CD5– Mantle Cell Lymphoma

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Abstract

Mantle cell lymphoma (MCL) typically expresses B-cell antigens and CD5 and overexpresses bcl-1 protein. However, unusual cases of bcl-1+ and CD5– MCL have been observed, posing a practical challenge for correct diagnosis and management. We identified 25 cases (48 samples) of bcl-1+ and CD5– lymphoma. CD5 expression was assessed by flow cytometric analysis alone (1 case), immunohistochemical analysis alone (17 cases), or dual flow cytometric/immunohistochemical methods (7 cases). The morphologic features were consistent with MCL with centrocytic cytomorphology in 20 cases and blastic variant in 5 cases. The t(11;14) was confirmed in 8 of 11 cases by fluorescence in situ hybridization of paraffin-embedded tissue. Cytogenetic analysis revealed the t(11;14) within a complex karyotype in 2 additional cases. These data show that MCL may lack CD5 expression. Evaluation of bcl-1 expression by immunohistochemical analysis or molecular genetics may be indicated if MCL is suspected clinically or morphologically despite a lack of CD5 expression.

Mantle cell lymphoma (MCL) is a distinct clinicopathologic entity recognized in the Revised European-American classification of lymphoid neoplasms1 and the current World Health Organization lymphoma classification.2 Most patients with MCL are elderly men who have an advanced stage of disease at diagnosis. Both nodal and extranodal involvement, including the spleen, bone marrow, gastrointestinal tract, or Waldeyer ring, are common. The clinical course is relatively aggressive, with poor response to conventional therapy. The common histologic features include effaced lymphoid architecture by a monomorphic lymphoid population with a vaguely nodular, diffuse, or mantle zone growth pattern. The classic cytomorphologic features include small to mediumsized lymphoid cells with irregular nuclear contours and scanty cytoplasm, closely resembling centrocytes. Blastic variants include a spectrum of intermediate to large cells with round or irregular nuclei and finely dispersed chromatin. MCL typically expresses B-cell antigens (CD19 and CD20), as well as CD5, and is CD10– and CD23–. The characteristic translocation, t(11;14)(q13;q32), between the immunoglobulin heavy chain and the cyclin D1 (bcl-1) genes results in overexpression of the cyclin D1/bcl-1 oncoprotein. Detection of bcl-1 by immunohistochemical analysis is highly specific for the diagnosis of MCL.1-5 Based on immunophenotyping by flow cytometric and immunohistochemical analysis, MCL usually can be separated from other low-grade B-cell lymphoproliferative disorders such as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), follicular lymphoma, marginal zone B-cell lymphoma (MZL), and hairy cell leukemia (HCL).

The ability to distinguish MCL from other low-grade B-cell lymphomas is extremely important because of the differences
in the treatment options and clinical course. In many cases, the overall histologic and cytomorphologic features suggest the diagnosis; immunophenotyping is clearly helpful for reaching the correct diagnosis and improves the diagnostic accuracy by some 10% to 45%. The value of immunophenotyping becomes more critical in the morphologic variants or in scanty specimens, such as those from fine-needle aspiration. However, undue reliance on one criterion (such as CD5 coexpression by B cells) may lead to an erroneous diagnosis. The prototypic MCL is CD5+ and bcl-1+ and CD10− and CD23−. If CD5 is negative, without investigation of bcl-1 expression, a diagnosis of low-grade lymphoma of a non-MCL type may be made. There are, however, unusual cases of bcl-1+ and CD5− B-cell lymphoma, which pose a practical challenge for correct diagnosis and management. It has been suggested these cases may represent a CD5− variant of MCL, and we present more data to support this hypothesis.

**Materials and Methods**

**Specimens**

We obtained bcl-1+ and CD5− B-cell lymphoma specimens from 25 patients (48 samples) from the IMPATH (New York, NY) database between February 1999 and November 2001. These included samples from blood, bone marrow, body fluids, fine-needle aspiration samples, and fresh tissues (lymphoid and extranodal) for flow cytometric analysis and formalin-fixed, paraffin-embedded tissues for immunohistochemical study. All MCL diagnoses initially were made at IMPATH before chemotherapy was given (except for case 17). Plasma cell neoplasms and HCL that were CD5− and bcl-1+ were not included in the study.

