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Letterer-Siwe disease: Immunohistochemical evidence for a proliferative disorder involving immature cells of Langerhans lineage*

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Summary. The morphological, ultrastructural and immunophenotypic properties of Histiocytosis-X (H-X) cells were investigated in a lymph node involved by Letterer-Siwe (L-S) disease. H-X cells were T6+ (CD1a), S-100+, T4+ (CD4) and HLA-DR+; in addition they were consistently T11+ (CD2) and were stained by antibodies directed against receptors for transferrin (T9), C3bi (OKM-1/CD11b), IgG-Fc (Leu-11/CD16) and Interleukin-2 (IL-2R/CD25). On immunostained cytosmears, T6+ cells were highly polymorphic and a prominent fraction (45%) showed immature morphology, characterized by lymphoid appearance. Cells expressing macrophage markers (ANAE, AACT, Leu-M3/CD14, PAM-1) were 10-fold fewer than T6+ cells and did not show a lymphoid morphology. At TEM level, H-X cells were characterized by poor content of LC granules and by the presence of myelin-like laminated bodies and of lysosome-like dense bodies. The immunophenotypic properties of H-X cells were compared to those of epidermal Langerhans cells (LCs) and of LCs present in lymph nodes of three cases of dermatopathic lymphadenitis. Epidermal LCs were T6+/HLA-DR+, and sometimes faintly T4+. Lymph node LCs were T6+, S-100+, T4+, HLA-DR+, and showed the same variety of surface receptors detected in H-X cells; furthermore, in a case with massive infiltration of the paracortex by T6+ cells, lymph node LCs were faintly T11+ and some of the T6+ cells had lymphoid aspect. Our findings suggest that the H-X cell population of L-S disease is not homogeneous, but is composed of discrete cell subsets with distinctive antigenic and morphological traits closely resembling those of cells of LC lineage at different maturational stages.

Key words: Histiocytosis X – Letterer-Siwe disease – Dermatopathic lymphadenitis – Langerhans cells – Immunohistology

Introduction

Letterer-Siwe (L-S) disease is an acute disseminated form of Histiocytosis X usually observed in early infancy and in the aged (Lichtenstein 1953). The histopathology of L-S disease is non-specific, being similar to that of the other forms of chronic disseminated Histiocytosis X (Hand-Schuller-Cristian disease) (Nezelof et al. 1979). However, several clinical criteria, including age of onset, tissue distribution of the lesions, and a less favorable prognosis, strongly suggest that L-S disease is a separate entity.

In recent years, several publications dealing with immunohistochemical characterizations of Histiocytosis X have appeared in the literature (Chollet et al. 1982; Thomas et al. 1982; Kahn et al. 1983; Harrist et al. 1983; Murphy et al. 1983; Beckstead et al. 1984; Bieber et al. 1985; Scarpelli 1986; Goldberg et al. 1986). It was established that Histiocytosis X lesions derive from abnormal proliferations of S-100+/T6+/HLA-DR+ dendritic cells closely resembling Langerhans cells (LCs). H-X cells, however, differ from typical LCs since they are often characterized by marked T4 expression (Harrist et al. 1983; Murphy et al. 1983; Beckstead et al. 1984), by immunoreactivity for C3b, C3bi and C3d antigen receptors (Bieber et al. 1985) and by weak positivity of myelo-monocytic antigens

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(Beckstead et al. 1984; Scarpelli 1986). It was therefore proposed that the unusual phenotype of H-X cells might be related to their state as "tumour cells" and/or to cell immaturity.

We describe here the morphological and antigenic properties of H-X cells in L-S disease using immunostained cytosmears. Our findings indicate that the H-X cell population is not homogeneous, but is composed of discrete cell subsets with distinctive morphological and antigenic traits; furthermore, similar properties were detected in normal cells of LC lineage present in dermatopathic lymphadenitis. Our observations raise the possibility that L-S disease is a proliferative disorder of LC precursors still able to reach full differentiation.

Materials and methods

The patient with Letterer-Siwe disease was a 11-month-old white female who presented with hepatosplenomegaly, superficial lymphadenopathy, cutaneous rash on the back, anaemia (Hb: 10.3 g/dl), thrombocytopaenia (23×10^9/l) and normal leukocyte counts (11.7×10^9/l); an inguinal lymph node was removed for diagnosis. The patient with Hyper-IgE syndrome (Buckley 1972) was a 9-month-old male who presented with recurrent infections, interstitial pneumonia, diffuse eczematous dermatitis, superficial lymphadenopathy, peripheral blood leukocytosis with eosinophilia, and marked serum hyper-IgE (7000 IU/ml); an axillary lymph node was biopsied. Lymph nodes involved by dermatopathic lymphadenitis were also obtained from two adult patients suffering of contact dermatitis. Fragments of normal skin were obtained from routine biopsy samples.

