Immune mediated glomerulonephritis (immune GN.) – a literature review

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The kidney is often the target of many aggressions of extra-renal origin. Its structure and function make it vulnerable and part-taking to the pathological changes than develop inside the living organism.

The increased blood presure inside the glomerular capillaries, its purpose in ultrafiltration and the negatively charged glycoproteins from the structure of the glomerular filtration barrier participate in increasing the sensitivity to the toxic action of exogenous or endogenous circulating substances.

Based on their pathogenesis, immune mediated glomerulonephritis may be divided into two categories:

1. glomerulonephritis caused by immune complexes deposited inside the glomerulus;
2. glomerulonephritis caused by anti-basal membrane antibodies.

1. Glomerulonephritis caused by immune complexes deposited inside the glomerulus

Studies regarding spontaneous and experimental glomerulonephritis have demonstrated that the immunological mechanisms play a very important role in glomerular pathology.

Based on recent reseach, in human pathology about 70-80% of immune glomerulonephritis are caused by the precipitation of immune complexes inside the glomerulus and in the pathology of companion carnivores about 77% of proteinuria cases are caused by immune mediated glomerulonephritis (Jergens A.E., 1987).

In the pathogenesis of glomerulonephritis caused by immune complexes there are two basic mechanisms involved in producing the structural changes inside the glomerulus, both of them triggering type III hypersensitivity reactions:

- circulating Atg-Atc immune complexes (preformed);
- Atg-Atc immune complexes formed "in situ" (inside the glomerulus).

Generally, immune based glomerulonephritis are characterized by the precipitation of immune complexes and complement fractions on the basal membranes and the mesangium as discontinuous deposits with a granular aspect that may be visualized through immunofluorescence and immuneperoxydasis methods.

These immunofluorescent granular deposits have an opposite aspect than those with a smooth, liniar, diffuse aspect caused by the precipitation of anti-basal membrane antibodies.

The pathogenicity of circulating immune complexes derives from their capacity to trigger a series of phenomena that have as a result the degradation of basal membranes (membranous and membrano-proliferative GN.) and mesangial cells (proliferative GN.).

Clinical symptoms are mainly characterized by severe proteinuria.

The pathogenesis of glomerulonephritis caused by the precipitation of circulating immune complexes

In causing immune mediated glomerulonephritis the circulating Atg-Atc immune complexes represent the main factor.

These complexes may contain bacteria, viruses, parasitic or tumoral antigens.

The pathogenicity and precipitation pattern of the immune complexes on the glomerular structures depend on their quantitative and qualitative aspects:

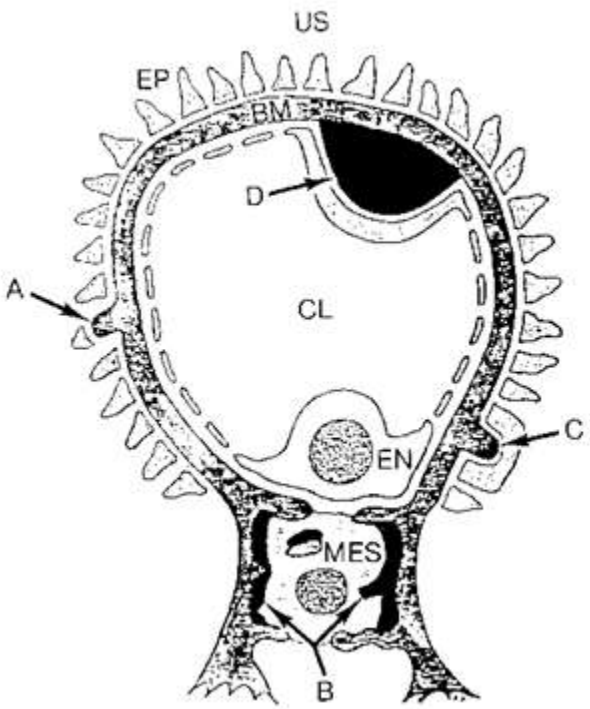
- the quantity of Atg-Atc complexes;
- the size of the complexes;
- molecular configuration;
- the afinity between the antibody and the antigen;
- electrical charge;
- solubility.

