Glomerulonephritis

Randa Farah MD

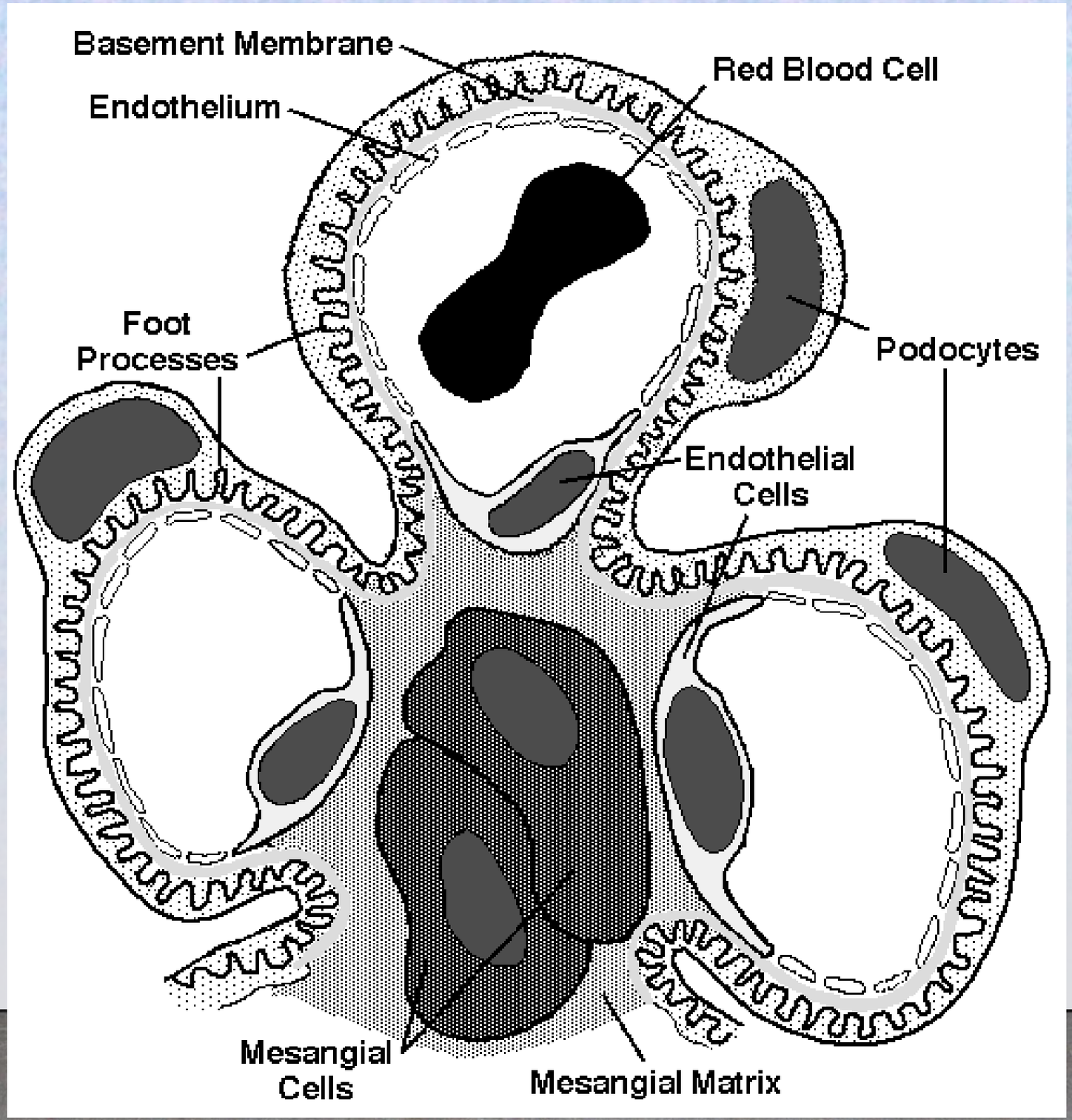
- Glomerulonephritis is inflammation of the glomeruli

- 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 and protein pass into the urine and are excreted

Normal structure of the glomerulus



Glomerular disease

- Glomerular disease are classified based on urine changes that manifest predominantly with

- **Nephrotic range** proteinuria and nephrotic urine sediment (fatty cast, oval bodies, few cell no casts)
- **Haematuria**, usually combination with proteinuria (which may be nephrotic range) with dysmorphic RBCs mixed with RBCs cast nephritic urine sediment

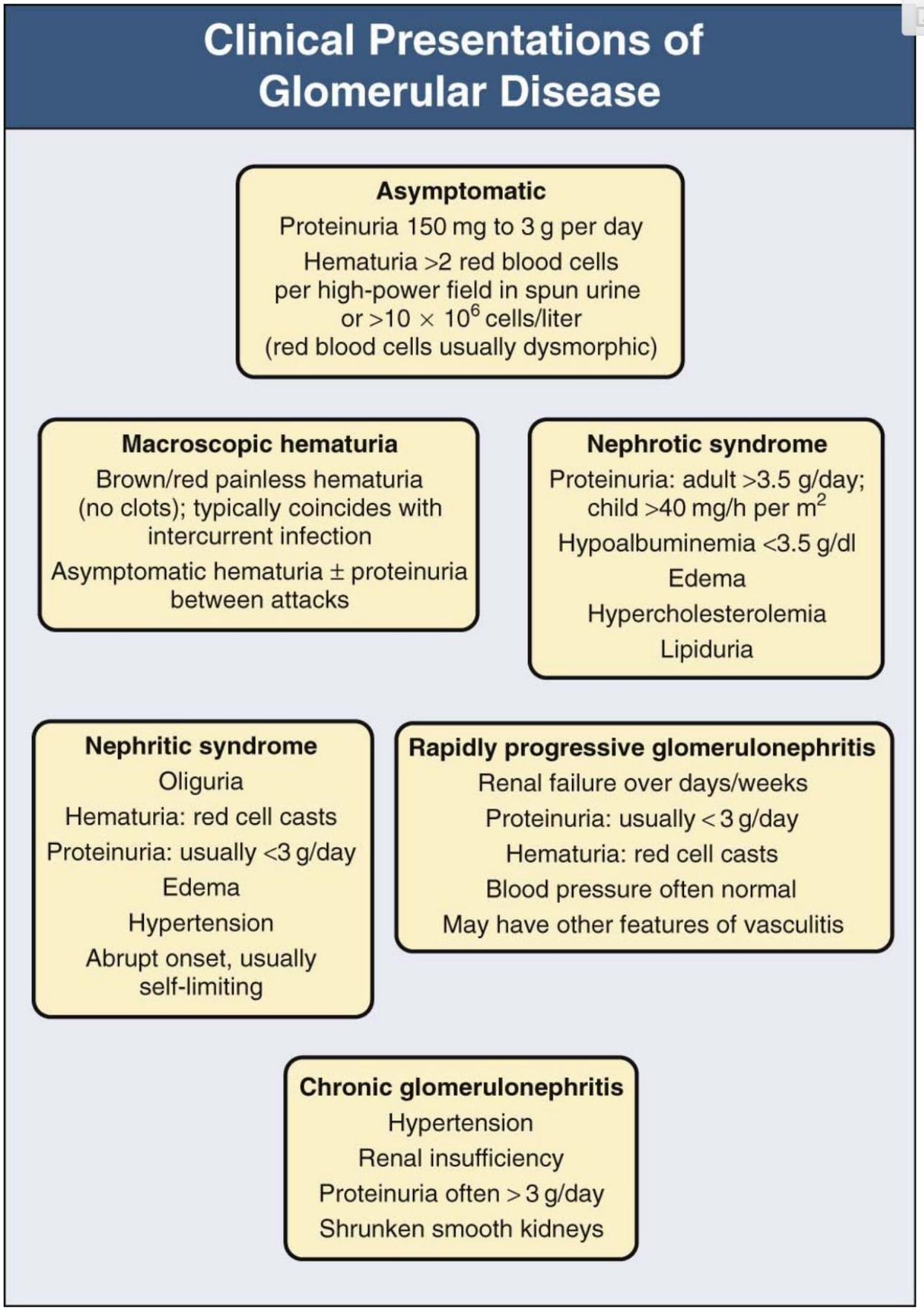


Figure 15.1: Clinical presentations of glomerular disease.

- **<u>Nephrotic syndrome :</u>**

  Nephrotic urine sediments

  Oedema

  Hypoalbuminemia

With hypercholesteremia and hypertriglyceridemia

- **<u>Nephritic syndrome</u>**

  Nephritic urine sediments

  with or without hypertension

  with or without elevated serum creatinine and oliguria

- **<u>Several glomerular disease</u>** typical manifest with both features of both nephritic and nephrotic syndrome for example: MPGN, Lupus nephritis

Pathogenies

- **Pathogenies** of nephrotic and nephritic syndrome disorders differs substantially,
- **There is clinical overlap** , Eg, several disorders may manifest with same clinical picture and presence haematuria and proteinuria dose not predict response to treatment or prognosis
- **It can be**

  Primary

  Secondary

clinical presentation

- Asymptomatic proteinuria
- Asymptomatic Haematuria
- Macroscopic haematuria
- Nephrotic syndrome
- Nephritic syndrome
- Rapidly progressive GN
- Chronic glomerulonephritis

Diagnosis of glomerular diseases

Glomerular disease usually suspected when screening or diagnostic testing reveals

elevated serum creatinine and/or abnormal urinalysis (haematuria , with or without cast proteinuria or both)

Clinical approach involves distinguishing predominate- nephritic form predominate- nephrotic features and identifying likely causes by patients age and associated illness

Diagnosis of glomerular diseases

- **History**

Haematuria, Foamy urine

Oedema (lower limb and periorbital oedema)

Elevated blood pressure

Multisystem disease associated with GN as

(Diabetes , Hypertension, amyloid, Hepatitis, lupus, vasculitis and malignancy)

Positive family Hx of renal disease or ESRD

- **Cont. History**

Family Hx of Alport's with hearing loss, Focal Segmental Glomerulosclerosis, Haemolytic Uremic Syndrome, uncommon familial IgA

Patient with Morbid obesity associated with FSGS

Medications use :

NSAIDs and interferon with minimal change

Penicillamine , mercury with membranous

Pamidronate, heroin with FSGS

Cyclosporin, tacrolimus and Oral contraception with HUS

- **Cont. History**

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 membranoproliferative GN)

Diagnosis of glomerular diseases

- Vital sign – includes Blood pressure , looking for hypertension
- Dependent pitting edema (lower limb or sacral 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 syndrome
- Palpable purpura in vasculitis, SLE, Cryoglobulinemia or endocarditis

