Progression of Glomerulonephritis to End-Stage Kidney Disease in a Cat with Nephrotic Syndrome

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(Received 28 May 2010/Accepted 20 August 2010/Published online in J-STAGE 3 September 2010)

ABSTRACT. A percutaneous renal biopsy was performed on a 3-year-old female Japanese domestic cat with pleural effusion, mild azotemia, hypoalbuminemia, hypercholesterolemia, and proteinuria. Glomerular lesions included mild diffuse hypercellularity and numerous capsular adhesions with characteristic outer protrusion of glomerular basement membrane. Diffuse and global granular deposits of IgG and C3 were detected along the capillary walls. Tubulo-interstitial changes were mild at the time of biopsy, but progression of the disease was predicted because of the many capsular adhesions of the glomerular tufts. The cat was fed a prescription diet without any other specific or symptomatic therapy after renal biopsy, and died 43 weeks after the biopsy. At necropsy, extensive tubulo-interstitial fibrosis and mononuclear cell infiltration had developed throughout the cortex and outer medulla, and most glomeruli had extensive global sclerosis or obsolescence with less prominent depositions of IgG and C3.

KEY WORDS: chronic renal failure, feline, glomerulonephritis, nephrotic syndrome, renal biopsy.

Glomerulonephritis is a common renal disease in dogs and cats and a major cause of chronic renal failure [5]. Urinalysis and blood biochemical examinations are useful in monitoring the disease, but definitive diagnosis and classification of glomerulonephritis is not possible without histologic examination. The World Health Organization (WHO) classification for human glomerular diseases [1] cannot be applied to veterinary species unless clinical parameters are correlated with pathologic findings through the progression of the disease. We report a case of protein-losing glomerulopathy in a cat, in which glomerular, tubular and interstitial lesions progressed considerably over the course of the disease.

A 3-year-old female Japanese domestic cat was presented with mild dyspnea and anorexia. Pleural effusion was evident radiographically, and 100 ml of transparent fluid was removed by thoracocentesis. Serum chemistry indicated mild azotemia, hyperproteinemia, hypoalbuminemia, and hypercholesterolemia with the following abnormal results (laboratory reference range in parentheses): blood urea nitrogen (BUN), 35.4 mg/dl (10–30 mg/dl); creatinine, 1.9 mg/dl (0.8–2.0 mg/dl); total protein, 3.8 g/dl (5.5–7.9 g/dl); albumen, 1.3 g/dl (2.1–3.4 g/dl); and cholesterol, 206 mg/dl (90–200 mg/dl) [8]. Urinalysis by reagent strips indicated proteinuria (4+) Blood was negative for feline leukemia virus antigen and feline immunodeficiency virus antibody by ELISA (SNAP® FIV/FeLV Combo Test, IDEXX Laboratories Inc., Westbrook, ME, U.S.A.). No antibody against feline coronavirus was detected by ELISA in a reference laboratory (IDEXX Laboratories Inc., Tokyo, Japan).

A percutaneous renal biopsy specimen, performed to confirm the presumptive diagnosis of glomerulopathy, was fixed in 10% formalin. Paraffin-embedded sections were stained with HE and periodic acid-Schiff (PAS). Immunohistochemistry to detect C3 or IgG was performed on paraffin sections by the streptavidin-biotin peroxidase method (Histofine Kit, Nichirei Corp., Tokyo, Japan) using primary antibodies against cat IgG (Kirkegaard & Perry Laboratories, Inc., Gaithersburg, MD) or cat C3 (Biogenesis, Poole, UK). The chromogen was diaminobenzidine. Sections were counterstained with hematoxylin.

One biopsy specimen containing more than 10 glomeruli was evaluated. All glomeruli had mild hypercellularity, at least partially attributed to mesangial hyperplasia. Glomerular tufts were adhered multifocally to Bowman’s capsule indicating previous damage with desquamation of glomerular epithelial cells (Fig. 1). Focal glomerulosclerosis or hyalinosis was noted at many adhesion sites. Thickening of the glomerular basement membrane (GBM) was not prominent in the PAS-stained sections. Patchy hypertrophy and hyperplasia of the parietal epithelial cells were also noted in the glomeruli. Interstitial mononuclear cell infiltration was minimal, and interstitial fibrosis was not recognized in the biopsy specimen. By immunohistochemistry, diffuse and global granular deposition of feline IgG and C3 was detected along the capillary walls (Fig. 2). An epon-embedded block for electron microscopic examination was made from the paraffin-embedded tissue. With transmission electron microscopy, many electron-dense deposits were in the...
subepithelial regions of glomerular capillary walls (Fig. 3). Thickening of the GBM was obvious but mild; many small projections between the subepithelial dense deposits protruded from the GBM. Loss or fusion of foot processes of the glomerular epithelial cells was evident.

