النادي الطبي

GENITOURINARY SYSTEM

SUBJECT : Pathology

LEC NO. : Three - part 2

DONE BY : ~~Johainah Taha - Areej Alqassem -~~ Fatima Abu Alasal

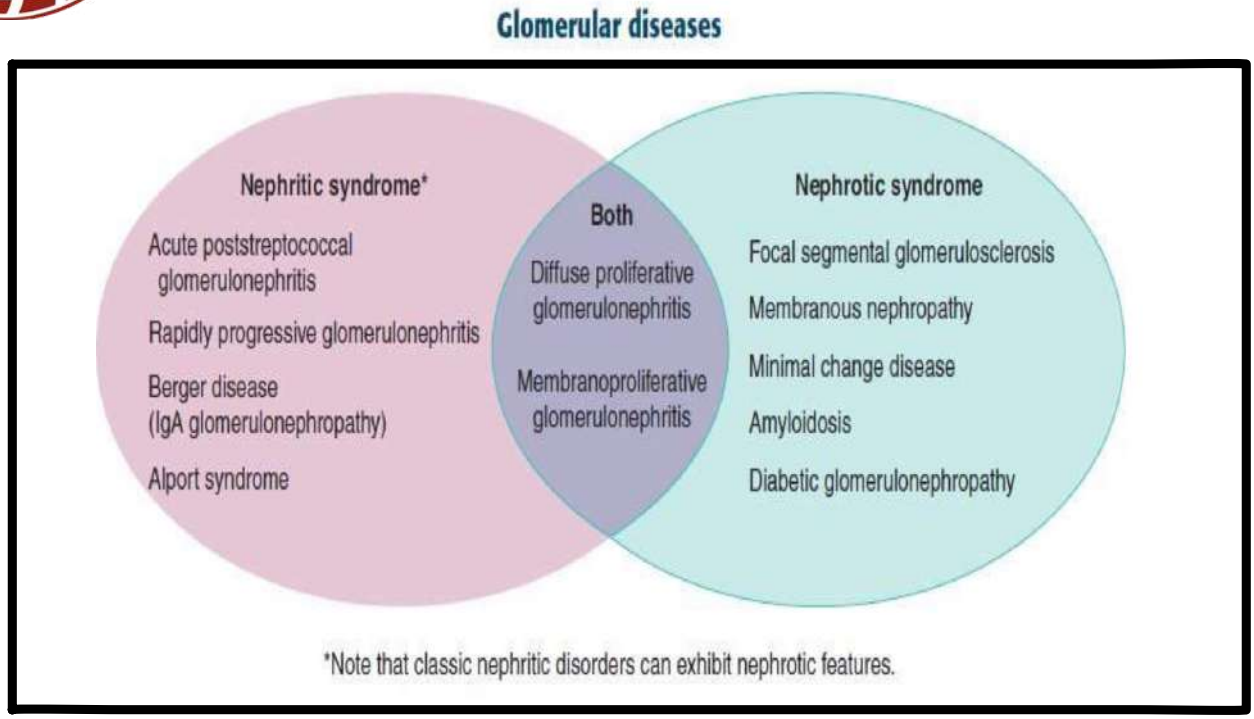
وَقُل رَّبِّ زِدْنِي عِلْمًا

Objectives

- Clinical manifestation of kidney disease
- understand the terminology of Renal diseases
- Discussion of Glomerular disease
- Nephrotic syndrome
- Nephritic syndrome
- Disease of blood vessels
- Urinary tract infection
- Analgesic nephropathy
- Acute Tubular Necrosis
- Hemolytic Uremic Syndrome
- Urolithiasis and hydronephrosis
- Renal Tumours RCC
- Bladder Tumours

