# Pathology – Lecture 3

## Renal Block

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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):

Glomerular Diseases can either be: Nephrotic, Nephritic, or even both syndromes at once.

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. They are generally immune mediated, by type II or type III hypersensitivity reactions, or idiopathic in nature. The lesions of the disease don't show hypercellularity, but are only fibrosed and hylanized forming sclerotic lesions. Lastly, Some of the diseases don't affect the juxtamedullary glomeruli.

(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. This type of edema is manifested by puffiness of a patient's face. The edema is further worsened by increased retention of salt and water. As fluid goes from the vessels to the interstitial tissue, plasma volume decreases. This decrease in plasma volume will reduce the GFR and the secretion of ANP. At this time, Aldosterone is also secreted to compensate for this drop in volume and pressure, ultimately worsening

the edema.

(d) Hyperlipidemia and hyperchomsterolemia are caused by increased hepatic lipoprotein synthesis. This is believed to happen by: (1) A reaction of the liver to albunemia (2) Problems resultant from transport and breakdown problems. At advanced stages of the syndrome, when the glomerular filtration membrane's permeability increases greatly, lipids can show up in the urine a condition called lipiduria.

Examining the Patient:

-The first test or procedure done to categorize the disease is a urine strip test (urine dipstick test). The test is done by inserting the sticks in the urine, and a result will come up within 120 seconds. The sticks may have as much as 10 pads that may show:

1. Glucose
2. Ketones
3. Blood
4. Protein
5. Nitrite
6. pH
7. Urobilinogen
8. Bilirubin
9. Leukocytes
10. Specific gravity

-Then renal function test (BUN, creatinine: serum, urine) are ordered.

-Radiological examinations.

-Kidney biopsy

-Lastly Electron microscopy.

(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. Is a disease of selective proteinuria, meaning that that only albumin is filtered and other proteins are spared. Theories attribute the disease to T-cell involvement with accompanying cytokines that act on nephrin synthesis.

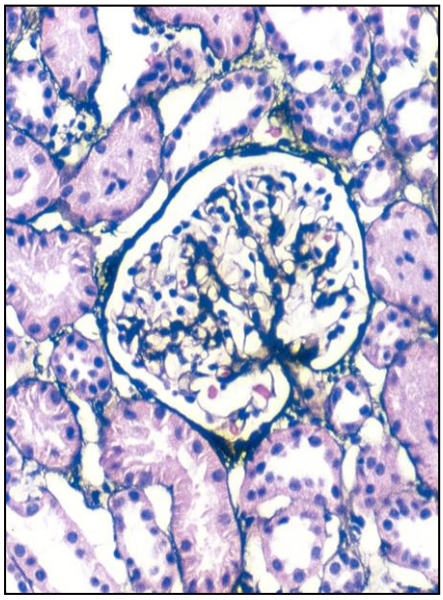
TABLE l: SUMMARY OF GLOMERULAR DISEASES

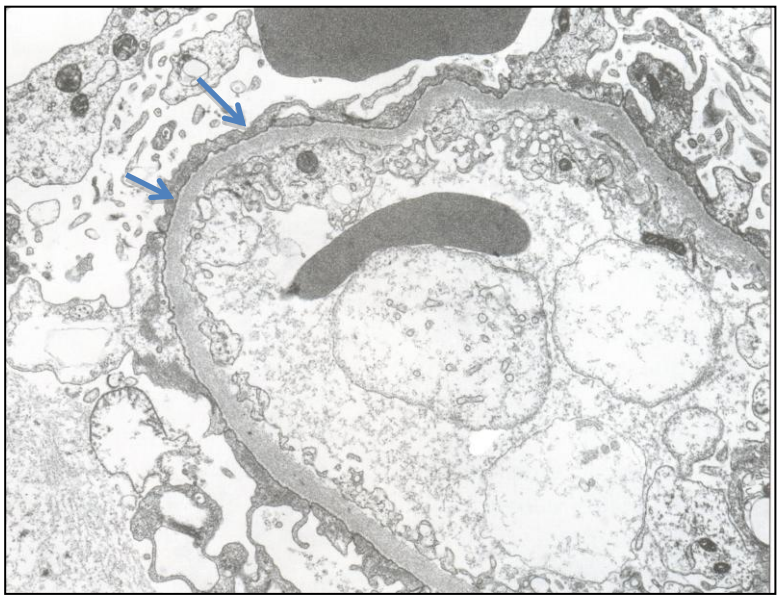
| TYPES | MORPHOLOGIC FINDINGS |
|---|---|
| A) Disorders manifest by the nephrotic syndrome | No visible basement membrane changes; fused epithelial foot process; lipid accumulation in renal tubular cells. |
| Minimal change disease (lipoid nephrosis) | No visible basement membrane changes; segmental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

