

Glomerular Injury in Domestic Cats and the Iberian Lynx (*Lynx pardinus*): A Comparative Review

María Ángeles Jiménez, Belén Sánchez and Laura Peña
*Facultad de Veterinaria, Universidad Complutense de Madrid
Spain*

1. Introduction

Glomerular lesions, in particular glomerulonephritis, were once considered rare in the domestic cat (Nash et al, 1979; Slawson & Lewis, 1979), but in the past decades, the diagnosis of these lesions has increased substantially possibly due to a better understanding and awareness of these diseases (DiBartola & Rutgers, 1994; Grant Maxie & Newman, 2007). Most of the feline glomerulonephritis reported to date are of immune-complex origin (Slawson & Lewis, 1979; Newman et al, 2007; Grant Maxie & Newman, 2007) although some fibrillary glomerulopathies such as glomerular amyloidosis (Boyce et al, 1984; DiBartola et al, 1985, 1986, Gruys 2004; Newman et al, 2007; Grant Maxie & Newman, 2007) and to lesser extent nonconglomerulopathies (Nakamura et al, 1996; Cavana et al, 2008) are also described.

The etiology is frequently elusive, though many associations with infectious and other diseases have been identified (Newman et al, 2007; Grant Maxie & Newman, 2007). In particular, association between certain viral diseases such as feline leukemia, feline immunodeficiency virus and feline infectious peritonitis are known to course with some degree of glomerular injury (Glick et al, 1978; Hayasi et al, 1982; Newman et al, 2007). Several reports also relate certain neoplasms with the presence of glomerular injury (Hayasi et al, 1982; Newman et al, 2007).

Primary glomerular diseases severe enough to cause the nephrotic syndrome are relatively uncommon in the domestic cat (Schwartz, 2007, as cited in Cavana et al, 2008) and in general lack relevance in most non-domestic felids (Newkirk et al, 2010). However, once renal failure ensues, the outcome is fatal and treatment is only palliative (Nash et al, 1979; DiBartola & Rutgers, 1994). Knowledge on the pathogenesis, type of injury, origin and similarities to human counterparts enables a better understanding of the disease which may permit earlier detection or its prevention. This becomes of even greater importance when considering endangered species such as the Iberian lynx (*Lynx pardinus*), with less than 200 individuals remaining in the wild and captivity (Guzman et al, 2002). The survival of a single animal becomes crucial.

The Iberian lynx is a large felid that has inhabited the Iberian Peninsula for over centuries (Garcia et al, 1997; García & Arsuaga, 1998). Nowadays this species is rated as “critically endangered” (Nowel & Jackson, 1996) and remaining samples are confined to two isolated

populations in southwestern Spain (Palomares et al, 2000; Guzmán et al, 2002; Rodríguez & Delibes, 2002). The population decline was exacerbated towards the mid twentieth century mainly because of habitat loss (Palomares et al, 1991) and lack of adequate prey (Moreno & Villafuerte, 1995). Studies have also shown a serious compromise of genetic variability in this species mostly due to inbreeding (Johnson et al, 2004).

Recovery and conservation efforts are at hand and continuous research on the ecology, welfare, natural pathogens or diseases regarding these animals is crucial for survival efforts. With this in mind, a histopathological survey was conducted through 1998-2006 in which glomerular lesions in a high number of the surveyed population were detected. This led to a thorough investigation of these lesions and how they could affect the overall survival of the species (Jiménez et al, 2008).

2. Glomerular disease in the domestic cat

Several types of glomerular injury have been reported in cats, all of which correspond to a certain extent with a human counterpart of the disease. The most frequent are the immune-mediated glomerulonephritis (membranous glomerulonephritis and membranoproliferative glomerulonephritis) and rarely have some fibrillary glomerulopathies been described.

Immune-mediated mechanisms causing glomerulonephritis involve deposition of soluble immune complexes within glomeruli or the formation of antibodies directed against antigens within the glomerular basement membranes (Valaitis, 2002; Newman et al, 2007; Grant Maxie & Newman, 2007). The former is the most frequent mechanism described in the cat and in domestic animals in general (Nash, et al, 1979; DiBartola & Rutgers, 1994; Newman et al, 2007). Immune-complex glomerulonephritis is usually associated with situations of prolonged antigenemia such as infectious diseases or neoplastic processes (Newman et al, 2007).

Glomerular diseases are classified according to the histopathologic and ultrastructural morphology of the glomeruli. In most cases disease is progressive and may secondarily affect the entire nephron (Valaitis, 2002; Grant Maxie & Newman, 2007). Most progress to chronic interstitial nephritis. In chronic terminal stages, the morphological aspect of the lesions may overlap and determination of the primary injury is hindered (Valaitis, 2002; Grant Maxie & Newman et al, 2007).

The clinical presentation courses with the nephrotic syndrome, end-stage renal disease or both (DiBartola & Rutgers, 1994). The former is characterized by subcutaneous edema, ascites, proteinuria, hypercholesterolemia, and hypoalbuminemia. Mild azotemia may be present. Proteinuria and moderate to marked azotemia together with polydipsia, polyuria or oliguria, vomiting and anorexia are more common with end-stage renal disease (DiBartola & Rutgers, 1994).

2.1 Membranous glomerulonephritis

The most common glomerular lesion in the domestic cat is diffuse membranous glomerulonephritis (Nash et al, 1979; Slauson & Lewis, 1979; Newman et al, 2007; Grant Maxie & Newman, 2007). Numerous studies have related the presence of this disease with renal failure and the nephrotic syndrome (Nash et al, 1979; Slauson & Lewis, 1979; DiBartola & Rutgers, 1994). Membranous glomerulonephritis is characterized by a segmental to diffuse thickening of the glomerular capillary basement membranes caused by subepithelial and intramembranous immunoglobulin deposits. These deposits are eventually

encompassed by the capillary basement membranes and reabsorbed (Valaitis, 2002; Newman et al, 2007). If antigenemia persists, glomerular capillary basement membranes are damaged beyond repair and undergo sclerosis. In this phase, renal basement membrane type IV collagen is replaced by abundant type III collagen (Martinez-Hernandez & Menta, 1983; Haralson et al, 1987). The membranes are no longer able to reabsorb immune deposits and the glomerulus terminally undergoes fibrosis with ultimate loss of the nephron (Valaitis, 2002). It is not uncommon to find various stages of membranous glomerular damage and sclerosis in a single case, particularly in those classified as most severe (Valaitis, 2002; Newman et al, 2007).

In the domestic cat, the immunoglobulin (Ig) deposits are frequently IgG or IgM and only rarely IgA (Newman et al, 2007). The location, composition and granular deposition of these deposits suggest that they are of immune-complex origin (DiBartola & Rutgers, 1994, Newman et al, 2007; Grant Maxie & Newman, 2007). However, in the majority of cases the type of antigen is not identified and therefore the disease is considered idiopathic and primary (Nash et al, 1979; Grant Maxie & Newman et al, 2007).

