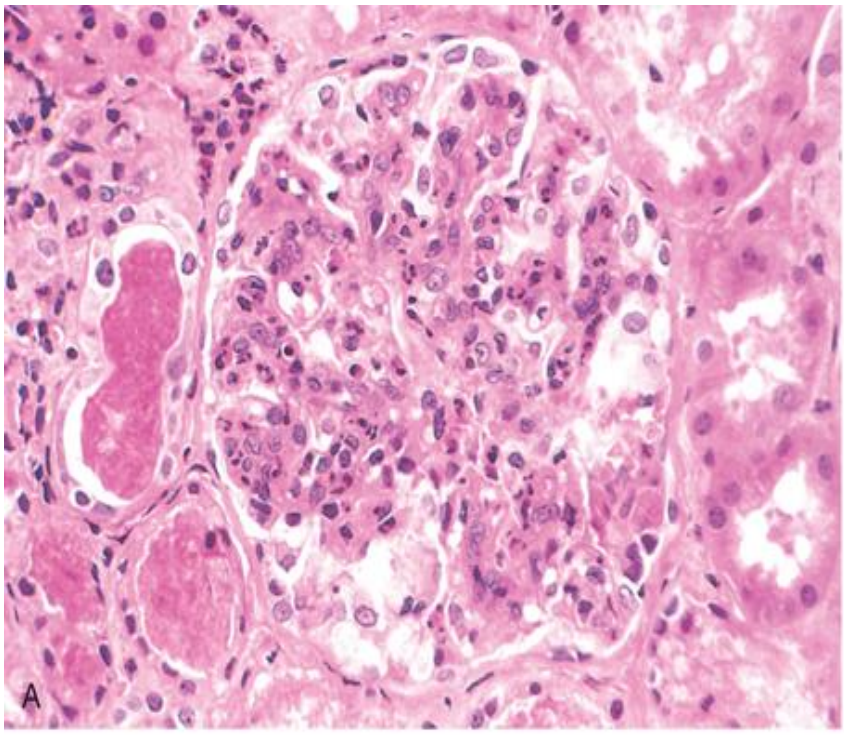
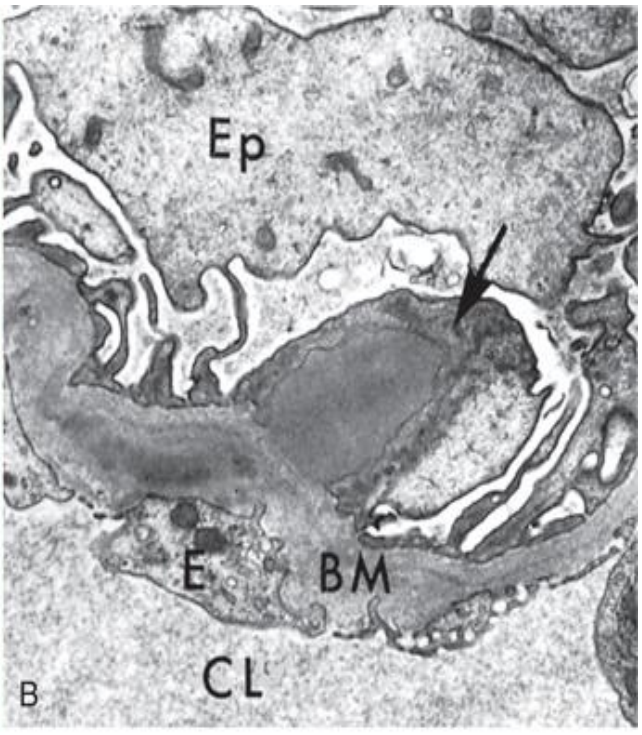




