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Angiomatoid malignant fibrous histiocytoma

Evidence for the histiocytic origin of tumor cells

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Summary. The results of an histological, immunocytochemical and electron microscopic study of an angiomatoid malignant fibrous histiocytoma are reported. Our results support an histiocytic, rather than an endothelial origin for the tumor cells.

Key words: Angiomatoid malignant fibrous histiocytoma – Histiocytic origin – Immunocytochemistry – Electron microscopy

Introduction

In 1979 Enzinger described a tumour with the combined features of haemangioma and histiocytoma, which he termed an "angiomatoid malignant fibrous histiocytoma". In this series, all 41 tumours described were found in the subcutaneous tissue of young adults. Two recent electron microscopic reports (Leu and Makek 1982; Sun et al. 1982) deal also with this type of tumour, whose histogenesis remains an enigma.

The purpose of this report is to present histological, electron microscopic and immunohistochemical evidence favoring the histiocytic origin of angiomatoid malignant fibrous histiocytoma.

Patient

An 18 year old male presented a small, firm subcutaneous nodule in his left axilla. The tumour had been growing slowly for approx. six months. It was excised with local anaesthesia. A check-up including biopsies of the liver and spleen revealed no metastasis. During the follow-up of 3 years, there was no evidence of local recurrence of the tumour or metastases.

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Material and methods

The firm tumour (3 × 2 × 1,5 cm) was sharply delimited. Its cut surface was yellow-brown with red spots. Samples were fixed in liquid formaldehyde (4%). For histology deparaffinized sections (5 μm) were stained with H+E, van Gieson's, Giemsa's, PAS, Prussian blue and reticulin stains (Gomori's technique). Incubations with antibodies and lectins were carried out on deparaffinized sections (5 μm). For immunohistology the unlabeled antibody enzyme method (Sternberger 1979) was used, as described in detail previously (Heitz et al. 1983). Rabbit antibodies (Dakopatts, Copenhagen) to factor XIII-related antigen (dilution 1:1000), chymotrypsin (E.C. 3.4.21.1; 1:1000), and lysozyme (E.C. 3.2.1.17; 1:2000) were applied. The histochemical reaction for peroxidase was carried out using 3,3′-diaminobenzidine-tetrahydrochloride (DAB; 0.05% w/v) and hydrogen peroxide (0.01% v/v) in 0.05 M Tris-HCl buffer (pH 7.6) for 1–6 min at room temperature. The sections were then fixed in aqueous osmium tetroxide (1%) for 20 min. Subsequently, staining of the same sections with Prussian blue was carried out. In addition, Ulex europaeus agglutinin I (UEA I; 1:100; MEDAC, Hamburg) coupled to horseradish peroxidase was applied for the visualization of endothelial cells. The peroxidase was localized as described above.

Control tissues. The endothelium of blood vessels of tissue adjacent to the tumour, from normal skin, from subcutaneous tissue and from capillary haemangiomas, served as control material for the reaction of factor VIII-related antigen and UEA I. Tissue from cutaneous histiocytomas and the inflamed area surrounding the tumours was used to test for chymotrypsin and lysozyme.

Technical controls included the use of phosphate-buffered saline as first, second, or third layer, and the ommission of hydrogen peroxide or DAB from the incubation medium of the histochemical reaction for the visualization of peroxidase.

For electron microscopic investigations, tissue blocks fixed in formaldehyde were postfixed in osmium-tetroxide (1%) and embedded in Epon. Semithin sections (1 μm) were stained with toluidin blue. Thin sections (660–800 nm) were stained with uranylacetate and lead citrate, and viewed in a Zeiss EM 9 electron microscope.

Results

Histologically, a layer of collagen fibers is evident at the periphery of the excised nodule which consists of infiltrates forming follicles, suggesting the structure of a lymph node. The infiltrates penetrate the adjacent adipose tissue and muscle. Some pseudocysts, devoid of endothelial cell lining and filled with erythrocytes (diameter up to 3 mm) and some small areas of haemorrhage, are irregularly distributed throughout the nodule (Fig. 1). The actual tumour tissue forms sharply delimited round or ovoid areas consisting of irregularly arranged large, oval, or spindle-shaped cells with a pale cytoplasm and indistinct cell boundaries (Fig. 2). Their nuclei are large, ovoid, and contain small nucleoli. Mitotic figures are uncommon. The cytoplasma often contains small deposits of haemosiderin. There are only a few irregularly arranged reticulin fibers. At the periphery of the nodules, there is a very dense infiltrate consisting mainly of macrophages and plasma cells, which contain coarse deposits of haemosiderin. In these areas there is a variable amount of collagen fibers and some thickwalled vessels.

