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Malignant Fibrous Histiocytoma

An Electron Microscopic Study of 17 Cases

Masazumi Tsuneyoshi[1], Munetomo Enjoji[1], and Norio Shinohara[2]

[1] Second Department of Pathology, Faculty of Medicine, Kyushu University, Fukuoka 812, Japan
[2] Department of Orthopedic Surgery, National Fukuoka Central Hospital, Fukuoka 810, Japan

Summary. The ultrastructural findings in 17 cases of malignant fibrous histiocytoma (MFH) are described. The tumors consisted of fibroblast-like cells and histiocyte-like cells in different proportions in different cases. Intermediate, undifferentiated, xanthomatous and multinucleated giant cells were also identified. In 12 of 17 cases myofibroblasts were evident. Acid phosphatase activity was detected cytochemically in the Golgi zone, endoplasmic reticulum and lysosomes (GERL) mainly within histiocyte-like cells, in three cases. These observations indicate that the GERL of the tumor cells are engaged in the formation of lysosomes. The polymorphic cellular composition, including undifferentiated cells, lends support to the concept that the MFH originates from a primitive multipotent undifferentiated mesenchymal cell.

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

Introduction

Malignant fibrous histiocytoma (MFH) has heretofore been considered probably to be of histiocytic origin (Kauffman and Stout 1961; Ozzello et al. 1963; O'Brien and Stout 1964), but more recently a possible origin from undifferentiated mesenchymal cells has been suggested (Fu et al. 1975, Taxy and Battifora 1977; Alguacil-Garcia et al. 1978; Weiss and Enzinger 1978; Lagacé et al. 1979; Reddick et al. 1979; Harris 1980; Enjoji et al. 1980). Ultrastructural descriptions of MFH created considerable interest among pathologists on account of the

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Offprint requests to: Dr. M. Enjoji, MD, Second Department of Pathology, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812, Japan

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variable cellular composition and the controversial histogenesis. We describe herein the fine structural characteristics of MFH and discuss the findings on the basis of a proposal concerning the histogenesis.

Materials and Methods

Seventeen cases of MFH were examined in our laboratory, using light and electron microscopy, during the period 1971 to 1979.

Tissues for light microscopy were processed in the usual manner following fixation in formalin. Sections were stained with haematoxylin and eosin. Special stains included Masson trichrome, silver impregnation for reticulin, periodic acid-Schiff, alcian blue and Prussian blue.

Electron microscopic examination was made on all seventeen cases. The fresh specimens were fixed in 3% glutaraldehyde solution (buffered pH 7.4). Some of the fixed blocks (3 cases), which were fixed for only 30 minutes by glutaraldehyde, were sectioned about 70 μ in a thickness of using a Vibrotome and were incubated for about 40 min in a modified Gomori medium for acid phosphatase reaction. The reacting and other prefixed specimens were 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 or only with lead citrate, and examined under a JEM 100 C electron microscope.

Results

Clinical Data

The clinical features of this series are summarized in Table 1.

Light Microscopic Findings

The seventeen cases in the present series included 13 pleomorphic tumors, one showing a typical storiform pattern and three tumors of myxoid variant of MFH. Each was composed of plump spindle, oval and polygonal cells with different degrees of atypia and pleomorphism, and presented poorly or well-

Table 1. Patient data of malignant fibrous histiocytoma

Case No.	Age	Sex	Location	Histological type
1	23	F	Thigh(rt.)	Pleomorphic type
2	36	M	Buttock(rt.)	Pleomorphic type
3	42	M	Thigh(rt.)	Pleomorphic type
4	45	M	Forearm(lt.)	Pleomorphic type
5	50	F	Upper arm(lt.)	Pleomorphic type
6	51	F	Shoulder(rt.)	Pleomorphic type
7	55	F	Chest wall(rt.)	Pleomorphic type
8	57	M	Thigh(rt.)	Pleomorphic type
9	59	M	Retroperitoneum	Pleomorphic type
10	65	F	Chest wall(lt.)	Pleomorphic type
11	68	F	Forearm(lt.)	Pleomorphic type
12	74	F	Thigh(rt.)	Pleomorphic type
13	76	M	Shoulder(lt.)	Pleomorphic type
14	76	M	Buttock(lt.)	Storiform type
15	55	M	Shoulder(lt.)	Myxoid variant
16	65	M	Thigh(rt.)	Myxoid variant
17	73	M	Upper arm(rt.)	Myxoid variant

