Glomerulonephritis in Dogs and Cats: Glomerular Function, Pathophysiology, and Clinical Signs

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ABSTRACT: Glomerulonephritis (GN) is a pathologic process associated with a multitude of primary diseases. In almost an equal number of cases, a significant concurrent illness cannot be found and GN is classified as idiopathic. Whatever the underlying cause, immune complexes form and initiate a series of events leading to glomerular injury. This leads to loss of normal function, resultant proteinuria, and potentially renal failure. Clinical signs often relate to the underlying disease, complications of hypoproteinemia, and uremia from renal failure.

Glomerulonephritis (GN) is a common cause of proteinuria in dogs and cats. The condition can be idiopathic or occur secondary to infectious agents, neoplasia, inflammatory diseases, endocrine diseases, and familial nephropathies. In most cases, glomerular injury is the result of a cascade of pathologic events that occur secondary to immune complexes formed or trapped in glomeruli. This injury disrupts the glomerular filter and its permselectivity, allowing proteins to be lost in urine.

GLOMERULAR ANATOMY AND FUNCTION

The functional unit of the kidney is the nephron, which consists of a glomerulus, Bowman’s capsule (a two-layered cellular envelope enclosing the tuft of capillaries that constitute the glomerulus of the kidney), and a renal tubule (Figure 1). Each glomerulus is supplied by an afferent arteriole, which connects with an efferent arteriole via a highly branched capillary system called the glomerular tuft.

Endothelial cells line the glomerular capillary lumen and contain fenestrae or pores. The glomerular basement membrane (GBM) surrounds the capillaries and may serve as the most important glomerular filter. The GBM and endothel-
lial cells have negatively charged sites that repel anions. Additionally, the GBM is believed to prevent passage of high-molecular-weight, noncharged molecules.

Mesangial cells support the GBM; these phagocytic cells are believed to remove filtration residues between the GBM and endothelial cells. The mesangial matrix surrounds the mesangial cells and appears to increase in volume in certain forms of GN.

The visceral epithelium lines the urinary or Bowman’s space and reflects back on itself to form the parietal epithelium, which is continuous with the proximal tubule. The epithelium consists of podocytes with numerous foot processes.

Spaces between foot processes, called slit pores, likely serve as yet another filter. They too are coated with negatively charged sialoproteins, which may also limit passage of smaller-molecular-weight nonionized particles.

Glomeruli prevent passage of molecules greater than 70,000 D and those with a net negative charge. Albumin is one of the major proteins lost in GN; it is approximately 65,000 D (small enough to pass through the filtration barriers), yet its passage is precluded to a large degree by normal glomeruli because of its net negative charge. This function of filtration, based on molecular size, charge, and shape, is referred to as permselectivity and is the basis of glomerular function. From Bowman’s space, filtrate continues on to the proximal tubule where proteins that escape the glomerular barrier are reabsorbed. A small amount of protein may remain in the urine of normal dogs.1

PATHOPHYSIOLOGY

Glomerular injury caused by GN in dogs and cats is immunologically mediated. In humans, dogs, and cats, the presence of immunoglobulins and complement factors bound to glomerular structures has been demonstrated.2–8 There are two mechanisms by which this immunologic damage is initiated:

- Preformed circulating antigen–antibody complexes are deposited or are trapped within glomeruli.
- Antigen is trapped in the glomerular capillary wall, and circulating antibodies form complexes with them.

Formation of anti-GBM antibodies in naturally occurring GN has not been proven in dogs or cats.

