Glomerulonephritis

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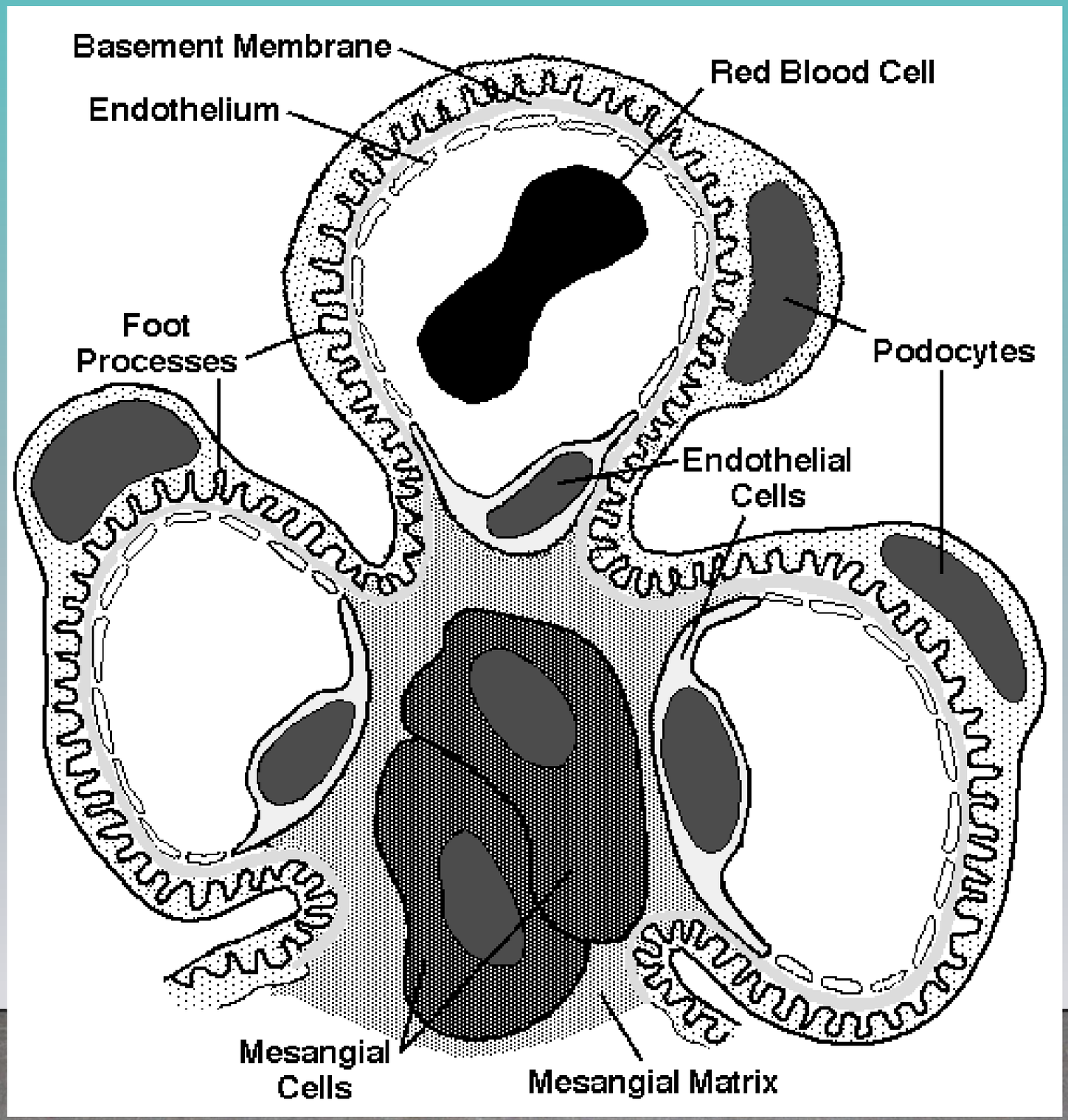
- Glomerulonephritis is inflammation of the glomeruli

- Glomerulopathy is a disease of the glomeruli when there is no evidence of inflammation.

- Glomerular Injury : impairment of selective filtering properties of kidney leading to decrease GFR

Molecules normally not filtered such as constituents of the blood, pass into the urine and are excreted

Normal structure of the glomerulus



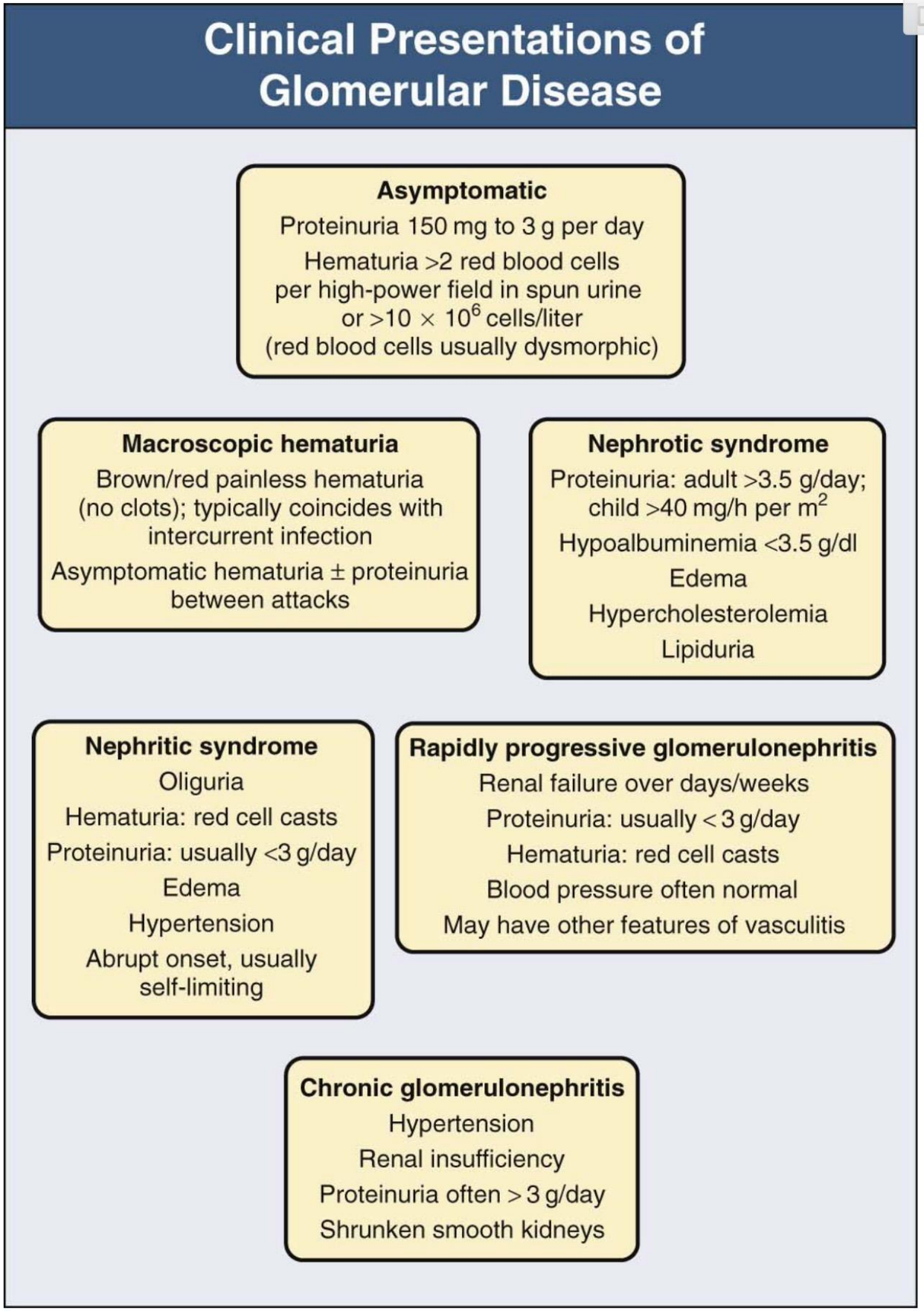


Figure 15.1: Clinical presentations of glomerular disease.

Possible Clinical Presentation

- Asymptomatic proteinuria
- Asymptomatic Hematuria
- Macroscopic hematuria
- Nephrotic syndrome
- Nephritic syndrome
- Rapidly progressive GN
- Chronic glomerulonephritis

History of glomerular disease

- Hematuria, Foamy urine
- Edema (lower limb and periorbital edema)
- HTN
- Multisystem disease associated with GN as
  (Diabetes , Hypertension, amyloid, lupus and vasculitis)
- Positive family Hx of renal disease or ESRD
- Family Hx of Alport's with hearing loss, Focal Segmental Glomerulosclerosis, Hemolytic Uremic Syndrome, uncommon familial IgA
- Patient with Morbid obesity associated with FSGS