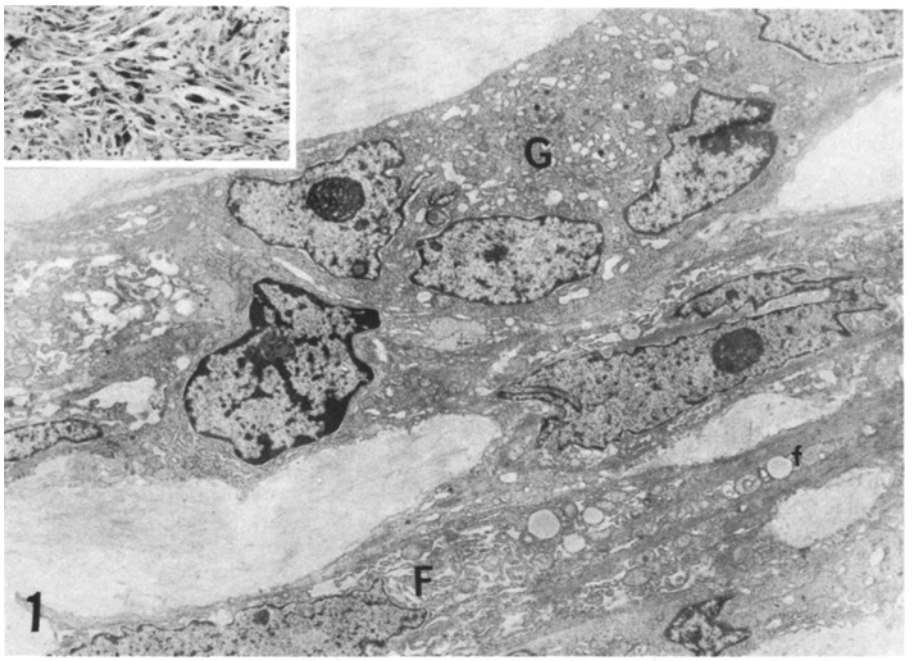
developed storiform patterns. The myxoid variant exhibited wide areas of a myxoid appearance and other tumors often had some myxoid areas. A gradual transition from one histological pattern to another was discernible. There were occasional aggregates of tumor giant cells, foam cells were sparse and inflammatory cells were rather numerous.

Electron Microscopic Findings

In all cases the tumors consisted of a heterogeneous cell population with variation in shape and size. Each was made up of several types of tumor cells which included undifferentiated, fibroblast-like, histiocyte-like, intermediate, xanthomatous and multinucleated tumor giant cells. However, two principal types, fibroblast-like and histiocyte-like, were always apparent, regardless of the area of the tumor examined.

The fibroblast-like cell was mostly spindle or polygonal in shape, with the cell membrane being either completely smooth or having a few short broad projections (Fig. 1). The nuclei were large and frequently contained nucleoli and the nuclear envelope often showed complicated folds or invaginations. The cytoplasm contained a scanty or more abundant population of organelles. The rough endoplasmic reticulum was well-developed, and frequently there was a slight dilatation of the cisternae. The Golgi zone and the smooth endoplasmic reticulum were sometimes well developed, abundant ribosomes, varying numbers of mitochondria and occasional lysosomes were also evident. Some of the fibroblast-like cells contained filament bundles with focal dense bodies in the peripheral area of the cytoplasm (Fig. 1). These cells were identical with myofibroblasts.

The second type, a histiocyte-like cell, presented more variable fine structure (Fig. 2). Individual cells of this type varied in shape and ranged from elongated to ovoid or stellate. The cell membrane was ruffled, and pseudopodia and filopodia were common. The nuclei were oval or indented with peripheral heterochromatin clumps. The bulky cytoplasm contained variable numbers of dense bodies of various sizes which were usually bounded by a distinct membrane and were probably lysosomal in nature. In some of these cells there was evidence of phagocytosis and erythrocytes or phagocytic vacuoles were detected in the cytoplasm (Fig. 3). The rough-surfaced endoplasmic reticulum was not conspicuous. Abundant ribosomes, moderate amounts of smooth endoplasmic reticulum vesicles, moderate-developed Golgi zones and mitochondria were identified. Occasional lipid droplets were also seen. Intracytoplasmic hyaline globules were noted in the histiocyte-like tumor cells in one cases examined under light microscopy. The globules were composed of a number of well or ill-defined bodies and a finely granular matrix. These bodies, of variable sizes with a round to ovoid contour, also had a varied electron density ranging from finely granular to electron-lucent (Fig. 4). Several characteristic Langerhans cell granules, flattened membrane enclosed structures with a central periodic core, were recognized in some histiocyte-like tumor cells of a postirradiation MFH (Tsuneyoshi and Enjoji 1980) (Fig. 5). "Nuclear body" type inclusions were sporadically visible in the nuclei of both histiocyte-like and fibroblast-like cells (Bouteille et al. 1967).



