

Original Articles

The Ultrastructure of Myxofibrosarcoma

A Study of 11 Cases

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Summary. An ultrastructural study of 11 myxofibrosarcomas is presented. The tumours were graded light-microscopically on a four-point scale according to cellularity, cell atypia and mitotic activity, as described in a previous paper: 3 were grade I, 2 grade II, 4 grade III and 2 grade IV.

Fibroblast-like and myofibroblast-like cells predominated in the grade I and II tumours, while histiocyte-like cells were relatively few; in grade III and IV tumours histiocyte-like cells predominated. The fibroblast-like cells were spindle-shaped with fairly smoothly outlined nuclei, and contained abundant parallel membranes and wide cisternae of endoplasmic reticulum. The histocyte-like cells were irregular in shape and showed indented nuclei with large nucleoli and coarse, peripherally arranged clumps of heterochromatin. The cytoplasm of these cells showed prominent pseudopodiae, microvillous projections, conspicuous systems of vesicles and vacuoles, inclusions of lipid and pigment, numerous lysosomal structures and large digestive vacuoles indicating auto- and exophagocytosis. The myofibroblast-like cells showed abundance of parallelly arranged cytoplasmic microfilaments with dense body-like structures and condensation at the plasmic membrane. Occasional cells appeared to be intermediate forms and primitive looking, undifferentiated cells were also encountered. A few multinucleated tumours cells were seen in the grade IV tumours. Thus, the present study shows the composite fibroblastic, myofibroblastic and histiocytic character of the tumour cells of myxofibrosarcoma; the grade III and IV tumours, with a tendency to contain solid areas, seem to be closely related to the pleomorphic type of malignant fibrous histiocytoma.

Key words: Myxofibrosarcoma – Fibroblast – Histiocyte – Myofibroblast – Sarcoma – Soft tissue tumour – Ultrastructure.

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Introduction

The name myxofibrosarcoma has frequently been used by pathologists as a descriptive term without definition. Myxofibrosarcoma has recently been described as an entity by us. It is characterized by the nodular growth of spindleshaped and irregular tumour cells exhibiting a varying degree of pleomorphism within a prominent, highly vascular myxoid matrix, predominantly seen superficially in the extremities of elderly people. The myxofibrosarcomas were divided into four histological grades. The higher the grade the worse the prognosis seemed. Myxofibrosarcomas are distinguished from other myxoid soft tissue tumours and tumour-like lesions, such as myxoid variants of nodular fasciitis, myxoma, myxoid liposarcoma, myxoid extraskeletal chondrosarcoma and embryonal rhabdomyosarcoma (Angervall et al., 1977). On the basis of the histological study, myxofibrosarcomas are believed to belong to the general category of fibroblastic and histiocytic malignant soft tissue tumours. High grade myxofibrosarcomas, with a tendency to contain solid areas seem to correspond to the "myxoid variant of malignant fibrous histiocytoma" recently described by Weiss and Enzinger (1977). For the purposes of their study, malignant fibrous histiocytomas in which 25% or more of the area was myxoid, were included in this variant.

The present study of 11 myxofibrosarcomas of different grades describes their ultrastructural characteristics. This provides a better basis for their definition and further helps to distinguish them from other myxoid soft tissue tumours.

Material

The material for the study comprised clinical histories, operation specimens, formalin-fixed tumour tissue, tissue blocks, routine histological sections, 1 micron thick sections of Epon-embedded tumour tissue and ultrathin sections for electron microscopy. All the 11 myxofibrosarcomas were consecutive cases examined at the Department of Pathology, Sahlgren's Hospital, Gothenburg, Sweden, during the years 1969 to 1977. Seven of the tumours were included in a previous study (Angervall et al., 1977).

All tumours were surgical specimens and 8 of them were primarily fixed and processed for an ultrastructural study; in 3 cases only formalin-fixed tumour tissue was available.

Methods

Five μ thick sections of formalin-fixed and paraffin-embedded tumour tissue were stained according to the haematoxylin-van Gieson method and with haematoxylin and eosin. Gordon's and Sweet's silver impregnation was used for demonstration of reticulin fibres, and the PAS-stain according to McManus, with and without prior digestion with diastase, was used to study the presence of glycogen. Alcian blue (Chroma-Gesellschaft) and toluidine blue stains were used at two different pHs, pH 2.5 and 0.5 and 4.0 and 0.5, respectively, for the examination of glucoseaminoglycans (nomenclature according to Jeanloz 1960) as described previously (Angervall et al., 1973; Kindblom and Angervall, 1975). These stains were performed with and without prior treatment of the sections with testicular hyaluronidase (hyalurinodase from bovine testes, type IV, Sigma) (Leppi and Stoward, 1965).

