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Anti-vimentin antibody reactivity with Reed-Sternberg cells of Hodgkin's disease*

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Summary. There are few data on the reactivity of Reed-Sternberg (RS) cells with antibodies against vimentin. In a preliminary survey of biopsy specimens from 16 cases of Hodgkin's disease (HD), we found that the anti-vimentin (V9) monoclonal antibody stained RS cells in 6 cases. We therefore examined vimentin expression on RS cells immunohistologically in 38 Bouin-fixed and paraffin-embedded lymph nodes with HD [lymphocyte predominance (LP) 4; nodular sclerosis (NS) 23; mixed cellularity (MC) 7; lymphocyte depletion (LD) 4]. The results were correlated with the histopathological features, the immunohistological phenotype of the RS cells, and the findings obtained from molecular genetics studies (available in 13 cases). RS cells were found to express strong and diffuse cytoplasmic staining for vimentin in 13 cases, all of the NS subtype. No differences in antigenic expression on RS cells were found between the vimentin-positive and negative cases within the NS subtype. DNA analysis revealed no B- or T-cell clonal populations in the tested samples. The results indicated that RS cells were immunostained by anti-vimentin (V9) antibody with a relatively high frequency, but only in the NS subtype of HD. This subtype, however, was heterogeneous according to vimentin immunostaining on RS cells. The significance of this finding concerning the RS cell origin in this subset is discussed.

Key words: Reed-Sternberg cells – Vimentin – Lymph node pathology – Immunohistology – DNA analysis

Introduction

The origin of the Reed-Sternberg (RS) cell of Hodgkin's disease (HD) remains undetermined (Anastasi and Variakojis 1988; Diebold and Audouin 1989; Lee 1987), although recent studies using sensitive immunohistochemical techniques have demonstrated that RS cells may express B- or T-cell-associated antigens (Agnarsson and Kadin 1989; Angel et al. 1987; Drexler et al. 1989; Falini et al. 1987; Kadin et al. 1988; Oka et al. 1988), in addition to some markers that were initially thought to be specific for HD including the CD 30 (Ki-1) antigen (Stein et al. 1985), CD 15 (Leu M1) (Carbone et al. 1986a; Hall and D'Ardenne 1987; Hsu and Jaffe 1984), CD 45 (leucocyte common antigen; LCA) (Chittal et al. 1988), and various activation antigens (Agnarsson and Kadin 1989; Diebold and Audouin 1989; Drexler et al. 1989). Moreover, there are reports of immunoglobulin gene rearrangements in some cases of HD, suggesting that these cases may be of lymphoid origin (Brinker et al. 1987; Drexler et al. 1989; Griesser et al. 1987; Weiss et al. 1986). In contrast, in a significant proportion of HD cases RS cells have been found to be negative for all of the lymphoid-associated antigens (Agnarsson and Kadin 1989; Falini et al. 1987), and gene rearrangement studies have revealed conflicting results (Knowles et al. 1986; Roth et al. 1988). The heterogeneity of marker expression found within the RS cell population may be related to the heterogeneity of the histological subtypes of the disease (Anastasi and Variakojis 1988; Carbone et al. 1987) which may help to explain the variable findings in molecular genetics studies (Agnarsson and Kadin 1989).

A previous study focussed on the microenvironmental organization of different stationary cells of the lymphoid tissues both in normal and pathological conditions. We employed an anti-vimentin (V9) monoclonal antibody (Osborn et al. 1984) to visualize fibroblastic reticulum cells (FRCs) in fixed and paraffin-embedded tissues (Gloghini et al. 1990). Since, to our knowledge, there are only sporadic and incomplete data in the literature regarding the reactivity of RS cells with antibodies against vimentin (Altmannsberger and Osborn 1987; Gabbiani et al. 1981; Norton et al. 1988; Simonton 1988) we performed a preliminary survey of biopsy specimens from 16 cases of HD. It was found that the V9 monoclonal antibody against vimentin stained RS cells

