Glomerular diseases

Normal anatomy
Fig. 1 Anatomy of the glomerulus and the juxtaglomerular apparatus

Hypersensitivity reactions
Mast cells covered with IgE antibodies bind parasitic antigens → inflammatory response, attraction of eosinophils → killing worms

Type I: Immediate hypersensitivity (anaphylaxis)
1st exposure to antigen → production of specific AB → their binding to mast cells (sensitization). Next exposure → allergen degranulates mast cells → release of histamine (immediate response) → vascular permeability, ↓airways, hives, conjunctivitis, rhinitis. Later: → leukotriens, prostaglandins, PAF, proteases (late phase) → localized anaphylaxis = atopy (asthma, hay fever, eczema, hives)

systemic anaphylaxis — circulatory shock, dyspnea, laryngospasm

Type II: Cytotoxic
Cell-mediated cytotoxicity requires prior binding of antibodies to target cells
- An epitope is present on a cell
  - a self-molecule in autoimmune diseases (errant or uncontrolled plasma cells produce antibodies against self-antigens)
  - a drug or microbial product passively adsorbed onto a cell surface
AB binds to the epitope and can stimulate cell damage by a number of effector mechanisms:
- AB + complement → opsonization → phagocytosis,
  extracellular release of toxic molecules → antibody-dependent cell-mediated cytotoxicity (ADCC)
- Activation of complement → membrane attack complex
- Activation of complement → C5b67 → bystander lysis ("innocent bystanders")
- Anchoring and activation of killer cells → ADCC

K(iller) cells: Lymphocyte-like cells (not B or T) that kill a variety of tumor cells and virus-infected cells but only after previous immunization (some authors: = natural killer cells, NK)

Type III: Immune-complex-mediated-hypersensitivity
Fig. 3 Immunologic reactions after an injection of heterologous protein

Dysbalance between the antigen and AB quantities (e.g., antibody in excess) → small complexes → they deposit in blood vessel walls → endothelial damage and inflammatory process
Deposition of complexes may reflect hemodynamic factors (glomeruli)

Type IV: Cell-mediated immune injury = delayed-type hypersensitivity
Slowly evolving (1-2 days). No circulating antibody but sensitized lymphoid cells
Resistant (intracellular) bacterium, herpes simplex and measles virus, foreign tissue, metals, chemicals etc.
First exposure → origin of antigen-specific memory T-lymphocytes; second exposure → their stimulation → lymphokines → activation of TH cells → ↑ TC, ↑ "angry" macrophages, ↑ K(ill)er cells, ↑ N(atural) K(iller) cells (= perhaps, do not require prior immunization) → indiscriminate phagocytosis, exudation. Macrophages → epitheloid cells → giant cells → granulomas
If exaggerated (= type IV) → granulomatous inflammation, contact dermatitis, transplant rejection. Where cell-mediated reactions do not eliminate the pathogen → tissue destruction

Inflammatory glomerular diseases
Three typical syndromes: nephritic, nephrotic and chronic glomerulonephritis (Fig. 4)
Immune diseases

Visceral epithelial cell (= podocyte) injury

Minimal change disease = lipoid nephrosis

Fig. 5: some mesangial proliferation, edematous podocytes, fusion (“loss”) of their foot processes

Focal segmental glomerulosclerosis (more serious degree of lipoid nephrosis)

- Focal = <50% of glomeruli are affected by light microscopy
- Diffuse = >50% affected
- Segmental = only a part of the glomerular tuft is involved

Glomerulosclerosis = obliteration (scarring) of capillary lumens

Both diseases result from primary injury of podocytes. Unclear podocyte damaging toxin – some lymphokine? React to glucocorticoids

Nephrotic syndrome

- heavy proteinuria (more than 3 g/day)
- hypoalbuminemia
- hyperlipidemia
- edema

Pathogenesis:
- Epithelial cell damage → distortion of slit diaphragms → proteinuria
- Loss of fixed negative charges of GBM → loss of (negatively charged) albumin
- Physicochemical changes in serum proteins (lipoid nephrosis, diabetes) → proteinuria
- Proteins between 50 000 – 200 000 daltons are lost (albumin, some IgG)

