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The Subcutaneous Fascial Analogue of Myositis Proliferans

Electron Microscopic Examination of Two Cases and Comparison with Myositis Ossificans Localisata

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Summary. Two cases of the so-called fascial analogue of myositis proliferans were investigated by histological and electron microscopic methods. It was found that the structure of the fascial variant corresponds almost completely to the true myositis proliferans localized within the musculature. The electron microscopic observations show a preponderantly histiocytic differentiation of the cells and strongly activated proliferating capillaries, and exclude a myogenic origin of the characteristic ganglion-like giant cells. Ultrastructurally a traumatic genesis appears possibly, the cells of the lesion could derive from multipotent cells of the microvasculature. The relations to myositis ossificans and fasciitis nodularis are discussed.

Zusammenfassung. 2 Fälle einer in der Faszie lokalisierten Variante der Myositis proliferans wurden histologisch und elektronenmikroskopisch untersucht. Dabei zeigt sich eine weitgehende Ähnlichkeit zur echten, intramuskulär lokalisierten Myositis proliferans. Die elektronenmikroskopischen Befunde ergeben eine überwiegend histiozytäre Differenzierung der Zellen und stark aktivierte proliferierende Kapillaren und schließen einen myogenen Ursprung der charakteristischen Ganglienzell-ähnlichen Riesenzellen aus. Auf Grund der Feinstruktur erscheint eine traumatische Genese möglich, wobei die Zellen ihren Ausgang von multipotenten Gefäßwandzellen nehmen könnten. Die Beziehungen zur Myositis ossificans und Faszitis nodularis werden diskutiert.

In 1960 Kern reported on pseudosarcomatous lesions of sceletal muscles and coined the term "myositis proliferans" for this disorder. Later Enzinger and Dulcey (1967) adding 33 cases mentioned 12 subcutaneous lesions of almost identical structure arising from the fascia or its close proximity. After these authors this process could be understood as a variant of fasciitis nodularis or of myositis proliferans.

Considerable interest was devoted to the histogenesis of cells in myositis proliferans, particularly of giant cells. Kern (1960) commented on the probable myoblastic nature, other authors (Enzinger and Dulcey, 1967; Tennstedt, 1972) suggested a fibroblastic origin. Recently the first electron microscopical examination of giant cells in myositis proliferans was done by Rose (1974) who unfortunately was not able to contribute to the histogenesis. According to our knowledge no electron microscopic study of the subcutaneous fascial analogue of myositis proliferans was undertaken till now.

Myositis ossificans localisata is another pseudosarcomatous lesion located in the cross-striated musculature, which easily can be confused with osteogenic

sarcomas (Ackerman, 1958; Möbius, 1963; Meffert and Weber, 1973; Uehlinger, 1973). A relation between myositis proliferans and myositis ossificans was considered as possible (cp. Kern, 1960) whereby the former disease was thought to be a "green stage" of myositis ossificans.

Material and Methods

2 cases of subcutaneous fascial analogues of myositis proliferans were available.

Case I. E.No. 3154/74. 68-year old man. For two weeks he suffered from increasing pain in the region of the left elbow joint. The patient's history was non-contributory, especially any form of prior injury was denied. At clinical examination a firm tumor of the size of a chestnut was palpated, its location was the superficial fascia of the extensor musculature immediately superior of the elbow joint. Under suspected diagnosis of sarcoma a wide local excision was done. The tumor was ill-defined, without a capsule, showed an "invasive" growth in the adjacent musculature and had a grayish color. The histological diagnosis was: subcutaneous analogue of myositis proliferans.

Case II. E.No. 15544/74. 53-year old woman. She observed a fastly growing lesion in the left groin for about four weeks. The patient noticed the process by accident, complaints were not present. The surgeon supposed a malignant process and performed a wide local excision. Macroscopically, an almond-sized tumor without sharp demarcation, but restricted completely to the fascia lata, was seen. Its color was grayish to whitish. Histologically the diagnosis of a subcutaneous analogue of myositis proliferans was made.

By reason of comparison a typical case of myositis proliferans and myositis ossificans is presented.

Case III. E.No. 5917/63. 35-year old woman. She noted a tumor in the left chest wall enlarging rapidly for few days. She did not remember the exact duration of the process or any mechanical trauma. A walnut-sized whitish tissue located in the left pectoralis muscle was removed by operation. Beacuse the demarcation from the surrounding muscle tissue was indistinct a part of the obviously healthy muscle was resected additionally. No hemorrhages or necroses were visible. The histological diagnosis was proliferative myositis.

