The morphology of immune mediated glomerulonephritis

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The kidney is often the victim of aggressions of extra-renal origin. It`s structure and functions make it susceptible to pathological changes that take place within the living organism.

The increased blood pressure inside the capillaries belonging to the glomeruli, the ultrafiltration function and the powerful negative charge of the local filtration glycoproteins are all elements that increase the sensibility of the kidney to the potentially damaging action of the exogenous or endogenous circulating substances.

Depending on the pathogenetic mechanisms, immune mediated glomerulonephritis may be:

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

1. Membranous glomerulonephritis

Membrane glomerulonephritis are characterized by the deposition of immune complexes [Ig G, Ig M, C3, membrane attack complexes (C5b-C9)] in all segments of the glomerulus (Trautwein, 2000).

The name of this type of lesion is borrowed from the Anglo-Saxon literature and illustrates the particular aspect of the basement membranes of the glomerular capillaries. However, in some situations it was possible to identify the antigen that forms the immune complexes retained at the glomerular level. Thus, membranous glomerulonephritis was observed in adenovirus infections in dogs, infestations with *Dirofilaria immitis* in dogs, infections with feline leukosis virus in cats (FeLV). Still, 70% of these cases remain idiopathic (Lees, 1997).

Immune complexes, regardless of their provenance, produce glomerular lesions through a similar pathogenetic mechanism. Electron-microscopy studies on dogs with idiopathic membranous glomerulonephritis have been able to deduce the evolutionary stages of this lesion.

In the first phase, very discrete, electron-dense immune deposits were observed on the epithelial surface of the glomerular basal membrane. Subsequently, there was a slight thickening of the basal membrane and a fusion of the podocyte processes over the immune deposits present at the membrane level with a diffuse and very rarely localized appearance. The podocytes appeared swollen and the podocyte processes also contained a granular material.

Subsequently the thickening of the basement membranes becomes evident through the new synthesized membrane material, visible between the membrane deposits and the basal membrane itself. It appears as small spots and spicules on the epithelial surface of the glomerular basal membrane, giving it a comb-like aspect easily identifiable in the silver impregnation (Moreau, 1989; Angus, 1990; Tennant, 1992; Vilafranca, 1994).

Studies on human membranous glomerulonephritis have revealed that spicules are actually extensions of the basement membrane consisting mainly of α3 and α5 chains of type IV collagen with laminin and fibronectin (Nevins, 1985; Verlander, 1998).

In late evolutionary stages, membranous spicules merge with the immune membranary deposits and the capillary wall thickens considerably. There is also a slight proliferation of the mesangial cells and a development of the mesangial matrix.

Finally, the glomerular basement membrane becomes distorted, folded, loses its polyanionic load and becomes highly permissive, especially for serum proteins. Thus, proteinuria and nephrotic syndrome can develop.

In 15% of cases, the evolution of the disease is favorable, the lesions being mostly reversible, in the rest of the cases a progressive evolution towards glomerular sclerosis is observed, following the obliteration of the capillaries (Moreau, 1989).

Clinically, membranous glomerulonephritis are most often accompanied by nephrotic syndrome (Moreau, 1989). Most membranous glomerulonephritis evolve as a generalized and global syndrome, being idiopathic (the composition of circulating immune complexes could not be identified) or being the expression of various pathological processes (infections, neoplastic processes, intoxication or autoimmune diseases) (Carpenter, 2002; Scott, 2001) .

Membranous glomerulonephritis can be an expression of old age (continuous synthesis of membranous material), heavy metal poisoning (gold, mercury), chronic septic diseases (pyometra in bitches), parasitic infestations, association with chronic interstitial nephritis (in dogs), systemic metabolic disorders (diabetes, thyroiditis) or idiopathic (unidentified immune complexes) (Jones, 1986).

2. Mesangial glomerulonephritis (mesangio-proliferative)

Histologically, mesangio-proliferative glomerulonephritis are dominated by cell proliferation, ultimately leading to a multicellular or polynuclear aspect of the Malpighi corpus (Oprean, 2002; Paul, 1991).

This type of immune mediated glomerulonephritis is the one most commonly seen, being dominated by the cellular and matriceal changes of the glomerular mesangium, morphologically translated into a more or less discrete increase in the cell numbers within its structure, as a result of the proliferation of the mesangial and endothelial cells, as well as the presence of inflammatory cells (polynucleated or mononucleated cells), the increase in mesangial matrix and the accumulation of mesangial deposits (Moreau, 1989; Pașca, 2006).

