American Journal of Pathology, Vol. 139, No. 3, September 1991

Rapid Communication

Coexpression of CD15 and CD20 by Reed-Sternberg Cells in Hodgkin's Disease

Lawrence R. Zukerberg, A. Bernard Collins, Judith A. Ferry, and Nancy L. Harris

From the James Homer Wright Pathology Laboratory of the Massachusetts General Hospital and the Department of Pathology, Harvard Medical School, Boston, Massachusetts

The immunophenotype of the Reed-Sternberg cells in Hodgkin's disease is heterogeneous among different cases; this heterogeneity has contributed to the continuing uncertainty regarding the normal counterpart of the Reed-Sternberg cell. In this study, the authors demonstrate coexpression of the B-cell marker, CD20, and the granulocyte associated antigen, CD15, by Reed-Sternberg cells in three of 20 cases of nodular sclerosis and mixed cellularity Hodgkin's disease using a double-labelling technique in one case and staining of serial sections in three cases. Additionally, the authors found that expression of CD20 occurred more often in tumors with a monomorphous proliferation of mononuclear and binucleate Hodgkin's and Reed-Sternberg cells, without numerous eosinophils or polymorphonuclear neutrophils. In contrast, expression of CD15 by Reed-Sternberg cells was associated with a greater granulocyte infiltrate. The presence or absence of fibrosis, plasma cells, and histiocytes did not correlate with antigen expression. These results suggest that there may be a continuum of antigen expression by Reed-Sternberg cells, with some cells expressing CD20, some CD15, and others expressing both antigens; cells coexpressing both CD15 and CD20 may represent an unstable intermediate in the process of antigen switching. The possibility that antigen expression by the neoplastic cells in a given case may modulate depending on the background infiltrate could explain the heterogeneity of immunophenotype among cases of Hodgkin's disease. (Am J Pathol 1991, 139:475–483)

The histology of Hodgkin's disease is variable, including four major recognizable subtypes. In all types, the malignant cell is presumed to be the Reed-Sternberg cell and its morphologic variants. Until recently, most observers have assumed that all subtypes represent the same disease process, differing only in the relative numbers of Reed-Sternberg cells and inflammatory cells. Recently, however, the application of monoclonal antibodies has shown that Reed-Sternberg cells in some of the different histologic subtypes can have different patterns of antigen expression. In the majority of nonlymphocyte predominance Hodgkin's disease, the Reed-Sternberg cells express the granulocyte-associated antigen CD15 (LeuM1) and the activation antigen CD30 (BerH2), and lack the B-cell antigen CD20 (L26) and the leukocyte common antigen (CD45).[1–5] In lymphocyte predominance Hodgkin's disease (LPHD), however, the Reed-Sternberg cells in most cases have been shown to express CD20 and CD45 and lack CD15; CD30 expression is variable.[6–8] This observation has been interpreted to suggest that LPHD is a distinct entity unrelated to other forms of Hodgkin's disease, possibly a B-cell lymphoma. However, none of the subtypes of Hodgkin's disease have absolutely consistent immunophenotypes; occasional cases of nodular sclerosis, mixed cellularity, and lymphocyte-depleted Hodgkin's disease express CD20 and CD45 and lack CD15 or CD30. Expression of T-lineage antigens has been reported in some cases.[9–10] Furthermore, inconsistency of antigenic expression has been observed in simultaneous and successive Hodgkin's biopsies.[11]

Recent studies that show clonally rearranged immunoglobulin genes and detection of bcl-2/J_H sequences in nodular sclerosis and mixed cellularity cases suggest a B-cell origin for at least some of these Hodgkin's subtypes, despite expression of CD15 and lack of

Accepted for publication June 20, 1991.

Address reprint requests to Dr. Nancy L. Harris, Department of Pathology, Warren 2, Massachusetts General Hospital, Boston, MA 02114.

CD20.[12–14] In an attempt to explain the heterogeneity in antigen expression among cases of Hodgkin's disease, we postulated that antigen expression by the neoplastic cells in a given case may modulate depending on cytokines and other factors associated with the background inflammatory cell infiltrate. If this were true, some cells might be expected to coexpress both CD15 and CD20 in the process of antigen switching. We looked for evidence of coexpression of these antigens by double-labelling experiments and staining of serial sections. We report coexpression of CD15 and CD20 by Reed-Sternberg cells in three cases of Hodgkin's disease (two nodular sclerosis and one mixed cellularity type), supporting the hypothesis of antigen modulation by Reed-Sternberg cells.

