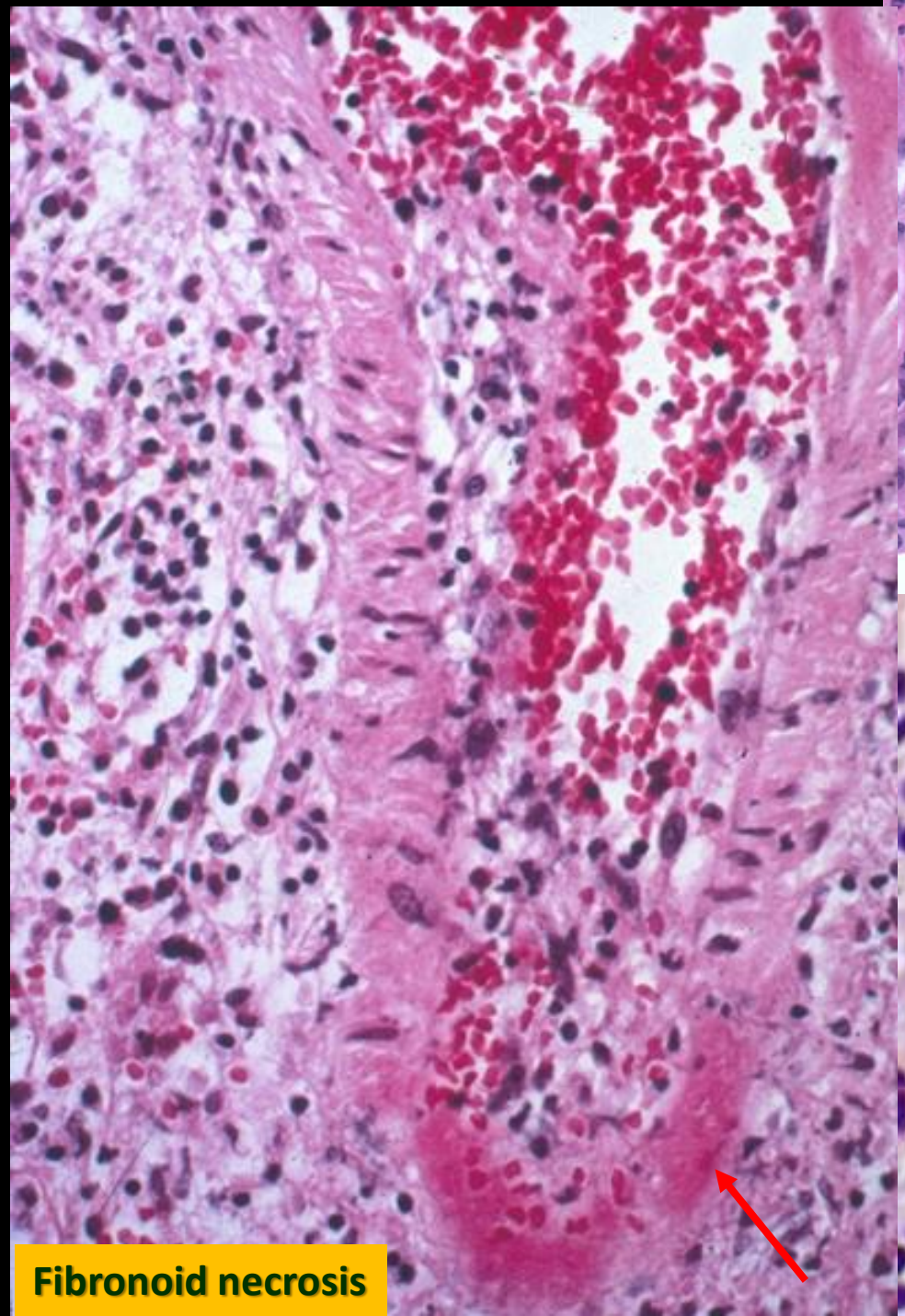
Category 1: Normal biopsy or nonspecific changes
Category 2: Antibody-mediated changes
Active ABMR; all 3 criteria must be met for diagnosis

1. Histologic evidence of acute tissue injury, including 1 or more of the following:
   - Microvascular inflammation (g > 0 and/or ptc > 0), in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 1 alone is not sufficient and g must be ≥ 1
   - Intimal or transmural arteritis (v > 0)[b]
   - Acute thrombotic microangiopathy, in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause

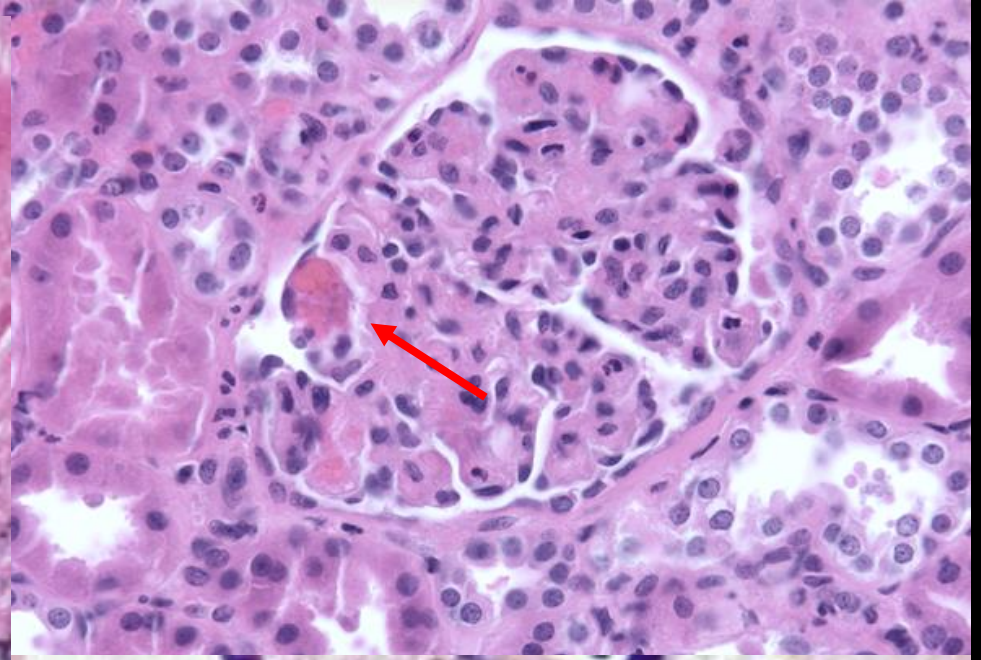




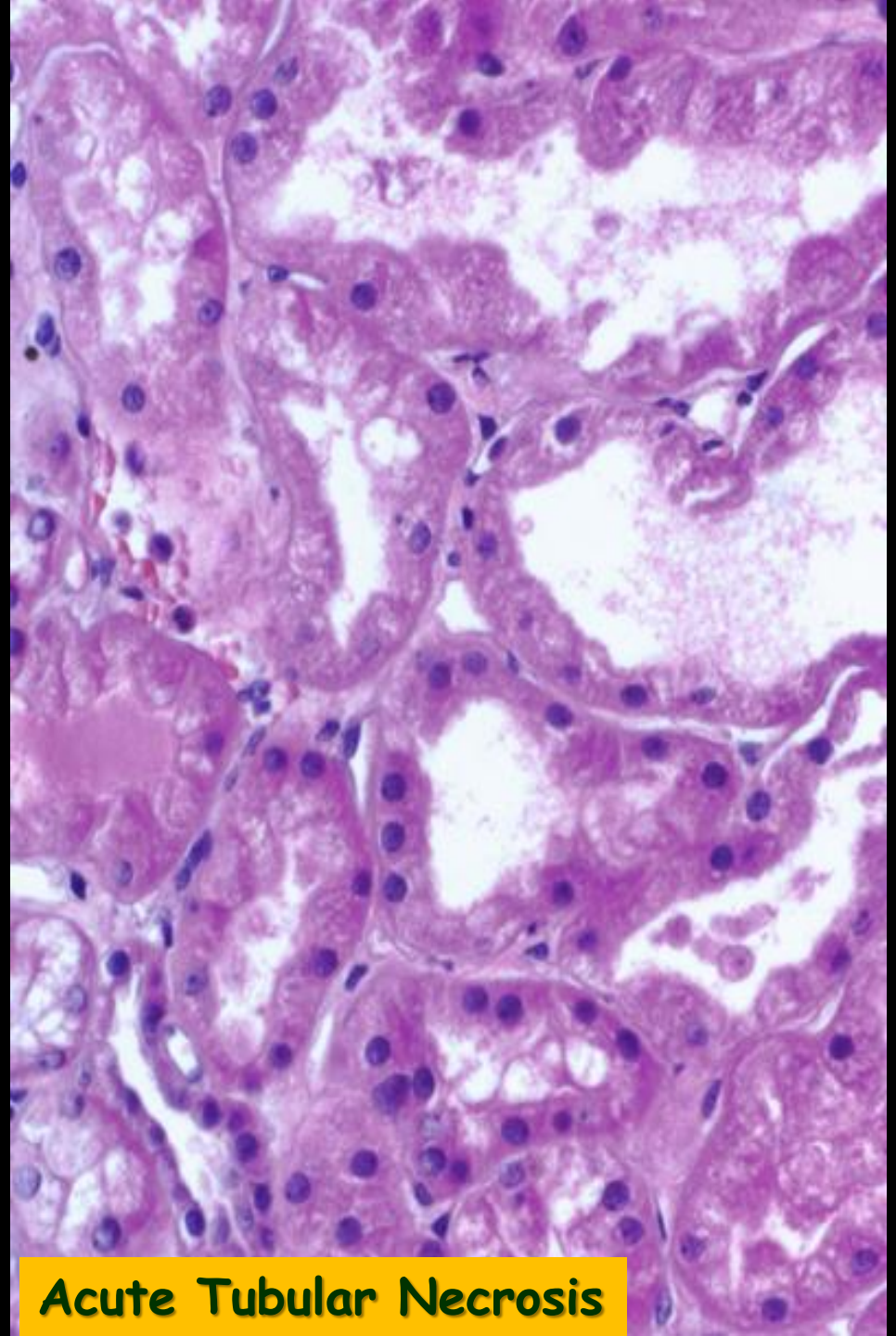
Capillaritis



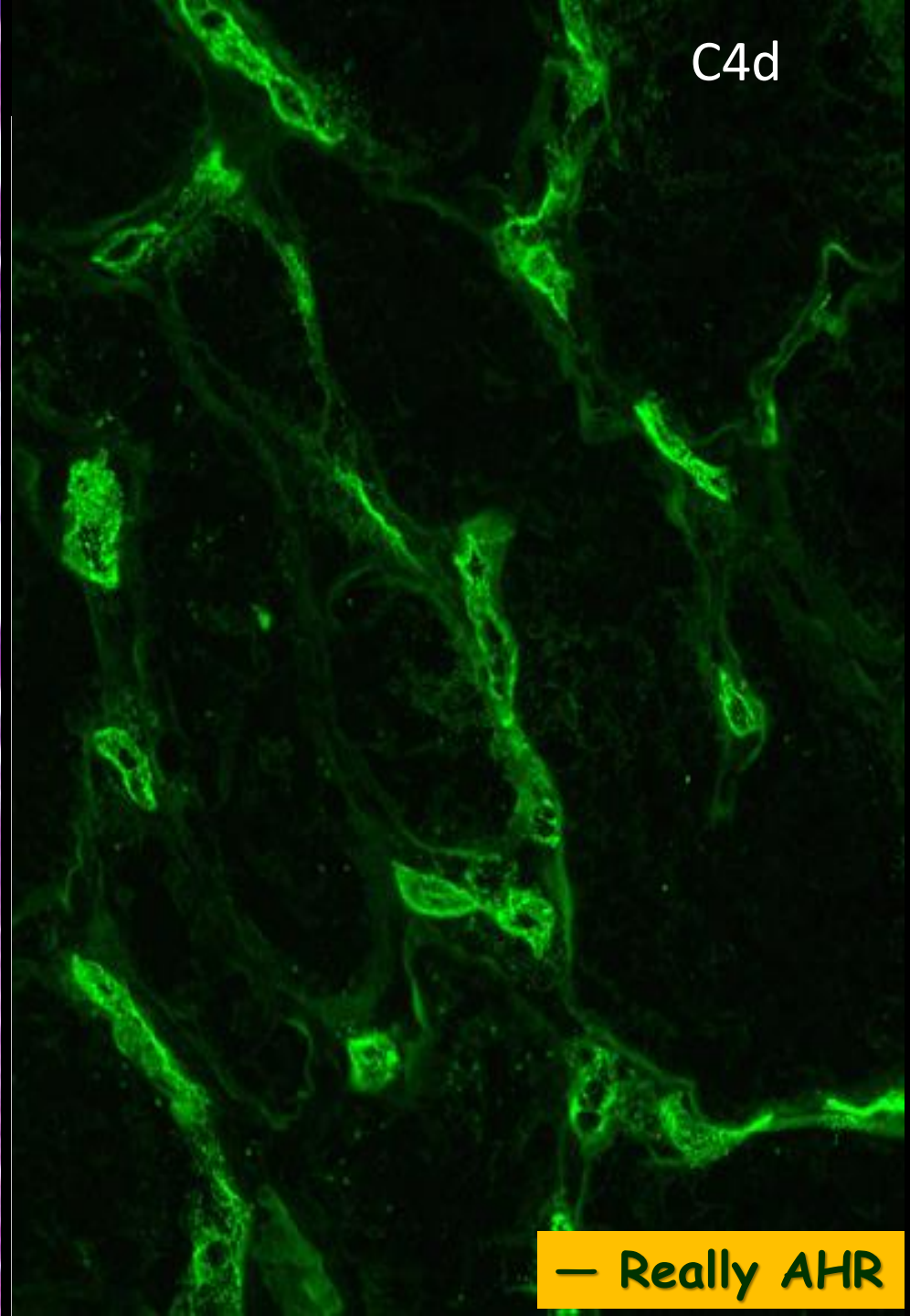
Fibronoid necrosis



Thrombotic Microangiopathy



Acute Tubular Necrosis



— Really AHR

2. Evidence of current/recent antibody interaction with vascular endothelium, including 1 or more of the following:

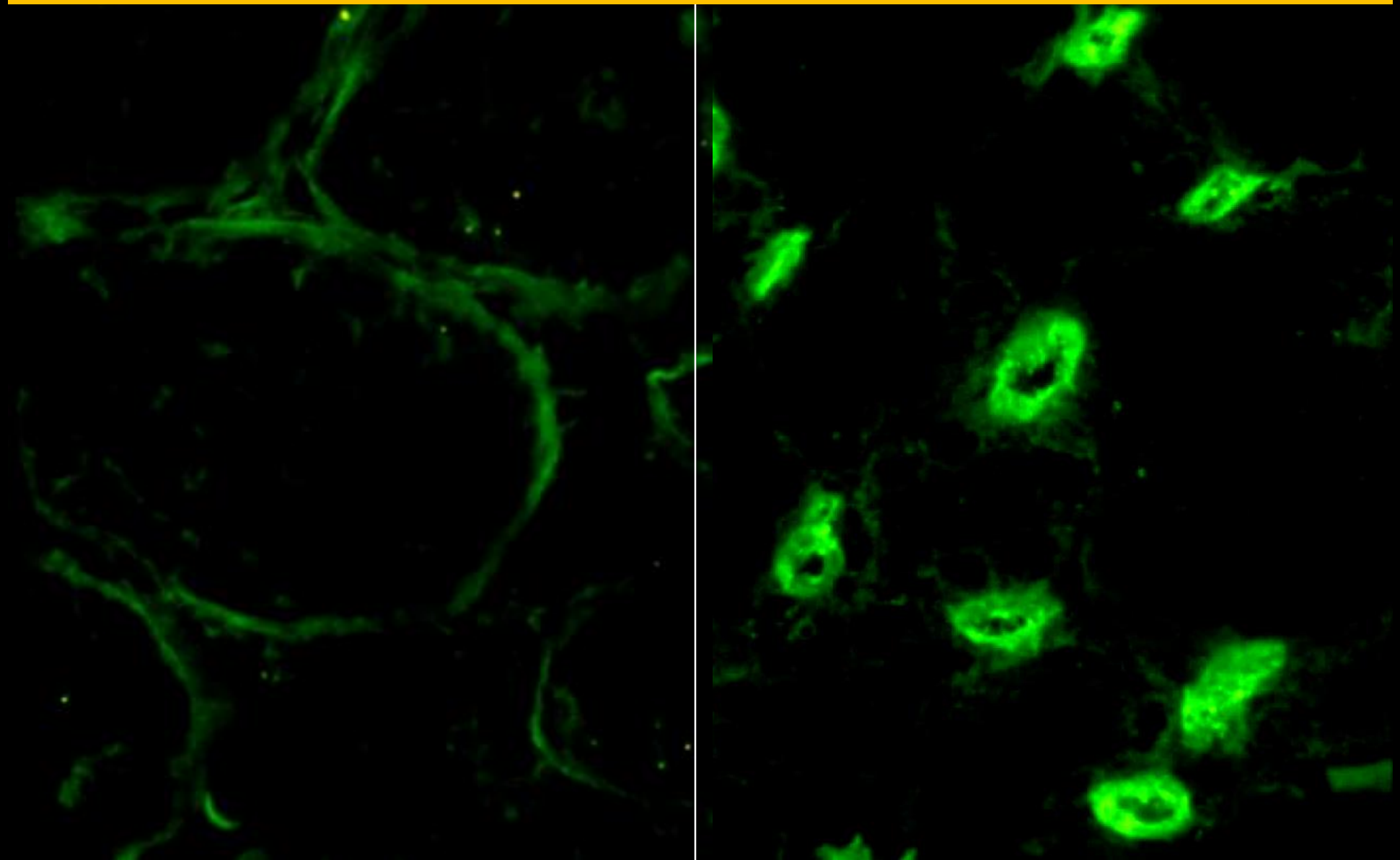
- Linear C4d staining in peritubular capillaries or medullary vasa recta (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
- At least moderate microvascular inflammation ([g + ptc] ≥2) in the absence of recurrent or de novo glomerulonephritis, although in the presence of acute TCMR, borderline infiltrate, or infection, ptc ≥ 2 alone is not sufficient and g must be ≥1
- Increased expression of gene transcripts/classifiers in the biopsy tissue strongly associated with ABMR, if thoroughly validated

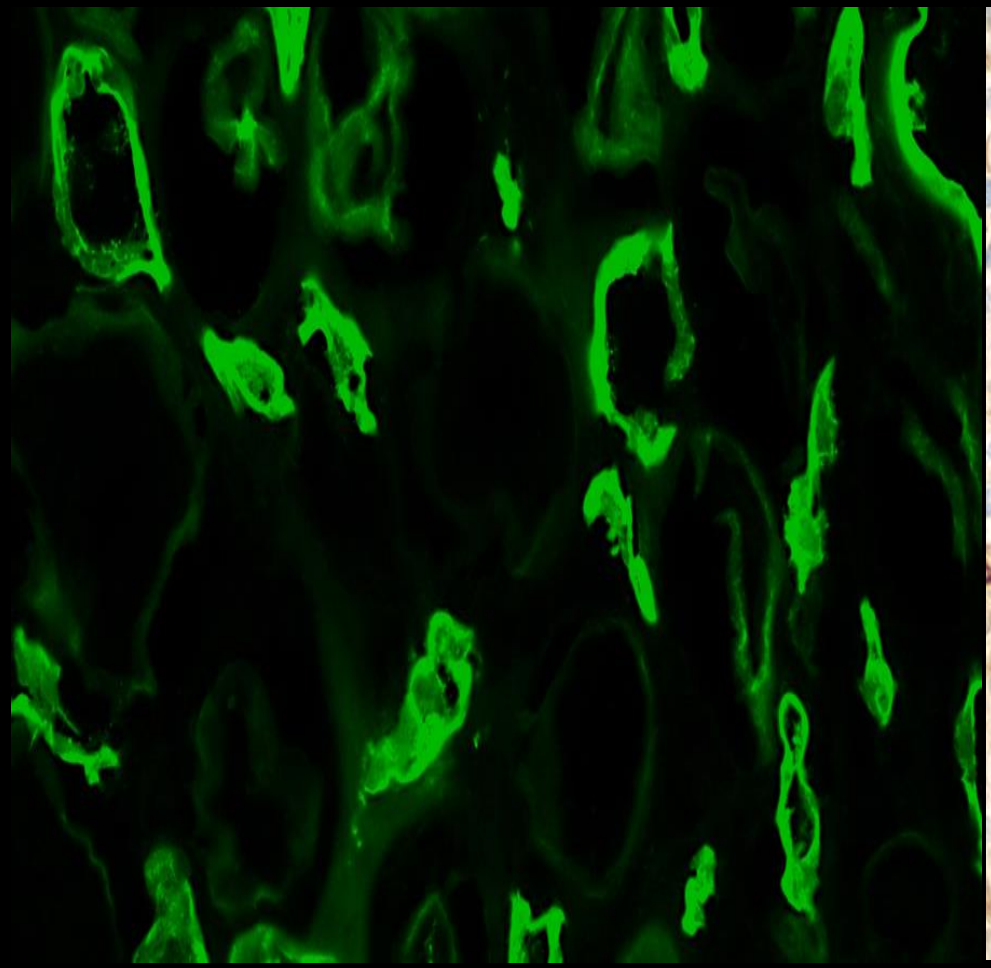
3. Serologic evidence of circulating donor-specific antibodies (DSA to HLA or other antigens). C4d staining or expression of validated transcripts/classifiers as noted above in criterion 2 may substitute for DSA; however thorough DSA testing, including testing for non-HLA antibodies if HLA antibody testing is negative, is strongly advised whenever criteria 1 and 2 are met

