Спасибо за приглашение

Thrombotic Microangiopathy: Pathology and Diagnosis

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University of Washington

Thrombotic Microangiopathy (TMA)

- What is it?

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  Corollary: Can we reliably agree on how to diagnose it?

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Thrombotic Microangiopathy; Definition

Wikipedia: **Thrombotic microangiopathy**, abbreviated **TMA**, is a pathology that results in thrombosis in capillaries and arterioles, due to an endothelial injury. It may be seen in association with thrombocytopenia, anemia, purpura and renal failure.

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Thrombotic Microangiopathy; Definition

Thrombotic microangiopathy (TMA) is the pathologic term for a condition characterized by microvascular changes including **thrombosis** in association with laboratory abnormalities of microangiopathic hemolytic anemia and thrombocytopenia.

Laszik, Kambham, and Silva in Heptinstall's Pathology of the Kidney, 7th ed. 2015

Thrombotic Microangiopathy
Constellation of Features

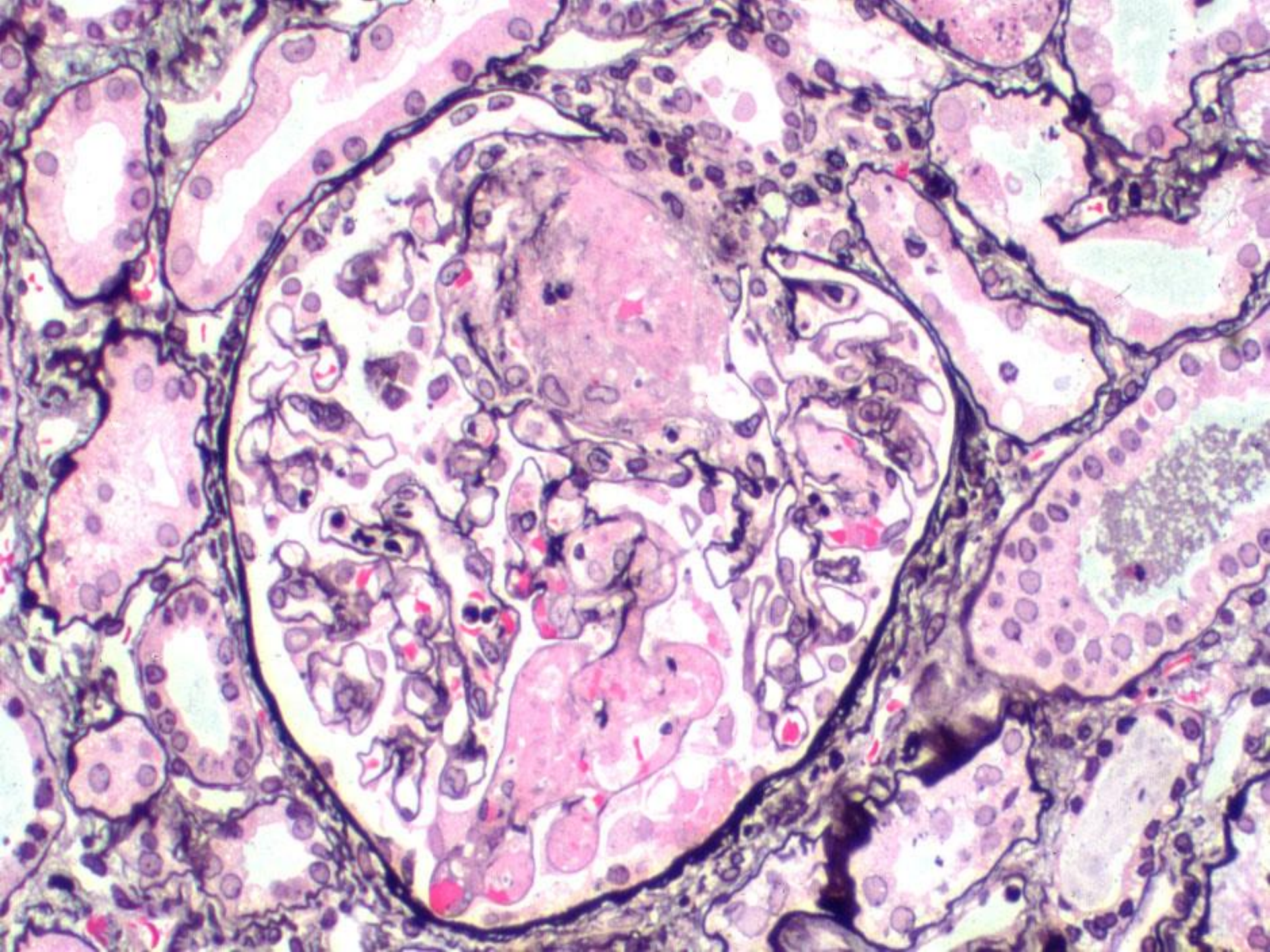
1) Microvascular thromboses (varies)
2) Hemolytic anemia (sometimes)
3) Thrombocytopenia (not always)
4) Vasculopathy of small arteries, arterioles, and capillaries (if looked for)
5) Variable organ involvement

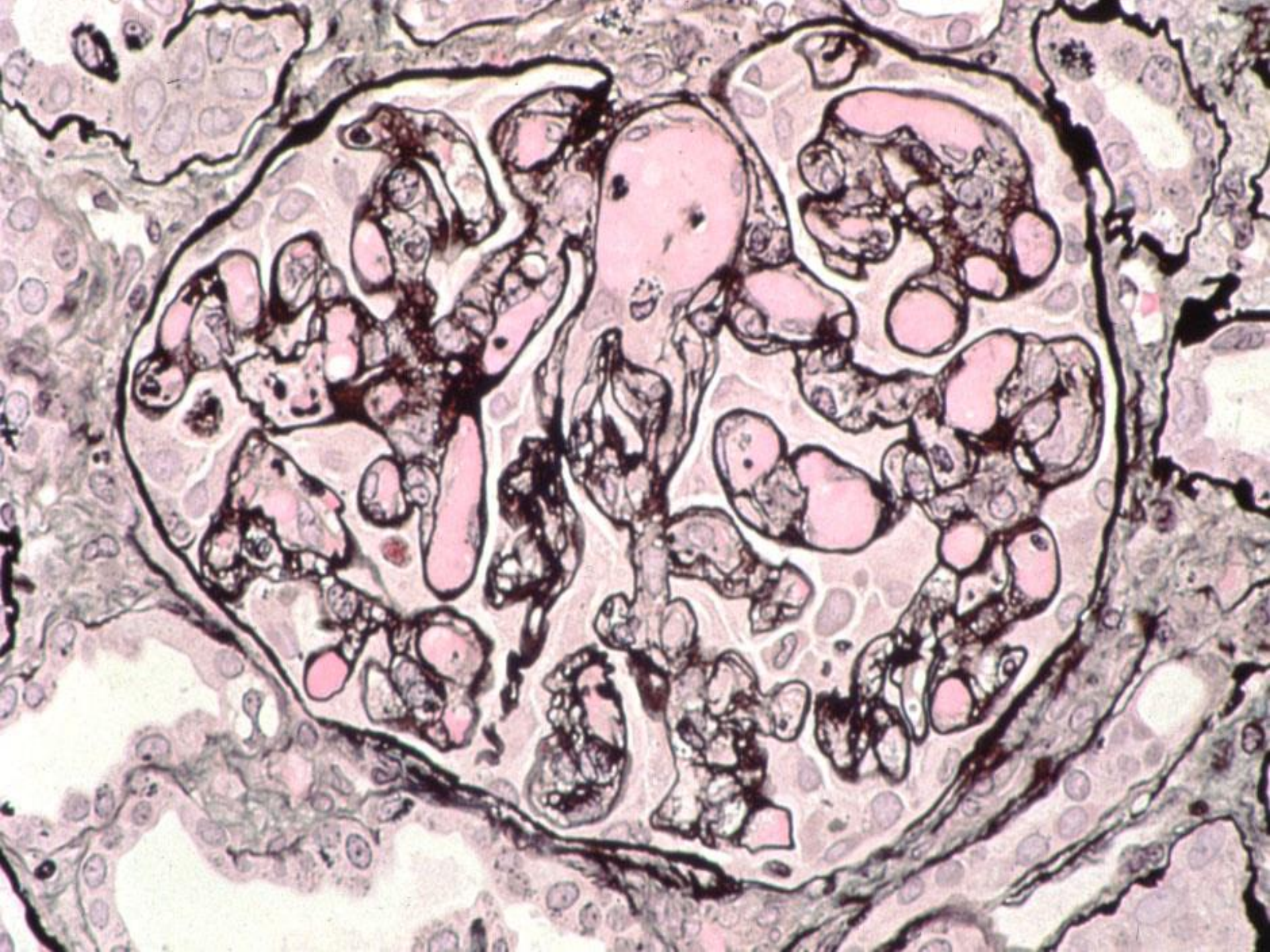
   Kidney: Involves glomerular capillaries, arteries and arterioles, or both.

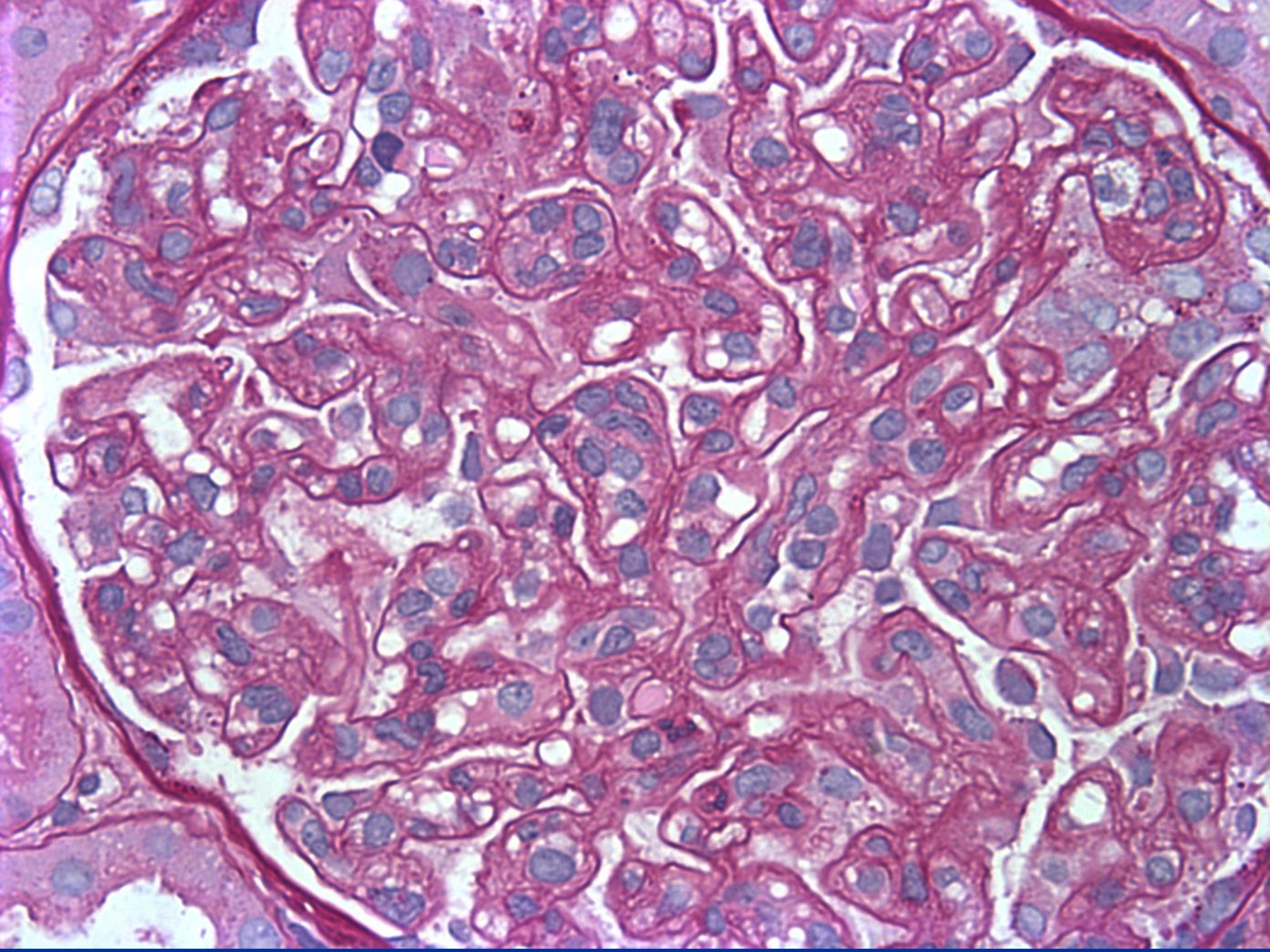
Thrombotic Microangiopathy – The Renal Pathology Perspective

TMA is a pattern of injury

- Glomerular
  - Endothelial injury (Endotheliosis)
  - Capillary wall injury (widening of the subendothelial space, duplication of basement membranes)
  - Mesangiolysis
  - Capillary microthromboses







HUS Lesions: Chronic

- Cellular interposition/
  double contour GBM
- Glomerular ischemic lesions:
  collapse
  corrugated GBM
  fibrosis of Bowman's capsule
- Glomerular obsolescence
- Intimal fibrosis
- Tubulointerstitial fibrosis

