Hairy Cell Leukemia Variant

Fact or Fiction

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Abstract

Hairy cell leukemia variant (HCL-V) is a poorly described, rare B-cell lymphoproliferative disorder typically positive for CD103 and CD11c, while lacking CD25. Splenic marginal zone lymphomas (SMZL) also have this unusual phenotype in 15% to 25% of cases, have other overlapping clinical or morphologic features, and are more common than HCL-V. The purpose of our study was to better characterize HCL-V and determine whether most cases could be distinguished from SMZL. Cases with an HCL-V phenotype were identified from our flow cytometry service, and 10 were selected for further study based on bone marrow or splenic tissue availability. All cases had cytologic features consistent with HCL-V, and 9 of 10 patients had lymphocytosis. Bone marrow involvement was mostly interstitial and/or sinusoidal without lymphoid nodules. Coexpression of preswitched with postswitched heavy chain isotypes, an unusual feature of HCL, was seen in 2 of 4 cases. This study better defines HCL-V and establishes that most cases do not represent SMZL.

Hairy cell leukemia variant (HCL-V) is a generally recognized rare B-cell lymphoproliferative disorder but has not been well described or defined in the literature.[1,2] As the name suggests, HCL-V is thought to share many clinical, morphologic, and immunophenotypic features with "classic" HCL, including splenomegaly and neoplastic lymphocytes with cytoplasmic projections or hairs. However, in contrast with HCL, patients with HCL-V typically have elevated WBC counts, easy-to-aspirate bone marrow, and neoplastic cells that only infrequently demonstrate reactivity for tartrate-resistant acid phosphatase (TRAP). In addition, while patients with HCL-V might have anemia or thrombocytopenia, the pancytopenia, neutropenia, and monocytopenia characteristically seen in classic HCL are not typically present. Moreover, most patients with HCL-V have a diminished or lack of response to conventional HCL therapies, including interferon alfa and cladribine.[1,3,4]

Splenic marginal zone lymphoma (SMZL) is a small B-cell lymphoproliferative disorder that also shares many clinical, morphologic, and immunophenotypic features with HCL-V and often is considered in the differential diagnosis.[5-7] SMZL primarily affects individuals older than 50 years and frequently involves the bone marrow and peripheral blood. Cytologically, the neoplastic lymphoid cells in SMZL characteristically have polar cytoplasmic villi, or hairs, and resemble HCL cells. Because of this feature, an older term for SMZL, used before marginal zone lymphomas were recognized entities, was splenic lymphoma with villous lymphocytes.[6] Immunophenotypically, HCL-V expresses the pan–B-cell antigens CD19, CD20, and CD22 and also typically is positive for CD103 and CD11c without CD25.[1,2,8] Approximately 15% to 25% of SMZL cases have

been reported to also express CD103 and CD11c and typically do not express CD25.[5,7]

Because HCL-V is not well described in the literature, is rare, and shares many unusual features with SMZL, which is a more common small B-cell lymphoproliferative disorder, we hypothesized that many cases thought to represent HCL-V based on immunophenotype and cytologic features might, in fact, represent SMZL. To study this question, lymphoproliferative disorders of mature small B cells with a CD103+, CD11c+, and CD25– phenotype were identified from our flow cytometry service. Bone marrow and other tissue biopsy specimens of these cases were studied to determine whether the histologic features more closely resembled SMZL or those described for HCL-V. In addition, heavy chain isotype studies, which potentially can distinguish SMZL from HCL-V, also were performed.[9]

Materials and Methods

Case Selection

Small B-cell lymphoproliferative disorders demonstrating unequivocal coexpression of CD11c and CD103 without CD25 were identified from searching our flow cytometry database between July 2000 and September 2003. We selected 10 cases for further study based on the availability of bone marrow core or splenic tissue biopsy specimens. Five cases were excluded because only peripheral blood and/or bone marrow aspirate specimens were available. Multiple specimens were reviewed for 5 patients. CBC count data also were obtained, when available. The University of Utah Institutional Review Board (Salt Lake City) approved the research use of these specimens (No. 11680).

