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Giant Cell Tumor of Soft Parts

An Ultrastructural Study

U. J. G. M. van Haelst and A. H. de Haas van Dorsser

Department of Pathology; Department of Orthopedic Surgery; Radboud Hospital; C. University Nijmegen; Nijmegen; The Netherlands

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Summary. The light-microscopic and ultrastructural findings in a case of so-called giant cell tumor of soft parts, localized at the dorsal side of the left foot of a 23-years-old male are described. An amputation of the lower extremity was performed and subsequently chemotherapy with adriamycin was given for 3 months. Despite the histology and cytologic malignant appearance and the evident vascular invasion, already present at the time of the first excision, the last known status 2 years later seems favorable. There are no pathologic lymph nodes in the groins and no signs of metastases on chest X-rays.

From the electron-microscopic study no definite conclusion can be drawn as regards the histogenesis of this tumor. We feel, as do others, that many of the principal mononuclear tumor cells are poorly differentiated mesenchymal cells. Some of the neoplastic cells, however, show ultrastructural features suggestive of chondro- or osteoblasts (a well-developed r.e.r. containing electron-dense material; multiple Golgi complexes; masses of glycogen; interdigitating cell membrane villi; cytoplasmic filaments; an extracellular amorphous matrix). Some of the larger tumor cells have the submicroscopic aspects of histiocytes as described in osseous, cutaneous, or pulmonary lesions of the histiocytosis X group. As yet undetermined cytoplasmic inclusion bodies constitute another rare observation in our material.

Key words: Giant cell tumor of soft parts — Histopathology — Ultrastructure.

Giant cell tumor of soft parts is a rare, probably fibrohistiocytic neoplasm, with a distinctive light-microscopic appearance which helps the histopathologist in its differentiation from other types of soft tissue sarcoma. Apart from a few single case reports (Merkow et al., 1971), two large papers dealing in particular with the gross and histologic aspects, the biologic behavior, and the results of treatment of this tumor, have appeared recently (Guccion-Enzinger, 1972; Soule-Enriquez, 1972; lit. by Mackenzie, 1975).

Further information is needed on the prognosis, histogenesis, and electron-microscopic appearances of this tumor and for these reasons we present this report. There have only been two previous ultrastructural studies of the lesion (Merkow et al., 1971; Fu et al., 1975).

Case History

The patient, a 23-years-old Caucasian male was referred to the Department of Orthopedic Surgery in January 1974 complaining of pain in the left foot during walking.

The previous history included surgical intervention for a monarthritis of the fifth metatarso-phalangeal joint of the left foot at the beginning of 1972, in a local hospital elsewhere. Histologic examination showed only nonspecific inflammation, locally suppurative. In October 1973, the patient underwent a synovial biopsy of the left medial ankle joint in the same

hospital. At that time the patient complained of a tender left ankle joint. Histologic examination showed chronic nonspecific inflammation.

The present physical examination showed a well-defined tumor on the dorsum of the left foot, over the area of the left navicular bone. The probable clinical diagnosis was a ganglion originating from the tendon of the extensor hallucis longus.

After a short period of conservative treatment without result, the patient was submitted to exploratory surgery under local anesthesia, in April 1974 in the outpatient ward. A $3 \times 3 \times 1$ cm tumor was removed. This was not easily separated from the fascia and tendons and grossly a malignant neoplasm was suspected.

The patient was admitted to the University Hospital the same day. On physical examination no metastases could be demonstrated. The laboratory results were normal. Pulmonary tomography revealed no metastases. On tomograms of the left foot local invasion of the navicular bone was suspected. Histologic examination demonstrated a paraskeletal malignant giant cell tumor. As a favorable course might be anticipated after wide excision, surgery was undertaken on May 6, 1974. However, the tumor was found to extend into the tendons and cuboid bone, and an amputation of the left lower leg was performed. Considering the extensive local invasion of the tumor, it was thought that the patient might benefit from chemotherapy prophylactically. Until August 20, 1974, adriamycin was administered (100 mg every 3 weeks, total dose 500 mg). This therapy had to be discontinued at the patients request due to alopecia and nausea. There were no signs of bone marrow toxicity or cardiac toxicity.

Follow-up studies have been carried out every 3 months since August 20, 1974. Recently (January 15, 1976) the patient was seen in the outpatient ward in good general condition walking with a well-fitting prosthesis. On physical examination, there were no signs of metastases; a few nonpathologic lymph nodes were palpable in the right and left groin. The laboratory results were normal. There were signs of metastases on the chest X-ray.

Material and Methods

The tissue for light microscopy was processed in the usual manner following fixation in formalin. Sections were stained with hematoxylin and eosin; Laguesse's reticulum stain; elastin-van Gieson stain; trichrome (Heidenhain); and Perls' iron stain.

For electron microscopy, fresh or formalin-fixed tissue was minced into 1 mm^3 blocks and fixed either in buffered osmic acid, pH 7.2, for 1 h or in 2.5% cacodylate-buffered glutaraldehyde, pH 7.4, for 2 h and then postfixed in osmic acid. Following dehydration in graded alcohols, the tissue blocks were embedded in Epon 812. Sections were mounted on formvar coated grids, stained with uranyl-acetate and lead citrate, and examined with a Siemens Elmiskop 101.

Results

Light-Microscopic Findings. At low magnification, the highly cellular tumor shows the well-known multinodular pattern in which the neoplastic nodules are separated by septa of dense, collagenous tissue (Fig. 1). In places, the tumor almost involves the epidermis, which is not ulcerated. Mononuclear, round-to-oval, or polyhedral cells with a relatively large, vesicular nucleus with one or two prominent nucleoli and a smooth, thick nuclear membrane, form the principal part of the neoplasm. The amount of cytoplasm varies; it is well circumscribed and stains acidophilic or amphophilic in H & E. In addition, the perinuclear part of the cytoplasm has a fine vacuolated aspect (Fig. 2A) and sometimes intracytoplasmic slits can be observed (Fig. 2B). The neoplastic cells are separated by collagen fibers or by a homogeneous interstitial substance as it appears in Heidenhain's aniline blue method and elastin-van Gieson's method. With Laguesse's method for reticulum, the reticulin pattern shows almost a biphasic arrangement because in some places the fibrils are arranged around nests of cells (Fig. 2C)

