PATHOLOGY TEAM 436

MEDICINE
KING SAUD UNIVERSITY

Nephrotic Syndromes

Revised by
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Objectives:

1. Recognize the five-major renal clinical syndromes.
2. Describe the main differential pathological diagnosis for each syndrome.
3. Perform a clinico-pathological correlation.
4. Describe the patterns of injury of each syndrome.

Black: Doctor's slides.
Red: important!
Green: Doctor's notes.
Grey: Extra.
Purple: Female's slides.
Blue: Male's slides.

Glomerular diseases:

- A biopsy is a must for diagnosis; unlike UTIs.
- Proteinuria occurs if and only if there is an effacement of podocyte.
- No hematuria or hypertension in nephrotic syndrome.
- nephrotic patients are prone to infection (protein loss).

https://www.youtube.com/watch?v=iAQkxTwnDWQ

Nephrotic syndrome:

Includes a group of conditions characterized by increased basement membrane permeability, permitting[1] the urinary loss of plasma proteins, particularly low-weight proteins such as albumin.

Clinical manifestations:

In all diverse causes of the nephrotic syndrome there is a **derangement**[2] in the capillary walls of the glomeruli that results in **increased** permeability to **plasma proteins** → allows protein to escape from the plasma into the **glomerular filtrate** →extremely **heavy proteinuria,** serum albumin is decreased→ **hypoalbuminemia** and a **drop in plasma colloid osmotic pressure**. → Increased release of **renin** from renal juxtaglomerular cells → Renin in turn stimulates the angiotensin-aldosterone axis→ promotes the retention of salt and water by the kidney. At the onset, **there is little or no: azotemia, hematuria, or hypertension**.

- **Heavy proteinuria** = proteins in urine = loss of 3,5 g/day
- Not accompanied by increased urinary **red cells or white cells. (No increased cells or no cells)**
- **Hypoalbuminemia** is often marked by Serum concentration of less than 3g/100 ML
- **Generalized edema** results from decreased **plasma colloid or oncotic pressure.** 'swelling eye'
- **Hyperlipidemia and hypercholesterolemia** are caused by increased hepatic lipoprotein synthesis. (fatty casts)
- Hypocalcemea.

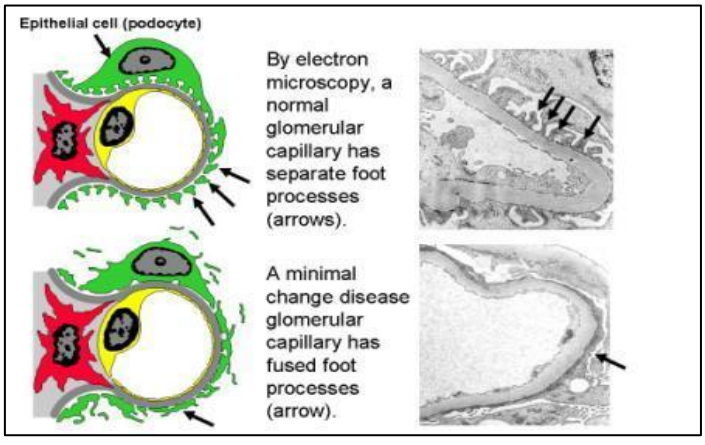
Nephrotic syndrome can be caused intrinsically by:

1-minimal change disease. 2-FSGS. 3-membranous glomerulonephritis.

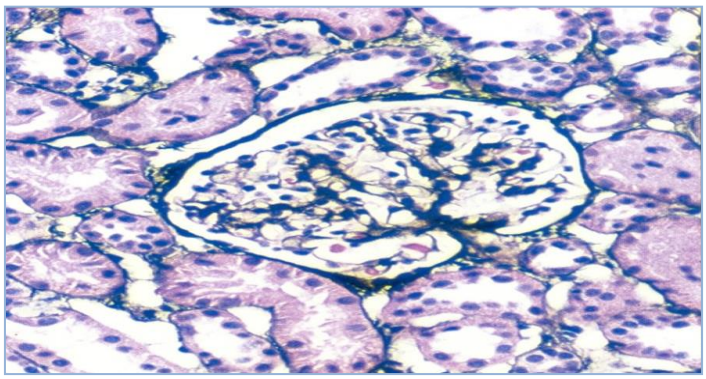
https://www.youtube.com/watch?v=4Y4PWTXjyEc

