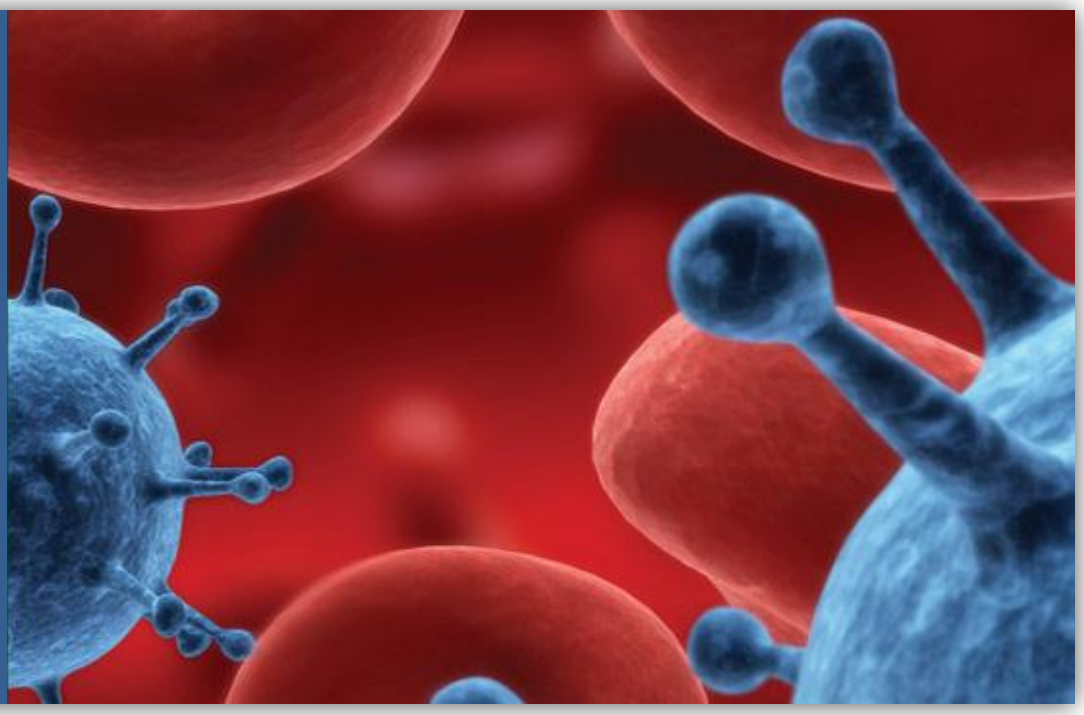
Immunology Team

Immuno Complex Nephritis



Team Members

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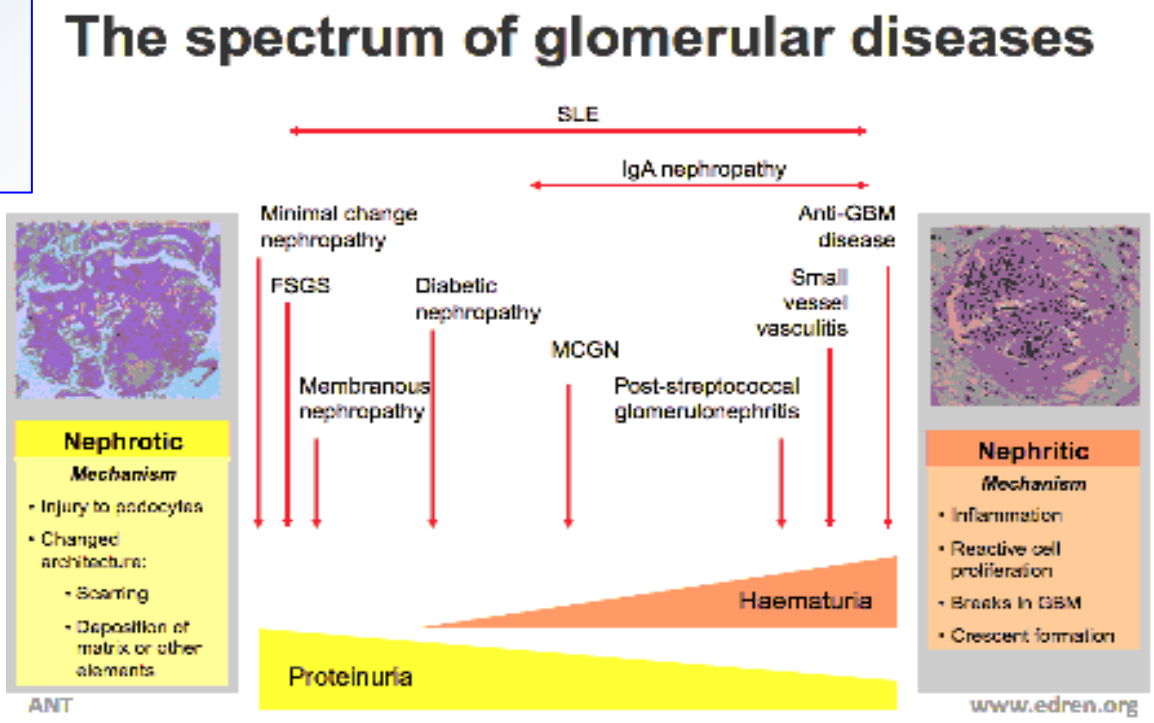
Objectives

