Banff Conference 2017

Pathology of Mixed Rejection in Renal Allografts

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Classification of Allograft Rejection

Clinicopathological

- Hyperacute
- Acute / Active
- Chronic active
- Chronic

Histopathological

- Tubulointerstitial / cellular
- Vascular / microvascular

Molecular / Immunopathological

- T cell mediated rejection (TCMR)
- Ab-mediated rejection (ABMR)
- Mixed rejection (TCMR / ABMR)

Mixed Allograft Rejection

- Concurrent TCMR & ABMR, with diagnostic features of both in the same biopsy
- Sequential & subsequent concurrent TCMR & ABMR in the life of the allograft
- Potential significant interactions between TCMR & ABMR
  - Which comes first ?
  - Does early TCMR predispose to later ABMR ?
  - Requires sequential biopsy studies to answer

Case of Mixed Rejection

- 63 year male; ESRD – type 2 diabetic
- DD renal Tx in February 2012
- 1A 1B 1DR mismatch
- Uneventful 1st year post-Tx; no allograft biopsies
- Stable function, eGFR 38.7
- Feb 2013: 1 year post-Tx protocol Bx (study-related):
- **Banff borderline TCMR** (g0,**i1,t1**,v0,ptc0,C4d0,cg0,mm0)
- Tubular vacuolation & calcifications, ? CNI effect
- 20% IF/TA (ci1,ct1,cv1,ah0)
- No EM features of TG or PTCBMML

Case of Mixed Rejection

- May 2014: Stable function, eGFR 37.4
- Proteinuria 0.15 g/day
- 2 years post-Tx protocol Bx (study-related):
- **Banff borderline TCMR** (g0,**i1,t1**,v0,ptc0,C4d0,cg0,mm1)
- 20% IF/TA (ci1,ct1,cv1)
- Nodular ah2, c/w diabetes +/- CNI effect
- IF studies –ve for immune complex GN
- No EM features of TG or PTCBMML
- GBM diffuse mild thickening, suggestive of recurrent diffuse diabetic GS

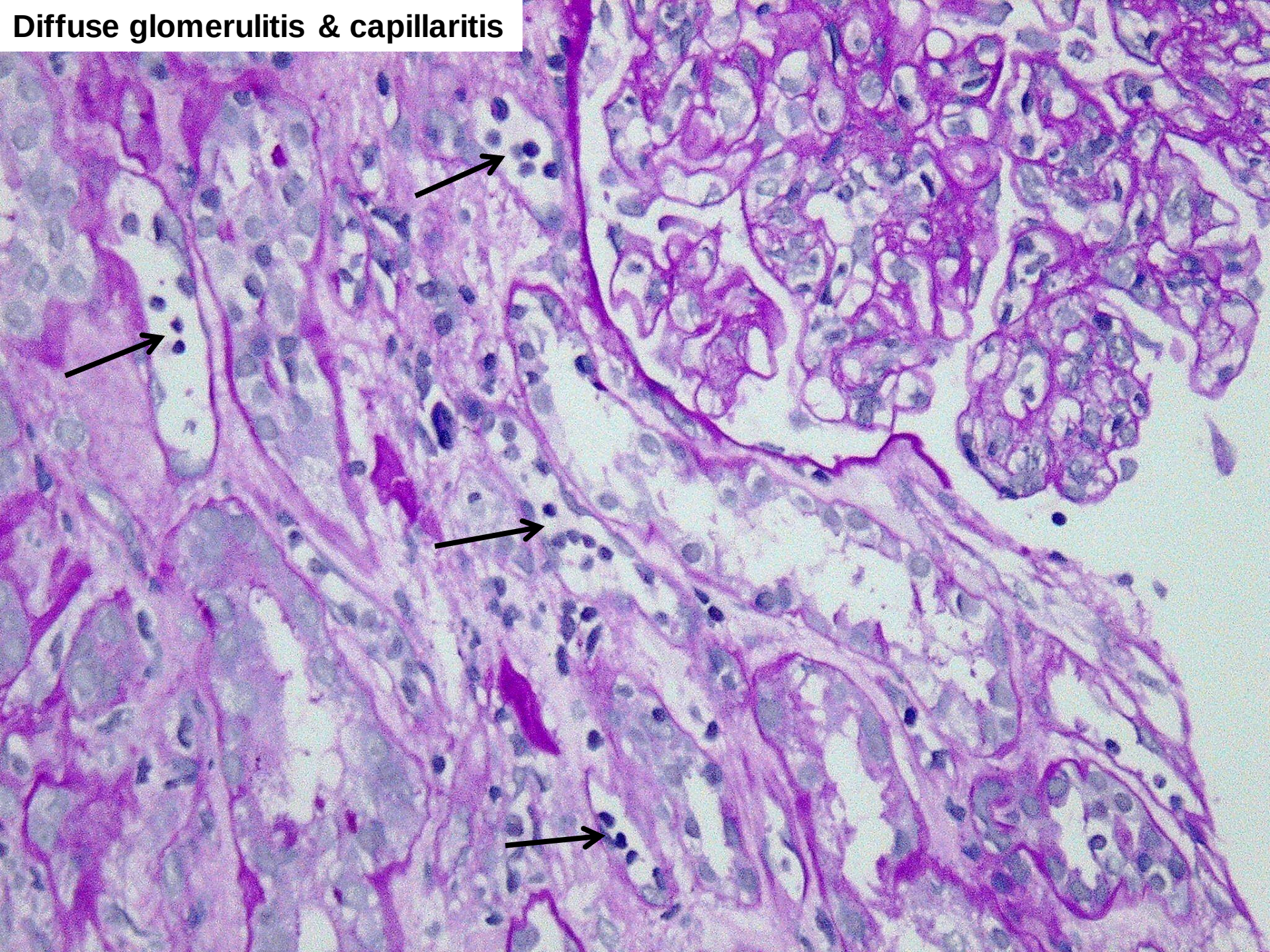
Case of Mixed Rejection

- May 2016: Stable function, eGFR 39
- Proteinuria 1.6 g/day, EBV+ve, DSA -ve
- 4 years post-Tx indication Bx:
- **Banff borderline TCMR** (g0,**i1,t1**,v0,ptc1,C4d0,cg0)
- 1 glomerulus with FSGS; moderate mesangial matrix expansion (mm2), c/w progressive recurrent diabetic GS
- 35% IF/TA (ci2,ct2,cv3)
- Nodular ah3, c/w diabetes +/- CNI effect
- IF studies –ve for immune complex GN
- No glom for EM, no PTCBMML

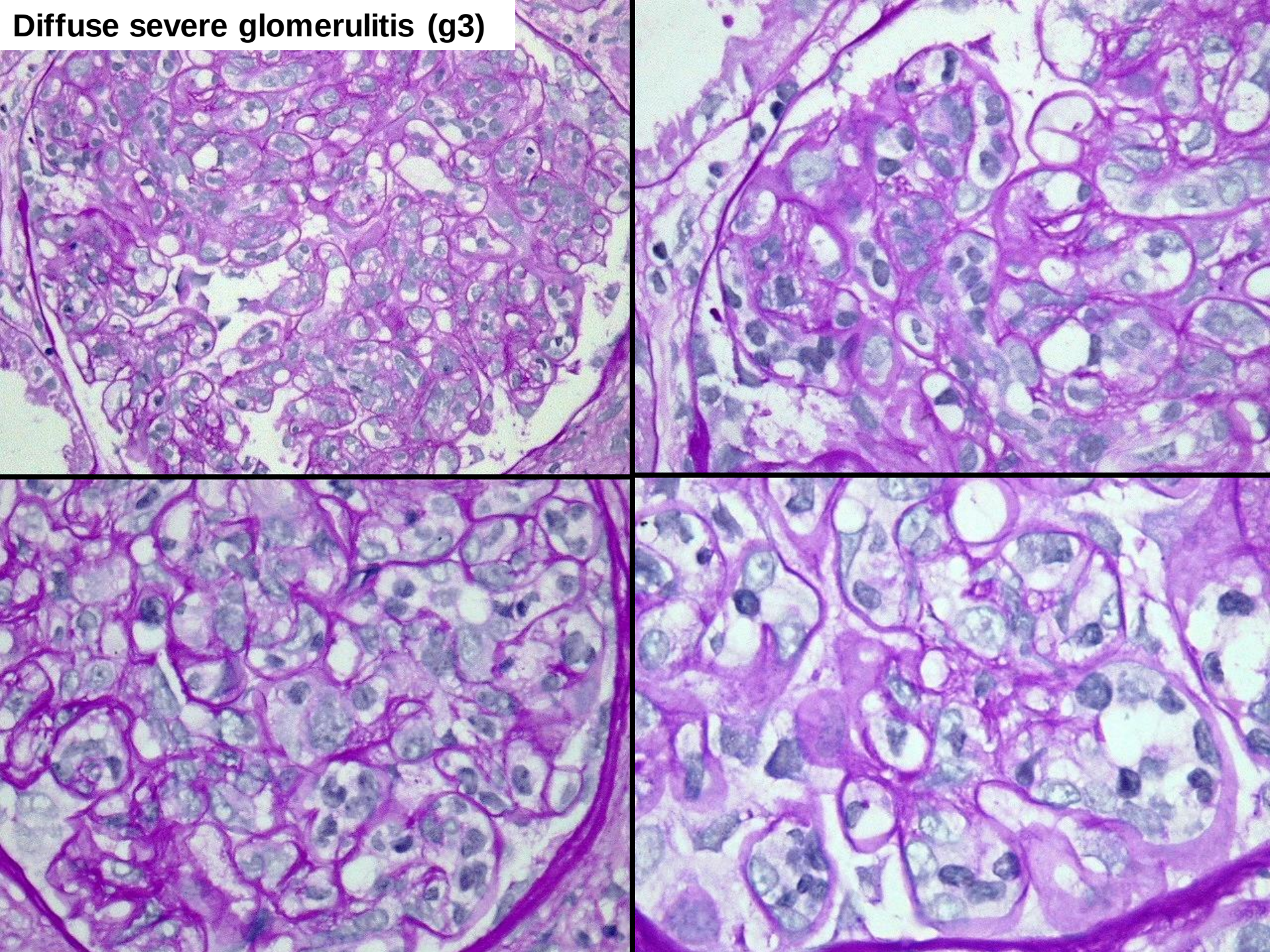
Case of Mixed Rejection

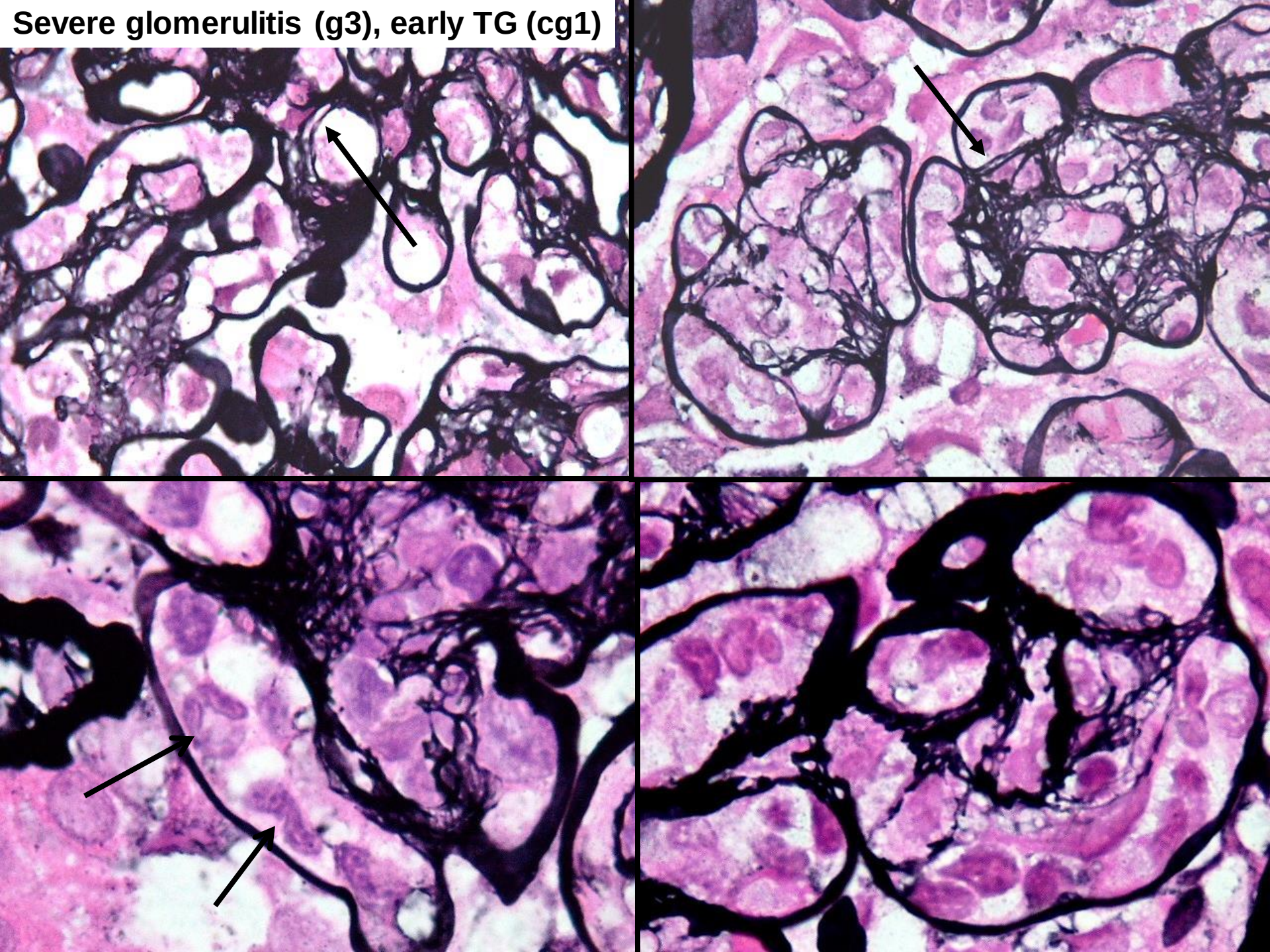
- December 2016: Rising serum Cr after being switched from CNI to rapamycin (due to EBV+), eGFR dropped to 29.2
- DSA +ve for class II anti-HLA: DQ7, highest MFI = 7843
- Almost 5 years post-Tx indication Bx:

Diffuse glomerulitis & capillaritis

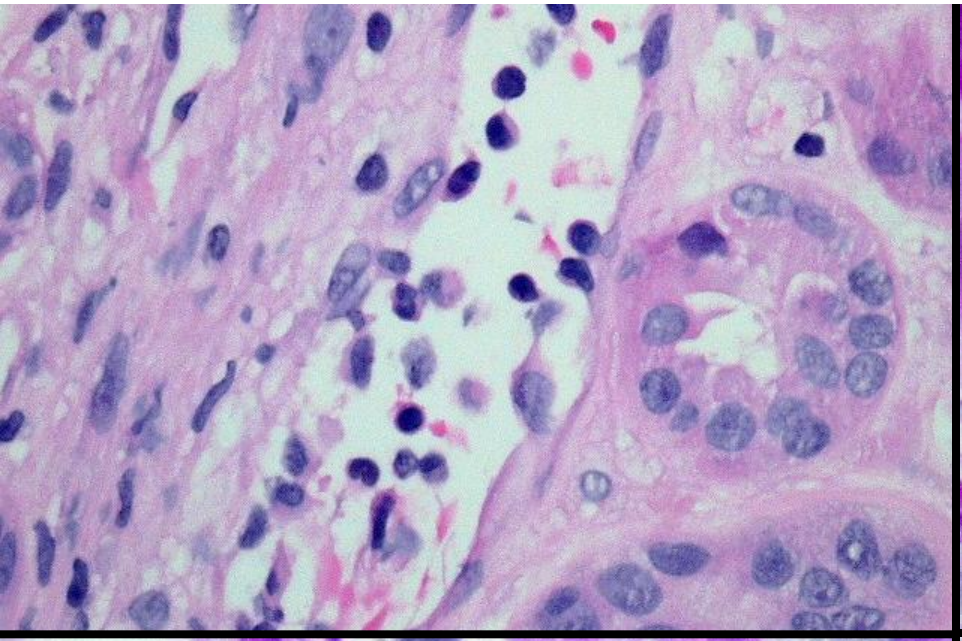


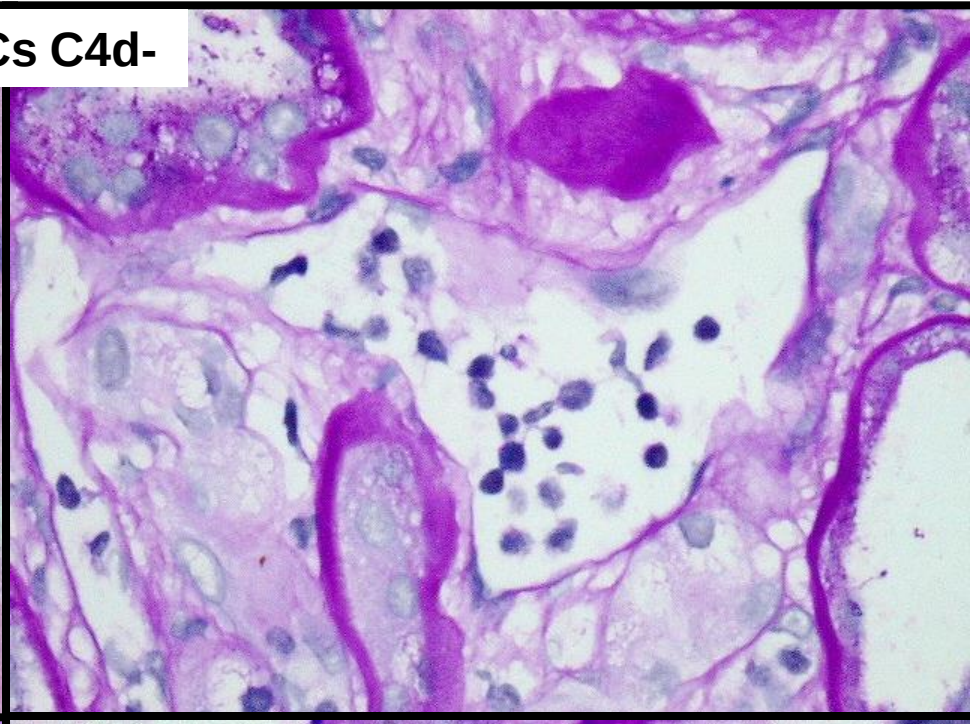
Diffuse severe glomerulitis (g3)