The injurious processes that result from immune complexes seem to be dependent on their intraglomerular location. Much of what is known about the pathophysiology is based on in vitro studies, but some general mechanisms are noteworthy. Once immune complexes have formed, there is a complex combination of complement activation, neutrophil and macrophage infiltration, platelet aggregation, activation of the coagulation cascade, and fibrin deposition. Neutrophils, macrophages, and mesangial cells produce oxidants and proteinases in response to immunoglobulins. Platelet activation and aggregation result in eicosanoid (thromboxane and leukotriene) formation and coagulation. Thromboxanes interfere with immune complex disposal, are chemotactic for neutrophils, and may decrease glomerular filtration rate through vasoconstriction and mesangial cell contraction.9 Increased urinary thromboxane excretion has been associated with GN and impaired immune complex clearance in animals.5,6,10–12 Nitric oxide is released by many cells during glomerular inflammation and can induce cytotoxicity. Platelets, as well as neutrophils, macrophages, endothelial cells, and mesangial cells, can release platelet-activating factor, which can neutralize negative charges in the glomerular capillary walls and enhance albuminuria.13 Platelet-activating factor and eicosanoids are chemotactants for neutrophils and macrophages, perpetuating a cycle of inflammatory mediator release.13 These injurious mediators cause morphologic changes within glomeruli. Mesangial cell and matrix proliferation and GBM thickening can occur, and with continued injury, glomerulosclerosis may develop. Eventually, irreversible damage to the glomerulus leads to a nonfunctional nephron.

HISTOLOGIC CLASSIFICATION

From a diagnostic standpoint, differentiation of idio-
pathic versus secondary GN is important because treatment hinges on eliminating the underlying disease in the latter. In humans, information gained from histopathologic, electron microscopic, and immunofluorescence studies allows for classification of GN. Immunofluorescence and electron microscopic findings have been described in veterinary patients, but widely accepted criteria for their categorization and hence clinical utility are lacking. It is hoped that an increase in the frequency with which they are performed in clinical cases will lead to greater utility.

In veterinary medicine, the condition is commonly categorized based on histopathologic descriptions (although there is disagreement in the literature as to the exact characteristics of each form9,14):

- **Membranous GN** (Figure 2) is characterized by a thickened GBM.
- **Proliferative (mesangio proliferative) GN** is characterized by glomerular hypercellularity with accumulation of mesangial matrix.
- **Membranoproliferative GN** (Figure 3) is a combination of hypercellularity and increased thickness of the GBM.
- **Glomerulosclerosis** is an increase in matrix and glomerular scarring.9
- **Minimal change disease** is characterized by normal to mild increases in mesangial cell proliferation, abnormalities of podocyte foot processes, and a lack of immunoglobulin deposition on immunofluorescence.14 Electron microscopy is required to confirm the diagnosis.

Glomerulosclerosis and minimal change disease are recognized less often in veterinary patients than in humans.14 The most frequently reported histologic form in dogs is variable, but most reported cases in cats are membranous GN,9,14,15

**DIAGNOSTIC DIFFERENTIALS**

For clinical purposes, GN is considered to be an idiopathic or secondary disease. In **idiopathic GN**, only the kidneys have evidence of pathologic involvement and no concurrent disease can be found. If a concurrent disease exists to which GN can be attributed, it is referred to as **secondary GN**. Significant associations have been found in 57% to 88% of dogs with GN (Table 1).2,16,17 Diseases that have been reported to be associated with GN include the following:

- One of the most frequent causes of secondary GN is **neoplasia**, which accounts for 17% to 40% of cases in various reports.2,16–19
- **Infectious diseases** may also be associated with GN (Table 1).7,20–26
  - **Heartworm disease** has been well documented experimentally as a cause of GN, and some naturally infected dogs have concurrent GN.2,16,27,28
  - Experimentally, **ehrlichiosis** causes transient proteinuria and mild glomerular changes during the acute phase, with proteinuria resolving over time.29
  - **Lyme disease** has been reported to cause a rapidly progressive form of GN in dogs.30
- **Glomerulonephritis** occurs in dogs with experimentally induced **diabetes mellitus** (DM), but evidence of GN occurring in dogs or cats with spontaneous DM is lacking.31
Spontaneous and iatrogenic hyperadrenocorticism are associated with GN in dogs.²,¹⁶,³²

Several breeds have been reported to have familial or genetically based forms of GN; the age of onset is variable but is generally within the first few years of life.²,¹⁶,³³–³⁷ In Doberman pinschers, sulfadiazine can cause a protein-losing nephropathy consistent with GN.³⁸

**SIGNALMENT**

Both dogs and cats are affected with GN, but it is recognized much more frequently in dogs. Most dogs with GN are older than 7 years.⁷,¹⁶,¹⁷,³⁹ In those breeds affected by familial GN, the age of onset can be much younger. There is no gender predisposition in dogs.