- 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.

These complexes keep circulating in the system then they are deposited in tissue and cause the disease.

Complexes of antibody with various microbial OR self-antigens induce type II or III hypersensitivity reactions in the kidney:



The spectrum is either acute damage to the glomeruli leading to proteinuria and might end up with hematuria (left mainly about protein loss) or extreme damage that the kidney can't hold the protein which leads to a drop in the osmotic pressure and that leads to fluid retention → edema (right mainly about tissue damage)

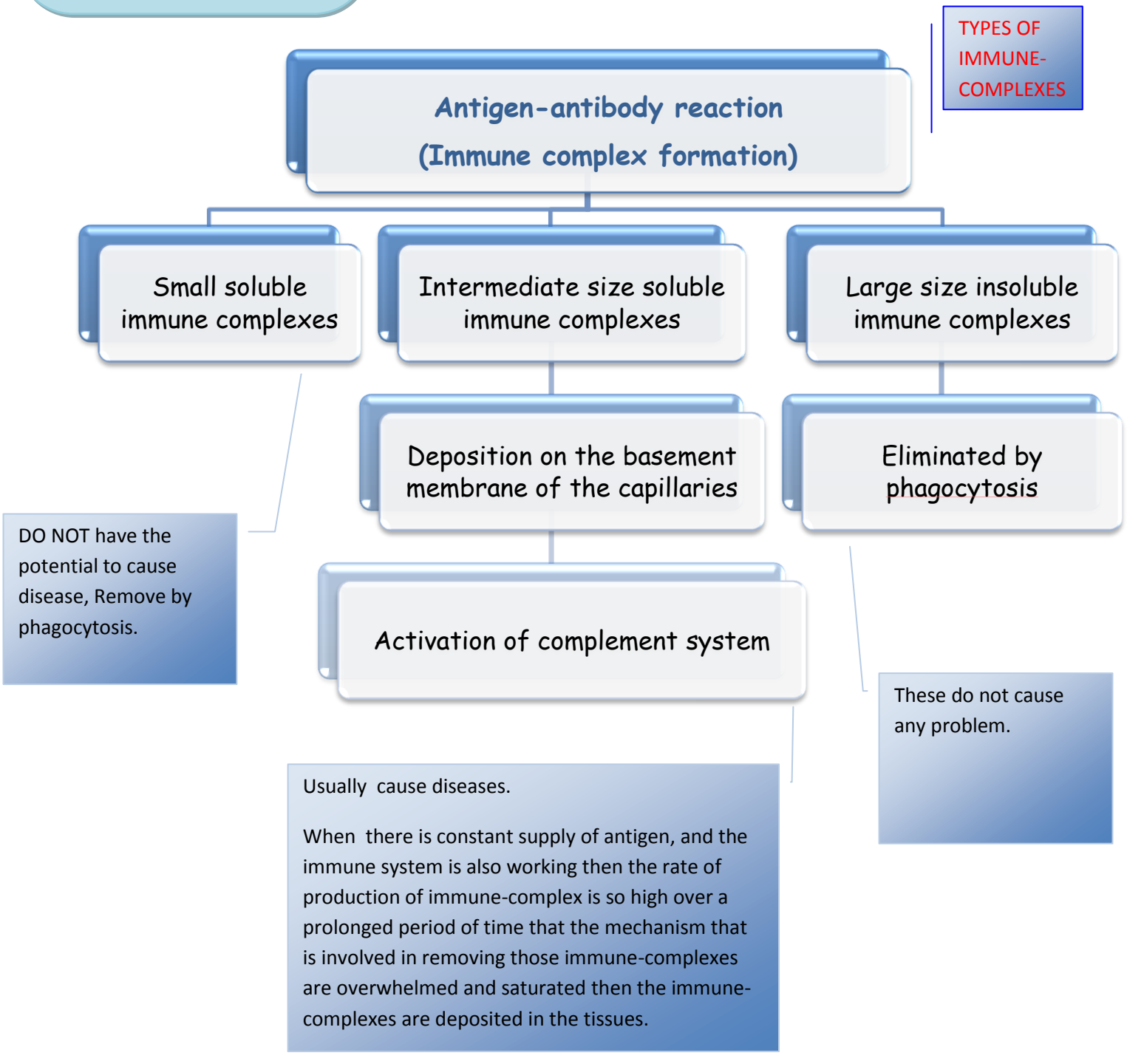
* Mainly nephritic is due to inflammation. And generally came with hematuria.

