Nucleolated Variant of Mantle Cell Lymphoma With Leukemic Manifestations Mimicking Prolymphocytic Leukemia

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Key Words: Mantle cell lymphoma; Nucleolated variant; Cyclin D1; t(11;14); Prolymphocytic leukemia; Blood; Lymph node

Abstract

Chronic lymphoproliferative disorders sometimes can be difficult to classify. We report 4 cases characterized by large cells with distinct central nucleoli, reminiscent of prolymphocytic leukemia, but shown on further workup to represent mantle cell lymphoma. At initial examination, the patients had generalized lymphadenopathy, splenomegaly, and a leukemic blood picture. The peripheral blood showed many large cells with round to slightly irregular nuclei, single central nucleoli, and a fair amount of pale cytoplasm. The picture was not typical of prolymphocytic leukemia because of the presence of generalized lymphadenopathy and the large size of the circulating abnormal cells. Immunophenotypic study showed that the large lymphoid cells were CD5+CD23– mature B cells with overexpression of cyclin D1, and cytogenetic study demonstrated the translocation t(11;14)(q13;q32) in 3 patients. Lymph node biopsy confirmed a diagnosis of mantle cell lymphoma, pleomorphic variant, in all 4 patients. This study documents the existence of an unusual leukemic form of mantle cell lymphoma with prominent nucleoli; the clinicopathologic features that distinguish it from other chronic lymphoproliferative disorders are discussed.

Mantle cell lymphoma (MCL) is a lymphoid malignant neoplasm of mature pregerminal center naive B cells that express CD5, surface IgM, and surface IgD, but not CD23. The hallmark of this lymphoma is overexpression of cyclin D1, attributable to t(11;14)(q13;q32) causing juxtaposition of the bcl-1 (cyclin D1) gene to the immunoglobulin heavy chain gene, or other mechanisms deregulating the bcl-1 gene.1 Besides the classic type characterized by small cells with hyperchromatic nuclei, the blastoid and pleomorphic variants also have been recognized.2,3 Peripheral blood and bone marrow involvement is not uncommon in MCL during the course of disease.4 In a report on the cytologic findings of MCL manifesting with a leukemic phase, Wong et al5 observed in 1 patient the occurrence of leukemic cells that superficially resembled oversized prolymphocytes. We since have observed 3 additional cases with this unusual cytologic appearance. We therefore performed a comprehensive cytologic, histologic, and immunologic analysis on these 4 cases.

Materials and Methods

Case Selection

During the period July 1994 to December 2000, 20 patients were given a diagnosis of leukemic MCL at the Queen Elizabeth Hospital, Hong Kong, People’s Republic of China. The diagnosis of MCL was established based on an immunophenotype of CD5+CD19+CD23– and overexpression of cyclin D1. This was supplemented by lymph node histologic features and cytogenetic findings of t(11;14)(q13;q32). The 4 cases included in the study all
showed distinct central nucleoli. One case had been included in a previous report on MCL in leukemic phase. The clinical records were reviewed. The peripheral blood films, bone marrow aspirate smears, and trephine and lymph node biopsy specimens were retrieved for study.

Cytologic and Histologic Studies

The blood films and bone marrow aspirate smears were stained with May-Grünwald Giemsa. Lymph node biopsy specimens from all 4 cases and trephine biopsy specimens from cases 1 through 3 were available for study. Specimens were formalin fixed, paraffin embedded, sectioned, and stained with H&E. The trephine biopsy specimens were decalcified in EDTA.

Immunohistochemical Studies

Sections cut from the lymph node biopsy specimens were immunostained with the following monoclonal antibodies: NCL-CD5-4C7 to CD5 (Novocastra, Newcastle-upon-Tyne, England); NCL-CD23-1B12 to CD23 (Novocastra); DCS-6 to cyclin D1 (Ventana, Tucson, AZ); 1F8 and Ber-MAC-DRC to CD21 and CD35, respectively, to highlight the follicular dendritic cell meshwork (Dakopatts, Glostrup, Denmark); and DO-7 to p53 protein (Dakopatts). The streptavidin-biotin-peroxidase complex detection system was used, using the Ventana ES automated immunostainer. Antigen retrieval was achieved by heating the slides in EDTA buffer at pH 8 in a pressure cooker for 2.5 minutes. An appropriate positive control was mounted on every slide to ascertain the validity of the stain.

Results

Clinical Findings

The patients were 3 men and 1 woman. Their mean age was 67.8 years (range, 65-73 years), and they had generalized lymphadenopathy and massive splenomegaly at the initial examination. The peripheral blood counts showed leukocytosis (13,900-50,900/µL [13.9-50.9 × 10^9 /L]) with a WBC count around 50,000/µL (50 × 10^9 /L) in 2 patients. Circulating mantle cells accounted for 40% to 66% of the leukocytes (mean, 54%). Cytogenetic studies showed complex chromosomal abnormalities with t(11;14)(q13;q32) in 3 patients.

