Virchows Arch [Pathol Anat] (1981) 391:323–335

Virchows Archiv A
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Malignant Fibrous Histiocytoma of Bone

Light Microscopic and Electron Microscopic Examination of Four Cases

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Summary. Malignant fibrous histiocytoma (MFH) of bone is a well-defined tumor by light microscopy but no agreement has been achieved concerning its histogenesis. We present the light and electron microscopic findings of four cases of MFH of bone. In case 1 multiple bone tumors were observed and in case 4 the tumor developed after irradiation. It was our aim to document the cytological variability and to arrange the findings in a histogenetic concept of primary intraosseous MFH. We observed some undifferentiated cells but mainly histiocyte- and fibroblast-like cells including intermediate forms, and several types of giant cells. We should emphasize the fact that there were also some large cells with a light microscopic resemblance to rhabdomyoblasts and with electron microscopic characteristics of myoblastic differentiation. From the ultrastructural point of view, therefore, MFHs seem to derive from a primitive mesenchymal stem cell rather than from the ordinary histiocyte. It is suggested that osteosarcoma and MFH of bone may have a common progenitor cell but it is important to make a clear clinico-pathological distinction between the tumors because of differing biological behavior.

Key words: Malignant fibrous histiocytoma – Bone – Ultrastructural cytology – Myoblastic differentiation – Undifferentiated mesenchymal stem cell – Relationship to osteosarcoma

Introduction

Since the first recognition of malignant fibrous histiocytoma (MFH) as a distinct bone tumor in 1972 by Feldman and Norman about 150 cases of such bone tumors have been reported in literature (cp. Dahlin 1978; Uehlinger and Haferkamp 1978; Dunham and Wilborn 1979), but less than 20 cases have been examined by the electron microscope.

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0340-1227/81/0391/0323/$02.60

The histological structure of these bone tumors is well defined and corresponds to that of their soft tissue counterparts. The essential criteria are the storiform tissue pattern (at least in some areas) and the presence of fibroblastic and histiocytic cells and giant cells (Spanier et al. 1975). However, ultrastructural examination supplies fine-structural details and thus may be helpful in diagnosing histologically uncertain cases (Roessner et al. 1979).

There are unanswered questions concerning the histogenesis of these tumors. Many authors are convinced that MFHs derive from histiocytic cells (Stout and Lattes 1967; Merkow et al. 1971; Yumoto et al. 1976; Roessner et al. 1979) but more recently another concept has been elaborated which postulates that the histiocyte is not the cell of origin but rather, an undifferentiated mesenchymal cell which develops along fibroblastic and histiocytic cell lines (Fu et al. 1975; Taxy and Battifora 1977; Alguacil-Garcia et al. 1978). Moreover, it was suggested that MFHs of bone may not be a histological entity at all but may be virtually dedifferentiated osteosarcomas (Uribe-Botero et al. 1977).

In principle, electron microscopic examination of tumors elucidates their cytological fine structure and may give data useful in histiogenesis. We investigated four cases of osseous MFH electron microscopically hoping to

(1) recognize the cytological variability of tumor tissue, and

(2) to arrange the findings in a histogenetic concept of primary intraosseous MFH.

Patients and Methods

Four cases of MFH of bone were examined light and electron microscopically.

Case 1: 28-Year Old Man. He was admitted to hospital because he suffered from bone pain. A lytic defect in his right proximal tibia was found on radiography. A thorough examination revealed a further area of radiolucency in his left proximal humerus. A biopsy was taken from the tibia and the diagnosis of fibrous histiocytoma of bone was made. 4 months later he noticed a swelling of the left toe. X-ray examination revealed an almost complete destruction of the end phalanx and ablation of the toe was performed. Light microscopic diagnosis: aggressive fibrous histiocytoma. Material was taken for electron microscopic examination. 3 months later a pea-sized skin nodule developed in the left forefoot. On histiological examination an aggressive fibrous histiocytoma was again diagnosed. The course of the disease suggested a malignant process. Later, the patient was lost to follow-up examinations.

Case 2: 66-Year Old Man. Because of bone pain in the right arm and a markedly reduced mobility of this limb X-ray examination was carried out. Ill defined confluent areas of radiolucency were seen in the right humerus (proximal metaphysis and caput humeri). Proximal humerus and joint-near parts of the scapula were removed surgically. The tumor had penetrated the cortex and invaded the surrounding muscular tissue. Histological diagnosis: malignant fibrous histiocytoma. The postoperative recovery was uneventful.

Case 3: 22-Year Old Man. The patient was operated on under the clinical suspicion of a malignant bone tumor (probably osteosarcoma) of the left proximal tibia. The tumor had completely penetrated the cortex of bone so that in paraosseous regions tumor tissue was also present. The tumor had a size of $6 \times 6 \times 5$ cm. Histologically a typical malignant fibrous histiocytoma of bone was diagnosed. X-ray examination demonstrated a second lesion in the left zygoma. On biopsy a metastasis was excluded and it was shown that there was a desmoplastic mesenchymal lesion without the structural pattern of fibrous histiocytoma.

Case 4: 60-Year Old Woman. 18 years ago an ablation of the breast was performed because of a left-sided breast cancer. The operation was followed by irradiation. 3 months before her death

she complained of pain and swelling of the left arm. After admission to hospital because of an attempt at suicide a rapid deterioration of her condition occurred and she succumbed to pneumonia. At autopsy a $5 \times 4 \times 4$ cm malignant fibrous histiocytoma of the left-sided proximal humerus was found which was interpreted as post-irradiation sarcoma. There were metastases in various thoracic vertebrae, lungs, liver and thyroid gland.