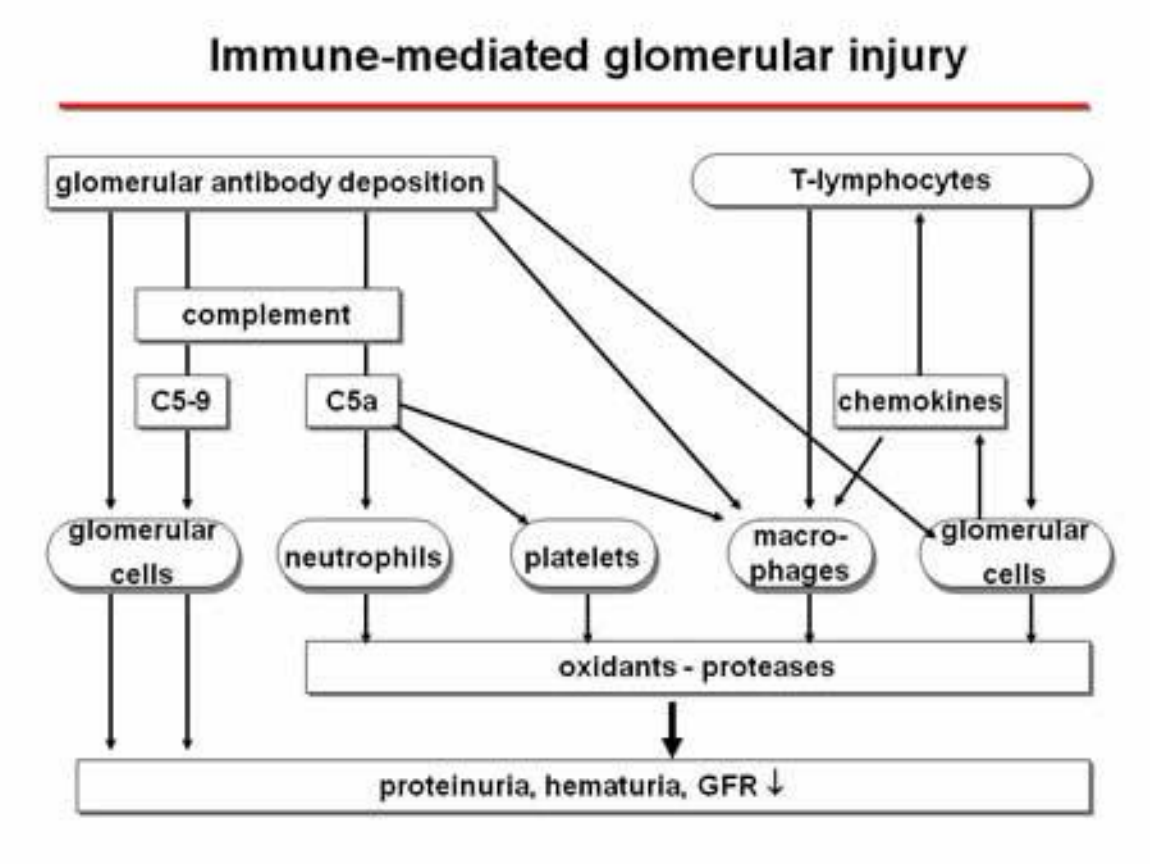
Immune-complex is an antigen binding to an antibody.

If the antigen is located in the tissue, it will cause damage directly where the antibody is in that area. But if the complex is in the blood it will cause damage where it is deposited eg. Joints, kidneys and skin.

Pathogenesis of immune-complex nephritis

(Type III hypersensitivity reactions)





The immune-complex is deposited in pores of the basement membrane of the glomeruli or there are antigens in the basement membrane that become targeted by the immune system.