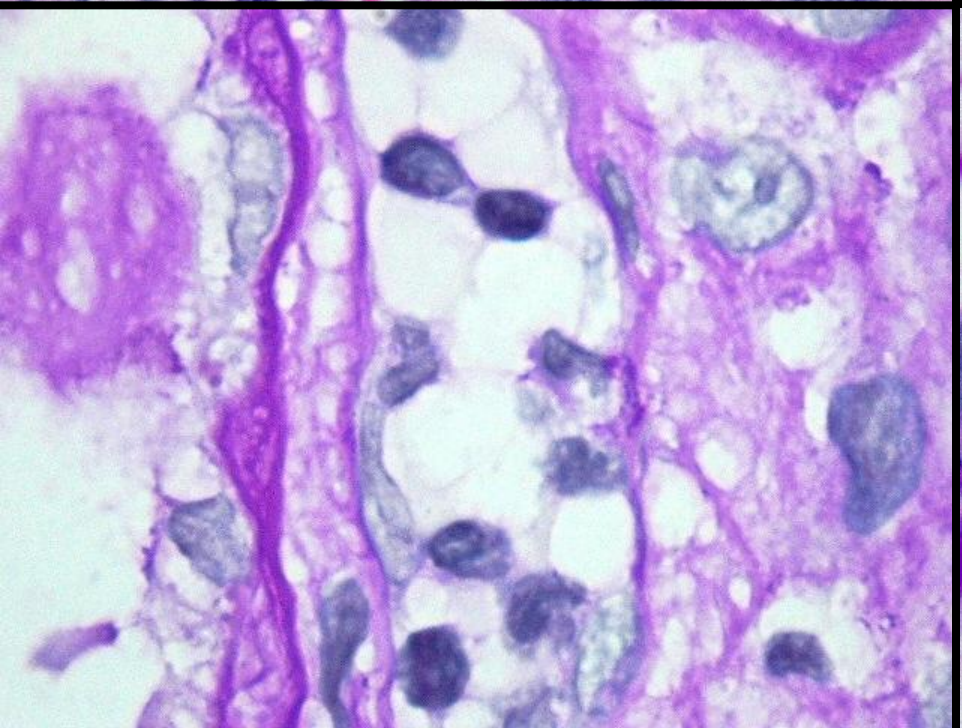


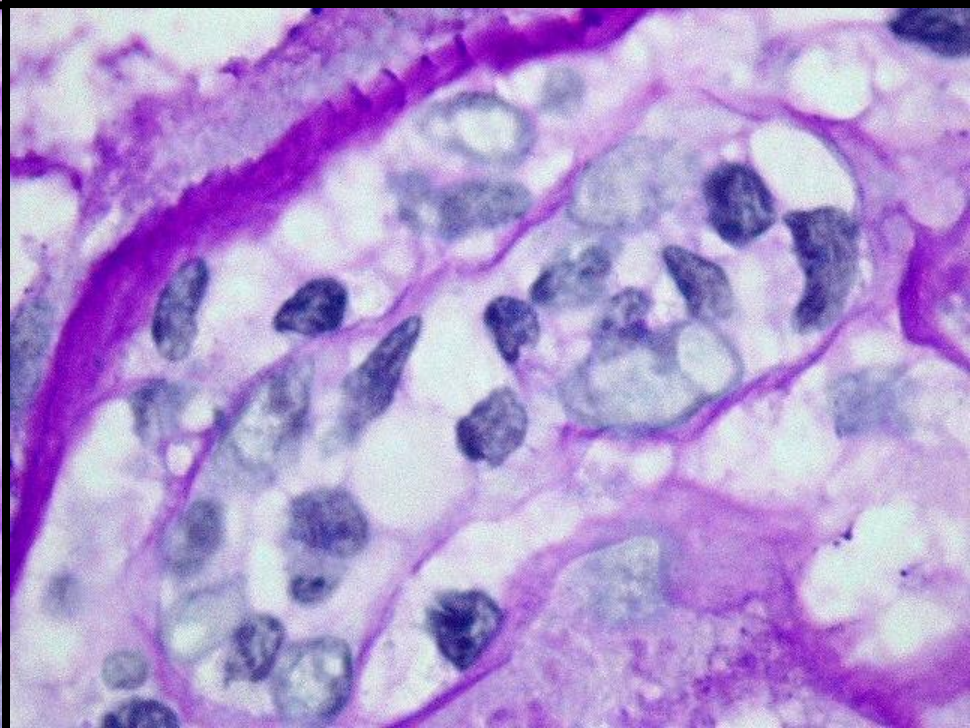

Severe glomerulitis (g3), early TG (cg1)

Diffuse ptc3 with mononuclear cells, PTCs C4d-

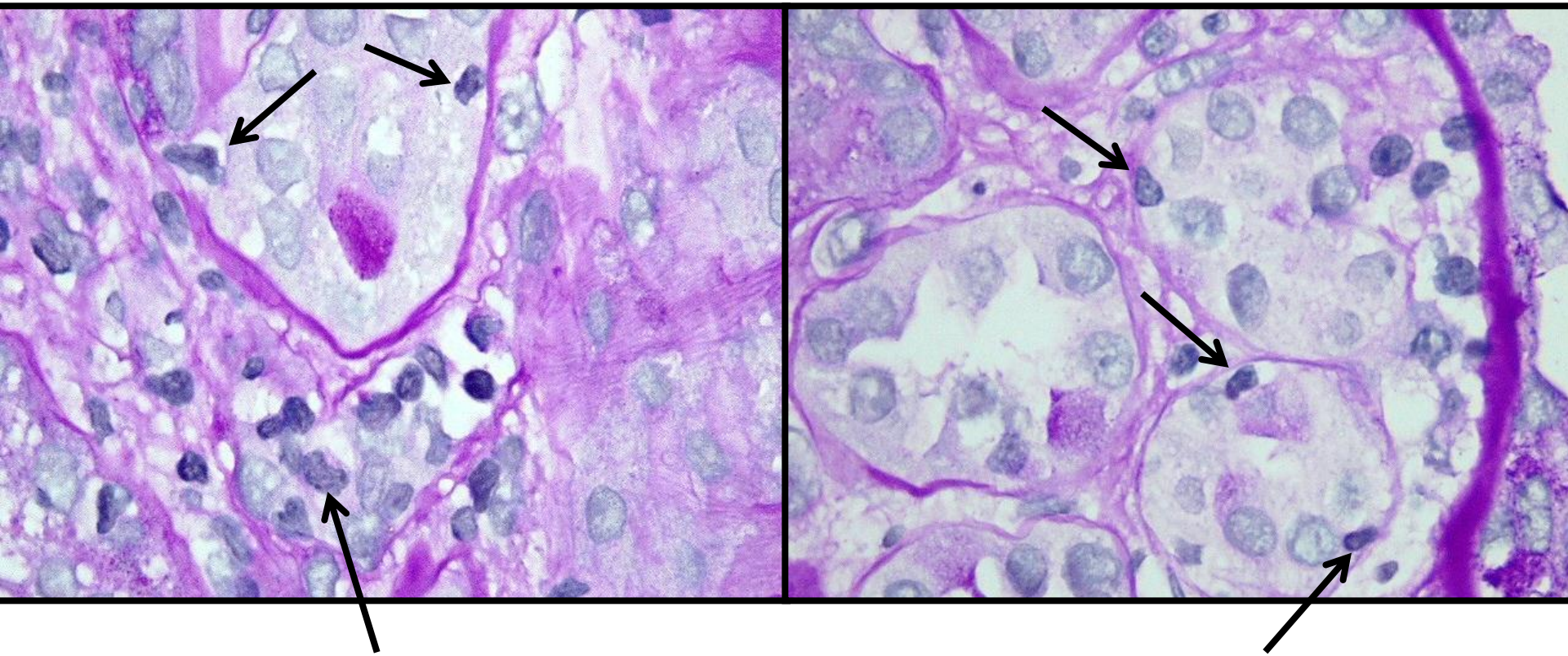




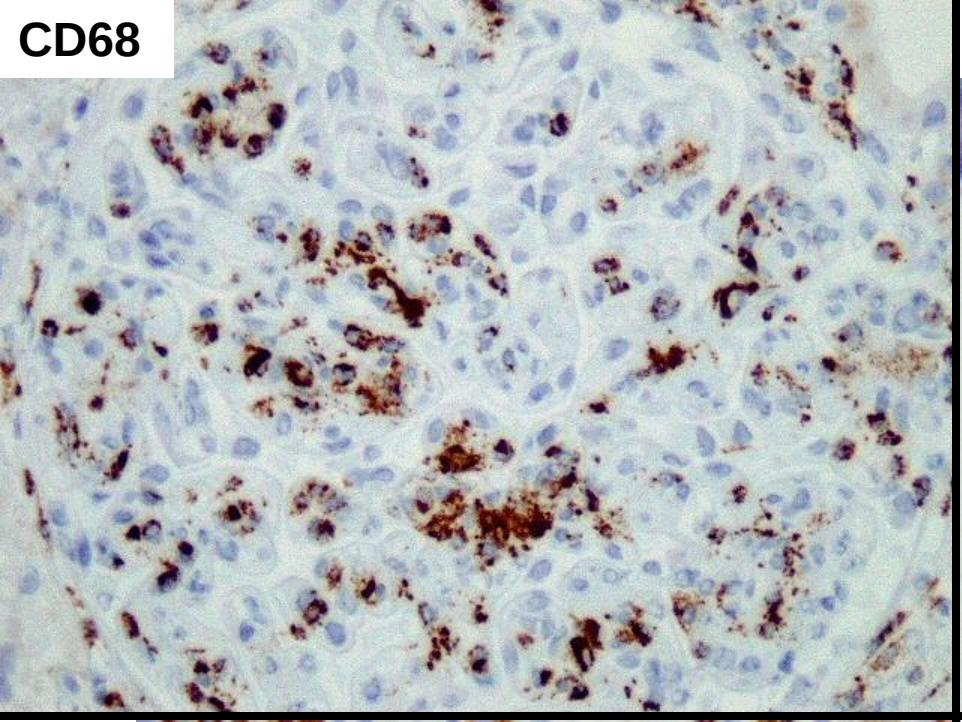


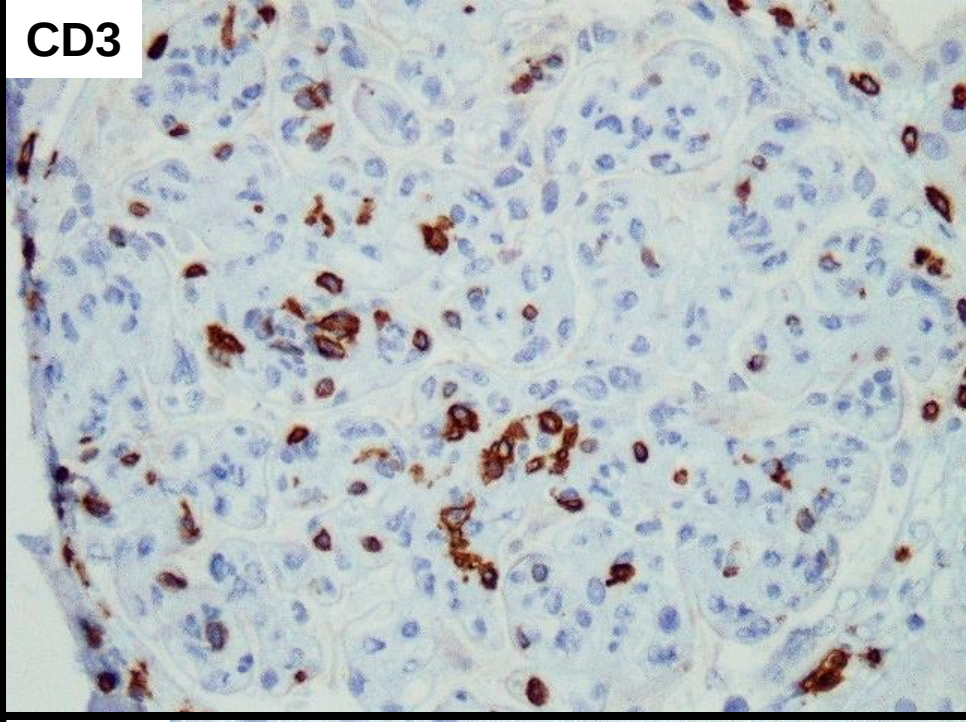


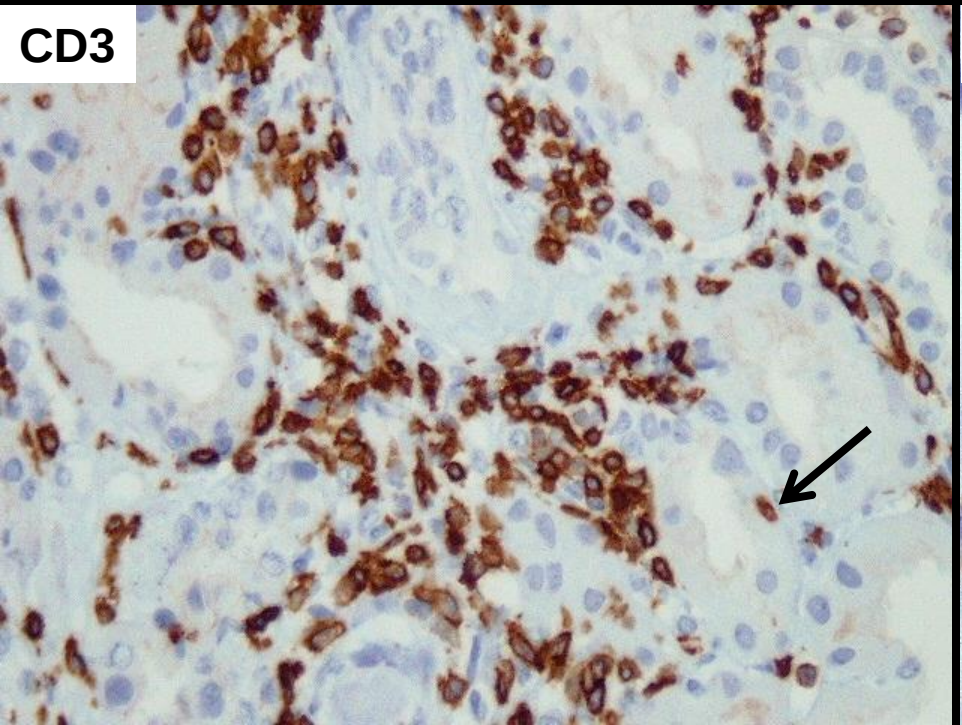
Foci of t1 tubulitis (arrows)



