

An Immunohistochemical Study of Proliferative Disorders of Histiocytes

Chan Il Park, Hee Jeong Ahn and Hoguen Kim

In an attempt to clarify the dual origin of histiocytes and to reclassify histiocytic proliferative disorders according to their immunohistochemical properties, normal histiocytes and histiocytes in selected proliferative disorders were stained, using the peroxidase-antiperoxidase method, for lysozyme, α 1-antichymotrypsin and for S-100 protein. The proliferated histiocytes of eosinophilic granuloma and Letterer-Siwe disease were strongly immunoreactive for S-100 protein. In histiocytic medullary reticulosis (HMR) and in histiocytic lymphoma, all three markers were found within the tumor cells. In fibrous histiocytoma and in juvenile xanthogranuloma, only a few weakly immunoreactive cells for S-100 protein were observed. Inflammatory malignant fibrous histiocytoma (MFH) (Xanthosarcoma) and xanthoma were immunoreactive for α 1-antichymotrypsin and lysozyme respectively. In MFH of the storiform-pleomorphic type and in atypical fibroxanthoma, stains using all of the histiocytic markers were negative. These results suggest that eosinophilic granuloma, Letterer-Siwe disease, fibroxanthoma and juvenile xanthogranuloma are proliferative disorders of T-zone histiocytes; HMR and histiocytic lymphoma are those of pluripotential stem cells capable of dual histiocytic differentiation; xanthoma and xanthosarcoma are monocytic proliferative disease; and MFH of the storiform-pleomorphic type and atypical fibroxanthoma are not true histiocytic diseases.

Key Words: Histiocyte proliferative disorder, T-zone histiocyte, monocyte/macrophage

The histiocytic proliferative diseases are a diverse group of disorders involving cells of the mononuclear phagocytic series (Van Furth *et al.* 1975; Van Furth 1976; Thomas *et al.* 1976; Shands and Axelrod 1977; Cohn 1978). At present, there is considerable confusion regarding the manner in which these diseases should be classified (Groopman and Golde 1981). Part of the uncertainty can be traced to the presence of marked phenotypic diversity among benign and malignant histiocytes.

The origin of histiocytes is still a matter of debate. Many experimental studies and clinical data suggest that tissue histiocytes are derived from marrow monoblasts (Maximow 1924; Thomas *et al.* 1976; Groopman and Golde 1981), although some recent work would seem to indicate that histiocytes may also be derived from other cell lines (Walker 1982; Bak-

ker *et al.* 1981). Marker studies of normal histiocytes and of histiocytic components in selected proliferative disorders suggest to some that there are at least two types of progenitor cells (Groopman and Golde 1981; Watanabe *et al.* 1983b), one being a monocyte-derived macrophage that is rich in lysozymes and α 1-antichymotrypsin (α 1-ACT) and the other being a T-zone histiocyte that contains S-100 protein but no lysozyme or α 1-ACT (Mason and Taylor 1975; Nakajima *et al.* 1982; Watanabe *et al.* 1983a, 1983b).

In this study, we attempt to clarify the dual origin of histiocytes by analyzing the immunohistochemical characteristics of various types of histiocytic proliferative disorders, with an eye toward reclassification of this group of diseases.

MATERIALS AND METHODS

Twenty-four cases representing ten different histiocytic proliferative disorders were selected from the pathology files of Severance Hospital, Yonsei University, from January, 1983 to June, 1986 (Table 1).

Four serial sections were cut from paraffin embedded blocks. Three sections were stained immunohisto-

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Department of Pathology, Yonsei University College of Medicine, Seoul, Korea

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Address reprint requests to Dr. C-I Park, Department of Pathology, Yonsei University College of Medicine, Seoul, Korea, 120-140

chemically for lysozyme, α 1-antichymotrypsin, and S-100 protein. The peroxidase-antiperoxidase technique was applied using commercial kits supplied by

DAKO-Immunoglobulin Ltd., Denmark. For normal control histiocytes, sections of lymph nodes and skin were selected.