1. Minimal change GN (lipoid nephrosis):

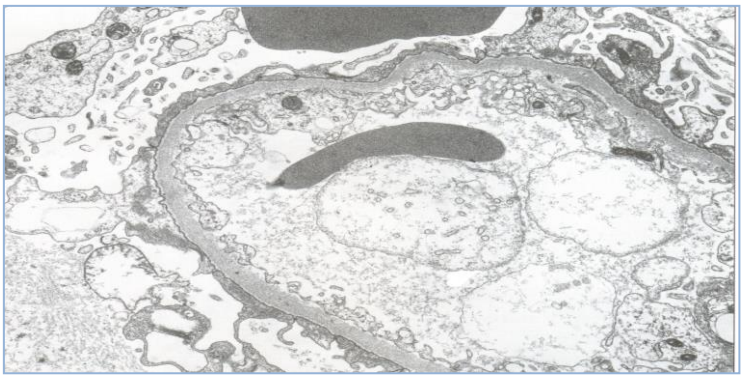
- Most common cause of nephrotic syndrome in **children** most commonly between the ages of 1 – 7 yrs.
- Light microscopy (LM) → **normal-appearing glomeruli.**
- **Electron microscopy (EM)** → normal except for the diffuse (effacement of epithelial foot processes* [3]) *it presents in all Nephrotic syndromes.
- **Immunofluorescence[4](IF)** → normal
- Most often this condition responds well to corticosteroid therapy. *More than 90% of children*
- The protein loss usually is confined to the smaller plasma proteins, chiefly *albumin* (selective proteinuria).



[1] To allow
[2] A disturbance (اختلال) of the regular order or arrangement.
[3] a podocyte reaction to injury or damage characterized by flattening of foot processes while the frequency of filtration slits is reduced, giving the appearance of a continuous cytoplasmic sheet covering the glomerular basement membrane.
[4] Antibodies tagged (labeled) with fluorochrome are used to localize.



Glomeruli appear unremarkable by light microscopy, and in young patients there is no tubulionterstial fibrosis, as in this patient.

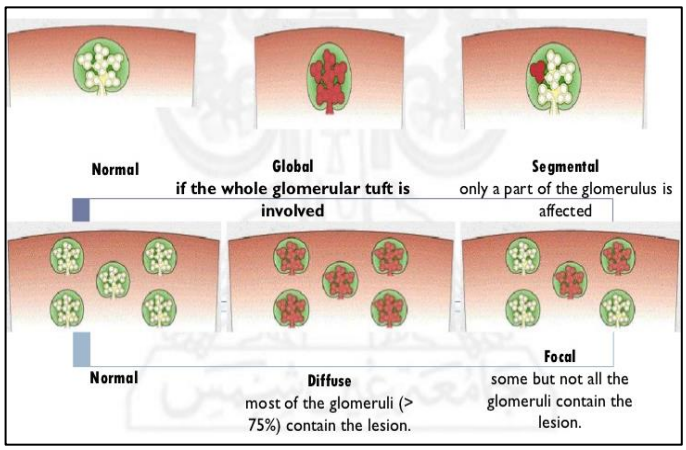


Extensive foot process effacement (lost) and microvillous transformation of visceral epithelial cells

2. Focal segmental glomerulosclerosis(FSGS):

https://www.youtube.com/watch?v=l7ZyAmGA98w&index=8&list=PLY33uf2n4e6P2hFA1_fxu-4IeTIDvwoDP

It's characterized histologically by **sclerosis**[5] affecting some glomeruli (**focal involvement**) and involving only segments of each affected glomerulus (**segmental involvement**).



