Classical Type Ehlers-Danlos Syndrome: Report of a Case and Review of Literature

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Ehlers-Danlos syndrome is a clinically and genetically heterogeneous group of connective tissue disorder characterized by skin hyperextensibility, joint hypermobility and tissue fragility. Currently it is classified into 6 major types, based on clinical and molecular characteristics and pattern of inheritance. Although no treatment is available for this disorder, it is important to recognize it when suspected and to prevent potential complications. We report a case of mild classical type Ehlers-Danlos syndrome (*Mitis* type according to Berlin classification) in a 25-year-old female who showed smooth and velvety skin with hyperextensibility, joint hypermobility, easy bruising and hyperpigmented, wrinkled scars.
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Key Word: Ehlers-Danlos syndrome

INTRODUCTION

Ehlers-Danlos syndrome (EDS) is a heritable, connective tissue disorder due to molecular defects affecting the synthesis, structure or function of the fibrillar collagens[1]. It shows clinical variability according to subtypes, although the principal manifestations include hyperextensible skin with a soft, velvety, doughy texture; joint hypermobility; easy bruising with brownish discoloration and dystrophic scars; and variable involvement of the internal organs[2]. In some cases it is life-threatening, but in many other cases the symptoms are so subtle that it remains undiagnosed. However, early recognition of this disorder has diagnostic and prognostic importance for patients, to reduce the risks and prevent potential complications.

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We herein report a case of EDS which showed representative features of mild classical type EDS (*Mitis* type according to Berlin classification[3]).

CASE REPORT

A 25-year-old woman presented with a 2-day history of spontaneous ecchymoses on both shins (Fig. 1). She reported that she had suffered from easy bruising to mild trauma and frequent gingival bleeding since childhood.

Examination showed a smooth, velvety and easily stretched skin, hypermobile finger, thumb and elbow joints (Fig. 2), multiple ecchymoses and hyperpigmented and wrinkled scars on the shins and knees. Results of laboratory tests including complete blood count, blood coagulation tests and liver function tests were within normal limits. There were no abnormalities on cardiovascular or ocular examination including echocardiography, chest/abdomen CT and slit-lamp biomicroscopy. In addition, there were no musculoskeletal findings of joint dislocations, scoliosis or pes planus. There was no family history of easy bruising, prolonged bleeding, joint hypermobility, or skin hyperextensibility.

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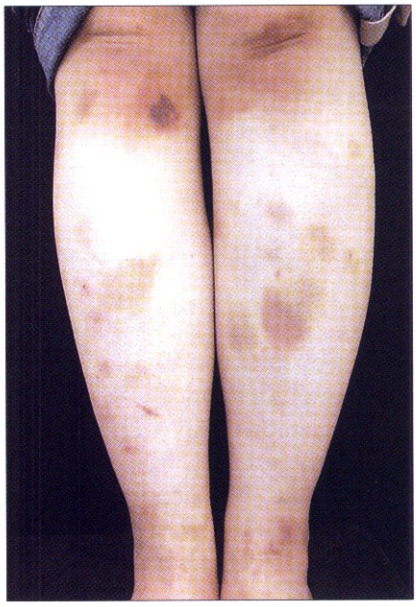

Fig. 1. Multiple ecchymoses and hyperpigmented and wrinkled scars on both shins and knees.

A biopsy specimen taken from the right shin showed some fragmented elastic fibers in the dermis. However, there was no abnormality, either in the thickness of skin or in the appearance of collagen fibers (Fig. 3).

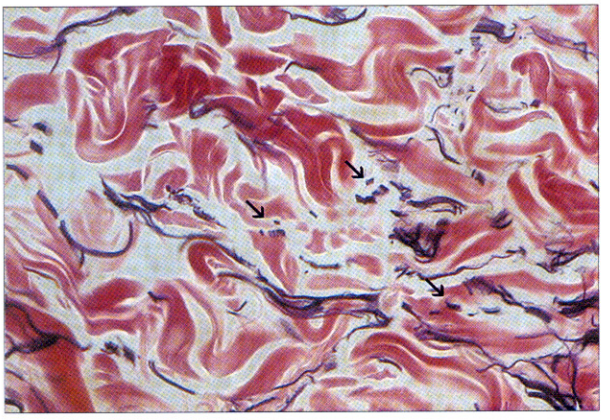

Fig. 3. Some fragmented elastic fibers in the dermis (Verhoeff-Van Gieson, × 400).

