

IMAGING DIAGNOSIS: FIBRODYSPLASIA OSSIFICANS PROGRESSIVA IN A CAT

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A 1-year-old female cat was presented for progressive alopecia, gait abnormalities, and stiffness. Radiography demonstrated multiple calcified lesions within the soft tissues of the cervical and thoracic spine, shoulder, and limbs. Postmortem computed tomography provided more detailed information on the distribution, pattern, and extension of lesions. In addition, computed tomography helped guide sample selection for histopathology. The final diagnosis was fibrodysplasia ossificans progressiva. This is a rare disorder of unknown etiology, characterized by fibrosis and heterotopic bone formation in connective tissues. To the authors' knowledge, this is the first report describing this disease in a European cat. © 2013 *Veterinary Radiology & Ultrasound*.

Key words: computed tomography, feline, fibrodysplasia ossificans progressiva, radiology.

Signalment, History, and Clinical Findings

A 1-YEAR-OLD, NEUTERED female domestic long-haired cat, born in Austria, was presented with a dull haircoat and a 2 week history of nonpruritic alopecia in the head region. At that time the animal was in good physical condition. Dermatological examination revealed bilateral symmetric alopecia of pinnae, periocular, and preauricular regions. Seborrhoeic dermatitis was detected dorsally, extending from the head to tail. The skin itself did not appear abnormal and scrapings were negative for *Demodex spp.* Fungal culture was positive for *Trichophyton terrestre*. Two weeks later, alopecia had progressed to involve the perioral region and diffuse hypotrichosis predominantly of primary hair was detected along the back. Hair on the pinnae had started to regrow, but remained short. Six weeks later, the owner noticed that the cat had progressive gait abnormalities, stiffness, and inability to jump. Biochemistry profile findings included marked elevation of inorganic phosphorous (2.5 mmol/l, reference range 0.8–1.9 mmol/l); lactate dehydrogenase (421.0 U/l, reference range <70 U/l); and cholesterol (4.9 mmol/l, reference range 1.8–3.9 mmol/l). The cat was serologically negative for feline immunodeficiency virus, feline leukemia virus, and had a coronavirus titer of 1:25. The complete blood count was normal. Orthopedic examination revealed gait abnormalities such as short

strides and stiffness of all limbs. Palpation of back and limb muscles identified marked diffuse hardening. Range of motion in shoulder, elbow, hip, and stifle joints was reduced, with restriction of both extension and flexion. Alopecia had extended to the inner thighs, ventrum, and back. The skin over the tarsal joints and medial thighs was hyperextensible and thin.

Imaging Diagnosis and Outcome

Radiography revealed bilateral heterotopic bone formation and small islands of calcification along the cervical and thoracic spine, shoulders, upper forelimbs, and upper hindlimbs (Fig. 1A, 1C). Due to a poor prognosis and deteriorating clinical condition, the cat was euthanized 4 months after the date of first presentation. Postmortem computed tomography (CT) (Fig. 1B, 1D) was performed and revealed multiple soft tissue calcifications consistent with heterotopic bone formation. Lesions resembled mature bone in the part that consisted of a more dense outer layer (compact bone) and a homogeneous less dense center (spongiform bone).

The borders of ossification seemed to be confluent with fasciae or aponeuroses, such as the superficial and deep fasciae of the trunk and the fascia genus and cruris. Calcified soft tissue lesions predominantly involved connective tissues of the shoulder region cervical and thoracic spine, and the aponeuroses and muscle fasciae of the axial skeleton and upper extremities (Fig. 2). The lesions were distributed in a bilaterally symmetrical pattern. For histological examination, sampled tissue lesions were fixed in 4% buffered formalin and additionally decalcified as needed (Decal[®],

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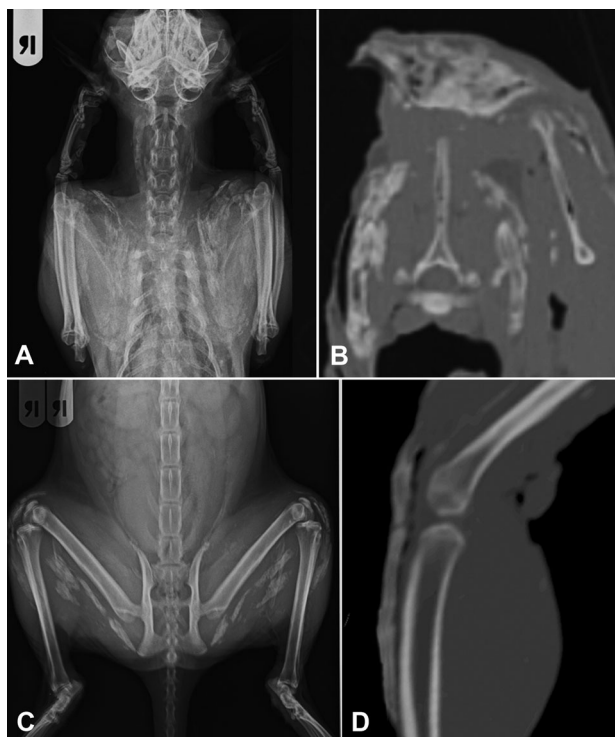