Cats with GN tend to be younger than dogs with the disease, averaging 3 to 4 years of age. Male cats appear to be affected more often (64% to 100%), but there has been no explanation for this finding.³,¹⁵,⁴⁰

**CLINICAL SIGNS**

In a recent retrospective study of 137 dogs with protein-losing glomerular disease, the most common clinical signs of GN and amyloidosis were anorexia, weight loss, and vomiting.¹⁶ It is likely in many cases that these signs relate to uremia as GN is believed to be a common cause of canine chronic renal disease.⁷ Renal failure was also noted frequently in cats with membranous GN.³,¹⁵,⁴⁰

Progressive, irreversible damage to the glomerulus renders the entire nephron nonfunctional. Polyuria/polydipsia and azotemia ensue when 66% and 75% of nephrons, respectively, become permanently nonfunctional. Patients with GN may demonstrate normal urine concentrating ability with concurrent azotemia. Assum-

**TABLE 1**

<table>
<thead>
<tr>
<th>Factors Associated with Glomerulonephritis</th>
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<tbody>
<tr>
<td><strong>Cats</strong></td>
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<tr>
<td>Infectious</td>
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<tr>
<td>Feline infectious peritonitis</td>
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<tr>
<td>Feline leukemia virus infection</td>
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<tr>
<td>Lymphoma</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Polyarthritis</td>
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<tr>
<td>Diabetes mellitus?</td>
</tr>
<tr>
<td>None</td>
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<tr>
<td><strong>Dogs</strong></td>
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<tr>
<td>Heartworm disease</td>
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<tr>
<td>Leishmaniasis</td>
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<tr>
<td>Lyme disease</td>
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<tr>
<td>Bacterial endocarditis</td>
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<tr>
<td>Pyometra</td>
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<tr>
<td>Ehrlichiosis</td>
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<tr>
<td>Canine adenovirus-2 infection</td>
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<tr>
<td>Chronic pyoderma</td>
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<tr>
<td>Lymphocytic leukemia</td>
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<tr>
<td>Transitional cell carcinoma</td>
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<tr>
<td>Lymphoma</td>
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<tr>
<td>Bronchogenic adenocarcinoma</td>
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<td>Doberman pinscher</td>
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<td>Bernese mountain dog</td>
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<tr>
<td>Beagle</td>
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<td>Soft-coated wheaten terrier</td>
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<td>Samoyed</td>
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<tr>
<td>Standard poodle</td>
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<tr>
<td>Golden retriever</td>
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<tr>
<td>Cocker spaniel</td>
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<tr>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Polyarthritis</td>
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<tr>
<td>Immune-mediated hemolytic anemia</td>
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<tr>
<td>Prostatitis</td>
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<tr>
<td>Chronic pancreatitis</td>
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<tr>
<td>Hyperadrenocorticism</td>
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<tr>
<td>Diabetes mellitus?</td>
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<tr>
<td>Corticosteroids?</td>
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<tr>
<td>Sulfadiazine</td>
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ing the patient does not have prerenal or postrenal azotemia, this can be explained by glomerulotubular imbalance in which the glomerular filtration rate decreases to a level of excretory failure (i.e., azotemia) before the loss of tubular function. Chronic renal failure seems to worsen the prognosis for survival for both dogs and cats with GN.