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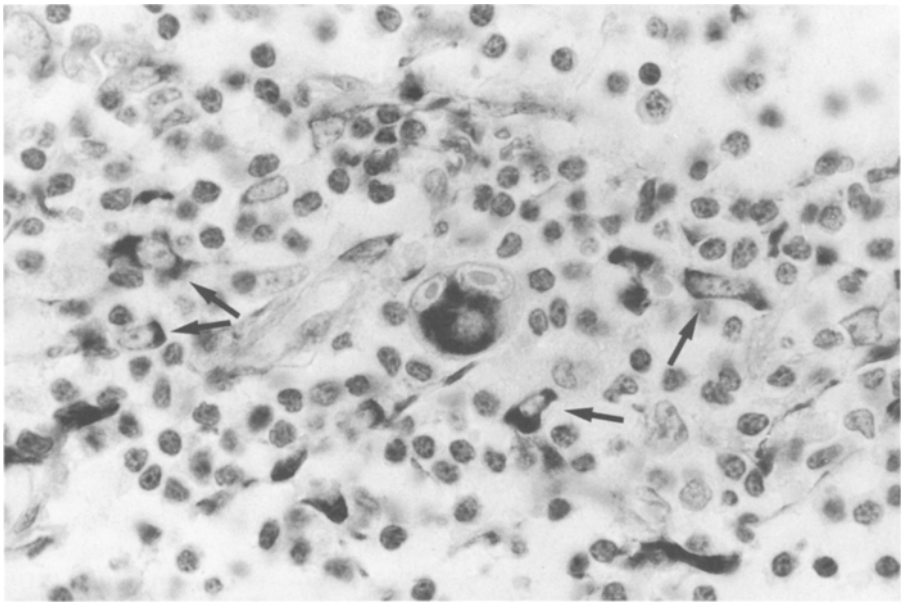

Fig. 1. A classic binucleated Reed-Sternberg cell shows strong and diffuse cytoplasmic positivity for vimentin. In addition, immunostaining for vimentin visualizes fibroblastic reticulum cells (*arrows*) and filamentous reticulum fibres. Bouin-fixed, paraffin-embedded section of lymph node with nodular sclerosing Hodgkin's disease; ABC; vimentin monoclonal antibody; haematoxylin counterstain; ×1,000 oil-immersion

in 6 specimens, all involved by nodular sclerosing HD (unpublished data). As a result of this finding, vimentin expression within the RS cell population was investigated in biopsy tissues from other cases and was correlated with the histopathological features, the immunophenotype of the RS cells and the findings available from molecular genetics studies.

Materials and methods

In our laboratory immunostaining for vimentin in combination with other antibodies is carried out routinely for diagnostic purposes. At the same time as the data presented were collected we tested 15 undifferentiated carcinomas, 56 sarcomas, 7 metastatic melanomas, 31 non-Hodgkin's lymphomas and 37 specimens (30 lymph nodes, 6 palatine tonsils, 1 lymphoid polyp of the large bowel) with reactive disorders. Such systematic examination has become necessary because of the widespread use of cell-differentiation markers in tumour pathology, particularly in the diagnosis of lymph node metastases and the need to document the distribution of vimentin in the various cell types present in normal and pathological tissues.

The biopsy specimens selected for study included 38 cases in which a pathological diagnosis of HD was established after examination of Bouin-fixed and paraffin-embedded sections routinely stained and immunohistologically labelled. Cases were subtyped histologically according to the Rye classification (Lukes et al. 1966).

Dewaxed sections were tested with a panel of selected antibodies, listed in Table 1 with their immunoreactivity. Fixed and paraffin-embedded tissues were used to obtain satisfactory morphological findings, particularly to detect RS cells clearly by employing anti-vimentin monoclonal antibody. Immunostaining was performed by using an avidin-biotin-peroxidase complex (ABC-Px) method (Hsu et al. 1981) as previously described (Carbone et al. 1986b). Negative controls were obtained by omission of the primary antibody and substitution with phosphate buffered saline. Since in each case variable numbers of RS cells stained positively with a given antibody, a case was considered to show positive staining if unequivocal staining for that antigen was demonstrated on several RS cells, according to Agnarsson and Kadin (1989).

