Biopsy Features of Kidney Allograft Rejection – *Banff 2017*

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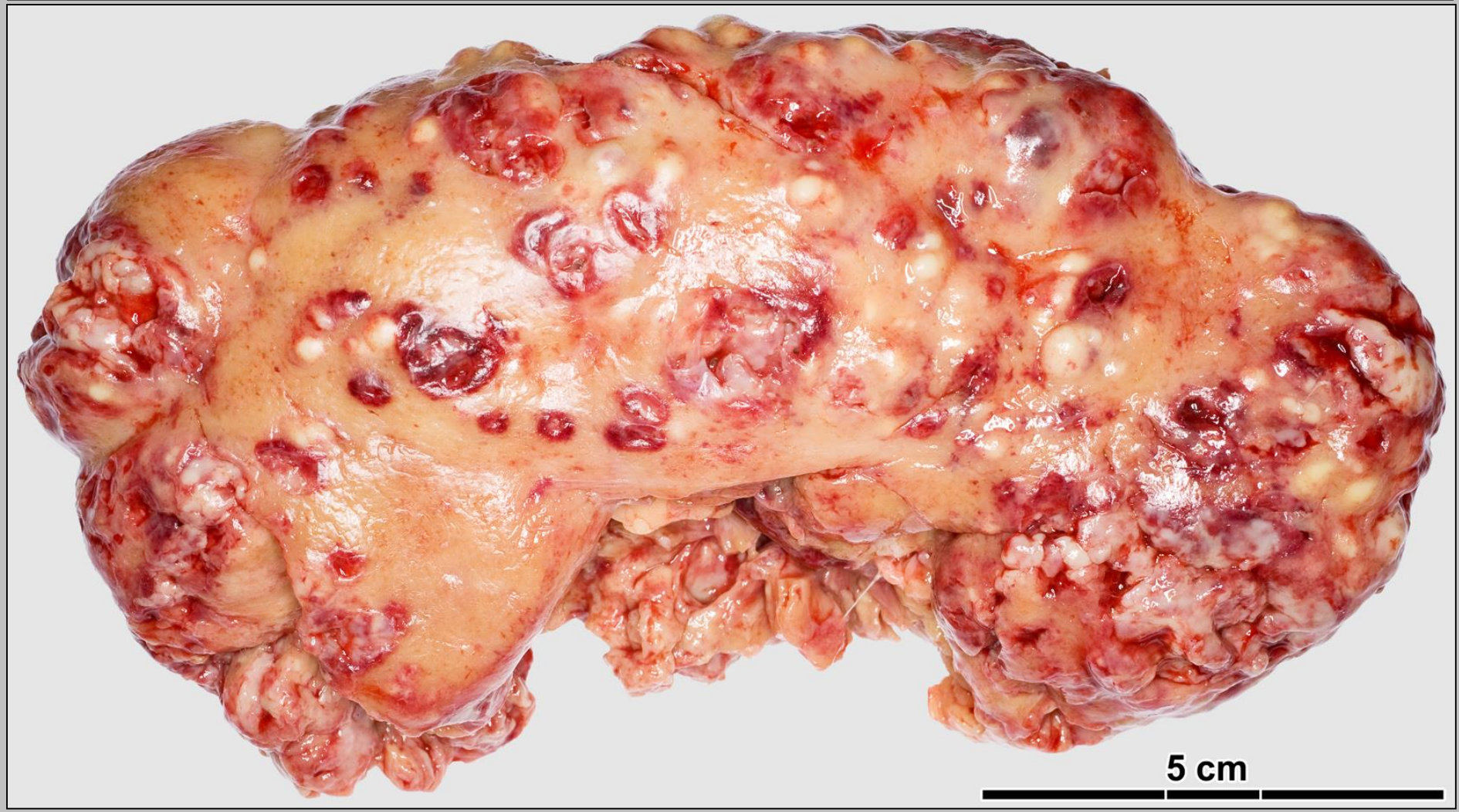
Treatment of allograft dysfunction should rely on the biopsy findings

Acute dysfunction treated empirically with pulse steroids. Sepsis developed; autopsy revealed prostatic hyperplasia, cystitis, and acute pyelonephritis with large abscesses



Causes of Allograft Dysfunction

Alloimmune	Non-alloimmune
Subsets of rejection	Polyoma virus NP
	Obstruction/pyelonephritis
	CNI-toxicity
	Glomerulonephritis
	Posttx diabetes, hypertension

Alloimmune and non-alloimmune injuries may coexist;

Rejection pathology has an intrinsic focal nature

Biopsy Processing for Optimum Interpretation

Sampling

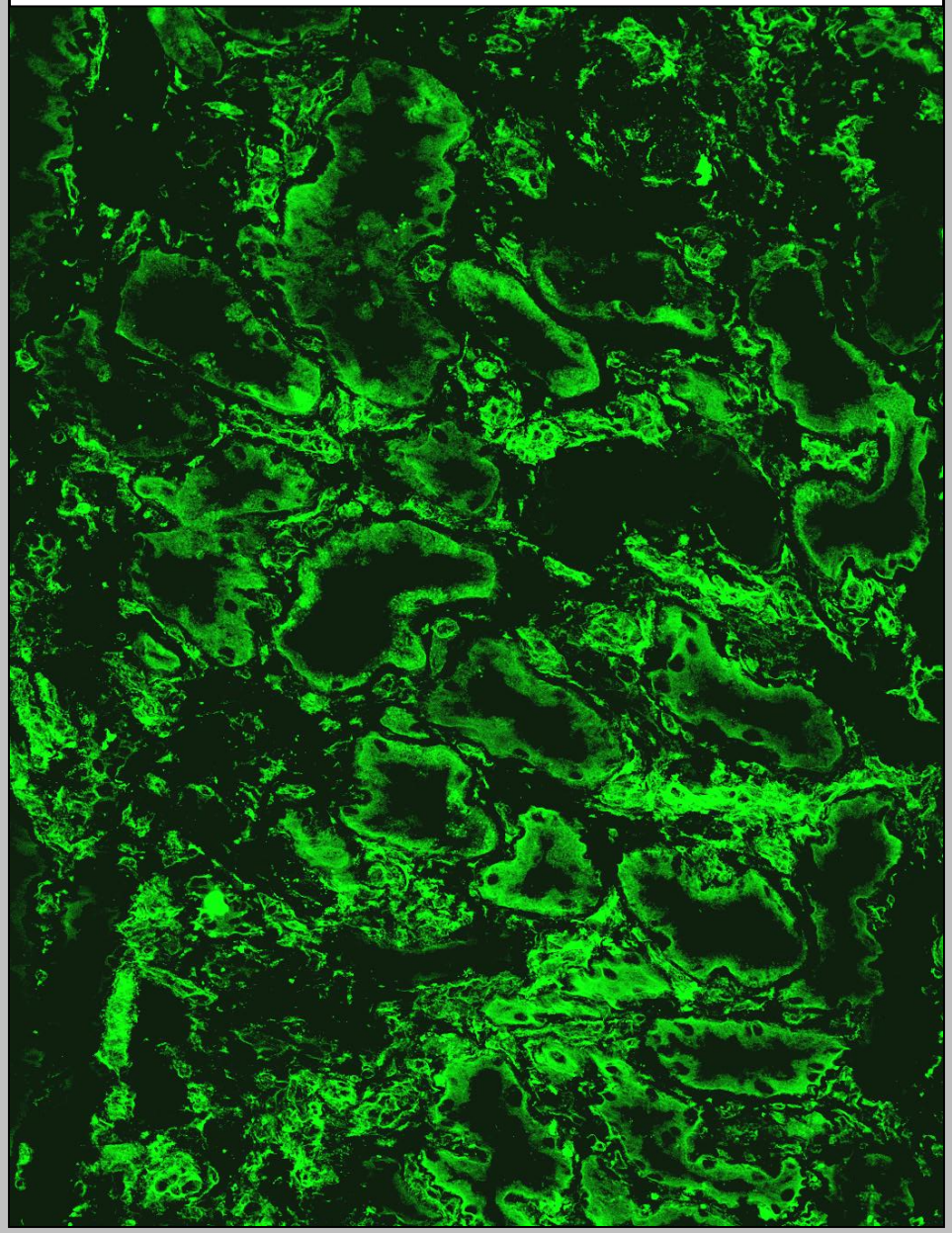
16-G needle; two cores

Frozen sections for IF and LM

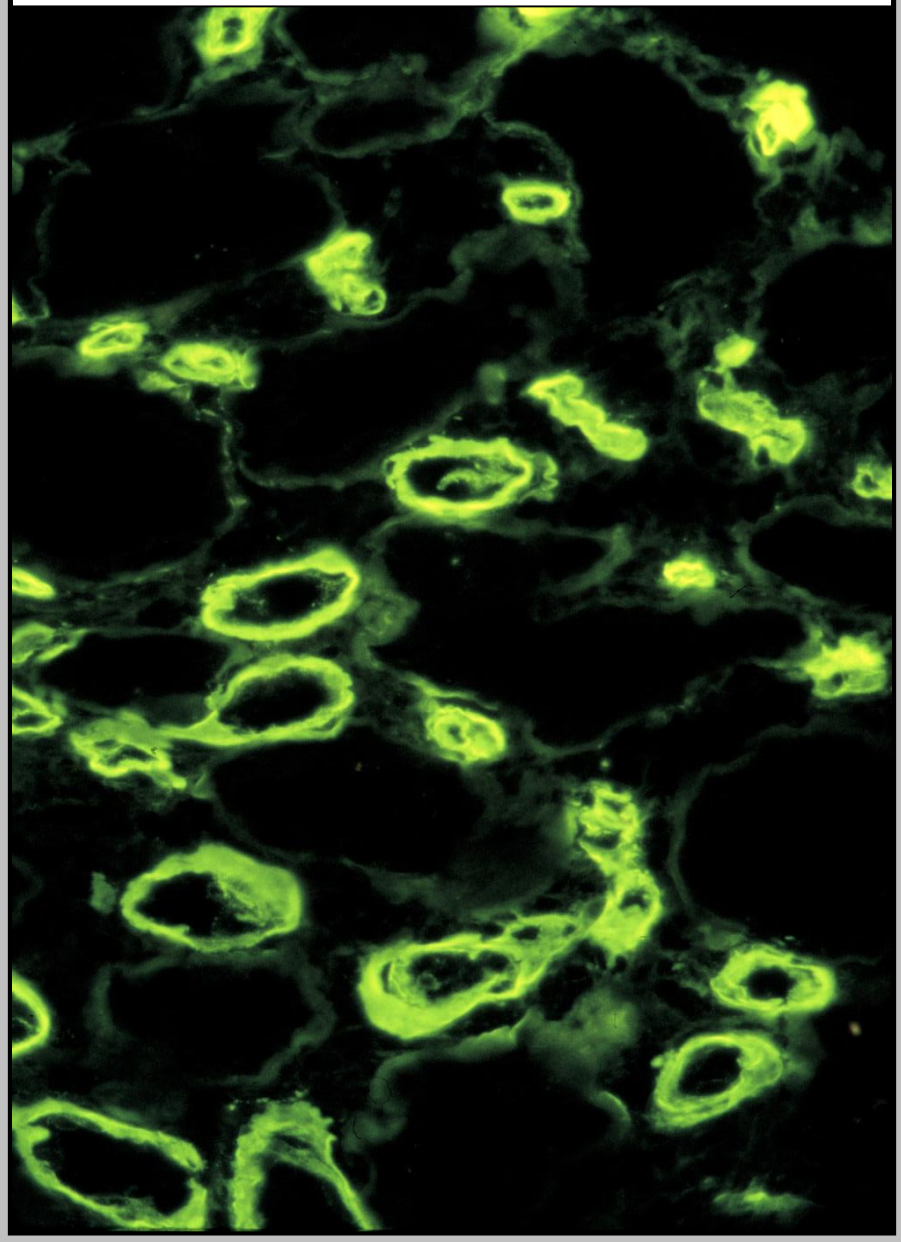
5 immunostainings;

