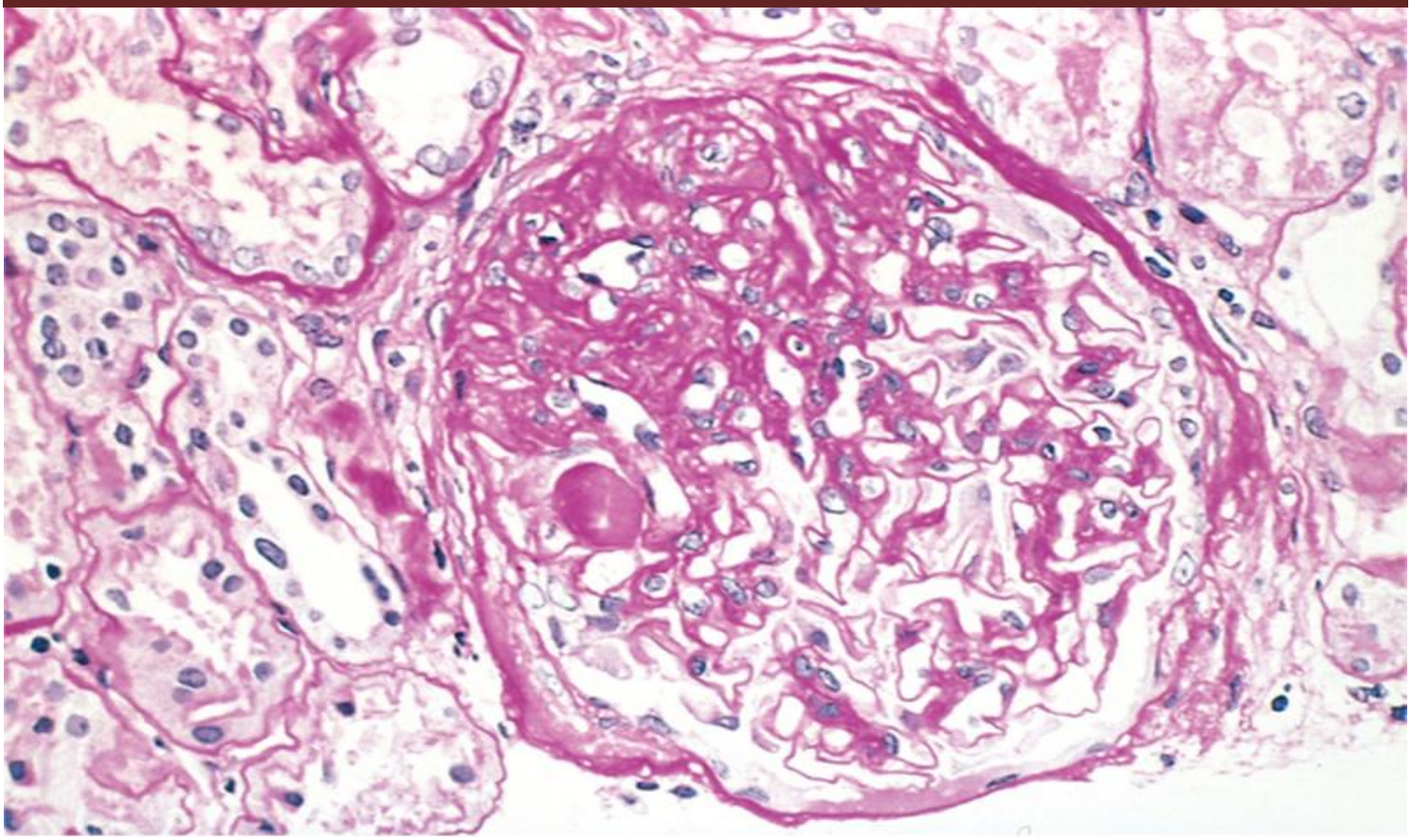

Lecture Four

Nephrotic Syndrome

432 ***Pathology*** *Team*

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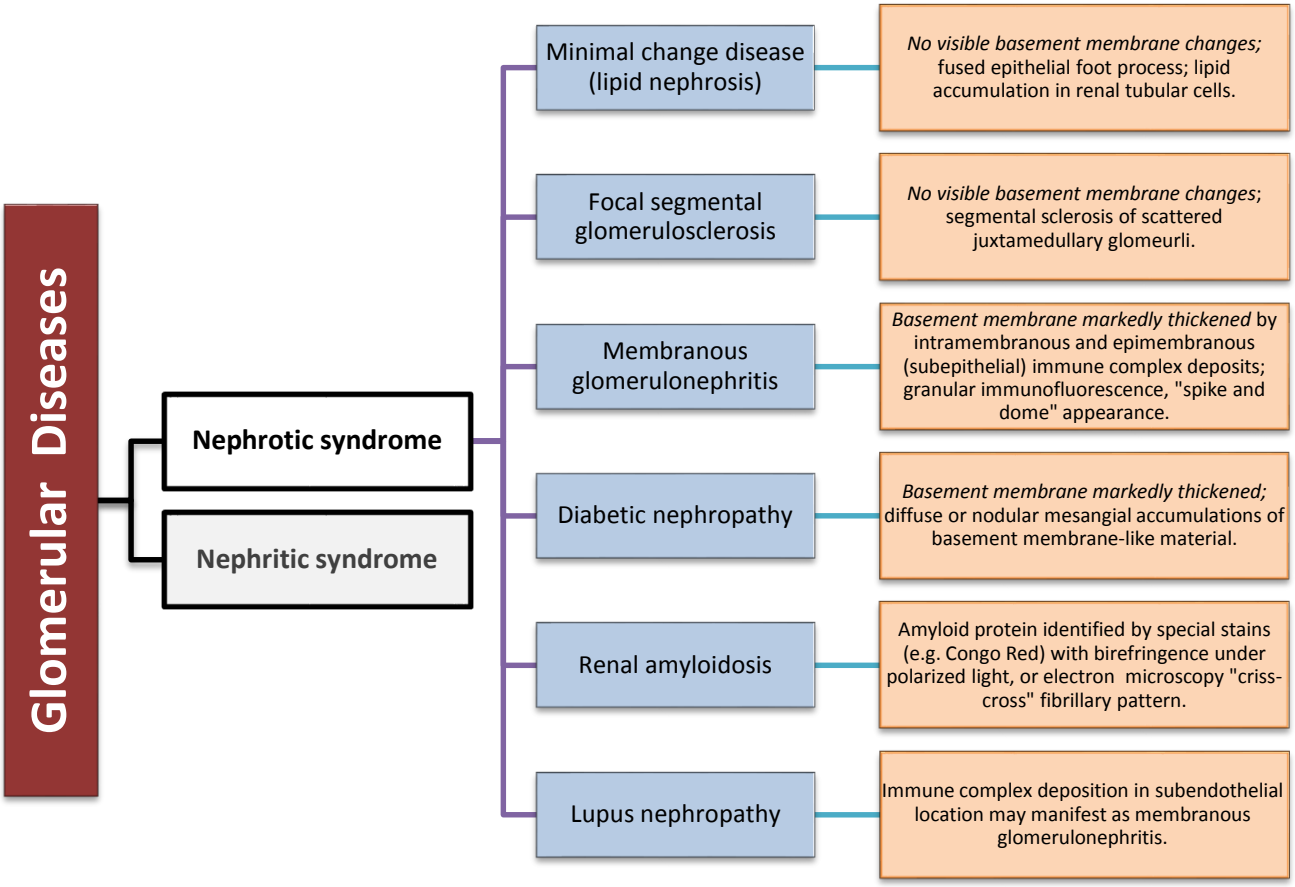
Reviewed By: Abdulrahman *Al-Akeel and* ***Ibrahim*** *Abunohaiah*

Renal Block

NOTE: female-side notes are written in purple.Red is important. Orange is explanation. Info in the handout not mentioned by Prof. Al-Rikabi are in GREY

Glomerular Diseases

Mind Map:



Terminology: **The following terms are used to describe the extent of glomerular injury:**

Diffuse	**All glomeruli are affected.**
Focal	**Some glomeruli are affected.**
Segmental	**Part of one glomerulus is affected.**
Global	**The entirety of one glomerulus is affected.**

Glomerular Diseases

Important note →Glomerular diseases are all immunologically mediated, the disease is determined of where this immunological reaction occurs.

