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Analysis of adhesion molecules in Ki-1 anaplastic large-cell lymphoma

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Abstract We analysed the expression of adhesion molecules on lymphoma cells in 13 patients with Ki-1 (CD30)-positive anaplastic large-cell lymphoma (Ki-1 ALCL; lymph nodes in 6, extranodal tumours in 6, and both lymph nodes and bone in 1). Very late activation antigen (VLA)-α4 (CD49d) and Hermes lymph node homing receptor (CD44) were constantly expressed in all specimens, and intercellular adhesion molecule-1 (ICAM-1; CD54) was frequently expressed in 10 of the 14 specimens. The expressions of lymphocyte function-associated antigen-1α (LFA-1α; CD11a) and VLA-α5 (CD49e) occurred in 5 of 14 and 4 of 14 specimens, respectively. The expressions of VLA-α2 (CD49b), endothelial leukocyte adhesion molecule-1, neural cell adhesion molecule (CD56) and E cadherin were always lacking. VLA-α6 (CD49f) was absent in all but one specimen. The expression of VLA-α5 on Ki-1 ALCL was high in subcutis-cutis but absent in lymph nodes. Furthermore, in one case, LFA-1α was detected in the primary lymph node, but was absent in a metastatic bone lesion. These results suggest that the expression of ICAM-1 is partially responsible for aleukemic behaviour in Ki-1 ALCL and, moreover, that the Ki-1 ALCL cells modify their expression of adhesion molecules at each of the involved organs.

Key words Ki-1 anaplastic large-cell lymphoma
Adult T-cell leukaemia/lymphoma · ATLL
Adhesion molecules

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Introduction

Ki-1 (CD30) anaplastic large-cell lymphoma (Ki-1 ALCL) was first described by Stein et al. in 1985 [27]. Patients with this disease have characteristic clinical behaviour with peripheral lymphadenopathy and extranodal tumour formation (subcutis-cutis, retroperitoneum, mediastinum, bone) [5, 8]. A leukaemic change is rarely observed [15, 29]. The characteristic histological features of Ki-1 ALCL are large cells with round or oval nuclei; one or more prominent nucleoli; and abundant, slightly amphophilic cytoplasm, showing cohesive growth patterns and paracortical or intrasinusoidal growth [4, 27]. Because of its histological characteristics, Ki-1 ALCL may be misdiagnosed as anaplastic carcinoma, melanoma or Hodgkin's disease. Immunophenotypic and genotypic analyses have revealed a frequent T-cell lineage [19, 27].

Recently, many lymphoid cell surface proteins which mediate adhesion to other cells and to the extracellular matrix have been identified. Several of these cellular adhesion molecules (CAMs) are also expressed by lymphoma cells and may mediate adhesion to tissue components during the metastatic process. Since haematopoietic neoplasms show a distinct organ preference it is reasonable to study the different constitutions of extracellular matrix [20, 21], basement membrane [31], and endothelial cells [2, 18] in various organs to examine the tendency for selection of specific organs for lymphoma cell involvement. Different combinations of CAMs might be expressed on Ki-1 ALCL cells in each involved tissue. To investigate this hypothesis, we studied the expression of CAMs including lymphocyte function-associated antigen-1α (LFA-1α; CD11a) and its ligand intercellular adhesion molecule-1 (ICAM-1; CD54), and endothelial leukocyte adhesion molecule-1 (ELAM-1), vascular cell adhesion molecule-1 (VCAM-1), neural cell adhesion molecule (NCAM; CD56), very late activation antigen (VLA)-α2 (CD49b), VLA-α4 (CD49d), VLA-α5 (CD49e), VLA-α6 (CD49f), CD44 and E cadherin in tissue specimens from patients with Ki-1 ALCL.

