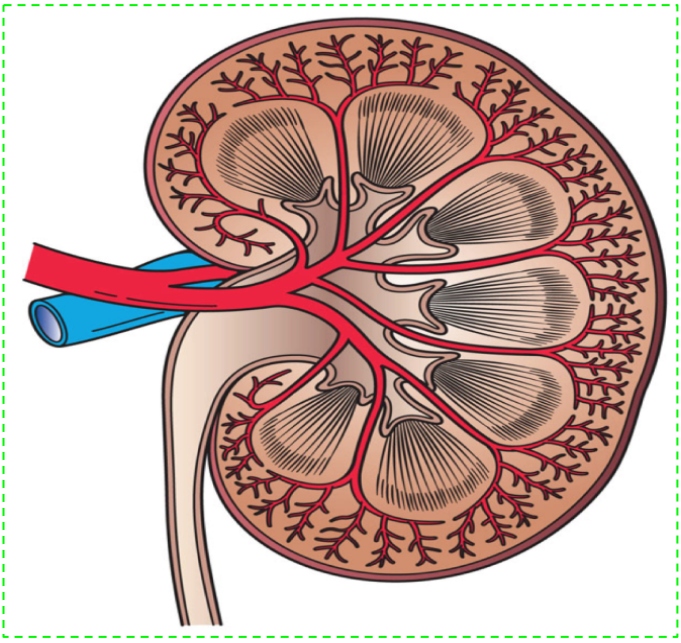
L1 Immune complex nephritis



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Objectives:

- Understand the importance of immune complexes in the pathogenesis of renal injury.
- Learn that immune complexes form in the circulation and may deposit in different tissues.
- Understand the dynamics of deposition of complexes which depend on the size and rate .
- Identify the different types of renal disease based on the site of deposition of the immune complexes.

Red: important
Purple: notes from doctor
Gray: extra

Hypersensitivity reactions:

can be divided into four types: type I, type II, type III and type IV, based on the mechanisms involved, size and time taken for the reaction to occur.

- ❖ The main hypersensitivity reactions in our lecture are type II and type III.

Hypersensitivity II:

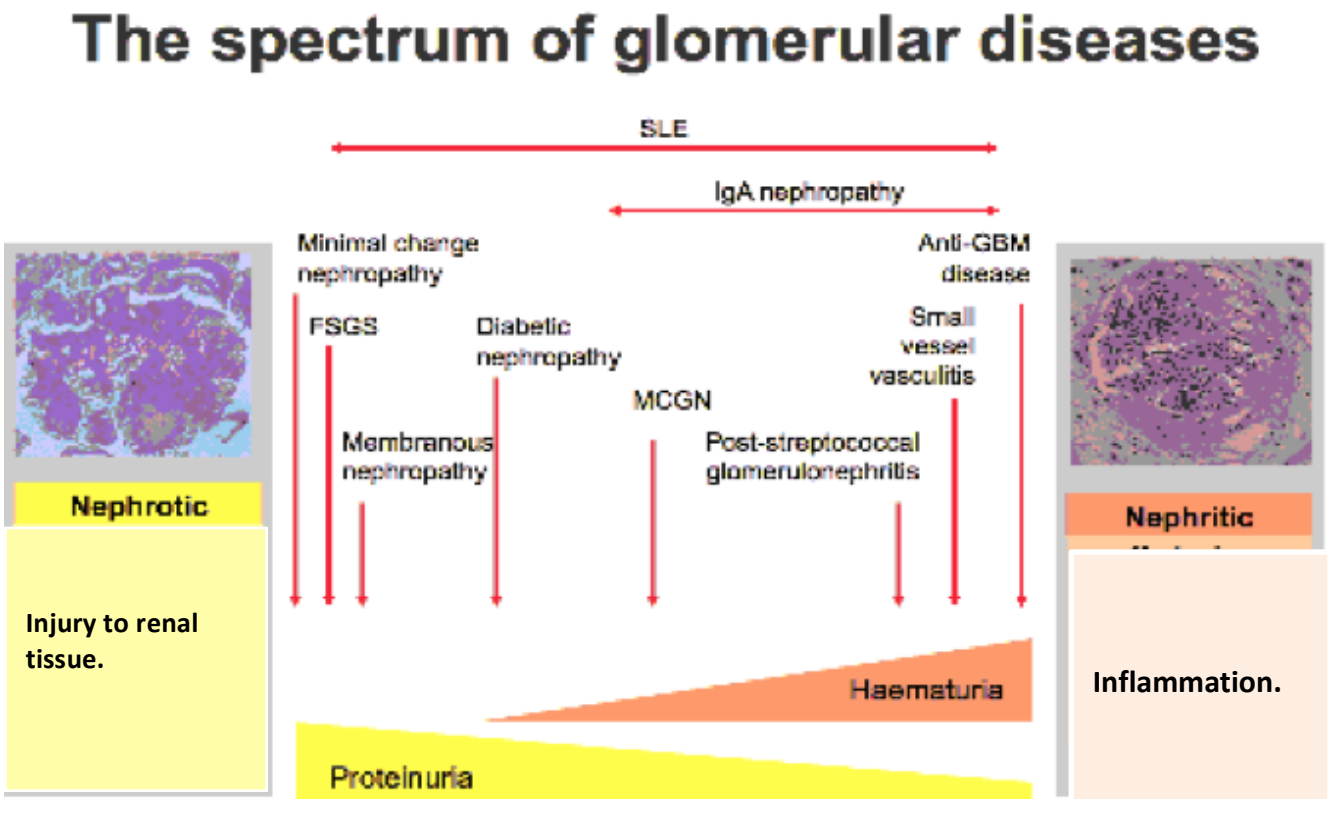
Antigens are part of the cell membrane of any tissue (HUMAN TISSUE) -> antibodies bind to them forming an immune complex -> induces inflammation.

