American Journal of Pathology, Vol. 141, No. 3, September 1992

Adhesion Receptor Profile of Thymic B-cell Lymphoma

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Primary thymic B-cell lymphoma is clinically characterized by aleukemic, highly aggressive local growth, infrequent distant metastasis, and infrequent secondary lymph node involvement. VLA-1 to VLA-6 are cell surface molecules binding to matrix molecules such as collagen, fibronectin, epiligrin, and laminin. VLA-4 additionally binds to VCAM-1 and ICAM-2, thus mediating intercellular adhesion. Other molecules involved in cell/cell adhesion are LFA-1 (CD11a/CD18), Mac-1(CD11b/CD18) and their ligand ICAM-1 (CD54), p150,95 (CD11c/CD18), LFA-3 (CD58), CD44, and LECAM-1. Twenty-three tumors, together with normal lymphoid tissue, were immunohistochemically examined to investigate the expression pattern of these molecules in thymic B-cell lymphomas and in their putative normal counterparts, namely thymic medullary B cells. Thymic B-cell lymphomas consistently lacked VLA-1,-2,-3,-5,-6, and CD11b, expressed ICAM-1 in 21 of 23 cases but were heterogenous for VLA-4, LFA-1, CD11c, LFA-3, CD44, and LECAM-1. Presence of LFA-1 correlated with LFA-3 expression (P = 0.029). The receptor profile of thymic B-cell lymphoma was reminiscent of the expressional status of normal thymic medullary B cells in some aspects but deviated in others: Assuming that, in terms of differentiation, thymic B-cell lymphoma is related to the asteroid variant of thymic medullary B cells, a propensity to down-regulate/lose VLA-4, CD11a, CD44, and LECAM-1 would have to be supposed in conjunction with a tendency to overexpress ICAM-1 and LFA-3. Sclerosis as an inconsistent phenomenon in thymic B-cell lymphoma was absent in 8 of 23 tumors. Presence of sclerosis correlated with LECAM-1 expression of the tumor cells (P = 0.038). Recent studies suggest that a locally growing/aleukemic phenotype of a B-cell neoplasia might be determined by the phenotype VLAs$^-$, LFA-1$^+$, ICAM-1$^+$, CD44$^-$, and LECAM-1$^-$. Our data corroborate this view. (Am J Pathol 1992, 141:729–741)

There is ample evidence to date that primary mediastinal B-cell lymphoma is a neoplasia with clinical, histologic, and immunologic features that, taken together, are rather unique.

Mediastinal B-cell lymphoma occurs in all age groups, but predominately in young women.[1–6] The typical localization is the anterior mediastinum, and a thymic involvement could be repeatedly demonstrated. Therefore, mediastinal B-cell lymphoma is regarded as a primary thymic tumor.[1,6–8] As a normal counterpart of this neoplasm, a recently described population of thymic medullary B cells has been proposed.[9–11]

Immunologically, thymic B-cell lymphoma is a tumor with immunoglobulin genes regularly rearranged[7,12,13] but with severe defects in expression of immunoglobulin constituents and HLA class I and II molecules.[3,4,5,14–17] Thymic B-cell lymphoma is immunohistochemically defined as CD5$^-$, CD10$^-$, CD19$^+$, CD20$^+$, CD21$^-$, CD22$^+$, CD30$^-$, CD37$^+$, CD40$^+$.[13,15,18,19]

Histologically, thymic B-cell lymphoma varies in cell size from medium to large, and Reed–Sternberg-like giant cells may be present in various amounts. As a peculiar feature, tumor cells regularly and rather abundantly display leptochrome cytoplasm,[20] which was typical enough for us to initially apply the term *mediastinal clear cell lymphoma (of B-cell type)* to this tumor.[3] In our experience, an inconsistent sclerosing reaction of the stroma may be present, which infrequently leads to partial scarry degeneration of the involved tissue. Sclerosis is regarded as typical of this tumor type by others,[2,4,6] however, and it was indeed one of the features of thymic B-cell lymphoma that was recognized first.[21,22]

In terms of tumor biology, it is a high-grade malignant lymphoma that, when misdiagnosed or unless treated with aggressive combined modality therapy, has a poor prognosis.[23–26] Thymic B-cell lymphoma is characterized by aggressive local growth often involving the lungs and, eventually, "metastasizes" to other organs such as liver and kidney. Secondary locoregional lymph node in-

Supported by the Tumorzentrum Heidelberg/Mannheim and the Bundesministerium für Forschung und Technologie (III-007-90/FVP7).

Accepted for publication March 12, 1992.

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volvement is uncommon, however, and generalized lymphomatous spread with bone marrow involvement or leukemia has not yet been reported.

Local versus disseminated growth or a leukemic phenotype of a malignant B-cell proliferation has recently been attributed to the presence *versus* the absence of surface molecules mediating adhesion or "homing," such as lymphocyte–endothelial cell adhesion molecule-1 (LECAM-1; *syn.* Leu-8 antigen), leukocyte function-associated antigen-1 (LFA-1; *syn.* CD11a/CD18), Hermes type cell adhesion molcules (CD44; *syn.* Hermes-3 homing receptor), and intercellular adhesion molecule-1 (ICAM-1). Inghirami et al[27] showed that B-chronic lymphocytic leukemia and small cell lymphocytic B-cell lymphomas differed in LFA-1 expression, and they hypothesized that absence of LFA-1 might be indicative of a leukemic phenotype. CD44 expression tended to be higher in diffuse, large B-cell lymphomas showing generalized lymph node involvement than in cases with more localized and contiguous growth.[28,29] B-cell lymphomas presenting as large, solitary tumor masses were found to be more frequently ICAM-1 positive than those displaying diffuse, wide-spread lymph node involvement and leukemia.[30] In low-grade malignant B-cell lymphomas, absence of ICAM-1 was statistically correlated with a leukemic spread.[31] Primary gastrointestinal B-cell lymphomas were found to be largely devoid of CD44 and LECAM-1.[32] Using the immunodeficient SCID mouse system, Walter et al[33] could show that Burkitt's lymphoma cell lines caused local tumor while autologous Epstein–Barr virus (EBV)-transformed lymphoblastoid cell lines (LCL) showed both local tumor formation and dissemination, thereby regularly involving the thymus. Immunophenotypically, these cell lines differed in their capacity to express CD11a, CD11c, CD44, and ICAM-1, which, as previously reported,[34–37] were detectable at higher levels in LCLs.[33]

These observations prompted us to investigate thymic B-cell lymphoma with a comprehensive panel of monoclonal antibodies against different classes of adhesion molecules (Table 1).

Material and Methods

Tumor Tissue and Lymphoma Typing

Fresh frozen tumor tissues from 23 patients with thymic B-cell lymphoma were collected during the last 5.5 years. The definite diagnose of thymic B-cell lymphoma was established on the basis of histologic criteria[3] and immunohistochemical data concerning CD19, CD20, CD22, immunoglobulin, HLA-A,- B,- C, and -DR expression.[9,16] In addition, all available data on tumor localization, spread, and the definite clinical Ann Arbor stage at the time of diagnosis were taken into account. In six cases, tumor tissue was sent to us as diagnostic lung biopsy (Table 3), but was finally regarded as thymic B-cell lymphoma infiltrating the lung. Normal neonate and infantile thymi (seven specimens) were obtained in the course of thoracic surgery for unrelated reasons; other normal (reactive) tissues were derived from traumatic spleens (two specimens), hyperplastic tonsils (five specimens), and

Table 1. *Adhesion Receptors Detected and Antibodies Used in This Study*

Antigen	MW (kDa)	Receptor for/function	CD No.	Clone	Isotype
Very late antigens					
VLA-α^1	210	Collagen/laminin	—	TS2/7	IgG1
VLA-α^2	170	Collagen/(laminin)	CDw49b	CLB-thromb/4	IgG1
VLA-α^3	130/25	Collagen/fibronectin/laminin/ epiligrin	—	J143	?
VLA-α^4	150	Fibronectin/VCAM-1/ICAM-2	CDw49d	HP2/1	IgG1
VLA-α^5	135/25	Fibronectin	—	SAM1	IgG2a
VLA-α^6	120/30	Laminin	CDw49f	GOH3	IgG2a
VLAβ_1	130	*Common β-chain of VLA-1-6*	CD29	K20	IgG2a
Leu-CAM family					
LFA-1 (α)	180	ICAM-1/ICAM-2	CD11a	25.3.1	IgG1
Mac-1	165	C3bi/zymosan/fibronogen/ fact.X/(ICAM-1?)	CD11b	BEAR1	IgG1
p150,95	150	C3bi/fibrinogen	CD11c	S-HCL3	IgG2b
LFA-1 (β)	95	*Common β-chain of CD11a,b,c*	CD18	MHM23	IgG1
Immunoglobulin superfamily					
ICAM-1	90	LFA-1	CD54	MEM-112	IgG1
LFA-3	60–65	CD2	CD58	BRIC5	IgG2a
Hermes type homing receptor					
CD44	80–95	Hyaluronate/venular high endothelium	CD44	A3D8	IgG1
Selectin					
LECAM-1	70–80	Human MECA-79 antigen (PNAd)	—	anti-Leu8	IgG2a

lymph nodes featuring chronic, nonspecific (including toxoplasmic) lymphadenitis (11 specimens).