For electron microscopy, small pieces from 8 of the tumours were immediately put into ice-cold OsO_4 according to Maunsbach (1966), fixed for 2 h, dehydrated in ethanol, embedded in Epon 812 and cut in an LKB Ultrotome III. In 6 cases, small pieces were also immersed in 2.5% glutaraldehyde in 0.1 M cacodylate buffer at pH 7.2 for 4 h and 4°C, washed in cold buffer, postfixed with 1% OsO_4 for 1 h and thereafter prepared in the same way as the OsO_4 -fixed material. In one case, only formalin-fixed tissue was available; small pieces were washed in 0.1 M sodium cacodylate buffer for 24 h, fixed for 3 h in icecold 1% OsO_4 in cacodylate buffer and prepared as previously described. Only paraffin-embedded material was available in two cases. Small pieces of tumour from selected areas of 20– $50\,\mu$ thick sections from the paraffin blocks were carefully deparaffinized in xylene, rehydrated in decreasing concentrations of ethanol and finally washed in cacodylate buffer, fixed in 1% OsO_4 and prepared as described above. One μ thick sections were stained with toluidine blue, and silver-to-grey sections were stained with uranyl acetate and lead citrate and examined in a Philips 200 electron microscope.

As in the previous study, the tumours in the present series were divided into 4 grades (see Table 1), according to the degree of tumour cellularity, cell atypia and prevalence of mitotic figures.

Results

Clinical Data

Information on the age and sex of the patients and size and location of the tumours is summarized in Table 1.

Case no.	Sex	Age (years	Location s)	Size (cm)	Histological grade
1	М	71	Subcutaneously, left calf	2.5	III
2	M	87	Subcutaneously, left calf	$9 \times 5 \times 5$	IV
3	M	25	Subcutaneously, left calf	3	П
4	F	66	Subcutaneously, right buttock	$10 \times 8 \times 7$	III
5	F	51	Subcutaneously, right lower arm	$9 \times 5 \times 3$	II
6	F	72	Subcutaneously, left thigh	$14 \times 8 \times 8$	IV
7	M	75	Intermuscular, right upper arm	$10 \times 6 \times 5$	III
8	F	35	Subcutaneously, right thigh	$13 \times 6 \times 2$	I
9	M	76	Intermuscular and subcutaneously, right thigh	$6 \times 5 \times 5$	III
10	F	45	Subcutaneously, temporal region, left	2.5	I
11	M	25	Intermuscular and subcutaneously, left calf	3	I

Table 1. Summary of clinical data for 11 patients with myxofibrosarcoma

Pathology

Light Microscopic Appearance

The light micorscopic characteristics of myxofibrosarcoma have previously been described in detail (Angervall et al., 1977).

Three tumours (cases 8, 10 and 11) were classified as grade I and 2 tumours (cases 3 and 5) as grade II. The grade I tumours showd a paucity of cells and the grade II tumours were poorly or moderately cellular and nodular in appear-

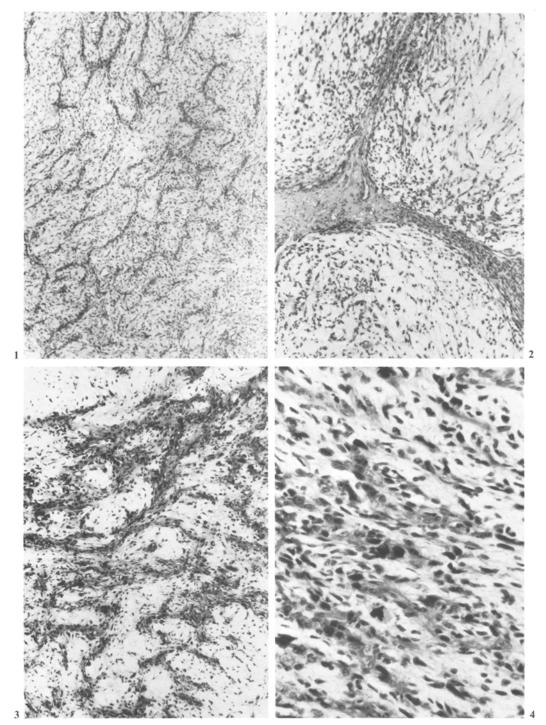


Fig. 1. Moderately cellular tumour area with a prominent plexiform capillary network and an abundant mucoid matrix. H & E, $\times 60$