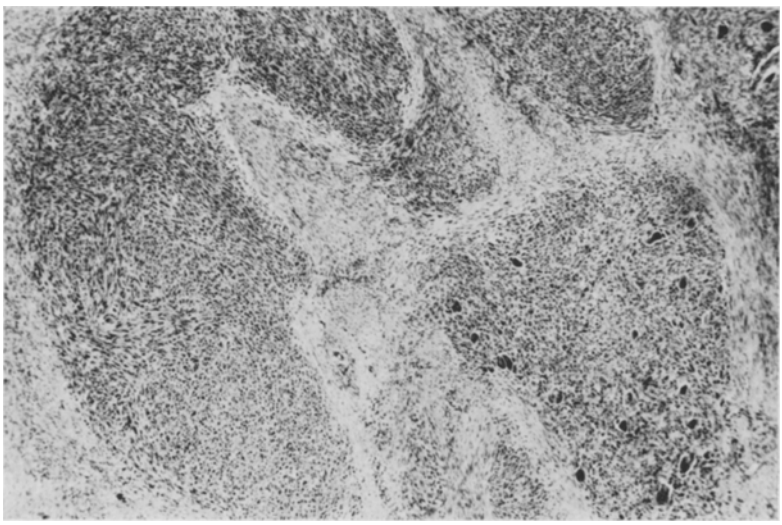
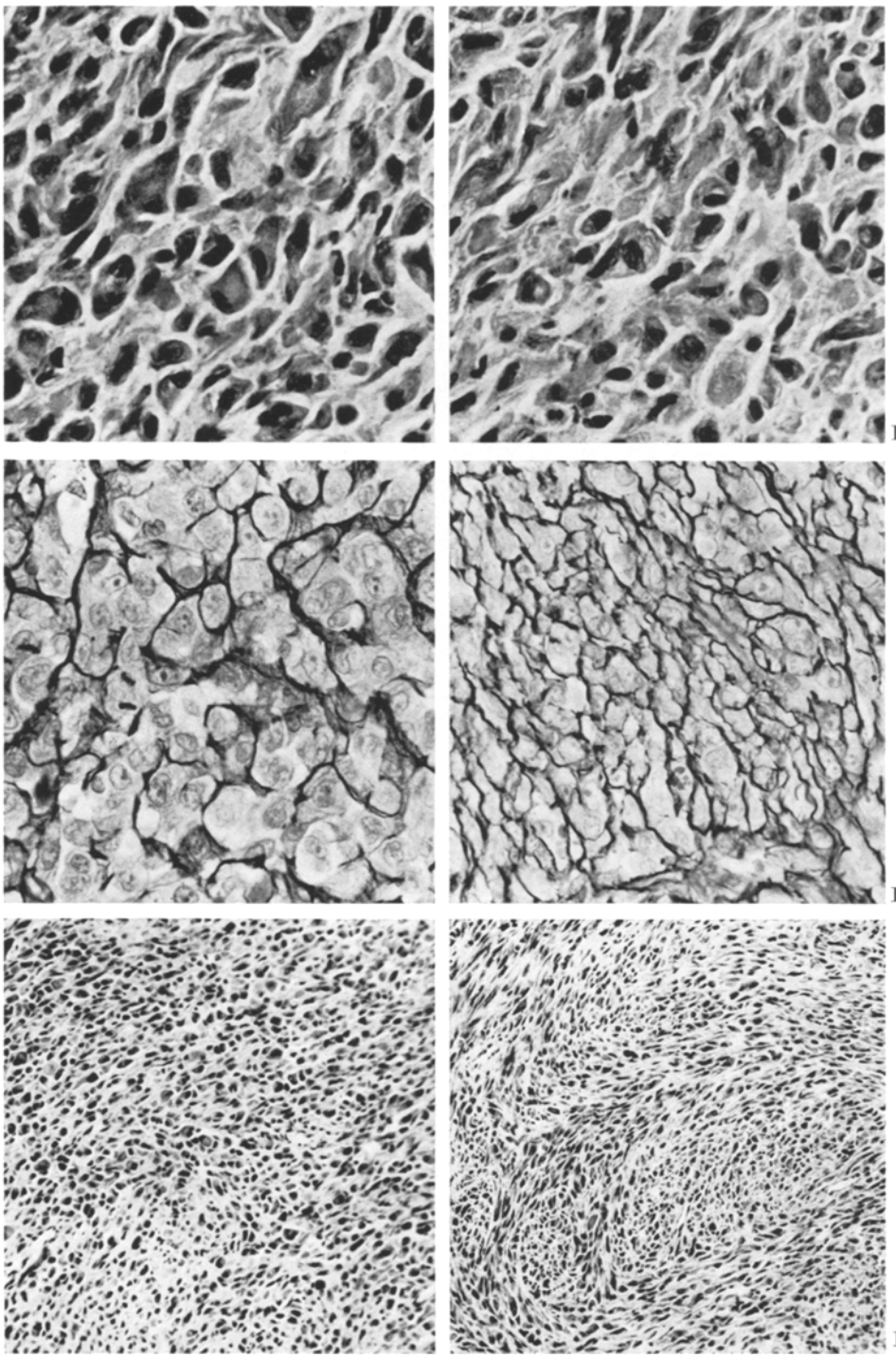


Fig. 1. A Low-power view with characteristic multinodular pattern. Several highly cellular nodules are separated by connective tissue septa. H & E stain; ×39

rather than between cells (Fig. 2D). In contrast to the relatively loose arrangement of the tumor cells in the center of the nodules (Fig. 2E), the spindle-shaped cells show evident bundle formation at the periphery, resembling sarcoma (Fig. 2F). The mitotic rate varies: at least one and sometimes up to three mitotic figures can be counted per high-power field (×400). Multinucleated giant cells are seen containing up to 50 nuclei, most often in the center of the cell. These cells sometimes have vacuoles in their cytoplasm and are focally intermixed with the mononuclear cells (Fig. 3A). We have found that groups of giant cells are present in the deeper parts of the tumor while this is seldom seen in the more superficial, subepidermal nodules. Foamy cells are not observed. There are no granulomatous features and almost no inflammatory cells. Small necrotic areas or extravasated red blood cells lie scattered throughout the tumor tissue. In such areas hemosiderin pigment can be demonstrated by Perls' stain. Gaping vascular spaces are frequently seen around the superficial nodules and in some of them tumor invasion is evident. Small foci of osteoid or chondroid formation are noted occasionally in the less cellular areas of the tumor (Fig. 3B). Some tumor cells contain PAS-positive cytoplasmic material. The Fontana-Masson silver method reveals no melanin; cross-striation is nowhere demonstrable with the PTAH stain. The sections of the bone underlying the neoplasm show no invasion.

Based upon the rate of mitotic activity, active nuclei with the prominent nucleoli, anaplasia and plemorphism of the neoplastic cells, the vascular invasion, and the extension of the lesion into the subcutaneous fat, we considered our case to be malignant.

Electron-Microscopic Observations. Submicroscopic examination of multiple sections reveals polyhedral cells with round-to-oval, regularly formed or extremely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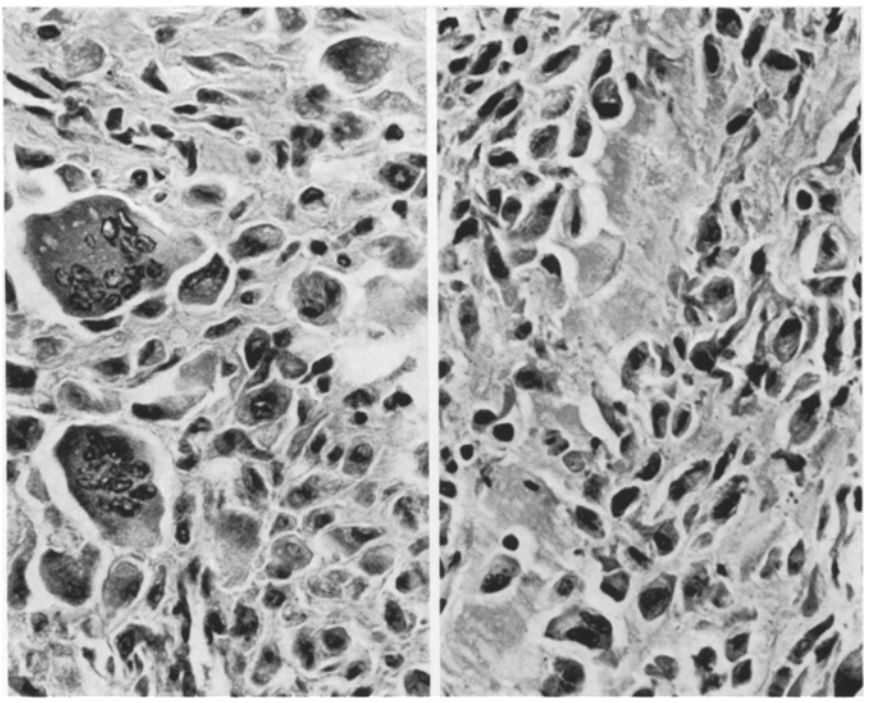

