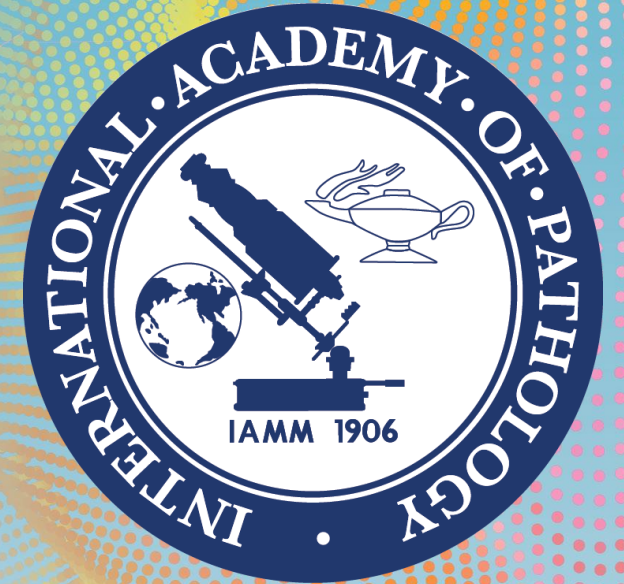


# Smoke and Mirrors

Dr Julia Chan

Royal North Shore Hospital



 The 48th Annual Scientific Meeting *of the*

Australasian Division of the  
International Academy of Pathology

# Disclosure of Relevant Financial Relationships

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No relevant financial relationships.

# HPC (70 y.o. male)

D0

- Surgery for hepatocellular carcinoma resection

D12

- Purulent discharge from drain – commenced on Augmentin DF

D17

- Presented to the emergency department for rash
- Started on right forearm and rapidly spread to other arm and legs
- Petechial/ purpuric rash, not painful or itchy
- Otherwise systemically well, no macroscopic haematuria or other urinary symptoms



# Past Medical History

- Hepatocellular carcinoma
  - Laparoscopic left lateral hepatectomy (Nov 2023)
  - Background of NASH cirrhosis (negative for hepatitis B and C)
- Colorectal carcinoma
  - AP resection 2020- low rectal cancer – had neoadjuvant therapy
  - Colectomy, colostomy in situ
- Type 2 diabetes mellitus
- Hypertension
- Atrial fibrillation
- COPD

# Medications

Carvedilol 25mg daily

Rosuvastatin 10mg daily

Trelegy Ellipta inhaler

Rivaroxaban

# SHx

Lives with wife

Ex-smoker, quit 1.5 years ago

Previous heavy drinker for 40 years  
(~approximately one crate  
beer/casket of wine daily)

Independent with ADLs and mobility

Nil IVDU

# Investigations - bloods

WCC 4.5	normal
Hb	128 (slightly low)
Platelet	290 (normal)
CRP	46.5 (H)
Coagulation screen	normal
Cr	149 (baseline 130),
eGFR	40 (baseline 50)
Albumin	22 [32-45 g/L]

# Investigations - urine

Urinalysis

Blood +++  
Protein +++

Microalbumin/Cr ratio

46.7 mg/mmol cr (H)

Microalbumin

714 mg/L (H)

Urine culture

Positive for E. Coli

# Investigations - Renal screen

C3 and C4	normal
ANA, ENA, ANCA	normal
IgA	5.25 (H)
Glomerular basement membrane IgG	37 (H) [<20]
Kappa free	64.2 (H)
Lamda free	44.2 (H)
serum EPG/IEPG	negative
Kappa/lamda ratio	normal
Rheumatoid factor	normal
ASOT	normal
anti-DNAse B	normal
Cryoglobulin	2%
CT KUB	no obstruction of renal tract

# Investigations - Infection screen

TB Quantiferon Gold	negative
HBV	negative
HCV	negative
HIV	negative
Strongyloides	negative
Swab (throat)	negative for strep
Swab (rash)	negative on Bacterial/ fungal/ AFB cultures

# Initial management

- Given antibiotics for E. Coli UTI
- Skin biopsy taken by dermatology
- Discharged from ED with outpatient follow-up planned

# However

- Seen in renal clinic 4 days later
  - Started having macrohaematuria

eGFR	29 (from 40)
Creatinine	198 (from 149)
Microalbumin/Cr ratio	277.3 mg/mmol cr
Microalbumin	5740 mg/L

- Plan for renal biopsy

# Clinical impression/ Clinical DDx

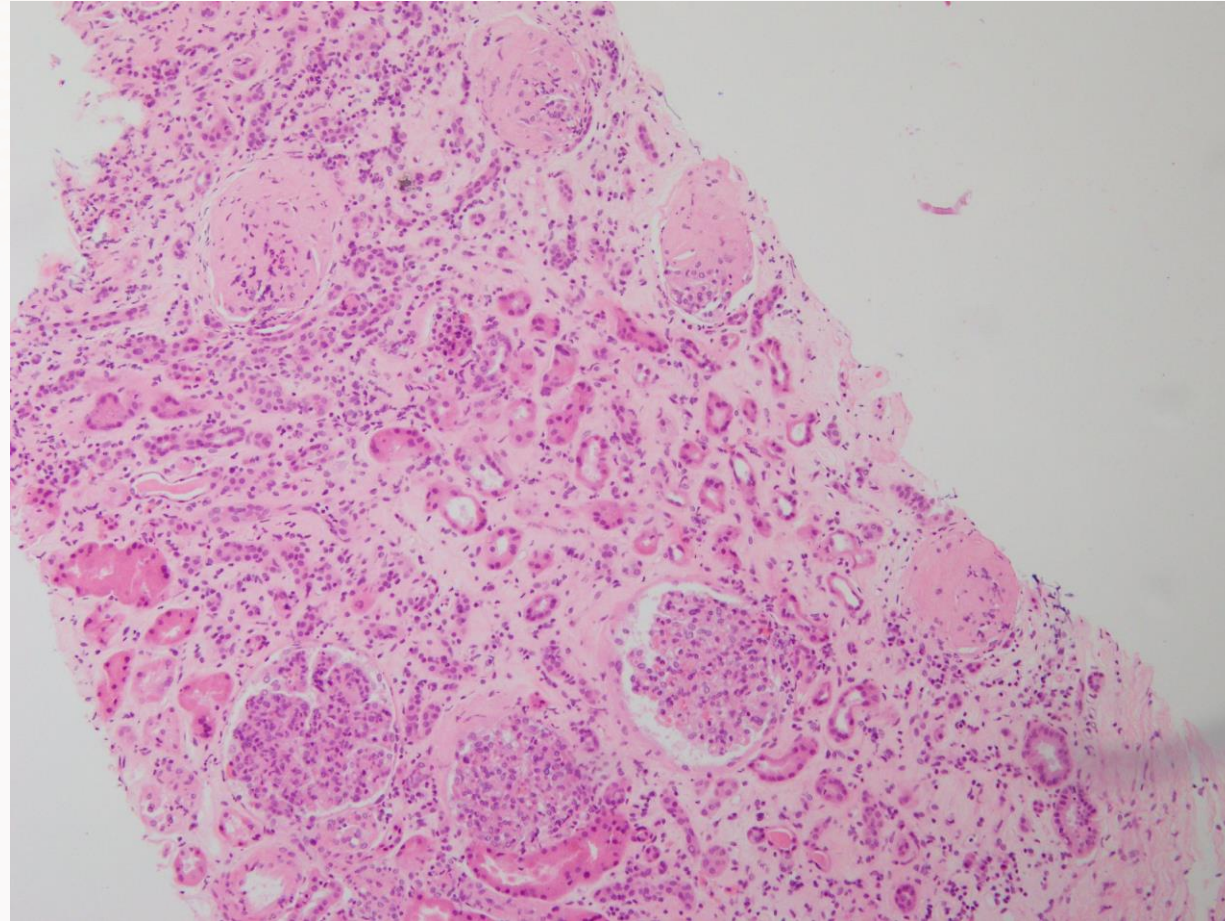
## Rash with declining kidney function

- Vasculitides
  - IgA vasculitis (HSP) (more common in children)
  - Cryoglobulinemia
  - Other vasculitides: ANCA, polyarteritis nodosa
- Infection associated
  - Poststreptococcal glomerulonephritis
  - Sepsis
- Autoimmune
  - Lupus nephritis (ANA would be abnormal)
  - Rheumatoid arthritis (rash not purpura)

