



CASE REPORT

Non-Familial Renal Amyloidosis in a Dog with Splenic Hemangioma

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ARTICLE HISTORY (14-389)

Received: August 01, 2014
Revised: January 05, 2015
Accepted: January 18, 2015

Key words:

Chronic Kidney Disease (CKD)
Dog
Hemodialysis
Renal amyloidosis
Splenic hemangioma

ABSTRACT

A 12-year-old, intact male, Labrador Retriever dog was referred to our hospital with a 1-week history of depression and azotemia that had not responded to symptomatic fluid therapy. Based on the history, clinical examination, CBC, serum biochemical analysis, urinalysis, and diagnostic imaging, the dog was tentatively diagnosed with glomerulonephropathy concurrent with a splenic tumor. Following a splenectomy and renal biopsy, renal amyloidosis and hemangioma were confirmed on histopathology. Despite intensive care with intermittent hemodialysis, the dog's condition deteriorated and died 12 days after admission. This case illustrates that splenic hemangioma can be related to renal amyloidosis.

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To Cite This Article: Lee CM, SG Kim, MH Kang, JH Sur, KD Eom, SW Jeong and HM Park, 2015. Non-familial renal amyloidosis in a dog with splenic hemangioma. *Pak Vet J*, 35(2): 257-259.

INTRODUCTION

Amyloidosis refers to a variety of diseases that have in common the extracellular deposition of fibrils formed by polymerization of proteins with a beta-pleated sheet conformation (Gillmore and Hawkins, 2013). Of the domestic animals, the dog is most commonly affected by amyloidosis. With the exception of the Chinese Shar-Pei dog, amyloid is deposited primarily in the glomeruli of affected dogs (Segev *et al.*, 2012).

The most common clinical features of renal amyloidosis in dogs are the same as those observed in other glomerular diseases: anorexia, vomiting, lethargy, polyuria, polydipsia, weight loss, and cachexia, all of which are nonspecific and consistent with chronic kidney disease (CKD). Cook and Cowgill (1996) have reported median amyloidosis survival times of 5 to 28 days. Renal amyloidosis is frequently idiopathic, but may be associated with chronic inflammation, infection, or neoplasia (Gillmore and Hawkins, 2013).

This case report illustrates the clinicopathologic findings and clinical course of non-familial renal amyloidosis due to a splenic tumor and describes the use of hemodialysis for intractable renal amyloidosis treatment.

History and clinical examination: A 12-year-old intact male Labrador retriever dog was referred to our hospital with a 1-week history of depression and azotemia.

Physical examination showed depression and pale mucous membranes. A firm, non-movable mass was palpable in the abdomen. Laboratory examination revealed anemia (hct 8%); azotemia (blood urea nitrogen 97 mg/dL; creatinine 4.5 mg/dL); hypoalbuminemia (1.1 g/dL); hyperglobulinemia (4.8 g/dL); hyperphosphatemia (10.7 mg/dL); and hyperkalemia (6.4 mmol/L). Biochemical findings suggested renal failure with a protein losing nephropathy. Urinalysis revealed severe proteinuria and isosthenuria, suggesting glomerulopathy including glomerulonephritis, amyloidosis, and glomerulosclerosis. Based on finding hypoalbuminemia and hyperglobulinemia, chronic immune stimulation and neoplasia were highly suspected.

Abdominal radiography revealed a large soft tissue density mass with decreased serosal detail in the cranioventral abdominal region (Fig. 1A). Abdominal ultrasonography showed cyst-like cavitated masses with mixed echogenicity on the spleen (Fig. 1B). Computed tomography (LightSpeed Plus, GE MEDICAL SYSTEM, USA) was performed to further evaluate the splenic mass and look for metastatic lesions. In the abdomen, the large mass with multiple hypo-attenuated cysts was surrounded by splenic parenchyma at the tail region (Fig. 2). The differential diagnosis at this stage included glomerular disorders concurrent with a splenic tumor.

Although evidence of metastatic disease was not found, the D-dimer level was significantly increased (D-dimer 9.3 mg/L). Serum protein electrophoresis revealed

hyperglobulinemia with remarkably elevated α -2 and β globulin, and hypoalbuminemia (Fig. 3). To prevent a thromboembolic disorder, enoxaparin (1 mg/kg, twice a day; Sanofi-Aventis, France) and clopidogrel (3 mg/kg, once a day; Sinil Pharm Ltd., Korea) were prescribed.

Treatment: Hemodialysis was intermittently performed to treat the azotemia. The dog was sedated with tiletamine-zolazepam (10 mg/kg; Virbac Laboratories, France) and medetomidine (0.2 mg/kg; Pfizer Korea., Korea) to facilitate central vein catheterization. A double lumen catheter was placed using a modified Seldinger technique. Intermittent hemodialysis was performed to reduce the azotemia. Hemodialysis was performed 3 times over a period of 5 days. The azotemia and serum abnormalities improved (Table 1), although they remained above the normal reference range. After hemodialysis, a laparotomy was performed, the splenic masses were resected (Fig. 4A), and tissues were collected for histopathology.