Large, insoluble complexes that are excessively formed are rapidly removed from the blood stream inside the kidney and phagocytosed by the monocytic-macrophage system (SMM) or partialy taken by the mesangial cells.

On the other hand, intermediary sized immune complexes formed in the presence of excess antigens remain in solution and may be deposited on the basal membrane of the glomerular capsule, of the vascular bundle and on the mesangium.

Through electron microscopy precipitated immune complexes may be visualized as irregular, electron-dense deposits, located under the endothelium (*subendothelial GN.*) or under the epithelium (*subepithelial GN.*), within the thickness of the basal membrane (*intramembranous GN.*) or the mesangium (*mesangial GN.)* (Slauson and Cooper, 2002) **(Schematic 1)**.

Schematic 1



THE MECHANISMS OF PRECIPITATION OF IMMUNE COMPLEXES IN THE GLOMERULUS

(after *Comeford*, 1968)

A – epithelial nodules;
B – mesangial deposits;
C – subepithelial deposits;
D – subendothelial deposits;
BM – basal membrane;
CL – capillary lumen;
EP – podocytic processes;
MES – mesangium;
US – filtration space;
EN – endothelial cells;

The subendothelial precipitation is common for circulating immune complexes with a high anionic charge (which does not allow them to pass through the glomerular basal membrane) and high afinity of the antibody for the antigen (which makes them difficult to be dissociated).

In contrast, the subepithelial precipitation is seen in immune complexes that have a cationic charge and a low afinity of the antibody to the antigen, which allows for the dissociation of the immune complex, the separate migration of the antigen and antibody through the glomerular basal membrane and the reconstitution of the complex on its subepithelial side.

The intramembranary depositing of the immune complexes is less common, in some cases representing an intermediary phase of the migration through the thickness of the glomerular basal membrane.

The depositing in the glomerular mesangium is particular for immune complexes with a neutral charge (Slauson and Cooper, 2002).

Finally, these antigen rich complexes don't determine a significant activation of the complement, hence they manifest a lower capacity in causing glomerular damage.

Also, it is important that any disease with a chronic evolution that prosuposes a prolongued exposure to antigens may stimulate the continuous formation of circulating immune complexes involved in the pathogenesis of immune mediated imflammations.

"*In situ*" formation of immune complexes

In contrast with the precipitation of "preformed" immune complexes we may also see the formation of "in situ" immune complexes directly within the walls of the glomerular capillaries.

This pathogenetic variant is supported by the observations done on spontaneous or experimental glomerulonephritis.

In situ, the formation of immune complexes is initiated by the circulating antigenic molecules of small or medium size that are able to penetrate the fenestrated endothelium of the capillary or small antigens that can easily pass through the *lamina densa* reaching the *lamina rara externa*, close to the visceral epithelial cells.

Also, the formation of immune complexes may be initiated by antibodies targeting structures of the glomerulus or antibodies that will be paired with antigens that are already fixated on the glomerular structures.

Antigens that are deposited inside the glomerulus may be specific for some glomerular components or nonspecific, trigerring an atraction for circulating antibodies that migrate through the basal membrane all the way to the already fixated antigens. Recent observations showed that the fixation of antigens on the glomerular structures is based on electrical phenomena. The positively charged antigens interact with the anionic glomerular structures (basal membrane, podocytic processes of the epithelial cells, mesangium).

The basal membrane has a strong negative charge due to the presence in its structure of polyanionic molecules such as syalo-glycoproteins and heparan-sulphate, thus facilitating the

passage of cationic molecular proteins, no matter of their nature and restricting the transit of anionic proteins (albumin) (Walker, F., 1973).

Antigens located inside the glomerular structures may be of endogenous or exogenous nature.

Endogenous antigens are represented by histone-DNA complexes, IgA and other immunoglobulin isotypes. Exogenous antigens are represented by various drugs and infectious agents (Slauson and Cooper, 2002).

The fixation of antigens on the glomerular antigens depend on the size, electrical charge, molecular arrangement and their carbohydrates content.

The selective permeability of the capillary wall given by the electricaly charged structural molecules has been demonstrated using feritine macromolecules (480 000 daltons) as markers. In normal conditions feritine anionic particles can pass through 100 nm wide endothelial pores, but cannot pass through the glomerular basal membrane due to the polianionic charge of the *laminei rara interna*.