Methods

To facilitate evaluation of the immunophenotype of the malignant cells, only cases with large numbers of Reed-Sternberg and Hodgkin's cells, usually in clusters or aggregates, were included. All cases of nodular sclerosis and mixed cellularity Hodgkin's disease from 1985 to 1990 (approximately 75 cases) were evaluated for areas with large numbers or syncytial aggregates of Reed-Sternberg and Hodgkin's cells. Twenty of the approximately 75 cases were selected. Cases were subclassified according to the Rye Classification for Hodgkin's Disease. The inflammatory response was evaluated by counting the number of neutrophils (using CD15), eosinophils (using a Giemsa stain), plasma cells, and histiocytes in 10 high power fields of "cellular" infiltrate diagnostic of Hodgkin's disease. Statistical analysis was done using ANOVA followed by multiple-range comparison tests (Fisher PLSD, Scheffe F-test, and Dunnett test).

Routine histologic sections were prepared from B5- or formalin-fixed, paraffin-embedded tissue and were stained with hematoxylin and eosin and Giemsa stains. Immunoperoxidase stains were done on B5-fixed (16 cases) or formalin-fixed (4 cases: nos. 4, 15, 19, 20), paraffin-embedded tissue sections with the avidin biotin complex technique[15] (Vector Laboratories Inc., Burlingame, CA). Tissue sections were stained with antibodies to CD15 (LeuM1, Becton Dickinson, San Jose, CA), CD45 (leukocyte common antigen, DAKO, Carpinteria, CA), CD20 (L26, DAKO), and CD30 (BerH2, DAKO).

To establish coexpression of antigen by single cells in cases that had both CD15 and CD20-positive cells, two procedures were used: 1) staining of serial sections (cases 1–3) with different antibodies, and 2) double staining with direct immunofluorescence (case 2 in which frozen tissue was available) as follows. Four micron cryostat-tissue sections were cut, air dried for 20 minutes, and prewashed in phosphate-buffered saline (PBS) buffer (pH = 7.4). Fluorescein isothiocyanate (green)-conjugated anti-CD15 (CD15–FITC, Becton-Dickinson) (dilution 1:20) and phycoerythrin (red)-conjugated anti-CD20 (CD20–PE, Becton-Dickinson) (dilution 1:20) were mixed; 100 μL was applied to the tissue sections, and the slides were incubated at room temperature for 30 minutes. Each antibody was also tested individually on adjacent sections. Slides were washed in PBS, three times, 5 to 7 minutes each, on a clinical rotator and coverslipped with aqua-mount mounting media (Lerner Laboratories Pittsburgh, PA). The sections were examined with a Zeiss Universal Fluorescence Microscope (Zeiss, Inc., Oberkocken, Germany) using vertical illumination for either fluorescein or rhodamine. Sections of tonsil and reactive lymph nodes and cases of Hodgkin's disease including lymphocyte predominance Hodgkin's disease (LPHD) not included in this study were used as controls.

Results

Histology and Immunophenotype (Table 1)

Neoplastic cells in three cases showed coexpression of CD15 and CD20; all three were CD30 positive and CD45 negative. Case 1 showed typical syncytial nodular sclerosis Hodgkin's disease with many admixed granulocytes (Figure 1A); greater than 90% of the syncytial Hodgkin's and Reed-Sternberg cells in this case showed strong staining for CD20 (membrane) and CD15 (membrane and paranuclear) on adjacent sections (Figure 1B, 1C). Case 2 also showed syncytial nodular sclerosis Hodgkin's disease, but differed (from case 1) in that the syncytial clusters of Hodgkin's cells had a more monomorphous appearance with fewer admixed inflammatory cells and lymphocytes (Figure 2A). The syncytia of Hodgkin's cells showed strong staining for CD20 (membrane) of all cells, and only occasional admixed CD15 positive cells (membrane and paranuclear) (Figure 2B, 2C). Double staining by direct immunofluorescence demonstrated occasional large cells within the syncytial clusters that coexpressed CD15 and CD20 (Figure 3). Case 3 showed mixed cellularity Hodgkin's disease with small clusters of Reed-Sternberg cells that could be seen on adjacent sections to express both CD15 and CD20. Similar to case 2, only rare granulocytes were present, but there were numerous admixed histiocytes.

The neoplastic cells in case 4 showed divergent phenotypes at two different sites within the same patient. Biopsy of a mediastinal mass showed typical Hodgkin's disease with numerous cytologically benign lymphocytes and admixed granulocytes (predominantly eosinophils)

Table 1. *Histologic and Immunophenotypic Findings*

Case	Histologic subtype	CD15	CD20	CD45	CD30	Granulocytic infiltrate (1–3+)‡
Coexpression of CD15 and CD20 (on same cells)						
1	NS	++	+	−	+	3+
2	NS	+	++	−	+	1+
3	MC	+	+	−	+	1+
Discordant expression of CD15 and CD20 at different sites						
4	a) Unclass*	−	++	++	−	1+
	b) Unclass†	+	−	−	+	3+
"B-cell" phenotype						
5	NS	−	++	++	−	1+
6	MC	−	+	−	−	1+
7	MC	−	+	+	+	1+
"Hodgkin's" phenotype						
8–16	NS	+ or ++	−	−	+	2–3+
17–18	MC	+	−	−	+	2+
"Null" phenotype						
19–20	NS	−	−	−	+	1–2+