Table 1. Pathological classifications for 24 patients

Diagnosis	No. of cases
Eosinophilic granuloma	3
Letterer-Siwe disease	2
Histiocytic medullary raticulosis	2
Histiocytic lymphoma (tonsil, skin)	2
Fibrous histiocytoma	2
Juvenile xanthogranuloma	1
Xanthoma	5
Atypical fibroxanthoma	1
Malignant fibrous histiocytoma	
Storiform-pleomorphic type	3
Inflammatory type (xanthosarcoma)	1
Sinus histiocytosis	2
Total	24

Table 2. Summary of immunohistochemical staining for α 1-antichymotrypsin, lysozymes and S-100 protein

Diagnosis	α 1-ACT	Lysozyme	S-100 protein
Eosinophilic granuloma	+	+	+++
Letterer-Siwe disease	+	+	+++
HMR	+/++	+++	+
Histiocytic lymphoma	+/+++	++	+
Fibrous histiocytoma	-	-	+
Juvenile xanthogranuloma	-	-	++
Xanthoma	-	++	-
MFH-inflammatory type	++	-	-
Atypical fibroxanthoma	-	-	-
MFH, storiform-pleomorphic type	-	-	-
Sinus histiocyte of LN	++	+	-
Langerhans cell of skin	-	-	++

α 1-ACT: α 1-antichymotrypsin

MFH : Malignant fibrous histiocytoma

HMR : Histiocytic medullary reticulosis

LN : Lymph node

- : All tumor cells are negative

+

++ : 20-50% of tumor cells are positive

+++ : 50% or more tumor cells are positive

RESULTS

The results of immunohistochemical staining for α 1-antichymotrypsin, lysozyme, and S-100 protein are summarized in Table 2.

Normal histiocytes

Histiocytes within the sinusoids of lymph nodes were immunoreactive for lysozyme and for α 1-antichymotrypsin but not for S-100 protein. In contrast, the cytoplasm of Langerhans cells of the epidermis was strongly positive for S-100 protein, although no lysozyme or α 1-antichymotrypsin was demonstrated. These results suggest that histiocytes within lymph nodes originate from bone marrow monoblasts and that Langerhans cells are T-zone histiocytes.

Histiocytosis X

Most of the histiocytes in eosinophilic granuloma and in Letterer-Siwe disease showed cytoplasmic immunoreactivity for S-100 protein (Fig. 1). Although some of the cells were also immunoreactive for α 1-antichymotrypsin and lysozyme, these cells were considered to be eosinophils and secondarily infiltrating reactive macrophages. Thus, it would appear that proliferating cells of the histiocytic type in histiocytosis X most likely originate from T-zone histiocytes.

Histiocytic medullary reticulosis and histiocytic lymphoma

Most of the tumor cells in histiocytic medullary reticulosis (HMR) and in histiocytic lymphoma stained intensely for α 1-antichymotrypsin and for lysozyme (Fig. 2). A few tumor cells also appeared to contain S-100 protein. Based on these results, it is suggested that HMR and histiocytic lymphoma may originate from pluripotential stem cells capable of dual histiocytic differentiation, thereby accounting for the coexistence of two kinds of histiocytes in these diseases.

