Diffuse Large B-Cell Lymphoma Occurring in Patients With Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

Clinicopathologic Features of 12 Cases

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Key Words: Large cell lymphoma; Lymphoplasmacytic lymphoma; Waldenström macroglobulinemia

Abstract

Of 92 patients with lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) treated at our institution, diffuse large B-cell lymphoma (DLBCL) also developed in 12 (13%). In 10 patients, DLBCL developed 12 to 128 months (median, 44 months) after the diagnosis of LPL/WM. Two patients had LPL/WM and DLBCL simultaneously. Clinicopathologic features at diagnosis of LPL/WM did not predict the risk of DLBCL. Onset of DLBCL was characterized by worsening constitutional symptoms, profound cytopenias, extramedullary disease, and organomegaly. Immunoglobulin light chain expression was identical in both LPL/WM and DLBCL. In situ hybridization for Epstein-Barr virus (EBV) in 8 cases of DLBCL was negative. Of 11 patients with clinical follow-up information available, 8 (73%) died within 10 months of diagnosis of DLBCL. DLBCL, most likely as a result of histologic transformation, occurs in a subset of patients with LPL/WM and is associated with aggressive clinical course and poor outcome. EBV is unlikely to be involved in transformation.

The World Health Organization classification defines lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) as a lymphoma of small lymphocytes with variable plasmacytoid differentiation that primarily involves bone marrow and is associated with serum IgM paraprotein. Immunophenotypic studies have shown that the neoplastic cells of LPL/WM express IgM and pan-B-cell antigens such as CD19, CD20, and CD22 and usually are negative for CD5, CD10, and CD23.

Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) are known to be at risk for developing diffuse large B-cell lymphoma (DLBCL), also known as Richter syndrome. Similarly, patients with LPL/WM may develop DLBCL, as has been described in isolated case reports and small series. However, a large series of these cases has not been reported. Furthermore, risk factors for developing DLBCL in patients with LPL/WM are poorly understood.

We describe 12 patients with LPL/WM in whom DLBCL also developed. This group is a subset of 92 patients with LPL/WM treated at our institution. In all 12 patients, immunoglobulin light chain expression was identical in LPL/WM and DLBCL, suggesting that the latter represents histologic transformation of LPL/WM. We retrospectively analyzed the clinicopathologic features at the time of diagnosis of LPL/WM of 10 patients who had LPL/WM and DLBCL sequentially and compared these features with those of the remaining 80 patients with LPL/WM in whom DLBCL did not develop, to determine whether any clinicopathologic features might correlate with subsequent development of DLBCL. We also assessed 8 cases for Epstein-Barr virus (EBV) to explore the potential role of EBV infection in the development of DLBCL.
Materials and Methods

We searched the files of the Department of Hematopathology, The University of Texas M.D. Anderson Cancer Center, Houston, from January 1995 through October 2002 for all cases of LPL/WM and then further selected the cases in which higher-grade lymphoma also was present. The diagnosis of LPL/WM was based on a combination of clinical, morphologic, laboratory, and immunophenotypic criteria as defined in the World Health Organization classification. Specifically, the following criteria had to be fulfilled: monoclonal IgM paraprotein in serum; bone marrow involvement by a B-cell neoplasm composed predominantly of small lymphocytes with a variable degree of plasmacytoid differentiation; monotypic B-cells positive for CD19 or CD20 and negative for CD5, CD10, and CD23; and a subsequent or concurrent biopsy specimen involved by higher-grade lymphoma. For the latter criterion, we identified 12 cases of DLBCL and 2 cases of classic Hodgkin disease. The latter had been reported previously. We excluded cases of WM without LPL; the cases of WM that were excluded had CLL/SLL or other types of non-Hodgkin lymphoma.

Clinical features and various laboratory parameters at the time of diagnosis of LPL/WM were used to calculate a prognostic index (PI) as proposed recently by Morel and colleagues. Briefly, the following parameters are used for the PI: age, 65 years or older; hemoglobin concentration, less than 12.0 g/dL (<120 g/L); leukocyte count, less than 10,000/µL (<4.0 × 10⁹/L); platelet count, less than 150 × 10⁹/L (<120 × 10⁹/L); and serum albumin level, less than 4.0 g/dL (<40 g/L). Each criterion is assigned a score of 1, and the cumulative score represents the PI. The risk for poor clinical outcome is considered low, intermediate, or high when the corresponding PI is 1 or less, 2, or 3 or more, respectively. The PI for the 10 patients with LPL/WM in whom DLBCL subsequently developed was compared with that for the other 80 patients with LPL/WM but without DLBCL.

