

## Cutaneous asthenia associated with Ehlers-Danlos syndrome in a Yorkshire terrier

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**Abstract :** Cutaneous asthenia or dermatosparaxis is an uncommon, congenital and inherited connective tissue disease of dog and cat, resembling Ehlers-Danlos syndrome (EDS) in man. EDS is characterized by loose, hyperextensible and, fragile skin, it is attributed to mutations in connective tissue gene. These mutations cause defects in type I or III collagen synthesis and as a result lack of strength or elasticity to skin, joint, ligament and vessels. EDS-affected animals often experience subcutaneous hematomas that have long bleeding times. The 4-years old male Yorkshire terrier was evaluated because of subcutaneous hematoma after stifle surgery. Clinical examination revealed a thin and hyperextensible skin and joint laxity. The degree of skin extensibility index was 23.4%, marked skin stretchy. Clinical diagnosis was confirmed by histopathological examination of a skin biopsy revealing reduced packing density of collagen fiber of skin.

**Key words :** collagenopathies, cutaneous asthenia, dermatosparaxis, dog, Ehlers-Danlos syndrome

Cutaneous asthenia or dermatosparaxis is a rare inherited connective tissue disease of dog and cat [1, 3, 5, 6] that resemble Ehlers-Danlos syndrome (EDS) in human [6, 9]. In veterinary medicine, EDS has been described in several species with collagenopathies [1, 6, 8]. EDS is characterized by loose, hyperextensible and fragile skin, which is attributed to mutations in connective tissue gene [2, 4]. These mutations cause defects in type I or III collagen synthesis and as a result lack of strength or elasticity to skin, joint, ligament, and vessels [1, 4, 9]. Thus, EDS-affected animals revealed clinically integumental, musculoskeletal, gastrointestinal, and cardiovascular signs [6, 7]. In dogs, cutaneous asthenia, also known as rubber puppy disease has been reported in English Springer Spaniels, Boxers, Beagles, Pembroke Welsh Corgies, German Shepherd Dogs, Saint Bernards, and Dachshunds [6, 9]. But literatures of EDS-affected dog are extremely few. Here, we describe the clinical and histopathologic findings in an dermatosparaxis-affected Yorkshire terrier.

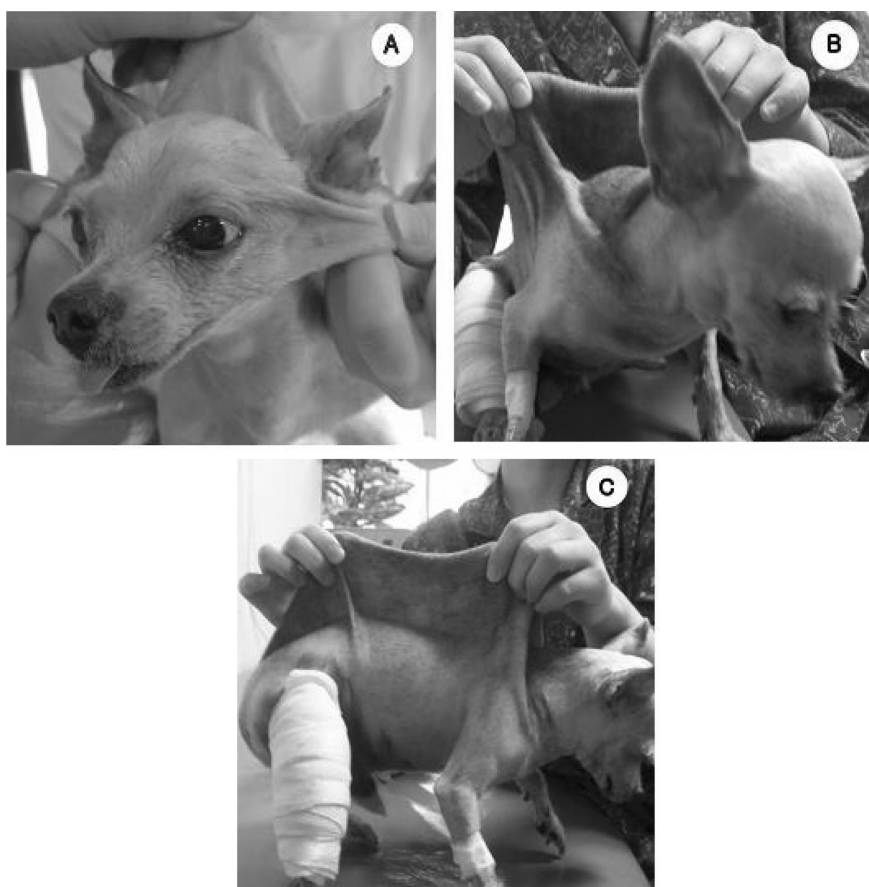
The 4-years old male Yorkshire terrier was referred for severe bruising of right stifle. The bruising was

