Monocytoid B-Cell Lymphoma: Its Evolution and Relationship to Other Low-Grade B-Cell Neoplasms

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Monocytoid B-cell lymphoma (MBCL) is a newly recognized B-cell neoplasm of uncertain histogenesis. The cytologic features of the neoplastic monocytoid B lymphocytes are virtually identical to those of hairy cell leukemia (HCL). As with HCL, progression of MBCL to a higher histologic grade is very unusual. However, whereas circulating leukemic cells are a characteristic feature of HCL, peripheral blood involvement has not been reported in MBCL. We recently studied a patient with MBCL of the spleen and axillary lymph nodes who developed peripheral blood involvement by MBCL cells. Unlike the cells of HCL, the circulating MBCL cells exhibited strong acid phosphatase activity that was tartrate sensitive. The leukemic cells had the antigenic phenotype IgMα, CD20+, CD11c+, CD5-, CD25(TAC)+, and PCA-1+. Immunogenetic studies of both lymph node and peripheral blood cells revealed identical immunoglobulin heavy-chain gene rearrangements. When compared with a series of HCL, the immunophenotype was similar except for the absence of CD1a and TAC. Progression of the MBCL to a large cell lymphoma, also expressing IgMα, was documented in an abdominal lymph node of this patient. Therefore, although rare, peripheral blood involvement by lymphoma cells may occur during the course of MBCL and should be distinguished from HCL with cytochemical and immunophenotypic studies. In addition, comparison of the clinical, pathologic, and immunologic features of MBCL with those of other low-grade B-cell neoplasms suggests that a close lineage relationship exists between MBCL and HCL.

M ONOCYTOID B-lymphocytes (MBLs) have been observed as a reactive component in a variety of inflammatory and neoplastic lymph node disorders. The malignant counterpart of these cells has recently been recognized, and the clinical and histopathologic features in a series of 21 patients with "monocytoid B-cell lymphoma" (MBL) have been described. Clinically, MBCL behaves as a low-grade lymphoma that involves lymph nodes almost exclusively and rarely evolves to a more aggressive lesion. In contrast to the findings in other low-grade B-cell neoplasms, no peripheral blood involvement by MBCL cells has been previously reported.

A specific combination of morphologic, immunologic, and clinical features makes MBCL a unique lymphoproliferative disorder. However, some of the clinical and pathologic features seen in MBCL are also observed in other low-grade B-cell neoplasms such as small lymphocytic lymphoma and, especially, hairy cell leukemia (HCL). Our purpose in this report is to detail the findings in an unusual case of MBCL that both peripheralized and evolved to a more aggressive histologic grade. In addition, we compared the clinical and pathologic findings in this case with those observed in other low-grade B-cell neoplasms.

CASE HISTORY

A 41-year-old man presented with complaints of malaise, fever, and a 15-lb weight loss occurring over a period of 4 weeks. Physical examination revealed left axillary and inguinal lymphadenopathy. On further workup, pancytopenia, retropertitoneal adenopathy, mild hepatomegaly, and marked splenomegaly were discovered. At laparotomy, a spleen weighing 1,500 g was removed. The splenic cords were diffusely infiltrated with monocytoid B cells; only a small amount of residual white pulp remained. MBLs were also sparsely present within the splenic sinuses. An axillary lymph node removed at the time of laparotomy also contained MBCL, but a splenic hilar lymph node contained a diffuse large-cell lymphoma (LCL). The bone marrow at the time of the patient's initial workup was not provably involved by a lymphoproliferative disorder. Systemic chemotherapy was begun with a regimen that included cyclophosphamide, adriamycin, VP-16, vincristine, bleomycin, cytosine arabinoside, methotrexate with leucovorin rescue, and prednisone. After the second cycle of chemotherapy, a routine peripheral blood analysis showed mild anemia (hematocrit 35%), a platelet count of 340 × 10^9/L and a WBC count of 4.5 × 10^9/L. The WBC differential at that time was 25% segmented neutrophils, 10% monocytes, and 65% "atypical" mononuclear cells. A repeat computed tomography (CT) scan of the abdomen revealed disappearance of the retropertitoneal lymphadenopathy. The peripheral adenopathy had also resolved. After four cycles of therapy, the drug regimen was changed to m-BACOD (bleomycin, adriamycin, cyclophosphamide, vincristine, methotrexate) due to pancytopenia. The patient is now asymptomatic, although immunologic studies show minimal bone marrow involvement by MBCL.

