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Myxoid malignant fibrous histiocytoma versus myxoid liposarcoma

A comparative ultrastructural study

Masazumi Tsuneyoshi, Hiroshi Hashimoto, and Munetomo Enjoji
Second Department of Pathology, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi Higashi-Ku Fukuoka 812, Japan

Summary. An ultrastructural comparison of 7 examples of myxoid malignant fibrous histiocytoma (myxoid MFH) with 6 of myxoid liposarcoma is described. Despite certain histological differences between the two, electron microscopy was more valuable in differentiating MFH from liposarcoma. Electron microscopically, MFH contained a variety of cell types including histiocyte-like, fibroblast-like, intermediate-type, xanthomatous, multinucleated tumor giant cells and undifferentiated cells. Liposarcoma was composed mainly of lipoblasts at various stages of differentiation with a minority of undifferentiated cells and fibroblast-like cells. In contrast to the component cells of the MFH, these lipoblasts were characterized by abundant cytoplasmic glycogen, numerous pinocytotic vesicles and a discontinuous basal lamina in addition to large lipid droplets.

Key word: Malignant fibrous histiocytoma – Liposarcoma – Sarcoma – Soft tissue neoplasms – Electron microscopy

Introduction

Myxoid malignant fibrous histiocytoma (myxoid MFH) and myxoid liposarcoma are the two major myxoid malignancies of the soft tissues. The two are usually differentiated by light microscopy, although they may at times pose difficult histopathological problems. There have been several ultrastructural studies on myxoid MFH (Alguacil-Garcia et al. 1978; Enjoji et al. 1980; Fu et al. 1975; Lagacé et al. 1979; Reddick et al. 1979; Taxy and

Offprint requests to: M. Enjoji at the above address

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Battifora 1977; Tsuneyoshi et al. 1981; Weiss and Enzinger 1977) and on myxoid liposarcoma (Bolen and Thorning 1980; Gould et al. 1979; Kalderon and Fethiere 1973; Lagacé et al. 1979; Wetzel and Alexander 1979), but there is apparently no documentation of an ultrastructural comparison between the two myxoid malignant tumors. We have now compared 7 samples of myxoid MFH and 6 of myxoid liposarcoma at the electron microscopic level and found that differences between the two tumors can be identified.

Materials and methods

Tissues from seven myxoid MFHs and six myxoid liposarcomas were used for both light and electron microscopy studies. The selection was made from cases registered in our laboratory from 1971–1981. Tissues for light microscopy were processed in the usual manner following fixation in formalin and sections were stained with haematoxylin and eosin. Special stains used included Masson trichrome, silver impregnation for reticulin, periodic acid-Schiff, alcian blue and Prussian blue. Electron microscopic examination was made on all 13 cases. The fresh specimens were fixed in 3% glutaraldehyde solution (buffered pH 7.4) and postfixed in 1% phosphate-buffered osmium tetroxyde. Following dehydration, the tissue blocks were embedded in Epon 812 and were cut using an LKB ultrotome III. Ultrathin sections were stained with uranyl acetate and lead citrate, and examined under a JEM 100C electron microscopy.

Results

Clinical data

The age and sex of the patients and location of the tumors are listed in Table 1.

Light microscopic findings

Myxoid MFH, as seen in seven cases, exhibited wide areas of tumor with a myxoid appearance, in which the cellular component was composed of plump spindle, oval and polygonal cells with different degrees of atypia and pleomorphism. The cells were arranged in a more or less well developed storiform pattern. Anastomosing capillary vessels were prominent (Fig. 1).

The six cases of myxoid liposarcoma also presented an abundant myxoid matrix, a plexiform capillary network and in general, a poorly cellular tumor cell population (Fig. 2). The cellular elements were stellate for the most part, and only occasionally were spindle or round cells seen. Some of the cells were unequivocal lipoblasts which had accumulated lipid to form either large single or multiple vacuoles in the cytoplasm.

Electron microscopic findings

Myxoid MFH (7 cases). In each of the cases, several cell types were identifiable; histiocyte-like, fibroblast-like, intermediate-type, xanthomatous, multinucleated tumor giant cells and undifferentiated cells. Among these, how-

Table 1. An ultrastructural study of myxoid malignant fibrous histiocytoma and myxoid liposarcoma

MFH			Liposarcoma		
Patient	Location	Survival	Patient	Location	Survival
1. 44 M	Thigh	Living (3 years 11 months)	1. 32 F	Thigh	Living (2 years (11 months)
2. 55 F	Shoulder	Died (2 years 6 months)	2. 37 F	Thigh	Living (3 years)
3. 59 M	Retroperitoneum	Died (1 year 1 month)	3. 56 F	Thigh	Living (15 years)
4. 67 M	Thigh	Died (2 years 9 months)	4. 60 F	Thigh	Living (10 months)
5. 70 M	Axilla	Living (1 year (1 month)	5. 52 F	Popliteal fossa	Living (20 years)
6. 73 M	Upper arm	Living (10 years)	6. 32 F	Retroperitoneum	Living (1 year)
7. 85 M	Forearm	Living (4 years)			

ever, the principal types were histiocyte-like, fibroblast-like and undifferentiated.

