Kidney Transplant Pathology
Chronic/Active Ab- Mediated Rejection
Banff Meeting 2022- 2024

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Meeting report

The Banff 2024 Kidney Meeting Report: Rejection as a spectrum of phenotypes and focus on differential diagnostic reasoning

Maarten Naesens [1,*,†], Candice Roufosse [2,**,†], Lynn D. Cornell [3,4], Mark Haas [5], Roslyn B. Mannon [6], Marjan Afrouzian [7], Enver Akalin [8], Nada Alachkar [9], Mariam P. Alexander [3], Serena M. Bagnasco [10], Ibrahim Batal [11], Georg A. Böhmig [12], Peter Boor [13], Verena Broecker [14], Anthony Chang [15], Marian Clahsen-Van Groningen [16,17], Shana M. Coley [18], Robert B. Colvin [19], Darshana Dadhania [20], Cinthia B. Drachenberg [21], Michelle Elias [22], Alton B. Farris [23], Agnes B. Fogo [24], Kevin Fowler [25], Ian W. Gibson [26], Valentin Goutaudier [27,28], Edmund Huang [29], Syed A. Husain [30], Annette M. Jackson [31], Jesper Kers [32,33], Željko Kikić [34],

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Meeting report

The Banff 2022 Kidney Meeting Report: Reappraisal of microvascular inflammation and the role of biopsy-based transcript diagnostics

Maarten Naesens [1,*,†], Candice Roufosse [2,**,†], Mark Haas [3], Carmen Lefaucheur [4], Roslyn B. Mannon [5], Benjamin A. Adam [6], Olivier Aubert [7], Georg A. Böhmig [8], Jasper Callemeyn [1], Marian Clahsen-van Groningen [9], Lynn D. Cornell [10], Anthony J. Demetris [11], Cinthia B. Drachenberg [12], Gunilla Einecke [13], Agnes B. Fogo [14], Ian W. Gibson [15], Philip Halloran [16], Luis G. Hidalgo [17], Catherine Horsfield [18], Edmund Huang [19], Željko Kikić [20], Nicolas Kozakowski [21], Brian Nankivell [22], Marion Rabant [23], Parmjeet Randhawa [24], Leonardo V. Riella [25], Ruth Sapir-Pichhadze [26], Carrie Schinstock [27], Kim Solez [28], Anat R. Tambur [29], Olivier Thaunat [30], Chris Wiebe [31], Dina Zielinski [7], Robert Colvin [32], Alexandre Loupy [7,‡], Michael Mengel [6,‡]

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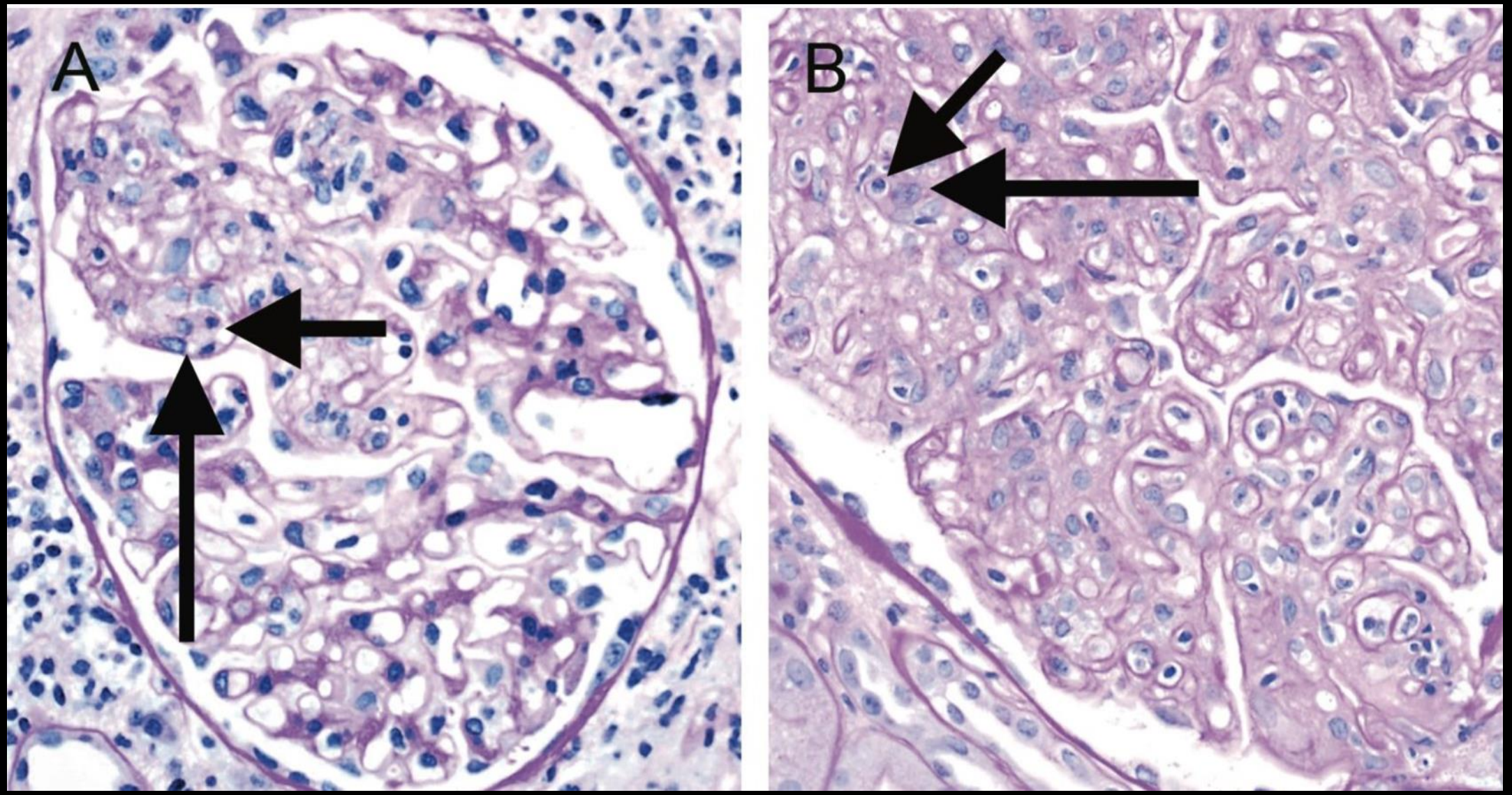
Updates of 2022 Banff Classification

Table S3: Phenotypes/subcategories of Banff 2022 Category 2: AMR/MVI, and changes to the Banff 2019 report. This table aligns with the classification of Table S1 but is in the format of the Banff 2019 report, per phenotype/subcategory. Changes to the Banff 2019 report are highlighted in red (deletions), green (additions) or italics (rewording).

Banff Category 2: Antibody-mediated rejection and microvascular inflammation/injury (AMR/MVI)
Active AMR; all 3 criteria must be met for diagnosis
1. Active lesions of AMR present, at least ~~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) • Acute thrombotic microangiopathy, in the absence of any other cause • ~~Acute tubular injury, in the absence of any other apparent cause~~ 2. *At least ~~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 • *Biopsy-based transcript diagnostics for AMR/MVI above a defined threshold*, if thoroughly validated *for use as substitute for MVI and available* 3. ~~Serologic~~ Evidence of circulating donor-specific antibodies (DSA to HLA or other antigens). If thorough testing for DSA (anti-HLA or other specificity) has not yet been performed, this should be done, *following the STAR guidelines.[1-3]. Detection of non-HLA antibodies (including ABO antibodies in ABO-incompatible transplantation) can be used as serologic Banff criterion for diagnosis of AMR, if the testing protocols are sufficiently standardized and clinically validated for the appropriate clinical context.* C4d staining ~~*or expression of validated transcripts/classifiers as noted above in criterion 2*~~ as noted above in Criterion 2 may substitute for DSA.

Banff Lesion Score g (Glomerulitis)

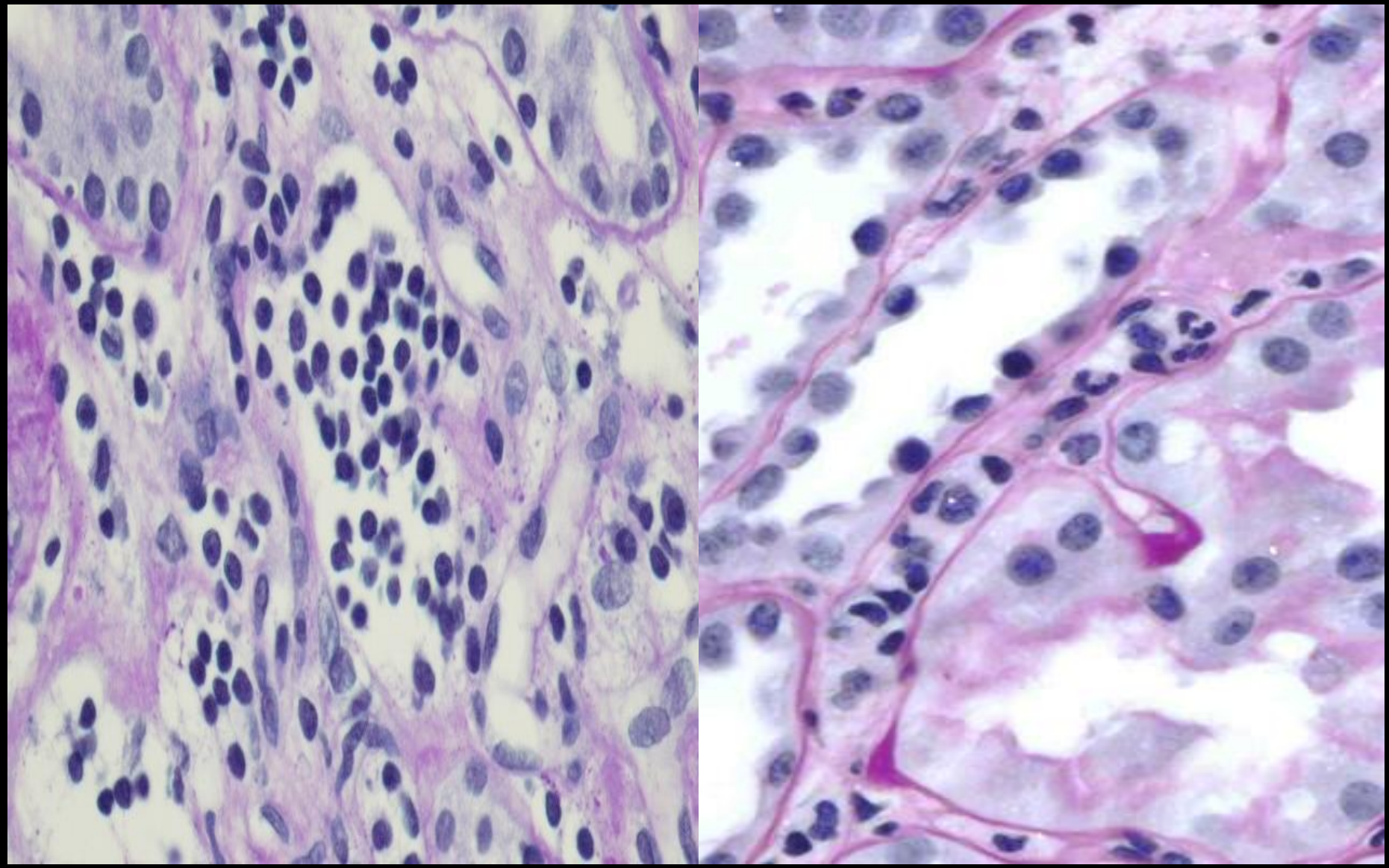


This is a synopsis of the thresholds for all Banff Lesion Scores

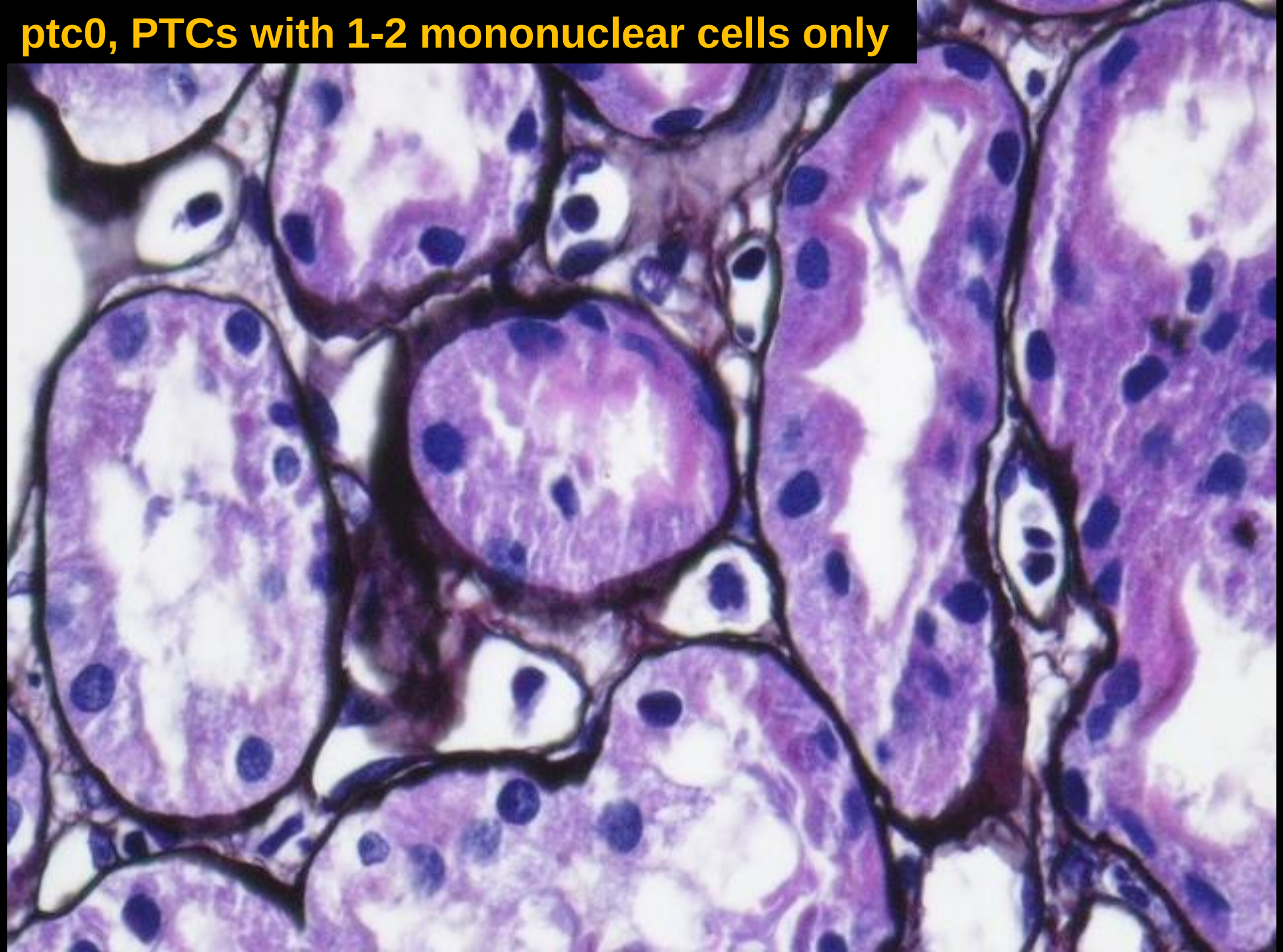
Banff lesion score,	Abbreviation	0	1	2	3
Interstitial inflammation	*i*	<10%	10-25%	26-50%	>50
Tubulitis	*t*	None	1-4/tubular cross section or 10 tubular epithelial cells	5-10	>10 or foci of tubular basement membrane destruction with i ≥ 2 and t2 elsewhere
Intimal arteritis	*v*	None	<25% luminal area lost	≥25% luminal area lost	Transmural and/or fibrinoid change and medial smooth muscle necrosis
Glomerulitis	*g*	None	<25%	25-75%	>75%
Peritubular capillaritis	*ptc*	<3 leukocytes/ PTC	≥1 leukocyte in ≥10% of PTCs with max. of 3-4/PTC	≥1 leukocyte in ≥10% of PTCs with max. of 5-10/PTC	≥1 leukocyte in ≥10% of PTCs with max. of >10/PTC
C4d	*C4d*	None	<10%	10-50%	>50%
Interstitial fibrosis	*ci*	≤5%	6-25%	26-50%	>50%
Tubular atrophy	*ct*	None	≤25%	26-50%	>50%
Vascular fibrous Intimal thickening	*cv*	None	≤25%	26-50%	>50%
GBM double contours	*cg*	None	1a: only by EM 1b: ≤25% by LM	26-50%	>50%
Mesangial matrix expansion	*mm*	None	≤25%	26-50%	>50%
Arteriolar hyalinosis	*ah*	None	Mild to moderate in ≥1	Moderate to severe in >1	Severe in many
Hyaline arteriolar thickening	*aah*	None	1 without circumferential	≥1 without circumferential	circumferential
Total inflammation	*ti*	<10%	10-25%	26-50%	>50%
Inflammation in the area of IFTA	*i-IFTA*	<10%	10-25%	26-50%	>50%

The user of this table should be familiar with the exact definitions underlying each individual Banff Lesion Score. Reliance on these thresholds alone without consideration of the regulatory statutes behind these scores is strongly discouraged. max.:, maximum; PTC, peritubular capillary.

