

# Classical Ehlers-Danlos syndrome: clinical, Histological and ultrastructural aspects

## Síndrome de Ehlers-Danlos clássica: aspectos clínicos, histológicos e ultraestruturais

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**Abstract:** A 12-year-old boy with difficulty in wound healing and scars of unusual appearance was examined. Thin, shiny and protruding skin, characterizing pseudotumoral lesions, was observed on his knees and elbows. Loose joints and increased skin elasticity were also observed. Light microscopy showed rare collagen bundles and loosely dispersed collagen fibers. Irregularly distributed elastic tissue was observed, and transmission electron microscopy revealed disorganized collagen fibers. In cross sections under high magnifications, fibers of varying diameters could be seen, as well as an irregular fiber outline. Scanning electron microscopy of the dermis showed disorganized collagen fibers, which were rarely arranged in bundles. Isolated and crossed-over fibers were also found.

**Keywords:** Collagen type V; Ehlers-Danlos syndrome; Microscopy, electron, scanning; Microscopy, electron, scanning transmission

**Resumo:** Paciente masculino de 12 anos relatou dificuldade em cicatrizar, seguido por cicatrizes de aspecto infrequente. A pele dos joelhos e cotovelos é fina, brilhante e protrusa, caracterizando pseudo-tumores. Além disso apresenta hiperelasticidade cutânea e articular. A microscopia óptica demonstrou raros feixes colágenos, as fibras colágenas encontram-se dispersas. O tecido elástico está presente e secundariamente irregular. A microscopia eletrônica de transmissão também observou fibras colágenas desorganizadas e com cortes transversais em grande aumento evidenciou diâmetros variados e contorno irregular das mesmas. A microscopia eletrônica de varredura da derme demonstrou raros feixes colágenos e fibras colágenas isoladas e entrecruzadas.

**Palavras-chave:** Colágeno tipo V; Microscopia eletrônica de transmissão; Microscopia eletrônica de varredura; Síndrome de Ehlers-Danlos

### INTRODUCTION

Collagen is an abundant structural protein found in all animals. In humans it comprises one third of total proteins, makes up three quarters of the dry weight of the skin and is the most prevalent component of the extracellular matrix.<sup>1</sup>

Twenty-eight different types of collagen composed of 46 different polypeptide chains have been identified in vertebrates, and many other proteins contain

collagenous domains.<sup>1</sup>

Collagen molecules are synthesized, secreted into the extracellular space and organized in fibrils that are in turn organized into tissue-specific macroaggregates.<sup>2</sup>

The central pathogenesis of Ehlers-Danlos syndrome (EDS) results from defects in collagen. Mutations were identified in structural collagen genes,

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as well as in genes coding for proteins involved in the processing of this protein.<sup>3</sup>

The hypothesis that EDS is a disorder of fibrillar collagen metabolism is well supported by the identification of specific defects in the collagen biosynthetic pathway that result in clinically different EDS forms.<sup>4</sup>

Three fundamental mechanisms of disease are known to produce EDS: a deficiency of collagen-processing enzymes, dominant negative effects of mutant collagen alpha-chains and haploinsufficiency.<sup>4</sup>

With recent advances, a simplified classification of EDS (Villefranche nosology, 1997) was suggested in which the disorder was divided into six main types.<sup>5</sup> This classification substitutes the old one, which consisted of nine types (type I to type IX), and is broken down into the following types: classical (previously types I and II); hypermobility (previously type III); vascular (previously type IV) kyphoscoliotic (previously type VI A/B); arthrochalasia (previously type VII A/B) and dermatosparaxis (previously type VII C).<sup>5</sup> Types V and VIII and the autosomal recessive type with a tenascin X deficiency are very rare and, as yet, insufficiently characterized.<sup>3,7</sup>

The classical, hypermobility, vascular and arthrochalasia types all possess a dominant autosomal inheritance, whereas the kyphoscoliotic and dermatosparaxis types are autosomal recessive.<sup>6</sup> Approximately 90% of EDS patients have either the classical or hypermobility type, while less than 10% have the vascular type.<sup>8</sup> The other three types comprise a small percentage of EDS cases.<sup>9</sup> Men and women of all races are equally affected by the disease.<sup>6</sup>