Materials and methods

Thirteen untreated patients with primary Ki-1 ALCL diagnosed in our institution from 1988 to 1992 were selected for study. Tissue specimens were obtained from lymph nodes in 6 patients, extranodal tissues in 6 patients (5 subcutis-cutis, 1 soft tissue), and both lymph node and bone tumour in 1 patient. The specimens were embedded in OCT (optium cutting temperature) compounds or snap-frozen in liquid nitrogen and stocked at –80° C until examination. Other parts of the tissues were fixed with B-5 solution, embedded in paraffin, and stained with haematoxylin and eosin, Giemsa, and silver impregnation. Immunostaining was performed by the avidin-biotin complex method (Vectastain). The monoclonal antibodies used in this study are listed in Table 1. Gene rearrangement of T-cell receptors (TcRs) and immunoglobulin heavy chain genes (JHs) was analysed by Southern blot method as previously described [19]. Investigation of the integration of human T-cell leukaemia virus type 1 (HTLV-1) proviral genome was performed with the Southern blot method [32]. The χ^2 test was applied for the statistical analysis of ICAM-1, LFA-1α, and VLA-α5 expression for each antibody between nodal and extranodal Ki-1 ALCL. Clinical and laboratory data were obtained from the charts of patients studied.

Table 1 Monoclonal antibodies used in this study (*ELAM* endothelial leukocyte adhesion molecule; *EMA* epithelial membrane antigen; *ICAM* intercellular adhesion molecule; *IL* interleukin; *LCA* leukocyte common antigen; *LFA* lymphocyte function-associated antigen; *NCAM* neural cell adhesion molecule; *VCAM* vascular cell adhesion molecule; *VLA* very late activation antigen)

Antibody	CD number	Source
Ki-1	CD30	Dakopatts
T11	CD2	Coulter Immunology
Leu4	CD3	Becton Dickinson
OKT4A+4	CD4	Ortho Diagnostic System
OKT8	CD8	Ortho Diagnostic System
B1	CD20	Coulter Immunology
Anti-IL2 receptor	CD25	Becton Dickinson
LCA	CD45	Dakopatts
VLA-α2	CDw49b	Immunotech
VLA-α4	CDw49d	Immunotech
VLA-α5	CDw49e	Immunotech
VLA-α6	CDw49f	Immunotech
ICAM-1	CD54	Becton Dickinson
LFA-1α	CD11a	Becton Dickinson
Leu44	CD44	Becton Dickinson
NCAM	CD56	Becton Dickinson
ELAM-1	–	British Bio-Technology
VCAM	–	British Bio-Technology
E cadherin	–	Takara Biomedical
EMA	–	Dakopatts

Results

Clinical and laboratory findings

The clinical features and laboratory findings are summarized in Table 2. The median age of patients was 61 years (range 14–80). Ten patients were male and 3 were female. Leukocytosis in excess of 10^4/µl was found in 5 patients. Atypical lymphoid cells were recognized in the peripheral blood of 5 (35%), 4 of which were HTLV-1 positive cases, but less than 3% of all white blood cell counts. According to the Ann Arbor staging system, 4 patients were stage I (30%), 3 were stage II (23%), 5 were stage III (38%) and 1 was stage IV (7%). The serum antibody against HTLV-1 was positive in 7 patients (53%), 6 of whom (46%) demonstrated the integration of HTLV-1 proviral DNA in the involved tissues.

Immunohistochemical studies and gene analysis

The results of immunohistochemical studies and Southern blot analysis are summarized in Table 3. All cases demonstrated strongly positive membranous and/or cytoplasmic reactions for Ki-1 (CD30) antigen on the lymphoma cells (Figs. 1, 2). CD4 was positive in all patients, CD3 was positive in 8 (57%) and CD25 (anti-interleukin 2α receptor) was positive in 12 (85%). Epithelial membrane antigen was positive in three cases of six HTLV-1 negative cases. All cases but one demonstrated the rearrangement of TcR gene and were considered to be

Table 2 Clinical and laboratory findings of CD30-positive anaplastic large-cell lymphoma (*AL* atypical lymphocytes; *ATLA* anti-human T-cell lymphotropic virus-1 antibody; *LDH* lactate dehydrogenase; LN=lymph node; WBC=white blood cell count, *M* male; *F* female)

