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Malignant Histiocytosis

Immunohistochemical Characterization on Paraffin Embedded Tissue

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Summary. Clinically, malignant histiocytosis is a malignant neoplasia with poor prognosis. Diseased are lymphnodes (especially cervical nodes), liver, spleen and bones. Few cases become leukemic. The cells show characteristic pale roundish, often indented nuclei, without large nucleoli and with abundant ill-defined cytoplasm. Phagocytosis of erythrocytes and leukocytes, as well as, hemosiderin deposits may serve as indicators for histiocytic, respectively macrophagic qualities. On touch preparation, tumor cells previously had been marked by acid phosphatase and non-specific esterase, as being histiocytic. – A comparable marking could be carried out on paraffin embedded material with lysozyme (muramidase) and alpha$_1$-antichymotrypsin, by the indirect immuno-peroxidase technique. No correlation could be proven between any special shape of tumor cells or between different grades of cellular atypism and presence or absence of the immunohistochemical reaction. The reaction with lysozyme and alpha$_1$-antichymotrypsin was also tested in other tumors and was found to be positive in a variety of different tumor cells showing degenerative changes, respectively necrobiosis. – But lysozyme and alpha$_1$-antichymotrypsin are markers characteristically found in histiocytes, respectively histiocytic tumor cells. They are apparently less distinct in MH with a larger number of immature histiocytic tumor cells.

Key words: Malignant histiocytosis – Immunohistochemical characterization of paraffin embedded material.

Zusammenfassung. Klinisch handelt es sich bei der malignen Histiocytose um eine maligne Neoplasie mit schlechter Prognose. Erkrankt sind Lymphknoten (besonders Halslymphknoten), Leber, Milz und Knochen bzw. Knochenmark. In einzelnen Fällen kann eine Ausschwemmung mit leukämischem Bild vorliegen. Die proliferierten Zellen zeigen charakteristischerweise blasse

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rundliche, oft eingebuchtete Kerne ohne große Nucleolen und reichlich unscharf umschriebenes Cytoplasma. Phagocytose von Erythrocyten und Leukocyten sowie Hämosiderinablagerungen dienen als Indikatoren für histiocytäre bzw. makrophage Eigenschaften der Tumorzellen. In Abdruckpräparaten wurden die Tumorzellen vorher schon cytochemisch durch eine positive Reaktion mit saurer Phosphatase und nichtspezifischer Esterase als histiocytär gekennzeichnet. Eine vergleichbare Kennzeichnung konnte am Paraffin-eingebetteten Material mit Lysozym (Muramidase) und Alpha$_1$-Antichymotrypsin durch die indirekte Peroxydase-Technik durchgeführt werden. Dabei ergaben sich keine Korrelationen zwischen besonderen Formen der Tumorzellen, unterschiedlichen Graden der Differenzierung und positiver oder negativer immunhistochemischer Reaktion. Die Reaktion mit Lysozym und Alpha$_1$-Antichymotrypsin wurde auch bei anderen Tumoren untersucht. Dabei fanden sich positive Ergebnisse bei mehreren Tumorzellen, die degenerative Veränderungen bzw. Nekrobiose aufwiesen. Aber Lysozym und Alpha$_1$-Antichymotrypsin zeigen Reaktionen, die typisch für Histiocyten bzw. histiocytäre Tumorzellen sind. Offensichtlich sind diese Reaktionen weniger ausgeprägt in Fällen mit MH, die eine größere Zahl unreifer Tumorzellen aufweisen.

Introduction

Malignant histiocytosis (MH), identical with "histiocytic medullary reticulosis" (Scott and Robb-Smith, 1939; Hardmeier et al., 1969; White et al., 1976; Huhn et al., 1978; Huhn and Meister, 1978), has to be included in the differential diagnosis of various malignancies, for example undifferentiated carcinomas or amelanotic melanomas. This diagnosis should be considered in lesions of lymphnodes particularly those, which cannot be classified as malignant lymphomas of Hodgkin- or non-Hodgkin type.

The purpose of this study is to examine to what extent immunohistochemical characterization of histiocytic tumor cells can be carried out on routine paraffin embedded material.

Applying the indirect immunoperoxidase technique, lysozyme (L) (muramidase) and alpha$_1$-antichymotrypsin (AC) were used as markers for histiocytic tumor cells (Motoi et al., 1978; Neville et al., 1978; Papamitriou et al., 1978).

Material and Methods

9 of 16 patients with MH, who previously had been characterized cytochemically and electronmicroscopically (Huhn et al., 1977; Huhn and Meister, 1977) served for testing the value of staining for lysozyme and alpha$_1$-antichymotrypsin as markers for enzymatic activity of histiocytic tumor cells. 5 µm sections of formalin fixed paraffin embedded tissue were used for the indirect immunoperoxidase technique with slight modifications, for example pronase pretreatment to reduce background staining (Burns, 1975; Heyderman and Neville, 1977; Witting, 1977; Meister et al., in press).

In controls, phosphate buffered solution (PBS) was used without antisera.

