Cutaneous asthenia (Ehlers–Danlos syndrome) in a cat

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1. Introduction
The Ehlers–Danlos syndrome (EDS), a group of inherited connective tissue diseases, is recognized in animals as well as in humans (1). Naturally occurring cases of this disease are reported in many species: horses (2–4), cats (5–9), dogs (10–13), calves, sheep, rabbits, and mink (2,13). However, this disease is rarely seen in cats and most of the reports available are descriptions of individual cases (3). Affected animals have hyperextensible and fragile skin (1,8). Delayed wound healing has been reported to be a complication of EDS in humans, using clinical and histologic criteria, while wound healing in dogs and cats with EDS appears to be similar to that of nonaffected animals (14). These disorders are also referred to as dermatosparaxis or cutaneous asthenia in animals (1). There is no therapy for the disease, but consistent management can allow affected cats to live long lives (8).

2. Case history
A 2-year-old, female, spayed crossbred cat, weighing 3.5 kg, was presented to the Department of Internal Medicine, Faculty of Veterinary Medicine, Istanbul University, with alopecia, loss of appetite, and hyperelasticity of the skin (Figure 1). Anorexia was evident for 4 days and the skin elasticity had been noted for 3 weeks. Generalized lymphadenopathy, an ulcerative wound on the left hind leg (Figure 2), and hyperextensibility of the skin were the abnormal findings detected on physical examination.

The rectal temperature was 38.4 °C and respiration rate was 18 breaths/min. The diagnostic work-up included a complete blood count, blood serum biochemistry panel, and urinalysis to rule out any internal disease associated with these skin lesions.

Mild leucocytosis (white blood cell count: 19.75 × 103 µL, reference range: 5.5–19.0) and hypoproteinemia (total protein: 5.2 g/dL, reference range: 5.9–8.5) were detected. Blood urea nitrogen (50 mg/dL, reference range: 15–34) concentration was slightly increased. The rapid tests of feline immunodeficiency virus (FIV), feline leukemia virus (FeLV) (FIV Ab/FeLV Ag Test Kit Anigen, BioNote, Inc., South Korea), and feline infectious peritonitis (FIP) (FCoV Ab Test kit Anigen, BioNote, Inc., South Korea) were found to be negative. Urinalysis findings were also normal. Due to the presence of alopecia, the trace element zinc was assayed by spectrophotometry and found to be 0.4 µg/mL, which was lower than the reference range (0.7–2.0 µg/mL).

The biopsy areas were chosen randomly. Punch biopsies (6 mm) of the lesional skin involving the left hind leg and the sacrocaudal region were obtained from the cat

Abstract: Ehlers–Danlos syndrome (EDS), or dermatosparaxis, is a rare hereditary disease of the connective tissue, which is characterized by skin hyperextensibility and laxity. In the present article, the case of a crossbred female spayed cat, at the age of 2 years, was presented with hyperelasticity of the skin, alopecia, and an ulcerative wound on the left hind leg. The animal’s dorsum was hyperextensible, smooth to the touch, and could be easily torn with minor traumas. To the best of the authors’ knowledge, the present report is the first documented feline case of cutaneous asthenia in Turkey.

Key Words: Cat, collagen disease, cutaneous asthenia, Ehlers–Danlos syndrome
using local anesthesia and the biopsy sites were allowed to heal by second intention. The biopsy samples were sent to the Department of Pathology for histopathological examination.

In an attempt to evaluate the collagen defect, a skin extensibility examination was performed. The skin over the dorsal lumbar region was stretched to the maximum point, without causing any discomfort, and the measurement was made carefully. The body length was measured from the occipital crest to the base of the tail. The skin extensibility index (SEI) was found to be increased by 22% than the reference value described as 19% (2).

The examination of skin scrapings and hair plucks did not reveal any parasites or mycotic infections. Histological skin samples were fixed in neutral 10% buffered formalin and routinely processed. Sections 5 μm thick were stained with hematoxylin and eosin (H&E) and Masson’s trichrome and were examined under light microscope. Histopathologically, there was intense neutrophilic infiltration, fibrosis, and necrosis in between short and irregular collagen fibers. The neutrophilic infiltration suggested a secondary inflammation process. Focal lipocytic proliferation in the dermis (Figure 3), irregular papillary structures, and fibroblastic hyperplasia (Figure 4) in the epithelial layer were detected. There was an increase in the number of fibrocytes around the hair follicles and nest formations of fibroblasts were observed in the sections stained with Masson’s trichrome. In some cases the abnormal fibers appeared outlined by increased numbers of fibroblast (5,7). In such cases, fibrocytes, which are not noticeable in the papillary and reticular layers of the normal dermis, have become visible. Fibrocytic and fibroblastic hyperplasia were seen underlying the epithelial layer and fibroblast cell increase and collagen deficiency were detected (Figure 5). All these histopathologic findings were compatible with feline cutaneous asthenia (15).