موضوع محاضرة اليوم

تذكير اي شي بالاحمر فهو شرح خارجي، اي شي بالاخضر فهو ملاحظات الدكتورة❤️

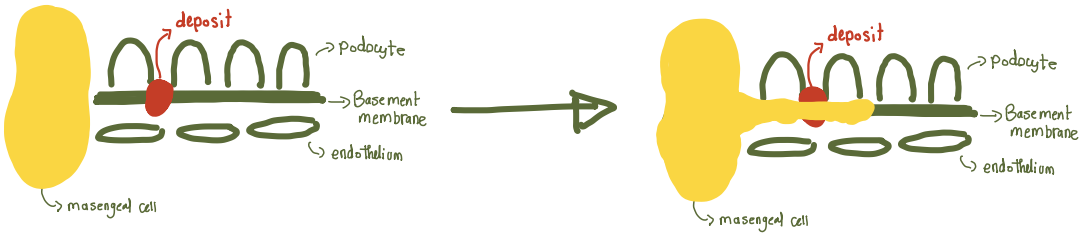


عشان نكون عارفين وين احنا، المرة الماضية درسنا عن **nephrotic diseases** و اليوم حنبلش بمرض بصير بال**nephrotic** و ال **nephritic**

4- membranoproliferative glomerulonephritis:

Membrano = thickening of the capillary membrane due to immune complex depositions.
Proliferative = masengeal cell proliferation (masengeal cells provide structural support to the glomerular tuft).

ركزوا هسا عالرسمة و الشرح الي بدي احكيه لانو مهم و بحبوه باسئلة البورد



هسا الي بصير هون انه ال**M cells** حتبدأ تعمل **proliferation** عبر ال**cytoplasm** لغاية ما توصل لنص ال**deposit** الي هو اصلا عبارة عن **immune comlex**، لما توصله حتقسمه لقسمين و كأنها كسرته بتعرفوا بشبهها بمين؟ جذور النباتات لما تكسر الصخور في الارض ✅
المهم هسا الشكل الي حينتج عنا هو خطين بنسميهم **tram track appearance** مهم جدا جدا و بحبوه بأسئلة البورد و يعتبر شي مميز جدا لهاد المرض

GENITOURINARY SYSTEM

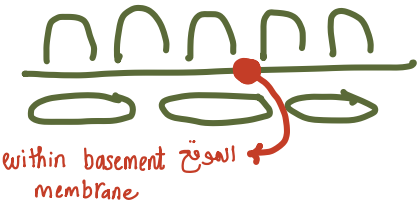
-Thick capillary membranes on H&E, often with 'tram-track' appearance
-Due to immune complex deposition (granular IF)
-Divided into two types based on location of deposits:

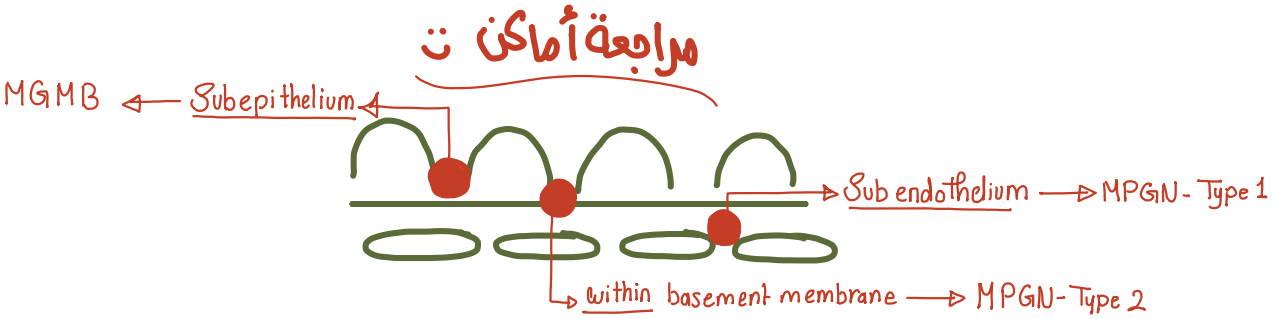
Type I

*subendothelial
*associated with HBV and HCV
*more often associated with tram-track