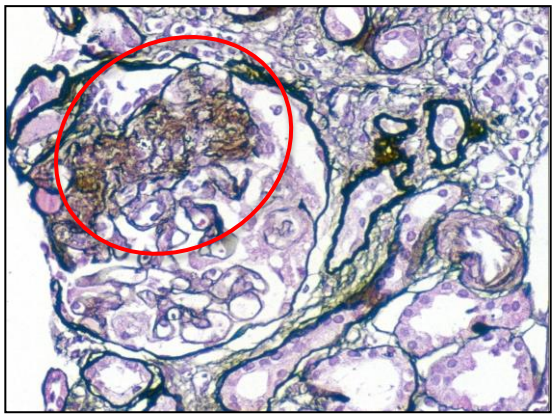
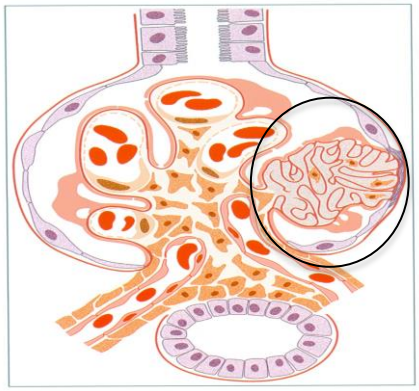
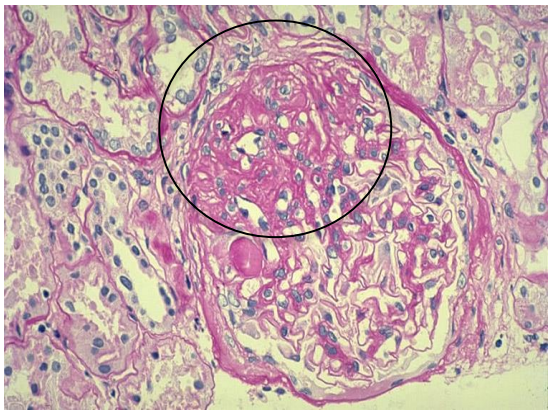
- **Injury to the podocytes is thought to represent the initiating event of primary FSGS.**
- Proteinuria is **nonselective**; and in general, the response to corticosteroid therapy is poor.

- **FSGS may be primary (idiopathic) or secondary to one of the following conditions:**
  - In association with **other conditions,** such as HIV nephropathy or heroin nephropathy.
  - As a secondary event in **other forms of GN** (e.g., **IgA nephropathy**).
  - As a maladaptation[6] to **nephron loss**.
  - In inherited or congenital forms. Autosomal dominant forms are associated with mutations in **cytoskeletal proteins and podocin**[7], both of which are required for the **integrity of podocytes**. In addition, a sequence variant in the apolipoprotein L1 gene (APOL1) on **chromosome 22** appears to be strongly associated with an increased risk of FSGS and renal failure in individuals of African descent.
- No immune complex deposits, Negative Immunofluorescence (normal).
- The typical segmental sclerotic lesion in FSGS is characterized by:

1- Obliteration of capillary loops.
2- Increased mesangial matrix, **without** deposits and with *Diffuse foot process effacement* by EM.
3- Deposition of Hyaline masses (**Hyalinosis**).
4- Lipid droplets.
5- Focal Deposition of IgM and complement are seen in IF.

- FSGS Initially affects Juxta-Medullary Glomeruli. In progression of the disease leads to global sclerosis of the glomeruli with pronounced tubular atrophy and interstitial firosis.

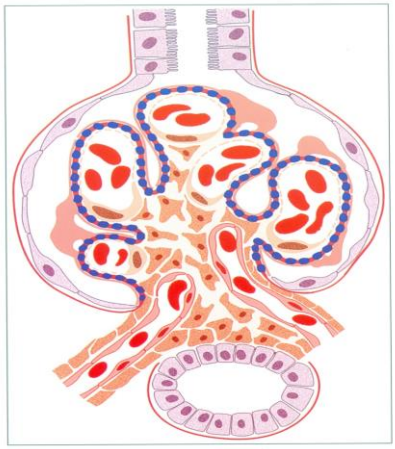
[5] Haedening of the tissue.
[6] سوء تكيّف
[7] is a protein component of the filtration slits of podocytes

- **collapsing glomerulopathy:** It is characterized by collapse of the glomerular tuft and podocyte hyperplasia. This is a more severe manifestation of FSGS that may be idiopathic or associated with HIV infection, drug-induced toxicities, and some microvascular injuries.

3. Membranous Nephropathy or glomerulonephritis:

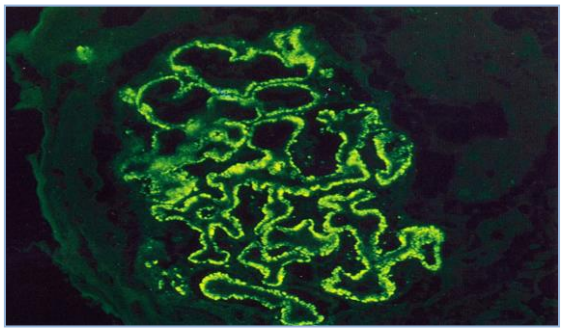
https://www.youtube.com/watch?v=zucxZw069kw&list=PLY33uf2n4e6P2hFA1_fxu-4IeTIDvwoDP&index=9