C4d Immunofluorescence

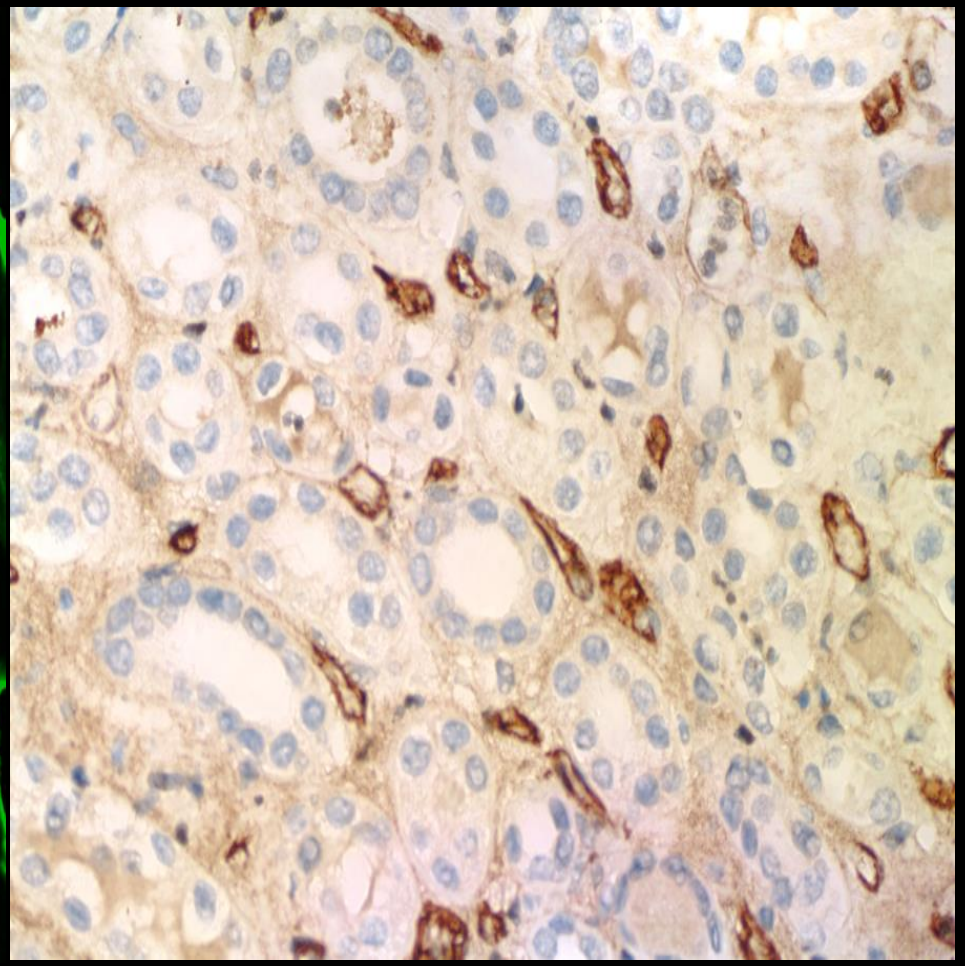
Acute Cellular Rejection

Acute Humoral Rejection



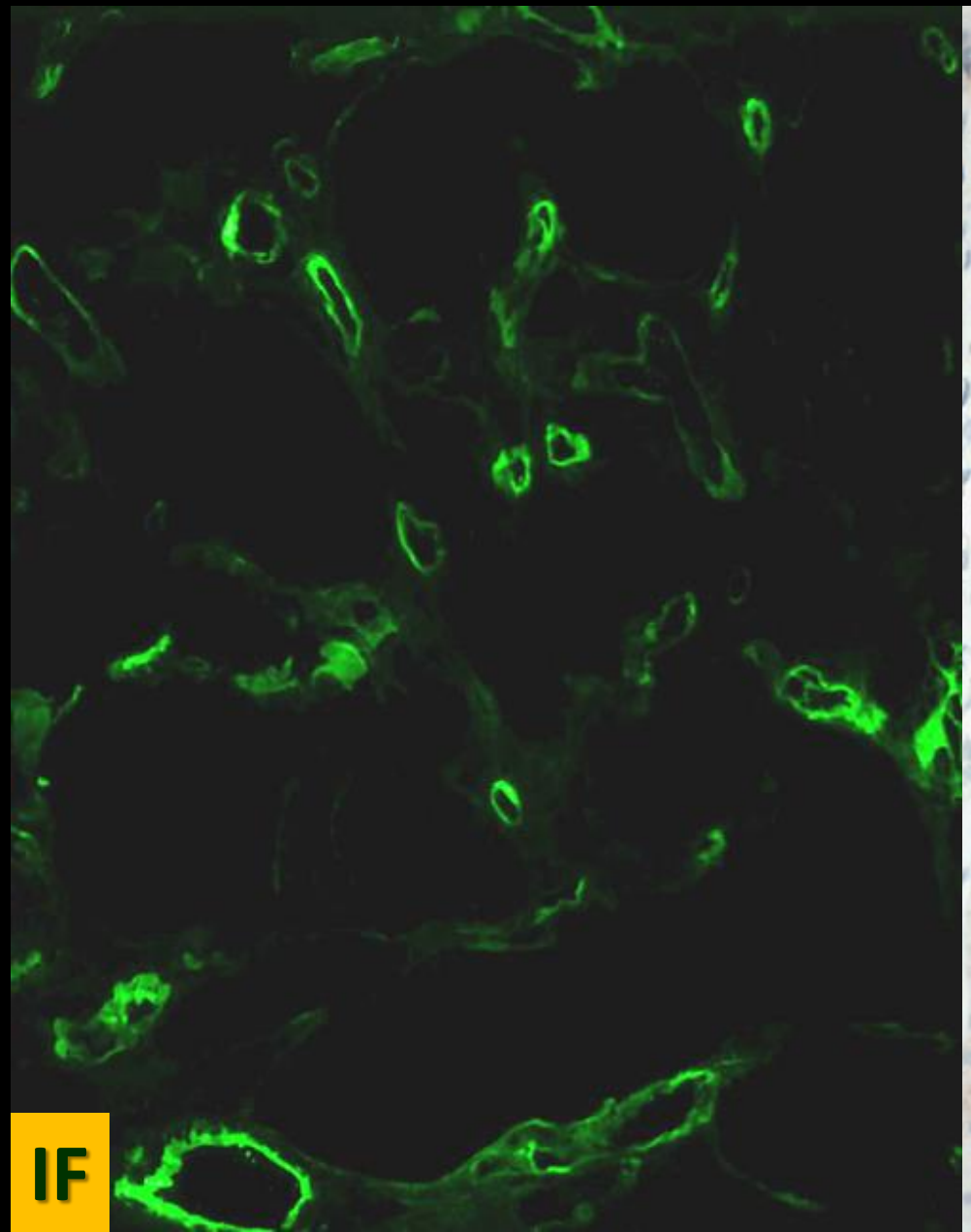


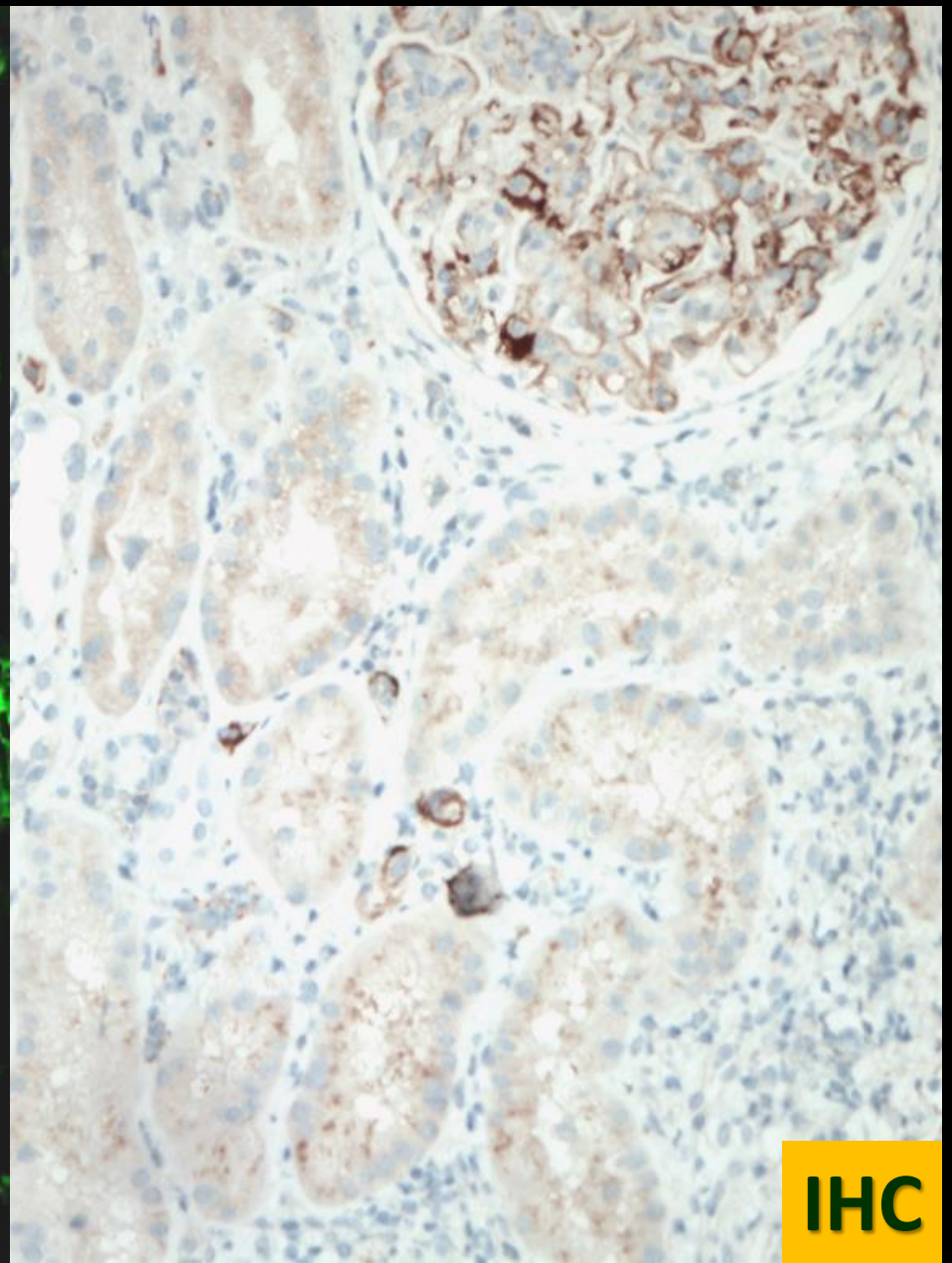
3-Step IF Technique



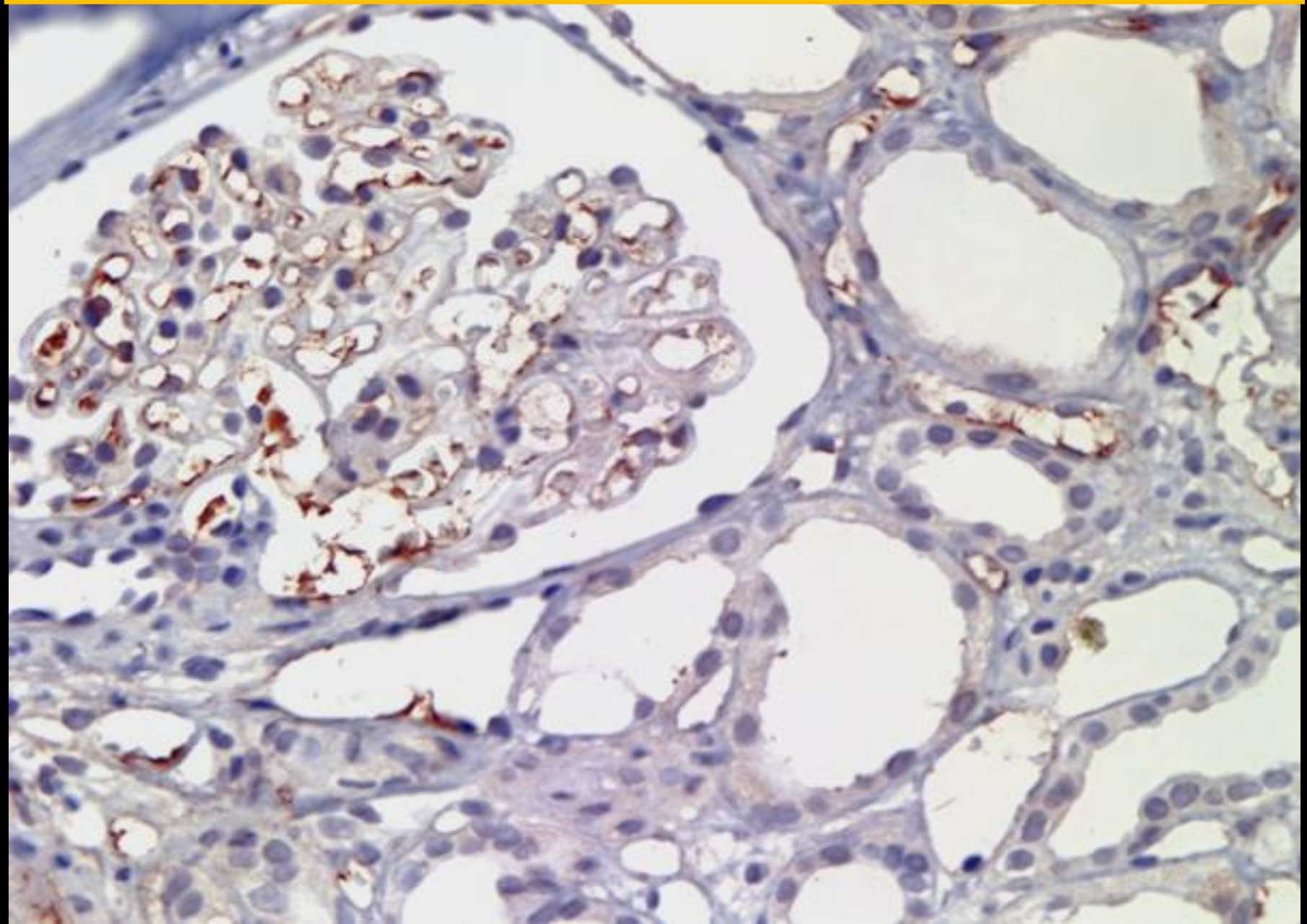
3-Step IP Technique

IF/frozen more sensitive than IHC/paraffin