Pronase was kindly supplied by Sigma Chemie GmbH, Neubiberg-München/Germany, antisera to lysozyme and alpha$_1$-antichymotrypsin by DAKO/Denmark and Boehringer-Ingelheim/Germany,

peroxidase-labelled goat anti rabbit IgG antibodies by Miles-Yeda-GmbH, Frankfurt/Germany and 3-amino-9-ethylcarbazole for demonstration of peroxidase activity by Sigma Chemie GmbH Neubiberg-München/Germany.

Positive reactions with L or AC were compared with each other and with the results which previously had been obtained for acid phosphatase, non-specific esterase and peroxidase in the same cases on imprint preparations (Huhn et al., 1977; Huhn and Meister, 1977).

Positively reacting cells were classified by their morphology as typical histiocytes (including xanthomatous cells) or fibroblast-like and intermediary cells. 3 grades of atypicality of tumor histiocytes were distinguished.

The immunohistochemical results were also related to other signs of histiocytic function such as phagocytosis of erythrocytes or leucocytes and haemosiderin deposits. All 16 cases were also studied by H & E, Giemsa, PAS, Prussian-blue stains and silver impregnation.

Results

Our material included 16 patients, the clinical data of which are summarized in Table 1.

Histologically a diffuse proliferation was found with infiltration of the diseased tissue by cells which showed roundish, occasionally kidney shaped, and rarely spindly nuclei and little fiber formation, if any (Fig. 1a). Many of the cells revealed abundant pale eosinophilic cytoplasm. With increasing atypicality, larger vesicular nuclei and distinct narrowing of the cytoplasmic rim became

Table 1. Clinical features

Patient	Age/sex	Inital symptom	Topographic distribution	Death
1.	29/m	pancreatic CA?	generalized LN, liver, spleen, bones, heart, lungs	14 mo.
2.	33/m	mediastinal TU	generalized LN, pleura, pericardium, subcutis	12 mo.
3.	42/f	osteolysis, maxilla	generalized LN, liver, spleen, bones; *leukemic*	2 mo.
4.	64/f	parotid TU	bone marrow	
5.	62/m	cervical LN-TU		3 mo.
6.	43/m	hepato-splenomegaly		
7.	36/m	epipharynx/cervical LN-TU		11 mo.
8.				6 mo.
9.	16/f	cervical/axillary LN-Tu	*leukemic*	
10.	70/f	skin TU, multiple		
11.	68/f	LN-TU, multiple	bone marrow	
12.	67/f	axillary LN-Tu		
13.	56/f	parotid TU		
14.	23/f	epipharynx/cervical LN-TU		
15.	41/f	vaginal TU	pelvic TU, hepato-splenomegaly, kidneys	12 mo.
16.	35/m	pelvic TU		

