Vitamin D Toxicosis in Cats: Natural Outbreak and Experimental Study

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ABSTRACT. A pathological study on 5 of 21 cats affected naturally with systemic calcinosis was performed. The animals ranged in age from 1 to 9 years. Hematology and serum chemistry analyses showed the elevated values of phosphorus, blood urea nitrogen and serum creatinine. X-ray examination disclosed the increased density of systemic bones. Histologically, marked calcification was present at the vascular walls of almost all the organs including the lungs, trachea, kidneys, heart, aorta, alimentary tracts, choroid plexus and bones. In the lungs, kidneys and stomach, the calcified lesions were associated with deposition of oxalate crystals. Serum chemistry showed more elevated values of 25-hydroxycholecalciferol (vitamin D) of the affected cats than the normal level. Retrospective examination revealed that these cats had been fed commercial pet foods containing a large amount of vitamin D (6,370 IU/100 g diet) from their young age, and its value was about ten times as much as that of the control food (680 IU/100 g diet). Pathological changes found in the cats from the experimental vitamin D toxicity were similar to those in the natural cases. In addition, tissue levels of calcium, phosphorous and zinc in the lungs and kidneys were markedly elevated in both natural and vitamin D-intoxicated cases. These findings suggest that long-term feeding of the pet food containing excessive vitamin D was responsible for the outbreak of the systemic calcinosis in the cats.

KEY WORDS: calcinosis, feline, hypervitaminosis D.


Systemic calcinosis is well known to be caused by hypervitaminosis D [2, 6–8, 12, 13, 15, 19] or hyperparathyroidism [5, 10, 16]. Natural occurrence of systemic calcinosis has been described in many domestic animals, such as cattle, horses, lambs and poultry; these cases were caused by ingestion of the plants containing agents with vitamin-D like biologic activity [13]. Some reports describe the occurrence of hypercalcemia associated with rodenticide poisoning in dogs [15] and cats [4]. There are also reports on soft tissue calcification in sucking puppies due to ingestion of milk containing high contents of vitamin A and D [8]. Sato et al. [17] have recently described the clinical and pathological findings of feline vitamin D toxicity caused by a commercial cat food containing excessive vitamin D. As reviewed elsewhere, the mechanism by which hyper-vitaminosis D induces systemic calcinosis is well known [1, 3].

Experimental studies on hypervitaminosis D have been reported in dogs [14, 19], cattle [2], horses [6] and swine [12]; all of the animals showed systemic calcinosis. In cats, however, there has been to date few reports on the experimental studies of vitamin D toxicity.

In this paper, we describe pathological findings of naturally-occurring hypervitaminosis D (systemic calcinosis) of cats. To confirm our diagnosis for the natural cases, we carried out the experimental study of dietary vitamin D toxicity of cats.

MATERIALS AND METHODS

Natural cases: From 1989 to 1990, systemic calcinosis of cats was commonly seen in Japan. Among these cats, surviving 3 cases and formalin-fixed tissue pieces of major organs from 2 dead cases were submitted to our department for pathological diagnosis. The animals ranged in age from 1 to 9 years. Clinically, chronic weight loss, anorexia episodic vomiting and signs of respiratory disturbance such as cough and difficulty in breathing were noted at the veterinary clinic, where hematology and serum chemistry analyses, and X-ray examination were performed. Complete necropsy was carried out on the three cases, and tissues including the liver, spleen, kidneys, heart, lungs, trachea, aorta, alimentary tract, lymph nodes of the superficial cervical and subiliac portions, brain, thyroid glands, parathyroid glands and bones (tumeri, femora and vertebrae) were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 6 μm, and stained with hematoxylin and eosin (HE). Selected tissues were stained with von Kossa method.

The content of vitamin D in the two commercial cat food, one of which (cat food A) had been fed to the affected cats from their young age, was analyzed by high-performance liquid chromatography (HPLC). Another cat food was also analyzed for vitamin D as reference control. In addition, wet matter concentrations of calcium, phosphorous, zinc, iron, and copper in the formalin-fixed lungs and kidneys from 4 affected cases were determined using atomic absorption spectroscopy, and values of those were analysed by two sample t test to determine significant differences from that of control.

