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Anaplastic large cell lymphoma, CD30/Ki-1 positive, expressing the CD15/Leu-M1 antigen

Immunohistochemical and morphological relationships to Hodgkin's disease*

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Summary. In this report we analyze the morphological and immunohistochemical findings observed in 5 cases of CD30/Ki-1 positive anaplastic large cell lymphoma, a recently recognized neoplastic entity. In comparison with the Ki-1 lymphomas so far described, these cases showed a fairly large number of Reed-Sternberg-like cells, often admixed with small lymphocytes and occasional eosinophils. Moreover, in all our cases immunohistochemical reactions detected the CD15/Leu-M1 antigen, together with markers of the T-lineage and of lymphoid activation. In previous studies the CD15/Leu-M1 antigen has been found in the majority of cases of Hodgkin's disease, but has been stated to be absent typically in Ki-1 lymphomas. Our results indicate that this antigen cannot be considered a reliable tool to distinguish between Ki-1 lymphomas and Hodgkin's disease. Furthermore, the morphological and immunohistochemical findings reported suggest that in some cases Ki-1 cell lymphoma and Hodgkin's disease may be closely related. They may represent different steps in the progression of the same lymphoproliferative disorder.

Key words: Anaplastic large cell lymphoma – Non-Hodgkin's lymphoma – Immunohistochemistry – Antigen expression

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Introduction

The anaplastic large cell lymphoma positive for the CD30/Ki-1 antigen (Ki-1 ALC-L) is an uncommon form of high grade non-Hodgkin's lymphoma, which has been recently recognized as a distinct pathological entity (Stein et al. 1986; Kadin et al. 1986). In the last few years, several reports have stressed the clinical relevance and the difficulty in the morphological recognition of the tumour (Kadin et al. 1986; Agnarsson and Kadin 1988; Weiss et al. 1988). Histologically, Ki-1 ALC-L may show a pattern of lymph node infiltration mimicking malignant histiocytosis, metastatic carcinoma or even melanoma. Occasionally, cases of Ki-1 ALC-L presenting fibrosis and Reed-Sternberg (RS)-like cells are not easily to distinguish from the nodular sclerosis type of Hodgkin's disease (HD). In these cases, diagnostic difficulties are further enhanced by the close immunophenotypic similarities shared by Ki-1 ALC-L and HD (Agnarsson and Kadin 1988; Weiss et al. 1988; Al Saati et al. 1986). Apart from their common expression of the CD30/Ki-1 antigen, formerly defined as a HD-related marker, both Ki-1 ALC-L and HD usually show positive immunostaining for a series of lymphoid activation antigens including Ia (HLA-DR), Tac (CD25/IL2-R), and epithelial membrane antigen (EMA). These immunological similarities have suggested a common origin of both Ki-1 ALC-L and HD from activated lymphoid cells (Stein et al. 1986). However, as all the cases of Ki-1 ALC-L reported in the literature have been unreactive to the CD15/Leu-M1 antigen,

while most cases of HD were positive, the expression of this antigen has been considered to be a sign of the differences between these diseases (Agnarsson and Kadin 1988).

We describe 5 cases of Ki-1 ALC-L expressing the CD15/Leu-M1 antigen. The morphological and immunological features observed in our cases suggest that some variants of ALC-L may be closely related to HD or even represent the progression of HD to a high grade malignant lymphoma.

Materials and methods

Case 1. A previously healthy 46-year-old man was investigated for an inguinal swelling. No fever, asthenia, night sweating or weight loss were complained of. Physical examination revealed enlargement of inguinal, axillary and cervical lymph nodes. A CT scan of the chest, abdomen, and pelvis was normal. An inguinal lymph node was removed and a diagnosis of ALC-L was made. Subsequent bone marrow biopsy was negative for lymphoma. The patient underwent chemotherapy (proMACE-CYTABOM protocol) and is still alive and in complete remission 7 months after diagnosis.