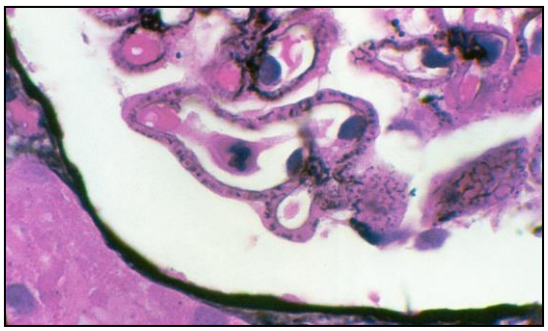
- An immune complex disease of an unknown etiology. Which is immune response against phospholipase A_2.
- It is a slowly progressive disease, characterized morphologically by the presence of subepithelial immunoglobulin-containing deposits along the GBM[8].
- Most common cause of Nephrotic Syndrome in Adults between 30-60 years old.

- **LM:**glomeruli may appear **normal** especially in early stage of the disease, but in severe cases we will see diffuse thickening of the **capillary** wall by the same method.
- **EM:** we can see subepithelial deposits which is the cause of thickening of the capillary wall. The subepithelial deposits is separated by small ***spike-like protrusion of GBM matrix***. 'spike and dome pattern' Dome = immune complex. Spikes: basement membrane.
- The spikes are formed as a reaction to the deposits, which can be visualized by silver stain.
  EM: spikes = white. Deposits = dark. Deposits Don't stain with silver 'not appears'.
- In about 85% of cases, membranous nephropathy is caused by autoantibodies that cross-react with antigens expressed by podocytes. In the remainder (secondary membranous nephropathy), it occurs secondary to other disorders, including:
  - Infection (chronic hepatitis B, syphilis, malaria).
  - Malignant tumors, particularly carcinoma of the lung, colon, and melanoma.
  - Systemic lupus erythematosus. Class 5
  - Exposure to inorganic salts (gold, mercury).
  - some drugs (penicillamine, captopril, nonsteroidal anti-inflammatory agents)
- Membranous glomerulonephritis is a slowly progressive disorder that shows little response to steroid therapy.
- Immunofluorescence microscopy in membranous nephropathy showing **diffuse, granular** IgG deposition along the capillary walls.

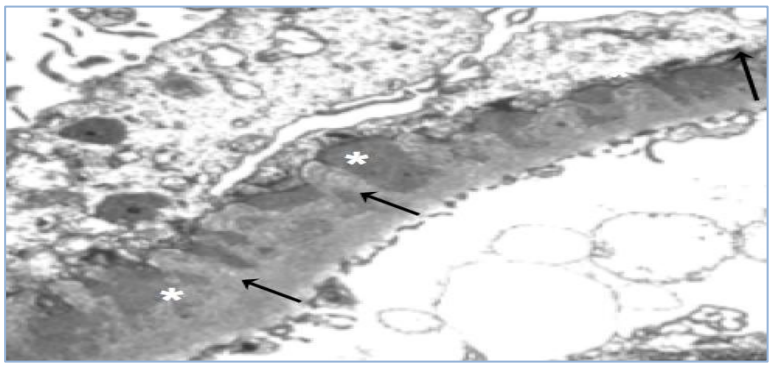
[8] Glomerular basement membrane



There is an evenly distributed granular capillary loop pattern of positively in membranous glomerulopathy

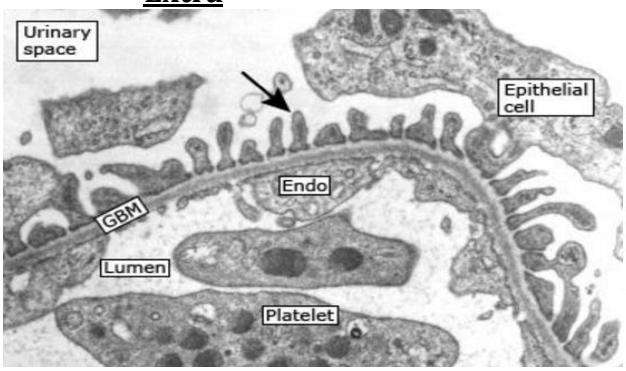


There are well-developed spikes and holes in tangential sections in stage-2 membranous glomerulopathy.