Experimental cases: Thirteen domestic cats, ranging from 2 to 3 months old and in body weight from 240 to 1,300 g, were used in this experiment. They were vaccinated for feline panleukopenia, rhinotracheitis and calcivirus. Ten
cats (Nos. 1–10) were orally given a commercial canned food mixed with vitamin D₃ solved in the oil at a dose of 15,000 IU/kg body weight every day. Out of them, eight cats (Nos. 1–8) died from 3 to 31 days after dosing. The remaining two survived vitamin D₃-dosed cats (Nos. 9 and 10) and all control cats (Nos. 11–13) were euthanized by the intravenous administration of pentobarbital (20.0 mg/kg) on the 40th day after dosing.

RESULTS

Clinical findings

Natural cases: X-ray graphy showed the increased density of the lungs, trachea, aorta, stomach and bones, especially in the vertebrae. Serum chemistry data from the 5 cats are shown in Table 1. In the cats, BUN, serum creatinine, phosphorous and 25-hydroxylcholecalciferol (vitamin D) were mildly to severely elevated.

Experimental cases: The cats (Nos. 1–10) given vitamin D₃ at 15,000 IU/kg developed clinical signs such as anorexia (10/10), progressive depression (9/10), weight loss (8/10), polydipsia (4/10), vomiting (3/10) and dehydration (1/10). In 6 of the 10 cats (Nos. 1–6), these signs became apparent within a week after the initiation of the dosing and died 1 to 2 days after the onset of the clinical signs. Two cats (Nos. 7 and 8) developed these signs 10 days after dosing. Other two cats (Nos. 9 and 10) showed little clinical abnormalities during the dosing period. Hematology and serum chemistry analyses in 4 cats (Nos. 7–10) revealed severely elevated values of BUN (average value: 49.7 mg/dl) and calcium (average value: 19.1 mg/dl). Control cats showed no abnormalities throughout the experimental period.

Gross lesions

Natural cases: The lungs and kidneys were hard in consistency and gritty on the cut surface. The walls of thoracic and abdominal aortae, and coronary arteries were moderately thickened, had a rough corrugated surface, and were gritty on the cut surface. In some cases, the ulcer was present in the gastric mucosa. Parathyroid glands were not swollen in all the cases.

Experimental cases: Variable numbers of whitish, gritty foci (calcification) were seen at the cortico-medullary junction of the kidneys in 6 cases. Control cats were unremarkable at necropsy.

Microscopic lesions

Natural cases: Marked calcification was present at the vascular walls of almost all the organs including the lungs, trachea, kidneys, stomach, heart, aorta and bones (Table 2). In addition, interstitial fibrosis and multiple foci of calcification were observed in the alveolar, bronchial and bronchiolar walls, and bronchial cartilage of the lungs. Lumens of the affected alveoli were dilated and occasionally

<table>
<thead>
<tr>
<th>Case number</th>
<th>Age (years)</th>
<th>Sex</th>
<th>BUN (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
<th>Ca (mg/dl)</th>
<th>P (mg/dl)</th>
<th>V.D. (mg/dl)</th>
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<td>1</td>
<td>1</td>
<td>F</td>
<td>119.5</td>
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<tr>
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<td>2</td>
<td>F</td>
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<td>M</td>
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<td>6</td>
<td>F</td>
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<td>5.1</td>
<td>5.1</td>
<td>8.6</td>
<td>72.2</td>
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</table>

a) Blood urea nitrogen. b) Calcium. c) Phosphorous.
d) 25-hydroxylcholecalciferol. e) Female. f) Male. g) Not examined.

Table 2. Distribution and severity of the calcified lesion of the natural cases

<table>
<thead>
<tr>
<th>Site</th>
<th>Case number</th>
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<th>2</th>
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<tr>
<td>Trachea</td>
<td>N.E.²</td>
<td>N.E.</td>
<td>+++</td>
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<tr>
<td>Heart</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Stomach</td>
<td>+++</td>
<td>+++</td>
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<td>+++</td>
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<td></td>
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<tr>
<td>Kidney</td>
<td>+++</td>
<td>+++</td>
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<tr>
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<td>Aorta</td>
<td>+++</td>
<td>N.E.</td>
<td>+++</td>
<td>+++</td>
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<td>Bone</td>
<td>N.E.</td>
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</table>

a) Severe: lesions detectable at low magnification.
b) Not examined.
c) Moderate: lesions easily discernible at moderate magnification.
contained macrophages and lymphocytes. Deposition of oxalate crystals was frequently observed in the alveolar walls (Fig. 1). The kidneys had scattered foci of calcification of the basement membrane of the renal tubules and Bowman’s capsule. Deposition of oxalate crystals (Fig. 2), and diffuse interstitial fibrosis with the narrowed tubular lumens were evident. The stomach showed calcification of the mucosa, submucosal tissue and muscle layer with a deposition of oxalate crystals. These gastric lesions were occasionally seen near old mucosal ulcers (Fig. 3). The walls of the coronary arteries were calcified and markedly thickened with fibrosis. Granular, calcified deposits were observed around blood vessels in the myocardium. Other sites of calcification included elastic fibers of the tracheal mucosa, and tunica intima to media of the thoracic and abdominal aortae. Systemic osteosclerotic changes were seen in all cases. The bone lesions were thin canals of the cortical bones with marked calcification of the pericanalicular bone tissue, and a retardation of osteoclastic absorption of the secondary spongiosa at the diaphysis.