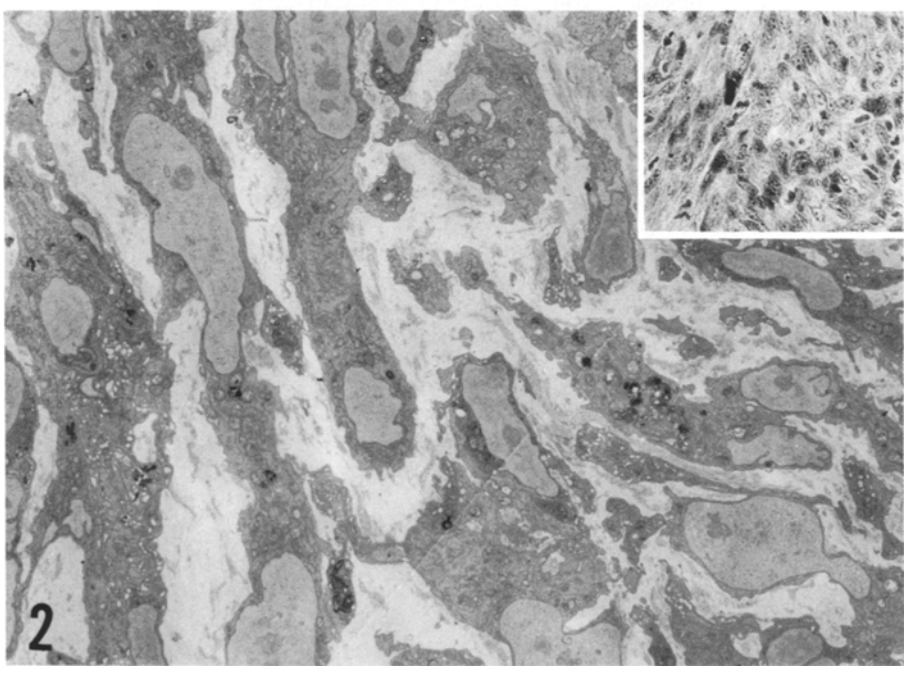
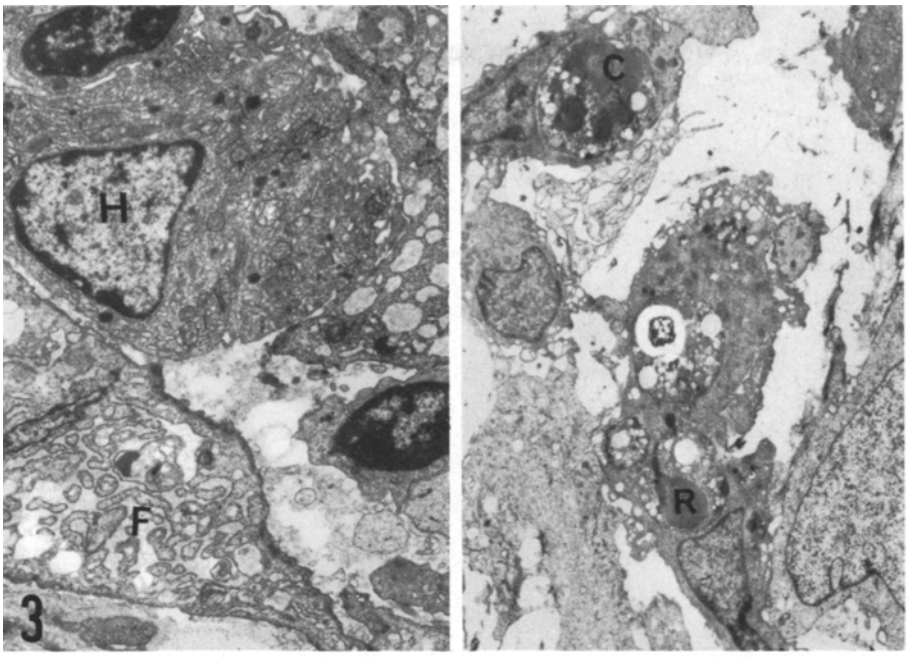