Representative fresh samples were obtained from 13 cases. They were collected during standard diagnostic procedures according to our multiparametric approach to lymphoproliferative disorders (Carbone et al. 1989). These samples were snap-frozen in liquid nitrogen and stored at −80° C. Genomic DNA was extracted from frozen tissues as described by Ceccherini-Nelli et al. (1987).

Table 1. Monoclonal antibodies used in this study

CD	Antibody	Source	Main specificity
	Vimentin	Boehringer (Mannheim, FRG)	Cells of mesenchymal origin
45	LCA[a]	Dakopatts a/s (Glostrup, Denmark)	Majority of human leucocytes
15	Leu M1	Becton-Dickinson (Mountain View, Calif.)	Granulocytes, Reed-Sternberg cells
30	BerH2	Dakopatts a/s (Glostrup, Denmark)	Hodgkin's and Reed-Sternberg cells, activated T- and B-cells
w75	LN1	Clonab-Biotest (Dreieich, FRG)	B-cells of germinal centre, macrophages, epithelioid cells
74	LN2	Clonab-Biotest (Dreieich, FRG)	B-cells of germinal centre and mantle zone, dendritic reticulum cells (HLA invariant chain)
43	MT1	Clonab-Biotest (Dreieich, FRG)	T-cells, macrophages, myeloid cells, B-cell subset
45RO	UCHL1	Dakopatts a/s (Glostrup, Denmark)	T-cells, macrophages, myeloid cells

CD, Cluster of differentiation, when applicable
[a] Leucocyte common antigen

Table 2. Number of cases of Hodgkin's disease positive for Vimentin, Leucocyte Common Antigen (LCA), Leu M1, BerH2 and B- and T-cell-associated antigens according to subtype

Subtype	Total	Vimentin (V9)	LCA (CD45)	Leu M1 (CD15)	BerH2 (CD30)	LN1 (CDw75)	LN2 (CD74)	MT1 (CD43)	UCHL1 (CD45RO)
LP	4	0	4	0	0	4	3	1	0
NS	23	13	1	22	19	3	15	0	0
MC	7	0	0	5	2	1	3	0	0
LD	4	0	0	4	4	0	3	0	0
Total	38	13	5	31	25	8	24	1	0

LP, Lymphocyte predominance; NS, nodular sclerosing; MC, mixed cellularity; LD, lymphocyte depletion

Either 10 or 20 μg of DNA was digested with the appropriate restriction enzyme for analysis of gene rearrangements. Size-fractionation of DNA fragments, Southern blotting, molecular hybridization and autoradiography were carried out as described by Ceccherini-Nelli et al. (1987). The probes used were the following: Ig heavy chain: 2.5 kb EcoRI fragment specific for Ig-J_H region (Flanagan and Rabbitts 1982); Ig κ light chain: 0.6 kb SacI fragment specific for the C_κ region (Bentley and Rabbits 1983); Ig λ chain: 8 kb EcoRI fragment specific for the C_λ region (Rabbitts and Forster 1983); TCR 0.7 kb HindIII-EcoRI fragment containing the Joining ($J_{\gamma 1}$) region (Lefranc and Rabbitts 1985); TCRβ: 0.6 kb HindIII-EcoRI fragment specific for the C_β region (Sims et al. 1984).

Plasmids were grown and purified by standard methods. Specific fragments were purified by the low-melting agarose procedure as described (Ceccherini-Nelli 1987). Probes were ^{32}P labeled by the multiprime DNA labelling system (Amersham, Buckinghamshire, UK) at specific activity 10^9 cpm/μg.

A rearrangement was defined as having occurred if, after digestion with restriction endonucleases, a new band was detected on hybridization. All rearrangements were determined using at least two different restriction enzymes.