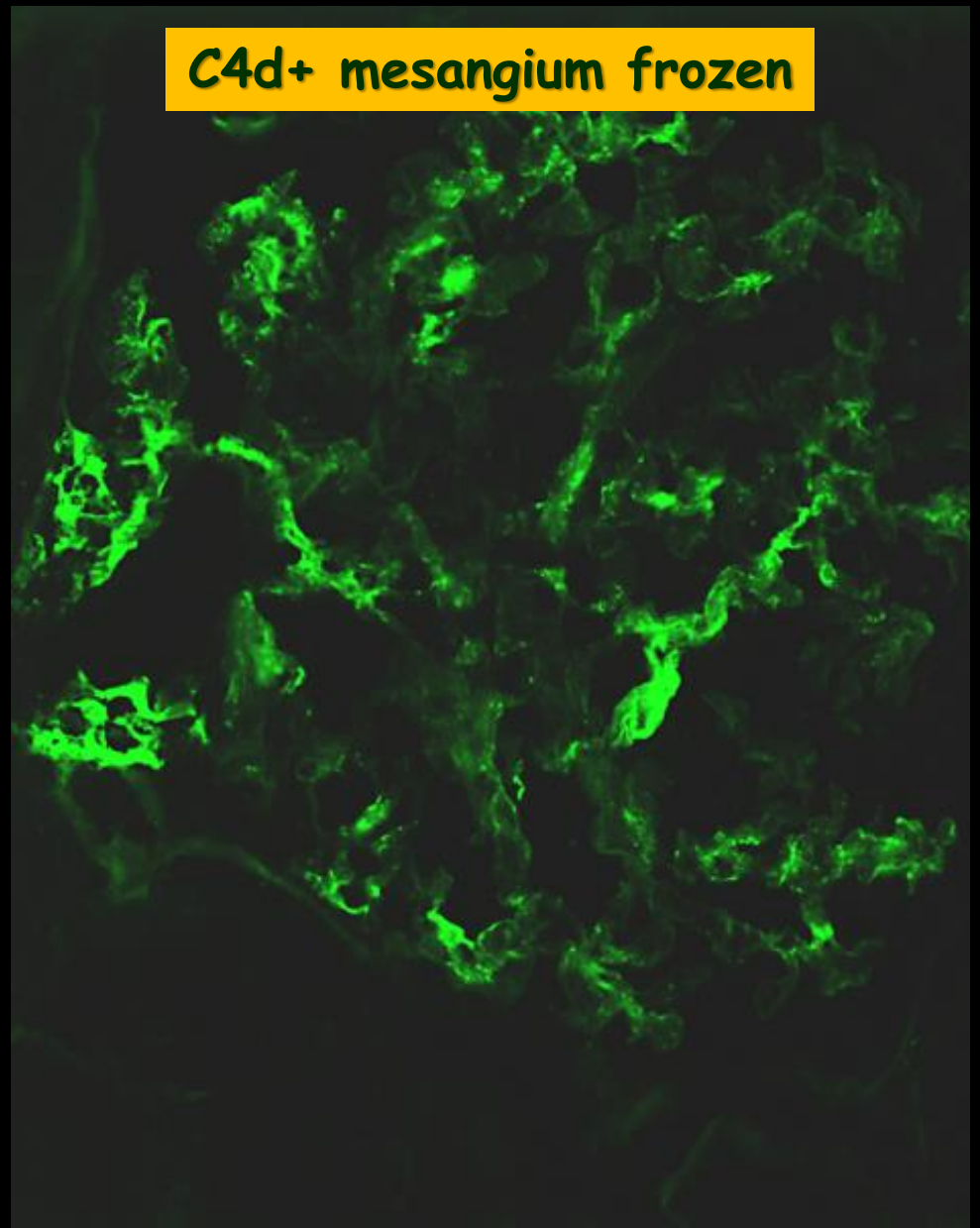


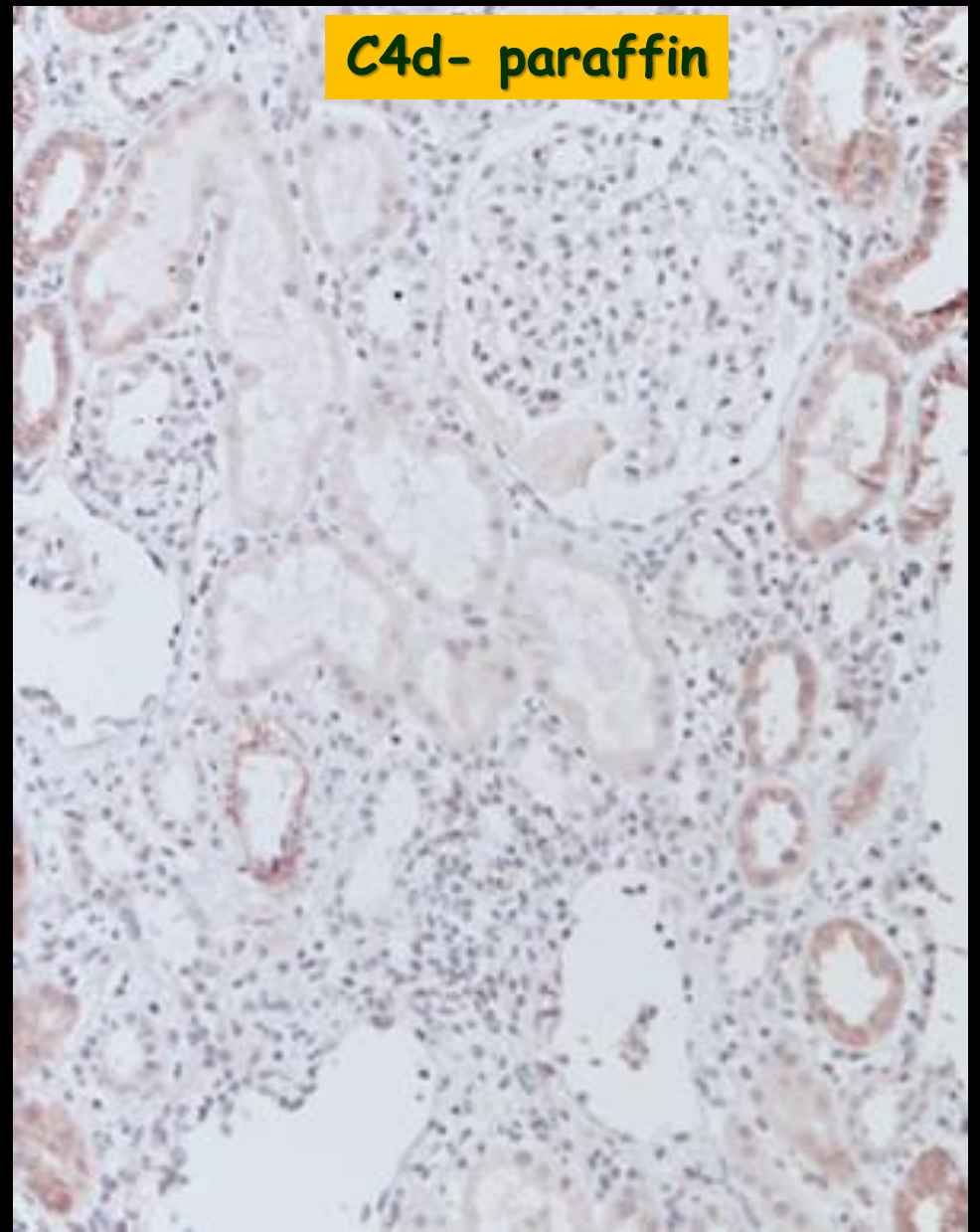


Fixed tissue may have plasma artifact



Normal kidney: Glomeruli stain in frozen, not paraffin





Updates of 2019 Banff classification

2- Chronic active ABMR; all 3 criteria must be met for diagnosis:

1. Morphologic evidence of chronic tissue injury,
2. Identical to criterion 2 for active ABMR
3. Identical to criterion 3 for active ABMR

Chronic active ABMR; all 3 criteria must be met for diagnosis

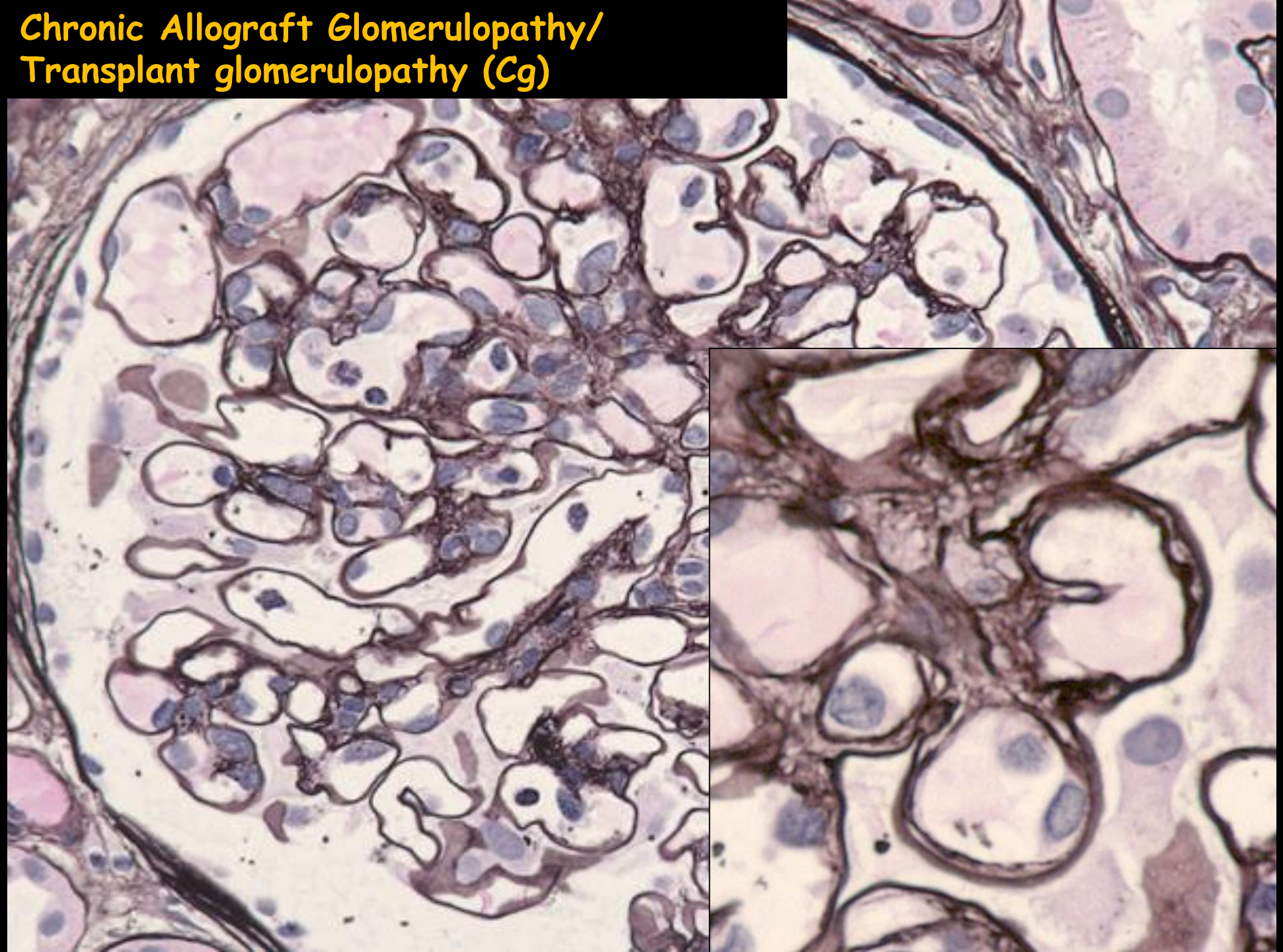
1. Morphologic evidence of chronic tissue injury, including 1 or more of the following:

Transplant glomerulopathy (cg > 0) if no evidence of chronic TMA or chronic recurrent/de novo glomerulonephritis; includes changes evident by electron microscopy (EM) alone (cg1a)

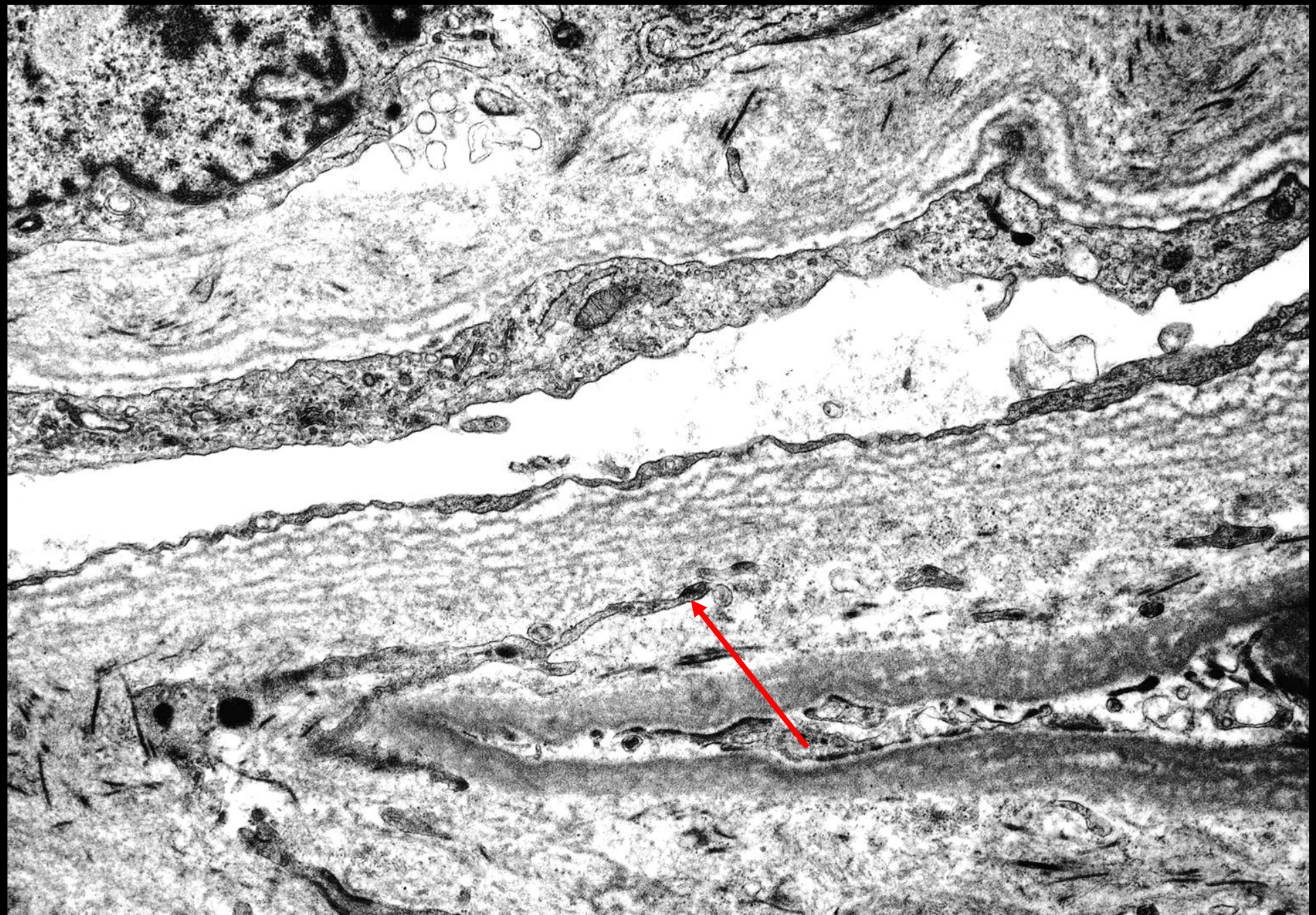
Severe peritubular capillary basement membrane multilayering (ptcml1; requires EM)

