Humoral rejection and hyperimmune patients

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Hystory I

- 1960 “donor specific antibodies” (DSA) first suggestion for a possible role in deteriorating renal function
- 1970 (Jeannet) – worse graft outcome when DSA are present
- 1990 (Halloran) - humoral rejection is clearly identified. Clinics and pathology are defined

Hystory II

- 1991, 1993 Feucht identifies “C4d” (byproduct after C4 metabolism) in peritubular capillaries of “high immunonologic risk” patients
- C4d was thereafter proposed as a specific marker for humoral rejection

Hystory III

- 1999 Collins: C4d staining within peritubular capillaries is associated to circulating antibodies against class I and II HLA donor antigens

HYPERACUTE REJECTION

Hyperacute

- Due to preformed antibodies. It is extremely rare.
- According to NAPRTCS data, incidence less than 0,25% (17/6.800 graft) in 15 years
- Routinary use of pre-graft cross-match makes it quite unlikely

Mechanism

- Preformed donor specific antibodies against ABO or HLA antigens (and other antigens?) bind to vessel endothelium and activate complement mediate response

histopathology

- Arteries: segmental and transmural fibrinoid necrosis of the wall with focal rupture of the elastic lamina.
- Glomeruli: partial thrombosis and necrosis of the tuft; capillary lumina are diffusely restricted by endothelial swelling and hyperplasia, mononuclear cells and neutrophils infiltration.
- Tubuli: swelling and vacuolization of the epithelial cells; small foci of inflammatory cells in the interstitium.
- Large areas of haemorrhagic extravasation due to necrosis of venules and of peritubular capillaries are commonly seen.

Therapy (largely uneffective)

- Steroid pulses
- Plasmaexchange /immunoadsorption
- Ev Ig
- Rituximab
- Bortezomib
- eculizumab

ACUTE/CHRONIC HUMORAL REJECTION

Mauyyedi JASN 2002

- 232 patients
- 81 with acute rejection
- 14 excluded
  - 9 no biopsy
  - 4 no IF
  - 1 no serum for DSA search

C4d vs donor specific antibodies

	N	DSA
C4d+	20	18 (90%)
C4d-	47	1 (2%)

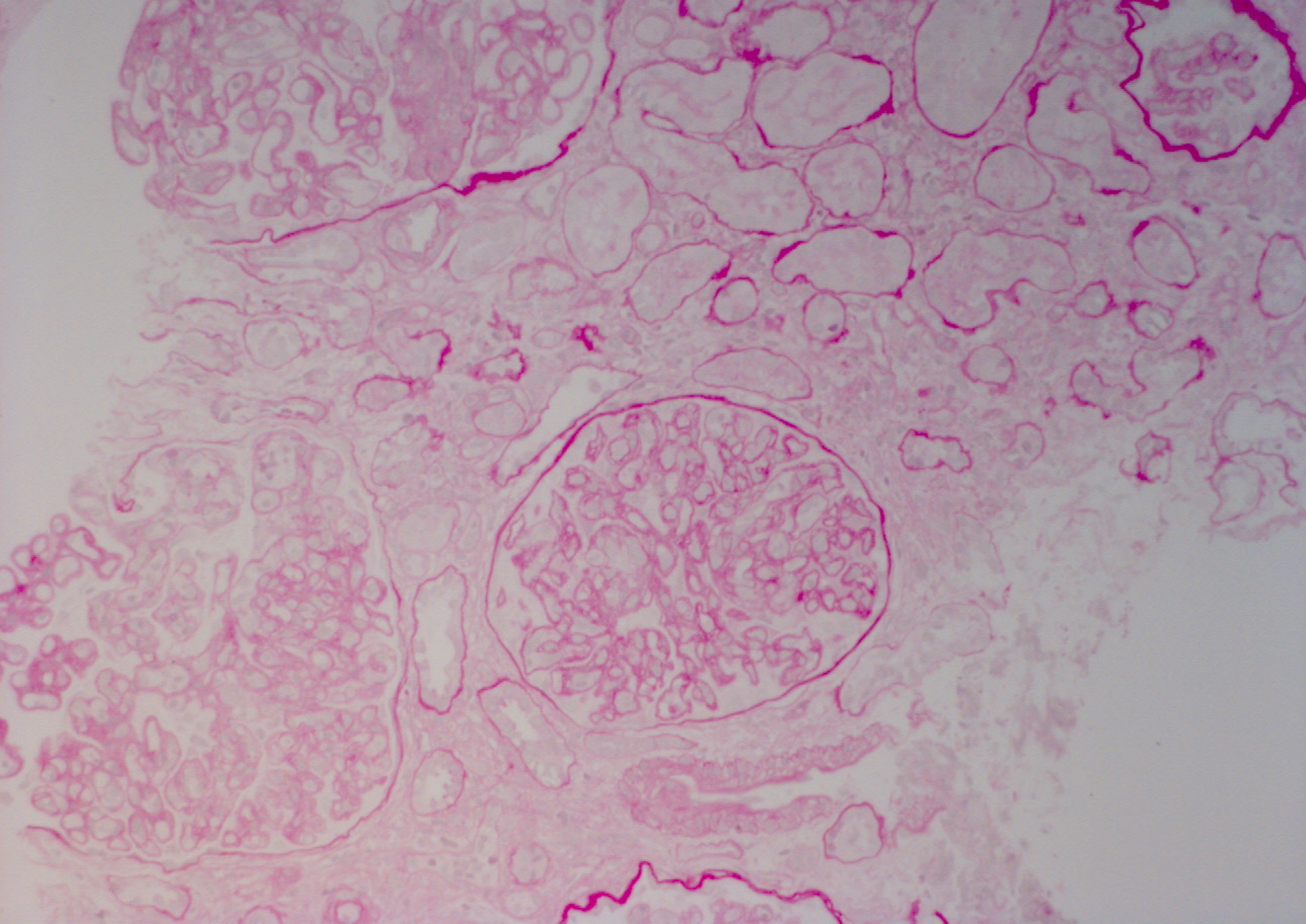
Antibody mediated rejection

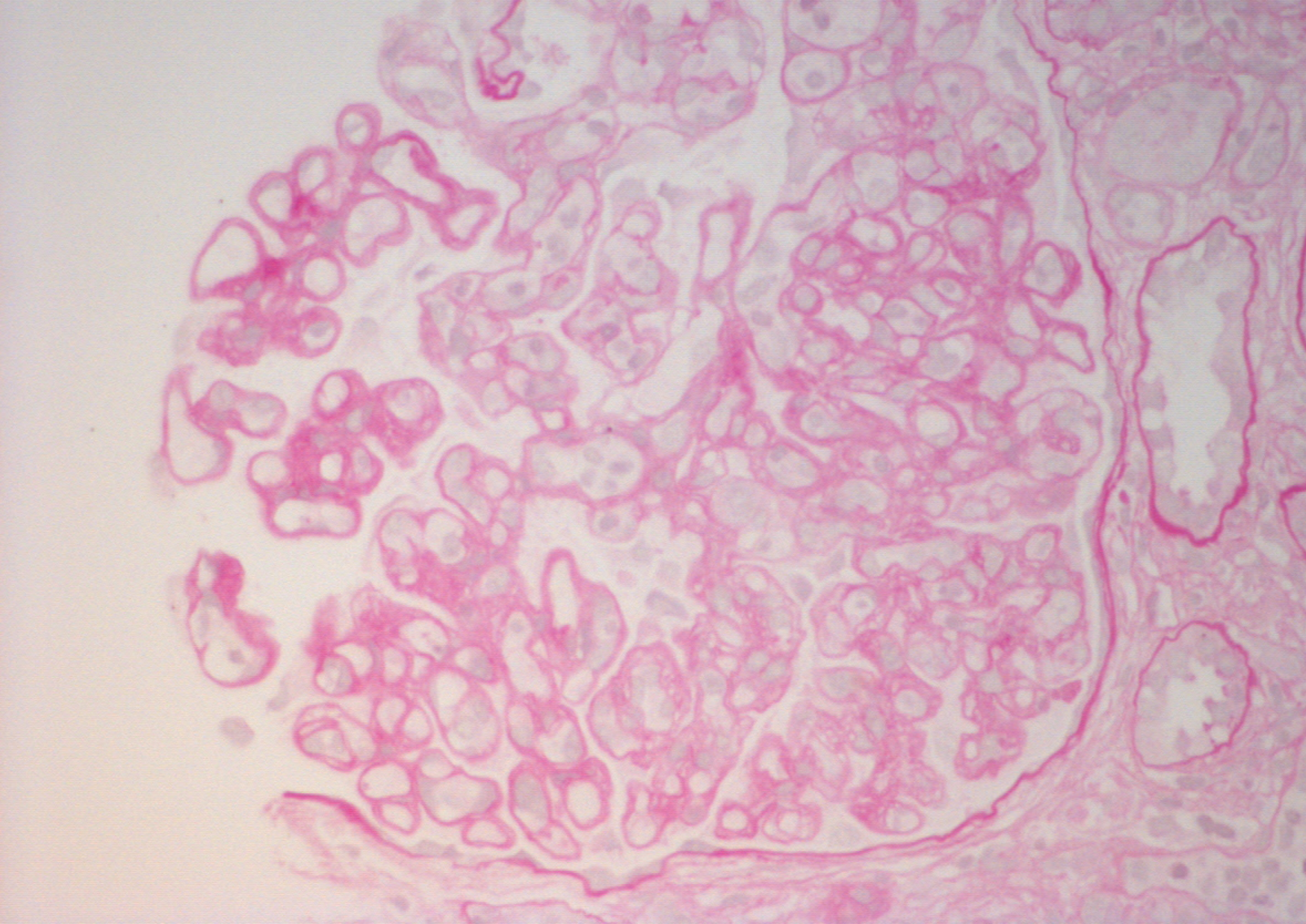
- Histology
  - acute tubular injury,
  - neutrophils and/or mononuclear cells in peritubular capilaries and/or glomeruli and/or capillary thrombosis, fibrinoid necrosis/intramural or transmural inflammation in arteries
- immunopathologic evidence: C4d or immunoglobulins deposition in peritubular capilaries
- serologic evidence: anti-donor antibodies

