

Immunohistochemical Study on Antigenic Phenotype of Langerhans Cell Histiocytosis

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Immunohistochemical study on 26 cases of Langerhans cell histiocytosis (LCH) using several leukocyte antibodies in addition to traditionally used markers (S-100 protein and peanut agglutinin) revealed that the proliferating cells of LCH expressed UCHL1, MT1 as well as classically known positivity for S-100 protein, HLA-DR and peanut agglutinin but were negative for OPD4. In comparison to S-100 protein peanut agglutinin (PNA) using a two stage method produced weaker staining and positively stained cells were sparse. Also in this study, a small proportion of proliferating cells in LCH was observed to be reactive for both myeloid/macrophage antigens (KPI, MAC 387 and lysozyme) and Langerhans cell marker (S-100 protein), verifying the existence of a hybrid form of histiocytes.

Key Words: Langerhans cell histiocytosis, antigenic phenotype, myeloid/macrophage antigens

Langerhans cell histiocytosis (LCH) is a proliferative disorder of histiocytes showing ultrastructural, histochemical, and immunohistochemical characteristics similar to Langerhans cells (LCs) and embraces various previously used terms such as histiocytosis X, Letterer-Siwe disease, Hand-Schüller-Christian disease and eosinophilic granuloma (Lichtenstein, 1953; Writing Group of the Histiocytic Society, 1987). The proliferating cells of LCH share common features with Langerhans cells (LCs) including positive staining for ATPase, S-100 protein and CD1a, characteristic binding of peanut agglutinin (PNA) and pathognomonic ultrastructure, Birbeck granules (Birbeck et al. 1961; Favara et al. 1983; Beckstead et al. 1984; Mierau et al. 1986; Ree and Kadin, 1986). Among these, positivity to S-100 protein and characteristic binding to PNA have been widely used as differential diagnostic point from other histiocytosis syndromes of macrophage origin,

which express lysozyme instead of S-100 protein and show nonspecific cytoplasmic binding of PNA.

But several recent studies have revealed that histiocytes of sinus histiocytosis with massive lymphadenopathy and dermatopathic lymphadenopathy, which had been thought as histiocytosis of macrophages origin, also express S-100 protein (Miettinen et al. 1987; Ruco et al. 1989; Eisen et al. 1990). Moreover the author recently observed that some proliferating cells of LCH express myeloid/macrophage markers suggesting antigenic ambiguity (Sung et al. 1992). Immunohistochemical study of LCH using several recently developed monoclonal antibodies, for leukocytes such as UCHL1, MT1 and OPD4, that have been widely used for immunophenotyping of hematologic diseases are scarce (Rabkin and Kjeldsberg, 1987; Hall et al. 1987; Azumi et al. 1988). In this study, the author performed immunohistochemical study on LCH using several commercially available leukocyte antibodies that work on paraffin embedded sections in addition to S-100 protein and peanut agglutinin (PNA). The main purpose of this study is twofold: the first is to evaluate immunophenotype of proliferating cells in LCH from a diagnostic point of view and the second is to investigate the nature of the proliferating cells in LCH using myeloid/macrophage markers besides S-100 protein.

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MATERIAL AND METHODS

Materials

Twenty-six cases of LCH with available paraffin blocks were obtained after reviewing pathologic files of the Severance Hospital and Wonju Christian Hospital from 1980 to 1991. The biopsy material comprised 22 cases from bone, 2 cases from lymph node and 2 cases from skin.

Methods

The formalin-fixed and paraffin embedded tissue blocks were sectioned and stained with hematoxylin-eosin for routine histologic examination. The immunohistochemical staining was performed by the labelled streptavidin method using LSAB kit (Dako, Santa Barbara, CA, USA) and DAB chromogen (Sigma chemical company, St. Louis, MO, USA). The primary antibodies used in this study are listed in Table 1. For excluding the possibility of immunostaining by nonspecific absorption mechanism, the author used antibody to albumin.

For PNA staining we incubated section with a 10 µg/ml concentration of biotinylated PNA (Vector Laboratories, Burlingame, CA, USA) after trypsinization and followed by avidin-biotin-complex (ABC)(Vector Laboratories) and DAB chromogen (Sigmacochemical company).