Peripheral edema or ascites, often thought to be common with protein-losing nephropathies, were found in only 3.7% of dogs with GN. In another retrospective report of dogs with GN, nephrotic syndrome (Figure 4) was appropriately defined as concurrent proteinuria, hypoproteinemia, hypercholesterolemia, and edema or ascites. Using these criteria, only 15% of 41 cases had nephrotic syndrome. Conversely, peripheral edema, ascites, and nephrotic syndrome are reported with a high prevalence in cats (62% to 75%); however, the criteria used for nephrotic syndrome were not well defined.

COMPLICATIONS

Hypertension, characterized by systolic pressures exceeding 160 mm Hg, is noted in many dogs (61%) with GN. Retinal hemorrhage or detachment may be seen as a sequela. Systolic blood pressure measurement is a simple procedure and should be done in all dogs and cats with GN. Systolic blood pressure in excess of 170 mm Hg on repeated measurements in dogs and cats is considered abnormal, and treatment should be considered, especially if the patient has clinical signs of hypertension. Patients with systolic pressures in excess of 200 mm Hg should be treated for hypertension.

Thromboembolic disease occurs in association with GN in dogs and cats. Aortic, pulmonary, mesenteric, and coronary arterial thrombi have been documented in dogs with protein-losing glomerular disease; a pulmonary arterial thrombus has been found in a cat with membranous GN. Antithrombin III is an important inhibitor of the coagulation cascade, and its deficiency (due to glomerular loss in the urine) is the most commonly proposed explanation for thromboembolic disease in patients with GN. Antithrombin III activity can be measured and may be low in protein-losing nephropathies; in one report, dogs with serum albumin concentrations less than 1.8 g/dl always had subnormal antithrombin III activity. Acute tachypnea and hindlimb weakness may be seen as a result of thromboemboli.

REFERENCES


Figure 4A

Figure 4A—Dog with nephrotic syndrome. (A) Pitting edema is present after digital pressure is applied to an edematous leg. (B) Clear abdominal fluid from the same patient. This was classified as a transudate.

Figure 4B

Figure 4B—Dog with nephrotic syndrome. (A) Pitting edema is present after digital pressure is applied to an edematous leg. (B) Clear abdominal fluid from the same patient. This was classified as a transudate.


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1. Dogs with GN tend to be ________ years of age.
   a. younger than 3  c. 4 to 7
   b. 3 to 4  d. older than 7

2. Cats with GN tend to be ________ years of age.
   a. younger than 3  c. 4 to 7
   b. 3 to 4  d. older than 7

3. ________ cats are most commonly affected with GN.
   a. Female  c. Male
   b. Siamese  d. Persian

4. Familial glomerulopathies have been reported in all of the following breeds except the
   a. corgi.  c. Doberman pinscher.
   b. cocker spaniel.  d. Bernese mountain dog.

5. Nephrotic syndrome is characterized by which combination of signs?
   a. hypoproteinemia, ascites and/or edema, hypernatremia, hypercholesterolemia
   b. hypoproteinemia, ascites and/or edema, azotemia, hypernatremia
   c. hypoproteinemia, azotemia, hypercholesterolemia, proteinuria
   d. hypoproteinemia, hypercholesterolemia, ascites and/or edema, proteinuria

6. The most common histologic form of GN seen in cats is
   a. mesangio proliferative.
   b. membranoproliferative.
c. membranous.
d. minimal change disease.

7. Secondary GN in dogs and/or cats has been documented in association with all of the following conditions except
   a. dirofilariasis.
   b. feline infectious peritonitis.
   c. lymphoma.
   d. hypothyroidism.

8. Potential complications of GN include all of the following except
   a. chronic renal failure.
   b. hypertension.
   c. diabetes mellitus.
   d. thromboembolic disease.

9. The most commonly accepted pathophysiologic cause of GN in dogs and cats is
   a. immune complex disease.
   b. apoptosis.
   c. hyperfiltration secondary to hypertension.
   d. toxins.

10. Systolic blood pressure should be measured in all patients with suspected GN, and hypertension should be treated if the systolic pressure exceeds ______ mm Hg.
    a. 200
    b. 140
    c. 120
    d. 80