Virchows Arch. A Path. Anat. and Histol. 367, 345—352 (1975)

Proliferative Myositis

A Case Report with Fine Structural Analysis

J. M. Gokel, P. Meister and G. Hübner

Department of Pathology, University of Munich (Head: Prof. Dr. M. Eder)

Received April 22, 1975

Summary. A report is given on a case of proliferative myositis in a 75 year old woman. By fine structural analysis it can be shown, that the charcateristic giant cells in proliferative myositis are mesenchymal cells with an intensive protein metabolism. They can be compared to fibroblasts; for a myogenic origin of these cells we found no evidence. Furthermore, various stages in the development and function of the proliferating cells were observed, by which the course of the disease can be explained.

Zusammenfassung. Es wird über einen Fall einer proliferativen Myositis bei einer 75 Jahre alten Frau berichtet. Die zur Klassifizierung der bei der proliferativen Myositis vorkommenden charakteristischen Riesenzellen durchgeführte elektronenmikroskopische Untersuchung ergab, daß es sich bei diesen Zellen um stoffwechselaktive mesenchymale Zellen handelt, die Fibroblasten ähnlichen sind. Anhaltspunkte für eine myogene Herkunft der Zellen ergaben sich nicht. Darüber hinaus konnten unterschiedliche Entwicklungs- und Funktionsstadien dieser Zellen beobachtet werden, die den Ablauf der Erkrankung verständlich machen.

In 1960, Kern described 7 cases of a rapidly growing process affecting the sceletal muscle which he named proliferative myositis (p.m.). Till now the largest series of cases was published by Enzinger and Dulcey (1967), who separated p.m. from nodular fasciitis and myositis ossificans. On microscopic examination a characteristic feature in p.m. is the appearance of large basophilic giant cells, the origin of which is not yet fully established. In the presented case a fine-structural analysis was performed to establish origin and significance of these giant cells.

Case Report

The patient, a 75 year old white woman, had noticed within a few weeks a rapidly growing mass on the inside of the left thigh. No history of trauma was given. The mass was painful on slight pressure and fairly movable. Surgery was performed and the mass found to be located in the proximal third of the musculus gracilis. The resected part of the muscle measured $8 \times 3 \times 2$ cm and showed a gray-white, ill-defined, not encapsulated lesion with irregular outline. Gross examination showed broad strands of fibrous tissue separating bundles of muscle fibres. The part in the center of the lesion was scarlike indurated. On microscopic examination there is found a break-up of muscle bundles by a proliferation of elongated spindle-shaped cells thus forming a characteristic "checkerboard-like" pattern. The lesion shows a variant pattern in the central, intermediate and peripheral areas. In the peripheral areas the muscle bundles are separated by a loose tissue of elongated spindle-shaped, oval and stellate cells (Fig. 1a). The lesion is ill defined and not encapsulated. The strands of proliferating cells become smaller toward the periphery thus leading without sharp borders to unaffected muscle tissue. The muscle fibres are virtually uninvolved in this area. Single foci of minimal inflammation with mononuclear cells are found.