Tissue Processing

From quick-frozen tissues, serial frozen sections of about 1.5 cm^2 in site and 4 to 6 μ in thickness were air-dried overnight, fixed in acetone for 10 minutes at room temperature, and immunostained immediately or stored at −20°C for 1 to 3 weeks.

Reagents

The monoclonal primary antibodies used in this study are listed in Table 1. They were gifts from colleagues (see Acknowledgement) or were supplied by Dianova, Hamburg, Germany and Becton Dickinson, Mountain View, California. A polyclonal biotinylated sheep antibody to mouse Ig (reactive with all mouse isotypes), a polyclonal biotinylated sheep antibody to rat Ig for detection of rat-derived GOH3, and a streptavidin-biotinylated peroxidase complex, all obtained from Amersham, High Wycombe, UK, served as a detection system for the primary antibodies.

Staining Procedure

The method is described in detail elsewhere.[38] Monoclonal antibodies in culture supernatants were used undiluted; ascites preparations were used as 1:2000 dilutions; purified reagents were used in a protein concentration of about 10 μg/ml. 3-Amino-9-ethylcarbazole was used as the substrate for the enzyme; the peroxidase reaction resulted in an intense red precipitate. The sections were faintly counterstained with Harris' hematoxylin.

Controls and Evaluation of Antigenic Densities

Negative controls were performed in each case without the primary antibody and, in a limited number of cases, by employing several irrelevant monoclonal antibodies of different mouse Ig isotypes directed against nonhuman antigens. No staining was observed, except for the reaction of granulocytes whose endogenous peroxidase was not destroyed.

Strongly stained stromal cells or endothelial cells or T lymphocytes and histiocytes, always present in combinations characteristic of the respective antigen under study, served as intrinsic positive controls. They also were taken as internal parameter for the maximal reactivity, which was regarded as "high antigenic density" and symbolized "+++." A definitely weaker staining intensity of the (neoplastic) B-cell population was characterized as "intermediate antigenic density" and symbolized "++." A very weak but clearly discernible staining was regarded as "low antigenic density" and symbolized "+." The absence of antigen was symbolized "−." Whenever the staining intensity within a (neoplastic) B-cell compartment was heterogenous, a simple semiquantitative statement was made. For comparative visualization of the entire B-cell population, a CD20 immunostaining was used.

Statistical Analysis

Fisher's exact test was applied for analysis of contingency tables.

Results

The results are summarized in Tables 2 and 3.

Serial immunostained sections of normal thymi showed that the population of medullary B cells (as shown by CD20[L26] [Figure 1a]) was devoid of VLA-α^1, -α^2, -α^3, -α^5, and -α^6, while expressing VLA-α^4 in high antigenic density (Figure 1b); the common VLA-β_1 chain was also detectable; however, the cells stained definitely weaker. Both cytomorphologic variants of thymic medullary B cells, i.e., the lymphoid and the asteroid variant,[10,11] further expressed CD44 and ICAM-1 in moderate (Figure 1d) and CD11a/CD18 in high amounts. CD11b and LFA-3 were undetectable within this population, and CD11c expression was restricted to the asteroid B-cell variant, which expressed CD11c at intermediate levels (Figure 1c). As compared with the cytologically and microtopographically defined forms of B-cell differentiation outside the thymus, thymic medullary B cells immunophenotypically resembled B cells within the extrafollicular compartments of the peripheral lymphoid tissues (i.e., marginal zone of spleen, intraepithelial B cells of tonsil, and sinusoidal B cells of lymph node), differing only in their mode of VLA-5 and ICAM-1 expression. They had far less in common with mantle zone B cells, follicular center B blasts, or plasma cells (Table 2).

Presence and extent of sclerosing reaction within thymic B-cell lymphoma varied considerably; the immunostained tumor specimens (mean diameter, about 1.5 cm) were used for a simple grading of sclerosis (Table 3). Eight of 23 cases did not evidence any signs of sclerosis; nine cases contained some fibrous bands that, by their arrangement, elucidated the alveolar growth pattern

Table 2. *Expression of Adhesion Molecules in Distinct B-cell Types Confined to Microtopographic Areas of Spleen, Tonsil, Lymph Node, and Thymus*

	Thymic medulla	Extrafoll. compartment*			Mantle zone			Follicular center			Plasma cells
		Spleen	Tonsil	L.n.	Spleen	Tonsil	L.n.	Spleen	Tonsil	L.n.	
VLA-α^1	−	−	−	−	−/+†	−/+	−/+	−	−	−	−
VLA-α^2	−	−	−	−	−/+ +	−/+ +	+/+ +	−	−	−	−
VLA-α^3	−	−	−	−	−/+ +	−/+	+	−	−	−	−
VLA-α^4	+ + +	+ +	+ + +	+ +	−/+ +	+ + +	+ + +	−	−	−	+ + +
VLA-α^5	−	+ +	+	− or +‡	+ +	+	+ +	−	−	−	− or +‡
VLA-α^6	−	−	−	−	−/+	+	−/+ +	−	−	−	− or + +‡
VLAβ_1	+ +	−	−	+	+	+	+	−	−	−	+ +
CD11a	+ + +	+ +	+ + +	+ + +	+ +	+	+ + +	−/+	−/+ +	+/+ + +	+ +
CD11b	−	−	−	− or +‡	−/+	−/+	−/+ + +	−	−	−	−
CD11c	−/+ +	−	−	+	−/+	−	−/+	−	−	−	−
CD18	+ + +	+ +	+ + +	+ + +	+ +	−/+	+ + +	−/+	+/+ + +	−/+ + +	− or + +‡
ICAM-1	+ +	−/+	−	−	−	−	−	−/+	−/+	−/+	−/+
LFA-3	−	−	−	−	−≫+ + +‖	−≫+ + +	−≫+ + +	−	−	−	−
CD44	+ +	+ +	+ +	−	+ +/+ + +	+ + +	+ +	−	−	−	−/+ + +
LECAM-1	+ + +	+ +	+ + +	−	+ + +	+ + +	+ + +	−	−	−	−/+ +

* Corresponding to marginal zone cells in spleen, intraepithelial B-cells in tonsil, and sinusoidal (monocytoid) B-cells in lymph node (L.n.); −, no detectable antigen; +, low; + +, intermediate; + + +, high antigenic density as compared with positive reference cells.

†Admixture of two subsets differing in antigen density.

‡ Variability among lymph nodes of different sites.

‖ Much more negative than positive cells.

