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Multiple dermatofibromas in a patient with Ehlers–Danlos syndrome: a case report

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Abstract

Background Dermatofibromas, also known as benign fibrous histiocytomas, are among the most common cutaneous soft-tissue lesions. Association of multiple dermatofibromas with some diseases was described and it has not been reported with Ehlers–Danlos syndrome before. We present a case with Ehlers–Danlos syndrome and multiple dermatofibromas.

Case presentation An 18-year-old Iranian woman presented with multiple purple nodules ranging from 0.5 to 1.5 cm in diameter, which were mobile and located on the proximal part of the lower limb. The dimple sign of these lesions was positive. During the physical examination, several features suggestive of Ehlers–Danlos syndrome were observed, including hyperextensibility and fragility of the skin, wide atrophic scars on the upper limb, hypermobility of joints and fingers, swan neck deformities of the digits, nodules on the knee, and striae alba on the leg. The patient was previously unaware of having Ehlers–Danlos syndrome. She had a history of asthma and atopic dermatitis. Family history was negative. A biopsy of the nodular lesions was performed, and the findings confirmed the diagnosis of dermatofibromas.

Conclusion We describe a patient with Ehlers–Danlos Syndrome who presented with multiple dermatofibromas. To our knowledge, this combination of findings is a previously unreported occurrence.

Keywords Multiple dermatofibromas, Ehlers–Danlos syndrome, Case report

Background

Ehlers–Danlos syndromes (EDS) comprise a group of relatively rare heritable connective tissue disorders characterized by defects in collagen synthesis or processing. These disorders are associated with a constellation of clinical manifestations, which may include skin hyperextensibility, joint hypermobility, and tissue fragility. The estimated overall prevalence of EDS is ~1 in 5000 individuals and encompass a spectrum of discrete disorders, with 13 recognized subtypes to date, each with its own clinical manifestations and diagnostic criteria. Among these subtypes, the underlying genetic alterations have been elucidated for 12 of these conditions, providing valuable insights into their molecular basis. Hypermobile Ehlers–Danlos syndrome (hEDS) is the most common type, but its genetic basis remains unknown, which makes diagnosis challenging since it relies on clinical evaluation [1, 2].

The correct clinical diagnosis of EDS can be established based on family history and clinical criteria, including the degree and nature of involvement of the skin, joints, and blood vessel walls [3]. The most common cutaneous manifestations are hyperextensibility, fragility, smooth, velvety skin that bruises easily, delayed wound healing,

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and thin, atrophic scars after wound healing [2]. The Beighton score is the most common method used for evaluating generalized joint hypermobility in hEDS [1].

Dermatofibromas, also called benign fibrous histiocytomas, are among the most common cutaneous soft-tissue lesions. They represent a benign dermal proliferation of fibroblasts that can arise as a reactive process following various triggers, such as trauma, injections, arthropod bites, or ruptured folliculitis, but often are idiopathic [4]. Dermatofibromas typically present as firm, often hyperpigmented, nodules 0.3–1.0 cm in diameter, but giant lesions larger than 3 cm in diameter have been described [5, 6]. Diagnosis is usually based on clinical appearance and histopathology. Multiple clustered dermatofibroma (MCDF) is a distinct variant of multiple dermatofibromas and is defined as a well-demarcated plaque composed of individual dermatofibromas [7].

Previous studies have explored potential links between EDS and various other conditions, including urinary incontinence. While multiple dermatofibromas have been associated with certain systemic diseases, with systemic lupus erythematosus (SLE) being the most prominent, followed by human immunodeficiency virus (HIV) infection [8, 9], this presentation has not been previously reported alongside EDS. Our case report describes a patient with a confirmed diagnosis of EDS who also exhibited multiple dermatofibromas.

Case presentation

An 18-year-old Iranian woman presented to the al-Zahra Hospital Dermatology Clinic with the chief complaint of multiple purple nodules that appeared about 2 years ago after trauma and fracture of her left elbow, on the proximal lower limb. The patient did not have a previous diagnosis, and it was her first consultation for these lesions.

