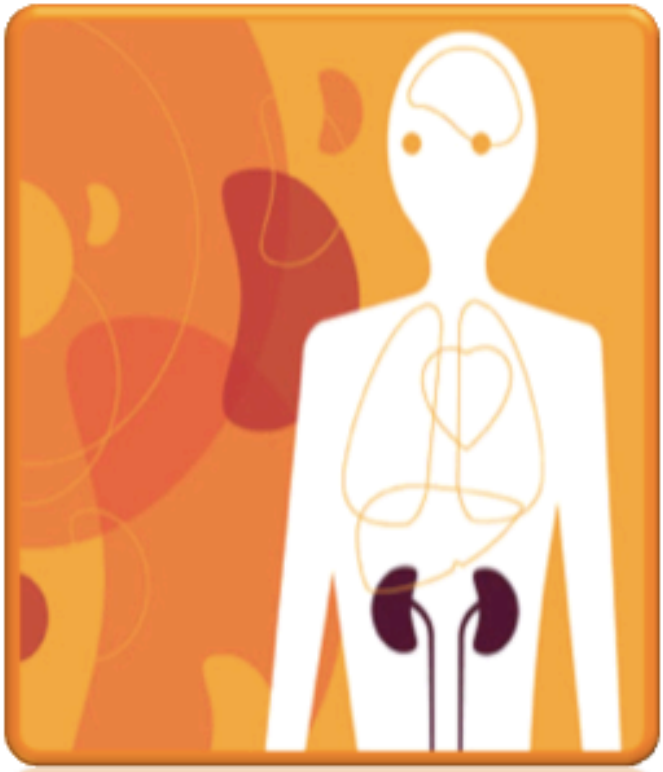


PATHOLOGY TEAM - 431

(Renal block)

Pathology of The Nephrotic, Nephritic and Chronic Kidney Disease

Bayan Al Nooh (LEADER)

Sadeem al dawas

Sara Almutairi

Afnan Alhargan

Wala'a Alshehri

Dalal Fatani

Sara Al anzi

Hadeel Helmi

Lama Al-Shwairkh

Hassah al-fozan

Reema Al anezi

Raghda Al-AmrI

Eman Al-Shahrani

Lama Mokhlis

HAZIM JOKHADAR (LEADER)

Mamdouh Al Enezi

Abdulelah Al Kapoor

Saad Kashogji

Majed Al Shammari

Bader Al Ghamdi

Khalid al Shibani

Abdullah Al Khowaiter

LECTURES THREE AND FOUR

PATHOLOGY OF THE NEPHROTIC, NEPHRITIC AND CHRONIC KIDNEY DISEASE

BY

DR. AMMAR AL RIKABI, PROFESSOR M.O. ALSOHAIBANI AND DR. HALA KFOURY

DEPARTMENT OF PATHOLOGY KING KHALID UNIVERSITY HOSPITAL

Contents:

- Important points
➔ Female Notes
➔ Male Notes
- Explanation

- Evaluation of glomerular disease (Terminology & Techniques).
- Glomerular Diseases:

Nephrotic Syndrome:	Nephritic Syndrome:	Other Glomerular Diseases:
1| Minimal Change Disease.	**1**| Posstreptococcal Glomerulonephritis.	**1**| IgA nephropathy.
2| Focal Segmental Golmerulosclerosis	**2**| Rapidly Progressive Glomerulonephritis.	**2**| Membranoproliferative Glomerulonephritis.
3| Membranous Gomerulonephritis .	**3**| Good Pasture Syndrome.	
4| Diabetic Nephropathy.		
5| Renal Amyloidosis.		
6| Lupus Nephropathy.		

- Renal Failure.
- Azotemia.

EVALUATION OF GLOMERULAR DISEASE

1] 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.

2] Techniques used for studying of glomerular diseases:

1. Light microscopy: using routine (haematoxylin and eosin) and special stains.
2. Immunofluorescence: antibodies tagged (labelled) with a fluorchrome are used to localize immunoreactants in the glomerulus.
3. Electron microscopy: ultrastructural studies of the glomerulus are used to features like the position and location of immune complex, basement membrane reactions and epithelial cell changes.

GLOMERULAR DISEASES (See table 1)

A) **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.

➔ Usually all glomerular diseases associated with NEPHROTIC syndrome are characterized by: Sclerosis & Fibrosis

(1) Classical manifestations:

(a) Massive **proteinuria** is generally characterized by excretion of more than 4 grams of protein per day. Unlike disorders with greater disruption of the glomerular structure, proteinuria in the nephrotic syndrome is not accompanied by increased urinary red cells or white cells.

(b) **Hypoalbuminemia** results from proteinuria and is often marked by a serum concentration of less than 3 g/100 ML.

(c) Generalized **edema** results from decreased plasma colloid or oncotic pressure. (without Red Blood Cells nor White Blood Cells in the urine)

(d) **Hyperlipidemia** and **hyperchomsterolemia** are caused by increased hepatic lipoprotein synthesis.

Why does this occur?

Due to the fusion of the foot processes (podocytes) leading to an increase in the permeability of the basement membrane. This leads to protein leakage Ex: albumin.

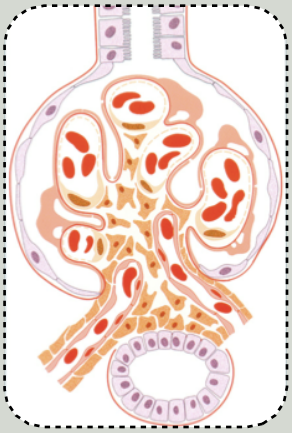
Minimal change disease - MCD

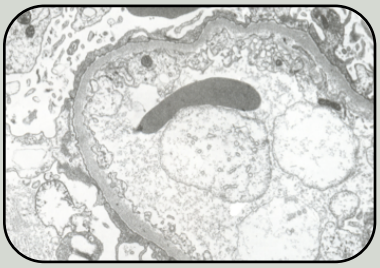
(lipoid nephrosis) is seen most often in young children but can also occur in older children and adults. It is the prototype of the nephrotic syndrome.