Bone marrow aspirate smears and clot sections, trephine biopsy specimens, and tissue biopsy specimens obtained at the time of initial diagnosis of LPL/WM and at the time of diagnosis of DLBCL were reviewed. LPL/WM was subtyped further as lymphoplasmacytoid, lymphoplasmacytic, or polymorphous. The pattern of infiltration in the bone marrow also was assessed and recorded as diffuse or nodular and interstitial.

Flow cytometry immunophenotypic studies were performed on bone marrow aspirate or tissue biopsy samples using a panel of antibodies specific for immunoglobulin κ and λ light chains, CD5, CD10, CD19, CD20, and CD23 as described previously. Other antibodies were used in a subset of these cases. Immunohistochemical studies were performed using fixed, paraffin-embedded tissue sections and the following antibodies: L26 (CD20; 1:700 dilution), immunoglobulin κ and λ light chains (1:10,000 dilution), Ki-67 (MIB-1; 1:20 dilution), and IgM (polyclonal, 1:3,000 dilution; DAKO, Carpinteria, CA); CD5 (1:50 dilution, Neomarkers, Fremont, CA); CD10 (1:70 dilution, Vector, Burlingame, CA); and CD23 (1:15 dilution, Novocastra, Burlingame, CA). In situ hybridization for EBV was performed in 8 cases using fixed, paraffin-embedded tissue sections and a probe specific for EBV-encoded small RNA (EBER). Cytogenetic studies were performed on bone marrow aspirate samples in 5 cases using conventional techniques as described previously.

Results

The study group included 8 women and 4 men with a median age of 56 years (range, 42-80 years). Ten patients were diagnosed with LPL/WM and DLBCL sequentially (cases 1-10), and 2 patients (cases 11 and 12) were diagnosed with LPL/WM and DLBCL simultaneously.

Clinical Findings in 10 Patients at the Time of Diagnosis of LPL/WM

There was a spectrum of signs and symptoms at the time of diagnosis, and patients had either indolent or aggressive disease. Two patients (cases 5 and 6) were first considered to have monoclonal gammopathy of undetermined significance before they became symptomatic and a definitive diagnosis of LPL/WM was made 2 and 4 years later, respectively. The remaining 8 patients were diagnosed initially with LPL/WM. Fatigue was the most common symptom, present in all patients. Fever, weight loss, and night sweats were reported in 2 patients (20%), 2 patients (20%), and 2 patients (20%), respectively. Two patients (cases 2 and 9) had headache and visual disturbance attributable to hyperviscosity. One patient (case 7) had multiple episodes of urticaria and rashes, so-called Schnitzler syndrome. Physical examination and computed tomography scans revealed no evidence of lymphadenopathy or hepatosplenomegaly in 9 patients. Chest and abdominal lymphadenopathy was present in 1 patient (case 3).

Serum monoclonal IgM was detected in all patients, with a median level of 1.500 mg/dL (15.0 g/L; range, 700-16,800 mg/dL [7.0-108.0 g/L]). Monoclonal immunoglobulin κ and λ light chains were detected in the serum of 6 and 4 patients, respectively. Other significant hematologic abnormalities included the following: anemia, with a hemoglobin concentration of less than 12.0 g/dL (<120 g/L; reference range, 14.0-18.0 g/dL [140-180 g/L]) in 9 patients (90%); leukopenia, with a leukocyte count of
1.600/µL (1.6 × 10^9/L; reference range, 4,000-11,000/µL [4.0-11.0 × 10^9/L]) in 1 patient (10%; case 10); and thrombocytopenia, with a platelet count of 113 × 10^3/µL (113 × 10^9/L; reference range, 140-440 × 10^3/µL [140-440 × 10^9/L]) in 1 patient (10%; case 5). One patient (case 9) had a serum albumin level of less than 4.0 g/dL (<40 g/L; reference range, 3.2-4.5 g/dL [32-45 g/L]). The PI based on clinical and hematologic parameters was determined to be low (0-1) in 5 patients, intermediate (2) in 3 patients, and high (3) in 2 patients.

Nine patients were treated with systemic chemotherapy. Cladribine was administered in variable combinations with other agents in 7 patients. These agents included cyclophosphamide, prednisone, fludarabine, chlorambucil, thalidomide, and rituximab. One patient was treated with melphalan and prednisone. One patient was treated with cyclophosphamide and vinblastine. Two patients treated with chemotherapy also underwent splenectomy to alleviate severe hemolytic anemia and thrombocytopenia during the course of disease. One patient did not receive therapy.