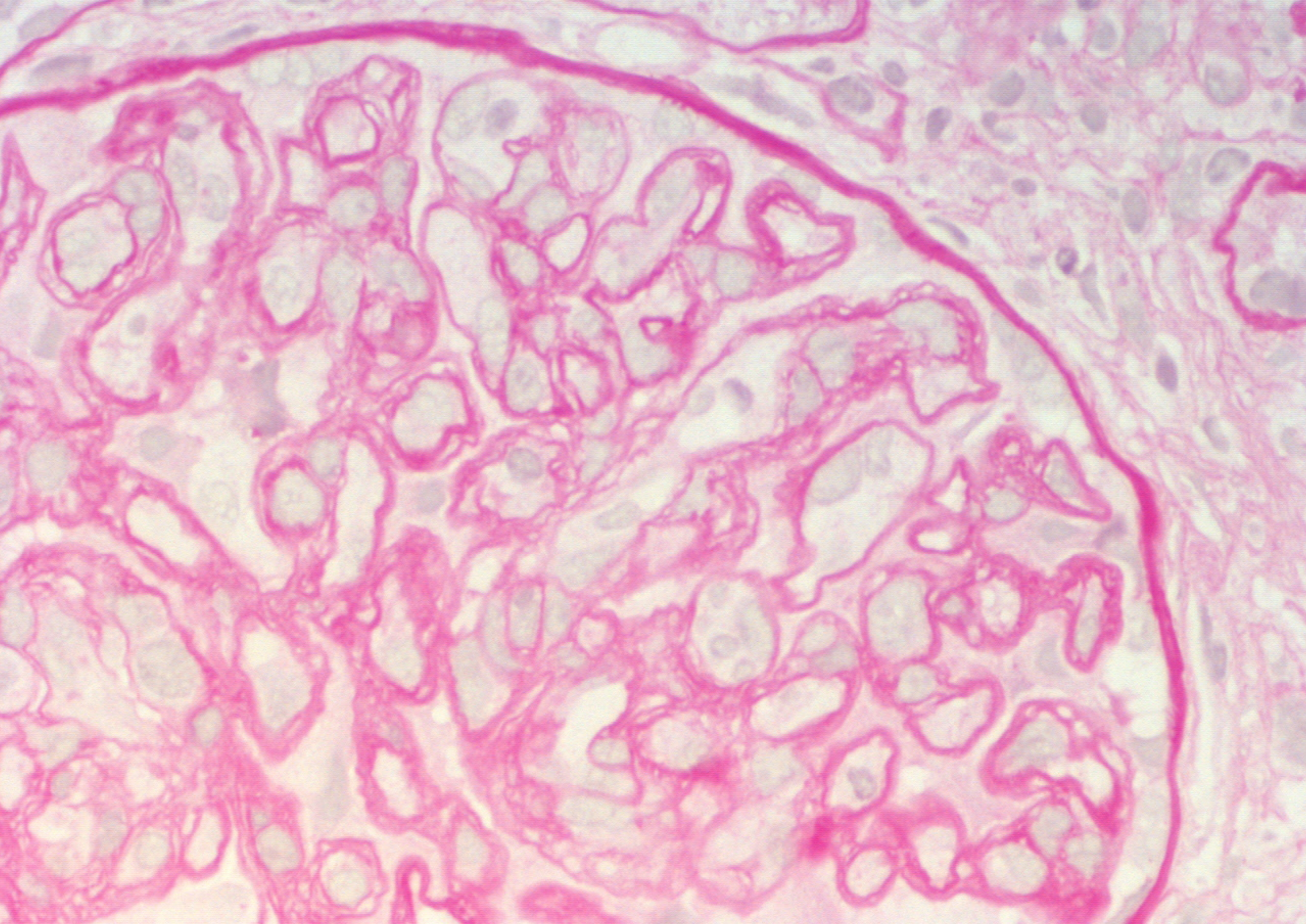
Racusen AJT 2003

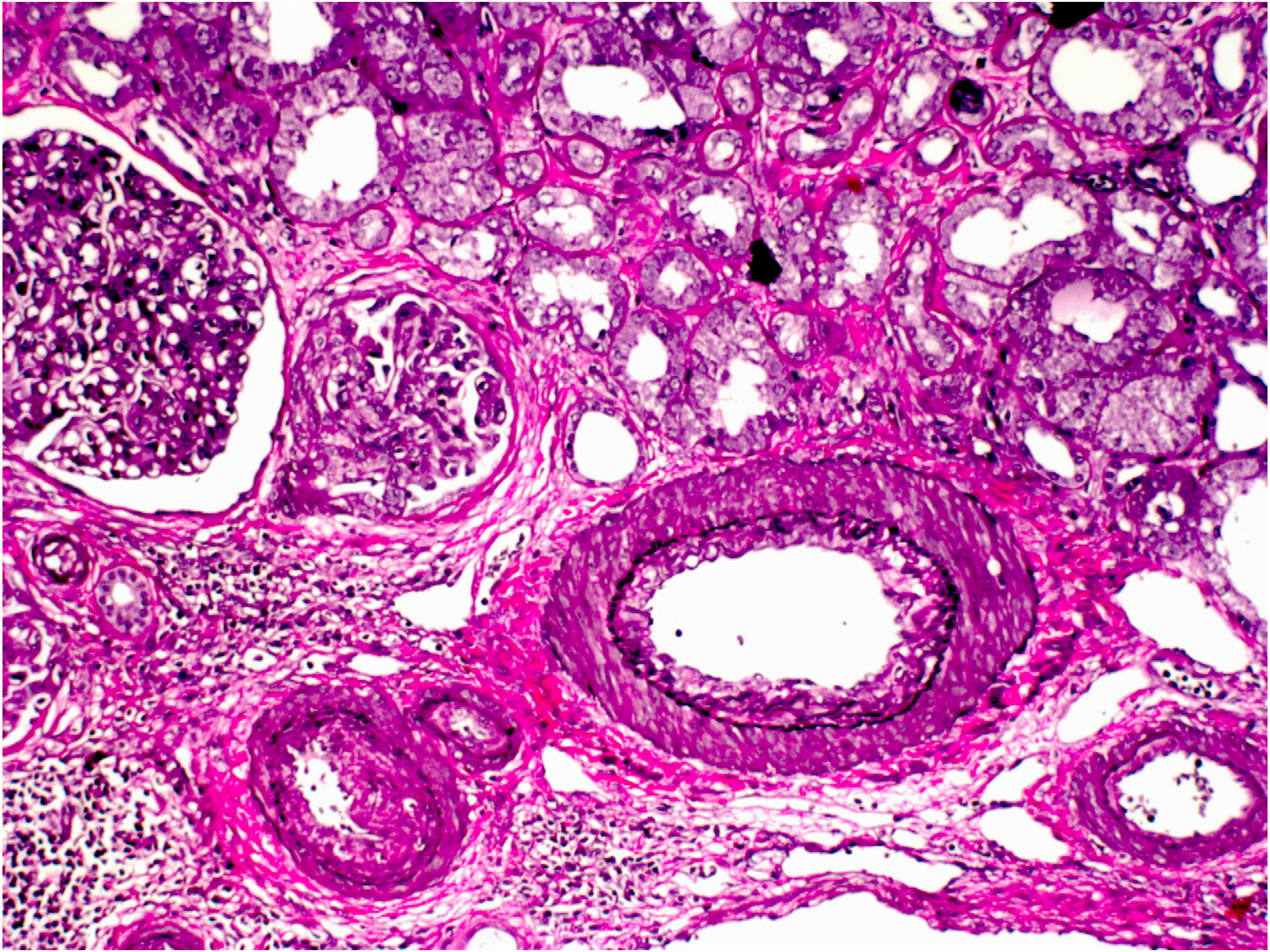
Worth noting:

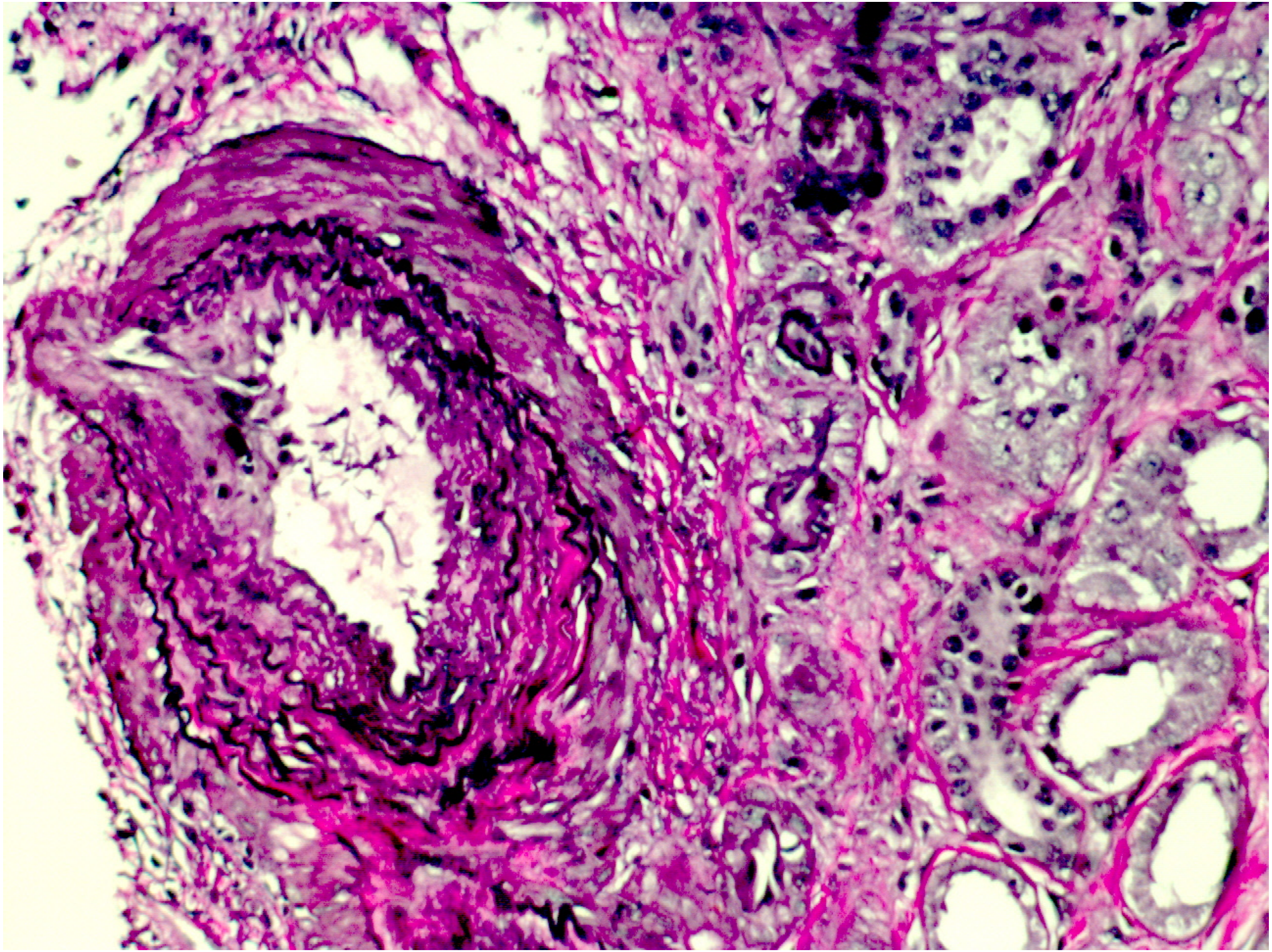
- Antibody mediated rejection (AMR) is evident in 32% of all biopsies performed during acute rejection
- C4d is a highly sensible (95%) and specific (96%) marker for AMR if in the right place (peritubular capillary)
- And it is pathognonomic only in cases of rejection