Flow Cytometric Analysis

Routine 4-color diagnostic flow cytometry studies were performed as previously described.[10] All 10 selected cases had at least 80% of the cells in the atypical lymphocyte gate showing expression of CD19, CD20, CD22, CD11c, and CD103 above isotype control levels without CD25, CD5, or CD10. Specific antibody clones related to identifying the HCL-V phenotype were CD11c (S-HCL-3), CD20 (L27), CD22 (S-HCL-1), and CD25 (2A3) obtained from BD Bioscience, San Jose, CA; CD19 (J4.119, HD237, 89B) from Beckman Coulter, Miami, FL; and CD103 (Ber-ACT8) from DAKO, Carpinteria, CA. Assessment of IgM, IgD, IgG, and IgA expression on the atypical lymphocytes was performed in a 3-color manner with CD11c, CD19, and anti–heavy chain affinity isolated goat F(ab')2 fragments labeled with fluorescein isothiocyanate obtained from Caltag Laboratories, Burlingame, CA. All antibodies were used as recommended by the manufacturers and directly conjugated with fluorescein isothiocyanate, phycoerythrin or phycoerythrin–cyanin 5.1. Analysis was performed using the EPICS XL-MCL cytometer and EXPO32 software (Beckman Coulter).

Morphologic and Immunohistochemical Studies

Tissue samples from each case were reviewed to assess for cytologic and histologic features. When available, material associated with each case, including H&E-stained sections of bone marrow core biopsy specimens, spleens, and lymph nodes, were obtained. Wright-Giemsa–stained bone marrow aspirate smears, peripheral blood smears, and cytocentrifuged specimens (lymph node and spleen specimens) prepared from specimens submitted for flow cytometry were examined. Immunohistochemical studies for CD20 (clone L-26; dilution 1:2,000; DAKO) and TRAP (clone ZY-9C5; dilution 1:100; Zymed, South San Francisco, CA) were performed on formalin- or B-5–fixed and paraffin-embedded sections of the bone marrow core biopsy specimens, spleens, and lymph nodes. Standard immunohistochemical techniques were used, including heat-induced antigen retrieval and avidin-biotin peroxidase detection on an automated immunostainer (Ventana, Tucson, AZ). Expression of each of the markers was evaluated in the lymphoid cells with atypical lymphoid features. Reticulin stains were performed on the paraffin-embedded bone marrow core biopsy specimens, using standard histochemical techniques. All bone marrow core biopsy specimens were evaluated for reticulin fibrosis, using a 4-tier scale (1+ to 4+).

Results

Patient Data

A total of 10 cases were included in this study based on the availability of bone marrow or splenic tissue biopsy specimens. The demographic and initial clinical information available for the patients is summarized in **Table 1** and **Table 2**. The patients included 8 men and 2 women with an average age of 77.7 years (range, 55-93 years). On initial examination or at the time of the first available CBC count, the average lymphocyte count ranged from 920 to 90,600/μL (0.92-90.6 × 10^9/L; average, 18,400/μL [18.4 × 10^9/L]), and 9 patients had an elevated WBC count and absolute lymphocytosis. Hemoglobin values ranged from 9.1 to 15.6 g/dL (91-156 g/L), with only 3 patients being anemic. Neutrophil counts ranged from 206 to 8,500/μL (0.21-8.5 × 10^9/L), with only 3 patients showing neutropenia, including 2 with mild neutropenia. Platelet values ranged from 71 to 211 × 10^3/μL (71-211 × 10^9/L), and 6 patients had thrombocytopenia. Monocyte counts ranged from 100 to 3,900/μL (0.1-3.9 × 10^9/L), and

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Table 1
Patient Information and Specimens Analyzed by Flow Cytometry

