
Focal
& Segmental
Glomerulosclerosis

## The cardinal feature is progressive glomerular scarring

**Early in the disease course, glomerulosclerosis is both focal, involving a minority of glomeruli, and segmental, affecting a portion of the glomerular globe.**

**FSGS is an important glomerulopathy because it has a high risk of progression to ESRD.**

# Primary or Idiopathic FSGS

- **Primary /Idiopathic FSGS accounts for approximately 20-30 % of all cases of the NS. It is becoming an increasingly common cause of NS in adults & remains a frequent cause in children.**

# Focal Segmental Glomerulosclerosis

Accounts for approximately 20% of cases of the nephrotic syndrome in children and 40% of such cases in adults

# Clinical Presentation

- >70% of patients present with signs and symptoms of nephrotic syndrome
  - Nephrotic range (>3.5 g/d) proteinuria
  - Generalized edema
  - Hypertension
  - Hypoalbuminemia
  - Hyperlipidemia
  - Microscopic hematuria
- Renal failure

**Table 1. Causes of Focal Segmental Glomerulosclerosis.**

| Type of Disease | Cause |
|---|---|
| Primary (idiopathic) form | Specific cause unknown; mediated by circulating permeability factors |
| Secondary forms | |
| Familial or genetic | Mutations in specific podocyte genes* |
| Virus-associated | Human immunodeficiency virus type 1, parvovirus B19, simian virus 40, cytomegalovirus, Epstein–Barr virus |
| Drug-induced | Heroin; interferons alfa, beta, and gamma; lithium; pamidronate; sirolimus; calcineurin-inhibitor nephrotoxicity; anabolic steroids |

| | |
|---|---|
| | anabolic steroids |
| Adaptive† | Conditions with reduced renal mass: oligomeganephronia, very low birth weight, unilateral renal agenesis, renal dysplasia, reflux nephropathy, sequela to cortical necrosis, surgical renal ablation, renal allograft, aging kidney, any advanced renal disease with reduced functioning nephrons<br>Conditions with initially normal renal mass: systemic hypertension, acute or chronic vaso-occlusive processes (atheroembolization, thrombotic microangiopathy, renal-artery stenosis), elevated body-mass index (obesity, increased lean body mass [e.g., bodybuilding]), cyanotic congenital heart disease, sickle cell anemia |

# FSGS vs MCD

- 1. Hematuria, Hypertension.
- 2. Nonselective proteinuria.
- 3. Poor response to corticosteroids.
- 4. >50% individuals develop ESRF within 10 y.
- 5. Adults in general fare even **less well** than children.

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# IgM nephropathy: timely response to a call for action

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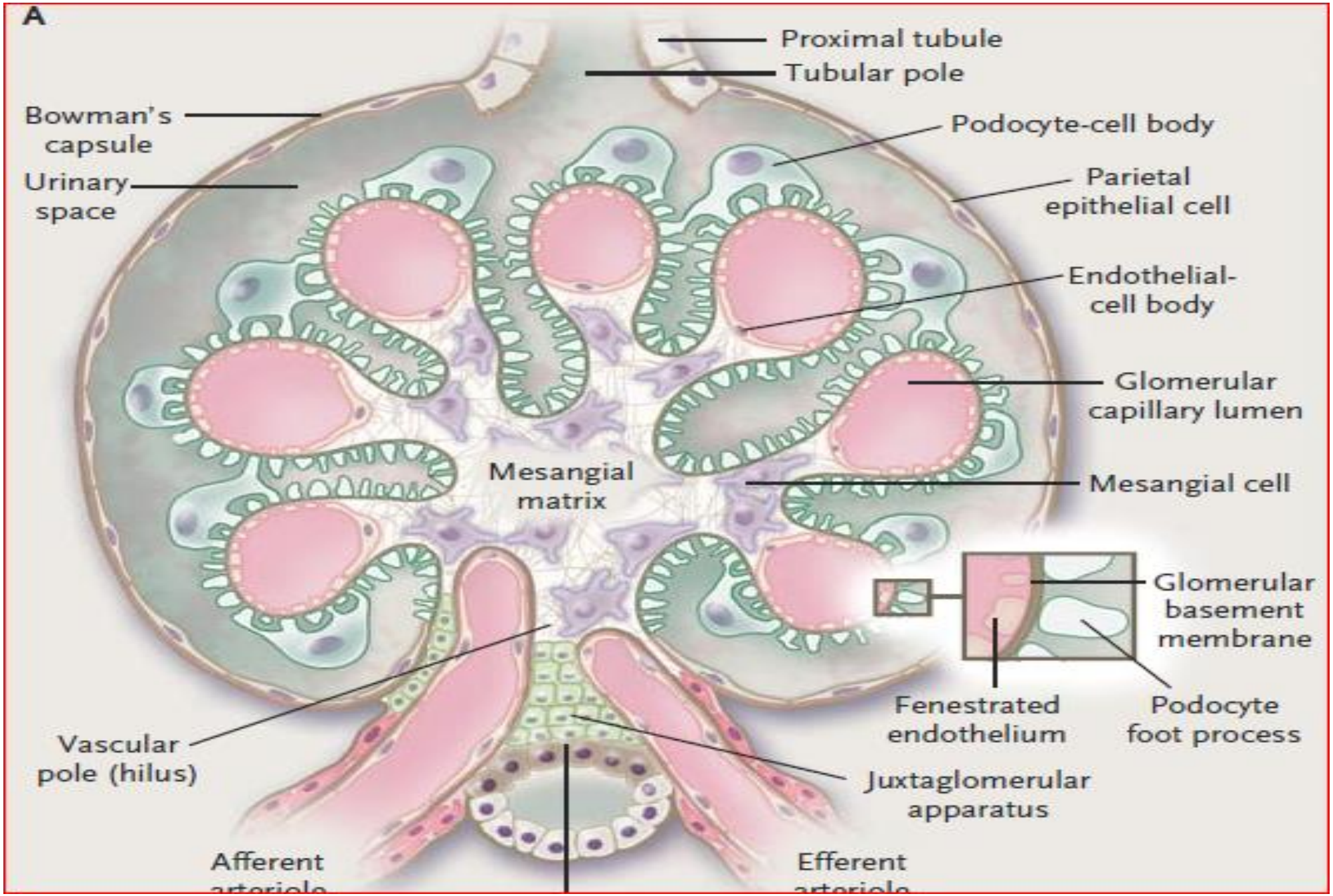
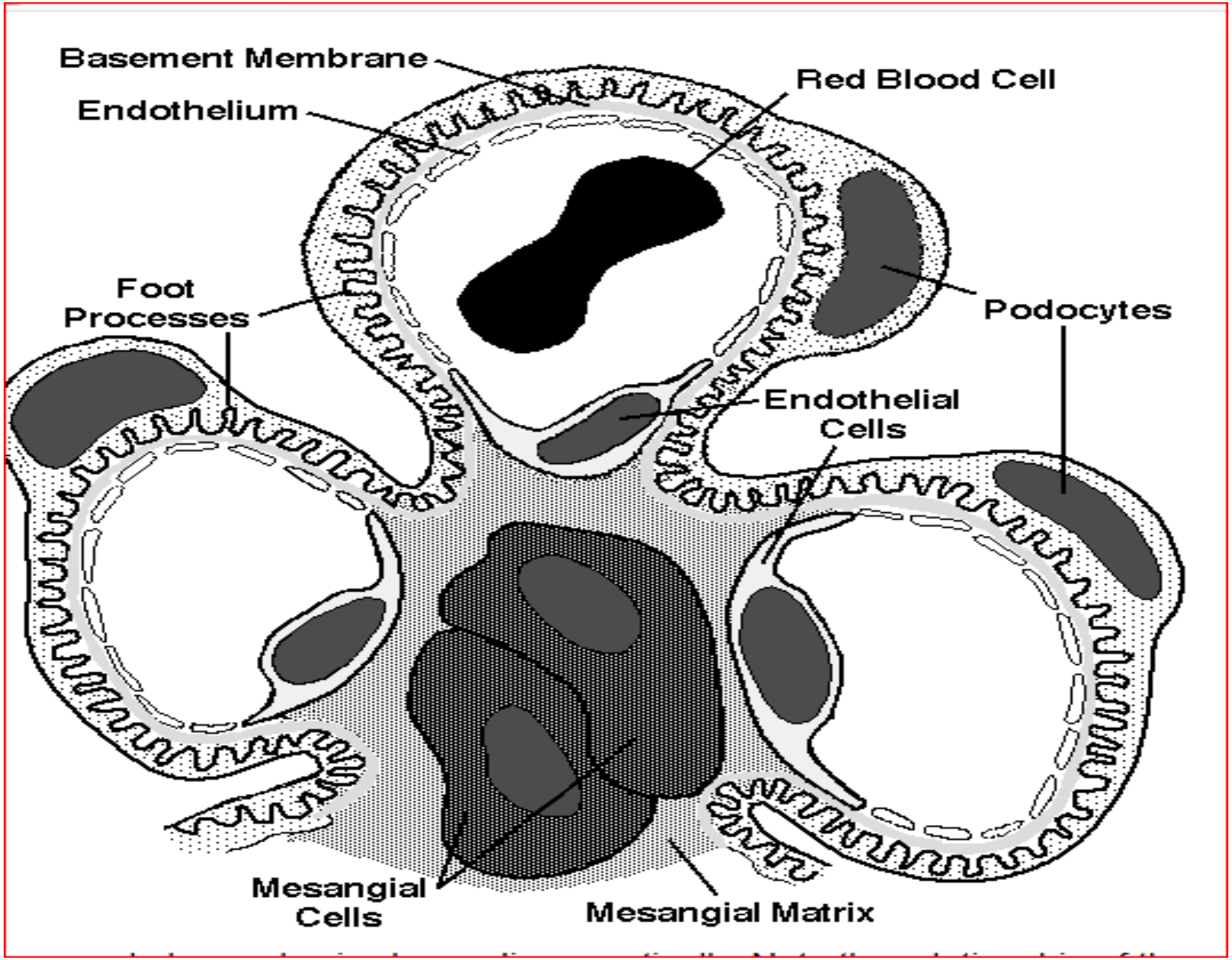
- MCD may transform to FSGS.
- Distinct clinicopathologic entity from the outset (beginning).
- In any case, **injury to podocytes** is thought to represent the initiating event of primary FSGS.
- As with MCD, **permeability-increasing factors produced by lymphocytes (cytokines)** have been proposed.