Membranous glomerulonephritis in the cat is usually progressive, age related and generally sufficiently slow for the animals to live a relatively normal life, even without treatment (Nash et al, 1979). Although, once renal failure ensues the outcome is fatal and treatment options are only palliative (Nash et al, 1979; DiBartola & Rutgers, 1994).

2.2 Membranoproliferative glomerulonephrits

Membranoproliferative glomerulonephritis is also a chronic, progressive renal disease, characterized by mesangial hypercellularity and diffuse thickening of capillary basement membranes and mesangium (Valaitis, 2002; Newman et al, 2007). According to the World Health Organization classifications of human glomerular diseases, there are three subtypes based on morphologic appearance. The changes that permit classification are not perceivable with light microscopy and have to be detected by immunofluorescence, immunohistochemistry or electron microscopy. Type I is characterized by subendothelial immune deposits in a granular pattern of immunoglobulins and complement components such as C3. Type II is characterized by intramembranous dense deposits of unknown composition and smaller quantities of complement. This type is also known as “dense deposit disease” and is suspected to be associated with autoimmunity. Type III is characterized by subendothelial and subepithelial deposits (Newman et al, 2007).

All three subtypes have been reported in domestic animals including cats (Newman et al, 2007). Type I is rare in the cat (Asano et al, 2008) and type III has only been reported in the cat (Inoue et al, 2001). Asano and collaborators (2008) described a single case of type I membranoproliferative glomerulonephritis in a young male Japanese domestic cat with nephrotic syndrome. Histopathology of a biopsy sample revealed mesangial hypercellularity with increased matrix and thickening of glomerular capillary basement membranes consistent with membranoproliferative glomerulonephritis. Double contours of glomerular capillary walls were also observed. Subendothelial and rare intramembranous dense deposits were identified ultrastructurally. No underlying infectious or other diseases were identified in this case.

Type III membranous glomerulonephritis has not been reported in domestic animals except rarely in the cat. Inoue and collaborators (2001) described a case of atypical membranous glomerulonephritis consistent with the type III category of the human classification system.

The case involved a two year old Japanese domestic cat with clinical evidence of glomerular injury and renal failure. Granular deposits of IgG and C3 in capillary walls and mesangium were identified by immunohistochemistry and subepithelial, subendothelial and intramembranous deposits were noted by electron microscopy. Both antibodies against feline infectious peritonitis and feline immunodeficiency viruses were detected in this animal however the relationship between infection and the renal lesions was unclear (Inoue K et al, 2001). Additionally, in 1978 a case series of 63 domestic cats revealed that one third of animals had glomerulonephritis possibly related to feline leukemia virus infection and associated viral hematopoietic neoplasms (Glick et al, 1978). The authors did not give a morphologic classification of the type of glomerulonephritis but described diffuse mesangial proliferation on light microscopy and electron dense subendothelial, subepithelial and intramembranous deposits. This description would closely fit with a type III membranoproliferative glomerulonephritis.

2.3 Fibrillary glomerulopathies

Fibrillary glomerulopathies are a specific category of human glomerular disease in which pathologic fibrillary materials are observed in the glomerulus (Korbert et al, 1994; Schwartz, 2007). The first step for diagnosis is to differentiate amyloid from other fibrillary deposits with either specific stains such as Congo red or ultrastructural evaluation (Korbert et al, 1994). To date glomerular amyloidosis, collagenofibrotic glomerulopathy and noncongoiphilic fibrillary glomerulopathy have been described in the domestic cat (Boyce et al, 1984; DiBartola et al, 1986; Nakamura et al, 1996; Cavana et al, 2008).

2.3.1 Glomerular amyloidosis

Amyloidosis is a known cause of glomerular injury in cats (Boyce et al, 1984; DiBartola et al, 1986; Van der Linde-Sipman et al, 1996). Amyloid is an extracellular fibrillar proteinaceous substance produced after incomplete proteolysis of several soluble amyloidogenic proteins. This substance is not a distinct chemical entity despite its uniform appearance and staining properties. Ultrastructurally, amyloid is composed of continuous, nonbranching fibrils of approximately 7.5 to 10 nm in diameter. Protein fibrils have a beta-pleated sheet conformation which confers the distinctive coloration and birefringence with Congo red staining (Kumar et al, 2010).

Several clinical settings course with different types of amyloid deposition. Reactive systemic amyloidosis (or secondary amyloidosis) is the most common form in domestic animals, including the cat (Van der Linde-Sipman et al, 1997; Gruys, 2004). Amyloid is derived from serum protein AA (serum amyloid associated), and is produced in excess as a result of chronic antigenic stimulation (inflammatory, infectious or neoplastic conditions) (Obici et al, 2005; Kumar et al, 2010). Another form is immunoglobulin-derived amyloidosis (primary or AL), in which amyloid is produced from immunoglobulin light chains in plasma cell dyscrasias as a product of monoclonal B-cell proliferation (Obici et al, 2005; Merlini et al, 2011). This type of amyloidosis is uncommon in domestic animals but has been described in the dog, cat and horse (Platz et al, 1997; Kim et al, 2005).

Both AA and AL amyloidosis occur in systemic or localized forms (Merlini et al, 2011). In the cat, particularly in Siamese and Oriental breeds, systemic AA is the most frequent type of amyloid (van der Linde-Sipman et al, 1997). AA amyloid has been described in liver, spleen, lung, pancreas and kidney (van der Linde-Sipman et al, 1997; Zini et al, 2008). On the

contrary, AL amyloidosis in the cat has been reported localized within neoplastic tissue of extramedullary plasmacytomas (Platz et al, 1997).

For the purpose of this chapter we will discuss only renal amyloidosis in cats. In the glomerulus, amyloid is first deposited in the mesangial area and subendothelium of glomerular capillaries and gradually accumulates compressing and obliterating endothelial and epithelial cells, and capillary loops. Amyloid is also deposited in the tubular basement membranes of the cortex and medulla. The physical presence of amyloid causes ischemia and pressure atrophy of the nephrons and subsequently secondary scarring (Grant Maxie & Newman, 2007). The cat differs from other species in that amyloid is deposited predominantly in the renal papilla and outer medulla with lesser involvement of the glomeruli (Grant Maxie & Newman, 2007).

Familial secondary amyloidosis is a known entity in Abyssinian cats (Boyce et al, 1984). In these animals, amyloid can have a systemic distribution affecting organs such as thyroid glands, stomach and colon, however clinical lesions are usually only related to renal amyloidosis (DiBartola et al, 1985). Similar to other cases of secondary amyloidosis in the cat, the glomeruli are less affected than the medullary interstitium (DiBartola et al, 1985; Grant Maxie & Newman, 2007). The mode of inheritance is still undetermined but some studies suggest a likely autosomal dominant trait with incomplete penetrance (Niewold et al, 1999).

2.3.2 Collagenofibrotic glomerulonephropathy

In various human and animal renal diseases, collagen fibrils accumulate in the mesangium as a secondary change to various glomerular injuries, including chronic forms of any of the previously described glomerulonephritis (Valaitis, 2002). Fibrillar collagen such as type III collagen should not be present in the glomerulus. Glomerular capillary basement membranes contain type IV collagen which is arranged in sheets instead of fibrils. Only small amounts of type III collagen are found in the renal interstitium and interstitial capillary basement membranes (Martinez-Hernandez & Menta, 1983; Kumar et al, 2010).