Fig. 2. Fibrous septa separate the tumour into lobules. H & E, $\times 60$

Fig. 3. Condensation of moderately pleomorphic tumour cells around delicate capillary-like vessels. H & E, $\times 120$

Fig. 4. Pleomorphic spindle-shaped and plump tumour cells. Some mitotic figures are seen. H & E, $\times\,300$

ance (Figs. 1 and 2). Most tumour cells were stellate or fusiform with bipolar cytoplasmic extensions. The cytoplasm was eosinophilic and occasionally contained small vacuoles. The nuclei were oval, with a granular chromatin structure, and contained one or rarely two nucleoli. Mitotic figures were few in number. The cells were frequently arranged in syncytium-like structures, enclosed by a conspicuous mucoid material. Delicate bundles of reticulin fibres and collagen were seen, often closely associated with tumour cells.

The 4 grade III tumours (cases 1, 4, 7 and 9) and 2 grade IV tumours (cases 2 and 6) were nodular, like the grade II tumours, but were generally more cellular and included some solid parts although the myxoid parts predominated (Figs. 3 and 4). The tumour cells were generally larger and more pleomorphic. These were plump, rounded or slender. The nuclei were large and irregularly shaped, with a coarse chromatin pattern, and exhibited one or more prominent nucleoli. Occasional cells contained small amounts of a PAS-positive granular substance, which was digested by diastase, i.e. compatible with glycogen. A few grotesque uni- or multinucleated tumour giant cells were found in the two grade IV tumours. Mitotic figures, some of which were polyploid, were frequently seen (Fig. 4).

A prominent plexiform pattern of capillary-like vessels was found in all the 11 tumours. It was most prominent in the poorly cellular myxoid areas (Fig. 1).

The abundant mucoid matrix stained with Alcian blue up to 0.1 M MgCl₂ and with Alcian blue at pH 2.5 and with toluidine blue at pH 4.0 but not at pH 0.5. The mucosubstance was digested by testicular hyaluronidase. The staining characteristics indicated the presence of hyaluronic acid and absence of sulphated glucoseaminoglycans, such as chondroitin sulphates (cf. Angervall et al., 1973; Kindblom and Angervall, 1975).

Electron Microscopic Appearance

Grade I and II

Fibroblast-like, spindle-shaped or stellate tumour cells with long and slender cytoplasmic extensions predominated. The nucleus was oval or elongated with occasional indentations and a fairly homogeneously dispersed chromatin and contained one or rarely two, usually small, nucleoli (Fig. 5). The cytoplasm contained abundant rough endoplasmic reticulum (RER) which appeared as both delicate parallel membranes and wide cisternae; some of the cisternae close to the cytoplasmic membrane were filled with a grey amorphous material (Figs. 6A and B). Distended cisternae, only partly studded by ribosomes, and prominent smooth endoplasmic reticulum (SER) were encountered in most cells of this type. The mitochondriae were oval or occasionally elongated and mostly showed incompletely traversing cristae. The Golgi zones were small or of moderate size (Fig. 6A). The cells were in areas parallelly arranged and the cytoplasmic extensions of neighbouring cells often interdigitated. No desmosome structures were found. The intercellular spaces were wide and filled by a moder-

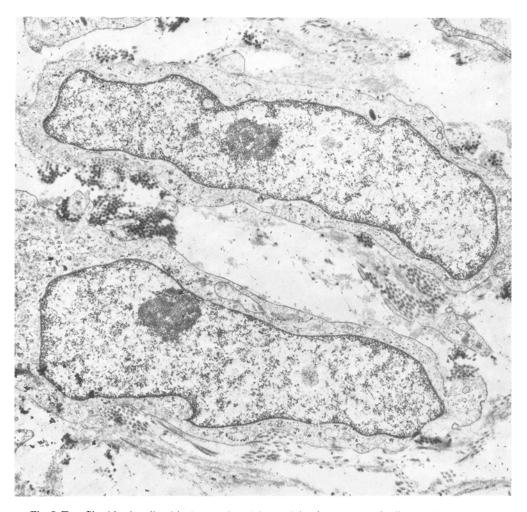
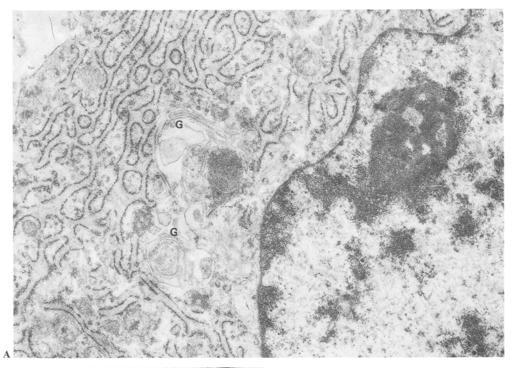


