Protein losing nephropathy (Proceedings)

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Proteinuria

Proteinuria can be pre-glomerular, glomerular, or post-glomerular in origin. Pathologic proteinuria is a persistent problem from glomerular damage, whereas functional proteinuria is generally transient. Infection or inflammation (including neoplasia) of the lower urinary tract can induce significant proteinuria, and urinary protein should always be evaluated in light of the urinary sediment and culture results and the clinical signs present. Non-glomerular renal diseases, such as pyelonephritis, severe chronic renal failure, or acute tubular necrosis may also cause proteinuria. Excessive protein delivery to the kidney ("pre-glomerular proteinuria") may lead to proteinuria, in conditions such as hemoglobinuria or multiple myeloma. Transient damage to the glomerulus from fever or heatstroke may cause transient proteinuria, but exercise does not appear to cause proteinuria in dogs as it does in people. The interval to determine whether proteinuria is persistent is not firmly established, but rechecking a month later seems clinically reasonable.

There are 4 tests in widespread use for detecting proteinuria. The urine dipstick is a semi-quantitative test that is a good screening test, but has many false positive results. Highly concentrated urine, alkaline urine, and feline urine are more likely to have false positive results. Any positive dipstick result should be confirmed with sulfosalicylic acid (SSA) turbidometric testing, which is a highly specific test.

Microalbuminuria tests for both dogs and cats are available. Microalbuminuria is defined as small amounts of albumin in the urine (1-30 mg/dl), a level that would not be detected by standard testing such as the urine dipstick or SSA test. The lower limit of the urine dipstick is urinary albumin 30 mg/dL. Detection of persistent or progressive microalbuminuria should prompt a careful search for infectious, inflammatory, metabolic, or neoplastic conditions that are causing secondary renal damage.

Microalbuminuria testing is not necessary for animals with overt proteinuria. Microalbuminuria can be used as an early screening test in apparently healthy animals with a predisposition to

renal disease, such as age, breed-associated predisposition to glomerular disease, or diseases associated with glomerular damage. A low positive test that is stable should be monitored; a high positive test or progressive increase in the level of microalbuminuria should prompt action (i.e., intensified diagnostic testing).

Quantification of the amount of protein using a protein:creatinine ratio (UPC) is warranted with a positive screening test, unless an obvious cause of proteinuria is present (i.e., hematuria, active urine sediment, positive culture). In healthy dogs, the UPC is less than 0.5. Values over 1 are considered abnormal. Values between 0.5 and 1 are questionable, and should be monitored for persistence or worsening. In cats with chronic kidney disease, a UPC over 0.4 is associated with shorter survival. In dogs, one UPC measurement is adequate to reliably estimate UPC when < 4. When monitoring changes in UPC over time, a change of 80% is needed to demonstrate a significant difference when the UPC is around 0.5, but only a 30% change is needed when the UPC is higher (around 12).

A consensus statement (Lees G, et al. JVIM 2005;19(3):377-385) recommends monitoring, investigating, or intervening depending on the level of proteinuria and the presence or absence of azotemia. In nonazotemic dogs and cats, microalbuminuria or a UPC > 0.5 prompts monitoring, a UPC > 1 prompts investigation, and a UPC > 2 prompts intervention. In azotemic dogs, intervention is recommended at a UPC > 0.5, whereas intervention is recommended at a UPC > 0.4 in azotemic cats.

Protein-losing Nephropathy

Protein losing nephropathies (PLN) include glomerulonephritis (GN), glomerulopathy, and amyloidosis. The normal glomerulus acts as a sieve to allow free filtration of small molecules, like urea, creatinine, sodium, water, etc. but restricts passage of larger or negatively charged molecules. Molecules the size of albumin or larger do not pass through the glomerulus unless damage has widened the pores or disrupted the charged surface. In glomerulonephritis, this damage is due to antigen-antibody complexes that "clog" the pores and activate complement, causing an inflammatory reaction. Platelet activation further exacerbates the damage to the glomerular capillary. Familial glomerulopathy is an inherited condition with abnormal glomerular collagen deposition leading to proteinuria and progressive renal failure. In amyloidosis, abnormal amyloid protein is deposited in the glomerulus. PLN may be fairly common in dogs, with cats having a lower incidence.

Diseases associated with glomerulonephritis in the dog include infectious diseases (heartworm disease, Ehrlichiosis, Lyme disease, Rocky Mountain Spotted Fever [RMSF], pyometra, chronic

bacterial infections, bacterial endocarditis, septicemia, Brucellosis, Leishmaniasis, Trypanosoma, and infectious canine hepatitis), neoplasia, inflammatory diseases (pancreatitis, systemic lupus erythematosus [SLE], polyarthritis, chronic skin disease, and prostatitis), and other conditions (Cushing's disease, diabetes mellitus). In cats, GN can be associated with feline leukemia virus, feline infectious peritonitis, mycoplasmal polyarthritis, neoplasia, pancreatitis, SLE, other immune diseases, and diabetes mellitus. In many cases, an underlying cause cannot be discovered, and these are classified as idiopathic. Amyloidosis can be a familial disorder in Shar Pei dogs and Abbysinian cats, and it can also occur in conjunction with chronic antigenic stimulation (i.e. chronic pyoderma, neoplasia). Breeds with a high incidence of familial glomerulopathy include Soft-coated Wheaton Terriers and English cocker spaniels. Familial PLN has been reported in many other breeds.