Fig. 1. Case 10. Electron micrograph showing fibroblast-like cells with well-developed rough endoplasmic reticulums (*F*). Two of the cells contain intracytoplasmic bundles of filaments with focal densities (*f*). There is a multinucleated giant cell of fibroblast-like type (*G*) (×5,000). Inset: Light micrograph of this pleomorphic tumor (H and E, ×90)

Fig. 2. Case 7. Histiocyte-like cells with abundant cytoplasm and cytoplasmic pseudopodia. Occasional lysosomes are evident (×5,000). Inset: Light micrograph of this pleomorphic tumor (H and E ×232)



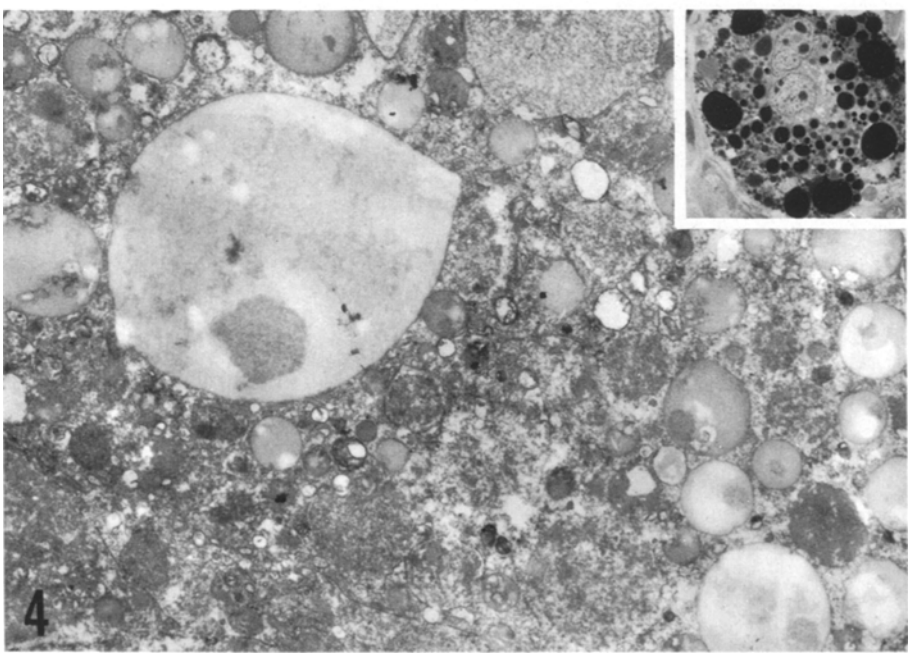


Fig. 3. Left: Case 3. Histiocyte-like cell containing lysosomes (*H*) and fibroblast-like cells having many dilated rough endoplasmic reticulums (*F*) (×9,700). Right: Case 17. Histiocyte-like cells with phagolysosomes, containing some degenerated cell (*C*) and erythrocyte (*R*) (×4,800)

Fig. 4. Case 8. Electron micrograph of intracytoplasmic hyaline globules showing round or ovoid contour and variable electron density (×8,300). Inset: Light micrograph of thick section of epoxy resin block showing these intracytoplasmic hyaline globules (toluidine blue stain, ×400)

