University of Basra
College of medicine

The kidney and the urinary tract system

Dr. Zainab A. Ameen
Iraqi board of histopathology and forensic medicine

Nephrotic Syndrome

-Caused by a derangement in glomerular capillary walls resulting in increased permeability to plasma proteins

-The manifestations of the syndrome include:

- **Massive proteinuria**: with the daily loss of 3.5 gm or more of protein
- **Hypoalbuminemia:** with plasma albumin levels less than 3 gm/dL
- **Generalized edema**
- **Hyperlipidemia and lipiduria**

.Nephrotic patients are particularly vulnerable to **infection**, especially staphylococcal and pneumococcal infections, probably due to loss of immunoglobulins in the urine

.**Thrombotic** and thromboembolic complications are also common in nephrotic syndrome, due in part to loss of endogenous anticoagulants (e.g., antithrombin III) in the urine

Causes of nephrotic syndrome

Causes	Approximate Prevalence (%)*	
	Children	Adults
Primary Glomerular Disease		
Membranous nephropathy	3	30
Minimal-change disease	75	8
Focal segmental glomerulosclerosis	10	35
Membranoproliferative glomerulonephritis and dense deposit disease†	10	10
Other proliferative glomerulonephritides (focal, "pure mesangial," IgA nephropathy)†	2	17
Systemic Diseases		
Diabetes mellitus		
Amyloidosis		
Systemic lupus erythematosus		
Drugs (nonsteroidal anti-inflammatory, penicillamine, heroin)		
Infections (malaria, syphilis, hepatitis B and C, HIV)		
Malignant disease (carcinoma, lymphoma)		
Miscellaneous (bee-sting allergy, hereditary nephritis)		

.The most frequent **systemic** causes of the nephrotic syndrome are **diabetes**, **amyloidosis**, and **SLE**

The most important of the **primary** glomerular lesions are **minimal-change disease** , **membranous** glomerulopathy , and **focal segmental glomerulosclerosis**

. **Minimal change** disease is most common in **children**, while **membranous** is most common in **older adults**, focal segmental glomerulosclerosis occurs at all ages

Minimal Change Disease

. Relatively benign disorder

. Diffuse effacement of foot processes of podocytes

. Detectable only by E.M, glomeruli that appear normal by L.M

. It is the most frequent cause of nephrotic syndrome in children, the peak incidence is 2 -6 years of age

. Unknown etiology and pathogenesis

. Highly selective Proteinuria(albuminuria)
. Normal blood pressure & normal renal function
. Dramatic response to corticosteroid therapy

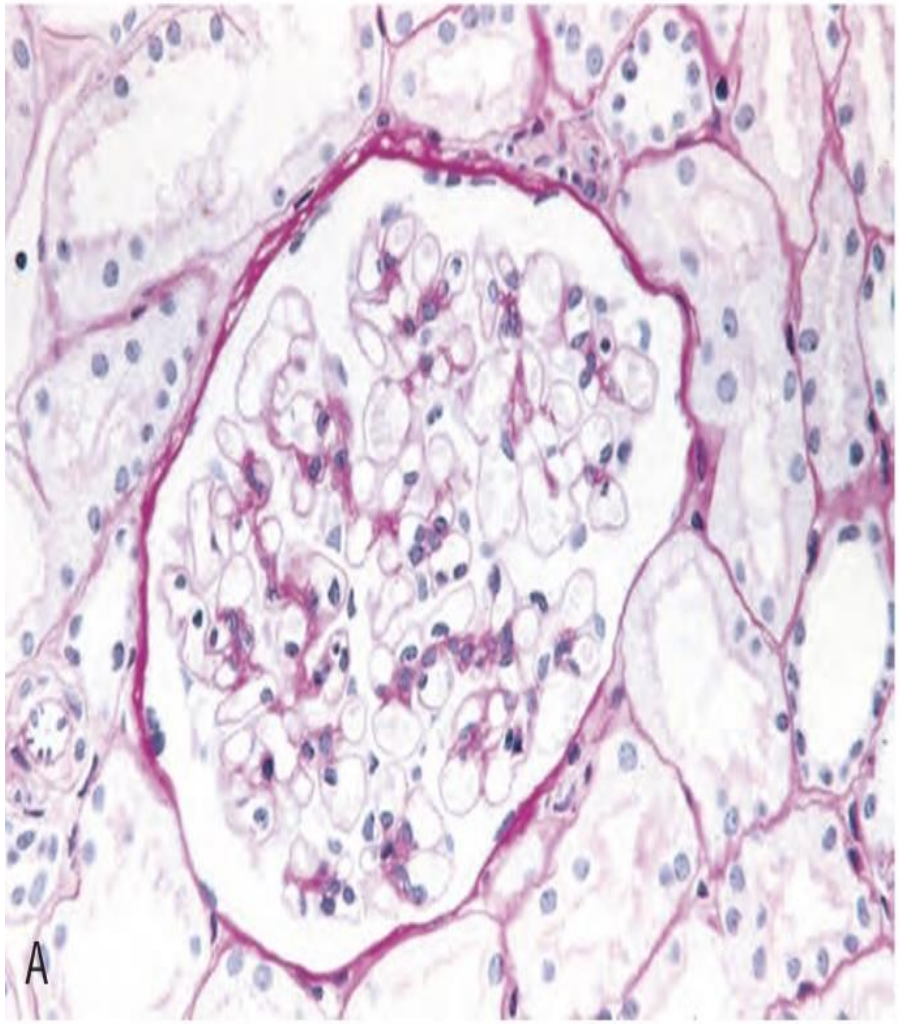
MORPHOLOGY

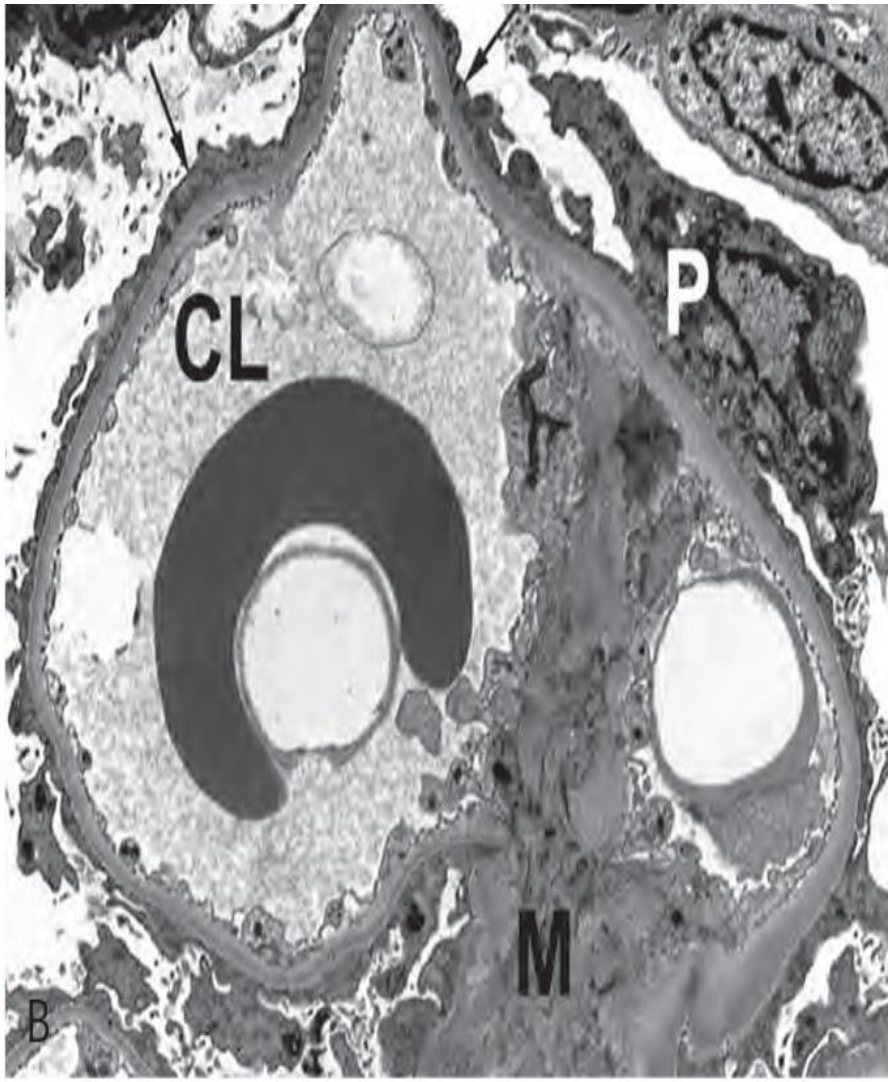
LM: The glomeruli are normal

IF : No Ig or complement deposits

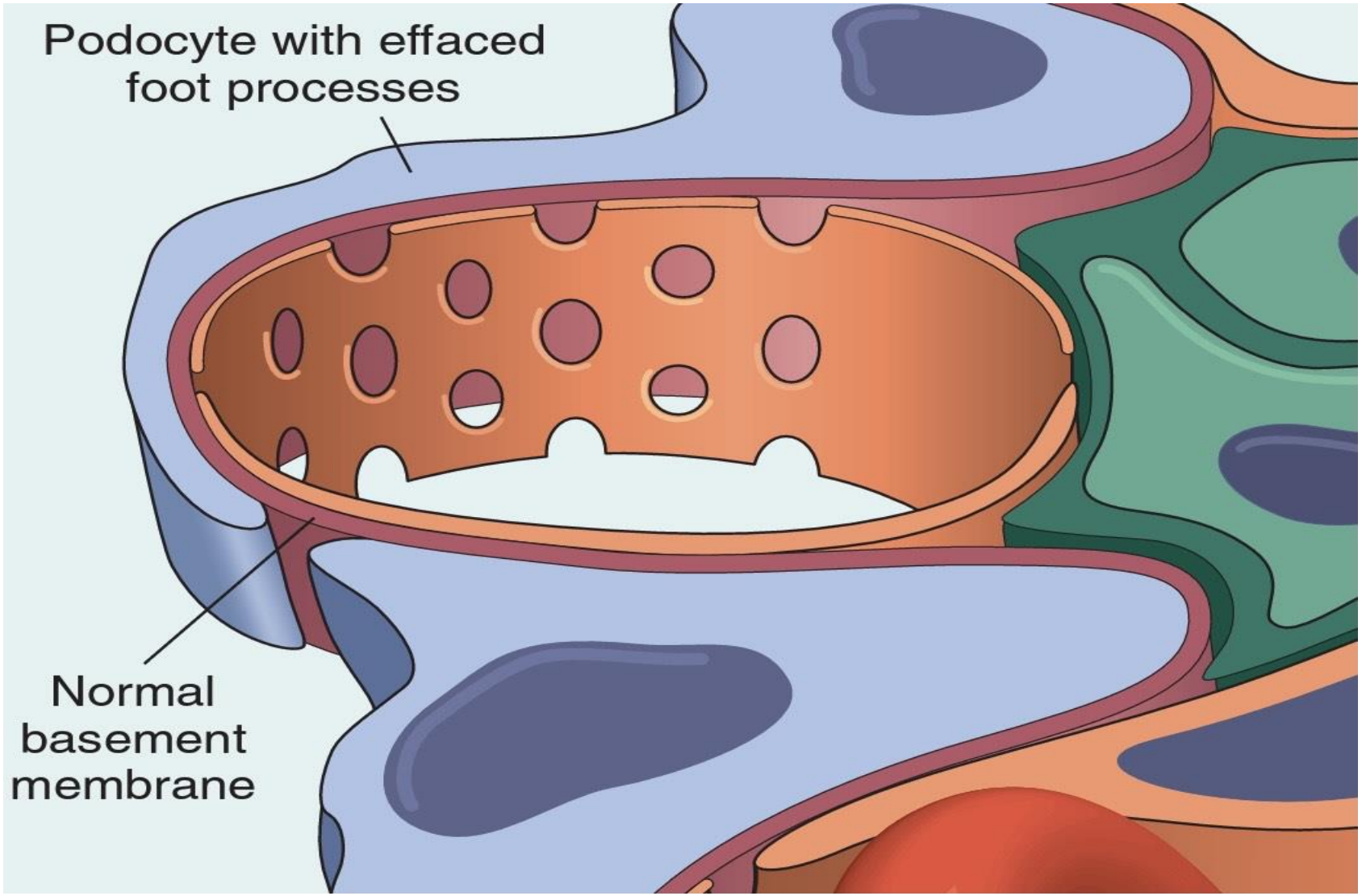
EM: The principal lesion is in the visceral epithelial cells, which show a uniform and diffuse **effacement** of foot processes

Minimal-change disease.
A:Light microscopy
B: Electron microscopy





Minimal change disease



Membranous Nephropathy

. Diffuse thickening of the glomerular capillary wall due to the accumulation of immune complex deposits along the **subepithelial** side of the basement membrane

. Approximately 80% of cases are primary

. **Clinical Features:** usually presents with the insidious onset of the nephrotic syndrome .