Whenever there is antigen-antibody reaction, it will start inflammation by activating complement ← the job of complement is to destroy the tissue when it is activated

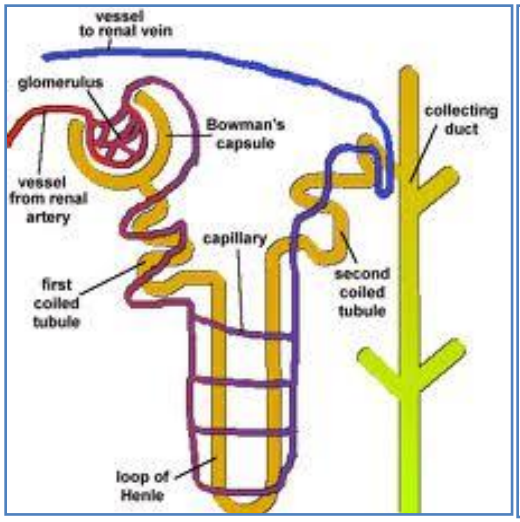
That is the cause of the destruction of the basement membrane of the glomerulus, there for there will be leakage of protein and blood and other substances.

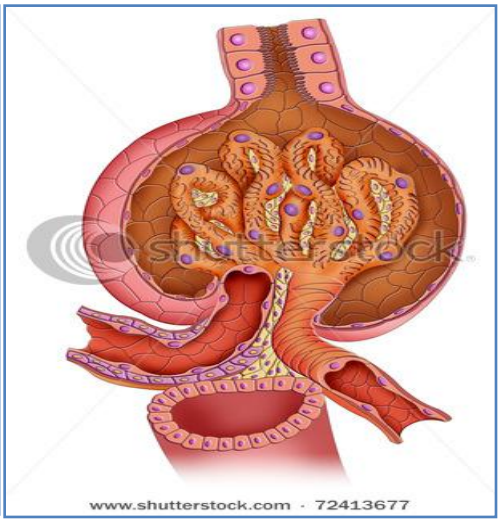
Site of deposition:

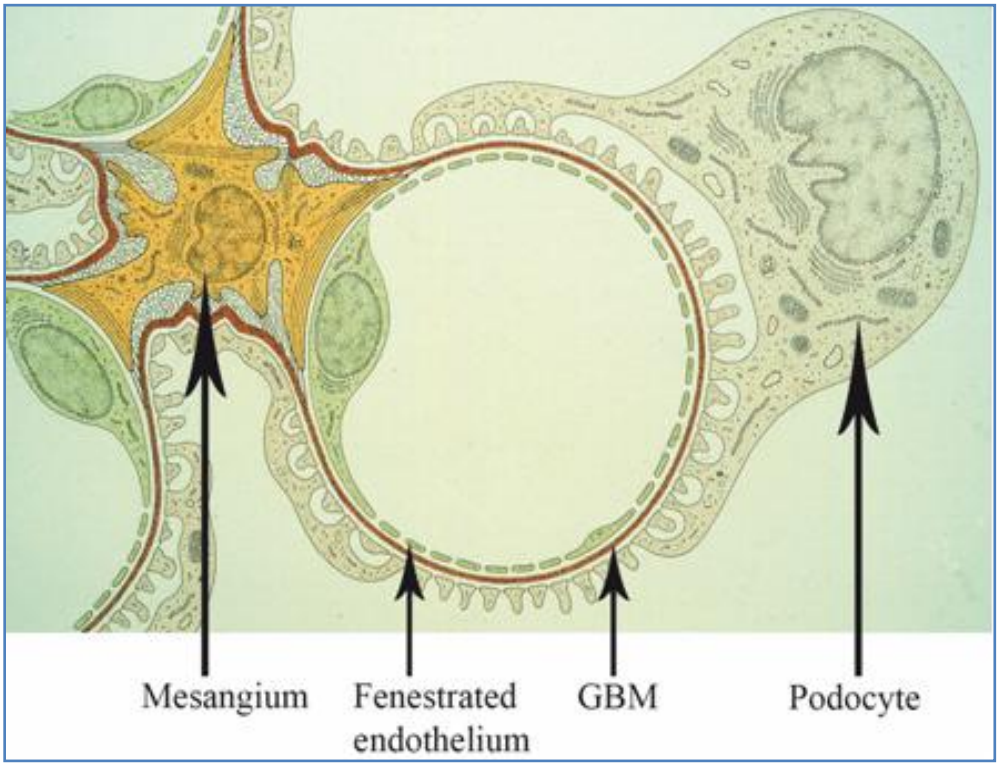
- Complexes accumulate in tissues where filtration of plasma occurs. This explains the high incidence of:
    1. Glomerulonephritis (deposition in the kidney)
    2. Vasculitis (deposition in the arteries)
    3. Arthritis (deposition in the synovial joints)

* The immune complex can deposit in any place but mainly in kidney, arteries and synovial joint.