Acetone-fixed cryostat sections and formalin-fixed paraffin embedded sections were prepared from lymph node and skin biopsies. Cytocentrifuge smears were prepared from the lymph node cell suspensions and from peripheral blood leukocytes obtained from the same patients.

Tissue sections were immunostained with one of the following antibodies whose specificity is listed in Table 1: OKT3, OKT4, OKT6, OKT9, OKT10, OKT11, OKT16, OKM-1, OKIa-1, OK-CLL (Ortho Pharmaceutical, Raritan, NJ, USA), Leu-7, Leu-M1, Leu-M3, anti-IL-2R (Becton Dickinson, Sunnyvale, CA, USA), DRC-1, To-15, anti-Factor VIII Related Antigens (F-VIII-RA), S-100 protein, α1-anti-chimotrypsin (AACT), lysozyme (Dakopatts, Denmark), B4 (Coulter Clone, Italy) and PAM-1 (Biondi et al. 1984).

Cryostat sections were incubated with biotin-conjugated horse anti-mouse serum, and then with avidin-biotin peroxidase complex (PK 4002; Vector Laboratories, Burlingame, CA, USA). The immune reaction product was developed with a final incubation with 0.03% H_2O_2 and 0.06% 3,3′-diaminobenzidine (BDH Chemicals, England) for 3–5 min. Endogenous peroxidase was inhibited by pre-incubation in 1% H_2O_2 in PBS for 30 min. Cryostat sections were also stained for α-naphtyl-acetate esterase (ANAE).

Paraffin sections were stained with haematoxylin-eosin; additional sections were immunostained for S-100 protein, AACT and lysozyme, using rabbit polyspecific sera. The reaction product was developed by avidin-biotin method as described above. Acetone-fixed cytocentrifuge smears were immunostained as previously described for cryostat sections.

Table 1. Antibody panel

Antibody	Antigen	Cellular distribution
OKIa-1	HLA-DR	B-lymphocytes, activated T lymphocytes macrophages and dendritic cells
OKT-6	CD 1a	Cortical thymocytes, Langerhans cells
OKT-11	CD 2	T-cells, receptor for sheep erythrocytes
OKT-3	CD 3	T-cells, associated with T cell receptor
OKT-4	CD 4	Helper T cells, macrophages, dendritic cells
OK-CLL	CD 5	T-cells, B-cell chronic lymphocytic leukemia
OKT-16	CD 7	T cells
OKT-8	CD 8	Cytotoxic/suppressor T cells, splenic sinusoidal cells
OKT-9		Transferrin receptor
OKT-10		Thymocytes, activated T cells, plasma cells
OKM-1	CD 11b	C3bi receptor, granulocytes, monocytes, macrophages, NK cells
Leu M3	CD 14	Mature monocytes and macrophages
Leu-M1	CD 15	Hapten X, myeloid cells, Reed-Sternberg cells
Leu-11	CD 16	Fc receptors on granulocytes, NK cells and some macrophages
PAM-1		Tissue macrophages
DRC-1		Follicular dendritic reticulum cells
B4	CD 19	B lymphocytes
To-15	CD 22	B lymphocytes
Anti-IL-2R	CD 25	Interleukin-2 receptor on T cells and macrophages
Leu-7		NK cells, nervous sheath
S-100		Interdigitating reticulum cells, Langerhans cells, numerous cells of non-haematopoietic origin
AACT		Myelo-monocytic cells and macrophages, activated T lymphocytes
Lysozyme		Myelo-monocytic cells and macrophages
F-VIII-RA		Endothelial cells, megakaryocytes, thrombocytes

For electron microscopy lymph node fragments were fixed for TEM at 4° C in 2.5% gluteraldehyde in phosphate buffer (pH 7.3) for 3 h. The fragments were then washed in PBS for 2 h and postfixed in 1.33% osmium tetroxide in PBS at 0° C. The small blocks were dehydrated in alcohol, transferred in toluene and embedded in EPON 812. Thin and ultrathin sections were cut on Reichert microtome and stained with lead hydroxide. The sections were examined in a Philips EM 400.