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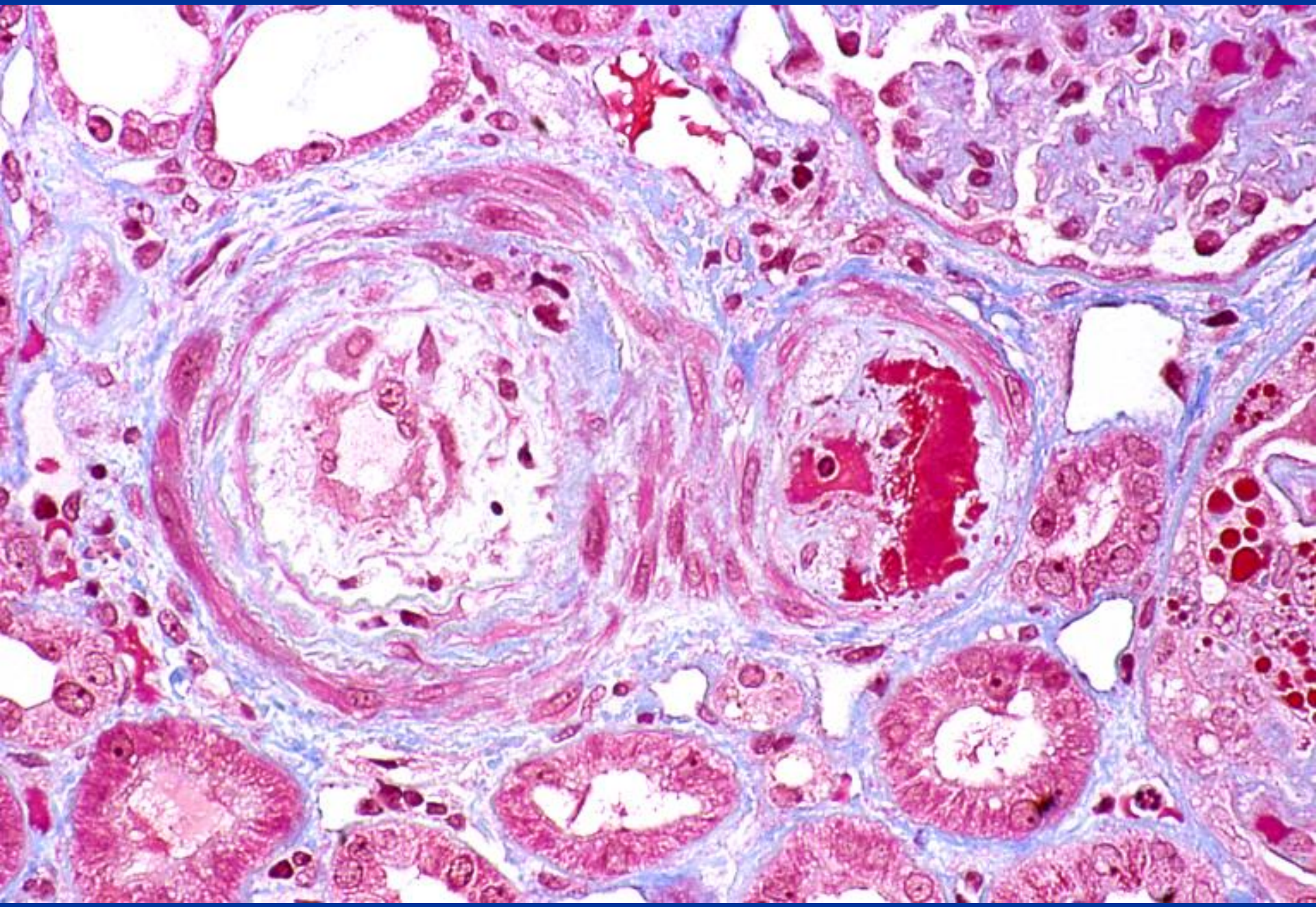
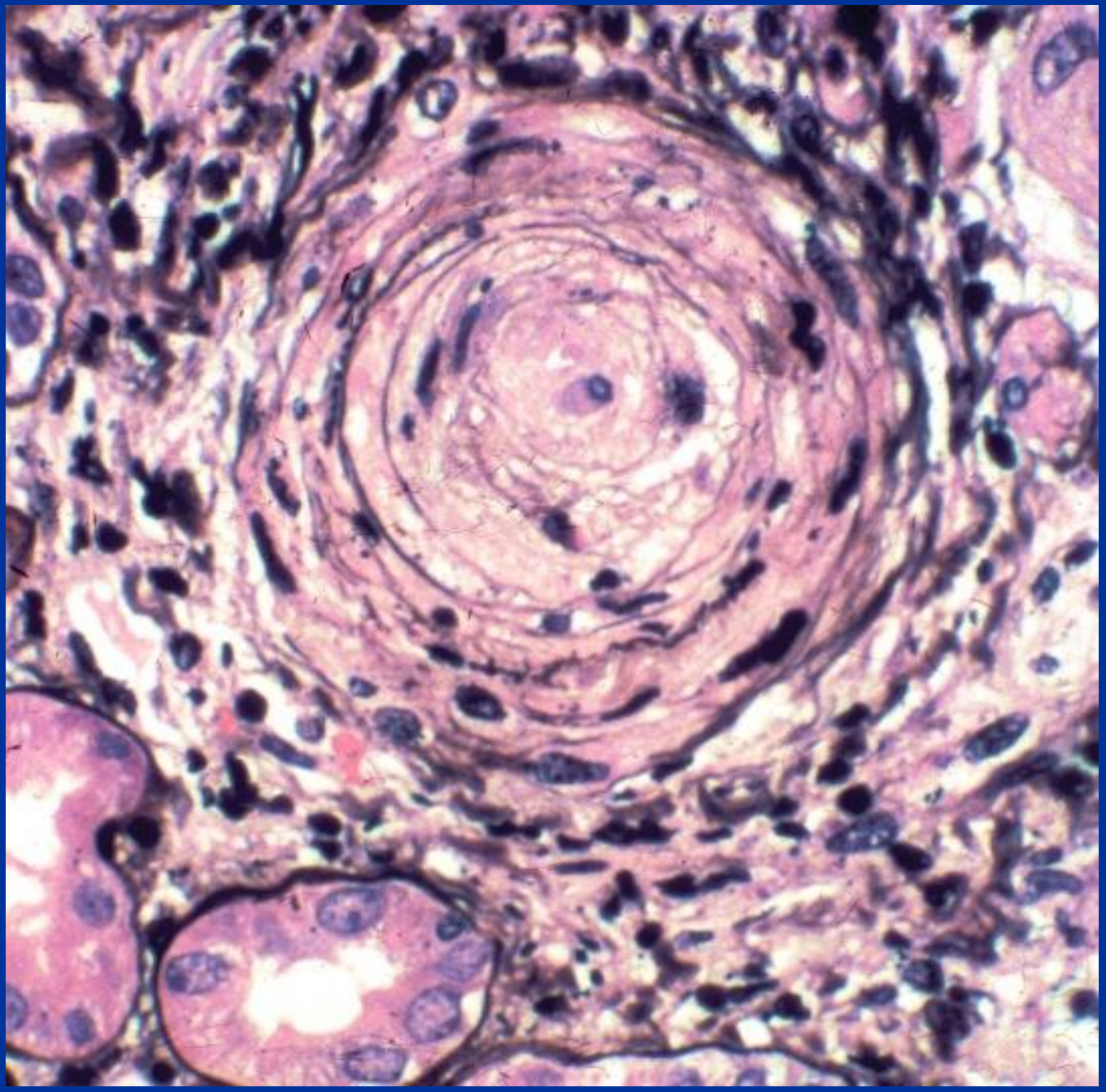
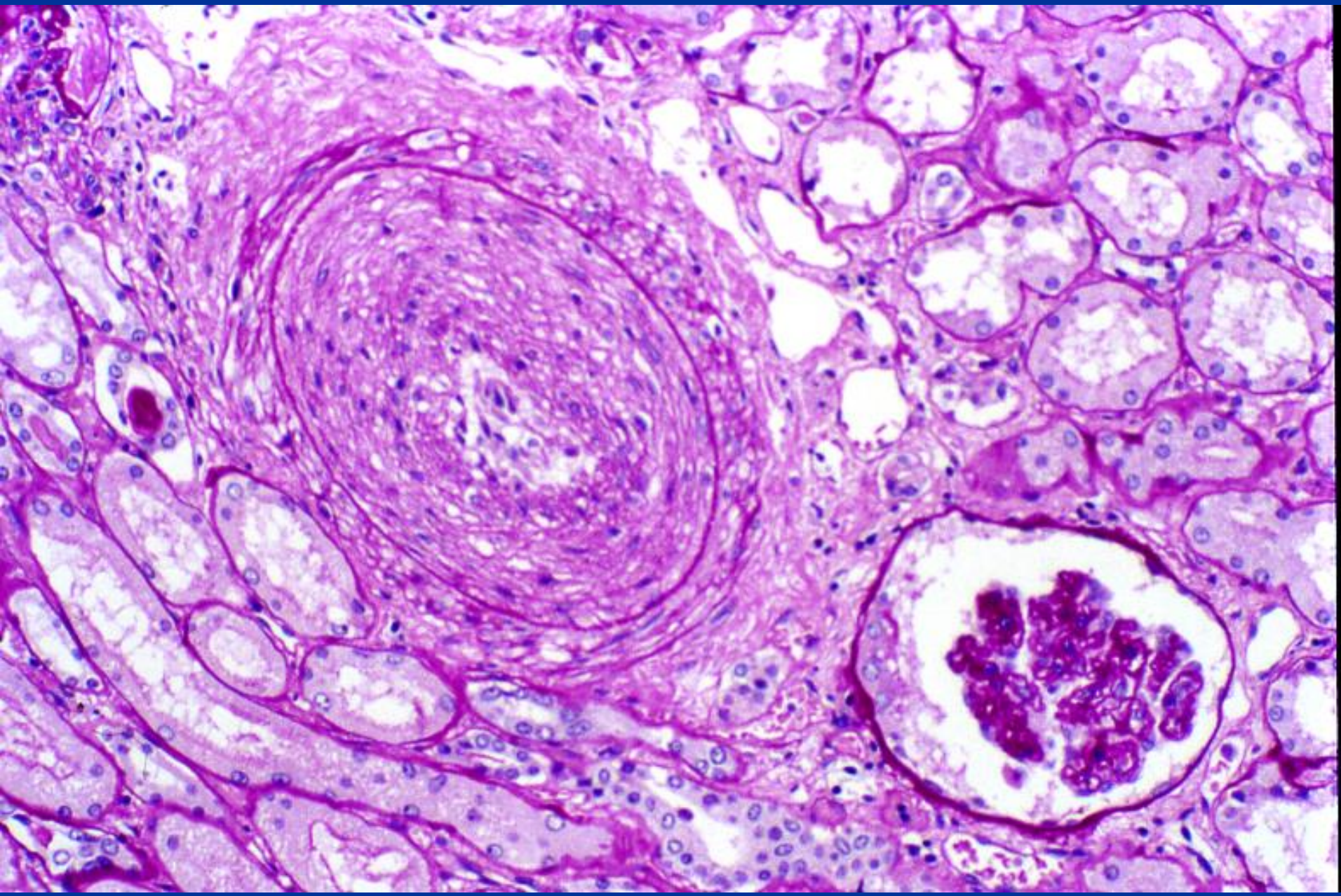
  - Mesangiolysis
  - Capillary Microthromboses
- Arterial/Arteriolar: (Acute)
  - Intimal swelling
  - Thromboses
  - Hyperplastic changes (“onionskinning”)







Thrombotic Microangiopathy – The Renal Pathology Perspective

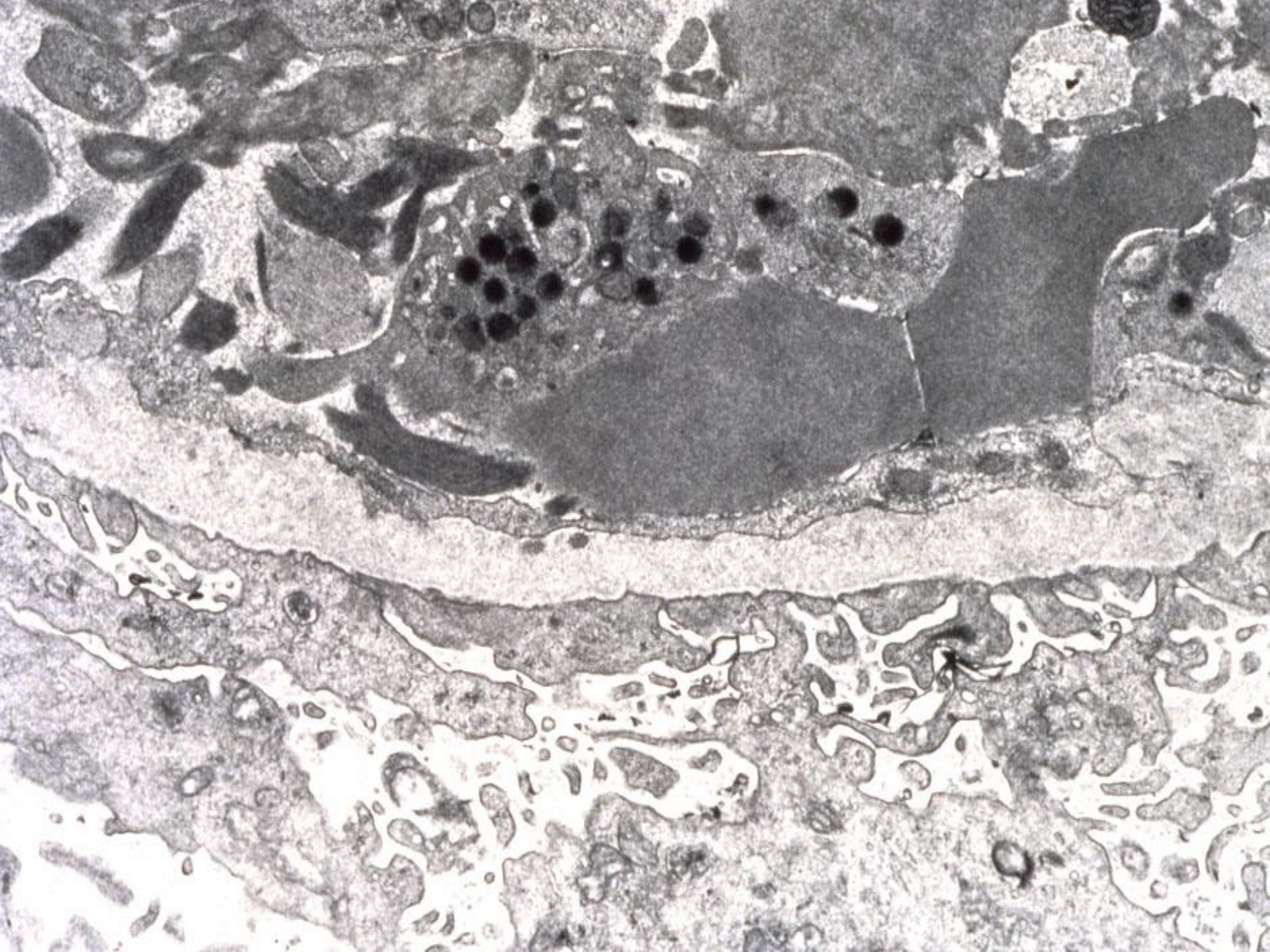
TMA is a pattern of injury

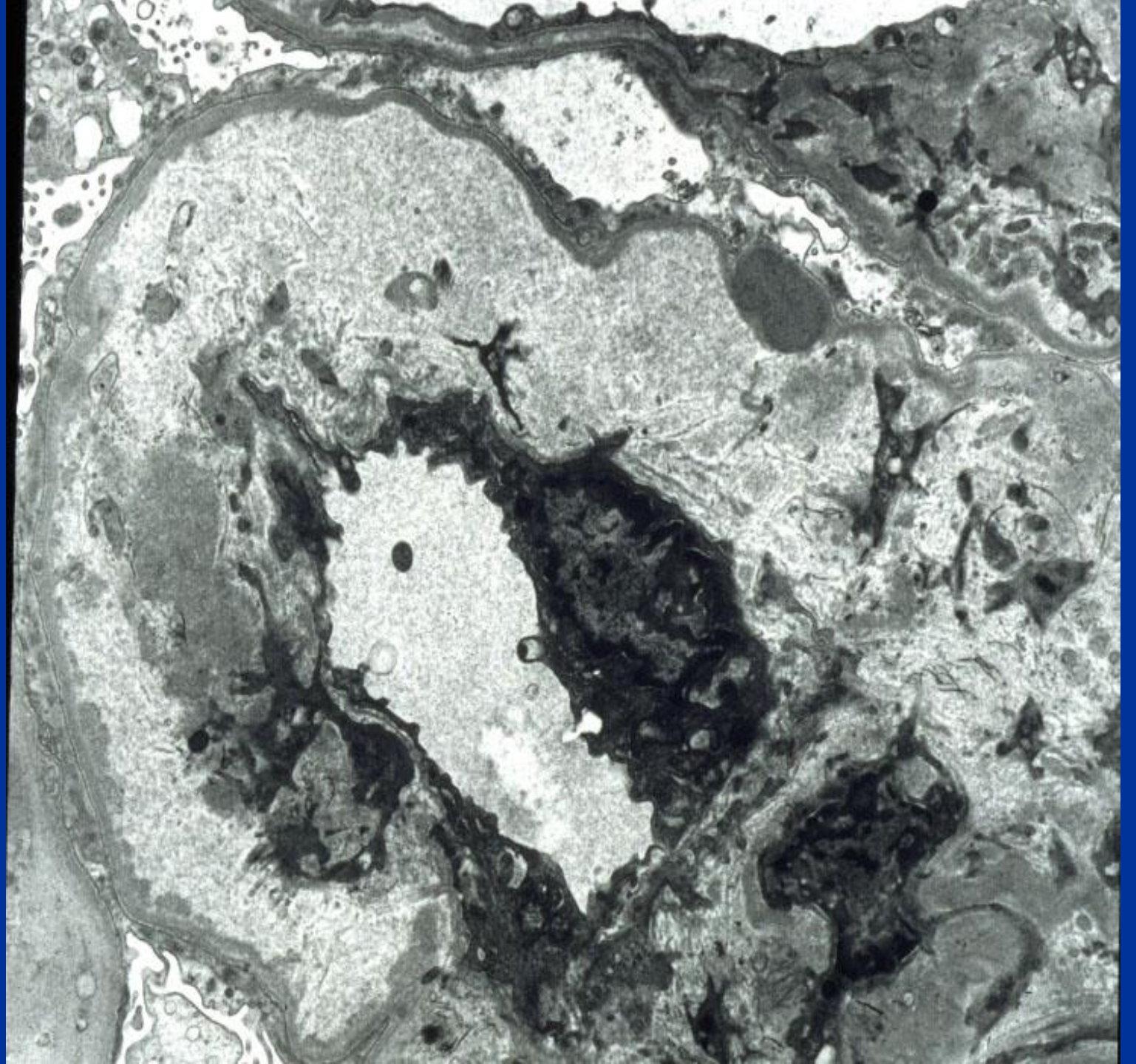
- Glomerular
  - Endothelial injury (Endotheliosis)
  - Capillary wall injury (widening of the subendothelial space, duplication of basement membranes)
  - Mesangiolysis
  - Capillary Microthromboses
- Arterial/Arteriolar:
  - Intimal swelling
  - Hyperplastic changes (“onionskinning”)
- Coagulation
  - Fibrin / platelet thrombi
  - Hemolysis / schistocytes

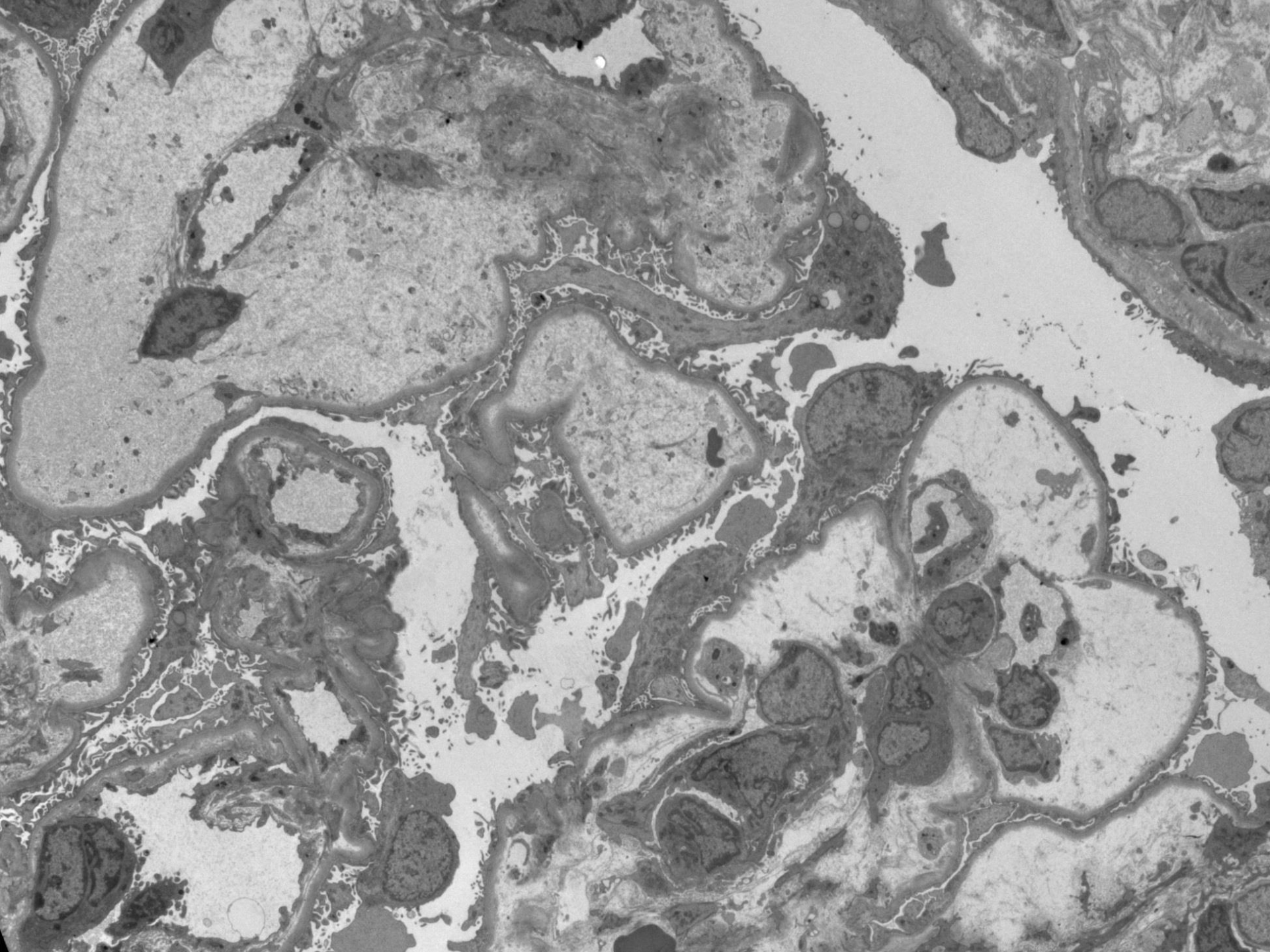
Cases of TMA may have all or only some (most common) of these features. Renal limited (and particularly glomerular limited) cases are common.