On physical examination, purple nodules with diameters ranging from 0.5 cm to 1.5 cm, which were mobile, were observed on the proximal part of the lower limb. The dimple sign of these lesions was positive (Fig. 1). Upon inspection, an abnormal shape of the fingers was visible, and during the examination of her whole body to detect any other signs and symptoms, we noted that the skin was hyperextensible and fragile, and wide atrophic scars were evident on the upper limb. Joints displayed hypermobility, especially in the fingers, and Swan-neck deformities of the digits were also apparent (Fig. 2). Some nodules were observed on her knee, and striae alba were present on her leg (Fig. 3). Skin-colored papules on the sides of the heel (piezogenic papules) were also seen, all of which are consistent with EDS.

The patient was the first child in her family, and her birth weight was 3.1 kg. She had normal growth and development during the fetal period. EDS symptoms appeared at the time of puberty as skin hyperextensibility, joint hypermobility, brittle skin, and susceptibility to ecchymosis. She mentioned a history of xerosis and atopic dermatitis since her infancy. She also had a history of respiratory disorders and had been diagnosed with asthma about 5 years ago, and inhalation corticosteroids had been prescribed for her for 2 years. She did not mention any history of cardiovascular, ophthalmic, skeletal, or gastrointestinal disorders. Family history was negative.

A biopsy of the nodular lesions was performed and showed fibrohistiocytic proliferation, acanthotic epidermis, and elongated rete ridges, which were suggestive of dermatofibroma (Fig. 4A, B). The patient was referred to a cardiologist and ophthalmologist. The result of the echocardiography was normal, and no abnormalities in the eyes were observed. Unfortunately, the patient was not cooperative for further diagnostic studies and abstained from genetic testing and any other diagnostic

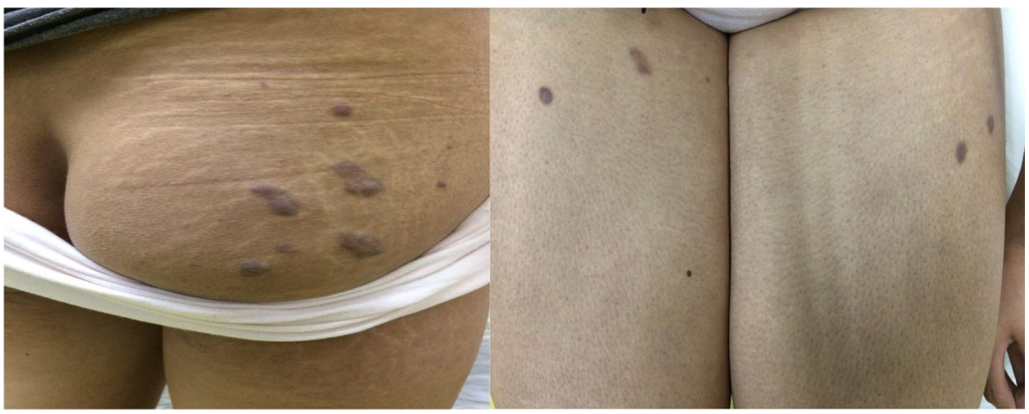

Fig. 1 Purple nodules with diameter of 0.5–1.5 cm, which are mobile have been seen on the proximal part of the lower limb