Samples for light microscopic investigation were fixed in 10% neutral formalin, embedded in paraffin and cut into 5 mμ thick sections. The following stains and reactions were performed: H&E, elastica-Domagk, Goldner's and Mallory's trichrome stain, silver impregnation after Gömöri, Sudan black for demonstration of lipids, Prussian blue, periodic acid-Schiff reaction, Alcian blue staining at different pH (0.5, 1.0 and 2.5) and the Alcian blue staining at different electrolyte concentration (CEC method after Scott and Dorling). For demonstration of lipids frozen sections were also used and stained with Sudan III.

Tissue for electron microscopic examination was fixed in ice-cold 2.5% glutaraldehyde (buffered with cacodylate buffer at pH 7.2) for 2 hours, postfixed in osmium tetroxide for 1 h and embedded in Mikropal. From case 4 material for electron microscopy was prepared by re-embedding formalin fixed tissue in Mikropal. Semithin sections were stained with toluidine blue, ultrathin sections were contrasted with uranyl acetate and lead citrate.

Results

Light Microscopy

The most characteristic histological feature was the storiform growth pattern, predominant in all cases. It is defined as a cartwheel-like or matting-like tissue structure. Although there were slight variations in the cytological findings, yet fibroblast-like and histiocyte-like cells could always be identified as the main cell types (Figs. 1, 2).

In spite of many cytological similarities there were also some marked differences between the tumors. Case 1 did not show striking cellular atypia. We found spindle-shaped fibroblast-like and relatively cytoplasm-rich histiocyte-like cells. The latter cellular elements seldom contained lipids or stored iron, their nuclei showed prominent nucleoli. Giant cells were rarely seen. A remarkable finding in this case was the presence of large cells with an excentric nucleus bearing some resemblance to rhabdomyoblastic cells (cp. Fig. 6 inset). In cases 2, 3 and 4 apart from spindle-shaped fibroblast-like cells more pleomorphic, histiocyte-like cells and many giant cells were observed. In places giant cells appeared also to be polymorphic or showed the features of Touton cells (especially in case 3 – Fig. 1c and Fig. 2 inset). Osteoclast-like giant cells were seldom noticed. Foamy cells were rarely detected. It is noteworthy that except for case 1 different regions of the same tumor showed a variable amount of intercellular substance. This was predominantly reticular and collagen fibers, and acid mucopoly-saccharides were scanty. In addition, varying numbers of interspersed inflammatory cells must be mentioned (lymphocytes and some granulocytes).

The metastases of case 4 showed essentially the same picture as the primary bone tumor.

Electron Microscopy

Ultrastructurally there was a broad spectrum of cytological pictures, but the majority of cells possessed structural characteristics of either histiocytes or fibroblasts, or of both cell types (Figs. 3, 4, 5).

