Renal Pathology
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2024

Audio 2

The Nephrotic Syndrome

- a clinical complex resulting from glomerular disease & includes the

following:

- (1) massive proteinuria (3.5 gm /day in adults).
- (2) hypoalbuminemia (≤ 3 gm/dL).
- (3) generalized edema
- (4) hyperlipidemia and lipiduria.
- (5) little or no azotemia, hematuria, or hypertension.

❑Causes of Nephrotic Syndrome

1-Primary Glomerular Diseases

2-Secondary (Systemic Diseases with Renal Manifestations)

❑Primary Diseases that Present Mostly with Nephrotic Syndrome

1-Minimal-change disease

2-Focal segmental glomerulosclerosis(FSGS).

3-Membranous nephropathy

4-membranoproliferativeGN type 1 (usually a combination of nephrotic/ nephritic syndrome)

B-Systemic Diseases with Renal Manifestations:

1. Diabetes mellitus.
2. Amyloidosis
3. Systemic lupus erythematosus
4. drugs (gold, penicillamine, "street heroin").
5. Infections (malaria, syphilis, hepatitis B, HIV).
6. Malignancy (carcinoma, melanoma).
7. Miscellaneous (e.g. bee-sting allergy)

Minimal Change Disease (Lipoid Nephrosis),nil disease, and foot process disease

➢ Essential Features :

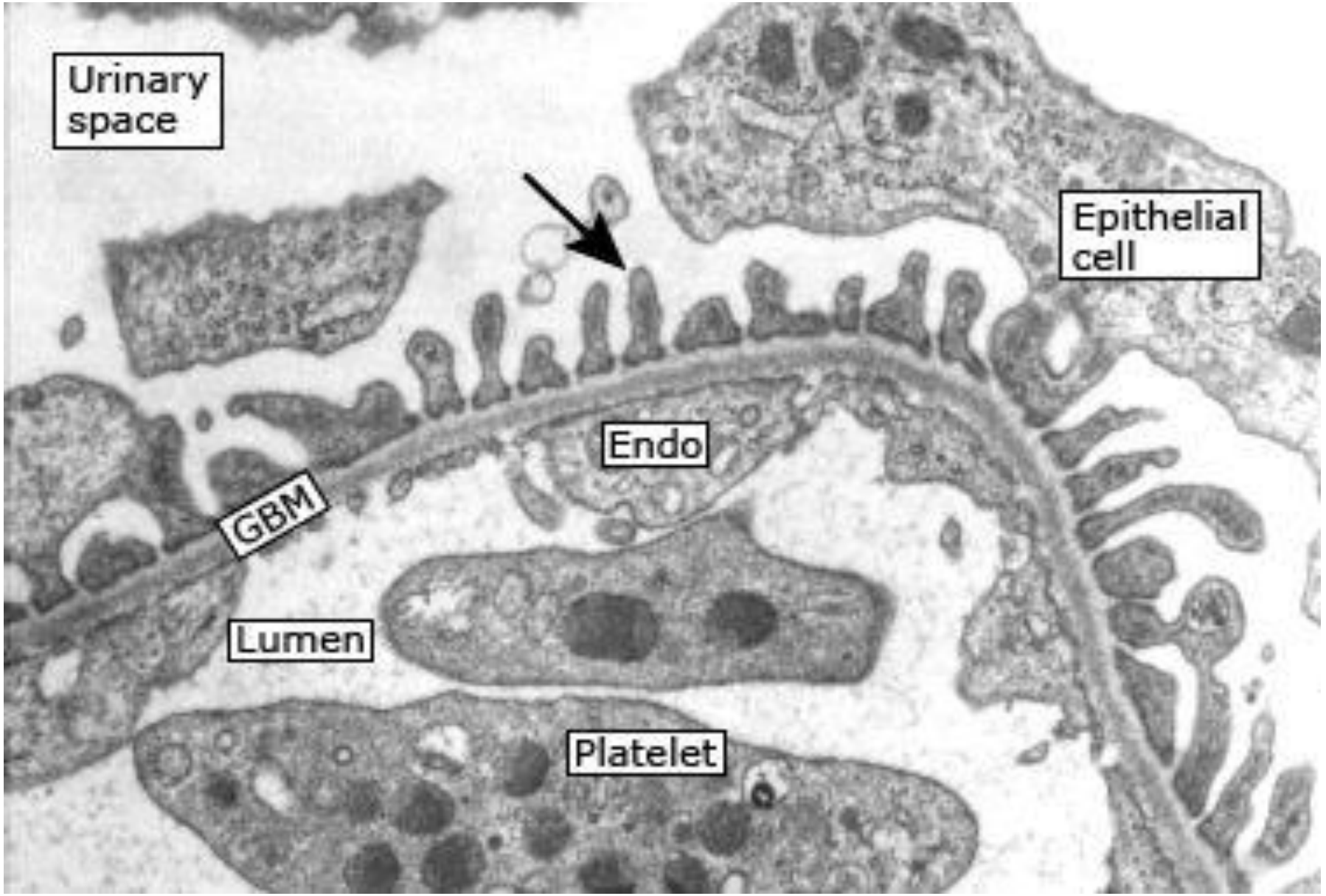
- MCG is the most frequent (about 65%) cause of the nephrotic syndrome in children.
- Although it may develop at any age, MCD is most common between ages 1 and 7 years.
- It is characterized by **G** that have a normal appearance by light microscopy, but when viewed with the **EM it** shows:

(1)diffuse effacement of podocyte foot processes

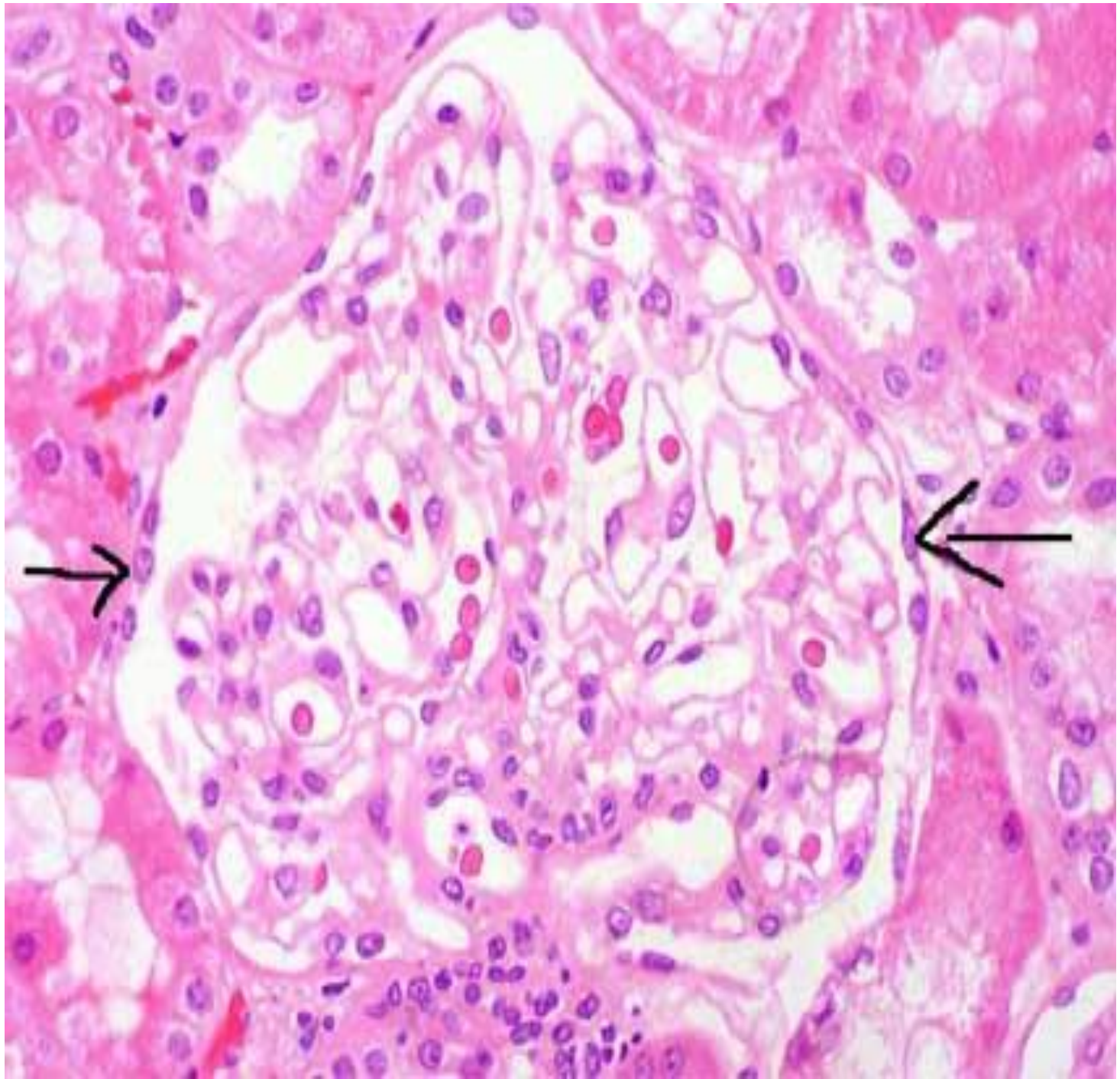
(2) Without antibody deposits.