Table 3 *Expression of Adhesion Molecules on Thymic Medullary B Cells and on Thymic B-cell Lymphomas*

Case No.	Site	VLA-α^4	VLA-β_1	CD11a	CD11c	CD18	ICAM-1	LFA-3	CD44	LECAM-1	Sclerosis*
1	Mediastinal mass	−/+	−/+	+ +	+ + +	+ + +	+ +	−	+	−	0
2	Lung	−/+ +	−/+	−	+ +	−/+	+ + +	+ + +	−	+ + +	1
3	Mediatinal mass	−	−	−	−/+	+ +/+ + +	+ +	−	+ +	+	2
4	Lung	+ +	+	−	+	+	+ + +	−	+	+	2
5	Mediastinal mass	−	−	−	−	−/+	−/+	−	+	−	1
6	Mediastinal mass	−/+ +	−/+	+	+ + +	+ + +	+ + +	+ + +	−/+ +	+/+ +	1
7	Mediastinal mass	−	−	−	−	−	+ +	+ + +	+	−	0
8	Mediastinal mass	−	−	+ +	−/+	−/+	+ +	+ + +	−	−	1
9	Lung	−	−	+ + +	+ + +	+ + +	+ + +	−	−	−	0
10	Mediastinal mass	−	−/+	+	+ + +	+	+ + +	+ + +	−/+	−	0
11	Lung	−	−	+	+	+ +	+ +	+ + +	+ + +	+ +	1
12	Mediastinal mass	+	+	−	−	−	+ +	−	−	−	2
13	Mediastinal mass	−	−	−	−	−	−	−	−	−	2
14	Mediastinal mass	−	−	−	−	−	+ + +	−	−	+ +	1
15	Mediastinal mass	−	−	+	+	+ + +	+ +	+ + +	+ +/+	−/+	1
16	Lung	−	−	−	−	−	+ +	−	−/+	+	2
17	Lung	−	−	−	−	−	+	−	−	−	1
18	Mediastinal mass	−	−	+	+ +	−	+ +	+ + +	−	−	0
19	Mediastinal mass	−	−	+ + +	+ + +	+ + +	+ +	+ + +	−	−	0
20	Mediastinal mass	−/+ + +	−/+	−	−	−	−	−	−	−	0
21	Mediastinal mass	−/+ +	−	−	−	−	+ + +	+ + +	−	+ +	1
22	Mediastinal mass	−	−	−	−	−	+ + +	−	−	−	2
23	Mediastinal mass	+ + +	−	−	−	−	+ + +	+ + +	−	+ + +	0

* Index of sclerosis; 0, no sclerosis; 1, low; 2, high degree of sclerosis; −, no detectable antigen; +, low; + +, intermediate; + + +, high antigenic density; x/y, composite pattern of antigen expression.

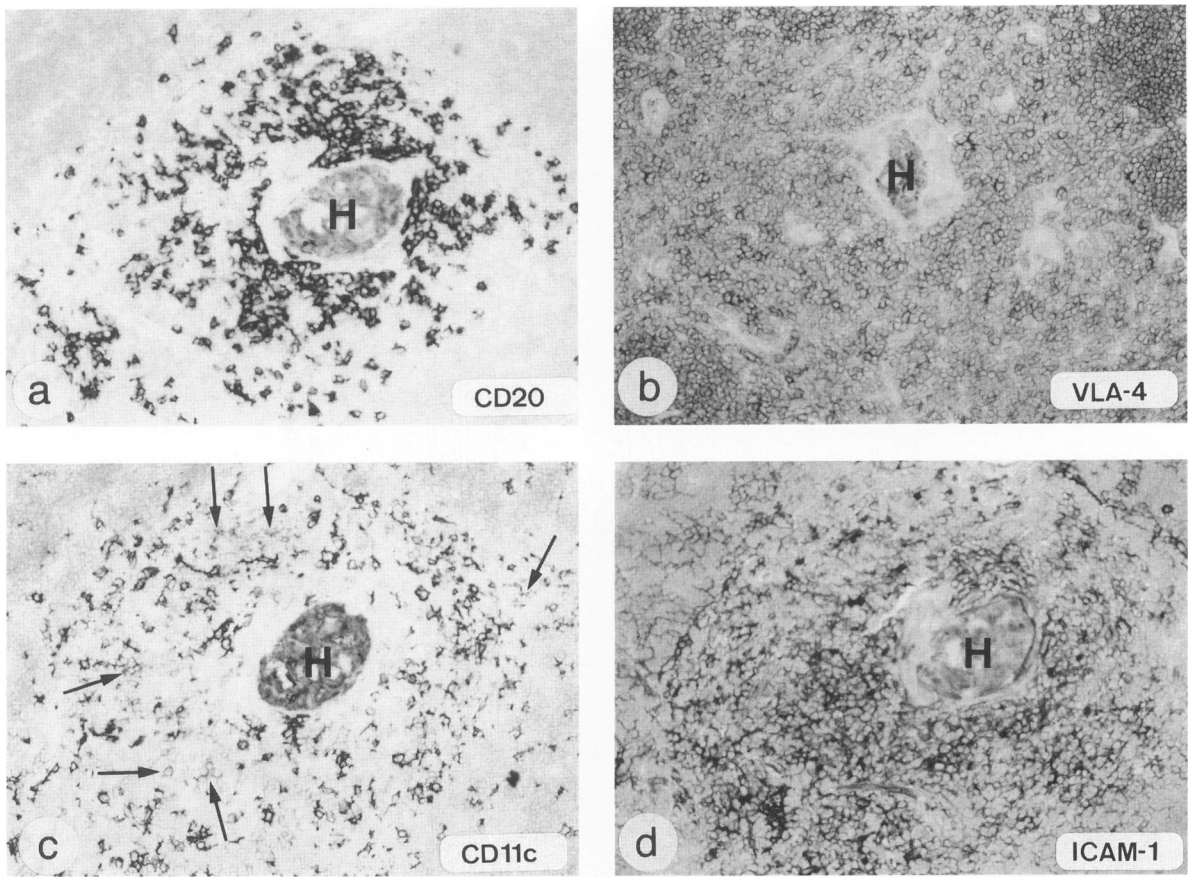

Figure 1. *Normal infantile thymus. Serial frozen sections stained with different monoclonal antibodies using an indirect immunoperoxidase technique and aminoethylcarbazole as the chromogen (dark grey to black) and a faint hematoxylin nuclear counterstain [same technique used for all figures].* **a**: *CD20(L26) reveals the entire medullary B-cell population surrounding a Hassall's corpuscle [H].* **b**: *Medullary B-cells and medullary and cortical thymocytes strongly express VLA-α^4.* **c**: *While the lymphocytic variant of medullary B-cells is CD11c$^-$, the asteroid B-cell variant (Hofmann et al[9,10]) express CD11c at intermediate levels (arrows, the strongly stained cells are medullary histiocytes);* **d**: *Strong expression of ICAM-1 in medullary B-cells and in a subset of thymic cortical and medullary epithelium* (**a–d**: *×128).*

(e.g., case 2, Figure 2c, and case 6, Figure 3e), and the remaining six tumors showed broad collagenous bands and foci of necrosis.

The adhesion receptor profiles of the 23 thymic B-cell lymphomas studied were homogenous in some aspects, but heterogenous in others (Table 3). Corresponding to the phenotype of medullary B cells, thymic B-cell lymphoma was negative for VLA-α^1 (Figure 2a), -α^2, -α^3 (Figure 2b), -α^5, and -α^6; in one single tumor (case 6), a subset of the neoplastic population expressed very low amounts of VLA-α^1. VLA-α^4 expression was markedly heterogenous: Only one tumor (case 23) expressed VLA-α^4 in an antigenic density comparable to that of normal medullary B cells; case 4 was VLA-α^4 positive throughout, albeit at a reduced antigenic level, and case 12 was only very faintly VLA-α^4-positive; five further cases were made up of an admixture of VLA-α^4-positive and VLA-α^4-negative tumor cells (e.g., case 2; Figure 2c).

VLA-β_1 was expressed in a pattern essentially corresponding to that of VLA-α^4, but at distinctly lower levels. Cases 21 and 23, although clearly VLA-α^4 positive (although only in parts of case 21), did not express any detectable VLA-β_1, and, *vice versa,* case 10 was weakly VLA-β_1 positive in the absence of any VLA-α chains.