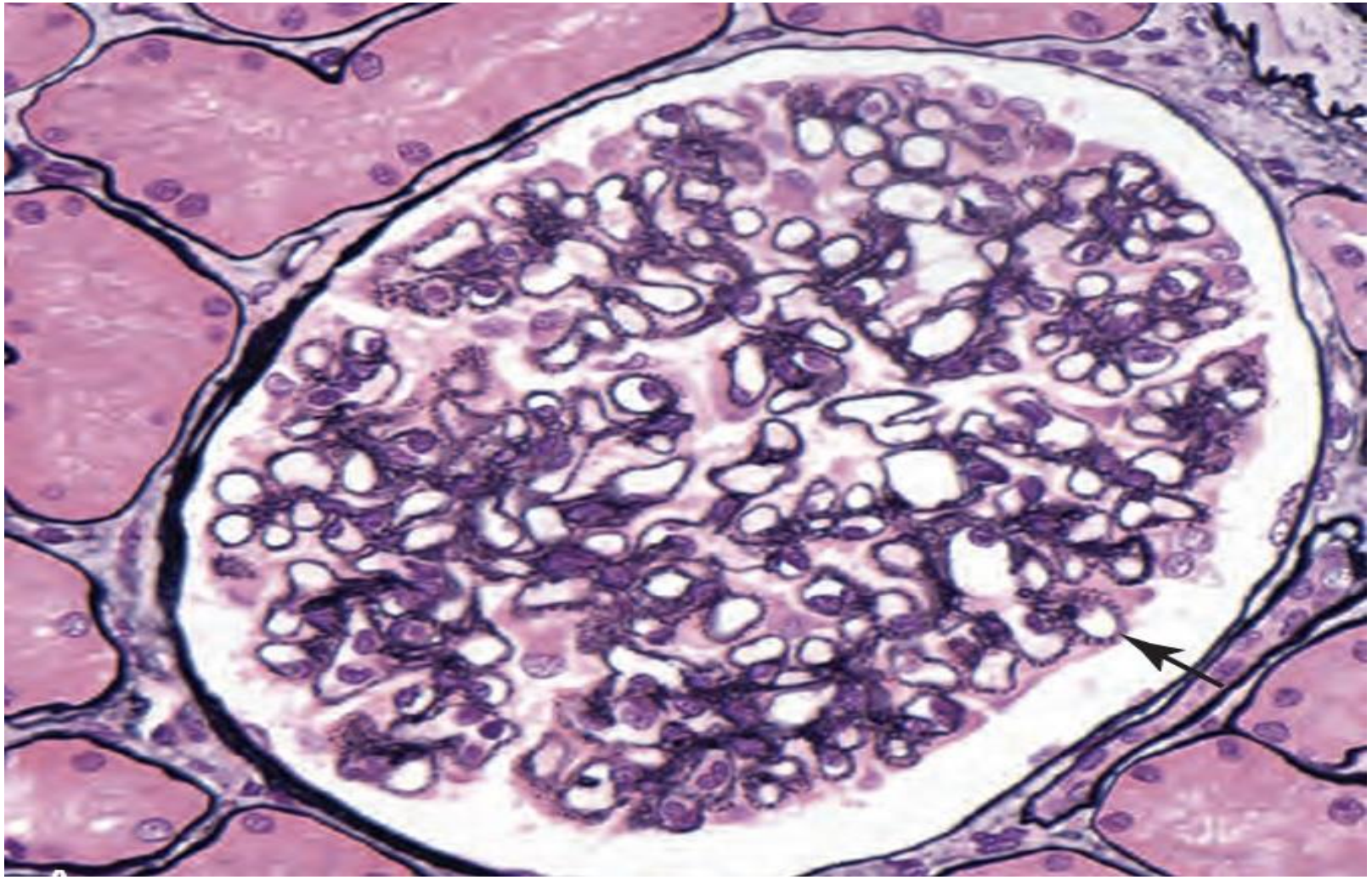
. The proteinuria is nonselective and usually does not respond well to corticosteroid therapy

. Complete or partial remissions may occur in up to 40% of patients

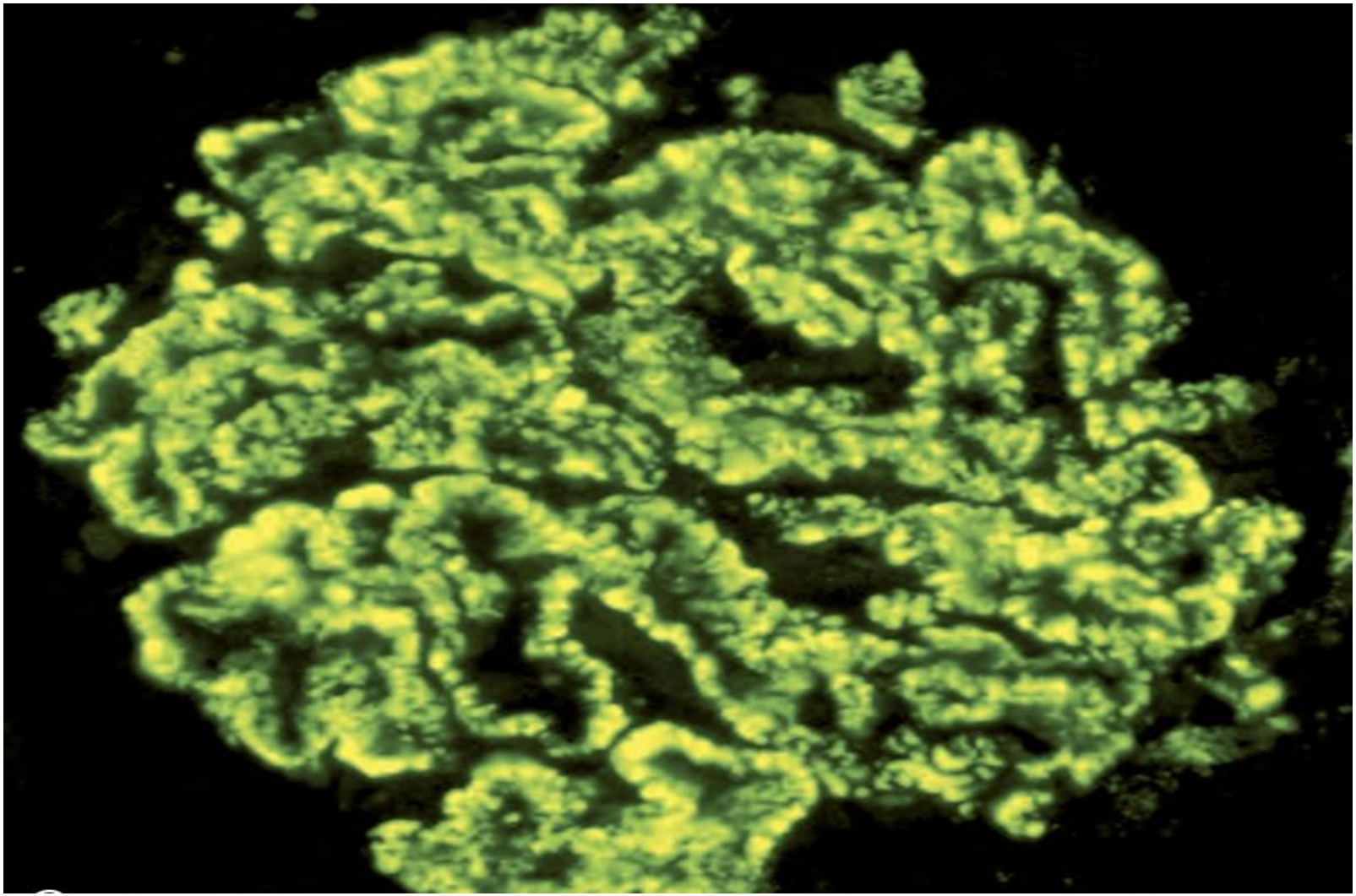
. Hematuria and mild hypertension are present in 15% to 35% of cases

MORPHOLOGY

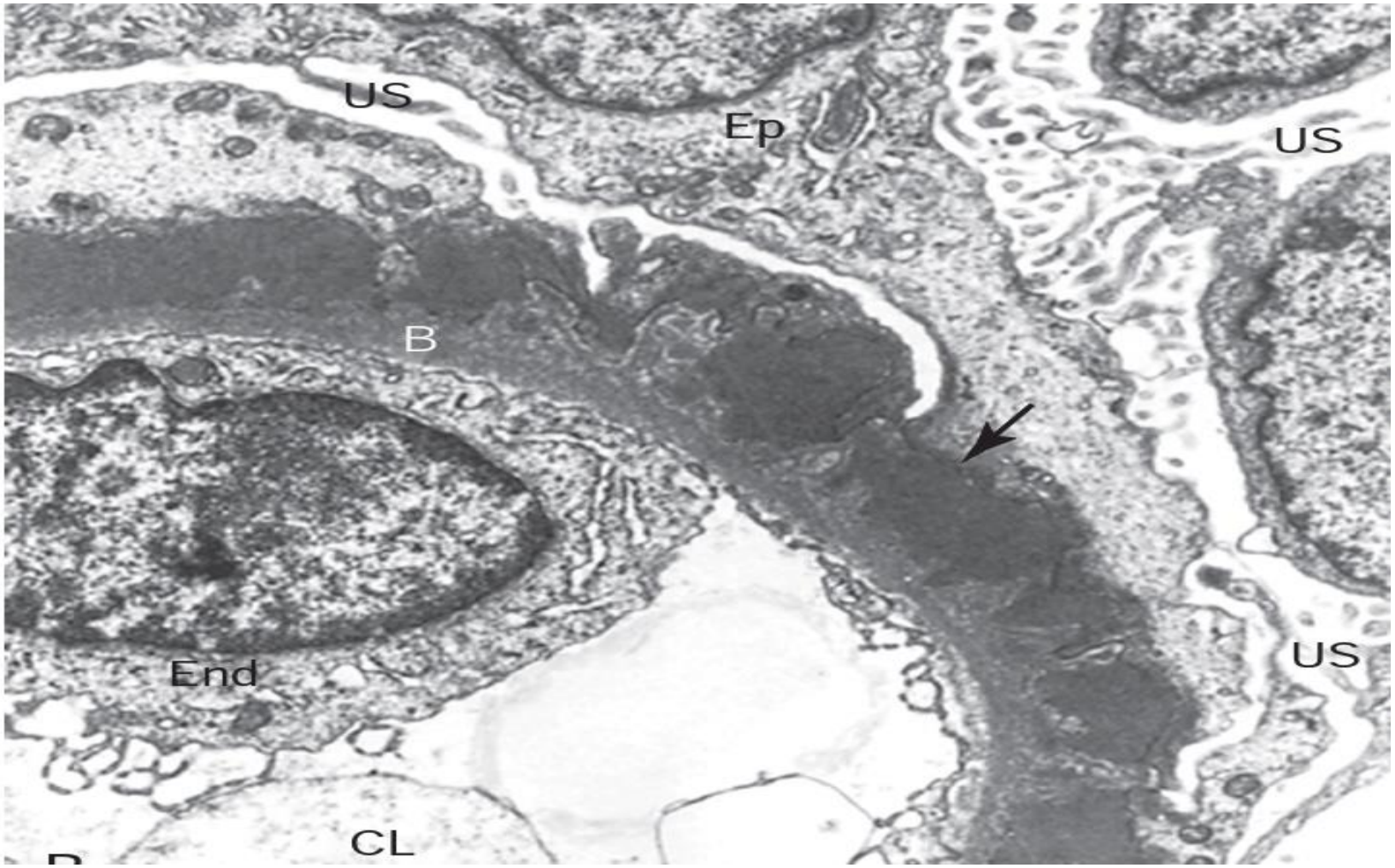
LM: Uniform, diffuse thickening of the glomerular capillary wall



