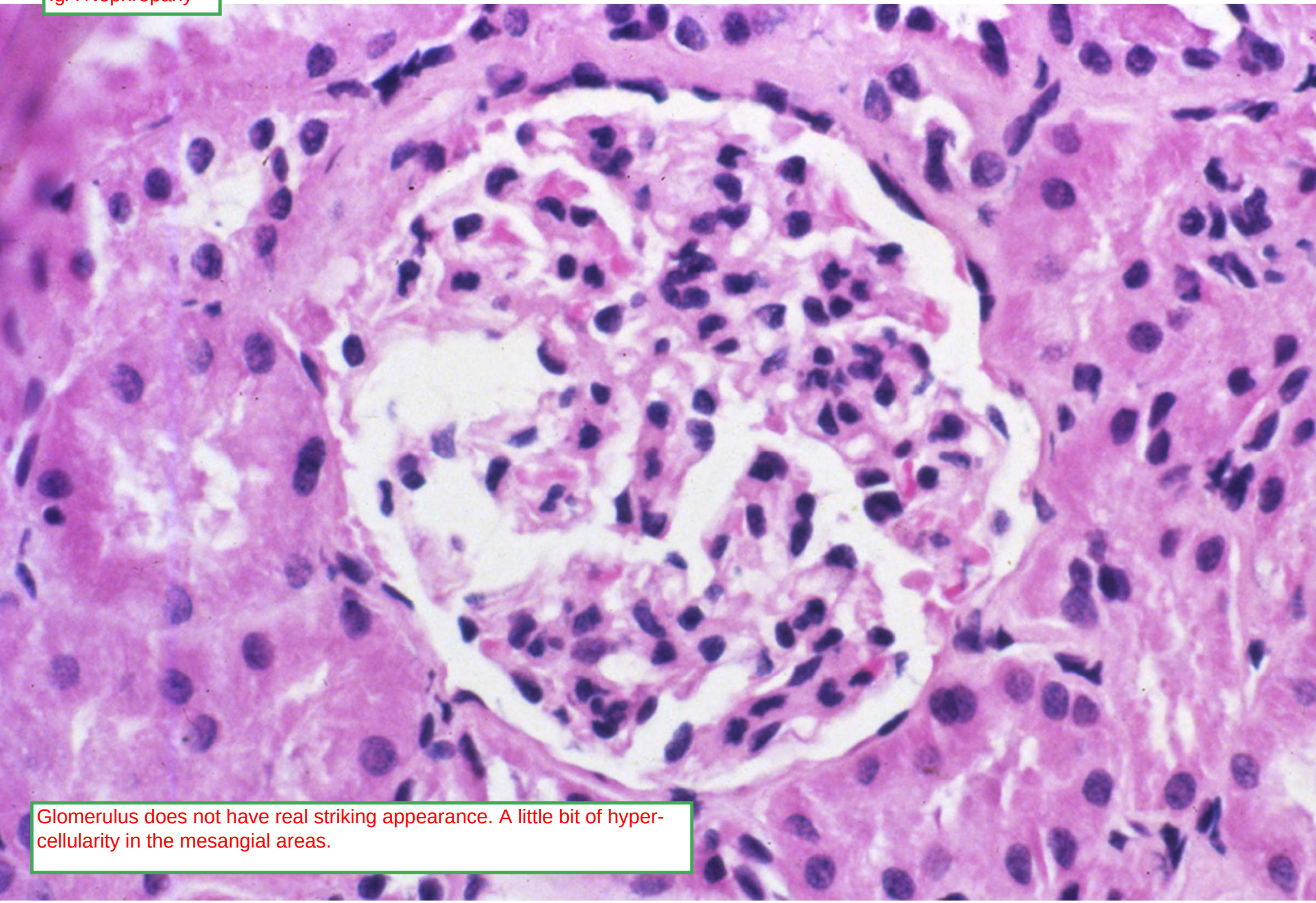
APPROVED

IgA nephropathy

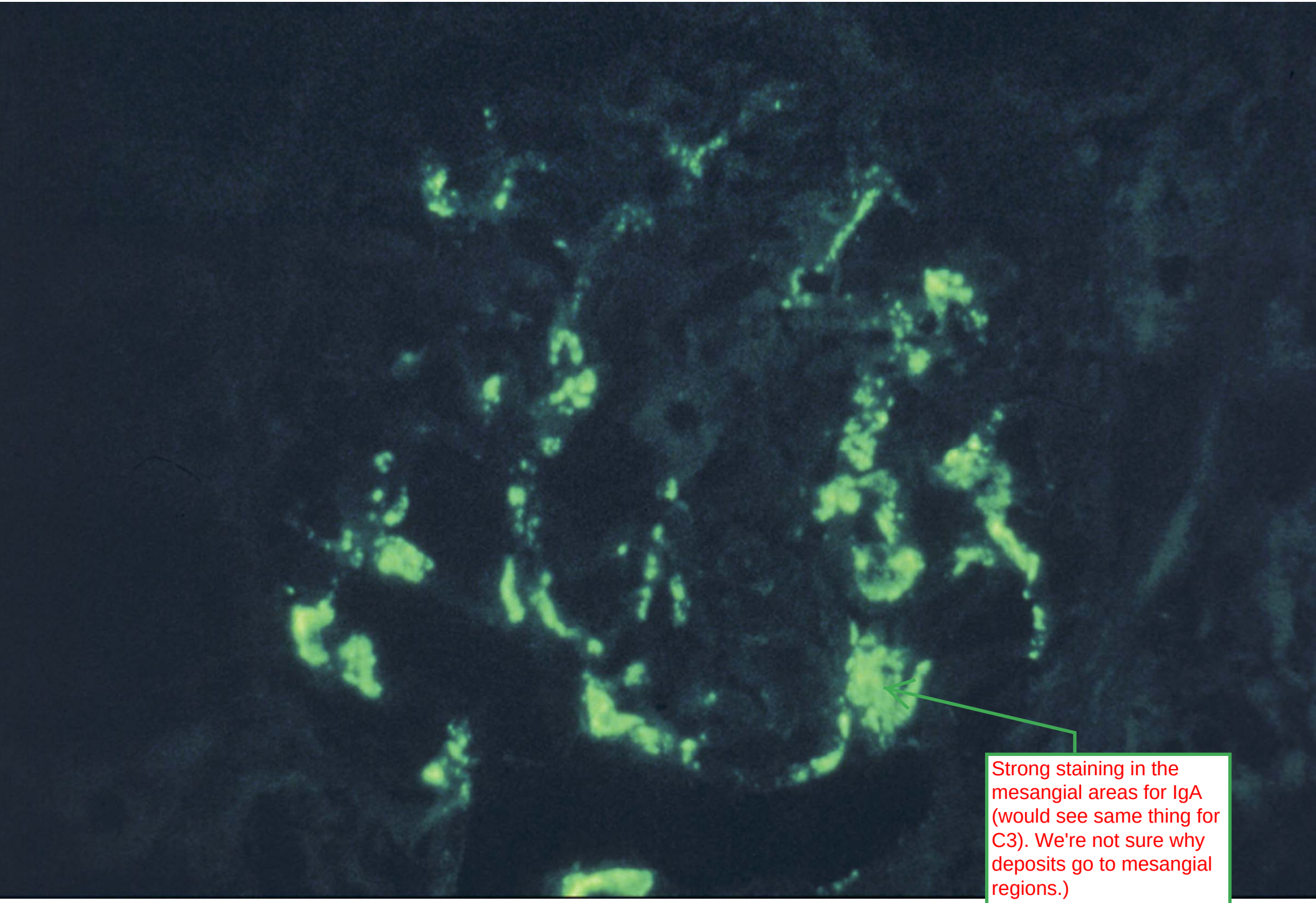
- **Pathogenesis**
  - **Antigens: unknown, possibly infection-associated ? complex of bacterial IgA-binding protein with IgA**
  - **Immune reactants: IgA, C3**
  - **Complex location: mesangial**
- **Histologic: Mesangial expansion/cellular proliferation**
- **Clinical: Recurrent hematuria, often immediately following URI; may progress to chronic renal failure; most common in young white males; systemic variant (Henoch-Schönlein purpura) with skin and GI vasculitis plus renal manifestations**

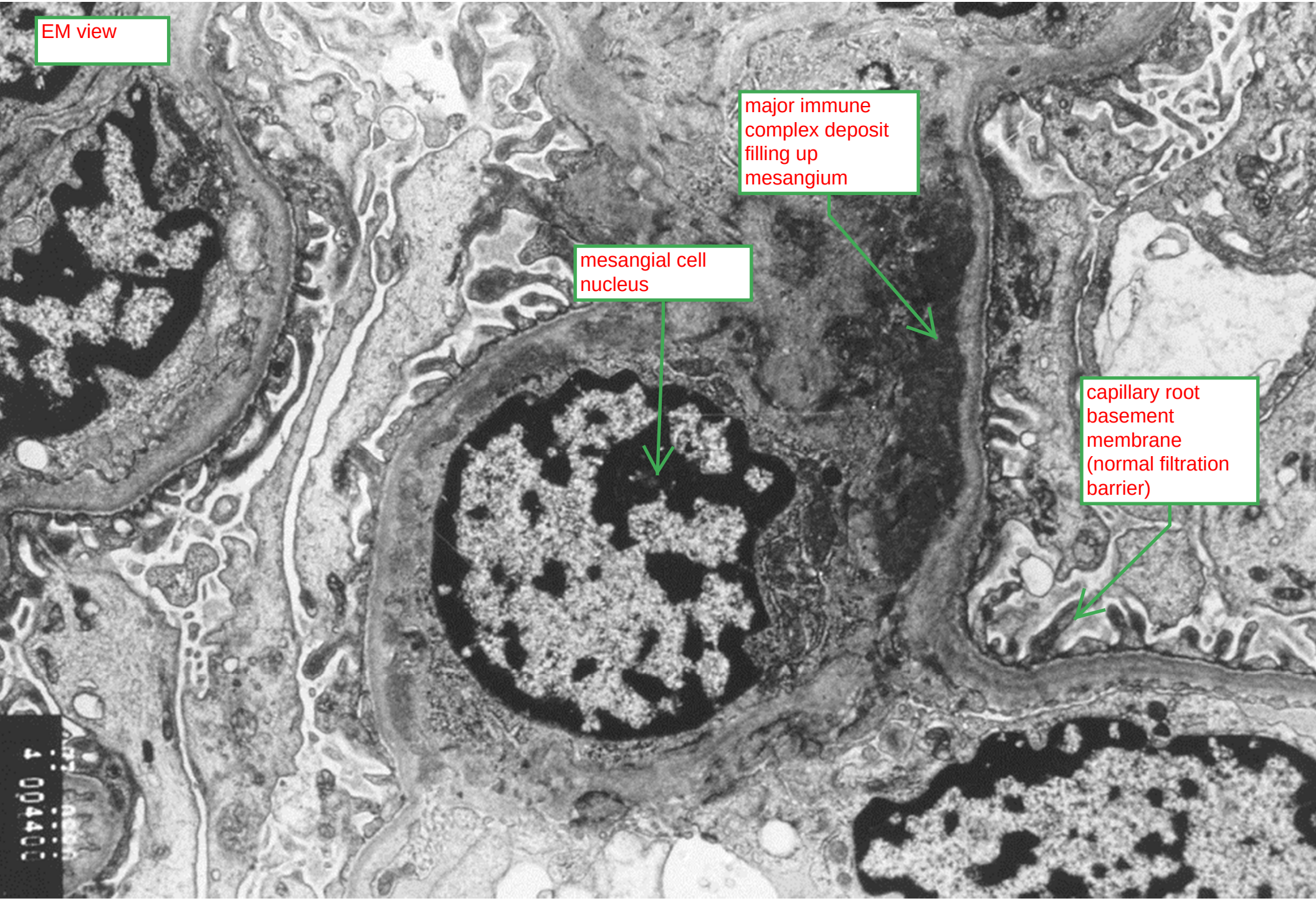
IgA nephropathy is another immune complex disease where the deposits are primarily mesangial deposits. IgA serves as a ligand for this bacterial protein. Patients frequently get disease after upper respiratory infection which leads to theory that it is infection induced.

IgA Nephropahy



Glomerulus does not have real striking appearance. A little bit of hyper-cellularity in the mesangial areas.

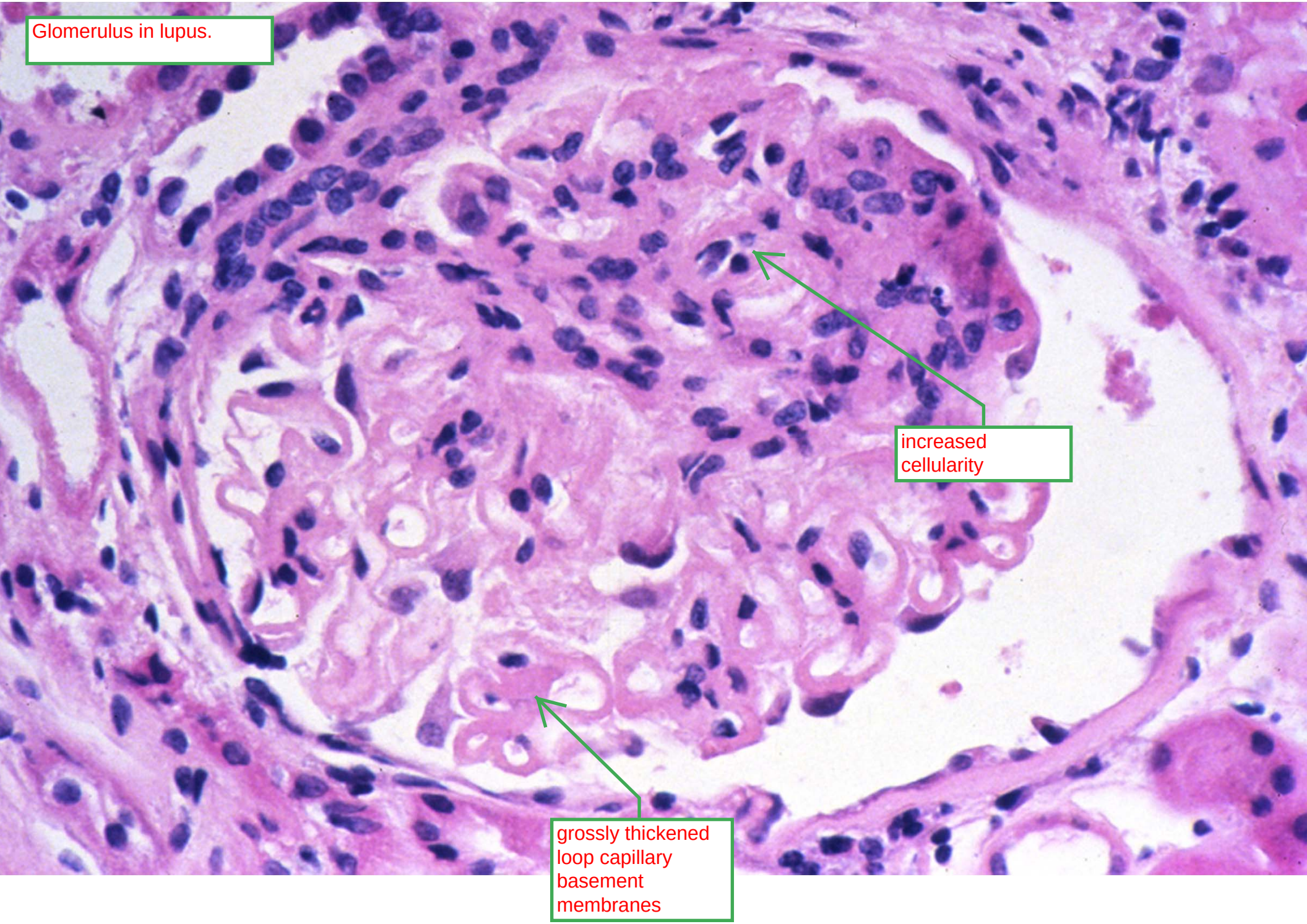

Strong staining in the mesangial areas for IgA (would see same thing for C3). We're not sure why deposits go to mesangial regions.)

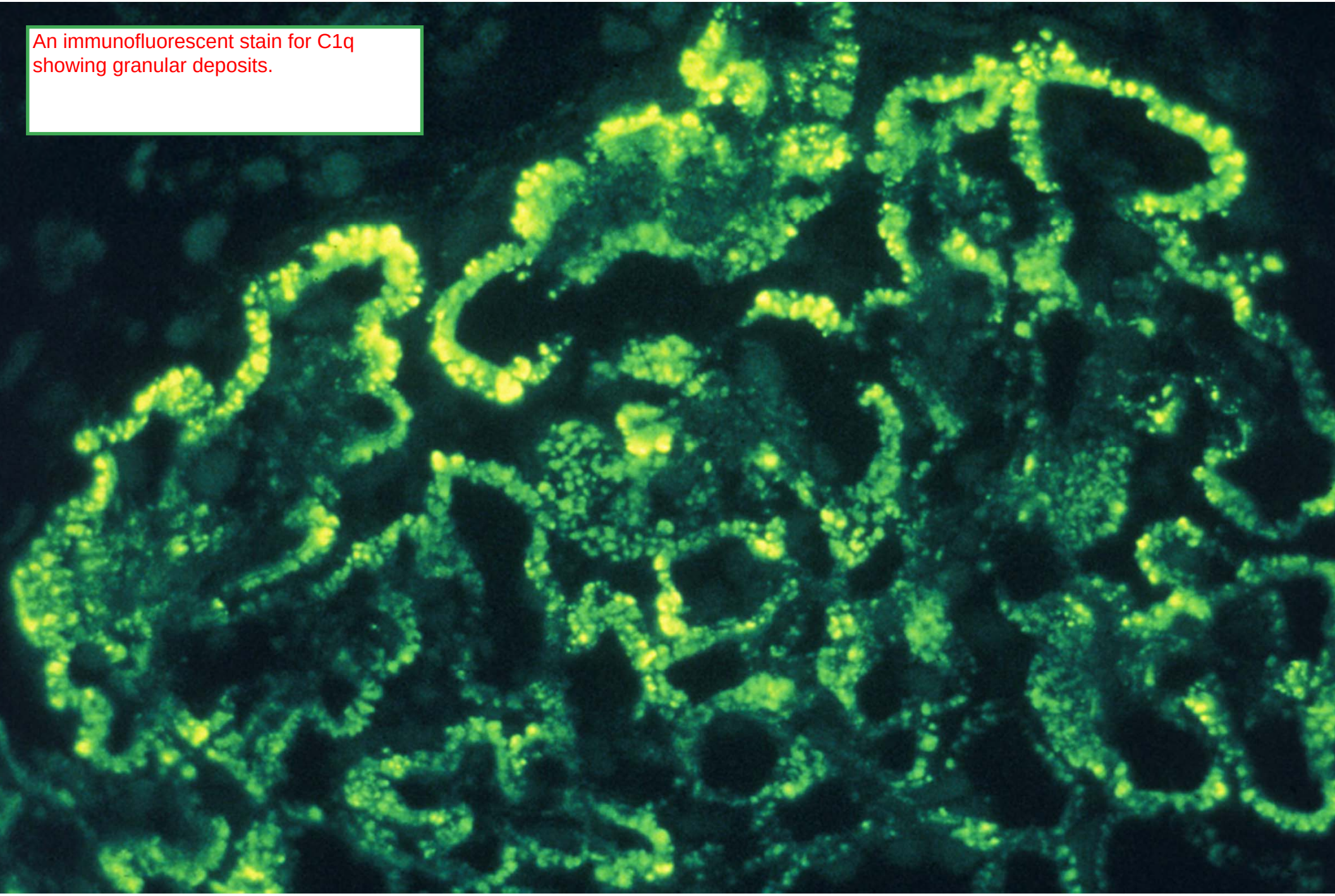

EM view
major immune complex deposit filling up mesangium
mesangial cell nucleus
capillary root basement membrane (normal filtration barrier)

