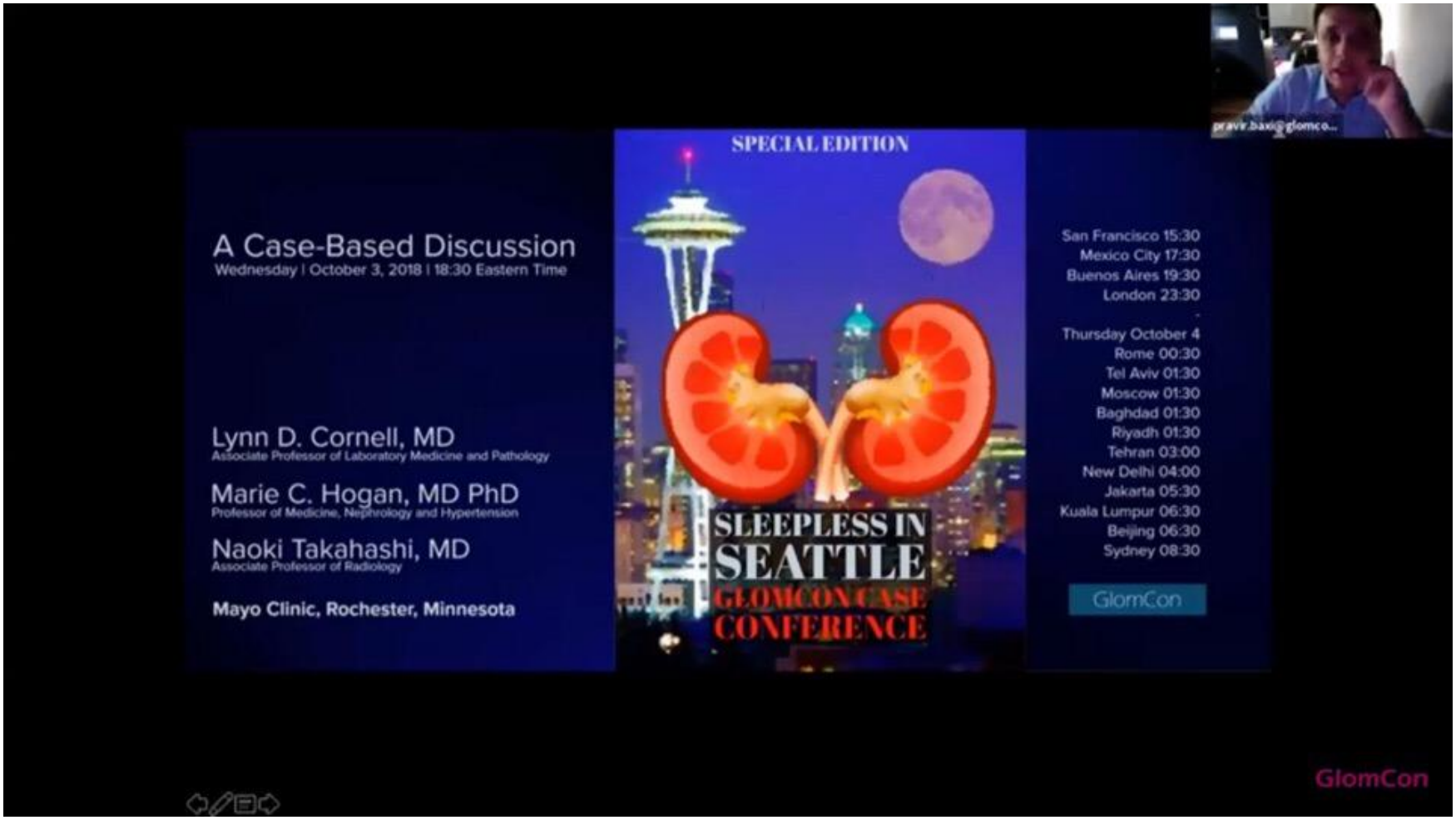

A Case-Based Discussion
Wednesday | October 3, 2018 | 18:30 Eastern Time
Lynn D. Cornell, MD
Associate Professor of Laboratory Medicine and Pathology
Marie C. Hogan, MD PhD
Professor of Medicine, Nephrology and Hypertension
Naoki Takahashi, MD
Associate Professor of Radiology
Mayo Clinic, Rochester, Minnesota
SPECIAL EDITION
SLEEPLESS IN SEATTLE
GLOMCON CASE CONFERENCE
San Francisco 15:30
Mexico City 17:30
Buenos Aires 19:30
London 23:30
Thursday October 4
Rome 00:30
Tel Aviv 01:30
Moscow 01:30
Baghdad 01:30
Riyadh 01:30
Tehran 03:00
New Delhi 04:00
Jakarta 05:30
Kuala Lumpur 06:30
Beijing 06:30
Sydney 08:30
GlomCon
GlomCon

Clinical presentation: Dr. Hogan

- Middle-aged man
- Initial presentation:
  - Abdominal pain distention & ascites
  - 5lb weight loss & loose stools
  - 6L paracentesis

Clinical presentation

- CT scan: pancreatic disease
- Serum IgG4 elevated
- Diagnosis: Autoimmune pancreatitis

Clinical presentation

- Initial treatment & response:
  - Prednisone x 2 mo. Symptoms improved (pain, distention, ascites).
  - 6 courses prednisone x 2 mo each without prolonged taper
  - Azathioprine x4 mo 1.5 yrs prior; no clear improvement …treatment stopped

Clinical presentation

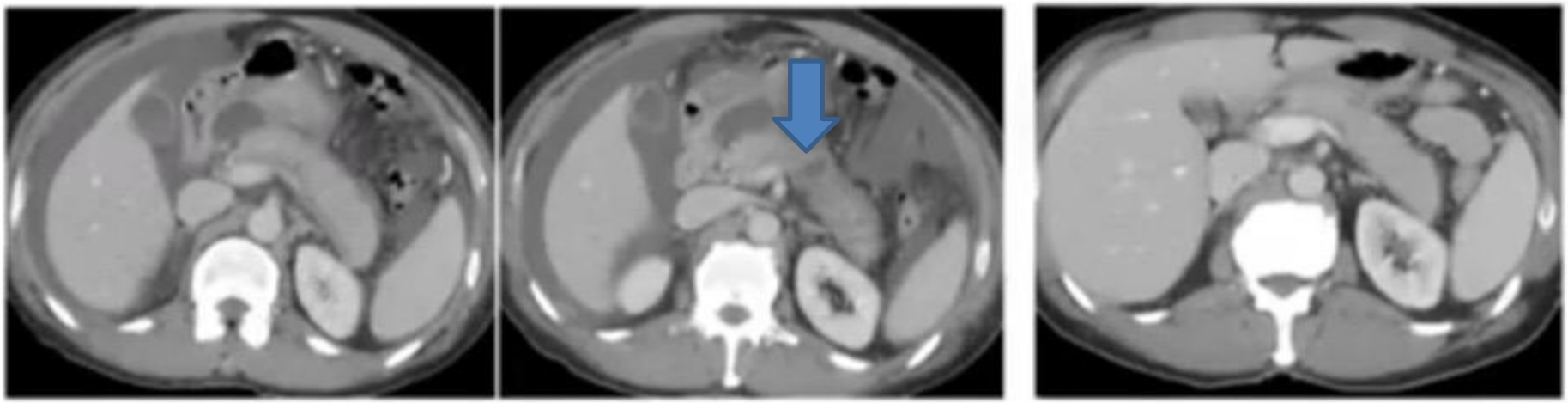
- 2 & 3 years after initial presentation:

  4-5 ERCPs

  - 2 with pancreatic stone extraction; immediate improvement in pain
  - Biliary and minor papilla sphincterotomies.

Radiology Studies: Dr. Takahashi

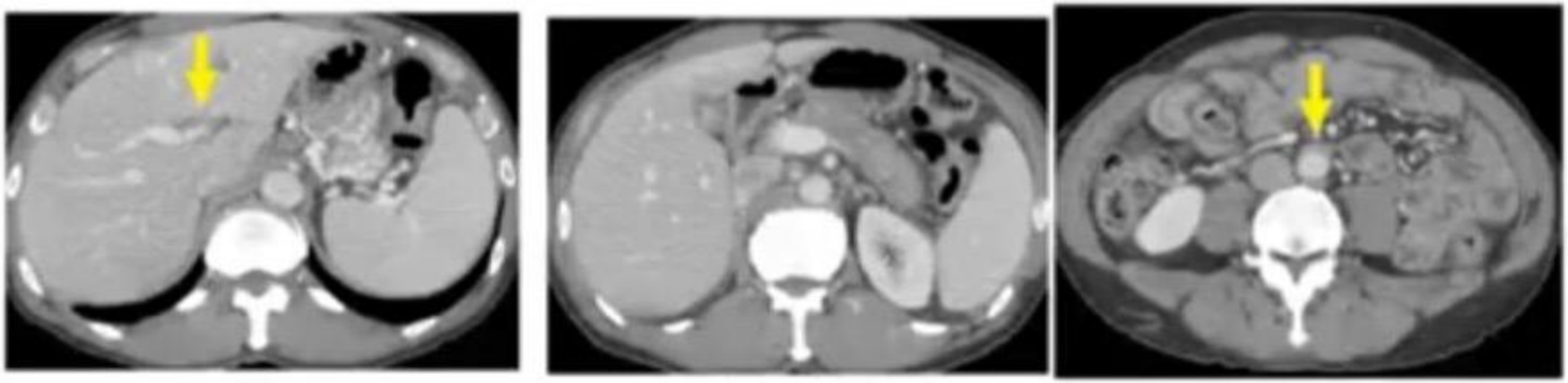
- Diffuse pancreatic enlargement with hypodense rim
- No biliary, renal or aortic involvement
- Peripancreatic fluid collection
- Large ascites



