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Paraffin section immunohistochemistry in the diagnosis of Hodgkin's disease and anaplastic large cell ($CD30^+$) lymphomas

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Summary. Morphological and immunohistological studies were carried out on a series of 137 lymphomas including $CD30^+$ anaplastic large cell (ALC) lymphomas (48 cases) and non-lymphocyte predominant Hodgkin's disease (HD) (89 cases), with the aim of assessing in situ expression of a combination of antibodies including anti-CD30/BerH2, epithelial membrane antigen (EMA), CD15 and CD45, in addition to other monoclonal antibodies suitable for paraffin tissues. A greater proportion of cases of ALC lymphomas than of HD exhibited positivity for CD45 (91.7% vs 17.6%), EMA (56.2% vs 4.5%), CD43 (53.6% vs 13.1%) and CD45RO (39.5% vs 3.5%), whereas Reed-Sternberg (RS) cells in HD most frequently expressed CD15 (93.2% vs 20.8%) antigen. Moreover, in 35 of 48 (72.9%) ALC lymphomas tumour cells expressed the $CD30^+$, $CD45^+$, $CD15^-$, EMA^- or $^+$ phenotypic profile, while in the same percentage (62/85) of HD cases RS cells were found to express the $CD30^+$, $CD45^-$, $CD15^+$, EMA^- profile. This study suggests that the differential expression of CD45, EMA, and CD15 may be used in the separation of ALC lymphomas and HD. However, co-expression of CD30, CD45 and CD15 antigens by RS cells in HD (14/85 cases, 16.5% in this series) and by tumour cells in ALC lymphomas (9/48 cases, 18.7% in this series) may be encountered in a non-negligible fraction of cases.

Key words: Hodgkin's disease – Anaplastic large cell lymphoma – Immunohistochemistry – In situ immunophenotyping – Monoclonal antibodies

Introduction

Ki-1 (later designated CD30) antigen, an activation-associated lymphocyte antigen (Stein et al. 1985) that is not lineage specific, was first recognized on Hodgkin and Reed-Sternberg (HRS) cells by Stein et al. (1982) using a monoclonal antibody (mAb) raised against the Hodgkin's disease (HD)-derived cell line L428. Subsequently, in situ expression of CD30/Ki-1 antigen was demonstrated in anaplastic large cell (ALC) lymphomas of either T- or B-cell origin that were therefore designated as Ki-1, ALC lymphomas (Stein et al. 1985); before the Ki-1 antibody had become available these lymphomas were variously diagnosed as malignant histiocytosis, metastatic carcinoma, melanoma or HD (Agnarsson and Kadin 1988; Pallesen 1990; Schwarting et al. 1989; Stein et al. 1985).

Because $CD30^+$ ALC lymphoma cells exhibit considerable morphological resemblance to HRS cells of HD in most cases (Agnarsson and Kadin 1988; Hall et al. 1988; Rosso et al. 1990) attempts to find morphological and immunohistological criteria to distinguish between these two lymphomas – especially between $CD30^+$ ALC lymphomas containing a proportion of HRS-like cells and lymphocyte-depleted variants of HD – have been performed (Hall et al. 1988; Leoncini et al. 1990; Rosso et al. 1990; Stein et al. 1991). However, diagnostic difficulties are increased by the close immunophenotypic similarities shared by ALC lymphomas and HD (Agnarsson and Kadin 1988; Weiss et al. 1988). Apart from their common expression of the CD30/Ki-1 antigen, both ALC lymphomas and HD usually show positive immunostaining for activation antigens, and may express B- or T-cell-associated antigens (Agnarsson and Kadin 1988, 1989; Angel et al. 1987; Chan et al. 1989; Delsol et al. 1988; Drexler et al. 1989; Falini et al. 1987; Griesser et al. 1987; Kaudewitz et al. 1989; Schmid et al. 1991; Schnitzer et al. 1988; Tashiro et al. 1989).

The present study reports the application of a combination of antibodies including anti-CD30/BerH2, CD15/LeuM1, epithelial membrane antigen (EMA), CD45/leucocyte common antigen (LCA), and other mAbs which are expected to identify T- or B-cell lineage on routinely processed tissues, with the aim of establishing the practical value of these markers in the diagnosis of HD and ALC lymphomas and in the separation of these entities.