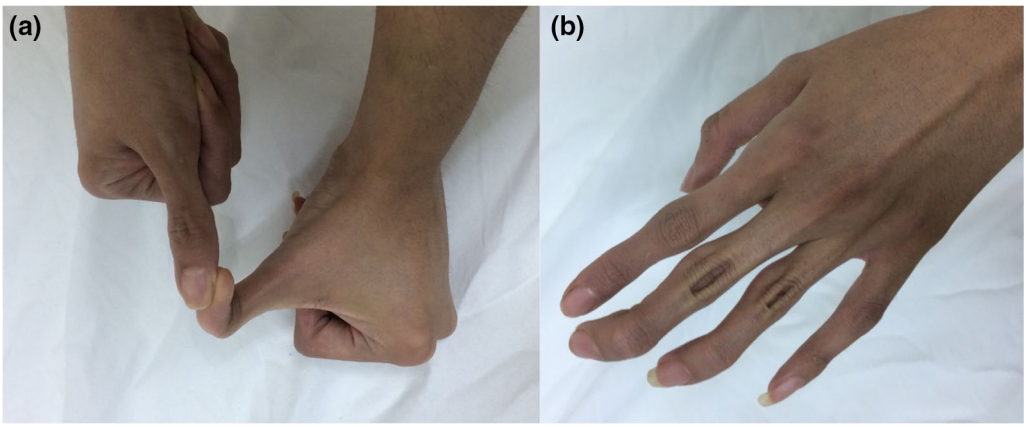

Fig. 2 **A** Hypermobile finger. **B** Swan-neck deformity of the digi

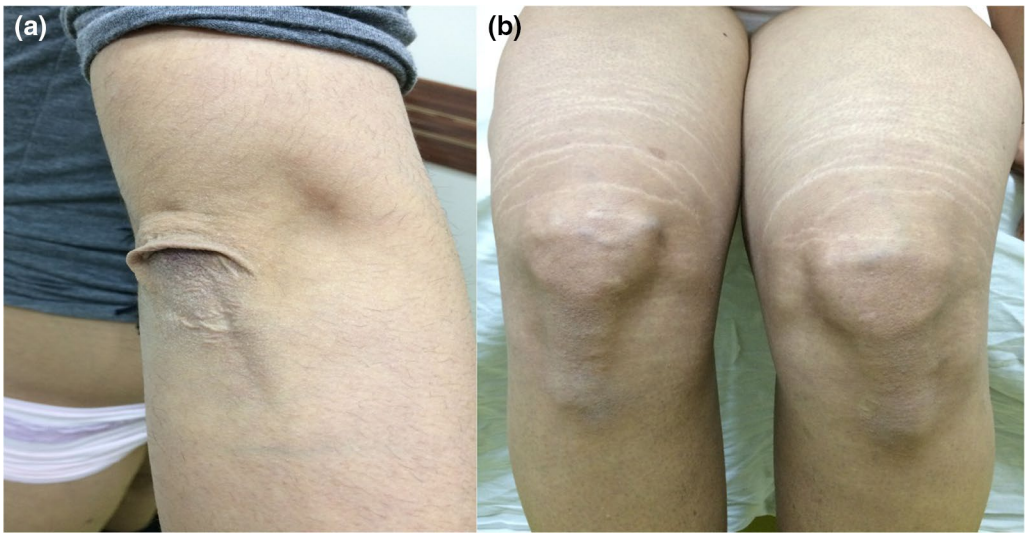

Fig. 3 **A** Atrophic scar on the elbow. **B** Striae alba on legs

assessments. Clinical diagnosis of classical EDS was established based on physical examination findings that met two major criteria (skin hyperextensibility, atrophic scarring, and generalized joint hypermobility) and two minor criteria (easy bruising and skin fragility). We also ruled out other connective tissue disorders that are included in the differential diagnosis of EDS. Finally, we educated the patient about both the benign nature of the dermatofibroma lesions and the importance of EDS follow-up.

Discussion and conclusions

Dermatofibroma, also known as benign fibrous histiocytomas, are common, benign, painless dermal nodules that are usually solitary and measure less than 1 cm. They often appear on the extremities of middle-aged women [10]. The pathogenesis of dermatofibromas is not fully understood. Histopathologically, dermatofibromas are caused by persistent inflammatory proliferation of either histiocytes, fibroblasts, or dermal dendritic cells.

