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Myxoid Liposarcoma

An Electronmicroscopic Study: Biological and Histogenetic Considerations

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Summary. Ten myxoid liposarcomas (ML) were studied ultrastructurally in an attempt to determine the histogenesis of this neoplasm and structural associations which might contribute to their relatively benign clinical behavior. The findings were compared with normal and neoplastic adipose tissue.

Three cell types were observed, i.e., "primitive" mesenchymal cells, intermediate cell types, and lipoblasts at various stages of development. The principle differences between the lipoblastic elements were the number and the size of intracytoplasmic fat vacuoles, the development of basement membrane-like material, micropinocytotic vesicles along the plasma membrane and the quantity and pleomorphism of mitochondria. The tumor vasculature was complex but consistently demonstrated a multilayered basal lamina. This finding has been described in neoplasms associated with a relatively good prognosis.

This study demonstrates that the better differentiated lipoblasts in ML share some features with normal brown fetal fat and hibernoma. It is, thus, suggested that ML may be derived from brown adipose tissue.

Key words: Myxoid liposarcoma – Histogenesis – Electron Microscopy – Hibernoma.

Myxoid liposarcoma (ML), the most frequent histologic expression of liposarcoma, represents one of the more commonly encountered soft tissue sarcomas. A number of studies have related the clinical-pathological features of ML over the past several decades (Ewing, 1942; Stout, 1944; Pack and Pierson, 1954; Enterline et al., 1960; Enzinger and Winslow, 1962; Kindblom et al., 1975). Although malignant, the neoplasm in characterized by local invasion and high recurrence rather than metastasis. The basis for this biological behavior has not been defined.

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Table 1. Clinical data of 10 Patients with ML

Sex	Age	Location of primary lesion	Treatment	Recurrences	Follow-up
M	50	Gluteal region	Simple excision	–	Free of disease at 42 months
M	47	Lower extremity	Wide excision and radiotherapy	3 at 4, 5, 8 years	Free of disease at 10 years
F	24	Retroperitoneum	Incomplete excision and chemotherapy	8 In 5 years	Alive with residual tumor at 7 years
M	47	Lower extremity	Wide excision	–	Free of disease at 4 years
F	33	Lower extremity	Wide excision	–	Free of disease at 4 years
F	40	Lower extremity	Wide excision	–	Free of disease at 2 years
M	44	Lower extremity	Wide excision	–	Free of disease at 3 years
M	34	Lower extremity	Wide excision	–	Free of disease at 18 months
F	25	Chest Wall	Wide excision	–	Free of disease at 4 years
F	46	Thigh	Wide excision	1 at 2 years	Free of disease at 4 years

Despite the relatively frequent occurrence of ML, there have been very few ultrastructural studies of this neoplasm (Scarpelli and Greider, 1962; Kalderon and Fethiere, 1973; Flenker, 1976; Gould et al., 1976; Feldman, 1979; Kindblom and Säve-Söderbergh, 1979). Accordingly, the histogenetic derivation of this sarcoma has not been established.

In an attempt to address these two issues (biology and histogenesis) we undertook a detailed ultrastructural study of ML. The results of our findings are compared and contrasted with normal and neoplastic adipose tissue.

Material and Methods

The clinical data are summarized in Table 1.

Surgical specimens were fixed in Bouin's solution or phosphate buffered 10% formalin. Paraffin sections were stained by H&E, Alcian blue, Hale's and Laidlaws's technique. Oil red "O" stains were performed on frozen tissue. For electron microscopy, fresh tissue from multiple sites was sliced into 1 mm^3 fragments and fixed in 2.5% glutaraldehyde in 0.1 M cacodylate buffer at pH 7.4. The tissue was postfixed in 1% osmium tetroxide, dehydrated in graded alcohols and embedded in Epon 812. 0.5 mμ thick sections were stained with toluidine blue. In each case, 15 to 20 selected blocks were studied. From appropriate areas, ultrathin sections were cut, stained with uranyl acetate and lead citrate, and examined with a transmission electron microscope.

Results

Light Microscopy

The histological features of ML required for the diagnosis included abundant myxoid stromal lakes, a plexiform capillary network and a generally poorly cellular tumor cell population (Fig. 1). The mucoid stroma stained avidly with Alcian blue and Hale's technique. Occasional erythropoietic cells were noted in this stroma. The vascularity was optimally appreciated with the reticulin stain. The neoplastic cells featured a round and somewhat pyknotic nucleus