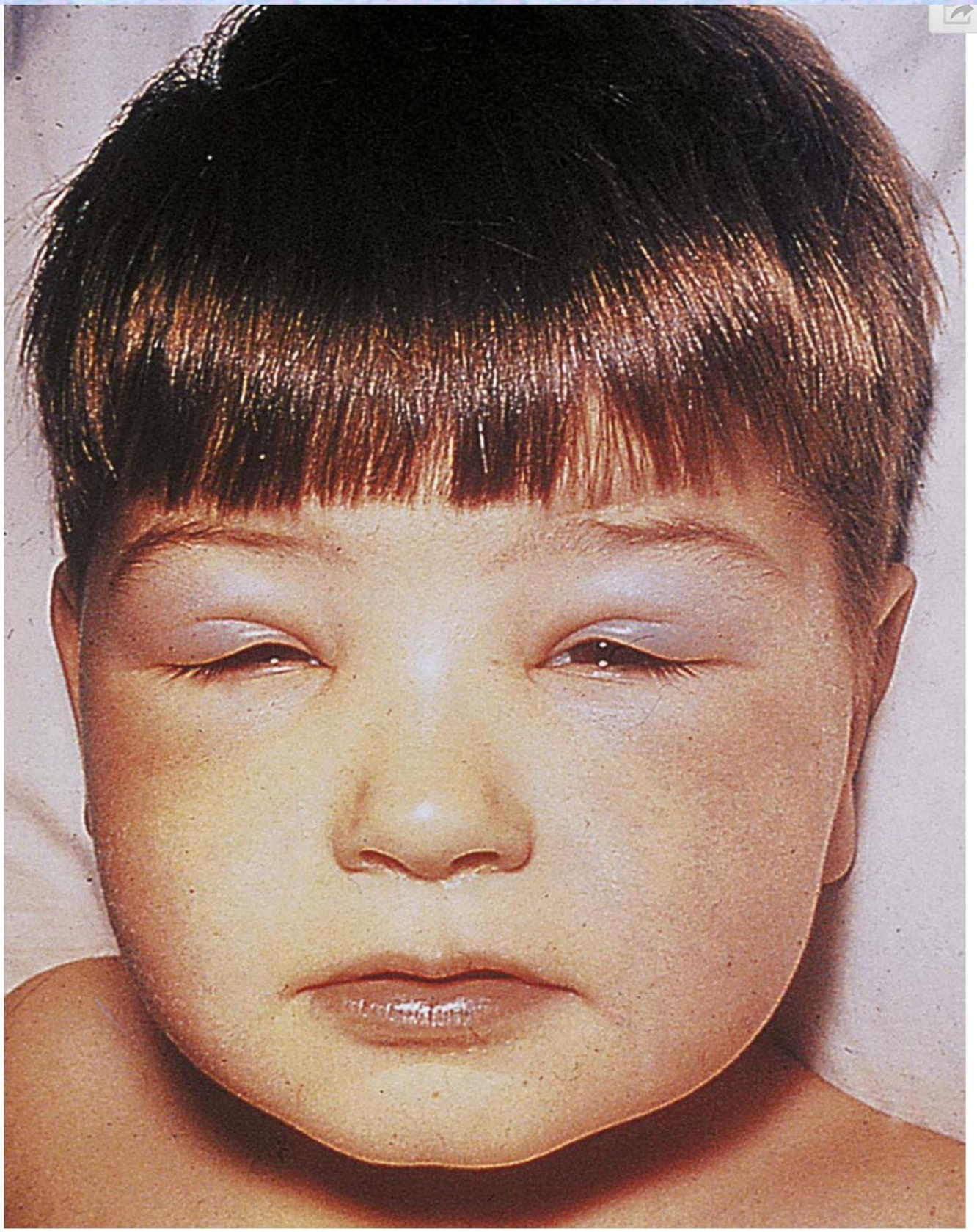


Figure 15.2: Nephrotic edema. Periorbital edema in the early morning in a nephrotic child. The edema resolves during the day under the influence of gravity.

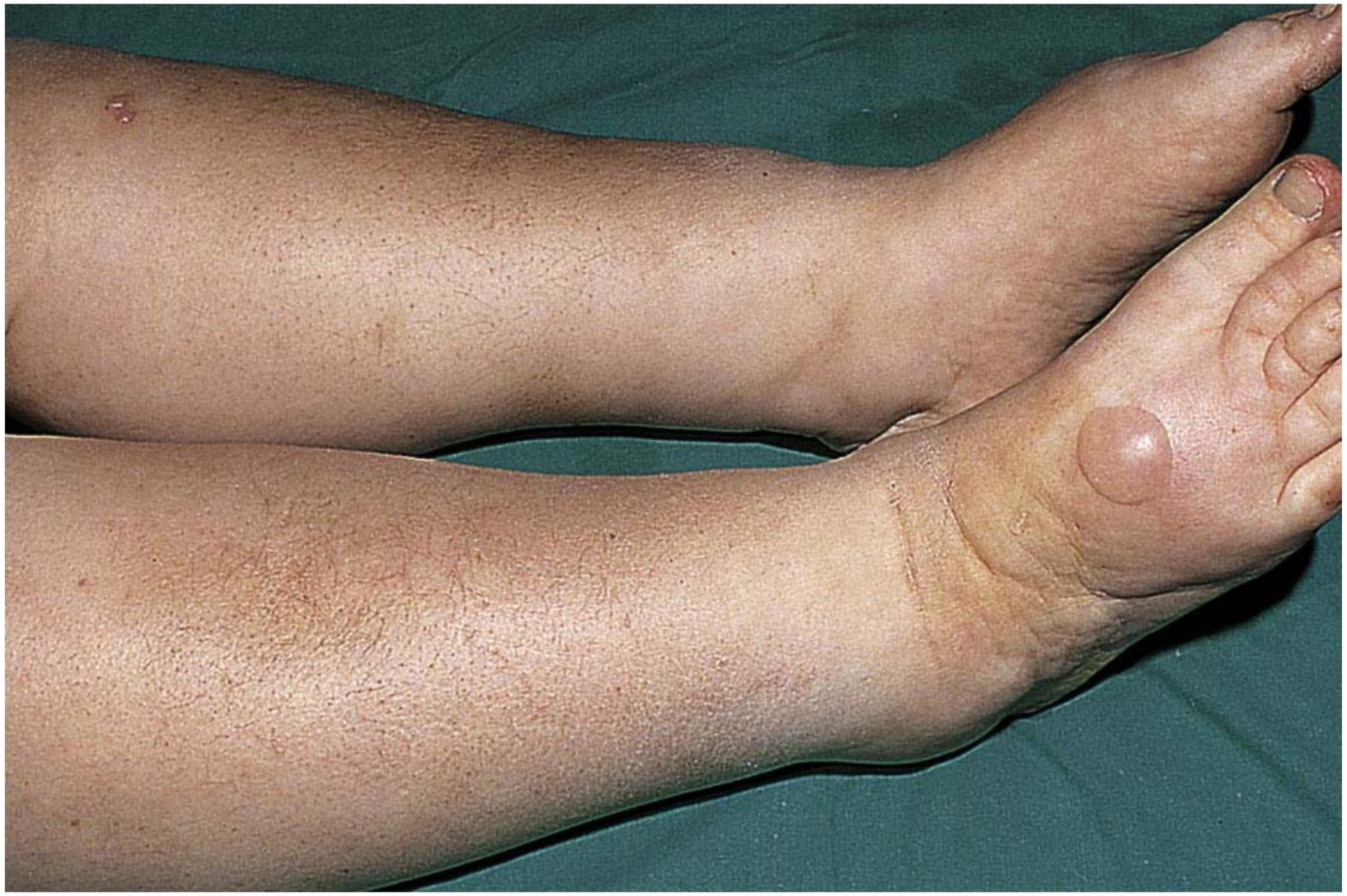


Figure 15.3: Nephrotic edema. Severe peripheral edema in nephrotic syndrome; note the blisters caused by intradermal fluid.

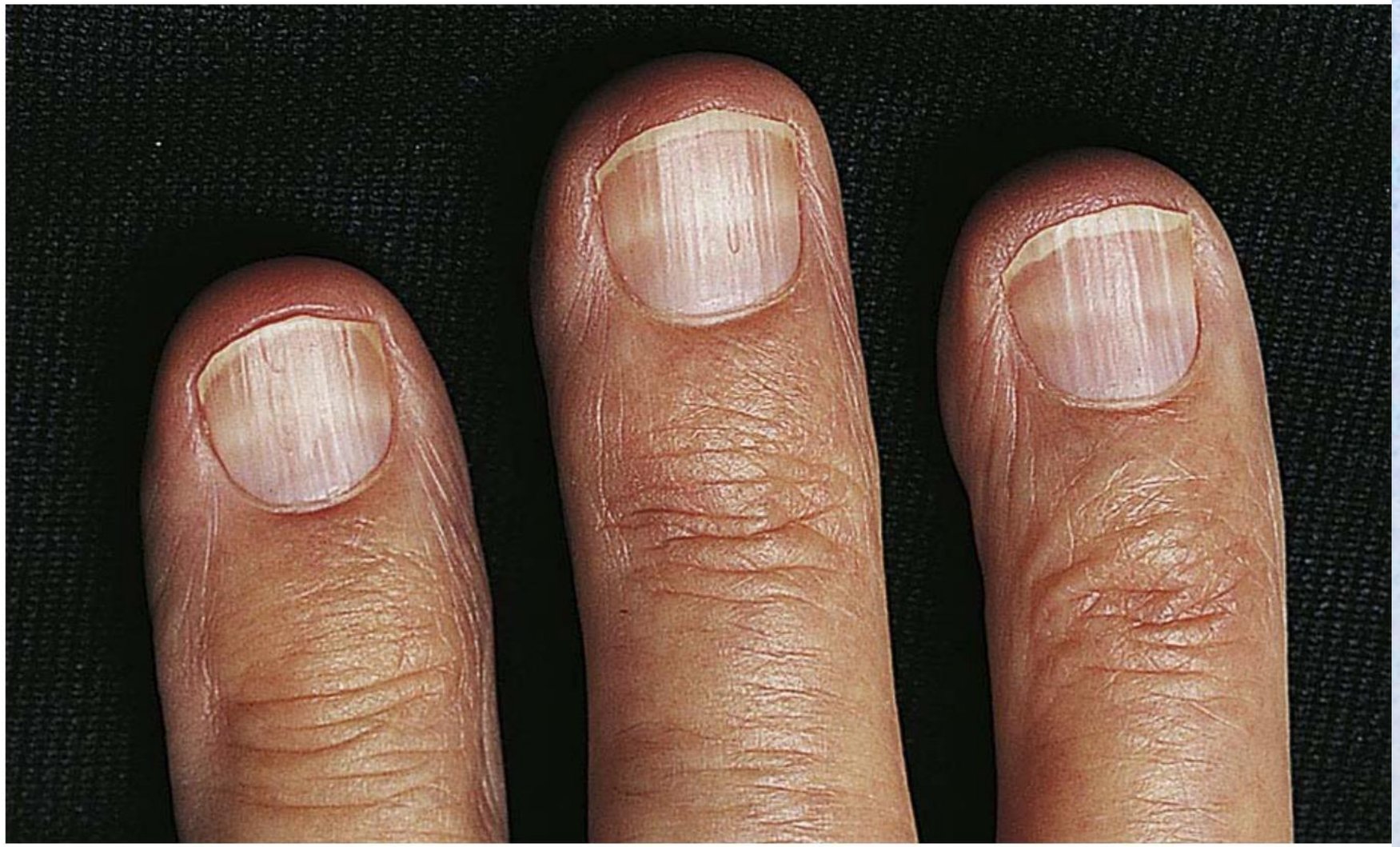


Figure 15.4: Muehrcke's bands in nephrotic syndrome. The white band grew during a transient period of hypoalbuminemia caused by the nephrotic syndrome.