Table 2. Age, sex and biopsy sites of the patients

Case No.	Age (yrs)	Sex	Biopsy site
1	36	M	Skull
2	4	F	Femur
3	18	F	Skull
4	1	M	Femur
5	2	M	Ulna
6	5	M	Rib
7	42	M	Mandible
8	21	M	Skull
9	14	M	Ulna
10	3	M	Lymph node
11	6	M	Skull
12	4/12	M	Rib
13	11	M	Vertebra
14	18	M	Clavicle
15	5	F	Vertebra
16	5	F	Clavicle
17	6	M	Clavicle
18	35	M	Rib
19	50	M	Scapula
20	14	F	Mandible
21	4	M	Clavicle
22	1/12	M	Skin
23	26	M	Mandible
24	7/12	M	Lymph node
25	4	F	Skull
26	4/12	M	Skin

Table 1. Primary antibodies and lectin used

Antibody	Predominant Reactivity	Source
UCHL1	Macrophage, T-lymphocyte	Dako
MT1	Macrophage, T-lymphocyte	Bio Test (Germany)
OPD4	T-lymphocyte (Helper)	Dako
HLA-DR	B-lymphocyte, Activated T-lymphocyte	Dako
	Langerhans cell, Macrophages	
KP1(CD68)	Macrophage, Myeloid cell	Dako
MAC 387	Macrophage, Myeloid cell	Dako
Elastase	Myeloid cell, Macrophages	Dako
Lysozyme	Macrophage, Myeloid cell	Dako
S-100 protein	Langerhans cell, Schwann cell,	Dako
	Melanocyte	
Albumin	Hepatocyte	BioGenex (San Ramon, CA, USA)
Peanut agglutinin	Histiocytes, Lymphoid cells	Vector
	Urothelium	

RESULTS

Clinical data

The age at the time of diagnosis ranged from 1

month to 50 years and there were 21 male and 5 female patients. Age, sex and biopsy sites of the patients are listed in Table 2.

Light microscopic findings

All cases showed characteristic histologic features

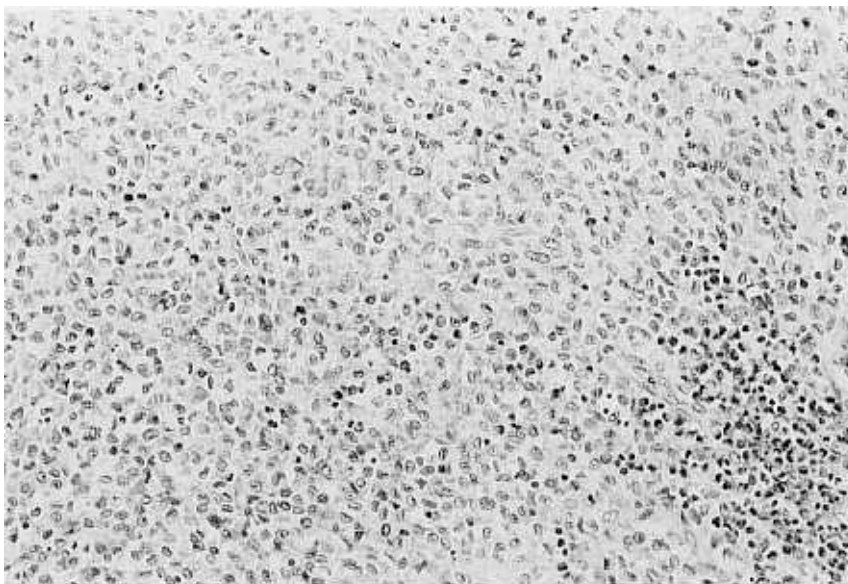


Fig. 1. LCH showing proliferation of histiocytes having abundant cytoplasm and grooved nuclei admixed with inflammatory cells (Hematoxylin-Eosin).