Collagenofibrotic glomerulonephropathy or primary glomerular fibrosis, is a type of primary nephropathy in humans characterized by an abundant accumulation of type III collagen in the glomerular subendothelial spaces and mesangium and marked increase in serum of type III procollagen peptides (Alchi et al, 2007; Ikeda et al, 1990; Shirota et al, 1995; Nakamura et al, 1996). Collagen fibrils show characteristic structural abnormalities displaying frayed or spiral forms and marked disarray (Ikeda et al, 1990). The cause and pathogenesis are unknown and whether the disease is primary or secondary to systemic disease remains controversial (Alchi et al, 2007).

Spontaneous renal diseases with collagen fibril deposition are rare in domestic animals but some cases have been described in dogs, pigs and cats (Koeman et al, 1994; Shirota et al, 1995; Nakamura et al, 1996). Nakamura and collaborators (1996) reported a case of renal glomerular fibrosis in a young female Japanese domestic cat with clinical evidence of renal failure. Histopathology revealed that most glomeruli contained mesangial sclerosis and capillary collapse. Immunohistochemistry identified the matrix content as type III collagen. Collagen fibrils were also identified in mesangial and subendothelial areas by electron microscopy and the structural characteristics resembled human collagenofibrotic nephropathy. The cause for these collagenofibrotic glomerulopathy-like lesions was not identified and thus were considered of primary origin. This cat was serologically positive

for feline leukemia virus, however the authors did not consider an association between infection and the renal lesions. Serum concentrations of type III procollagen peptides were not evaluated in the feline case.

2.3.3 Nonconglomerular fibrillary glomerulonephritis

Nonconglomerular fibrillary glomerulonephritis is believed by some authors to represent a new entity among the primary glomerulonephritis (Alpers, 1992; Schwartz et al, 2002). This disease is characterized by randomly oriented, non-branching fibrils of approximately 10-22 nm diameter in the mesangial matrix and glomerular capillary basement membranes of glomeruli. Fibrils are heterogeneous and appear to be of immune complex origin. The exact chemical nature of the fibrils remains unknown (Alpers, 1992; Schwartz et al, 2002; Hvala et al, 2003).

A single case of nonconglomerular fibrillary glomerulonephritis has been reported in an adult female European shorthair cat with clinical evidence of renal disease (Cavana et al, 2008). The renal lesions consisted of thickened glomerular capillary basement membranes and Bowman's capsules. Capillary basement membranes were PAS positive and Congo red negative. Electron microscopy revealed subepithelial and subendothelial randomly scattered fibrillary deposits in the capillary basement membranes. Fibrils were larger than amyloid fibrils, measuring between 18-26 nm in diameter. Mesangial expression of IgG and IgM was detected by immunohistochemistry. The animal had a lymphoplasmacytic enteritis that was considered a possible source of immune stimulation. Concomitant systemic diseases, such as inflammatory, autoimmune or neoplastic processes, have been occasionally associated with this entity in humans (Ozawa et al, 1991; Masson et al, 1992; Hvala et al, 2003).

3. Glomerular injury in the Iberian lynx

Uncommon diseases are often described in non-domestic endangered animals, many times associated with deficient genetic diversity, captivity conditions or both. Little has been reported on health aspects of the Iberian lynx and research on this approach has become a priority for current conservation programs. There have been several cases reported of *Mycobacterium bovis* infection in the Iberian lynx (Briones et al, 2000; Aranaz et al, 2004). Disease was likely acquired by preying on infected animals (Briones et al, 2000). Our group also reported a generalized immune depletion apparently unrelated to infectious agents or other systemic diseases after evaluating lymphoid tissues in a representative portion of the population during the years 1998-2003 (Peña et al, 2006). A feline leukemia virus infection outbreak in the Doñana National Park population of Iberian lynxes was reported during a six month period between 2006 and 2007 (Meli et al, 2010, 2011). During this period, six animals died presumably due to the infection (Meli et al, 2011). Sequence analysis revealed homology with a strain originally identified in domestic cats suggesting co-infection between species (Meli et al, 2011; Geret et al, 2011). Prior to this time, the reported prevalence of feline leukemia virus in the same population was relatively low (Luaces et al, 2008) and evidence of lesions or death directly associated with the viral infection was unknown.

During the years 1998-2006, a thorough histopathological investigation on necropsied Iberian lynxes revealed the presence of glomerulonephritis in an important percentage of the surviving population, both free-ranging and captive (Jiménez et al, 2008). The disease was chronic, progressive and age related. None of the animals in this study died from renal

disease nor was there evidence of clinical disease in the small percentage of animals with available urinalyses. Proteinuria and low urine specific gravity were detected in few of these animals which may suggest some degree of glomerular filtration impairment. However the quality and accuracy of the samples and obtainment methods were unaccounted for and thus interpretation of these results may be inexact.

Histopathology of the glomerular lesions revealed a focal, diffuse membranous glomerulonephritis of variable severity in all animals regardless of their age, sex and captivity or free-ranging conditions. The only exception was found in a 44 day old cub without any evidence of renal lesions. The number and severity of affected glomeruli varied within samples and these factors were used to evaluate the overall severity of the disease in each animal.

Glomerular changes included segmental to diffuse glomerular capillary basement membrane thickening, decreased glomerular tuft cellularity, diffusely enlarged Bowman's epithelium, synechia between glomerular tufts and Bowman's capsules and Bowman's capsule fibrosis. In more severe cases the number of sclerotic glomeruli increased within the sample. Glomerular capillary basement membranes appeared thickened with PAS and silver stains (Fig.1 and Fig.2), and in sclerotic glomeruli, the mesangium stained blue with Masson's trichromic stain revealing the presence of collagen (Fig.3). Additional changes in the renal parenchyma included interstitial lymphoplasmacytic aggregates and fibrosis (Fig.3), and intratubular mineralization and protein casts. Both fibrosis and inflammation were significantly associated with severity and together with the glomerular sclerosis, were considered secondary to the membranous glomerulonephritis and not primary changes.