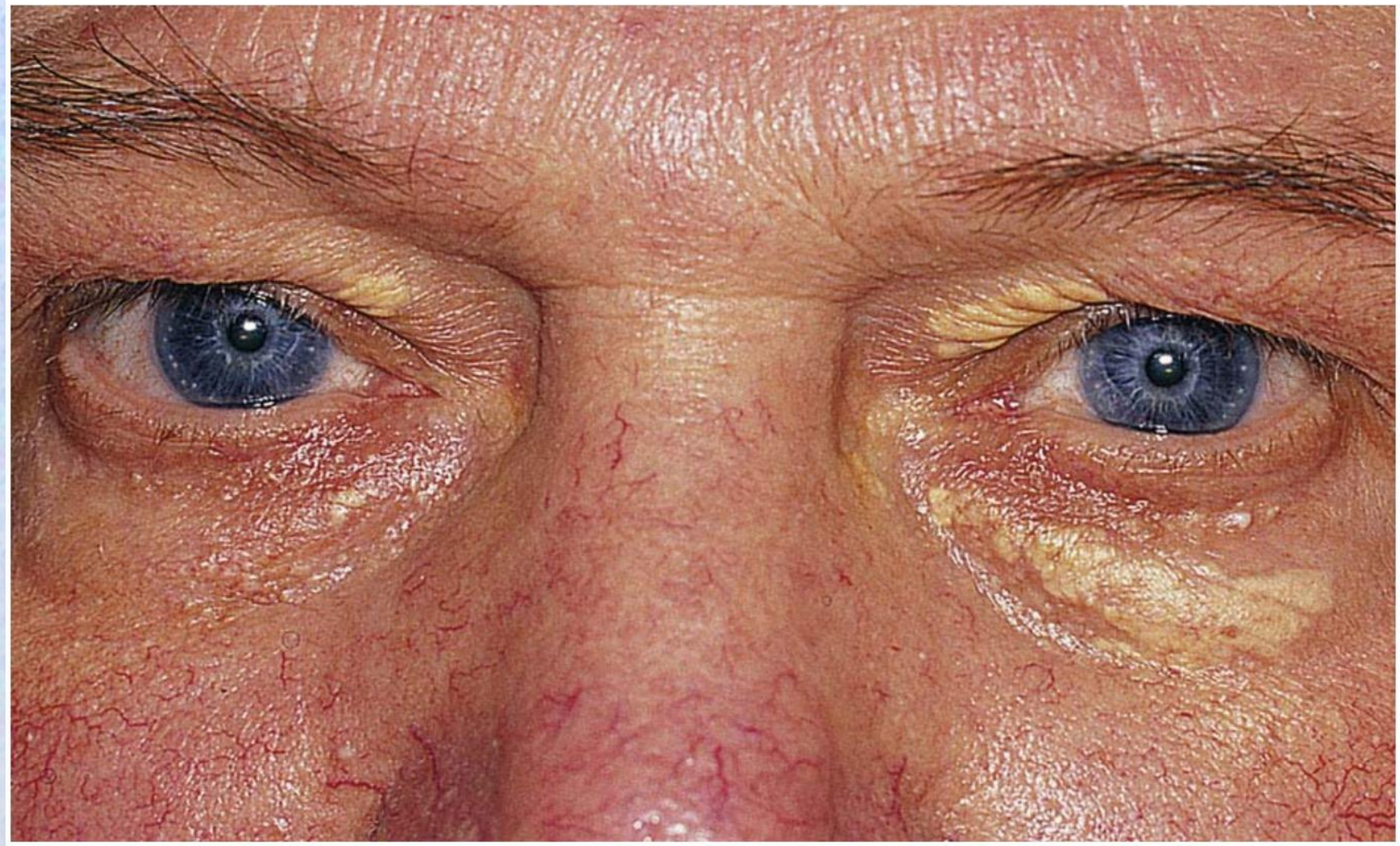


Figure 15.5: Xanthelasmas in nephrotic syndrome. These prominent xanthelasmas developed within a period of 2 months in a patient with recent onset of severe nephrotic syndrome and serum cholesterol level of 550 mg/dl (14.2 mmol/l).

Diagnosis of glomerular diseases

- **<u>Investigations</u>**

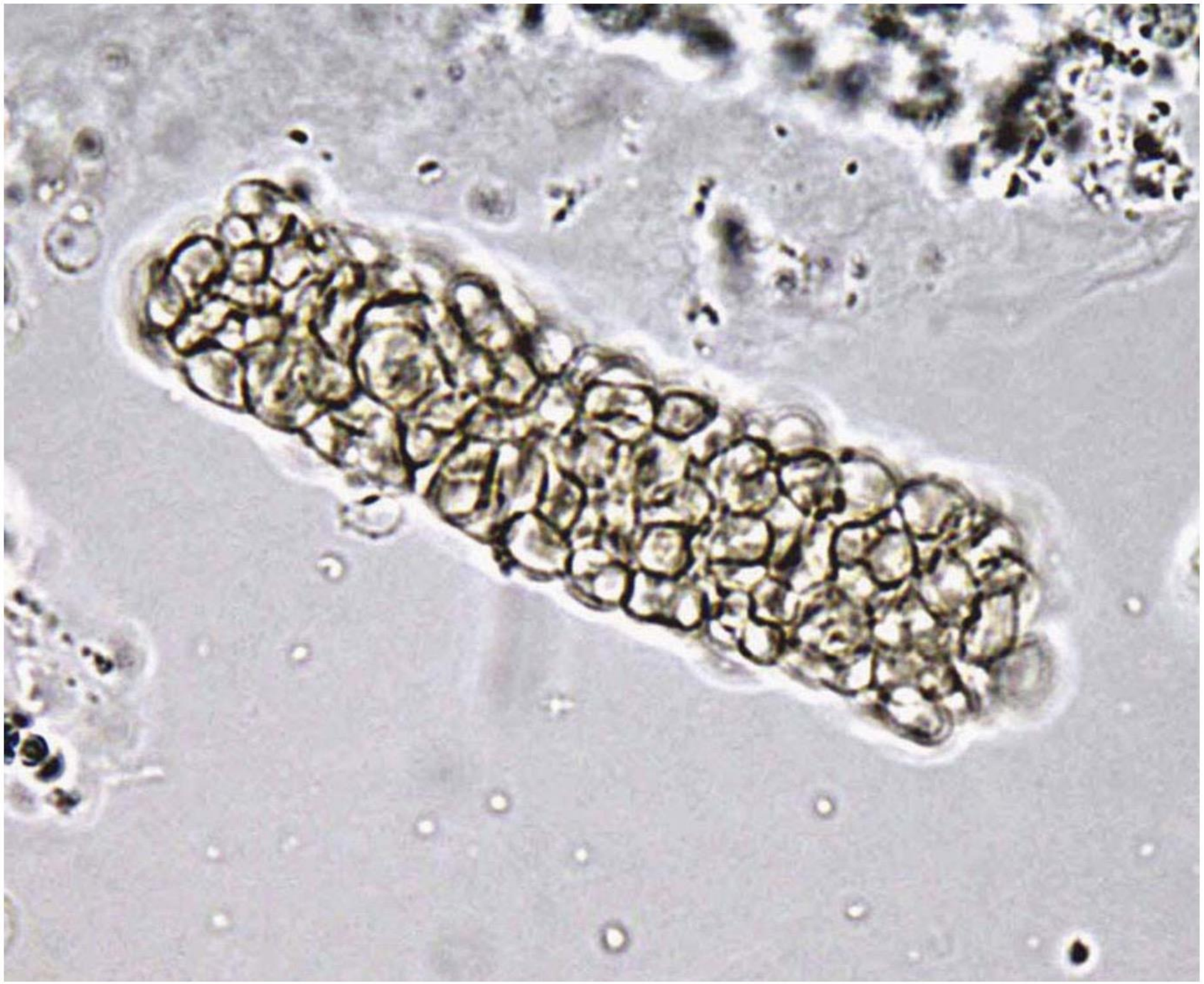
  Renal function (Creatinine, urea, electrolytes)

  Urine analysis (Looking for protein and blood)

  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)



- **<u>Investigations</u>**

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

Hepatitis B , hepatitis C and HIV Infection

Complement level (C3, C4 and CH50)

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

Renal biopsy

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	

Nephritic syndrome

Haematuria with variable degree of proteinuria usually dysmorphic or often RBCs cast

Often ≥ of the following elements are present :

Oedema, Hypertension, elevated serum creatinine and oliguria

It can be primary or secondary

Diagnosis is based on History, physical examination and sometimes renal biopsy

Treatment and prognosis varies by cause

Nephritic syndrome

The syndrome can be

Acute (serum creatinine rises over many weeks or less)

Chronic (renal insufficiency may progress over years)

Or can be

Primary

Secondary

Nephritic syndrome

Acute glomerulonephritis

Postinfectious glomerulonephritis

Rapidly progressive glomerulonephritis (RPGN)

Membranoproliferative glomerulonephritis

Chronic glomerulonephritis

IgA nephropathy

Hereditary nephritis (Alport syndrome)

Thin basement membrane disease

Postinfectious / Diffuse proliferative GN

- Occurs after infection, usually with a nephrogenic strain of group A beta- haemolytic streptococcus.
- Onset 1 – 4 weeks after upper respiratory / cutaneous infection
- Symptoms and signs range from

Asymptomatic haematuria (in about 50%) and mild proteinuria to full-blown nephritis with microscopic or gross haematuria (cola-colored, brown, smoky, or frankly bloody urine), proteinuria (sometimes nephrotic-range), oliguria, oedema, hypertension, and renal insufficiency.

- Fever is unusual and suggests persistent infection.
- Renal failure that causes fluid overload with heart failure and severe hypertension requiring dialysis affects 1 to 2% of patients.

Postinfectious / Diffuse proliferative GN

- **Antistreptolysin O level**

  The most common laboratory evidence of recent streptococcal infection

  Remains elevated for several months in about 75% of patients with pharyngitis and in about 50% of patients with impetigo

  It is not specific

Urinalysis

Typically shows proteinuria (0.5 to 2 g/m^2/day); dysmorphic RBCs; WBCs; renal tubular cells; and possibly RBC, WBC, and granular casts.

C3 and total hemolytic complement activity (CH50) levels

Decreased during active disease and return to normal within 6 to 8 weeks in 80% of PIGN cases

PIGN- **Biopsy specimens**

Light microscopy (LM)

Diffuse glomerular proliferation and cellular infiltration

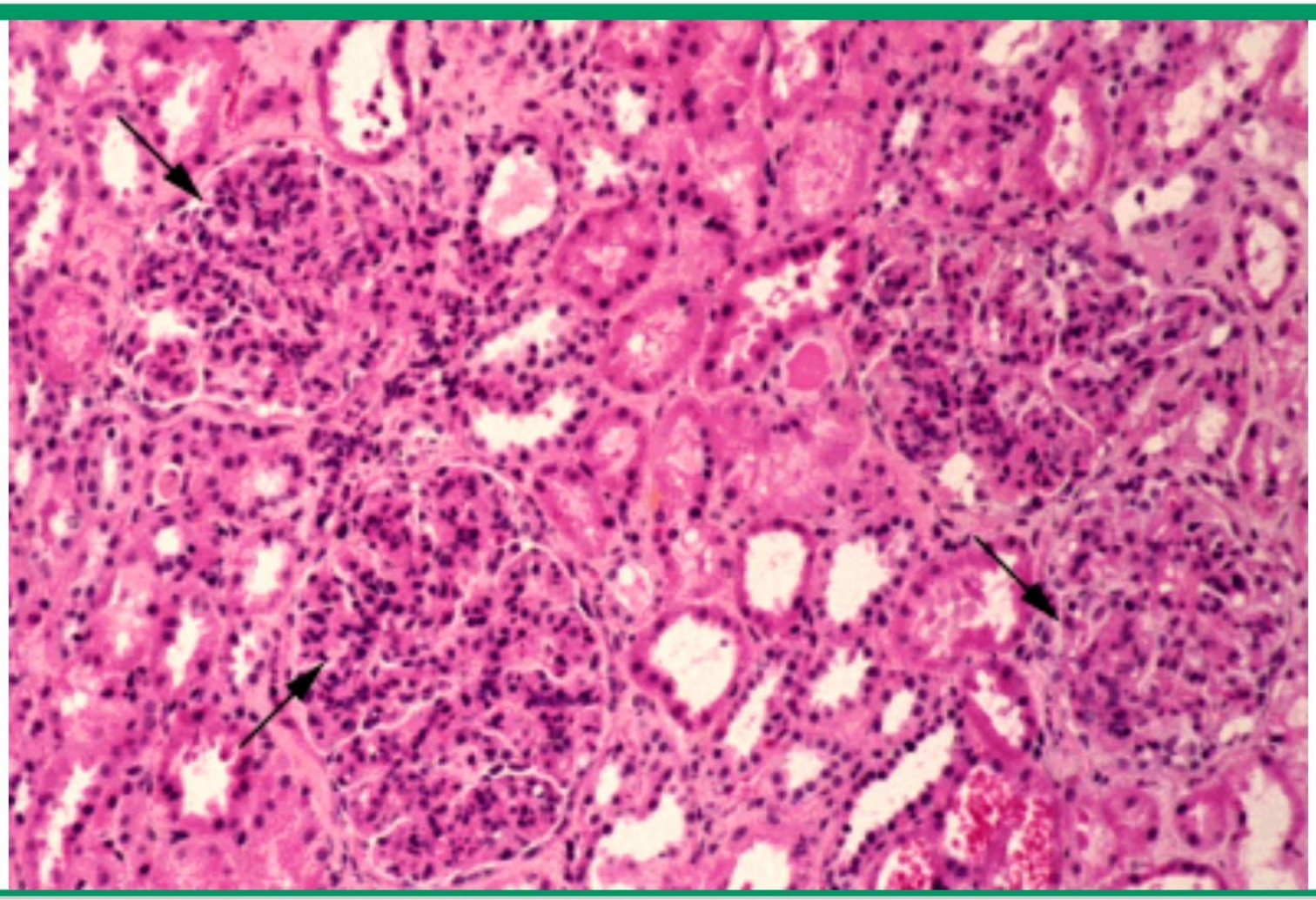
Immunofluorescence (IF)