Case number	Age (years)	Sex	Biopsy site	Other involved organs	WBC ($\times 10^3$/µl)	AL (%)	LDH (IU/l)	ATLA	Proviral DNA	Stage
1	64	M	LN:axillar	LN:paraaorta	7300	1	1505	+	+	III
2	68	F	LN:inguinal	LN:paraaorta Subcutis	13100	2	760	+	+	IIIE
3	14	F	LN:mesenteric	LN:paraaorta	7900	0	598	–	–	II
4	54	M	LN:neck	LN:paraaorta Mediastinum	13900	0	978	+	–	III
5	47	M	LN:neck	–	7300	0	357	–	–	IIA
6	68	F	LN:neck	–	3700	0	1469	+	+	IA
7	61	M M	LN:inguinal Bone	LN:neck	11500	1	2152	+	+	IIIE
8	64	M	Subcutis	Mediastinum	7900	0	455	+	+	IIE
9	80	M	Subcutis-cutis	–	1400	0	412	–	–	IE
10	73	M	Subcutis	–	4300	0	199	–	–	IE
11	76	M	Subcutis	–	3800	3	745	+	+	IE
12	65	M	Subcutis	–	7800	1	518	–	–	IV
13	64	M	Soft tissue	Skin	13400	0	243	–	–	IIIE

Table 3 Immunological and genetic study (*G* germ line; *IL-2R* interleukin 2 receptor; *N* null type; *ND* not done; *R* rearranged band; *T* T cell; *7′* lymph node, *7″* bone; *a* some CD20 positive cells are present, Cβ1 TcR cβ, digested with *Eco* RI enzyme, Cβ2 TcR cβ, digested with *Hind* III enzyme, Jγ TcR Jγ, *IH* immunoglobulin heavy chain genes)

Case number	CD30 Ki-1	CD2 T11	CD3 Leu4	CD4 OKT4A+4	CD8 OKT8	CD20 B1	CD25 IL-2R	CD45 LCA	EMA	Cβ1	Cβ2	Jγ *Eco* RI	JH *Hind* III	Pheno-type	Geno-type
1	+	+	+	+	−	−	+	+	−	G	G	R	G	T	T
2	+	+	−	+	−	−	+	+	−	G	G	G	G	N	N
3	+	+	−	+	−	a	+	+	+	R	R	R	G	N	T
4	+	+	−	+	−	−	−	−	−	G	R	R	G	N	T
5	+	+	+	+	+	−	−	+	−	R	R	G	G	T	T
6	+	+	+	+	−	−	+	+	−	G	R	R	G	T	T
7′	+	−	+	+	−	−	+	+	−	R	G	R	G	T	T
7″	+	−	+	+	−	−	+	+	−	R	G	R	G	T	T
8	+	+	+	+	−	−	+	+	−	R	G	R	G	T	T
9	+	+	−	+	−	−	+	+	+	G	G	R	G	T	T
10	+	−	+	+	−	−	+	−	−	G	G	ND	G	T	T
11	+	+	−	+	−	−	+	−	−	R	G	G	G	N	T
12	+	+	−	+	−	−	+	+	−	G	G	R	G	N	T
13	+	−	−	+	−	−	+	+	+	G	G	R	G	N	T

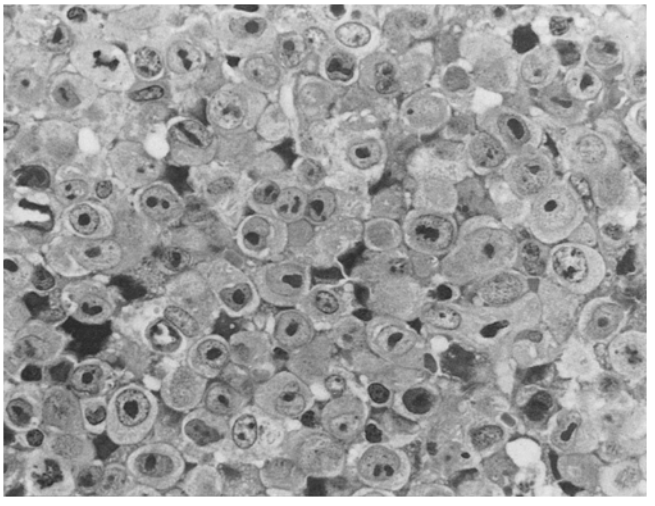

Fig. 1 CD30 positive anaplastic large-cell lymphoma (ALCL). Diffuse and cohesive proliferation of lymphoma cells with large round or oval nuclei and distinct nucleoli. Lymph node [Case 2, haematoxylin and eosin (H & E) ×400

