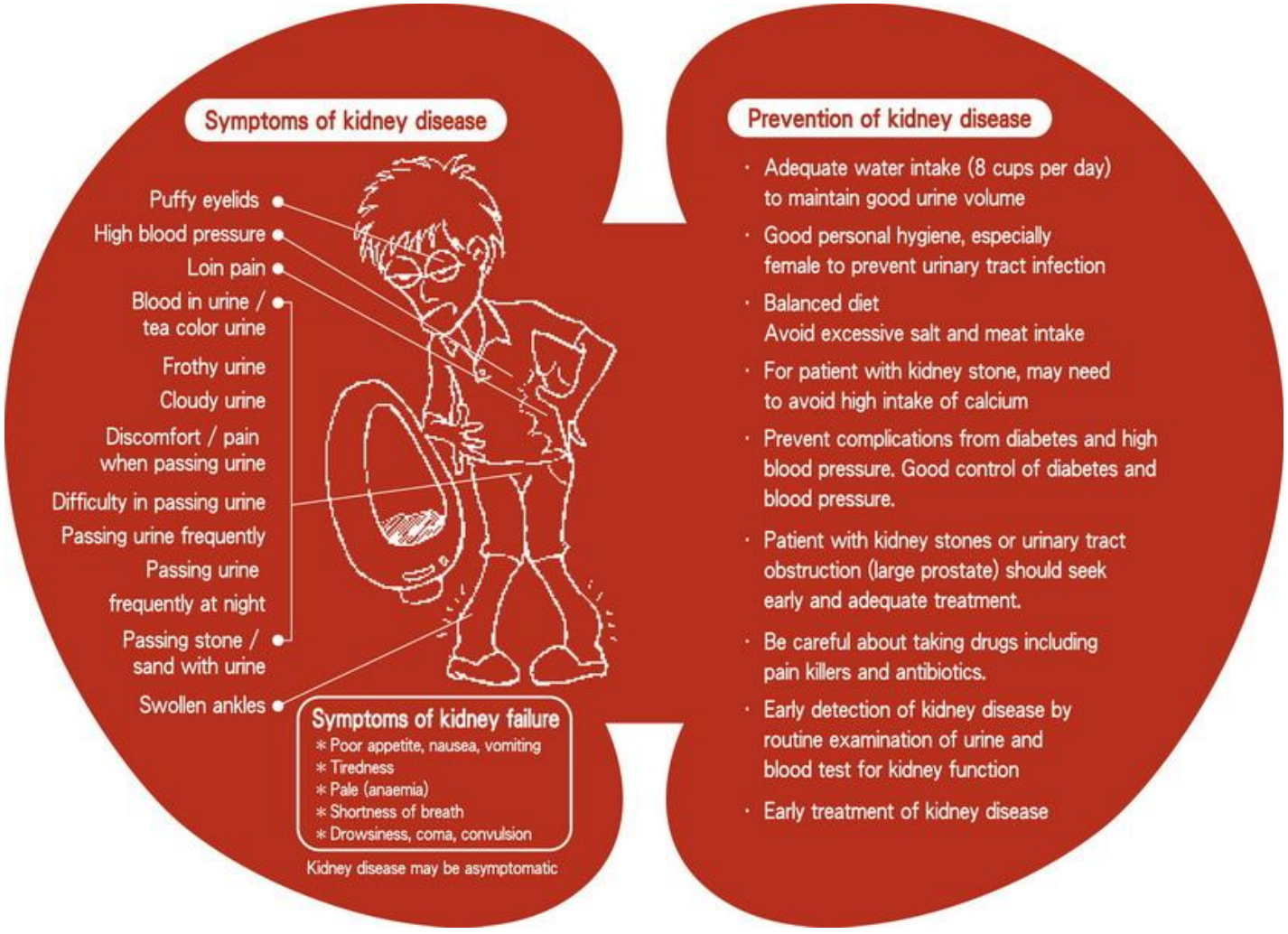
The Major 5 Clinical Syndromes E.2



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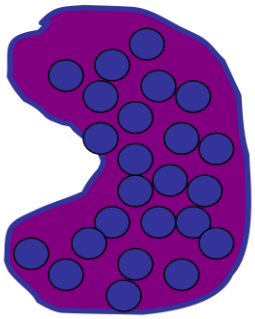
It is Adequate for Studying this Lecture

