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Immunohistochemical study of the abnormal cells in Langerhans cell histiocytosis (Histiocytosis x)

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Summary. The immunophenotypic properties of the abnormal cells in routine specimens from 16 cases of Langerhans cell histiocytosis (LCH) were examined. In five cases, cryostat sections were also available. The abnormal cells expressed a similar phenotype and were positive for HLA-DR, S-100 protein, peanut agglutinin (PNA), CD1a, CD4 and several macrophage-associated markers, including CD11c, CDw32 and CD68 (the latter detectable in routine sections with antibody KP1). Staining with CD14, CD35 (C3b receptor), and CD11b (C3bi receptor) was negative with the exception of one of the cases in which a proportion of the cells showed faint positivity with CD11b. Staining for pan-T-cell (CD2, CD3, CD5) and pan-B-cell (CD19, CD22) antigens was negative in all lesions. It is concluded that LCH expresses a characteristic phenotype with some heterogeneity with regard to macrophage markers and that immunohistochemical methods in cryostat sections and routine specimens form a useful supplement to other techniques for the diagnosis of this condition.

Key words: Langerhans cell histiocytosis – Immunohistochemistry

Introduction

The term "Histiocytosis x" is now being replaced with the less mystifying and partly self-explanatory term "Langerhans cell histiocytosis" (Writing Commitee for the Histiocytosis Society 1987). It has been established that the abnormal cells in these conditions are very similar to the normal Langerhans cells of the epidermis (Nakajima et al. 1982; Murphy et al. 1983; Bhan et al. 1984). The "x" may, however, still be appropriate as questions regarding aetiology, prognosis and treatment are largely unsolved; and knowledge of the pathobiology of the disease is only fragmentary.

Heterogeneity with respect to the expression of various cell markers has been shown to exist in the abnormal cells of LCH (Bos et al. 1984; Hall et al. 1987; Groh et al. 1988; Pallesen 1988; Ruco et al. 1988) and the rapidly expanding field of immunohistochemical markers offers possibilities to recognize details still more intricate with regard to differentiation and cell function. This may ultimately be meaningful in uncovering the pathogenesis.

However, reports of LCH with extensive immunohistochemical investigations are still few and mostly casuistic. In the present study we have examined routine specimens and cryostat sections from 16 patients with LCH with respect to their immunophenotypic properties employing a panel of antibodies intended to confirm and extend the existing information regarding the LCH phenotype.

Material and methods

Twenty-two biopsy specimens from 16 cases of Langerhans cell histiocytosis (LCH) were drawn from the files of the Laboratory of Paediatric Pathology and the Department of Pathology, Rigshospitalet (see Table 1). The samples had been obtained during the period 1968 to 1988. Estimation of organ involvement was based on biopsy findings and clinical and paraclinical parameters. Organ dysfunction was determined according to the criteria outlined by Lahey (1975).

Formalin fixed and paraffin embedded specimens were processed according to standard procedures and stained with monoclonal antibodies reactive with routine specimens (see Table 2), as described in detail elsewhere (Davey et al. 1987). In five cases, fresh biopsy samples were also available and these

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Table 1. Clinical data from 16 cases of Langerhans cell histiocytosis