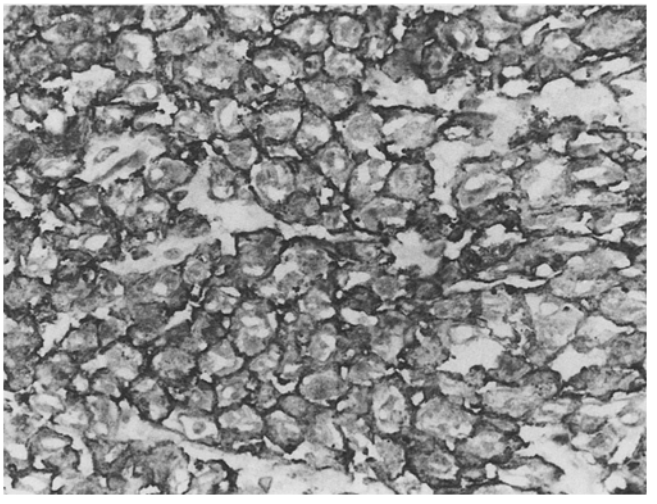

Fig. 2 Infiltrating large neoplastic cells show a constantly positive reaction for Ki-1 (CD30). Lymph node [case 4, avidin-biotin complex (ABC) staining ×400]

T-cell lymphoma. In one case (case 3) of T-cell lymphoma, most of the lymphoma cells showed T-cell marker and some were CD20-positive also; but because gene analysis revealed the rearrangement of TcR β and γ genes and no rearrangement of JH gene, the case was diagnosed as T-cell lymphoma. One case (case 2) expressed neither CD3 or CD20 nor rearrangement of TcRs or JH, and this case was diagnosed as null-cell type. Lymphoma cells obtained from two different sites (lymph node and bone tumour) in case 7 had the same clonality of TcRs and proviral DNA of HTLV-1.

Adhesion molecules on Ki-1 ALCL

Table 4 lists the expression of each in Ki-1 ALCL. Ki-1 ALCL strongly expressed VLA-α4 (14/14 100%), CD44 (14/14 100%) and ICAM-1 (10/14 71%; Fig. 3), but in all cases lacked the expression of VLA-α2, ELAM-1, NCAM, and E cadherin. VLA-α5 and LFA-1α were expressed in 5 of 14 specimens (35%) and 6 of 14 specimens (42%), respectively. Only case 13 expressed VLA-α6 on the lymphoma cells of the retroperitoneal tumour, and only 2 cases (case 5 and 11) demonstrated VCAM-1.

Comparing the expression of CAMS between lymph nodes and extranodal tissues, the lymphoma cells in the subcutis-cutis displayed a higher incidence of positive reactions for ICAM-1, LFA-1α, and VLA-α5 than those in the lymph node: that is ICAM-1 6/7 (85%) versus 4/7 (57%); LFA-1α 4/7 (57%) versus 2/7 (28%) and VLA-α5 4/7 (57%) versus 0/7 (0%), respectively. VLA-α5 showed significantly higher expression on the lymphoma

Table 4 Analysis of adhesion molecules on CD30-positive anaplastic large-cell lymphoma

Case number	Biopsy site	ICAM -1	LFA -1α	VLA -2α	VLA -4α	VLA -5α	VLA 6α	CD44	ELAM -1	VCAM -1	NCAM	E cadherin
1	LN	+	–	–	+	–	–	+	–	–	–	–
2	LN	+	–	–	+	–	–	+	–	–	–	–
3	LN	+	–	–	+	–	–	+	–	–	–	–
4	LN	+	+	–	+	–	–	+	–	–	–	–
5	LN	–	–	–	+	–	–	+	–	+	–	–
6	LN	–	–	–	+	–	–	+	–	–	–	–
7	LN	–	+	–	+	–	–	+	–	–	–	–
	Bone	–	–	–	+	–	–	+	–	–	–	–
8	Subcutis	+	+	–	+	+	–	+	–	–	–	–
9	Subcutis	+	+	–	+	+	–	+	–	–	–	–
10	Subcutis	+	+	–	+	+	–	+	–	–	–	–
11	Subcutis	+	–	–	+	–	–	+	–	+	–	–
12	Subcutis	+	+	–	+	+	–	+	–	–	–	–
13	Soft tissue	+	–	–	+	–	+	+	–	–	–	–