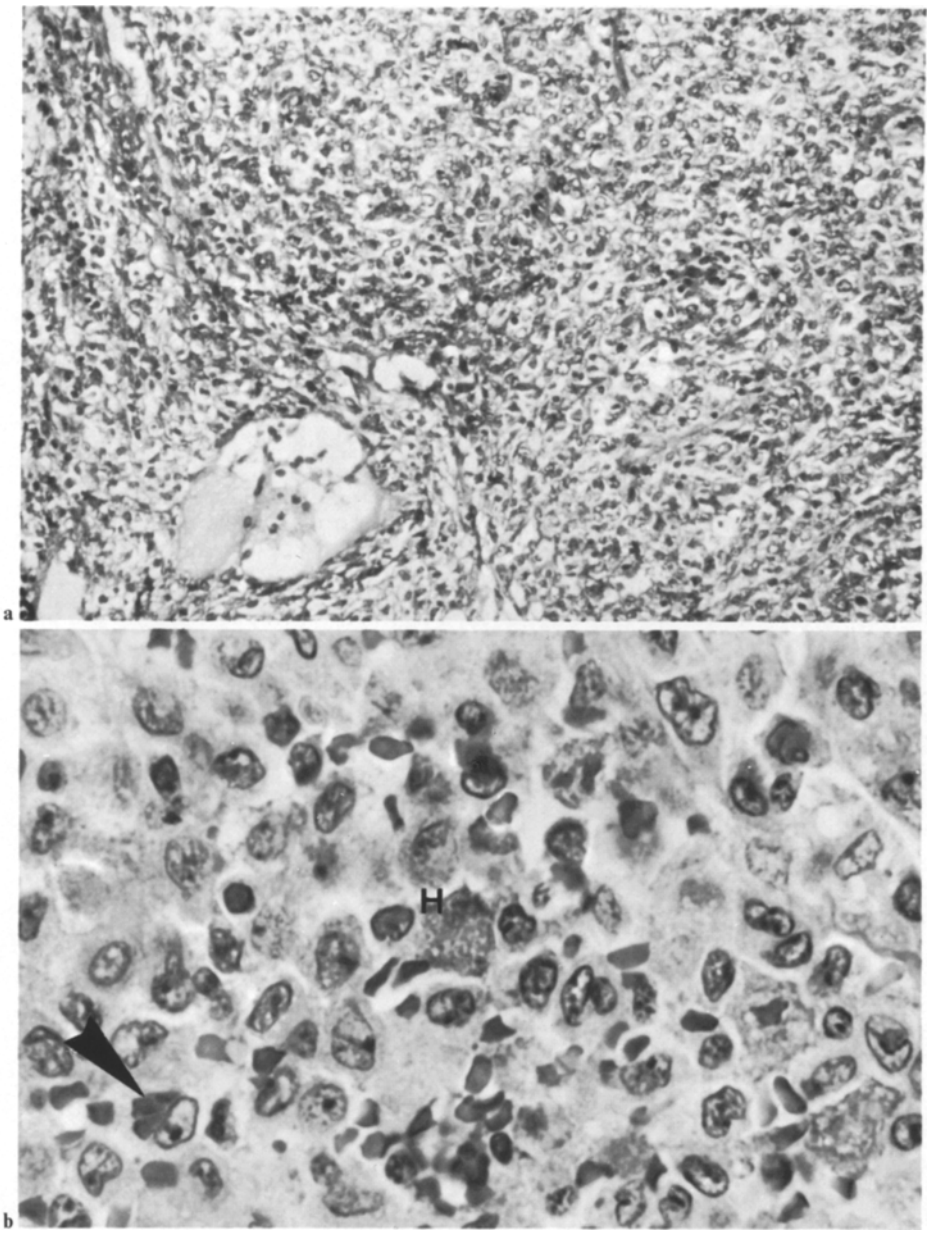

Fig. 1. a Lymphnode with MH, showing obliterated architecture by proliferated cells with pale roundish nuclei, without marked atypism (our grade I) and without distinct nucleoli. Ill-distinct cell borders. H & E, ×63. **b** MH with marked atypism, with irregular nuclei and occasional large nucleoli (our grade III). Phagocytosis of erythrocytes (→). Hemosiderin-ladden tumor cell with dark granular cytoplasm (*H*). H & E, ×400

Table 2. Histological and immunohistochemical findings

Patient	Atypism	Mitoses	Erys-phagocytosis-leucos		Hemo-siderin	Lyso-cyme	Alpha$_1$-antichymo-trypsin
1.	+	+	+	+	++	+++	+++
2.	+++	++	+	○	+	++	+++
3.	+++	+++	○	○	(+)	+	++
4.	++	+			○	+	+
5.	+++	++	++	++	○	+	+
6.							
7.	++	++	+	○			
8.							
9.	++	+	+	+	(+)	(+)	+
10.						○	○
11.	+	○	+	○		+	+
12.	++	++	+	○	○	++	++
13.	++	++	+	+	?	+	++
14.	++	+	++	++	○	++	+
15	+	++	++	++	+	(+)	+
16.	++	++	++	++	○	++	++

evident (change in nuclear/cytoplasmic ratio). Few cases, especially with marked atypicality, showed Hodgkin-, or Sternberg-like cells. However, no multinucleated giant cells without nuclear atypicality like Touton-cells, were found.

Mitoses were almost always found with MH. They were of varying number and sometimes atypical. There was a sprinkling of inflammatory cells between the tumor histiocytes, these were chiefly neutrophilic with some eosinophilic granulocytes. Only exceptionally were there spindle cells, with a suggestion of storiform pattern and slight focal formation of reticulin fibers. Only one case contained xanthomatous cells. Occasionally tumor histiocytes presented a finely granular eosinophilic cytoplasma, which was also PAS-positive. Phagocytosis of erythrocytes and leukocytes, chiefly neutrophilic granulocytes, was considered as the main evidence for histiocytic nature of tumor cells. The ingested material was frequently surrounded by a halo. Also evaluated as histiocytic feature were haemosiderin deposits (Fig. 1 b) which were emphasized by Prussian-blue stains.

The pertinent histological and cytological features are summarized in Table 2. They are compared with the the staining with lysozyme (L) (muramidase) and alpha$_1$-antichymotrypsin (AC). Positive reaction with L and AC was expressed by finely granular, occasionally somewhat coarser orange brown structures, which were to some extent located along the cell membrane (Fig. 2a, b; Fig. 3a, b). Histiocytic tumor cells of varying configuration and different grades of atypicality would show a positive reaction, including multinucleated giant cells and even spindle cells with fiber formation. Cells of similar appearance could also be negative. A positive reaction, sometimes of coarser quality, was seen around ingested erythrocytes or leukocytes. Haemosiderin-laden tumor cells were frequently and characteristically found to be negative with L and AC stains.