Results

In Letterer-Siwe disease lymph node architecture was completely effaced by a cell population composed of a proliferation of medium-large cells with oval, indented or lobated nuclei and with weakly basophilic cytoplasm (Fig. 1). Some mitotic figures were occasionally observed. On cryostat sections (Table 2), H-X cells were T6+ (CD1a), T4+ (CD4) and HLA-DR+. Furthermore, H-X cells were immunostained by antibodies directed against receptors for transferrin (T9), C3bi (OKM-1/CD11b), IgG-Fc (Leu-11/CD16), and Interleukin-2 (anti-IL-2R/CD 25). Unexpectedly, H-X cells were consistently immunoreactive for T11 (CD2) which is known to recognize the T lymphocyte receptor for sheep erythrocytes. H-X cells were weakly ANAE+ and myeloperoxidase-negative;

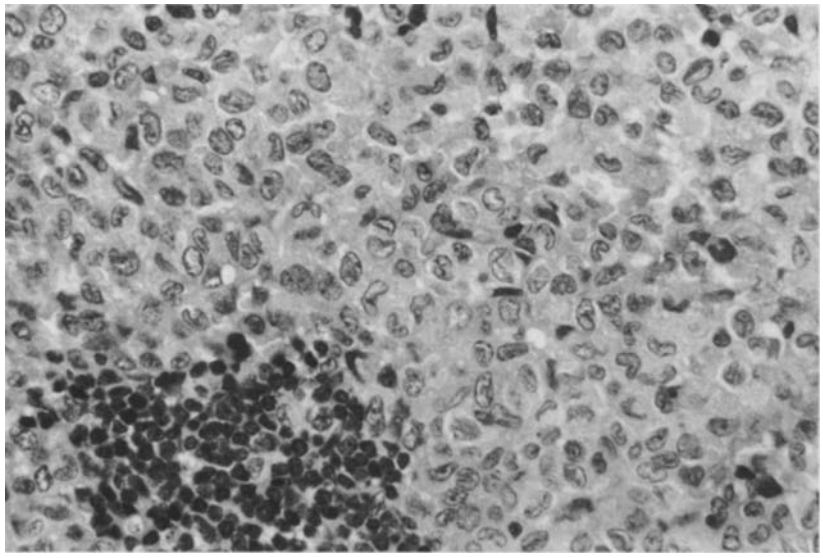

Fig. 1. Letterer-Siwe disease. The lymph node architecture is effaced by a cell population composed of elements with abundant cytoplasm and with oval, lobated or folded nuclei. A residual B cell follicle is present on the left

Table 2. Immunohistochemical characterization of Histiocytosis X cells and of Langerhans cells on cryostat sections from lymph nodes and skin

Histology	Age	HLA-DR	T6 (CD 1)	T11 (CD 2)	T4 (CD 4)	OKM-1 (CD 11)	LEU-11 (CD 16)	PAM-1	LEU-M3 (CDw 14)	T9	TAC (CD 25)
Letterer-Siwe disease (lymph node)	0.9	++	++	++	++	++	+	+	+	++	+
Dermatopathic lymphadenitis Hyper-IgE syndr.	0.7	++	++	+/−	++	++	+/−	−	−	++	+/−
Dermatopathic lymphadenitis Contact dermat.	45	++	++	−	+	+	+/−	−	−	+	+/−
Dermatopathic lymphadenitis Contact dermat.	42	++	++	−	+	+/−	+/−	−	−	+	+/−
Normal skin (3 cases)		++	++	−	+/−	−	ND	−	−	ND	−

Histiocytosis X and Langerhans cells were not reactive with the following antibodies: T1 (CD5), T3 (CD3) T16 (CD7), T8 (CD8), T10, Leu-M1 (CD15), B4 (CD19), To-15 (CD22), Leu-7, DRC-1, Factor VIII-RA. (++) Most of the cells are positive. (+) Numerous cells are positive. (+/−) Some cells are positive