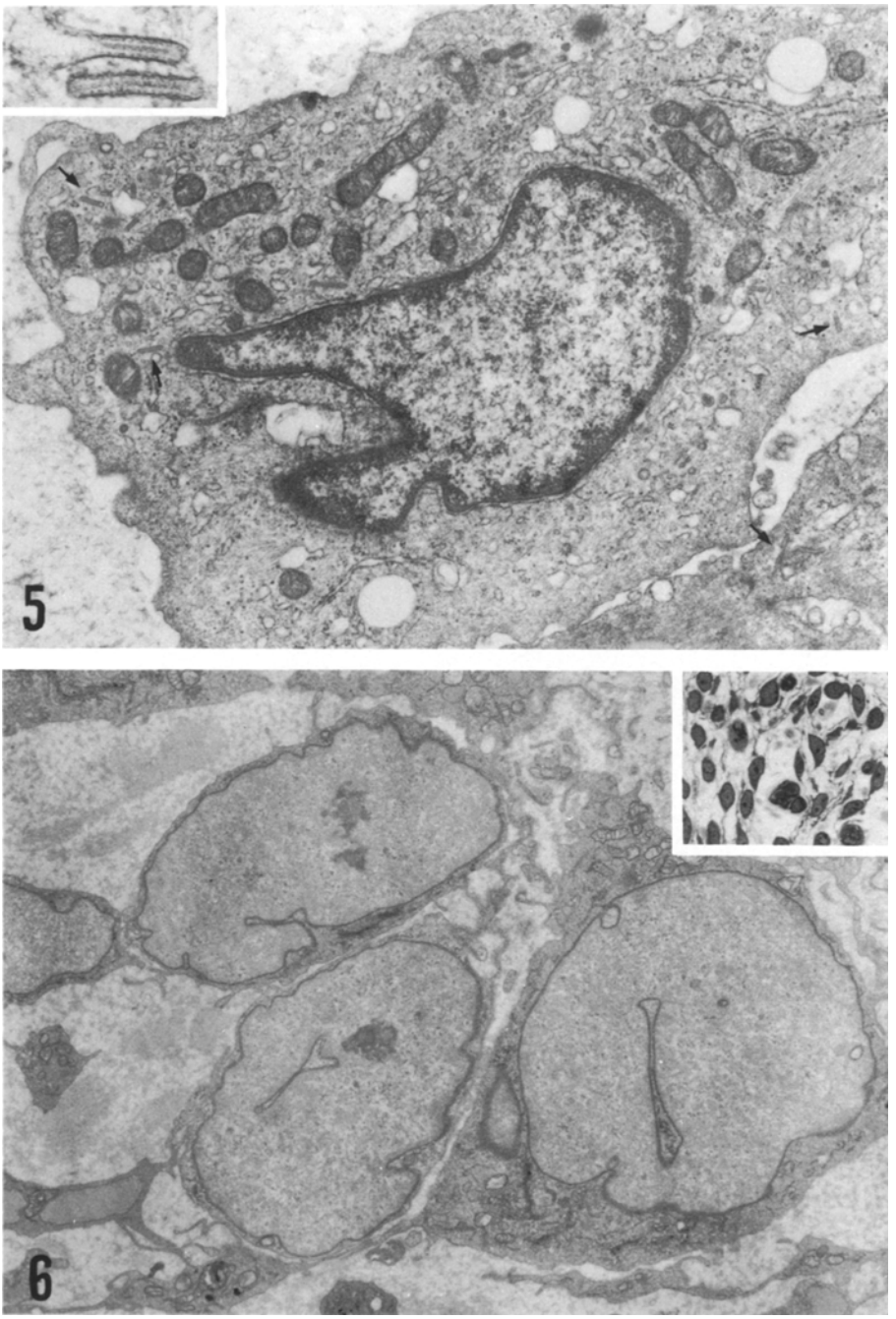
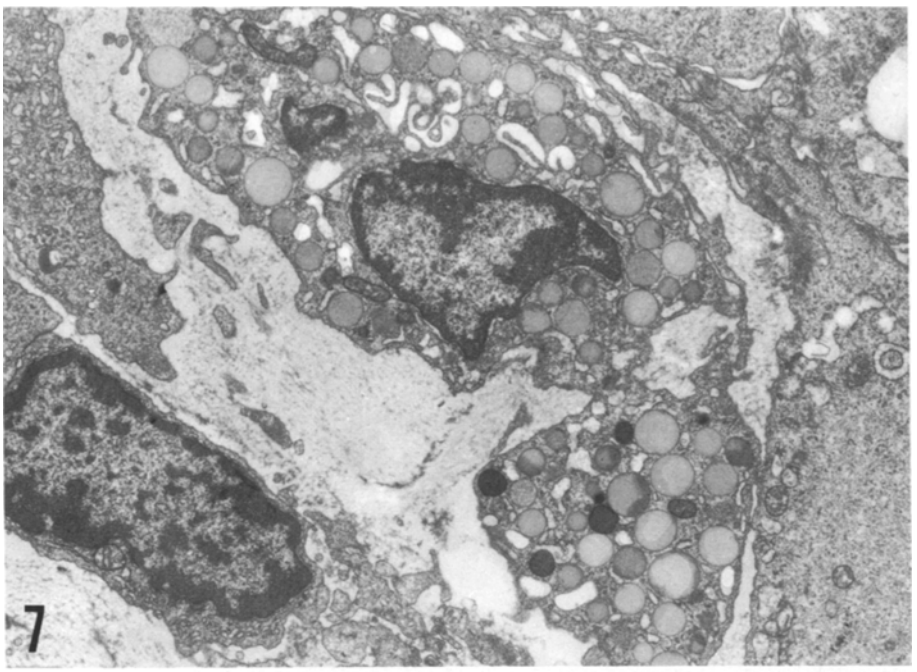