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

Postinfectious / Diffuse proliferative GN

Prognosis

Good prognosis

- **Treatment**

Supportive care

May include restriction of dietary protein, sodium, and fluid and, in more severe cases, treatment of edema and hypertension . Dialysis is occasionally necessary.

Antimicrobial therapy is preventive only when given within 36 hours of infection and before glomerulonephritis becomes established.

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

Membranoproliferative glomerulonephritis

- A group of immune-mediated disorders characterized histologically by glomerular basement membrane (GBM) thickening and proliferative changes on light microscopy.
- There are 3 types, each of which may have primary (idiopathic) or secondary causes.
- Primary forms affect children and young adults between ages 8 and 30 and account for 10% of cases of nephrotic syndrome in children;
- Secondary forms tend to affect adults > 30.
- Men and women are affected equally. Reported familial cases of some types suggest genetic factors play a role in at least some cases.
- Many factors contribute to hypocomplementemia.

Membranoproliferative GN[32]

- **Symptoms and signs are:**

  Nephrotic syndrome in 60 to 80% of cases.

  Nephritic syndrome (acute glomerulonephritis) are presenting features in 15 to 20% of cases of type I and III disease and in a higher percentage of type II disease.

  At diagnosis, 30% of patients have hypertension and 20% have renal insufficiency; hypertension often develops even before glomerular filtration rate (GFR) declines

Membranoproliferative GN

- *Classification based on Electron microscopy*

Type I: - Systemic immune complex disorder (eg, systemic lupus erythematosus , mixed cryoglobulinemia, Sjögren syndrome)

- Chronic infection (eg, bacterial endocarditis , HIV infection , hepatitis B or C infection , visceral abscess, ventriculoatrial shunt infection)

- Cancer (eg, chronic lymphocytic leukemia , lymphomas , melanoma)

- Other disorders (eg, partial lipodystrophy, C2 or C3 deficiencies, sarcoidosis , thrombotic microangiopathies)

Type II: - Complement activation

-BM deposits (dense deposit disease)

Type III : as type I with Subendothelial and sub endothelial deposition

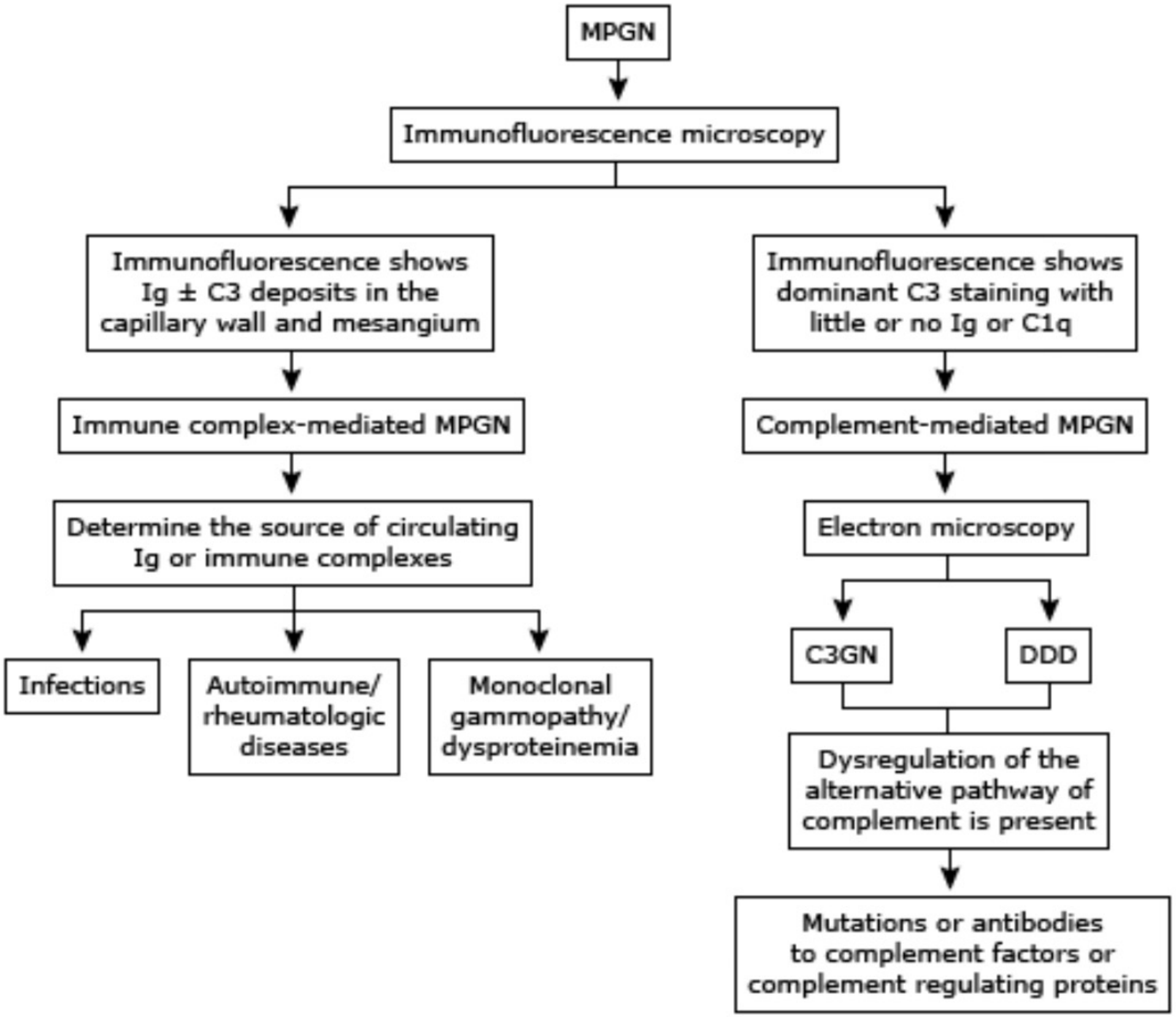
MPGN Prognosis

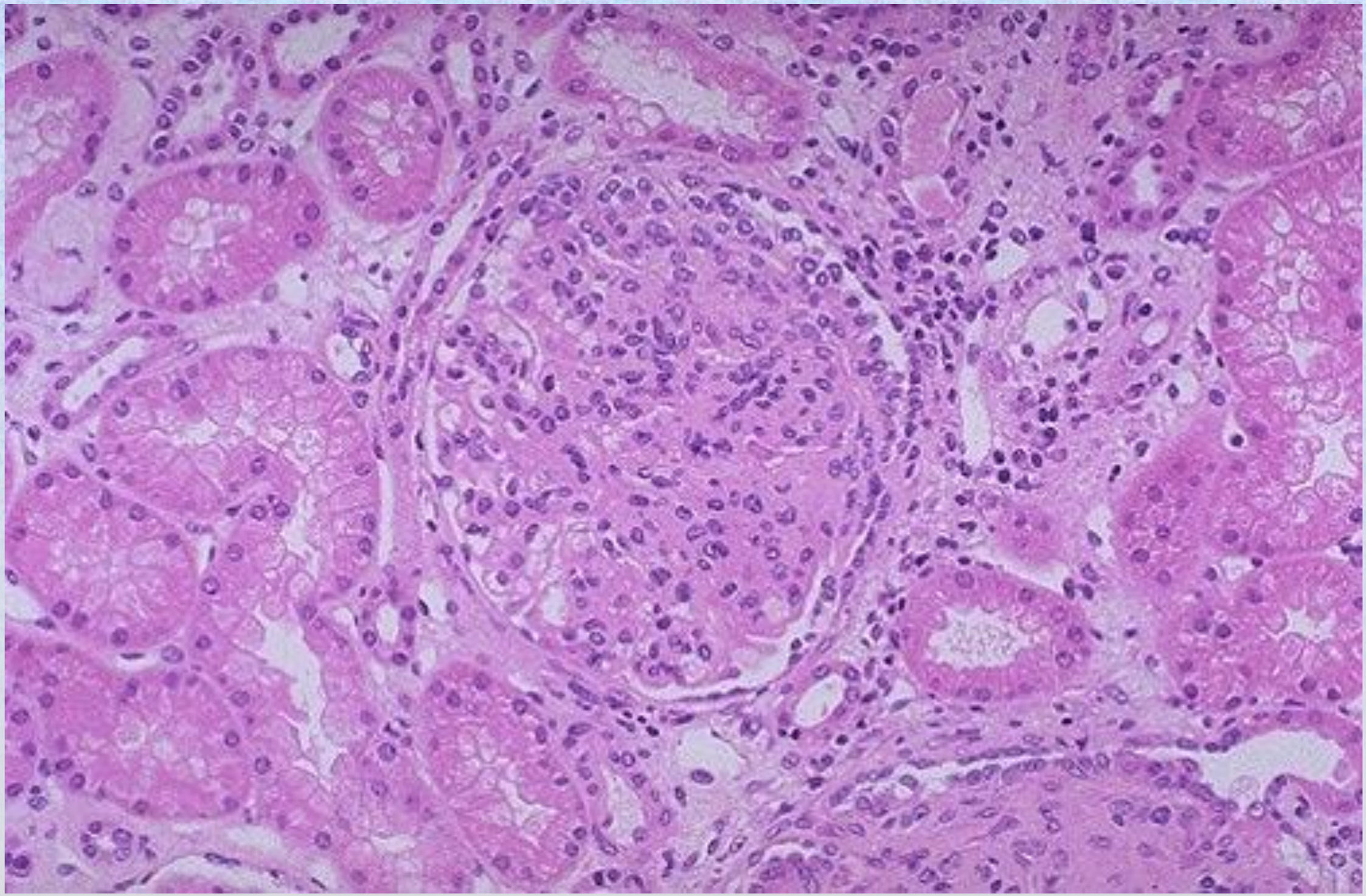
- Prognosis is good if a condition causing secondary membranoproliferative glomerulonephritis is successfully treated
- ESRD occurs in 50% of patients at 10 years and in 90% at 20 years
- Type I MPGN recurs in 30% of kidney transplantation patients
- Type II MPGN recurs in 90% but, despite this high recurrence rate, leads to graft loss only infrequently.
- Outcome tends to be worse if proteinuria is in the nephrotic range.