Banff Lesion Score ptc (Peritubular Capillaritis)

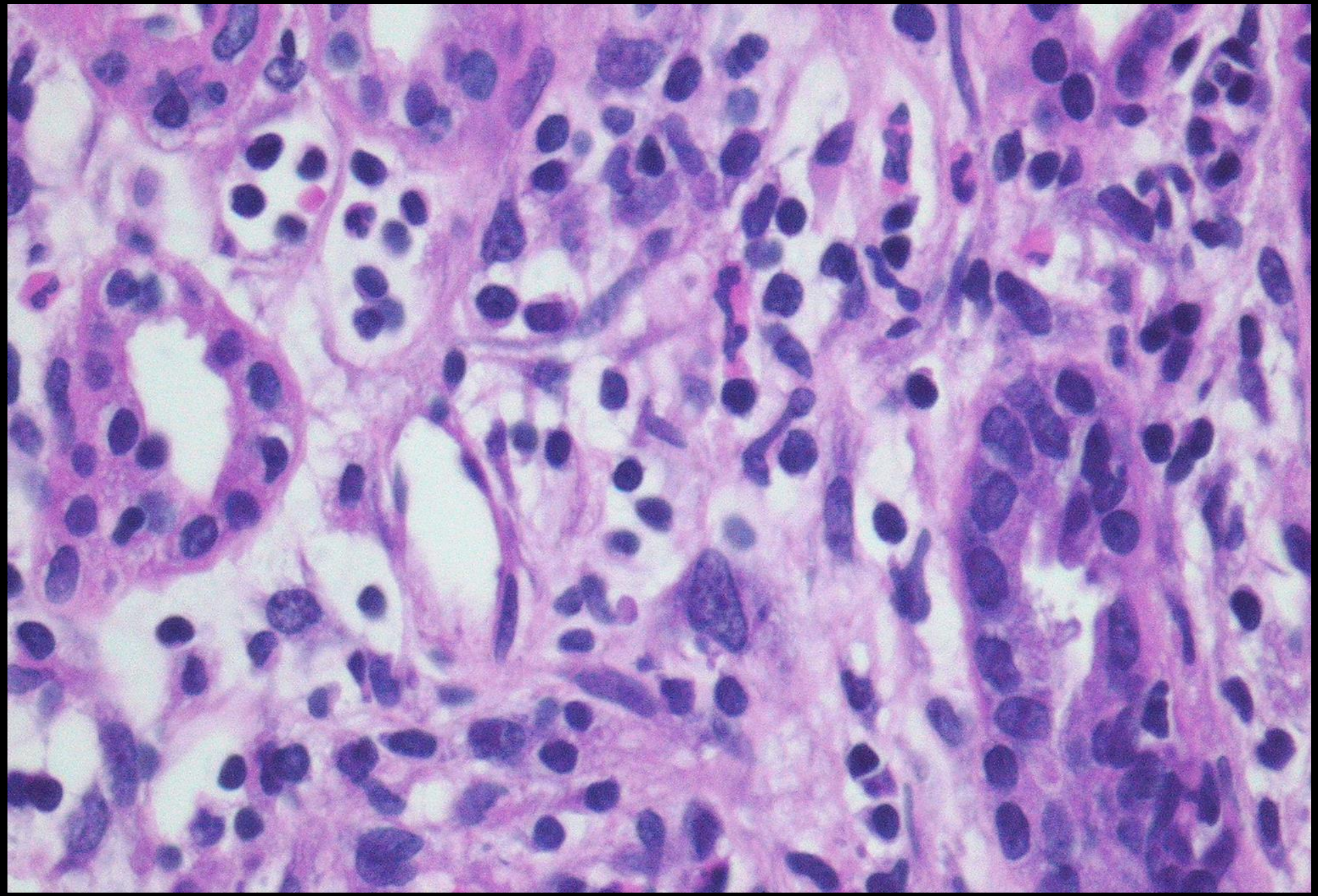


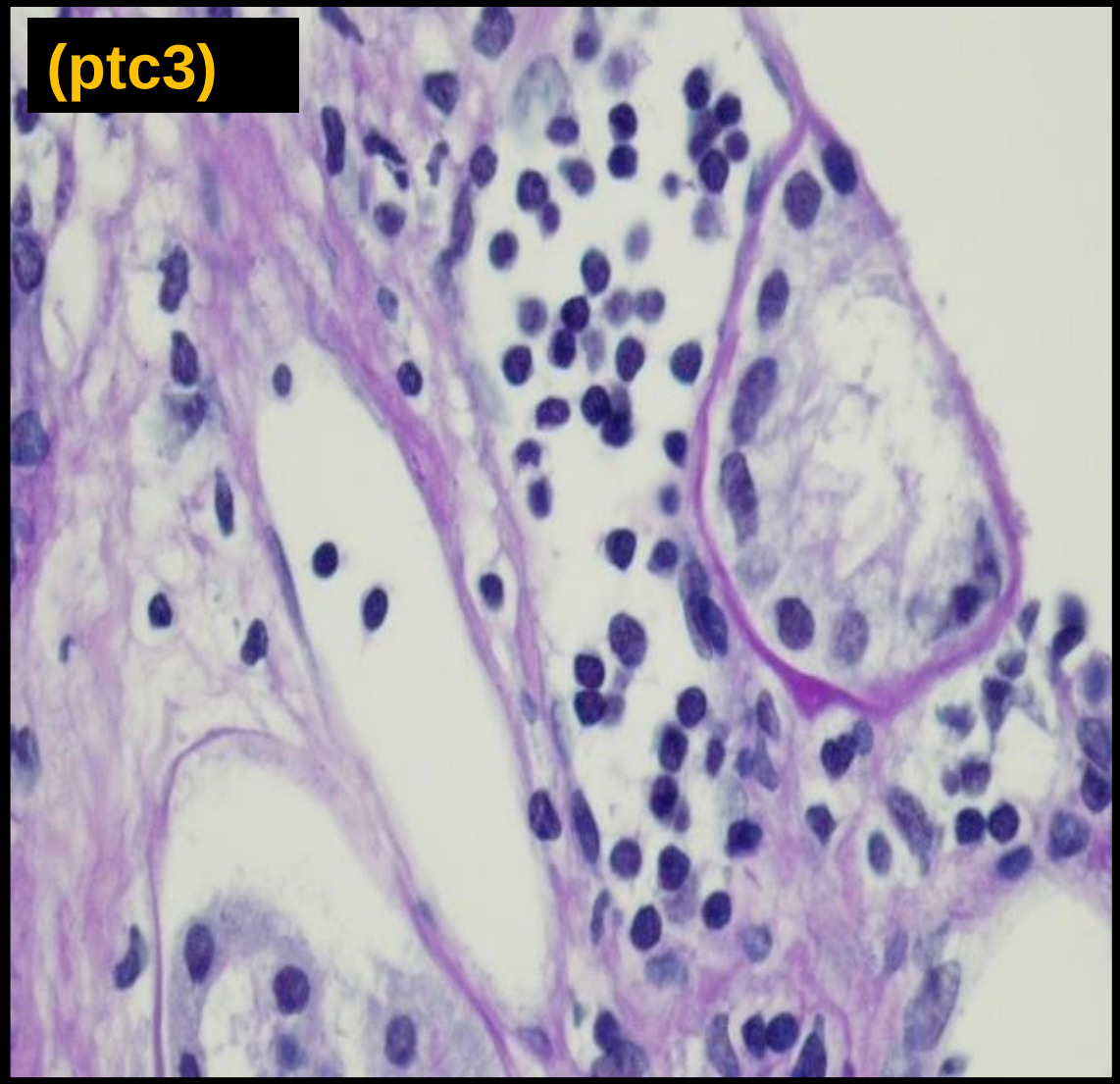
ptc0, PTCs with 1-2 mononuclear cells only

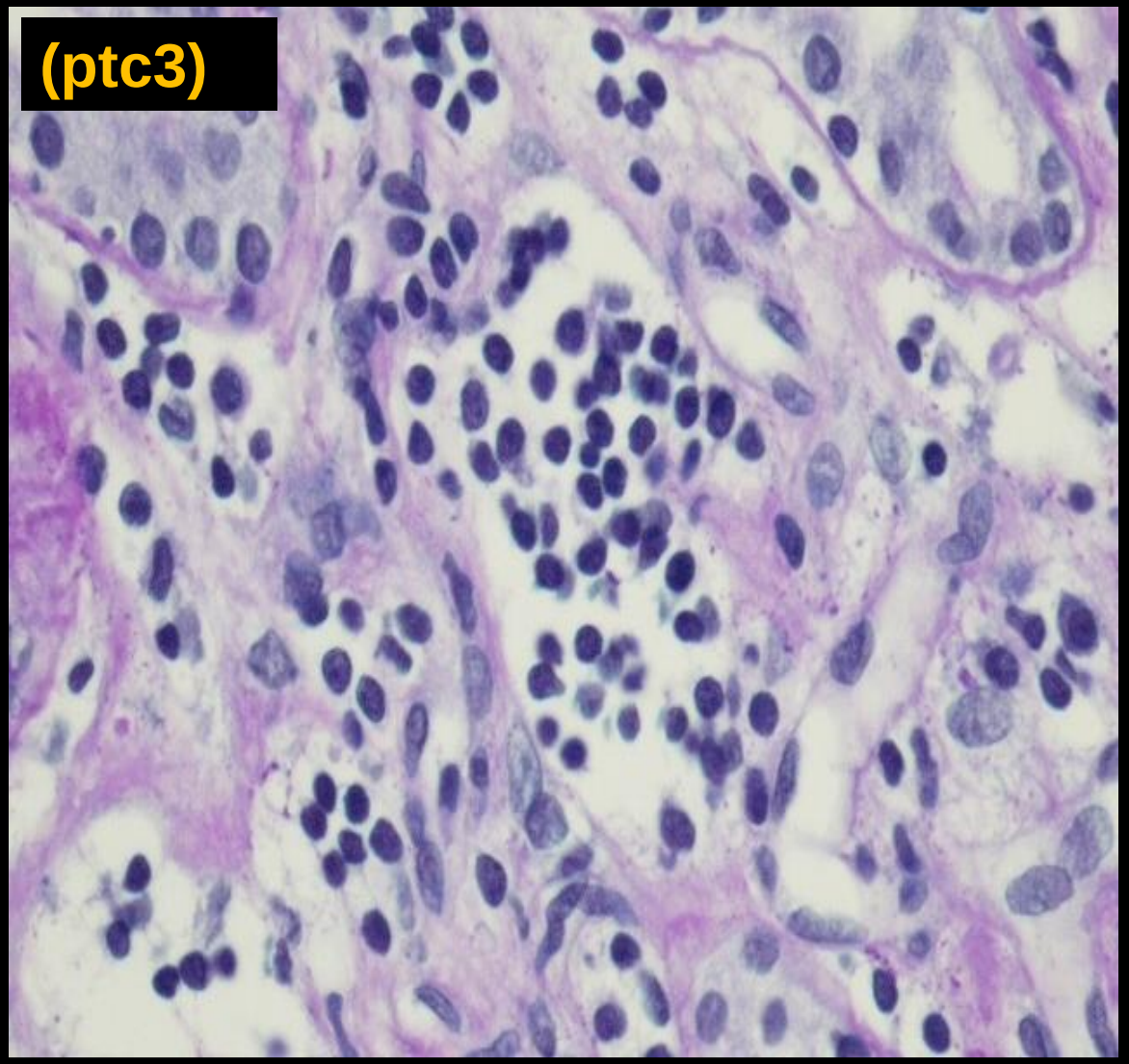


ptc1*, mononuclear cells only

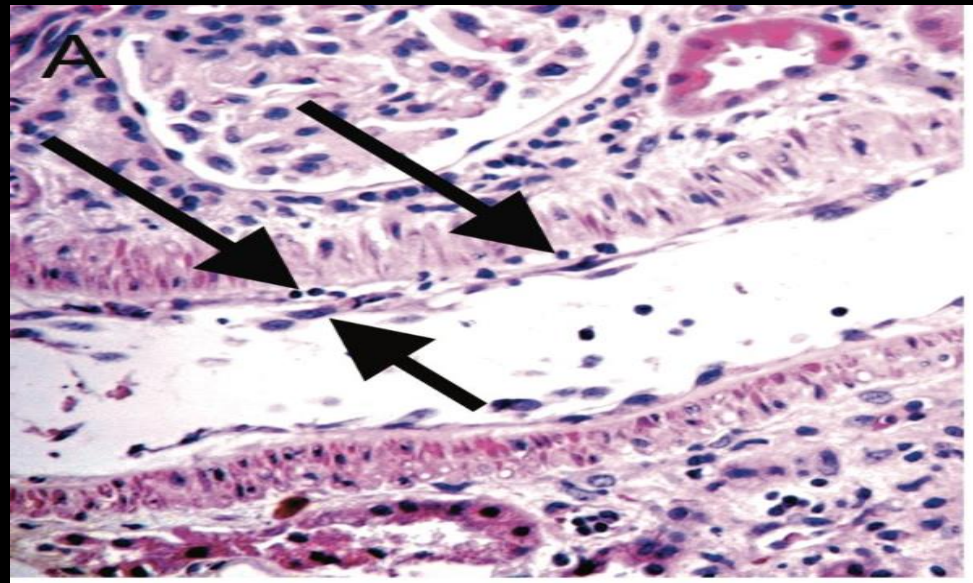
7 days post-Tx, AbMAR, ptc2, PMNLs & mononuclear cells

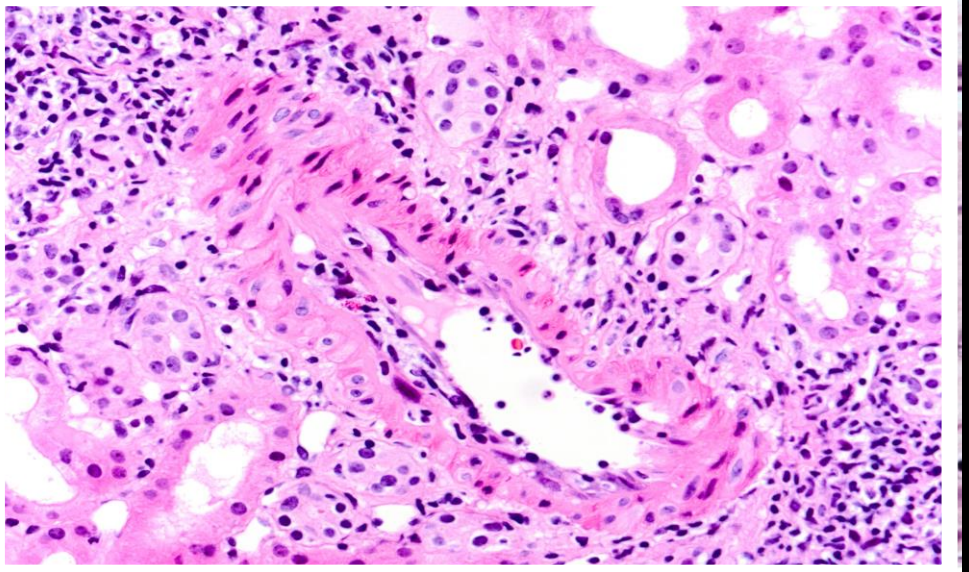


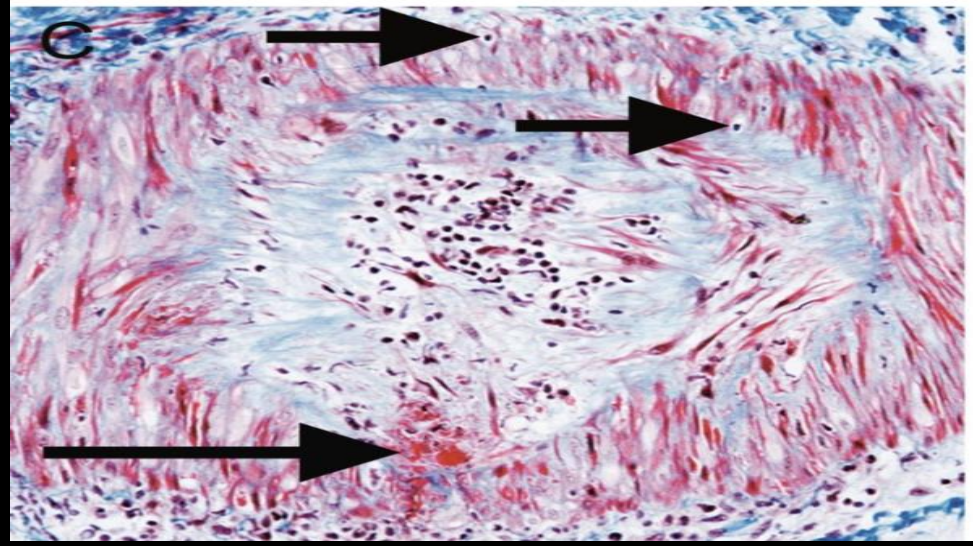

(ptc3)