Dogs with PLN may initially be asymptomatic. Early signs of disease include weight loss or lethargy. With severe proteinuria, hypoalbuminemia may lead to ascites or peripheral edema, but this is not a common initial sign. Renal failure (i.e. azotemia with isothenuria) is NOT necessary to diagnose PLN. In fact, early recognition of PLN allows intervention to delay the onset of renal failure. Many veterinary patients are presented only when signs of renal failure or uremia become apparent. These signs may include polyuria/polydipsia, anorexia, nausea, and vomiting. Signs of the underlying disease may also be present.

Diagnosis

Diagnosis of PLN involves documenting significant proteinuria. Low amounts (trace to 1+) of protein may be normal in well-concentrated urine (> 1.035 specific gravity), but this level of proteinuria in dilute urine may be significant. An active urine sediment or positive urine culture may indicate lower urinary tract disease, and proteinuria should be re-evaluated after appropriate therapy. Renal proteinuria can be caused by conditions other than PLN, including hemoglobinuria, myoglobinuria, Bence-Jones proteinuria with multiple myeloma, fever, stress, renal congestion, and extreme environmental temperatures. The urine protein:creatinine ratio (UPC) is a good predictor of 24-hour urine protein excretion and is much easier to obtain. A UPC of > 1.0 is abnormal.

After diagnosing PLN, standard tests to uncover any potentially treatable cause include complete blood count, serum chemistry panel, urinalysis, urine culture, titers for common tick borne diseases (Borrelia, Ehrlichia canis, RMSF) and heartworm testing in dogs, feline leukemia virus testing in cats, thoracic radiographs to screen for neoplasia, and usually abdominal imaging (radiograph or ultrasound). Other tests would be dependent on individual case

characteristics.

Renal Biopsy

Renal biopsies can be obtained by a percutaneous needle biopsy ("Tru-Cut") with ultrasound guidance, by keyhole or open laparotomy, or laparoscopy. Renal biopsy should not be performed unless results of a coagulation profile and/or bleeding time are normal. Renal biopsy samples should be preserved in formalin for light microscopy, and another sample preserved in a medium appropriate for immunofluorescent (freezing or Michel's medium) or immunohistochemical staining, and potentially for electron microscopy (formalin with gluteraldehyde). Special biopsy processing of the light microscopy portion is recommended (i.e., evaluating thin sections, special stains including H&E, PAS, trichrome, and Congo red if amyloid is suspected). Immunofluorescent or immunohistochemical staining for IgA, IgG, IgM, and complement (C3) is recommended for all biopsies. Electron microscopy is generally reserved for questionable cases. If moderate to severe renal failure is already present, the results of the biopsy are unlikely to alter treatment or the course of the disease.

In people, the histopathologic type of GN is used to determine appropriate therapy and is correlated to outcome. In veterinary medicine, we have been limited by lumping all GN into a single category; more attention to specific classification may improve our ability to effectively treat and render an accurate prognosis. Membranoproliferative glomerulonephritis (MPGN) is probably the most common type of canine GN and is characterized by thickened capillary loops and mesangial hypercellularity. MPGN Type I, also called mesangiocapillary GN, is caused by infectious diseases. MPGN Type II is uncommon in dogs. A rapidly progressive form of MPGN with tubular necrosis and interstitial inflammation tentatively associated with *Borrelia burgdorferi* infection in dogs has been recognized.

Membranous nephropathy is the second most common GN in dogs and the most common in cats and affects males more than females. It is generally an idiopathic disease. The basement membrane becomes thickened with immune complex deposits. Immunosuppressive therapy may be warranted with this type of GN. Progression may be slower, and spontaneous remission has been reported.

Proliferative glomerulonephritis encompasses several types of GN in humans (anti-GBM disease, postinfectious GN, IgA nephropathy) that are poorly characterized in dogs. Histologically, there is mesangial cell proliferation. Antibodies directed against the glomerular basement membrane (anti-GBM disease) has not been described in dogs or cats. IgA nephropathy in people occurs in young adult males and is characterized by intermittent micro-

or macroscopic hematuria. Many dogs are positive for IgA on immunofluorescence, but this may reflect the polymeric nature of IgA and nonspecific binding in dogs.

Hereditary Nephritis includes a variety of inherited glomerular defects of the basement membrane collagen type IV. Light microscopic changes include membranoproliferative or sclerosing GN, but electron microscopy is necessary to make a definitive diagnosis.

