Circulating Immune complex

Immune complexes are formed every time when antibody meets and bind to antigen, and generally they are removed effectively by **the mononuclear phagocyte system following complement activation,** but occasionally they persist and eventually deposit in a range of tissues and organs. Persistence of antigen from continued infection or in autoimmune disease can lead to immune-complex disease. Immune complexes can form both in the circulation, leading to systemic disease or at local sites such as the lung. Immune-complex deposition is most likely where there is **high blood pressure**. The site of immune-complex deposition depends partly on the size of the complex , in the kidney: small immune complexes can pass through the glomerular basement membrane; large complexes are unable to cross the membrane and accumulate between the endothelium and the basement membrane or the mesangium.

Complement helps to disrupt immune complexes. RBC bear's a receptor for **C3b** for transporting complement-containing IC to the spleen for removal. Complement deficiencies lead to formation of large, insoluble complexes which deposit in tissues. Charged antigens have tissue-binding properties, particularly for the glomerulus, and help or assist to localize complexes to the kidney.

Kidney disorders that initiated & mainly mediated by an immune response

• Renal infections with renotrophic pathogens, including uropathogenic Escherichia coli ,BK virus, Leptospira spp., Mycobacterium tuberculosis and HIV

• Extrarenal infections including septic kidney injury, immune complex-mediated nephritis (for example, post-infectious glomerulonephritis and endocarditis.

• Systemic autoimmunity against ubiquitous antigens with renal inflammation, including IgA nephropathy or Henoch– Schönlein purpura, lupus nephritis, Sjögren's syndrome, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, and antibody-mediated haemolytic uraemic syndrome.

• Immune responses against renal antigens, including anti-glomerular basement membrane (anti-GBM) autoimmune disease and allograft rejection

Anti-neutrophil cytoplasmic antibodies (ANCAs)

Definition :Anti-neutrophil cytoplasmic antibodies (ANCAs) are a group of autoantibodies, mainly of the IgG type, against antigens (The c-ANCA antigen is specifically proteinase 3 (PR3) and p-ANCA antigens include myeloperoxidase (MPO) in the cytoplasm of neutrophil granulocytes and monocytes.

ANCAs are associated with small vessel vasculitides including:

1. Granulomatosis with polyngitis (previously known as **Wegener's granulomatosis**),
2. Microscopic polyangiitis,
3. Primary pauci-immune necrotizing crescentic glomerulonephritis.
4. Eosinophilic granulomatosis with polyangiitis (previously known as **Churg-Strauss syndrome**).
5. Drug induced vasculitides.

Clinical Symptoms

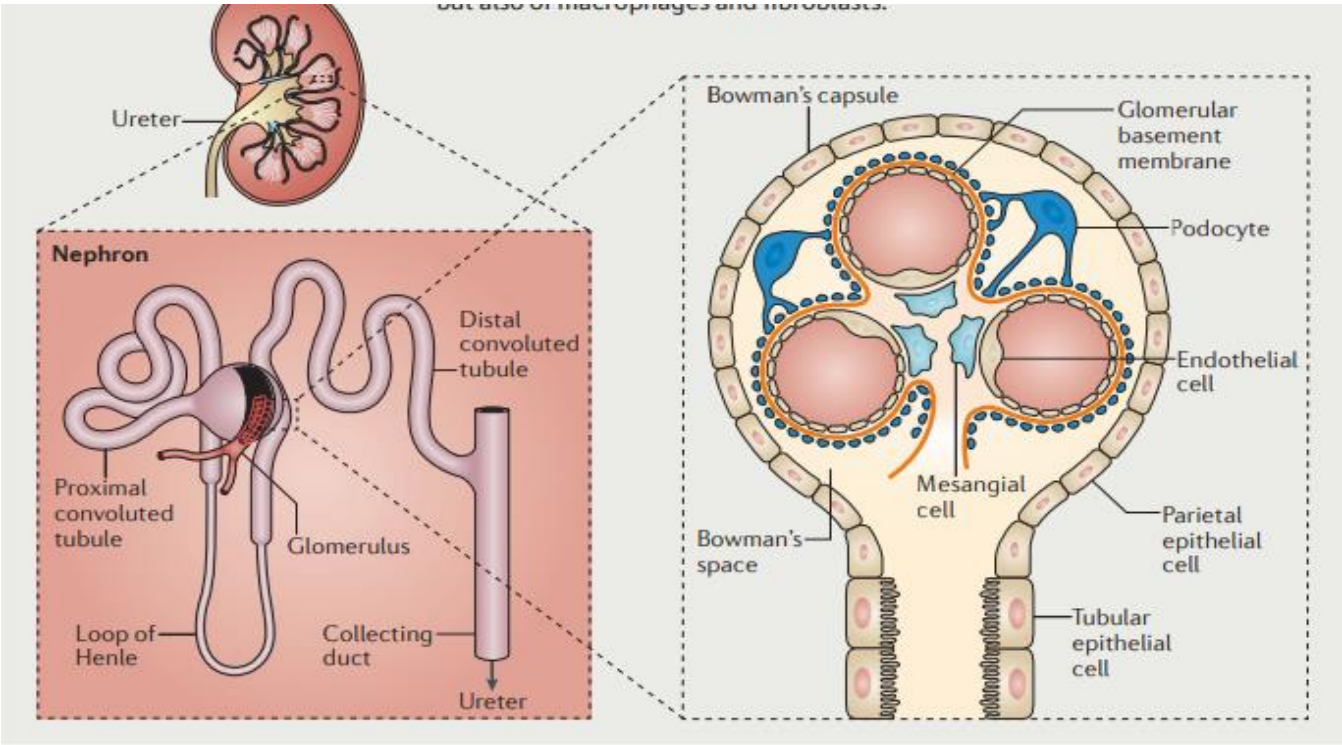
Fever, malaise, palpable purpura, arthralgia, myalgia, weight loss haematuria, proteinuria in kidney, cough, dyspnea and haemoptysis

