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NOTE

Pathology

Severe calcification of systemic blood vessel walls caused by continuous hypercalcemia in a cat with congenital hypothyroidism

Yusuke TANAKA[1)], Michio OOIKE[2)], Kenichi WATANABE[1)], Noriyuki HORIUCHI[1)] and Yoshiyasu KOBAYASHI[1)]*

[1)]Department of Veterinary Medicine, Obihiro University of Agriculture and Veterinary Medicine, Nishi 2-11, Inada-cho, Obihiro, Hokkaido 080-8555, Japan
[2)]Ooike Animal Hospital, Minami 5-46-21, Nishi 19, Obihiro, Hokkaido 080-8555, Japan

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ABSTRACT. A 97-day-old male Japanese domestic cat was diagnosed as congenital hypothyroidism. During the treatment, continuous hypercalcemia was detected. Although fluid therapy was performed, the cat died at the age of 1785 days. At autopsy, both parathyroid glands were enlarged, and elastic arterial walls were increased in thickness and hardness. Histopathological examination revealed hyperplasia of both parathyroid glands and interstitial fibrosis of bilateral kidneys. Severe calcification of the tunica media and tunica externa in systemic elastic and muscular arteries were also observed. These calcifications were considered to be due to renal secondary hyperparathyroidism. In the present case, hypothyroidism might have caused hyperparathyroidism through renal failure. In veterinary medicine, this is the first reported case of hypothyroidism accompanied with hyperparathyroidism.

KEY WORDS: calcification, congenital hypothyroidism, hypercalcemia, hyperparathyroidism

Functional neoplasms of parathyroid glands, renal failure, and some malignant tumors, such as anal sac gland carcinoma and T cell lymphoma in dogs, can cause hypercalcemia. These diseases promote secretion of parathyroid hormone (PTH) or parathyroid hormone-related protein (PTH-rp) directly or indirectly. Excessive PTH or PTH-rp causes calcification of internal organs, such as the lungs, endocardium, kidneys, and stomach, as well as tunica intima and tunica media of vessels in these organs through an imbalance between calcium and phosphorus concentrations in the blood [7, 12].

Feline congenital hypothyroidism is an uncommon endocrine disease that mainly occurs in kittens [10]. Defect in thyroid hormone biosynthesis and hypoplasia of thyroid gland has been known as the cause of feline congenital hypothyroidism [8]. In veterinary medicine, cases of hypothyroidism accompanied with hyperparathyroidism have not been previously reported. Here, we present a case of feline congenital hypothyroidism accompanied with continuous hypercalcemia caused by hyperparathyroidism.

A 97-day-old male Japanese domestic cat exhibited hypodynamia, anorexia, vomiting, and constipation. The size of the animal was small, which was inappropriate for the age. A broad head, short and thick neck, and short extremities were also observed. At the initial admission, slight increases in blood urea nitrogen (BUN), creatinine, and calcium were detected. The concentration of serum thyroxin (T4) was below the detection limit (<0.1 μg/d*l*) (Reference interval (RI): 0.8–3.9 μg/d*l*); in contrast, the thyroid-stimulating hormone (TSH) concentration was markedly high (1.4 *n*g/m*l*) (RI: <0.3 *n*g/m*l*). From these clinical findings, the kitten was diagnosed as congenital hypothyroidism. Administration of L-thyroxin using a dosage of 17 μg/kg continued for 12 days. However, the continuous high-dose administration of L-thyroxin worsened its hypodynamia. Thus, the treatment was discontinued. Serum T4 was below the detection limit at 127 and 136 days of age. To avoid the occurrence of side effects, continuous low-dose L-thyroxin therapy was applied. Dose adjustments were carried out from 1.0 to 11 μg/kg based on the serum T4 level. Although serum T4 was detected from 298 to 1,497 days of age, the value was still below the reference range (Table 1).