Case	Sex	Age at diagnosis	Organ involvement	Therapy[a]	Age at last follow-up visit
1	M	$1^{1}/_{12}$ y	Ear, skin, bones lymph node,	Pred., vinbl., CHOP, VP16	$7^{7}/_{12}$ y
2	M	$^{5}/_{12}$ y	Ear, skin, bones	Pred.	$10^{1}/_{12}$ y
3	M	$2^{2}/_{12}$ y	Ear, skin, bones	Pred.	$8^{6}/_{12}$ y
4	F	9 y	Ear, skin, lymph node	Pred., vinbl.	$16^{4}/_{12}$ y
5	F	$^{3}/_{12}$ y	Skin, lymph node	Pred.	$8^{2}/_{12}$ y
6	M	$^{10}/_{12}$ y	Lymph node, lung	Pred.	$2^{8}/_{12}$ y
7	M	$^{6}/_{12}$ y	Lymph node, bones gingival mucosa	Pred., CHOP, mtx., VP16, vinbl. IFN	$6^{9}/_{12}$ y
8	M	$^{11}/_{12}$ y	Skin, bones, bone marrow	Pred., vinbl., CHOP, IFN	$1^{10}/_{12}$ y (dead)
9	F	$3^{5}/_{22}$ y	Unifocal bone	Pred.	$9^{3}/_{12}$ y
10	M	6 y	Bones	Pred.	18 y
11	F	$^{3}/_{12}$ y	Skin, bones	Pred.	$6^{2}/_{12}$ y
12	F	1 y	Bones, lung	Pred.	$3^{7}/_{12}$ y
13	M	$1^{11}/_{12}$ y	Bones	Pred.	$4^{7}/_{12}$ y
14	M	1 y	Bones	Pred.	$5^{3}/_{12}$ y
15	F	8 y	Skin	Not known	Not known
16	F	30 y	Skin, bones	Pred.	41 y

[a] pred. = prednisone; vinbl. = vinblastine; CHOP = cyclophosphamide, oncovin, adriamycin, prednisone; VP16 = etoposide-VP16 mtx = methotrexate; IFN = alfa-interferon-2

Table 2. Details of the antibodies of this study

Antibody	CD designation (and/or antigen)	Source (and/or reference)
T-cell associated		
OKT6	CD1a	Ortho Diagnostics
anti-Leu-5	CD2	Becton Dickinson
anti-Leu-4	CD3	Becton Dickinson
anti-Leu-3	CD4	Becton Dickinson
anti-Leu-1	CD5	Becton Dickinson
anti-Leu-2	CD8	Becton Dickinson
UCHL1*	CD45RO	DAKOPATTS
anti-Tac	CD25 (IL-2 receptor)	(Uchiyama et al. 1981)
B-cell associated		
4KB128	CD22	DAKOPATTS
B4	CD19	Coulter Clone
L26*	B-cell related	DAKOPATTS
Macrophage/myeloid cell associated		
OKM1	CD11b (C3bi receptor)	Ortho Diagnostics
KB90	CD11c (p150,95 molecule)	DAKOPATTS
anti-Leu-M3	CD14	Becton Dickinson
KB61	CDw32 (FcyII receptor)	(Pulford et al. 1986)
To5	CD35 (C3b receptor)	DAKOPATTS
Y1/82A	CD68	(Davey et al. 1988)
EBM/11	CD68	DAKOPATTS (Kelly et al. 1988)
KP1*	CD68	(Warnke et al. 1989)
R4/23	FDC related**	DAKOPATTS
NP57*	Neutrophil elastase	DAKOPATTS (Ralfkiaer et al. 1989)
Miscellaneous		
Anti-HLA-DR	HLA-DR	Becton Dickinson
CR4/43*	HLA-DR	Mason DY (unpublished)
LCA*	CD45	DAKOPATTS
Ki-1	CD30	DAKOPATTS
Ber-H2*	CD30	DAKOPATTS
PNA*	Peanut agglutinin	DAKOPATTS
S-100*	S-100 protein	DAKOPATTS

* antibodies reactive with routine specimens;
** FDC = follicular dendritic cell

were processed as described previously. In brief, specimens were embedded in OCT-compound®, frozen in a mixture of 2-methylbutane and dry ice and stored at −80° C until sectioning. Cryostat sections were airdried overnight at room temperature, fixed in acetone for 10 minutes and then stained with the antibodies listed in Table 2 using either a three-stage immunoperoxidase method (Ralfkiaer et al. 1986) or the alkaline phosphatase-anti-alkaline phosphatase (APAAP) technique (Cordell et al. 1984).

Positive controls were performed by staining lymphoid organs with benign hyperplasia or malignant lymphomas of known immunological phenotypes; and negative controls by omitting one or more of the immunohistochemical reagents (Ralfkiaer et al. 1986).