* Subcapsular focus of syncytial Hodgkin's disease.
† Adjacent mediastinal mass suggestive of nodular sclerosis type without fibrous bands on biopsy specimen.
‡ 1+ = <100; 2+ = 100–200; 3+ = >200 cells/10 hpf.
NS = nodular sclerosis subtype; MC = mixed cellularity subtype.

and both diagnostic Reed-Sternberg cells and mononuclear variants. No fibrous bands were seen, but because of small sample size distinction between nodular sclerosis and mixed cellularity Hodgkin's disease was not possible. Immunoperoxidase stains on the mediastinal node showed that the atypical cells were negative for CD20 and CD45 and strongly expressed both CD15 and CD30. An adjacent cervical lymph node showed a small focus of tumor composed of a syncytium of Hodgkin's and Reed-Sternberg cells with only rare admixed lymphocytes and virtually no granulocytes, histiocytes, or plasma cells. The aggregate of Hodgkin's cells was CD20 and CD45 positive, and CD15 and CD30 negative.

Three cases (5–7) had a B-cell phenotype; they expressed CD20 and lacked CD15. Two cases were CD45 positive and only one expressed CD30. Case 5 was classified as nodular sclerosis Hodgkin's disease and was similar to case 2, with monomorphous clusters of Hodgkin's and Reed-Sternberg cells separated by thick bands of collagen; although numerous admixed lymphocytes were present, granulocytes were virtually absent. Cases 6 and 7 showed mixed cellularity Hodgkin's disease with small clusters of Reed-Sternberg cells admixed with numerous lymphocytes, plasma cells and histiocytes. Both cases were unusual in that there was a paucity of granulocytes.

Of the remaining 13 cases, 11 showed a classic Hodgkin's disease phenotype (CD15+, CD30+, CD20−, CD45−); all cases were associated with a moderate-to-marked granulocytic infiltrate. The Reed-Sternberg cells in two cases did not express either CD15 or CD20 although both were CD30+.

Inflammatory Reaction (Table 2)

The average number of inflammatory cells in 10 high power fields was compared for the four immunophenotypic groups: coexpression, b-cell, Hodgkin's, and null. (For this exercise, Case 4a was considered B-cell and 4b as Hodgkin's phenotype.) For neutrophils, eosinophils, and total granulocytes, the average number was lowest in the B-cell group and highest in the Hodgkin's group, with the coexpression group having an intermediate number. Analysis of variance (ANOVA-single factor model), comparing the immunophenotypic groups and inflammatory components showed significance for eosinophils [$F(3,17) = 4.895$; $P = .0124$] and total granulocytes [$F(3,17) = 3.86$; $P = .0283$]. Further analysis of these groups using multiple-range comparison tests showed significant mean differences between the B-cell group and Hodgkin's group for both eosinophils and total granulocytes ($P < 0.05$), and between the Hodgkin's and coexpression groups for eosinophils ($P < 0.05$); other mean differences were not significant. Analysis of variance for histiocytes, plasma cells, and neutrophils alone was not significant when compared with the four immunophenotypic groups. Although there were no significant difference in numbers of histiocytes or plasma cells between the four groups by ANOVA, there were half as many histiocytes and twice as many plasma cells on average in the null group as in the other three.

Discussion

The lineage of the malignant cell in Hodgkin's disease is unknown. In the majority of cases, Reed-Sternberg cells