Glomerulonephritis, New basement membrane (arrows) is growing between the deposits(stars), leading to a spike appearance on silver stain.

Extra



Diabetic nephropathy: (nodular diabetic glomerulosclerosis)

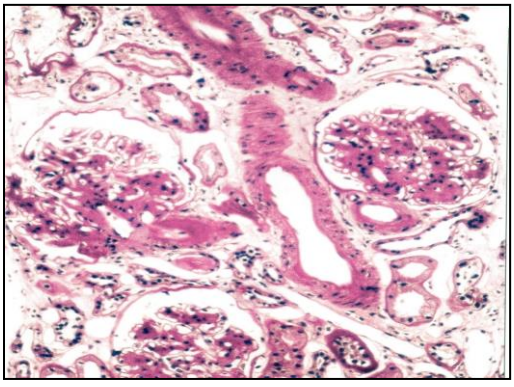
The lesions in diabetic nephropathy are characterized by **arteriolar hyalinization, mesangial matrix expansion** and **glomerular basement thickening**.

- Diabetic nephropathy usually associated with diabetic retinopathy (eyes abnormalities).
- Electron microscopy demonstrates striking increase in **thickness of the glomerular basement membrane**. Thickening of **vascular** basement membrane is one of the earliest morphologic changes in diabetes mellitus (long standing non-controlled diabetes).

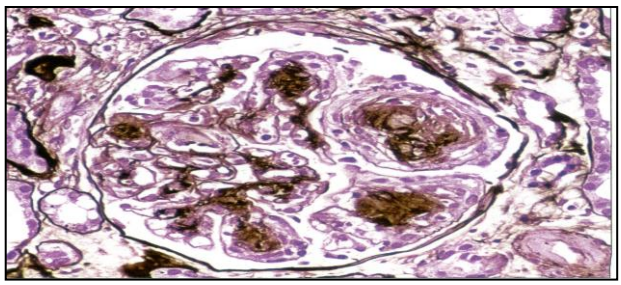
- **An increase in mesangial matrix** with time results in two characteristic morphologic patterns:
  1) **Diffuse glomerulosclerosis** is marked by a diffusely distributed increase in mesangial matrix.
  2) **Nodular glomerulosclerosis** is marked by nodular accumulations of mesangial matrix material (Kimmelstiel-Wilson nodules)*.

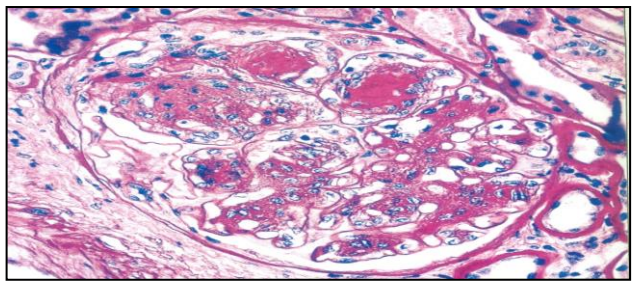
*قبل يوصل المريض لهذه المرحلة (**Kimmelstiel-Wilson nodules**) لا يعتبر nephrotic لكن إذا وصل لها نصنفه المرض على طول nephrotic.
In PAS stain we see the nodules.

Immunofluorescence (IF) → Linear IgG (The previous diseases had granular immune complexes).



The lesions in diabetic nephropathy are characterized by arteriolar hyalinization, mesangial matrix expansion and glomerular basement thickening.



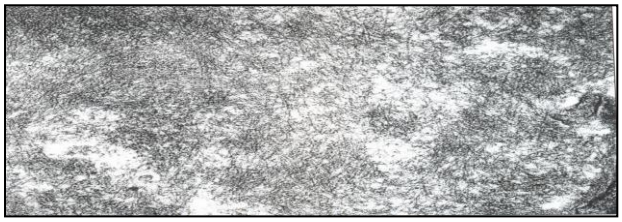


The lamellated appearance of the Kimmelstiel-Wilson nodule characteristic of the nodular sclerosis form of diabetic nephropathy is shown, along with arteriolar hyalinization (hyaline material not cells) and surrounding tubulointerstitial fibrosis.