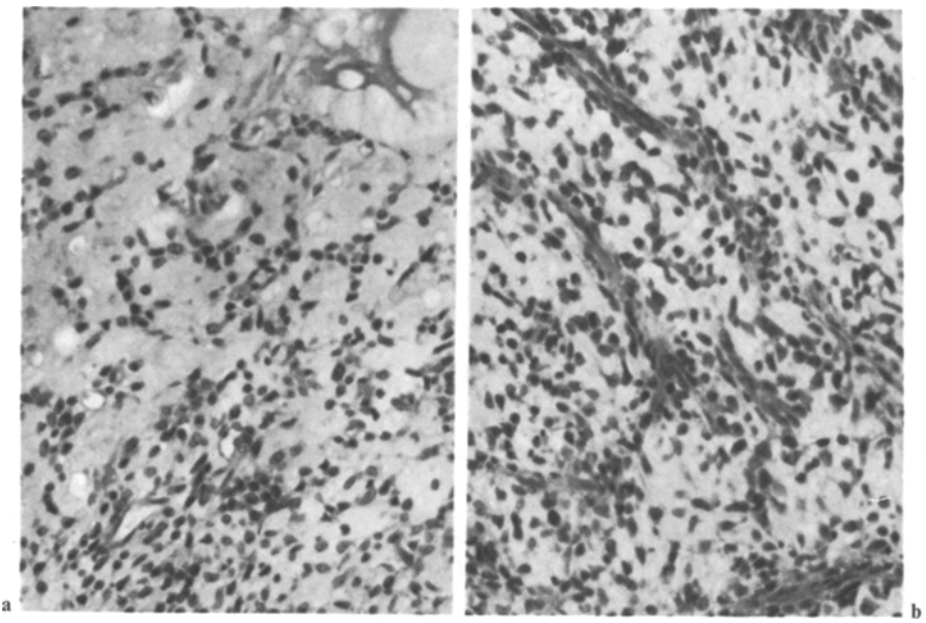


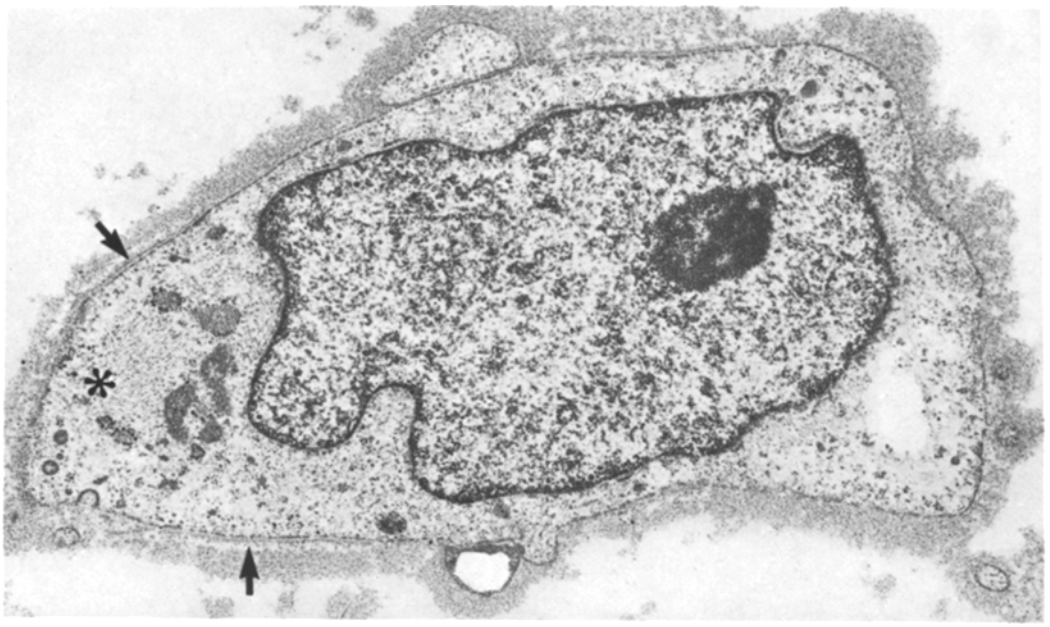
Fig. 1.a Typical area in a ML showing the abundance of the myxoid matrix with "mucus-lakes" (*top-right*). A few multivacuolated lipoblasts are present within a population of round to stellate cells. **b** Focus in a tumor in which the plexiform vascular pattern is prominent

with scant cytoplasm and ill-defined cytoplasmic borders. Necrosis was not evident neither was nuclear pleomorphism. Mitoses were observed with extreme rarity. Fat stains revealed an occasional cell which contained multivacuolated cytoplasmic neutral lipid.

Electron Microscopy

Three principal cell types were observed; "primitive" mesenchymal cells, intermediate cell types and lipoblasts at various stages of differentiation.