Lecture Five

Nephritic syndrome

432 ***Pathology*** *Team*

Done By: Abdulmajeed *Al-Jasser*

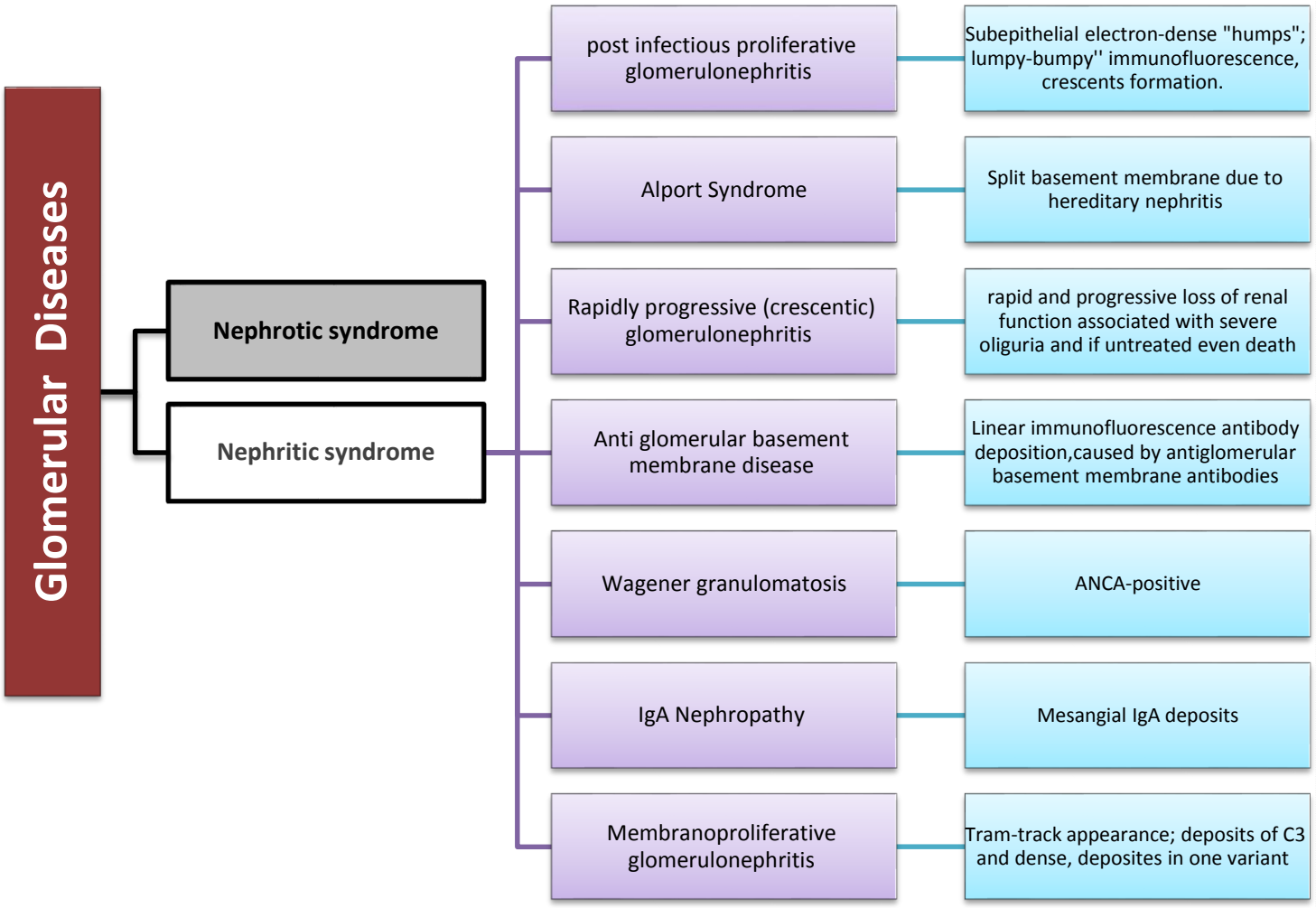
Reviewed By: Amal *Al-Sinan and* ***Roqaih*** *Al-Dueb*

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:



NEPHRITIC SYNDROME

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.

Clinical findings:

1) **Mild proteinuria.**
2) **Mild edema.**
3) **Oliguria.**
4) **Azotemia** (Increased urea and creatinine levels in blood due to decreased GFR)
5) **Hypertension** (due to Fluid retention / increased renin secretion, when there is glomerular disease, it will compromised the blood circulation of the glomeruli so the renin will secrete).
6) **Smoky brownish urine.**
7) **Hematuria** could be microscopic or macroscopic RBCs. Results from leakage of dysmorphic RBC directly from glomerular capillaries into the Bowman space. Many of the RBC are aggregated into the shape of the renal tubules and embedded in a proteinaceous matrix forming RBC casts that can be observed in the urine. Proteinaceous is the one which cause these RBCs to adhere to each other. The hemodynamic changes caused by the rupture lead to a reduction in the glomerular filtration rate (GFR).

