Case Report

Early Stage of Chronic Kidney Disease with Renal Injury Caused by Hypertension in a Dog

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1. Introduction

The close association between progression of kidney damage and systemic hypertension is well known in human and small animal medicine [1–5]. However, in cases when kidney disease with systemic hypertension is diagnosed from clinical symptoms and laboratory test results, a renal biopsy is required to determine whether renal injury is induced by persistent hypertension or whether it is the preexisting kidney disease. This report presents a case of a dog with nonazotemic early stage of chronic kidney disease probably caused by hypertensive renal injury.

2. Case Presentation

A 10-year-old spayed female Papillon weighing 4.0 kg presented with a history of persistent hematuria and pollakiuria. Concurrent bladder calculi, a mammary gland tumor, and nonazotemic early stage of chronic kidney disease with contracted kidneys were noted in this dog. The dog underwent cystectomy, unilateral mastectomy, and intraoperative renal biopsy. On the basis of histopathological analysis of renal biopsy results, it was suspected that renal injury of the dog was caused by persistent hypertension, and a follow-up examination revealed severe hypertension. The dog was treated with a combination of an angiotensin-converting enzyme inhibitor and calcium channel blocker. The treatment produced a good outcome in the dog, and there has been no progression of the chronic kidney disease for over 2 years.
fixed with 10% neutral buffered formalin and embedded in paraffin with a routine procedure, and 2 µm thick sections were cut serially. For observation using a conventional light microscope, sections were stained with hematoxylin-eosin, periodic acid Schiff, periodic acid methenamine-silver, Masson’s trichrome, and elastica van Gieson stains. Immunohistochemistry was performed using goat polyclonal antibodies against dog immunoglobulin (Ig) G, IgA, IgM, and complement C3 as primary antibodies (Bethyl Laboratories, Montgomery, Tex, USA).

**Histopathology.** There were about 20 glomeruli in the observed sections. Diffusely and globally observed changes in the glomeruli were wrinkling of the glomerular basement membrane, collapse of the glomeruli, and thickening of Bowman’s capsule (Figure 1). Severe interstitial fibrosis and tubular atrophy with periodic acid Schiff-positive cast formation were observed (Figure 1). Mononuclear cell infiltration by lymphocytes and plasma cells was also observed in the interstitium. Hyaline degeneration, thickening of tunica media, and luminal narrowing were observed in the small arteries and arterioles (Figure 1). Positive signals for IgM and complement C3 were observed in the glomeruli, small arteries, and arterioles (Figure 1). No positive signals were detected for IgG or IgA.

These histopathological findings resembled those of hypertensive renal injury in human [6], and this findings suspected that systemic hypertension has persisted in the dog. Although systolic blood pressure (SBP) could not be measured previously because this dog has an aggressive behavior, evaluation of the SBP was retried according to the Doppler method (Model 811-B; Parks Medical Electronics, Las Vegas, Nev, USA). Urinary protein/creatinine ratio (UPC) was determined after confirmation of non-bacteriuria. From the careful evaluation according to the standardized procedure [7, 8], the dog’s SBP was considered over 180 mm Hg. The UPC was found to be 0.34. Therefore, the dog was clinically diagnosed as IRIS stage 1 CKD (pCre: <125 µmol/l) with severe hypertension (SBP: >180 mm Hg) and borderline proteinuria (UPC: 0.2–0.4). Since renal injury induced by persistent hypertension was suggested from the findings of renal biopsy, antihypertensive therapy was initiated.

Changes in SBP and pCre are shown in Figure 2. The SBP did not fall below 180 mm Hg after administration of the angiotensin-converting enzyme inhibitor (ACEI) benazepril (0.69 mg/kg p.o. once or twice daily) treatment. Although the calcium channel blocker (CCB) amlodipine (0.35 mg/kg p.o. once daily) was added to the benazepril treatment, this combination of antihypertensive agents only induced temporarily antihypertensive action. Informed consent was
obtained from the dog owner for replacing the type of ACEI, that is, for replacing benazepril with temocapril (0.11 mg/kg p.o. once daily), before increasing the dosage of amlodipine or adding of a different class of antihypertensive agents. This change in ACEI was effective; the dog's SBP gradually decreased to within the normotensive range and became stable. The dog has been treated with a combination of amlodipine and temocapril for over 2 years and has managed to stay clinically healthy having IRIS stage 1 CKD with nonproteinuria (UPC: <0.2).

3. Discussion

In human medicine, the term hypertensive nephrosclerosis (HN) was used to describe the renal injury caused by essential hypertension [9]. Although human HN is usually diagnosed solely on clinical grounds, importance of the pathological analysis of renal biopsy results has been pointed out recently [10, 11]. The most typical features of HN are vascular lesions such as hyaline degeneration and sclerosis. The most common glomerular change of HN is an ischemic change featured by collapse of the capillary tufts with wrinkling of the basement membrane [6]. Tubulointerstitial lesions are frequently observed in the cases of HN [6, 12]. Thickening of Bowman’s capsule with collapse of glomerular tufts and interstitial fibrosis are regarded as changes in the case of long-standing hypertension. Although histopathological evidence from the renal biopsy was sufficient to diagnose the renal injury of the dog to be caused by persistent hypertension, hypertension in the present case could not be diagnosed as essential. Although laboratory test results and clinical symptoms did not suggest the presence of predisposing causes of canine secondary hypertension such as diabetes, hyperadrenocorticism, acute renal failure, or hypothyroidism, the dog was not diagnosed as the essential hypertension in the strict sense, because concurrent urolithiasis and mammary gland tumor were demonstrated in the dog.

In the present case, immunopositive signals for IgM and C3 were clearly detected in the glomeruli, small arteries, and arterioles. Although immunohistochemical examinations have not been fully performed even in human HN, depositions of IgM and C3 have been considered as the most common findings; these depositions are not considered to be the primary cause of glomerular damage but as nonspecific accumulation and deposition in areas of injured tissue [6].

ACEI and CCB are commonly used as antihypertensive agents in dogs and cats [7]. In the present case, co-administration of ACEI and CCB improved systemic hypertension without increasing pCre or exacerbating the dog’s condition. Interestingly, a tangible and gradual decrease in the blood pressure was seen after the type of ACEI used was changed from benazepril to temocapril. Temocapril belongs to the newest generation of ACEIs, which are commercially available for dog therapy in our country; temocapril results in long-lasting preferential biliary excretion and has high bioavailability. However, it is difficult to explain why temocapril was more effective than benazepril in this dog. Similar to temocapril, benazepril is also an ACEI that causes long-lasting and preferential biliary excretion. Significant antihypertensive effects of benazepril in dogs with CKD involving systemic hypertension have already been demonstrated experimentally and clinically in previous reports [9, 13]. Although the findings from the present case indicated that temocapril is an effective antihypertensive agent, its superiority to other ACEIs has not yet been demonstrated.

References