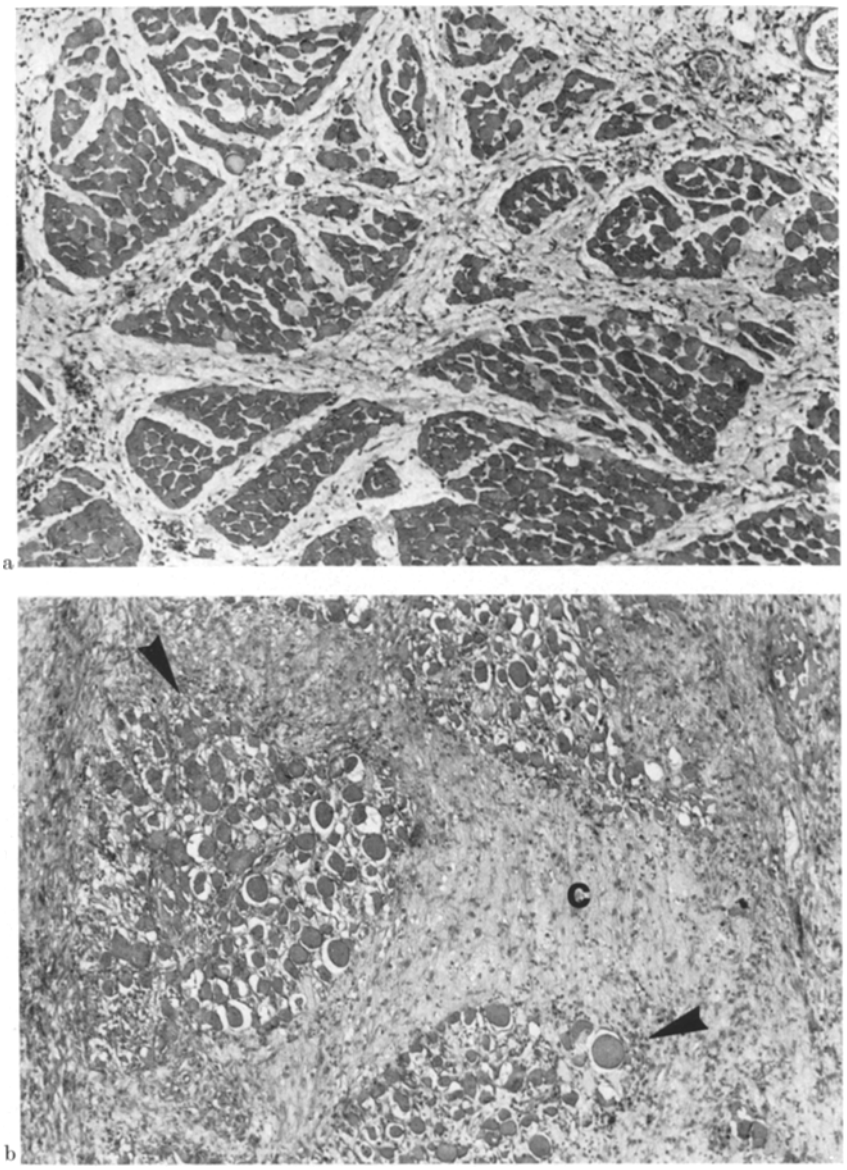

Fig. 1a and b. Proliferative myositis (p.m.). (a) Low-power picture of peripheral area illustrating "checkerboard-like" pattern produced by strands of proliferating spindle-shaped cells with remnants of well preserved striated muscle tissue. HE ×48. (b) Low-power picture of intermediate and central area in p.m. Severely damaged, degenerating muscle tissue of intermediate area (arrows); broad streaks of collagenous fibres replacing muscle tissue in the central area (*c*)

In contrast the muscle bundles and fibres of the intermediate area are severely damaged. The bundles are broken up by tissue of densely packed big spindle-shaped cells and groups of large giant cells; in both mitotic figures are common. The muscle fibres differ greatly in diameter, are atrophic or even necrotic (Fig. 1b).

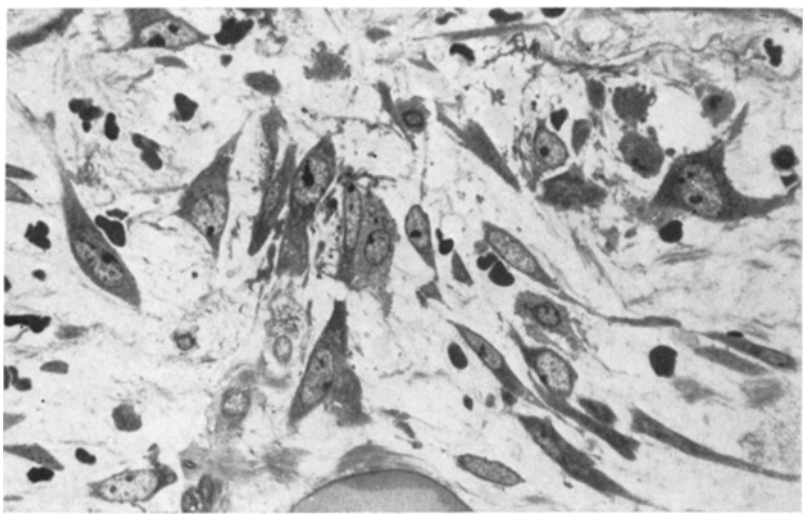

Fig. 2. Proliferative myositis. Intermediate area illustrating a group of typical, "ganglionlike" giant cells