A
Proximal tubule
Tubular pole
Bowman's capsule
Urinary space
Podocyte-cell body
Parietal epithelial cell
Endothelial-cell body
Glomerular capillary lumen
Mesangial matrix
Mesangial cell
Glomerular basement membrane
Fenestrated endothelium
Podocyte foot process
Vascular pole (hilus)
Juxtaglomerular apparatus
Afferent arteriole
Efferent arteriole


Basement Membrane
Endothelium
Red Blood Cell
Foot Processes
Podocytes
Endothelial Cells
Mesangial Cells
Mesangial Matrix

- **The deposition of hyaline masses in the glomeruli** represents the entrapment of plasma proteins and lipids in foci of injury where sclerosis develops.
- **IgM and complement proteins** commonly seen in the lesion are also believed to result from nonspecific entrapment in damaged glomeruli.

# MORPHOLOGY

- **Immunofluorescence microscopy:**
- **It reveals nonspecific trapping of immunoglobulins, usually IgM & complement in the areas of hyalinosis.**

# Morphology

- The disease first affects only some of the glomeruli (**Focal**) & initially only the juxtamedullary glomeruli.
- Eventually all levels of the cortex are affected.
- Lesions occur in some tufts (**Segmental**) within a glomerulus.

- Key factor in the pathogenesis
  - "**Podocyte damage and loss**"

# Podocytopathy

Podocytes that are targeted by cellular stresses, such as permeability factors (external causes) or disease causing mutations (intrinsic defects), respond by the reorganization of their actin cytoskeleton, leading to foot-process effacement.

**Various aspects of podocytopathy**

- **The affected glomeruli exihibit:**

1. Increased mesangial matrix,
2. Obliterated capillary lumens
3. Deposition of hyaline masses & lipid droplets.

# Global Sclerosis:

Occasionally , glomeruli are completely sclerosed with or without **interstitial fibrosis**

# Pathologic variants

1. Collapsing variant→ESRD
2. Glomerular tip lesion variant
3. Cellular variant
4. Perihilar variant
5. Not otherwise specified (NOS) variant. Most common

# Pathological Variants

- **Tip variant**
  - Involving the part of the glomerulus near the origin of the proximal tubule
- **Perihilar variant**
  - Sclerosis of the vascular pole
- **Cellular variant**
  - Hypercellularity of the capillary space
- **Collapsing variant**
  - With ≥1 glomeruli with global or segmental collapse

Progress more rapidly to ESRD

# Morphology

- **EM** shows **effacement of foot processes**. Global sclerosis may be found occasionally.
- **Collapsing glomerulopathy- Collapse** of the entire glomerular tuft & podocyte hyperplasia.