Proliferative glomerulonephritis may evolve either globally, affecting the whole glomerulus, or segmental, thus affecting some glomerular lobules.

In the case of pure mesangio-proliferative glomerulonephritis, the mesangial and matriceal changes are exclusively confined to the axial region of the glomerulus, without modifying the caliber of the glomerular capillaries (Moreau, 1989).

In segmental glomerulonephritis, hyperplasia located inside the structure of the glomerulus (glomerular polynucleosis) can produce a marked reduction in the caliber of glomerular capillaries due to external compression, down to complete stenosis, reduction of glomerular perfusion and sclerosis (Jergens, 1987; Perchereau, 1996).

In electron microscopy, the fusion of the podocyte pedicels can be observed. Extra-membranary deposits are exceptionally observed in electron microscopy, but by means of immunohistochemistry, regular, homogeneous or granular deposits may be revealed sub-endothelially along the glomerular basal membrane containing IgG and IgM, without the C3 fraction of the complement (Trautwein, 2000).

Most cell proliferations are mediated by complement and platelet-derived factors. It has been shown that the increase in cell numbers and mesangial matrix is accompanied by an increase

in PDGF (platelet derived growth factor) expression secreted by endothelial cells and PDGF receptor proteins, demonstrating that cell proliferation is based on autocrine mechanisms.

These proliferative phenomena result in segmental and even general glomerular sclerosis, glomerular capillary collapse and adhesions between the vascular bundle and the Bowman capsule (Jones, 1986).

The quantitative and qualitative balance of these lesions is indispensable in the histological prognosis.

Occurrence of segmental or global proliferative glomerulonephritis was observed in infections with *Leishmania sp*. in dogs, mink plasmocytosis, infections with *Streptococcus zooepidermicus* in horses and chickens, etc. (McGavin, 2007).

3.Membrane-proliferative glomerulonephritis (mesangio-capillary)

Membrane-proliferative glomerulonephritis (MPGN), also called mesangio-capillary glomerulonephritis, is a morphoclinic entity that is characterized by proliferation of the mesangial cells and at the same time by the thickening of the glomerular basal membrane, thus meeting both aspects of membranous and mesangio-proliferative glomerulonephritis (Nakatsuji, 1998; Nevins, 1985).

These morphological aspects are considered to be intermediate lesions that end in generalized chronic glomerulonephritis, leading to chronic renal failure (Jergens, 1987). The structural changes within this type of lesion explain why the animals, respectively, show hematuria and nephritis concomitant with proteinuria and nephrotic syndrome.

Membrane-proliferative glomerulonephritis may be associated with systemic features or well-defined pathologies (secondary GN) or, as in most cases, can be idiopathic (primary).

Membrane-proliferative glomerulonephritis, as an autosomal dominant recessive disease, has been described in 20 Berneese Sheepdogs, with ages between 2 and 5 years, who had renal failure and severe proteinuria syndrome. It seems that the infection with *Borrelia burgdorferi* represents a triggering factor of the pathological process (Bernard, 1991; Gough, 2004).

Based on the clinical and pathological aspects in both humans and animals, there are 3 types of membrane-proliferative glomerulonephritis: type I, II and III, the last being very little known and controversial (Cotran, 1999; Roitt, 1992).

a. Type I GNMP

Type I membrane-proliferative glomerulonephritis are characterized histologically by an increased lobulation of the glomeruli caused by the proliferation of the mesangial cells and of the mesangial matrix.

The process of epithelial and membrane proliferation may be extended to the whole glomerule, from the vascular pole to the urinary one, or localized to several capillary loops (glomerular lobules).

In the first situation, the vascular bundle is retracted, more or less shrunken, partially thrombosed or with sclerosis (Moreau, 1989).

In the second situation, the affected glomerular loops appear compact, the rest of the capillaries being permeable.

On the whole, this category of glomerulonephritis is represented by severe lesions that do not allow healing without sequelae. The walls of the glomerular capillaries appear thickened as a result of subendothelial deposits consisting of immune complexes containing immunoglobulins (Ig G, Ig M) and the C3 fraction of the complement (nephrotic factor C3).

Highlighting within the structure of the deposited immune complexes of C1q and C4 fractions indicates that complement activation following the classical pathway plays an important role in the pathogenesis of type I GNMP.