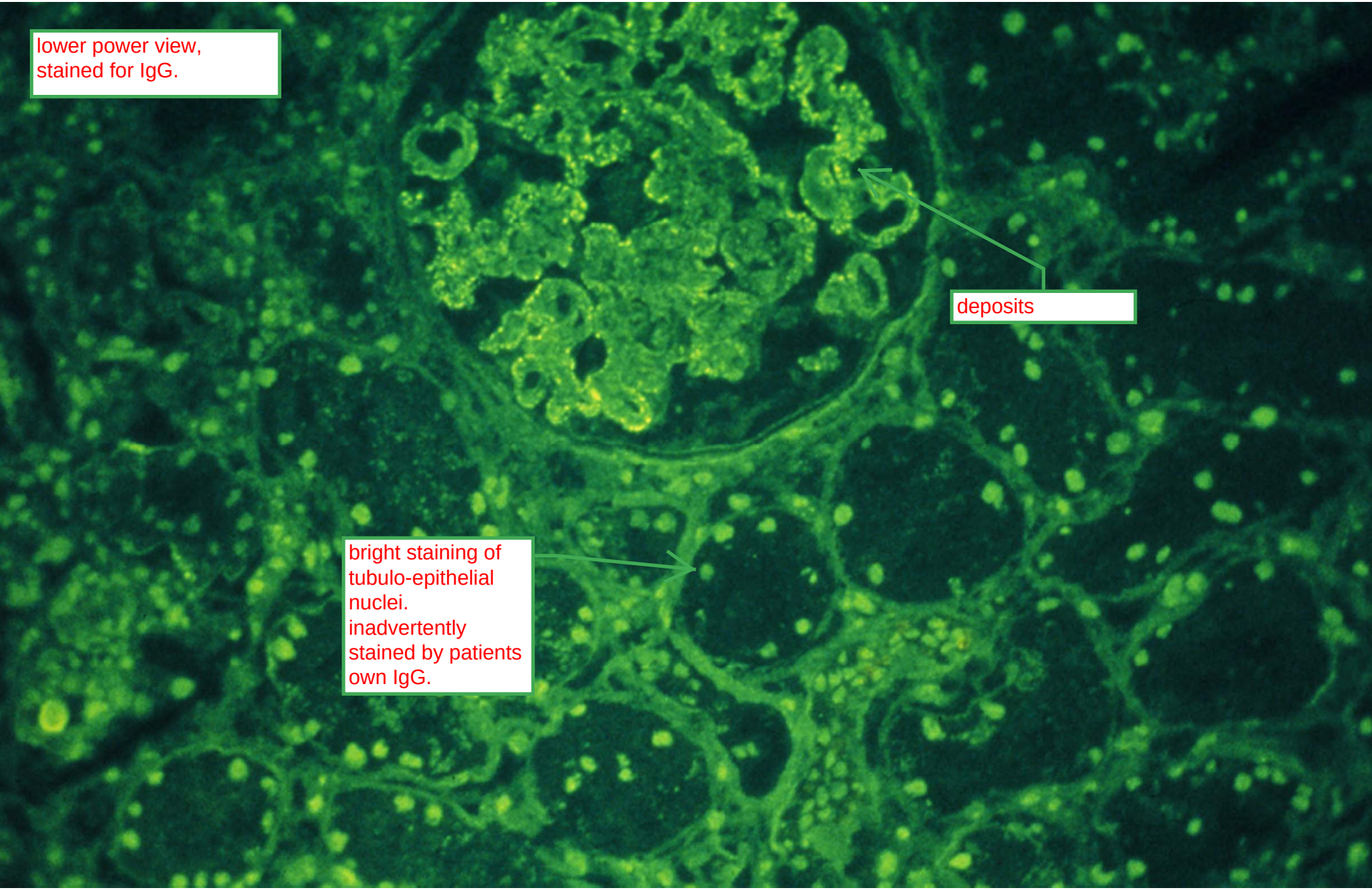
Systemic lupus erythematosus

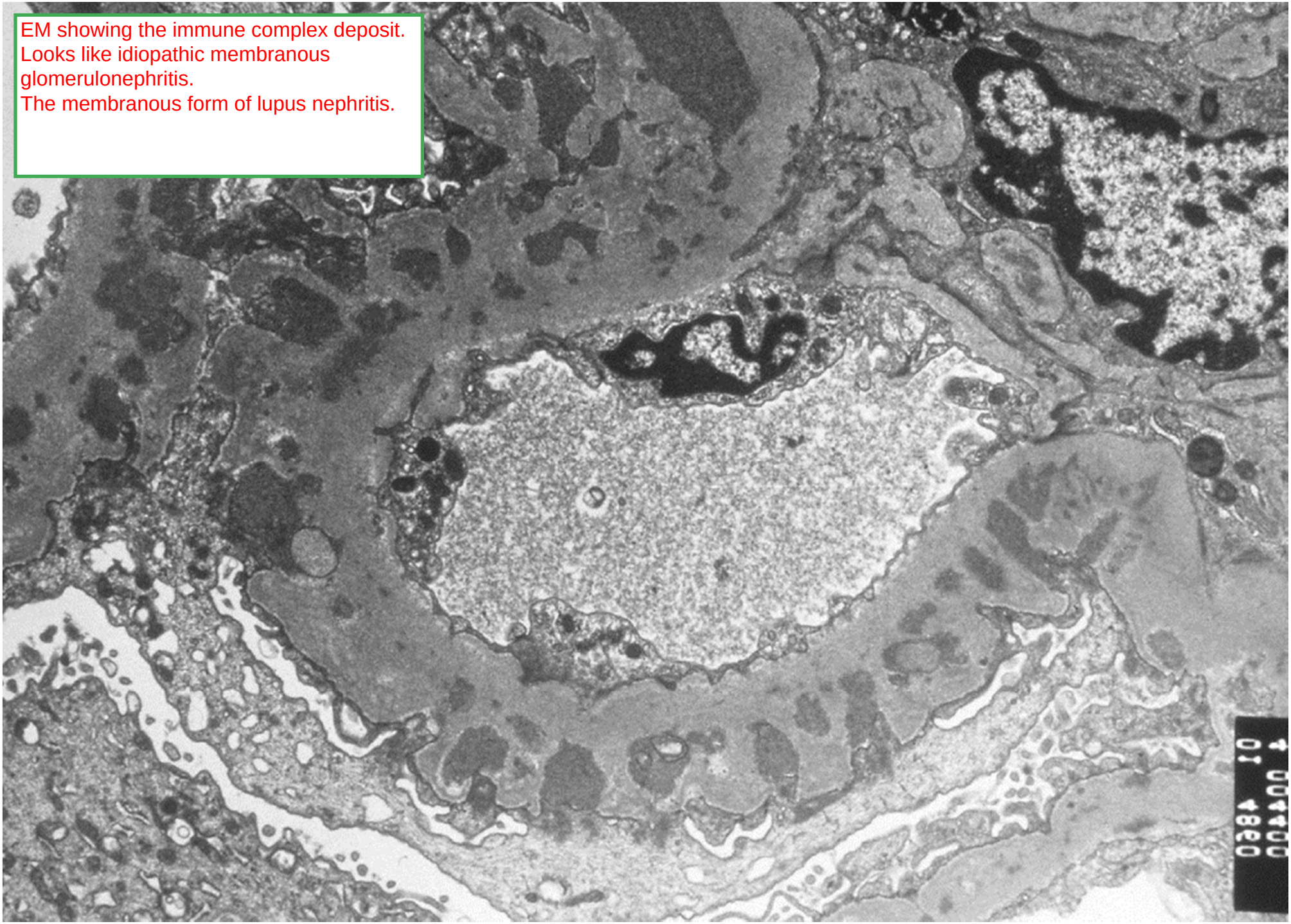
- **Pathogenesis**
  - **Antigens: DNA, RNA, nucleoproteins**
  - **Immune reactants: IgG, IgM, IgA, various complement components**
  - **Complex location: mesangial, subendothelial, and/or subepithelial**
- **Histologic: Highly variable, including many histologic patterns described previously; tubuloreticular inclusions on EM**
- **Clinical: Similarly variable, including any of the symptom complexes described previously; most common in young black women**

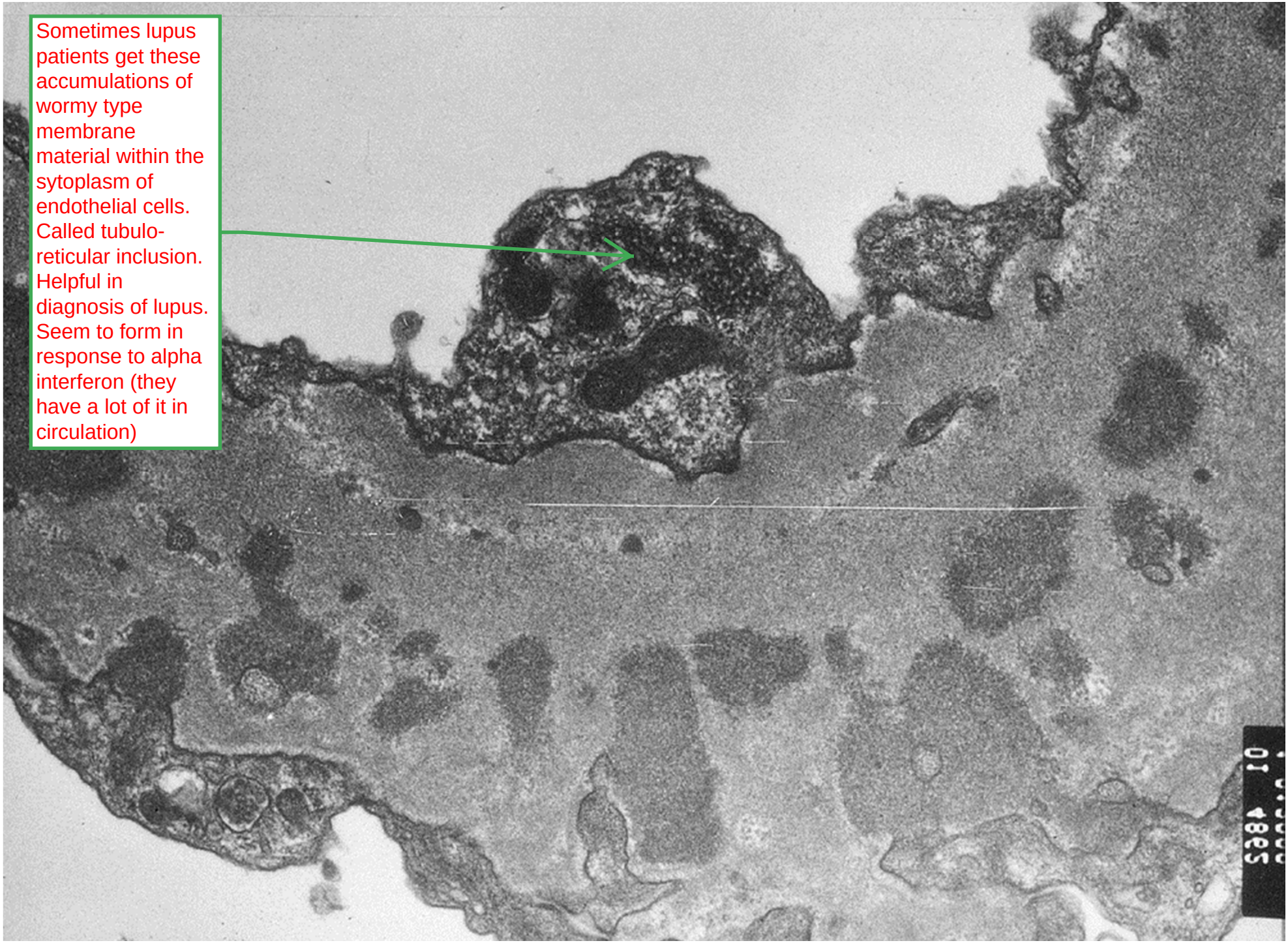
Seen frequently on the renal biopsy service. Immune complexes in this disorder tend to have a whole of different things in them: different immunoglobulins, complement, etc. Deposits can be anywhere. There is a mesangial form that looks a lot like IgA nephropathy. There is a membranous form with subendoethelial deposits that look a lot like membrano-proliferative glomerulonephritis. Lupus can look like anything. Clinical presentation is highly variable.

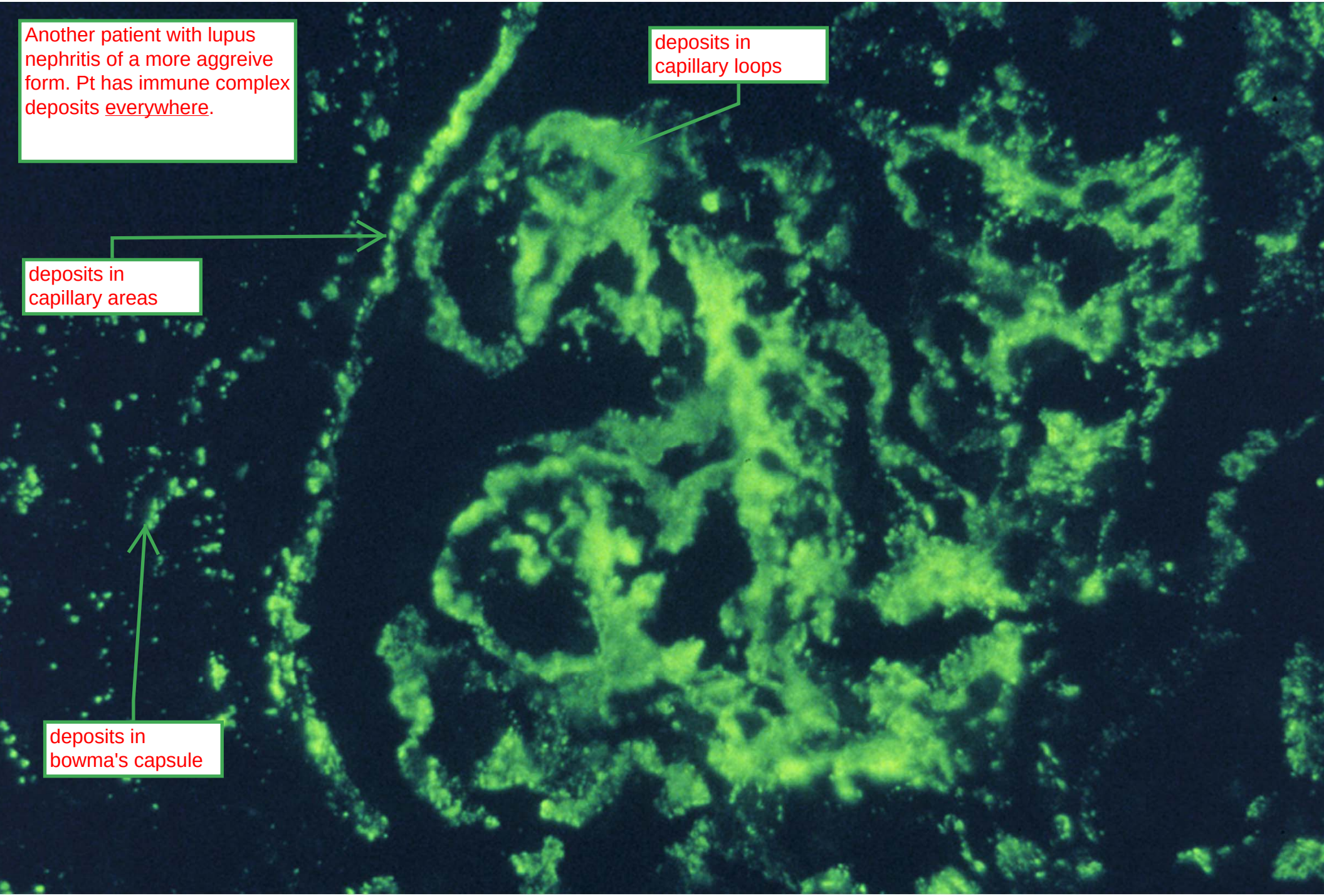

Glomerulus in lupus.
increased cellularity
grossly thickened loop capillary basement membranes


An immunofluorescent stain for C1q showing granular deposits.


lower power view,
stained for IgG.
deposits
bright staining of
tubulo-epithelial
nuclei.
inadvertently
stained by patients
own IgG.


EM showing the immune complex deposit.
Looks like idiopathic membranous glomerulonephritis.
The membranous form of lupus nephritis.


Sometimes lupus patients get these accumulations of wormy type membrane material within the sytoplasm of endothelial cells. Called tubulo-reticular inclusion. Helpful in diagnosis of lupus. Seem to form in response to alpha interferon (they have a lot of it in circulation)


Another patient with lupus nephritis of a more aggreive form. Pt has immune complex deposits everywhere.
deposits in capillary loops
deposits in capillary areas
deposits in bowma's capsule

part II

Glomerulonephritis

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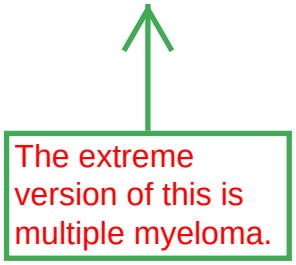
Copyright Statement

So we just talked about immune complexes in glomerulonephritis but we will now move on to other etiologies. First up: monoclonal protein deposition (MPD). They are produced by malignant or pre-malignant plasma cells.