During the treatment for congenital hypothyroidism, BUN and creatinine increased from 298 and from 1,365 days of age, respectively. Moreover, an increase in calcium was noted at 525 days of age, and hyperphosphatemia was also observed later. Although fluid therapy was performed by a clinician, the abnormal values of BUN, creatinine, calcium, and phosphorus were not improved (Table 1). The concentrations of ionized calcium, intact-PTH, and PTH-rp measured at 525 days of age were 2.1 nmol/*l* (RI: 1.22–1.5), 7.1 *p*g/m*l* (RI: 8.0–25.0), and 1 pmol/*l* (RI: 0–1.5), respectively. Ultrasonographic examination at 1757 days of age disclosed enlarged bilateral parathyroid glands. Unfortunately, the cat died at 1,785 days of age and was subjected to autopsy at the

*Correspondence to: Kobayashi, Y.: kyoshi@obihiro.ac.jp

Table 1. Chronological summary of dosage of L-thyroxin and biochemical examination of blood test

Days old		97	127	136	298	525	1,365	1,392	1,497	1,784
Dosage of L-thyroxin (μg/kg)		17	NA	1.0	4.75	7.9	9.0	NA	11.0	NA
T4 (μg/d*l*)	(RI: 0.8–3.9)	BDL	BDL	BDL	0.1	0.5	0.7	0.4	0.7	BDL
BUN (mg/d*l*)	(RI: 20–30)	30.8	-	-	61.8	45.0	55.1	77.0	52.0	167.7
Creatinine (mg/d*l*)	(RI: 0.8–1.8)	2.6	-	-	1.5	1.7	2.6	2.8	2.9	2.0
Calcium (mg/d*l*)	(RI: 6.2–10.2)	11.2	-	-	-	15.0	19.7	22.1	15.0	11.4
Phosphorus (mg/d*l*)	(RI: 4.5–8.1)	-	-	-	-	4.1	7.2	8.1	9.4	13.8

BUN, Blood urea nitrogen; RI, Reference interval; NA, Administration of L-thyroxin was not carried out; BDL, Below the detection limit (<0.1 μg/d*l*). -: The value was not examined.

Fig. 1. Walls of the aortic arch, descending aorta, thoracic aorta, abdominal aorta, celiac aorta, and cranial mesenteric artery are increased in thickness due to diffuse calcification.

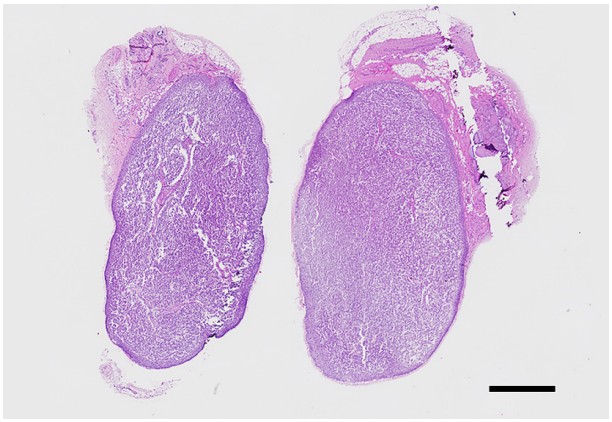

Fig. 2. Only a few normal thyroid gland tissues are observed next to the enlarged parathyroid glands. Hematoxylin and eosin stain, bar=1,000 μm.