Case IV. E.No. 1321/75. 30-year old woman. For three months the patient preceived a lump in the musculature of the right thigh, which was very painful. Radiographically periphere dense areas and a sharp demarcation were found, the angiographic examination yielded a tumor with numerous vessels. Frozen sections during operation gave the diagnosis of myositis ossificans. Therefore a wide local excision of the walnut-sized lesion within the quadrizeps musculature was performed.

Furthermore 5 cases of fasciitis nodularis (E.No. 5224/58, 6773/58, 14607/67, 17629/70, 812/72) with typical clinical data and characteristical histological features were added and compared with the cases I to IV.

For the histological examination material was fixed in buffered 4% neutral formalin. In case I, II and IV tissue for electron microscopic investigation was taken from specimens fixed in formalin shortly, postfixed in 3% glutaraldehyde (3 hours, 4 C) and osmium tetroxide (1 hour, 4° C) and embedded in usual manner in Epon. Then ultrathin sections were made.

Histological stains and histochemical reactions: H & E, elastica-v. Gieson, Goldner's trichrome stain, methylgreen pyronin, Feulgen stain, cresyl violet, PAS, digestion with amylase followed by PAS reaction, colloidal iron reaction (Hale)-PAS, alcian blue pH 0.5, 1.0 and 2.5, digestion of sections by hylase and following staining with alcian blue, alcian blue (pH 2.5)-PAS.

Results

I. Light Microscopy

a) Fascial Analogue of Myositis Proliferans. In both the cases the lesions took their origin from the fascial connective tissue and replaced it in this area. In case I the lesion enchroached on the adjacent musculature separating widely

single muscle cells. In places it showed an "invasive" growth into subcutaneous adipose tissue. A capsule was always missed accordingly. The basic structure was a fibrous tissue which was exceedingly endowed with capillary vessels in some places exhibiting proliferating endothelial cells, whereas in other areas a fiber-rich connective tissue poor of vessels predominated (Fig. 1 a). In capillary-rich regions the connective tissue was structured in a myxoid-like fashion with slit-like spaces, between the formed elements amorphous ground substance was enclosed (Fig. 1 b). This intercellular substance obviously contained acid mucopolysaccharides as evidenced by the positive Hale and alcian blue reaction (the latter was strongest at pH 0.5). Because of the slight diminishing of the mucopolysaccharide stains after hylase digestion the presence of hyaluronic acid was inferred.

The cells observed were spindle-shaped, oval or stellate resembling fibroblast-like cells. Mostly they contain large rounded or elongated nuclei with distinct nuclear membranes and a moderate content of chromatin distributed evenly throughout the nucleus or seldom arranged in large irregular clumps. The most striking feature are giant cells (Fig. 1 b). There are to be differentiated two types: 1. Some cells possess several nuclei localized in the center, which show similarities to nuclei of endothelial cells, and have a moderately abundant eosinophilic cytoplasm. 2. The vast majority of giant cells reveals abundant, sometimes granular or vacuolated basophilic cytoplasm when stained with H & E and faint red after Goldner's stain, and a pale vesicular, eccentrally placed nucleus containing one or, rarely, two prominent nucleoli which are deep blue or purple. The latter cells bear some resemblance to ganglion cells, but search for Nissl substances (cresyl violet stain) was unsuccessful. Occasional typical mitotic figures were noted in fibroblast-like and giant cells. Scattered throughout the lesion some lymphocytes and mononuclear cells were discerned, they were concentrated at the periphery of the lesion especially around small vessels.

In addition two pecularities of case I must be mentioned. First, a solitary focus of osteoid formation was seen; second, two cavities filled with erythrocytes and fibrin clots and lined by flattened mesenchymal cells were observed.

b) Cases for Comparison. Our case of typical *myositis proliferans* exhibited a fibrous tissue in the pectoralis muscle separating the muscle cells but left the muscle fibers uninvolved. Single muscle fibers show stronger degenerative cytoplasmic changes pointing to trophic disturbances, which finally result in death of muscle cells. The quality of cellular composition of the lesion was undistinguishable from the fascial analogue, but the quantity of giant cells was clearly higher in myositis proliferans than in the fascial analogue. Moreover the rich content of vessels seen in fascial analogue seemed to be less conspicious. It appears, besides, to be worth to stress that scattered lymphocytes at the periphery accentuated perivascularly were present (Fig. 2).