Hypersensitivity III:

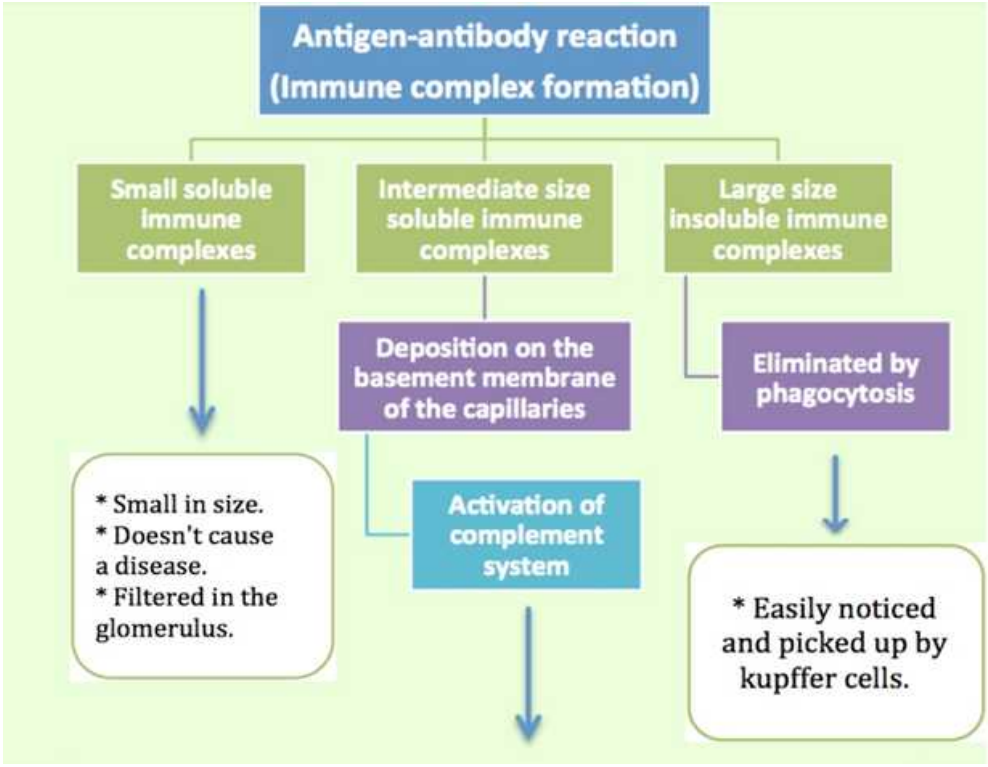
Microbial Antigens are circulating in the blood -> antibodies bind to them forming an immune complex.

Immune Complex Nephritis :

Complexes of antibody with various microbial (non-self antigens) or self antigens induce type II or III hypersensitivity reactions in the kidney.



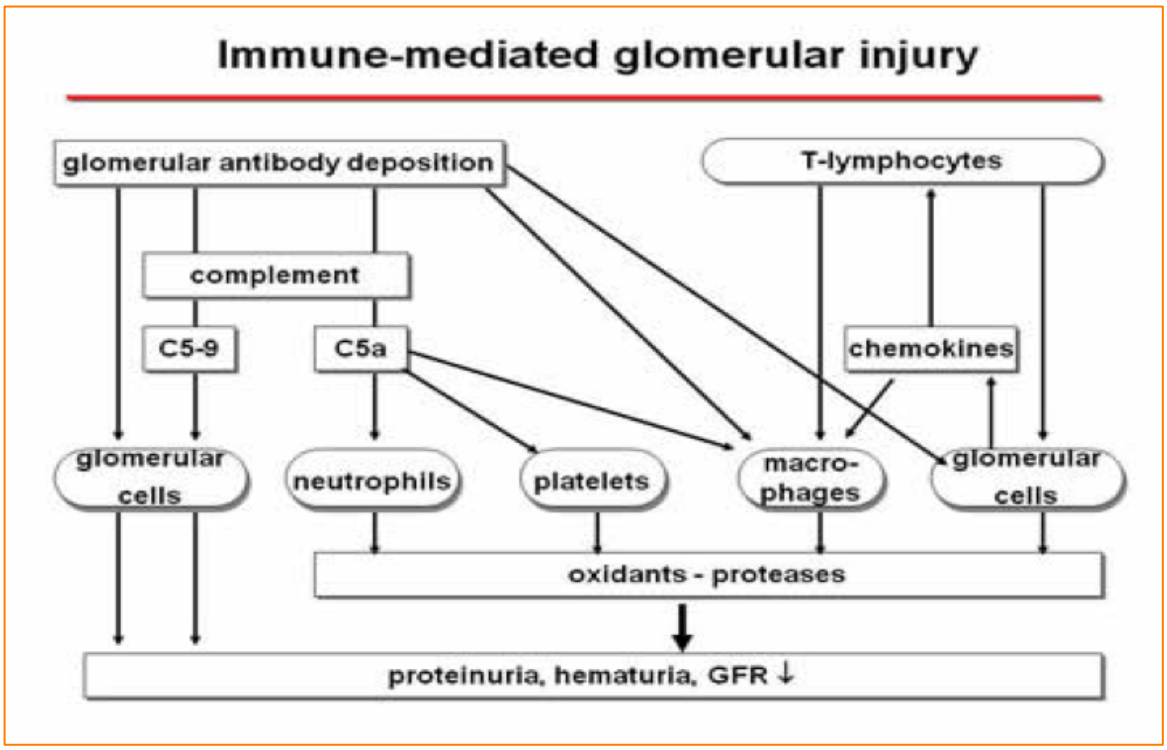
Pathogenesis of immune-complex nephritis (Type III hypersensitivity reactions)