MPGN- treatment

- Corticosteroids for children with nephrotic-range proteinuria
- Dipyridamole and aspirin for adults
- Kidney transplantation for patients with ESRD
- Underlying disorders are treated when possible. Specific therapy is probably not indicated for patients with non-nephrotic–range proteinuria, which usually suggests slow progression.

Proposed classification of MPGN





IgA Nephropathy
Mesangioproliferative GN

- IgA nephropathy is a nephritic syndrome, a form of chronic glomerulonephritis characterized by the deposition of IgA immune complexes in glomeruli.
- Most common primary glomerulonephritis
- It occurs at all ages, with a peak onset in the teens and 20s;
- Affects men 2 to 6 times more frequently than women;
- More common in whites and Asians than in blacks

Pathogenesis

- Cause is unknown, but evidence suggests that there may be several mechanisms, including

  Increased IgA1 production, Defective IgA1 glycosylation causing increased binding to mesangial cell, decreased IgA1 clearance, a defective mucosal immune system, overproduction of cytokines stimulating mesangial cell proliferation, familial clustering has also been observed, suggesting genetic factors at least in some case

IgA Nephropathy
Mesangioproliferative GN

The most common manifestations are:

Persistent or recurrent macroscopic haematuria

Asymptomatic microscopic haematuria with mild proteinuria.

Gross haematuria usually begins 1 or 2 days after a febrile mucosal (upper respiratory, sinus, enteral) illness

Mimicking acute postinfectious glomerulonephritis , except the onset of haematuria is earlier (coinciding with or immediately after the febrile illness).

RPGN with crescentic IgA nephropathy <10%

- IgA nephropathy usually progresses slowly;
- Renal insufficiency and hypertension develop within 10 years in 15 to 20% of patients.
- Progression to ESRD occurs in 25% of patients after 20 years.
- IgA nephropathy is diagnosed in childhood, prognosis is usually good.
- Recurs in 20-60% of transplants

- **Risk factors for progressive deterioration in renal function include the following:**
- Proteinuria > 1 g/day
- Elevated serum creatinine level
- Uncontrolled hypertension
- Persistent microscopic hematuria
- Extensive fibrotic changes in the glomerulus or interstitium
- Crescents on biopsy

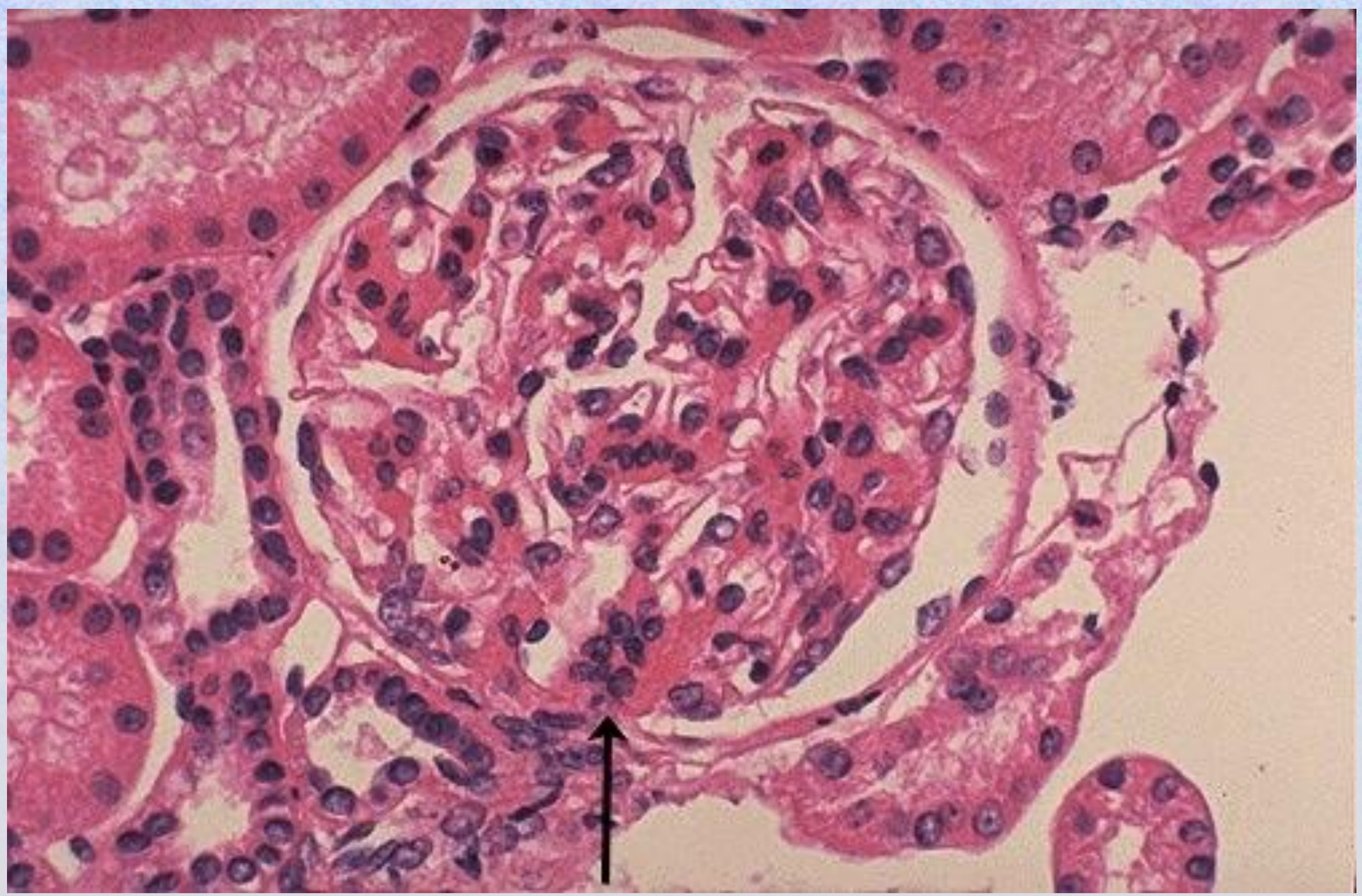
Prognostic Markers at Presentation in IgA Nephropathy

Clinical	Histopathologic
Poor Prognosis	
Hypertension	Mesangial hypercellularity
Renal impairment	Endocapillary proliferation
Severity of proteinuria	Segmental glomerulosclerosis
Hyperuricemia	Tubular atrophy
Gross obesity	Interstitial fibrosis
Duration of preceding symptoms	Capillary loop IgA deposits
Increasing age	Crescents (controversial)
Good Prognosis	
Recurrent macroscopic hematuria	
No Impact on Prognosis	
Gender	Intensity of IgA deposits
Serum IgA level	

Figure 22.9: Prognostic markers at presentation in IgA nephropathy. None of the clinical or histopathologic adverse features, except capillary loop IgA deposits, are specific to IgA nephropathy.

IgA biopsy

- Light microscopy (LM)
  - Increased mesangial matrix
  - Mesangial proliferation
  - Focal sclerosis (FSGS)
- Immunofluorescence (IF) – mesangial IgA
- Electron microscopy (EM) – mesangial deposits



IgA Treatment

- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) for

  hypertension , serum creatinine > 1.2 mg/dL or macroalbuminuria (urinary protein > 300 mg/day) and with a target urinary protein of < 500 mg/day

- Corticosteroids for progressive disease, including increasing proteinuria, especially into the nephrotic range, or increasing serum creatinine level

- Normotensive patients with intact renal function (serum creatinine < 1.2 mg/dL and only mild proteinuria (< 0.5 g/day) usually are not treated beyond angiotensin inhibition and omega-3 fatty acids (fish oil).

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 :

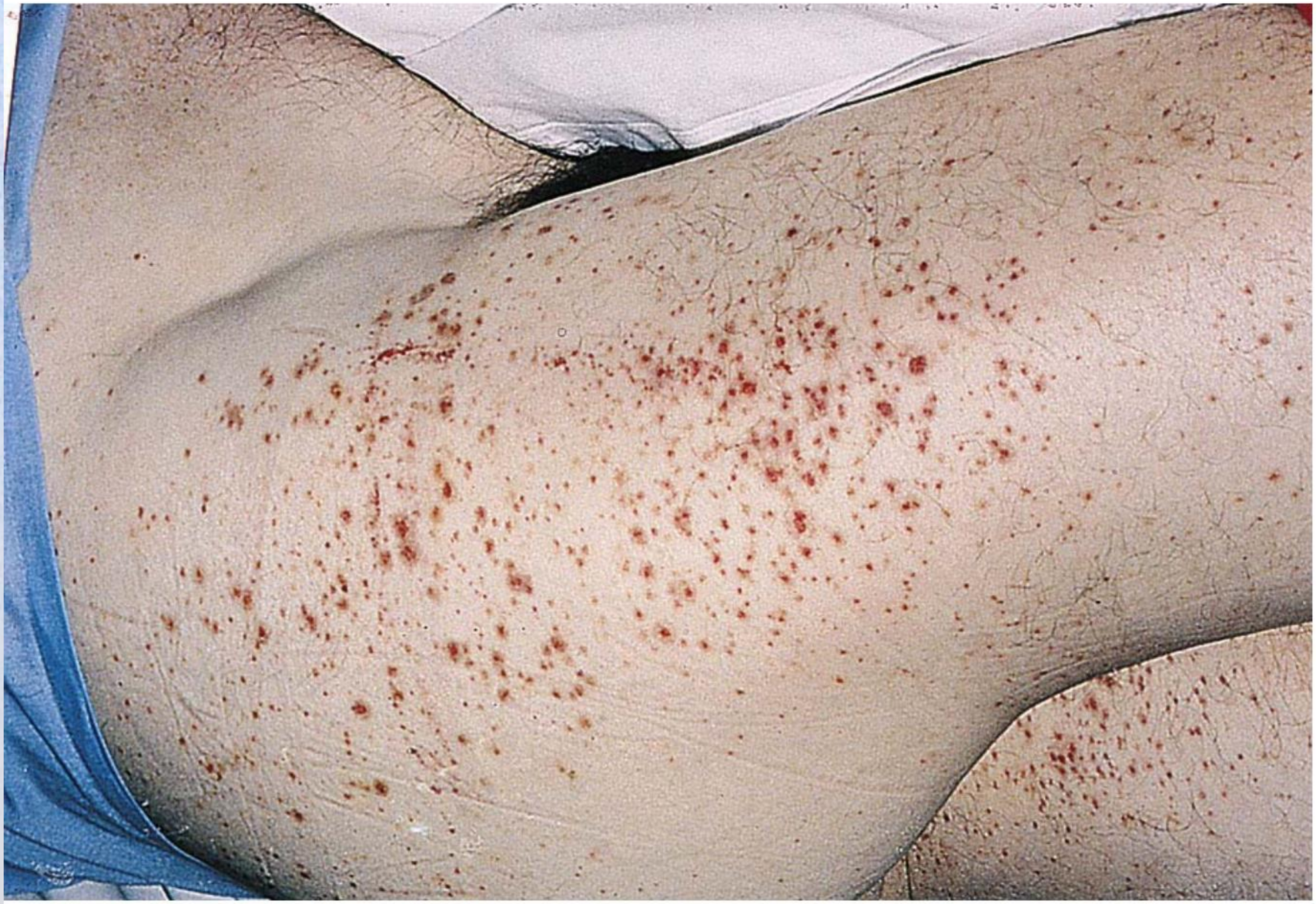
  Purpuric skin rash

  Arthritis

  Gastrointestinal symptoms (abdominal pain)

Self limiting illness

Confirm diagnosis by skin or kidney biopsy



Crescentic GN
Rapidly progressive GN

- Nephritic syndrome

- Damage to glomerular vessels, egress of inflammatory cells and fibrin into Bowman's space, proliferation of epithelial cells

- Pathologic diagnosis accompanied by extensive glomerular crescent formation (ie, >50% of sampled glomeruli contain crescents which can be seen in a biopsy specimen)

- If untreated, progresses to ESRD over weeks to months.

