Glomerular Disease

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Glomerular disease is an important cause of chronic renal failure in human patients and has been increasingly recognized in veterinary medicine in recent years. The two important glomerular diseases of domestic animals are glomerulonephritis and glomerular amyloidosis. Proteinuria is the hallmark of glomerular disease, and the term *nephrotic* syndrome traditionally has been used to describe patients with proteinuria, hypoalbuminemia, hypercholesterolemia, and edema or ascites.

Glomerulonephritis

Immune-complex glomerulonephritis is a disease of glomeruli caused by deposition of immunoglobulin or complement in the glomerular capillary wall. Immune complexes generally deposit in the glomerular filter in one of two ways. Soluble circulating immune complexes can be trapped in the glomeruli under conditions of antigen-antibody equivalence or slight antigen excess. In antibody excess, immune complexes tend to be large and insoluble and are rapidly removed from the circulation by phagocytic cells. In large antigen excess, immune complexes do not readily bind complement and are less likely to produce immune injury. Immune complexes also may be formed *in situ* either in response to endogenous glomerular antigens, endogenous non-glomerular antigens or exogenous antigens deposited or "planted" in the glomeruli. Immune complexes may be deposited in a *subepithelial, subendothelial* or *intramembranous* locations in glomeruli. Complexes also may deposit in the mesangium. Immune complex deposition in glomeruli may decrease the amount of fixed negative charge and enhance filtration of negatively-charged circulating macromolecules (e.g. albumin). Complement activation results in membrane damage and proteinuria. Soluble complement components (e.g. C3a, C5a) also recruit inflammatory cells. Platelet activation and aggregation occur secondary to endothelial damage or antigen-antibody interaction and exacerbate glomerular damage by release of a variety of mediators. These mediators cause activation and proliferation of mesangial cells and endothelial cells, vasospasm and increased coagulation. Mesangial cells contribute to glomerular inflammation by release of eicosanoids, cytokines, and growth factors and by increased matrix production. Inflammatory cells also contribute to glomerular injury. Neutrophils and macrophages localize in the glomeruli in response to soluble mediators including complement components, platelet activating factor, platelet-derived growth factor, and eicosanoids. Activated neutrophils release reactive oxygen species and proteinases, leading to further damage. Macrophages produce proteinases, oxidants, eicosanoids, growth factors, cytokines, complement fragments, and coagulation factors. Several infectious and inflammatory diseases have been associated with glomerular deposition or *in situ* formation of immune complexes in domestic animals. In most cases, however, the antigen source or underlying disease process is not identified and the glomerular disease is referred to as idiopathic.

Amyloidosis

Amyloidosis refers to a diverse group of diseases characterized by extracellular deposition of fibrils formed by polymerization of protein subunits with a specific biophysical conformation called the β-pleated sheet. This specific biophysical conformation is responsible for the unique optical and tinctorial properties of amyloid deposits as well as their insolubility and resistance to proteolysis *in vivo*. Amyloid deposits have a homogeneous, eosinophilic appearance when stained by hematoxylin and eosin and viewed by conventional light microscopy. They demonstrate green birefringence after Congo red staining when viewed under polarized light. The clinical diagnosis of amyloidosis is based on this finding. Reactive (secondary) amyloidosis is a systemic syndrome characterized by tissue deposition of amyloid A protein (AA amyloid) which is an amino terminal fragment of the acute phase reactant, serum amyloid A protein (SAA). Naturally-occurring systemic amyloidosis in domestic animals is an example of reactive amyloidosis. Familial amyloid syndromes in the Abyssinian, Siamese and Oriental shorthair breeds of cat and in the Shar Pei, Beagle and English foxhound breeds of dog are additional examples of reactive systemic amyloidosis in veterinary medicine. Diseases that have been observed in association with reactive systemic amyloidosis in the dog include chronic infectious or non-infectious inflammatory diseases and neoplasms, but there is no discernible associated inflammatory or neoplastic disease in the majority of dogs and cats presented with reactive systemic amyloidosis.