* Not effectively picked up by the kupffer cells.
* Able to deposit in the tissues
* Rate of production: like in SLE (autoimmune disease)
* Causes a disease.

(The antigens are self-proteins, which mean that the immune complexes are continuously released in high amounts over a prolonged period of time). These high amounts can't be effectively picked up by reticular endothelial system. And excessive amounts keep on circulating and eventually it will deposit in different tissues (like kidneys for example arterioles of the glomerulus are highly convoluted and the pressure inside is high so the chance of immune complexes to deposit is high) and start inflammation (the most dangerous immune complexes are the medium sized ones)

KUPFFER CELLS: are specialized macrophages located in the LIVER



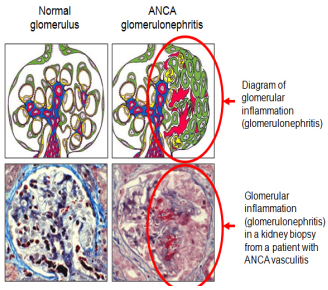
*Glomerulonephritis it's an injury initiated by the immune complexes deposited in tissues ⟶ activate complements (C5-9\ c5a) ⟶ infiltration of different cells (neutrophils\platelets\macrophages\glomerular cells) and activation of T cells lead to the release of chemokines and more inflammatory cells aggregation ⟶ destruction of the tissue (glomeruli) ⟶ ↓ GFR , proteinuria and hematuria.

* Macrophages are the cells causing a connection between innate immunity (first line of defense mainly here phagocytosis) and adaptive immunity (2nd line of defense which is divided into humoral immunity (Abs) and cellular immunity (T-cells)).

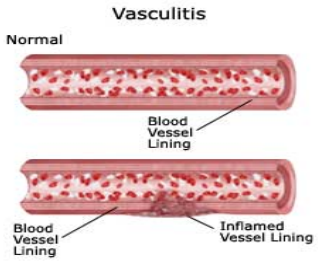
Remember: the constant release of inflammatory cells and enzymes to defeat the infected area will increase the risk to move to the next stage (Acute glomerulonephritis) ⟶ (Chronic glomerulonephritis)

Where do they deposit mostly?

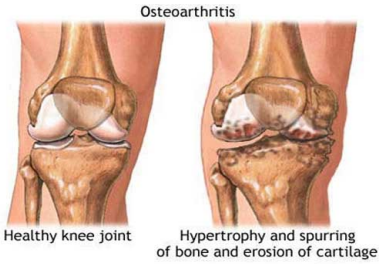
- Complexes accumulate in tissues where filtration of plasma occurs. This explains the high incidence of:



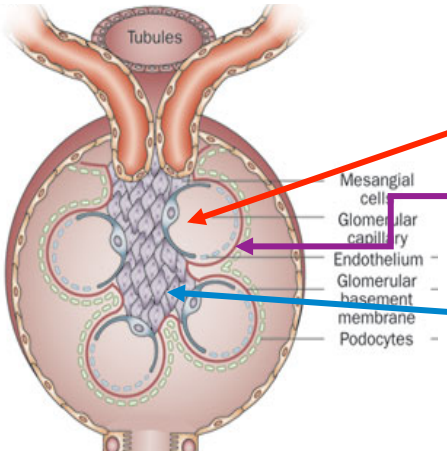
Glomerulonephritis (deposition in the kidney)



Vacuities (Deposition in the arteries)



Arthritis (Deposition in the synovial joints)



Immune complex deposition cause injuries in:

Endocapillary injury: present with
Hematuria, proteinuria, ↓GFR, inflammatory lesion " the symptoms will be clear"

Epithelial injury: present with
Necrotic range, proteinuria, no inflammatory lesion (no clear symptoms)

Meningeal injury: present with
Microscopic Hematuria, proteinuria. (no clear symptoms)

The symptoms depend on the site of immune complex deposition.