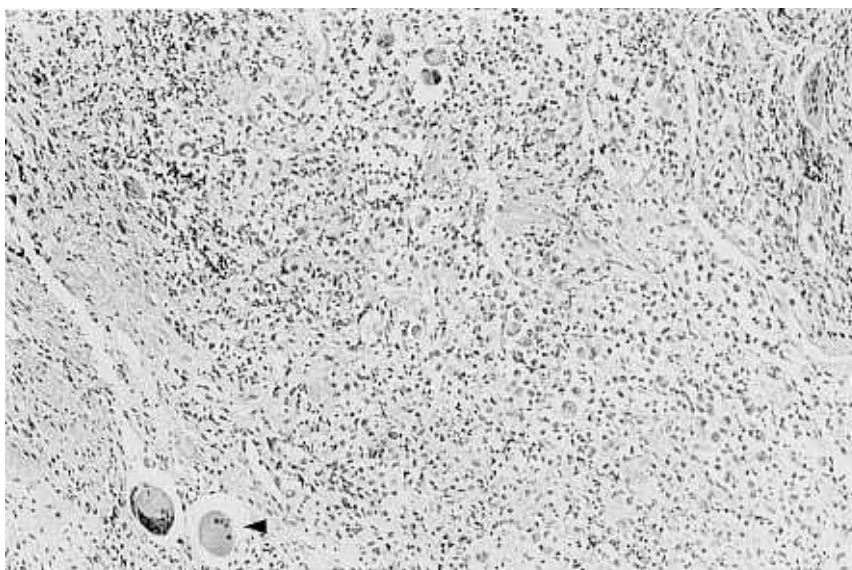


Fig. 2. Multinucleated giant cells with grooved nuclei of LCH cells (◁) and round nuclei of xanthoma cells (◀)(Hematoxylin-Eosin).

of LCH. The main proliferating cells were large mononuclear cells having abundant cytoplasm and characteristic grooved nuclei forming sheets (Fig. 1). The associated inflammatory cells infiltration, including eosinophils and lymphocytes, varied from case to case. Multinucleated giant cells were frequently observed and their morphologic features of nuclei varied. Some of them showed grooved and irregular nuclei of LCH cells and others showed round small nuclei of xanthoma cells (Fig. 2).

Table 3. Results of immunohistochemical staining

Antibody & Lectin	Results of staining		
	Negative	Focally Positive	Diffusely Positive
UCHL1		9/26	15/26
MT1		1/26	19/26
OPD4		0/26	0/26
DR		5/26	11/26
KP1		19/26	0/26
MAC387		17/26	0/26
Elastase		0/26	0/26
Lysozyme		17/26	0/26
S-100 Protein		0/26	26/26
Albumin		0/26	0/26
Peanut Agglutinin		26/26	0/26

Immunohistochemical staining

The results of immunohistochemical staining are summarized in Table 3. All cases showed diffuse cytoplasmic or nuclear staining with antibody to S-100 protein (Fig. 3).

Twenty-four cases showed a positive reaction for UCHL1 and twenty cases showed a positive reaction for MT1 (Fig. 4). UCHL1 and MT1 staining were intense and membranous. There were no cases reactive for OPD4 or Elastase. Sixteen cases showed positive staining for HLA-DR and most of the staining was confined to the paranuclear area except those cases from skin which demonstrated intense membranous staining of LCH cells in addition to positive staining of normal LCs at the epidermis (Fig. 5). LCH cells reactive for KP1, Mac 387 and lysozyme were observed in 19, 17 and 17 cases respectively although positive LCH cells were few in number. KP1 showed either intracytoplasmic coarse granular pattern or paranuclear staining (Fig. 6). MAC 387 revealed a dendritic pattern of staining (Fig. 7). except for LCH cells, which was not detected by immunostaining with other myeloid/macrophage markers. In general myeloid/macrophage markers were positive in less than 10% of LCH cells in each case except one in which about thirty percent of the LCH cells demonstrated positive re-