Type II

*intramembranous
*associated with C3 nephritic factor





طيب خلينا شوي نشرح فكرة C3 و شو علاقة type 2 فيها
لو بتتذكروا الcomplement system فكنا حكينا انه الC3 عن طريق انزيم C3 convertase بتعطينا C3A + C3B
هدول المرضى حيكون عندهم antibody ضد هاد الانزيم الي اسمه C3 convertase، فحيربط فيه و يعمل اله stablizing و blocking لهيك C3 ما حاكون قادرة اكسرها مما يؤدي الى overactivation الها و ايضا نقصان بالC3 serum و بالتالي inflamation و damage
و هاد ال autoantibody عند هدول المرضى بنسميه C3 nephritic factor

يلا ننتقل عالسلايدات...

وقل رب زدني علماً

Membranoproliferative GN(MPGN)

- Membranoproliferative glomerulonephritis (MPGN) **is a pattern of glomerular injury on kidney biopsy with characteristic light microscopic changes, including hypercellularity and thickening of the glomerular basement membrane (GBM). MPGN is a histologic lesion and not a specific disease entity.**
- Also called **hypocomplementemic**, lobular or mesangiocapillary glomerulonephritis
- Histologic lesion, not a specific disease entity
- MPGN should be diagnosed with **specific etiology or underlying cause (such** as C3GN, immune complex mediated, monoclonal), **not as types I - III**

بنعتبر هاد المرض **complicated** لانه ممكن يكون **nephrotic** او **nephritic** و ركزوا عالامور الي ركزتلكم عليها الدكتور (أي شي قرأته حيكون هايلايت باللون الاصفر و الشي المهم جدا باللون الاخضر)
بهاد المرض حيصير عنا **hypercellularity** في **masengeal cell** و**endothelial cell**
الله **types 3** حسب ال**morphologic changes** الي تصير بال**glomeruli**، بس هسا صار التصنيف حسب **pathogenesis** و ال**cause**، و الي معظم اسبابها بتكون **immune complex** او **monoclonal**

Essential features:

- A morphologic pattern of glomerular injury, characterized by endocapillary and mesangial hypercellularity, mesangial and subendothelial deposits and duplicating of glomerular basement membrane.
- Idiopathic membranoproliferative glomerulonephritis (MPGN) thought to be a diagnosis of exclusion

هسا هون حيصير عنا **subendothelial deposition** حتيجي ال **mesangial cell** و تمتد بين ال**endothelium** و ال **basement membrane** و لهذا حيصير عنا **thickening** لل **basement membrane**

Clinical features

- Either immunoglobulin (polyclonal or monoclonal) mediated or complement mediated.
- **Immunoglobulin mediated:** due to infections, autoimmune diseases, paraproteinemias
- **Complement mediated:** dysregulation of alternative pathway due to genetic or acquired abnormalities in regulatory factors
- Traditional classification based on electron microscopy findings: MPGN type I (subendothelial and mesangial deposits), MPGN II (intramembranous dense ribbon-like deposits) and MPGN III (subendothelial and subepithelial deposits)

- Newer classification based on immunofluorescence emphasizing pathophysiology: Immune complex / monoclonal immunoglobulin mediated MPGN (activation of classic complement pathway) and C3 glomerulopathies (including dense deposit disease, C3 glomerulonephritis and CFHR5 nephropathy, activation of alternate complement pathway)
- MPGN lesion due to immune complex now referred to simply as MPGN
- Poor prognostic signs including nephrotic syndrome, an elevated serum creatinine and hypertension at presentation, crescents and tubulointerstitial disease on biopsy

2 3

اذا التصنيف الجديد بيعتمد على السبب، يا immune complex deposition يا وجود C3 nephrotic factor
الاصل انه احنا هسا فاهمينهم لانو انشرحوا فوق

