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Familial renal amyloidosis in a Shar Pei dog

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Abstract : Familial renal amyloidosis was found in a four-year-old male Shar Pei dog. The dog had intermittent fever with signs of renal failure. Another sibling of this dog also showed subclinical signs of renal amyloidosis. Despite aggressive therapy with peritoneal dialysis, the dog died after 10 days of the first presentation. With special staining for amyloid, the renal amylodosis was confirmed.

Key words: canine, familial, renal amyloidosis, renal failure, shar Pei

Familial renal amyloidosis in Shar Pei dogs is characterized by autosomal recessive inheritance, early onset of age (mean age 4.1 years), female predilection (2.5 times higher incidence), episodes of fever and swollen hocks, and progressive chronic renal failure with severe proteinuria [3, 6, 9, 10]. Similar renal amyloidosis has been reported in other dog breeds [2, 7]. Clinical signs were closely related to renal failure (including vomiting, anorexia, lethargy, polydipsia, polyuria, weight loss, and dehydration) with a history of intermittent fever and joint swelling (commonly called Shar Pei fever or Shar Pei swollen hock syndrome) [3, 4]. Major laboratory findings were included azotemia, hyperphosphatemia, hypocapnia, isosthenuria, proteinuria, and hypercholesterolemia. According to literature, all dogs had medullary deposition of amyloid, and 9 of 14 (64%) had glomerular involvement [2, 4]. As a result, as few as 25% to 43% of affected Shar Pei dogs have proteinuria. In severe cases, amyloid deposits could be also found in other organs including liver, spleen, stomach, lung and pancreas and caused to thromboembolism [1, 5, 10]. Affected Shar Peis may be an animal model of familial Mediterranean fever in humans [3].

A 4-year-old intact male Shar Pei dog was referred at Veterinary Teaching Hospital of Kangwon National University with the primary complaints of persistent anorexia, fluctuant fever, vomiting, progressive weight loss and polyuria/polydipsia for last 2 weeks. In physical examination, the dog was lethargic with high fever (rectal temperature 39.7°C). Both hock joints were found to be swollen. Complete blood cell count showed leukocytosis ($22.1 \times 10^3/\mu l$; reference range: $6\text{-}17 \times 10^3/\mu l$) and eosinophilia ($8.7 \times 10^3/\mu l$; reference range: $0\text{-}1.3 \times 10^3/\mu l$), suggesting either parasitic or immune mediated diseases. The dog was polycytemic ($9 \times 10^6/\mu l$; reference range: $5.5\text{-}7.5 \times 10^6/\mu l$) and severely dehydrated, suggesting polycythemia might be due to severe dehydration.

Serum biochemistry revealed severe azotemia (blood urea 162 mg/dl; reference range: 7-28 mg/dl; creatinine 12.3 mg/dl; reference range: 0.9-1.7 mg/dl), hyperphosphatemia (20 mg/dl; reference range: 2.4-6.1 mg/dl) and hyperakalemia (7.9 mmol/l; reference range: 2.4-6.1 mmol/l). Biochemical findings strongly suggested severe renal failure. Urinalysis revealed low urine specific gravity (1.010; reference range: 1.015-1.030), severe proteinuria (3+ in dipstick) and aciduria (pH 5.0), suggesting renal cause of renal failure (particularly glomerular diseases).

Abdominal radiography revealed no abnormalities in renal location and dimension. On ultrasound examination, the kidneys were normal in shape and size with poor corticomedullary definition and a hyperechoic cortex (Fig. 1) suggesting renal parenchymal disease. Based on history of familial etiology, clinical findings with renal failure and echocardiographic findings with renal parenchymal involvement, the case was tentatively diagnosed as a familial renal amyloidosis.

In this case, initially we performed peritoneal dialysis (925 ml Hartman solution with 75 ml 20% dextrose and 500U of heparin, 45 min dwell time, exchange every 2 hrs) for 24 h, to lessen azotemia and hyperkalemia.