The specimen of *myositis ossificans* showed an organoid pattern with zonal differentiation as known from literature (Ackerman, 1958). In the center a cell-rich mesenchymal tissue with several multinucleated giant cells resembling so-called epulis type was to be observed. Here interlacing cell bundles and areas comprising a loose connective tissue with neutral and acid mucopolysaccharides in profusion and some capillary vessels were found. The tissue was surrounded by a zone of osteoid tissue showing a good differentiation and an organoid pattern.

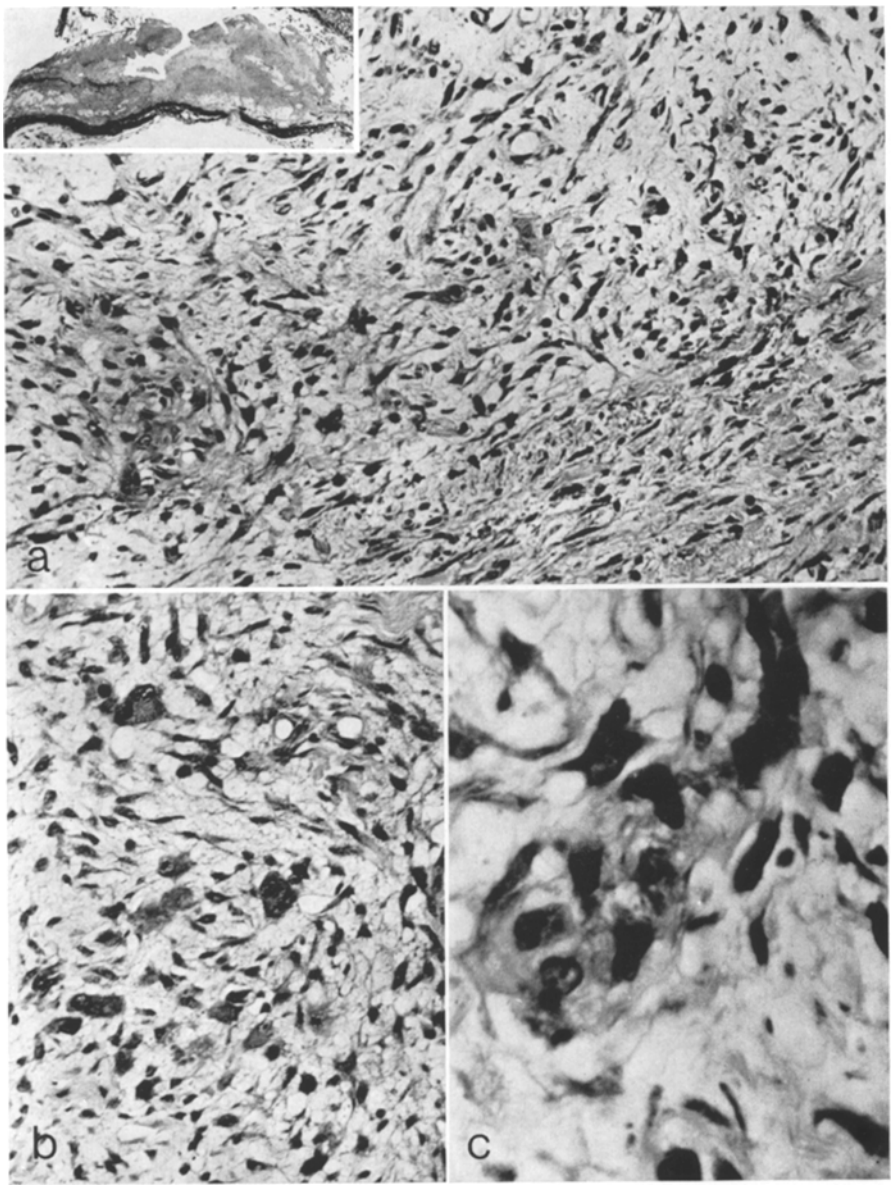

Fig. 1a—c. Typical fascial analogue of myositis proliferans. (a) There are fiber-rich regions (lower right) and areas with a fibrous tissue in a myxoid like fashion showing numerous capillary vessels (HE, 180:1). Inset demonstrates the fascial origin (v. Gieson, 5:1). (b) Characteristic multinucleated giant cells in a myoxid-like tissue (HE, 180:1). (c) Capillary vessel with swollen endothelial cells mimicking a giant cell (HE, 720:1)

The outermost zone consisted of a layer of proliferating mesenchymal cells which showed transition into osteoblasts. In this region the mucopolysaccharide stains were clearly positive.