Types of immune-mediated renal injury

Antibody-mediated Injury:

- Membranous glomerulonephritis
- IgA nephropathy
- Membrano-proliferative glomerulonephritis
- Post infectious glomerulonephritis
- Anti-glomerular basement membrane disease

1-Post Infectious Glomerulonephritis (GN) (Post-streptococcal):

It is an acute glomerulonephritis induced by streptococcal infection.
but What is the acute glomerulonephritis?

it is considered as a Diffuse proliferative GN (ProliferativeGN) **ALL GLOMERULI IS EFFECTED NOT ONLY PARTS OF IT**

Diffuse proliferation of glomerular cells **THEY PROLIFERATE**

frequent infiltration of leukocytes (especially neutrophils)

Hypocomplementemia
because it is consumed in the immune process
(inflammation)

Granular deposits of IgG & complement on the Glomerular Basement Membrane

***is the typical features of immune complex disease**

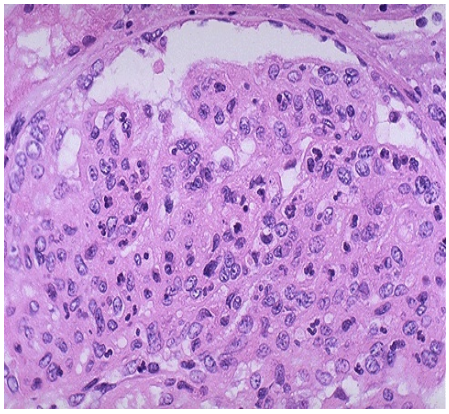
Etiology	• known streptococcal types called: nephritic strains • more common in children
clinical presentation	• 7-14 days *after* pharyngitis. • 14-21 days *after* (skin infection) Abrupt onset (Acute nephritic syndrome)
Antibody	• IgG antibodies cross react to the glomeruli
antigene	• Strep antigens which trigger the antibodies
hypersensitivity	• type III
pathogenesis	•Circulating immune complexes during filtration in the glomerulus deposit in the kidney •Immune complexes activate complement

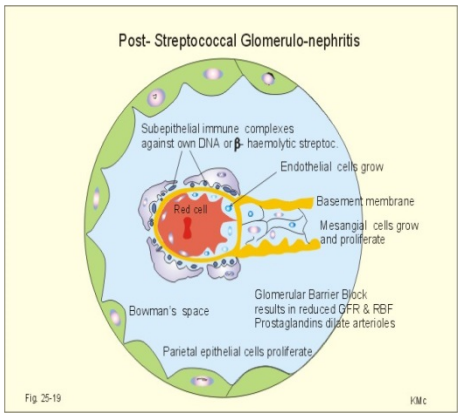
Abrupt : SUDDEN

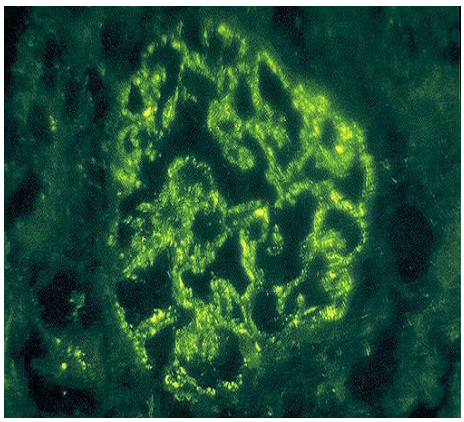
Diagnosis:

** Culture: In most children bacterial culture will be negative

Anti –streptolysin-O antibody(ASO)	The anti-DNAse B titre
is not the best indecator of streptococcal skin sepsis	is a better indicator of streptococcal skin sepsis
Cholesterol and lipids in skin suppress the ASO antibody response	is not affected by skin lipids