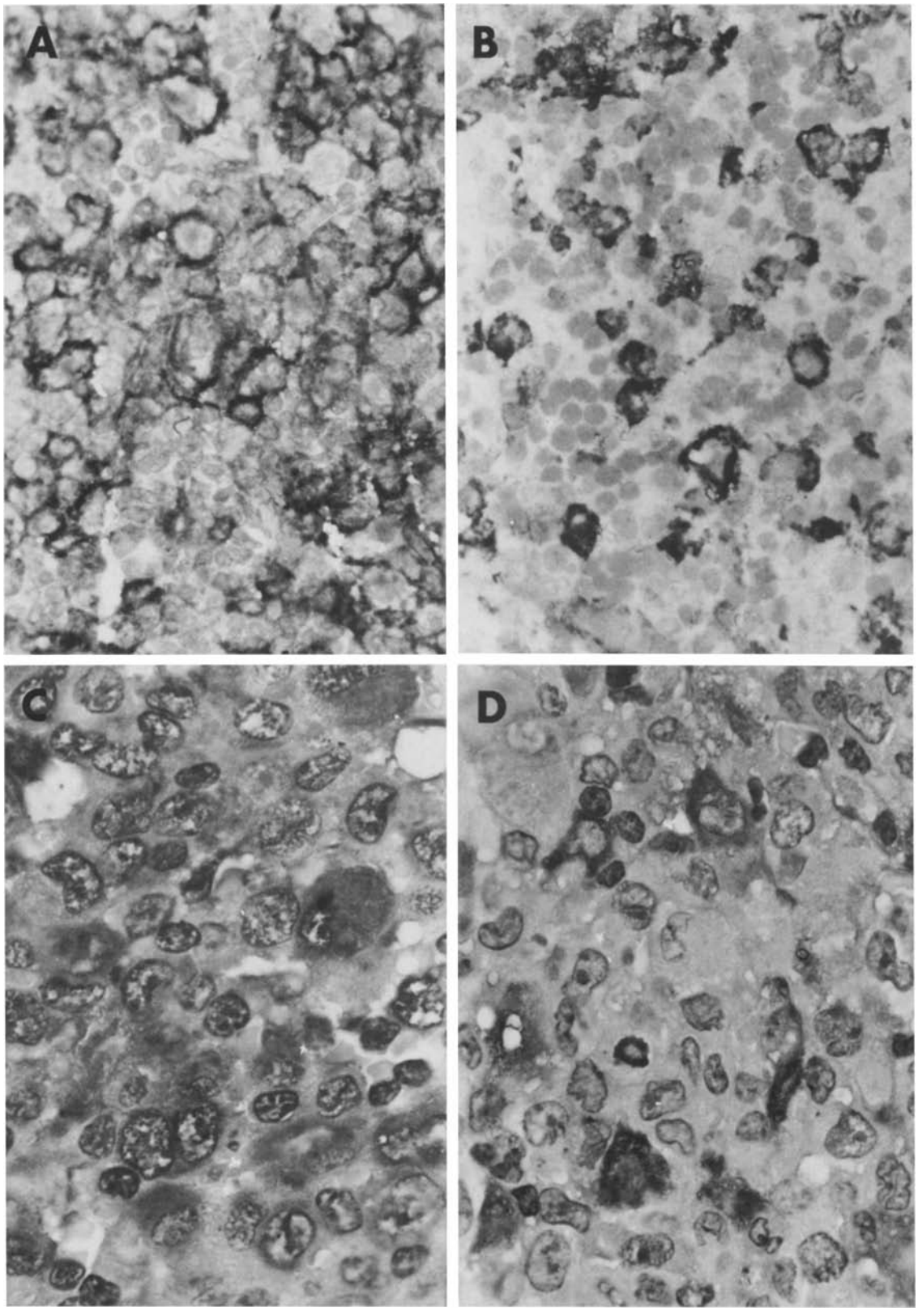

Fig. 2. Letterer-Siwe disease. Frozen sections immunostained for T6 (**A**) and PAM-1 (**B**), and paraffin sections immunostained for S-100 (**C**) and (AACT) (**D**). The number of T6+ cells is comparable to that of S-100+ cells and is higher than that of cells expressing the macrophage markers PAM-1 and AACT. Some AACT+ cells have folded nuclei suggesting a possible relation to H-X cells (ABC-peroxidase, ×400)

