Severe renal failure in a dog resembling human focal segmental glomerulosclerosis.

Severe Renal Failure in a Dog Resembling Human Focal Segmental Glomerulosclerosis

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Summary

A case of renal disease in a dog resembling human focal segmental glomerulosclerosis is presented. A kidney biopsy from this animal showed focal glomerular sclerosis, with variable distribution, affecting the perihilar and peripheral segments of the glomerular tuft. Non-sclerotic glomeruli were markedly enlarged. Interstitial fibrosis in association with tubular atrophy affected approximately 20% of the area of the biopsy. Immunofluorescence labelling showed immunoglobulin M deposits entrapped in segmental sclerotic areas and ultrastructural examination revealed segmental sclerosis and obliteration of capillaries, vacuolation of podocytes and diffuse effacement of foot processes. The dog was humanely destroyed 1 month later. At necropsy examination there was severe end-stage kidney disease with interstitial fibrosis involving more than 60% of the renal tissue. The clinical course and the microscopical, immunofluorescence and ultrastructural findings in this case have similarity to focal segmental glomerulosclerosis in man.

Keywords

dog; glomerulosclerosis; kidney; renal failure

Primary focal segmental glomerulosclerosis (FSGS) is a major cause of the nephrotic syndrome and progression to end-stage renal disease (ESRD) in people (Crosson, 2007). The 10-year survival rate for nephrotic patients with primary FSGS is approximately 50%, but the prognosis for nephrotic patients is dependent on the response to treatment, irrespective of age at onset. In people, 60–70% of patients resistant to treatment develop ESRD after 5–10 years. The diagnosis of FSGS is based on the presence of areas of glomerular sclerosis and tuft collapse that are both focal (some glomeruli are affected, but not all) and segmental (a segment of the glomerulus is affected). Segmental hyalinosis, glomerular deposits that are positive for immunoglobulin (Ig) M and/or complement factor 3 (C3) by immunofluorescence labelling, as well electron microscopical evidence of effacement of epithelial cell foot processes, may often be seen, but are not required for diagnosis. The clinical hallmarks of FSGS include proteinuria, nephrotic syndrome and frequently the progressive loss of renal function (Chun et al., 2004).

The idiopathic form of FSGS is most commonly recognized, but secondary FSGS can occur in association with reflux nephropathy, obesity, human immunodeficiency virus (HIV) infection and sickle cell disorder, as well as other medical conditions (D'Agati, 2003). There is an estimated recurrence rate for FSGS of approximately 30–40% in renal transplant patients, which suggests that the pathogenesis is not exclusively the result of intrinsic kidney disease. A 'circulating factor' that causes recurrent FSGS has been widely reported; however, the identity of factor has not been described (Crosson, 2007 and Deegens et al., 2007). The present report describes a dog with severe renal failure and pathological findings compatible with human FSGS.

A 2-year-old, neutered female, mixed breed dog was referred with a 2-month history of polyuria, polydipsia, weight loss and weakness. The mucous membranes were pale and dry. Haematological examination revealed a mild normochromic normocytic anaemia (packed cell volume 32.5%; reference range 37.1–57%), while serum biochemistry showed elevated serum creatinine (539.2 μmol/l; reference range 26.5–132.6 μmol/l) and blood urea nitrogen (67.8 mmol/l; reference range 4.9–17.8 mmol/l), hyperphosphataemia (2.90 mmol/l; reference range 0.94–2.13 mmol/l) and low total protein (44 g/l; reference range 54–82 g/l). Urinalysis revealed a specific gravity of 1.015, while the protein/creatinine ratio was 9.1 (reference range < 0.5). Sediment and urine cultures were negative. The dog was serologically negative for Leishmania donovani (immunofluorescent antibody test), Ehrlichia spp. and Dirofilaria immitis (SNAP™; IDDEX Laboratories, Westbrook, USA). On the basis of these findings, a diagnosis of chronic renal failure was made. An abdominal ultrasound investigation showed the kidneys to be normal.

