

62-Year-Old Woman with Periorbital Edema and Fatigue

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Disclosures

- DSMB: EMD Serono
BMS
- Investigator: Sonoma, Cabaletta, Astra Zeneca
- Consultant: Electra
Leerink Partners
- Expert Testimony

62-Year-Old Woman

PMH: H/O MCA stroke with residual mild hemiparesis (2015)

Bronchiectasis

H. Pylori, treated

Raynaud's phenomenon

MED: Furosemide, prn for occasional ankle edema (years); Chinese herbs

Occasional amphetamines

FH: Gastric cancer

SH: Born in China. Married. Three children. No tobacco. Rare alcohol.

August 2024

- Upper and lower endoscopies to evaluate iron deficiency anemia, and s/p treatment of H. Pylori
- Within days, progressive fatigue: needing to rest during usual walks
daytime naps
lassitude
- Sensation of feeling swollen throughout body

Next Steps?

September 2024

- Fatigue, dyspnea, lassitude continue
- Physical exam shows no edema; left hand contracture; normal RR and O2 Sat on room air; lungs clear
- Laboratory evaluation:
 - CRP 4.3 (0- 5 mg/L)
 - ALT/AST 80s
 - Uric acid normal
 - Scr 0.6; eGFR >100
 - No proteinuria
 - RF 271 (< 13)
 - ANA 1:1280, speckled pattern

Antinuclear Antibodies (ANAs)

- Two assay methods: -indirect immunofluorescence using the human epidermoid carcinoma (HEp-2) cell line as substrate (BWH)
 -solid phase assay
- IIF: pattern (homogeneous, speckled, nucleolar, centromere)
 titer—above 1:160

▼ **TABLE 1.** Target antigens and associated diseases for nuclear patterns

Pattern (ICAP)	Code	Antigen association	Disease association
Homogeneous	AC-1	dsDNA, nucleosomes, histones	SLE, drug-induced lupus, juvenile idiopathic arthritis
Speckled	AC-2,4,5	hnRNP, U1RNP, Sm, SS-A/Ro (Ro60), SS-B/La, RNA polymerase III, Mi-2, Ku	MCTD, SLE, SjS, DM, SSc/PM overlap
Dense fine speckled	AC-2	DFS70/LEDGF	Rare in SLE, SjS, SSc
Fine speckled	AC-4	SS-A/Ro (Ro60), SS-B/La, Mi-2, TIF1γ, TIF1β, Ku, RNA helicase A, replication protein A	SjS, SLE, DM, SSc/PM overlap
Large/coarse speckled	AC-5	hnRNP, U1RNP, Sm, RNA polymerase III	MCTD, SLE, SSc
Centromere	AC-3	CENP-A/B (C)	Limited cutaneous SSc, PBC
Discrete nuclear dots	AC-6,7		
Multiple nuclear dots	AC-6	Sp100, PML proteins, MJ/NXP-2	PBC, SARD, PM/DM
Few nuclear dots	AC-7	p80-coilin, SMN	SjS, SLE, SSc, PM, asymptomatic individuals
Nucleolar	AC-8,9,10		
Nucleolar homogeneous	AC-8	PM/Scl-75, PM/Scl-100, Th/To, B23/nucleophosmin, nucleolin, No55/SC65	SSc, SSc/PM overlap
Nucleolar clumpy	AC-9	U3-snoRNP/fibrillarin	SSc
Nucleolar punctate	AC-10	RNA polymerase I, hUBF/NOR-90	SSc, SjS
Nuclear envelope	AC-11,12		
Smooth nuclear envelope	AC-11	Lamins A,B,C, or lamin-associated proteins	SLE, SjS, seronegative arthritis
Punctate nuclear envelope	AC-12	Nuclear pore complex proteins (i.e., gp210)	PBC
Pleomorphic	AC-13,14		
PCNA-like	AC-13	PCNA	SLE, other conditions
CENP-F-like	AC-14	CENP-F	Cancer, other conditions

High Titred Rheumatoid Factor

- Rheumatoid arthritis
- Sjogren's Syndrome
- Cryoglobulinemia (Hepatitis C)

First Rheumatology Visit, September 2024

- Complaints of fatigue and shortness of breath persist. No joint pain.
- Normotensive, normal O2 saturation. Left sided weakness secondary to prior CVA with contracture left hand. Question skin thickening distal fingers. Normal cardiac exam. Rhonchi at the left base. Joints normal. No proximal muscle weakness. Question of some periorbital swelling. No edema.

Labs, First Rheumatology Visit, Sept 2024

- ESR, CRP: normal
- CPK: 107
- Myositis antibody panel: normal
- Positive RNP antibody
- Negative anti Scl 70
- C3, C4, CH50 all normal
- Urine normal; UPCR normal
- CT chest: bronchiectasis; ? Mild ILD right base

Some definitions

- Undifferentiated connective tissue disorder: does not fulfill classification criteria of a single disorder (e.g., Raynaud's and ILD, normal exam, positive ANA and negative extractable antigens)
- Overlap Syndrome: Features of two or more rheumatic disorders (e.g., erosive inflammatory arthritis, positive ANA, negative extractable antigens)
- Mixed Connective Tissue Disease: connective tissue disorder with features of ILD, myositis, Raynaud's, arthritis; high anti RNP antibodies characteristic

Scleroderma



Scleroderma

- Rare disorder: incidence 8-56 new cases/million /year
prevalence 38-341 cases/million (increased due to improved survival)
female preponderance
- CTD with the highest mortality: cum. survival 75% @ 5 years
63% @ 10 years
lung disease vs. renal disease in the past
- Features: Chronic
Immune mediated; vascular involvement
Over 95% have Raynaud's
Multisystem involvement (skin, gastrointestinal, pulmonary, vascular, renal)
- Increased risk of malignancy, especially lung (~1/3 of all cancers) and skin

Scleroderma Subtypes

- Limited skin disease: (CREST); vascular disease, calcifications, pulmonary hypertension
- Diffuse skin disease: accelerated skin disease early lung fibrosis; risk of renal crisis, cardiac involvement
- Scleroderma and overlap syndrome
- Scleroderma sine (no skin involvement)

Second Rheumatology Visit, Nov 2024

- Profound fatigue continues; ADL affected; shortness of breath with activities
- Exam: minimal periorbital swelling; no edema
no skin thickening over hands
negative nailfold microscopy
no synovitis
no muscle weakness

Labs at Second Rheumatology Visit, Nov 6 2024

- CPK 589
- TSH normal
- Prescribed 20 mg prednisone

Thanksgiving Eve 2024

- 2 AM: knocked on son's door, asking to be driven to other son's home, located down the street
- Brought to ED
- On arrival: Alert, oriented
Recalled confusion
BP 226/143 HR 81, reg O2 sat 98%

Evaluation in the ED

- WBC 21,000
- H/H: 14.8/45.7
- Platelet: 44,000
- LDH 1120

- CRP 41
- Cre 1.05 (baseline 0.6), K 3.1
- Urinalysis with 3+ blood and 2+ protein
- Urine sediment 10 RBC/hpf

- Lactate 2.6
- ibili 1.0
- NT-proBNP 1354

- CT Head: 7 mm left parietal lobe parenchymal hemorrhage

Next Steps?

Clinical Features and Diagnosis of Scleroderma Renal Crisis

Diagnostic criteria (essential)

New-onset BP >150/85 mm Hg or obtained at least twice over 24 hr

Increase ≥ 20 mm Hg from usual systolic BP

AKI stage 1 or higher: >50% increase in serum creatinine from stable baseline or an absolute increase of $26.5 \mu\text{mol/L}$

Captopril Started

Supportive evidence (desirable)

Microangiopathic hemolytic anemia on blood film, thrombocytopenia, and other biochemical findings consistent with hemolysis

Findings consistent with accelerated hypertension on retinal examination

Microscopic hematuria on urine dipstick or RBCs on urine microscopy

Oliguria or anuria

Renal biopsy with typical features of SRC, including onion-skin proliferation within the walls of intrarenal arteries and arterioles, fibrinoid necrosis, and glomerular shrinkage

Flash pulmonary edema

AKI, Acute kidney injury; BP, blood pressure; RBC, red blood cell; SRC, scleroderma renal crisis.