The majority of spindle or polygonal cells were either histiocyte-like or fibroblast-like. The histiocyte-like cell had a more variable fine structure. The most characteristic feature was the presence of ruffled cytoplasmic prolongations. The bulky cytoplasm contained variable numbers of lysosomes and small numbers of mitochondria, Golgi complexes and rough endoplasmic reticulum (Figs. 3–5). In some of the cells, phagocytized erythrocytes or lipid vacuoles were detected in the cytoplasm. The nuclei were oval or indented, and had peripheral heterochromatin clumps. The fibroblast-like cell had a cell membrane which was either completely smooth or had a few short broad projections. The cytoplasm contained a scanty or more abundant population of organelles. There was a moderately well developed rough endoplasmic reticulum with slightly dilated cisternae and abundant ribosomes, varying numbers of mitochondria and occasional lysosomes (Fig. 5). Nuclei were fusiform and had dispersed chromatin, prominent nucleoli and sometimes nuclear bodies. Some of the fibroblast-like cells contained filament bundles with focal dense bodies in the peripheral area of the cytoplasm. These cells were identified as myofibroblasts.

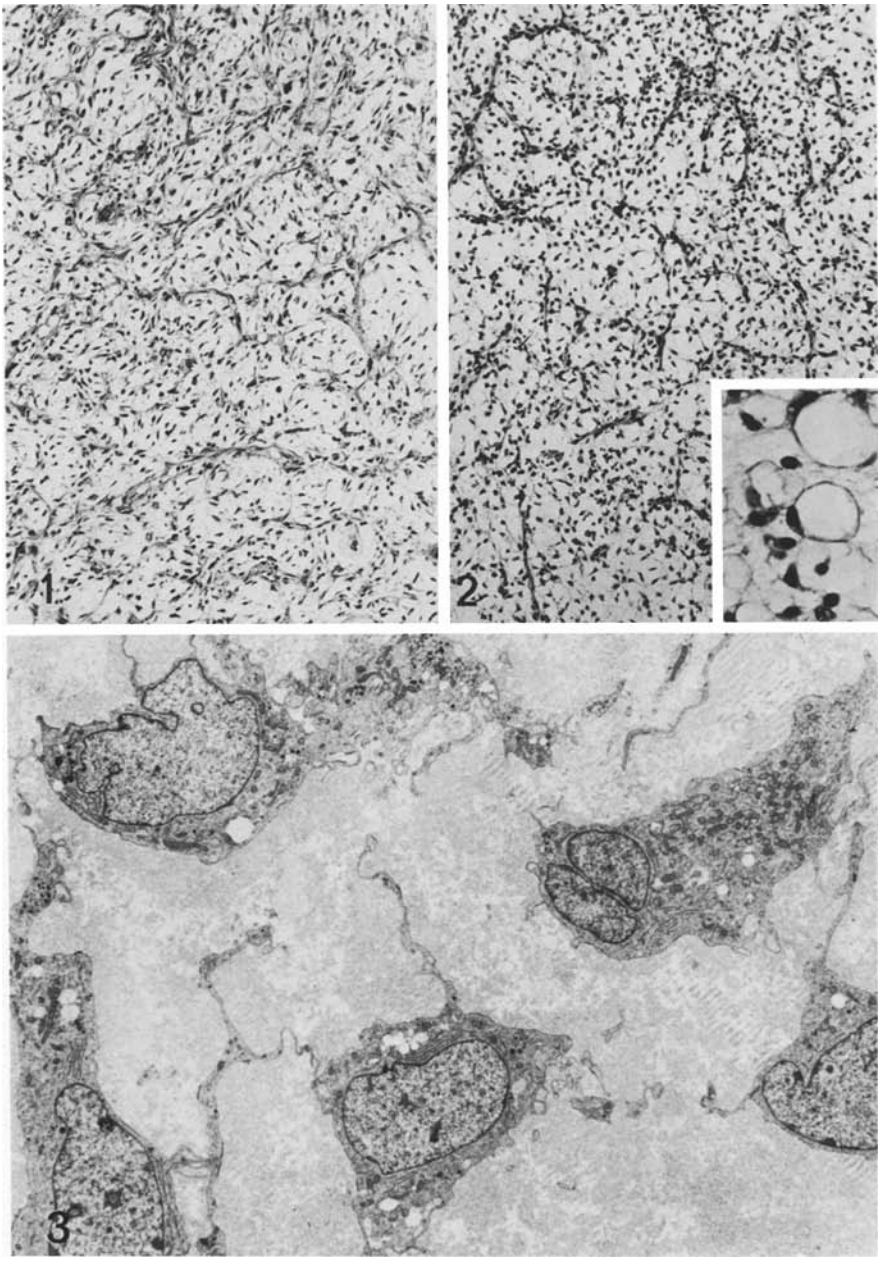


Fig. 1. Light micrograph of myxoid MFH. The tumor cells are arranged haphazardly or as a perivascular growth and are separated by myxoid matrix (× 100)

Fig. 2. Light micrograph of myxoid liposarcoma showing round to stellate cells and a plexiform capillary pattern on an myxoid background (× 100). *Inset:* Lipoblasts with lipid droplets (× 400)

Fig. 3. Electron micrograph of myxoid MFH. Histiocyte-like cells with cytoplasmic prolongations and intracytoplasmic lysosomes are scattered. The extracellular matrix contains fine granular material (× 4,400)

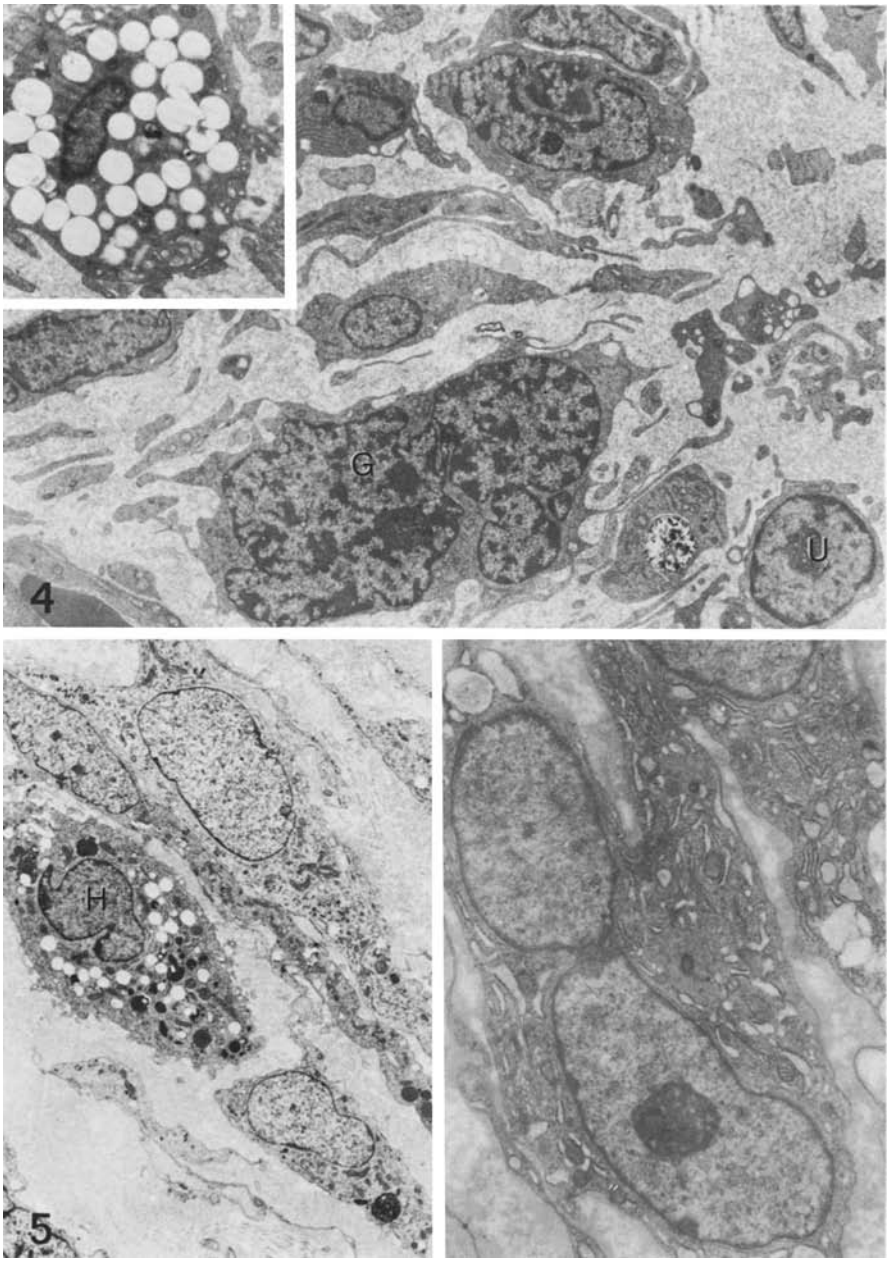


Fig. 4. Myxoid MFH composed of an admixture of histiocyte-like cells, giant cell (*G*) and undifferentiated cell (*U*) (× 6,800). *Inset:* Xanthomatous cell with accumulation of lipid droplets and cytoplasmic prolongations (× 6,800)