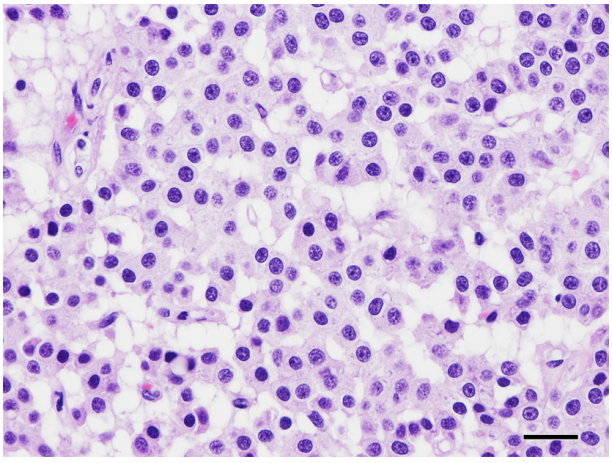

Fig. 3. Parathyroid gland. Chief cells with abundant lightly eosinophilic cytoplasm are observed. There is no nuclear atypia, pleomorphism, or mitosis in these chief cells. Hematoxylin and eosin stain, bar=20 μm.

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At autopsy, the size of the left and right parathyroid glands was 7.5 × 5 × 3 and 6.5 × 4.5 × 3 mm, respectively. The apparent thyroid gland tissues were not grossly observed. Systemic arterial walls were increased in thickness and hardness, and the changes were severe in the aortic arch, descending aorta, thoracic aorta, abdominal aorta, celiac aorta, and cranial mesenteric artery (Fig. 1). In the subcutis of the limbs, cervical region, and trunk, whitish hard sandy masses, 5 to 15 mm in diameter, were scattered. Both kidneys were atrophied (left side: 16 × 20 × 17 mm; right side: 14 × 21 × 16 mm), and the sternum exhibited an S-shape.

Histopathological examination revealed bilateral marked enlargement of parathyroid glands (Fig. 2). Bilateral parathyroid

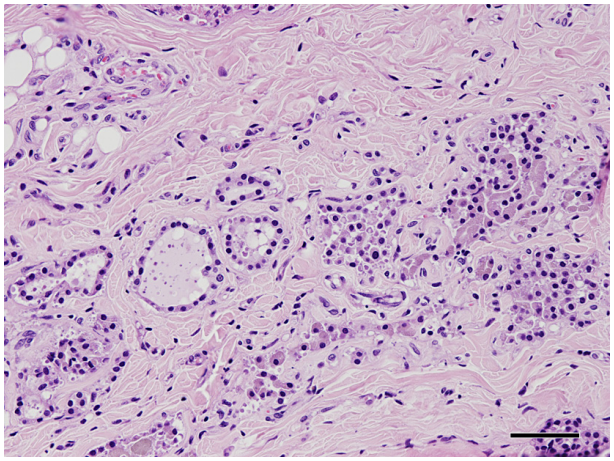

Fig. 4. Thyroid gland. The follicles is small in number. In collagen-rich interstitium, there are only a few follicles filled with colloid. There are also multifocal clusters formed by follicular cells with large pale eosinophilic cytoplasm (right side of the image). Hematoxylin and eosin stain, bar=50 μm.

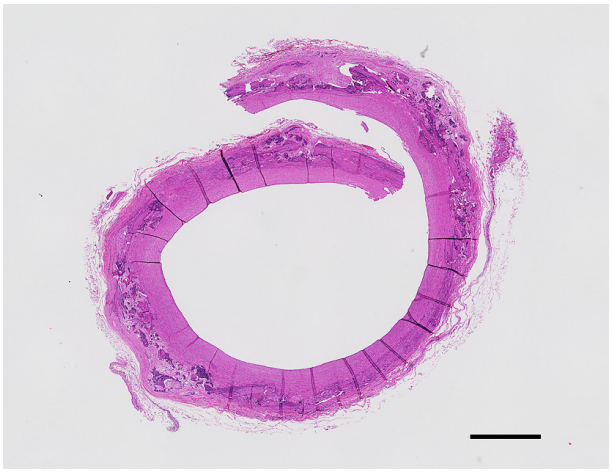

Fig. 5. Thoracic aorta. There is calcification of the tunica media and externa. In contrast, the tunica intima is normal. Hematoxylin and eosin stain, bar=1,000 μm.

