Diagnosis of Acute and Chronic Antibody-Mediated Rejection: Banff Classification and Pathologic Correlates of Graft Survival

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1. Pathology of acute ABMR in kidney: histology, C4d, DSA, and the 2013 Banff classification

2. Pathology of chronic, active ABMR in kidney: transplant glomerulopathy, DSA, and the 2013 Banff classification

3. Pathologic factors influencing graft survival following treatment of active ABMR

Statement of Disclosure

Mark Haas serves as a paid consultant on pathology adjudication committees for two industry-sponsored clinical trials:

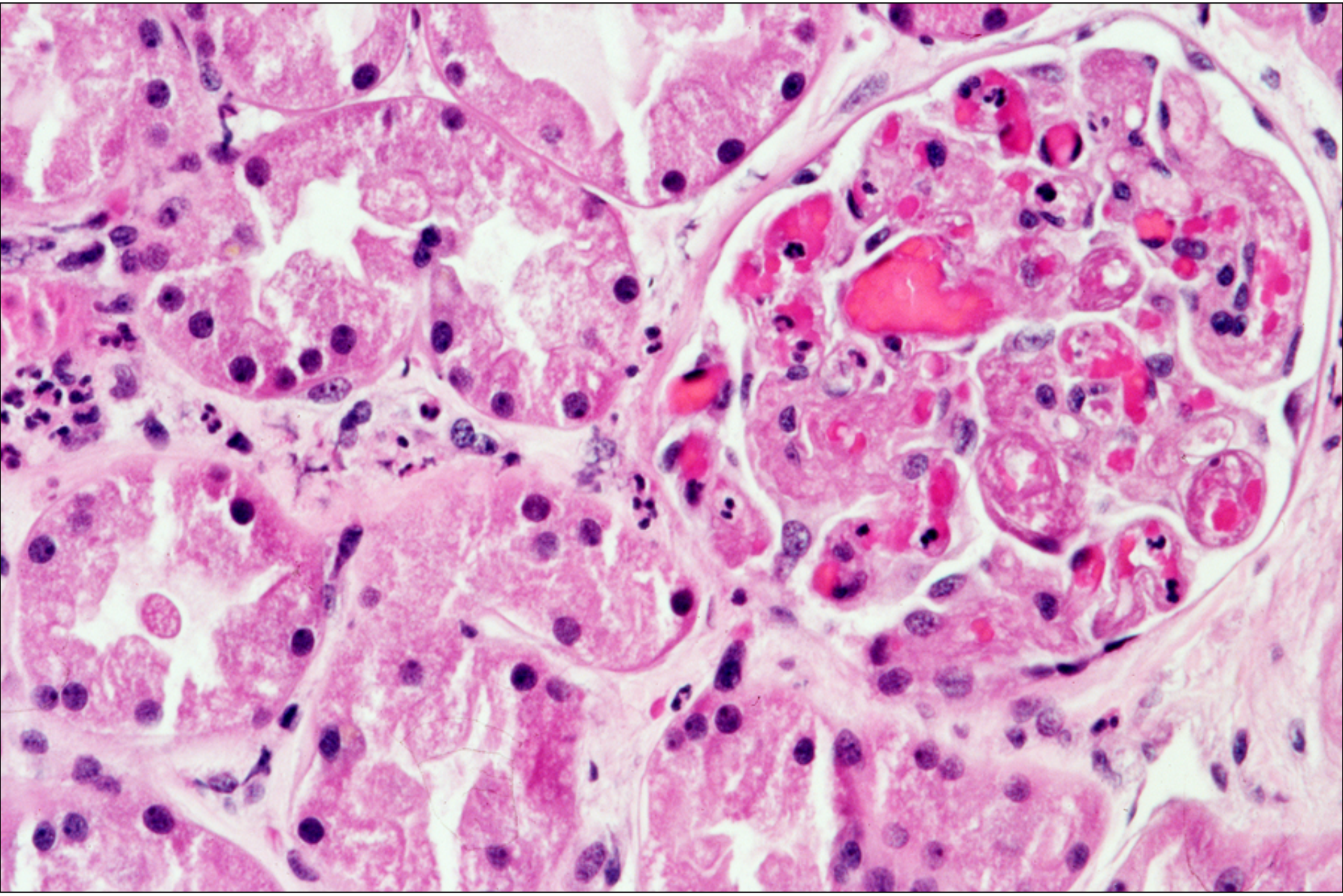
Shire ViroPharma – Treatment of Acute ABMR

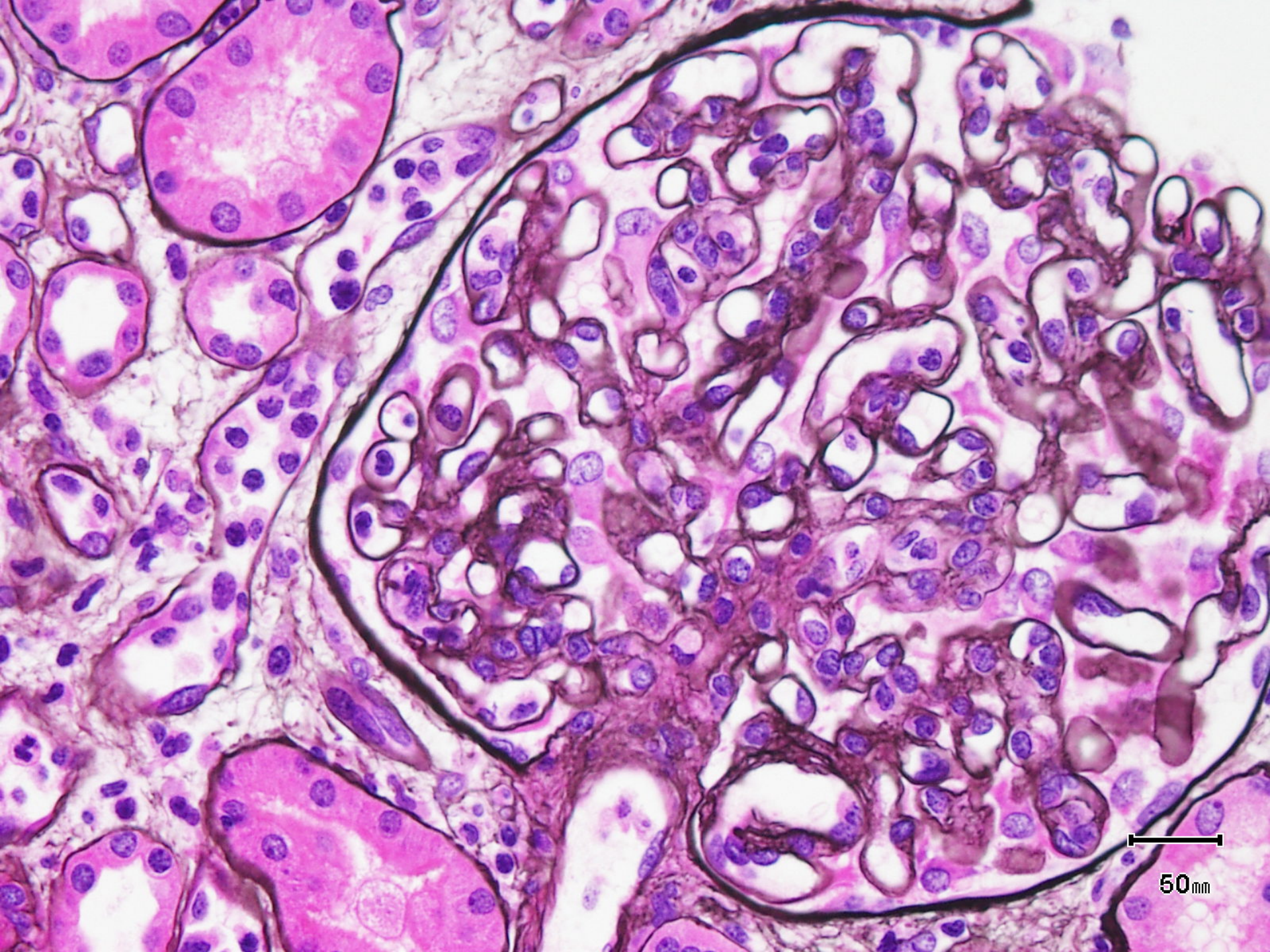
AstraZeneca – Treatment of Proliferative Lupus Nephritis

Neither represents a conflict of interest relevant to any of the material presented in this talk.