Therapy resulted in partial remission in 5 patients, complete clinical remission in 1 patient, and stable disease in 2 patients. One patient’s tumor was chemo-resistant with no significant reduction of serum paraprotein or tumor load. All 6 patients with partial or complete remission had 1 or more relapses.

The clinicopathologic features of the 10 patients in whom DLBCL subsequently developed were compared with those of the 80 patients with LPL/WM in whom DLBCL did not develop Table 1. Except for a female predominance, there were no significant differences in the clinicopathologic features for these 2 groups.

### Table 1

**Characteristics of Patients With LPL/WM at the Time of Initial Diagnosis of LPL/WM**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>WM Without DLBCL (n = 80)</th>
<th>WM With DLBCL (n = 10)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>62 (34-80)</td>
<td>64 (42-80)</td>
<td>1.98</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>.08</td>
</tr>
<tr>
<td>Female</td>
<td>30 (38)</td>
<td>7 (70)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50 (63)</td>
<td>3 (30)</td>
<td></td>
</tr>
<tr>
<td>Initial prognostic index</td>
<td></td>
<td></td>
<td>.17</td>
</tr>
<tr>
<td>Low (0-1)</td>
<td>44 (55)</td>
<td>5 (50)</td>
<td></td>
</tr>
<tr>
<td>Intermediate (2)</td>
<td>24 (30)</td>
<td>3 (30)</td>
<td></td>
</tr>
<tr>
<td>High (3-4)</td>
<td>12 (15)</td>
<td>2 (20)</td>
<td></td>
</tr>
<tr>
<td>Bone marrow lymphocytic infiltrate &lt;50%</td>
<td>43 (54)</td>
<td>5 (50)</td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>37 (46)</td>
<td>5 (50)</td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>16 (20)</td>
<td>1 (10)</td>
<td>.68</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>14 (18)</td>
<td>0 (0)</td>
<td>.2</td>
</tr>
</tbody>
</table>

**DLBCL**, diffuse large B-cell lymphoma; LPL, lymphoplasmacytic lymphoma; WM, Waldenström macroglobulinemia.  

* Data are given as number (percentage) unless otherwise indicated. P values were generated from Student’s t and Fisher exact tests.  
† Two patients with concurrent diagnoses of LPL/WM and DLBCL were excluded.

### Clinical Findings in 10 Patients at the Time of Diagnosis of DLBCL

The interval from the initial diagnosis of LPL/WM to DLBCL ranged from 12 to 128 months (median, 44 months) in 10 patients Table 2. At the time of onset of DLBCL, all patients complained of profound fatigue. Night sweats, fever, and weight loss were reported by 4 patients (40%), 6 patients (60%), and 6 patients (60%), respectively. One patient (case 2) had Bell palsy as a result of lymphomatous dissemination to the central nervous system. Two patients (cases 3 and 8) had multiple cutaneous nodules. Physical examination and computed tomography scans revealed generalized...