The "primitive" mesenchymal cells were characterized by a round to oval nucleus with occasional focal indentation of the nuclear membrane. Chromatin was finely dispersed and somewhat condensed toward the nuclear membrane; occasional nucleoli were seen. Mitotic figures were extremely rare, only one was observed in this cell type among the ten cases examined. The thin rim of cytoplasm contained few organelles, i.e., monoribosomes, polyribosomes, rare mitochondria and brief profiles of rough endoplasmic reticulum. The cell membrane were often coated by a layer of lightly osmiophilic finely granular material (Fig. 2). More cytodifferentiated mesenchymal cells demonstrated indented nuclei with prominent nucleoli. In addition to the above cited organelles, these cells contained occasional Golgi zones, coated vesicles and bundles of microfilaments. The cell membranes were similarly coated by an interrupted layer of granular material. Subplasmalemmal osmiophilic condensations



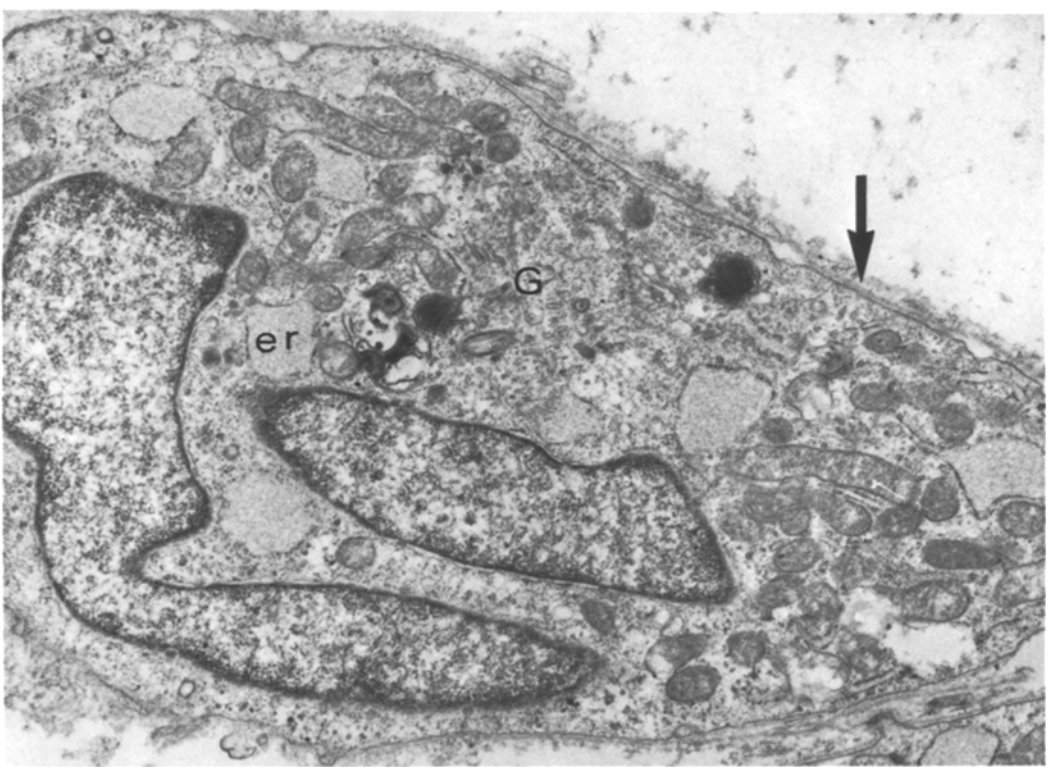
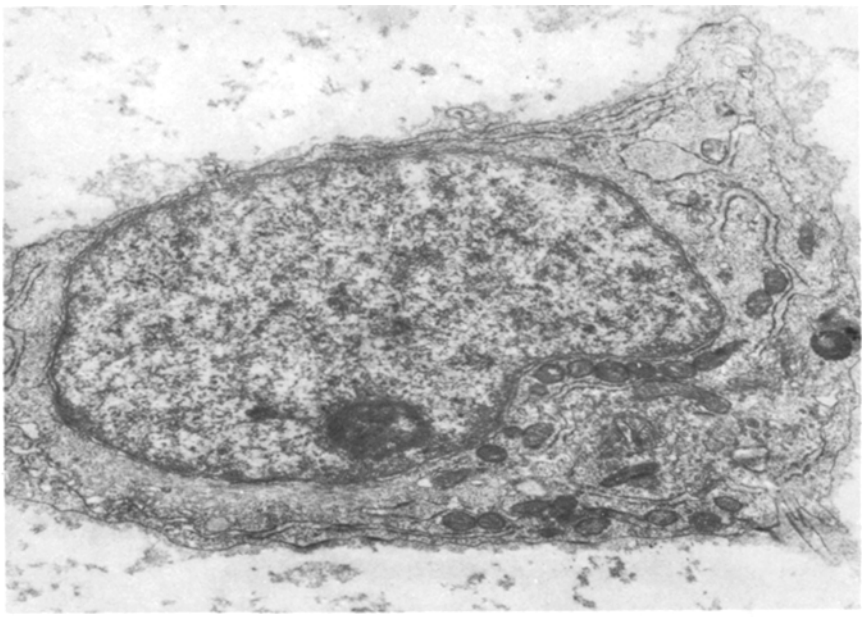


Fig. 2. Electron micrograph demonstrating a "primitive" mesenchymal cell characterized by a somewhat indented nucleus. Microfilaments are seen (asterisk) in cross section in the cell cytoplasm. The plasma membrane is covered by a thick layer of a granular material. An irregular discontinuous basement membrane (*arrow*) is evident. ($\times$ 11,600)