Case 2. A 45-year-old woman presented with nausea, vomiting, temperature, loss of weight, fatigue, and night sweats. At physical examination, the spleen was palpated 2 cm below the left costal margin. Endoscopy showed a large ulcerated mass on the lesser curvature of the stomach. Multiple biopsies revealed a pattern consistent with high grade malignant lymphoma. Chest X-rays and Jamshidi needle biopsy were unremarkable, while bipedal lymphangiography was positive. At laparotomy, the tumour extended to the pancreas, intestine, peritoneum, perigastric and retroperitoneal nodes. A sample of neoplastic tissue was taken and a diagnosis of ALC-L was made. The patient was treated with CHOP-CVP, with transient partial remission. She died 5 months after diagnosis, when she was in a resistant phase.

Case 3. A previously healthy, 62-year-old man presented with diffuse lymph node swelling, loss of weight, fever and night sweating. A CT scan of the chest and abdomen revealed retroperitoneal bulky disease. Bone marrow aspirate and Jamshidi needle biopsy were unremarkable. An inguinal lymph node biopsy was performed and fixed in 10% formalin. A diagnosis of high grade non-Hodgkin's lymphoma, unclassified, was made. A second lymph node was removed from the latero-cervical region, snap-frozen in liquid nitrogen, and stored at −80° C. Immunophenotyping on paraffin and frozen sections allowed a preliminary diagnosis of ALC-L. The patient underwent aggressive chemotherapy (CHOP-Bleo), but rapidly died of progressive disease.

Case 4. A 23-year-old female presented with temperature and latero-cervical lymph node enlargement, lasting 2 weeks. Physical examination, total body CT scan, bone marrow Jamshidi needle biopsy, and laboratory investigations did not reveal significant findings. The patient underwent a lymph node biopsy which showed the histological pattern of ALC-L. "Mantle" field radiation therapy was performed. The patient is still alive and in complete remission 10 months after diagnosis.

Case 5. A 34-year-old woman presented with fever, weight loss, night sweats, and severe dyspnoea. She had a previous history of Hodgkin's disease, nodular sclerosing type (stage IIB, with "bulky" mediastinal tumour), which had been treated with MOPP-ABVD and radiotherapy, obtaining complete remission. A CT scan showed a huge mediastinal mass with infiltration of both the lungs. A biopsy was performed during thoracotomy and a diagnosis of ALC-L was made. Residual Hodgkin's disease was not observed. Abdominal ultrasonography, bipedal lymphangiography, and Jamshidi needle biopsy were negative. Laboratory findings were within normal limits with the exception of BSR (72 mm/1st hour). Autologous bone marrow transplantation was planned. The patient died of rapidly progressive disease, while she was receiving induction therapy with Endoxan and Mitoxantrone.

Formalin- or B5-fixed, paraffin-embedded tissue samples were available in all instances. In case 3, frozen tissue specimens had also been obtained. 3 μm thick paraffin sections were stained with H-E, Giemsa, P.A.S., and Gomori silver impregnation for reticulin fibres.

Immunohistochemistry was performed both on paraffin and frozen sections by the APAAP technique (Cordell et al. 1984), using the monoclonal antibodies listed in Tables 1 and 2. In case 1, immunohistochemical procedures were performed by the streptavidin-peroxidase conjugate (SP) method, as already described (Shi et al. 1988). The specific antisera to lysosyme and protein S-100 were used following the PAP technique (Sternberger 1986). Enzyme digestion was never performed. Positive controls were provided by normal tonsils. Reactivity of Leu-M1 and Ber-H2 was also tested in sections from cases of nodular sclerosis and mixed cellularity HD. Negative controls were obtained by substituting the primary antibodies with normal mouse serum.

Results

In all the cases, lymph nodes showed an almost complete effacement of the normal structure due to proliferation of anaplastic large cells. Neoplastic elements spread through marginal and cortical sinuses, extended to the interfollicular areas with partial sparing of follicles (Fig. 1), and were either dispersed or arranged in cohesive sheets. In all cases, variable fibrosis was also noticed. In some areas, thin and irregular fibrous septa crossed the neoplastic infiltrates, producing a vaguely nodular pattern. Anaplastic elements were characterized by large nuclei with medium-sized or prominent nucleoli and a broad, faintly basophilic or clear rim of cytoplasm (Fig. 2). Several cells presented distinctive RS-like features. These cells were often surrounded by a fairly regular rim of small, normal-appearing lymphocytes (Fig. 3). A variable number of reactive histiocytes and sparse eosinophils were also present. In all cases, mitotic figures were numerous and mostly restricted to anaplastic large cells.