**CG may be associated with HIV inf drug-induced toxicities. It has a poor prognosis.**

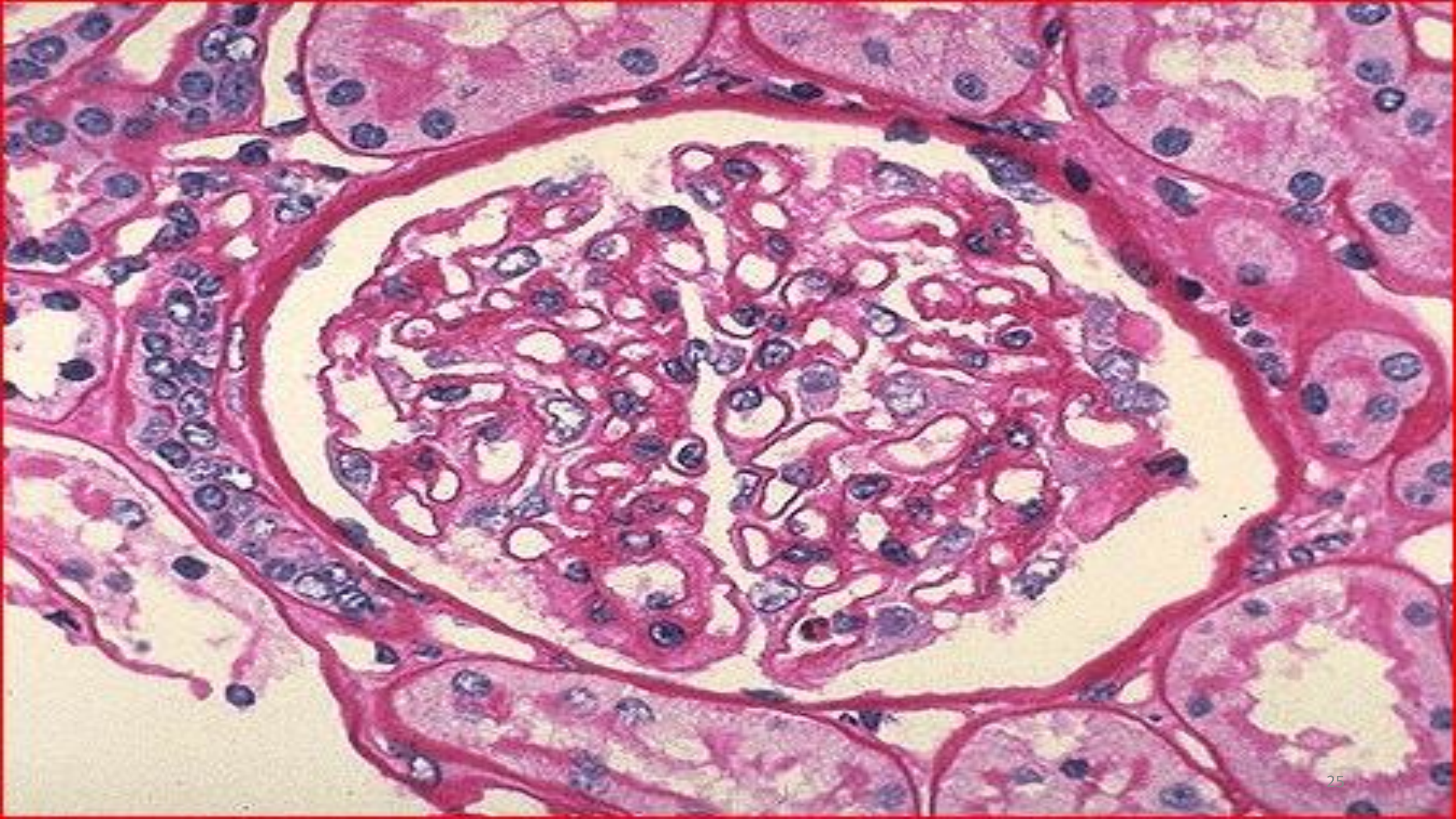
- ***Primary/Idiopathic FSGS***

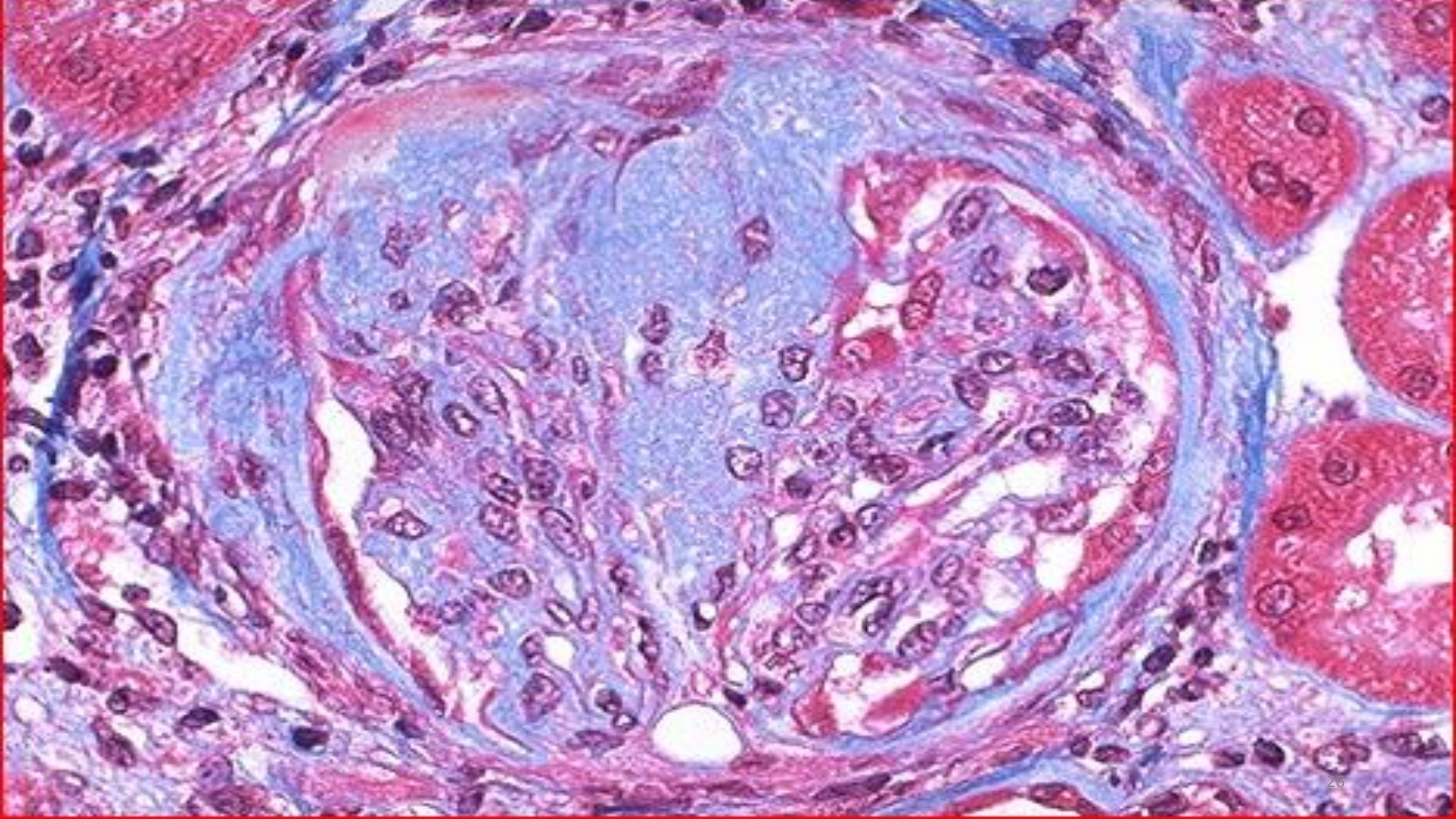
- ***Hereditary diseases***
  - Sickle cell disease

- ***Viral infections***
  - HCV, HIV
  - Cytomegalovirus
  - Epstein-Barr virus
  - Parvovirus B19

- ***Drugs/Toxic agents***
  - Interferon-α, pamidronate, lithium, gold, **heroin (IV)**

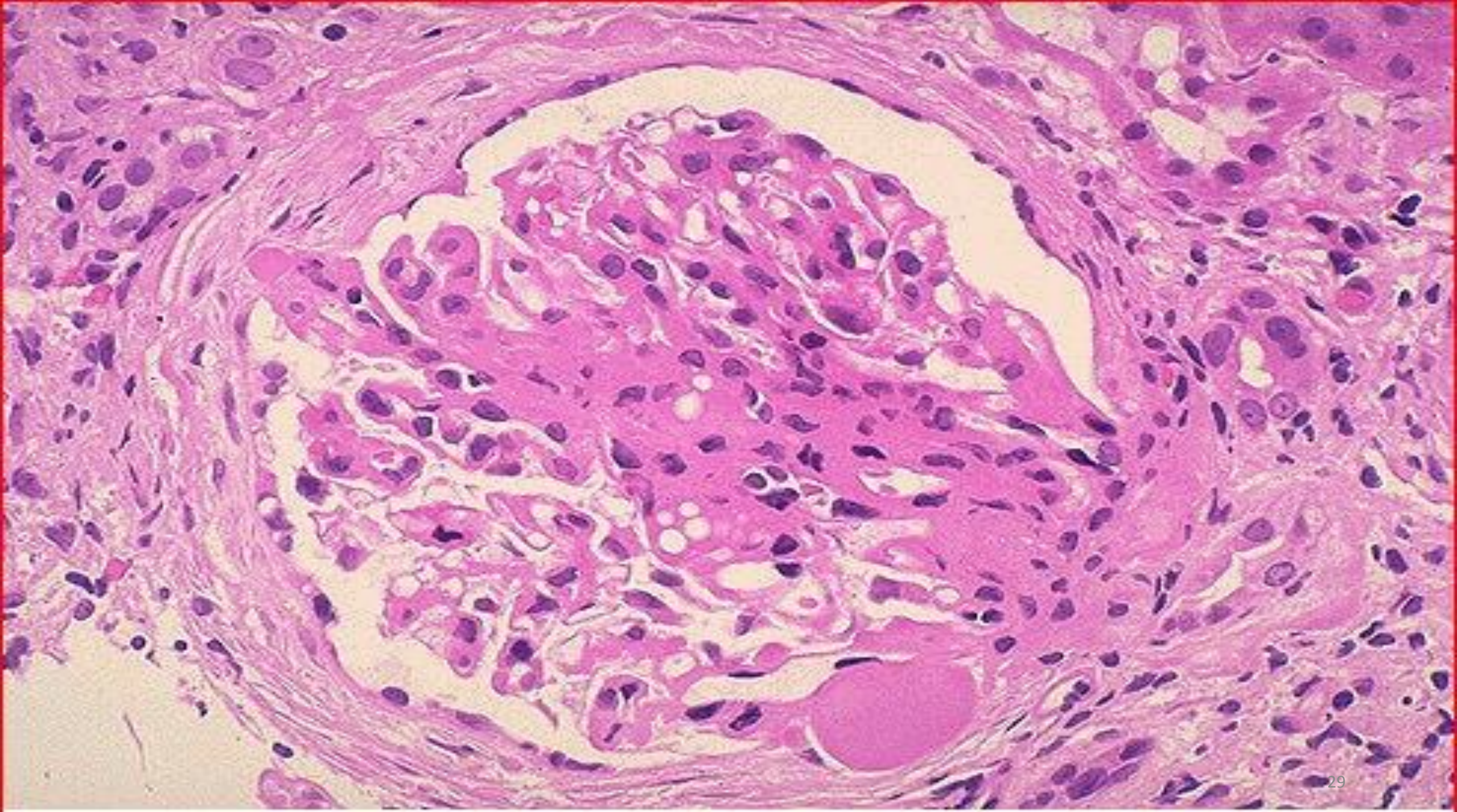
- ***Ischemia***
  - Renal artery stenosis
  - Hypertensive kidney disease
  - Calcineurin inhibitors (CNIs) nephrotoxicity
  - Acute and chronic renal allograft rejection
  - Cholesterol crystal embolism
  - Cyanotic congenital heart disease