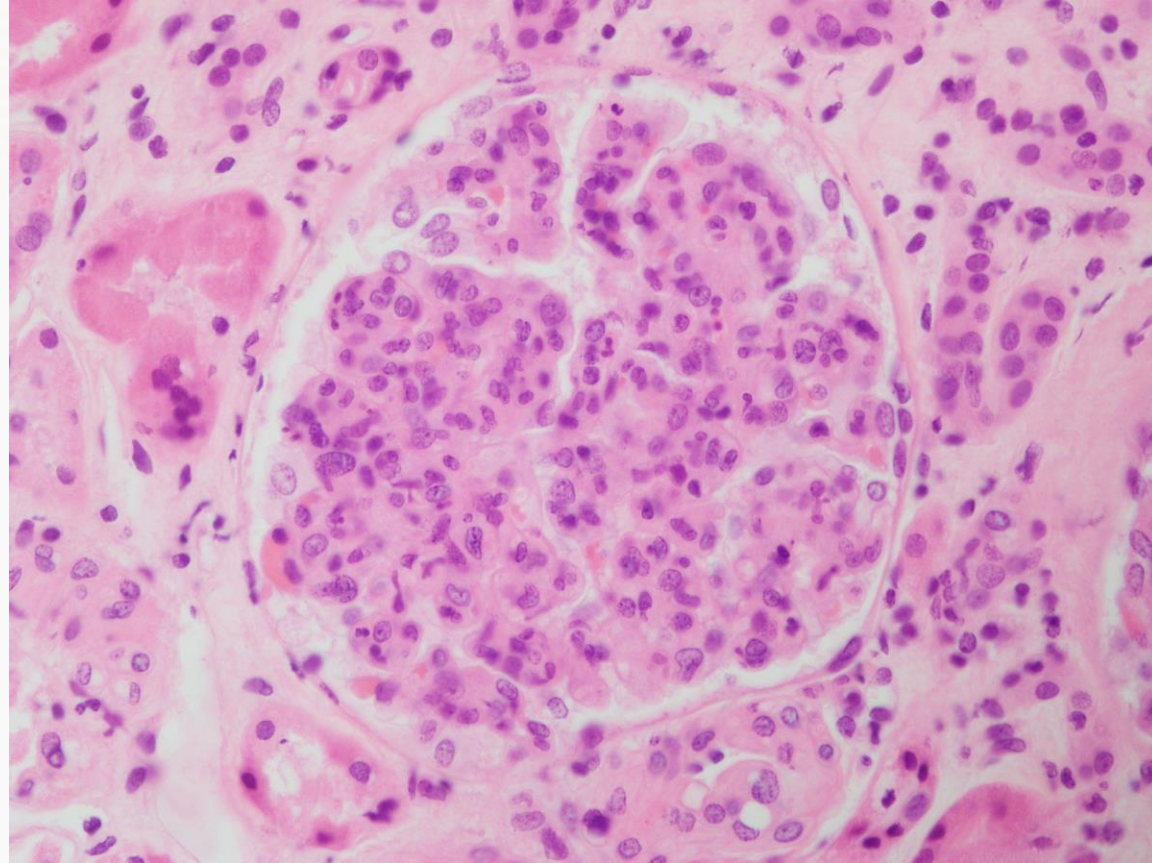
# Renal Biopsy:

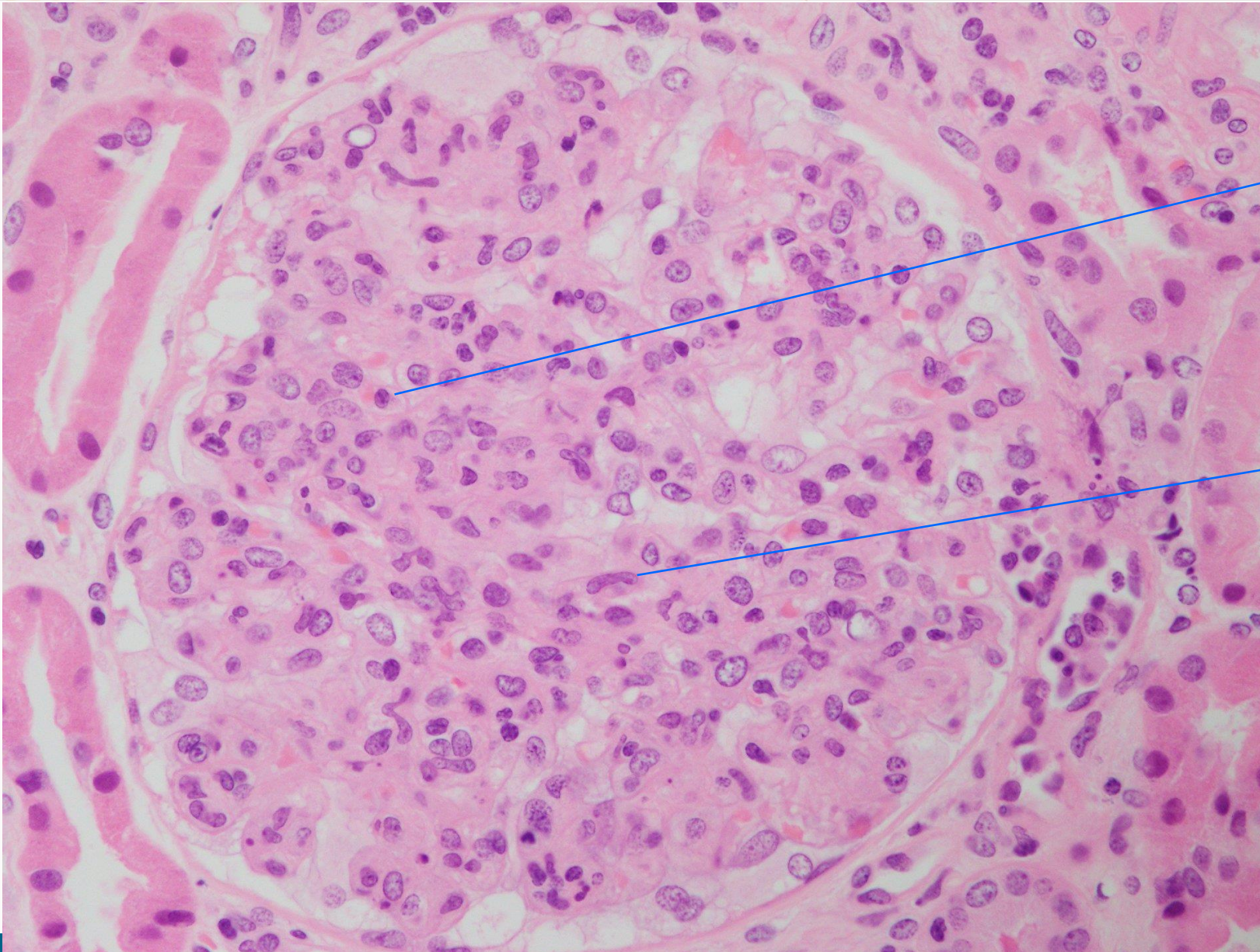
Light microscopy

# Sclerotic glomeruli



# Hypercellular and lobulated



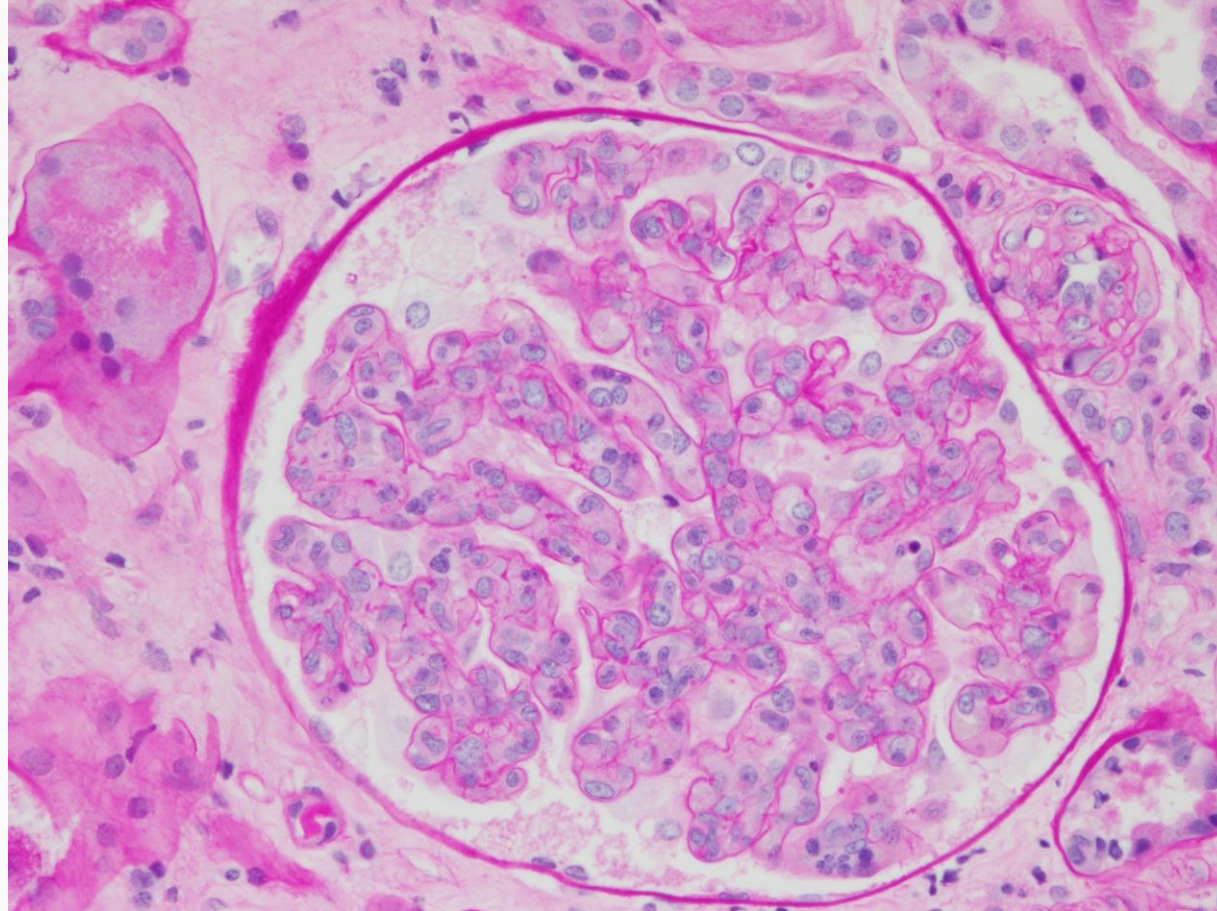


Neutrophil

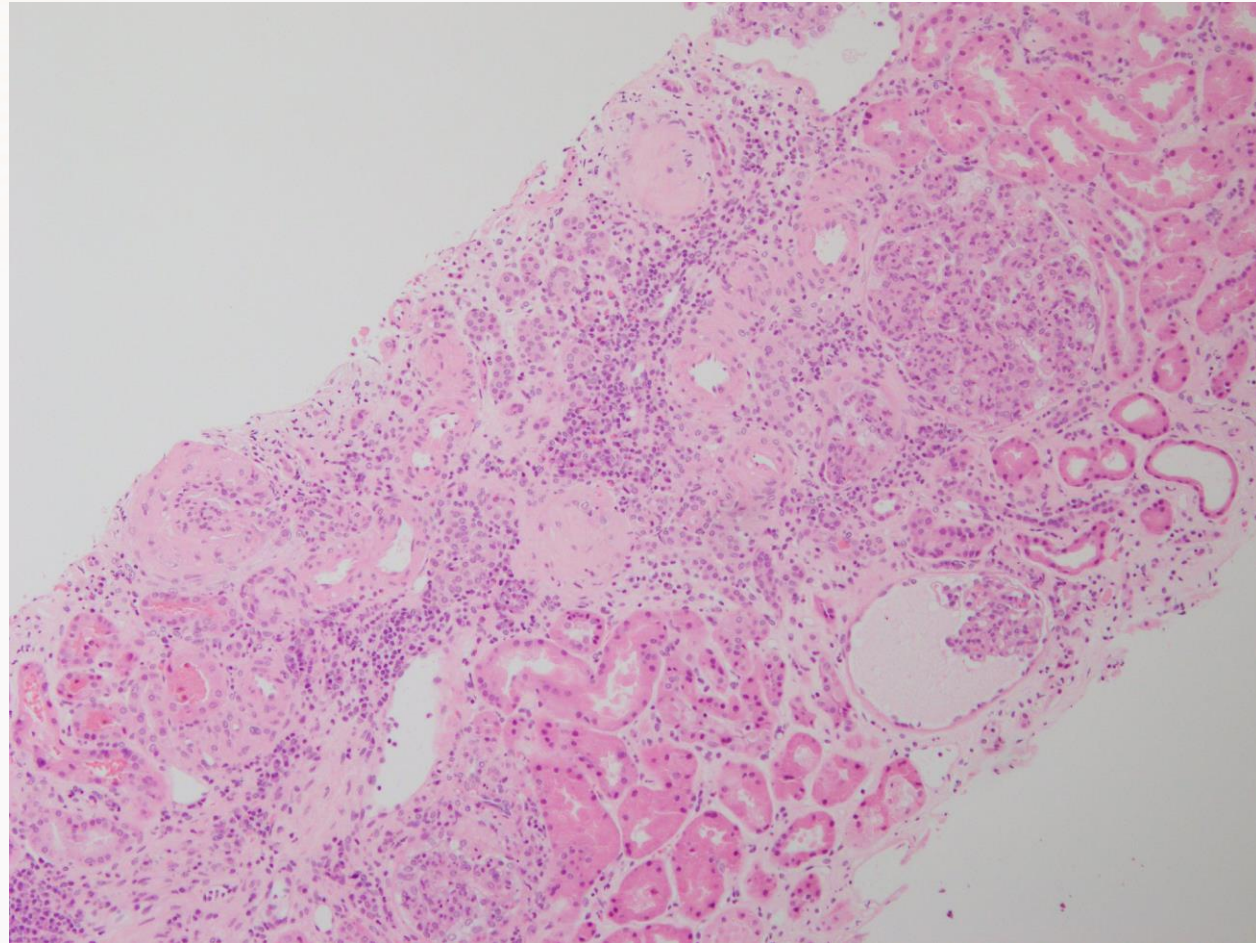
Monocytes (horseshoe shape)