Immunohistochemical results are summarized in Table 3. All the cases showed expression of the CD15/Leu-M1 antigen (Fig. 4) and resulted positive for fixation-resistant markers of T-lineage and lymphoid activation. In case 3, immunohistochemical tests performed on frozen sections further confirmed the T-cell origin of the lymphoproliferative disorder.

Table 1. Monoclonal antibodies (mAbs) and policlonal antisera employed in paraffin sections

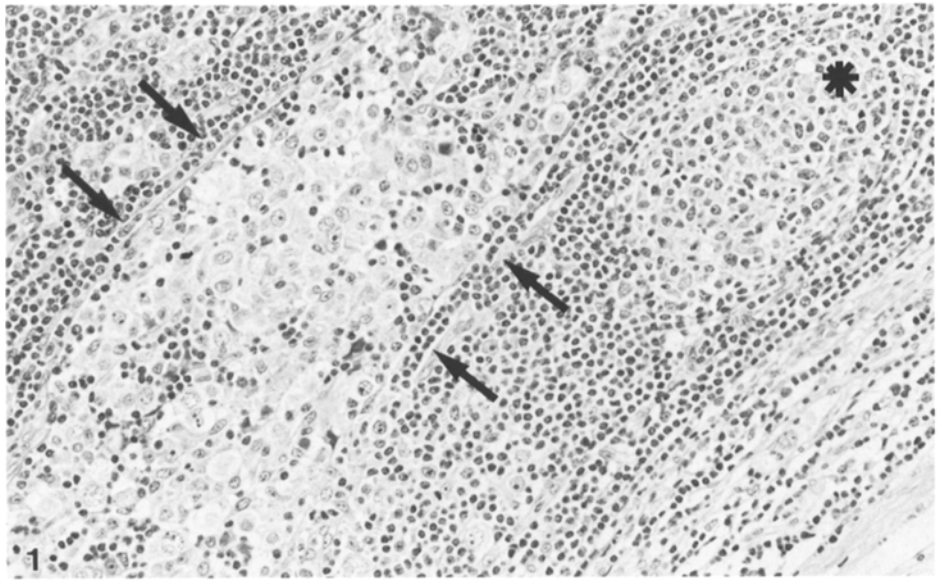
mAb/source	specificity: CD and target cells
LC/DAKO	CD45; leukocyte common antigen (LCA); pan-leukocyte
4KB5/DAKO	CD45RA; LCA epitope restricted to B cells and T subsets
L26/DAKO	33 KD antigen expressed by B cells
LN1/CLONAB	CDw75; antigen expressed by mature B cells
LN2/CLONAB	CD74; antigen of B cells and monocytes
MB1/CLONAB	CD45R; 180 KD antigen expressed by B cells
MB2/ CLONAB	Unclustered B cell antigen
MT2/CLONAB	CD45R; B cells, prevalently of the follicular mantle
C3bR/DAKO	CD35; B cells, dendritic reticulum cells
UCHL1/DAKO	CD45RO; LCA epitope restricted to T cells
MT1/CLONAB	CD43; T cells, myeloid and erythroid precursors, Langerhans cells, monocytes and macrophages
Leu-M1/BD	CD15; RS cells, cells of myelomonocytic origin
Ber-H2/Prof. Stein	CD30; fixation-resistant epitope of Ki-1 antigen expressed by activated lymphoid cells, RS cells and ALC-L elements
HLA-DR/DAKO	MHC class II antigen; B cells and activated T cells
LN3/CLONAB	HLA-DR epitope
Tü9/CLONAB	RS cells
EMA/DAKO	Epithelial membrane antigen expressed by non-lymphoid cells, plasma cells, RS cells, and high grade lymphoma elements
MAC 387/DAKO	Macrophages
KP1/Dr. Mason	CD68; macrophages
anti-IgA1-1gA2/BD	Immunoglobulin-producing B cells
IgM/DAKO	Immunoglobulin-producing B cells
Kappa/DAKO	Immunoglobulin-producing B cells
Lambda/DAKO	Immunoglobulin-producing B cells
S 100/DAKO	Protein S-100, expressed by Langerhans cells and interdigitating reticulum cells
Lysozyme/DAKO	Muramidase, expressed by cells of histiocytic lineage