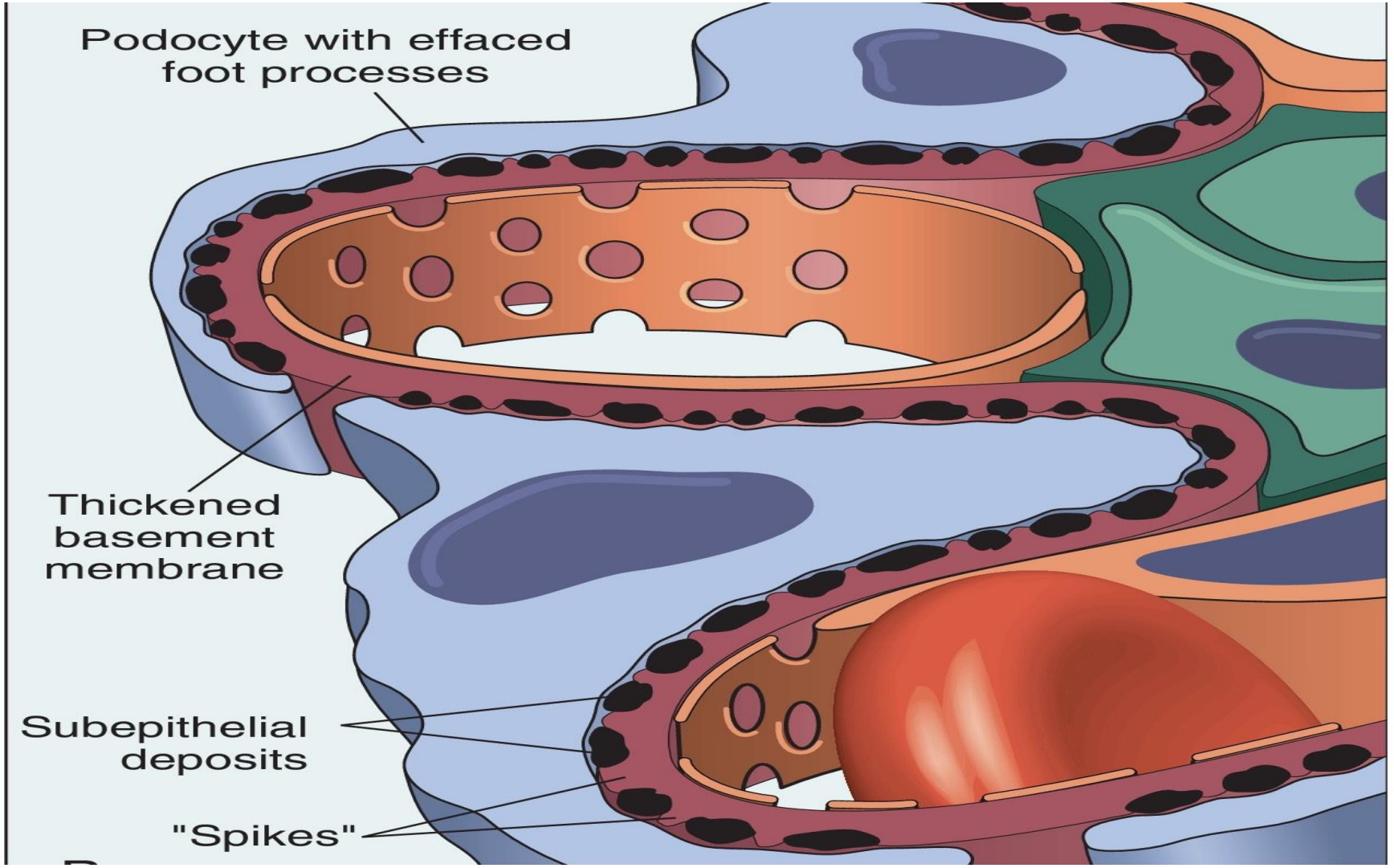
IF : Granular deposits of IgG and C3 along GBM.



EM: irregular electron dense deposits containing immune complexes between the basement membrane and the overlying epithelial cells, with effacement of podocyte foot processes



Membranous Nephropathy



Focal Segmental Glomerulosclerosis (FSGS)

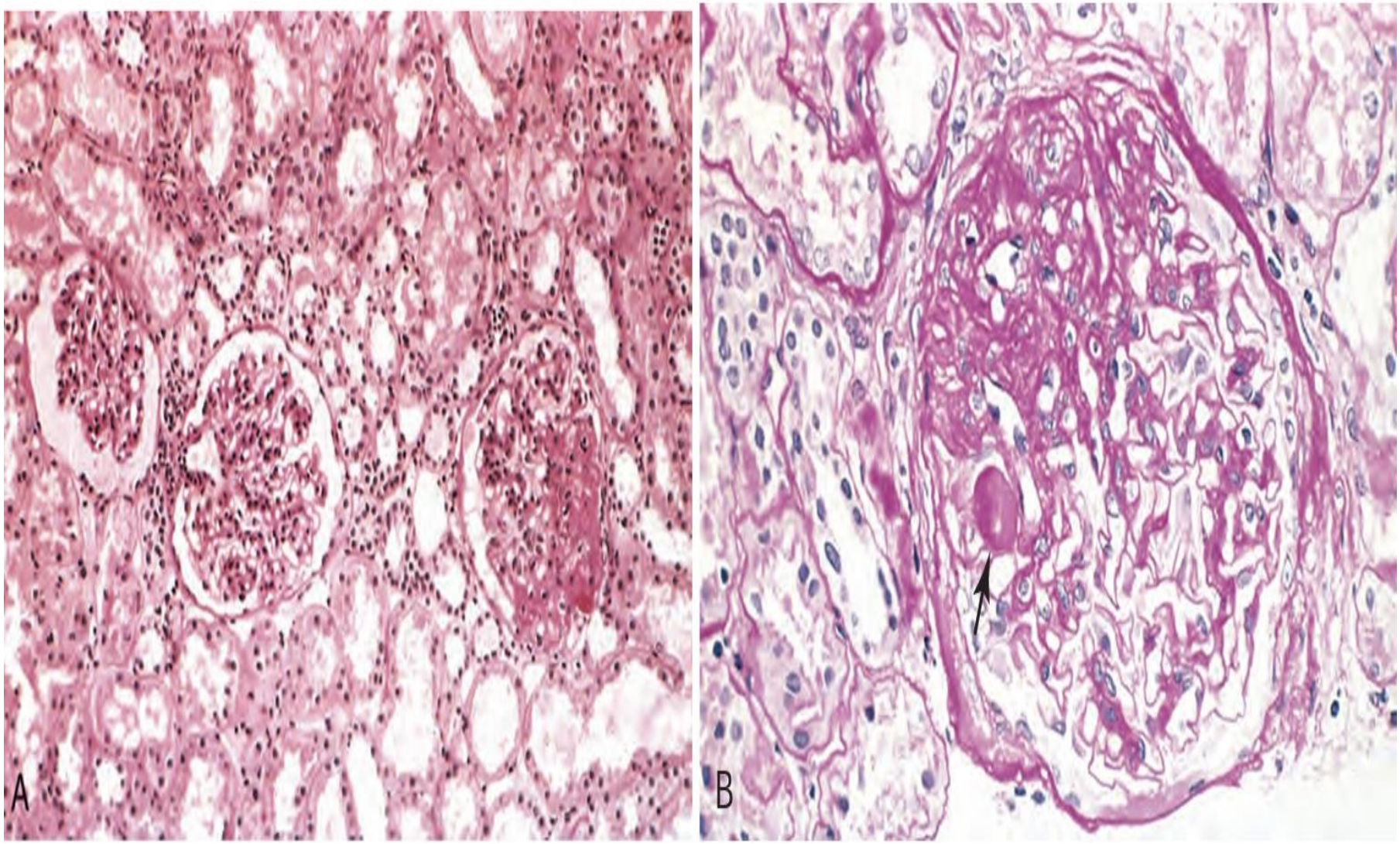
. The most common cause of nephrotic syndrome in adults

.The lesion is characterized by sclerosis of some, but not all, glomeruli (focal), and in the affected glomeruli, only a portion of the capillary tuft is involved (segmental)

. Hypertension, microscopic hematuria, and some degree of azotemia are commonly present

. Primary (idiopathic) or Secondary
. Little tendency for spontaneous remission
.Response to corticosteroid therapy is is poor

Focal segmental glomerulosclerosis



Membranoproliferative Glomerulonephritis (MPGN)

. It is responsible for 10% of NS in children and adults.

. Idiopathic (Primary) or Secondary.

. Characterized histologically by alterations in the glomerular basement membrane, proliferation of glomerular cells, leukocyte infiltration, and the presence of deposits in mesangial regions and glomerular capillary walls

. It is divided into two major types :

Type-I (most common):deposition of immune complexes containing IgG and complement

Type-II (Dense Deposit Disease) unknown material deposition

MORPHOLOGY

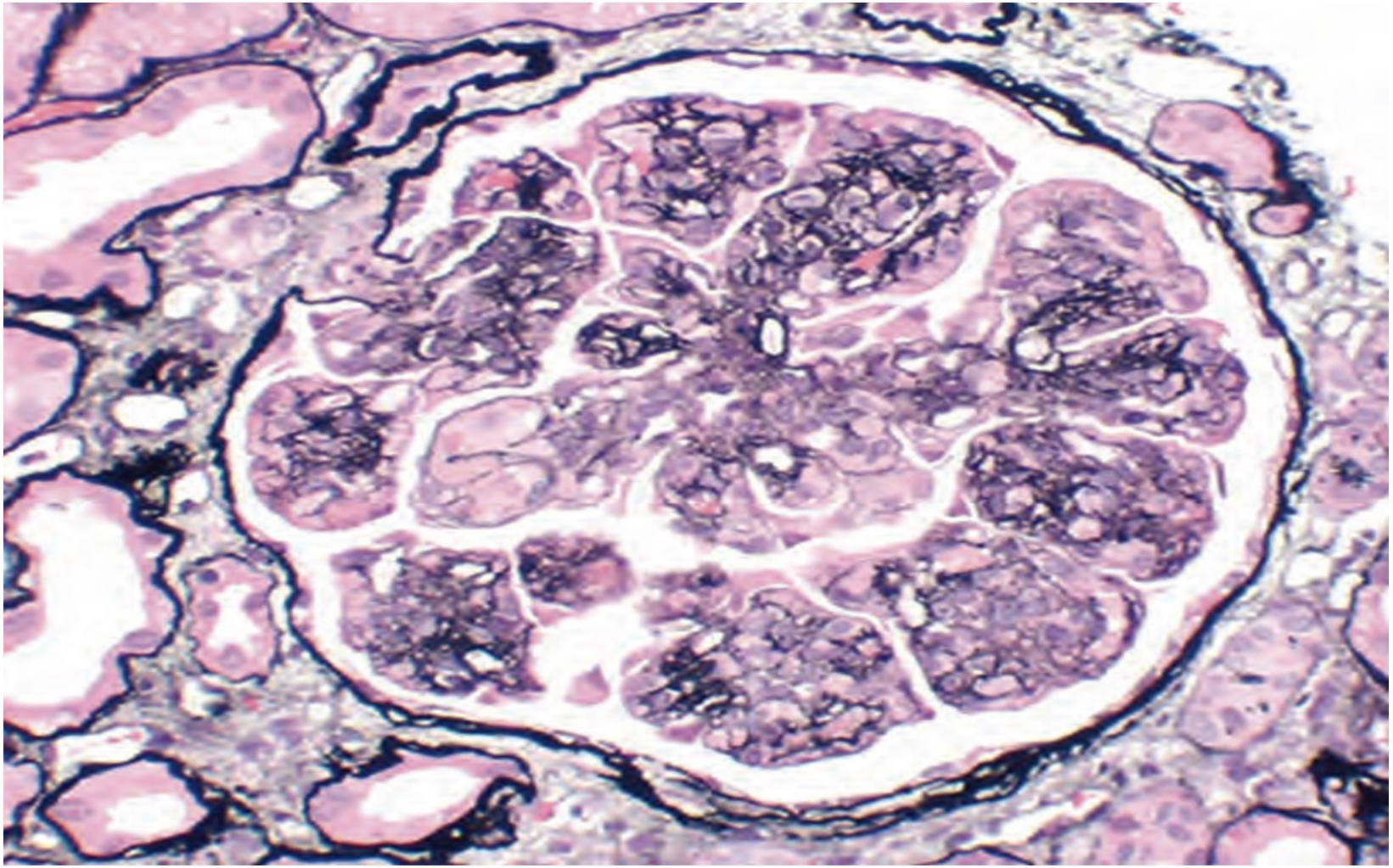
LM:

The glomeruli are large and hypercellular with an accentuated “lobular” contour, this is caused by proliferation of mesangial cells and increased mesangial matrix with the infiltrating leukocytes.