Results

The clinical features are summarized in Table 1. The median age of the 16 patients (9 male, 7 female) at the time of diagnosis was $1^4/_{12}$ years (range: $^3/_{12}$–30 years). Two patients had localized disease (one with a unifocal bone lesion, one with skin involvement only). The remaining fourteen patients had disseminated disease with involvement of either bone and soft tissue(s) or soft tissue in two or more sites. Organ dysfunction was evident in one patient at the time of diagnosis (case 1), and during progression of the disease in another (case 8). The treatment regimens (see Table 1) consisted of prednisone in all patients with additional chemotherapeutic agents in four. Two patients received alfa-interferon-2 treatment during the course. Median follow-up in the patients was $5^3/_{12}$ years (range: $^{11}/_{12}$–12 years). One patient was lost to follow-up. One patient (case 8) with disseminated disease never went into remission and died from organ dysfunction. The remaining fourteen patients were in remission at the latest control visit, however, 3 patients (cases 1, 7 and 16) experienced relapses during the course.

The lesions from various tissues (Table 3) exhibited similar histological features. All cases showed infiltrates of large cells with reniform or grooved nuclei, evenly dispersed chromatin, and abundant eosinophilic cytoplasm (Fig. 1). Occasional multinucleate giant cells were present in all bone lesions. Necrotic foci with accumulation of eosinophils were noted in the bone lesions and also in two lymph node specimens.

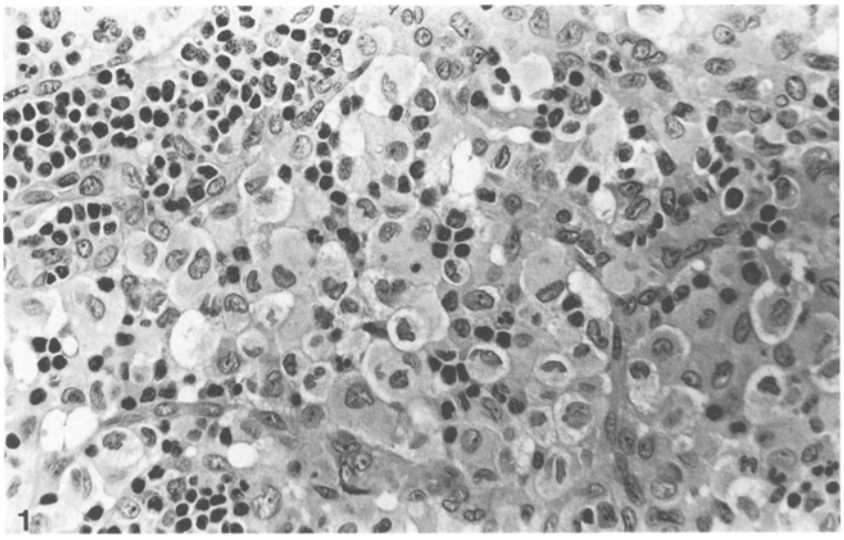
Results from the immunohistochemical examination of routine specimens are summarized in Table 3 and illustrated in Figs. 2 and 3. In all cases, the abnormal cells showed nuclear and cytoplasmic positivity for S-100 protein. Staining for PNA was also positive in all lesions. Both surface membrane and cytoplasmic positivity was seen; and many cells showed prominent paranuclear dots (see Fig. 2), corresponding possibly to the Golgi region (Rhee and Kadin 1986).