Fully revised with Dr.Hala Kfouri

PATHOLOGY OF THE KIDNEY

Glomerular diseases – How to name them:

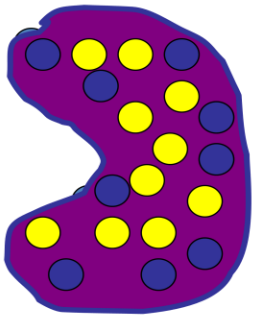
- Diffuse OR focal related to the no. of glomeruli affected
- Global OR segmental in how ONE glomeruli is affected



Diffuse:
all the Glomeruli
Blue = abnormal

Global

ALL OF IT affected



Focal:
some of the Glomeruli
blue = abnormal
Yellow = normal

Segmental

ONLY A SEGMENT affected

When Doing Kidney Biopsy, We look through 3:

1- Histopathology
2- Fluorescent Microscopy
3- Electron Microscopy

Adequacy of a biopsy:

8 glomeruli should be present (biopsy for transplant: 10 glomeruli + 2 artery → adequate
7 glomeruli + 1 artery → the borderline)

Primary → the disease or pathology is originated and placed in the same organ (Kidney)
Secondary → a general disease in the body that affected this organ (Kidney)

	"PRIMARY"	"SECONDARY"
Site	Kidney is the only organ involved or predominantly involved (it might be a systemic disease)	Kidney is one of the many organs involved. Disease is systemic, like: • *Hypertention* • *SLE* • *Metabolic disorders* • *Polyarteritis nodosa*
Comment	With inflammatory component =Glomerulonephritis Without inflammatory component = Glomerulopathy	
Histology	The "Same" Glomerular Injury	

THE MAJOR 5 CLINICAL SYNDROMES:

1- Nephrotic syndrome :

Mainly

heavy **proteinuria** (proteins in urine) ((body loss of 3,5 g/day)) – **hypoalbuminemia** – edema - lipiduria, **hyperlipidemia.**

- Severe Glomerular Abnormalities

May or may not be accompanied by **Hematuria** depending upon the underlying disease.

2- Nephritic syndrome:

Mainly **hematuria** (RBCs in urine), red blood cells casts, **edema, hypertension, abnormal renal function** and HYPERCELLULARITY

- Glomerular Abnormalities

Nephritis = **inflammation** in/of the kidney

3- Asymptomatic Hematuria (Proteinuria):

Mainly Microscopic Hematuria With Rbcs Casts - proteinuria ((usually <1 gram/24 hours)) - normal renal function.

- subtle/mild glomerular abnormalities

IgA nephropathy - Glomerular Basement Membrane Abnormalities

4- Rapidly progressive Glomerulonephritis (RPGN)

Rapid deterioration of renal function, and is related to CRESCENT.

5- Chronic renal failure

Chronic uremia = end of all renal diseases → end stage renal disease (ESRD; uremia)

CHRONIC = FIBROSIS

THE BASIC STRUCTURAL PATTERNS OF GLOMERULAR INJURY

1) Epithelial Cell Disease (Minimal Change Disease)
2) Focal Segmental Glomerulosclerosis
3) Membranous Nephropath

→ ***Nephrotic Injury***

4) Diffuse Proliferative Glomerulonephritis
5) Membranoproliferative Glomerulonephritis
6) Focal Proliferative and Necrotizing Glomerulonephritis

→ ***Nephritic Injury***

7) Crescentic Glomerulonephritis → ***Crescentic***

8) Mesangial Proliferative Glomerulonephritis
9) Basement Membrane Abnormalities

→ ***Asymptomatic***

10) Focal Global Glomerulosclerosis → ***Chronic Renal Failure***

I. THE NEPHROTIC SYNDROME (NEPHROSIS)

➢ It is characterized by:

- No Hypercellularity
- Proteinuria: (> 3.5g/24 H)
- Hypoalbuminemia.
- Hyperlipidemia And Lipiduria
- Edema (The Most Obvious)