Pathogenesis of MPGN:

- ❑ Different pathogenic mechanisms are involved in the development of MPGN.
- ❑ Most cases of type I MPGN are caused by **circulating immune complexes, but** the inciting Ag is not known.
- ❑ Like many other GNs, type I MPGN may also occur in association with other known disorders (**secondary MPGN),such as SLE, hepatitis B & C, chronic liver disease or infected A-V shunt**

***Different pathogenic mechanisms are involved in the development of MPGN either :**
1- Immunoglobulin mediated, due to infections, autoimmune diseases, paraproteinemia.
2- Complement mediated: dysregulation of alternative pathway due to genetic or acquired abnormalities in regulatory factors

GENITOURINARY SYSTEM

كثير مهمة الصفحة

Very important

Type I: classical

- MPGN pattern of injury with discrete subendothelial and mesangial electron dense deposits

Mostly immune complex deposition indicating activation of classic complement pathway and some alternative complement pathway (overlaps with C3 glomerulonephritis)

- Distinguished from new category of C3 glomerulopathies by prominent Ig or C1q

Primary MPGN mostly affecting adolescents and young adults.

- > 50% with nephrotic syndrome
- 10 - 20% with acute nephritis syndrome
- ~50% with low C3
- May be secondary to chronic infections (e.g. hepatitis C), autoimmune diseases (e.g. SLE), paraproteinemias, alpha-1-antitrypsin deficiency and malignancies
- ~50% renal survival at 10 years
- Recurs in ~30% of children 6 - 12 months after transplantation
- MPGN due to a monoclonal gammopathy or complement mediated disease with a higher risk of graft recurrence than immune complex mediated MPGN secondary to infection or autoimmune disease

Membranoproliferative Glomerulonephritis (MPGN), when caused by a monoclonal gammopathy or complement-mediated disease, carries a higher risk of recurrence after a kidney transplant compared to MPGN caused by immune complex-mediated factors like infection or autoimmune diseases. The underlying monoclonal gammopathy or complement-related issues contribute to a more challenging post-transplant scenario for individuals with MPGN.

Very important

Type II MPGN (dense-deposit disease)

- Essential diagnostic feature based on the presence of highly electron dense ribbon-like deposits of the glomerular basement membrane
  Now categorized under C3 glomerulopathies
- **Cause: excessive complement activation**
- **autoantibody against C3 convertase called C3 nephritic factor (it stabilizes the enzyme and lead to uncontrolled cleavage of C3 and activation of the alternative complement pathway).**
- **Result: Hypocomplementemia;**
- **Can be acquired by infections or monoclonal paraprotein**
- **Average age at diagnosis: 14 years**
- **Typically present with renal insufficiency, nearly all with hematuria and 33% with nephrotic syndrome**
- **Also deposits in basement membranes of spleen, choroid and retina**
- **Poorer prognosis than type I; 50% have renal failure in 10 years; 80 - 100% recur after renal transplant**

الي عليهم اخضر كثير مهمين و شرحناهم فوق

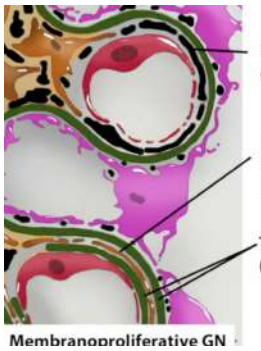
و الdeposition هاي مو بس بتكون بالkidney ممكن برضه تكون بالspleen و ال retina