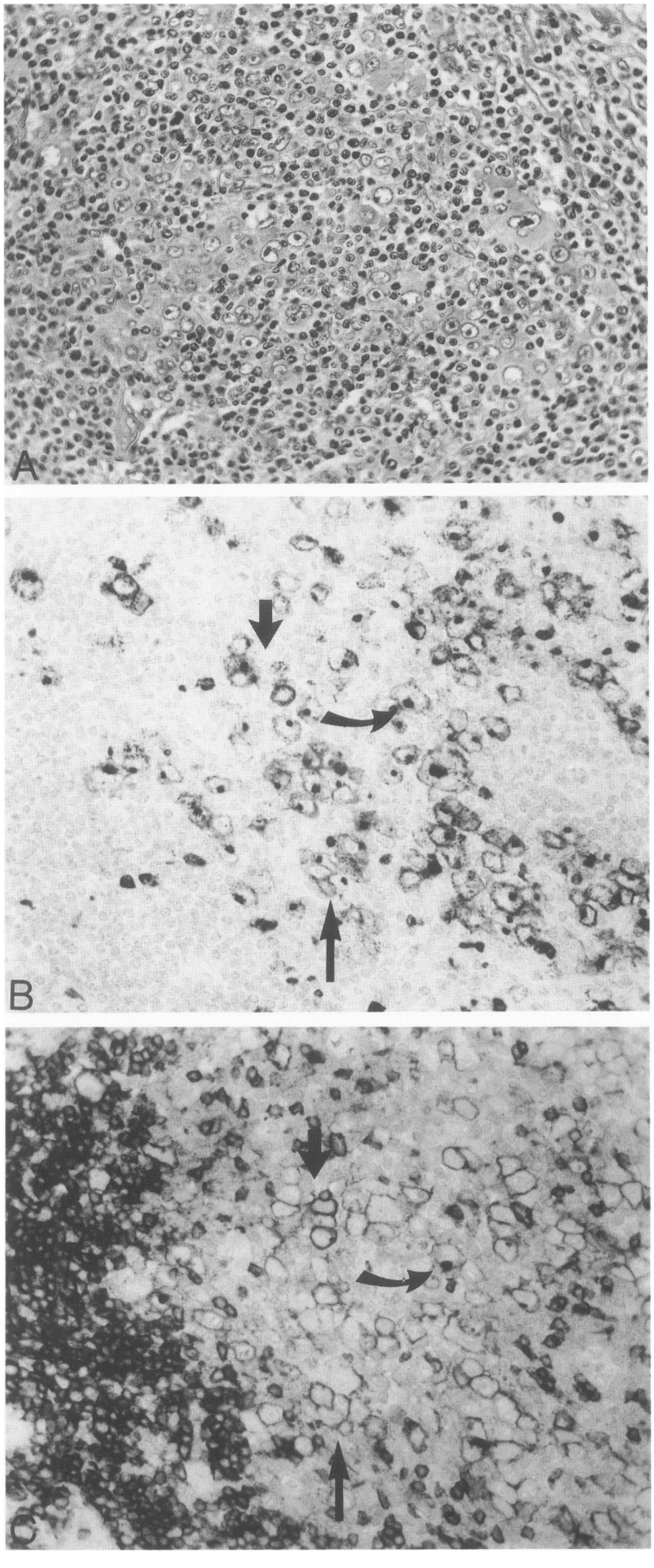

Figure 1. *(Case 1) Aggregate of Hodgkin's and Reed-Sternberg cells with numerous admixed lymphocytes* (**A**, *H&E* ×*313*). *Same field on adjacent sections shows that most of the Hodgkin's cells are CD15+ (membrane and paranuclear)* (**B**, ×*313*) *and CD20+ (membrane)* (**C**, ×*313*). *Arrows highlight similar cell groups for orientation.*