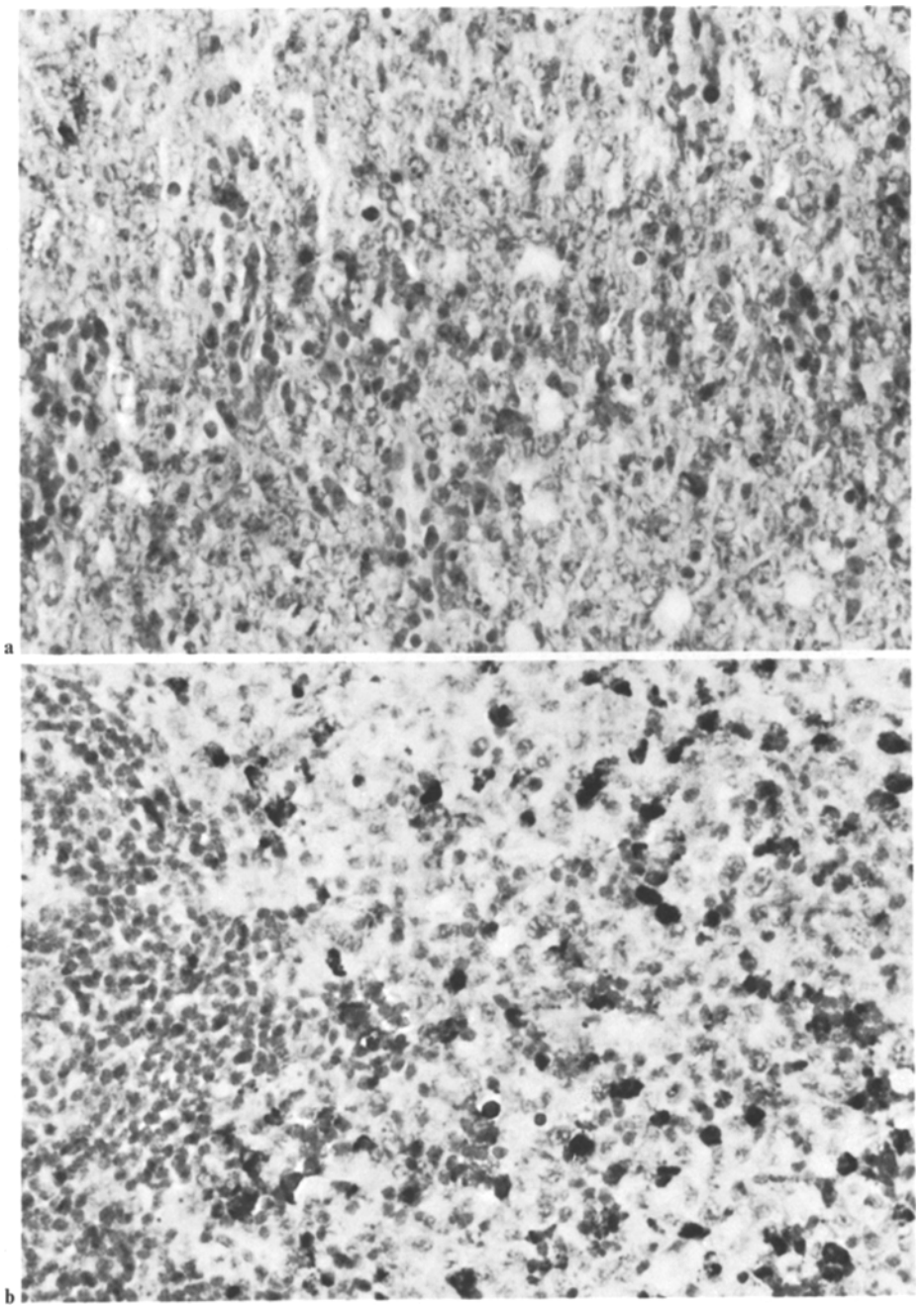

Fig. 2. a Lymphnode with MH: case with only moderate number of cells marked by lysozyme. Positive cells contain greyish to black cytoplasmic granules and are not easily recognizable by the applied magnification. Lysozyme, × 100. **b** Same case with easily recognizable marked cells by alpha$_1$-antichymotrypsin. Left margin: remnant of lymphfollicle. Alpha$_1$-antichymotrypsin, × 100