Pathogenesis:

1) Antigen antibody reaction (Immune complex), which is **hypersensitivity reaction type 3.** Antigen may be bacterial, viral, tumor antigens or any antigen like bee sting.

Because of antigen antibody reaction → activation of complement: C3a and C5a →they induce chemo taxis → attract neutrophils, which attack the glomerulus → neutrophils release its lysosomal enzymes → damage of the glomerulus → glomerulonephritis.

Immune complexes may occur in two sites:

1- **In blood circulation** → go to kidney, which is very vascular → accumulate → inflammatory reaction → diseased kidney.
2- **In situ (موضعي)**, antigens get fixed to the basement membrane → antibodies form the complexes on site.

2) Antigen stimulates T- lymphocytes to secrete cytokines which cause damage. Injury to podocytes and/or glomerular basement membrane.

A- Nephrotic Syndrome

Nephrotic Syndrome includes a group of conditions characterized by increased basement membrane permeability, permitting the urinary **loss of plasma proteins**, particularly low-weight proteins such as **albumin**.

> ***REMEMBER:*** **Syndrome** is collection of symptoms and signs.
> **Disease** is collection of symptoms, signs, radiological features, pathological features and laboratory features.

Classical manifestations:

1. **Massive proteinuria** is the first symptom more than 3.5 gram per day.
   Unlike other disorders with greater disruption of the glomerular structure, proteinuria in the nephrotic syndrome is not accompanied by increased urinary red cells or white cells.
2. **Edema (pitting edema)** on the face or limb and sometimes it is generalized (**anasarca**).results from decreased plasma colloid or oncotic pressure.
3. **Hyperlipidemia** and **hypercholesterolemia** are caused by increased hepatic lipoprotein synthesis due to hypoalbuminemia
4. **Hypoalbuminemia** results from proteinuria and is often marked by a serum concentration of less than 3 g/100 ML.
5. **Lipiduria**

There are 2 types of proteinuria:

1) Selective (excrete only albumin). That is happens in nephrotic syndrome and that is why the patients have hypoalbuminemia

2) Not selective (excrete albumin and globulin), usually in nephritic syndrome.

NOTE: All the diseases that cause nephrotic syndrome don't have inflammation.

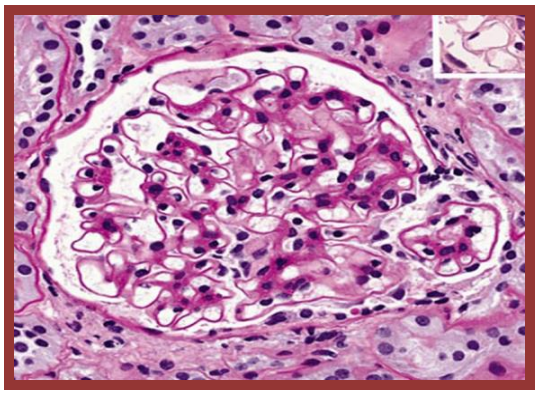
Types of Nephrotic Syndrome: (classified upon its immune complex deposit site, and we have to do a biopsy to classify the disease)

1/ Minimal change disease (MCD)

Also called **Minimal change glomerlopathy** or **Lipoid nephrosis.**
Which like to cause nephrotic syndrome in **children** but can also occur in older children or adults

Pathogenesis:

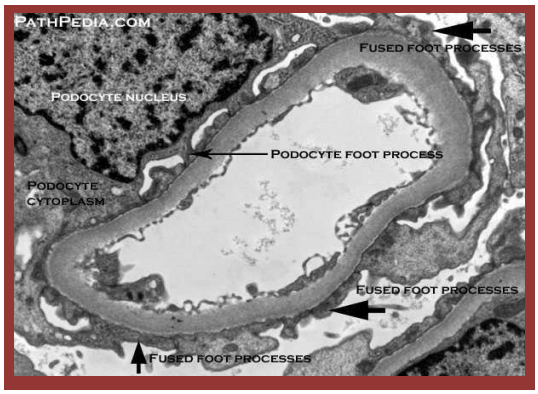
Lipid-laden renal tubules (lipids are intracytoplasmic in tubular cells) particularly in cells of proximal convoluted tubules.