Capillaritis with large mononuclear cells with reniform nuclei


CD68


CD3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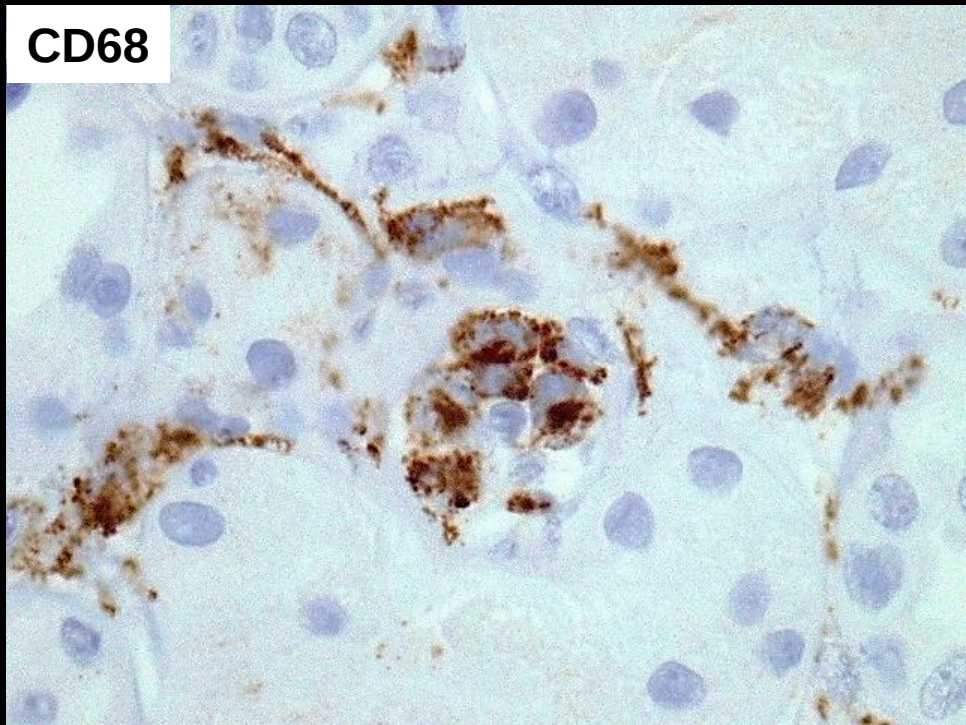
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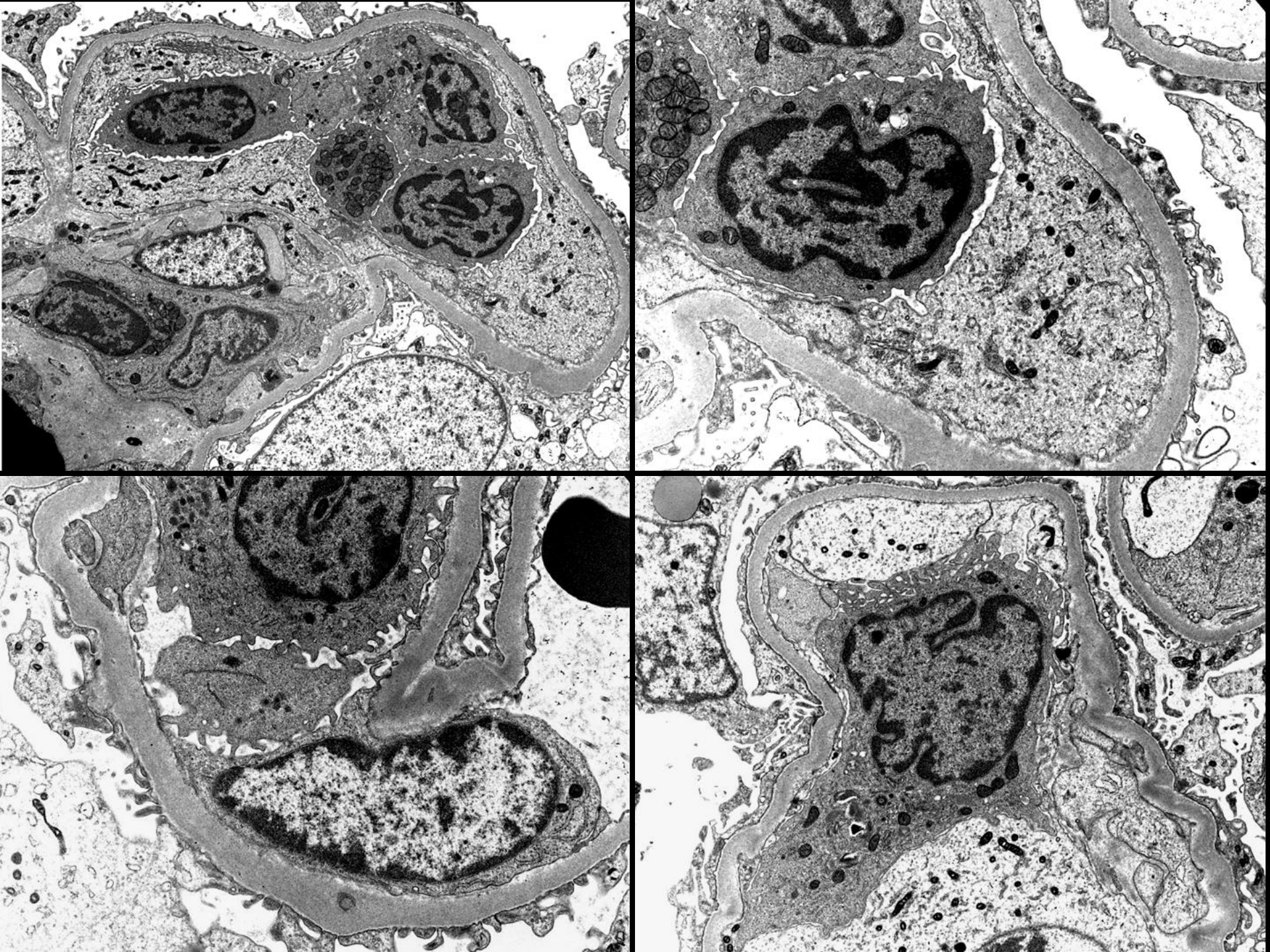
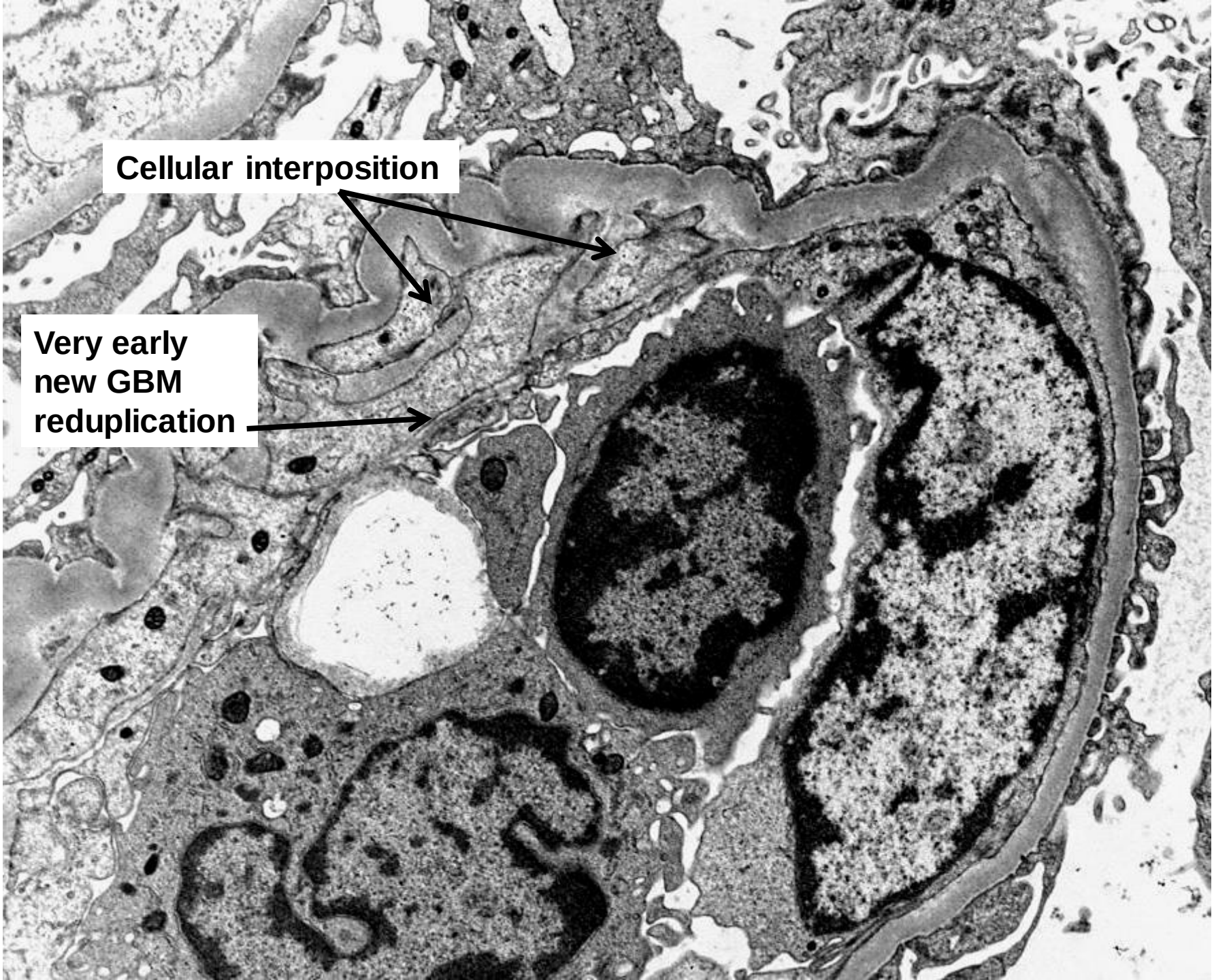
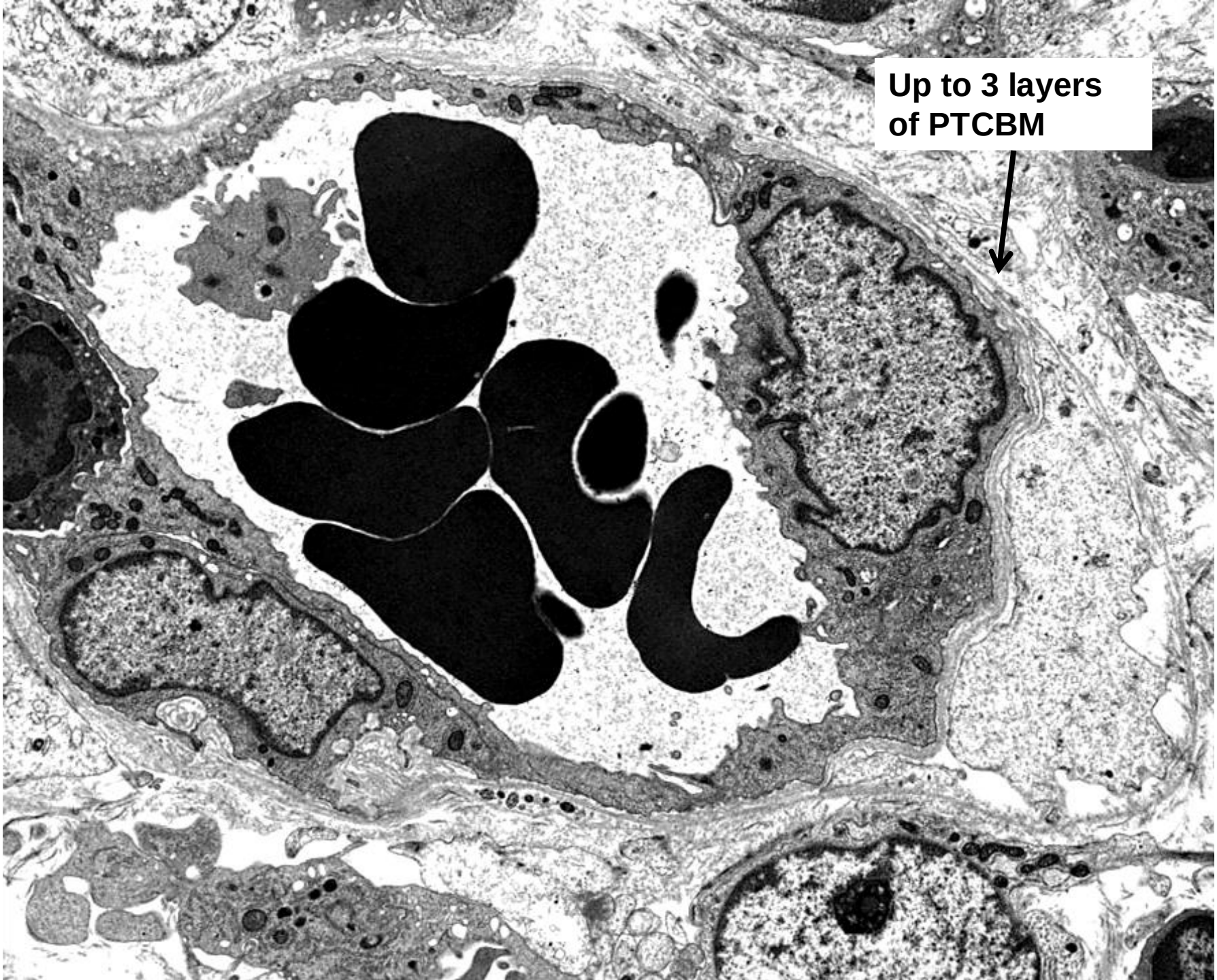