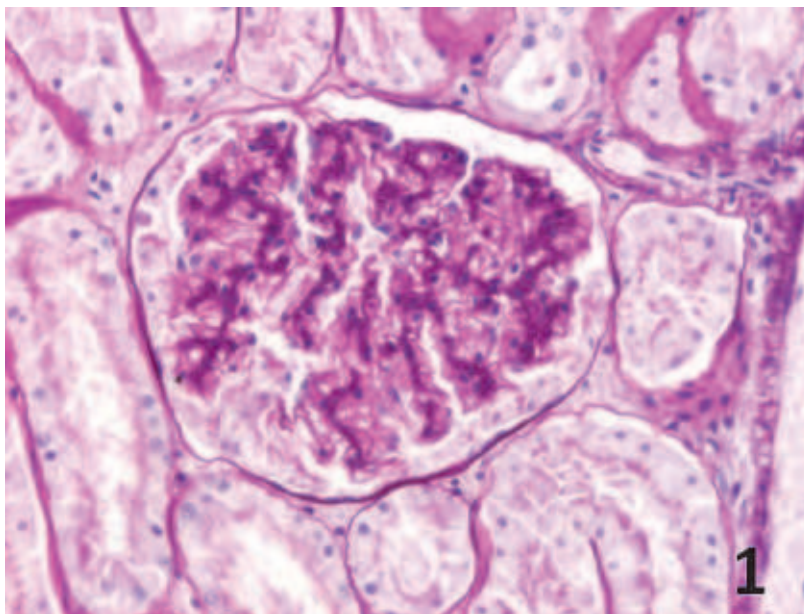


Fig. 1. Iberian Lynx. Kidney. PAS stain. Glomerulus with diffusely thickened capillary basement membranes, 20X

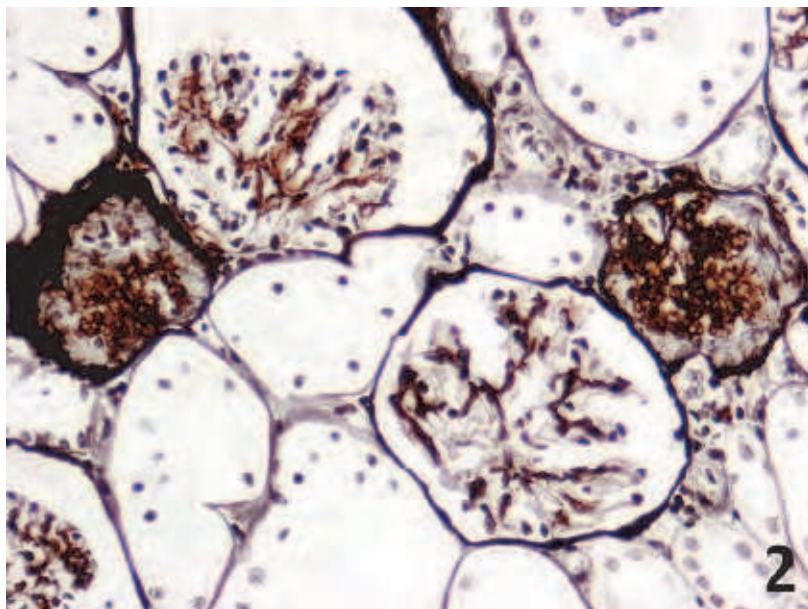


Fig. 2. Silver stain of glomeruli with membranous glomerulonephritis and glomerulosclerosis, 20X

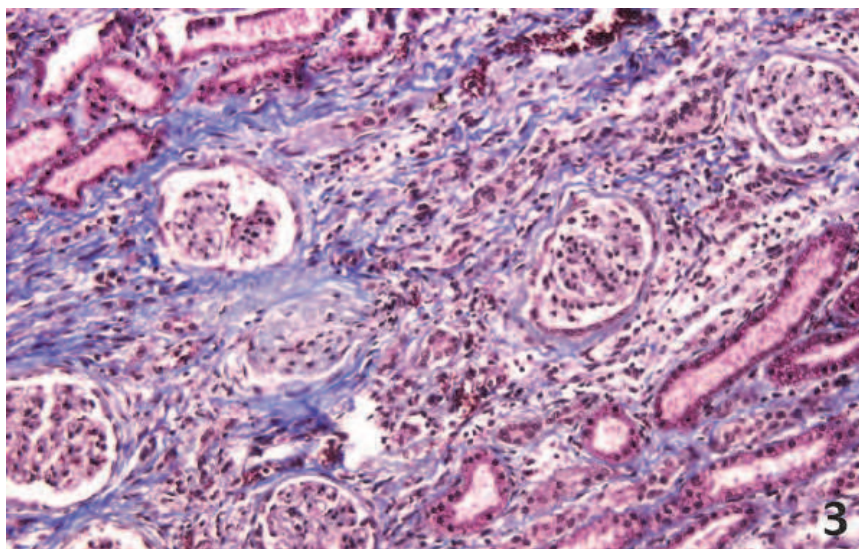


Fig. 3. Masson's trichrome stain. Chronic interstitial nephritis with fibrosis and sclerotic glomeruli, 10X

Increased amounts of laminin, type IV collagen and fibronectin were identified in affected basement membranes. As the severity of the lesions increased, glomerular tufts contained

higher amounts of laminin and the amount of type IV collagen decreased. IgG and IgM were identified in early lesions and expectedly were negative in sclerotic glomeruli. As was previously mentioned when describing membranous glomerulonephritis, immune complexes are present during initial stages and as severity progresses, the capacity of basement membranes to reabsorb these complexes is hindered. IgA was consistently negative. Readers are referred to Jimenez et al, 2008 for a more detailed discussion on these cases.

Electron microscopy of selected samples showed irregularly thickened up to twice normal width glomerular capillary basement membranes (Fig.4). Sparse intramembranous, large, scattered, irregular electron-dense deposits were noted, often surrounded by electron lucent spaces (Fig.5). Similarly, randomly distributed electron lucent areas in the capillary basement membranes were observed and interpreted as areas of immune deposit resorption. Foot processes in affected areas were variably blunted, fused or effaced. Degeneration of endothelial cells and rarely epithelial cells was also observed. The presence of IgG and IgM was corroborated within the electron dense deposits with immunogold labeling (Fig.6). Electron dense deposits were not observed in subepithelial or subendothelial areas (Jimenez et al, 2008).

No fibrillary deposits of any type were noted within the sampled areas, ruling out amyloidosis or other fibrillary glomerulopathies. Sclerotic glomeruli would have been expected to contain some amount of fibrillar collagen accumulation given the intensely blue staining with Masson's trichromic stain, however only moderate membranous lesions were sampled for electron microscopy. The ultrastructure of sclerotic glomeruli was not evaluated.

The origin of the circulating immune-complexes is elusive and the membranous glomerulonephritis of the Iberian lynx remains idiopathic for the majority of cases. Hence this disease may be a primary affection in the Iberian lynx. Only a small number of animals showed evidence of systemic diseases such as mycobacteriosis or malignant neoplasms (cutaneous squamous cell carcinomas) (Jimenez et al, 2009). Both processes are chronic, course with debilitation and are known causes of persistent antigenemia that may be associated with immune-complex glomerulonephritis. Feline coronavirus and feline leukemia viruses were rarely detected by PCR in the animals during the 1998-2006 study period and never associated with histopathological evidence of disease. It is unlikely that in these instances the renal lesions were related with infection. However, even if an association between antigenemia in these cases and the membranous glomerulonephritis existed, there would still be an important number of animals in which the origin of the immune-complexes remained unaccounted for.

