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Case Report

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Efficacy and Complications of Palliative Irradiation in Three Scottish Fold Cats with Osteochondrodysplasia

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Case 1

An intact female Scottish Fold (SF) cat under 12 months of age was presented to the Veterinary Medical Teaching Hospital at the Nippon Veterinary and Life Science University (VMTH-NVLU) for exercise intolerance because of chronic pain of several month duration. Upon palpation, she was almost immobile and was unwilling to be touched. Her limbs were short, thick, and deformed; huge plantar exostoses and misshapen toenails were evident. The plantar skin was stretched because of the exostoses. The tail was thick and inflexible. No treatment had been administered.

Radiography of the 4 limbs, tail (Fig. 1), abdomen, and chest was performed. Radiographs of the forelimbs revealed new bony proliferations on the carpal, fifth metacarpal, and phalangeal bones. The distal metacarpal bones and phalanges were short, thick, and misshapen. On the hindlimbs, new bony proliferations were observed on the tarsal, metatarsal, and phalangeal bones. These bones were also short, thick, and misshapen. The radiograph of the tail showed bony proliferations and the caudal vertebrae were short and malformed. The intervertebral spaces were reduced and the caudal vertebrae were in direct contact. No other bone lesions were detected on radiographic examination of the thorax and abdomen.

Based on the breed, signalment, clinical signs, and radiographic findings, the cat was diagnosed with SF osteochondrodysplasia (SFOCD). The owner abandoned the cat because of the severity of the disease. The cat was adopted by one of our staff, and informed consent was obtained from the individual. Radiation therapy (RT) was performed on the limbs on the right side as palliative treatment for chronic pain. To evaluate the efficacy and complications, only the unilateral limbs were irradiated. The treatment plan was developed based on the X-ray CT[a] images using 3D treatment planning software.[b] During the treatments, the cat was anesthetized and placed in a recumbent position on a vacuum bag immobilization device[c] that conformed to the patient's shape. Although artificial skin was used to wrap the limbs (to regulate the dose), blocks, wedges, and a multileaf collimator were not used. Palliative RT was performed using a 4 MV X-ray linear accelerator.[d] The protocol consisted of 6 fractionated doses of 1.5 Gy each on a Monday–Wednesday–Friday schedule for a total dose of 9 Gy.

Clinical signs were resolved within 2 weeks from the start of RT. After the course of radiotherapy, radiography was performed regularly (Fig. 1). Progression of disease was not detected. No acute complications including alopecia, pigmentation, and moist desquamation occurred. There were no radiographic differences between the treated and untreated sides. At 38 months, the cat presented with signs of severe pain in the limbs on the left side that had not been irradiated. Radiation therapy was performed on the left forelimbs and hindlimbs according to the protocol described above. The cat was monitored for 60 months. At 60 months, late radiation complications including alopecia, bone or nerve necrosis, and tumorigenesis were not observed (Fig. 2). The cat readily walked, ran, and jumped. Radiography revealed no change in the bone lesions.

Case 2

A 2-year-old castrated male SF cat was referred to the VMTH-NVLU for chronic hindlimb pain of

Abbreviations:

Gy	gray
LD-RT	low-dose radiation therapy
RT	radiation therapy
SF	Scottish Fold
SFOCD	Scottish Fold osteochondrodysplasia
VMTH-NVLU	Veterinary Medical Teaching Hospital at the Nippon Veterinary and Life Science University