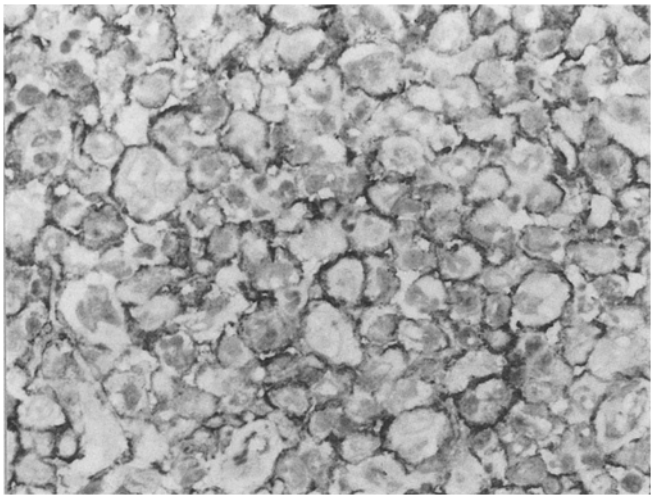

Fig. 3 Neoplastic cells of nodal ALCL show positive membranous reaction for intercellular adhesion molecule-1 (CD54). (Case 4, ABC staining ×400)

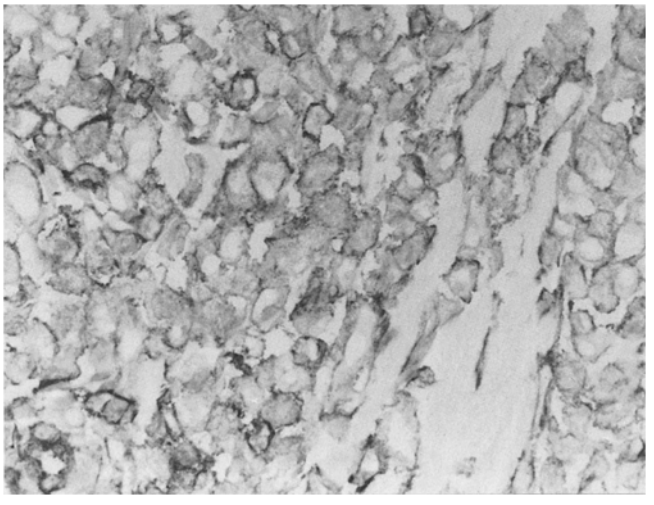

Fig. 4 Neoplastic cells of extranodal ALCL cells show a positive reaction for very late activation antigen-α5 (CDw49e). Subcutis (case 9, ABC staining ×400)

cells in the subcutis-cutis (Fig. 4; P=0.035), but there was no significant relationship of ICAM-1 and LFA-1α.

In case 7, LFA-1α expression was detected on the lymphoma cells in the lymph node, but was not detected in the bone tumour. There was no difference in histological, phenotypic, and genotypic characteristics of the tumour at that site (Fig. 5).

No statistical difference in the expression of CAMS was found between HTLV-1 negative cases and HTLV-1 positive cases.

Discussion

Analyses of CAMs on non-neoplastic and neoplastic lymphocytes have been reported by many authors in recent years. In non-neoplastic B-cells, different expressions of VLAs have been demonstrated during B-cell differentiation [17]. Stauder et al. reported that ICAM-1 was found in 44% of low-grade and 30% of high-grade B-cell lymphomas [26]. In thymic B-cell lymphoma, ICAM-1 was highly expressed, but VLA-1, 2, 3, 5, and 6 were repeatedly lacking, and VLA-4, LFA1α, and CD44 were heterogeneous [6]. Baldini et al. showed that VLA-α4 was almost constantly expressed, but the expression of VLA-α3 showed a low incidence with a low level of intensity in B-cell lymphoma. In contrast, in the presence of chronic B-cell leukaemia, the expression of VLA-α3 was higher and that of VLA-α4 was low [1].

A few studies have been conducted on T-cell lymphoma. Circulating memory T-cells expressed an increased level of LFA-1α, VLA-α3, VLA-α5, and VLA-α6 [24]. Peripheral T-cell lymphoma in the central nervous system, muscle, gastrointestinal tract and nasopharynx exhibited NCAM [14], and the infiltrating cells in cutaneous T-cell lymphoma expressed LFA-1, LFA-3, ICAM-1, VLA-4, and VLA-5 [28].