.The GBM is thickened, and often shows a“doublecontour” or “tram-track”

IF: IgG and C3 are deposited in a granular pattern

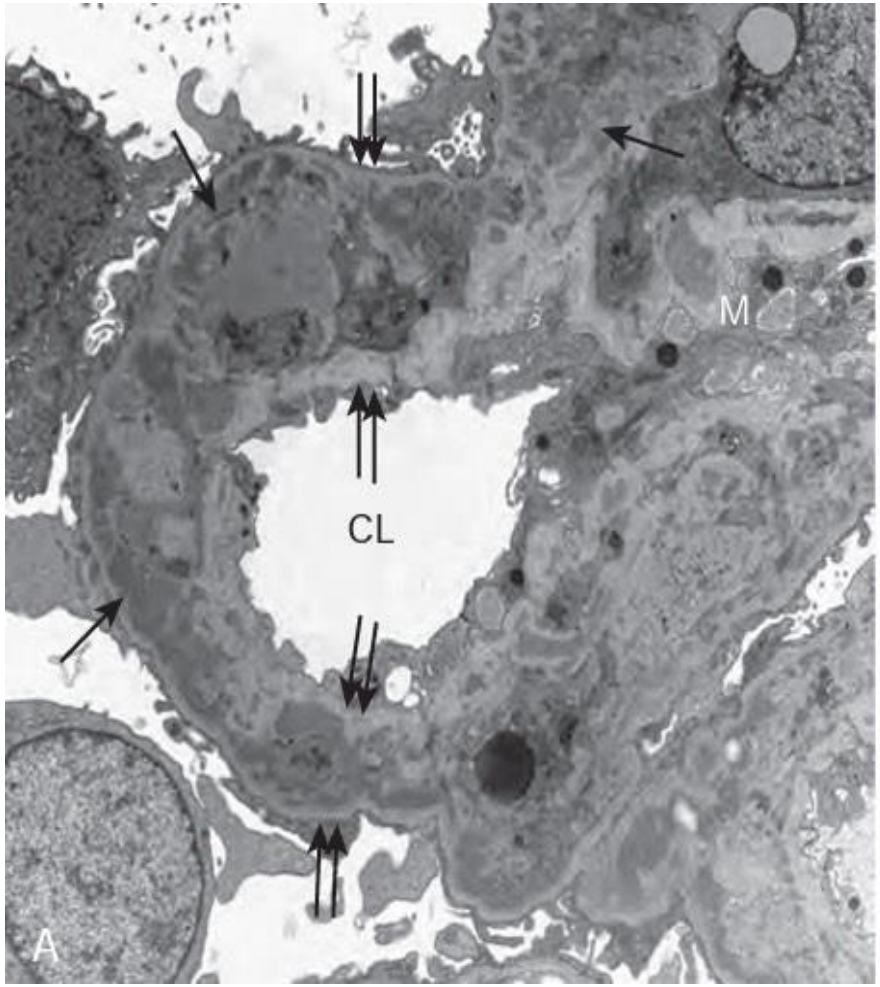
Membranoproliferative glomerulonephritis: showing mesangial cell proliferation, increased mesangial matrix , GBM thickening, accentuation of lobular architecture

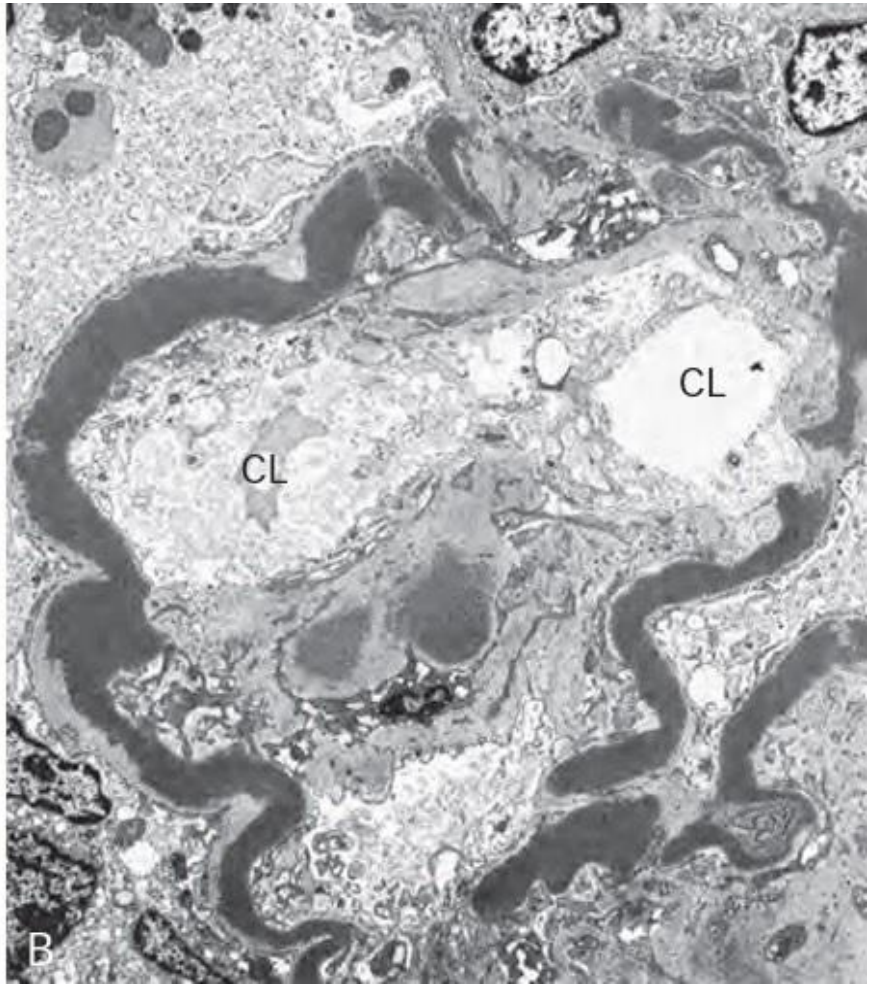


Electron microscopy of MPGN

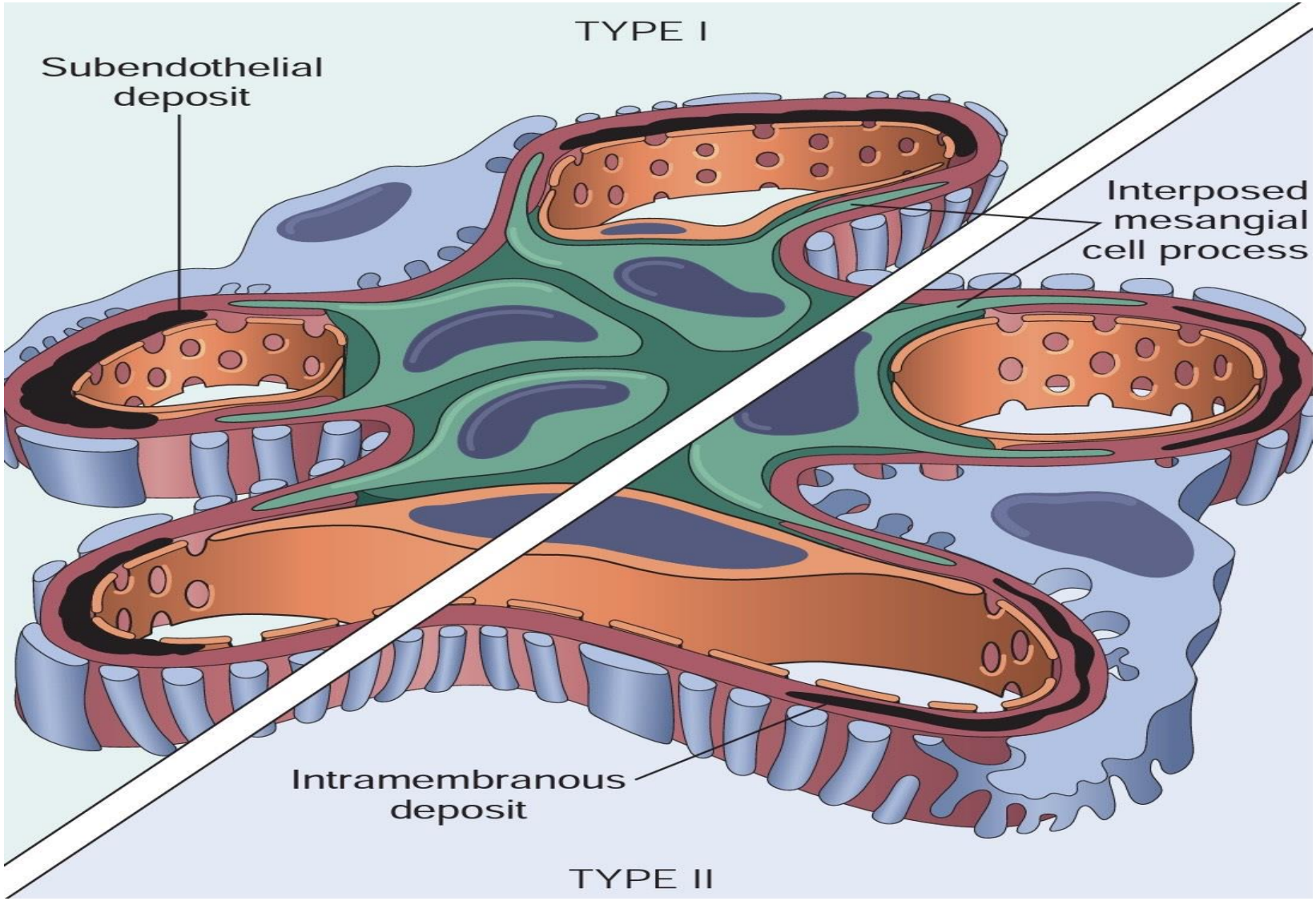
.Type I (A): discrete deposits (arrows) incorporated into the glomerular capillary wall between duplicated (split) basement membranes (double arrows), and in mesangial regions (M)