Table 1

<table>
<thead>
<tr>
<th>Case No./ Sex/Age (y)</th>
<th>Clinical Features</th>
<th>Hb (g/dL)</th>
<th>Plt (× 10^9 /L)</th>
<th>WBC (× 10^9 /L)</th>
<th>N</th>
<th>L</th>
<th>M</th>
<th>E</th>
<th>MC</th>
<th>Cytogenetic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/65</td>
<td>History of rheumatoid arthritis treated by methotrexate; generalized lymphadenopathy and massive splenomegaly; normal serum immunoelctrophoresis but free kappa light chain detected in urine; given CVP; DOD, 13 mo</td>
<td>10.6</td>
<td>199</td>
<td>13.9</td>
<td>32</td>
<td>22</td>
<td>4</td>
<td>2</td>
<td>40</td>
<td>46,XY[18]</td>
</tr>
<tr>
<td>2/M/73</td>
<td>Marked weight loss, generalized lymphadenopathy, massive splenomegaly; borderline elevated IgG (16.8 g/L [reference range, 7-16 g/L]); given CVP; DOD, 6 wk.</td>
<td>11.0</td>
<td>52</td>
<td>2.75</td>
<td>26</td>
<td>23</td>
<td>4</td>
<td>1</td>
<td>46</td>
<td>38~45,X,–Y,add(3)(q29),–9,–10(t(11;14)(q13;q32),add(13)(q34),del(17)(p13),add(21)(q22),+mar[cp7]/46,XY[12]</td>
</tr>
<tr>
<td>3/F/68</td>
<td>Marked weight loss, generalized lymphadenopathy, massive splenomegaly; diffuse increase in immunoglobulin levels (IgG, 17.9 g/L [reference range, 7-16 g/L]; IgM, 5.1 g/L [reference range, 0.4-2.3 g/L]; IgA, 6.2 g/L [reference range, 0.7-4 g/L]) with IgM lambda and free lambda light chain detected in serum and urine, respectively; given CVP; DOD, 4 mo</td>
<td>9.5</td>
<td>69</td>
<td>50.9</td>
<td>21</td>
<td>9</td>
<td>3</td>
<td>1</td>
<td>66</td>
<td>40,X,–X,–5,–8,–9,–10,add(10)(q22q26),t(11;14)(q13;q32),–13,der(16)t(13;16)(q11;q24),–17,add(19)(p13.3),–20,–21,der(22)(t(6;22)(q11;p11),+mar1, +mar2,+mar3[5]/46,XX[5]</td>
</tr>
<tr>
<td>4/M/65</td>
<td>Marked weight loss, generalized lymphadenopathy, hepatosplenomegaly; normal immunoglobulin levels; given CVP; alive with disease, 5 mo</td>
<td>10.7</td>
<td>106</td>
<td>48.7</td>
<td>29</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>64</td>
<td>49,X,7t(Y;11)(q12;p22),+del(3)(p11p21),add(5)(q35),+7i(8)(q10),?inv(10)(p11q22),t(11;14)(q13;q32),+13,–15,add(15)(q26),der(17)t(17;26)(p11;p11),+18i[1]/46,XY[9]</td>
</tr>
</tbody>
</table>

CVP, cyclophosphamide, vincristine, prednisolone; DOD, died of disease; MC, mantle cells (given as percentage of leukocytes).

*Unless stated otherwise, values are given in Système International (SI) units; conversions to conventional units are as follows: IgA, IgG, and IgM, divide by 0.01 for mg/dL; hemoglobin (Hb; g/dL SI), divide by 0.01 for mg/dL; platelets (Plt; × 10^9 /L SI), divide by 1.0 for × 10^3 /µL; WBC (× 10^9 /L SI), divide by 0.001 for /µL. Values for neutrophils (N), lymphocytes (L), monocytes (M), and eosinophils (E) are percentages, which are conventional units; to convert to SI, multiply by 0.01 for the proportion of 1.00.
chemotherapy that included cyclophosphamide, vincristine, and prednisolone with poor response. Three patients died in 6 weeks to 13 months (mean, 6 months), while 1 patient was alive with disease after 5 months.

**Cytologic Findings**

In all 4 cases, the abnormal circulating lymphoid cells were predominantly (>90%) large cells (3-4 times the size of an RBC) and had round, angular to irregular nuclei with slightly clumped chromatin; a prominent, often single nucleolus; and a fair amount of pale basophilic cytoplasm. Occasional giant cells (>4 times the size of an RBC) with markedly folded nuclei, multiple nucleoli, and only a narrow rim of cytoplasm could be found in cases 2 through 4. In the marrow aspirate smears, similar large cells were found and accounted for about 50% of the marrow nucleated cells (range, 20%-69%).

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**Image 1** Partial karyotype showing t(11;14)(q13;q32) in case 2 (G-banding with trypsin-Giemsa).