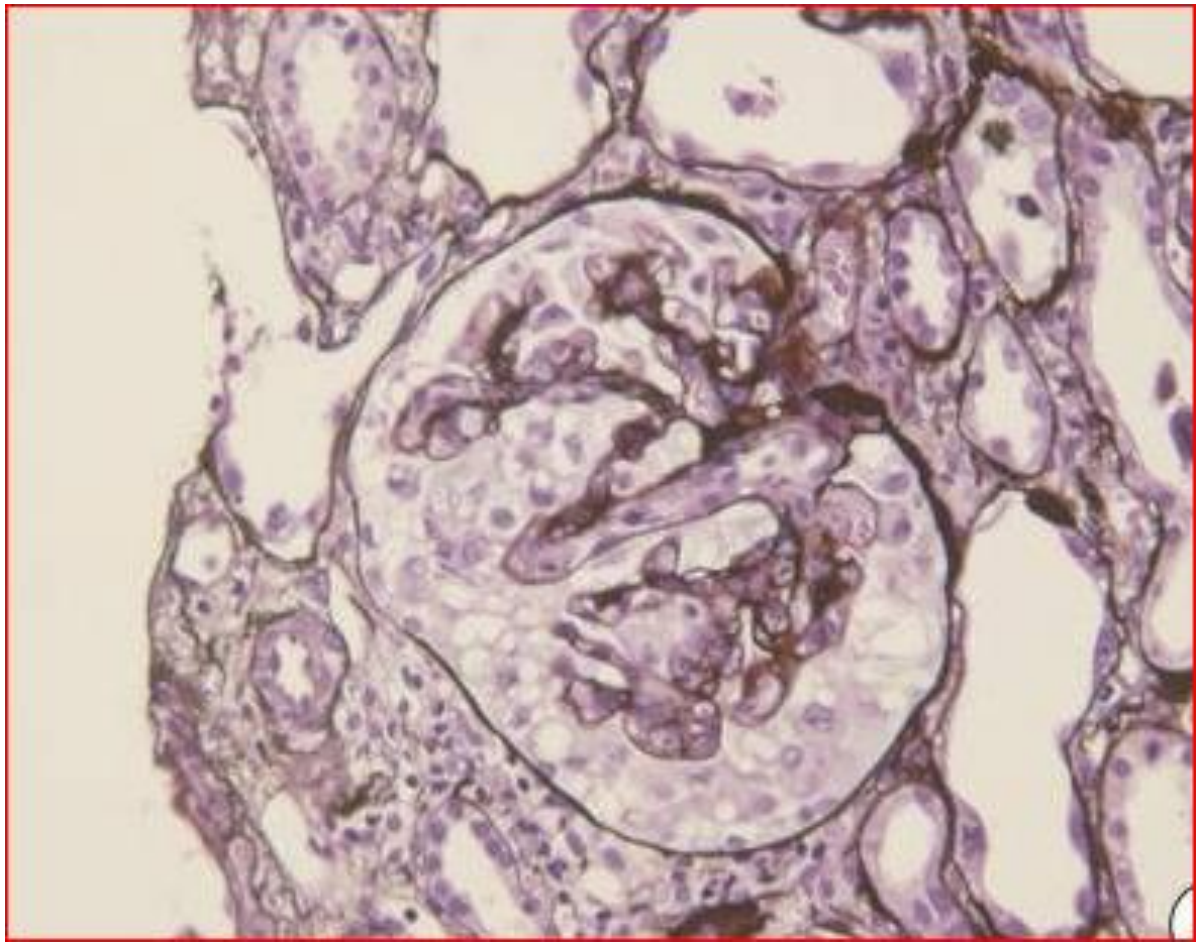


**This trichrome stain of a glomerulus in a patient with focal segmental glomerulosclerosis (FSGS) demonstrates blue collagen deposition. FSGS accounts for about a sixth of cases of nephrotic syndrome in adults and in children. FSGS is most often a primary disease, but it can be secondary to other conditions.**

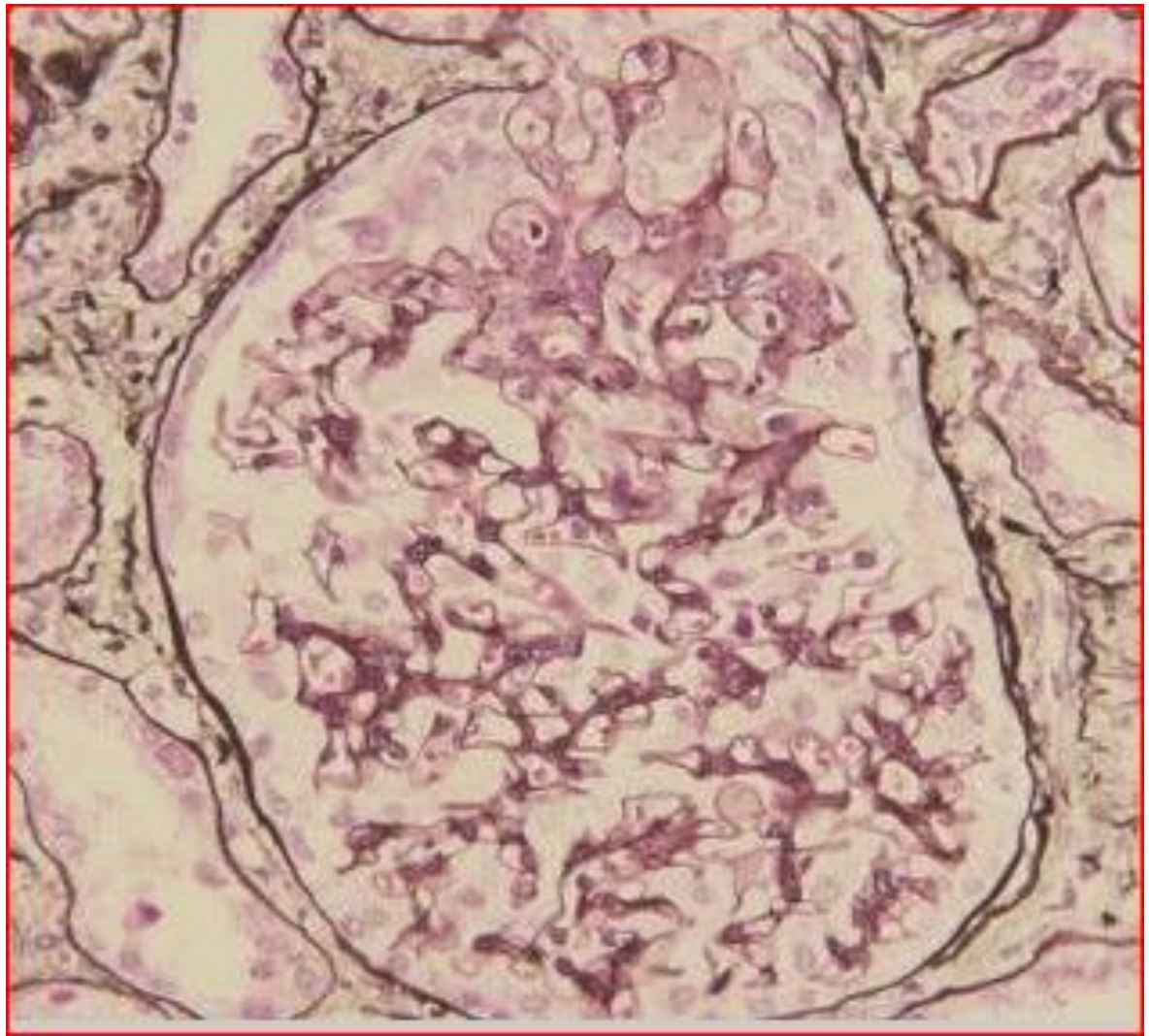
**This is focal segmental glomerulosclerosis (FSGS). An area of collagenous sclerosis runs across the middle of this glomerulus. As the name implies, only some (focal) glomeruli are affected and just part of the affected glomerulus is involved (segmental) with the sclerosis. In contrast to minimal change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