A B

Fig. 3. (A) Mononuclear cells with pleomorphic bilobed nuclei are intermingled with benign-appearing multinucleated giant cells in deeper parts of tumor. H & E stain; ×390. (B) Field of tumor showing pleomorphic tumor cells surrounded by osteoid material. H & E stain; ×390

pleomorphic, deeply indented and lobulated nuclei with a narrow rim of condensed chromatin around the nuclear membrane. They contain one or two huge nucleoli with a prominent filamentous nucleolonema and a pars amorpha (Fig. 4). Occasionally peculiar intranuclear bodies or membrane-bound filaments are observed. The cytoplasmic membranes of the loosely and irregularly arranged tumor cells are smooth while microvillous or plump interdigitating cytoplasmic processes are present between the tightly grouped cells (Fig. 5). The intercellular spaces may be narrow and empty looking or irregularly enlarged and partially filled with electron-dense amorphous material with dark granules. In places, the pres-

Fig. 2. (A) Multiple bizarre tumor cells in loose arrangement with pink staining cytoplasm and a faintly vacuolated juxtanuclear appearance. H & E stain; ×390. (B) Tumor cells with small, slitlike clear spaces in their cytoplasm. H & E stain; ×390. (C) Small area of tumor showing fine reticulum enclosing groups of cells. Compare with Figure 1D. Laguesse's reticulum stain; ×390. (D) In contrast with previous figure, reticulin fibers in this part of tumor surround each tumor cell individually. Laguesse's reticulum stain; ×390. (E) Central part of neoplastic nodule showing loose arrangement of tumor cells. Compare with Figure 2F. H & E stain; ×100. (F) At periphery of nodule, spindle cells are arranged in bundles with fibrosarcomatous aspect. H & E stain; ×100

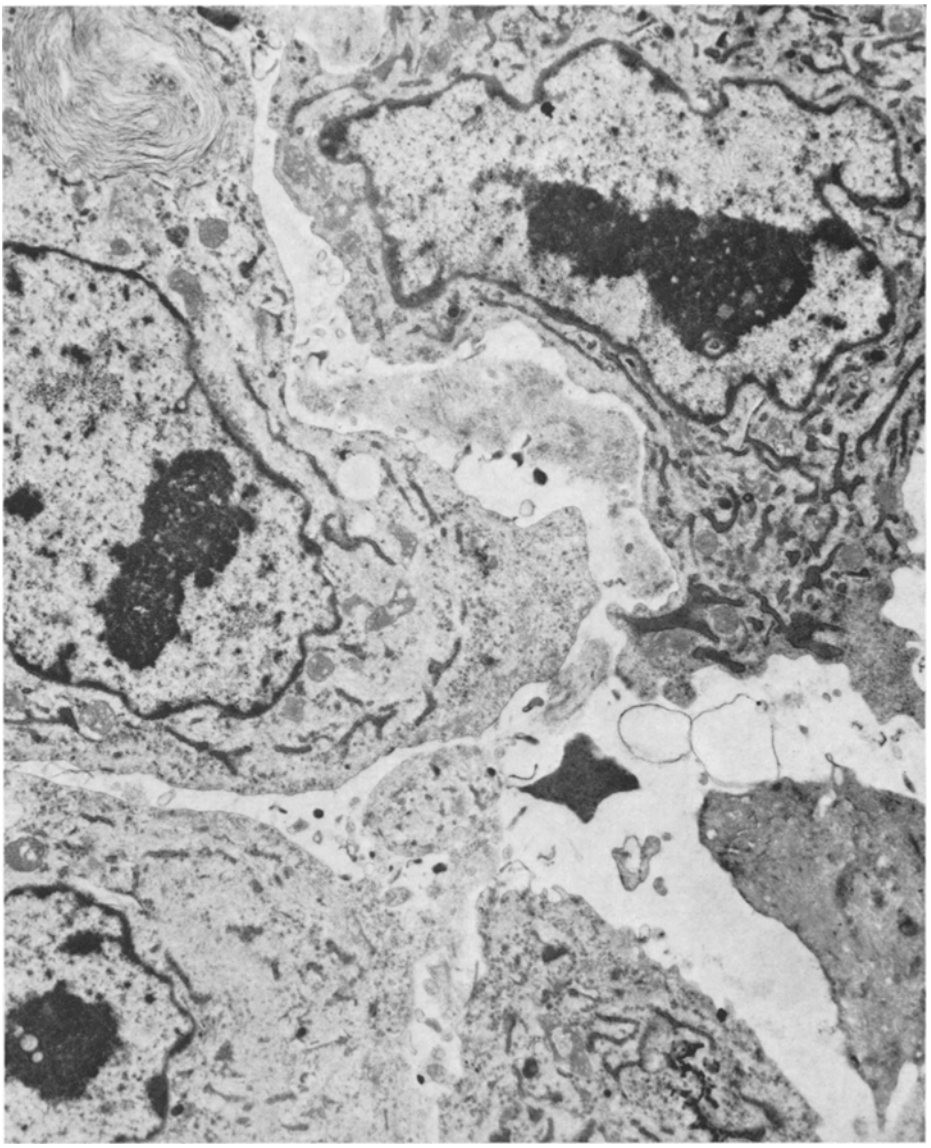

Fig. 4. Electron micrograph of four neoplastic cells with large indented nuclei and prominent nucleoli. Notice well-developed rough endoplasmic reticulum containing electron-dense material. ×10,000

ence of fibrils with a periodicity of reticulin or collagen fibers is noted (Fig. 6). Occasionally a primitive junction between a tumor cell and the intercellular matrix can be observed.

The cytoplasm contains abundant, closely packed slender microfilaments so that in some cells the cytoplasm shows little besides filaments (Fig. 7). In most