Fig. 5. Two fibroblastic cells with elongated nuclei containing homogeneously dispersed heterochromatin and a single nucleolus. The intercellular space shows some collagen fibre bundles and grey amorphous material. × 7,500

ately dense amorphous material and some bundles of ordinary cross-banded collagen fibres were seen, often closely associated with the external cell surface (Fig. 5). Occasionally, small segments of the cells were enclosed by basement membrane-like material.

The abundance of cytoplasmic microfilaments was a strinking feature of some cells. The filaments were parallelly arranged and most prominent peripherally in the cytoplasm or in the perinuclear area (Fig. 7). The filaments had a diameter of 7.5–10 nm and lacked periodicity. Structures similar to dense bodies and condensation of the filaments at the cytoplasmic membrane were occasionally found, but no well-developed "attachment-sites" were seen.

Histiocyte-like cells, mostly polygonal in shape, were relatively few in number but were found intermingling with the fibroblast-like cells in all the grade I



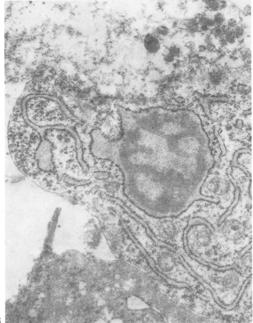


Fig. 6. A Detail of a fibroblast-like cell showing anastomosing parallel membranes of RER and a Golgi zone (G). The nucleus contains small heterochromatin clumps and a nucleolus. B Parallel membranes of RER continuous with cisternae, studded by ribosomes and filled with grey, amorphous material. $\times 20,000$

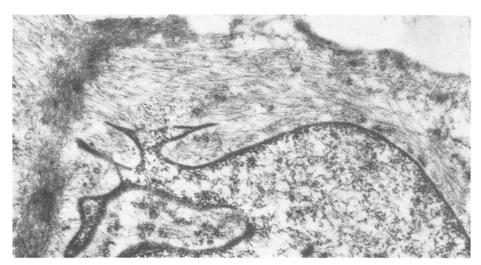


Fig. 7. An irregular indented nucleus surrounded by abundant parallelly arranged cytoplasmic filaments with focal condensation. $\times 25{,}000$

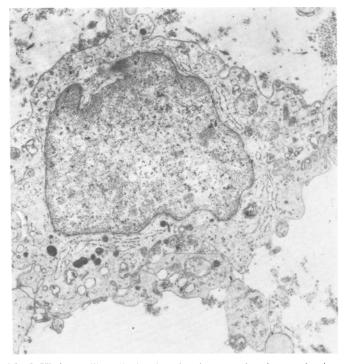
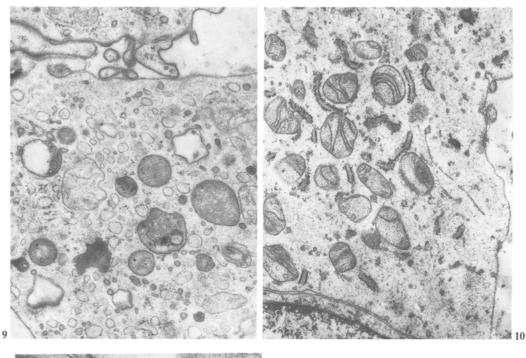


Fig. 8. Histiocyte-like cells showing abundant cytoplasmic vacuoles, lysosomal structures, inclusions and large, rounded mitochondriae. The cytoplasm shows a ruffled contour with pseudopodiae. $\times\,6,000$



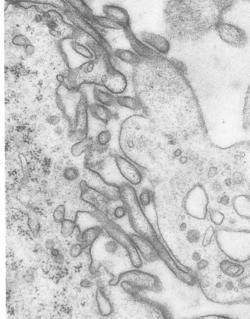


Fig. 9. Cytoplasmic detail showing abundant vesicles, vacuoles, lysosomal structures and lipid inclusions. $\times 16,000$

Fig. 10. Rounded and polygonal mitochondriae with short or traversing cristae associated with short profiles of RER. $\times 20,000$

Fig. 11. Cell surface showing prominent cytoplasmic microvillous projections and pinocytosis vesicles. $\times 25,000$