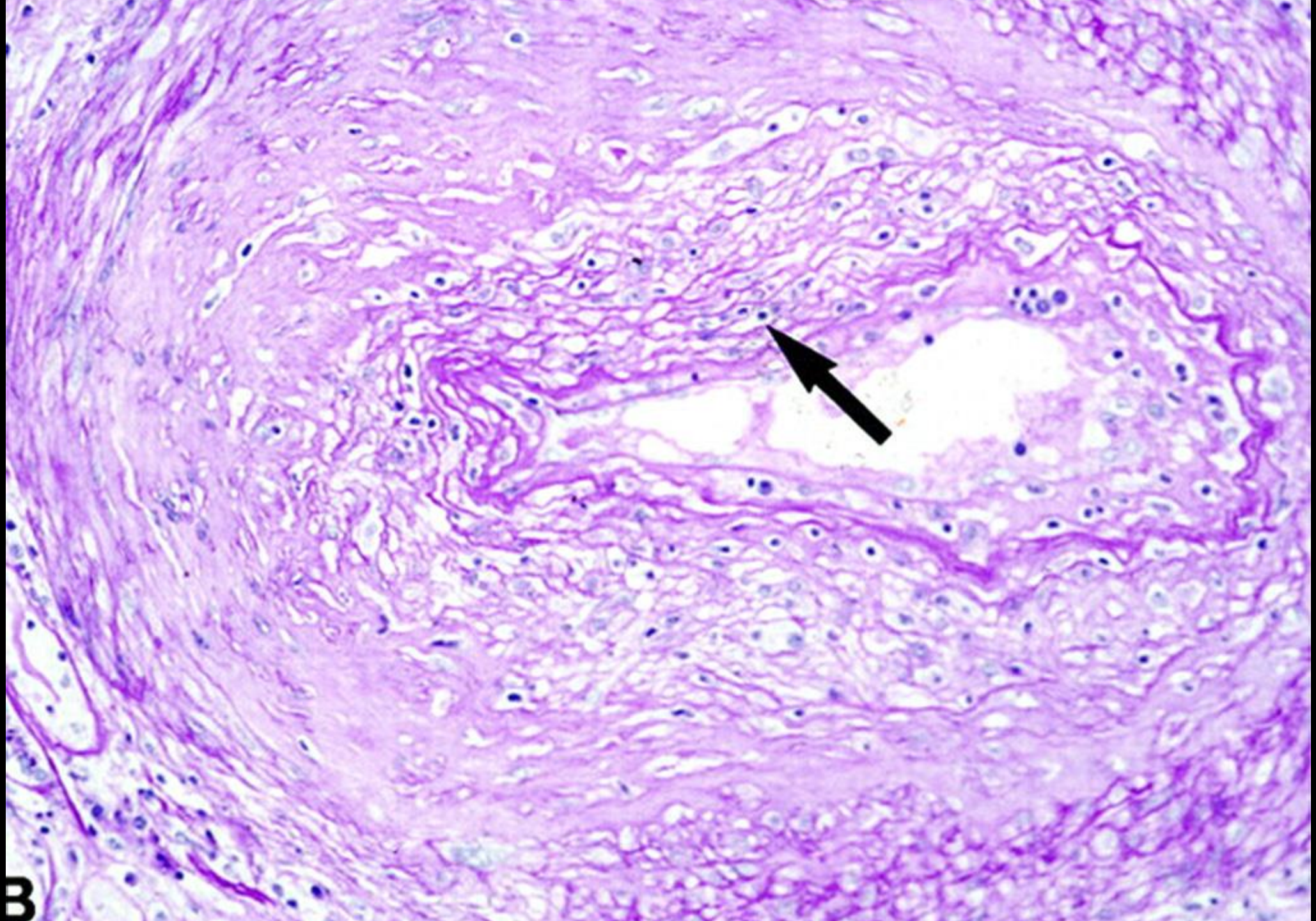
Arterial intimal fibrosis of new onset, excluding other causes; leukocytes within the sclerotic intima favor chronic ABMR if there is no prior history of TCMR, but are not required

Chronic Allograft Glomerulopathy/ Transplant glomerulopathy (Cg)



3 years post-Tx, PTC BM multilayering (up to 7 layers)

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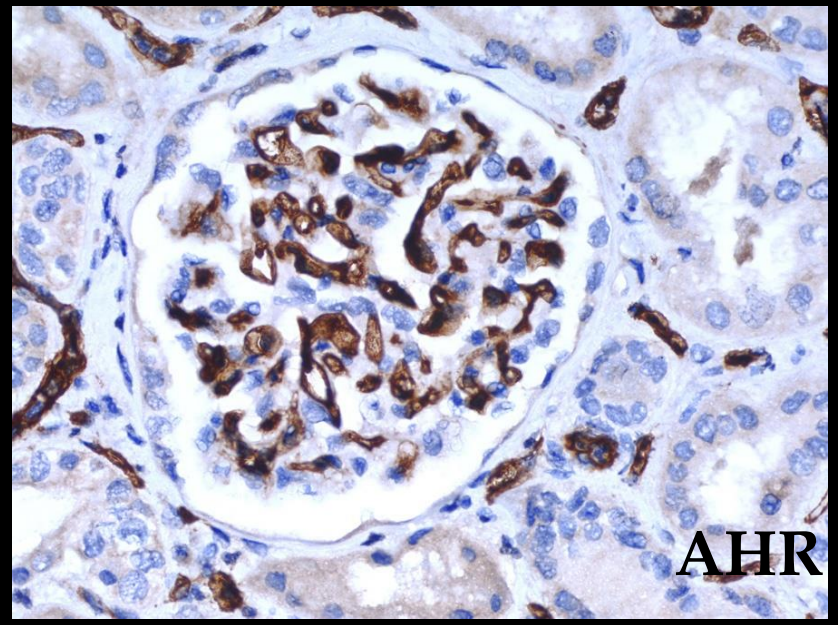
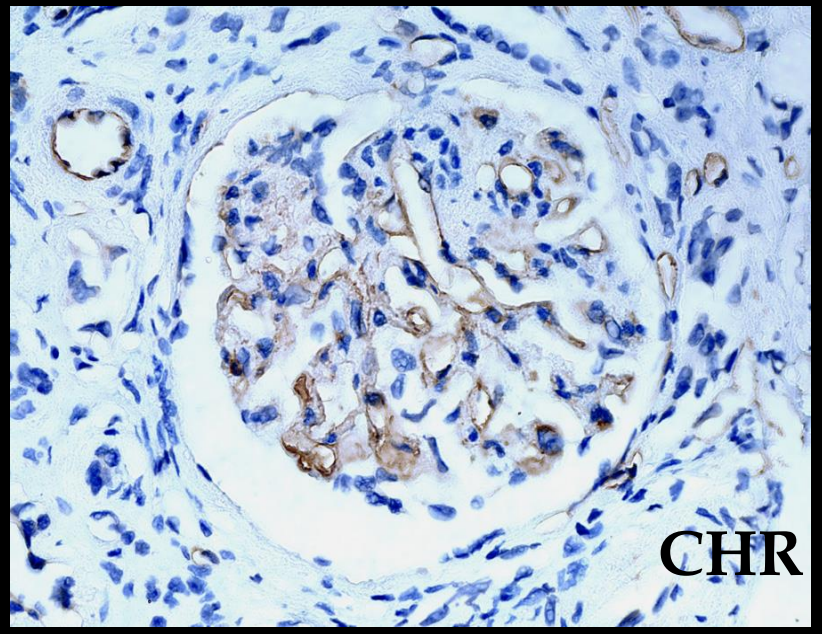
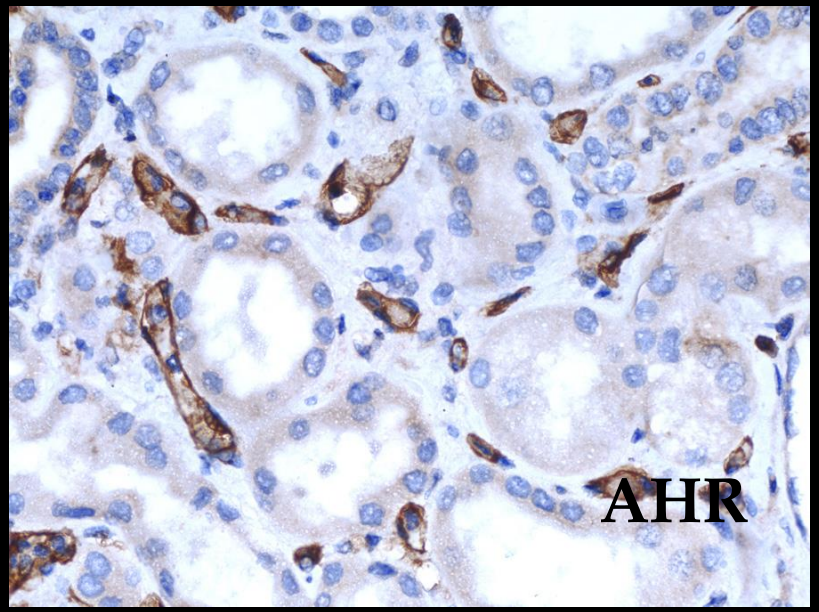
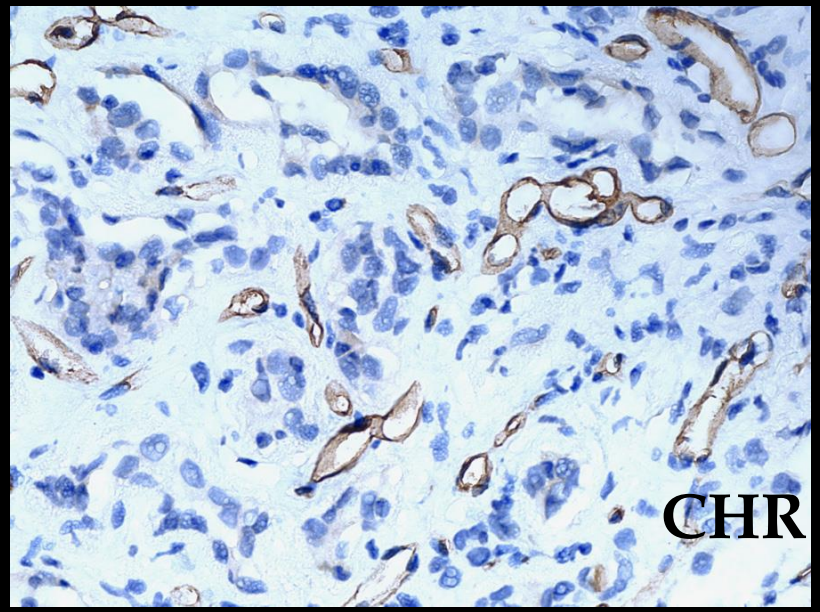
C4d









Updates of 2019 Banff classification

3- *Chronic (inactive) ABMR*

1. cg > 0 and/or severe ptcml (ptcml1)
2. Absence of criterion 2 of current/recent antibody interaction with the endothelium
3. Prior documented diagnosis of active or chronic active ABMR and/or documented prior evidence of DSA

Updates of 2019 Banff classification

4- C4d staining without evidence of rejection;