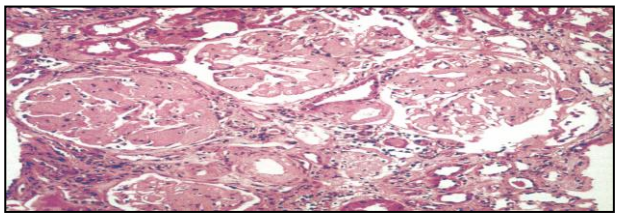
Renal amyloidosis: "with Smokers"

- Predominantly subendothelial and mesangial amyloid deposits are characteristic.
- The amyloidosis can be identified by reactivity of amyloid with special stains (e.g. Congo Red*, crystal violet, thioflavin T) and by birefringence[9] under polarized light. It is also demonstrated by a characteristic crisscross fibrillary pattern of amyloid by electron microscopy.
- Most often, there are associations with chronic inflammatory diseases, such as rheumatoid arthritis or plasma cell tumors such as multiple myeloma.

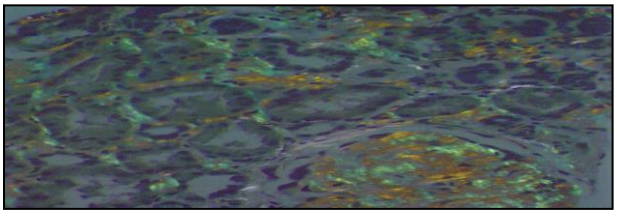
*تقدر تكتشف المرض عن طريق صبغة ال Congo Red بعدين تسوي **polarization** ويطلعلك تحت **apple-green birefringence** وأيضا يعطيك ألوان مخلفة مع انكسار الضوء عن طريق تحريك العدسة لل**microscope**ال



Randomly oriented, **8-10nm fibrils**, typical of amyloid within the mesangium.



Massive amyloid deposits are present in glomeruli and arterioles

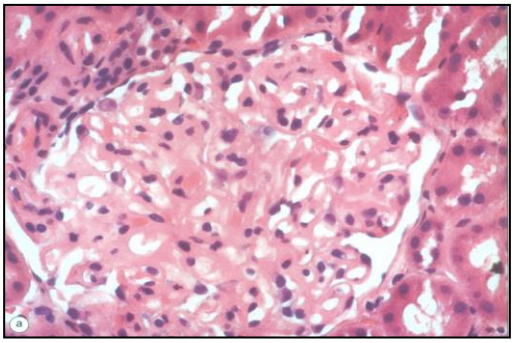


Tubular involvement with amyloid is verified by **apple-green birefringence** under polarized light.

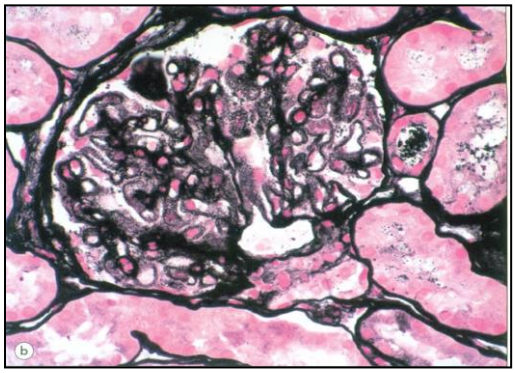
[9]transmitting light unequally in different directions. (انكسار الضوء)

Lupus nephropathy:

- SLE is an inflammation of the kidney; SLE can also damage the skin, joints, nervous system and virtually any organ or system in the body because antibodies act **against DNA**. It is an autoimmune and systemic disease.
- These antibodies accumulate in subendothelial.



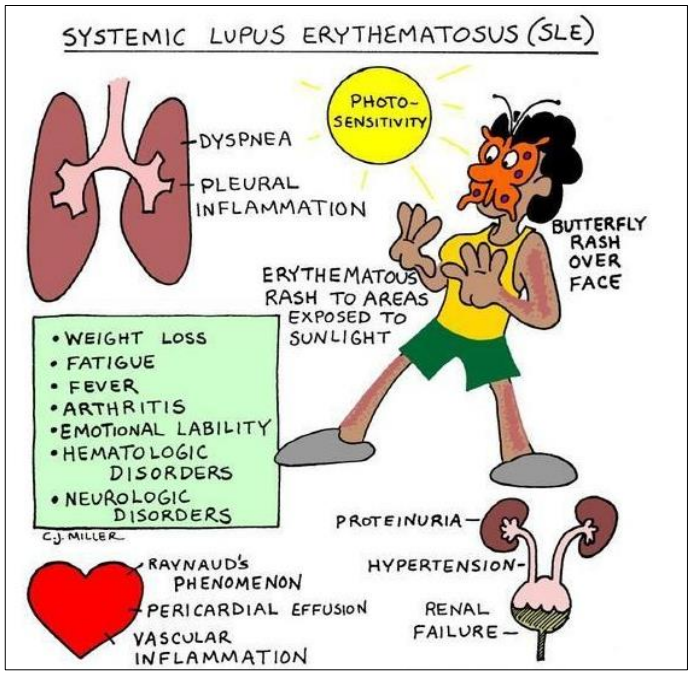
a) Class V lesion or lupus membranous glomerulopathy. There is diffuse thickening of the peripheral capillary walls associated with an increase in mesangial matrix.