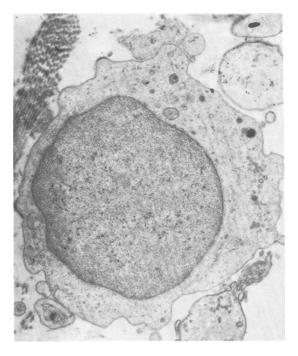
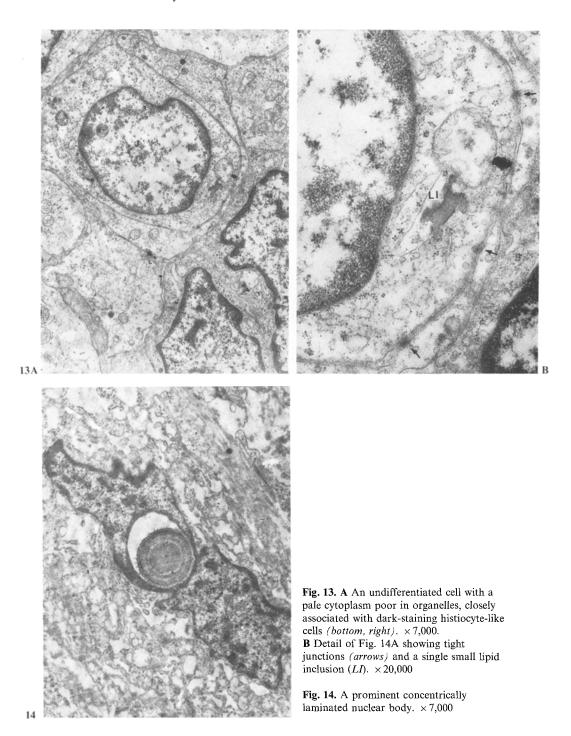
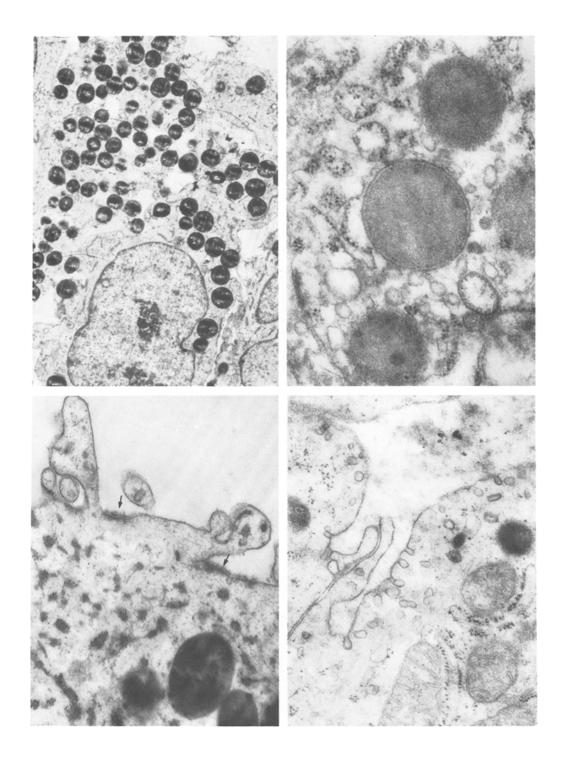


Fig. 12. An undifferentiated rounded cell with a pale cytoplasm containing few organelles and a nucleus with evenly distributed chromatin. A few small vesicles and lysosomal structures are present (top, right). × 6,000

and II tumours. The nuclei of these cells were often segmented or convoluted, the chromatin was irregularly dispersed in clumps, with heterochromatin condensed at the periphery, and one or two prominent nucleoli were found. The cytoplasm was more abundant than in the spindle-shaped cells and the cytoplasmic ground substance stained grey. The cytoplasm contained abundant characteristically membrane-bound lysosomes of variable size and density, other cytoplasmic inclusions without delimiting membranes and occasional lipid droplets (Figs. 8 and 9). The systems of vesicles and vacuoles were prominent and the Golgi zones were large. The mitochondria were abundant and had a rounded shape. Some of them were large, with incomplete irregular or traversing, sometimes branching, cristae (Fig. 10). The sparse RER mostly appeared as short parallel membranes; polysomes were more abundant. Occasional cells of this type included microfilaments as in the spindle-shaped, fibroblast-like cells, although usually less abundant. Pseudopodiae, microvillous cytoplasmic processes and deep cytoplasmic indentations were characteristic features of most cells (Fig. 11).