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Materials and methods

Morphological and immunohistological studies were carried out on a series of 137 lymphomas occurring in adult patients. They included $CD30^+$ ALC lymphomas (48 cases) and HD (89 cases). The morphological criteria used for the identification of ALC lymphomas were those described by Agnarsson and Kadin (1988). The Rye modification of the Lukes and Butler classification was used to classify HD (Lukes et al. 1966). Lymphocyte predominant HD was not included in this study, since this histological subtype seems to be a phenotypically distinct (Chittal et al. 1988) and is possibly an unrelated disease.

In all cases mAbs suitable for paraffin tissues – LCA (CD45), BerH2 (CD30), LeuM1 (CD15), EMA, vimentin, LN1 (CDw75), LN2 (CD74), LN3, L26 (CD20), MB1/MT2 (CD45R), MB2, CD3, UCHL1 (CD45RO), Leu22/MT1 (CD43), KP1 (CD68), anti-cytokeratin (MNF116), – were used, as previously reported (Carbone et al. 1990a). In addition, for BerH2, vimentin and CD3 antibodies the avidin-biotin-peroxidase complex (ABC) method was employed by using the ABC Elite kit supplied by Vector (Burlingame, Calif., USA). The immunoreactivity along with the source of all these commercially available antibodies have been reported in separate papers (Carbone et al. 1990a, c, 1992). A case was considered to show positive staining if unequivocal staining for that antigen was demonstrated on several HRS cells, according to Agnarsson and Kadin (1989). In several cases of both ALC lymphoma and HD groups, frozen section material was available for study. Data from the immunophenotype on frozen sections were used only to confirm findings and are not included in this report.

Results

The results from staining 48 cases of ALC lymphoma are shown in Table 1 and compared with 89 cases of HD including the major histological subtypes, with the exception of lymphocyte predominant HD.

In 13 cases a presumptive T-phenotype was ascribed on the basis of the presence of CD43 and CD45RO and/or CD3 immunoreactivity on the tumour cells, whereas in 16 cases ALC lymphoma cells showed CDw75 and/or CD20 B-cell-associated antigens. Fourteen cases could not be categorized using the antibodies available. In 5 cases ALC lymphoma cells expressed the CD68 histiocyte-associated antigen; tumour cells in these cases exhibited either T-cell (1 case) and B-cell (1 case) origin or null phenotype (3 cases). Two of these cases have been reported previously (Carbone et al. 1990a).

In all cases every neoplastic cell stained with the BerH2 (CD30) antibody (Fig. 1); the staining was intense, on the cell membranes, and commonly associated with a dot-like pattern in the paranuclear Golgi area. The ALC lymphoma cells immunoreacted with CD45 (Fig. 2) and CD74 mAbs in almost all cases, whereas immunoreactivity with vimentin, MB2, LN3 and EMA (Fig. 3) antibodies was noted in more than half of the evaluated cases (see Table 1). In 10 cases (20.8%) anaplastic cells were found to express CD15 (Fig. 4); the staining was on the cytoplasm with a diffuse or a dot-like pattern. In the majority (7/10) of $CD15^+$ cases, 30–50% of malignant cells were labelled.

Of considerable interest was the expression of the $CD30^+$, $CD45^+$, $CD15^-$, $EMA^{+\text{ or }-}$ profile by tumour cells in 35 of 48 (72.9%) ALC lymphomas, while the

Table 1. Immunophenotypes in cases of $CD30^+$ anaplastic large cell (ALC) lymphomas and Hodgkin's disease (HD)

Histological diagnosis	No. of cases	Immunohistological markers expression (no. of positive cases/no. of tested cases)														
		CD30	CD45	CD15	EMA	LN3[a]	Vim	CDw75	CD74	CD45R	MB2[a]	CD20	CD3	CD43	CD45RO	CD68	MNF116
ALC lymphoma	48	48/48	44/48	10/48	27/48	28/35	35/44	20/43	44/48	15/41	37/48	15/28	7/43	22/41	17/43	5/46	0/37
HD[b]	89																
NS	65	64/65	13/63	61/65	2/65	45/58	50/64	23/61	65/65	1/64	22/64	8/47	0/32	9/60	1/63	0/52	0/11
MC	18	17/18	1/17	16/18	1/18	11/17	7/18	4/18	18/18	0/17	6/18	2/13	1/ 9	2/18	2/18	0/14	0/ 5
LD	6	6/ 6	1/ 5	6/ 6	1/ 6	5/ 5	4/ 6	2/ 6	6/ 6	0/ 5	1/ 6	1/ 6	1/ 3	0/ 6	0/ 5	0/ 4	0/ 1