CD11a was expressed in high amounts in two cases (Figure 3a) and twice in intermediate amounts. Most thymic B-cell lymphomas of our series, however, lacked this molecule completely or were only very weakly CD11a positive, thus deviating from normal thymic medullary B cells. All thymic B-cell lymphomas were CD11b negative (Figure 3b). By contrast, thymic B-cell lymphomas differed considerably in their ability to express CD11c: five tumors showed an overall overexpression (Figure 3c), and two others were entirely CD11c positive at a level comparable to that of the asteroid variant of thymic medullary B cells; 10 cases were clearly CD11c negative throughout (Figure 3d), and two tumors were composed of weakly CD11c-positive and CD11c-negative cells. The common β-chain of Leu-CAM, i.e., CD18, was detectable in heterogenous antigenic densities generally corre-

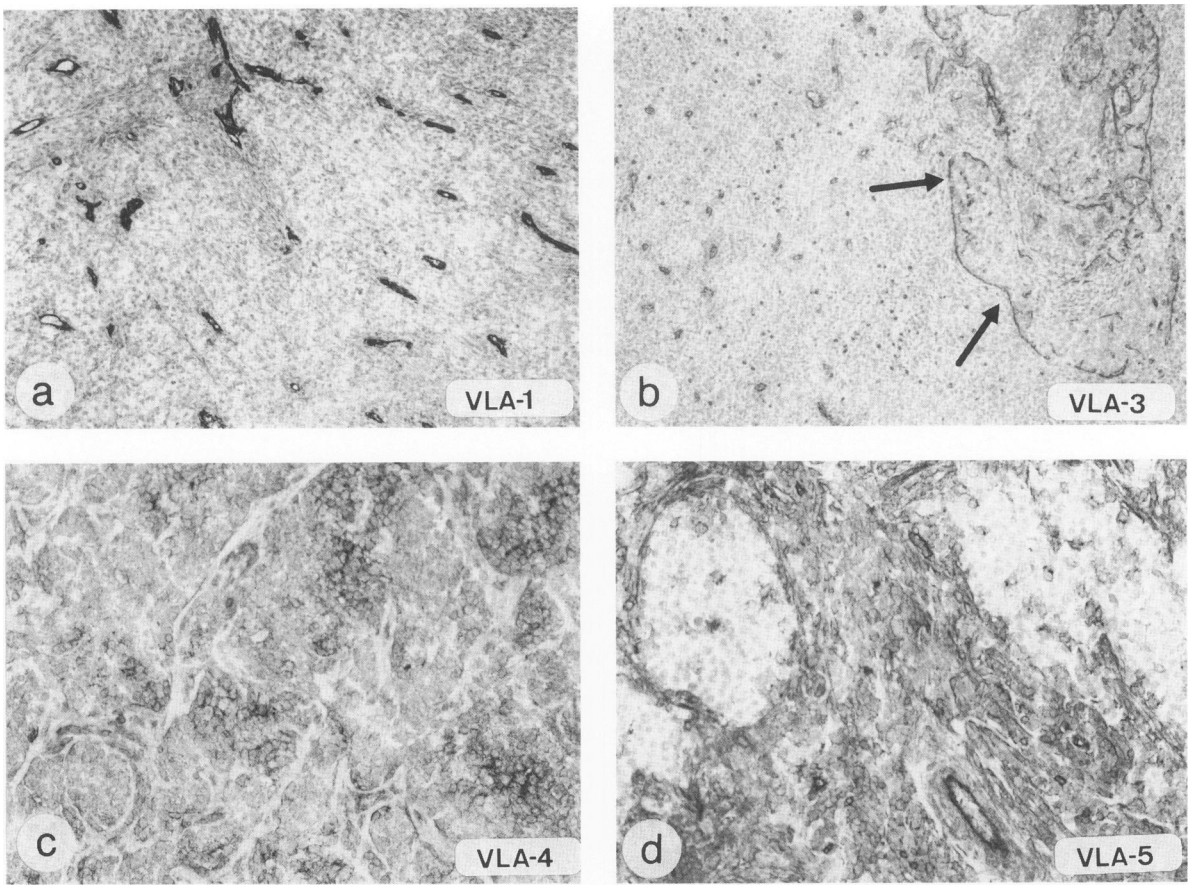

Figure 2. *VLA expression in thymic B-cell lymphoma.* **a**: *Case no. 3 is completely devoid of VLA-α^1; strongly VLA-α^1-positive endothelial cells serve as positive intrinsic controls (×64).* **b**: *Case no. 15 lacks any detectable VLA-α^3; thymic remnants are highlighted as a VLA-α^{3+} cellular network (×64).* **c**: *Case no. 2 is composed of an admixture of VLA-α^{4-} and VLA-α^{4++} tumor cells; the low degree of sclerosis in this case is visible as a filigran meshwork of unstained fibrillar structures (×128).* **d**: *Case no. 1; the neoplastic population is VLA-α^{5-} while vascular endothelium, stromal cells and the reactive mononuclear infiltrate express this molecular in high to moderate amounts (×128).*

sponding to those of all Leu-CAM α-chains expressed by an individual tumor; however, case 18 showed no CD18 expression whereas CD11c was detectable in intermediate and CD11a in low antigenic density. In cases No. 2 and 10, CD18 was detectable in lower antigenic density than CD11c. This indicates single chain expression or relative overexpression of the α-chain in a minority of tumors. By contrast, a relative overexpression of the β-chain was observed in cases 3 and 15.

Except for three cases (cases 5, 13, and 20), thymic B-cell lymphomas were entirely ICAM-1 positive. Compared with the intermediate level of ICAM-1 expression in normal thymic medullary B cells, there was an overexpression of this molecule in nine of our tumors (Figure 3e). LFA-3 was expressed either very strongly (11 cases) or was lacking entirely (12 cases). There was a statistically significant correlation between LFA-3 expression and presence of LFA-1 ($P = 0.029$). CD44 subdivided thymic B-cell lymphoma into a positive and a negative subgroup of about equal size, and three tumors were composed of CD44-positive and CD44-negative cells (Figure 3g). Patterns of LECAM-1 expression were likewise heterogenous in thymic B-cell lymphoma; only two tumors corresponded to reactive medullary B cells by their high antigenic density (Figure 3f). Although incongruous at the individual level (e.g., case 23), presence of LECAM-1 on tumor cells was statistically correlated with presence of sclerosis ($P = 0.038$).

Discussion

We have shown that thymic B-cell lymphoma has an adhesion receptor status that can be summarized as VLA-α^{1-}, -α^{2-}, -α^{3-}, -α^{5-}, -α^{6-}, CD11b$^-$, ICAM-1$^+$, and which is heterogenous for VLA-α^4, CD11a, CD11c, LFA-3, CD44, and LECAM-1. Thus, the receptor profile of thymic B-cell lymphomas is similar to the expressional status of normal thymic medullary B cells, especially concerning ICAM-1, VLA-α^1, -α^2, -α^3, -α^5, and -α^6, which are absent in medullary B cells but expressed on (subsets of) mantle zone B cells. Nevertheless, similarity has its limits:

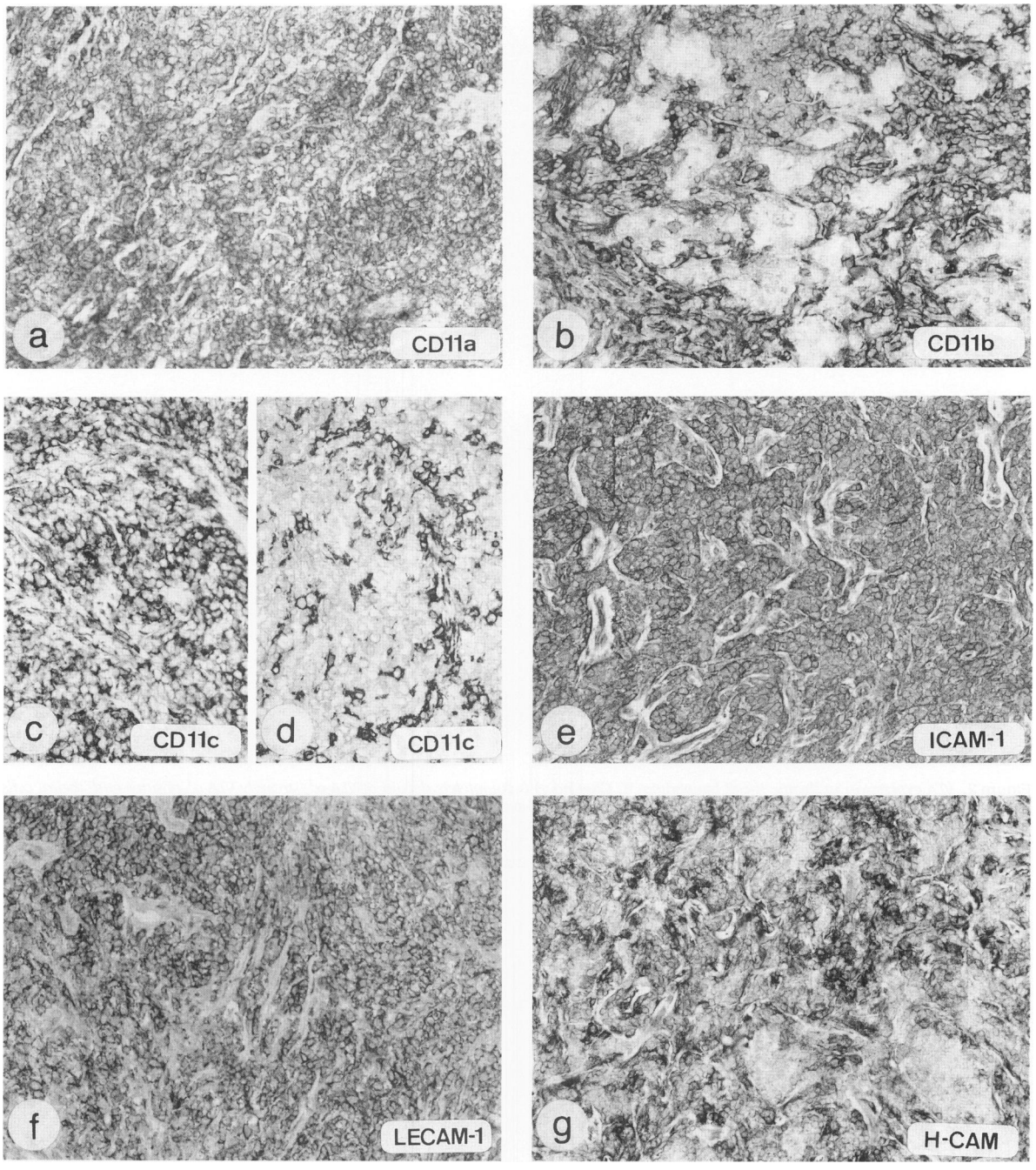

Figure 3. *Expression of Leu-CAMs, CD44, and LECAM-1 in thymic B-cell lymphoma.* **a**: *Case No. 9 shows strong expression of CD11a on tumor cells with minimal sclerosis.* **b**: *Case no. 15: The malignant B-cells are CD11b$^-$ whereas stromal cells and a subset of the reactive mononuclear infiltrate is CD11b$^+$; sclerosis is minimal.* **c**: *All tumor cells of Case no. 6 strongly express CD11c.* **d**: *By contrast, Case no. 7, is a CD11c$^-$ tumor containing CD11c$^+$ dendritic interstitial cells;* **e**: *Like the majority of thymic B-cell lymphomas, Case no. 6 strongly expresses ICAM-1; there is a low degree of sclerosis visible as unstained fibrillar structures.* **f**: *Case no. 2: LECAM-1 is detectable in high antigenic density within the neoplastic population; low degree of sclerosis.* **g**: *Case no. 6 shows heterogenous expression of CD44 within the tumor cell population: some of the neoplastic cells show an intermediate level of expression, while the majority is CD44$^-$; high levels of CD44 are confined to dendritic interstitial cells (***a–g**: *×128).*

Assuming that, in terms of tumor differentiation, thymic B-cell lymphoma is related to the asteroid variant of thymic medullary B cells, a propensity to down-regulate/lose VLA-α^4, CD11a, CD44, and LECAM-1 would have to be supposed in conjunction with a tendency to overexpress LFA-3 and ICAM-1.

Currently, there are no published data on expression of VLA proteins in B-cell lymphomas. We observed VLA-

3, -4, and -5 in acute B lymphoblastic leukemia (B-ALL), VLA-2,-3,-4 and -5 expression in chronic B-lymphocytic leukemia (B-CLL), and VLA-4 and -5 expression in hairy cell leukemia (HCL). By contrast, primarily aleukemic B-cell lymphoma types, with very few exceptions, showed VLA expression restricted to VLA-4, which was regularly detectable in plasmacytomas and was inconsistently present in follicular center cell lymphomas.[39] Accordingly, VLA-4 is the only member of the VLA- (*syn.* β_1-integrin) family that is to some extent expressed in thymic B-cell lymphoma. VLA-4 on B cells was shown to bind to the IICS region of fibronectin[40]; VLA-4 is also involved in cell–cell interaction because it has been shown to bind the vascular cell adhesion molecule VCAM-1,[41,42] and the intercellular adhesion molecule ICAM-2[43] and to co-mediate B-T and B-B lymphocyte aggregation.[42] Our data confirm Hemler's observation[44] of the relative abundance of VLA-α^4 as compared with the level of VLA-β_1-expression, which seems to be typical of lymphoid cells in general. It is not clear whether these abundant VLA-α^4-chains mate with another type of β-chain or are expressed as monomers.

CD11a represents the α-chain of LFA-1. On B cells, LFA-1 is involved in homotypic adhesion, activation, proliferation, differentiation, and, by its capacity to bind to high endothelial venules, in lymphocyte homing.[45] Known ligands for LFA-1–mediated adhesion are ICAM-1 and ICAM-2.[46,47] In B-cell ontogeny, LFA-1 is first detectable at the surface IgM^+ B-cell stage,[45] and, correspondingly, is lacking on B-ALL.[48] Clayberger et al[49] showed that LFA-1 is absent in most common and B-ALLs and in Burkitt's lymphomas, but is expressed in most nodal B-cell lymphomas of low and intermediate grade of malignancy. Inghirami et al[27] found LFA-1 to be a marker that differentiates between B-CLL ($LFA\text{-}1^-$) and small cell lymphocytic lymphoma ($LFA\text{-}1^+$). Caligaris-Cappio et al[50] showed that, in contrast to LFA-1-negativity of B-CLL and HCL, lymphomas originating in the germinal center, and thus corresponding to a sessile stage in B-cell development, are $LFA\text{-}1^+$. Here we show that most thymic B-cell lymphomas are devoid of LFA-1. Although it is conceivable that LFA-1 to some extent determines the pattern of growth and spread in B-cell neoplasia (see below), Medeiros et al[51] and Horst et al[29] failed to find a significant correlation between mode of LFA-1 expression and clinical course in diffuse large cell lymphoma.

The *CD11c* molecule is also known as p150,95, Leu-M5, or S-HCL3.[45] Like CD11b, CD11c—in conjunction with CD18—is able to bind C3bi[45] and fibrinogen.[52] Because it was found to interact with a counter-receptor on stimulated epithelium, it is also regarded as an adhesion molecule.[53] Schwarting et al[54] were the first to describe the now established expression of CD11c in HCL. CD11c was further detected in a minority of B-CLLs[55] and immunocytomas (lymphoplasmacytoid lymphoma).[56] Mielke and Möller[38] demonstrated CD11c expression in cases of primary gastrointestinal B-cell lymphoma that had an immunoprofile corresponding to extrafollicular B cells. In their first description of this antigen, Schwarting et al[54] stated that medullary B cells of the thymus are $CD11c^-$ (which is in contrast to our detection of a $CD11c^+$ subpopulation). This may be accounted for the fact that the asteroid B-cell variant[9,10] had not yet been described. Corresponding to the differential CD11c expression in thymic medullary B cells, this antigen was heterogeneously expressed in our series of thymic B-cell lymphomas (as previously published for a smaller series of cases by Möller et al.[18]). Investigating the CD11c expression in thymic B-cell lymphoma, Brandter et al[13] found two of two cases to be $CD11c^+$, and Al-Sharabati et al[19] showed eight of eight cases to be $CD11c^-$.

ICAM-1 (CD54) is a 90-kDa integral membrane glycoprotein with five immunoglobulinlike domains.[57] The generally low expression of B cells can be enhanced by lectin stimulation, and it therefore has been classified as activation antigen.[44] ICAM-1 is a ligand of LFA-1[45] and probably also of CD11b/CD18,[58] thus mediating adhesion. With very few exceptions, thymic B-cell lymphomas express ICAM-1 in abnormally high levels. Against the background of the typical presentation of thymic B-cell lymphoma as a locally growing tumor, this finding neatly corresponds to observations of Boyd et al,[30] who demonstrated higher amounts of ICAM-1 in lymphomas that appeared as large solitary tumor masses compared with those displaying widespread lymph node involvement. Stauder et al[31] reported a correlation between lack of ICAM-1 and a leukemic phenotype in cases of low-grade malignant B-cell lymphomas. In diffuse large cell lymphoma, presence *versus* absence of ICAM-1 was not correlated with mode of spread or clinical course.[29]

LFA-3 was detectable in about half of the cases of thymic B-cell lymphomas studied. LFA-3 expression statistically correlated with expression of LFA-1. Co-expression of these two receptors was observed in Burkitt's lymphoma lines. The existence of a co-modulating mechanism was suggested because both LFA-1 and LFA-3 can be induced by interleukin-4.[59] This mechanism might be operative also in thymic B-cell lymphoma.