FIG. 1. A–D: Antemortem radiographic and postmortem computed tomographic (CT) images of a cat with fibrodysplasia ossificans progressiva: (A) dorsoventral radiograph of head, neck, thorax, and forelimbs; (B) transverse CT image at the level of shoulders (right shoulder removed); (C) ventrodorsal radiograph of the caudal abdomen, pelvis, and hindlimbs; and (D) thick slab reformatted sagittal CT image of the right hindlimb. Images demonstrate bilateral heterotopic bone formation and small islands of calcification confluent with muscles, fasciae, and aponeuroses.

Quartett Immundiagnostika und Biotechnologie Vertriebs GmbH, Berlin). Tissues were then embedded in paraffin wax, sectioned, and stained with hematoxylin and eosin (HE). Histopathological examinations of the musculoskeletal connective tissue lesions revealed marked proliferations of regular arranged, interlacing bundles of cell-rich collagenous tissue containing capillaries. Associated with connective tissue proliferations there were nodular perivascular localized aggregations of lymphocytes, mainly associated with larger vessels. Furthermore widespread areas of cartilaginous metaplasia and endochondral ossification with formation of trabecular structures and bone marrow were evident within the thickened connective tissue (Fig. 3). Fibrodysplastic areas showed distinct borders relative to unaltered tissue. Adjacent muscle fibers had a markedly reduced diameter, thickening of epimysium, and an increase in the number of internal, localized nuclei. Additionally scattered in these regions, mild infiltrations by mastocytes were identified. Similar areas of fibroplasia were found in the dermis, tongue, epineurium and perineurium of peripheral nerves and around moderately enlarged popliteal lymph nodes. Foci of ossification could be found at the base of upper lip

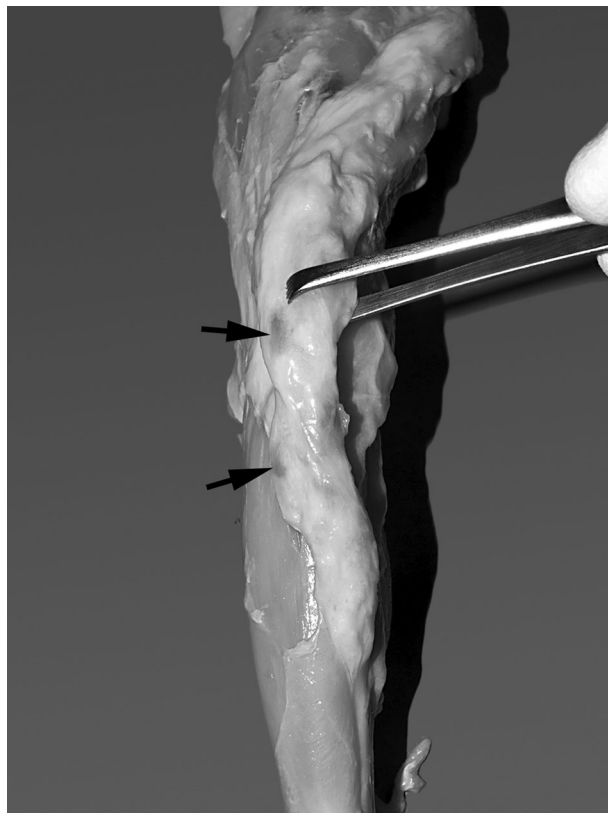


FIG. 2. Postmortem gross dissection photograph of the right hindlimb illustrating severe thickening and induration of fascia in the cranial portion of the sartorius muscle (forceps) with foci of ossification (arrows).

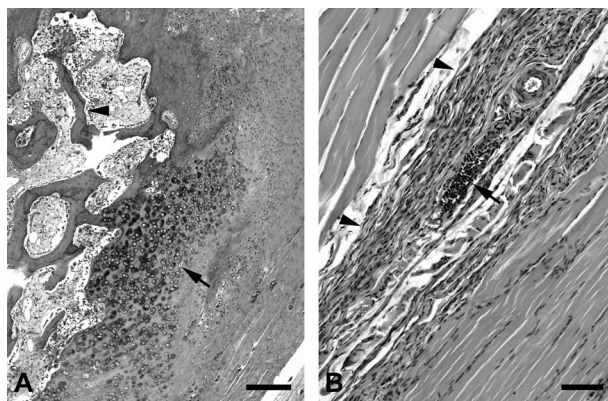


FIG. 3. Photomicrographs of muscle fascia. (A) Large areas of cartilaginous metaplasia (arrow) and endochondral ossification (arrowhead) with formation of marrow within the thickened connective tissue. HE, Bar = 400 μm . (B) Proliferation of cell-rich, collagenous tissue (arrowheads), and focal aggregations of lymphocytes (arrow); HE, Bar = 150 μm .

sinus hair only. Mastocytosis was most intensive in the dermis of most skin samples. Other necropsy findings included moderate follicular hyperplasia of the spleen, hyperplasia of sternal lymph nodes, and serohemorrhagic pericardial effusion. Within the lungs, moderate alveolar edema, scattered thrombi as well as mild perivascular infiltrated by

lymphocytes were found. Based on results of diagnostic imaging and histopathological examination, the diagnosis fibrodysplasia ossificans progressiva was made.

