NOTE *Surgery*

Fibrodysplasia Ossificans Progressiva-like Condition in a Cat

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ABSTRACT. Fibrodysplasia ossificans progressiva (FOP)-like condition was diagnosed in a Japanese domestic cat with stiffness, marked atrophy of the muscles, and limited mobility of all joints in both the pelvic limbs. Etretinate, a retinoid, was used for medical management; however, no improvement in the clinical signs was observed. Inheritance of the disorder has not yet been demonstrated. Furthermore, the clinical signs and histopathological findings of feline FOP-like condition in the present case differed from those of the previously reported cases.

KEY WORDS: feline, fibrodysplasia ossificans progressiva, heterotopic ossification.

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Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder of the connective tissues with progressive, generalized, and disabling heterotopic ossification [3, 4]. In humans, the clinical and anatomical features of FOP are characterized by congenital malformation of the great toes with a hallux valgus deformity; first evidence of painful swelling of soft tissues involving tendons, ligaments, fascias, and skeletal muscle; and progression of the ossification from the dorsal, axial, cranial, and proximal regions to the ventral, caudal, and distal regions of the body [3, 4]. In addition, the pathogenesis of human FOP has been reported to be associated with the overexpression of bone morphogenetic protein (BMP)-4 [9]. Currently, there are no reports on the availability of definitive treatment and prophylaxis for FOP. The patient may have a shortened life span due to respiratory failure resulting from disability of the chest wall [1, 4, 15].

On the other hand, limited information is available on FOP-like condition in the field of veterinary medicine because there are very few published reports on naturally occurring heterotopic ossification in animals [2, 5–8, 11–14]. Thus far, only 6 cases of cats with FOP-like condition have been reported, and these were limited to the United States [12–14] and Canada [7]. The prevalence and inheritance of feline FOP-like condition remain unknown. In this report, we describe a case of a Japanese domestic cat with FOP-like condition and compare it with the 6 previously reported cases.

A castrated male Japanese domestic cat (age, 1 year and 3 months; body weight, 4.5 kg) was referred to us due to pelvic limb stiffness. Five months prior to referral, the patient exhibited lameness of the left pelvic limb and a stiff left tarsal joint. During the following 3 months, the right tarsal joint and both stifle joints successively became stiff. The cat\rquote s condition deteriorated gradually and eventually led to a loss of voluntary motion of the bilateral pelvic limbs. Traumatic injury was not observed, and the patient experienced occasional pain when the pelvic limbs were touched. No genealogical information was available.

The initial physical examination revealed bilateral stiffness and marked atrophy of the femoral and crural muscles, and a limited mobility on both sides of the hip, stifle, and tarsal joints. The patient had fever (39.9°C) and experienced pain during palpation of the pelvic limbs; however, trauma and swelling of the pelvic limbs were not observed. The results of neurological examination indicated that both the pelvic limbs exhibited loss of postural reactions and spinal reflexes could hardly be observed. However, responses to superficial and deep painful stimuli were observed in both the pelvic limbs. The values of hematological and routine serum biochemical tests were within the normal reference ranges, except for a significant increase in the serum creatine kinase (CK) concentration (1,077 mg/d*l*) and slight increase in the serum aspartate aminotransferase (AST) (66 U/*l*) and glucose (187.7 mg/d*l*) concentrations (Table 1). Analysis of the CK isozyme pattern revealed the CK-MM, CK-MB, and CK-BB concentrations to be 944.5, 65.7, and 56.0, respectively. The results of serologic tests for toxoplasmosis, feline immunodeficiency virus, and feline leukemia virus were negative (Table 1). Coombs'test was negative, and antinuclear antibody was not detected (Table 1). Radiography revealed multiple areas of well-defined mineralization in the right caudal thigh and crural muscles, around the right stifle and ankle joints, and in the left proximal and caudal thigh muscles (Fig. 1). Such ectopic mineralization was not observed in the other regions.

No abnormality was observed following the insertional activity on electromyography of both the pelvic limbs. The motor nerve conduction velocities of the bilateral ulnar and tibial nerves were within the normal ranges. Computed tomography (CT) revealed ectopic columnar mineralization with a pulp-like structure and smooth margins in the intermuscular area between the right semitendinosus and semimembranosus muscles (Fig. 2a); multiple irregular and