For electron microscopy, similar skin samples were fixed in 4% paraformaldehyde, postfixed in osmium tetroxide, and embedded in low-viscosity Spurr spin. Ultrathin sections were cut, counterstained with 0.5% uranyl acetate and lead citrate, and examined with a Zeiss 902A electron microscope. Electron microscopy revealed an irregular, disorganized pattern and the decrease of the collagen fibers (Figure 6). Normally, collagen fibers constitute 70% of the proteins of the dermis. In contrast to normal skin, diminished collagen fibers were seen in the present case.

Initial therapy included saline infusion (20 mL/kg intravenously (IV)) (Isotonic NaCl®, 500 mL, Eczacıbaşı Baxter, Turkey), ceftriaxone disodium (Rocephine® IV amp., 1 g, Roche, Turkey; 25 mg/kg, q12 h, IV), vitamin C (Redoxon® IV amp., 500 mg/5 mL, Bayer, Turkey; daily 50 mg/kg, IV), dexamethasone (Bepanthene® amp., 500 mg/2 mL, Roche, Turkey; 0.5 mL, 2 times every other week, intramuscularly), and vitamin E (Ephynal®, 300 mg, Bayer, Turkey; 300 IU/day, per os (PO)). The drugs were applied for 10 days. Because of decreased appetite and water consumption, serum infusion therapy was advised.
An antibiotic was also given for mild leucocytosis and skin lesions. Vitamin C, dexpanthenol, and vitamin E were essential for a healthy skin. A protected environment was recommended to the owner because of the hyperelasticity of the skin.

The second referral happened 10 days after the first referral. Blood was withdrawn for hematology and blood serum biochemistry analyses. Leucocytosis was healed and total protein was detected within normal ranges. With this treatment, the appetite was increased and the mobility was markedly improved. The sections of the skin where the samples were taken had been healed completely, but the hyperelasticity of the skin remained the same.

The therapy of the patient was continued with vitamin C and zinc (Zinco-C tab.®, 15 mg, Berko, Turkey; 50 mg/kg/day, PO) and vitamin E (Evicap® cap. 100 mg, Koçak Pharma, Turkey; 100 IU/day, PO) for 1 month. Collagen (hydrolyzed) (Collagen for Pets® tab., Alfa Natural Company, USA) was also used once per day for 2 months. The cat’s general condition status was good, including the skin elasticity. The owners were instructed to continue with the current vitamins, especially with vitamin C, for 6 months and to refer to our policlinic in the event of any abnormal situations occurring.

The clinical picture and the histopathological findings were compatible with feline cutaneous asthenia. Diagnosis was made step by step as described above.

3. Results and discussion
The terms of cutaneous asthenia, dermatosparaxis, and EDS denote a disease complex that includes several hereditary congenital defects of dermal connective tissue in man and in various animal species (5–10,12). Feline cutaneous asthenia is a very rare, inherited disorder of collagen production in cats. The clinical picture of the affected cat is characterized by skin hyperextensibility and fragility, compatible with the signs and symptoms described for cats with cutaneous asthenia (5–10, 12).

Due to the cat’s young age and its symptoms, the SEI and histopathologic results were all compatible with a congenital defect in the present case. Breed predispositions of the individual animal species to asthenia are reported. In cats, Himalayans and domestic shorthairs are the predisposed breeds (2). In this report, our patient was a mixed-breed household cat. Genetic analysis as a diagnostic tool could not be performed as the patient was a stray cat, found on the street while she was a kitten.

It is very unusual to see the complete syndrome of cutaneous fragility, articular laxity, and ocular abnormalities in the same animal. The cutaneous form is the most commonly seen (12). In this patient, only the cutaneous form of the disease was present. The SEI was also higher (22%) than the reference value and the cutaneous hyperextensibility was remarkable in this patient.

In the present case, morphologic changes were seen in dermal collagen in light microscopic examination. Collagen fibers showed alterations in arrangement and length and were characterized by shortening, disarray, curling, and uneven size. The disorganization of the collagen fibrils is also a characteristic feature observed in feline patients with EDS (7), as well as the findings of disorganization of collagen fibrils on electron microscopy (3,5,8,15). Cutaneous asthenia is a congenital form of feline skin fragility syndrome (FSFS) that has also been reported in young cats. Histologically, some cases of cutaneous asthenia are difficult to distinguish from acquired skin fragility with differentiation based on signalment, history, and SEI. Histopathology of skin biopsies in FSFS reveals marked epidermal and dermal atrophy although the skin of the animals is not hyperextensible (16).
There is no specific treatment protocol for this disease. In spite of any therapy, some authors suggest the oral administration of vitamin C, which is necessary for collagen synthesis in cats (50 mg/animal, daily) (2). However, secondary manifestations of the disease, such as joint laxity, must confer a more guarded prognosis (2,6,17). Despite the poor prognosis, the patient must be taken care of to avoid causing any skin injuries.

To the knowledge of the present authors, this is the first report of cutaneous asthenia in cats or any other animal species in Turkey.

References