**Experimental cases:** Organs abnormally calcified were the lungs, trachea, kidneys, heart, stomach and choroid.

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**Fig. 1.** Lung of a natural case (No. 3). Interstitial fibrosis, marked calcification and deposition of oxalate crystals (arrows) at the alveolar walls. Infiltration of macrophages into alveolar lumens. HE × 66.

**Fig. 2.** Kidney of a natural case (No. 2). Interstitial fibrosis and marked calcification at the basement membrane of renal tubules and Bowman’s capsule. Deposition of oxalate crystals in the tubular lumens (arrows). HE × 66.
plexus (Table 3). These findings were consistent with those of the natural cases except for the absence of the lesion in the aorta and bone of experimental cases. In these organs affected, elastic fibers and basement membranes of the vascular walls (Fig. 4), renal tubules (Fig. 5), internal elastic membrane of the arteries, and lamina muscularis mucosae of the stomach (Fig. 6a) were preferably calcified. Von Kossa stain disclosed a mild to moderate calcification in the tissues such as the lungs, trachea, kidneys, heart, stomach (Fig. 6b) and choroid plexus. None of the control cats showed an abnormal calcification described above.

Tissue levels of calcium, phosphorus and zinc in the lungs and kidneys of natural and experimental cases were shown in Tables 4 and 5. Both natural and vitamin D-intoxicated cases showed higher concentrations of calcium, phosphorus and zinc in the lungs and kidneys than control cats (Tables 4 and 5). Values of phosphorus and zinc in the lung of natural cases were significantly higher than those of control (phosphorus; p<0.001, zinc; p<0.01).

DISCUSSION

The pathological condition of our natural cases is systemic calcinosis. The nature and distribution of the lesions are almost consistent with those described in the recent study [17], and are similar to those of hypervitaminosis D in other domestic animals [1, 2, 5, 7]. The cause of this feline disease seems not to be primary or

Table 3. Distribution and severity of the calcified lesion of the experimental cases

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Vitamin D-intoxicated cases were fed a commercial canned food added with 15,000 IU/kg body weight of vitamin D. 

a) Moderate: lesions easily discernible at moderate magnification.
b) Severe: lesions detectable at low magnification.
c) Mild: lesions few and minimal.
d) No lesions.
secondary hyperparathyroidism because there are no findings of the bone absorption and the chief cell hyperplasia in the parathyroid [5, 10, 16]. Retrospective examination revealed that the affected cats had ingested the commercial cat foods containing much larger amount of vitamin D than daily requirement of cats [9]. Serum chemistry of these cats showed the elevated value of 25-hydroxycholecalciferol (vitamin D). From these findings, we postulated that the cause of the natural cases (systemic calcinosis) was hypervitaminosis D due to the ingestion of excess vitamin D in the cat food A. In this study, experimental vitamin D-intoxication could reproduce the same lesions as in the natural cases. The number of the cases affected with systemic calcinosis dramatically decreased after the company reduced the amount of vitamin D in the cat food A. Therefore, it could be concluded that the cause of the systemic calcinosis fulfilled in Japan from 1989 to 1990 was the cat food containing excess vitamin D. The origin of oxalate crystals in the calcified lesions remains unclear because the amount of oxalate in the discussed cat food was not estimated yet.

Contrary to the natural cases, experimental cases had no calcified lesions in the bones and aortae. Calcification in the bones developed in the cats by treatment with vitamin D for eight months [4] and some chronic cases of the cattle affected with hypervitaminosis D [2]. Therefore, it seems
appropriate that, in the bones and aortae, calcification can occur for a relatively long period exposure of excess vitamin D. Alternatively, in the vascular system, the coronary artery appeared to be more preferentially affected by vitamin D toxicity since almost all the experimental cats for a short period had calcified lesions in the coronary arteries but not in the small or large arteries of any other organs.

REFERENCES

VITAMIN D TOXICOSIS IN CATS