Pathogenesis of symptoms (Fig. 7)
Hypersensitivity reactions type II:

Antibodies directed against the intrinsic GBM antigens

- Antiglomerular basement membrane nephritis = “idiopathic” crescentic GN
  - Antigen: noncollagenous portion of the α3 chain of type IV collagen
  - Complement and mediators → focal glomerular necrosis, crescent formation → end-stage renal failure
  - Anti-GBM antibodies bind in a linear pattern to the GBM (without electron-optically dense deposits)

Goodpasture’s syndrome: antigens in GBM and alveolar basement membrane in the lungs → focal proliferative GN and hemorrhagic pneumonitis. Crescents, uremia

Hypersensitivity reactions type III: Immune complex formation = immune complex disease

- Glomerulus is highly susceptible to the entrapment or formation of immune complexes
- Detection: electron microscopy, immunofluorescence (granular appearance)
- The nature of the antigen → whether subepithelial or subendothelial deposition
- Location of the complexes → type of injury and clinical manifestations. However, histopathology does not correlate well with clinical syndroms

Subepithelial deposits

Subepithelial deposits

- Postinfectious GN
  - circulating cationic antigen (A, β-hemolytic streptococci)
  - Fig. 9: „humps“ formed by immunocomplexes

Membranous nephropathy

- idiopathic form (=unknown antigens) – autoimmune disease? Experimental model: filtered autoantibody; antigen present in situ (glycoprotein on podocyte cell membrane). Common, variable course, treatment - ?
- in systemic disease
  - systemic lupus erythematosus – lupus nephritis (AB against DNA)
  - hepatitis B
  - tumor antigens
Fig. 11 (Membranous GN): Precipitation of immunoglobulins on the outer surface of the GBM ("spikes" → complete incorporation of Ig into the membrane)

Table 1

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Subepithelial deposits ↔ injury to the podocytes: membrane attack complex C5b-9 → fusion of the foot processes

Clinical manifestations: typically nephrotic
Distortion of slit diaphragms → proteinuria
Activated complement is not in contact with circulating inflammatory cells → lack of inflammatory cell infiltration → proteinuria lasts for a long time, but little damage

Subendothelial and mesangial deposits

Rather rarely: entrapped anionic antigens (e.g., DNA in lupus) and circulating antibodies → in situ immune complex formation
More often Fig. 8 (right side): entrapment of preformed circulating immune complexes
• Lupus autoantigens
• Tumor neoantigens
• Postinfectious GN:
  - Streptococci → nephritogenic strains, bacterial endocarditis, pneumonitis, meningitis, abscesses etc. Acute diffuse proliferative GN, mostly mild, rarely crescents
  - hepatitis B, malaria
Sometimes no known source of antigenic stimulation:
- **Berger’s disease** = IgA nephropathy
  Upper respiratory infection. Circulating IgA → deposition in mesangium → mesangial proliferation, no cellular infiltrates. **Focal proliferative GN.** Mostly benign course
- **Schönlein-Henoch purpura**
  Skin IgA deposits → purpura; arthritis, hemorrhagic gastroenteritis, nephritis (mostly benign). **Focal proliferative GN**
- **Membranoproliferative GN**
  C3 nephritic factor activates complement → ↓complement
  Circulating immune complexes → mostly end stage renal failure

**Inflammatory response**
- Complexes generate C3a and C5a in contact with circulation → chemotaxis
- Activation of Hageman factor → ↑coagulation cascade
- Damaged endothelium → cytokines and autacoids (local hormones) → ↑adhesion molecules → activation of endothelial and inflammatory cells

Local glomerular inflammation → breaking filtration membrane → ↑porosity, hematuria, proteinuria blocking of glomerular capillaries → ↓permeability → hypervolemia, uremia (azotemia)

**Clinical manifestations:** typically nephritic syndrome:
- active urine sediment: red cells, white cells, cellular and granular casts
- mild to moderate proteinuria
- ↓GFR Fig. 13: Mechanisms causing reduction of GFR in the nephritic syndrome
  Recovery more rapid, but severe inflammation → irreversible cell injury → glomerulosclerosis