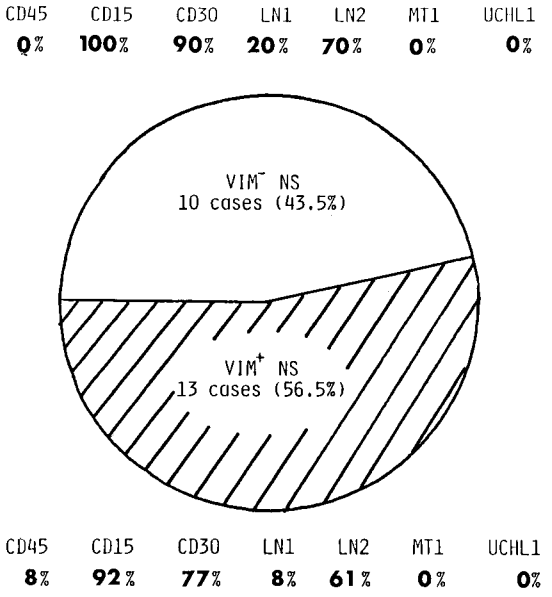

Fig. 2. Percentage of cases of nodular sclerosing (*NS*) Hodgkin's disease positive for the tested markers, according to the results of immunostaining for vimentin (*VIM*)

Results

Cases were subtyped according to the Rye classification (Lukes et al. 1966) as follows: lymphocyte predominance (LP), 4; nodular sclerosis (NS), 23; mixed cellularity (MC), 7; and lymphocyte depletion (LD), 4. Cases of each subtype of HD staining positively for CD45 (LCA), CD15 (Leu M1), CD30 (BerH2) and the various B- and T-cell markers tested are shown in Table 2.

Between 30% and 100% of the RS and Hodgkin mononuclear cells of all cases of LP showed a slight to moderate reactivity in the plasma membrane for CD45, whereas this positivity was rare in cases of NS and absent in the other cases. With the exception of the LP type, almost all cases of HD were found to express the CD15 (Leu M1) antigen, with 70–100% of the RS and Hodgkin mononuclear cells showing a strong reactivity in the plasma membrane and cytoplasm. CD30 (BerH2) was expressed less frequently than CD15 in both the NS and the MC groups and was not expressed in the LP cases. In the NS and MC groups, 20–75% of the RS cells showed a moderate to strong reactivity in the plasma membrane and cytoplasm for CD30 (BerH2). Regardless of subtype CD74 (LN2) and/or CDw75 (LN1) B-cell-associated antigens were found to be expressed in a high proportion of cases, with 60–90% and 15–60% of RS cells showing moderate to strong reactivity in the cytoplasm and plasma membrane. One case of LP subtype expressed both B- and T-cell (CD 43, MT1) antigens.

In 13 of the cases (34%) 20–70% of the RS cells and Hodgkin mononuclear cells were found to express vimentin (Table 2, Fig. 1). All these cases were of the NS type and represented more than half of the tested cases in this group (13/23; 56.5%). In the vimentin-positive cases one or more additional antigens were expressed. No substantial differences in antigenic expression on RS cells were found between the vimentin-antigen-positive and negative cases within the NS subgroup (Fig. 2).

Usually, the immunostained mononuclear or multinucleate RS cells exhibited strong and diffuse cytoplasmic positivity for vimentin (Fig. 1). In each case variable numbers of RS cells stained positively with vimentin antibody. Endothelial cells, FRCs, "histiocytes" (monocyte-macrophage related cells) and plasma cells were the

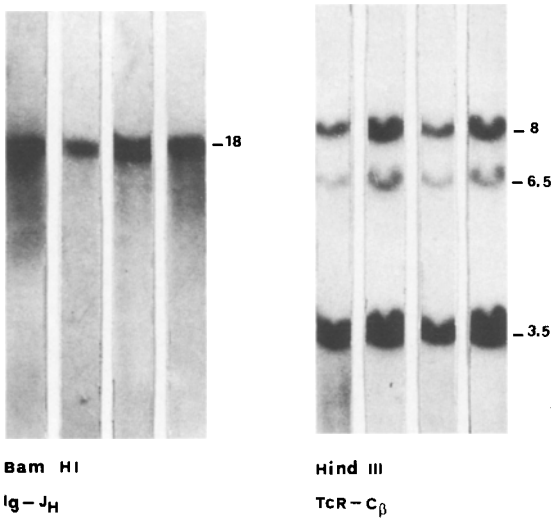

Fig. 3. Southern blot of genomic DNA from 4 cases of vimentin-positive Hodgkin's disease hybridized with TCR-C_β and Ig-J_H. DNAs were digested with the reported enzymes. Germ-line fragments are indicated in kilobase units

other cell types immunostained, while very few lymphocytes were immunoreactive. Epithelioid cells were variably immunostained. Elongate FRCs (Fig. 1) intimately attached to reticulum fibres exhibited strong cytoplasmic positivity for vimentin. Immunostaining for vimentin visualized their cytoplasmic extensions in addition to filamentous reticulum fibres which coursed between lymphocytes and, sometimes, between RS cells. Immunostained FRCs were particularly numerous in cases of NS.