There is neither sarcolemmal proliferation nor any other evidence of attempted muscle regeneration. The giant cells show an abundant, deeply staining basophilic cytoplasm with sometimes small cytoplasmic vacuoles. They tend to occur in groups loosely arranged in nests and have one or two eccentrically placed vesicular nuclei with prominent nucleoli (Fig. 2). They bear a resemblance in size and shape to ganglion cells and are embedded in a mucoid matrix with few collagenous fibres. In this matrix an increased amount of acid mucopolysaccharides can be demonstrated by special staining procedures. The central area of the lesion shows a network of collagenous fibres, which has replaced the muscle tissue. The loosely dispersed giant cells often show degeneration.

Electron Microscopic Investigation

To correlate lightmicroscopic and fine structural findings tissue was examined from peripheral, intermediate and central areas of the lesion. Since only formalin-fixed and paraffin-embedded material was available the tissue had to be reembedded and processed as described earlier (Hübner, 1970).

The elongated spindle-shaped cells in the *peripheral areas* have big nuclei and nucleoli and a small cytoplasm (Fig. 3a). The chromatin in the nuclei is regularly distributed. A few elongated mitochondria, a well developed ergastoplasm and many polyribosomes are found in the cytoplasm. The cisternae of the rough endoplasmic reticulum are small and filled with a homogenous material. Very rarely small fat droplets are found in the cytoplasm, while small clumps of fibrillary material without regular striation are to be seen in the extracellular space.

The giant cells which are found in the *intermediate area* between degenerating muscle bundles show big nuclei with regularly distributed chromatin and large nucleoli, which are often arranged transversely to the longer axis of the nucleus