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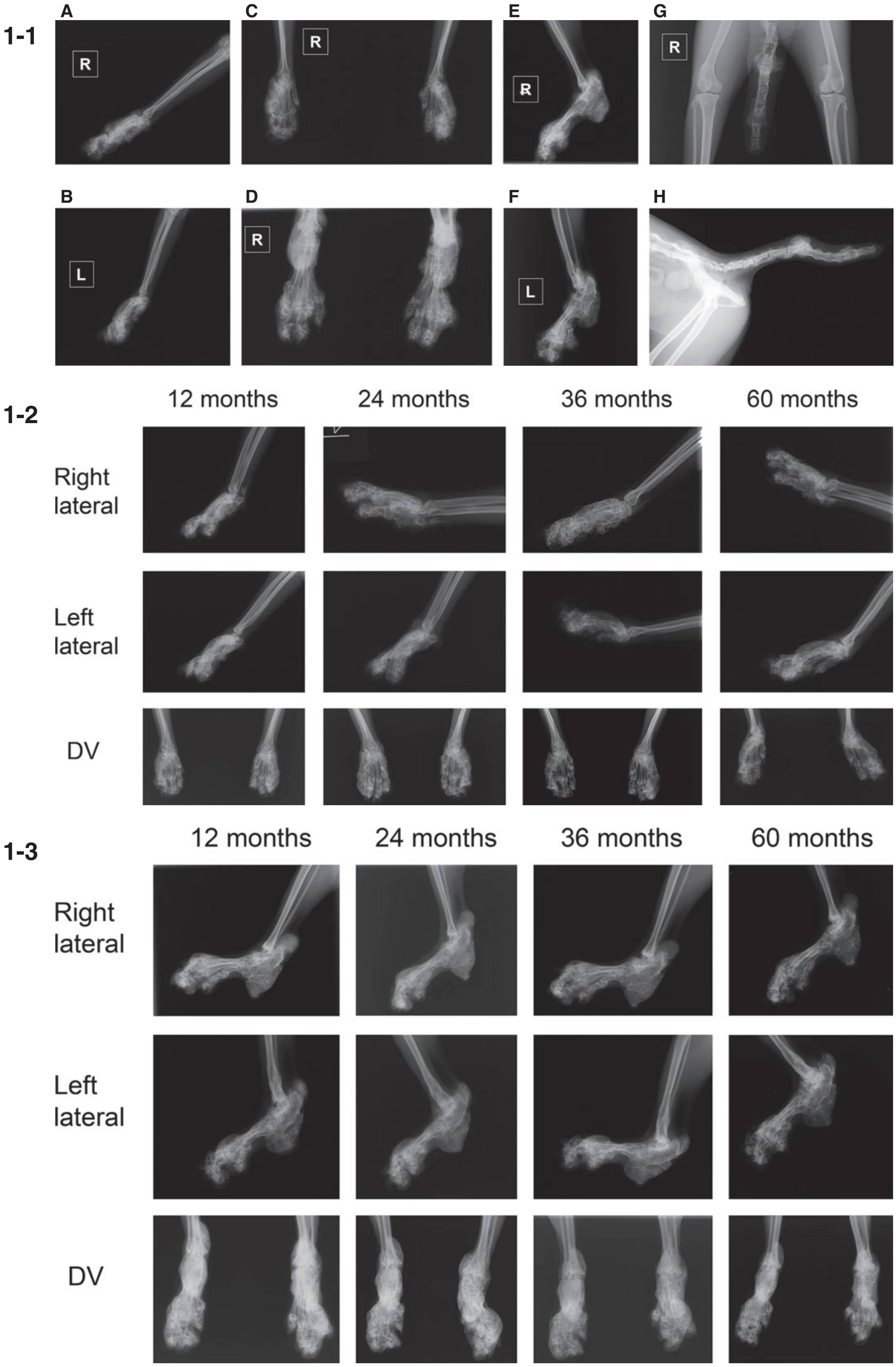

Fig. 1. Radiographs of the limbs and tail of the cat in case 1. 1–1 Radiographs at initial diagnosis (0 month). (**A**) Right carpus (lateral). (**B**) Left carpus (lateral). (**C**) Both carpi (dorsoventral, DV). (**D**) Both tarsi (DV). (**E**) Right tarsus (lateral). (**F**) Left tarsus (lateral). (**G**) Tail (ventrodorsal, VD). (**H**) Tail (lateral). 1–2 Serial radiographs of the forelimbs at 12, 24, 36, and 60 months. Radiographic findings did not change over time. 1–3 Serial radiographs of hindlimbs at 12, 24, 36, and 60 months. Radiographic findings did not change over time.