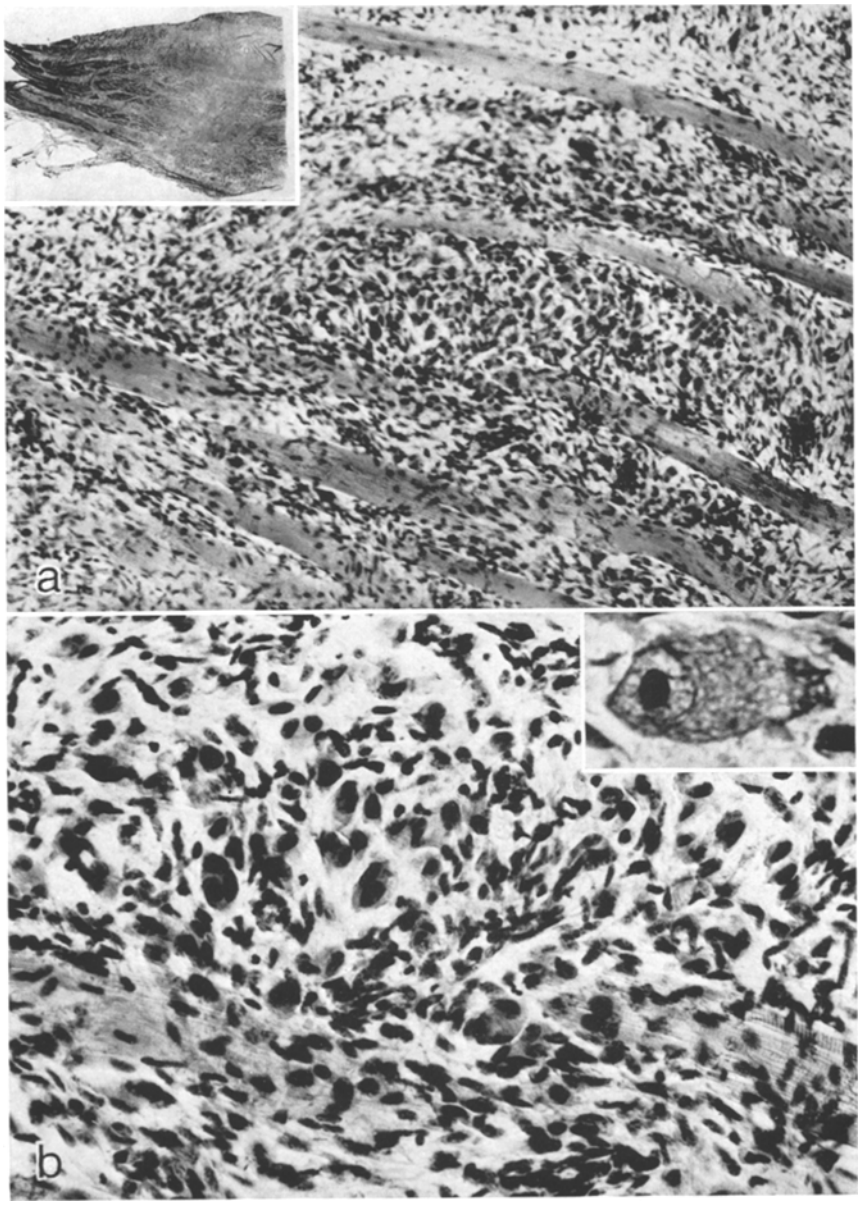

Fig. 2a and b. Histological picture of myositis proliferans. (a) The proliferating mesenchymal cells of the lesion separate the muscle cells (HE, 180:1, inset 5:1). (b) Fibroblast- and histiocyte-like cells intermingled with giant cells (HE, 180:1). Some giant cells exhibit ganglion-like nuclear structures (inset, HE, 720:1)

Histologically the fasciitis nodularis consists of a tissue composed of proliferations of predominating spindle-shaped fibroblasts, a rich network of reticulum fibres and discrete accumulations of lymphocytes, plasma cells and leukocytes

