Clinical Course of FSGS.

- There is little tendency for spontaneous remission in idiopathic FSGS, and responses to corticosteroid therapy are variable.
- In general, children have a better prognosis than adults do.
- Progression to renal failure occurs at variable rates.

- About 20% of patients follow an unusually rapid course, with intractable massive proteinuria ending in renal failure within 2 years.
- Recurrences are seen in 25% to 50% of patients receiving allografts

Membranoproliferative Glomerulonephritis (MPGN)

- Is best considered a pattern of immune-mediated injury rather than a specific disease.
- There are two groups

I. Type 1

- Characterized by deposition of immune complexes containing IgG and complement

II. Type II

- Called *dense deposit disease* in which activation of complement appears to be the most important factor.

- MPGN accounts for up to 10% of cases of nephrotic syndrome in children and young adults
- Some patients present only with hematuria or proteinuria in the nonnephrotic range
- but many others have a combined nephrotic-nephritic picture

Pathogenesis of Type 1

- There is evidence of immune complexes in the glomerulus and activation of both classical and alternative complement pathways.

-The antigens involved in idiopathic MPGN are unknown.

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Morphology

- Light microscope:

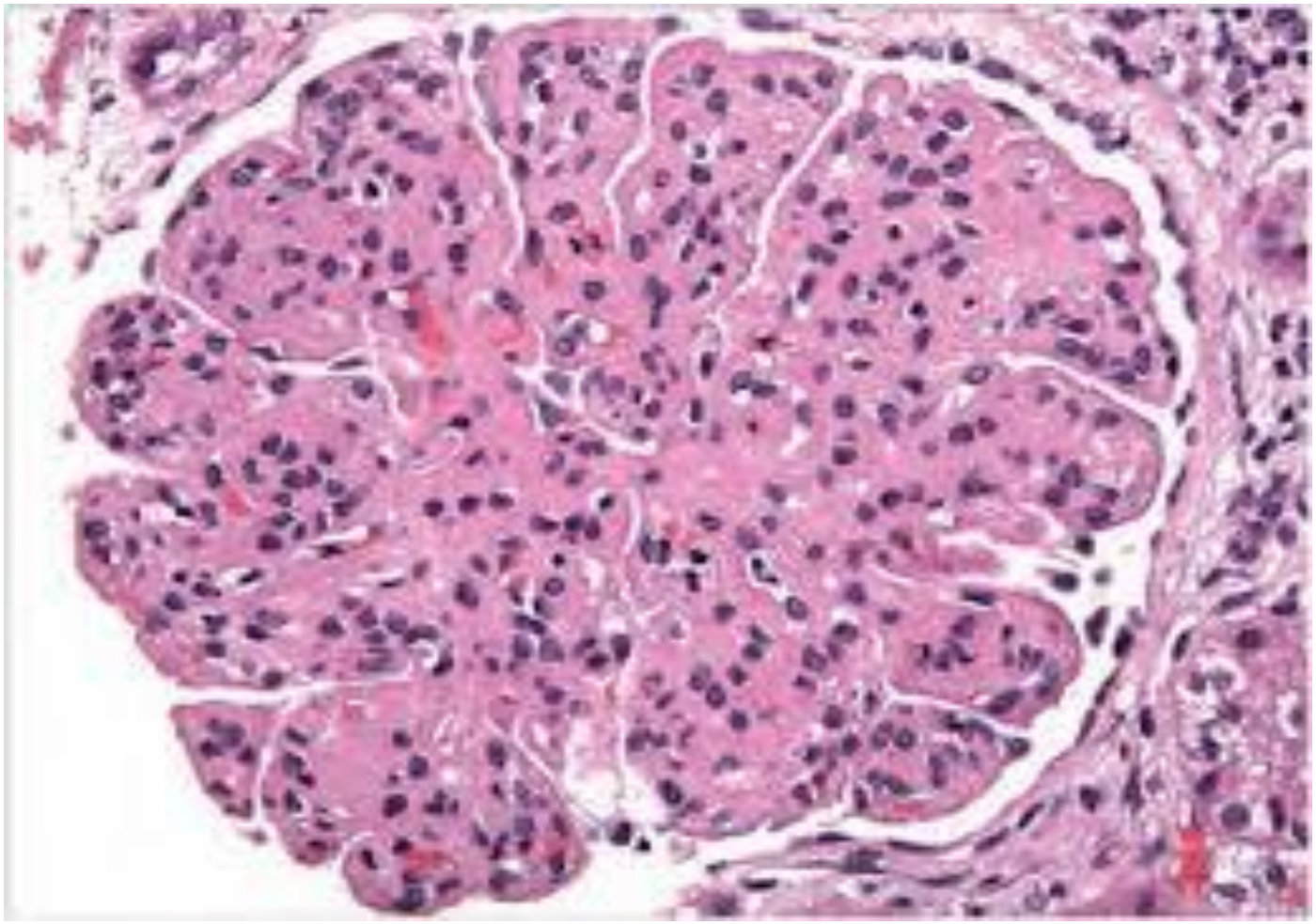
1. The glomeruli are large and hypercellular.