Fig. 5. Myxoid MFH. *Left:* An admixture of histiocyte-like cell (*H*) with filopodic extensions, lysosomes and lipid droplets (× 4,300). *Right:* Fibroblast-like cell with prominent rough endoplasmic reticulum showing some dilatation (× 8,200)

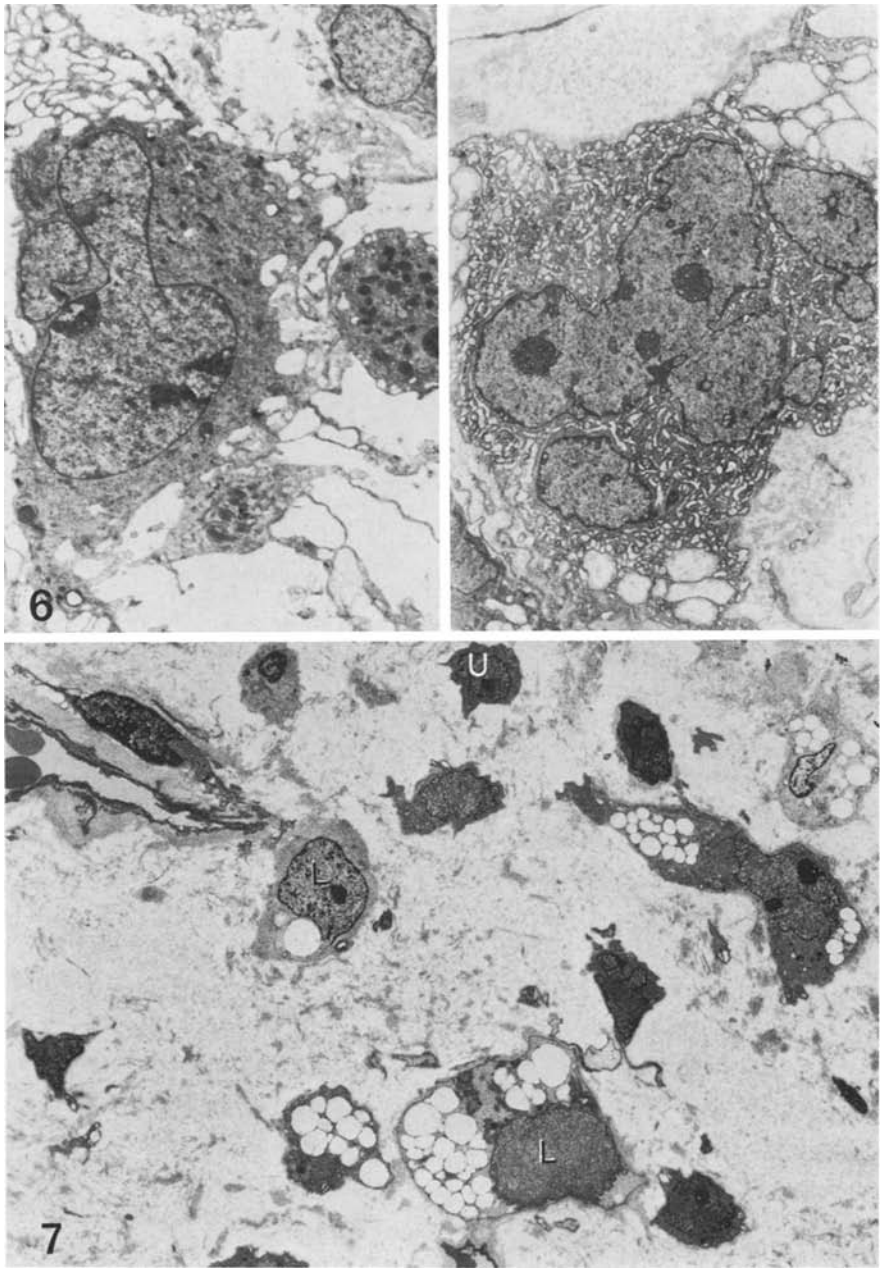


Fig. 6. Multinucleated giant tumor cell of myxoid MFH. *Left:* Histiocyte-like type having abundant lysosomes and cytoplasmic prolongations (× 3,300). *Right:* Fibroblast-like type having prominent rough endoplasmic reticulum and cytoplasmic extensions (× 3,300)