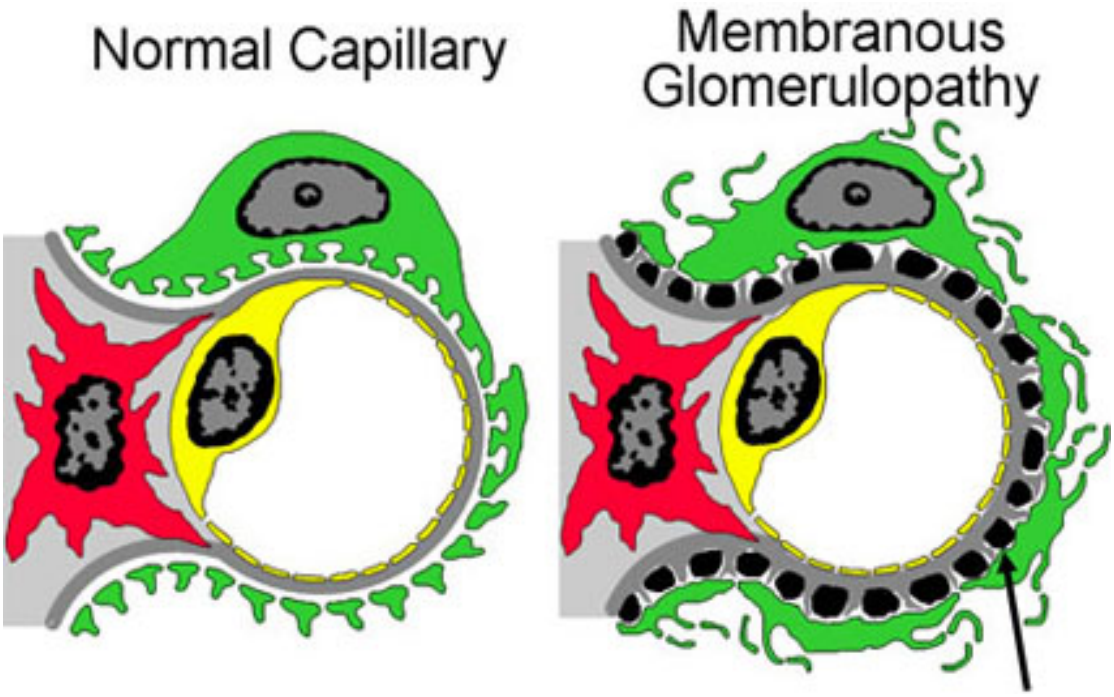






the immune deposits are distributed in the capillary loops in a granular, bumpy pattern because of the focal nature of the deposition process.
It can be tested by IMMUNOFLUORESCENCE

2-Membranous Glomerulonephritis (Membranous nephropathy) :

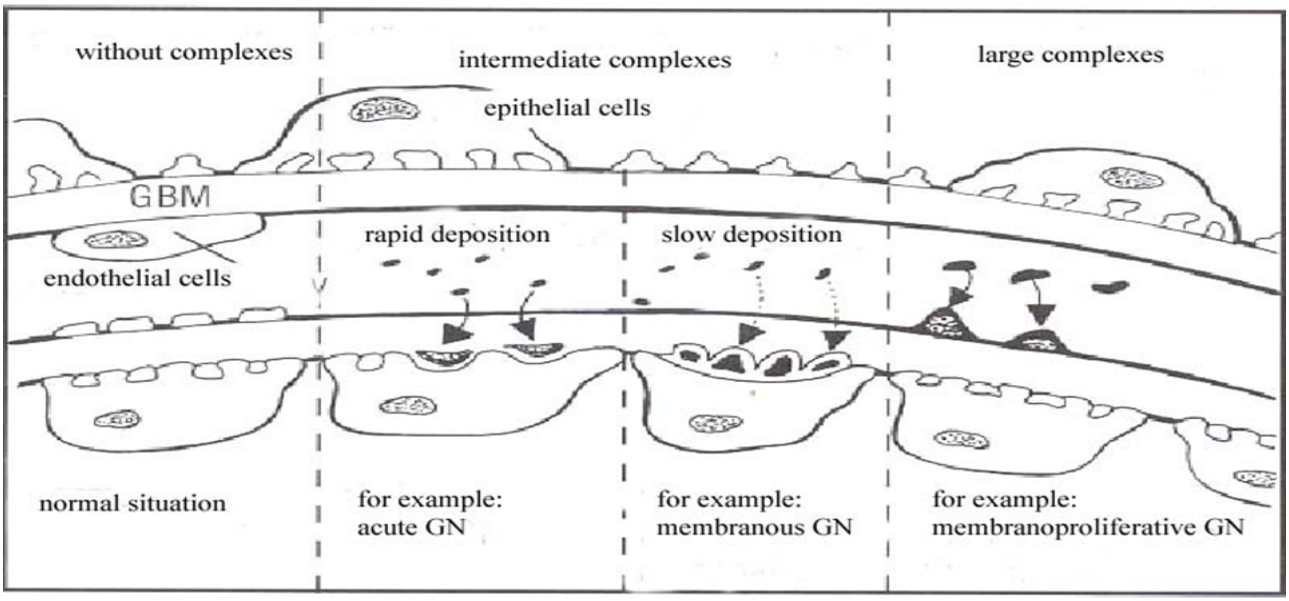


- A slowly progressive disease
- considered as a form of chronic immune-complex nephritis
-Most common between 30 - 50 years

3- Membranoproliferative Glomerulonephritis MPGN OR Mesangiocapillary (GN):

<table>
<tr><td colspan="2">It is a chronic progressive glomerulonephritis that occurs in older children and adults, it has 2 main types</td></tr>
<tr><td>Type II MPGN
Also known as : dense deposit disease</td><td>Type I MPGN (80% of cases)</td></tr>
<tr><td>The fundamental abnormality is :
- Excessive complement activation.
- Some patients have autoantibody against C3 convertase called: C3 nephritic factor.
- Characterized by intramembranous dense deposits</td><td>-Circulating immune complexes have been identified
-May occur in association with hepatitis B&C antigenemia,extra-renal infections or SLE
- Characterized by subendothelial and mesangial deposits
DR mention the following Q : Give an example of MPGN?
answer: Hepatitis B or C and SLE
.</td></tr>
</table>

Note the complex is large because it has a lot of antibodies or a lot of complement and it can't pass through the glomeruli so it affects the mesangial cell only
"the issue is small because of complex's large size" , remember we said that the medium size deposits are the most sever



3-IgA Nephropathy (Berger disease):

