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Reciprocal/dichotomic expression of vimentin and B cell differentiation antigens in Reed-Sternberg's cells

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Summary. An immunohistochemical study of 63 cases of Hodgkin's disease was undertaken using formalin-fixed paraffin embedded tissue sections. The antibodies used were against L26, LN-1, LN-2, EMA (epithelial membrane antigen), Leu-M1, Vimentin, UCHL-1, S-100, and lysozyme. Hodgkin's disease could be divided into three groups: the first group was LN-1 +/L26 +/vimentin −, the second LN-1 −/L26 +/vimentin +, and the third LN-1 −/L26 −/vimentin +). Sixteen cases of follicular lymphomas were also examined and were all positive for LN-1 and L26 and negative for vimentin. Thus the vimentin negativity of the first group, including 7 nodular lymphocyte-predominant cases, gives further evidence of their germinal center B-cell origin. Since vimentin is expressed mainly in the immature stage of B-lymphocytes, the second group of Hodgkin's disease may represent immature B-cell Hodgkin's disease. In the third group, vimentin was present in Reed-Sternberg's (RS) and Hodgkin's (H) cells in 45 of the 48 cases (92.5%). In none of 48 cases were these cells positive for S-100 or lysozyme, but strong vimentin-positivity still suggested monocytic or histiocytic origin. The results of our study suggest, at least, divergent origin of RS's and H's cells.

Key words: Hodgkin's disease – Nodular paraglanuloma – Vimentin – Immunoperoxidase

Introduction

Vimentin is the major intermediate filament polypeptide and is often utilized to differentiate epithelial and mesenchymal neoplasms immunohistochemically (Osborn et al. 1977; Osborn and Weber 1983). Vimentin is the most primitive intermediate filament and cells can switch production of specific intermediate filaments (along with differentiation) to either glial (Dahl et al. 1981; Prochiantz et al. 1982; Schnitzer et al. 1981; Yen and Fields 1981), myogenic (Bennet et al. 1979; Granger and Lazarides 1979) or epithelial lines (Herman et al. 1983; Ramaekers et al. 1983b). The main intermediate filament of haematopoietic cells is vimentin, and its quantiative expression and organization is highly variable within the different lineage of these cells. Thus, vimentin is well organized in monocytes into a rich filamentous network through the whole cytoplasm, while it disappears completely during the maturation of erythrocytes and megakaryocytes (Dellagi et al. 1983).

An immunohistochemical study of vimentin expression in lymphocytes and lymphoid organs has been reported by Giorno (1985). He found that lymphocytes in the periarteriolar lymphoid sheath of the spleen as well as macrophages and fibroblastic reticulum cells were reactive to monoclonal antibodies directed against vimentin. Giorno and Sciotto (1985) also reported that vimentin immunostaining was of limited usefulness in the diagnosis of non-Hodgkin's lymphomas.

Recently we found that many of RS's and H's cells were strongly positive with vimentin immunostaining in paraffin sections (Tamaru et al. 1988). This, coupled with the paucity of the similar studies on non-Hodgkin's lymphomas, prompted us to investigate vimentin expression in Hodgkin's and non-Hodgkin's lymphomas.

Materials and methods

Sixty-three cases of histopathologically proven non-treated Hodgkin's disease and sixteen cases of follicular lymphomas were selected for study. All tissues used in this study were formalin fixed and paraffin embedded. In most cases, the tissues

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were from lymph nodes. However, tissue from the spleen (one case of Hodgkin's disease) was also included.

Six lymph nodes with follicular hyperplasia were similarly processed and served as non-neoplastic controls. The antibodies used included mouse monoclonal antibodies against Leu-M1 (Becton-Dickinson), LN-1, LN-2 (all Techniclone International), L26, UCHL-1, EMA and Vimentin (all DAKO), and purified rabbit antibodies to Lysozyme and to S-100 recognizing both A and B subunits (all DAKO).