The *immunocytochemical analysis* fails to detect either factor VIII-related antigen immunoreactivity or binding of UEA I in the tumour cells. Endothelial cells of the capillaries in the tumour are clearly outlined (Fig. 3). Chymo-

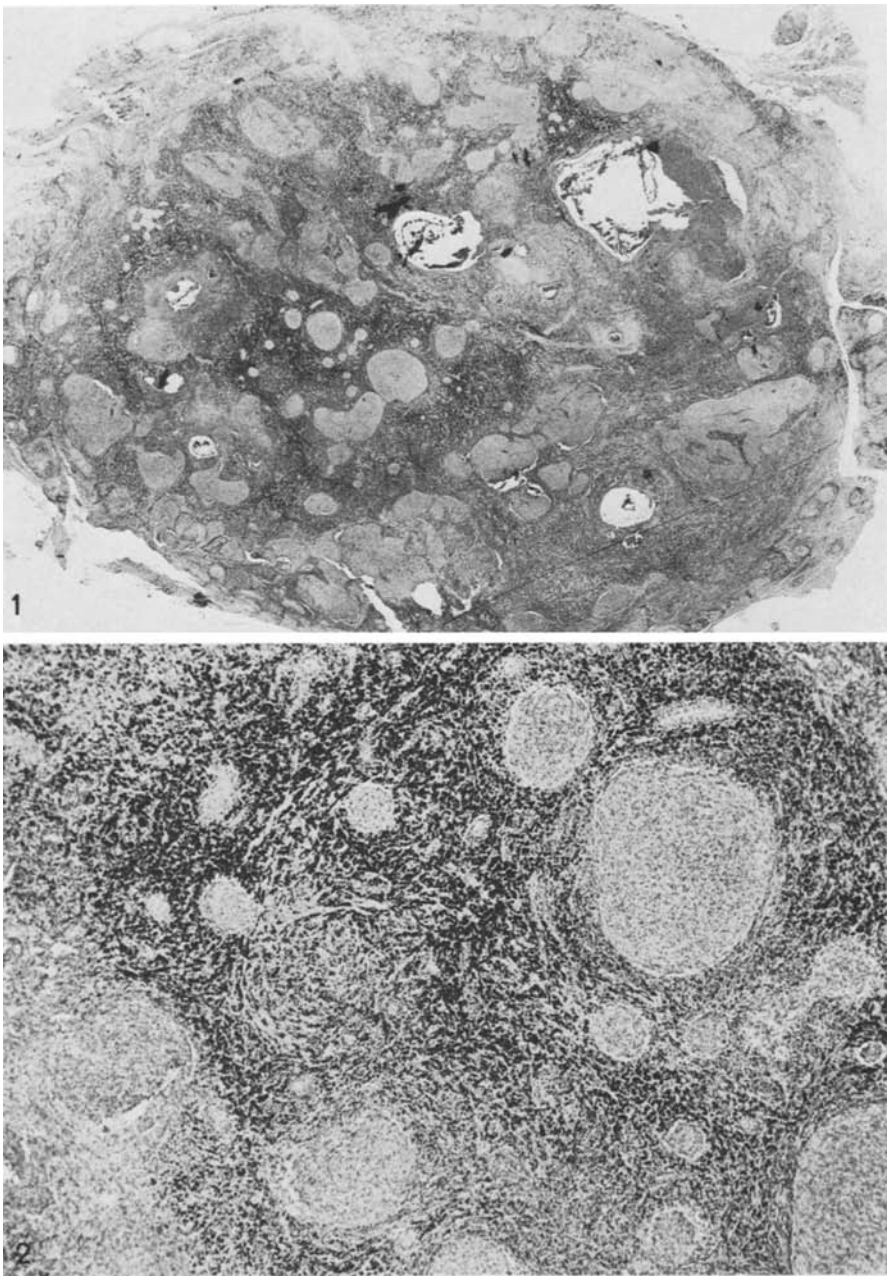
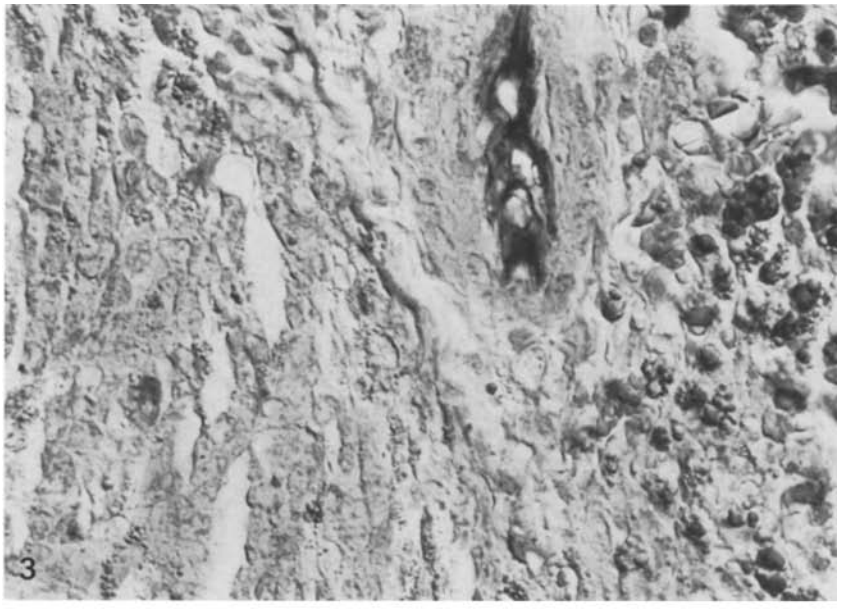