Minimal change disease is characterized by the absence of lesions on light microscopy; electron microscopy is necessary. Because there is only one well-described case report of minimal change disease in a dog, prognosis cannot be predicted, but this disease is steroid-responsive in humans.

Glomerulosclerosis is an end-stage lesion in response to any glomerular injury. Focal segmental glomerulosclerosis is common in people and is likely underdiagnosed in dogs.

Amyloidosis is characterized by acellular material in the glomerulus. When stained with Congo red, these deposits are red with conventional light microscopy and a birefringent apple green when viewed with polarized light.

Complications

Between 50 to 85% of dogs with PLN have hypertension. Hypercoagulability is also a common finding. Urinary loss of the natural anticoagulant antithrombin III and platelet hyper-responsiveness contribute to thromboembolus formation. Thromboemboli most commonly lodge in the pulmonary vasculature, causing acute onset dyspnea with minimal radiographic changes.

Therapy

Protein restriction decreases the amount of proteinuria and the protein trafficking in the renal tubules. A renal diet, containing a restricted quantity of high quality protein should be prescribed.

Perhaps the single most beneficial therapy for PLN is angiotensin converting enzyme (ACE) inhibition. ACE inhibitors have been proven to decrease proteinuria and delay onset of renal failure in dogs. Enalapril (0.25-0.5 mg/kg PO q 12-24 hrs) is a commonly used drug; benazepril is showing promise. Because ACE inhibitors can decrease renal blood flow, reevaluation of a chemistry panel for worsening azotemia 1 week after starting therapy or dose adjustment is advised. These drugs can be used in normotensive patients as well as hypertensive patients, although blood pressure should be monitored.

Aspirin at a dose of 0.5 mg/kg q 12-24 hours will inhibit platelet aggregation while decreasing the risk of side effects seen at standard doses. It has a wider safety margin than anticoagulants such as coumadin, which require meticulous monitoring to avoid serious hemorrhagic events. It is used to decrease the risk of thromboembolic complications, and because platelet aggregation and fibrin deposition in the glomerulus may contribute to the pathogenesis of PLN.

In people, response to various immunosuppressive protocols varies with specific type of GN. There is no evidence of efficacy in dogs or cats, and these drugs should be used with caution and based on results of renal biopsy. Corticosteroids are associated with proteinuria and are not recommended in dogs unless underlying disease is steroid-responsive (i.e., systemic lupus erythematosus). Corticosteroids may be helpful in cats. Cyclosporine was not beneficial in controlled study of dogs with GN. Other immunosuppressive drugs, such as azathioprine (2 mg/kg PO q 24-48 hours in dogs only) or cyclophosphamide (50 mg/m2 PO q 24 hours for 3 to 4 days, then off for 3 to 4 days) may be used but their benefit has not been proven. Mycophenolate mofetil (CellCept), a relatively new immunosuppressive agent used for human transplant recipients, is showing some promise in treating certain types of GN in people, most notably, lupus nephritis. No data is available for dogs with GN.

There is no effective treatment for established amyloidosis. Colchicine (0.01-0.03 mg/kg PO q 24 hours) given during febrile episodes in Shar Peis may decrease amyloid deposition. There is no evidence of effectiveness once renal failure has occurred. The primary side effect is gastrointestinal upset. Dimethylsulfoxide (DMSO, 90 mg/kg orally or SQ 3 times a week) has questionable benefit. Anorexia, nausea, and unpleasant odor are side effects.

Many drugs are available to help control hypertension. In the setting of PLN, ACE inhibitors make a logical first choice, because of their combined antihypertensive and antiproteinuric effects. If blood pressure is not adequately controlled by ACE inhibitors or dose escalation is contraindicated, other agents can be added. Angiotensin receptor blockers (i.e., losartan, candesartan) are commonly used in conjunction with ACEi in people, but experience in veterinary medicine is limited. In people, hypotension is a limiting side effect. Because diuretics commonly cause volume depletion and hypokalemia, they are not routinely used, although spironolactone, an aldosterone antagonist diuretic, is used by some clinicians. Short term use until peripheral edema is controlled can be considered.

Once renal failure has developed, most standard therapies for renal failure are appropriate, with a few caveats about fluid therapy. In the hospitalized patient, substituting a colloidal fluid (Hetastarch, Dextran) for all or part of the crystalloid fluid (saline, lactated ringers solution) may decrease development of peripheral edema. Subcutaneously administered fluids may not be

absorbed well in the presence of hypoalbuminemia.

Prognosis

The outcome of PLN has previously been considered poor, with a median survival time of 1 month. In cases with moderate to severe renal failure, this likely still holds true. Resolution of PLN is possible is the underlying condition can be treated, but this is uncommon. With the advent of ACE inhibition, survival in dogs with PLN without renal failure has been extended, and survival times over 1 to 2 years is not uncommon in my clinical practice.