Abbreviations: CD = Designated number of characterized molecules, proposed at the Fourth international Workshop on Leukocyte Differentiation Antigens (Vienna, February 1989); BD = Becton Dickinson

Table 2. Monoclonal antibodies (mAbs) employed in frozen sections

mAb/source	specificity: CD and target cells
T6/DAKO; OKT6/ORTHO	CD1a; Langerhans cells, thymocytes
T11/DAKO; OKT11/ORTHO	CD2; T cells expressing SBC-R
T3/DAKO; UCHT1/Dr. Beverley	CD3; T cell receptor associated molecule
T4/DAKO; anti-Leu-3a/BD	CD4; T cell subsets (helper); macrophages
T1/DAKO; anti-Leu-1/BD	CD5; T cells and B cell subsets
Tü33/Dr. Ziegler	CD6; mature T cells; B cell subsets
anti-LEU-9/BD	CD7; T cells expressing IgM-R
T8/DAKO; anti-Leu-2a/BD	CD8; T cell subsets (suppressor)
C3bR/DAKO; OKM1/ORTHO	CD11b; T cell subsets (NK); granulocytes
anti-Leu-M5/BD; p150,95/DAKO	CD11c; T cell subsets (NK); macrophages
Mo2/Dr. Todd	CD14; monocytes and macrophage subsets
Macrophage/DAKO	Monocytes and macrophages
Ber-MAC3/Prof. Stein	Macrophages
DRC1/DAKO	Follicular dendritic cells
CD19/DAKO; anti-Leu-12/BD	CD19; B cells
anti-Leu-16/BD	CD20; B cells
CD22/DAKO; anti-Leu-14/BD	CD22; B cells
IL2-R/DAKO	CD25; activated B and T cells; macrophages
Ki-1; Ber-H2/Prof. Stein	CD30; activated B and T cells
Ki-24/Prof. Stein	CD70; activated B and T cells
Ki-27/Prof. Stein	activated B and T cells
HLA-DR/DAKO	MHC class II antigen expressing cells
PC (Ki-67)/DAKO	Proliferating cells
LC/DAKO	CD45; pan-leukocyte antigen (LCA)