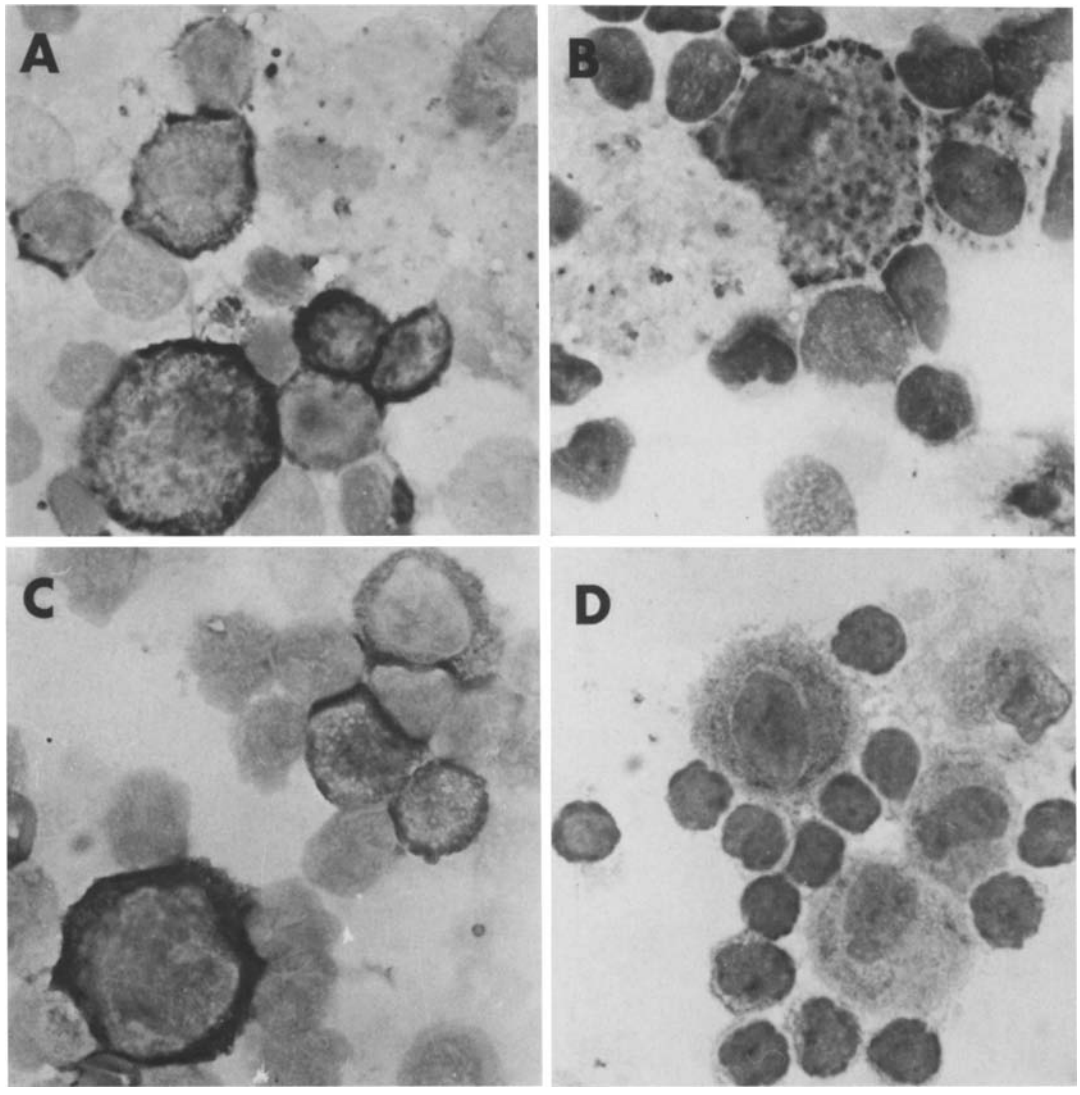

Fig. 3. Immunostained cytosmears prepared from the lymph node cell suspensions. (**A**) Letterer-Siwe disease. T6+ cells are highly polymorphic and consist of lymphoid, medium-sized and large cells. (**B**) Letterer-Siwe disease. The macrophage antigen PAM-1 is present in medium-sized and large cells only. (**C**) Dermatopathic lymphadenitis associated with Hyper-IgE syndrome. T6+ cells show the same polymorphism of L-S disease. (**D**) Dermatopathic lymphadenitis. Three T11+ large cells whose morphology is consistent with a Langerhans origin. (ABC-peroxidase, × 1000)

they were not stained by antibodies directed against Hapten X (Leu-M1/CD15), B cells (B4/CD19; To-15/CD22), T cells (T3/CD3; T1/CD5; T16/CD 7; T8/CD8) and NK cells (Leu-7). Cells expressing the macrophage markers ANAE, PAM-1 and Leu-M3/CDw14 were numerous, but were fewer than T6+ cells (Fig. 2A). Some eosinophils, scattered mature (T3+, CD3) T lymphocytes, and rare B cell nodules were present in the lesion (Fig. 1).