Recent work on molecular cloning and immunochemistry of CD44 shows that this antibody cluster defines an immunologically related but structurally very diverse family of membrane proteoglycans and glycoproteins. The classic form of the CD44 molecule is the 80- to 90-kDa hyaluronate binding form involved in high endothelial venule-binding, which is designated CD44H (*H* derived from *hematopoietic*).[60] Various isoforms of CD44 have been described that have one (or more) additional extra-

cellular domain(s). As far as investigated, CD44 monoclonal antibodies (MAb) recognize different although broadly overlapping epitopes on CD44 molecules[61]; however, it cannot be excluded that some individual CD44 clones are restricted to certain molecular variants. Immunoprecipitation lysates of tonsillar lymphocytes with CD44 (A3D8) used in this study gave rise to an 85- to 95-kDa band,[61] indicating that (at least) the classic form of the CD44 molecule is recognized by this antibody. During B-cell ontogeny, CD44 is expressed in high amounts during the very early phase and is transiently abrogated during the pre-B cell and follicular center stage of development.[28,62] In diffuse large B-cell lymphoma, aberrant CD44 expression was observed to be heterogenous and was reported to be associated with more disseminated disease.[29,63] Correlation of a CD44-positive phenotype and poor prognosis were already suggested by Jalkanen et al.[64] We found CD44 expressed in about half of the thymic B-cell lymphoma cases. We agree with Picker et al[28] in their statement that this molecule is not in itself indicative of a disseminative phenotype in B-cell neoplasia.

LECAM-1, also known as "lymph node homing receptor" on lymphocytes, Leu-8, or LAM-1, is an 80- to 90-kDa glycoprotein with lectin activity and thus a member of the so-called selectin family of surface molecules.[65,66] On B cells, LECAM-1 is differentially expressed along the differentiation pathway[67]; it is up-regulated when the B cell acquires CD20[68] and is transiently down-regulated or shed during the follicular center blast stage[69] and after *in vitro* activation.[69] This molecule plays a role not only in the tissue sequestration of B cells by binding to high endothelial venules (through physical interactions with the peripheral lymph node addressin),[70] but also in regulating B-cell differentiation.[71] LECAM-1 expression in B-cell neoplasias has been previously studied by several authors,[32,39,72–77] who agreed on the almost regular expression of this molecule in B-CLL, HCL, and mantle zone lymphoma. The overall paucity of LECAM-1 in follicular center cell lymphoma[74,78] corresponds to the LECAM-1 status of the putative normal counterpart, i.e., follicular center B cells. In thymic B-cell lymphoma, LECAM-1 expression was restricted to a minority of our cases, thus confirming data by Menestrina et al[2] and Brandter et al.[13] In this study, a statistical correlation between occurrence of sclerosis and LECAM-1 expression of thymic B-cell lymphoma emerged.

Comparative studies on expression of CD11/CD18, ICAM-1, and LFA-3 on Burkitt's lymphoma and EBV-transformed LCL showed that expression of CD11/CD18, ICAM-1, and LFA-3 is generally absent or very low in Burkitt's lymphoma cell lines. It also was shown that Burkitt's lymphoma cell lines growing in aggregates (as well as LCL, which tend to grow in large cell clumps) have a definitely higher amount of these antigens compared with cell lines growing as single cells.[34–37] Thus, it is likely that the adhesion receptor profile of a malignant B-cell clone greatly determines its mode of growth and its propensity to disseminate. Available data on adhesion receptor expression in locally growing, aleukemic B-cell neoplasias can be compiled to a phenotype that appears to be VLA (1 to 6)$^-$,[39] ICAM-1$^+$,[30,31] LFA-1$^+$,[27,31,50] CD44$^-$,[29,64] and LECAM-1$^-$.[74,77] Thymic B-cell lymphoma, which is characterized by the absence of most VLAs, down-regulation of CD44 and LECAM-1, and overexpression of ICAM-1, is a B-cell tumor paradigmatically contributing to the connection between local growth and the adhesion receptor profile just mentioned. Deviations from this receptor profile, e.g., absence of LFA-1 and presence of CD44 and LECAM-1 in individual cases of thymic B-cell lymphoma, may confer a "metastatic" potential to the neoplastic clone and thus may influence the clinical course and prognosis.

Acknowledgment

The authors thank L. Boumsell, Institut de Recherches sur les Maladies du Sang, Université de Paris VIII, France, for the antibody K20; M. E. Hemler, Division of Tumor Virology, Dana-Faber Cancer Institute, Boston, Massachusetts, for the antibody TS2/7; P. W. Modderman, Central Laboratory of the Netherlands Red Cross Blood Transfusion Service, Amsterdam, The Netherlands, for the antibodies CLB-thromb/4 and GOH3; L. J. Old, Memorial Sloan-Kettering Cancer Center, New York, New York, for the antibody J143; A. J. McMichael, John Radcliff Hospital, Oxford, United Kingdom, for the antibody MHM23; V. Horejsí, Institute of Molecular Genetics, Czechoslovak Academy of Sciences, Prague, Czechoslovakia, for the antibody MEM-112; S. Menges, S. Westenfelder, and J. Moyers for technical assistance; and C. Raulfs for linguistic advice.

References

1. Addis BJ, Isaacson PG: Large cell lymphoma of the mediastinum: A B-cell tumour of probable thymic origin. Histopathology 1986, 10:379–390
2. Menestrina F, Chilosi M, Bonetti F, Lestani M, Scarpa A, Novelli P, Doglioni C, Todeschini G, Ambrosetti A, Fiore-Donati L: Mediastinal large-cell lymphoma of B-type, with sclerosis: Histopathological and immunohistochemical study of eight cases. Histopathology 1986, 10:589–600
3. Möller P, Lämmler B, Eberlein-Gonska M, Feichter GE, Hofmann WJ, Schmitteckert H, Otto HF: Primary mediastinal clear cell lymphoma of B-cell type. Virchows Arch [A] 1986a, 409:79–92
4. Perrone T, Frizzera G, Rosai J: Mediastinal diffuse large-cell lymphoma with sclerosis. Am J Surg Pathol 1986, 10:176–191