Rearrangements of the Ig heavy and light chain genes and of TCRγ and TCRβ genes were analysed in 13 cases (7 of the NS, 2 of the LP, 2 of the MC and 2 of the LD subtypes), including 4 vimentin-positive cases. Organization of Ig and TCR loci was analysed by Southern blot hybridization analysis of the genomic DNA restriction fragments obtained by enzymatic digestions with at least two different restriction enzymes. The technique is sensitive and reliable enough to detect a B- and/or T-cell clonal proliferation when it represents about 1–2% of the cellular population in the pathological sample. Only germ-line bands were detected in all 13 cases with the Ig gene probes and the TCR probes (Fig. 3). Therefore no B- or T-cell clonal populations were present in the HD cases analysed.

Discussion

Gabbiani et al. (1981), in their report concerning immunochemical identification of intermediate-sized filaments in human neoplastic cells, mentioned that RS cells of a case of HD examined were stained by vimentin antibodies. Six years later Altmannsberger and Osborn (1987), in their review of mesenchymal tumour markers, stated that most Hodgkin's lymphomas were vimentin positive. Simonton (1988), reviewing her experience with a commercially available monoclonal anti-vimentin (BGAV) antibody reported that it labelled mononuclear and classic RS cells of HD uniformly. In neither review, however, were there detailed data about these findings. Recently, Norton et al. (1988), who studied 10 cases of malignant lymphomas and 1 case of HD of the NS subtype, diagnosed in infarcted lymphoid tissue, found that anti-vimentin (V9) antibody stained the tumour cells in HD. In contrast, RS cells failed to react with the anti-vimentin antibody 43βE8 used by Gown and Vogel (1985).

The present study demonstrates that RS cells were immunostained by anti-vimentin (V9) monoclonal antibody in one-third of the 38 analysed cases of HD. This relatively high frequency of vimentin antigen on RS cells in HD clearly indicates that this is not an occasional finding. It is noteworthy that vimentin antigen was present only in RS cells of NS subtype, and was absent in LP, MC and LD subtypes; moreover, vimentin expression was found only in a proportion of the NS cases regardless of the other immunophenotype findings (see Fig. 2).

Immunostaining reactions with other antibodies documented that CD45 (LCA) was usually negative on RS cells in NS, LD and MC subtypes; it was present only in LP cases and in one case of NS subtype; this case showed also positivity for CD15 (LeuM1), CD30 (BerH2), CDw75 (LN1), CD74 (LN2) antigens. The CD15 (LeuM1) antigen was present on RS cells in 82% of our cases, thus confirming its usefulness as a marker of HD. RS cells were found to express CD15 (LeuM1) antigen in 22 of the 23 cases of NS subtype. The CD30 (BerH2) antigen was expressed less frequently than CD15 (LeuM1) in the NS and MC groups. Both antigens were not expressed in the LP cases. A high frequency of CD74 (LN2) and/or CDw75 (LN1) B-cell antigens was found irrespective of the subtype of HD. Therefore, in this study V9 vimentin antibody selectively failed to immunoreact with RS cells of LP, MC and LD subtypes as both CD15 (LeuM1) and CD30 (BerH2) did in the LP cases and CD45 (LCA) in the MC and LD subtypes.