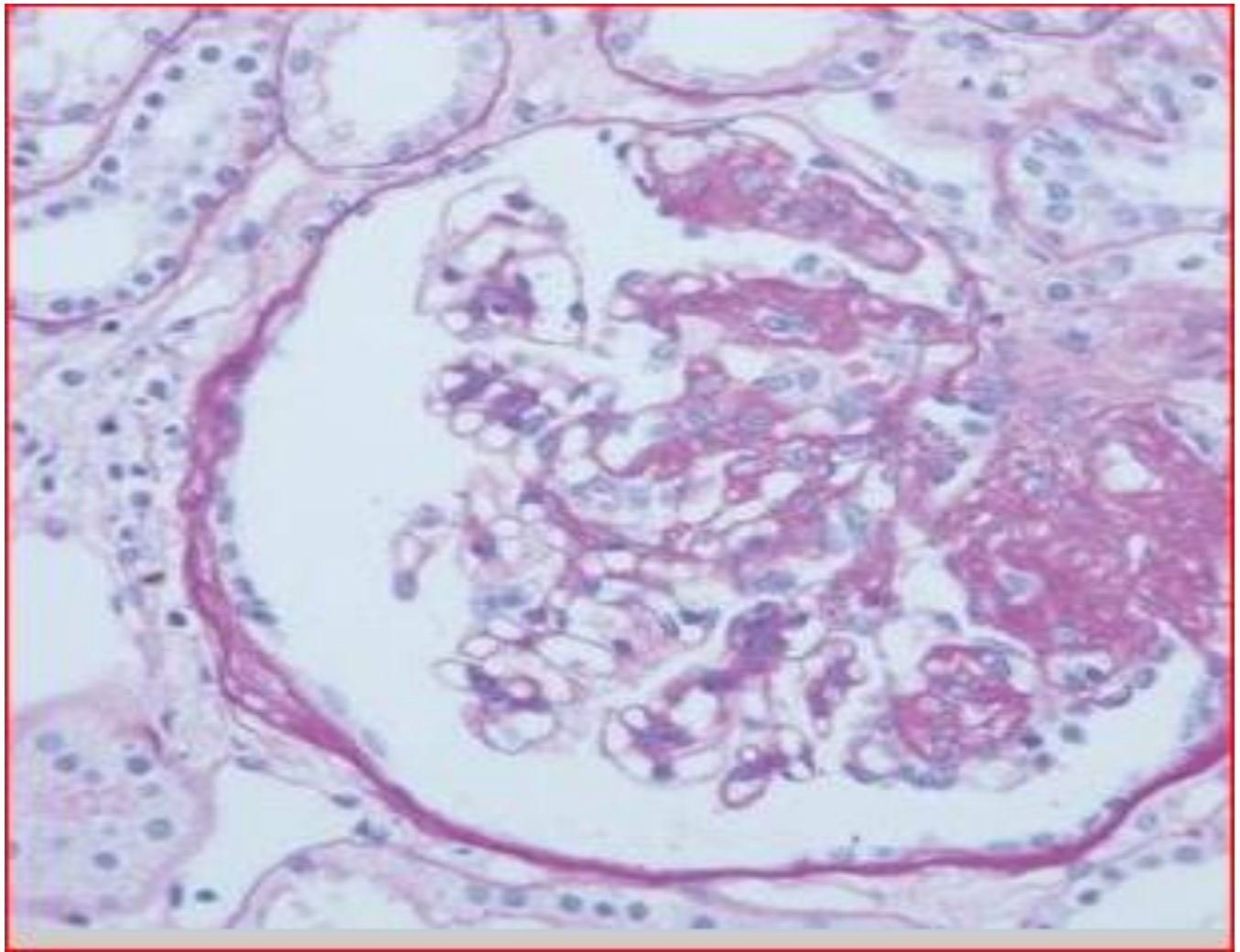
# Capillary collapse and podocyte hyperplasia are characteristic features of the collapsing variant.



# In the tip variant, segmental lesion involves the glomerular tuft next to the tubular pole.



The perihilar variant is diagnosed when sclerosis or hyalinosis are present in perihilar lesion in more than half of the sclerotic glomeruli.



# Columbia Classification

Practical Application of Columbia Classification for Focal Segmental Glomerulosclerosis

# FSGS (NOS)

**Inclusion criteria**

At least 1 glomerulus with segmental increase in matrix obliterating the capillary lumina. There may be segmental glomerulus capillary wall collapse without overlying podocyte hyperplasia.

**Exclusion criteria**

Exclude perihilar, cellular, tip, and collapsing variants.

# Perihilar variant

Inclusion criteria

At least 1 glomerulus with perihilar hyalinosis, with or without sclerosis. >50% of glomeruli with segmental lesions must have perihilar sclerosis and/or hyalinosis.

Exclude cellular, tip, and collapsing variants.

# Cellular variant

- Inclusion criteria
- At least 1 glomerulus with segmental endocapillary hypercellularity occluding lumina, with or without foam cells and karyorrhexis.
- **Exclusion criteria**
- Exclude tip and collapsing variants.

# Tip variant

**Inclusion criteria**

At least 1 segmental lesion involving the tip domain
(outer 25% of tuft next to origin of proximal tubule).
The tubular pole must be identified in the defining lesion.
The lesion must have either an adhesion or confluence of podocytes with parietal or tubular cells at the tubular lumen or neck. The tip lesion may be cellular or sclerosing.

**Exclusion criteria**

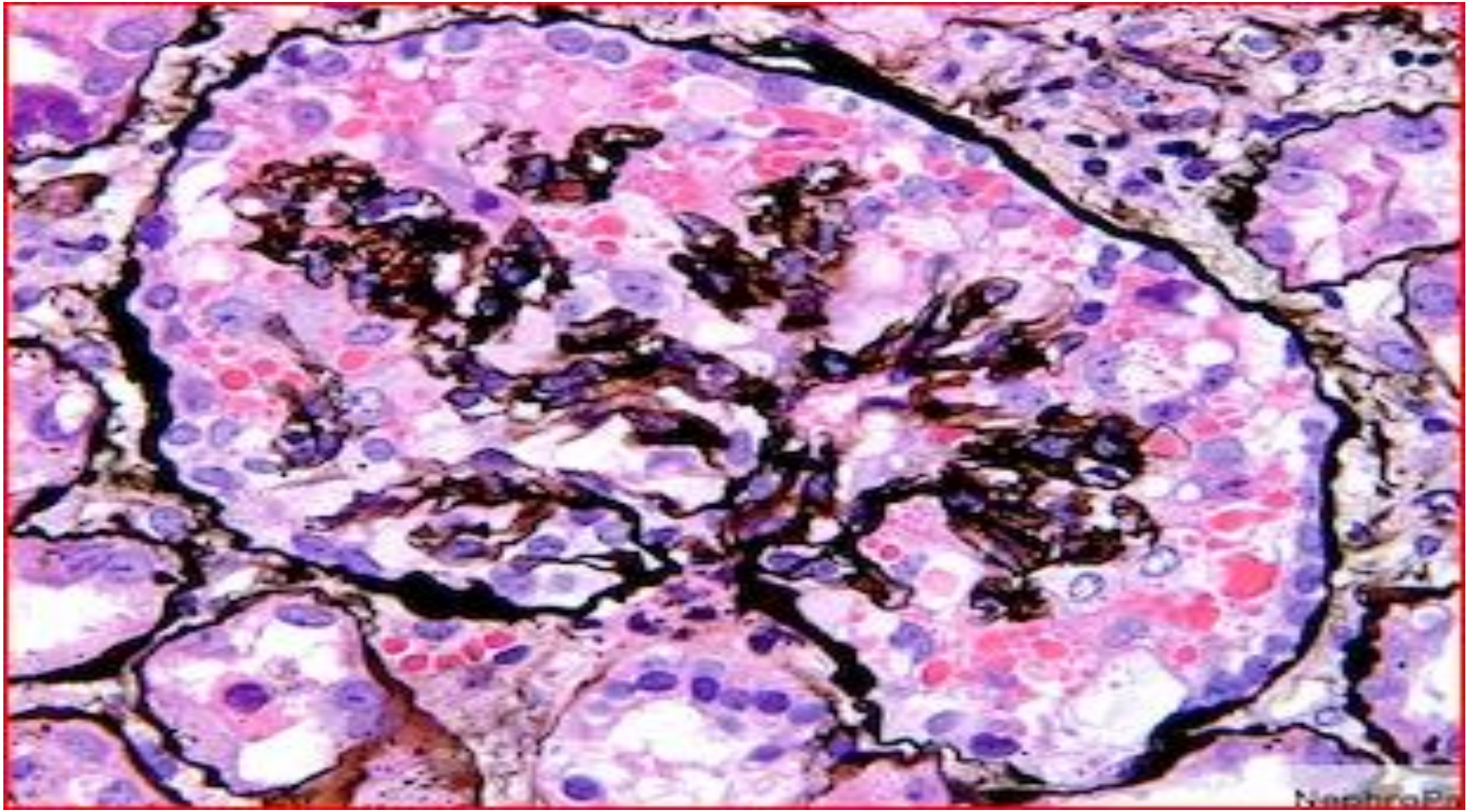
Exclude collapsing variant.
Exclude any perihilar sclerosis.

