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Clusterin expression in elastofibroma dorsi

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Summary. Background: Elastofibroma dorsi is a benign soft tissue lesion composed of abnormal elastic fibers. Degenerated elastic fibers in skin and liver are associated with clusterin, an apoprotein that shares functional properties with small heat shock proteins. We evaluated the staining pattern and possible role of clusterin in elastofibroma dorsi. Material and methods: Twenty-one subcutaneous elastofibromas from the scapular region were evaluated with Elastica van Gieson and Orcein stains, immunohistochemically with antibodies to clusterin, smooth muscle actin, S-100, vimentin and CD34 and correlated with clinical data with respect to physical trauma. Results: Clusterin correlated with the staining pattern of Elastica van Gieson and labelled abnormal broad coarse fibrillar and globular elastic fibers in all elastofibromas. Orcein stains additionally identified fine oxytalan fibers which were not stained by clusterin. Clusterin staining was observed only on the outside of the elastin fibers, while the cores of fibers and globules were unstained. 4/21 elastofibromas showed cellular nodules with a myxoid/collagenous stroma. The round to oval cells showed cytoplasmic staining with vimentin and clusterin; CD34 labelled mostly cell membranes. The cells lacked SMA and S-100 expression. The central areas of the nodules were devoid of elastic fibers, but the periphery contained coarse fibers and globules. 9/11 patients, for whom clinical data were available, reported trauma to the scapular region. Conclusion: Many investigated ED were associated with trauma, which supports a reactive/degenerative etiology of ED. The abnormal large elastic fibers in all ED were enveloped by clusterin. Clusterin deposition may protect elastic fibers from degradation and thus contribute indirectly to the tumor-like presentation of ED.

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Introduction

Elastofibroma dorsi (ED), originally described by Järvi and Saxén (1961), is a benign connective tissue lesion characterized by the accumulation of abnormal elastic fibers. Under physiological conditions, elastic fibers are responsible for the resilient properties of various organs, with highest concentrations in aorta and lung. In subcutaneous tissues and skin, several types of elastic fibers are described. In the reticular dermis, the elastic fibers are large fibrils which primarily consist of elastin. They are horizontally oriented and extend vertically into the papillary dermis, either as bundles of microfibrillar oxytalan fibers or as cross-linked elaunin fibers (Wolff et al., 2008). In cell culture experiments it has been shown that elastin is produced by skin fibroblasts and smooth muscle cells (Giro et al., 1984; Kajiya et al., 1997). Although the metabolic turnover of elastic fibers is very slow, elastic fibers are continuously degraded. Degradation is associated with a number of pathological conditions, e.g. actinic damage, genodermatoses, systemic genetic diseases and ED (Wolff et al., 2008). Histologically, elastic fibers can be detected by Elastica van Gieson or Orcein stains. Immunohistochemical investigations of ED revealed expression of CD34, factor XIIIa, vimentin, lysozym, prominin 2 (CD133), fibronectin, laminin and myoglobin in fibroblasts and matrix components (Fukuda et al., 1987; Govoni et al., 1988; Kumaratilake et al., 1991; Nakamura et al., 1991; Kahn and Hanna, 1995; Mojica and Kuntzman, 2000; Kayaselcuk et al., 2002; Hisaoka and Hashimoto, 2006; Gun et al., 2007; Yamazaki, 2007; Kuroda et al., 2008). ED can occur at different anatomical sites (Austin et al., 1983; Cross et al., 1984; Tsutsumi et al., 1985; De Nictolis et al., 1995;

Sakatani et al., 2000; Nishida et al., 2003), but the main locations are subcutaneous and deep soft tissues of the scapular region (Nagamine et al., 1982; Haney, 1990; Fletcher et al., 2002; Kara et al., 2002; Chandrasekar et al., 2008; Kourda et al., 2009), in particular between lower scapula and chest wall deep to the latissimus dorsi and rhomboid major muscles, where ED are often attached to the ribs (Fletcher et al., 2002). The etiology of ED is still unknown. There is some debate as to whether ED is a true neoplasm or if physical stress contributes to ED development (Fletcher et al., 2002).