. Type II (B) : There are dense homogeneous deposits within the GBM





MPGN

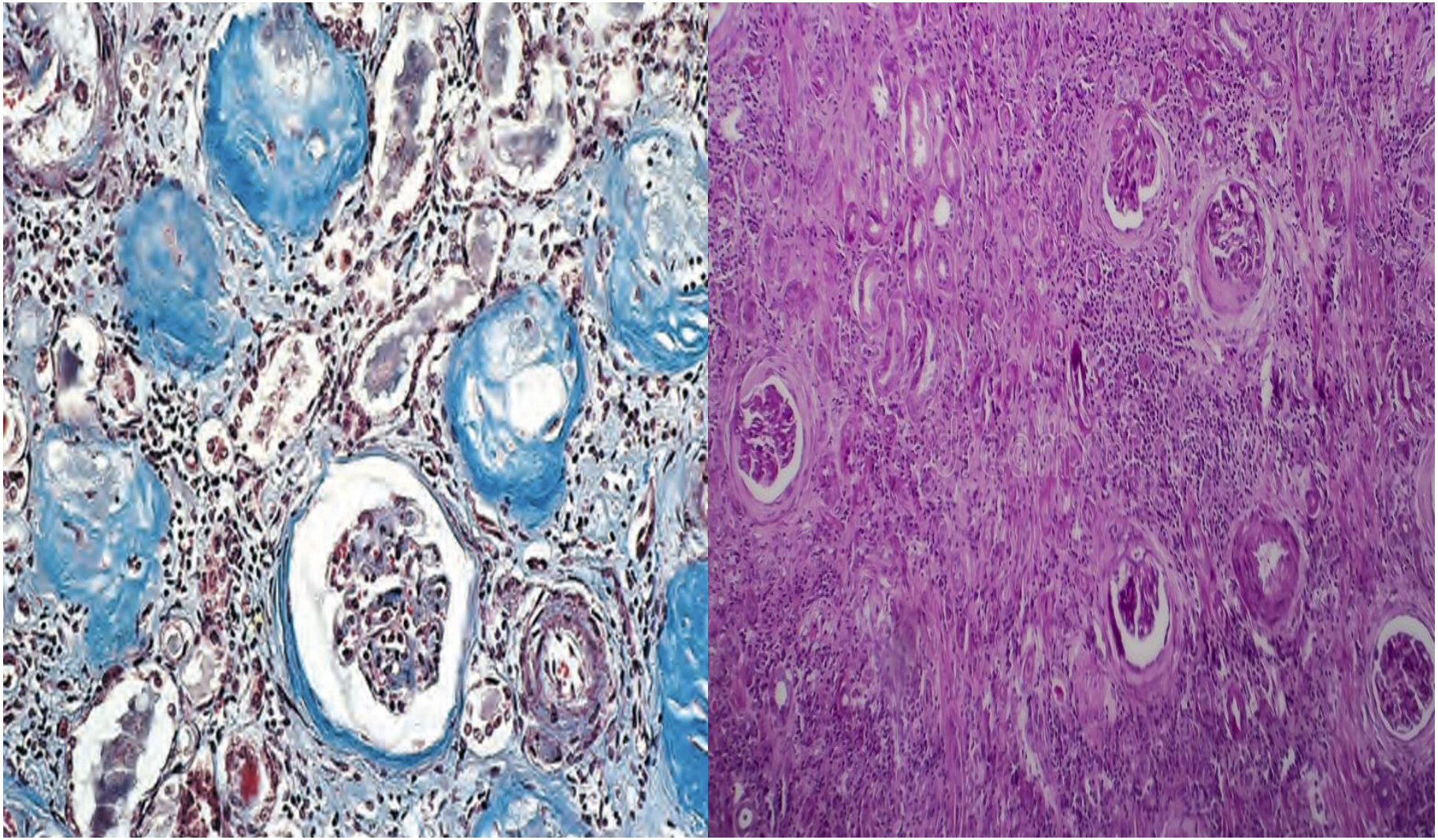

TYPE I
Subendothelial deposit
Interposed mesangial cell process
Intramembranous deposit
TYPE II

Chronic Glomerulonephritis

. **End-stage** glomerular disease that result from many types of glomerulonephritis
. The kidneys are **symmetrically** contracted and have diffusely granular cortical surfaces

.The glomerular **histology**:
Early: may still show evidence of the primary disease.
Late : eventually ensues **obliteration of glomeruli**, transforming them into acellular eosinophilic masses , tubular atrophy and interstitial fibrosis.
. Slowly progresses to renal insufficiency or death from uremia

Chronic Glomerulonephritis



Glomerular Lesions in Systemic Diseases

Systemic Lupus Erythematosus (SLE)
(lupus nephritis)

. Up to **50%** of SLE patients have clinically significant renal involvement.

. All of the glomerular lesions are the result of deposition of **immune complexes** that are regularly present in the mesangium or along the entire basement membrane.

. Six patterns of glomerular disease are seen in SLE:

- **Minimal mesangial lupus nephritis (class I)**

. very uncommon.

. Immune complex deposition in the mesangium , identified by IF and EM, normal LM.

- **Mesangial proliferative lupus nephritis (class II)**

.Characterized by mesangial cell proliferation, often accompanied by accumulation of mesangial matrix.

- **Focal lupus nephritis (class III)**

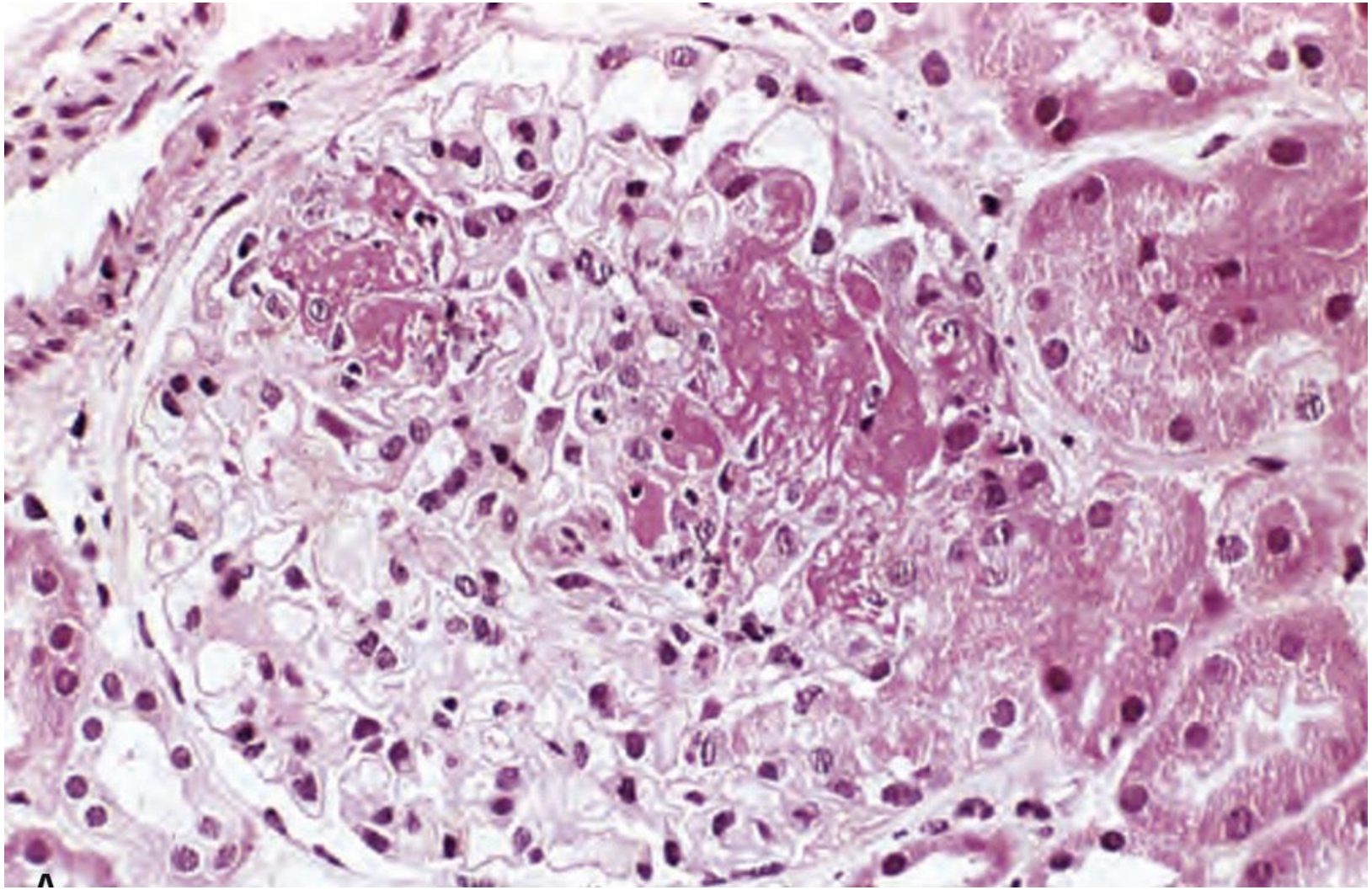
. Defined by involvement of fewer than 50% of all glomeruli.

. Affected glomeruli may exhibit swelling and proliferation of endothelial and mesangial cells associated with leukocyte accumulation

. Mild hematuria and proteinuria.

.Some patients progress to diffuse glomerulonephritis.

Focal lupus nephritis



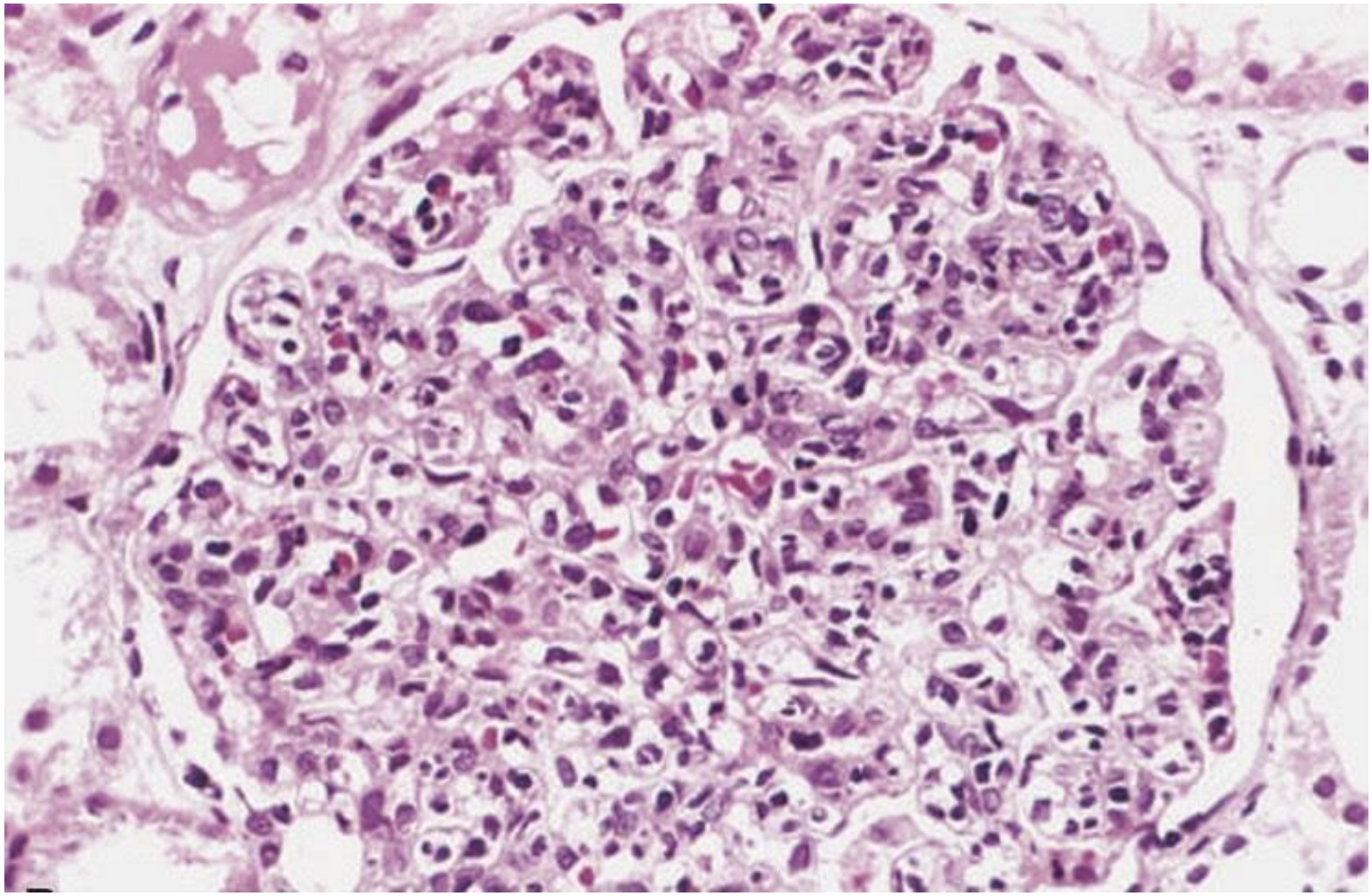
- **Diffuse lupus nephritis (class IV)**

. The **most common** form of lupus nephritis
. The lesions are similar to those in class III, but differ in extent