Histopathologic Features Associated with Antibody-Mediated Acute Rejection
(K. Trpkov et al., Transplantation 61: 1586-1592, 1996)

Finding	Ab+ Rejection	Ab- Rejection	P Value
Severe arteritis	10/24	0/20	**0.001**
Infarction	9/24	0/20	**0.002**
PMNs in PTC	11/24	1/20	**0.003**
Glomerulitis	11/24	2/20	**0.01**
Fibrin thrombi (glom and vasc)	11/24	3/20	0.05
Dilation of PTC	8/24	2/20	0.08
PMNs in glomeruli	7/24	3/20	NS
Moderate or severe tubulitis	12/24	19/20	**0.002**

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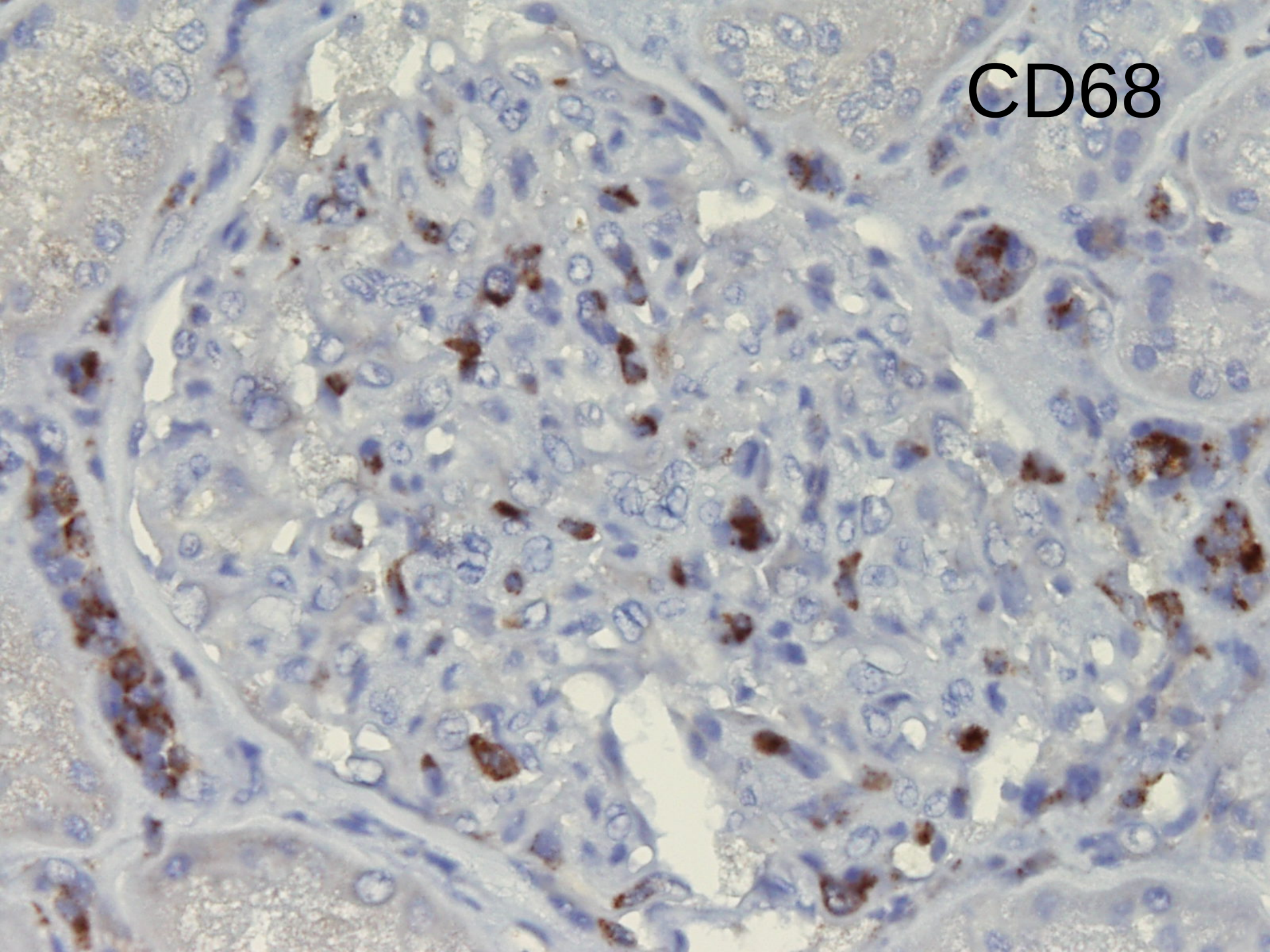
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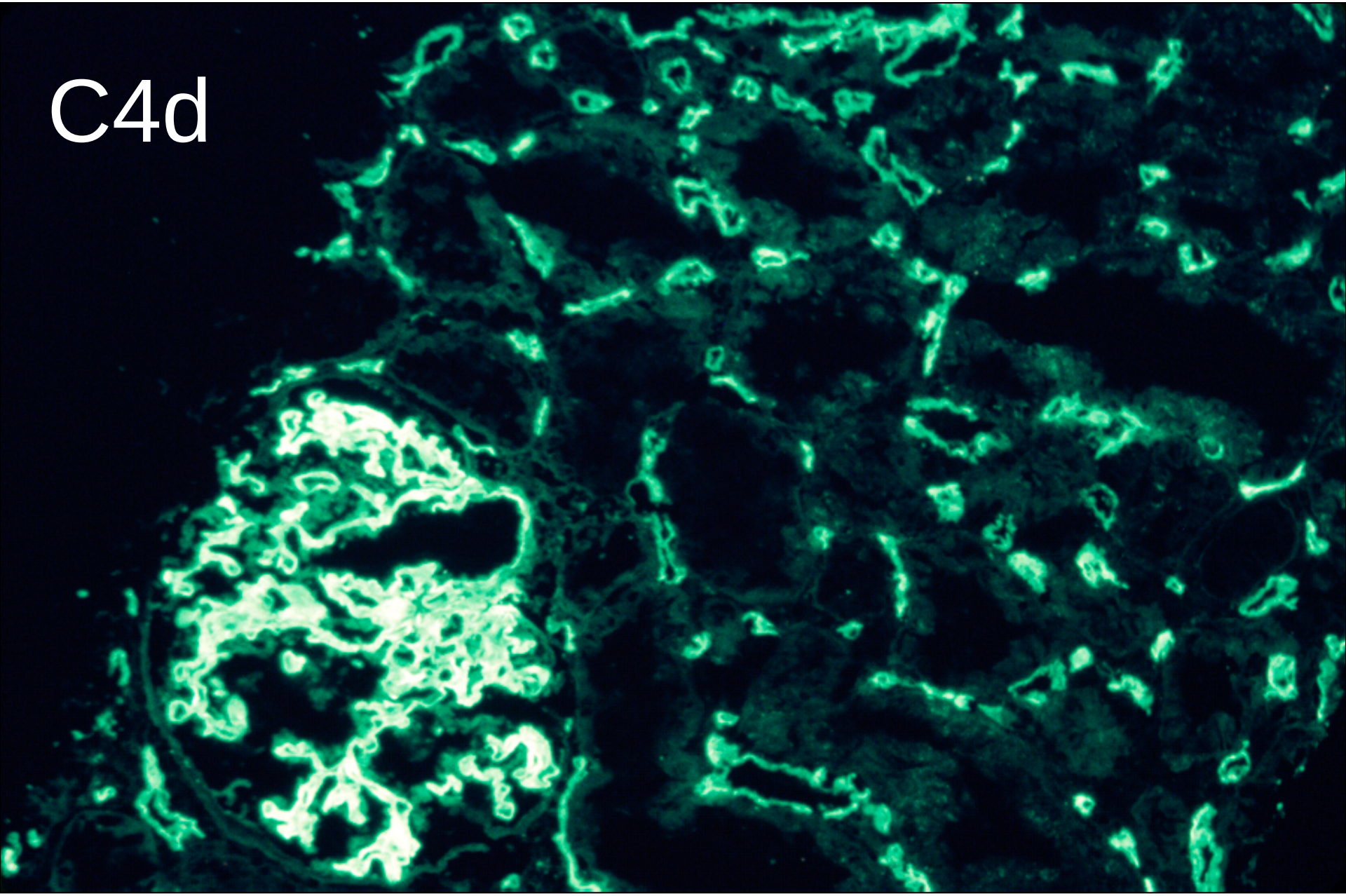