HE, PAS, trichrome, and elastin for LM

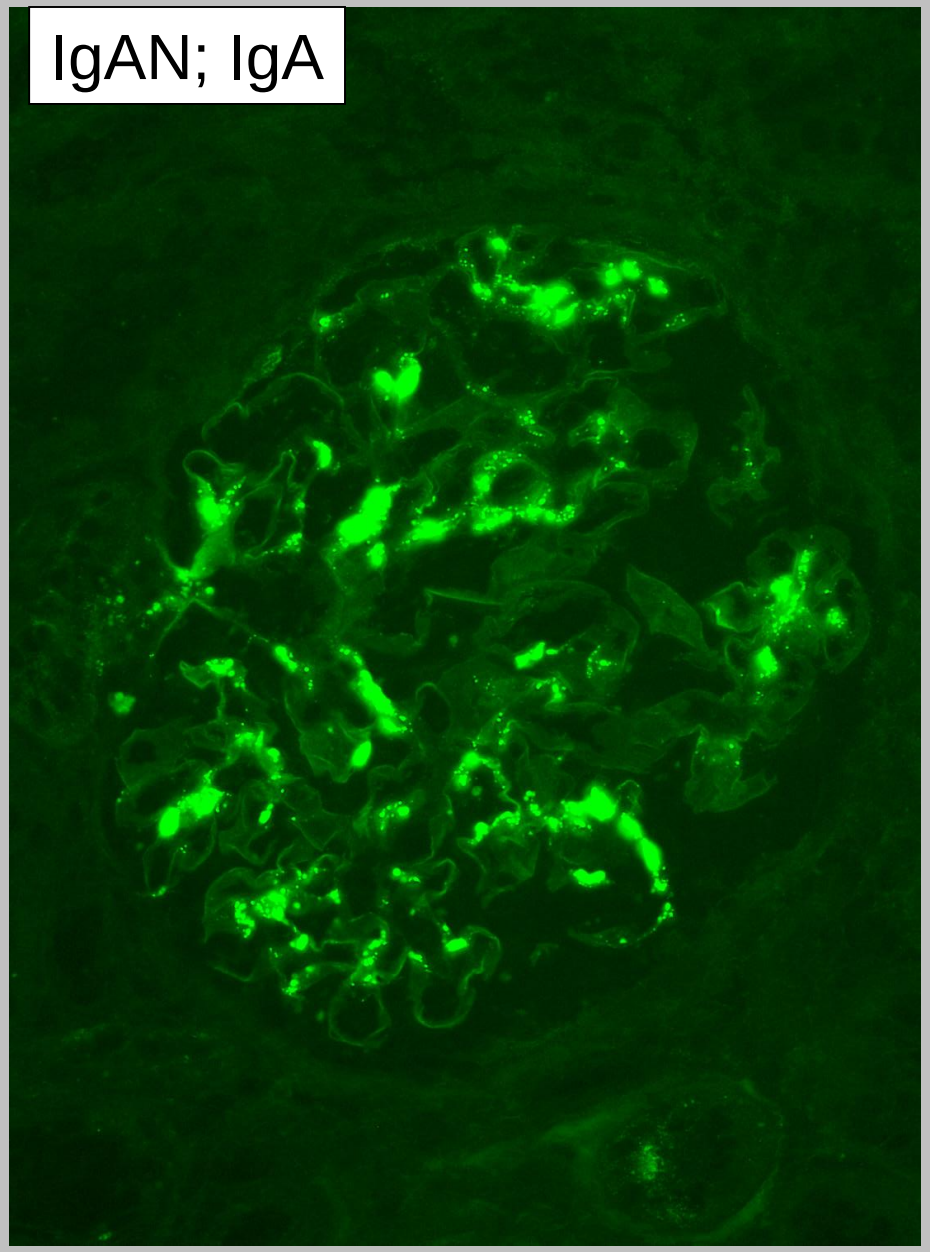
Tubular HLA-DR expression - TCMR

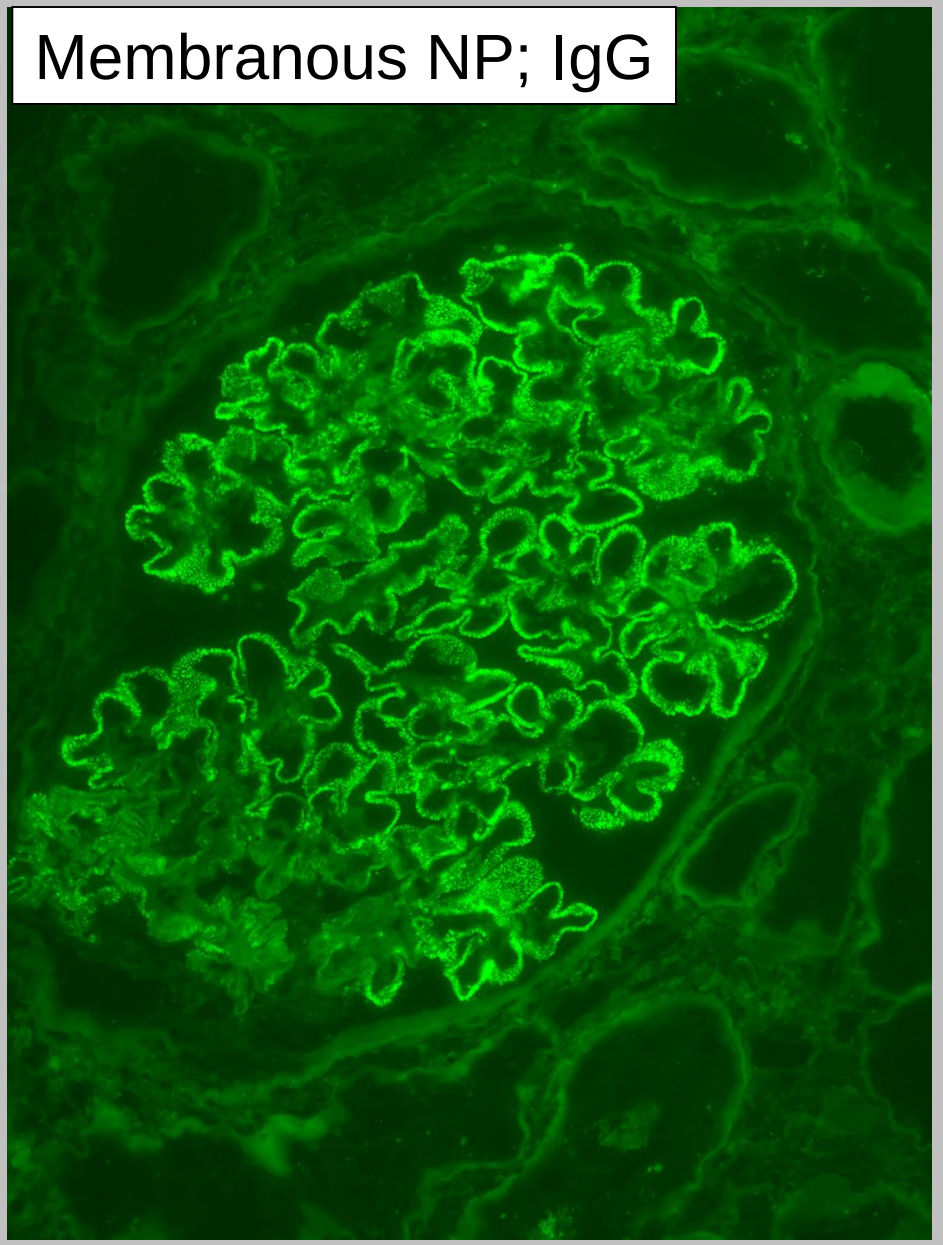


C4d-positive peritubular capillaries - ABMR

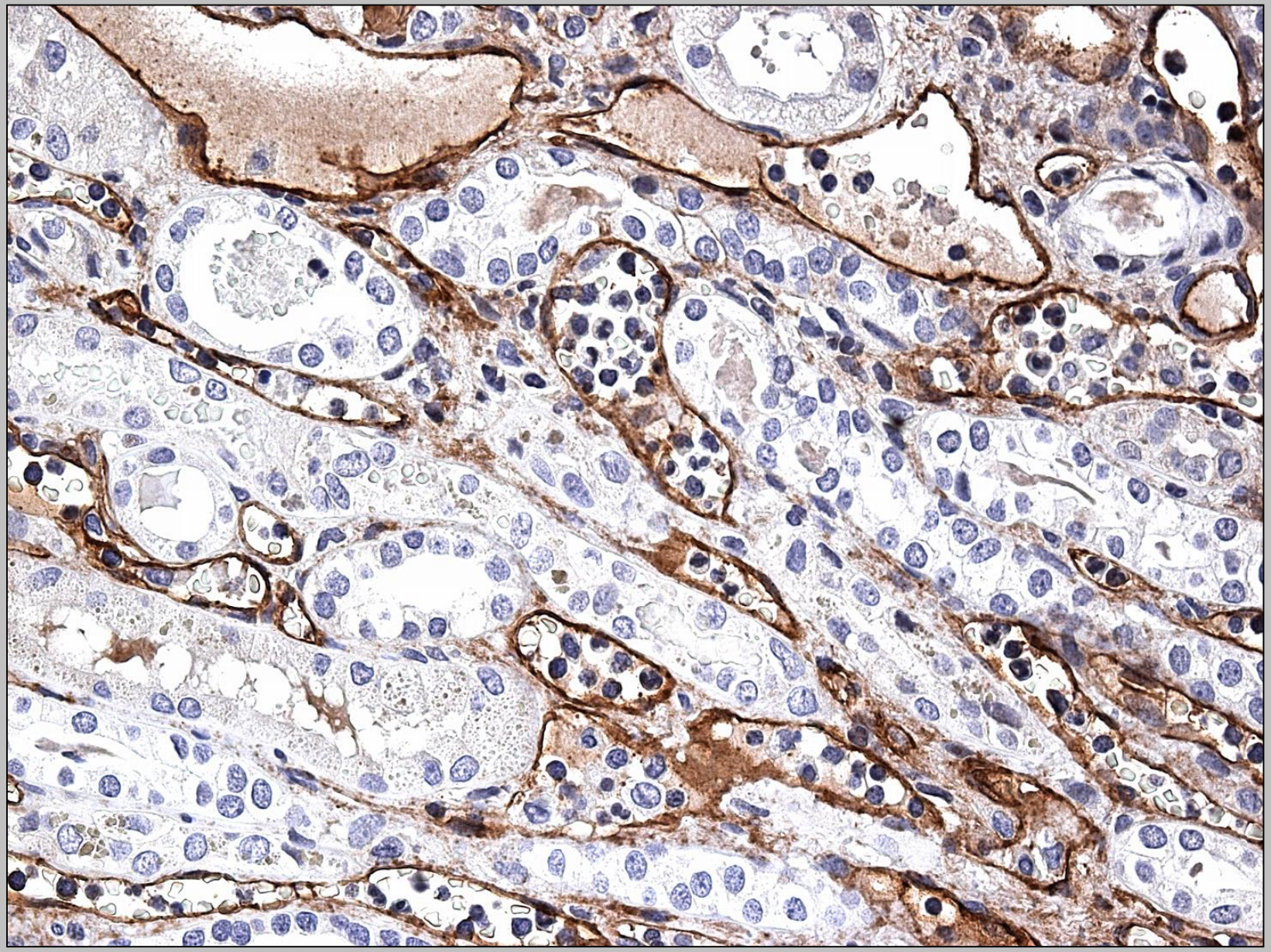


IgG, IgA, IgM, C3 for checking immune deposits

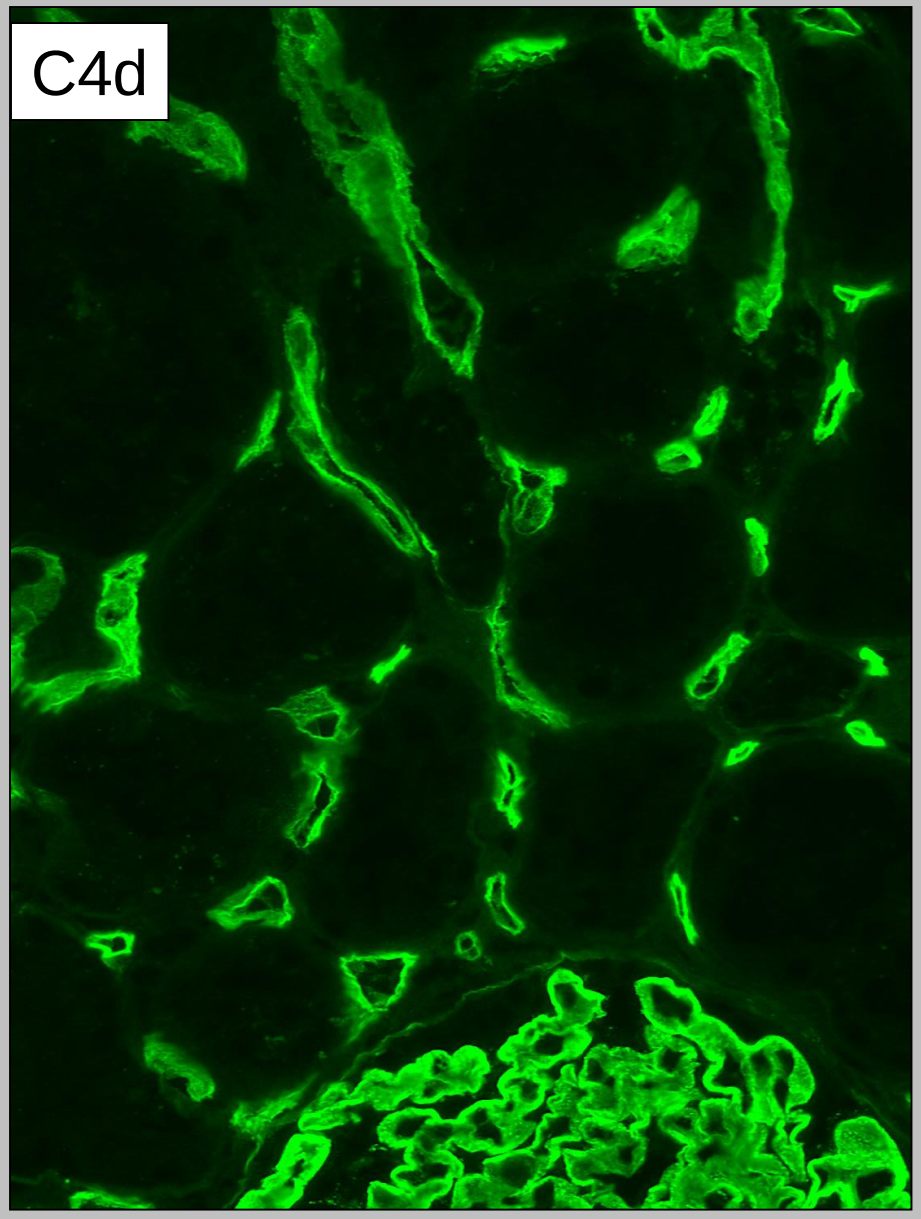


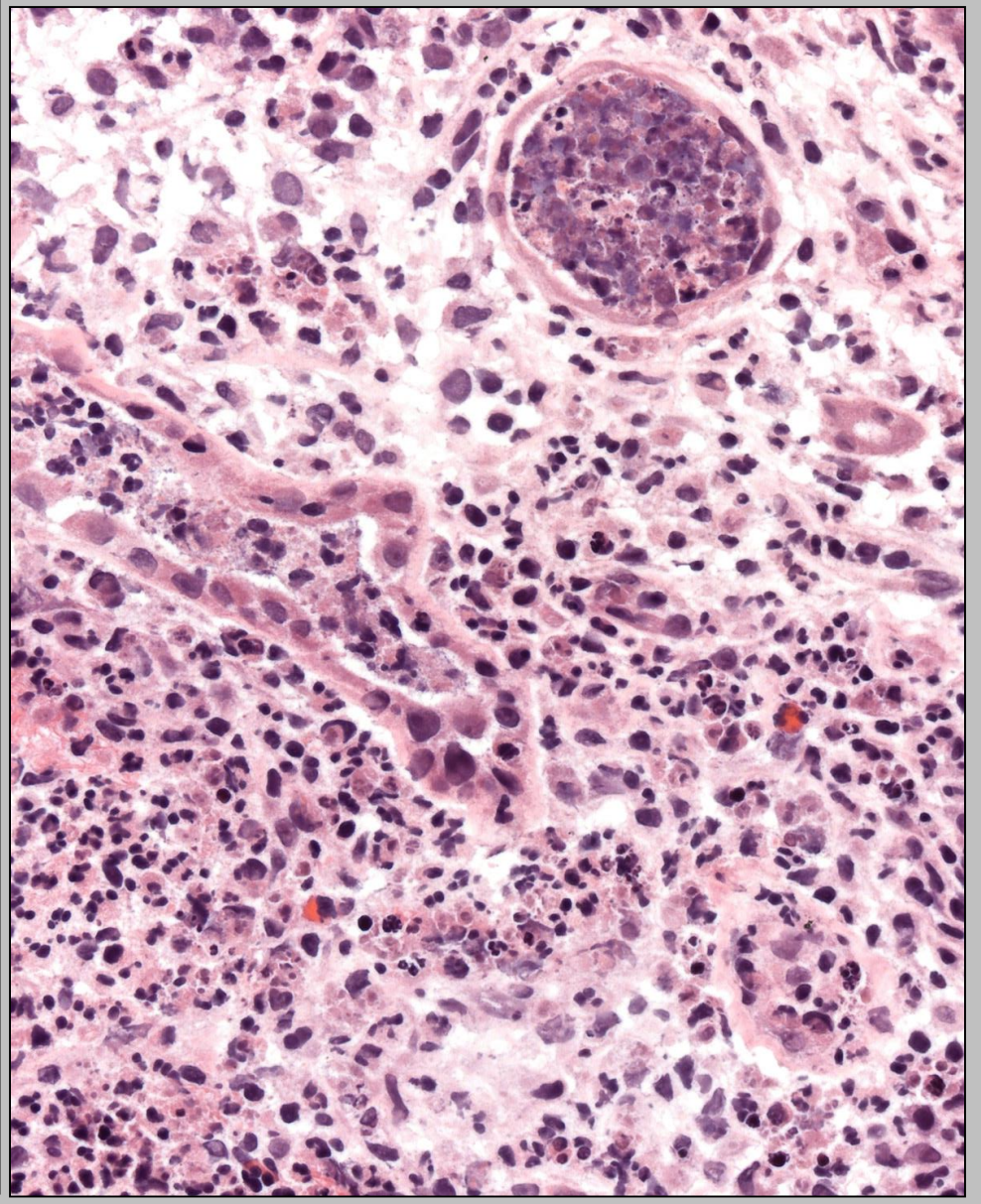


C4d IHC on paraffin sections works well; less sensitive than that of on frozen sections



Evaluation of frozen sections may provide relevant information about active ABMR, vascular TCMR or acute pyelonephritis





Biopsy Processing for Optimum Interpretation

Sampling

16-G needle; two cores

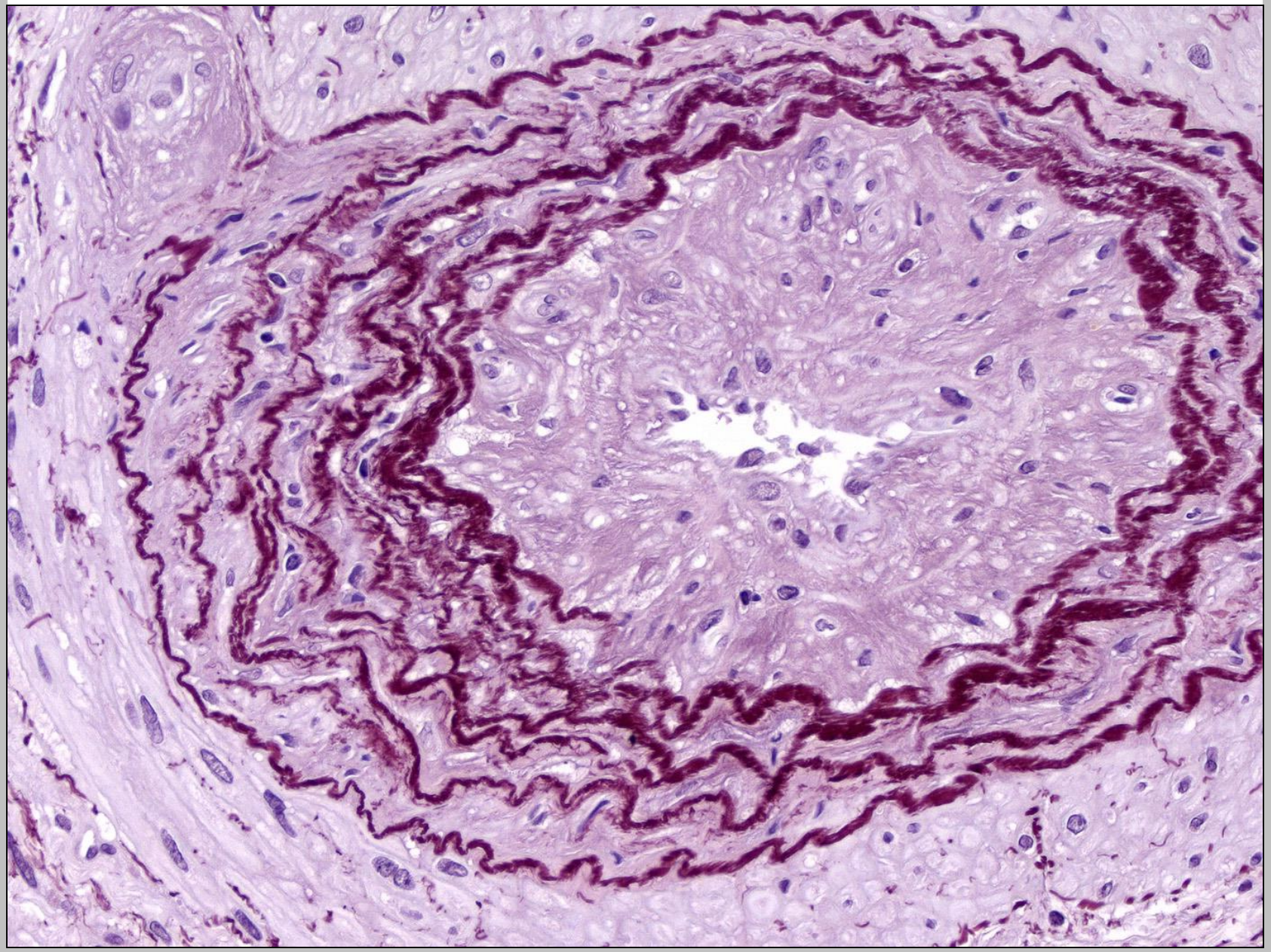
Frozen sections for IF and LM

5 immunostainings;
HE, PAS, trichrome, and elastin for LM evaluation

Paraffin sections for LM

HE, PAS, trichrome, Jones, elastin

Elastin differentiates rejection-induced intimal fibrosis from hypertension-induced fibroelastosis



Biopsy Processing for Optimum Interpretation

Sampling

16-G needle; two cores

Frozen sections for IF and LM

5 immunostainings;
HE, PAS, trichrome, and elastin for LM evaluation

Paraffin sections for LM

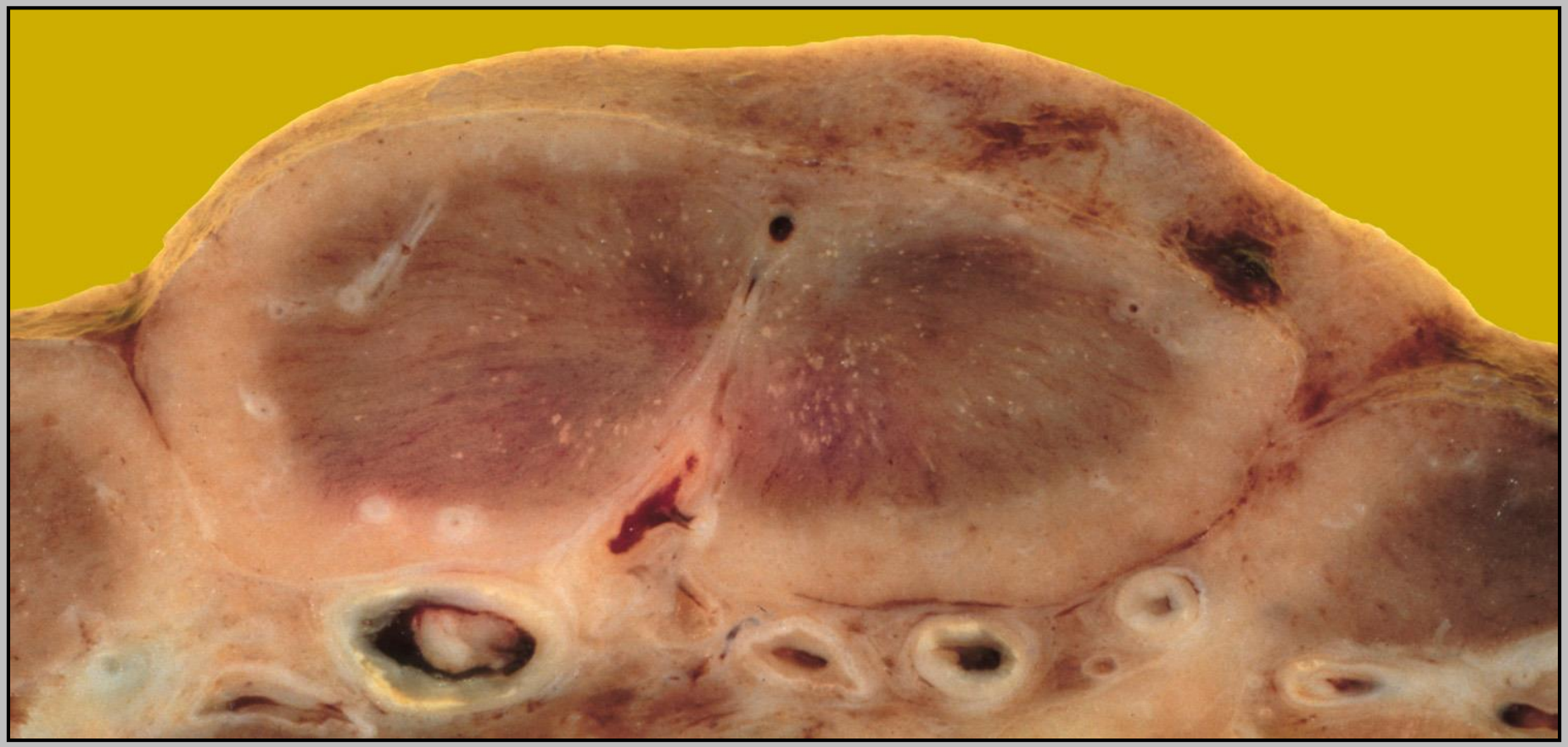
HE, PAS, trichrome, Jones, elastin
Severity of lesions: Banff grades

EM

Fixation and embedding in each case

Extrarenal arteries ± arcuate arteries are not present in the biopsy sample, therefore, important site of injury is not evaluated.

Rejection-induced obliterative intimal fibrosis ➔ IFTA in the supplied parenchyma



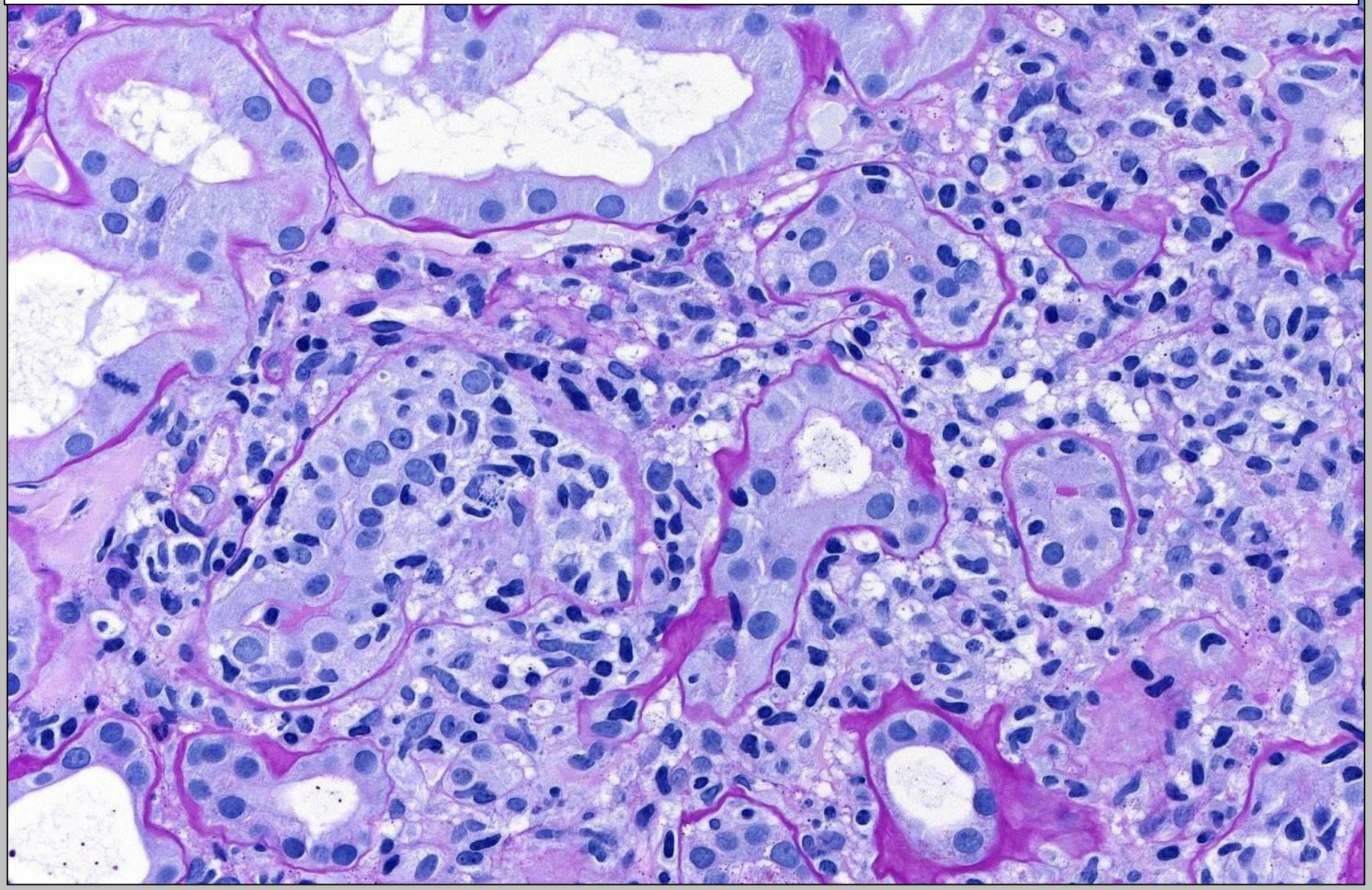
The Banff 2017 Kidney Meeting Report: Revised diagnostic criteria for chronic active T cell-mediated rejection, antibody-mediated rejection, and prospects of integrative endpoints for next-generation clinical trials

Haas et al. AJT 2018;18:293-307

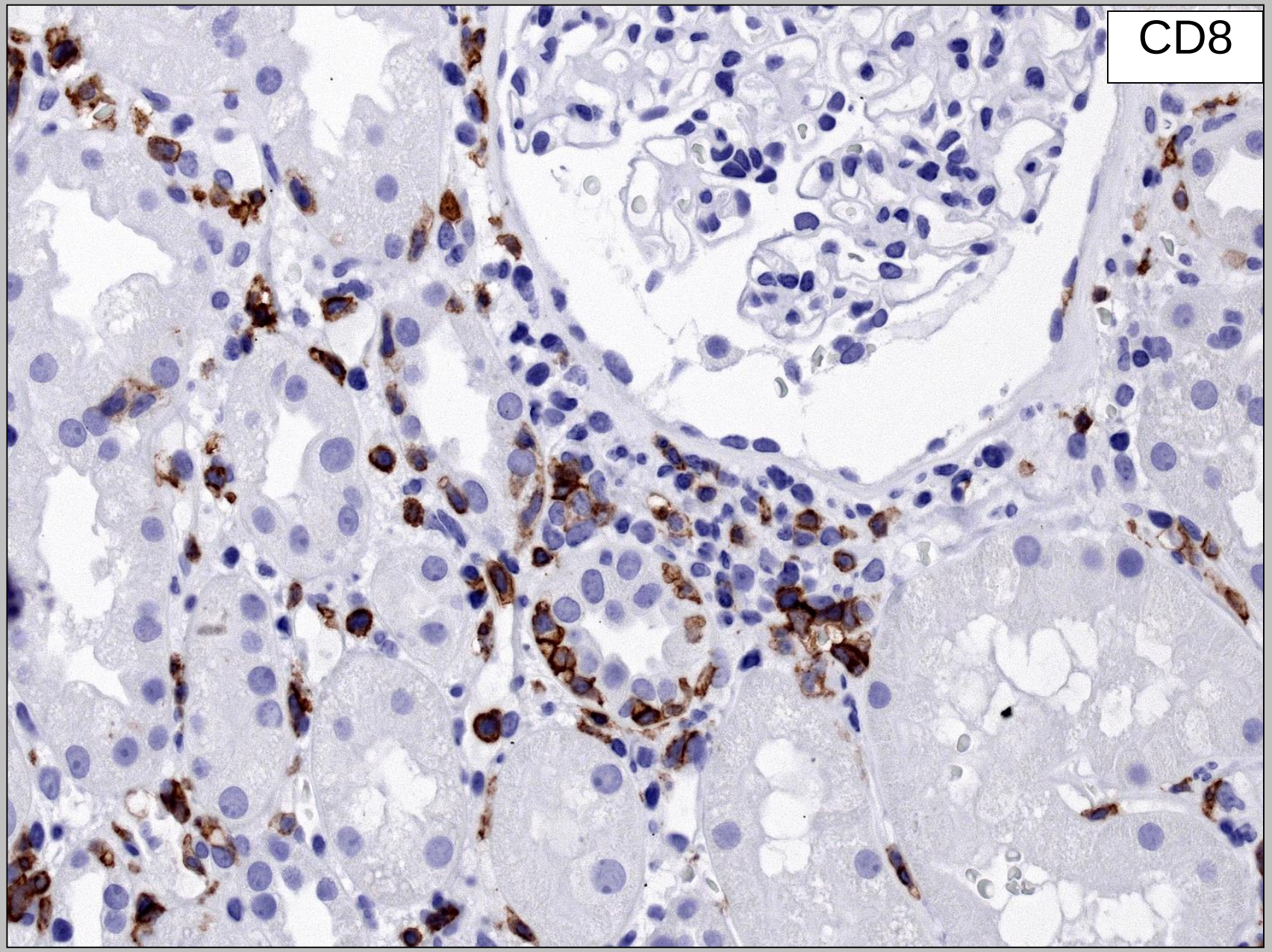
T cell-mediated	Borderline	Antibody-mediated
Acute		Active
Chronic active		Chronic active

