Renal Pathology
Glomerular diseases
L2

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TABLE 14.1 Glomerular Diseases

Primary Glomerular Diseases
Minimal-change disease
Focal segmental glomerulosclerosis
Membranous nephropathy
Acute postinfectious glomerulonephritis
Membranoproliferative glomerulonephritis
IgA nephropathy
Dense deposit disease
C3 glomerulonephritis
Glomerulopathies Secondary to Systemic Diseases
Lupus nephritis (systemic lupus erythematosus)
Diabetic nephropathy
Amyloidosis
Glomerulopathy secondary to multiple myeloma
Goodpasture syndrome
Microscopic polyangiitis
Granulomatosis with polyangiitis
Henoch-Schönlein purpura
Bacterial endocarditis–related glomerulonephritis
Thrombotic microangiopathy
Hereditary Disorders
Alport syndrome
Fabry disease
Podocyte/slit-diaphragm protein mutations

IgA, Immunoglobulin A.

Table 14.2 Summary of Major Primary Glomerular Diseases

Disease	Most Frequent Clinical Presentation	Pathogenesis	Glomerular Pathology		
			Light Microscopy	Fluorescence Microscopy	Electron Microscopy
Minimal-change disease	Nephrotic syndrome	Unknown; podocyte injury	Normal	Negative	Effacement of foot processes; no deposits
Focal segmental glomerulosclerosis	Nephrotic syndrome; nonnephrotic range proteinuria	Unknown: reaction to loss of renal mass; plasma factor?	Focal and segmental sclerosis and hyalinosis	Usually negative; IgM and C3 may be present in areas of scarring	Effacement of foot processes; epithelial denudation
Membranous nephropathy	Nephrotic syndrome	In situ immune complex formation; PLA2R antigen in most cases of primary disease	Diffuse capillary wall thickening and subepithelial "spike" formation	Granular IgG and C3 along GBM	Subepithelial deposits
Membranoproliferative glomerulonephritis (MPGN) type I	Nephrotic/nephritic syndrome	Immune complex	Membranoproliferative pattern; GBM splitting	Granular IgG, C3, C1q and C4 along GBM and mesangium	Subendothelial deposits
C3 glomerulopathy (dense deposit disease and C3 glomerulonephritis)	Nephrotic/nephritic syndrome; nonnephrotic proteinuria	Activation of alternative complement pathway; antibody-mediated or hereditary defect in regulation	Mesangial proliferative or membranoproliferative patterns	C3	Mesangial, intramembranous and subendothelial electron-dense or "waxy" deposits
Acute postinfectious	Nephritic syndrome	Immune complex	Diffuse endocapillary	Granular IgG and	Primarily

Disease	Most Frequent Clinical Presentation	Pathogenesis	Glomerular Pathology		
			Light Microscopy	Fluorescence Microscopy	Electron Microscopy
Acute postinfectious glomerulonephritis	Nephritic syndrome	Immune complex mediated; circulating or planted antigen	Diffuse endocapillary proliferation; leukocytic infiltration	Granular IgG and C3 along GBM and mesangium	Primarily subepithelial humps
IgA nephropathy	Recurrent hematuria or proteinuria	Immune complexes containing IgA	Mesangial or focal endocapillary proliferative glomerulonephritis	IgA ± IgG, IgM, and C3 in mesangium	Mesangial and paramesangial dense deposits
Anti-GBM disease (e.g. Goodpasture syndrome)	Rapidly progressive glomerulonephritis	Autoantibodies against collagen type IV α3 chain	Extracapillary proliferation with crescents; necrosis	Linear IgG and C3; fibrin in crescents	No deposits; GBM disruptions; fibrin
Pauci-immune glomerulonephritis	Rapidly progressive glomerulonephritis	Anti-neutrophil cytoplasmic antibody	Extracapillary proliferation with crescents; necrosis	Fibrin in crescents	No deposits; GBM disruptions; fibrin

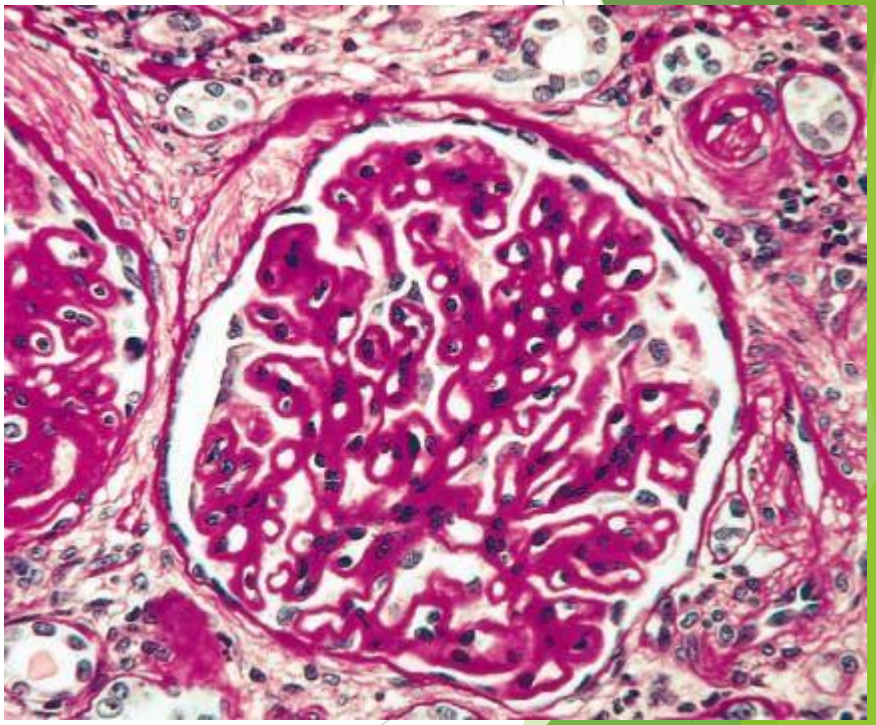
GBM, Glomerular basement membrane; *IgA*, immunoglobulin A; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M.

Membranous GN

- Characterized by uniform thickening of the capillary wall due to diffuse deposition of electron dense deposits on epithelial aspect of GBM.
- It usually presents in adults between the ages of 30 and 60 years and follows an indolent and slowly progressive course
- Adults 30%, children 5%.
- 85% Idiopathic, 15% Secondary.

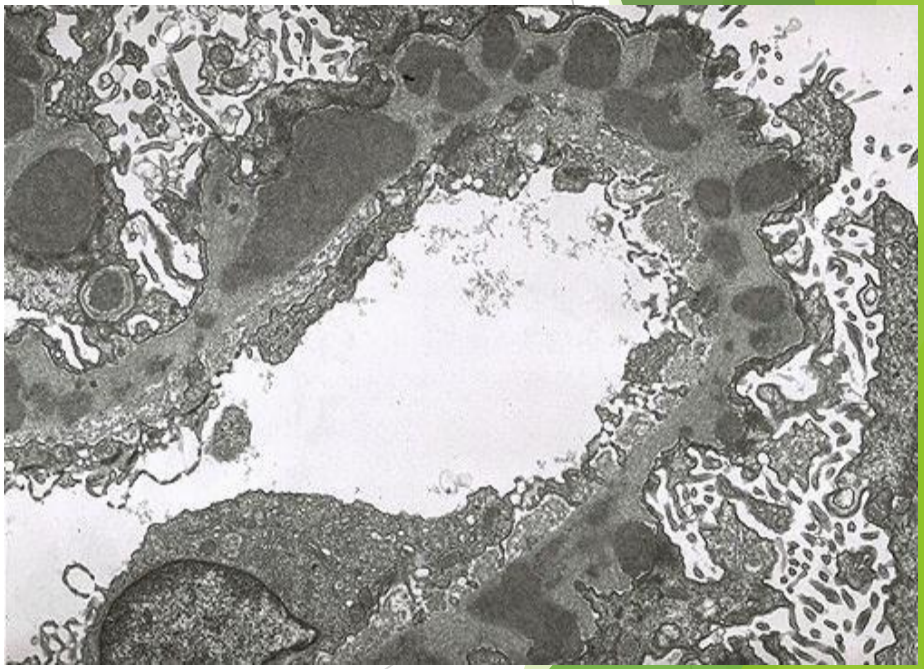
Membranous GN

The main histologic feature is **diffuse thickening** of the capillary wall (GBM glomerular basement PAS stain