Another characteristic aspect of this type of glomerulonephritis is the so-called "mesangial interposition", which consists of the interposition of the cells and the mesangial matrix between the endothelium and the glomerular basal membrane. This phenomena confers a double contour to the glomerular basal membrane or the appearance of "tram rails", easily observable in silver impregnation and PAS staining methods.

In dogs, type I membrane-proliferative glomerulonephritis predominantly develops as an idiopathic disease (Trautwein, 2000) However, some data suggest that it is sometimes possible to associate this type of lesion with systemic, bacterial (leishmaniasis and boreliosis in dogs) and viral infections (feline infectious peritonitis, cat leukosis, equine infectious anemia, African swine fever) or neoplasia. (Brostoff, 1991; Dambach, 1997; Oprean, 2000; Perianu, 1997).

b. GNMP Type II (Dense Deposit Disease)

The histological features are represented by the marked thickening of the PAS-positive basal glomerular membrane. The mesangium may be loose due to mesangial cell or matrix proliferation.

The definitive diagnosis surges following the electron-microscopy highlighting of the deposits constituted by a dense, osmophilic material, in the thickness of the lamina densa of the basal glomerular membrane and the mesangium.

The same characteristic of "mesangial interpositioning" is also found in the second type of membrane-proliferative glomerulonephritis (Cotran, 1999). Also, through immunohistochemistry, it has been observed that they are mainly constituted from the C3 fraction of the complement and properdine.

In the pathology of glomerulonephritis in humans, the participation of IgG auto-antibodies against C3-convertase, called C3-critical factors (C3NeF), has been noted. The basal membrane stabilizes C3-convertase, the C3bBb enzyme of the alternative complement activation pathway and continues to deactivate C3 cleavage in C3b and C3a.

Continuous activation of the complement gradually leads to the consumption of this element (hypocomplementemia). The level of the C3 fraction will be very low, but the C1q and C4 fractions will remain within normal limits.

c. Type III GNMP consists in the presence of immune deposits on both sides of the basal membrane at the same time (sub-endothelial and sub-epithelial). The lesion appears to be a type I variant (Cheville, 1994).

Ig A Nephropathy (Berger's Disease)

IgA nephropathy is the most common form of glomerulonephritis in humans, a common cause of asymptomatic hematuria. It can be observed in dogs and experimentally in mice (Bernard, 1991)

From a morphological point of view it is characterized by mesangial deposits of IgA, proliferation of the mesangial cells and expansion of the mesangial matrix (Brostoff, 1991).

According to the histological criterion, this glomerular lesion falls into the category of membrane-proliferative glomerulonephritis.

The research of the collective Bené (1984) established that the disease appears following the synthesis at abnormal levels of IgA or the synthesis of abnormally assembled IgA. In the first case, the abnormal IgA synthesis is due to the prolonged exposure of the mucous membranes to an antigen represented by a pathogen over the course of respiratory and digestive infections that

surmounts the cleansing ability of the macrophageal-monocytic system, IgA which is then deposited in the glomerular level, in the glomerular mesangium (Day, 1988).

The amount of complex circulating Ig A is directly proportional to the severity of the infection in the case of abnormal synthesis. In the second situation, the immune deposits that are found in the mesangium are composed of IgA1-glycosylated with an abnormal structure. Due to these abnormal structures of IgA1, the asialoglycan-proteins (macrophage receptors) cannot bind the macrophages of the macrophageal-monocytic system to initiate phagocytosis, favoring mesangial precipitation (Brostoff, 1991).

Glomerular lesions due to the deposits of immune complexes containing IgA have been observed frequently in patients with hepatic cirrhosis. Studies on mice with induced cirrhosis by carbon tetrachloride intoxication have revealed the presence of circulating IgA with abnormal structure but also located on the glomerular basal membranes.

he presence of C3 fraction in the structure of the mesangial deposits and that of the final components of the complement, except for the C1 and C4 fractions, suggests that activation of the complement following the alternative pathway mediated by IgA plays an important role in the pathogenesis of these types of mesangial-proliferative glomerulonephritis (Bovee, 1984; Braun, 1995).

The diagnosis of IgA nephropathy is based on the immunofluorescence highlighting of IgA deposits present in the glomerular mesangium (McCluskey, 1983). The highest prevalence of IgA glomerular deposits was observed in dogs with enteritis and hepatitis (Osborne, 1973). In the examined patients, co-deposits of IgM and IgG (Osborne, 1973) were also highlighted.