Monoclonal Protein Deposition (Plasma Cell Dyscrasias)

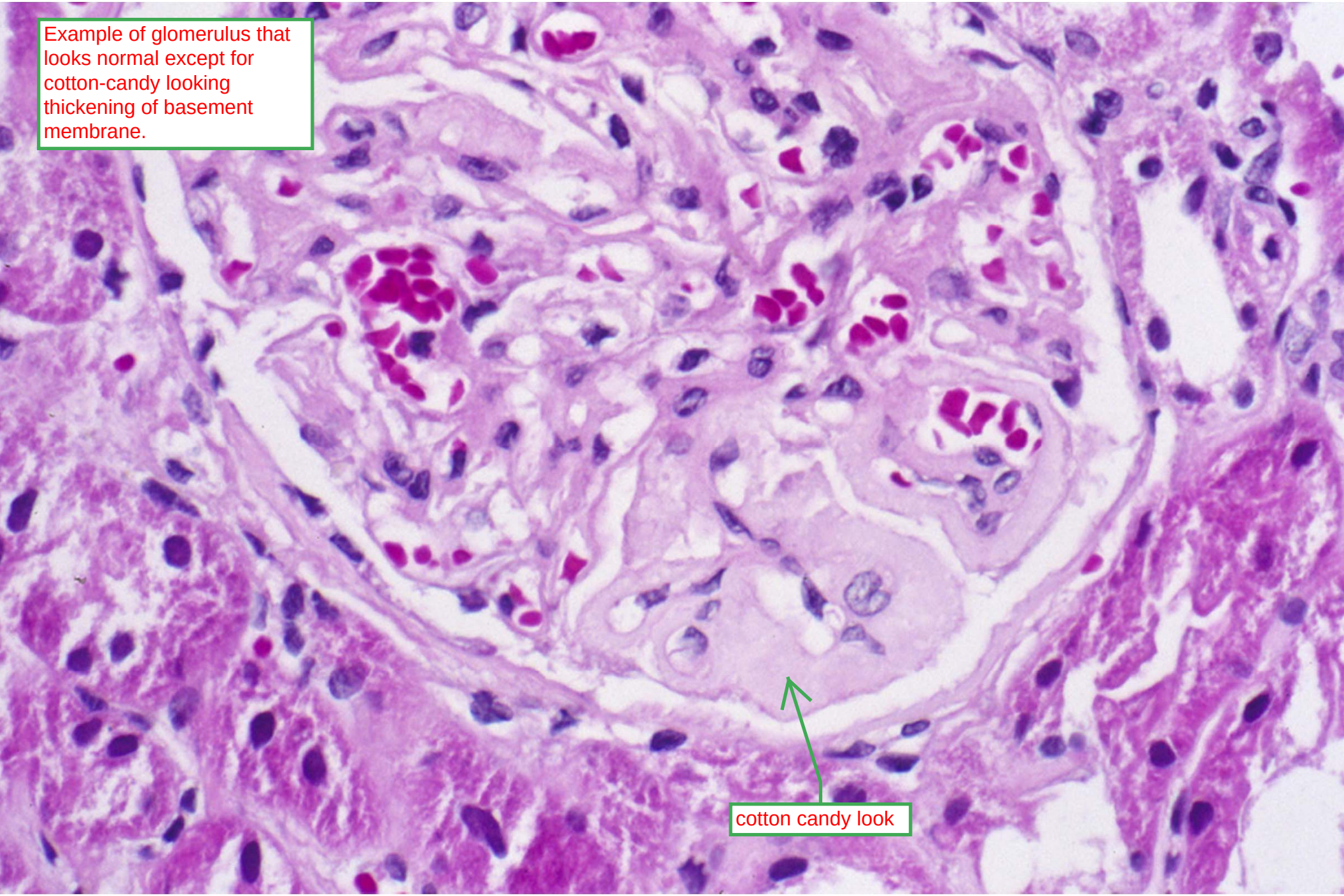


The extreme version of this is multiple myeloma.

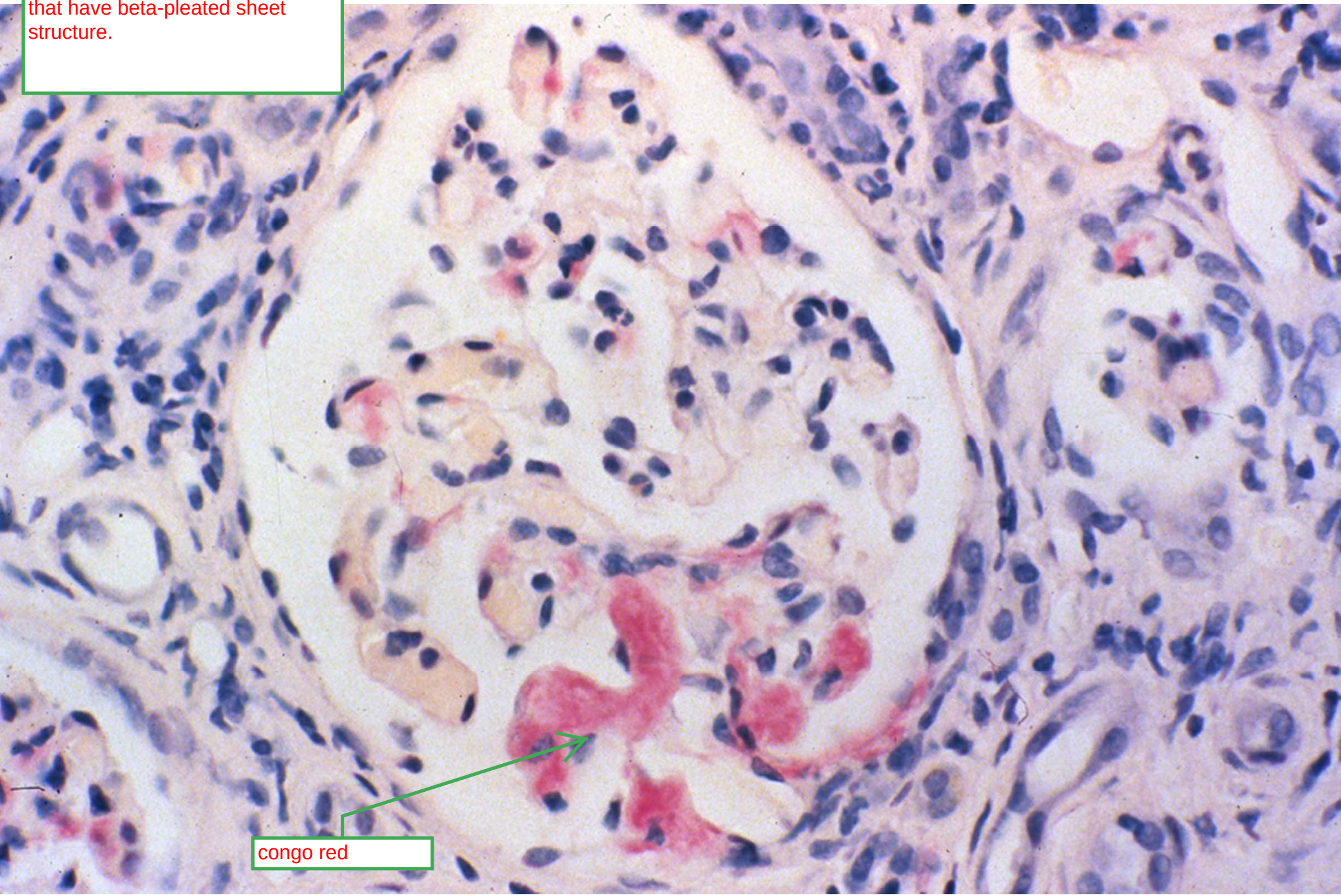
Primary (AL) Amyloidosis

- **Pathogenesis: Glomerular/vascular deposition of amyloid (abnormal protein with β-pleated sheet structure) containing monoclonal immunoglobulin light chains produced by clonal plasma cells (myeloma, MGUS)**
- **Histologic: Diffuse expansion of mesangium/capillary loop basement membranes by amyloid deposits**
- **Clinical: Proteinuria/nephrotic syndrome, often progressing to renal failure; most common in adults**

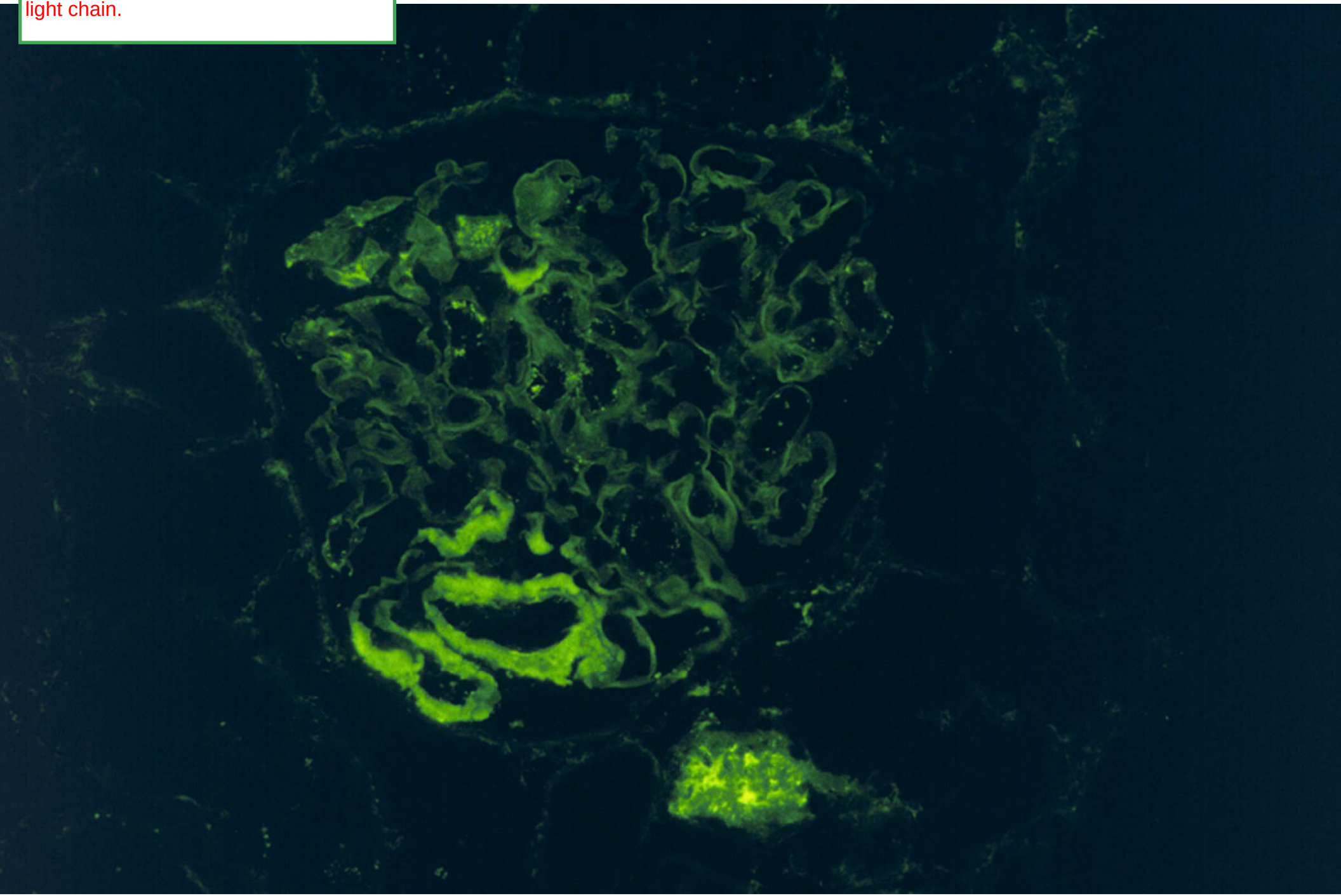
Most common MPD is primary amyloidosis. There is deposition in the kidneys and other places in the body but mainly located in glomerulus and blood vessels in kidneys. Amyloid is an abnormal protein that contains monoclonal light chains that fold into a beta pleated sheet structure. Somethign about this abnormal folding causes it to form little fibrillar structures that are seen in EM pictures.

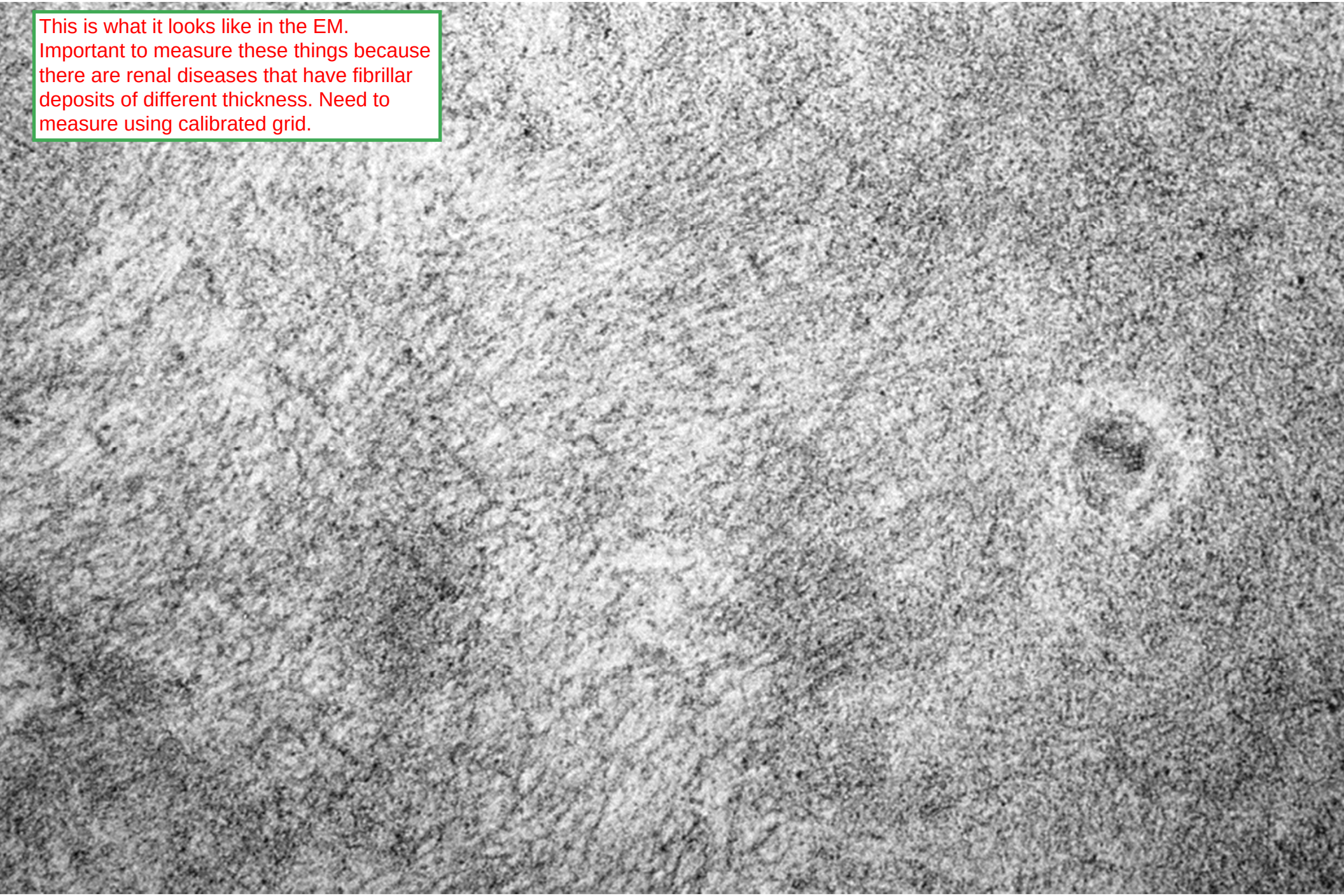

Example of glomerulus that looks normal except for cotton-candy looking thickening of basement membrane.
cotton candy look

Congo red stain --> binds protein that have beta-pleated sheet structure.



Immunfluorescent stain for Ig-Lambda light chain.

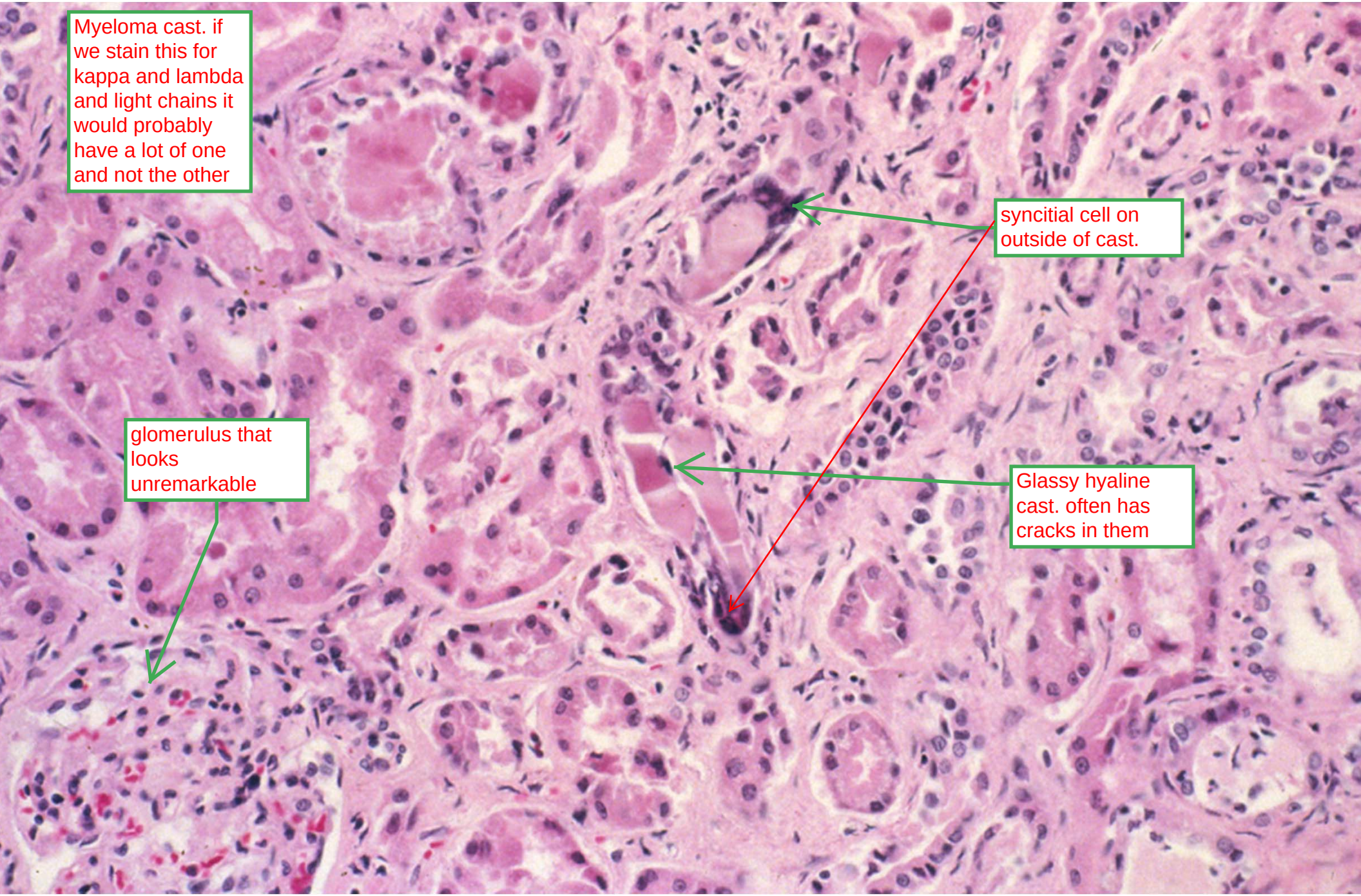



This is what it looks like in the EM.
Important to measure these things because there are renal diseases that have fibrillar deposits of different thickness. Need to measure using calibrated grid.