Remainder of cells  
endothelial

# PAS-stain showing no double contours

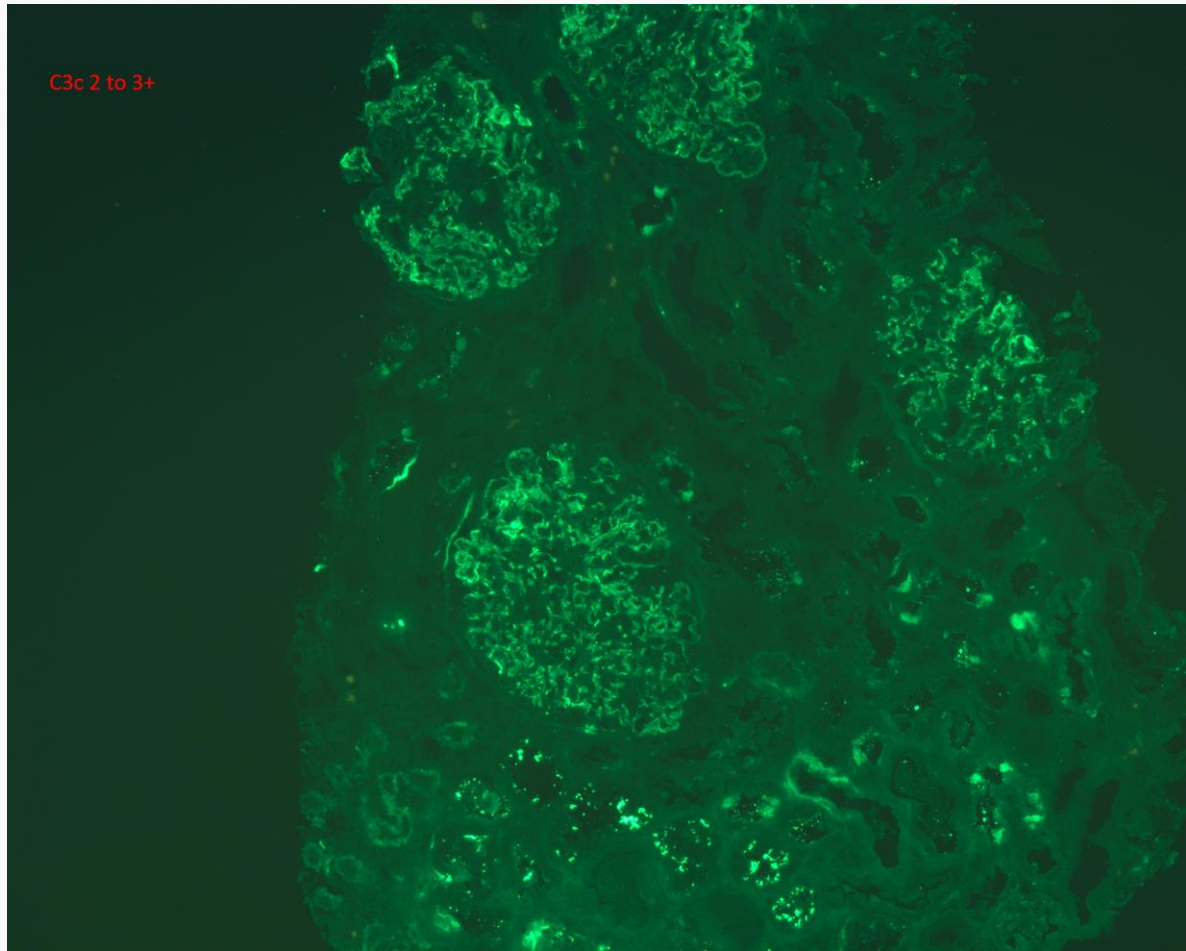


# Interstitial inflammation

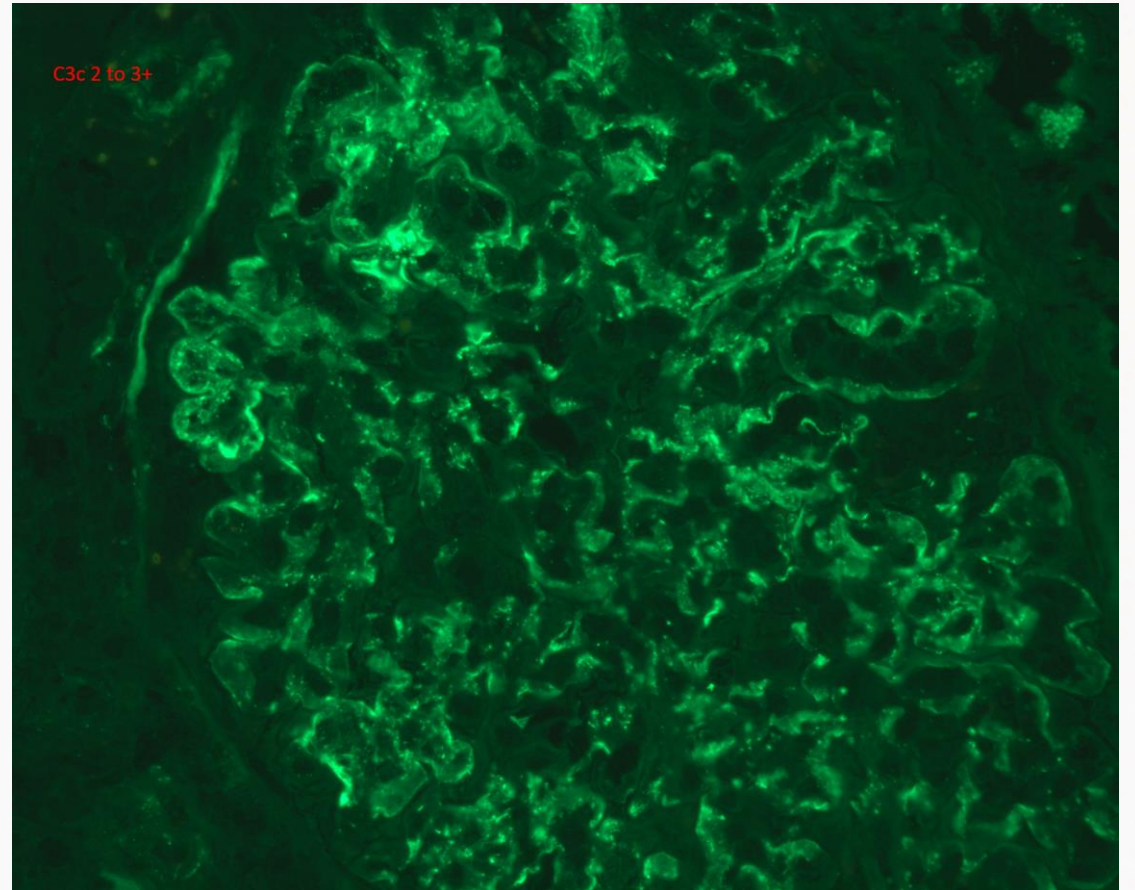


# Renal Biopsy:

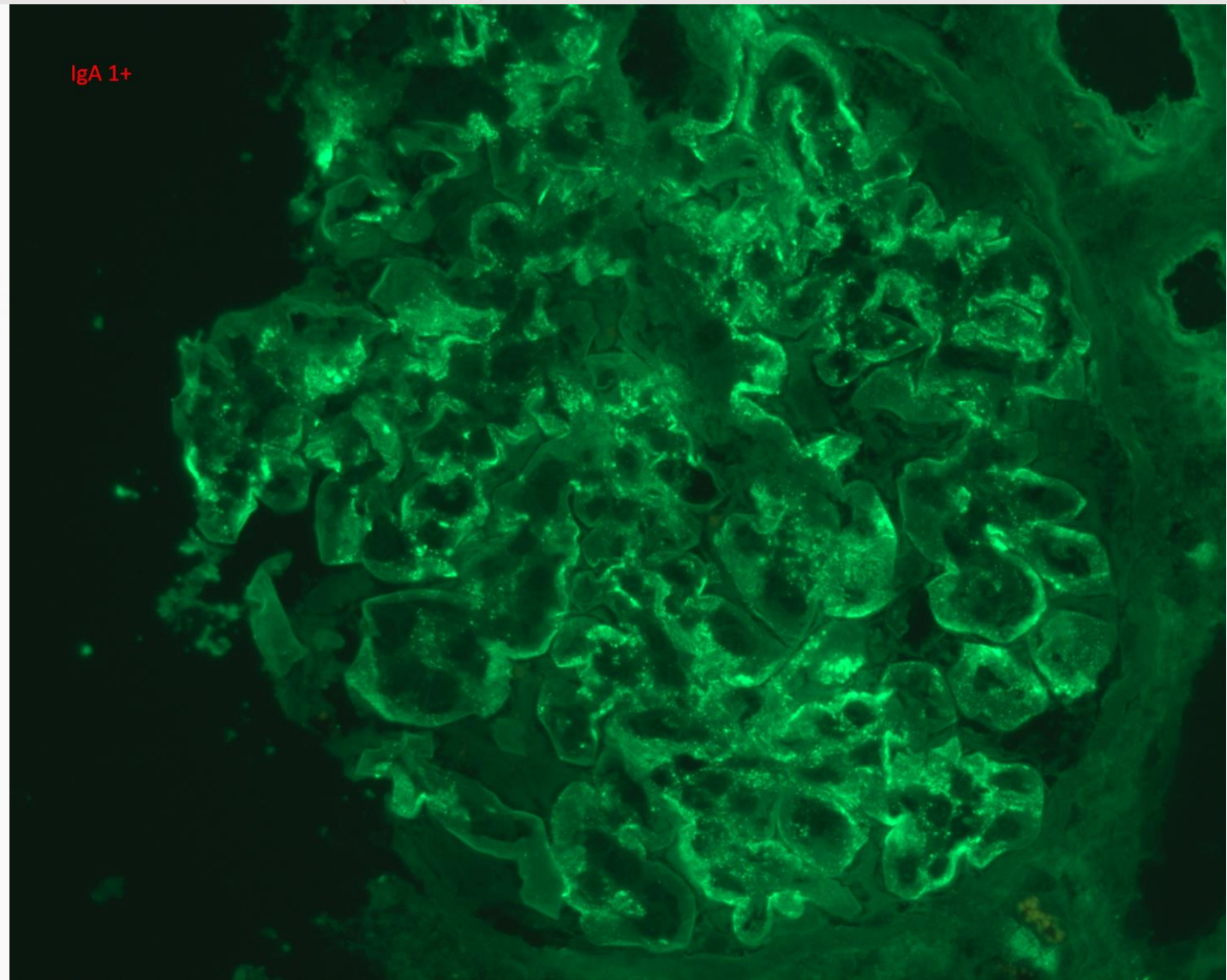
## Immunofluorescence



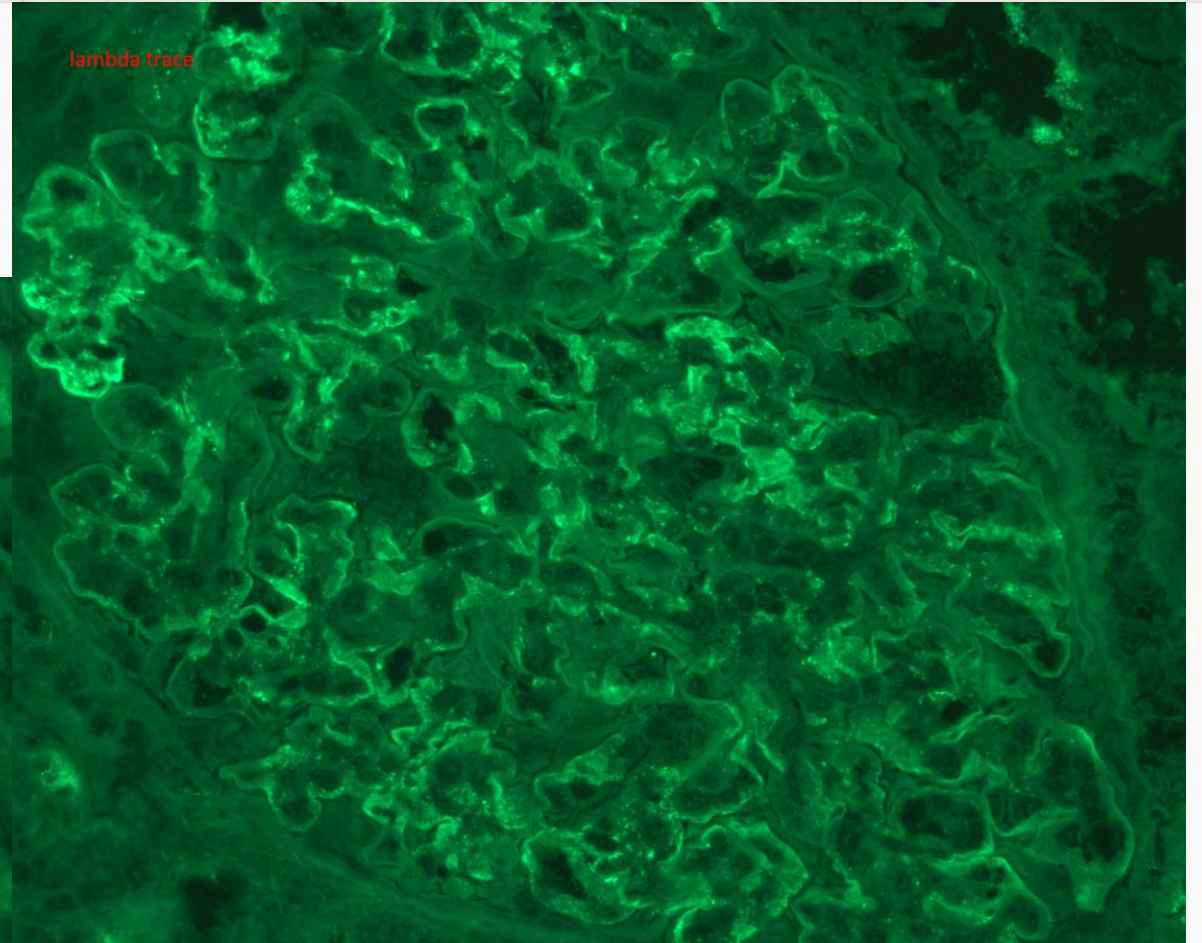
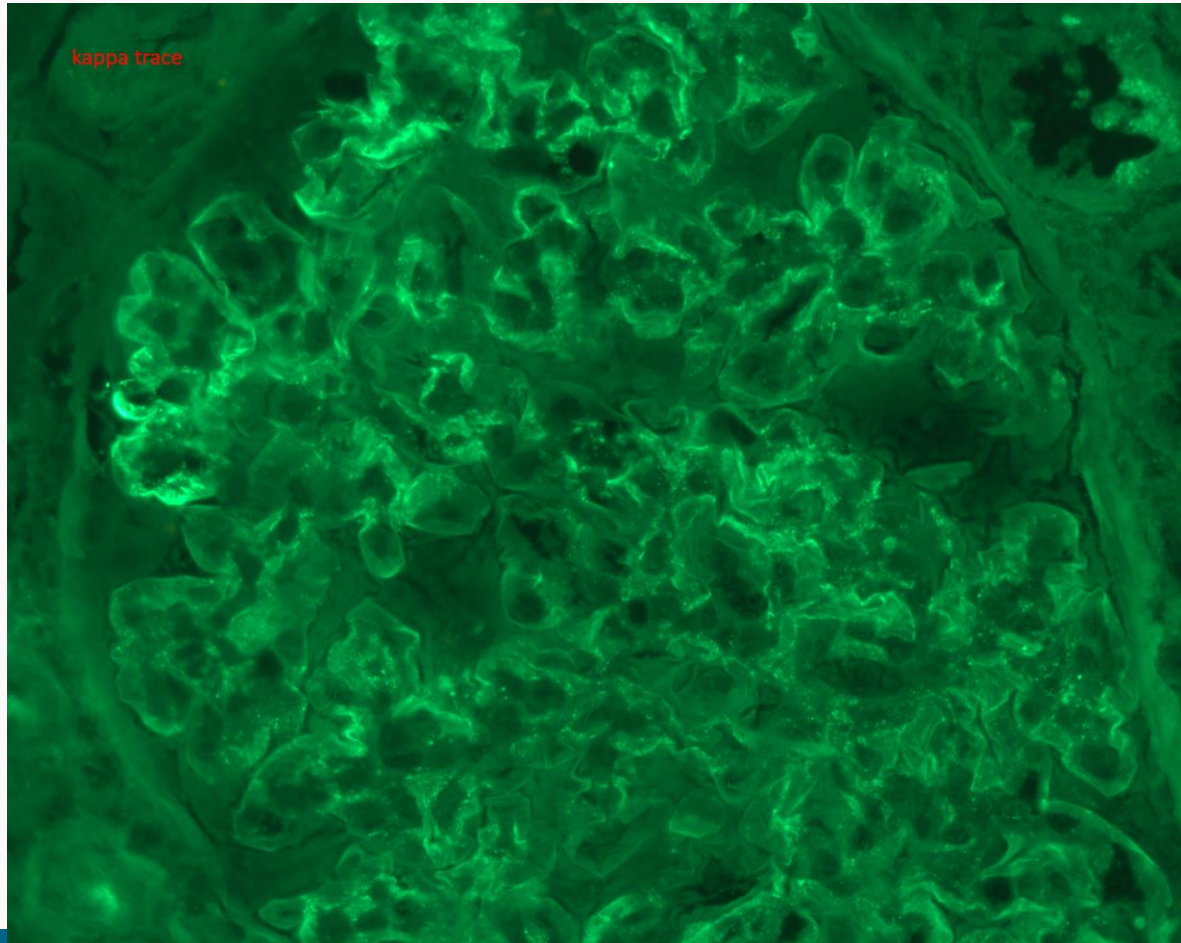