Cellular interposition
Very early new GBM reduplication

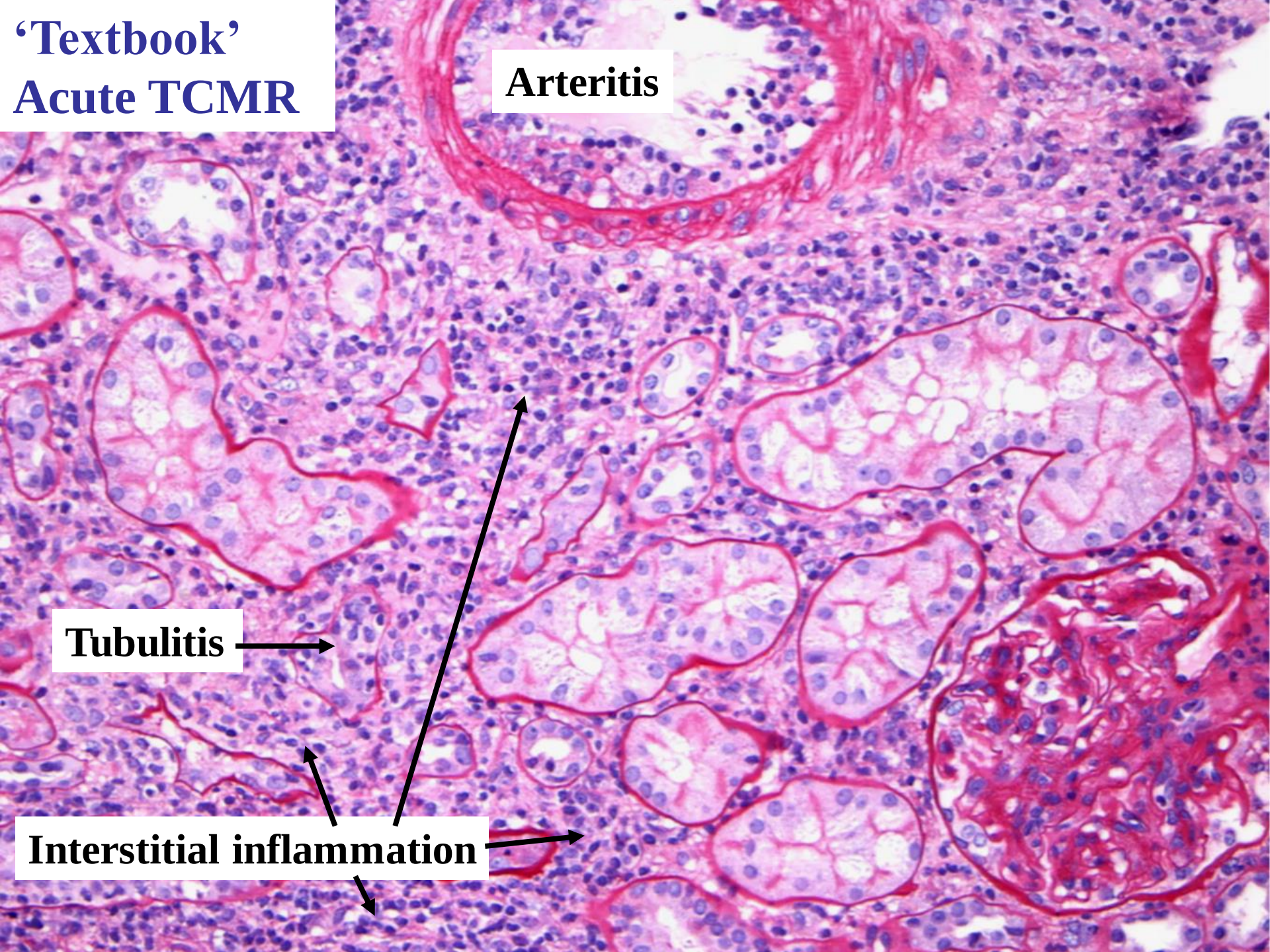

Up to 3 layers
of PTCBM

Case of Mixed Rejection

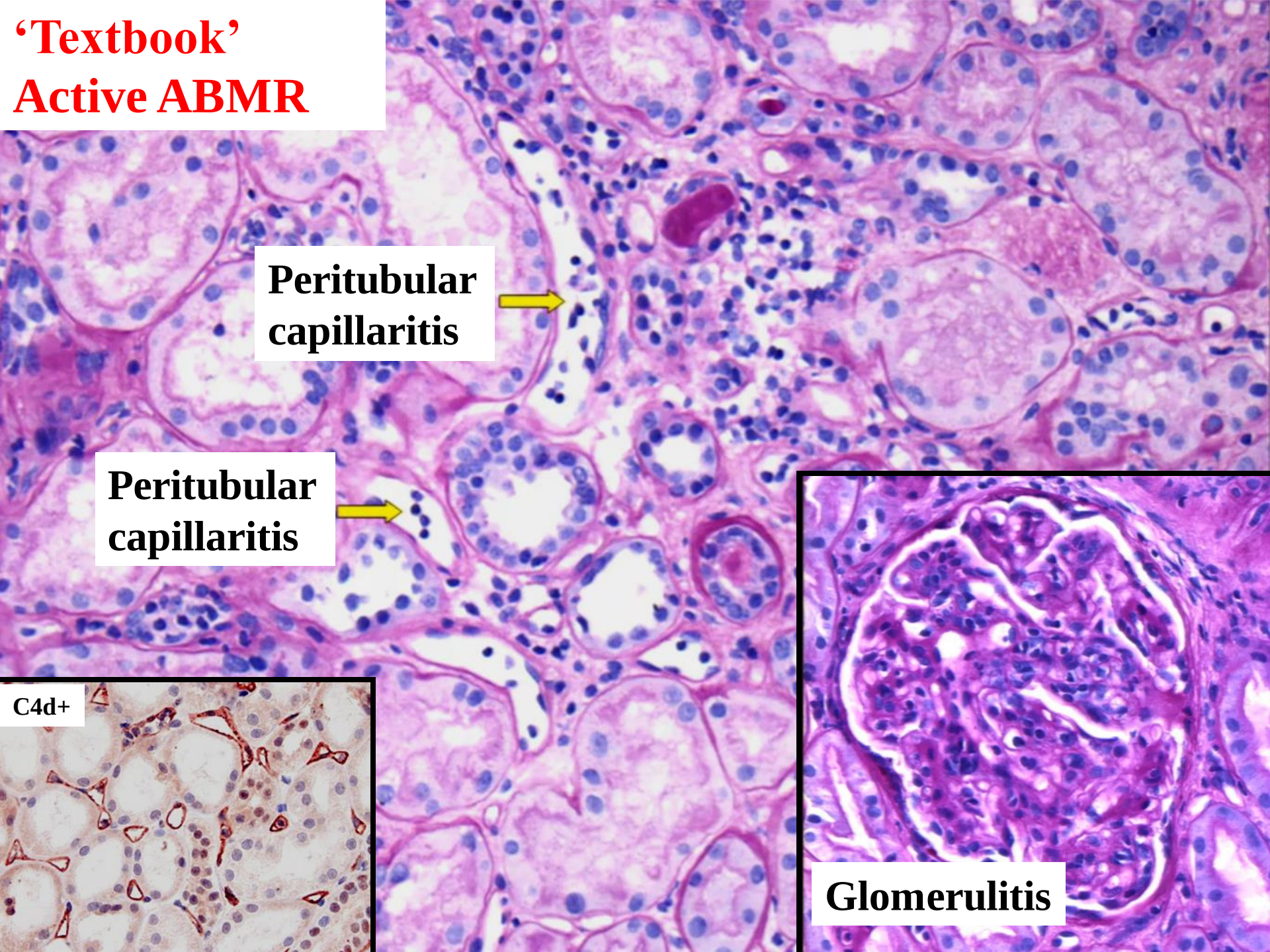
- December 2016: Rising serum Cr after being switched form CNI to rapamycin (due to EBV+), eGFR 29.2
- DSA +ve for class II anti-HLA: DQ7, highest MFI = 7843
- Almost 5 years post-Tx indication Bx:
- **C4d negative chronic active ABMR** with severe Tx glomerulitis (g3), diffuse peritubular capillaritis (ptc3), and early TG (cg1,mm1)
- Concurrent **Banff borderline TCMR** (i1,t1,v0)
- 40% IF/TA (ci2,ct2,cv2)
- Nodular ah3, c/w diabetes +/- CNI effect
- IF studies –ve for immune complex GN
- EM: Glomerulitis, GBM thickening with very early focal reduplication, no significant PTCBMML (3 layers)

Case of Mixed Rejection

- Persistent continuing low-grade **Banff borderline TCMR** over 4 years post-Tx
- At just under 5 years post-Tx, developed *de novo* DSA (anti-HLA class II: DQ7)
- Progressed to mixed rejection phenotype with **chronic active ABMR** & concurrent persisting **Banff borderline TCMR**
- Recurrent diffuse diabetic GS


‘Textbook’
Acute TCMR
Arteritis
Tubulitis
Interstitial inflammation

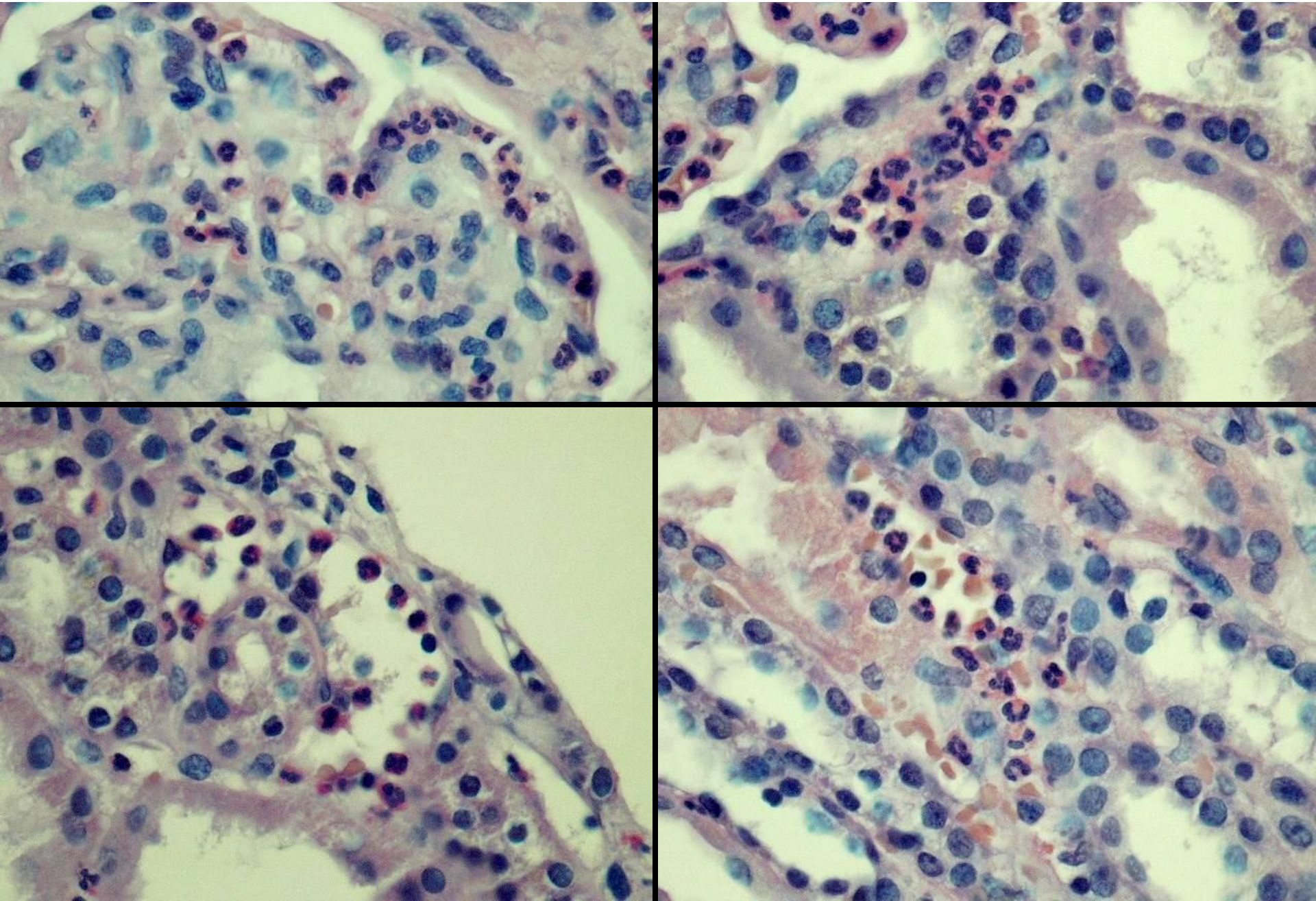
‘Textbook’ Active ABMR



Reappraisal of Lesions of Allograft Rejection

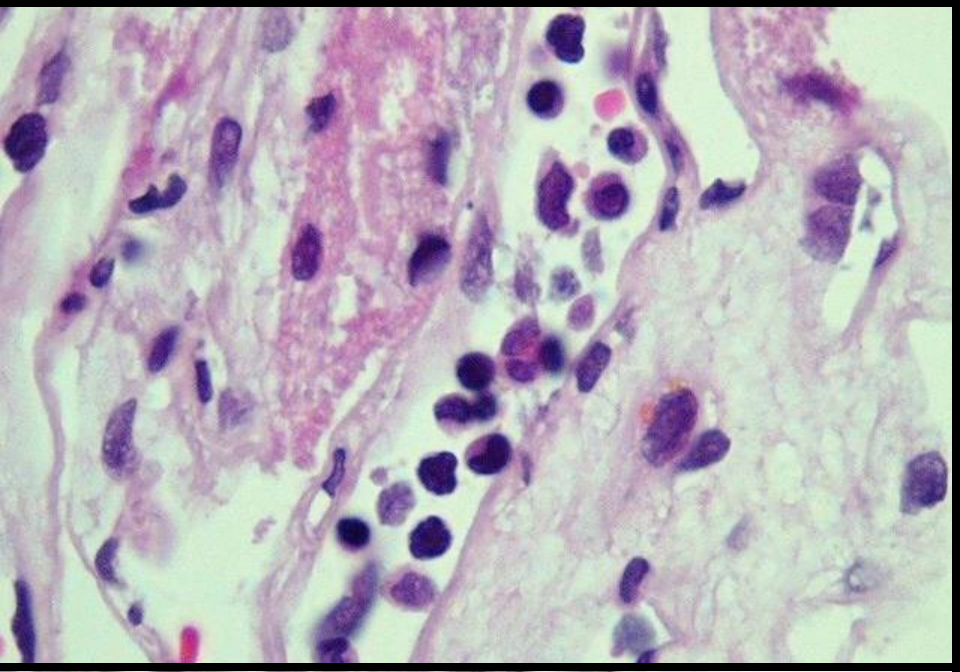
Acute / Active Lesions	TCMR	ABMR
• Interstitial inflammation	✓✓	-
• Lymphocytic tubulitis	✓✓	-
• Glomerulitis	✓	✓✓
• Peritubular capillaritis	✓	✓✓
• Vasculitis / intimal arteritis	✓	✓
• PTC C4d deposition	-	✓✓
Chronic Lesions		
• TG (Tx glomerulopathy)	✓	✓✓
• PTCBMML	?	✓✓
• IF/TA	✓	✓
• Arterial intimal fibrosis	✓	✓

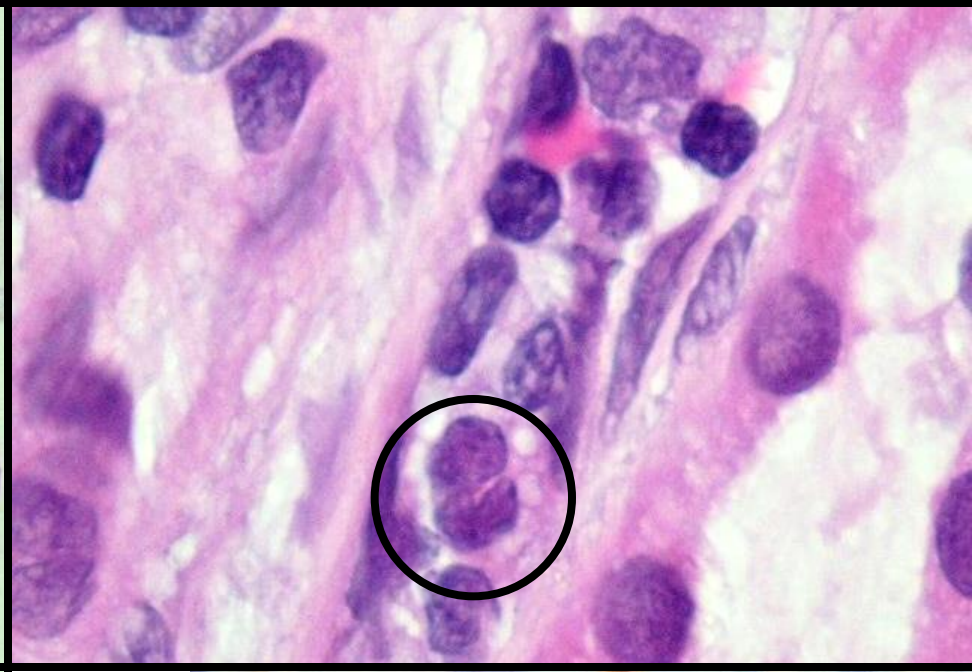
13 days post-Tx, anuric, pre-sensitized with class I/II (A11,B39,DR13) DSA:
Acute ABMR: g3,i1,t0,v1,ptc3, diffuse C4d+; diffuse severe neutrophilic MVI

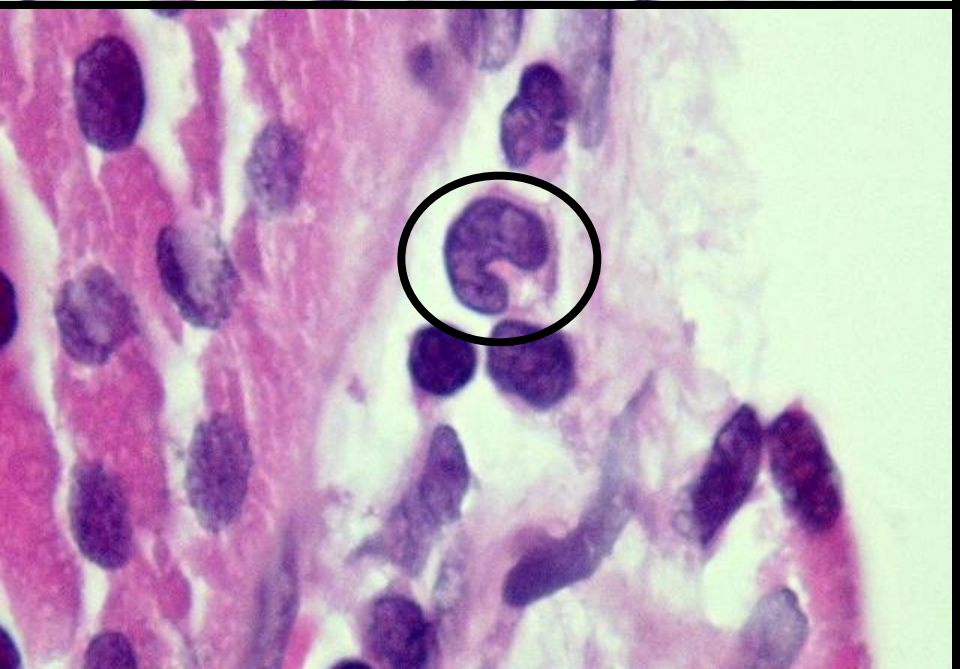


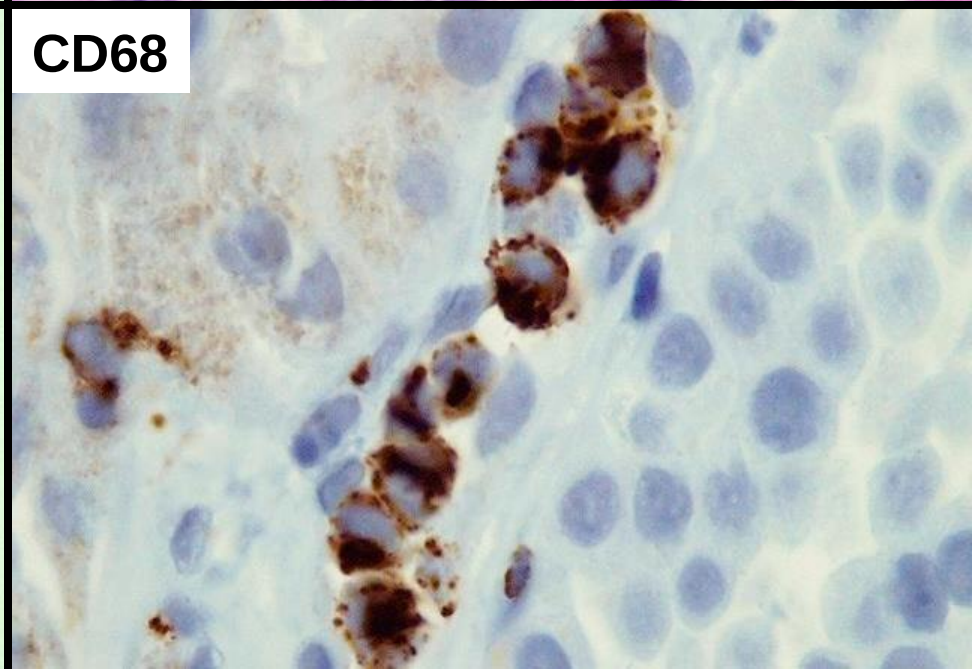
9 years post-Tx; *de novo* class II (DQ7) DSA: g3,i1,t1,v0,ptc3,cg1,mm0,ci2,ct2,cv1,ah3

Chronic active ABMR: Diffuse severe mononuclear capillaritis with large convoluted nuclei (circled).