**Cytomorphologic Studies**

Cytocentrifuge preparations from bone marrow or peripheral blood and touch imprints from fresh tissue were prepared from flow cytometric specimens for cytologic correlation. Whenever there was sufficient lymphoid or extranodal tissue, a portion of the tissue was fixed in formalin and embedded in paraffin for morphologic correlation. Paraffin sections also were prepared from bone marrow core biopsy specimens, using standard procedures after decalcification for 40 minutes (Rapid bone decalifier, American Master*Tech Scientific, Lodi, CA). H&E sections from the original formalin-fixed, paraffin-embedded tissue blocks were used for histologic diagnosis in the majority of cases.

**Immunophenotypic Studies**

Multicolor flow cytometric analysis was performed with fresh cell suspensions in accordance with guidelines outlined in the US-Canadian Consensus Conference on flow cytometric

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**Table II**

**CD5− and bcl-1+ Mantle Cell Lymphoma Case Summary**

<table>
<thead>
<tr>
<th>Case No./Sex/ Age (y)</th>
<th>Type of Study</th>
<th>Tissue Studied</th>
<th>t(11;14)*</th>
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</thead>
<tbody>
<tr>
<td>1/M/69</td>
<td>IHC</td>
<td>Lymph node</td>
<td>ND</td>
</tr>
<tr>
<td>2/M/71</td>
<td>IHC/FCM</td>
<td>Bone marrow, small bowel (2 specimens)</td>
<td>+</td>
</tr>
<tr>
<td>3/M/76</td>
<td>IHC/FCM</td>
<td>Lymph node</td>
<td>+</td>
</tr>
<tr>
<td>4/M/73</td>
<td>IHC/FCM</td>
<td>Right and left tonsil (2 specimens)</td>
<td>ND</td>
</tr>
<tr>
<td>5/M/66</td>
<td>IHC</td>
<td>Stomach, colon</td>
<td>ND</td>
</tr>
<tr>
<td>6/F/100</td>
<td>IHC</td>
<td>Duodenum</td>
<td>ND</td>
</tr>
<tr>
<td>7/F/62</td>
<td>IHC</td>
<td>Skin</td>
<td>ND</td>
</tr>
<tr>
<td>8/F/74</td>
<td>IHC</td>
<td>Tonsil, cecum</td>
<td>+</td>
</tr>
<tr>
<td>9/F/74</td>
<td>IHC</td>
<td>Lung</td>
<td>–</td>
</tr>
<tr>
<td>10/F/58</td>
<td>IHC/FCM</td>
<td>Lymph node, colon (2 specimens), salivary gland, bone marrow</td>
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</tr>
<tr>
<td>11/F/61</td>
<td>IHC/FCM</td>
<td>Bone marrow (7 specimens), colon</td>
<td>–</td>
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<td>12/F/62</td>
<td>IHC/FCM</td>
<td>Bone marrow, peripheral blood</td>
<td>+</td>
</tr>
<tr>
<td>13/F/71</td>
<td>IHC†</td>
<td>Lymph node</td>
<td>+</td>
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<td>14/F/66</td>
<td>IHC</td>
<td>Tonsil</td>
<td>ND</td>
</tr>
<tr>
<td>15/F/82</td>
<td>IHC/FCM</td>
<td>Lymph node, peripheral blood</td>
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<td>IHC</td>
<td>Lymph node</td>
<td>ND</td>
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<tr>
<td>17/M/56</td>
<td>FCM</td>
<td>Peripheral blood, skin</td>
<td>+</td>
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<tr>
<td>18/F/66</td>
<td>IHC</td>
<td>Lymph node, pharynx (2 specimens)</td>
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</tr>
<tr>
<td>19/M/79</td>
<td>IHC†</td>
<td>Colon</td>
<td>ND</td>
</tr>
<tr>
<td>20/M/69</td>
<td>IHC</td>
<td>Small bowel</td>
<td>+</td>
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<td>21/M/73</td>
<td>IHC</td>
<td>Lymph node</td>
<td>+</td>
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<tr>
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<td>ND</td>
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<tr>
<td>23/F/77</td>
<td>IHC</td>
<td>Bone marrow</td>
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<tr>
<td>24/M/63</td>
<td>IHC</td>
<td>Tonsil, pancreas</td>
<td>ND</td>
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<tr>
<td>25/M/62</td>
<td>IHC</td>
<td>Lymph node, stomach</td>
<td>ND</td>
</tr>
</tbody>
</table>

FCM, flow cytometric; IHC, immunohistochemical; ND, not done.