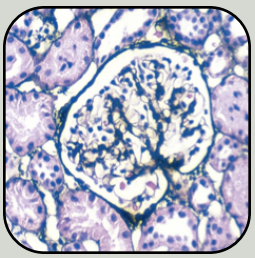
➔ HIGH proteinuria

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

2) Light microscopy demonstrates normal-appearing glomeruli.
➔ that's why it's called minimal change disease.
3) Electron microscopy is normal except for the disappearance or fusing of epithelial foot processes.







4) Most often, this condition responds well to corticosteroid therapy.

5) Patients are more prone to thrombosis & infections.

TYPE	MORPHOLOGIC FINDINGS
A] Disorders manifest by the nephrotic syndrome	
Minimal change disease (lipid nephrosis)	No visible basement membrane changes; fused epithelial foot process; lipid accumulation in renal tubular cells.
Focal segmental glomerulosclerosis	No visible basement membrane changes; segmental sclerosis of scattered juxtamedullaryglomeurli.
Membranous glomerulonephritis	Basement membrane markedly thickened by intramembranous and epimembranous (subepithelial) immune complex deposits; granular immunofluorescence, "spike and dome" appearance.
Diabetic nephropathy	Basement membrane markedly thickened; diffuse or nodular mesangial accumulations of basement membrane-like material.
Renal amyloidosis	Amyloid protein identified by special stains (e.g. Congo Red) with birefringence under polarized light, or electron microscopy "criss-cross" fibrillary pattern.
Lupus nephropathy	Immune complex deposition in subendothelial location may manifest as membranous glomerulonephritis.
B] Disorders manifest by the nephritic syndrome	
Post-streptococcal glomerulonephritis rapidly progressive (crescentic) glomerulonephritis	Subepithelial electron-dense "humps"; lumpy-bumpy" immunofluorescence, crescents formation, antineutrophil cytoplasmic antibody (ANCA) - negative forms with immune complexes or antiglomerular basement membrane antibodies; ANCA-positive (pauci-immune) form with Wegener granulomatosis.
Goodpasture syndrome	Linear immunofluorescence antibody deposition caused by antiglomerular basement membrane antibodies.
Alport syndrome	Split basement membrane due to hereditary nephritis.
C] Other glomerular disorders	
IgA nephropathy (Berger disease)	Mesangial IgA deposits.
Membranoproliferative glomerulonephritis	Tram-track appearance; deposits of C3 and dense deposits in one variant.

General Informations:

➔ 3 kinds of Investigations should be done when dealing with glomerular disease:

1) Light Microscopy.
2) Electron Microscopy.
3) Immunofluorescence.

- Minimal Change Disease is also called:
  1. Lipoid Nephrosis.
     (Sometimes the renal tubule appear vaculated "lipid vacuole".
  2. Minimal Glomerulosclerosis.

- MCD is a very important disease for 2 reasons:

  1. Most common cause for nephrosis in children & young adult.
  2. Got an excellent prognosis.

- Bee stings could lead to MCD.

- Proteinuria:
  - Selective ➔ Albumin loss.
  - non-selective ➔ Albumin & Globulin loss.

Focal segmental glomerulosclerosis is clinically similar to minimal change disease but occurs in somewhat older patients. It is characterized by sclerosis within capillary tufts of the deep juxtamedullary glomeruli with focal or segmental distribution.

1. Focal distribution is involvement of some, but not all of the glomeruli.
2. Segmental distribution is involvement of only a part of the glomerulus.

➔ Causes:
1. primary (Idiopathic): very common.
2. Secondary: could be due to:
- HIV. - IgA nephropathy.

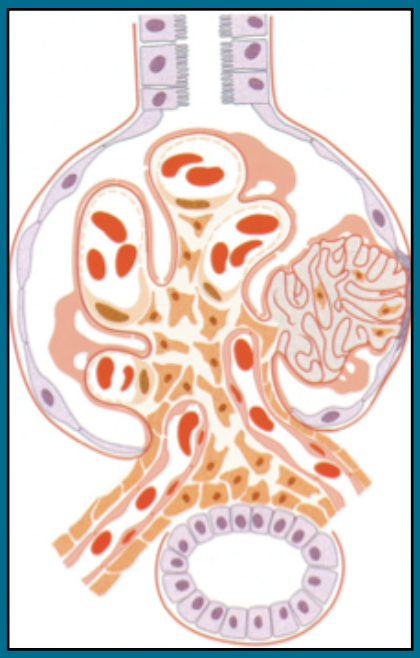
- FSGS likes to affect the juxtamedullary nephron.

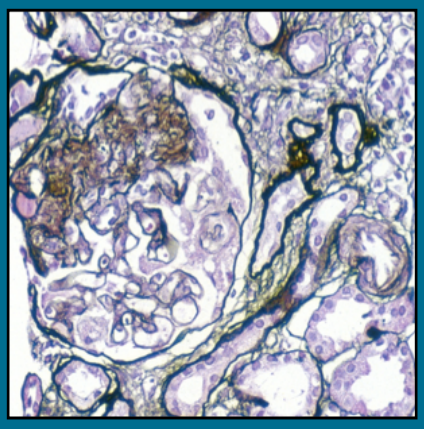
- Under L.M.
1. Hyalinization and fibrosis to the blood vessels.
2. ↑ in the mesangial matrix.
3. Collapse of part of the glomeruli.
4. Adhesions between the affected segment and bowman's capsule, called "synechiae".