NOTE: The RBC casts are a sign of a disease affecting the glomerulus.

Pathogenesis:

Nephritic syndrome is an immune mediated disease and this immune reaction is usually an immune complex, so:

This immune complex→creates an inflammatory reaction→activation of the complement by the alternative pathway→accumulation of C3a & C5a→chemotaxis of neutrophils→contribution of the damage which occurred in the blood vessels→the blood vessels inside the glomerulus react to this contribution→mesangial& endothelial proliferation.

REMEMBER: **diffuse (rapid) proliferative glomerulonephritis can occur the following:**

- **Type 1** → Anti basement membrane anti bodies (Good pasture syndrome).
- **Type 2** → Post infectious glomerulonephritis / SLE class 4.
- **Type 3** → Wagener granulomatosis (Pauci-immune).

1- Post streptococcal glomerulonephritis:

Also called **acute post infectious proliferative glomerulonephritis.**
It is the prototype of the nephritic syndrome. It is immune complex disease with the antigen being of streptococcal origin.
This disease is common in young people.

It's usually occurs 1-4 weeks following upper respiratory tract infection (mainly throat infection by Group A β-hemolytic streptococci) → the child starts having edema→ Changing in urine color → Development of nephritic syndrome.

Also this disease can follow other infections:

1) Tonsillitis.
2) Streptococcal impetigo.
3) Infected insect bites.
4) Staphylococcal infection.
5) Viral infection.

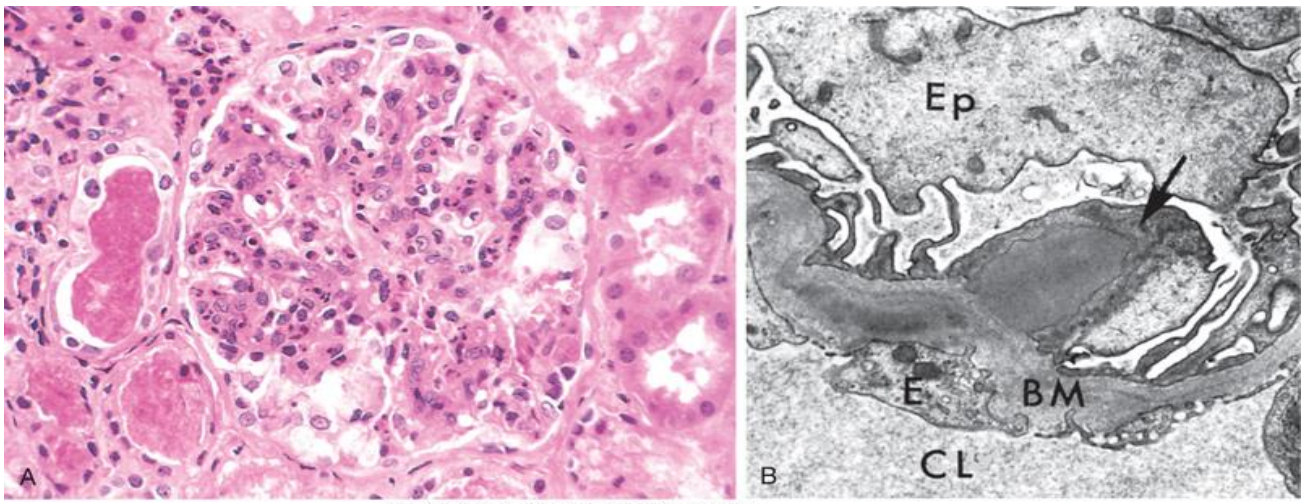
Part of these proteinaceous within this bacteria acts as antigen lead to activation of the complement. With nephritogenic strains of group A β-hemolytic streptococci.

Causes

1- SLE (Class four). **2- Viral Diseases.** **3- Autoimmune diseases.**

Microscopic finding:

LM: Neutrophils within and outside the capillaries. Proliferation of the glomeruli (mesangial and epithelial cells). Glomerulus becomes very big. Hypercellular enlarge.
EM: dense subepithelial "humpy bumpy " and intramembranous deposits of fibrin and RBCs in Bowman's space
IF: IgG or/and C3 deposits on subepithelial mesangial areas forming mass (granular)



Kumar et al: Robbins Basic Pathology, 9e.

