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Short Communication

Langerhans' Cell Histiocytosis: Expression of Leukocyte Cellular Adhesion Molecules Suggests Abnormal Homing and Differentiation

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***Langerhans' cell histiocytosis (LCH) is characterized by an accumulation of cells with a Langerhans' cell (LC) phenotype. Most patients present with solitary skin or bone lesions, but multi-organ lesions may appear. Twenty-two LCH-tissue sections from 13 children and adolescents, with lesions at different sites, were investigated for the expression of leukocyte cellular adhesion molecules. Surprisingly, the LCH cells showed expression for CD2 in 11 lesions. Staining of LCH cells for CD11a and CD11b was positive in six and three lesions, respectively. Staining for CD11c, CD44, CD54, and CD58 was found consistently positive in all lesions. The strong reactivity for CD54 (intercellular adhesion molecule-1) and CD58 (leukocyte function antigen-3) is in contrast with the epidermal LC. LCs in culture are known to up-regulate the expression of CD54 and CD58. These changes are thought to reflect the* in vivo *situation during migration of activated LCs from the skin to the draining lymph node. It can be concluded that the abnormal cells in LCH not only share characteristics with the epidermal LC, but have additional characteristics of the activated LC, a cell capable of migration. The presumed immunological dysregulation in LCH may affect the expression of cellular adhesion molecules, reflected by the inconsistent expression of CD11a and CD11b and the unexpected expression of CD2. These features may contribute to migration of LCs to aberrant sites in combination with abnormal persistence and proliferation.** (Am J Pathol 1994, 144:466–472)*

Langerhans' cell histiocytosis (LCH) is characterized by an abnormal accumulation and proliferation of Langerhans' cells, cells that normally reside in the epidermis. Most patients affected by the disease are children. The clinical manifestations of LCH in these patients may be variable: some patients present with skin involvement, whereas others present with solitary or multiple bone lesions. Lymph nodes may also be involved. In the most severe cases, the patients present with multi-organ localization. Currently LCH is considered an unusual immunological reaction rather than a malignancy, but the pathogenesis of LCH remains unknown.[1]

Immunohistochemically, LCH cells are known to stain positively for CD1a and S-100.[2,3] Various other markers, such as CD4, LN-2 (cytoplasmic, major histocompatibility complex [MHC] class II antigen), LN-3 (membrane MHC class II antigen), and vimentin were found to be positive in LCH cells.[3–5] Ultrastructurally, the presence of Birbeck granules in the cytoplasm of the tumor cells is characteristic for LCH.[2] With these immunohistochemical and ultrastructural characteristics, LCH cells resemble the epidermal Langerhans' cell.

Cellular adhesion molecules mediate cell-cell and cell-matrix adhesion and play an important role in several other cell functions.[6,7] Several families of ad-

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hesion molecules have been identified, such as the integrins, the immunoglobulin (Ig) superfamily, and the lymphocyte homing receptors. Adhesion molecules that have been associated with adhesive functions and migration of leukocytes are referred to as leukocyte adhesion molecules.[8] These leukocyte adhesion molecules play a role in migration of leukocytes and in antigen presentation as accessory molecules, in which they facilitate antigen-independent adhesion and provide costimuli for T lymphocytes.[9,10] In LCH, lesions may occur at different sites and may remain solitary or evolve to multiple site lesions. The presumed immunological dysregulation in LCH may affect Langerhans' cells in their function and also affect the expression of cellular adhesion molecules, resulting in an accumulation of cells with a Langerhans' cell phenotype at aberrant sites. So cellular adhesion molecules are likely to play an important role in the pathogenesis of LCH. To investigate the expression of leukocyte adhesion molecules of LCH cells, we studied LCH tissue of 13 patients using immunohistochemical methods.

Materials and Methods

Patients

Frozen tissue of 13 pediatric and adolescent patients (eight male and five female) with a histologically confirmed diagnosis of LCH was collected; in four cases primary and recurrent lesions were available. Age at time of diagnosis ranged from 3 months to 22 years. The clinical data of the patients were stratified according to the criteria of the Histiocyte Society:[11] (I) single bone lesion, isolated skin disease, or solitary lymph node involvement; (II) multiple bone or skin lesions, or multiple lymph node involvement; and (III) multi-organ involvement. For routine histology, sections of formalin-fixed, paraffin-embedded tissue were stained with hematoxylin and eosin.