C3c: 2 to 3+ granular capillary wall and mesangial staining.



IgA: 1+ granular capillary wall and mesangial staining



Kappa and lambda: trace granular capillary wall and mesangial staining



# IF

IgG	negative to trace granular capillary wall and mesangial staining
IgM	negative
Fibrinogen	negative

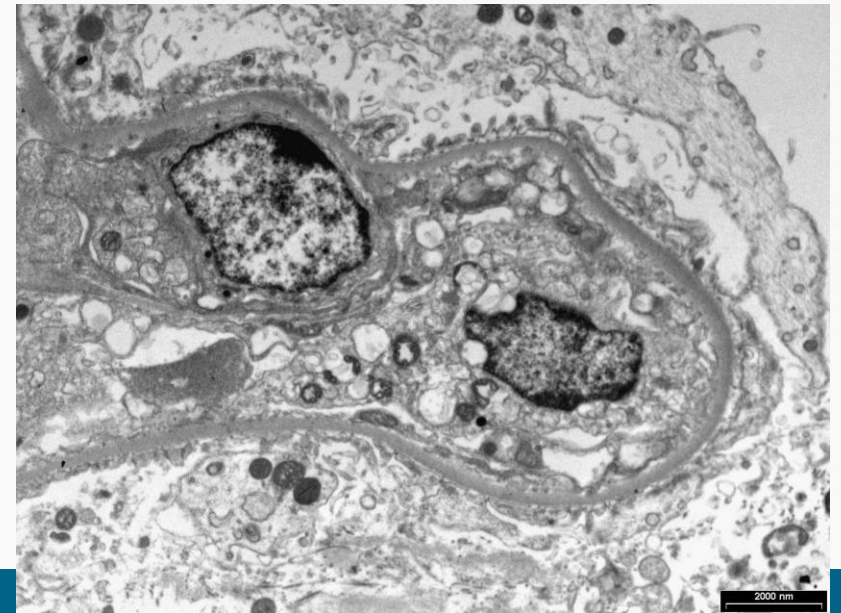
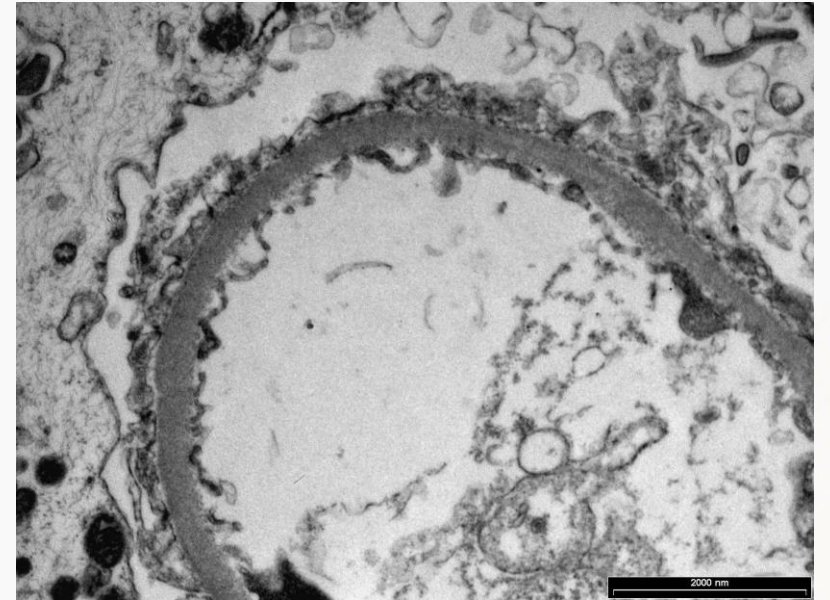
# Summary of renal biopsy