Fig. 3. Electron micrograph shows an intermediate cell whose cytoplasm contains dilated cisternae of rough endoplasmic reticulum (*er*), numerous pleomorphic mitochondria, polyribosomes, a Golgi area (*G*) and lysosomes. The plasma membrane is covered by a rather regular basement membrane (*arrow*). ($\times$ 11,200)



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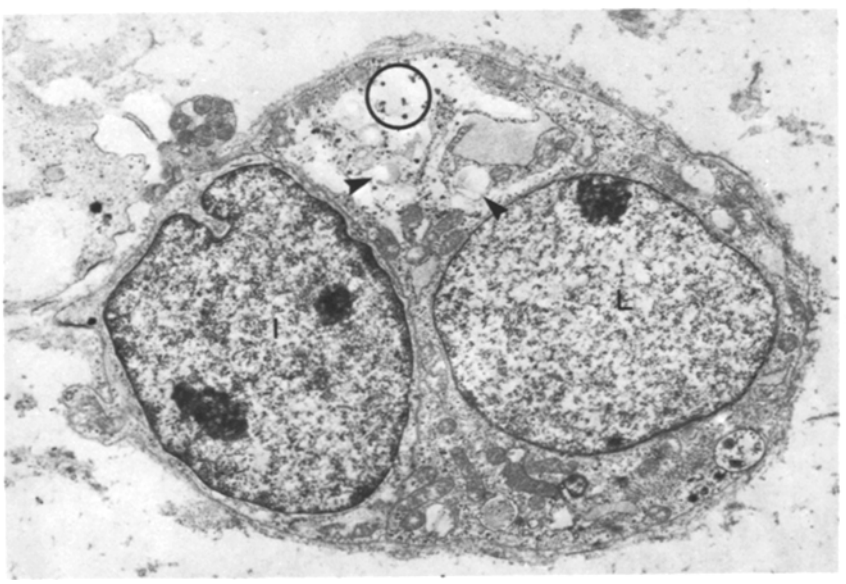

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Fig. 4. Intermediate cell showing nuclear indentation, dilated cisternae of rough endoplasmic reticulum containing a finely granular material resembling the extracellular matrix. A striking microfibrillary network is localized around the nucleus. Pleomorphic mitochondria and prominent Golgi are readily seen. (× 8,960)

Fig. 5. Electron micrograph showing an intermediate cell (*I*) in close association to a poorly differentiated lipoblast (*L*). In the latter, note pleomorphic mitochondria, dilated cisternae of rough endoplasmic reticulum, β-glycogen particles (circle) and lipidic microvacuoles (*arrow-head*). (× 5,920)

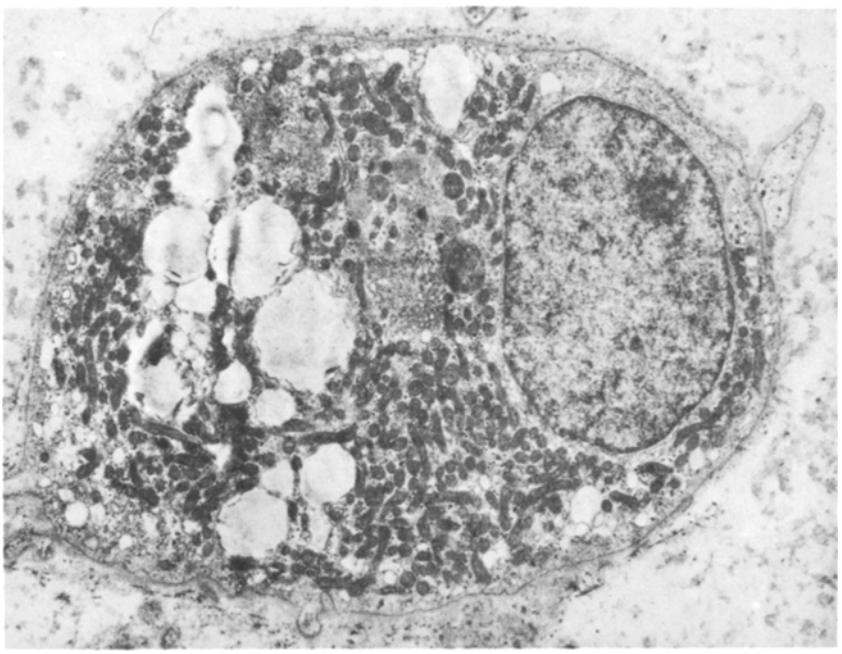

Fig. 6. Electron micrograph demonstrating a better differentiated lipoblast with an eccentric nucleus, numerous pleomorphic mitochondria and coalescing lipid vacuoles. Lysosomes and Golgi zone are also apparent. (× 7,360)

suggestive of hemidesmosomal structures and an irregular discontinuous basal membrane-like material were also noted.

