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Case Report

Canine renal failure syndrome in three dogs

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Three dead dogs were brought to the College of Veterinary Medicine, Kyungpook National University for study. Clinically, all the dogs showed emaciation, anorexia, depression, hemorrhagic vomiting and diarrhea for 7~10 days before death. All the clinical signs were first noted for about one month after feeding the dogs with commercial diets. At necropsy, all 3 dogs had severe renal damage with the same green-yellowish colored nephroliths in the renal pelvis. They also showed systemic hemorrhage and calcification of several organs, which might have been induced by uremia. Microscopically, necrosis, calcification and calculi were detected in the renal tubules, and especially in the proximal convoluted tubules and collecting ducts of the kidney. These findings were supportive of a mycotoxic effect, and especially on their kidneys. However, the precise cause of the toxic effect in these cases of canine renal failure could not be determined.

Key words: canine renal failure syndrome, fungal toxin, kidney, nephrolith

During March 2004, 3 dead dogs were brought to the College of Veterinary Medicine, Kyungpook National University to elucidate the causes of their deaths. One was a 2-year old male Shitzu (case No. 1) and the other dogs were an 18-months-old female Shitzu (case No. 2) and a Malamute (case No. 3), respectively. All dogs showed emaciation, anorexia, depression, hemorrhagic vomiting and diarrhea for 7~10 day before death. These clinical signs had occurred after feeding them diets made by one company for about over a month. The owners reported that the appetite of their dogs was excellent, their activity level was normal and no weight loss had been noted before feeding them the new food. Blood data were obtained from local animal hospitals and also our college laboratory before the deaths of the 3 dogs. Values for the complete blood count using Hemavet (Drew Scientific, USA) showed anemia and thrombocytopenia in all dogs. The blood chemistry was analyzed by an analyst (Hemagen Diagnostic, USA) and an automatic dry chemistry analyzer (Fuji Dry-Chem ; Fuji Photo Film, Japan). The values of the serum chemistry profile are shown in Table 1. The blood urea nitrogen, creatinine and phosphorus levels were severely increased, but the sodium and chloride levels were decreased. The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were normal or mildly increased, respectively. Data of serum chemistry indicated severe renal failure and mild hepatic damage.

At necropsy, all the dogs showed systemic hemorrhage in the heart, lung, liver, stomach, intestine, spleen and kidney. A urine-like odor could be smelled in the oral cavity of case No. 2, which also had an ulcerated mucosal layer of the oral cavity, tongue and stomach. Hemorrhage and hypertrophy were observed in the heart. The lungs were severely congested and hemorrhagic, and the liver was necrotic and hemorrhagic with an enlarged gall bladder. Hemorrhage was also noted in the gastrointestinal tracts. The spleen showed atrophy and signs of hypovolemia, which might have been to systemic hemorrhage. In the spleen of case No. 3, hemorrhagic infarction was detected at several sites. In case No. 1, the hemorrhagic right kidney was smaller than the left kidney, and the left kidney had severe yellow-white mottled areas near the cranial part, and there was hemorrhage at the caudal part. These mottled areas were assumed to be infarction and calcification. Small brown foci were detected in the pale kidney of case No. 2. Irregular whitish spots were distributed on the surface of the kidney in case No. 3. Upon dissecting the kidneys, all 3 dogs had calculi with same green-yellow color, but the paste and the uroliths showed different sizes and shapes in the renal pelvis (Fig. 1a). Case No. 1 had also the same calculi in its hemorrhagic bladder and urethra. The urethrolith (9 × 4 × 4 mm in size) had a bullet-like shape. The collected calculi from the kidney, bladder and urethra were smeared on a slide and then observed under a microscope. All the calculi from the kidney, bladder and urethra consisted of a number of calcium carbonate-like crystals and miscellaneous amorphous crystals.