Degenerated proteins are known to expose their hydrophobic domains on the surface of the protein. Molecular chaperones (heat-shock proteins) assist in the folding of newly synthesized proteins and are able to promote refolding after damage by physical trauma and other types of cellular injury. They bind to and stabilize the exposed hydrophobic domains of the target proteins and help regulate folding with cycles of controlled binding and release (Aigelsreiter et al., 2007). Clusterin (apolipoprotein J) is a highly conserved multifunctional glycoprotein. Clusterin action resembles that of small heat-shock proteins (sHsps). The broad tissue and fluid distribution indicates that clusterin has a fundamental biological role (Blaschuk et al., 1983; Poon et al., 2000; Jones and Jomary, 2002). Unlike sHsps, clusterin is a secreted protein and the first chaperone to be identified in the extracellular space (Humphreys et al., 1999; Poon et al., 2000). In previous studies, we demonstrated that clusterin is associated with degenerated and abnormal elastic fibers in aged human and mouse skin (Janig et al., 2007), as well as with human liver disease associated with liver fibrosis and cholestasis (Aigelsreiter et al., 2009). UV-induced elastic fiber degeneration could be prevented by adding clusterin (Janig et al., 2007). The role of clusterin in carcinogenesis is still unclear but it appears to play a role in tumorigenesis of various organs (Rizzi and Bettuzzi; Xie et al., 2002; Mazzarelli et al., 2009; Panico et al., 2009; Redondo et al., 2009; Sala et al., 2009), such as lymphomas (Saffer et al., 2002; Nascimento et al., 2004) and soft tissue tumor development (Grogg et al., 2005; Lourda et al., 2007). The aim of our study was to elucidate the role of the stress-associated protein clusterin and to document the properties and distribution of *clusterin* in a collection of subcutaneous ED.

Materials and methods

Samples of formaldehyde-fixed and paraffin-embedded human ED (n=21) were obtained from the BioBank of the Medical University of Graz, Austria. Clinicopathological data concerning patient's gender, age, tumor size, history of physical stress, and recurrence rate were collected. Sections were stained with hematoxylin-eosin (H-E), Elastica van Gieson and Orcein stain according to a standard procedure. For immunohistochemical detection of clusterin, sections were submitted to antigen retrieval in Cell Conditioner1 CC1 (CC1950-124 2L), subsequently incubated for 30 min with monoclonal mouse antibody to human clusterin (Clone 41D, Upstate Biotechnology, Lake Placid, NY) at 1: 5000 dilution. The reaction was visualized using the Incubation with Ventana Ultra View DAB Kit (760-500) on Ventana Benchmark. For negative control the primary antibody was omitted. Immunohistochemical detection of smooth muscle actin (SMA; Sigma Aldrich, monoclonal mouse antibody, A2547, clone 1A4), Vimentin (Histoprime, monoclonal mouse antibody, E034M), S-100 (Dako, monoclonal rabbit antibody, Z311) and CD34 (Eubio, monoclonal mouse antibody, Ab-1, clone QBEnd/10) was performed following the manufacturer's instructions.

Results

Tumor size and volume of 21 subcutaneously located ED ranged from 32 to 165 cm^2 (mean: 78 cm^2). All ED were poorly circumscribed. The cut surface revealed yellow fatty tissue interlaced with gray-white fibrous tissue bands (Fig. 1A). Histologically, ED were composed predominantly of collagenous fibrous tissue with islands of adipose tissue (Fig. 1B). Amorphous globular and thick abnormal fibrillar elastic material was embedded in a cell-poor collagenous fibrous background (Fig. 1C). Orcein stains displayed numerous globular elastic fibers with serrated appearance (Fig. 1D), thick tubular structures with occasional branching, but also microglobular elastin fibers and fine thin microfibrillar oxytalan fibers (Fig. 1E). Antibody to human clusterin labeled all elastic fibers and globules within the collagenous areas strongly (Figs. 1F-H, 2C-D). Clusterin was identified on the outside of the fibers. In cross sections of these fibers, the core was completely unstained (Fig. 1G-H).

4/21 ED displayed numerous collagenous and/or myxoid nodules (Fig. 2A,B). In some lobules cellularity was low, others revealed clusters of oval polygonal vimentin positive cells in lobular arrangement. The centers of these nodules were devoid of broad thick elastin fibres but displayed globular elastin deposits. Towards the periphery of these nodules the elastin fibers became larger and displayed a serrated surface. Antibody to clusterin labelled the globular material and the outer surface of large serrated elastin fibers at the periphery of the nodules. The core of the fibers was unstained (Fig. 2C). In addition to the abnormal elastic fibers, some, but not all cells within the nodule showed a strong cytoplasmic staining with antibody to clusterin (Fig. 2D). Immunohistochemistry with antibody to CD34 revealed a hetereogenous staining pattern. Most, but not all cells revealed a staining of cell membranes (Fig. 2E). Within the cellular areas round large cells with abundant cytoplasm and a prominent nucleus were found in close proximity to broad coarse branching elastic fibers and fine fibrils (Fig. 2F). None of these cells reacted with antibodies to smooth muscle actin (Fig. 2G) and S-100 (Fig. 2H). (For staining details see Table 1).