The blocks were sectioned at 5 μm, and the slides then deparaffinized through descending grades of ethanol. Following a ten-min wash in PBS (pH 7.2), the slides were incubated in a bath containing methanol and 0.5% H_2O_2 to inhibit endogenous peroxidase for 30 min, treated with normal serum (rabbit serum for monoclonal antibodies, swine serum for others) for 30 min, incubated first with each primary antiserum, washed, and then with biotinylated rabbit anti-mouse (for Leu-M1, LN-1, LN-2, L26, UCHL-1, EMA and Vimentin) or -swine (for others) anti-serum. After washing, the slides were incubated with the avidin-biotin peroxidase complex, which was developed using diaminobenzidine-HCl with 0.3% H_2O_2. The sections were then counterstained with methylgreen and dehydrated prior to microscopic evaluation. Each case was evaluated for the extent and nature of each antibody positivity.

Results

The results obtained in 63 cases of Hodgkin's disease of different histological types are summarized in Table 1.

LN-2 was considered to be present in RS's and H's cells in 56 of the 63 cases (88.9%), Leu-M1 in 40 cases, L26 in 15 cases, LN-1 in 10 cases, EMA in 6 cases, and Vimentin in 45 cases. L26 and LN-1 showed staining related to the surface membrane with, in some instances, intense localized positivity in discrete areas adjacent to the nucleus (Figs. 1, 2a). The staining of EMA was membranous with occasionally weak cytoplasmic staining. LN-2 showed diffuse cytoplasmic reactivity, as well as intense localized paranuclear staining. Leu-M1 exhibited an intense membrane and a diffuse cytoplasmic staining pattern, predominantly in the paranuclear regions. RS's and H's cells exhibited various staining patterns of vimentin such as diffuse positivity in the entire cytoplasmic area and localized positivity in the paranuclear region, or the combination of both (Figs. 3, 4a). Frequently, a crescent-shaped area along with a half circumference of the nuclear membrane or the cytoplasmic membrane was strongly stained (Figs. 4b, c).

Leu M1 and Vimentin, in cases of mixed cellular (MC), lymphocyte depleted (LD) and nodular sclerosing (NS) Hodgkin's disease, were expressed threefold or more frequently than in cases of lymphocyte predominant (LP) Hodgkin's disease (Table 1). None of L26 and LN-1 positive cases, which consisted of 7 nodular LP and 3 MC cases and only 5 of 15 L26 positive cases were vimentin positive (Table 2). Namely, all LN-1-positive cases (including all EMA-positive cases) were negative for vimentin and Leu-M1 (Figs. 2b, c).

One nodular sclerosis case of syncytial variant was L26 positive. However, this case was negative for LN-1 and EMA and positive for Leu-M1 and Vimentin.

LN-2 reactivity was seen within most RS's and H's cells in all four major subgroups of Hodgkin's disease. Of these 63 cases, however, non-reactivity for LN-2 was noted in 4 cases of mixed cellularity,

Table 1. Immunoreactivities of Reed-Sternberg and Hodgkin cells with antiseras on each subtype (%)