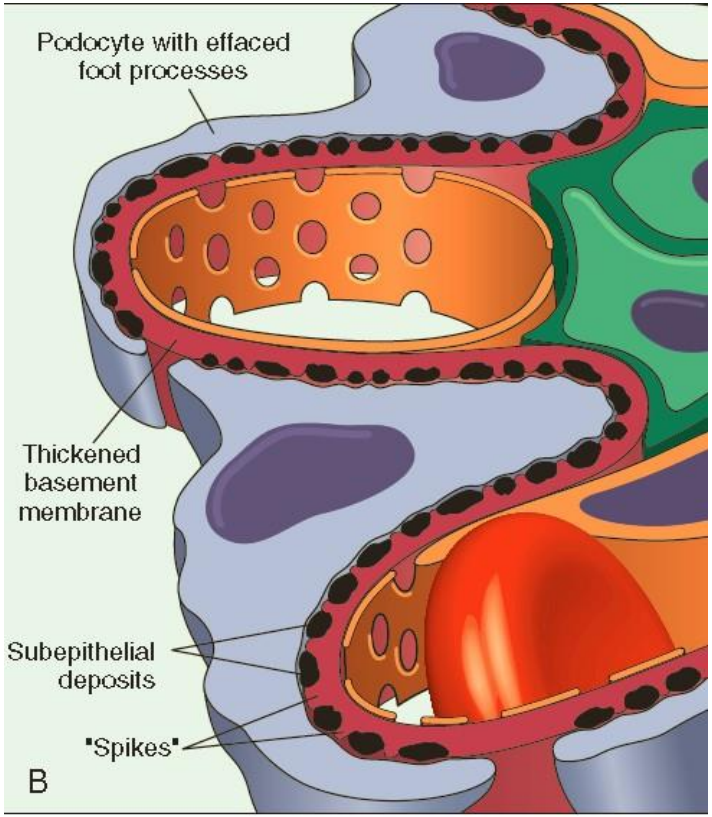


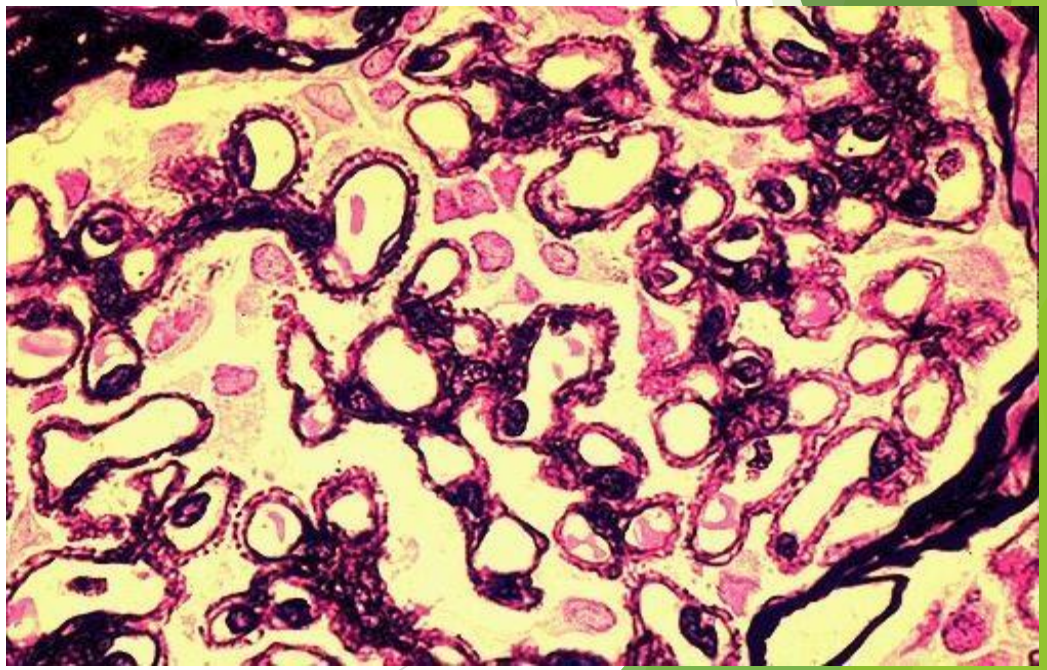
Membranous GN

EM reveals that thickening is caused by **subepithelial** deposits, which nestle against the GBM & are separated from each other by small, spike~~-like protr~~usions of GBM matrix that form in reaction to the deposits (**spike & dome pattern**)

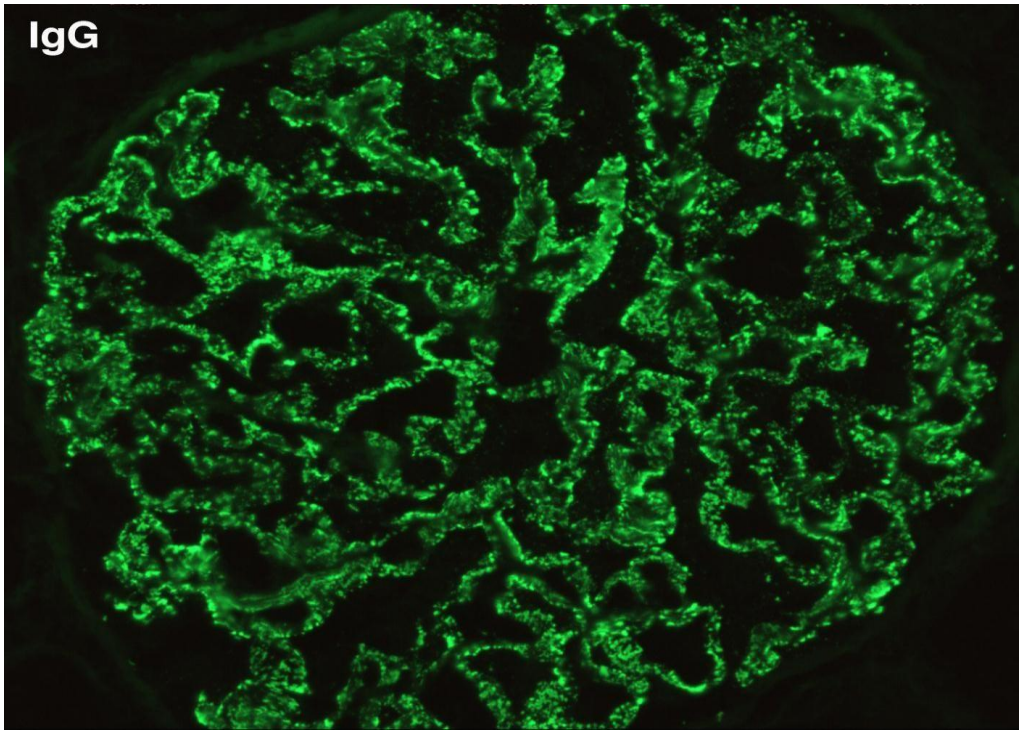


Membranous GN





Membranous GN

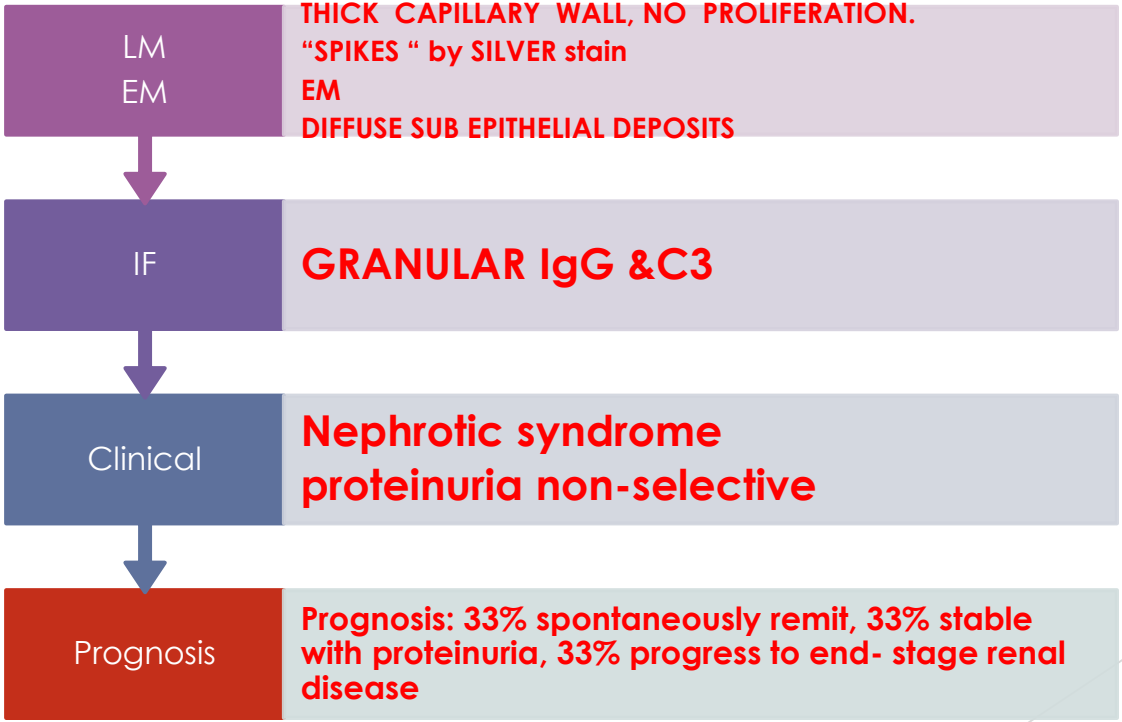


IF microscopy demonstrates that the granular deposits contain both immunoglobulins & complement

Membranous GN

- Sudden onset full-blown nephrotic syndrome
- In contrast to MCD, the proteinuria is nonselective
- Usually fails to respond to corticosteroid therapy
- Secondary causes should always be ruled out
- Variable prognosis:
  - Proteinuria persists in >60% of patients
  - ~40% progress to renal failure over 2 to 20 years.
  - 10-30% benign course partial or complete remission of proteinuria.

Membranous GN (cont)



Nephritic Syndrome

- Acute, rapidly progressive, or chronic
- Manifestations
  - Hematuria
  - Variable proteinuria
  - Impaired renal function(increase in blood urea & serum creatinine)
  - Hypertension
  - Edema

Nephritic Syndrome

- **caused by inflammatory lesions of glomeruli**
- The lesions have in common **proliferation of the cells** within the glomeruli + an infiltrate of leukocytes.
- **Injury the capillary walls** → permitting blood to pass into the urine → lead to a reduction in the GFR.
- **Reduced GFR** →oliguria, fluid retention, and azotemia
- **Hypertension** is caused by both the fluid retention and augmented renin release from the ischemic kidneys
- may be **primary glomerular** diseases, such as postinfectious glomerulonephritis (GN) and various forms of crescentic GN, or **secondary to systemic** disorders such as systemic lupus erythematosus.