Myeloma Cast Nephropathy

- **Pathogenesis: Tubular plugging and epithelial injury caused by casts composed of monoclonal immunoglobulin light chain produced by myeloma cells (usually does not coexist with AL amyloidosis)**
- **Histologic: Hyaline casts in renal tubules with associated multinucleate syncytial cells**
- **Clinical: Renal failure in patient with multiple myeloma**

Some light chains produced by neoplastic cells have a tendency to form amyloid and get hung up glomerulus and cause problems there. There are other monoclonal proteins that don't tend to do that and get out into urinary space instead. Light chains are very small proteins and its fairly easy for them to slip through the glomerular filter. Can form casts and plug the distal tubules. Casts cause an inflammatory rxn and cause acute renal failure, which is difficult to treat. Histology shows cast that have a glassy hyaline appearance.


Myeloma cast. if we stain this for kappa and lambda and light chains it would probably have a lot of one and not the other
syncitial cell on outside of cast.
glomerulus that looks unremarkable
Glassy hyaline cast. often has cracks in them

Now moving on to outside of capillary loop and talking about some things that don't involve particular kinds of deposits. We will concentrate on visceral epithelial cells.

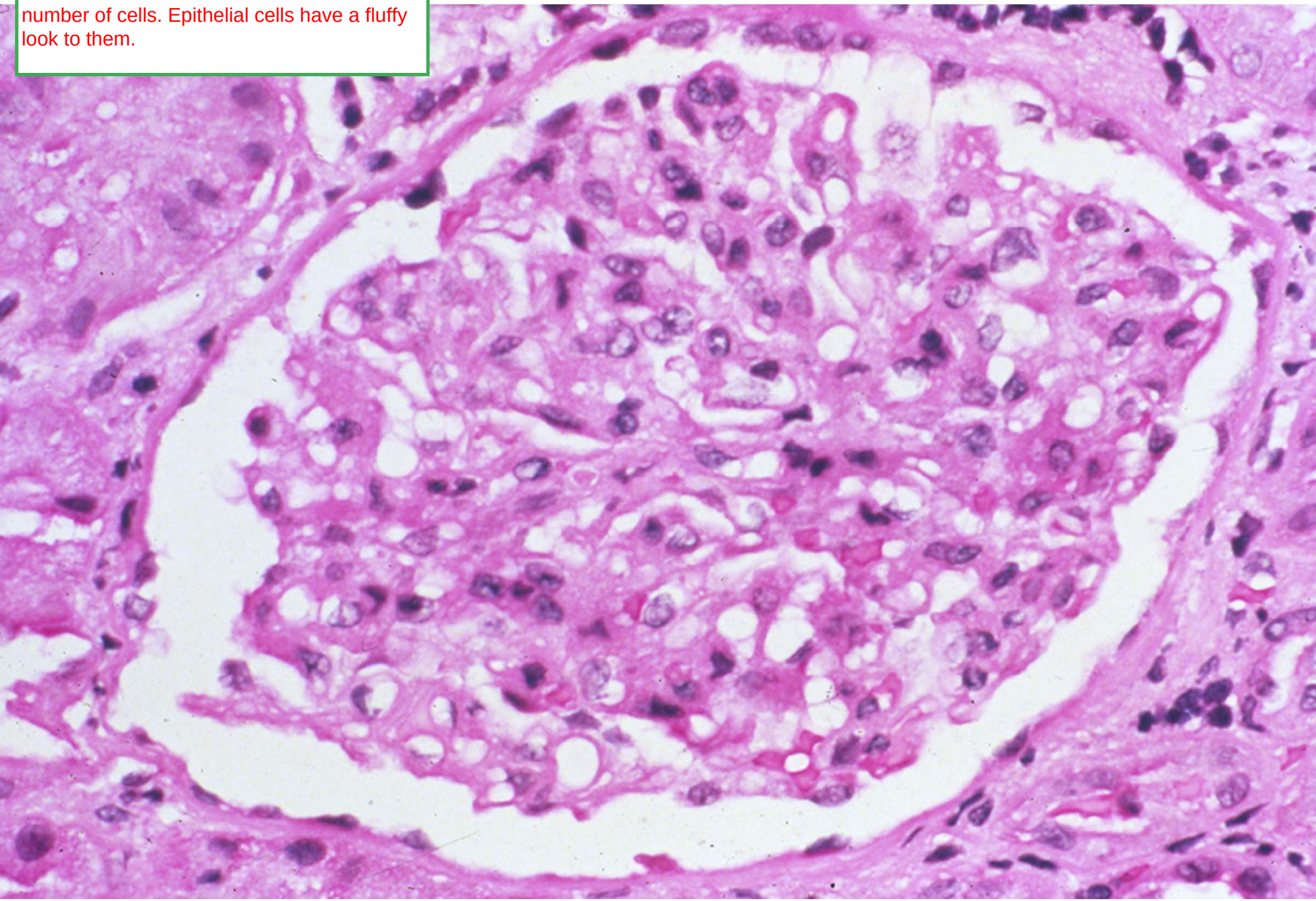
Epithelial Cell Damage

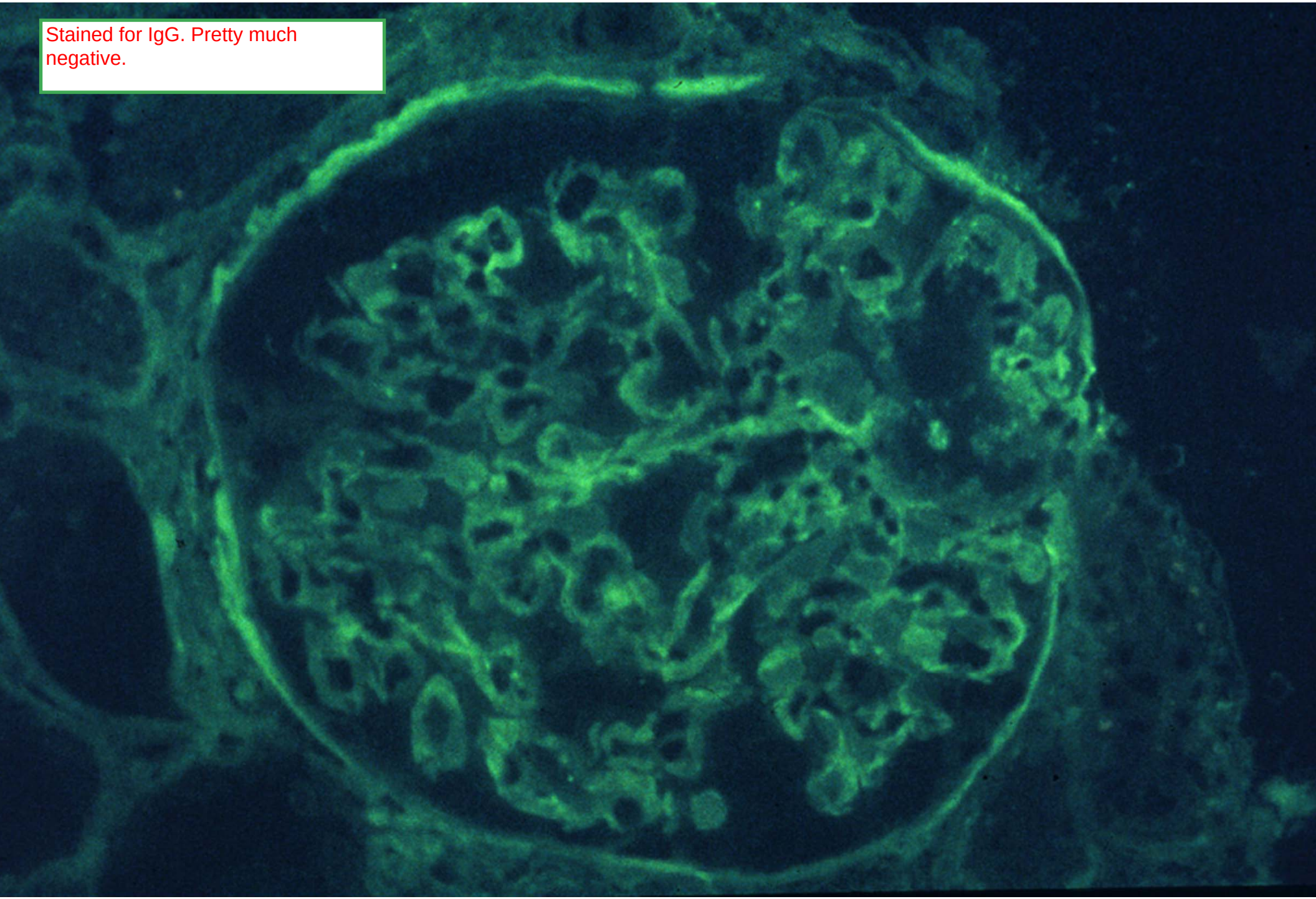
Minimal change disease (nil lesion, lipoid nephrosis)

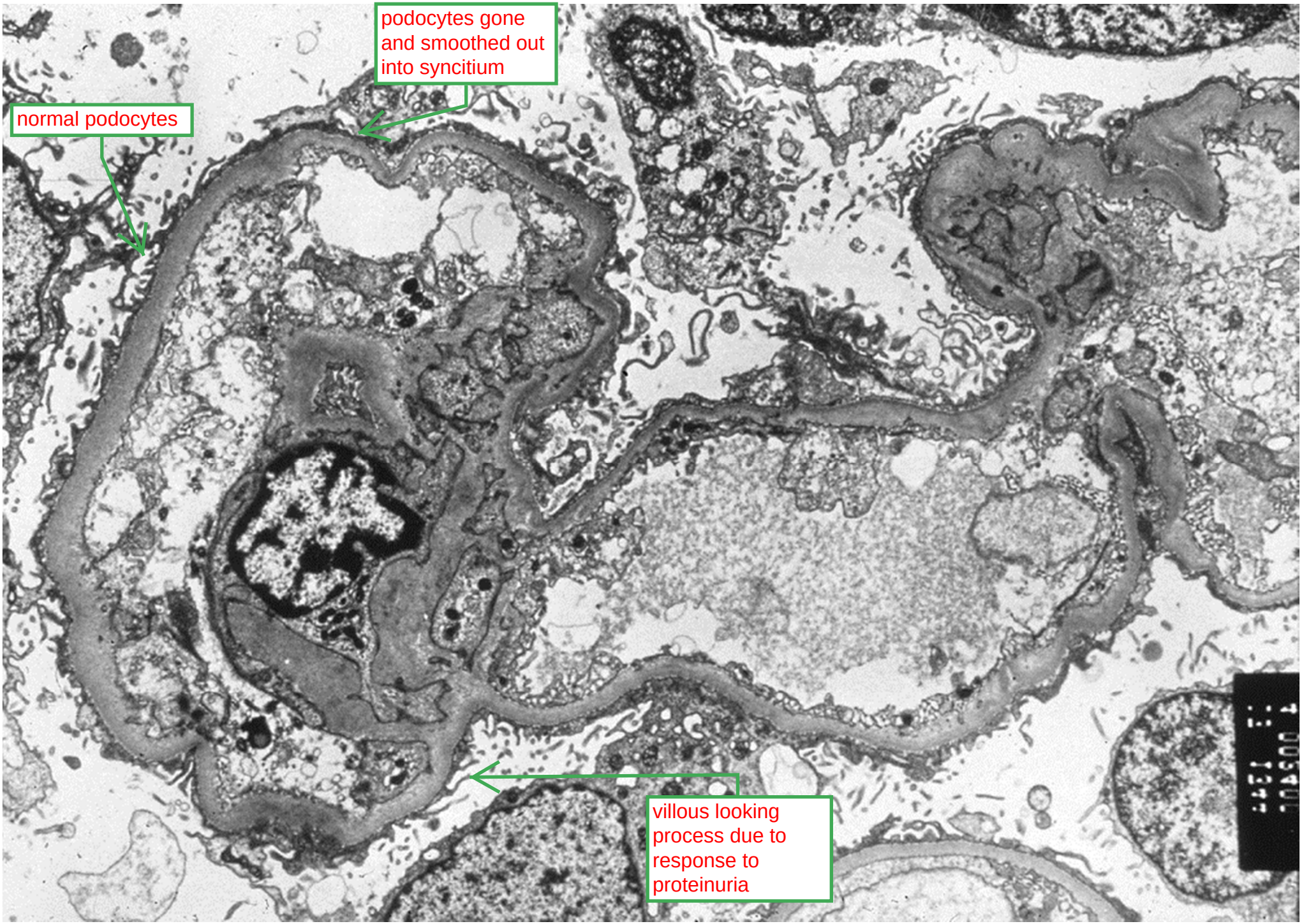
- **Pathogenesis: Damage to visceral epithelial cell foot processes**
  - **? Cytokine**
  - **Nonsteroidal anti-inflammatory drugs (NSAIDs)**
- **Histologic: Normal or mildly altered histology; foamy histiocytes may be present in glomeruli and tubules**
- **Clinical: Proteinuria/nephrotic syndrome, generally responsive to steroids; most common in children (NSAID-associated form often seen in adults)**

Might encounter Minimal Change Disease (MCD) this on pediatric rotations. There is an idiopathic form in children. Adults get it from NSAIDs. Believed to involved some cytokine that damages podocytes. Patients usually get better with steroids.

Glomerulus in child with MCD. Normal number of cells. Epithelial cells have a fluffy look to them.

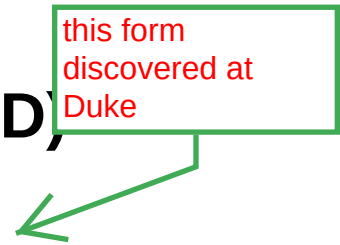


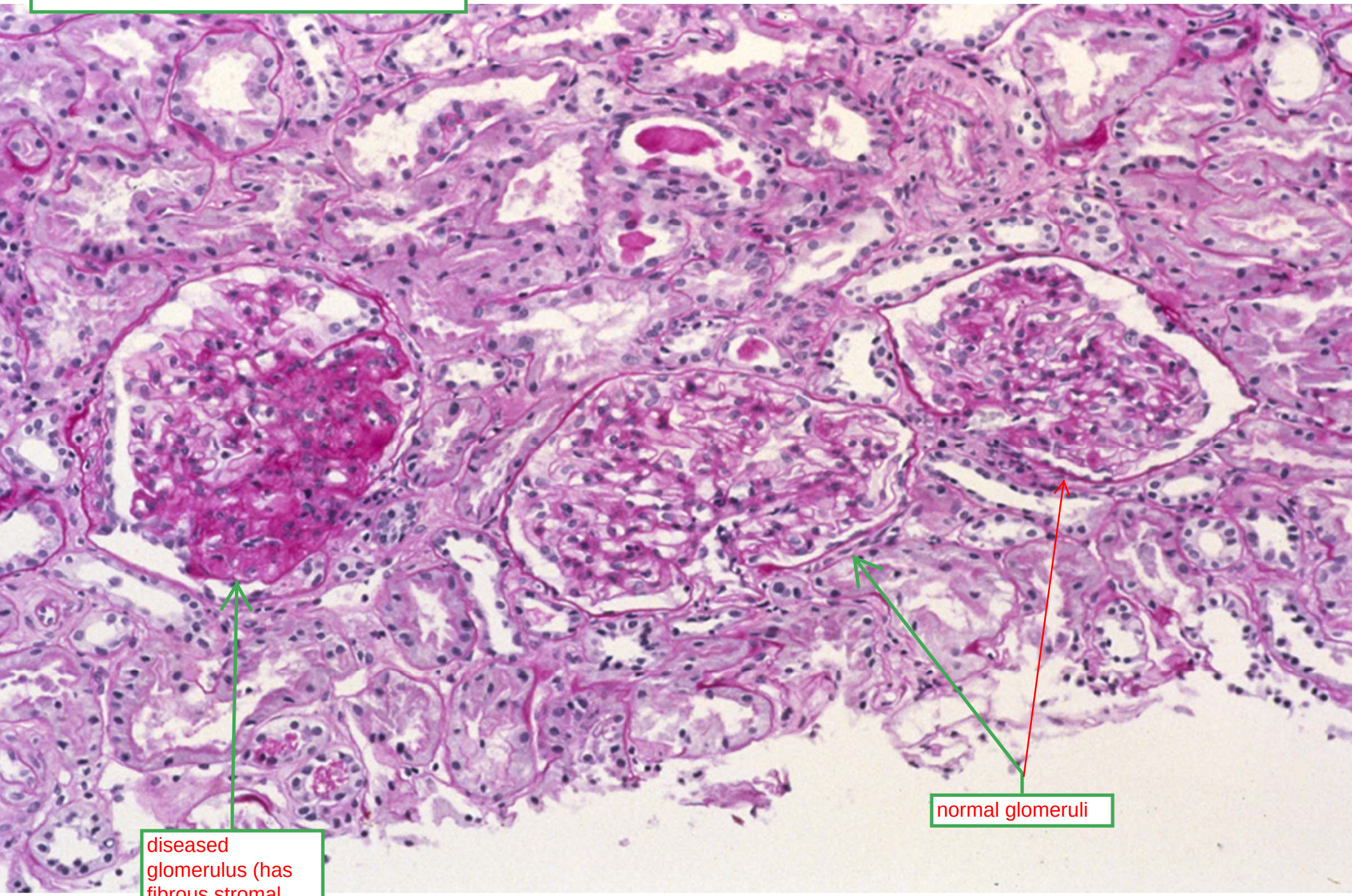

Stained for IgG. Pretty much negative.