**Diffuse endocapillary proliferative glomerulonephritis, with dominant C3 and some IgA on IF**

# EM

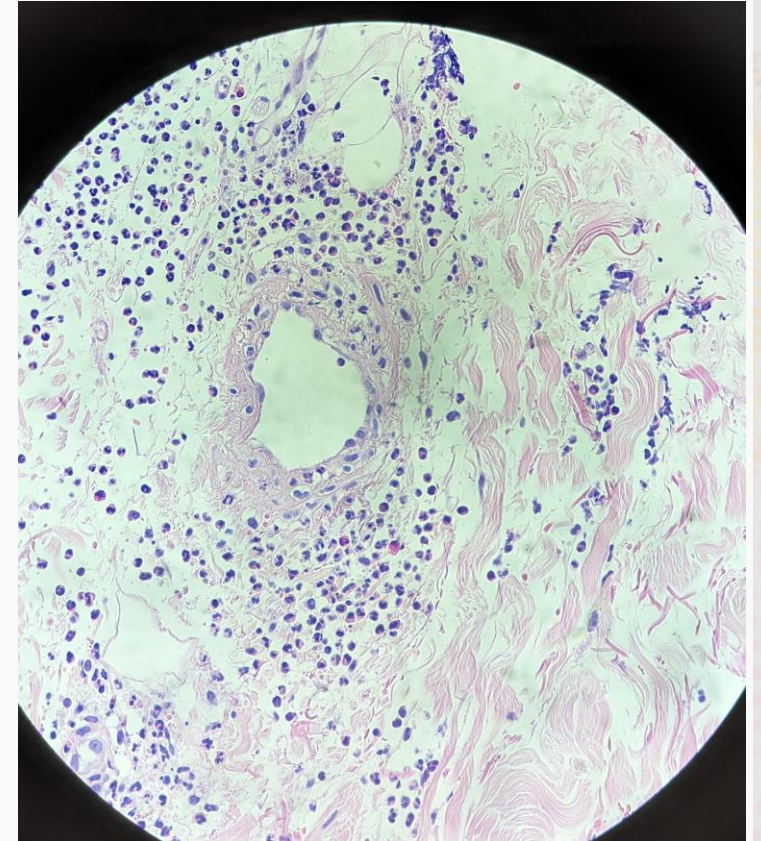
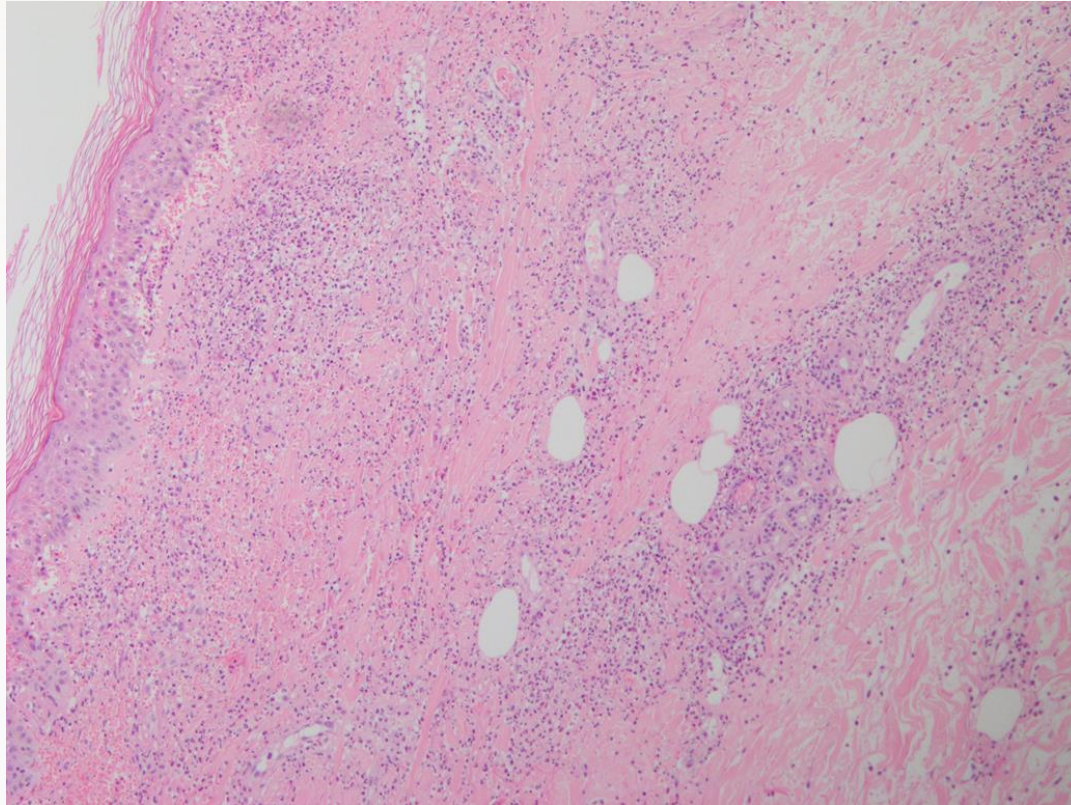
Moderate to severe foot process effacement. No deposits.

No diagnostic features of an immune complex glomerulonephritis are present. The diagnostic glomeruli may not have been included in the EM sample.

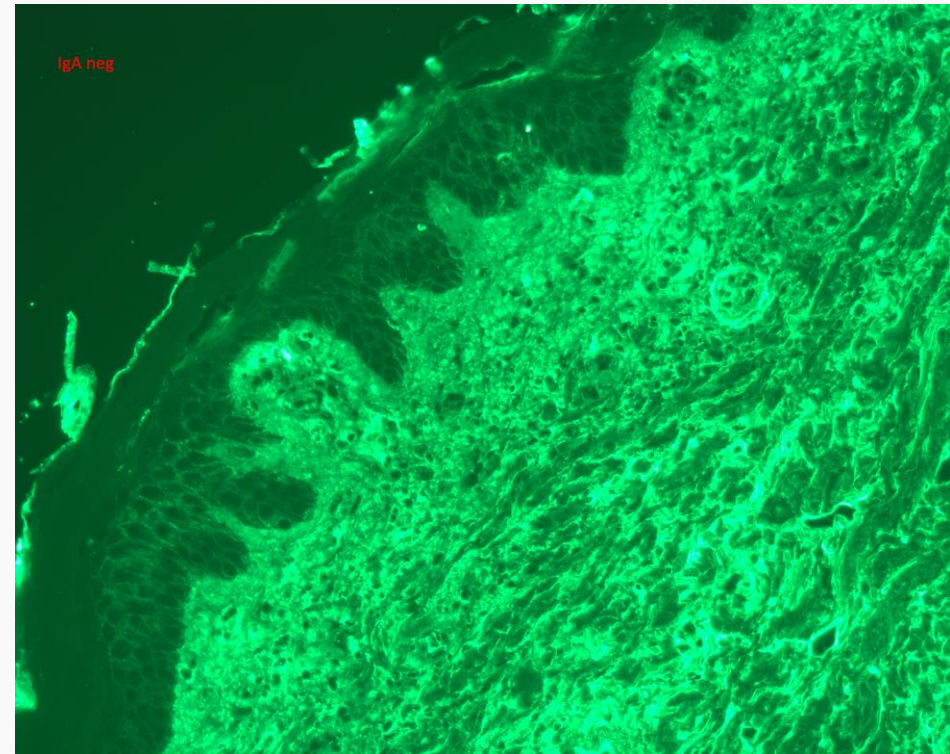
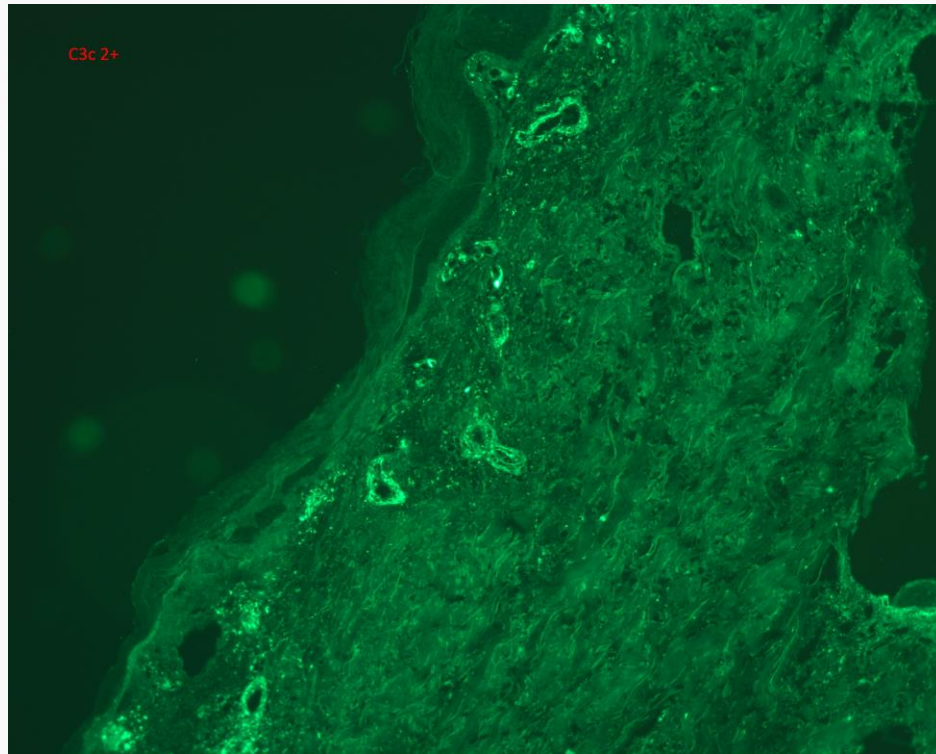


# Skin biopsy

- Leukocytoclastic vasculitis
- Occasional eosinophils seen
- Stains for microorganisms negative



# Skin IF: C3 (2+) and IgA (neg)

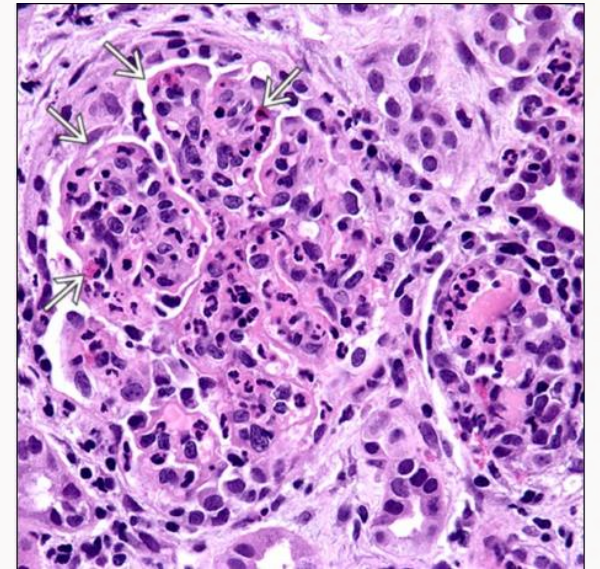


# DDx of the renal biopsy

- **IgA dominant acute postinfectious glomerulonephritis**
- Streptococcal postinfectious glomerulonephritis
- Non-streptococcal postinfectious glomerulonephritis
- C3 glomerulonephritis
- IgA nephropathy
- Cryoglobulinemic glomerulonephritis
  