C4d

C4d and Early Graft Loss

(H.E. Feucht et al, Kidney Int 43: 1333-8, 1993)

- 93 renal allografts biopsied for early dysfunction (mean 11 days post-transplant)
- 43 biopsies – diffuse PTC C4d
  - 18 graft losses in 1st year (58% graft survival)
- 8 biopsies – focal PTC C4d
  - 3 graft losses in 1st year (63% graft survival)
- 42 biopsies – C4d negative in PTC
  - 4 graft losses in 1st year (90% graft survival)
- 3/4 cases of graft loss in C4d- group were C4d+ on a later biopsy
- C4d+ associated with re-transplant, elevated PRA

C4d Staining in Renal Allografts: correlation with donor-specific Ab

- Collins et al, JASN 10: 2208-14, 1999
  100% of AR with +DSA were C4d+
  No C4d in DSA- AR, CSA toxicity
- Maueyyedi et al, JASN 13: 779-787, 2002
  30% of early AR C4d+ - 90% had anti-donor antibody
  2 morphologic subtypes of AMR - capillary, arterial
  Arterial (fibrinoid necrosis) had worse outcome
- Bohmig et al, JASN 13: 1091-9, 2002
  21/24 C4d+ cases had DSA by flow cytometric XM
  50% of C4d- biopsies had DSA
  93% specificity, 31% sensitivity (IHC on paraffin sections)

Diagnostic Criteria for Acute AMR in Renal Allograft Biopsies

(L.C. Racusen et al, Am J Transplant 3: 1-7, 2003)

1. Morphologic evidence
    a. Neutrophils and/or monocytes/macrophages in PTC and/or glomeruli (peritubular capillaritis; glomerulitis)
    b. Arterial fibrinoid necrosis
    c. Thrombi in glomerular capillaries, arterioles, and/or small arteries
    d. Acute tubular injury, without other apparent causes
2. Immunohistologic evidence
    a. Diffuse C4d in PTC
    b. Immunoglobulin and/or complement in arterial fibrinoid necrosis
3. Serologic evidence
    a. Circulating antibodies to donor HLA or other specific anti-donor antibodies at the time of biopsy

Loupy et al (Paris), Am J Transplant 9: 2561-2570, 2009

Compared clinical, pathologic parameters in DSA-positive renal transplant recipients at 1 year post-transplant based on findings on a 3-month protocol biopsy :

Subclinical ABMR (14 patients)
C4d+ with glomerulitis and/or PTC WBC margination

Suspicious but not diagnostic (22 patients)
C4d- with glomerulitis and/or PTC WBC margination

No ABMR (9 patients)
C4d-, no glomerulitis or PTC WBC margination

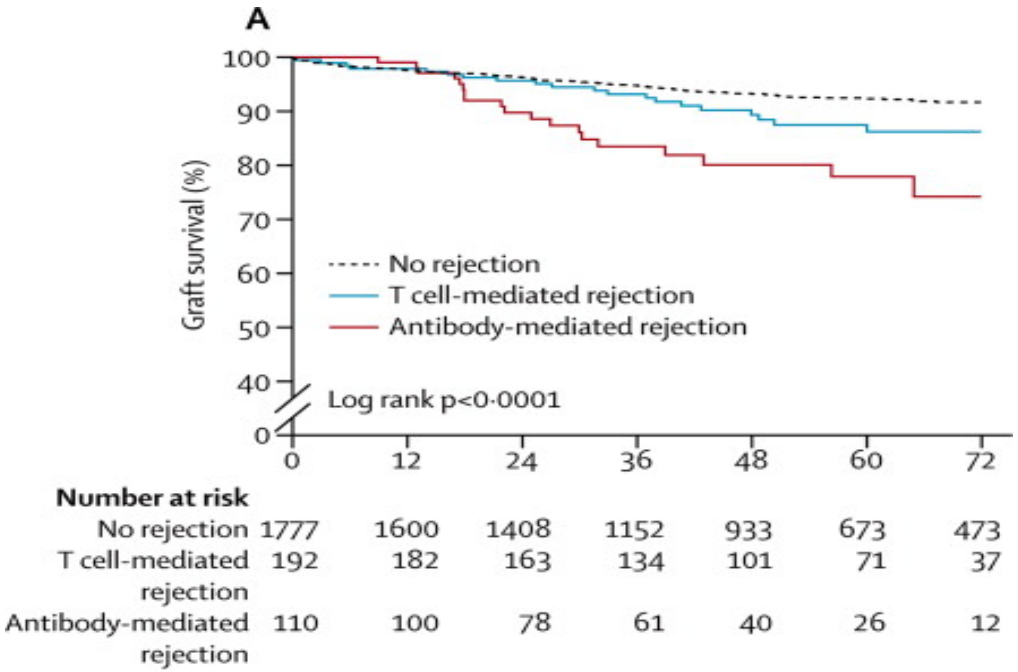
Loupy et al (Paris), Am J Transplant 9: 2561-2570, 2009

Findings 1 year post-transplantation:

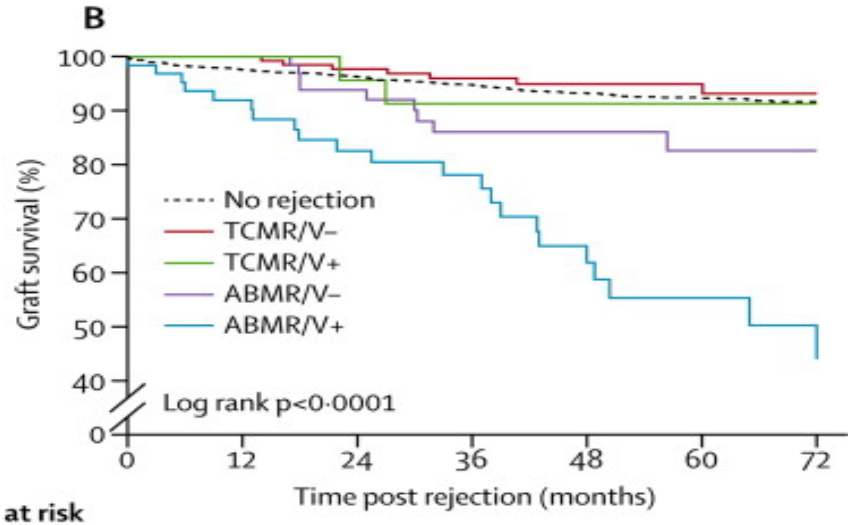
SC ABMR (14): Mean GFR 39 +/- 14
(C4d+, g/ptc+) 100% with TA/IF (ci + ct >0)
43% with transplant glomerulopathy

"Suspicious" (22): Mean GFR 46 +/- 18
(C4d-, g/ptc+) 77% with TA/IF
18% with transpl. glomerulopathy

No ABMR (9): Mean GFR 62 +/- 19
(C4d-, g/ptc-) 33% with TA/IF
0% with transplant glomerulopathy



Number at risk							
No rejection	1777	1600	1408	1152	933	673	473
T cell-mediated rejection	192	182	163	134	101	71	37
Antibody-mediated rejection	110	100	78	61	40	26	12