- E.M./ Affected foot processes of podocytes.

- Immunefluorescence/ May find IgM and C_3 deposits, although the etiology isn't immunological, but these substances are entrapped.

LIGHT MICROSCOPE





Prognosis:

- Not good.
- May develop azotemia.
- Renal Failure

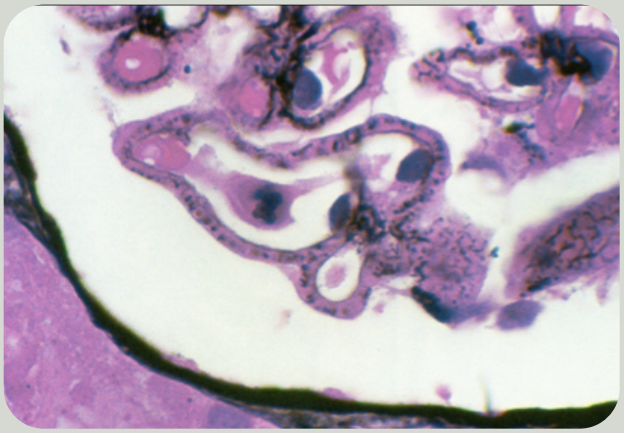
Membranous glomerulonephritis is an immune complex disease of unknown etiology.

(1) This disease is a major primary cause of the nephrotic syndrome.

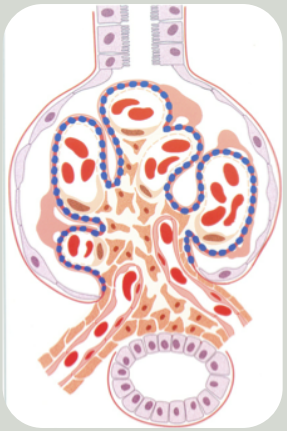
(2) Incidence is highest in teenagers and young adults.

(3) The diagnosis should be suspected when the nephrotic syndrome is accompanied by azoemia (increased concentrations of serum urea nitrogen and creatinine).

(4) Morphologic characteristics include greatly thickened capillary walls which are visible by light microscopy and visible by electron microscopy as a 5- to 10-fold thickening of the basement membrane.

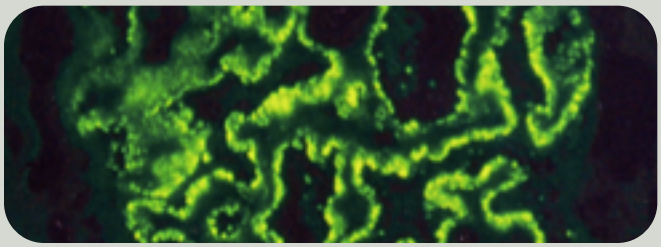


(5) Ultrastructural findings include numerous electron-dense immune complexes in intramembranous and epimembranous (epithelial) locations within and on the basement membrane. This immune complex disease can be mimicked in an animal model resulting from multiple repeated injections of foreign protein.



(6)With special stains, a "spike and dome" appearance resulting from the extension of basement membrane between and around the immune deposits is seen; the spikes are basement membrane material and the domes are immune complex deposits.

(7) Granular deposits of immunoglobulin G (IgG) or C3 are apparent on immunofluorescence. Granular immunofluorescence is a general characteristic of immune complex disease.



(8) Membranous glomerulonephritis is a slowly progressive disorder that shows little response to steroid therapy.

(9) It (membranous glomerulonephritis) is seen in 10% of patients with systemic lupus erythematosus (SLE) and other associations sometimes include hepatitis B, syphilis, or malaria infection; drugs, such as gold salts or penicillamine or malignancy.

(10) The disorder sometimes causes renal vein thrombosis, which was previously thought to be an etiologic factor.

Nephrotic syndrome + Azotemia = membranous glomerulonephritis

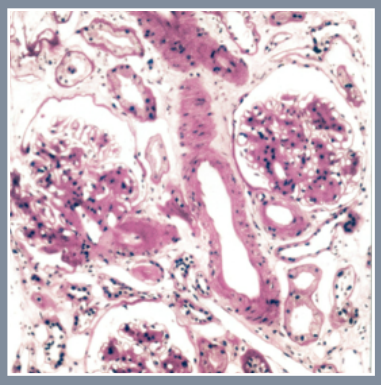
- The antigen in SLE is an Anti-DNA antibody.
- Incidence increased in females more the males.

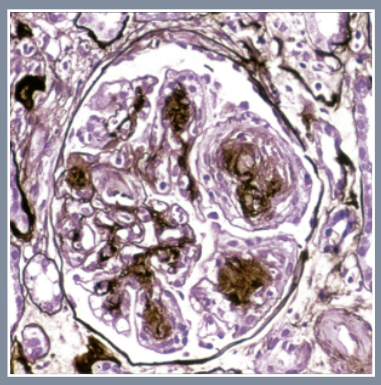
Why do patients develop such a disease ?

- Because they develop type III hypersensitivity reaction. These circulating immune-complexes are high in their molecular weight and are deposited in highly vascularized organs e.g. the kidney, more specifically the subepithelial layer of filtration barrier.

- The disease got long clinical course, it can last from 2- 20 years.

LIGHT MICROSCOPE





Diabetic nephropathy

(1)Often, this disease is clinically manifested by the nephrotic syndrome.(Can cause nephritic syndrome).
(2) Electron microscopy 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.
(3) An increase in mesangial matrix results in two characteristic morphologic patterns:

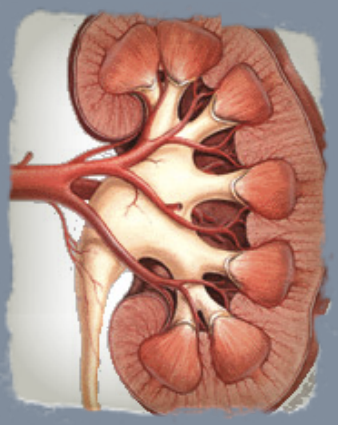
(a) Diffuse glomerulosclerosis is marked by a diffusely distributed increase in mesangial matrix. May develop renal Failure.