Fibrous histiocytoma, juvenile xanthogranuloma and xanthoma

In fibrous histiocytomas (dermatofibroma) and

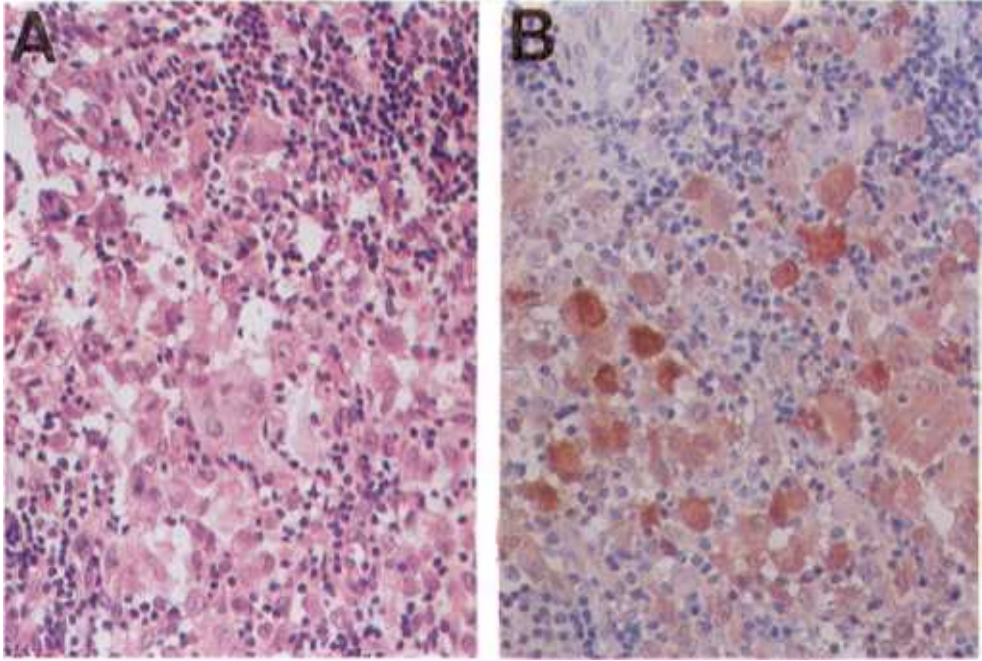


Fig. 1. Eosinophilic granuloma showing positive immunoperoxidase staining for S-100 protein, (A) H & E, $\times 200$; (B) S-100 protein, $\times 200$

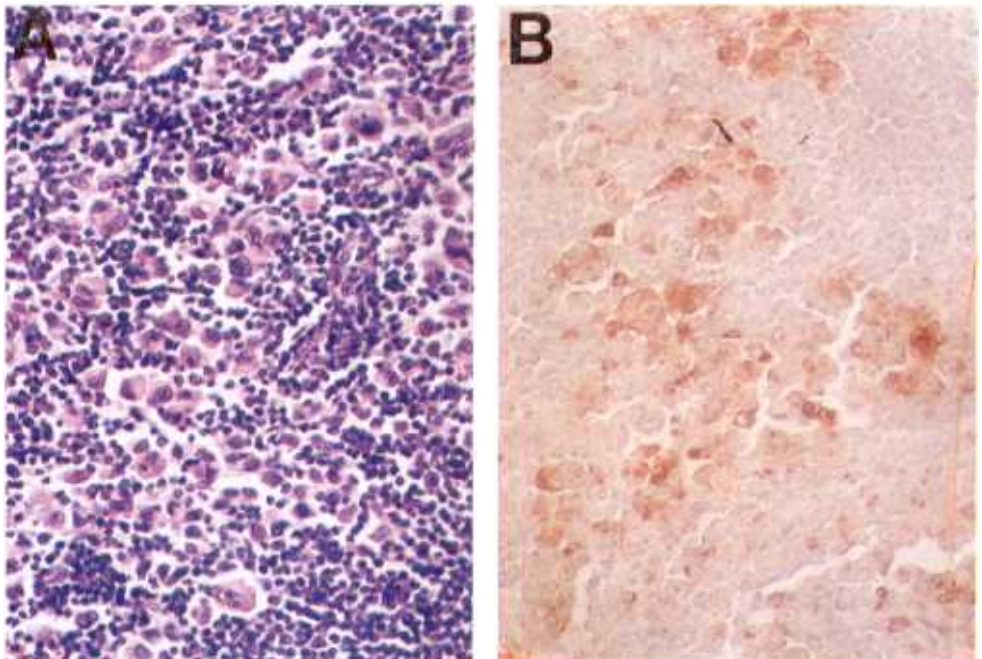


Fig. 2. Lymph node of histiocytic medullary reticulosis, (A) Proliferating cells with nuclear atypism in the sinusoid. H & E, $\times 200$; (B) Atypical cells showing positive reaction for lysozyme. Lysozyme, $\times 200$