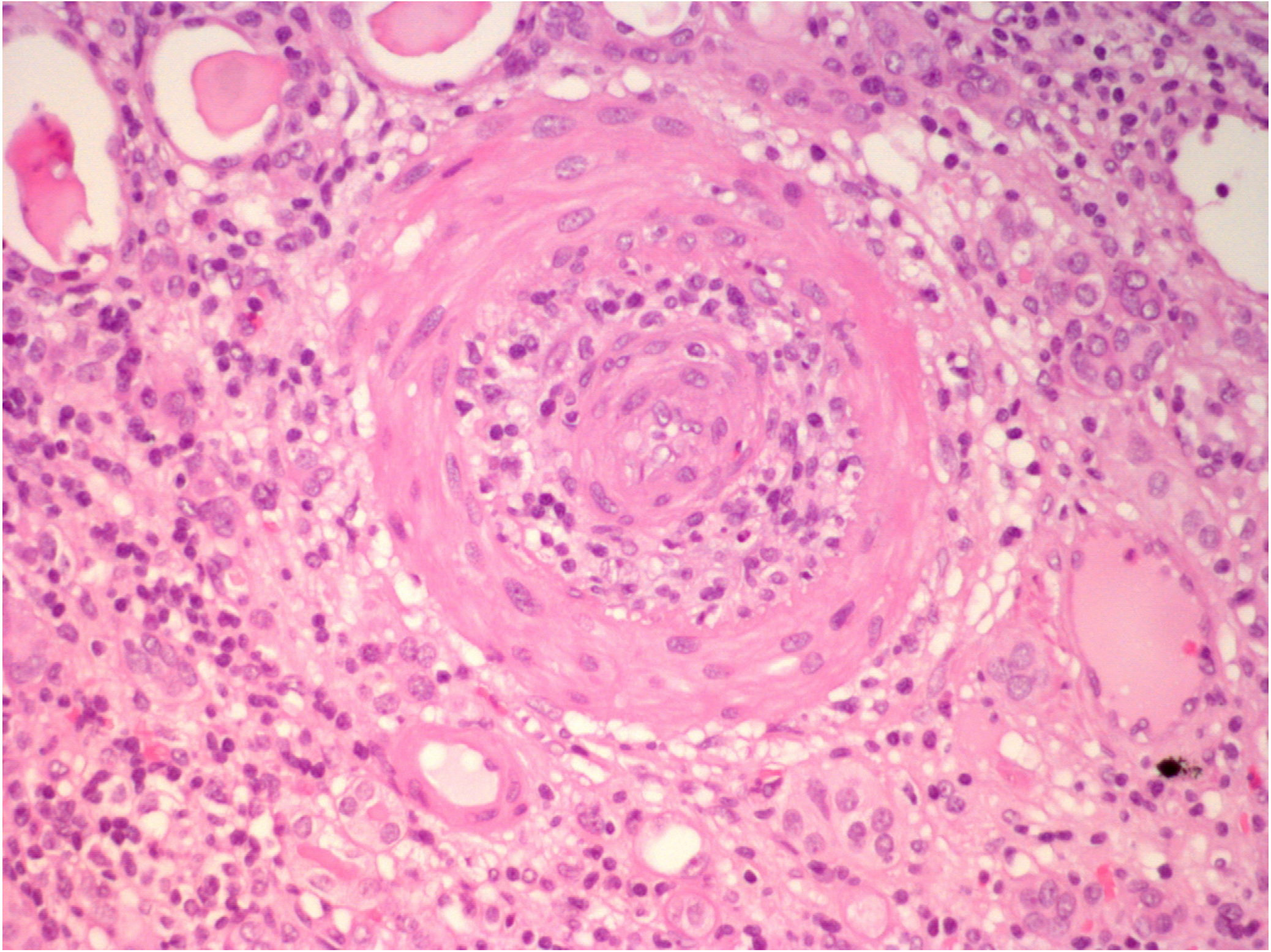




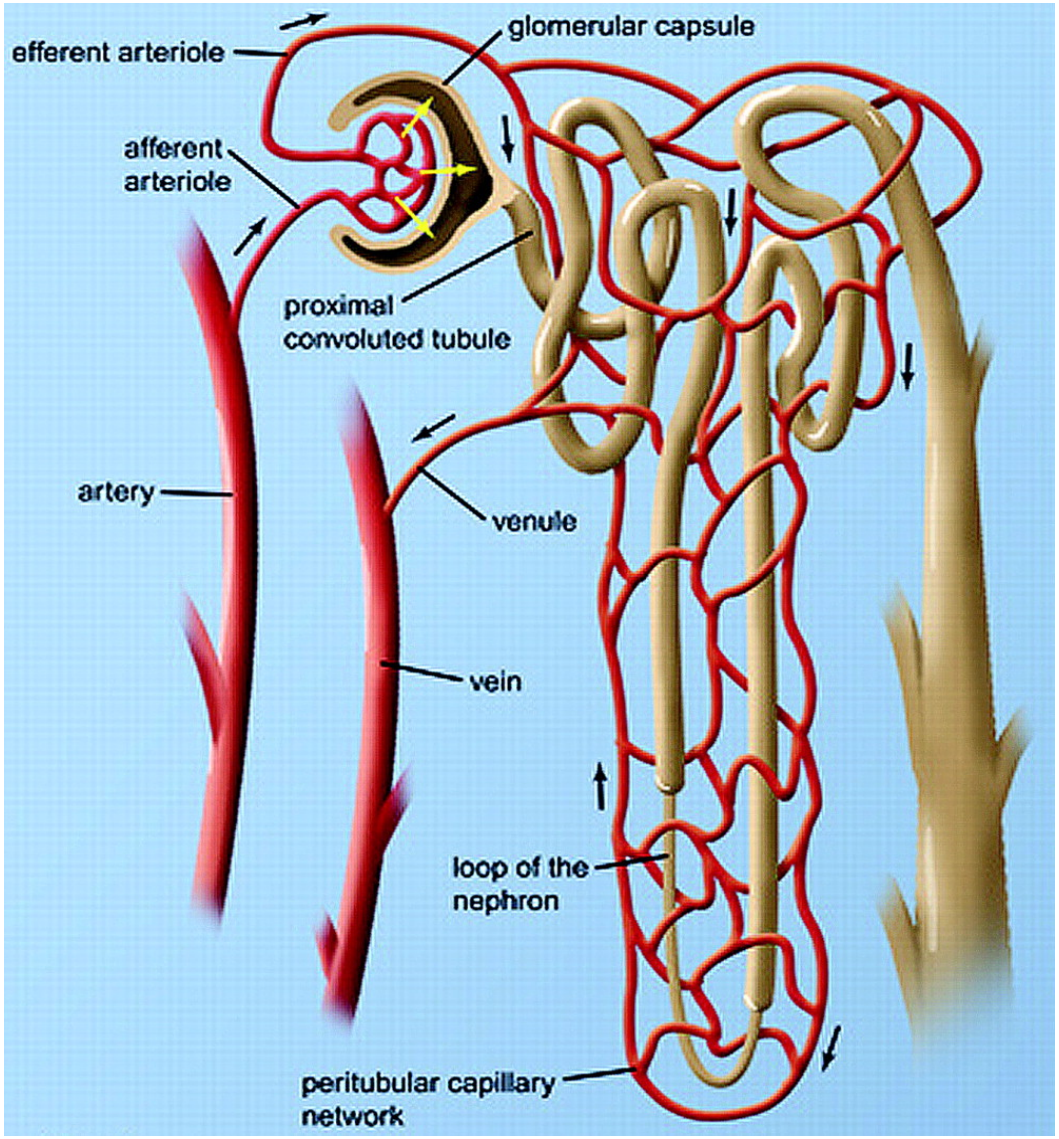




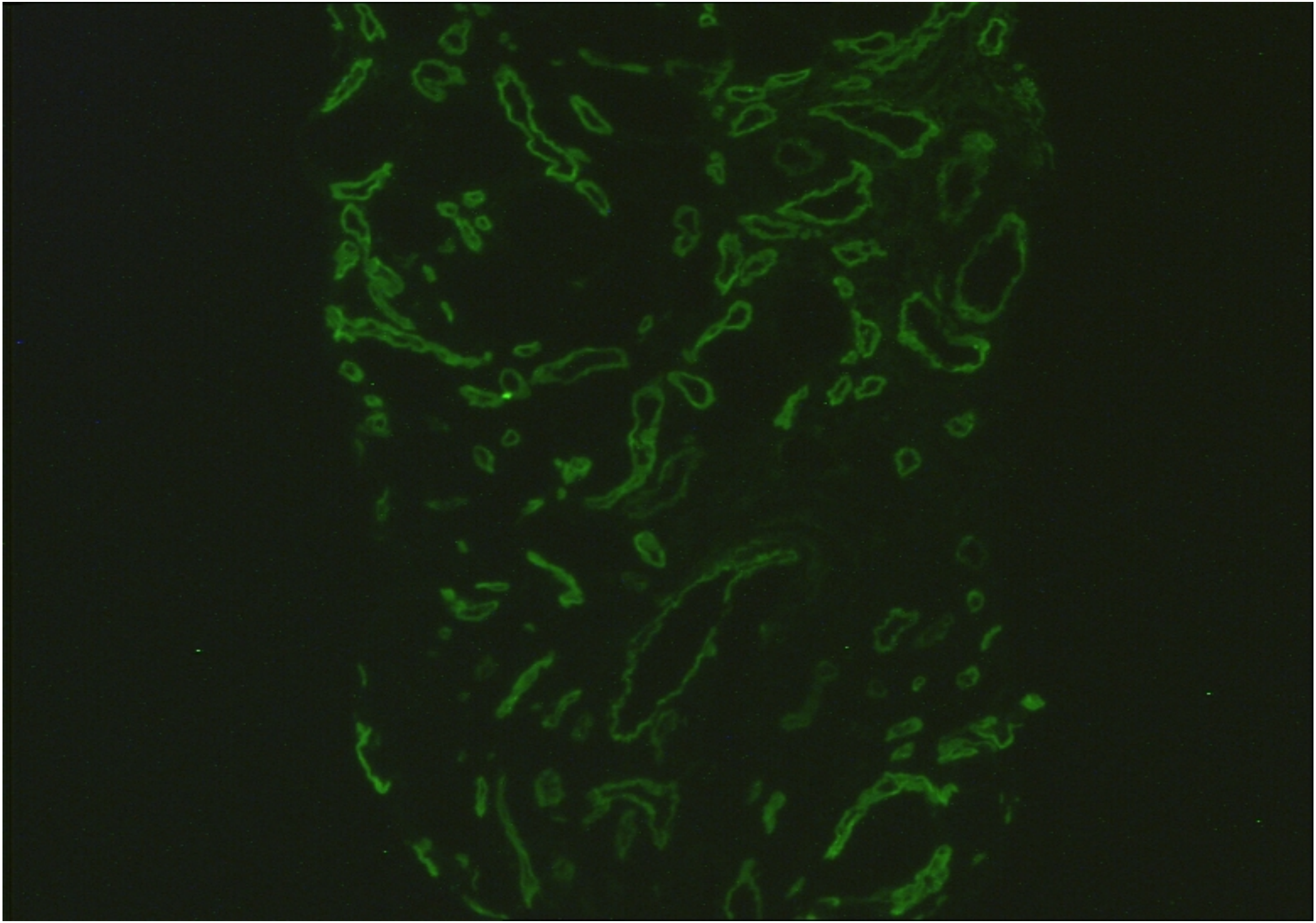


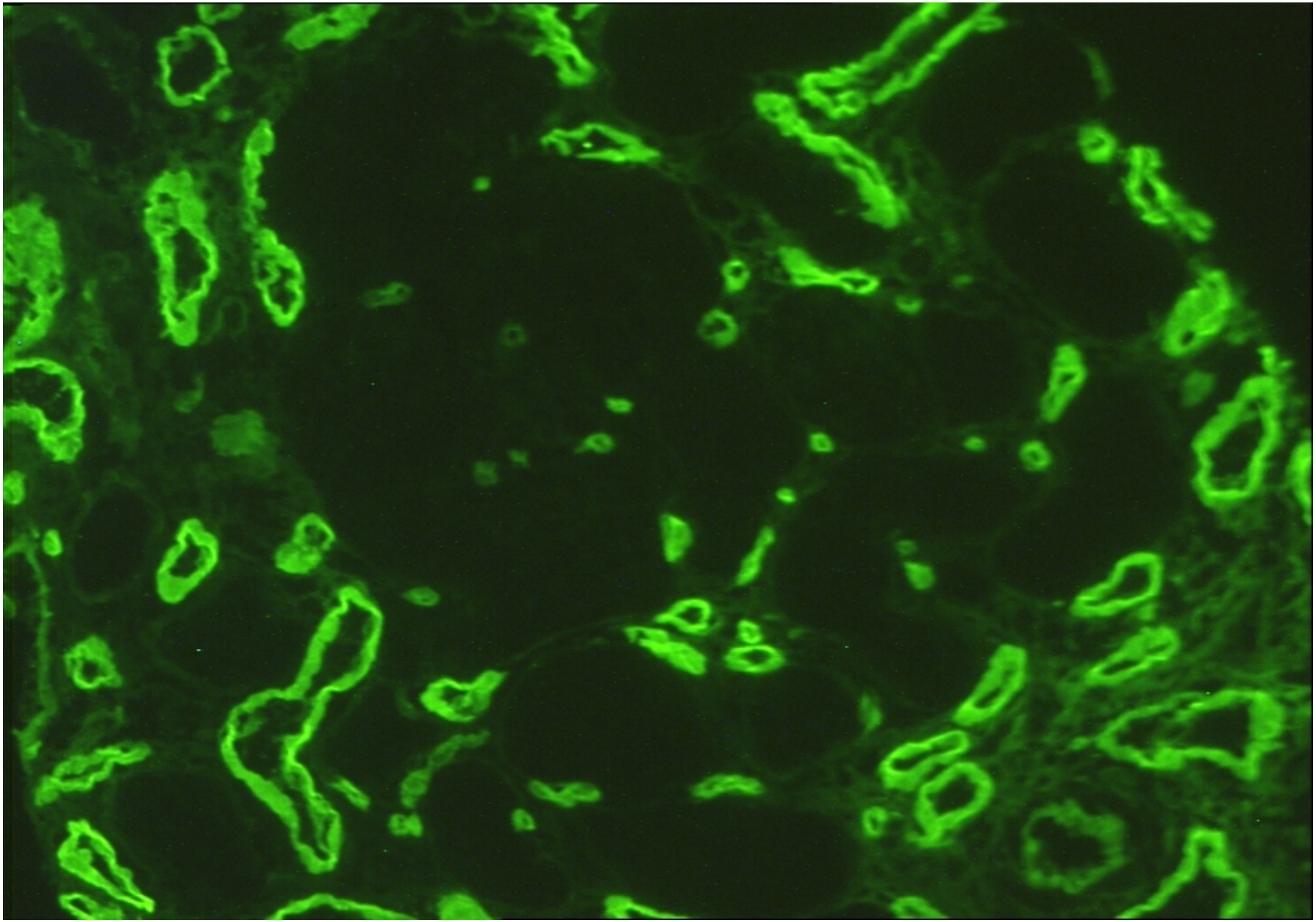


The microvasculature of the nephron.



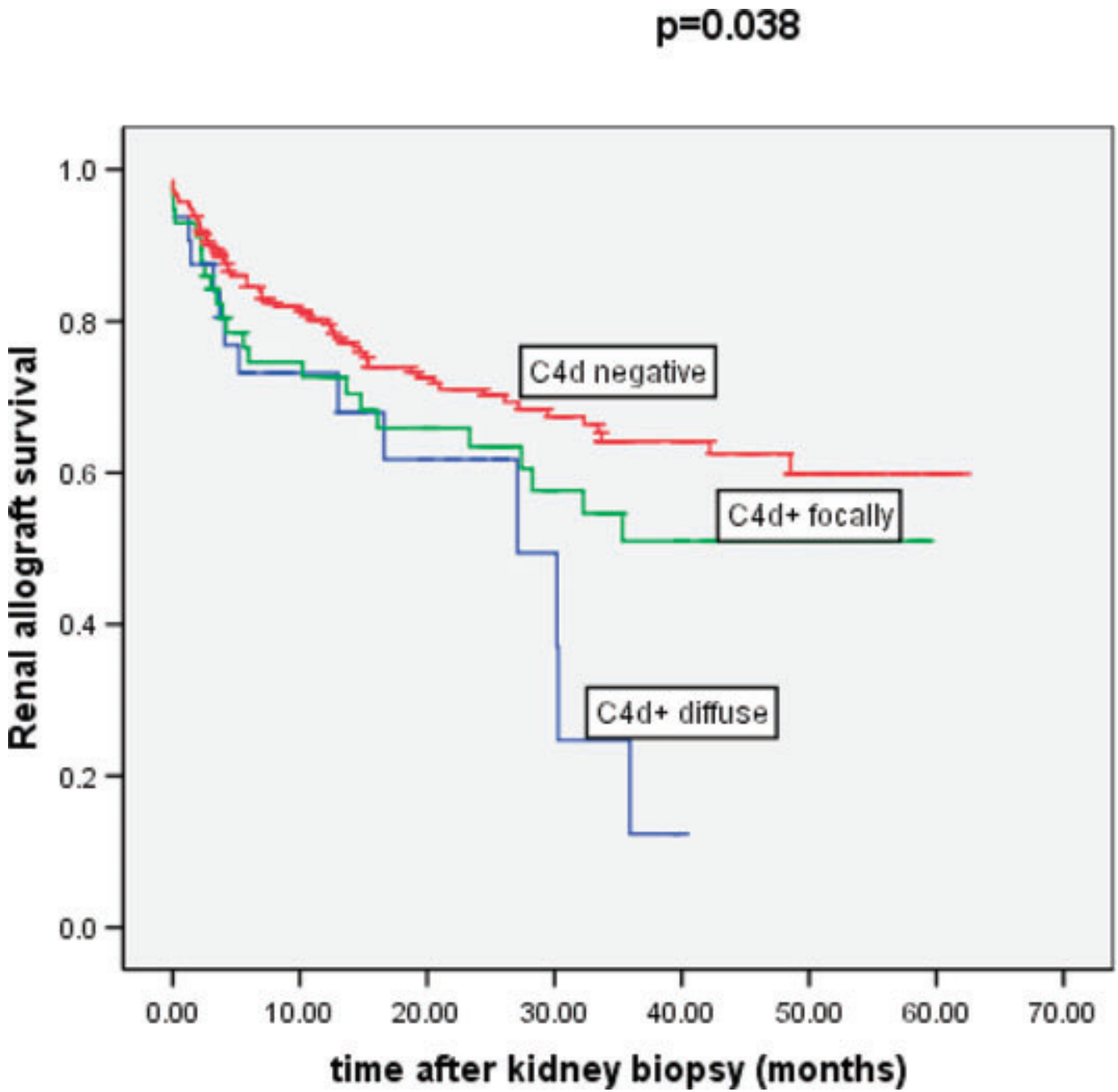
Nangaku M JASN 2006;17:17-25





Iterative Biopsies

- C4d may disappear 2-3 weeks after DSA disappearance
- Its persistence may associate with chronic rejection



American Journal of Transplantation 2009; 9: 812–819

DONOR SPECIFIC ANTIBODIES

Antibody mediated rejection

- Preformed antibodies
- *de novo* antibodies
  - Against class I or II anti HLA antigens
  - MICA
  - Agonistic antibodies against the Angiotensin II type 1 receptor (AT1R-AA)
  - Others (Anti-vimentine,….)

What are MICA?

- MICA = Major-histocompatibility-complex class I–related chain A (MICA) antigens
- are surface glycoproteins with functions related to innate immunity .
- are expressed on endothelial cells, dendritic cells, fibroblasts, epithelial cells, but not on peripheral-blood lymphocytes.
- Therefore, antibodies directed against MICA are not detected with the methods generally used for routine cross-match.

N Engl J Med 2007;357:1293-300.

Agonistic antibodies against the Angiotensin II type 1 receptor (AT1R-AA)

- Classically reported a rejection with severe hypertension
- Hystology: endarteritis, transmural arteritis and/or fibrinoid vascular necrosis (Banff IIb or Banff III)
- Is it a "true-rejection" or an autoimmune phenomenon triggered in the permissive allogeneic and postiischemic inflammatory enviroment?

Dragun N Engl J Med 2005; 352: 558–69

- Prospectic study on 2000 patients: circulating alloantibodies shorten 1 and 2 years graft survival (Terasaki PI, Transplantation 2005; 80: 1194.).
- De novo DSA associate with worse graft outcome (Colvin RB. JASN 2007; 1046).
- Also antibodies against other antigens (MICA) lead to poor graft outcome (Zou Y NEJM 2007; 357: 1293.).