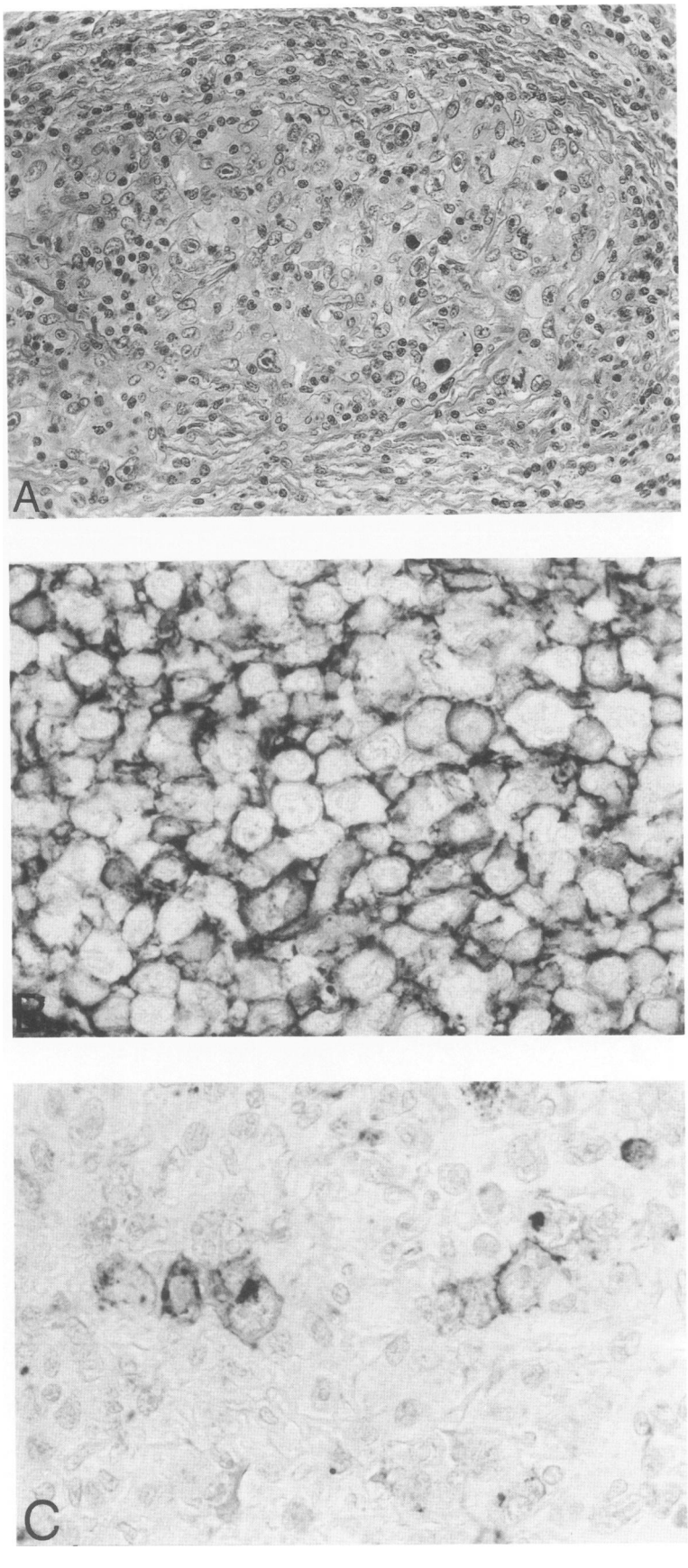

Figure 2. *(Case 2) Syncytial aggregate of Hodgkin's and Reed-Sternberg cells with few admixed inflammatory cells and lymphocytes* (**A**, *H&E* ×*313*). *All cells show strong staining for CD20 (membrane)* (**B**, ×*500*) *and occasional cells are also CD15+ (membrane and paranuclear)* (**C**, ×*500*).