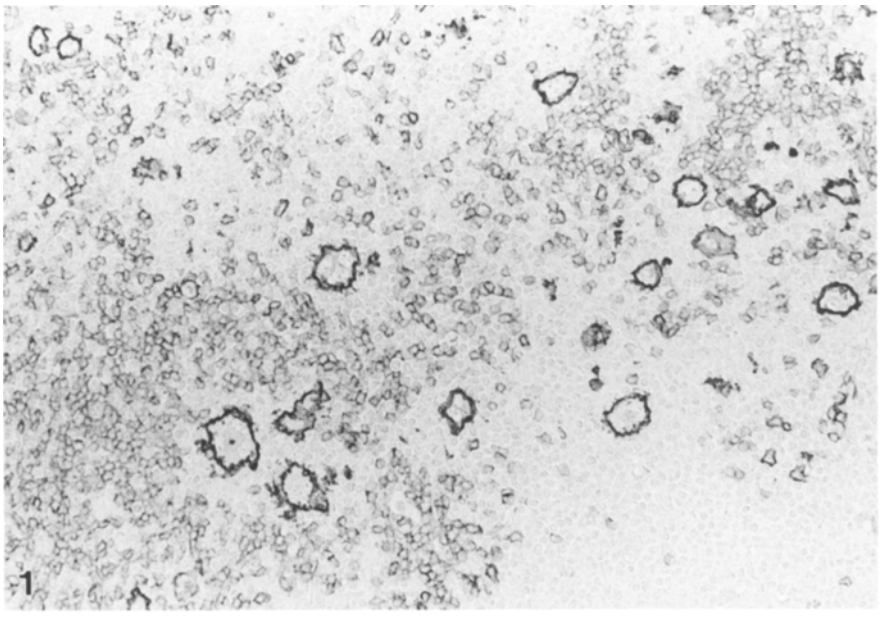
Subtype	Case No.	Reactivities of R-S and H cells with antisera					
		L26	LN-1	LN-2	EMA	Leu-M1	Vimentin
LP	11	7/11 (63.6)	7/11 (63.6)	11/11 (100)	4/11 (36.4)	3/11 (27.3)	4/11 (36.4)
MC	32	7/32 (21.9)	3/32 (9.4)	28/32 (87.5)	2/32 (6.3)	18/32 (56.3)	24/32 (75.0)
LD	5	0/5 (0)	0/5 (0)	4/5 (80.0)	0/5 (0)	5/5 (100)	5/5 (100)
NS	15	1/15 (6.7)	0/15 (0)	13/15 (86.7)	0/15 (0)	14/15 (93.3)	12/15 (80.0)
Total	63	15/63 (23.8)	10/63 (15.9)	56/63 (88.9)	6/63 (9.5)	40/63 (63.5)	45/63 (71.4)

LP, lymphocyte predominant; MC, mixed cellularity; LD, lymphocyte depletion; NS, nodular sclerosis

Table 2. L26 Positive cases

Case No	Age/sex (y)	Subtype	Reactivities of R-S and H cells with antisera				
			LN-1	LN-2	EMA	Leu-M1	Vimentin
1	8/M	LP (nod)	+	+	−	−	−
2	19/M	LP (nod)	+	+	−	−	−
3	57/M	LP (nod)	+	+	−	−	−
4	13/F	LP (nod)	+	+	+	−	−
5	17/M	LP (nod)	+	+	+	−	−
6	18/M	LP (nod)	+	+	+	−	−
7	35/M	LP (nod)	+	+	+	−	−
8	22/M	MC	+	+	+	−	−
9	42/F	MC	+	+	+	−	−
10	?/M	MC	+	+	−	−	−
11	4/M	MC	−	+	−	+	+
12	30/M	MC	−	+	−	+	+
13	54/M	MC	−	+	−	−	+
14	61/F	MC	−	±	−	−	+
15	20/F	NS (syn)	−	+	−	+	+

LP (nod), lymphocyte predominant (nodular subtype); MC, mixed cellularity; NS (syn), nodular sclerosis (syncytial variant)