† Fluorescence in situ hybridization, except cases 12 and 17, which were done by standard karyotypic analysis. Flow cytometric analysis at another institution showed CD5− lymphoma.

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analysis. Briefly, cell suspensions from solid tissues were prepared using a manual dispersion method. Isolated cells were preincubated in RPMI 1640 medium supplemented with 10% fetal bovine serum to minimize nonspecific binding of antibodies. Erythrocytes in bone marrow and blood specimens were lysed with a 0.008% solution of ammonium chloride. Cells were washed with phosphate-buffered saline and incubated with cocktails of antibodies conjugated to fluorescein isothiocyanate (FITC), phycoerythrin (PE), peridinin chlorophyll protein, or allophycocyanin. The antibody cocktails were prepared by Becton Dickinson Immunocytometry Systems (San Jose, CA). The relevant antibody cocktails are listed in Table 2, in which CD5 (clone UCHT2) was labeled with FITC. In some cases, additional staining with PE-conjugated CD5 (also clone UCHT2) was performed when FITC-conjugated CD5 intensity was thought to be equivocal. Data acquisition was performed on a FACScalibur flow cytometer (Becton Dickinson Immunocytometry Systems), and the data were analyzed with CellQuest software (Becton Dickinson Immunocytometry Systems). The levels of antigen expression were depicted on multiple dual-parameter scattergrams. Antigen negativity was defined as having the same fluorescent intensity as the negative control and the isotype control. Nonviable cells in the tissue samples were excluded by using 7-amino actinomycin D or propidium iodide.

Immunohistochemical studies were performed with 4-µm sections from formalin-fixed, paraffin-embedded tissue. Briefly, after deparaffinization, the specimens were treated with low pH (5.95 ± 0.05) buffer for CD20 and CD3 staining or with high pH (9.5 ± 0.05) for CD5 and bcl-1 staining and then autoclaved at 105°C for 3 minutes. Immunostaining was performed using a labeled streptavidin-biotin procedure in a TechMate 500 autostainer (Ventana Medical Systems, Tucson, AZ), and the colorimetric reaction was completed with diaminobenzidine (Sigma, St Louis, MO). The relevant antibodies used in routine diagnosis were as follows: CD20 (L-26, 1:200, DAKO), CD3 (polyclonal, 1:1,500, DAKO), CD5 (4C7, 1:2,000, Novocastra, Newcastle upon Tyne, England), and bcl-1 (DCS-6, 1:500, Neomarkers, Fremont, CA). A valid CD5 stain was accepted when the positive external control (tonsil or lymphoid tissue) and internal control (ie, admixed nonneoplastic T cells) samples were positive. A negative staining result was defined as absence of staining in the target cells as seen in the negative control sample. Cases with weak or focal staining were designated as positive.

### Cytogenetics and Fluorescence In Situ Hybridization

Peripheral blood or bone marrow cells were cultured overnight with parallel samples, unstimulated and stimulated with pokeweed and phytohemagglutinin mitogens. Colcemid, 0.1 mL (10 µg/mL), was added to cultures for 30 minutes. The cells were fixed in methanol/acetic acid (3:1) after hypotonic treatment in a 0.075-mol/L concentration of potassium chloride. G-banding was performed using trypsin and Giemsa staining. Karyotypes were described according to the 1995 International System for Human Cytogenetic Nomenclature.