At initial presentation

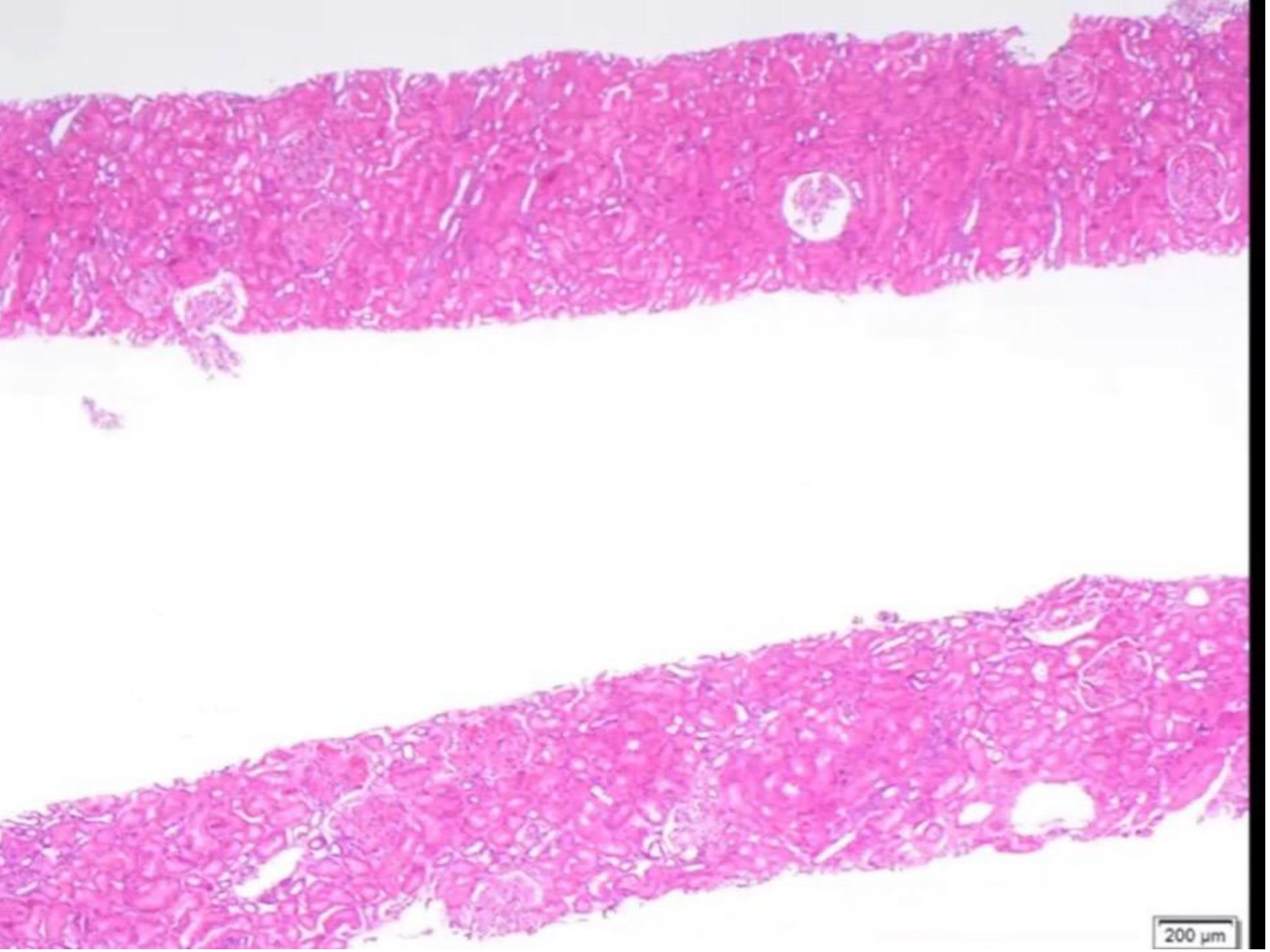
4 years after initial presentation

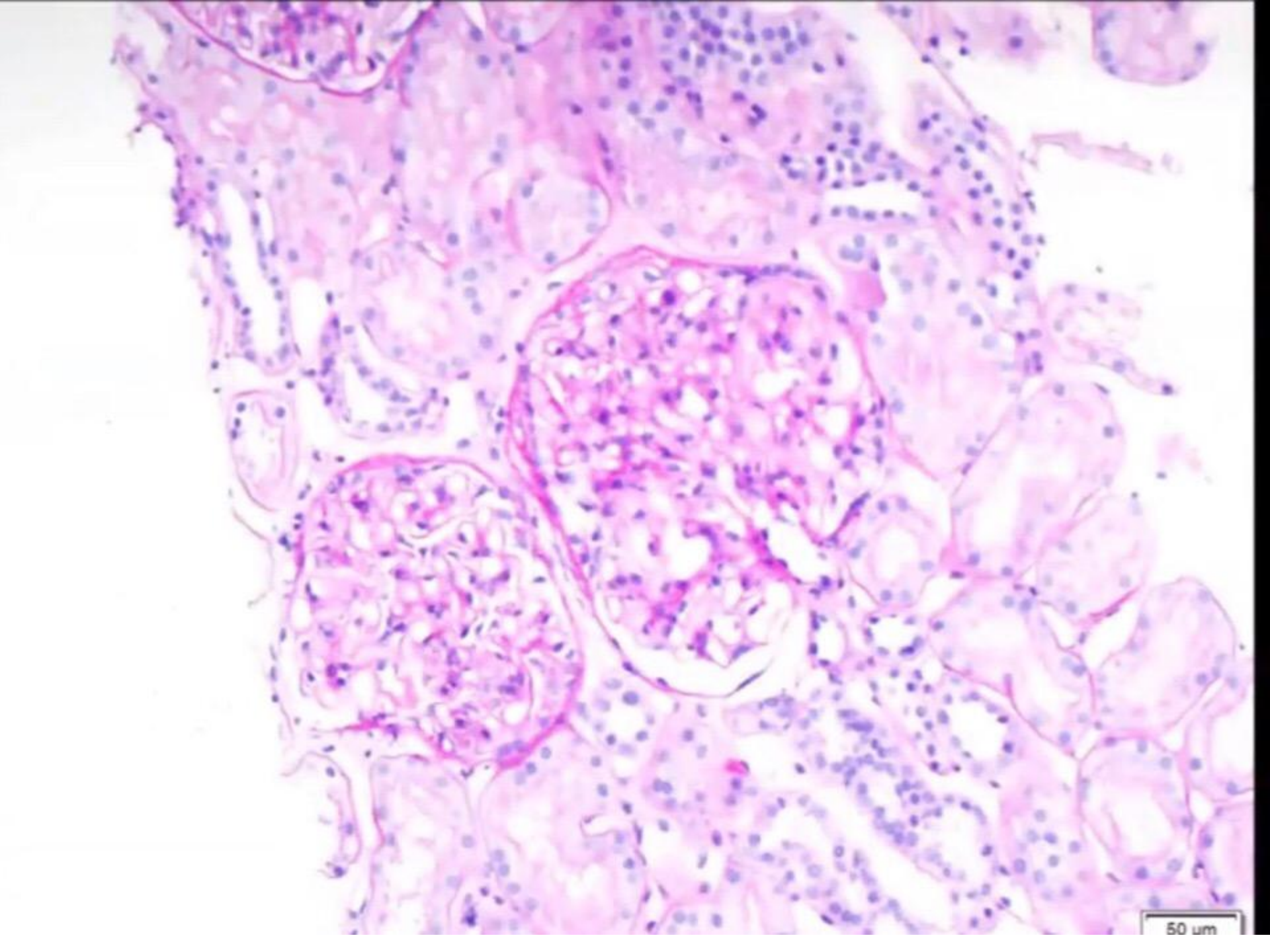
- Biliary involvement (narrowing of portal vein)
- Diffuse pancreatic enlargement (relapse)
- Mild retroperitoneal fibrosis