Fig. 5. Case 10. Histiocyte-like cells with abundant cytoplasm containing characteristic Langerhans cell granules (arrow) (×16,200). Inset: High magnification of two Langerhans cell granules (×75,000)

Fig. 6. Case 16. Undifferentiated tumor cells are relatively small and have a scanty cytoplasm with few organelles (× 6,500). Inset: Light micrograph of thick section of epoxy resin block (toluidine blue, × 380)



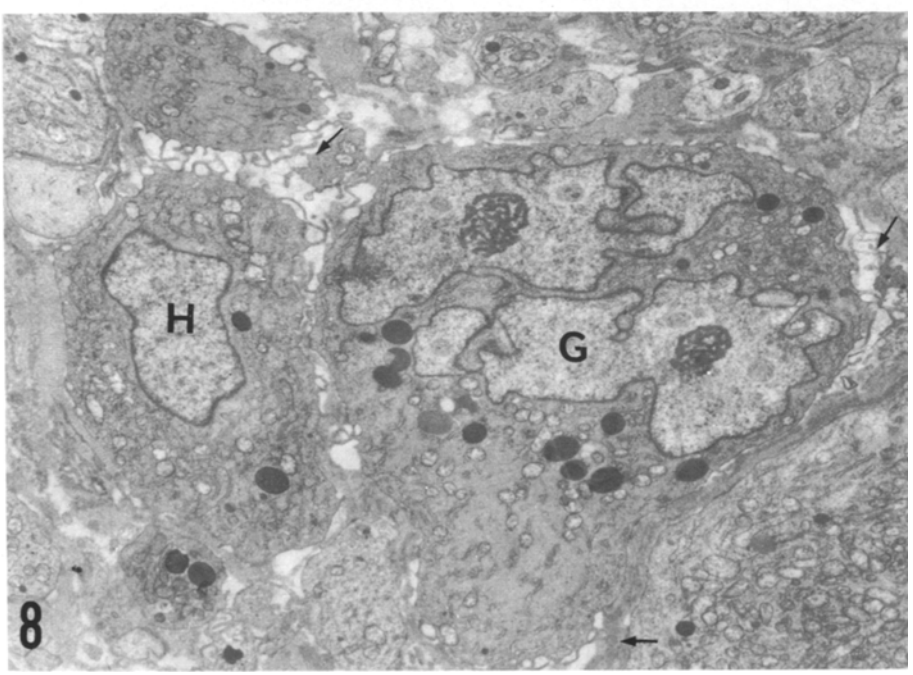
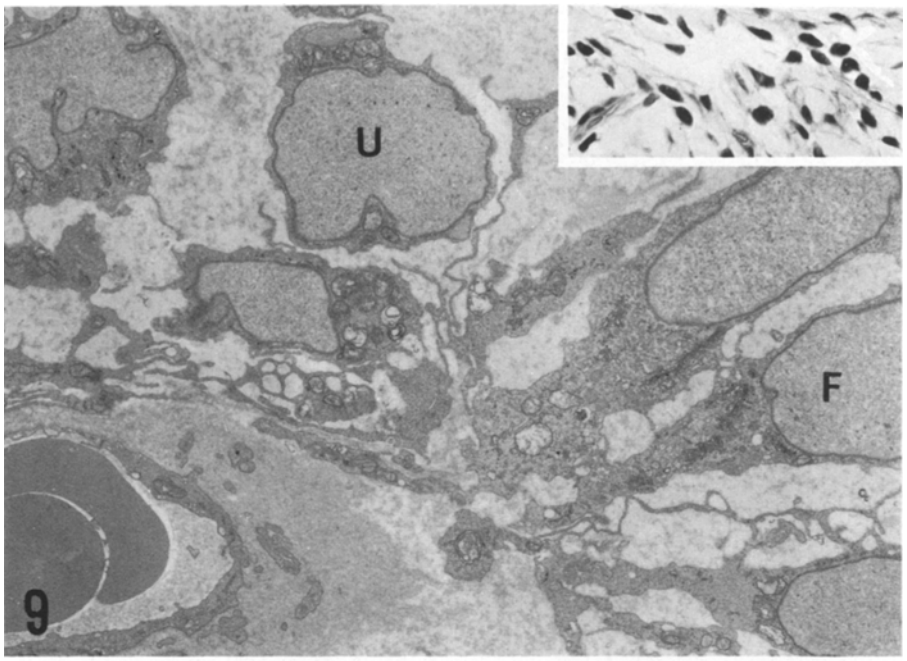