Acute TCMR; Banff Grades IA and IB

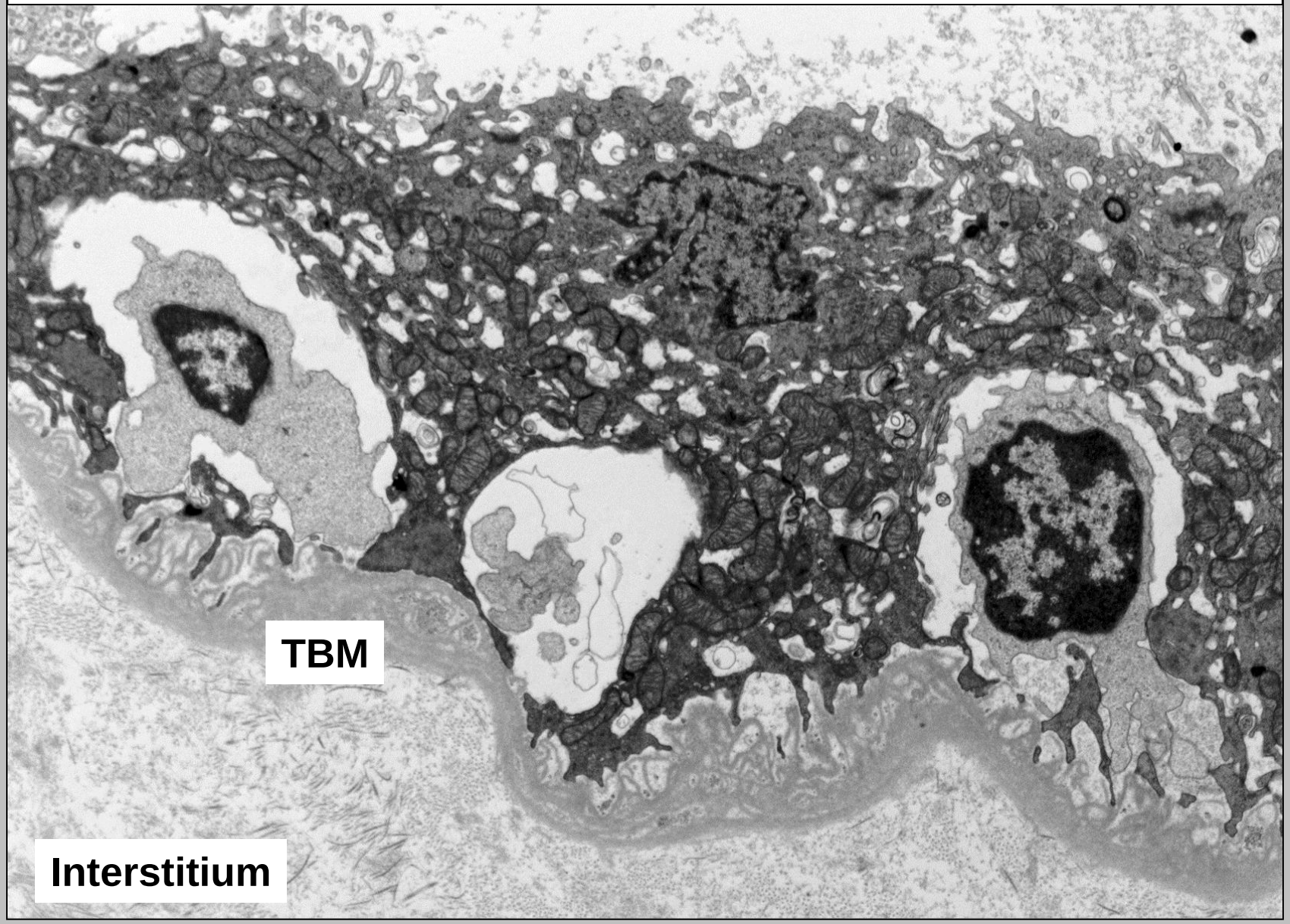
Interstitial infiltrates involving >25% of nonsclerotic cortex (**i2 or i3**) and moderate or severe tubulitis (**t2 or t3**)



Infiltrating cells: mixture of $CD8^+$ and $CD4^+$ T-lymphocytes > macrophages > plasma cells > NK cells

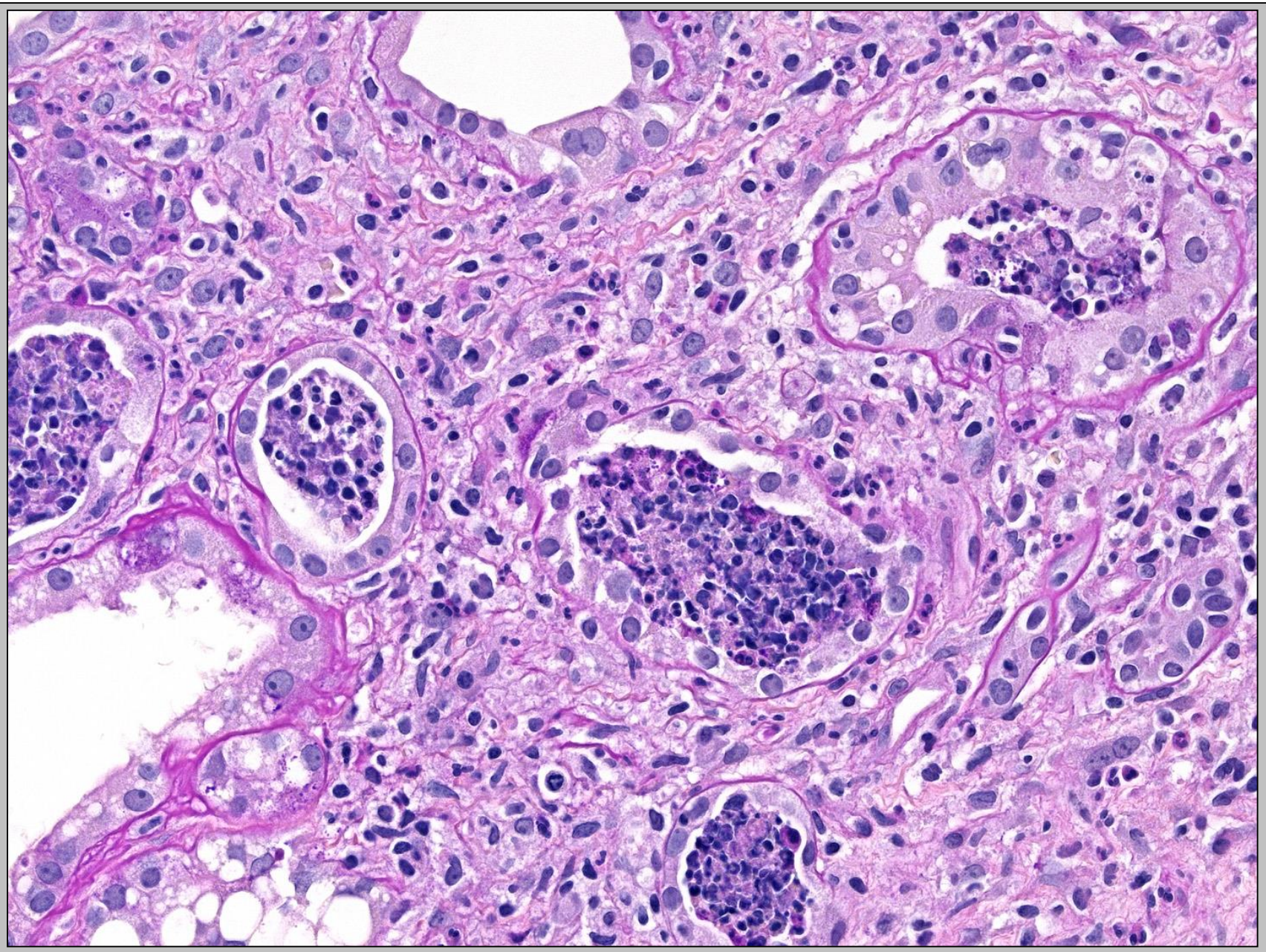


Apoptosis of tubular cells in the vicinity of intratubular T-lymphocytes (contact-dependent cellular cytotoxicity)



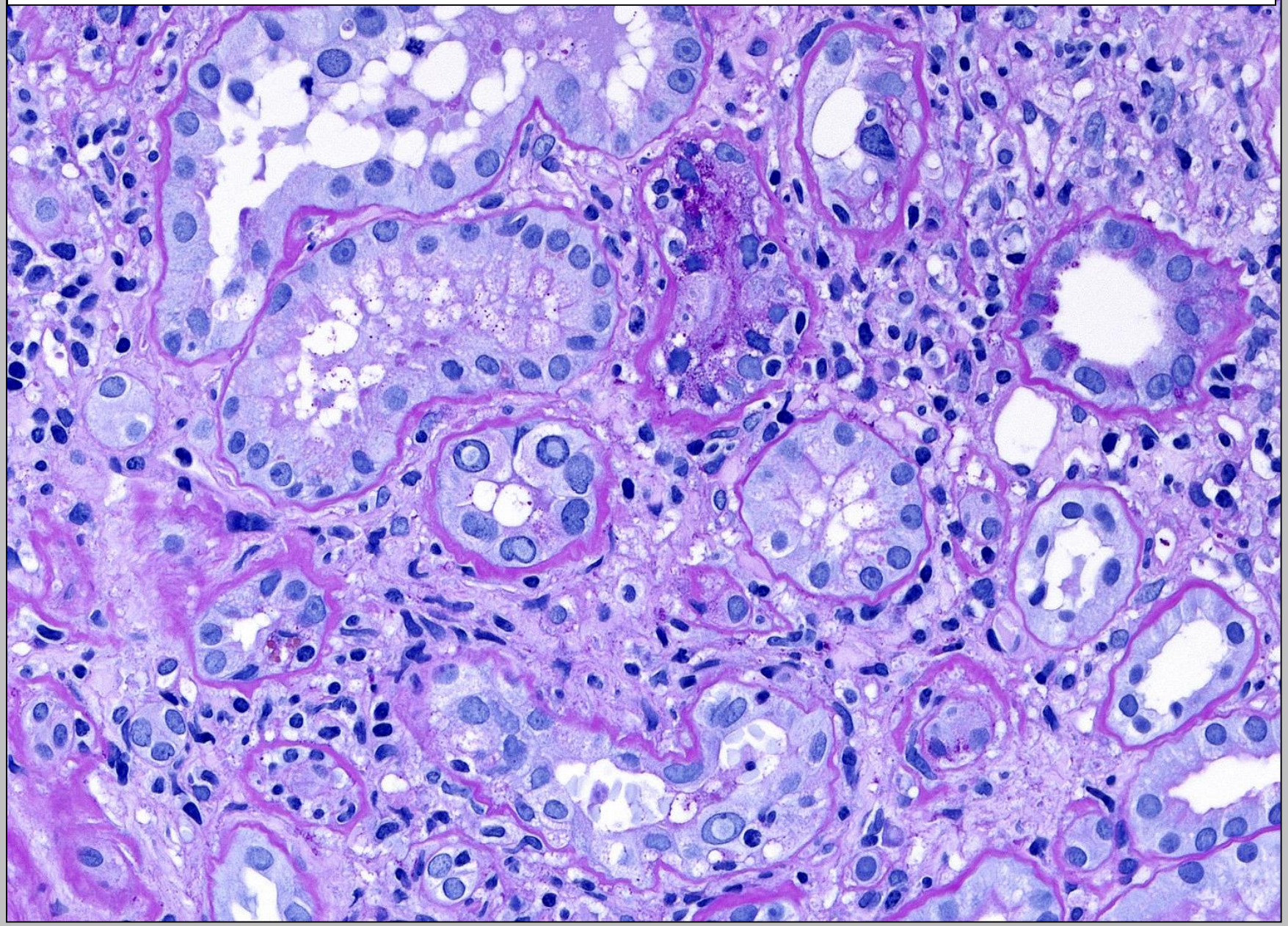
Diff. dg of acute TCMR Banff Grade I: acute pyelonephritis

- neutrophils in infiltrates and pus casts

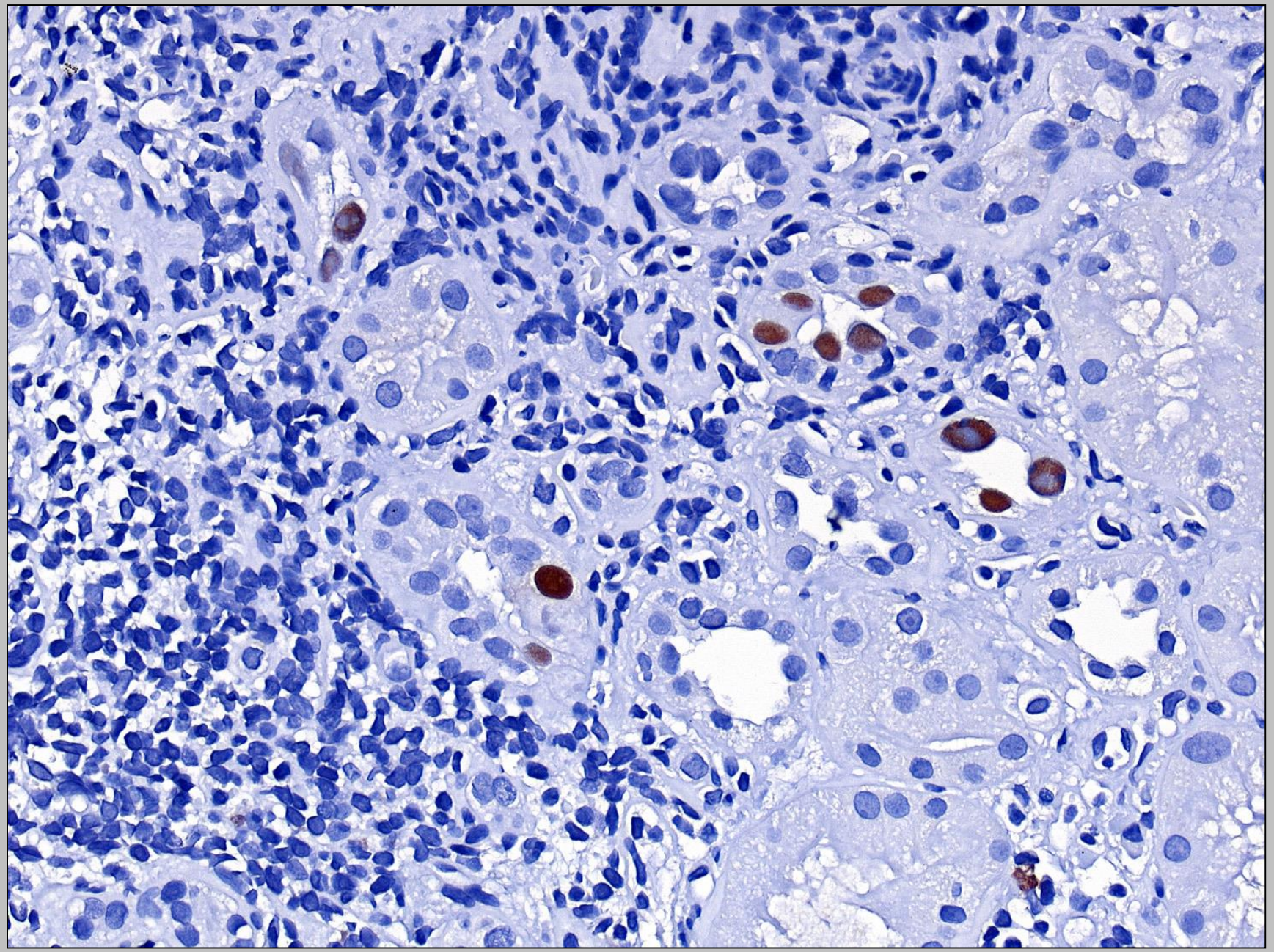


Diff. dg of acute TCMR Banff Grade I:

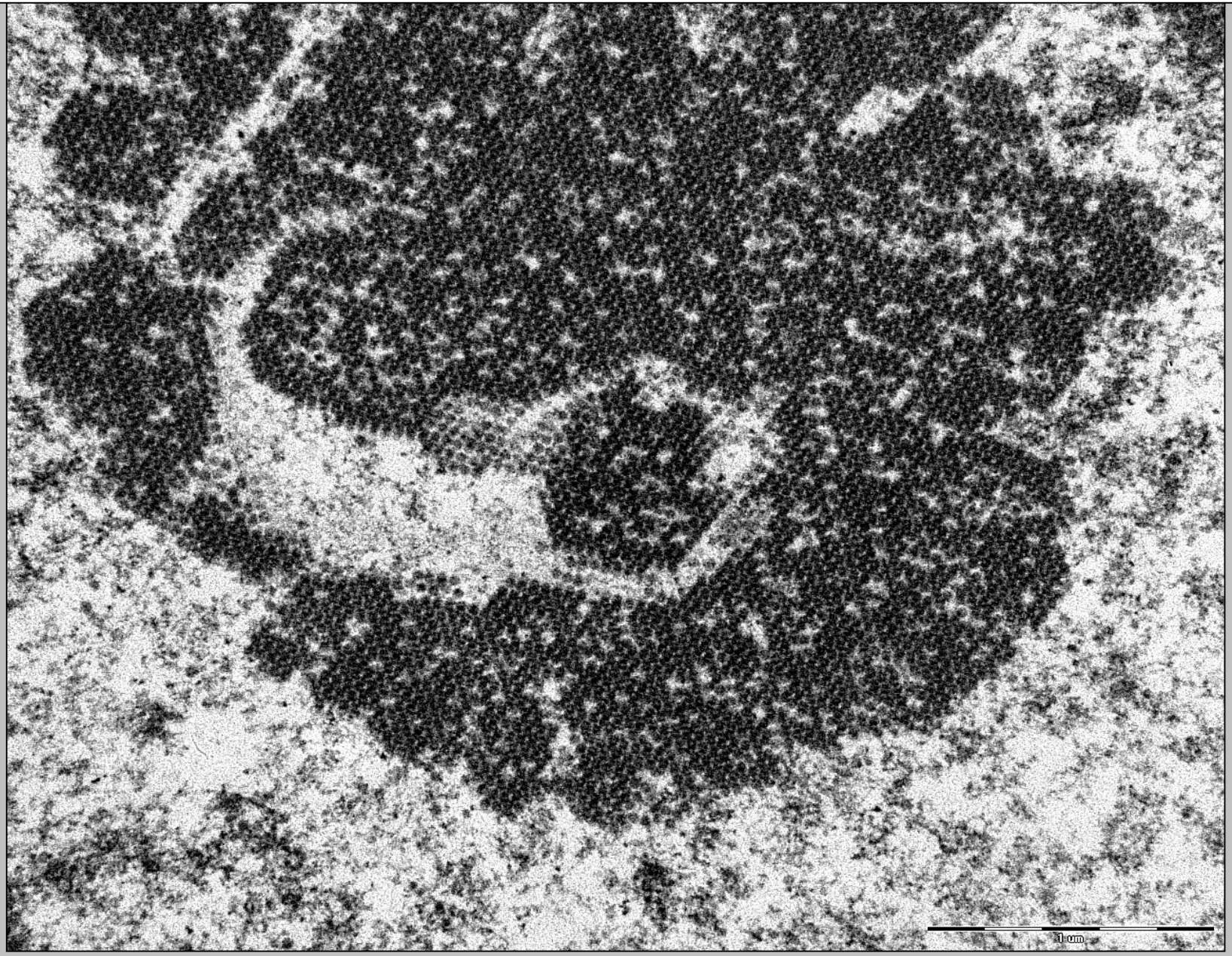
PVN - interstitial infiltrates, tubulitis, inclusions



Confirmation of PVN: Simian virus large T antigen staining

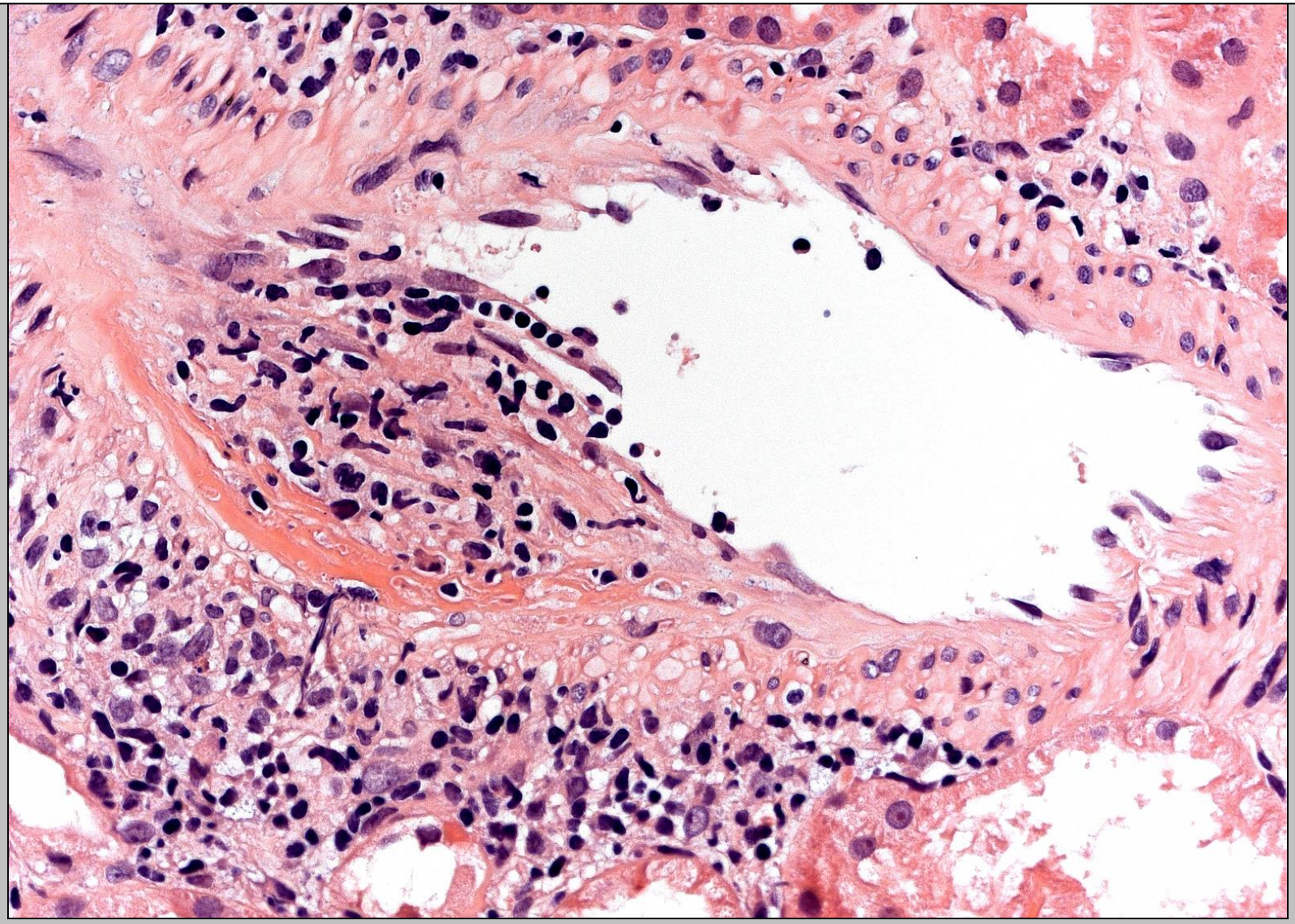


EM (labour extensive and not sensitive): polyoma virions are 40 nm in diameter; arranged in a paracrystalloid structure



Acute TCMR, Banff Grades II and III
”vascular rejection”

Intimal arteritis: lymphocytes ± monocytes in the intima
Transmural arteritis and/or fibrinoid necrosis medial SMCs