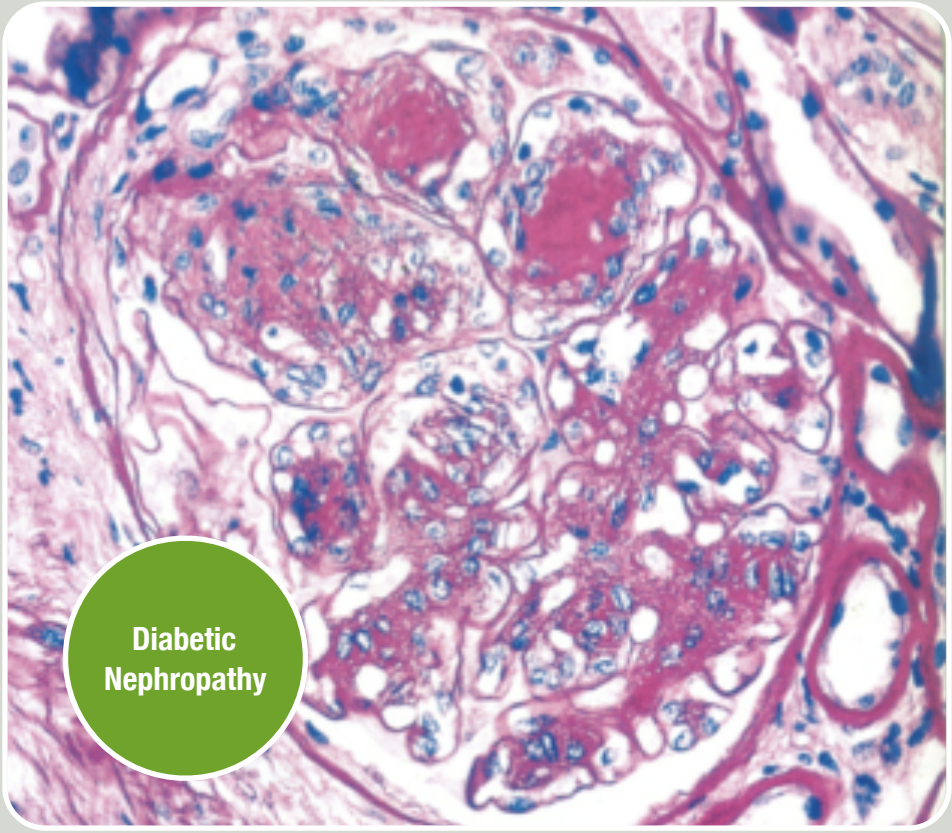
(b) Nodular glomerulosclerosis is marked by nodular accumulations of mesangial matrix material (Kimmelstiel-Wilson nodules).

➔ Associated with retinopathy.
➔ Clinical Presentation:
1. Proteinuria. 2. Tubulo-interstial fibrosis.

- Renal complications of diabetes militus?

1. Necrotizing Papillitis.
2. Pyelonephritis.
3. Diabetic Nephropathy.





Renal amyloidosis

(1)This condition is another cause of the nephrotic syndrome.
(2) Predominantly subendothelial (Blood vessels) and mesangial (Kidney) amyloid deposits are characteristic.
(3) The amyloidosis can be identified by reactivity of amyloid with special stains [e.g. Congo Red (will stain the amyloid in brown, Apple green) , crystal violet, thioflavin T) and by birefringence under polarized light. It is also demonstrated by a characteristic criss-cross fibrillary pattern of amyloid by electron microscopy.
(4) Most often, there are associations with chronic inflammatory diseases, such as rheumatoid arthritis or plasma cell tumours such as multiple myeloma.

- Acute Phase Protein? is a protein secreted from the liver, but during chronic inflammation.

- Light chain of an antibody can cause amyloidosis.

Lupus nephropathy = Lupus nephritis

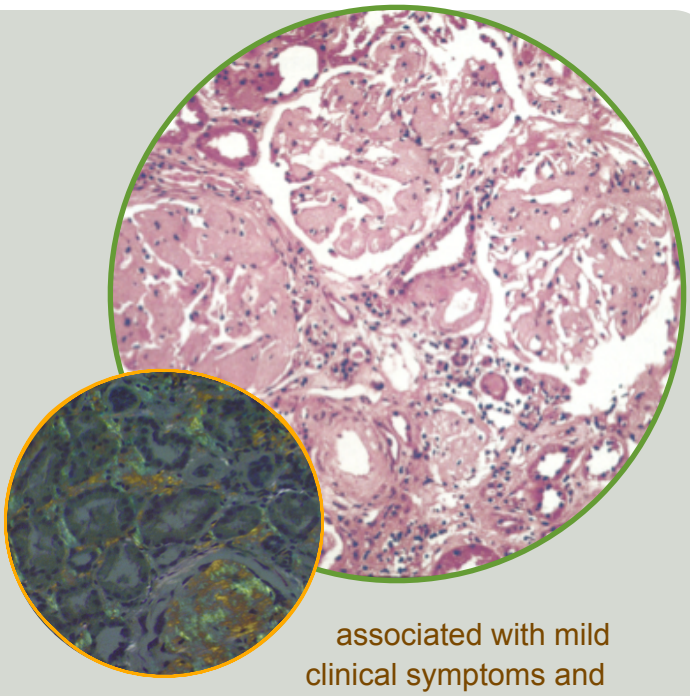
(a) This is the renal component of SLE; the severity of the renal lesion often determines the overall prognosis in patients with SLE. It is often manifest as the nephrotic syndrome but many cases also have major nephritic features.(It can cause nephrotic or nephritic syndrome).