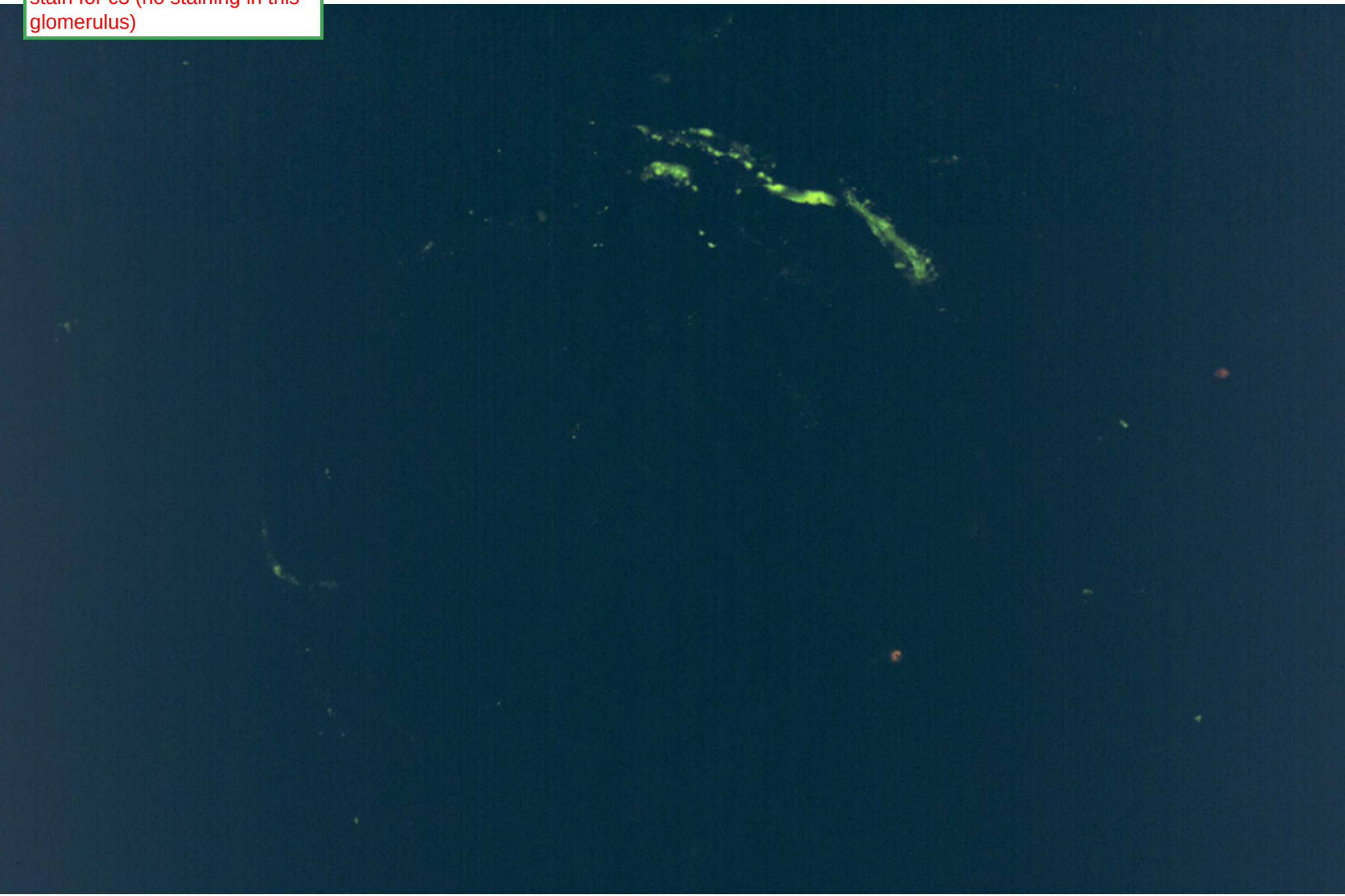

podocytes gone and smoothed out into syncitium
normal podocytes
villous looking process due to response to proteinuria

Focal segmental glomerulosclerosis

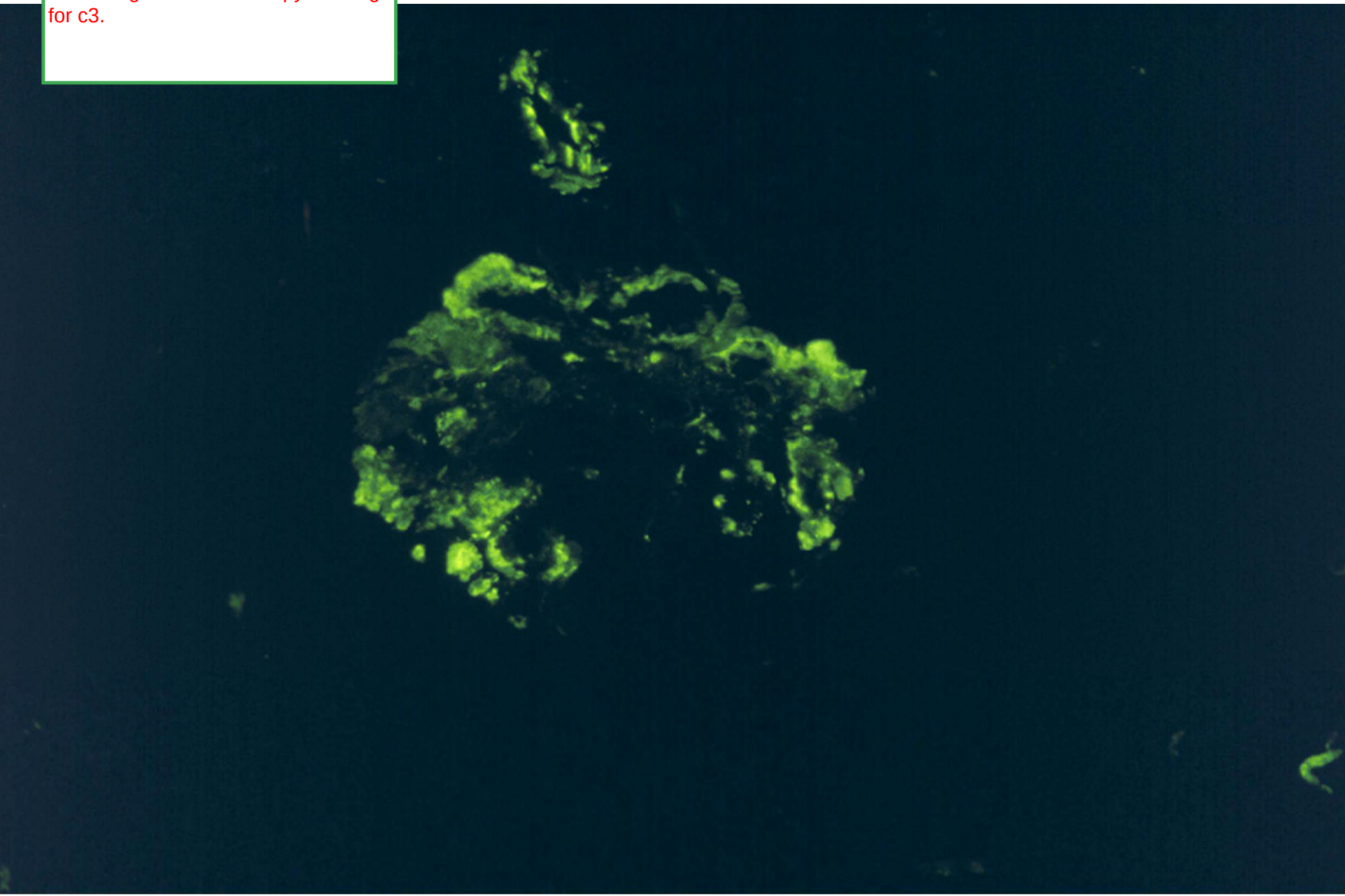
- **Pathogenesis: Damage to visceral epithelial cell foot processes**
  - **Primary (pathogenesis unclear, ? similar to MCD)**
  - **Secondary (sickle cell disease, obesity, HIV)**
  - **Heritable (podocin, nephrin, alpha-actinin, TRPC6)**
- **Histologic: Focal, segmental sclerosis of glomeruli**
- **Clinical: Proteinuria/nephrotic syndrome, often progressing to chronic renal failure; generally unresponsive to steroids**

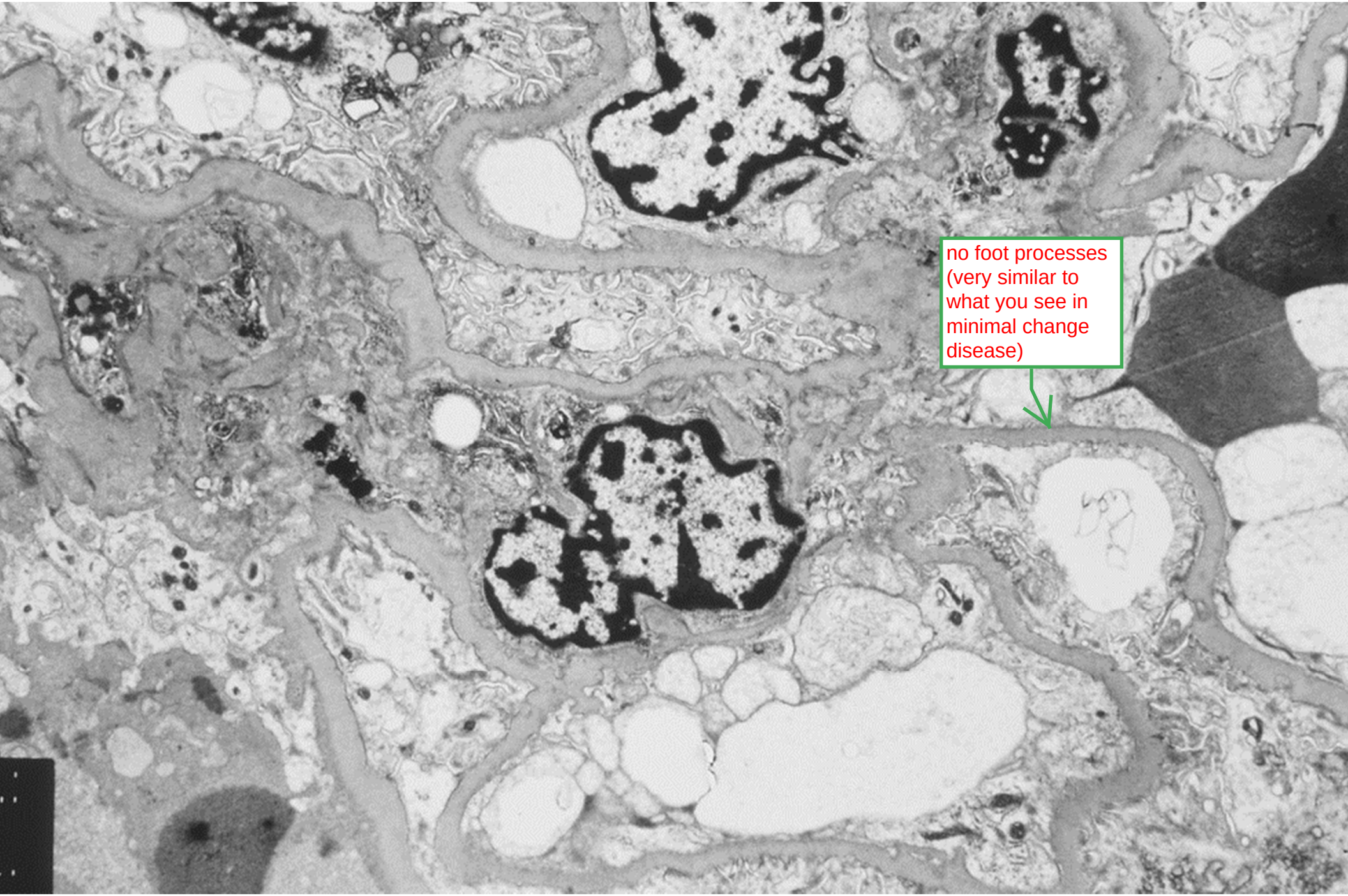



focal segemental glomerulosclerosis
diseased glomerulus (has fibrous stromal tissue)
normal glomeruli

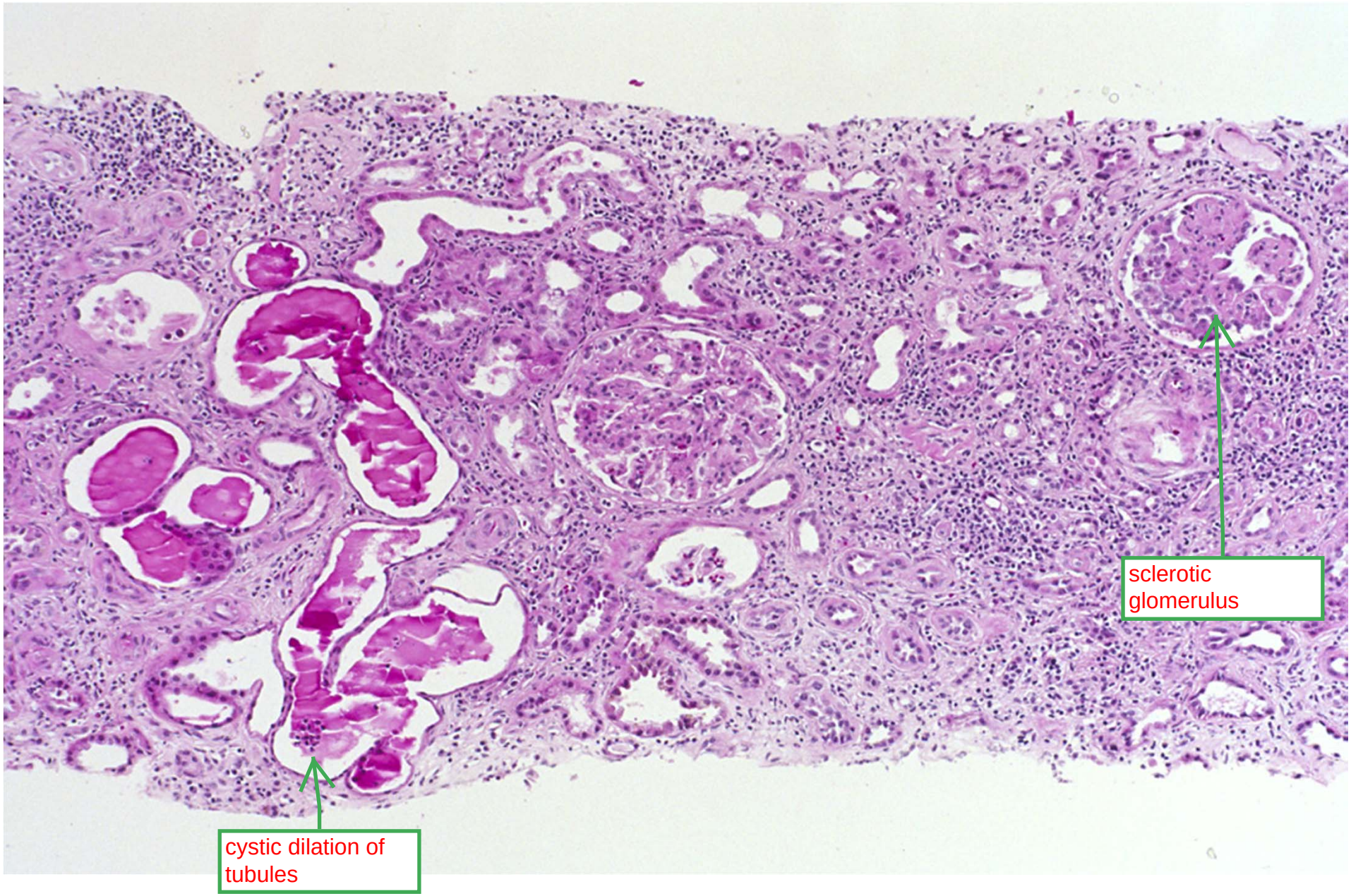

stain for c3 (no staining in this glomerulus)

sclerotic glomerulus. clumpy staining for c3.




no foot processes (very similar to what you see in minimal change disease)

HIV-associated nephropathy (HIVAN)



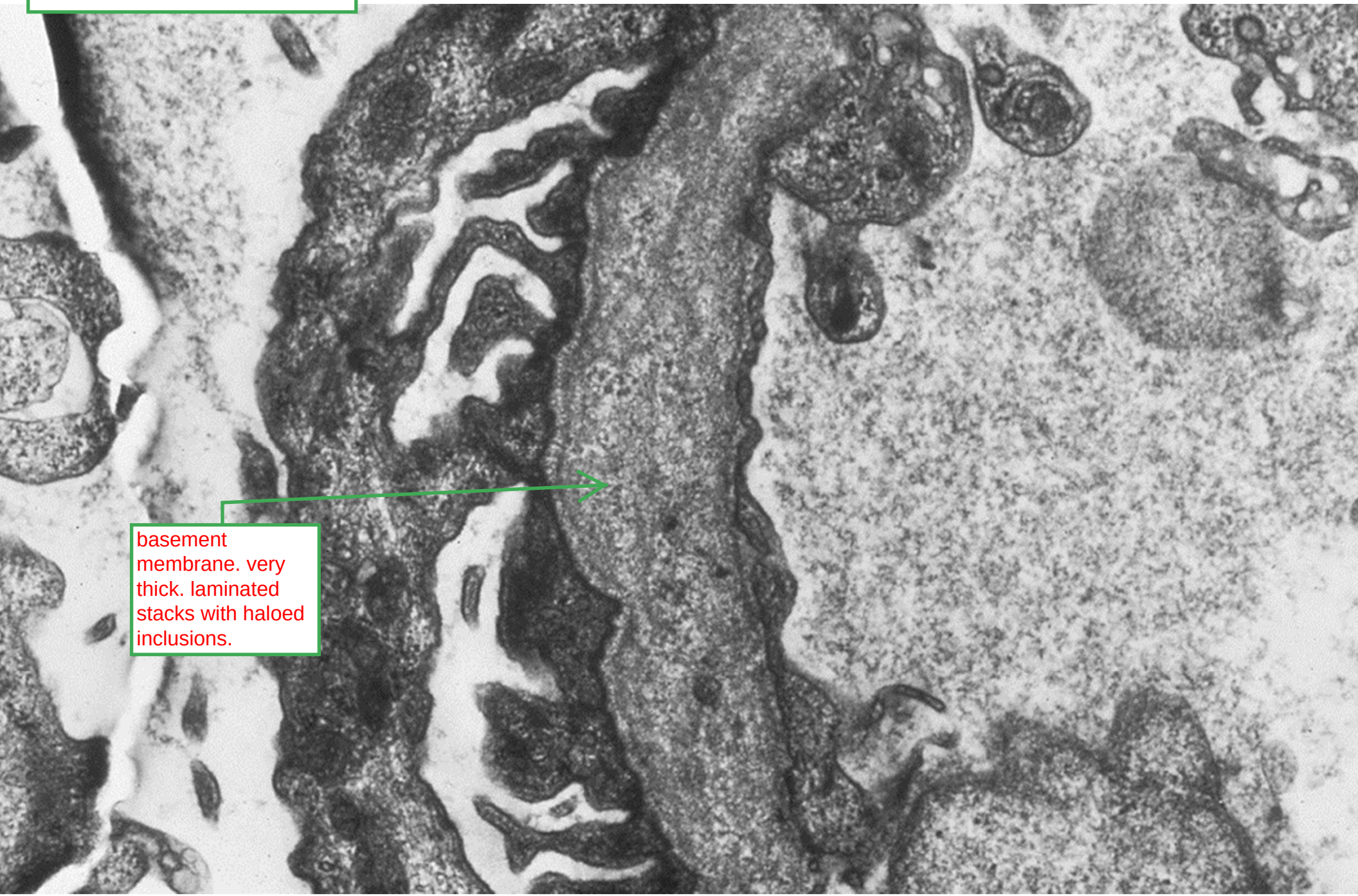
Intrinsic Defects of Glomerular Basement Membrane

Alport's syndrome (hereditary nephritis)

- **Pathogenesis: Mutations in genes encoding α chains of type IV collagen; defective collagen biosynthesis**
  - **X-linked: α5**
  - **Autosomal recessive: α3, α4**
- **Histologic: Variable; alternate thinning, thickening, and splitting of capillary basement membranes seen by electron microscopy**
- **Clinical: Hematuria, proteinuria; chronic progressive renal failure; deafness, eye abnormalities (cornea, lens)**

Sees about one case a year. Type 4 collagen is important in basement membranes.