Immune deposits were also detected by immunohistochemistry and electron microscopy in approximately 76% of the spleens from animals during the 1998-2006 study period. Deposits were located in splenic arteriolar basement membranes. These basement membranes were also thickened, particularly in areas with the deposits. Similar electron-lucent spaces surrounded the electron dense deposits. Immunoglobulins were also identified as IgG and IgM (Fig.7). This finding conveys the possibility of a systemic immune-complex disease of uncertain etiology also responsible for the glomerular lesions. An autoimmune origin for this disease was speculated given the apparent lack of a defined cause for the lesions and that lesions do not appear to be secondary to tissue damage (Jimenez et al, 2009; Jacobson et al, 1997). An inherited cause for this disease has also been hypothesized. Given the low genetic diversity of the Iberian lynx (Johnson et al, 2004), an inherited trait or predisposing genetic condition could easily show in a high number of the population. These possibilities together with the identification of the circulating causative antigens are currently under study.

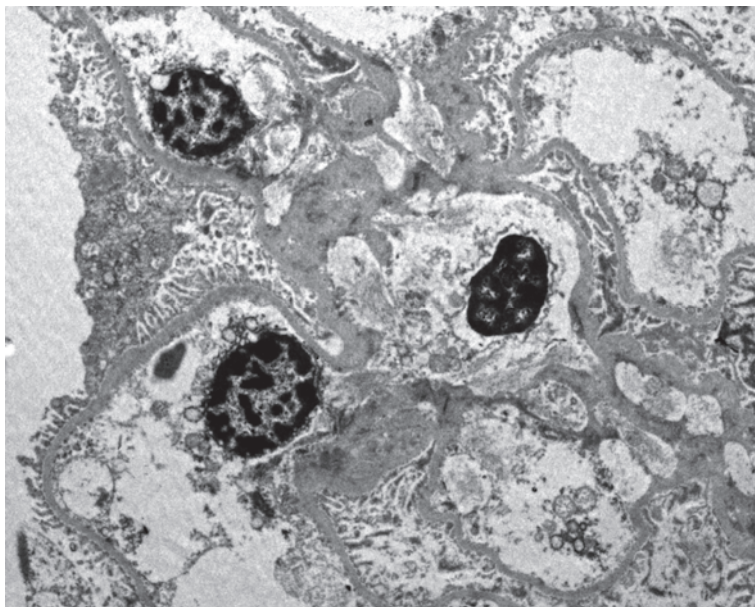


Fig. 4. Iberian lynx. Renal glomerulus. Electron microscopy. Multifocally and segmentally thickened capillary basement membranes with intramembranous electron dense deposits.

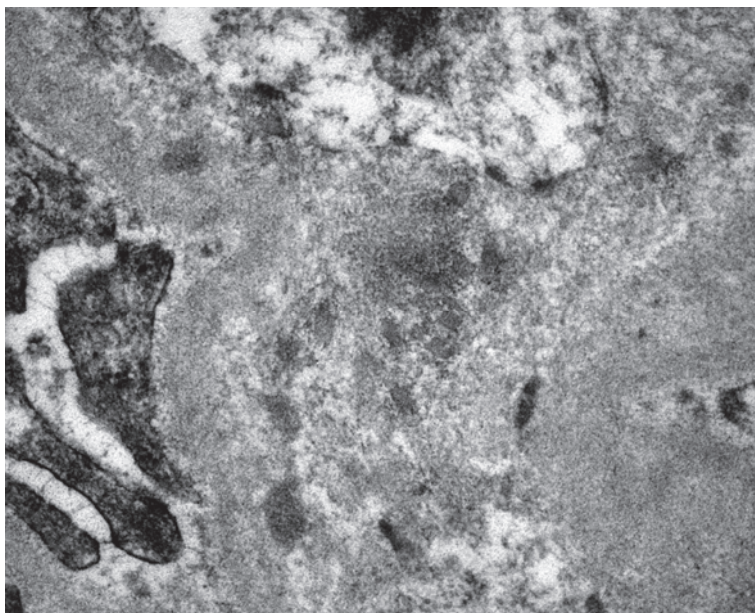


Fig. 5. Iberian lynx. Glomerular capillary basement membrane. Electron microscopy. Detail of intramembranous electron dense deposits and electron-lucent peripheral areas.

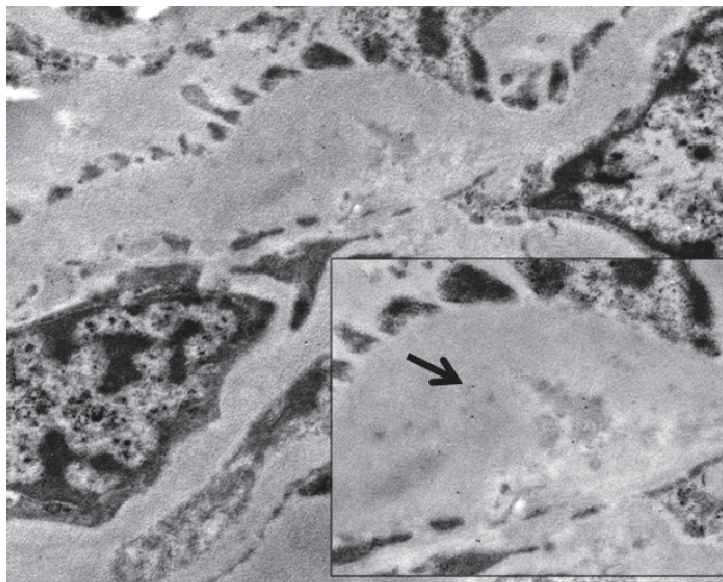


Fig. 6. Iberian lynx. Renal glomerulus. Immunogold labeling of IgM. Thickened capillary basement membranes with intramembranous electron dense deposits and colloid gold labeling of IgM. Inset: Detail of labeled gold particles

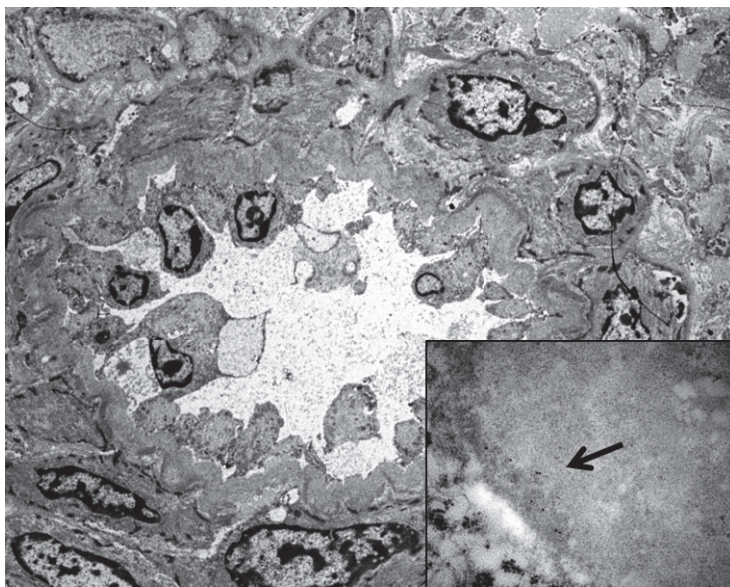


Fig. 7. Iberian lynx. Splenic follicular arteriole. Diffusely thickened capillary basement membrane with intramembranous linear electron dense deposits. Inset: Detail of positive labeling for IgG.