Number at risk							
No rejection	1777	1600	1408	1152	933	673	473
TCMR/V–	139	136	121	101	77	54	29
TCMR/V+	26	26	23	20	15	12	4
ABMR/V–	73	68	56	42	28	19	7
ABMR/V+	64	52	41	32	21	12	9

Lefaucheur et al (Paris), Lancet 381: 313-9, 2013

Banff 2013 Classification of Antibody-Mediated Rejection (ABMR) in Renal Allografts

Acute/Active ABMR; all 3 features must be present for diagnosis[a]

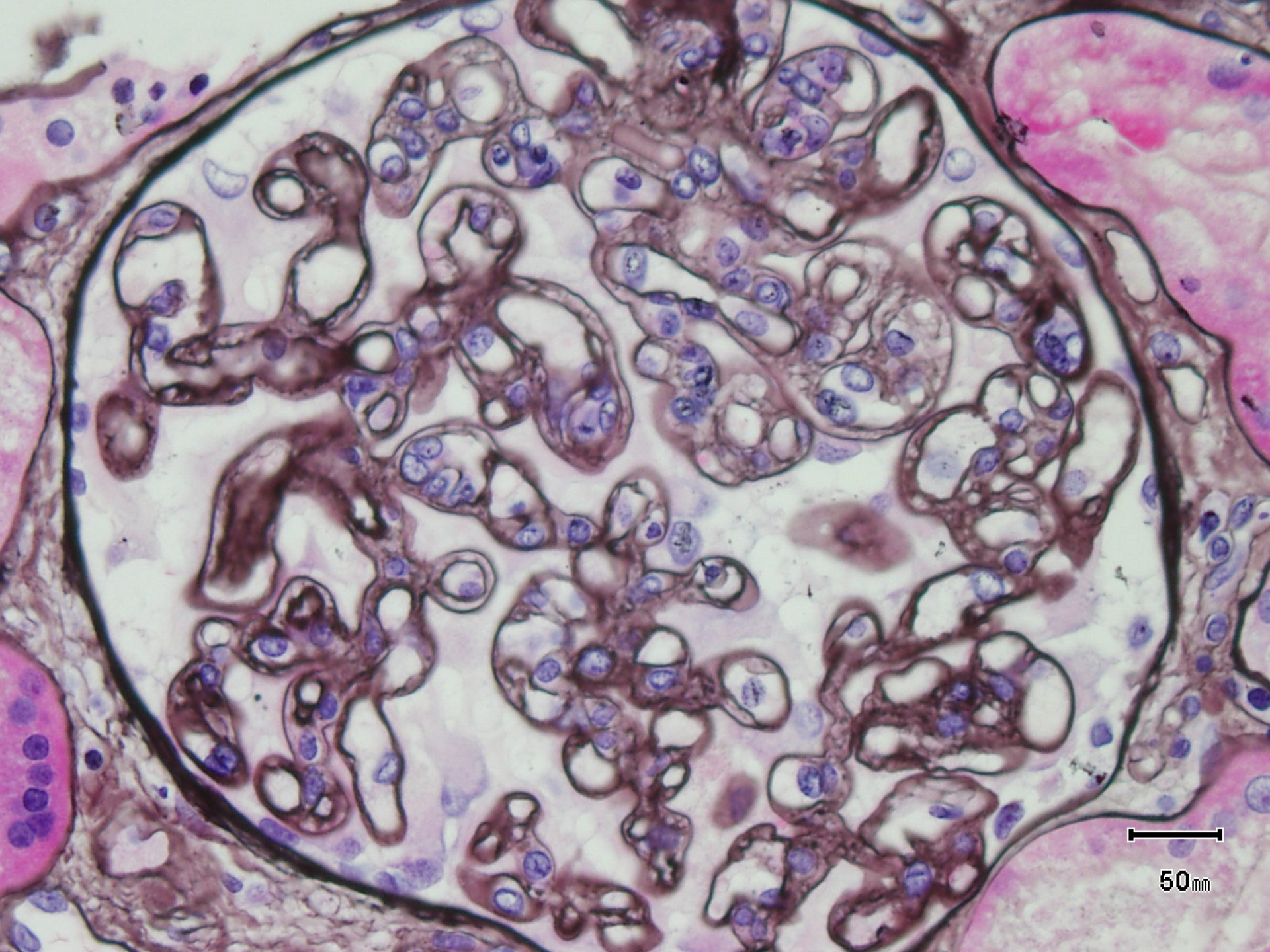
1. Histologic evidence of acute tissue injury, *including one or more of the following*:
   - Microvascular inflammation (g > 0[b] and/or ptc > 0)
   - Intimal or transmural arteritis (v > 0)[c]
   - Acute thrombotic microangiopathy, in the absence of any other cause
   - Acute tubular injury, in the absence of any other apparent cause
2. Evidence of current/recent antibody interaction with vascular endothelium, *including at least one of the following*:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation ([g + ptc] ≥2)[d]
   - Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, *if thoroughly validated*
3. Serologic evidence of donor-specific antibodies (HLA or other antigens)

[a] These lesions may be clinically acute, smoldering, or subclinical. Biopsies showing two of the 3 features may be designated as "suspicious" for acute/active ABMR.

[b] Recurrent/de novo glomerulonephritis should be excluded

[c] These lesions may be indicated of ABMR, TCMR, or mixed ABMR/TCMR

[d] In the presence acute T cell-mediated rejection, borderline infiltrates, or evidence of infection, ptc ≥2 alone is not sufficient to define moderate microvascular inflammation and g must be ≥1.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Different Etiologies of Transplant Glomerulopathy

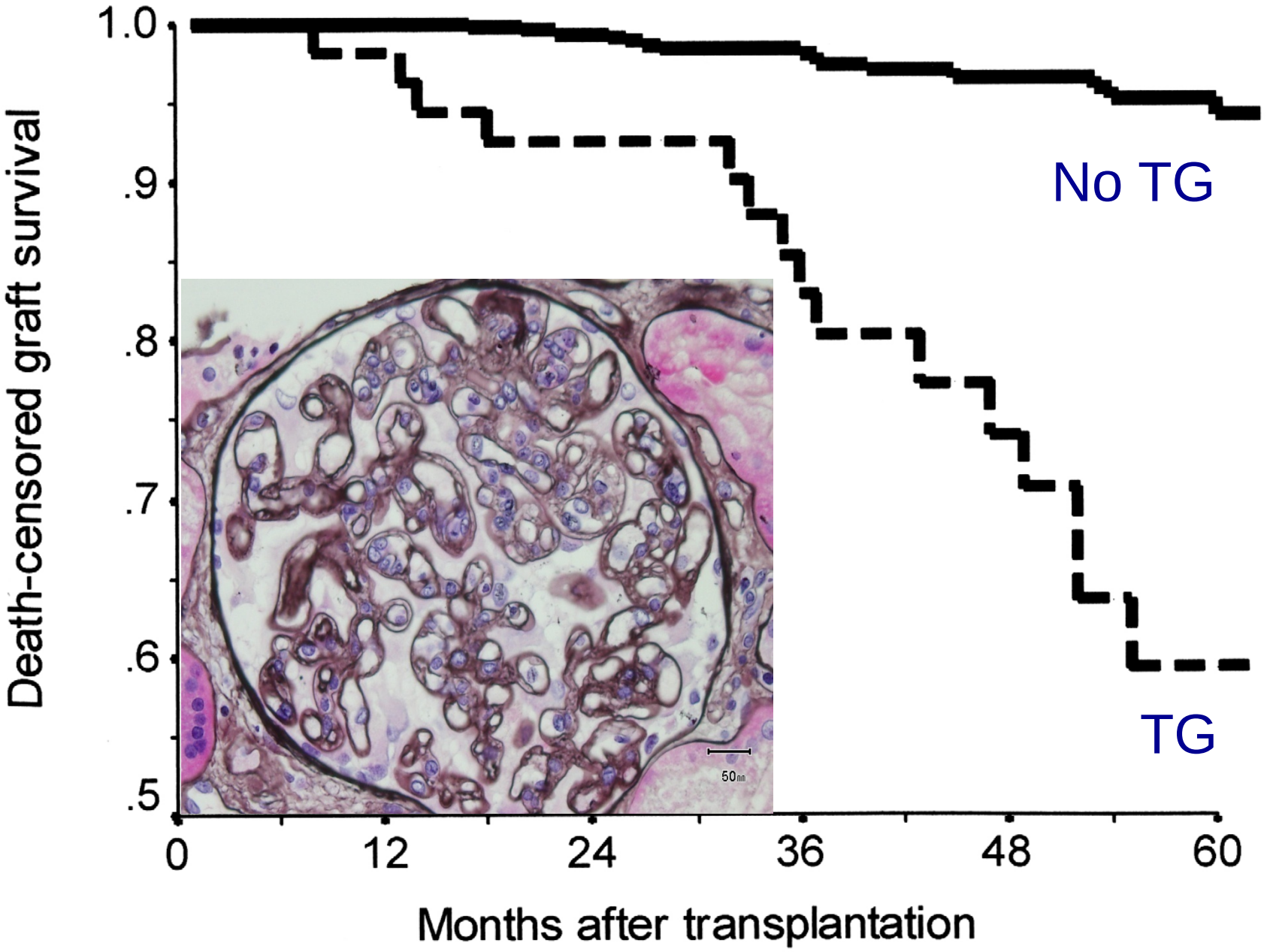
1. Chronic/Persistent Antibody-Mediated Rejection
   (73% of for-cause biopsies with TG at mean of 5.5 yrs post-transplant were C4d+, had concurrent DSA, or both;
   Sis et al, AJT 7: 1743-1752, 2007)