Evolution: hypothesis

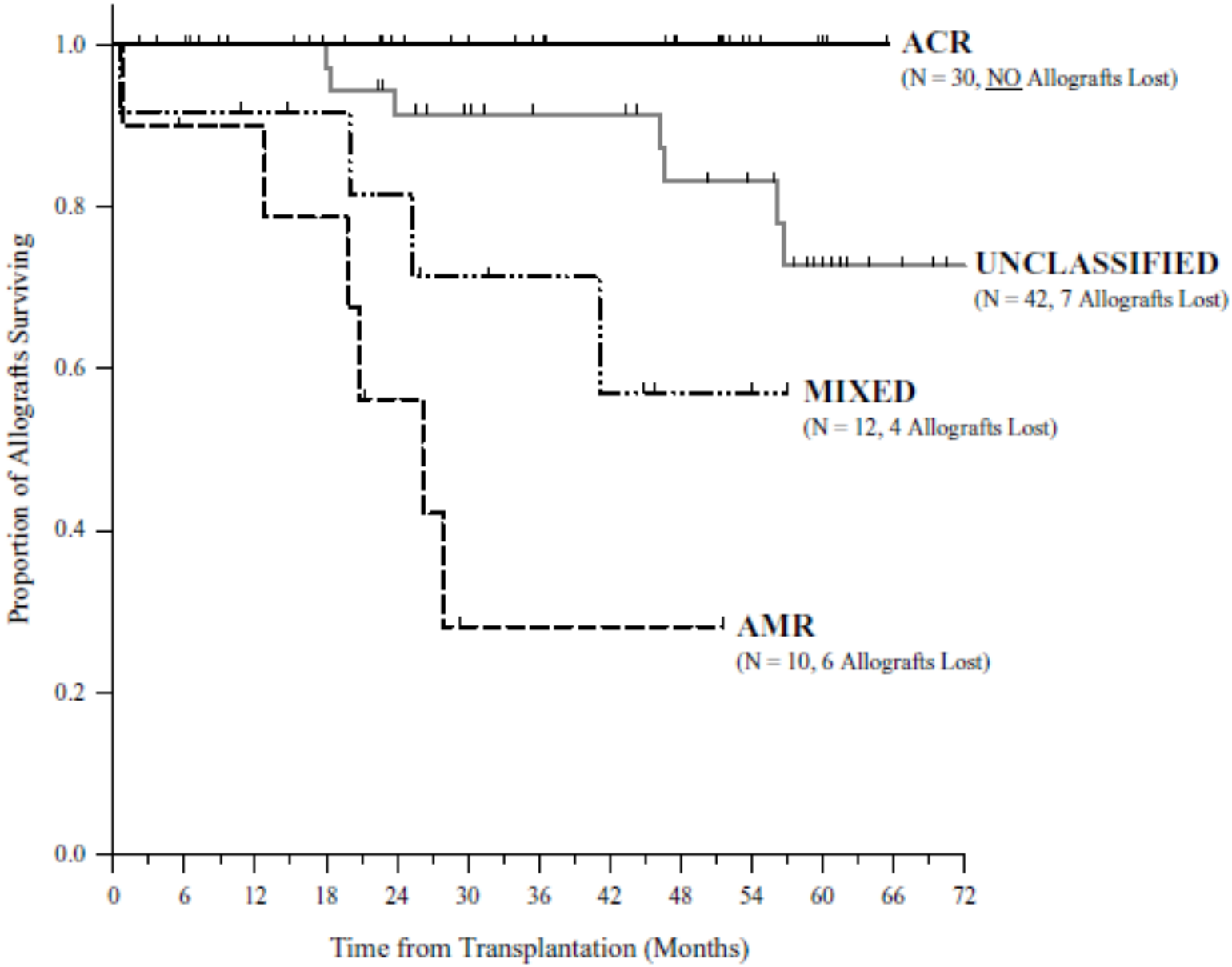
1. Development of circulating antibodies
2. Deposition of C4d in the renal tissue
3. Acute humoral rejection
4. Organ disfunction - evidence of chronical rejection is often already present

Table 5: Association of HLA antibodies with graft failure (serum creatinine >4.0 mg/dL)

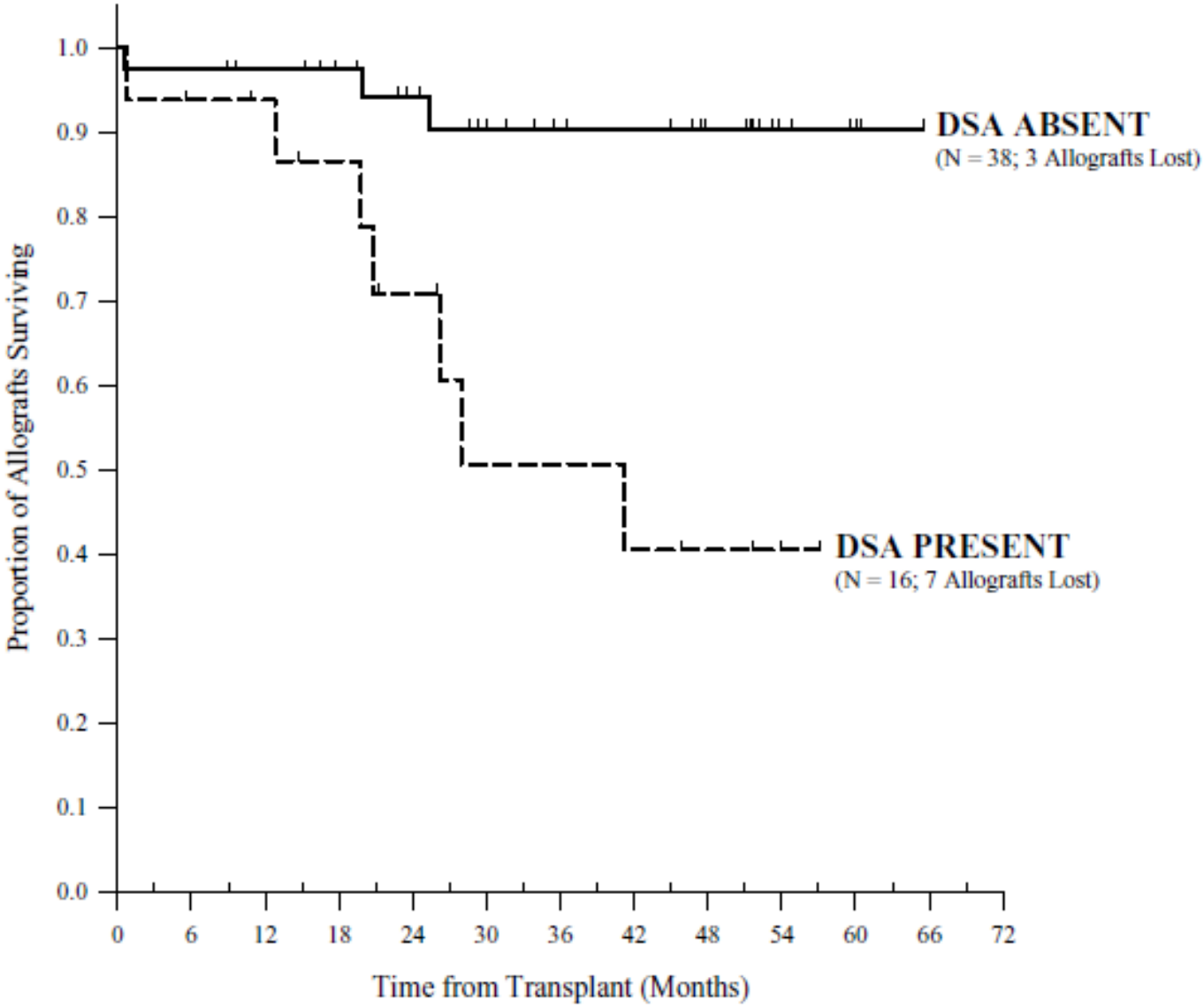
	SCr (mg/dL)		p-Value
	<4.0	>4.0 or fail	
HLA antibody	11	21	
No antibody	18	4	0.0006
DSA	2	13	
No antibody	18	4	0.000004
NDSA	9	8	
No antibody	18	4	0.05
De novo* HLA antibody	5	6	0.03
No antibody	18	4	

**De novo* antibody: After transplantation, if the patient had no antibodies for at least six months and then developed antibodies, these antibodies were defined as being *de novo*.

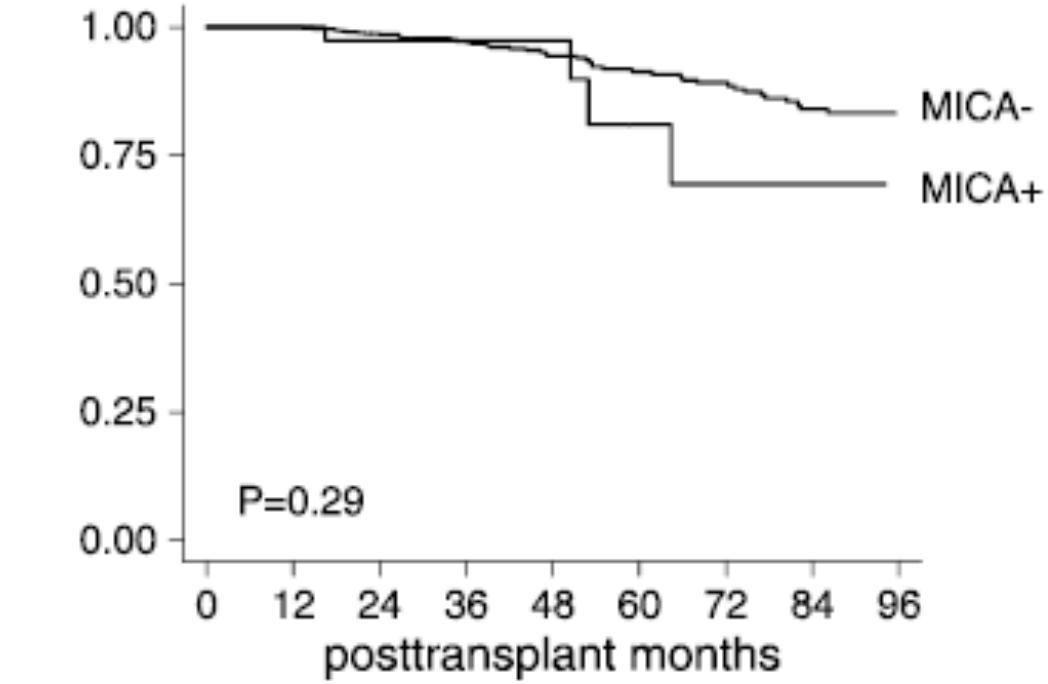
American Journal of Transplantation 2007; 7: 864–871