Fig. 7. Case 3. Xanthomatous cell containing membrane bound lipid droplets ($\times$ 13,000)

Fig. 8. Case 6. Multinucleated tumor giant cell of histiocyte-like type (*G*) having lipid droplets and delicate cytoplasmic prolongations (arrows). Histiocyte-like cells (*H*) with filopodia-like projections (arrow). ($\times$ 6,800)



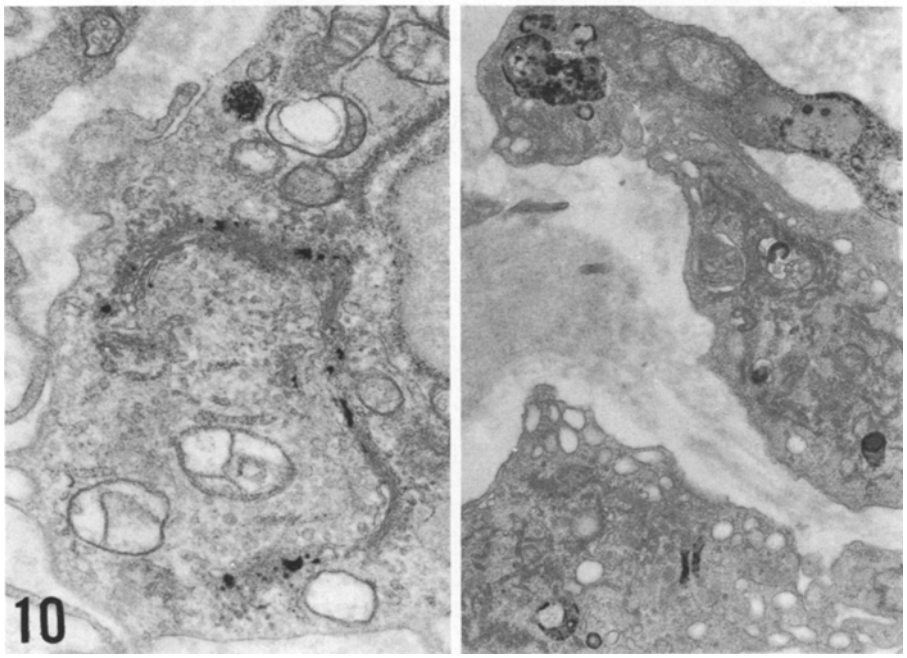


Fig. 9. Case 16. Electron micrograph of a myxoid tumor showing undifferentiated cells (*U*) and spindle cell of fibroblast type (*F*). The extracellular matrix contains a finely granular material (× 10,000). Inset: Light micrograph of the myxoid tumor (× 380)

Fig. 10. Left: Case 16 (× 24,000). Right: Case 7 (× 25,000). Electron micrograph of cytochemistry for acid phosphatase. A crystalline precipitate of lead phosphate reaction product in Golgi zone, endoplasmic reticulums and lysosome

In addition to the above two cell types, lesser numbers of other cell types were identified. Some tumor cells exhibited morphological characteristics intermediated between those of fibroblasts and histiocytes and were difficult to classify. These intermediate tumor cells displayed considerable variation in configuration and organelle composition but had a well-developed rough endoplasmic reticulum with dilated cisternae and occasional lysosomes in the abundant cytoplasm. Undifferentiated tumor cells were irregularly distributed, and were characterized by being relatively small and ovoid or polygonal and by having a smooth cell surface and a round or indented nucleus (Fig. 6). The thin rim of the cytoplasm of these cells contained few such organelles as ribosomes and mitochondria. In a greater cyto-differentiation of the above cells, the nuclei were often indented and the cytoplasm displayed pseudopod-like extensions and more substantially developed intracytoplasmic organelles. Xanthomatous tumor cells were rarely observed and were characterized by filopodic cytoplasmic extensions, empty vesicle and membrane-bound lipid droplets which appeared either as empty spaces or homogeneous electrondense material (Fig. 7). Multinucleated giant cells having two or more nuclei were not common and showed irregular, often deeply indented nuclear membranes and cytoplasmic invaginations. The giant cells could be separated into two types, fibroblast-like and histiocyte-like. The former cells were featured by a well-developed rough endoplasmic reticulum (Fig. 1), and the latter by the presence of numerous delicate cytoplasmic prolongations, occasional lysosomes and scanty mitochondria and ribosomes (Fig. 8).