Two percutaneous ultrasound-guided biopsies were collected with an 18-gauge Tru-cut-type needle and the samples were fixed in 10% neutral buffered formalin for histological investigation and in 2.5% buffered glutaraldehyde for electron microscopy. Renal biopsies were processed for light microscopy, immunofluorescence labelling for IgG, IgM, IgA and C3 (Aresu et al., 2008) and electron microscopy. For histological examination, sections (4 μm) were stained with haematoxylin and eosin (HE), Masson's trichrome, periodic acid-Schiff (PAS), methenamine silver–PAS (PASM) and acid fuchsin orange G (AFOG) (Kriz, 2003). The percentage of interstitial fibrosis was evaluated using an ocular grid and pointcounting on trichrome-stained sections of renal cortex.

For transmission electron microscopy (TEM), the tissue was post-fixed in 2% osmium (in distilled water) for 1.5 h, dehydrated in graded acetone and embedded in Epon. Semithin sections were stained with azure methylene blue. Ultrathin sections were counterstained with uranyl acetate and lead citrate. For ultrastructural studies, a Philips EM 420 was used.

The two renal core biopsies had a cortico-medullary ratio of 7:1. A total of 35 glomeruli were present and 11 of these showed global sclerosis. Fifteen of the remaining 24 glomeruli showed discrete segmental sclerosis with increased matrix and adhesion of Bowman's capsule. The distribution of sclerosis was variable within the glomerular tuft, affecting the perihilar and peripheral segments (Fig. 1a, b). AFOG staining showed matrix deposition with obliteration of capillaries and diffuse wrinkling of the glomerular basement membrane. Signs of scattered segmental endocapillary hypercellularity with foam cells and macrophages were present, associated with hypertrophic epithelial cells characterized by PAS-positive droplets. The level of interstitial fibrosis in association with tubular atrophy was estimated to be 20% (Fig. 1c). There was moderate and patchy interstitial inflammatory infiltration of lymphocytes and plasma cells with few macrophages. Immunofluorescence labelling revealed IgM deposits with a segmental distribution in three of five glomeruli in the sclerotic area. No specific distribution, either granular or linear, was evident, while labelling for IgG, IgA and complement C3 was negative. Ultrastructural examination of two glomeruli showed segmental areas of sclerosis and obliteration of capillaries (Fig. 2a). There was vacuolation of podocytes and diffuse effacement of foot processes (Fig. 2b). A diagnosis of FSGS was made.

Fig. 1.

Renal biopsy. (a) Glomerulus showing segmental scar with adhesion to Bowman's capsule (arrow). PAS. × 400. (b) Glomerulus showing focal obliteration of the capillary lumina overlying hypertrophic and hyperplastic podocytes (arrow). PAS. × 400. (c) Two glomeruli with normal microscopical appearance. AFOG. × 200.