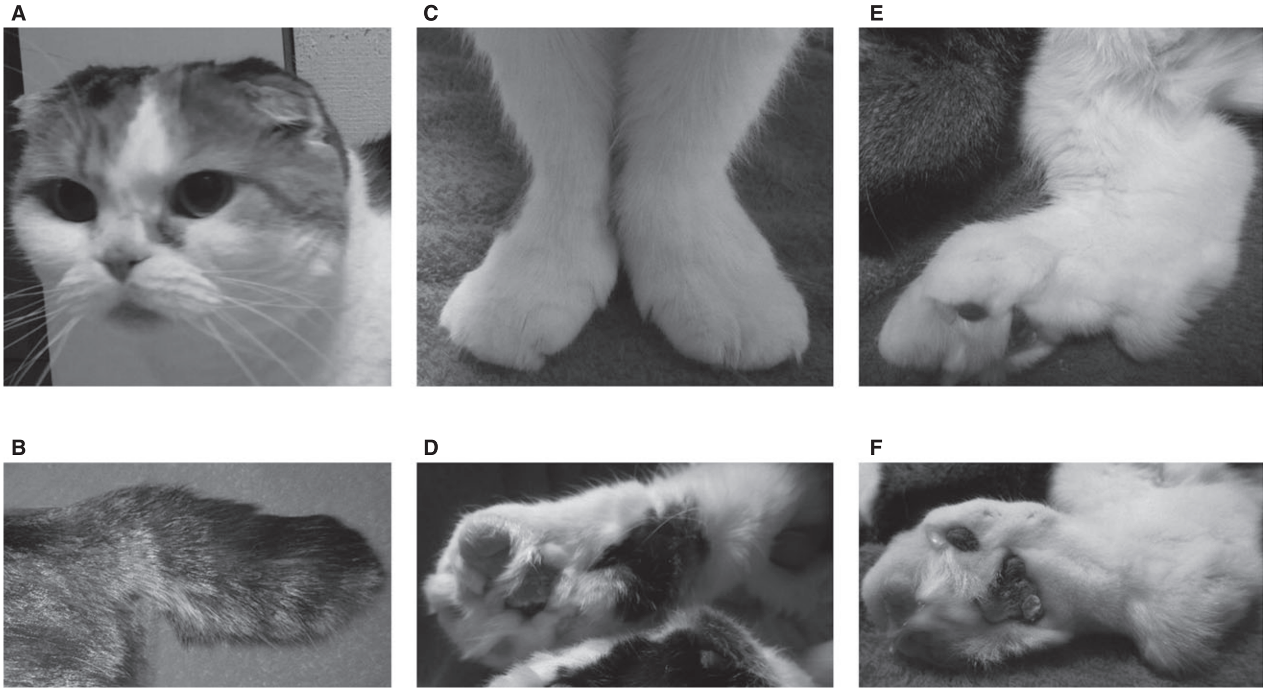

Fig. 2. The cat in case 1 at 60 months after irradiation. Although all limbs and tail were distinctly short, thick, and deformed, the lesions did not differ from those at initial diagnosis. (**A**) Facial appearance with folded ears. (**B**) Tail. (**C**) Forelimbs. (**D**) Phalanges and pads of forelimbs. (**E**) Right hindlimb. (**F**) Phalanges and pads of the hindlimb.

3 months duration. The clinical signs had been controlled by meloxicam administration, but recurred when the medication was withdrawn. The cat was unwilling to allow his hindlimbs to be palpated. Although his limbs were short, obvious deformities were not observed.

Radiography of the 4 limbs, tail, abdomen, and chest was performed. New bone proliferation was observed on the calcaneal bones of the left hindlimbs and there were bilateral tarsal osteophytes. No other bone lesions were observed radiographically on the forelimbs or tail.

The cat was diagnosed with SFOCD and monitored for 59 months. To relieve the chronic pain, both hindlimbs were irradiated according to the protocol described above. Clinical signs resolved within 1 month from the start of RT. Acute adverse effects were not observed at the irradiated sites. After the course of RT, radiographs were performed routinely. At 4 months, plantar exostosis was observed. The exostosis progressed gradually until 26 months; however, at 59 months no further progression was observed. The right tarsal joint osteophytes gradually progressed until 50 months, but at 59 months did not show further progression. No late complications were observed during this period. The cat was stable and did not require meloxicam.

Case 3

A 1.5-year-old female intact SF cat was presented to the VMTH-NVLU for right hindlimb lameness of 1 year duration. She could not jump up. She was reluctant to allow palpation of her right hindlimb and would not land on it. No treatment had been administered.