Banff 2017 Classification of Rejection

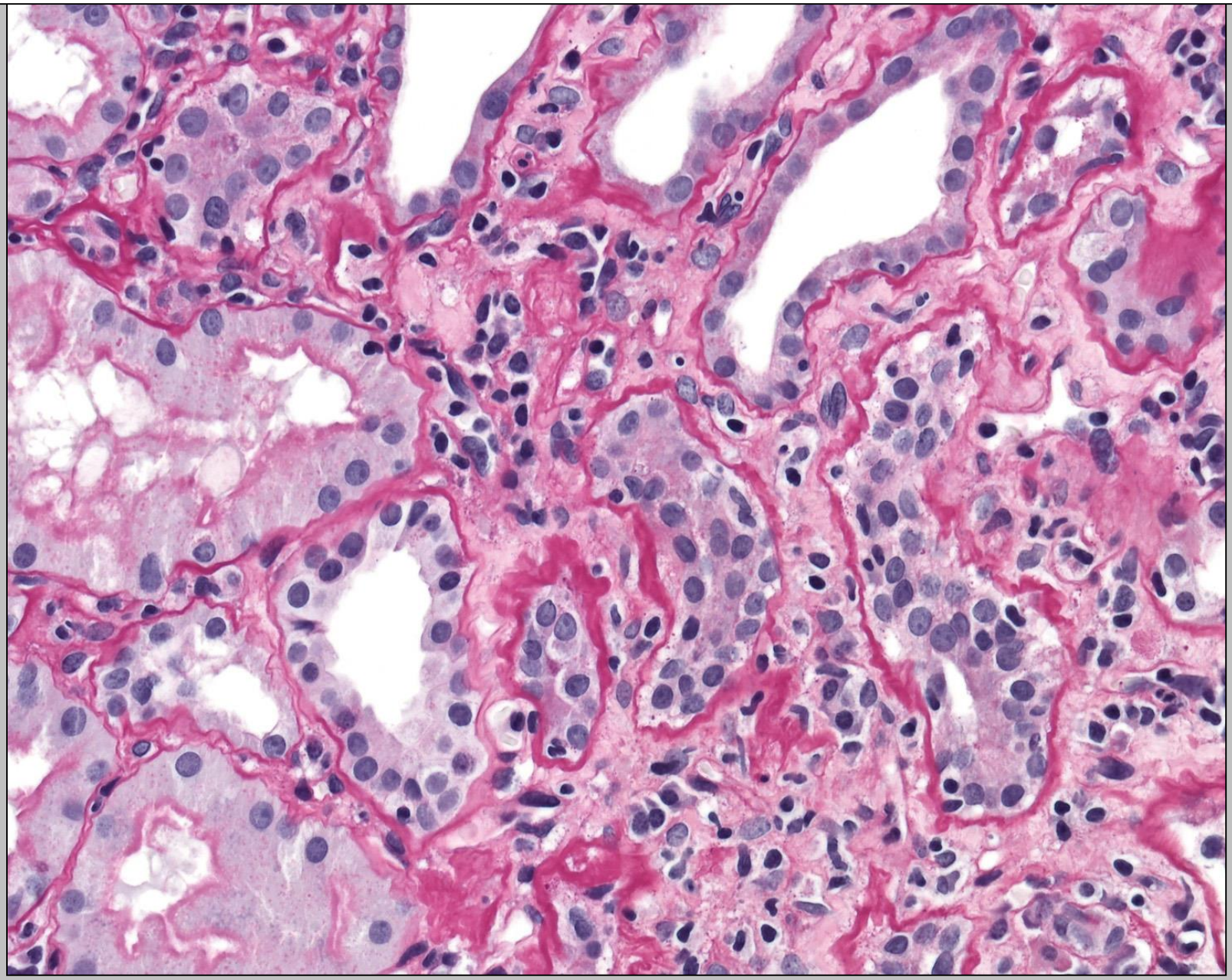
AJT 2018;18:293-307

T cell-mediated	Borderline	Antibody-mediated
Acute		Active
Chronic active[x]		Chronic active

[x]A biopsy fulfilling the criteria for chronic active TCMR should not be given a second diagnosis of Borderline or acute TCMR

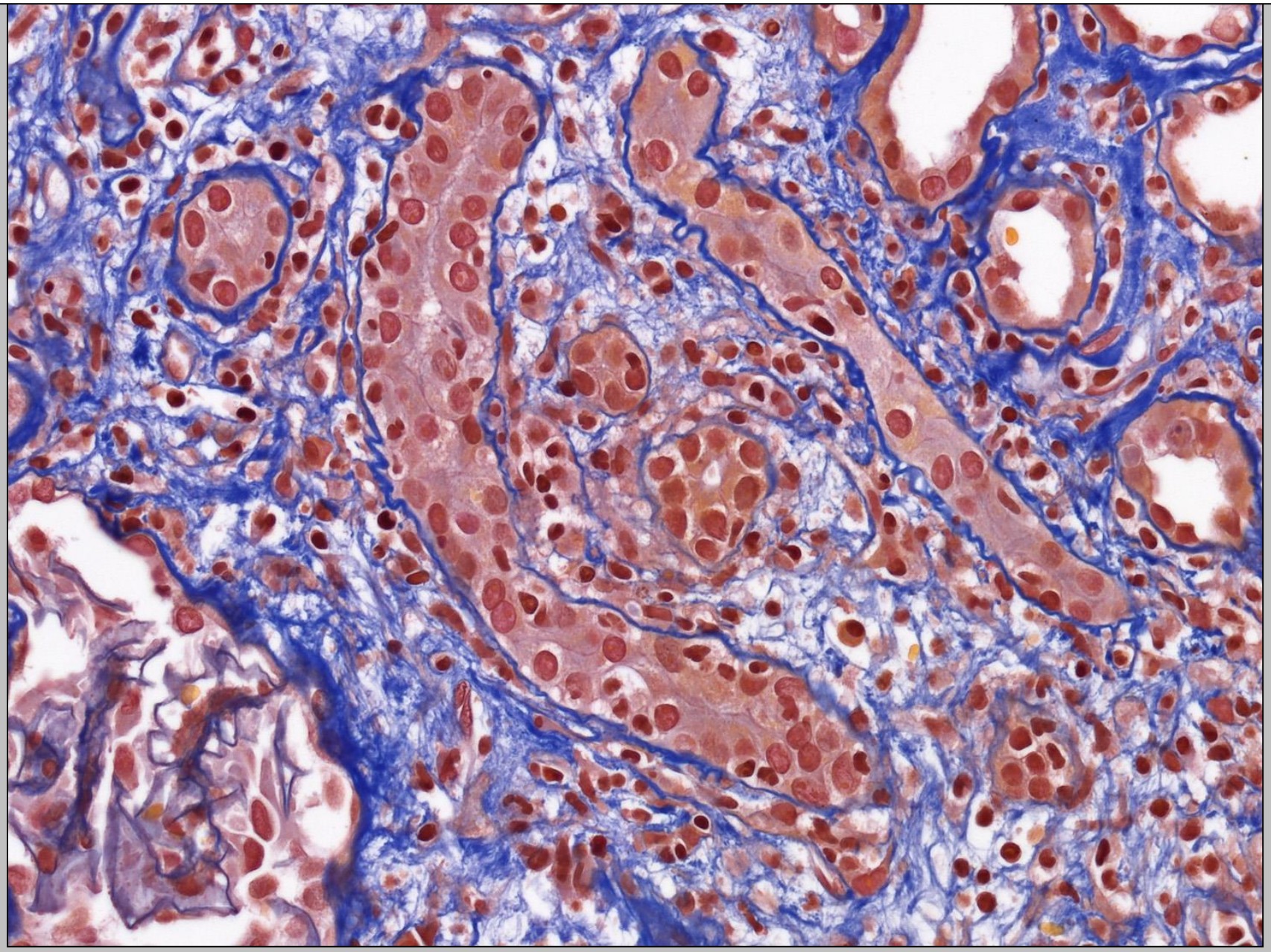
Chronic active TCMR; Banff Grades IA and IB

Interstitial inflammation in area of IFTA (i-IFTA) with marked tubulitis

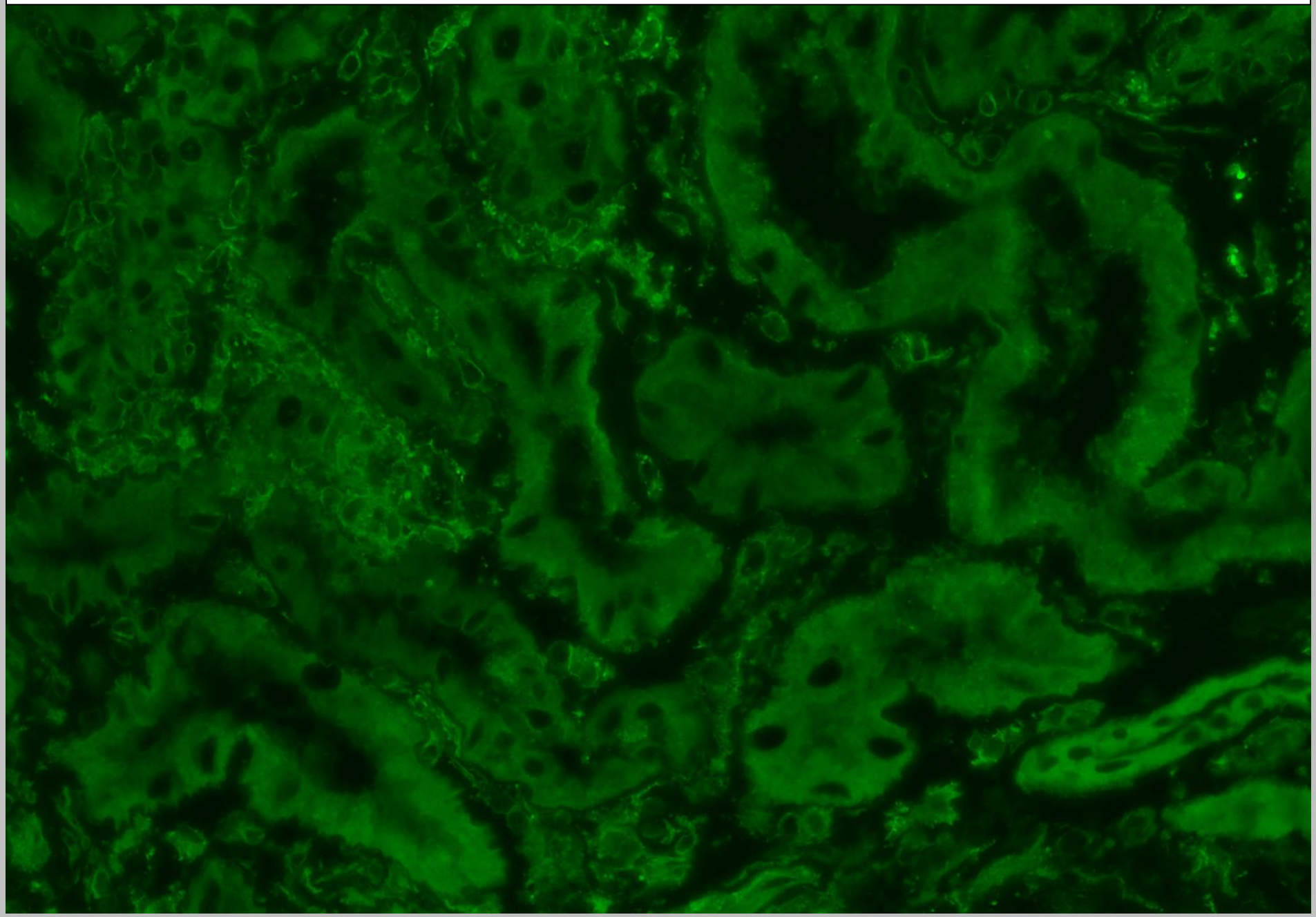


Chronic active TCMR; Banff Grades IA and IB

Interstitial inflammation in area of IFTA (i-IFTA) with marked tubulitis

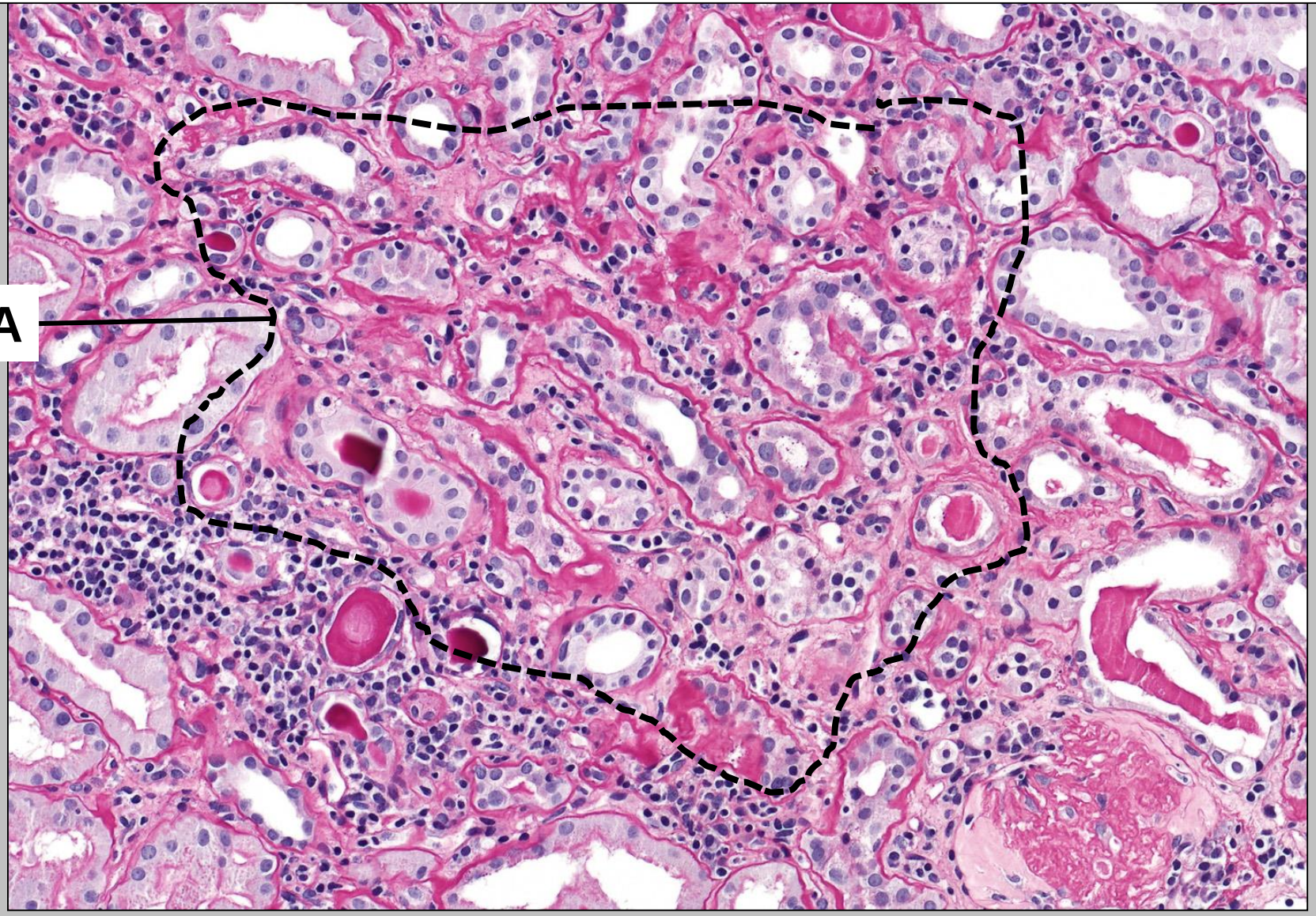


Tubular HLA-DR expression in chronic active TCMR



Chronic active TCMR; Banff Grades IA and IB

Definition: interstitial inflammation involving >25% of sclerotic cortical parenchyma (**i-IFTA 2 or 3**) with moderate or severe tubulitis (**t2 or t3**)



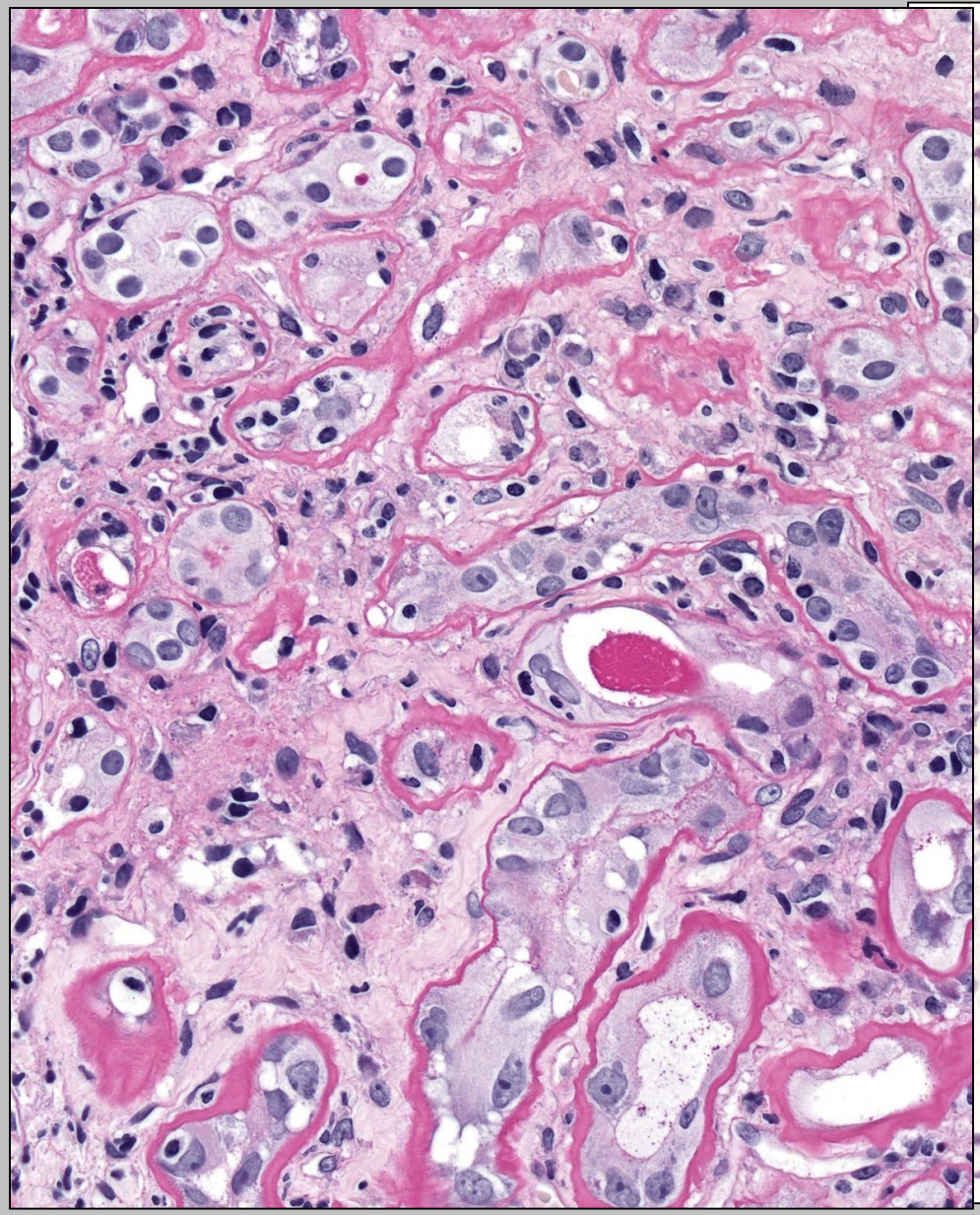
i-IFTA in TCMR

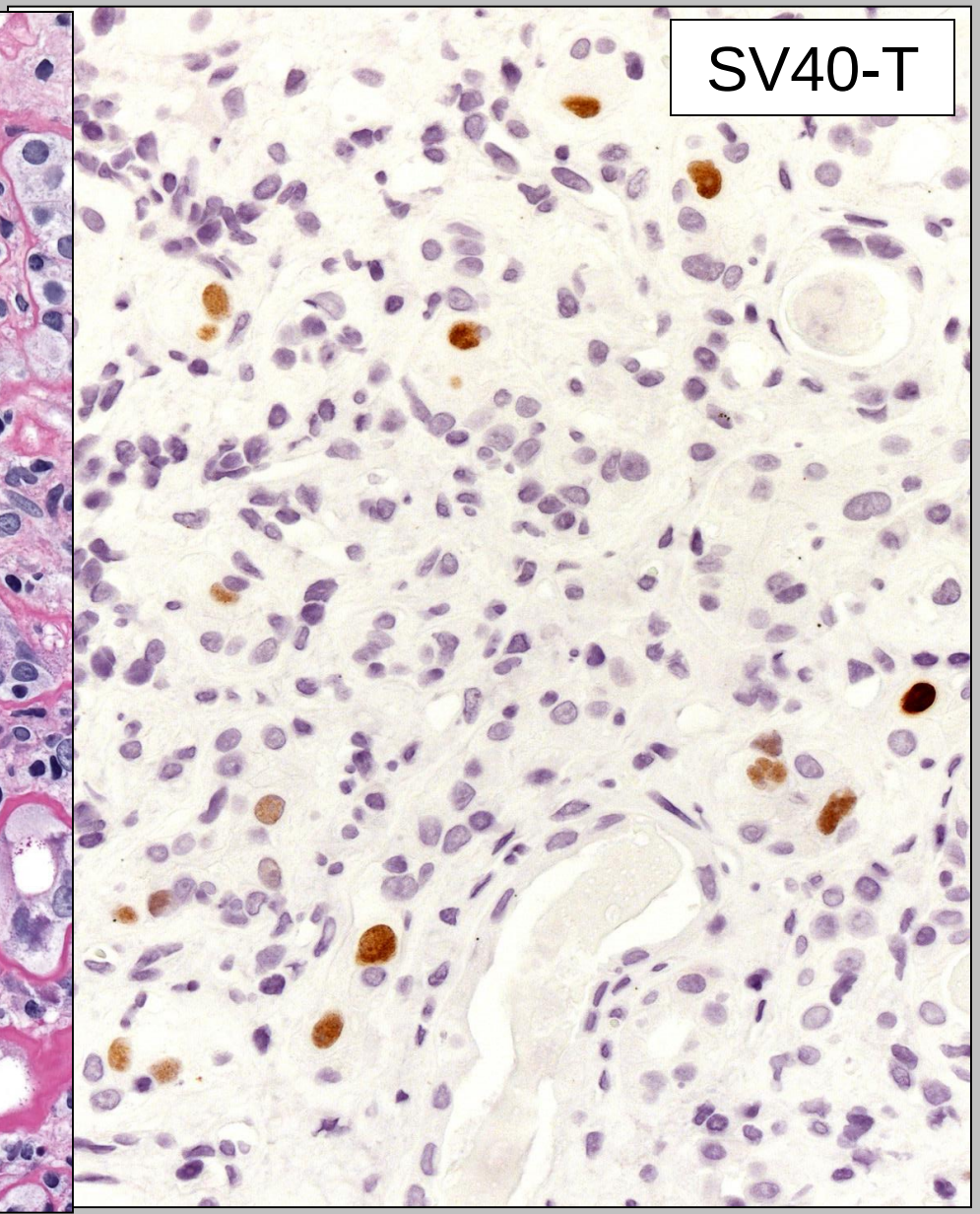
Nonspecific lesion; morphologic correlate of active injury