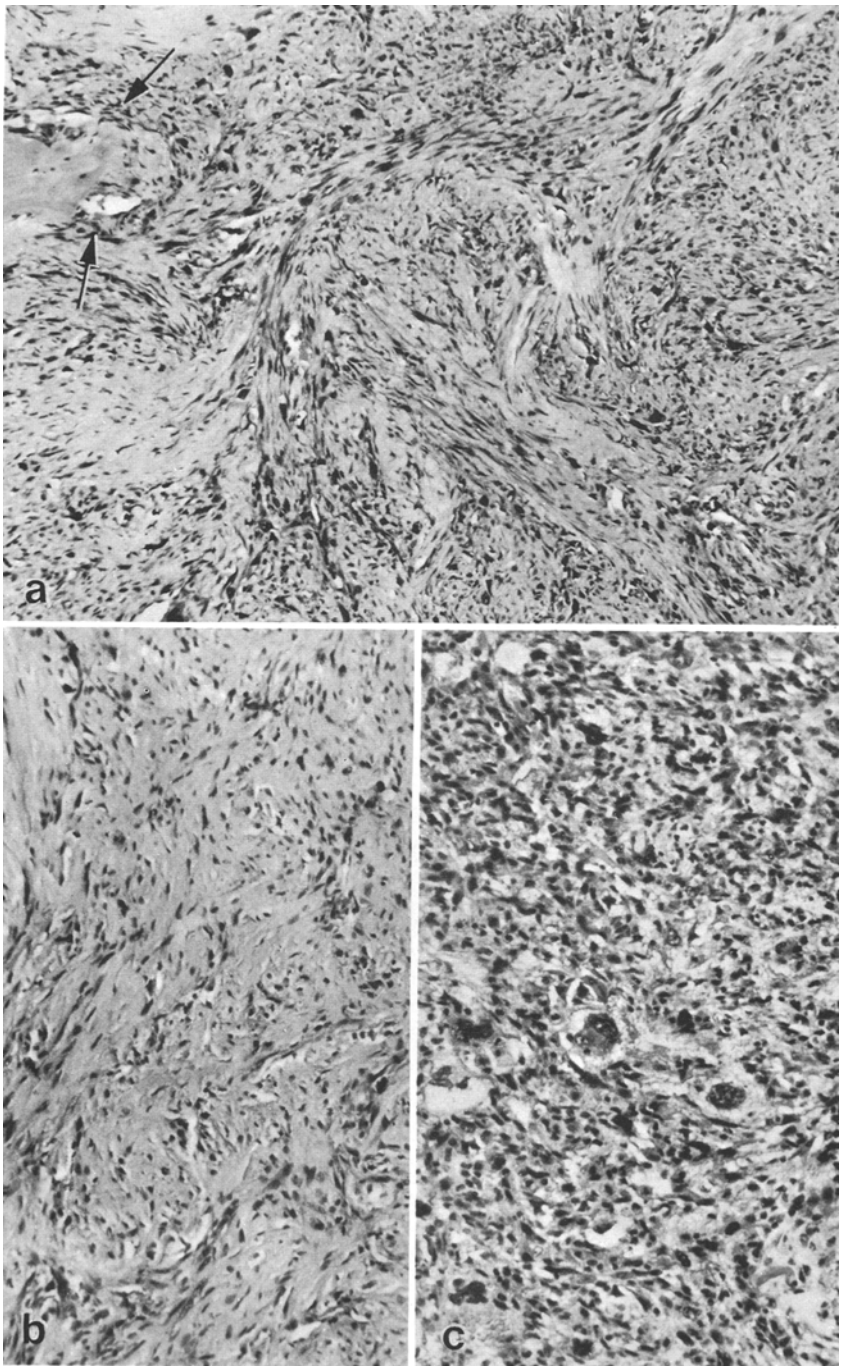

Fig. 1 a–c. Histological features of malignant fibrous histiocytoma of bone. **a** Interwoven fascicles of fibroblast-like cells form the storiform growth pattern. Note scattered larger atypical cells. Bony trabeculum (→) (HE, 160:1). **b** The storiform growth patterns is visible. There are predominantly fibroblast-like cells and a moderate amount of partly hyalinized intercellular substance (HE, 160:1). **c** The picture is dominated by histiocyte-like cells. Moreover, some Touton-like giant cells are also detectable (HE, 160:1)

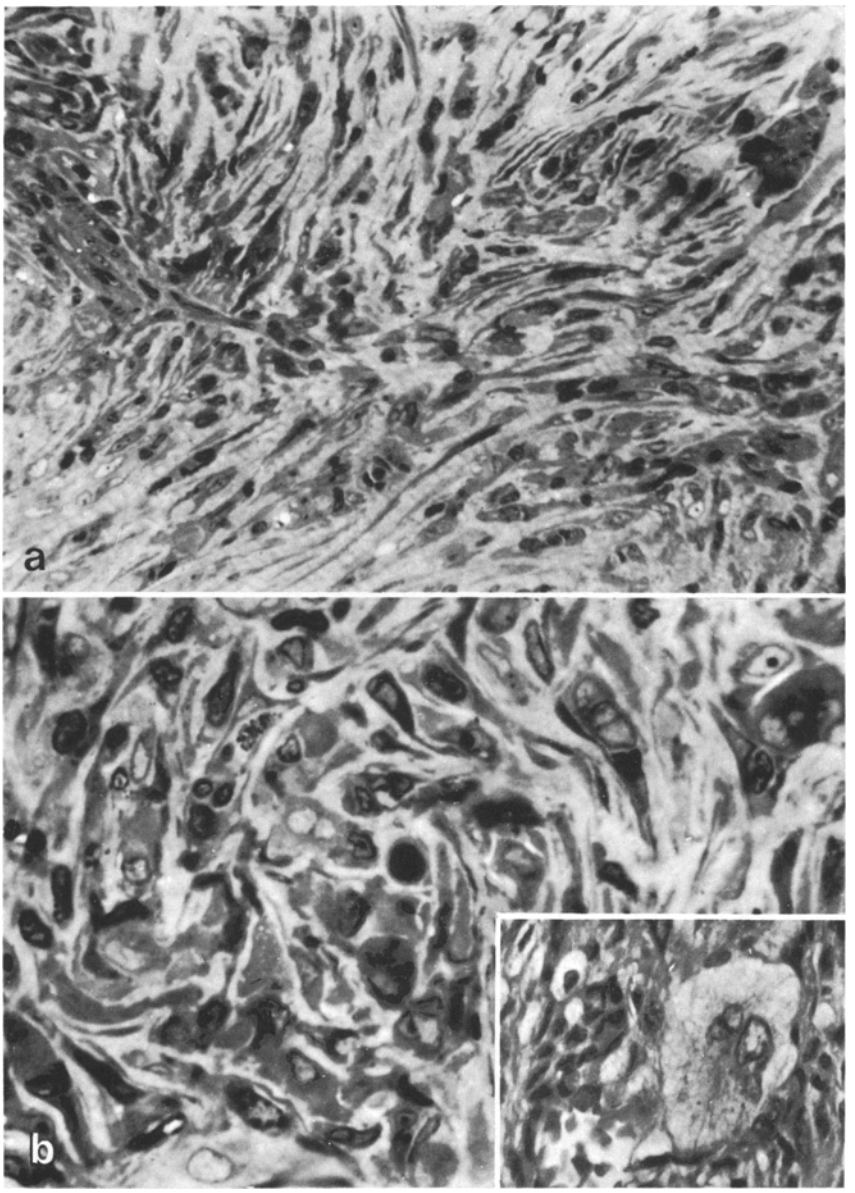

Fig. 2a, b. The two main cellular constituents of malignant fibrous histiocytoma of bone are shown. **a** Spindle-shaped fibroblast-like cells in fascicular arrangement (semithin section, toluidine blue, 380:1). **b** Somewhat more voluminous histiocyte-like cells with irregular large nuclei and some prominent nucleoli (semithin section, toluidine blue, 960:1). *Inset:* Two giant cells are visible, they bear resemblance to Touton cells and osteoclasts, resp. (HE, 480:1)