AJT 2009; 9: 1063–1071



AJT 2009; 9: 1063–1071



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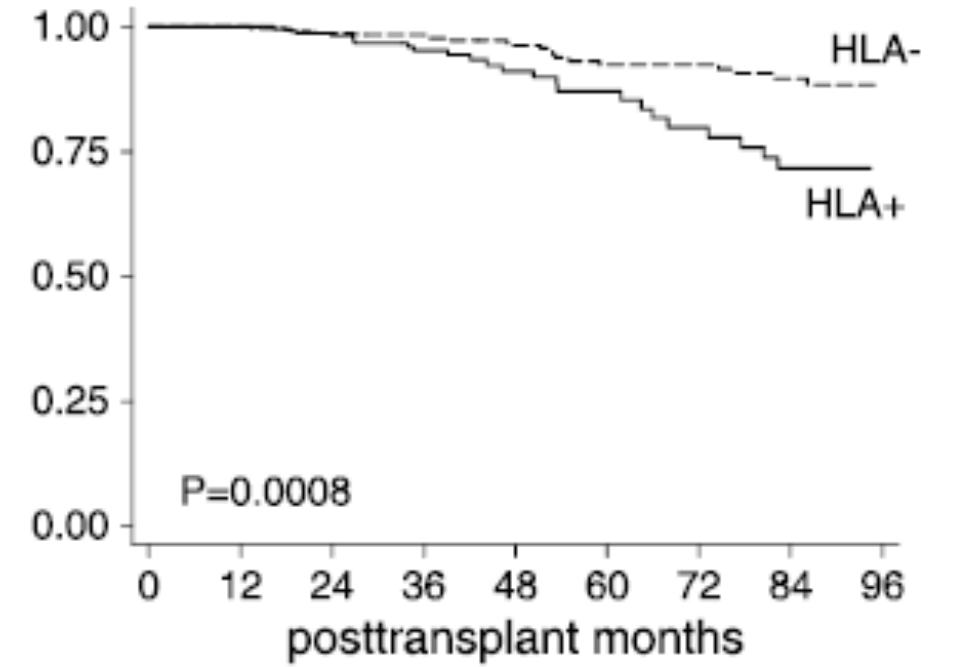

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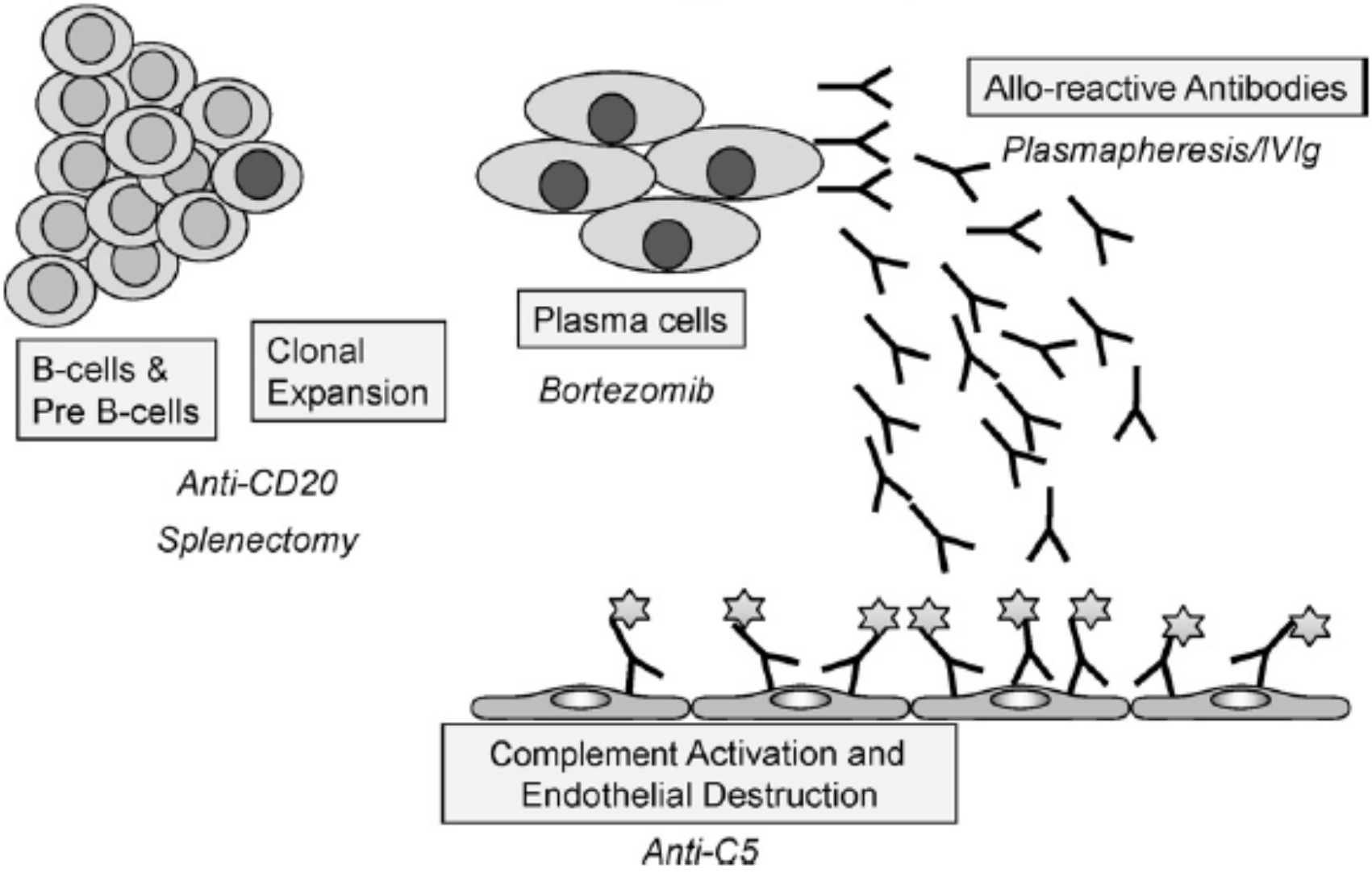
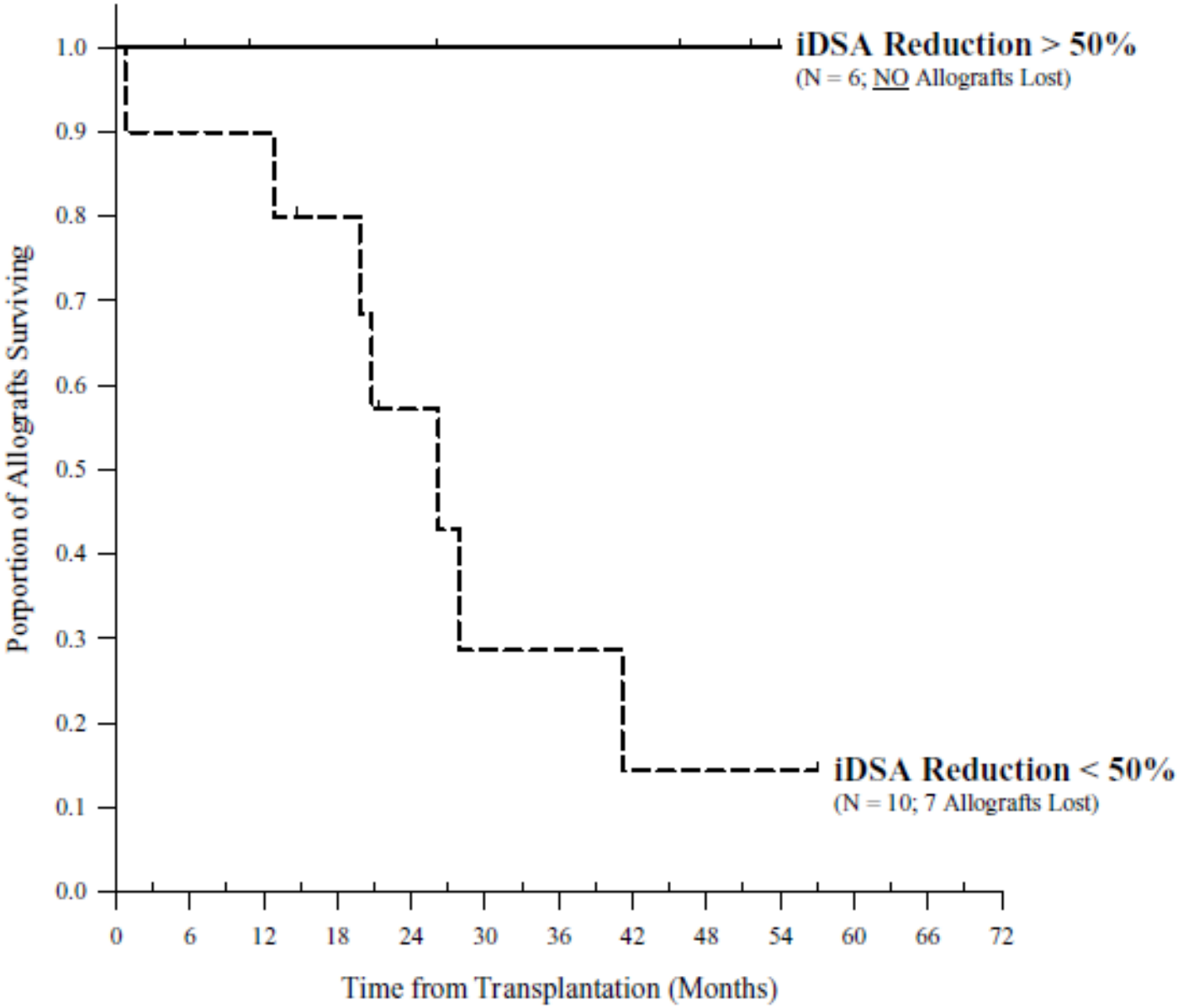
Transplantation 2012;93: 1258-1264