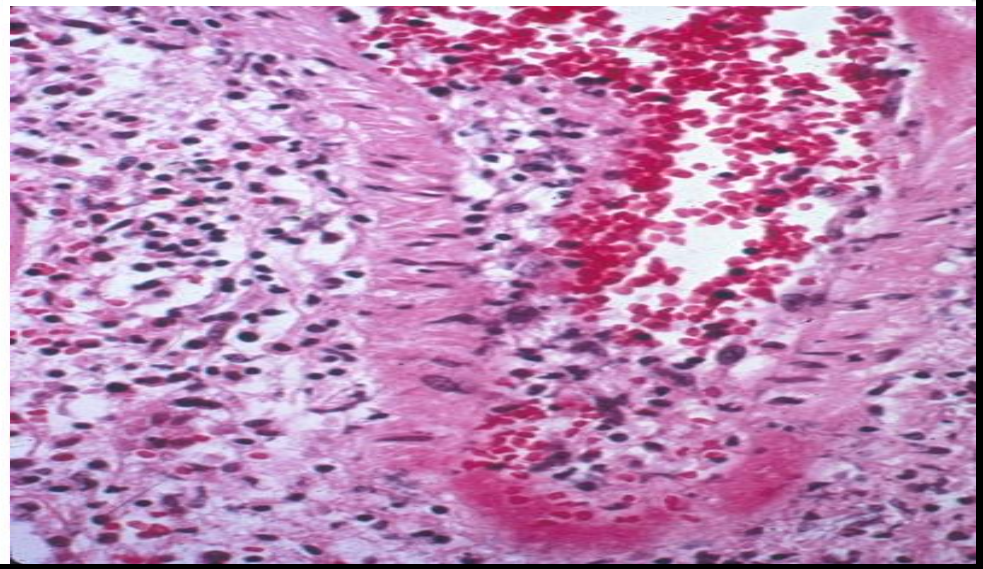

(ptc3)

Banff Lesion Score v (Intimal Arteritis)

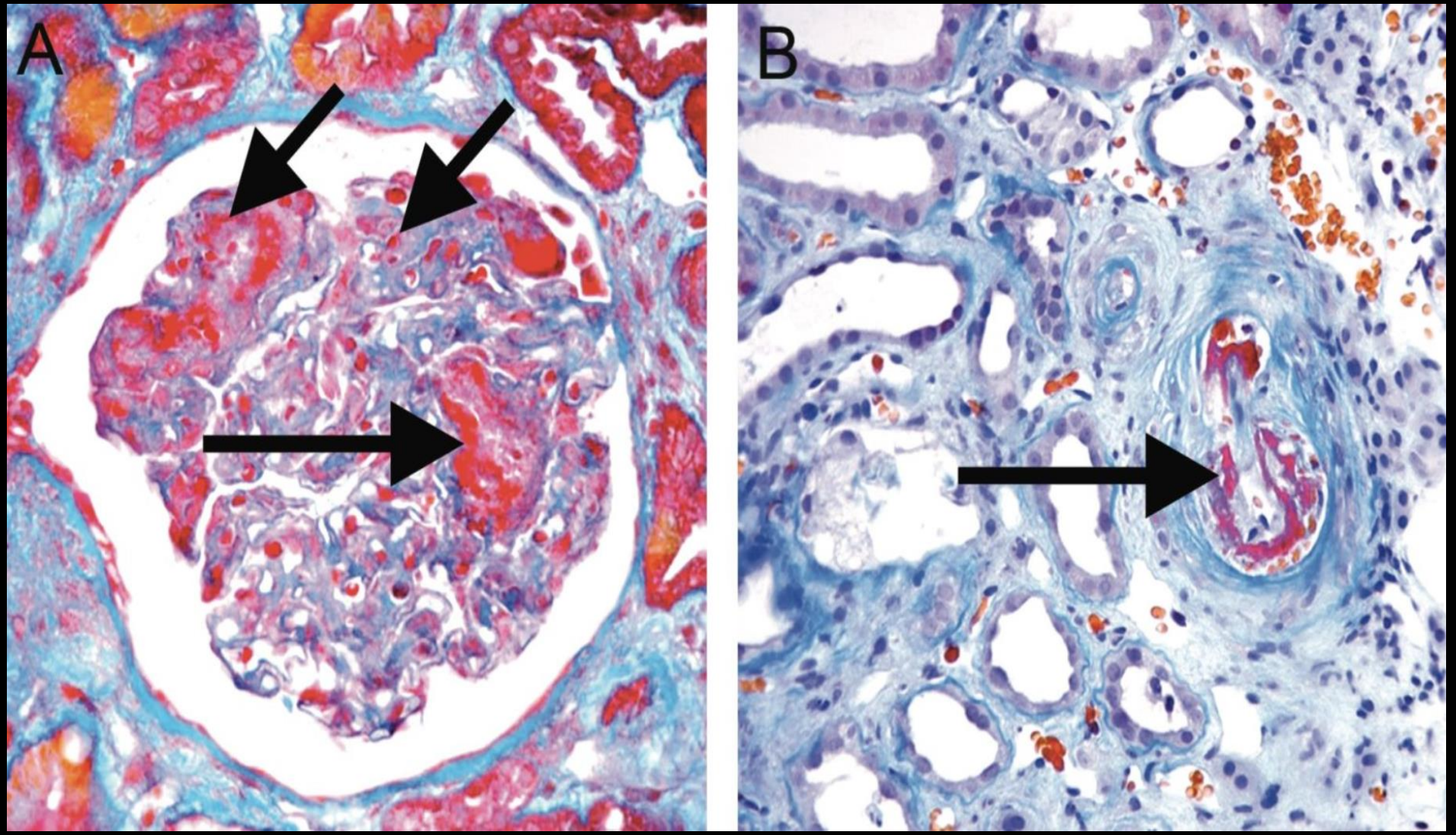








Acute Thrombotic Microangiopathy (TMA)



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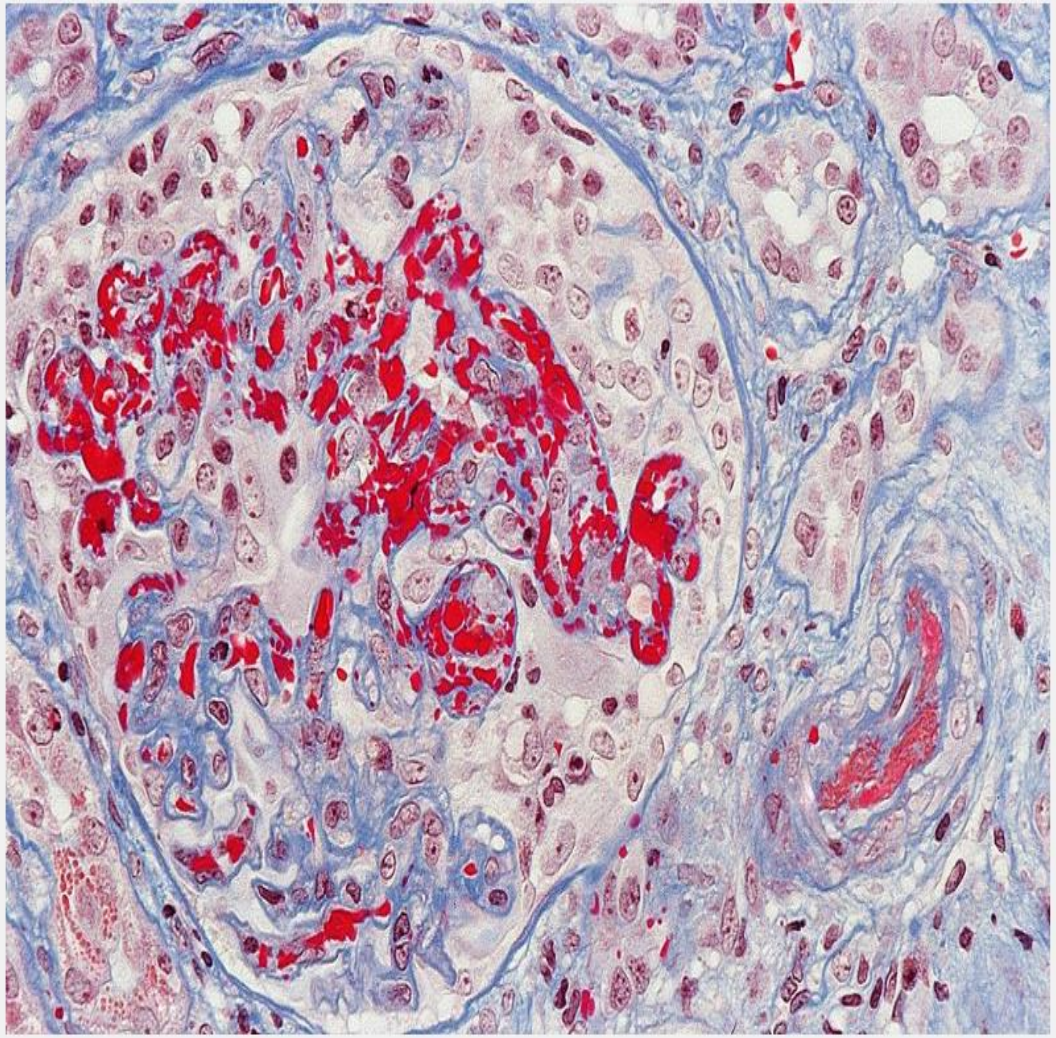
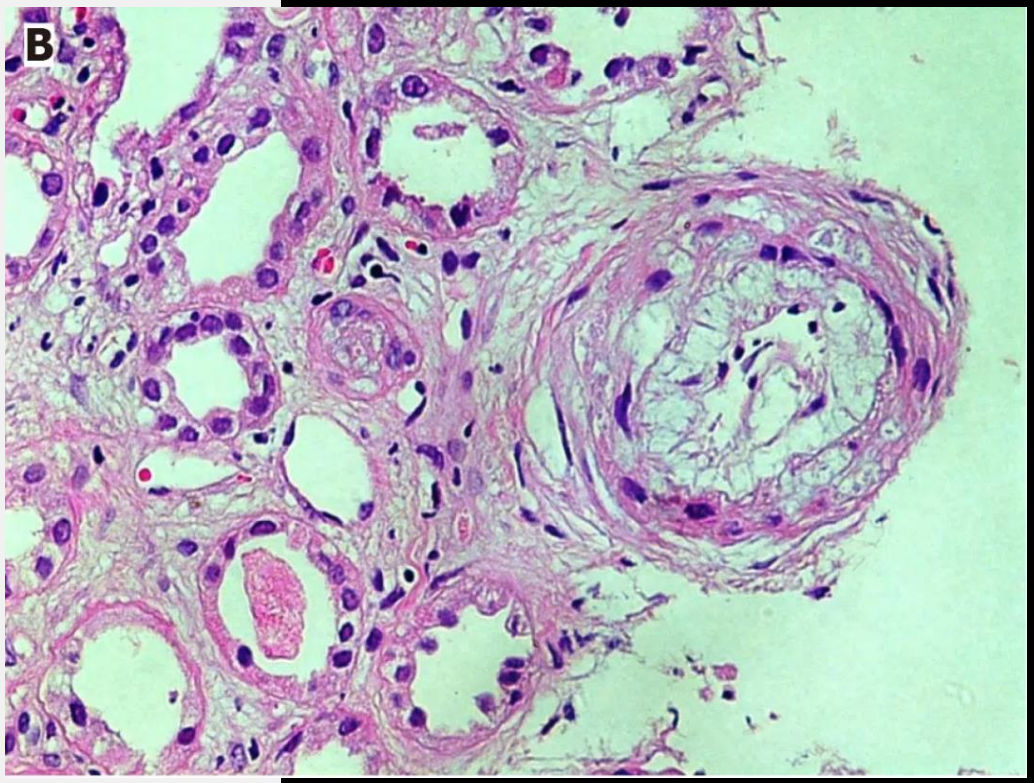
Check for updates

Thrombotic Microangiopathy in the Renal Allograft: Results of the TMA Banff Working Group Consensus on Pathologic Diagnostic Criteria

Marjan Afrouzian[1], Nicolas Kozakowski[2], Helen Liapis[3], Verena Broecker[4], Luon Truong[5], Carmen Avila-Casado[6], Heinz Regele[2], Surya Seshan[7], Josephine M. Ambruzs[8], Alton Brad Farris[9], David Buob[10], Praveen N. Chander[11], Lukman Cheraghvandi[12], Marian C. Clahsen-van Groningen[13,14], Stanley de Almeida Araujo[15], Dilek Ertoy Baydar[16], Mark Formby[17,18], Danica Galesic Ljubanovic[19], Loren Herrera Hernandez[20], Eva Honsova[21], Nasreen Mohamed[22], Yasemin Ozluk[23], Marion Rabant[24], Virginie Royal[25], Heather L. Stevenson[1], Maria Fernanda Toniolo[26] and Diana Taheri[27,28]*

TMA in renal allograft can be a challenging diagnosis





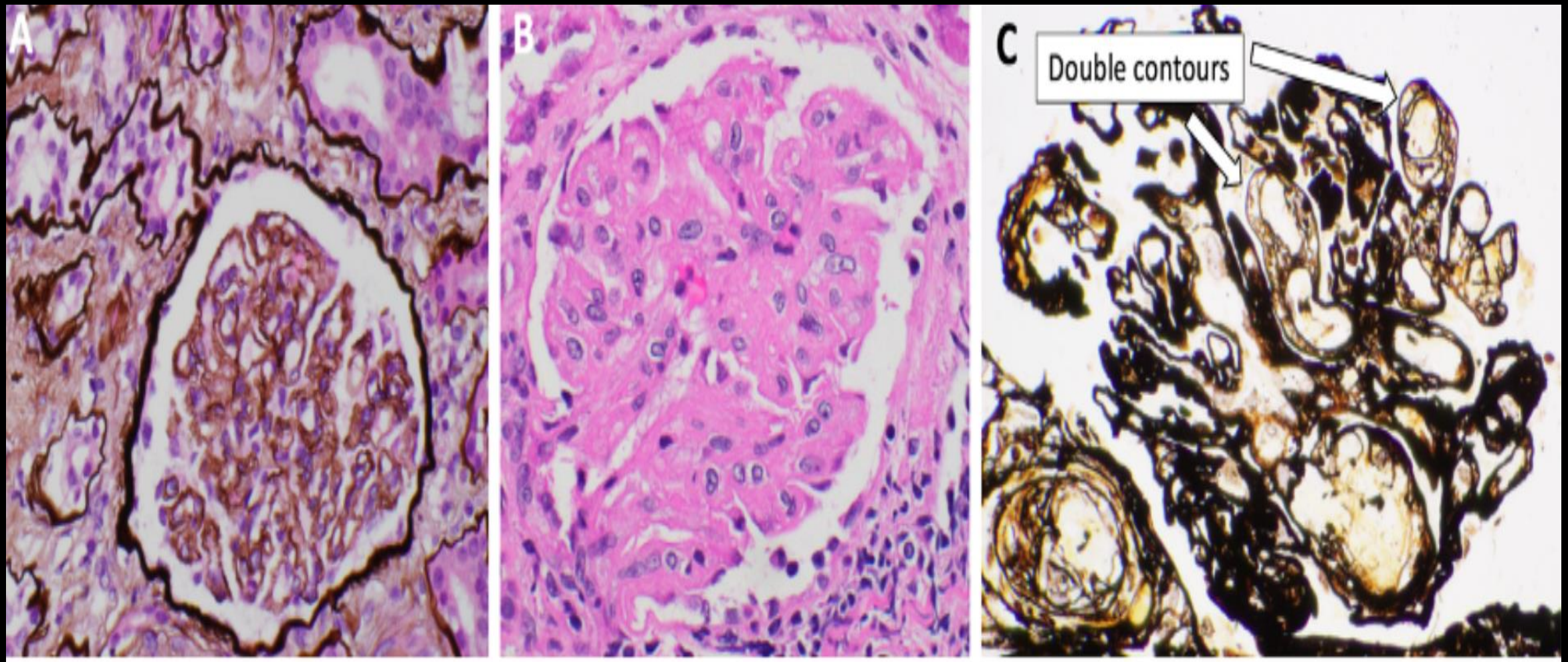
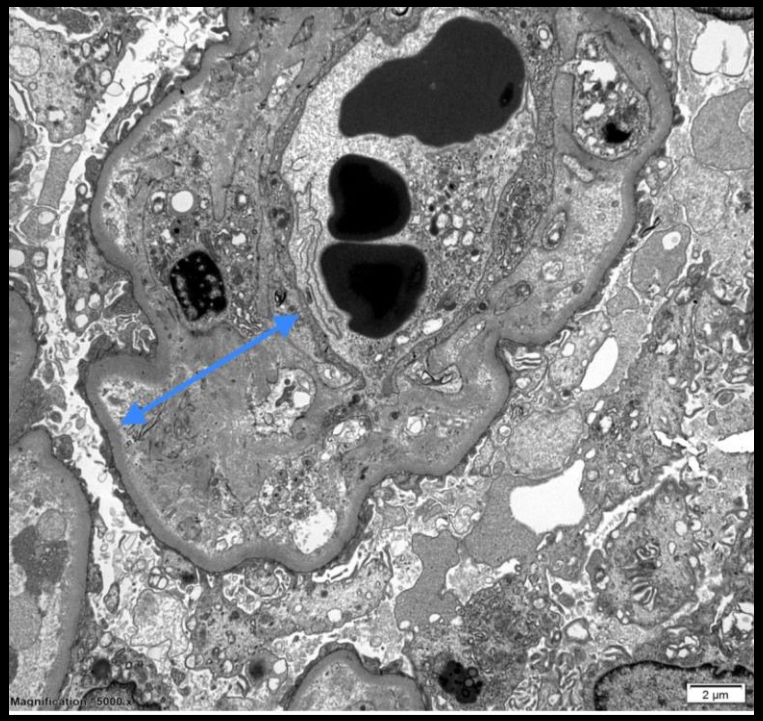


Figure 3: Glomerular ischemic changes (Chronic TMA) A) wrinkling in the glomerular tuft (JMS) B) bloodless ischemic glomerulus with mesangial collaps (H&E) C) Double contours in capillary walls (JMS)