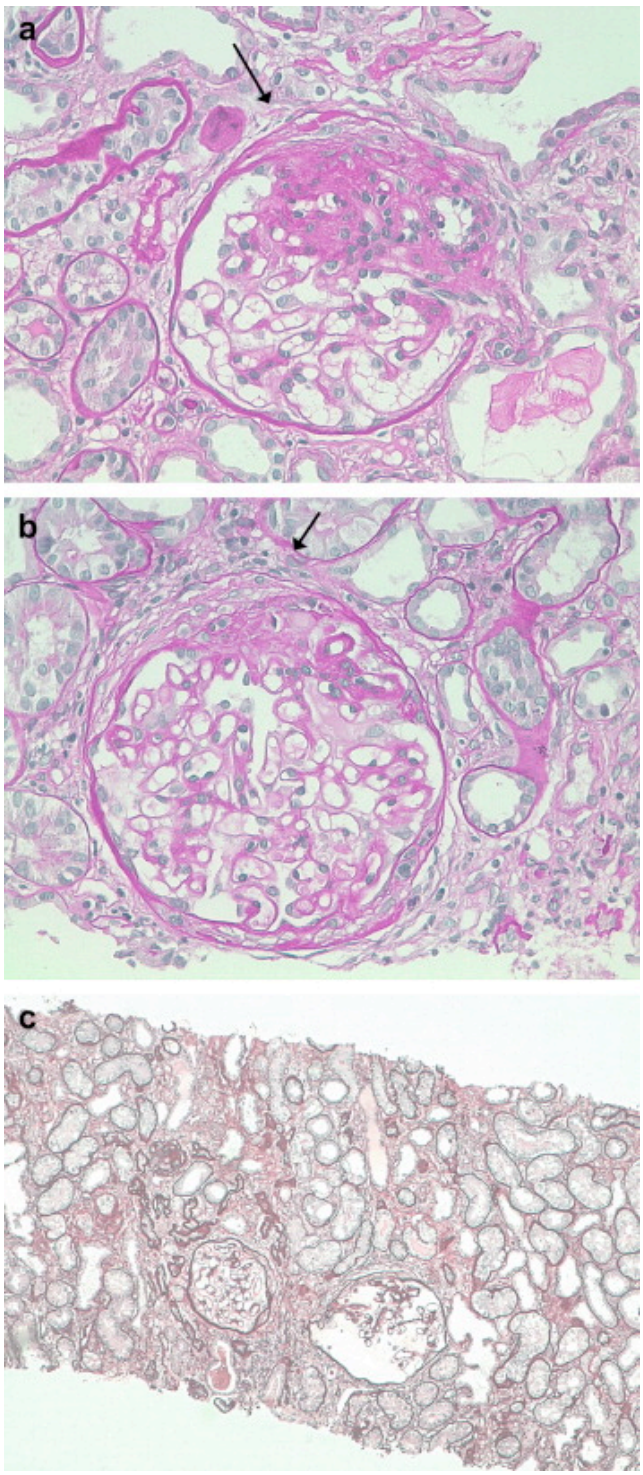
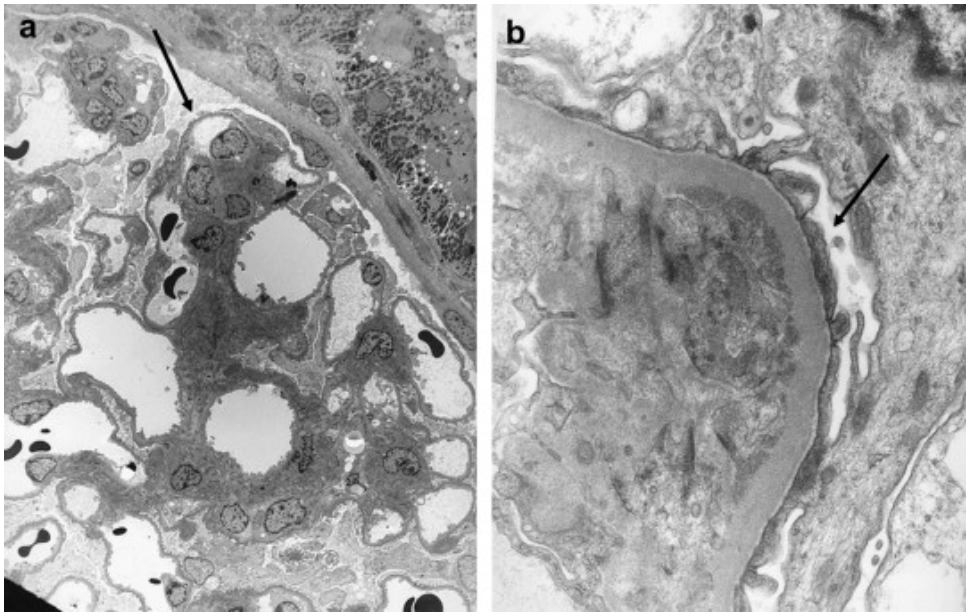


Fig. 2.