Fig. 7. Electron micrograph of myxoid liposarcoma showing an admixture of lipoblasts at various stages of differentiation (*L*) and undifferentiated cells (*U*). The extracellular matrix contains a finely granular material (× 2,000)

The undifferentiated cell was irregularly distributed, was characterized by a relatively small size and ovoid or polygonal shape, and had a smooth surface and a round or indented nucleus. The thin rim of cytoplasm contained only a few organelles such as ribosomes and mitochondria (Fig. 4). In some instances there was partial differentiation, however, the nuclei were often indented and the cytoplasm displayed pseudopod-like extensions and more substantially developed intracytoplasmic organelles.

Some tumor cells showed morphologically intermediate characteristics between the histiocyte-like and the fibroblast-like cells. Rare xanthomatous histiocytes were characterized by filopodic cytoplasmic extensions, empty vesicles, membrane-bound lipid and some lysosomes (Fig. 4). Multinucleated giant cells, though not common, contained two or more nuclei with irregular, often deeply indented nuclear membranes and showed cytoplasmic invaginations. These giant cells could be separated again into two types; fibroblast-like and histiocyte-like. The former cells were characterized by well developed rough endoplasmic reticulum (Fig. 6) and the latter by the presence of numerous delicate cytoplasmic prolongations, occasional lysosomes and scanty mitochondria (Figs. 4 and 6).

The extracellular space was made up of finely granular osmiophilic material, occasional microfibrils and sometimes collagen.

Myxoid liposarcoma (6 cases). The tumor cells were isolated for the most part, but were occasionally grouped into small clumps. Three major cell types were observed; lipoblasts at various stages of differentiation, fibroblast-like cells and undifferentiated cells (Fig. 7).

The first type included cells which were clearly recognizable as lipoblasts at various stages of development. The cytoplasm contained variable numbers of lipid droplets that either retained their individuality or fused into a giant single droplet. The lipid droplets were generally of medium electron density, although some were nearly electron-lucent. They occupied most of the cytoplasm and were homogeneously opaque and frequently bounded by a limiting membrane. The larger cells were the multivacuolated and univacuolated (signet-ring). Mitochondria were generally plentiful, and were often focal in distribution. They were small in size with a dense matrix and varied from round to fusiform. Prominent pools of glycogen and smooth endoplasmic reticulum were frequently seen. Lysosomes and Golgi apparatus were rare. Occasional bundles of microfilaments and rough endoplasmic reticulum were present. Free ribosomes were scattered throughout the cytoplasm. In addition to the above cited organelles, microtubular inclusions were occasionally recognized in some lipoblasts (Fig. 8). The nuclei displayed smooth to complex contours with deep indentations. The nuclear chromatin was unevenly dispersed and had a moderate peripheral condensation. One or two prominent nucleoli were present, and nuclear bodies were occasionally seen. The cytoplasmic border was smooth and the cell membrane with numerous pinocytotic vesicles was coated by an irregular discontinuous basal membrane-like material. Less mature lipoblasts were round or stellate with some elongated forms (Fig. 9). The cytoplasm contained comparatively few