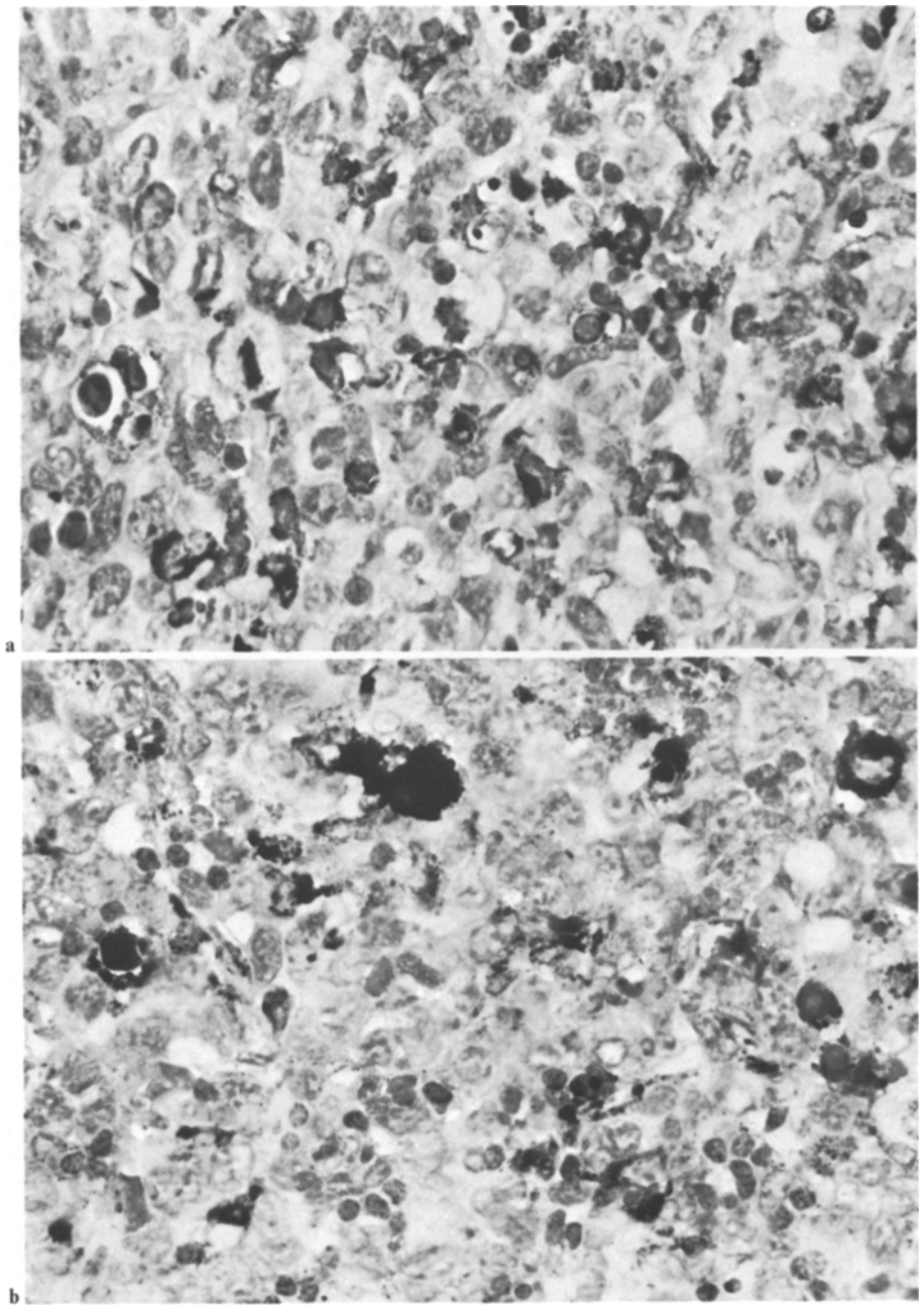

Fig. 3. a Area of MH with marked atypism. Positive gray-granular cytoplasmic marking does not reveal preferences for any special cell-forms. Lysozyme, ×400. **b** Positive cells of MH stand out even more distinctly and are densely packed by black granules with alpha$_1$-antichymotrypsin. Alpha$_1$-antichymotrypsin, ×400