- The hypercellularity is produced both

a. by proliferation of cells in the mesangium and endothelial cells

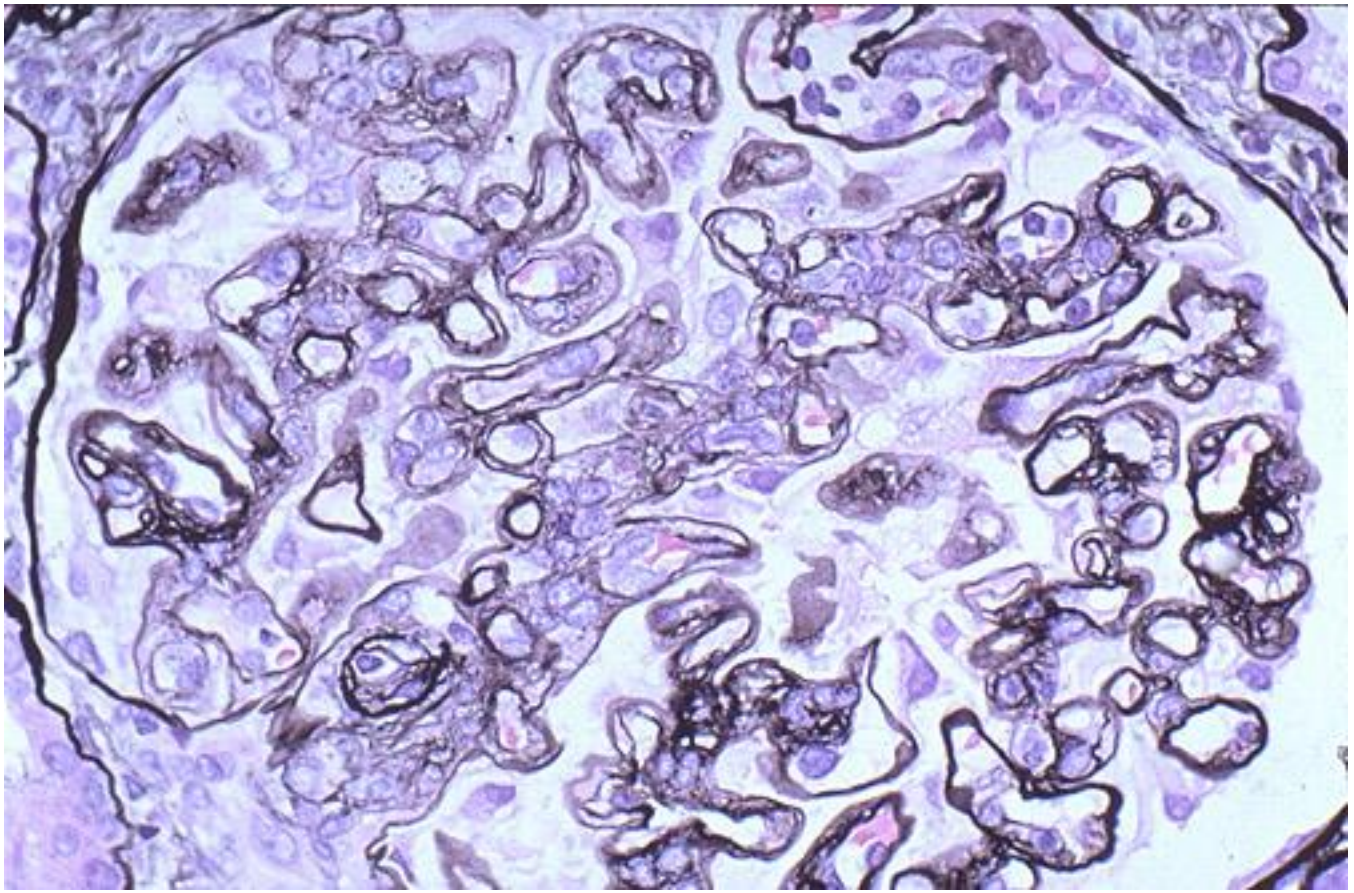
b. Infiltrating leukocytes.