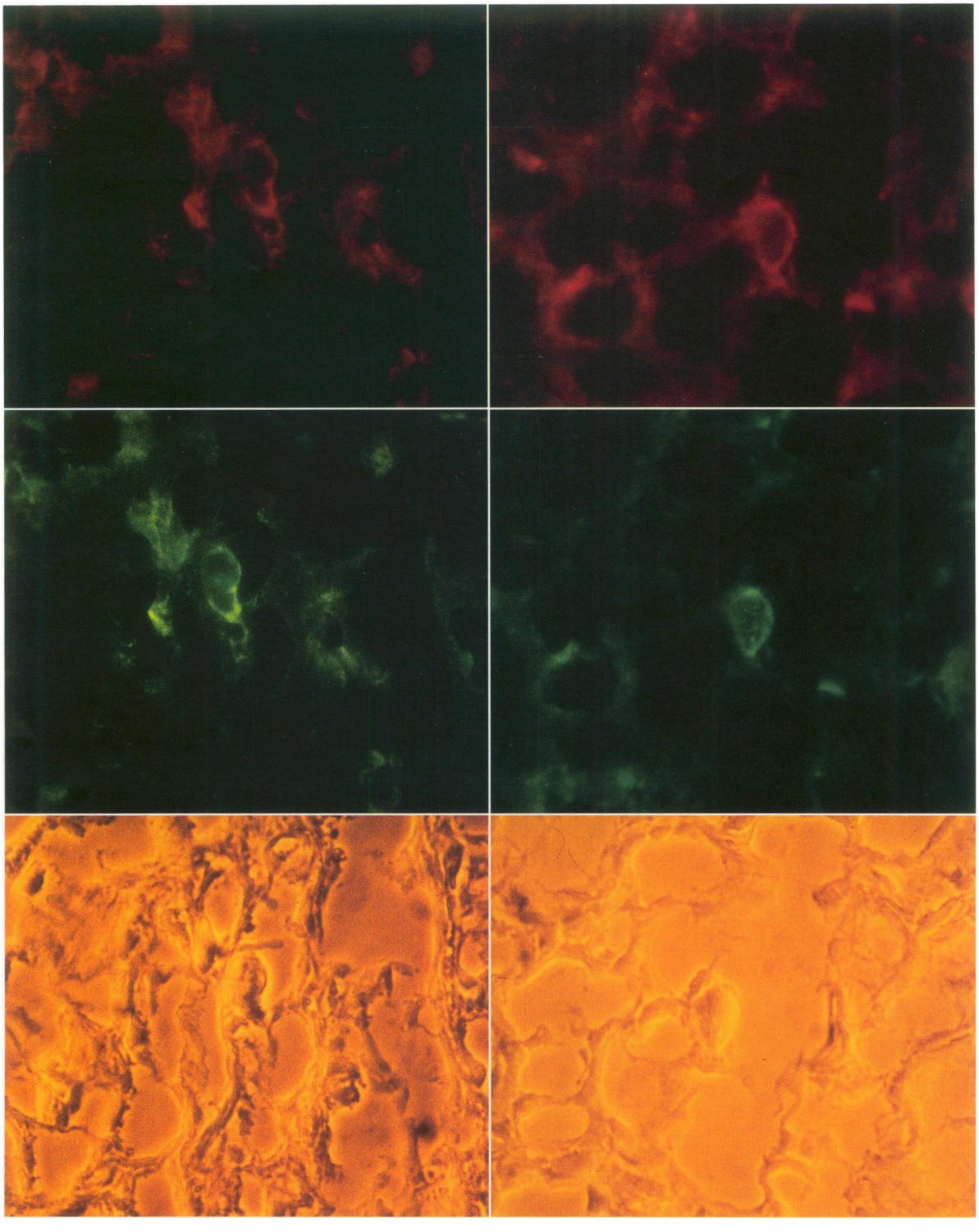

Figure 3. *Double staining by direct immunofluorescence demonstrates occasional large cells within the syncytial clusters of case 2 that coexpress CD20 (red)* (**A, D,** ×*850*) *and CD15 (green)* (**B, E,** ×*850*). *Note the paranuclear staining with CD15* (**B**); *it is not present with CD20* (**A**). *The cells visualized with phase contrast* (**C, F,** ×*850*) *are compatible with Reed-Sternberg and Hodgkin's cells.*

Table 2. *Inflammatory Reaction*

	Coexpression	B-cell	Hodgkin's	Null
Neutrophils [F(3,17) = 1.316; P = .3019]†	108.3 (166.0)*	18.7 (13.1)	145.8 (132.9)	40 (28.3)
Eosinophils [F(3,17) = 4.895; P = .0124]	16.7 (5.8)	13.8 (24.2)	87.9 (49.1)	33 (24.0)
			$P < 0.05$	
	$P < 0.05$			
Total granulocytes [F(3,17) = 3.86; P = .0283]	125 (168.9)	32.5 (33.7)	233.8 (118.7)	73 (52.3)
			$P < 0.05$	
Histiocytes [F(3,17) = .154; P = .9258]	186.7 (271.6)	187.5 (224.4)	186.7 (172.4)	90 (14.1)
Plasma cells [F(3,17) = .43; P = .7339]	21.7 (24.7)	23.7 (30.9)	24.9 (40.2)	55 (35.4)

* Mean number of cells/10 hpf (×40) (SD).
† One Factor ANOVA.

and their variants lack leukocyte common antigen and T– or B–cell-associated antigens and express the granulocyte-associated antigen CD15 and the activation antigen CD30.[1–5] Occasional cases have been reported in which the neoplastic cells express B-lineage antigens, particularly with the antibody L26, which detects an intracytoplasmic domain of CD20.[3–8,16] The majority of CD20 positive cases are lymphocyte predominant type; these cases usually lack CD15, and it has been postulated that they represent B-cell neoplasms that are different from classic Hodgkin's disease (nodular sclerosis/mixed cellularity).[6–8]

In this study, we found that the majority (55%) of cases of mixed cellularity and nodular sclerosis Hodgkin's disease had a classic phenotype (CD15+, CD30+, CD20−, CD45−), whereas a minority (15%) had a B-cell phenotype (CD20+, CD15−). In three cases (15%), we found coexpression of CD15 and CD20 on the same cells. The finding that the same cell coexpresses CD15 and CD20 suggests that one of these antigens is not lineage specific, and that cases of Hodgkin's disease that express one of these antigens and lack the other may not reflect different lineages, as previously believed, but may represent different phases of antigen expression by the same neoplastic cell type. There may be a continuum in antigen expression from CD20+ to CD15+, with the double staining cells possibly representing an unstable intermediate in the process of antigen switching.

Several lines of evidence favor the conclusion that the CD15 antigen is nonlineage specific, and that the neoplastic cell is more likely to be a B lymphocyte than a granulocyte-macrophage lineage cell. First, the CD15 antigen is expressed by nonlymphoid cells, and has been reported in activated T cells, cytomegalovirus-infected cells, and some T-cell lymphomas,[17–19] it is therefore not restricted to monocyte/macrophage cells. Second, the CD20 antigen has been extensively studied and found to be a highly specific marker for B cells.[16,20] Third, there is evidence from molecular genetic studies that Reed-Sternberg cells in some cases of typical Hodgkin's disease can have rearranged immunoglobulin genes.[12–13]

The Hodgkin's phenotype (CD15+, CD30+, CD20−, CD45−) that was seen in cases 8 through 18 was associated with the presence of a moderate-to-marked reactive inflammatory infiltrate, containing eosinophils and neutrophils, whereas the B-cell phenotype (CD15−, CD30−, CD20+, CD45+) in cases 5 through 7 was associated with the absence of such an infiltrate. The double staining cases were heterogeneous: case 1 had a marked granulocytic infiltrate and strongly expressed CD15, whereas case 2, which was associated with a scanty inflammatory infiltrate, strongly expressed CD20 and weakly expressed CD15. In case 4, expression of CD15 was seen in a node with a prominent granulocytic infiltrate, whereas CD20 expression was seen in a node with no granulocytic background.