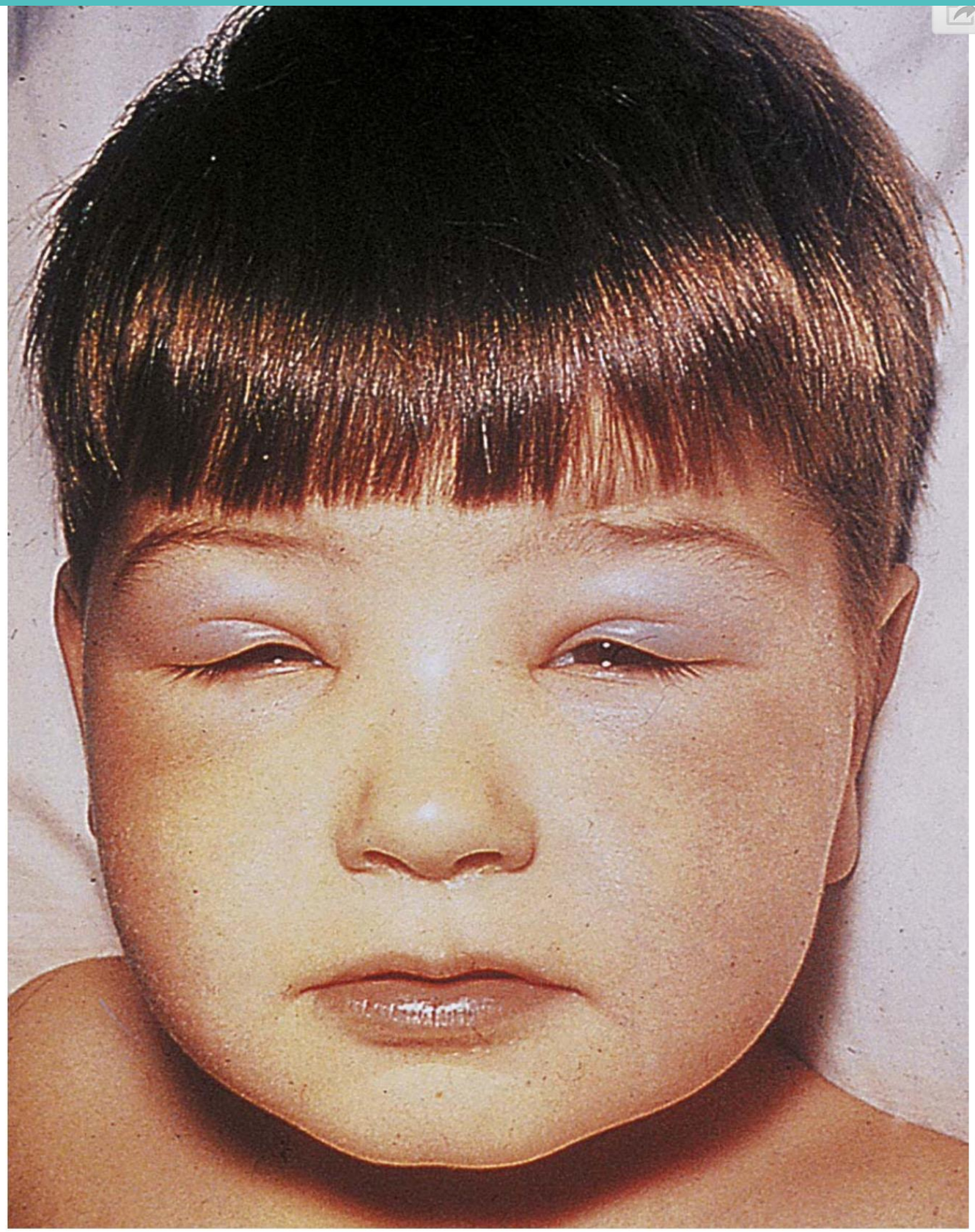


Figure 15.2: Nephrotic edema. Periorbital edema in the early morning in a nephrotic child. The edema resolves during the day under the influence of gravity.

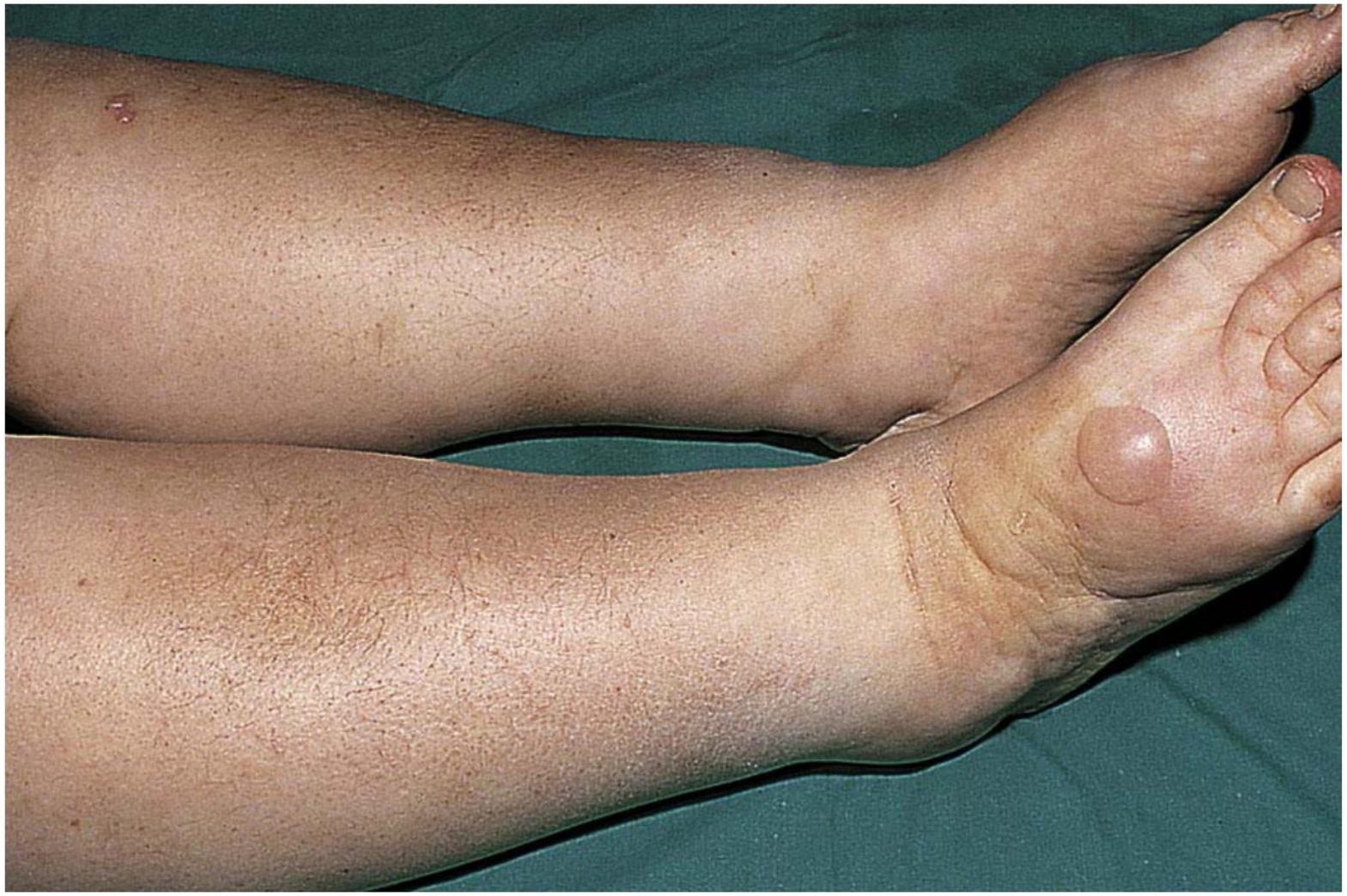


Figure 15.3: Nephrotic edema. Severe peripheral edema in nephrotic syndrome; note the blisters caused by intradermal fluid.

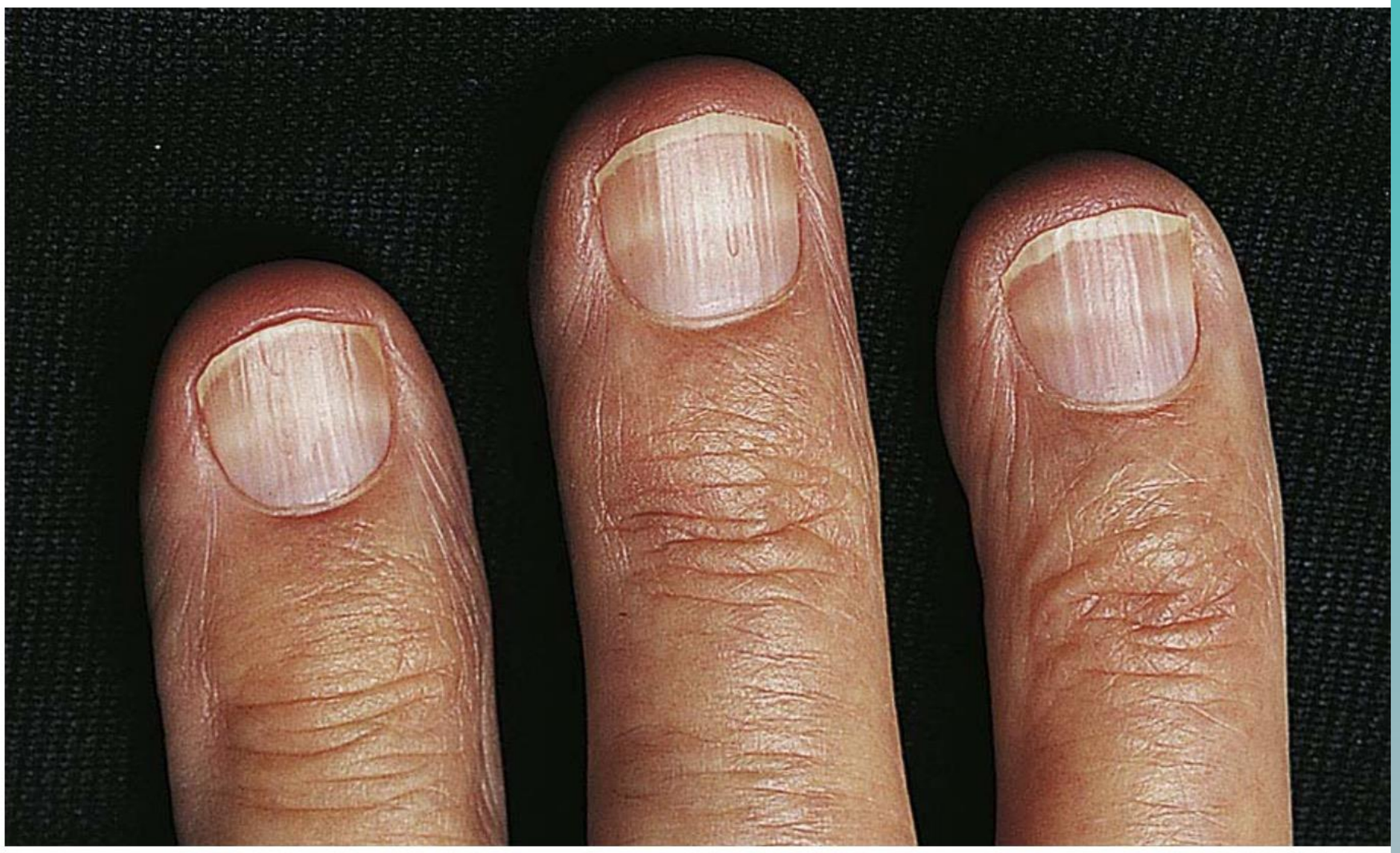


Figure 15.4: Muehrcke's bands in nephrotic syndrome. The white band grew during a transient period of hypoalbuminemia caused by the nephrotic syndrome.