The pathogenesis of all forms of glomerulonephritis in SLE involves deposition of DNA and anti DNA complexes within the glomeruli. This causes an inflammatory responses 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: Normal by light, electron and immunofluorescence microscopyc.(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. ➔ low complementemia

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. (got nephritic syndrome).

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. (The worst of all, can develop renal failure).

B] Nephritic syndrome

Is characterized by inflammatory rupture of the glomerular capillaries, with resultant bleeding into the urinary space; proteinuria and edema may be present but usually are mild.

(1) Clinical findings:

(a) **Oliguria**

(b) **Azotemia** (which is elevation of blood urea nitrogen and creatinine levels due to decreased glomerular filtration rate/GFR).

(c) **Hypertension**

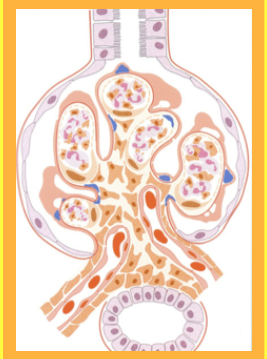
(d) **Hematuria** results from leakage of red cells directly from glomerular capillaries into the Bowman space. Many of the red cells are aggregated into the shape of the renal tubules and embedded in a proteinaceous matrix forming red cells casts that can be observed in the urine. So either you will see freely RBCs or RBCs cast in the urine. Patient often reports having **"smoky brown urine"**. Red cell casts can degenerate and become pigmented granular casts (RBCs cast).

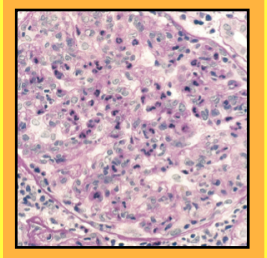
(e) Patient also may has proteinuria and hypoalbuminemia (which is causing edema) but with much less extent than the nephrotic syndrome.

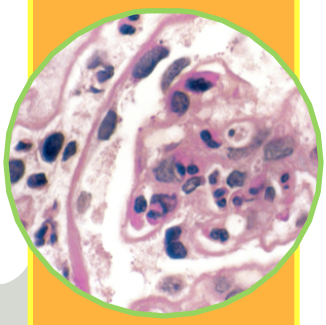
(2) **Posstreptococcal glomerulonephritis** (acute exudative proliferative glomerulonephritis) is the prototype of the nephritic syndrome. It is immune complex disease with the antigen being of streptococcal origin. (It is type 3 hypersensitivity reaction).
This disorder most often follows or accompanies infection (tonsillitis, streptococcal impetigo, infected insect bites) with nephritogenic strains of group A B-hemolytic streptococci. Sometimes cause by staphylococci or viruses like influenza or respiratory viruses and others.

> Only the " nephritrogenic" strains of **B-hemolytic streptococci** can cause glomerular disease.

Acute post-infectious glomerulonephritis







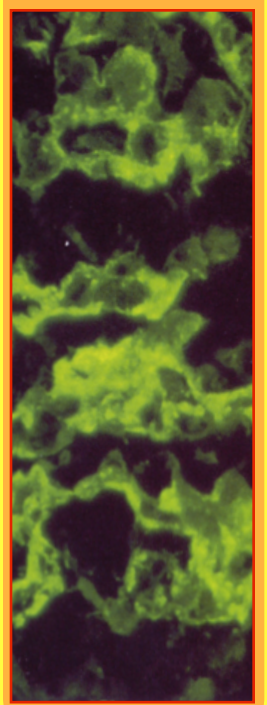
Complete recovery in almost all children and many adults follow. A very minority develops rapidly progressive glomerulonephritis.
Several laboratory abnormalities are characteristic, including urinary red cells and red cell casts, azotemia, decreased serum C3 and increased titers of anticationic proteinase as an evidence of recent streptococcal infection.

An intense inflammatory reaction involving almost all glomeruli in both kidneys result in:

1. Innumerable punctuate hemorrhages on the surface of both kidneys.
2. Enlarged, hypercellular, swollen, blood less glomeruli with proliferation of mesangial and endothelial cells and sometimes neutrophilic infiltration.
3. Glomerular basement membrane of normal thickness and uniformity despite the extensive inflammatory changes.
4. Characteristic electron-dense **"humps"** on the epithelial side of basement membrane with subepithelial localization.
5. 'Lumps-bumpy" immunofluorescence (extremely coarse granular immunofluorescence for IgG or C3).

> We do immunofluorescence (anti C3 – anti IgG), and we will find them (+) in subepithelial layer. Then we look for complement in circulation we'll find it decreased (Hypocomplementemia). Then when we do anti- streptolysin O (ASO) test, it will be increased -type of protein for detection of strept. Infections-. Then ESR is increased. Finally, C reactive protein is increased.

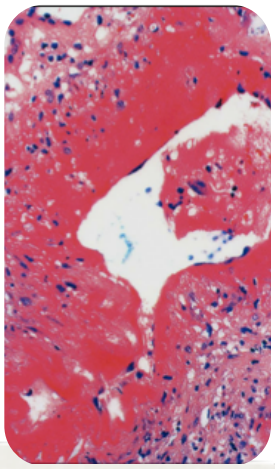
Immuno-fluorescence



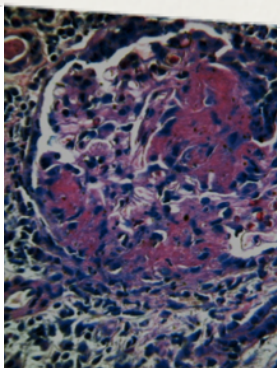
(3) **Rapidly progressive (crescentic) glomerulonephritis (RPGN).**

(a) RPGN usually presents with the nephritic syndrome that progresses rapidly to renal failure within weeks or months. The disorder is histologically defined by the formation of crescents between the Bowman's capsule and the glomerular tuft which result from deposition of fibrin in the Bowman space and from proliferation of parietal epithelial cells of the Bowman capsule. Cells of monocytic origin are often involved.