Reproduced from Lynch BM, Stern EP, Ong V, Harber M, Burns A, Denton CP. UK Scleroderma Study Group (UKSSG) guidelines on the diagnosis and management of scleroderma renal crisis. Clin Exp

Serum autoantibodies in systemic sclerosis

Antigen	ANA staining pattern	Approximate frequency in all patients (%)	Clinical associations	Organ involvement
Scl-70 (topoisomerase-1)	Speckled	10 to 40	dcSSc	Lung fibrosis, isolated pulmonary hypertension less likely
Centromere	Centromere (kinetochore)	15 to 40	lcSSc	Pulmonary hypertension, esophageal disease, "protection" from lung fibrosis and renal disease
RNA polymerase III	Fine speckled nucleolar	4 to 25	dcSSc	Renal, skin, malignancy

Characteristics and clinical associations of the different autoantibodies that may be seen in scleroderma. dcSSc and lcSSc refer to diffuse and limited cutaneous systemic sclerosis, respectively.

ANA: antinuclear antibody; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis.

Adapted from: Nihtyanova SI, Denton CP. Autoantibodies as predictive tools in systemic sclerosis. Nat Rev Rheumatol 2010; 6:112.

The Hematologist Perspective

- Consult Question: Why is the patient thrombocytopenic?
- Hematology Response 1: Ugh, not another thrombocytopenia consult
- Hematology Response 2 (and the appropriate response): Snap out of it and first assess for anything alarming

The Hematologist Perspective

Are there findings to suggest a dangerous diagnosis?

Yes!

Hemoglobin Trend: 14.8 -> 11.9 in 16 hours

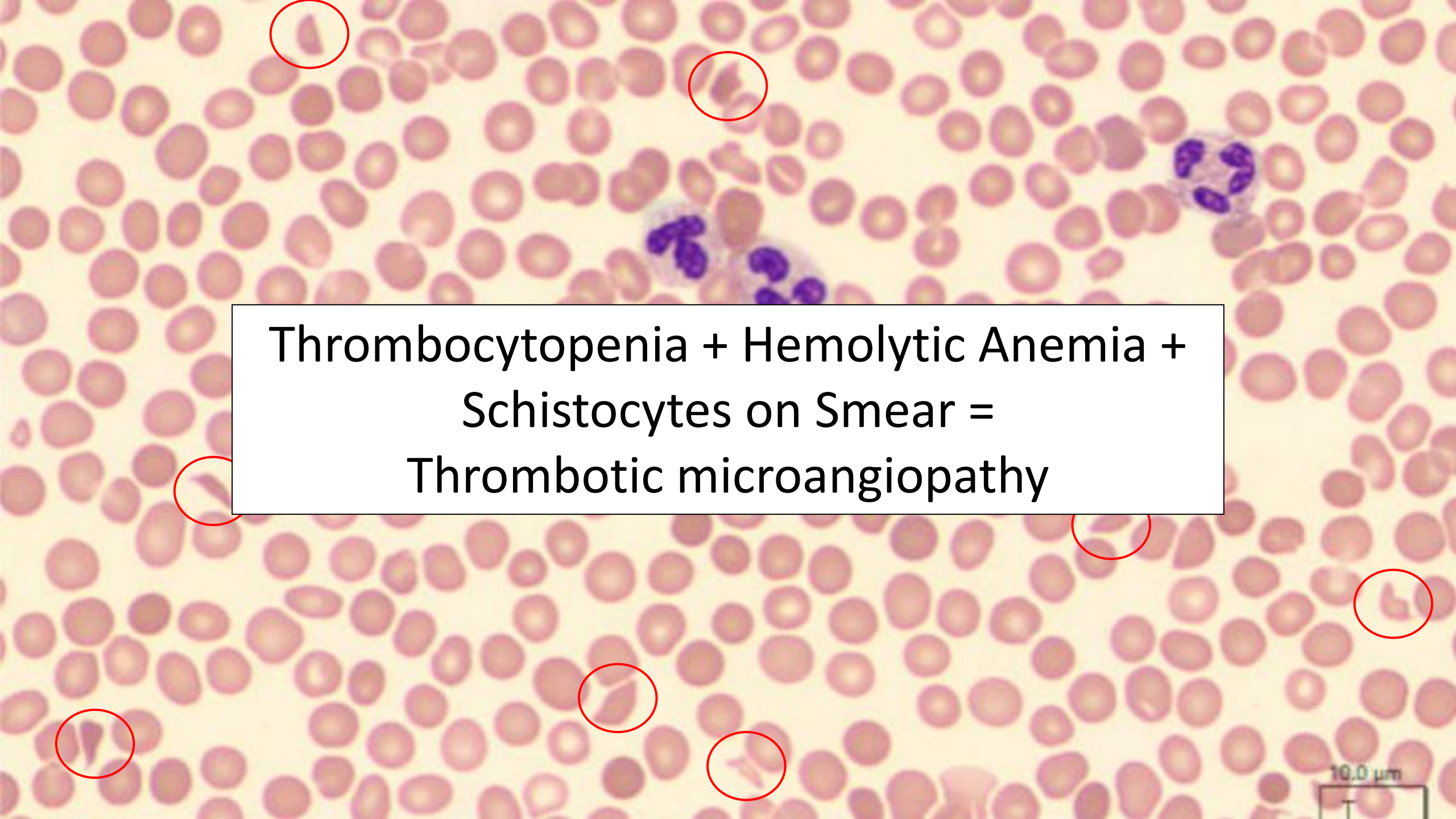
Elevated retic count, indirect bilirubin, LDH

Undetectable haptoglobin

Creatine: 0.67 -> 1.05



10.0 μm



Thrombocytopenia + Hemolytic Anemia +
Schistocytes on Smear =
Thrombotic microangiopathy

The Hematologist Perspective

Primary TMA Syndromes

- TTP
- Shiga toxin-mediated HUS
- Complement-mediated (aHUS)
- Drug-induced

“Secondary” TMA Syndromes

- DIC
- Systemic infection
- Malignant HTN
- Rheumatic: Scleroderma renal crisis, antiphospholipid antibody syndrome
- Preeclampsia/HELLP
- Transplant associated TMA
- Malignancy/Chemo associated

The Hematologist Perspective

Primary TMA Syndromes

- TTP ← Can't miss
- Shiga toxin-mediated HUS
- Complement-mediated (aHUS)
- Drug-induced

“Secondary” TMA Syndromes

- DIC
- Systemic infection
- Malignant HTN
- Rheumatic: **Scleroderma renal crisis**, antiphospholipid antibody syndrome
- Preeclampsia/HELLP
- Transplant associated TMA
- Malignancy/Chemo associated

Most likely

PLASMIC Score for TTP

Predicts ADAMTS13 deficiency in suspected thrombotic thrombocytopenic purpura (TTP) with high discrimination.