- It is relatively uncommon, affecting 10 to 15% of patients with glomerulonephritis

- Occurs predominantly in patients 20 to 50 years.

RPGN- Clinical presentation

- Manifestations are usually insidious, with weakness, fatigue, fever, nausea, vomiting, anorexia, arthralgia, skin rash and abdominal pain.
- About 50% of patients have edema and a history of an acute influenza-like illness within 4 weeks of onset of renal failure, usually followed by severe oliguria.
- Nephrotic syndrome is present in 10 to 30%.
- Hypertension is uncommon and rarely severe.
- Patients with anti-GBM antibody disease Granulomatous with Polyangiitis and Microscopic may have pulmonary hemorrhage, which can manifest with hemoptysis or be detectable only by finding diffuse alveolar infiltrates on chest x-ray (pulmonary-renal syndrome or diffuse alveolar hemorrhage syndrome).
- Progression to End stage renal disease in most of untreated patient within weeks to months

Crescentic GN
Rapidly progressive GN

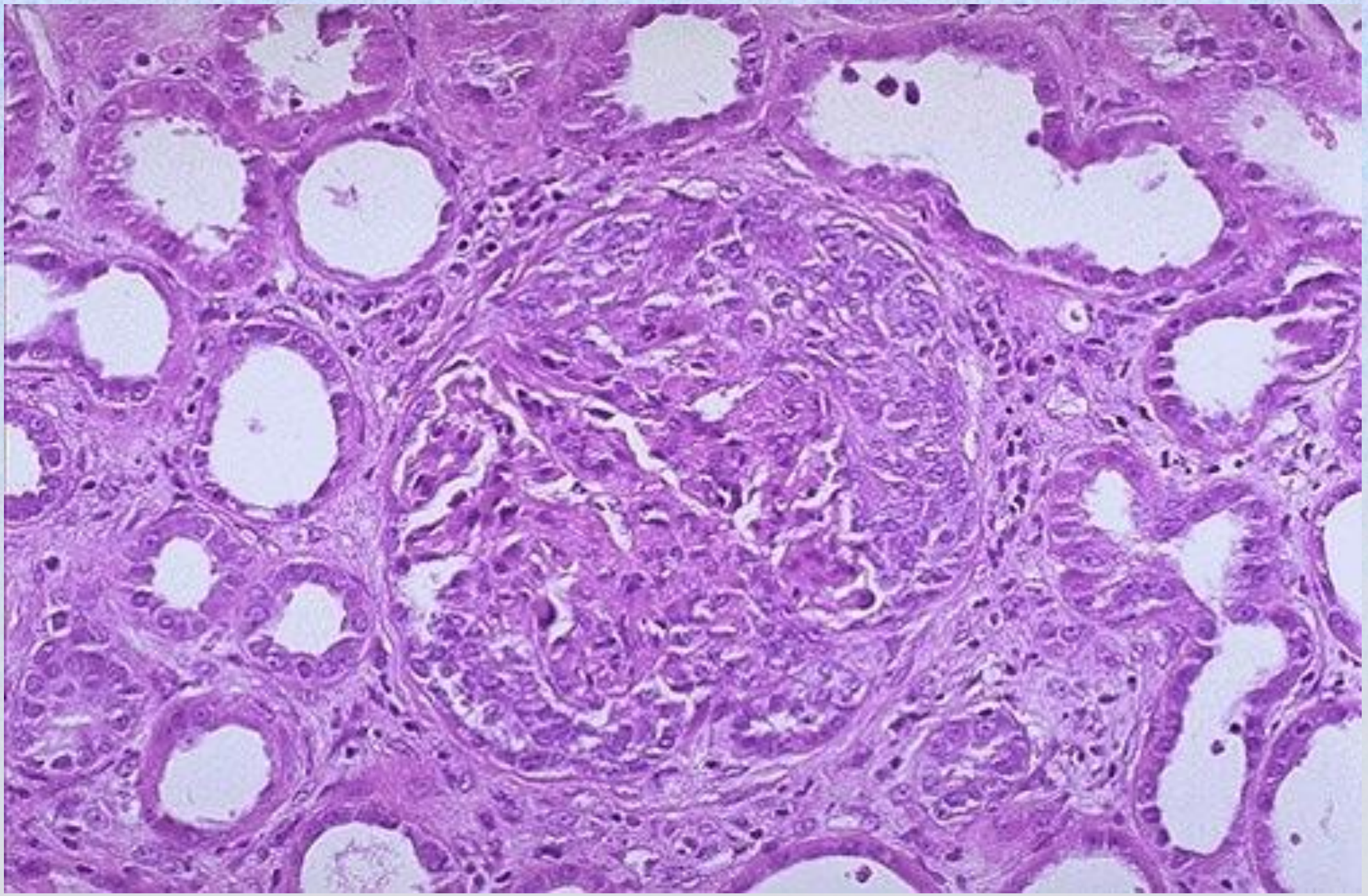
- Pathogenesis
  - Type I – anti-GBM antibodies
    - **Immunofluorescent staining of renal biopsy tissue demonstrates linear IgG deposits.**
    - **Combination of glomerulonephritis and alveolar hemorrhage=** Goodpasture's disease
  - Type II – immune complexes
    - Idiopathic or secondary to autoimmune disease or other GN
      - SLE, HSP, IgA nephropathy, Postinfectious GN
  - Type III – pauci-immune
    - Idiopathic or secondary to systemic vasculitis
      - granulomatosis with polyaniitis (GPA) antiproteinase 3-ANCA or myeloperoxidase-ANCA, and systemic vasculitis.
      - microscopic polyangiitis

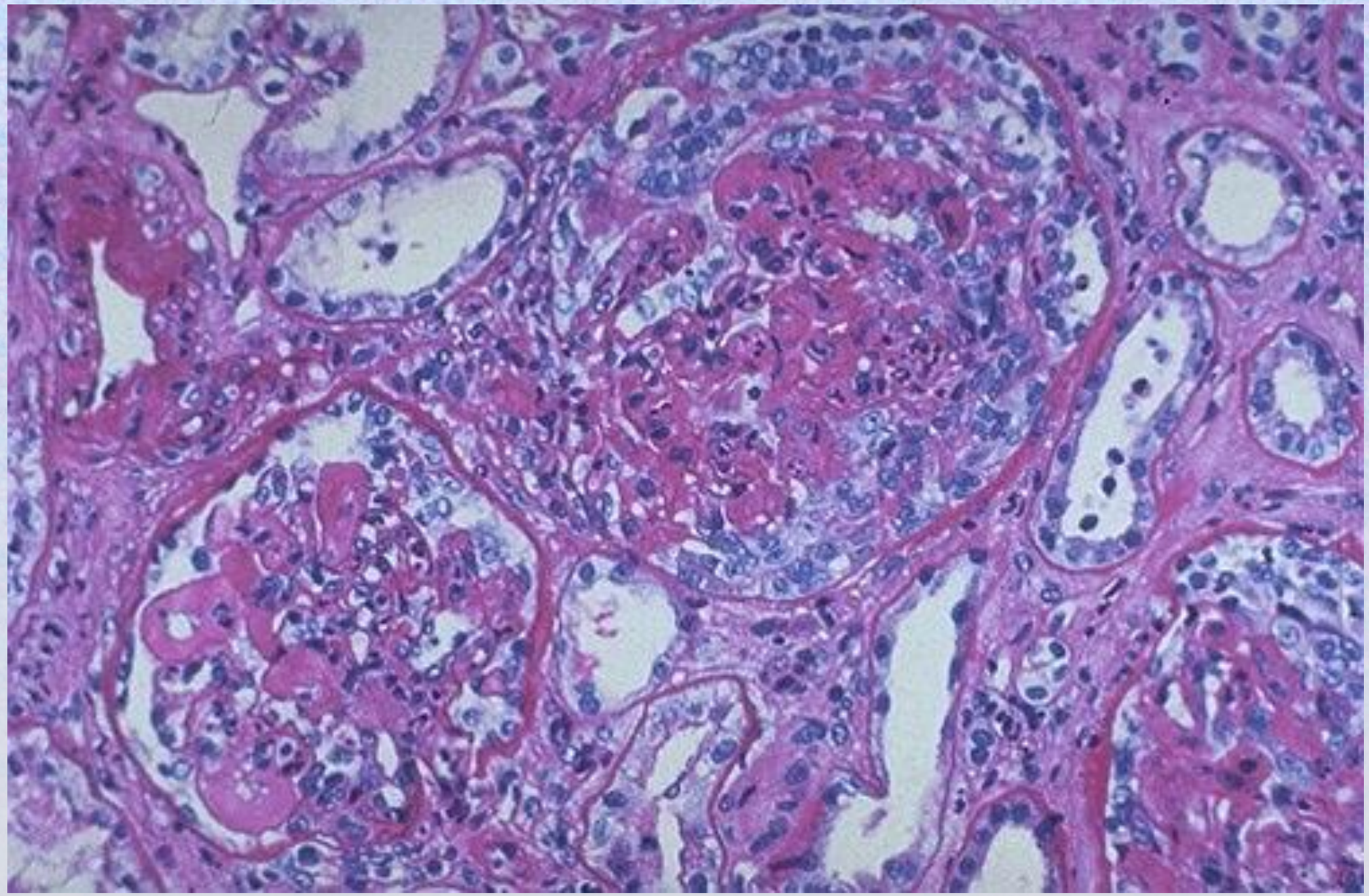
Crescentic GN
Rapidly progressive GN- Treatment

- Corticosteroids
- Cyclophosphamide
- Rituximab
- Plasma exchange

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





- Nephrotic syndrome / Proteinuria
  - Proteinuria (> 3.5g protein / day)
  - Hypoalbuminemia < 3.5 g/dl
  - Oedema
  - Hypercholesterolemia, Lipiduria

Glomerular diseases associated with nephrotic syndrome

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

Pathophysiology –Nephrotic syndrome

- Proteinuria occurs because of changes to capillary endothelial cells, the glomerular basement membrane (GBM), or podocytes, which normally filter serum protein selectively by size and charge.

Complication of Nephrotic syndrome

- Results in urinary loss of macromolecular proteins, primarily albumin but also opsonins, immunoglobulins, erythropoietin, transferrin, hormone-binding proteins (including thyroid-binding globulin and vitamin D-binding protein), and antithrombin III. Deficiency of these and other proteins contribute to a number of complications as :
  - Oedema (including ascites and pleural effusions)
  - Anaemia
  - Changes in thyroid function test results (among patients previously hypothyroid, increased dose requirement for thyroid replacement hormone)
  - Dyslipidaemia
  - Chronic kidney disease

Complication of Nephrotic syndrome

- Hypercoagulability and thromboembolism (especially renal vein thrombosis and pulmonary embolism, which occur in up to 5% of children and 40% of adults)
- Protein undernutrition in children (sometimes with brittle hair and nails, alopecia, and stunted growth)
- Proximal tubular dysfunction (acquired Fanconi syndrome) secondary to toxic effects of large amounts of protein that they reabsorb)

Diagnosis- Nephrotic syndrome

- Urine random (spot) protein/creatinine ratio ≥ 3 or proteinuria ≥ 3 g/24 hours
- Blood urea nitrogen (BUN) and creatinine concentrations vary by degree of renal impairment.
- Serum albumin often is < 2.5 g/dL (25 g/L).
- Total cholesterol and triglyceride levels are typically increased.