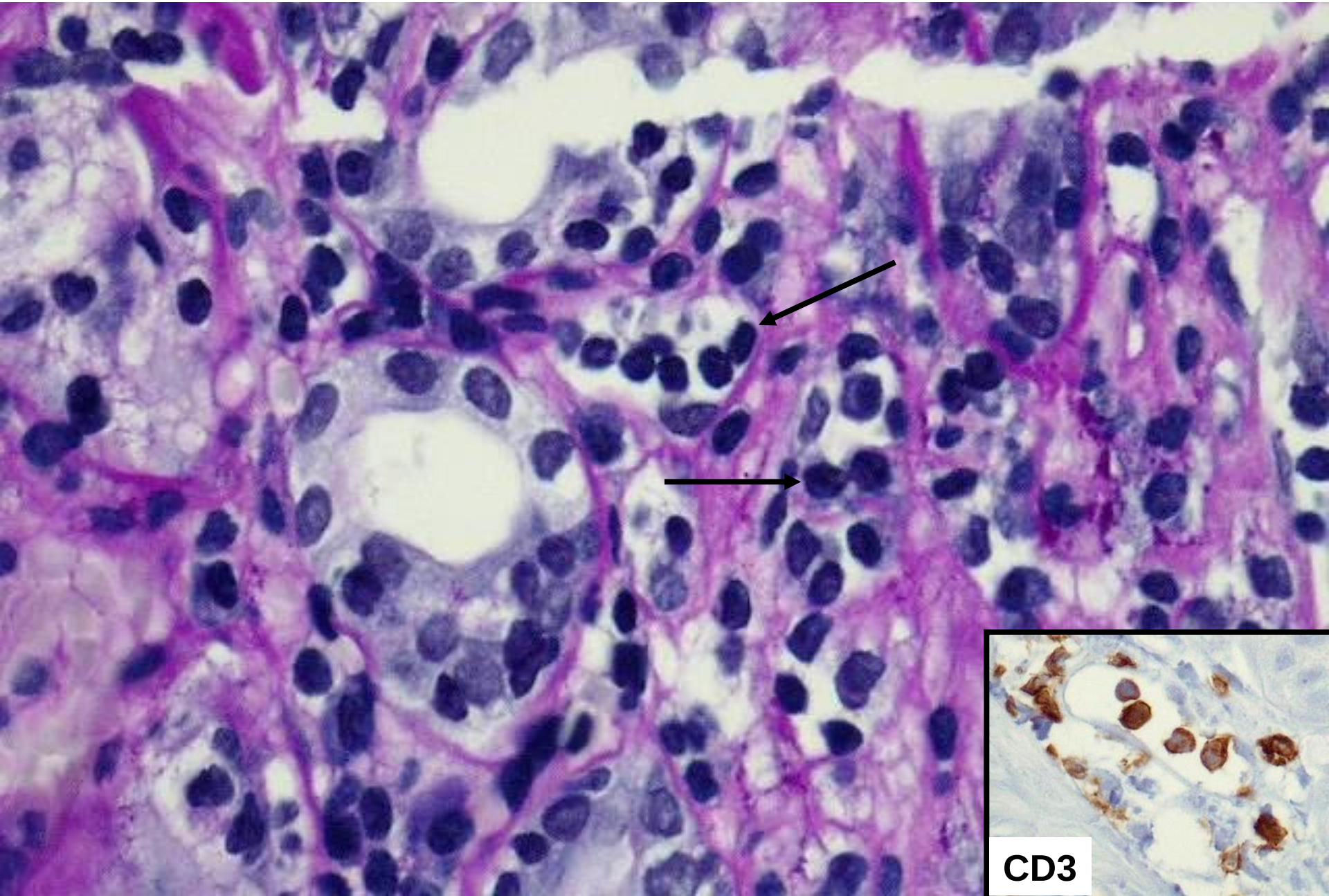




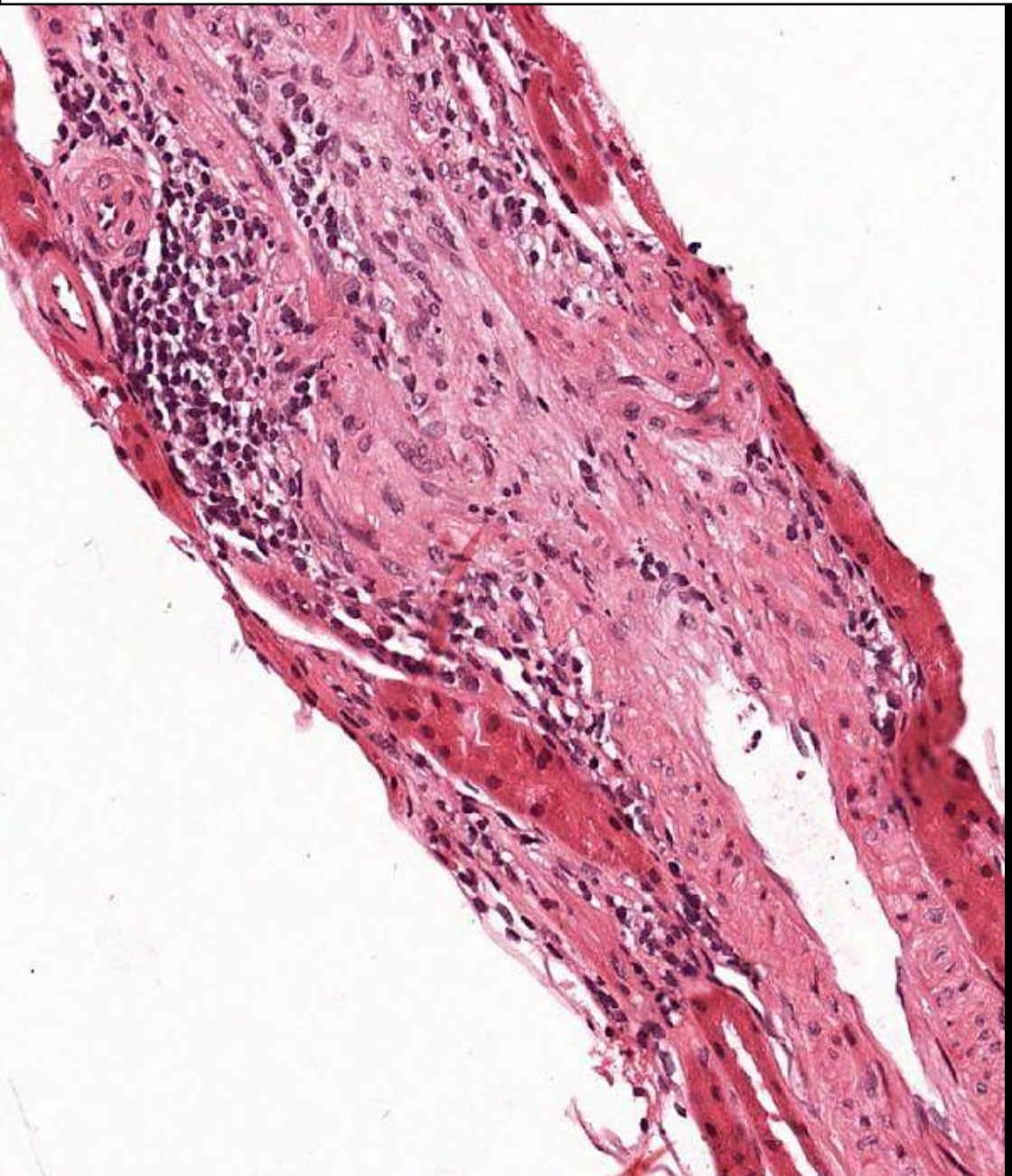


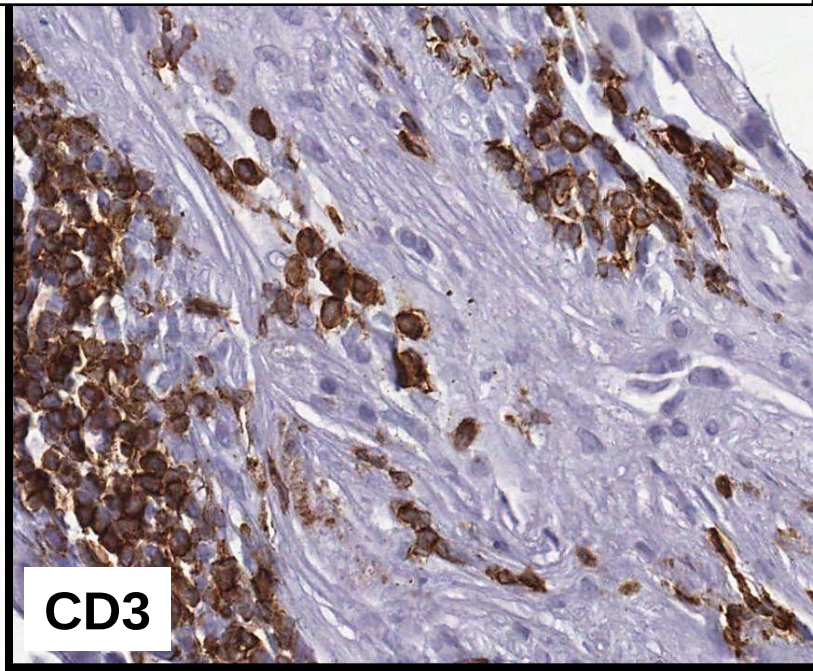


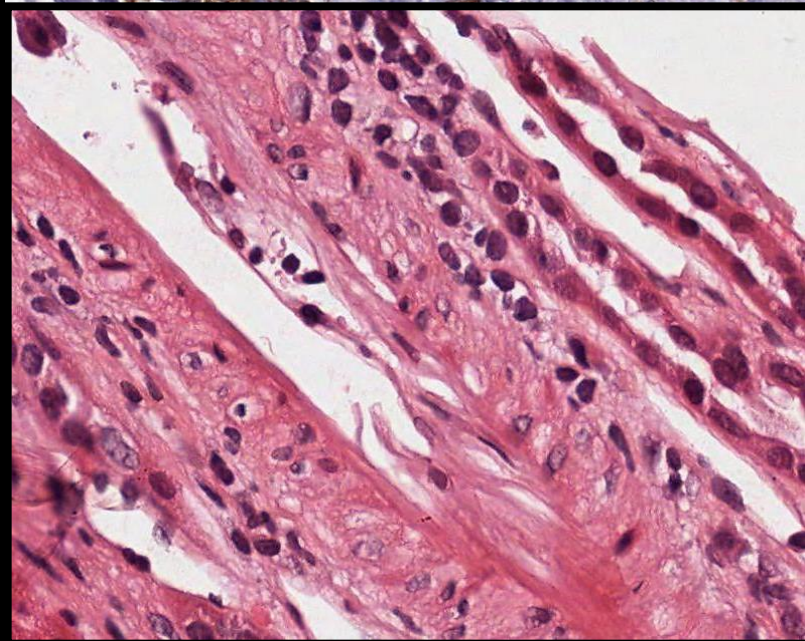
Peritubular capillaritis in acute TCMR: Banff IB, g0,i3,t3,v0,ptc2
Predominantly small hyperchromatic mononuclear CD3+ T cells



5 years post-Tx allograft Bx, stable function, class II (DQ9) DSA: Isolated V lesion with transmural arteritis (g0,i0,t0,v3,ptc2), C4d-







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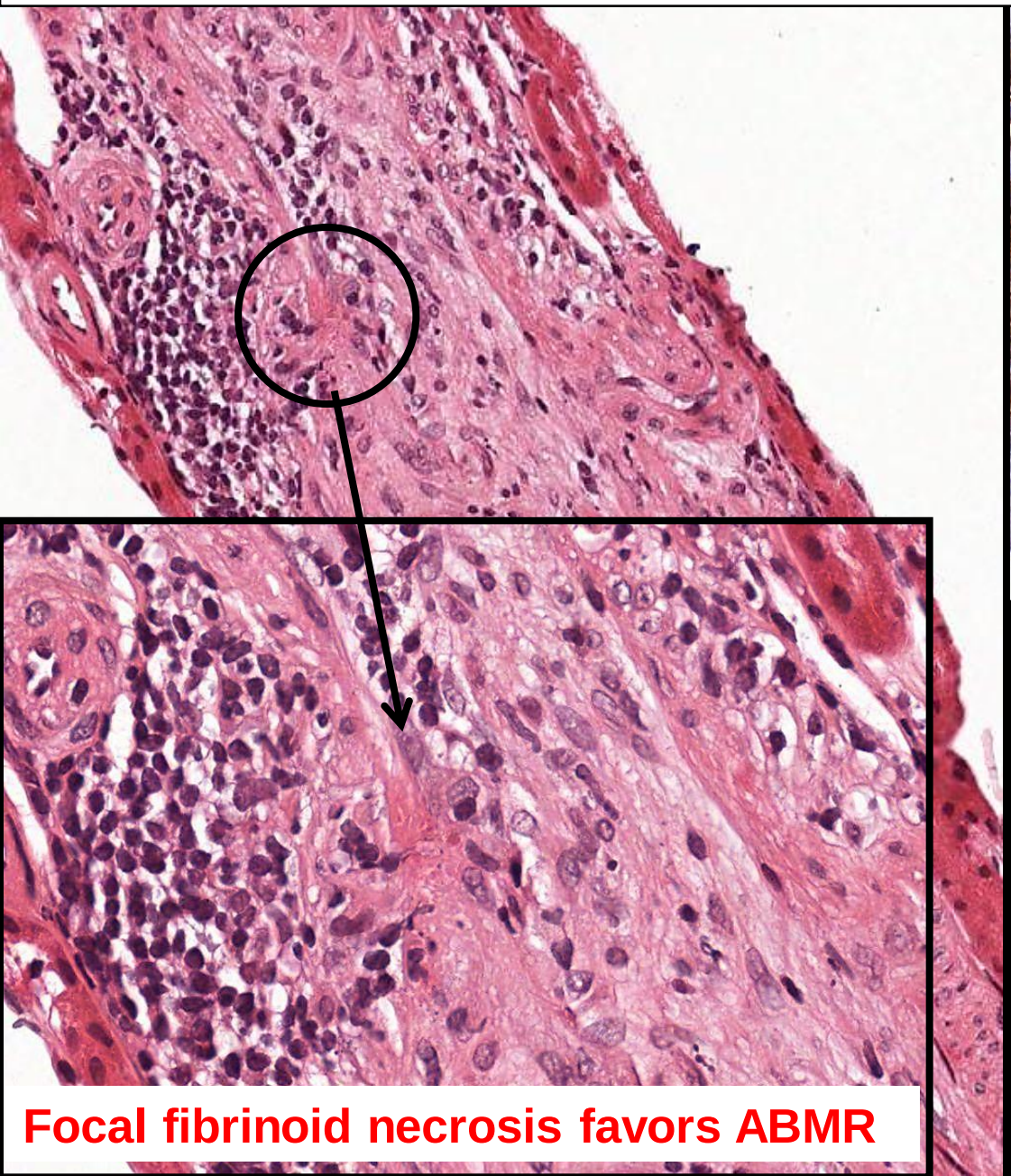