Related to chronic underimmunosuppression

Diff. dg.: PVN, resolving pyelonephritis, ABMR, GN

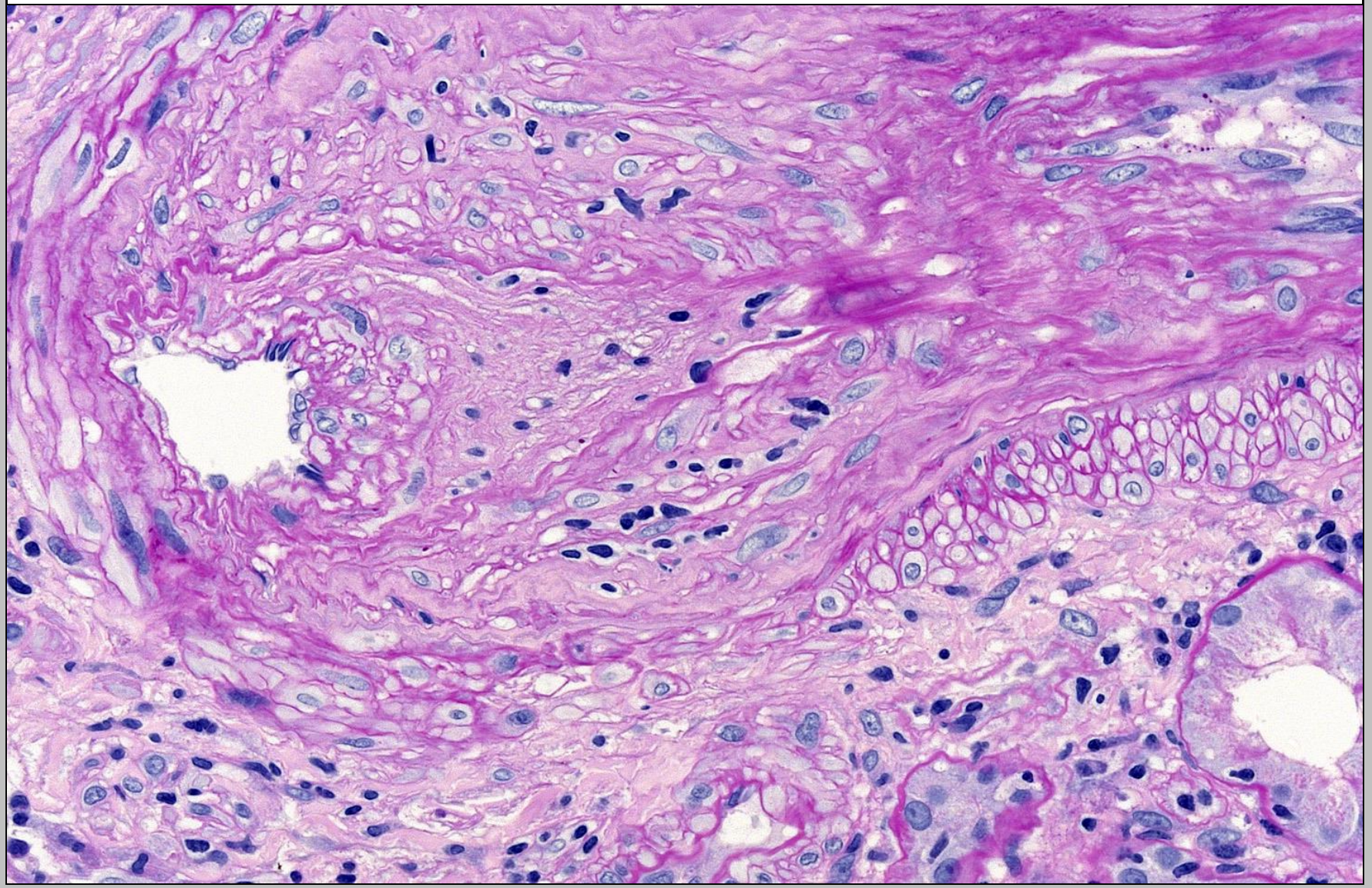
i-IFTA with tubulitis in polyoma virus nephropathy





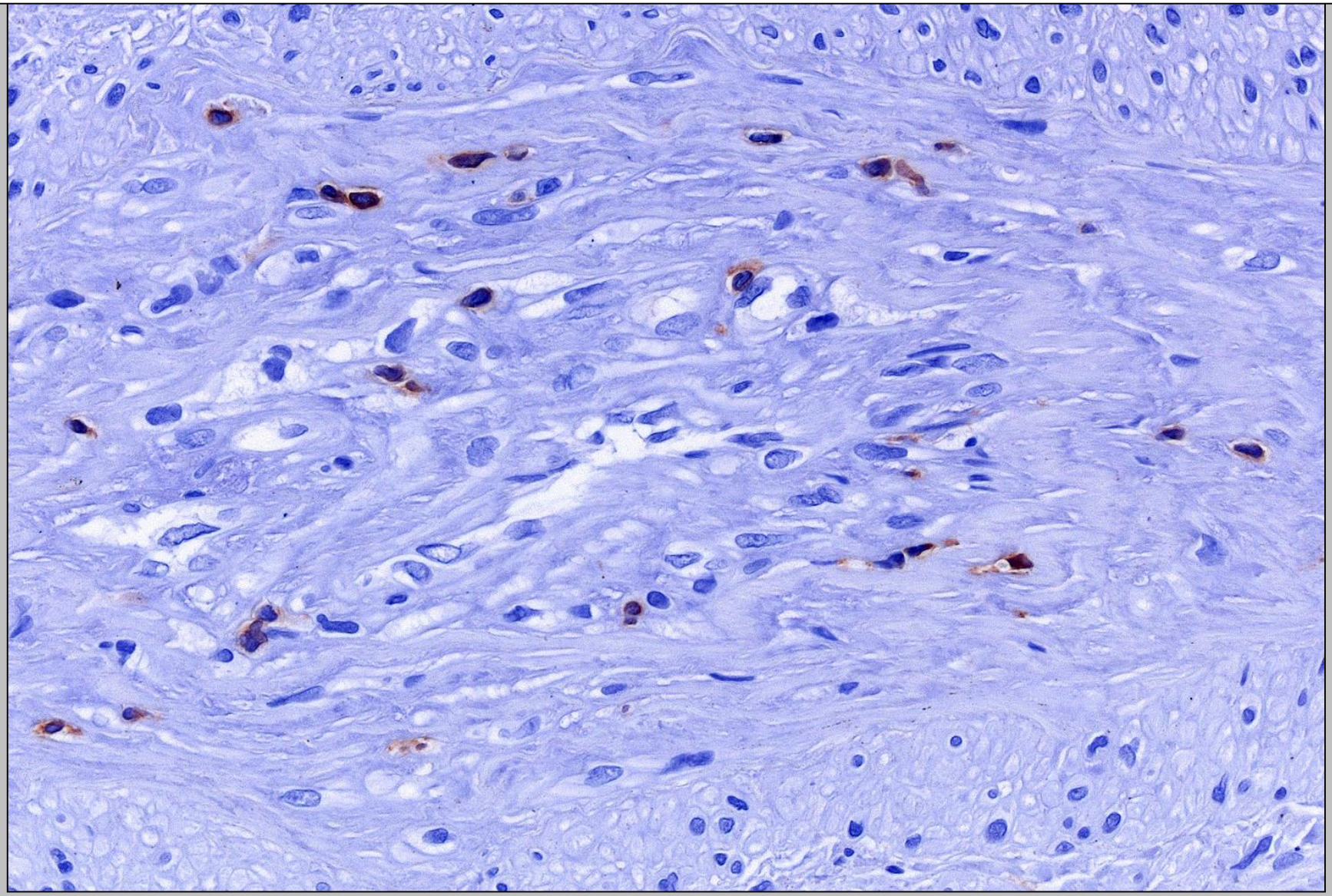
Chronic active TCMR; Banff grade II

Chronic transplant arteriopathy: arterial intimal fibrosis with mononuclear inflammation in fibrosis and formation of neointima



Chronic active vascular TCMR; Banff grade II

Significant fraction of mononuclear cells proved to be T-cells on CD3-staining

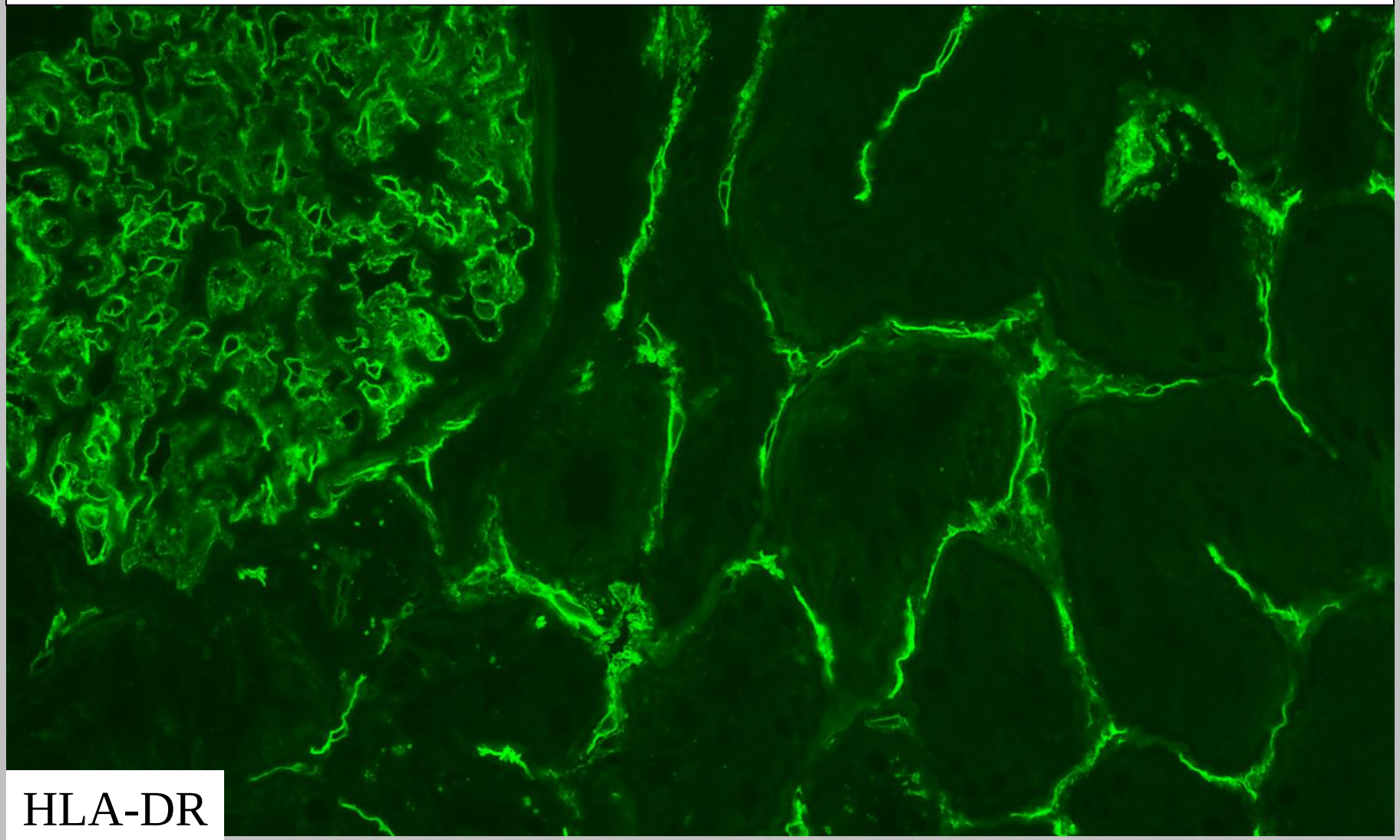


Banff 2017 Classification of Rejection

AJT 2018;18:293-307

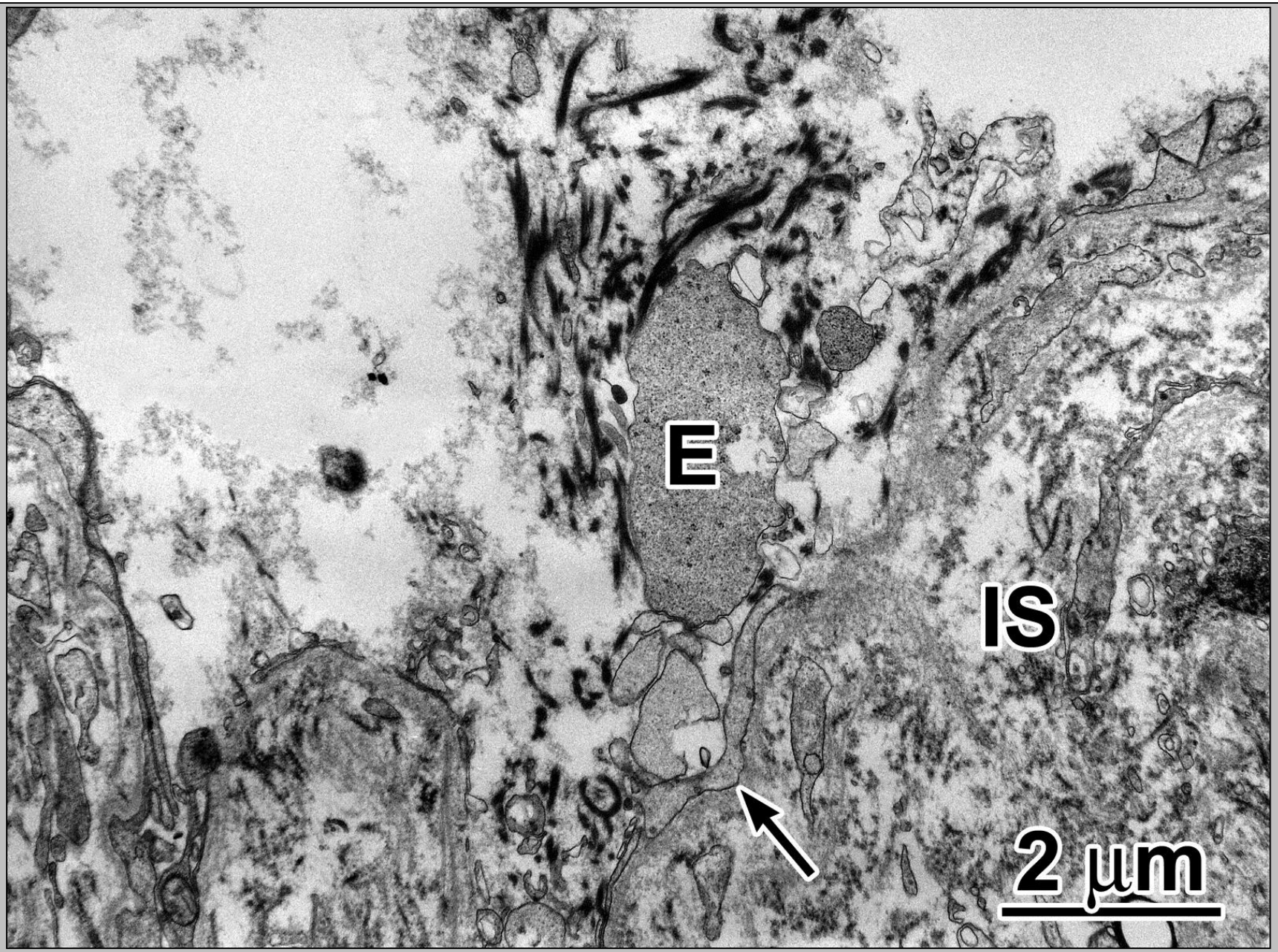
T cell-mediated	Borderline	Antibody-mediated
Acute		**Active**
Chronic active		Chronic active

Endothelial cells express HLA antigens
Anti-HLA DSAs (IgG3, IgG1) bind to the endothelium, activate the classical complement pathway and the MAC induces endothelial injury



HLA-DR

DSA-induced cytotoxic lysis of the PTC endothelial layer with fibrin deposits and denudation of the BM



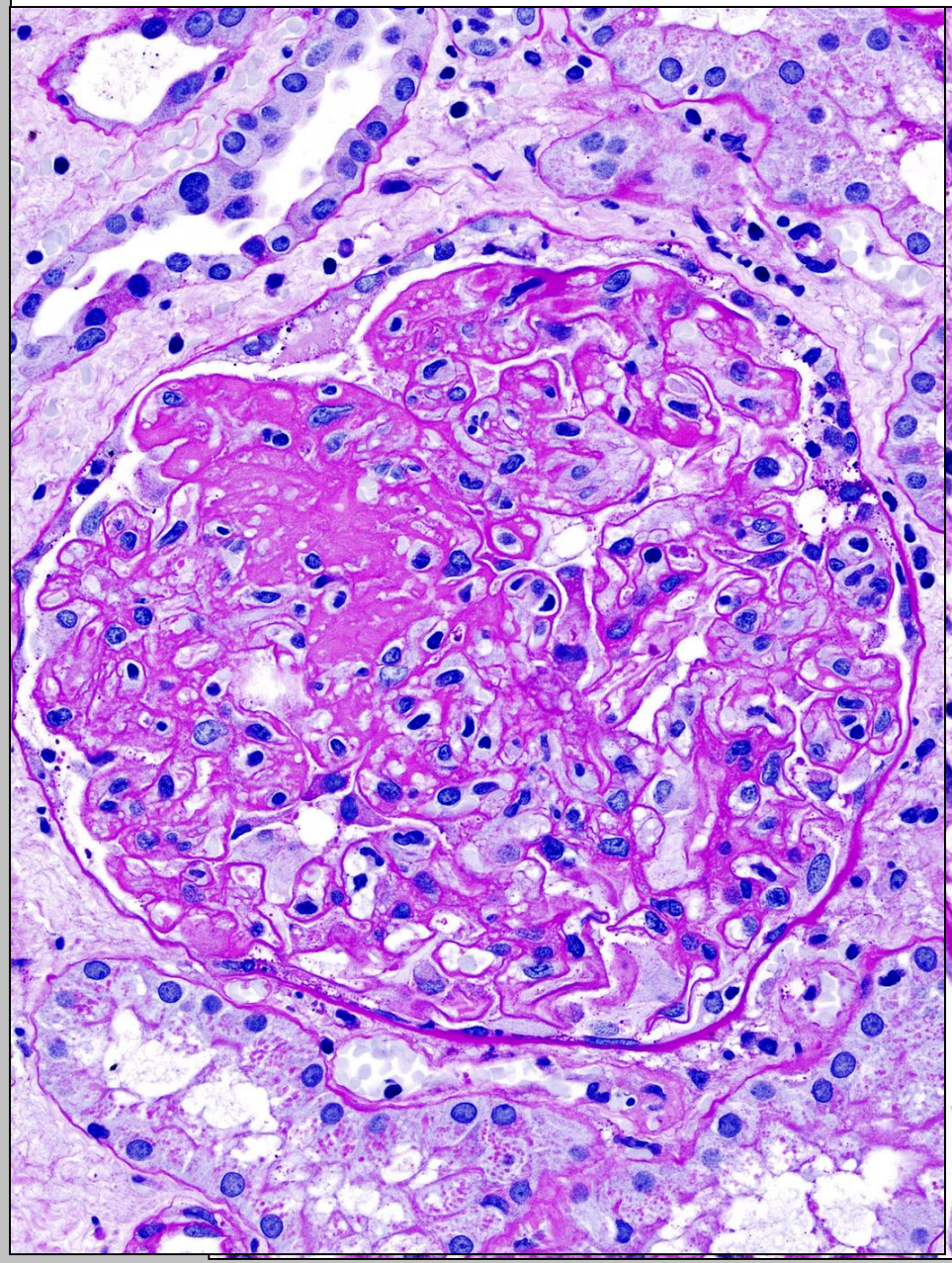
Diagnostic Criteria of Active ABMR[X]

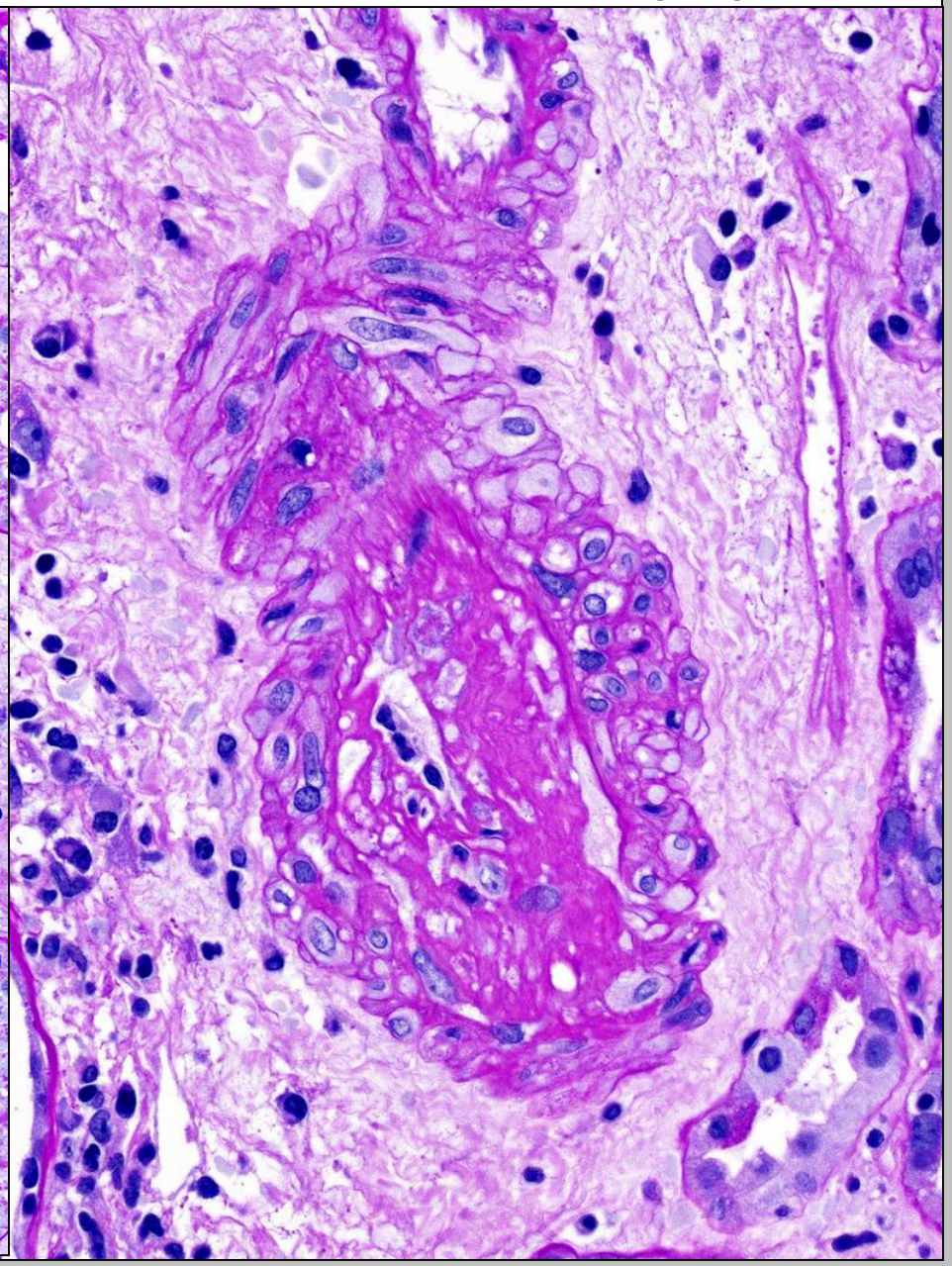
Histological evidence of acute tissue injury