Histopathological Features:

LM: appears normal

EM: Effacement (fusion) and adhesion and loss of foot process (flat podocytes). (There is damage of podocytes; the podocytes may detach leaving openings on the basement membrane)
The thing we can't see it under the microscope is that the basement membrane losses its negativity, so with fusion of podocytes there will be increase in permeability.



NOTE: we only see the position of the immune complex deposition under the EM

Prognosis:

It has a **good** prognosis; most of patients may regress spontaneously or with steroid for a short period of time. It is rarely to progress. But it is more progressive in adults and older children. Most often, this condition responds well to corticosteroid therapy.

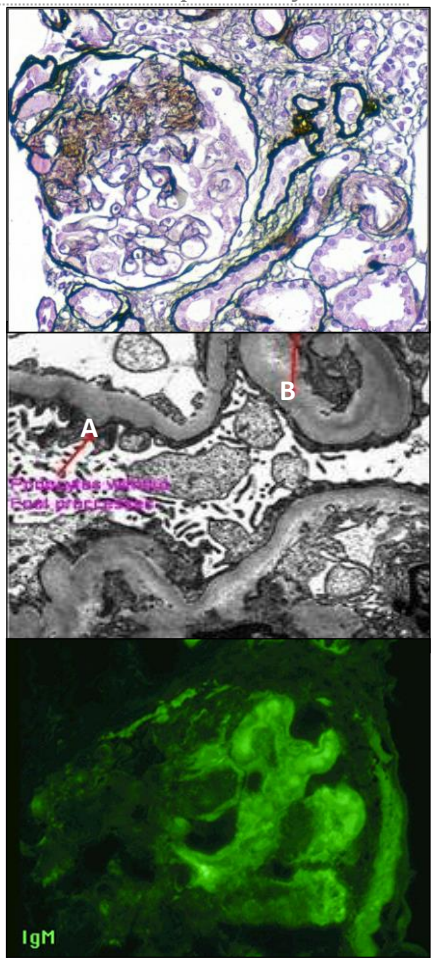
2/Focal segmental glomerulosclerosis

Patient present with nephrotic syndrome and Hypertension (rare)

Causes

- **Idiopathic**
- **HIV infection**
- **Heroin addicted**
- **Secondary to other glomerular disease** (ex. IgA nephropathy, which called Berger's disease, not Buerger's disease)

Histopathological Features:



LM: sclerosis within capillary (capillary collapsed, fibrosed and adhesion with Bowman's capsule) tufts of the deep juxtamedullary glomeruli with focal or segmental distribution.

EM: (A) Fusion of podocytes
(B) Thickening and fibrosis of basement membrane

IF: usually negative, but may see IgM and C3.
Immunofluorescence is a technique for determining the location of an antigen (or antibody) in tissues by reaction with an antibody (or antigen) labeled with a fluorescent dye. Always, it used in immunologic mediated diseases.

Prognosis:

40% or more develops chronic renal failure. They take corticosteroid.