Thrombotic Microangiopathy Electron Microscopy

- Marked expansion of lamina rara interna
- Endothelial cell swelling
- Fibrin and platelet deposition
- Mesangiolysis

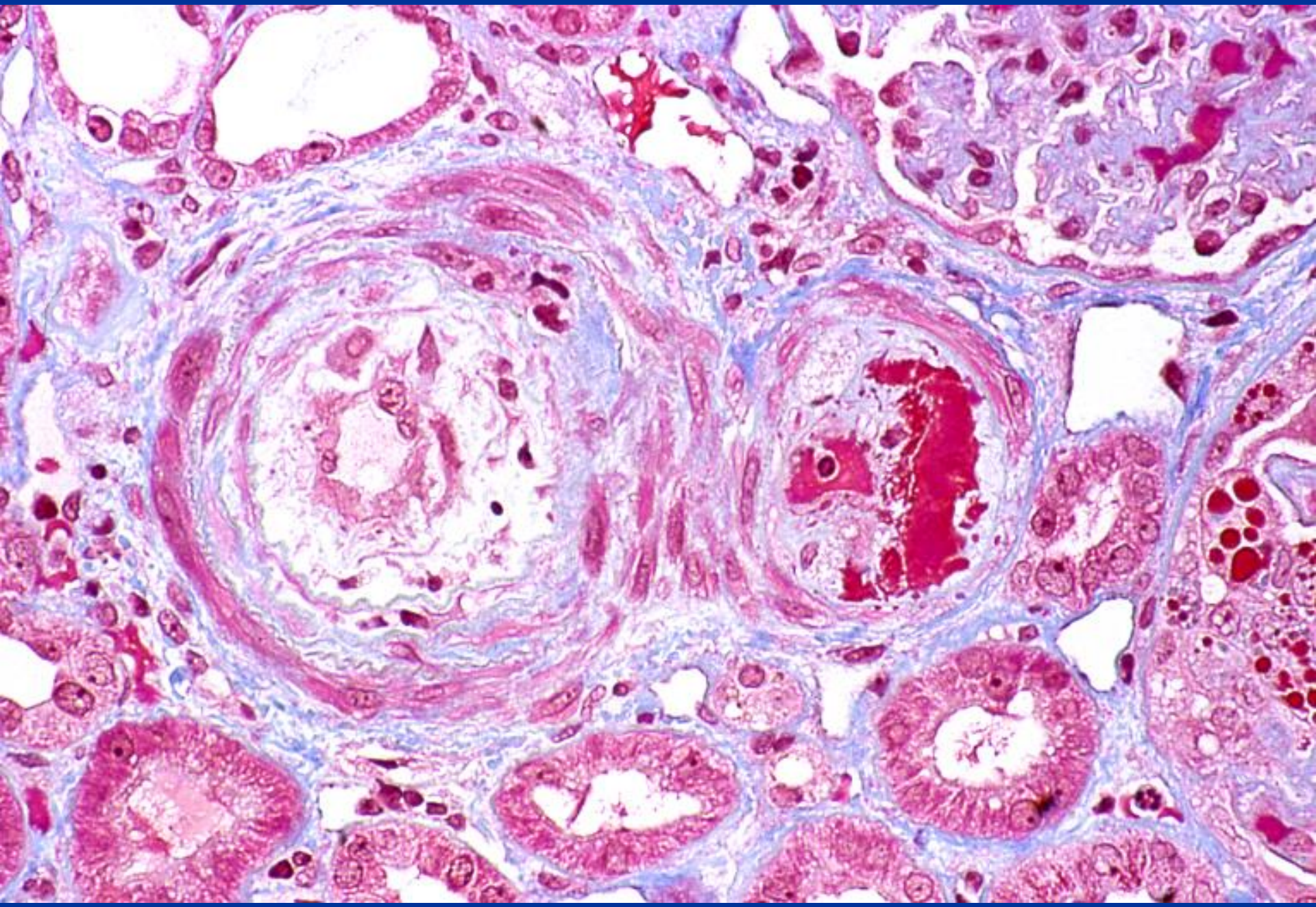






Diagnosis of TMA

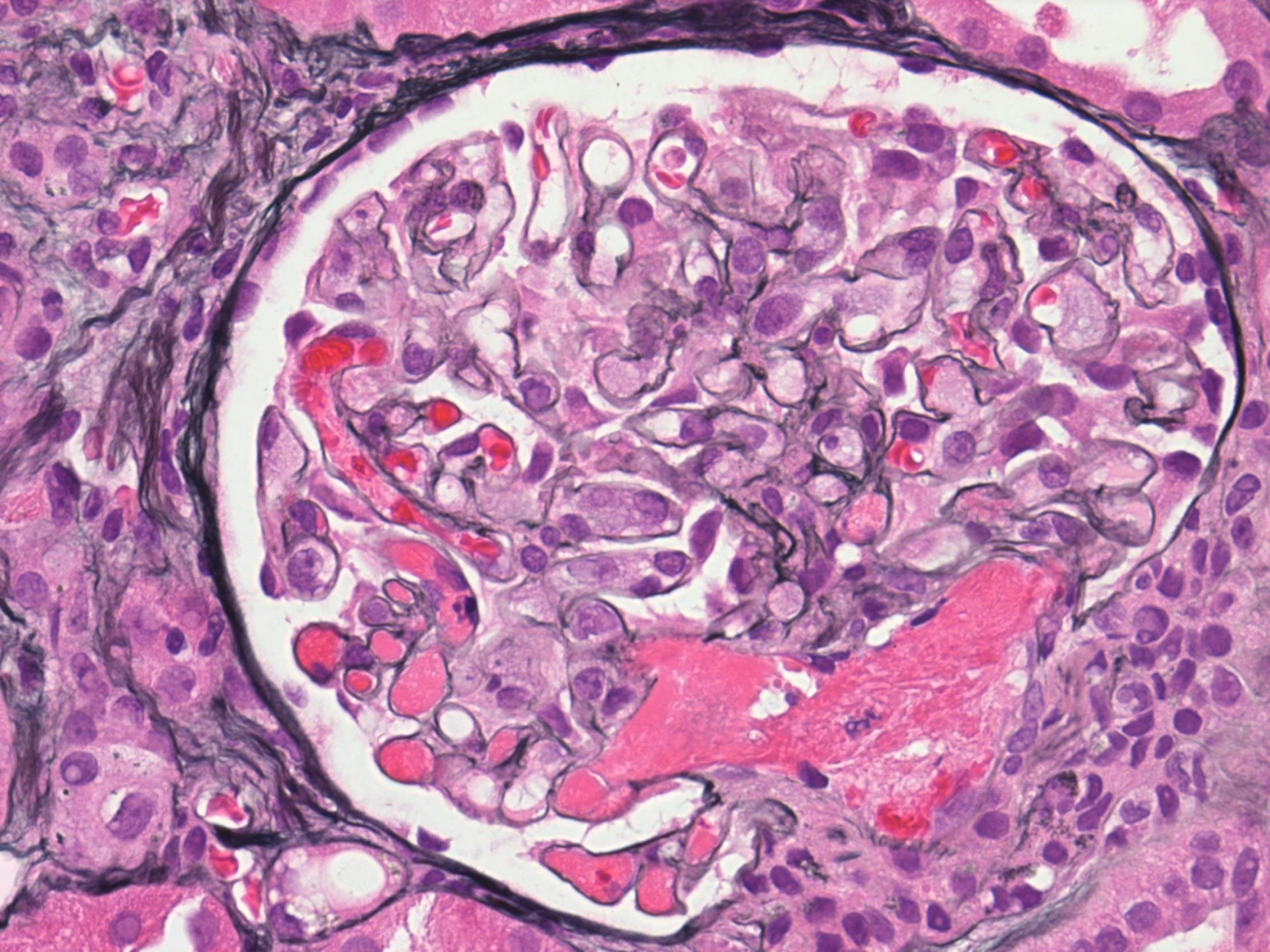
What are the minimal criteria to establish a pathologic diagnosis?



Diagnosis of TMA

What are the minimal criteria to establish a pathologic diagnosis?

Thrombosis?



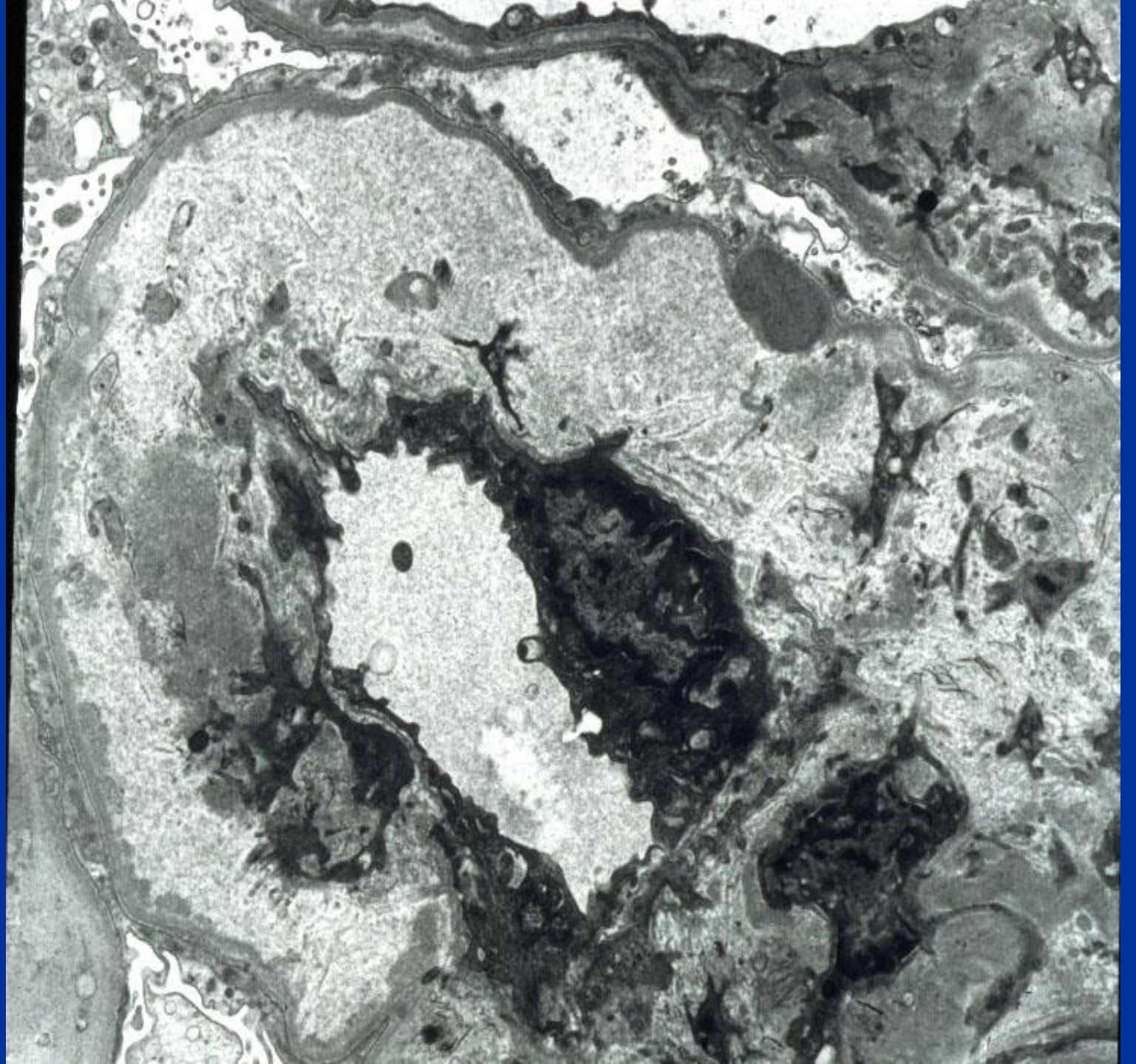
Diagnosis of TMA

What are the minimal criteria to establish a pathologic diagnosis?

Thrombosis?

If not thrombosis, what then?

Is glomerular involvement sufficient?

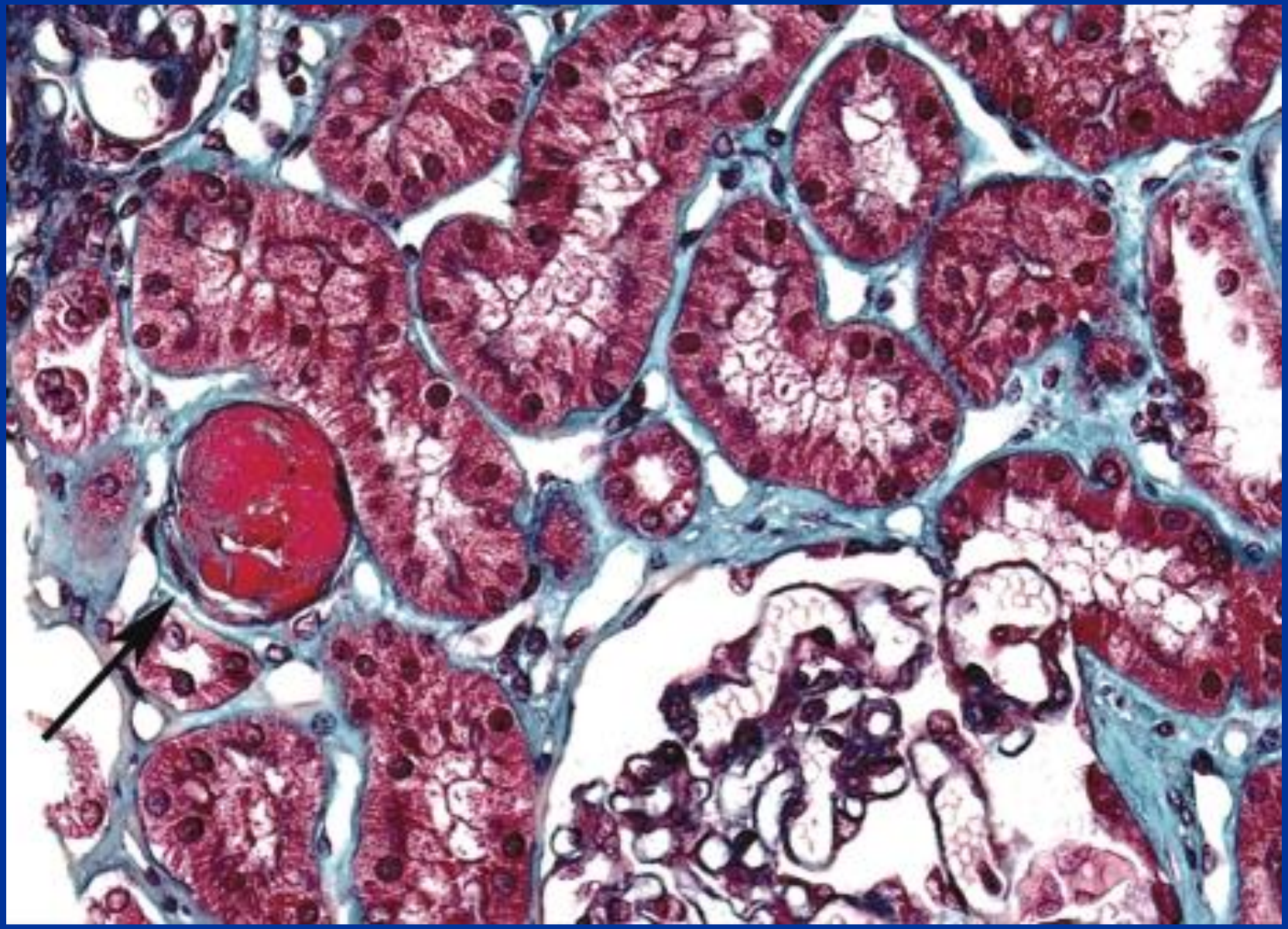


A clinicopathologic study of thrombotic microangiopathy in IgA nephropathy

El Karoui K, Hill GS, Karras A, Jacquot C, Moulonguet L, Kourilsky O, Frémeaux-Bacchi V, Delahousse M, Duong Van Huyen JP, Loupy A, Bruneval P, Nochy D.