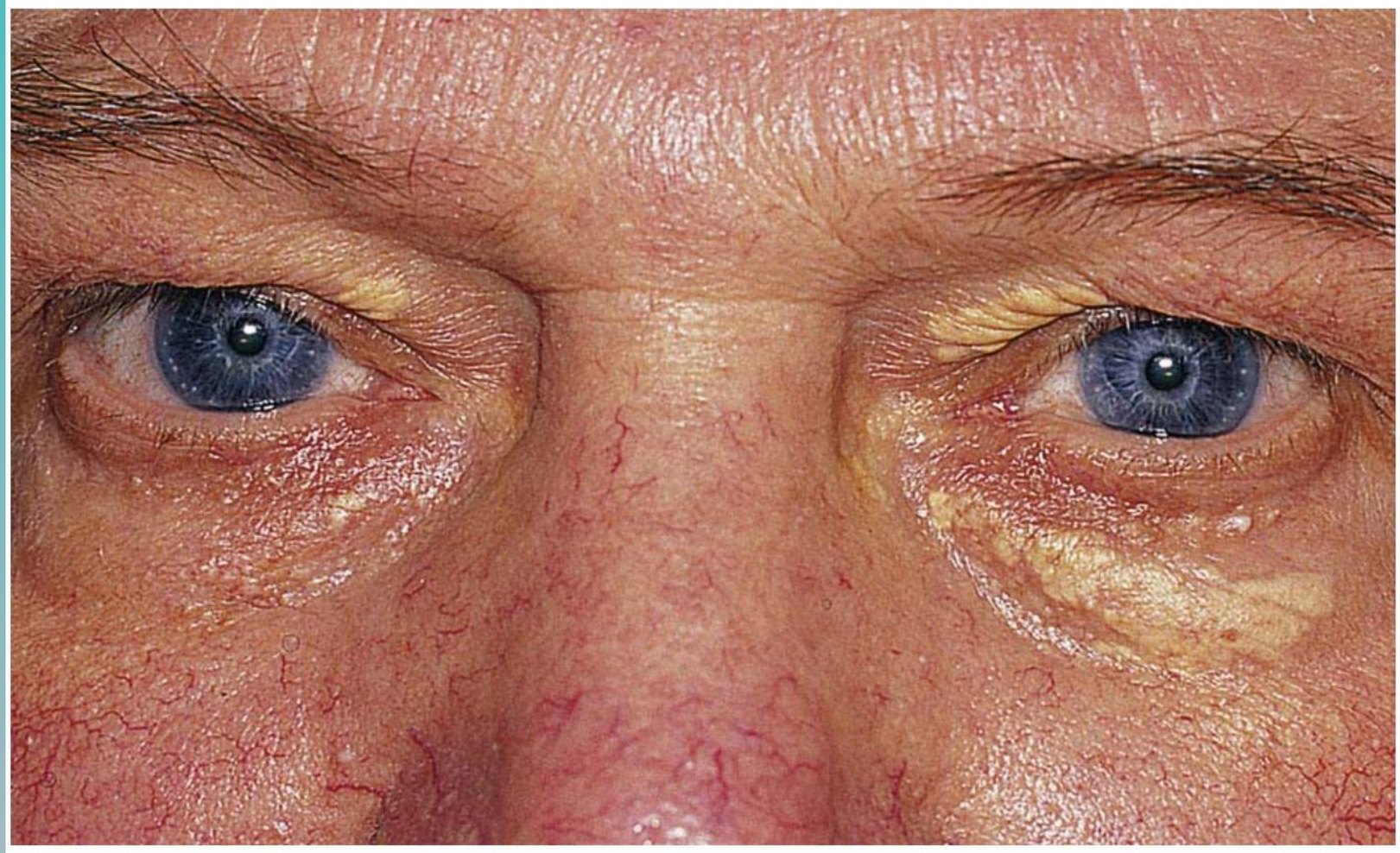


Figure 15.5: Xanthelasmas in nephrotic syndrome. These prominent xanthelasmas developed within a period of 2 months in a patient with recent onset of severe nephrotic syndrome and serum cholesterol level of 550 mg/dl (14.2 mmol/l).

History

- Medications use :

NSAIDs and interferon with minimal change

Penicillamine , mercury with membranous nephropathy

Pamidronate, heroin with FSGS

Cyclosporin, tacrolimus and Oral contraception with HUS

- Hx of recent or persistent infection (as streptococcal, infective endocarditis and viral infection)

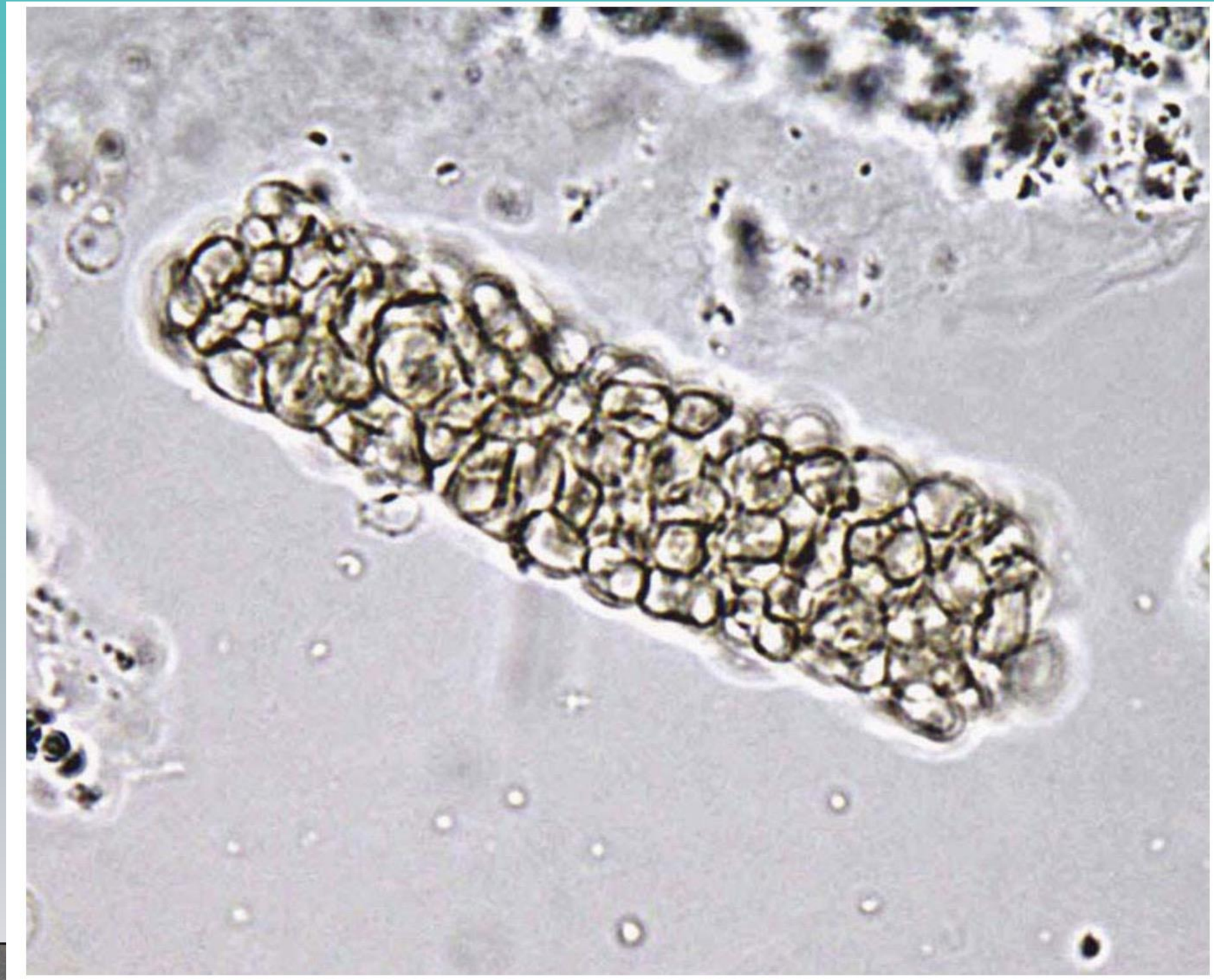
- Hx of malignancy (solid as lung ,breast and GI with membranous nephropathy OR Hodgkin's Lymphoma in minimal change and Non HL in membranoprolifertive GN)

Physical examination

- Hypertension
- Dependent pitting edema
- Periorbital edema
- Genital edema, abdominal wall, ascites and pleural effusion
- Xanthelasma in nephrotic syndrome
- Muehrcke's bands (white nails and white bands in nephrotic syndrome)
- Pulmonary sign in Pulmonary renal sydrome
- Palpable purpura in vasculitis, SLE, Cryoglobulinemia or endocarditis

Laboratory Studies

- Renal function
- Urine analysis (proteinuria and hematuria)
- Urine microscopy (dysmorphic RBCs, RBCs cast)
- 24 hr urine collection for protein or/and Spot urine protein and creatinine ratio
- serology as ANA, Anti DNA (lupus) , RF, Cryoglobulins (cryoglobulinemia) , anti GBM, ANCA (vasculitis), Antistreptolysim O titer (poststerptococcal GN)



- Urine electrophoresis for monoclonal light chain or heavy chain (myeloma-associated amyloid or light chain deposition disease

- Hepatits B , hepatits C and HIV Infection

- Complement level (C3, C4 and CH50)

Hypocomplementemia in Glomerular Disease

Pathway Affected	Complement Changes	Glomerular Diseases	Nonglomerular Diseases
Classical pathway activation	C3 ↓, C4 ↓, CH50 ↓	Lupus nephritis (especially class IV), mixed essential cryoglobulinemia	
	+ C4 nephritic factor	Membranoproliferative GN type 1	
Alternative pathway activation	C3 ↓, C4 normal, CH50 ↓	Poststreptococcal GN GN associated with other infection* Endocarditis, shunt nephritis, hepatitis B Hemolytic-uremic syndrome	Atheroembolic renal disease
	+ C3 nephritic factor	Membranoproliferative GN type II (Dense Deposit Disease)	
Reduced complement synthesis	Acquired		Hepatic disease Malnutrition
	Hereditary C2 deficiency Factor H deficiency	Lupus nephritis Familial hemolytic-uremic syndrome Membranoproliferative GN type II	

- Renal US (normal size, Vs Small (chronic Renal disease) or large kidneys (DM, Amyloidosis or HIV)

- Renal Bx

Presentation of glomerular disease

- Nephrotic syndrome / Proteinuria
  - Proteinuria (> 3.5g protein / day)
  - Hypoalbuminemia < 3.5 g/dl
  - Oedema
  - Hypercholesterolemia, Lipiduria
- Nephritic syndrome / Haematuria
  - Haematuria
  - Oligouria
  - Proteinuria < 3g/day
  - Hypertension
  - Edema

- Progressive renal failure
  - — Renal failure over days/ weeks
  - — proteinuria < 3 g/day
  - — hematuria : RBCs cast
  - — Other features of vasculitis
- Chronic Glomerulonephritis
  - — HTN
  - — Renal insufficiency
  - — Proteinuria often > 3 g/ day
  - — Small kidneys