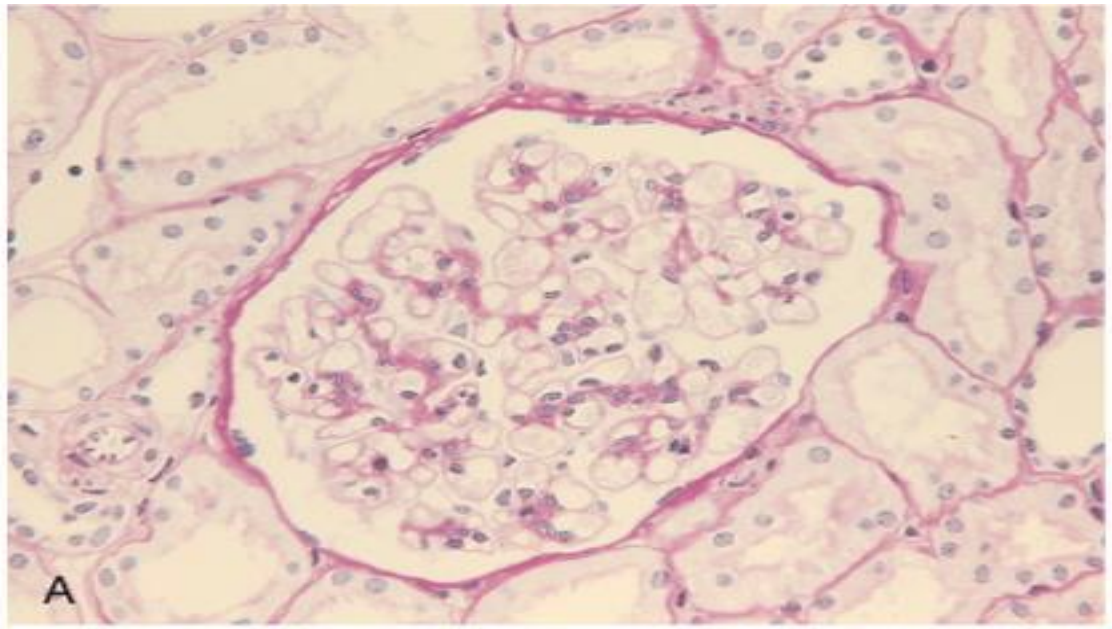
- **Pathogenesis:** The pathogenesis of podocyte injury, which is the underlying mechanism of proteinuria in MCD is **unknown** & it may be the result of nonimmune causes.

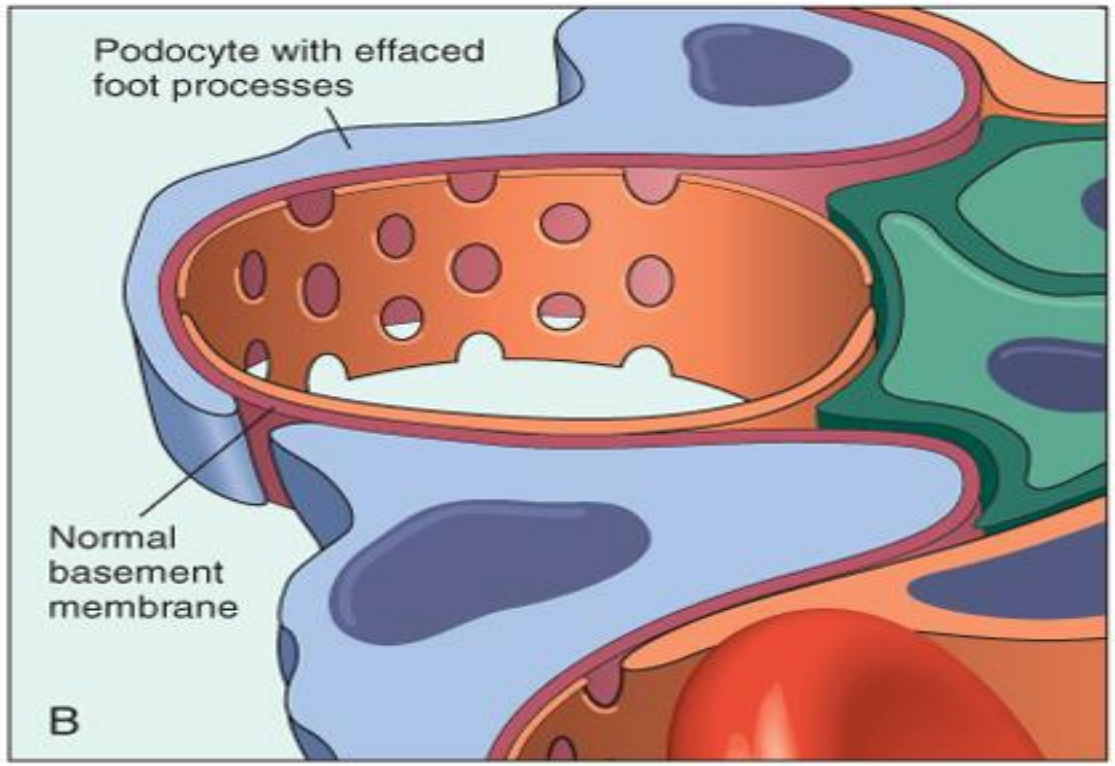
Normal Glomerulus by electron microscope



Normal Glomerulus Normal glomerulus. See the cellularity of the glomerular tuft. The arrows indicate nuclei of parietal epithelial cells covering the Bowman's capsule. In vivo the Bowman's space is narrower than seen in conventionally processed tissue. (H&E, X300).







Minimal change disease.