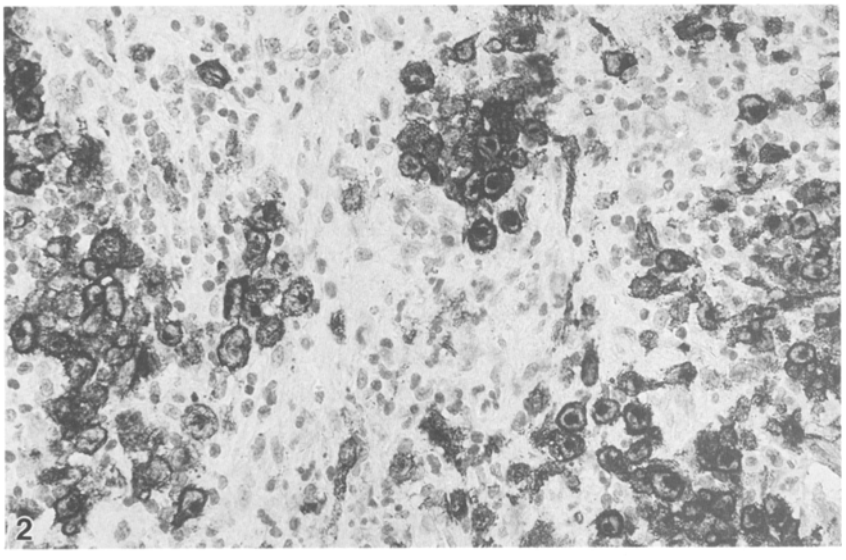
HLA-DR and CD68 was expressed in 16 and

Table 3. Phenotypic data on routine specimens from 16 cases of Langerhans cell histiocytosis

Case	Tissue	CD45 LCA	PNA	S-100	HLA-DR CR4/43	CD68 KP1	NP57	CD45RO UCHL1	L26	CD30 BerH2
1	lymph node	−	+	+	+	+/−	+/−	−	−	−
2	bone	−	+	+	+	+/−	−	−	−	−
3	bone	+	+	+	+	+/−	+/−	+	−	−
4	subcutis	−	+	+	+	+/−	−	+	−	−
	lung	−	+	+	+	+/−	−	−	−	−
5	lymph node	−	+	+	−	−	−	+	−	−
6	lung	−	+	+	−	+/−	−	−	−	−
	lymph node	−	+	+	−	−	−	−	−	−
7	gingiva	−	+	+	+	+/−	+/−	−	−	−
	lymph node	−	+	+	+	−	−	−	−	−
	lymph node	+/−	+	+	+	+/−	−	−	−	−
8	bone	−	+	+	+	+/−	−	−	−	−
9	bone	−	+	+	−	+/−	−	+	−	−
10	bone	−	+	+	+	+/−	−	+/−	−	−
	bone	−	+	+	+	+/−	−	+/−	−	−
11	bone	−	+	+	+	+/−	−	−	−	−
12	lung	−	+	+	+	+/−	−	−	−	−
	bone	+/−	+	+	−	−	−	−	−	−
13	bone	−	+	+	+	+/−	−	−	−	−
14	bone	−	+	+	−	+/−	−	+	−	−
15	skin	ND	ND	ND	+	+/−	ND	ND	ND	−
16	skin	−	+	+	+	+/−	−	+	−	−

+ = labelling of a majority of the abnormal cells; +/− = labelling of a proportion of the abnormal cells; − = no staining of the abnormal cells. ND = not done





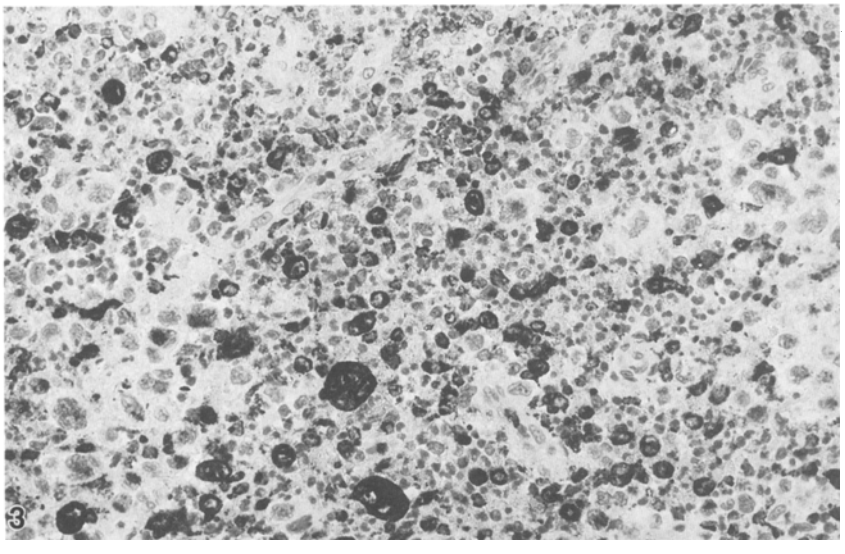


Fig. 1. Biopsy from lymph node showing typical LCH infiltrate composed of large cells with reniform or grooved nuclei and abundant pale cytoplasm. H&E. Original magnification: 400