Tumor cells defined as histiocyte-like showed relatively voluminous cytoplasm with small cytoplasmic microvillus-like projections and a large folded, hyperlobated or irregularly indented nucleus. Sometimes formations resembling so-called nuclear blebs were detectable (especially in case 1, cp. Fig. 6a). The heterochromatin was mostly uniformly distributed or arranged in little lumps, a condensation of chromatin at the nuclear periphery was not infrequently seen. The nucleolus, if visible, was large, this fact and the existence of several nuclear bodies of different types indicated nuclear hyperactivity (Fig. 4a, b). The cytoplasm contained a complex system of mitochondria, vesicles and vacuoles as well as some slender tubes of rough endoplasmic reticulum (Fig. 3a, b). We found some lysosomes here and there (Fig. 3d). In addition, large lipid containing vacuoles of digestive type, membraneous structures and occasionally siderin granules were noted. There were few typical lipid droplets. Golgi zones were sometimes prominent. In case only 1 glycogen granules were identified within the cytoplasm and the nucleus of some cells (Figs. 3a, 4c).

The fibroblast-like cells were mostly of elongated shape and contained an elongated, but often rather irregular nucleus. The size of the nucleoli varied. Within the cytoplasm rough endoplasmic reticulum dominated the picture (Fig. 5a). Beside tubes of rough endoplasmic reticulum with parallel membranes cisterna-like extensions of this organelle system occurred. Other cytoplasmic constituents were mitochondria, ribosomes and a moderately developed Golgi apparatus.

Both the cell types and their intermediate forms were found to contain filaments of 60–100 Å diameter in the cytoplasm (Fig. 4a, b). There were great variations in the amount of filaments and in their arrangement. In histiocyte-like cells they seemed to be mostly unordered, whereas in fibroblast-like cells a parallel arrangement was sometimes obvious, a pattern typical for myofibroblasts (Fig. 5b). The latter cells were especially prominent in case 2. Occasionally such filament bundles showed small densities which strengthened the resemblance to smooth muscle cells (Fig. 6b, c). A surrounding discontinuous basement membrane-like material was sometimes seen, but a continuous basement membrane was always lacking (Fig. 6a).

In case 1 a special cell form was noted. It had an irregular, activated nucleus and the cytoplasm was characterized by abundant filaments of 100–130 Å in diameter. They were occasionally deposited in small and short bundles but the great majority of filaments were unordered, although several filaments again lay parallel to each other. Frequently filamentous structures replaced a great part of the other cytoplasmic organelles such as mitochondria, small tubules of rough endoplasmic reticulum and ribosomes. There were often numerous subplasmalemmal vesicles suggesting micropinocytosis and a basement membrane-like structure in close proximity to the outer plasma membrane. Thus, these cells revealed certain characteristics of myoblastic differentiation (Fig. 6a).

In addition to the cells described above undifferentiated cells with a high nuclear-cytoplasm ratio and an activated nucleus were seen. Their cytoplasm contained few organelles which consisted mainly of ribosomes and some mitochondria. Between these undifferentiated cells and the more differentiated ones intermediate forms occurred. Most of the giant cells possessed cytoplasmic