Vimentin is a 58 kDa protein originally isolated from mouse 3T3 fibroblasts (Franke et al. 1978). It is the most widely distributed intermediate-filament protein, since it is expressed in virtually all mesenchymal cells. The expression of vimentin should be related to the process of cell differentiation (Lazarides 1982; Osborn and Weber 1982) more than to tumour histogenesis (Brown et al. 1987). Different cell types in lymphoid tissues may express this antigen immunohistologically, and studies performed on frozen sections (Giorno 1985; Giorno and Sciotto 1985; Möller et al. 1988) as well as paraffin-embedded sections (Azumi and Battifora 1987; Gown and Vogel 1984) of lymphoid tissues have documented that monoclonal antibodies against vimentin are reactive with a number of cell types, including the FRCs. The results of our previous study (Gloghini et al. 1990) employing anti-vimentin (V9) monoclonal antibody in fixed and paraffin-embedded lymphoid tissues confirmed previous data, demonstrating that endothelial cells, FRCs and "histiocytes", especially of the tingible body macrophage type, were the main cell types immunostained, while very few lymphocytes were immunoreactive. How-

ever, by using the same anti-vimentin (V9) monoclonal antibody in frozen sections of reactive lymphoid tissues B- and T-cells expressed vimentin in amounts comparable to those of histiocytes, fibroblasts and endothelial cells (Möller et al. 1988) with the exception of germinal centre cells. Thus, the demonstration of vimentin expression in RS cells does not provide evidence of their origin. In fact, vimentin expression does not exclude the view that in this subset of NS cases RS cells may derive from lymphoid cells. The expression of CDw75 (LN1) and/or CD74 (LN2) B-cell-associated antigens and the CD30 (BerH2) antigen in RS cells within the subset of vimentin-positive cases could confirm this hypothesis. Recent studies, however, have indicated that the expression of aberrant B- or T-cell markers is not an uncommon finding in granulocyte/monocyte/histiocyte-related neoplastic cells (Hsu and Hsu 1989), and that CD30 expression is not an exclusive property of T- or B-cells, but it can be present in human macrophages (Andreesen et al. 1989; Hsu and Hsu 1989). Therefore, according to these recently published findings we can speculate that the vimentin expression on RS cells may indicate a non-lymphoid-cell origin taking into consideration the wide distribution of this intermediate-filament protein in the FRCs/histiocytes/monocytes-macrophages present in the lymphoid tissues.

Interestingly, an immunofluorescence study on fixed sections with a monospecific antiserum to fibronectin revealed abundant cytoplasmic fibronectin in RS cells from 5 patients with NS-HD (Resnick and Nachman 1981). Based on this finding, the authors concluded that the RS cell is derived from the macrophage cell line.

Data suggesting phenotypic heterogeneity in the RS cells among different cases of NS have been critically reviewed by Anastasi and Variakojis (1988). Variability of antigen expression in NS does not appear to be limited to markers associated with B- and T-cells. Leu M1 appears to vary in expression in the NS subtype as well (Chittal et al. 1988). In addition, reports of monocyte/macrophage/histiocyte antigen expression in HD support the possibility that there is a subset of cases of NS that have this phenotype (Anastasi and Variakojis 1988).

As immunophenotypic analyses have shown variable phenotypic expression, molecular genetics studies have demonstrated variable findings with respect to gene rearrangements indicating that among cases of NS-HD there is no specific genotype (Knowles et al. 1986; Brinker et al. 1987; Griesser et al. 1987; Roth et al. 1988). There were no rearrangements of either the immunoglobulin gene or the TCR gene in the 13 samples analysed in the present study, which also included 4 vimentin-positive NS cases.

In conclusion, the results of this study demonstrated that RS cells were found to express vimentin only in the NS subtype of HD, this finding being present in 56.5% of NS cases. The view that this histological subtype shows immunophenotypic heterogeneity has been further supported by the detection of a subset of cases in which RS cells expressed vimentin. The significance of this finding concerning the possible origin of RS cells in this subset is unclear, because vimentin alone is not a completely reliable marker of tumour histogenesis. In addition, the basic mechanisms that regulate vimentin production are still obscure. Additional cases of NS-HD should be analysed in order to confirm the present results and to extend the correlation of vimentin expression on RS cells with their immunophenotypic and genotypic profiles. Moreover, a larger number of cases of LP, MC and LD subtypes should be analysed to assess whether RS cells of HD other than the NS subtype are really negative for vimentin, as suggested by this study.

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