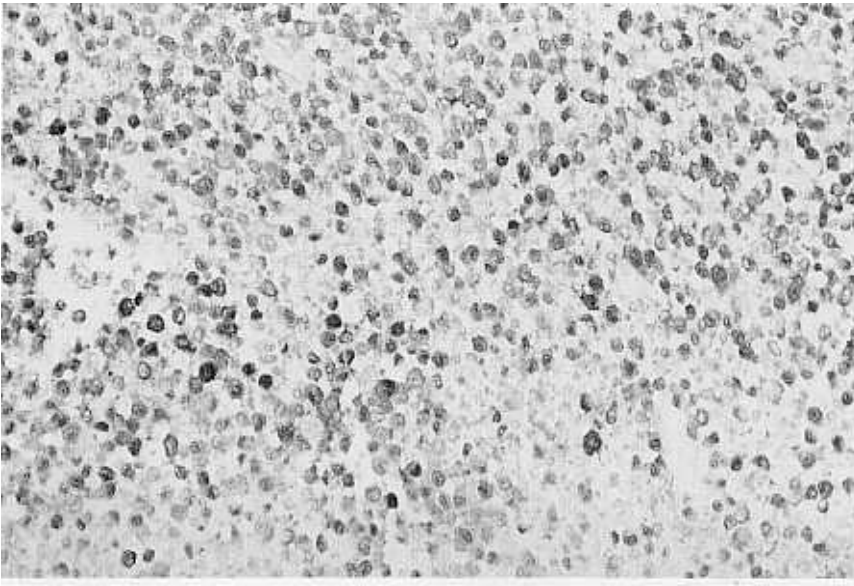


Fig. 3. LCH immunostained with S-100 protein showing diffuse positivity of LCH cells.

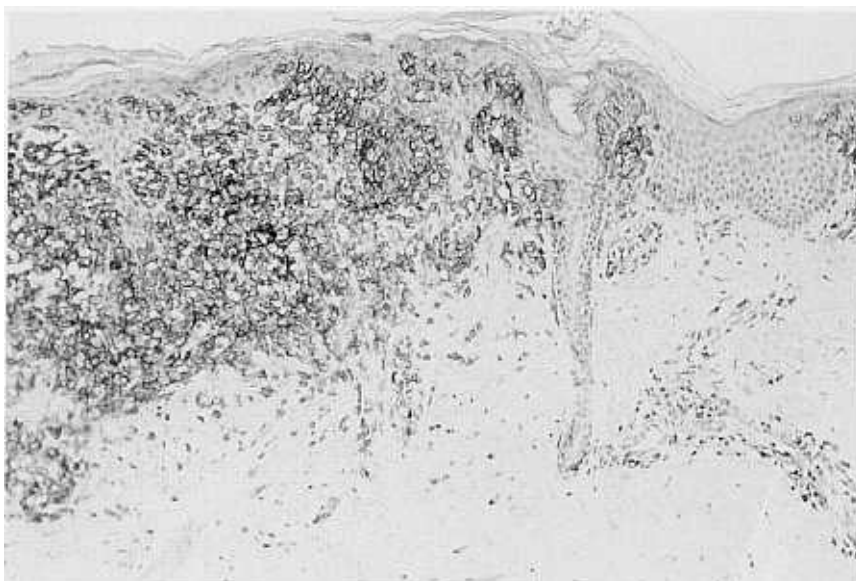


Fig. 4. LCH of skin immunostained with MT1 showing intense membrane staining of LCH cells.