### Table 2

**Clinical Features of LPL/WM and DLBCL in 12 Patients**

<table>
<thead>
<tr>
<th>Case No/</th>
<th>Sex/</th>
<th>Prognostic Index</th>
<th>Interval (mo)†</th>
<th>Site of DLBCL</th>
<th>Therapy</th>
<th>Outcome (mo)</th>
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</thead>
<tbody>
<tr>
<td>1/F/A9</td>
<td>0</td>
<td>128</td>
<td>BM</td>
<td>H-CVAD</td>
<td>Died (1)</td>
<td></td>
</tr>
<tr>
<td>2/F/A9</td>
<td>0</td>
<td>41</td>
<td>BM, LN</td>
<td>H-CVAD</td>
<td>Died (3)</td>
<td></td>
</tr>
<tr>
<td>3/F/80</td>
<td>2</td>
<td>12</td>
<td>Skin</td>
<td>H-CVAD</td>
<td>Died (3)</td>
<td></td>
</tr>
<tr>
<td>4/F/81</td>
<td>1</td>
<td>46</td>
<td>BM</td>
<td>H-CVAD</td>
<td>Died (5)</td>
<td></td>
</tr>
<tr>
<td>5/M/74</td>
<td>3</td>
<td>36</td>
<td>BM</td>
<td>H-CVAD</td>
<td>Died (5)</td>
<td></td>
</tr>
<tr>
<td>6/M/66</td>
<td>1</td>
<td>108</td>
<td>BM</td>
<td>H-CVAD, rituximab</td>
<td>Died (5)</td>
<td></td>
</tr>
<tr>
<td>7/F/A6</td>
<td>1</td>
<td>50</td>
<td>BM, LN</td>
<td>CHOP</td>
<td>Died (5)</td>
<td></td>
</tr>
<tr>
<td>8/F/73</td>
<td>2</td>
<td>29</td>
<td>Skin</td>
<td>CHOP, RT</td>
<td>Died (10)</td>
<td></td>
</tr>
<tr>
<td>9/M/67</td>
<td>3</td>
<td>46</td>
<td>Pleura</td>
<td>CHOP, MINE, rituximab</td>
<td>Lost to follow-up (7)</td>
<td></td>
</tr>
<tr>
<td>10/F/42</td>
<td>2</td>
<td>12</td>
<td>BM, LN</td>
<td>H-CVAD, rituximab, SCT, BEAM, RT</td>
<td>Alive without disease (8)</td>
<td></td>
</tr>
<tr>
<td>11/F/51</td>
<td>0</td>
<td>2</td>
<td>BM</td>
<td>Cladribine, cyclophosphamide, rituximab</td>
<td>Alive with disease (7)</td>
<td></td>
</tr>
<tr>
<td>12/M/48</td>
<td>4</td>
<td>0</td>
<td>Maxilla</td>
<td>CHOP, INF-α, rituximab, RT</td>
<td>Alive with disease (98)</td>
<td></td>
</tr>
</tbody>
</table>

BEAM, carmustine, etoposide, cytarabine, and melphalan; BM, bone marrow; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL, diffuse large B-cell lymphoma; H-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and prednisone; LPL, lymphoplasmacytic lymphoma; MINE, mesna, ifosfamide, mitoxantrone, and etoposide; RT, local radiation therapy; SCT, autologous stem cell transplantation.

† Age, sex, and prognostic index at the time of diagnosis of LPL/WM.

‡ Interval from the diagnosis of LPL/WM to the diagnosis of DLBCL.
lymphadenopathy in 7 patients (70%) and splenomegaly in 5 patients (50%). Two patients (20%; cases 3 and 9) had hepatomegaly and pleural effusions.

Nine patients (90%) had severe anemia with a hemoglobin concentration that ranged from 6.6 to 10.0 g/dL (66-100 g/L; median, 7.5 g/dL [75 g/L]). Six patients (60%) had leukopenia, with a total leukocyte count of less than 4,000/µL (<4.0 × 10^9/L), and 6 patients (60%) had thrombocytopenia, with a platelet count of less than 100 × 10^9/µL (<100 × 10^9/L). Serum lactate dehydrogenase levels were elevated to greater than twice normal (reference range, 313-618 IU/L) in 8 patients (80%). Mild hypercalcemia (calcium level, 11.0 mg/dL [2.75 mmol/L]; reference range, 8.4-10.4 mg/dL [2.10-2.60 mmol/L]) was found in 1 patient. Monoclonal IgM in the serum was detected in all patients, and the level ranged from 100 to 6,200 mg/dL (1.0-62.0 g/L; median, 800 mg/dL [8.0 g/L]). The onset of DLBCL was the first sign of relapse in 2 patients who were in partial remission with low serum monoclonal IgM levels (<500 mg/dL [<5.0 g/L]). In 1 patient (case 9), the onset of DLBCL was accompanied by a falling IgM level from 600 to 100 mg/dL (6.0 to 1.0 g/L) during a 4-month period. The monoclonal immunoglobulin light chain in the serum was identical to that present at the time of diagnosis of LPL/WM.

Five patients (cases 1-5) were treated with hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone). Two patients received hyper-CVAD combined with rituximab (cases 6 and 10). Case 10 also received autologous stem cell transplant and BEAM (carmustine, etoposide, cytarabine, and melphalan). Two patients (cases 7 and 8) received CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). One patient (case 9) was treated with CHOP, MINE (mesna, ifosfamide, mitoxantrone, and etoposide), and rituximab. In addition to these regimens, 2 patients (cases 8 and 10) also were treated with local radiation therapy.

Eight (89%) of 9 patients with clinical follow-up available died within 10 months of the diagnosis of DLBCL, with a median survival of 5 months. At last follow-up, only 1 patient (case 10) was alive without disease (8 months after the diagnosis of DLBCL). One patient (case 9) was lost to follow-up 7 months after the diagnosis of DLBCL.