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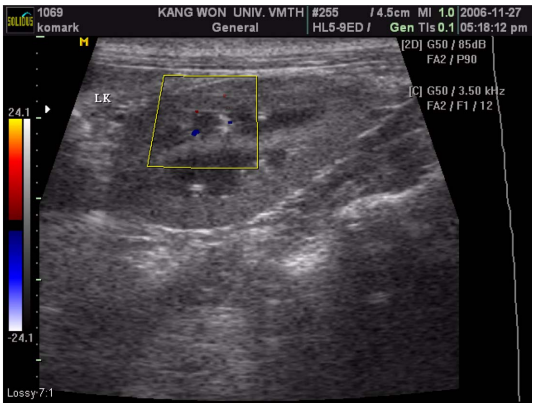

Fig. 1. Ultrasonographic findings in the kidney. Kidney was normal in shape and size with poor corticomedullary definition and a hyperechoic cortex. Blood flow in renal arteries and veins were remarkably reduced, suggesting chronic renal parenchymal disease.

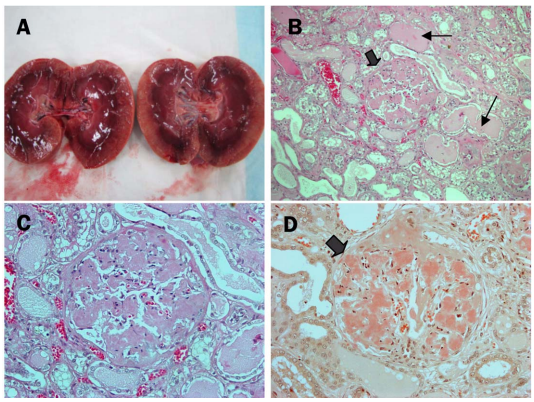

Fig. 2. Gross (A) and histopathology (B to D) of kidney. Grossly, both kidneys were pale, waxy and of normal size (A). Histologically, lesions of the kidneys were characterized by tubular degeneration, necrosis and multifocal mineralization and the hypocellular glomerular tufts (thick arrow of B). The renal tubules usually contained eosinophilic proteineous and cellular casts in the lumina (thin arrows of B). The glomerular loops were replaced by amorphous, finely fibrillar to waxy, eosinophilic material (C). The homogenouse material deposited in the renal corpuscles was confirmed as amyloid in the Congo red stain (D). Note the pink colored material in the glomerular tuft (thick arrow). B and C, H&E stain; D, Congo red stain. Magnification B = ×200, C and D = ×400.

To facilitate urine production, 10% mannitol (CJ Pharmaceuticals, Korea) and furosemide (3 mg/kg; Handok Pharmaceuticals, Korea) were administered intravenously. In addition, to alleviate gastrointestinal disturbance (i.e. vomiting), metoclopramide (0.3 mg/kg; Shin-Il Pharmaceuticals, Korea) and cimetidine (5 mg/kg; CJ Pharmaceuticals, Korea) were also administered intravenously. However, hyperkalemia persisted after 24 h peritoneal dialysis. Sodium bicarbonate (2 mmol/kg; Sanpoong Pharmaceuticals, Korea) was infused slowly over 30 min with 10% calcium gluconate (CJ Pharmaceuticals, Korea) in a separate fluid line (0.5-1.0 ml/kg over 15 min). The clinical signs of dog showed waxing and waning over the first week of treatment. The dog had peritoneal dialysis for 3 consecutive days. during the first week After the first week of treatment, clinical signs were gradually improved. In laboratory tests performed after the first week of treatment, the level of blood urea (27 mg/dl) and creatinine (2.5 mg/dl) were almost returned to normal range. Serum phosphorus was back to 3.5 mg/dl. However serum potassium level was decreased to 1.6 mmol/l.

