Membranoproliferative Glomerulonephritis

• MPGN is characterized by alterations in the GBM and mesangium and by proliferation of glomerular cells.
• 5% to 10% of cases of primary nephrotic syndrome in children and adults.
• Some individuals present only with hematuria or proteinuria in the non-nephrotic range; others have a combined nephrotic-nephritic picture.

• Types of MPGN:
• 1-type I is (about 80% of cases).
• 2-type II
Type I MPGN

- circulating immune complexes similar to chronic serum sickness but the inciting antigen is not known.
- It occurs in association with:
  1- hepatitis B and C antigenemia.
  2- SLE.
  3- infected A-V shunts.
  4- extra-renal infections with persistent or episodic antigenemia.
Type II MPGN (*dense-deposit disease*)

- The fundamental abnormality appears to be *excessive complement activation* which may be caused by several mechanisms not involving antibodies.

- Some patients have an *autoantibody against C3 convertase* called *C3 nephritic factor*, which is believed to stabilize the enzyme and lead to uncontrolled cleavage of C3 and activation of the alternative complement pathway.

- Hypocomplementemia is more marked in type II due to:
  -
• **Morphology**

• **LM**

• both types of MPGN are similar.

• The glomeruli are large with an accentuated **lobular appearance** and show **proliferation of mesangial and endothelial cells** as well as infiltrating leukocytes.

• The **GBM is thickened** and the glomerular capillary wall often shows a double contour or "**tram track,**" appearance especially evident in silver or PAS stains.

• The **tram track** appearance is caused by "**splitting** of the **GBM** due to the inclusion within it of processes of mesangial and inflammatory cells extending into the peripheral capillary loops (MPGN II).
Membranoproliferative GN, showing mesangial cell proliferation, basement membrane thickening, leukocyte infiltration, and accentuation of lobular architecture.
Schematic representation of patterns in the two types of membranoproliferative GN. In type I there are subendothelial deposits; type II is characterized by intramembranous dense deposits (dense-deposit disease). In both, mesangial interposition gives the appearance of split basement membranes when viewed by light microscopy.
This silver stain demonstrates a double contour of the basement membranes ("tram-tracking") that is characteristic of MPGN (arrows).
• **IF**
  
  • C3 is deposited in an irregular granular pattern.
  
  • IgG and early complement components (C1q and C4) are often also present (immune complex pathogenesis).
  
  • **Type I MPGN** is characterized by discrete subendothelial electron-dense deposits.
  
  • "splitting" of the GBM (tram track) occurs when the mesangial cell (which has a macrophage-like function) goes after subendothelial immune deposits.
IF Granular deposition of immune complexes characteristic of circulating and in situ immune complex deposition
EM-MPGN type I a mesangial cell at the lower left that is interposing its cytoplasm at the arrow into the basement membrane leading to splitting" of the GBM (tram track).
• In **type II lesions** the lamina densa and the subendothelial space of the GBM are transformed into an irregular, ribbon-like, extremely electron-dense structure, resulting from the deposition of material of unknown composition, giving rise to the term **dense-deposit disease**.

• C3 is present in irregular chunky and segmental linear foci in the basement membranes and in the mesangium in characteristic circular aggregates (**mesangial rings**).

• IgG , C1q and C4 are usually absent.
EM-dense deposits in the basement membrane of MPGN type II. There are dark electron dense deposits within the basement membrane that often coalesce to form a ribbon-like mass of deposits (arrows)
• **Clinical Course**
• Nephrotic syndrome (in 50% of cases).
• MPGN may begin as acute nephritis or mild proteinuria.
• The prognosis of MPGN is generally poor.
• No remission.
• 40% progressed to end-stage renal failure.
• 30% had variable degrees of renal insufficiency.
• the remaining 30% had persistent nephrotic syndrome without renal failure.
• **Dense-deposit disease has a worse prognosis.**
• It tends to recur in renal transplant recipients
The Nephritic Syndrome

• Pathogenesis:

• proliferation of the cells within the glomeruli accompanied by a leukocytic infiltrate →

• injures the capillary walls permitting escape of red cells into the urine →↓ GFR →

• oliguria, reciprocal fluid retention, and azotemia.