Prognosis:

Complete recovery in almost all children and many adults follow.
A very minority develops rapidly progressive glomerulonephritis.

Laboratory testing:

1) Urinary red cells and red cell casts.
2) Azotemia
3) Decreased serum C3
4) Increased titers of anticationic proteinase (as an evidence of recent streptococcal infection)

An intense inflammatory reaction involving almost all glomeruli in both kidneys results in (Characteristics):

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 (a lot of neutrophils within the capillaries & outside them).
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) **High power:** There are RBCs & fibrin in the bowman's space due to the inflammatory reaction that caused damage to the basement membrane and it is leaking protein, RBC & fibrin.
6) **Immunofluorescence:** There are chunks of positive immune complexes either containing IgG/C3 or both of them. The large deposits could be mesangial/ subepithelial and they called "humpy-bumpy".

2- Alport syndrome (congenital/hereditary nephritis):

It is a disease that usually affects children (especially males).

Pathogenesis:

This disease refers to a group of hereditary glomerular diseases caused by mutations in gene encoding for certain protein chain (α-5 chain), which forms the collagen IV which enters into the composition of the glomerular basement membrane and causes structural abnormality in it.

Clinical findings:

1) **Deafness.**
2) **Various eye disorders** (including lens dislocation), posterior cataracts and corneal dystrophy.
3) **Nephritic syndrome.**

You can see this disease in SLE (Class four) & in type (1, 2 & 3) proliferative glomerulonephritis.

Microscopic finding:

- Biopsy is almost normal. (We only see the abnormalities on the electrical microscope).

- EM: Irregular glomerular basement membrane thickening (areas are thick and areas are thin) with foci of splitting of the lamina densa.

Prognosis:

Often progressing to end stage renal disease by 30 years of age.

3- Rapidly progressive (crescentic) glomerulonephritis (RPGN)

A- RPGN usually presents with the nephritic syndrome that progress 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.

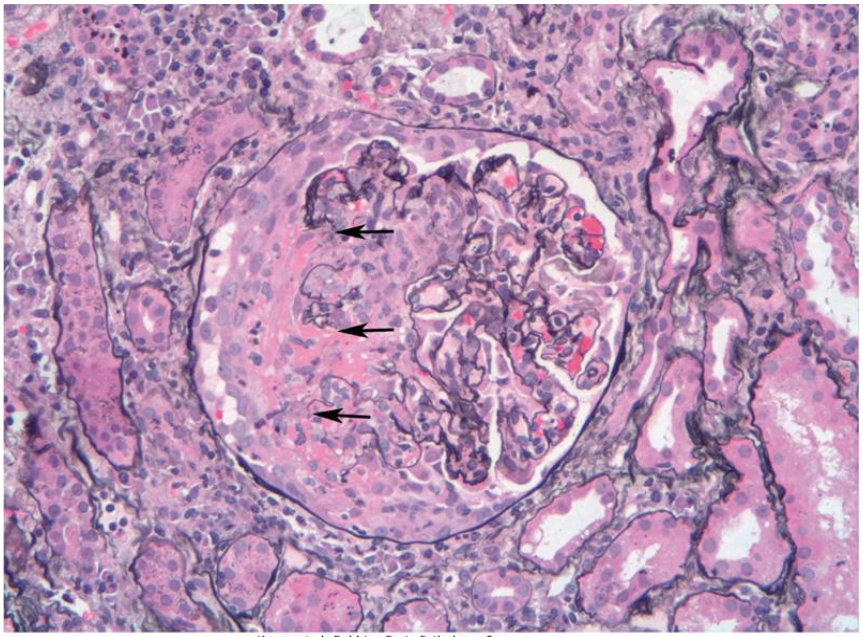
B- The etiology is post streptococcal in approximately 50% of cases with immune complex deposition; other immune complex forms of RPGN include, among others, lupus nephropathy and IgA nephropathy.

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

D- RPGN can also be of the pauci-immune type. This means that in these cases RPGN is without immune complex deposition or anti glomerular basement membrane antibodies. This third type of RPGN is associated with anti neutrophilic cytoplasmic antibodies (ANCAs), in contrast to the immune complex or anti glomerular basement membrane forms of RPGN, which are ANCA-negative. The ANCA-negative forms of RPGN are designated type I when RPGN is of the anti-glomerular 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.