Fig. 2. Biopsy from LCH skin lesion stained for PNA. The abnormal cells are strongly positive with both cell surface and cytoplasmic positivity. Paranuclear dots (possibly corresponding to the Golgi region) are prominent in a majority of the cells. Original magnification: 400

Fig. 3. Biopsy from a LCH bone lesion stained with CD68 (antibody KP1). There is a strong labelling of both multinucleate giant cells and reniform LCH cells. Original magnification: 250

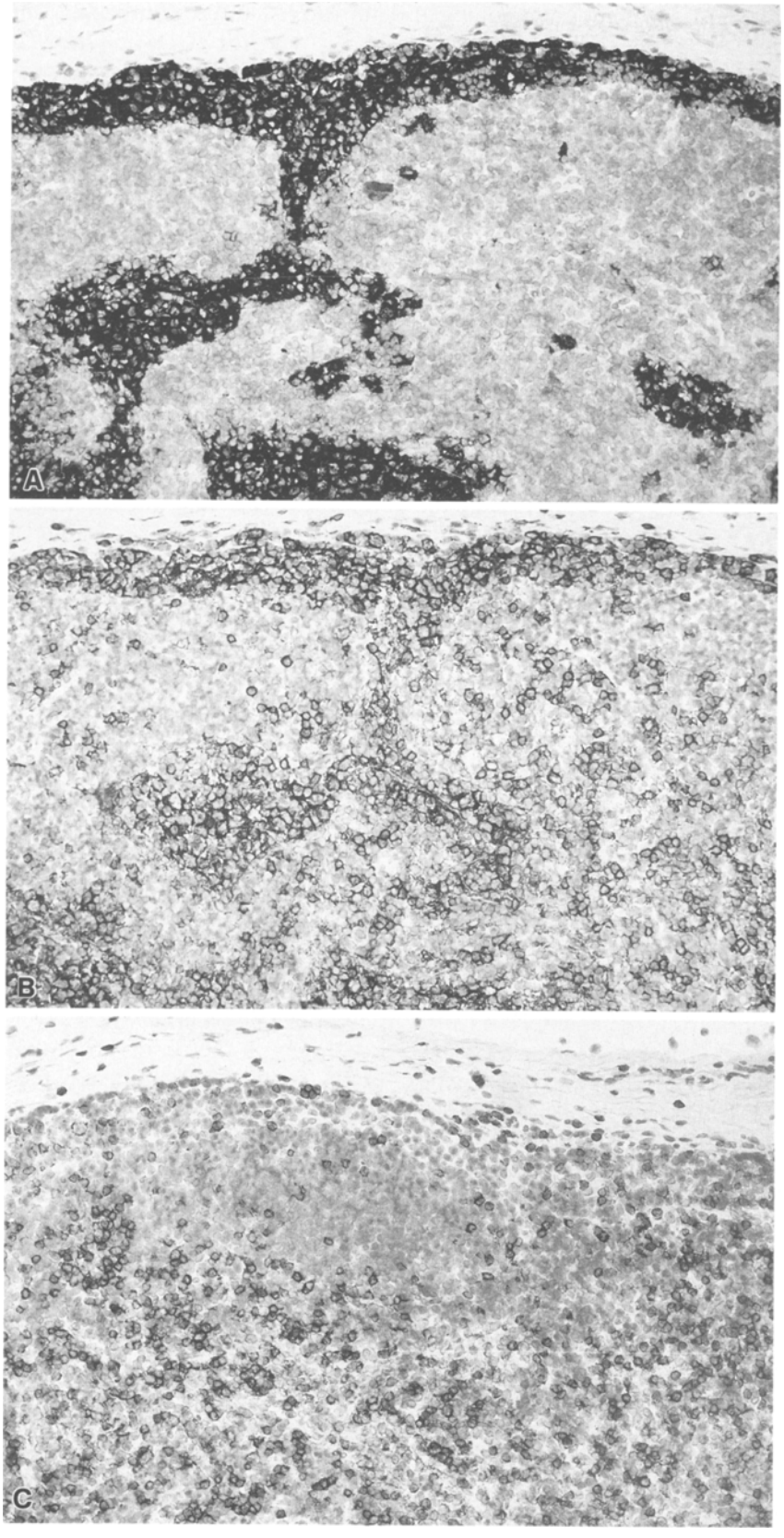


Fig. 4. Biopsy from a lymph node with LCH infiltrates. The abnormal cells are positive with CD1a **A** and CD4 **B**, but negative for a pan T-cell marker CD3 **C**. Original magnification: 100

Table 4. Phenotypic data on cryostat sections from 5 cases of Langerhans cell histiocytosis

Markers	Case 2 bone	Case 6 lymph node	Case 7 lymph node	Case 15 skin	Case 16 skin
T-cell associated					
CD1a	+	+	+	+	+
CD4	+	+	+	+	+
CD2-3-5-8	−	−	−	−	−
CD25	+	−	−	ND	+
B-cell associated					
CD19-22	−	−	−	−	−
Myeloid/Macrophage associated					
CD11b	ND	−	−	−	+
CD11c	+	+	+	+	+
CD14	−	−	−	−	−
CDw32	+	+	−	+	+
CD35	ND	−	−	−	−
CD68	+	+/−	−	+	+/−
R4/23	ND	−	−	−	−
LCA	+	+	+	−	+

+ = labelling of a majority of the abnormal cells; +/− = labelling of a proportion of the abnormal cells; − = no staining of the abnormal cells; ND = not done

18 specimens, respectively. The most abundant staining was seen with HLA-DR which labelled a majority of the infiltrating cells. CD68 reacted with both giant cells and reniform LCH cells (see Fig. 3), but only a proportion of the latter cells were positive. In all cases, staining with CD68 was confined to the cytoplasm of the cells, and labelling of the nuclei was not observed.