Table 1. Laboratory findings of the patient

WBC	8,000/μl	BUN	18.9 mg/dl	CK	1,077 mg/dl
Neutrophils	6,480/μl	Crea	1.2 mg/dl	CK-MM	994.5 mg/dl
Lymphocytes	800/μl	Glu	187.7 mg/dl	CK-MB	65.7 mg/dl
Monocytes	320/μl	Alb	3.52 g/dl	CK-BB	56.0 mg/dl
Eosinophils	400/μl	Glob	4.18 g/dl	Ca	10.11 mg/dl
RBC	$11.43 \times 10^6/\mu l$	AST	66 U/l	P	2.12 mg/dl
Hb	19.6 g/dl	ALT	52 U/l	Mg	2.30 mg/dl
PCV	54%	ALP	66 U/l	Na	153 mEq/l
MCV	56 fl	TBil	0.4 mg/dl	K	3.7 mEq/l
MCHC	17.1 g/dl	TCho	68 mg/dl	Cl	116 mEq/l
Plt	$257 \times 10^3/\mu l$				
TP	8.7 g/dl		FeLV	Negative	
			FIV	Negative	
			Toxoplasmosis	<8	
			Coombs test	Negative	
			Antinuclear antibody	Negative	

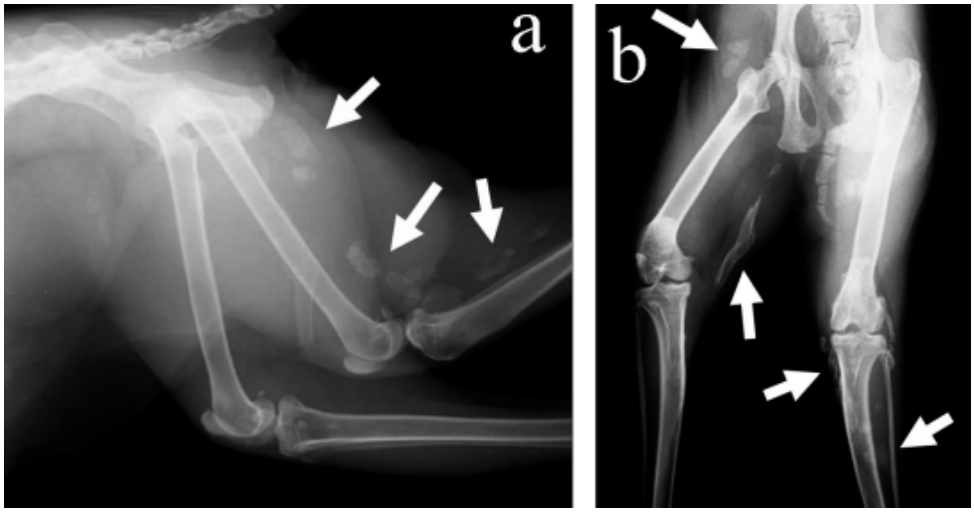

Fig. 1. Lateral (a) and ventrodorsal (b) radiographic findings of the hindquarter. White arrows indicate multiple areas of well-defined ectopic mineralization in both the pelvic limbs.

smooth clumpy mineralization in the intermuscular area of the left semimembranosus, semitendinosus, adductor, and biceps femoris muscles (Fig. 2a); and multiple columnar and clumpy mineralization with a pulp-like structure partially around the left popliteal, superficial digital flexor, and gastrocnemial muscles (Fig. 2b).

Two biopsy samples were obtained—one from the right semimembranosus area and the other from the left superficial digital flexor muscular area. Intraoperative findings revealed partially firm and thickened fibrosing and calcifying fascias and an intermuscular rigid and white osteoid structure with a luminal myeloid tissue. The samples were fixed in 10% neutral buffered formalin and decalcified, if required. They were then embedded in paraffin and cut to obtain 4-μm thick sections. The sections were stained with hematoxylin and eosin as well as Masson's trichrome dye. Histopathological examination revealed endochondral ossification with a normal osteogenetic process and fibrous proliferation of the fascias (Fig. 3a). In addition, bridging and networking of the osseous tissue with the luminal myeloid tissue were observed. Atrophy and lysis of myocytes occurred due to the compression of the fascial ossification (Fig. 3b); however, no inflammatory cellular infiltration was observed. Based on the clinical signs and the results of diagnostic imaging and histopathological examination, a definitive diagnosis of FOP-like condition was made.

The patient was administered with etretinate (Tigason®, Chugai Pharmaceutical Co., Tokyo, Japan), a synthetic vitamin A derivative (retinoids), at a dose of 1.0 mg/kg (PO, SID). However, the clinical signs did not improve, and radiographic examination 144 days after the initial presentation revealed new mineralization in the pelvic limb. Oral administration of etretinate was then withdrawn, and the owner did not permit any further follow-up examinations and therapeutic trials.