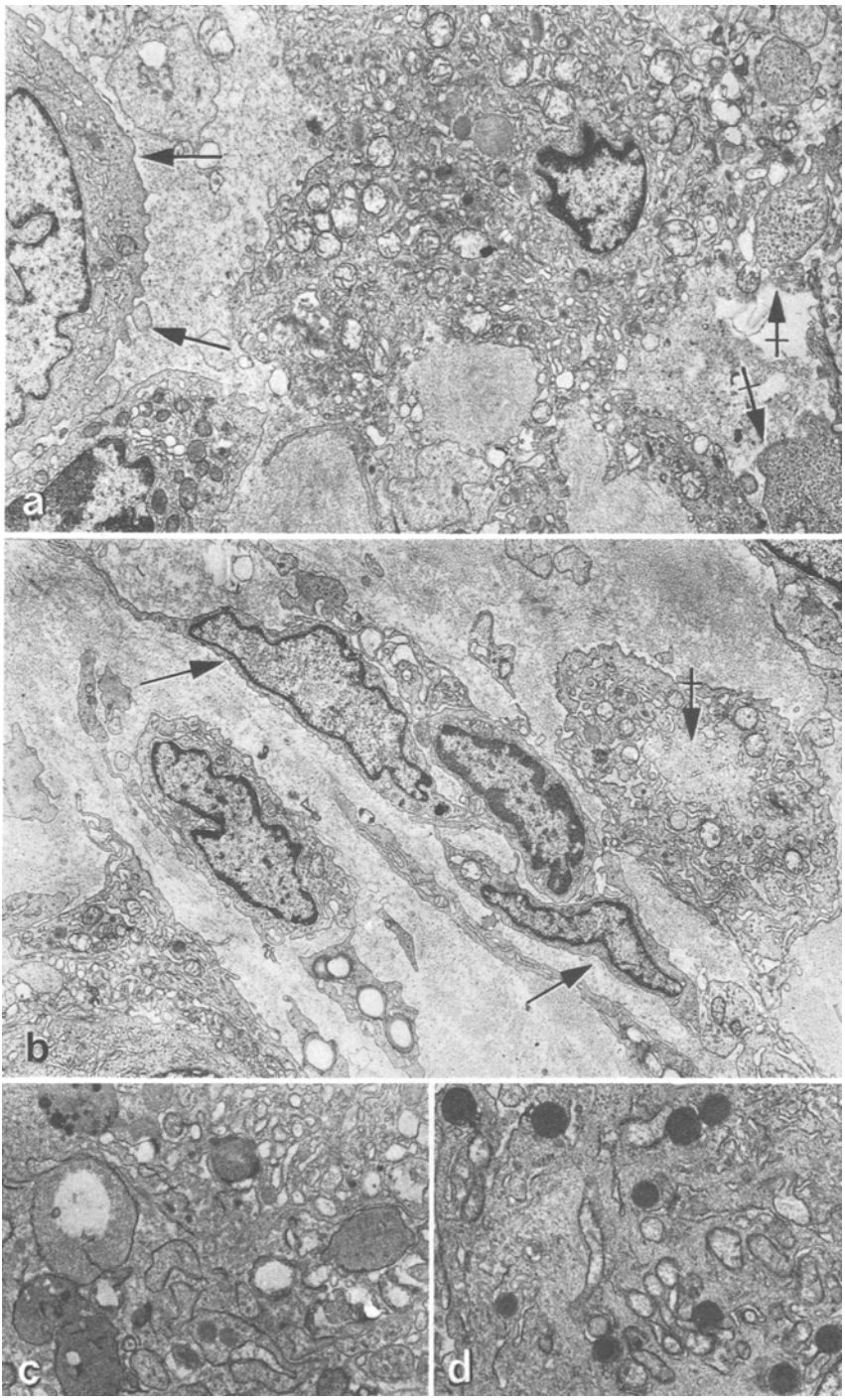

Fig. 3a–d. Examples of histiocyte-like cells are demonstrated. **a** The organelle content of the cells is relatively typical for histiocytic cells: tubules of smooth endoplasmic reticulum and vesicles, some lysosomal structures, mitochondria and a clearly visible Golgi apparatus. Furthermore, a part of an undifferentiated cell (→) and cytoplasmic projections with glycogen granules (↠) can be seen (7,820:1). **b** Apart from elongated and uncharacteristic mesenchymal cells (→) several histiocyte-like cells are present. There are some lipid droplets within the cytoplasm. Note the intracytoplasmic filaments (↠) (6,450:1). **c** and **d** Structures of the Golgi zone and some lysosomal elements are visible (10,200:1)