The functional relationship between the neoplastic Hodgkin's and Reed-Sternberg cells in Hodgkin's disease and the inflammatory background infiltrate is not understood fully. Several recent studies suggest that production of cytokines by the neoplastic cells may be responsible for the tissue eosinophilia and fibrosis.[21–23] It is also theoretically possible that the presence of specific types of inflammatory cells could alter antigen expression by the neoplastic cells, although direct evidence for such an interaction is lacking. The findings in our study suggest the possibility that, in the absence of the classic inflammatory background, the Hodgkin's and Reed-Sternberg cells express a B-lineage antigen and often CD45, whereas in the presence of the typical inflammatory infiltrate of eosinophils and/or neutrophils, these antigens are lost, and CD15 and CD30 are expressed. Whether the change in antigen expression by Reed-Sternberg cells is the cause or the effect of the change in the inflammatory background remains to be elucidated.

Coexpression of Hodgkin's and B-cell markers on the

same cell forms an addition to the growing body of evidence supporting the B-cell nature of the Reed-Sternberg cell.[12–14,24] We postulate that the Reed-Sternberg cell in most cases of Hodgkin's disease may be of B-cell origin, even though B-lineage antigens are usually not detectable. Under some conditions, the cells may express B-cell associated antigens, whereas under other conditions the cells develop a Hodgkin's phenotype, with partial or complete loss of B-cell associated antigens and expression of CD15 and CD30. The pattern of antigen expression is likely to be related in some way to host-tumor cell interaction, but the nature of the interaction and the chronologic sequence of antigen expression or loss is speculative at this time. However, the possibility that Reed-Sternberg cells can modulate antigen expression would explain the confusing heterogeneity of antigen expression in Hodgkin's disease, with some cells in a given case expressing CD15 and CD30, others CD20, some expressing both antigens, and some cases showing a change in antigen expression over time.[11] If our hypothesis is correct, it would explain the frequent association of Hodgkin's disease with B-cell lymphoma.[25–30] This hypothesis would also suggest that lymphocyte predominance Hodgkin's disease may be related to other subtypes of Hodgkin's disease rather than a separate entity, distinct from other types of Hodgkin's disease by virtue of a different neoplastic cell lineage. It would also explain the presence of clonally rearranged immunoglobulin genes and detection of bcl-2/J_H sequences in some cases of Hodgkin's disease that lack B-lineage associated antigens.[12–14]

In summary, we report the coexpression of CD15 and CD20 by Reed-Sternberg cells in rare cases of Hodgkin's disease. We also observed that lack of CD20 and expression of CD15 was associated with an increasing inflammatory infiltrate, suggesting that antigen expression by Reed-Sternberg cells may vary depending on the background cellularity. In addition, our results support a B-cell origin for the Reed-Sternberg cell in some cases of Hodgkin's disease.