Platelet count $<30 \times 10^9/L$

No 0

Yes +1

Hemolysis

Reticulocyte count $>2.5\%$, haptoglobin

No 0

Yes +1

5 points

PLASMIC Score

Intermediate

risk

Risk group

6 %

Risk of severe ADAMTS13 deficiency (defined as ADAMTS13 activity level $<15\%$)

Copy Results

Next Steps

Yes 0

Yes 0

Yes +1

INR <1.5

No 0

Yes +1

Creatinine $<2.0 \text{ mg/dL}$ ($176.8 \mu\text{mol/L}$)

No 0

Yes +1

The Hematologist Perspective

Consult Day 1:

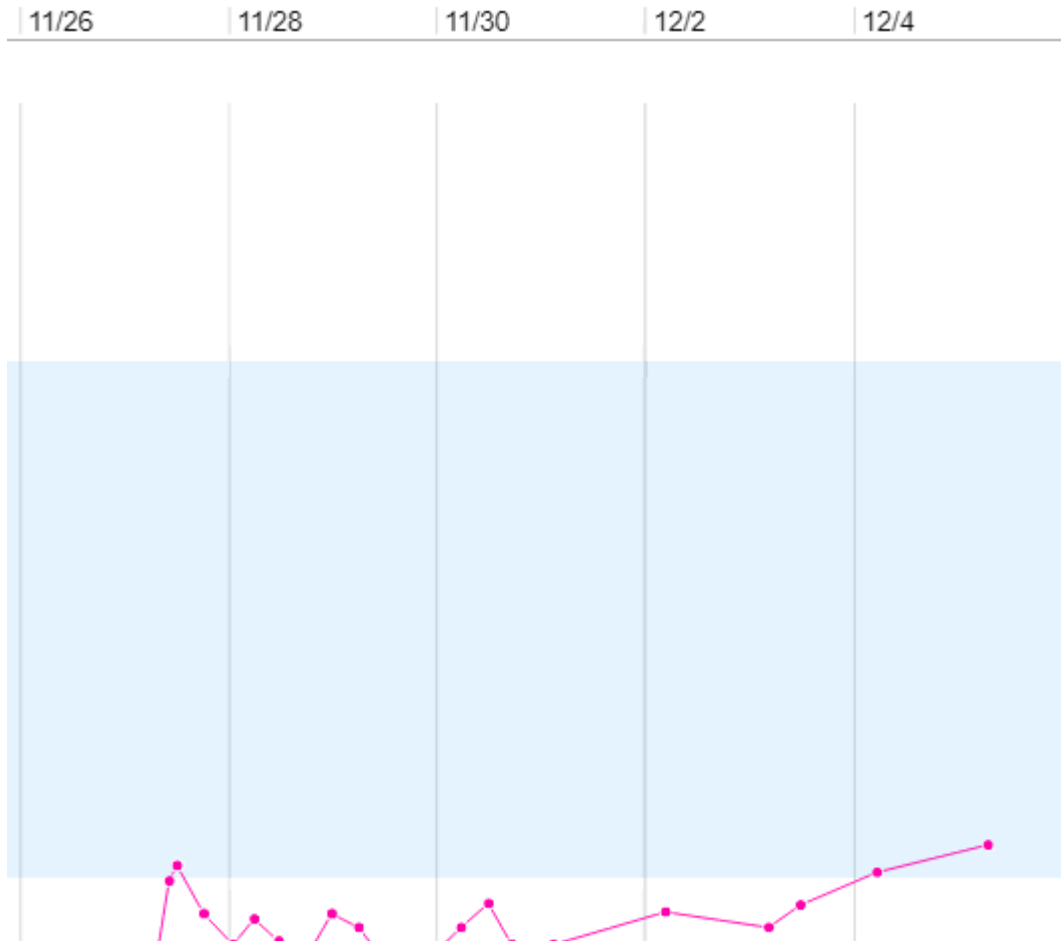
“Given history of rheumatologic disorder, markedly elevated blood pressure on admission, a rise in her creatinine of >0.3 , and recent steroid use, scleroderma renal crisis is highest on the differential. Send ADAMTS13 but defer plasmapheresis for TTP.”

Early the Following Morning:

“Overnight with appropriate management of scleroderma renal crisis, the patient’s hemoglobin and platelet counts decreased and her mental status worsened. This increases concern this morning for TTP. We will therefore plan to initiate plasmapheresis while waiting for the ADAMTS13 result.”

Working Diagnosis: TTP

- Plasmapheresis started to treat presumptive TTP pending ADAMTS13



Dates as Rows

Print

PLT	
Ref. Range & Units	150 - 450 K/uL
12/03/24 04:15	121 ▼
12/02/24 04:31	130 ▼
12/01/24 02:42	111 ▼
11/30/24 17:10	111 ▼
11/30/24 11:47	135 ▼
11/30/24 05:28	121 ▼
11/29/24 23:48	107 ▼
11/29/24 17:08	104 ▼
11/29/24 12:02	101 ▼
11/29/24 05:55	121 ▼
11/28/24 23:43	129 ▼
11/28/24 18:27	106 ▼
11/28/24 11:31	113 ▼
11/28/24 05:52	126 ▼
11/28/24 01:01	111 ▼
11/27/24 18:16	129 ▼
11/27/24 12:06	157 ▼

← Plasmapheresis initiated

Hospital Course, Peri and Post TTP, Nov-Dec 2024

- Hypertension continues. Calcium channel blocker added to ACEi
- Scr rises (1.09 to 1.81)
- Microalbuminuria
- Thrombocytopenia persistent but not worse
- Echo: LVEF 65%; RSVP: 63 mm HG

BWH MGRs

David E. Leaf, MD, MMSc

Associate Professor of Medicine, Harvard Medical School

Director of Clinical and Translational Research in Acute Kidney Injury

Division of Renal Medicine, Brigham and Women's Hospital

BWH Medical Grand Rounds

February 28, 2025

Is this TTP?

PLASMIC Score for TTP

Predicts ADAMTS13 deficiency in suspected thrombotic thrombocytopenic purpura (TTP) with high discrimination.

INSTRUCTIONS

Use in hospitalized adult inpatients with suspected thrombotic thrombocytopenic purpura (TTP) who might benefit from early initiation of plasma exchange while awaiting ADAMTS-13 results. Do not use in patients who have already undergone plasma exchange (i.e., intermediate and high risk groups, in whom therapeutic plasma exchange must be initiated immediately).

When to Use ▼ Pearls/Pitfalls ▼ Why Use ▼

Platelet count $<30 \times 10^9/L$	No 0	Yes +1
Hemolysis Reticulocyte count $>2.5\%$, haptoglobin undetectable, or indirect bilirubin $>2.0 \text{ mg/dL}$ ($34.2 \mu\text{mol/L}$)	No 0	Yes +1
Active cancer Treated for cancer within the past year	No +1	Yes 0
History of solid-organ or stem-cell transplant	No +1	Yes 0
MCV $<9.0 \times 10^{-14} \text{ L}$ ($<90 \text{ fL}$)	No 0	Yes +1
INR <1.5	No 0	Yes +1
Creatinine $<2.0 \text{ mg/dL}$ ($176.8 \mu\text{mol/L}$)	No 0	Yes +1

5 points PLASMIC Score

Intermediate risk

6 % Risk of severe ADAMTS13 deficiency (defined as ADAMTS13 activity level $<15\%$)

Copy Results Next Steps

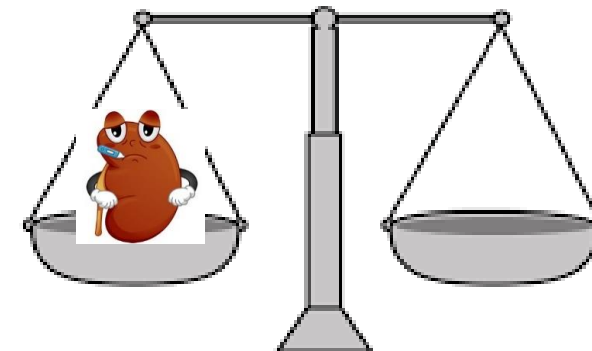
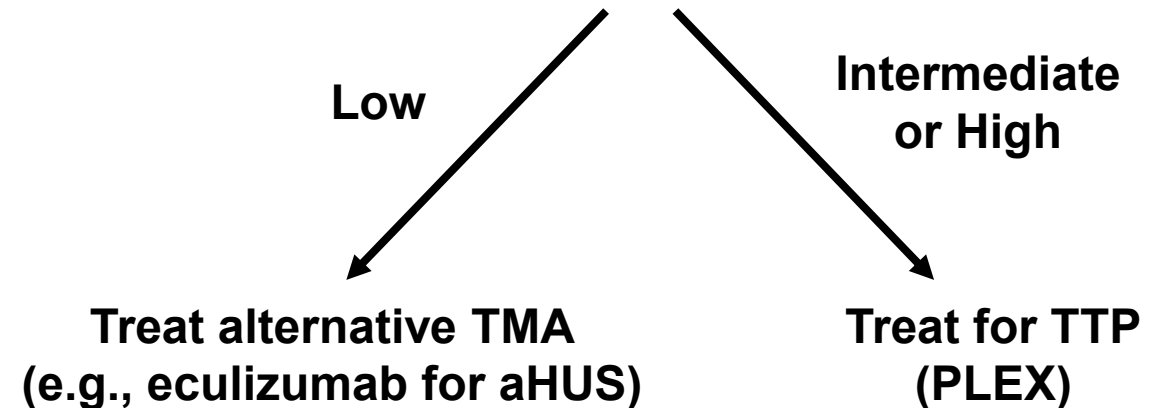
Next Steps Evidence Creator Insights