MPGN



2. The glomeruli have an accentuated “lobular” appearance due to the proliferating mesangial cells and increased mesangial matrix
3. The GBM is thickened, and often shows a “double-contour” or “tram-track” appearance, or splitting especially evident in silver stain and resulted from of new basement membrane synthesis in response to subendothelial deposits of immune complexes

Silver stain in MPGN



4. Between the duplicated basement membranes there is inclusion or interposition of cellular elements, which can be of mesangial, endothelial, or leukocytic origin

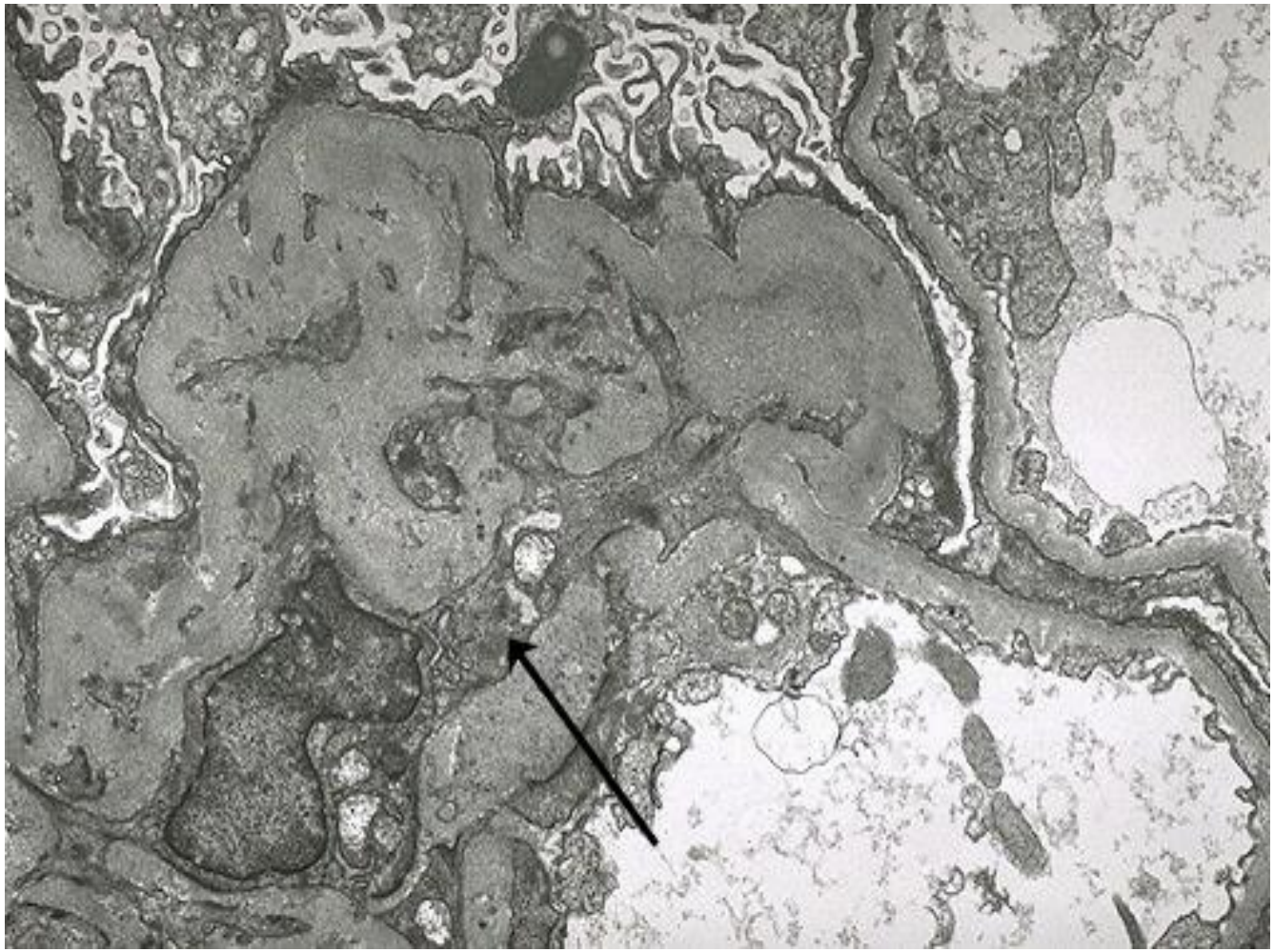
Electron microscope

- Characterized by the presence of discrete **subendothelial electron-dense deposits.**

Immunofluorescence

- Granular deposition of igG and C3 along with early complement components (C1q and C4) .

EM of type 1 MPGN



Clinical Features.

- Most patients with primary MPGN present in adolescence or as young adults with nephrotic syndrome and a nephritic component manifested by hematuria or, more insidiously, as mild proteinuria.
- Few remissions occur spontaneously and the disease follows a slowly progressive but unremitting course.

- Some patients develop numerous crescents and a clinical picture of RPGN.
- About 50% develop chronic renal failure within 10 years.
- Treatments with steroids, immunosuppressive agents, have not proven to be of any benefit.

Type II MPGN
Dense Deposit Disease

- Most patients with dense-deposit disease (formerly called type II MPGN) have abnormalities resulting in excessive activation of the alternative complement pathway.
- These patients have a consistently decreased serum C3 but normal C1 and C4, the early components of complement pathway.
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- In the alternative complement pathway, C3 is directly cleaved to C3b
- The reaction depends on the initial activation of C3 by substances as bacterial polysaccharides, endotoxin, via pathway involving Factors B and D.
- This leads to the generation of C3bBb, the alternative pathway C3 convertase.

- Normally, this C3 convertase is labile
- More than 70% of patients with dense-deposit disease have a circulating autoantibody termed *C3 nephritic factor (C3NeF)* that binds the alternative pathway C3 convertase and protects it from inactivation

- This favors persistent C3 activation and hypocomplementemia.
- C3NeF, an antibody present in the serum of individuals with Dense deposit disease, acts at as properdin, serving to stabilize the alternative pathway C3 convertase, thus enhancing C3 activation and consumption, causing hypocomplementemia.