In our case, the clinical, radiographic and CT findings

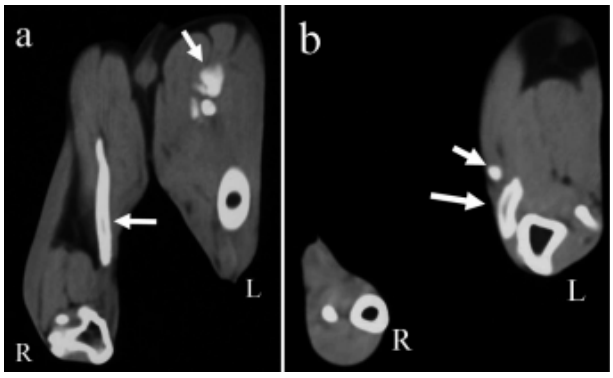

Fig. 2. Cross-sectional computed tomographic (CT) findings of the pelvic limbs at the thigh (a) and crural (b) level. White arrows indicate multiple ectopic mineralization in the intermuscular areas.

suggested progressive ectopic intermuscular mineralization and no cutaneous and subcutaneous mineralization, and the histopathological findings revealed endochondral ossification. The findings were similar to human FOP. However, our patient exhibited no deformity of the paw digits similar to the congenital malformation of the great toes that is typically observed in humans with FOP. Therefore, we definitively diagnosed the present case as an FOP-like condition. No deformity of the paw digits has been observed in the previous reports on feline FOP-like condition [7, 12–14]. In addition, inheritance of the disorder could not be demonstrated in this case as well as in the 6 previously reported feline cases. It remains unknown whether feline FOP-like condition is an autosomal dominant disorder similar to that observed in humans.

In our case and the 6 previously reported cases, the clinical findings and the regions of ectopic ossification varied. The differences in the clinical signs and predisposed regions may depend on the pathogenesis; however, no studies on the pathogenesis of feline FOP-like condition have been reported. In humans, the pathogenesis of FOP remains unknown; however, FOP was shown to be associated with the overexpression of BMP-4 [3, 4, 9]. Hence, it is imperative to carry out further investigations on the expression level of BMP-4 in individual cases of feline FOP-like condition. Furthermore, other pathogenic factors may be associated with feline FOP-like condition because its clinical features differed from those in humans.

Although in the previous cases, the feline patients with FOP-like condition were treated with vitamin E and selenium [7] or prednisone followed by disodium etidronate [13], neither of these therapeutic regimens was effective. In humans with FOP, disodium etidronate and prednisone have been demonstrated to have limited effects on FOP, and prolonged administration resulted in osteomalacia and impairment of ossification in the normal bone [1, 3, 4]. Therefore, these therapeutic strategies are not currently recommended. In our case, etretinate, a retinoid, was used for medical management. Retinoids are regarded as potential therapeutic agents for human FOP because of their ability to inhibit the differentiation of mesenchymal tissue into cartilage and/or bone [15]. However, in the present case, etretinate showed no effects on the progression of heterotopic ossifications. Other plausible therapeutic approaches for FOP include cyclooxygenase-2 inhibition, anti-angiogenic therapy, radiation, and gene therapy with BMP antagonists [3, 4]. Further investigations on feline FOP-like condition are required to determine whether these therapeutic strategies are clinically effective.

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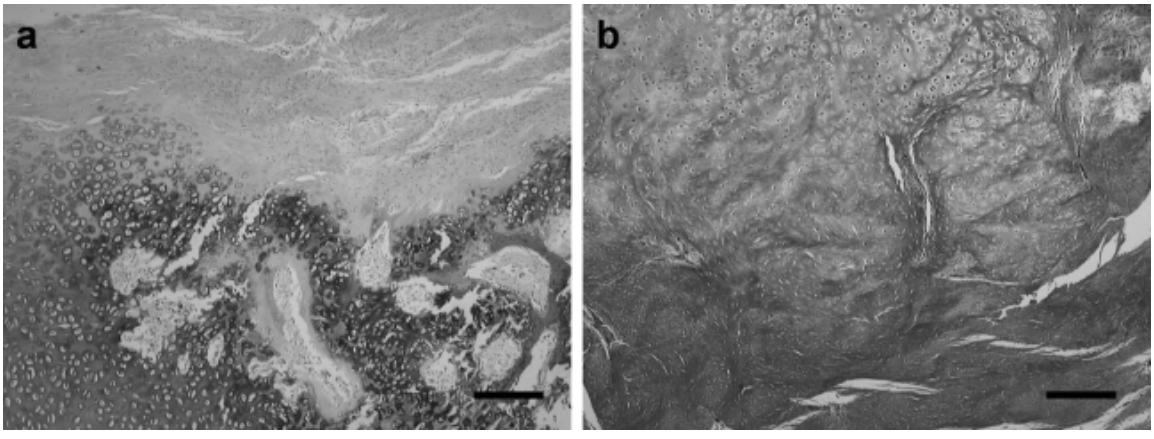

Fig. 3. Histopathological findings of the biopsy samples obtained from the left superficial digital flexor muscle. The sections were stained with hematoxylin and eosin (a) and Masson's trichrome dye (b). Endochondral ossification was observed with a normal osteogenetic process and fibrous proliferation of the fascias. Scale bar=250 μm.

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