Acute Diffuse Proliferative GN

- **Post infectious GN:**
- **strep., pneumococc., staph., measels, mumps, Hep. B&C**

POSTSTREPTOCOCCAL GN

- Acute nephritic syndrome presents 1 - 4weeks after a strep infection of throat or skin.
- Group A ,B -hemolytic

- **Light microscopy**
  - Diffuse proliferation , leukocytic infiltration
- **EM**
  - subepithelial humps
- **IF**
  - granular IgG & C3 in GBM & Mesangium

Poststrep GN (cont)

- Pathogenesis
  - Nephritogenic strains >90%
  - ASO titer increase
  - Immune complex disease/ circulating or implanted Ag or both.
  - Decrease in serum complement.
  - Implicated Ags **streptococcal exotoxin B (Spe B) and streptococcal glyceraldehyde-3-phosphate dehydrogenase (GAPDH) affinity for glomerular proteins and plasmin**

Poststrep GN (cont)

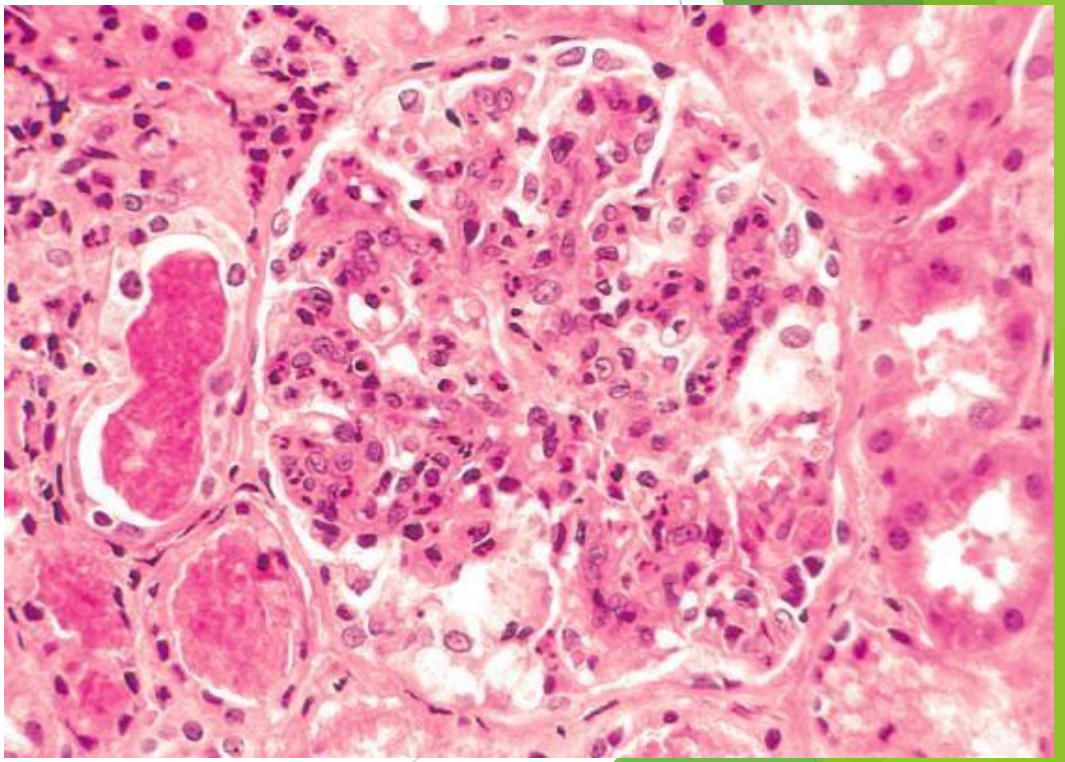
- Clinical picture
- fairly common , usually children (6 - 10 years
- Urine---- red cell casts ; proteinuria mild
- Prognosis
- children >95% recovery ,1% RPGN ,2% CRF
- Adults 15-50% develop ESRD

Post infectious GN
LM morphology

Most characteristic change increased cellularity of all glomeruli (nearly all glomeruli) caused by

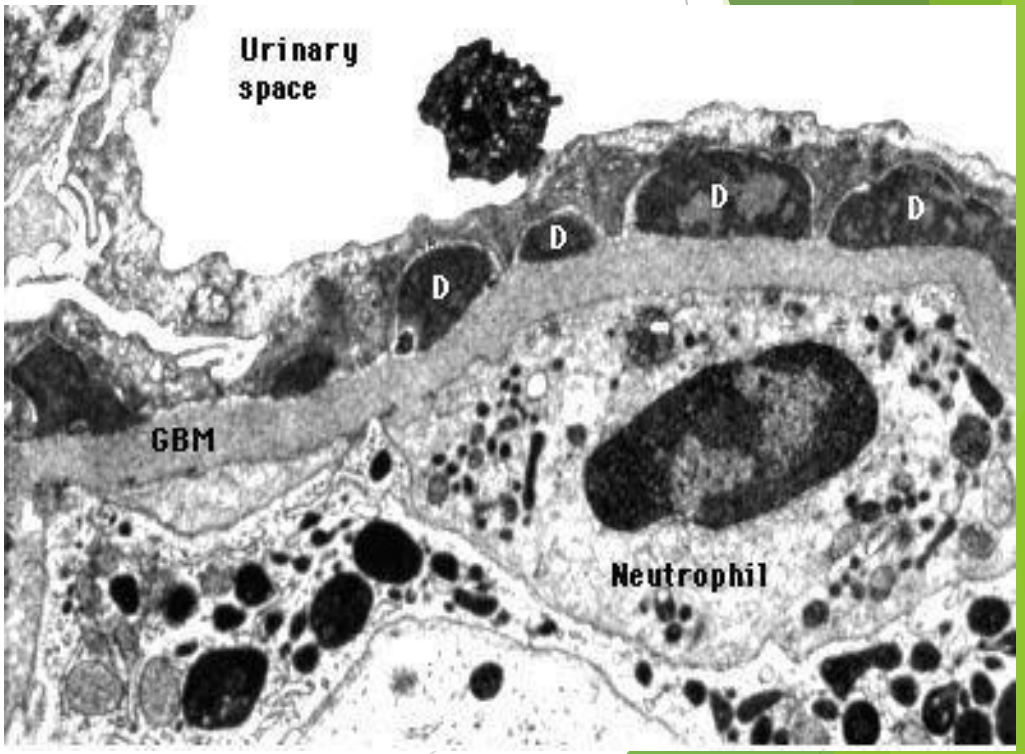
(1) proliferation & swelling of endothelial & mesangial cells

(2)by infiltrating neutrophils & monocytes.



Post infectious GN
EM morphology

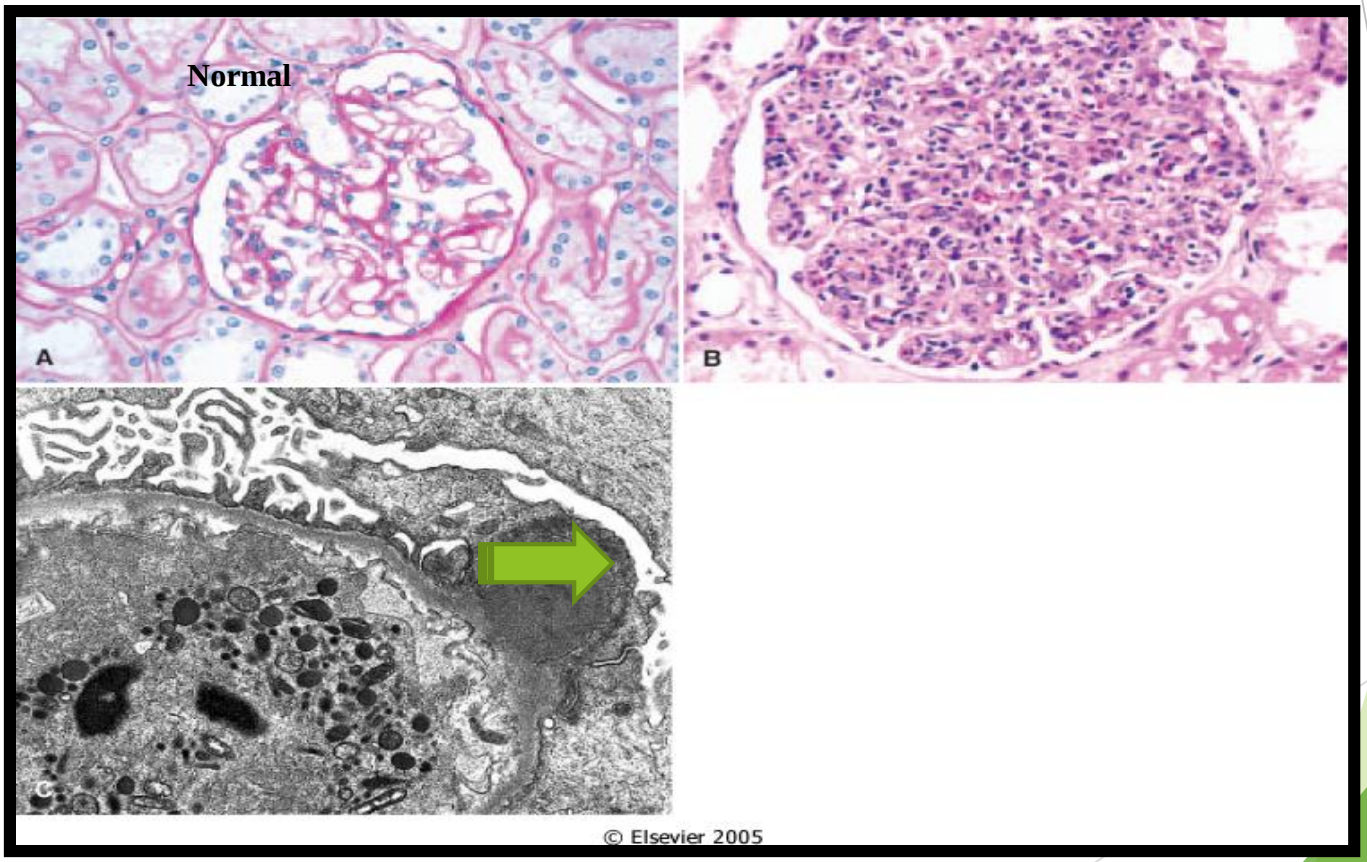
EM: shows deposited immune complexes as **subepithelial "humps"** (on the epithelial side of GBM)
IF: scattered granular deposits of IgG & complement within the capillary walls