• Hypertension is probably a result of both the fluid retention and some augmented renin release from the ischemic kidneys.
Acute Postinfectious (Poststreptococcal) Glomerulonephritis

- deposition of immune complexes resulting in diffuse proliferation and swelling of resident glomerular cells and frequent infiltration of leukocytes, especially neutrophils.
- **Exogenous antigens:**
  - 1-poststreptococcal GN.
  - 2-Infections by organisms as pneumococci and staphylococci
  - 3-infections by several common viral diseases such as mumps, measles, chickenpox, and hepatitis B and C.
- **Endogenous antigens** as occur in SLE
Poststreptococcal GN

- It develops in a child 1-4 wks after the individual recovers from a group A streptococcal infection.
- Only certain "nephritogenic" strains of $\beta$-hemolytic streptococci are capable of evoking glomerular disease.
- In most cases the initial infection is localized to the pharynx or skin.
- **LM**
  - uniformly increased cellularity of the glomerular tufts in all glomeruli ("diffuse").
  - The increased cellularity is caused both by proliferation and swelling of endothelial and mesangial cells and by a neutrophilic and monocytic infiltrate.
- Sometimes there is necrosis of the capillary walls.
- "crescents" within the urinary space in response to the severe inflammatory injury.
Post-streptococcal glomerulonephritis is due to increased numbers of epithelial, endothelial, and mesangial cells as well as neutrophils in and around the capillary loops (arrows)
• **IF**
  
  • reveals scattered **granular deposits of IgG and complement** within the **capillary walls and some mesangial areas**.
  
  • These deposits are usually cleared over a period of about 2 wks.

• **EM**
  
  • shows deposited immune complexes arrayed as **subendothelial, intramembranous**, or, most often, **subepithelial "humps"** nestled against the GBM.

• **Mesangial deposits** are also occasionally present
APGN
immune deposits are distributed in the capillary loops in a granular, bumpy pattern because of the focal nature of the deposition process.
EM-Typical electron-dense subepithelial "hump(arrow) and intramembranous deposits.

BM, basement membrane; CL, capillary lumen; E, endothelial cell; Ep, visceral epithelial cells (podocytes)
Clinical Course

- abrupt onset.
- malaise, a slight fever, nausea, and the nephritic syndrome.
- oliguria, azotemia, and hypertension are only mild to moderate.
- gross hematuria.
- Mild proteinuria.
- Serum complement levels are low during the active phase of the disease.
- ↑serum anti-streptolysin O antibody titers.
- Recovery occurs in most children in epidemic cases.
- Some children develop rapidly progressive GN due to severe injury with crescents or chronic renal disease due to secondary scarring.
- The prognosis in sporadic cases is less clear.
- In adults 15% to 50% of individuals develop end-stage renal disease over the ensuing few years or 1 to 2 decades.
- in children the prevalence of chronicity after sporadic cases of acute postinfectious GN is much lower.
IgA Nephropathy (Berger Disease)

- is one of the most common causes of recurrent microscopic or gross hematuria
- It usually affects children and young adults.
- begins as an episode of gross hematuria that occurs within 1 or 2 days of a nonspecific upper respiratory tract infection.
- the hematuria lasts several days and then subsides only to recur every few months.
- It is often associated with loin pain.
- The pathogenic hallmark is the deposition of IgA in the mesangium
• Some have considered IgA nephropathy to be a localized variant of Henoch-Schönlein purpura, also characterized by IgA deposition in the mesangium.