The intermediate cells, more numerous than primitive mesenchymal cells, were disposed singly and in clusters. When observed individually, the cells were elongated with spindle shaped indented nuclei which, in transverse section, produced a bi or multilobulated appearance. (Fig. 3) When clustered, nuclei were generally round. Chromatin was finely granular and condensed along the nuclear membrane. The cytoplasm was characterized by a striking microfibrillary network localized perinuclearly. (Fig. 4) Moderate numbers of polymorphic mitochondria were admixed among other cytoplasmic organelles. Filamentous, rod-shape and C-shaped mitochondrial forms were often identified. A poorly developed Golgi zone was occasionally observed in the concavity of nuclear depressions. Other organelles included limited numbers of dense lysosomes, monoribosomes and polyribosomes, dilated rough endoplasmic reticulum which contained finely granular material indistinguishable from the extracellular matrix, and rare β-glycogen particles. Occasional pinocytotic vesicles and osmiophilic condensations were noted along the cell membranes. A discontinuous but well formed layer of basement membrane-like material was often evident.

A third cellular population, about equal numerically to the intermediate cell type, was composed of lipoblasts at various stages of development. Less mature forms were round to elongated and often in close apposition to each other (Fig. 5). The nuclei were generally round but occasionally pleomorphic.

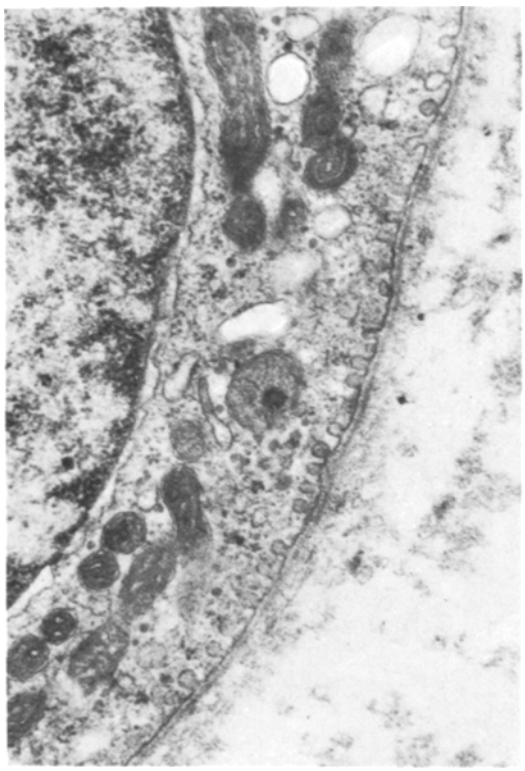

Fig. 7. Higher magnification showing a well-defined basement membrane with a striking pinocytotic activity. Glycogen rosettes and a mitochondrion whose matrix contain a round focal condensation are observed. (×20,700)

The cytoplasm contained organelles similar to the intermediate cells, i.e., moderate amounts of dilated cisternae of rough endoplasmic reticulum, bundles of microfilaments, mono and polyribosomes, variable numbers of pleomorphic mitochondria, and β-glycogen particles. The most notable additional feature was the presence of irregularly shaped small cytoplasmic lipid vacuoles, both membrane and non-membrane bound. The cell surface was coated by a discontinuous layer of basement membrane-like material.

Better differentiated lipoblasts were present in many areas of each tumor. These cells varied considerably in shape and were characterized by peripheral, somewhat crescentic nuclei with prominent nucleoli. Cytoplasmic components varied from one cell to another. In some the cytoplasm was occupied in large measure by pleomorphic rod-filamentous mitochondria with a dense matrix and moderately developed cristae. Other portions of cytoplasm contained irregular coalescent lipid vacuoles lacking limiting membranes (Fig. 6). Other organelles included variable numbers of lysosomes, poorly developed Golgi, polyribosomes, β-glycogen particles and clusters of glycogen rosettes. Striking pinocytotic activity and deep surface recesses were seen along the cell membrane (Fig. 7). Discontinuous basement membrane-like material was present, often