Case No./Sex/Age (y)	Specimen	Time*
1/M/65	BMA	—
2/M/91	WB	—
3/M/80		
A	BMA	—
B	BMA	9
C	BMA	25
4/F/93	BMA	—
5/M/71		
A	WB	—
B	WB	2 d
C	WB	5
D	BMA	1
6/M/82	BMA	—
7/M/79		
A	Spleen	—
B	LN	16
8/M/55		
A	WB	—
B	Spleen	3
C	BMA	15
9/F/88	WB	—
10/M/73		
A	Spleen	—
B	LN	10

BMA, bone marrow aspirate; LN, lymph node; WB, whole blood.
* Time elapsed between specimens, in months unless otherwise indicated.

monocytosis was present in 6 patients. No patient had monocytopenia. Only 2 patients had cytopenias involving more than 1 lineage, primarily anemia and thrombocytopenia.

Flow Cytometric Findings

The specimens used for flow cytometric immunophenotyping for each case are listed in Table 1. All cases had a mature monoclonal B-cell immunophenotype (CD19+, CD20+, and CD22+) and also were positive for CD103 and CD11c and lacked CD25, CD5, and CD10 **Image 1**. Restriction of the λ light chain was present in 6 cases and κ in 4 cases. Multiple specimens from different time points were analyzed by flow cytometry for 5 patients, and all had similar phenotyping results compared with one another. Cryopreserved viable cells were available in 4 cases and were evaluated for IgD, IgM, IgG, and IgA expression. As summarized in **Table 3**, 2 cases expressed IgG alone, while 1 expressed IgG and IgM, and 1 expressed IgD with IgA and partial IgG. Representative flow cytometric data for the case (case 8) that demonstrated expression of preswitched IgD with postswitched IgG and IgA heavy chain isotypes are shown in **Image 2**. Because essentially all of the cells expressed IgD, one can infer that some of the same cells coexpress IgD with IgG or IgA.

Morphologic and Immunohistochemical Findings

Specimens were available from 9 cases that could be evaluated for cytologic features and included 5 marrow aspirate smears, 5 peripheral blood smears, and 1 lymph node **Table 4**. The atypical lymphocytes identified in all of these cases were somewhat variable in size and typically demonstrated scant to moderate cytoplasm with hair-like cytoplasmic projections and round to oval nuclei with clumped chromatin **Image 3**. Definitive nucleoli were identified in only 1 case.

Bone marrow core biopsy specimens from 9 cases were available for morphologic evaluation and immunohistochemical or other staining studies **Table 5**. The core biopsy specimens for cases 2 and 9 were obtained at the time of the submitted whole blood specimens, while the core biopsy specimen for case 10 was obtained approximately 1 year before the spleen specimen. All others were obtained with the bone marrow aspiration specimens submitted for flow cytometric immunophenotyping.

The percentage of bone marrow involvement in these cases ranged from 10% to 90%. Review of the bone marrow infiltrates morphologically and by CD20 immunohistochemical analysis demonstrated a predominantly interstitial pattern in 4 cases, a predominant sinusoidal pattern in 4 cases, and a