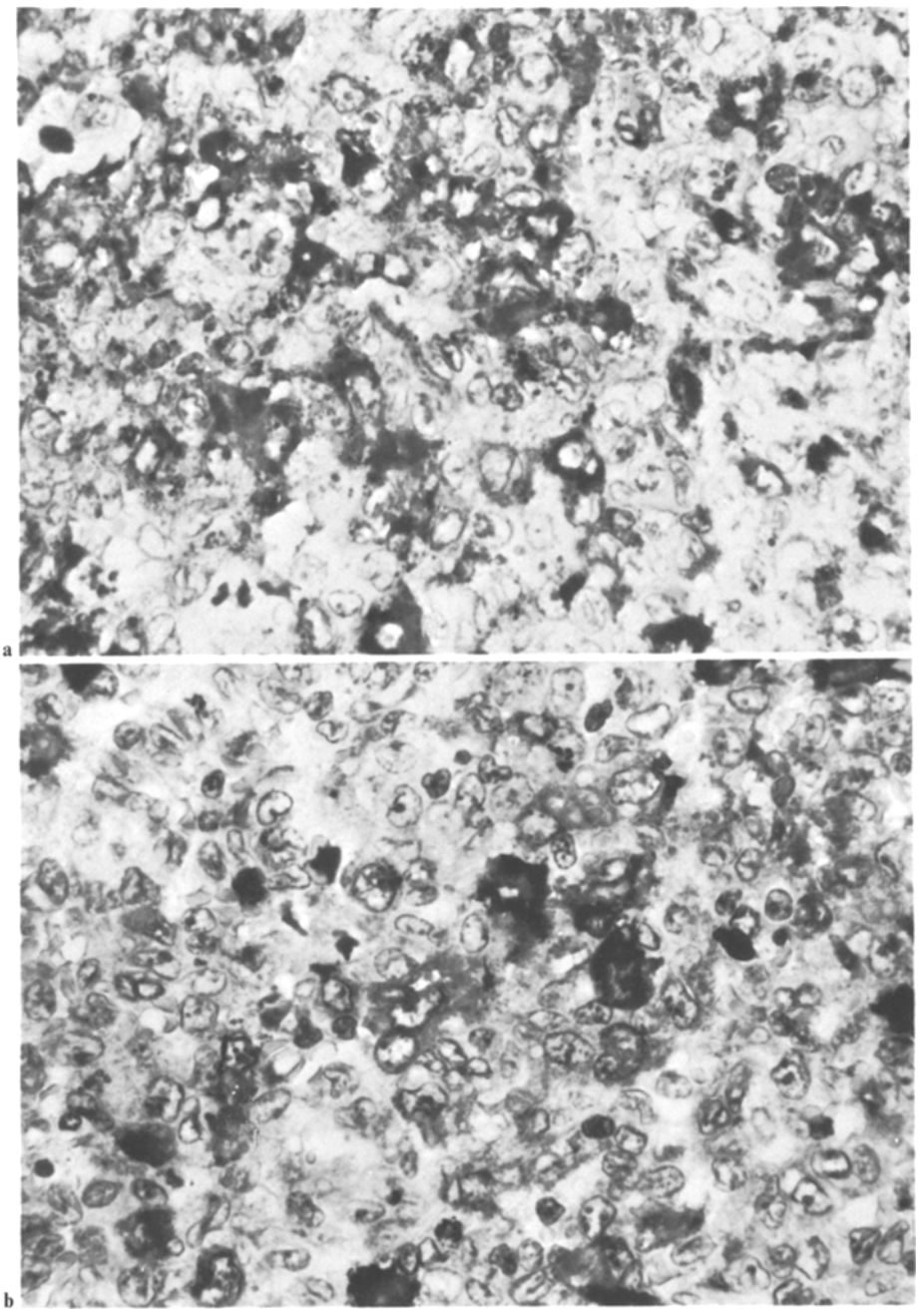

Fig. 4. a Comparison with cases of histiocytosis X, showing less atypism and frequently indented nuclei. As a rule, a higher number of cells shows positive marking with lysozyme. Lysozyme, ×400. **b** Histiocytosis X, also with more distinct granulation by alpha$_1$-antichymotrypsin. Alpha$_1$-antichymotrypsin, ×400