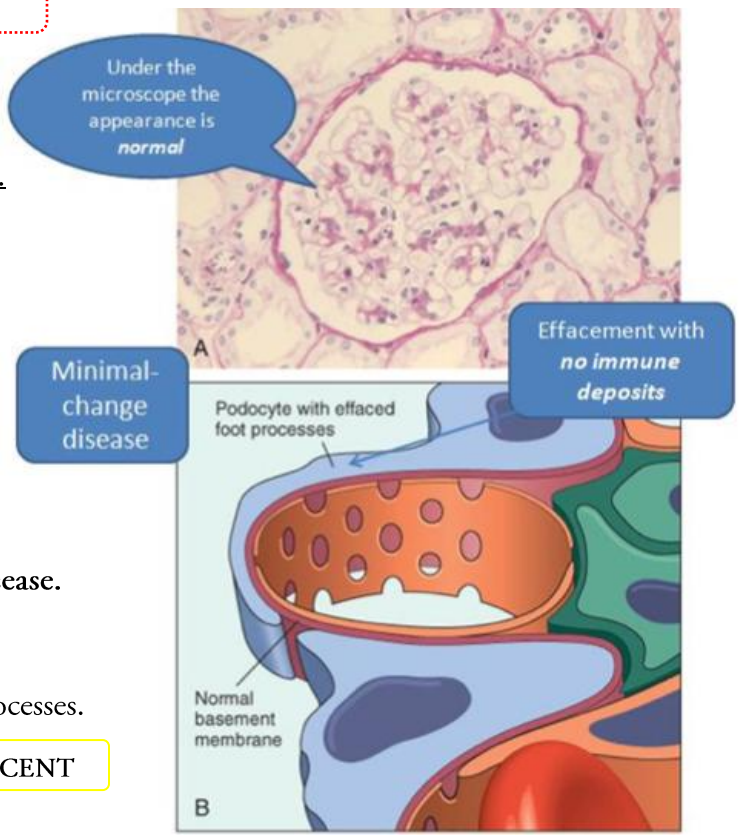
- The structural abnormality ***shared by all the nephrotic conditions*** with heavy proteinuria **is**
  → **the *SIMPLIFICATION OR FUSION OF THE CELL FOOTPROCESSES.***

  It Show much less glomerular inflammation and proliferation than other syndromes.
  The Sclerosing Glomerulopathies ***Predominate in this group.***

- due to increase glomerular permeability
- Causes vary according to age:
  - In children the nephrotic syndrome is almost always caused by **A Lesion Primary To The Kidney.**
  - In adults the nephrotic syndrome is often due to **Renal Manifestations Of Asystemic Disease.**

Minimal-Change Disease (Lipoid Nephrosis)

- *DIFFUSE* EPITHELIAL CELL DISEASE
- It is a benign disorder
  that is the most common cause of nephrotic syndrome in children.
  (The peak incidence is between age 2 and 3)
- **Morphology:**
  - **Light Microscopy:** normal glomeruli.
  - **Electron Microscope:**
    uniform and diffuse effacement
    of the foot processes of the podocytes.
  - **Immunofluorescence Microscopy:** negative
- **Pathogenesis:**
  - **No good experimental model of minimal change disease.**
  - **The proteinuria has been attributed to:**
    A T-cell derived factor
    that causes podocyte damage and effacement of foot processes.



CAN'T BE DIAGNOSED FROM HISTOLOGY OR IMMUNOFLOURESCENT

MCQs

10 years old child presented with 1 month history of lower limb edema a& puffiness of the face, what is the most likely diagnosis? **Nephrotic Syndrome.**

What will his blood test show? Hypo / hyper / normal Albuminemia, Lipidemia ?? **Hypoalbuminemia - Hyperlipidemia.**