Table 2
CBC Count Data for Patients Included in the Study

Case No.	Time*	WBC, /μL (× 10^9/L)	Hemoglobin, g/dL (g/L)	Lymphocytes, /μL (× 10^9/L)	Monocytes, /μL (× 10^9/L)	Neutrophils, /μL (× 10^9/L)	Platelets, × 10^3/μL (× 10^9/L)
1	0	4,300 (4.3)	12.2 (122)	920 (0.92)	400 (0.4)	2,900 (2.9)	141 (141)
2	+2 d	17,700 (17.7)	10.8 (108)	13,100 (13.1)	400 (0.4)	4,200 (4.2)	168 (168)
3	0	26,600 (26.6)	11.2 (112)	15,200 (15.2)	800 (0.8)	8,500 (8.5)	88 (88)
4	0	102,900 (102.9)	12.3 (123)	90,600 (90.6)	1,000 (1.0)	1,000 (1.0)	109 (109)
5	+6 mo	23,000 (23.0)	9.1 (91)	14,900 (14.9)	500 (0.5)	5,800 (5.8)	80 (80)
6	–5 mo	24,500 (24.5)	15.6 (156)	20,600 (20.6)	1,000 (1.0)	2,900 (2.9)	211 (211)
7	+37 mo	12,400 (12.4)	12.2 (122)	6,600 (6.6)	2,100 (2.1)	3,700 (3.7)	128 (128)
8	0	9,400 (9.4)	11.9 (119)	6,000 (6.0)	100 (0.1)	3,100 (3.1)	116 (116)
9	–27 d	17,600 (17.6)	13.2 (132)	12,800 (12.8)	2,600 (2.6)	1,400 (1.4)	245 (245)
10	0	3,970 (3.97)	13.0 (130)	3,600 (3.6)	155 (0.16)	206 (0.21)	71 (71)

* Time elapsed between CBC data and evaluation of first flow cytometry specimen.

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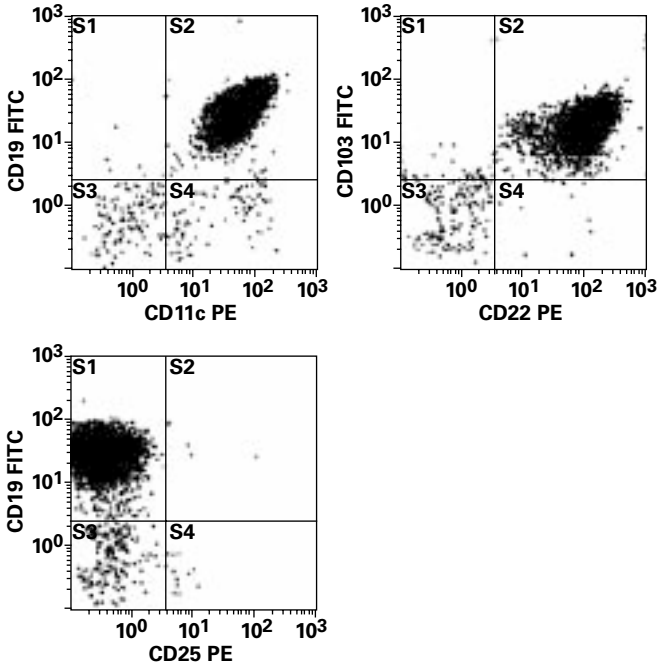

Image 1 Flow cytometric dot plots from a representative case demonstrating a CD19+, CD22+ B-cell population with coexpression of CD11c (**A**) and CD103 (**B**), without CD25 (**C**). FITC, fluorescein isothiocyanate; PE, phycoerythrin.