Interphase fluorescence in situ hybridization (FISH) was performed using a dual-colored probe for the IgH (immunoglobulin heavy chain) locus and for the CCND1 (cyclin D1) locus (both from VYSIS, Downers Grove, IL) according to the manufacturer’s recommendation. Briefly, 60-µm sections were cut from each block, as was a control block containing normal spleen tissue. After deparaffinization and rehydration, nuclei were harvested, resuspended in fetal bovine serum, and applied to slides. The probe was added to the slides after standard pretreatment and sealed under a coverslip. The slides and probe were codenatured at 90°C for 10 minutes and hybridized overnight at 37°C. Posthybridization washes were performed according to the VYSIS rapid wash method. A total of 200 to 500 nuclei from each block were scored by 2 observers (C.F.S. and C.S.B.) using a fluorescent microscope. Normal cells had 2 red and 2 green probe signals. Cells positive for the t(11;14)(q13;q32.3) had 1 red, 1 green, and 2 orange fusion signals.

### Results

#### Clinical Data

Twenty-five cases of CD5– and bcl-1+ lymphomas were identified, representing 10.6% (25/235) of the total MCL cases seen during the same period. There were 18 men and 7
women (M/F ratio = 2.6:1). Ages ranged from 38 to 100 years (median, 69 years). In 12 cases, 2 or more sites were involved. Lymph nodes were involved in 10 cases; the gastrointestinal tract in 9 cases; bone marrow, peripheral blood, or both in 7 cases; and tonsil in 4 cases. Other organs involved included skin, lung, submandibular gland, and pancreas (Table 1). Since IMPATH is a referral laboratory, staging for many cases included in the study was done locally. Therefore, the percentage of patients who had multiorgan involvement may be an underestimate. For example, for case 5, gastric and colonic biopsy specimens were analyzed in this laboratory, but the patient had widespread lymphadenopathy and splenomegaly when he was examined initially.

Follow-up data were available for 4 cases. One patient (case 10) had stage IVb disease and was treated with multiple regimens of chemotherapy (including fludarabine; cladribine; a combination of cyclophosphamide, doxorubicin [hydroxydaunomycin], vincristine [Oncovin], and prednisone [CHOP]; rituximab), radiation, and allogeneic bone marrow transplantation in early 2001. She died of disease 2 years after the diagnosis. The second patient (case 8) with stage III disease was treated with hyper-CVAD (cyclophosphamide, vincristine, Adriamycin [doxorubicin], and dexamethasone) and has persistent disease. The third patient (case 2) had stage IIb disease, was treated with 8 cycles of CHOP, and has been free of disease for 9 months. The fourth patient (case 17) was diagnosed with “marginal zone lymphoma” in 1988, treated with splenectomy and multiple regimens of chemotherapy, and now has persistent stage IV disease.

Morphologic Features

As seen in classic CD5+ MCL, both nodal and extranodal tissue involvement by CD5– MCL occurred. In the patients with gastrointestinal involvement, multiple lymphomatous polyps were seen. Histologically, most cases manifested with either nodular or diffuse patterns. Because some biopsy specimens were small, however, the histologic pattern was difficult to determine in some cases. Nevertheless, at least half of the cases showed a recognizable nodular pattern. Distinct expansion of the mantle zone surrounding the germinal centers was evident in about one third of the cases Image 1. Cytologically, the neoplastic cells in 20 of 25 cases showed a monotonous population of atypical small to medium lymphocytes with irregular and indented nuclei, moderately coarse chromatin, inconspicuous nucleoli, and scant cytoplasm (centrocytic type) Image 2. Monocytoid differentiation was seen occasionally. Five of 25 cases demonstrated larger cells with dispersed or vesicular chromatin, small nucleoli, and frequent mitosis, corresponding to the blast variant. Scattered histocytes were associated with both cell types.

Lymphoma cells in peripheral blood samples in cases of centrocytic MCL were small to medium lymphocytes with moderately clumped chromatin and irregular, indented, and cleaved nuclear contours Image 3. The pattern of bone marrow involvement by centrocytic MCL may be nodular (with or without a paratrabeicular component) or diffuse. The marrow with large cell variant MCL showed a diffuse infiltrative pattern.

Immunophenotyping

Seventeen cases were studied by immunohistochemical analysis alone. These cases included 23 samples (Table 1). The neoplastic B cells in all cases (both typical centrocytic and large cell variants) clearly showed CD20+ B cells with strongly positive bcl-1 nuclear staining (Image 1). CD5 staining highlighted the same T-cell population as did CD3 (used as an internal control), and no visible CD5 staining was seen on the B cells. The negative CD5 staining of B cells was a constant finding in the cases with multiple samples obtained at different locations and/or at different times; some patients had undergone chemotherapy, but others had not. Lack of CD5 was not associated exclusively with any morphologic subtypes.