2. Hepatitis C
   - Need to differentiate from recurrent or de novo MPGN, using IF and/or EM
   - Possibly related to TMA associated with anti-cardiolipin antibodies

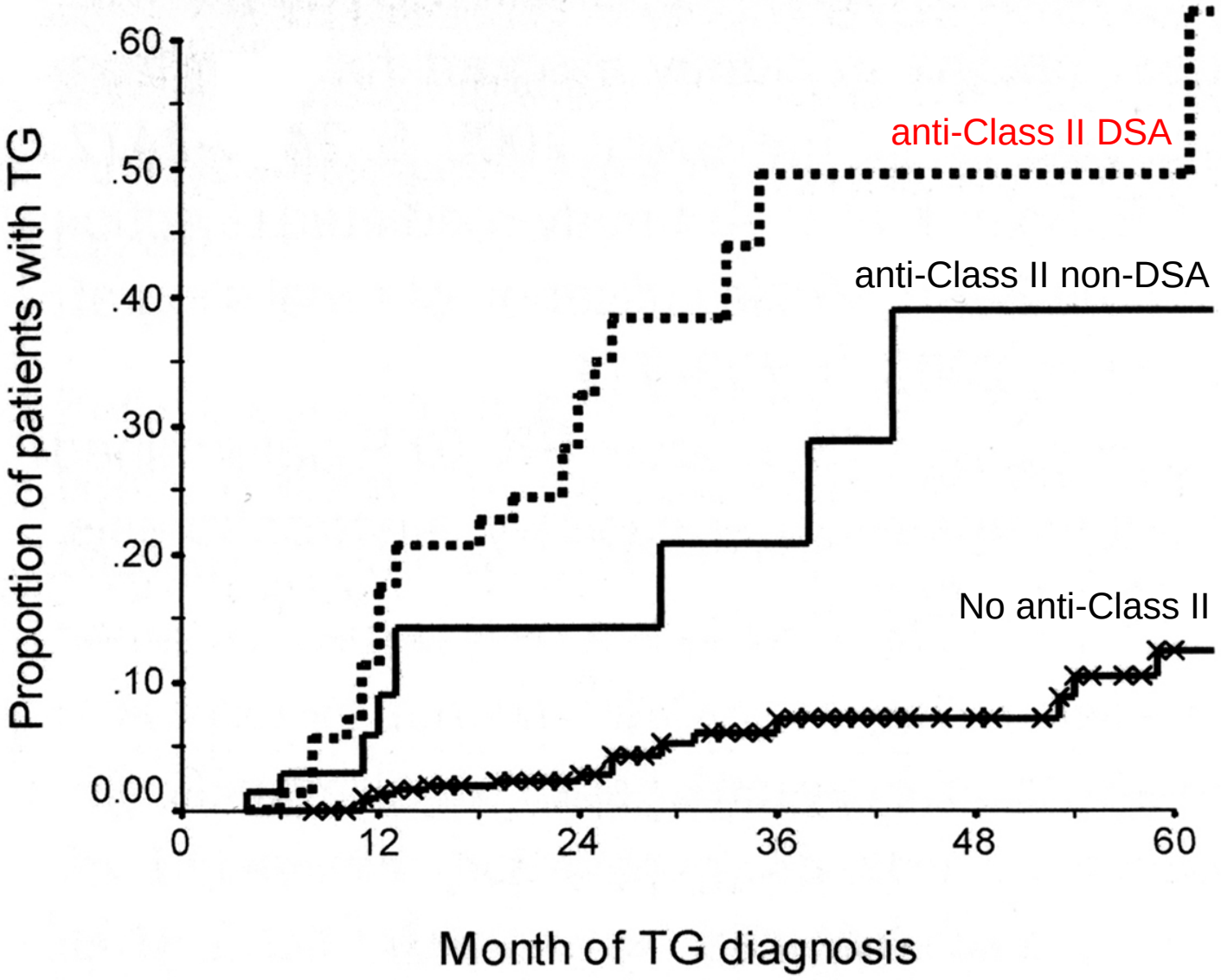
3. Other forms of TMA

4. Cell-Mediated Rejection?

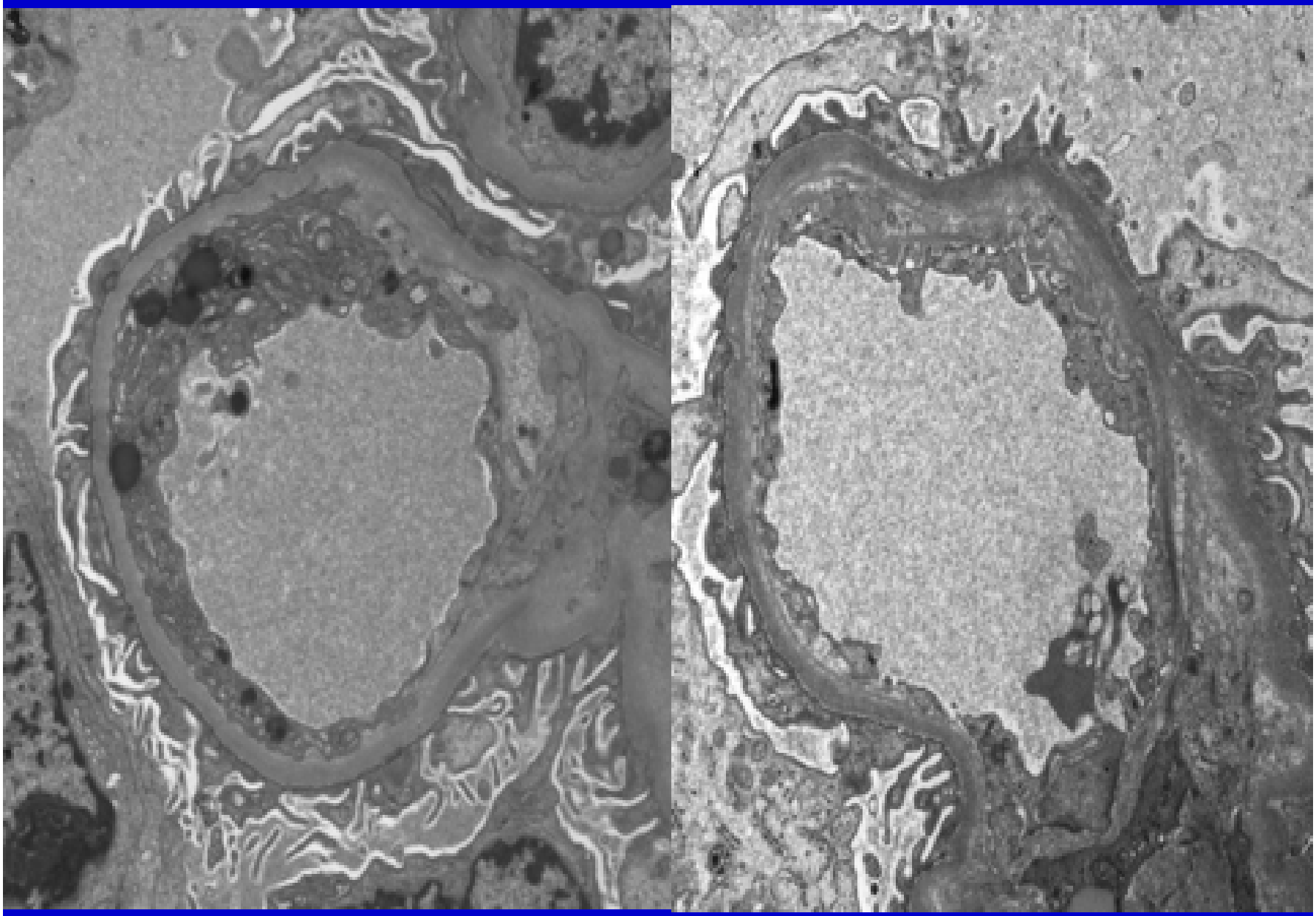
ref: Baid-Agrawal et al, Kidney Int. 80: 879-885, 2011