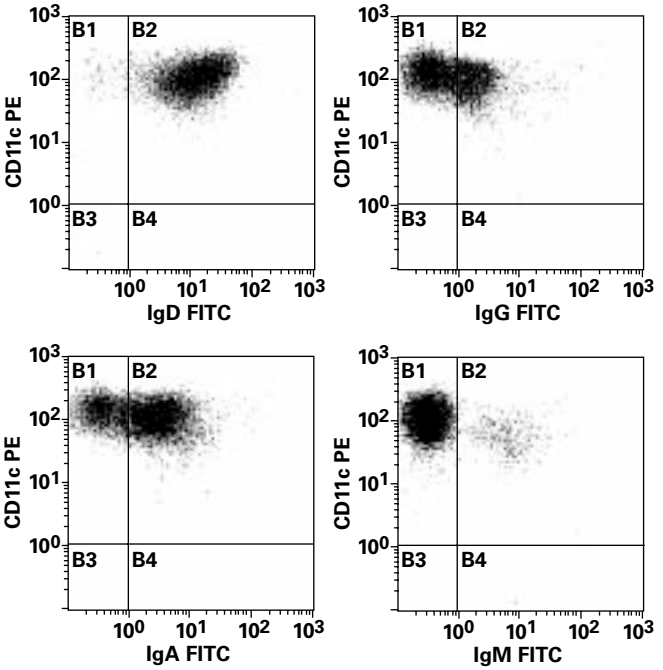

Image 2 (Case 8) Flow cytometric immunoglobulin heavy chain isotype analysis showing expression of IgD (**A**), partial IgG (**B**), and IgA (**C**) without significant IgM (**D**). FITC, fluorescein isothiocyanate; PE, phycoerythrin.

diffuse pattern in 1 case **Image 4** (Table 5). Secondary patterns also were observed in 5 cases, eg, some sinusoidal involvement was observed in 2 cases with mostly interstitial disease. However, only 1 case demonstrated a lymphoid aggregate that was nonparatrabecular in location, small, and not well-defined, even after CD20 staining. Splenic tissue specimens were available in 3 cases (7A, 8B, 10A) and all showed complete effacement with diffuse involvement of the red and white pulp by the atypical CD20+ B cells. Lymph node specimens were available in 2 cases (7B, 10B) and also demonstrated complete effacement with diffuse involvement by the CD20+ atypical lymphoid infiltrate. Immunohistochemical

Table 3
Flow Cytometric Data for IgG, IgM, IgD, and IgA

Case No.	IgG	IgM	IgD	IgA
3C	+	–	–	–
6	+	+	–	–
8B	+/–	–	+	+
9	+	–	–	–

+, positive; –, negative; +/–, partial expression.

Table 4
Morphologic Features of Lymphocytes in Smears and Cytocentrifuged Preparations

Case No.	Specimen	Size	Cytoplasm	Projections	Nucleoli
1	BMA	Small	Scant	Yes	No
2	WB	Medium	Moderate	Yes	No
3B	BMA	Small to medium	Scant	Few	No
4	BMA	Small to medium	Scant	Yes	No
5A	WB	Medium	Moderate	Yes	No
5B	WB	Medium	Moderate	Yes	No
5D	BMA	Medium	Moderate	Yes	No
6	BMA	Small	Scant	Yes	No
7	LN	Small	Moderate	Yes	No
8A	WB	Medium	Moderate	Yes	No
9	WB	Medium	Moderate	Yes	Yes

BMA, bone marrow aspirate; LN, lymph node; WB, whole blood.

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staining for TRAP was performed in all cases and was clearly positive in only 2 (cases 3 and 7). Staining for reticulin fibers was evaluated in 7 bone marrow specimens and demonstrated at most only mild fibrosis (1-2+).

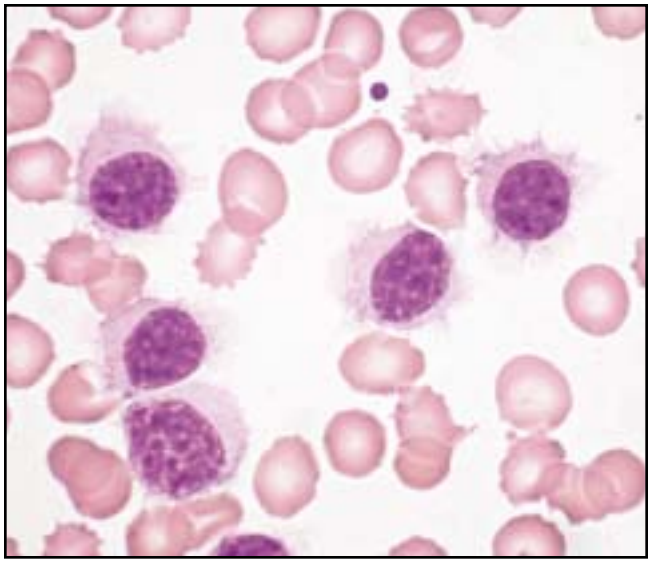

Image 3 Cytologic features from a representative case (Wright stain, ×1,000).