[a] No cluster of differentiation assigned
[b] Reaction with the respective antibody of Hodgkin's and Reed-Sternberg cells is reported

NS, Nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depletion

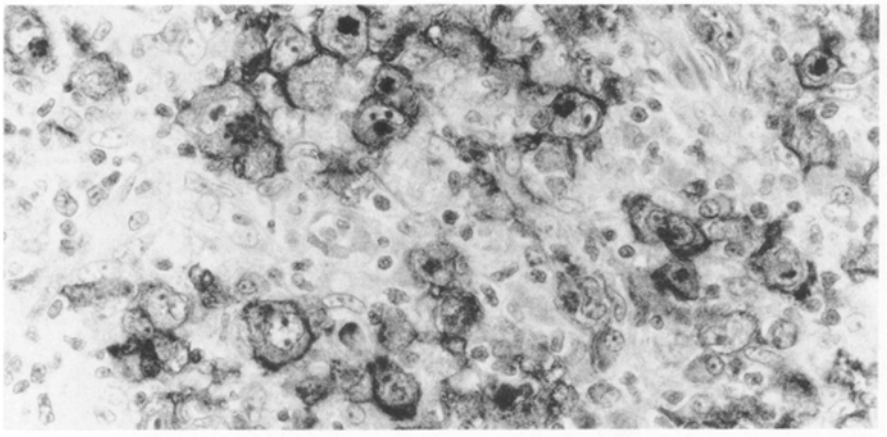

Fig. 1. Anaplastic large cell lymphoma. Neoplastic cells stain with the BerH2 (CD30) antibody. Large cells show membrane labelling and paranuclear dot-like reaction product. Bouin-fixed, paraffin-embedded section, avidin-biotin-peroxidase complex immunostaining, haematoxylin counterstain, ×630

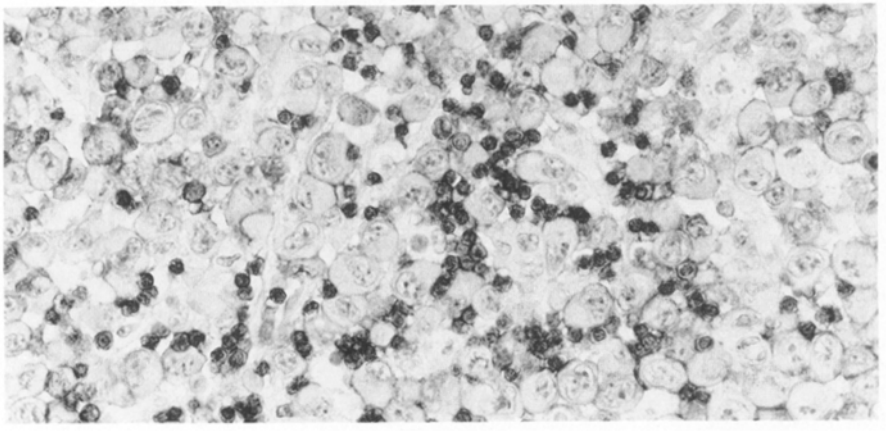

Fig. 2. Anaplastic large cell lymphoma. Nearly all anaplastic large cells show a membrane staining for CD45. Note positive strong staining of surrounding small lymphocytes. Bouin-fixed, paraffin-embedded section, avidin-biotin-peroxidase complex immunostaining, haematoxylin counterstain, ×400

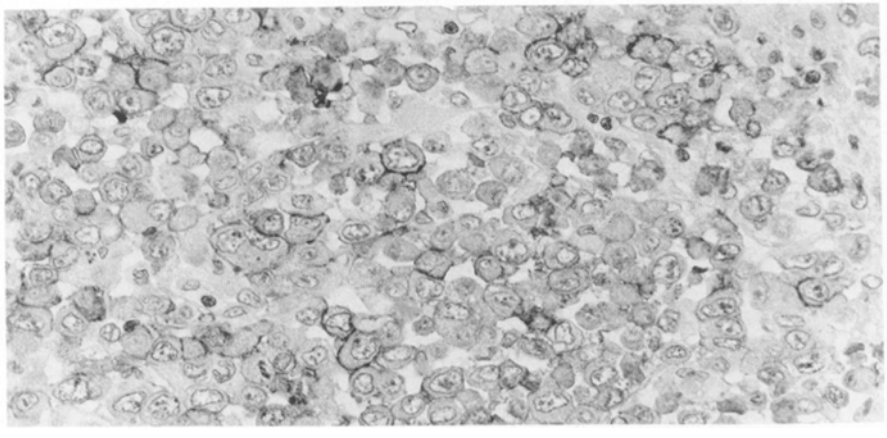

Fig. 3. Anaplastic large cell lymphoma. Staining pattern for epithelial membrane antigen is of membranous and contiguous cytoplasmic type. Bouin-fixed, paraffin-embedded section, avidin-biotin-peroxidase complex immunostaining, haematoxylin counterstain, ×400