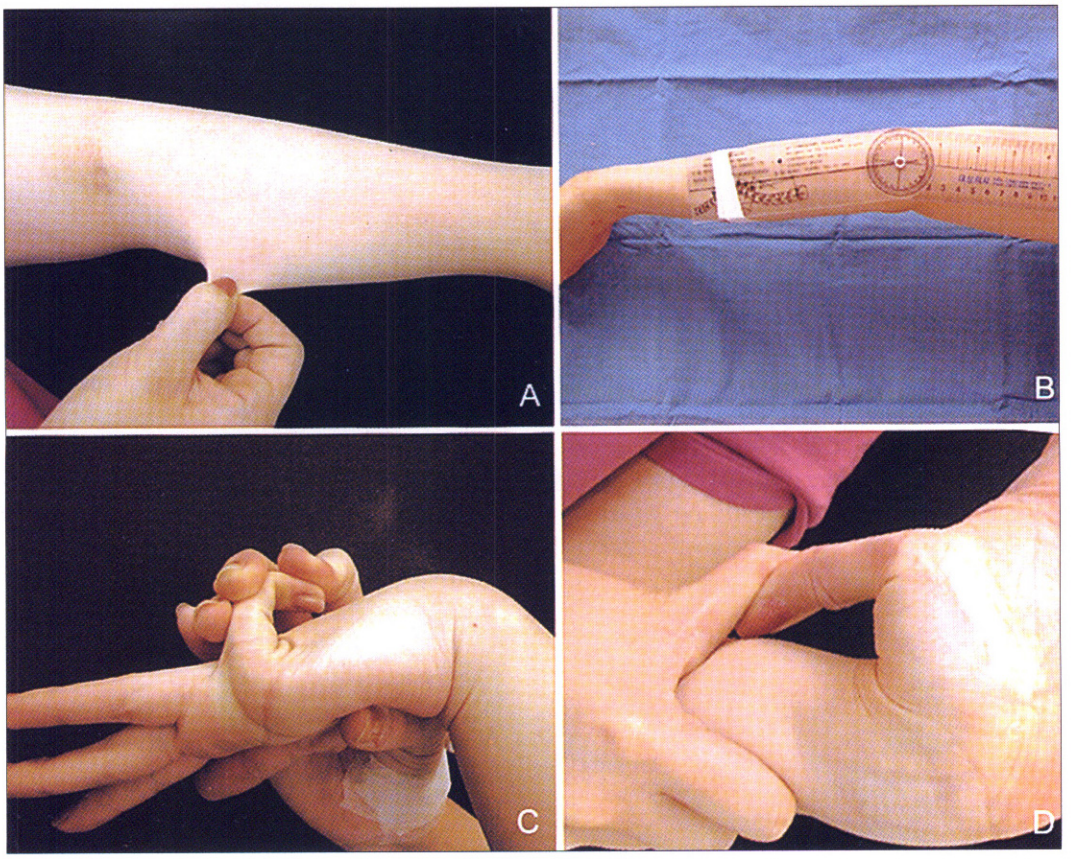

Fig. 2. (A) Smooth, velvety and easily stretched skin. (B) Hyperextension of elbow > 10 degrees. (C) Dorsiflexion of little finger > 90 degrees. (D) Passive apposition of thumb to flexor forearm.

No therapy was initiated and she was advised to avoid physical trauma, such as skin laceration or vigorous exercise, and to have regular evaluations.