Fig. 1. Angiomatoid malignant fibrous histiocytoma with characteristic nodular proliferation, haemorrhagic cysts, and a dense inflammatory infiltrate resembling a lymph node metastasis. H+E, ×7.5

Fig. 2. Tumour nodules surrounded by a dense infiltrate with coarse deposits of haemosiderin. H+E, ×40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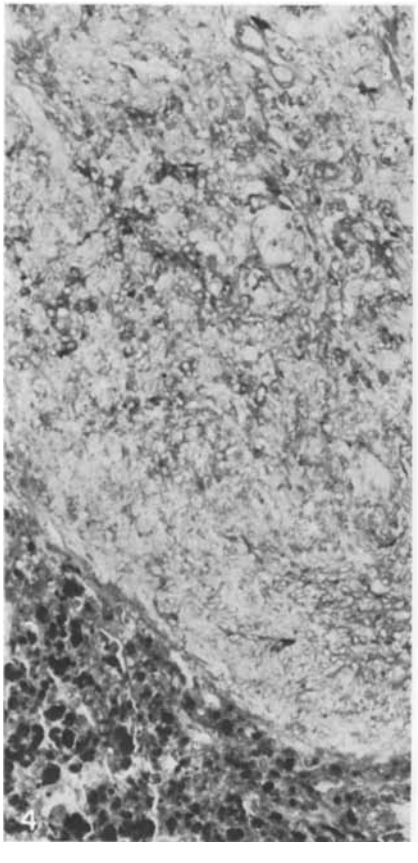
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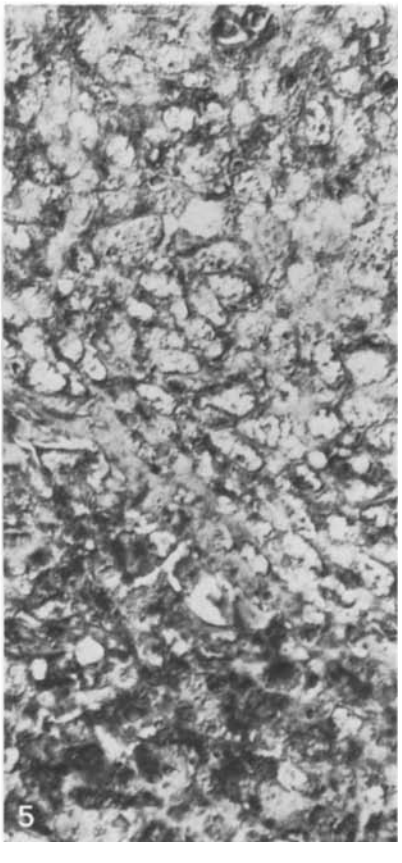
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trypsin and lysozyme-immunoreactivities are present in a large number of the tumour cells. In many cells, the immunocytochemical reaction product and finely granular haemosiderin deposits are co-localized in the cytoplasm (Fig. 4 and 5). The fine haemosiderin deposits are distinctly different from the coarse deposits present in histiocytes and in the plasma cells of the inflammatory reaction surrounding the tumour.

In the *control tissues*, endothelial cells are made visible both by the immunoreaction for factor VIII-related antigen and by UEA I. Histiocytes can be recognized by their reactions to antisera directed against chymotrypsin and lysozyme. All technical control reactions were invariably negative.