Immunohistology

Immunoperoxidase staining using a biotin-streptavidin (Dako, Glostrup, Denmark) peroxidase method[12] was performed on frozen, acetone-fixed sections from tissue stored at −80 C. The peroxidase label was visualised using 3-amino-9-ethylcarbazol (AEC, Aldrich), together with H_2O_2. Slides were counterstained with hematoxylin. When possible, staining was performed on serial sections. Frozen, acetone-fixed sections of normal skin (n = 3) were used as controls. In addition, LCs in uninvolved skin and mucosa of appropriate LCH lesions served as internal controls. Characteristics of the antibodies are listed in Table 1.

Indirect Immunofluorescence

Indirect immunofluorescence double-staining was performed using frozen, acetone-fixed sections from the mucosal lesion of patient no. 9. Sections were preincubated with normal goat serum, diluted in 10% phosphate-buffered saline. Binding of monoclonal antibody T6 (Dako) directed against CD1a, was visualized with anti-IgG2a fluorescein isothiocyanate-conjugated goat anti-mouse Ig, and binding of

Table 1. *Antibodies Used*

MAb	Cluster	Ligand	Source	Cellular distribution	Function
T6	CD1a		D	Cortical thymocytes, LC	Unknown
Leu5	CD2	CD58	BD	E-rosette receptor on T lymphocytes	Adhesion and activation of T lymphocytes
T11	CD2	CD58	CO	E-rosette receptor on T lymphocytes	Adhesion and activation of T lymphocytes
LFA-1α	CD11a	CD54	VL	Leukocytes	Adhesive functions of leukocytes
CR3	CD11b	iC3b, CD54	BD	Mac-1, monocytes, macrophages, granulocytes, LC	Adhesive functions of leukocytes
B-ly6	CD11c	Fibrinogen, iC3b,	O (ref. 32)	p150, 95, monocytes, macrophages, granulocytes, LC	Adhesive functions of leukocytes
NKI-P1	CD44	Hyaluronate, fibronectin, collagen	SP	HCAM, widely distributed	Homing of lymphocytes, binding to ECM
My13	CD54	CD11a	CC	ICAM-1, monocytes, epithelial cells, fibroblasts	Initial adhesion in antigen-presentation, cell-endothelium adhesion
TS2/9	CD58	CD2	TS	LFA-3, widely distributed	Initial adhesion in antigen-presentation, T-cell activation

LC, Langerhans' cells; CD, cluster of differentiation; HCAM, homing cellular adhesion molecule; ICAM-1, intercellular adhesion molecule-1; ECM, extracellular matrix

D: Dako, Glostrup, Denmark; BD: Becton Dickinson, Erembodegem, Belgium; CO: Coulter, Luton, England; VL: Dr. R.A.W. van Lier, Central Laboratory, Bloodtransfusion, Amsterdam, The Netherlands; O: Own laboratory; SP: Dr. S.T. Pals, University of Amsterdam, The Netherlands; CC: Dr. C. Civin, John Hopkins Oncology Center, Baltimore, MD; TS: Dr. T.A. Springer, Harvard Medical School, Boston, MA.

monoclonal antibody T11 (Coulter, Luton, England), directed against CD2, was visualized with anti-IgG1 rhodamine B isothiocyanate-conjugated goat anti-mouse Ig.

Results

Histopathology

The histopathological diagnosis of LCH was established according to the criteria of the Histiocyte Society, including CD1a-stains of the LCH cells in 12 patients.[11] In the bone lesions, many eosinophilic granulocytes were scattered among the LCH cells. Lymphocytes were also present, but to a much lesser extent than the eosinophilic granulocytes. Multinucleated giant cells were seen in most of these lesions. In general, the bone lesions showed the typical appearance of the formerly called eosinophilic granuloma. In the skin lesions, the LCH cells were seen in the papillary dermis, and among these cells, lymphocytes were present. Only few eosinophilic granulocytes were seen. The lesion involving a lymph node of patient no. 12 consisted of LCH cells extending into the sinusoidal spaces. The areas of LCH cells were predominantly located in the paracortex leaving the follicles intact. Many sinus histiocytes were scattered among the LCH cells. Relatively few lymphocytes were found within the fields of LCH cells.