If I see post-infectious diffuse proliferative glomerulonephritis with crescent --> rapidly progressive proliferative glomerulonephritis --> may to renal failure



Wegener's granulomatosis



There are three types of disease:

1- **Type III proliferative and crescentic glomerulonephritis** (Pauci (scanty) -immune glomerulonephritis): You don't see immune complexes although, it is immune disease. This disease is called Wegener granulomatosis (C-ANCA), and sometimes been Microscopic polyangitis (P-ANCA). Not common and it causes vasculitis because it is immune mediated (antibody-antigen complexes) which is accumulating in the wall of blood vessels lead to create necrosis which is called fibrinoid necrosis. To diagnose this disease we do ANCA test. Also it may be associated with discoloration of bone to brown, nasal symptoms (such as bleeding) and respiratory symptoms (such as dyspnea).

2- Type I: associated with Anti-basement membrane antibodies that encompass a number of diseases, most notably being Good Pasture Syndrome: a disease in which antibodies attack the glomerular and alveolar basement membranes.
This type is important to diagnose because patients can benefit from plasmaphoresis: plasma is separated from the cells in the blood, the cells are suspended in saline, a plasma substitute or donor plasma), and the reconstituted solution may be returned to the patient. The procedure is used to remove excess antibodies from the blood

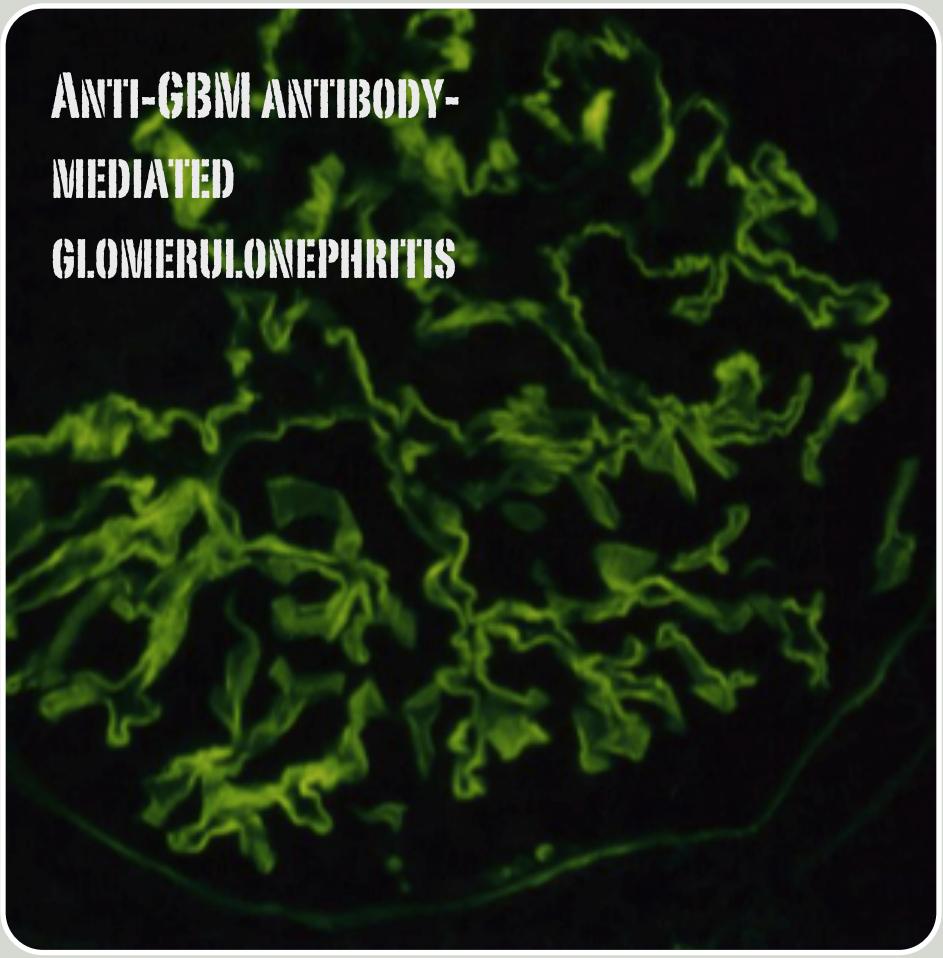
3- Type II: is associated with diseases of immune-complex deposition and include:

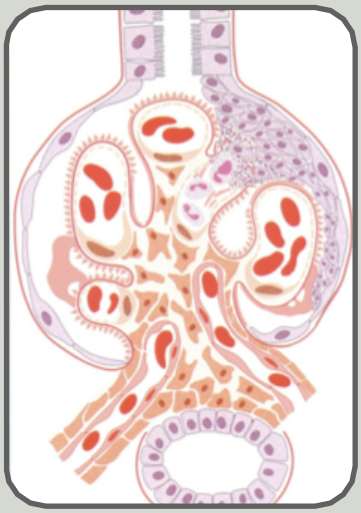
- SLE
- Post-infectious glomerulonephritis.
- IgA nephropathy
- Hench-Sholien purpora: HSP is a systemic vasculitis (inflammation of blood vessels) and is characterized by deposition of immune complexes containing the antibody IgA, which may hit the kidney. The disease causes palpable purpura (small hemorrhages); often with joint and abdominal pain.