References

1. Hsu SM, Jaffe ES: LeuM1 and peanut agglutinin stain the neoplastic cells of Hodgkin's disease. Am J Clin Pathol 1984, 82:29–32
2. Dorfman RF, Gatter KC, Pulford KAF, Mason DY: An evaluation of the utility of anti-granulocyte and anti-leukocyte monoclonal antibodies in the diagnosis of Hodgkin's disease. Am J Pathol 1986, 123:508–519
3. Chittal SM, Caveriviere P, Schwarting R, Geredes J, Saati TA, Rigal-Huguet F, Stein H, Delsol G: Monoclonal antibodies in the diagnosis of Hodgkin's disease. The search for a rational panel. Am J Surg Pathol 1988, 12:9–21
4. Meideros LJ, Weiss LM, Warnke RA, Dorfman RF: Utility of combining anti-granulocyte and anti-leukocyte antibodies in differentiating Hodgkin's disease from non-Hodgkin's lymphoma. Cancer 1988, 62:2475–2481
5. Hall PA, D'Ardenne AJ, Stansfeld AG: Paraffin section immunohistochemistry. II. Hodgkin's disease and large cell anaplastic (Ki1) lymphoma. Histopathology 1988, 13:161–169
6. Pinkus GS, Said JW: Hodgkin's disease, lymphocyte predominant type, nodular-further evidence for a B-cell derivation: L&H variants of Reed-Sternberg cells express L26, a pan B-cell marker. Am J Pathol 1988, 133:211–217
7. Coles BF, Cartun RW, Pastuszak WT: Hodgkin's disease, lymphocyte-predominant type: Immunoreactivity with B-cell antibodies. Mod Pathol 1988, 1:274–278
8. Bishop PW, Harris M, Smith AP, Elsam KJ: Immunophenotypic study of lymphocyte predominance Hodgkin's disease. Histopathology 1991, 18:19–24
9. Casey TT, Olson SJ, Cousar JB, Collins RD: Immunophenotype of Reed-Sternberg cells: A study of 19 cases of Hodgkin's disease in plastic embedded sections. Blood 1989, 74:2624–2628
10. Kadin ME, Muramoto L, Said J: Expression of T-cell antigens on Reed-Sternberg cells in a subset of patients with nodular sclerosing and mixed cellularity Hodgkin's disease. Am J Pathol 1988, 130:345–353
11. Chu WS, Abbondanzo SL, Frizzera G: Comparison of immunophenotypes in simultaneous and successive lymph node biopsies involved by Hodgkin's disease. Mod Pathol 1991, 4:406A
12. Sundeen J, Lipford E, Uppenkamp M, Sussman E, Wahl L, Raffeld M, Cossman J: Rearranged antigen receptor genes in Hodgkin's disease. Blood 1987, 70:96–103
13. Weiss LM, Strickler JG, Hu E, Warnke RA, Sklar J: Immunoglobulin gene rearrangements in Hodgkin's disease. Hum Pathol 1986, 17:1009–14
14. Stetler-Stevenson M, Crush-Stanton S, Cossman J: Involvement of the bcl-2 gene in Hodgkin's disease. J Natl Cancer Inst 1990, 82:855–858
15. Hsu SM, Raine L, Fanger H: The use of avidin–biotin–peroxidase complex (ABC) in immunoperoxidase techniques: A comparison between ABC and unlabelled antibody (PAP) procedures. J Histochem Cytochem 1981, 29:577–580
16. Mason DY, Comans-Bitter WM, Cordell JL, Verhoeven MAJ, van Dongen JJM: Antibody L26 recognizes an intracellular epitope on the B–cell-associated CD20 antigen. Am J Pathol 1990, 136:1215–1222
17. Hanjan SNS, Kearney JF, Cooper MD: A monoclonal antibody (MMA) that identifies a differentiation antigen on human myelomonocytic cells. Clin Immunol Immunopathol 1982, 23:172–188
18. Wieczorek R, Burke JS, Knowles DM: Leu-M1 antigen expression in T-cell neoplasia. Am J Pathol 1985, 121:374–380
19. Rushin JM, Riordan GP, Heaton RB, Sharpe RW, Cotelingam JD, Jaffe ES: Cytomegalovirus-infected cells express LeuM1 antigen; A potential source of diagnostic error. Am J Pathol 1990, 136:989–995
20. Clark EA, Ledbetter JA: Structure, function, and genetics of

human B cell associated surface molecules. Adv Cancer Res 1989, 52:81–149

21. Ben-Ezra J, Sheibani K, Swartz W, Stroup R, Traweek ST, Kezirian J, Rappaport H: Relationship between eosinophil density and T-cell activation markers in lymph nodes of patients with Hodgkin's disease. Hum Pathol 1989, 20:1181–1185
22. Kadin ME, Agnarsson BA, Ellingsworth LR, Newcom SR: Immunohistochemical evidence of a role for transforming growth factor beta in the pathogenesis of nodular sclerosing Hodgkin's disease. Am J Pathol 1990, 136:1209–1214
23. Samoszuk M, Nansen L: Detection of interleukin-5 messenger RNA in Reed-Sternberg cells of Hodgkin's disease with eosinophilia. Blood 1990, 75:13–16
24. Jaffe ES: The elusive Reed-Sternberg cell. N. Engl J Med 1989, 320:529–31
25. Brecher M, Banks PM: Hodgkin's disease variant of Richter's Syndrome. Report of eight cases. Am J Clin Path 1990, 93:333–339
26. Casey TT, Cousar JB, Mangum M, Williams ME, Lee JT, Greer JP, Collins RD: Monomorphic lymphomas arising in patients with Hodgkin's disease. Correlation of morphologic, immunophenotypic, and molecular genetic findings in 12 cases. Am J Pathol 1990, 136:81–94
27. Hansmann ML, Fellbaum CH, Hui PK, Lennert K: Morphological and immunohistochemical investigation of non-Hodgkin's lymphoma combined with Hodgkin's disease. Histopathology 1989, 15:35–48
28. Hansman ML, Stein H, Fellbaum C, Hui PK, Parwaresch MR, Lennert K: Nodular paragranuloma can transform into high-grade malignant lymphoma of B type. Hum Pathol 1989, 20:1169–75
29. Sundeen JJ, Cossan J, Jaffe ES: Lymphocyte predominant Hodgkin's disease nodular subtype with coexistent "large cell lymphoma": Histological progression or composite malignancy? Am J Surg Path 1988, 12:599–606
30. Williams J, Schned A, Cotelingam JD, Jaffe ES: Chronic lymphocytic leukemia with coexistent Hodgkin's disease. Implications for the origin of the Reed-Sternberg cell. Am J Surg Path 1991, 15:33–42