Abbreviations: CD = Designated number of characterized molecules, proposed at the Fourth International Workshop on Leukocyte Differentiation Antigens (Vienna, February 1989); BD = Becton Dickinson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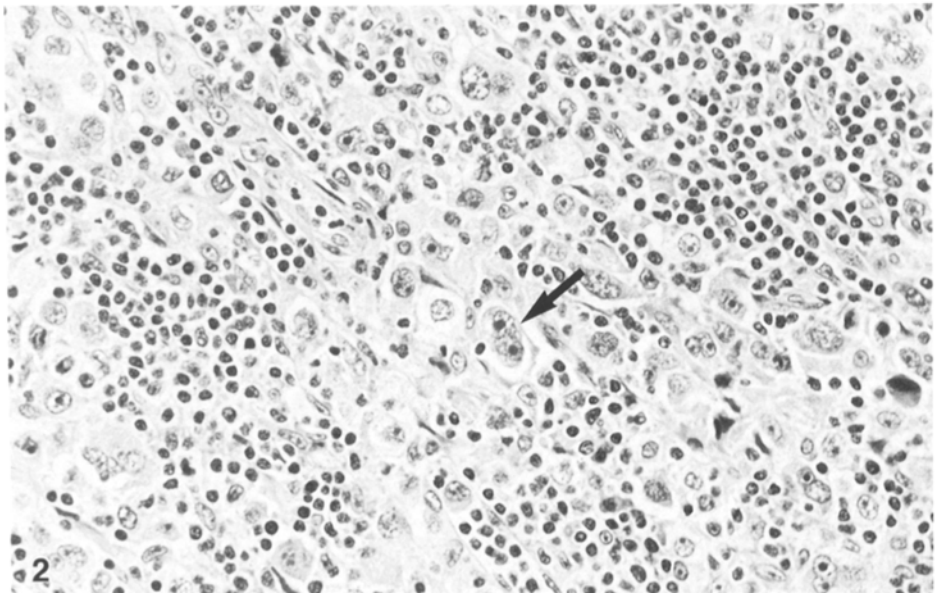
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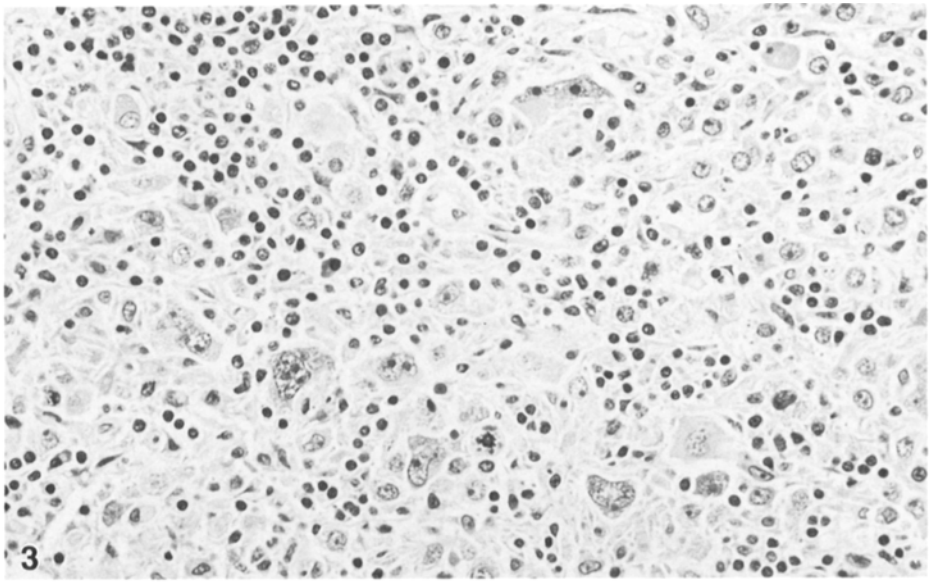
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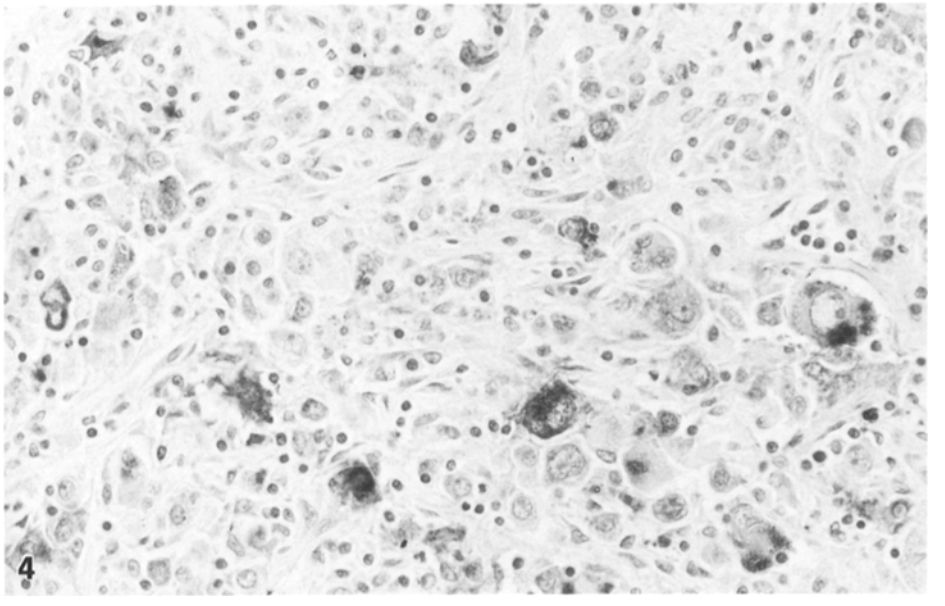
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Table 3. Main immunohistochemical findings observed in the reported cases in paraffin sections