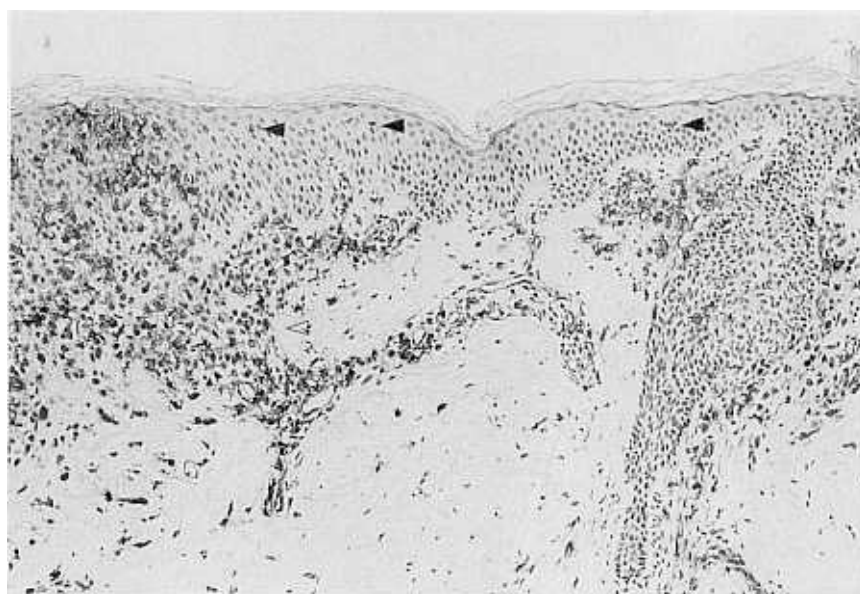


Fig. 5. LCH of skin immunostained with HLA-DR showing intense membrane staining of LCH cells (◁) and LCs in the epidermis(◀).

action for KP1. Because the associated inflammatory cells infiltration might hinder accurate evaluation, positive reaction was evaluated at the areas showing sheet-like, monotonous proliferation of LCH

cells relatively devoid of inflammatory cells infiltration. The majority of associated multinucleated giant cells showed positive reaction for myeloid/macrophage markers (Fig. 8) but a significant proportion

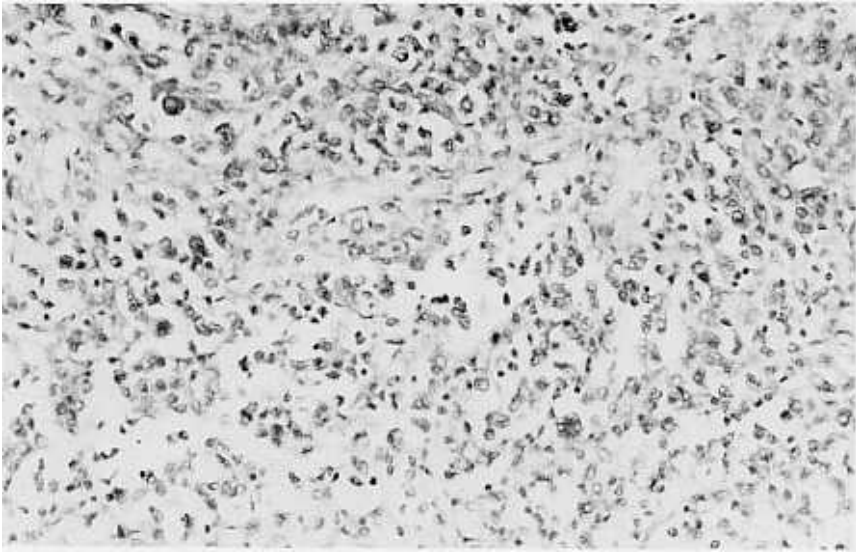


Fig. 6. LCH immunostained with CD 68 showing paranuclear positivity.

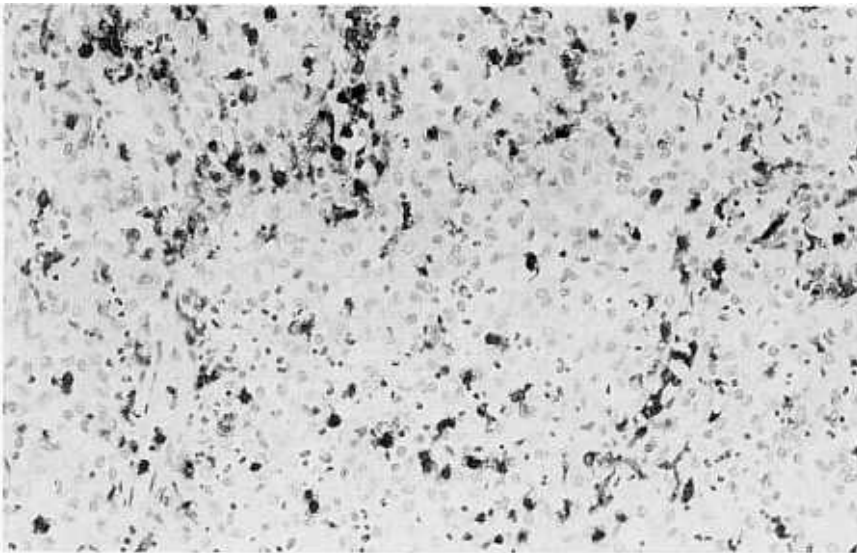


Fig. 7. LCH immunostained with MAC 387 showing scattered dendritic cells within LCH cells.

of them also showed positive staining for S-100 protein (Fig. 9) especially in those cells with grooved nuclei. The immunostaining using antibody to albumin revealed negative reaction with giant cells excluding the possibility of nonspecific

staining by passive absorption.