Despite the prevalence of these lesions within the population, the progress appeared to be slow. Animals seem to be able to live normally. This is similar to what is observed in domestic cats with membranous glomerulonephritis. However, the impact and consequences of this disease are yet far from known and caution on how this species will be able to confront overlapping renal injuries is warranted.

It is interesting to mention that glomerular lesions have also been described in other non-domestic felids. The most important have been secondary to systemic amyloidosis. Systemic AA amyloidosis has been described in black-footed cats (*Felis nigripes*) and cheetahs (*Acinonyx jubatus*) (Terio et al, 2008; Papendick et al, 1997). In both species, despite the systemic distribution, renal amyloidosis was the significant cause of morbidity and mortality. It is interesting to highlight that in the cheetah amyloidosis was associated with underlying systemic inflammatory diseases and was only observed in captive animals (Papendick et al, 1997). Contrarily, in the black footed cats amyloidosis was not associated with inflammatory conditions and was also detected in a young, free-ranging animal. Familial amyloidosis is suspected in this species (Terio et al, 2008). In both species, amyloidosis was more severe in the medulla than in glomeruli, similar to what is observed in domestic and Abyssinian cats.

Glomerulosclerosis has also been described in captive cheetahs. The lesion resembled human diabetic glomerulopathy. Hypertension, possibly associated with stress, dietary, and genetic factors, was speculated as a possible cause for the disease (Bolton & Munson, 1999).

Primary glomerular injury was considered a rare condition when surveying renal lesions of non-domestic felids of some zoological collections (Newkirk et al, 2010). Glomerular lesions similar to those described in the Iberian lynx with high prevalence in the free-ranging population as well as in captivity, and apparent primary origin, have not been described in other non-domestic felids.

4. Conclusions

The comparative study of diseases among different species often helps respond questions and elucidate unsolved enigmas of pathogenesis. The glomerular disease here reported appears to be unique for the Iberian lynx when considering non-domestic felids. The fact that this disease has not been reported previously in other non-domestic felids does not mean a similar entity may not exist. The study of these species is often difficult given the many interfering factors usually revolving these animals. Such factors include difficult access to wild-life populations, sample numbers compromised due to endangerment or limited access to captive populations among others. Often information is limited when encountering certain diseases or other situations regarding health and answers many times are sought in comparative pathology.

The purpose of this review was to compare the membranous glomerulonephritis of the Iberian lynx with the different types of glomerular injury reported, particularly in the domestic cat because of the close relationship and the extensive research available on the latter. Hopefully, the continuous study of these diseases will reveal new insights on pathogenesis, treatment or even prevention of these entities.

5. Acknowledgements

This research was supported by the Spanish Ministry of Environment, Research Project 90/2002, the Junta de Andalucía, Project CGL2004-00346/BOS, Red Nacional de Parques Nacionales, Project 17/2006, and TRAGSATEC, Project 244-2010.

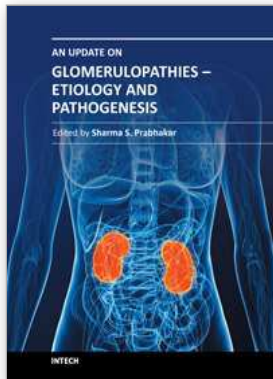
6. References

- Alpers C.E. (1992). Immunotactoid (microtubular) glomerulopathy: an entity distinct from fibrillary glomerulonephritis? *American Journal of Kidney Disease*, Vol.19, pp. 85-191
- Aranaz, A.; De Juan, I.; Montero, N.; Sánchez, C.; Galka, M.; Delso, C.; Alvarez, J.; Romero, B.; Bezos, J.; Vela, A.I.; Briones, V.; Mateos, A. & Domínguez, L. (2004). Bovine tuberculosis (*Mycobacterium bovis*) in wildlife in Spain. *Journal of Clinical Microbiology*, Vol.42, No.6, pp. 2602-2608
- Asano, T.; Tsukamoto, A.; Ohno, K.; Ogihara, K.; Kamiie, J. & Shirota, K. (2008). Membranoproliferative glomerulonephritis in a young cat. *Journal of Veterinary Medical Science*, Vol.70, No.12, pp. 1373-1375
- Bolton, L.A. & Munson, L. (1999). Glomerulosclerosis in captive cheetahs (*Acinonyx jubatus*). *Veterinary Pathology*, Vol.36, pp. 14-22
- Boyce, J.T.; DiBartola, S.P.; Chew, D.J. & Gasper, P.W. (1984). Familial renal amyloidosis in Abyssinian cats. *Veterinary Pathology*, Vol.21, No.1, (January), pp. 33-38
- Briones, V.; De Juan, I.; Sánchez, C.; Vela, A.I.; Galka, M.; Montero, N.; Goyache, J.; Aranaz, A.; Mateos, A. & Domínguez, L. (2000). Bovine tuberculosis and the endangered Iberian lynx. *Emerging Infectious Diseases*, Vol.6, No.2, pp. 189-191
- Cavana, P.; Capucchio, M.T.; Bovero, A.; Ripanti, D.; Catalano, D.; Scaglione, F.E.; Miller, J.; Blunden, T. & Farca, A.M. (2008). Nonconophilic fibrillary glomerulonephritis in a cat. *Veterinary Pathology*, Vol.45, pp. 347-351
- DiBartola, S.P.; Benson, M.D.; Dwulet, F.E. & Cornacoff, J.B. (1985). Isolation and characterization of amyloid protein AA in the Abyssinian cat. *Laboratory Investigations*, Vol.52, No.5, (May), pp. 485-489
- DiBartola, S.P.; Tarr, M.J. & Benson, M.D. (1986). Tissue distribution of amyloid deposits in abyssinian cats. *Journal of Comparative Pathology*, Vol.96, No.4, (July) pp.387-398
- DiBartola, S.P. & Rutgers, H.C. (1994). Diseases of the kidney. In: *The cat, diseases and clinical management*. 2nd Ed.; Sherding, R.G.; pp. 1711-1717, Saunders, Philadelphia
- Garcia, N.; Asuaga, J.L. & Torres, T. (1997). The carnivore remains from the Sima de los Huesos Middle Pleistocene Site (Sierra de Atapuerca, Spain). *Journal of Human Evolution*, Vol.33, pp.155-174
- Garcia, N. & Asuaga, J.L. (1998). The carnivore remains from the hominid-bearing Trinchera-Galeria, Sierra de Atapuerca, Middle Pleistocene site (Spain). *Geobiosphere*, Vol.31, pp. 659-674
- Geret, C.P.; Cattori, V.; Meli, M.L.; Riond, B.; López, G.; Vargas, A.; Simón, M.A.; López-Bao, J.V.; Hofmann-Lehmann, R. & Lutz, H. (2011). Feline leukemia virus outbreak in the critically endangered Iberian lynx (*Lynx pardinus*): high-throughput sequencing of envelope variable region A and experimental transmission. *Archive of Virology*, (February 8), Epub ahead of print
- Glick, A.D.; Horn, R.G. & Holscher, M. (1978). Characterization of feline glomerulonephritis associated with viral-induced hematopoietic neoplasms. *American Journal of Pathology*, Vol.92, pp. 321-332
- Grant Maxie, M. & Newman, S.J. (2007). The urinary system. In: *Pathology of Domestic Animals*. 5th Ed.; Jubb, K.V.F.; Kennedy, P.C. & Palmer, N.; pp. 425-522, Elsevier Saunders, Edinburgh,
- Gruys, E. (2004). Protein folding pathology in domestic animals. *Journal of Zhejiang University Science*, Vol.5, No.10, pp. 1226-1238, ISSN 1009-3095