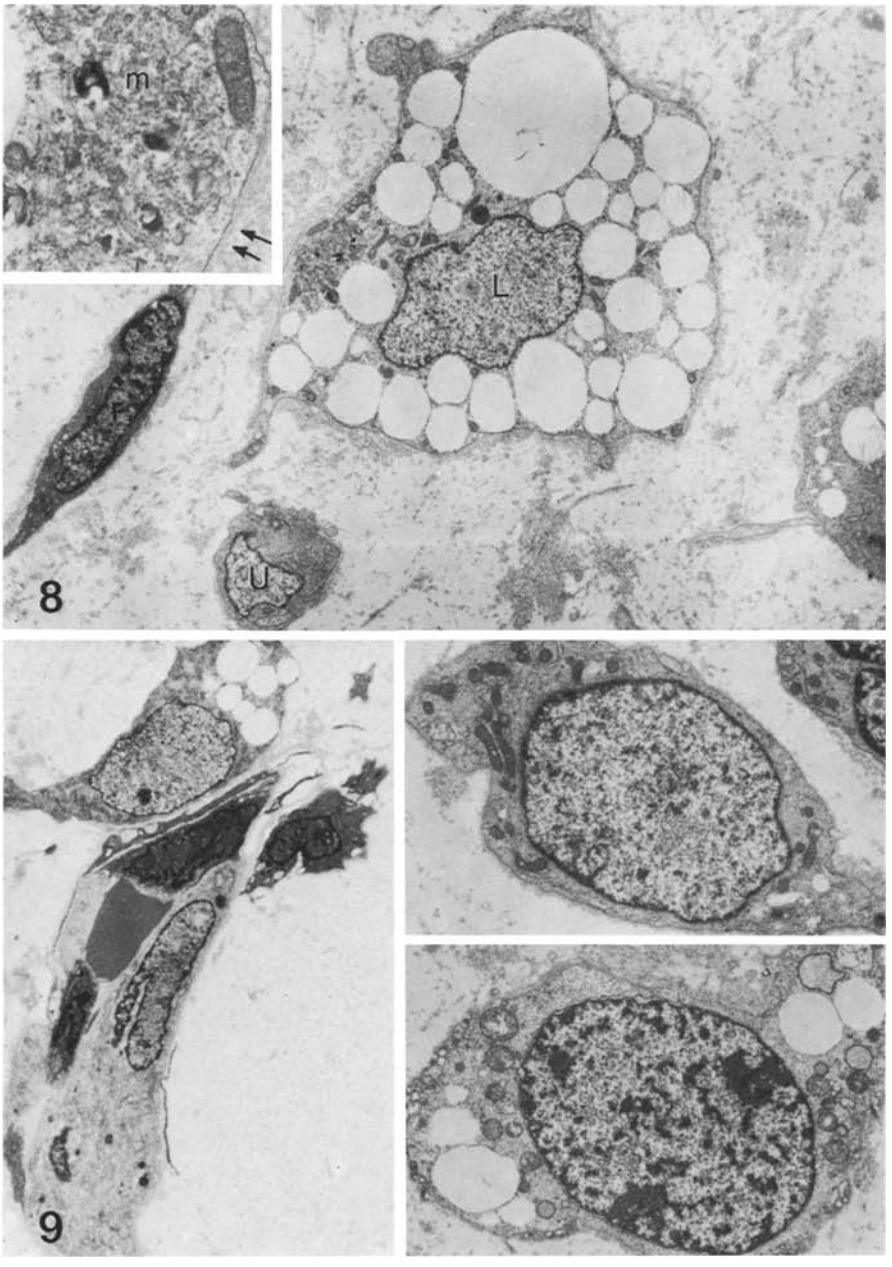
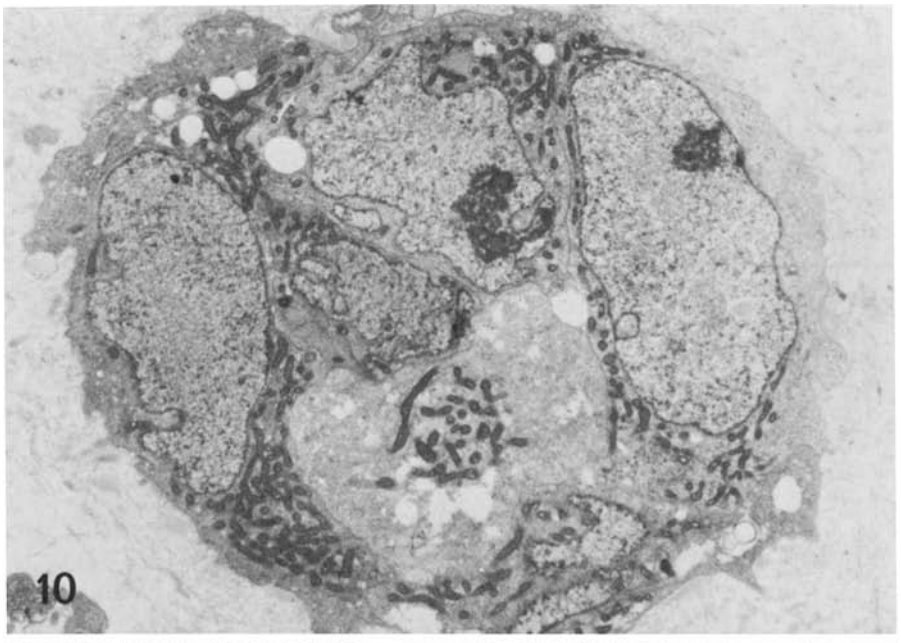


Fig. 8. Myxoid liposarcoma composed of undifferentiated cell (*U*), spindle (fibroblast-like) cell (*F*) and well differentiated lipoblast (*L*) showing multivacuolated form (×6,800). *Inset:* Intracytoplasmic microtubular inclusion (*m*). The plasma membrane is covered by basal lamina (*arrows*) (×23,600)