Classification of glomerular disease

- How many glomeruli?
  - Focal = only some glomeruli
  - Diffuse = all glomeruli affected
- How much of a single glomerulus?
  - Segmental = only part of the glomerulus
  - Global = the entire glomerulus
- Primary vs Secondary
  - primarily renal disease vs renal complication of systemic disease

Glomerular diseases associated with nephrotic syndrome

- Primary
  - Minimal change disease
  - Membranous GN
  - Focal segmental glomerulosclerosis (FSGS)
- Secondary
  - Diabetic nephropathy
  - Amyloidosis

Complication of Nephrotic syndrome

- Infection : caused by

  a- loss of immunoglobulin

  b- the edema act as culture media

  c- malnutrition

  d- use of immunosupressive agent

- Acute renal failure: prerenal failure, Acute tubular necrosis and renal vein thrombosis

- Growth retardation in paediatrics and malnutrition

- Hypercoagulability (thrombosis) : lead to arterial and venous thrombosis

a- higher concentration of factor I,II,V,VII,VIII,X and fibrinogen

b- lower level of anticoagulant as antithrombin III

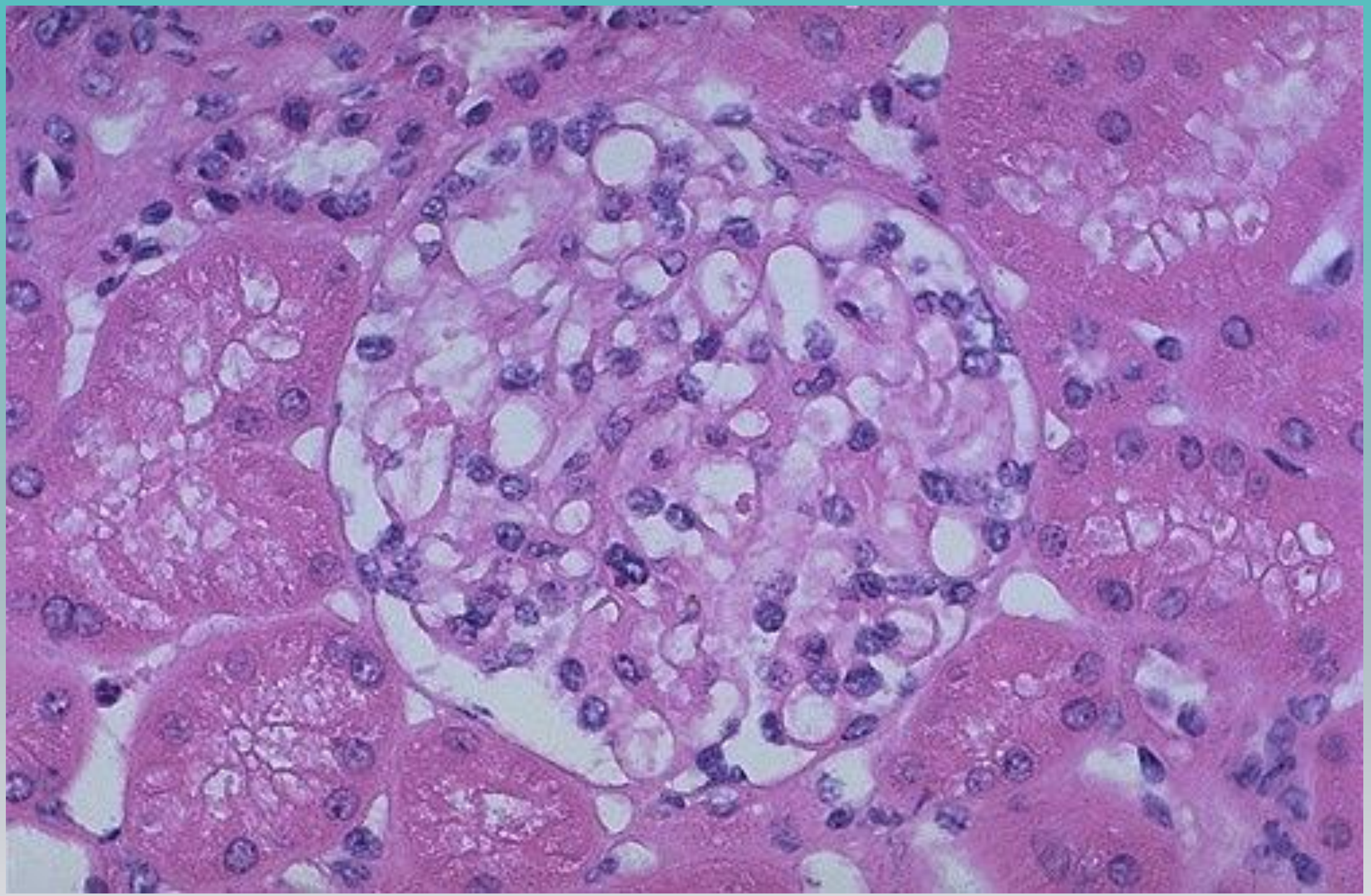
c- decrease fibrinolysis

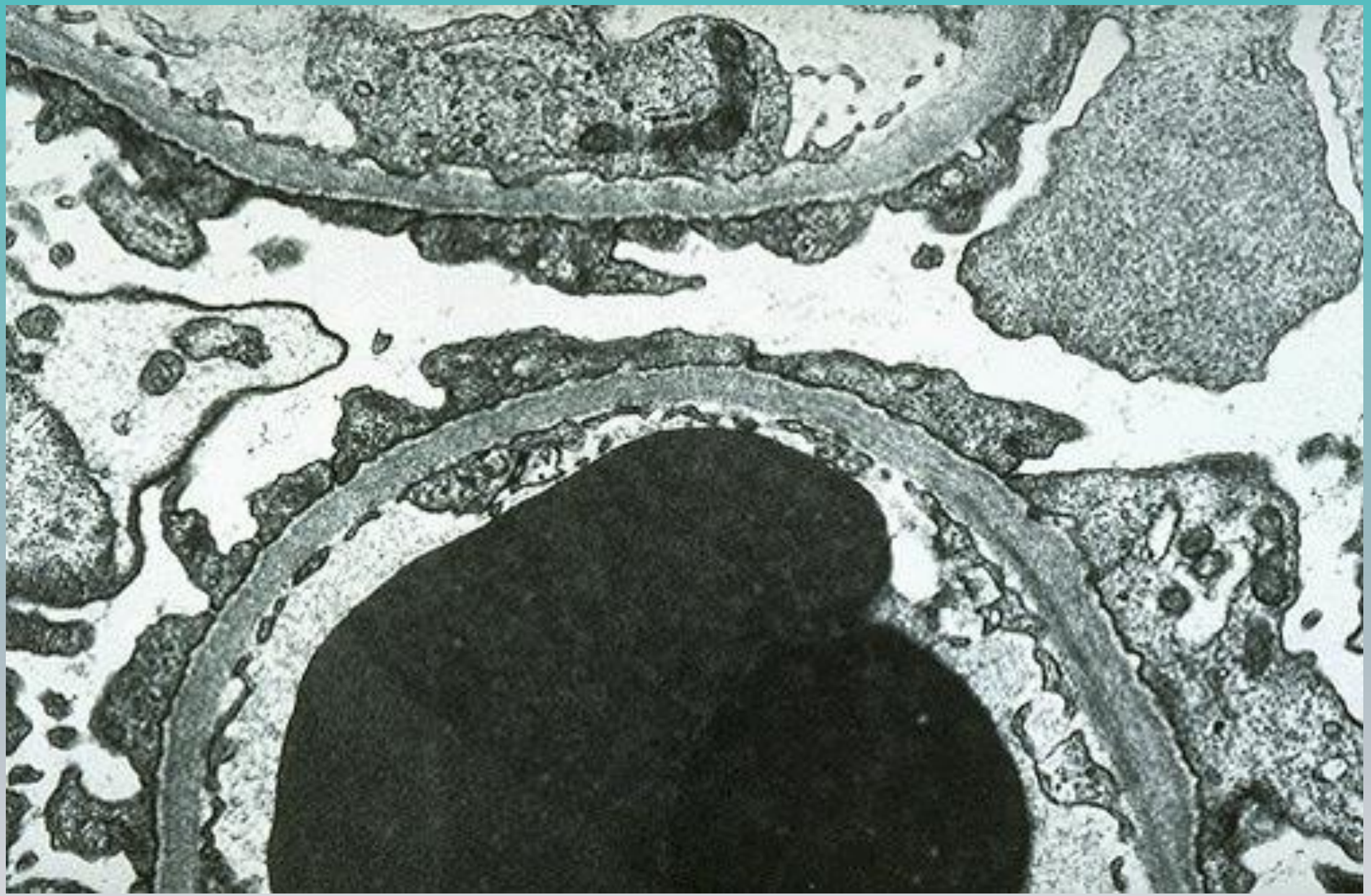
d- higher blood viscosity

e- increase platelet aggregation

Minimal change disease

- Commonest cause of nephrotic syndrome in children
- Can occur in adults
- Characterised by
  - Lack of glomerular changes on light microscopy
  - Lack of immune deposits
  - Good response to steroids
  - Electron microscopy (EM) – Fusion of podocyte foot processes
- Pathogenesis
  - Circulating factor causing damage to podocytes (glomerular epithelial cells)





Minimal change disease

- Most cases of minimal change disease are idiopathic
- it can be secondary yo drugs, malignancy or allergens

Factors Associated with the Onset of Nephrotic Syndrome in Minimal Change Disease
Drugs
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Interferon alfa
Lithium: rare (usually causes chronic interstitial nephritis)
Gold: rare (usually causes membranous nephropathy)
Allergy
Pollens
House dust
Insect stings
Immunizations
Malignancy
Hodgkin's disease
Mycosis fungoides
Chronic lymphocytic leukemia: uncommon (usually associated with membranoproliferative glomerulonephritis)

Membranous GN

- The most common cause of nephrotic syndrome in adults
- Idiopathic (85%) or secondary (15%) to:
  - Neoplasms (lung, colon, melanoma)
  - Autoimmune disease (SLE, thyroiditis)
  - Infections (Hep B, syphilis, malaria)
  - Drugs (Penicillamine, gold)
- 40% progress to chronic renal failure (CRF)
- Pathogenesis
  - Subepithelial immune deposits
  - Thickening of BM between deposits – eventually envelopes and covers the deposits

Clinical Features of Membranous Nephropathy

Rare in children – <5% of total cases of nephrotic syndrome

Common in adults – 15% to 50% of total cases of nephrotic syndrome, depending on age. Increasing frequency after age 40 years.