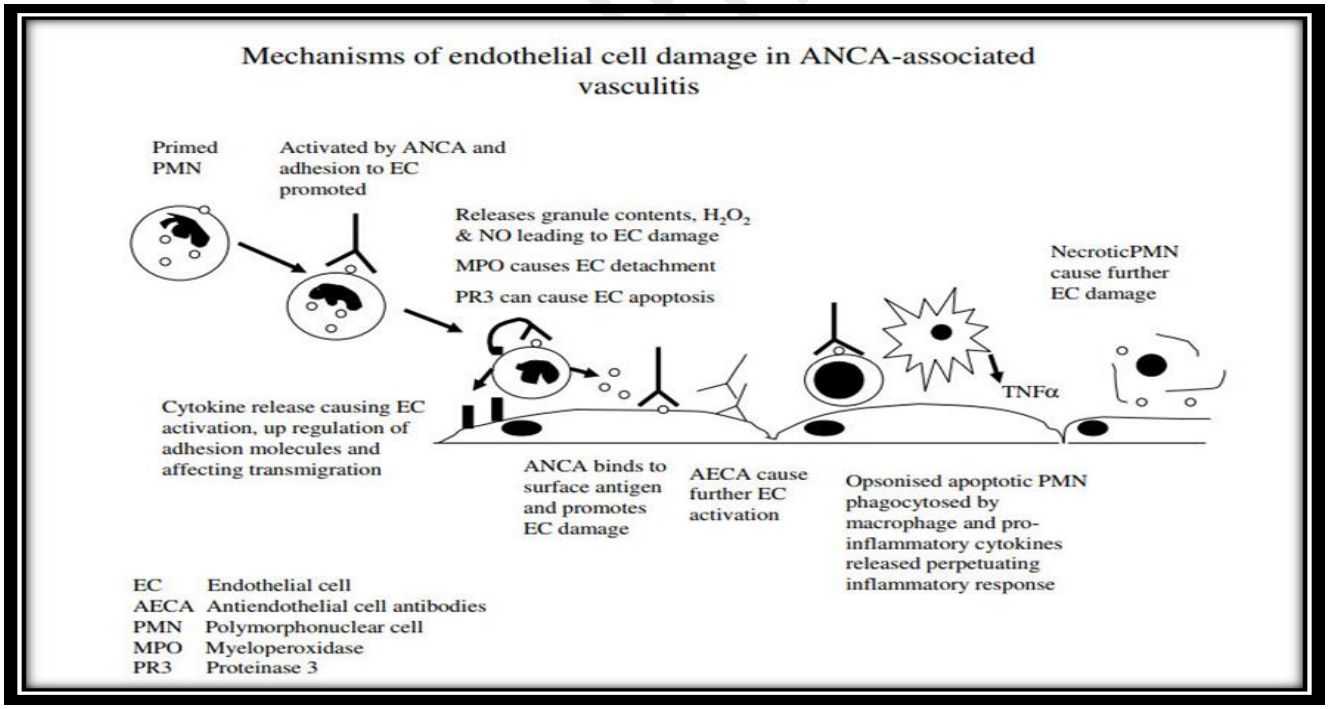
Pathogenesis and immunity

The antibodies have a direct pathological role in the formation of small vessel vasculitides, MPO and PR3 specific ANCA can activate neutrophils and monocytes through their Fc and Fab'2 receptors. The activated neutrophils can then adhere to endothelial cells where degranulation occurs. This releases free oxygen radicals and lytic enzymes, resulting in damage to the endothelium via the induction of necrosis and apoptosis. neutrophils release chemoattractive signalling molecules that recruit more neutrophils and B cells to the endothelium, acting as a positive feedback loop. All these cells and antibodies and cytokine destroy the small blood vessels and form vasculitides

Treatment

1- Immunosuppression drugs 2- Plasma exchange 3- cyclophosphamide and azathioprine.


Ureter
Nephron
Distal convoluted tubule
Proximal convoluted tubule
Glomerulus
Loop of Henle
Collecting duct
Ureter
Bowman's capsule
Glomerular basement membrane
Podocyte
Endothelial cell
Mesangial cell
Parietal epithelial cell
Bowman's space
Tubular epithelial cell


Mechanisms of endothelial cell damage in ANCA-associated vasculitis
Primed PMN
Activated by ANCA and adhesion to EC promoted
Releases granule contents, H_2O_2 & NO leading to EC damage
MPO causes EC detachment
PR3 can cause EC apoptosis
NecroticPMN cause further EC damage
TNFα
Cytokine release causing EC activation, up regulation of adhesion molecules and affecting transmigration
ANCA binds to surface antigen and promotes EC damage
AECA cause further EC activation
Opsonised apoptotic PMN phagocytosed by macrophage and pro-inflammatory cytokines released perpetuating inflammatory response
EC Endothelial cell
AECA Antiendothelial cell antibodies
PMN Polymorphonuclear cell
MPO Myeloperoxidase
PR3 Proteinase 3