Post infectious GN

- Most commonly present as acute nephritic syndrome
- Fever, nausea, gross hematuria, & mild proteinuria.
- Serum complement levels are low during the active phase of the disease.
- Serum anti–streptolysin Oantibody titers are elevated in poststreptococcal cases.
- Recovery occurs in most children with poststreptococcal disease

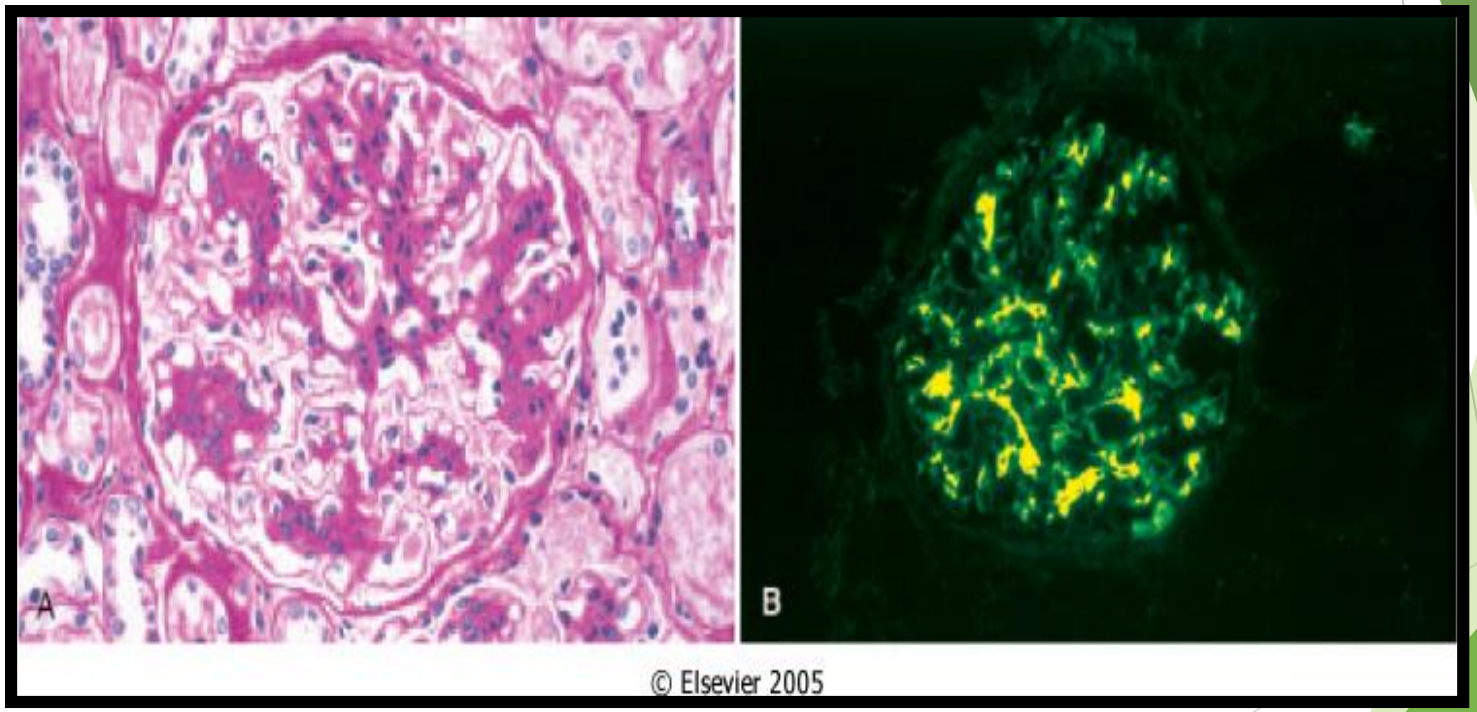
Acute proliferative GN



IgA Nephropathy (IgA-N)

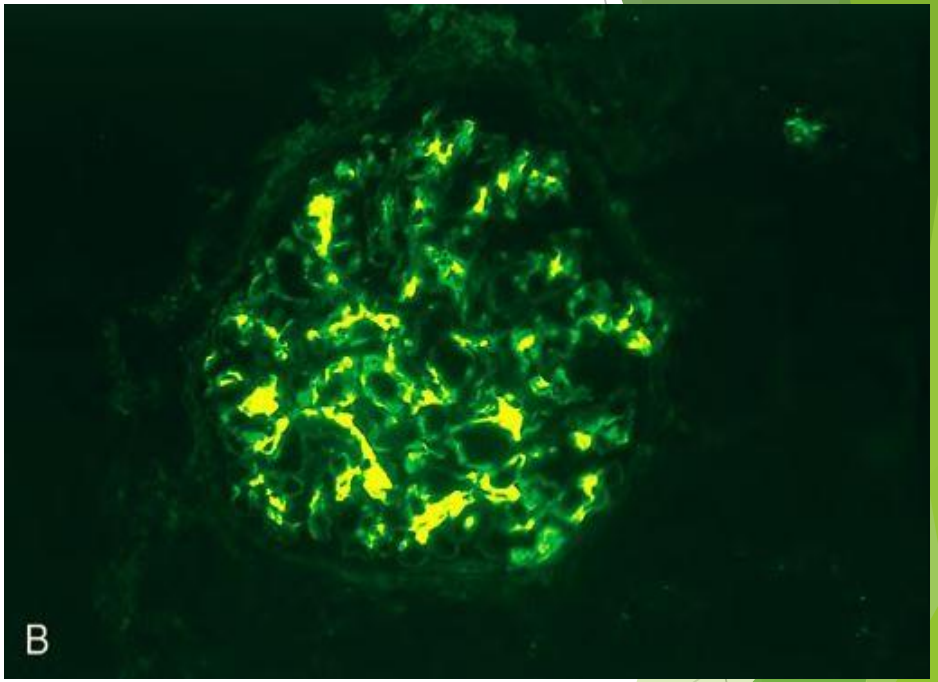
- GN characterized by the presence of prominent IgA deposits in the mesangial regions.
  - Commonest type of GN
  - Children & young adults
  - Usually 1 to 2 days after URTI
  - Microscopic or gross hematuria
- LM ----- normal / mesangioprolif / focal or diffuse prolif.
- EM ---- electron dense deposits in the mesangium
- IF ---- diffuse , usually global mesangial IgA in all cases .

IgA Nephropathy



IgA Nephropathy

Different **LM** findings but whatever the histologic lesions, the pathognomonic feature by **IF** is the deposition of **IgA** and C3, in the **mesangial region. (diagnostic)**



Pathogenesis of IgA-N

- Activation of **alternative pathway of complement**
- Genetic or acquired abnormality leading to **increase IgA** synthesis by mucosal surfaces after antigenic stimulation → Circulating IgA aggregates or complexes entrapped in mesangium and activate alternative pathway.
- Increased frequency in individuals with celiac disease in liver disease (secondary IgA nephropathy).

IgA - Nephropathy

- Prognosis
  - initial benign course but slowly progressive
  - 20 - 50% progress to CRF in 20 years
- Bad prognostic features
  - old age
  - heavy proteinuria
  - Hypertension
  - sclerosis
- 20 - 60% recur in transplants.

Membranoproliferative (mesangiocapillary) GN

- Characterized histologically by alterations in the basement membrane, proliferation of glomerular cells and leukocyte infiltration.
  - Children and young adults
  - nephrotic syndrome, nephritic syndrome, proteinuria, hematuria or nephrotic/nephritic.
- Secondary
  - chronic immune complex disorder (SLE, HCV, HIV)
  - malignant conditions (CLL, lymphoma, melanoma)
  - *MPGN type I* and *dense deposit disease* (formerly *MPGN type II*).

MPGN

Type I

- The antigens Mostly are proteins derived from infectious agents e.g., hepatitis C & B viruses;

1. "planted" antigens: after first binding to or becoming trapped within glomerular structures.
2. Contained in preformed immune complexes deposited from the circulation.

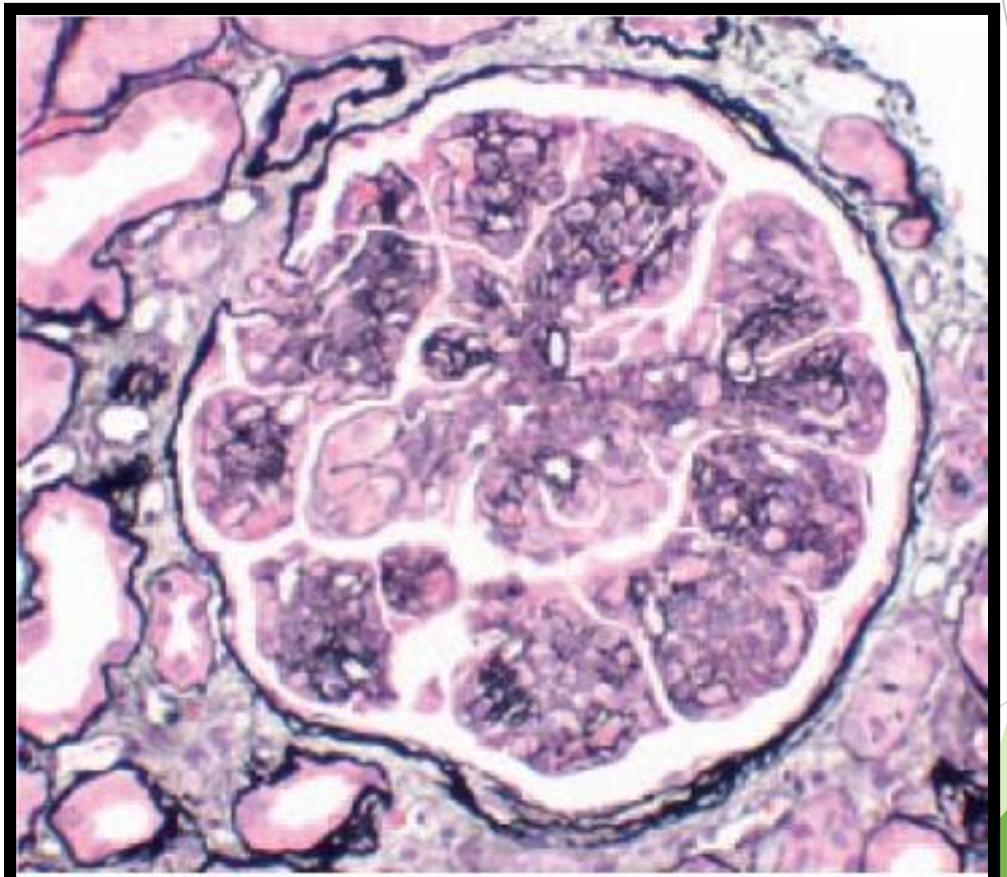
Dense Deposits disease

- **Complement dysregulation**
- Autoantibody against C3 convertase (called C3 nephritic factor)
- Ab stabilizes the enzyme
  uncontrolled cleavage of C3 & activation of the alternative complement pathway