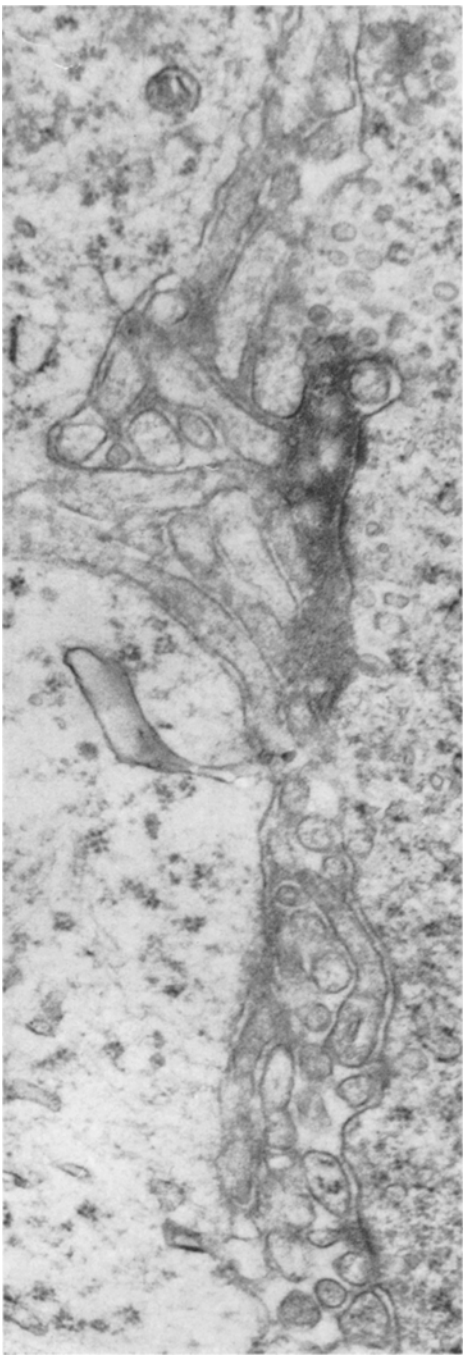

Fig. 5. Parts of two cells in close apposition with microvilli and intergiditating cytoplasmic processes. ×35,100

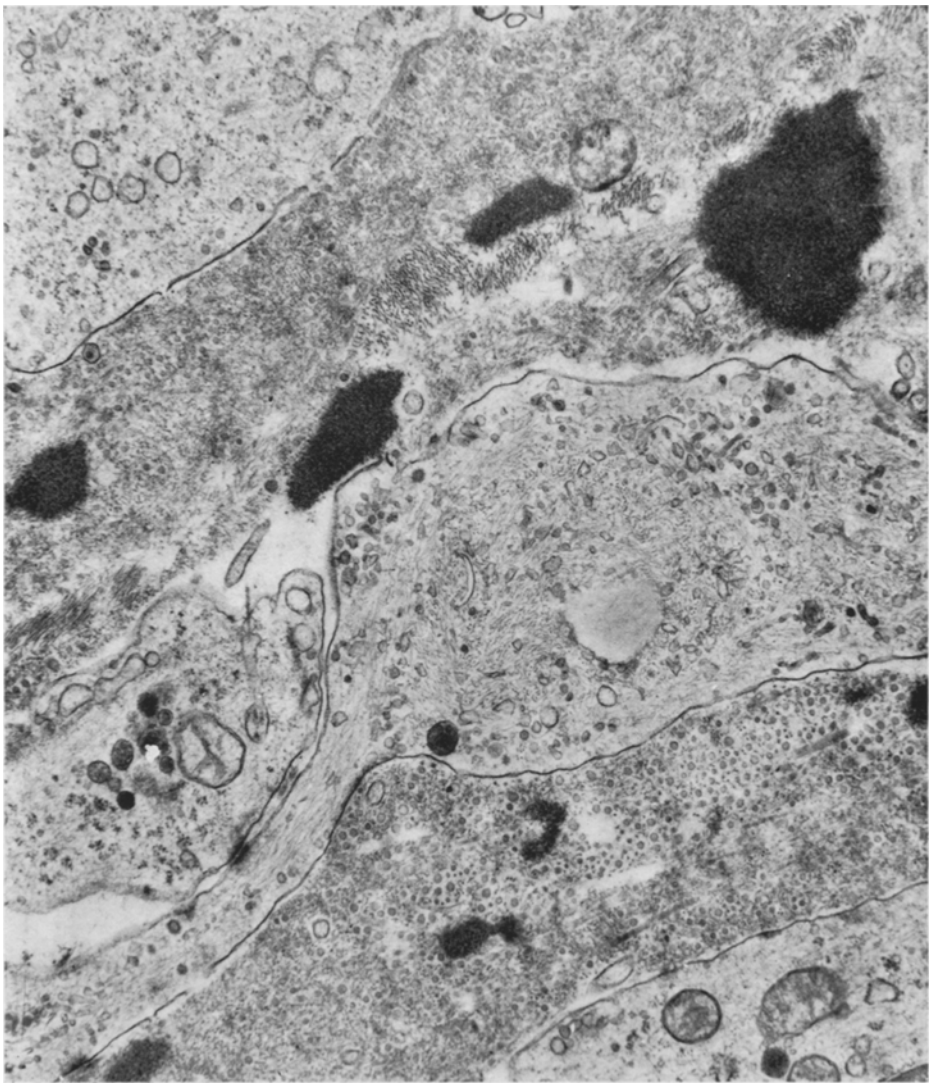

Fig. 6. Electron micrograph of some of the extracellular material shows groups of short, small, and large fibrils. Very electron-dense amorphous material can be seen at different places. ×21,300

cells interconnecting profiles of rough endoplasmic reticulum are arranged in a more or less parallel array; their cisternae are slightly dilated and filled with semidense material (Fig. 4). Small, round lipid droplets can be seen lying free or in association with profiles of endoplasmic reticulum. Their number, however, varies from cell to cell (Fig. 8). Masses of glycogen are quite prominent in some cells. In general, the dispersed or compactly grouped mitochondria are small

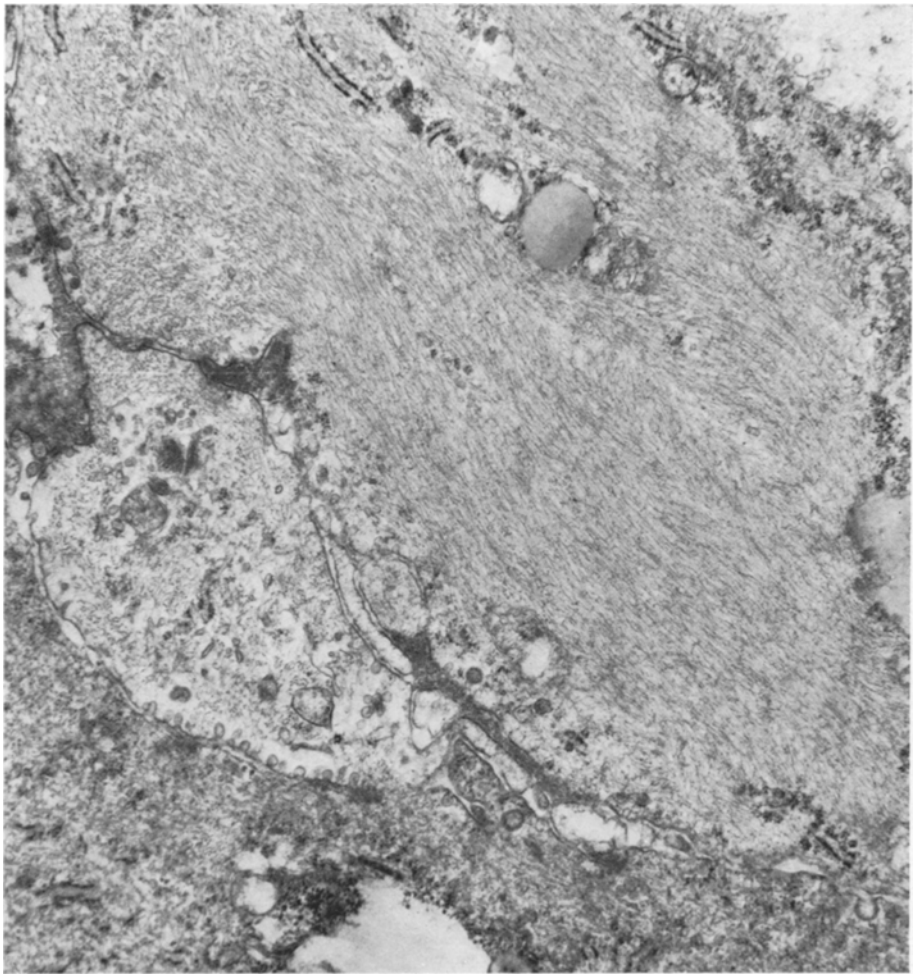

Fig. 7. Large number of small intracytoplasmic filaments almost completely fills part of a tumor cell. Some rough endoplasmic reticulum lamellae, free polyribosomes, and lipid droplets are focally present. ×20,000