Immunostains were performed in 3 cases with decalcified core biopsy specimens. Two of these had lack of CD5 expression also seen in other, nondecalcified soft tissues. Therefore, lack of CD5 expression does not seem to be an artifact of decalcification in these cases.

Samples from 7 cases were studied by immunohistochemical and flow cytometric analysis, and the phenotypes, including positive bcl-1 expression, were confirmed by immunohistochemical analysis. All cases showed monoclonal B cells with negative CD5 expression. Negativity for CD5 also was consistent in different biopsy specimens from the same patient Image 4. Flow cytometric analysis alone was performed in 1 case in which the patient had a history of “marginal zone B-cell lymphoma”; the case was CD5+. The positive bcl-1 expression was confirmed by subsequent examination of a skin biopsy specimen (case 17). The intensity of CD20 and light chain expression usually was moderate. CD10 usually was negative. CD23 was dimly positive in 4 samples from 3 patients. The expression of CD11c was variable. Because of the negative CD5 and dim CD23 expression, 2 cases had been misinterpreted based on flow cytometric analysis alone and subsequently were reclassified after evaluation of histomorphologic features and immunohistochemical results.

FISH and Conventional Cytogenetics

FISH study on paraffin-embedded tissue was performed in 11 cases in which paraffin-embedded tissue was available. Eight of these cases (2, 3, 8, 10, 13, 18, 20, and 21 [Table 1])
Image A, Colonic biopsy specimen from a case of lymphomatous polyposis (×40).

B, Mantle cell lymphoma (MCL) from a lymph node biopsy specimen with centrocytic cell type (×100).

C, Blastic variant MCL from a lymph node biopsy specimen (×200). Note that CD5 stains the same population as does CD3.
showed positive t(11;14) fusion signals. Among the remaining 3 cases, 1 sample (case 5) showed 20% of cells with extra signals, and 8% of cells showed extra signals that included 1 or 2 fusion signals. The other 2 cases were negative. Complex karyotypes were seen by standard cytogenetic analysis in samples from 2 cases without paraffin blocks for FISH study. One peripheral blood sample (case 17) showed t(11;14) in addition to +der(3),t(1;3)(23;p23), t(5;5)(q33;p15),+mar, and the second was a bone marrow sample (case 12) that showed t(11;14), del(2)(q13;q37), add(3)(q25), +7, +12, and add(17)(q25). Both were confirmed to be bcl-1+ by immunohistochemical analysis of subsequent biopsy specimens.

Discussion

We reported 25 cases (48 samples) of CD5− B-cell lymphoma with positive bcl-1 expression, morphologic features, and molecular genetic analysis results that are consistent with MCL.

CD5 expression was not detected in any cases by flow cytometry on fresh tissue (conjugated with FITC or PE) and/or immunohistochemical analysis on formalin-fixed, paraffin-embedded tissue at different sites and at different times. The sensitivity of CD5 staining by immunohistochemical analysis with the monoclonal antibody 4C7 is considered to be similar to that of the flow cytometric method as previously reported. Morphologically, these cases had features similar to their CD5+ counterparts and showed either a diffuse or nodular pattern with centrocytic or blastic cytologic features. Eight of 11 cases studied by FISH demonstrated the t(11;14) translocation. We believe these cases represent an antigenic variant of MCL, which has no detectable CD5 expression by flow cytometric and/or immunohistochemical methods. This is the largest series with comprehensive analysis of this subset of MCL.