Diagnosis- Nephrotic syndrome

- **Testing for secondary causes of nephrotic syndrome**
  - Serum glucose or glycosylated Hb (HbA1C)
  - Antinuclear antibodies
  - Hepatitis B and C serologic tests
  - Serum and urine protein electrophoresis
  - Cryoglobulins
  - Rheumatoid factor
  - Serologic test for syphilis (eg, rapid plasma reagin)
  - HIV antibody test
  - Complement levels (C3, C4)

Prognosis- Nephrotic syndrome

- Prognosis varies by cause.
- The prognosis generally is favourable in corticosteroid-responsive disorders.
- In all cases, prognosis may be worse in the presence of the following:
  - Infection
  - Hypertension
  - Significant azotaemia
  - Haematuria
  - Thromboses in cerebral, pulmonary, peripheral, or renal veins
- The recurrence rate is high in kidney transplantations with focal segmental glomerulosclerosis

Treatment- Nephrotic syndrome

- Treatment of causative disorder
- Angiotensin inhibition
- Sodium restriction
- Statins
- Diuretics for excessive fluid overload
- Rarely, nephrectomy

Minimal change disease

- Commonest cause of nephrotic syndrome in children 4-8 years (80% to 90%),
- It also occurs in adults (10 to 20% of adult nephrotic syndrome
- Most cases of minimal change disease are idiopathic
- It can be secondary to drug use (especially nonsteroidal anti-inflammatory drugs [NSAIDs]) and hematologic cancers (especially Hodgkin lymphoma).

Diagnosis:

- Sudden onset of unexplained nephrotic-range proteinuria that is mainly albumin
- Normal renal function
- Non-nephritic urine sediment
- In adults with idiopathic nephrotic syndrome diagnosis by renal biopsy
- In children, the diagnosis can be suspected (and treatment begun) based on the typical presentation

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)

Kidney biopsy- Minimal change disease

- Characterized by

  Lack of glomerular changes on light microscopy

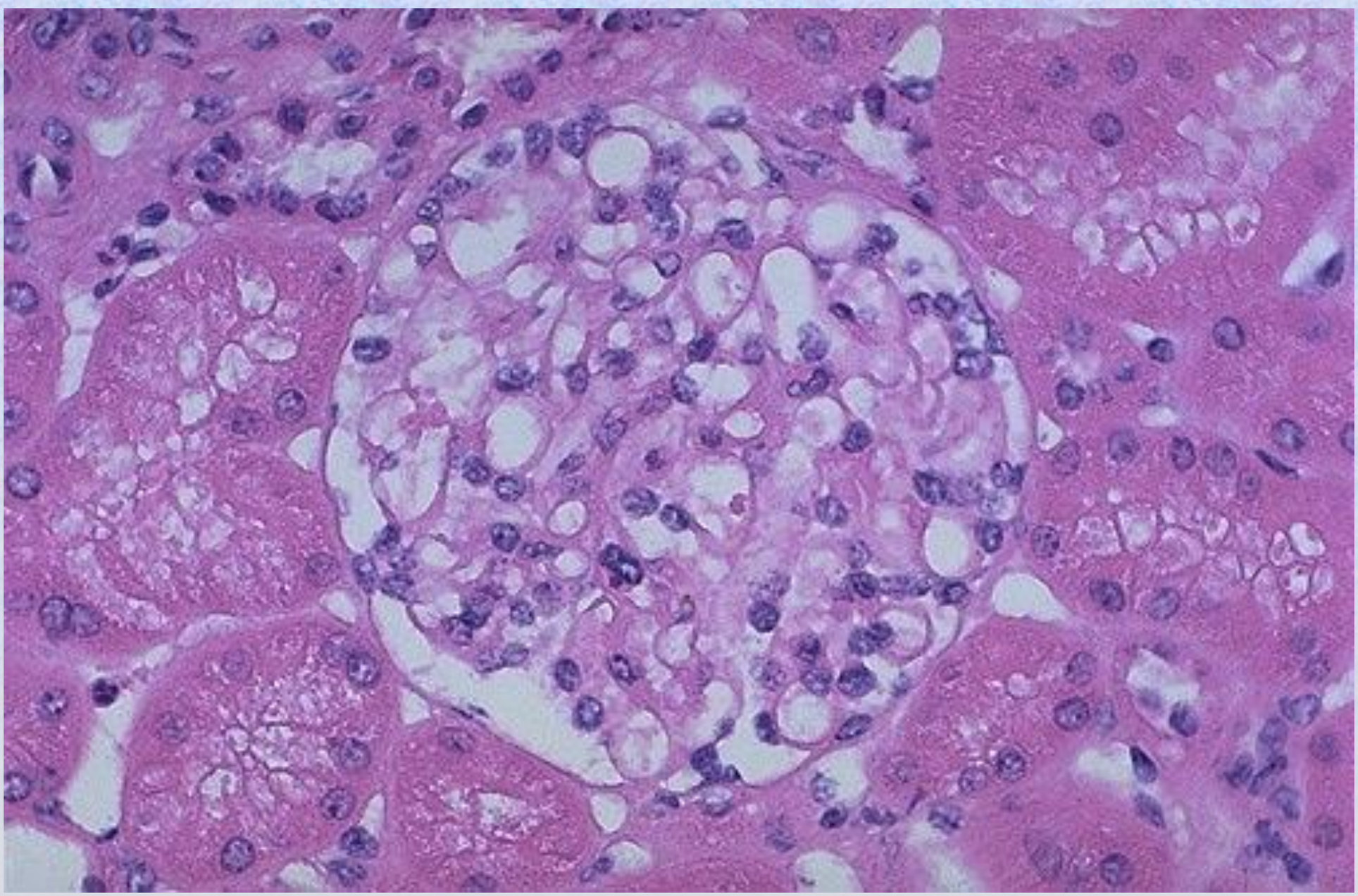
  Lack of immune deposits

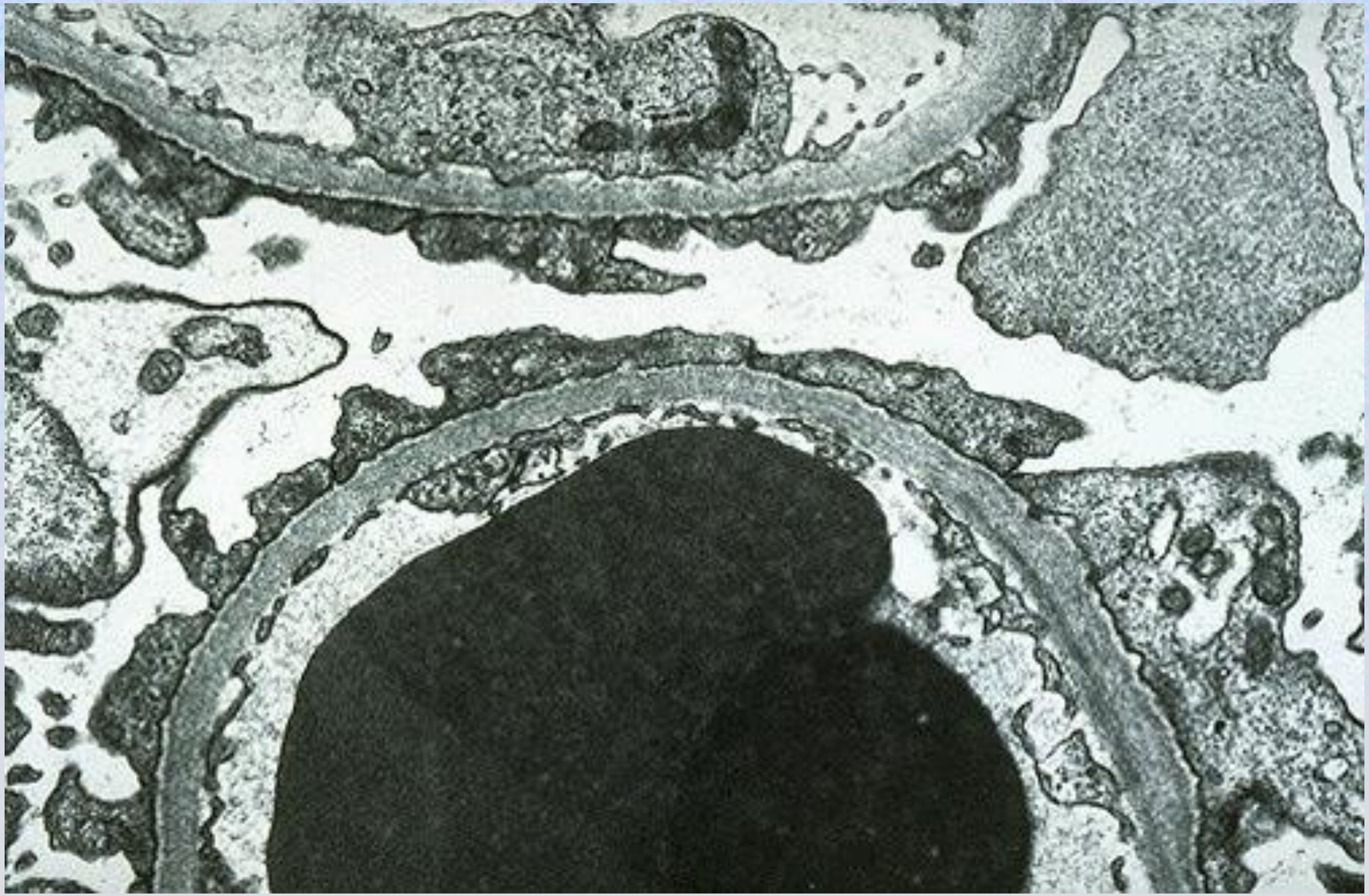
  Good response to steroids

  Electron microscopy (EM) – Fusion of podocyte foot processes

  Pathogenesis

  Circulating factor causing damage to podocytes (glomerular epithelial cells)





Treatment – MCD

- Treatment includes measures to clear proteinuria, reverse hypovolemia, and reduce oedema.
- Corticosteroids are the treatment of choice, leading to complete remission of proteinuria in most cases.
- Recurrence is common, however. Options for steroid-sparing therapy and steroid-resistant cases include cyclophosphamide, chlorambucil, mycophenolate, rituximab, and tacrolimus

Membranous GN

- The most common cause of nephrotic syndrome in adults
- Idiopathic (85%) or secondary (15%) to:
    - Drugs (eg, gold, penicillamine, nonsteroidal anti-inflammatory drugs [NSAIDs])
    - Infections (eg, hepatitis B or C virus infection, syphilis, HIV infection)
    - Autoimmune disorders (eg, systemic lupus erythematosus [SLE])
    - Thyroiditis
    - Cancer
    - Parasitic diseases (eg, malaria, schistosomiasis, leishmaniasis)
- 40% progress to chronic renal failure (CRF)

- **<u>Pathogenesis</u>**

  Subepithelial immune deposits

  Thickening of BM between deposits – eventually envelopes and covers the deposits

- Membranous nephropathy (MN) is rare in children and, when it occurs, is usually due to hepatitis B virus infection or SLE.