Males > females in all adults groups

Caucasians > Asians > African-Americans > Hispanics

Nephrotic syndrome in 60% to 70%

Normal or mildly elevated BP at presentation

"Benign" urinary sediment

Non-selective proteinuria

Tendency to thromboembolic disease (DVT, RVT, PE)

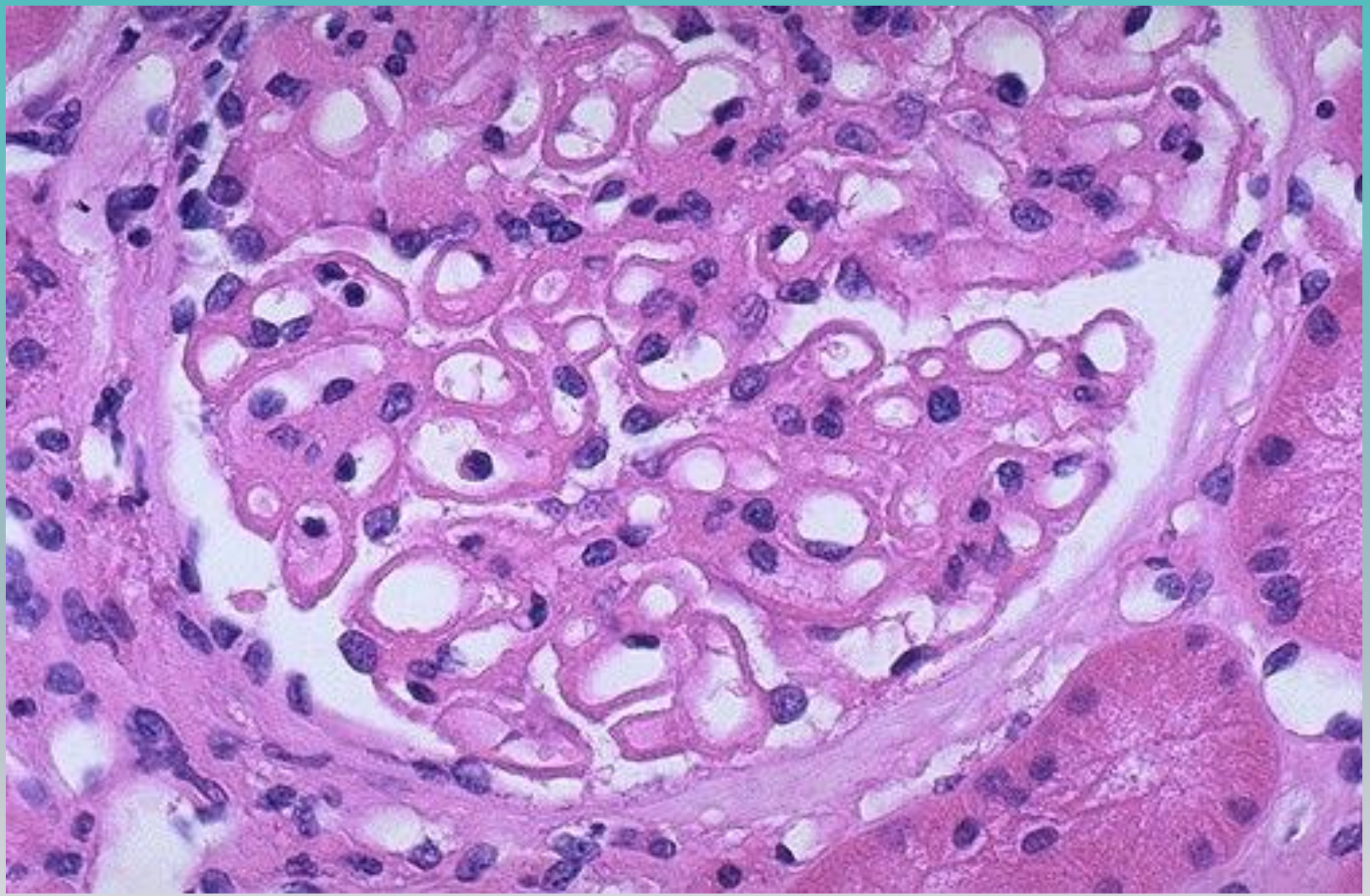
Secondary causes: infection, drugs, neoplasia, systemic lupus erythematosus

Major causes of membranous nephropathy

Idiopathic - may represent autoantibody against a podocyte antigen such as PLA2R
Systemic lupus erythematosus (WHO Class V)
Drugs:
Penicillamine
Bucillamine
Gold salts
Anti-TNF therapy
Tiopronin
NSAIDs
Hepatitis B virus
Hepatitis C virus (rare)
Malignancy (may not be causative)
Hematopoietic cell transplant / GVHD
Status post renal transplantation
Sarcoidosis (uncommon)

Membranous GN

- Light microscopy (LM)
  - Thickened capillary BM
  - BM spikes on silver stain
- Immunofluorescence (IF) – diffuse granular IgG and C3 GBM staining
- Electron microscopy (EM) – subepithelial deposits



Focal Segmantal Glomerulosclerosis

- Histologic lesion rather than disease
- Idiopathic or primary FSGS: typically presented with nephrotic syndrome
- Secondary FSGS : typically presents with non nephrotic proteinuria and renal insufficiency
  - Reduced renal mass with adaptive response to glomerular hypertrophy or hyper filtration (chronic reflux / pyelonephritis / interstitial nephritis)
  - Systemic infection (HIV)
  - Toxin (Heroin, interferon and pamidronate, cyclosporine)
- Genetic disease

Focal Segmental GlomeruloSsclerosis

- Characterized by:
  - Sclerosis of portions of some, not all glomeruli
  - Often progresses to chronic renal failure (CRF)
  - Recurs in 25-50% renal transplants Light microscopy (LM)
  - Focal segmental sclerosis
    - Some normal glomeruli
- Immunofluorescence (IF)
  - IgM and C3 deposition in sclerotic areas
- Electron microscopy (EM)
  - Fusion of podocyte foot processes

Focal Segmantal Glomerulosclerosis

- Clinical presentation:

Either asymptotic proteinuria or full nephrotic syndrome

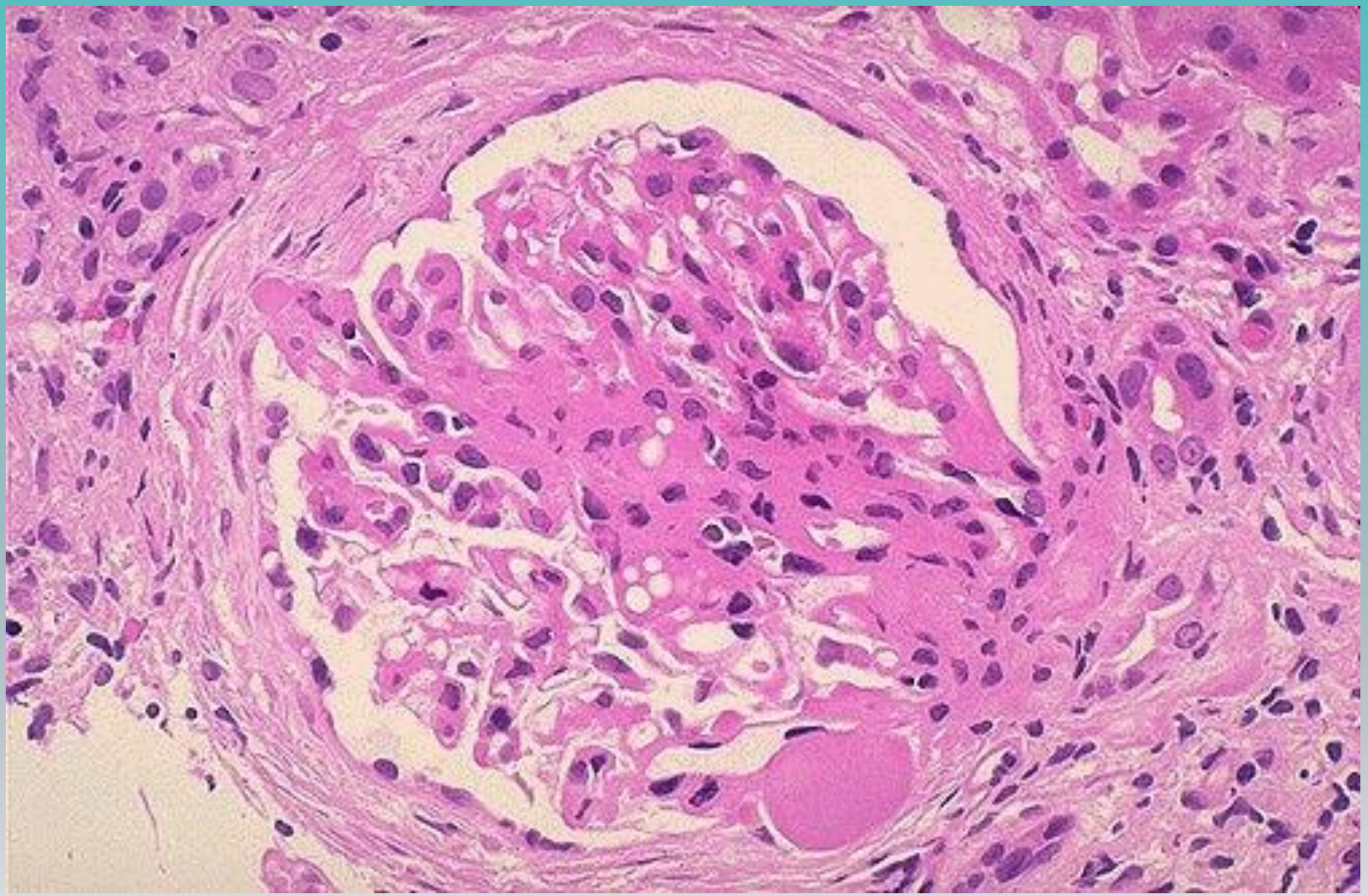
Edema

Hypertension

Microscopic hematuria

decreased GFR

— Secondary FSGS typically have lower level of proteinuria (subnephrotic proteinuria with normal albumin)



Glomerular diseases associated with nephritic syndrome

- Primary
  - Postinfectious / Diffuse proliferative GN
  - Membranoproliferative GN
  - IgA nephropathy (Mesangioproliferative GN)
  - Crescentic GN