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Morphology

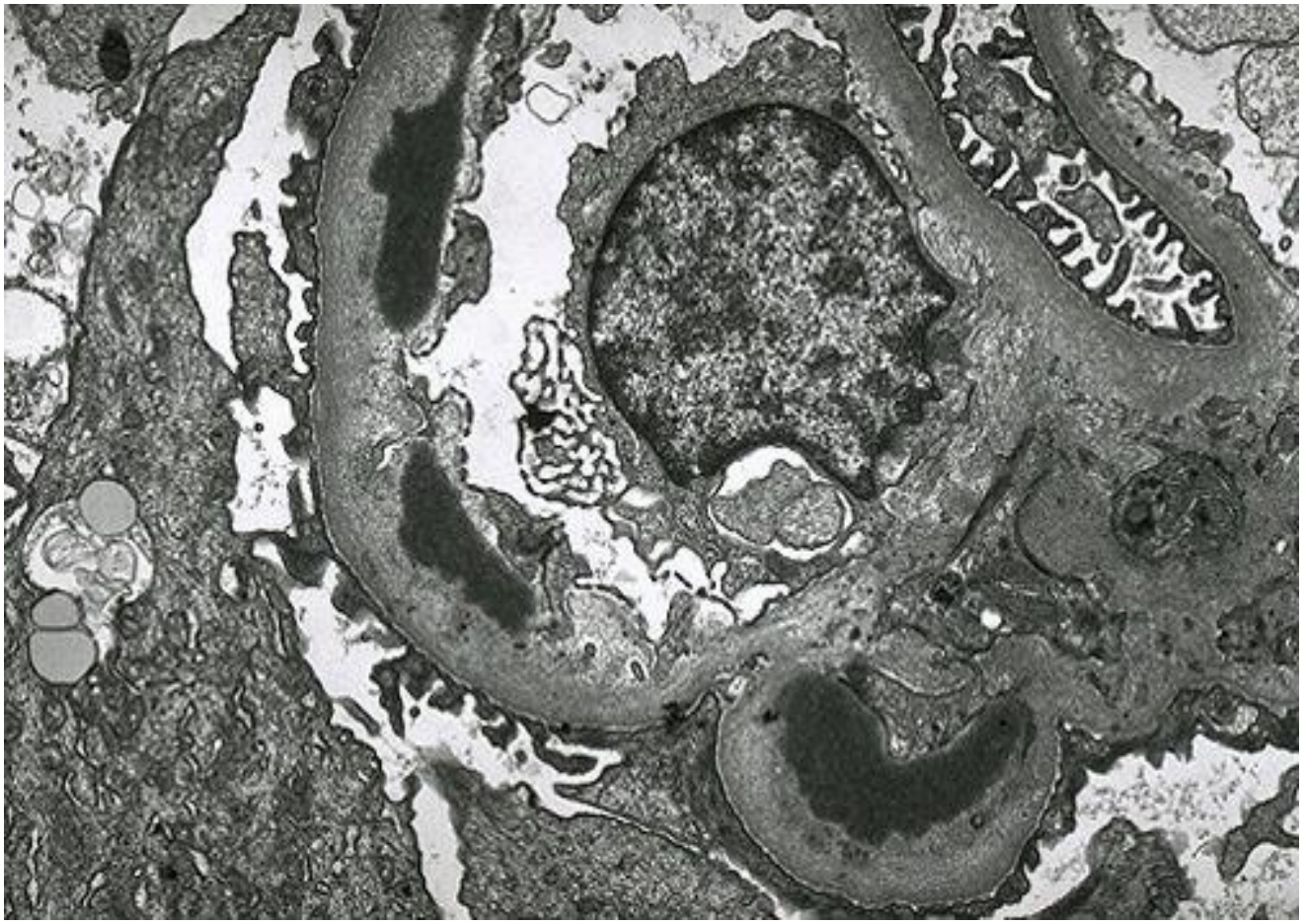
Light Microscopy:

- Most cases show histologic appearance similar to type 1

Electron microscopy:

- Permeation of the lamina densa of the GBM by a ribbon-like, homogeneous, extremely electron-dense material of unknown nature

EM of dense deposit disease



By immunofluorescence

- C3 is present in irregular granular or linear foci in the basement membranes on either side but not within the dense deposits.
- IgG is usually absent,
- C1q and C4 are absent

Clinical Features.

- Dense deposit disease primarily affects children and young adults.
- The clinical presentation

a. Nephritic syndrome with hematuria

b. And/or nephrotic syndrome with proteinuria

- The prognosis is poor, with about half of these patients progressing to end-stage renal disease.
- There is a high incidence of recurrence in transplant recipients;
- dense deposits may recur in 90% of such patients, although renal failure in the allograft is much less common.

Isolated glomerular syndromes

IGA nephropathy or Berger disease

- Characterized by presence of

1. Recurrent hematuria
2. Deposition of IgA in the mesangium
3. Is the most common type of glomerulonephritis worldwide

Pathogenesis.

- Current evidence favors a “multi-hit” etiology for this disorder involving several steps.

- IgA, the main Ig in mucosal secretions
- Is present in plasma at low concentrations, mostly in monomeric form
- The polymeric forms being catabolized in the liver.

- In patients with IgA nephropathy, levels of plasma polymeric IgA are increased, but increased production is not sufficient to cause this disease.

- In this disease , an abnormality causes aberrant glycosylation of polymeric IgA that causes increased levels of polymeric IgA in the plasma
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- A genetic influence is suggested by the occurrence of this condition in families and in HLA-identical siblings

- It is believed that in IgA nephropathy there is is a hereditary or acquired defect that leads abnnormal glycosylation of the IgA molecule) prior to their secretion by B cells.

- This aberrantly glycosylated IgA1 is either deposited by itself in glomeruli or it elicits an autoimmune response and forms immune complexes in the circulation with IgG autoantibodies directed against the abnormal IgA molecules.