The morphology of immunostained cells was investigated further on cytocentrifuge smears prepared from the lymph node cell suspension (Table 3). T6+ cells accounted for 43% of total cells, and were characterized by a variety of aspects (Fig. 3A); 45% of T6+ cells were small lymphocyte-like cells; 34% were medium-sized cells with clearly discernable cytoplasm and round nuclei; 21% were large cells with eccentrically located nuclei. On cytosmears, 14% of T11+ cells were large cells with round or lobated nuclei. PAM-1+ cells were about 10-fold less numerous than T6+ cells and were medium-large cells only (Fig. 3B). Expression of macrophage markers by H-X cells was also investigated on paraffin sections where some cells with lobated or folded nuclei were AACT+

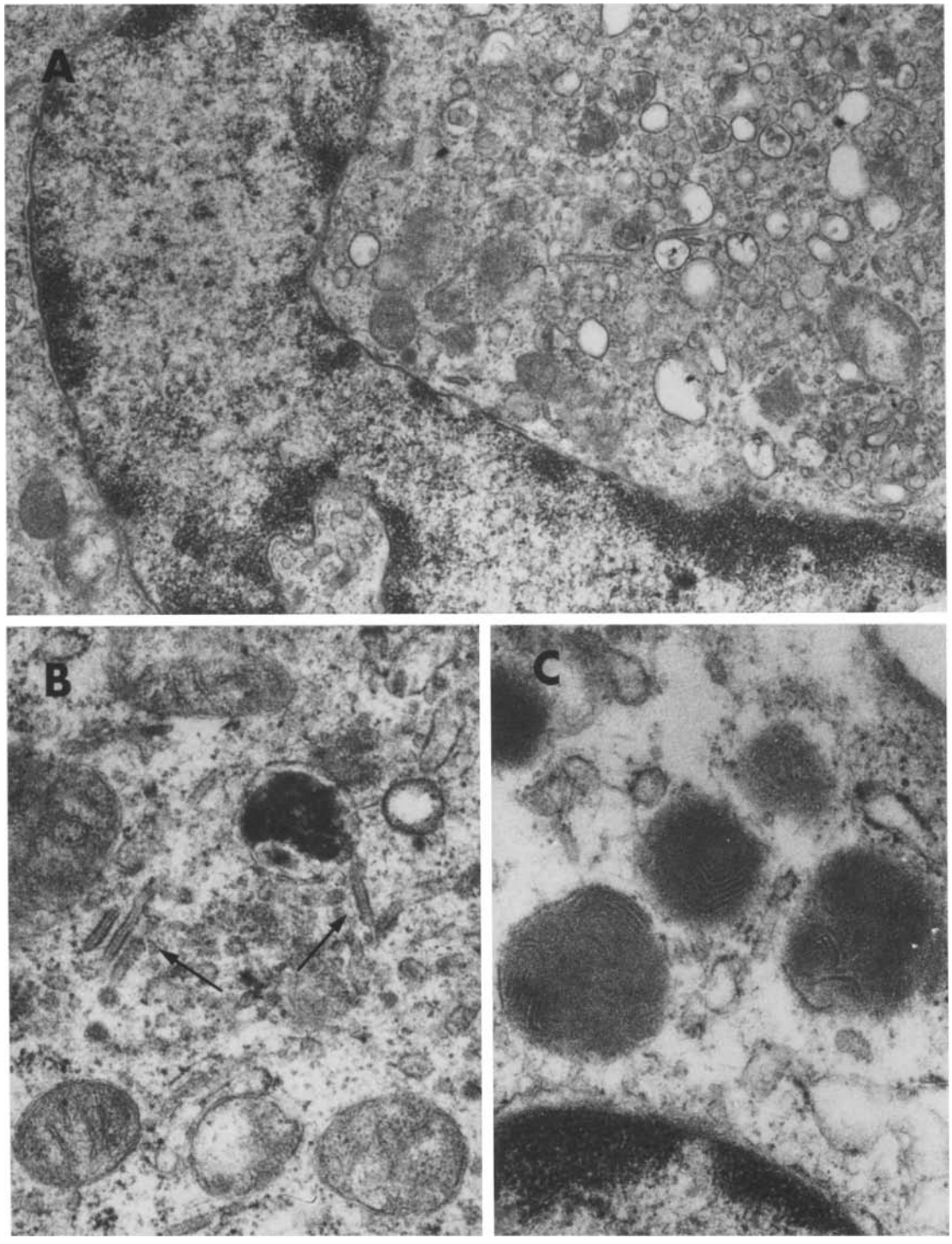

Fig. 4. (**A**) A lymph node cell containing some Langerhans' granules in the cytoplasm (×340000). (**B**) A higher magnification of the granules showing the zipper-like structure (×45000). (**C**) A cytoplasmic detail of a lymph node cell containing myelin-like laminated bodies (×45000)

(Fig. 2D); furthermore, H-X cells were consistently S-100-positive (Fig. 2C) and lysozyme-negative.