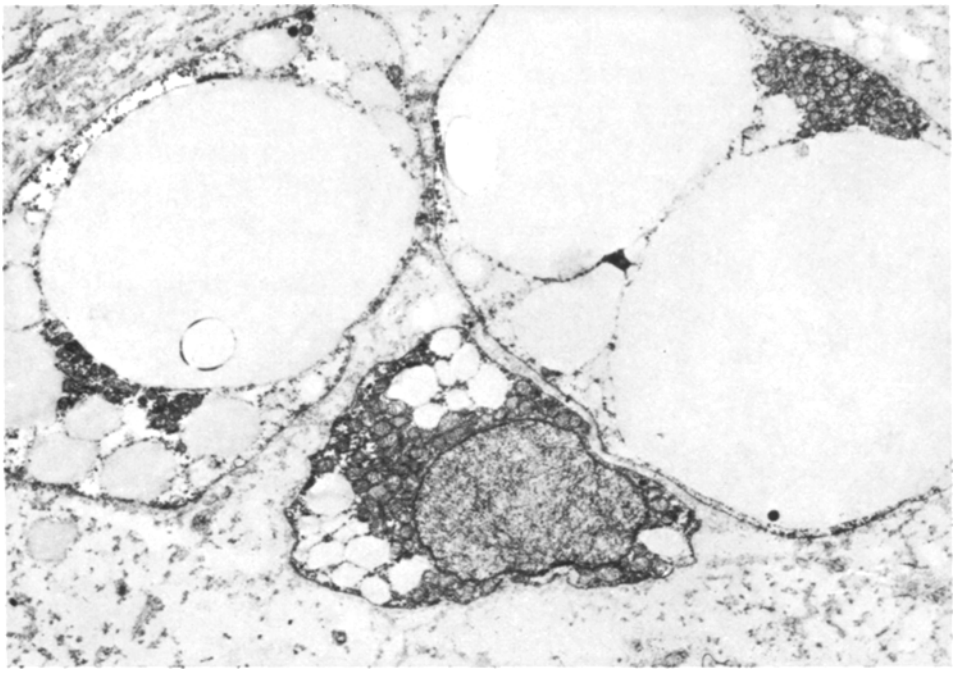

Fig. 8. Electron micrograph with three well differentiated lipoblasts characterized by a cytoplasm which contains coalescing membrane-bound lipid vacuoles, clusters of mitochondria and glycogen particles. Aggregates of finely granular and poorly osmiophilic material are observed within the intercellular matrix. (×2,840)

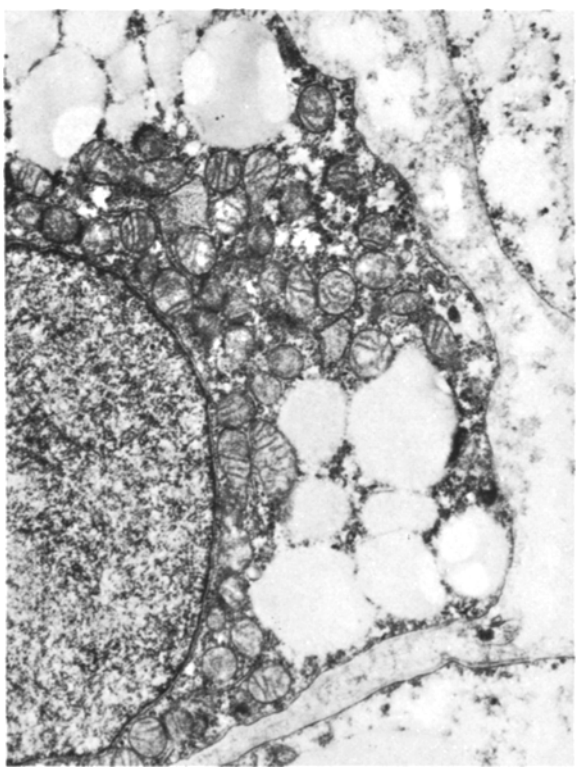

Fig. 9. Higher magnification from Fig. 8 showing abundant pleomorphic mitochondria, lipid vacuoles and glycogen rosettes. A discontinuous irregular basement membrane is seen along the cell borders. (×10,800)

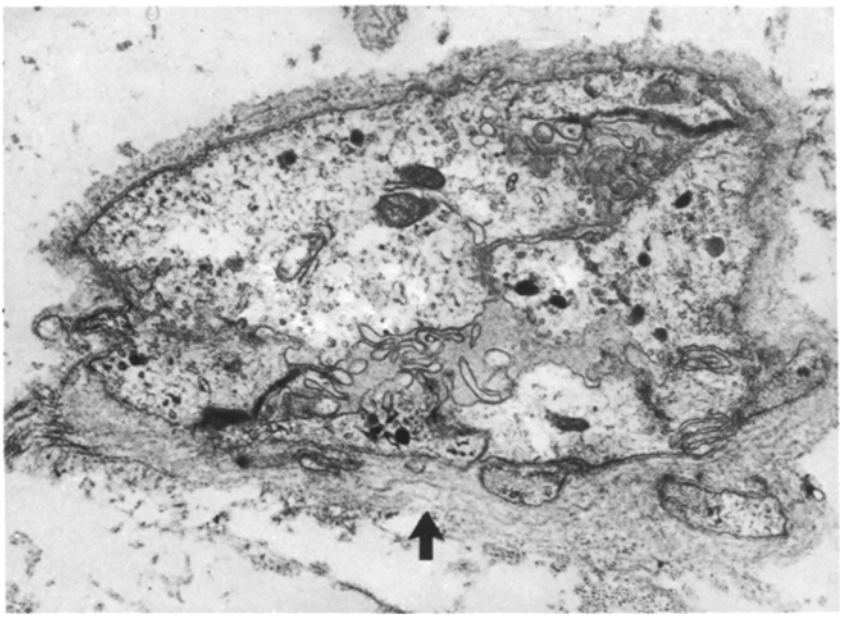

Fig. 10. Electron micrograph shows a tangential section through a vessel with hyperplastic endothelial cells. Notice the striking pinocytotic activity and the multilayered basement membrane (*arrow*). (×8,960)

in association with a layer of a finely granular material. Well-differentiated voluminous lipoblasts were occasionally observed (Figs. 8 and 9). Their cytoplasm was nearly filled with large membrane-bound lipid vacuoles. Variable numbers of round to elongated mitochondria were admixed with vesicles of endoplasmic reticulum. Surface pinocytotic activity was evident; the cell membranes were often coated by an ill-defined layer of finely granular material.