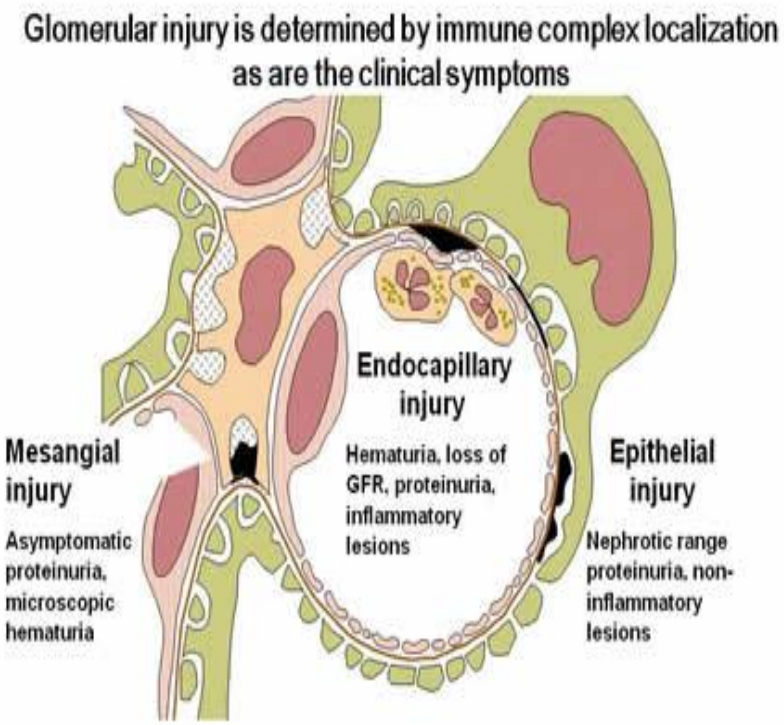
Nephron and glomerulus







Normal cut section of the glomerulus



Sites of deposition of the immune-complexes:

1. **The mesangial → sever damage because of the access to cytokines and other cells.**
2. **Under endothelial cells (sub endothelium)→ most likely to cause damage because it has access to cells involved in the inflammatory reaction.**
3. **On the outer side of the basement membrane(epithelium)→ will cause slow damage but not severe as the previous two.**

Types of immune-mediated renal injury:

Any injury in the podocyte will cause proteinuria.

Antibody-mediated Injury:

- Membranous glomerulonephritis.
- IgA nephropathy.
- Membranoproliferative glomerulonephritis.
- Post infectious glomerulonephritis.
- Antiglomerular basement membrane disease. (good pasture syndrome)

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

Usually present after respiratory infection.

If the sudden onset it will be Acute nephritic syndrome.

Presentation:

- 7-14 days *after* pharyngitis.
- 14-21 days *after* (skin infection).
- Abrupt onset (Acute nephritic syndrome).
- Strep antigens trigger antibodies that cross-react to glomeruli.
- Circulating immune complexes during filtration in the glomerulus deposit in the kidney.
- Immune complexes activate complement.

Diffuse means: involving all the glomeruli in the kidney.

Proliferative means: increase of the size of the cells.

Features of Acute glomerulunephritis:

- Diffuse proliferative GN (PGN) __Post Infectious Glomerulonephritis
- Diffuse proliferation of glomerular cells and frequent infiltration of leukocytes (especially neutrophils)
- Typical features of immune complex disease :

- Hypocomplementemia

- Granular deposits of IgG & complement on GBM

Poststreptoccal GN

- Caused by known streptococcal types called: nephritic strains
- In most children bacterial culture will be negative
- Anti –streptolysin-O antibody (ASO) will be the only evidence
- The anti-DNAse B titre is a better indicator of streptococcal skin sepsis than the
- ASO titre.
- Cholesterol and lipids in skin suppress the ASO antibody response

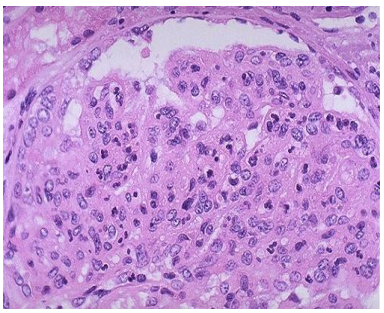
but not the anti-DNAse B antibody titre**.**