and show an opaque osmiophilic matrix with short, disorganized cristae (Fig. 8). A number of well-developed Golgi complexes can be noted within some cells. Evidence of phagocytic activity is minimal and the so-called Langerhans cell granules are never observed. Occasionally viruslike particles are noted free within the cytoplasm of tumor cells.

Multinucleated cells are large, contain multiple nuclei, and are bordered by a smooth, delicate cell membrane. Their cytoplasm is characterized by a large number of small, ovoid, or elongated mitochondria which are uniformly distributed (Fig. 9). The rough endoplasmic reticulum is sparse with nondilated cisternae.

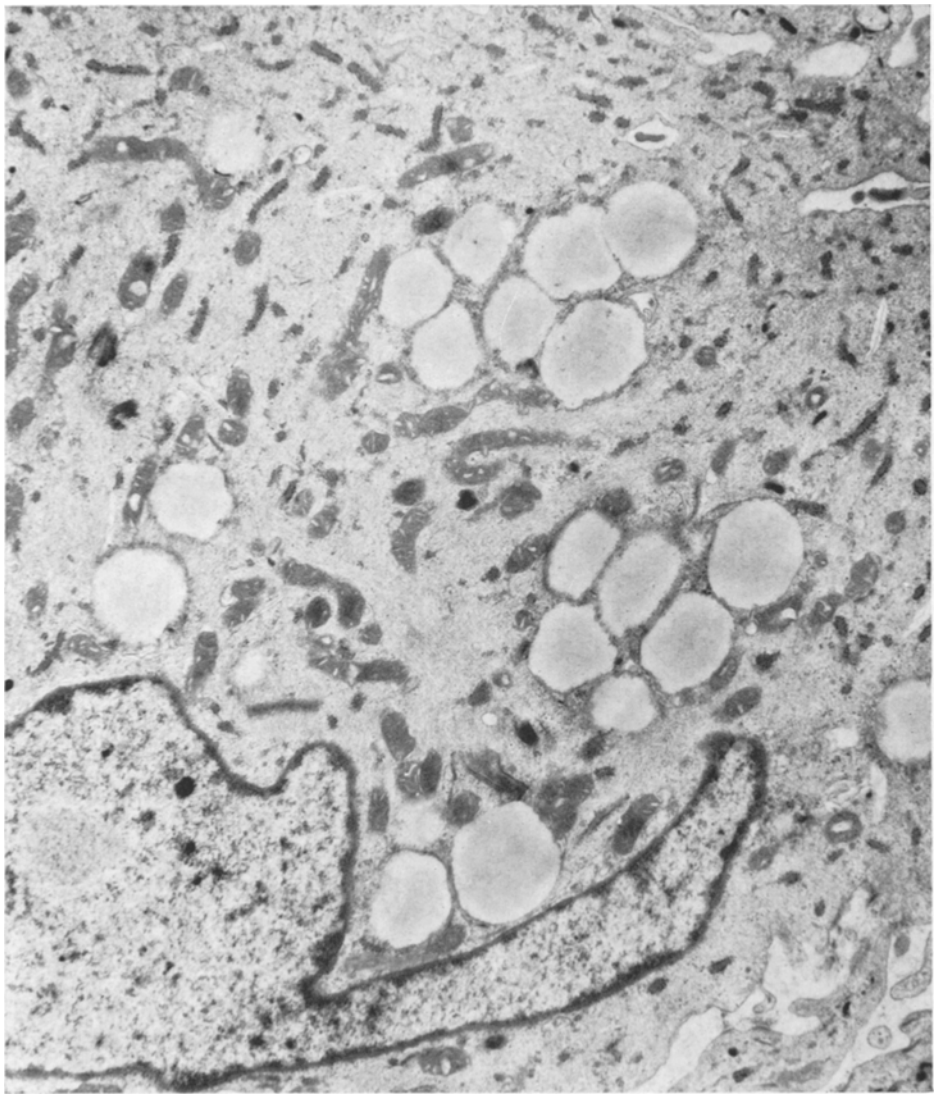

Fig. 8. Aggregated fat droplets and small, dark mitochondria can be observed in some of large tumor cells. ×15,000

Three remarkable findings in certain tumor cells are worth mentioning. First the occurrence of solitary or grouped needle- or spindle-shaped empty "slits" in the cytoplasm (Fig. 10). These spaces show no evident relation to other cell organelles and are not bordered by a distinct membrane. They contain some membranous osmiophilic material.

The other peculiar observation constitutes the presence of irregular polyhedral or oval inclusion bodies, delimited by a membrane (Fig. 11). They contain very