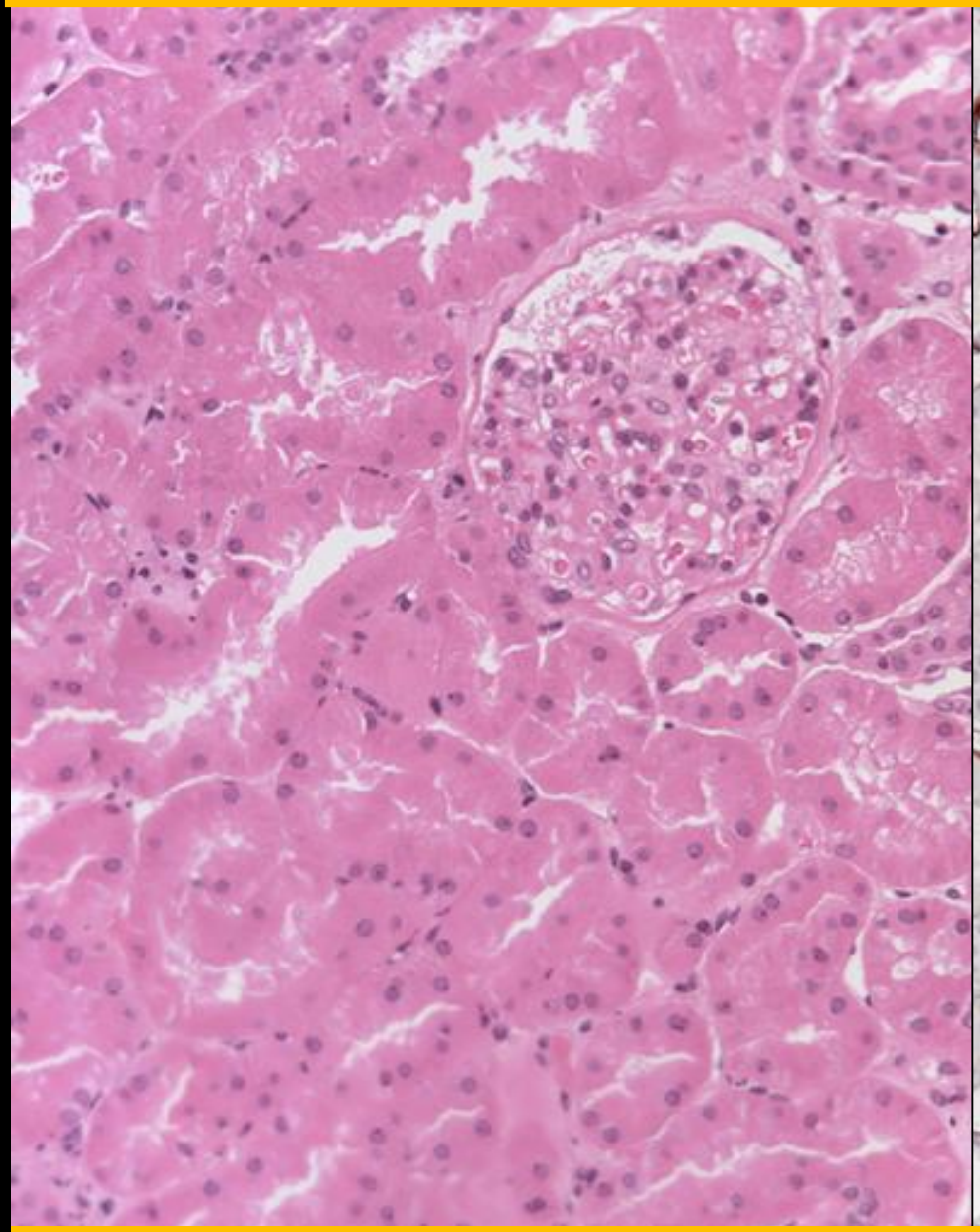
- ***all 4 features must be present for diagnosis***

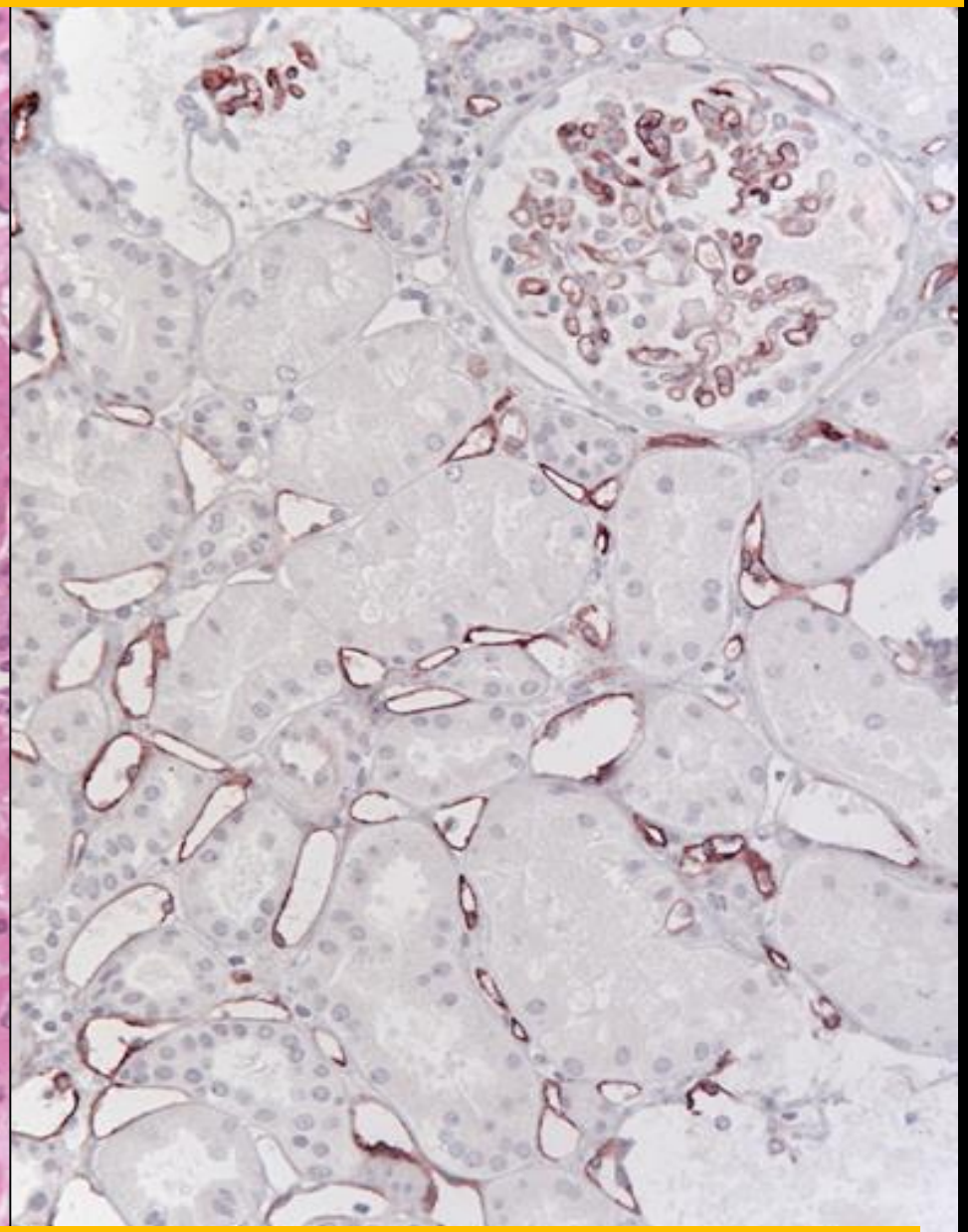
1. Linear C4d staining in peritubular capillaries

(C4d2 or C4d3 by IF on frozen sections, or C4d>0 by IHC on paraffin sections)

2. Criterion 1 for active or chronic active ABMR not met
3. No molecular evidence for ABMR as in criterion 2 for active and chronic active ABMR
4. No acute or chronic active TCMR, or borderline changes