expression of the $CD30^+$, $CD45^+$, $CD15^+$, $EMA^{+\text{ or }-}$ profile was found in 9 of 48 (18.7%) cases. Other phenotypes were observed in the remaining 4 cases (see Table 2).

HD cases were subtyped according to the Rye classification (Lukes et al. 1966) as follows: nodular sclerosis (NS), 65; mixed cellularity (MC), 18; and lymphocyte depletion (LD), 6. Cases of each subtype of HD staining positively for BerH2 (CD30), CD45, CD15, EMA, and the various markers tested, including B- and T-cell markers, are shown in Table 1. In 33 cases staining of some or the majority of HRS cells with antibodies that recognize antigens on B-lymphocytes (CDw75, 29 cases; MB2, 29 cases; CD20, 11 cases) was seen. These cases included 26 of the 62 NS, 5 of the 18 MC and 2 of the 6 LD. Regardless of subtype, CD74 or LN3 were found to be expressed in all cases or in a high proportion of cases, respectively; whereas CD43, CD45RO and CD3 T-cell-associated antigens were found to be expressed only in a small fraction of cases (13.1%, 3.5% and 4.5%, respectively). In 61 of 88 cases (69.3%) HRS cells were found to express vimentin; however, in the NS subtype vimentin expression was found in 50 of 64 cases (78.1%). Only in 1 case was staining with CD45R

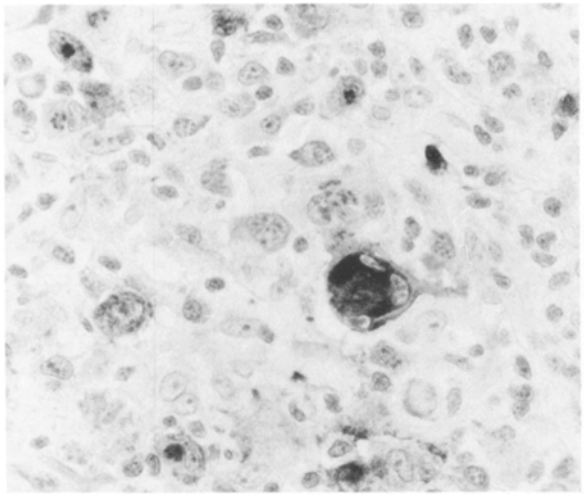

Fig. 4. Anaplastic large cell lymphoma. Some anaplastic large cells show a cytoplasmic staining for anti-CD15 (LeuM1) antibody with a dot-like paranuclear positivity. Bouin-fixed, paraffin-embedded section, avidin-biotin-peroxidase complex immunostaining, haematoxylin counterstain, × 630

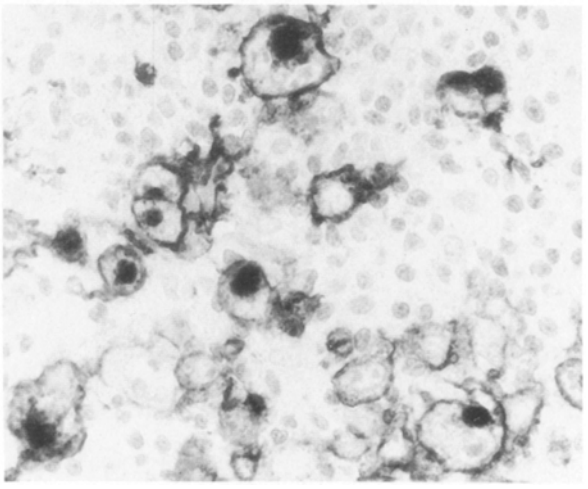

Fig. 5. Hodgkin's disease, nodular sclerosis subtype. Reed-Sternberg cells are strongly positive for anti-CD15 (LeuM1) antibody. The staining pattern is clearly membrane-associated, with a dot-like paranuclear (Golgi area) positivity. Bouin-fixed, paraffin-embedded section, avidin-biotin-peroxidase complex immunostaining, haematoxylin counterstain, × 630