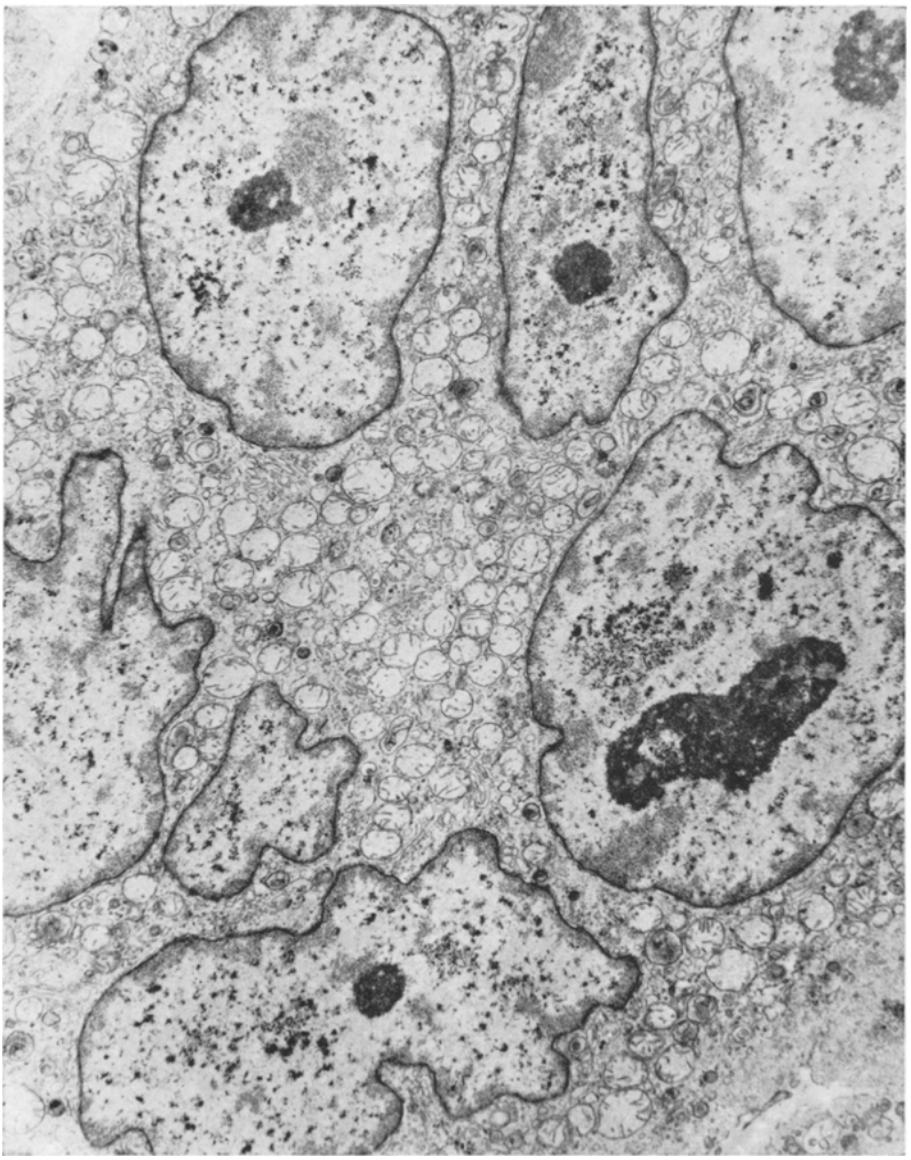

Fig. 9. Multinucleated giant cell with prominent nucleoli and large number of small mitochondria in cytoplasm. Phagocytic activity not present. ×10,000

dense, osmiophilic material and slightly curved, fibrillar or tubular structures lying in a semidense, fine granular background.

The presence of accumulated smooth, slender tubular structures in the paranuclear regions of some tumor cells represents another uncommon but interesting finding in our material (Fig. 12).

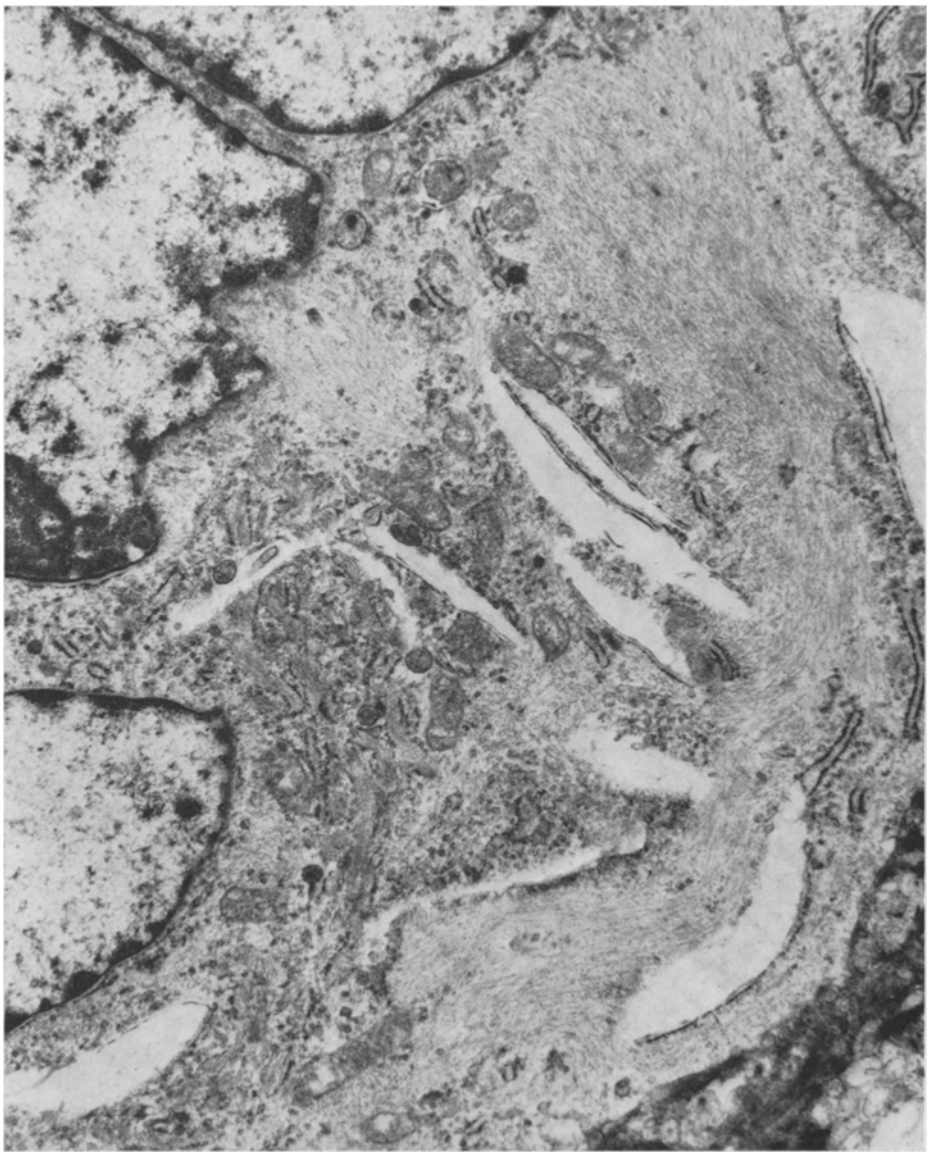

Fig. 10. Part of neoplastic cell with extremely lobulated nucleus (upper left corner) and intracytoplasmic clefts along rough endoplasmic reticulum. Residual membranes of endoplasmic reticulum can be seen within these "slits". ×15,000

Discussion

Notwithstanding the high mitotic rate, varying from one to three or four mitoses per high-power field, the vascular invasion and the pleomorphic, active nuclei with one or two large nucleoli, the biological behavior of the tumor in our case seems to be favorable from the follow-up of 2 years. No distant metastases