Clinical findings

Most animals with glomerular disease are middle-aged or older at presentation. There is no sex predilection, but approximately 75% of cats with GN are males. Any breed can be affected by glomerular disease but, familial forms of membranoproliferative GN have been reported in soft-coated Wheaten terriers (thought to be associated with abnormal processing of dietary antigens), Brittany spaniels (associated with hereditary deficiency of the third component of complement) and Bernese Mountain dogs (often associated with positive serology for *Borrelia burgdorferi*). Hereditary defects of glomerular basement membrane type IV collagen occur as an autosomal recessive trait in English Cocker spaniels and as an X-linked dominant trait in male Samoyed dogs. Basement membrane

defects are also suspected to occur in Doberman pinschers and Bull terriers. Familial renal amyloidosis occurs in young Abyssinian, Siamese and Oriental shorthair cats and in Shar Pei dogs. Familial amyloidosis has also been reported in Beagles and English foxhounds.

Animals with glomerular disease may present in one of six possible ways: (1) signs may be related to the presence of chronic renal failure if more than 75% of the nephron population has become non-functional (e.g. anorexia, weight loss, lethargy, polyuria, polydipsia, vomiting) and this presentation unfortunately is most common; (2) signs may be related to an underlying infectious, inflammatory or neoplastic disease; (3) proteinuria may be an incidental finding detected during diagnostic evaluation of another medical problem; (4) signs may be related to classical nephrotic syndrome as described above (e.g. ascites, subcutaneous edema); (5) signs may be related to thromboembolism (e.g. sudden onset of dyspnea with pulmonary thromboembolism, sudden onset of paraparesis with iliac or femoral artery embolism); or (6) sudden blindness may occur due to retinal detachment resulting from systemic hypertension.

Physical examination findings frequently are related to the presence of chronic renal failure and uremia. Other physical findings may be related to the presence of underlying infectious, inflammatory or neoplastic diseases. Affected Shar Pei dogs may have a previous history of so-called “Shar pei fever” (episodic joint swelling usually involving the tibiotarsal joints and high fever that resolve within a few days, regardless of treatment). Some physical findings may be related to severe protein loss (e.g. ascites, edema, poor body condition, poor haircoat). Retinal hemorrhages, vascular tortuosity, and retinal detachment may occur due to systemic hypertension.

On urinalysis, marked proteinuria in presence of an inactive urinary sediment is the hallmark of glomerular disease. Hyaline and granular casts and lipid droplets occasionally may be seen in the sediment. Either glomerulonephritis or amyloidosis can lead to chronic renal failure with the expected biochemical abnormalities (e.g., azotemia, hyperphosphatemia, metabolic acidosis). Hypoalbuminemia occurs in up to 75% of dogs with amyloidosis and in 60% of dogs with glomerulonephritis whereas hypercholesterolemia occurs in up to 60% of dogs with glomerulonephritis and in 90% of dogs with amyloidosis. Mild to moderate hypercholesterolemia may be a non-specific finding in cats with renal disease. The hypercholesterolemia in patients with glomerular disease may be due in part to increased hepatic synthesis of cholesterol-rich lipoproteins secondary to chronic hypoalbuminemia. Assessment of the urine protein/creatinine ratio avoids the confounding effect of total urine solute concentration (i.e. specific gravity) on qualitative assessment of proteinuria. It is correlated with 24-hour urinary protein loss but easier to measure (i.e. does not require a 24-hour urine sample). The normal urine protein/creatinine ratio is < 0.4 in dogs and cats. The magnitude of increase in urine protein/creatinine ratio is roughly correlated with nature of glomerular disease. Results are highest in dogs with glomerular amyloidosis (often more than 10) and lowest in those with interstitial renal disease (usually less than 10). Animals with glomerulonephritis have very variable results (normal to more than 30). The presence of pyuria or marked hematuria can make the urine protein/creatinine ratio unreliable (i.e. produce false positive results). Measurement of fibrinogen and antithrombin III concentrations may identify animals at risk for thromboembolism. Ultimately, renal biopsy is the only reliable way to differentiate glomerulonephritis from glomerular amyloidosis.