The preservation of the *ultrastructure* is less than optimal, due to the primary fixation of the tissue in formaldehyde. A variable amount of desmosome-like structures are present between adjacent cells. The ovoid nuclei show peripheral chromatin condensation and small nucleoli (Fig. 6). In the cytoplasm of many tumour cells, electron-dense lysosomes containing haemosiderin are conspicuous. Pinocytic vesicles are lacking. In several tumour cells fine cytofilaments are present, sometimes in concentric arrangement around the nuclei. The intercellular spaces are often irregularly widened and contain an electron-dense basal lamina-like material, which includes some collagen fibers. Plasma cells and macrophages contain fragments of phagocytosed erythrocytes and polymorphous lysosomes with haemosiderin granules (Fig. 7).

Discussion

According to Enzinger (1979), a tumour must fulfill the following criteria to be classified as angiomatoid malignant fibrous histiocytoma: 1) Nodular proliferation of spindle cells, 2) presence of small cysts filled with blood, small haemorrhages and deposits of haemosiderin, and 3) dense inflammatory infiltration of lymphocytes and plasma cells, resembling a lymph node metastasis.

In Enzinger's series of 41 patients, the tumours occurred for the most part in young people (mean age 13 years, range 6 months to 43 years) and were localized in the subcutaneous tissue of the limbs (35 tumours). Some patients suffered from loss of weight, fever and anaemia. In 11 patients, the tumour recurred locally (most often within 1 year after excision), 5 patients had metastases, and 3 patients died thereof. The only therapy

Fig. 3. Clearly outlined endothelium of a small vessel. Absence of peroxidase reaction product in the tumour (*left*). Ulex europaeus agglutinin I. Differential interference contrast optics, × 500

Fig. 4. Immunoreactive chymotrypsin in many tumour cells. Coarse haemosiderin deposits in the surrounding tissue (*bottom*). Unlabeled antibody enzyme method for chymotrypsin, counterstaining with Prussian blue. × 125

Fig. 5. Immunoreactive lysozyme present in the cytoplasm of tumour cells (*top*). Unlabeled antibody enzyme method differential interference contrast optics, × 500