Derivation and external validation of the PLASMIC score for rapid assessment of adults with thrombotic microangiopathies: a cohort study



Pavan K Bendapudi, Shelley Hurwitz, Ashley Fry, Marisa B Marques, Stephen W Waldo, Ang Li, Lova Sun, Vivek Upadhyay, Ayad Hamdan, Andrew M Brunner, John M Gansner, Srinivas Viswanathan, Richard M Kaufman, Lynne Uhl, Christopher P Stowell, Walter H Dzik, Robert S Makar

PLASMIC Score for TTP



Thrombotic Microangiopathy (TMA) Classification

Primary TMA Syndromes

- ~~TTP~~
- Shiga toxin-mediated HUS
- Drug-induced
- Complement-mediated (aka, “aHUS”)

- Coagulation-mediated
- Metabolism-mediated

Usually present in children
<1 year old

“Secondary” TMA Syndromes (Systemic disorders)

- DIC
- Systemic infection
- Malignancy
- Preeclampsia/HELLP
- Malignant HTN
- HSCT-TMA
- Solid organ transplant (CNI-mediated)
- Rheumatic: SLE/MCTD
 - Scleroderma/SRC
 - APS/CAPS

aHUS

(“complement-mediated TMA”)

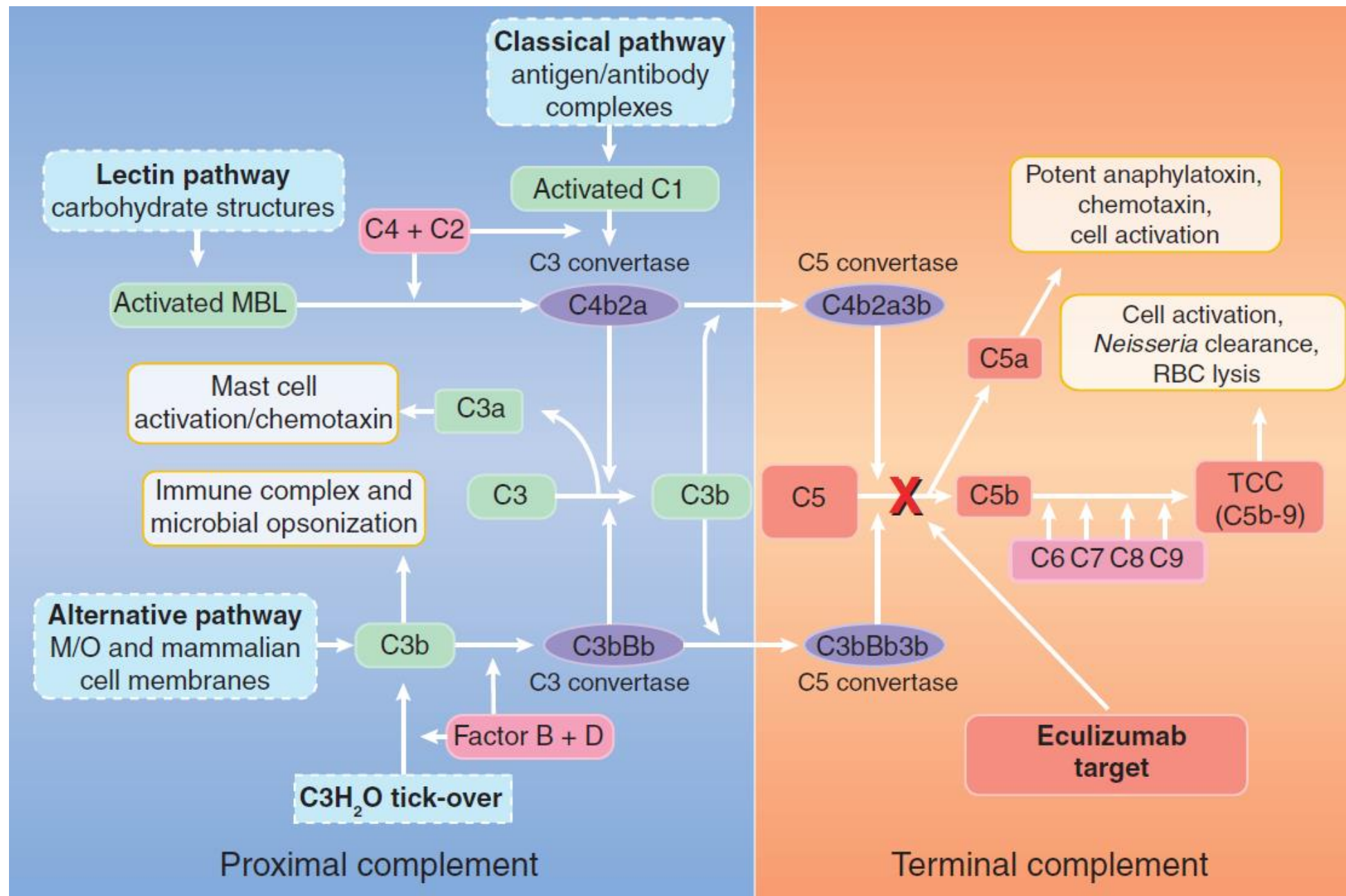
- AKI w/ 2+protein and 3+blood
- ANA (speckled) / MCTD
- Female

SRC

(“Scleroderma Renal Crisis”)

- AKI w/ 2+protein and 3+blood
- ANA (speckled) / MCTD
- Female

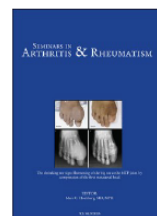
- Age 64
- h/o Raynaud's
- Recent steroid use
- Presentation w/ severe HTN
- Pulmonary HTN / ?ILD
- Low-grade myositis





Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Studying the Role of C5-Inhibition Therapy in Scleroderma Renal Crisis-Induced Thrombotic Microangiopathy – A Review of Literature

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ARTICLE INFO

Keywords:

Systemic sclerosis
Scleroderma renal crisis
Eculizumab

ABSTRACT

Background: The pathogenesis of scleroderma renal crisis (SRC) remains poorly understood but a growing body of evidence suggests that activation of the complement system may be involved in the disease. Recent studies have shown that Eculizumab (monoclonal antibody directed against the complement component C5) is effective in treating patients with SRC who present with symptoms of thrombotic microangiopathy (SRC-TMA).

Objectives: In this study, we conducted a systematic review to characterize the published experience of the presentation and outcome of patients with SRC who were treated with C5 inhibitor, Eculizumab.

Methods: A literature search was conducted from inception to December 2022 using Medical Subject Headings (MeSH) terms for 'scleroderma', 'scleroderma renal crisis, and 'Eculizumab'. We included case reports, case series, and observational studies which reported the use of Eculizumab with or without Angiotensin-converting enzyme inhibitors (ACE-I) for the treatment of scleroderma renal crisis (SRC) in patients with systemic sclerosis. **Results:** The study included 17 patients, all of whom were treated with Eculizumab. Additionally, the use of ACE-I was reported in 11/17 (64.7%) patients. Further, plasmapheresis was used in 9/17 (52.9%), steroids in 5/17 (29.4%), cyclophosphamide in 3/17 (17.6%), calcium channel blockers in 3/17 (17.6%), and Rituximab in 3/17 (17.6%) patients. Renal replacement therapy was required in 11/17 (64.7%) patients. 14/17 patients (82.3%) were reported to have clinical (renal or hematologic) improvement with Eculizumab therapy (Table 1).