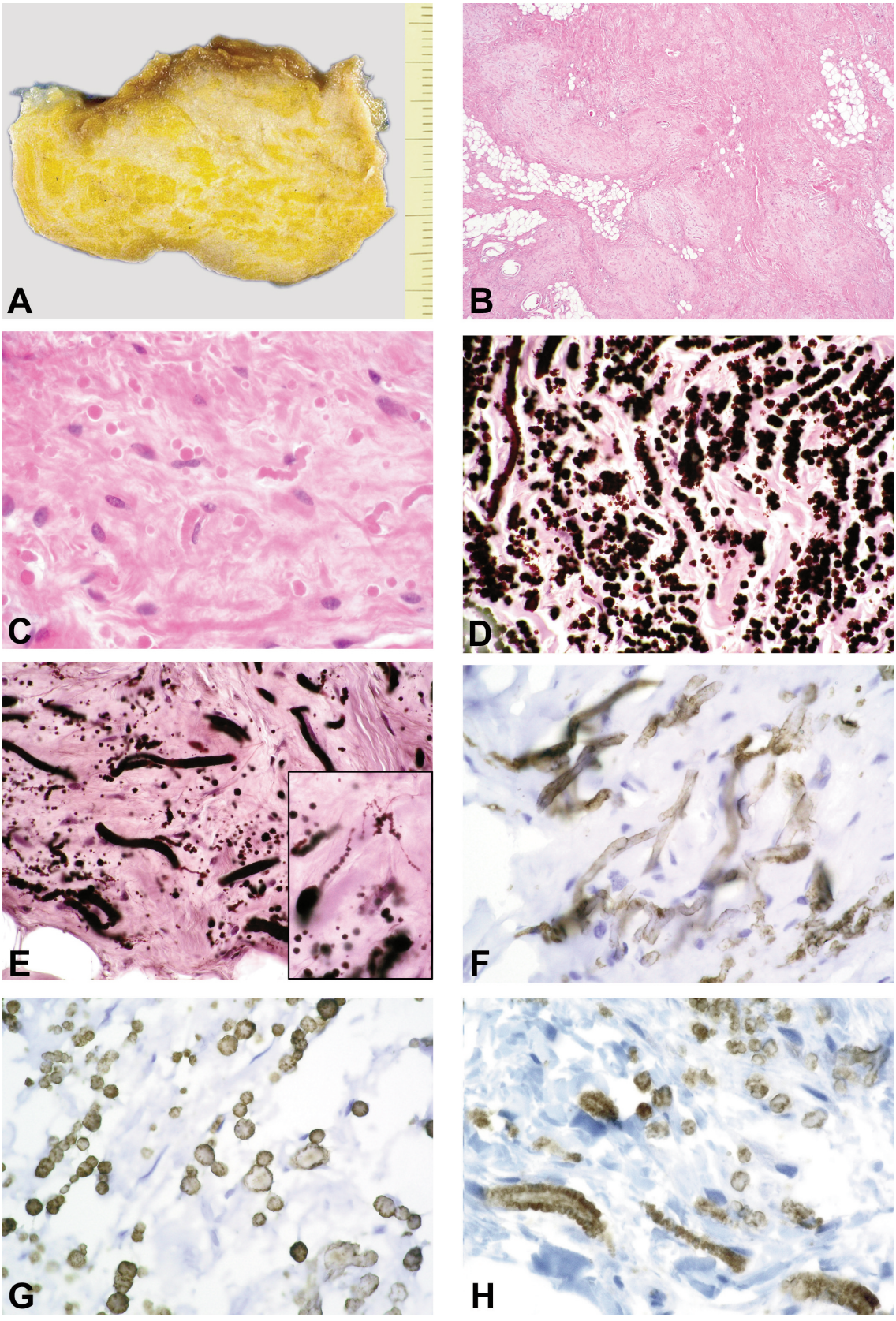

Fig. 1. A. Macroscopic image of the cut surface of a poorly circumscribed elastofibroma dorsi (ED) from a subcutaneous location consisting of yellow fat and gray-white fibrous areas. **B.** Microscopic overview of ED on H.E. stained section. The tumor is composed of collagenous tissue, thickened eosinophilic elastic fibers and adipose tissue. **C.** Microscopic detail of ED on H.E. stained section. The tumor is composed of collagenous tissue with intermingled enlarged and globular abnormal eosinophilic elastic fibers. **D.** Microscopic detail of ED. Orcein stains highlights black thickened abnormal globular elastic fibers. **E.** Microscopic detail of ED on Orcein stained section. In the center fine oxytalan fibers can be noticed, at the periphery thick branches of abnormal elastic fibers are documented, both stain positive on Orcein. The fine oxytalan fibers become globular structures and are associated with thick elastic fibers (inset). **F.** Microscopic detail of ED. Immunohisto-chemistry with antibody to clusterin reveals that branching thick abnormal elastic fibers are heavily decorated with clusterin on the outside of the fibers. Their staining pattern resembles that of Orcein stain. **G-H.** Microscopic detail of ED. Immunohisto-chemistry with antibody to clusterin: A high proportion of abnormal elastic fibers display a peculiar staining pattern. The staining intensity is higher at the margins of the serrated elastic fibers, leaving the core unstained. B, x 2; C-F, x 40; G, H, insert in E, x 60

Correlation with physical trauma was possible in 11/21 patients, since 3 patients died of unrelated causes and 7 were lost for follow-up. Two patients reported a history of trauma or injury to the scapular region, and seven patients reported prolonged physical exposure to the region were the ED arose (details of trauma or physical exposure are listed in Table 2).

Discussion

The pathognomonic histological appearance of ED allowing a confident diagnosis contrasts with the lack of understanding of its etiology. Originally, ED was believed to represent a degenerative/ reactive process with production of abnormal, partly globular elastic fibers and fibrous tissue after preceding chronic microtrauma to the affected area (Järvi et al., 1969; Haney, 1990). A number of case