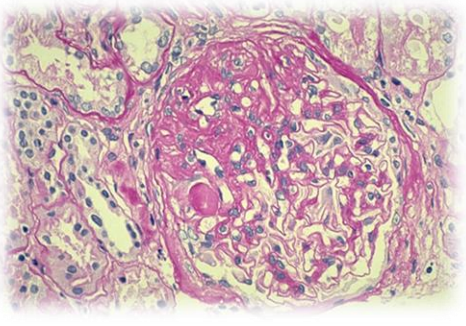
CHILD??? →→ MAINLY PODOCYTE INJURY

FOCAL AND SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

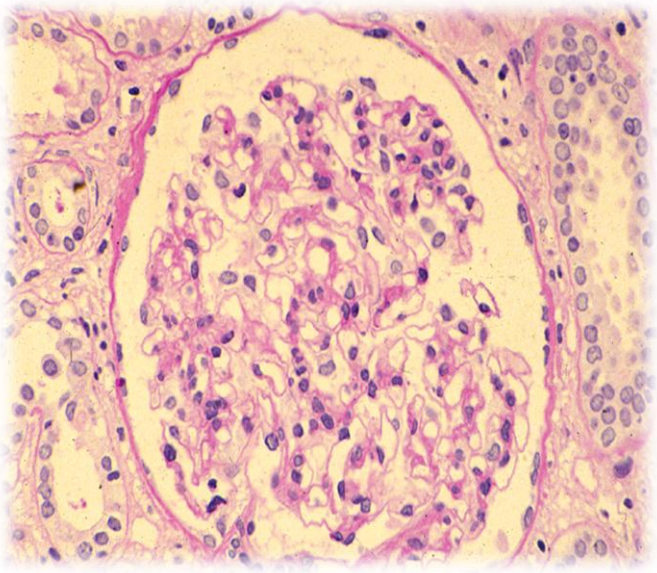
DEFINITIONS:

Focal: Not all glomeruli in kidney.
Segmental: Not the whole of the glomerulus.

((Sclerosis = fibrosis)).



MEMBRANOUS GLOMERULONEPHRITIS (MGN)



- **Histological Characteristics:**
  - Thickening of the membrane.
  - IgG depositions along the epithelial side of the capillary (on the **epithelial side**).
  - Spikes are present perpendicular to the basement membrane IgG is leaving from the B.M → it shows such shapes
  - Lumen of the capillaries is open (normal).

Note: Compare the glomeruli
basement membrane *to the* **tubule membrane** *to see the thickened*

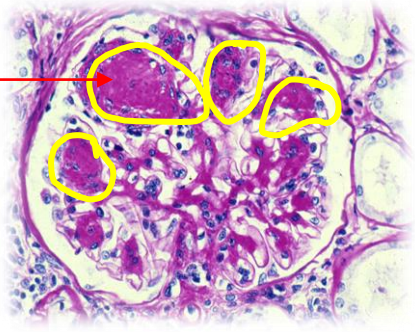
- **Etiology (Associated Conditions):**
  1. Autoimmune diseases.
  2. Infectious diseases. Ex. Hepatitis B
  3. Drugs.
  4. Miscellaneous. Ex. Malignancies

MGN is usually IDIOPATHIC
The variety of causes linked to MGN minimizes the fact that
in many instances the relationship is tentative and the etiologic implication is unproven.

- **Pathophysiology:**
  - In situ formation - of subepithelial Immune complex.
  - Nephrotic Syndrome.
  - **4 stages:** Normal – Spikes – Mild to prominent thickening.
  - **IgG:** finely granular along the glomerular capillary wall.

Diabetic Nephropathy

This is *PAS (+)* →



NODULAR GLOMERUSCLEROSIS.
It happens to diabetic patients.

To Differentiate From Amyloid → Amyloid Is *PAS (-)*
→ Amyloid Fibrils are 10-12 µnm by Epithelial Membrane

II. ACUTE NEPHRITIC SYNDROME

CAUSES:

1- Acute Post-Streptococcal Glomerulonephritis
2- Membrano- Proliferative Glomerulonephritis
3- Systemic Lupus Erythematosis.