A

Glomerulus appears normal, with a delicate basement membrane

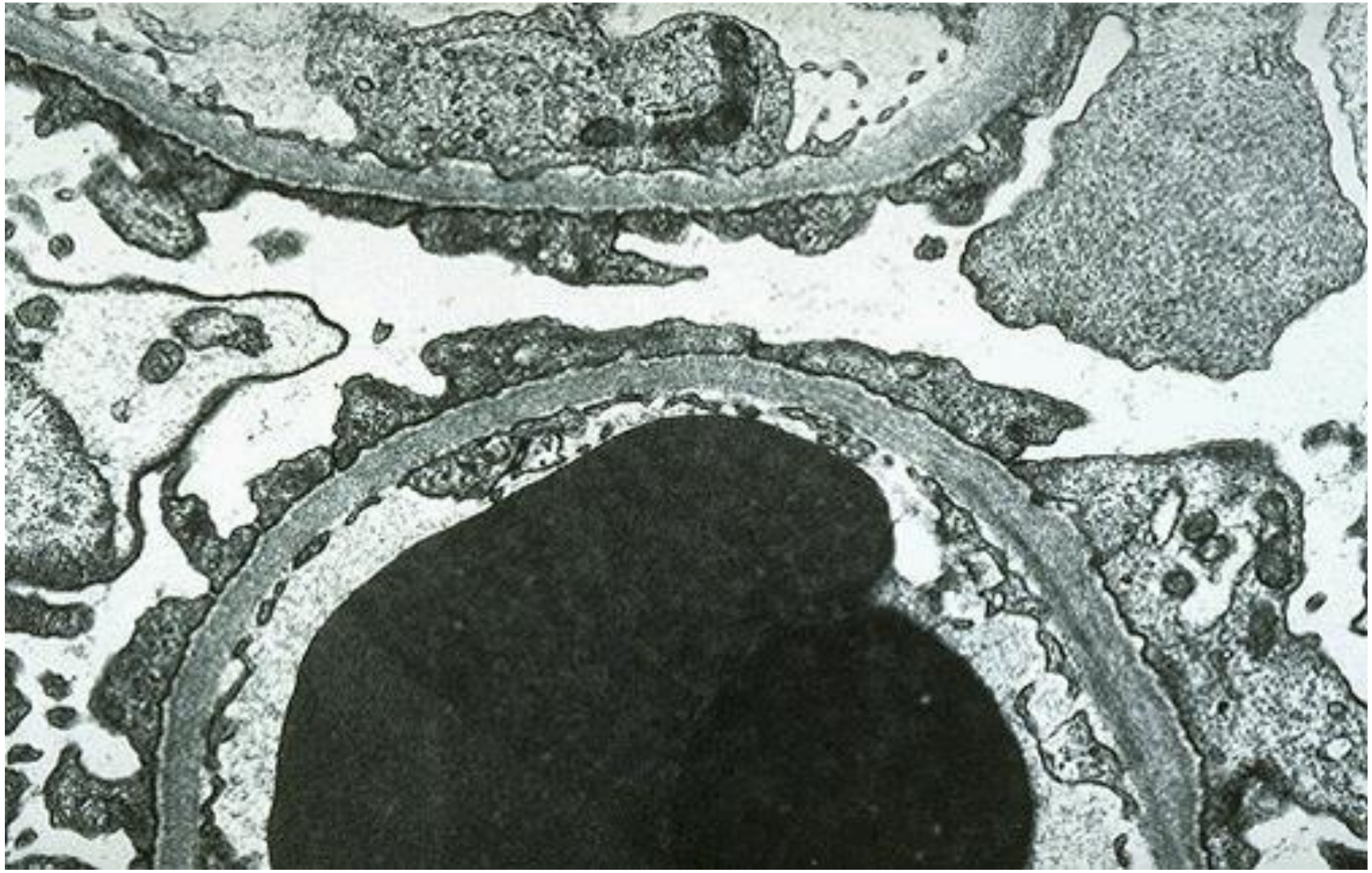
B

diffuse effacement of foot processes of podocyteswith no immune deposits.

Morphology

- **LM**
- the glomeruli appear normal.
- **IF**
- negative
- **EM**
- **uniform and diffuse effacement of the foot processes of the podocytes**.
- No immune deposits

MCD-EM the capillary loop in the lower half contains two electron dense RBC's. Fenestrated endothelium is present and the BM is normal. The overlying epithelial cell foot processes are fused (arrows).



MCD Clinical Course

- nephrotic syndrome in an otherwise healthy child.
- no hypertension
- renal function preserved
- selective proteinuria (albumin)
- prognosis is good .
- Treatment : corticosteroids 90 % of cases
- < 5 % develop chronic renal failure after 25 years
- In Adults with minimal change disease the response is slower and relapses are more common.

Membranous GN(MGN)=Membranous Nephropathy MN)

- A slowly progressive disease, most common in the 30-50 years age group, characterized by the presence of:

(I) Diffuse thickening of the capillary wall,

(II)subepithelial immunoglobulin-containing deposits.

- **Pathogenesis**
- MGN is a form of **chronic immune complex nephritis**.
- Although circulating complexes of known exogenous (e.g., hepatitis B virus) or endogenous (DNA in SLE) Ag can cause MGN,
- it is now thought that most idiopathic MGN are induced by Abs reacting in situ to endogenous, or, planted **G** Ags.

Types of Membranous glomerulonephritis :

1-Idiopathic (85% of cases):

- **Most common cause of nephrotic syndrome in nondiabetic adults**
- Idiopathic autoimmune glomerular disease characterized by diffuse subepithelial immune complex deposition with nephrotic range proteinuria, without known systemic cause.
- Thickening of glomerular basement membrane and subepithelial deposition of immune complexes (silver stain, spike)
- Anti-PLA2R autoantibodies
- Circulating autoantibodies bind to an autoantigen on the surface of the podocytes resulting in in situ immune complex formation that activates the lectin complement pathway and causes podocyte injury and proteinuria
- 2 major target antigens are now firmly recognized: the M type phospholipase A2 receptor 1 (PLA2R) (~70%) and the thrombospondin type 1 domain containing 7A (THSD7A) (2 - 5%)

2-Secondary membraneous nephropathy

- **(1) infections (HBV, syphilis, schistosomiasis, malaria).**
- **(2) malignant tumors (lung, colon and melanoma).**
- **(3) autoimmune diseases as SLE .**
- **(4) inorganic salts exposure (gold, mercury).**
- **(5) drugs (penicillamine, captopril,NSAID).**

•Morphology

•**LM**

•**diffuse thickening of the GBM**.