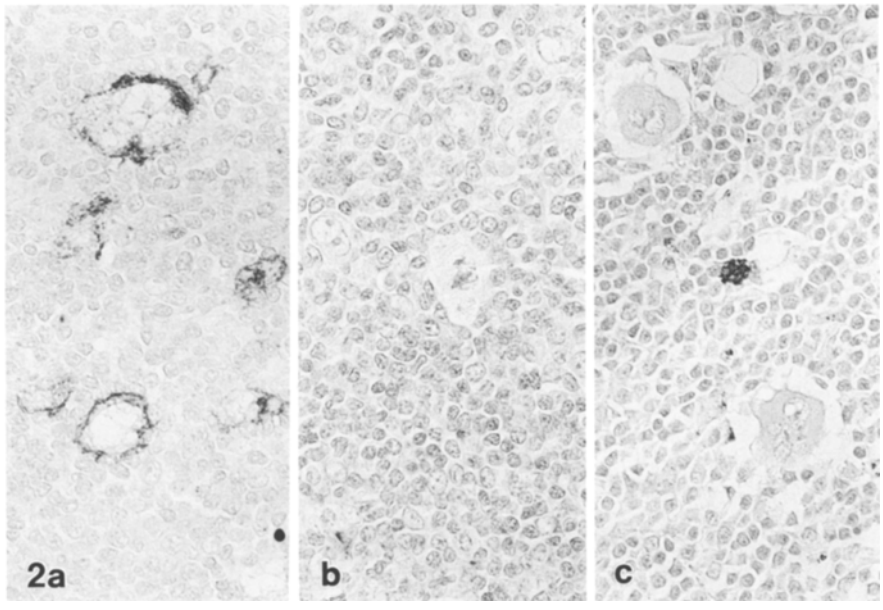


Fig. 1. Hodgkin's disease, nodular lymphocyte predominant type (corresponding to nodular paragranuloma). The RS's and H's cells demonstrating reactivity with L26 as strong positivity of the cell surface membrane and localized deposits adjacent to nucleus (avidin-biotin-peroxidase, counterstained with methyl-green, × 200)

Fig. 2a–c. Same case as in Figure 1. **a** LN-1 antibody staining showing same immunoreactive pattern to L26 antibody on RS's and H's cells (× 400). **b** and **c** None of RS's and H's cells showing positivity with vimentin and Leu-M1 (× 400). (all; avidin-biotin-peroxidase, counterstained with methyl-green)

1 case of lymphocyte depletion and 2 cases of nodular sclerosis Hodgkin's disease.

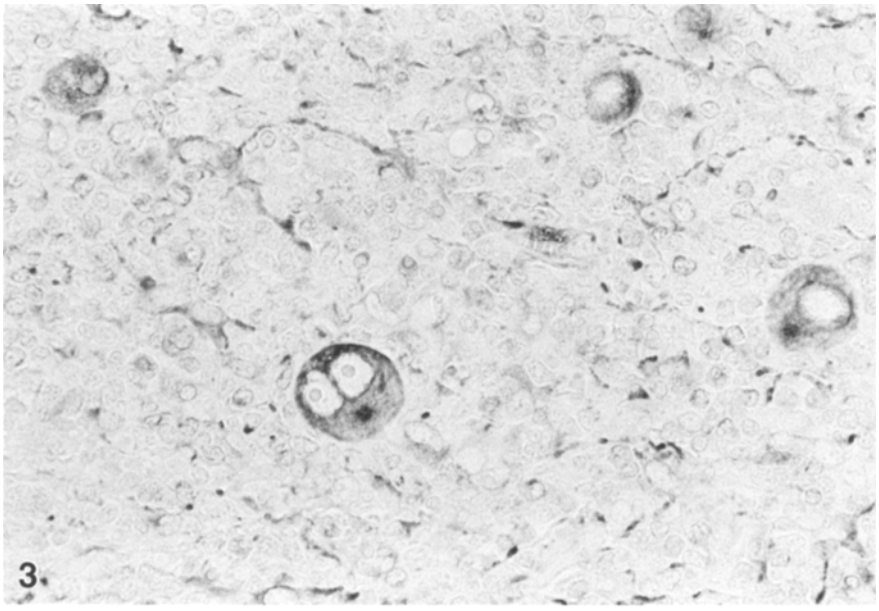
None of the cases showed positivity for S-100, UCHL-1 or lysozyme.

All of 16 follicular lymphomas were positive for LN-1, LN-2, and L26, and negative for vimentin (Fig. 5a), Leu-M1, UCHL-1, lysozyme and S-100.

Staining characteristics, of reactive lymph nodes with LN-1, LN-2, L26, UCHL-1 and S-100 antibodies, were similar to those previously reported (Epstein et al. 1984; Ishii et al. 1986; Norton et al. 1986; Watanabe et al. 1983). Vimentin was positive in reticular cells of the T-zone, the endothelial cells and some perivascular cells of post-capillary venules and capillaries, in macrophages and weakly so in follicular dendritic cells. Occasionally, small and medium-sized lymphocytes in the mantle zone and para-cortical area exhibited positivity on the nuclear membrane.