5. Lamarre L, Jacobson JO, Aisenberg AC, Harris NL: Primary large cell lymphoma of the mediastinum. Am J Surg Pathol 1989, 13:730–739
6. Davis RE, Dorfman RF, Warnke RA: Primary large-cell lymphoma of the thymus. Hum Pathol 1990, 21:1262–1268
7. Kataoka T, Oyama A, Suzuki H, Kurita S, Ariyoshi Y, Ota K, Suchi T, Hayashi H, Osada H, Takashi T, Ueda R: B-cell lymphoma of probable thymic origin: case report. Jpn J Clin Oncol 1988, 18:371–378
8. Möller P, Hofmann WJ, Mielke B, Otto HF: Das primär mediastinale, hellzellige B-Zell-Lymphom ist ein epithelassoziiertes Thymuslymphom. Pathologe 1989a, 10:234–239
9. Hofmann WJ, Momburg F, Möller P, Otto HF: Intra- and extrathymic B cells in physiologic and pathologic conditions. Immunohistochemical study on normal thymus and lymphofollicular hyperplasia of the thymus. Virchows Arch [A] 1988a, 412:431–442
10. Hofmann WJ, Momburg F, Möller P: Thymic medullary cells expressing B lymphocyte antigens. Hum Pathol 1988b, 19: 1280–1287
11. Isaacson PG, Norton AJ, Addis BJ: The human thymus contains a novel population of B lymphocytes. Lancet 1988 ii: 1488–1490
12. Scarpa A, Bonetti F, Menestrina F, Menegazzi M, Chilosi M, Lestani M, Bovolenta C, Zamboni G, Fiore-Donati L: Mediastinal large-cell lymphoma with sclerosis. Virchows Arch [A] 1987, 412:17–21
13. Brandter LB, Smith CIE, Hammarström L, Lindemalm C, Christensson B: Clonal immunoglobulin gene rearrangements in primary mediastinal clear cell lymphoma. Leukemia 1989, 3:122–129
14. Yousem SA, Weiss LM, Warnke RA: Primary mediastinal non-Hodgkin lymphomas: a morphologic and immunologic study of 19 cases. Am J Clin Pathol 1985, 83:676–680
15. Möller P, Moldenhauer G, Momburg F, Lämmler B, Eberlein-Gonska M, Kiesel S, Dörken B: Mediastinal lymphoma of clear cell type is a tumor corresponding to terminal steps of B cell differentiation. Blood 1987a, 69:1087–1095
16. Möller P, Herrmann B, Moldenhauer G, Momburg F: Defective expression of MHC class I antigens is frequent in B-cell lymphomas of high-grade malignancy. Int J Cancer 1987b, 40:32–39
17. Momburg F, Herrmann B, Moldenhauer G, Möller P: B-cell lymphomas of high-grade malignancy frequently lack HLA-DR, -DP, and -DQ antigens and associated invariant chain. Int J Cancer 1987, 40:598–603
18. Möller P, Matthaei-Maurer DU, Hofmann WJ, Dörken B, Moldenhauer G: Immunophenotypic similarities of mediastinal clear-cell lymphoma and sinusoidal (monocytoid) B cells. Int J Cancer 1989b, 43:10–16
19. Al-Sharabati M, Chittal S, Duga-Neulat I, Laurent G, Mazerolles C, Al-Saati T, Brous set P, Delsol G: Primary anterior mediastinal B-cell lymphoma. Cancer 1991, 67:2579–2587
20. Nakamine H, Masih AS, Strobach RS, Duggan MJ, Bast MA, Armitage JO, Weisenburger DD: Immunoblastic lymphoma with abundant clear cytoplasm: A comparative study of B- and T-cell types. Am J Clin Pathol 1991, 96:177–183
21. Miller JB, Variakojis D, Bitran JD, Sweet DL, Kinzie JJ, Golomb HM, Ultmann JE: Diffuse histiocytic lymphoma with sclerosis: a clinicopathologic entity frequently causing superior venacaval obstruction. Cancer 1981, 47:748–756
22. Waldron Jr JA, Dohring EJ, Farber LR: Primary large cell lymphomas of the mediastinum: an analysis of 20 cases. Semin Diagn Pathol 1985, 2:281–295
23. Lichtenstein AK, Levine A, Taylor OR, Boswell W, Rossman S, Feinstein DI, Lukes RJ: Primary mediastinal lymphoma in adults. Am J Med 1980, 68:509–514
24. Levitt LJ, Aisenberg AC, Harris NL, Linggood RM, Poppema S: Primary non-Hodgkin's lymphoma of the mediastinum. Cancer 1982, 50:2486–2492
25. Trump DL, Mann RB: Diffuse large cell and undifferentiated lymphomas with prominent mediastinal involvement. Cancer 50:277–282, 1982
26. Jacobson JO, Aisenberg AC, Lamarre L, Willett CG, Linggood RM, Miketic LM, Harris NL: Mediastinal large cell lymphoma: An uncommon subset of adult lymphoma curable with combined modality therapy. Cancer 1988, 62:1893–1898
27. Inghirami G, Wieczorek R, Zhu BY, Silber R, Dalla-Favera R, Knowles D: Differential expression of LFA-1 molecules in non-Hodkin's lymphoma and lymphoid leukemia. Blood 1988, 72:1431–1434
28. Picker LJ, Medeiros LJ, Weiss LM, Warnke RA, Butcher EC: Expression of lymphocyte homing receptor antigen in non-Hodgkin's lymphoma. Am J Pathol 1988, 130:496–504
29. Horst E, Meijer CJLM, Radaszkiewicz T, Ossekoppele GJ, Van Krieken JHM, Pals ST: Adhesion molecules in the prognosis of diffuse large-cell lymphoma: Expression of a lymphocyte homing receptor (CD44), LFA-1 (CD11a/18), and ICAM-1 (CD54). Leukemia 1990a, 4:595–599
30. Boyd AW, Dunn SM, Fecondo JV, Culvenor JG, Dührsen U, Burns GF, Wawryk SO: Regulation of expression of human intercellular adhesion molecule (ICAM-1) during lymphohematopoietic differentiation. Blood 1989, 73:1896–1903
31. Stauder R, Greil R, Schulz TF, Thaler J, Gattringer C, Radaskiewicz T, Dierich MP, Huber H: Expression of leukocyte function-associated antigen-1 and 7F7-antigen, an adhesion molecule related to intercellular adhesion molecule-1 (ICAM-1) in non-Hodgkin lymphomas and leukemias: possible influence on growth pattern and leukaemic behaviour. Clin Exp Immunol 1989, 77:234–238
32. Möller P, Eichelmann A, Mechtersheimer G, Koretz K: Expression of β_1-integrins, HCAM (CD44), and LECAM-1 in primary gastro-intestinal B-cell lymphomas as compared to the adhesion receptor profile of the gut-associated lymphoid system, tonsil, and peripheral lymph node. Int J Cancer 1991, 49:846–855
33. Walter J, Möller P, Moldenhauer G, Schirrmacher V, Pawlita M, Wolf J: Local growth of a Burkitt's lymphoma versus disseminated invasive growth of the autologous EBV immortalised lymphoblasoid cells and their somatic cell hybrids in SCID mice. Int J Cancer 1991, 50:265–273
34. Rickinson AB, Gregory CD, Young LS: Viruses and cancer risks: Outgrowth of Epstein-Barr virus-positive Burkitt's lymphoma in the immune host. Med Oncol Tumor Pharmacother 1987, 4:177–186