•**IF**

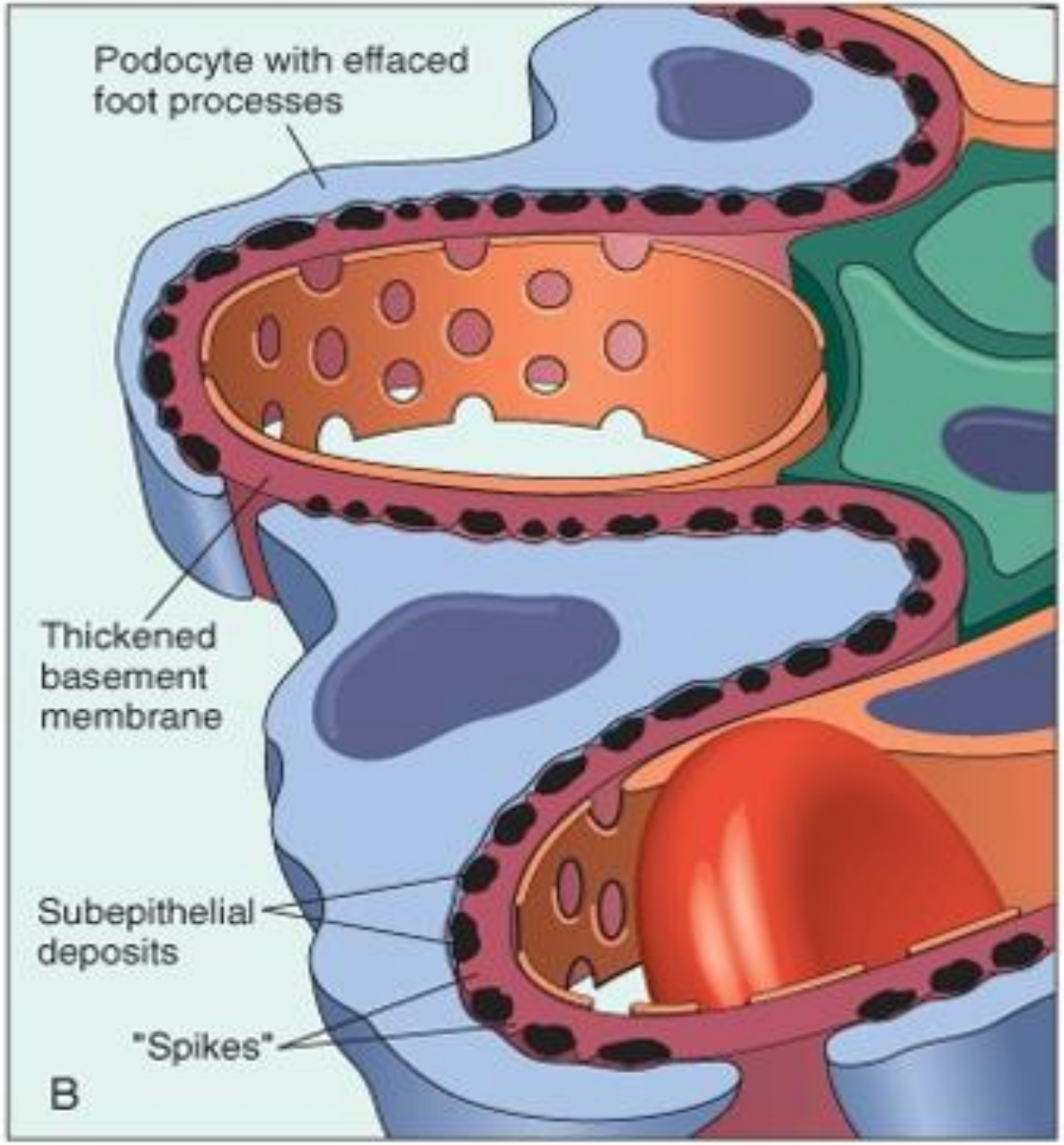
•**deposits** of immunoglobulins and complement along the GBM (IgG)

•By **EM**

(1) the podocytes show effacement of foot processes, &

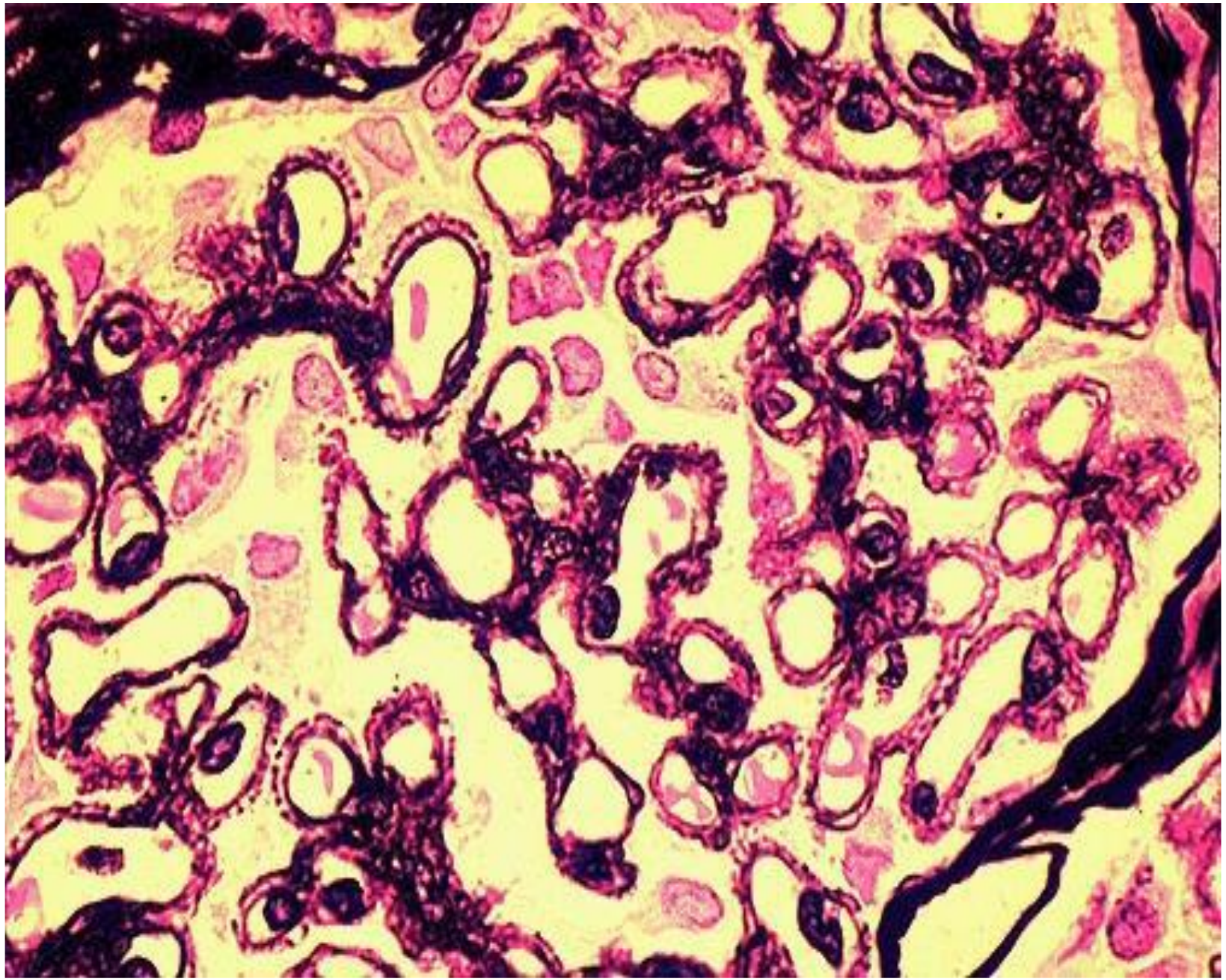
(2) the diffuse thickening of the GBM is caused in part by subepithelial dome deposits that nestle against the GBM & are separated from each other by small, spike like protrusions of GBM matrix that form in reaction to the dome deposits, resulting in a (spike & dome pattern).

(3)As the disease progresses, these spikes close over the deposits, incorporating them into the GBM.