**Type II or IV: Crescent formation and cell-mediated immunity**

Fig. 14. Severe damage of capillary wall → leaks (rents) in GBM → fibrinogen and other plasma components ("whole blood") enter Bowman’s space → proliferation of all components (of aggressive white cells, endothelial and epithelial, mesangium, epitheloid and giant cells), leakage of fibrin. **Hypersensitivity reaction type II or IV**

**Crescents** = accumulation and proliferation of extracapillary cells
→ compression of the glomerular tuft → rapid renal failure
Crescentic glomerulonephritis (>50% glom.) ⇔ rapidly progressive GN

**Etiology:**
- any severe nephritic condition → 50% of patients
- antiglomerular basement membrane nephritis = idiopathic crescentic GN (if no antibodies are detectable), see above
- ANCA-positive disorders
**Vascular diseases**

A variety of *systemic* diseases → injury of the renal arteries (e.g., hypertension → nephrosclerosis)

Two acute disorders:

**Systemic vasculitis and antineutrophil cytoplasmatic antibodies**

Acute systemic process of arteries.
- **Large vessel** arteritides, e.g., classic form of *polyarteritis nodosa* → distal glomerular ischemia (no inflammation) → ↓GFR  
- Glomerular tuft is directly involved, e.g., *microscopic form* of polyarteritis nodosa or Wegener’s granulomatosis (i.e., with no evident extrarenal involvement). They were summarized under the *pauci-immune necrotizing GN* characterized specifically by novel circulating autoantibody → antineutrophil cytoplasmic antibody = ANCA

ANCA → respiratory burst of phagocytic cells → release of free radicals → degranulation → injury to endothelial cells → focal (= < 50% glomeruli affected) *proliferative GN*, glomerular necrosis, crescents, active urine sediment. Malign course
- hypersensitive vasculitis diseases connected with drugs (penicillin, sulfonamides etc.)

**Thrombotic microangiopathies**

Injured endothelial cell loses its natural thromboresistance → platelet activation → thrombi in the lumen → possibly fibrinoid necrosis and fibrin deposition into media

Include: *Hemolytic-uremic syndrome:* thrombocytopenia, *microangiopathic hemolytic anemia,* *thrombosis of glomerular capillaries* → ↓renal function

Pathogenesis of thrombotic microangiopathies:
- verotoxin-producing *Escherichia coli* → damage to endothelia (infantile diarrhea); also immunosuppressives and chemotherapy
- Willebrand factor → platelet aggregation; autoantibody against inhibitors of platelet aggregation
- antibody-mediated endothelial injury in hyperacute renal transplant rejection

**Metabolic and toxic**

*Amyloidosis*

Plasma cell disorder → ↑immunoglobulin in serum → primary amyloidosis, e.g., in multiple myeloma

Chronic inflammatory diseases → secondary amyloidosis

Infiltration of GBM etc. with amyloid fibrils → nephrotic syndrome

Diabetes

Increased synthesis of extracellular substances → thickness of the GBM and mesangial matrix and *glomerulosclerosis* (= hyaline deposits or scarring within glomeruli)

Fig. 15: *Proliferative sclerotic GN:* advanced mesangial proliferation → narrowing and destruction of capillaries

*Nephrotic syndrome.* Generalized microangiopathy → nephropathy, retinopathy and neuropathy

**Collagen IV hereditary defect – Alport’s syndrome**

Congenital defect of collagen, X-linked (mild in females), GBM very thin or multilayered, sclerotic changes. Myopia and deafness. Nephritic syndrome

**Chronic glomerulonephritis**

Not an unknown form of GN, but a common final pathway for many glomerular diseases

Experimentally: 5/6 nephrectomy → ↑single nephron GFR (= hyperfiltration)

Loss of nephrons → hyperperfusion → hyperfiltration → sclerosis of glomeruli

Proteinuria, RBCs and casts, ↓GFR, occassionally nephrotic syndrome

Stable or goes on to the end stage renal disease

**Drugs and toxins**

Captopril, gold, antibiotics...

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