- Secondary
  - HSP
  - Systemic vasculitis
  - SLE
  - Systemic sclerosis

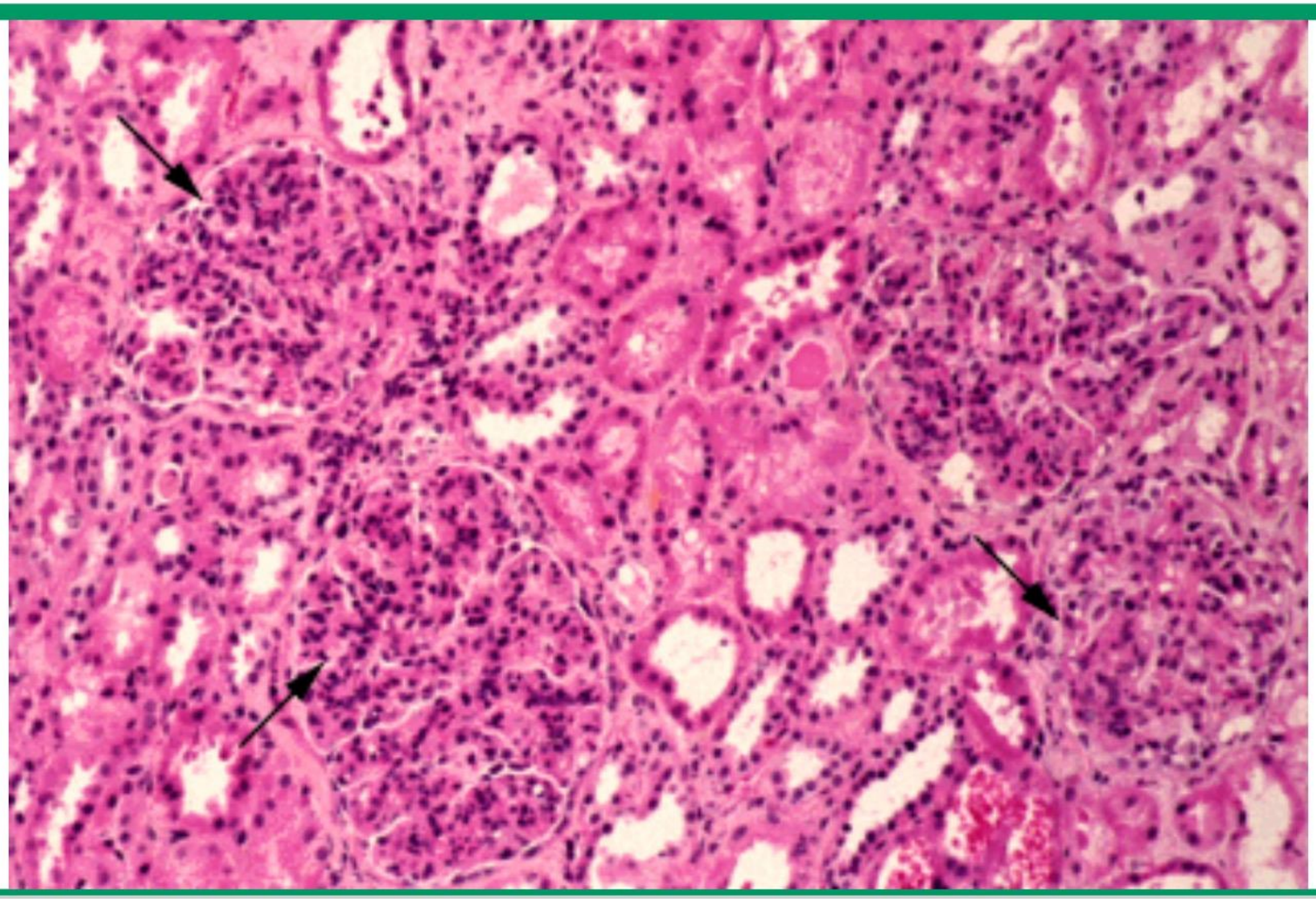
Postinfectious / Diffuse proliferative GN

- Characterised by
  - Onset 1 – 4 weeks after upper respiratory / cutaneous infection with Group A ®-haemolytic streptococci
  - Can occur after a number of other bacterial, viral and parasitic infections
  - Elevated antistreptococcal antibody and decreased C3
  - Secondary to anti-strep antibodies binding to glomerular components
  - Usually resolves within 6 weeks
  - Edema, hematuria and hypertension with acute kidney injury

Postinfectious / Diffuse proliferative GN

- Light microscopy (LM)
  - Diffuse glomerular proliferation and cellular infiltration
- Immunofluorescence (IF)
  - Granular BM IgG, IgM, C3
- Electron microscopy (EM)
  - Dome shaped Subepithelial deposits

Postinfectious glomerulonephritis



Low-power light micrograph showing diffuse, proliferative glomerulonephritis as may be seen in postinfectious glomerulonephritis. The glomeruli are so hypercellular (arrows) that open capillary lumens cannot be seen, and the glomeruli may be hard to distinguish from the surrounding interstitium.

Courtesy of Helmut Rennke, MD.

Graphic 80304 Version 2.0

Membranoproliferative GN

- **Presented with variety of finding** :

- Microscopic hematuria

- No proteinuria , mild proteinuria to nephrotic syndrome

- Severe GN with reduced GFR with HTN

- Low complements

Membranoproliferative GN

- *Classification based on Electron microscopy*

Type I: - Immune complex disease

- Idiopathic or secondary to Neoplasm, Autoimmune disease, Infections, Drugs
- - Subendothelial immune complexes

Type II: - Complement activation

- -BM deposits (dense deposit disease)
- ***Type III :*** as type I with Subendothelial and sub endothelial deposition

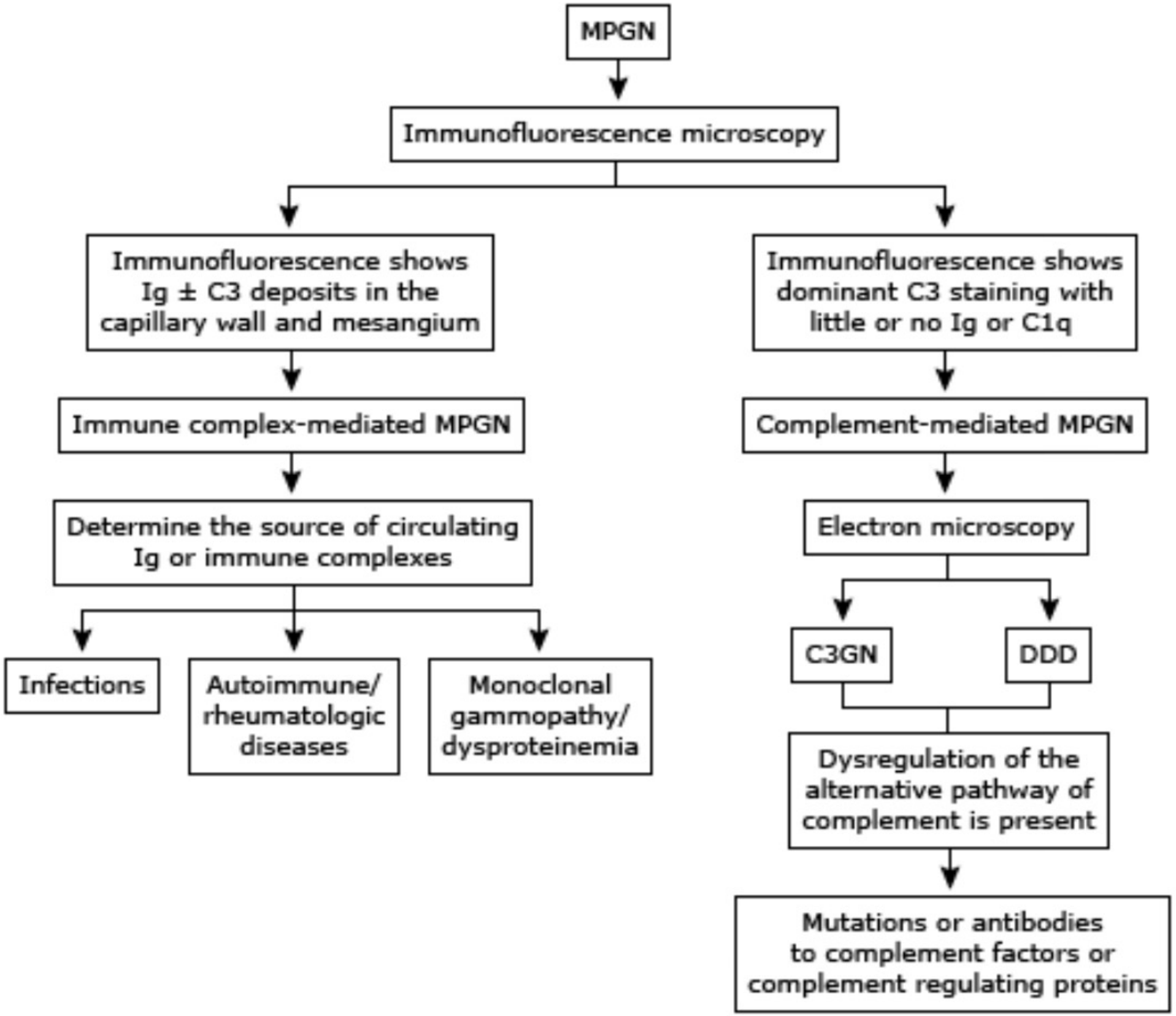
- 50% progress to chronic renal failure (CRF)