DISCUSSION

EDS is a clinically, biochemically, and genetically diverse group of disorders characterized by joint laxity and common dermal features[4]. Although prior classification of EDS included 11 subtypes, Beighton et al.[5] proposed a new, simplified classification based primarily on the cause of each type, and major and minor diagnostic criteria have been defined (Table 1). The major criteria of classical type EDS include skin hyperextensibility, widened atrophic scars as a manifestation of tissue fragility, and joint hypermobility. Skin hyperextensibility is measured at a neutral site by pulling up the skin until resistance is felt. Thin, atrophic papyraceous scars occur mostly on pressure points, for example, knees, elbows, forehead, or chin. Scars become wide and remain as a dark discoloration of the skin. Joint hypermobility is assessed by the Beighton scale, and a score of at least five out of nine defines hypermobility[5]. In other subtypes, generalized joint hypermobility without atrophic scars (hypermobility type), arterial/intestinal/uterine fragility and characteristic facial appearance (vascular type), muscle hypotonia, scoliosis and scleral fragility (kyphoscoliosis type), congenital hip dislocation (arthrochalasia type), and redundant skin (dermatosparaxis type) are principal clinical features[5].

It has been noted that EDS occurs in approximately 1 case per 440,000 people[6]. However, it is often difficult to reach a diagnosis of EDS in less severely affected individuals[7]. Taking the circumstances into consideration, the prevalence of all forms of EDS is estimated to be 1 case per 5,000 people[8]. Among the 19 cases which have been reported in Korean literature (Table 2), some patients were diagnosed with EDS during childhood, whereas others who had mild symptoms and signs remained undiagnosed until they were in their twenties. In mild cases, the condition was scored by the degree of joint hypermobility, skin extensibility, wrinkled scarring and bruising (Table 3). And those who had scores of 7 or greater were considered as patients with EDS. In our case, the patient showed joint hypermobility of the little finger, thumb and elbow;

Table 1. Classification of the Ehlers-Danlos Syndrome According to the Villefranche Nosology[5]

Villefranche classification	Former classification	Major diagnostic criteria	Inheritance pattern	Biochemical defect
Classical	Gravis Mitis	Skin hyperextensibility Widened atrophic scars Joint hypermobility	AD	Mutation in COL5A1/COL5A2
Hypermobility	Hypermobile	Skin involvement Generalized joint hypermobility	AD	Unknown
Vascular	Arterial-ecchymotic	Thin, translucent skin Arterial/intestinal/uterine fragility or rupture	AD	Mutation in COL3A1
Kyphoscoliosis	Ocular-scoliotic	Generalized joint laxity Severe muscle hypotonia at birth Scoliosis at birth, progressive Scleral fragility and rupture of the ocular globe	AR	Mutation in PLOD1
Arthrochalasis	Arthrochalasis multiplex congenita	Severe generalized joint hypermobility, with recurrent subluxations Congenital bilateral hip dislocation	AD	Deletion in COL1A1/COL1A2
Dermatosparaxis	Human dermatosparaxis	Severe skin fragility Sagging, redundant skin	AR	Mutation in type 1 collagen N-peptidase

Table 2. Review of Ehlers-Danlos Syndrome Reported in Korean Literature

Case	Sex/Age	Clinical manifestations	Family history	Classification	Reference No.
1	M/47	Skin hyperextensibility Multiple joint dislocation Easy bruising, Cigarette paper scars	5 similar cases in 3 generations	Classical	9
2	F/1	Skin hyperextensibility Joint hypermobility Congenital hip dislocation		Arthrochalasis	10
3	F/8	Skin hyperextensibility Joint hypermobility Radiohumeral subluxation Congenital hip dislocation		Arthrochalasis	10
4	M/25	Skin hyperextensibility, Easy bruising		Classical	11
5	F/39	Skin hyperextensibility Cigarette paper scars Molluscoid pseudotumor	Mildly affected a 6-year-old daughter	Classical	12
6	M/25	Skin hyperextensibility Joint hypermobility Chronic joint pain		Hypermobility	13
7	M/21	Skin hyperextensibility Joint hypermobility Joint dislocation	Similar findings in his sister	Hypermobility	14
8	M/26	Skin hyperextensibility Joint hypermobility Dystrophic scars	Similar findings in his sister	Classical	15
9	F/3	Skin hyperextensibility, Easy bruising Subcutaneous spheroids Joint hypermobility	Similar findings in her great-grand- mother	Classical	16
10	F/4	Joint hypermobility, Easy bruising		Hypermobility	17
11	F/26	Skin hyperextensibility Joint hypermobility Easy bruising, Cigarette paper scars	Easy bruising in her mother	Hypermobility	17
12	M/5	Joint hypermobility, Scoliosis, Pes planus	Case 13 is his sister	Kyphoscoliosis	18
13	F/3	Joint hypermobility, Pes planus	Case 12 is her brother	Kyphoscoliosis	18
14	F/1	Joint hypermobility Muscular hypotonicity		Kyphoscoliosis	19
15	M/21	Skin hyperextensibility Cigarette paper scars	Similar findings in his maternal grandmother, mother and brother	Classical	20
16	F/25	Skin hyperextensibility Cigarette paper scars Molluscoid pseudotumor Joint hypermobility, Scoliosis		Kyphoscoliosis	21
17	F/5	Skin hyperextensibility Joint hypermobility Ocular findings (oscillopsia, corneal opacity, blue sclera)		Kyphoscoliosis	22
18	M/25	Skin hyperextensibility Cigarette paper scars Molluscoid pseudotumor Joint hypermobility		Classical	23
19	M/19	Skin hyperextensibility Cigarette paper scars Joint hypermobility	Similar findings in his maternal grandfather and mother	Classical	24