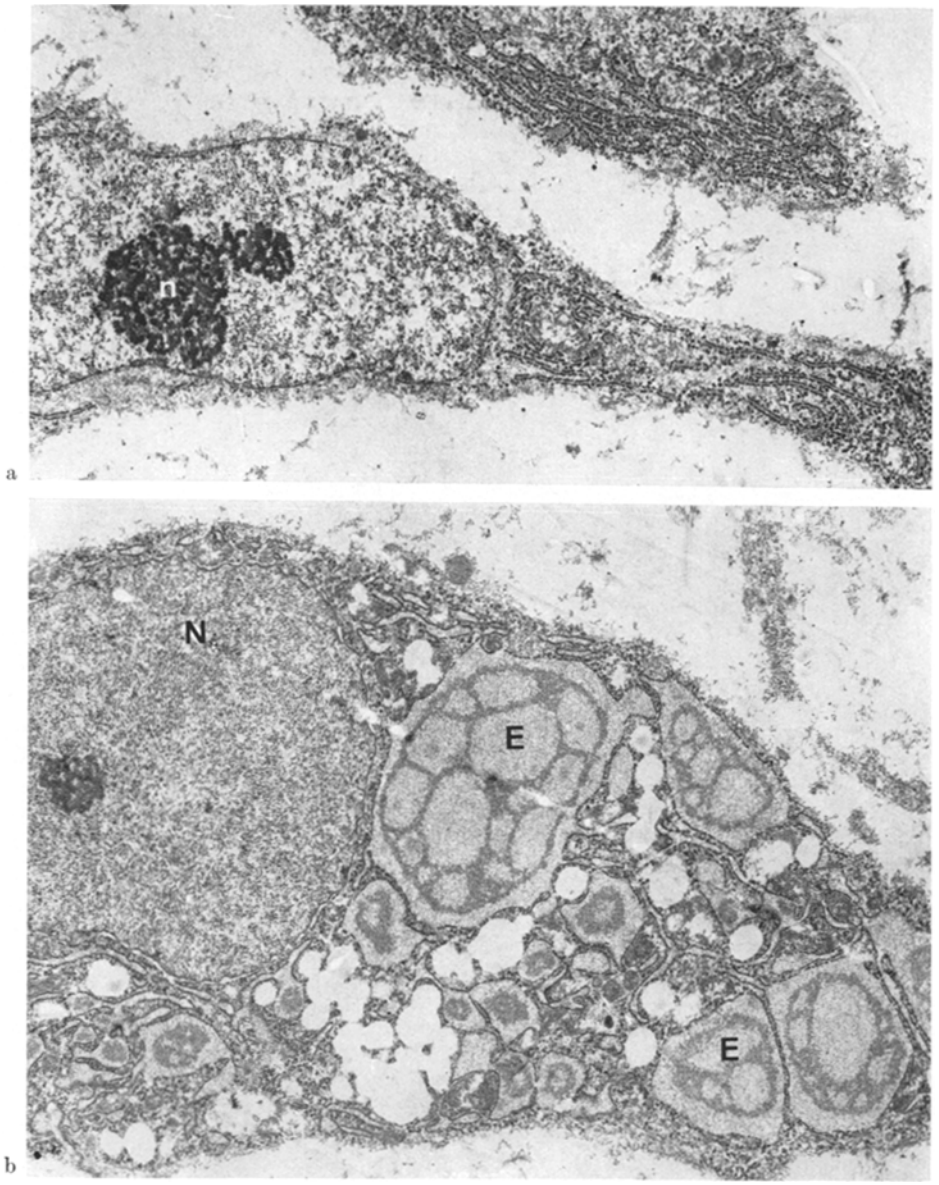

Fig. 3a and b. Fine structure of proliferating cells in proliferative myositis. (a) Spindle-shaped cell from the peripheral area with big nucleus, double nucleoli (*n*) and many profiles of ergastoplasm in the cytoplasm. Arch. Nr. 6956, ×8000. (b) Giant cell from the intermediate area at the same magnification as (a). Dilated cisternae of the ergastoplasm (*E*) containing a multilayered material. *N* nucleus. Arch. Nr. 6974, ×8000

(Fig. 3b). Mitotic figures are common. The ergastoplasm of these cells is well developed, the cisternae are dilated and often filled with a moderate electron dense multilayered material. Between the lamellae of the ergastoplasm many