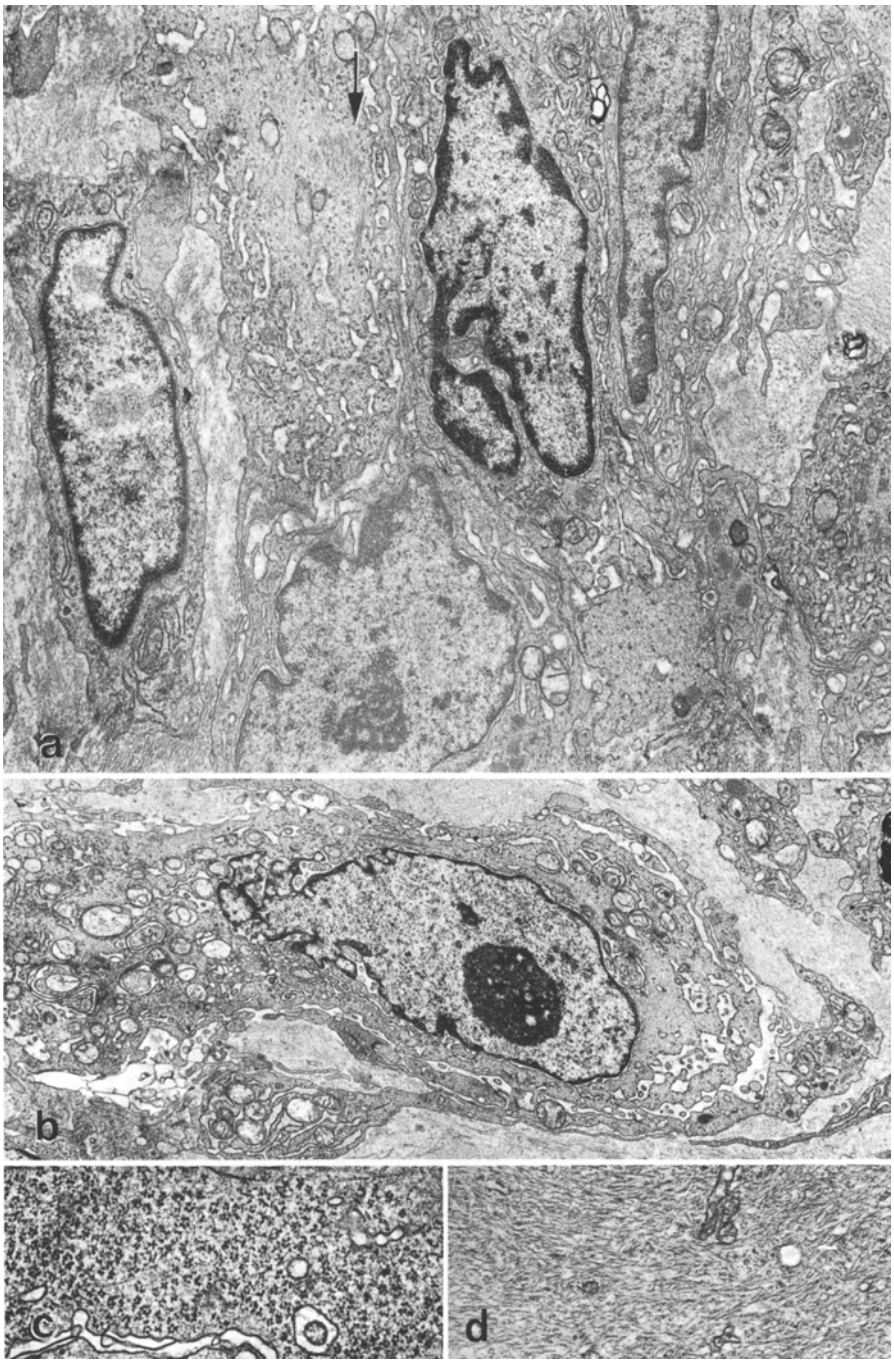

Fig. 4a–d. Histiocyte-like cells and intermediate forms between histiocyte- and fibroblast-like cells are seen. **a** Note the nuclear activity with several nuclear bodies and the filaments in an intermediate cell. These filaments have a diameter of 60–100 A (→). The cells are closely approximated (9,800:1). **b** The nucleus of this histiocyte-like cell contains a large nucleolus (7,820:1). **c** Numerous glycogen granules (22,200:1). **d** 100 A filaments, which are known to be a constituent of the cytoskeleton (12,600:1)

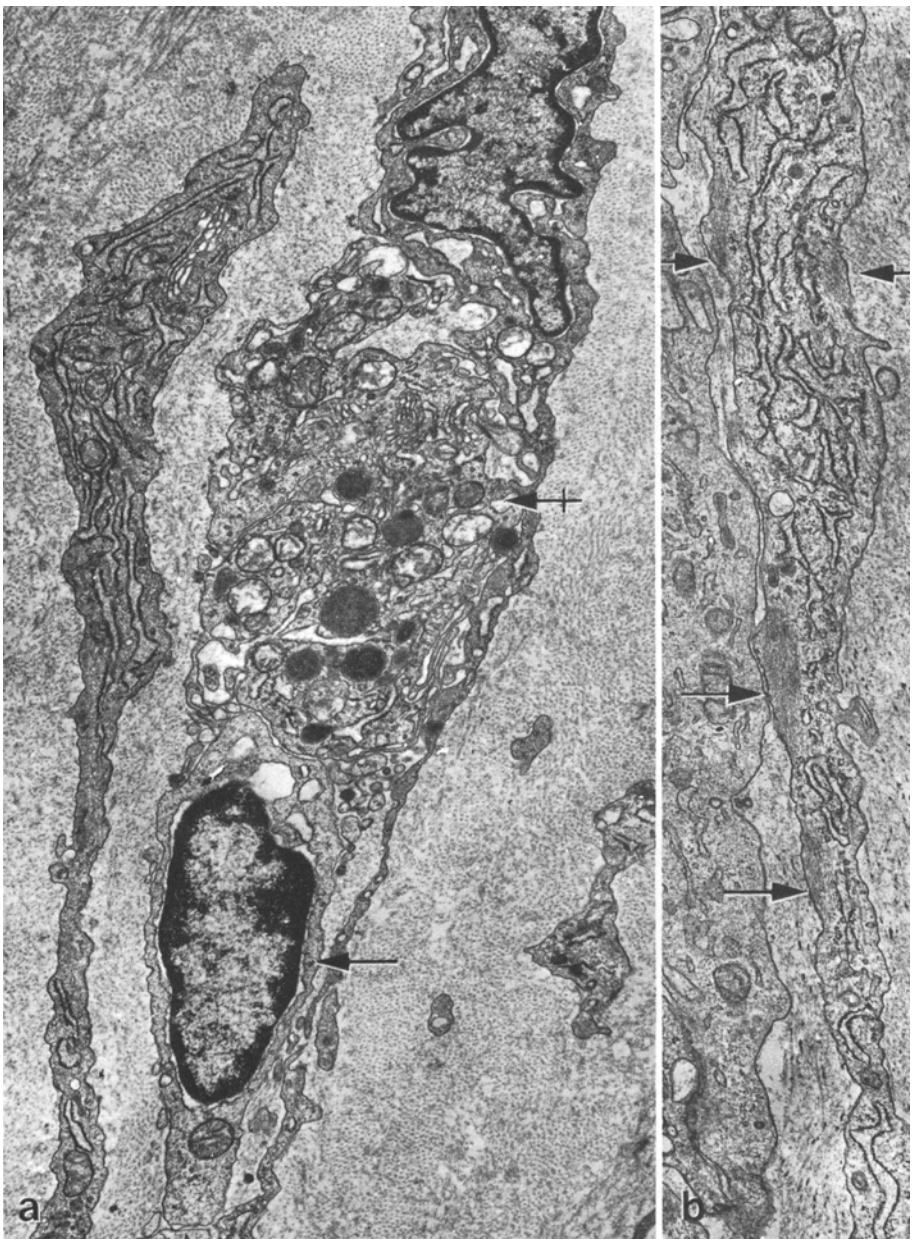

Fig. 5a, b. Variants of fibroblast-like cells. **a** Typical fibroblast-like cells besides undifferentiated (→) and histiocyte-like cells (↠) (12,900:1). **b** Microfilament bundles in a fibroblast-like cells (→) produce a myofibroblast-like picture (17,200:1)