MPGN

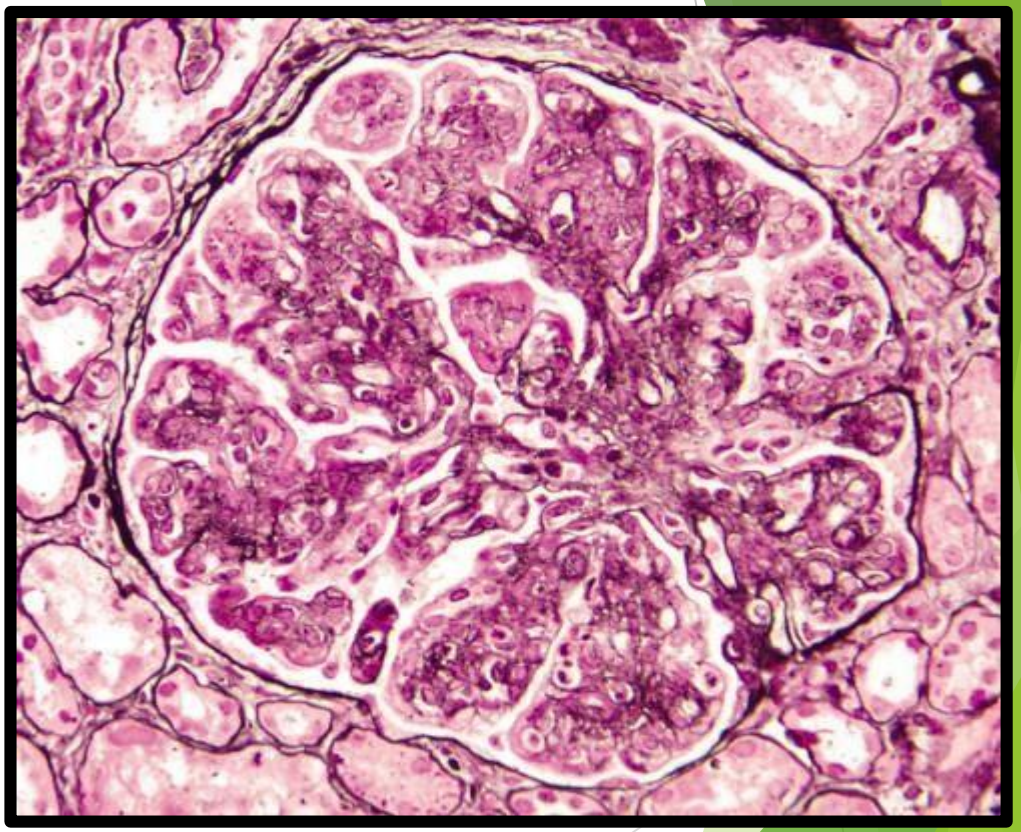
- Light microscopy:
  - enlarged glomeruli, proliferation + infiltration of inflammatory cells, lobular accentuation, thickening of capillary walls ”reduplication” of glom capillary “tram-tracking”, crescents may be seen.
  - tubulointerstitial changes & vascular changes of HT.
- EM type I
  - subendothelial deposits, circumferential mesangial interposition, increase in mesangial cells & matrix.
- IF type I
  - C3 ,C1q,C4 in granular pattern in mesangial area.

MPGN



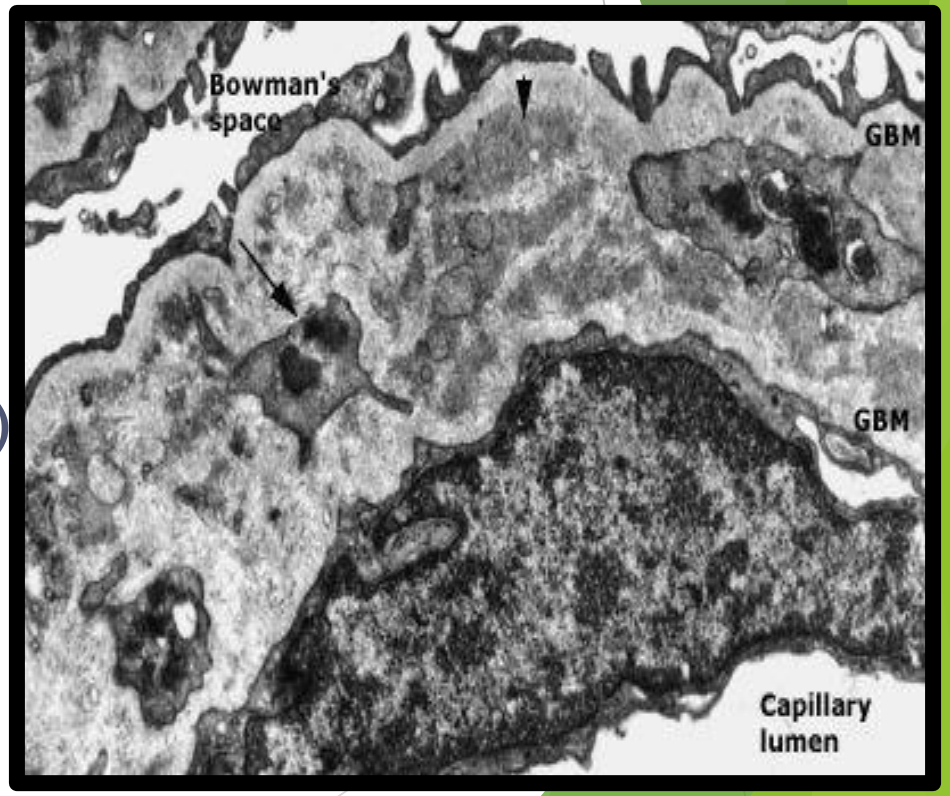
MPGN

Glomeruli are large, have an accentuated **lobular** appearance; proliferation of mesangial & endothelial cells as well as infiltrating leukocytes



MPGN EM

Marked thickening of the glomerular capillary wall by immune deposits (short arrow) & by interposition of mesangial cell processes (long arrow)