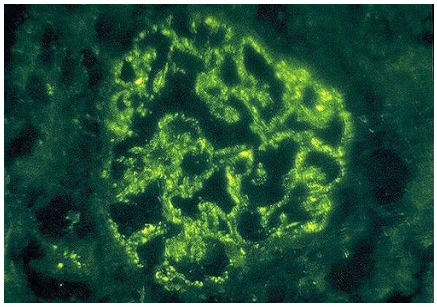
In most children bacterial culture will be negative → because they took antibiotic for pharyngitis. So we use (ASO).

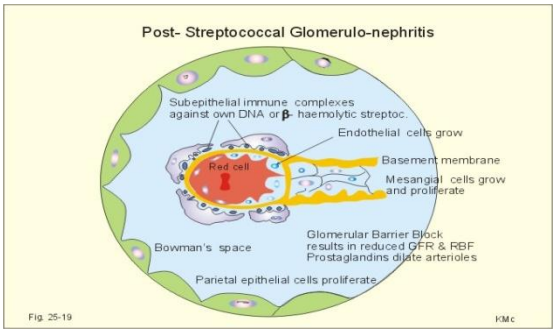
but in case of skin infection the ASO will NOT be useful or a good indicator. So the best one is The anti-DNAse B titre in this case.

Post streptococcal GN. Diffuse Proliferative GN

(Generalized damage to glomeruli)







The immune deposits are distributed in the capillary loops in a granular, bumpy pattern because of the focal nature of the deposition process.

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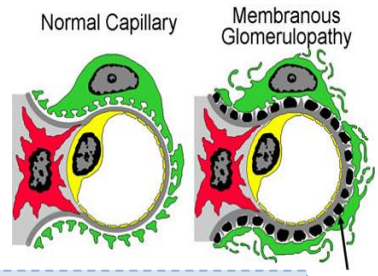
2. Membranous Glomerulonephritis (Membranous nephropathy)



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

(Membranous Glomerulonephritis is one of the intrinsic renal diseases that causes nephrotic syndrome that is found in the blood capillaries)

In the membranous glomerulopathy the immune complex deposit on basement membrane.

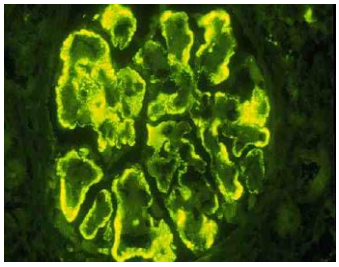
MPGN: involve mesngial cells and sub endothelial layer of capillaries.

3. Membranoproliferative Glomerulonephritis (MPGN) OR Mesangiocapillary GN

It is a chronic progressive glomerulonephritis that occurs in older children and adults

2 main types :

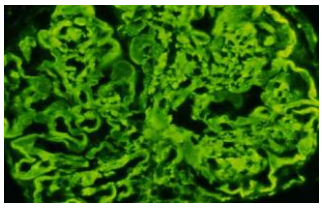
Type I MPGN (80% of cases)



The 'high-lighted green' seen in IF is only seen on the edges with negativity in the capillaries (capillaries not involved)

- Circulating immune complexes have been identified (type 3 hypersensitivity reaction)
- May occur in association with hepatitis B&C antigenemia, extra-renal infections or SLE
- Characterized by subendothelial and mesangial deposits

Type II MPGN Also known as : dense deposit disease (DDD) .



The IF observed is dense everywhere (equal thickness)