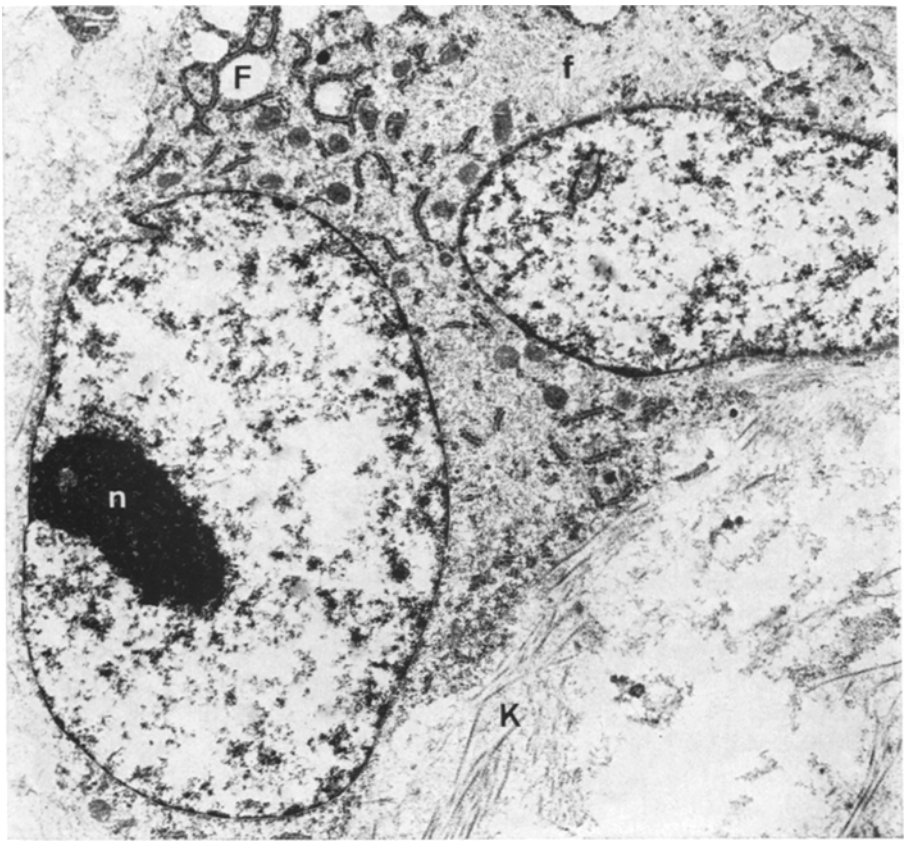

Fig. 4. Binucleated giant cell of the central area in proliferative myositis. In the cytoplasm narrow cisternae of the ergastoplasm, small mitochondria, many fine filaments (*f*) and some fat droplets (*F*). In the lower right collagenous fibres (*K*) in the interstitium. *n* nucleus. Arch. Nr. 6970, × 9000

free ribosomes are dispersed. Some cells contain no ergastoplasm but numerous free ribosomes. In the interstitium many loosely distributed fine filaments and very few typical collagenous fibrils are observed.

In the *central area* of the lesion many giant cells have pycnotic nuclei with clumped chromatin (Fig. 4). While some cells show a still well developed ergastoplasm others have distended cisternae of the rough endoplasmic reticulum with a loss of ribosomes. In the cytoplasm aggregated fat droplets and sometimes loose bundles of fine filaments are found. Sometimes these fibres are localized in deep cytoplasmic invaginations. The cells are not in contact with each other. They show no desmosomes or other spezialized forms of cell contact; a basement membran could not be seen. Fine structural features resembling those of rhabdomyoblasts or even nerve cells could not be demonstrated in any cell of the different areas of p.m.

Discussion

The presented case demonstrates the typical clinical symptoms and morphological pattern of proliferative myositis (p.m.) and can be compared with the observations of Kern (1960), Enzinger and Dulcey (1967) and Mackenzie (1970). The p.m. is a benign lesion of the sceletal muscle and characterized by an ill-defined swelling of the muscle with irregular outline. The main histologic features are a break-up of muscle bundles by a fibroblastic proliferation, degeneration of muscle tissue and the appearance of basophilic giant cells. The rapidly growing muscular lesion, the ill-defined, irregular outline and the many mitoses may cause difficulties in diagnosis and are responsible for the confusion of p.m. with malignant tumors. In fact, 14 cases out of 33, described by Enzinger and Dulcey (1967), were initially mistaken for mesenchymal tumors. In 8 cases the lesion was thought to be a rhabdomyosarcoma. It is obvious that in contrast to p.m. rhabdomyosarcomas or fibrosarcomas display more cellular polymorphism and atypical mitotic figures. Sarcomas also do not show the quite regular break-up of muscle bundles with a "checkerboard-like" pattern characteristic for p.m. When the p.m. is confused with ganglioneuroma the diagnosis is made on the appearance of the giant "ganglion-like" cells alone (Stout, 1947). Histochemical examination (Enzinger and Dulcey, 1967) as well as our electron microscopic investigation give no support to a neurogenic origin of these cells.

P.m. rarely causes tenderness or pain and occurs mostly in older patients (average age 50 years). The condition is unknown in children, and male predominate with a ratio of 4:3 (Mackenzie, 1970). The older age in p.m. is important in differential diagnosis versus subcutaneous nodular fasciitis. Nodular fasciitis occurs over a wider age range and reveals histologically more granulomatous appearance and a greater vascular and inflammation component (Konwaler, Keasbey and Kaplan, 1955; Hutter, Stewart and Foot, 1962). As Kern (1960) thought the large basophilic "ganglion-like" cells of p.m. to be myoblastic cells rather than fibroblasts, Enzinger and Dulcey (1967) looked upon them as modified fibroblasts. Our electron microscopic study did not reveal any features which would support a myogenic origin of these cells. There is also no convincing evidence that these cells differentiate towards smooth muscle cells. However, they obviously represent modified active fibroblasts of unusual size and shape.