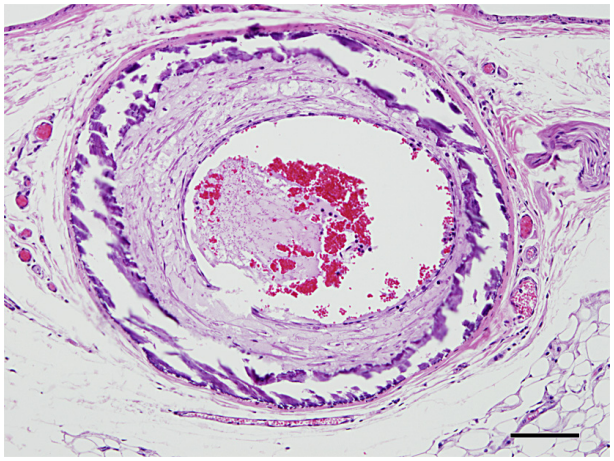

Fig. 6. Mesenteric artery. Although severe calcification is observed at the tunica media and tunica externa, tunica intima is normal. Hematoxylin and eosin stain, bar=100 μm.

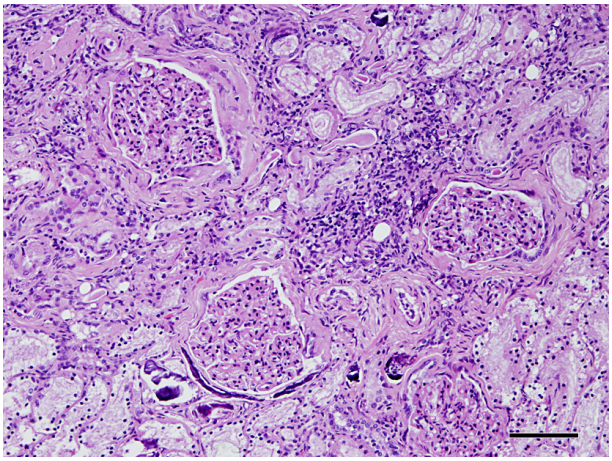

Fig. 7. Kidney. There is focal fibrosis, mononuclear cell infiltration, and calcification of renal tubules and Bowman's capsules. Hematoxylina and eosin stain, bar=100 μm.

glands were composed of closely packed chief cells with abundant lightly eosinophilic cytoplasm. There was no nuclear atypia, pleomorphism, mitosis, or invasion into surrounding tissues in these chief cells (Fig. 3). In both thyroid glands, the follicles was small in number. Only a few follicles lined by low cuboidal follicular cells were filled with colloid. There were multifocal clusters formed by follicular cells with large pale eosinophilic cytoplasm in collagen-rich interstitial connective tissue (Fig. 4). Severe calcification of blood vessel walls was observed in both elastic arteries and muscular arteries of systemic organs and tissues (spleen, kidneys, heart, lungs, adrenal glands, tongue, stomach, mesentery, cerebrum, cerebellum, pituitary gland, and cranial dura matter). In both types of arteries, the tunica media and tunica externa were severely damaged; in contrast, the tunica intima was normal (Figs. 5 and 6). Although the calcification of systemic blood vessel walls was severe, the pathologic changes in parenchymal cells in systemic visceral organs were minimal except for in the kidneys. In the kidneys, calcification of renal tubules and Bowman's capsules, interstitial fibrosis, and glomerulosclerosis were observed (Fig. 7). The calcification of lungs was evident in capillary, venous, and arterial walls. In stomach, the calcification was localized in arterial walls of submucosa and muscular layer. Subcutaneous whitish masses were composed of depositions of calcium in the dermis, subcutaneous tissues, and cutaneous muscles. In the thighbone, the Howship's lacunae was expanded, and an increase in fibroblasts around the bone trabeculae was also observed.

On the basis of the macroscopic and histopathologic findings, the bilaterally enlarged parathyroid glands were diagnosed as hyperplasia. The cause of parathyroid gland hyperplasia is mainly categorized as renal failure, nutritional imbalances, or primary

[12]. Due to the presence of clinical and histopathological evidence of severe renal damage, the cause of the present hyperplasia was considered to be renal failure.