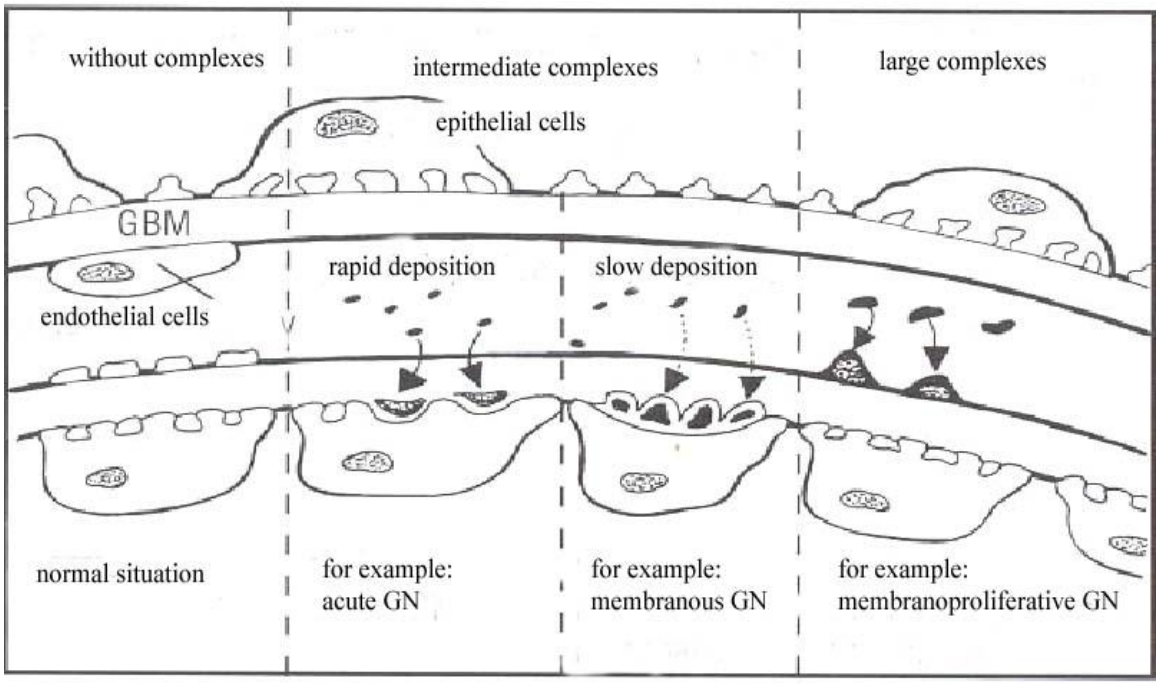
The fundamental abnormality is :

- Excessive complement activation.
- Some patients have autoantibody against C3 convertase called: C3 nephritic factor.
- Characterized by intramembranous dense deposits

The difference between type 1 and 2:

- Type1: main type, involve hepatitis B&C antigenemia, extra-renal infections or SLE. Deposit on subendothelial and mesangial.
- Type 2: intramembranous dense deposits.

Membranoproliferative GN



4. IgA Nephropathy (Berger disease)

The most common form of primary glomerulonephritis in the

world

- Affects children and young adults

- Begins as an episode of gross hematuria (blood in the urine) that occurs within 1-2 days of a non specific upper respiratory tract infection

The differnce between **Post Infectious Glomerulonephritis and IgA Nephropathy (Berger disease) is kidney lesion or (renal diesaese) appear (occur) after one to two weeks, but here within 1-2 days the patient precent with heamaturia .**

An easy way 2 help u memorize:

Think of Berger disease as like a 'Hamburger'

*Who eats hamburgers? Kids and young adults (not elderly)

* coz it's a 'hamburger' it contains blood (hematuria)

*How is any 'hambuger' eaten? Via the mouth down the throat next 2 the resp. track so (RTI)

IgA Nephropathy

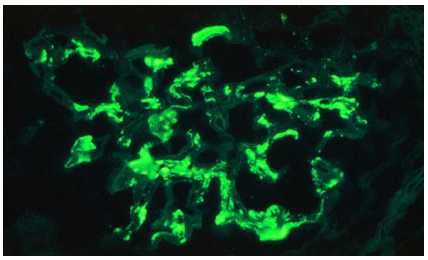
- The pathogenic hallmark is :

- Deposition of IgA & complement C3 in the mesangium

- There is evidence of : Activation of complement by the alternative pathway (serum complement C2 and C4 will be normal)

There are 3 pathways for compliment activation:

classical (starts from C1-C4, C2, C3,C5…) Latin (starts from -C4,C2,C3…) and alternative which starts from C3-C5….) that why both C1 and C4 are within norm. range



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

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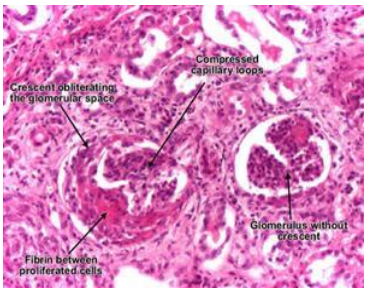
5. Rapidly Progressive (Cresentic) Glomerulonephritis (RPGN)

- 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



Rapidly Progressive (Cresentic) Glomerulonephritis cresent = moon (the capillaries in the glomurulus look tike a half moon)

Crescentic GN: patient present with both pulmonary and renal deposition.