subcutaneous hematoma after stifle surgery because of bilateral medial patella luxation (grade II) and right cruciate ligament rupture. The owner informed that the dog had fragile skin and history of bruising, since 8 months of age. On physical examination, the dog revealed predominant periodontitis, alopecia, skin fragility and hypermobility, and carpal and tarsal joint laxity. Especially, the skin showed marked stretchy, fragile and thinly over the trunk. Skin elasticity was also decrease, as well as the penlight penetrated thinly skin and the dermal vessels are exposed (Fig. 1, 2). Skin hyperextensibility appears over the torso and head except for extremities. Skin bruising was detected around neck and abdomen. Otherwise the dog appeared healthy, and no other abnormalities were found. There was no ophthalmic symptom and we don't obtain pedigree history.

To determine the skin laxity, skin extensibility index (SEI) was calculated as objective measurements. SEI was examined as follows: skin extensibility index (%) = [height of fold of skin over lumbar region (cm)/ distance from occipital to base of tail (cm)] × 100.

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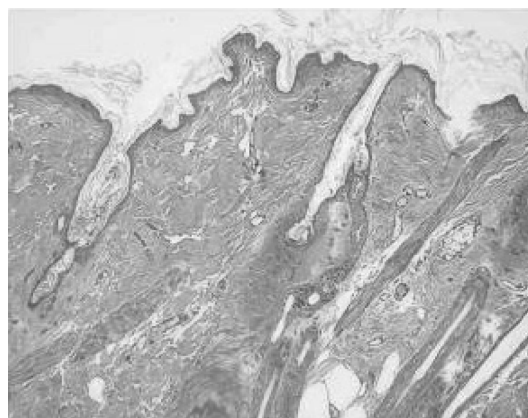
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**Fig. 1.** A Yorkshire terrier with skin hyperextensibility by Ehlers-Danlos syndrome or cutaneous asthenia. This case showed excess cutaneous laxity on the head (A) and dorsum (B) with gentle traction. The hyperextensible skin was severe thinly and showing the dermal vessels through the other side. The copious bruising was noted around the right thigh and lower abdomen after stifle surgery (C).

Vertical height of extensible skin (dorsolumbar skin fold) was 7.5 cm and body length (from the base of the tail to the occipital crest) was 32 cm, therefore calculated SEI was 23.4% (Table 1). On laboratory result, WBC, ALP, AST and ALP were mildly elevated (Table 2).

Skin biopsy was performed using a 4-mm skin biopsy punch and skin specimens obtained from the dorsum was fixed in 10% formalin-glutaraldehyde solution, and stained with hematoxylin-eosin. Histopathologically, there were a diffuse in the dermis layer and a loose in the hypodermis layer, and moreover there were decreased dense collagen fiber of dermis and number of hair follicles (Fig. 3). This case was diagnosed as EDS based on the SEI increased and collagen fiber decreased.



**Fig. 2.** Histologic micrograph of dorsal dermis from Ehlers-Danlos syndrome showing decreased dense collagen fiber of skin. Note lack, shortened and fragmented dermal collagen bundles (H&E stain,  $\times 200$ ).

