Immune Mechanisms of Glomerular Injury
Glomerular disease

- One of the commonest causes of end-stage renal failure worldwide, especially in younger patients
- Various types, defined histologically, with distinct clinical features and natural histories
- Immunologically mediated, involving different immune mechanisms in the various types
- Treatment with immunosuppressive drugs, e.g. prednisolone and cyclophosphamide, is often effective in some types

Glomerulonephritis

- Inflammation of the glomeruli,
- leading to damage to the glomerular capillary wall (proteinuria, hematuria) and
- reduction in glomerular filtration rate (renal failure)
CLINICAL MANIFESTATIONS OF RENAL DISEASE

Acute Nephritic syndrome
Nephrotic syndrome
Asymptomatic hematuria
Asymptomatic proteinuria
Acute renal failure
Chronic renal failure

Nephritic
- Hematuria
- Proteinuria
- Hypertension
- Hypoalbuminemia
- Oliguria (GFR↓, Cr↑, BUN↑)
- Edema (salt and water retention)

Nephrotic
- Proteinuria (“nephrotic range” >3.5g/24h)
- Hypoalbuminemia
- Severe Edema
- Hyperlipidemia
- Lipiduria

**Acute Renal Failure**
- Oliguria, /anuria, recent azotemia
- Glomerular, interstitial, vascular, ATN

**Chronic renal failure (uremia)**
- Azotemia (elevated BUN, s. creatinine, decreased GFR)
- Cl. Sign symptoms
- Biochemical abnormality

**Chronic renal failure (uremia)**

Four Stages:
- **Diminished renal reserve:** GFR....50%
  asymptomatic, BUN & S. Creatinine... normal
- **Renal Insufficiency:** GFR....20-50%
  Azotemia, anemia, HTN
- **Renal Failure:** GFR....20-25%
  Edema, met. Acidosis, Hypocalcemia. (Uremia)
- **ESRD:** GFR....<5%
  terminal stage of uremia

**Classifications of glomerulonephritis**

**Clinical** - description of a
e.g. nephrotic syndrome, RPGN

- **Histological** - renal biopsy findings, e.g. membranous nephropathy, crescentic GN
- **Immunological** - based on serology or immunofluorescence, e.g. immune-complex, anti-GBM

*Each histological type of GN tends to present in a particular way, but with considerable overlap*

Classification of glomerulopathies

- **Clinical**: primary x secondary
- **According time period**: acute x subacute x chronic
- **According renal biopsy**: focal x segmental x diffuse
- **According number of cells**: non-proliferative x proliferative
- **According immunofluorescence**: Glomerular diseases

**Primary GN**
- no underlying systemic disease, e.g. IgA nephropathy

**Secondary GN**
- due to systemic disease, e.g. SLE

**Other glomerulopathy**
- inherited, e.g. Alport’s syndrome
- secondary, e.g. diabetes, amyloid

**Primary Glomerulonephritis**

**Acute diffuse proliferative GN**
**Rapidly progressive GN**
Membranous GN
Lipoid nephrosis (minimal change disease)
Focal segmental glomerulosclerosis
Membranoproliferative GN
IgA Nephropathy
Chronic GN

- Secondary (Systemic) Diseases
  - Systemic lupus erythematosus
  - Diabetes mellitus
  - Amyloidosis
  - Goodpasture’s syndrome
  - Polyarteritis nodosa
  - Wagener’s granulomatosis
  - Henoch-Schonlein purpura
  - Bacterial endocarditis

- Hereditary Disorders
  - Alport’s syndrome
  - Fabry’s disease

Nomenclature of glomerular injury

- Diffuse - all glomeruli

- Focal - some glomeruli, others unaffected

- Global - the whole glomerulus

- Segmental - only part of the glomerulus

Immunological

 Antibody mediated

- In situ immune complex
  --fixed intrinsic tissue Ag
  --planted Ag (exo &endo)
- **Circulating immune complex** (endo & exogenous)
- **Cytotoxic** antibody
- **T-cell mediated**
- **Alternate complement pathway**

**In Situ Immune Complex**

- **Anti-GBM Antibody induced Nephritis**
  -- Ab. against fixed Ag. of normal GBM
  -- IF..... linear pattern of staining for Abs.
  -- NC1 of a- chain of Collagen IV
  -- RPGN

- **Heymann Nephritis**
  -- Ab binds glomerular epithelial cell memb
  ...... complement activation..... shedding of immune aggregates
  -- IF..... Sub-epithelial deposits, granular

- Antibodies against planted antigens
  Abs react in situ with Ags planted in glomeruli
  -- DNA, nuclear proteins
  -- bacterial products, immune complexes

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- **Trapping circulating Ag-Ab complexes in glomeruli**

- Complexes localize due to their physiochemical properties & hemodynamic factors
- Complexes have no immunologic specificity for glom. Constituents
- Exogenous or endogenous Ags
- Activation of Complement
- Leucocytes + endoth. Or mesangial cells
- **E/M.....S/Endoth. or S/Epith.**
• IF.....S/enoth. Or S/epith. or BM, or mesangium, granular
  Type III reaction – immune complex-mediated hypersensitivity
- The reaction of antibody with antigen generates immune complexes. In some cases, large amounts of immune complexes can lead to tissue damage
  They deposited in various tissues
  \[\text{↓}\]
  induce complement activation and ensuing inflammatory response

Antigens can be:
• Endogenous – for example DNA in SLE
• Exogenous – bacteria, viral, parasitical Ag

Location of immune deposits in the glomerular capillary wall

Antibodies to Glomerular Cells
• Antibodies may react with cellular components and cause injury by cytotoxic and other mechanisms

Cell mediated immunity in GN

• Sensitized T cells

Cause & progression

Alternative Compliment pathway

• MPGN II
  Delayed – type hypersensitivity (Type IV)
T lymphocytes may also recognize antigen

When they do, a mononuclear cell infiltrate may accumulate at the site of Ag concentration and lead to the elaboration of toxic products and tissue injury
THANKS