Undifferentiated, primitive-looking, rounded cells, with smoothly outlined nuclei and evenly distributed, finely granular chromatin throughout the nucleus and no or one small nucleolus were seen associated with the fibroblast-like and the histiocyte-like cells. The scant, light-staining cytoplasm contained few short profiles of RER and oval or rounded mitochondriae and only a few scattered small lysosomes (Fig. 12). No distinct Golgi zones were encountered. These cells were usually seen to be intimately associated with each other or with cells showing signs of histiocytic or fibroblastic differentiation (Fig. 13A). Some tight-junctions were seen between the cells (Fig. 13B).





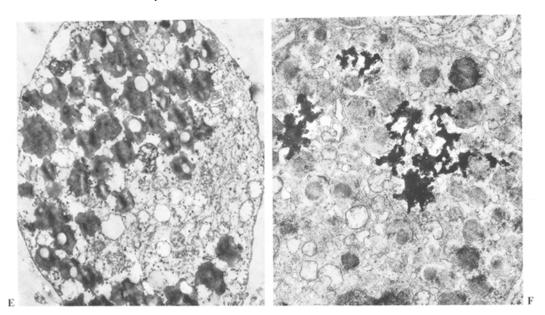


Fig. 15. A Numerous, large, dense lysosomal structures within a histiocyte-like cell. ×5,000. B A lysosome-like body, dense inclusions without limiting membrane and numerous vesicles. ×45,000. C Club-shaped cytoplasmic projections and segments of cytoplasmic membrane coated on the outer aspect with a thin layer of dense material and with cytoplasmic condensation on the inner side. ×30,000. D Pinocytosis vesicles at the surface of two histiocyte-like cells. The few segments of RER are closely associated with mitochondriae. ×33,000. E Cytoplasmic extension containing abundance of partly dissolved lipid inclusions. ×7,000. F Dense granular hemosiderin-like inclusions, lipid inclusions and lysosomal structures. ×20,000

Grade III and IV

The histiocyte-like cells predominated and showed the same characteristic features as in the grade I and II tumours. The nuclei were usually larger, even more irregular in shape and had multiple, very large nucleoli. Nuclear bodies, some large and laminated, others small, rounded and granular, were found (Fig. 14). Glycogen granules could be seen, both within the nucleus and in the cytoplasm. The abundance of dense lysosomes, vesicles, pinocytosis vesicles, lipid droplets and inclusions, some of which were hemosiderin-like, were even more prominent than in the grade I and II tumours (Fig. 15A-F). Segments of the cytoplasmic membrane, in varying stages of invagination, were coated on the outer aspect with a 50-70 nm thick layer of dense material, fibrillar in structure at high magnification. The inner surface of these segments showed a condensed, dense material (Fig. 15C). Numerous large digestive vacuoles containing fragments of mitochondria, RER and membrane structures were seen indicating auto- and exophagocytosis (Figs. 16A and B). As in the grade I and II tumours, these cells occasionally contained fairly abundant cytoplasmic microfilaments. Basement membrane-like material was rarely seen partly enclosing the tumour cells. A few single tight-junction structures were seen.

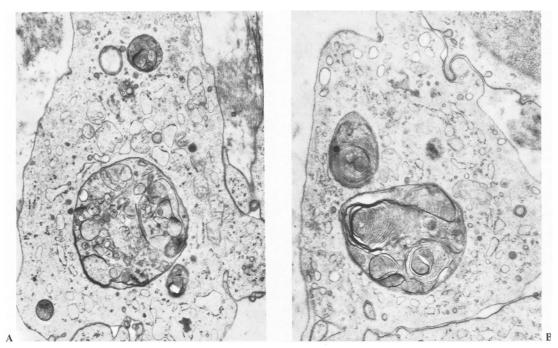


Fig. 16 A and B. Large digestive vacuoles filled with remnants of organelles and multilaminated structures. $\times\,15,000$

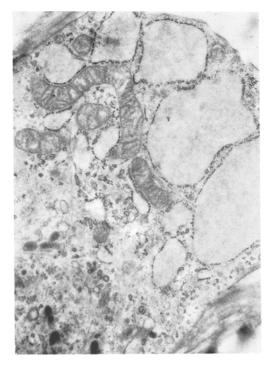
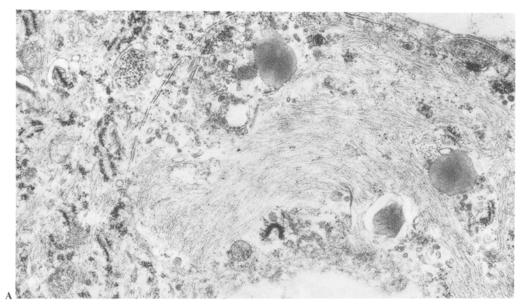