3/Membranous glomerulonephritis

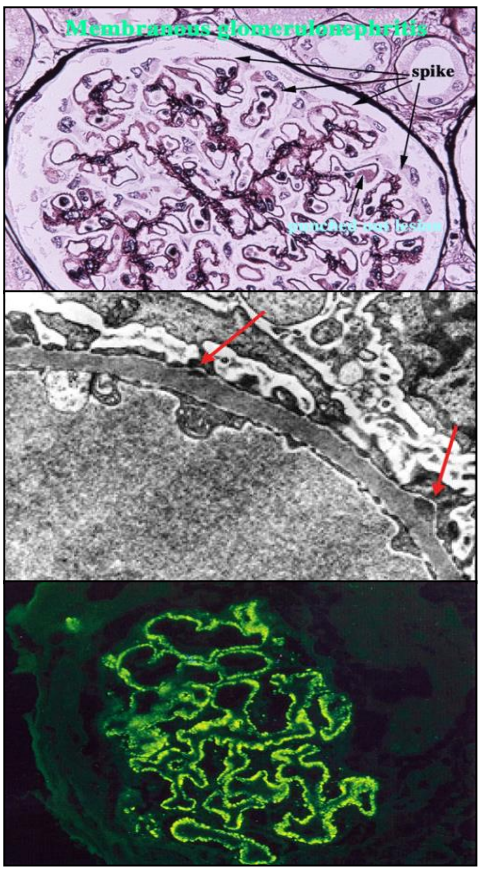
Membranous glomerulonephritis→Spike and dome appearance

Most common cause of nephrotic syndrome in **adults**
The diagnosis should be suspected when the nephrotic syndrome is accompanied by azotemia (a medical condition characterized by abnormally high levels of nitrogen-containing compounds, such as urea, creatinine).

Causes:

- **Idiopathic**
- **Secondary to hepatitis B, or SLE (Systemic lupus erythematosus)**
- **Cancer**
- **Drugs** such as **gold salts** and **penicillamine** which are used for treatment of Rheumatoid Arthritis, Syphilis, and Malaria, also patient who use Captopril for hypertension.

Histopathological Features:



LM: basement membrane is very thick.

EM: subepithelial deposition of immune complex (cause the thickened basement membrane between epithelium and basement membrane). "Spikes and domes" appearance (immune complexes) underneath the basement membrane.

IF: positive. Granular deposition of IgG and complement C3 in subepithelium. (Important).

Prognosis:

Slowly progressive disorder that shows little response to steroid therapy.
The disorder sometimes causes renal vein thrombosis, which was previously thought to be an etiologic factor.

4/ Diabetic nephropathy

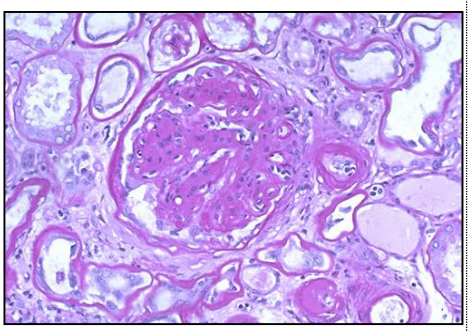
Cause:

Uncontrolled diabetes.

LM: will be either

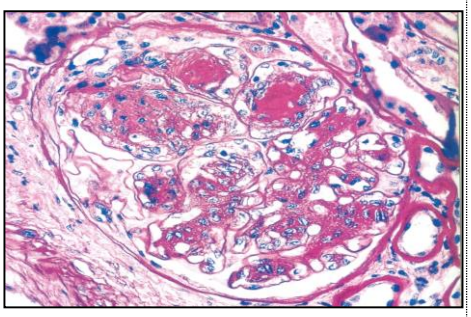
1) **Diffuse glomerulosclerosis**: thickening of the glomerular capillary walls (accumulation of basement membrane like material in the wall of these capillaries and the mesangium), diffuse increase in mesangial matrix and mesangial cell proliferation ending in sclerosis.

1)

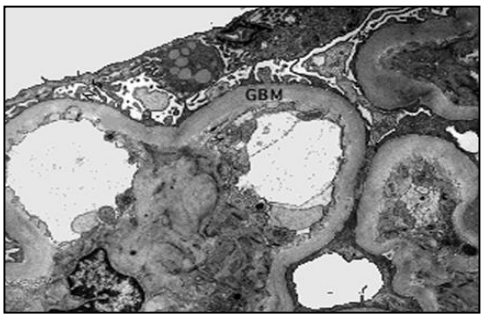


2) **Nodular glomerulosclerosis (Kimmelstiel Wilson nodules/ lesion):** nodule formation in the mesangium. These nodules are spherical and eosinophilic, with a central acellular area. It is pathogonomic of diabetes.