Discussion

According to Giorno and Sciotto (1985), less than 50% of non-Hodgkin's lymphomas were immunoreactive to monoclonal antibodies against vimentin. They did not find any correlation of vimentin expression with immunophenotypic or histopatho-



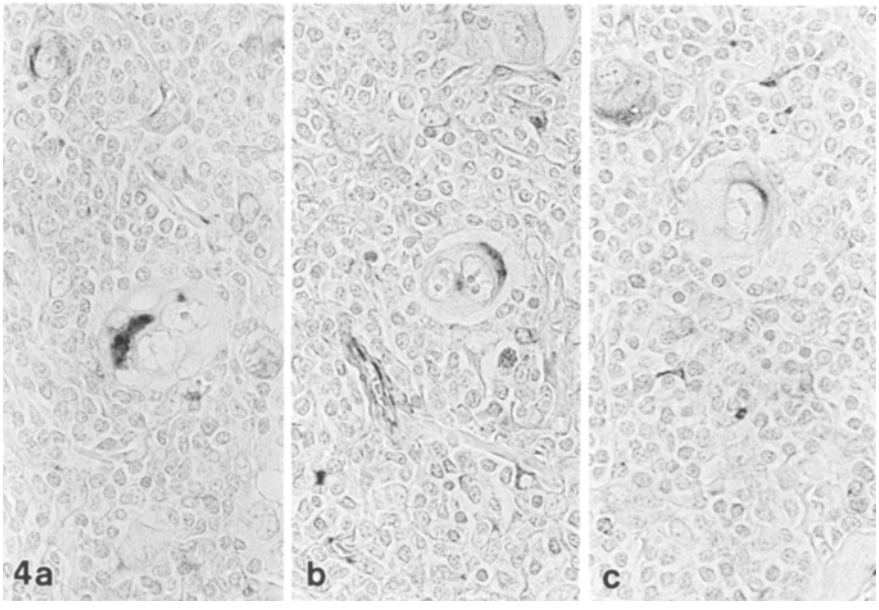


Fig. 3. RS's and H's cells showing intense staining with vimentin. A so-called mirror image diagnostic cell showing diffuse cytoplasmic and localized paranuclear staining. Fibroblastic reticulum cells, histiocytic cells and a few small lymphocytes also are immunoreactive for vimentin (avidin-biotin-peroxidase, counterstained with methyl-green, ×400)

Fig. 4. a RS's cell showing only localized paranuclear staining (×400). **b** and **c** Positive reactions in crescent-shaped area along with half circumference of the cytoplasmic membrane and the nuclear membrane of RS's cell (×400). (all; avidin-biotin-peroxidase, counterstained with methyl-green)

logical categories of malignant lymphomas. They studied 28 B-cell and 2 T-cell lymphomas but Hodgkin's disease was not included. Few other papers have dealt with vimentin expression in lymphomas, examined by polyclonal antibodies and immunofluorescence techniques. Among them, 5 and 4 Hodgkin's lymphomas were included in Kahn's (1983) and in Ramaeker's report (1983a) respectively, but whithout any detailed comments.

We found that in 45 of 63 cases of Hodgkin's disease, RS's and H's cells were strongly positive for vimentin. This frequency exceeded that of Leu-M1 reactivity in our series by almost 10 percent. It was found that the incidence of vimentin and Leu-M1 antigen expression in four subtypes of Hodgkin's disease showed a similar tendency; namely, only in 3 or 4 of 11 LP type were RS's and H's cells positive with vimentin or with Leu-M1 immunostaining, while 80 to 100 percent of NS and LD cases contained RS's and H's cells reactive to both antibodies.

RS's and H's cells are established as the neoplastic elements of Hodgkin's disease but the derivation of these cells remains speculative. It has been suggested by various investigators that these cells originate from macrophages (Kadin et al. 1978; Kaplan and Gartner 1977; Long et al. 1977; Mir and Kahn 1983; Mori et al. 1985; Oka et al.