Skin and joint involvement are very significant, and dermatologists should therefore be aware of this condition. However, the disease can also affect other systems and organs such as blood vessels, eyes and the gastrointestinal tract.<sup>3</sup>

Classic type EDS tends to be the easiest to recognize.<sup>9</sup> Patients present with different cardinal signs such as articular hypermobility, extremely fragile soft hyperextensible skin, hemosiderotic scars and cutaneous pseudotumors.<sup>3,10,11</sup> Complications, such as hernias, prolapse of pelvic organs, premature arthritis and cervical insufficiency, may occur.<sup>9,12</sup>

Patients with the classic type have mutations in type V collagen (COL5A1 and COL5A2 genes), presumably because of negative dominant effects.<sup>4,5,7,8</sup> Nevertheless, two studies showed that haploinsufficiency of COL5A1 may be more common.<sup>11,13</sup>

#### CASE REPORT

A 12-year-old boy presented with a complaint of very difficult wound healing, followed by the formation of scars of unusual appearance. The patient

also reported loose joints and an increase in skin elasticity.

On examination, innumerable slightly prominent, chestnut-colored scars were observed on the anterior face of his legs. Thin, shiny protruding skin characterizing a pseudotumoral lesion could be seen on the knees and elbows. An ulceration was also observed on the left knee (Figure 1). Nails were normal and varicose veins were found in the ankles. Mosaic-like atrophic scars were observed on his forearms (Figure 2).

The patient's face was normal although there was an excessive number of scars on his forehead. Joints and skin were easily hyperextended (Figure 3). Laboratory tests were normal.

Light microscopy of hematoxylin-eosin stained sections of skin showed an epidermis with a slightly altered contour and ectatic vessels in the papillary and reticular dermis. Rare irregular collagen bundles of various sizes were observed in the reticular dermis, where collagen was mainly found loosely dispersed (Figure 4A). Verhoeff staining showed disorganized elastic tissue (Figure 4B).

Transmission electron microscopy (TEM) also revealed disorganized collagen fibers, which were seen in cross and longitudinal sections in the same field in a non-parallel arrangement (Figure 5A). In cross sections under high magnifications, fibers of varying diameters could be seen, as well as an irregular fiber outline (Figure 5B).

Scanning electron microscopy (SEM) of the dermis showed disorganized collagen fibers, which were rarely arranged in bundles (Figure 6).

Isolated and crossed fibers were also found.



FIGURE 1(A,B): Clinical aspects showing scars on the patient's legs and pseudotumoral lesions on his knees

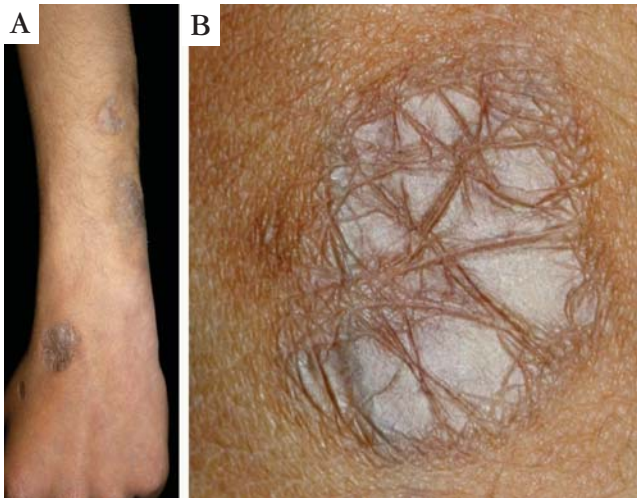


FIGURE 2 (A,B): Atrophic scars on the patient's forearm. Detail showing a mosaic-like aspect