(a) Lipid-laden renal tubules (lipids are intracytoplasmic in tubular cells)

particularly in cells of proximal convoluted tubules. Lipoproteins are reabsorbed from excretion.

(b) Electron microscopy is normal except for the disappearance or fusing of epithelial foot processes.

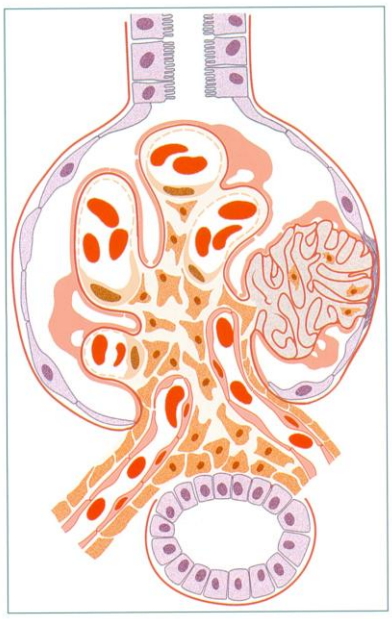


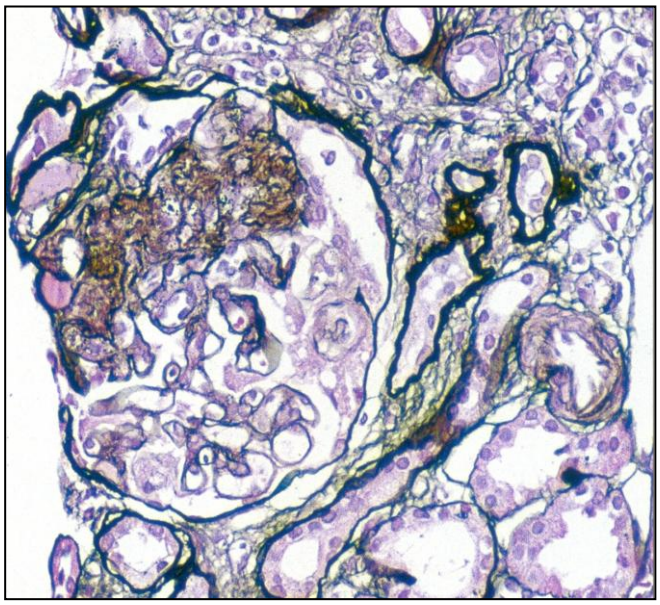


(A) Regular H&E slide of minimal change disease. The histology of the disease looks normal, with no chang level of microscopy. There is no tubulionterstial fibrosis, as in this patient. (B) Electron Microscopy of minim disease (lipoid nephrosis) shows no structural changes except for flattening of the foot processes (podocyte basement membrane shown by pointed arrows, while everything else looks normal.

(c) Most often, this condition responds well to corticosteroid therapy, showing excellent prognosis. It is important for the disease to be diagnosed at an early stage that's for it have the best prognosis it can and avoid complications.

**3] Focal segmental glomerulosclerosis** is clinically similar to minimal change disease but occurs in somewhat older patients, very common in adults. It is characterized by sclerosis within capillary tufts of the deep juxtamedullary glomeruli with focal or segmental distribution. Podocytes effacement maybe seen by EM, but not under a light microscope.