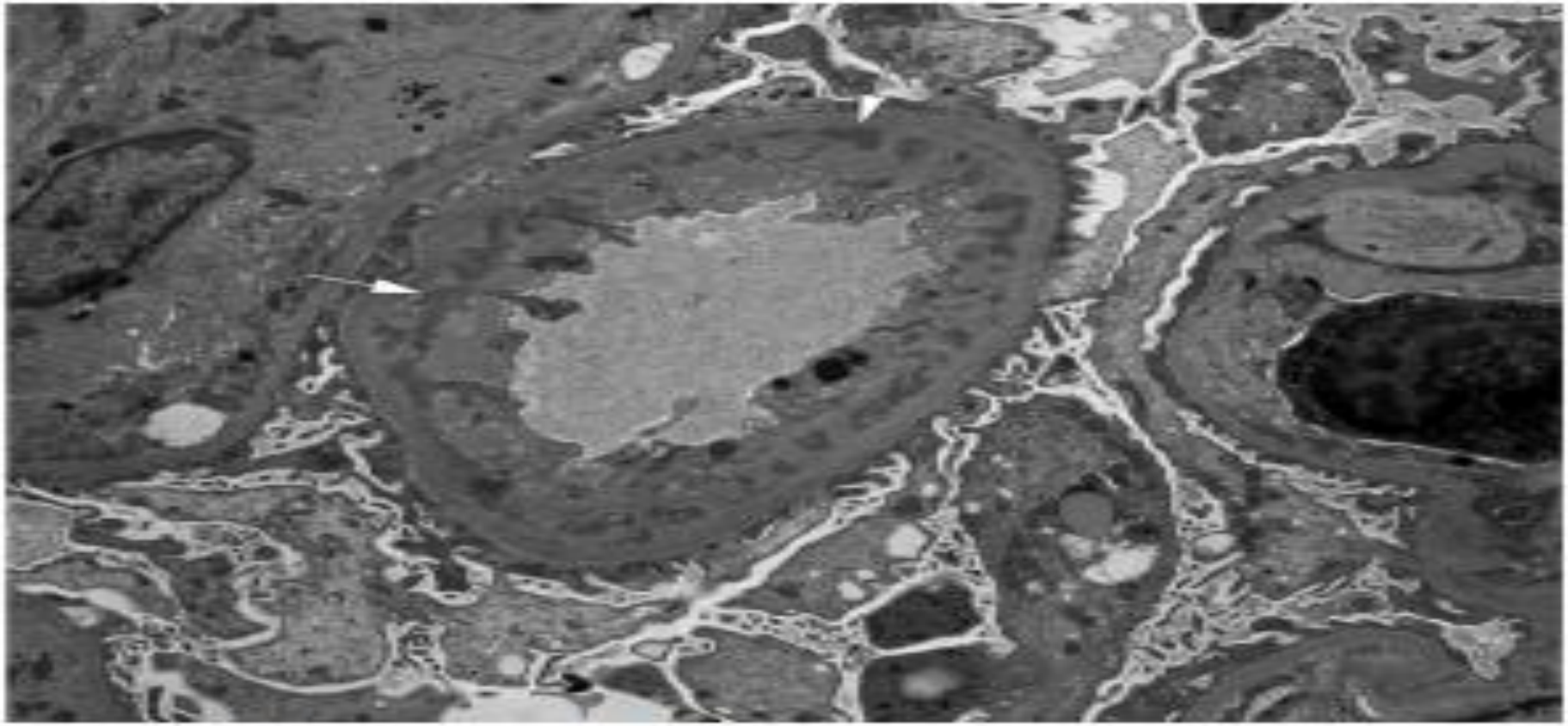
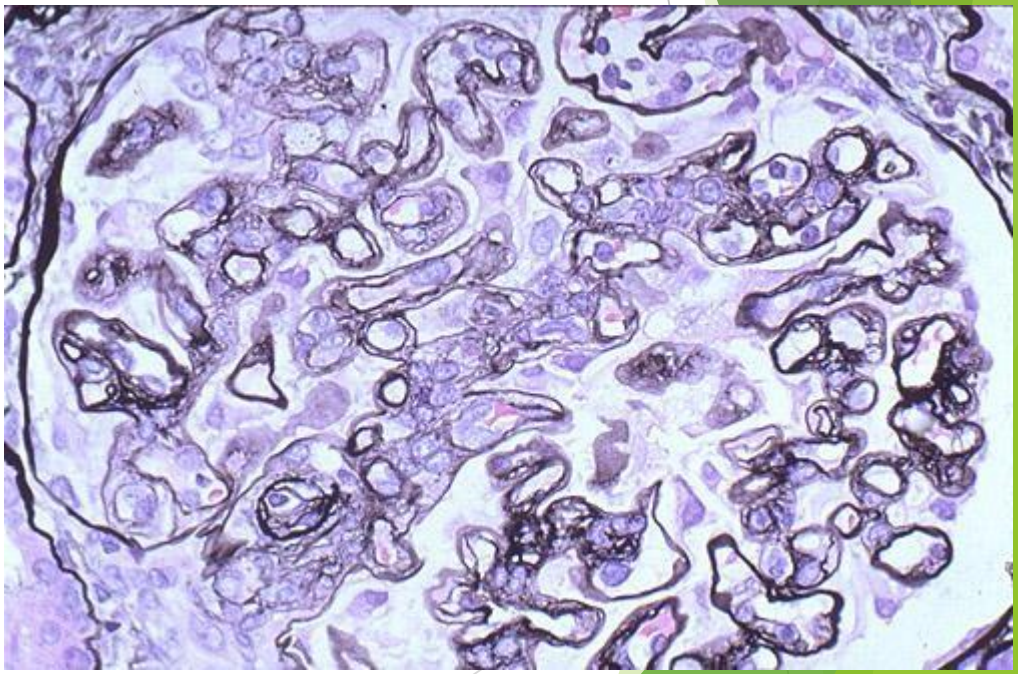


Figure 6. Membranoproliferative glomerulonephritis with subendothelial deposits (arrows) and new basement membrane material between the interposed cell and endothelium (electron microscopy).

MPGN
LM morphology

The GBM is thickened, and the glomerular capillary wall often shows a **double contour**, or "**tram track**," appearance, especially evident with use of silver



Dense Deposit Disease (DDD)

Pathogenesis of Dense deposits disease (previously Type II MPGN):

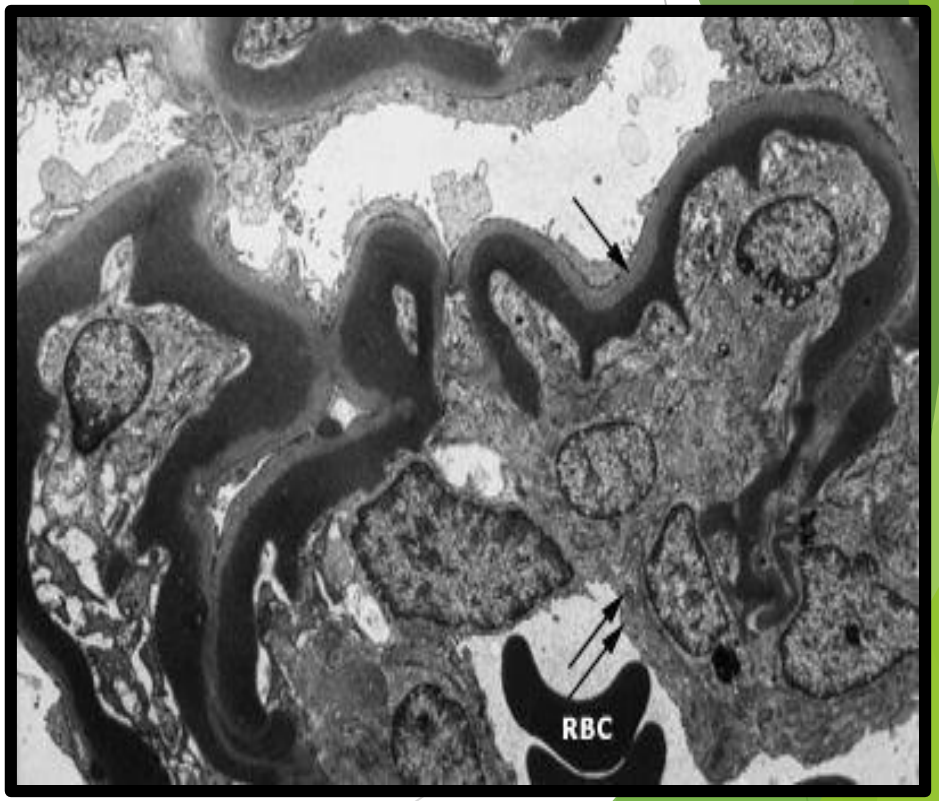
- Patients have abnormality that lead to activation of alternative pathway of complement. They have persistent low C3 , normal C1 & C4.
- >70% have C3 nephritic factor ***(C3NeF)***, an auto Ab that stabilizes C3 convertase leading to persistence of C3 degradation & hypocomplementemia.
- Mutation of factor H, or autoantibodies to factor H.

Dense Deposit Disease (DDD)

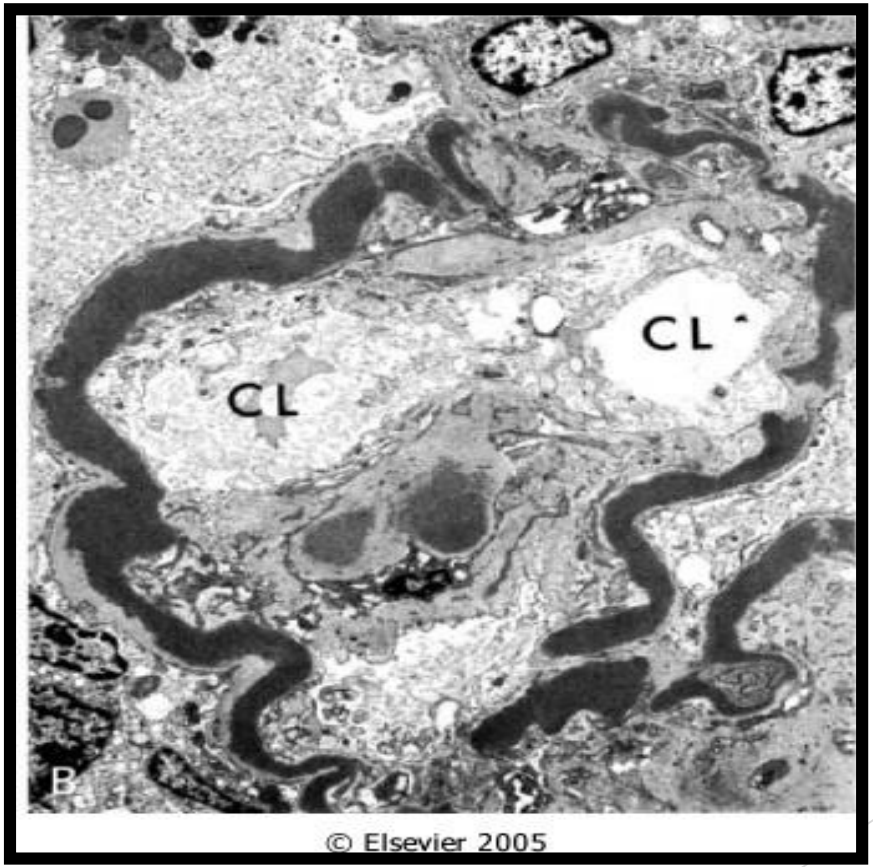
- Dense deposits disease (previously Type II MPGN)
- LM
  - similar to type I: The glomeruli are hypercellular, the capillary walls show duplicated basement membranes, and the mesangial matrix is increased
- EM
  - lamina densa transformation into an irregular , ribbon - like ,extremely electron dense structure.(Dense Deposit Disease) DDD.
- IF
  - granular mesangial & short or discontinuous linear capillary loop deposits of C3. No early complement components or Igs.