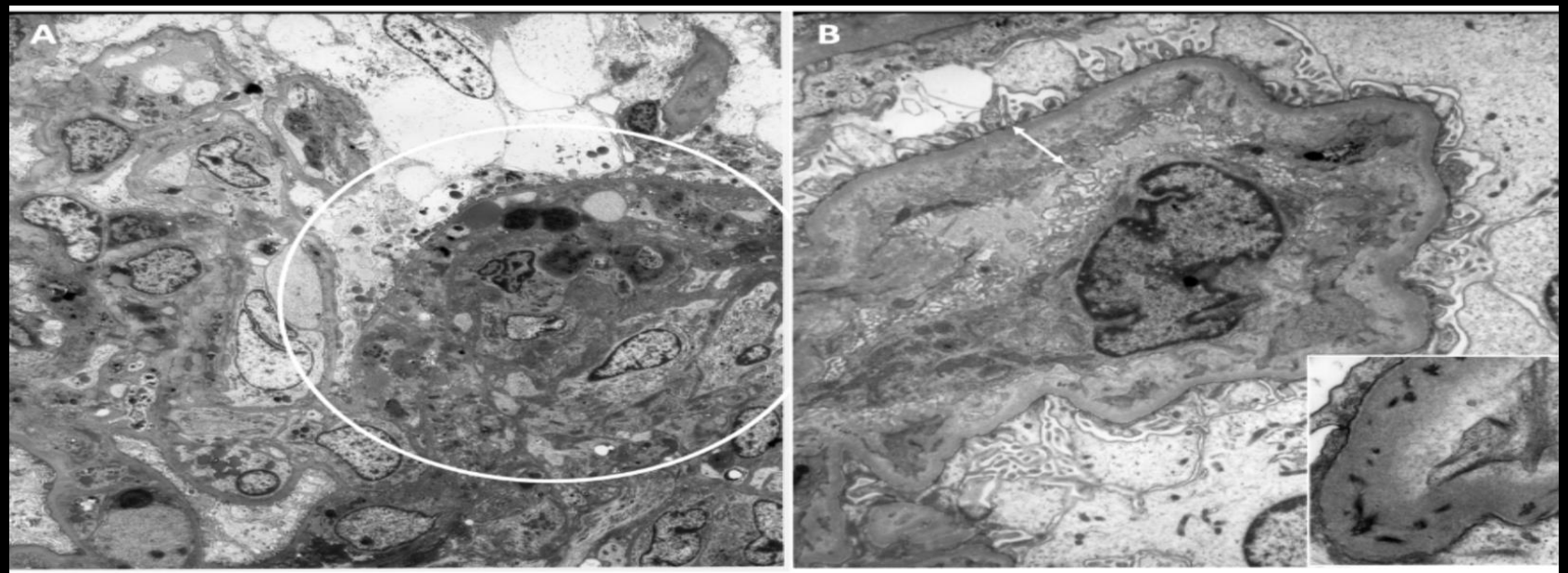
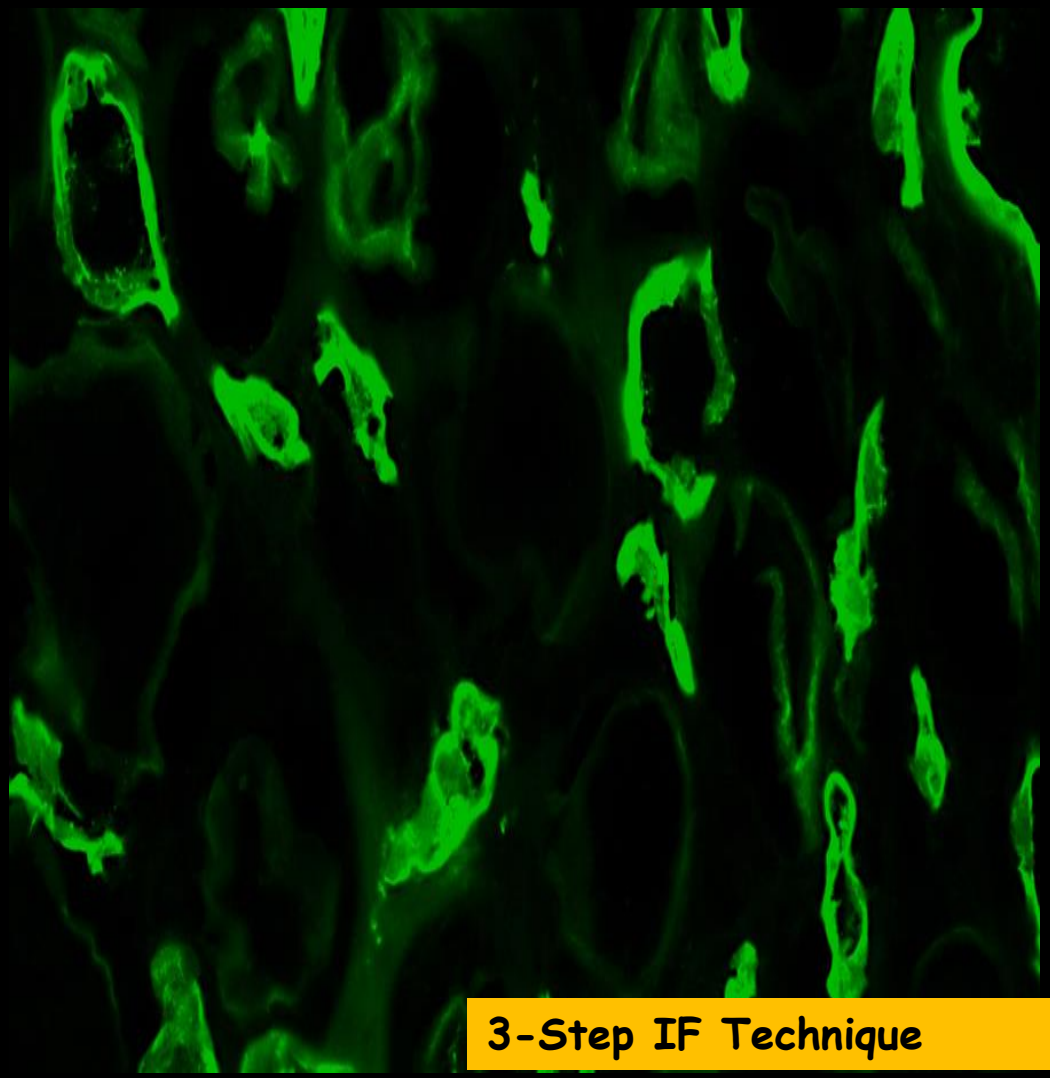
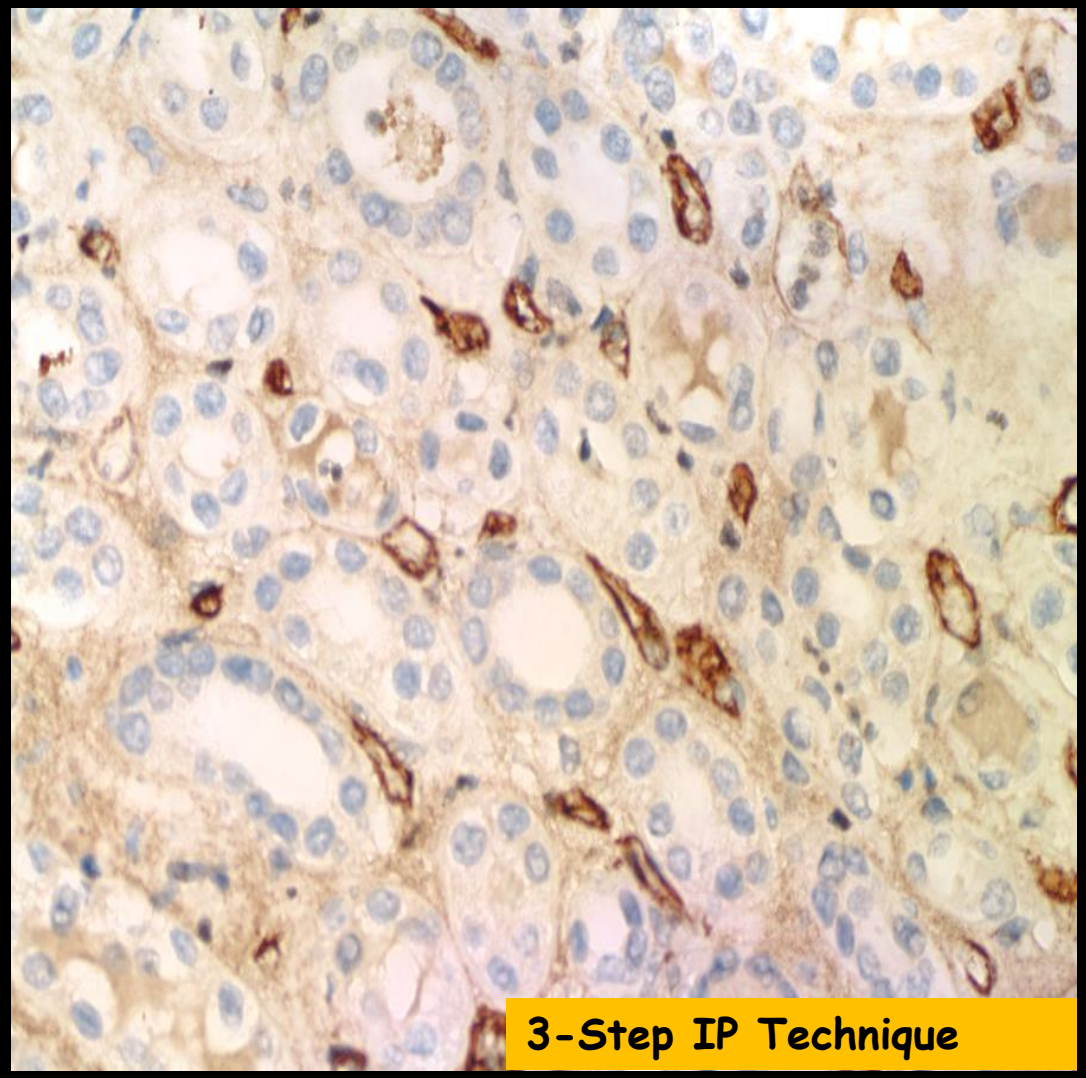


Figure 9: A) Occluded capillary lumina with endocapillary cells, debris and fibrin B) Subendothelial widening and duplication of GBM (inlet)

Banff Lesion Score C4d



3-Step IF Technique

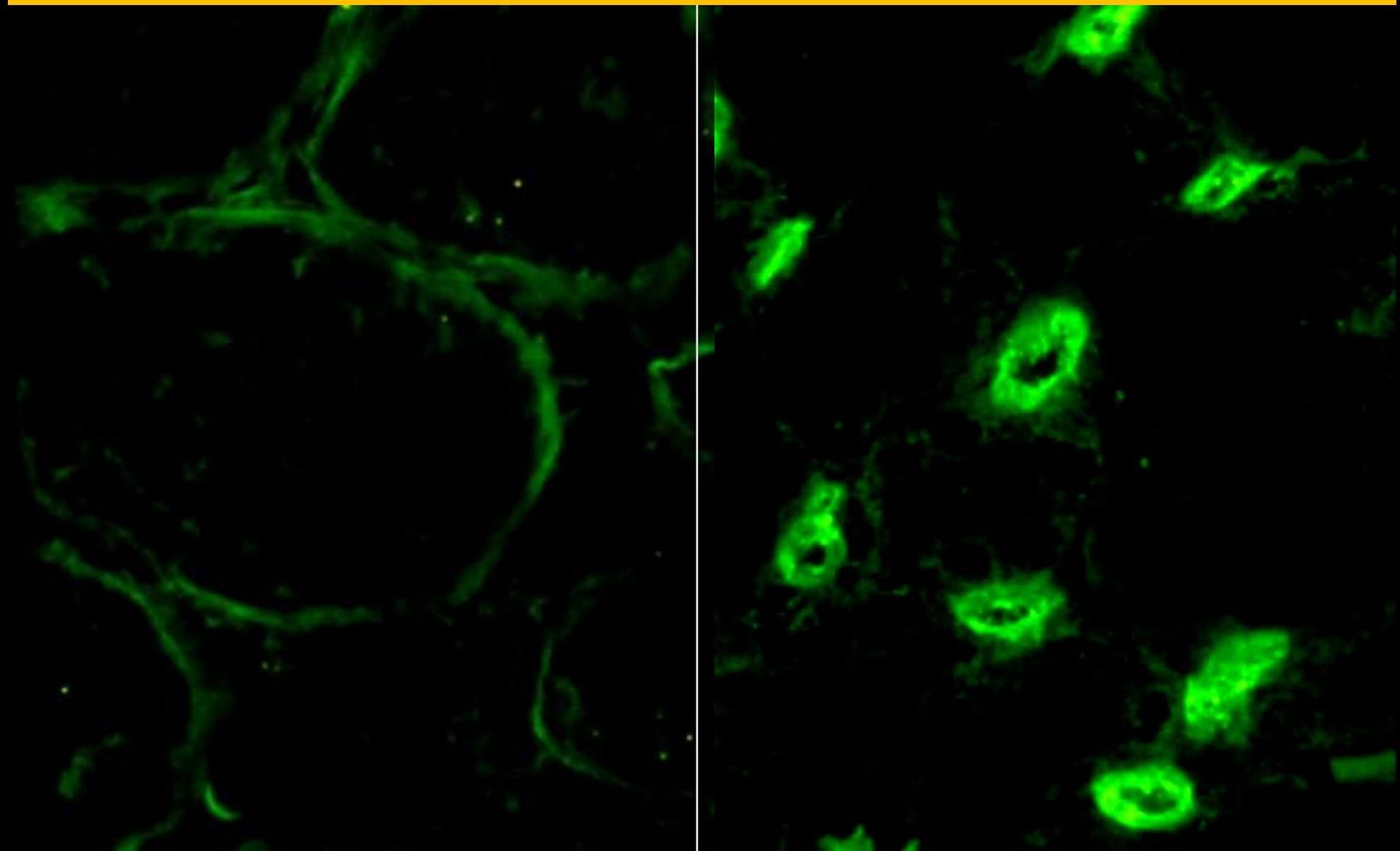


3-Step IP Technique

C4d Immunofluorescence

Acute Cellular Rejection

Acute Humoral Rejection



C4d scoring in peritubular capillaries (PTC)

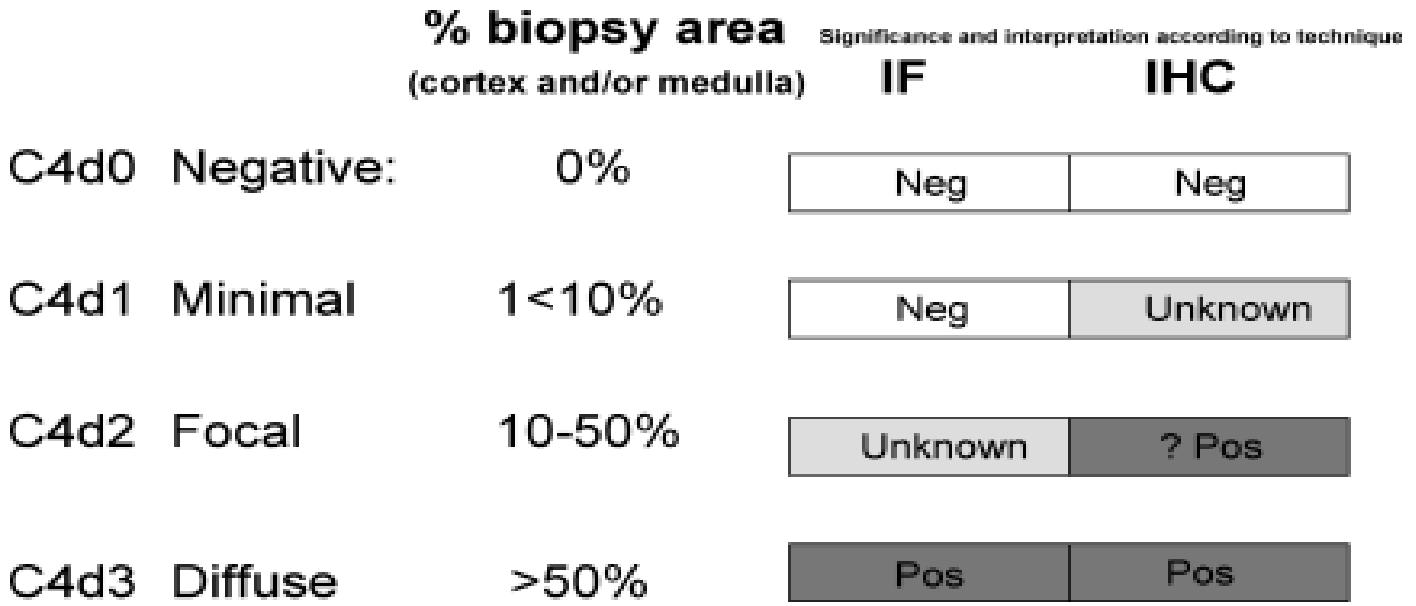


Figure 1: C4d scoring in peritubular capillaries (PTC) and influence of staining method. The interpretation of C4d staining should be adjusted for the applied technique. Immunohistochemistry (IHC) on paraffin section is usually less sensitive by about one grade level (i.e. diffuse staining on IF [cryosections] can be seen as focal on IHC [paraffin sections]). Therefore, the report should indicate the actual % of tissue involved and the potential clinical significance. For example, diffuse positive C4d by IF or IHC is highly correlated with circulating antidonor antibody. Focal positive C4d by IHC is possibly equivalent to diffuse positive IF, and should be retested on IF, if possible. However, for focal positive C4d by IF and for minimal C4d by IHC, the clinical significance is unknown.