J Am Soc Nephrol. 2012;23:137-48.

TMA or Not?



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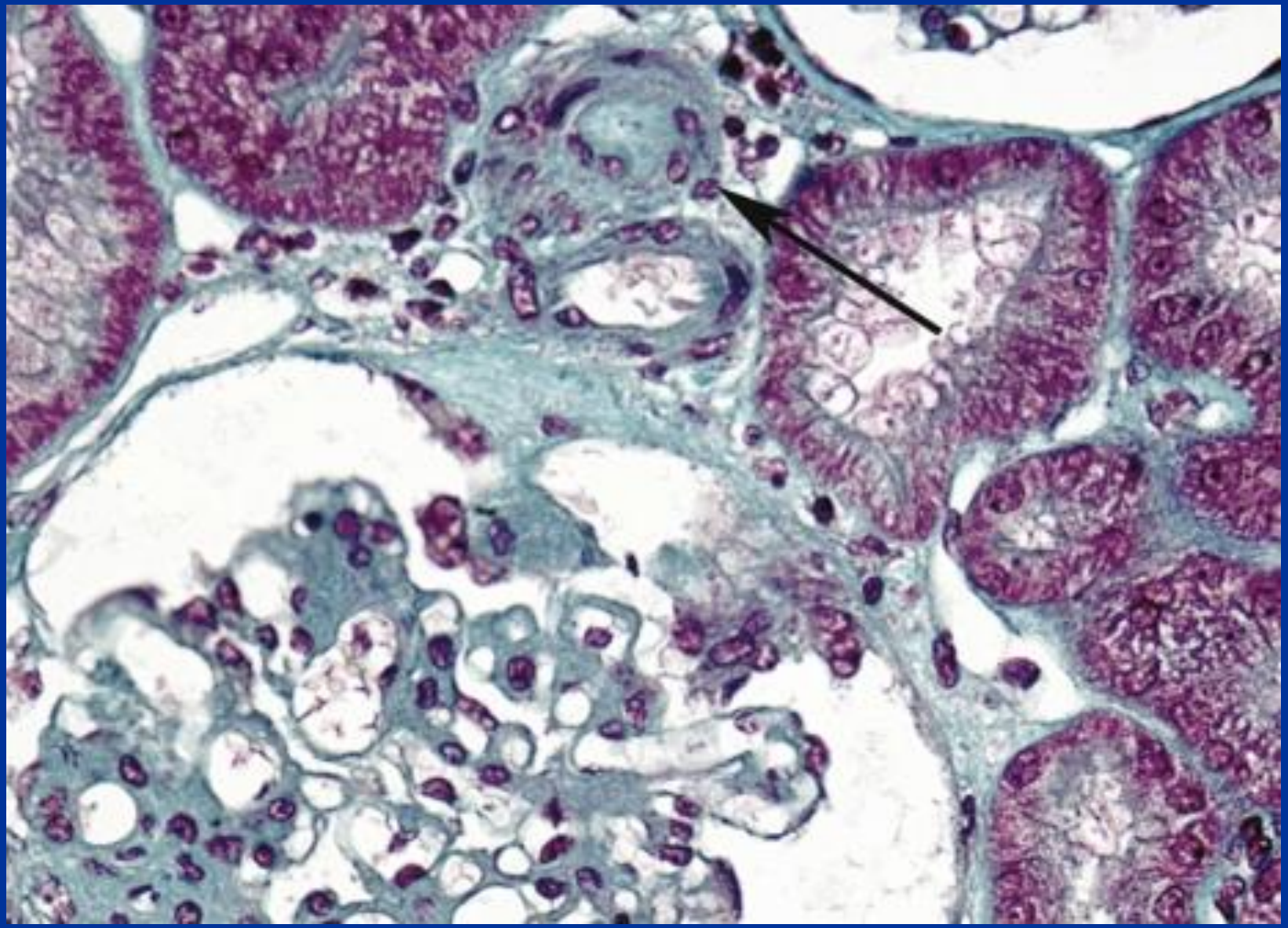

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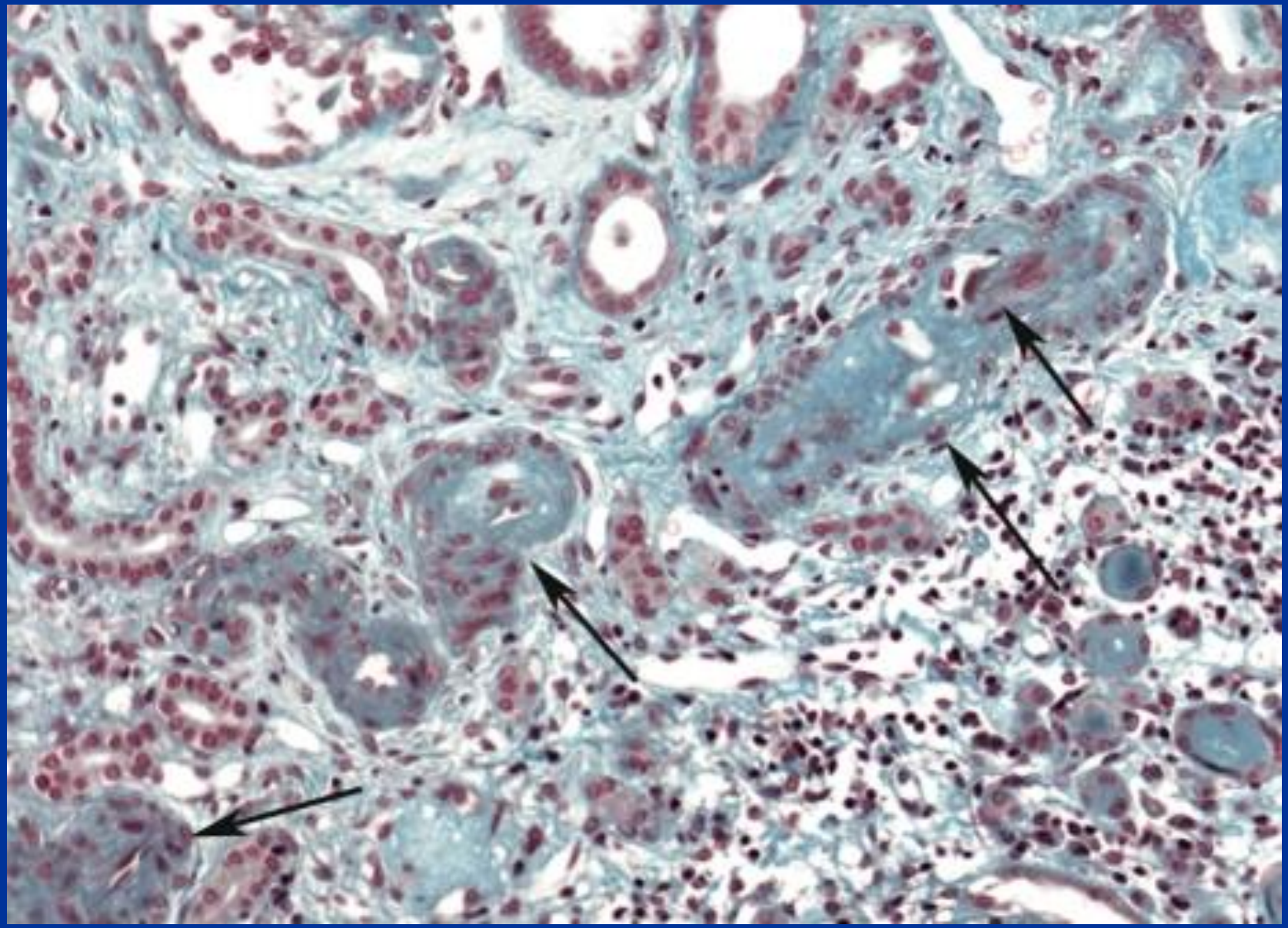


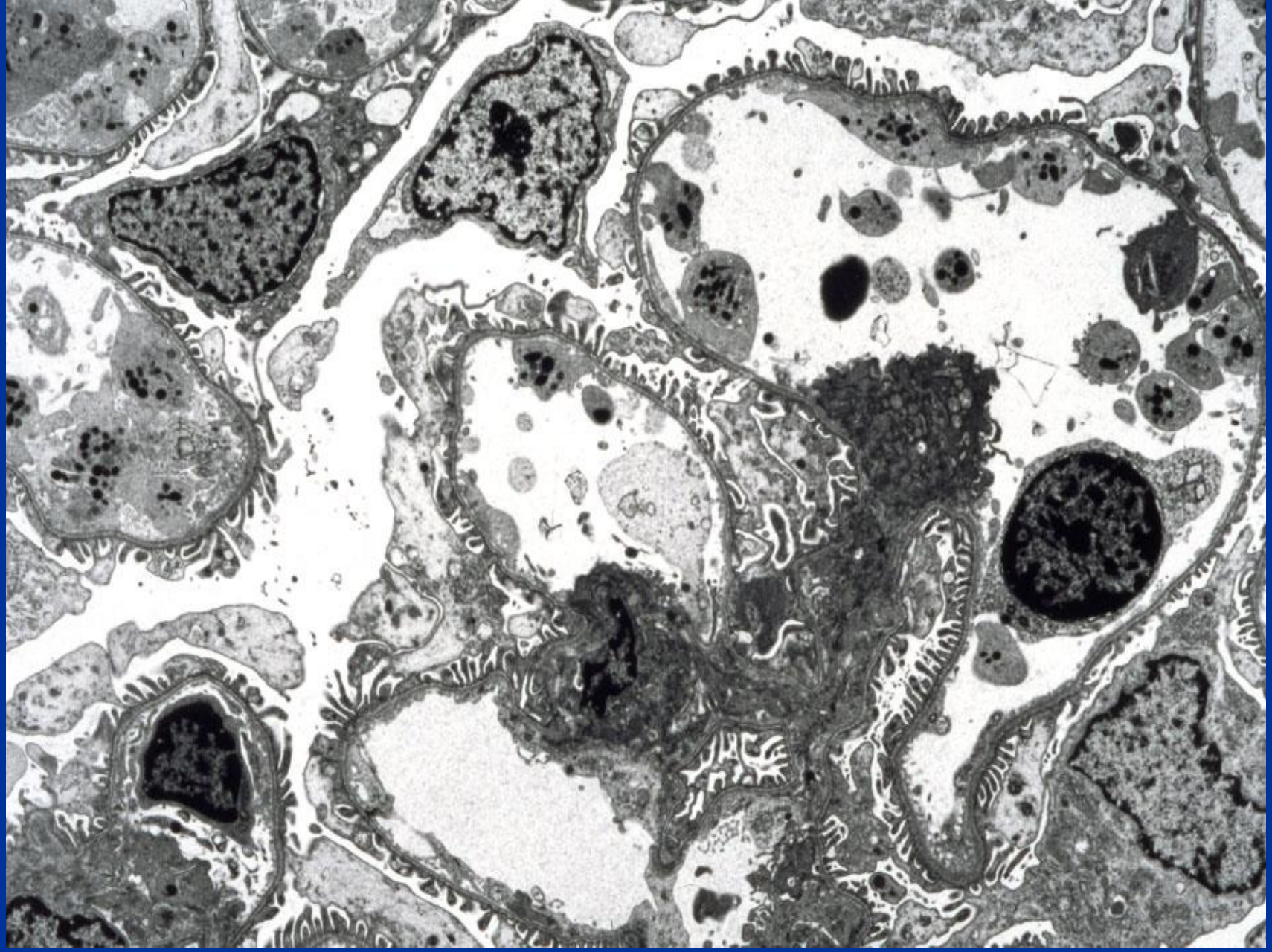
El Karoui K, Hill GS, Karras A, et al. A clinicopathologic study of thrombotic microangiopathy in IgA nephropathy. J Am Soc Nephrol. 2012 Jan;23(1):137-48.

Thrombotic Microangiopathy Pathogenesis

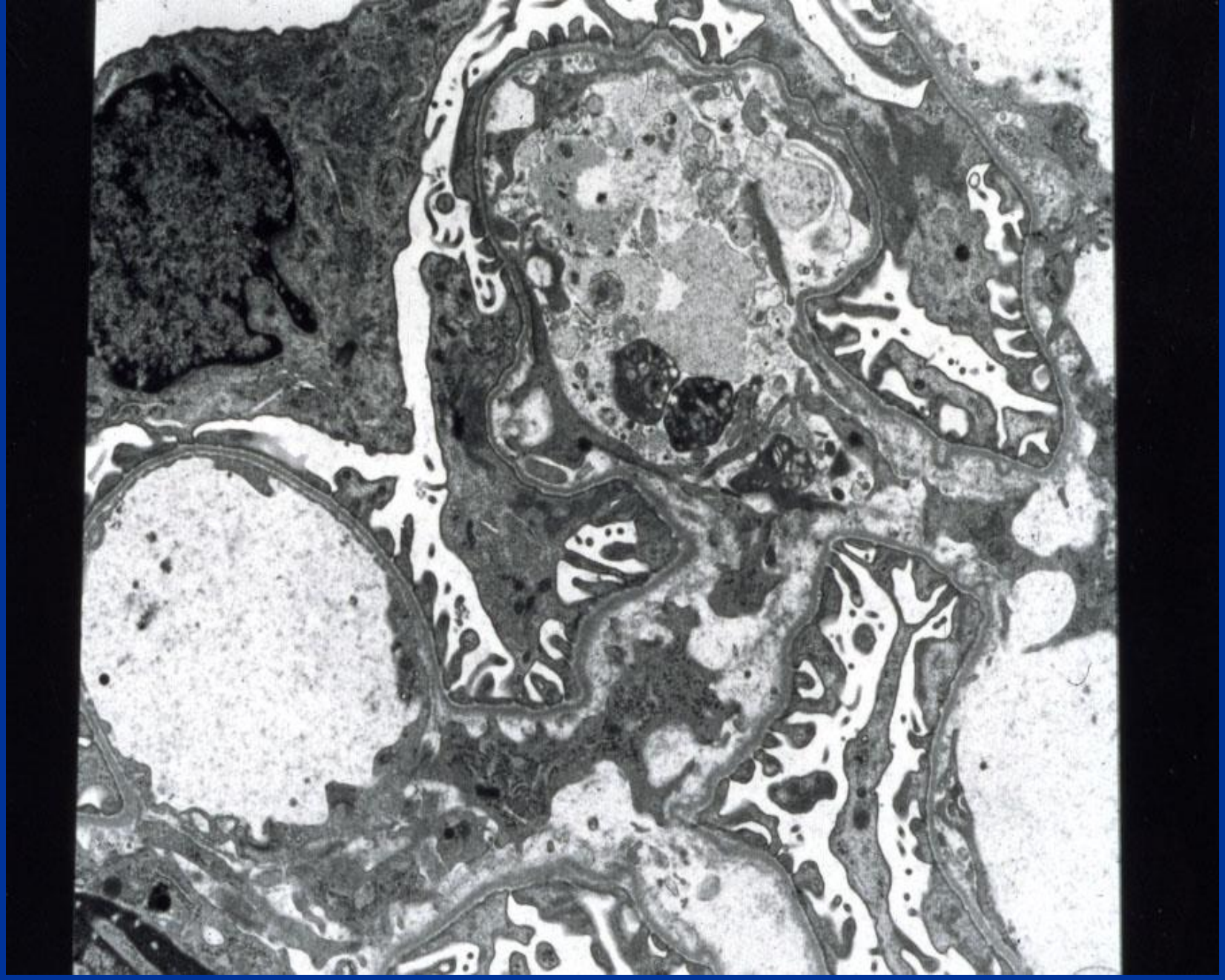
A Rat Model of Endothelial Injury and TMA

- Induced by goat anti-rat endothelial cell antibody
- Clinical: Renal insufficiency, proteinuria, hemolysis, diminished platelet counts
- Early lesion: Intracapillary platelet/ fibrin thrombi
- Mesangiolysis
- Recovery