Some dermatofibromas clearly arise as a reactive process following traumas, injections, arthropod's bites, or ruptured folliculitis [4]. Also, in literature, there are reports of multiple dermatofibroma that suggesting association with some diseases including systemic lupus erythematosus as most dominant and then HIV infection. The study that reported multiple dermatofibromas with human immunodeficiency virus (HIV) infection in three men suggests immunosuppression as the basic mechanism for incidence of multiple dermatofibromas [9]. There are examples of patients who developed dermatofibromas while taking oral prednisone (with SLE) or

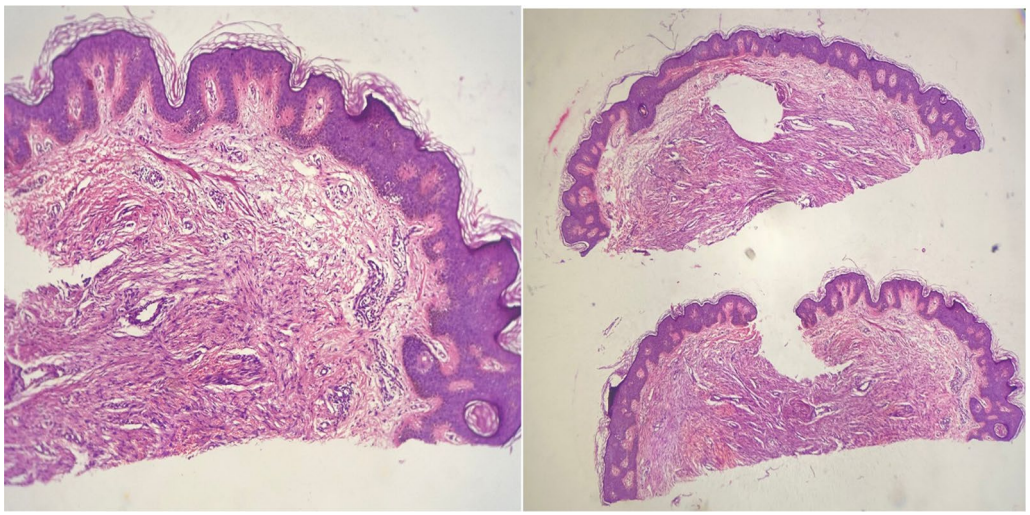

Fig. 4 There are papilomatous and acanthotic epidermis with basal layer pigmentation. In dermis, grenz zone and admixture of fibroblasts, histocytes, and blood vessels are seen

occurrence of new dermatofibromas related to increase in corticosteroid dosage and a dramatic reduction in the number of dermatofibromas when corticosteroid treatment was discontinued. This indicates that immunosuppressive therapies also may play a role in the pathogenesis of dermatofibroma [4, 10, 11]. In addition, some other conditions in comorbidities with multiple dermatofibromas have been reported including dermatomyositis, Sézary syndrome, hepatitis C, hepatocellular carcinoma, Hashimoto's thyroiditis, myasthenia gravis, chronic myeloid leukemia, and Sjögren's syndrome, and recently, a survey was published that showed new onset of multiple dermatofibromas in site of the shunt area after renal transplantation in patients [12–20].

Our patient was diagnosed with asthma 5 years ago and used an inhaled corticosteroid for 2 years. The lesions developed 1 year after withdrawing the inhaled corticosteroid. Considering the lack of systemic effects and the 1-year gap, we believe the inhaled corticosteroid is unlikely to be a factor in the development of multiple dermatofibromas (MD). Regarding the left elbow trauma and fracture, despite the initial suspicion, the different anatomical locations and the presence of multiple lesions make the association questionable.

Ehlers–Danlos syndromes are a group of inherited connective tissue disorders that can exhibit either an autosomal dominant or autosomal recessive inheritance pattern. These disorders frequently result from genetic alterations in genes responsible for encoding collagen proteins or enzymes involved in the modification of collagen [1]. In 2017, the International Classification of Ehlers–Danlos syndromes (EDS) underwent a revision, resulting in the delineation of 13 unique subtypes, with EDS hypermobility type being by far the most common and some types being quite rare. This updated classification system was based on a comprehensive analysis of the phenotypic features and the corresponding molecular pathogenesis associated with each subtype. The molecular basis is known in all subtypes except for hypermobile EDS [1, 2, 21]. Nevertheless, genetic testing is not performed for every patient, and the 2017 diagnostic criteria do not provide explicit guidance on the recommended scope of genetic analysis [1].