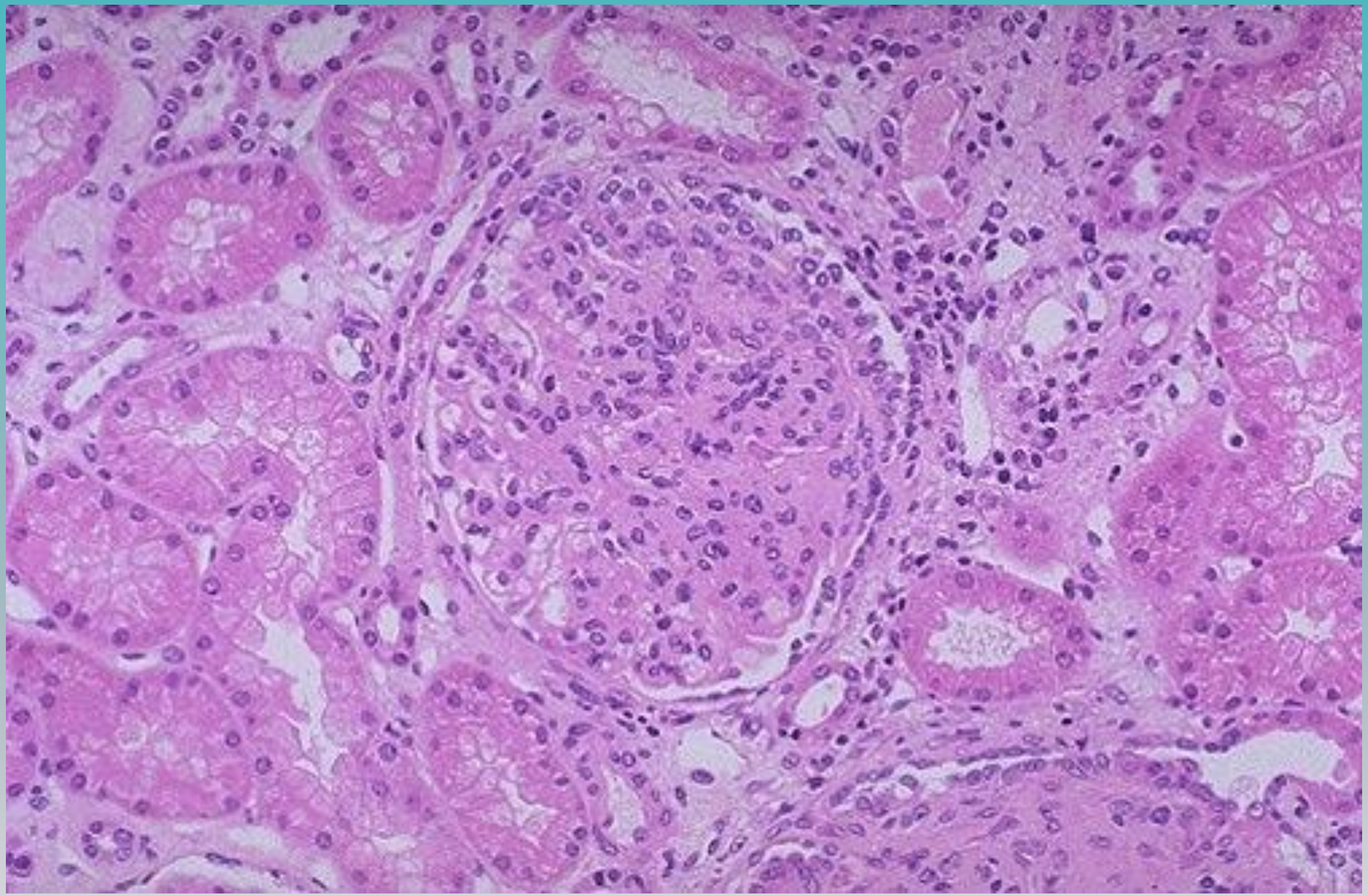
- High recurrence rate in renal transplants

Membranoproliferative GN

- Light microscopy (LM)
  - Mesangial proliferation
  - Thickened capillary loops
  - Glomerular hypercellularity due to mesangial proliferation
  - Mesangial interposition – double GBM's and silver stain (Type I)
- Immunofluorescence (IF)
  - Type I: Granular BM and mesangial IgG, IgM, C3
  - Type II: Granular BM C3
- Electron microscopy (EM)
  - Type I: Subendothelial deposits and mesangial interposition
  - Type II: Dense deposits in GBM

Proposed classification of MPGN





IgA Nephropathy
Mesangioproliferative GN

- Most common primary glomerulonephritis

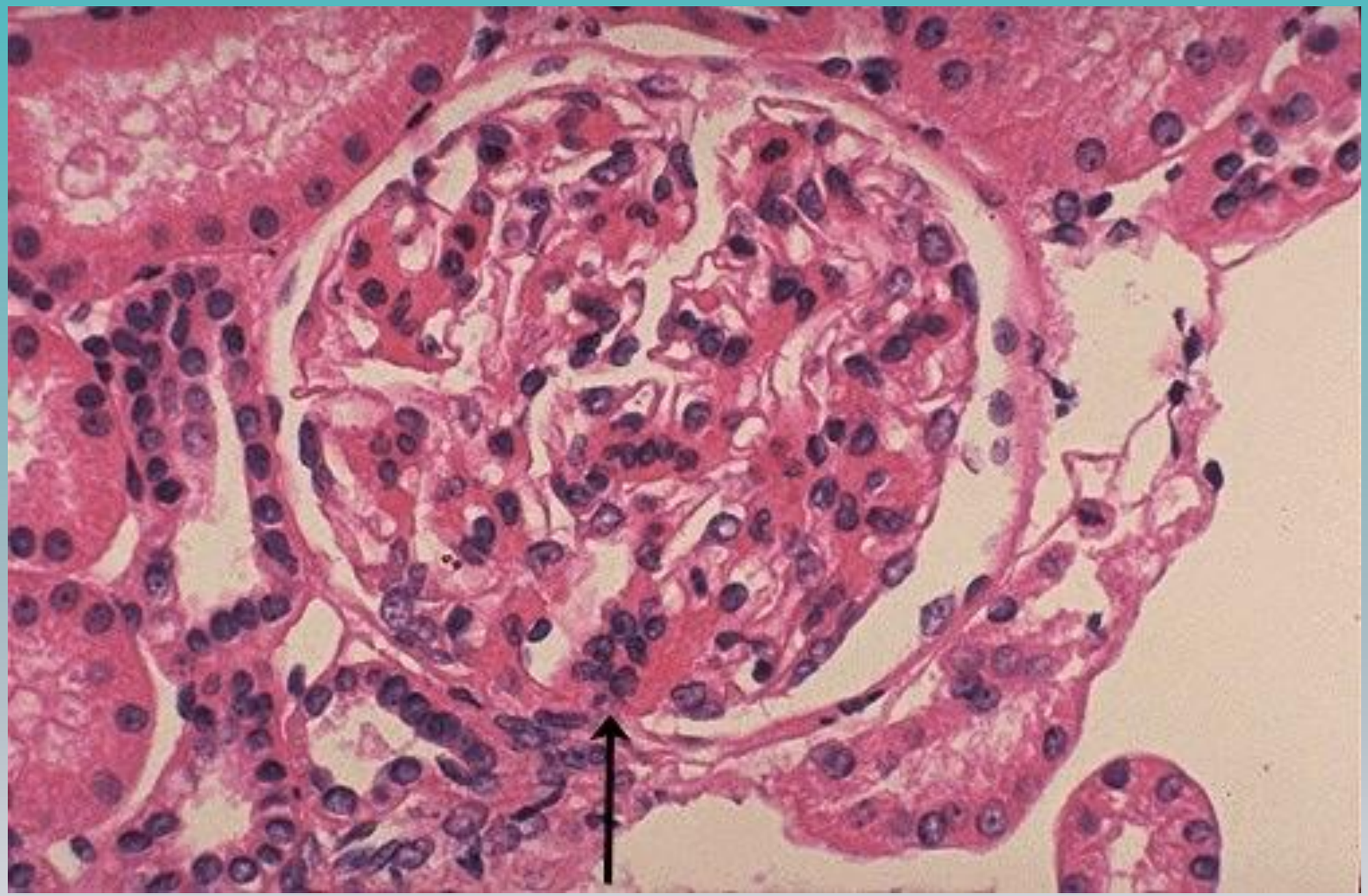
- More common among Asian an caucasians
- ***Pathogenesis***
  - Increased mucosal IgA secretion in response to inhaled/ingested antigens
  - Glomerular (mesangial) deposition of IgA
- ***Characterised by :*** - most common clinical presentation is episodic macroscopic hematuria (single or recurrent) provoked by mucosal infection

- Microscopic hematuria with or without proteinuria during routine examination

- Acute kidney injury with crescentic IgA nephropathy

Mesangioproliferative GN

- 50% progress to chronic renal failure (CRF)
- Recurs in 20-60% of transplants
- Varying histology
- Light microscopy (LM)
  - Increased mesangial matrix
  - Mesangial proliferation
  - Focal sclerosis (FSGS)
- Immunofluorescence (IF) – mesangial IgA
- Electron microscopy (EM) – mesangial deposits



Honcech-Schonlein Purpura (HSP)

- Small vessel vasculitis affecting the skin, joint ,gut with kidney
- The nephritis associated with HSP is characterized by mesangial IgA deposition
- Clinical presentation :

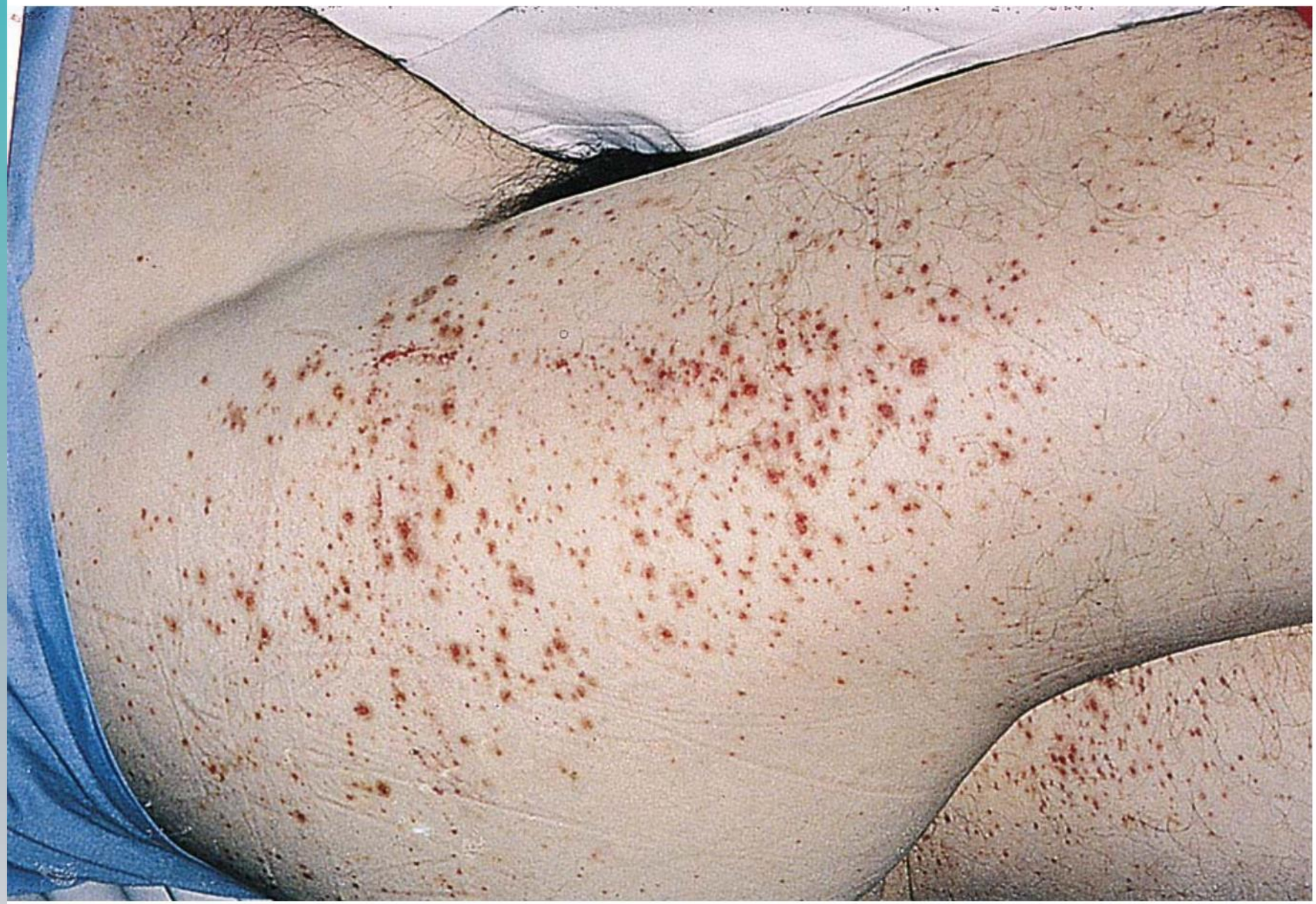
  Purpuric skin rash

  arthritis

  Gastrointestinal symptoms (abdominal pain)