The stroma was composed of abundant granular and fine fibrillar material, but only scant collagen. Numerous vessels were observed.

The tumor vasculature, whether arteriolar, venular, or capillary, displayed prominent endothelial cells. A multilayered basal lamina was consistently noted often in close association with granular aggregates of the extracellular stroma, the latter probably correspond to mucopolysaccharides (Fig. 10). Pericytes, in addition to their usual features, occasionally contained large aggregates of glycogen.

Discussion

Adipose tissue is metabolically active and labile. Species differences, age, nutritional status, environmental temperature, body site, and technique of tissue processing along with the lability contribute to the complexity of the topic (Napolitano, 1965). The developmental biology, structure, lipid composition, and physiological responses of the principal types of adipose tissue have been

Table 2. Comparative ultrastructural features

	White adipose tissue	Brown adipose tissue
Volume of cell	120 μ	25–40 μ
Cytoplasmic vacuoles	Coalescing inclusions (Single unilocular)	Several small inclusions
Mitochondria		
Number	±	++++
Pleomorphism	±	+++
Glycogen	−	+
Cytoplasmic membranes		
SER	+	−
Golgi	±	±
Plasma membranes		
Pinocytosis	+++	++
Basement membrane	±	++
Focal condensations	−	++
Interstitium		
Vessels	+	++++
Nerves	±	++
Collagen	±	+

described; (Napolitano, 1963; Tedeschi, 1965; Wasserman, 1965; Merklin, 1973; Seemayer et al., 1975) the salient comparisons essential to the discussion of ML will be considered.

Comparative ultrastructural features between brown and white adipose tissue are summarized in Table 2. The principle differences are cell volume, mitochondrial number and pleomorphism, cytoplasmic membrane systems development, glycogen content, and extent of innervation and vascularization. A morphological spectrum exists between multilocular brown fat and unilocular white fat in developmental biology (Sheldon, 1965). However, when fully developed the two types of adipose tissue are structurally, biochemically and functionally distinct (Das Gupta, 1970).

The literature contains a limited number of ultrastructural studies of ML (Scarpelli and Greider, 1962; Kalderon and Fethiere, 1973; Flenker, 1976; Gould et al., 1976; Feldman, 1979; Kindblom and Säve-Söderbergh, 1979). An early study, a detailed correlative cytochemical and electron microscopic analysis of a myxoid liposarcoma, described five principle cell types (Scarpelli and Greider, 1962). Significant features included abundant and pleomorphic mitochondria, limited cytoplasmic membrane systems, surface pinocytotic activity and discontinuous basal lamina. The mitochondria were considered similar that described in brown fat (Lever, 1957). It was, therefore, suggested that the mitochondria in the tumor "may represent the type of mitochondrion associated with embryonic fat cells".

A comparative ultrastructural study between one case of myxoid liposarcoma and pleomorphic liposarcoma denoted significant differences between the two (Kalderon and Fethiere, 1973). It was suggested that both were derived from

Table 3. Comparative ultrastructural features

	Hibernoma	ML
Volume of cells	25–75 μ	25–70 μ
Cytoplasmic vacuoles	Several small inclusions	Several small inclusions to coalescing
Mitochondria		
Number	++++	+to+++
Pleomorphism	+++	++to+++
Matricial inclusions	+	±
Glycogen	scant	scant
Cytoplasmic Membranes		
RER	+	+to++
SER	+	+
Golgi	±	++
Plasma membranes		
Pinocytosis	+to+++	+to+++
Basement membrane	+++	+to+++
Focal condensations	−to+++	+to++
Interstitium		
Vessels	+++	+++
Relation of vessels to cells	+++	+to++
Reticulin	±	+
Myxoid matrix	−	+++

white fat. The neoplasm considered to represent myxoid liposarcoma is described and illustrated as demonstrating mitotic figures and conspicuous nuclear hyperchromasia and pleomorphism.

Another fine-structural study of a single case of ML depicts two principal types, multivacuolar lipocytes and fibroblast-like cells. It was concluded that the ML contained cells which resembled fetal fat (Flenker, 1976).

Describing the comparative electron microscopic findings between intramuscular myxoma and ML, Feldman (1979) emphasized the extensive content of cytoplasmic lipid in ML. Gould and colleagues (1976) described ultrastructural comparisons between hibernoma, ML and pleomorphic liposarcoma. In ML, the cells were round to spindle shaped and contained lipid or finely floculent material within cytoplasmic vacuoles. Focal basal lamina formation was also noted. It was concluded that the ability to form membrane-bound cytoplasmic lipid and basal lamina reflected a degree of cytodifferentiation in hibernoma and ML, neither of which was present in pleomorphic liposarcoma.