Post-infectious glomerulonephritis (post-streptococcal glomerulonephritis)

- One of **the most frequent causes** of nephritic syndrome **in childhood** may be seen in adult but less typical.
- **Associated with group A streptococcal infection**, (less commonly other infections).
- **Clinically:**
  hematuria ("tea colored urine") – oliguria – edema – hypertension.
- **Morphologically :**
  1- Enlarged and hypercellular glomeruli with polys.
  2- Mesangial and endothelial cells increased.
  3- Epithelial crescent are NOT COMMON (but may occur)
  4- ImmunoFluorescent demonstrates classic **"lumpy bumpy"** pattern staining for IgG or C3.
  Humps are >> Subepithelial (on the epithelial membrane)

Clinical improvement: several weeks – **Recovering from Proteinuria and Hematuria:** several months

Membranoproliferative Glomerulonephritis(MPGN)

As the name indicates, it **involves** both the glomerular capillary wall (Double thickening) & the glomerular tuft (proliferation). Mostly affects Children. Has 2 major types (type I/subendothelial deposit AND type II/dense deposit disease)

- **CLINICAL ASPECT:**
  Type I: "present mainly with nephritic syndrome"
  - Proteinuria (but < 3.5)
  - Hematuria >>>nephritic feature
  - Decreased **C3** level.
  - Increased **ASO** titer.

  Type II:
  - Mainly in children and young adults.
  - Mainly with nephrotic (proteinuria is higher)
  - Renal insufficiency.

MPGN-II (DENSE DEPOSIT DISEASE):
Not of immune complex origin
In BM. Material, there're alterations (instead of deposits)
With abnormalities in basement membrane

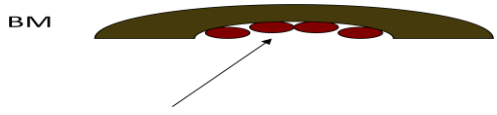
Unlike **MPGN-I** which is of immune complex origin & With complement system activation

- **IT COULD BE:**
  - Primary (Idiopathic) (we don't know what is the reason).
  - Secondary

- **ASSOCIATED CONDITIONS**
  - SLE
  - Sjogren's Syndrome.
  - Complement deficiencies.
  - Chronic infection
    (Endocarditis, Hepatitis, Malaria)

SJOGREN'S SYNDROME:
autoimmune syndrome affects certain glands in the body.
(salivary glands, lachrymal glands: tears)
→ decrease water production.

- **SECONDARY MPGN: secondary to:**
  - Hepatitis B or C (most frequent with MPGN)
  - Sickle cell Disease or Trait
  - Malignancy.



CIC of known, unknown or suspected origin (from inside)
Compliment sys. activation <<<in type I

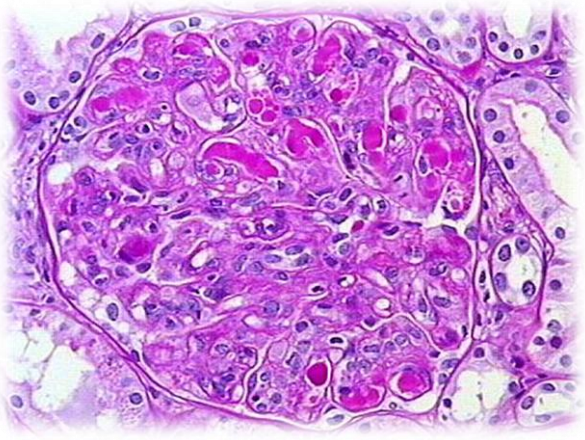
➢ **PATHOGENESIS**

Type I:

- Immune Complex Disease.
- C3 activation.
- Antigens.

Type II:

C3 nephritic factor (C3NeF)
activate the alternative complement pathway
→elaboration of biologically active complement fragments



➢ **MORPHOLOGY** (both types are similar)

- **ELECTRON MICROSCOPY**
  - Alterations to the basement membrane
  - Proliferation to glomerular cells (in the mesangium)
  - Leukocyte infiltrations.
  - Lobular architecture.
- **IMMUNOFLUORESCENT MICROSCOPY**

Type I
- **C3** : Peripheral lobular pattern
- **IgG:** Similar pattern

Type II
- **C3** : Widespread deposition

Lupus Nephritis

- **It affects** any organ of the body (the brain, blood vessels, lungs, kidney). More **frequent in** women than in men.
- Renal involvement occurs in about 70% of SLE (systemic lupus erythematosus) patients.
  Most patients have anti-dsDNA antibodies and are hypocomplementemic.
- The **histological changes** in lupus nephritis
  vary from mild mesangial cell proliferation to severe diffuse proliferative glomerulonephritis.
- About half of the patients with lupus nephritis have the **diffuse proliferative form** (i.e. the most severe form)
- ImmunoFluorescent and Electron Microscopy **reveal**
  mesangial and subendothelial immune complex deposits containing IgG, IgM, IgA, and C3.
  These complexes often contain ss- and ds- DNA.