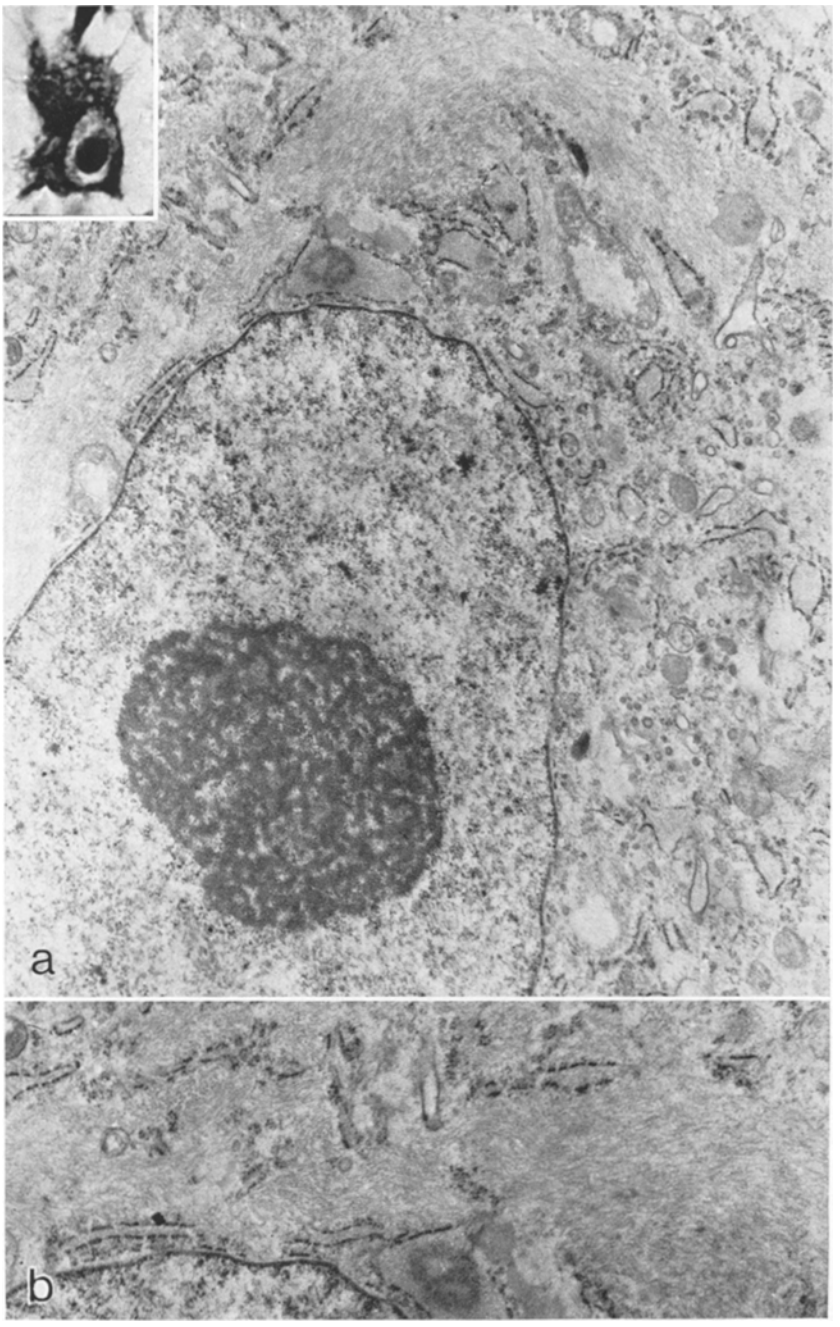

Fig. 3a and b. Electron microscopic demonstration of a ganglion-like giant cell. Besides a varying organelle content juxtanuclear bundles of microfilaments are prominent. Note the enlarged nucleolus (a, 13500:1). (b) Microfilament bundles in greater detail. The filaments are without periodicity and appear wavy arranged (20500:1)