reports support this theory. An ED in an unusual location, the foot, developed after intensive dance and aerobic exercise (Cross et al., 1984). A traumatic genesis is reported in colonic ED which developed after a preceding endoscopic resection of an adenoma (Sakatani et al., 2000).The occurrence of ED in unusual locations without a history of trauma, for example in the ocular region (Austin et al., 1983; Hsu et al., 1997), and the observation of multiple ED in the same patients raised the theory of a possible neoplastic nature of ED. One patient had bilateral subscapular and a gastric ED (Enjoji et al., 1985), the other had deep bilateral ED located near the femur and in the subscapular region (Nishida et al., 2003). One report investigating 170 ED in a large fishingmen community in Japan suggests a genetic predisposition, since about 1/3 of these lesions showed a familial distribution, typically with multiple family members affected (e.g. 4/7 siblings in one family). They also describe a relatively high incidence of ED on the upper extremity and shoulder area, and state that 161/170 reported patients were farmers and manual laborers (working as fishingmen), thus in our opinion indirectly supporting the trauma related genesis (Nagamine et al., 1982).

In our study, the elastin fibers in all ED were of globular and/or fibrillar structure. Clusterin reacted with

Table 1. Special stains and immunohistochemistry results of ED with proliferation nodules.

	Elastica van Gieson	Orcein	Clusterin	CD34	SMA , S-100
pat 6	fine oxytalan fibers neg. thick elastic fibers pos.	fine oxytalan fibers pos. thick elastic fibers pos.	fine oxytalan fibers neg. thick elastic fibers pos.	50-60% of cells pos	neg.
pat 10	fine oxytalan fibers neg. thick elastic fibers pos.	fine oxytalan fibers pos. thick elastic fibers pos.	fine oxytalan fibers neg. thick elastic fibers pos.	40-50% of cells pos	neg.
pat 11	fine oxytalan fibers neg. thick elastic fibers pos.	fine oxytalan fibers pos. thick elastic fibers pos.	fine oxytalan fibers neg. thick elastic fibers pos.	50-60% of cells pos	neg.
pat 12	fine oxytalan fibers neg. thick elastic fibers pos.	fine oxytalan fibers pos. thick elastic fibers pos.	fine oxytalan fibers neg. thick elastic fibers pos.	30-40% of cells pos	neg.

pos.: positive; neg.: negative

Table 2. Available Clinical Data of ED.