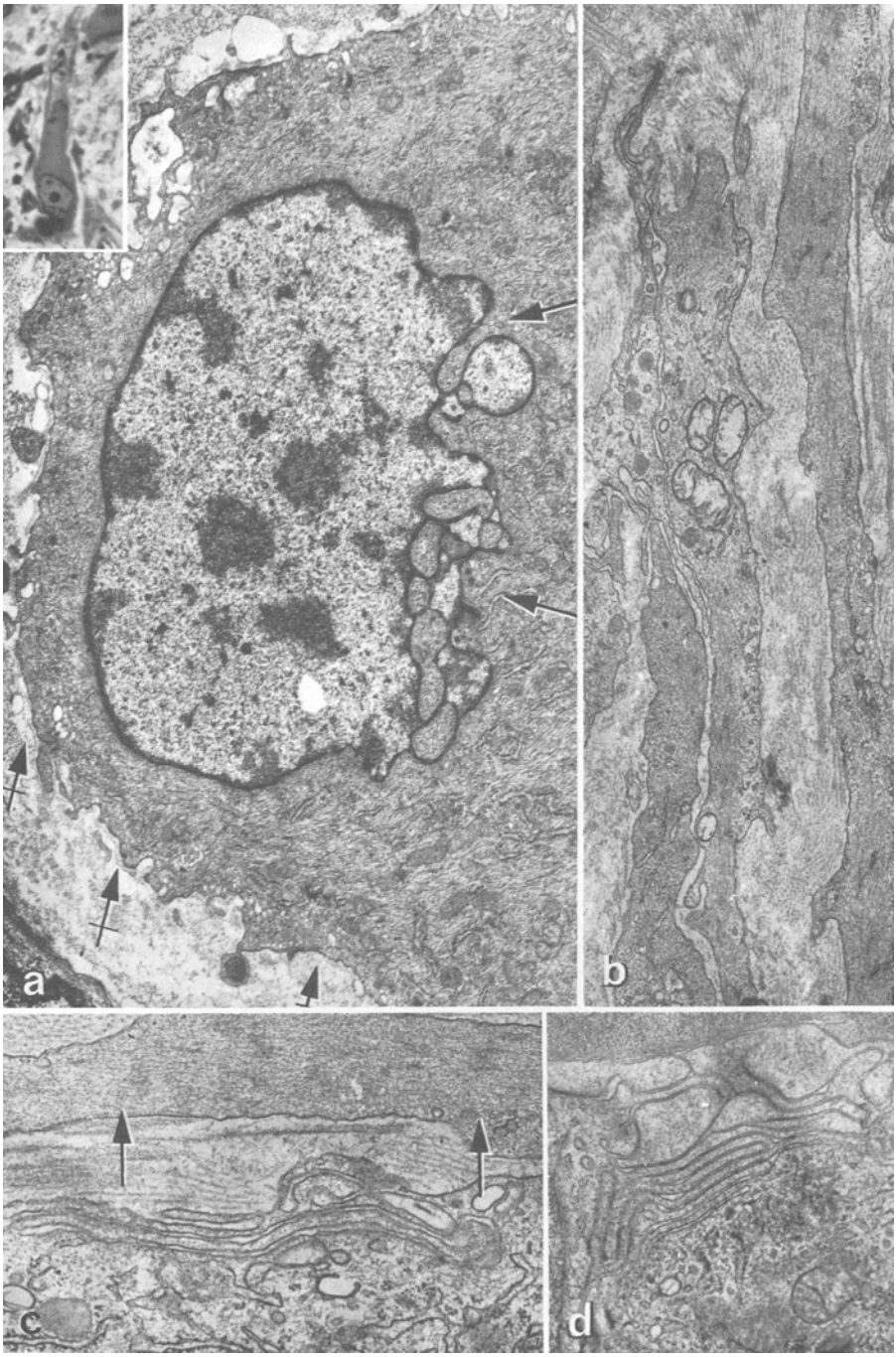

Fig. 6. **a** A large cell form case 1. There are nuclear blebs (→), numerous 100 A-filaments within the cytoplasm, subplasmalemal microfilaments, micropinocytotic vesicles and a discontinuous basement membrane-like substance (+) (9,660:1). Inset: Semithin section of a large rhabdomyoblast-like cell (Toluidine blue, 960:1). **b** Microfilaments almost completely replace the other organelles. Scattered dense bodies and some micropinocytotic vesicles strengthen the resemblance to myoblastic differentiation. **c** Part of a myoblastic differentiated cell with microfilaments running along the cell axis (→). A histiocyte-like cell shows complex membrane foldings caused by the parallel arrangement of cellular processes (22,200:1). **d** Cellular interdigitations of histiocyte-like cells (15,900:1)

features of histiocyte-like cells, the ultrastructural aspect even seemed occasionally to resemble osteoclasts.

The cell density of the tissue samples varied. Only in occasional specimens were interdigitations of tumor cells detectable (Fig. 6d). The cells mostly lay either close to each other without intercellular substance between them and without intercellular junctions, or they were separated by thin fibrils and mature collagen fibers. In case 1 a cross-banded substance like fibrous long spacing collagen was occasionally demonstrated.