Fig. 9. Myxoid liposarcoma. *Left:* Moderately differentiated lipoblast closely adherent to a capillary (×2,800). *Right upper:* Less mature lipoblast with a few lipid droplet. The plasma membrane is covered by basal lamina (×9,800). *Right lower:* Moderately differentiated lipoblast (×9,800)



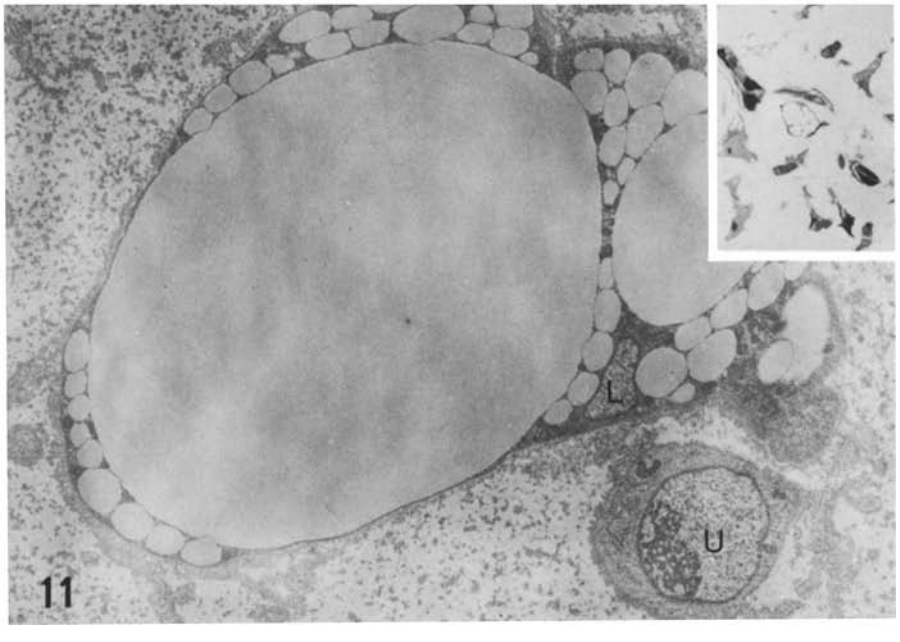


Fig. 10. A cell cluster composed of several lipoblasts in close apposition. Focal aggregates of mitochondria and glycogen (× 6,400)

Fig. 11. Well differentiated lipoblast (*L*) showing multivacuolated form and undifferentiated cell (*U*) (× 6,600). *Inset:* Light micrograph of thick section of epoxy resin block (toluidine blue, × 440)

lipid droplets which were unevenly distributed, although there were moderate amounts of other organelles, such as rough endoplasmic reticulum, microfilaments, and mitochondria which contained moderate amounts of glycogen. Moderately differentiated lipoblasts varied in shape and contained moderate numbers of lipid droplets (Fig. 9). Other intracytoplasmic organelles in these cells were numerous mitochondria, focal aggregates of glycogen, sparse lysosomes, poorly differentiated Golgi complex or ribosomes. The combination of these organelles varied from one cell to another. Several less mature or moderately differentiated lipoblasts were occasionally seen in close apposition and the cell cluster appeared to be a single multinucleated giant cell (Fig. 10). Well differentiated lipoblasts were either multinucleated or univacuolated (Figs. 8 and 11). The cytoplasm was filled with multiple lipid vacuoles of varying sizes, but in some lipoblasts the lipid droplets fused into a giant single droplet and the so-called "signet-ring" cell was characterized by a peripheral nucleus with a prominent necleoli. The lipoblasts were often found closely adherent to a capillary (Fig. 9).

The second cell type was a fibroblast-like cell which was elongated and had a spindle shaped indented nucleus (Fig. 8). The cytoplasm contained more or less well developed organelles. The rough endoplasmic reticulum were sometimes well developed. Abundant ribosomes, varying numbers of mitochondria and filament bundles were evident.

The third type was an undifferentiated cell, unevenly distributed and characterized by a round to oval nucleus in which chromatin was finely dispersed (Figs. 8 and 11). The cytoplasm was scanty and contained few such organelles as ribosomes, mitochondria and rough endoplasmic reticulum. Occasional bundles of microfilaments were seen in the cytoplasm. The cell membranes were covered by a layer of granular material.

The loose extracellular stroma contained amounts of moderately electron-dense and finely granular material comparable with mucopolysaccharide, small numbers of collagen fibrils, or other non-crossbanded, filamentous material.