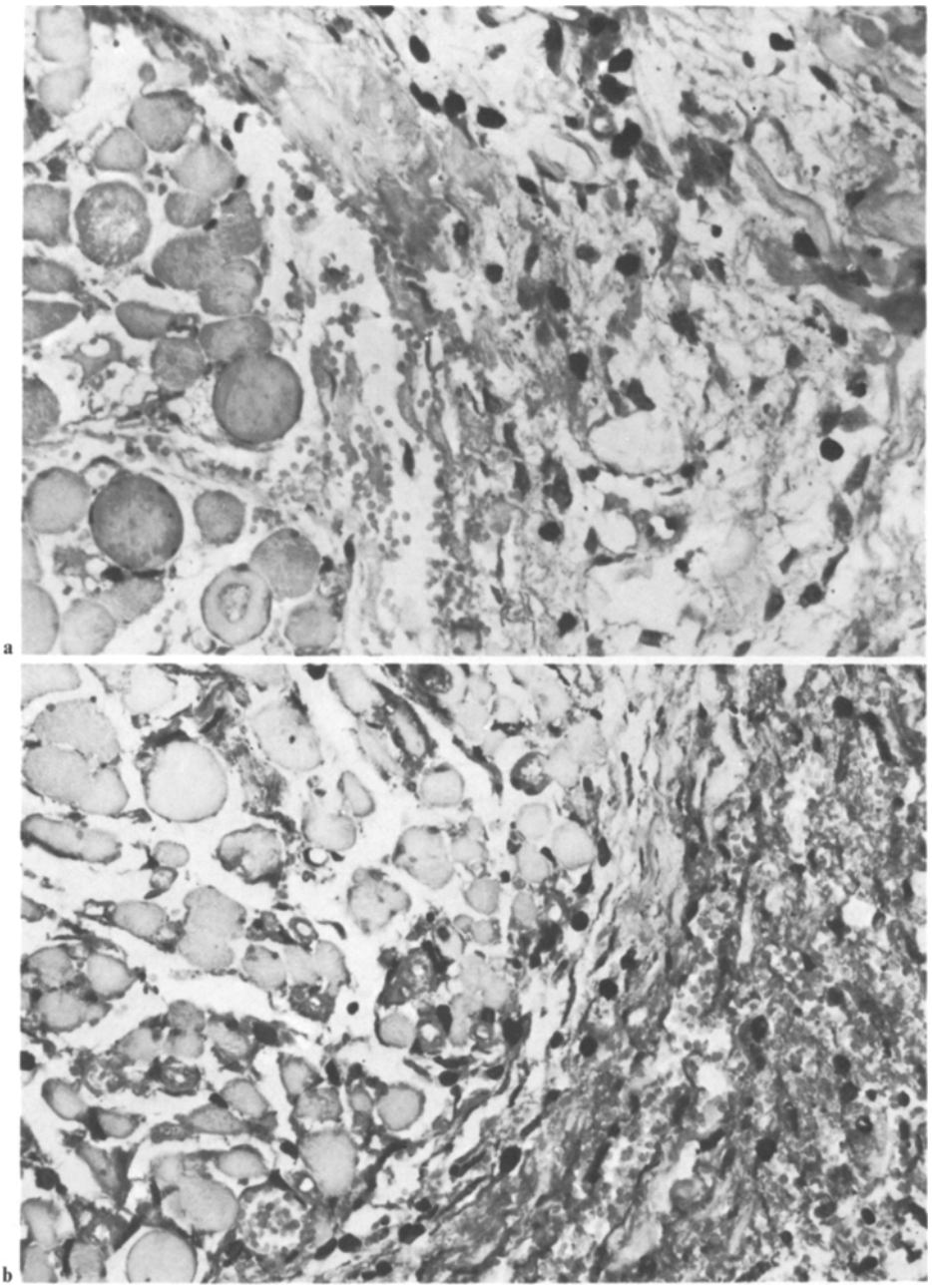

Fig. 5. a Granulation tissue and skeletal muscle: obligatory staining of histiocytes and neutrophilic granulocytes by lysozyme. Lysozyme, ×100. **b** Also in granulation tissue distinct, dark stains with alpha$_1$-antichymotrypsin. Alpha$_1$-antichymotrypsin, ×100

Table 3. Comparison between cytochemistry and immunohistochemistry on paraffin sections.

Patient	Acid	Phos-phatase	Non-specitic esterase	Perox-idase	PAS	Lyso-cyme	Alpha$_1$-antichymo-trypsin
1.	+++		++	○	+	+++	+++
2.	+++		++	○	+	++	+++
3.	++		++	○	+	+	++
4.	○		○	−	−	+	+
5.	+++		++	○	○	+	+
6.							
7.	++		++	○	○		
8.							
9.	++		+++	○	+	+	+
10.	○		○	−	−	−	−
11.	++		++	○	+	+	+
12.	○		○	−	−	++	++
13.	○		○	−	−	+	+
14.	++		++	○	○	++	+
15.	○		○	−	−	(+)	++
16.	○		○	−	−	++	++

The number of cases studied is too small to draw conclusions as to possible relations between positive reactions with L or AC and grade of cellular atypism or mitotic rate.

In 9 cases, in addition to immunohistochemical studies, the results of the previously performed cytochemical examinations were also available. Concordant positive reactions with L and AC and acid phosphatase and non-specific esterase became evident; peroxidase was regularly negative (Table 3).

Discussion

MH constitutes a multifocal malignant neoplastic process involving most frequently lymph nodes, spleen, liver, bone marrow and lungs. The clinical course may imitate a malignant lymphoma and can rapidly lead to death (Rappaport, 1966; Huhn et al., 1978; Huhn and Meister, 1978). Only lately some improvement was achieved by polychemotherapy including Adriamycin (Alexander and Daniels, 1977; Huhn et al., 1979).

Histiocytes are defined by their function as *phagocytes*. Phagocytosis of erythrocytes and of leucocytes, as well as, haemosiderin deposits may serve as indicators of histiocytes, also in neoplasias (Meister et al., in press). These features are, however, not restricted only to histiocytic tumorcells. Moreover, these features are neither obligatory nor ubiquitous in histiocytic tumors. They are also not easily recognized.

As cytochemical reactions can only be carried out on fresh cells or with frozen tissue, they may be easier available to clinicians, procurring the material, than for pathologists.

For pathologists a method has to be conceived, whereby histiocytic tumors can be characterized, p.e. immunohistochemically, on routine paraffin embedded tissue.

The search for a marker of histiocytic tumor cells is based immunohistochemically 1. on studies of the normal distribution of lysozyme in men, which could be demonstrated in granulocytes, monocytes and in "macrophages" (histiocytes) in lymphnodes and spleen (Klockars and Reitamo, 1975; Mason and Taylor, 1975; Heyderman and Neville, 1977). – 2. Additionally alpha$_1$-antichymotrypsin could be demonstrated in histiocytes and reticulum cells, but not in granulocytes or lymphocytes (Papamitriou et al., 1978). – Thus, lysozymes and alpha$_1$-antichymotrypsin were considered as markers for histiocytic tumor cells (Motoi et al., 1978; Neville et al., 1978; Papamitriou et al., 1978). Elevated lysozymes could also be demonstrated in serum and urine of patients with MH (Scully et al., 1977). So far, an elevation of serum values is not yet known for alpha$_1$-antichymotrypsin.

In this study a modified immunoperoxidase technique was applied (Burns, 1975; Heyderman and Neville, 1977; Meister et al., in press).

Regular histiocytes, with reactive proliferation, showed an indistinct positive (dark brown) reaction with lysozyme, chiefly along the cell periphery, which could be seen practically in all cells. In granulocytes the deposits were distinctly granular and somewhat coarser.

Coarser deposits also were found around ingested granulocytes in histiocytic tumor cells, and in histiocytic tumor cells in vicinity of focal necrosis, probably as sign of cellular degeneration. A more impressive positive reactivity was seen with alpha$_1$-antichymotrypsin in reactively proliferated histiocytes and in histiocytic tumor cells. – In histiocytic tumors also the possibility of a mixture of positive tumor cells and reactive histiocytes has to be considered especially around foci of necrosis.