mAb/CD	Case 1	Case 2	Case 3[a]	Case 4	Case 5
LC/CD45	+/− (m)	−/+ (m)	−	−/+ (m)	−
4KB5/CD45RA	−	−	−	−	−
LN1/CDw75	−	−	−	−	−/+ (w)
MB2	−	−/+ (w)	+ (w)	−	−
MT1/CD43	+/− (m)	−	−/+ (m)	−	+/− (m)
UCHL1/CD45RO	+/− (m)	−/+ (m)	−	−/+ (m)	+ (m)
Leu-M1/CD15	+/− (s)	−/+ (m)	−/+ (m)	+/− (m)	+/− (m)
Ber-H2/CD30	+ (m)	+ (m)	+ (s)	+/− (m)	+/− (m)
LN3 (HLA-DR)	+/− (m)	ND	+ (m)	ND	ND
EMA	+/− (m)	−	+/−	−	+/− (s)
MAC 387	−	−	−	−	−

Abbreviations: − = all or most cells positive; +/− = more than 50% of the cells positive; −/+ = less than 50% of the cells positive; − = no cell positive; ND = not done; s = strong labelling; m = moderate labelling; w = weak labelling.

[a] Case 3 was also tested in frozen sections, showing the following phenotype: CD1a +, CD4 +, CD5 +, CD8 −, CD11b −, CD11c −, CD14 −, CD19 −, CD20 −, CD22 −, CD25 +, CD30 +, CD70 +. Immunostaining for CD2, CD3, CD6, and CD7 produced unreliable results

Discussion

Ki-1 ALC-L and HD have been reported to be closely related diseases (Stein et al. 1986). Gene rearrangement studies proved that in Ki-1 ALC-L and HD, neoplastic cells may be either of B- or T-lineage (O'Connor et al. 1987a; O'Connor et al. 1987b). Immunohistochemical investigation gave strong indications that both neoplasms originated from activated lymphoid cells (Stein et al. 1986; Agnarsson and Kadin 1988). The neoplastic elements of Ki-1 ALC-L and HD are usually characterized by the expression of a series of activation markers, including Ia (HLA-DR), Tac (CD25/IL2-R), transferrin receptor (CD71/TRF-R), and EMA (Stein et al. 1986; Al Saati et al. 1986; Stein et al. 1987; Agnarsson and Kadin 1988). The immunohistochemical affinity between Ki-1 ALC-L and HD is further stressed by their frequent non-reactivity for the leukocyte common antigen (Falini et al. 1989). Moreover, the occurrence of various immunophenotypic profiles (B, T, mixed or null) has been reported in both Ki-1 ALC-L and HD (Stein et al. 1986; Stein et al. 1987; Agnarsson and Kadin 1988). On morphological grounds, some subtypes of HD, such as the syncitial variant of the nodular sclerosis type, may be quite indistinguishable from Ki-1 ALC-L, being characterized by sheets of atypical cells with single element necrosis, as well as by an interfollicular pattern of lymph node infiltration with sparing of B-cell areas (Blaunstein and Lewkow 1987). However, Ki-1 ALC-L may show histological features reminiscent of HD, such as interstitial or band fibrosis and nodular appearance (Stein et al. 1987). The recently proposed possibility of an association of Ki-1 ALC-L with HD (Pileri et al. 1989) further stresses the relationships between these neoplasms and emphasizes the difficulties occurring in their differential diagnosis. Ki-1 ALC-L may be separated from HD on the basis of a series of morphological features, including the marked pleomorphism of infiltrates, the sinusoidal pattern of nodal involvement, the cohesive appearance of neoplastic sheets, and the high mitotic rate (Stein et al. 1987; Agnarsson and Kadin 1988). Moreover, lacunar cells and the regular admixture of normal lymphocytes and neoplastic cells, both common findings in HD, are usually absent. A crucial role in differentiating Ki-1 ALC-L from HD has been assigned to immunohistochemistry (Agnarsson and Kadin 1988). In fact, the CD15/Leu-M1 antigen has been reported to be typically absent in Ki-1 ALC-L, whereas it is observed in the majority of HD cases, except for the lymphocyte predominance type. Leu-M1 antigen, formerly defined as "X Hapten"