At TEM level, most of the cells show cytoplasm rich in smooth endoplasmic reticulum, coated vesicles, few mitochondria and a characteristic lobulated nuclear shape. Some of the cells are characterized by the presence of cytoplasmic Langerhans'

Table 3. Percentage and morphology of positive cells on immunostained cytocentrifuge smears obtained from the lymph node cell suspensions

Diagnosis	Age	Antibody	% of total cells	Morphology of positive cells		
				Small	Medium	Large
Letterer-Siwe disease	0.9	T6	43	45	34	21
		PAM-1	5	0	48	52
		T11	35	52	34	14
Dermatopathic lymphadenitis Hyper-IgE synd.	0.7	T6	5	23	37	40
		PAM-1	3	0	45	55
		T11	36	70	27	3
Dermatopathic lymphadenitis Contact dermat.	45	T6	4	0	15	85
		PAM-1	7	0	12	88
		T11	40	88	12	0
Reactive Foll. Hyperplasia* (6 cases)		T6	0.5–0.01	0	13–32	68–87

Cytocentrifuge smears were prepared from lymph node mononuclear cell suspensions and were immunostained by avidin-biotin immunoperoxidase technique. Positive cells were divided in small, medium-sized and large, according to their morphology, and the percentage of each subtype was determined. Small cells: lymphocyte-like cells with round nuclei and scanty cytoplasm. Medium-sized cells: cells with clearly discernable cytoplasm and round centrally located nuclei. Large cells: cells with abundant cytoplasm and eccentrically located round, indented or lobated nuclei. * Some T6+ dendritic cells could be demonstrated in the subcapsular region on cryostat sections

granules (Birbeck granules) (Fig. 4). Moreover, two other types of cytoplasmic organelles were observed; they were previously described as lysosome-like and myelin-like laminated bodies (Fig. 4C).

In the case of dermatopathic lymphadenitis associated with the Hyper-IgE syndrome, T6+ cells were densely packed in the paracortex. These cells were also faintly T11+; in addition, numerous T9+, OKM-1+, Leu-11+ and TAC+ cells were also observed. On cytosmears, some Langerhans-like cells were T11+, and T6+ cells were highly polymorphic as observed in L-S disease (Fig. 3C, D) (Table 3). In the additional two cases of dermatopathic lymphadenitis, T6+ cells were less numerous, and were characterized by dendritic morphology; some of the dendritic-like cells were T9+, OKM-1+, Leu-11+ and TAC+. Cytosmears prepared from one of these cases and from 6 reactive lymph nodes contained only a few T6+ medium-large cells. On paraffin sections, Langerhans-like cells were S-100-positive, AACT-negative and lysozyme-negative.

T6+ cells were not detected on peripheral blood immunostained cytocentrifuge smears prepared from the same patients.

Immunoreactivity for T11 could not be demonstrated in epidermal LCs present in three normal skin samples (Table 3); LCs were T6+/HLA-DR+ and occasionally faintly T4+.

Discussion

We describe here a case of L-S disease in which H-X cells were characterized by previously unreported properties such as polymorphic cytology, immunoreactivity for the T-cell associated antigen CD2, and presence of peculiar cytoplasmic organelles known as myelin-like laminated bodies (MLB) and lysosome-like dense bodies (LDB).

The morphological heterogeneity of H-X cells was demonstrated on immunostained cytosmears; actually, T6+ cells were characterized by a variety of cytological aspects ranging from lymphocyte-like cells to large dendritic cells. A similar spectrum of T6+ cells was detected in a case of prominent dermatopathic lymphadenitis. Thus, the presence of polymorphic T6+ cells is not restricted to L-S disease, but may be observed in other conditions characterized by accelerated LC turn-over. The most likely interpretation for this finding is that H-X/LC populations were composed of discrete cell subsets expressing different maturational stages. Accordingly, we may speculate that some cases of L-S disease originate from proliferative disorders of immature cells already committed to the LC lineage. This interpretation might also help to understand some distinctive traits of the disease such as multiorgan involvement and a highly aggressive clinical course. It should be pointed out that non-dendritic T6+ cells have not been pre-

viously described in H-X or in dermatopathic lymphadenitis. Furthermore, T6+ lymphocyte-like cells were not demonstrated in lymph nodes or spleen containing lymphocyte-like cells immunoreactive for S-100 protein (Uccini et al. 1986). This discrepancy might be due either to our technical approach, namely the use of immunostained cytosmears, and/or to the rarity of the reported cases (both patients were under one year of age).