Self limiting illness

Confirm diagnosis by skin or kidney biopsy



Crescentic GN
Rapidly progressive GN

- Characterised by
  - Glomerular crescents formation
    - Accumulation of cells in Bowman's space
    - Inflammatory cells, fibrin and epithelial cell proliferation
    - Compression of glomerulus
  - Rapidly progressive clinical course
- Pathogenesis
  - Damage to glomerular vessels
  - Egress of inflammatory cells and fibrin into Bowman's space
  - Proliferation of epithelial cells

Clinical presentation

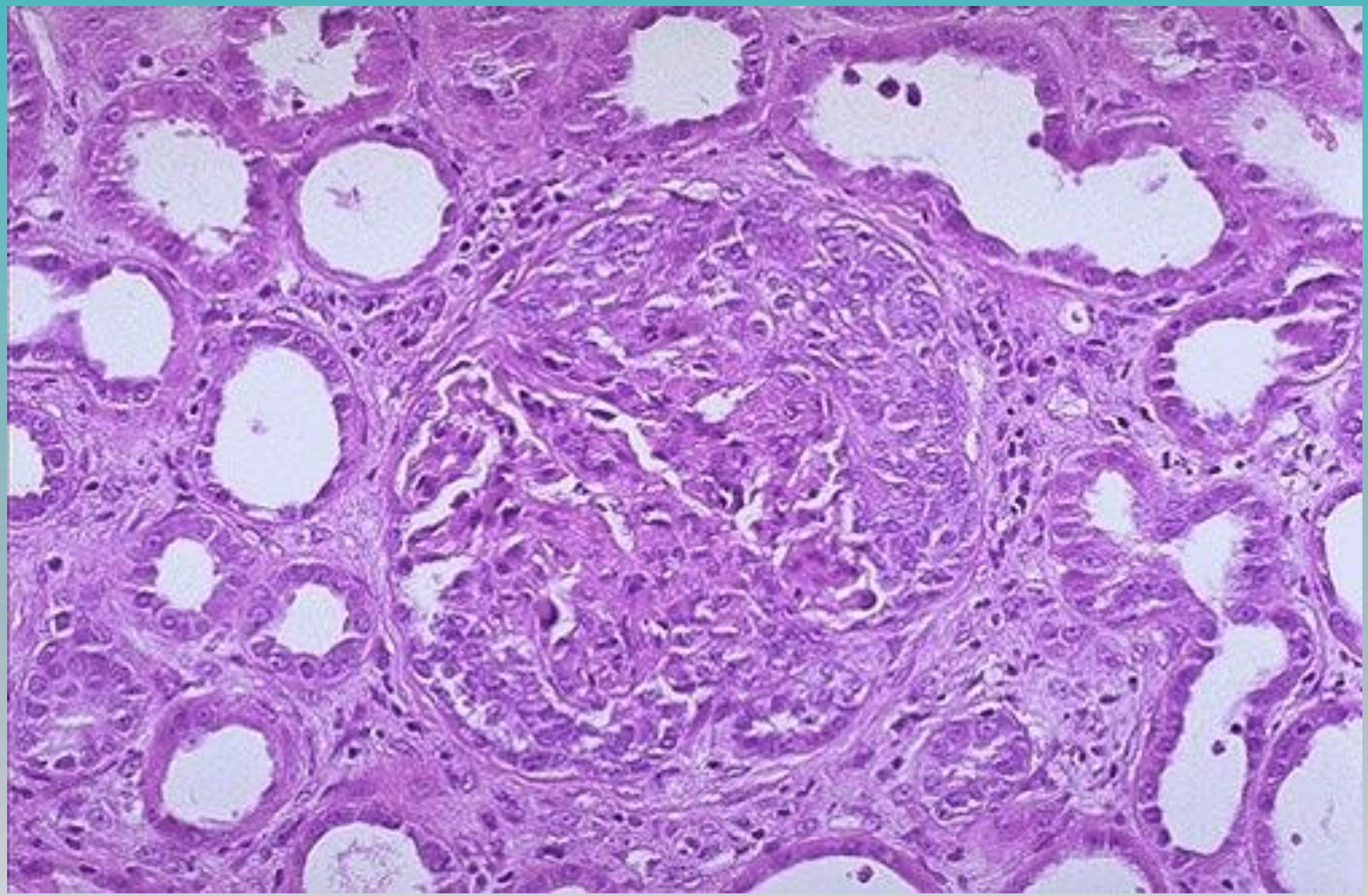
- Presented with acute onset macroscopic hematuria, decrease UOP and oedema
- renal insufficiency is present with all cases , Urine analysis reveals RBCs and RBCs cast with proteinuria
- AntiGBM , Granulomatous with Polyangitis and Microscopic Polyangitis may have pulmonary symptoms
- Systemic complaints as fatigue, weight loss and skin rash
- progression to End stage renal disease in most of untreated patient within weeks to months

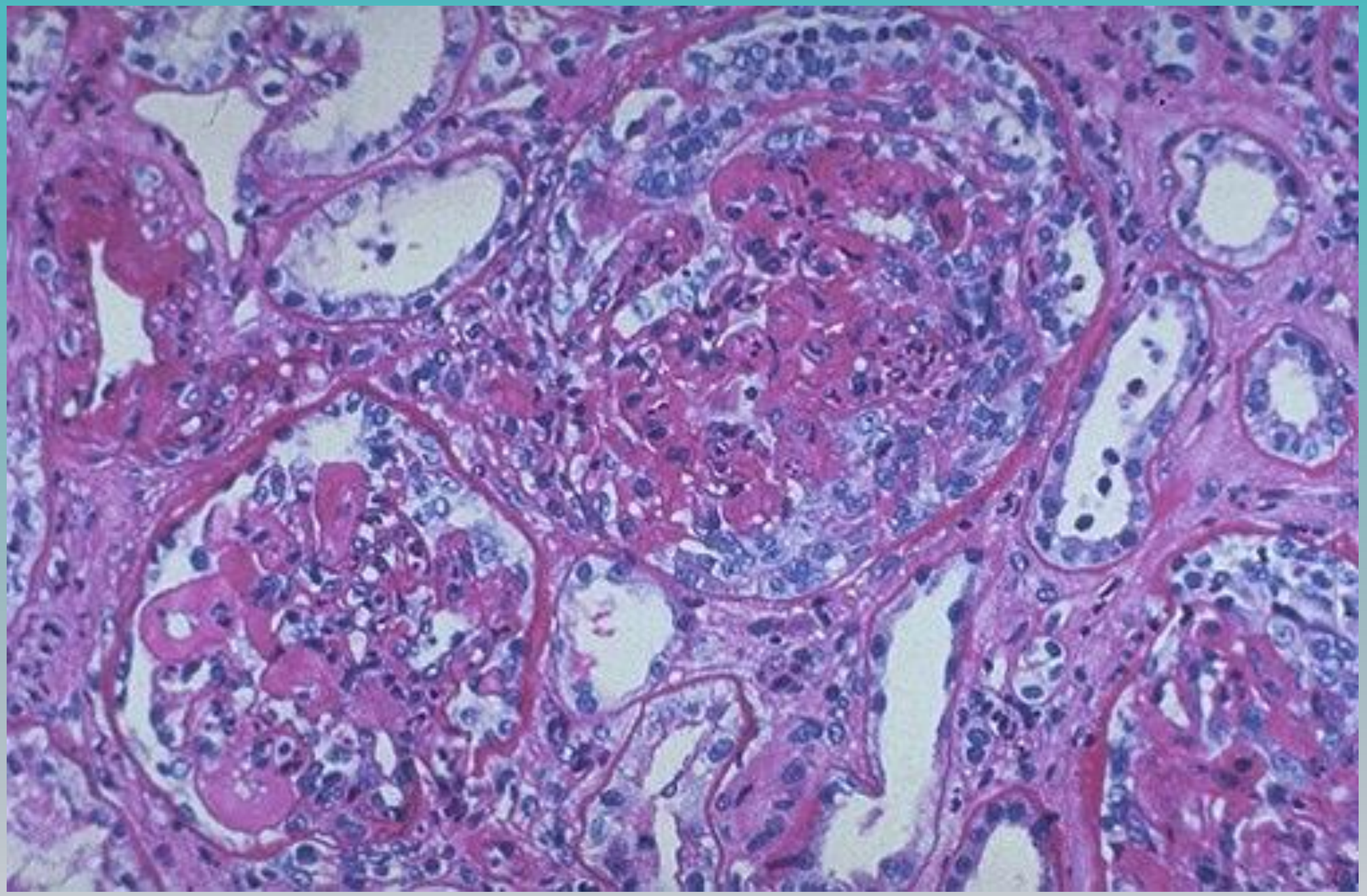
Crescentic GN
Rapidly progressive GN

- Pathogenesis
  - Type I – anti-GBM antibodies
    - linear deposition of IgG
    - May bind to alveolar BM in lung = Goodpasture's disease
  - Type II – immune complexes
    - Idiopathic or secondary to autoimmune disease or other GN
      - SLE
      - HSP
      - IgA nephropathy
      - Postinfectious GN
  - Type III – pauci-immune
    - Idiopathic or secondary to systemic vasculitis
      - granulomatosis with polyaniitis (GPA)
      - microscopic polyangiitis

Crescentic GN

- Light microscopy (LM)
  - Cellular crescents of epithelium and inflammatory cells
  - Fibrotic crescents
- Immunofluorescence (IF)
  - Type I: linear IgG
  - Type II: granular IgG
  - Type III: no deposits
- Electron microscopy (EM)
  - Type II: subendo, mesangial and subepi deposits





Thank you