TREATMENT

Therapeutic Approaches For Crossing Antibody Barriers to Solid Organ Transplantation



R.A. Montgomery et al. / Seminars in Immunology *23 (2011) 224– 234*



AJT 2009; 9: 1063–1071

TABLE 1. Therapeutic agents used against DSAs in the treatment of antibody-mediated rejection and the evidence supporting their role

Therapy	Action	Evidence supporting the treatment[a]
Plasmapheresis (PP)[b]	Decrease the titer and block the effect of DSA	Low, benefit not consistently demonstrated
Immunoadsorption (column)	Decrease the titer of DSA	Low, seems beneficial
IVIG	Decrease the titer and block the effect of DSA	Very low
Bortezomib	Decrease production of DSA	Very low
Corticosteroids	Decrease inflammation caused by DSA in graft and decrease production of DSA, suppression of T cells	Very low
Anti-thymocyte preparations	Reduce production of DSA by decreasing Helper T cells, suppression of T cells	Very low
Eculizumab	Block complement activation resulting from DSA activation	Very low
Mycophenolate	Block the effect and decrease production of DSA, suppression of T cells	Very low
Rituximab	Decrease production of DSA	Very low
Cyclophosphamide	Decrease production of DSA	Very low
Deoxyspergualin	Decrease production of DSA, suppression of T cells	Very low
Splenectomy	Decrease production of DSA	Very low
Tacrolimus	Decrease production of DSA, Suppression of T cells	Very low

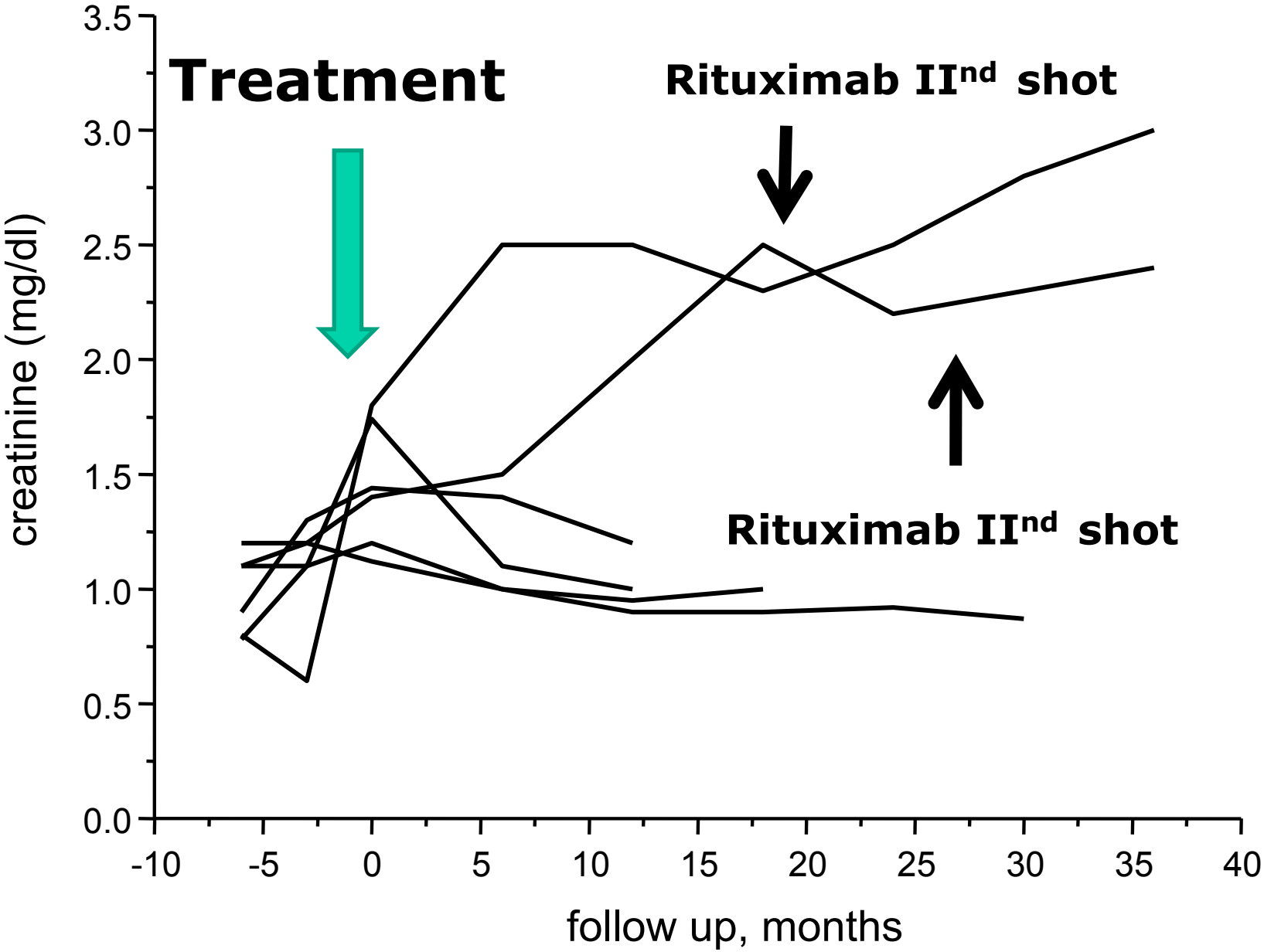
[a] According to the GRADE system, as described in the *Materials and Methods* section.
[b] Plasmapheresis may have other effects, which block the effect of DSA, including removal of other circulating factors such as complement (*28, 62–65*).

Transplantation 2012;94: 775Y783

PERSONAL EXPERIENCE

- 6 patients (4 M,2 F)
- Identified DSA
- Hystology positive for antibody mediated rejection
- C4d positivity on Peritubular capillaries

- Immunoadsorption /plasmaexchange
- Rituximab 1-2 infusions
- CD 19 + < 1% total lymphocytes


Treatment
Rituximab IInd shot
Rituximab IInd shot
creatinine (mg/dl)
follow up, months
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-10
-5
0
5
10
15
20
25
30
35
40

DESENSITIZATION

Sensitized patients

DSA removal (immunoadsorption or plasma exchange), DSA inactivation (high-dose intravenous immunoglobulins) enable successful positive-crossmatch kidney transplantation with good short- to intermediate term outcomes

Nat. Rev. Nephrol. 6, 297–306 (2010);

However:

Antibody-mediated rejection can occur subclinically and in time results in chronic injury to the renal microvasculature, transplant glomerulopathy, interstitial fibrosis, and tubular atrophy

Nat. Rev. Nephrol. 6, 297–306 (2010);

and

- acute antibody mediated rejection (AMR) occurs in 20–50% of positive crossmatch transplantations.
- AMR is usually reversed:1 year survival close to 90%
- but 3, 5 or 8 years survival significantly worse than “standard”

Nat. Rev. Nephrol. 6, 297–306 (2010);

Conclusion I

- Donor Specific Antibodies worsen graft outcome
- They may be directed toward several different antigens
- No treatment is clearly proven to be efficacious

In conclusione II

- Desensitization protocols are clearly effective in the short - medium time but long term effect is still to be determined
- In pediatric age, due to long life expectation, it is probably too early to recommend routine use, out of specific trial