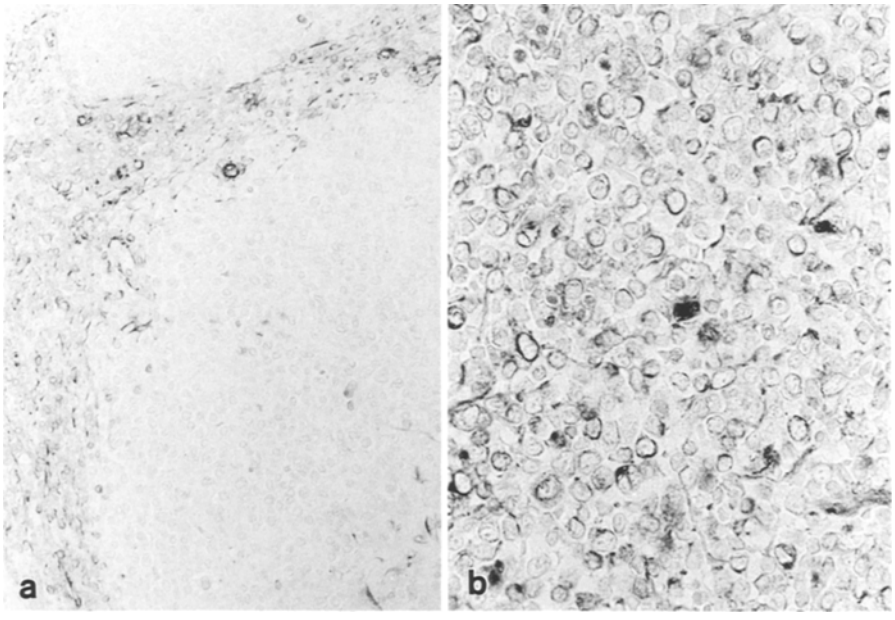


Fig. 5. a A case of follicular lymphoma stained with vimentin. None of lymphoma cells show positive reaction with vimentin. Outside the neoplastic follicle, capillaries and a few lymphocytes are vimentin positive (×200). **b** A case of diffuse large T-cell lymphoma. Lymphoma cells demonstrating reactivity with vimentin as positivity of a diffuse cytoplasmic pattern and crescent-shaped paranuclear pattern in one side of the cytoplasm (×400). (**a** and **b**; avidin-biotin-peroxidase, counterstained with methyl-green)

1988; Payne et al. 1982; Ree et al. 1981; Strauchen 1984; Stuart et al. 1977), T-lymphocytes (Biniaminov and Ramot 1974; Kadin et al. 1985; Stein et al. 1985), B-lymphocytes (Boecker et al. 1975; Cossman et al. 1977; Garvin et al. 1974; Kadin et al. 1974; Leech 1973; Linch et al. 1985; Pinkus and Said 1988; Poppema 1980; Poppema et al. 1985; Poppema et al. 1979a; Poppema et al. 1979b; Stein et al. 1986; Taylor 1976; Timens et al. 1986; Weiss et al. 1986), granulocytes (Stein et al. 1982b), interdigitating reticulum cells (Beckstead et al. 1982; Hsu et al. 1986; Hsu et al. 1985; Kadin 1982; Poppema et al. 1982) or unclassified cells (Stein et al. 1982a).