- Why IgA dominant acute postinfectious GN is favored
  - Histology of acute proliferative glomerulonephritis
  - Dominant C3 followed by IgA on IF

# Streptococcal post-infectious GN

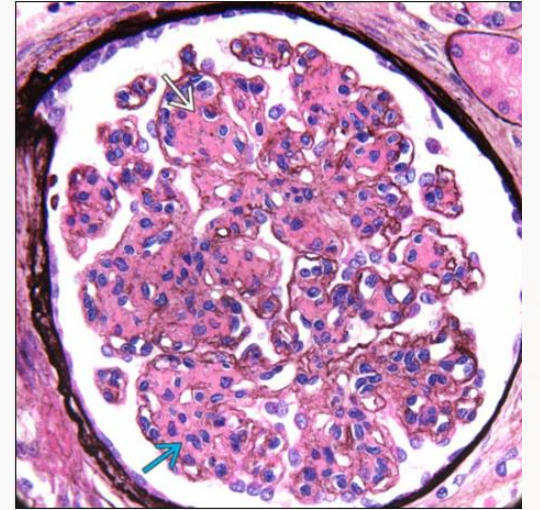
- Streptococcus pyogenes, group A, beta-haemolytic
- Acute immune complex disease, activates alternative complement pathway
- Low C3, positive ASO or anti-DNAse B
- Microscopy: diffuse, global involvement;  
exudative proliferative pattern  
(accentuated lobularity with abundant neutrophils)
- IF: C3 positive (can get C3-dominant in later stages), IgG
  - IgA rare
- EM: subepithelial deposits



# Non-streptococcal postinfectious GN

- Acute GN occurring after exposure to infectious agent other than group A Streptococcus
- Staphylococcus most common cause in older patients (~ 50%)
- Hypocomplementemia in 30-50%
- LM (similar to PSAGN): Diffuse proliferative most common, often exudative; crescents may be present
- IF: **IgG and C3**, IgA absent
- EM: subepithelial deposits

# C3 glomerulonephritis



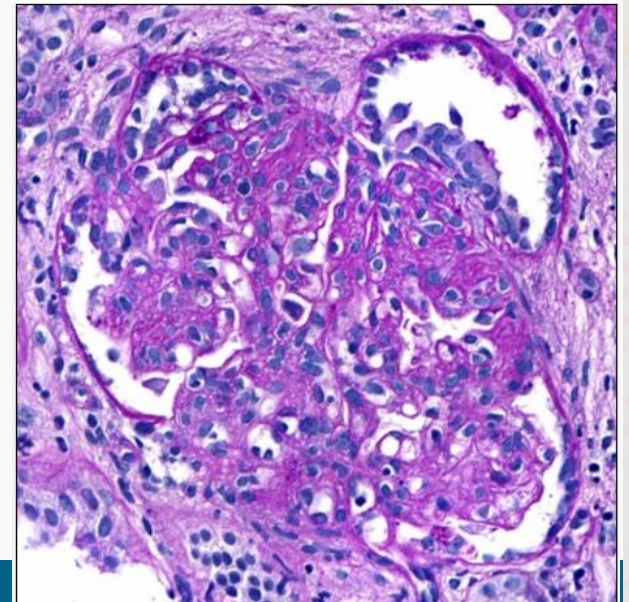
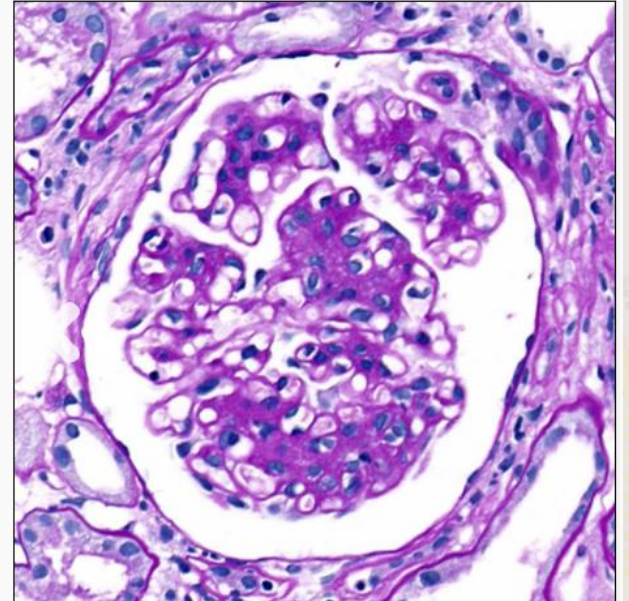
- Dysfunction of alternative complement pathway
- Low C3 in ~ 40% with normal C4
- LM: Various patterns (Membranoproliferative (MPGN) most common- mesangial hypercellularity; GBM double contours)
- IF: **Prominent granular C3 deposits** in mesangium and GBM; IgG, IgM, IgA, &/or C1q may be present but at least 2 levels of intensity less than C3
- EM: Amorphous deposits in mesangium, subendothelial electron-dense deposits

# IgA nephropathy

LM: Mesangial hypercellularity (focal or diffuse) and focal segmental glomerulosclerosis

IF: IgA mesangial deposits (100%), C3 (90%),  
lambda > kappa

EM: Amorphous, electron-dense deposits in  
mesangium



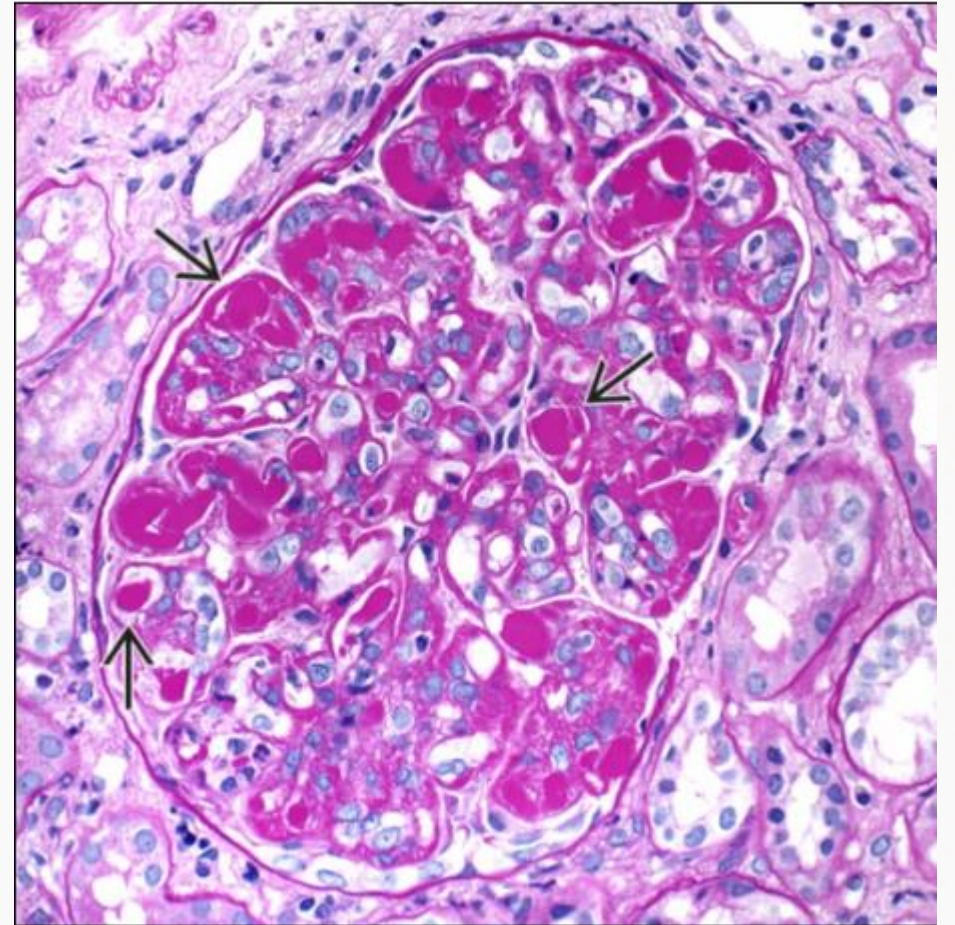
# Cryoglobulinemic glomerulonephritis

Pseudothrombi, MPGN

IF:

Type 1: > 90%  $\kappa$ -light chain and ~ 85% IgG

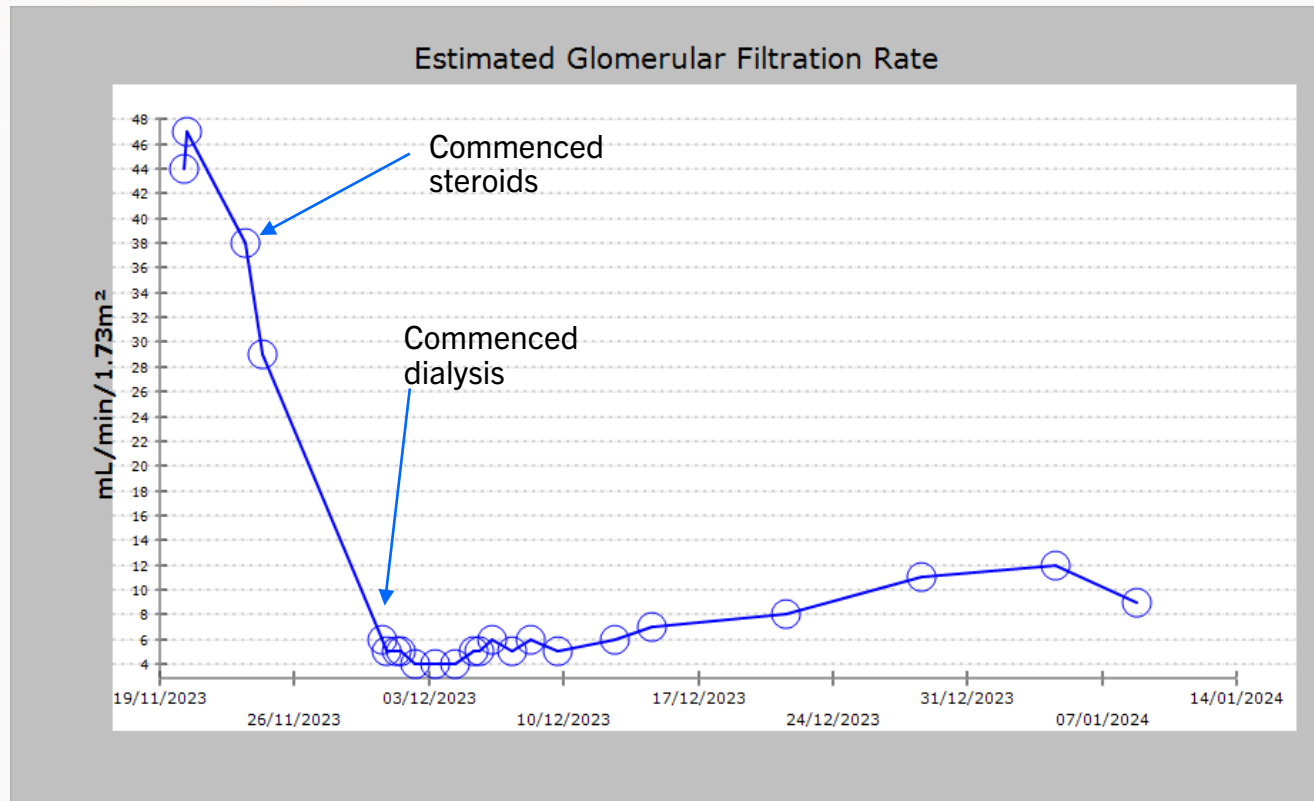
Mixed: IgG, IgM, C3, C1q



# Summary table of ddx on biopsy

vs IgA postinfectious GN	Similarities	Differences
Strep/ non-strep	LM findings	IF: IgA absent
C3 GN	High intensity C3 on IF	LM: MPGN, double contours
IgA nephropathy		LM: Mesangial hypercellularity IF: IgA > C3 Lambda > kappa
Cryoglobulinaemic GN		LM: pseudothrombi IF: Not IgA dominant

# Patient's progress



Covid and pneumonia in Jan  
→ needed to wean off steroids

March- drainage of abdo abscess around HCC resection site

# IgA-dominant postinfectious glomerulonephritis

# Clinical features

Most frequent in older patients

Average age at diagnosis 60 years

61% of patients 65 years or older

M>F (3.9:1)

Underlying diabetes mellitus in 55%

Other predisposing: malignancy (6%), IVDU (4%), alcoholism (4%)

Site of infection:

Skin (51%): cellulitis, surgical wound infection, abscess

Infectious agent

Classically staphylococcus infection,

But other pathogens also associated e.g. gram negative bacteria

# Clinical features

Mean time from onset of infection to renal disease was 4 weeks

## Renal presentations

- Renal failure (acute or rapidly progressive)
- Haematuria
- Proteinuria
- Hypertension

Hypocomplementaemia in 69%

## Prognosis

- 16% full recovery
- 43% persistent renal dysfunction
- 41% ESRD

# Relation to the vasculitic rash

A paper from 2013 (Satoskar et al), found that out of 37 patients diagnosed with culture-proven staphylococcus infection-associated GN with glomerular IgA deposits, 22% had an accompanying purpuric skin rash with LCV

# Pathology

Endocapillary proliferative and exudative glomerulonephritis  
Identical to poststreptococcal GN

In 33%- pure mesangial proliferative GN and 4% crescentic GN

IF: IgA sole or dominant immunoglobulin

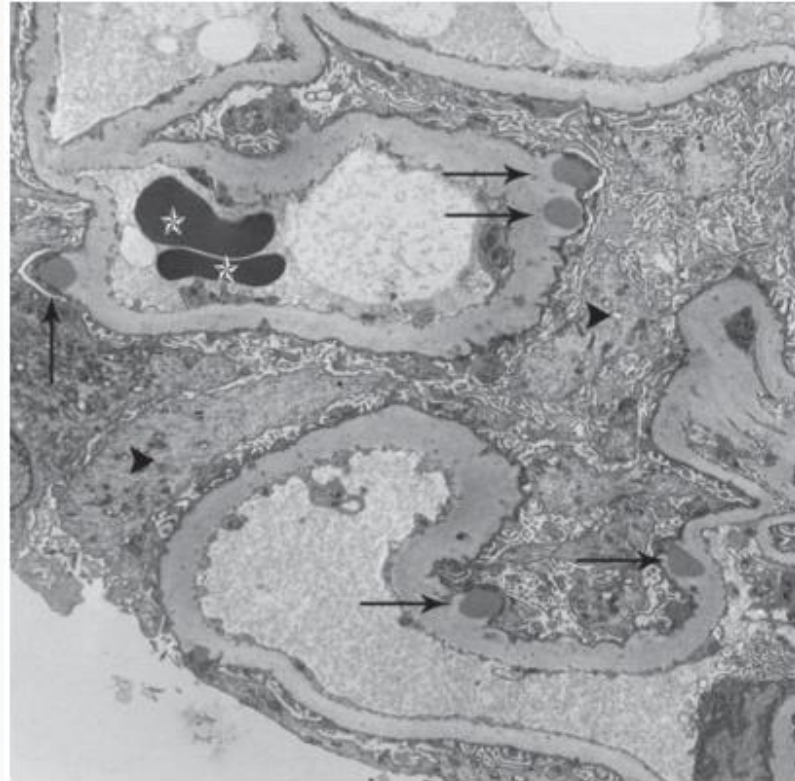
+/- weaker staining for IgG and/or IgM

High-intensity staining for C3, stronger than IgA in majority

Punctate deposits

EM: Mesangial electron-dense deposits + sub-epithelial deposits (with hump shaped appearance)

# Electron Microscopy



Hump-shaped subepithelial  
electron-dense deposits (arrows)

# Pathogenesis

- Not well understood
- Likely host-pathogen interactions
- Activation of selective IgA responses
- Staphylococcus enterotoxin (acts as superantigen)/ other cell surface antigens
- Possible role of diabetic milieu
  - Increased serum IgA and Ig-A containing immune complexes in diabetics

# Treatment

- First choice of treatment – treating infection e.g. antibiotics
- No definite evidence for use of steroids
  - E.g. Anjali *et al.* report worse outcomes due to immunosuppression
  - E.g. Okuyama *et al.* case report where patient responded to steroids in addition to antibiotics

# Conclusion

- Consider IgA-dominant postinfectious glomerulonephritis in elderly patient with comorbidities (especially diabetes) presenting with acute kidney injury/ haematuria/ proteinuria
- Pathology: Endocapillary proliferative and exudative glomerulonephritis
- IF: IgA dominant/ co-dominant with C3 staining > IgA
- EM: Mesangial + subepithelial deposits
- Poor prognosis

# References

- Colvin & Chang (2023). Diagnostic Pathology: Kidney Diseases. Elsevier
- Nasr, S. H., & D'Agati, V. D. (2011). IgA-dominant postinfectious glomerulonephritis: a new twist on an old disease. *Nephron Clinical Practice*, 119(1), c18-c26.
- Satoskar, A. A., Molenda, M., Scipio, P., Shim, R., Zirwas, M., Variath, R. S., ... & Nadasdy, T. (2013). Henoch-Schönlein purpura-like presentation in IgA-dominant Staphylococcus infection-associated glomerulonephritis—a diagnostic pitfall. *Clinical Nephrology*, 79(4), 302-312.
- Some of the images used in the DDX section are from ExpertPath (Elsevier Health)
- Okuyama, S., et al. "Successful treatment of post-MRSA infection glomerulonephritis with steroid therapy." *Clinical nephrology* 70.4 (2008): 344.