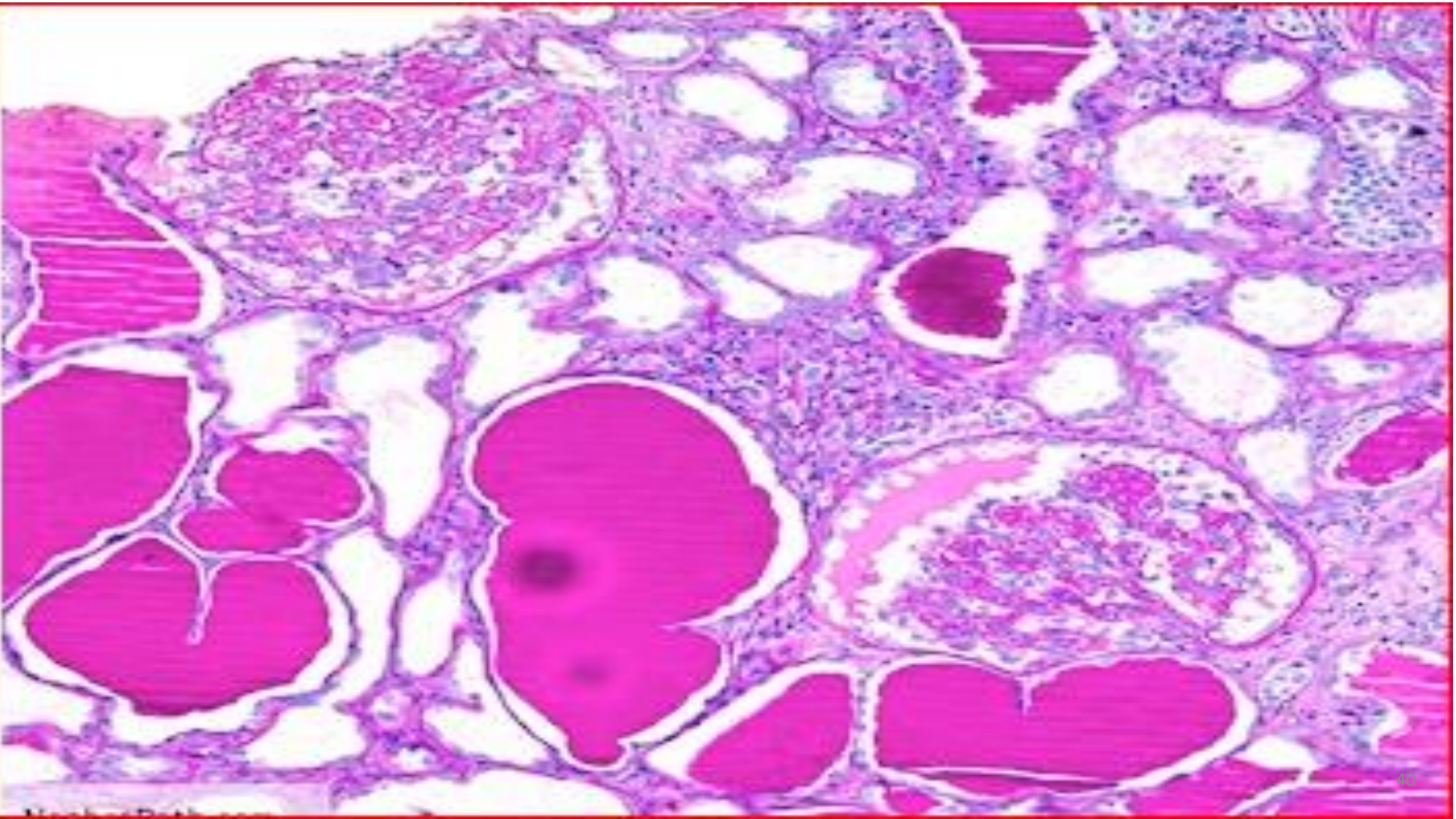
# Collapsing variant

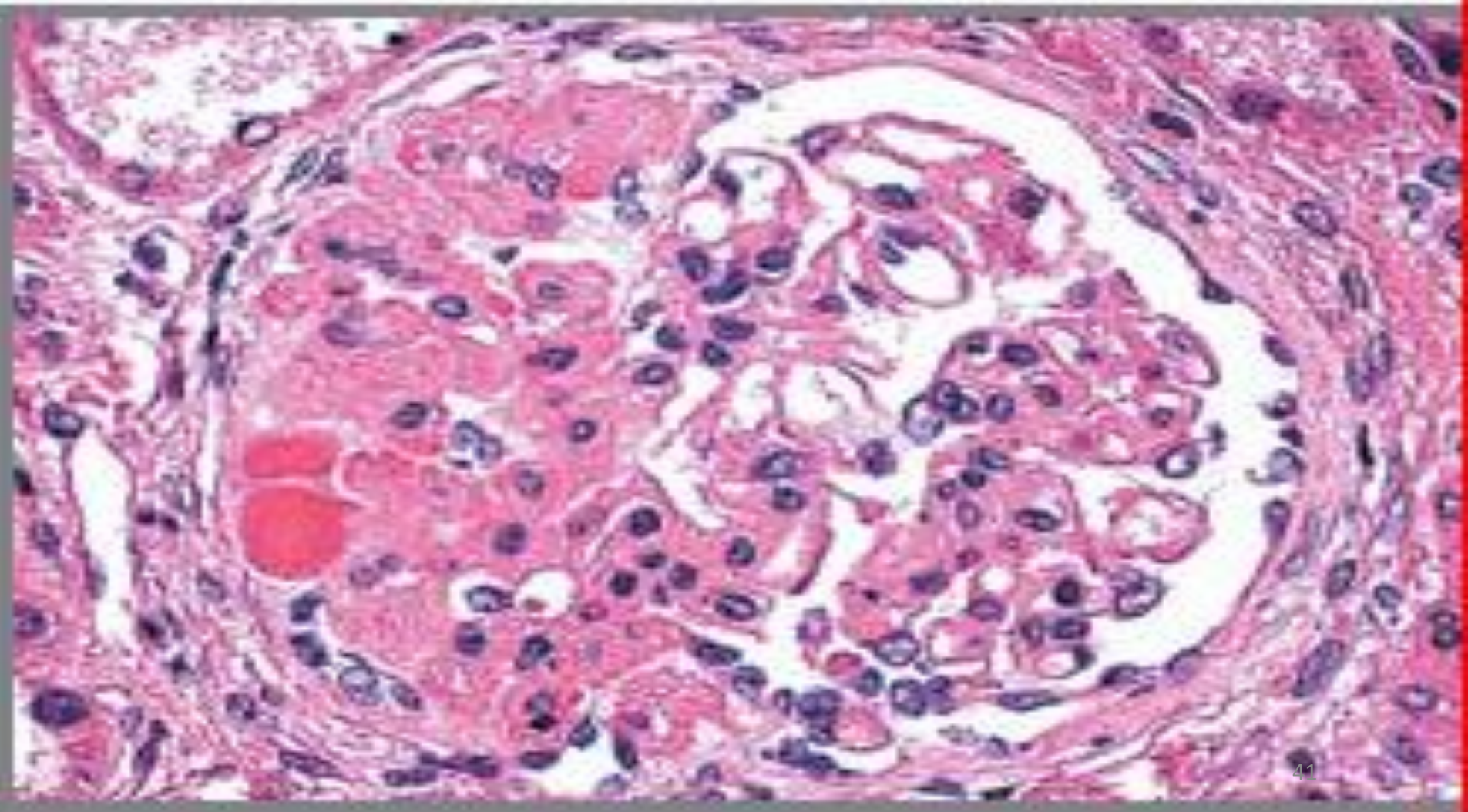
At least 1 glomerulus with segmental or global collapse and overlying podocyte hypertrophy and hyperplasia.