The disease can be either: (A) primary: idiopathic (B) Secondary: associated with hypertension, Diabetes, secondary to another glomerular disease.

(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.
(c) The disease manifests with nonselective proteinuria.
(d) Even though the diseases is not considered an autoimmune disease, you may find immune deposits of IgM and C3 with immunofluorescence after they are entrapped. This entrapping is largely due to the high molecular weight of these immune complexes.
(e) The prognosis is much worse than that of minimal change.

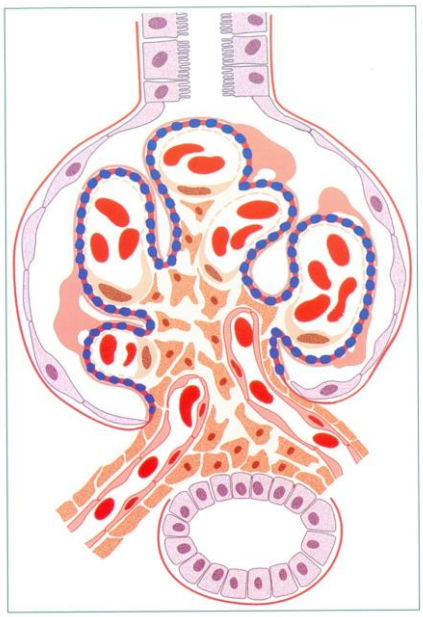
4] Membranous glomerulonephritis is an immune complex disease of unknown etiology. Most common cause in adults, and is one of the most common autoimmune diseases.

(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).

(A) Illustrative representation of Focal segmental glomerulosclerosis. There is sharply defined segmental sclerosis (shown by the arrow), defined as obliteration of capillary loops and increased matrix, without deposits of immune complexes and with diffuse foot process effacement by EM (Not shown). Adhesions can also be present. (B) Regular H&E of FSGS that shows increased matrix with obliteration of capillary lumina, frequently with hyalinosis and adhesions, as seen here.

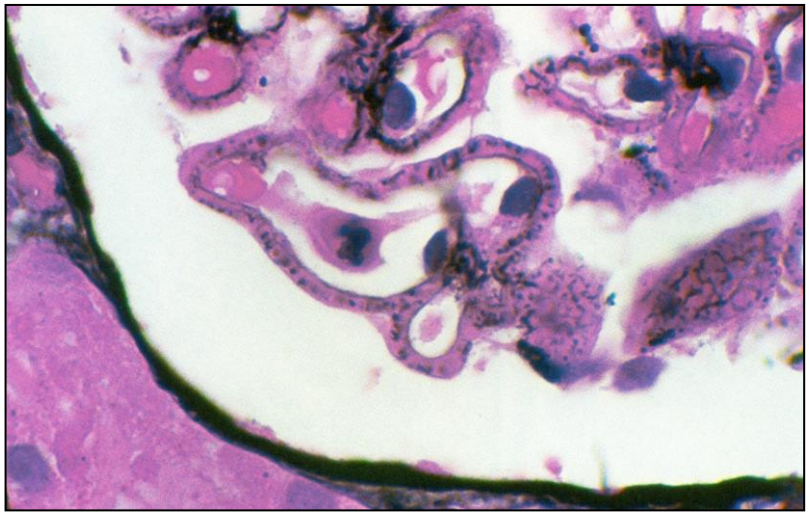
(d) Morphologic characteristics include greatly diffused thickened capillary walls, which are visible by light microscopy and visible by electron microscopy as a 5- to 10-fold thickening of the basement membrane.

(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.



This is visual representation of Membranous glomerulopathy. There is no evident proliferation by light microscopy, with global subepithelial deposits, which may be visualized by light microscopy by the glomerular basement membrane spike reaction on silver stain.