Table 3. Diagnostic Scoring System of the Classical Type Ehlers-Danlos Syndrome[7]

Clinical features	Score	Presented case
1. Joint hypermobility		
A. Dorsiflexion of little finger > 90 degrees with forearm flat on table	1	1
B. Passive apposition of thumb to flexor forearm	1	1
C. Hyperextension of elbow > 10 degrees	1	1
D. Hyperextension of knee > 10 degrees	1	
E. Forward flexion of trunk so that palms of hand rest easily on floor	1	
2. Skin extensibility		
A. < 4 cm	0	
B. 4 cm	1	
C. 5 cm	2	
D. 6 cm	3	
E. 7 cm	4	
F. 8 cm	5	
3. 'Cigarette paper', wrinkled scarring		
A. Left elbow and forearm	1	
B. Right elbow and forearm	1	1
C. Left knee	1	1
D. Right knee	1	
E. Forehead	1	
4. Bruising		
A. No history or clinical evidence	0	
B. Positive history of mild bruising, no clinical evidence	1	
C. Positive history of moderate bruising with or without skin findings	2	
D. Moderate bruising on physical examination	3	3
E. Marked bruising on physical examination	4	
F. Gross bruising on physical examination	5	

skin extensibility less than 4 cm; wrinkled scars on both knees; and moderate bruising upon physical examination.

On histopathologic examination, most patients show no abnormalities of collagen or elastic fibers, except for those with vascular type. They show dermal thinning, usually to half or three quarters of normal thickness, and relatively abundant elastic fibers that appear shortened and fragmented[25]. In electron microscopic studies, some have reported no difference to the normal control, whereas, others have observed abnormalities, such as fibroblasts with the paucity of rough-surfaced endoplasmic reticulum, a reduced number of fibroblasts, an underdeveloped endoplasmic reticulum, and small, sparse collagen bundles[7,25].

EDS should be distinguished from cutis laxa, pseudoxanthoma elasticum, Marfan's syndrome, Turner's syndrome and cartilage-hair hypoplasia syndrome. In EDS, the skin is hyperextensible but not lax, and it recoils quickly. In cutis laxa, there is lax, pendulous skin and loss of elastic tissue in the dermis. In pseudoxanthoma elasticum, the skin may be lax, but is yellowish and characterized histologically by the presence of calcification. Other diseases mentioned above can also be distinguished by their associated features[26].

No treatment is currently available for EDS. Therefore, palliative and preventive care is applicable to all forms of EDS. Although not evaluated in a large group of patients with EDS, prevention is based on common sense and clinical experience, and it is important to reduce the risks and prevent potential complications[7,27]. For example, as patients with atrophic or cigarette scars can be expected to have a poor cosmetic outcome after surgical pro-

cedures, it is recommended to avoid non-essential surgery or invasive procedures. Patients should avoid physical trauma that could cause skin lacerations, and they should wear protective clothing when taking exercise. Sports that cause heavy joint strain, for example, weight lifting or stretching, are discouraged. Patients should also avoid standing or working on hardened floors for long periods and wear supportive, cushioned shoes to reduce foot, knee, hip, or back pain. Finally, regular evaluation of the skin, joints, heart or eyes is important for maintenance[4,27].

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