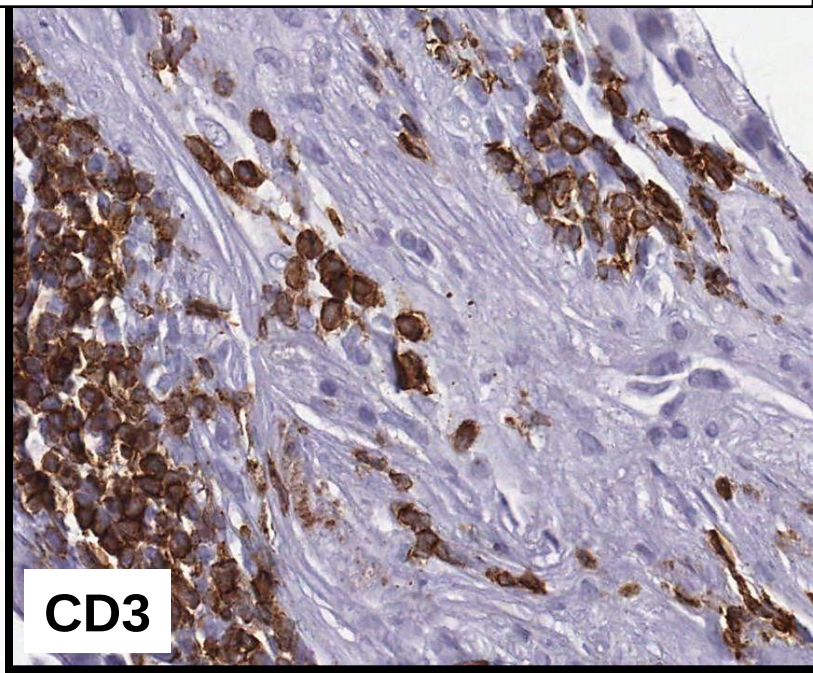

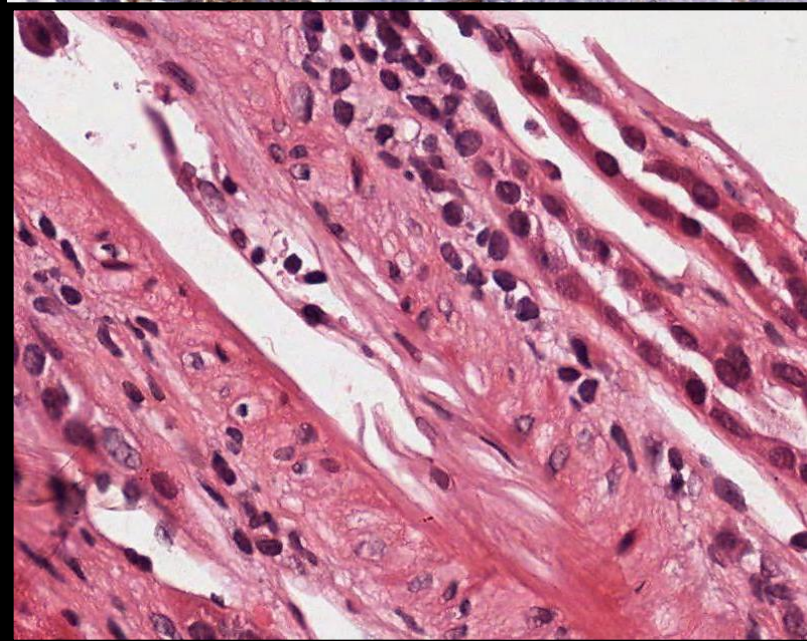

Focal fibrinoid necrosis favors ABMR

Evolution and Clinical Pathologic Correlations of *De Novo* Donor-Specific HLA Antibody Post Kidney Transplant

C. Wiebe[a,†], I. W. Gibson[b,c,†], T. D. Blydt-Hansen[d], M. Karpinski[e], J. Ho[e], L. J. Storsley[e], A. Goldberg[d], P. E. Birk[d], D. N. Rush[e] and P. W. Nickerson[a,c,*]

American Journal of Transplantation 2012; 12: 1157–1167

UNIVERSITY OF MANITOBA

- 315 low-risk renal transplants with no preexisting DSA
- Sequential HLA DSA screening using FlowPRA beads
- Protocol (n=215) and indication (n=163) allograft biopsies
- 15% (47/315) developed *de novo* DSA at 4.6 +/- 3.0 years, associated with either stable graft function / indolent dysfunction / acute graft dysfunction
- 10 year graft survival significantly worse with *dn*DSA compared with no DSA (57% vs 96%, $p < 0.0001$)
- Development of *dn*DSA associated with nonadherence to immunosuppressive therapy (49% vs 8%, p=0.035)

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Prior to *dn*DSA detection:
- **Significantly more B/TCMR at 0 – 6 months in *dn*DSA+ cohort**

Table 2: Clinical pathologic course before dnDSA detection

	No dnDSA (n = 268)	Total dnDSA (n = 47)	dnDSA adherent subgroup (n = 24)	dnDSA nonadherent subgroup (n = 23)
Non-adherence	8%	49%***	0%	100%
DGF requiring dialysis	12%	11%	8%	13%
Clinical rejection, 0–6 months	13%	28%*	29%*	26%
Subclinical rejection, 0–6 months	15%	26%	30%	22%
6-Month protocol biopsy, n	151	37	18	19
g	0.02 ± 0.2	0.03 ± 0.2	0.05 ± 0.2	0.0 ± 0.0
i	0.37 ± 0.6	0.62 ± 0.8*	0.33 ± 0.6	0.90 ± 0.9**
t	0.41 ± 0.7	0.62 ± 0.9	0.28 ± 0.7	0.95 ± 1.0**
v	0.01 ± 0.1	0.03 ± 0.2	0.06 ± 0.3	0.0 ± 0.0
ptc	0.11 ± 0.4 (n = 46)	0.60 ± 0.9 (n =30)**	0.14 ± 0.5 (n =14)	1.0 ± 1.0 (n =16)**
C4d+	0% (n =16)	10% (n =31)	7% (n =14)	12% (n =17)
cg	0.02 ± 0.2	0.03 ± 0.2	0.05 ± 0.2	0.0 ± 0.0
ci	0.53 ± 0.6	0.57 ± 0.7	0.56 ±0.7	0.58 ± 0.7
ct	0.65 ± 0.6	0.62 ± 0.6	0.61 ± 0.6	0.63 ± 0.6
cv	0.36 ± 0.6	0.36 ± 0.6	0.44 ± 0.7	0.29 ± 0.5
Clinical rejection, 7–12 months	3%	6%	0%	13%*
12-Month serum Cr. (μmol/L)	113 ± 44	116 ± 44	121 ± 44	110 ± 45
dnDSA onset (months)	–	56 ± 36	51 ± 37	60 ± 34
Month proteinuria ≥0.5 g/d	51 ± 40 (n =43)	67 ± 34 (n =25)	70 ± 40 (n =7)	66 ± 33 (n =18)
Month Cr ≥ 25% baseline	34 ± 31 (n =33)	68 ± 31 (n =29)***	79 ± 28 (n =7)***	65 ± 32 (n =22)***

Significance level compared to the No dnDSA group *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

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Prior to *dn*DSA detection:

- **Significantly more B/TCMR at 0 – 6 months in *dn*DSA+ cohort**
- **More TCMR lesions (i/t), and more ptc, at 0 – 6 months in the *dn*DSA+ cohort; particularly in nonadherent DSA+ subgroup**

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Month proteinuria ≥0.5 g/d	51 ± 40 (n =43)	67 ± 34 (n =25)	70 ± 40 (n =7)	66 ± 33 (n =18)
Month Cr ≥ 25% baseline	34 ± 31 (n =33)	68 ± 31 (n =29)***	79 ± 28 (n =7)***	65 ± 32 (n =22)***

Significance level compared to the No dnDSA group *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$.

Evolution and Clinical Pathologic Correlations of *De Novo* Donor-Specific HLA Antibody Post Kidney Transplant

American Journal of Transplantation 2012; 12: 1157–1167

C. Wiebe[a,†], I. W. Gibson[b,c,†], T. D. Blydt-Hansen[d], M. Karpinski[e], J. Ho[e], L. J. Storsley[e], A. Goldberg[d], P. E. Birk[d], D. N. Rush[e] and P. W. Nickerson[a,c,*]

- **At time of *dn*DSA detection, more ABMR – related pathology (g/ptc/C4d+/cg) in *dn*DSA+ cohorts**

Table 3: Pathologic correlations with patient phenotypes at the time of dnDSA detection

	Acute dysfunction dnDSA	Indolent dysfunction dnDSA	Stable function dnDSA	Dysfunction no dnDSA	Stable function no dnDSA
n	14	15	18	55	213
Clinical rejection, 0–6 months	36%*	27%*	22%	24%*	10%
Nonadherence	100%***	53%***	6%	16%*	6%
Month dnDSA positive	60 ± 35	61 ± 31	49 ± 31	–	–
Month protein, ≥0.5 g/d	63 ± 38	70 ± 33	–	51 ± 40	–
Month Cr ≥ 25% baseline	63 ± 34	73 ± 28	–	34 ± 31	–
Biopsy, n	12	13	14	35	27
Month of biopsy	63 ± 34	71 ± 26	53 ± 46	27 ± 21	24 ± 2
Creatinine at biopsy	490 ± 420***	156 ± 59***	118 ± 44	189 ± 180**	106 ± 31
g	0.92 ± 0.8***	0.92 ± 0.8***	0.14 ± 0.4	0.20 ± 0.5	0.04 ± 0.2
i	2.0 ± 1.1***	1.07 ± 0.8**	0.50 ± 0.8	0.74 ± 1.0	0.37 ± 0.6
t	2.0 ± 1.0***	0.54 ± 0.5**	0.35 ± 0.6	0.60 ± 0.9**	0.11 ± 0.3
v	0.08 ± 0.3	0 ± 0	0.21 ± 0.8	0.03 ± 0.2	0 ± 0
ptc	2.20 ± 0.7***	1.92 ± 1.0***	0.93 ± 1.0***	0.27 ± 0.6	0.04 ± 0.2
C4d+	80%***	39%**	57%***	0%	4%
cg	0.25 ± 0.5**	0.92 ± 1.2***	0 ± 0	0.14 ± 0.4	0 ± 0
ci	1.17 ± 0.6*	1.62 ± 0.5***	0.50 ± 0.7	1.37 ± 0.7***	0.67 ± 0.6
ct	1.25 ± 0.6	1.85 ± 0.7***	0.93 ± 0.5	1.46 ± 0.6**	0.93 ± 0.6
cv	0.75 ± 0.8	0.78 ± 0.6	0.57 ± 0.7	0.67 ± 0.7	0.41 ± 0.6
Months of follow-up post-dnDSA detection	29 (1–69)	45 (1–88)	19 (0–128)	–	–
Graft failure	57%***	40%***	0%	15%***	0%

Significance level compared to the Stable Function No dnDSA group *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Evolution and Clinical Pathologic Correlations of *De Novo* Donor-Specific HLA Antibody Post Kidney Transplant

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American Journal of Transplantation 2012; 12: 1157–1167

- **At time of *dn*DSA detection, more ABMR – related pathology (g/ptc/C4d+/cg) in dnDSA+ cohorts**
- **More TCMR pathology (i/t) in *dn*DSA+ cohorts with dysfunction; i.e. c/w mixed ABMR/TCMR, particularly with nonadherence & acute dysfunction**

Table 3: Pathologic correlations with patient phenotypes at the time of dnDSA detection

	Acute dysfunction dnDSA	Indolent dysfunction dnDSA	Stable function dnDSA	Dysfunction no dnDSA	Stable function no dnDSA
n	14	15	18	55	213
Clinical rejection, 0–6 months	36%*	27%*	22%	24%*	10%
Nonadherence	100%***	53%***	6%	16%*	6%
Month dnDSA positive	60 ± 35	61 ± 31	49 ± 31	–	–
Month protein, ≥0.5 g/d	63 ± 38	70 ± 33	–	51 ± 40	–
Month Cr ≥ 25% baseline	63 ± 34	73 ± 28	–	34 ± 31	–
Biopsy, n	12	13	14	35	27
Month of biopsy	63 ± 34	71 ± 26	53 ± 46	27 ± 21	24 ± 2
Creatinine at biopsy	490 ± 420***	156 ± 59***	118 ± 44	189 ± 180**	106 ± 31
g	0.92 ± 0.8***	0.92 ± 0.8***	0.14 ± 0.4	0.20 ± 0.5	0.04 ± 0.2
i	2.0 ± 1.1***	1.07 ± 0.8**	0.50 ± 0.8	0.74 ± 1.0	0.37 ± 0.6
t	2.0 ± 1.0***	0.54 ± 0.5**	0.35 ± 0.6	0.60 ± 0.9**	0.11 ± 0.3
v	0.08 ± 0.3	0 ± 0	0.21 ± 0.8	0.03 ± 0.2	0 ± 0
ptc	2.20 ± 0.7***	1.92 ± 1.0***	0.93 ± 1.0***	0.27 ± 0.6	0.04 ± 0.2
C4d+	80%***	39%**	57%***	0%	4%
cg	0.25 ± 0.5**	0.92 ± 1.2***	0 ± 0	0.14 ± 0.4	0 ± 0
ci	1.17 ± 0.6*	1.62 ± 0.5***	0.50 ± 0.7	1.37 ± 0.7***	0.67 ± 0.6
ct	1.25 ± 0.6	1.85 ± 0.7***	0.93 ± 0.5	1.46 ± 0.6**	0.93 ± 0.6
cv	0.75 ± 0.8	0.78 ± 0.6	0.57 ± 0.7	0.67 ± 0.7	0.41 ± 0.6
Months of follow-up post-dnDSA detection	29 (1–69)	45 (1–88)	19 (0–128)	–	–
Graft failure	57%***	40%***	0%	15%***	0%

Significance level compared to the Stable Function No dnDSA group *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Evolution and Clinical Pathologic Correlations of *De Novo* Donor-Specific HLA Antibody Post Kidney Transplant

American Journal of Transplantation 2012; 12: 1157–1167

C. Wiebe[a,†], I. W. Gibson[b,c,†], T. D. Blydt-Hansen[d], M. Karpinski[e], J. Ho[e], L. J. Storsley[e], A. Goldberg[d], P. E. Birk[d], D. N. Rush[e] and P. W. Nickerson[a,c,*]

- **Pathology in *dn*DSA+ cohort showed progressive chronic active ABMR +/- TCMR**
- **Mixed ABMR/TCMR rejection in 75% (9/12) of nonadherent acute dysfunction dnDSA+ subgroup and 43% (6/14) of indolent dysfunction subgroup**
- **Strong trend to B/TCMR episodes at 0 - 6 months post-Tx, preceding development of *dn*DSA**
- **Prior TCMR was a risk factor for subsequent development of *dn*DSA and ABMR**

Evaluation of C1q Status and Titer of *De Novo* Donor-Specific Antibodies as Predictors of Allograft Survival

C. Wiebe[1,2,*], A. J. Gareau[1], D. Pochinco[2], I. W. Gibson[2,3], J. Ho[1,4], P. E. Birk[5], T. Blydt-Hasen[6], M. Karpinski[1], A. Goldberg[5], L. Storsley[1], D. N. Rush[1] and P. W. Nickerson[1,2,4]

American Journal of Transplantation 2016;

UNIVERSITY OF MANITOBA

- **C1q status correlated with *dn*DSA titer**
- ***dn*DSA titer correlated with TCMR, ABMR & mixed AR**
- **42 biopsies at time of *dn*DSA detection:**
  - **24% (n=10) had ABMR only**
  - **52% (n=22) had mixed ABMR / TCMR**
  - **24% (n=10) had no significant rejection**
- **Recipients with mixed rejection more likely to progress to graft loss (64%) compared to ABMR alone (30%)**
- **Further emphasizes the mixed pattern of alloimmune-mediated injury associated with *dn*DSA, and the need for combined T and B cell interventions**

Evaluation of C1q Status and Titer of *De Novo* Donor-Specific Antibodies as Predictors of Allograft Survival

C. Wiebe[1,2,*], A. J. Gareau[1], D. Pochinco[2], I. W. Gibson[2,3], J. Ho[1,4], P. E. Birk[5], T. Blydt-Hasen[6], M. Karpinski[1], A. Goldberg[5], L. Storsley[1], D. N. Rush[1] and P. W. Nickerson[1,2,4]