Radiography of the 4 limbs, tail, abdomen, and chest was performed. Bony proliferations were detected on the tarsal, metatarsal, and calcaneal bones bilaterally. Osteophytes were also found around both tarsal joints. The radiograph of the tail revealed that the caudal vertebrae were short and malformed. No lesions were observed on the forelimbs.

Based on the signalment and radiographic findings, the cat was diagnosed with SFOCD. Radiation therapy was administered to both hindlimbs according to the protocol described above. Clinical signs resolved within 1 month from the start of RT. Acute adverse effects were not observed. Routine radiographs taken over a period of 16 months did not show any progression of the bone lesions. At 48 months, we observed new deformities around both tarsi, but her activity had not declined. She was followed up for 72 months, and had no problems. Late complications were not observed.

Discussion

Low-dose radiation therapy (LD-RT) is normally administered for the treatment of inflammatory and degenerative diseases including painful heel spur, tennis/golfer's elbow, painful osteoarthritis, and hyperproliferative syndromes in humans.[1–4] Although the specific mechanisms underlying the analgesic effect are yet to be ascertained, it could be attributed to anti-inflammatory activity.[1] In veterinary medicine, although animal models of arthritis treated with LD-RT were used for experimentation,[5] limited data are available on the clinical cases of dogs and cats. Low-dose radiation therapy for SFOCD was described in one SF cat;[6] however, further studies with a larger sample size and long-term follow-up period are warranted.

The SF cat was developed in the Perthshire region of Scotland in the early 1960s. A pure white cat with forward-folded ears was found on a local farm in 1961. This cat with the naturally occurring anomaly was the ancestor of the Scottish Fold breed. The breed was registered with the British Cat Fancy in 1966, but was outlawed in England in 1974 because of deafness and limb abnormalities (osteochondrodysplasia). The breed continued to be bred in the United States and was registered in 1972.[7–9] Scottish Fold cats have a characteristic appearances that include folded-ears, large round eyes, a gentle nose curve, and thick, short limbs. Because of its sweet appearance and friendly personality,[7] the SF is one of the popular breeds in Japan.

Osteochondrodysplasia is a well-known inherited disease in the SF cat.[8,9] This disease is inherited as an autosomal incomplete dominant trait. The folded-ear allele has been called Fd.[10] Homozygous cats (Fd/Fd) are affected with severe osteochondrodysplasia. Heterozygous cats (Fd/fd) develop a milder form of the disease.[10,11] Fold-to-normal mating has been recommended to avoid producing homozygous cats.[7,9] Homozygous cats with normal ears are called Scottish Shorthairs and do not develop the disease.[9] This disorder is characterized by distal limb and tail skeletal deformities.[7] Histopathologic findings include defective maturation and dysfunction of cartilage.[12] Clinical signs include lameness and exercise intolerance, such as reluctance to jump and run resulting from chronic pain. As osteochondrodysplasia affects the typical cat's agile and athletic lifestyle, the quality of life can be disrupted.

This disease is an inherited disorder, and supportive therapies including oral remedies, surgery, and RT aimed at palliation of chronic pain are employed.[6,11–13] The effects of medical treatments, including nonsteroidal anti-inflammatory drugs, glycosaminoglycans, and pentosan polysulfate are limited. As SFOCD develops at an early age, long-term drug administration is not realistic.[11,12] In one report, osteotomy resulted in a temporary analgesic effect; however, lameness recurred after 48 weeks.[13] Hubler et al. reported that irradiation to both hindlimbs in 1 SF cat relieved pain; however, new bone proliferation was evident 28 months after RT.[6] Although RT has been considered to be a promising treatment option for SFOCD, long-term evaluation of efficacy and late complications have not been adequately conducted. The aim of this case report was to evaluate the long-term efficacy and adverse effects in 3 SFOCD cats treated with RT.