Alport's Syndrome

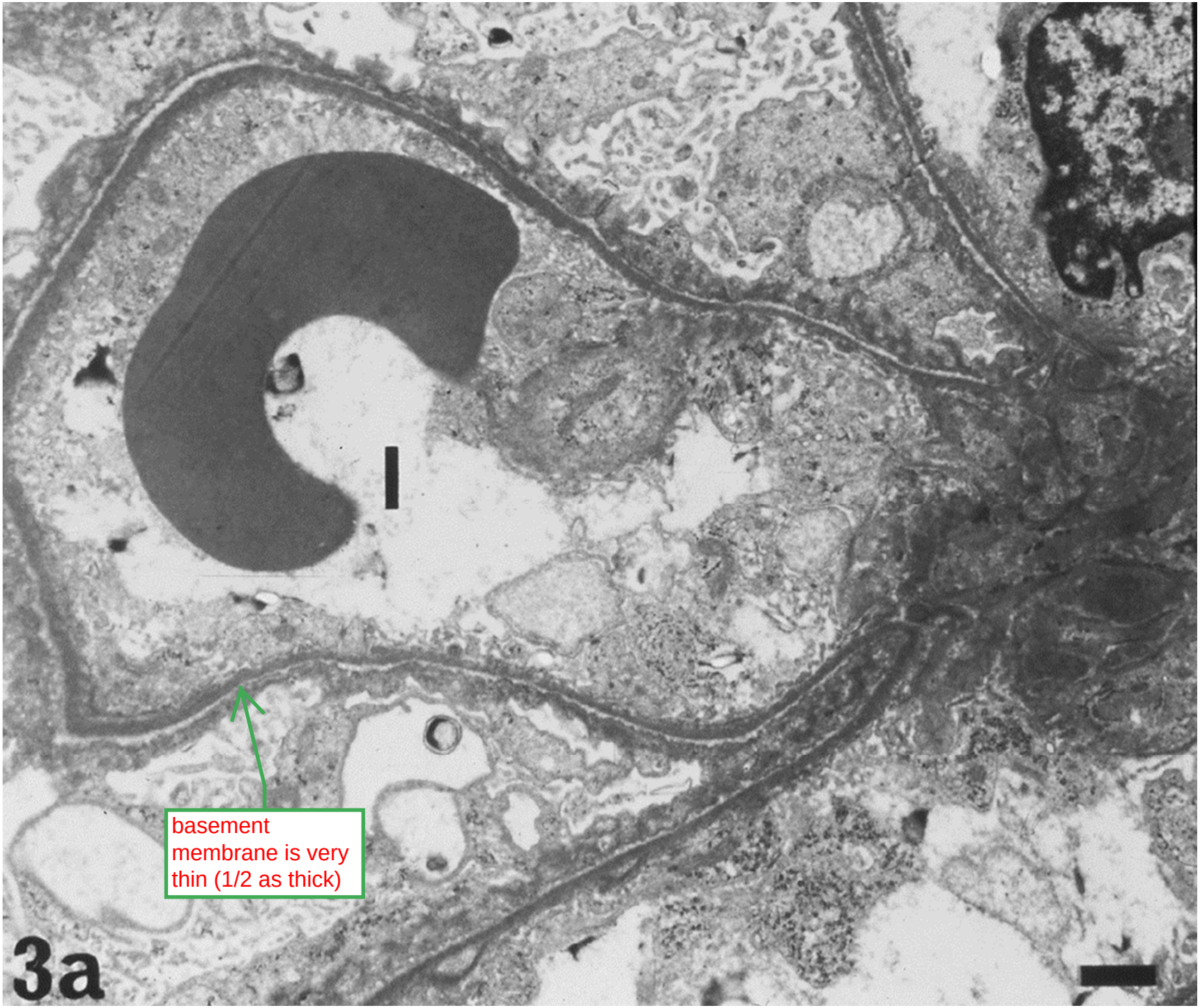


Benign recurrent hematuria (thin basement membrane syndrome)

- **Pathogenesis: Heritable defect in gene encoding α3 or α4 chain of type IV collagen (usually dominant inheritance)**
- **Histologic: Generally only minor abnormalities; diffuse thinning of glomerular basement membranes seen by electron microscopy**
- **Clinical: Microscopic or macroscopic hematuria; generally indolent course**

1/2 as thick

Looks sort of like minimal change disease.


basement membrane is very thin (1/2 as thick)
3a

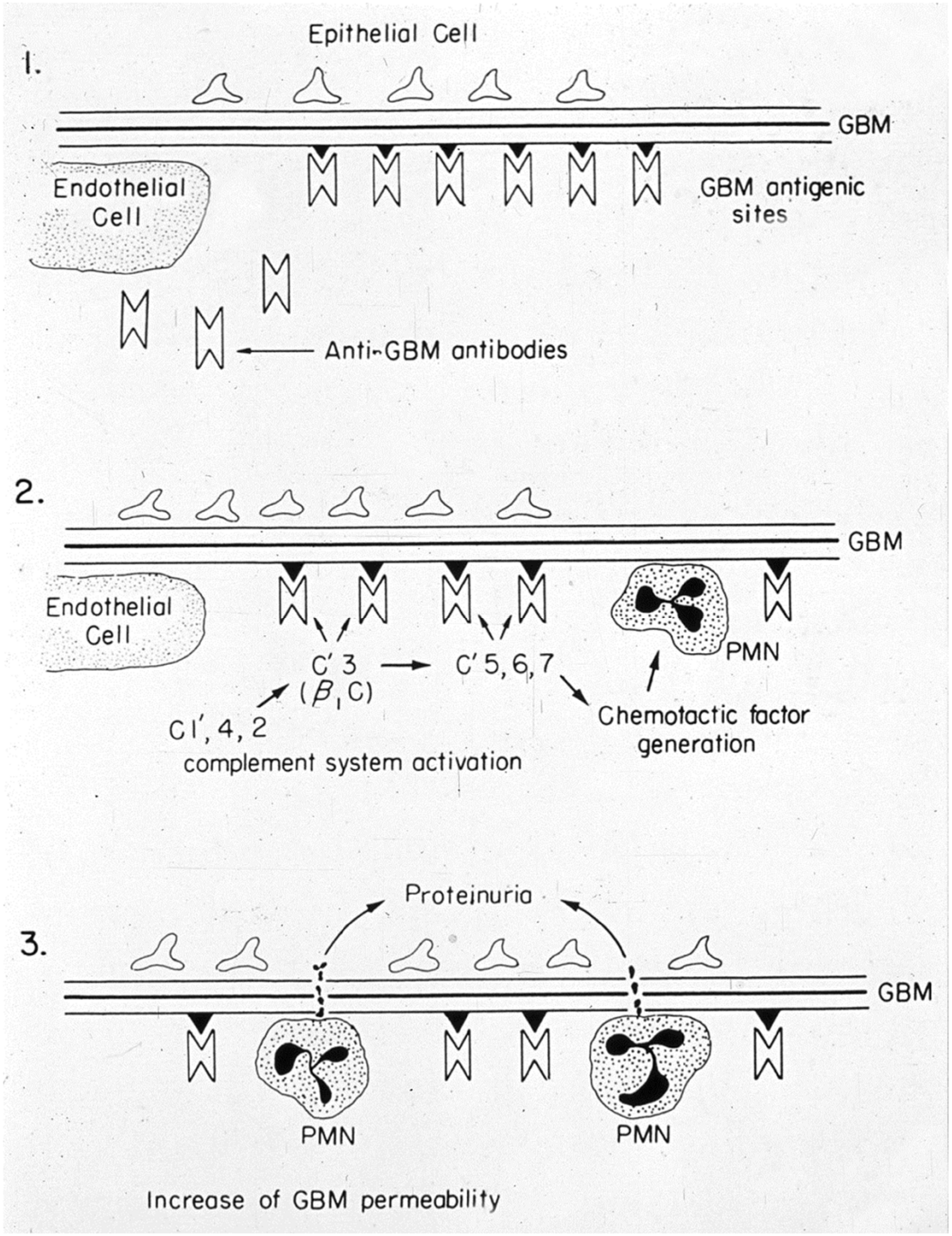
Antibodies Against Glomerular Basement Membrane

Goodpasture's syndrome

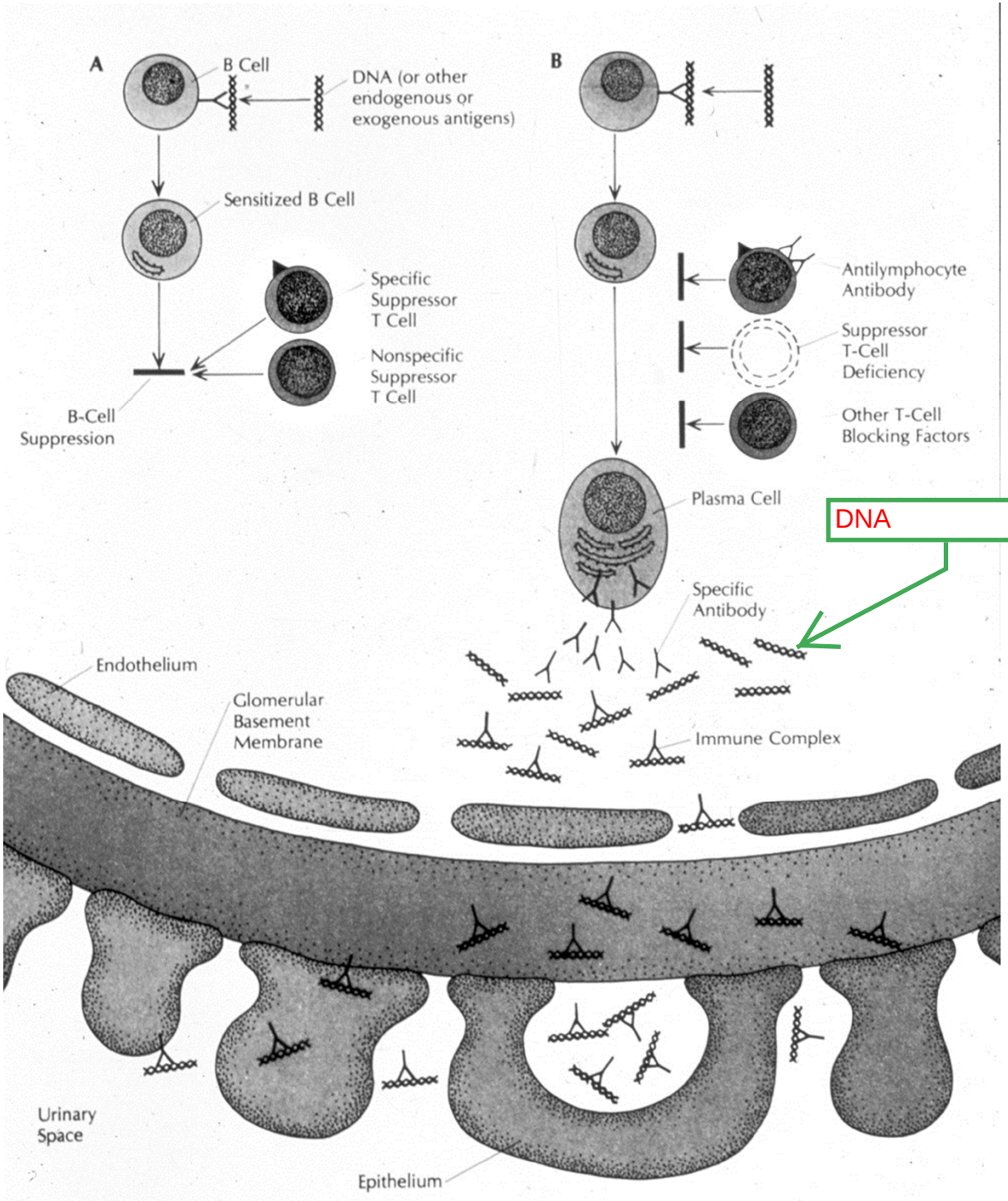
- **Pathogenesis: Production and binding of autoantibody (IgG) to α3 chain of type IV collagen**
- **Histologic: Focal segmental necrotizing glomerulonephritis, frequently with crescents**
- **Clinical: Rapidly progressive glomerulonephritis with pulmonary hemorrhage/hemoptysis; may present as isolated renal disease (referred to as "anti-glomerular basement membrane antibody glomerulonephritis") or pulmonary disease; most common in young males**

Patients make antibody against alpha3. Goodpastures is classified as a pulmonary-renal syndrome because it affects both lungs and kidneys. Most common in males.

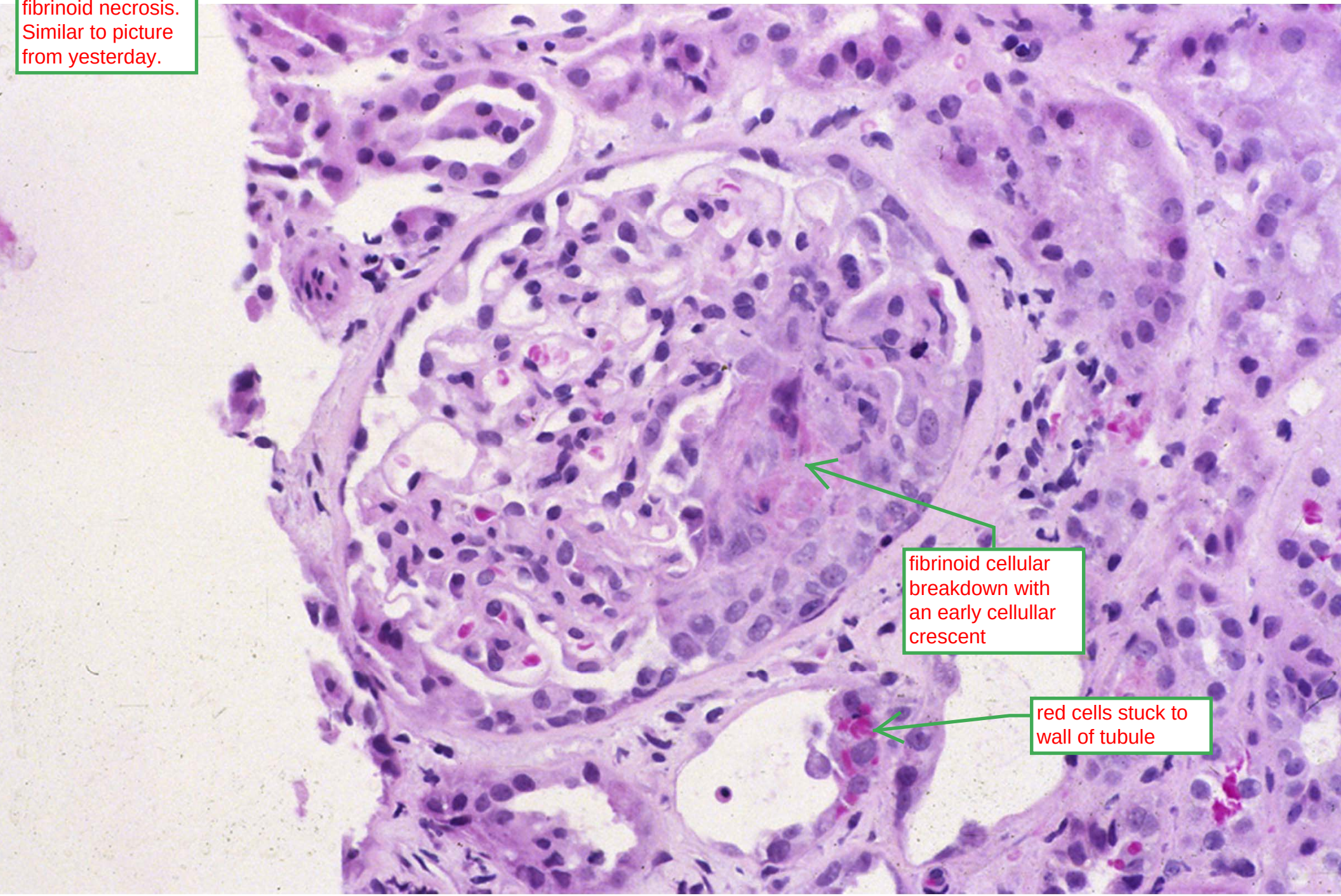
Cartoon of hypersensitivity reaction. (1) Anti-glomerular basement membrane antibodies bind alpha3 of collagen. (2) complement binds and chemotactic signals bring in neutrophils (3) neutrophils damage the basement membrane and blood is released into urinary space



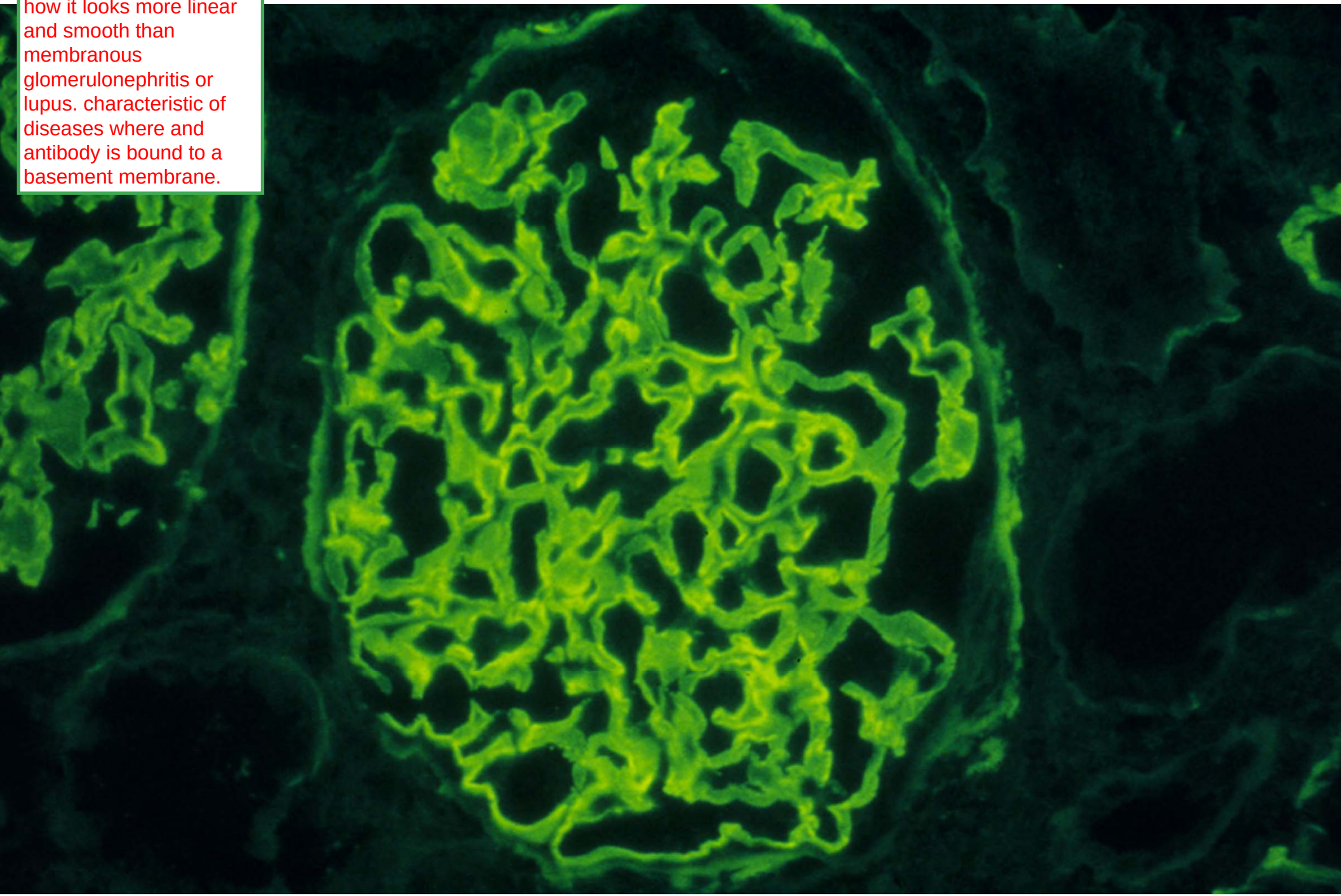
Showing this slide kind of late but he wants to illustrate a type 3 hypersensitivity reaction to compare it with a type 2 reaction (previous slide). This is an example of lupus.