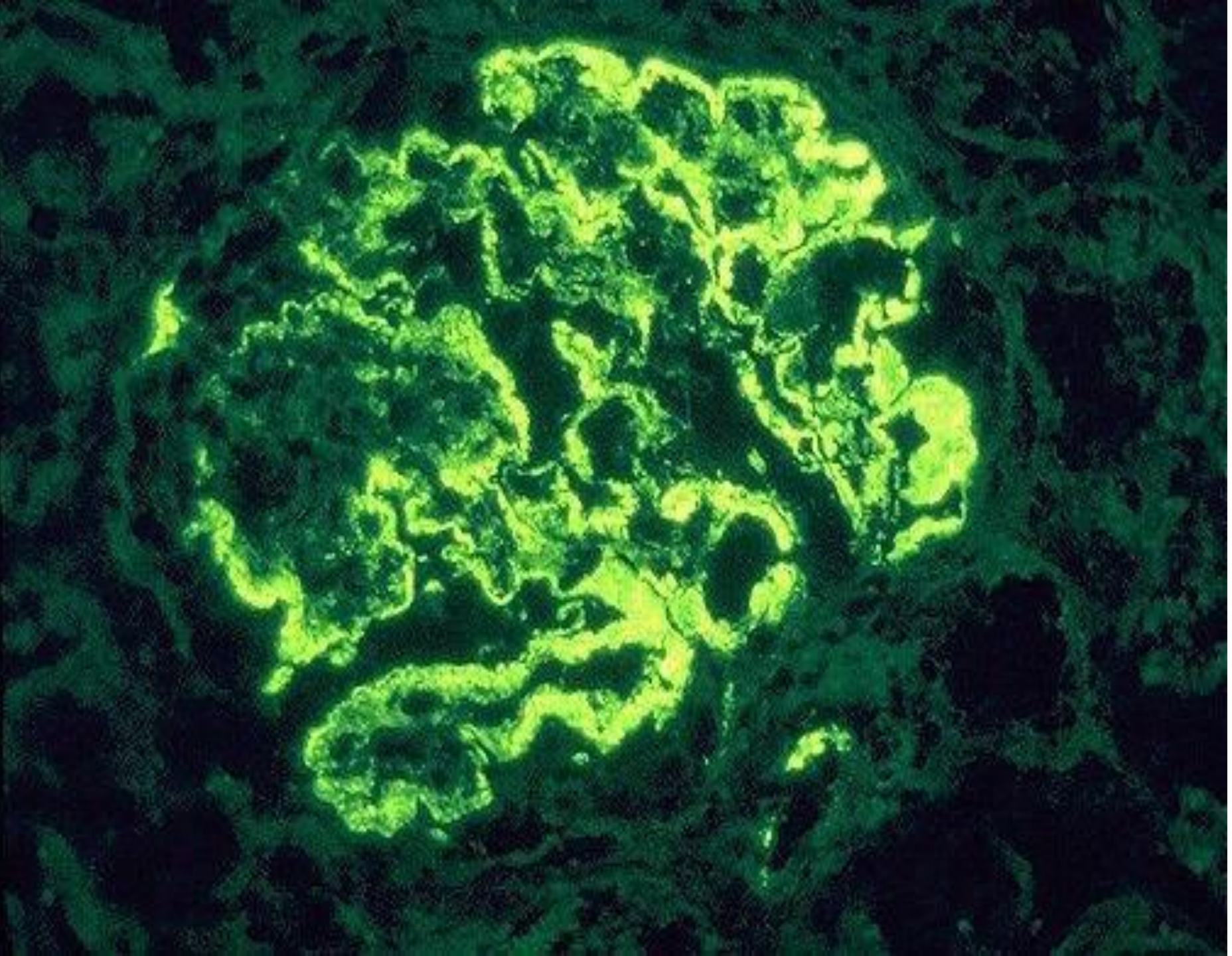


Membranous nephropathy.

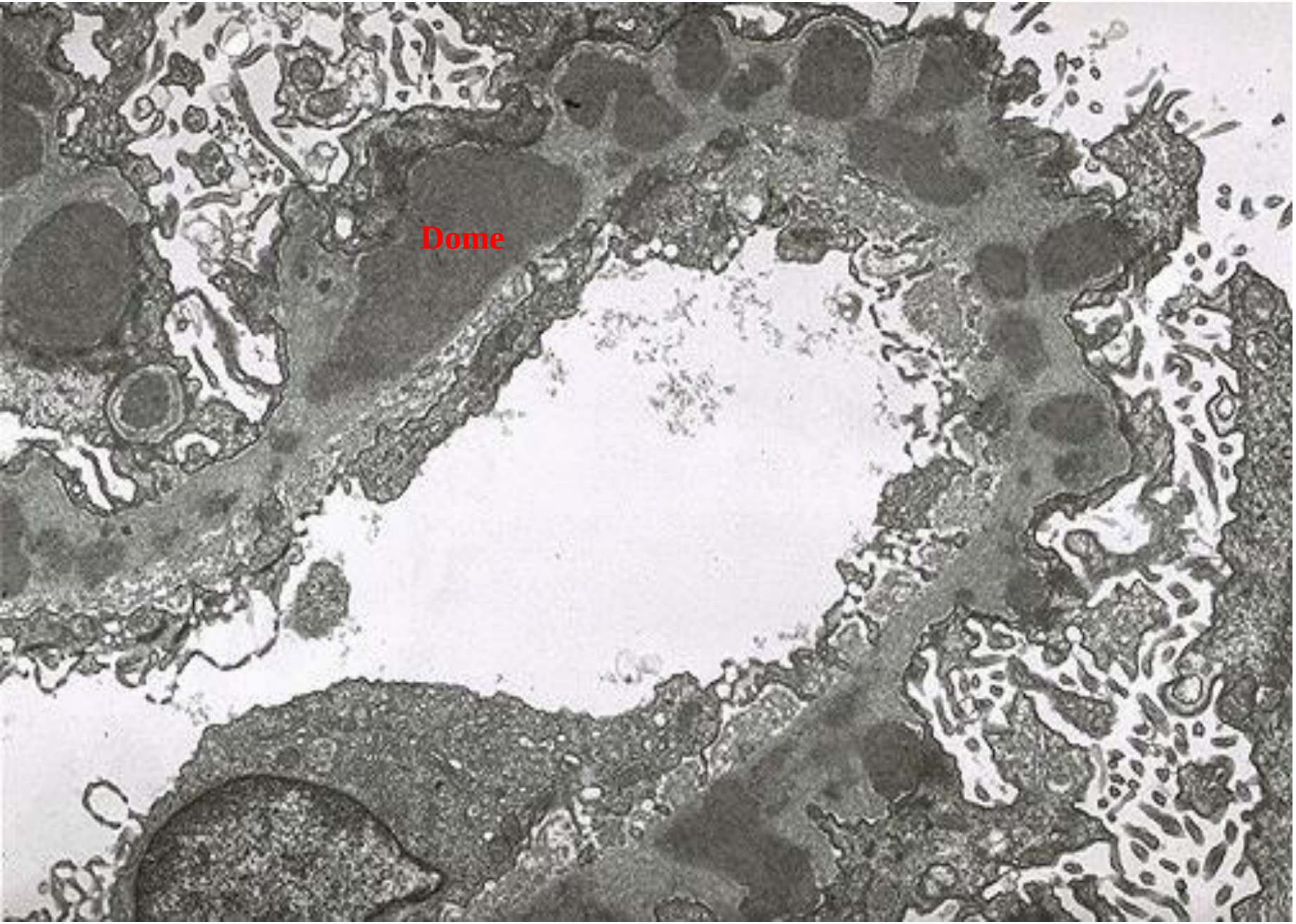
Sub epithelial deposits and the presence of "spikes" of basement membrane material between the immune deposits.



A silver stain (black). Characteristic "spikes" seen with membranous glomerulonephritis as projections around the capillary loops.



Membranous GN IF: Finely granular staining for IgG, predominately IgG4, presents uniformly in a subepithelial distribution in all glomeruli



EM-

("spike and dome" pattern).

Clinical Course

- Clinically, idiopathic MGN characterized by **insidious development of the nephrotic syndrome**, usually without antecedent illness.
- **In contrast to MCD**,

(I) the proteinuria is nonselective,

(II) does not usually respond to corticosteroid therapy((**poor response to corticosteroid therapy)).**

- **Secondary causes of MGN should be ruled out.**

Prognosis:

- **60% of cases → proteinuria persists**
- **About 40%→progressive disease and renal failure 2 to 20 yr.**
- **30% →partial / complete remission of proteinuria.**

Focal and Segmental Glomerulosclerosis (FSGS)

- Essential features
- **Glomerular** lesion characterized histologically, by;

A. sclerosis affecting some, but, not all **G** (**focal** involvement) & involving only some (**segments**) of each affected **G**

B. often associated with the **nephrotic syndrome,** can occur:

(1) in **association** with other known conditions, e.g., **HIV nephropathy, heroin nephropathy**;

(2) As a secondary event in other forms of GN(e.g., **[IgA] nephropathy**);

(3) as a **maladaptation after nephron loss.**

(4) in **inherited or congenital** forms resulting from mutations affecting cytoskeletal or related proteins expressed in podocytes (e.g., nephrin), i.e., nonimmune cause;

- (**Nephrin a transmembrane glycoprotein, is the major component of the slit diaphragms between adjacent foot processes)**
- (5) as an **primary or idiopathic** FSGS, which accounts for **20% to 30%** of all cases of the nephrotic syndrome.
- It is becoming an **increasingly common** cause of nephrotic syndrome in **adults (35%)** & remains a frequent cause in children.