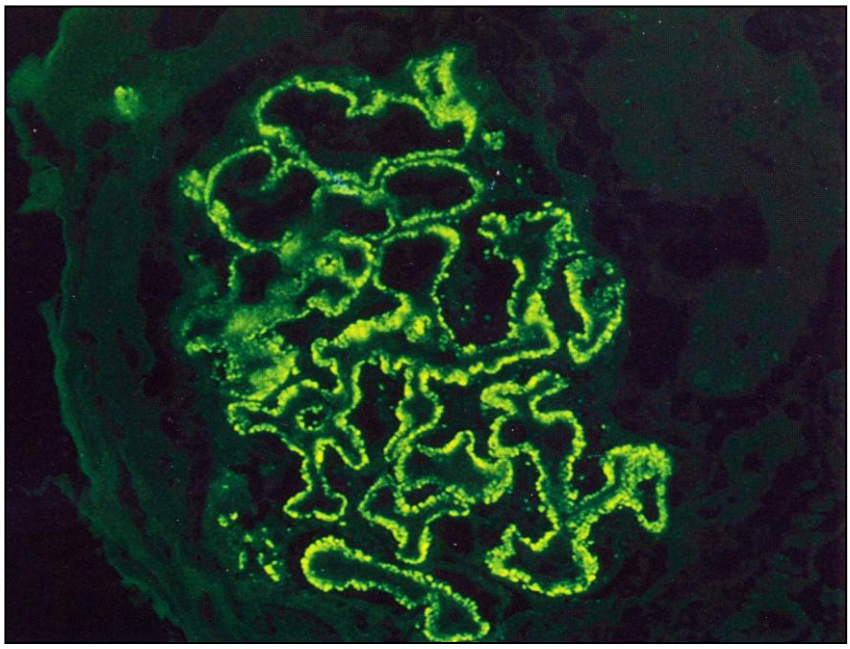
(f) With special stains, a "spike and dome" appearance resulting from the extension of basement membrane between and around the immune deposits is seen; the spikes are basement membrane material and the domes are immune complex deposits.



(g) Granular deposits of immunoglobulin G (IgG) or C3 are apparent on immunofluorescence. Granular immunofluorescence is a general

characteristic of immune complex disease. How does it undergo sclerosis? The immune deposits are catabolized by the basement membrane in a way. This leaves empty spaces, which are patched up by membrane like material at first. Then these spaces are hylanized with granulation tissue to become thickened.

Now the disease is thought to be mediated by these complexes' interaction with renal auto-antigens. There is also some susceptibility linked to people with changes in the HLA locus.



Immunofluorescence of renal tissue showing capillary loop pattern of positive membranous glomerulopathy by the stain.

(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 (used to treat Rheumatoid arthritis) or penicillamine (also an immunosuppressior used to treat Rheumatoid Arthritis) or malignancy. It also associated with captopril and even with reactions to an exogenous antigen.

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

- Clinical course of membranous glomerulonephritis:
- About 90% of cases are idiopathic
- Shows non-selective proteinuria
- Some patients (40%) may progress to have renal failure, but this usually happens at a time frame of 15 – 20 years.
- Others have a benign case, which may have remission of proteinuria.

## 5] Diabetic nephropathy

Is a non-mmune mediated nephrotic syndrome.

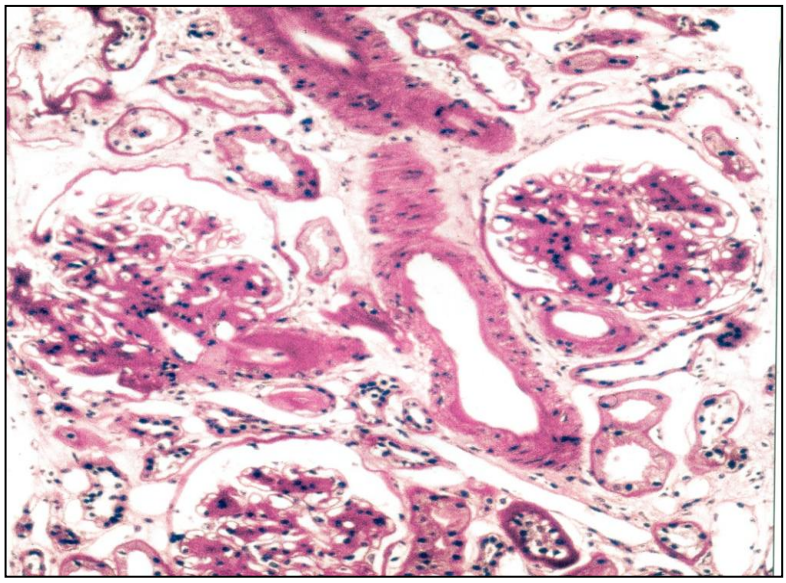
(a) Often, this disease is clinically manifested by the nephrotic syndrome.