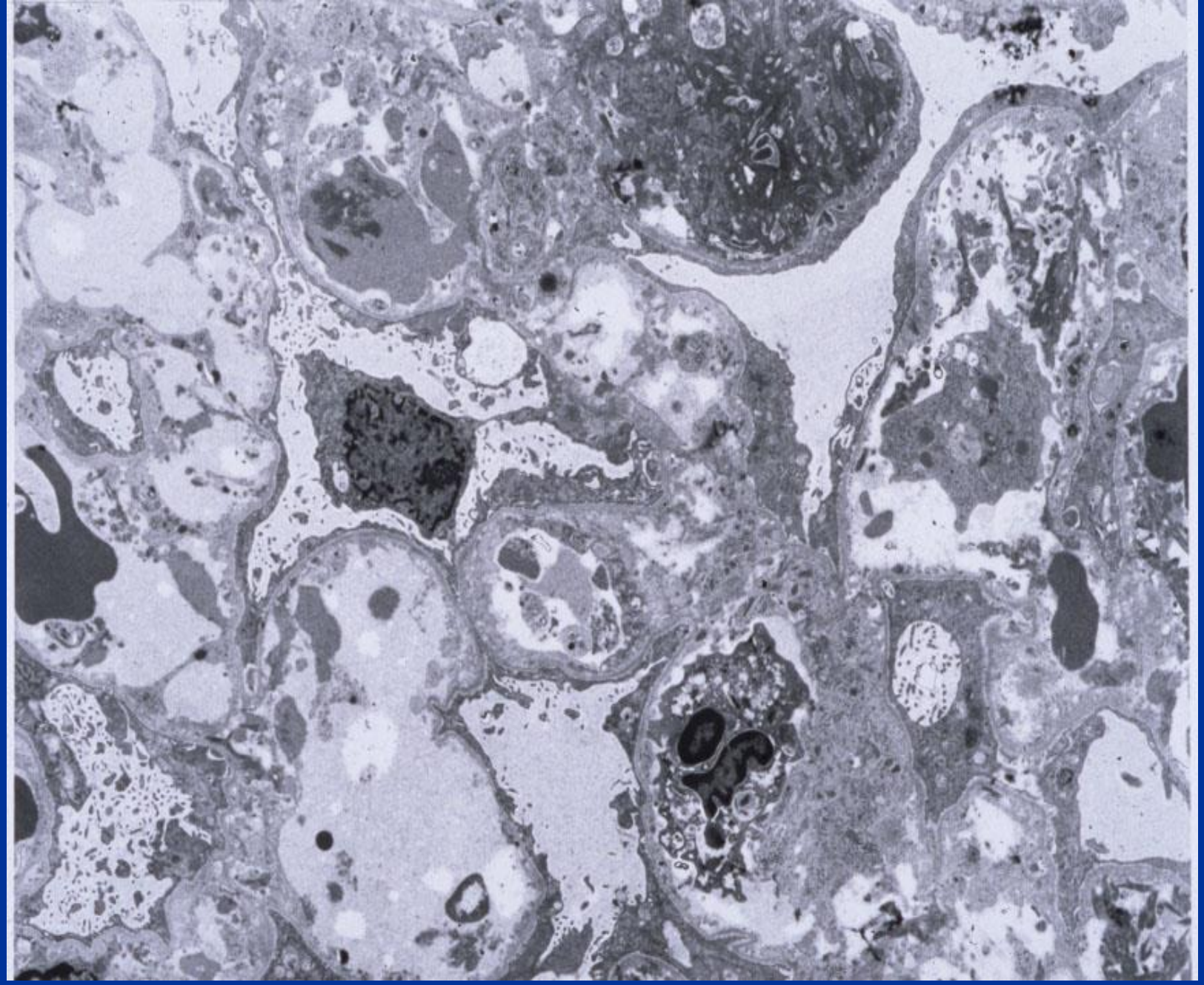
Kidney Int 1997; 52:182-94



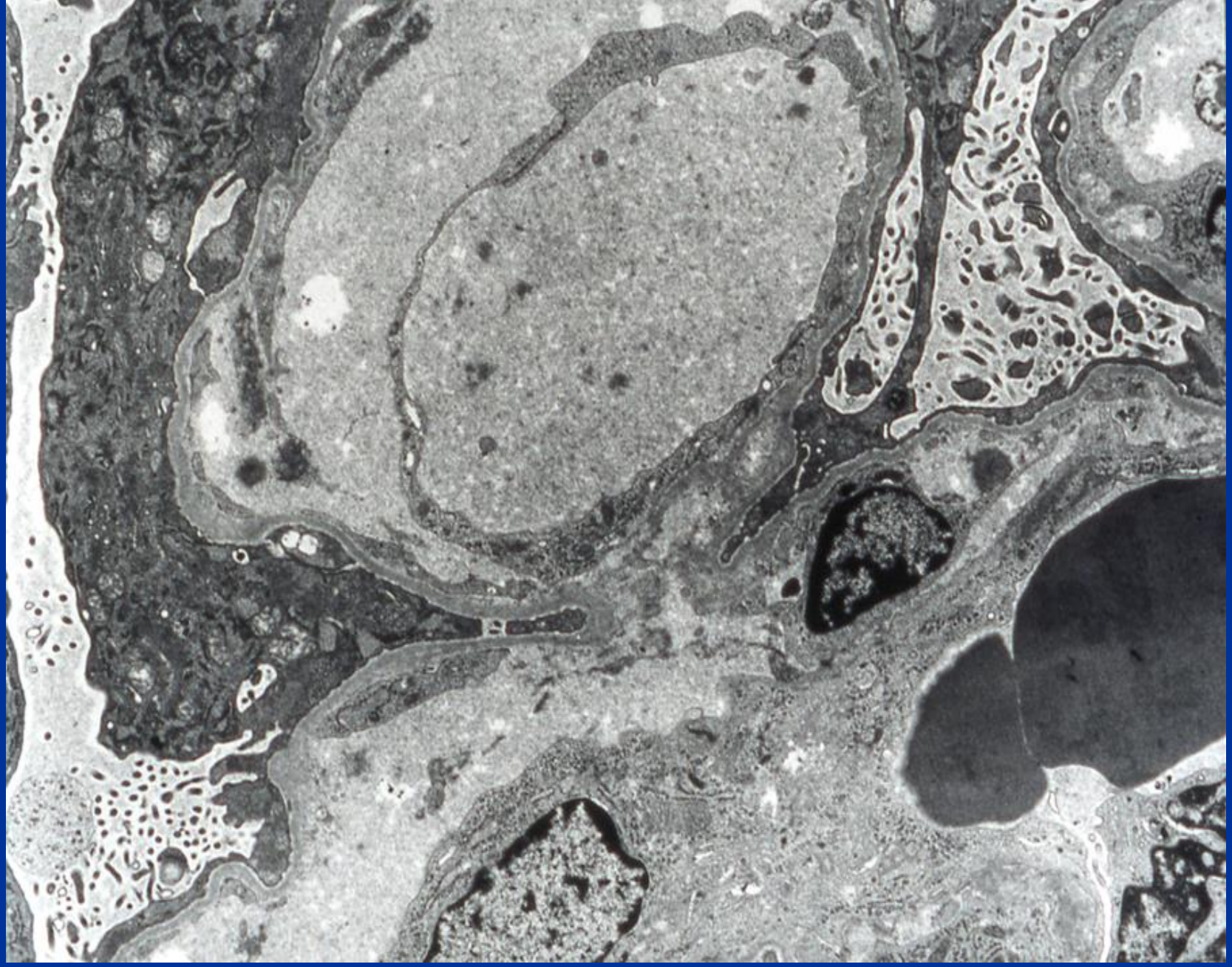
Anti-GEN antibody: Ten Minutes



Anti-GEN antibody: 24 Hours

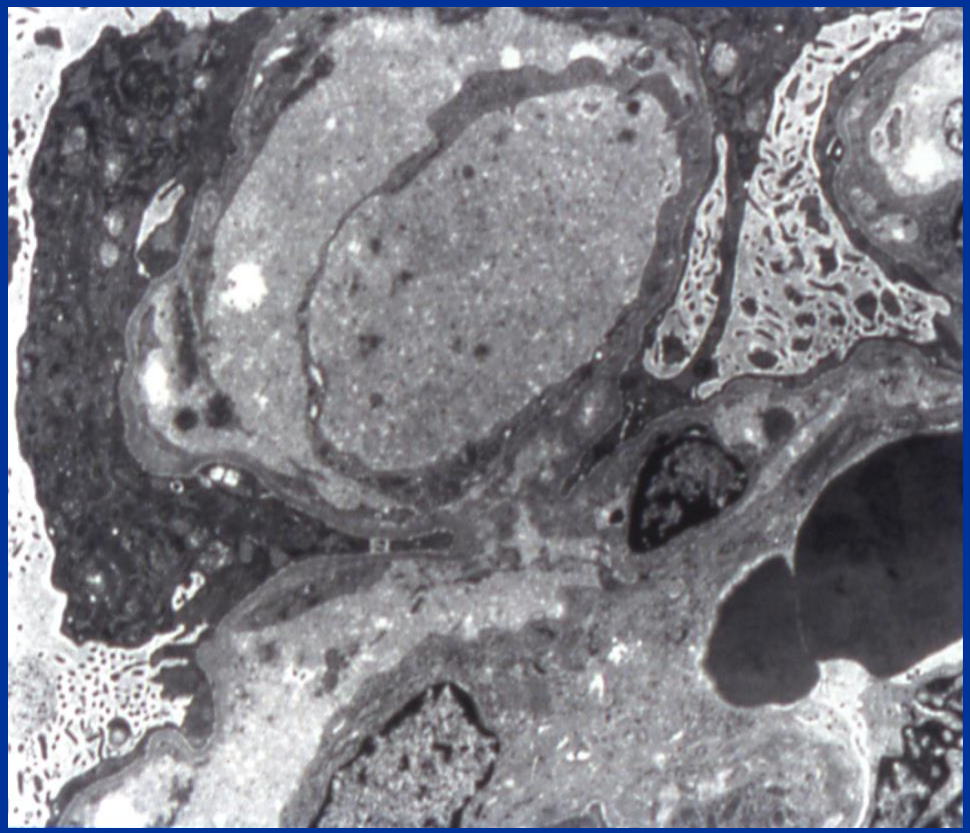


Anti-GEN antibody: 72 Hours

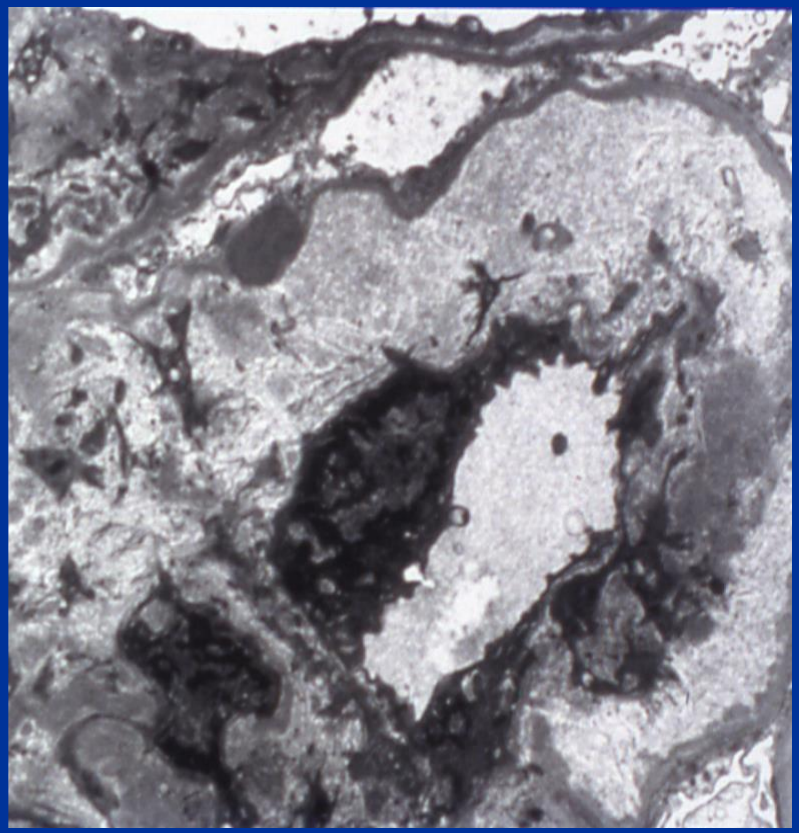


Anti-GEN antibody: 5 Days

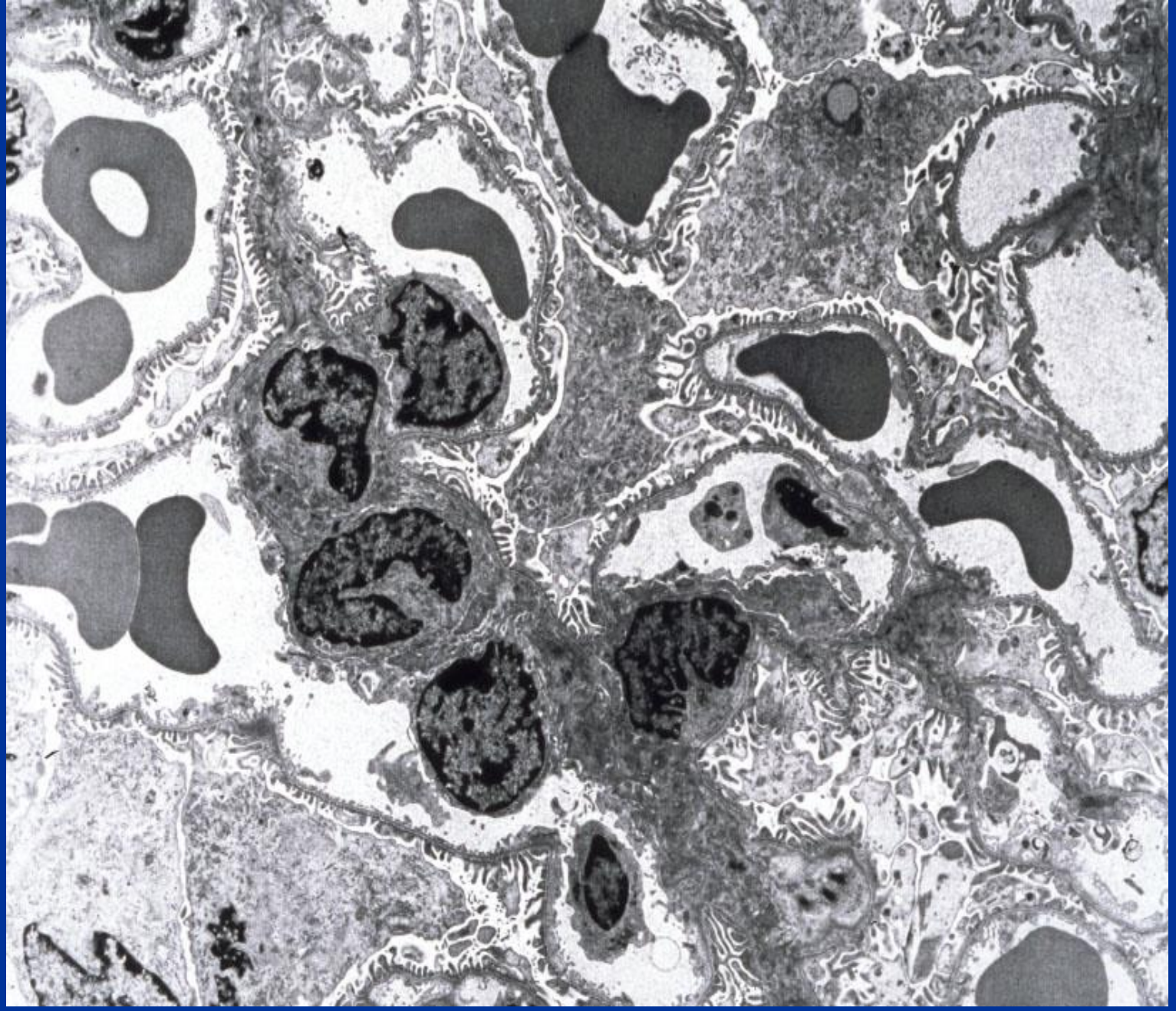
Thrombotic Microangiopathy



Rat



Human



Anti-GEN antibody: Ten Days

Thrombotic Microangiopathy Pathogenesis

- Endothelial cell injury

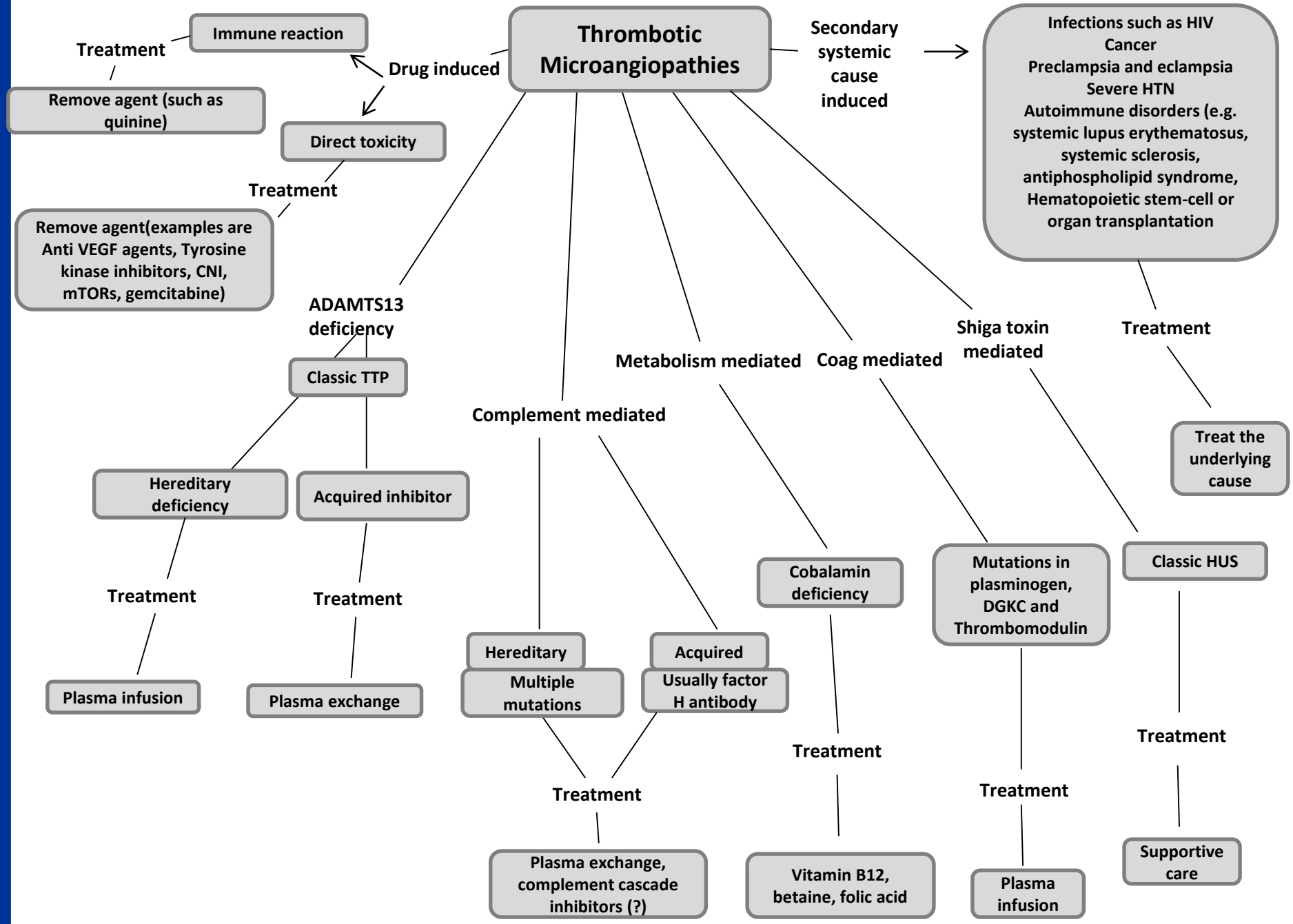
Thrombotic Microangiopathy

- Hemolytic – Uremic syndrome
- Thrombotic thrombocytopenic purpura
- Malignant hypertension
- Eclampsia/Pre-eclampsia
- Post-partum renal failure
- Oral contraceptives
- Infections
- Allograft transplant rejection
- Scleroderma
- Systemic lupus erythematosus
- Anti-phospholipid antibody syndrome
- Heredity
- Radiation
- Disseminated intravascular coagulation
- Drugs/toxins