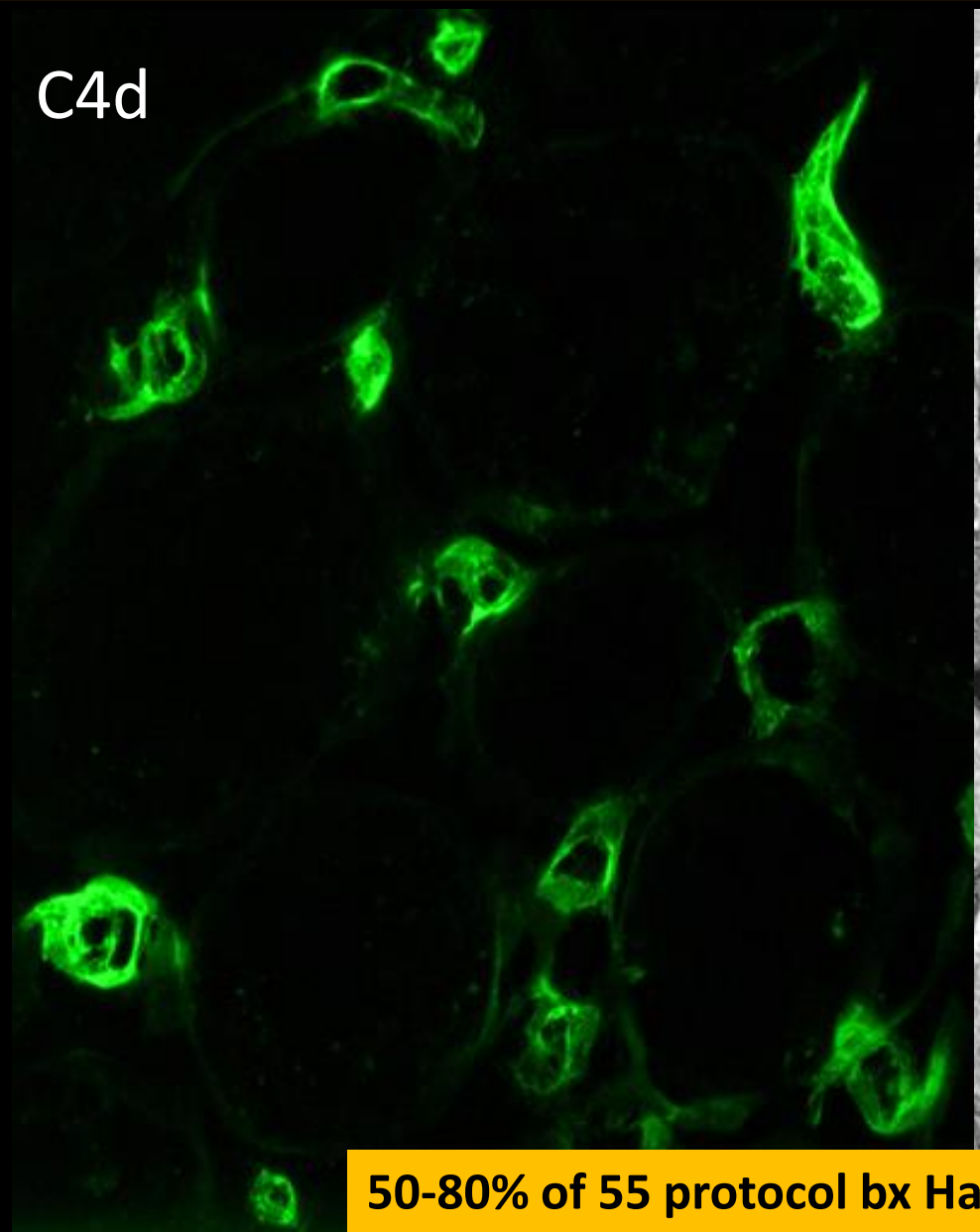
"Normal" Protocol Biopsy with C4d+

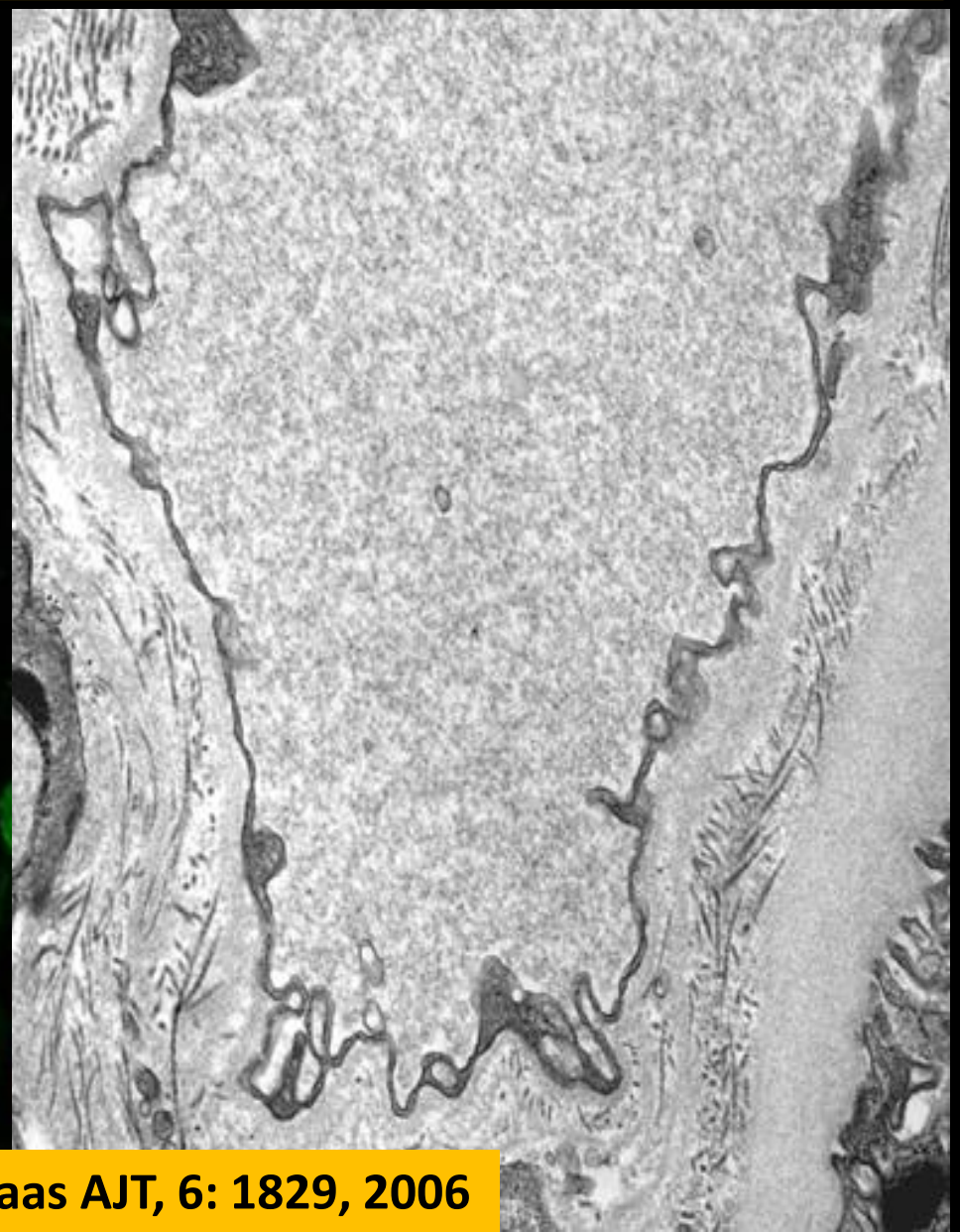




2-4% of 501 protocol bx in 1st yr Mengel AJT, 5: 1050, 2005

ABO incompatible allograft
Protocol bx 3 months





50-80% of 55 protocol bx Haas AJT, 6: 1829, 2006

A major residual issue within the classification

- The category of CA ABMR encompasses lesions with:
- Severe activity and mild chronicity (eg, g3 ptc3 cg1 ci0 ct0 C4d3),
- Those with mild activity and severe chronicity (eg, g1 ptc1 cg3 ci3 ct3 C4d0),
- Intermediate cases.
- Thus a simple diagnosis of CA ABMR gives treating clinicians limited information for appropriate treatment options.
- Although the addition of individual Banff lesion scores to the diagnostic line of the report is interpretable by experienced clinicians, it may confuse some clinicians who are unfamiliar with subtleties of the Banff system

Banff Kidney Questionnaire 2019

Survey results on reporting of chronic active T cell–mediated rejection (CA TCMR), chronic active antibody-mediated rejection (CA ABMR), and Banff i threshold for borderline Lesions

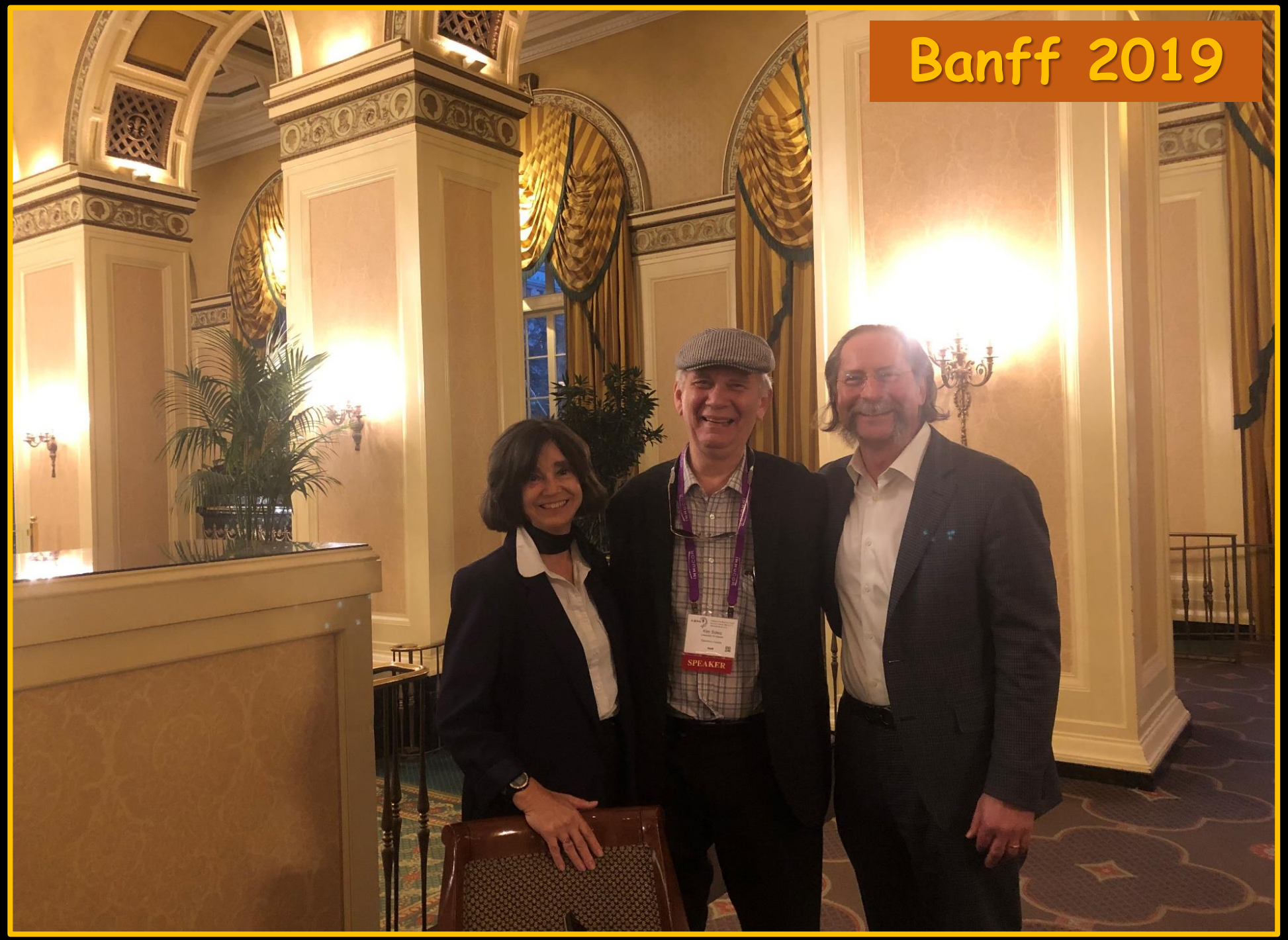
	Preferred diagnosis wording				
CA TCMR	CA TCMR + borderline or acute TCMR	CA TCMR +active component meeting criteria for BL or acute TCMR	CA TCMR	Acute TCMR+ moderate inflammed IFTA	Other
i1 t2 ti2 iIFTA3 ci2 ct2 +noMVI	**46%**	33%	20%	0%	1%
i2 t2 ti2 iIFTA3 ci2 ct2 + noMVI	**61%**	21%	5%	12%	1%
i1 t2 ti2 iIFTA3 ci2 ct2 v1 + noMVI	**70%**	12.5%	6.5%	10%	1%
CA ABMR	Current wording: CA ABMR	CA ABMR +specify g and ptc scores	CA ABMR +mild/moderate/severe activity/chronicity	ABMR +mild/moderate/severe activity/chronicity	Other
	14%	26%	27%	**29%**	4%

	Preferred threshold		
Borderline (suspicious) for acute TCMR	Inflammation in <10% of nonsclerotic cortex (i0 t > 0)	Inflammation in 10%-24% of nonsclerotic cortex (i1 t > 0)	Inflammation in 5%-24% of nonsclerotic cortex (with t > 0)
	15%	**82%**	3%

At the 2013 Banff conference in Comandatuba, Bahia, Brazil, a new Banff Working Group was formed, the "Clinical and Laboratory Assessment of Highly Sensitized Patients Working Group", later referred to as the "Antibody-Mediated Injury Working Group" .

key points

- ABMR in the kidney shows a wide range of clinicopathologic features that are not adequately represented in the current Banff diagnostic classification. we need to re-assess the usefulness of the current ABMR categories.
- the presence of features of more than one disease is usual in late renal allograft biopsy samples, typically some components of calcineurin inhibitor toxicity, donor disease (arteriosclerosis) , and chronic rejection, sometimes with recurrent disease.
- The Nephropathologist, together with the Nephrologist, must try to determine the principal pathological processes that are present and decide which treatments might be of potential benefit.


Banff 2019
SPEAKER

Thank You For Your Attention

The Smithfield Street Bridge, Pittsburgh, Pennsylvania Sep 2019