In a recent report on the ultrastructure of 10 cases of liposarcomas including 2 cases of myxoid liposarcoma and 1 case of predominantly myxoid liposarcoma with round-cell areas, Kindblom and Säve-Söderbergh (1979) have shown the presence of spindle and stellate shaped cells whose rough endoplasmic cisternae were filled with an amorphous and granular material of varying density. Similar material was observed within membrane-bound vesicles and vacuoles which appeared to be ruptured and the contents of which extruded into the extracellular space. Lipid cytoplasmic vacuoles were observed in most cells. From this study, it has been stated that a relationship could exist between myxoid and round-cell liposarcoma. Based upon the "variegated cellular appearance of the different

subtypes of liposarcoma", it was suggested that all liposarcomas could represent histogenetically a single entity.

Ultrastructural studies of hibernoma (Levine, 1972; Dardick, 1978) have demonstrated a range of cell size (25–75 mμ), well-developed basal lamina, lysosomes with transition to lipofuscin granules, abundant pleomorphic mitochondria, fat vacuoles of variable size, poorly-developed membrane and Golgi systems, cytoplasmic and rare pinocytotic vesicles and an intercellular space containing abundant capillaries and fine reticulin fibers.

We have compared our ultrastructural findings in ML with a previously studied hibernoma (Seemayer et al., 1975). The comparative features are summarized in Table 3. The configuration of cytoplasmic vacuoles in hibernoma and the better differentiated lipoblasts of ML is similar. The vacuoles in each are membrane bound and often fused. Pleomorphic, abundant mitochondria, a constant in hibernoma, are observed both within better differentiated lipoblasts and the intermediate cell type of ML. Mitochondrial matricial dense bodies described in hibernoma were rarely seen in ML. In both neoplasms limited amounts of glycogen are present. Cytoplasmic membranes are generally poorly developed in hibernoma and the primitive mesenchymal cells and well-developed lipoblasts of ML. In contrast intermediate cells and poorly developed lipoblasts of ML contain a well-developed cytoplasmic membranous system, the content of which is indistinguishable from the extracellular granular matrix. These observations are in agreement with previous histochemical (Enzinger and Winslow, 1962) and electron microscopic findings (Kalderon and Fethiere, 1973) which suggested that one cell type in ML synthesized mucopolysaccharides which are deposited as extracellular matrix, thus accounting for the mucoid quality of the tumor. ML and hibernoma share some features of plasma membrane differentiation. Pinocytotic activity is observed in both although it was most apparent in better differentiated lipoblasts of ML. A well-defined basement membrane delineates cell contours in hibernomas and the better differentiated lipoblasts of ML. However, in all three cell types of ML, basement membrane formation of varying development is demonstrable. The subplasmalemmal focal condensations in "primitive" mesenchymal cells, intermediate cells and poorly differentiated lipoblasts are also present in hibernoma. The relation of tumor cells to the vascular network in ML appears less organoid than hibernoma, yet, the prominent vascularity of ML is reminiscent of hibernoma and human brown adipose tissue.

In summation, hibernoma and ML share many ultrastructural features, particularly when comparisons are drawn between the better differentiated lipoblasts of ML and hibernoma. The structural similarities include cell volume, cytoplasmic lipid vacuoles, pleomorphic, abundant mitochondria and features of plasma membrane differentiation. Although the vascular network of ML does not reproduce the intimate cell-vessel relation observed in hibernoma, it is nevertheless unique. The most notable difference between the two was reflected by the cytoplasmic membrane system which is rarely observed in hibernoma but well-developed in the intermediate cell and immature lipoblast of ML. The dilated cisternae of rough endoplasmic reticulum containing a material similar to the extracellular matrix and the prominent Golgi in ML are probably responsible for the abundant extracellular myxoid matrix.

The multilayered basal lamina of the vasculature of ML deserves consideration. This feature has been described in association with human and experimental epithelial neoplasms associated with a favorable prognosis (Tarin, 1969; Gould et al., 1972; Cooper and Waisman, 1973). Similar findings have been reported in granular cell tumor of soft tissue (Cooper, 1974), low grade vascular neoplasms (Ramsay, 1966) and the myxoid variant of malignant fibrous histiocytoma (Lagacé et al., 1979). The significance of this observation is, as yet, unclear. However, its striking concurrence with neoplasms which pursue a relatively indolent course suggests a possible role in tumor containment.

Hibernoma has been viewed for more than 60 years as a tumor derived from brown adipose tissue, a concept supported by structural and biochemical studies. The histogenesis of liposarcomas, particularly the common myxoid variant, remains unsettled. Our findings suggest that ML may be derived from brown adipose tissue. This hypothesis is supported by a number of ultrastructural features common to ML, hibernoma and normal brown fat. Prospective studies of myxoid liposarcoma should include electron microscopy, biochemical assays of lipid and mitochondrial cytochrome systems, tissue culture, and inoculation into "nude" athymic mice, the latter to study the dynamics of invasion and tumor vascularization.

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