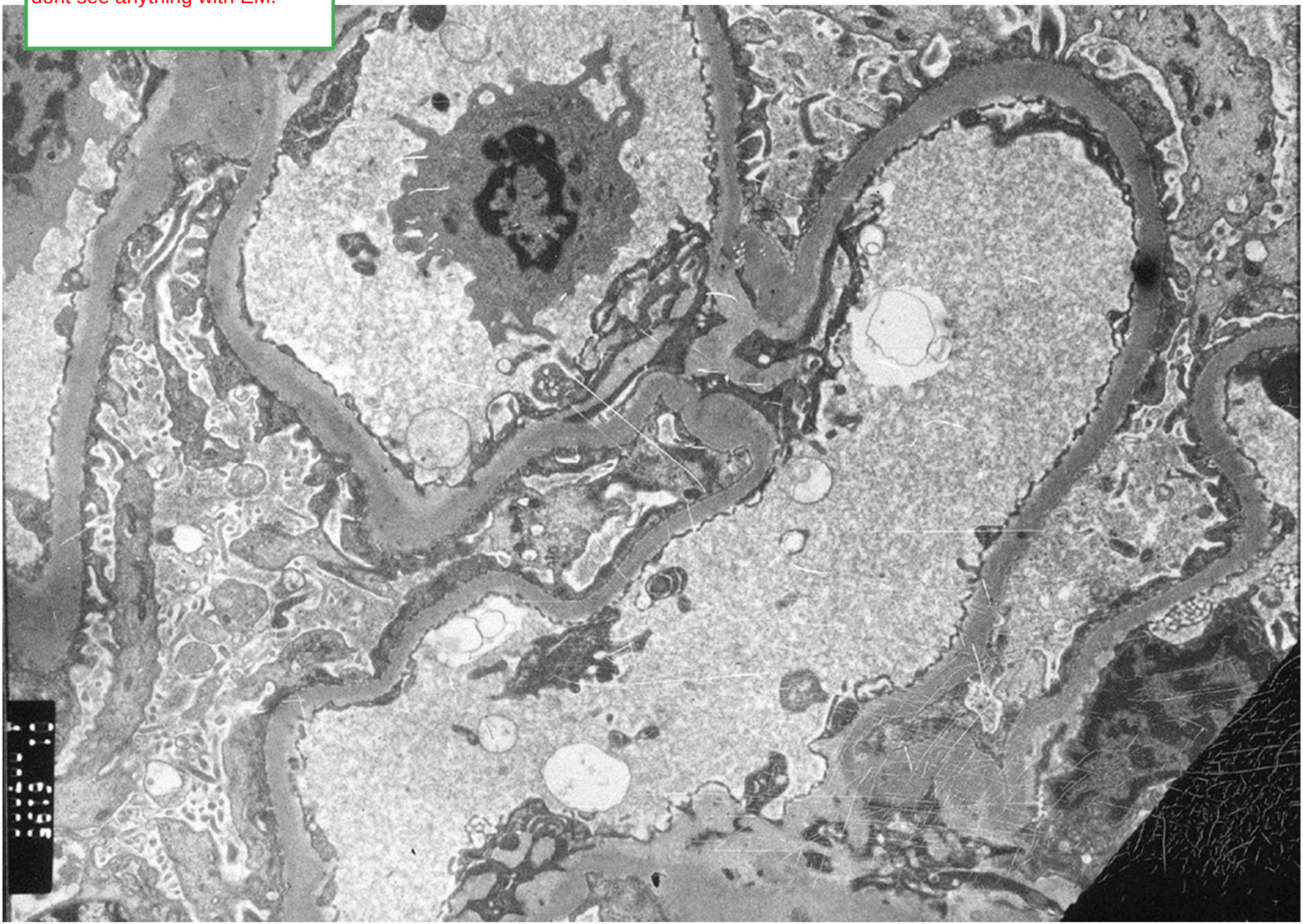
Examples of fibrinoid necrosis. Similar to picture from yesterday.



stained for IgG. notice how it looks more linear and smooth than membranous glomerulonephritis or lupus. characteristic of diseases where and antibody is bound to a basement membrane.



dont see anything with EM.



Endothelial Cell Damage

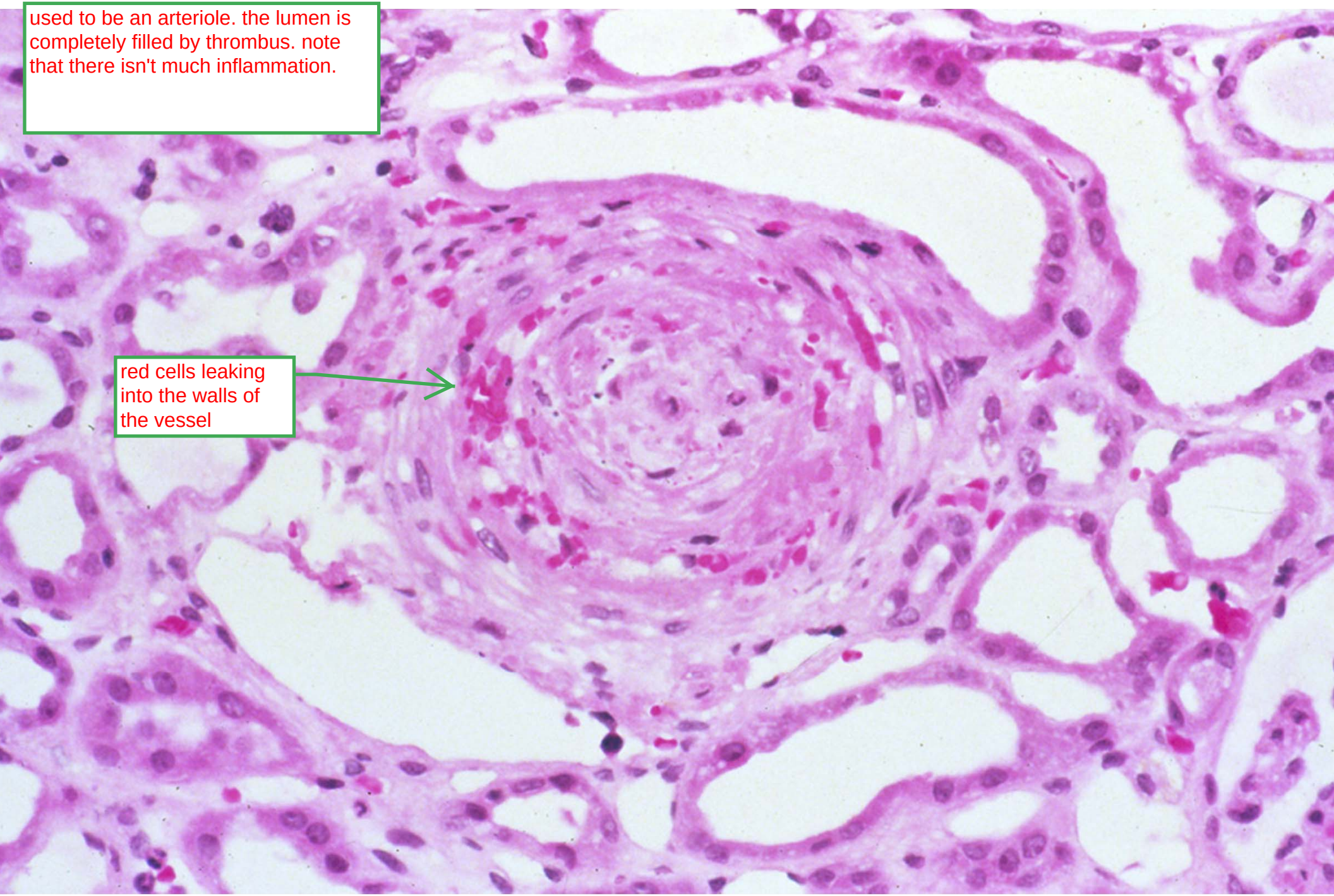
Thrombotic microangiopathies

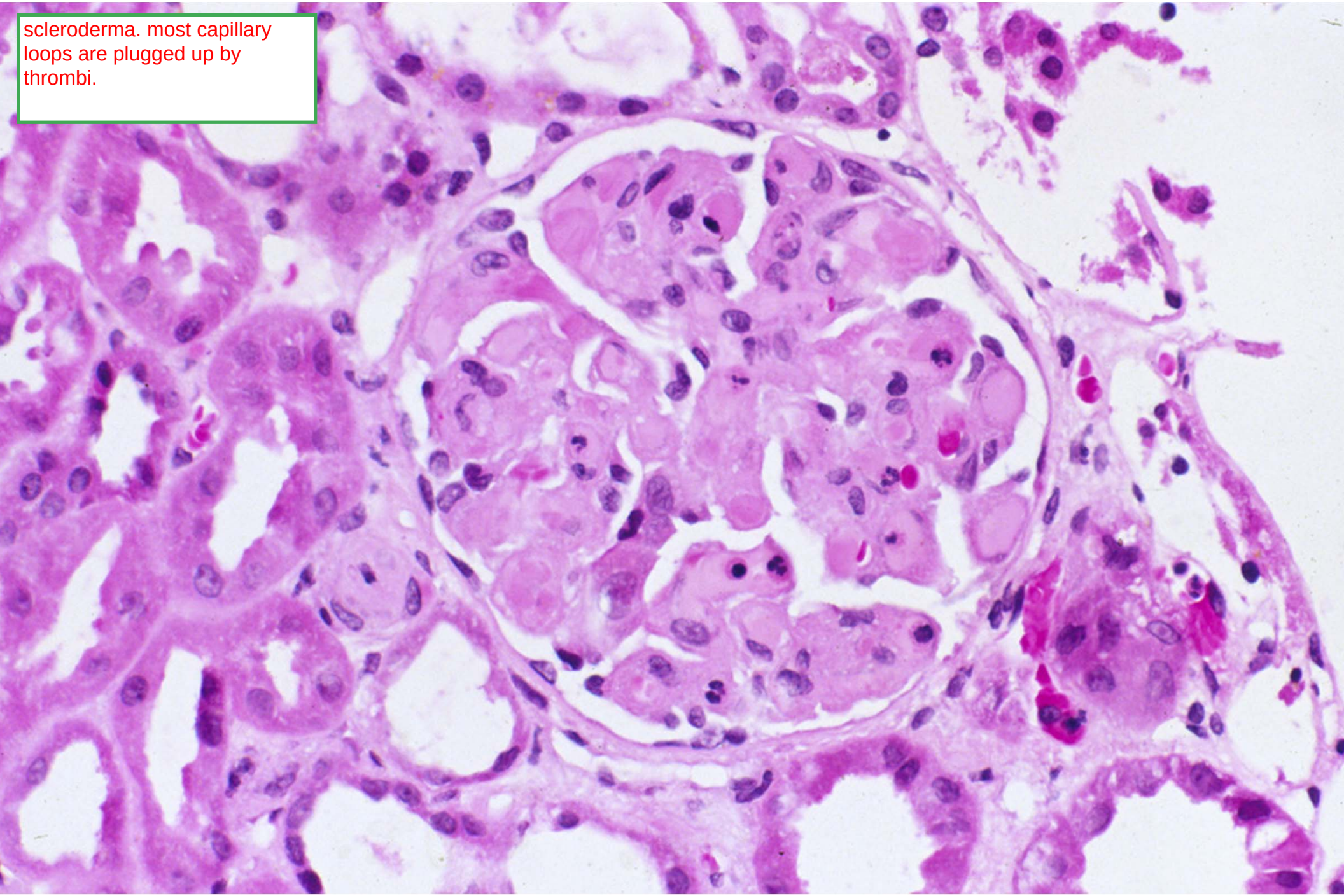
- **Pathogenesis: Damage to endothelium of glomerular capillaries/arterioles/small arteries**
  - **Verotoxin (Enterohemorrhagic E. coli O157:H7)**
  - **Shear forces (malignant hypertension)**
  - **Complement regulatory factor deficiency**
    - **Hereditary**
    - **Autoantibody**
  - **Other**
- **Histologic: Endothelial and subendothelial damage and fibrin thrombi in capillaries, arterioles, and arteries**
- **Clinical: Acute renal failure with or without other systemic manifestations; variable course**

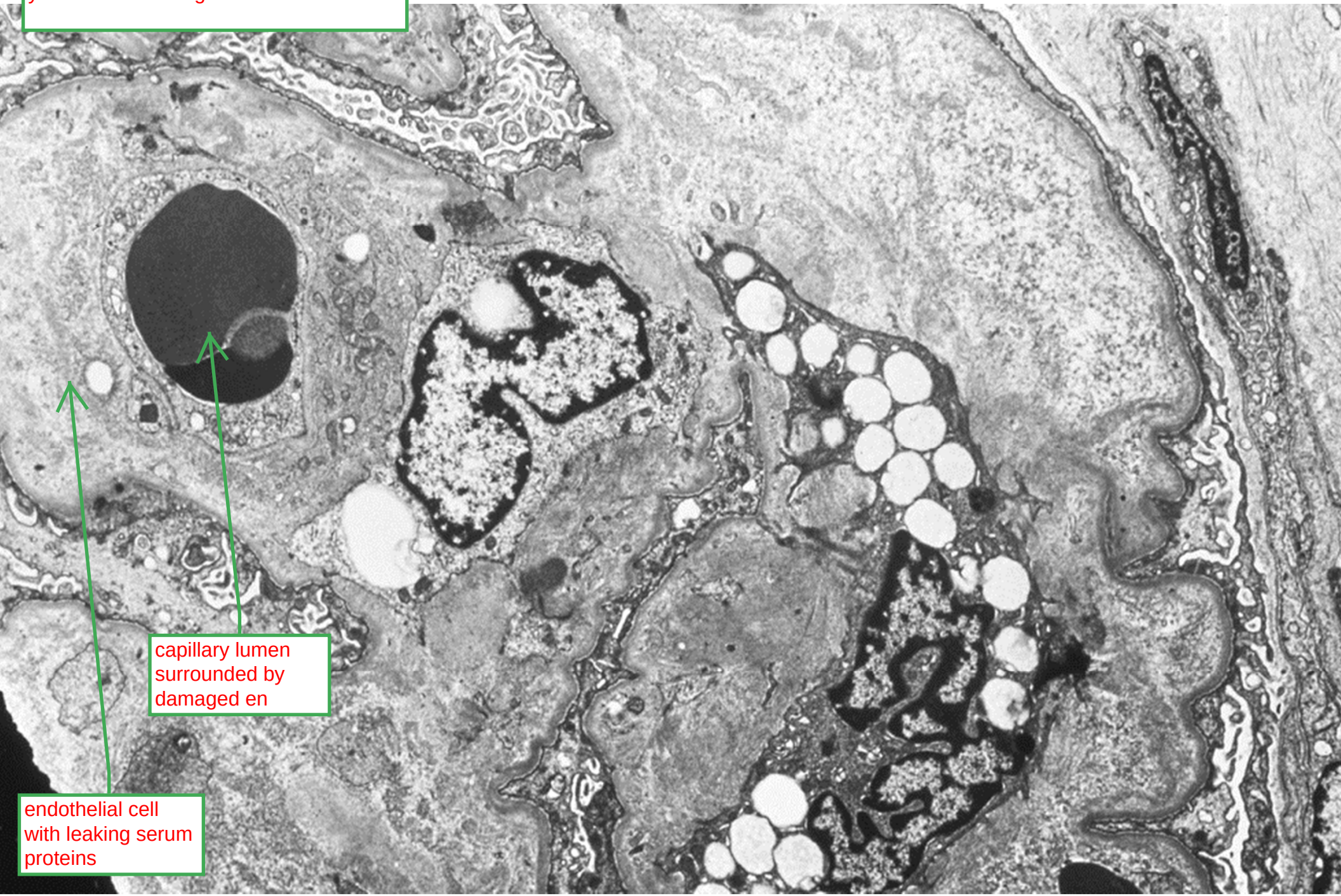
Thrombotic microangiopathies: “The three-letter disorders”

- **HUS - hemolytic uremic syndrome**
- **TTP - thrombotic thrombocytopenic purpura**
- **PSS - progressive systemic sclerosis**
- **HTN - malignant hypertension**
- **CNI - calcineurin inhibitor toxicity**
- **DIC - disseminated intravascular coagulation**
- **SLE - systemic lupus erythematosus**

Also called "three letter disorder." These are the names for them. In general just understand that there are several things that lead to this particular renal pathology.


used to be an arteriole. the lumen is completely filled by thrombus. note that there isn't much inflammation.
red cells leaking into the walls of the vessel

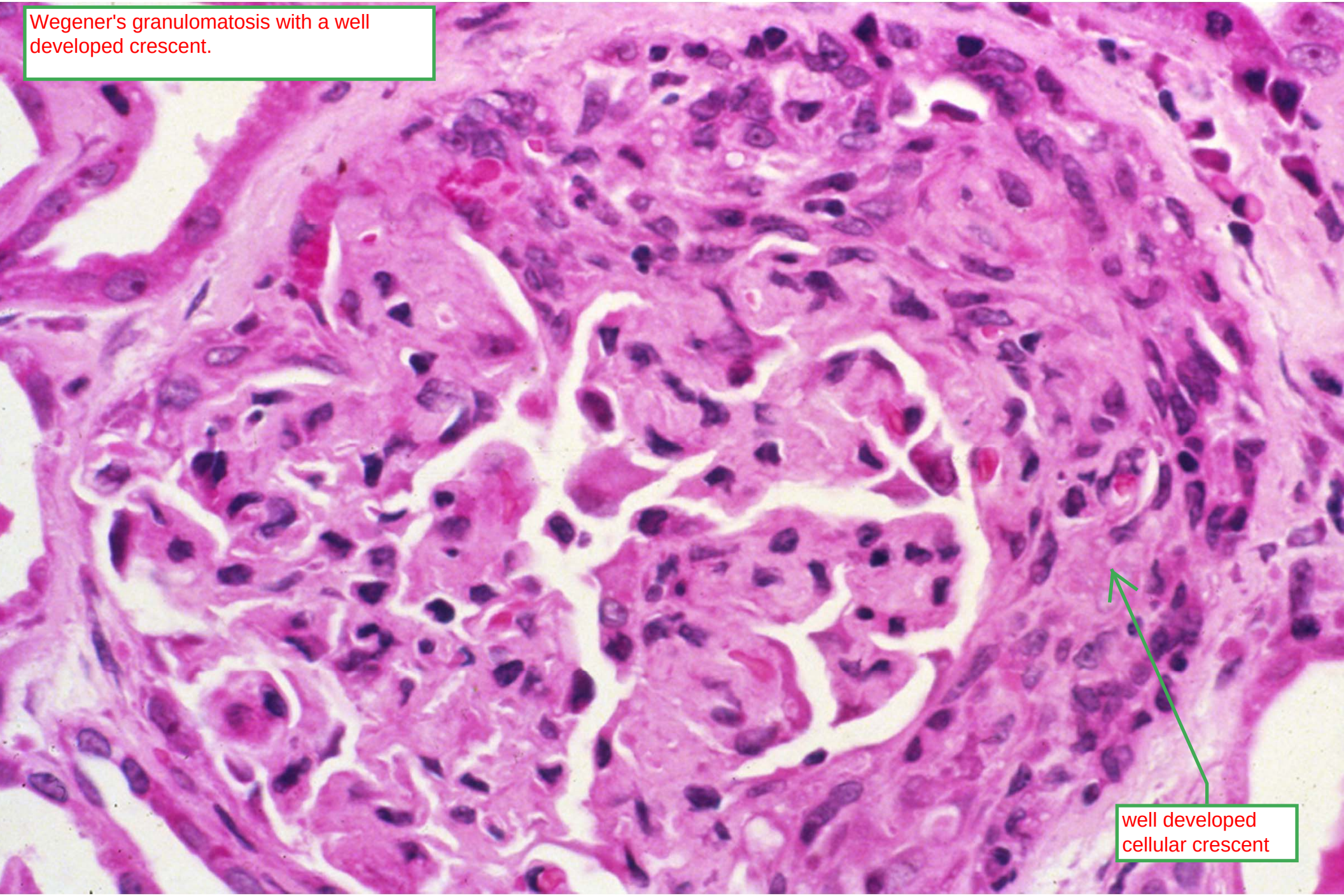

scleroderma. most capillary loops are plugged up by thrombi.