Evidence of antibody interaction with vascular endothelium

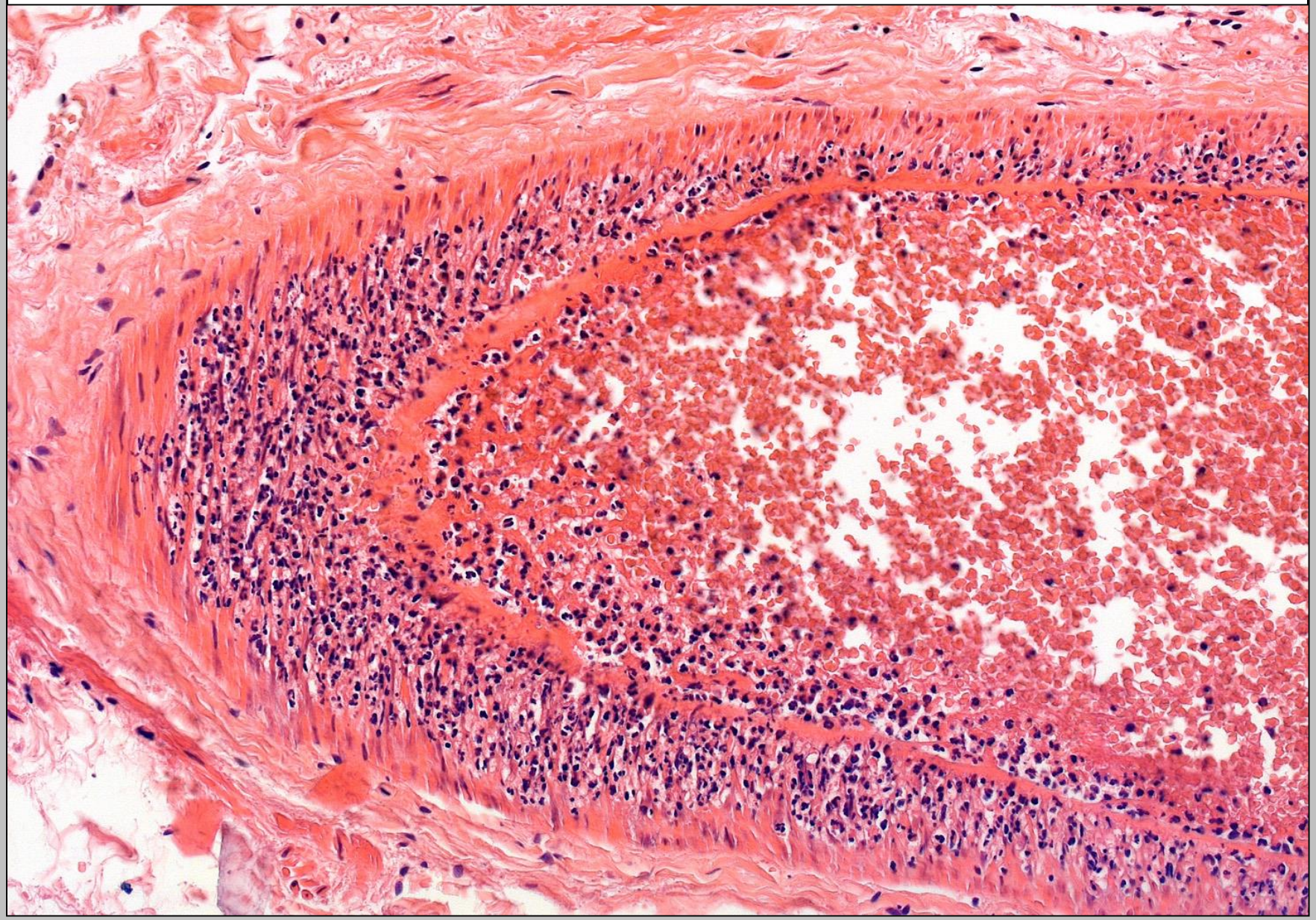
[X]May be clinically acute, smoldering, or subclinical; therefore, the misleading older term “Acute/active ABMR” was simplified to active ABMR

Evidence of acute tissue injury: glomerulitis, glomerular thrombi, and arteritis; not shown acute tubular injury

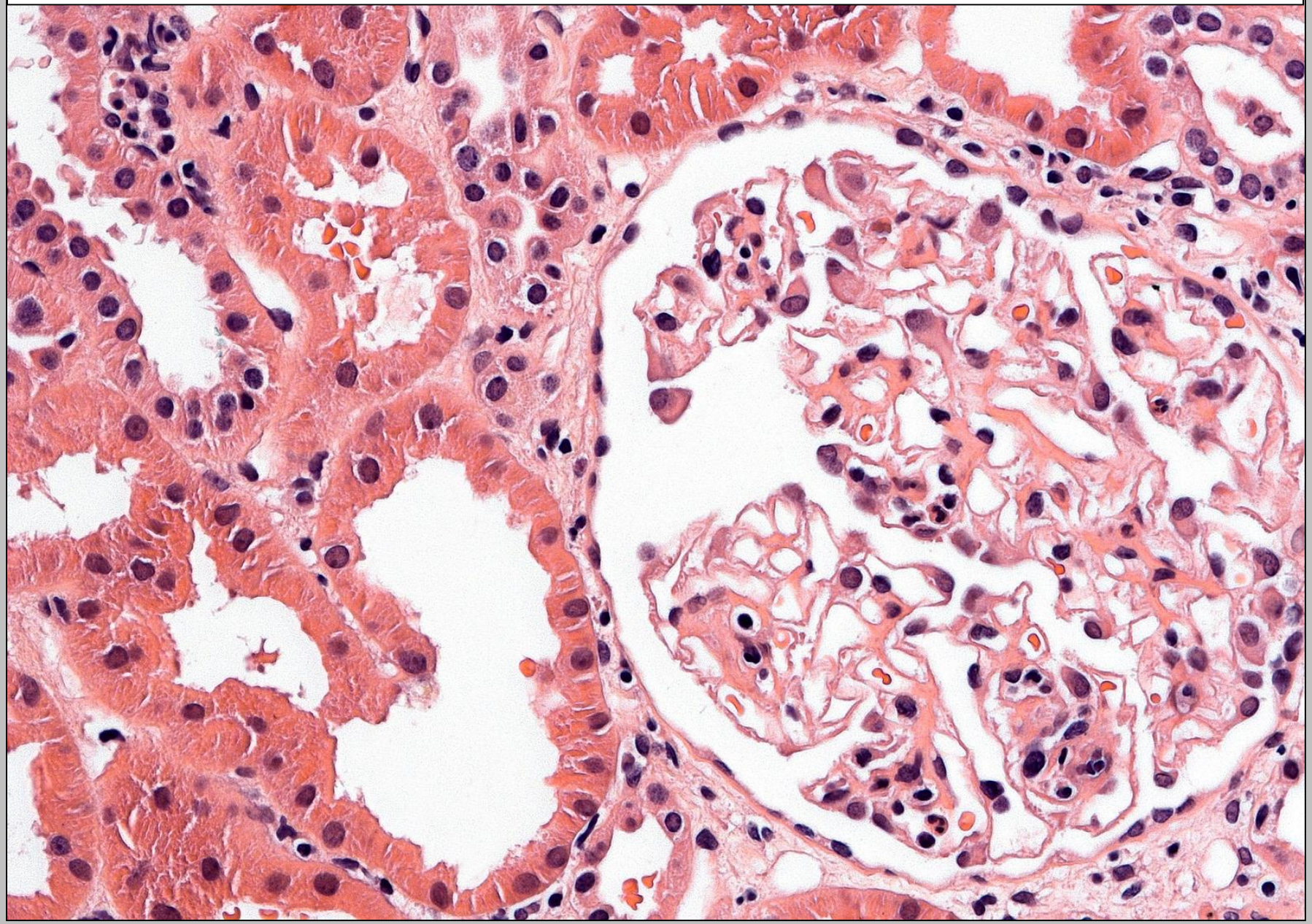




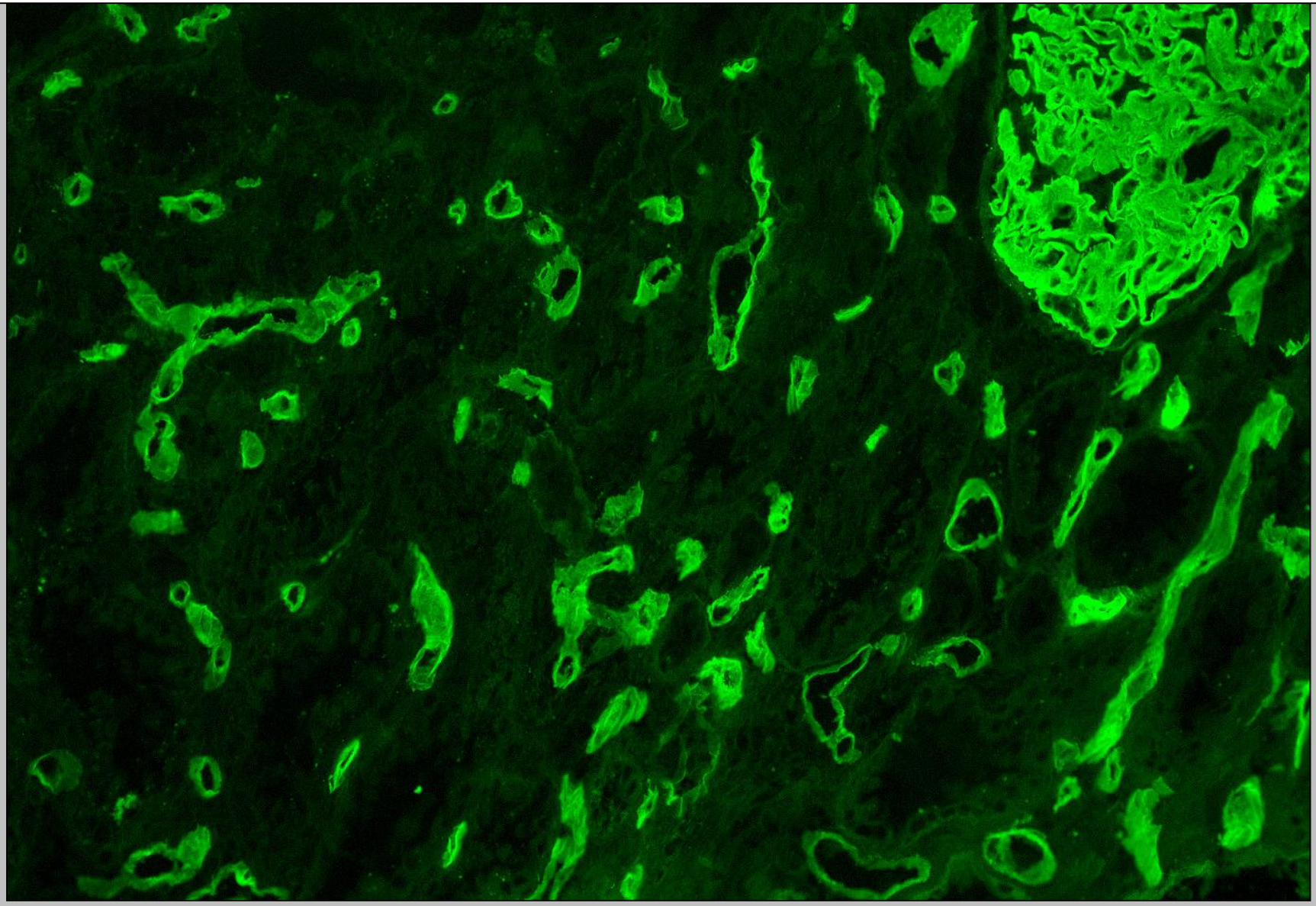
Transmural arteritis in a large artery (not sampled by the biopsy)



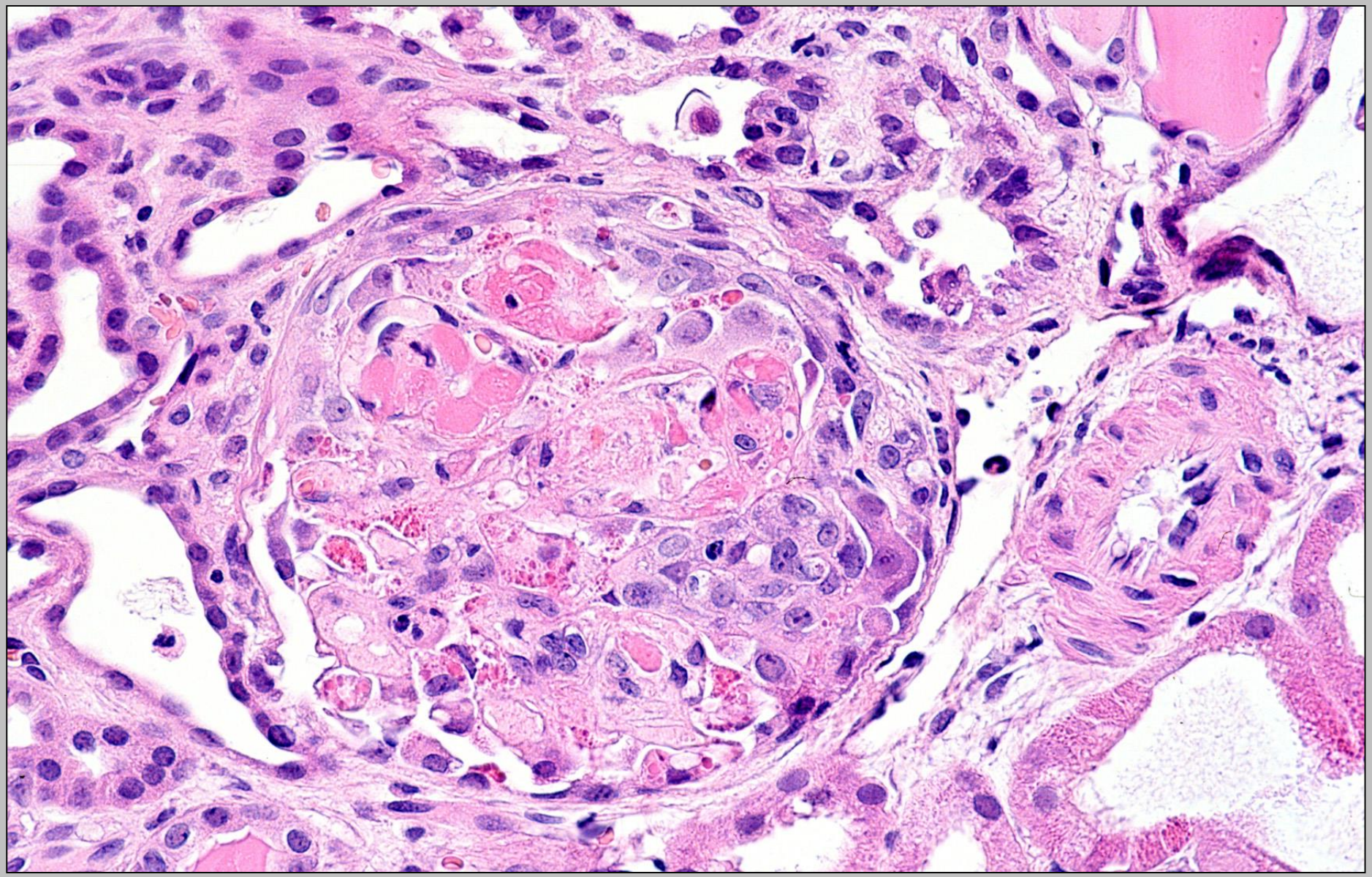
Microvascular inflammation (glomerulitis and peritubular capillaritis) is the most constant feature of active ABMR



Evidence of antibody interaction with vascular endothelium: C4d-positive PTCs
Very high specificity for the presence of DSAs if positive



Acute dysfunction, thrombi in glomeruli; C4d-negative: consider CNI-induced or recurrent TMA



What is the diagnosis in cases where DSA testing is not available or potentially false negative?

ABMR if

MVI score ≥1 and C4d-positive

MVI score ≥2 and C4d-negative

Molecular tests still have limitations and are not yet approved as diagnostic tests

The categories “suspicious for active ABMR” “suspicious for chronic active ABMR” are eliminated

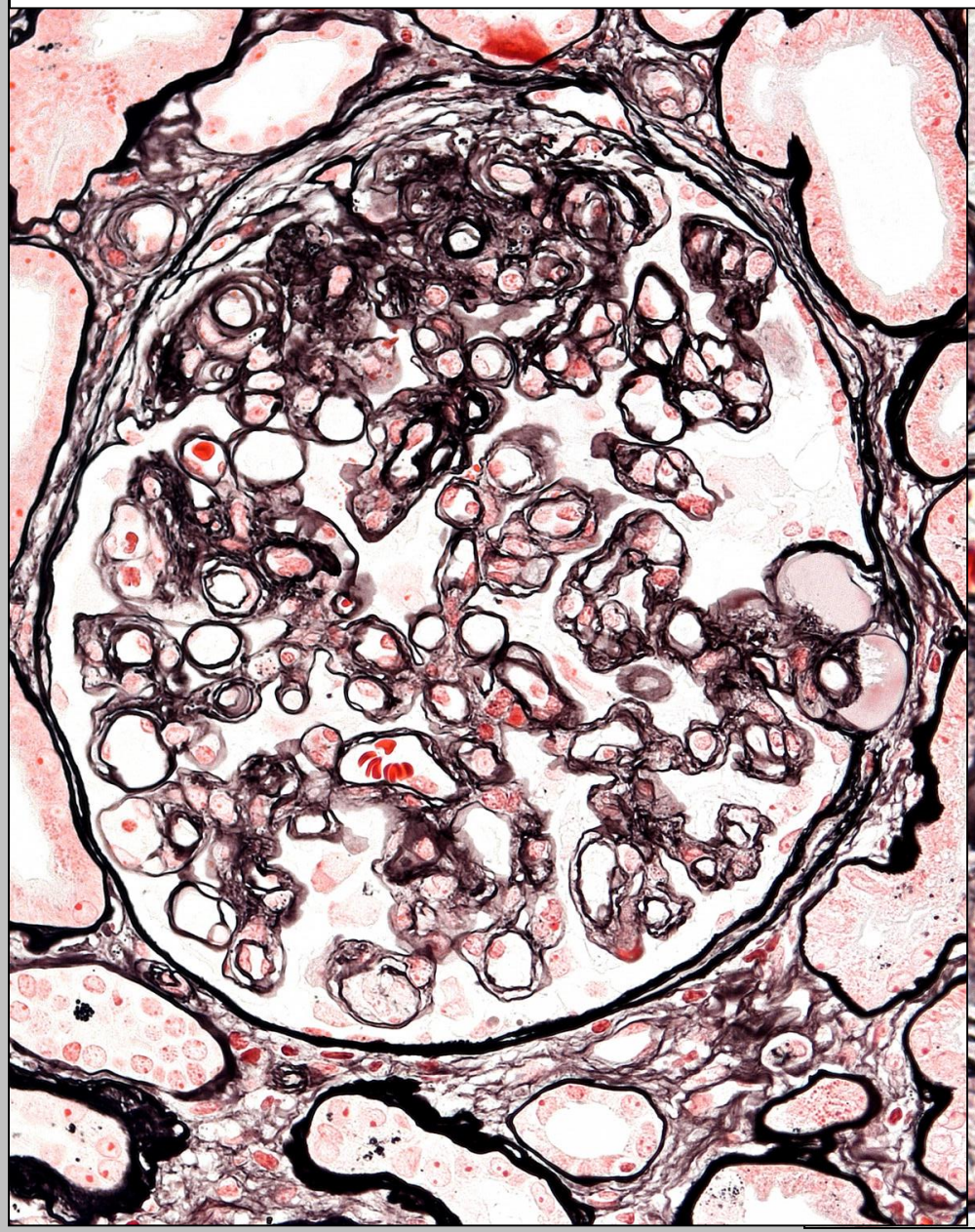
Banff 2017 Classification of Rejection

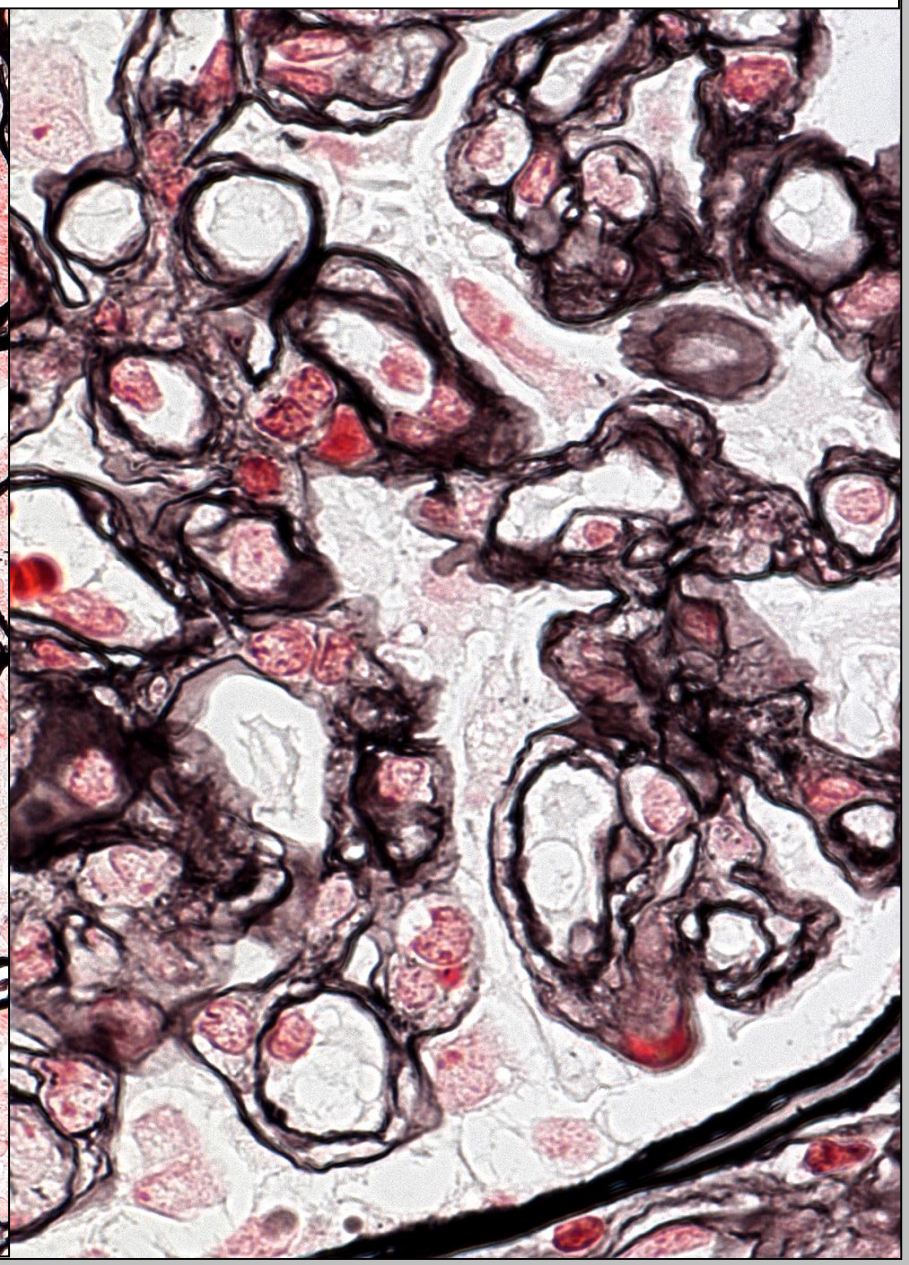
AJT 2018;18:293-307

T cell-mediated	Borderline	Antibody-mediated
Acute		Active
Chronic active		**Chronic active**

