LECTURES THREE AND FOUR

PATHOLOGY OF THE NEPHROTIC, NEPHRITIC

AND CHRONIC KIDNEY DISEASE

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EVALUATION OF GLOMERULAR DISEASE

1] **Terminology**: The following terms are used to describe the extent of glomerular injury:

(a) Diffuse - all glomeruli are affected.
(b) Focal - some glomeruli are affected.
(c) Segmental - part of one glomerulus is affected.
(d) Global - the entirety of one glomerulus is affected.

2] **Techniques used for studying of glomerular diseases:**

(a) Light microscopy: using routine (haematoxylin and eosin) and special stains.
(b) Immunofluorescence: antibodies tagged (labelled) with a fluorchrome are used to localize immunoreactants in the glomerulus.
(c) 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.

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

(2) **Minimal change disease** (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.

TABLE 1: SUMMARY OF GLOMERULAR DISEASES

TYPES	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 juxtamedullary glomeurli.
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.

(a) Lipid-laden renal tubules (lipids are intracytoplasmic in tubular cells) particularly in cells of proximal convoluted tubules.
(b) Light microscopy demonstrates normal-appearing glomeruli.
(c) Electron microscopy is normal except for the disappearance or fusing of epithelial foot processes.
(d) Most often, this condition responds well to corticosteroid therapy.

3] **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.
(a) Focal distribution is involvement of some, but not all of the glomeruli.
(b) Segmental distribution is involvement of only a part of the glomerulus.

4] **Membranous glomerulonephritis** is an immune complex disease of unknown etiology.
(a) This disease is a major primary cause of the nephrotic syndrome.
(b) Incidence is highest in teenagers and young adults.
(c) The diagnosis should be suspected when the nephrotic syndrome is accompanied by azoemia (increased concentrations of serum urea nitrogen and creatinine).
(d) 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.
(e) 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.
(f) 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.
(g) Granular deposits of immunoglobulin G (IgG) or C3 are apparent on immunofluorescence. Granular immunofluorescence is a general characteristic of immune complex disease.
(h) Membranous glomerulonephritis is a slowly progressive disorder that shows little response to steroid therapy.
(i) 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.
(j) The disorder sometimes causes renal vein thrombosis, which was previously thought to be an etiologic factor.

5] **Diabetic nephropathy**

(a) Often, this disease is clinically manifested by the nephrotic syndrome.

(b) 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.

(c) An increase in mesangial matrix results in two characteristic morphologic patterns:

(1) Diffuse glomerulosclerosis is marked by a diffusely distributed increase in mesangial matrix.

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

6] **Renal amyloidosis**

(a) This condition is another cause of the nephrotic syndrome.

(b) Predominantly subendothelial and mesangial amyloid deposits are characteristic.

(c) The amyloidosis can be identified by reactivity of amyloid with special stains (e.g. Congo Red, 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.

(d) Most often, there are associations with chronic inflammatory diseases, such as rheumatoid arthritis or plasma cell tumours such as multiple myeloma.

7] **Lupus nephropathy**

(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.

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.

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.

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.

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) Haematuria 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. The

(e) patient often reports having "smoky brown urine". Red cell casts can degenerate and become pigmented granular casts.

(2) **Posstreptococcal glomerulonephritis** (acute proliferative glomerulo-nephritis) is the prototype of the nephritic syndrome. It is immune complex disease with the antigen being of streptococcal origin.

(a) This disorder most often follows or accompanies infection (tonsillitis, streptococcal impetigo, infected insect bites) with nephritogenic strains of group A B-hemolytic streptococci.

(b) Complete recovery in almost all children and many adults follow. A very minority develop rapidly progressive glomerulonephritis.

(c) 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.

(d) 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).

(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 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 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) Antiglomerular 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 antiglomerular 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 deaflines 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 is mutation in the gene for the 5 chain of type IV collagen.
         d. Irregular glomerula basement membrane thickening with foci of splitting of the lamina densa are seen by electron microscopy.

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-Schonlein vasculitis disease.

(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.

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