Microscopic evaluation of the splenic mass revealed a hemangioma with necrosis (Fig. 4B). The kidney lesions were characterized by acellular material in the glomeruli that was homogeneously eosinophilic when stained with hematoxylin-eosin stain. Numerous proteinaceous casts were identified in the renal tubules (Fig. 5A). Congo red staining revealed deposition of homogeneous bright orange material in the glomeruli, confirming renal amyloidosis (Fig. 5B).

Despite intensive care and intermittent hemodialysis, the dog died 12 days after hospitalization. With the owner's approval, a postmortem examination was performed. Grossly, multiple firm nodules were palpable in the lungs. Histopathologic examination revealed numerous areas of calcification in the alveolar walls and alveolar infiltration by macrophages. Based on the histopathology results, secondary uremic pneumonitis was suspected as the cause of death.

DISCUSSION

Renal amyloidosis in dogs primarily involves the glomerulus and less frequently the cortical and medullary interstitium. An exception to this pattern occurs in the Chinese Shar Pei breed, in which renal medullary lesions are reported to predominate. In this case, glomerular amyloid deposition was revealed. Interstitial nephritis was suspected to be a secondary pathologic change caused by the advanced glomerular amyloidosis.

Hemangiomas are defined as benign vasoformative neoplasms with vascular structures closely resembling normal blood vessels. Hemangiomas are histologically classified into 6 subtypes: capillary; cavernous; mixed capillary and cavernous; arteriovenous; venous; and granulation tissue (Gamlem and Nordstoga, 2008). The splenic tumor in this case showed cavernous structures with well-differentiated endothelial cells lining the walls of the blood-filled cavities and surrounded by homogeneous necrotic material.

Renal amyloidosis has been reported to commonly occur concurrently with other diseases, especially chronic inflammatory conditions and neoplasia (Nakagawa *et al.*, 2012). In one human patient with a splenic tumor and

Table 1: Profiles of blood urea nitrogen and creatinine during intermittent hemodialysis (IHD) in a Labrador Retriever dog

	Before IHD	After 1 st IHD	After 2 nd IHD	After 3 rd IHD	Reference range
Blood urea nitrogen	97	81	71	56	8-26 mg/dl
Creatinine	4.5	3.6	3.6	3.0	0.5-1.3 mg/dl

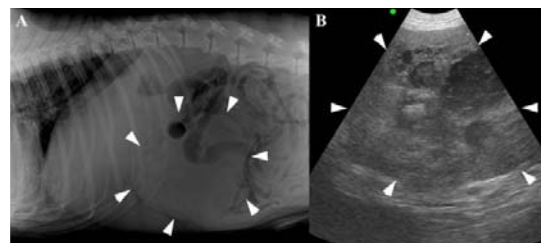


Fig. 1: Right lateral abdominal radiograph (A). A large round soft tissue density mass was revealed in the cranioventral abdomen (white arrowheads) causing deviations in the positions of the liver, kidney, and small intestine. Decreased serosal detail was found. (B). Mixed echogenicity was observed on ultrasonographic examination of the cavitated splenic mass.

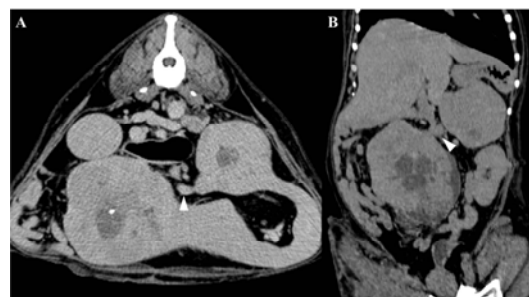


Fig. 2: CT images of splenic masses at the head and tail of the spleen. Both transverse (A) and dorsal (B) images revealed nonhomogeneous masses with distinct margins at the head and tail regions with iso-attenuating opacity relative to the spleen. A splenic lymph node was detected (white arrowhead). Mineralization was seen within the mass. Deviations in the positions of abdominal organs were observed. The left side of the dog is to the right on the image.

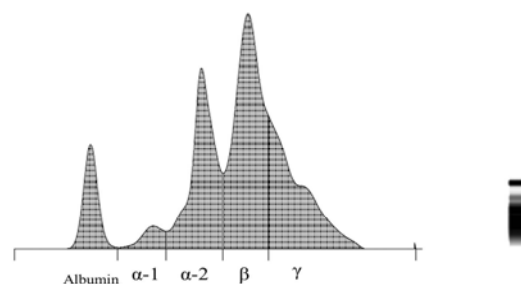


Fig. 3: Serum protein electrophoresis showing markedly decreased albumin fraction, and increased α -2 and β fractions. The albumin:globulin ratio was 0.1.

amyloidosis, the nephrotic syndrome resolved after splenectomy, suggesting that the splenic tumor caused the amyloidosis (Gillmore and Hawkins, 2013). In our case, the dog did not show improvement after removal of the tumor.