Discussion

All of the monoclonal small B-cell lymphoproliferative disorders examined in the present study were selected for inclusion based on having a particular phenotype, CD103 positivity with bright CD22 and CD11c and without CD25, CD5, and CD10. Although not specific, this immunophenotype is most consistent with the entity termed HCL-V.[8] The only other small B-cell lymphoproliferative disorders that express CD103 with any degree of regularity are HCL and SMZL.[5,11,12] Although HCL usually is positive for CD103, CD22, and CD11c, cases of HCL were unlikely to have been selected because large studies have demonstrated that more than 99% are CD25+.[11] In addition, other features seen with most of our cases, including lymphocytosis, and notable lack of pancytopenia, monocytopenia, and severe neutropenia are all typical of HCL-V but would be unusual for HCL.[1,2] Approximately 15% to 25% of SMZL cases have been reported to be CD103+, and most of these typically express CD22 and CD11c without CD25.[5,7] Moreover, atypical lymphocytosis of villous lymphocytes and the lack of pancytopenia also may be seen with SMZL.[5,6] Therefore, the main differential diagnosis for our cases would be between HCL-V and SMZL.

Although there are few studies reported in the literature, the pattern of bone marrow involvement of HCL-V is thought to resemble HCL, which characteristically is described as being predominantly interstitial.[1,2] However, intravascular (sinusoidal) infiltrates have also been reported in up to 73% of cases of HCL, usually in combination with interstitial involvement,[13] although rare cases with pure sinusoidal involvement have been reported.[14] Distinct neoplastic lymphoid nodules in bone marrow biopsy specimens typically are not found in HCL. Conversely, studies of bone marrow involvement by SMZL typically have shown a mixed pattern of involvement, with neoplastic lymphoid nodules the most frequently identified pattern.[13,15] Although intravascular (sinusoidal) involvement also is identified frequently and initially was proposed to be a possible hallmark for SMZL,[16,17] subsequent studies confirmed that it typically occurs in combination with other patterns, primarily lymphoid nodules, and is not unique to SMZL.[13,15]

The morphologic features of marrow involvement in our series were similar to those reported for HCL. Specifically, definitive well-formed neoplastic lymphoid nodules typical of

Table 5
Summary of Bone Marrow Morphologic Features Based on Review of H&E, Histochemical Staining for Reticulin, and Immunoperoxidase for CD20 and TRAP

Case No.	Cellularity (%)	Percentage of Involvement*	Predominant Pattern	Secondary Pattern	TRAP	Reticulin†
1	70-80	20-30	Interstitial	Aggregate; diffuse	–	1-2+
2	70	40	Interstitial	NA	–	1+
3A	30	30-40	Sinusoidal	Interstitial	+	ND
B	10-20	10	Sinusoidal	Interstitial	+/–	ND
4	10	30	Sinusoidal	Interstitial	–	1+
5D	40-50	40	Sinusoidal	NA	–	ND
6	50	10-30	Interstitial	Sinusoidal	–	1+
8A	60	30-40	Interstitial	Sinusoidal	–	1+
C	20-30	70	Interstitial	Sinusoidal	–	1+
9	30	60	Sinusoidal	NA	–	1+
10	100	90	Diffuse	NA	–	1+

NA, not applicable, significant secondary pattern not identified; ND, test not done owing to lack of material; TRAP, tartrate-resistant acid phosphatase; +, positive; –, negative; +/–, partial expression.
* Percentage of the bone marrow involved by atypical CD20+ B cells.
† Graded on a 4-tier scale.