35. Gregory CD, Murray RJ, Edwards CF, Rickinson AB: Down-regulation of cell adhesion molecules LFA-3 and ICAM-1 in Epstein-Barr virus-positive Burkitt's lymphoma underlies tumor cell escape from virus-specific T cell surveillance. J Exp Med 1988, 167:1811–1924
36. Patarroyo M, Prieto J, Ernberg I, Gahmberg CG: Absence, or low expression, of leukocyte adhesion molecules CD11 and CD18 on Burkitt lymphoma cells. Int J Cancer 1988, 41:901–907
37. Billaud M, Rousset F, Calender A, Cordier M, Aubry JP, Laisse V, Lenoir GM: Low expression of lymphocyte function-associated antigen (LFA-1) and LFA-3 adhesion molecules is a common trait in Burkitt's lymphoma associated with and not associated with Epstein-Barr virus. Blood 1990, 75:1827–1833
38. Mielke B, Möller P: Histomorphologic and immunophenotypic spectrum of primary gastro-intestinal B-cell lymphomas. Int J Cancer 1991, 47:334–343
39. Möller P, Eichelmann A, Koretz K, Mechtersheimer G: Adhesion molecules VLA-1-6 define discrete stages of peripheral B lymphocytic development and characterize different classes of B cell neoplasias. Leukemia 1992, 6:256–264
40. Garcia-Pardo A, Wayner EA, Carter WG, Ferreira OC Jr: Human B lymphocytes define an alternative mechanism of adhesion to fibronectin. The interaction of the $\alpha 4\beta 1$ integrin with the LHGPEILDVPST sequence of the type III connecting segment is sufficient to promote cell attachment. J Immunol 1990, 144:3361–3366
41. Osborn L, Hession C, Tizard R, Vassallo C, Luhowskyj S, Chi-Rosso G, Lobb R: Direct cloning of vascular cell adhesion molecula 1 (VCAM-1), a cytokine-induced endothelial protein that binds to lymphocytes. Cell 1989, 59:1203–1211
42. Hemler ME, Elices MJ, Parker C, Takada Y: Structure of the integrin VLA-4 and its cell-cell and cell-matrix adhesion functions. Immunol Rev 1990, 114:45–65
43. Seth R, Salcedo R, Patarroyo M, Makgoba MW: ICAM-2 peptides mediate lymphocyte adhesion by binding to CD11a/CD18 and CD49d/CD29 integrins. FEBS Lett 1991, 282:193–196
44. Hemler ME: VLA proteins in the integrin family: Structures, functions, and their role on leukocytes. Annu Rev Immunol 1990, 8:365–400
45. Patarroyo M, Makgoba MW: Leucocyte adhesion to cells. Molecular basis, physiological relevance, and abnormalities. Scand J Immunol 1989, 30:129–164
46. Marlin SD, Springer TA: Purified intercellular adhesion molecule-1 (ICAM-1) is a ligand for lymphocyte function-associated antigen 1 (LFA-1). Cell 1987, 51:813–819
47. Staunton DE, Dustin ML, Springer TA: Functional cloning of ICAM-2, a cell adhesion ligand for LFA-1 homologous to ICAM-1. Nature 1989, 339:61–64
48. Miedema F, Tromp JF, Van't Veer MB, Poppema S, Melief CJM: Lymphocyte function-associated antigen 1 (LFA-1) is a marker of mature (immunocompetent) lymphoid cells. A survey of lymphoproliferative diseases in man. Leukemia Res 1985, 9:1099–1104
49. Clayberger C, Medeiros LJ, Link MP, Warnke RA, Wright A, Koller TD, Smith SD, Krensky AM: Absence of cell surface LFA-1 as a mechanism of escape from immunosurveillance. Lancet 1987, ii:533–536
50. Caligaris-Cappio F, Bergui L, Schena M, Chilosi M, Marchisio PC: Cell-cell and cell-matrix adhesion structures may influence the growth pattern of chronic lymphoid malignancies. Leukemia 1989, 3:167–169
51. Medeiros LJ, Weiss LM, Picker LJ, Clayberger C, Horning Sj, Krensky AM, Warnke RA: Expression of LFA-1 in Non-Hodgkin's lymphoma. Cancer 1989, 63:255–259
52. Loike JD, Sodeik B, Cao L, Leucona S, Weitz JI, Detmers PA, Wright SD, Silverstein SC: CD11c/CD18 on neutrophils recognizes a domain at the N terminus of the Aa chain of fibrinogen. Proc Natl Acad Sci 1991, 88:1044–1048
53. Stacker SA, Springer TA: Leukocyte integrin p150,95 (CD11c/CD18) functions as an adhesion molecule binding to a counter-receptor on stimulated endothelium. J Immunol 1991, 146:648–655
54. Schwarting R, Stein H, Wang CY: The monoclonal antibodies αS-HCL1 (aLeu-14) and αS-HCL3 (aLeu-M5) allow the diagnosis of hairy cell leukemia. Blood 1985, 65:974–983
55. De la Hera A, Alvarez-Mon M, Sanchez-Madrid F, Martinez C, Durantez A: Co-expression of Mac-1 and p150,95 on $CD5^+$ B cells. Structural and functional characterization in a human chronic lymphocytic leukemia. Eur J Immunol 1988, 18:1131–1134
56. Visser L, Shaw A, Slupsky J, Vos H, Poppema S: Monoclonal antibodies reactive with hairy cell leukemia. Blood 1989, 74:320–325
57. Staunton DE, Marlin SD, Stratowa C, Dustin ML, Springer TA: Primary structure of ICAM-1 demonstrates interaction between members of the immunoglobulin and integrin supergenefamilies. Cell 1988, 52:925–933
58. Smith CW, Marlin SD, Rothlein R, Toman C, Anderson DC: Cooperative interactions of LFA-1 and Mac-1 with intercellular adhesion molecule-1 in facilitating adherence and transendothelial migration of human neutrophils in vitro. J Clin Invest 1989, 83:2008–2017
59. Rousset F, Billaud M, Blanchard D, Figdor C, Lenoir GM, Spits H, de Vries JE: IL-4 induces LFA-1 and LFA-3 expression on Burkitt's lymphoma cell lines. Requirement of additional activation by phorbol myristate acetate for induction of homotypic cell adhesions. J Immunol 1989, 143:1490–1498
60. Stamenkovic I, Aruffo A, Amiot M, Seed B: The hematopoietic and epithelial forms of CD44 are distinct polypeptides with different adhesion potentials for hyaluronate-bearing cells. EMBO J 1991, 10:343–348
61. Picker LJ, de los Tuyos J, Telen MJ, Haynes BF, Butcher EC: Monoclonal antibodies against the CD44 [In(Lu)-related p80], and Pgp-1 antigens in man recognize the Hermes class of lymphocyte homing receptors. J Immunol 1989, 142:2046–2051
62. Horst E, Meijer CJLM, Radaszkiewicz T, van Dongen JJM, Pieters R, Figdor CG, Hooftman A, Pals ST: Expression of a human homing receptor (CD44) in lymphoid malignancies and related stages of lymphoid development. Leukemia 1990b, 4:383–389
63. Pals ST, Horst E, Ossekoppele GJ, Figdor CG, Scheper RJ, Meijer CJLM: Expression of lymphocyte homing receptor as

a mechanism of dissemination in non-Hodgkin's lymphoma. Blood 1989, 73:885–888

64. Jalkanen S, Joensuu H, Klemi P: Prognostic value of lymphocyte homing receptor and S phase fraction in Non-Hodgkin's lymphoma. Blood 1990, 75:1549–1556
65. Tedder TF, Isaacs CM, Ernst TJ, Demetri GD, Adler DA, Disteche CM: Isolation and chromosomal localization of cDNAs encoding a novel human lymphocyte cell surface molecule, LAM-1. Homology with the mouse lymphocyte homing receptor and other human adhesion proteins. J Exp Med 1989, 170:123–133
66. Imai Y, True DD, Singer MS, Rosen SD: Direct demonstration of the lectin activity of gp90MEL, a lymphocyte homing receptor. J Cell Biol 1990, 111:1225–1232
67. Lanier LL, Loken MR: Human lymphocyte subpopulations identified by using three-color immunoflourescence and flow cytometry analysis: Correlation of Leu-2, Leu-3, Leu-7, Leu-8, and Leu-11 cell surface antigen expression. J Immunol 1984, 132:151–156
68. Kansas GS, Dailey MO: Expression of adhesion structures during B cell development in man. J Immunol 1989, 142: 3058–3062
69. Kansas GS, Wood GS, Engleman EG: Maturational and functional diversity of human B lymphocytes delineated with anti-Leu-8. J Immunol 1985, 134:3003–3006
70. Berg EL, Robinson MK, Warnock RA, Butcher EC: The human peripheral lymph node vascular addressin is a ligand for LECAM-1, the peripheral lymph node homing receptor. J Cell Biol 1991, 114:343–349
71. Murakawa Y, Strober W, James SP: Monoclonal antibody against the human peripheral lymph node homing receptor homologue (Leu 8) inhibits B cell differentiation but not B cell proliferation. J Immunol 1991, 146:40–46
72. Garcia CF, Weiss LM, Warnke RA: Small noncleaved cell lymphoma: An immunophenotypic study of 18 cases and comparison with large cell lymphoma. Hum Pathol 1986, 17:454–461
73. Michie SA, Garcia CF, Strickler JG, Dailey MO, Rouse RV, Warnke RA: Expression of the Leu-8 antigen by B-cell lymphomas. Am J Clin Pathol 1987, 88:486–490
74. Carbone A, Manconi R, Poletti A, Gloghini A, De Paoli P, Volpe R: Expression of Leu-8 surface antigen in B-cell lymphomas. Correlation with other B-cell markers. J Pathol 1988, 154:133–140
75. Strickler JG, Medeiros JL, Copenhaver CM, Weiss LM, Warnke RA: Intermediate lymphocytic lymphoma: An immunophenotypic study with comparison to small lymphocytic lymphoma and diffuse small cleaved cell lymphoma. Hum Pathol 1988, 19:550–554
76. Kimby E, Mellstedt H, Bjorkholm M, Holm G: Clonal surface structures related to differentiation, activation and homing in B-cell chronic lymphocytic leukemia and monoclonal lymphocytosis of undetermined significance. Eur J Haematol 1989, 43:452–459
77. Spertini O, Kansas GS, Munro JM, Griffin JD, Tedder TF: Regulation of leucocyte migration by activation of the leucocyte adhesion molecule-1 (LAM-1) selectin. Nature 1991, 349:691–694
78. Pals ST, Meijer CJLM, Radaszkiewicz T: Expression of the human peripheral lymph node homing receptor (LECAM-1) in nodal and gastrointestinal Non-Hodgkin's lymphomas. Leukemia 1991, 5:628–631