2)



Both types have arteriolar hyaline deposits.



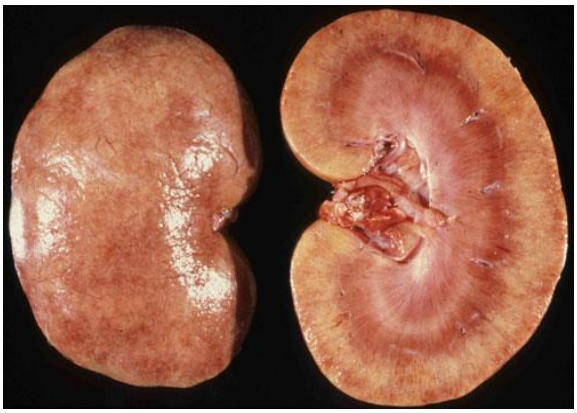
EM: demonstrates striking increase in thickness of the glomerular basement membrane. Thickening of vascular basement membranes observable by electron microscopy is one of the earliest morphologic changes in diabetes mellitus.

IF: We don't found deposit of immune complexes in both of them, but may found IgM and C3 complex in diffuse glomerulosclerosis, which is not pathogenesis but trapped from circulation.

Prognosis:

The end result of diabetic nephropathy is scarred non-functioning kidneys.
We have to control the diabetic and improve live quality of the patient to delay the complication which one of them is diabetic nephropathy.

5/ Renal Amyloidosis

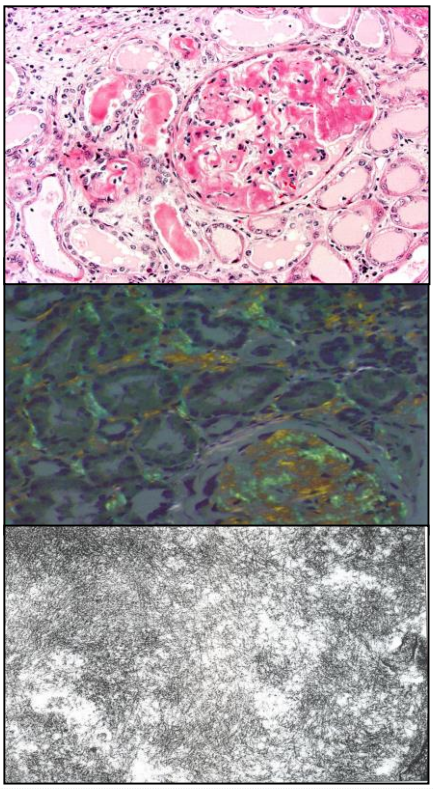


Amyloid deposition in kidneys

Amyloid is a kind of protein that is secreted by the liver or plasma cells. **If the patient have cancer in plasma cells (Multiple Myeloma)**, results in increase amyloid AL which get deposit in kidney, liver, spleen, ets .
Amyloid AA is associated with any chronic disease especially Osteomyelitis, Tuberculosis, Bronchiectasis and Rheumatoid Arthritis

Patient presents with nephrotic syndrome symptoms and chronic disease.

Biopsy: Glomeruli are enlarged and sclerotic



LM: Predominantly subendothelial and mesangial amyloid deposits are characteristic.

We stain Amyloid with a special stain called **Congo Red** (Which turns amyloid **brown**) then by birefringence under polarized light it turns to **apple green.**

EM: It is demonstrated by a characteristic criss-cross fibrillary pattern (tangled of fibrillary or fibrin of protein).

No treatment for the amyloidosis

6/ Lupus nephropathy

SLE is systemic, autoimmune disease, and one of its manifestations is nephrotic syndrome or nephritic syndrome.

> Autoimmune disease: when the body loses the capability to differentiating between what is self and what is non-self, and it reacts against its own antigen. For examples, antibody against blood vessels, antibodies against DNA.