- In children it is important to distinguish **FSGS** cause of the nephrotic syndrome from **MCD** , because the clinical courses and prognosis are markedly different:
- **Unlike MCD, patients with FSGS have**

(1)Nonselective proteinuria,
(2) Higher incidence of hematuria & hypertension
(3) Generally, a poor response to corticosteroid therapy, with 50% of cases developing RF within 10 years of diagnosis.
Adults in general feel even less well than children.

Pathogenesis

- The pathogenesis of primary FSGS **is unknown**.
- In any case, nonimmune injury to the podocytes is thought to represent the initiating event of primary FSGS **(as** with MCD)& is the underlying mechanism of proteinuria.
- The **permeability-increasing factors produced by lymphocytes** have been proposed in both MCD & FSGS.

- The recurrence of proteinuria in some persons with FSGS, who receive **renal allografts**, sometimes within 24 hours of transplantation, supports the idea that a **circulating mediators is the cause of the damage to podocytes.**

- The deposition of **hyaline masses** in the **G** in FSGS represents the entrapment of plasma proteins & lipids in foci of injury where sclerosis develops.

- IgM & complement proteins commonly seen in the lesion are also believed to result from nonspecific entrapment in damaged **G**.

Morphology

- **Microscopically** :

FSGS is characterized by both focal & segmental lesions occurring in

1) some segments within a G & sparing of the others (hence the term "segmental"),

2) the disease first affects only some of the G (hence the term "focal").

- **The affected G exhibit**

(a) Increase **mesangial matrix,**

(b) deposition of hyaline masses (hyalinosis) & lipid droplets in the affected G (PAS+, trichrome red, silver negative) and endocapillary foam cells or lipoid droplets in focal glomeruli, , causing….

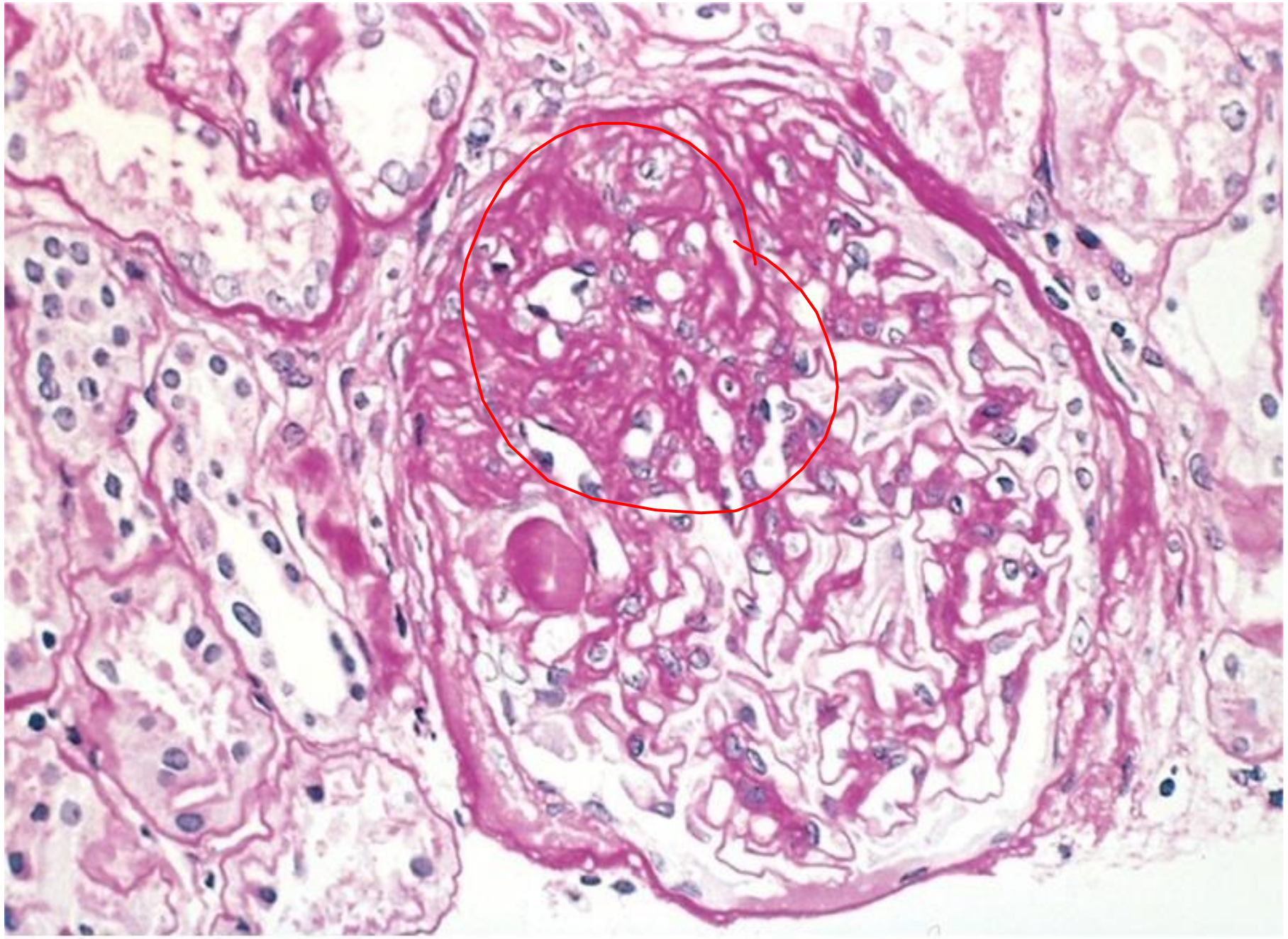
(C) obliteration of the capillary lumens

- **immunofluorescence M often reveals nonspecific trapping of immunoglobulins, usually IgM, & complement, in the areas of hyalinosis.**
- **Focal tubular atrophy with interstitial fibrosis, hyaline thickening of afferent arterioles**
- **Note: the defining glomerular lesions may not be sampled in needle core biopsy due to their focal nature**