Syndromes of Thrombotic Microangiopathy

James N. George and Carla M. Nester

N Engl J Med 371:654-666; 2014



Modified from Kevan Jhaveri (NephronPower Blog) who adapted from George and Nester, NEJM 2014; 371: 654-66

Drug Induced Thrombotic Microangiopathy

- Chemotherapy
  - Mitomycin
  - Gemcitabine
  - Radiopharmaceuticals
- Immunomodulatory
  - Cyclosporine
  - Tacrolimus
  - Rapamycin
  - OKT3
  - Interferon
- Anti-Angiogenic
  - VEGF Inhibitor
- Antiplatelet Agents
  - Clopridogel
  - Ticlopidine
- Other
  - Quinine

Drug-Induced Thrombotic Microangiopathy Mechanisms of Injury

Mechanism	Key Factors	Drugs Implicated
Toxicity to Endothelial Cells	Cumulative Dose	Cancer Chemotherapy (Mitomycin, Gemcitabine, Radiopharmaceuticals), Calcineurin Inhibitors, Anti-platelet agents
Acute, Immune Mediated	Not dose dependent – antibodies directed to platelets (quinine) and ADAMTS13 (anti-platelet agents)	Quinine, Anti-platelet agents
Acquired ADAMTS 13 Deficiency		Rarely reported; Antiplatelet agents
Interference with podocyte/endothelial cell axis of VEGF signaling		Anti-VEGF antibodies

Calcineurin Inhibitors and TMA

Cyclosporine and Tacrolimus have similar mechanisms of toxicity

Non-TMA related toxicities:

- Vasoconstriction
- Tubular cell toxicity
- Interstitial fibrosis

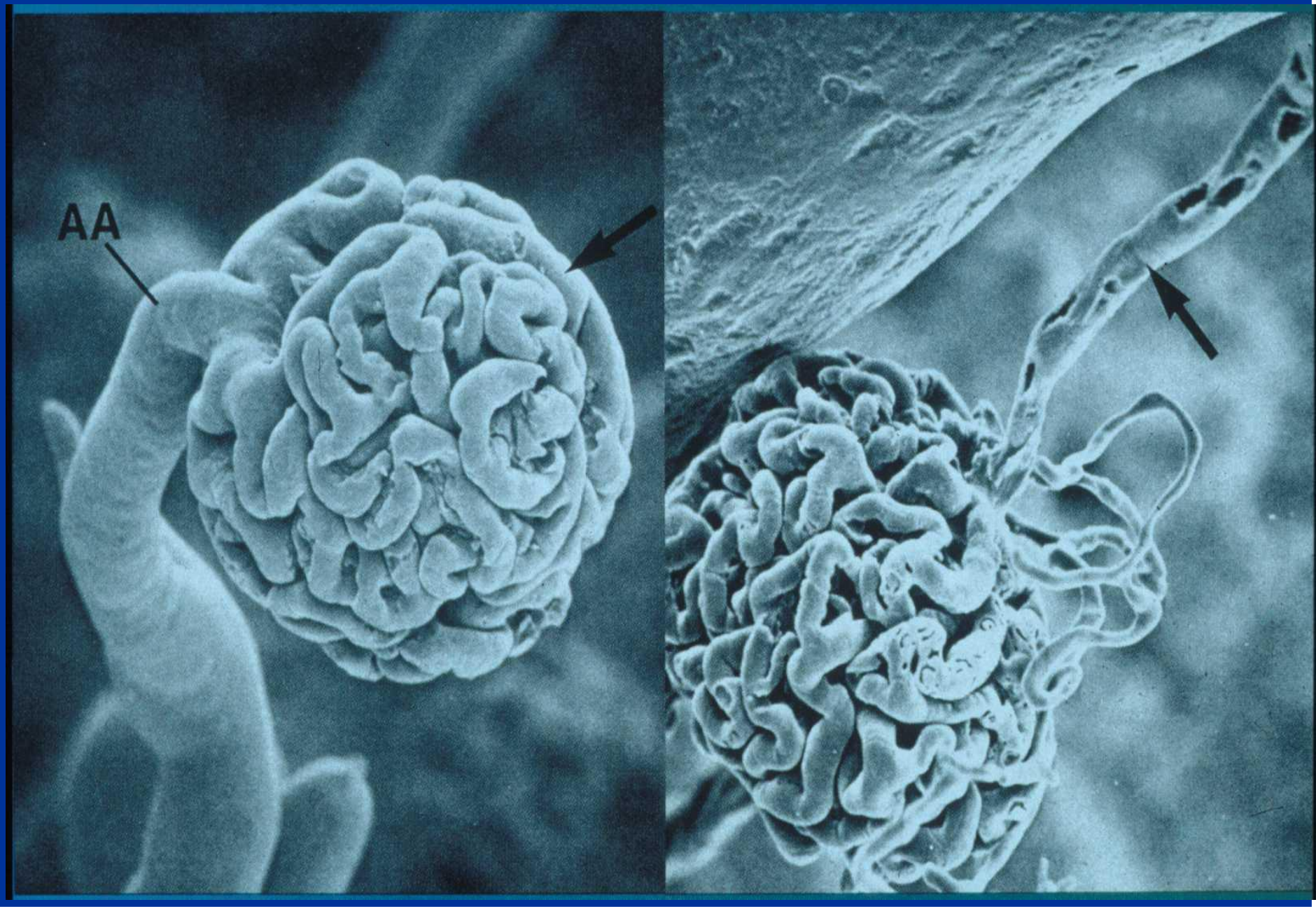
Possibly related toxicity

- Arteriolopathy

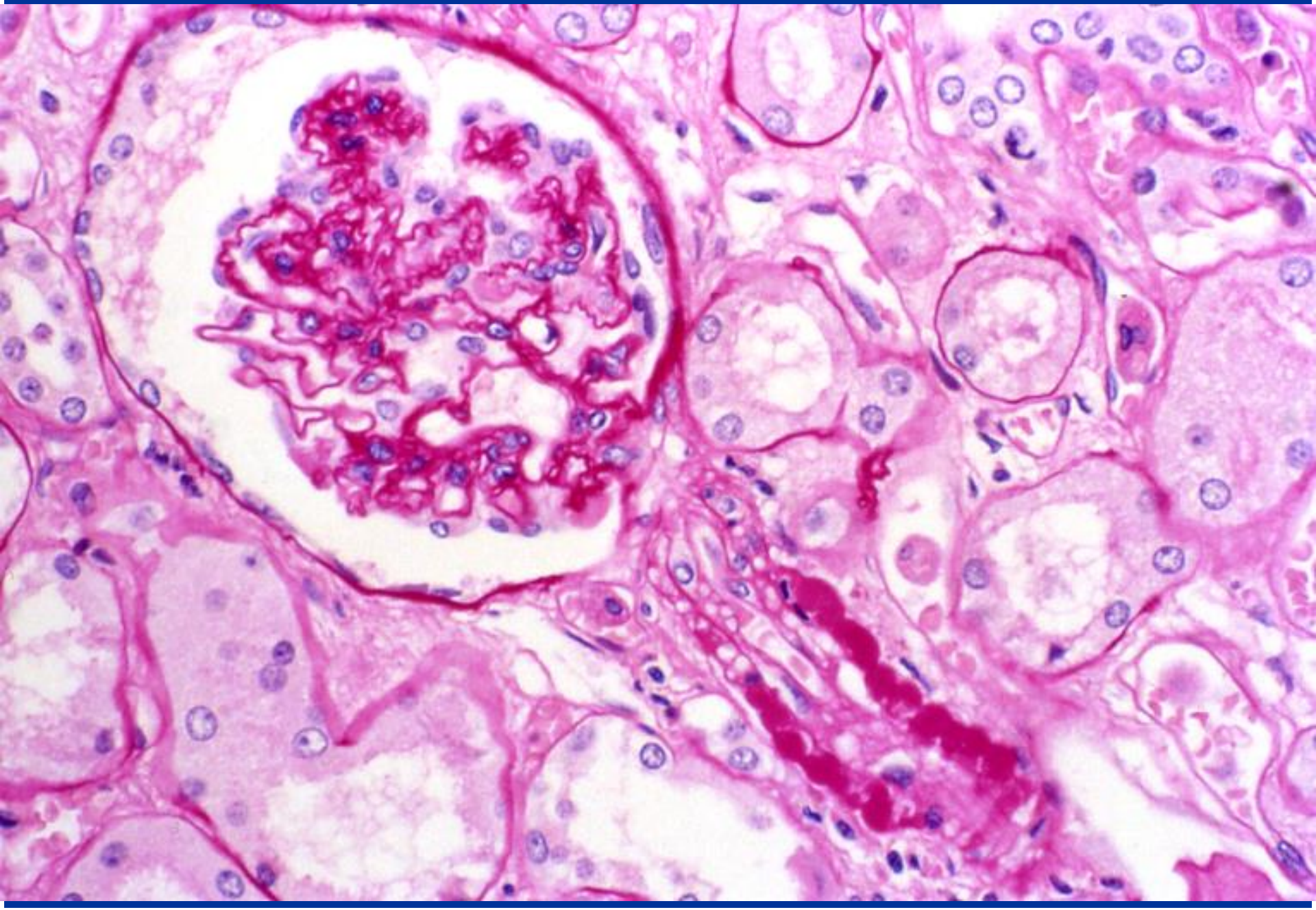
Probable etiologic injury in TMA

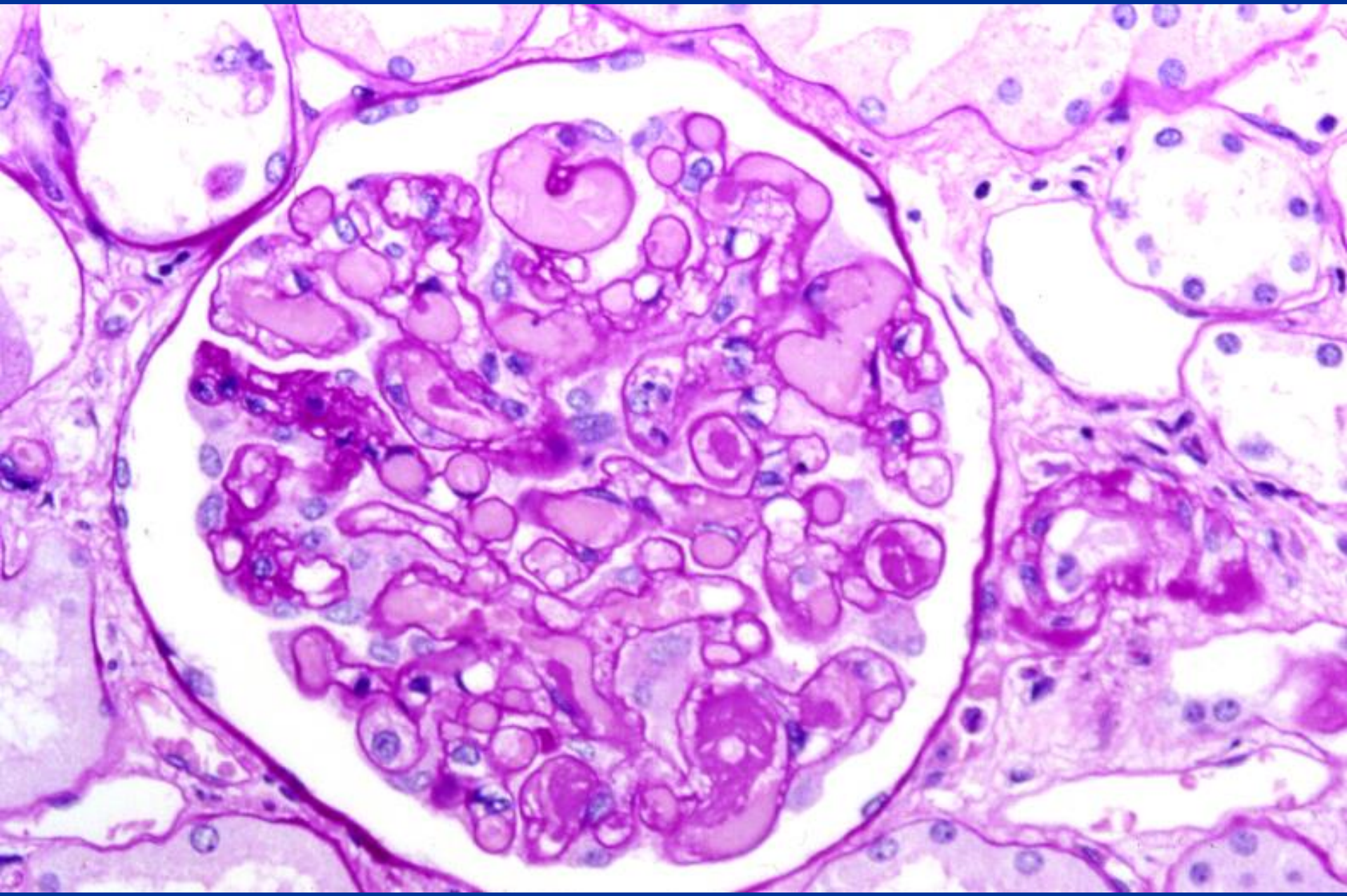
- Endothelial toxicity
- No evidence of altered ADAMTS 13 activity

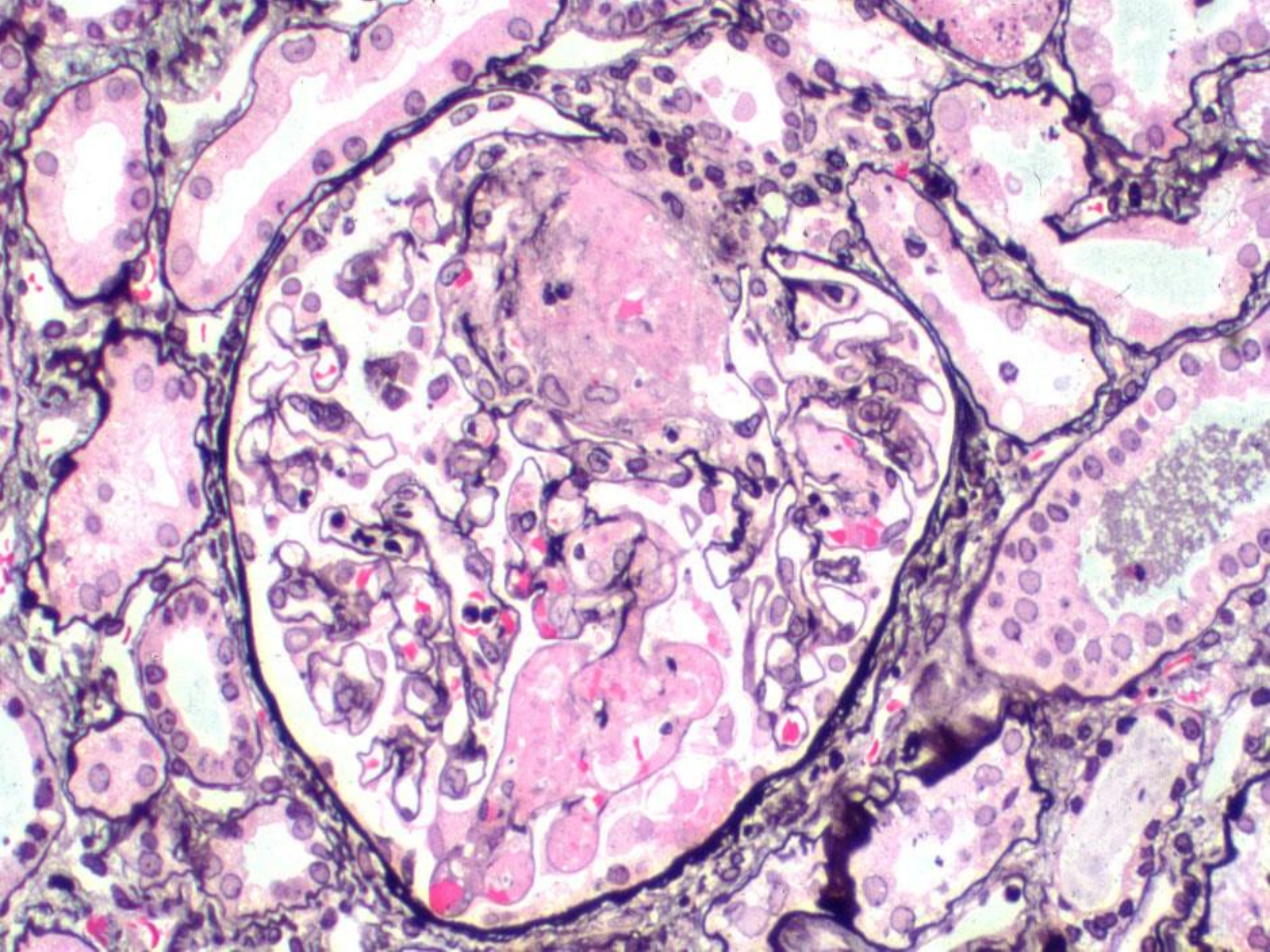
Calcineurin Inhibitor Induced Vasoconstriction