Leucocyte common antigen (CD45), UCHL1 (CD45RO) and neutrophil elastase (antibody NP57) was expressed by a varying proportion of the abnormal cells in 3, 8 and 3 specimens, respectively (see Table 3). In contrast, staining with L26 (against a B-cell associated antigen) and CD30 (Ki-1) was negative in all cases.

Results from the immunohistochemical examination of cryostat sections (available in 5 cases) are summarized in Table 4 and illustrated in Fig. 4.

The abnormal cells showed a similar phenotype and were positive for CD1a and CD4, but negative for other T-cell associated antigens, including CD2, CD3, CD5 and CD8. Two cases were positive for CD25 (against the IL-2 receptor). Staining for B-cell antigens (CD19 and CD22) was negative.

With respect to the expression of macrophage associated markers, the five cases were remarkable similar. Four cases were positive with CD68 and CDw32 (FcgammaII receptor); and 5 cases were positive with CD11c (p150,95 molecule). All cases were negative with CD14, CD35 (C3b receptor) and a follicular dendritic cell antigen (antibody R4/23). Staining for C3bi receptor (CD11b) showed a faint positivity in one lesion. The remaining specimens were CD11b negative. Staining for LCA in cryostat sections was positive in four of five cases.

Discussion

In the present report we have studied routine specimens and cryostat sections from 16 LCH patients with respect to the immunophenotypic properties of the abnormal cells. The results confirm and extend previous studies and indicate that LCH lesions show a characteristic phenotype and are positive for HLA-DR, S-100 protein, PNA and CD1a (a thymic cortical T-cells antigen that is also present on normal Langerhans cells).