Discussion

Nine previous feline cases of fibrodysplasia ossificans progressiva have been reported to our knowledge in the veterinary literature.¹⁻⁸ All of them were reported outside Europe. Locations included the United States of America ($N = 5$), Japan ($N = 1$), and Brazil ($N = 1$). Some of these cases were identified as progressive ossifying myositis³ or generalized myositis ossificans¹, a former misnomer for fibrodysplasia ossificans progressiva. The term myositis ossificans circumscripta continues to be used to describe non-hereditary forms of heterotopic ossification. Fibrodysplasia ossificans progressiva has been described in young adult to middle-aged cats of both sexes and various breeds including Maine Coon, Himalayan as well as mongrel, domestic longhair and shorthair cats. Clinical findings similar to those described in the cat of the current study have been previously reported in a case series of three cats.²

It is unclear if genetic components play a role in the pathogenesis of feline fibrodysplasia ossificans progressiva. In humans, most cases of fibrodysplasia ossificans progressiva arise as a result of spontaneous mutations of bone morphogenetic proteins.⁹ Genetic transmission is autosomal dominant and can be inherited from either parent. Skeletal abnormalities such as microdactyly of the great toe and missing phalanges have also been reported. Cardiac muscle and smooth muscle are typically not involved in human fibrodysplasia ossificans progressiva.

In most previous reports of feline fibrodysplasia ossificans progressiva, inflammatory infiltration, and involvement of mastocytes, as evident in human patients¹⁰ were not mentioned. The role of mastocytes in the pathophysiologic mechanism of fibrodysplasia ossificans progressiva is unclear, but their abundance in connective tissue could induce cell-mediated processes such as fibroproliferation. Prostaglandin 2 (PGD_2), produced by mast cells, might also explain the alopecia observed in the cat of the current report. Elevated levels of localized PGD_2 have been found in balding scalp tissues of men, which supports our theory of a possible causal link between PGD_2 , mast cells, and hair loss.¹¹ One previous report was found describing skin lesions in a cat diagnosed with fibrodysplasia ossificans progressiva.⁷ In this report, macroscopic findings such as alopecia and seborrhoea were comparable to our observations, however histopathologic findings differed in that they included acanthosis and vacuolar degeneration of the epidermal, mucinous change of the superficial der-

mal layer, and *Malassezia* yeast. Furthermore it cannot be excluded that cutaneous lesions described are coincidental issues.

Heterotopic bone formation (defined as development of extraskeletal bone tissue that is often atypical) was of a higher grade and organization in the paravertebral cervical and thoracic regions in the cat of our report, whereas it appeared as loosely associated calcified regions aligned with the course of the fascial planes in other regions. Progression of heterotopic bone formation in human patients is strongly influenced by environmental factors such as soft-tissue trauma (e.g. surgical procedures) and viral illnesses.¹⁰ Long bones may also have a distinctly thickened compact bone. Single human case studies reported irregular periosteal new bone growth on the ulna, tibia, and fibula.⁵ Osseous structures in the cat of our report did not appear abnormal. Histopathologic characteristics of soft tissue lesions for most previously reported feline cases were comparable to those in our case. The distribution pattern seemed to vary in some extent. Other differential diagnoses for soft tissue calcifications in cats may include calcinosis circumscripta, metastatic calcification, hypervitaminosis A or D.¹² These differentials were excluded in the cat of our report because calcified soft tissue lesions were consistent with mature heterotopic bone rather than dystrophic or metastatic calcification.

CT was a helpful adjunct for the necropsy examination in that it assisted in characterization, localization, and histopathologic sampling of the soft tissue calcifications. One limitation of our study was that the CT examination was performed after the left forelimb and right hindlimb had been removed. This reduced the quality of the CT images and made interpretation difficult in some projections. The use of thick slab transverse slice reformatting was helpful for demonstrating the extent of shoulder involvement.

In conclusion, this is the first reported case of feline fibrodysplasia ossificans progressiva in Europe. Fibrodysplasia ossificans progressiva should be included in the differential diagnosis list for cats with progressive, multifocal areas of heterotopic bone formation involving connective tissues. Molecular genetic examinations of affected cats should be attempted to determine whether there are mutations in the bone morphogenetic pathway, similar to human patients. Cats could be a useful natural animal model for improving understanding of the pathophysiology of this painful, disabling disorder in humans, and for developing new treatments.¹³

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