**Exclusion criteria**

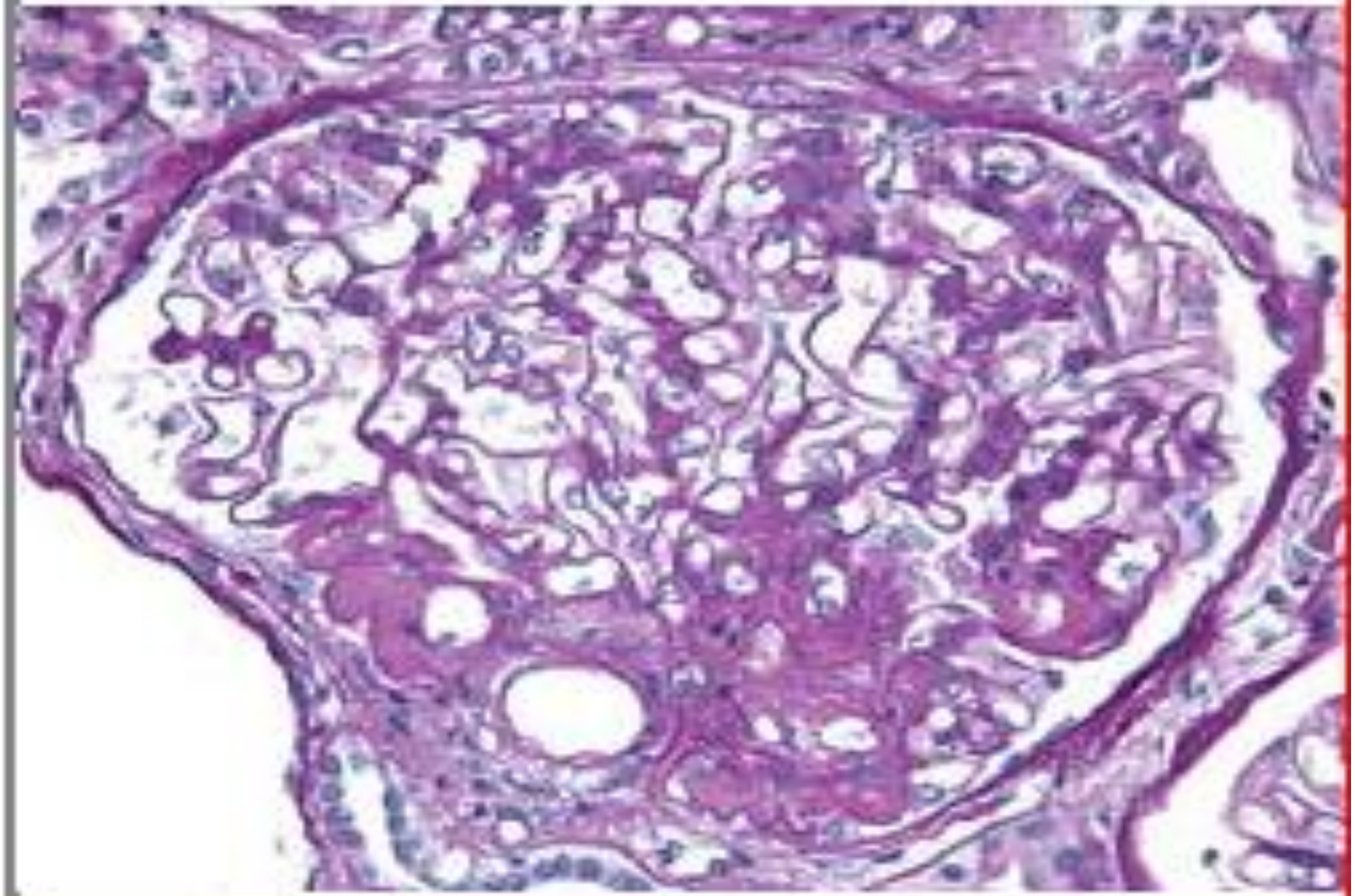
None.





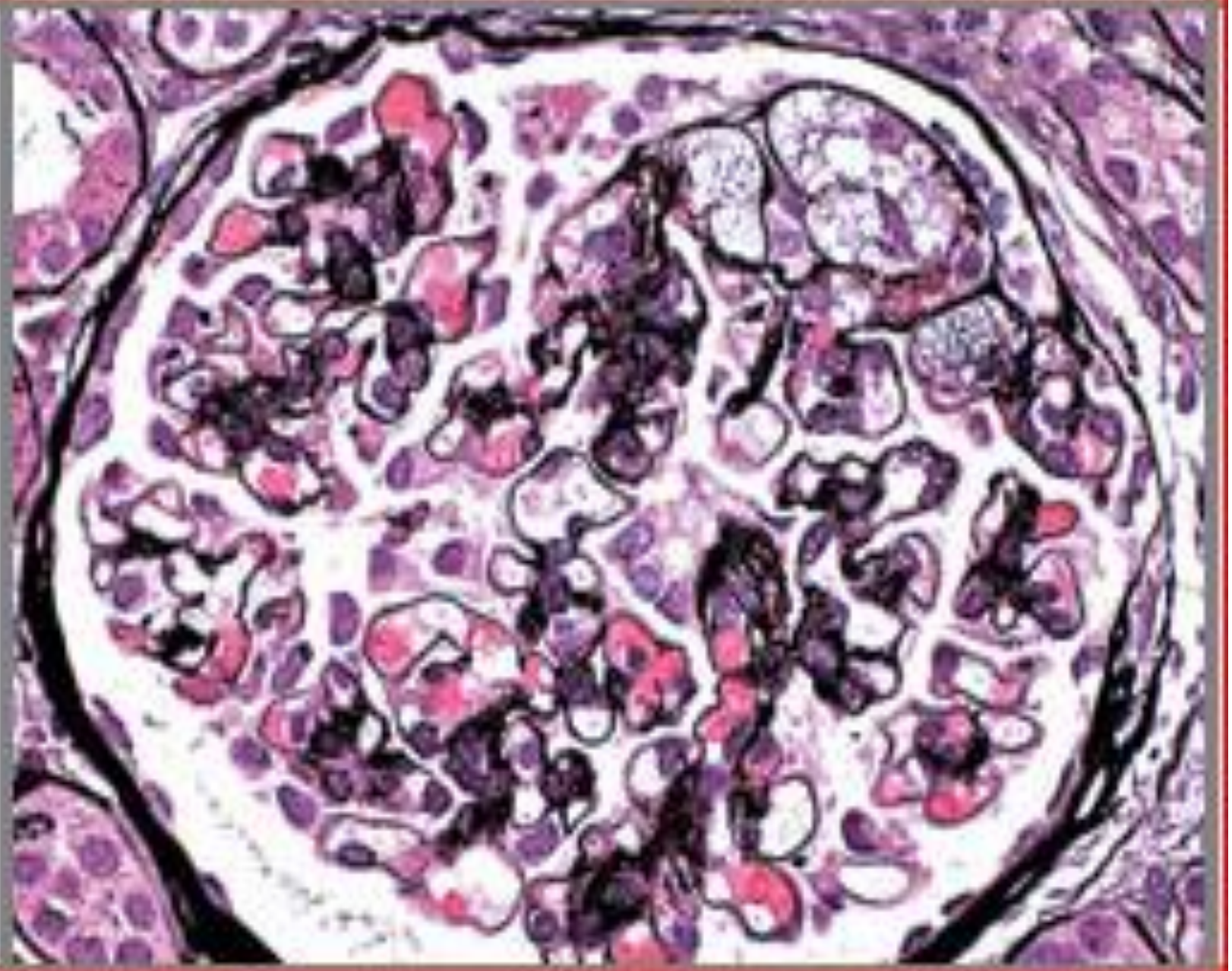
| Histologic Subtype | Glomerular Lesion |
| --- | --- |
| NOS |  |

# Perihilar



- Perihilar hyalinosis and sclerosis involving the majority of glomeruli with segmental lesions.
- Perihilar lesions are located at the glomerular vascular pole.
- In adaptive FSGS, there is usuallly glomerular hypertrophy (glomerulomegaly).
- Foot-process effacement is relatively mild and focal, which probably reflects the heterogeneous adaptive responses of glomeruli.

# Cellular



Expansile segmental lesion with endocapillary hypercellularity, often including foam cells and infiltrating leukocytes, with variable glomerular epithelial-cell hyperplasia.