Clinical management

If possible, identify and treat any underlying predisposing inflammatory or neoplastic disease process (i.e. remove the offending antigen if possible). If chronic renal failure is present, it is treated according to the principles of conservative medical management of chronic renal failure (e.g. dietary restriction of phosphorus, phosphorus binders, H2-blockers). Supportive treatment of hypertension may include a low salt diet (< 0.3% on a dry matter basis). Angiotensin converting enzyme (ACE) inhibitors (e.g. enalapril, benazepril) decrease glomerular capillary hydraulic pressure by decreasing post-glomerular arteriolar resistance and thus decrease proteinuria. Although this beneficial effect must be balanced against their potential to aggravate azotemia, it is well accepted that ACE inhibitors slow the progression of chronic renal disease in human patients independent of their effect of systemic blood pressure. In one study of dogs with glomerulonephritis, enalapril (0.5 mg/kg PO q12-24h) decreased proteinuria (as assessed by urine protein/creatinine ratio), decreased blood pressure, and slowed progression of renal disease in dogs. The calcium channel blocker amlodipine also may be used in the management of hypertension.

No studies in veterinary medicine are available to demonstrate effectiveness of any specific therapy for glomerulonephritis. Immunosuppressive drugs (e.g. corticosteroids, azathioprine, cyclophosphamide, chlorambucil, cyclosporine, mycophenolate) may be tried. Corticosteroid administration actually can cause proteinuria in dogs, and one retrospective study suggested that corticosteroid therapy may be detrimental in dogs with glomerulonephritis. Corticosteroids may be beneficial (or at least not detrimental) in cats with glomerulonephritis. Azathioprine (2.2 mg/kg PO q24h) may be tried for immunosuppression in dogs (but not cats) with idiopathic glomerulonephritis. Azathioprine should not be used in cats because they metabolize the drug very slowly and develop bone marrow suppression and severe leukopenia when given dosages similar to those used in dogs. Demonstration of treatment effectiveness is confounded by the variable biological behavior of the disease (e.g., some spontaneously resolve, some have stable proteinuria for long periods of time, and some progress to endstage renal failure).

In dogs, an aspirin dosage of 0.5-1.0 mg/kg PO once a day may selectively inhibit platelet cyclooxygenase without preventing the beneficial effects of prostacyclin formation (e.g. vasodilatation, inhibition of platelet aggregation) and may decrease the risk of thromboembolism. Omega-3 polyunsaturated fatty acids (ω-3 PUFA) (e.g. fish oil) may suppress glomerular inflammation and coagulation by interfering with production of pro-inflammatory prostanoids.

No specific therapy has been shown to be beneficial in treatment of amyloidosis. Dimethylsulfoxide (DMSO) may decrease the concentration of the acute phase reactant serum amyloid A protein (SAA) and may improve renal function by reduction of interstitial inflammation and fibrosis in the kidney. One case report in a dog with amyloidosis showed a beneficial effect (e.g. less proteinuria, improved glomerular filtration rate) of DMSO when used at a dosage of 90 mg/kg/wk administered subcutaneously. Another study of several affected dogs showed no effect of DMSO (i.e. dogs had similar amounts of amyloid in their kidneys at necropsy as in renal biopsies taken before instituting DMSO treatment). Colchicine impairs the release of SAA from hepatocytes by binding to microtubules and preventing its secretion. Colchcicine (0.03 mg/kg/day) may be beneficial in Shar Pei dogs with recurrent fever and joint swelling (so-called "Shar pei fever") that may be at risk for development of systemic amyloidosis, but no prospective placebo-controlled study is available to support this treatment.

Prognosis

Amyloidosis is a progressive disease with a poor prognosis. Affected animals often are in renal failure at the time of presentation and generally live less than 1 year after diagnosis. Glomerulonephritis has a variable course and a poor prognosis should not be given unless there is evidence of progression to chronic renal failure. The following may outcomes may occur in dogs and cats with glomerulonephritis: spontaneous remission, stable course with ongoing proteinuria for several months to years, or progression to chronic renal failure over months to years.

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