In the pleomorphic MFH, the cell population consisted of the several different cell types described. The relative numbers of cells depended on the portions examined within the tumor. In the storiform tumor, the cell population was mainly a mixture of fibroblast-like cells, histiocyte-like cells and intermediate cells, although the fibroblast-like cells predominated. In the myxoid variant, several cell types were observed. Among them, undifferentiated, fibroblast-like and histiocyte-like cells were noted in most cases (Fig. 9). The extracellular matrix of the myxoid tumor was made up of finely granular material with occasional microfibrils and rarely collagen.

Tumor cells showing specific cyto-differentiation towards lipoblasts or rhabdomyoblasts were not seen.

Cytochemistry for Acid Phosphatase by Electron Microscopy (3Cases)

Acid phosphatase activity was detected in numerous intracytoplasmic locations, mainly in the histiocyte-like cells. A coarse, crystalline precipitate of lead phosphate reaction product was identified in Golgi zones, endoplasmic reticulum, primary lysosomes and residual bodies of the tumor cells (Fig. 10).

Discussion

Following early ultrastructural studies of MFH (Merkow et al. 1971; Fu et al. 1975), there is now a more distinct appreciation of the tumor cell types (Taxy and Battifora 1977; Alguacil-Garcia 1978; Lagace et al. 1979; Reddick et al.

1979; Harris 1980). In addition to fibroblast-like and histiocyte-like cells, several different tumor cell types were detected in the tumor; i.e., intermediate-type, xanthomatous, multinucleated tumor giant cells and undifferentiated cells. The present electron microscopic study of 17 MFH again revealed the two major cell types, fibroblast-like and histiocyte-like cells and in addition confirmed much the same cellular composition as described above. Although the relative numbers of these cells varied with the tumors or even in different portions of the same tumor, on morphological grounds, each cell type appeared to participate in the neoplastic process.

The presence of an undifferentiated cell type in MFH was described by Fu et al. (1975) and by Alguacil-Garcia et al. (1977) and in an atypical fibrous histiocytoma of the humerus by Saito and Caines (1977). The undifferentiated cells were identified, albeit in small numbers, in all 17 cases of the present series. The presence of these cells led to the proposal of Fu et al., that MFH originates from undifferentiated mesenchymal cells, an alterative to the view of Kauffman and Stout'.

A striking discovery was the finding of Langerhans cell granules in some histiocyte-like tumor cells in a postirradiation MFH (Tsuneyoshi and Enjoji 1980). Another was that intracytoplasmic hyaline globules were detected ultrastructurally in histiocyte-like tumor cells of an MFH. These globules have also been detected in other human malignant tumors (Dekker and Krause 1973; Mori et al. 1974) and, on the basis of their staining and ultrastructural details, were considered to be lipoprotein or glycoprotein. Myofibroblasts having bundles of intracytoplasmic myofilaments with dense bodies were regarded as a common constituent in MFH by Churg and Kahn (1977) and by Harris (1980). These cells were detected in the majority of cases of our series, and were essentially identical to fibroblasts, probably having a contractile function.

Depending on subtypes or histological patterns of MFH, the cellular composition of tumors was variable. The pleomorphic tumor had a great variety of cell types, whereas the storiform tumor was composed mainly of fibroblast-like cells and a lesser number of histiocyte-like and intermediate cells. The myxoid variant tumor consisted principally of undifferentiated cells and two partially cyto-differentiated cell lines, invariably toward histiocyte-like and fibroblast-like cells. In addition, no tumor cells displayed lipoblastic, rhabdomyoblastic or any other specific cyto-differentiation.

Acid phosphatase activity detected by cytochemical electron microscopy was found in Golgi zones, endoplasmic reticulum and the lysosomes (GERL) of tumor cells, particularly of histiocyte-like cells, in three cases examined. The GERL of the tumor cells probably contributes to the formation of lysosomes. This activity has not previously been reported in cases of MFH.

The exact histogenesis of MFH remains uncertain. Several authors (Fu et al. 1975; Taxy and Battifora 1977; Alguacil-Garcia et al. 1978; Weiss and Enzinger 1978; Reddick et al. 1979; Harris 1980; Enjoji et al. 1980) reported that rather than an histiocytic origin (Merkow et al. 1971; Yumoto et al. 1979; Miller et al. 1980), there was a wide range of potential differentiation from the undifferentiated cells actively participating in the neoplastic process, thus, these cells were converted to fibroblast-like, histiocyte-like, intermediate-type, xanthoma-

tous and multinucleated giant tumor cells. On the basis of the present ultrastructural and cytochemical studies, the demonstration of various tumor cell types admixed with undifferentiated cells and intermediate forms supports this concept.

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