Fig. 17. Prominent, peripherally located distended cisternae of RER filled with grey material, closely associated with elongated mitochondriae. ×25,000



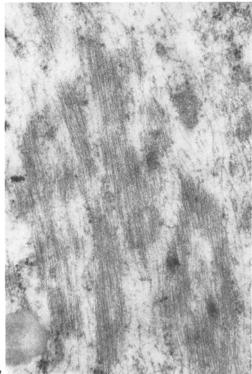


Fig. 18. A Detail of two cells with lipid inclusions, few profiles of RER and polysomes and systems of vesicles. Abundant parallelly arranged cytoplasmic filaments are seen. ×20,000. B Area with focal condensations of cytoplasmic filaments. ×70,000

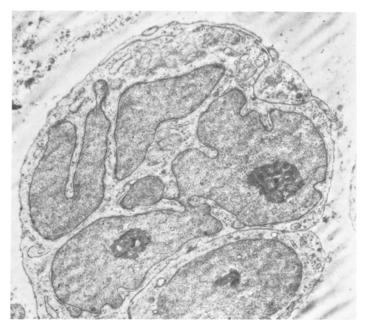


Fig. 19. A multinucleated giant-cell with evently distributed chromatin throughout the nuclei and prominent nucleoli. The cytoplasm contains some short profiles of RER, polysomes and rounded mitochondriae. To the bottom a neighbouring cell with a single nucleus. $\times 5,000$

Fibroblast-like cells, similar to those which predominated in the grade I and II tumours, were less common but found in all grade III and IV tumours. Generally, they showed larger nuclei with more abundant chromatin and larger nucleoli. Occasional large nuclear bodies were seen. The wide cisternae of RER were even more prominent. The cisternae of RER were seen to communicate with exceedingly large, smooth, membrane-limited vacuoles distended by a grey amorphous material, similar to that in the intercellular spaces. The vacuoles and RER cisternae were intimately associated with mitochondria, some of which were large and elongated (Fig. 17). Parallelly arranged cytoplasmic filaments were conspicuous in some cells, being the predominant organelle (Fig. 18A). A few dense-body-like structures were seen (Fig. 8B). The fibroblast-like cells also exhibited a few scattered dense lysosomes and in areas the cytoplasm of the cells showed pseudopodiae-like structures as well as some pinocytotosis vesicles. Collagen fibres of ordinary cross-banded type were seen intercellularly, closely associated with the cell surfaces.

Undifferentiated cells, as in the grade I and II tumours, were found predominantly in the most cellular areas and were closely associated with both fibroblast-like and histiocytic cells. At low magnification they were clearly distinguished by their small size, regular contour and pale-staining cytoplasm and nucleus. Occasionally, these cells contained a few lysosomes and systems of vesicles and dilated segments of RER and occasional pseudopodiae.

A few multinucleated giant cells were seen. The multiple nuclei, rarely more than 3 in the sections, were segmented or convoluted, showed a finely granular,

evenly distributed, chromatin, similar to that of the undifferentiated cells, and exhibited one or two nucleoli (Fig. 19). The cytoplasmic features parallelled in most respects those of the undifferentiated cells, i.e. organelles in a scant pale-staining cytoplasm. Multinucleated giant cells were seen to be in intimate contact with cells of undifferentiated type (Fig. 19).

Abundant blood vessels of capillary-like type occurred throughout the tumour. When cut transversely, some of them were seen to be built-up of one or two endothelial cells surrounded by a thin basal lamina. Other vessels were wider and composed of several endothelial cells forming a single row of cells sometimes projecting into the lumen and enclosed by basal lamina. Pericytes were observed along the endothelial wall of these vessels. The endothelial cells often showed signs of phagocytic activity. Smooth muscle cells were not found around any of the vessels studied. Tumour cells of all types were frequently seen intimately associated with the vessels.

Discussion

Light microscopically, the myxofibrosarcomas showed a great variation in cellularity, atypia and mitotic activity and only the high grade tumours, which included some solid parts, exhibited features suggestive of a histocytic origin.