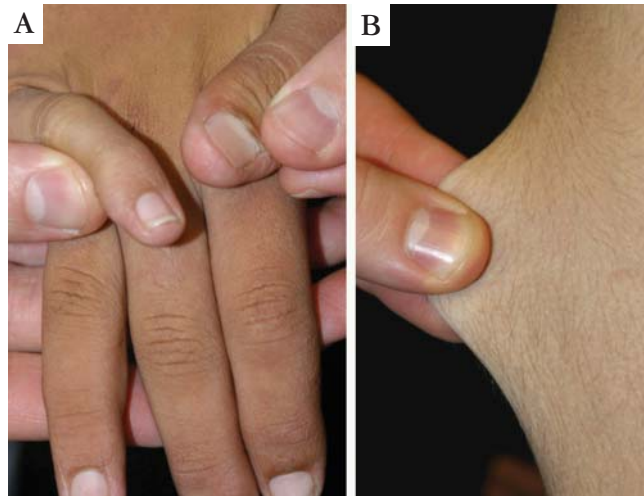


FIGURE 3 (A,B): Skin and joint hyperelasticity

### DISCUSSION

The Ehlers-Danlos syndrome comprises a group of hereditary disorders of the connective tissue characterized by variable skin hyperelasticity with an increased tendency to abnormal healing.<sup>3, 7, 14</sup> In the classic type, patients present with joint hypermobility; extremely fragile, soft, hyperextensible skin; hemosiderotic scars; and cutaneous pseudotumors.<sup>3, 10, 11</sup>

In the case described here light microscopy revealed skin of normal thickness with loosely arranged collagen fibers and rare organized bundles; elastic tissue was present and disorganized.<sup>3</sup>

Hermans-Lê et al. described thinner skin and collagen bands and also elastic fibers of various shapes and sizes with a disorganized appearance.<sup>14</sup> Giunta et al. described some areas with both large and small collagen fibers. They also observed areas with disrupted dermal architecture and agglutinated elastic

fibers. These elastic changes may be secondary to the collagen disturbance, since the elastic fibers are not primarily affected in EDS.<sup>10</sup>

Similarly to light microscopy, TEM showed disorganized collagen fibers with varying outlines and diameters in the transverse sections. These findings have already been reported in the literature.<sup>7</sup> Collagen tissue with a cauliflower-like appearance has been reported in the literature but was not found in our case.<sup>3, 5</sup>

SEM also revealed irregularly distributed collagen fibers that did not aggregate well. Isolated and crossed fibers confirmed this abnormal aggregation of collagen. To date only one study using SEM showed this inability of collagen fibers to aggregate.<sup>15</sup>

These histological and ultrastructural findings are similar to those found in the literature and help to elucidate the pathogenesis of this classical dermatological condition. □