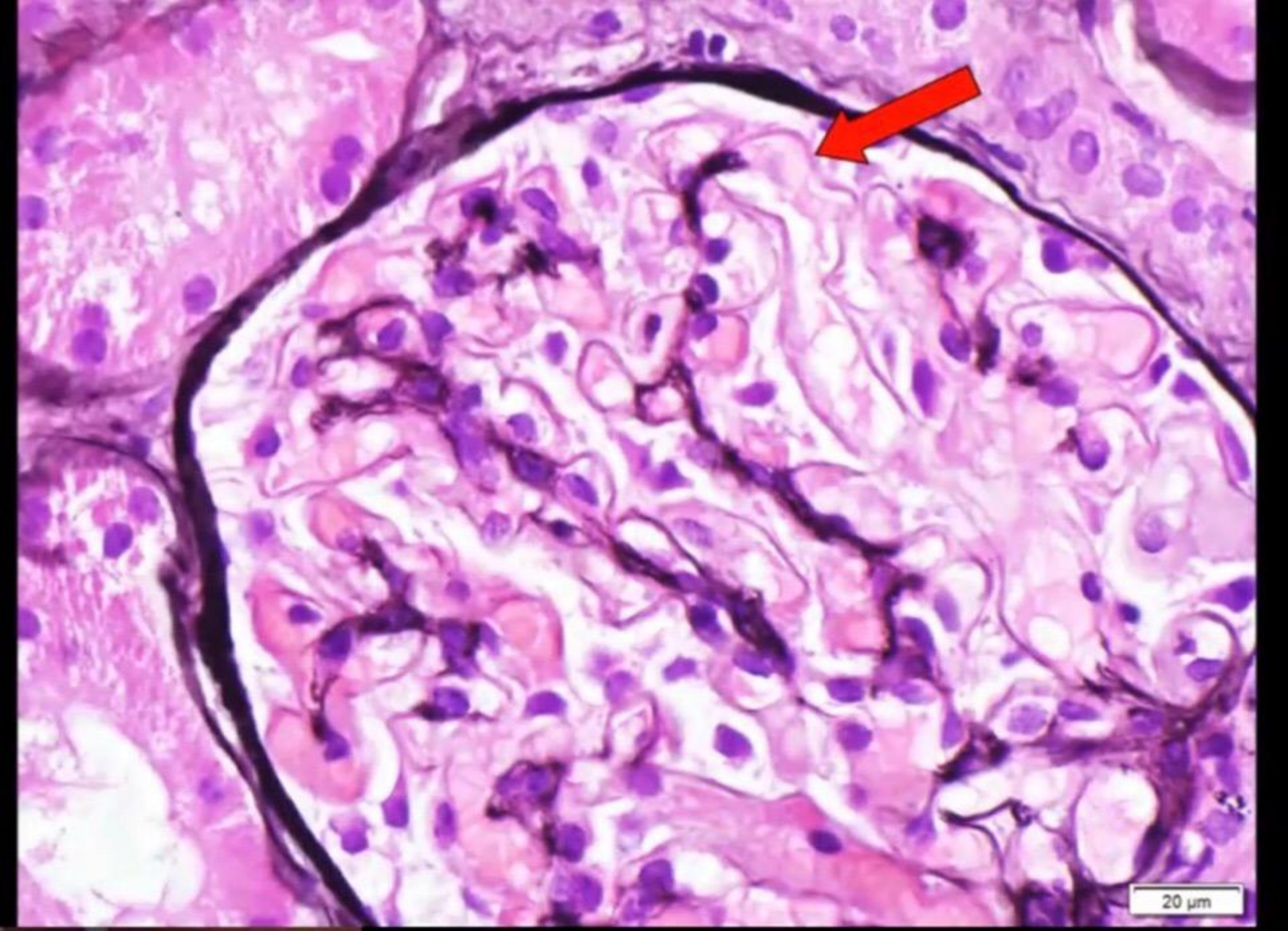


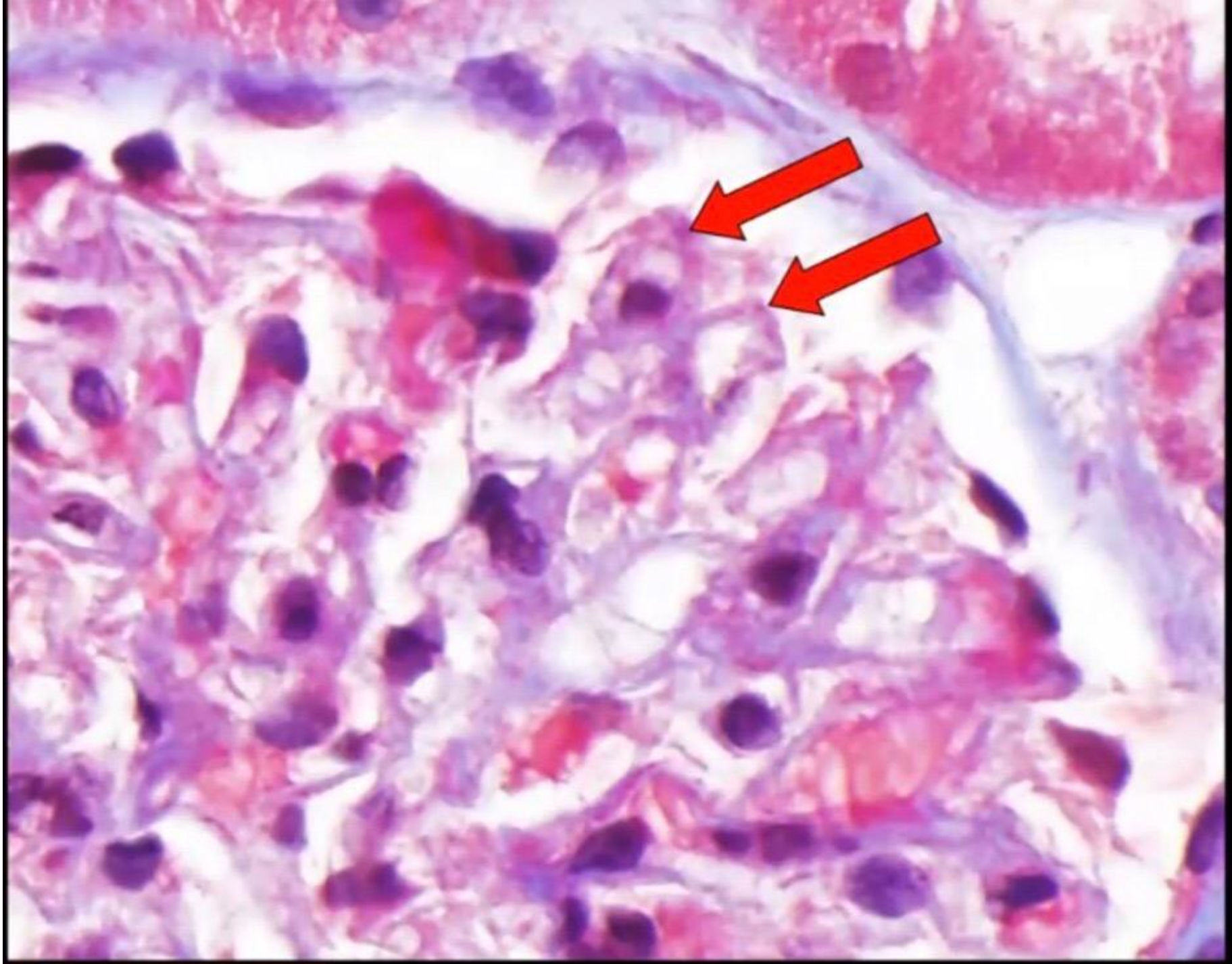
Nephrology Referral: Dr. Hogan

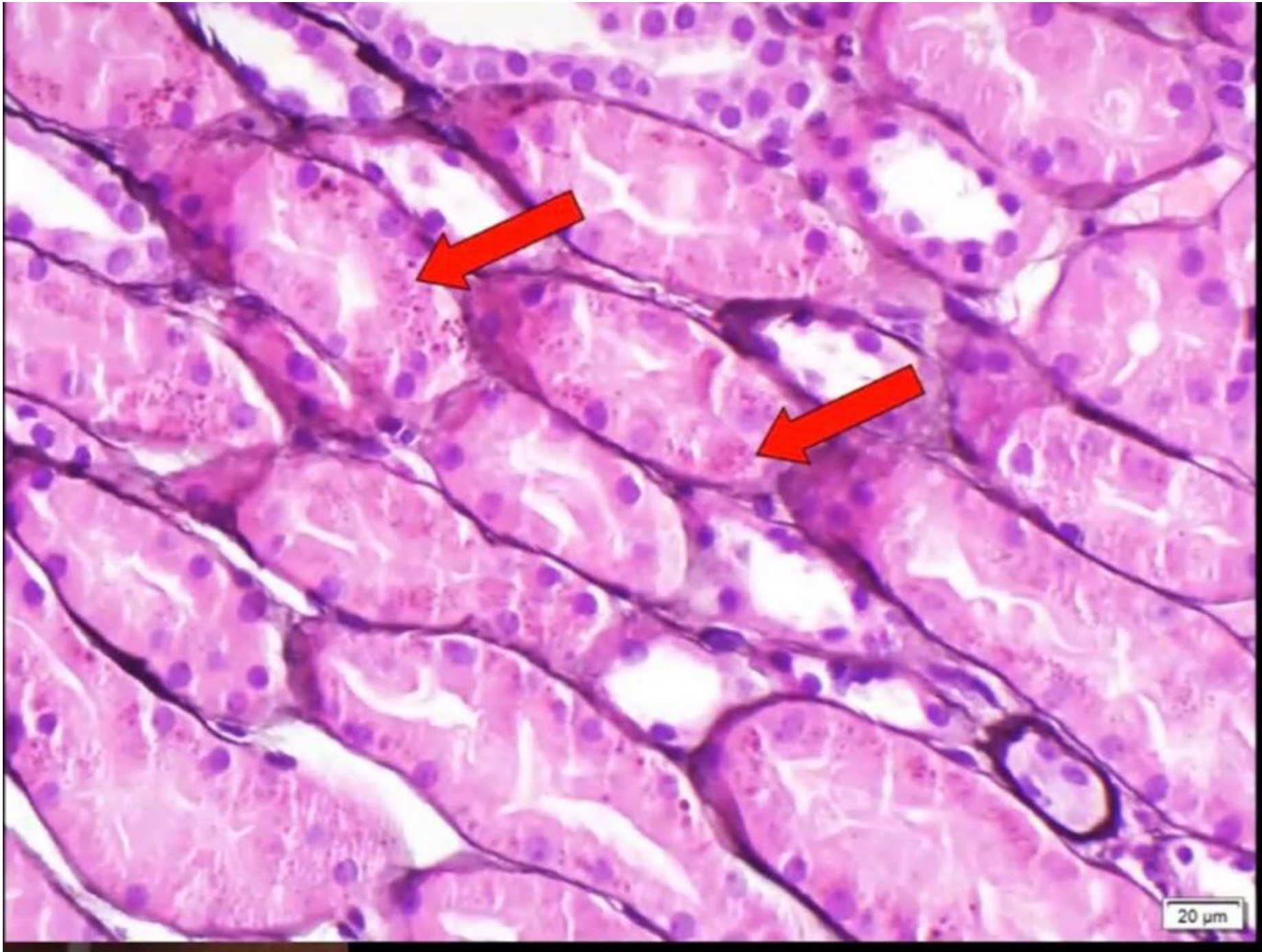
- Frothy Urine x 6mo. Off steroids 6mo.
  - Torsemide 5mg for edema x 2wk
- **EXAM:**
  - Wt 64kg. BMI:21. BP129/83. HR82.
    No edema
- **LABS:**
  - ESR 68; Creatinine 1.1.g/dL. Serum PLA2R-ve.
  - Alk Phos 125 (45-115); AST 60 (4-48)
  - Predicted 24hr urine protein 4g