(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 (Kimrnelstiel-Wilson nodules).

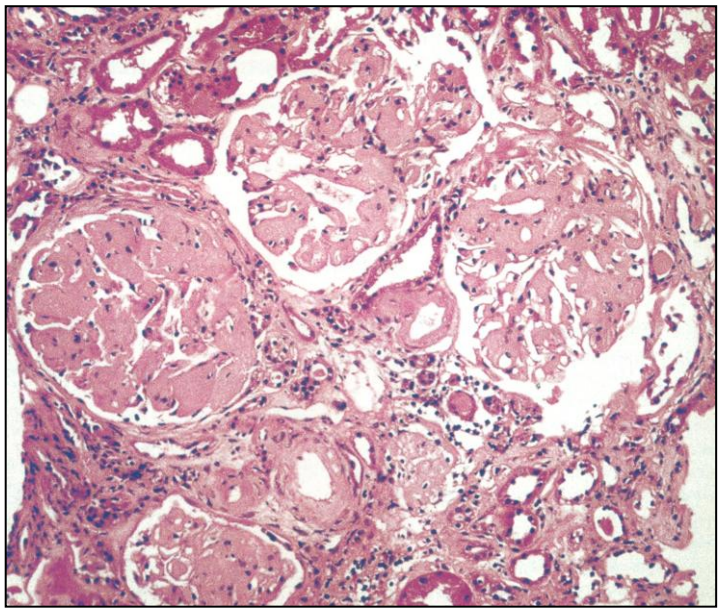


H&E of Renal tissue showing lesions of diabetic nephropathy that are characterized by (1) arteriolar hyalinization, (2) mesangial matrix expansion and (3) glomerular basement thickening.

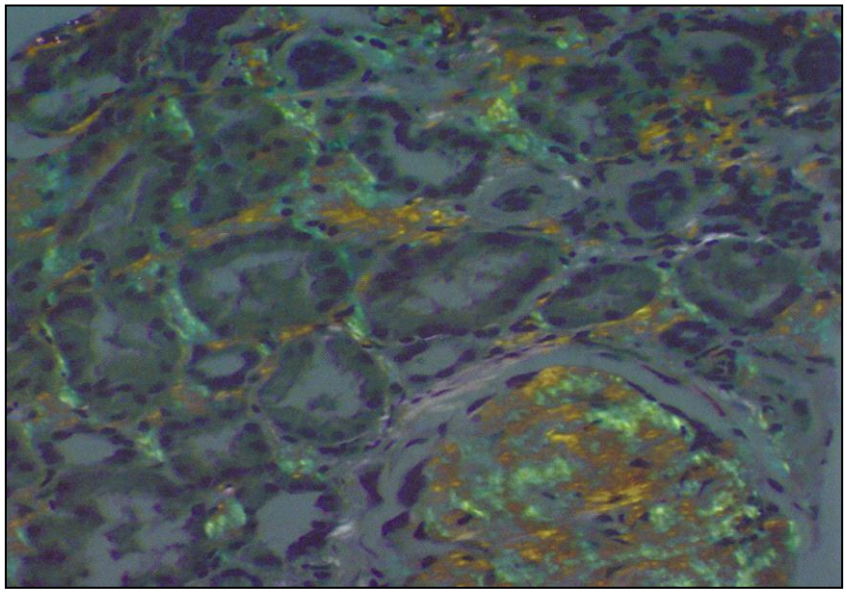
**6] Renal amyloidosis**

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

(b) Predominantly global 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.



Tubular involvement with amyloid is verified by apple-green birefringence under polarized light.

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

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