	age	tumor size (cm)	physical trauma	recurrence
pat 1	65	7x3x3	Fell on right shoulder five years before tumor diagnosis	no
pat 2	69	6.9x6x3.5	no trauma reported/remembered	no
pat 3	69	8.5x2x6.7	repeated carrying of heavy weight with right arm during former occupation as bookkeeper (repetitive movements at register)	no
pat 4	48	9x3x8	leg-length discrepancy: patient is forced to carry bags on left shoulder/arm	no
pat 5	46	11x9x6	carries bags on left shoulder	no
pat 6	57	5x5x5	carries (often heavy) rucksacks when hiking (hobby) or shopping	no
pat 7	68	8x5.5x2	carries (often heavy) rucksacks when hiking (hobby) or shopping	no
pat 8	52	7x4x3	pat played soccer in club (hobby)	no
pat 9	74	5x4x5	pat suffers from chronic dizziness for about 30 years - repeated injuries by falls and hospital stays in course of this disease	no
pat 10	57	7.5x6x2.5	no trauma or overload reported/remembered	yes
pat 11	49	10.5x7x4.5	patient was employed as gardener for over 30 years, did monotonous, repeated lifting with right arm (repotting)	no

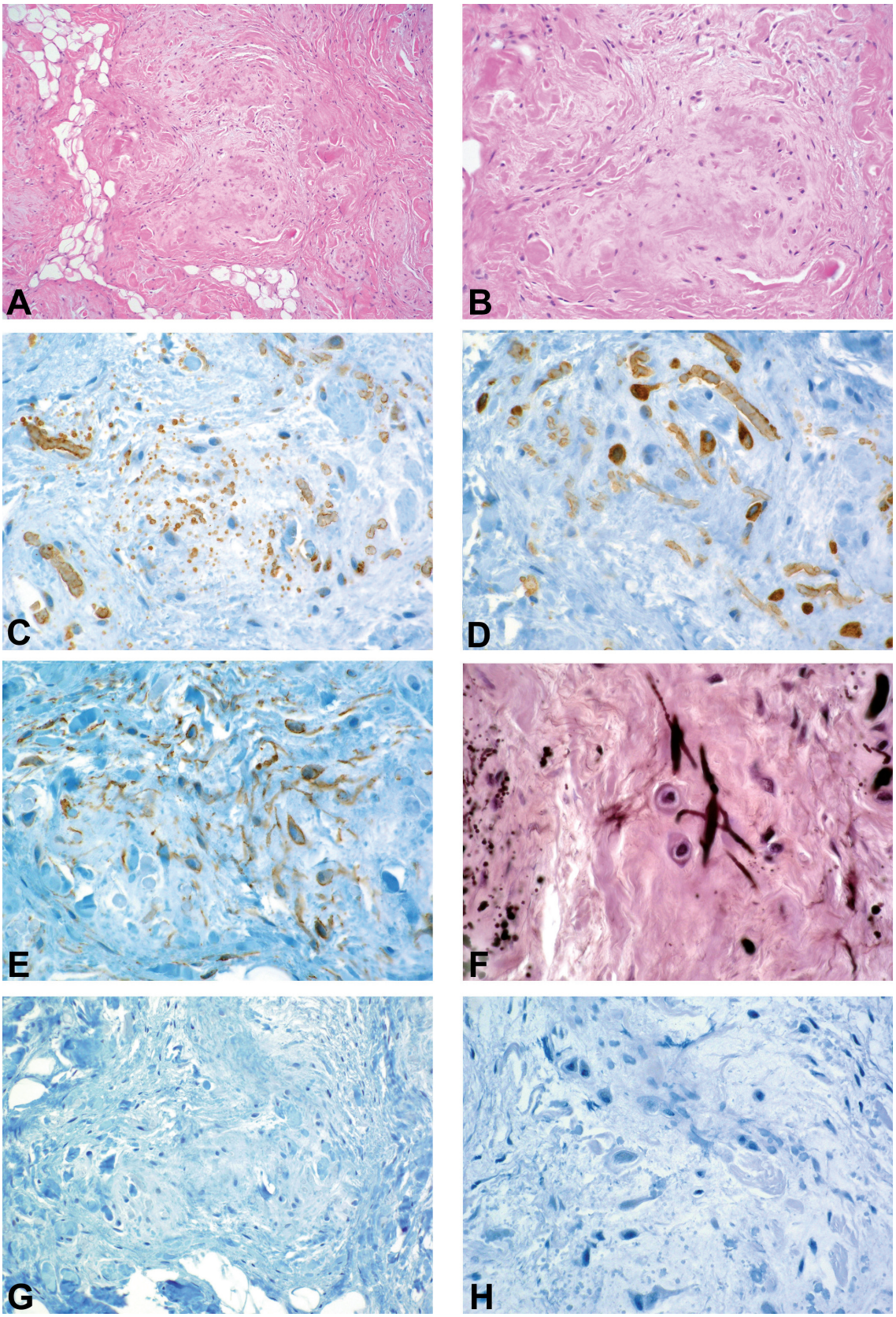

Fig. 2. A-B. Microscopic overview and detail of ED on H.E. stained section. The center of a cellular / proliferation nodule is composed of several fibroblasts and abnormal elastic fibers. **C, D.** Microscopic overview of ED. Immunohisto-chemistry with antibody to clusterin: cellular nodule contains oval cells (fibroblasts) with strong cytoplasmic staining. The abnormal elastic fibers at the periphery of the nodule are decorated with clusterin. **E.** Microscopic detail of ED. Immunohisto-chemistry with antibody to CD34: The cell membranes of fibroblasts in the center of proliferation nodule stain with CD34. Note the spindle cell morphology and CD34 positive cell dendrites of fibroblasts. **F.** Microscopic detail of ED on Orcein stained section. The two round cells with a prominent nucleus are reminiscent of a chondroid-like metaplasia. **G, H.** Microscopic detail of ED, immunohisto-chemical stained sections with antibodies to smooth muscle actin (SMA) **(G)** and S-100 **(H)**. The cells in the center of cellular / proliferation nodule are negative for SMA and S-100. A, x 4; B, x 10; C-E, G, x 40; F, H, x 60

both globular and fibrillar elastic fibers. In the nodular areas, large elastic fibers were found at the periphery of the nodules while the central area was devoid of globular and broad fibrous elastin. The center contained only small elastin globules. Clusterin was demonstrated on the outside of the globules and of abnormal branching elastic fibers, e.g. clusterin enveloped/ coated the thick abnormal fibers. No reaction of clusterin with fine oxytalan fibers was found, suggesting that clusterin envelopes abnormal