SLE CLASSIFICATION

Classification of Lupus Nephritis (IMP):

Class I: Minimal Mesangial lupus nephritis

Mesangial:
there're proliferations but the capillaries are NOT obliterated

Class II: Mesangial proliferative lupus nephritis (mild mesangial)

Class III: Focal and segmental necrosis and proliferation.

Class IV: Diffuse segmental (IV-S) or global (IV-G) lupus nephritis (more than 50% of gloom affected

Class V: Diffuse membranous lupus nephritis ((may occur in combination with class III or IV))

Class VI: Advanced sclerosing lupus nephritis (It is more sclerosing and then becomes fibrtic) >> **90% sclerotic glomeruli**

The pathologist **should indicate**

- **the grade** (mild, moderate, severe) **of** tubular atrophy
- **Severity** of Arteriosclerosis or Other Vascular Lesions
- Interstitial Inflammation and Fibrosis

III. RAPIDLY PROGRESSIVE GN - NEPHRITIC SYNDROME CRESCENTIC GN: CR-GN

A. DEFINITION:

It is a clinical condition with **rapid and progressive decline in renal function** and active **urine sedimen**

Usually characterized by an **inflammatory process that results in the formation of cellular crescents within Bowman's space** (crescents).

Takes a Crescentic Appearance as: Parietal cells of Bowman's capsule proliferate + a monocyte/macrophage infiltrate.

Crescent is an extracapillary proliferation (it forms outside of capillary tuft)

B. SIGN AND SYMPTOMS:

- Rapid decline in renal function (over several days or few weeks).
- Active urine sediment.
- Usually no edema and no hypertension.
- Renal failure and death result in weeks to months.

C. CAUSES:

Idiopathic or primary crescentic glomerulonephritis caused by autoimmune diseases.

According to its autoimmune cause, it can be divided into three types:

➢TYPE I: ANTI-GBM DISEASE: (GBM: glomerular basement membrane)

Deposits of IgG ((Linear)), often with C3, on **the GBM.**

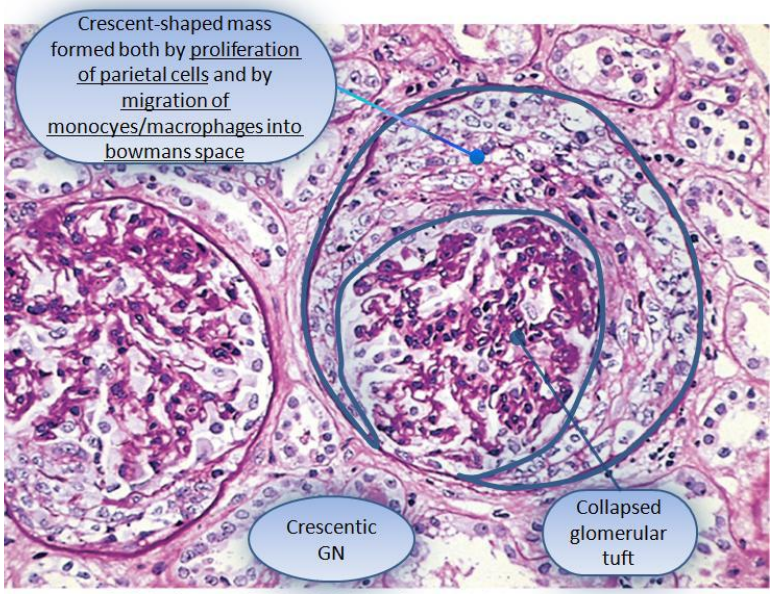
Goodpasture Syndrome :

Sometimes they also bind to **pulmonary capillaries** →producing: pulmonary hemorrhages & with renal failure.