Intermittent hemodialysis is a renal function replacement modality that is defined by short, efficient hemodialysis sessions (Bloom and Labato, 2011). In this case, IHD for stabilization was performed because of the refractory uremia.

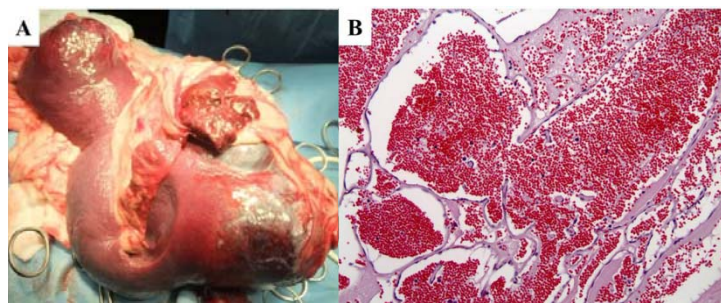


Fig. 4: A) Grossly enlarged spleen with irregular surface caused by the mass. B) Histopathology revealed the splenic mass filled with homogeneous eosinophilic material interspersed with vascular spaces, and completely encircled by a single layer of endothelial cells. H & E stain; 200 X.

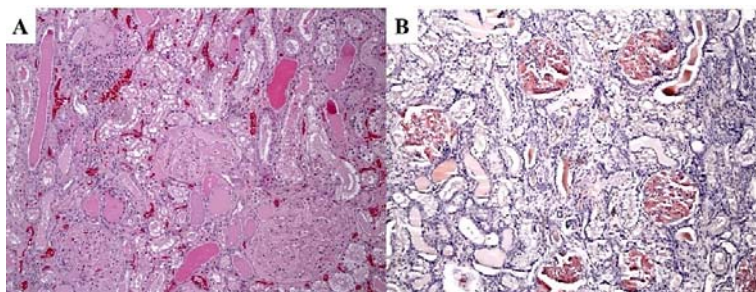


Fig. 5: Histopathology of the kidney (A, B). Kidney lesions exhibited homogeneous eosinophilic staining with hematoxylin-eosin stain and were characterized by tubular inflammation, multifocal mineralization, and acellular glomerular material that expanded the mesangium. The renal tubules contained an eosinophilic proteinaceous substance and cellular casts in the lumina (A). Congo red staining confirmed the homogeneous material deposited in the glomerular structures as amyloid. H & E stain (A); Congo red stain (B). 100 X.

In animals with glomerular disease, increased serum globulin concentrations may occur because of increased concentrations of α -globulins, such as α -2 lipoprotein, and β globulins (Sabattini and Bettini, 2009). Elevated concentrations of α and β globulins in this dog indicated a nephrotic syndrome caused by the renal amyloidosis.

Thrombosis has been reported as a complication of renal diseases including amyloidosis. Dehydration leads to hyperviscosity and slowing of blood flow with subsequent thrombus formation. The accompanying elevation of plasma α -globulins which have antifibrinolytic activity, contribute to this process (Sabattini and Bettini, 2009).

Changes in the lungs including edema, inflammation, and calcification which occur in patients with uremia, are referred to as the pulmonary renal syndrome (von Vigier *et al.*, 2000). Histopathologic results of the dog in this case showed inflammatory changes with calcification of alveolar spaces which might have been present for several months.

Amyloidosis in dogs and cats is usually diagnosed after renal failure has developed and has a poor prognosis (Bloom and Labato, 2011). Several conditions that potentially predispose animals to develop renal amyloidosis include neoplastic, immune-mediated, and infectious diseases. Evaluation of dogs with proteinuria is warranted because amyloidosis primarily manifests as a protein losing nephropathy in dogs, with the exception of the Chinese Shar Pei breed (Nakagawa *et al.*, 2012). Renal biopsy is the definitive method for diagnosing amyloidosis. Although the optimal treatment for amyloidosis is still unclear, early diagnosis may improve prognosis. In conclusion, splenic hemangioma caused non-familial renal amyloidosis in this dog, and the condition was unresponsive to medical therapy.

Author's contribution: CM Lee was the patient's veterinary doctor. SG Kim and MH Kang participated in all medical aspects of this case. JH Sur interpreted the histopathology data. KD Eom interpreted the diagnostic imaging data. SW Jeong performed the surgery. HM Park provided guidance on the case and the report. All authors interpreted the data, critically revised the manuscript for important intellectual content, and approved the final version.

Acknowledgement: This paper was written as part of Konkuk University's research support program for its faculty on sabbatical leave in 2014.

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