Calcineurin Inhibitor Toxicity: Arteriolopathy







Calcineurin Inhibitor Induced TMA
Presentation

Usually manifests as acute renal failure

- Renal failure may be only manifestation
- Usually diagnosed by renal biopsy
- Increased susceptibility with sirolimus
- Inconstant association with supratherapeutic drug levels

Calcineurin Inhibitor Induced TMA
Outcome

- Reversible
- Outcome better than most other forms of HUS/TTP/TMA
- Calcineurin Inhibitor induced TMA is usually drug specific (i.e., cyclosporine induced TMA is not necessarily predictive of tacrolimus induced TMA, and vice versa)
- Benefit of plasma exchange remains unproven

Gemcitabine-induced TMA

Initially approved as a therapeutic for metastatic pancreatic cancer, now used for numerous other malignancies

Incidence:

- TMA association first reported in 1994.
- Incidence is low- 8/2586 patients (0.31%) in one study (Cancer 2004; 2664)

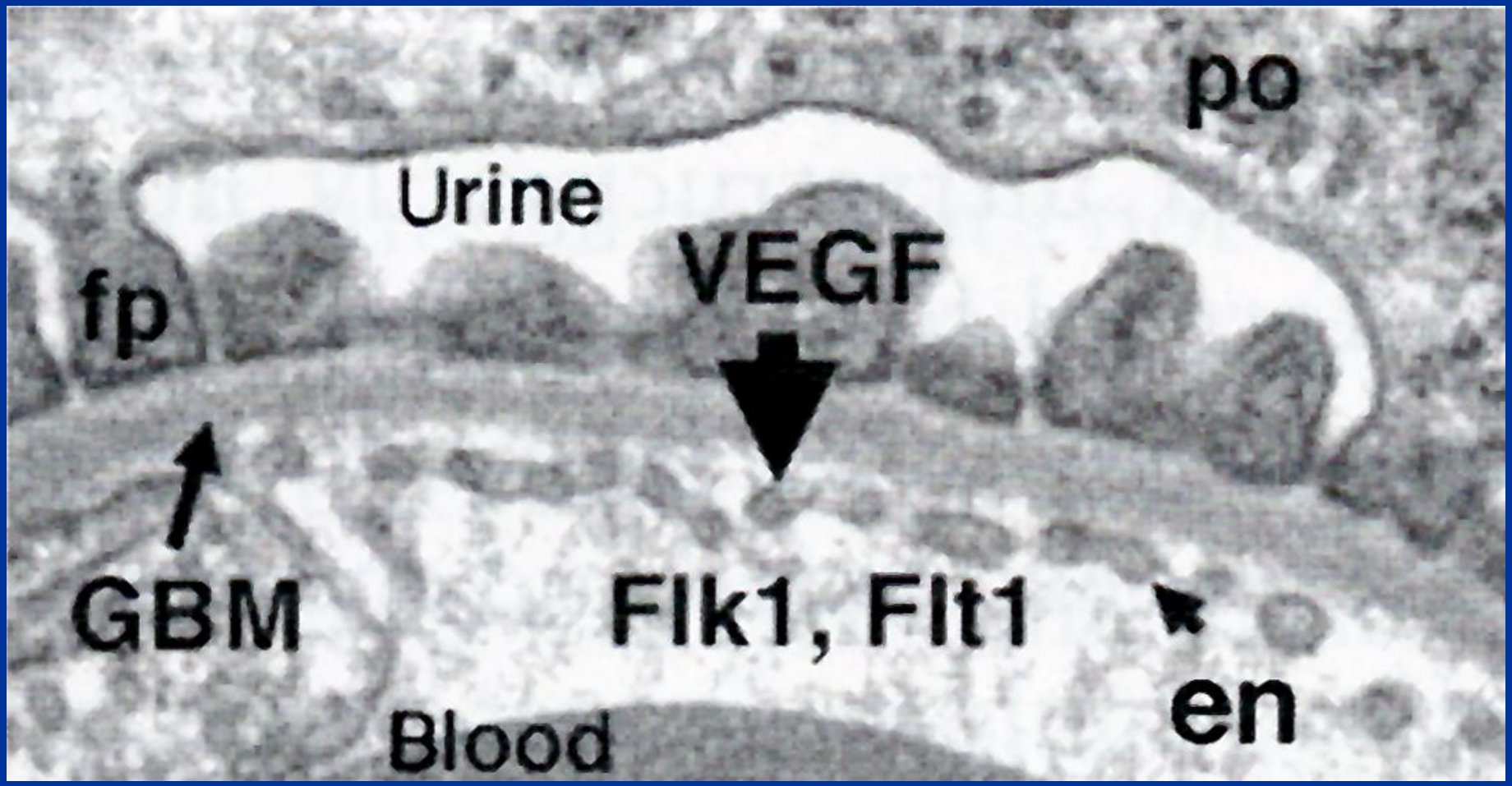
Presentation:

- Onset is variable. TMA may develop months or even years after last dose

Mechanism:

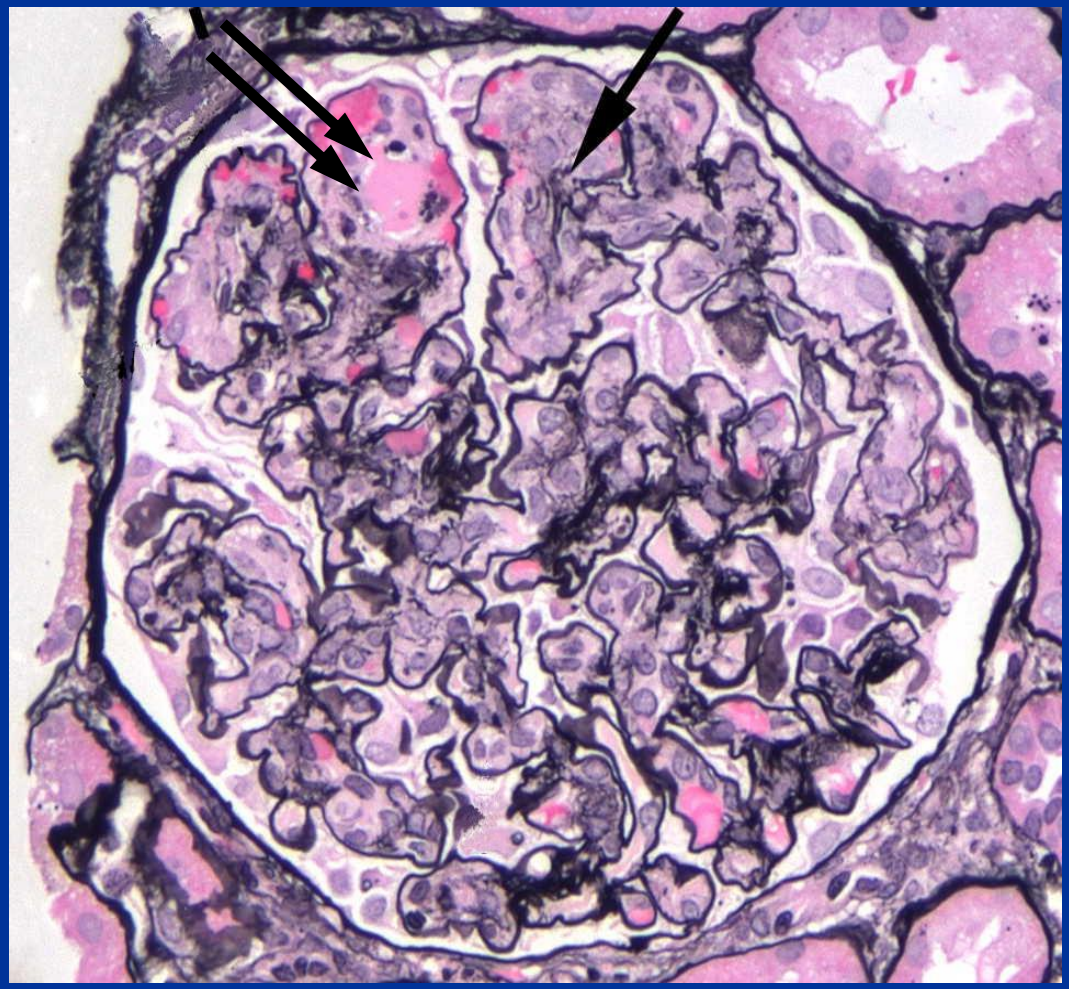
- Presumed endothelial toxicity. Dose-dependent associations not well established.

VEGF (Vascular Endothelial Growth Factor) and TMA



Eremina, et al
J. Clin. Invest. 2003; 111:707

Anti-VEGF Antibody and TMA
A Renal Biopsy Study



V Eremina, JA Jefferson, et al. NEJM 2008

Kidney diseases associated with anti-vascular endothelial growth factor (VEGF): an 8-year observational study at a single center.

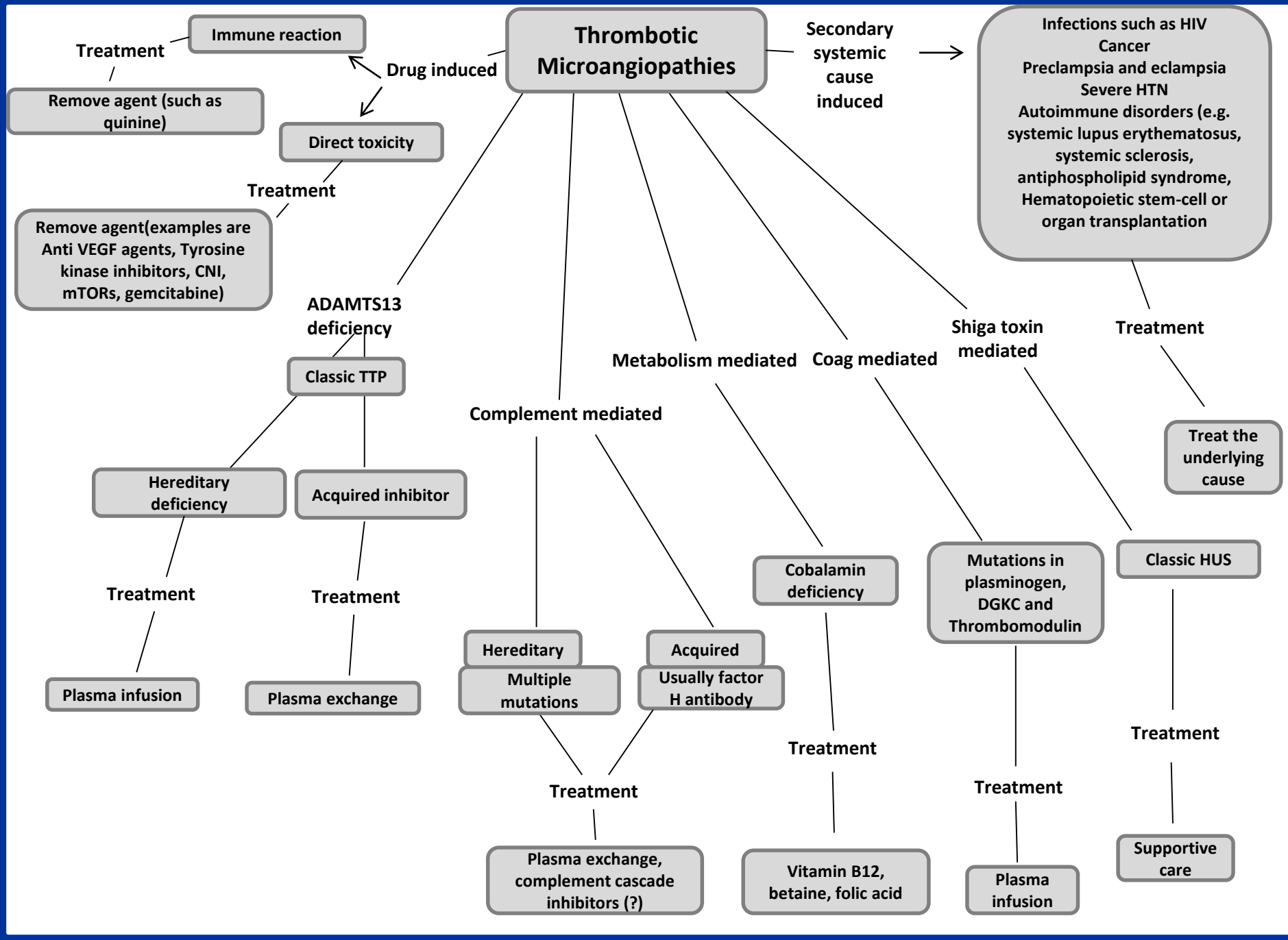
- 100 biopsied cases 2006-2013
- 73% showed TMA
  - 50% were renal-limited (i.e., no hemolytic anemia)
- Hypertension and proteinuria resolved after drug discontinued (recurred in 3/3 who were re-challenged)

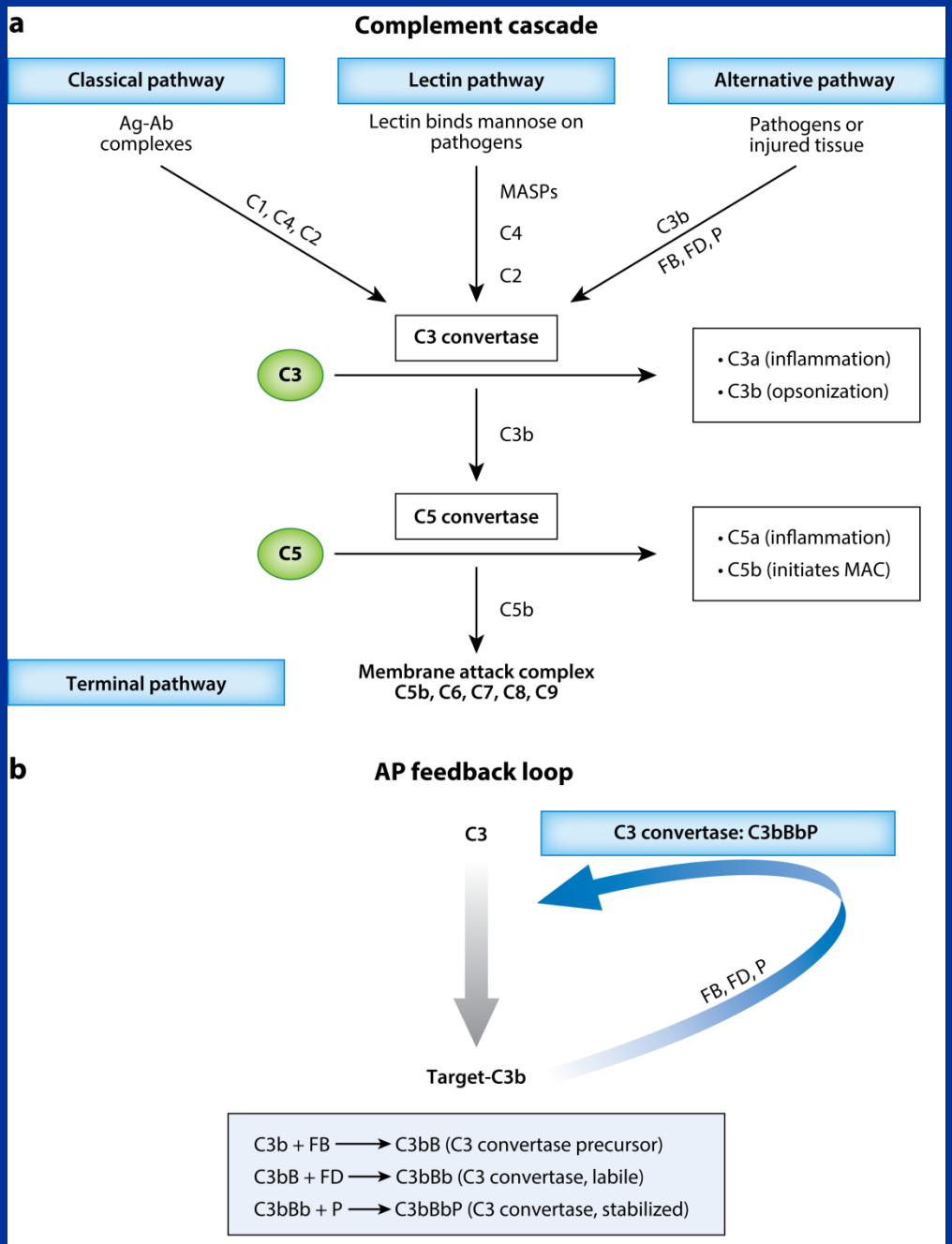
Izzedine H et al. Medicine 2014

Drug Induced Thrombotic Microangiopathy (TMA)