Ultrastructurally, most cells in all the tumours could be classified as being either of fibroblast-like or of histiocyte-like type, the two types showing marked differences: the fibroblast-like cells exhibited abundant, wide cisternae of RER, small or moderately sized Golgi zones, sometimes abundant cytoplasmic filaments and moderate numbers of oval or elongated mitochondriae, while the histiocyte-like cells showed pseudopodiae, pinocytic vesicles, dense inclusions and lysosomes, large digestive vacuoles, prominent Golgi zones and abundant, mostly large and rounded mitochondria. The cells of predominantly fibroblast-like type, which showed signs of phagocytosis, and the mainly histiocyte-like cells with wide cisternae of RER and cytoplasmic filaments may be regarded as intermediate forms.

Tumours of all grades, but especially the grade I and II tumours, included cells with abundant parallelly arranged cytoplasmic microfilaments. There were tumour cells showing features described as characteristic for myofibroblasts. Similar cells have previously been described in malignant fibrous histiocytomas and, interestingly, also in cardiac myxomas and in a tumour described as "fibromyxosarcoma" (Churg and Kahn, 1977; Feldman et al., 1977; Leak et al., 1967). The myofibroblasts described in malignant fibrous histiocytoma and cardiac myxoma have exhibited such prominent features of leiomyoblastic differentiation that it does not seem possible to make a clear distinction between the two types of cells. The findings of myofibroblast-like cells with more or less distinct leiomyoblastic features within myxofibrosarcoma as well as malignant fibrous histiocytoma may explain the difficulties that can arise when distinguishing fibroblastic histiocytic tumours from leiomyomatous tumours, such as atypical fibroxanthoma of skin from cutaneous leiomyosarcoma (Dahl and Angervall, 1974; Dahl, 1976).

A dual fibroblastic-histiocytic pattern has been found in dermatofibrosarcoma protuberans (Ozello and Hamels, 1976), atypical fibroxanthoma (Weedon

and Kerr, 1975; Barr et al., 1977), malignant fibroxanthoma (Merkow et al., 1971; Fu et al., 1975; Taxy and Battifora, 1977) and malignant giant cell tumour of soft parts (Alguacil-Garcia et al., 1977). This feature seems also to apply to myxofibrosarcomas, at least the high grades. A clear distinction between fibroblastic and histiocytic cells and also between these and the myofibroblast-like cells is not always possible in these tumours. The presence of undifferentiated primitive looking cells with or without slight indications of histiocytic or fibroblastic differentiation, suggests that they may be stem cells for the fibroblast-like and histiocyte-like tumour cells in myxofibrosarcomas.

Light microscopically, the grade I and II tumours can be misinterpreted as myxoid liposarcoma, extraskeletal myxoid chondrosarcoma or benign myxoma (Angervall et al., 1977). The ultrastructural demonstration of both fibroblast-like and histiocyte-like cells may help to distinguish the low grade myxofibrosarcomas from these tumours (Kindblom and Säve-Söderbergh, in press; Enzinger and Shiraki, 1972; Smith et al., 1976; Fu and Kay, 1974; Feldman et al., 1977).

The ultrastructural appearance varied depending on histological grade. The differences, however, were mainly quantitative and appeared to follow a continuous scale from the low grade tumours, predominantly composed of fibroblast-like and the primitive looking cells and relatively few histiocyte-like cells, to the high grade tumors with abundance of histiocyte-like cells. The size, irregularity and amount of heterochromatin clumps of the nuclei increased with increasing histological grade, as did the number and size of nucleoli and digestive vacuoles and lysosomes in the histiocyte-like cells and the wide cisternae of RER in the fibroblast-like cells. These ultrastructural differences between the low and high grade tumours are thought to reflect a higher cellular and nuclear activity of the high grade tumours which, light microscopically, was seen as high mitotic activity and prominent cellular and nuclear polymorphism.

Tumours of all 4 grades had several light microscopical features in common: myxoid structure, nodularity, plexiform vascular pattern, and they lacked a distinct storiform pattern as can be seen in malignant histiocytic tumours. Ultrastructurally, all tumours exhibited a variable distribution of fibroblast-, histiocyte- and myofibroblast-like cells. Light microscopically, the entirely myxoid grade I and II tumours presented no obvious features suggestive of histiocytic differentiation. Electron microscopically, these tumours showed predominantly fibroblast- and myofibroblast-like cells and relatively few histiocyte-like cells. A histiocytic origin was more evident for the grade III and IV tumours, particularly those with solid areas corresponding to the myxoid variant of malignant fibrous histiocytoma, as described by Weiss and Enzinger (1977), and we feel it justified to use the term "myxoid variant of malignant fibrous histiocytoma" for high grade myxofibrosarcomas with a tendency to contain solid areas.

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