**Image 2A** (Case 3), Peripheral blood sample showing a predominance of large cells that superficially resemble oversized prolymphocytes (Romanowsky, ×400). **B** (Case 4), The large mantle cells have round to irregular nuclei with somewhat lacy chromatin, single distinct nucleoli, and an appreciable amount of pale cytoplasm (Romanowsky, ×1,000). **C** (Case 3), Occasional giant cell with a hyperlobulated nucleus and a narrow rim of cytoplasm can be found (Romanowsky, ×1,000).
Histologic Findings

The lymph node architecture was effaced by a vaguely nodular to diffuse infiltrate of small to medium-sized lymphoid cells that had irregular to folded nuclei, mixed with some larger cells with a single and distinct nucleolus. Prolymphocytes, paraimmunoblasts, and proliferation centers were not found. The trephine biopsy specimens showed an interstitial to nodular infiltrate of a mixed population of small, medium to large cells with prominent nuclear irregularities. No paratrabecular accentuation was demonstrated.

Immunohistochemical Findings

The lymphoma cells expressed CD5 but not CD23. Strong nuclear staining for cyclin D1 also was demonstrated. p53 protein was positive only in case 2. In all 4 cases, irregular meshwork of follicular dendritic cells could be highlighted by simultaneous staining for CD21 and CD35.
Discussion

MCL was first characterized in the Kiel Classification in 1974 as “centrocytic lymphoma.” It was not until the early 1990s that the term “mantle cell lymphoma” was used to specify a mature B-cell lymphoma with a distinctive immunophenotype of CD5+ CD23−, translocation t(11;14)(q13;q32), and overexpression of the cyclin D1 gene. Cyclin D1 overexpression has become a defining feature and also has helped in recognizing the broader morphologic spectrum of MCL. Cytologically, the mantle cells often are described as being small to medium-sized with clefted nuclei and scanty cytoplasm. The leukemic form of mantle cell lymphoma has also been described.

In the present report, we describe the unusual cytologic findings in 4 cases of pleomorphic variant of MCL in leukemic phase characterized by prominent single nucleoli. Unlike the variant form of hairy cell leukemia, the leukemic mantle cells have less condensed chromatin and do not show cytoplasmic projections. The nucleolated leukemic mantle cells resemble oversized prolymphocytes because of the presence of a single central nucleolus and an appreciable amount of pale cytoplasm, but the nuclear/cytoplasmic ratio is higher. Cytologically, this type of leukemic MCL can be distinguished from prolymphocytic leukemia by the large size of the circulating tumor cells. The presence of giant hyperlobulated cells with a high nuclear/cytoplasmic ratio on careful scrutiny of the blood films also may help in the differentiation. Furthermore, the clinical manifestations are unusual for prolymphocytic leukemia, which usually is associated with splenomegaly but no peripheral lymphadenopathy. The tumor cells showed an immunophenotypic profile of CD5+ CD23−, and all of them exhibited overexpression of cyclin D1, with t(11;14)(q13;q32) demonstrated in 3 cases. Although cyclin D1 overexpression with or without the translocation t(11;14) has been described in occasional cases of chronic lymphocytic leukemia (CLL) or prolymphocytic leukemia, lymph node histologic features, which are of great help for the differentiation between MCL and CLL, are lacking in most of the reported cases. In fact, it has been shown that a substantial proportion of cases previously classified as CLL with t(11;14)(q13;q32) should be reclassified as MCL or other entities on histologic examination of the lymph node or spleen. Levy et al described a subset of probable MCL-related tumors with tumor cells showing prominent nucleoli. Schlette et al also suggested that some cases of cyclin D1−positive, t(11;14)-positive prolymphocytic leukemia should best be classified as “prolymphocytoid variant” MCL. It is unfortunate that a lymph node biopsy specimen was available in only 1 of the 4 cases reported by them. On the other hand, the availability of lymph node biopsy specimens in all 4 of our cases confirmed the diagnosis of MCL. The lymph nodes in both CLL and prolymphocytic leukemia usually contain paraimmunoblasts and pseudofollicular proliferation centers, features that were absent in our cases. Furthermore, irregular follicular dendritic cell meshwork, a characteristic histologic feature of MCL but not CLL or prolymphocytic leukemia, can be found in our cases.
Our cases probably correspond to the leukemic phase of the large cell variant of plasmocytic MCL described by Zoldan et al., although the lymph node biopsy specimens in our cases did not show a pure large cell component. They are distinguishable from the blastoid variant of MCL, which is composed of small to medium-sized lymphoblast-like cells with fine chromatin and inconspicuous nucleoli. It is important to distinguish MCL in leukemic phase from CLL and prolymphocytic leukemia because the prognosis and treatment are different. It has been shown that the efficacy of purine analogue for the treatment of these mature B-cell lymphoproliferative disorders probably is different. Fludarabine is less effective in MCL than in CLL and prolymphocytic leukemia. It also has been suggested that the chimeric anti-CD20 monoclonal antibody, rituximab, has moderate activity in MCL but not in CLL and small lymphocytic lymphoma.

References