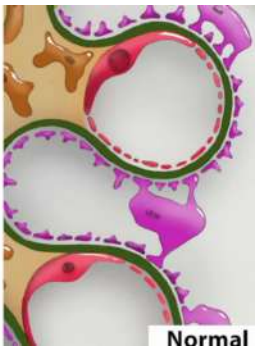
وقل رب زدني علماً

GENITOURINARY SYSTEM

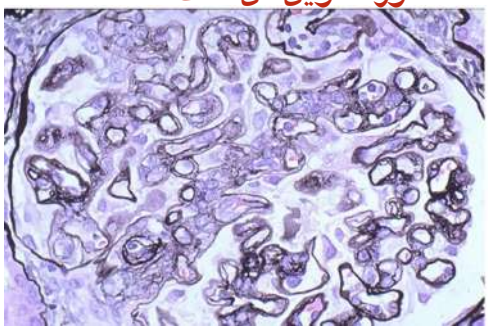
❖ **Morphology**

- ❑ **Light Microscope**
- ❑ Both types of MPGN are similar by LM.
- ❑ Glomeruli are large with accentuated **lobular appearance** and show **proliferation of mesangial and endothelial cells** as well as infiltrating leukocytes.
- ❑ (Mesangial and endocapillary hypercellularity with lobular accentuation),Irregular thickening of glomerular basement membrane by interposition of mesangial cells between endothelium and basement membrane, Forming double contour / tram track appearance (PAS or silver stain)
- ❑ Crescents in ~20% cases
- ❑ Neutrophils (exudate) may present
- ❑ May have immune complex aggregates forming hyaline thrombi in capillary lumina
- ❑ The **tram track** appearance is caused by "**splitting**" **of the GBM** due to the inclusion within it of processes of mesangial & inflammatory cells extending into the peripheral capillary loops.