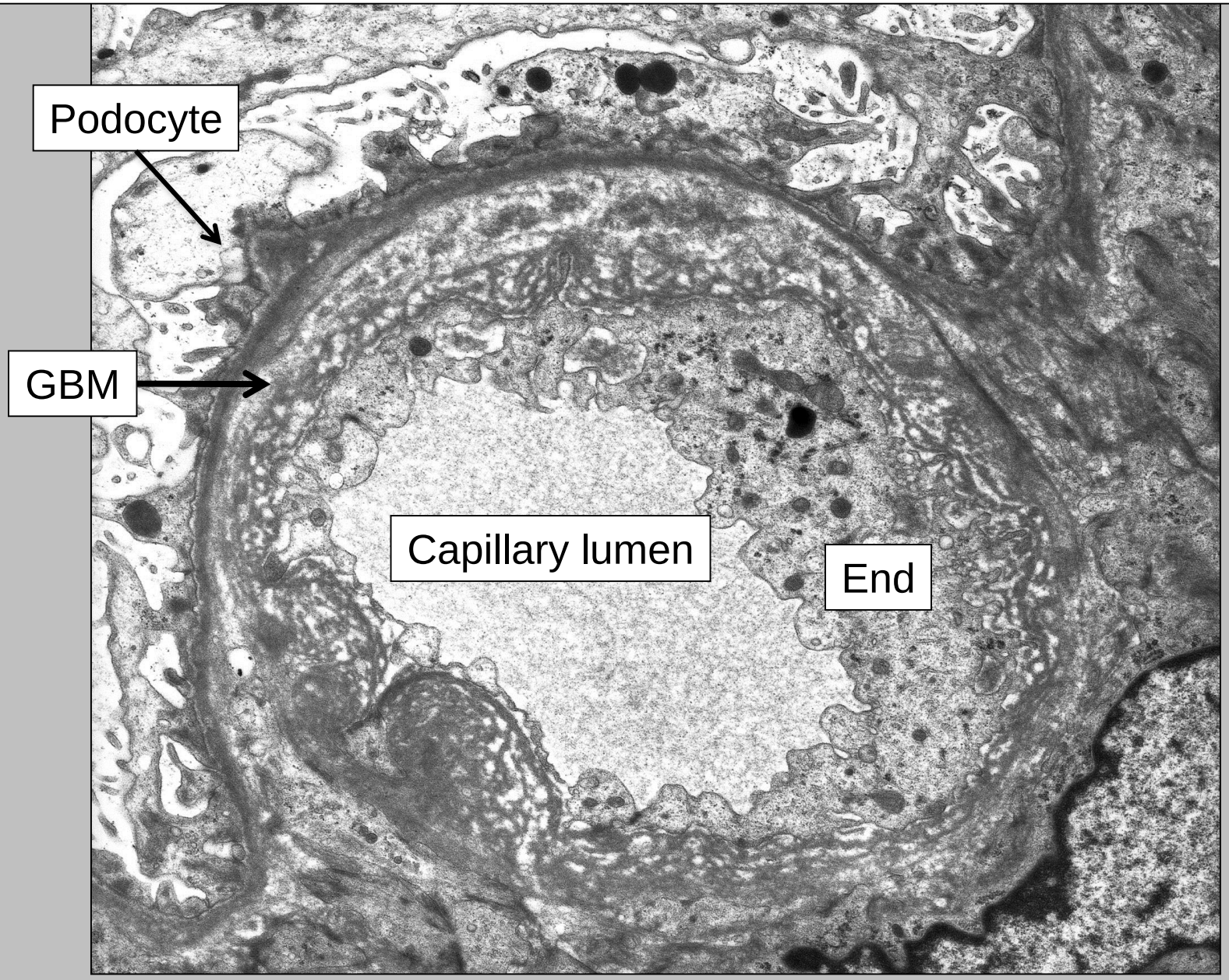
Chronic vascular injury is present (transplant glomerulopathy, PTCBM multilayering, new-onset arterial intimal fibrosis)

Transplant glomerulopathy (TG): diffusely double contoured loops – irreversible lesion

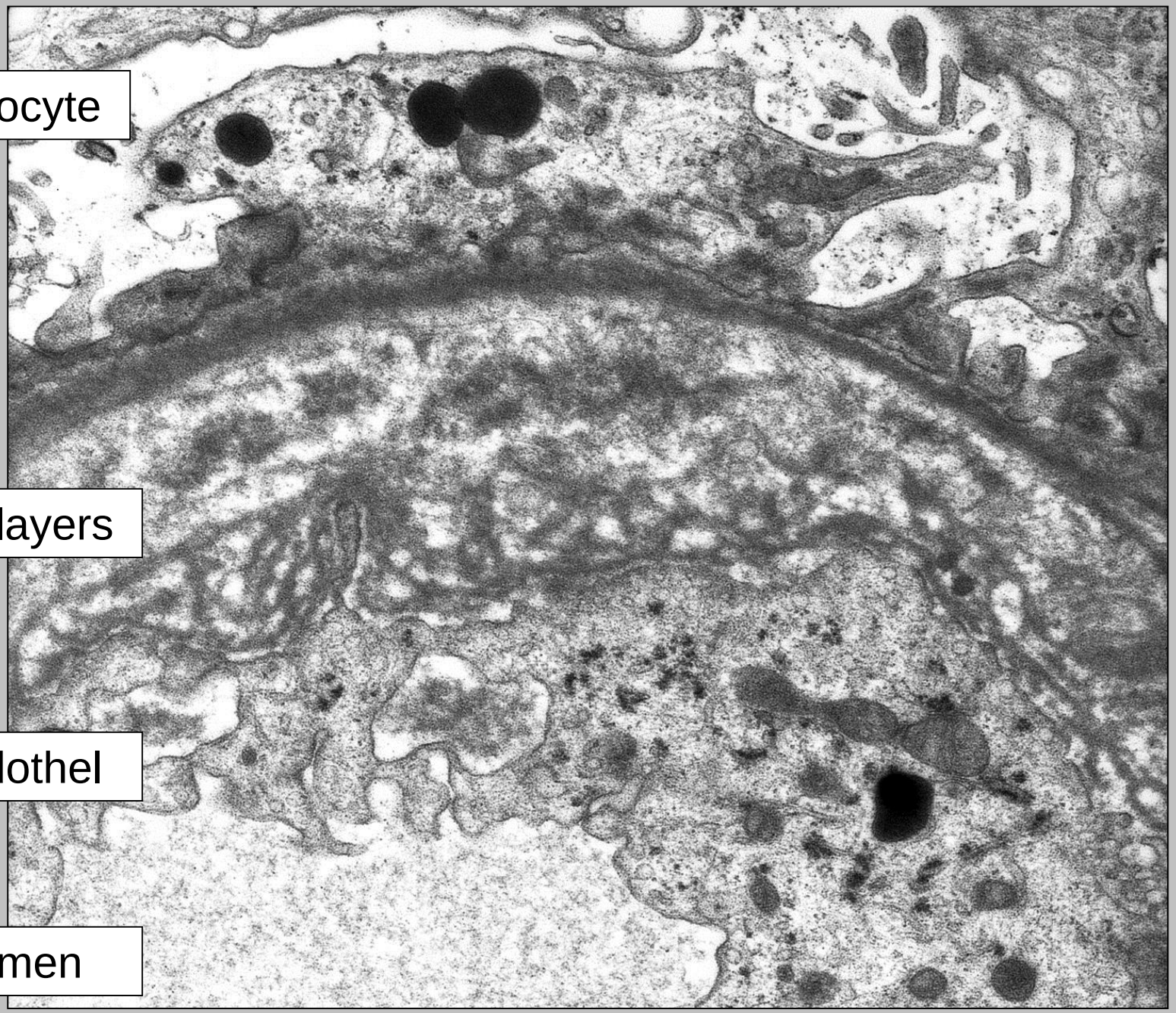




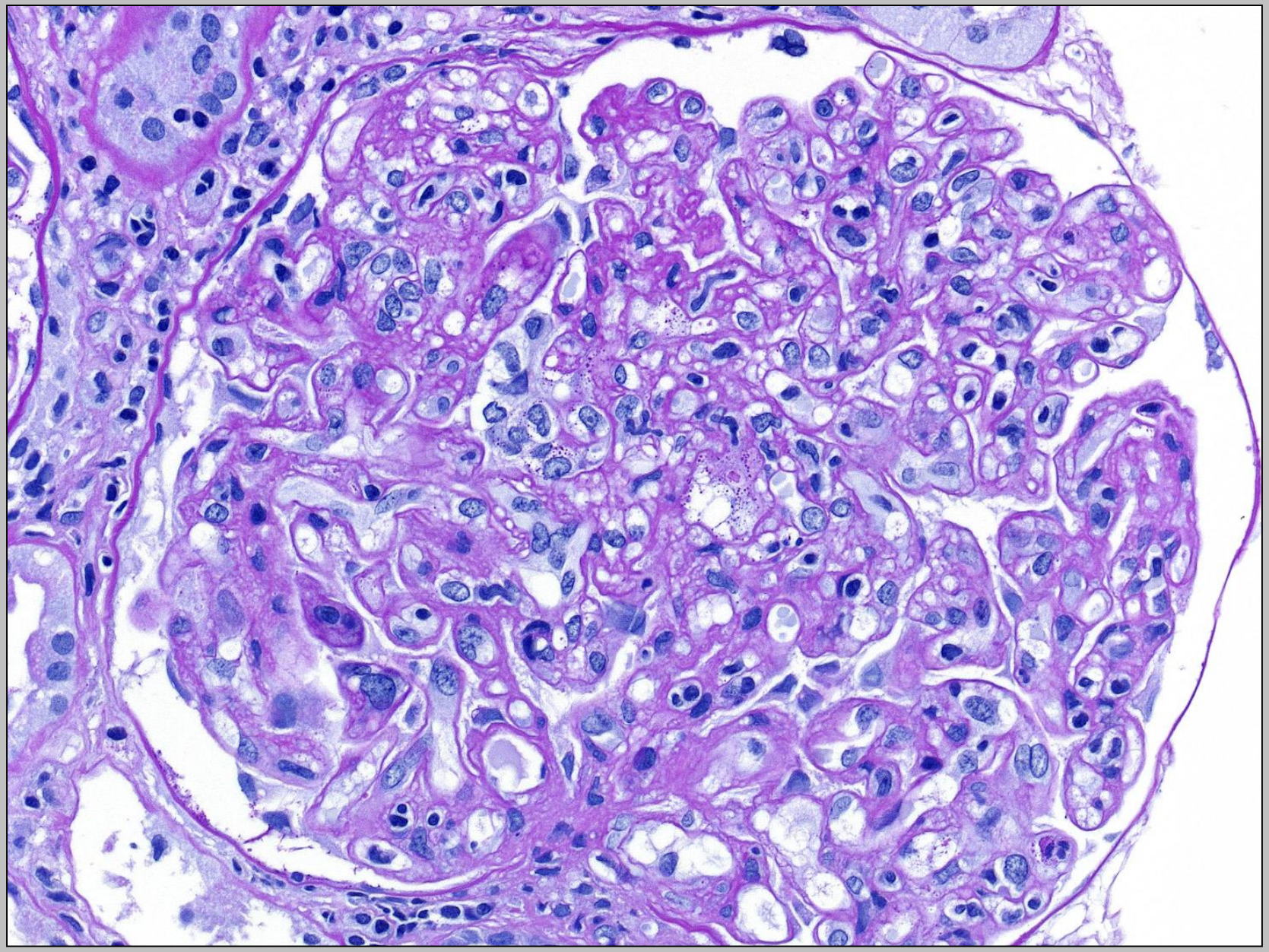
TG on EM: thickened endothelial layer, no fenestrae; several new BM layers



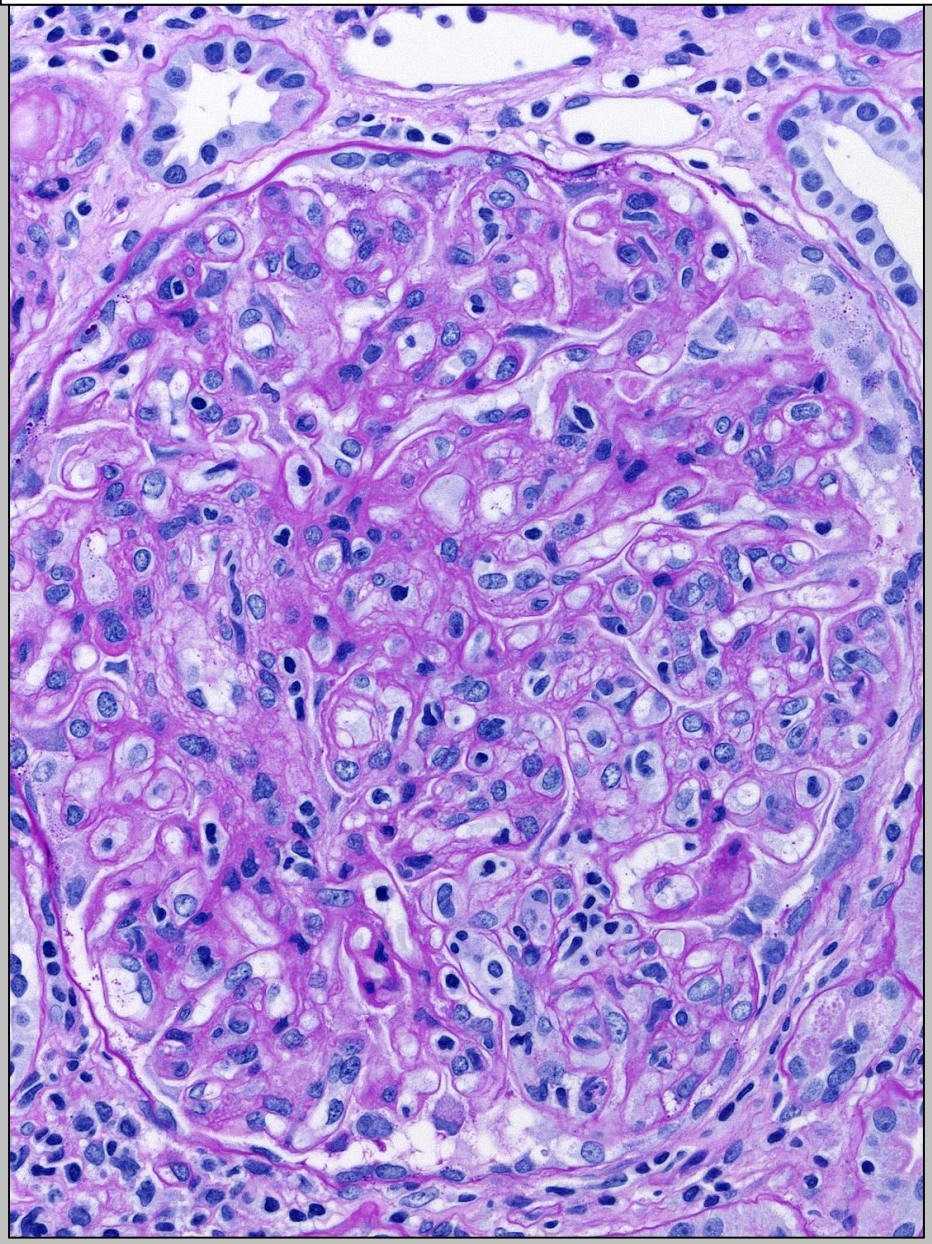
Transplant glomerulopathy at higher magnification

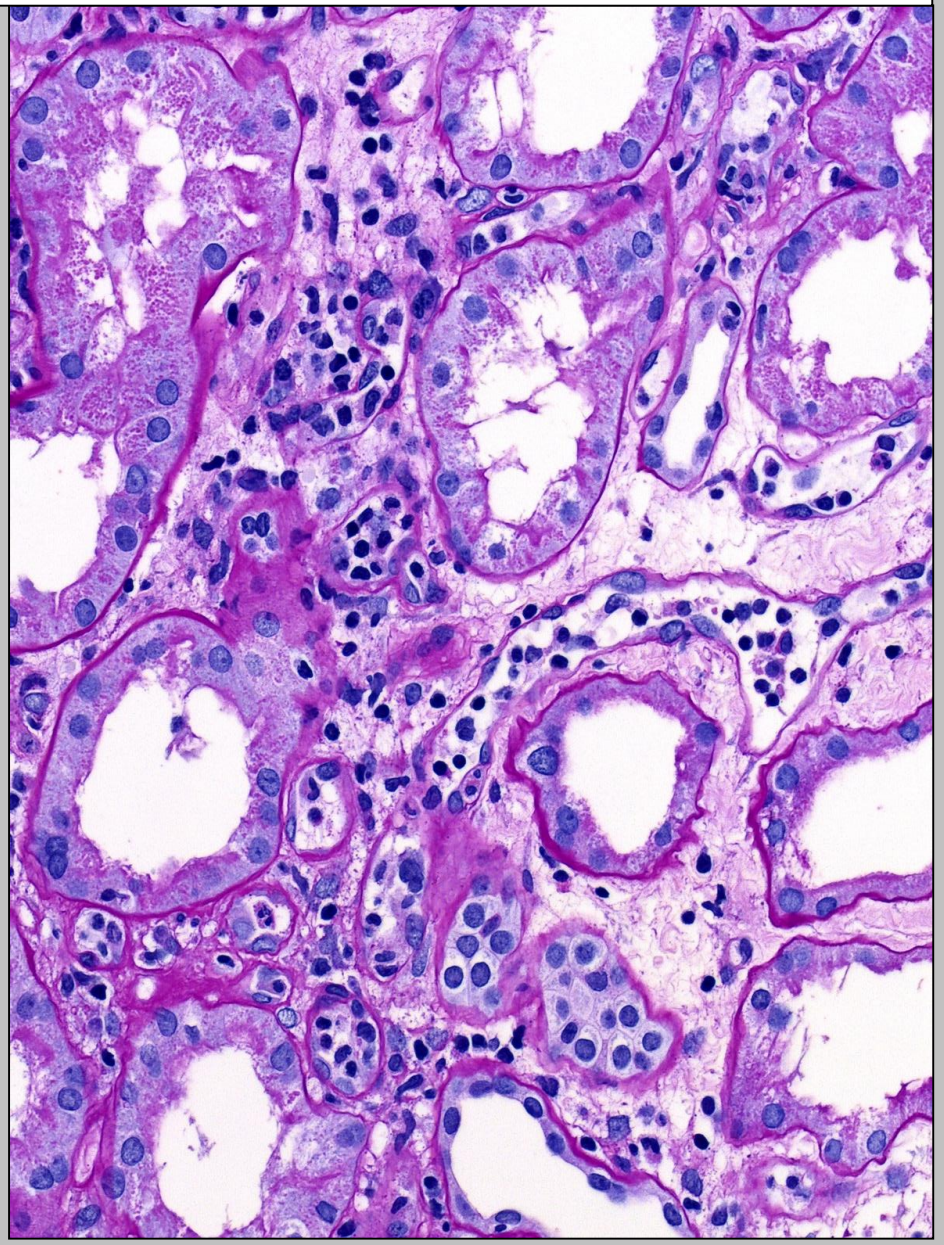


Diff. dg. of transplant glomerulopathy: recurrent or *de novo* proliferative GN; clue: no immune complexes on IF



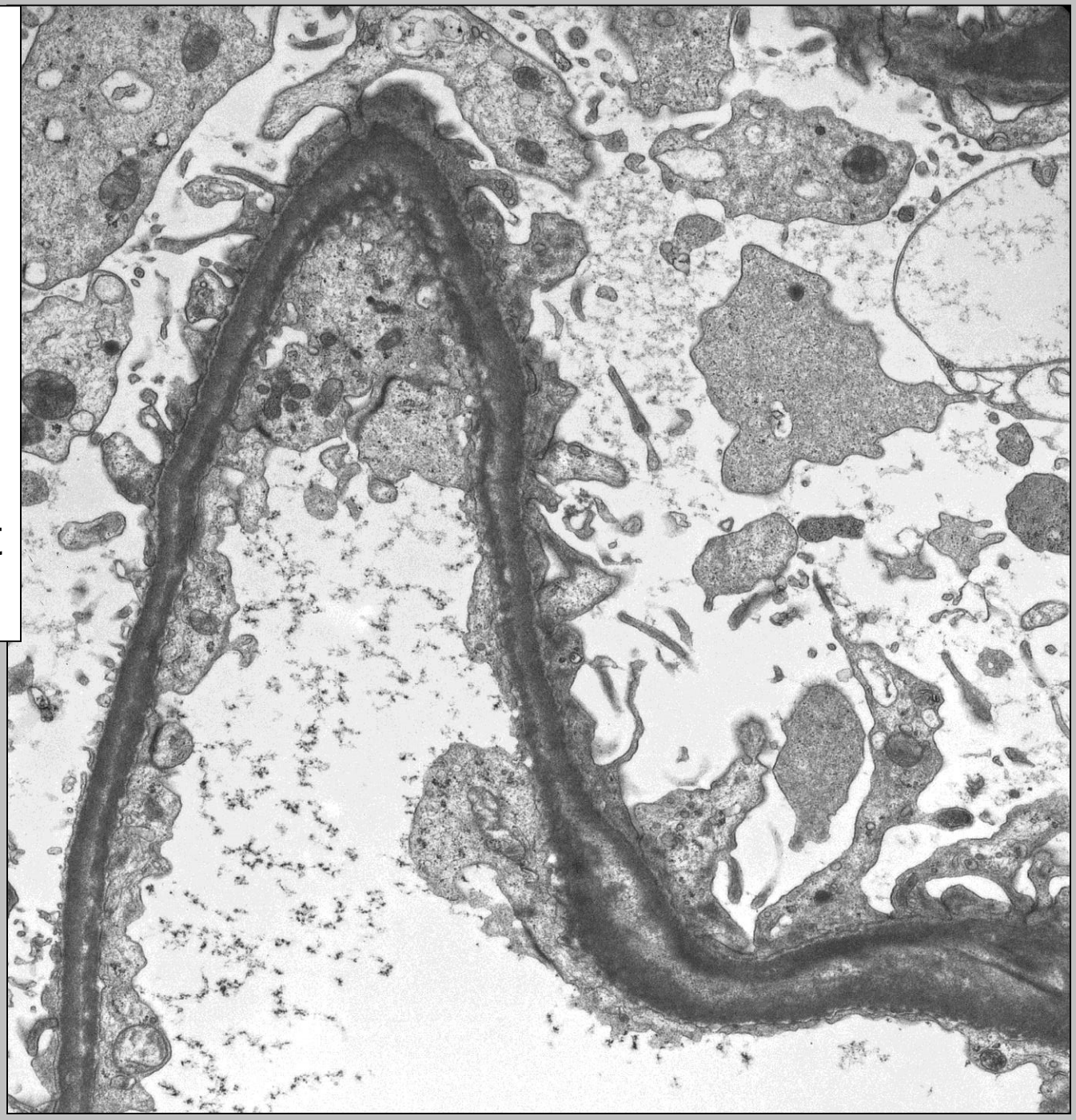
C4d+, TG, and at least moderate MVI (g+ ptc ≥2) indicate chronic active ABMR