American Journal of Transplantation 2008; 8: 753

Updates of 2022 Banff Classification

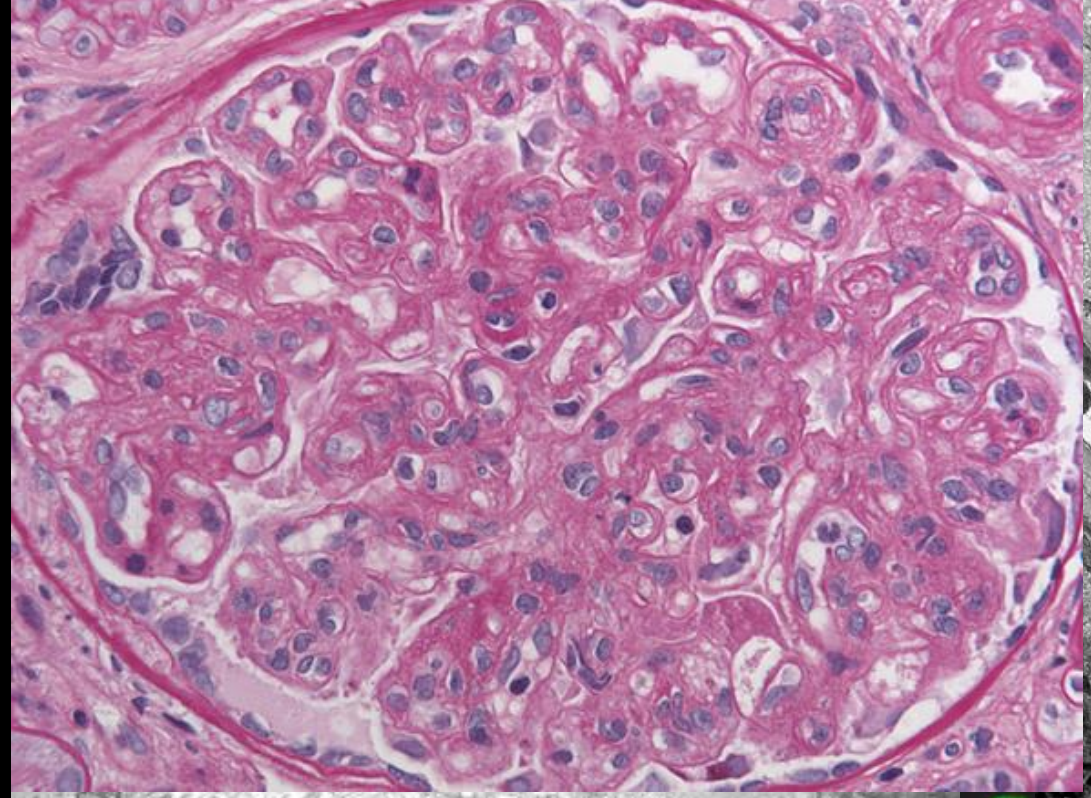
Chronic active AMR; all 3 criteria must be met for diagnosis

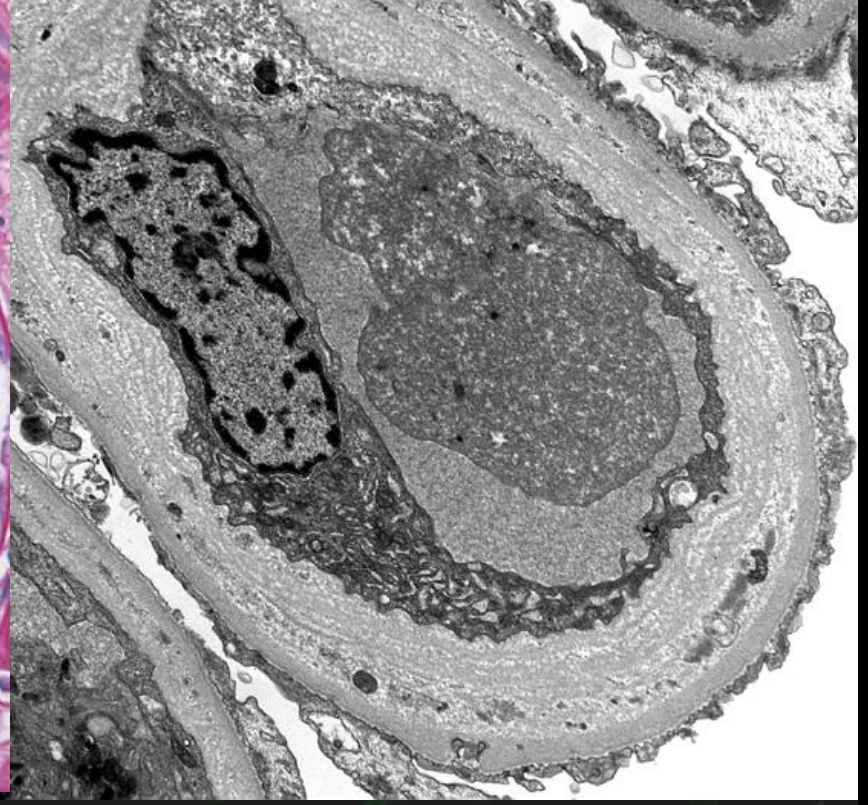
1. *Chronic lesions* of AMR present, ~~Morphologic evidence of chronic tissue injury, including~~* at least 1 ~~or more~~ of the following:
   - Transplant glomerulopathy (cg > 0) if no evidence of chronic TMA or chronic recurrent/de novo glomerulonephritis; includes changes evident by electron microscopy (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~~
2. Identical to criterion 2 for active AMR, above
3. Identical to criterion 3 for active AMR, above, including strong recommendation for DSA testing whenever criteria 1 and 2 are met.

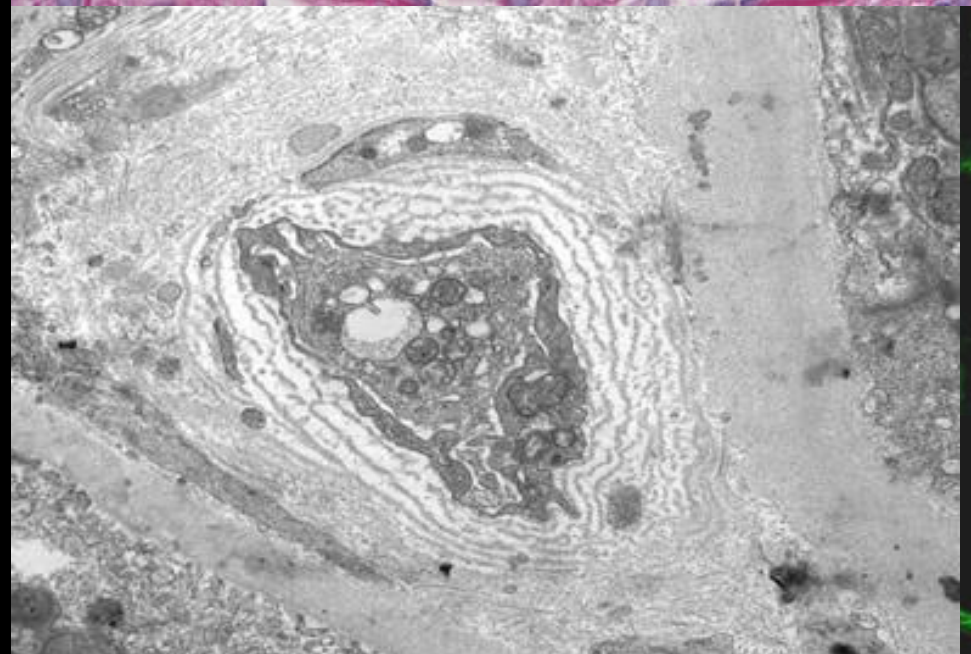
~~Biopsies meeting criterion 1 but not criterion 2 with current or prior evidence of DSA (posttransplant) may be stated as showing chronic AMR, however remote DSA should not be considered for diagnosis of chronic active or active AMR~~

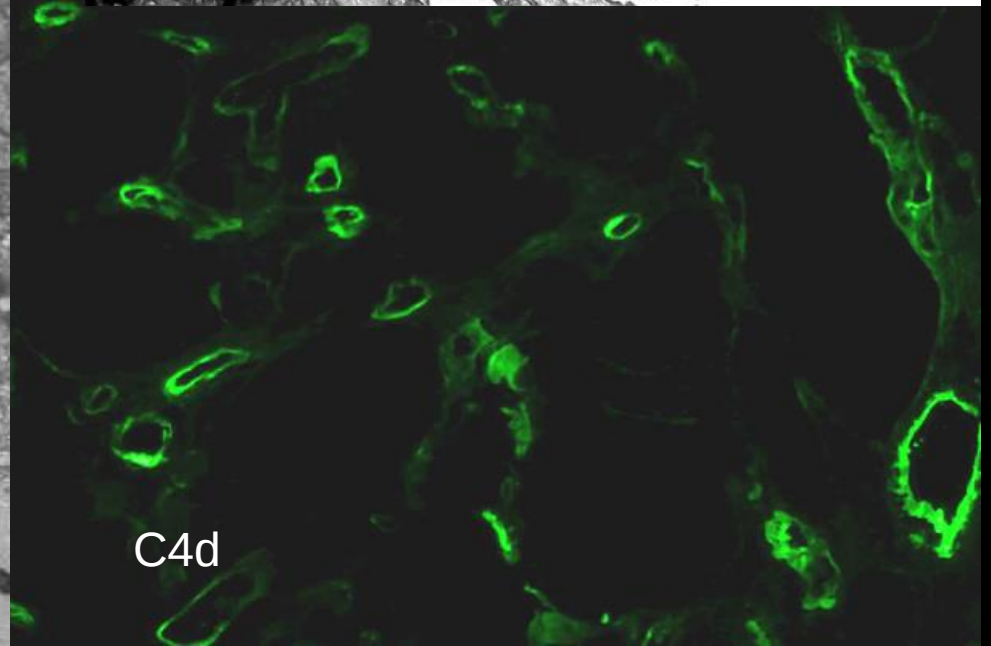
Chronic ~~(inactive)~~ AMR; all 3 criteria must be met for diagnosis

1. cg > 0 and/or severe ptcml (ptcml1)
2. Absence of criterion 2 ~~*of current/recent antibody interaction with the endothelium*~~ *as defined for active and chronic active AMR, above*
3. Prior documented diagnosis of active or chronic active ABMR and/or documented prior (post-transplant) and/or current evidence of DSA (*DSA as defined in above criterion 3 for active AMR)*