Crescentic glomerulonephritis (Jones silver methenamine stain).

Note the areas of necrosis with rupture of capillary loops (arrows) and destruction of normal glomerular structures ,and the adjacent crescent-shaped mass of proliferating cells and leukocytes filling the urinary space. The segmental distribution of the necrotizing and crescentic GN is typical of ANCA (antineutrophil cytoplasmic antibody)-associated crescentic GN.



4- Anti glomerular basement membrane disease:

Also called **Good pasture syndrome.**

AGBMD caused by the formation of antibodies (anti glomerular basement membrane antibodies), which are directed against antigen in the glomerular and pulmonary alveolar basement membranes.

It usually affects young males.

LM: It can be characterized by the formation of crescent.

(The crescent consists of parietal epithelial cells with some inflammatory cells)

At some stages of proliferation will lead to rupture of the basement membrane→RBCs &fibrin goes to Bowman's space → reactive proliferation of parietal cells →they will form the crescent

IF: Immunofluorescence: Linear deposition of IgG & C3 along the basement membrane (not granular).

Prognosis:

If there is crescent that means the damage in the glomerulus is sever.

The prognosis in children is better than adults & elders.

C3 is typically markedly decreased.

Clinical manifestations include:

1) Nephritic syndrome.
2) Pneumonitis with hemoptysis (hemorrhagic pneumonitis). If he have this disease affecting the lungs and cause necrotizing the basement membrane.
3) Peak incidence in men in their mid-20s.
4) RPGN crescentic morphology with linear immunofluorescence.
5) Alport syndrome.

Causes:

1) **Post infectious glomerulonephritis**
2) **SLE**
3) **Pauci immune glomerulonephritis**

Treatment: Plasmapheresis

5- Wagener granulomatosis:

Also called **Pauci-immune glomerulonephritis**

NOTE: Pauci means absent of occur in very little amount.

Wagener granulomatosis is 3 type of diffuse proliferative glomerulonephritis and a type of vasculitis (Fibrinoid necrosis), there are no immune deposits. When I do Immunofluorescence for immune complex I can't find them.
This is a type of RPGN which the IF is negative or almost negative i.e .pauci-immune.

Increased Anti-neutrophil cytoplasmic antibodies (ANCA).

The glomerulus is hypercellular & showing some proliferation.
This disease can affect (Kidneys, Nose & Respiratory system), and is progressive.

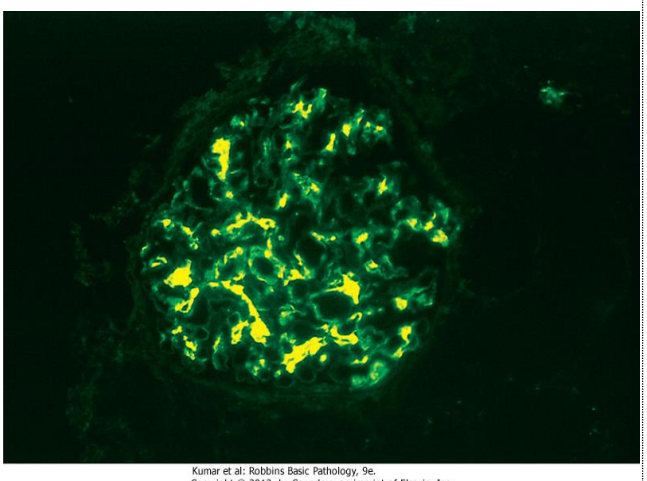
6- IgA Nephropathy:

Also called **Berger disease**
It is **the most common cause of nephritis** in worldwide (especially west).

IgA nephropathy is characterized by benign **recurrent hematuria** in children (only microscopic hematuria), usually following an **infection**, lasting 12 days, and usually of **minimal clinical significance.**

Pathogenesis:

It is also characterized by over production of IgA → This IgA form immune complex→get deposited in the mesangium of the glomerulus.
A lot of mesangial proliferation &mesangial deposits, with increased mesangial matrix.



Kumar et al: Robbins Basic Pathology, 9e.
Copyright © 2013 by Saunders, an imprint of Elsevier Inc.