The tissues were immediately fixed in 10% neutral

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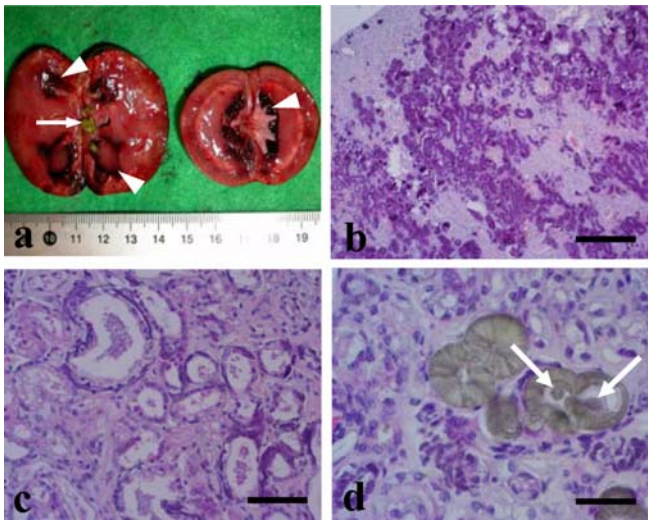

Fig. 1. Kidney of a dog. a (case No. 1.); Nephroliths (arrow) with green-yellow color in the pelvis, and hemorrhage spots (arrow head) are found in both kidney. b (case No. 1.); Severe calcification in the tubules of the cortex and hemorrhage. c (case No. 2); Necrosis of the proximal convoluted tubules and protein casts in the lumen of the tubules, including calcification in the basement membrane. d (case No. 2); Calcium and green-yellow crystals (arrow) are deposited in the tubules of the cortex. H&E stain, Scale bars for b & c; 50 μm, d; 25 μm.

buffered formalin for light microscopy; they were then routinely processed and embedded in paraffin. Sections were cut at 4 μm thickness and they were stained with hematoxylin and eosin (H&E).

Microscopically, the lesions of the 3 dogs were similar to each other. The heart, lung, liver, stomach, intestine, spleen and kidney tissues were hemorrhagic in accordance with the gross findings. Calcification was also detected in the basement membrane of the lumen of the bronchioles, alveolar wall and cerebellum, and this was markedly observed in the cardiac muscles. In the multifocally ulcerated stomach, broad calcification in the mucosal layer was observed. The mucosal layers of the tongue and intestinal tract were focally ulcerated, inflammatory and hemorrhagic. Mild centrilobular hemorrhage and necrosis were observed in the liver specimens. Mild fatty changes could often be detected. In the left kidney of case No. 1, severe calcification was detected in the cortex (Fig. 1b), which was the identical site of the grossly observed yellow-white mottled areas. In the medulla, many collecting tubules of the renal papilla were full of calculi. In the bladder of case No. 1, there were desquamation of epithelial cells, hemorrhages and cystitis. There was marked necrosis of the proximal convoluted tubules in the cortex, and protein casts were found in many tubules with interstitial nephritis (Fig. 1c). Specifically, severe damages of the kidneys were observed in all 3 dogs. Calcification and calculi in the tubules and collecting ducts were largely detected in the area of the cortex, and most calculi were round with many lines radiating from their centers (Fig. 1d). A few calcium cores of calculus or amorphous crystals were observed in the tubules.

Until now, there have been several reports that pet foods were contaminated with fungal toxins such as ochratoxins [11,12], aflatoxins [9,12], and fumonisins [1-3,13]. Here, we describe the clinical, serological, gross and histopathological findings of 3 dead dogs with renal failure that occurred after feeding them one company's dog food.