Already by light microscopy differences between central, intermediate and peripheral areas of p.m. can be distinguished, which may express variant stages of development of p.m. This concept is supported by the electron microscopic findings of functional differences in the cells of the different areas. Based on these findings the following concept of pathogenesis in p.m. results: the most recent changes in p.m. are to be seen in the peripheral areas of the lesion; here a proliferation of immature fibroblasts takes place. The fibroblasts have many free ribosomes as evidence of a high level protein synthesis. The muscle bundles are spread apart by strands of proliferating cells but the muscle cells are virtually uninvolved. In the intermediate area numerous mitoses and large, occasionally multinuclear giant cells appear. They show dilated ergastoplasmic cisternae and apparently are responsible for the formation of the abundant ground

substance. Here the muscle bundles are severely impaired and show cellular degeneration, atrophy and even necroses. The centrally located broad septa of fibrous connective tissue represent the oldest area of p.m.; muscle tissue, here, has degenerated and vanished; only few large cells can be seen, which form collagenous fibres and may show marked degenerative changes.

The cause of p.m. still remains unknown. Enzinger and Dulcey (1967) suggested that some type of injury to fascia, muscle or the supplying vasculature precedes the appearance of the lesions. But a history of preceding injury in chronical and topographical relation with p.m. is just mentioned in about one third of the cases (Enzinger and Dulcey, 1967).

Still unexplained up to now is the origin of the initial proliferating cells. In our case capillaries and small veins with swollen endothelial cells became evident in the intermediate area. By electron microscopic examination they featured beside Weibel-Palade granula numerous free ribosomes and an ergastoplasm similar to that of the proliferating fibroblasts. However, neither a transition of endothelial cells into perivascular proliferating interstitial cells nor a proliferation of interstitial cells with Weibel-Palade granula, which are characteristic for endothelial cells, could be demonstrated. Therefore it remains undecided, if the initial cell proliferation in p.m. starts with a proliferation of endothelial cells or if endothelial cells are only secondly involved reacting to an unknown injury.

In all cases, which were published, the lesion was treated by surgical excision; so the biological behaviour and prognosis of untreated p.m. is unknown. A possible relationship to myositis ossificans was discussed, as some cases of p.m. showed local calcification or bone formation. Ackerman (1958) suggested p.m. to be an immature, "green-stick" variety of myositis ossificans. However in p.m. calcification rarely occurs and is never very impressive; the zonal phenomenon with varying maturity of ossification typical for myositis ossificans could never be observed.

It appears possible that p.m. is a self-limited process and may heal spontaneously with scarring. Recurrences could not be observed during a period of 1 to 16 years in any of the published cases. Also two patients observed in our institute are 5 and 7 years after surgical treatment without recurrence (Meister, 1975). In the presented case the postoperative course was uneventful; one year following surgical excision there is no evidence of local recurrence.

We are greatly endebted to Mrs. U. Faszekas and Miss B. Wojtek for their skilful technical assistance.

References

Ackerman, L. V.: Extraosseous localized nonneoplastic bone and cartilage formation (so called myositis ossificans). Clinical and pathological confusion with malignant neoplasms. J. Bone Jt. Surg. **40**, 279–298 (1958)

Enzinger, F. M., Dulcey, F.: Proliferative myositis. Report of thirty-three cases. Cancer (Philad.) **20**, 2213–2223 (1967)

Hübner, G.: Zur Feinstruktur von formalinfixiertem Biopsie- und Autopsiematerial nach Paraffineinbettung. Virchows Arch. Abt. A **351**, 155–167 (1970)

Hutter, R., Stewart, F., Foote, F.: Fasciitis. Cancer (Philad.) **15**, 992–1003 (1962)
Kern, W. H.: Proliferative myositis: a pseudosarcomatous reaction to injury. Arch. Path. **69**, 209–216 (1960)
Konwaler, B., Keasbey, L., Kaplan, L.: Subcutaneous pseudosarcomatous fibromatosis (fasciitis). Amer. J. clin. Path. **25**, 241–252 (1955)
Mackenzie, D. H.: The differential diagnosis of fibroblastic disorders. Oxford and Edinburgh: Blackwell Scientific Publications 1970
Meister, P.: Personal communication, 1975
Stout, A.: Ganglioneuromata of the sympathetic nervous system. Surg. Gynec. Obstet. **84**, 101–110 (1947)

Dr. J. M. Gokel
Prof. Dr. P. Meister
Prof. Dr. G. Hübner
Pathologisches Institut der Universität
D-8000 München 2
Thalkirchner Str. 36
Federal Republic of Germany