Microscopic finding:

LM: proliferative of the mesangium.
It looks like focal segmental glomerulonephritis.

IF: IgA deposits in mesangial regions.

IgA nephropathy can be a component of the Henoch-Schonleinpurpura* (Hypersensitivity angiitis).
A variety of systemic diseases are associated with IgA nephropathy such as liver failure, celiac disease (diseases that characterized by over production of IgA).

REMEMBER: **You have to differentiate between:**
Berger Disease = IgA nephropathy
Buerger's disease = Thromboangiitis obliterans (inflammation and thrombosis of small and medium arteries and veins of the hands and feet. It is strongly associated with use of tobacco products)

7- Membranoproliferative glomerulonephritis:

This disease could be nephritic or nephrotic syndrome.
Endocapillary proliferation, (endothelial cells are proliferated)

Clinical characteristics: include slow progression to chronic renal disease.

Histological characteristics: include both basement membrane thickening and cellular proliferation.

There is **splitting in the glomerular basement membrane**.
It affects the endothelial & mesangial cells.
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.

It is either:

A- Idiopathic → it's found in 10% of the cases and it will cause only nephrotic syndrome.
B- Proliferative: two types:

1- Type I (Membranoproliferative glomerulonephritis) most common.

An immune complex nephritis associated.

* Henoch-Schonleinpurpura: a systemic syndrome involving the skin (purpuric rash), gastrointestinal tract (abdominal pain), Joints (Arthritis), and kidneys.

Microscopic finding:

LM: it has a striking tram-track appearance. Proliferation in endothelial cells.
EM: Accumulation of immune complex (sub-endothelial deposition).
IF: there are IgG & C3 (sub-endothelial & mesangial).

Causes:

1) **SLE**
2) **Hepatitis B or C** (C is more common)
3) **Unknown antigen**

2- Type II (Dense Deposit Disease) (DDD)

DDD is characterized by Irregular electron-dense material (complement protein) deposited within the glomerular basement membrane (So, it's a complement disease).

It has a tram-track appearance that is not as apparent as that of type I.

Pathogenesis:

Over production of C3 and they are activated by the alternative pathway.
Replacement of glomerulus basement membrane by thick band of C3.
The possible cause is an IgG autoantibody (C3 nephritic factor) with specificity for the C3 convertase of the alternate complement pathway.

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) Hypertesnion 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.

Summary (from Robbins)

The 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.**

Questions from Pathology Recall book

1/ What causes the leakage of RBCs into the urine?
Inflammatory repture of glomerular capillaries with escape of RBCs into the Bowman space.

2/ What is the immunofluorescence pattern in case of Goodpasture disease?
Linear IgG

3/ What is the electron microscopy finding in Alport syndrome?
GBM splitting.

4/ What is the typical infection associated with PIGN?
Group A B- hemolytic streptococci which cause tonsillitis, impetigo.

5/ What predispose a patient to rebidly progressive glomerulonephritis?
Streptococcal infection, lupus, vasculitis, and cryoglobulinemia.

6/ List the 3 charcteristic findings in Goodpasture disease?

1- Alveolar damage
2- Glomerulonephritis
3- Antibody deposition along alveolar and GBM.

7/ What is the pathology of Berger disease?

Mesangial IgA deposition, diffuse mesangial preliferation.

Case 1 / An 8 year-old boy is brought to the pediatrician's office with a 2 day history of malaise, fever of 38.8 , nausea, and vomiting. His mother reports that he has decreased urine output and that his urine is a dark, smoky color. His blood pressure is slightly elevated, and there is some swelling of his hands and feet and around his eyes. He has been is good health except for a sore throat a week or so ago. What is the most likely the diagnosis?

A- Poststreptococcal infection.
B- Aloprt Syndrome.
C- Goodpasture disease.
D- Berger disease.

Case 2/ A renal biopsy from an adult who presented with progressive renal failure and hematuria reveals linear deposits of IgG within the glomeruli. Which of the following types of autoantibodies is most likely to be present in this individual?

A- Antibasement membrane antibodies.
B- Anticentromere Antibodies.
C- Antidouble-stranded DNA antibodies.
D- Anti-smooth muscle antibodies.

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

The cases from case files Pathology book

Answers:

- Case 1 / A
- Case 2 / A

432 Pathology Team

*Good Luck ^_^*