The results of PNA staining using a two step method after trypsinization were as follows; all cases showed a positive reaction but LCH cells showing a specific membrane and a paranuclear

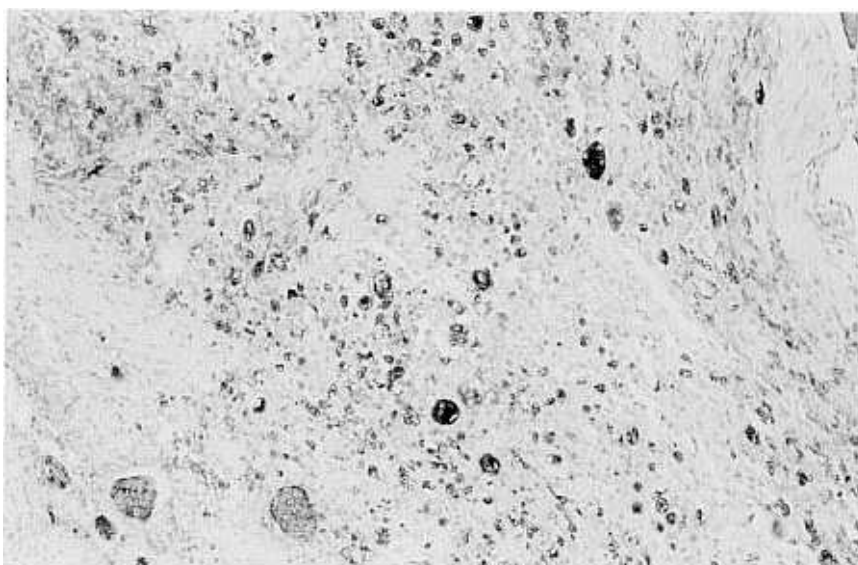


Fig. 8. Multinucleated giant cells of LCH showing positivity to CD68.

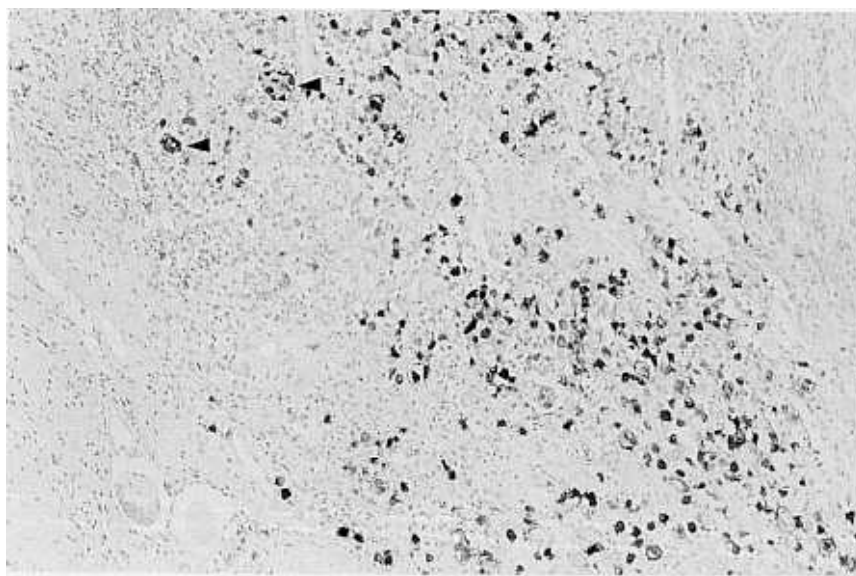


Fig. 9. Multinucleated giant cells of LCH showing positivity to S-100 protein.

staining pattern (Fig. 10) were less than twenty percent of the LCH cells in each case and the majority of them showed diffuse nonspecific cytoplasmic reaction.