MATERIALS AND METHODS

All excised tissues were fixed in 10% neutral buffered formalin, embedded in paraffin, and stained with hematoxylin and eosin for routine histologic examination. Portions of each tissue sample were embedded,6,7

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snap-frozen in isopentane precooled in liquid nitrogen. Surface immunoglobulin expression was evaluated with the direct technique on cryostat-cut sections. A modification of the avidin-biotin complex (ABC) technique was used for evaluation of other membrane-associated antigens. Immunophenotypic analysis of peripheral blood cells was performed on mononuclear cell suspensions with a Coulter Epics 742 flow cytometer (Coulter, Hialeah, FL); 5,000 cells were counted for each antibody determination. A large panel of antibodies was used in these studies. Included were antibodies directed against the lymphoid-associated antigens CD2, CD3, CD4, CD5, CD8, CD19, CD20 (Coulter), CD7 (Becton Dickinson, Mountain View, CA), terminal deoxynucleotidyl transferase (Bethesda Research Laboratory, Gaithersburg, MD), and the immunoglobulin light and heavy chains (TAGO, Burlingame, CA). The myeloid-directed antibodies My4 (CD14), My7 (CD13), and My9 (CD33) from Coulter and Leu-M5 (CD11c) from Becton Dickinson were also used. Markers for CD10 (Coulter) and CD25 (Becton Dickinson) completed the antibody panel. Cytochemical reactions for Sudan black B, myeloperoxidase, acid phosphatase with and without tartrate inhibition, and esterase with a-naphthyl butyrate as substrate were performed on peripheral blood smears according to standard methods. High-molecular-weight DNA was digested with appropriate restriction endonucleases, and Southern blot hybridizations with nick-translated probes were used for evaluation of immunoglobulin and T-cell receptor gene rearrangements. Immunoglobulin gene probes were derived from the plasmids pHuiH, pHuxc, and pHuAc2, a gift from Dr Phil Leder. The T-cell receptor b-chain probe was prepared from the plasmid piurkat-2 provided by Dr Tak Mak.

RESULTS

Morphologic findings. Axillary lymph node sections showed an interfollicular infiltration by atypical lymphoid cells (Fig 1). Abundant pale cytoplasm, often with relatively distinct cell borders, and small vesicular nuclei with occasional “monocytoid” features were characteristics of the neoplastic lymphoid cells. Only a few scattered Malpighian corpuscles were present in sections of the spleen. The splenic cords contained a diffuse infiltrate of atypical lymphocytes with cytoplasmic features similar to those observed in the axillary lymph node; the splenic sinuses were open and also contained scattered MBL (Fig 2). The histologic findings in the spleen were therefore virtually identical to those seen in HCL. However, unlike HCL, no pseudo-sinuses (blood lakes) were apparent. The splenic hilar lymph node sections showed a diffuse LCL which was classifiable according to the Working Formulation as being of the large noncleaved cell type (Fig 3). This lymph node was completely involved by LCL; no transitional area with MBCL was evident.

Peripheral blood smears taken after the second cycle of chemotherapy showed a predominant population of atypical cells (Fig 4). Homogeneous round to reniform nuclei and moderately abundant cytoplasm showing occasional projections made HCL a diagnostic possibility. However, the atypical cells contained acid phosphatase that was sensitive to tartrate inhibition (Fig 5). Cytochemical studies for Sudan black, peroxidase, and nonspecific esterase yielded no
Fig 4. Monocytoid B-cell lymphoma cells in peripheral blood. The cells are slightly larger than normal lymphocytes and have abundant pale-gray cytoplasm with poorly defined cytoplasmic borders. Occasional nucleoli are seen. Cytologically, these cells cannot be distinguished from those seen in hairy cell leukemia (Wright-Giemsa, original magnification ×1,000).

Fig 5. (A) Acid phosphatase without tartrate inhibition is strongly positive in most circulating MBCL cells. (Original magnification ×1,000.) (B) The acid phosphatase activity is completely inhibited in the presence of tartrate. (Original magnification ×1,000.)

