**Babylon University Fourth Stage**

**Colleague of Medicine Lecture 1**

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**Urinary tract Pathology**

**Glomerular diseases**

Glomerular diseases constitute one of the major problems in nephrology.

They are divided to:

*Primary glomerular diseases*: in which, the kidney is the only or predominant organ involved.

*Secondary glomerular diseases*: in which the glomeruli injured secondary to several systemic diseases such as systemic immunological diseases (systemic lupus erythematosus), vascular disorders (hypertension), metabolic diseases (diabetes mellitus), and some hereditary conditions such as Fabry disease.

**Glomerular Diseases**

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| **PRIMARY GLOMERULOPATHIES** |
| |  |  |  | | --- | --- | --- | |  |  | Rapidly progressive (crescentic) glomerulonephritis | |  |  | Membranous glomerulopathy | |  |  | Minimal-change disease | |  |  | Focal segmental glomerulosclerosis | |  |  | Membranoproliferative glomerulonephritis | |  |  | IgA nephropathy | |  |  | Chronic glomerulonephritis | |
| **SYSTEMIC DISEASES WITH GLOMERULAR INVOLVEMENT** |
| |  |  |  | | --- | --- | --- | |  |  | Systemic lupus erythematosus | |  |  | Diabetes mellitus | |  |  | Amyloidosis | |  |  | Goodpasture syndrome | |  |  | Microscopic polyarteritis/polyangiitis | |  |  | Wegener granulomatosis | |  |  | Henoch-Schönlein purpura | |  |  | Bacterial endocarditis | |
| **HEREDITARY DISORDERS** |
| |  |  |  | | --- | --- | --- | |  |  | Alport syndrome | |  |  | Thin basement membrane disease | |  |  | Fabry disease | |

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**Clinical manifestations**

The clinical manifestations of glomerular disease are clustered into the five major glomerular syndromes.

Both the primary glomerulopathies and secondary glomerulopathies can result in these syndromes.

**The Glomerular Syndromes**

| **Syndrome** | **Manifestations** |
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| Nephritic syndrome | Hematuria, azotemia, variable proteinuria, oliguria, edema, and hypertension |
| Rapidly progressive glomerulonephritis | Acute nephritis, proteinuria, and acute renal failure |
| Nephrotic syndrome | >3.5 gm/day proteinuria, hypoalbuminemia, hyperlipidemia, lipiduria |
| Chronic renal failure | Azotemia ➙ uremia progressing for months to years |
| Isolated urinary abnormalities | Glomerular hematuria and/or subnephrotic proteinuria |

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**Microscopical changes of glomerular diseases**

The glomerulopathies are characterized by one or more of the following basic microscopical features.

**1- Hypercellularity.**

The hypercellularity is result from one or more combinations of the following:

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|  | **•** | *Cellular proliferation* of mesangial or endothelial cells. |
|  | **•** | *Leukocytic infiltration*. |
|  | **•** | *Formation of crescents*.  Crescents are composed of proliferating parietal epithelial cells and infiltrating leukocytes.  Fibrin, which leaks into the urinary space, through ruptured basement membranes, is the molecule that elicits the crescentic response. |

**2- Basement membrane thickening.**

By light microscopy, this change appears as thickening of the capillary walls

By electron microscopy such thickening takes one of two forms:

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|  | **•** | Deposition of immune complexes, on the endothelial or epithelial side of the basement membrane or within the membrane itself. |
|  | **•** | Thickening of the basement membrane due to increased synthesis of its protein components, as occurs in diabetic glomerulosclerosis. |

**3- Hyalinosis and sclerosis.**

*Hyalinosis*, accumulation of material called hyaline which is homogeneous and eosinophilic extracellular material. Hyaline is made up of plasma proteins that have escaped from the circulation into glomerular structures. Hyalinosis is usually a consequence of endothelial or capillary wall injury and typically the end result of various forms of glomerular damage.

*Sclerosis is* characterized by accumulations of extracellular collagenous material, either in the mesangial areas as is often the case in diabetic glomerulosclerosis, or involving the capillary loops, or both.

Because many of the primary glomerulopathies are of unknown cause, they are often classified by their histology.

The histologic changes can be further subdivided according to their distribution into:

*According to distribution:*

*Diffuse*: involving all glomeruli;

*Global*: involving the entire glomerulus;

*Focal*: involving only a proportion of the glomeruli;

*Segmental*: affecting a part of each glomerulus;

Other subdivision according to distribution:

*Capillary loop*: affecting predominantly capillary loop

*Mesangial*: affecting predominantly mesangial regions.