Discussion

Separation of myxoid MFH from myxoid liposarcoma is essential, although it is not always difficult using light microscopy (Enjoji et al. 1980). We know of no report regarding an ultrastructural comparison between these two malignant myxoid tumors, although Reddick et al. (1979) did report liposarcoma and pleomorphic rhabdomyosarcoma. In line with the results of Lagacé et al. (1979), electron microscopy of myxoid MFH demonstrated four principal cell types; primitive mesenchymal cells, spindle cells of fibroblastic and histiocytic nature, and multinucleated giant cells. In addition, lesser numbers of the cell types such as intermediate cells (both fibroblastic and histiocytic) and xanthomatous cells were found. The ultrastructural findings in myxoid liposarcoma have been described (Bolen and Thorning 1980; Gould et al. 1979; Kalderon and Fethiere 1973; Lagacé et al. 1979; Wetzel and Alexander 1979). According to these authors, the tumors con-

Table 2. An ultrastructural study of myxoid malignant fibrous histiocytoma and myxoid liposarcoma

	MFH	Liposarcoma
Cell type	Histiocyte-like cell Fibroblast-like cell Intermediated cell Xanthomatous cell Multinucleated giant cell Undifferentiated cell	Well differentiated lipoblast multivacuolated lipoblast univacuolated (signet-ring) Moderately differentiated lipoblast Less mature lipoblast round to stellate cell Fibroblast-like cell Undifferentiated cell
Cytoplasmic border	Ruffled	Smooth
Lipid droplet	− or + lysosomal lipid	+ to + + + small to large
Mitochondria	+	+ + to + + + small dense, focal
Lysosome	Prominent (histiocyte-like cell)	Sparse
Rough E.R.	+ + to + + + (fibroblast-like cell)	− to +
Smooth E.R.	+	+ to + + +
Golgi complex	+	− to +
Glycogen	− to +	+ to + + +
Free ribosome	+ to + +	+ to + +
Filament	− to + + +	− to + +
Pinocytotic vesicle	− to +	+ to + + +
Basement membrane	−	+
Others		Microtubular inclusion Cell cluster

sisted of three main cell types, i.e. primitive mesenchymal cell, intermediate cell types, and lipoblasts at various stages of development. The principal differences were the number and the size of intracytoplasmic fat vacuoles and the amount of basement membrane-like material.

The comparative ultrastructural features are summarized in Table 2. The myxoid MFH was composed of several cell types, such as histiocyte-like, fibroblast-like, intermediate-type, xanthomatous, multinucleated tumor giant cells and undifferentiated cells, and our previous studies revealed histiocyte-like, fibroblast-like cells and undifferentiated cells to be the three major cell types (Enjoji et al. 1980; Tsuneyoshi et al. 1981). The myxoid liposarcoma, in contrast, consisted principally of lipoblasts at various stages of differentiation with a minority of undifferentiated and fibroblast-like cells. The lipoblasts were characterized by abundant and pleomorphic mitochondria, limited cytoplasmic membrane systems, abundant cytoplasmic glycogen, numerous pinocytotic vesicles, and discontinuous basal lamina, in addition to large lipid droplets.

The essential difference between the two was thus the presence or abscence of lipoblasts. As mentioned previously by Lagacé et al. (1979), there

is a morphological spectrum of lipoblasts; the less mature, of round or stellate form, moderately differentiated lipoblasts of varying shapes and mature differentiated lipoblasts of multinucleated and univacuolated or signet-ring forms. The cells in earlier stages of differentiation contained a few or several smaller lipid droplets, but in later stages, the lipid droplets appeared as larger coalescent masses filling the cytoplasm (Napolitano 1963). The electron microscopic features of liposarcoma that served to help differentiate this tumor from the MFH were, in addition to the size and distribution of the lipid droplets, the shape of the tumor cells that contained the lipids, the relative paucity of lysosome-like granules, and the increased lipid accumulation in the cell cytoplasm. Furthermore, certain features in the liposarcoma including focal aggregates of abundant and pleomorphic mitochondria, abundant cytoplasmic glycogen, numerous pinocytotic vesicles and basal lamina investment appeared somewhat distinctive when compared to those of the cells seen in the MFH. Other cytoplasmic organelles such as Golgi complexes, free ribosomes and filaments were present in both MFH and liposarcoma. Xanthomatous cells seen in MFH were different from the lipid-filled cells of the liposarcoma with respect to the distribution and size of lipid droplets, and of some other cellular features (Bolen and Thorning 1980; Lagacé et al. 1979). For the undifferentiated type cells, electron microscopic features were similar in both liposarcoma and MFH. These undifferentiated cells were occasionally encountered in both types of tumors and had rounded nuclei and a scanty cytoplasm containing a few organelles. The characteristic amorphous matrix of the liposarcoma was substantially similar, electron microscopically, to that of the MFH except that there were fewer fibrils and collagen fibers in the liposarcoma.

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