At the ultrastructural level, cells with LC granules were extremely rare in L-S disease; this finding is well in keeping with the presence of immature LCs since LC granules cannot be demonstrated in the indeterminate reticulum cells which are the putative precursors of LCs in the skin (Murphy 1985). In L-S disease, several cells contained MLB and LDB; these latter organelles were originally described as distinctive of a benign perinatal LC disorder known as "Self-healing reticulohistiocytosis" (Hashimoto and Pritzker 1973). Our findings do not support this interpretation and suggest the possibility that MLB and LDB represent ultrastructural markers for a variety of LC disorders perhaps occurring during the first year of age.

H-X cells and immature LCs were consistently T11+ (CD2), and lacked other T cell antigens (CD3,5,7). CD2 expression by LCs was not previously described and could not be demonstrated by us in epidermal LCs and in two additional cases of dermatopathic lymphadenitis. Thus, it seems likely that CD2 reactivity is not a constitutive trait of LCs, but is a transitory event occurring during differentiation. CD2, also known as T cell erythrocyte receptor and LFA-2, is a 50 kD glycoprotein involved in cell-adhesion and in cell-activation (Alcover et al. 1987). CD2 is mostly present on T-lymphocytes, but is also expressed by NK cells (Lanier et al. 1986) and in some rare cases of acute myeloblastic leukaemia (Mirro et al. 1985); furthermore, CD2 antigen was recently detected on normal rat macrophages (Williams et al. 1987). These findings suggest that CD2 expression by LC/H-X cells does not necessarily imply that they belong to the T cell lineage.

The immunohistochemical characterization of L-S disease has demonstrated that H-X cells have surface receptors for transferrin (T9), C3bi (OKM1/CD11b), IgG-Fc (Leu-11/CD16) and IL-2 (Tac/CD25). The reactivity of H-X cells for C3bi has already been demonstrated (Beckstead et al. 1984; Bieber et al. 1985), but the expression of the other receptors has not been previously reported. We have observed that lymph node LCs may have a repertoire of surface receptors similar to that of H-X cells and that epidermal LCs lack immunoreactivity for receptor antigens; this variability might depend on different stages of cell activation and/or differentiation. The observation that isolated or cultured LCs have biologically active receptors for complement, IgG-Fc and IL-2 (Stingl et al. 1977; Nezelof et al. 1977; Stainer et al. 1986), support our interpretation.

It is generally believed that LCs derive from a bone marrow precursor closely related to that of the myelomonocytic lineage (Goordyal and Isaacson 1985). This interpretation is also supported by the recent demonstration that skin repopulation by LCs is preceded by the appearance of intradermal PAM-1+ macrophages (Murphy et al. 1986). In L-S disease, PAM-1+ cells were less numerous than T6+ cells and were always medium-large in size. These findings suggest either that T6+ cells and PAM-1+ cells belong to unrelated lineages, or that macrophage antigens were expressed by a minority of medium-large T6+ cells. Alternatively, the more immature cells present in the lesion were capable of a dual differentiation towards macrophages and LCs. The finding that some PAM-1+/AACT+ cells showed H-X cell morphology may indicate that they were part of the abnormal cell proliferation. Furthermore, the observation that the number of PAM-1+ cells strictly parallels that of cells markedly ANAE+, Leu-M3+ and AACT+, may indicate that two cell populations, one with enzymatic and phenotypic traits of macrophages and the other with those of LCs, were co-existing in the same lesion.

Circulating T6+ cells could not be demonstrated in the peripheral blood. Thus, even in conditions in which the LC turn-over seems to be accelerated, acquisition of T6 antigen expression is an event which takes place in the extra-vascular compartment. In skin lesions, an increase in the number of intraepidermal T6+ cells is usually associated with an accumulation of PAM-1+ macrophages in the superficial dermis (Murphy et al. 1986). According with our observations, these two cell populations might derive from the same uncommitted precursor whose terminal differentiation is most probably driven by local microenvironmental factors.

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