Immunohistology

A summary of the results is given in Table 2. In all 20 lesions investigated, the LCH cells were strongly positive for CD1a. In patient no. 12, the CD1a staining confirmed the presence of large sheets of LCH cells within the sinusoidal spaces. In 11 lesions from seven patients, LCH cells expressed CD2. The LCH cells that were positive for CD2 showed a weaker but distinct staining compared to the T lymphocytes present in most lesions. CD2 staining was predominantly seen at the surface of the cell, although in some cases an additional granular, cytoplasmic staining seemed to be present. Not all, but a major subset of CD1a-positive cells was positive for CD2 (range 10 to 25%), as demonstrated in serial sections and in case no. 9 by double immunofluorescence. LCH cells expressing CD2 were found in LCH lesions from bone, skin, as well as lymph node (see Figure 1).

Examination of the LCH cells for β2 integrin expression showed that CD11c was found positive in all cases. In contrast, staining of the LCH cells for CD11b was only seen in three out of 15 lesions investigated. Within the lesions, many cells positive for CD11b were seen, probably representing macrophages and eosinophilic granulocytes. For CD11a, in six out of 19 lesions positive LCH cells were found, and in three of these cases, a markedly strong and distinct staining was observed (see Fig-

Table 2. *Results*

Patient no.	Sex	Age*	Lesion	SHS†	CD1a	CD2	CD11a	CD11b	CD11c	CD44	CD54	CD58
1	m	22 yr	Bone	I	++	–	–	–	++	++	++	++
2	m	2.5 yr	Bone	I	++	–	ND	ND	++	++	ND	++
3	m	15 yr	Bone	I	++	–	++	+	++	++	++	++
4	f	10 yr	Bone	I	++	+	++	++	++	++	++	++
5	f	1 yr	Skin	II	++	+	–	ND	++	+	ND	++
6	m	2 yr	Bone	II	++	+	–	–	++	++	++	++
6	m	2 yr	Bone	II	++	–	–	–	++	++	++	ND
6	m	2 yr	Bone	II	ND	+	–	ND	++	++	++	+
7	m	9 mo	Skin	III	ND	ND	+	ND	++	++	+	ND
8	m	1 yr	Mucosa	III	+	–	–	ND	++	++	+	++
8	m	1 yr	Mucosa	III	++	–	++	ND	++	++	++	++
9	f	4.5 yr	Bone	III	++	–	–	–	++	++	++	++
9	f	4.5 yr	Mucosa	III	++	++	–	–	++	++	++	++
10	m	2.5 yr	Bone	III	++	–	+	–	++	++	+	+
11	f	1 yr	Skin	III	++	+	+	ND	++	++	+	++
12	m	2.5 yr	Lymph node	III	++	+	–	+	++	++	++	++
13	f	1 yr	Mucosa	III	++	–	–	–	++	++	++	++
13	f	1 yr	Skin	III	++	++	–	–	++	ND	++	++
13	f	1 yr	Mucosa	III	++	++	ND	–	++	++	++	++
13	f	1 yr	Bone	III	++	++	–	–	++	++	++	++
13	f	1 yr	Bone	III	++	ND	ND	–	++	++	++	++
13	f	1 yr	Bone	III	++	+	–	–	++	++	++	++

* Age at time of diagnosis
† Stratification according to the Histocyte Society (ref. 11). ND, not done; –, negative staining; +, weak staining; ++, strong staining.

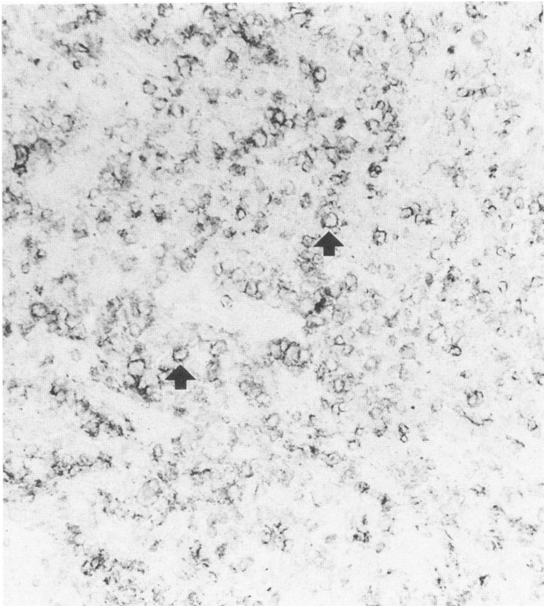

Figure 1. *Staining for CD2 in the mucosal lesion in case no. 9. A subset of the LCH cells positive for CD1a also shows positivity for CD2 (arrows). (140×; immunoperoxidase).*

ure 2). Similar to the expression of CD2, not all, but a subset of LCH cells expressed CD11a and CD11b, although the relative number of positive cells exceeded the cells positive for CD2 (range 25 to 75%).