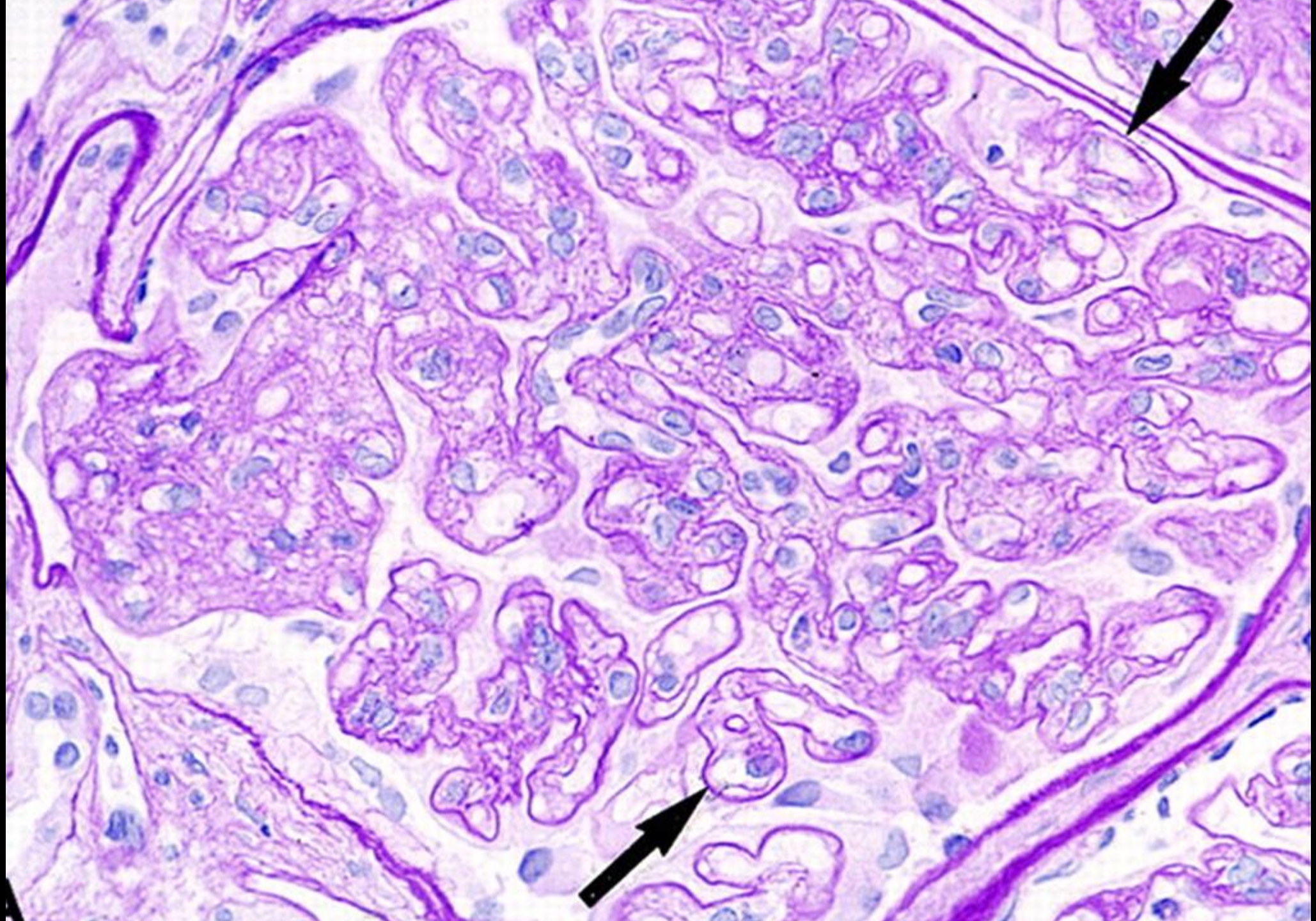


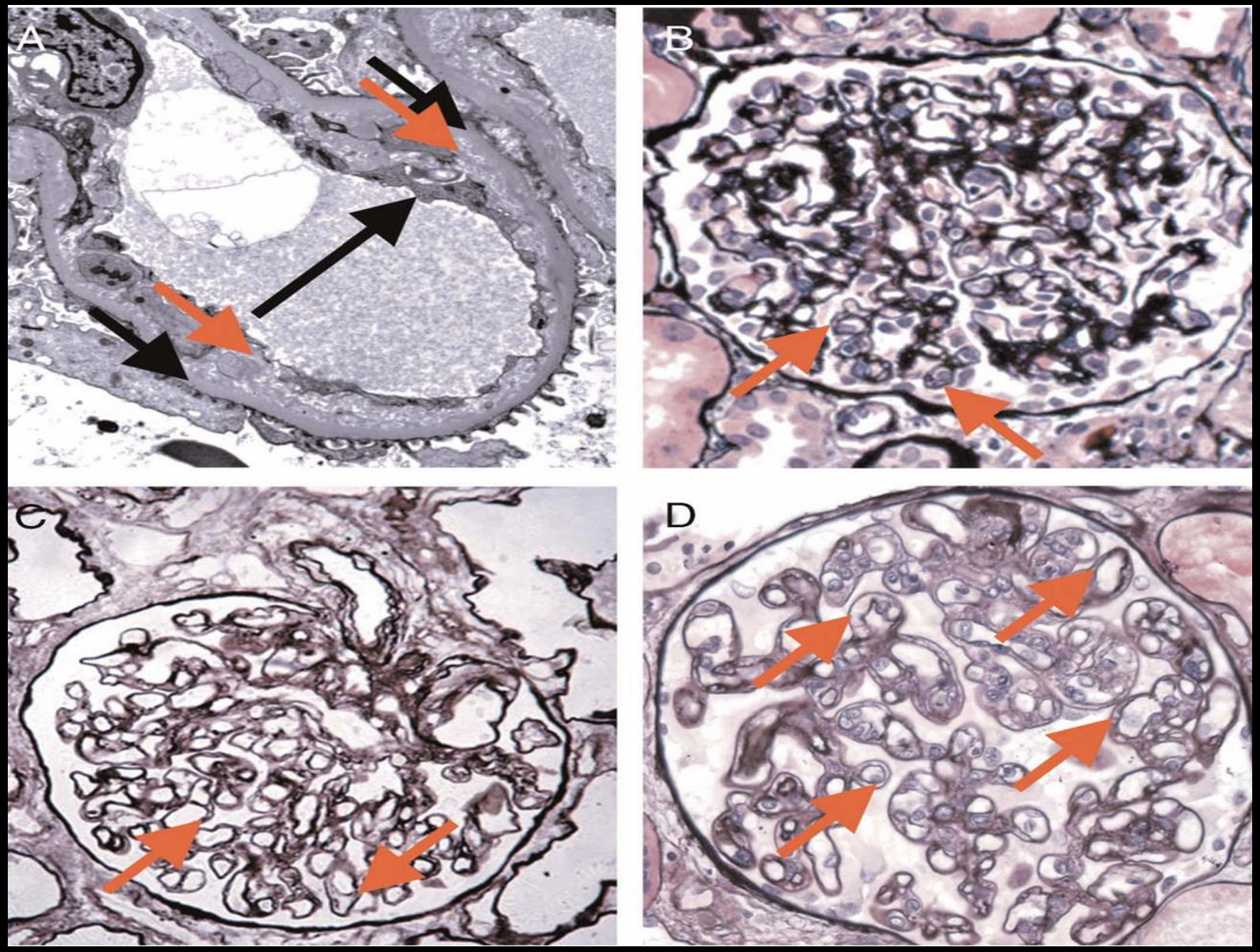

C4d

Quantitative Criteria for Double Contour- cg Score

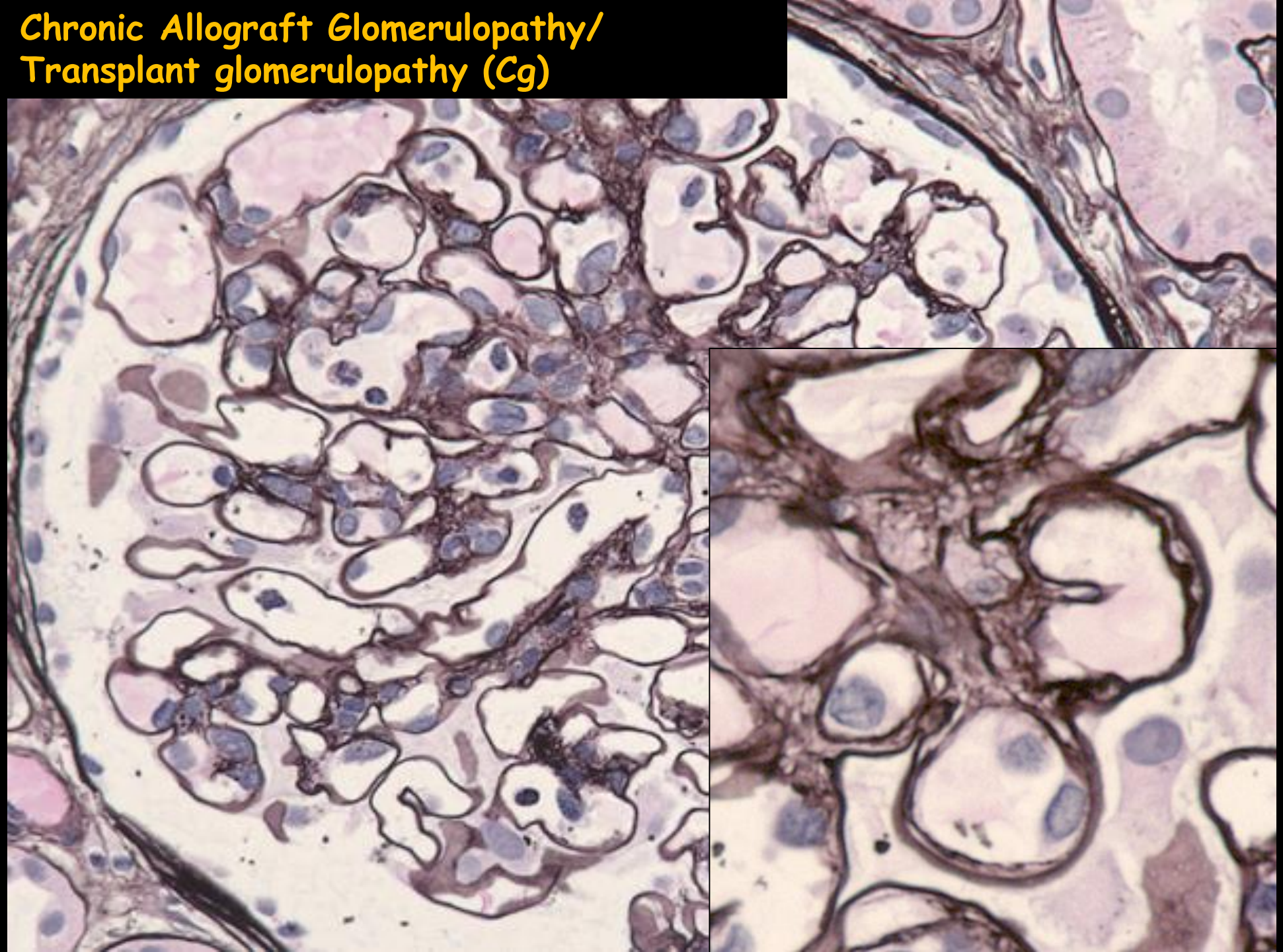
Quantitative criteria for scoring degree of double contours in diagnosing TG

cg0	No GBM double contours by LM or EM (no TG)
cg1a	No GBM double contours by LM but GBM double contours in at least 3 glomerular capillaries by EM with associated endothelial/subendothelial changes
cg1b	GBM double contours in 1–25% of capillary loops by LM in the most affected glomerulus
cg2	GBM double contours in 26–50% of capillary loops by LM in the most affected glomerulus
cg3	GBM double contours in ≥50% of capillary loops by LM in the most affected glomerulus

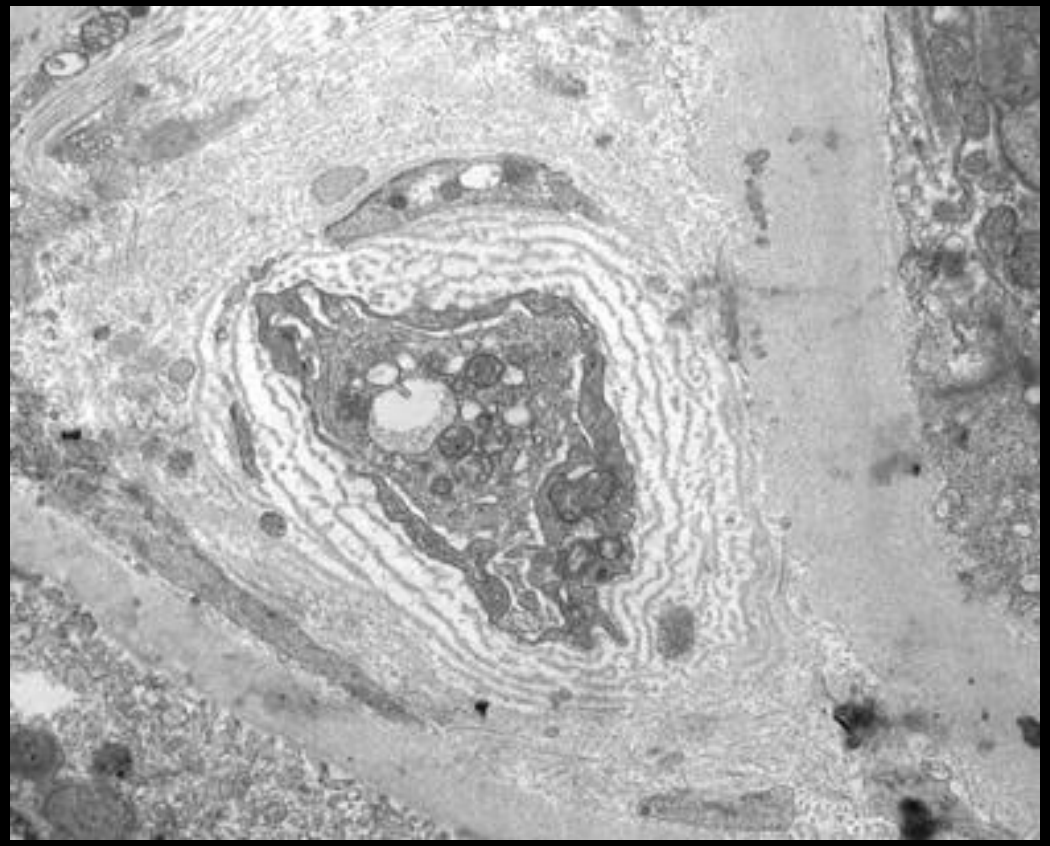


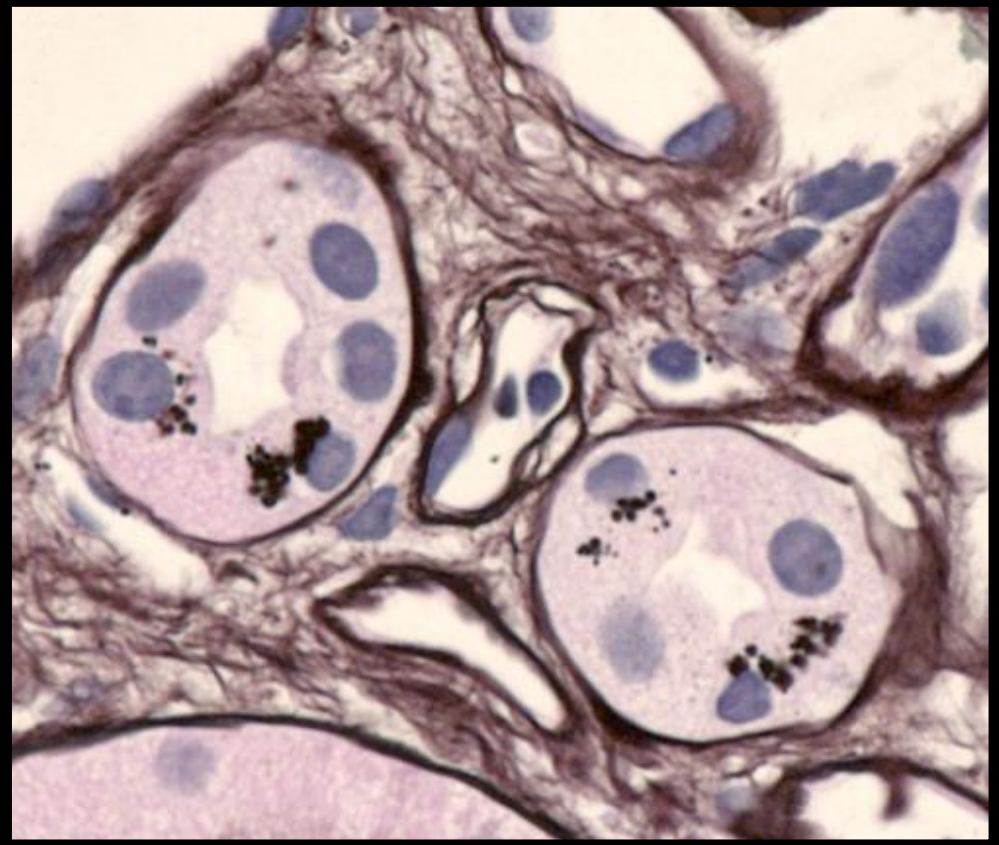

A
B
C
D

Chronic Allograft Glomerulopathy/ Transplant glomerulopathy (Cg)