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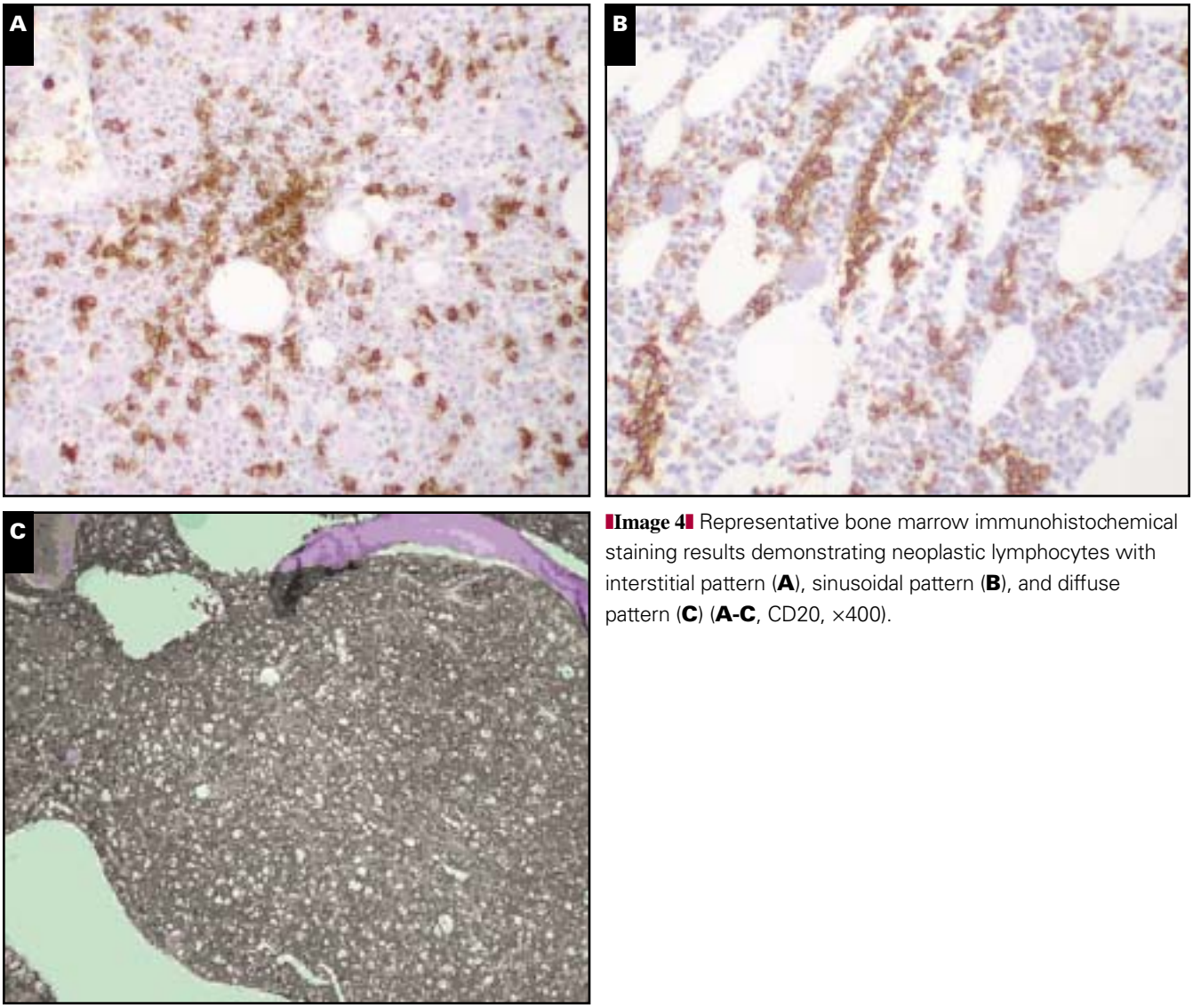

Image 4 Representative bone marrow immunohistochemical staining results demonstrating neoplastic lymphocytes with interstitial pattern (**A**), sinusoidal pattern (**B**), and diffuse pattern (**C**) (**A-C**, CD20, ×400).