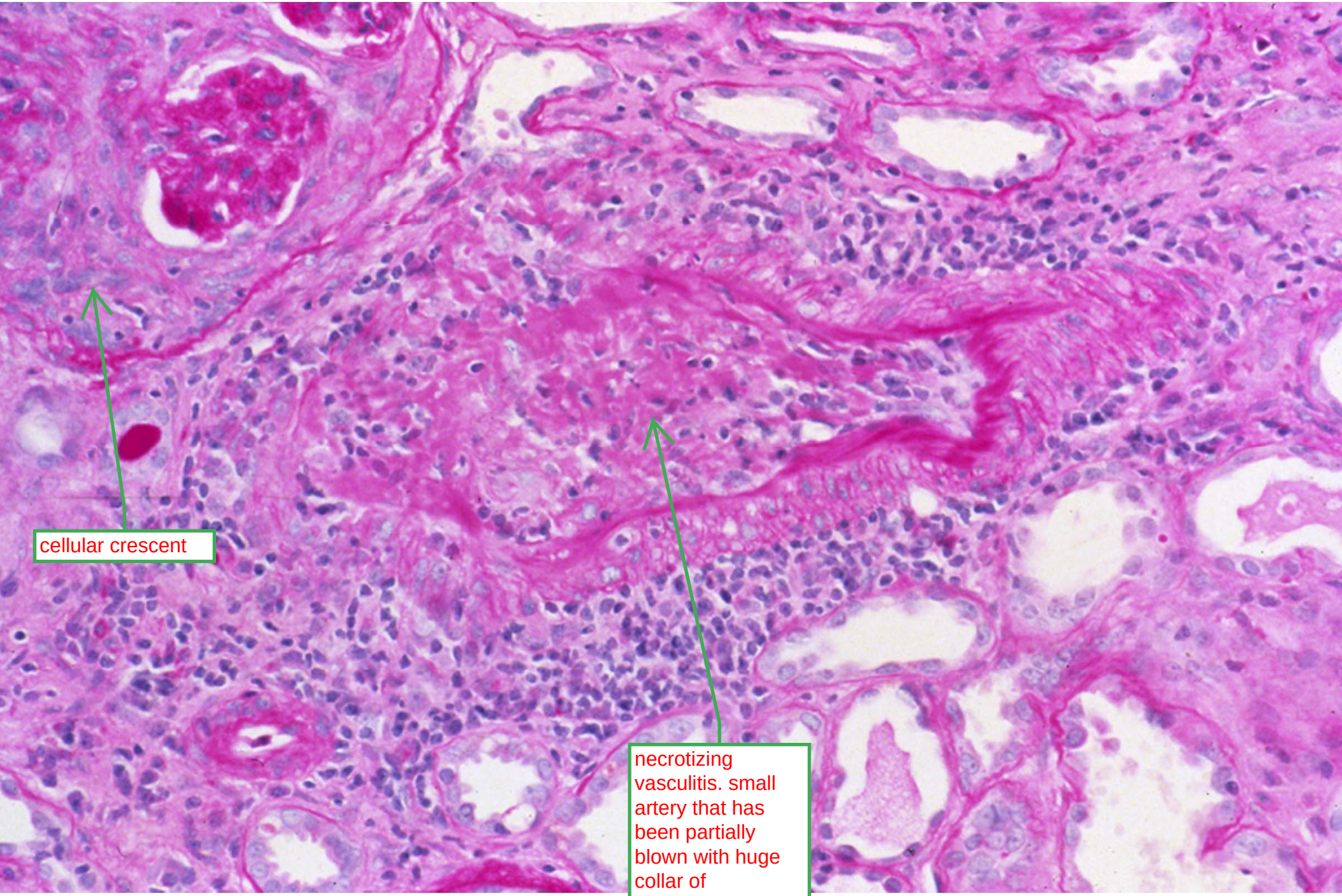

you can see damage to endothelium
capillary lumen surrounded by damaged en
endothelial cell with leaking serum proteins

Anti-neutrophil cytoplasmic antibody (ANCA) glomerulonephritis

- **Pathogenesis: Damage to vascular endothelium and walls (especially glomerular capillaries) by neutrophils activated by anti-neutrophil cytoplasmic antibodies (ANCA)**
- **Histologic: Focal segmental necrotizing glomerulonephritis, often with crescents; necrotizing, inflammatory vasculitis**
- **Clinical: Nephritic syndrome, often with systemic manifestations**
  - **Wegener's granulomatosis (often c-ANCA, pulmonary-renal syndrome)**
  - **Microscopic polyangiitis (often p-ANCA, often renal-localized)**
  - **Churg-Strauss syndrome (associated with asthma, eosinophilia)**

Similar pathogenesis to goodpasture's syndrome.


Wegener's granulomatosis with a well developed crescent.
well developed cellular crescent

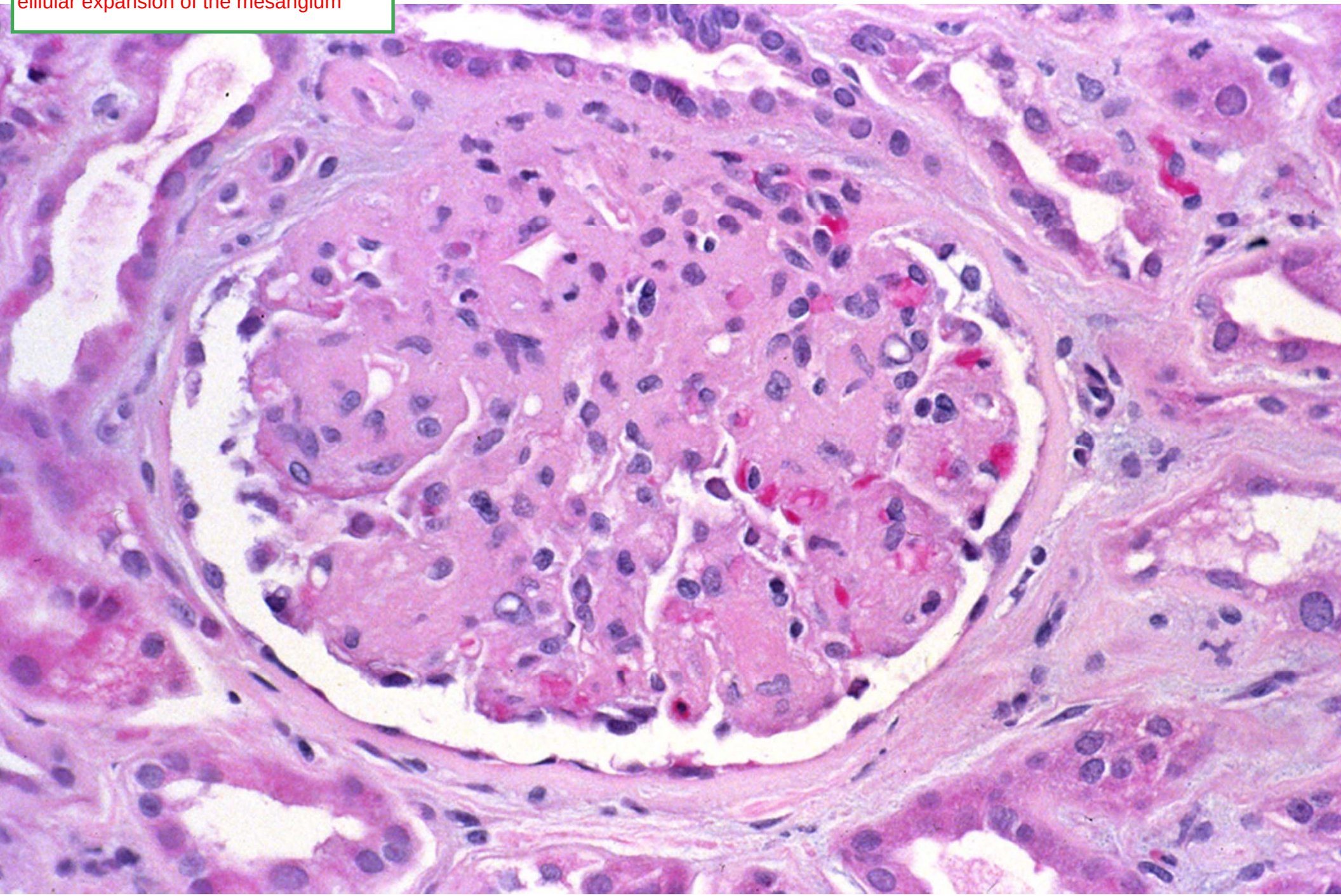

cellular crescent
necrotizing vasculitis. small artery that has been partially blown with huge collar of inflammatory cells around it

Diabetic nephropathy

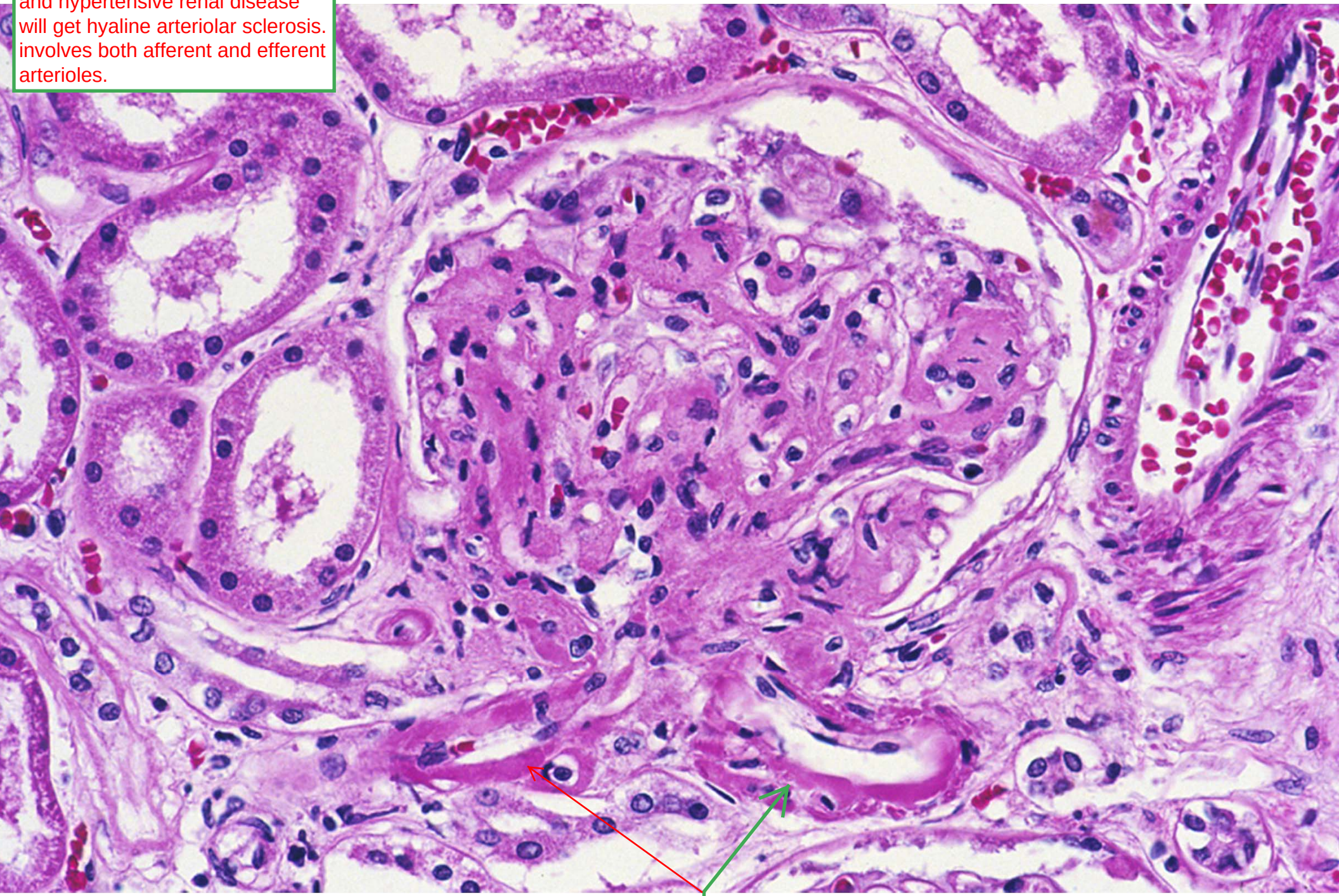
- **Pathogenesis: Probably involves non-enzymatic glycosylation of tissue proteins**
- **Histologic: Arteriolar sclerosis (afferent and efferent arterioles); diffuse, focally nodular mesangial expansion and capillary loop thickening**
- **Clinical: Chronic renal failure, frequently with superimposed acute disorders (pyelonephritis, papillary necrosis)**

We do hemoglobin-a1c test to check for this.

Example of diabetic nodule. hypoc-
elllular expansion of the mesangium

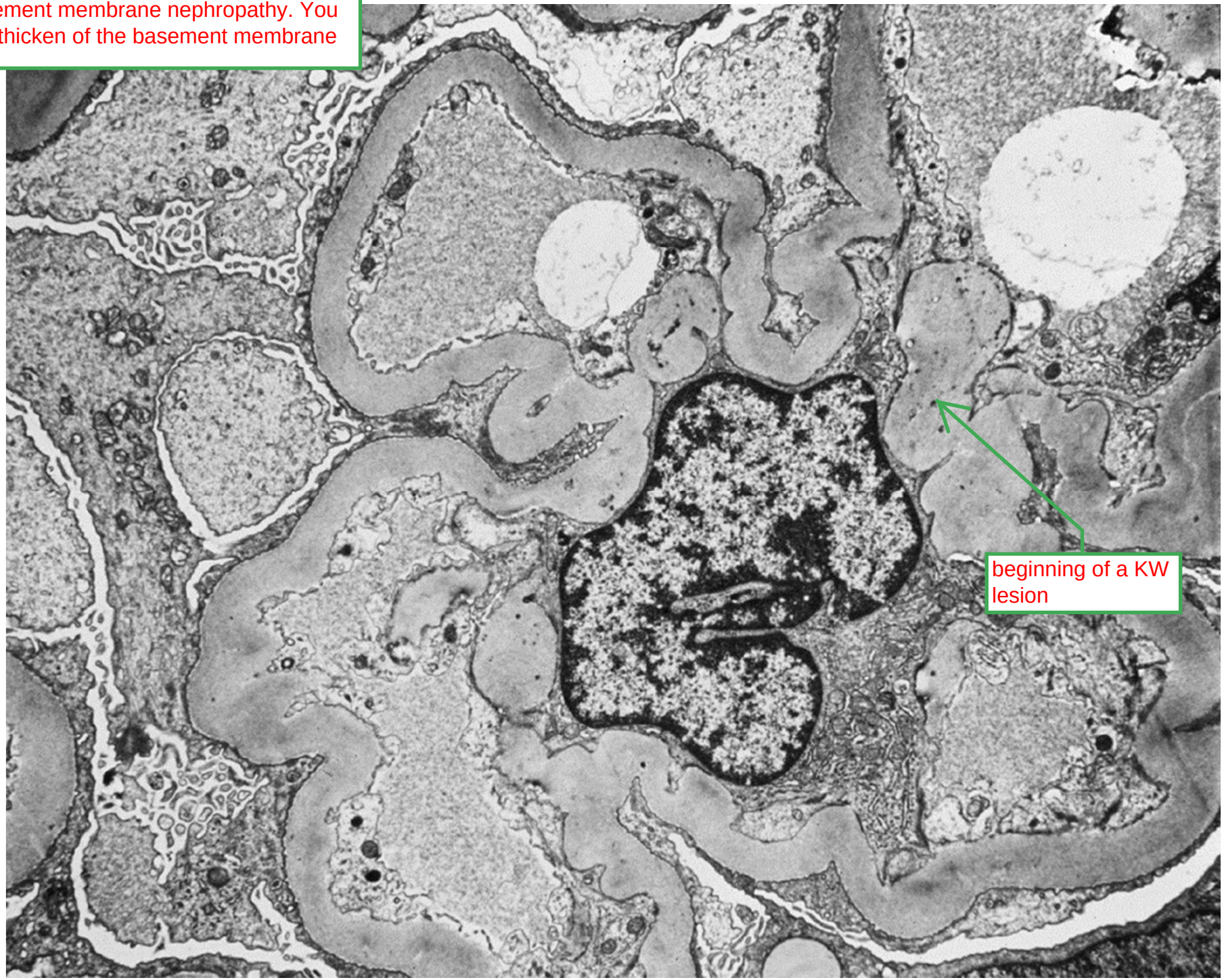


patients with diabetic nephropathy and hypertensive renal disease will get hyaline arteriolar sclerosis. involves both afferent and efferent arterioles.



Afferent and efferent arterioles (both are thickened and hyalinized

EM shows you the opposite of thin basement membrane nephropathy. You see thicken of the basement membrane

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