The correct diagnosis can be made only by demonstrating the characteristic bile duct abnormalities by specialized imaging such as endoscopic retrograde cholangio-pancreatography or magnetic resonance cholangiography.

Lecture No. 10-11

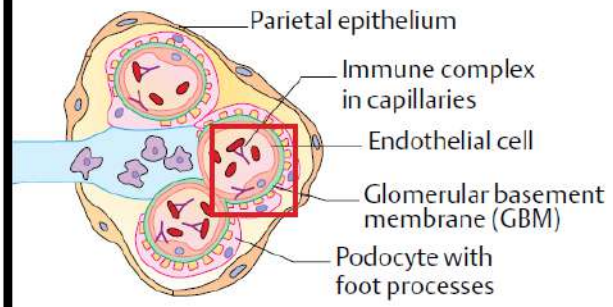
Renal diseases

Many renal diseases have underlying immunological mechanisms. Antibody-mediated effects are primarily involved, whereas cellular mechanisms are less important. Immunological diseases of the kidney mainly affect the glomerulus, which is most likely due to its filter function. Circulating antibody-mediated renal diseases are induced in three mechanisms, circulating performed immune complexes accumulate subendothelially on the capillary aspect of the basement membrane, alternatively antibodies may react in situ with the glomerular basement membrane or with antigens of the visceral epithelial cells.

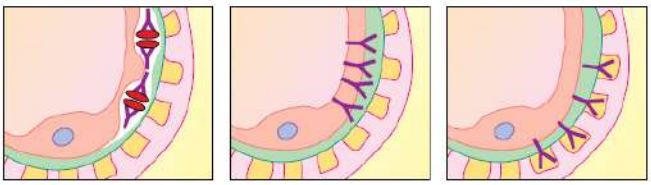
Antibody deposits can cause direct damage to epithelial or endothelial cells of glomerulus due to complement activation and pore formation. On the other hand, the antibodies can also bind to the FC receptors of monocytes, macrophages, granulocytes and platelets. This leads to the activation, or in the case of platelets aggregation of the cells. The glomerular damage can cause two distinct symptom complexes: the nephrotic syndrome and the nephritis syndrome.

Differentiation Between Nephrotic Syndrome and Nephritic Syndrome

Typical Features	Nephrotic	Nephritic
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular venous pressure	Normal/low	Raised
Proteinuria	++++	++
Hematuria	May/may not occur	+++
Red blood cell casts	Absent	Present
Serum albumin	Low	Normal/slightly reduced