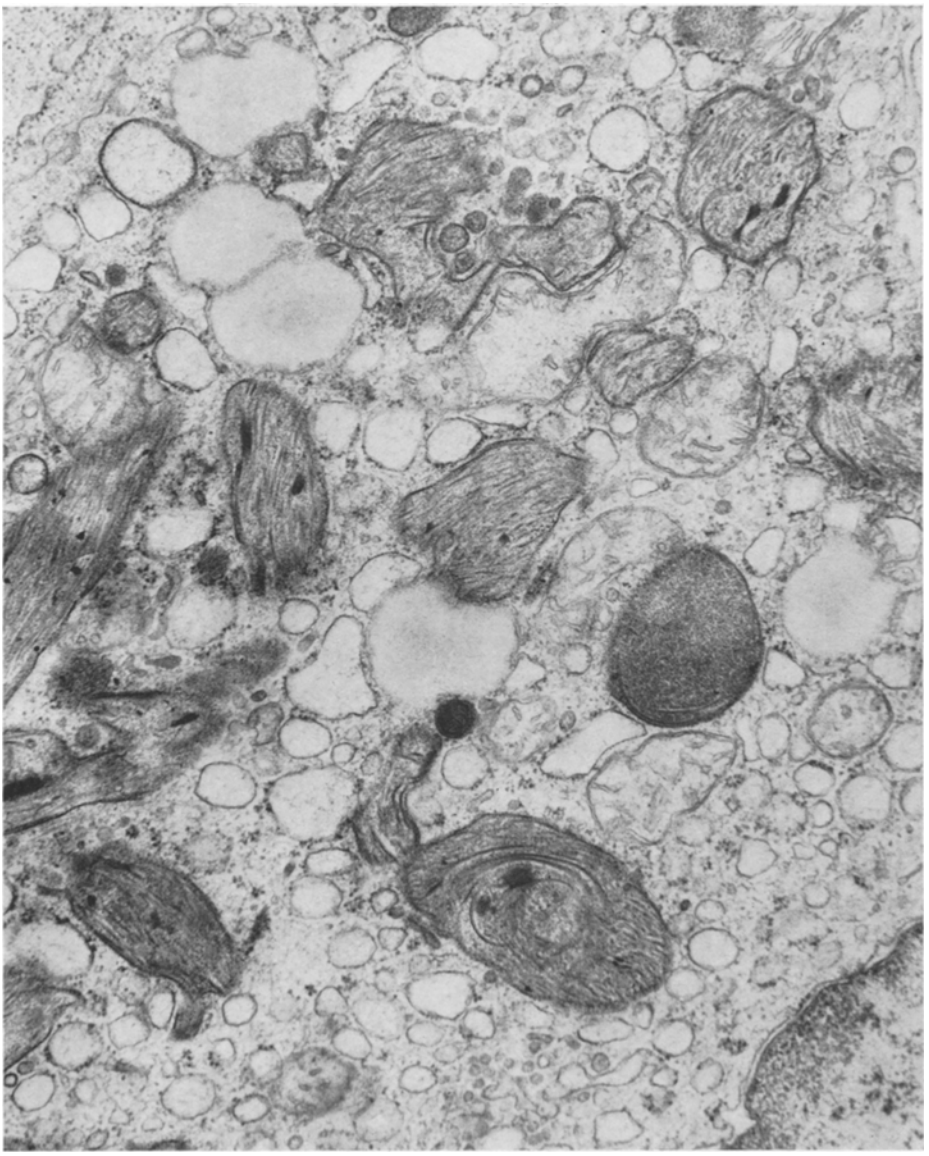

Fig. 11. Electron micrograph of portion of tumor cell with peculiar inclusionlike bodies with diameter of 0.5–1.5 micron, in cytoplasm. ×32,500

and no suspicious lymph nodes in the groins are present. The fact that we are dealing with the superficial type of tumor and that an amputation of the involved limb was performed shortly after local excision of the lesion, are likely to be of significance in this respect. Our case illustrates the problem that the ultimate fate of patients with this type of soft tissue neoplasm is difficult to predict.

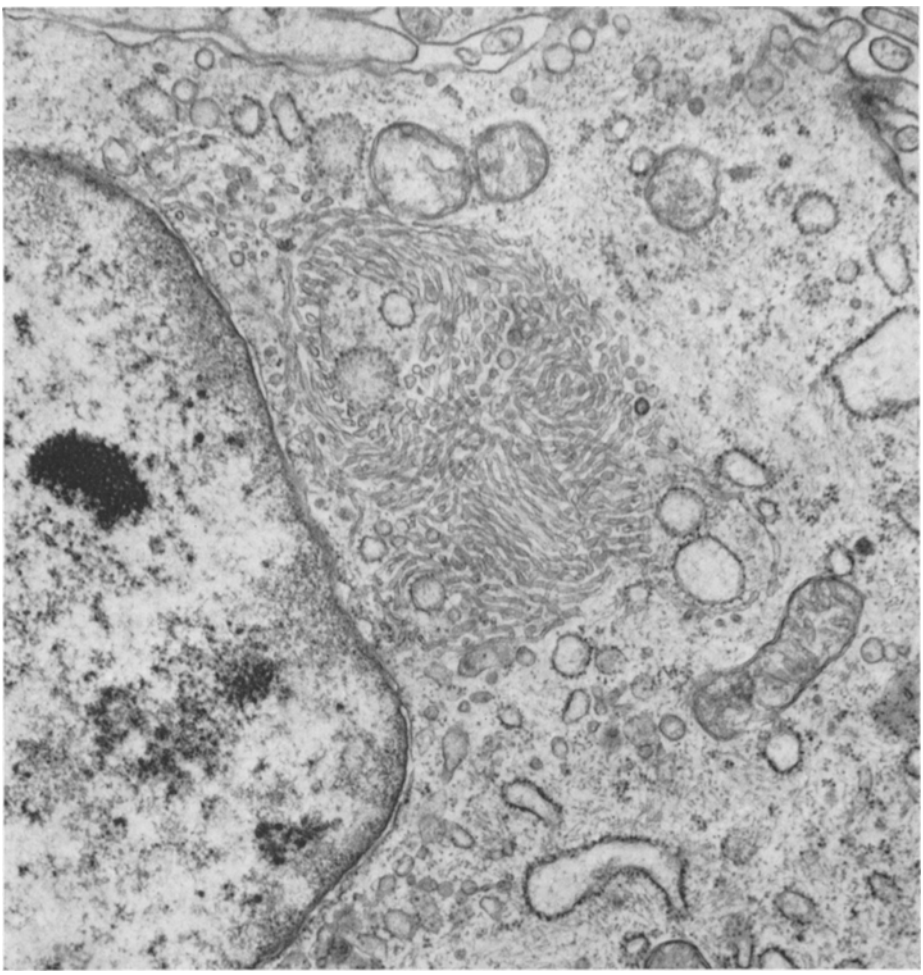

Fig. 12. Complex of smooth, branching tubular structures in close relation or continuous with outer leaflet of nuclear membrane as observed in some of neoplastic cells. ×30,000

We believe that malignant giant cell tumor of soft parts is probably a variant of mesenchymal fibrohistiocytic sarcoma and that its unique light-microscopic appearance justifies its separation from malignant fibrous histiocytoma (malignant fibroxanthoma; fibroxanthosarcoma). For this reason it is also worthwhile to correlate our fine structural findings to those described by Merkow et al. (1971) and Fu et al. (1975) in the lesions last mentioned (see Table 1). As regards the cell population, these neoplasms have a large variety of mesenchymal cells in common, in which one or the other cell type can prevail. Even at the electron-microscopic level, however, the real nature and origin of many individual neoplastic cells remain questionable. A fairly good correlation can also be demonstrated as regards the fine structural nuclear and cytoplasmic findings in the main cell type of each of the three variants mentioned above. Moreover, according to Merkow et al.

(1971), these electron-microscopic manifestations support the light-microscopic suspicion of malignancy in our case.

Further comment should be made on some aspects of three cellular elements namely (1) a prevalent type of tumor cells; (2) the cellular elements with some histiocytic features and (3) the multinucleated giant cells.

1. Many of the main principal cell type are characterized by a typical, elaborate endoplasmic reticulum with cisternae containing an electron-dense substance. Furthermore, the cytoplasmic filaments, the interdigitation with neighboring cells, the presence of lipid droplets, and well-developed Golgi complexes and the appearance of the extracellular matrix with its amorphous substance which corresponds to previous descriptions of chondroid or osteoid, are features seen in osteoblasts (Ghadially-Mehta, 1970), or chondroblasts (Spjut et al., 1971; Levine-Bensch, 1972; Steiner et al., 1973). In addition, it is interesting to note that osteoblastic differentiation with osteoid and bone formation, or chondroblastic differentiation with cartilage formation, have been described and demonstrated by Guccion-Enzinger (1972, Fig. 12) in their light-microscopic study of thirty-two cases of giant cell tumor of soft parts. This finding applies to our case, although sites of chondroid or osteoid formation are relatively scarce. One can also state that the lack of clear delineation of the cell membrane, as seen in light-microscopy, and the relatively small amount of glycogen in the tumor cells, might be against the theory of a chondroblastic origin for the predominant type of tumor cell.