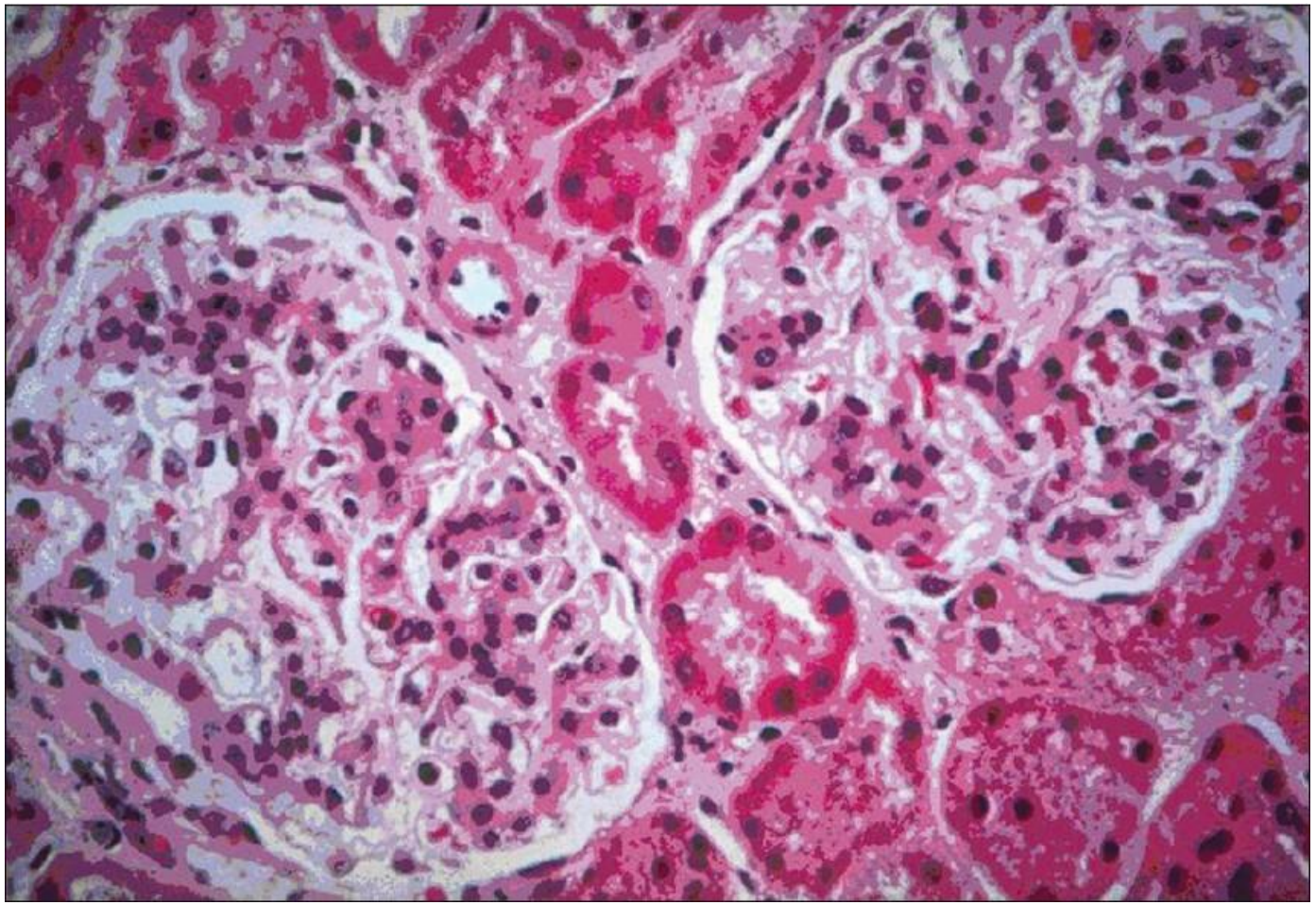
- The immune complexes are deposited in the mesangium;
- alternatively, the abnormal IgA1 is deposited in the mesangium with sub-sequent formation of immune complexes in situ.
- The mesangial immune deposits then activate mesangial cells to proliferate, produce increased amounts of extracellular matrix, and secrete numerous cytokines and growth factors.