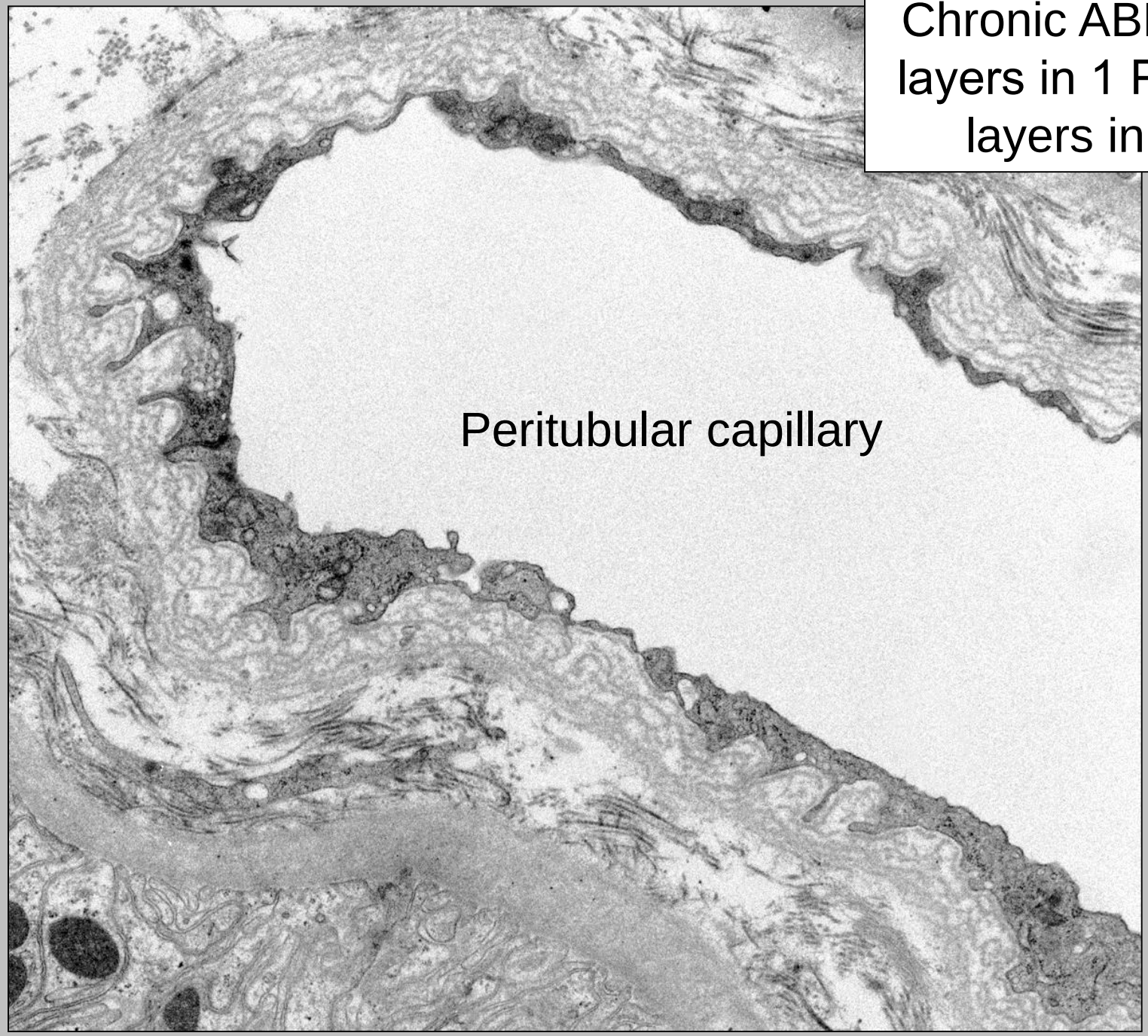




EM can provide evidence on chronic tissue injury:

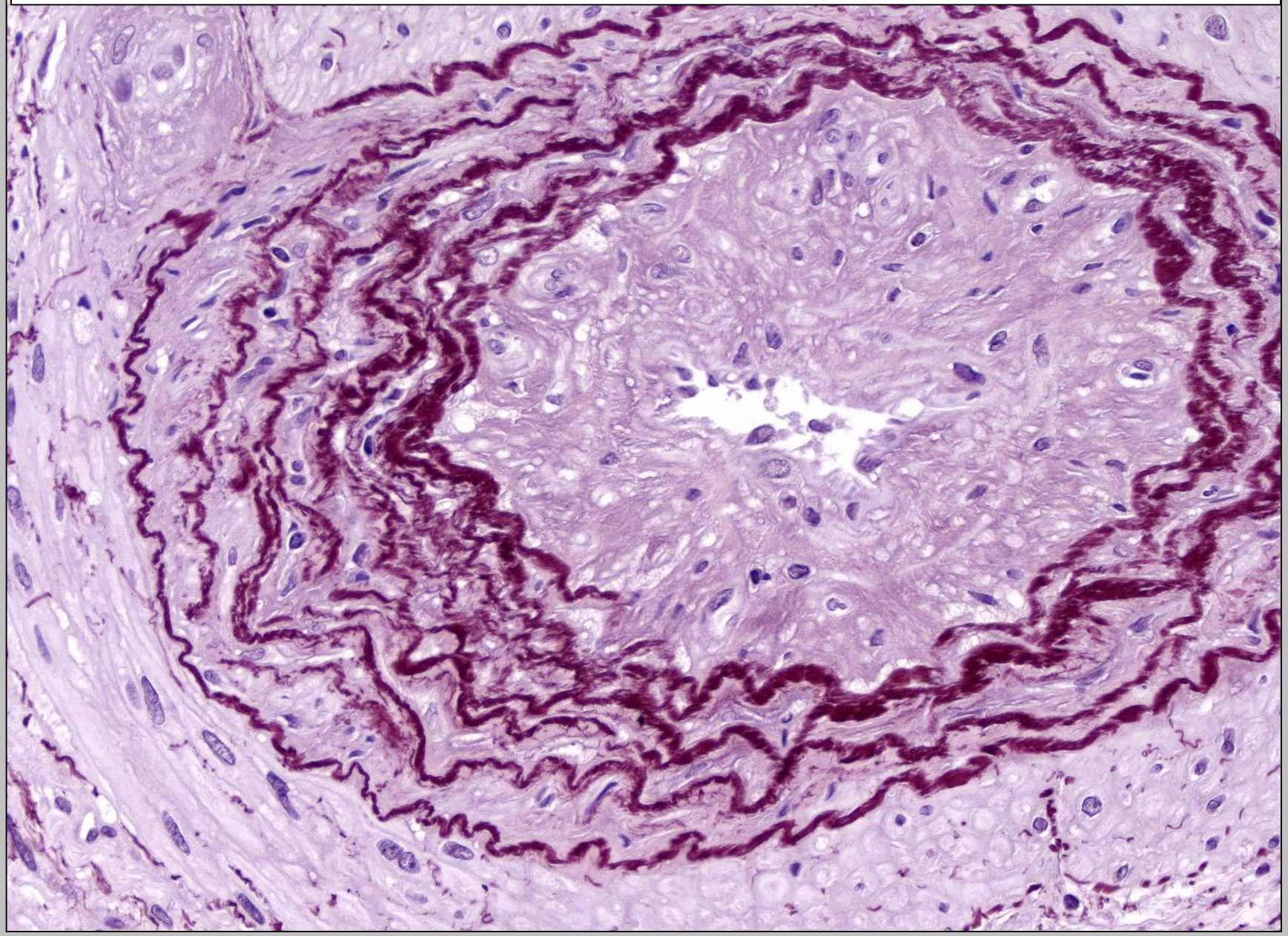
“Early TG”
LM is negative (Banff cg1a); doubled GBM in at least 3 capillaries



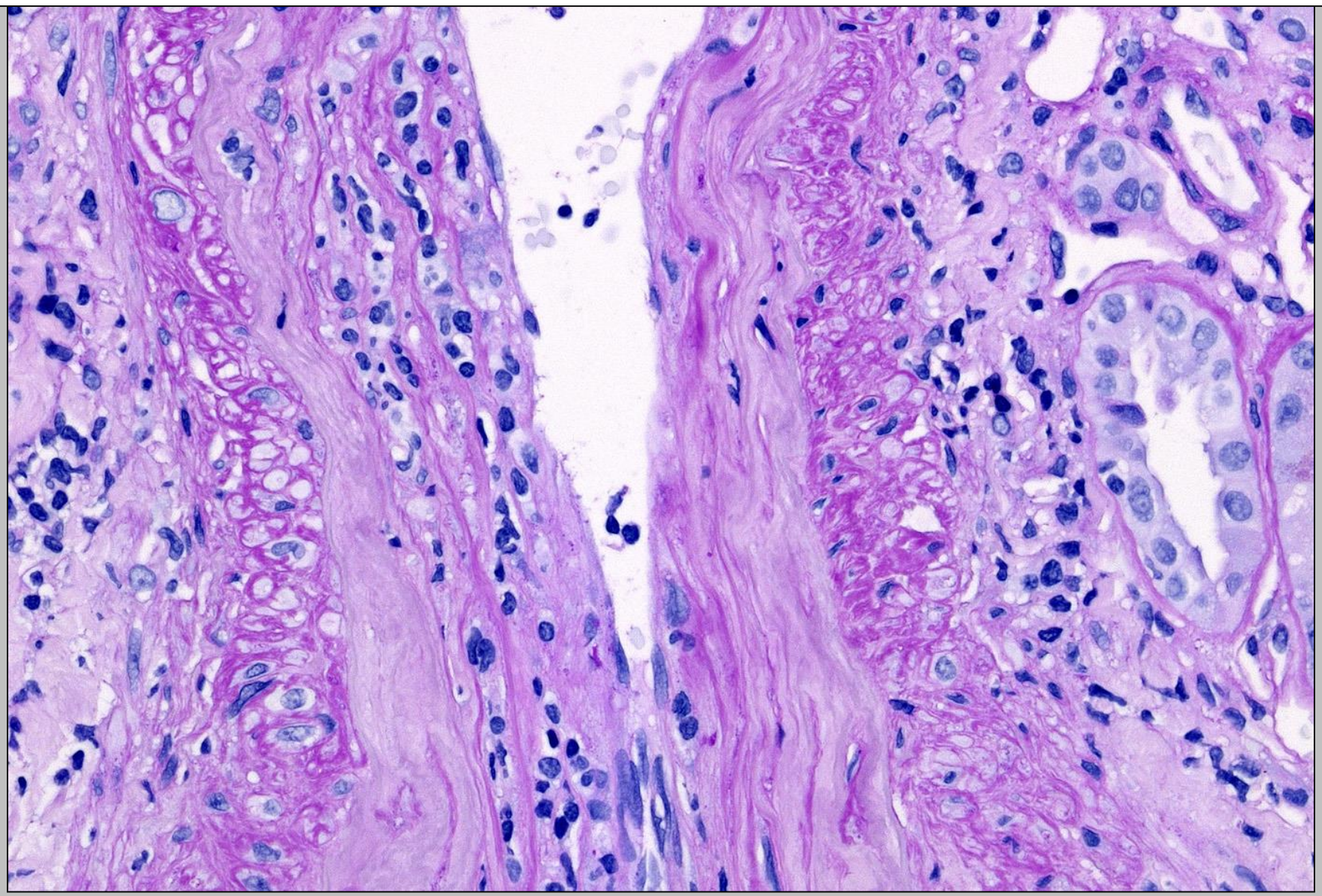


Chronic ABMR: ≥7 BM layers in 1 PTC and ≥5 layers in 2 PTCs

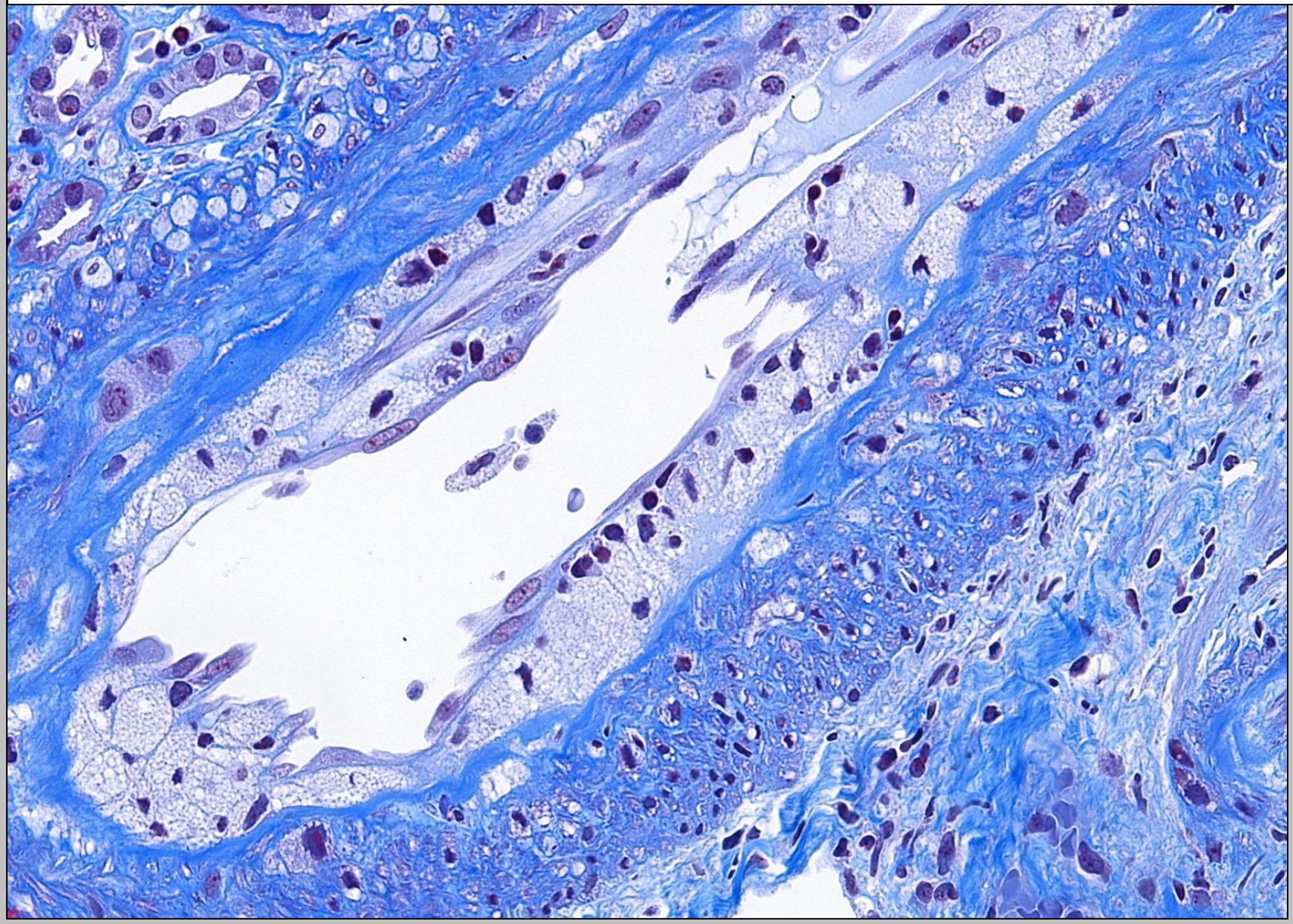
New-onset intimal fibrosis – less sensitive marker than the capillary BM lesions observed on EM



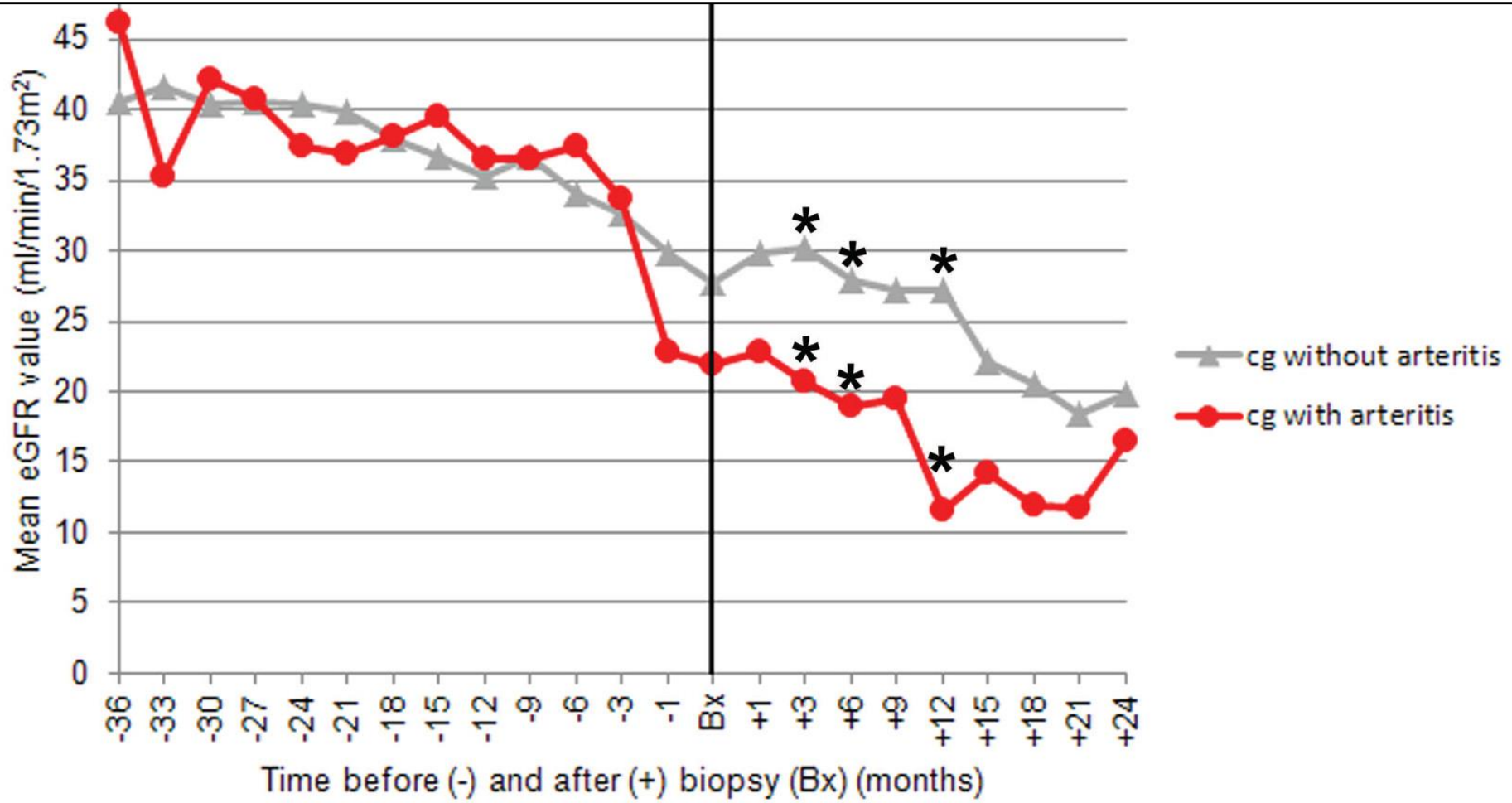
Active arteritis within the sclerotic intima can be present in cases with transplant glomerulopathy
- may be the feature of ABMR *per se* or mixed rejection



Intimal foamy macrophages are characteristic for chronic active ABMR

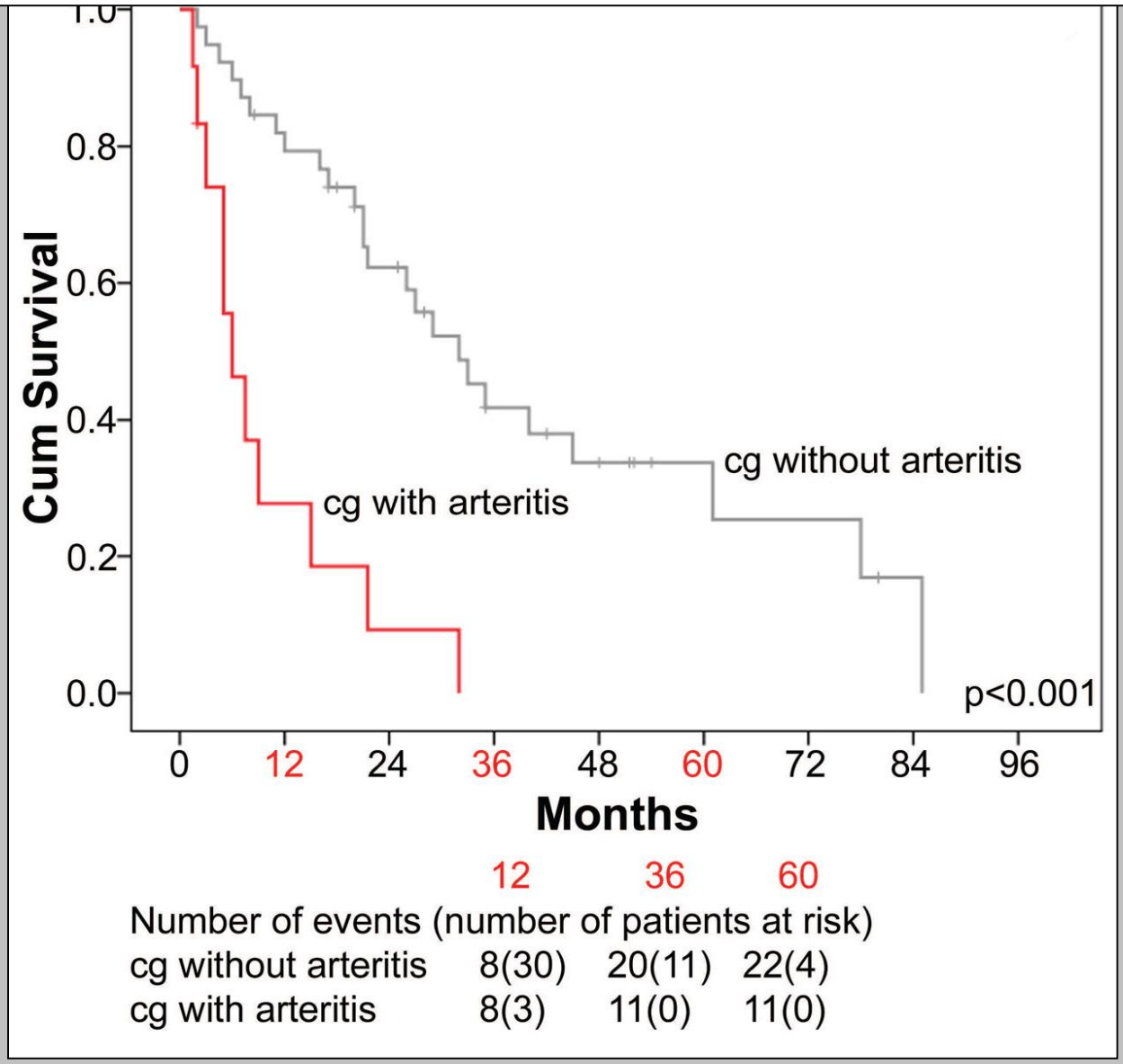


The renal function in transplant glomerulopathy with arteritis was significantly poorer than in that in transplant glomerulopathy without arteritis 3, 6 and 12 months post-biopsy



Dobi et al. Morphologic features and clinical impact of arteritis concurrent with transplant glomerulopathy. Pathol Oncol Res 2016, 22: 15-25

The graft survival in transplant glomerulopathy with arteritis was significantly poorer than in that in transplant glomerulopathy without arteritis



Biopsy lesions indicating acute TCMR

(three lesions are correct)

A. Interstitial inflammation involving more than 25% of nonsclerotic cortical parenchyma

B. Moderate or severe tubulitis

C. Arteritis

D. Linear C4d staining in peritubular capillaries

Biopsy lesions indicating active ABMR

(three lesions are correct)

A. Linear C4d staining in peritubular capillaries

B. At least moderate microvascular inflammation (glomerulitis and peritubular capillaritis ≥2)

C. Arteritis

D. Interstitial fibrosis and tubular atrophy

Biopsy lesions indicating chronic active ABMR

(three lesions are correct)

A. Transplant glomerulopathy

B. Linear C4d staining in peritubular capillaries

C. At least moderate microvascular inflammation (glomerulitis and peritubular capillaritis ≥2)

D. Moderate or severe tubulitis