Renal biopsy. (a) Glomerulus showing an increase in mesangial matrix and partial obliteration of capillary lumina (arrow). (b) Extensive effacement of foot processes (arrow). TEM. × 3,500.

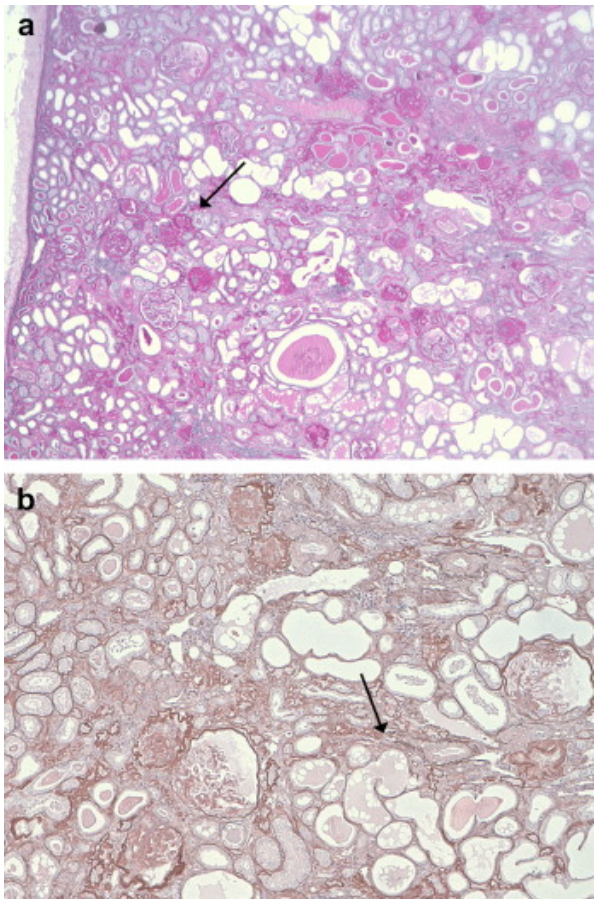


Therapy including 24 h of intravenous fluid infusion, famotidine (0.5 mg/kg q24 h per os), metoclopramide (0.2 mg/kg q12 h intravenously) and a commercial renal diet was administered. Two weeks after initial presentation, the dog had not shown any improvement in clinical condition and laboratory findings were compatible with persistent azotaemia, proteinuria and anaemia. Glucosuria was also evident, with abnormal renal glucose excretion. Due to the continuing poor clinical condition, the dog was humanely destroyed 1 month later.

Formalin-fixed specimens of liver, lung, heart, intestine, stomach, pancreas, brain and both kidneys were submitted for pathological evaluation. No significant lesions were detected in any organs other than the kidneys. Both kidneys were pale and firm with an irregular surface. Transverse sections of the entire kidneys were examined. Approximately 80‑90% of glomeruli were totally sclerotic, with an increase in mesangial matrix effacing the glomerular capillaries (Fig. 3a). The remaining glomeruli had thickening of Bowman's capsule and markedly thickened and prominent capillary loops with numerous synechiae. Diffuse tubular ectasia was present. Mild to severe chronic tubulointerstitial nephritis, characterized by multifocal infiltration of lymphocytes and plasma cells, was evident. The extent of interstial fibrosis was more than 60% in the kidney sections examined; a diagnosis of end-stage kidney disease was made (Fig. 3b).

Fig. 3.

Kidney taken at necropsy examination. (a) Low-power view of kidney with diffuse glomerular sclerosis and diffuse tubular atrophy (arrow). PAS. × 200. (b) Low-power view of kidney with diffuse tubular ectasia and the presence of protein granular casts in the lumina (arrow). AFOG. × 300.



