Glomerular diseases in dogs and cats

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Lisa Gardbaum discusses, in the first of a two-part article, the pathogenesis, classification and diagnosis of glomerular disease in canines and felines

GLOMERULAR diseases are an important cause of renal disease in dogs. The incidence in randomly selected dogs is reported to be between 43 and 90 per cent, with the incidence increasing with age (mean eight years)[1].

They are also seen in cats, but are considered uncommon. Most of this article will, therefore, relate to the disease in dogs.

A vast majority of the glomerular diseases that occur in cats and dogs are secondary to a systemic infectious, neoplastic or non-infectious inflammatory disease (Tables 1a and 1b). In approximately 50 per cent of cases, however, no identifiable concurrent disease is apparent at the time of presentation, either because it has resolved or is occult.

Occult disease may become overt months after initial diagnosis of glomerular disease, necessitating continual monitoring and assessment, as treatment of these underlying diseases is by far the most important aspect in the management of affected animals. The most common forms seen in the dog and cat are amyloidosis and glomerulonephritis. Familial glomerulopathies also occur in several breeds and often manifest at an early age.

The renal cortex contains scattered glomeruli and tubules within the interstitium.

The glomerulus is a tuft of highly branched capillaries, which invaginate into the proximal tubules

(Figures 1a and 1b).

The afferent arteriole enters to form the glomerular capillary tuft and exits as the efferent arteriole. The capillary loops are supported by mesangial cells and the mesangial matrix.

The capillary tuft is covered by a glomerular basement membrane (GBM) and is lined by a layer of interdigitating visceral epithelial cells (podocytes).

The glomerular filtration barrier consists of endothelium, GBM and podocytes. This acts as a filter, across which an ultrafiltrate of the plasma is formed. It is freely permeable to water and small solutes, but normally retains most macroglobules, such as proteins.

Proteinuria results when there is disruption of the filtration barrier, which may be caused by the deposition of immune complexes and/or complement within the glomerulus (glomerulonephritis), amyloid (amyloidosis), a change in the composition of the GBM (congenital or acquired) or injury to the endothelial cells or podocytes (minimal change disease).

Damage to the mesangial cells can also occur, but does not usually cause significant proteinuria as the GBM is unaffected. Proteinuria induces tubular damage, leading to progressive nephron loss due to the direct toxic effect of the protein on the tubules, which leads to interstitial inflammation, fibrosis and cell death due to obstruction of the tubules by the casts. The classification of glomerulonephritis is based on the site of immune complex deposition (subendothelial, subepithelial or mesangial) and the associated immunological responses (Table 2). Immune complexes may be circulating and trapped in mesangial or subendothelial cells, or form in situ.

Clinical signs

The clinical signs associated with glomerular disease can vary. Animals may be asymptomatic, or signs may reflect the underlying disease process.

There may be non-specific signs of weight loss, lethargy and anorexia, or signs consistent with chronic renal failure if azotaemia is present. If proteinuria is severe, hypoalbuminaemia may lead to ascites or peripheral oedema due to the resulting decrease in plasma oncotic pressure (Figure 2). Sodium retention is thought to also contribute to oedema formation. Thromboembolism is one of the most serious complications of glomerular disease and is more commonly seen in cases of amyloidosis and membranous nephropathy, where proteinuria is likely to be marked.

The incidence of thromboembolism may be underestimated due to the difficulty in identifying its presence. Pulmonary thromboembolism is most common, and this often manifests as severe dyspnoea, but can occur elsewhere.

The cause of the hypercoagulable state is thought to be mainly due to loss of antithrombin III

(ATIII), a protease inhibitor that modulates fibrin formation. Being of a similar size and charge to albumin, it is lost in the urine to a similar degree. Although measuring levels of ATIII may help determine those cases most needing anti-thrombotic therapy, other factors are also thought to contribute to thromboembolism, such as increased thromboxane B2 levels (an inducer of platelet aggregation), platelet hypersensitivity caused by hypercholesterolaemia, increased fibrinogen concentrations leading to increased fibrin complex formation and platelet aggregation, and release of other coagulation factors.

Hypertensive damage may manifest as neurological signs or retinal or cardiac changes. Hypertension is reported in up to 80 per cent of dogs with glomerular disease, and thought to be due to sodium retention and the generation of vasoactive factors (rennin or angiotensin II).