When comparing our findings with ultrastructural observations of the main cells of the conventional giant cell tumor of bone (Horie, 1961; Hanaoka et al., 1970; Steiner et al., 1972), there appears to be a strong similarity between the stromal cells of these tumors (e.g., Fig. 9 in Steiner et al., 1972) and the predominant cells in our case (e.g., Fig. 4). Although opinions about histogenesis vary, the authors consider the stromal cells in the giant cell tumor of bone to be connective tissue cells with features suggestive of fibroblasts and histiocytes, rather than osteoblasts (Steiner et al., 1972).

Focusing on the presence of the intracytoplasmic filaments, the latter might suggest smooth muscle cells. However, the absence of paranuclear clustering of mitochondria, of pinocytotic vesicles, of a complete or incomplete basement lamina limiting individual tumor cells, as described for the normal smooth muscle cell and for leiomyosarcoma (Tobon et al., 1973; Darby et al., 1975), does not support that contention. In general, it can be said that the significance of the type of cytoplasmic filaments we are dealing with here remains obscure and nonspecific. Their presence has been described in a great variety of malignant tumor cells (Bernhard, 1969; Haguenau, 1969).

2. Some observations on a rather small number of cells remain of interest. The presence of "slits" or cleftlike spaces in the cytoplasm (Fig. 10) should be noted. Similar structures are known to be present in the normal granular pneumocytes (type II) and have also been described in the cells of a bronchiolar-alveolar tumor of primary alveolar origin (Basset et al., 1974). The same applies to the presence of the smooth, slender tubular structures depicted in Figure 12. In our material, however, these tubules occur in the paranuclear regions of the cytoplasm while in the human or murine pulmonary tumors (adenomas and adenocarcinomas)

Table 1

	Fibroxanthosarcoma (metastatic lesion) (Merkow et al., 1971)	Malignant Fibrous Histiocytomas (Fu et al., 1975)	Giant Cell Tumor of Soft Parts (Van Haelst et al., 1976)
Cell Population (Cell types)	1 dark- and light-staining cells (histiocytic cells) 2 fibroblasts 3 Xanthoma-type cells 4 giant cells	1 fibroblastlike cells 2 histiocytelike cells 3 immature cell (stem cell) 4 Xanthomatous cells 5 giant cells	1 undifferentiated cells (stem cell) 2 cells suggesting chondro- or osteoblast differentiation 3 histiocytic cells 4 fibroblasts 5 giant cells
	Neoplastic cells of type 1	*Neoplastic cells of type 2*	*Neoplastic cells of type 2 and 3*
Enlarged, hyperchromatic lobular nuclei	++[a]	+ (oval/kidney-shaped)	+
Nuclear projections	+[a]		+
Prominent nuclear envelope	+		++
Spheroidal nuclear body	+[a]	+	occasionally
Nuclear membrane-bound filaments	rarely[a]		+
Dense nucleoli	+		++
Solitary r.e.r. Abundant r.e.r.	+ (in light cells) + (in dark cells)	+ (and abundant s.e.r.)	+ (abundant in type 2)
Small mitochondria Giant mitochondria	+ (in light cells) + (in dark cells)[a]		+ −
Lysosomes	numerous	+	small; not numerous
Golgi complexes	prominent	prominent	prominent
Lipid bodies	+		+
Glycogen	infrequent		++ (in some cells)
Intracytoplasmic filaments	+[a]	+ (in 1 case)	++
Interdigitation of plasmalemma	+ (and microvilli)	+	+ (and microvilli)

Desmosomelike structures	+[a]	+	+ (infrequent; half-desmosomes between cells and matrix)
Viruslike particles	frequent		occasionally
Annulate lamellae	frequent[a]		—
Tubular structures (in e.r.)		+	—
			cleftlike spaces[b]
			undetermined inclusion bodies[b]
			paranuclear tubular structures[b]
	Cells of type 2	*Cells of type 1*	
Lobular nucleus	+	elongated nucleus/invaginations	
R.e.r.	abundant	abundant	
Cytoplasmic filaments	+	+	
	Cells of type 4	*Cells of type 5*	*Cells of type 5*
Mitochondria	numerous and small	numerous/small	numerous/small
Coiled nucleolus	+		+
		Cells of type 3	*Cells of type 1*
Cell surface		Smooth	Smooth
Nucleus		round; relatively large	round; relatively large
Cytoplasm		small	small
R.e.r.		rare	rare
Golgi complexes		rare	rare
Lysosomes		small	—
Extracellular space	amorphous mat. (hyaline?) fibrin	a few collagen fibers immature fibers microfilaments	a few collagen fibers and microfilaments with focal electron-dense material

[a] Electron-microscopic manifestations suggesting malignancy in fibroxanthosarcoma (Merkow et al., 1971)
[b] Additional findings in histiocytic cells (type 3)

mentioned above, they appear to be localized within the nuclei of the tumor cells (Coalson et al., 1970; Flaks-Flaks, 1970; Kuhn, 1972). For the time being, it is uncertain whether these findings can enhance our insight into the nature of the cells of the giant cell tumor of soft parts. In this respect we would refer to a recent publication by Wang et al. (1976) on giant cell carcinoma of the lung. These authors state that the cellular origin of this tumor is not completely clarified and express an opinion as to whether it originates from epithelial or from primitive multipotential cells.

Cytoplasmic "slits" have also been described in typical histiocytes (macrophages) with extremely lobulated nuclei in lesions of the eosinophilic granuloma type (Morales et al., 1969; Figs. 6 and 7). In contrast to their findings, extensive investigation of many slides of our material could not convincingly demonstrate the presence in the cytoplasm of so-called Birbeck's granules (Langerhans'cell granules). In our view, demonstration of these granules strongly supports the histiocytic or macrophage nature of a cell, an opinion supported by the literature on this subject (van Haelst, 1969; Morales et al., 1969; Shamoto, 1970; Vernon et al., 1973).

Although inclusion bodies (see Fig. 11) are rarely observed in our material, their presence may be of some interest. Until now, the real nature of these structures (phagocytozed material? pigment granules? parasitic remnants?) is uncertain. As far as we know, there have been no previous reports of such bodies, neither in the tumor we are dealing with here, nor in other neoplasms of epithelial or mesenchymal origin.

3. The light- and electron-microscopic appearance of the multinucleated giant cells is the same as that of the giant cells described in other tumors of soft tissue e.g., leiomyosarcoma (Salm-Sissons, 1972; Darby et al., 1975), of bone e.g., giant cell tumor, of cartilage e.g., chondroblastoma, or even of normal osteoclasts. In contrast, they do not have the epithelial features which have been demonstrated in giant cells occurring in tumors of epithelial origin, such as carcinomas of the thyroid or pancreas (Rosai, 1968).

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Dr. U. van Haelst
Department of Pathology
C. University of Nijmegen
Geert Grooteplein Z 24
Nijmegen
The Netherlands