Clinical Findings in 2 Patients With Concurrent LPL/WM and DLBCL

Two patients (cases 11 and 12) were diagnosed with de novo LPL/WM and DLBCL simultaneously. One patient (case 11) complained of increasing fatigue, weight loss, night sweats, and progressive dyspnea on exertion owing to severe anemia (hemoglobin concentration, 7.4 g/dL [74 g/L]). Another patient (case 12) complained of weight loss and left upper toothache and gum swelling that was unresponsive to antibiotic treatment. Subsequent radiologic study revealed a mass in the left maxilla with destruction of the maxillary sinus and cervical lymphadenopathy. The patient also had pancytopenia and hypoalbuminemia, a hemoglobin concentration of 8.3 g/dL (83 g/L), a total leukocyte count of 3,300/µL (3.3 × 10^9/L), and a platelet count of 105 × 10^9/µL (105 × 10^9/L). Both patients had IgM κ monoclonal protein in the serum, 500 and 5,600 mg/dL (5.0 and 56.0 g/L), respectively.

Case 11 was treated with cladribine, cyclophosphamide, and rituximab. Case 12 was treated with CHOP, α-interferon, and local radiation for DLBCL. The patient declined cladribine and cyclophosphamide treatment and received rituximab only for persistent LPL/WM after the DLBCL was resolved. Both patients are alive with disease, 7 and 98 months after initial diagnosis, respectively.

Pathologic Findings

Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

Bone marrow aspirate smears, clot sections, and biopsy sections were reviewed. In each case, LPL/WM was observed as a lymphoplasmacytic infiltrate that was predominantly nodular and interstitial in 8 cases (67%) or diffuse in 4 cases (33%) Image 11 and Image 21. These neoplasms were classified further as lymphoplasmacytid in 7 (Images 1C and 2C), lymphoplasmacytic in 4, and polymorphous in 1. The median tumor burden in the bone marrow biopsy specimen was 50% of total cellularity (range, 20%-95%). Flow cytometry immunophenotypic studies in all cases demonstrated that each tumor was of B-cell lineage and negative for CD5, CD10, and CD23. The neoplasms were positive for monotypic immunoglobulin light chain in all cases, κ in 8 and λ in 4, which corresponded to the isotype identified in the serum.

Diffuse Large B-Cell Lymphoma

DLBCL was first detected in the bone marrow (n = 5), skin (n = 2), pleura (n = 1), and maxilla (n = 1) and concurrently in bone marrow and lymph node (n = 3). In each case, large cells were increased with frequent mitotic figures. The large cells resembled centroblasts in 9 cases (75%) and immunoblasts in 3 cases (25%). In bone marrow biopsy sections (Image 1A) and aspirate smears (Image 1B), the large cells showed oval to irregular nuclear contours, dispersed chromatin, and a moderate amount of cytoplasm. Proliferation rate, assessed in 7 cases using the MIB-1 (Ki-67) antibody, showed approximately 40% to 70% positive cells. Immunophenotyping by flow cytometry (n = 5), immunohistochemical analysis (n = 3), or both (n = 4) demonstrated monotypic immunoglobulin light chain, 8 κ
and 4 λ, identical to the isotype identified in the neoplastic cells of the corresponding LPL/WM cases.

In 8 cases of DLBCL involving bone marrow, a variable amount of low-grade LPL/WM also was present in the background. Lymph node biopsy specimens obtained from the cervical region in 2 patients (cases 2 and 7) showed diffuse effacement of the architecture by a proliferation of large cells. In case 10, a supraclavicular lymph node was assessed by fine-needle aspiration that showed numerous large cells and small lymphocytes in the background. Concurrent bone marrow aspiration and biopsy specimens in all 3 cases showed DLBCL. Skin biopsy specimens obtained from the upper back (case 3) and the breast (case 8) revealed diffuse infiltration of the dermis by large cells dissecting between collagen bundles. Mitotic figures were identified easily (Images 2A and 2B). Concurrent bone marrow aspiration and biopsy specimens from both patients (cases 3 and 8) showed low-grade LPL/WM, one lymphoplasmacytoid, and the other lymphoplasmacytic, involving 20% (Image 2C) and 90% of the medullary space, respectively.

Pleural and maxilla biopsy specimens (cases 9 and 12) showed sheets of large cells within a background of small lymphocytes and mature plasma cells. The bone marrow aspiration and biopsy specimens showed low-grade lymphoplasmacytic LPL/WM in case 9 and lymphoplasmacytoid LPL/WM in case 12.