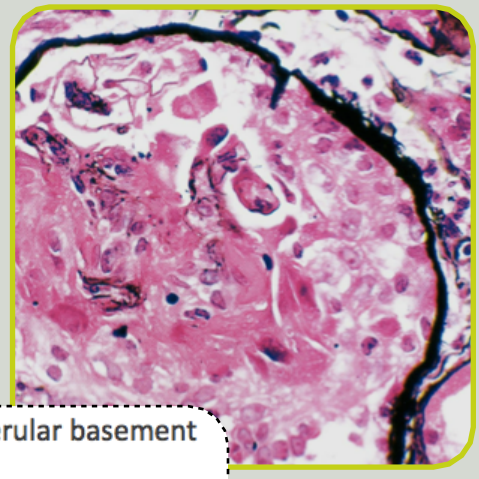
(b) The etiology is poststreptococcal in approximately 50% of cases with immune complex deposition; other immune complex forms of RPGN include, among others, lupus nephropathy and IgA nephropathy.

(c) Anti-glomerular basement membrane antibodies (non streptococcal) are characteristic in approximately 10% of cases; these cases often present clinically as Goodpasture syndrome.

(d) RPGN can also be of the **pauci-immune type**. This mean that in these cases RPGN is without immune complex deposition or anti-glomerular basement membrane antibodies. This third type of RPGN is associated with antineutrophilic cytoplasmic





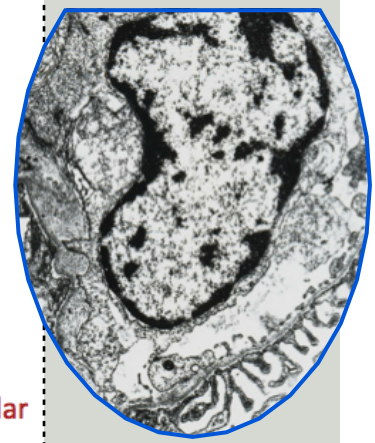


antibodies (ANCAs), in contrast to the immune complex or antiglomerular basement membrane forms of RPGN, which are ANCA-negative.

The ANCA-negative forms of RPGN are designated type I when RPGN is of the antiglomerular basement membrane antibody type and type II when it is of the immune complex type. The ANCA-positive pauci-immune form of RPGN is designated type III.

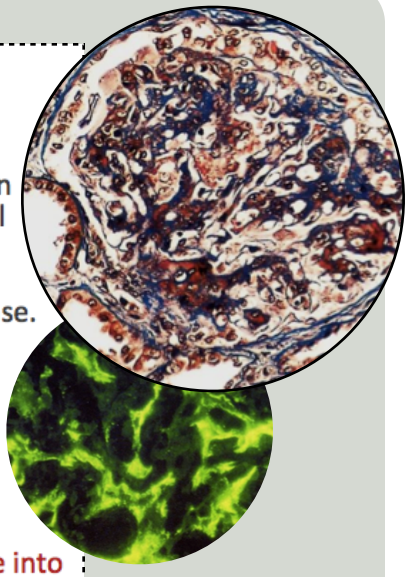
(4) **Good pasture syndrome (antiglomerula basement membrane disease).**
- (a) The cause is the formation of antibodies (antiglomerular basement membrane antibodies), which are directed against antigen in the glomerular and pulmonary alveolar basement membranes.
- (b) Flourescent antibody studies for Igg demonstrate positive **linear** immunofluorescence.
- (c) Clinical manifestations include:
  1. Nephritic syndrome.
  2. Pneumonitis with hemoptysis (hemorrhagic pneumonitis).
  3. Peak incidence in men in their mid-20s.
  4. RPGN crescentic morphology with linear immunofluorescence.
  5. **Alport syndrome**:
     - a. This disease is a hereditary nephritis associated with nerve deaf lines and ocular disorders, such as lens dislocation and cataracts.
     - b. Clinical characteristics include the nephritic syndrome, often progressing to end stage renal disease by 30 years of age.
     - c. The causes are mutation in the gene for the 5 chains of type IV collagen.
     - d. Irregular glomerular basement membrane thickening with foci of splitting of the lamina densa are seen by electron microscopy.

ALPORT SYNDROME



Is an X-linked disease, affects mostly boys.

C] Other glomerular diseases



(1) IgA nephropathy (Berger disease) is an extreme common entity defined by deposition of IgA in the mesangium.

(a) Most frequently, the disease is characterized by benign recurrent hematuria in children, usually following an infection, lasting 12 days, and usually of minimal clinical significance.

(b) Focal glomerulonephritis may be the presenting feature.

c) IgA nephropathy can be a component of the Henoch-Schonleinvasculitis disease.

d) There is mesangial cell and matrix increase, with mesangial deposits.

e) Definitive diagnosis is made by immunofluorescence, showing dominant or codominant staining with IgA in a predominantly mesangial pattern.

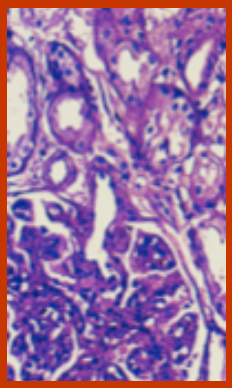
(2) Membranoproliferative glomerulonephritis

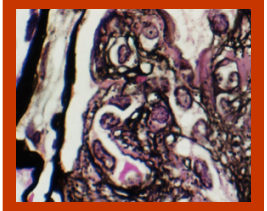
(a) Clinical characteristics include slow progression to chronic renal disease.