Mycotoxicosis is a serious problem, particularly in tropical and subitropical countries where the climate is moist and warm, and these factors facilitate and accelerate fungal growth [3]. The most frequent toxigenic fungi are *Aspergillus, Penicillium* and *Fusarium* species and they produce aflatoxins, ochratoxins, fumonisins, trichothecenes and zearalenone [5-7]. The characteristics of each toxin are as follows [5-7]. Aflatoxins are potent carcinogens that are produced by *Aspergillus flavus* and *A. parasiticus* in peanuts, maize and some other nuts and oilseeds. Ochratoxin A is a kidney toxin and probable also a carcinogen. It is produced by *Penicillium verrucosum* in cereal grains in cold climates by *A. carbonarium* in grapes, wines and vine fruits, and by *A. ochracues* that is sometimes in coffee beans. The same fungi that produce ochratoxins also produce another nephrotoxin, citrinin. Fumonisins, which may cause esophageal cancer, are formed by *Fusarium moiliforme* and *F. proliferatum*, but only in maize. Trichothecene are highly immunosuppressive and zearalenone causes estrogenic effects. Both are produced by *F. graminearum* and the related species. These mycotoxins are found in foodstuffs and they are not destroyed by normal processing or cooking since they are heat-stable [5,7].

Acute aflatoxicosis is rare in domestic animals, except dogs, because of the inordinately large amounts of contaminated feed that an animal would have to ingest at one time to show this malady. Aflatoxicosis in dogs is characterized by hemorrhage and centrilobular to massive hepatocellular necrosis in the acute case, and lipidosis and necrosis of the hepatocytes, biliary hyperplasia, and fibrosis and celluar atypia of hepatocytes in the chronic case [8]. Fumonisins have known to be hepatotoxic and nephrotoxic, and so induce apoptosis of hepatocytes and the proximal tubule epithelial cells, and fumonisins can also induce liver and esophageal cancer [9].

In this case, the histopathological findings were supportive of a toxic effect, and especially on the proximal convoluted tubules of the kidney and partially on the liver. Moreover, the calculi, systemic hemorrhages and calcification in several organs of the 3 dogs were compatible with uremia. The cause of canine renal failure in our cases did not seem to be toxification by aflatoxins and fumonisin since specific lesions in liver that are caused by theses toxins were not detected in spite of the mild hepatic damage. Therefore, there is a high possibility that the renal failure in our cases may have been produced by fungal nephrotoxins in the diet,

especially ochratoxins and/or citrinin, as was previously reported on a homepage of a pet diet company. However, the precise cause of renal failure could not be determined.

The clinical, serological, gross and histopathological lesions of the 3 dogs were similar to each other and they showed the same composition and color of nephroliths. In our cases, the color of all nephrolith from the 3 dogs was greenish-yellow, which seemed to be associated with the hemorrhage that consequently led to bilirubinemia. Ling *et al.* [6] reported that struvite, apatite (calcium phosphate) and urate were found in uroliths from females, and oxalate, cystine, silica and brushite were significantly more prevalent in males when they compiled and statistically analyzed the selected data from a large number of canine urinary calculi that were collected from 11,000 specimens between July 1981 and January 1994. They also reported that the prevalence of canine uroliths differs between different ages and between the sexes. However, in our 3 cases, all the calculi were mainly composed of calcium carbonate-like crystals that were identical to each other despite of the different ages and sexes. Based on the above description, our cases supported a hypothesis that the same toxic material(s) might have damaged the kidney of these dogs and then led to death. Calcium carbonate crystals are commonly seen in the urine of horses, but they may occasionally be found in the urine of dogs and cats [11]. However, to the best of our knowledge, there have been no previous reports of concurrent fungal toxin-induced renal failure and nephrolithiasis that were mainly composed of calcium carbonate-like crystals in dogs.

However, we couldn't determine the exact toxins and fungi for these three cases. It is not easy to define a mycotoxicosis when the diagnosis depends upon mycological identification of a species rather than on identifing the mycotoxin itself. However, the clinical, serological and morphological similarities between our cases, the general toxic nephropathy and the relationship between the incidence of canine renal failure syndrome after feeding with the same dog diet in some countries, and the fungal toxins that have been reported in the raw materials at pet food factorys suggest that the canine renal failure syndrome might have been induced by mycotoxicosis. This report presents evidences that support the mycotoxic hypothesis of diet-induced nephropathy and it gives some directions for future investigations.

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