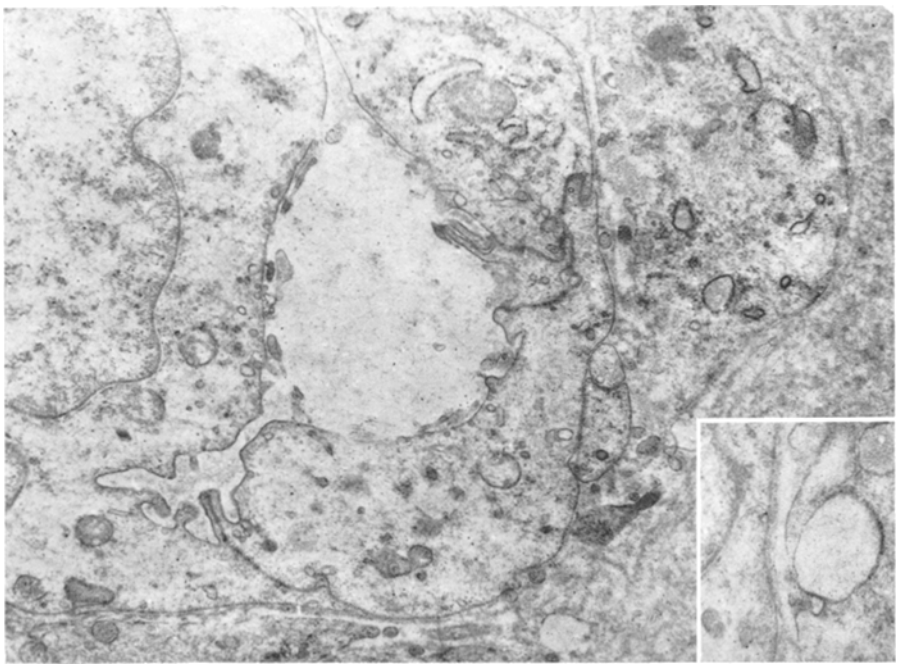

Fig. 4. Example of an activated capillary vessel. The endothelial cells are swollen and enveloped by a basement membrane. On the right side a clearly activated pericytic cell is visible 13500:1). The inset demonstrates a regular endothelial basement membrane (20500:1)

with predilection of the latter cells in the periphery of the lesions. Focally edematous and myxoid regions are visible. Collagen fibers are sparse. Additionally the occurrence of giant cells is to be mentioned; they contain some nuclei placed in the center, and an indistinctly bounded cytoplasm with polyhedral or elongated shape.

II. Electron Microscopy

a) Fascial Analogue of Myositis Proliferans. The lesion consists of mesenchymal cells of somewhat varying ultrastructure including giant cells, and numerous capillaries as demonstrated by light microscopy. The roundish mesenchymal cells show a round to ovoid nucleus, seldom with shallow indentations, which has a rather evenly distributed chromatin. In the cytoplasm a moderate, but in the single cell varying content of rough endoplasmic reticulum partially forming cisternae and sacs, and mitochondria can be observed. The Golgi apparatus is well-developed. Free ribosomes are detected as polysomes, in the cytoplasm some cells contain collagen fibers surrounded by membranes. The giant cells whose nuclei possess large nucleoli have a similar organelle equipment. However, filaments encountered not frequently in the majority of mesenchymal cells are often seen in the giant cells. Their diameters are 50 to 70 Å and they are distributed randomly in the cytoplasm or more often arranged in bundles (Fig. 3). No periodicity, attachment sites or Z-lines were detected. Occasionally, lipid droplets without limiting mem-