Conclusion: These findings should prompt testing on a larger cohort of SRC-TMA patients. This would help us determine whether aggressive treatment combining ACE-I and Eculizumab can target the various underlying endothelial, inflammatory, and immunologic mechanisms involved in SRC-TMA, and improve patient outcomes.

Treatment	RRT	Improvement	Outcome
Eculi, ACEi, CCB, PLEX	Yes	Hematologic	Death from SSc related cardiomyopathy
Eculi, ACEi, CCB, PLEX	Yes	Renal	Alive
Eculi, ACEi	Yes	No	Alive, requiring dialysis
Eculi, ACEi	No	Renal/Hematologic	Alive
Eculi, ACEi, PLEX, steroids	No	Renal/Hematologic	Alive
Eculi, ACEi	Yes	No	Alive, requiring renal transplant
Eculi, ACEi, PLEX, steroids, CYC	No	No	Death during hospitalization
Eculi, ACEi	Yes	Hematologic	Alive, requiring dialysis
Eculi, ACEi, PLEX, CYC	No	Hematologic	Alive
Eculi, ACEi, RTX	Yes	Hematologic	Alive, requiring dialysis
Eculi, ACEi, CYC	No	Hematologic	Alive
Eculi, RTX, steroids	Yes	Hematologic	Death during follow up period
Eculi, RTX	Yes	Hematologic	Death during follow up period
Eculi, PLEX	No	Renal/Respiratory	Alive
Eculi, PLEX, steroids	Yes	Renal/Hematologic	Alive
Eculi, PLEX, steroids, FFP	Yes	Hematologic	Alive, requiring dialysis
Eculi, PLEX, BB, CCB	Yes	Renal, hematologic, skin, cardiac	Alive

Hospital Course, December 2024

- Complement panel sent
- Plasmapheresis discontinued
- Captopril continued
- No corticosteroids
- Eculizumab initiated
- Right heart catheterization confirmed pulmonary hypertension (normal pcwp) and sildenafil started
- Family declined repeated recommendations for renal biopsy
- Physical therapy, rehabilitation