- Guzman, J.N.; Garcia, F.J.; Garrote, G.; Perez de Ayala, R. & Iglesias, M.C. (2002): Iberian lynx (*Lynx pardinus*) distribution and current conservation status in Spain. In: *Proceedings of the International Seminar on the Iberian Lynx, Andujar, Spain, (October)*, pp. 18-20
- Haralson, M.A.; Jacobson, H.R. & Hoover, R.L. (1987). Collagen polymorphism in cultured rat kidney mesangial cells. *Laboratory Investigation*, Vol.57, pp. 513-523
- Hayasi, T.; Ishida, T. & Fujiwara, K. (1982). Glomerulonephritis associated with feline infectious peritonitis. *Japanese Journal of Veterinary Science*, Vol.44, pp. 909-916
- Hvala, A.; Ferluga, D.; Vizjak, A. & Koselj-Kajtna, M. (2003). Fibrillary nonconglomerular renal and extrarenal deposits: a report on 10 cases. *Ultrastructural Pathology*, Vol.27, pp. 341-347
- Ikeda, K.; Yokoyama, H.; Tomosugi, N.; Kida, H.; Ooshima, A. & Kobayashi, K. (1990). Primary glomerular fibrosis: a new nephropathy caused by diffuse intraglomerular increase in atypical type III collagen fibers. *Clinical Nephrology*, Vol.33, pp. 155-159
- Inoue, K.; Kami-Ie, J.; Ohtake, S.; Wakui, S.; Machida, S. & Shirota, K. (2001). Atypical membranoproliferative glomerulonephritis in a Cat. *Veterinary Pathology*, Vol.38, pp. 468-470
- Jacobson, C.N.; Gange, S.L.; Rose, N.R. & Graham, N.M. (1997). Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clinical Immunology and Immunopathology*, Vol.84, pp. 223-243
- Johnson, W.E.; Godoy, A.; Palomares, F.; Delibes, M.; Fernández, M.; Revilla, E. & O'Brien, S.J. (2004). Phylogenetic and Phylogeographic analysis of Iberian lynx populations. *Journal of Heredity*, Vol.95, No.1, pp. 19-28
- Jimenez, M.A.; Sanchez, B.; Perez-Alenza, M.D.; Garcia, P.; Lopez, J.V.; Rodriguez, A.; Muñoz, A.; Martinez, F.; Vargas, A. & Peña, L. (2008) Membranous glomerulonephritis in the Iberian lynx (*Lynx pardinus*). *Veterinary Immunology and Immunopathology*, Vol.121, pp. 34-43
- Jimenez, M.A.; Sanchez, B.; García, P.; Pérez-Alenza, M.D.; Carrillo, E.; Moreno, F.J. & Peña, L. (2009). Diseases of the Iberian lynx: Histopathological survey, lymphoid depletion, glomerulonephritis and related clinical findings, In: *Iberian lynx ex situ conservation, an interdisciplinary approach*. Vargas, A.; Breitenmoser, C.; & Breitenmoser, U.; Fundación Biodiversidad, UICN Cat Specialist Group
- Kim, D.Y.; Taylor, W.; Eades, S.C. & Cho, D.-Y. (2005). Systemic AL amyloidosis associated with multiple myeloma in a horse. *Veterinary Pathology*, Vol.42, pp. 81-84
- Koeman, J.P.; Biewenga, W.J. & Gruys, E. (1994). Proteinuria associated with glomerulosclerosis and glomerular collagen formation in three Newfoundland dog littermates. *Veterinary Pathology*, Vol.31, pp. 188-193
- Kumar, V.; Abbas, A.K.; Fausto, N. & Aster, J.C. (2010). Diseases of Immunity. In: *Robbins and Cotran Pathologic Basis of Disease, eighth Ed.*; Kumar, V.; Abbas, A.; Fausto, N. & Aster, J.C.; ISBN 978-1-4160-3121-5, Philadelphia, PA
- Luaces, I.; Doménech, A.; García-Montijano, M.; Collado, V.M.; Sánchez, C.; German Tejerizo, J.; Galka, M.; Fernández, P. & Gómez-Lucía, E. (2008). Detection of Feline leukemia virus in the endangered Iberian lynx (*Lynx pardinus*). *Journal of Veterinary Diagnostic Investigation*, Vol.20, pp. 381-385