Radiation therapy controlled pain caused by SFOCD over a long period of time in all 3 cases (59–72 months). Control of inflammation responsible for chronic pain is considered the mechanism for the analgesic effect of RT in SFOCD.[6] Some mechanisms of anti-inflammation have been proposed in humans, such as improvement in blood perfusion, release of various cytokines and enzymes, modulation of molecule expression, effect on the local vegetative nervous system and innate immune system, and alterations in the pH values.[1,5,14,15] However, specific mechanisms underlying the analgesic effect are yet to be elucidated. The local nervous system, including C fibers, could play an important role in the analgesic effect. Nerves are considered to be radio-resistant, and the tolerance dose 50 for 5 years of nerve system was reportedly 75 Gy in humans.[16] When C fibers are damaged by RT, they can extend over a period of 3–4 years. Pain did not completely resolve in all 3 cases: the clinical signs including immobility and hypoactivity improved after RT; however, all 3 cats experienced pain when their limbs with lesions were stretched. Therefore, a fractionated dosage of 1.5 Gy for a total dosage of 9 Gy could have a lethal effect on the nerves. In addition, SFOCD develops at a young age.[10,12] As lesion development was advanced, it is possible that the peak pain sensation has passed in all 3 cats, which is perhaps why they could control the pain for a longer period of time. Histopathologic findings of SFOCD were characterized by defective maturation and dysfunction of cartilage.[12] In order to clarify the long-term maintenance of the analgesic effect and histopathologic changes caused by RT, further histopathologic examinations when they die (ie, necropsy) are warranted.

A gradual progression of bone lesions was observed in the cats in cases 2 and 3. The radiographic findings of the right-sided limbs that were irradiated earlier did not differ from the left-sided limbs that were irradiated later in the case 1 cat. Radiation therapy is considered to relieve pain but not to suppress the advance of bone disease. Interestingly, the cat in case 1 showed apparent improvement of clinical signs after the initial RT, although no treatment was performed on the lesions on the left-sided limbs. The reduction of pain in the right-sided limbs might have allowed the total pain fall below a threshold that results in the onset of clinical signs.

Late complications including alopecia, necrosis, and tumorigenesis at irradiation sites were not observed. As SFOCD develops at an early age, there is concern whether late adverse effects occur.[17] The RT protocol we used was based on a single case report.[6] A more proper protocol should be developed that considers the long-term efficacy and occurrence of late complications. In addition, using additional RT for recurrence of pain should be evaluated. Although further follow-up is required, these 3 cases could continue without any difficulties for a long time.

Scottish Fold osteochondrodysplasia can develop in both homozygous and heterozygous cats with folded ears. The Case 1 cat was considered homozygous because all limbs were affected and the clinical signs were severe. Mild lesions only in the hindlimbs were observed in the cats in cases 2 and 3; therefore, they were considered heterozygous. Although polymerase chain reaction can be used to determine whether they were homozygous or heterozygous,[18,19] the test was not performed because genomic DNA could not be obtained from all 3 cats. Genetic confirmation is required to predict the severity of SF disease. As all 3 cats showed satisfactory clinical improvement after RT, this could be an effective treatment for the cats with SFOCD of varying severities. Although RT is an effective and promising regimen for SFOCD, it is only a supportive treatment. To eradicate SFOCD completely, identification of the responsible gene is warranted. The fundamental resolution for SFOCD is to restrict the breeding of cats with this gene. Determination of the responsible gene would facilitate the production of SF cats free from osteochondrodysplasia. Scottish Fold breeding with SFOCD is cruel. In several countries and states, breeding of cats with SFOCD is prohibited. Scottish Shorthairs have the same characteristics as SF and do not develop SFOCD because of the absence of the defective gene described above. Therefore, breeding of Scottish Shorthairs is recommended instead of SF. In addition, SFOCD is considered to resemble congenital contractural arachnodactyly (Beals syndrome or Marfan's syndrome). This condition is characterized by crumpling of the ear pinnae and contracture of the digits,[20,21] and may have application as a disease model for SFOCD.

Radiation therapy could relieve pain for a long period of time in cats with SFOCD. No complications occurred in these 3 cases, although further lifelong follow-up is required. Radiation therapy has possibilities as a viable treatment option for SFOCD.

Footnotes

[a] Asteion Super4 Edition, Toshiba Medical Systems Corporation, Tochigi, Japan.
[b] XiO, CMS Japan, Tokyo, Japan.
[c] VACUFORM, MICROSPACE SYSTEM, Garbsen, Germany.
[d] PRIMUS, Toshiba Medical Systems Corporation, Tochigi, Japan.

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