In our study on Ki-1 ALCL, all cases but one were identified as T-cell lymphoma. The analysis of CAMs of Ki-1 ALCL showed constant expression (100%) of VLA-α4 and CD44, and high expression of ICAM-1 (71%). LFA-1α and VLAα5 were heterogeneous. VLA-

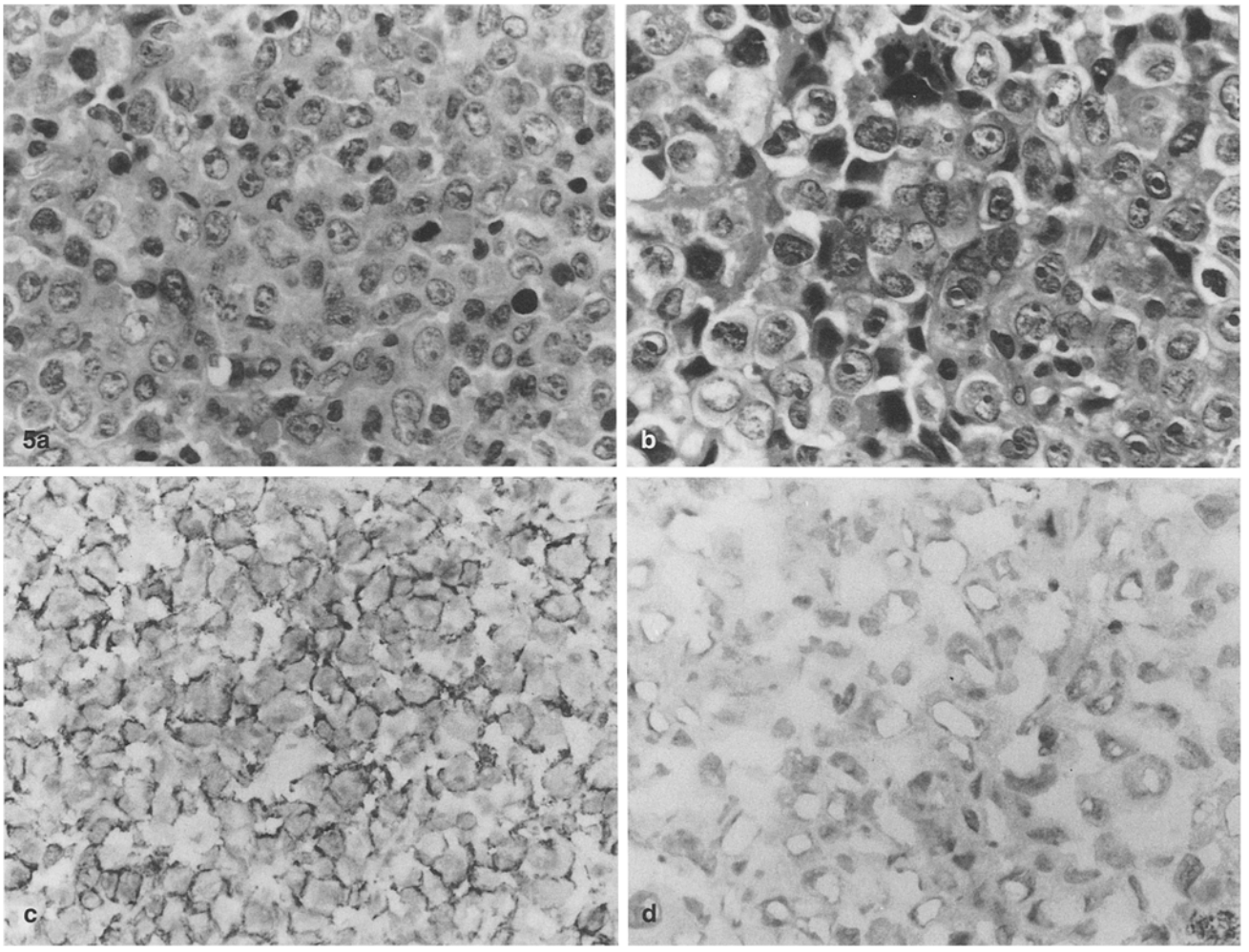

Fig. 5a–d CD30-positive ALCL cells in case 7 have similar morphologic features in lymph node as a primary lesion (**a**) and in bone as a metastatic lesion (**b**; both H & E ×400). However lymphocyte function-associated antigen-1α was positive in lymph node (**c**) but negative in bone (**d**, ABC staining ×400)

α2, ELAM, NCAM, and E cadherin were always lacking.