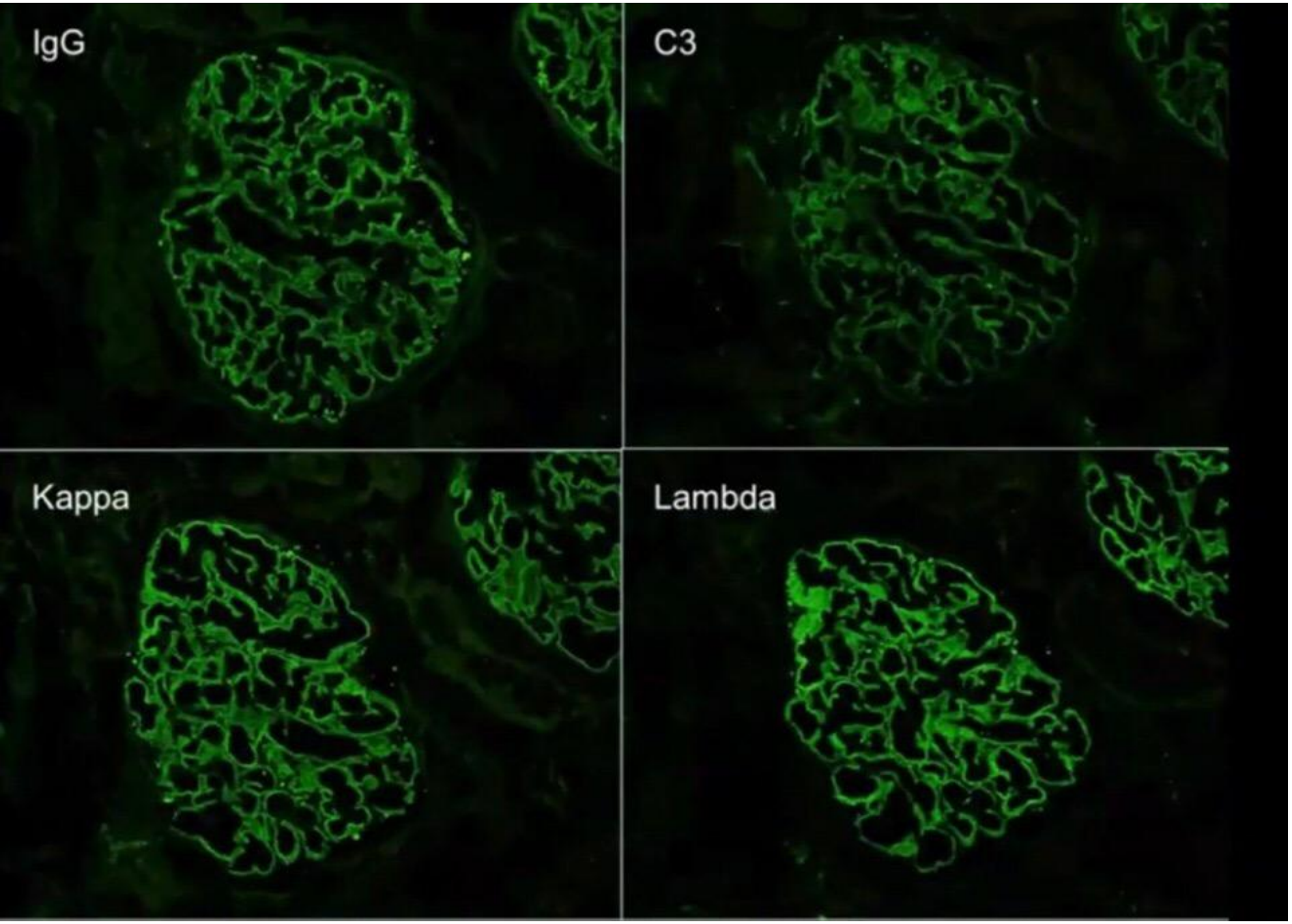

200 µm

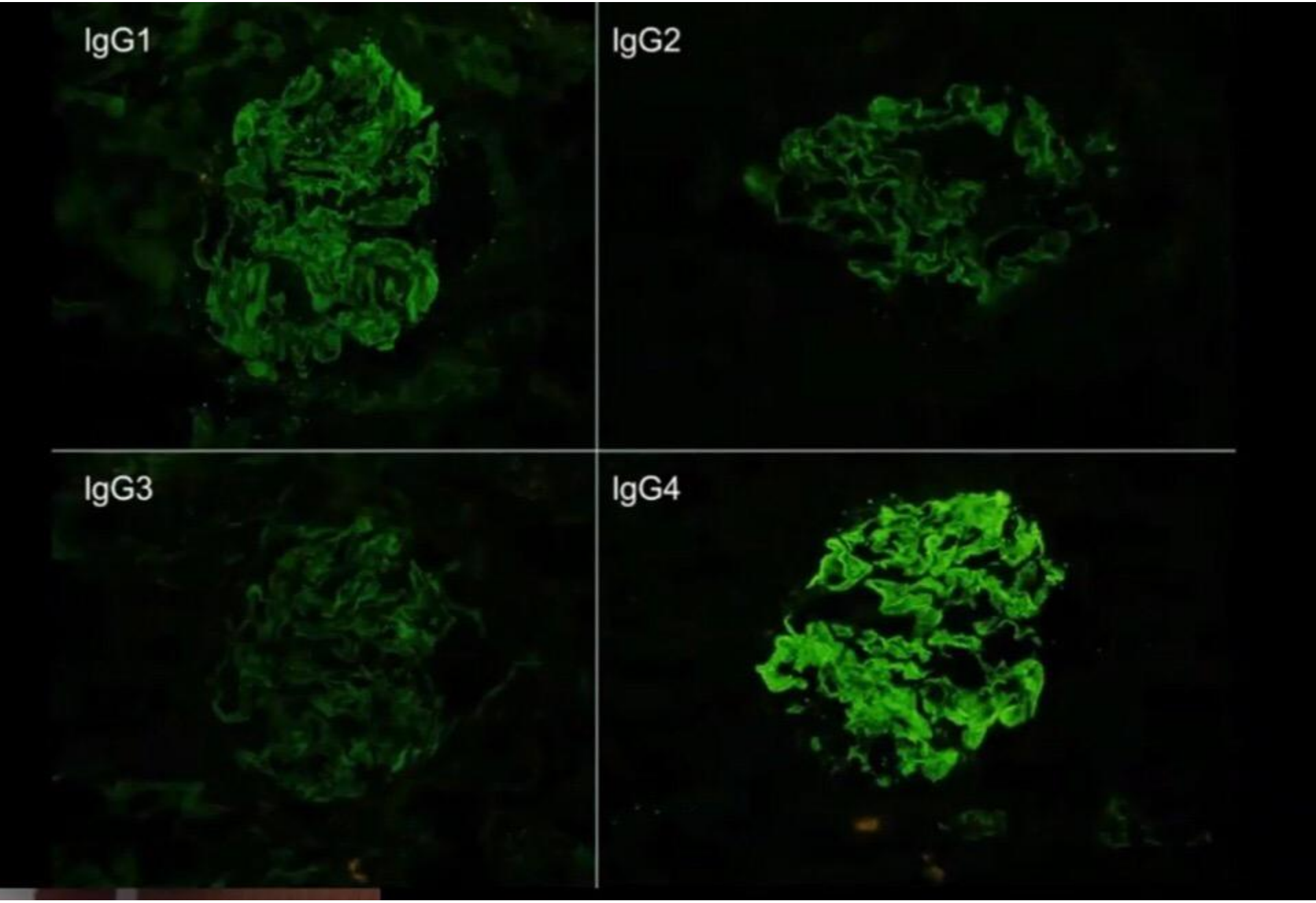

50 µm

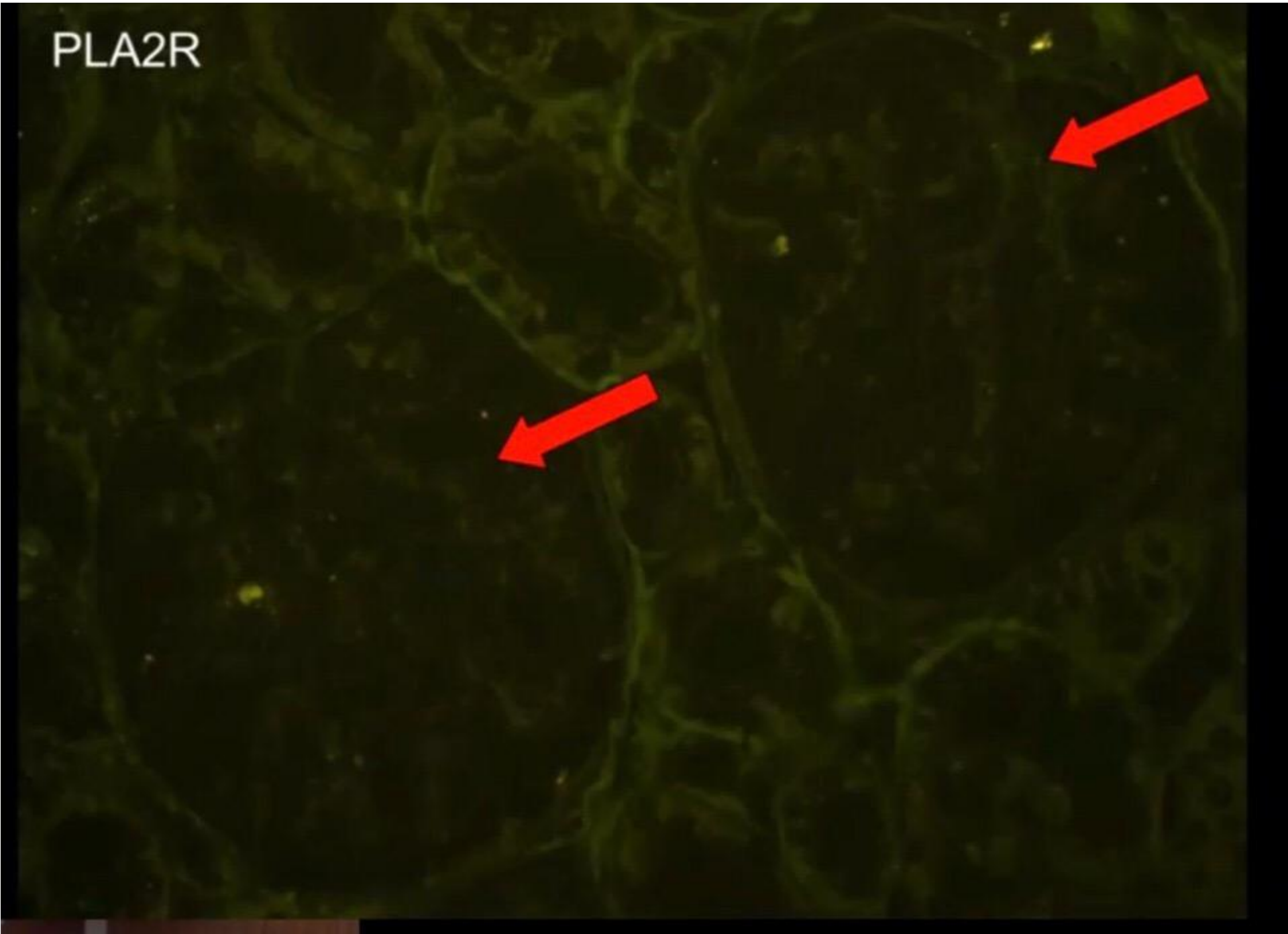

20 µm

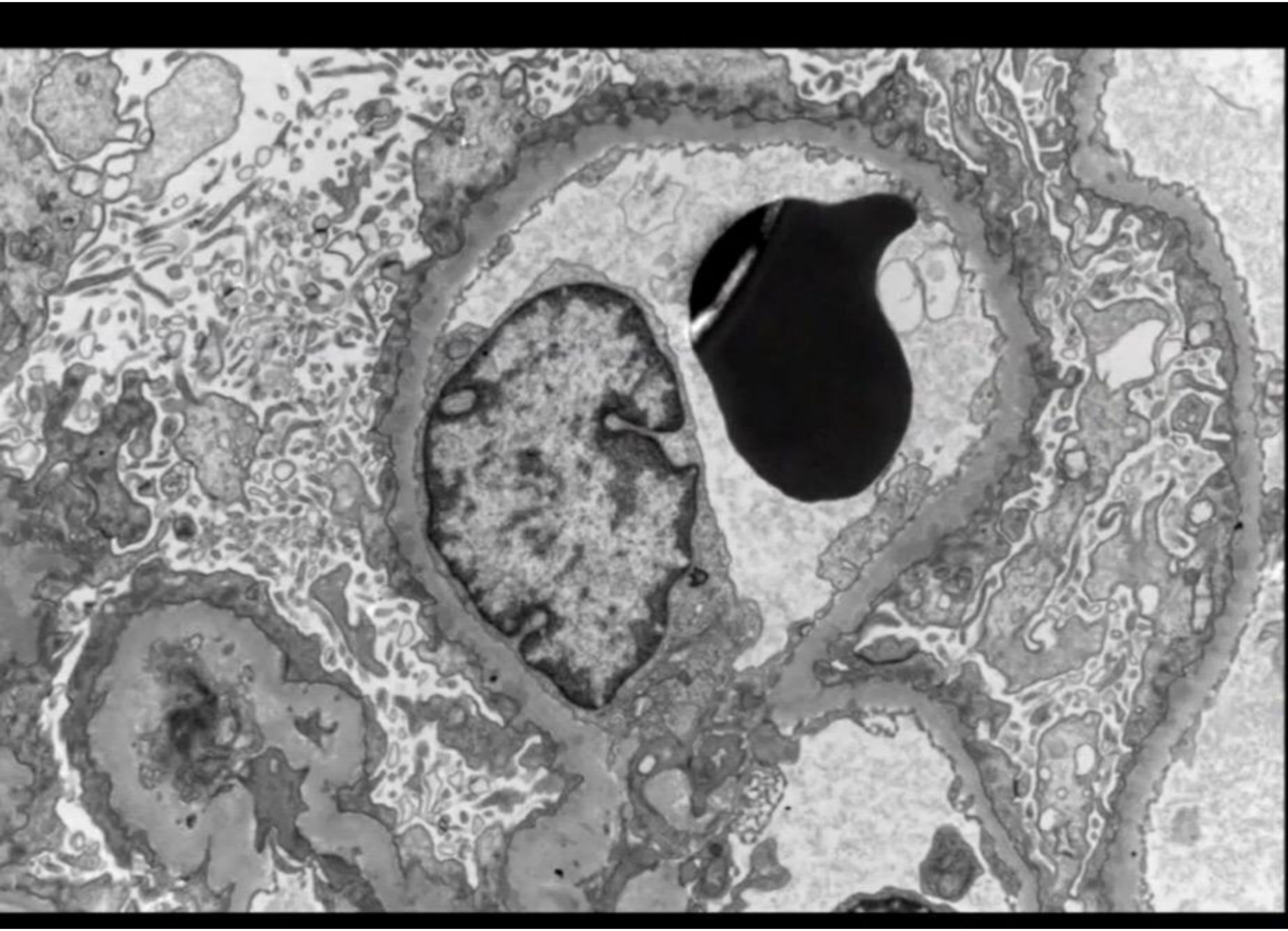


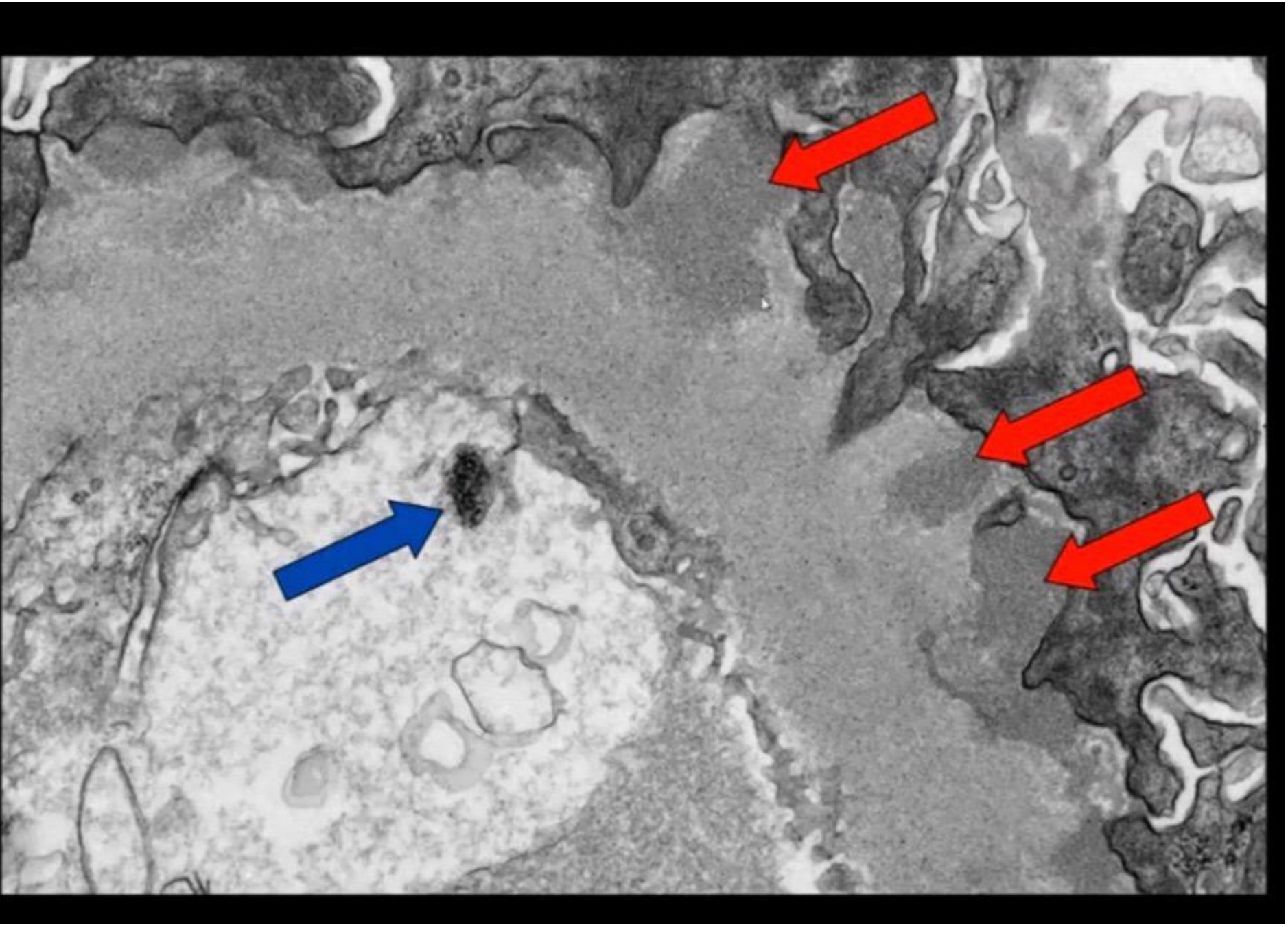

20 µm


IgG
C3
Kappa
Lambda


IgG1
IgG2
IgG3
IgG4


PLA2R



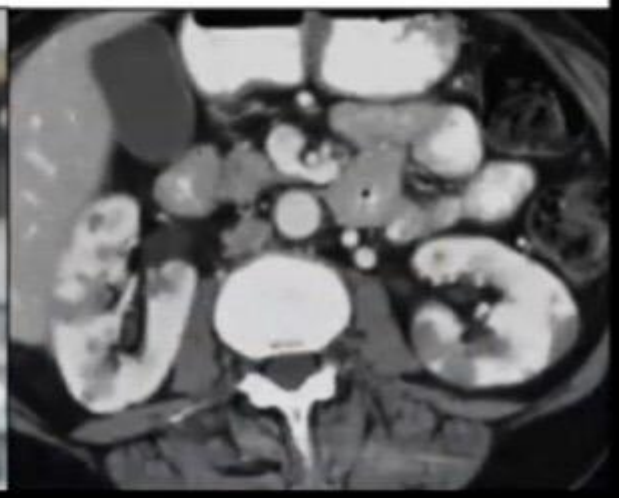


Diagnosis

Kidney, needle biopsy:
IgG4-related membranous glomerulonephritis (IgG4-MGN)

IgG4-Related Disease (IgG4-RD)

- Recently recognized systemic immune-mediated disease
- Predominantly affects middle-aged to older men
- Often presents as inflammatory masses
  - Can mimic neoplasms



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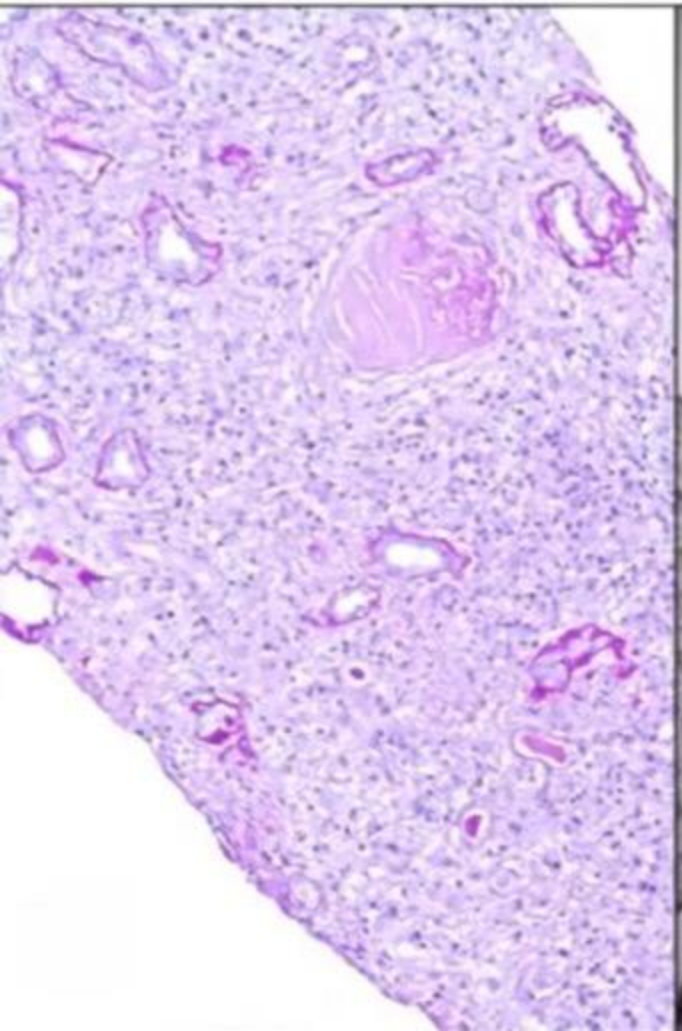
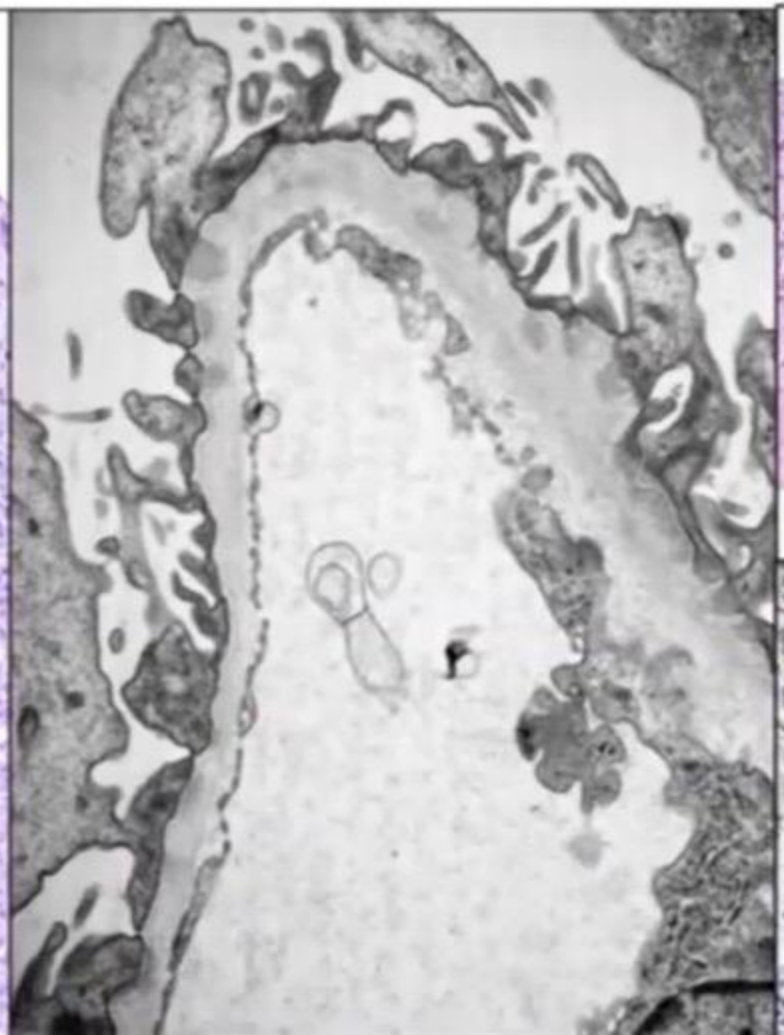
Patterns of renal involvement by IgG4-RD