When experimentaly cationized feritine is capable to penetrate the trilamellar basal membrane reaching the subepithelial space and even the filtration space.

The strong negative charge of the glomerular basal membrane works as a selective electrical filter, permissive for neutral and cationic molecules and nonpermissive for anionic molecules (albumin). Even more, the electrostatic barrier represented by the glomerular basal membrane is meant to permanently maintain the distance between the podocytic processes of the epithelial cells.

We may conclude that the electrical charge of the molecules (particles) that need to pass through this barrier is more important than their size, thus transiting can be done more easily for the larger cationic molecules than for the smaller anionic ones.

When the negative electrical charge of the barrier is lost podocytes increase their volume, the podocytic processes are reduced and the membranary pores are destroyed. Thus, from a functional point of view, the barrier against the positively charged molecules is destroyed leading to proteinuria.

Loss of polyanions from the glomerular basal membrane determines the accumulation inside the mesangium of immunoglobulin and complement macromolecules.

The hypothesis of glomerulonephritis caused by the formation of immune complexes "*in situ*" is supported by observations made following experimental immunization with *Dirofilaria immitis* in dogs. *Dirofilaria immitis* antigens were administered directly in the renal artery after wich the changes of the glomerular basal membrane were observed. Secondarily, circulating antibodies reacted with the antigens deposited on the basal membrane, finally forming Atg-Atc immune complexes ("in situ") (Grauer and col., 1988; Muramatsu and col., 1988).

The role of the complement system

A special part in triggering glomerular lesions is due to the classical path of activation of the complement system.

The major immunopathogenetic effect is represented by the chemotactic atraction of neutrophils and monocytes to the site where immune complexes are fixated on the surface of the basal membrane through C3a and C5a fractions of the complement.

Neutrophils are capable to phagocytose immune complexes but also produce alterations of the glomerular basal membrane through the release of their one lysosomal enzymes (elastasis, G catepsin, collagenasis and oxygen free radicals). Also, oxygen free radicals (singlet oxygen, superoxyde) may determine the activation of mesangial cells.

Circulating monocytes that are atracted through chemotaxis in the damaged glomeruli and mesangial cells with phagocytic properties actively participate in the glomerular inflammatory process. Both cell types produce and release chemokines, activation factor for blood plateles, prostaglandines (PGE2), metabolites of arachidonic acid, oxygen free radicals and platelet procoagulating factors.

Using experimental models it has been shown that the complement fraction C5b-C9, the complement membranary atack complex participated in the alteration of the glomerular basal memebrane, thus increasing its permeability (Gharaee-Kermani and col., 1996).

Fractions C3a and C5a (anaphylatoxins) of the complement determine the release of histamine from the basophilic granulocytes and increases the vascular permeability which favours the precipitation of an even larger amount of immune complexes in the capillary wall.

This process in which the vasoactive amines induce an increase in the vascular permeability and subsequently the depositing of a larger amount of circulating complexes is called "anaphylactic atraction" (Slauson and Cooper, 2002).

Another consequence of the damages brought to the glomerular basal membrane is the activation of the blood platelets. Exposed membranary collagen initiates the activation of blood plateles with the release of excessive quantities of vasoactive amines such as histamine or serotonin.

Blood plateles amplify even more the glomerular lesions, the basal membranes loosing all their anionic charge, determining the precipitation of an even larger number of immune complexes at this level, the continuous atraction of neutrophils and the passage of proteins in the urinary filtrate becomes unstopabble (Wyers M., 1976).

Another important event is the activation of the XII factor (Hageman Factor) by exposing the glomerular basal membrane which initiates the intrinsic coagulation in such a way that fibrin deposits may be visualized in some forms of glomerulonephritis.

The activated Hageman Factor determines in its turn the activation of the complement system which increases the capillary permeability and the atraction of neutrophils (through mechanisms already discussed).

In conclusion, the cascade of inflammatory mechanisms triggered after the precipitation of circulating immune complexes or after their formation "*in situ*" following different causes is perpetuated endlessly affecting the integrity of the glomerular basal membrane and its permeability.

Still, the glomerular response to these injuries is somewhat monomorphic, being represented mostly by the thickening of the glomerular basal membranes, cellular proliferation and finally sclerosis.

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