• Henoch-Schönlein purpura is a systemic syndrome involving the skin (purpuric rash), gastrointestinal tract (abdominal pain), joints (arthritis), and kidneys.
Pathogenesis

• 1- It is associated with an abnormality in IgA production and clearance.
• IgA is increased in 50% of patients with IgA nephropathy due to increased production in the marrow.
• circulating IgA-containing immune complexes are present in some individuals.
• A genetic influence is suggested by the occurrence of this condition in families and in HLA-identical siblings, and by the increased frequency of certain HLA and complement phenotypes in some populations
• 2-abnormality in glycosylation of the IgA immunoglobulin→ ↓ plasma clearance of IgA → deposition in the mesangium.
• 3-the absence of C1q and C4 in glomeruli points to activation of the alternative complement pathway.
• 4-increased IgA synthesis in response to respiratory or gastrointestinal exposure to environmental agents (e.g., viruses, bacteria, food proteins) may lead to deposition of IgA and IgA-Ag complexes in the mesangium, where they activate the alternative complement pathway and initiate glomerular injury.
• 5-IgA nephropathy occurs with increased frequency in individuals with celiac disease and in liver disease where there is defective hepatobiliary clearance of IgA complexes (secondary IgA nephropathy).
Morphology

• **1-focal proliferative GN**
  - The glomeruli may be normal or may show mesangial widening and segmental inflammation confined to some glomeruli.

• **2-diffuse mesangial proliferation (mesangioproliferative)**

• **3-overt crescentic GN.**

• **IF**

• *mesangial deposition of IgA* often with C3 and properdin and smaller amounts of IgG or IgM.

• Early components of the classical complement pathway are usually absent
IF demonstrates positivity with antibody to IgA. The pattern is that of mesangial staining.
• **EM**

• Electron-dense deposits in the mesangium.

• The deposits may extend to the subendothelial area of adjacent capillary walls in a minority of cases usually those with focal proliferation.
Hereditary Nephritis

• Hereditary nephritis refers to a group of hereditary glomerular diseases caused by mutations in GBM proteins.

• *Alport syndrome*, in which nephritis is accompanied by nerve deafness and various eye disorders, including lens dislocation, posterior cataracts, and corneal dystrophy.

• **Pathogenesis:**
  
  • The GBM is largely composed of type IV collagen, which is made up of heterotrimerers of \(\alpha_3\), \(\alpha_4\), and \(\alpha_5\) type IV collagen
  
  • Mutation of any one of the \(\alpha\) chains results in defective heterotrimer assembly and thus the disease manifestations of Alport syndrome.
Morphology

• Glomeruli appear unremarkable until late in the course when secondary sclerosis may occur.
• Interstitial cells take on a foamy appearance as a result of accumulation of neutral fats and mucopolysaccharides (foam cells) as a reaction to marked proteinuria.
• With progression, there is increasing glomerulosclerosis, vascular sclerosis, tubular atrophy, and interstitial fibrosis.
• EM
• the BM of glomeruli appears thin and attenuated early in the course.
• Late in the course, the GBM develops irregular foci of thickening or attenuation with pronounced splitting and lamination of the lamina densa, yielding a "basket-weave" appearance
LM-The renal tubular cells appear foamy (arrows) because of the accumulation of neutral fats and mucopolysaccharides. The glomeruli show irregular thickening and splitting of basement membranes.
thin and attenuated BM in Alport syndrome
• **Clinical Course**
  • X-linked as a result of mutation of the gene encoding α5 type IV collagen.
  • Males > females and are more likely to develop renal failure.
  • Rarely, inheritance is autosomal recessive or dominant, linked to defects in the genes that encode α3 or α4 type IV collagen.
  • presentation at age 5-20 yrs with gross or microscopic hematuria and proteinuria.
  • overt renal failure occurs between 20- 50 yrs of age
Rapidly Progressive (Crescentic) Glomerulonephritis

- RPGN is a clinical syndrome and not a specific etiologic form of GN.
- Clinically, it is characterized by rapid and progressive loss of renal function with features of the nephritic syndrome.
- With severe oliguria and if untreated death from renal failure within weeks to months.
- The histologic picture is characterized by the presence of crescents (crescentic GN).
- These are produced in part by proliferation of the parietal epithelial cells of Bowman's capsule in response to injury and in part by infiltration of monocytes and macrophages.
Pathogenesis