CD44 was strongly expressed by the LCH cells, as was the case for most of other inflammatory cells within the specimen. Staining for CD54 (Figure 3) and CD58 also revealed strong positivity of LCH cells, but in contrast most other cells showed only weak expression. In addition, a distinct endothelial staining for CD54 was found in some cases. In the control sections of normal skin, CD1a positive LCs were found to express CD11c, CD54 (both weak), CD44, and CD58 (both moderate staining). Expression of CD2, CD11a, and CD11b was not observed.

Discussion

Within the immune system associated with the skin, Langerhans' cells are considered important antigen-presenting cells. After cutaneous antigen contact, the Langerhans' cells are supposed to migrate to the draining lymph node and present the antigens to the surrounding T lymphocytes in the paracortical zone, thus functioning as interdigitating dendritic cells.[13,14] The migration and homing of these Langerhans' cells depends on cellular adhesion molecules, as does migration of other leukocytes.

In LCH, currently regarded an immunological dysfunction of unknown origin,[1] lesions may not only be present in the skin or in lymph nodes, the normal sites of occurrence of the Langerhans' cells, but many other sites may be affected. The presumed immunological dysregulation in LCH may affect Langerhans' cells in their function and also affect the expression of cellular adhesion molecules resulting in a migration and accumulation of Langer-

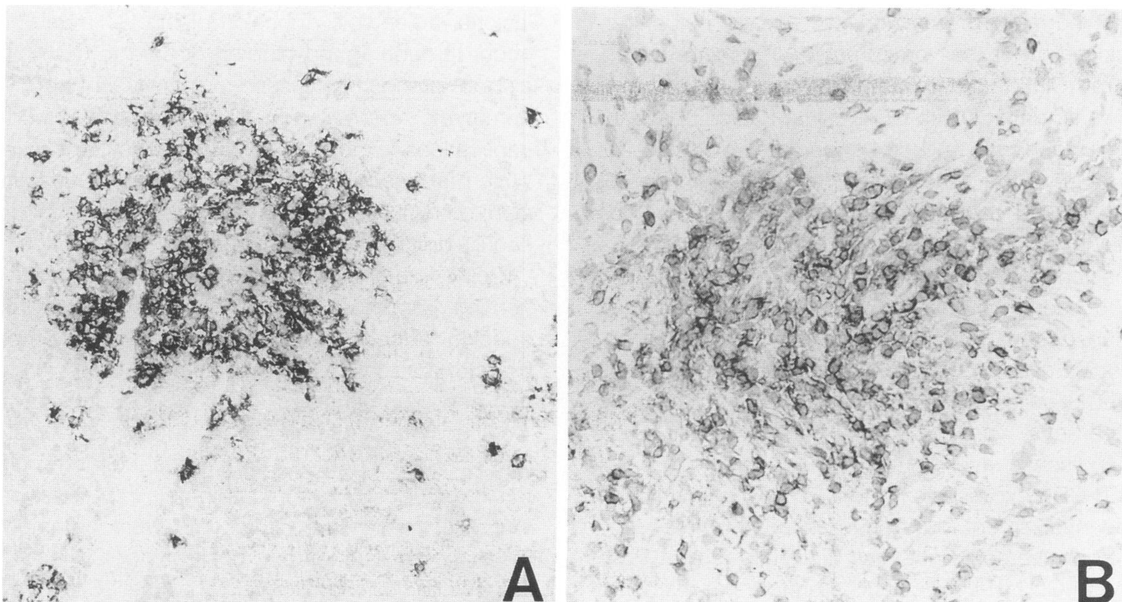

Figure 2. *Staining for CD1a* (**A**) *and CD11a* (**B**) *in the bone lesion in case no. 3. In addition to the LCH cells, lymphocytes and macrophages are positively stained for CD11a.* (**A**: *140×;* **B**: *224×; immunoperoxidase).*