DISCUSSION

The classification of proliferative disorders of



Fig. 10. LCH showing paranuclear positivity to PNA staining.

histiocytes has not been settled and has undergone multiple revisions as that of malignant lymphoma mainly due to our increasing knowledge about mononuclear phagocyte and immunoregulatory effector (M-PIRE) system (Foucar and Foucar, 1990). The classification of 'Histiocyte Society' basically divides histiocyte disorders into three types according to its cell of origin and clinical behavior (Writing Group of the Histiocyte Society, 1987). Among them LCH has been believed to be a proliferative disorder of histiocytes closely related to Langerhans cells due to its morphologic, histochemical, and immunohistochemical similarities. Langerhans cells, characterized histochemically for the first time by Paul Langerhans in 1868, are now categorized into immune accessory cells. They are characterized morphologically by dendritic processes and Birbeck granules, histochemically by positive ATPase reaction, and immunophenotypically by expression of S-100 protein, CD1a, HLA-DR, Fc receptor (Birbeck *et al.* 1961; Favara *et al.* 1983; Beckstead *et al.* 1984; Mierau *et al.* 1986; Ree and Kadin, 1986). But there are some immunophenotypic differences between proliferating cells of LCH and its normal counterpart. Unlike normal LC, LCH cells may express CD4, complement receptors, Fc-IgG receptors and other activation markers (Favara *et al.* 1983; Beckstead *et al.* 1984; Bieber *et al.* 1985).

Among the many phenotypic characteristics, pos-

itive reaction to S-100 protein and characteristic PNA binding pattern (membranous and paranuclear dot) have been used as a supportive tool for the diagnosis of LCH due to its applicability on formalin-fixed and paraffin-embedded blocks. But recently, many useful monoclonal lymphoid and histiocytic markers which work on routinely processed paraffin blocks have been developed and they have been actively used as diagnostic and research tools. There is little diagnostic difficulty in the case of typical presentation of LCH especially if it reveals positive immunostaining reaction to S-100 protein. But under the circumstances of unusual clinical findings, such as isolated lymph node involvement, and if it reveals atypical morphologic features, there will be some diagnostic difficulties and we will rely much more on immunophenotypic characteristics for confirmatory diagnosis. But there are few studies evaluating the immunoreactivities of LCH cells with recently developed lymphohistiocytic markers, such as UCHL1, OPD4 and MT1 (Rabkin and Kjeldsberg, 1987; Hall *et al.* 1987; Azumi *et al.* 1988). So this study applied several recently developed leukocyte monoclonal antibodies, mainly used for the diagnosis of T-cell lymphoma. The results of this study showed that the significant fraction of proliferating cells showed positive staining for MT1 and UCHL1 despite the fact that the majority of the cases were from decalcified material. This is not an unexpected

finding due to the fact that both of these antibodies recognize histiocytic lineage. MT1 recognizes an antigen of 190, 110 and 100 kd, which is expressed on T-cells, myeloid cells and macrophages (Dobson *et al.* 1986). UCHL1 recognizes an epitope on the low molecular 180 kd-isoform of the leukocyte common antigen, which is expressed on most thymocytes, activated T-cells, and cells of myelomonocytic lineage (Smith *et al.* 1986). So they are non-lineage specific markers that work on paraffin embedded sections. Considering the facts that these markers are mainly used for the diagnosis of T-cell lymphoma and that some cases of LCH with atypical pictures may mimic T-cell lymphoma morphologically, we must be cautious upon interpreting the results of positive staining to these non-lineage specific markers as in the case of granulocytic sarcoma. OPD4 was originally described as marker for helper/inducer T-lymphocytes subset in paraffin sections (Yoshino *et al.* 1989) but recent study reports that it is reactive with CD45RO but differs from UCHL1 by the absence of monocyte reactivity (Poppema *et al.* 1991). The result of this study that none of the cases revealed positive reaction to OPD4 corresponds to the above mentioned characteristics of this antibody. Positivity to HLA-DR was demonstrated in 16 out of 26 cases and the majority of positive reactions were paranuclear dot pattern. Because all cases without decalcification procedure showed diffuse positive staining, the low positive rate of LCH cells to HLA-DR in this study was probably due to antigen loss during decalcification procedure.