Fig 6. Bone marrow showing involvement by monocytoid B-cell lymphoma. The appearance is indistinguishable from bone marrow involvement by HCL. However, a reticulin fibrosis is not present (hematoxylin & eosin, original magnification ×312).

Fig 7. DNA hybridization studies of axillary lymph node and peripheral blood mononuclear cells. Identical clonally rearranged immunoglobulin heavy-chain genes are evident with all three restriction endonucleases.

DISCUSSION

MBLs have recently been recognized as a reactive component in a variety of benign and neoplastic lymph node disorders. The morphologic features of MBL originally prompted designations such as "monocytoid cells" and "immature sinus histiocytes." However, studies by our laboratory, as well as others, documented the presence of B-lymphocyte antigens and polyclonal immunoglobulins on the surface of these cells. Recently, the malignant counter-
part of these reactive cells has been described; immunologic studies revealed a monoclonal pattern of surface immunoglobulin expression. We proposed the term MBCL for this newly recognized neoplastic disorder.

We recently reported the clinical and histopathologic features of MBCL in a series of 21 patients. Most of these patients had limited stage disease (I or II). In this series, MBCL behaved clinically as a low-grade neoplasm, and survival times were relatively long. The survival times may be long, in part, because MBCL usually does not progress to a more aggressive histologic grade. In addition, although peripheralization of malignant cells occurs in virtually all types of non-Hodgkins lymphomas and is common in well-differentiated lymphocytic lymphoma (WDLL), intermediate lymphocytic lymphoma (ILL), and especially in HCL, no case of MBCL with peripheral blood involvement has been previously reported.

We recently studied the evolution of MBCL in a patient with disease involving peripheral lymph nodes and spleen. A diffuse LCL was discovered in a splenic lymph node at the time of splenectomy. A leukemic phase of the MBCL was first noted several months after the initial diagnosis while the patient was undergoing chemotherapy. Immunophenotypic and antigen receptor gene rearrangement studies showed that the MBCL, the LCL, and the peripheral blood mononuclear cells were components of the same disease. Monoclonal expression of IgMA was present in all three tissue samples, and identical clonally rearranged immunoglobulin heavy-chain genes were detected in both the axillary lymph node and the peripheral blood MBCL cells.

Progression of WDLL to a higher histologic grade is not an uncommon event. Approximately 10% to 15% of these low-grade lymphomas undergo a Richter’s-like transformation to LCL. In addition, WDLL may occasionally undergo a prolymphocytic transformation. Because of its close genotypic relationship with WDLL, ILL presumably can also evolve in a similar fashion. In contrast to WDLL, however, there is no good evidence that HCL undergoes such changes. There are occasional reported cases of coincident LCL and HCL, but clonal evolution of one to the other has not been demonstrated. Like HCL, it is unusual for MBCL to evolve into a more aggressive form. In our recent series of 21 patients with MBCL, only one patient other than the one we report in this article has undergone histologic progression. Therefore, at least with respect to its tendency not to progress to a higher grade lymphoma, MBCL appears to be biologically more closely akin to HCL than to any other low-grade B-cell neoplasm.

MBCL and HCL are also very similar histologically. Indeed, as reported previously, the morphologic appearance of MBCL in lymph nodes is virtually identical to that of HCL. Both disorders may involve lymph node sinuses and interfollicular areas in a pattern characteristic of a leukemic infiltrate. MBCL and HCL differ, however, in their tendency to involve extranodal sites (Table 1). Spleen and bone marrow involvement, both of which are characteristic features of HCL, are rare in MBCL. In our recently reported series, only two of 21 patients had splenomegaly; neither of these patients underwent splenectomy, however, and histologic confirmation of lymphomatous involvement is not available. In addition, only two of nine patients in that series whose bone marrow was examined had disease in this site; in both cases, the lymphomatous infiltrate was primarily parabascular in location and was not associated with a reticulin fibrosis. Both of these findings are unusual features in HCL.

Cytologically, the circulating MBCL cells were indistinguishable from hairy cells. Other peripheral blood findings, however, were not typical of HCL. Specifically, pancytopenia was absent, and the circulating malignant cells were the predominant component of a normal WBC count. The platelet count was normal, and the hematocrit was depressed only slightly. The presence of circulating MBCL cells in this case is a novel finding, but the exact incidence of this occurrence is not known. Although seemingly rare, because of the apparent silent nature of the process, peripheral blood involvement by MBCL, albeit slight, may be more common than realized.