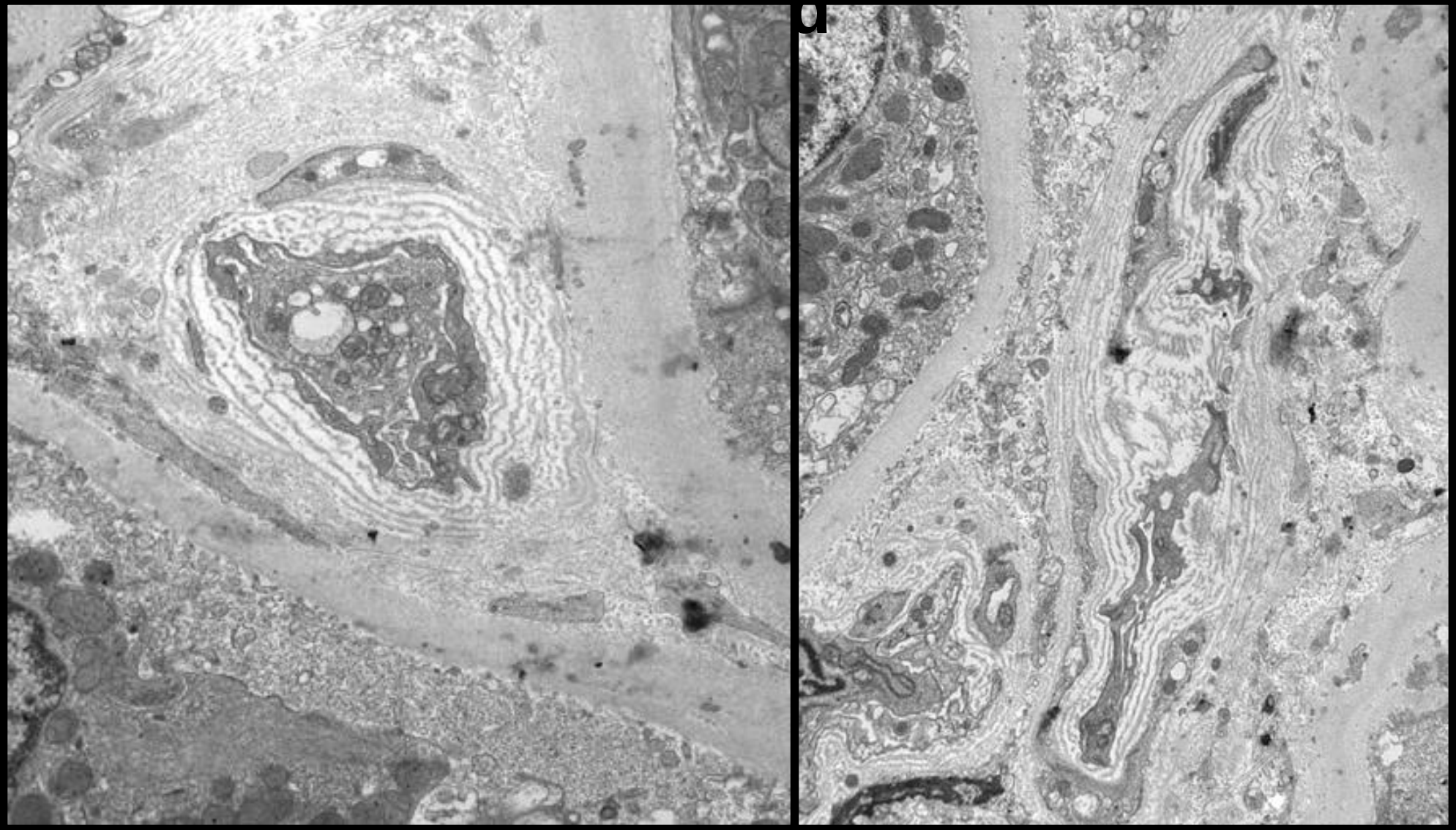


Peritubular Capillary Multilamination

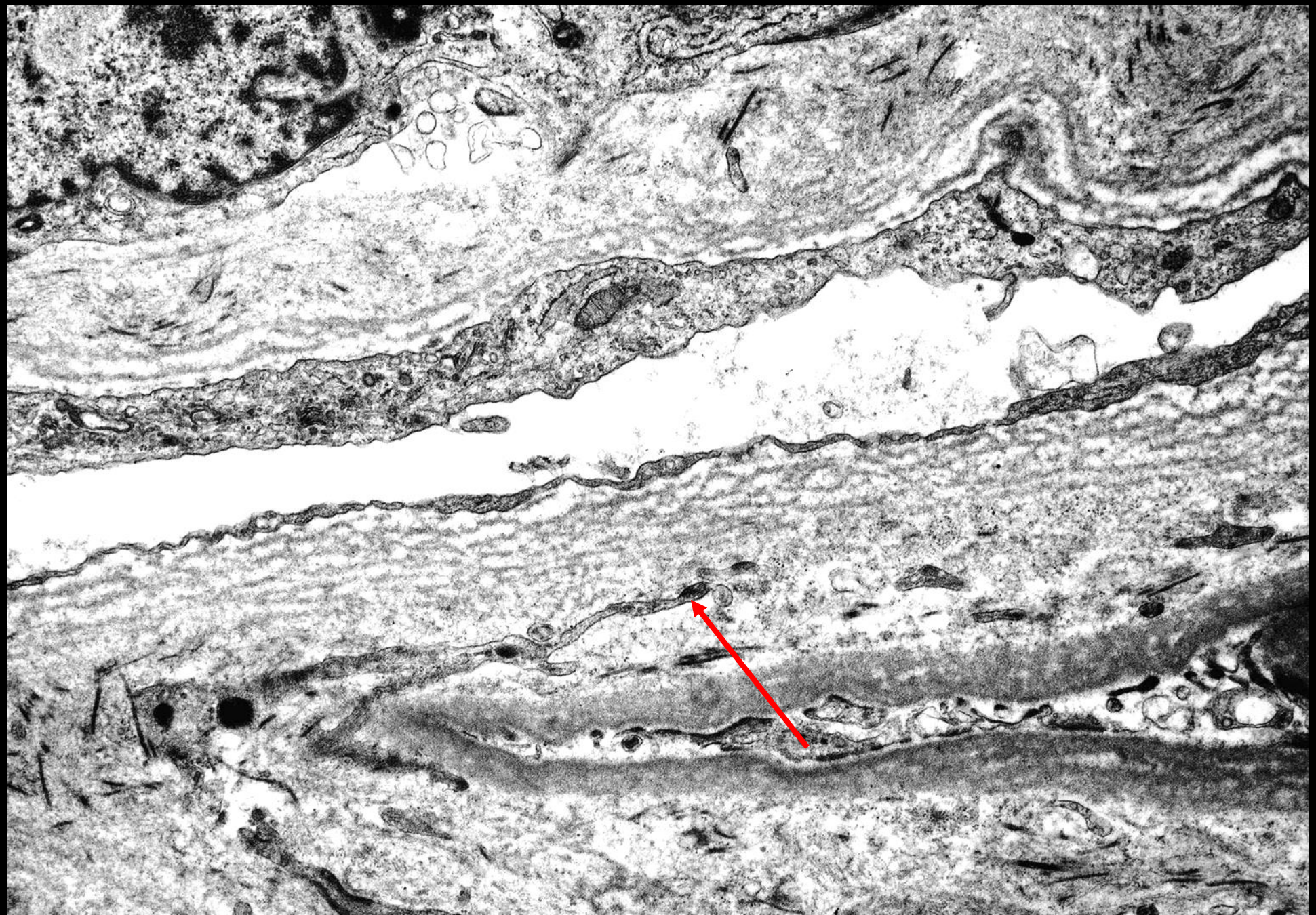


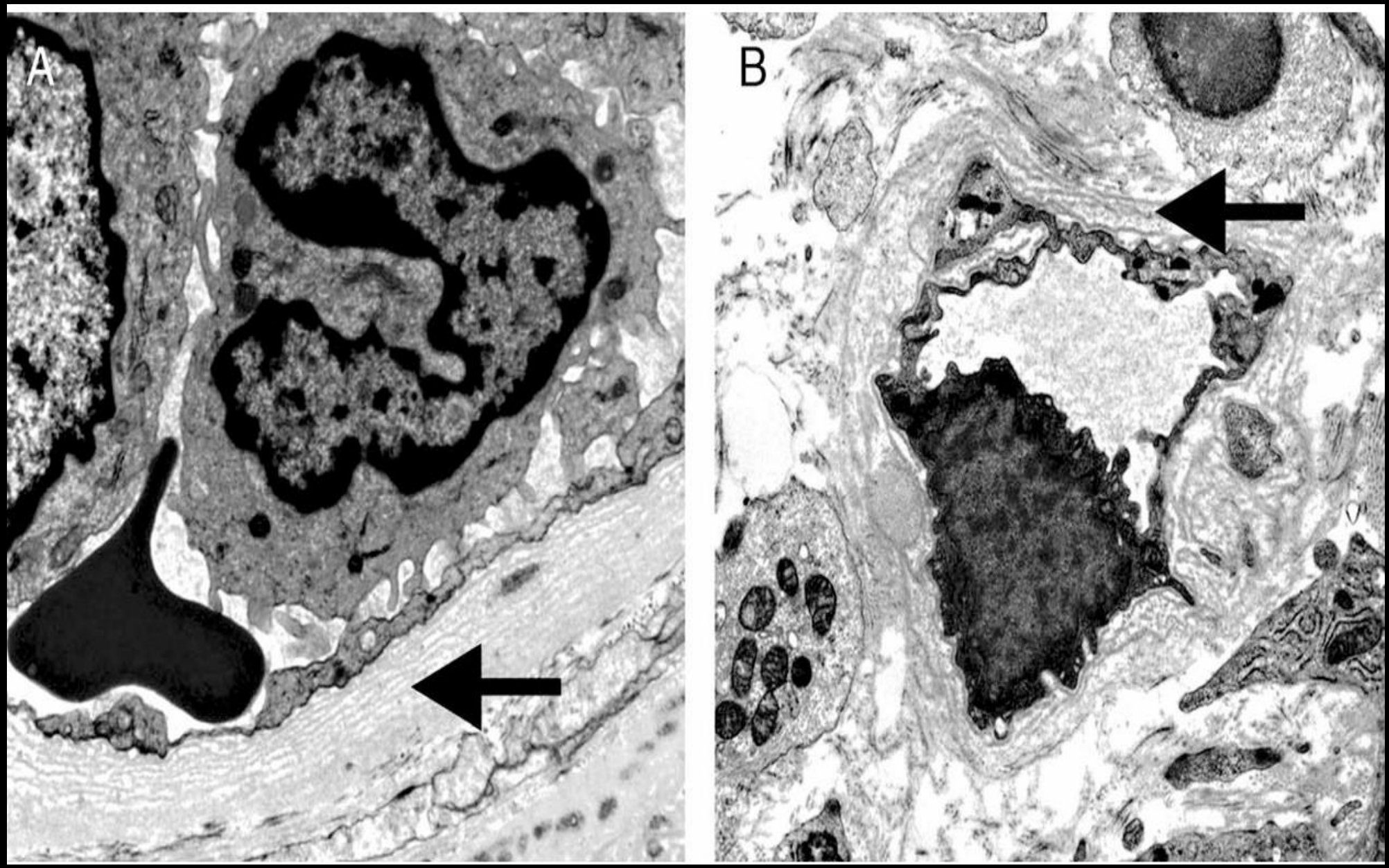


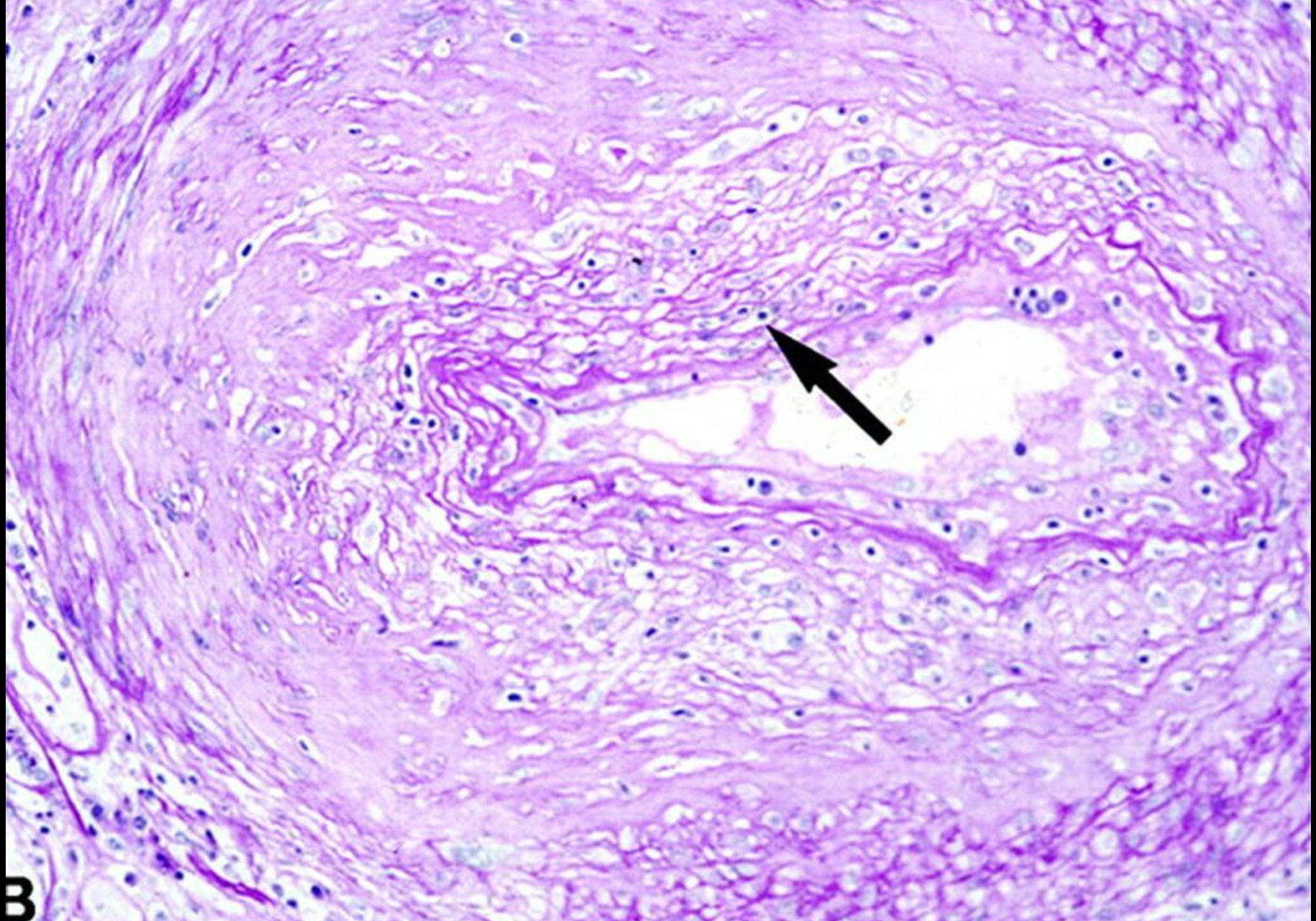
Peritubular Capillary Multilamination



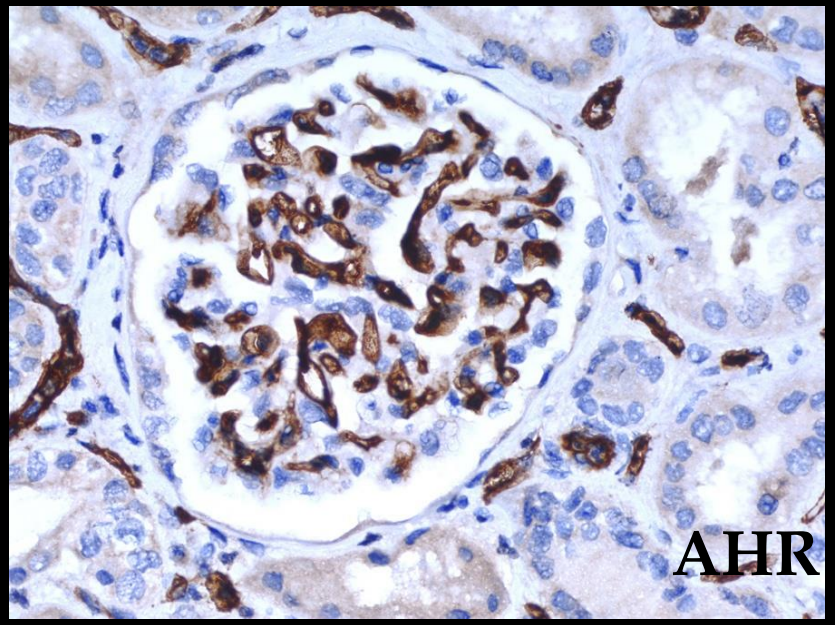
3 years post-Tx, PTC BM multilayering (up to 7 layers)

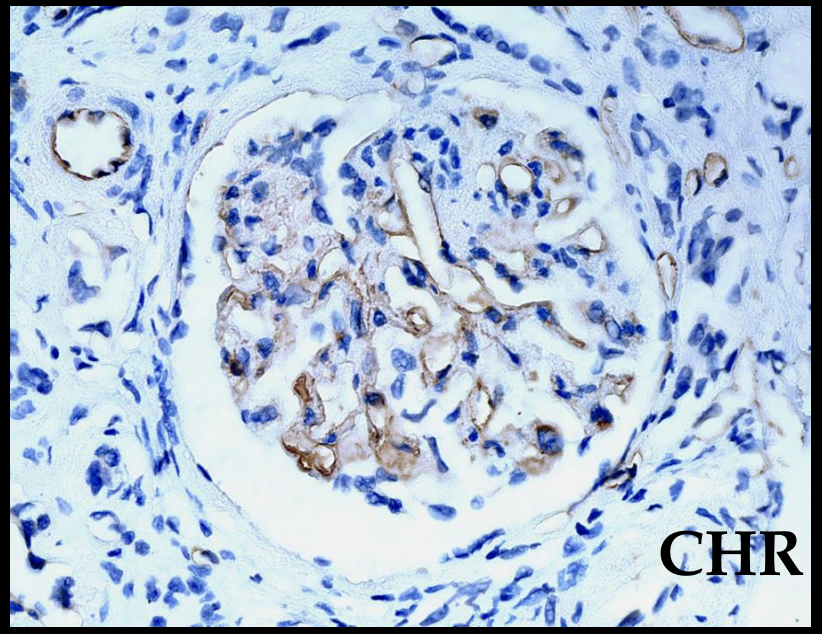


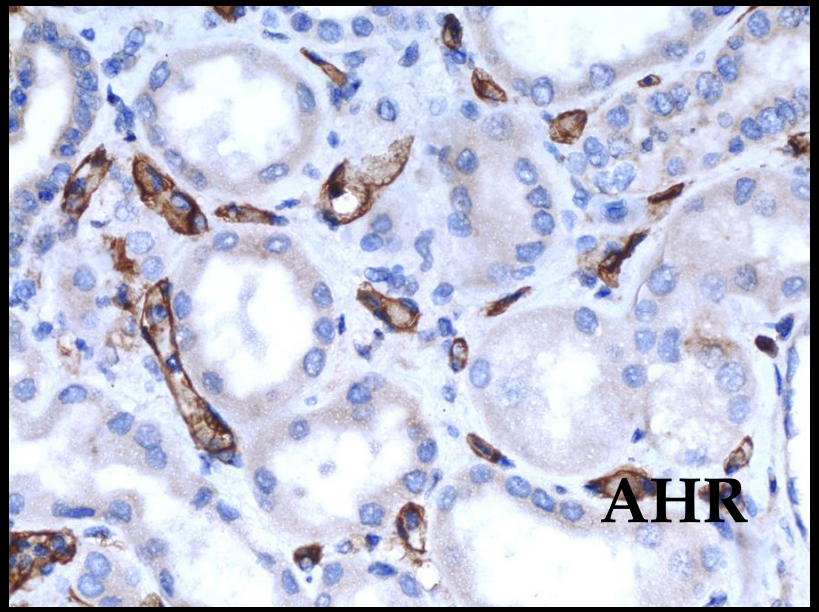

A
B

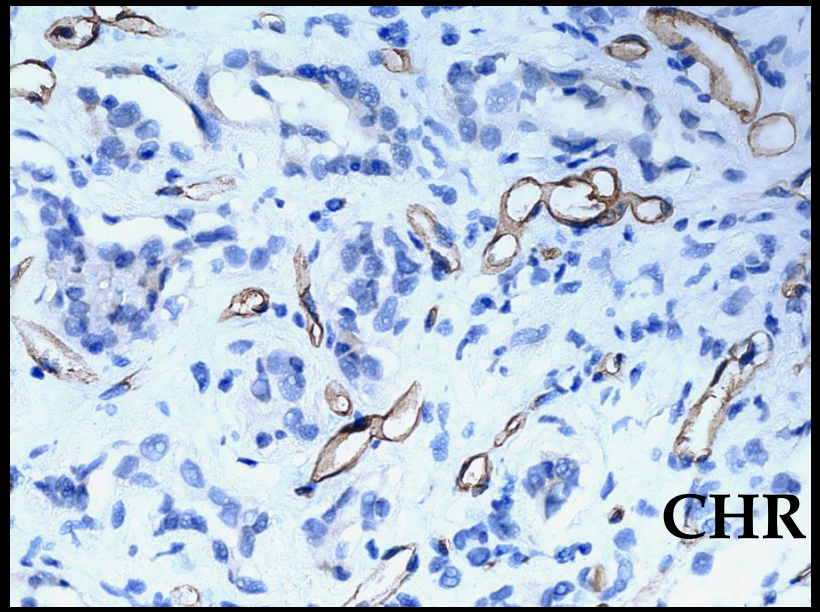

B

C4d





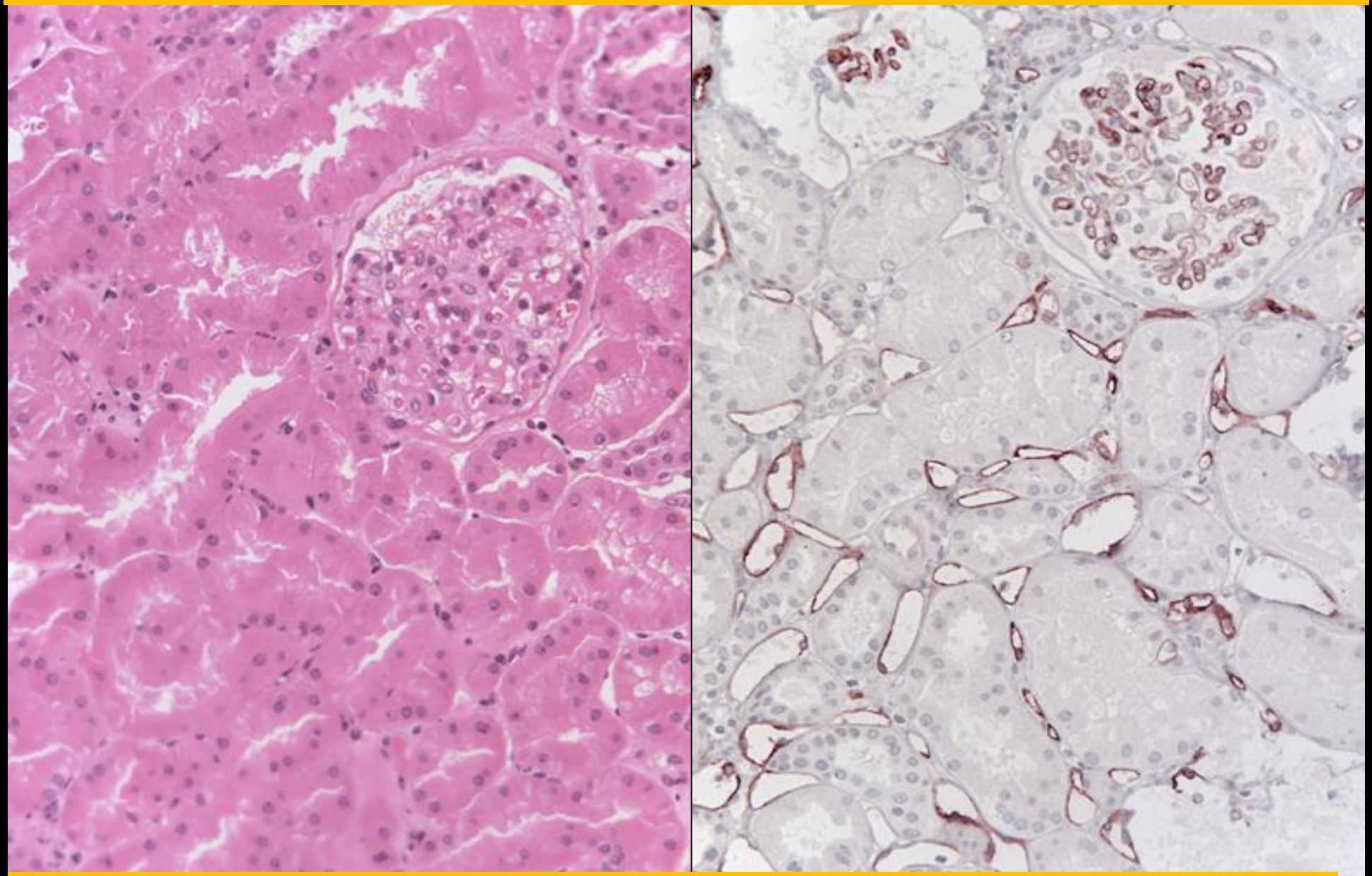




C4d staining without evidence of rejection; all 4 features must be met for diagnosis[c]