A handful of cases of CD5− MCL have been documented sporadically. An abstract from Kaptain et al discussed 7 cases of CD5− and bcl-1+ MCL. Their cohort contained 5 men and 2 women, aged 38 to 80 years, and all cases showed a diffuse histologic pattern. The authors concluded that CD5− and cyclin D1+ MCL had clinical
features similar to the CD5+ counterparts. However, 3 cases showed unusually long survival. A single case reported by Bell et al was a 78-year-old man with lymph node, spleen, peripheral blood, and bone marrow involvement. The lymphoma was CD5– and had the t(11;14) translocation as revealed by cytogenetic and polymerase chain reaction studies. Therefore, CD5– MCL was diagnosed. MCL without CD5 expression has been observed in a few studies and constitutes approximately 11% of the cases; these data are similar to those for our cohort. However, no separate study was performed on the subset of CD5– cases reported in these articles. In a review by Arber and Weiss, CD5 was expressed in only 79.9% of nonleukemic MCLs but in 93% of leukemic MCLs. In addition, Shapiro et al noted 10 cases of CD5– MCL in their series of 40 cases of CD5– lymphoproliferative disorders based on flow cytometric analysis. These data support the concept that a subset of MCLs may not have detectable CD5 expression.

Additional karyotypic abnormalities besides the t(11;14) translocation have been reported frequently in MCL. There were 2 cases with a complex karyotype in our series. The case with peripheral blood and bone marrow involvement (case 12) was a blastic variant, which demonstrated bcl-1 staining on the bone marrow core biopsy specimen. The abnormality of chromosome 17 in this case may be associated with the leukemic phase of MCL, as proposed by Onciu et al. The peripheral blood sample from case 17 also showed a complex karyotype; recent follow-up on a skin biopsy specimen from this patient showed bcl-1 positivity, confirming involvement by MCL.

The differential diagnosis of bcl-1+ hematologic malignant neoplasms includes HCL, plasma cell neoplasia, rare cases of so-called atypical CLL/SLL and splenic MZL/lymphoplasmacytic lymphoma. HCL can be easily excluded because MCL lacks CD25 and CD103 expression by flow cytometric analysis, and it lacked the classic HCL histologic features in our series. Plasma cell myeloma can be excluded because all cases in our series showed a lymphoma phenotype (CD45 bright and CD19 and CD20 moderate), and none of these cases resembled plasma cells morphologically. With regard to the atypical CLL/SLL, we relied more on the classic histologic features to differentiate MCL from the rarely reported CLL/SLL or prolymphocytic variants. In addition, the intensity of CD20 and surface immunoglobulin is dimmer in CLL/SLL. Most cases of atypical CLL or prolymphocytic leukemia are bcl-1–, although rare cases were reported as positive. Some of the bcl-1+ atypical CLL and prolymphocytic cases have been identified as MCL.
Therefore, it is possible that the cases of bcl-1+ atypical CLL and prolymphocytic leukemia may be a heterogeneous group. Although bcl-1 expression has been reported in some cases of splenic MZL, relatively recent studies have not demonstrated the t(11;14) in well-documented cases of splenic MZL.3,42 None of our cases resembled lymphoplasmacytic lymphoma.

Other differential diagnoses for CD5– lymphomas include nodal MZL and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) origin. Nodal MZL is a low-grade and usually localized lesion, and it features monocytoid B-cell proliferation with expansion of the marginal zone. A monocytoid B-cell proliferation with lymphoepithelial lesions and focal follicular hyperplasia is characteristic of MALT lymphoma. The neoplastic cells are generally CD5– with rare exceptions.33,34 Both of these lymphomas are bcl-1–.

As IMPATH is a referral laboratory, we do not have extensive staging and follow-up data. However, the clinical manifestation of CD5– MCL does not seem substantially different from that of its CD5+ counterpart, since many patients had multiorgan involvement at diagnosis. However, a larger cohort with close follow-up is needed to determine any significant difference in clinical outcome between this variant and the classic phenotype.

We identified a cohort of MCL cases without detectable CD5 expression, which may be a potential pitfall for this diagnosis. With flow cytometric and immunohistochemical studies becoming the standard of care in diagnosing lymphoma and fine-needle aspiration being used more widely, it is important to recognize this variation of CD5 expression and the limitations of flow cytometric and immunohistochemical analysis, especially when only a limited panel is used for lymphoma classification. Undue reliance on 1 criterion (such as CD5 coexpression by B cells) may lead to an erroneous diagnosis. Evaluation of cyclin D1/bcl-1 expression by immunohistochemical analysis or molecular genetics is indicated if MCL is suspected clinically or morphologically despite lack of CD5 expression.

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References