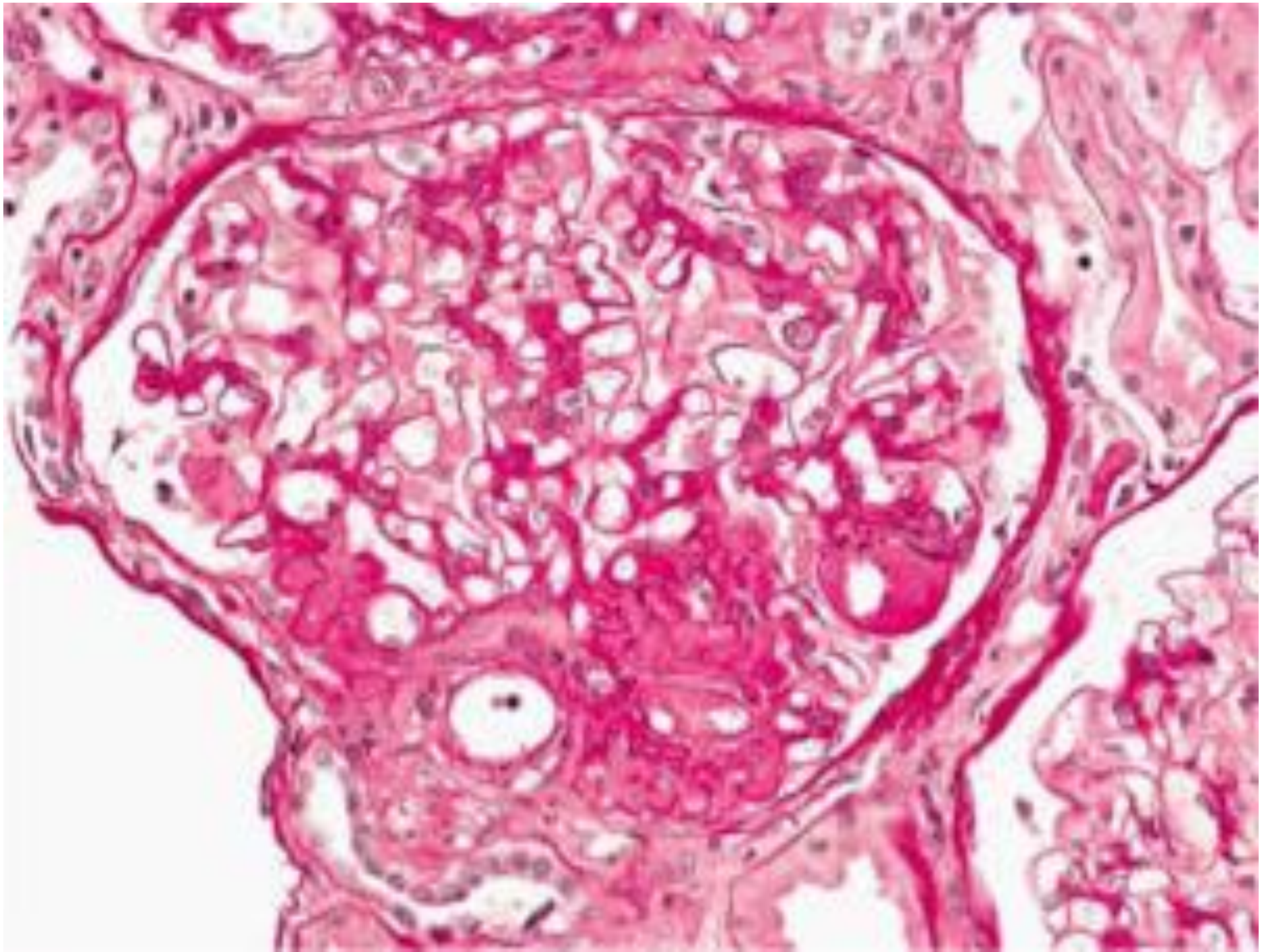
- On EM, as in MCD, the podocytes exhibit **effacement of foot processes,**

- Clinically, there is **little tendency for spontaneous remission** of idiopathic FSGS, & responses to corticosteroid therapy are poor.

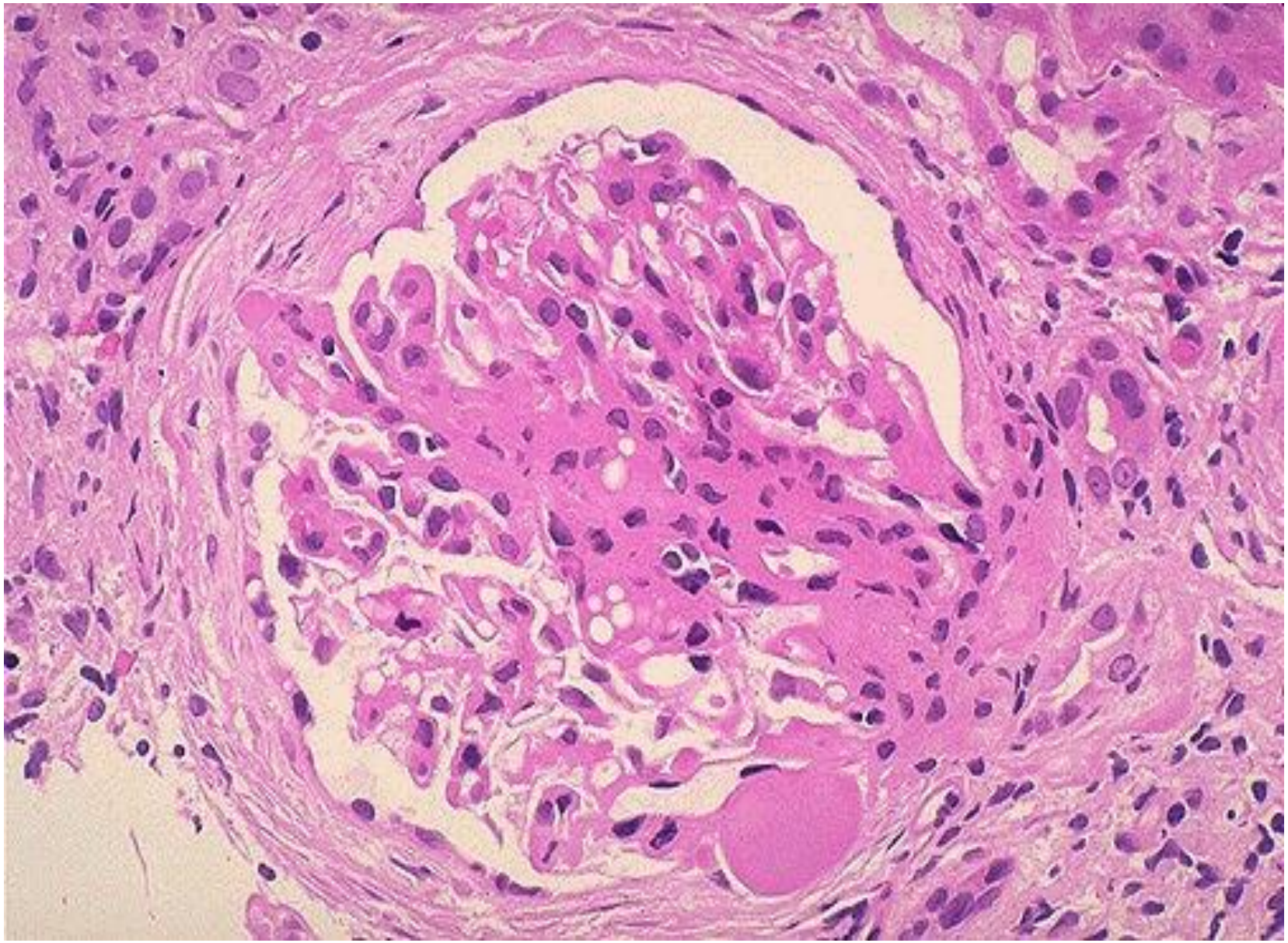
- **Progression** of FSGS, with time, leads to **global sclerosis** of the **G** with pronounced tubular atrophy & interstitial fibrosis, a picture difficult to differentiate from other forms of chronic **G** disease, with progression to RF occurring in 50% of FSGS patients after 10 years.



HP view of **focal & segmental glomerulosclerosis (FSGS),**seen as a mass of **scarred, obliterated capillary lumens with accumulations of matrix material,** that has replaced a portion of the glomerulus.



- This is focal segmental glomerulosclerosis (FSGS).
- An area of collagenous sclerosis runs across the middle of this glomerulus.
- As the name implies, only some (focal) glomeruli are affected and just part of the affected glomerulus is involved (segmental) with the sclerosis.
- In contrast to minimal change disease, patients with FSGS are more likely to have non-selective proteinuria, hematuria, progression to chronic renal failure, and poor response to corticosteroid therapy.