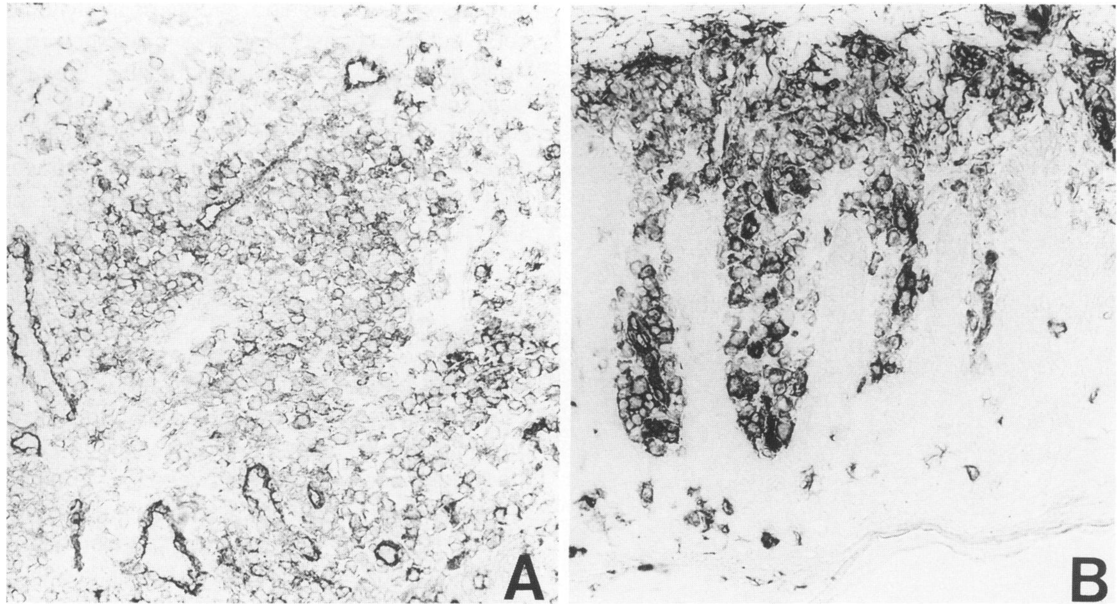

Figure 3. *LCH staining for CD54 in the mucosal lesion in case no. 9* (**A**) *and in the skin lesion in case no. 13* (**B**). (**A** *and* **B**: *140×; immunoperoxidase*).

hans' cells at aberrant sites. This implies an important role of cellular adhesion molecules in the pathogenesis of LCH.

The reactivity with CD2, a molecule essential to adhesion on T lymphocytes and thymocytes,[15] was described earlier in a case of LCH involving a lymph node[16] and, more recently, in four additional cases of LCH.[17] The presence of the CD2 molecule on the surface of LCH cells is unexpected, as CD2 is not normally present on the surface of Langerhans' cells, nor their precursors.[18] In other species, eg, rat, CD2 may be found on macrophages. CD2 shows similarities with CD4,[19] that is also observed on macrophages and on Langerhans' cells. CD2 is the receptor for CD58 (leukocyte function antigen-3) [LFA-3], and the interaction of these cell-surface molecules plays a role in initial antigen-independent adhesion of cells and in antigen-presentation by $CD58^+$ dendritic cells to $CD2^+$ T lymphocytes, and in subsequent T-cell activation.[10,20] In the formerly reported case by Ruco et al the presence of CD2 on LCH cells was thought to represent immature Langerhans' cells in Letterer-Siwe (multi-organ LCH) disease involving lymph node.[16] However, we found CD2 expression not only in cases with lymph node involvement, but also in patients with skin and bone involvement, including a solitary lesion. Positivity for CD2 of LCH cells is therefore not restricted to patients with multi-organ disease, nor to specific sites. Remarkably, in different lesions within the same patient, we found expression of CD2 and CD11a in one lesion together with a complete lack in the other (case nos. 6, 9, 13 for CD2 and case no. 8 for CD11a). Moreover, for CD2, CD11a, and CD11b we found that not all but only subsets of CD1a-positive cells expressed these adhesion molecules. The above findings may reflect differences in the microenvironment of the lesions and subsequent responsiveness of the LCH cells to diverse stimuli. As CD2 is expressed by LCH cells in some lesions, homotypic adhesion of the LCH cells may occur through ligand binding of CD2 to CD58, that also is strongly expressed on the LCH cells. This homotypic aberrant adhesion may have important implications for the biological behavior of the cells. Which factors are able to induce the CD2 expression on LCH cells, and the significance of this, should be further investigated.