Fig. 1. Lymph node section showing a sinusoidal infiltrate composed of anaplastic large cells (*arrows*). A secondary follicle with evident germinal centre (*asterisk*) is spared by the neoplastic process. H-E ×250

Fig. 2. Neoplastic elements are characterized by pleomorphic nuclei with medium-sized or prominent nucleoli and by abundant pale cytoplasm. Reed-Sternberg – like cells are present among tumor sheets (*arrow*). H-E ×400

Fig. 3. Fairly regular rims of small, normal-appearing lymphocytes surround anaplastic large cells. Sparse histiocytes are also noticeable. H-E ×400

Fig. 4. Neoplastic cells show strong membrane and cytoplasmic expression of CD15/Leu-M1 antigen. Immunoalkaline phosphatase (APAAP) method ×600

and more recently ascribed to the cluster 15 of leukocyte differentiation antigens, is normally expressed by cells of the myelomonocytic lineage (Hsu and Jaffe 1984). This antigen corresponds to a sugar moiety linked to membrane or cytoplasmic lipids and proteins. On the basis of its resistance to routine fixation and embedding procedures, the CD15/Leu-M1 antigen has been evaluated extensively in samples of human neoplastic tissues. The frequent expression of this antigen by RS cells produced preliminary reports that put forward CD15/Leu-M1 antigen as being the most reliable marker in HD (Hsu and Jaffe 1984). However, subsequent studies have demonstrated that CD15/Leu-M1 positivity is also found in other neoplastic lymphoproliferative disorders, including high grade T- and B-cell lymphomas (Meis et al. 1986), as well as in cases of carcinoma (Sheibani et al. 1986). Recently, immunoreactivity for the CD15/Leu-M1 antigen has been reported in one of three ALC-L cases, expressing T-lineage markers (Hall et al. 1988). In this case, a preliminary enzyme digestion was required to obtain positive immunostaining. Our results indicate that a strong expression of the CD15/Leu-M1 antigen may be detected in a certain proportion of cases of Ki-1 ALC-L without any enzyme treatment. This finding clearly stresses the unreliability of CD15/Leu-M1 staining as a tool for distinguishing between Ki-1 ALC-L and HD. Both the immunohistochemical and morphological features of our cases emphasize that in some instances Ki-1 ALC-L may be closely related to HD. As a matter of fact, all the cases herein reported displayed histological features consistent with high grade malignant lymphoma, but also showed morphologic findings typically observed in HD. In particular, the pleomorphism of the neoplastic populations, mainly composed of large to medium-sized anaplastic cells, the sinus infiltration with sparing of follicles, the cohesive appearance of the infiltrates and the high mitotic index were similar to those observed in the so-called common type of Ki-1 ALC-L (Second International Workshop on Ki-1 Anaplastic Large Cell Lymphoma 1988). However, neoplastic elements often showed the features of RS cells and were frequently surrounded by a fairly regular rim of normal-appearing small lymphocytes, as seen in HD.

In conclusion, our cases were characterized by morphological and immunohistochemical features intermediate between HD and Ki-1 ALC-L. As in some cases of ALC-L related to HD (Pileri et al. 1989), these findings may reflect blastic transformation of RS cell clones. Sundeen et al. (1988) have recently reported the possibility that lymphocyte predominant HD may precede or transform into non-Hodgkin's lymphoma of large cell type and B-cell derivation. Our results suggest that such a progression may also take place between HD and Ki-1 ALC-L. Our findings, however, differ from those of Sundeen et al. (1988) In that Ki-1 ALC-L was preceded by nodular sclerosing HD and displayed T-cell phenotype. Furthermore, while in Sundeen's series the large cell lymphomatous component did not affect the clinical course, which was comparable to that seen in lymphocyte predominant HD, in our series the histological progression was associated with the biological progression of the disease.

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