The pathogenesis of all forms of glomerulonephritis in SLE involves deposition of DNA and anti DNA complexes within the glomeruli. This causes an inflammatory response that may cause proliferation of the endothelial, mesangial and/or epithelial glomerular cells and in severe cases necrosis of the glomeruli.

The World Health Organization has divided SLE glomerular disease into five classes:

Class one: Patient doesn't have the nephrotic syndrome's symptoms. **His kidney is totally normal.** (Later one he will develop the disease)(This is seen in less than 5% of SLE patients).

Class two: Mesangial lupus glomerulonephritis is seen in 10 to 25% of cases and is associated with mild clinical symptoms and immune complex deposits in the mesangium.

Class three: **Focal proliferative lupus glomerulonephritis** is seen in 20 to 35% of patients. Here one or two foci within an otherwise normal glomerulus show swelling and proliferation of endothelial and mesangial cells with neutrophilic infiltration or fibrinoid deposits and capillary thrombi. (He will have nephritic syndrome not nephrotic). One of renal causes of acute glomerulonephritis

Class four: Is **diffuse proliferative glomerulonephritis** and is seen in 35% to 60% of SLE patients. The histological features are similar to the one described in class 3 but are more diffuse. In this condition, immune complexes deposition create an overall thickening of the capillary walls which resemble rigid "wire loops" on light microscopy.

Class five: Is **membranous lupus glomerulonephritis** occurs in 10 to 15% of cases. 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.

Summary (from Robbins)

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 A2 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.**

Questions from Pathology Recall book

1/ Name the site of immune complex deposition in the SLE.

- Subendothelial.

2/ With which technique can most accurately detect the position of immune complex?

- Electron microscope

3/ What stimulates hepatic lipoprotein synthesis?

- Hypoalbuminemia

5/ To what does ''lipoid nephrosis" refer?

- The presence of numerous lipid droplets in tubules and fat bodies in the urine

6/ What therapy is used for lipoid necrosis?

- Steroids, relapses more common in adults.

7/ What is the characteristic staining pattern in membranous glomerulonephritis?

- Spike and dome appearance (spikes are basement membrane, domes are intracellular deposits)

9/ What 2 drugs cause membranous glomerulonephritis as a potential side effect?

- Gold salts
- Penicillamine

10/ How long before the diabetic nephropathy affects the kidneys?

- Usually after 10-20 years, accompanied by retinopathy, coronary artery disease, and peripheral vascular disease.

11/ What is the treatment of amyloidosis?

- There is no treatment for it

12/ What part of the nephron is typically affected diabetic glomerulosclerosis?

- The mesangial matrix is increased.

Case 1 / A 30-year old female patient presents with onset of peripheral edema. Physical examination finds hypertension and bilateral pedal edema. Urinalysis finds massive proteinuria, and evaluation of her serum finds elevated levels of cholesterol. A silver stain of a renal biopsy specimen reveals a characteristic ''spike and some'' pattern, and electron microscopic y finds a uniform deposition of small electron dense deposits in a subendothelial location. Which of the following immunofluorescence patterns is most characteristic of this patient's renal disease?

A. Granular pattern of IgA and C3
B. Granular pattern of IgG and C3
C. Linear pattern of IgD and C4
D. Linear pattern of IgE and C4

Case2 / A 45-year old woman with a long term history of poorly controlled diabetes mellitus is found to have proteinuria. A renal biopsy reveals hyaline arteriosclerosis of the afferent and efferent arterioles along with Kimmelstiel-Wilson lesions in a few of the glomeruli. Which of the following is the most likely the diagnosis?

A. Diffuse proliferative glomerulonephritis
B. Focal segmental glomerulosclerosis
C. Membranous glomerulonephropathy
D. Nodular glomerulosclerosis

اللهم إني استودعتك ما قرأت و ما حفظت و ما تعلمت فرده عليّ عند حاجتي اليه انك على كل شيء قدير

432 Pathology Team
Good Luck ^_^

The cases are from case files Pathology book

Answers:

- Case 1 / B
- Case 2 / D