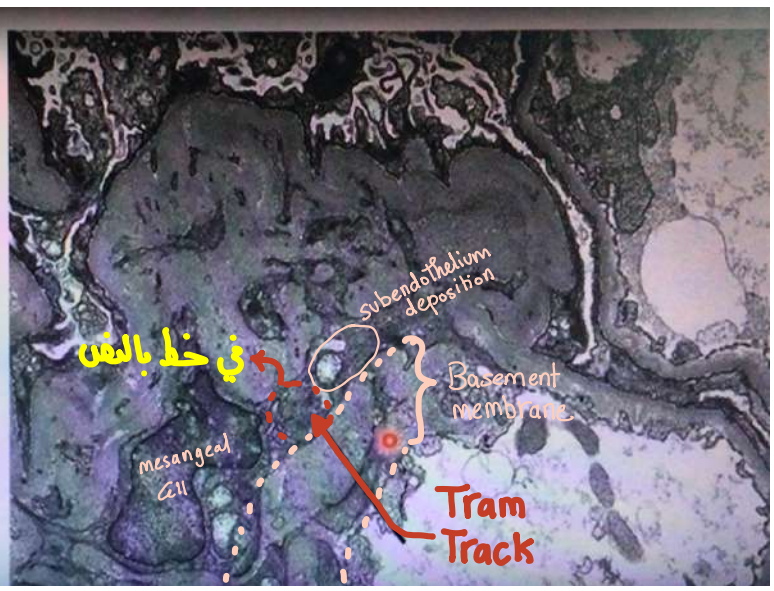




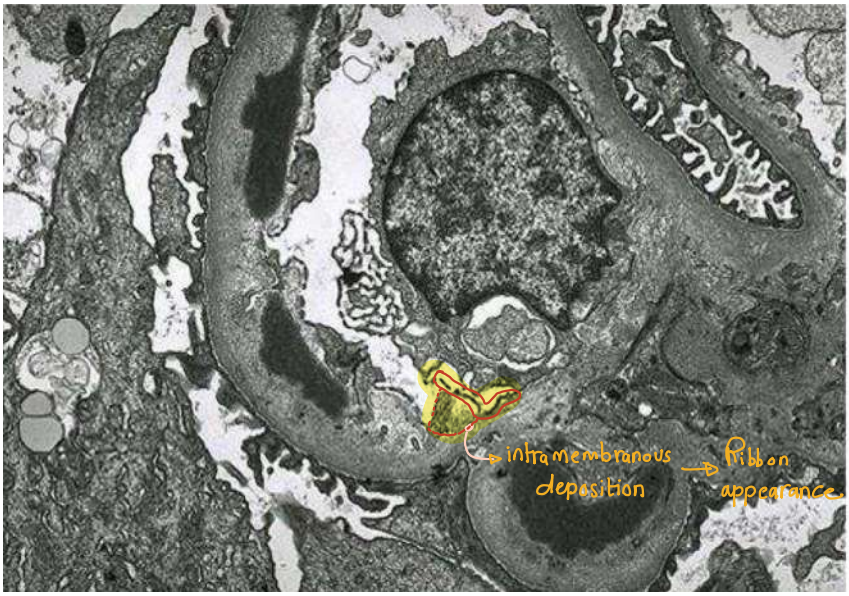
صور حلوين من النت



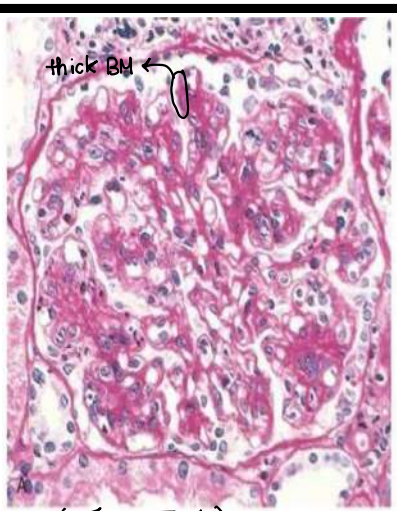
- ❑ This electron micrograph demonstrates a mesangial cell at the lower left that is interposing its cytoplasm at the arrow into the basement membrane, leading to splitting and reduplication of basement membrane that is piled up above the mesangial cytoplasm in this micrograph.
- ❑ This is MPGN. These characteristic EM changes occur when the mesangial cell (which has a macrophage-like function) goes after subendothelial immune deposits, but makes a mess of the basement membrane in the process.



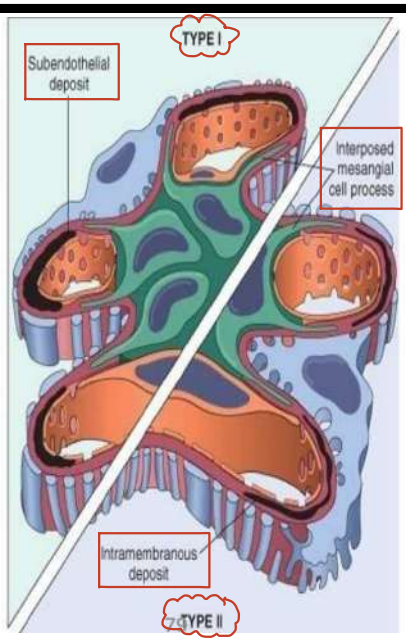
وقل رب زدني علماً



- The electron micrograph above demonstrates dense deposits in the basement membrane typical for dense deposit disease.
- **These dark electron dense deposits within the basement membrane often coalesce to form a ribbon-like mass of deposits, as seen in the electron micrograph below.**