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- **42 biopsies at time of *dn*DSA detection:**
  - **24% (n=10) had ABMR only**
  - **52% (n=22) had mixed ABMR / TCMR**
  - **24% (n=10) had no significant rejection**
- **Mixed ABMR / TCMR rejection is common at time of *dn*DSA onset**
- **Recipients with mixed rejection more likely to progress to graft loss (64%) compared to ABMR alone (30%)**
- **Further emphasizes the mixed pattern of alloimmune-mediated injury associated with *dn*DSA, and the need for combined T and B cell interventions**

Early Versus Late Acute Antibody-Mediated Rejection in Renal Transplant Recipients

Christina Dörje,[1,7] Karsten Midtvedt,[1] Hallvard Holdaas,[1] Christian Naper,[2] Erik H. Strøm,[3] Ole Øyen,[1] Torbjørn Leivestad,[1,4] Tommy Aronsen,[5] Trond Jenssen,[1,6] Linda Flaa-Johnsen,[1] Jørn Petter Lindahl,[1] Anders Hartmann,[1] and Anna Varberg Reisæter[1,4]

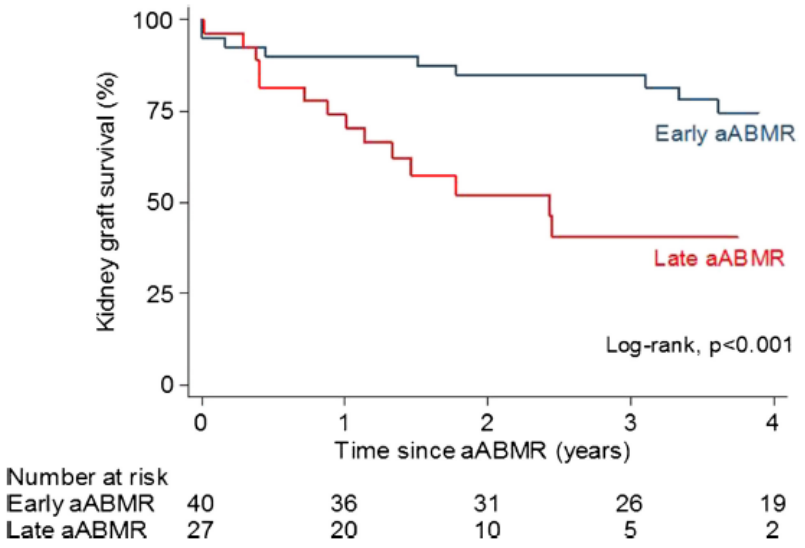


FIGURE 1. Kaplan–Meier estimates of graft survival (non-death-censored) in patients with early aABMR versus late aABMR.

TABLE 2. Biopsy findings at rejection

Banff	Early aABMR (n=40), n (%)	Late aABMR (n=27), n (%)
Concomitant acute TCMR and aABMR	25 (63)	26 (96)
C4d positive	32 (80)	26 (96)
Transplant glomerulopathy	0 (0)	10 (37)
Borderline	8 (20)	13 (48)
IA or IB	5 (12)	11 (41)
IIA or IIB	12 (30)	2 (7)

aABMR, acute antibody-mediated rejection; TCMR, T-cell–mediated rejection.

- **n = 67 ABMR biopsies**
- **40 early (< 3 m) presensitized**
- **27 late (> 3 m) de *novo* DSA**
- **Late ABMR had poorer graft survival**

Mixed ABMR / TCMR in:

- **63% of early ABMR (42% ≥ grade IA)**
- **96% of late ABMR (48% ≥ grade IA)**
- **Mixed rejection phenotype was associated especially with nonadherence in younger recipients**

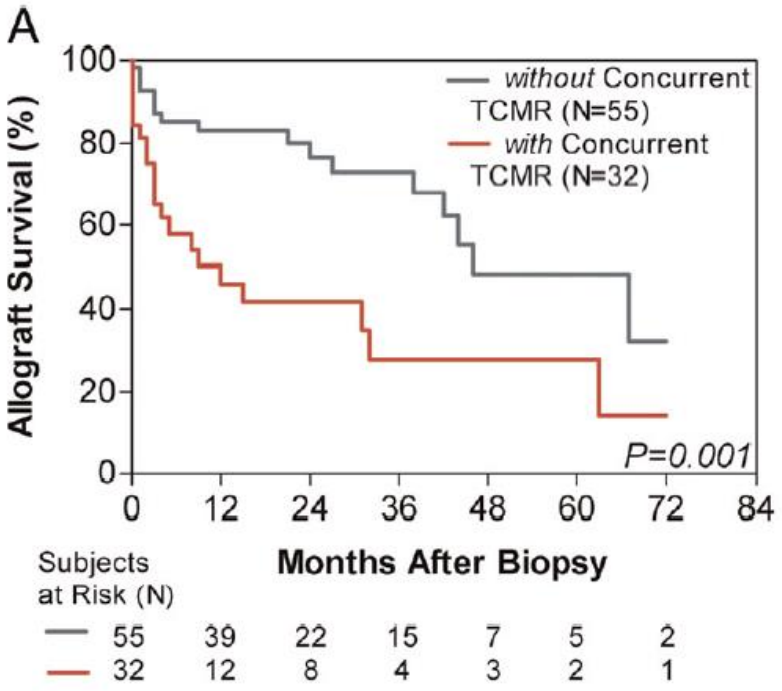
(*Transplantation* 2013;96: 79–84)

Concurrent Acute Cellular Rejection Is an Independent Risk Factor for Renal Allograft Failure in Patients With C4d-Positive Antibody-Mediated Rejection

Marie Matignon,[1,2,3] Thangamani Muthukumar,[1,2,4] Surya V. Seshan,[5] Manikkam Suthanthiran,[2,4] and Choli Hartono[2,4,6,7]

- **n = 87 C4d+ ABMR**
- **37% (32/87) showed concurrent acute TCMR grade 1 or 2**
- **Concurrent TCMR a risk factor for graft failure**

Kaplan-Meier Graft Survival Analysis



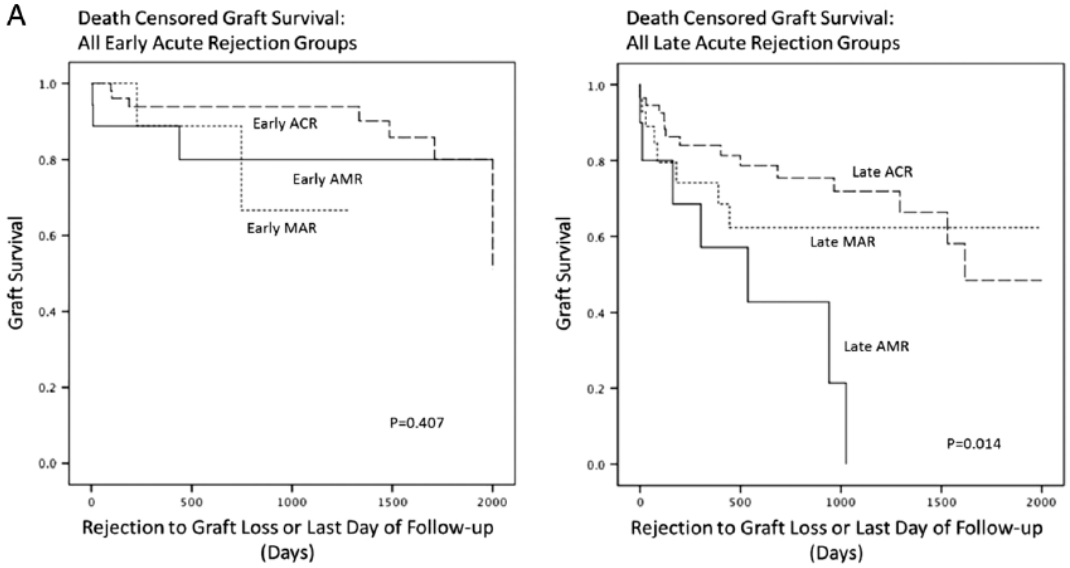
64% of graft failures in the 1st year post-Bx occurred in the mixed rejection subset

(*Transplantation* 2012;94: 603–611)

Acute Rejection Clinically Defined Phenotypes Correlate With Long-term Renal Allograft Survival

Jill C. Krisl, PharmD,[1,2] Rita R. Alloway, PharmD, FCCP,[3] Adele Rike Shield, PharmD,[4] Amit Govil, MD,[3] Gautham Mogilishetty, MD,[3] Michael Cardi, MD,[5] Tayyab Diwan, MD,[2] Bassam G. Abu Jawdeh, MD,[3] Alin Girnita, MD, D-AHBI,[3] David Witte, MD,[3] and E. Steve Woodle, MD, FACS[2]

- **n = 182 recipients with biopsy-proven 1st acute rejection (AR) episode**
- **Evaluated impact of time of AR (early 0-6 months vs late > 6 months post-Tx) and type of rejection (TCMR vs ABMR vs mixed TCMR / ABMR – MAR) on graft & patient survival**



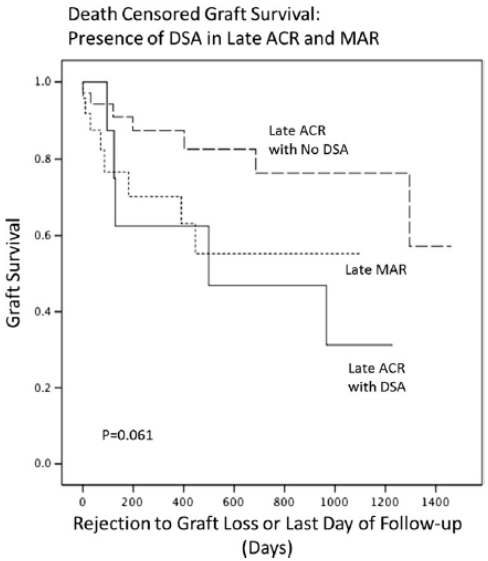


FIGURE 2. Death-censored graft survival: presence of DSA in late ACR and MAR.

- **For all rejection types, late AR had poorer graft survival than early AR**
- **MAR had poorer graft survival than pure TCMR; late ABMR did worst**

(*Transplantation* 2015;99: 2167–2173)

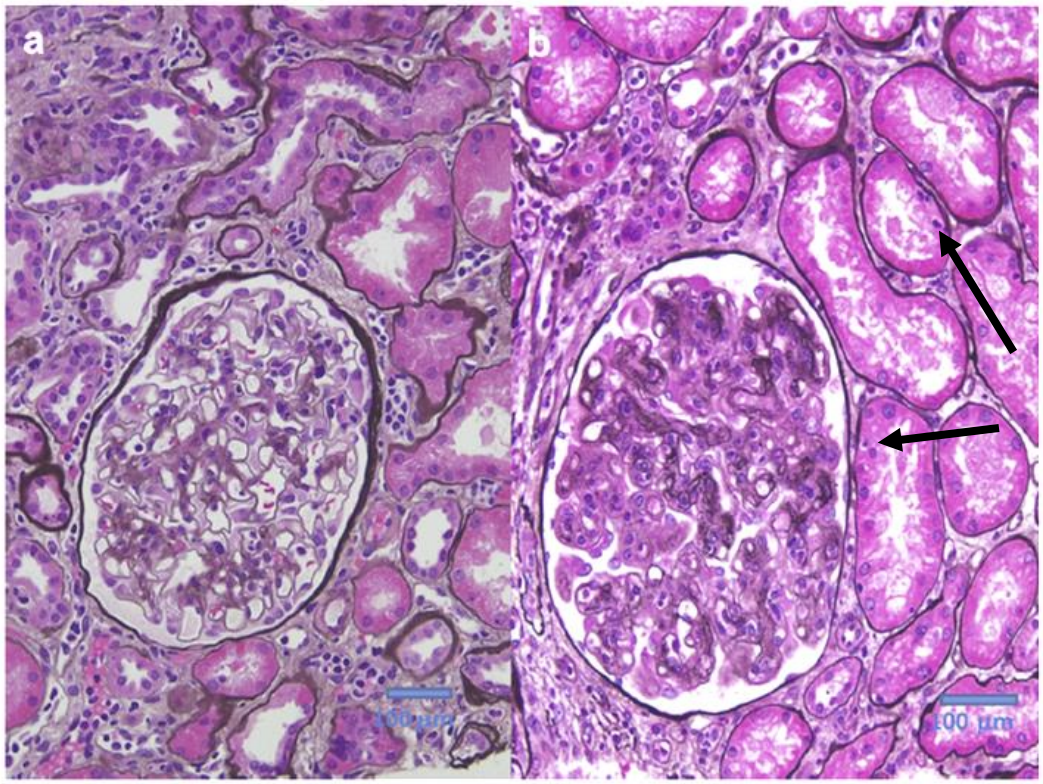
Differences in pathologic features and graft outcomes in antibody-mediated rejection of renal allografts due to persistent/recurrent versus *de novo* donor-specific antibodies

Kidney International (2017)

Mark Haas[1], James Mirocha[2], Nancy L. Reinsmoen[3], Ashley A. Vo[4], Jua Choi[4], Joseph M. Kahwaji[4], Alice Peng[4], Rafael Villicana[4,5] and Stanley C. Jordan[4]

Type 1 ABMR:

- **Presensitized,**
- **<1 year post-Tx**
- **Acute dysfunction**
- **Acute / active ABMR with g/ptc**
- **27% cg>1**
- **27% concurrent B/TCMR**



Type 2 ABMR:

- ***dn*DSA (class II)**
- **>1 year post-Tx**
- **Indolent dysfunction**
- **Chronic active ABMR with g/ptc/cg/ci/ct**
- **53% cg>1**
- **72% concurrent B/TCMR**

Figure 1 | Photomicrographs of representative biopsies showing (a) type 1 and (b) type 2 ABMR. The biopsy of the type 1 lesion, performed 4 months after transplantation, shows acute or active ABMR with glomerulitis and prominent peritubular capillaritis; there is no transplant glomerulopathy (TG) or cell-mediated rejection. The biopsy of the type 2 lesion, performed 23 months after transplantation, shows chronic, active ABMR with TG in addition to glomerulitis and peritubular capillaritis. There are also several tubules with tubulitis seen above and to the right of the glomerulus. Jones methenamine silver stain, original magnification X200 (both panels).

Differences in pathologic features and graft outcomes in antibody-mediated rejection of renal allografts due to persistent/recurrent versus *de novo* donor-specific antibodies

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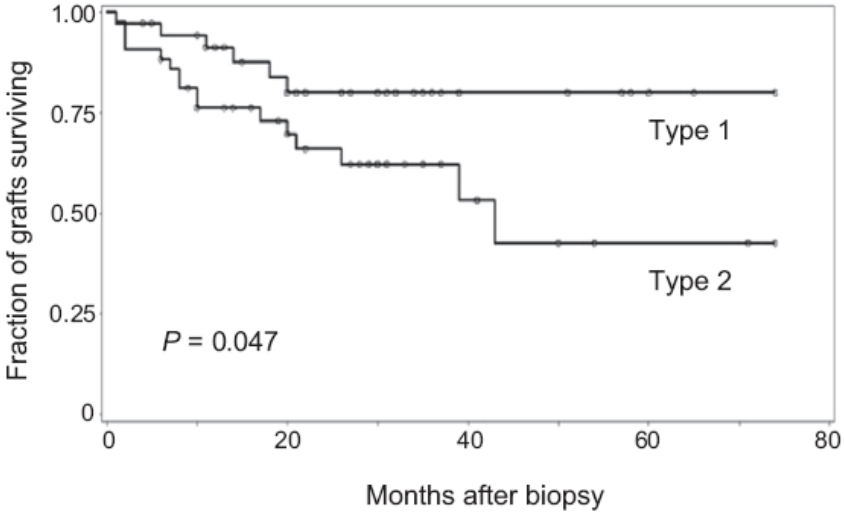

Figure 2 | Kaplan–Meier analysis of death-censored graft survival in patients with type 1 ($n = 37$) and type 2 ($n = 43$) antibody-mediated rejection. Small circles on each curve indicate censored values (time since transplantation to last follow-up without graft loss). The 2 curves are significantly different ($P = 0.047$) by log-rank analysis.