-most common from of primary glomerulonephritis in the world

- Affects children and young adults

- Begins as an episode of gross hematuria that occurs within 1-2 days of a non specific upper respiratory tract infection

The pathogenic hallmark is :

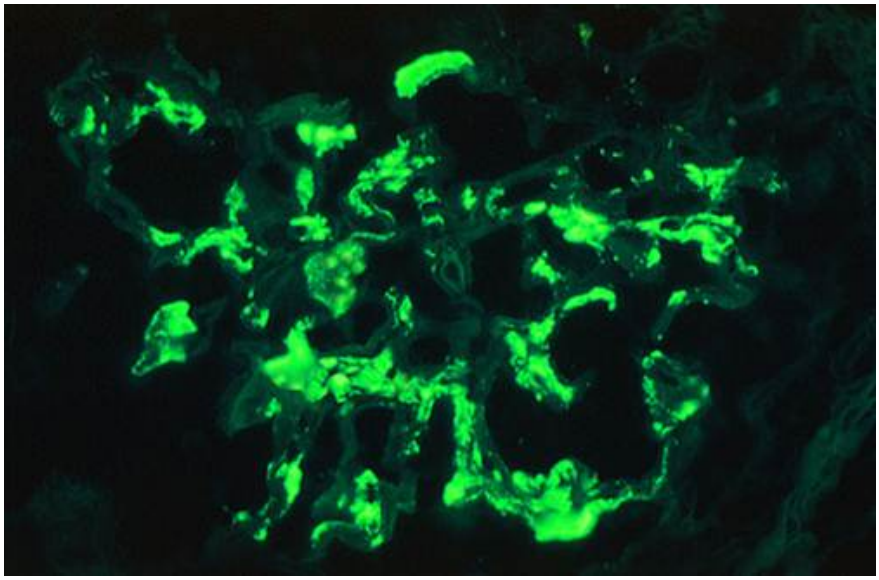
1-Deposition of IgA & complement C3 in the mesangium only!

2-There is evidence of :

Activation of complement by the alternative pathway "because it's faster" (serum complement C2 and C4 will be normal)

important note:

As we took on foundation block
Alternative pathway"activated by bacterial products " :
it include C3,c5,c6,c7,c8,c9
so that's why C2 & C4 are normal because they belong to the classical pathway Not the alternative!!



This immunofluorescence pattern demonstrates positivity with antibody to IgA. The pattern is that of mesangial deposition in the glomerulus. This is IgA nephropathy.

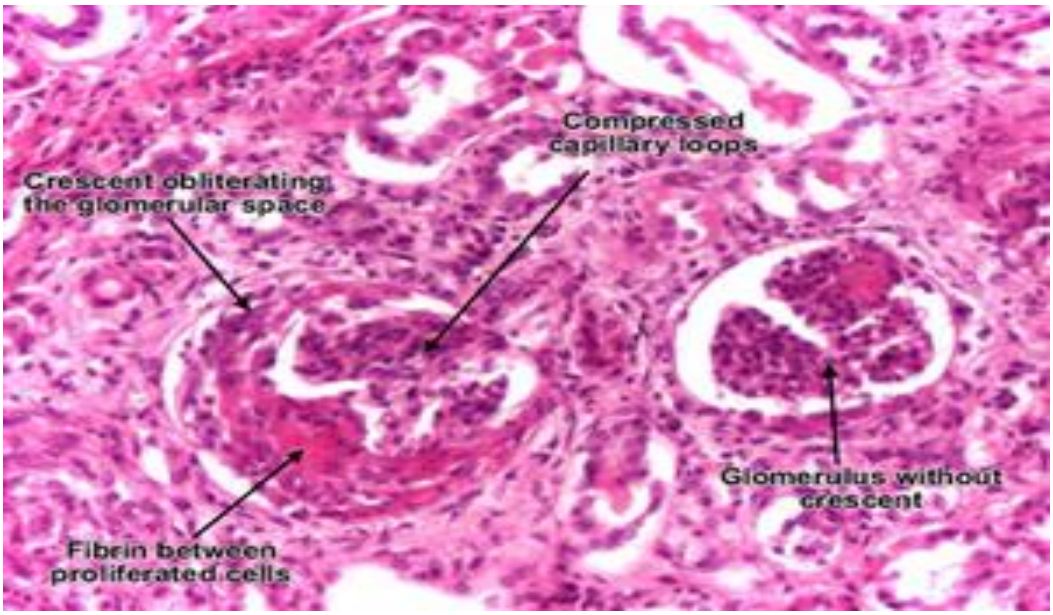
Rapidly Progressive (Cresentic) Glomerulonephritis (RPGN)