elastic material only after fiber alignment to elastic fibers has occurred. Deposition of clusterin on the surface of the abnormal proteins shields them from the surrounding microenvironment, similar to observations in cholestatic liver diseases, where clusterin accumulated on the outside of bile plugs leaving the cores unstained (Aigelsreiter et al., 2009). To our knowledge, regression of ED does not occur, or at least has not been reported. One explanation may be that clusterin deposition prevents degradation of these abnormal elastic fibers. Clusterin deposition may therefore indirectly contribute to the persistence of these lesions. In some of our subcutaneous ED, cellular nodules were observed with oval to round, vimentin and CD34-positive cells with abundant cytoplasm lacking S-100 and SMA expression. Some cells in the proliferation nodules displayed features of chondroid-like metaplasia but lacked S-100 and SMA expression. This led us to interpret the cells within the nodules as fibroblasts and a likely source of the abnormal elastic fibers. We speculate that elastin is secreted by these cells and aligned in the periphery of the nodules. As we have clinical information about trauma in only 1 of these 4 cases, we were not able to correlate the traumatic nature. These "proliferation nodules", however, could represent an early phase in the development of ED, where local proliferation of cells with abnormal elastin production is initiated, probably as response to trauma. It is likely that in ED attached to the chest wall and ribs additional cell types such as chondrocytes or specialized myofibroblasts contribute to elastic fiber production. The observation of cellular cytoplasmic staining with clusterin allows the speculation that the same cell/ fibroblast in ED is capable of producing abnormal elastic fibers and clusterin.

In summary, the majority of our patients with subcutaneous ED in the scapular region reported physical trauma to the affected area. All ED shared the pattern of deposition of clusterin on the surface of the abnormal elastin fibers and globules, but not around the fine elastic fibrils. We thus conclude that abnormal elastofibrogenesis is the initial event, possibly as a reaction to physical stress/trauma, and that clusterin deposition constitutes a secondary event. Clusterin deposition prevents degradation of these fibers and may indirectly contribute to persistent tumor-like accumulation of abnormal elastic material in the affected tissues. The mechanism of clusterin deposition and the cell type responsible for clusterin production remains unclear and should be the topic of further investigations.

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