4. Anti-basal membrane glomerulonephritis

The name of this category of glomerulonephritis is reserved for the glomerular lesions produced by intrinsic anti-antigen antibodies of the basal membrane, which through interaction lead to the accumulation of membrane immune deposits.

The experimental prototype is called *Masugi nephritis* or *toxic nephritis* and was obtained in mice by injecting them with anti-kidney antibodies, prepared on rabbits by immunization with mouse kidney tissue.

Glomerulonephritis produced by anti-basal membrane antibodies is an autoimmune disease with severe and rapid evolution consisting of the formation of anti-basal membrane antibodies and their storage in renal tissue or other extrarenal tissues, more specifically in the glomerulus and sometimes, but not always, in the walls of the pulmonary alveoli. The origin of these antibodies is still unknown.

This disease was experimentally reproduced in sheeps and dogs and used to elucidate the evolution of glomerular lesions with immune etiology (Bruijn, 1989). In this regard, circulating antibodies, produced by experimental immunization with heterologous antigenic basal membrane antigens, react with their endogenous antigens.

The diagnosis of this glomerulonephritis consists in highlighting the linear deposits located on the external face of the glomerular capillaries, in the sub-epithelial space, consisting of anti-basal membrane antibodies and IgG. IgM and IgA have been more rarely observed (Vilafranca, 1994).

5. Sclero-hyaline glomerulonephritis (chronic)

Sclero-hyaline glomerulonephritis are the most severe forms of glomerular lesions, represented by the advanced evolution of the lesions with degenerative effect on the structural and functional integrity of the glomerulus.

All degenerative glomerular lesions linked to membranary deposists, represented by immune complexes or by other pathological constituents or by proliferation of reactive cells, slowly disappear, being replaced by an irreversible process of fibrosis (collagenization), with the increase in mesangial matrix and the disappearance of glomerular capillaries. The glomeruli become hypocellular and non-functional (Morel-Maroger, 1984; M.V.M. The Merck Veterinary Manual, 1998).

Macroscopically, in the kidneys, glomerulosclerosis is manifested by a reduction in volume and a wrinkled aspect of the surface. On the sectioned surface, the cortex is atrophied, with a granular and yellowish appearance, due to the lipid accumulation (Fontaine, 1989).

The histological aspect is conditioned by the evolutionary stage of the disease. In the early stages, we may see lesions of mesangio- or membrane-proliferative glomerulonephritis. Progressive hyalinization of glomeruli can be frequently observed by transforming them into an eosinifilic acellular block. The hyaline is the result of the absobtion of accumulated plasmatic proteins, the increase in mesangial matrix and collagenization (Cotran, 1999).

The process can be generalized (involving all glomeruli) or focused. In addition, glomerulosclerosis can affect the entire glomerular structure (global) or only portions of the glomerular (segmental), presenting a nodular or segmental aspect at the level of the affected glomeruli. Over time, fibrous scars are formed in which vague remnants of the structure of the vascular bundle can be distinguished.

The process of glomerular sclerosis severely affects the functionality of the nephron. Due to the particularities of the renal blood circulation, the disruption of the bloodstream in the glomerulus subsequently affects all structures irrigated from the efferent arteriole. Thus, the uriniferous tubes are subjected to hypoxia with the decreasing and then disruption of blood flow to the glomerulus. The result of hypoxia is death by apoptosis of the tubular epithelial cells. In addition, chronic proteinuria that accompanies glomerulosclerosis stimulates tubular nephrocyte apoptosis (Duffy, 1983; Euzeby, 1989).

Many factors contribute to the acceleration of glomerulosclerosis. High levels of protein in food, increased blood pressure in functional glomeruli as a result of hypertensive diseases, cytokines and platelet growth factors ultimately lead to the acceleration and expansion of the process of sclerosis. These factors favor the alteration of the glomerular functional components, producing hyperfiltration and lesions of the capillary endothelium, activation of the mesangial cells and an increase of the mesangial matrix synthesis, degeneration of the visceral epithelium and finally the appearance of glomerular inter-epithelial synechiae (visceral parietal epithelium). (McGavin, 2007)

Glomerulosclerosis is not only the final phase of glomerulonephritis, but is also the termination form of all chronic kidney damage that results in the structural and functional alteration of the nephrons (Fontaine-Verdier, 2003).

Medium-intensity glomerulosclerosis have been observed in old dogs without however being able to determine the cause of the injury and occasionally in dogs with diabetes and hypertension by eosinophilic glycoprotein deposits in the mesangial matrix (McGavin, 2001).

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