MPGN II/ DDD

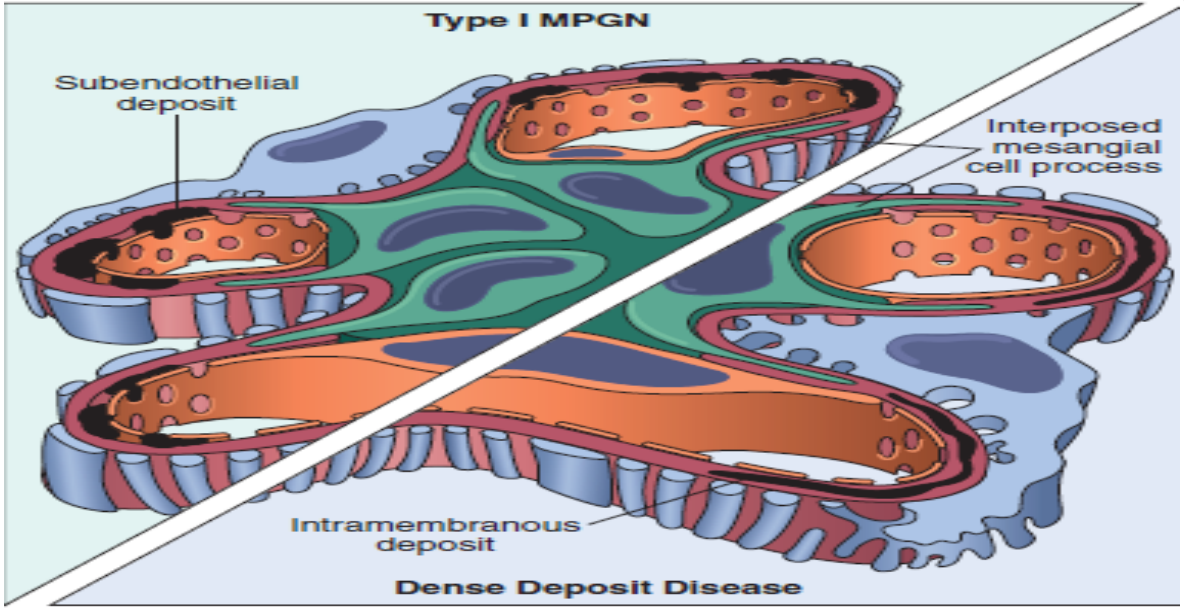
There are **dense** homogeneous deposits within the basement membrane. **Ribbon-like appearance** of subendothelial & intramembranous material



Dense Deposit Disease (DDD)

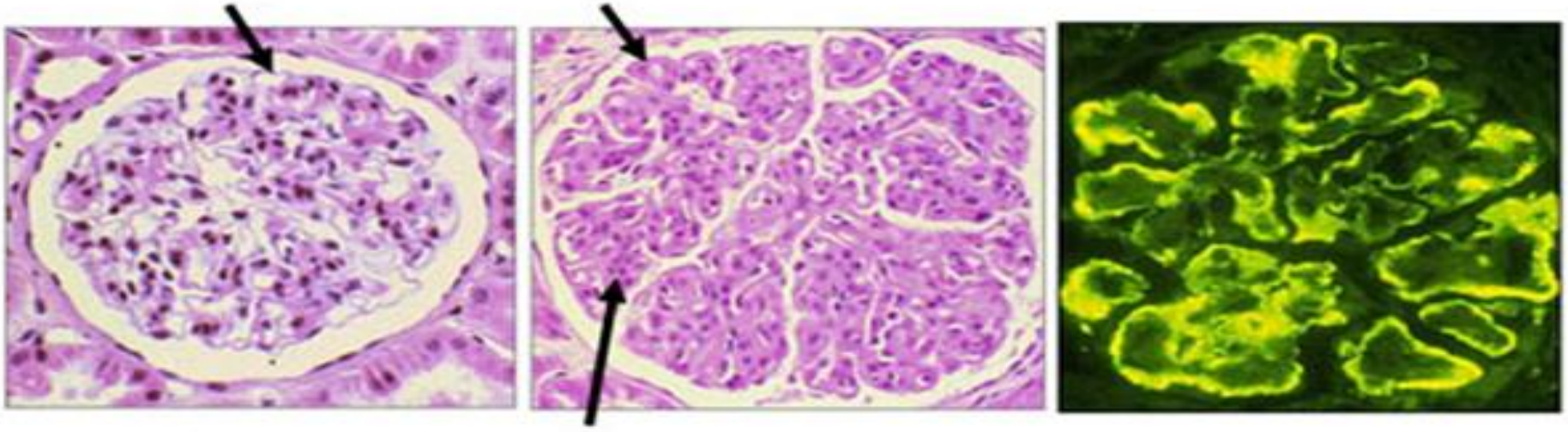


Schematic representation of patterns in two types of MPGN.

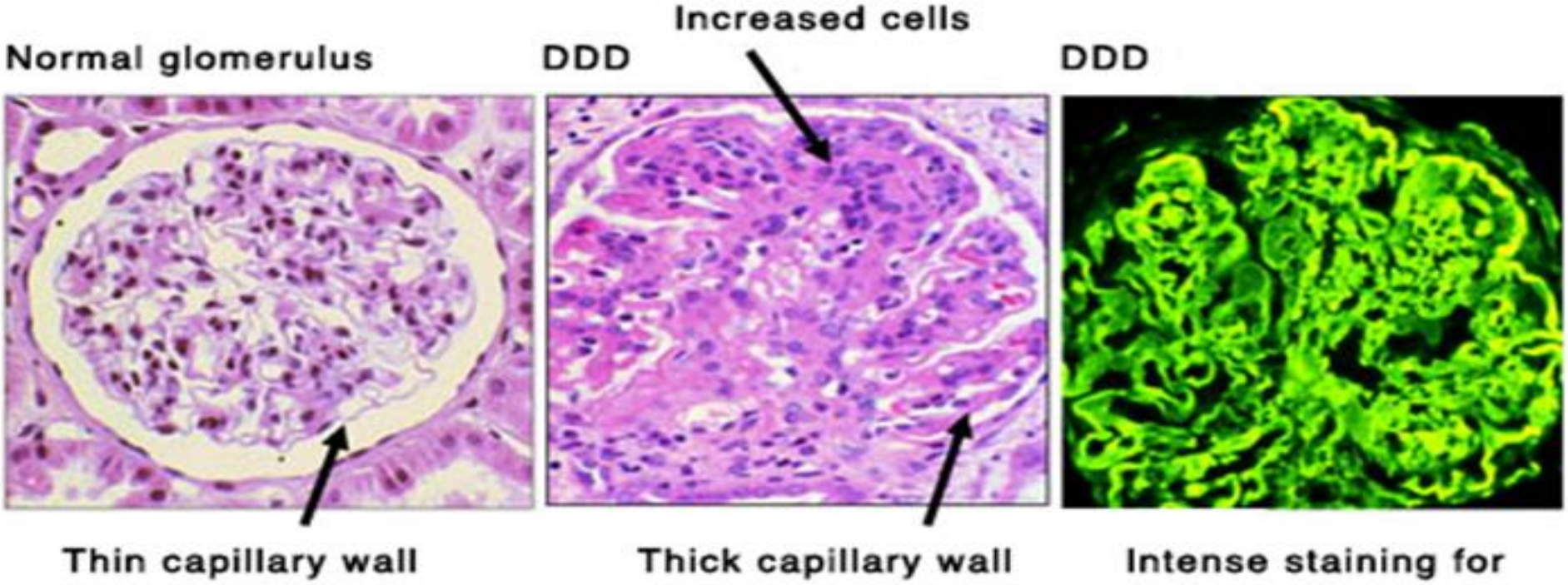


In type I: Subendothelial deposits.
In dense deposit disease: Intramembranous dense deposits. In both types:
Mesangial interposition gives appearance of split basement membranes viewed by light microscopy.

Membranoproliferative Glomerulonephritis Type I Glomerulus Viewed by Light Microscopy (left) and Immunofluorescence Microscopy (right)



Dense Deposit Disease (Membranoproliferative Glomerulonephritis Type II) Glomerulus Viewed by Light Microscopy (left) and Immunofluoresence Microscopy (right)



MPGN clinical manifestations

- **MPGN type I is more common than DDD.**
- **Clinical course:**
- **The principal mode of presentation (50% of cases) is the nephrotic syndrome, may begin as acute nephritis or mild proteinuria.**
- **Prognosis:**
- **Generally poor.**
- **40% progress to end-stage renal failure, 30% had variable degrees of renal insufficiency, and the remaining 30% had persistent nephrotic syndrome without renal failure.**
- **Dense-deposit disease has a worse prognosis, and it tends to recur in renal transplant recipients**

Hereditary Nephritis

- A group of heterogeneous hereditary - familial renal diseases associated with glomerular lesions.

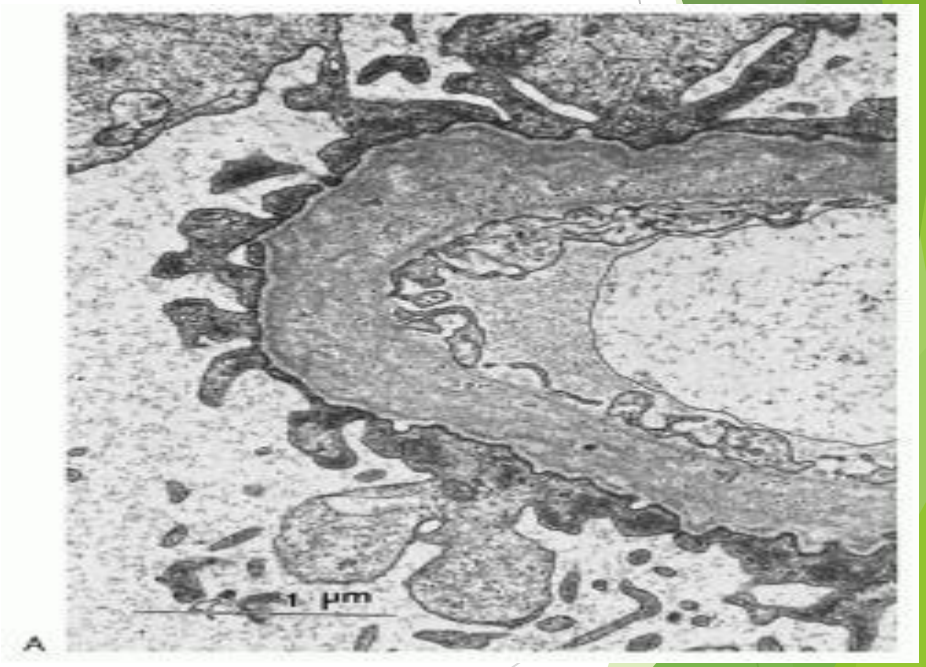
- Alport syndrome
  - Nephritis + nerve deafness + eye disorders.
  - Males > females
  - X-linked, AR or AD
  - LM - Normal glomeruli early in the disease, secondary sclerosis later, Foam cells in the interstitium.