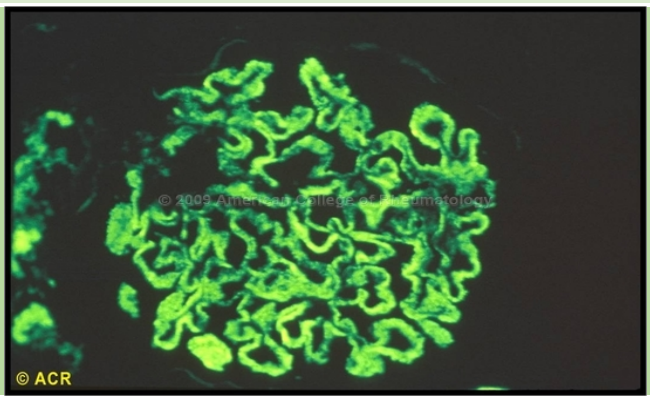
Bad ,going to have renal failure

- ✓ RPGN is a clinical syndrome and not a specific form of GN
- ✓ In most cases the glomerular injury is immunologically mediated
- ✓ A practical classification divides CrGN into three groups on the basis of immunologic findings

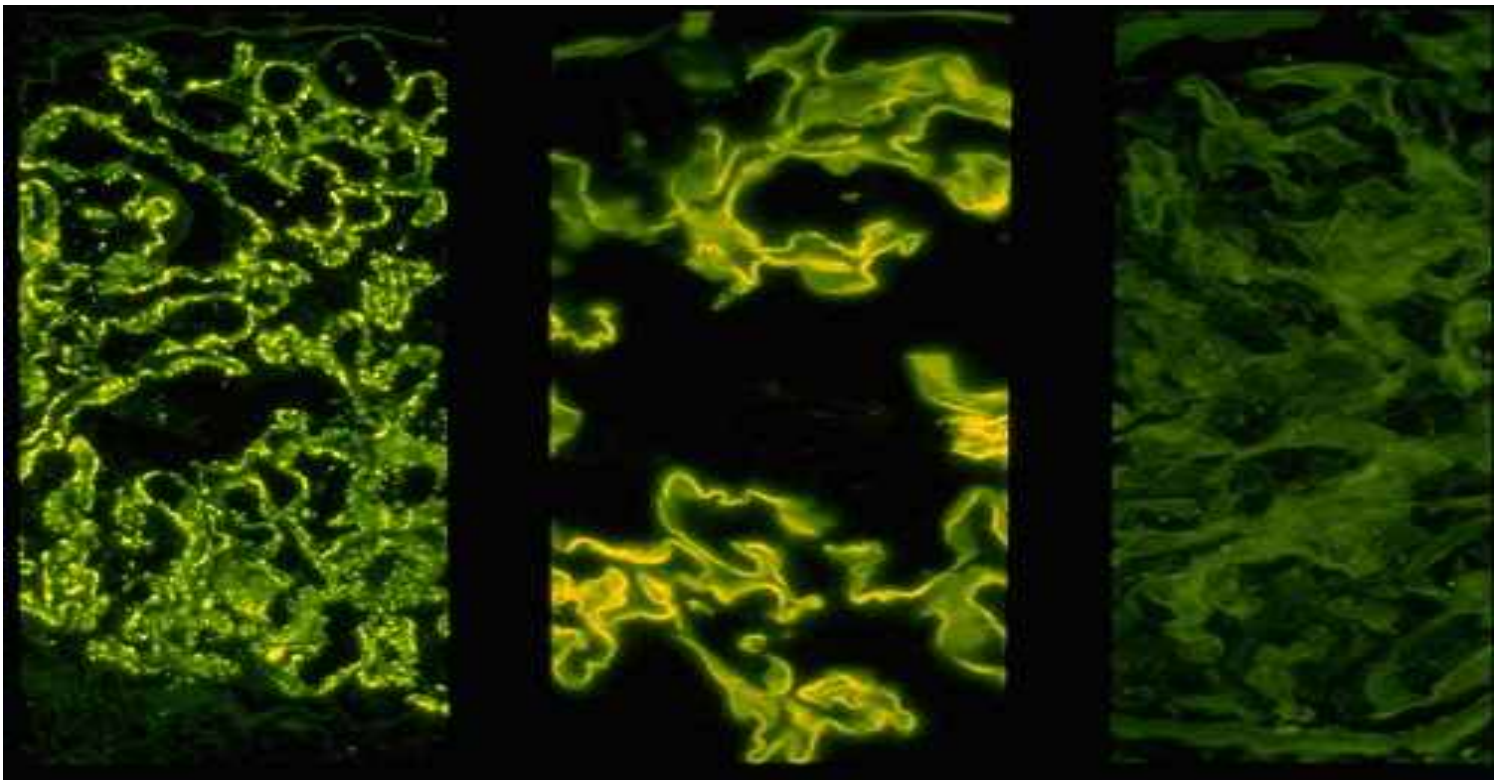
Types:

- ⊖ **Type I (Anti-GBM antibody) (Cresentic GN)**
- ⊜ **Type II (Immune complex - mediated Cresentic GN)**
- ⊛ **Type III (Pauci-immune) Cresentic GN**



Type I (Anti-GBM antibody)	Type II (Immune complex - mediated Cresentic GN)	Type III (Pauci-immune) Cresentic GN
✓ Characterized by linear deposition of IgG and C3 on the GBM	✓ May occur as a complication of any of the immune complex nephritides Post infectious, SLE, IgA nephropathy	✓ Defined by the lack of anti-GBM antibodies.
✓ Goodpasture syndrome (an example)	✓ Characteristic granular (microscopically): ✓ A lumpy-bumpy pattern of staining of the GBM for immunoglobulin and complement	Most cases are associated with: Anti-neutrophil cytoplasmic antibodies in serum (ANCA) and systemic Vasculitis
✓ Antibodies bind also in the pulmonary alveolar capillary basement membranes		