Neither by lysozyme nor by alpha$_1$-antichymotrypsin did all tumor cells stain positively. Some "typical" histiocytes or xanthomatous cells would be either positive or negative with both reactions. The same was true for spindle cells with fibroblastic appearance. Thus, by the applied immunohistochemical methods, histiocytic qualities of tumor cells became evident, which not always could be predicted by routine H & E or Giemsa stains. – Cells with ingested erythrocytes or with haemosiderin deposits were often negative (Mann et al., 1979; Meister et al., in press). Concerning ingested granulocytes, there may be a marked positive reaction with lysozyme.

Cell imprints originally had shown mostly strongly positive acid phosphatase, positive non-specific esterase, weak or negative reaction with PAS and negative peroxidase (Huhn et al., 1978). In this study it could be shown, that all these cases showed also some degree of positive marking with L and AC on paraffin embedded material. With tumor histiocytes the degree of differentiation is reflected cytochemically by the content of enzymes (chiefly hydrolases), and ultrastructural to some degree by the content of lysosomes (Huhn and Meister, 1978).

As cellular atypism may be an indicator of dedifferentiation, MH was graded accordingly from I. highly differentiated, II. moderately differentiated, to III.

with low differentiation and anaplasia. Mann et al. (1979) and Sheibani et al. (1979), also compared differentiation, respectively cellular atypism in MH with evidence of enzymatic activity with L. Mann et al. (1979) included in their grading additionally the degree of phagocytosis. They found an almost ubiquitous positive reaction in absence of atypism and with rare phagocytosis, similar to the reaction in reactive histiocytes (group I). Their group II without atypism but with marked phagocytosis showed only slight positive reaction. Group III with marked atypism and Hodgkin- or Sternberglike cells, revealed neither phagocytosis nor positive marking with L. Interesting was a negative correlation between phagocytosis and positive enzymatic reaction, which was also found in single cells in our material (Meister et al., in press). Contrary to Mann et al. (1979), Sheibani et al. (1979) stressed a positive reaction with L in tumor histiocytes of all grades of differentiation. The problem of finding reproducible criteria for grading in MH becomes evident. – In our study the reaction to L or AC was rather compared to the atypism of individual cells, than to different grades of MH as a collective of cells. Our limited experience shows evidence of negative reactions with L and AC with small immature histiocytic cells, with some cases of MH, but also with reactive histiocytic proliferation and histiocytosis X (unpublished data). Besides regional differences in atypism in one tumor, also chronological variations are possible. Mann et al. (1979) described one case, which with the course of time changed from their grade I to grade III, expressing loss of differentiation.

Our series of cases did not reveal any rules as to interdependancies between cellular atypism and grade of reaction with acid phosphatase or non-specific esterase and grade of reaction with lysozyme or alpha$_1$-antichymotrypsin. Differences between repeated biopsies were seen in one case, which not only revealed less atypism at second biopsy, but also an association of these cells with a more marked reaction with L and AC. In contrast, another case with almost exclusively atypical spindle cell histiocytes showed almost ubiquitous finely granular positive reaction with L and AC.

Finally, all included cases, even with negative cytochemical reactions for acid phosphatase or non-specific esterase showed some degree of positive reaction with L or AC. Thus chances to pick up positive cells by immunohistochemistry on histological sections appears to be superior to cytochemical evaluation by smears.

The distinction between MH, without marked atypism, and proliferating "histiocytosis X", may only be possible electronmicroscopically, with typical Langerhans-granula in histiocytosis X, which neither can be found in MH, nor with reactively proliferated histiocytes. Transitions between MH and histiocytosis X cannot be proven.

Typical "histiocytosis X" is characterized by large histiocytes, which show an almost omnipresent positive reaction with L and AC (Fig. 4a, b) and multinucleated giant cells without atypism.

An almost omnipresent positive reaction with L and AC was also found with reactive proliferation of histiocytes, for example in non-specific granulation tissue (Fig. 5a, b).

Positive reactions also could be found in a variety of other tumor cells especially with cellular degeneration and necrosis as in examined control cases of liposarcoma, rhabdomyosarcoma or carcinoma (Meister et al., in press).

Distinct were positive reactions with L and AC in malignant melanomas which in contrast to MH, however, were also positive in controls using PBS instead of anti-sera.

Because of similar light microscopical and clinical findings MH has to be differentiated from malignant lymphomas and neoplasias of myelogenous cells and other tumors of the monocyte-histiocyte-reticulum cell system. Additional cytochemical, immunohistochemical and fine structural studies allow a differentiation from lymphomas and myelosis (Stein, 1976; Huhn and Meister, 1978). Inspite of some differences, a relationship of MH to monocytic leukemia (Basset and Nezeloff, 1966), as well as, to tumors of interdigitating reticulum cells may be considered.

In summary, *immunohistochemical characterization* of tumor cells by *lysozyme (L)* and *alpha$_1$-antichymotrypsin (AC)* has to be considered as a valuable tool for identification of histiocytic neoplasias, especially MH. Immunohistochemical findings have to be evaluated in conjuntion with routine H & E sections, to eliminate possibly wrong positive findings in none-histiocytic, degenerating tumor cells of different histogenesis. But also the possibility of negative reactions, because of immaturity of histiocytic tumor cells must be considered. This consideration is expecially supported by our impression, that small, immature histiocytic (tumor) cells appear to be more apt to lack positive reactions with L and/or AC.

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