- Martinez-Hernandez, A. & Menta, P.S. (1983). The basement membrane in pathology. *Laboratory Investigation*, Vol.48, pp. 656-677
- Masson, R.G.; Rennke, H.G. & Gottlieb, M.N. (1992). Pulmonary hemorrhage in a patient with fibrillary glomerulonephritis. *New England Journal of Medicine*, Vol.326, pp. 36-39
- Meli, M.L.; Cattori, V.; Martinez, F.; López, G.; Vargas, A.; Simón, M.A.; Zorrilla, I.; Muñoz, A.; Palomares, F.; López-Vao, J.V.; Pastor, J.; Tandon, R.; Willi, B.; Hofmann-Lehmann, R. & Lutz, H. (2009). Feline leukemia virus and other pathogens as important threats to the survival of the critically endangered Iberian lynx (*Lynx pardinus*). *PLoS One*, Vol.4, No.3, e4744
- Meli, M.L.; Cattori, V.; Martinez, F.; López, G.; Vargas, A.; Palomares, F.; Lopez-Bao, J.V.; Hofmann-Lehmann, R. & Lutz, H. (2010). Feline leukemia virus infection: a threat for the survival of the critically endangered Iberian lynx. *Veterinary Immunology and Immunopathology*, Vol.134, No.1-2, (March 15), pp.61-67
- Merlini, G.; Seldin, D.C. & Gertz, M.A. (2011). Amyloidosis: Pathogenesis and new therapeutic options. *Journal of Clinical Oncology*, (April 11) Epub ahead of print
- Moreno, S. & Villafuerte, R. (1995). Traditional management of scrubland for the conservation of rabbits *Oryctolagus cuniculus* and their predators in the Doñana National Park, Spain. *Biological Conservation*, Vol.118, pp. 183-193
- Nakamura, S.; Shibata, S.; Shiota, K.; Abe, K.; Uetsuka, K.; Nakayama, H.; Goto, N. & Doi, K. (1996) Renal glomerular fibrosis in a cat. *Veterinary Pathology*, Vol.33, pp. 696-699
- Nash, A.S.; Wright, N.G.; Spencer, A.J.; Thompson, H. & Fisher, E.W. (1979). Membranous nephropathy in the cat: a clinical and pathological study. *Veterinary Records*, Vol.105, No.4, (July 28), pp. 71-77
- Newkirk, K.M.; Newman, S.J.; White, L.A.; Rohrbach, B.W.; Ramsay, E.C. (2010). Renal lesions in nondomestic felids. *Veterinary Pathology*, Vol.
- Newman, S.J.; Confer, A.W. & Panciera, R.J. (2007). Urinary System. In: *Pathologic Basis of Veterinary Disease*. 4th Ed.; McGavin, M.D.; Zachary, J.F.; pp. 613-692, Mosby Elsevier, St Louis
- Niewold, T.A.; van der Linde-Sipman, J.S.; Murphy, C.; Tooten, P.C. & Gruys, E. (1999). Familial amyloidosis in cats: Siamese and Abyssinian AA proteins differ in primary sequence and pattern of deposition. *Amyloid*, Vol.6, No.3, (September), pp. 205-209
- Nowel & Jackson, (1996). Wildcats-status survey and conservation action plan. IUCN/SS Gland, Switzerland
- Obici, L.; Perfetti, V.; Palladini, G.; Moratti, R. & Merlini, G. (2005). Clinical aspects of systemic amyloid. *Biochemistry and Biophysics Acta*, Vol.1753, No.1, pp. 11-22
- Ozawa, K.; Yamabe, H.; Fukushi, K.; Osawa, H.; Chiba, N.; Miyata, M.; Seino, S.; Inuma H.; Sasaki, T.; Yoshikawa, T. (1991). Case report of amyloidosis-like glomerulopathy with hepatic involvement. *Nephron*, Vol.58, pp. 347-350
- Palomares, F.; Rodriguez, A.; Laffite, R. & Delibes, M. (1991). The status and distribution of the Iberian lynx (*Felis pardina*, Temminck) in Coto de Doñana area, SW Spain. *Biological Conservation*, Vol.57, pp. 159-169
- Palomares, F.; Delibes, M.; Revilla, E. (2000). Iberian lynx in a fragmented landscape: predispersal, dispersal and postdispersal habitats. *Conservation Biology*, Vol.14, No.13, pp. 809-818

- Papendick, R.E.; Munson, L.; O'Brien, T.D. & Johnson, K.H. (1997). Systemic AA amyloidosis in captive cheetahs (*Acinonyx jubatus*). *Veterinary Pathology*, Vol.34, No.6, pp. 549-556
- Peña, L.; García, P.; Jiménez, M.A.; Benito, A.; Pérez Alenza, M.D. & Sánchez, B. (2006). Histopathological and immunohistochemical findings in lymphoid tissues of the endangered Iberian lynx (*Lynx pardinus*). *Comparative Immunologic and Microbiologic Infectious Disease*, Vol.29, No.2-3, pp. 114-126
- Platz, S.J.; Breuer, W.; Geisel, O.; Linke, R.P. & Hermanns, W. (1997). Identification of lambda light chain amyloid in eight canine and two feline extramedullary plasmacytomas. *Journal of Comparative Pathology*, Vol.116, pp. 45-54
- Poli, A.; Falcone, M.L.; Bigalli, L.; Massi, C.; Hofmann-Lehmann, R.; Lombardi, S. & Bendinelli, M. (1995). Circulating immune complexes and analysis of renal immune deposits in feline immunodeficiency virus-infected cats. *Clinical Experimental Immunology*, Vol.101, pp. 254-258
- Rodríguez, A. & Delibes, M. (2002). Internal structure and patterns of contraction in the geographic range of the Iberian lynx. *Ecography*, Vol.25, No.3, pp. 314-328
- Schwartz, M.M. 2007. Glomerular diseases with organized deposits. In: *Heptinstall's pathology of the kidney. 6th Ed.*; Jennette, J.C.; Olson, J.L.; Schwartz, M.M. & Silva, F.G.; Lippincott Williams & Wilkins, Philadelphia
- Schwartz, M.M.; Korbert, S.M. & Lewis, E.J. (2002). Immunotactoid glomerulopathy. *Journal of the American Society of Nephrology*, Vol.13, pp. 1390-1397
- Shirota, K.; Masaki, T.; Kitada, H.; Yanagi, M.; Ikeda, Y.; Une, Y.; Nomura, Y. & Jothy, S. (1995). Renal glomerular fibrosis in two pigs. *Veterinary Pathology*, Vol.32, pp.236-241
- Slauson, D.O. & Lewis, R.M. (1979). Comparative pathology of glomerulonephritis in animals. *Veterinary Pathology*, Vol.16, pp.135-164
- Terio, K.A.; O'Brien, T.; Lamberski, N.; Famula, T.R. & Munson, L. (2008). Amyloidosis in black-footed cats (*Felis nigripes*). *Veterinary Pathology*, Vol.45, No.3, pp. 393-400
- Valaitis, J. (2002). Renal glomerular disease. In: *Atlas of electron microscopy with histopathological bases and immunofluorescence findings*, p. 99, ASCP Press, Chicago,
- Van der Linde-Sipman, J.S.; Niewold, T.A.; Tooten, P.C.J.; de Neijts-Backer, M. & Gruys, E. (1997). Generalized AA-amyloidosis in Siamese and Oriental cats. *Veterinary Immunology and Immunopathology*, Vol.56, pp.1-10
- Zini, E.; Hauser, B.; Meli, M.L. & Glaus, T. M. (2008). Transient laboratory changes in a cat with repeated hepatic hemorrhages due to amyloidosis. *Veterinary Record*, Vol.162, pp. 24-26



An Update on Glomerulopathies - Etiology and Pathogenesis

Edited by Prof. Sharma Prabhakar

ISBN 978-953-307-388-0

Hard cover, 276 pages

Publisher InTech

Published online 06, September, 2011

Published in print edition September, 2011

The book has fourteen chapters which are grouped under different sections: Immune System and Glomerulonephritis, Animal Models of Glomerulonephritis, Cytokines and Signalling Pathways, Role of Cells and Organelles in Glomerulonephritis and Miscellaneous. While the purpose of this volume is to serve as an update on recent advances in the etio-pathogenesis of glomerulopathies, the book offers the current and broad based knowledge in the field to readers of all levels in the nephrology community.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

María Ángeles Jiménez, Belén Sánchez and Laura Peña (2011). Glomerular Injury in Domestic Cats and the Iberian Lynx (*Lynx pardinus*): A Comparative Review, *An Update on Glomerulopathies - Etiology and Pathogenesis*, Prof. Sharma Prabhakar (Ed.), ISBN: 978-953-307-388-0, InTech, Available from: <http://www.intechopen.com/books/an-update-on-glomerulopathies-etiology-and-pathogenesis/glomerular-injury-in-domestic-cats-and-the-iberian-lynx-lynx-pardinus-a-comparative-review>

INTECH

open science | open minds

InTech Europe

University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike-3.0 License](#), which permits use, distribution and reproduction for non-commercial purposes, provided the original is properly cited and derivative works building on this content are distributed under the same license.