Six of thirteen cases demonstrated the integration of HTLV-1 proviral genome and were considered to be adult T-cell leukaemia/lymphoma. However, no significant difference was demonstrated between HTLV-1 negative and HTLV-1 positive Ki-1 ALCL cells in the expression of CAMs studied in this research, which suggests that in Ki-1 ALCL, HTLV-1 infection dose not influence on the expression of CAMs on their lymphoma cells.

Several studies have reported on the correlation between CAMs on neoplastic cells and clinical behaviour in haematopoietic malignancies. Inghirami et al. [13] showed that chronic B-cell lymphocytic leukaemia and B-cell small lymphocytic lymphoma had different LFA-1α expressions and these researchers hypothesized that the absence of LFA-1α might indicate a leukaemic change. Möller et al. [17] demonstrated that the leukaemic phenotype of B-cell malignancies may depend on the presence of VLA-5. Boyd et al. [3] reported that patients with large and solitary tumours in B-cell lymphoma were more often found to have ICAM-1 expression by lymphoma cells than were those with systemic lymph node swelling and overt leukaemia. Several authors have suggested that a local growth and aleukaemic blood picture in B-cell lymphoma might be related to the phenotype of VLAs(–) [17], LFA-1(+) [13, 26], ICAM-1(+) [3, 26], CD44(–) [12], and LECAM-1(–) [25]. Our cases with Ki-1 ALCL frequently showed mass formation and no overt leukaemic changes. Our findings on the expression of ICAM-1 in lymphoma cells correspond to previous results, but VLA-4 was constantly positive and CD44 was highly expressed. This difference may be attributed to the specificity of the Ki-1 ALCL or to the cell lineage.

Interestingly, Ki-1 ALCL cells showed different levels of CAM expression in different organs. The populations of VLA-α5-, ICAM-1- and LFA-1α-positive lymphoma cells in the subcutis-cutis were greater than in the lymph nodes. VLA-α5 was expressed significantly more frequently in the subcutis-cutis than it was in the lymph node. VLA-α5 is known to bind to the RGD (Arg-Gly-Asp) domains of fibronectin [11, 23]. In our study, lymphoma cells in both nodal and extranodal tissues con-

stantly expressed VLA-α4, which is known to bind not only to the CS-1 alternatively spliced domain of fibronectin [9, 30] but also to VCAM-1 [7]. VCAM-1 was expressed on the lymphoma cells only in case 5. These results indicate that Ki-1 ALCL cells in the subcutis-cutis may employ fibronectin by using both domains of RGD and CS-1. Hemler et al. reported increased expression of VLA-α5 in peripheral T lymphocytes prompted by stimulation [11], and suggested that VLA-5 was acquired in the periphery, perhaps having been involved in lymphocyte extravasation and migration through tissue [10]. Using Nalm-6 cells and BMS2 stromal cells, Miyake et al. demonstrated that high affinity for fibronectin achieved through VLA-4 and VLA-5 might be needed for Nalm-6 cell migration [16]. Ki-1 ALCL cells in the subcutis-cutis may have a higher affinity for fibronectin than do those in the lymph nodes by determined through use of both VLA-α4 and VLA-α5.

Additionally, the lymphoma cells in case 7 exhibited different expression of LFA-1α between the lymph node and bone tumour despite their similar morphology and their same phenotype and genotype. Roos used T-cell hybridoma and reported that LFA-1 was required for efficient metastasis of T-cell hybridoma [22]. Our data do not correspond with those findings. There are two possible interpretations for these results. Tumour cells in the lymph node might acquire the ability to lack LFA-1α and then metastasize to the bone. Secondly, after metastasis, Ki-1 ALCL cells in the bone lack LFA-1α or simply do not exhibit it. However, our results may indicate that Ki-1 ALCL cells are able to change the expression of their CAMs between the primary site and the metastatic lesion. Further examination is necessary to address this question.

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