In the present case, although the concentration of PTH at 525 days of age was normal, we considered that the hypercalcemia was caused by increased concentration of PTH for several reasons. Firstly, hyperplasia of parathyroid glands is associated with production and secretion of PTH [9, 12]. The present case had marked hyperplasia of bilateral parathyroid glands. The findings suggested that they also secrete abundant PTH and cause hypercalcemia. Secondly, the presence of expanded Howship's lacunae and abundant fibroblasts around the thighbone trabeculae also suggested the enhanced secretion of PTH. Thirdly, deformities in keel bones are often observed in laying hens that require continuous high bone resorption to lay eggs [11]. The S-shaped deformity in the sternum in the present case was probably attributed to long-term bone resorption like in laying hens. Although the examination of PTH was performed only at 525 days of age, the value would have probably been high if measured after this point.

Arterial medial and intimal calcifications are common lesions in animals with renal failure and toxicosis with vitamin D [7], which are also known to cause calcification of the parenchyma in the lungs, endocardium, kidneys, and stomach [7]. In the present case, severe calcification of blood vessel walls was observed in the tunica media and tunica externa in systemic elastic and muscular arteries. In addition, although the calcification of blood vessels was severe, that of parenchymal cells of the visceral organs was minimal. These distributions are atypical in severe and continuous hypercalcemia.

In human medicine, calciphylaxis is known as a disease in which calcification is observed specifically in blood vessel walls. In this condition, calcified systemic small- to medium-sized blood vessel walls cause local ischemia and functional disorder of organs and tissues [4]. Cutaneous blood vessels are frequently damaged, and the lesions may induce small vessel thrombosis and painful and non-treatable skin ulcers, which are essential for diagnosis of calciphylaxis [4]. Although the pathogenesis of calciphylaxis remains unclear, abnormalities of blood clotting factor were suspected as risk factors [3]. These predisposed conditions include antiphospholipid syndrome and deficiency of protein C, protein S, or antithrombin [3]. In the present case, the absence of calcification and thrombosis in cutaneous blood vessel walls, and of skin ulcers did not concur with the lesions of calciphylaxis.

The hypothyroidism in this case was suspected to be congenital because of the age, low value of T4, and high value of TSH [10, 13]. Because histological findings of thyroid glands of the present case were consistent with those of the reported case of thyroid gland hypoplasia in kittens [14], the cause of congenital hypothyroidism in the present case was considered to be a congenital thyroid hypoplasia. Hypothyroidism can cause renal dysfunction through decreasing renal blood flow and glomerular filtration [2, 5]. The chronically damaged kidneys in the present case were probably attributed to congenital hypothyroidism. Although hypothyroidism was not associated with hyperparathyroidism directly, hypothyroidism may cause hyperparathyroidism through renal failure.

In humans, an association between thyroid hormones and vascular calcification has been studied. Klotho produced by distal nephron and matrix GLA protein (MGP) produced by vascular smooth muscle are known as inhibitors of vascular calcification. Because the circulating level of triiodothyronine (T3) is positively associated with levels of Klotho and MGP, T3 is considered to prevent vascular calcification by up-regulation of those calcification inhibitors [1, 6]. In veterinary medicine, there are no study revealing an association between T3 and these calcification inhibitors. Although the T3 value was not examined directly, the present case was diagnosed as congenital thyroid gland hypoplasia. Therefore, as in humans, hypothyroidism may contribute to an atypical distribution of calcification in blood vessel walls of the present case. Further studies of similar cases are required to elucidate the mechanism. Importantly, clinicians should pay close attention to the values of not only T4 and TSH, but also BUN, creatinine, calcium, phosphorus, and PTH in cats with congenital hypothyroidism, to prevent occurrence of renal failure and renal secondary hyperparathyroidism.

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