(if there is **no pulmonary involvement** → it is a pure type I CrGN).

Patient present with **hemoptysis (blood-streaked sputum)** and **renal failure.**

Usually in **males**



➢TYPE II: IMMUNE COMPLEX-MEDIATED:

Means it could be secondary to

SLE, MPGN, IgA nephropathy and many things.

You will see complex deposition on the glomeruli.

TYPE III: PAUCI IMMUNE (ANCA-ASSOCIATED):

Pauci- refers to few or some.

From the name you can imagine that there is not as much immune interaction.

There are no anti-GBM Ab's or immune complexes to be found.

The causative agent is the Antineutrophil Cytoplasmic Ab.

It is a complication of Vasculitides

Microscopic form (same as) PAN -Wegener's granulomatosis - Churg-Strauss syndrome - Drug-induced vasculitides.

Other primary glomerulonephritides:
post-infectious GN, IgA nephropathy, MPGN, etc.
Systemic diseases (SLE, RA, Henoch-Schonlein purpura)

D. **MORPHOLOGY:**

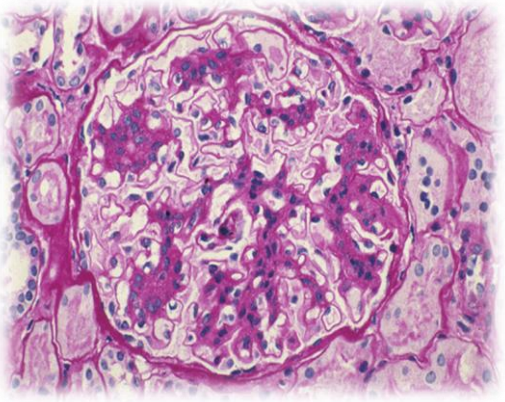
- Grossly kidney is enlarged with:
  - Tiny Reddish Dots.
  - Pale and Smooth Surface.
- Microscopically:

In The Crescent and the collapsed, fragmented capillary tuft: Mononuclear cells + you may see giant cells.
(Monocytes, Epithelioid Cells, Proliferated Parietal Epithelial Cells From Bowman's Capsule, Polymorphonuclear Neutrophils)

> **RPGN is a reversible disease if** the problem is treated early by immunosuppressant.
> **but if** it becomes fibrous (the crescent) → the kidney is gone.

IV. ASYMPTOMATIC HEMATURIA (PROTEINURIA)

- Hematuria or proteinuria (persistent micro-hematuria)
- Normal renal function (early during the course)
  (that's why we call it Asymptomatic)
- Not associated with hypertension or edema



CHARACTERIZED MORPHOLOGICALLY BY EITHER:

- Focal necrotizing AND/OR inflammatory lesions of the glomeruli.
- Basement membrane anomalies that result in greater capillary fragility.

V. END STAGE RENAL DISEASE

I. Chronic Renal Failure **May come from:** Azotemia Active urine sediment (variable) Proteinuria (variable) Past history of RPGN, nephrotic syndrome or nephritic syndrome Hypertension **Definition:** End-stage renal disease is with widespread global glomerular obsolescence (sclerosis), tubular atrophy, interstitial fibrosis, and variable degree of arterial & arteriolar sclerosis. A more precise diagnosis can often be established by immunohistochemical and ultrstructural studies.	**A. Extent of the problem;** Medical costs and ESRD **B. Uremic syndrome** 1. Skin manifestations - pruritus, uremic "frost", skin 2. Cardiac manifestations - uremic pericarditis 3. Neurological manifestations - peripheral neuropathy 4. Pulmonary complications - pneumonitis and hemorrhage 5. Hematopoietic manifestations - anemia, bleeding diathesis 6. Skeletal abnormalities - renal osteodystrophy (secondary hyperparathyroidism) 7. Other - metabolic imbalances **C. Pathogenesis of uremic syndrome** 1. Uremic "Toxins" 2. Middle molecules 3. The "Trade off" hypothesis
II. Treatment of End Stage Renal Disease	A. Supportive therapy B. Dialysis C. Renal transplantation