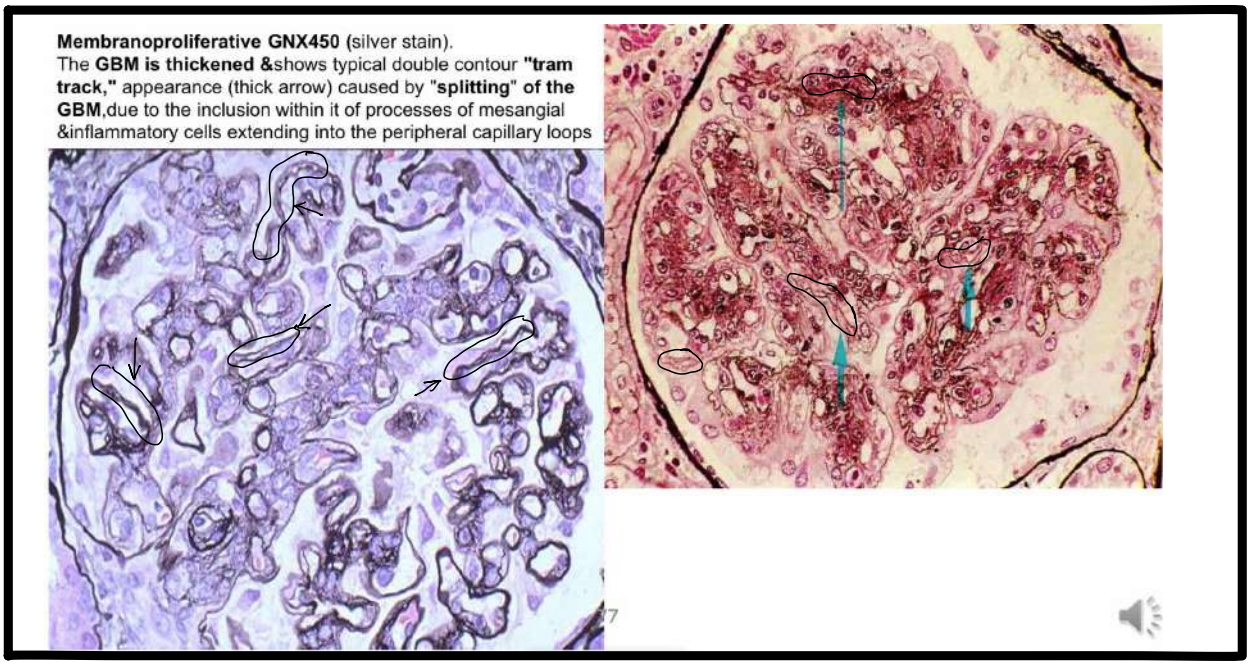


(Tram-Track)
بتحسوا وكأنه BM مقطع بالنص



A, MPGN, showing BM thickening, WBC infiltration, mesangial cell proliferation, & lobular architecture accentuation.
B, Schematic representation of patterns in the two MPGN types
★In **type I,**there are **subendothelial** deposits;
★**type II** is characterized by **intramembranous dense deposits**(dense-deposit disease).
In both types I&II, mesangia interposition gives the appearance of split BM when viewed by light microscopy.

Very important

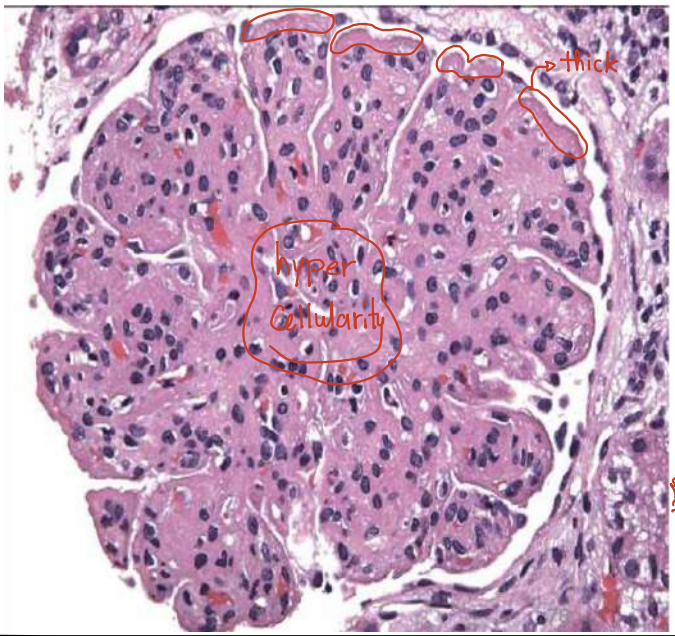


- **Types I & II have different ultrastructural & immunofluorescence microscopic features.**
- **Type I MPGN** is characterized by discrete **subendothelial electron-dense deposits**.
  - By immunofluorescence M, **C3** is deposited in an **irregular granular pattern, & IgG** & early complement components (C1q & C4) are often also present, indicative of an immune complex pathogenesis.
- **Type II MPGN-C3 alone in GBM**
  - In **type II lesions** the lamina densa & 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 & segmental linear foci in the BMs & in the mesangium but the IgG & the early components of the classical complement pathway (C1q & C4) are usually **absent**.