Hered. Nephritis (cont.)

- EM ----GBM shows irregular thickening, lamination, splitting (**"basketweave"** appearance)
- Defective GBM synthesis, mutation in encoding for alpha-5 chain of collagen type IV.
- Gross hematuria-- mostly males 5 - 20 yrs
- CRF in 20 yrs

Alport syndrome

Early: GBM is thin & attenuated
Later: develops irregular foci of thickening, splitting and lamination, yielding a "**basket-weave** "appearance.



RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

- **Clinically - rapid and progressive loss of renal function with severe oliguria and (if not treated) death from renal failure within weeks or months.**
- **Histologically- presence of crescents in most glomeruli.**
- **RPGN is not a single disease it is a syndrome which could be caused by a number of diseases both primary of kidney and systemic diseases.**

CLASSIFCATION AND PATHOGENESIS OF(RPGN) ACCORDING TO IMMUNOFLUORESCENCE FINDING

- 1- ***Anti-GBM antibody–mediated crescentic GN:*** Linear pattern for IgG & C3 (12%)
  - Anti glomerular basement membrane disease
    - anti bodies to G.B.M , could cross react with pulmonary alveolar B.M to produce the clinical syndrome of lung hemorrhage and renal failure (Good Pasture`s syndrome).
- 2-***Immune complex–mediated crescentic GN:*** Granular pattern for IgG & C3 (44%)
  - Immune complex disease
    - post infect., SLE, IgAnN, HSP
    - idiopathic

RPGN (cont)

- 3- ***Pauci-immune type crescentic GN:*** **Immunofl. Negative (44%)**
  - **most have ANCA in serum (ANCA Associated RPGN)**
    - **some associated with systemic vasculitis**
    - **the rest no association (idiopathic).**

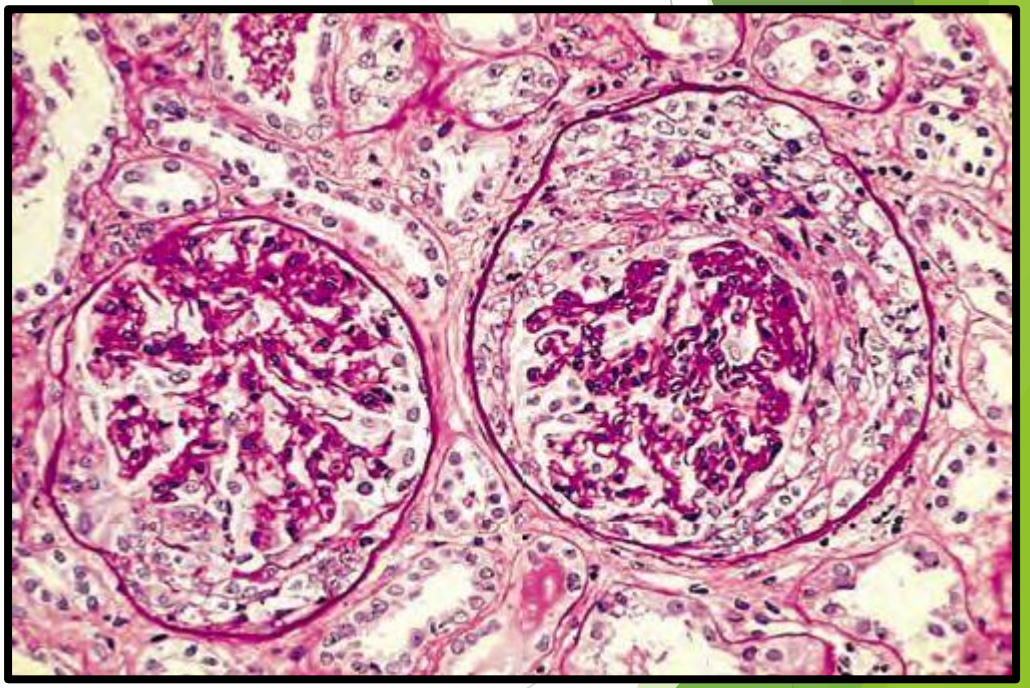
MORPHOLOGY OF RPGN
RPGN (cont)

- **Light microscopy** (CRESCENTIC GN)
  - > 50 - 75% of glomeruli contain crescents obliterating Bowman capsule and compressing the underlying glomeruli which could show normal, or focal proliferative changes.
- **EM**
  - rupture of GBM only or with electron dense deposits
- **IF**
  - linear, granular or none.

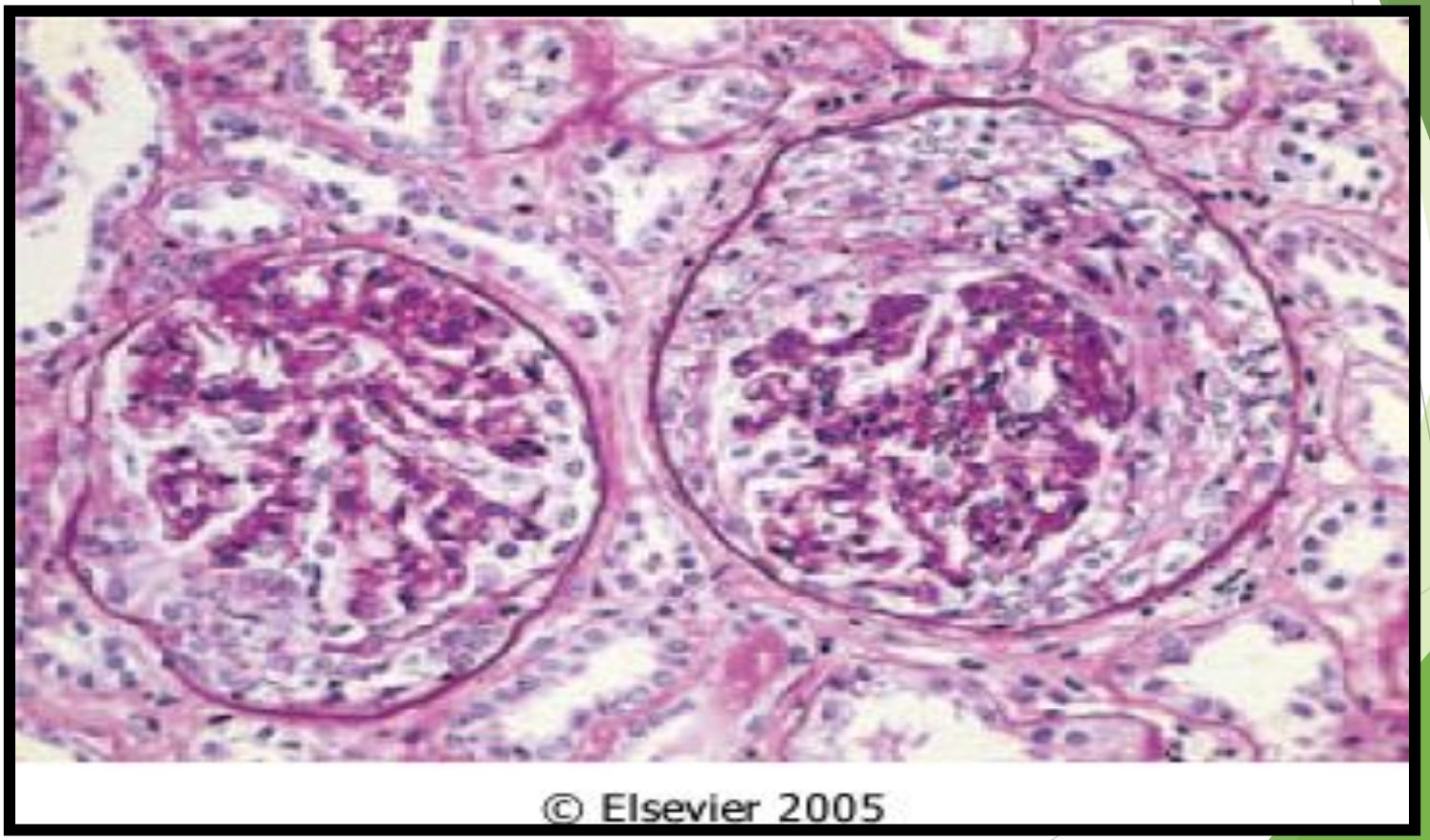
MORPHOLOGY OF RPGN

LM

Collapsed glomerular tufts and **crescent-shaped** mass of proliferating parietal epithelial cells & leukocytes internal to Bowman capsule



Cresentric GN



Prognosis of (RPGN)

- Prognosis depends roughly on the fraction of the involved glomeruli.
- Milder forms may subside but renal involvement is usually progressive leading to oliguria.
- Therapy
  - Plasmapheresis (***Immune complex–mediated crescentic GN usually doesn't respond)***
  - steroids
  - cytotoxic drugs
- Some patients requires long term dialysis, and renal transplant.

The end

Good luck