Table 2. Major immunophenotypes of anaplastic large cell (ALC) lymphomas and Hodgkin's and Reed-Sternberg cells in Hodgkin's disease, as shown by the application of a combination of markers on paraffin sections

Immunophenotypes[a]	ALC lymphomas	Hodgkin's disease		
		NS	MC	LD
CD30+ CD45+ CD15− EMA+	19/48	–	–	–
CD30+ CD45+ CD15− EMA−	16/48	1/63	–	–
CD30+ CD45+ CD15+ EMA+	6/48	–	–	1/5
CD30+ CD45+ CD15+ EMA−	3/48	12/63	1/17	–
CD30+ CD45− CD15− EMA−	2/48	3/63	1/17	–
CD30+ CD45− CD15+ EMA−	–	44/63	14/17	4/5

[a] Other immunophenotypic profiles included:
CD30+ CD45− CD15+ EMA+ in 2/63 NS-HD and 1/48 ALC lymphomas;
CD30− CD45− CD15+ EMA− in 1/63 NS-HD;
CD30+ CD45− CD15− EMA+ in 1/48 ALC lymphomas; and
CD30− CD45− CD15− EMA− in 1/17 MC-HD
NS, Nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depletion; EMA, epithelial membrane antigen

present, whereas no staining with CD68 or MNF116 was observed in any case.

Both anti-LeuM1 (CD15) and BerH2 (CD30) mAbs showed parallel membranous and dot-like cytoplasmic staining patterns (Fig. 5). Almost all cases of HD were found to express the CD15 antigen (83/89, 93.2%). BerH2 (CD30) was expressed more frequently than CD15. In the NS, MC and LD groups, 20–75% of the HRS cells showed a moderate to strong reactivity for BerH2 (CD30). A slight to moderate reactivity in the plasma membrane for CD45 was seen in 13 of 63 cases of NS (20.6%) and rarely in the other cases. EMA antigen was rarely expressed in the HD cases (4/89, 4.5%).

It was noteworthy that the expression of the $CD30^+$, $CD45^-$, $CD15^+$, EMA^- profile was found in 62 of 85 (72.9%) cases (Table 2), while the expression of the $CD30^+$, $CD45^+$, $CD15^+$, $EMA^{-\text{ or }+}$ profile was observed in 14 of 85 (16.5%) HD cases. Other less frequent phenotypic profiles were encountered in the remaining 9 evaluated cases (see Table 2).

Discussion

ALC lymphoma, first described as an entity in 1985 by Stein et al., is consistently associated with expression of the Ki-1/CD30 antigen. However, CD30 antigen which is also expressed in many cases of immunoblastic T-cell lymphoma and pleomorphic T-cell lymphoma and in some B-cell lymphomas (Schwarting et al. 1989), may be found in almost all HD cases (Carbone et al. 1990b; Chittal et al. 1988; Ree et al. 1989; Stein et al. 1985).

ALC lymphomas are heterogeneous in their cell lineage (O'Connor et al. 1987). Previous reports have demonstrated variable phenotypes, most frequently T-cell (Agnarsson and Kadin 1988; Chan et al. 1989; Delsol et al. 1988; Kaudewitz et al. 1989; Schnitzer et al. 1988; Tashiro et al. 1989). Morphological features of these lymphomas include tumour cell pleomorphism, sinus infiltration, a trabecular pattern, fibrosis, single cell necrosis, and a prominent plasma cell infiltrate (Agnarsson and Kadin 1988; Carbone et al. 1990a; Stein et al. 1985) in addition to HRS-like cells (Agnarsson and Kadin 1988; Carbone et al. 1990a).