CD44 is a member belonging to the lymphocyte homing receptors and is associated with site-specific adhesion and extravasation of lymphocytes, but also with regulation of CD2-CD58 interaction and, augmentation of leukocyte adhesion and T-cell activation by epitopic modulation of CD2.[21,22] The normal epidermal Langerhans' cell is reported to express CD44, and in culture this expression may increase,[23] although these data were obtained in mice. As we found strong positivity for CD44 on the LCH cells, this may suggest that the LCH cells resemble the activated normal Langerhans' cell. With regard to the function of CD44, its expression on LCH cells may not only be involved in site-specific

adhesion, but CD44 expression may also have other important implications. Ligand binding of CD44 on LCH cells may stimulate production of cytokines, as has been shown for monocytes.[22] This may influence the microenvironment of LCH lesions and result in expression of adhesion molecules and further cytokine release by other inflammatory cells. For the LCH cells that also express CD2, modulation by CD44 may further stimulate these properties, resulting in an aberrant microenvironment and persistence of LCH lesions.

With regard to the expression of CD11a (LFA-1, the $\alpha L\beta 2$ integrin) of normal Langerhans' cells conflicting data exist. Freshly isolated Langerhans' cells have been reported to be negative,[24] whereas cultured Langerhans' cells may be negative or positive for CD11a.[25,26] CD11a interactions are of particular interest regarding antigen-presentation of dendritic cells to T lymphocytes. CD11a is a receptor for CD54 intercellular adhesion molecule-1, and this binding supposedly initiates and facilitates cell adhesion on both T cells and antigen-presenting cells.[9,10] Being a professional antigen-presenting cell, one would expect the Langerhans' cells to express CD11a. In LCH, out of 19 lesions only six showed positive staining for CD11a in the LCH cells. It is therefore clear that LCH cells, like Langerhans' cells in culture, are capable of CD11a expression. Because the LCH cells also strongly express CD54, the concurrent expression of CD11a and CD54 may facilitate homotypic adhesion as well.

Although normal Langerhans' cells in the skin have been described to express the $\beta 2$ leukocyte integrins CD11b ($\alpha M\beta 2$) and CD11c ($\alpha X\beta 2$),[24,26] we could not demonstrate the expression of CD11b in normal skin LCs. This may be due to differences in techniques used; however, considering the other studies, it seems clear that normal LCs only express CD11b at low levels. The LCH cells consistently express CD11c as described previously.[27] Staining for CD11b was positive in only three out of 15 lesions investigated, confirming earlier observations of variable CD11b staining of LCH cells,[16,27] possibly being different from the epidermal Langerhans' cells.

The LCH cells we investigated were strongly positive for CD54 and CD58. Normal Langerhans' cells in the skin do also express CD54 and CD58, but at a low level.[26,28] However, upon activation by antigen contact, Langerhans' cells strongly increase the expression of accessory molecules involved in antigen presentation, such as MHC class II,[29] and this activation facilitates the migration of the epidermal Langerhans' cell. In short term culture of Langerhans' cells, that is thought to resemble the conversion of these cells to interdigitating dendritic cells during their migration to draining lymph nodes, changes in adhesion molecule expression together with loss of Birbeck granules and CD1a expression are taking place.[26,29–31] In addition to up-regulation of MHC class II antigens, an increase of CD54 and CD58 and a decrease of the $\beta 2$ integrins CD11b and CD11c expression occurs[26,29] and CD11a may appear, although on this point conflicting data exist.[25] Most of our results are in keeping with the initial changes during culture of human epidermal Langerhans' cells that are related to activation and subsequent migratory capacities.

We can conclude that LCH cells resemble, at least in part, the activated epidermal Langerhans' cells, cells with migratory capacities. Also, LCH cells may have differentiation abnormalities with preservation of epidermal Langerhans' cell characteristics and concommitant altered expression of adhesion molecules. This may explain the occurrence at aberrant sites of cells with a Langerhans' cell-like appearance. The immunological dysregulation presumably to underlying LCH, may either cause this aberrant homing, or maintain the persistence of LCH lesions.

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