Extra:

RPCGN: is one of the most impor. Glomular diseases because
*it causes nephritic syndrome.
*rapidly progresses (may lead to loss of kidney within 2-3 weeks)
* doesn't respond well to treatment easily.

Types of Rapidly Progressive (Cresentic) Glomerulonephritis (RPGN)

Type 2 (Immune complex-mediated Cresentic GN):

May occur as a complication of any of the immune complex nephritides:
*Post infectious
*SLE
*IgA nephropathy

Characteristic granular (lumpy-bumpy) (when using IF)pattern of staining of the GBM for immunoglobulin & complement

Type 1 (Anti-GBM Antibody) cresentic GN

Characterized by linear deposition of IgG and C3 on the GBM

- Goodpasture syndrome:
Body forms self Ag against own basement membrane
Antibodies bind also in the pulmonary alveolar capillary basement membranes

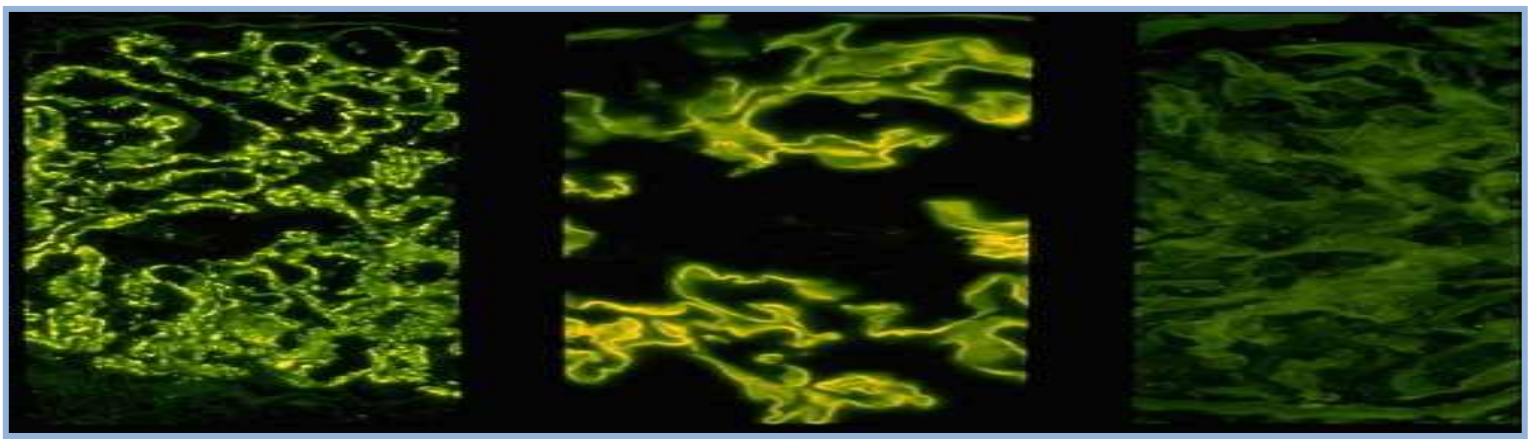
(So it may be seen in both the kidney and lungs)

Type 3 (Pauci-immune) Cresentic GN):

- Defined by the lack of anti-GBM antibodies.

- Most cases are associated with: Anti-neutrophil cytoplasmic antibodies in serum (ANCA) and systemic vasculitis

(Pauci = missing
so in this disease there are no AB or complement found in IF)



Take home message :

*Immune complexes underly the pathogenesis of many of the glomerulo-nephritides. (many of the GN diseases are of immune nature not caused by toxins or organisms)

*Activation of the complement system is an integral part of the process,(because its activation will lead to injury of the surrounding tissue in the form of inflammation and recruitment of more inflammatory cells and mediators) and measurement of the complement proteins help in diagnosis and follow-up of patients.

*Immunofluoresence of renal biopsy demonstrate the presence of immune complexes and confirm the diagnosis. (E.g. if linear = type 1 CrGN - if there is a ‘spike and dome appearance = membranous glomerulonephritis)

Questions :

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1. The cause of Immune complex nephritis is:

   A. Small immune complexes.

   B. Intermediate immune-complexes.

   C. Large immune-complexes.

2. Typical features of immune complex disease :

   A. Hypocomplementemia

   B. Hypercomplemntemia.

   C. Positive anti-DNAse B antibody titre**.**

3. **The only evidence to diagnose post-streptococcal glomerulo-nephritis:**

   A. Anti-streptolysin O titer (ASO)

   B. Gram stain.

   C. Ig G test.