In the last few years, several reports have stressed difficulty in the morphological recognition of ALC lymphomas (Agnarsson and Kadin 1988; Carbone et al. 1990a; Hall et al. 1988; Leoncini et al. 1990; Stein et al. 1991; Weiss et al. 1988). In particular, cases of ALC lymphoma with fibrosis and HRS-like cells are not easily to distinguish from the NS subtype of HD; however,

the syncytial variant of the NS type of HD may be indistinguishable from ALC lymphoma (Rosso et al. 1990). It is noteworthy that the ALC lymphomas and HD share close immunophenotypic similarities (Agnarsson and Kadin 1988; Weiss et al. 1988). Recent studies have demonstrated that HRS cells as tumour cells in ALC lymphoma may express B- or T-cell-associated antigens (Agnarsson and Kadin 1989; Angel et al. 1987; Drexler et al. 1989; Falini et al. 1987; Griesser et al. 1987; Schmid et al. 1991; Weiss et al. 1986) in addition to CD15 (Hall and D'Ardenne 1987; Hsu and Jaffe 1984) and CD45 (Chittal et al. 1988), while in a significant proportion of cases HRS cells have been found to be negative for all the lymphoid-associated antigens (Agnarsson and Kadin 1989; Falini et al. 1987). The occurrence of cases characterized by morphological and immunohistochemical features intermediate between HD and ALC lymphoma has also been reported (Leoncini et al. 1990; Rosso et al. 1990; Stein et al. 1991).

In the present study 89 and 48 cases showed histological features consistent with the conventional diagnosis of HD and ALC lymphomas, respectively. In paraffin sections of fixed tissue 20–75% HRS cells of nearly all HD cases, and every atypical cell and HRS-like cell of all ALC lymphomas reacted with anti-CD30 mAb.

Major differences between HD and ALC lymphomas were found with the use of CD15, CD45 and EMA mAbs. Anti CD15 mAb stained HRS cells in 83 of 89 (93.2%) HD cases, but it stained atypical cells only in 10 of 48 (20.8%) ALC lymphomas; an opposite pattern of staining was obtained with CD45 antibody, ALC lymphoma cells showing CD45 expression more often than did HRS cells of HD (44/48, 91.7% vs 15/85, 17.6%). Immunoreactivity with EMA antibody was noted in 27 of 48 (56.2%) ALC lymphoma cases and in only 4 of 89 (4.5%) HD cases. Moreover, CD43 and CD45RO T-cell-associated antigens were found to be expressed in 22 of 41 (53.6%), and 17 of 43 (39.5%) ALC lymphomas whereas both these antigens were found to be expressed by HRS cells only in a small proportion of HD cases (see Table 1). Immunoreactivity with CD45R, CD3 and CD68 was noted in 15 of 41 (36.6%), 7 of 43 (16.3%) and 5 of 46 (10.9%) ALC lymphomas, whereas these antigens were exceptionally present or absent in HD cases. No substantial differences were found concerning the expression of the other antibodies tested, including vimentin. Vimentin expression by ALC lymphoma cells and HRS cells of HD has been reported in recently published papers (Carbone et al. 1990b; Gustmann et al. 1991). In this study immunoreactivity with vimentin was noted in a high proportion of the evaluated HD (69.3%) and ALC lymphoma (79.5%) cases.

Thus a significantly greater proportion of cases of ALC lymphomas than of HD exhibited positivity of atypical large cells for CD45, EMA, CD43 and CD45RO, whereas HRS cells in HD most frequently expressed CD15 antigen (see Table 1). These data confirm the findings of other authors (Agnarsson and Kadin 1988; Chan et al. 1989; Chittal et al. 1988; Hall et al. 1988; Leoncini et al. 1990; Penny et al. 1991), including the results of a previous study (Delsol et al. 1988) indicating that expression of CD15 antigen could be detected on up to 20% of cases of ALC lymphomas. CD15 staining in the tumour cells of ALC lymphomas differed from that in HRS cells of HD because it usually lacked membrane reactivity. In this study the application of a combination of antibodies anti-CD30, CD45, CD15 and EMA indicated that ALC lymphomas and HD could express two different major immunophenotypes, the $CD30^+$, $CD45^+$, $CD15^-$, $EMA^{+\text{ or }-}$ profile in 35 of 48 (72.9%) ALC lymphomas and the $CD30^+$, $CD45^-$, $CD15^+$, EMA^- profile in the same percentage (62/85) of HD.

These data suggest that the differential expression of CD45, EMA and CD15 may be used in the separation of these pathological entities in conjunction with careful histopathological assessment. In addition, the results indicate that expression of other heterogeneous, albeit less frequent, phenotypes by both these entities (see Table 2) together with the non-negligible co-expression of CD30, CD45 and CD15 antigens by HRS cells (in 14/85, 16.5% HD cases) and by ALC lymphoma cells (in 9/48, 18.7% cases) make a search for additional markers able to define the diagnostic significance of these phenotypic variants desirable.

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