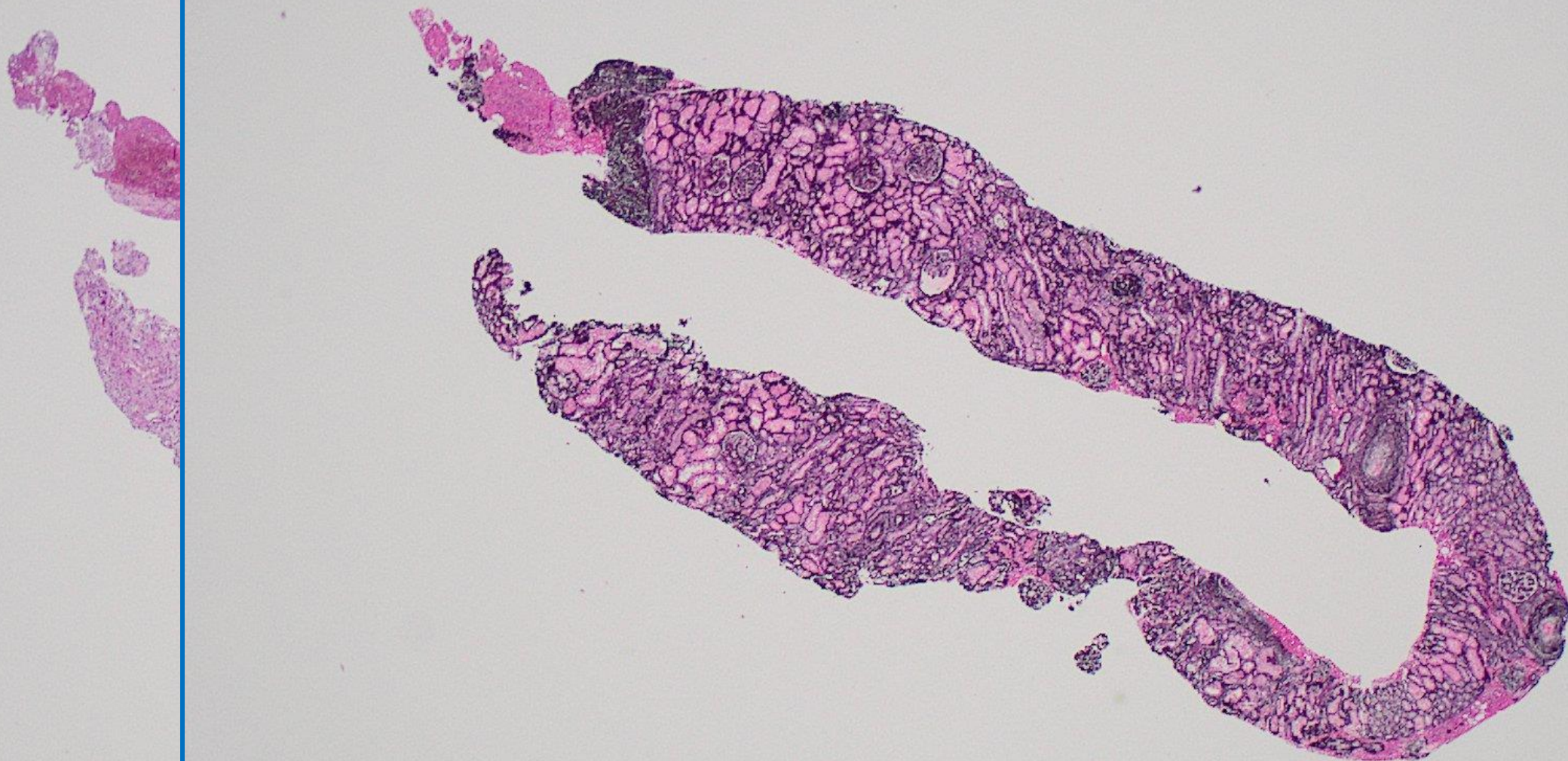
Subsequent Developments, 2024-2025

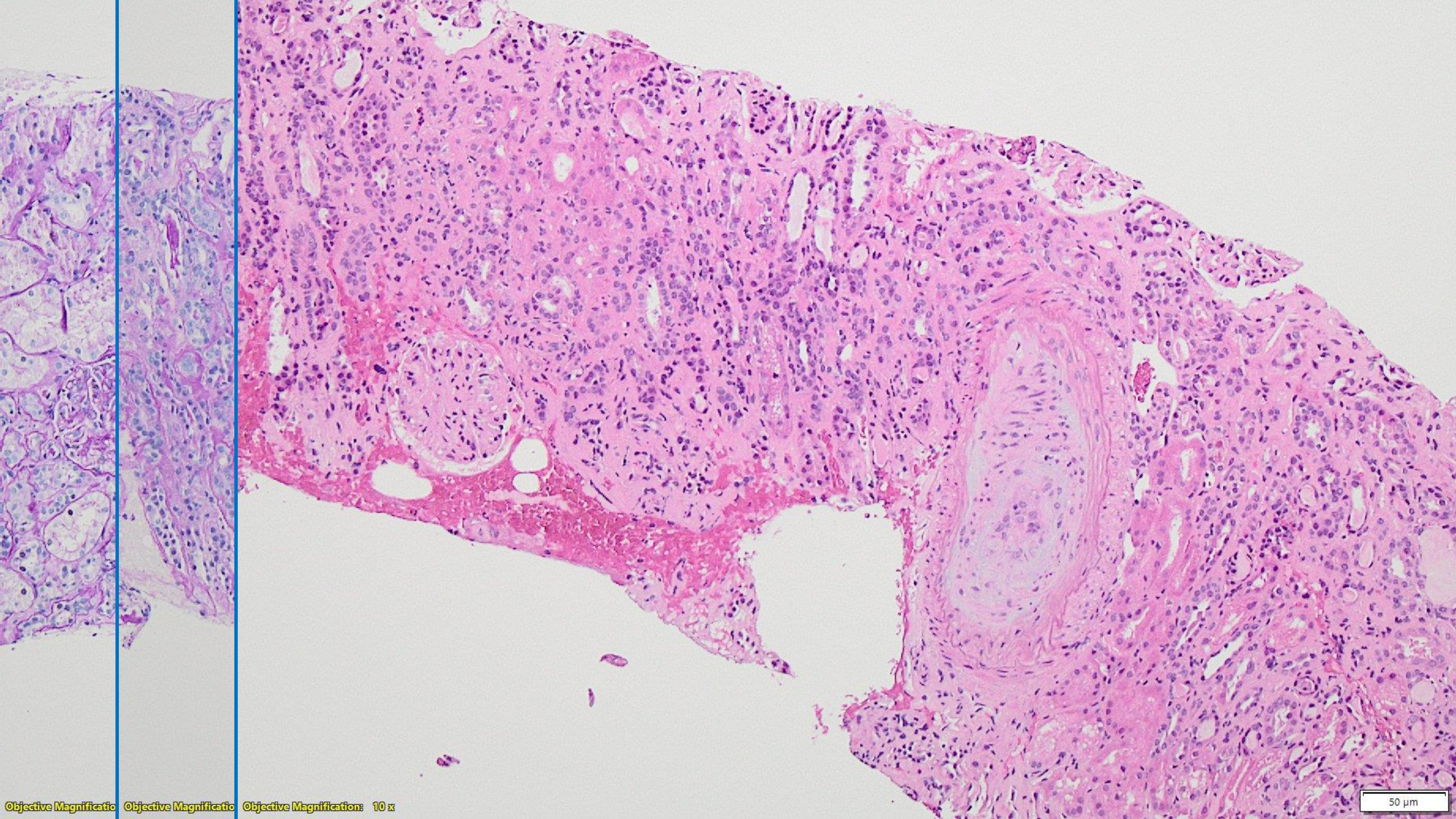
- Complement panel returned nondiagnostic for aHUS
- Eculizumab continued temporarily
- Progressive dyspnea with features of volume overload, LVEF 50%, abnormal diastolic dysfunction, RV dilatation
- Cardiac MRI with features of interstitial fibrosis
- AKI, hypokalemia (Scr 1.45; MALB/Cr ratio 1062.3, 3+ blood)

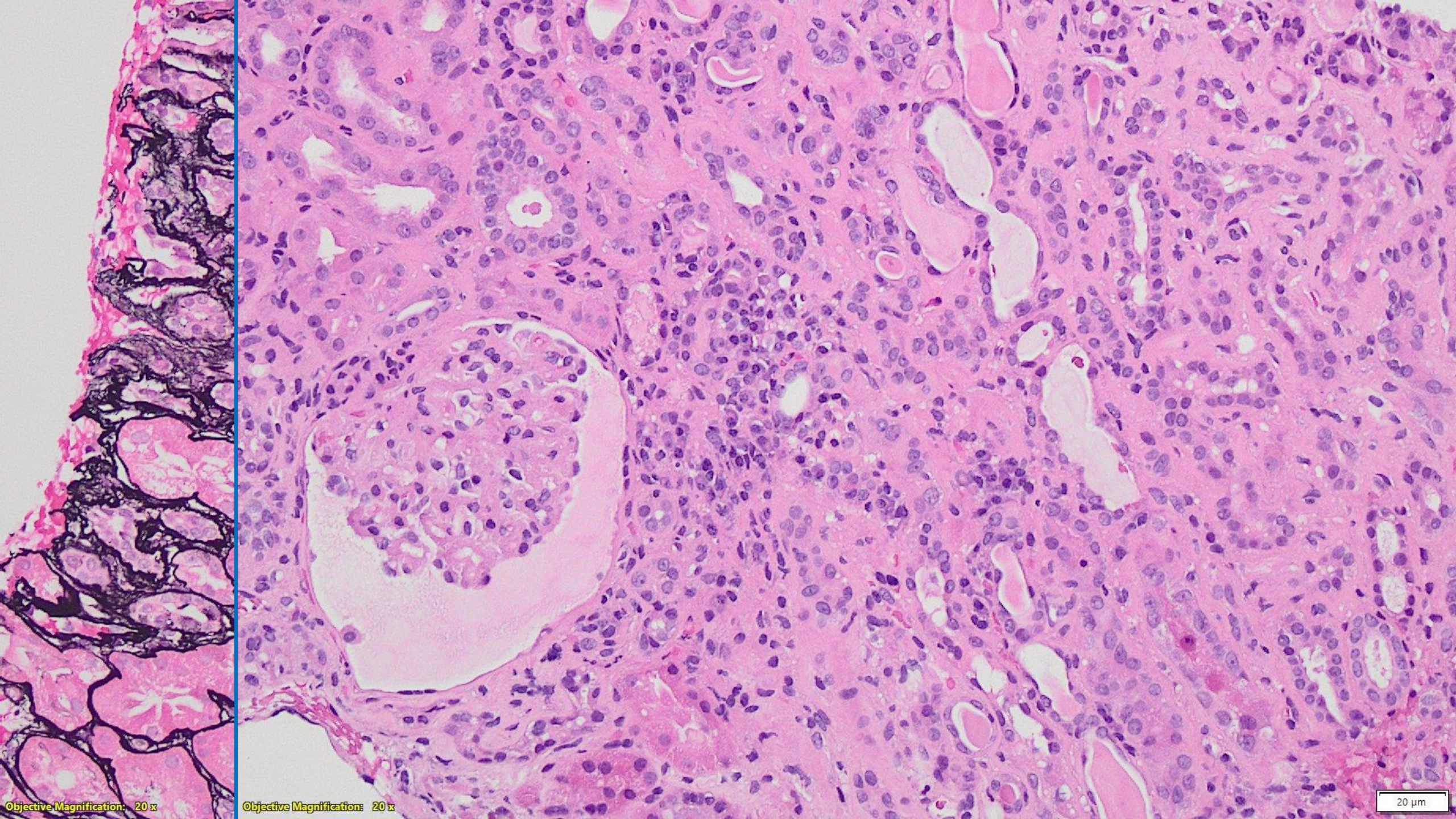
Kidney Biopsy

Sujal Shah, M.D.