The immunophenotypic findings in the current case are similar to those previously reported for MBCL. When these findings are compared with those in a series of cases of HCL, some minor differences are apparent (Table 2). The receptor for IL-2 (TAC antigen) was not present on MBCL.

### Table 1. Distinguishing Clinical and Pathologic Features of Low-Grade B-Cell Neoplasms

<table>
<thead>
<tr>
<th>Feature</th>
<th>MBCL</th>
<th>HCL</th>
<th>WDLL</th>
<th>ILL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominant sites of involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Spleen</td>
<td>−</td>
<td>+</td>
<td>−/−</td>
<td>+</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TRAP</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Transformation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(to a higher histologic grade)</td>
<td>−</td>
<td>−</td>
<td>−/+</td>
<td>NS</td>
</tr>
</tbody>
</table>

Abbreviations: MBCL, monocytoid B-cell lymphoma; HCL, hairy cell leukemia; WDLL, well-differentiated lymphocytic lymphoma; ILL, intermediate lymphocytic lymphoma; TRAP, tartrate-resistant acid phosphatase; NS, not studied.

Present in >50% of cases (+); present in <10% of cases (−); present in 10% to 50% of cases.

### Table 2. Immunologic Comparison of Small Lymphocytic Neoplasms

<table>
<thead>
<tr>
<th>Antibody</th>
<th>MBCL</th>
<th>HCL</th>
<th>WDLL</th>
<th>ILL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD5</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD3</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD2</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD19</td>
<td>−/+</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD20</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Monoclonal slgs</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>CD11c</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>CD25</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>PCA-1</td>
<td>−/+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
</tbody>
</table>

Present in majority (>80%) of cases studied (+); absent in majority (>80%) of cases (−); not consistently present or absent (−/+).

Abbreviation: slgs, surface immunoglobulins.
cells but has typically been detected in HCL.20,21 The CD5 (Leu-1) antigen is expressed on most malignant cells in WDLL and IDL and is a useful diagnostic feature, its presence has not been reported in HCL. Positivity for CD5 is also usually not observed in MBCL and was not detected in the current study. However, exceptions to this may exist.23 The presence of acid phosphatase isoenzyme V, as detected by its resistance to tartrate inhibition, is a diagnostic feature in HCL.24 The circulating MBCL cells in our patient contained strong acid phosphatase activity, but this activity was inhibited by tartrate. Furthermore, all other MBCL which we have examined to date have also been TRAP negative (K. Sheibani, unpublished observation).

Although these minor immunophenotypic and cytochemical differences are useful for distinguishing between the two diseases, there is sufficient similarity between HCL and MBCL to suggest a close lineage relationship. For example, the myelomonocytic antigen CD1lc (Leu-M5), which is rarely present in other B-cell neoplasms,25 has been consistently detected in both HCL and MBCL.26 Moreover, the similar pattern of lymph node involvement by the two neoplasms and the tendency of both not to transform also suggest a closely related histogenesis.

There is a “sequence” of low-grade B-cell malignancies, classified as small lymphocytic lymphomas in the Working Formulation, that conforms to the corresponding scheme of normal B-cell differentiation and ranges from WDLL through ILL to lymphoplasmacytoid lymphoma, the most differentiated of the group. These small lymphocytic lymphomas share many features, both collectively and between individual pairs. Previous immunologic26,27 and functional28 studies on HCL suggest that clonal expansion in this disease occurs at a level of differentiation between that of WDLL and multiple myeloma. Because of the clinical, pathologic, and immunologic similarities to HCL, our studies suggest that the origin of MBCL occupies a closely adjacent site to the origin of HCL and is perhaps derived from cells that are close to plasma cells in differentiation.

Peripheral blood involvement of MBCL, as reported in this article, obscures a prime feature that differentiates this disease from HCL. In the peripheral blood, the only distinguishing features between the two disorders are the differences in TAC expression and TRAP reactivity. The current case suggests that peripheralization of MBCL should also be considered when a cytologically typical case of HCL is discovered to be “atypical” because of TRAP and TAC negativity and/or there are clinical findings at presentation that are unusual for HCL.

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