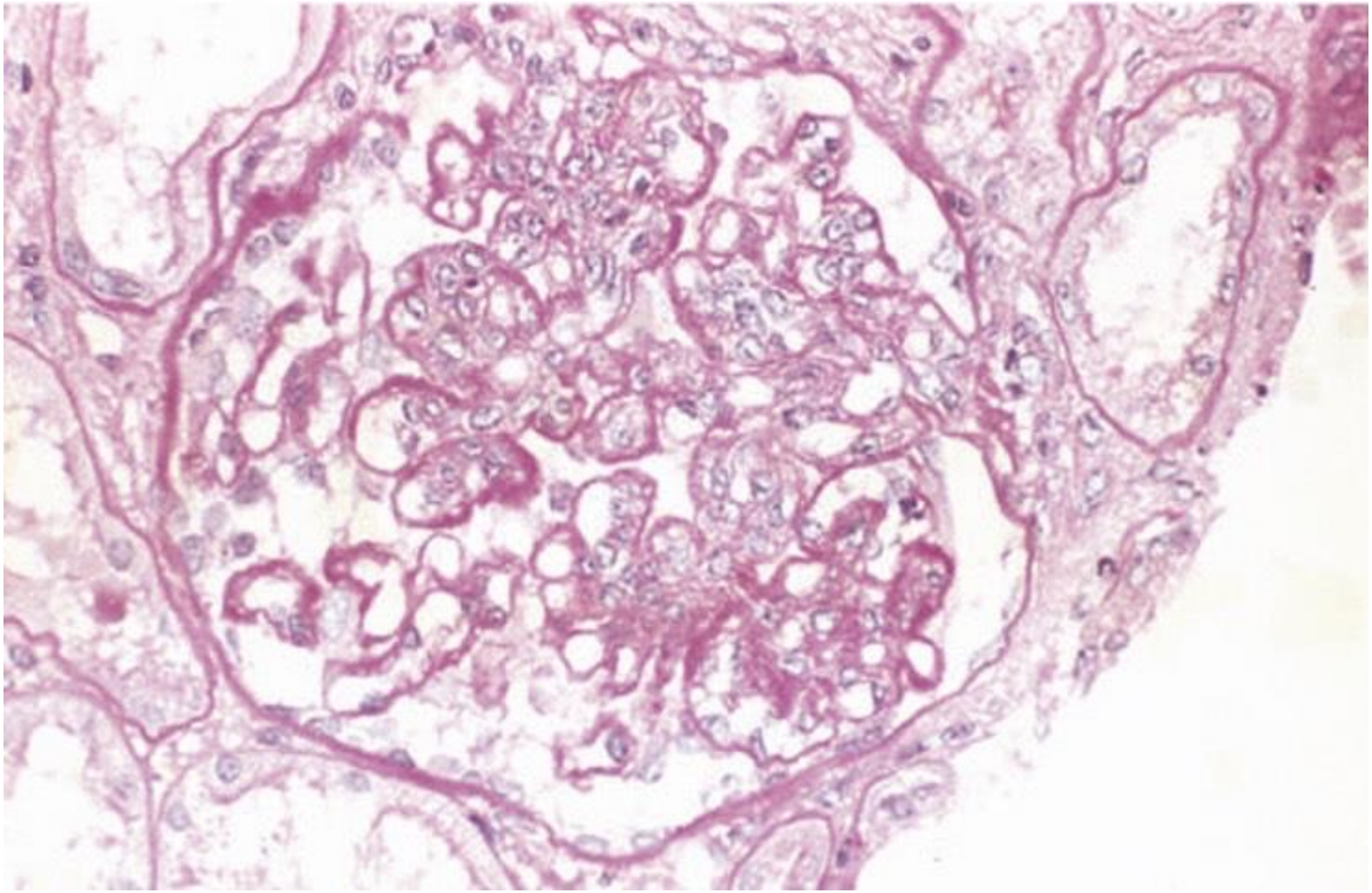
. Circumferential thickening of the capillary wall, forming "**wire loop**" structures may be seen on LM

. Patients are usually **symptomatic** , showing hematuria and proteinuria , Hypertension and mild to severe renal insufficiency.

Diffuse lupus nephritis



Diffuse lupus nephritis (wire loop lesion)



- **Membranous lupus nephritis (class V)**

  - Diffuse thickening of the capillary walls.

  - The lesion is usually accompanied by severe proteinuria , and may occur concurrently with focal or diffuse lupus nephritis.

- **Advanced sclerosing lupus nephritis (class VI)**

  - Sclerosis of more than 90% of the glomeruli, and represents end-stage renal disease.

Diabetic Nephropathy

. The kidney is a primary target for diabetes

. Three lesions are involved in the kidney:

1.Glomerular lesions

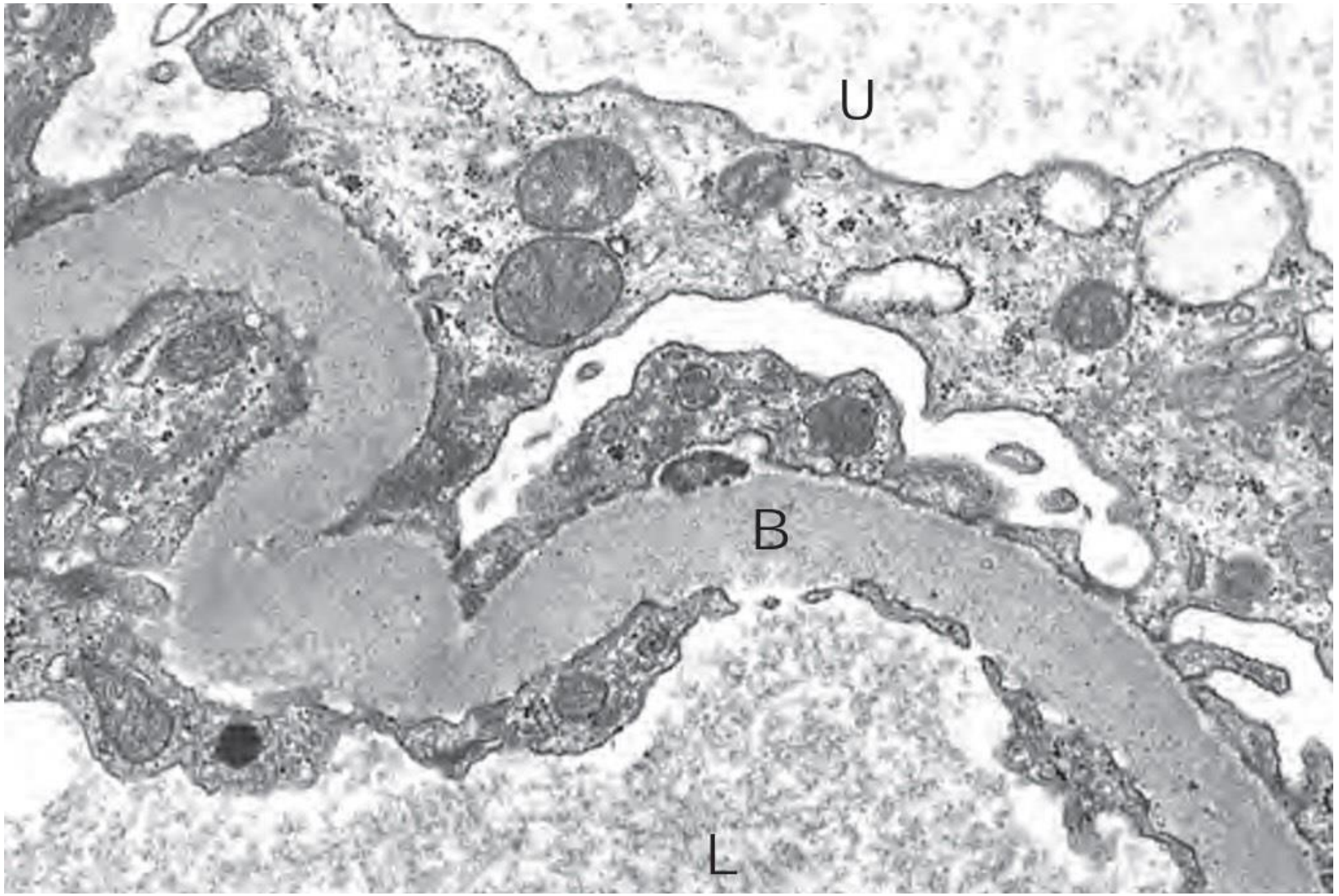
2.Renal vascular lesions

3.Pyelonephritis

.The most important **glomerular** lesions are :

- **Capillary BM thickening**
- **Diffuse mesangial sclerosis**
- **Nodular glomerulosclerosis**

Electron micrograph of a renal glomerulus showing markedly thickened glomerular basement membrane (B) in a diabetic patient



Diabetic glomerulosclerosis

Two forms

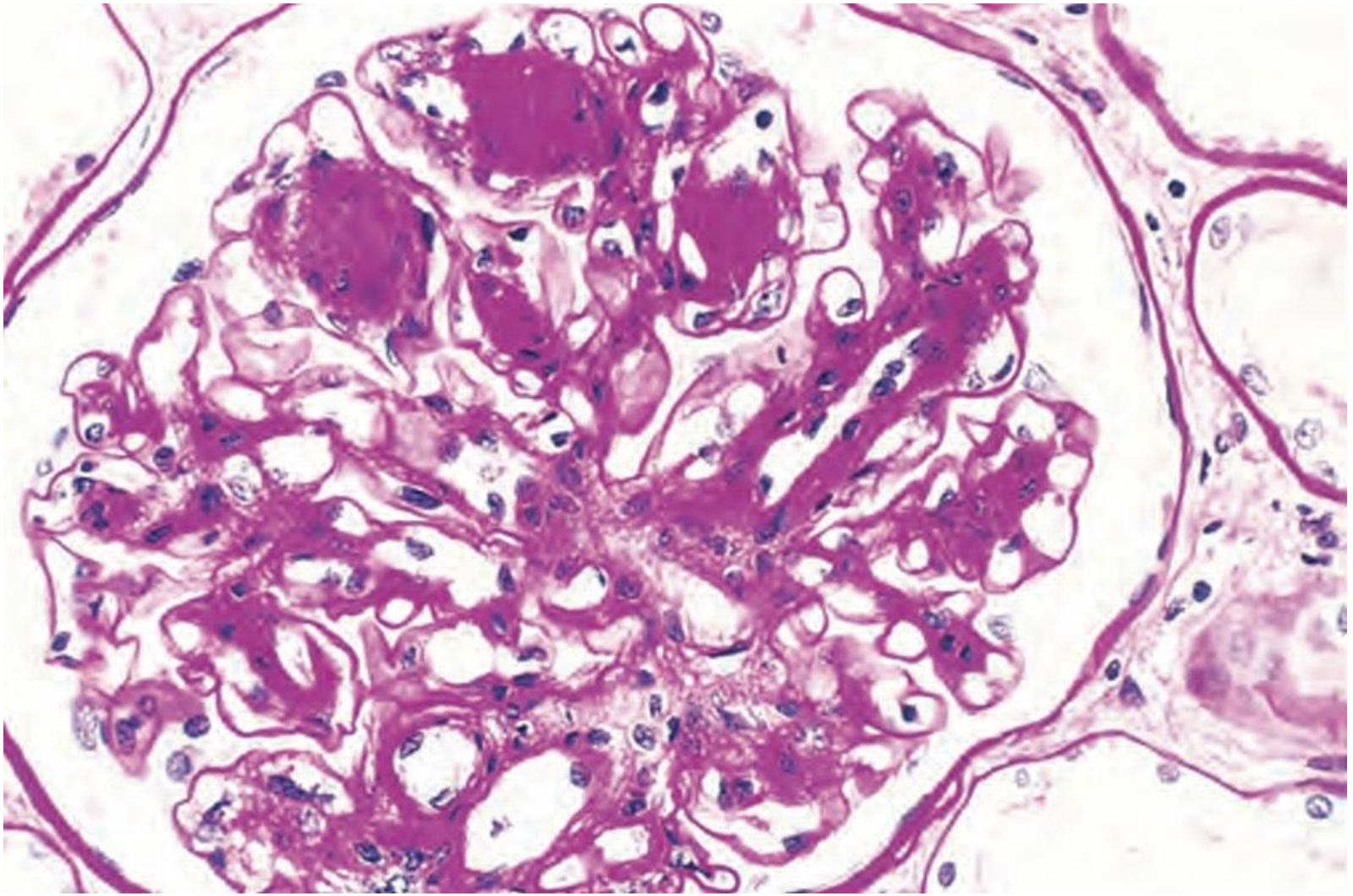
- **Diffuse glomerulosclerosis**: diffuse deposition of hyaline material in the mesangium.