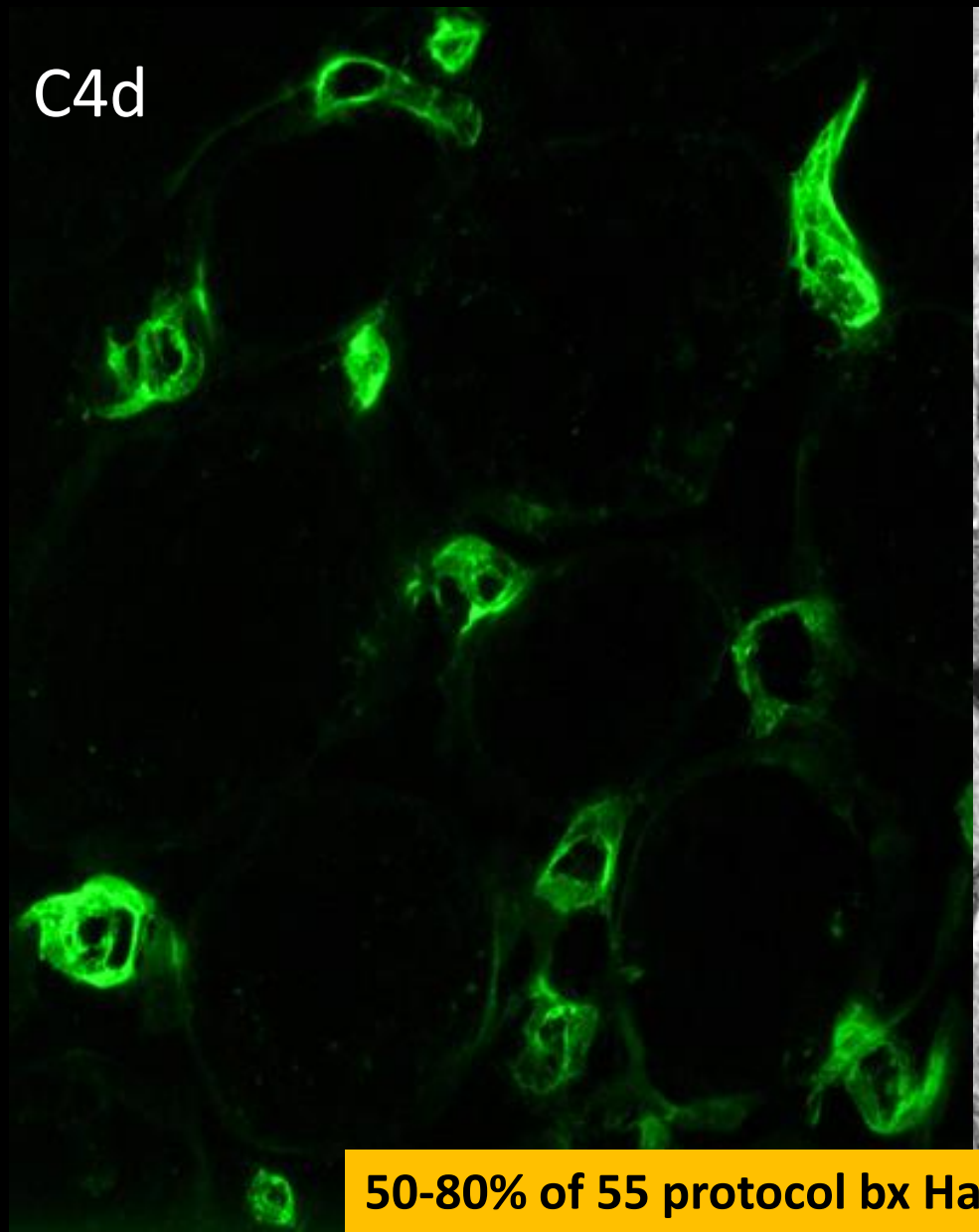
1. Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
2. Criterion 1 for active or chronic active AMR not met
3. *Negative biopsy-based transcript diagnostics* for AMR/*MVI* as in criterion 2 for active and chronic active AMR
4. No acute or chronic active TCMR, or borderline changes

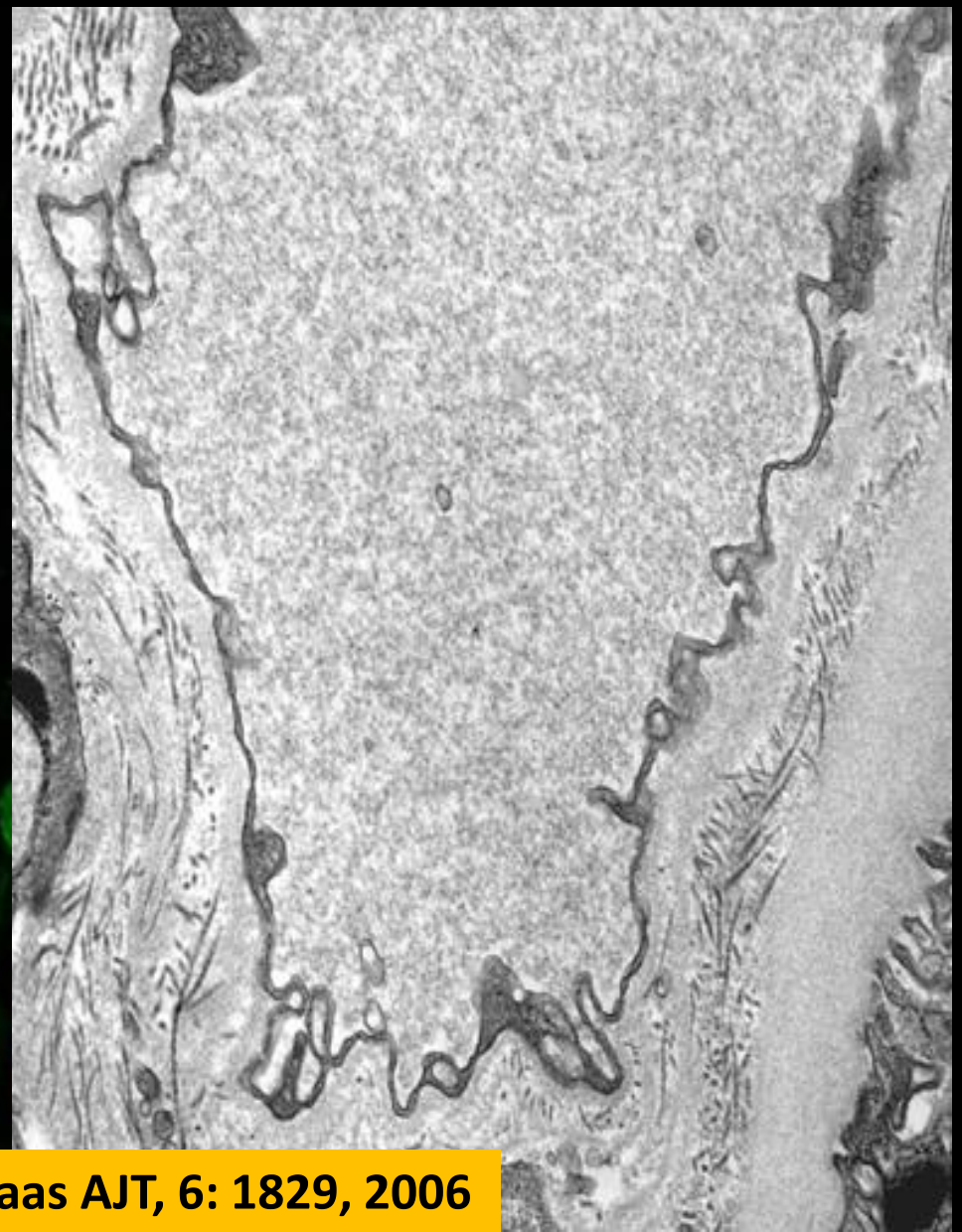
"Normal" Protocol Biopsy with C4d+



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

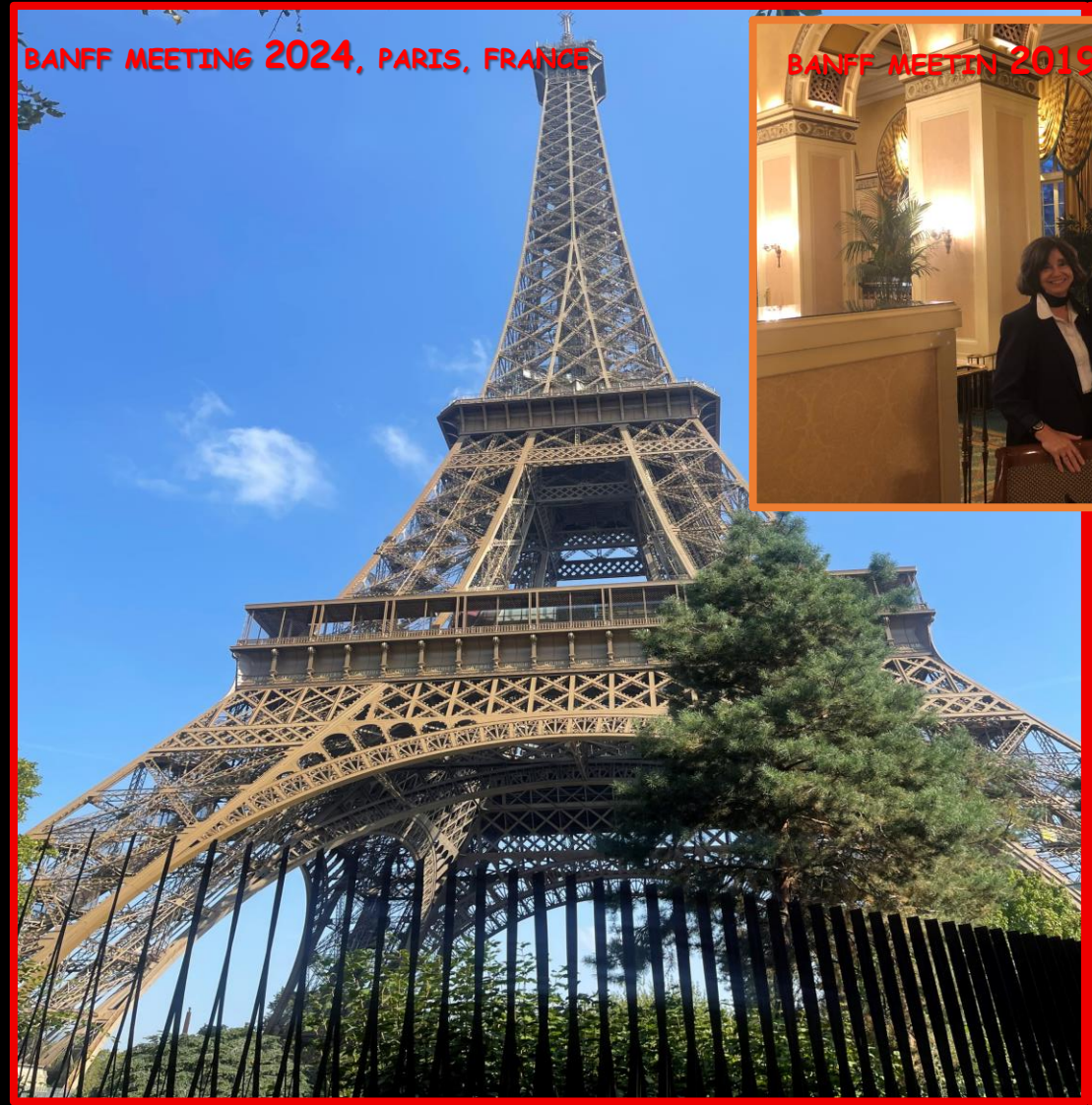
ABO incompatible allograft
Protocol bx 3 months



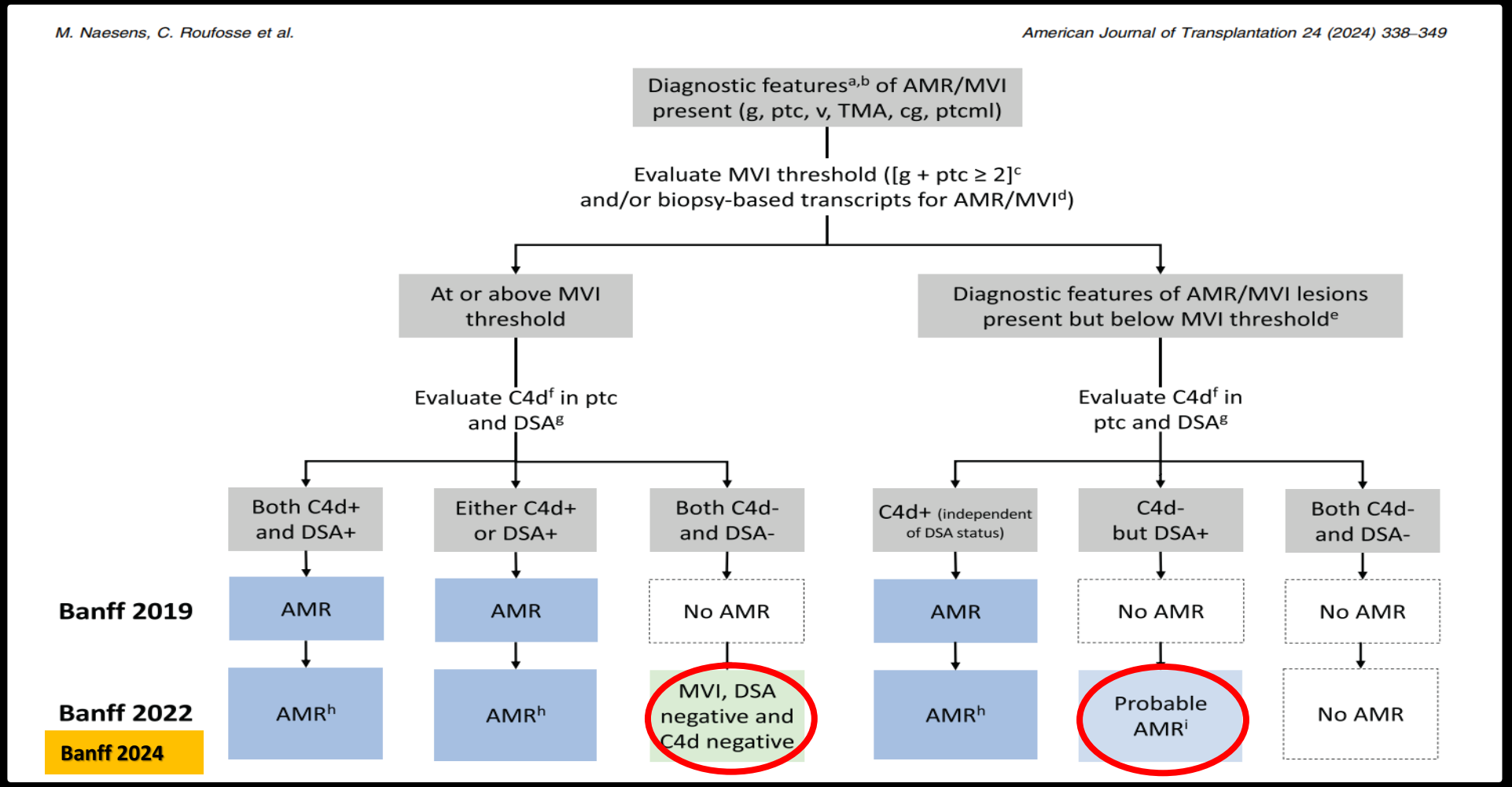


50-80% of 55 protocol bx Haas AJT, 6: 1829, 2006

Thank you for Listening- Any Questions?



Flowchart of the Banff 2022 Classification for Category 2: Antibody-mediated rejection and microvascular inflammation/injury (AMR/MVI).



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