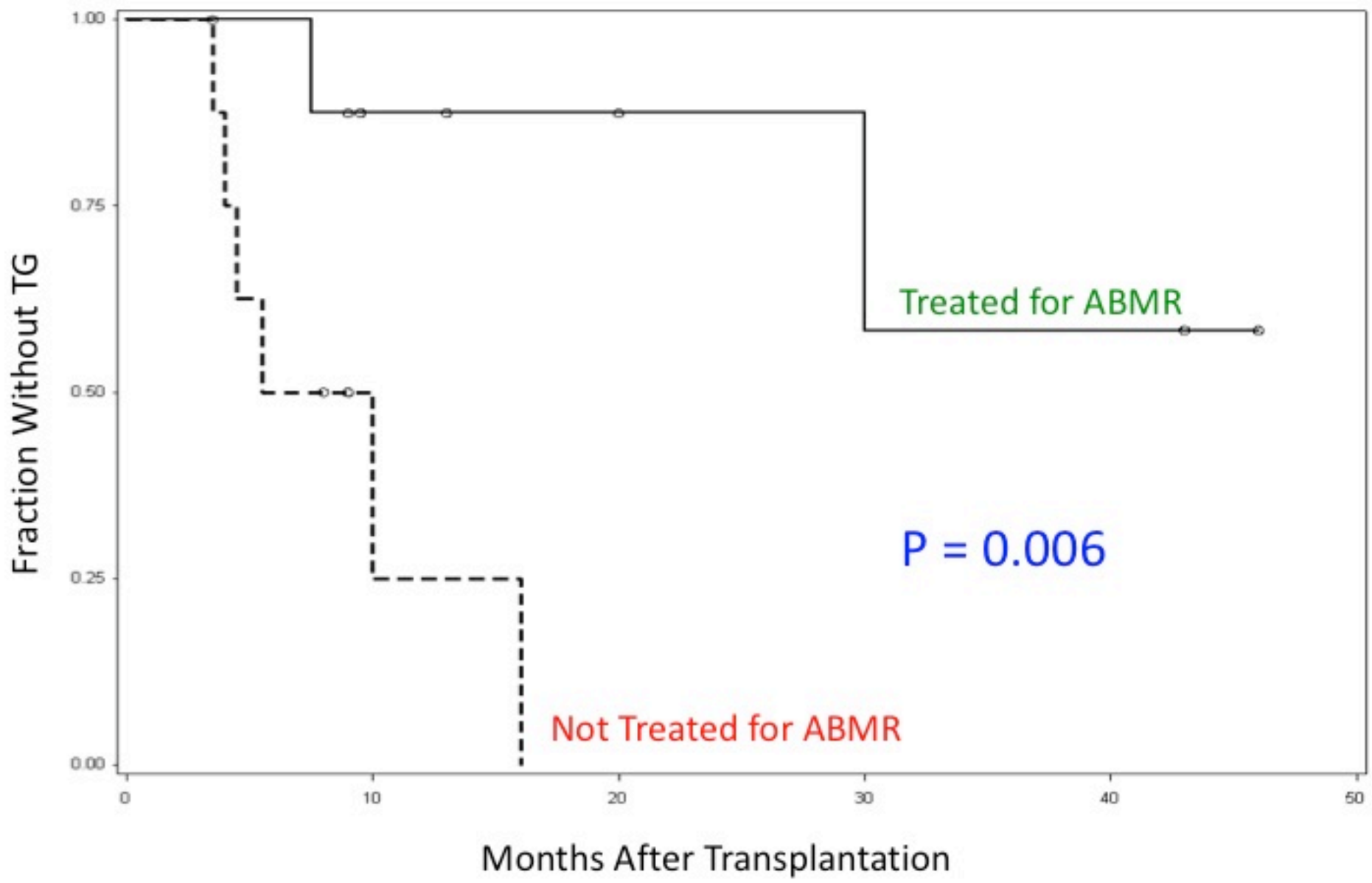
Cosio et al, AJT 8: 492-6, 2008



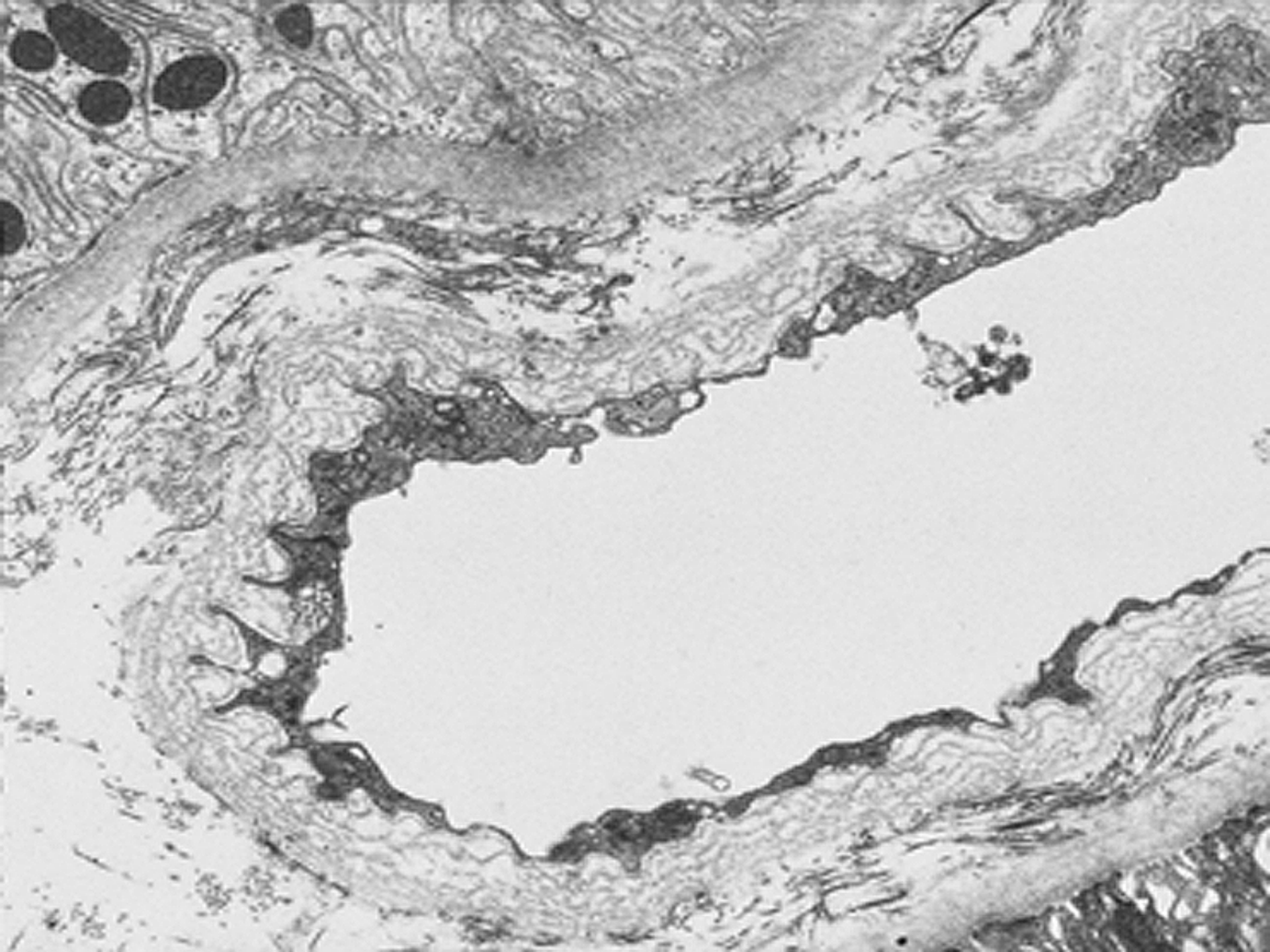
Gloor et al, AJT 7: 2124-32, 2007

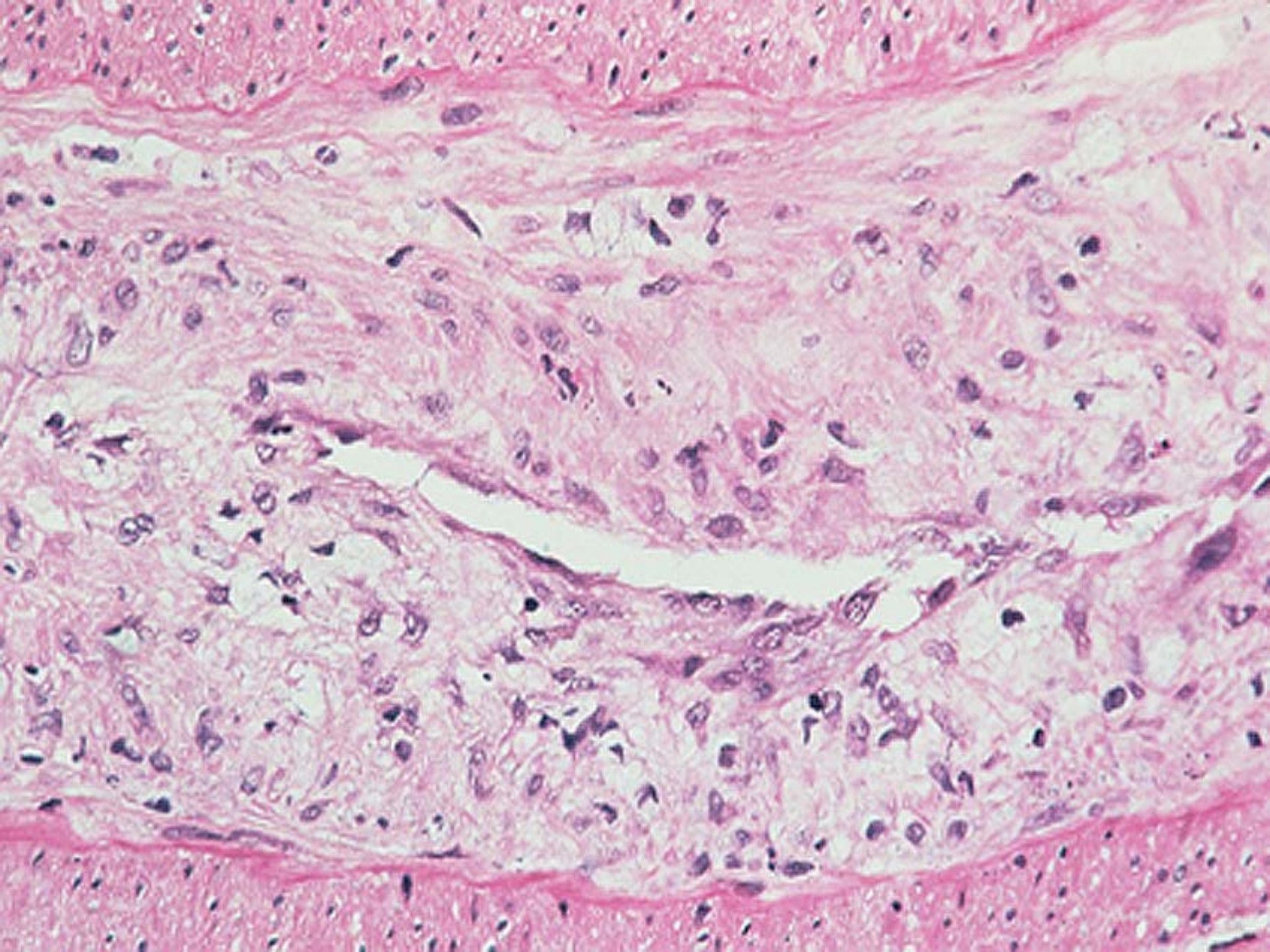


Biopsies ≤3 mo post-transplant with MVI, DSA, glom. endothelial EM changes



Haas and Mirocha, AJT 11: 2123-31, 2011





Banff 2013 Classification of Antibody-Mediated Rejection (ABMR) in Renal Allografts (continued)

Chronic, Active ABMR; all three features must be present for diagnosis[f]

1. Morphologic evidence of chronic tissue injury, *including 1 or more of the following*:
   - Transplant glomerulopathy (cg >0)[g], if no evidence of chronic TMA
   - Severe peritubular capillary basement membrane multilayering (requires EM)[h]
   - Arterial intimal fibrosis of new onset, excluding other causes
2. Evidence of current/recent antibody interaction with vascular endothelium, *including at least one of the following*:
   - Linear C4d staining in peritubular capillaries (C4d2 or C4d3 by IF on frozen sections, or C4d > 0 by IHC on paraffin sections)
   - At least moderate microvascular inflammation ([g + ptc] ≥2)[i]
   - Increased expression of gene transcripts in the biopsy tissue indicative of endothelial injury, *if thoroughly validated*
3. Serologic evidence of donor-specific antibodies (HLA or other antigens)

[f] In the absence of evidence of current/recent antibody interaction with the endothelium (those features in section 2), the term active should be omitted; in such cases DSA may be present at the time of biopsy or at any previous time post-transplantation.

[g] Includes GBM duplication by electron microscopy only (cg1a) or GBM double contours by light microscopy

[h] ≥7 layers in 1 cortical peritubular capillary and ≥5 in 2 additional capillaries, avoiding portions cut tangentially

[i] In the presence acute T cell-mediated rejection, borderline infiltrates, or evidence of infection, ptc ≥2 alone is not sufficient to define moderate microvascular inflammation and g must be ≥1.