Pauci : means less or deficiency

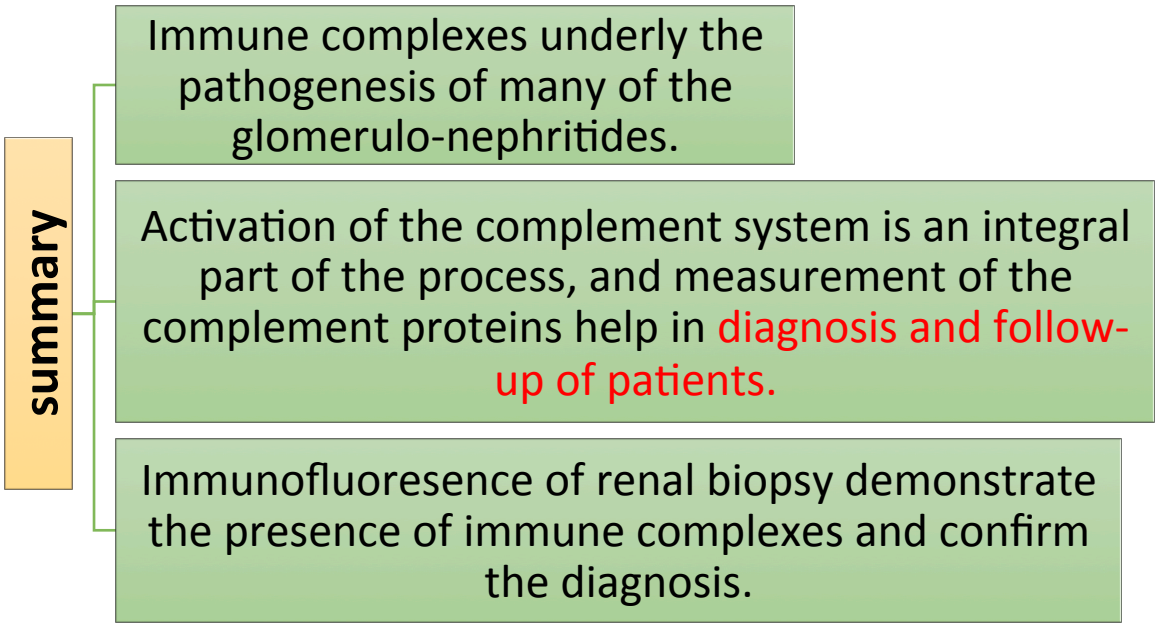


Granular staining (Immune complex)

Linear staining (Anti-GBM)

No antibody staining (Pauci associated with vasculitis)

AN EXTRA SMART ART , to refresh your memories.



SAQs:

1) Poststreptococcal GN Caused By :
nephritic strains.

2) The best indicator of streptococcal skin sepsis is? , and WHY is it better than ASO titer:
A- The anti-DNAse B titer.
B- Because of Cholesterol and lipids in skin suppress the ASO antibody response but not the anti-DNAse B antibody titre.

3)Membranoproliferative Glomerulonephritis Type I association with:
- hepatitis B&C antigenemia,
- extra-renal infections or SLE

4) What is the difference between Type I and II Membranoproliferative Glomerulonephritis:
Type I: Characterized by subendothelial and mesangial deposits
Type II: Characterized by intramembranous dense deposits

5) What is the pattern of staining of the GBM in Type II (Immune complex - mediated Cresentic GN):
Lumpy bumpy pattern.

MCQs:

1) Vasculitis deposition of complex in the:

A- Kidney.
B- arteries.
C- Synovial joints.
D- All of the above.
Answer : B

2) In Post infection Glomerulonephritis presentation there is an abrupt Onset in. :
A- pharyngitis.
B- Skin infection.
C- Acute nephrotic syndrome.
D- Non of the above.
Answer: C

3) In Diffuse proliferation GN there is a Diffuse proliferative of glomerular cells and frequent infiltration of leukocytes especially:
A- Macrophages
B- Lymphocytes.
C- Plasma Cells.
D- Neutrophils.
Answer: D

4) Typical features of immune complex disease :
A- Hypocomplementemia.
B- Granular deposits of IgG & complement on GBM.
C- Hypercomplementemia.
D- A+B
Answer: D

5) Membranous Glomerulonephritis is:
A- Slowly Progressive.
B-A form of chronic immune-complex nephritis.
C-A form of acute immune-complex nephritis.
D- A+B
Answer: D

6) In IgA Nephropathy There is evidence of Activation of complement by
A- the alternative pathway
B- Lectin pathway.
C- Classic pathway.
D- All.
Answer: A

7) Type I (Anti-GBM antibody) (Cresentic GN) Characterized by linear deposition of
A- IgA& C3 on the GBM.
B- IgM & C2 on the GBM.
C- IgG & C3 on GBM.
D- IgG & C2 on GBM.
Answer: C