There are diagnostic criteria for hypermobile Ehlers–Danlos syndrome (hEDS) provided by International Consortium on Ehlers–Danlos Syndromes and Related Disorders with the Beighton score used for assessing joint hypermobility in patients with EDS. A revised clinical criterion for hypermobile EDS and set of diagnostic clinical criteria for all of EDS subtypes are also proposed by Malfait *et al*. in 2017. Based on revised diagnostic clinical criteria for EDS, a patient must meet specific criteria for a suggestive diagnosis of classical Ehlers–Danlos Syndrome (cEDS). Firstly, the patient must exhibit the major criterion of skin hyperextensibility and atrophic scarring. In addition to this major criterion, the patient must also have either the second major criterion, generalized joint hypermobility, and/or at least three minor criteria including easy bruising, soft, doughy skin, skin fragility, molluscoid pseudotumors, subcutaneous spheroids, hernia, epicanthal folds, complications of joint hypermobility, and family history of a first-degree relative who meets clinical criteria [1].

In our case, since the patient was not sufficiently cooperative, we were unable to perform genetic testing for EDS. We established a clinical diagnosis of EDS,

with a high suspicion of the classical type, based on physical examination findings that met two major criteria (skin hyperextensibility, atrophic scarring, and generalized joint hypermobility) and two minor criteria (easy bruising and skin fragility). The absence of multiple fractures, short stature, and bluish sclerae in infancy are distinguishing features of osteogenesis imperfecta [22, 23]. In patients with Marfan syndrome (MFS), disorders of the cardiovascular system, musculoskeletal system, and eyes, as well as tall stature, are common symptoms. In our case, the lack of lens abnormalities confirmed by slit-lamp examination, a normal echocardiography report, and normal stature helped us exclude MFS [24]. Cutis laxa is characterized by an absence of skin elasticity, leading to loose and sagging skin. Unlike in EDS, when tension is applied to and then released from the skin of patients with cutis laxa, it does not return to its original position due to the loss of elastin [25, 26]. Other disorders that can closely mimic EDS in clinical presentation, such as Loeys–Dietz syndrome, arterial tortuosity syndrome, lateral meningocele syndrome, tenascin-X deficiency, Stickler syndrome, Ullrich congenital muscular dystrophy, and occipital horn syndrome (OHS), did not match the clinical manifestations observed in our case [27].

A comprehensive search of relevant databases, including Embase, Medline, Web of Science, and Google Scholar, revealed no prior reports of patients with both Ehlers–Danlos Syndrome (EDS) and multiple dermatofibromas. While a causal relationship between multiple dermatofibromas and EDS cannot be definitively established based on our single case observation, this unusual clinical presentation highlights the need for continued observation and reporting of such cases.

Abbreviations

EDS	Ehlers–Danlos syndrome
MCDF	Multiple clustered dermatofibroma
HIV	Human immunodeficiency virus
hEDS	Hypermobile Ehlers–Danlos syndrome
MFS	Marfan syndrome
OHS	Occipital horn syndrome

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Author contributions
1. FM: visiting and examining the patients and forming diagnostic and therapeutic plans for the patients, as well as the patient's representative for reporting in the form of a case report, performing histologic examination on the biopsy specimens, and obtaining and preparing pathology photos. 2. MB: corresponding author, gathering and documenting all medical information related to the patient, taking the photos of patient, making a substantial contributing to the concept and design, and writing the first draft of the case report. 3. ZT: resident in charge of following up with the patients, taking an accurate history, conducting skin biopsy, and revising the manuscript critically for important intellectual content. 4. ETT: resident in charge of following up with the patients, taking an accurate history, conducting skin biopsy, and revising the manuscript critically for important intellectual content. 4. ETT: gathering articles related to the case, contributing to the writing of the article, making a substantial contributing to the concept and design, writing the largest share of the report, and involving in the patient's care.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article (and its additional information files).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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