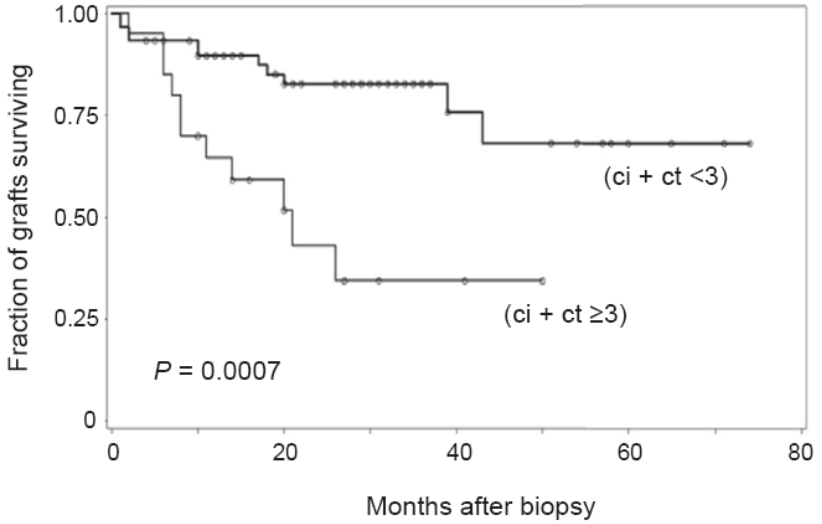

Figure 3 | Kaplan–Meier analysis of death-censored graft survival in patients with antibody-mediated rejection with absent or mild interstitial fibrosis and tubular atrophy (IF/TA) (sum of Banff ci and ct scores <3; $n = 60$) and with at least moderate IF/TA (sum of Banff ci and ct scores ≥3; $n = 20$). Small circles on each curve indicate censored values (time since transplantation to last follow-up without graft loss). The 2 curves are significantly different ($P = 0.0007$) by log-rank analysis.

Almost all patients treated aggressively following diagnosis of ABMR with high-dose IVIG / rituximab +/- plasmapheresis, and for concurrent TCMR Banff IA or higher with steroids +/- thymoglobulin

Differences in pathologic features and graft outcomes in antibody-mediated rejection of renal allografts due to persistent/recurrent versus *de novo* donor-specific antibodies

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In cases of ABMR, a significant predictor of development of graft loss was a mixed rejection phenotype, with concurrent TCMR of Banff grade IA or higher

Table 3 | Predictors of death-censored graft loss

A. Univariate analysis

Predictor	Hazard Ratio (95% CI)	*P* Value
Age	1.01 (0.99–1.04)	0.33
Male gender	0.74 (0.32–1.70)	0.33
Live donor	1.97 (0.85–4.56)	0.12
Biopsy indication: progressive dysfunction	1.48 (0.64–3.46)	0.36
Interval transplant to biopsy ≥ 84 months	2.56 (1.05–6.22)	0.038
Type 2 versus type 1 ABMR	2.51 (0.98–6.43)	0.054
C4d score 2–3 versus 0–1	1.16 (0.43–3.15)	0.77
cg score ≥ 1	2.31 (0.98–5.42)	0.054
Chronic, active versus acute/active ABMR	1.97 (0.84–4.63)	0.12
(ci + ct) ≥ 3	3.88 (1.67–9.05)	0.002
CMR, Banff grade 1a or higher	2.48 (1.07–5.75)	0.037
TMA	2.58 (0.75–8.84)	0.13
Presence of anti-HLA DQ DSA	1.53 (0.62–3.76)	0.36
Decrease in RIS score > 2	0.21 (0.06–0.70)	0.012

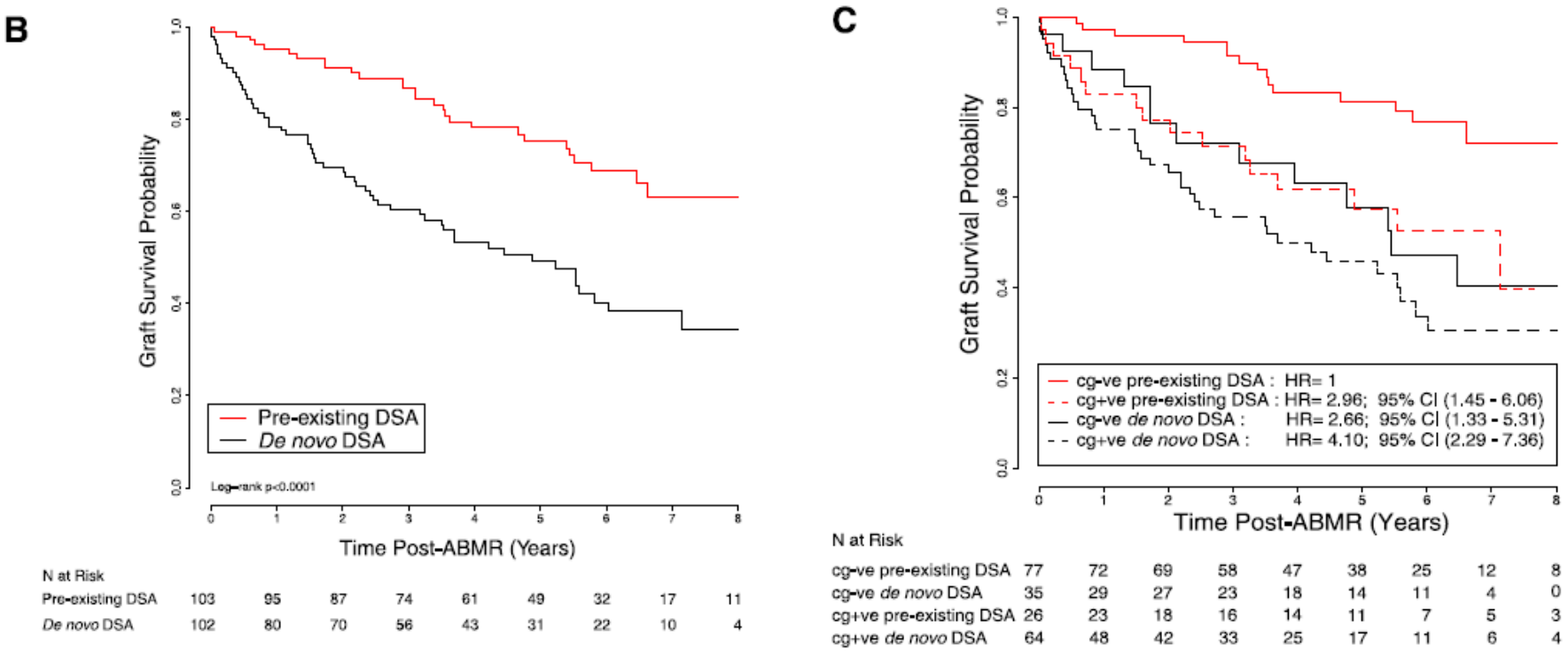
B. Multivariable analysis

Predictor	Hazard ratio	95% CI	*P* value
(ci + ct) ≥ 3	2.98	1.26–7.06	0.013
Decrease in RIS score > 2	0.23	0.07–0.79	0.020
CMR, Banff grade 1a or higher	2.19	0.93–5.15	0.074

Question: ***Is the lymphocytic tubulitis with intraepithelial CD3+ T cells seen in association with type 2 ABMR (mixed rejection phenotype) of the same biological significance as the lymphocytic tubulitis with intraepithelial CD3+ T cells seen in pure TCMR ?***

Antibody-Mediated Rejection Due to Preexisting versus *De Novo* Donor-Specific Antibodies in Kidney Allograft Recipients

Olivier Aubert,* Alexandre Loupy,*†‡ Luis Hidalgo,§‖ Jean-Paul Duong van Huyen,¶ Sarah Higgins,** Denis Viglietti,*†† Xavier Jouven,* Denis Glotz,*†† Christophe Legendre,*†‡ Carmen Lefaucheur,*†† and Philip F. Halloran‖‡‡



- **Multicentre study of ABMR (5 European / 2 N. American centres)**
- **Poorer graft survival for *de novo* DSA cohort, especially if TG+**

Antibody-Mediated Rejection Due to Preexisting versus *De Novo* Donor-Specific Antibodies in Kidney Allograft Recipients

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Table 2. Histology, DSA, and renal function at the time of ABMR-proven biopsy

Parameters	Preexisting Anti-HLA DSA ABMR (*n*=103)	*De Novo* Anti-HLA DSA ABMR (*n*=102)	*P* Value
Histology			
g (0–3), mean (SD)	1.71 (1.02)	1.06 (0.91)	<0.001
ptc (0–3), mean (SD)	1.76 (0.98)	1.66 (1.00)	0.47
C4d positive, *n* (%)	53 (51.46)	39 (42.39)	0.13
cg (0–3), mean (SD)	0.48 (0.94)	1.28 (1.15)	<0.001
i (0–3), mean (SD)	0.61 (0.92)	1.23 (1.01)	<0.001
t (0–3), mean (SD)	0.59 (0.90)	1.01 (1.11)	0.003
v (0–3), mean (SD)	0.32 (0.65)	0.22 (0.60)	0.29
ci (0–3), mean (SD)	0.96 (1.04)	1.60 (0.92)	<0.001
ct (0–3), mean (SD)	0.99 (0.99)	1.60 (0.91)	<0.001
cv (0–3), mean (SD)	1.26 (1.00)	1.44 (0.98)	0.2
ah (0–3), mean (SD)	0.97 (0.92)	1.53 (1.05)	<0.001
Immunology at the time of the ABMR biopsy			
Anti-HLA DSA class 1, *n* (%)	40 (38.83)	26 (25.49)	
Anti-HLA DSA class 2, *n* (%)	63 (61.17)	76 (74.51)	0.02
Anti-HLA DSA MFI, median [IQR]	2561 [1252–6937]	7295 [1948–11,814]	<0.001
Renal function			
eGFR, ml/min per 1.73 m^2, mean (SD)	39.00±18.26	41.65±21.19	0.34
Proteinuria, g/g creatinine, mean (SD)	0.51±1.05	1.51±2.51	<0.001

g, glomerulitis; ptc, peritubular capillaritis; cg, transplant glomerulopathy; i, interstitial inflammation; t, tubulitis; v, endarteritis; ci, interstitial fibrosis; ct, tubular atrophy; cv, arteriosclerosis; ah, arteriolar hyaline thickening; MFI, mean fluorescence intensity.

More proteinuria, TG & IF/TA in *de novo* DSA ABMR (later 'for cause' biopsies)

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Table 2. Histology, DSA, and renal function at the time of ABMR-proven biopsy

Parameters	Preexisting Anti-HLA DSA ABMR (*n*=103)	*De Novo* Anti-HLA DSA ABMR (*n*=102)	*P* Value
Histology			
g (0–3), mean (SD)	1.71 (1.02)	1.06 (0.91)	<0.001
ptc (0–3), mean (SD)	1.76 (0.98)	1.66 (1.00)	0.47
C4d positive, *n* (%)	53 (51.46)	39 (42.39)	0.13
cg (0–3), mean (SD)	0.48 (0.94)	1.28 (1.15)	<0.001
i (0–3), mean (SD)	0.61 (0.92)	1.23 (1.01)	<0.001
t (0–3), mean (SD)	0.59 (0.90)	1.01 (1.11)	0.003
v (0–3), mean (SD)	0.32 (0.65)	0.22 (0.60)	0.29
ci (0–3), mean (SD)	0.96 (1.04)	1.60 (0.92)	<0.001
ct (0–3), mean (SD)	0.99 (0.99)	1.60 (0.91)	<0.001
cv (0–3), mean (SD)	1.26 (1.00)	1.44 (0.98)	0.2
ah (0–3), mean (SD)	0.97 (0.92)	1.53 (1.05)	<0.001
Immunology at the time of the ABMR biopsy			
Anti-HLA DSA class 1, *n* (%)	40 (38.83)	26 (25.49)	
Anti-HLA DSA class 2, *n* (%)	63 (61.17)	76 (74.51)	0.02
Anti-HLA DSA MFI, median [IQR]	2561 [1252–6937]	7295 [1948–11,814]	<0.001
Renal function			
eGFR, ml/min per 1.73 m^2, mean (SD)	39.00±18.26	41.65±21.19	0.34
Proteinuria, g/g creatinine, mean (SD)	0.51±1.05	1.51±2.51	<0.001

g, glomerulitis; ptc, peritubular capillaritis; cg, transplant glomerulopathy; i, interstitial inflammation; t, tubulitis; v, endarteritis; ci, interstitial fibrosis; ct, tubular atrophy; cv, arteriosclerosis; ah, arteriolar hyaline thickening; MFI, mean fluorescence intensity.

More interstitial inflammation & tubulitis in *de novo* DSA ABMR. Is it TCMR?

Antibody-Mediated Rejection Due to Preexisting versus *De Novo* Donor-Specific Antibodies in Kidney Allograft Recipients

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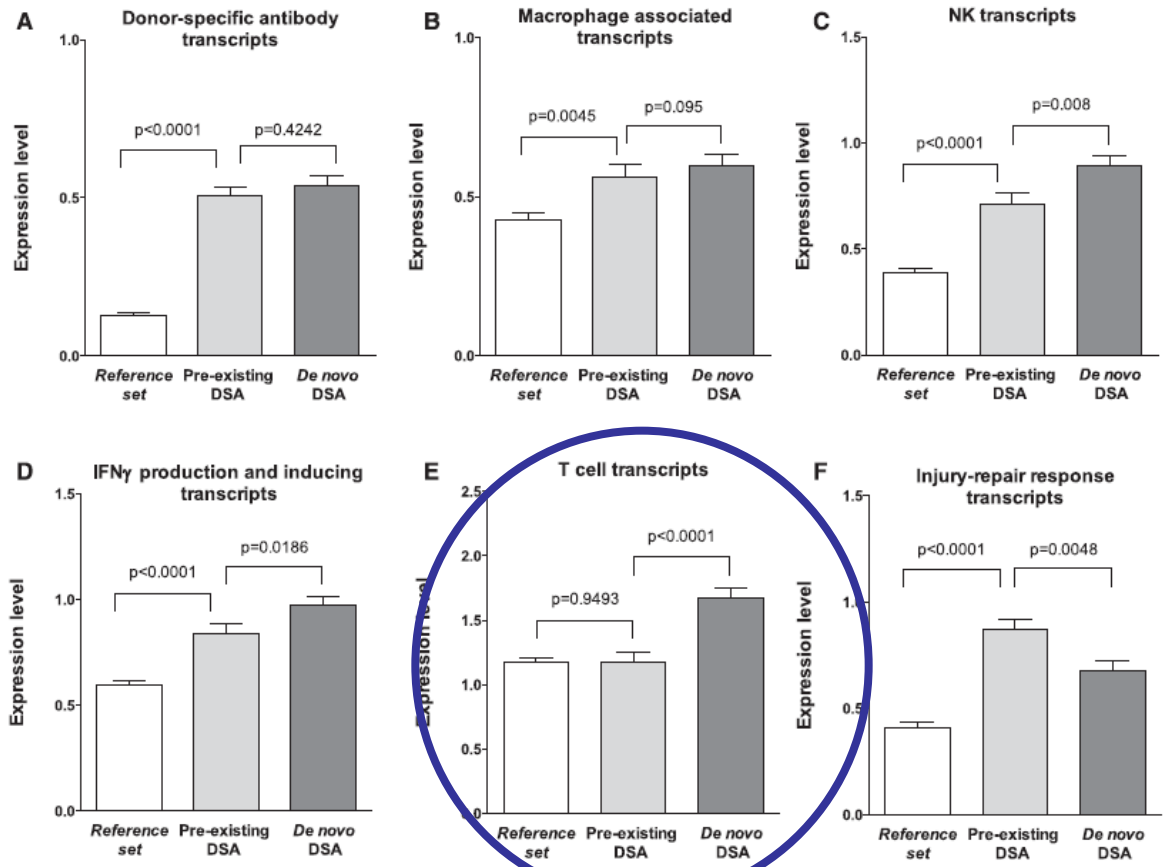

Figure 3. Molecular biopsy scores according to DSA characteristics. Data are on the basis of 666 kidney allograft biopsies assessed for intragraft gene expression of the PBTs ([A] endothelial DSA-selective transcripts, [B] macrophage-inducible transcripts, [C] natural killer cell [NK] transcripts, [D] IFNγ production and inducing transcripts, [E] T cell transcripts, [F] injury–repair response transcripts) according to circulating anti-HLA DSA and ABMR status (reference set without ABMR, preexisting DSA ABMR, and *de novo* DSA ABMR). The T bars indicate SEM and DSA denotes anti-HLA DSA.

Effector T cell transcripts significantly higher in the later *de novo* DSA ABMR cohort, c/w concurrent active TCMR, i.e. true mixed ABMR / TCMR rejection in type 2 ABMR

Mixed Allograft Rejection

- Early TCMR in months 0 - 6 post-Tx may be causal in the subsequent development of *de novo* DSA and ABMR
- Concurrent TCMR is not uncommon in the setting of late ABMR with *de novo* DSA; contributing to graft dysfunction and accelerated graft loss
- Pathologists need to boldly make the diagnosis of mixed ABMR / TCMR rejection
- Expect to find a mixed pattern of rejection in context of an under-immunosuppressed allograft recipient due to nonadherence +/- clinical complications of drug toxicity
- Anti-T cell as well as anti-B cell therapy should be considered to aggressively treat mixed rejection phenotype

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