- **Nodular glomerulosclerosis** (Kimmelstiel - Wilson nodules):

The glomerular lesions take the form of ovoid or spherical, often laminated, nodules of matrix situated in the periphery of the glomerulus

The nodular and diffuse forms are usually combined

Diffuse and nodular diabetic glomerulosclerosis



Tubular and Interstitial Diseases

1. Ischemic or toxic tubular injury
2. Inflammatory(tubulointerstitial nephritis)

1. Acute Tubular Necrosis (ATN):

-ATN is characterized by destruction of renal tubular epithelial cells either from ischemia or nephrotoxins lead to loss of renal function (most common cause of ARF)

Ischemic ATN:

Occurs after shock produced by sepsis, burns, trauma, blood loss.

Nephrotoxic ATN:

caused by:

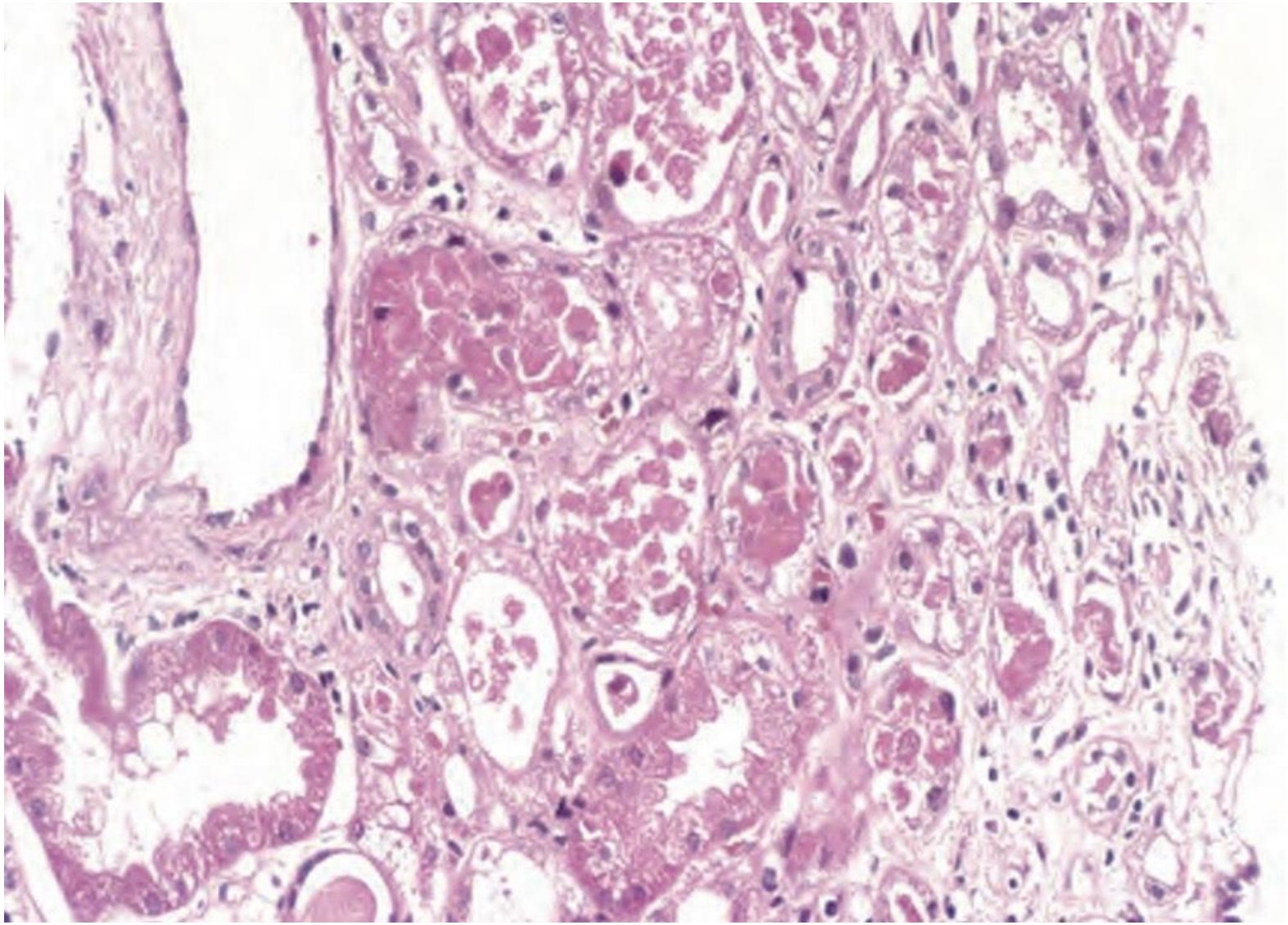
Drugs : gentamycin ,cephalosporin.

Toxins : heavy metals such as mercury.

Morphology:

Focal tubular epithelial necrosis at multiple points in the proximal tubule along the nephron with large skip areas, often with ruptured basement membrane.

Acute tubular injury



Tubulointerstitial Nephritis (TIN) :

Inflammatory injuries of the tubules and interstitium with sparing of glomeruli.

-In cases of TIN caused by bacterial infection , the renal pelvis is predominantly involved(pyelonephritis).

-The term interstitial nephritis is reserved for TIN that are non bacterial in origin (viral infections, drugs, metabolic disorders, irradiation)

Tubulointerstitial nephritis can be acute or chronic.

Acute tubulointerstitial nephritis has a rapid clinical onset and is characterized histologically by interstitial edema, often accompanied by leukocytic infiltration of the interstitium and tubules, and tubular injury.

Chronic interstitial nephritis : there is infiltration with predominantly mononuclear leukocytes, prominent interstitial fibrosis, and widespread tubular atrophy.

Pyelonephritis and Urinary Tract Infection

Pyelonephritis is one of the most common diseases of the kidney and is defined as inflammation affecting the tubules, interstitium, and renal pelvis.

It occurs in two forms :

1. Acute pyelonephritis : is a common suppurative inflammation, caused by bacterial infection , it is an important manifestation of **UTI** , which can involve lower (cystitis ,prostatitis ,urethritis) or upper (pyelonephritis) urinary tract.

- The majority of cases are associated with **lower UTI** which is very common.
- **E-coli** is the most common causative agent.

- The bacteria reach the kidneys from the lower urinary tract (**ascending infection**) which is the most common or the blood stream (**hematogenous infection**)

.

Predisposing factors to Acute PN are:

1. **Urinary tract obstruction**:BPH, uterine prolapse, stone.
2. **Vesico-ureteral reflux**
3. **Instrumentation**
4. **Diabetes mellitus**
5. **Pregnancy**
6. **Immunosuppression & Immunodeficiency**
7. **Pre-existing renal lesions**
8. **Gender and age**

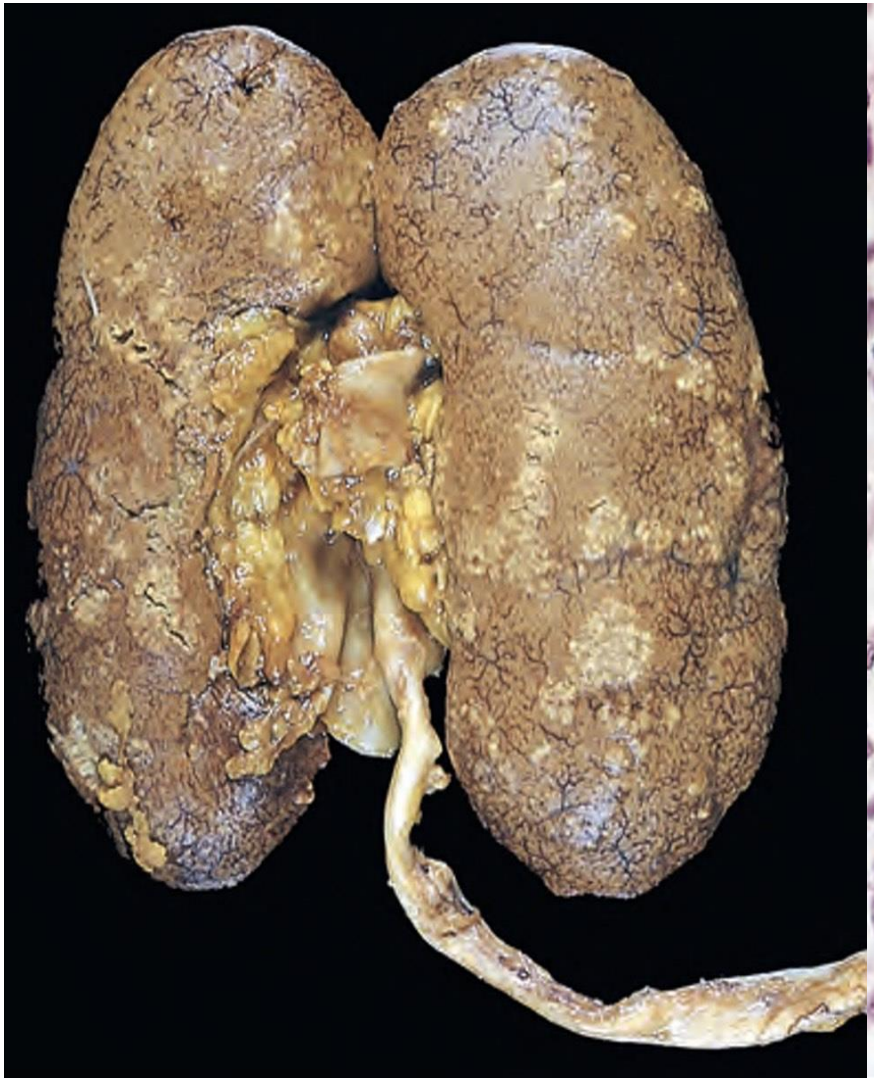
Clinical features : sudden onset loin pain with fever , chills, nausea , malaise , dysuria , frequency and urgency

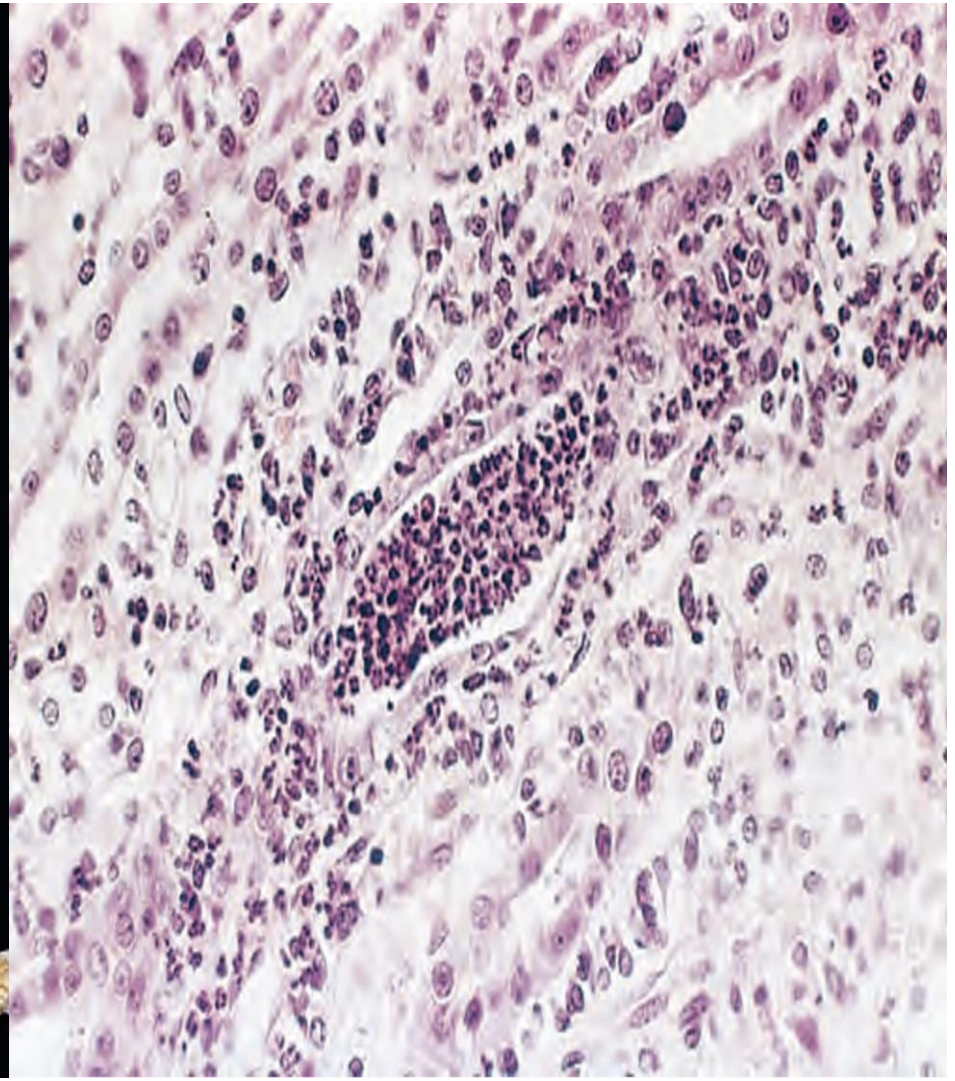
Morphology

One or both affected kidneys are enlarged or normal in size, with discrete yellow raised abscesses, which may coalesce to form single large area of suppuration

Histologically : patchy interstitial suppurative inflammation , intratubular aggregate of neutrophiles , tubulitis and tubular necrosis.