Morphology

Light microscopy:

- The glomeruli show mesangial widening increased mesangial cells (mesangioproliferative glomerulonephritis),

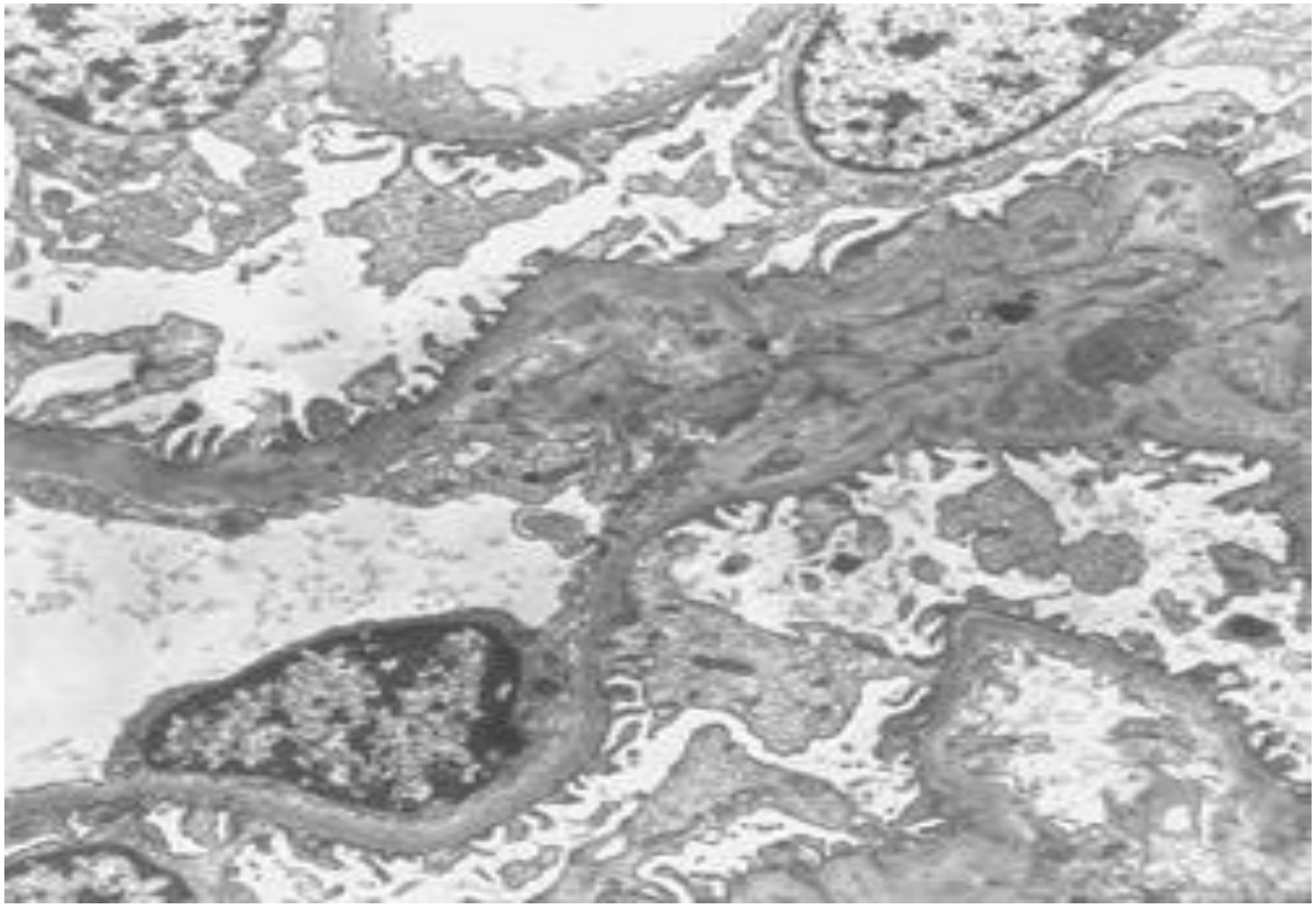
IgA nephropathy



EM:

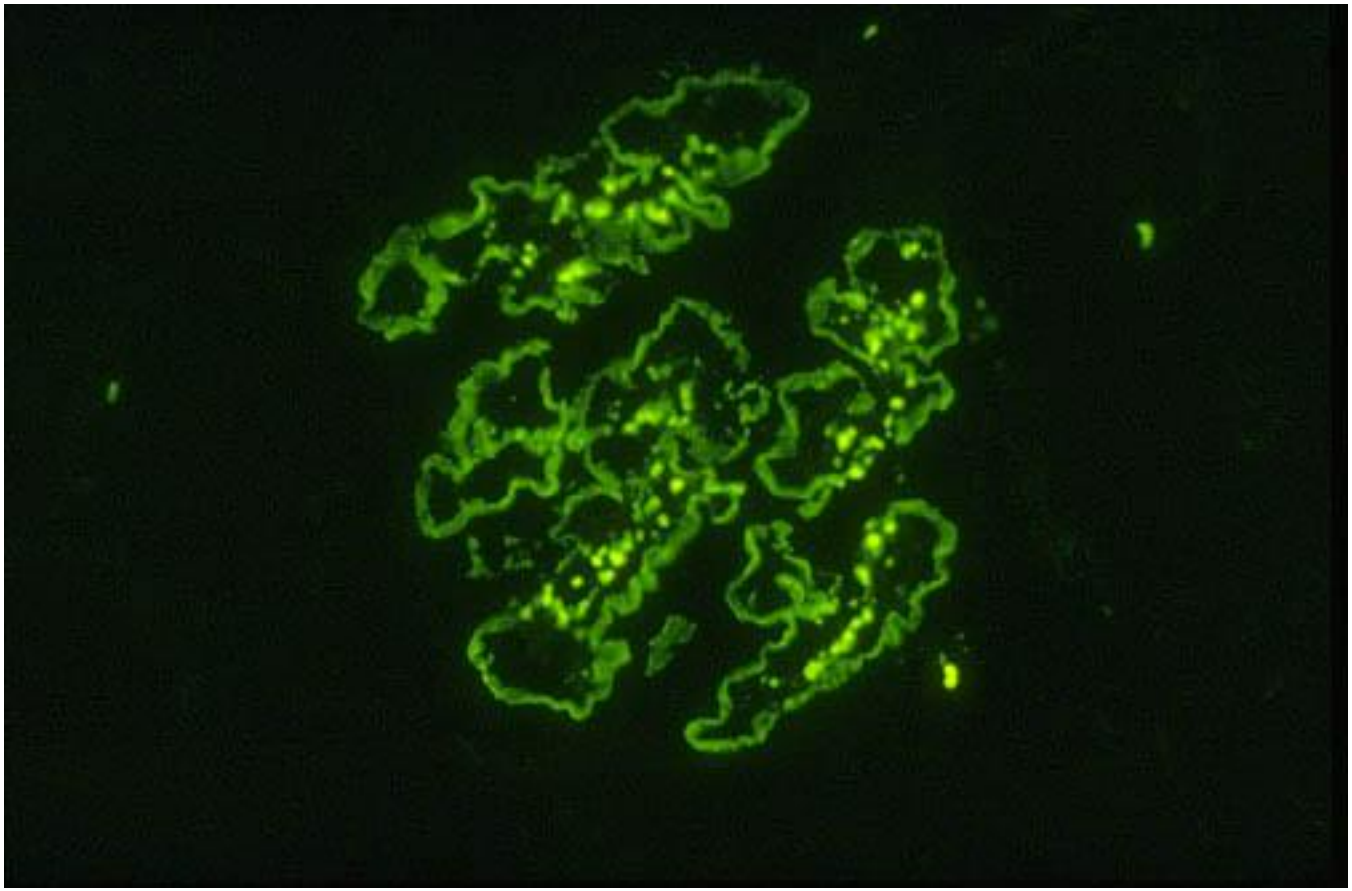
- Electron-dense deposits predominantly in the mesangium;

IgA nephropathy



- **Immunofluerescense**

- Granular deposition of IgA in the mesangium



Clinical Features.

- The disease affects people of any age, most commonly older children and young adults.
- Many patients present with gross hematuria after an infection of the respiratory or, less commonly, gastrointestinal or urinary tract;
- 30% to 40% have only microscopic hematuria, with or without proteinuria;
- 5% to 10% develop acute nephritic syndrome, including some with rapidly progressive glomerulonephritis.

- The hematuria typically lasts for several days and then subsides, only to return every few months.
- The subsequent course is highly variable.
- Many patients maintain normal renal function for decades.
- Slow progression to chronic renal failure occurs in 15% to 40% of cases over a period of 20 years.