The key diagnostic finding in animals with glomerular disease is a raised urine protein/creatinine (UPC) ratio on urinalysis. A UPC of more than 0.5 in a urine sample free of inflammation or macroscopic haematuria is considered abnormal. As a general rule, mild proteinuria (0.5 to two) tends to be associated with tubulointerstitial disease, whereas UPCs greater than or equal to two tend to suggest the presence of glomerular disease.

The highest UPCs are most commonly seen with amyloidosis and membranous nephropathy, and are also seen with hereditary nephritis and minimalchange disease. These forms of glomerular disease are also most commonly associated with the “nephrotic syndrome”, where a combination of hypercholesterolaemia, hypoalbuminaemia, proteinuria and ascites/oedema is present. Although this syndrome is pathognomonic for glomerular disease, it is only seen in about 15 per cent of affected dogs. Partial nephrotic syndrome can also be seen without oedema/ascites, in about 50 per cent of cases.

Studies have shown that the presence of increasing magnitudes of microalbuminuria suggests damage to the glomerular filtration barrier and cases with microalbuminuria are likely to go on to develop overt proteinuria[2]. The urine-specific gravity is variable with glomerular disease. The presence of renal azotaemia with an intact concentrating ability (tubulointerstitial imbalance) is suggestive of glomerular disease.

Urinary casts are often seen and are thought to be proteins packaged in a form that will protect renal tubular epithelium from their potentially damaging effects.

Biochemistry findings include azotaemia and hyperphosphataemia in advanced cases with concurrent renal failure (53 per cent of dogs with glomerulonephritis and 23 per cent of dogs with amyloidosis), hypoalbuminaemia in animals with marked hypoproteinuria (60 to 70 per cent of cases), and hypercholesterolaemia reported in 80 per cent of cases of glomerulonephritis and 86 per cent of dogs with amyloidosis.

It is believed that hypoalbuminaemia stimulates hepatic protein synthesis, including lipoproteins

leading to hypercholesterolaemia. Hyperlipidaemia may also be present and may perpetuate glomerular and tubulointerstitial damage.

With ultrasound imaging, the kidneys may appear normal, small and irregular or large. There may be increased echogenicity of the cortex, loss of corticomedullary differentiation or pelvic dilation. Thorough investigations should be performed in an attempt to identify any underlying systemic diseases, including careful physical examination, any signs of joint swellings, skin or abdominal masses or gingivitis or pyoderma.

Investigations should include:

• radiographic and ultrasonographic imaging;

• bloods including haematology for evidence of immunemediated haemolytic anaemia or thrombocytopaenia;

• serology for regional infectious disease (*Borrelia burgdorferi,* dirofilariasis) and antinuclear antibody;

• arthrocentesis if polyarthritis is suspected; and

• brain MRI and cerebrospinal fluid sampling if neurological signs are evident.

In cases where proteinuria does not improve or worsens over time with either non-specific treatment and/or treatment of identifiable underlying disease, renal biopsy should be considered to determine the type of glomerular disease present so specific treatment may be implemented. Those dogs with early renal failure or very severe proteinuria should also be considered for biopsy, but this is contraindicated in advanced renal failure.

For evaluation of glomerular disease, only renal cortical tissue needs to be biopsied. Including the medulla leads to an increased risk of haemorrhage and infarction, and should be avoided. Surgical, laparoscopic or percutaneous Tru-Cut biopsies can be attained. With Tru-Cut biopsies, at least two samples (more than 10mm long) should be taken with either a 16g or 18g needle. Once collected, the largest piece should be placed in formalin for light microscopy. The other piece should be divided into two, with one placed in a fixative suitable for electron microscopy (EM); for example, four per cent formalin and one per cent glutaraldehyde in a sodium phosphate buffer. One piece should either be frozen or placed in a fixative suitable for immunofluorescent microscopy (IFM) such as Michel’s solution.

Light microscopy is usually sufficient to diagnose the type of glomerular disease in advanced cases. EM is required to identify small immune complex deposits and the exact location of the deposits and damage to the GBM. IFM further defines the disease by determining the specific

nature of the deposits. Unfortunately EM and IFM are not readily available in the UK.

Classification of glomerular disease

• Glomerulonephritis

– Membranoproliferative glomerulonephritis (MPG) is the most common form in dogs (20 to 60 per cent of cases), with a median age of 10 years. It is rare in cats.

Histologically, there is thickening of the capillary walls and increased glomerular/mesangial cellularity (Figures 3a and 3b).

It is further typed, based on the location of the immunecomplexes within the glomeruli. MPG may be idiopathic, but is usually due to an underlying systemic disease process.