The cat had been fed a prescription diet (Feline k/d® cat food, Hill’s-Colgate Japan, Tokyo) for renal disease but no other specific or symptomatic therapy was provided. Proteinuria was persistent during the first 4 months after the renal biopsy, but was not evaluated afterward. The azotemia progressively increased in severity until the cat’s death 43 weeks after the biopsy (Fig. 4).

At necropsy, both kidneys were firm with a fine granular surface. Histologically, renal lesions were more severe than at the time of the initial biopsy (Fig. 5). Most glomeruli had global sclerosis or obsolescence, but approximately 2% of the 270 glomeruli evaluated had only minimal to mild sclerosis, but diffuse and global GBM thickening and moth-eaten appearance in PAS-stained sections (Fig. 5). With Masson’s trichrome stain, orange to red deposits were scattered along capillary walls in nonsclerotic glomeruli. No
amyloid deposition was detected with Congo red stain. Deposition of IgG and C3 was less prominent than in the original biopsy specimen. With electron microscopy, accumulation of basement membrane-like matrix and capillary collapse were observed in the sclerotic or obsolescent glomeruli. Renal tubules were atrophied; tubular and vascular walls through the cortex and outer medulla were mineralized; the renal interstitium was expanded by fibrosis and mononuclear cell infiltration. These renal changes were consistent with sclerosing glomerulonephritis with progression to end-stage kidney. The main extra-renal lesions included cutaneous and pulmonary edema; mild hypertrophy and hyperplasia of the parathyroid glands; and calcification of the large arteries, lung, and gastric mucosa, consistent with renal secondary hyperparathyroidism.

Histologically, the lesion in the renal biopsy specimen could be classified as membranous nephropathy because there were prominent granular IgG and C3 deposits in the glomeruli and many subepithelial electron-dense deposits with protrusion of GBM around them as described in human [1] as well as feline cases [8, 12]. Segmental capsular adhesion was associated with glomerulosclerosis in this case, but was not consistent with focal segmental glomerulosclerosis according to the criteria for classification of human glomerular diseases [1]. Segmental sclerosis and capsular adhesion can develop in membranous glomerulonephropathy, especially in the advanced stage in cats [8, 12]. However, marked thickening of GBM suggestive of advanced membranous glomerulopathy was not seen in the original biopsy specimen from this case. Ultrastructural changes of GBM in the biopsy specimen resembled those of stage I membranous nephropathy based on WHO classification of human diseases [1]. However, in previous studies, sequential ultrastructural staging (I–IV) of the development of electron-dense GBM deposits, as done in human membranous glomerulopathy, was unrewarding for the disease in dogs and cats [8, 12].

The glomerulopathy in this cat progressed from nephrotic syndrome at the time of renal biopsy to end-stage chronic renal failure in 43 weeks. In human medicine, the classification of glomerular disease reflects the clinical and histopathological characteristics of each category [1]. In cats, only membranous glomerulopathy has been well studied; the morphologic characteristics have prognostic value [7, 8, 12]. In the present case, despite the mildness of GBM lesions, the prognosis was poor because of many irreversible glomerular changes such as capsular adhesions, focal sclerosis/hyalinosis, and extensive GBM deposits. These irreversible glomerular changes might be an indication for treatments to minimize or delay the progression of the disease. Wright et al. [12] stated that the most important factor influencing the outcome of glomerular disease was not simply thickening of GBM, but the occurrence of progressive glomerular sclerosis. The persistent proteinuria in this case may have contributed to the development of tubulointerstitial changes; proteinuria has been implicated in tubular injury in human patients as well as in experimental models of protein-losing glomerulonephropathy [2].

It is not clear whether the WHO classification of human glomerular diseases [1] could be applied to feline diseases, because there are few reports on other types of glomerulonephritis in cats [4]. Renal biopsy is a relatively safe procedure [3, 10]; its use in cases of suspected glomerular disease, especially before azotemia has developed, is needed to establish the clinico-pathological classification of glomerular diseases in animals. The diagnosis should be based on light and electron microscopic and immunohistochemical findings [11]; clinical and histopathological changes of the cases need to be monitored throughout the course of the disease. Formalin-fixed/paraffin-embedded tissue was used for electron microscopy and immunohistochemistry in this
study because only one small biopsy specimen was available. However, for optimal pathological examination of renal biopsy specimens, glutaraldehyde fixative and fresh frozen sections should be used for electron microscopy and immunohistochemistry, respectively. Light microscopic evaluation should be performed on sections stained with HE, PAS, periodic acid-methenamine silver, Masson’s trichrome and Congo red. The clinical and pathological trials would make it possible to make early diagnosis of the renal diseases for timely application of therapeutic interventions that may slow or halt disease progression [6].

REFERENCES