To elucidate the immunophenotypic characteristics of RS's and H's cells we employed 8 other antibodies, including those against L26, LN-1, LN-2, UCHL-1, EMA, Leu-M1, S-100 and lysozyme. When the results of immunostaining obtained with these different antibodies were compard, it was evident that there was a reciprocal relationship between expression of Leu-M1 or vimentin, and B-cell markers. The nodular variety of LP Hodgkin's disease has been suggested to be of follicular B-cell origin (Pinkus and Said 1988; Poppema et al. 1979b; Stein et al. 1986; Timens et al. 1986). In our study, 7 nodular LP cases were L26 and LN-1 positive and vimentin negative. Since LN-1 is known to be expressed by germinal B lymphocytes (Epstein et al. 1984), our finding is consistent with the views advanced by Poppema (1979b) and by Stein (1986). Moreover, we found that all 16 cases of follicular lymphomas were also negative for vimentin. Therefore, vimentin negativity of nodular LP cases provides further evidence of their germinal B-cell origin. Since Giorno and Sociotto's (1985) and Moller's (1988) papers are apparently the only two reports existant concerning vimentin expression of lymphoma cells studied with immunohistochemical methods, we investigated 37 B-cell and 10 T-cell lymphomas and 6 mycosis fungoides cases. Neoplastic cells in 7 of 10 T-cell lymphomas and 5 of 6 of the mycosis fungoides cases were strongly positive for vimentin immunostaining. These included two each of diffuse large cell type (Fig. 5b), mixed cell type and of HTLV-1 related pleomorphic type and one case of AILD-like T-cell lymphoma. Three other cases were weakly positive and only one case was completely negative. Among 37 B-cell lymphomas, 6 of 13 diffuse large cell lymphomas and one of 6 diffuse mixed and small cleaved cell cases were strongly positive and 26 other cases were negative for vimentin immunostaining. Giorno and Sociotto (1985) reported that 2 cases of follicular large cell lymphoma were vimentin-positive and Moller's report (1988) indicated that 2 of 18 follicular lymphomas were vimentin-positive. However, none of 16 follicular lymphomas, regardless of their cellular types, were positive in our series.

The data presented in this paper indicate that Hodgkin's disease can be divided into three types on the basis of different pattern of antigen expression by RS's and H's cells. The first of these (10 cases) is characterized by expression of L26 and LN-1 (often associated with EMA), and absence

of vimentin and Leu-M1. Seven of these 10 cases were nodular LP type. These cases can be interpreted as cases in which RS's and H's cells originated from germinal center B-cells. The second group (5 cases) expresses L26 and vimentin with the absence of LN-1 and EMA. In B lymphocytes, vimentin is expressed especially in their immature stage, while in T lymphocytes, monocytes and granulocytes, vimentin expression is retained through all stages of maturation (Dellagi et al. 1983). Therefore, the second group may represent such immature B-cell Hodgkin's disease. Leu-M1-positivity in 3 of 5 cases in this grop may due to aberrant gene expression. The third group which comprise the largest one (48 cases) shows expression of vimentin and/or Leu-M1 with the absence of L26, LN-1 and EMA. Mori et al. (1985) recently reported immunoelectron microscopic evidence of the presence of lysozyme and alpha-1-antitrypsin in the cytoplasm of RS's and H's cells. Activity of lysosomal enzymes (acid phosphatase) has also been observed in RS's and H's cells (Kaplan and Gartner 1977; Mikata et al. 1981). Recently Leu-M1 expression is recognized on some lymphomas and monocytic/histiocytic cells (Kornstein et al. 1986; Meis et al. 1986; Swerdlow and Wright 1986). Moreover, it is observed that LN-2 expresses on not only B-lymphocytes but also on monocytic/histiocytic cells (Epstein et al. 1984). Although in none of these 48 cases were RS's and H's cells positive to S-100 or lysozyme, strong positivity against vimentin antibody coupled with Leu-M1 positivity still suggest monocytic or histiocytic origin of these cells. The fact that the immunohistochemical properties of RS's and H's cells were not all alike was demonstrated only by using of 5 monoclonal antibodies. The results of our study suggest the divergent origin of these cells. For the determination of haematopoietic tumour cell lineage, results of phenotypic analysis must be judged carefully, since the problem of aberrant gene expression or lineage infidelity is known in these tumours (Smith et al. 1983). Although genotypic analysis of Hodgkin's disease have been reported with inconstant conclusions- (Mikata 1988) similar data should in future, shed the light on the nature of Hodgkin's disease.

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