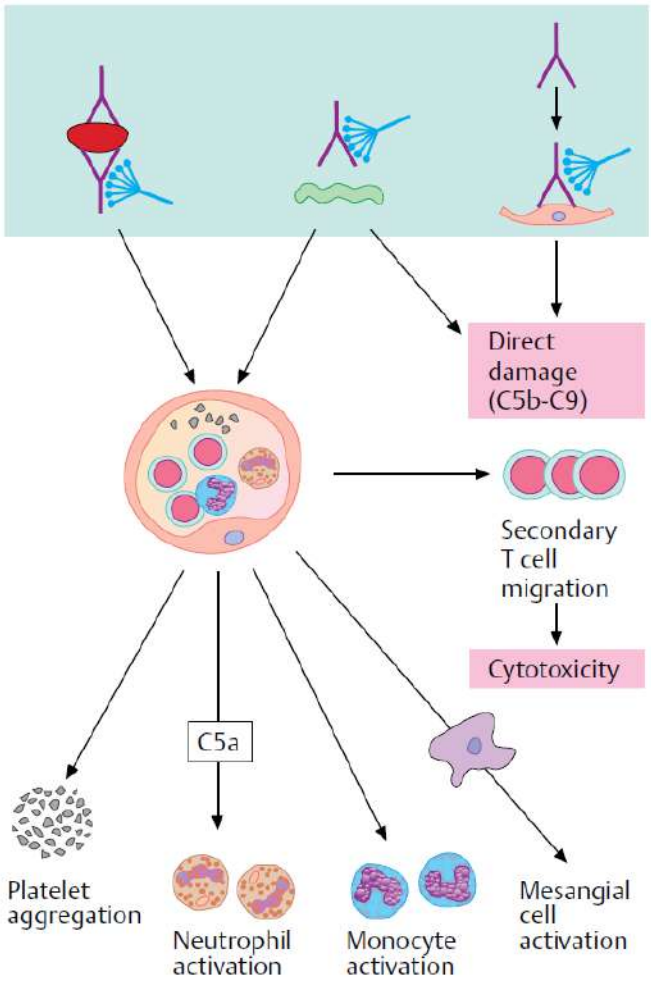
1. Anatomy



2a. Immune complex deposition

2b. Anti-GBM Ab

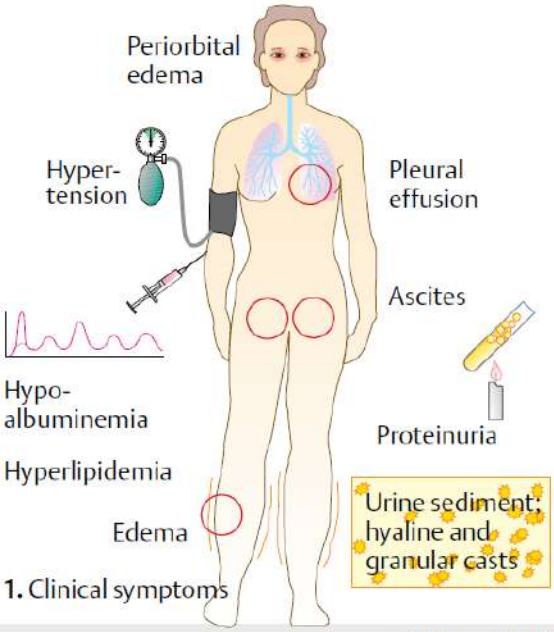
2c. Anti-epithelial cell Ab



Proteases, eicosanoids, NO, cytokines, growth factors

3. Mediators of glomerular damage

A. Mechanisms

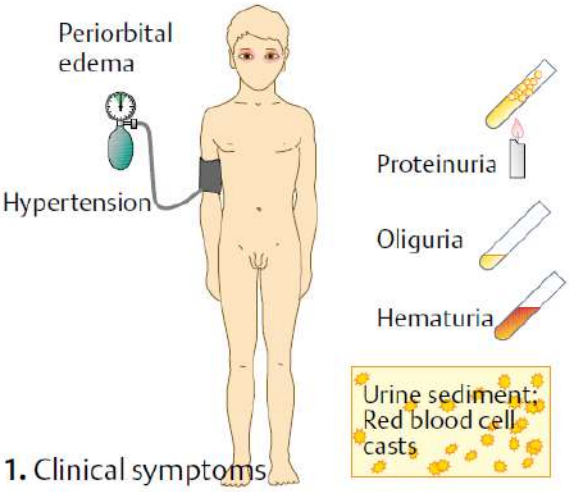


1. Clinical symptoms

	Children	Adults
Membranous glomerulonephritis	5%	20%
Lipoid nephrosis minimal change GN	60%	10%
Focal segmental glomerulosclerosis	10%	10%
Membranoproliferative glomerulonephritis	10%	5%
Proliferative GN (focal, IgA....)	10%	15%
Systemic diseases: diabetes, SLE, amyloidosis...	5%	40%

2. Causes of nephrotic syndrome

B. Nephrotic syndrome



1. Clinical symptoms

Postinfectious GN
Rapidly progressive GN
IgA nephropathy

2. Causes of the nephritic syndrome

C. Nephritic syndrome

Antineutrophil cytoplasmic antibody associated glomerulonephritis

Patients with ANCA-associated glomerulonephritis are usually aged from 40 to70 years and most have had a flu-like illness with arthralgia and myalgia a few days or weeks prior to the onset of renal disease or vasculitis. A spectrum of vasculitis is seen, ranging from disease limited to the kidneys in about a quarter of cases to a systemic vasculitic process with pulmonary involvement in about half the patients. ANCA-associated glomerulonephritis is now the commonest form of crescentic or rapidly progressive glomerulonephritis.

The renal lesion is characterized by few or no deposits of immunoglobulin or complement in the kidney **(so-called pauci-immune glomerulonephritis)** and by necrosis and crescent formation

Two pattern of antineutrophil cytoplasmic antibody (ANCA) reactivity are important clinically: generalized cytoplasmic staining **(cANCA)** and a perinuclear pattern **(pANCA)**. Most cANCA sera react with a serine proteinase called proteinase 3 (PR3), while most pANCA sera react with myeloperoxidase (MPO). A further pattern is associated with inflammatory bowel disease, particularly ulcerative colitis, some cANCA/ Panca positive sera react with neutrophil antigens other than PR3/MPO.

Raised ANCA titres are generally detectable during active granulomatosis with polyangiitis, and rising titres may herald a relapse. There has been debate whether ANCAs are pathogenic in vasculitis or simply a marker, but there is mounting evidence that they are pathogenic. The exact pathogenesis of granulomatosis with polyangiitis is not completely understood, but T cells, B cells, neutrophils and endothelial cells have all been implicated in the process.

Lecture No. 12-13

Membranous glomerulonephritis

Membranous glomerulonephritis can occur at any age, with the peak incidence in adults aged between 30-50 years and is characterized by the formation of immune complexes on the subepithelial surface of the basement membrane. The antibodies react in situ with endogenous podocyte antigens. The majority (70-80%) of patients with primary MN have circulating autoantibodies to **M-type phospholipase A2 receptor (PLA2R),** a transmembrane receptor that is expressed in glomerular podocytes. Antibodies to thrombospondin type-1 domain containing 7A protein (THSDA7A) and neutral endopeptidase have been identified in smaller subsets of patients.

Typical features include diffuse thickening of the basement membrane with fusion of the foot processes. The inhomogeneous distribution of the IgG and C3 deposits results in