Although the laboratory findings were favorable, the dog was still oliguric. Without diuretic treatment, the dog could not voluntarily urinate. Ten day after the first visit, the dog died suddenly with signs of severe dyspnea. With owner's consent, the dog was necropsied. Lungs were filled with fluid and blood and appeared to be atelectatic. Grossly, both kidneys were diffusely tan, waxy and of normal size (Fig. 2A). There were hemorrhages and congestions in pancreas and gastrointestinal tracts. The gastric fundus was abnormally thickened with luminal ulceration and hemorrhage.

In histopathological examination, abnormal proliferation of mucosal and muscular layers of stomach. The kidney lesions were characterized by diffuse tubular degeneration, necrosis and multifocal mineralization and hypocellular glomerular tufts (Fig. 2B). The glomerular loops were filled and expanded by homogenous eosinophilic material and the basement membrane and Bowman's capsule were hyalinized and highly thickened (Fig. 2C). The dilated renal tubules usually contained eosinophilic proteineous and cellular casts in the lumina. Small numbers of lymphocytes and plasma cells were infiltrated in the interstitium. In the Congo red stain, the homogenouse material deposited in the renal corpuscles was confirmed as amyloid, as shown in Fig. 2D.

Familial renal amyloidois is an autosomal recessively inherited disease and known as familial Shar Pei fever due to intermittent fever fluctuating 40-42°C [4, 9]. The fever is generally self-limiting and lasting for 12-36 h. Another common clinical sign often accompanying the fever is swelling of a joint, usually the hock (tibiotarsal) joint and is known as Swollen Hock

Syndrome. According to recent study, affected Shar Pei dogs have increased levels of the cytokine interleukin-6 (IL-6), which is involved with the fever response and production of acute phase reactant proteins [8]. Disrupted regulation of IL-6 is involved in the pathogenesis in Shar Pei with renal amyloidosis [8]. The progression of disease with intermittent fever observed in this case might be closely related to disrupted IL-6 regulation.

Colchicine is a drug currently being recommended in Shar-Pei with renal amyloidosis [2]. However, no controlled studies have been done to prove the usefulness of colchicine in preventing renal amyloidosis, although anecdotal reports suggested that it did help to retard the progression of renal amyloidosis. However, in our case, because the dog was initially severely oliguric and pre-existing gastrointestinal disturbances, we were unwilling to use colchicine. In fact, our case was controlled with frequent peritoneal dialysis with symptomatic therapy, although colchicine was not administered.

Problems for managing this case were properly maintaining fluid and electrolyte balance with adequate energy supply. Especially in dogs with renal failure, if dogs were rapidly volume expanded and remained oliguric or anuric, the initial fluid calculation would cause rapid overhydration and pulmonary edema if continued. In our case, the main cause of death might be, in part, pulmonary edema by overhydration due to sudden deterioration of renal function. Although we assessed urine output, central venous pressure and amount of fluid infused were regularly monitored, the assessment was only valid in situation while the dog was receiving peritoneal dialysis. With peritoneal dialysis, the fluid could not accumulate in the extracelluar space. However, without peritoneal dialysis, the fluid could rapidly accumulate in the extracelluar space, if the infused fluid was excessive. The amount of fluid loaded should be reduced in this case, although the renal function appeared to be normal in biochemical tests. Probably sudden deterioration of renal function, although it was not detected in biochemical tests, might facilitate the fluid accumulation in this case.

Another sibling of this dog was suffering subclinical renal amyloidosis and had no abnormalities in biochemical tests related to renal function, except mild proteinuria (+1). Since this disease is autosomal recessively inherited, the other dog is possibly carrier state. The causative gene for renal amyloidosis has not been identified and research is currently underway at the University of Missouri College of Veterinary Medicine (Pers. Com. Dr. Gary Johnson). If DNA test for this disease can be developed, affected dogs can be easily screened out from breeding stocks. This will significantly reduce the number of affected dog in a short period of time.

In conclusion, we firstly reported a rare case of familial renal amyloidosis in Shar Pei dog in Korea.

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