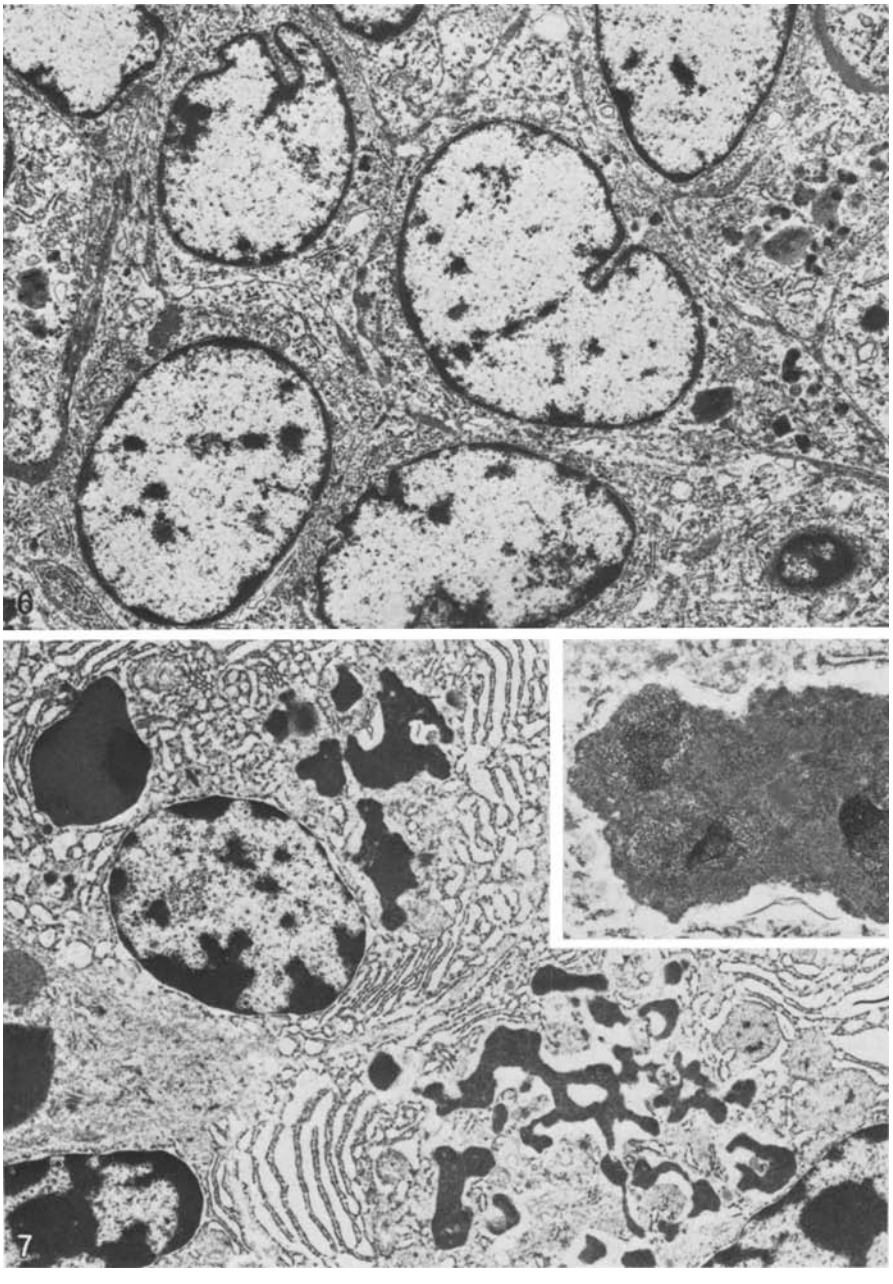

Fig. 6. Group of tumour cells with large ovoid nuclei. The cytoplasma contains unevenly distributed polymorphous lysosomes, × 5,500

Fig. 7. Intersitital plasma cells with phagocytosed fragments of erythrocytes, × 5,500. *Inset*: Compound siderosome in the cytoplasma of a plasma cell with iron containing particles, × 14,000

is surgical excision. Enzinger did not find any correlation between the histological grade of differentiation and the biological behaviour of the tumour.

Enzinger considered angiomatoid malignant fibrous histiocytoma to be a proliferation of fibroblast-like and histiocyte-like cells. He found a storiform pattern of growth in only three tumours and cellular lipoid storage and multinucleated giant cells in a further four tumours. He did not consider the tumour to be of vascular origin. In this context it is interesting to consider some of the diagnoses made by pathologists of the tumours referred to Enzinger: Haemorrhagic cyst, (sclerosed) haemangioma, haemangiosarcoma, histiocytoma, and plasmacytoma.

Few other reports have dealt with identical or similar tumours. They have been classified as haemangioendothelioma of lymph nodes (Gall and Rappaport 1958, 1966) or as "cellular angioma" and as "vascular lesion with histiocyte-like or fibroblast-like cells" at electron microscopy (Sun et al. 1982). In our opinion, another tumour, in which striated and smooth muscle fibers were components found at electron microscopy, does not meet the above-mentioned criteria (Leu and Makek 1982).

The tumour presented in this report fulfilled Enzinger's criteria. In our opinion, the mixture of nodular tumour tissue with the inflammatory reaction is characteristic for malignant fibrous histiocytoma, but presents a real diagnostic problem. The electron microscopic findings do not exclude an endothelial origin for the lesion. In contrast, the results obtained in this study by immunocytochemistry point to an *histiocytic origin* of at least some of the tumour cells. The storage of haemosiderin in tumour cells containing chymotrypsin- and lysozyme-immunoreactivity is an important argument in favor of an histiocytic origin. Furthermore, the lack of factor VIII-related antigen and of the binding of UEA I to tumour cells, argues against an endothelial origin. The reactions used in this study can be considered specific, as specific cells could be visualized in control tissues, and all technical controls were invariably negative.

Plasma cell iron was a very prominent feature in our case. This is uncommon, but has been described in conditions of local iron overload secondary to haemorrhage or tissue necrosis (DeLellis 1971), in alcoholics or patients with refractory anaemia, porphyria cutanea tarda, plasma cell dyscrasia, and haemochromatosis (McCurley et al. 1984).

In our opinion, the results presented in this study argue strongly in favor of a predominantly histiocytic origin of the tumour. Our findings therefore support Enzinger's hypothesis (1979). The relationship of angiomatoid malignant fibrous histiocytoma to a tumour of similar histological appearance, the aneurysmal (malignant) fibrous histiocytoma of the skin (Santa Cruz and Kyriakos 1981), remains to be established. The histological characteristics of histiocytic haemangioma (Rosai et al. 1979) are different from those of angiomatoid malignant fibrous histiocytoma despite the similarity of the terms.

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