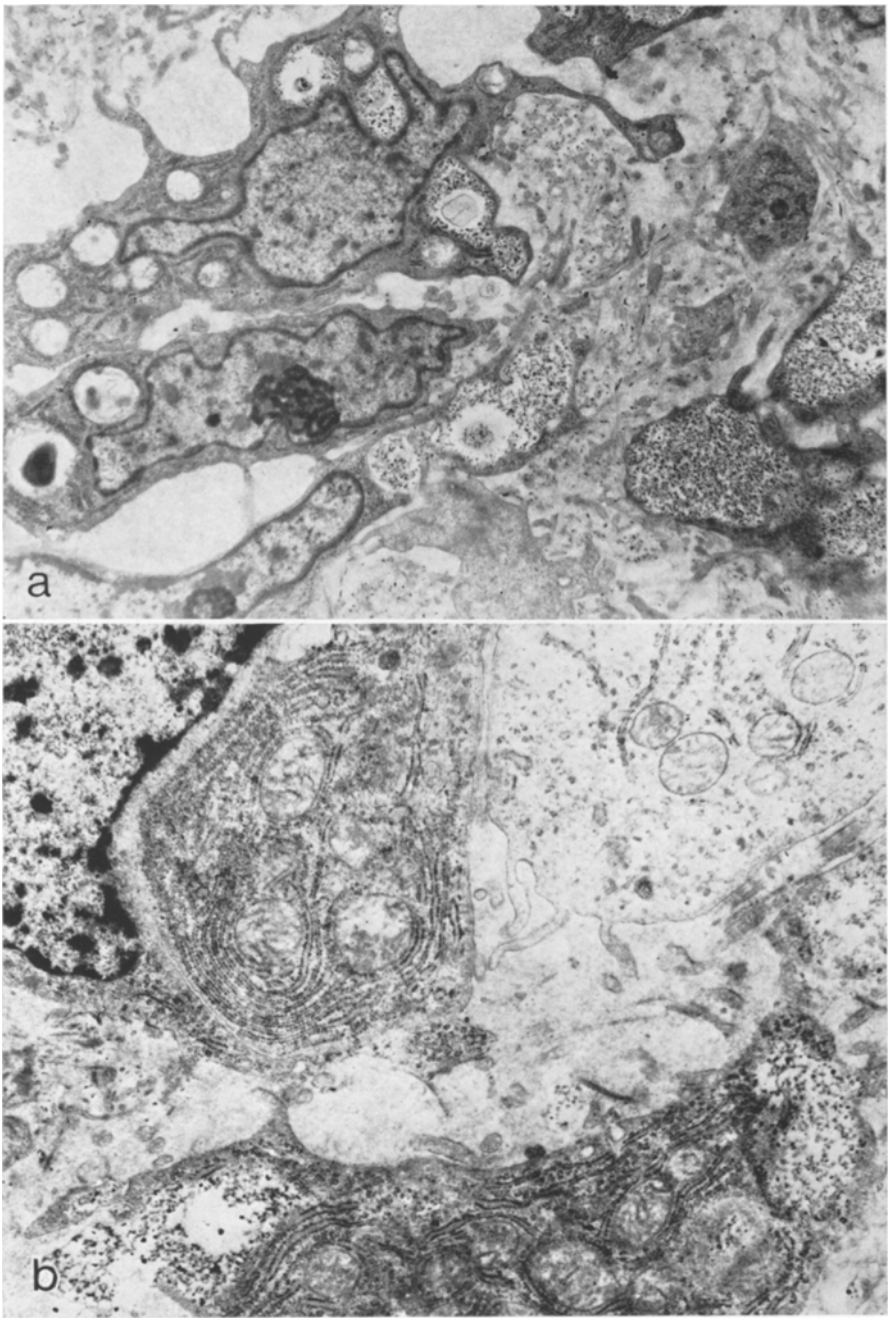

Fig. 5a and b. Myositis ossificans with varying differentiated cellular structures. The cells show a different organelle content. (a) Chondrocyte-like proliferating cells reveal irregular nuclear contours, a dense cytoplasm and a varying amount of glycogen granules (10800:1). (b) Fibrolast- and histiocyte-like cells as well as a transitional chondroblast-like form (14400:1)

brane and locally accentuated vesicles resp. autophagosomes could be observed. The mesenchymal cells did not exhibit intercellular junctions, as desmosomes, or basement membrane-like material.

Activated, hypertrophied and swollen endothelial cells with microvillous projections on their luminal side were a prominent feature of capillaries (Fig. 4). Their nuclei were indented and lobulated, in the cytoplasm pinocytotic vesicles, several mitochondria and a small amount of rough endoplasmic reticulum were present. Between the endothelial cells tight junctions are discernible, and they are surrounded by a basement membrane. Beneath the endothelial cells pericytes are to be found. They appear partially unactivated, but in many places they are in an active stage with hypertrophied cytoplasm. The pericytes are enveloped by a basement membrane. In their vicinity the aforementioned mesenchymal cells can be detected which reveal an almost identical nucleus and organelle content, but the basement membrane is lacking.

