A 12 year-old boy was examined with difficulty in wound healing and abnormal scars since early childhood. Light microscopy showed loosely and disperse dermal collagen with rare bundles, fibroblasts show an irregular morphology. The hair fibrous sheath presented a normal parallel distribution of the collagen fibers with normal spindle shaped fibroblasts. Transmission electron microscopy also found disorganized collagen fibers, which were seen in a same field in longitudinal and cross sections. With high magnifications an amorphous substance was seen near to loose collagen fibers, which showed variable diameters in cross sections. Scanning electron microscopy of the dermis showed disorganized collagen fibers, with higher magnification important collagen disarrangement was observed with isolated and crossed-over fibers.
ARTICLE

Light and Electron Microscopy of Classical Ehlers-Danlos Syndrome

Hiram Larangeira de Almeida Jr.
Eduardo Bicca
Nara Moreira Rocha
Luis Antônio Suita de Castro
Introduction

Ehlers-Danlos syndrome (EDS) is characterized by collagen changes, with various clinical manifestations due to mutations in the collagen structural genes or in proteins involved in collagen processing in tissues (1). A simplified classification of EDS was suggested by Villefranche (2) who identified six clinical types, substituting the previous types numbered from I to IX: classical type (previously types I and II); hypermobility type (previously type III); vascular type (previously type IV) kyphoscoliosis type (previously type VI A/B); arthrochalasia type (previously type VII A/B) and dermatoparaxis type (previously type VII C).

The classical type is inherited as an autosomal dominant genetic trait, and together with the hypermobility type, accounts for about 90% of EDS cases (2). It is secondary to mutations in type V collagen (genes COL5A1 and COL5A2) (4-7) and is characterized by marked joint hypermobility, with soft hyperextensible skin, hemossiderotic scars and cutaneous pseudotumors (6, 7). Other manifestations such as hernias, pelvic prolapse, premature arthritis, and cervical insufficiency are possible (6). This disease can also affect the blood vessels, eyes and the gastrointestinal tract (3).

Case Report

A 12 year-old boy was examined in our outpatient clinic. The mother reported some difficulty in wound healing and abnormal scars
since early childhood, there was no history of congenital hip dislocation or recurrent subluxations, excluding the arthrochalasia subtype of EDS.

Skin examination identified shiny and protruding skin in the elbows (Figure 1a) and knees characterizing the pseudo-tumoral lesions, as well as innumerable brown atrophic scars, mainly in the anterior aspect of the legs (Figure 1b). Face, nails, hairs and blood examinations were normal. Joints and skin were easily hyperextended. Sagging and redundant skin typical of dermatoparaxis was not seen.

Light microscopy showed an epidermis with a slight alteration in its contour. Abundant ectasic vessels were seen in the dermis. Collagen was seen loosely and disperse with rare bundles, fibroblasts showed an irregular morphology (Figure 2a). With Verhoeff’s staining elastic tissue showed an irregular distribution. Interestingly, the hair fibrous sheath presented a normal parallel distribution of the collagen fibers with normal spindle shaped fibroblasts (Figures 2 b and c).

Transmission electron microscopy (TEM) also found disorganized collagen fibers, which were seen in a same field in longitudinal and cross sections (Figure 3a). Small collagen bundles near isolated collagen fibers could be found (Figure 3b) as well as elastic fibers with an irregular outline. With high magnifications, an amorphous substance was seen near to the loose collagen fibers (Figure 3c) and in cross sections; fibers with variable diameters and an irregular contour were observed (Figure 3d).

Scanning electron microscopy (SEM) of the dermis showed disorganized collagen fibers together with some bundle formation (figures 4a, b and d). With higher magnification, an important collagen disarrangement was observed in some areas, in which isolated and
crossed-over fibers were seen (Figure 4 e). Normal collagen shows a regular distribution (Figures 4 c and f)

Discussion

The Ehlers-Danlos syndrome comprises a group of genodermatoses characterized by skin hyperelasticity and abnormal healing secondary to mutations in collagen and collagen-related proteins.

In this morphological characterization of a classical EDS case, we could demonstrate collagen changes with light microscopy, with paucity of collagen bundles and irregular fibroblasts in a disorganized dermis. Interestingly, the hair fibrous sheath had a normal appearance, with fusiform cells and parallel distribution of collagen, which suggests that these fibroblasts represent a different cell subpopulation, which has been already proposed on a molecular level (8). Some investigations also pointed out the concept of different skin fibroblasts subsets (9, 10).

Similarly, TEM showed some disorganized loose collagen fibers, with an irregular outline and various diameters in the cross-sections, which were already reported in the literature (6, 10, 11). There are few reports on the use of SEM in dermal diseases. In accordance to our results, only one report with SEM in EDS showed the inability of collagen fibers to aggregate (12). Up to now, the correlations between the phenotype and mutation patterns or ultrastructural changes were not suggested, since this condition is very rare.
References


Legends

Figure 1- a. pseudotumoral scar in the elbow. b. multiple aberrant scars in the lower leg.

Figure 2- Light microscopy. a. irregular collagen fibers and fibroblasts morphology (HE x 400). b. normal follicular fibrous sheath (HE x 100). c. detail of the normal follicular fibrous sheath with parallel distribution of the collagen and fusiform cells (HE x 400).

Figure 3 – Transmission electron microscopy. a. irregular distribution of collagen fibers, seen in longitudinal and cross sections (x12,000). b. small collagen bundle (arrow) and an elastic fiber (EF) with irregular outline (x12,000). c. detail of the collagen fibers with an amorphous material (x30,000). d. irregular and aberrant contour of collagen fibers on cross sections(x 50,000).
Figure 4 – Scanning electron microscopy. a, b and d. irregular distribution of collagen fibers, with some bundles formation and isolated fibers (x 3,500). d. detail of an irregular area without bundle formation showing individualized and crossed-over collagen fibers (x 7,000). c and f. normal collagen (x 1,500).
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