EDS or cutaneous asthenia is a rare disease in veterinary and human medicine, which is a group of inheritable collagen mutation in connective tissue genes [4, 9]. Collagen, glue-like protein of connective tissue, defect reduce mechanical properties of skin, joints, ligaments, and blood vessels. Thus, EDS is characterized by skin hyperextensibility, joint hypermobility and fragility of skin and blood vessels [6, 8]. The clinical and histopathological findings were consistent with the diagnosis of EDS [5, 6]. In human medicine, EDS have been divided ten subtypes based on mode of inheritance and biochemical defect and clinical signs [2, 4, 9]: Type I; gravis, Type II; mitis, Type III; benign familial hypermobility, Type IV; ecchymotic or arterial, Type V; x-linked, Type VI; ocular, Type VII; arthrochalis multiplex congenita, Type VIII; periodontal form, Type IX; x-linked cutis laxa, skeletal, and Type X; fibronectin deficient. In veterinary medicine, EDS is described with cutaneous asthenia that is results from abnormalities in the biosynthesis of collagen and disturbance in connective tissue function [3, 7, 8]. According to lack of collagen bundle, these diseases are commonly manifested soft tissue hyperextensibility or fragility, for instance; skin

fragility (dermatosparaxia), skin laxity (cutaneous asthenia) or joint laxity, and periodontitis [3, 5, 6]. Skin laxity was principally produced also in this case. Cutaneous asthenia was first identified in cattle and then, reported many species, sheep, cat, dog, and mink. But classification of collagenopathies in veterinary medicine is insufficient because rare genetic, biochemical and ultrastructural studies have been carried out [6]. This case was evaluated lack of dense collagen fiber in the extensible and thin skin on microstructural and clinical studies. The skin extensibility index is used to quantitate the extensibility of affected dorsolumbar skin. SEI has been used as common criterion for clinical identification of EDS in dog and cat [3, 8]. Normally, SEI of non-affected dog is 8% to 15% [3, 5], but this case was 23.4%. More significantly, the skin of EDS-affected animal is fragile and easily laceration [1, 2]. Consequently, readily manifests subcutaneous hematomas produced by minimal trauma and poor wound healing in EDS [2, 5, 9]. In this case, the copious bruising area of surgical stifle and ecchymosis around the abdomen are typical clinical features caused by fragile vessels. These signs are like EDS subtype I, II, III and IV [3, 6, 8]. Cutaneous asthenia resembling EDS type I-III is cause by a deficiency of type I procollagen-N-peptidase, which lead to accumulation of partially processed type I procollagen [1, 8]. Collagen fibers of affected animals were irregular arranged and lost mechanical strength [1, 3]. In light and electron microscopic study, collagen bundle were loosely integrated and separated on ground substance. Collagen fibers appeared fragmented and isolated [6, 8]. The principal manifestation of ultrastructural finding was the disorganization in collagen fibril of dermis, for example; loosely fibril packing, variation in fiber diameter and disarray arrangement of collagen fiber [3, 6]. Lacked and fragmented dermal collagen

**Table 1.** Clinical appearance of this case

Index	Torso	Shoulder/ elbow	Thigh/stifle	Carpal	Tarsal
ROM* increased	-	-	-	+	+
Joint laxity	-	-	+	+	+
Dislocation	-	-	+	-	-
Skin bruising	+	-	+	-	-
Pendulous skin	-	-	-	-	-
SH†	+	-	-	-	-

\*ROM (range of motion), † SH (skin hyperextensibility).

**Table 2.** Results of hematological analysis

CBC count		Differential count		Chemistry	
WBC ( $10^3/\text{ul}$ )	25.45	Neutrophils seg	87	ALT (IU)	97
RBC ( $10^6/\text{ul}$ )	3.73	Lymphocyte	7	AST (IU)	73
HB (g/dl)	9.2	Monocyte	6	ALP (IU)	318
PCV %	27.3	Eosinophil	0	BUN (mg/dl)	21
MCV fl	73	Basophil	0	Creatinine (mg/dl)	0.45
MCHC %	33.6				

bundles were eminently observed also in this case. It is clinically important to perceive cutaneous asthenia. This abnormality are easily lacerated and presented large wound [2, 3]. In human and veterinary practical management, tape closure has been indicated to reduce large scar [3]. However, dog and cats suffer with cutaneous asthenia appear to have a normal life span, if ensure caution and free from trauma [3]. In this case, the bruising and wound were treated with carefully nursing and general post-operative treatment. On follow up after treatment, the surgical wound and bruising recovered but skin and joint laxity persisted.

This case is first report of cutaneous asthenia associated with EDS in a dog in Korea. Skin extensibility index and histological evaluation were useful for the diagnosis of cutaneous asthenia. The prominent signs of this rare disease were skin and joint laxity as also as poor wound healing that result in congenital abnormalities in the biosynthesis of collagen. Therefore, the affected animals were required carefully nursing and caution in trauma.

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