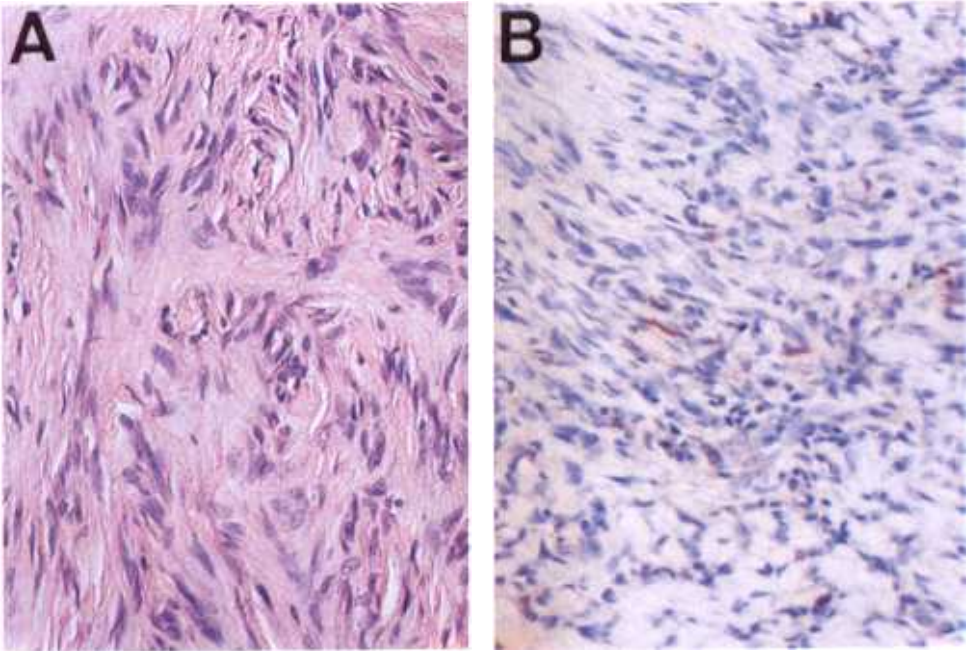


Fig. 3. Fibrous histiocytoma. Proliferating spindle cells show positive reaction for S-100 protein. (A) H & E, $\times 200$; (B) S-100 protein $\times 200$

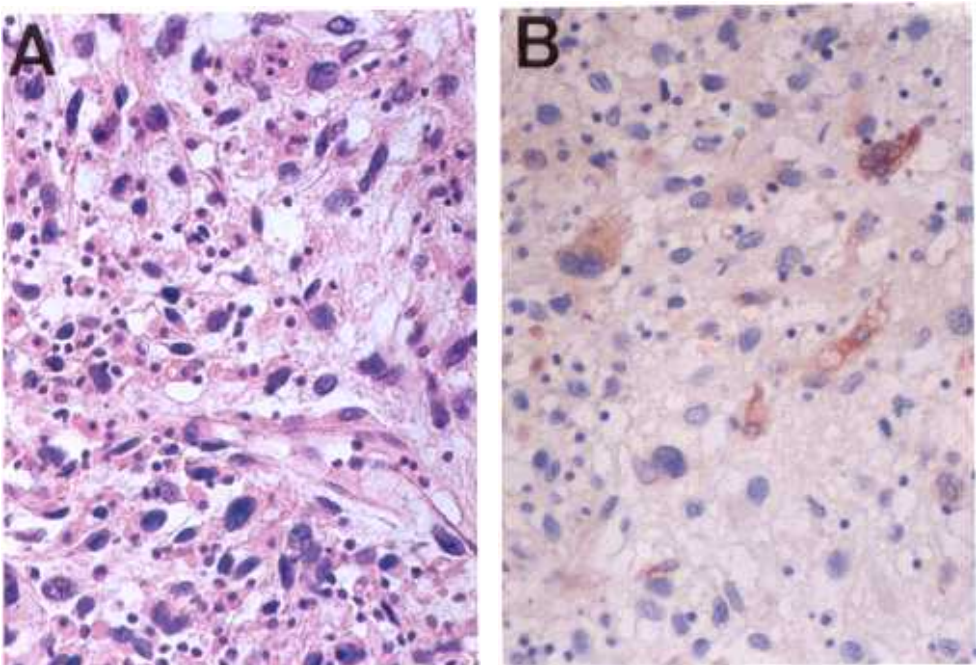


Fig. 4. Inflammatory type malignant fibrous histiocytoma showing tumor cells stained positively for $\alpha 1$ -antichymotrypsin. (A) H & E, $\times 200$; (B) $\alpha 1$ -antichymotrypsin, $\times 200$

juvenile xanthogranuloma, some of the fusiform tumor cells appeared positive for S-100 protein, but there were no neoplastic cells having α 1-antichymotrypsin or lysozyme (Fig. 3). In contrast, the proliferated histiocytes in xanthoma were positive only for lysozyme. These results suggest that fibrous histiocytomas and juvenile xanthogranulomas originate from T-zone histiocytes, and that xanthomas are derived from monocyte/macrophages.