The histopathological, immunofluorescence and electron microscopical findings in this case were consistent with human FSGS. To the authors' knowledge, this is the first description of FSGS in a dog. The key pathogenesis of FSGS is correlated to podocyte damage (Kambham et al., 2001). The initial injury to podocytes leads to further damage mediated by cytokine release, mechanical stress and further loss of polarity, resulting in sclerosis and scarring of the glomerulus (Kriz, 2003). Inflammatory infiltration leads to mesangial matrix deposition, promoting the collapse of glomeruli. The cellular infiltrate and cytokine secretion also damages tubular epithelial cells and some tubular epithelial cells may undergo transformation to mesenchymal cells, which contributes to the fibrosis (Rodríguez-Iturbe et al., 2005 and Aresu et al., 2008). Moreover, renal vascular and glomerular sclerosis is a consequence of high blood pressure and the exaggerated extracellular matrix formation in mesangial and vascular smooth muscle is an adaptive response to the increased tension during chronic kidney damage (Chun et al., 2004).

In people, the progression of FSGS does not correlate with age, sex or the presence of haematuria (Korbet, 1999). Neither the percentage of glomeruli with segmental scars nor the percentage of glomeruli with global sclerosis is predictive of outcome. Only the extent (more than 20%) of interstitial fibrosis has consistently been shown to predict a poor prognosis. Earlier studies demonstrated that global and segmental sclerosis involving more than 20‑30% of glomeruli is poor prognostic factor (Chun et al., 2004). In contrast, there are often cases with histological features that are so mild that they may be difficult to distinguish from 'minimal change disease' (MCD), which carries a more favourable prognosis (D'Agati, 2003). Controversy still persists as to whether FSGS may represent an evolutionary stage of MCD. The diagnosis of a focal disease such as FSGS is, in fact, established by the finding of at least one abnormal glomerulus. Distinguishing early lesions of FSGS from a possible form of MCD can be difficult. Since the lesions are segmental, sclerosis in some portion of the glomerular tuft could be missed in a single section (Howie, 1994). In these cases, serial sections of the renal biopsy can help follow the glomerular tuft and the possible presence of a segmental area of sclerosis.

In dogs, advanced lesions are generally classified as end-stage kidneys. The major problem in canine renal disease is the lack of availability of renal biopsies when clinical signs of renal disease are mild and the opportunity for follow-up during treatment is minimal. Irrespective of the nature of the primary glomerular disease, renal fibrosis is considered to be the common final pathway by which glomerulonephritis with variable aetiology progresses to end-stage renal failure. It is therefore important to identify factors that participate in the initiation of tubulointerstitial inflammation and subsequent interstitial fibrosis during progressive glomerular injury (Strutz and Neilson, 2003). The identification of IgM deposits in the lesions of the present case suggests a possible initiating factor. No immunofluorescence examination was performed in the kidneys collected at post-mortem examination, due to the severe damage and diffuse glomerulosclerosis that was present.

The canine secondary form of focal and mesangial sclerosis also occurs in renal diseases characterized by a decreased number of glomeruli, such as experimental unilateral nephrectomy or obesity. Nephron loss causes compensatory hypertrophy of remnant glomeruli with increased volume and increased glomerular pressure, leading to systemic hypertension. The end result is capillary collapse and mesangial sclerosis (Brown et al., 1997). Experimental studies consider primary and secondary FSGS to be two distinct morphological entities and point out that the first is a more aggressive and destructive glomerulopathy (Rennke and Klein, 1989). In contrast, the mechanisms of glomerular and interstitial injury in these cases appear similar (Kriz, 2003). In canine medicine, such data are not yet available and further clinical studies must focus on the role of the renin‑angiotensin system in preventing glomerular capillary hypertension and improving clinical investigation to detect the nephrotic syndrome, a hallmark of FSGS.

In Italy, many cases of end-stage kidney disease are reported in dogs with severe renal leishmaniosis. Focal and segmental mesangial alterations have been described as part of the multiple immune-mediated lesions in leishmaniosis, but have never been regarded as primary aspects of the disease (Zatelli et al., 2003). There was no evidence for an infectious aetiology in the present case and an immunological reaction mediated by IgG and complement was excluded due to the results of the immunofluorescence studies. The origin of FSGS in the present case was therefore considered to be idiopathic.

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