***Instructor in Pathology, Harvard Medical School
Associate Pathologist, Brigham and Women's Hospital***



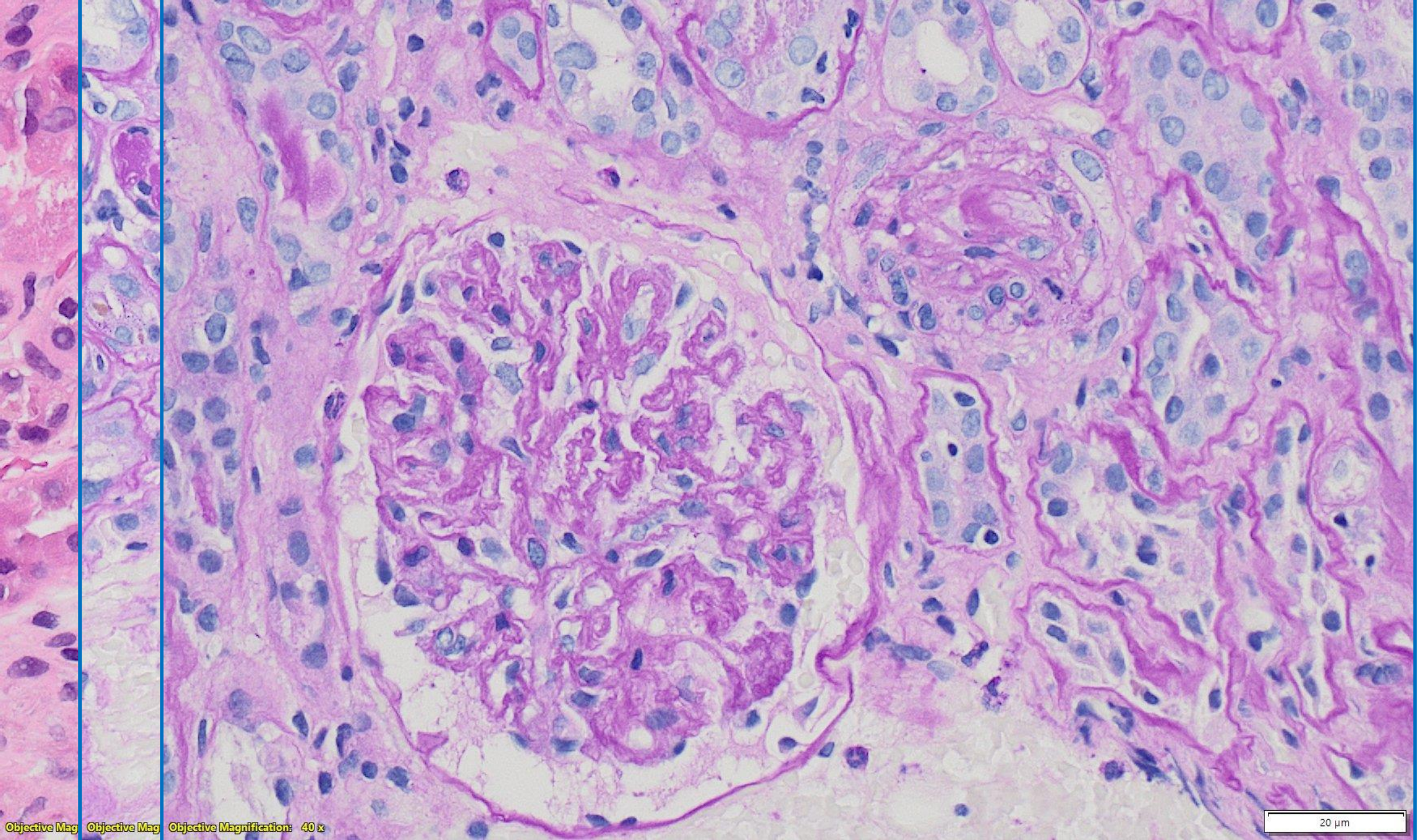


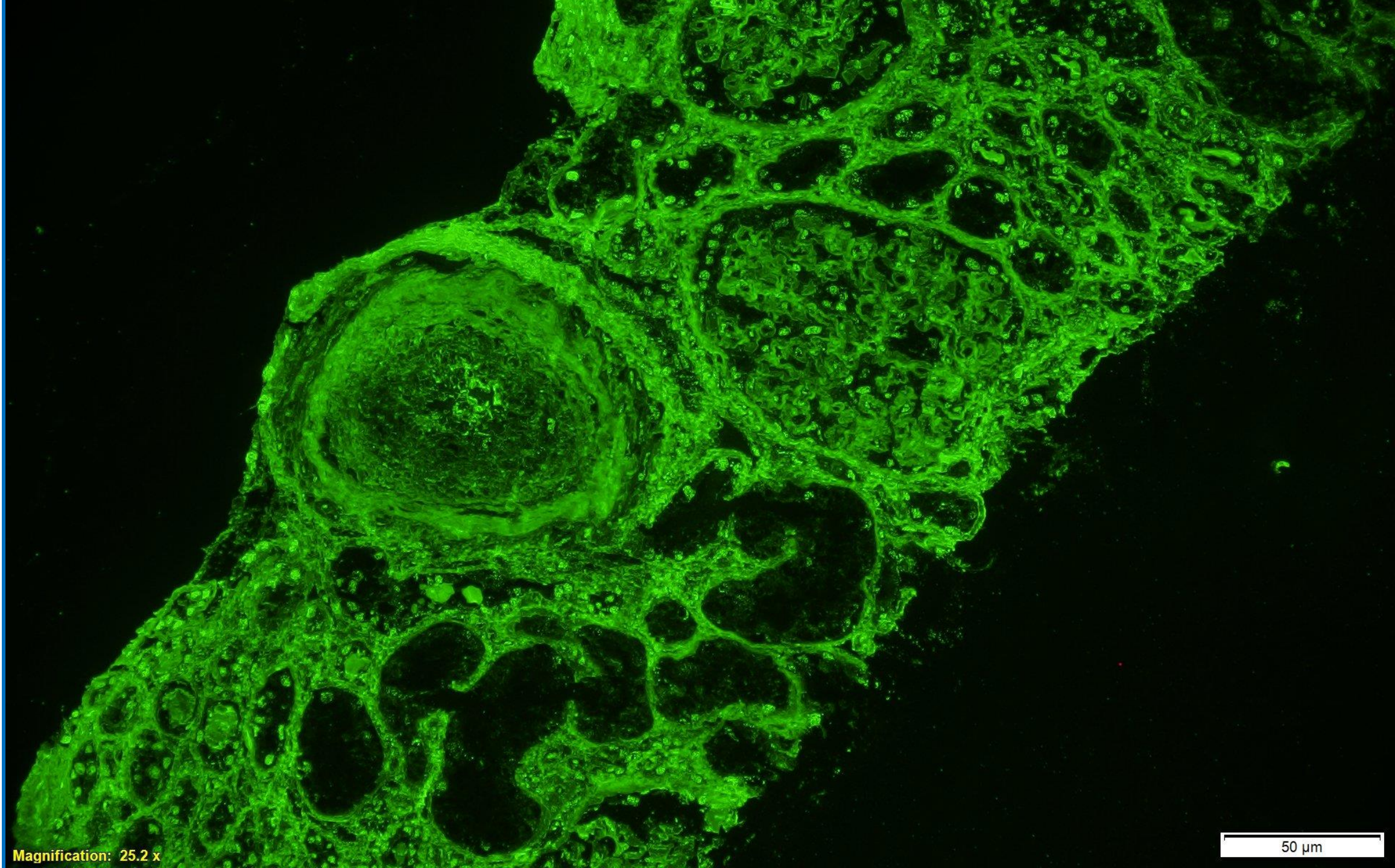


Objective Magnification: 20 x

Objective Magnification: 20 x

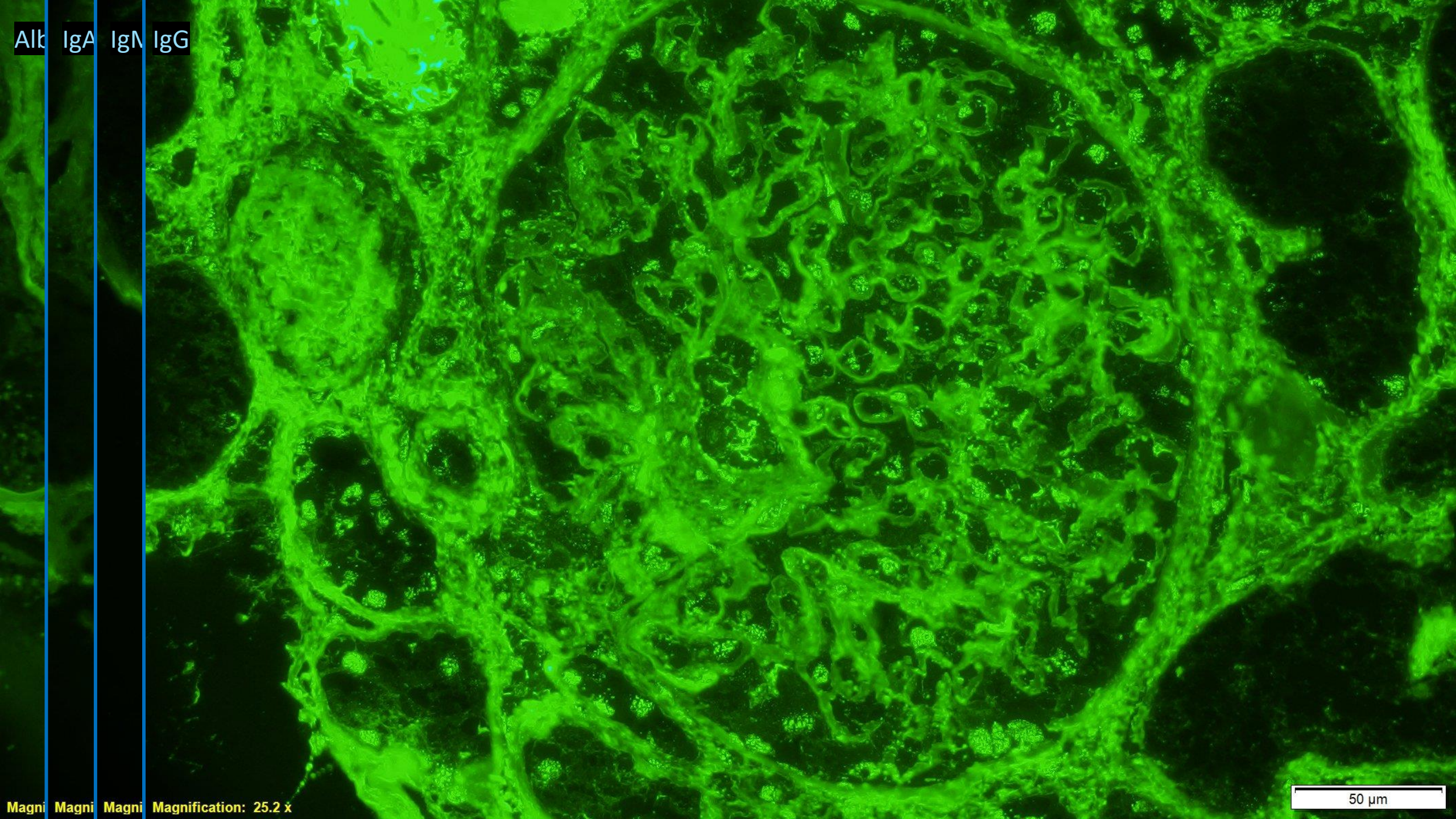
20 μ m





Magnification: 25.2 x

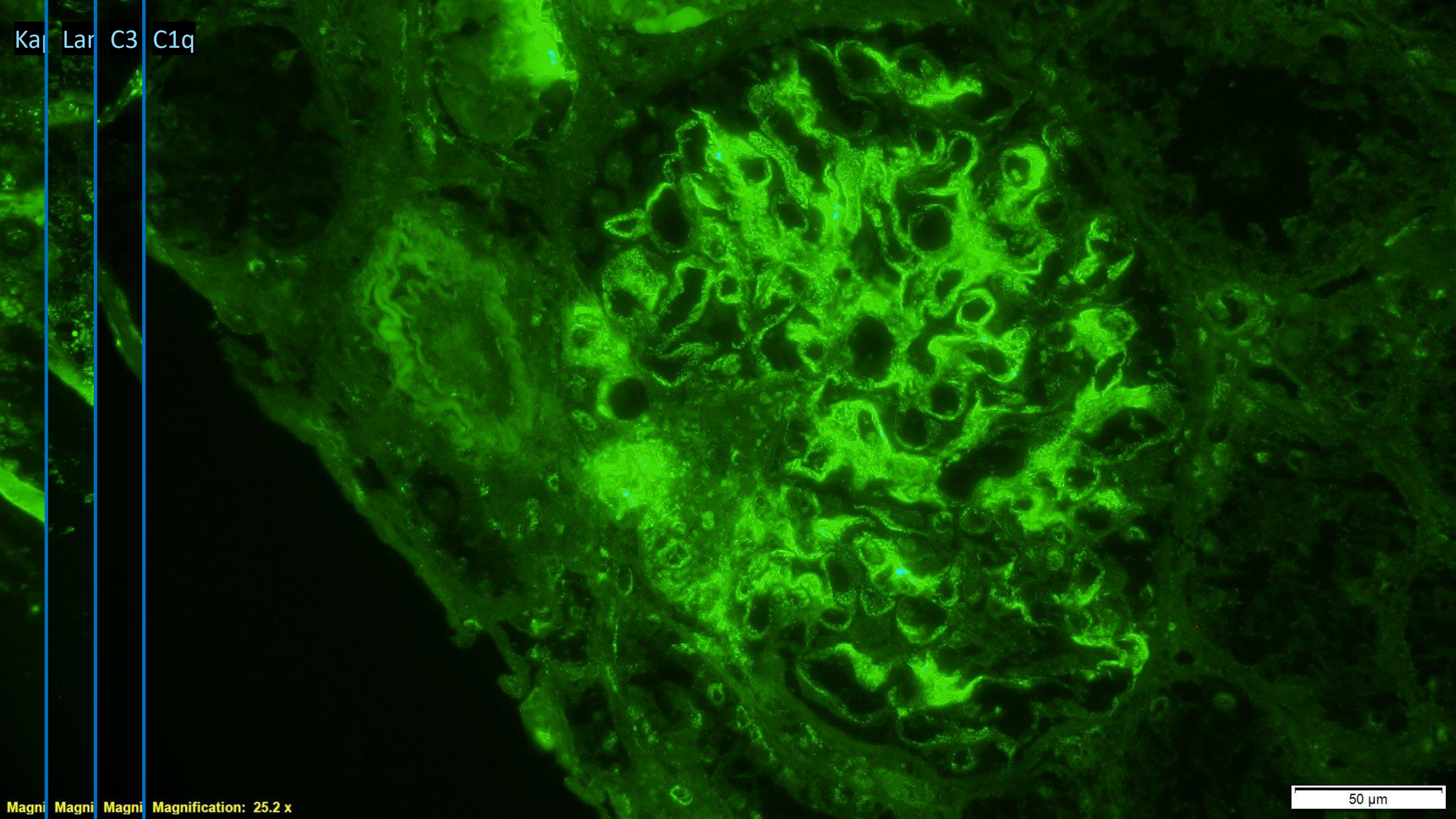
50 μ m



Alb IgA IgM IgG

Magni Magni Magni Magnification: 25.2 x

50 μm



Ka Lar C3 C1q

Magni Magni Magni Magnification: 25.2 x

50 μm

DIAGNOSIS

- **KIDNEY PARENCHYMA WITH:**

- **CHRONIC-ACTIVE THROMBOTIC ANGIOPATHY**

- ARTERIAL INTIMAL MUCOID DEGENERATION, ENDOTHELIAL CELL SWELLING, CONCENTRIC (“ONION-SKIN”) REMODELING, AND GLOMERULAR HYPOPERFUSION

- **IMMUNE COMPLEX-MEDIATED GLOMERULOPATHY**

- EXTENSIVE MESANGIAL DEPOSITS WITH “FULL-HOUSE” REACTIVITY
 - STRONG NUCLEAR STAINING FOR POLYCLONAL IgG (TISSUE ANA EFFECT)

- THE FINDINGS ARE CONCERNING FOR A **SYSTEMIC AUTOIMMUNE CONDITION** WITH **OVERLAP FEATURES**, WITH FEATURES TYPICALLY SEEN IN SCLERODERMA AND LUPUS NEPHRITIS

- **MILD CHRONIC CHANGES** OF THE PARENCHYMA, INCLUDING:

- GLOBAL GLOMERULOSCLEROSIS (9% OF GLOMERULI)
 - TUBULAR ATROPHY AND INTERSTITIAL NEPHRITIS (< 10% OF THE CORTEX)
 - SEVERE ARTERIAL AND ARTERIOLAR SCLEROSIS

Final Thoughts

- Entities of MCTD and Scleroderma; Scleroderma Sine
- Differential diagnosis of thrombotic microangiopathy
- Fibrotic changes can not be reversed; treatment focused on preventing further damage from uncontrolled inflammation
- Value of coordinated, multispecialty care

Special Thanks

- Dylan Kotliar, MD, PH.D (rheumatology fellow)
- Michael Weinblatt MD (primary rheumatologist)
- Helmut Rennke MD