	MCG	FSGN
Hematuria	_	+
Hypertension	_	+
Proteinuria	Selective	Non-selective
Respond to corticosteroid therapy	Good	Poor

Columbia University classification: perihilar, cellular, tip lesion, collapsing and not otherwise specified ; correlates with prognosis

Collapsing glomerulopathy

Essential features

- A morphologic type of FSGS.
- At least 1 glomerulus with capillary loop collapse and prominence of overlying podocytes or parietal epithelial cells
- Worse prognosis than other variants of focal segmental glomerulosclerosis; supersedes other variants if others present in biopsy.
- May be idiopathic or associated with viruses, genetics, drugs, vascular injury and autoimmune diseases
- CC with Nephrotic range proteinuria
- Elevated serum creatinine at presentation

Answer those question

Q1:Which of the following is true about primary membranous nephropathy?

- Active periglomerular inflammation and rupture of Bowman capsule
- Little or no immunoglobulin or complement deposits by immunofluorescence
- Most common cause of idiopathic nephrotic syndrome in nondiabetic adults worldwide
- Significant mesangial or endocapillary hypercellularity
- Which of the following is true about minimal change glomerulopathy?

Q2:Which of the following is true about minimal change glomerulopathy?

- Interstitial inflammation and fibrosis are usually absent
- It is the most common type of nephrotic syndrome in adults
- Monoclonal antibody therapy should be the first line therapy
- Pretreatment biopsy is always done

Q3:Which of the following signs and symptoms is common in minimal change disease?

- Azotemia
- Hypertension
- Macrohematuria
- Selective proteinuria

What is Nephritis ?

- It is essentially an inflammation of the kidney

Q:What is the types of nephritis ?

- Acute nephritic syndrome
- Chronic glomerulonephritis

Q:Essentrial Features ?

❑ Proliferation of the cells in glomeruli& leukocyte infiltrate
→Injured capillary walls →escape of RBCs into urine
→↓GFR →oliguria, fluid retention, and azotemia.

❑ Hypertension (a result of both the fluid retention and some augmented renin release from kidneys).

Nephritic Syndrome: Presentation

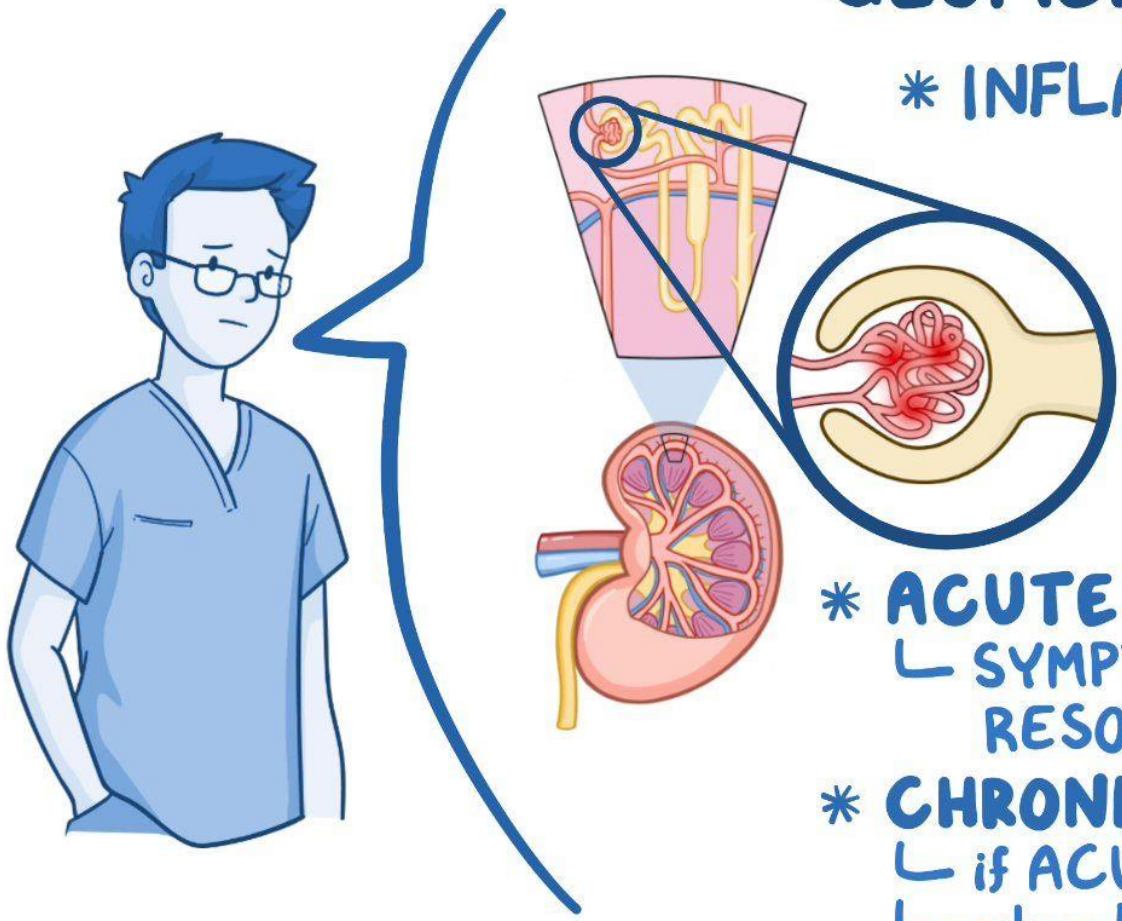
- **PHAROH**
- ***P**roteinuria*
  - *<3.5g/1.73m2/day*
- ***H**ematuria*
  - *Abrupt onset*
- ***A**zotemia*
  - *Increased creatinine and urea*
- ***R**BC Casts*
- ***O**liguria*
- ***H**TN*

Click to add text

Peripheral Edema/Puffy Eyes

"Smoky Urine"

GLOMERULONEPHRITIS



* INFLAMMATION of the GLOMERULI
  * **PRIMARY**
    - STARTS in GLOMERULI
  * **SECONDARY**
    - GLOMERULI are AFFECTED by SYSTEMIC DISEASE
* **ACUTE**
  - SYMPTOMS DEVELOP SUDDENLY & RESOLVE w/ TREATMENT
* **CHRONIC**
  - if ACUTE DISEASE NOT TREATED
  - when DISEASE PROCESS DEVELOPS SLOWLY
    - → IRREVERSIBLE FAILURE of KIDNEYS

Glomerular diseases mostly presenting with Nephritic syndrome:

I. Infectious diseases
   A. Poststreptococcal glomerulonephritis[a]
   B. Nonstreptococcal postinfectious glomerulonephritis
      1. Bacterial: infective endocarditis, "shunt nephritis," sepsis, pneumococcal pneumonia, typhoid fever, secondary syphilis, meningococcemia
      2. Viral: hepatitis B, infectious mononucleosis, mumps, measles, varicella, vaccinia, echovirus, and coxsackievirus
      3. Parasitic: malaria, toxoplasmosis

II. Multisystem diseases: SLE, vasculitis, Henoch-Schönlein purpura, Goodpasture's syndrome

III. Primary glomerular diseases: mesangiocapillary glomerulonephritis, Berger's disease (IgA nephropathy), "pure" mesangial proliferative glomerulonephritis

IV. Miscellaneous: Guillain-Barré syndrome, irradiation of Wilms' tumor, self-administered diphtheria-pertussis-tetanus vaccine, serum sickness

[a]Most common cause.
Abbreviation: SLE, systemic lupus erythematosus.
Source: RJ Glassock, BM Brenner: HPIM-13.