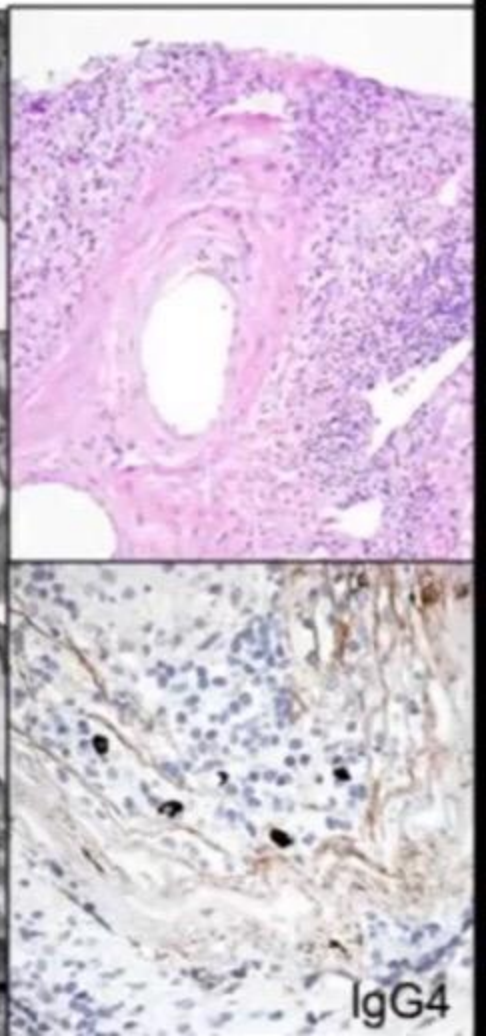
Tubules and interstitium:
IgG4-related tubulointerstitial nephritis

Glomeruli:
Membranous glomerulonephritis

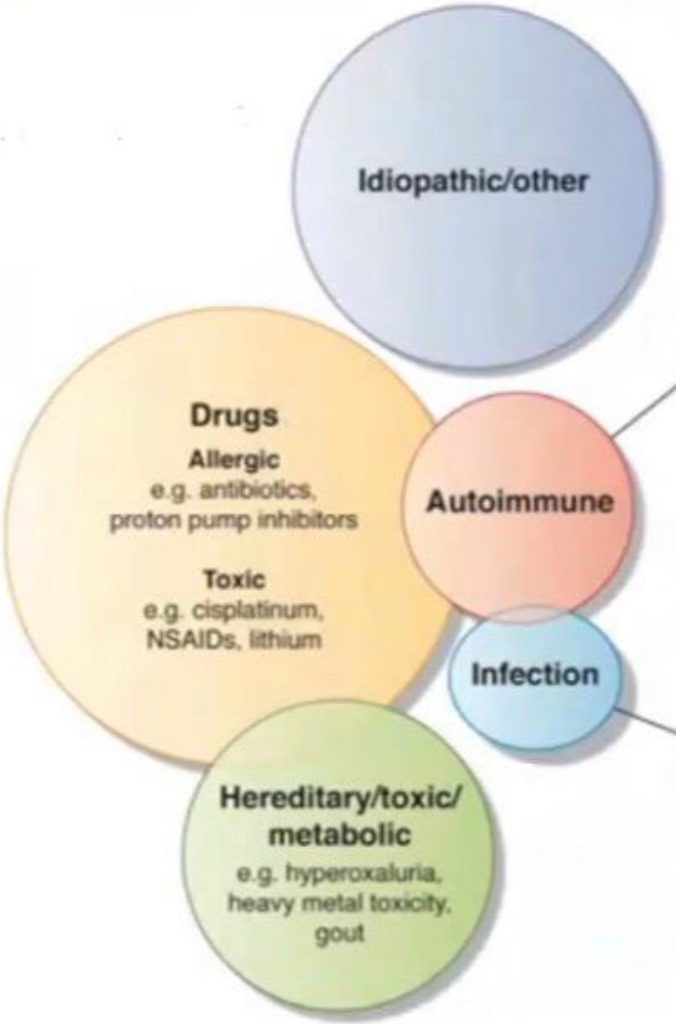
Vessels:
IgG4 plasma cell arteritis







Categories of tubulointerstitial nephritis/ nephropathy



Autoimmune

With tubulointerstitial immune complex deposits

Associated with systemic disease:
- IgG4-associated systemic disease
- Sjogren syndrome
- Systemic lupus erythematosus (with glomerular disease)

Primary in kidney:
- Idiopathic hypocomplementemic TIN with extensive immune deposits
- Giant cell tubulitis with TBM immune deposits (?drug reaction)
- Associated with glomerular disease (e.g. membranous glomerulonephritis)

Without immune complex deposits
- Anti-tubular basement membrane nephritis (linear TBM staining for immunoglobulin)
- TINU syndrome
- Sarcoidosis
- Other

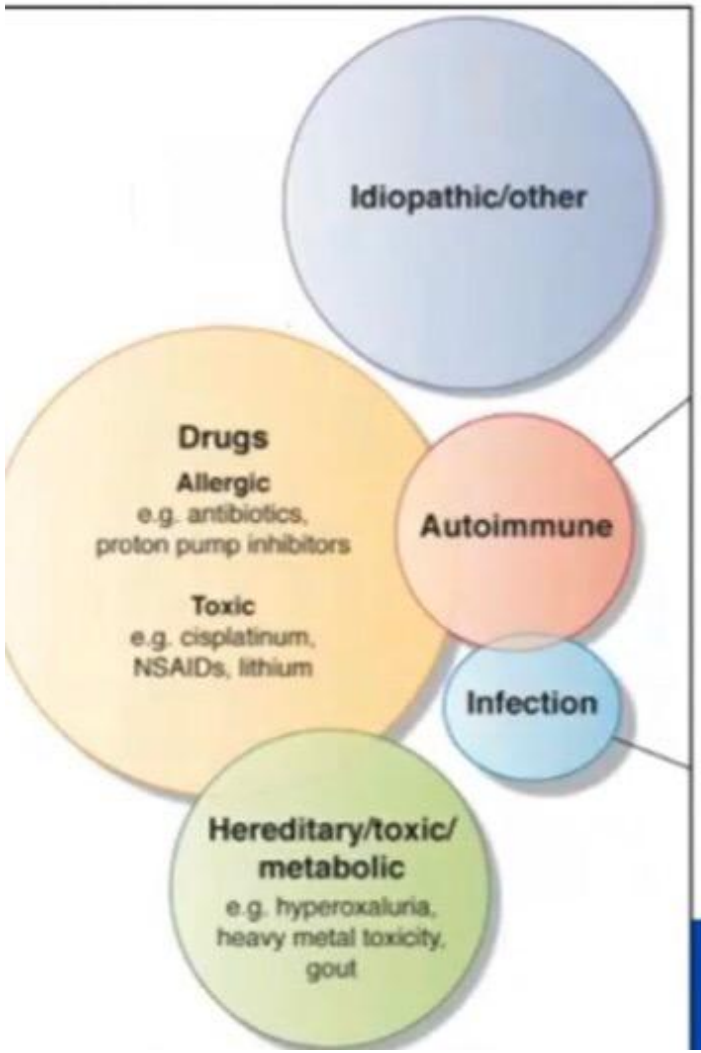
Infection

Direct infection (viral, bacterial, other)
e.g. BK polyomavirus interstitial nephritis (may show TBM deposits), acute pyelonephritis

Reactive
e.g. post-streptococcal

Cornell, *Kidney Int*, Nov 2010

IgG4-related tubulointerstitial nephritis (IgG4-TIN)



Part of a systemic immune-mediated disease

IgG4-TIN first recognized in association with autoimmune pancreatitis (AIP)

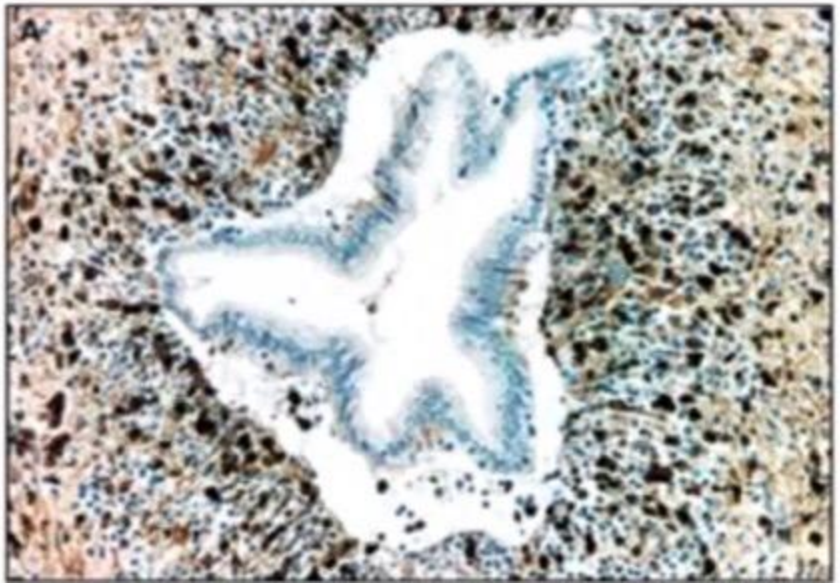
Cornell LD, Chicano SL, Deshpande V, Collins AB, Selig MK, Lauwers GY, Barisoni L, Colvin RB. Pseudotumors due to IgG4 immune-complex tubulointerstitial nephritis associated with autoimmune pancreatocentric disease. Am J Surg Pathol. 2007 Oct;31(10):1586-97

Autoimmune Pancreatitis (AIP)

- Hamano 2001: ↑ serum IgG4 in AIP, hypergammaglobulinemia in AIP mostly IgG4

Hamano et al: High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med*, 344: 732-8, 2001