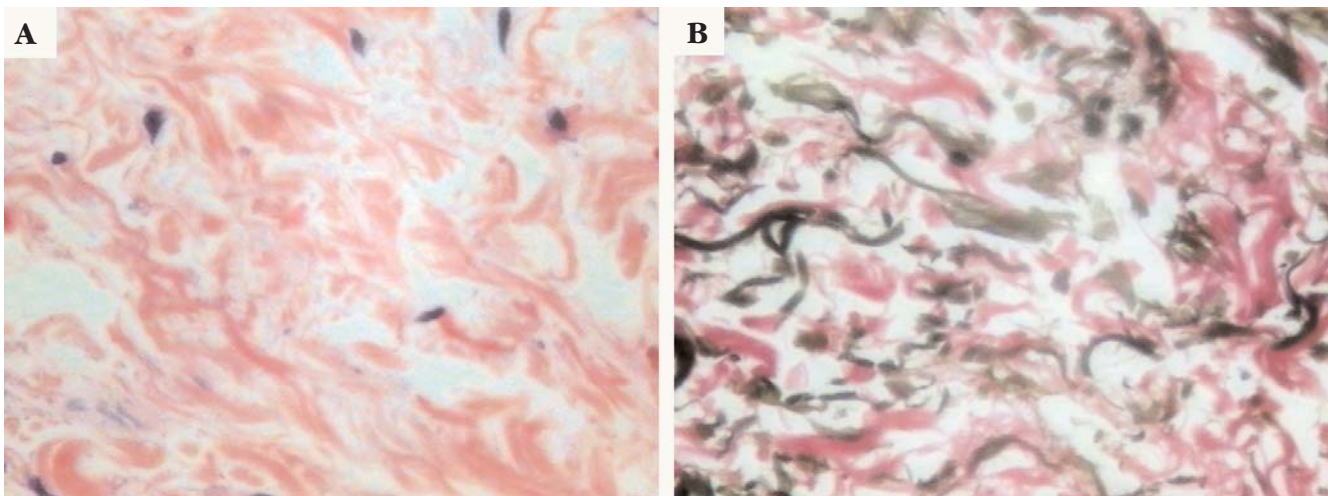
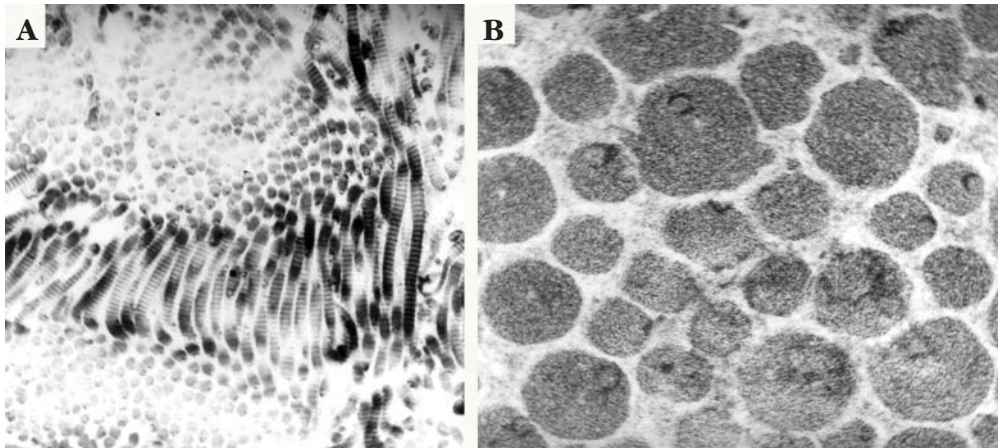
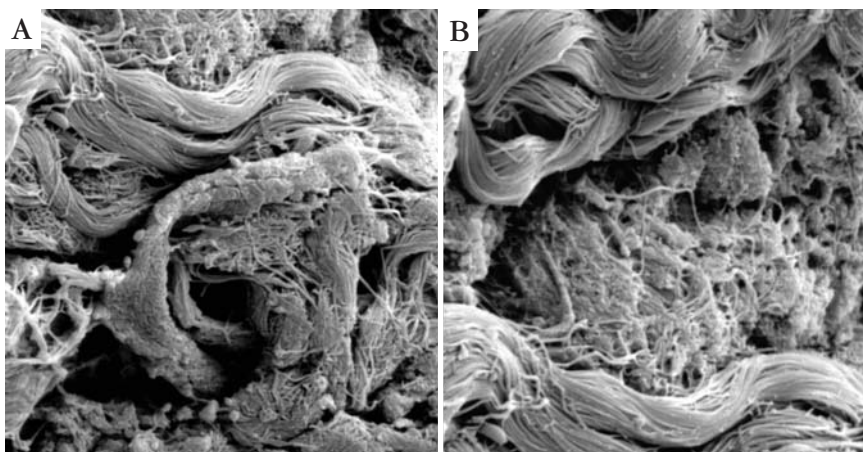


FIGURE 4: A. Light Microscopy - loose collagen without; regular bundles in the reticular dermis (HE x 400); B. elastic fibers present in the normal quantity but with an irregular distribution (Verhoeff x 400)





**FIGURE 5:** Transmission electron microscopy- **A.** disorganized collagen fibers, which were seen in cross and longitudinal sections (x 12,000) **B.** fibers of varying diameters with irregular outlines(x 85,000)



**FIGURE 6 (A,B):** Scanning Electron Microscopy - Irregular distribution of dermal collagen fibers, with some arranged in bundles and some isolated (x 3,600)

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