PNA is a plant-derived lectin that has a high affinity for glycoproteins that contain the terminal sequence β -D-galactose-(1-3)-N-acetyl-D-galactosamine (Damjanov, 1987). PNA stains cells of M-PIRE system and it has been used for differential diagnosis of proliferative disorders of histiocytes (Howard and Batsakis, 1982; Ree and Kadin, 1986; Ree and Kadin, 1987). Some reported high sensitivity and specificity of PNA staining for LCH (Ree and Kadin, 1986; Ree and Kadin, 1987; Mclelland and Chu, 1988). But there has been many debates on these facts (Kanitakis *et al.* 1988; Rabkin *et al.* 1990), so this study evaluated PNA as a marker of LCH.

The results showed that only a small fraction of LCH cells in each case showed specific paranuclear and membrane staining patterns. Immunohistochemical staining using lectin has many variables (Rabkin *et al.* 1990). Among these, the most important one is survival of the lectin binding site after

tissue processing. This study included 22 cases of bone biopsy which needed decalcification process and the author performed PNA staining by a two step method using biotinylated PNA which was reported to be a less sensitive method than a three-step method (Rabkin *et al.* 1990). But comparing the results of PNA staining with those of S-100 protein immunostaining which showed diffuse staining in all cases, The author found no advantage of PNA staining over S-100 protein immunostaining in the diagnosis of LCH.

In this study about two thirds of the cases showed KP1, MAC 387 and lysozyme besides S-100 protein in a small fraction of LCH cells but there was no case reactive for Elastase. DAKO-CD68, KP1 detects a glycoprotein with a molecular weight of approximately 11kD, probably associated with lysosomal granules and it stains macrophages in a wide variety of human tissue (Pulford *et al.* 1989). Normal LCs of epidermis in the two included cases revealed negative reaction to KP1.

DAKO-MAC 387 reacts with human cytoplasmic antigens expressed in granulocytes, blood monocytes and tissue histiocytes (Flavell *et al.* 1987). Its immunogen is purified peripheral blood monocyte component and it also did not label normal LCs in the epidermis. DAKO-Elastase reacts with human neutrophil elastase, a neutral protease which is found principally in the primary granules of human neutrophils, but is also present in small amounts in some human monocytes (Dewald *et al.* 1975; Pulford *et al.* 1988). Traditionally it has been known that the proliferating cells of LCH is S-100 protein positive and showed a lack of lysozyme (Watanabe *et al.* 1983; Park *et al.* 1988). But sinus histiocytosis with massive lymphadenopathy, probably of macrophage origin, reveals ambiguous phenotype (both S-100 protein and lysozyme positive) and there is a report demonstrating that LCH cells can also reveal myeloid/macrophage markers in addition to S-100 protein (Miettinen *et al.* 1987; Ruco *et al.* 1989; Eisen *et al.* 1990; Sung *et al.* 1992). In this study the positive reaction of LCH cells to KP1, MAC 387 and lysozyme is verified but is observed only in a small fraction of LCH cells. So KP1, MAC 387 and lysozyme can't be used as diagnostic markers of LCH. Also noted was a staining pattern of MAC 387. It demonstrated dendritic cells among sheets of LCH cells which probably represent tumor infiltrating dendritic histiocytes undetected hitherto after S-100 protein immunostaining due to masking of these cells by diffuse and intense positivity of LCH cells.

The result of this study that a minority of LCH

cells expressed hybrid phenotype of macrophages and LCs suggests the existence of transitional cells of histiocytes. There are several well-established transitional cells among M-PIRE system showing hybrid phenotype. such as lining cells of the spleen (Foucar and Foucar, 1990). LCs and macrophages have common a progenitor and several in vivo and in vitro studies support the fact that LCs and macrophages are not entirely separate families of M-PIRE system (Nezelof et al. 1977; Murphy et al. 1986).

In summary, this study demonstrated that the most reliable marker of LCH, especially in decalcified material, is S-100 protein and also that proliferating cells of LCH express UCHL1 and MT1 re-emphasizing lineage nonspecificity of these markers. Also noted was a dual expression of S-100 protein and myeloid/macrophage markers in a minority of LCH cells.

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