It has also been identified as a familial disease in Bernese mountain dogs and Brittany spaniels, and a severe form has been seen associated with infection with *Borrelia burgdorferi* (Lyme's disease), with a higher incidence in Labradors and golden retrievers[3].

– Membranous glomerulonephritis is also a common form of glomerular disease in dogs (10 to 45 per cent of cases) and is the most common form in cats, in which other forms are very uncommon. The mean age in dogs is eight years and three years in cats. It is characterised by thickening of the capillary loops, but normal cellularity within the glomeruli.

It is more common in males than females in both species. Due to the lack of inflammatory response, this form is sometimes referred to as a glomerulonephropathy, rather than a glomerulonephritis. Proteinuria in these cases may be massive and, therefore, may present with nephrotic syndrome.

– Proliferative glomerulonephritis is seen in two to 16 per cent of cases. Histologically, there is mesangial cell hyperplasia and mesangial complex proliferation. The median age in dogs is seven to nine years. Proteinuria and renal failure are the most common presentations.

• Amyloidosis

Amyloidosis is one of the most common glomerular diseases in dogs, accounting for approximately 25 per cent of cases. With the exception of Abyssinians and Siamese breeds, it is rare in cats.

Females appear to be affected more than males. Beagles, English foxhounds and collies may be at increased risk and it may be familial in the former two. As with membranous nephropathy, it may be associated with massive proteinuria and nephrotic syndrome, with or without thromboembolism.

It is defined as the extracellular deposition of fibrils formed by polymerisation of proteins with a beta-pleated sheet conformation. These proteins (amyloid A) are formed from serum amyloid A protein (SAA), an acute-phase protein produced by hepatocytes, in response to macrophage-derived cytokines released in inflammatory diseases. This is known as reactive amyloidosis. It is by far the most common form seen in cats and dogs and tends to occur in older animals.

Amyloid is first deposited in the mesangial regions and then to the subendothelial aspect of the GBM. This is seen under light microscopy as homogenous acellular, eosinophilic material when stained with haematoxylineosin (Figures 4a and 4b), and stains an apple green colour with Congo red stain with polarising microscopy (Figure 5). Other organs, such as the liver, spleen, adrenals and gastrointestinal tract, may also be involved, although clinical signs associated with this are rare. As with glomerulonephritis, a chronic systemic disease is thought to trigger reactive amyloidosis, although this may be unidentifiable in 50 per cent of cases.

A familial form of reactive amyloidosis is recognised in the Abyssinian cat and the Shar Pei dog, where amyloid is deposited within the glomeruli, but mainly within the medulla. These animals are more likely to develop azotaemia than proteinuria. Familial amyloidosis is also recognised in Siamese. Oriental-shorthaired cats, where concurrent liver deposition can lead to hepatic rupture and haemorrhage.

Affected Shar Peis are normally younger dogs (median four years) and often have a predisposition phase, with a history of recurrent pyrexia and swelling of the tibiotarsal joints prior to the development of renal amyoidosis, which may be similar to familial Mediterranean fever seen in humans.

• Hereditary nephritis

This is a group of inherited glomerular diseases that are a result of a defect in the GBM collagen (type-IV). They should be considered in any young dog presented with signs of glomerular disease, and have been reported in several dog breeds, including the springer spaniel, bull terriers, Dalmatians and, rarely, in Samoyeds (Table 3). In springer spaniels and Samoyeds, terminal renal failure normally develops by two years of age, whereas in bull terriers and Dalmatians survival can be as long as 10 years. A familial immune-mediated glomerulonephritis is seen in soft-coated wheaten terriers, together with a protein-losing enteropathy.

• Minimal change disease

This is a common cause of nephrotic syndrome in humans and has been reported in dogs. No glomerular lesions are identified by light microscopy and immunoglobulin deposition is not seen with IFM, but podocyte foot process abnormalities are detected by EM. It is important to diagnose this form of glomerular disease, as it is extremely sensitive to corticosteroid treatment.

• Glomerulosclerosis

This often develops as an endstage lesion in response to glomerular injury or decreased functioning renal mass.

When nephron numbers are reduced in renal failure, the remaining nephrons hypertrophy in response, and hyperfunction, leading to glomerular injury and glomerulosclerosis, and a progressive reduction in renal function.

Proteinuria in cases of glomerulosclerosis secondary to renal disease tends to be mild. Glomerulosclerosis can also develop secondary to hypertensive renal damage, and in dogs with diabetes mellitus.

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