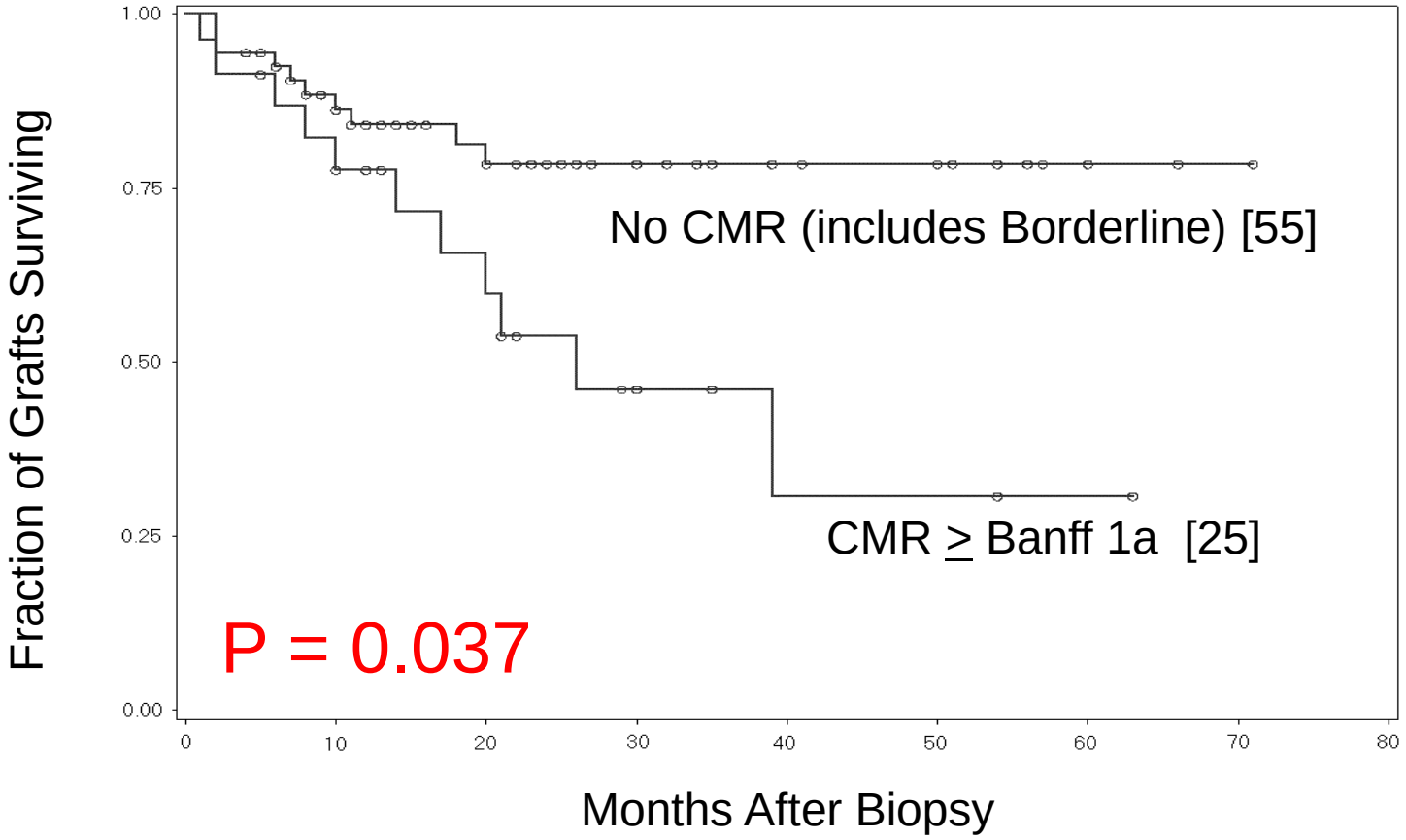
Comparison of Predictive Value of Banff 2013 vs. Banff 2007 Criteria for Chronic, Active ABMR

De Serres et al (Quebec), Am J Transplant 16: 1515-25, 2016

123 patients, single center, indication bx Jan 2006 – Oct 2014
45 reached combined endpoint of graft loss or doubling of SCr

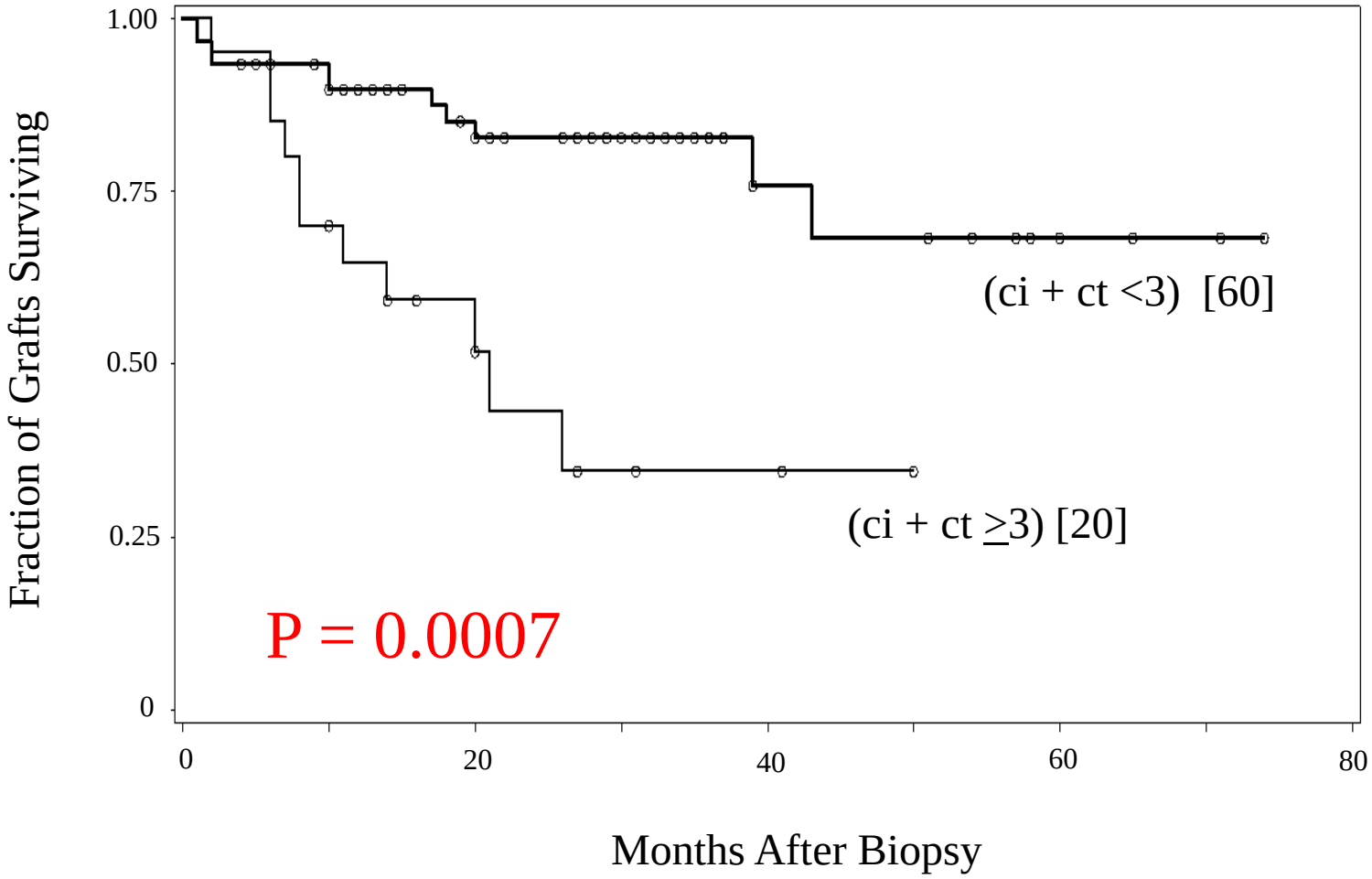
	Banff 2007	Banff 2013
% with CAABMR	18%	36%
HR of CAABMR for combined endpoint	1.6 [0.7-3.8]	2.5 [1.2-5.2]

Graft Survival After Treatment
"Pure" ABMR vs Mixed ABMR/TCMR
80 cases: 37 Type 1, 43 Type 2



P = 0.073 by multivariable analysis

M Haas et al, Kidney Int, 2017



P = 0.013 by multivariable analysis

M Haas et al, Kidney Int, 2017

Thank you for your attention. Any questions?