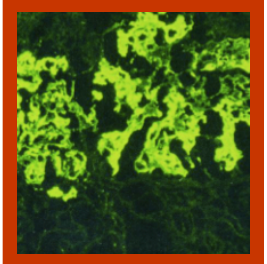
(b) Histological characteristics include **both basement membrane thickening and cellular proliferation.**

(c) The disease is marked by reduplication of the glomerular basement membrane into two layers due to expansion of the mesangial matrix into the glomerular capillary loops; this results in a characteristic tram- track appearance best seen with silver stains.

MPGN type I







It should not be confused with **membranous glomerulonephritis**, a condition in where the basement membrane is thickened, but the mesangium is not.

(d) **Disease occurs in two forms:**

1. Type I is an immune complex nephritis associated with an unknown antigen. It has a striking tram-track appearance.

There is often very prominent complement deposition in MPGN with prominent mesangial and coarse, chunky peripheral loop deposits, corresponding to the subendothelial deposits.

2. Type II (dense deposit disease) has a tram-track appearance that is not as apparent as that of type I.

1. Irregular electron-dense material deposited within the glomerular basement membrane is characteristic. C3 is demonstrable adjacent to but not within the dense deposits and serum C3 is characteristically markedly reduced.
2. The possible cause is an IgG autoantibody (C3 nephritic factor) with specificity for the C3 convertase of the alternate complement pathway.

Asymptomatic Hematuria:

- **Hematuria or proteinuria (persistent microhematuria).**
- **Usually normal renal function (early in the course)**
- **Usually no hypertension or Edema.**
- **Condition characterized morphologically by focal necrotizing of inflammatory lesions of glomeruli, or by basement membrane anomalies that result in capillary fragility.**

RENAL FAILURE

A] General considerations

(1) Renal failure can be acute or chronic and can result from any of the glomerular or tubulointerstitial lesions diseased in the preceeding sections.
(2) Azotemia (elevated urea and creatinine) of renal origin is always an associated feature.
(3) In advanced stages, renal failure results in uremia; the term uremia denotes the biochemical and clinical syndrome characteristic of symptomatic renal disease.

B] Major clinical characteristics of uremia

(1) Azotemia (elevated urea and creatinine)
(2) Acidosis resulting from the accumulation of sulfates, phosphates and organic acids.
(3) Hyperkalemia.
(4) Abnormal control of fluid volume.

(a) An early characteristic is the inability to concentrate urine; a later manifestation is the inability to dilute urine.
(b) Sodium and water retention can result in congestive heart failure.

(5) Hypocalcemia caused by failure to synthesize the active form of Vitamin D, hypocalcemia can lead to renal osteodystrophy.
(6) Anemia caused by decreased secretion of erythropoietin.
(7) 'Hypertension caused by hyperproduction of rennin.

C] Other clinical characteristics of uremia include anorexia, nausea and vomiting; neurologic disorders, ranging from diminished mental function to convulsions and come; bleeding caused by disordered platelet function; accumulation in the skin of urochrome and other urinary pigments and fibrinous pericarditis.

NON-RENAL CAUSES OF AZOTEMIA

A] **Pre-renal azotemia:**

This condition results from decreased renal blood flow due to blood loss, decreased cardiac output, systemic hypovolemia (as in massive burns), or peripheral pooling of blood due to marked vasodilatation (as in grame-negative sepsis). It is characterized by increased tubular reabsorption of sodium and water, resulting in oliguria, concentrated urine and decreased urinary sodium excretion.

(1) **Measurement of urinary sodium** is diagnostically significant in the delineation of the oliguria of shock.
(a) **Oliguria** may be caused by decreased renal blood flow with consequent decreased glomerular filtration rate, in which case tubular reabsorption of sodium is maximaly increased and urinary sodium is low.
(b) **Oliguria** may be a manifestation of acute tubular necrosis, in which case tubular reabsorption is greatly impaired and urinary sodium is not decreased.

(2) **The BUN:** creatinine ratio is characteristically greater than 15 due to a combination of both decreased glomerular filtration and increased tubular reabsorption of urea.

B] **Post-renal azotemia**:
Results from mechanical blockage (obstruction) of urinary flow.
- BUN is an abbreviation of Blood Urea Nitrogen.

Robbin's Summary

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 non-immune 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.

Nephritic Syndrome

- The nephritic syndrome is characterized by hematuria, oliguria with azotemia, proteinuria, and hypertension.
- **The most common cause** is immunologically mediated glomerular injury; lesions are characterized by proliferative changes and leukocyte infiltration.
- **Acute postinfectious glomerulonephritis** typically occurs after streptococcal infection in children and young adults but may occur following infection with many other organisms; it is caused by deposition of immune complexes, mainly in the subepithelial spaces, with abundant neutrophils and proliferation of glomerular cells. Most affected children recover; the prognosis is worse in adults.
- **IgA nephropathy**, characterized by mesangial deposits of IgA-containing immune complexes, is the most common cause of the nephritic syndrome worldwide; it is also a common cause of recurrent hematuria; it commonly affects children and young adults and has a variable course.
- **Hereditary nephritis (Alport syndrome)** is caused by mutations in genes encoding GBM collagen; it manifests as hematuria and slowly progressing proteinuria and declining renal function; glomeruli appear normal by light microscopy until late in the disease course.

Rapidly Progressive Glomerulonephritis

- **RPGN** is a clinical entity with features of the nephritic syndrome and rapid loss of renal function.
- **RPGN is commonly** associated with severe glomerular injury with necrosis and GBM breaks and subsequent proliferation of parietal epithelium (crescents).
- **RPGN may be immune-mediated**, as when autoantibodies to the GBM develop in anti-GBM antibody disease or when it arises consequent to immune complex deposition; it also can be pauci-immune, associated with antineutrophil cytoplasmic antibodies.

PATHOLOGY TEAM