**Pathogenesis of glomerular diseases**

The immune mechanisms underlie **most** forms of primary glomerulopathies and **many** of the secondary glomerular disorders.

**Immune mechanisms of glomerular injury**

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| **1- Antibody-mediated injury** |
| **A-In situ immune complex deposition** |
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| **B- Circulating immune complex deposition** |
| |  |  |  | | --- | --- | --- | |  |  | Endogenous antigens (e.g., DNA, tumor antigens) | |  |  | Exogenous antigens (e.g., infectious products) | |
| **C- Cytotoxic antibodies** |
| **2-CELL-MEDIATED IMMUNE INJURY** |
| **3-ACTIVATION OF ALTERNATIVE COMPLEMENT PATHWAY** |

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| GBM, glomerular basement membrane. |

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**1-Antibody mediated injury**

**A- Antibodies reacting in situ within the glomerulus**

**I- Anti-GMB antibody–induced glomerulonephritis**

In this type of injury *antibodies are directed against intrinsic fixed antigens that are normal components of the GBM, the GBM antigen that is responsible for classic anti-GBM antibody–induced glomerulonephritis is a component of the* α3 *chain of collagen type IV*.

Often the anti-GBM antibodies cross-react with other basement membranes, especially those in the lung alveoli, resulting in simultaneous lung and kidney lesions *(Goodpasture syndrome)*.

Anti-GBM antibody–induced glomerulonephritis are characterized by:

Light microscope: severe crescentic glomerular damage.

Immunofluorescent microscope: diffuse linear pattern.

Clinically: rapidly progressive glomerulonephritis.

**II- Antibodies against planted antigens**

*Antibodies can react in situ with antigens that are not normally present in the glomerulus but are “planted” there*.

Planted antigens include:

DNA, nucleosomes, and other nuclear proteins.

Bacterial products.

Large aggregated proteins (e.g., aggregated immunoglobulins, which deposit in the mesangium because of their size).

Immune complexes themselves.

Free antigen.

Complement.

Immunofluorescent microscope: granular staining similar to the pattern found in circulating immune complex nephritis.

**III- Heymann nephritis**

Antibody binding to glomerular epithelial cell membrane is followed by complement activation and then shedding of the immune aggregates from the cell surface to form the characteristic subepithelial deposits.

Electron microscopy the glomerulopathy is characterized by the presence of numerous discrete deposits along the *subepithelial aspect* of the basement membrane.

Immunofluorescence microscopy is *granular* rather than linear.

Clinically: membranous nephropathy.

***Note:*** **anti-GBM antibody disease** and **Heymann nephritis** are autoimmune diseases, caused by antibodies to endogenous tissue components. **What triggers these autoantibodies is unclear**.

***B- Circulating immune complex glomerulonephritis***

*In this type of glomerular disease, the injury is caused by the trapping of circulating antigen-antibody complexes within* *glomeruli.*

Antigen-antibody complexes are formed in the circulation and then trapped in the glomeruli, where they produce injury.

Two types of antigens that trigger the formation of circulating immune complexes

1. Endogenous antigen, as in SLE
2. Exogenous antigen, as microbial antigens: bacterial products (streptococci), the surface antigen of hepatitis B virus, hepatitis C virus antigens, some tumor antigens are also thought to cause immune complex–mediated nephritis.

Light microscope: the glomeruli showed leukocytic infiltration and proliferation of mesangial and endothelial cells.

Electron microscopy: reveals the immune complexes as electron-dense deposits that lie in the mesangium, between the endothelial cells and the GBM (subendothelial deposits), or between the outer surface of the GBM and the podocytes (subepithelial deposits). Deposits may be located at more than one site in a given case.

Immunofluorescence microscopy: the immune complexes are seen as granular deposits along the basement membrane, in the mesangium, or in both locations

Clinically: membranous or membranoproliferative type of glomerulonephritis.

**C- Antibodies to glomerular cells**

Antibodies against glomerular cell antigens may react with cellular components and cause injury by cytotoxic mechanisms.

Antibodies to mesangial cell antigens, for example, can cause mesangiolysis; antibodies to endothelial cell antigens cause endothelial injury.

**2- Cell-mediated immunity in glomerulonephritis**

Although antibody-mediated mechanisms cause many forms of glomerulonephritis, there is now considerable evidence that sensitized T cells cause some forms of glomerular injury.

**3- Activation of alternative complement pathway**

Alternative complement pathway activation occurs in the entity called dense-deposit disease, also referred to as *membranoproliferative glomerulonephritis.*