Ruco et al. (1988) have reported one LCH case in which the abnormal cells expressed the T-cell associated antigen CD2. The cells showed some signs of immaturity (lymphoid appearance and few Birbeck granules) and it was concluded that the expression of CD2 may be a transitory phenomenon during LCH differentiation. Pallesen (1988) also reported weak expression of CD2 in one of two cases of LCH cases, but morphological signs of immaturity were not mentioned. In the present study, CD2 expression was not seen in any of the 5 cases in which cryostat sections were available. Staining for other T-cell antigens was also negative with the exception of the helper-cell associated CD4 antigen, which is not T-cell specific, but also expressed by both "classical" tissue macrophages and accessory cells (Wood et al. 1985). In the present study, staining for CD45RO (antibody UCHL1) showed cytoplasmic positivity in 8 specimens. This is in keeping with the observation that UCHL1 is not strictly T-cell specific but may also be expressed by macrophages (Norton and Isaacson 1989).

B-cell antibodies (CD22, CD19, L26) did not show any reactivity with the abnormal cells and this is in accordance with several other immunohistochemical studies of LCH (Bos et al. 1984; Hall et al. 1987; Groh et al. 1988; Ruco et al. 1988) with the exception of the study by Pallesen (1988) in which 2 cases showed staining for the B-cell associated antigen CD24.

Heterogeneity of LCH cells has also been documented in relation to the expression of macrophage and myeloid cell associated markers. In a study of 21 cases of LCH (Groh et al. 1988) 18 of 29 lesions showed positivity with antibody VIM12 (against the C3bi receptor). Only one of four cases in the present study showed a faint reactivity for

this marker. Staining for C3b receptor was negative, and this is in keeping with other reports of LCH (Ralfkiaer et al. 1985; Pallesen 1988; Hall et al. 1987). However, Groh et al. (1988) found C3b receptor expression (DAKO-C3bR) in 18 of their 29 LCH specimens. The reasons for these discrepancies is not clear but may reflect differences in differentiation or maturation. The CD11c antigen was expressed strongly in all five cases in this study and this is in accordance with results published by Pallesen (1988), Meyer et al. (1988) and Hall et al. (1987). Groh et al. (1988) found expression of this antigen in 7 of 29 specimens.

Expression of the macrophage antigen CD68 has been demonstrated in cryostat sections of LCH by staining with antibodies Ki-M6 (Groh et al. 1988, Meyer et al. 1988) and EBM11 (Hall et al. 1987). Groh et al. (1988) and Meyer et al. (1988) found that 18 of 29 and 6 of 8 specimens were positive, respectively. In five cases in which cryostat sections were available we found that four cases were CD68 (EBM11) positive in a variable proportion of the abnormal cells. Furthermore, with a novel antibody, (KP1) which may be used to detect the CD68 antigen in routine specimens (Pulford et al. 1986), staining was observed in a proportion of the cells in 18 of 22 specimens. This antibody does not react with normal Langerhans cells (Warnke et al. 1989) and may prove useful for the recognition of LCH in routine sections.

In a double labelling study of 7 cases, Barbey et al. (1987) documented reactivity in 30–40% of cells in LCH lesions with antibody to the IL-2-receptor (CD25). This antibody reacts with cultured LC, but does not react with normal Langerhans cells. The authors suggested that this marker may provide a means of evaluating disease activity in LCH. In the present report we found IL-2-receptor expression in lesions from 2 patients (case 2: bone lesion; case 16: skin lesion). Both patients had disseminated disease. One patient (case 2) went into remission and has shown no recurrence after almost ten years of follow up. The other patient (case 16), who presented with multiple bone lesions, went into remission but had recurrence with perianal skin involvement after 10 years. Thus, in the present report, the occurrence of IL-2-receptor expression does not appear to give any meaningful correlation to disease activity.

In summary, 22 routine specimens and 5 cryostat sections from 16 Langerhans cell histiocytosis patients were examined with respect to their immunophenotypic properties. The abnormal cells were positive for HLA-DR, S-100 protein, PNA, CD1a, CD4 and macrophage-associated markers including CD11c, CDw32 and CD68. A novel antibody, KP1 which detects CD68 in routine specimens showed staining in 18 of 22 specimens and this marker, which does not reacts with normal Langerhans cells, may prove helpful in the evaluation of routine specimens. It is concluded that LCH expresses a characteristic phenotype and that immunohistochemical methods are a useful adjunct to other diagnostic methods in LCH.

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