- ↑ IgG4+ plasma cells in lesions



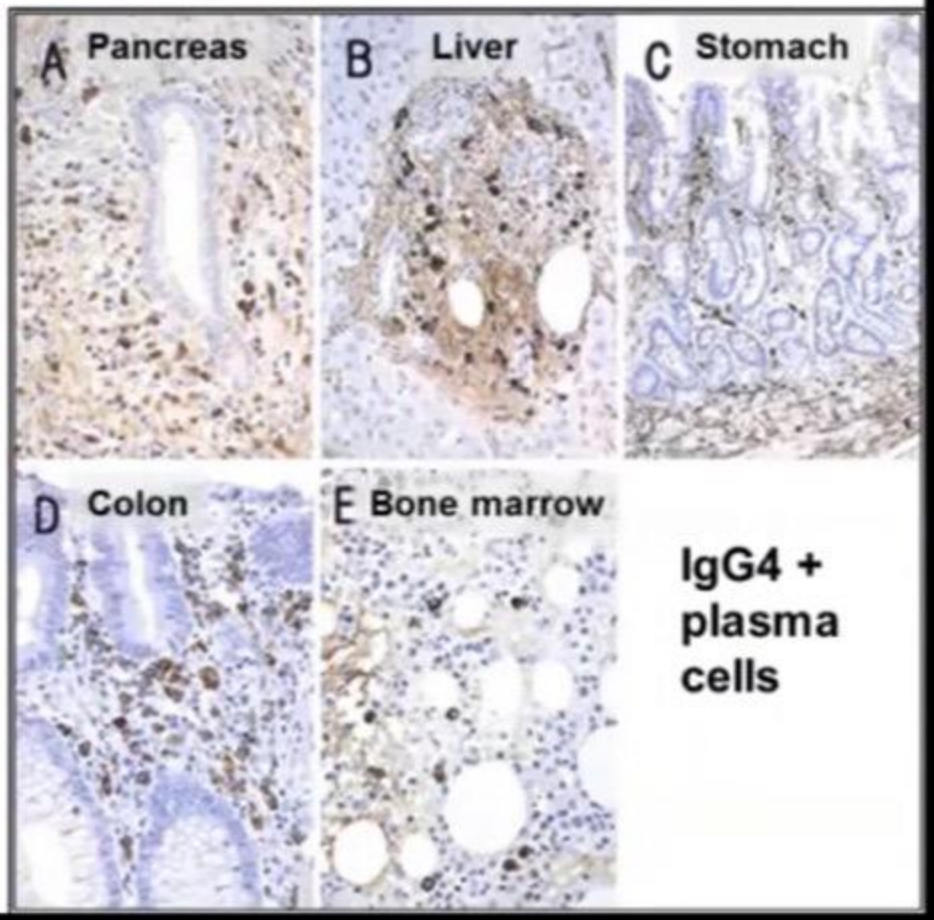
IgG4+ plasma cells in pancreas

Aoki et al *Histopath*, 47:147, 2005

AIP and systemic disease

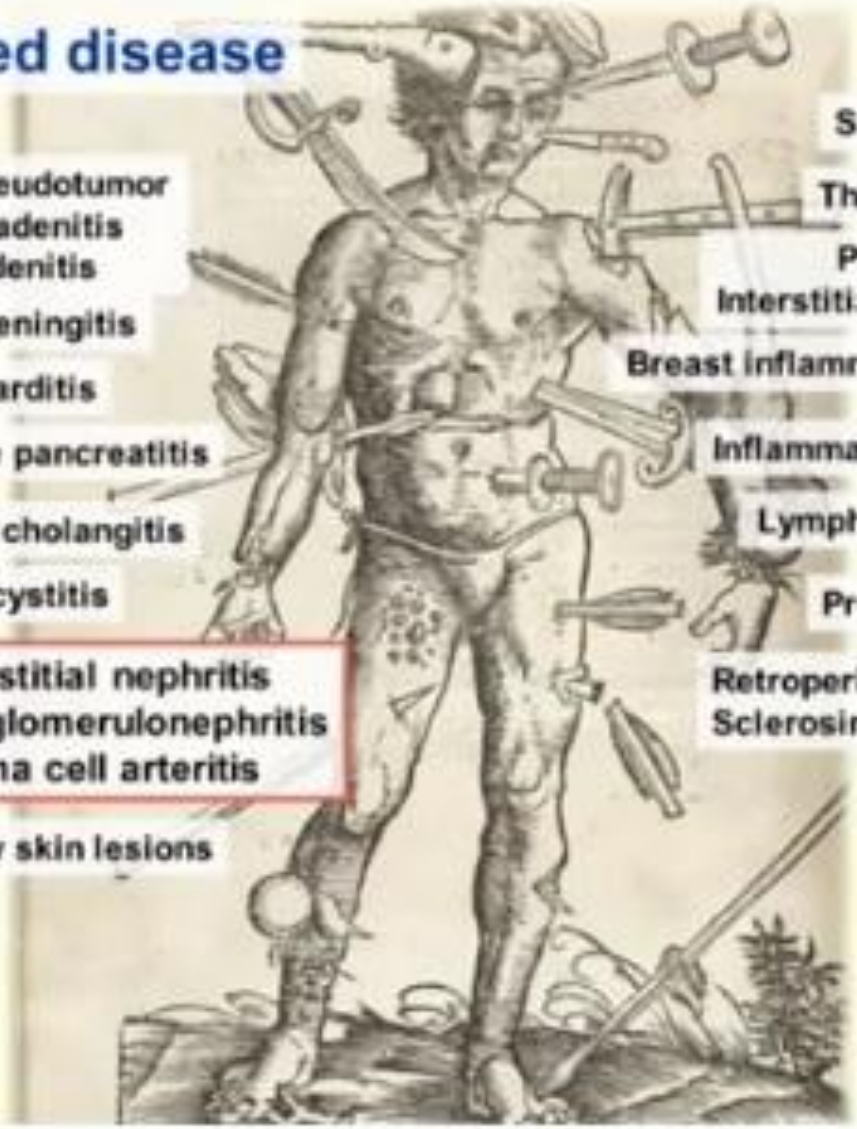
Kamisawa 2003: AIP patients have IgG4+ plasma cells in tissues outside of the pancreas

- Peripancreatic tissue
- Bile duct
- Gallbladder
- Liver
- Gastric mucosa
- Colonic mucosa
- Salivary glands
- Lymph nodes
- Bone marrow



T Kamisawa et al. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; 38(10):982-4.

IgG4-related disease



Orbital pseudotumor
Dacryoadenitis
Sialadenitis

Pachymeningitis

Pericarditis

Autoimmune pancreatitis

Sclerosing cholangitis

Cholecystitis

Tubulointerstitial nephritis
Membranous glomerulonephritis
IgG4-plasma cell arteritis

Inflammatory skin lesions

Sinusitis

Thyroiditis

Pleuritis
Interstitial pneumonitis

Breast inflammatory pseudotumor

Inflammatory aneurysm

Lymphadenopathy

Prostatitis

Retroperitoneal fibrosis
Sclerosing mesenteritis

Hans von Gersdorff, 1529

IgG4-related disease (IgG4-RD): Histopathology

Striking histologic similarities among affected organs

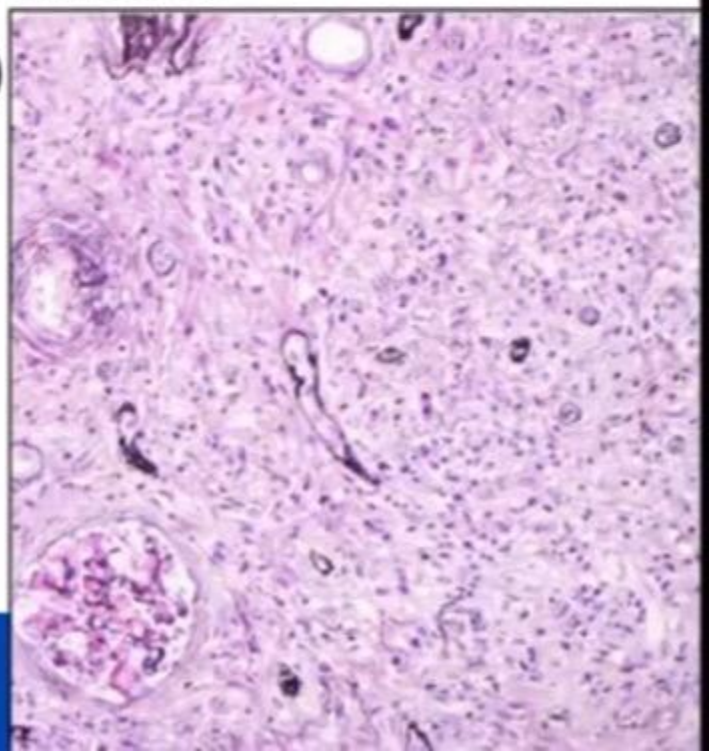
Three major histopathological features associated with IgG4-RD:

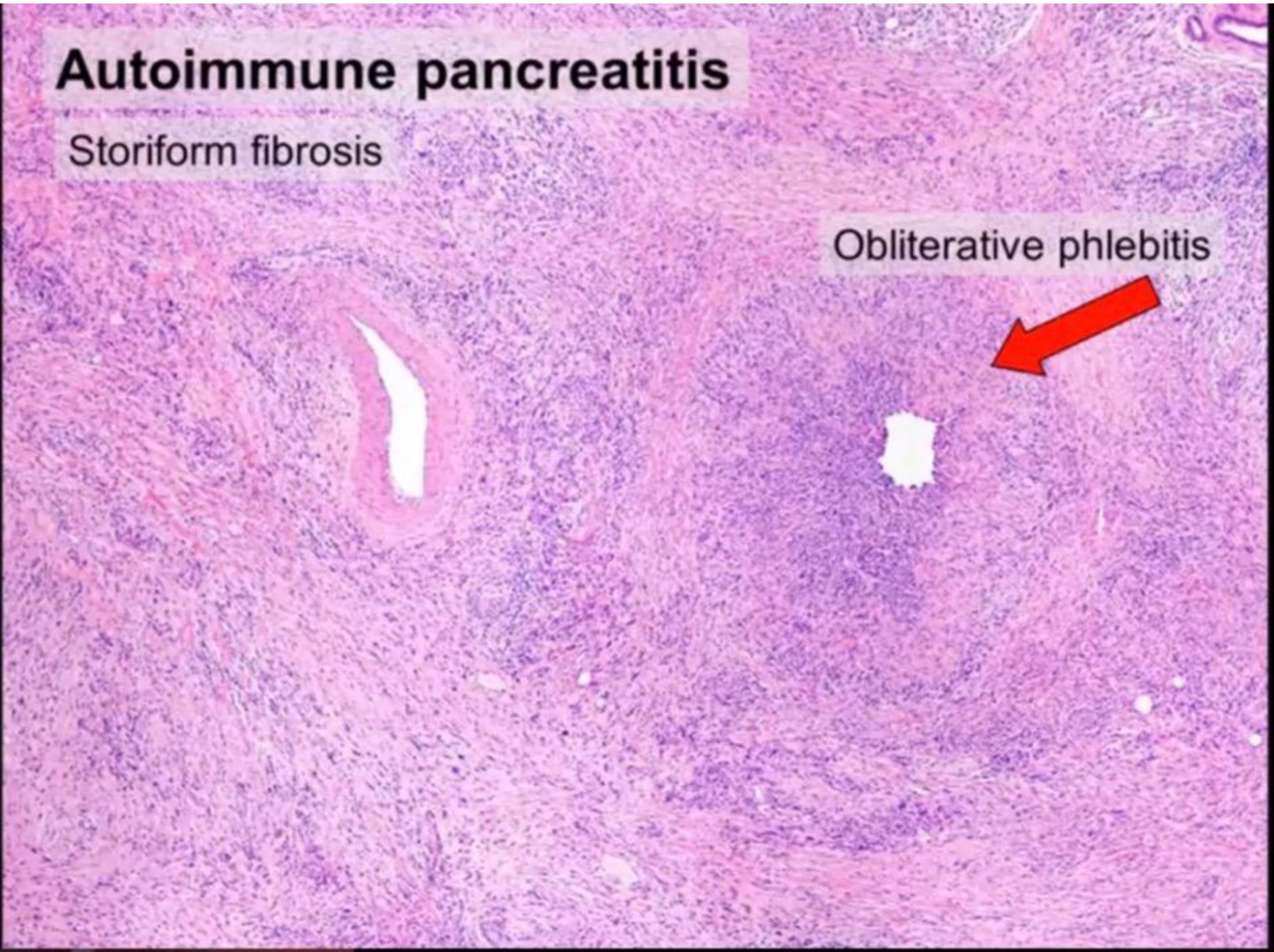
(1) Dense lymphoplasmacytic infiltrate

(2) Fibrosis ("storiform pattern")

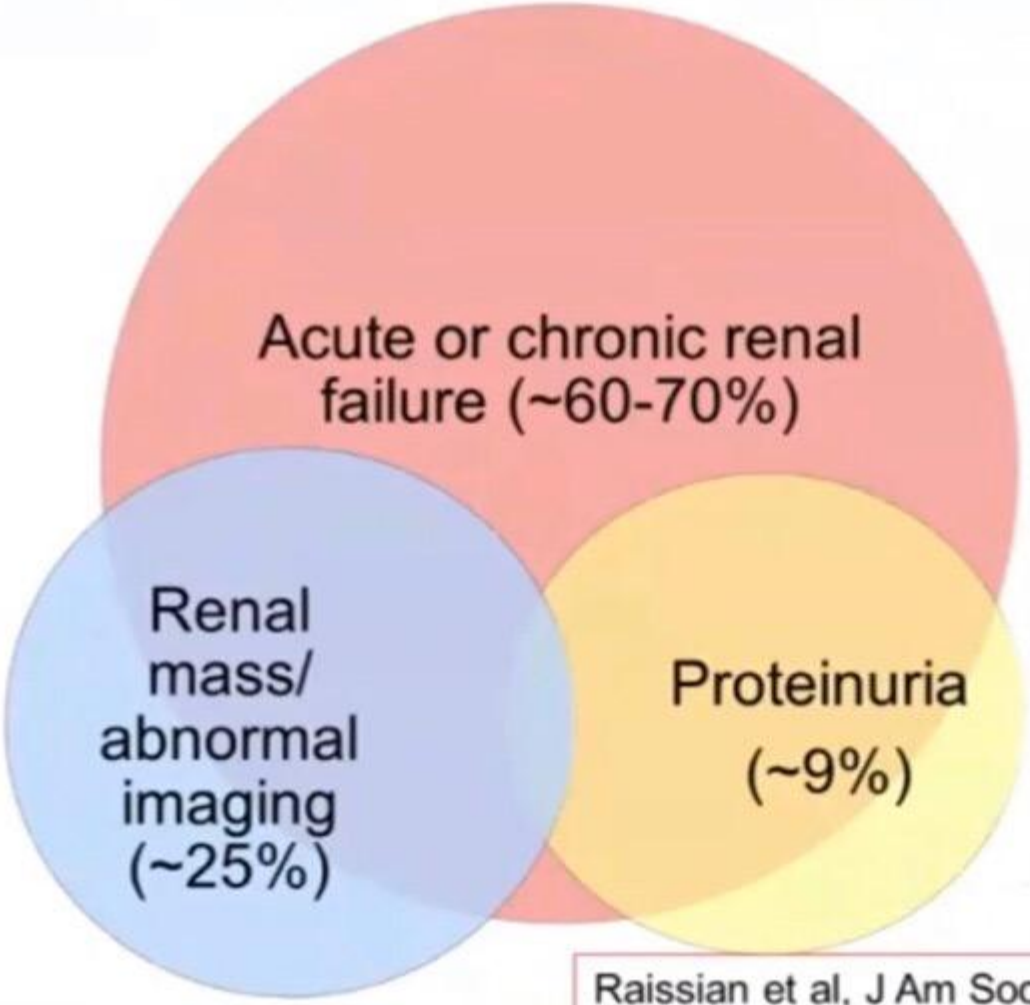
(3) Obliterative phlebitis

Typical histologic appearance is considered the "gold standard" for diagnosis of IgG4-RD