The intercellular substance consists of collagen fibers or of a granular or amorphous substance, resp.

b) Myositis Ossificans. The cells situated in a granular or fine fibrillar ground substance containing also collagen fibers show preponderantly a stellate shape with numerous cytoplasmic processes. The amount of cytoplasm and the organelle content vary remarkably (Fig. 5), but there exist numerous transitional forms, so that the morphological pictures of the same basic cell seem to vary considerably in their appearances. Relatively undifferentiated cells can be found with few ergastoplasmic tubes and some mitochondria. Cells with abundant rough endoplasmic reticulum arranged in part in stacked parallel arrays and partially surrounding mitochondria are also noticed. A picture noteworthy to comment on is the focal accumulation of glycogen granules in some cells. Furthermore, a well-developed Golgi apparatus, varying contents of free ribosomes, lysosomal structures and vesicles measuring nearly 800 Å in diameter and occasionally some subplasmalemmal scattered microfilaments must be mentioned. The nuclei ovoid to stellate show an evenly distributed chromatin or coarse chromatin deposits approximately dependent on the cytoplasmic picture. We had the impression that the more histiocyte-like cells are endowed with the former, the more fibroblast-like cells with the latter nuclear variant. Desmosomes or basement membrane-like material could not be detected.

Moreover, some capillary vessels were examined. Their endothelial cells are activated with the typical cytoplasmic organelles. Pericytes are also to be seen, but these cells appeared to be resting.

Discussion

The histological description of the subcutaneous tumors presented here as case I and II confirms the great morphological similarity to myositis proliferans. The only difference to the true myositis proliferans localized within the musculature is the smaller quantity of ganglion-like giant cells. Besides clinical differences the presence of these cells, however, distinguishes them clearly from the fasciitis nodularis which otherwise has a similar basic structure (Konwaler *et al.*, 1955; Hutter *et al.*, 1962; Miller, 1964; Stiller and Katenkamp, 1973). Moreover our electron microscopical investigation revealed an identical structure of giant cells

compared to Rose's report (1974) related to the myositis proliferans. Thus the designation "subcutaneous fascial analogue of myositis proliferans" seems to be correct.

The cells of the lesion are mesenchymal cells with round nuclei and a relatively uncharacteristic organelle content. Corresponding to their organelle equipment and in accord with the histochemical findings their function must be anabolic and katabolic together. The aspect of the ganglion-like giant cells at ultrastructural level appears more histiocytic than fibroblastic. Accordingly the giant cells are surely not myogenic cells as already supposed by light microscopical findings (Enzinger and Dulcey, 1967). Only occasionally multinucleated giant cells are discerned which partially may have an endothelial origin.

On the extraction of the cells of the lesion generally no precise assertion is possible. By reason of numerous proliferating capillaries with activated endothelial cells and pericytes, and the resemblance of the latters with perivascular "tumor" cells, a deriving from cells of vessel walls could be conceivable in analogy to the dermatofibroma or histiocytoma cutis resp. (Katenkamp and Stiller, 1975). The absence of basement membrane-like material would not contradict this theory, because pericytes moving from the vessels are known to lose their basement membrane (Movat and Fernando, 1964).

In comparison to myositis ossificans a random focal distribution of osteoid tissue in myositis proliferans or its fascial analogue when present at all, and the lack of the typical ganglion-like giant cells in the former condition speak against a relationship and consequently against the assumption that myositis proliferans is a "green stage" of myositis ossificans. Also, the clinical course and the electron microscopic findings suggest this.

However, the ultrastructural results can be used only precautiously for differentiation between myositis proliferans and ossificans. Indeed, the cells in myositis ossificans are more organelle-rich (especially more rough endoplasmic reticulum and ribosomes) and the nucleus possesses another shape and chromatin distribution, but it can not from morphology alone be excluded, that these cells could have developed from cells of myositis proliferans if one remembers the multipotency of mesenchymal cells. Also, the extensive participation of pericytes on proliferation in myositis proliferans (or their fascial analogue) in comparison to the non-activated pericytes in myosits ossificans could easily be explained merely on the basis of the duration of the process if taking into the account autoradiographic examinations on the cell derivation in granulation tissues at different times (Oehmichen and Grüninger, 1973; Sumrall and Johnson, 1973; Büchner *et al.*, 1974).

The etiology of the myositis proliferans and of their fascial analogue remains open. The decisive role of any local injury is accepted (Enzinger and Dulcey, 1967; Heyden *et al.*, 1970). The profusion of giant cells in intramuscular lesions and their smaller number in extramuscular locations is perhaps compatible with the idea, that the injury primarily affects the muscle cells. The histiocyte-like organelle content of numerous tumor cells also speaks in favour of that.

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