Malignant fibrous histiocytoma (MFH)

Included in this study were tumors of the storiform-pleomorphic type and the inflammatory type, according to the classification of Enzinger and Weiss (1983). In cases of the storiform-pleomorphic type, all three immunohistochemical stains gave negative results. However, in the inflammatory type of xanthosarcoma, many histiocyte-like tumor cells and pleomorphic giant cells were immunoreactive for α 1-antichymotrypsin though negative for lysozyme and S-100 protein (Fig. 4). Finally, the immunohistochemical pattern of staining in atypical fibroxanthomas was identical to that of the storiform-pleomorphic type of MFH.

DISCUSSION

On the basis of the study, we propose a cell of origin for each of the histiocytic proliferative disorders represented, as summarized in Table 3.

Lichtenstein (1964) proposed the term histiocytosis X to encompass Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma. Although these diseases differ from each other with respect to organ involvement and prognosis, they are unified by the presence of proliferating large histiocytes. Numerous data indicate that these histiocytes are similar to epidermal Langerhans cells. Ultrastructurally, the characteristic inclusions (histiocytosis X bodies) resemble the Birbeck granules found in Langerhans cells (Tarnowski and Hashimoto 1967; Shamoto 1970; Corrin and Basset 1979; Kato *et al.* 1981). Our study confirms the suggested similarities between these two types of cells by showing that they possess similar immunohistochemical characteristics (Takahashi *et al.* 1981; Nakajima *et al.* 1982; Watanabe *et al.* 1983a, 1983b). Our study also suggests that histiocytosis X is the result of a proliferation of T-zone histiocytes.

In the case of HMR and histiocytic lymphoma, most of the tumor cells bear the immunohistochemical characteristics of monocytes, although a small pro-

Table 3. The proposed cell of origin of the histiocytic proliferative diseases by their immunohistochemical characteristics

Diagnosis	Proposed cell of origin
Eosinophilic granuloma	T-zone histiocyte
Letterer-Siwe Disease	
HMR	Pluripotential stem cell
Histiocytic Lymphoma	
Fibrous histiocytoma	T-zone histiocyte
Juvenile xanthogranuloma	
Xanthoma	Monocyte/Macrophage
MFH-inflammatory type	
Atypical fibroxanthoma	Not histiocyte
MFH, storiform-pleomorphic type	
Sinus histiocyte of LN	Monocyte/Macrophage
Langerhans cell of skin	T-zone histiocyte

MFH : Malignant fibrous histiocytoma

HMR : Histiocytic medullary reticulosis

LN : Lymph node

portion have features of T-zone histiocytes. Although some authors (Imamura *et al.* 1971) believe that these neoplasms are derived from T-zone histiocytes by virtue of the presence of Birbeck granules in their cytoplasm, the presence of lysozyme has been demonstrated repeatedly (Mendelsohn *et al.* 1980; Meister and Nathrath 1980; Roholl *et al.* 1985). The presence of features of both monocytes and T-zone histiocytes would suggest that the cells in question originate from pluripotential stem cells that are capable of dual differentiation.

Fibrous histiocytoma and juvenile xanthogranuloma are generally considered soft tissue tumors of histiocytic origin (Fu *et al.* 1975; Hajdu 1979; Boulay 1982). Immunohistochemical studies have shown that they contain S-100 protein (Watanabe *et al.* 1983a) but no α 1-antichymotrypsin- or lysozyme-positive cells. Because α 1-antichymotrypsin can be found at any stage of monocyte/macrophage differentiation, these benign fibrohistiocytic tumors seem not to be monocytic diseases. In xanthoma, it is difficult to explain why proliferated cells contain only lysozyme without α 1-antichymotrypsin.

Watanabe *et al.* (1983b) have speculated that all MFHs are monocyte-derived. But, in this study, the immunohistochemical staining pattern of the storiform-pleomorphic type was completely different

from that of the inflammatory type. The absence of immunoreactivity for all of the histiocytic markers in the storiform-pleomorphic type of MFH suggests that the neoplasm more likely originates from undifferentiated mesenchymal cells than from histiocytes. In the inflammatory type of MFH, the histiocyte-like tumor cells as well as the tumor giant cells showed the same immunohistochemical properties as the monocyte-derived histiocytes. It is possible that the storiform-pleomorphic type of MFH and the inflammatory type of MFH are different entities histologically and immunohistochemically. Atypical fibroxanthoma is another disorder, previously thought to be histiocytic, that appears not to be histiocytic on this basis of immunohistochemical study.

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