SMZL were not seen, and most cases showed mixed patterns of interstitial intravascular (sinusoidal) involvement. The exceptions were 2 cases that showed exclusive sinusoidal involvement, 1 case with exclusive interstitial involvement and 1 with diffuse bone marrow involvement. Other features of our cases that varied from those characteristically seen in bone marrow biopsy specimens of HCL included the absence of increased reticulin fibrosis and lack of TRAP staining, which are typical of HCL-V.[1,2] Therefore, the marrow features observed in our cases are most consistent with HCL-V rather than SMZL or HCL.

The histologic features of HCL-V in the spleen also are not well described in the literature but are thought to closely resemble HCL with primarily involvement of the red pulp.[1,2] SMZL in contrast, shows predominantly white pulp involvement.[6,12,18] The 3 cases with splenic material in our series all showed diffuse effacement with marked red pulp involvement. The white pulp was overrun from the red pulp neoplasm and not clearly visible or distinct. Although not definitive because of the extent of disease involvement, these findings are more consistent with HCL-V rather than SMZL.

Most of the atypical lymphocytes in our cases had hair-like cytoplasmic projections and other cytologic features similar to HCL cells. There was no clear evidence of hair polarity as described for SMZL cells.[1] Moreover, the atypical lymphocytes did not seem to be smaller than classic HCL cells, as has been described for SMZL.[1] It is interesting that only 1 case had significant numbers of atypical lymphocytes with prominent nucleoli similar to prolymphocytes. It is possible, however, that our inability to identify nucleoli in some cases could be related to suboptimal smear quality. Although prominent nucleoli have been reported to be a typical finding in HCL-V,[1,2] our series suggests that they may not be present or easily visible in many cases that have may other features of HCL-V.

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Evaluation of immunoglobulin heavy chain isotype expression represents another way to possibly differentiate HCL-V from SMZL. An unusual feature of HCL, not typically observed with other B-cell lymphoproliferative disorders, is the expression of preswitched (IgM/IgD) and postswitched (IgG/IgA) immunoglobulins by the same cells in approximately 40% of cases related to differential RNA processing.[9] In contrast, SMZL cells characteristically express IgM with IgD and lack IgG or IgA.[12,18] Our finding of IgG expression without other isotypes in 2 of 4 cases and coexpression of preswitched with postswitched immunoglobulin on the same cells in the other 2 cases further supports our cases as being more similar to HCL than SMZL. The only other study of heavy chain isotype expression in HCL-V also seemed to find coexpression of preswitched and postswitched isotypes in 1 or 2 of 11 cases examined, along with a majority of cases expressing IgG.[1] However, that study used only fluorescence microscopy and, therefore, might not have been sensitive enough to detect all cases showing coexpression of preswitched and postswitched isotypes.

In conclusion, the clinical, morphologic, and isotype expression findings suggest that most if not all of our CD103+ B-cell lymphoproliferative disorder cases represent what often is called HCL-V. Because HCL-V is thought to be rare and had not been well characterized in the literature, this study extends what is known about this entity and confirms it can be clinically, immunophenotypically, or morphologically distinguished from HCL and SMZL. In addition, it suggests that peripheral blood B-cell lymphoproliferative disorders with a CD103+, CD11c+, CD25– phenotype would, on inspection of bone marrow and other tissue biopsy specimens, most likely represent cases of HCL-V rather than peripheralized SMZL. This study also has better established that HCL-V closely resembles HCL in many respects, including the pattern of bone marrow infiltration. However, distinguishing HCL-V from HCL using immunophenotypic and other criteria is important because patients with HCL-V seem to have different clinical features and poor responses to conventional HCL therapies.[1,3,4] Further studies are needed to better define how HCL-V might be related to HCL or whether it should be considered a distinct clinicopathologic entity.

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