- Deep vein thrombosis is more frequent in MN

- Renal vein thrombosis is more frequent in MN and is usually asymptomatic, but may manifest with flank pain, hematuria, and hypertension

Diagnosis of MN

- Anti-Phospholipase A2 Receptor (Anti-PLA2R) Antibody (found in 70-80% of patients with idiopathic membranous nephropathy
- Evaluation for secondary causes
- Diagnosis is suggested by development of nephrotic syndrome, particularly in patients who have potential causes of membranous nephropathy (age group or evidence of secondary causes) .
- Proteinuria is in the nephrotic range in 80%. Laboratory testing is done as indicated for nephrotic syndrome .
- The glomerular filtration rate (GFR), if measured, is normal or decreased.
- Confirm diagnosis by renal biopsy

Prognosis

- About 25% of patients undergo spontaneous remission, 25% develop persistent, non-nephrotic–range proteinuria, 25% develop persistent nephrotic syndrome, and 25% progress to end-stage renal disease .
- **Risk of progression to renal failure is highest among patients with**
  - Persistent proteinuria ≥ 8 g/day, particularly men age > 50 years
  - An elevated serum creatinine level at presentation or diagnosis
  - Biopsy evidence of substantial interstitial inflammation

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)

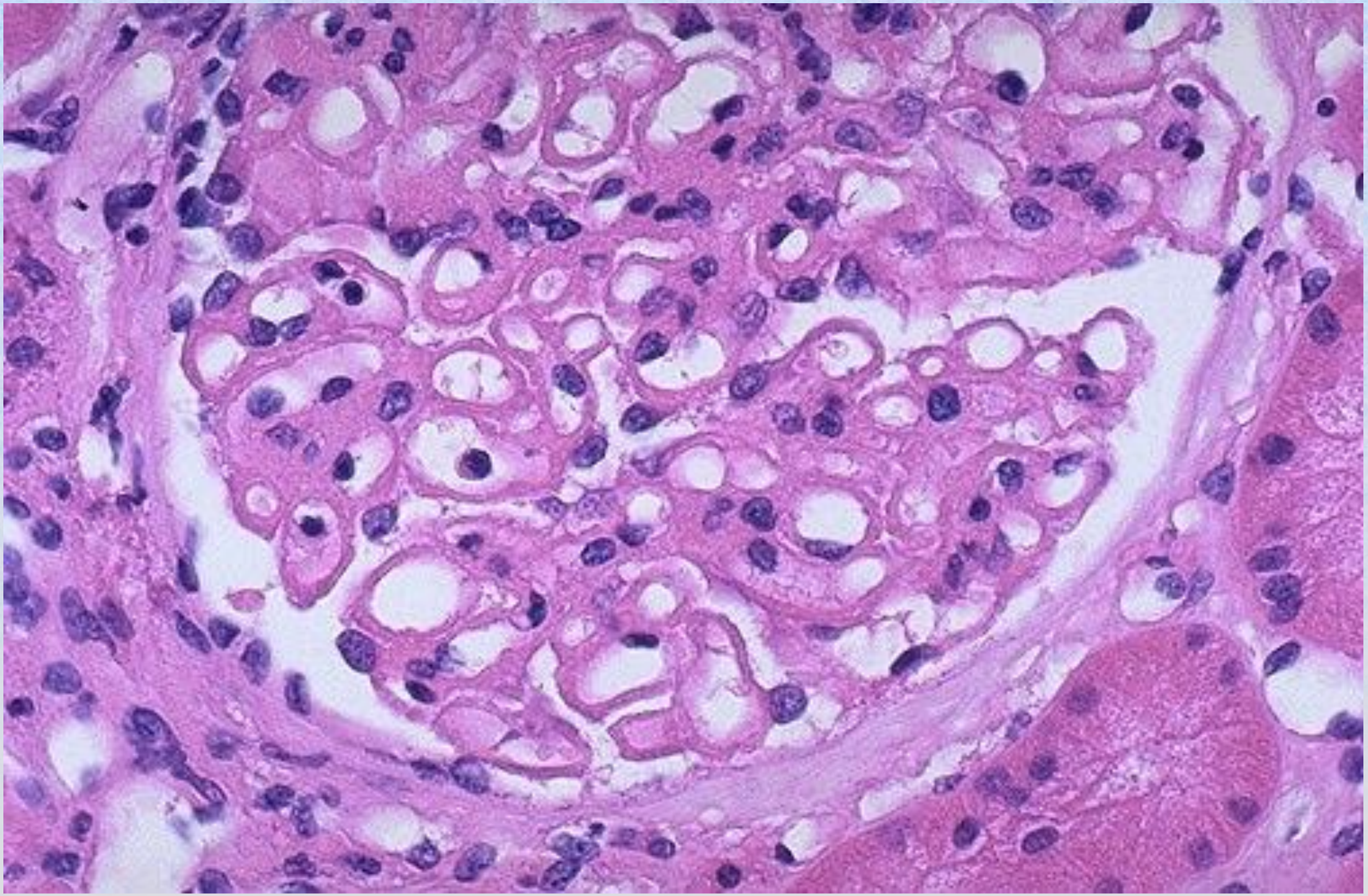
Secondary causes: infection, drugs, neoplasia, systemic lupus erythematosus

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



Treatment MN

- Treatment of secondary causes and of nephrotic syndrome as indicated
- Immunosuppressive therapy for patients at high risk of progression idiopathic memebranous
    - Asymptomatic patients with non-nephrotic–range proteinuria do not require treatment; Monitor renal function (eg, twice yearly when apparently stable).
    - Nephrotic-range proteinuria and asymptomatic or who have oedema that can be controlled with diuretics and treat for nephrotic syndrome.
    - Hypertension with MN should be given an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) to reduce proteinuria.
    - Kidney transplantation for patients with end-stage renal disease

Focal Segmental Glomerulosclerosis

- The most common cause of idiopathic (or primary) nephrotic syndrome among adults in the US
- Histologic lesion rather than disease
- Idiopathic or primary FSGS: typically presented with nephrotic syndrome

- **Secondary FSGS** :
  - Drugs (eg, heroin, lithium, interferon alfa, pamidronate, cyclosporine, or NSAIDs [causing analgesic nephropathy]),
  - Atheroembolic disease affecting the kidneys,
  - Obesity
  - HIV infection (see HIV-associated nephropathy), and disorders causing nephron loss (eg, reflux nephropathy, subtotal nephrectomy,
  - Renal dysgenesis [eg, oligomeganephronia: renal hypoplasia with a decreased number of nephrons])
  - Familial cases exist. Genetic disease

Clinical presentation-FSGS

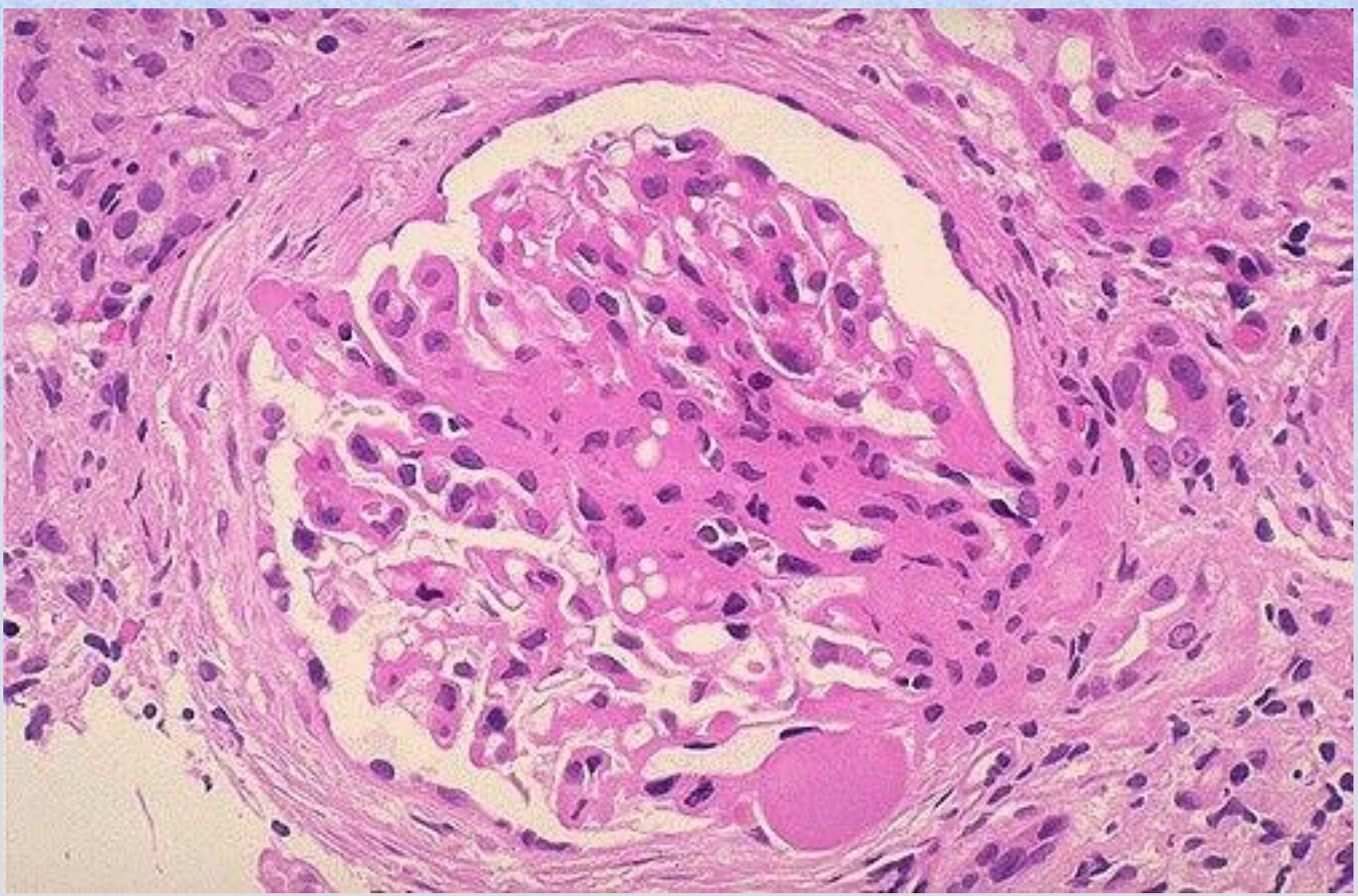
- Heavy proteinuria, hypertension, renal dysfunction, oedema, or a combination.
- Sometimes the only sign is asymptomatic proteinuria that is not in the nephrotic range.
- Microscopic haematuria is occasionally present.

Diagnosis

- Renal biopsy, when possible, with immunostaining and electron microscopy
- FSGS is suspected in patients with nephrotic syndrome, proteinuria, or renal dysfunction with no obvious cause, particularly patients who have disorders or use drugs associated with FSGS.
- Urinalysis is done and blood urea nitrogen (BUN), serum creatinine, and 24-hour urinary protein excretion or spot urinary protein: creatinine ratio are measured.

Renal biopsy –FSGS

- 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



Morphologic Variants of Focal Segmental Glomerulosclerosis

1. FSGS, not otherwise specified (also known as classic FSGS)
2. FSGS, perihilar variant
3. FSGS, cellular variant
4. FSGS, collapsing variant (also known as collapsing glomerulopathy)
5. FSGS, tip variant

Prognosis – FSGS

- Prognosis is poor.
- Spontaneous remissions occur in < 10% of patients.
- Renal failure occurs in > 50% of patients within 10 years; in 20%, end-stage renal disease occurs within 2 years despite treatment and is more likely if patients have significant tubulointerstitial fibrosis.
- The disorder is more rapidly progressive in adults than in children.
- Collapsing FSGS, which is typical in association with IV drug abuse or HIV infection), suggests more severe disease and rapid progression to renal failure.
- Pregnancy may exacerbate FSGS.

Treatment- FSGS

- Angiotensin inhibition
- Corticosteroids and sometimes cytotoxic drugs for idiopathic focal segmental glomerulosclerosis (FSGS)
- Treatment often is not effective.
- Kidney transplantation for patients with end-stage renal disease

Thank you