(b) Silver methenamine (jones) stains reveal a spike and dome pattern to be present along the peripheral capillary loops where the wall of the capillaries cut tangentially; there is a moth-eaten appearance of the capillary wall.

Membranous lupus glomerulonephritis*:

In class 5, the patients have severe nephrotic syndrome and there is thickening of the capillary walls due to deposition of basement membrane like material as well as immune complexes.



*يشبه تماما ال **Membranous glomerulonephritis** ولكن يختلف عنه في التسميه **Secondary Membranous glomerulonephritis** لأن المريض عنده **lupus** بالإضافة يختلف في **"full house" immunofluorescence**

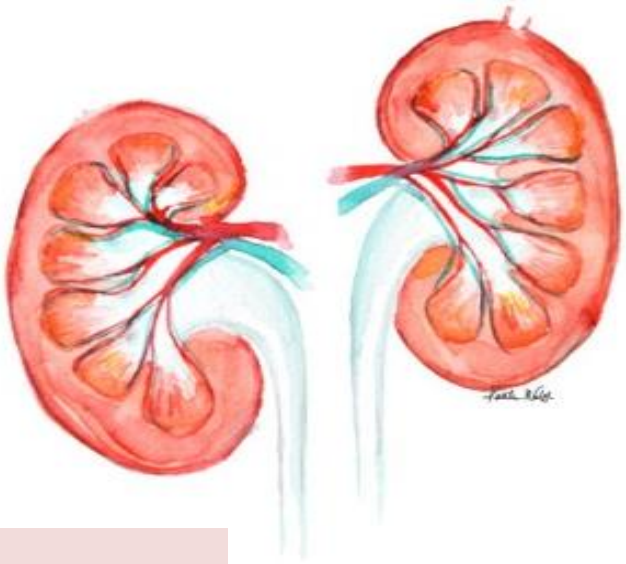
"Full house" immunofluorescence: This means quite simply that all five major immunofluorescent stains on a renal biopsy (IgM, IgG, IgA, C3, and C1q) are all positive. **بينما** ال**Membranous glomerulonephritis** يظهر فيه فقط immunoglobulin G (IgG) or C3

SUMMARY

The Nephrotic Syndrome

- The nephrotic syndrome is characterized by proteinuria, which results in hypoalbuminemia and edema.
- Podocyte injury is an underlying mechanism of proteinuria, and may be the result of nonimmune causes (as in minimal-change disease and FSGS) or immune mechanisms (as in membranous nephropathy).
- *Minimal-change disease* is the most frequent cause of nephrotic syndrome in children; it is manifested by proteinuria and effacement of glomerular foot processes without antibody deposits; the pathogenesis is unknown; the disease responds well to steroid therapy.
- *FSGS* may be primary (podocyte injury by unknown mechanisms) or secondary (e.g., as a consequence of previous glomerulonephritis, hypertension, or infection such as with HIV); glomeruli show focal and segmental obliteration of capillary lumina, and loss of foot processes; the disease often is resistant to therapy and may progress to end-stage renal disease.
- *Membranous nephropathy* is caused by an autoimmune response, most often directed against the phospholipase A_2 receptor on podocytes; it is characterized by granular subepithelial deposits of antibodies with GBM thickening and loss of foot processes but little or no inflammation; the disease often is resistant to steroid therapy.
- MPGN and dense deposit disease are now recognized to be distinct entities. MPGN is caused by immune complex deposition; dense deposit disease is a consequence of complement dysregulation. Both may present with nephrotic and/or nephritic features.

"اللهم لا سهل إلا ما جعلته سهلًا و أنت تجعل الحزن إذا شئت سهلًا"



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القادة

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