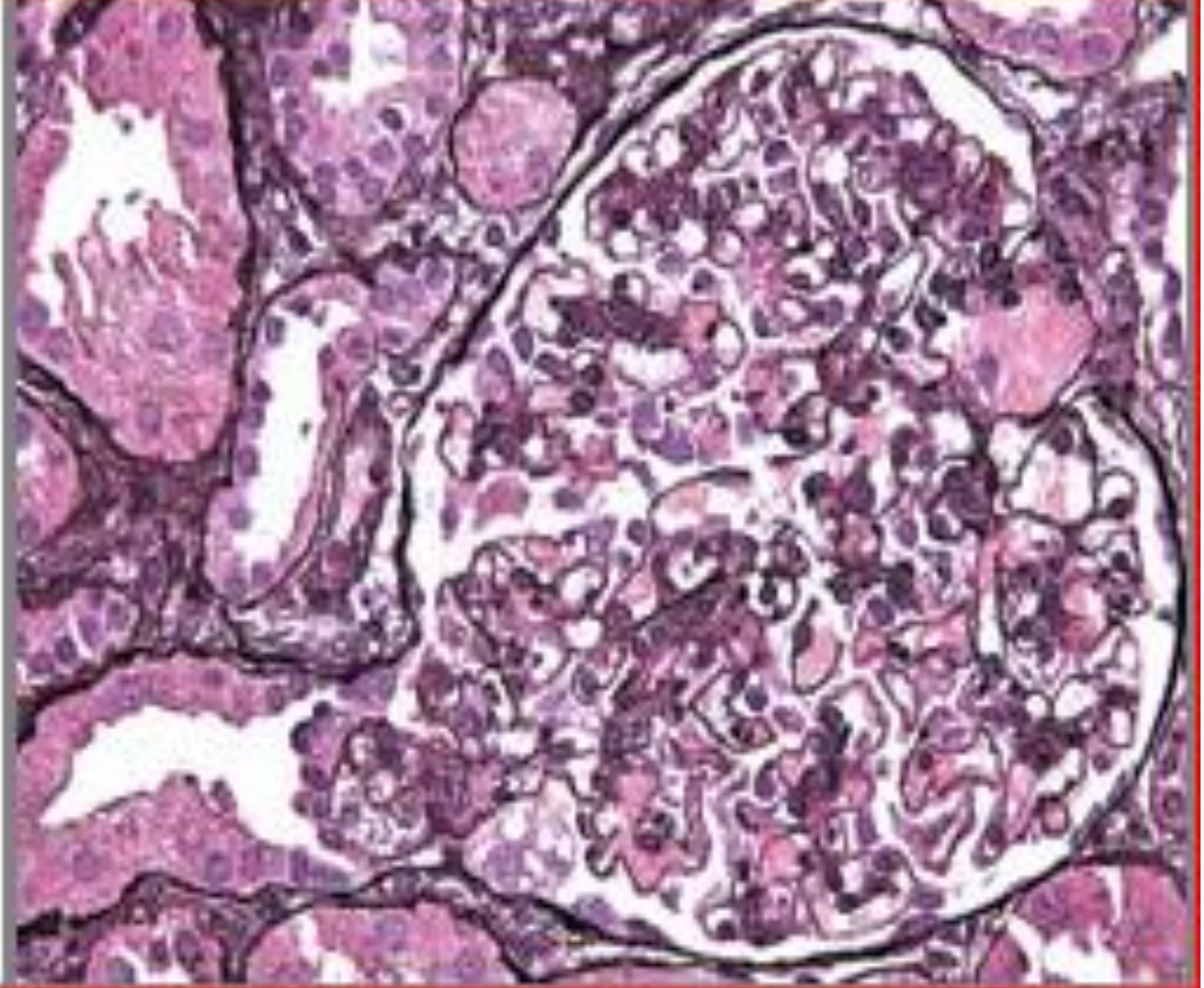
There is usually severe foot-process effacement.

Usually primary, but also seen in a variety of secondary forms.

This is the least common variant.

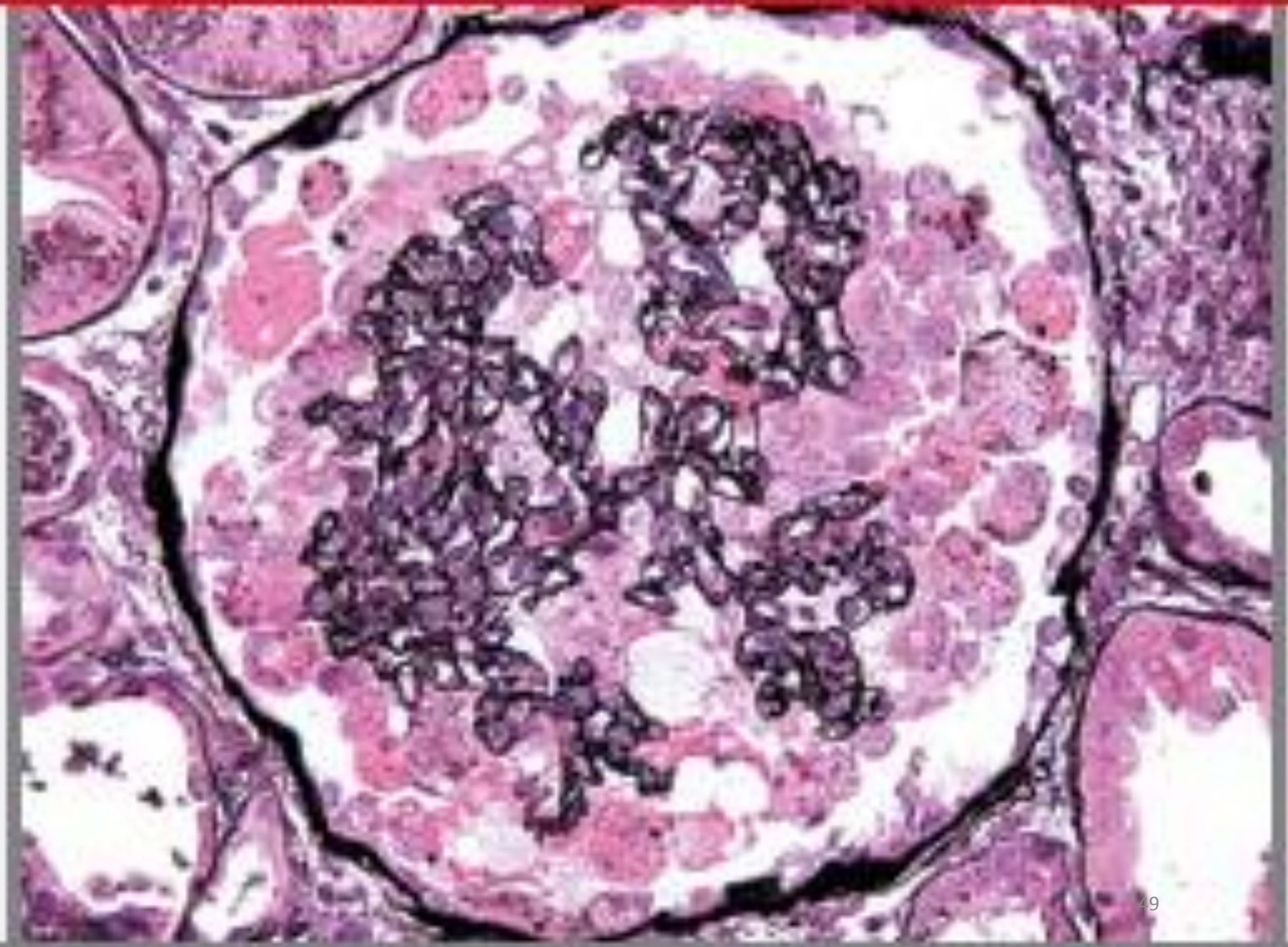
It is thought to represent an early stage in the evolution of sclerotic lesions.

Tip



- Segmental lesion involving the tubular pole, with either adhesion to tubular outlet or confluence of podocytes and tubular epithelial cells.
- Compared with other variants, it has the least tubular atrophy and interstitial fibrosis.
- There is usually severe foot-process effacement.

# Collapse



Implosive glomerular-tuft collapse with hypertrophy and hyperplasia of the overlying visceral epithelial cells.

Hyperplastic glomerular epithelial cells may fill the urinary space, resembling crescents.

Severe tubular injury and tubular microcysts are common.

There is usually severe foot-process effacement.

Primary or secondary to

- Viruses: HIV-1, parvovirus B19, SV40, EBV, CMV, hemophagocytic syndrome
- Drugs: pamidronate and interferon
- Vaso-occlusive disease: atheroemboli, calcineurin inhibitor nephrotoxicity, and chronic allograft nephropathy

Most aggressive variant of primary FSGS with black racial predominance and severe nephrotic syndrome.

Worst progmosis, with poor responsivity to glucocorticoids and rapid course to renal failure.

described: FSGS, not otherwise specified (NOS) or the classic type; cellular variant; collapsing variant; perihilar variant; and tip variant.[5-7] In brief, tip variant of FSGS necessitates the exclusion of collapsing variant and presence of at least one glomerulus with segmental lesion involving the tip domain of the glomerular capillary tuft. In the perihilar variant, the segmental sclerotic lesion is situated at the vascular pole and requires the exclusion of collapsing, tip, or cellular lesion. The cellular variant needs exclusion of collapsing and tip lesions, and is defined by segmental endocapillary hypercellularity occluding lumina in at least 1 glomerulus.[5-8] Collapsing variant was defined by collapse of at least 1 capillary loop with hyperplasia and hypertrophy of overlying visceral epithelial cells, irrespective of the presence of other variants of FSGS. In cases where none of these definitions