Discussion

Malignant fibrous histiocytomas of bone show the same ultrastructural characteristics as malignant fibrous histiocytomas of soft tissue and thus cannot be distinguished from them cytologically or structurally. The light microscopic findings in our four cases of osseous MFH are in congruence with the observations on these tumors reported in the literature (McCarthy et al. 1979). In case 1, apart from fibroblast- and histiocyte-like cells relatively large cells resembling myoblastic elements could be seen. Despite its histologically benign features this tumor must also be considered to be malignant because of aggressive behavior and occurrence in several bones. The latter phenomenon may be explained by multifocal tumor origin but the possibility of intraosseous metastases cannot be excluded with certainty. In cases 2, 3 and 4 cellular pleomorphism was more striking and beyond fibroblast-like and histiocyte-like cells lipid storing cells, bizarre, Touton-like and osteoclast-like giant cells were also observed. Although the light microscopic examination of cytology revealed certain quantitative differences the growth pattern of all tumors was almost exclusively storiform.

The electron microscopic investigation confirmed and widened our knowledge on the cytological structure seen light microscopically. There was a broad scale of cellular features ranging from undifferentiated to differentiated cells with some resemblance to defined mesenchymal cell types. Moreover, numerous intermediate forms were detected. Many cells possessed structural characteristics in common with histiocytes and some also with fibroblasts, including myofibroblasts (for comparison see Inada et al. 1976; Angervall et al. 1979). The giant cells seemed to be derived from histiocytic cells, some of them superficially resembled osteoclasts. While the presence of numerous xanthoma cells is reported in the literature (Inada et al. 1976; Yumoto et al. 1976; Roessner et al. 1979) these cells were seldom observed in our cases by electron microscopy. Some cells in case 1 have the structural traits of myoblastic cells.

Interestingly Weiss and Enzinger (1978) reported that fibrous histiocytomas and rhabdomyosarcomas are sometimes confused in daily histological practise, and they demand evidence of cross-striation for rhabdomyosarcoma diagnosis. It is widely accepted that rhabdomyoblasts are not a constituent of fibrous histiocytomas. Yet in 1977 Churg and Kahn mentioned rhabdomyoblast-like cells in semithin sections of malignant fibrous histiocytomas of soft tissue. These, however, were interpreted as a large cell variant of myofibroblasts after electron microscopic examination. Likewise Taxy and Battifora (1977) pointed to occasional rhabdomyoblast-like strap-shaped giant cells. In case 1 we found cells with structural traits of myofibroblasts and also several large cells with

obviously myoblastic differentiation. We have observed comparable cells in embryonal rhabdomyosarcomas (Katenkamp et al. 1979) but are not aware of similar ultrastructural observations in MFHs of bone.

Some other ultrastructural findings in our cases are remarkable because they have very seldom been reported in the literature. These are the special nuclear configuration of several histiocyte-like cells ("nuclear blebs") noticeable also in fibrous histiocytomas of the skin (Auböck 1975; Katenkamp and Stiller 1975), the occurrence of some cross-banded structures like fibrous long spacing collagen, reported only recently by Angervall et al. (1979) in a MFH of bone after irradiation, and the sparsity of intercellular junctions which are usually common in MFHs (cp. Churg and Kahn 1977; Johnson et al. 1978; Roessner et al. 1979).

In spite of intensive search no Langerhans organelles could be found in tumor cells. Yet such organelles seem to occur in fibrous histiocytomas of the soft tissue and bone (Newland et al. 1975; Alguacil-Garcia et al. 1977; Tsuneyoshi and Enjoji 1980). As is well known these organelles are most frequently observed in cells of histiocytosis X. Langerhans granules are thought to be correlated to the phagocytic activity of histiocytic cells (Wolff 1972), they seem to be of no cytogenetic significance.

In principle, fibroblasts and histiocytes are functionally defined cells, their organelle composition only reflects a momentary functional state. It is well documented that a lot of mesenchymal cells can act as fibroblasts or histiocytes. However ordinary (monocyte-derived) tissue histiocytes can modulate their cytological picture only in a fibroblastic direction. The fact that several mesenchymal cell types with intermediate forms were found in our cases speaks against the definition of MFHs of bone as being tumors of ordinary tissue histiocytes. We suggest that the cytology of MFH is the result of modulation and differentiation of an undifferentiated mesenchymal stem cell.

Osteoblasts and chondroblasts were not seen, nor did osteoid formation or calcification occur. Therefore the diagnosis of osteosarcoma is not permitted. Nevertheless many cellular modulations of MFH can also be found in osteosarcomas and the electron microscopic picture at low magnification may be quite similar to such tumors. Our recent electron microscopic findings permit the conclusion that osteosarcomas develop from primitive mesenchymal stem cells (Katenkamp et al. 1978). Our present results lead to a similar interpretation for osseous MFHs and may indicate a common progenitor cell for both the tumors. This idea is in sharp contrast to the view of other authors (cp. Roessner et al. 1979), but a possible relationship has already been suggested by Dahlin (Dahlin et al. 1977). However, despite a possible "joint" stem cell, a clear distinction between osseous MFH and osteosarcoma is mandatory, since the tumors are said to have different biological behavior (Spanier et al. 1975; Feldman and Lattes 1977).

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Accepted January 9, 1981