Acute pyelonephritis





2.Chronic pyelonephritis (CPN)

.It is a disorder where chronic tubulointerstitial inflammation and scarring involve the pelvis and calyces with repeated attacks of inflammation and healing

. Bacterial infection plays a dominant role, but other factors (vesicoureteral reflux, obstruction) predispose to repeat episodes of acute pyelonephritis

It can be divided into two types:

1.Reflux CPN

-Most common cause of CPN

-Begins in infants and children with congenital vesico-ureteral reflux

2. Obstructive CPN

-recurrent infection superimposed on diffuse or localized obstructive lesions lead to repeated bouts of renal inflammation and scarring

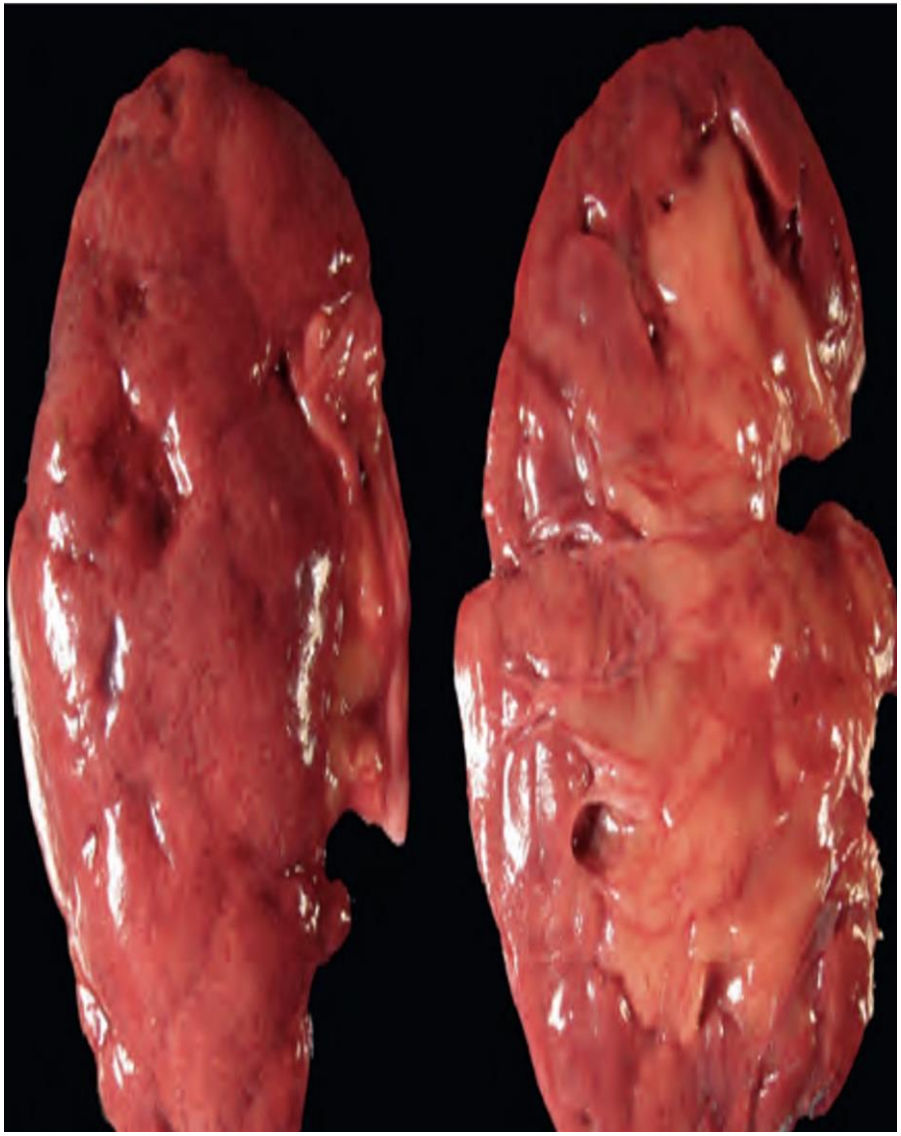
Morphology

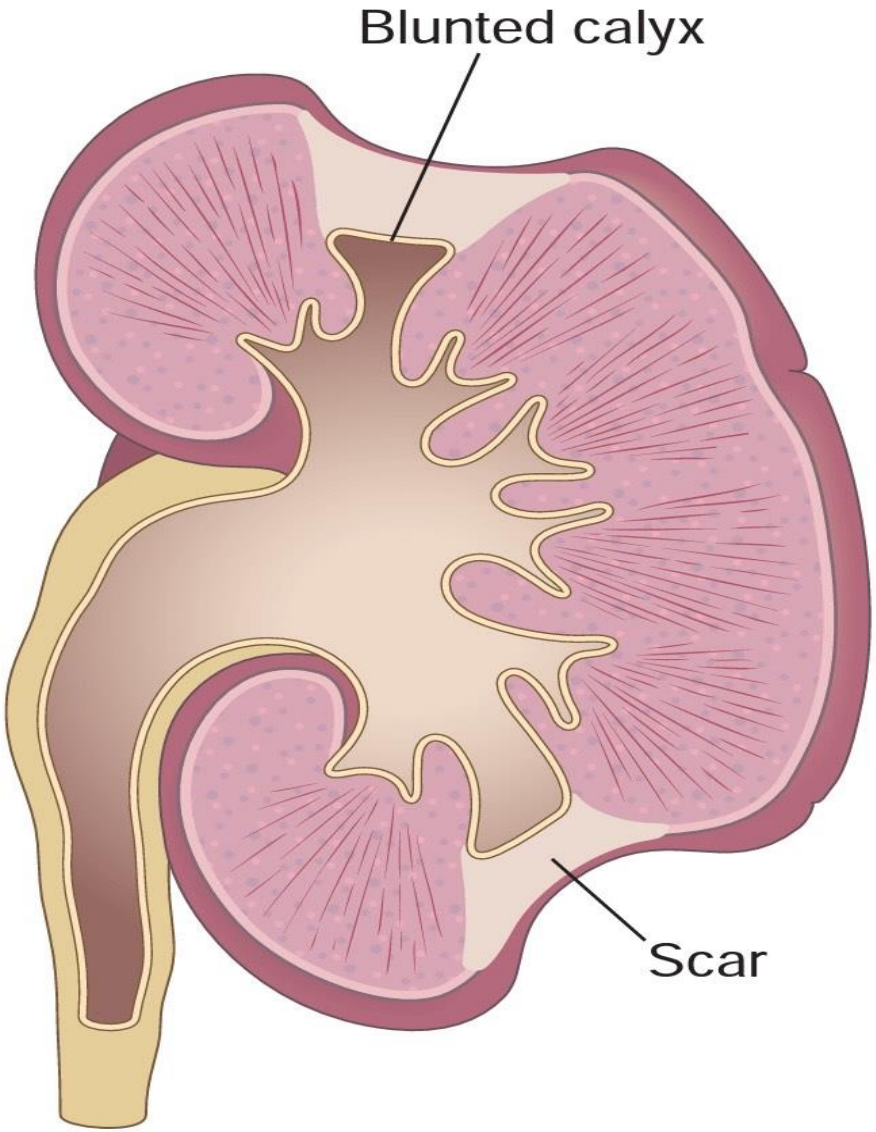
Gross : Asymmetrical small contracted kidney with irregular scarring and deformity of pelvis and calyces

Histology :

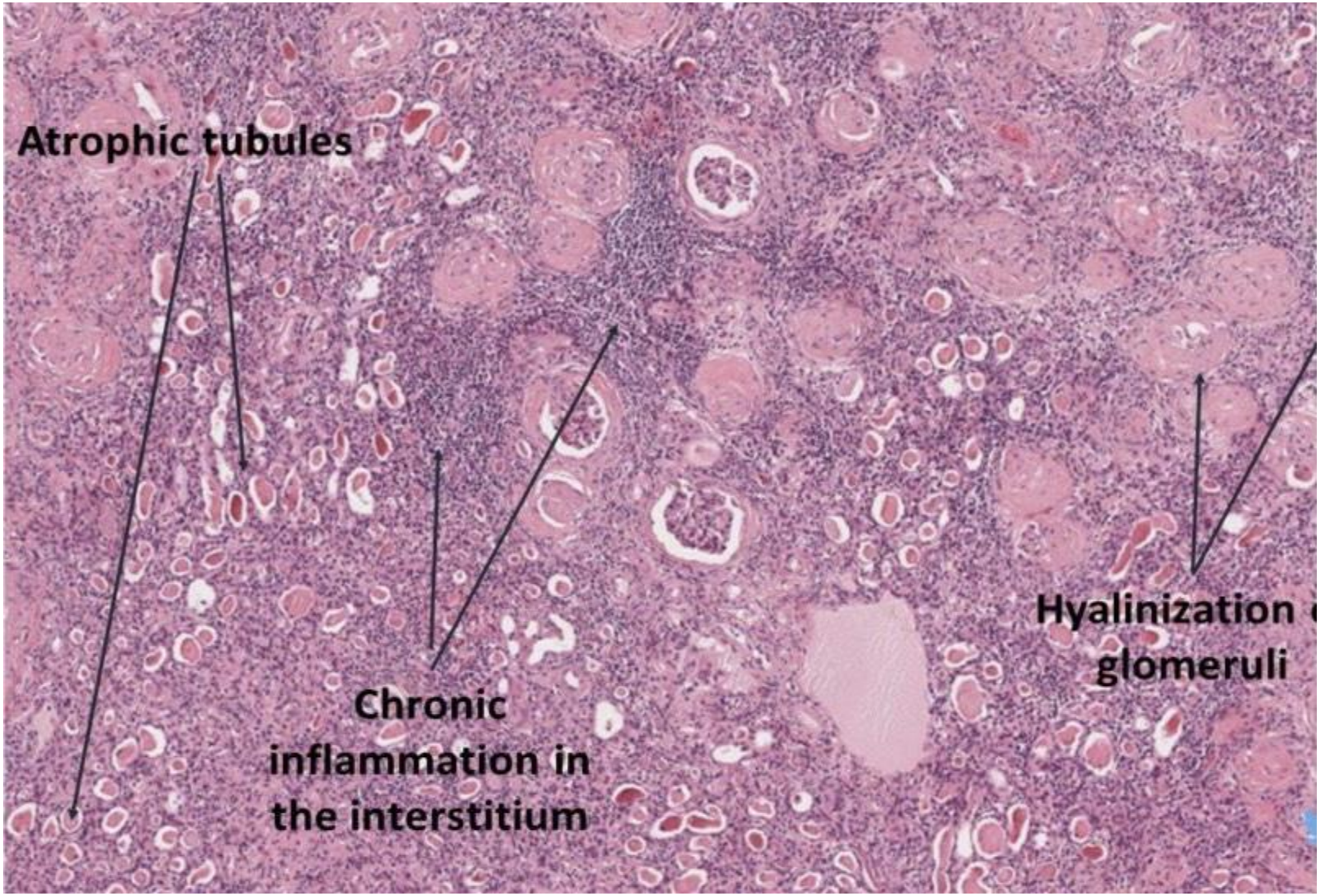
- Chronic inflammatory cell infiltration(lymphocytes, plasma cells and macrophages) in the interstitial tissue with fibrosis
- Atrophy, destruction, and loss of some tubules, remaining tubules are dilated and contain eosinophilic colloid casts resembling thyroid follicles (Thyroidization)
- Arteriolosclerosis
-Glomrulosclerosis

Chronic pyelonephritis





Chronic pyelonephritis



Chronic pyelonephritis