Clinical Course

- ❑ Clinically, 50% of MPGN cases presented with **nephrotic syndrome**, although it may begin as acute nephritis or mild proteinuria.
- ❑ prognosis poor.
- ❑ No remission.
- ❑ 40% progress to end-stage renal failure.

- ❑ 30% had variable degrees of renal insufficiency. the remaining 30% had persistent nephrotic syndrome without RF.
- ❑ **Dense-deposit disease (type II) has a worse prognosis.**
- ❑ **It tends to recur in renal transplant recipients**

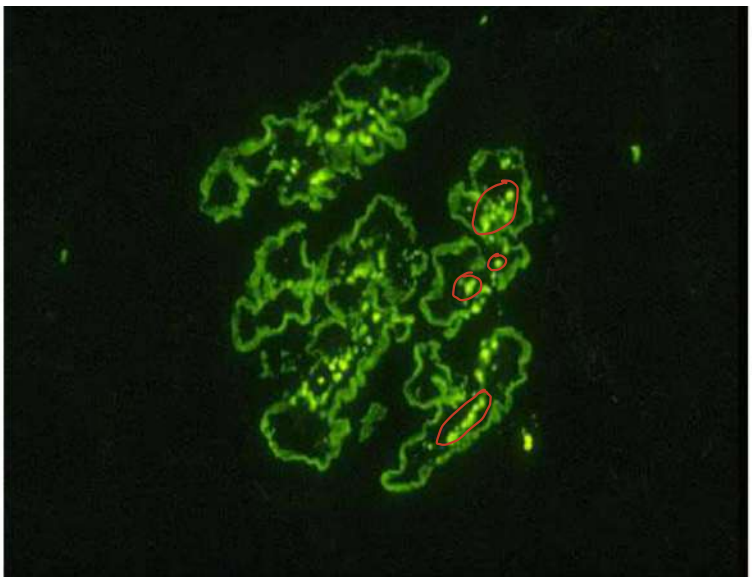


- **Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury on kidney biopsy with characteristic light microscopic changes, including hypercellularity and thickening of the glomerular basement membrane (GBM).**
- MPGN is a histologic lesion and **not** a specific disease entity. As such, the discovery of the lesion of MPGN in a kidney biopsy is the start of an exploratory process leading to a diagnosis, not an end in itself.
- **Q:What serologic test is often positive with MPGN?**
- **Answer C3 Nephritic factor (C3NeF) it is an autoantibody directed into C3 convertase and found in MPGN when there is hypocomplementemia**

وقل رب زدني علماً

Very important

مهم جدا نقارن بينهم



- The bright deposits scattered along capillary walls and in the mesangium by immunofluorescence microscopy with antibody to complement component C3 are typical for dense deposit disease (formerly called membranoproliferative glomerulonephritis, type II). Dense deposit disease produces a nephritic syndrome.
- Most patients have detectable circulating C3 nephritic factor, an IgG autoantibody.

Regarding renal biopsy examination Tram track appearance is a characteristic feature of:

a) Membranoproliferative GN
b) Membranous nephropathy
c) Focal segmental glomerulosclerosis
d) Crescentic GN

. Regarding renal biopsy EM examination Subendothelial immune-complex deposits is a characteristic feature of:

a) Membranoproliferative GN
b) Membranous nephropathy
c) Focal segmental glomerulosclerosis
d) Crescentic GN