Primary kidney or systemic disease.
In most cases the glomerular injury is immunologically mediated.
CrGN is divided into 3 groups on the basis of immunologic findings.
Type I (Anti-GBM Antibody):
(12%)
linear deposits of IgG and, C3 on the GBM.
The anti-GBM antibodies also bind to pulmonary alveolar capillary basement membranes to produce the clinical picture of pulmonary hemorrhages associated with renal failure (Goodpasture).
Anti-GBM antibodies are present in the serum and are helpful in diagnosis.
Plasmapheresis which removes pathogenic antibodies from the circulation is beneficial.
• **Type II (Immune Complex) (44%)**:  
  - Idiopathic  
  - Postinfectious/infection related  
  - Systemic lupus erythematosus (SLE)  
  - Henoch-Schönlein purpura/IgA nephropathy  
• **Type III (Pauci-Immune) ANCA Associated (44%)**:  
  - Idiopathic  
  - Wegener granulomatosis  
  - Microscopic angiitis  
• **LM**  
  - Glomeruli show segmental necrosis and GBM breaks with resulting proliferation of the parietal epithelial cells in response to the exudation of plasma proteins (fibrinogen) into Bowman's space.  
  - These distinctive lesions of proliferation are called **crescents** due to their shape as they fill Bowman's space.
Crescentic GN (PAS stain). The collapsed glomerular tufts and the crescent-shaped mass of proliferating cells and leukocytes internal to Bowman's capsule.
IF micrograph of a glomerulus CGN demonstrates positivity with antibody to fibrinogen.
• **IF**
  • strong *linear staining* of deposited IgG and C3 along the GBM *Type I (Anti-GBM Antibody)*.

• **EM**
  • deposits are not visualized because the endogenous collagen IV antigen to which the antibody is reacting is diffusely distributed, and so the large lattices of antigens and antibodies that occur in deposited immune complexes are not formed.
  
• distinct ruptures in the GBM may be seen.
Pauci-Immune (Type III) Crescentic Glomerulonephritis

- It is defined by the lack of anti-GBM antibodies or significant immune complex deposition detectable by IF and EM.
- Most of these individuals have antineutrophil cytoplasmic antibodies in the serum (ANCA).
- Type III CrGN is a component of a systemic vasculitis such as microscopic polyangiitis or Wegener granulomatosis.
- When pauci-immune CrGN is limited to the kidney it is called idiopathic.
- IF& EM for immunoglobulin and complement are negative and there are no deposits detectable by electron microscopy.
Clinical Course

• The onset of RPGN is by *nephritic syndrome* except that the oliguria and azotemia are more pronounced.

• Proteinuria sometimes approaching nephrotic range may occur.

• Some of these persons become anuric and require long-term dialysis or transplantation.

• The prognosis can be roughly related to the number of crescents.

• When No. of crescents in less than 80% of the glomeruli have a better prognosis than those with higher percentages of crescents
Chronic Glomerulonephritis

- It is an important cause of end-stage renal disease presenting as chronic renal failure.
- Among all individuals who require chronic hemodialysis or renal transplantation, 30% to 50% have the diagnosis of chronic GN.
- It probably represents the end stage of a variety of entities:
  - 1-CrGNs.
  - 2-FSGS.
  - 3-MGN.
  - 4-IgA nephropathy.
  - 5-MPGN.
  - 6-Idiopathic (20% of cases).
Morphology

- Classically, the kidneys are symmetrically contracted.
- LM
- Scarring of the glomeruli (obliteration of the glomeruli).
- Marked interstitial fibrosis; tubular atrophy
- Small and medium-sized arteries are frequently thick walled, with narrowed lumina, secondary to hypertension.
- Lymphocytic and plasma cells are present in the fibrotic interstitial tissue.
- The markedly damaged kidneys are designated end-stage kidneys
Chronic GN.
A MT stain shows complete replacement of virtually all glomeruli by blue-staining collagen.