Autoimmune pancreatitis
Storiform fibrosis
Obliterative phlebitis

IgG4-Related Kidney Disease (IgG4-RKD): Primary indication for biopsy



Raissian et al, J Am Soc Nephrol July 2011
Saeki et al, Kidney Int, Nov 2010
Buglioni et al (abstract, ASN 2018)

IgG4-RKD: Laboratory features

- ↑ Serum IgG4 in 67%
- Hypocomplementemia in ~50%
- Peripheral blood eosinophilia in ~30%
- +ANA (mostly low titer) in ~30%

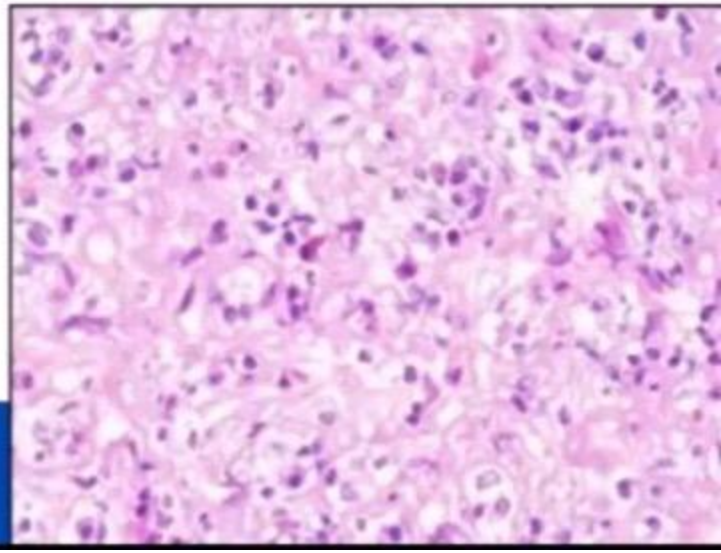
Raissian et al, J Am Soc Nephrol July 2011
Buglioni et al (abstract, ASN 2018)

IgG4-TIN: Light microscopy

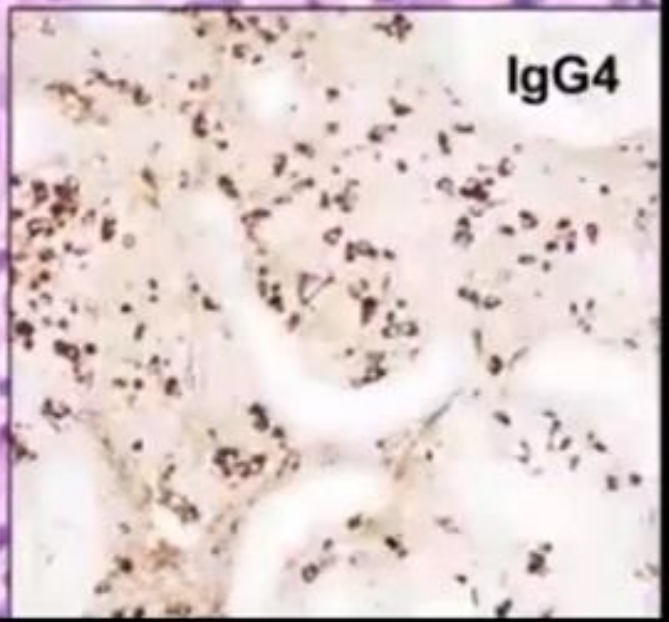
- Plasma cell-rich interstitial infiltrate

  Eosinophils often numerous
- Expansile interstitial fibrosis, “storiform” pattern
- Variable degrees of fibrosis/inflammation
- Increased IgG4+ plasma cells

  >10 cells per 40x field

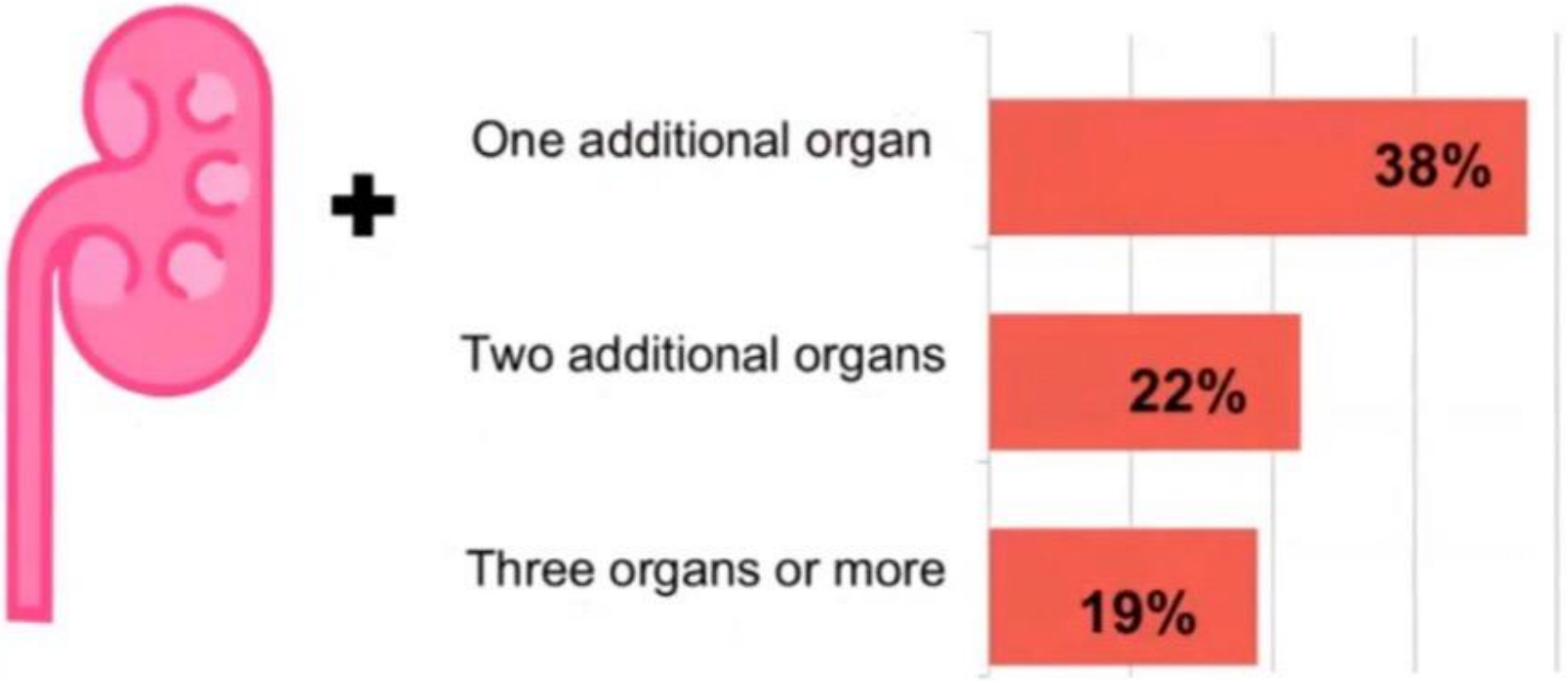


Plasma cells & eosinophils in infiltrate



Multi-organ involvement in IgG4-RKD

Besides kidney, nearly **80%** have other organ involvement by IgG4-RD



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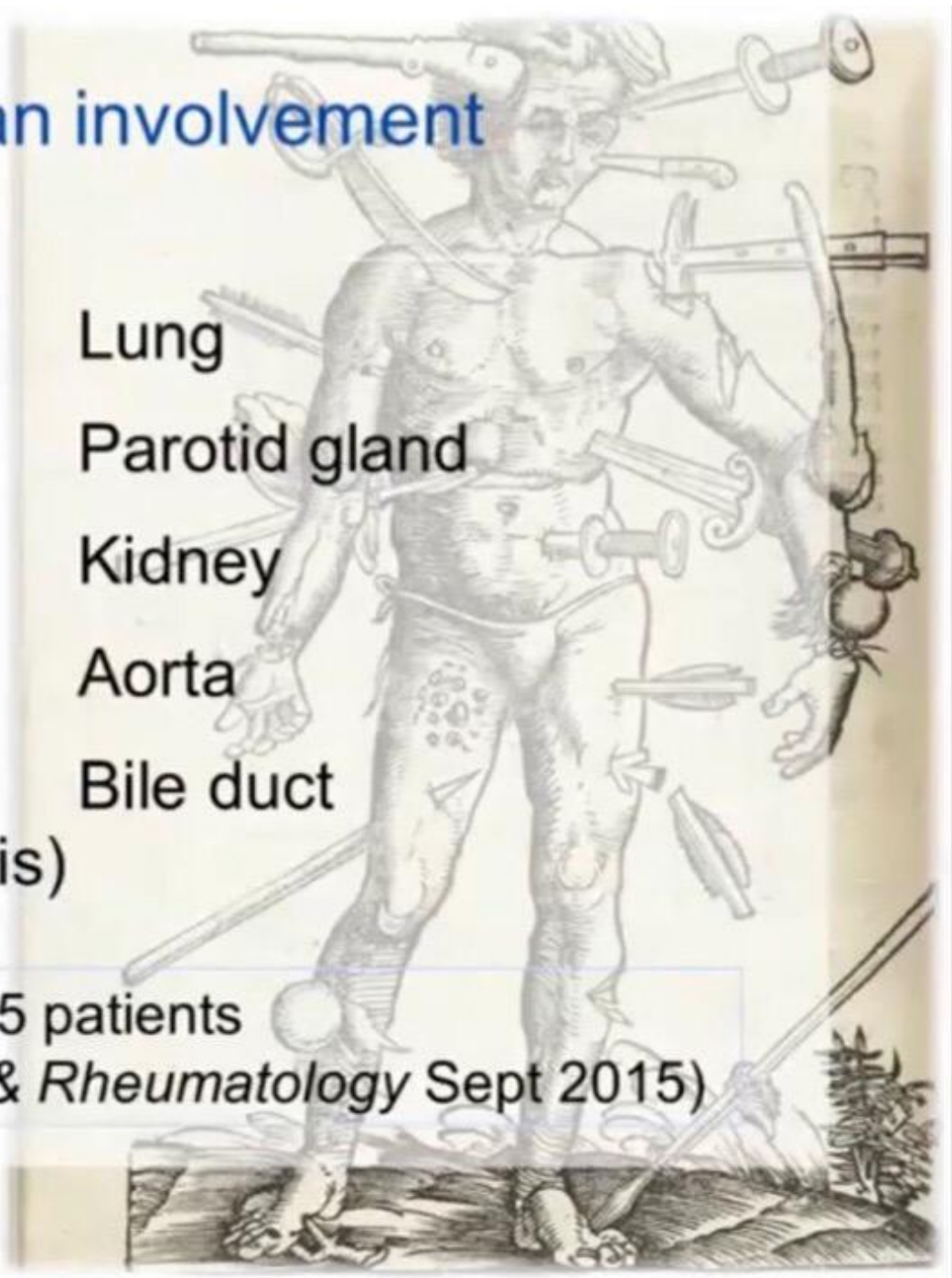
A Buglioni et al (102 IgG4-RKD cases, unpublished)

Most common organ involvement in IgG4-RD

- Submandibular gland
- Lymph nodes
- Orbit
- Pancreas
- Retroperitoneum (retroperitoneal fibrosis)
- Lung
- Parotid gland
- Kidney
- Aorta
- Bile duct



Present in ≥10% of 125 patients
(ZS Wallace, *Arthritis & Rheumatology* Sept 2015)

IgG4-RD:
Treatment and Response to Therapy

- Treatment indicated in patients with active and symptomatic disease
- Response to immunosuppressive treatment in ~90% of patients (~2-4 weeks)
  - Steroids usually first-line treatment
  - Rituximab an alternative

IgG4-RD:
Treatment and Response to Therapy

High relapse rate (~70% following rituximab response)

Predictors of relapse:

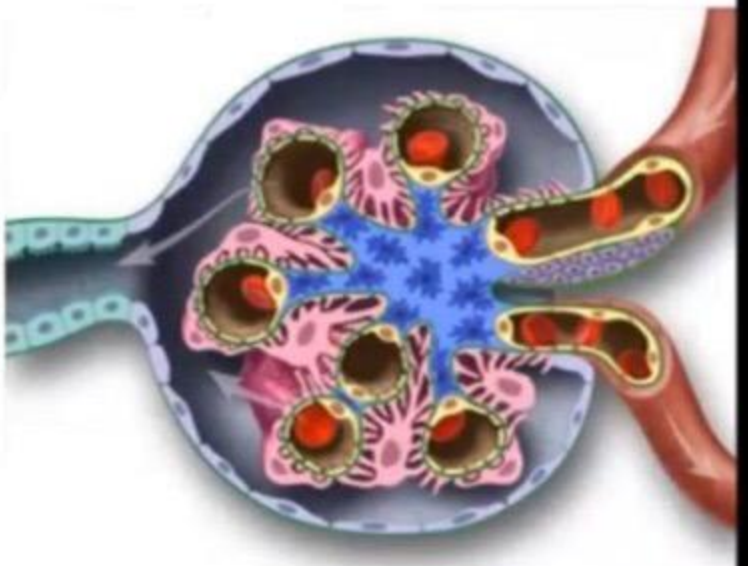
Elevated baseline (pre-treatment):

- Serum IgG4
- Serum IgE
- Circulating eosinophils

ZS Wallace et al, *Rheumatology* 2016; 55

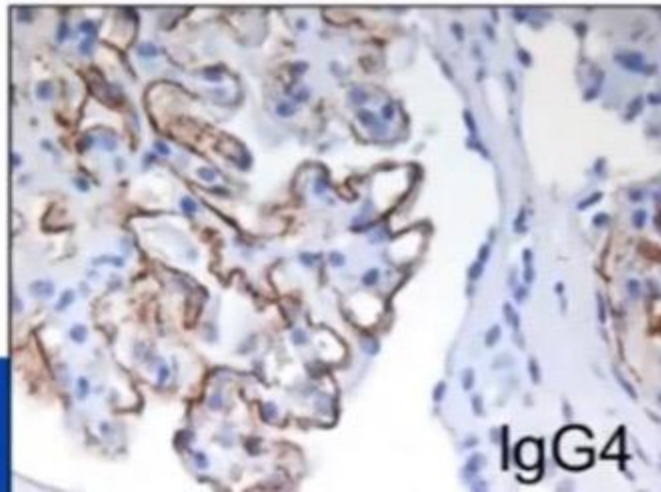
Glomerular diseases in IgG4-RD

- Membranous glomerulonephritis (MGN)
- IgA nephropathy
- Membranoproliferative GN
- Minimal change disease
- Other GN, not well-defined
- Diabetic glomerulosclerosis



Membranous glomerulonephritis (MGN)

- MGN may be primary ("idiopathic") or secondary
  - Secondary to autoimmune disease, infections, medications, cancers, other conditions
  - Primary MGN is IgG4-dominant
- MGN: most common glomerular disease in IgG4-RD
  - ~7% of IgG4-TIN have MGN
  - Different pattern of involvement of IgG4-RD—not "inflammatory"



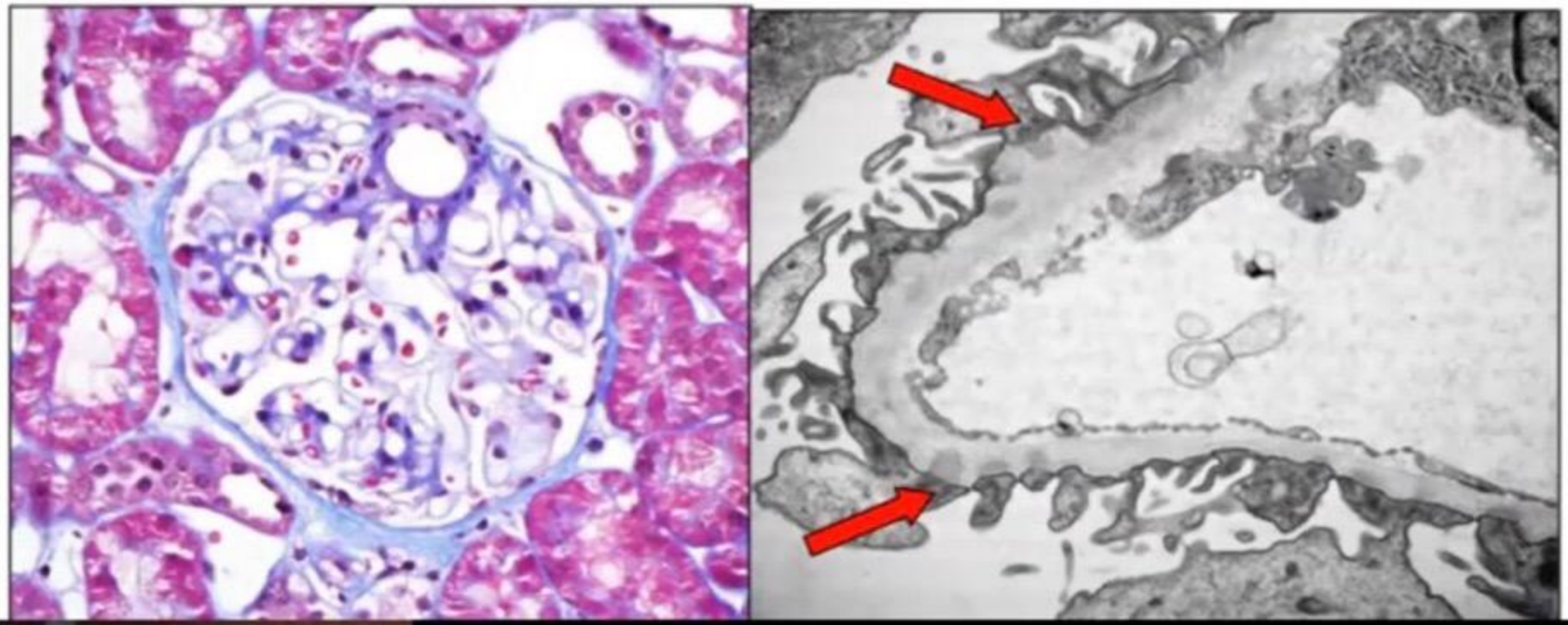
MGN in IgG4-RD: Mayo case series

- 9 patients with MGN and IgG4-RD
- Clinical presentation
  - Proteinuria
    - Ave 8.3 g/day; range 1.7-16
  - ↑ Creatinine in 6 patients
    - Ave 2.2 mg/dl (range 0.8-6.6)
    - 1 patient with ARF due to TIN

Alexander MP, Larsen CP, Gibson IW, Nasr SH, Sethi S, Fidler ME, Raissian Y, Takahashi N, Chari S, Smyrk TC, Cornell LD. Membranous glomerulonephritis is a manifestation of IgG4-related disease. Kidney Int. 2013 Mar;83(3):455-62

MGN in IgG4-RD: Mayo case series

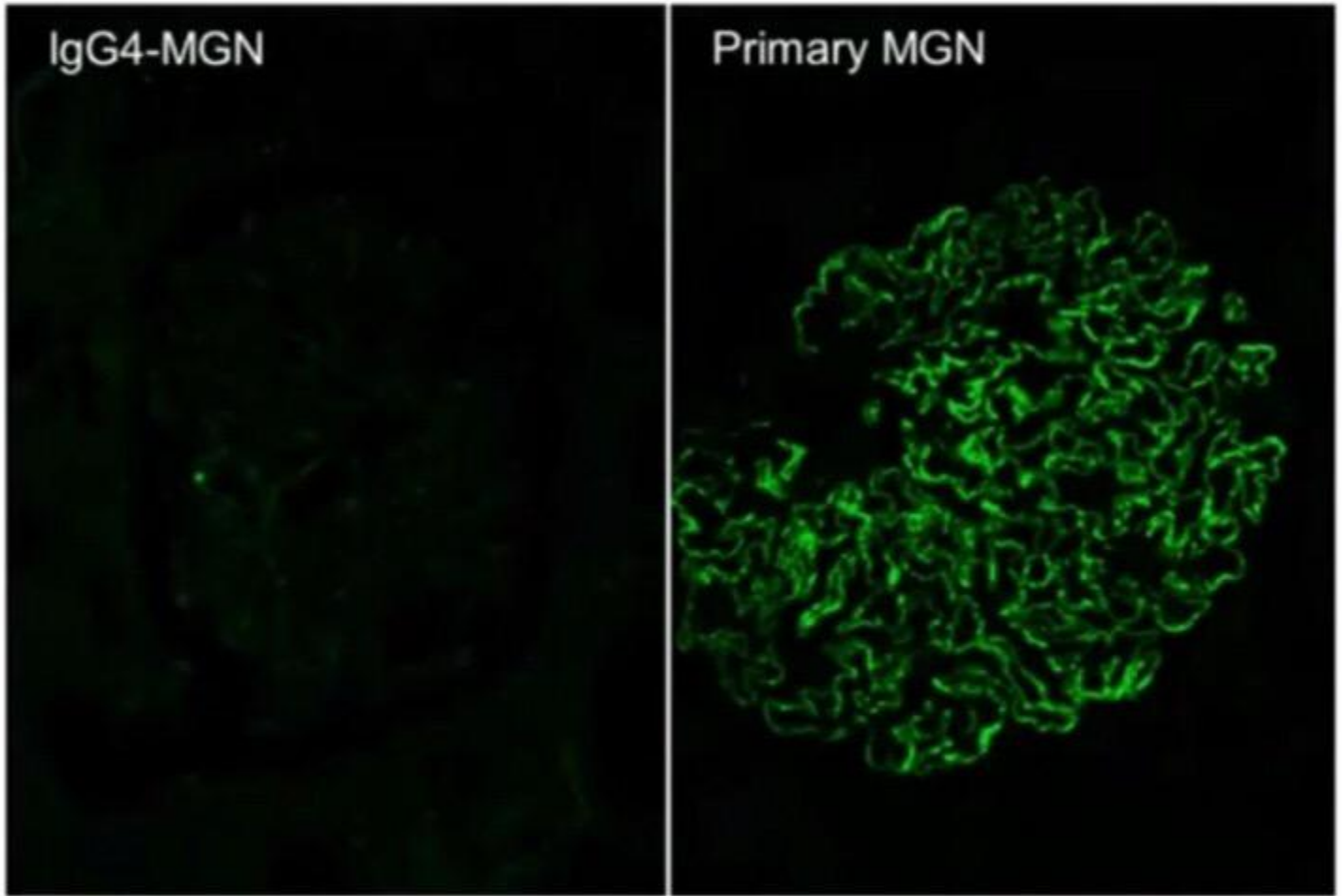
- All patients had IgG4-TIN or had extra-renal involvement by IgG4-RD
- 56% (5/9) had IgG4-TIN, sometimes focal



PLA2R staining in IgG4-MGN

Immunostaining for phospholipase A2 receptor (PLA2R)
Negative in IgG4-MGN

Argues that IgG4-MGN is secondary



Key points: IgG4-related kidney disease

Most common pattern of involvement is "*inflammatory*": IgG4-TIN

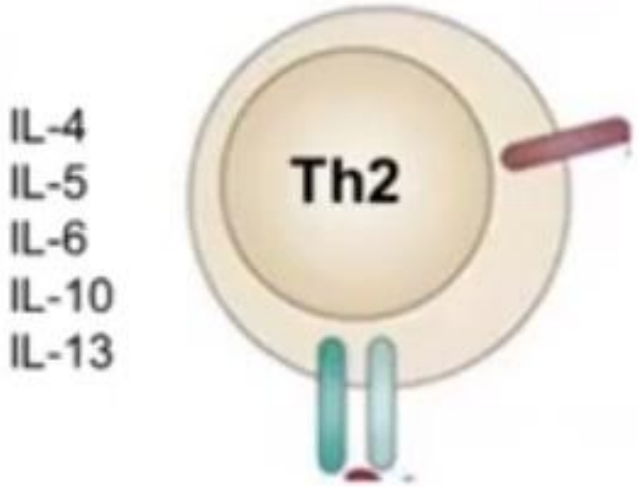
Analogous to other organs involved

Proteinuria/nephrotic syndrome in patients with systemic IgG4-RD is likely MGN

Only one small case series of IgG4-MGN; treatment & expected response is unknown

Pathogenesis of IgG4-RD (Dr. Cornell)

- Poorly understood
- Postulated chronic allergic disorder
  - Many patients have a history of allergy
  - Cytokine profile more suggestive of allergy (Th2)



Treatment & Clinical Follow Up (Dr. Hogan)

Treatment

- 3 rounds of rituximab (375mg/m^2)
  - Quantiferon status, Bactrim, ARB
  - Monitor CD20 cell counts, reassuring if remain undetectable
- Monitored q4-6 months
  - No further immunosuppressive therapy

Treatment & Clinical Follow Up (Dr. Hogan)

Latest follow-up (3 years post-rituximab, 7 years after initial presentation):

- Creatinine 0.81 mg/dL, serum albumin 4.5 g/dL
- No proteinuria
- Amylase/lipase & liver function tests normal
- No evidence of other organ involvement by IgG4-RD
- Not on maintenance immunosuppression

Background

- Steroids are effective therapy in > 90% of IgG4-RD cases
- True steroid-refractory disease is rare
- Relapse is common during steroid taper or after cessation of steroid therapy
- Rituximab (RTX) is also highly effective therapy for IgG4-RD, even in steroid resistant or refractory cases
- Relapse is also common after RTX therapy

Ghazale and Chari, Gut 2007; Hart et al, Gut 2012

Clinical Trial:

Treatment of IgG4-Related Disease with Revlimid and Rituximab (TIGR^2)