Summary

- Drug Induced TMA may be limited to the kidney
- Mechanisms of drug induced injury are diverse
  - Endothelial toxicity
  - Immune mechanisms (autoantibody formation)
  - Podocyte/endothelium homeostatic axis perturbations
- Mechanisms are generally distinct from those identified in cases of TTP/HUS
  - ADAMTS 13 rarely implicated
- Established therapeutic options are limited


Thrombotic Microangiopathies
Drug induced
Immune reaction
Treatment
Remove agent (such as quinine)
Direct toxicity
Treatment
Remove agent(examples are Anti VEGF agents, Tyrosine kinase inhibitors, CNI, mTORs, gemcitabine)
Secondary systemic cause induced
Infections such as HIV
Cancer
Preclampsia and eclampsia
Severe HTN
Autoimmune disorders (e.g. systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome,
Hematopoietic stem-cell or organ transplantation
Treatment
Treat the underlying cause
ADAMTS13 deficiency
Classic TTP
Hereditary deficiency
Acquired inhibitor
Treatment
Plasma infusion
Treatment
Plasma exchange
Complement mediated
Hereditary
Multiple mutations
Acquired
Usually factor H antibody
Treatment
Plasma exchange, complement cascade inhibitors (?)
Metabolism mediated
Cobalamin deficiency
Treatment
Vitamin B12, betaine, folic acid
Coag mediated
Shiga toxin mediated
Mutations in plasminogen, DGKC and Thrombomodulin
Treatment
Plasma infusion
Classic HUS
Treatment
Supportive care



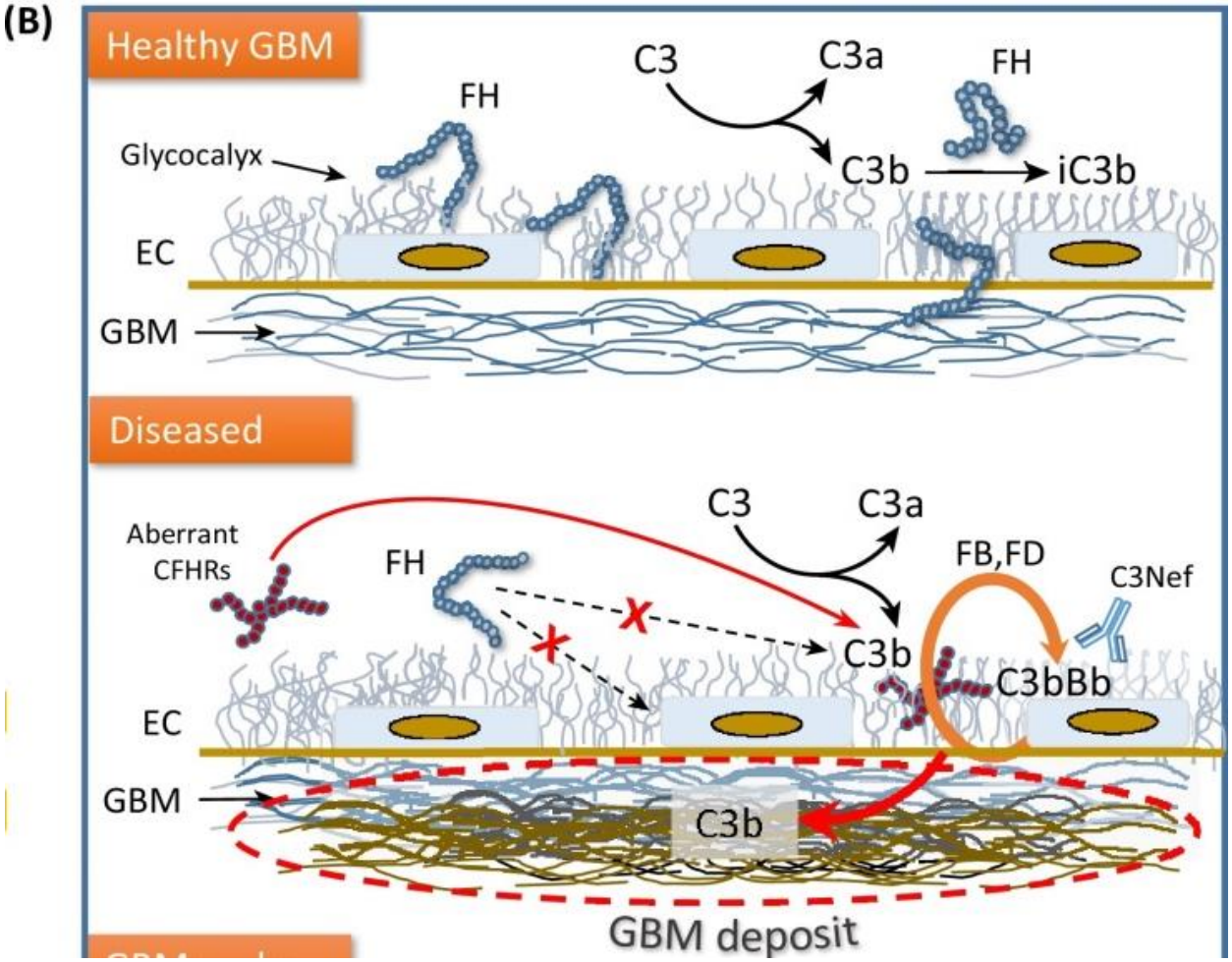
Liszewski MK, et al. 2017.
Annu. Rev. Pathol. Mech. Dis. 12:25–52

Atypical HUS and Complement

- **Loss of function in regulatory genes:**
- **Factor H: secreted, produced in liver**
- **Membrane cofactor protein (MCP): transmembrane, expressed systemically**
- **Factor I**
- **Gain of function in activating genes:**
- **C3, Factor B**
- **Autosomal recessive or dominant, variable penetrance**

Noris 2003, Richards 2003, Pickering/Cook 2011

COMPLEMENT DYSREGULATION IN aHUS



Mastellos DC, et al. Trends in Immunology 38: 383-394, 2017

% of genetic mutations in aHUS

	Children		Adults	
	France	Italy	France	Italy
N=	230	152	289	121
CFH, CFH hybrid	17.4	35.6	30	21.4
MCP	19.4	9.2	9	3.3
CFI	3.4	2.6	9	4.9
C3	9.5	3.9	8	4.9
CFB	.5	nd	1	nd
Anti-CFH ab	9.1	3.9	3.8	1.6
THMD	0	7.8	0	.8
Combined	1.7	nd	2	nd
DGKE	4.7	nd	0	nd

Fakhouri et al Lancet 2017

KDIGO 2016 Controversies Conference

Atypical Hemolytic Uremic Syndrome and C3 Glomerulopathy

This presentation is based on: Goodship T. et al., Kidney Intl (2017) 91:539-551.

aHUS: Laboratory Analysis

- Investigations should focus on determining the underlying etiology and excluding other diagnoses.
- Measure ADAMTS13 activity to diagnose or exclude thrombotic thrombocytopenic purpura (TTP).
- Investigation for STEC-HUS should be routine in all patients with presumed aHUS.

aHUS: Laboratory Analysis

- Serum/plasma levels of complement proteins should be measured in all patients with primary aHUS prior to plasma therapy.
  - C3 levels will be low in 30-50% of aHUS cases.
  - Low C3 levels are also noted in acute STEC-aHUS and pneumococcal aHUS.

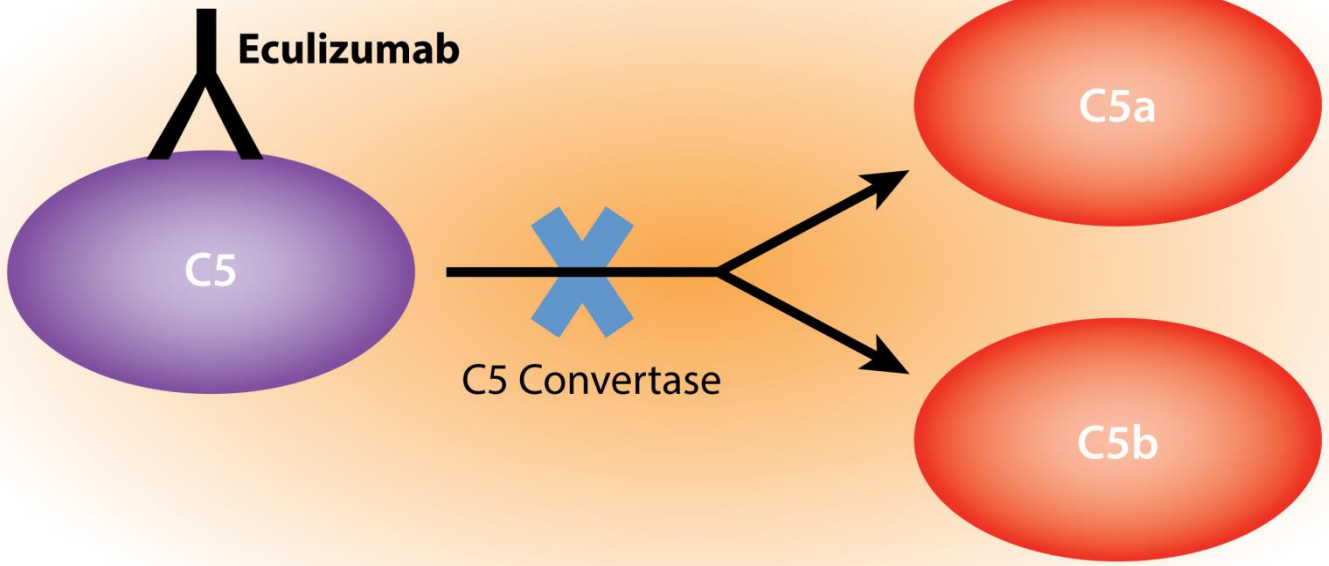
aHUS: Genetic Testing

- The minimum set of genes that should be screened includes *CFH*, *CD46*, *CFI*, *C3*, *CFB*, *THBD*, *CFHR1*, *CFHR5*, and *DGKE*.
- Genetic testing should also include the risk haplotypes *CFH-CFHR3* and MCP_{ggaac} as they modify disease penetrance and severity.
  - Delays in obtaining results from genetic or molecular diagnostic studies should not prevent a clinical diagnosis or postpone treatment, as early anticomplement treatment is crucial to preserve renal function and avoid irreversible sequelae.

aHUS: Acquired Drivers of Disease

- Acquired drivers of disease are autoantibodies to complement proteins or protein complexes that impair normal function.
- The best-studied acquired drivers are FH autoantibodies, which are usually seen in association with deletion of the *CFHR3* and *CFHR1* genes.

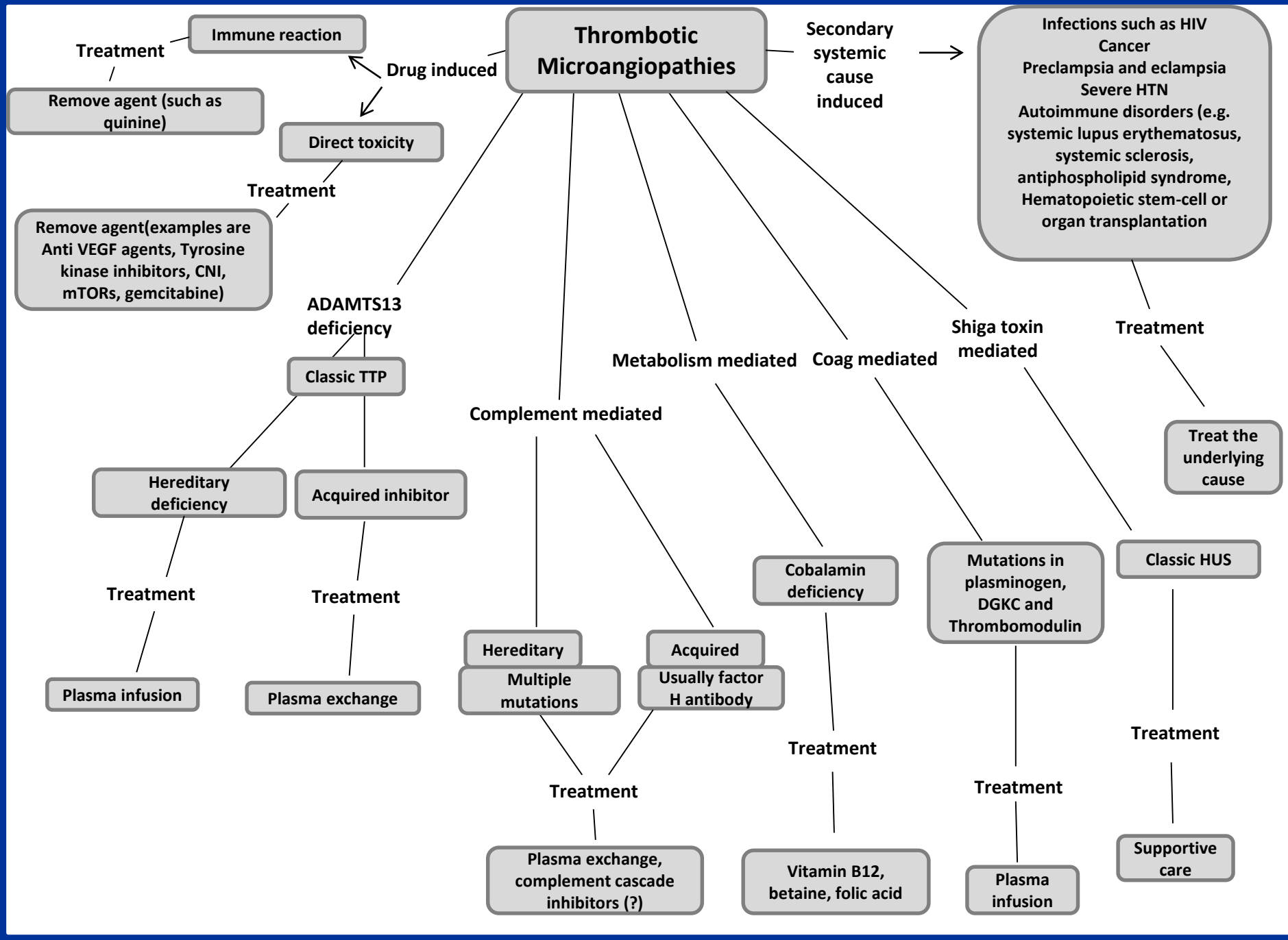
Eculizumab: Mechanism of Action



Liszewski MK, et al. 2017.
Annu. Rev. Pathol. Mech. Dis. 12:25–52

Eculizumab in complement-mediated HUS

- Rates of ESRD/death have dropped significantly
  - 6-15% vs 48-64% in pre-eculizumab era
  - Earlier treatment leads to better outcomes
- Eculizumab is now recommended as first line therapy for aHUS
  - Plasma Exchange if eculizumab is not available
- Optimal dosing and duration of therapy remain unclear


Thrombotic Microangiopathies
Drug induced
Immune reaction
Treatment
Remove agent (such as quinine)
Direct toxicity
Treatment
Remove agent(examples are Anti VEGF agents, Tyrosine kinase inhibitors, CNI, mTORs, gemcitabine)
Secondary systemic cause induced
Infections such as HIV
Cancer
Preclampsia and eclampsia
Severe HTN
Autoimmune disorders (e.g. systemic lupus erythematosus, systemic sclerosis, antiphospholipid syndrome,
Hematopoietic stem-cell or organ transplantation
Treatment
Treat the underlying cause
ADAMTS13 deficiency
Classic TTP
Hereditary deficiency
Acquired inhibitor
Treatment
Plasma infusion
Treatment
Plasma exchange
Complement mediated
Hereditary
Multiple mutations
Acquired
Usually factor H antibody
Treatment
Plasma exchange, complement cascade inhibitors (?)
Metabolism mediated
Cobalamin deficiency
Treatment
Vitamin B12, betaine, folic acid
Coag mediated
Shiga toxin mediated
Mutations in plasminogen, DGKC and Thrombomodulin
Treatment
Plasma infusion
Classic HUS
Treatment
Supportive care

TMA: Summary

- Pathologic features are not etiologically specific (and thrombi may not be present in the chronic stage)
- Pathogenesis involves endothelial injury, often with multiple "hits"
  - (e.g. genetic mutations and polymorphisms, autoantibodies; environmental factors)
- Microbiology of infection-related HUS is constantly changing
  - Non-O157:H7 strains are becoming more common
- Complement inhibition has revolutionized the management of aHUS
  - Non-complement causes of HUS remain to be identified
  - Role of complement dysregulation in other forms of TMA is uncertain


Thank you