In cases 2 and 4, large lymphoma cells also were identified in the peripheral blood, 21% and 15%, respectively. Tumor cells also were detected in the cerebrospinal fluid of case 2.

In situ hybridization for EBER performed on fixed, paraffin-embedded tissue sections of 1 lymph node, 2 skin, and 5 bone marrow biopsy samples was negative.

Cytogenetic data obtained from bone marrow aspirate samples were available for 3 patients (cases 1, 8, and 10).
with LPL/WM before developing DLBCL and also were available for 3 patients (cases 1, 5, and 6) at the time of diagnosis of DLBCL. All samples obtained at the time of LPL/WM diagnosis were diploid. Samples obtained at the time of DLBCL diagnosis showed complex cytogenetic abnormalities in 2 cases. In 1 case (case 6), −Y was identified in 4 of 20 metaphases 

Discussion

LPL/WM is a low-grade B-cell lymphoma that accounts for approximately 2% of all hematologic cancers and affects approximately 1,500 Americans per year.16,17 The clinical evolution of LPL/WM is variable, but most patients have a chronic and indolent clinical course with a median survival of 60 months. Rare cases of high-grade non-Hodgkin lymphoma evolving from LPL/WM have been reported in the literature as isolated case reports and small series.2-10 A large series of these cases has not been reported previously. In this article, we describe 12 patients with LPL/WM in whom DLBCL also developed.

The frequency of DLBCL in patients with LPL/WM at our institution is 13%, higher than the 5% frequency estimated by Kyrtsonis et al3 and higher than the 3% to 10% frequency reported for patients with B-cell CLL/SLL in whom histologic transformation to DLBCL (Richter syndrome) develops.18-21 The high frequency of transformation in patients with LPL/WM at our hospital may reflect the selection bias of a large referral center rather than a true frequency of DLBCL.

In search of risk factors for an adverse prognosis in patients with LPL/WM, previous studies have identified the following variables to be important: older age (>60-70...
years in different studies), male sex, poor performance status, cytopenias, cryoglobulinemia, hypoalbuminemia, high β₂-microglobulin value, heavy tumor burden, organomegaly, and poor response to treatment. Among these, advanced age and cytopenia are uniformly considered important. In a simple model based on age, blood cell counts, and the serum albumin level, Morel and colleagues showed that a PI of 1 or less, 2, and 3 or more corresponded to low-, intermediate-, and high-risk groups with 5-year survival rates of 87%, 62%, and 25%, respectively. Most of the patients in the present study were younger than 65 years (7/12 [58%]) or female (8/12 [67%]). At the time of diagnosis of LPL/WM, 3 patients (30%) were in the intermediate-risk group, whereas 2 patients (20%) were in the high-risk group. Comparison of the 10 patients with LPL/WM in whom DLBCL developed (excluding 2 patients with simultaneous LPL/WM and DLBCL) with the 80 patients with LPL/WM at our institution in whom DLBCL did not develop revealed that the PI at the time of initial diagnosis of LPL/WM did not predict risk of DLBCL. The presence or absence of lymphadenopathy or splenomegaly also did not correlate with DLBCL. Most likely, the causative events leading to DLBCL evolve during the time course of the disease. EBV also does not seem to be implicated in the process of transformation as in situ hybridization for EBER performed in 8 cases was negative.

Some studies have suggested that polymorphous histologic features and complex cytogenetic abnormalities in LPL/WM predict a poorer prognosis. The results of the present study support this view. Only 1 patient (case 10) had polymorphous LPL/WM, and this patient had both anemia and leukopenia at time of diagnosis of LPL/WM. Cytopenias worsened during a 1-year period and culminated in pancytopenia when DLBCL was diagnosed. Complex cytogenetic abnormalities, including deletion of 6q16 and 6q21, were identified in 2 of 3 patients with cytogenetic data available at the time of diagnosis of DLBCL. Deletion of 6q, in the region spanning q13 to q25, is the most common structural abnormality in LPL/WM and also has been reported in many other types of lymphoma.

In 1 patient (case 8), extramedullary DLBCL arose when bone marrow involvement was reduced to 20% after chemotherapy, suggesting that reduced tumor burden in bone marrow may not reduce the risk of DLBCL at extramedullary sites. As shown in the present study, DLBCL may occur as the first sign of relapse when the patients are in partial clinical remission with relatively low levels of serum paraprotein, or the onset of DLBCL may coincide with a falling serum IgM level as a result of tumor dedifferentiation. Thus, early diagnosis of DLBCL depends not only on laboratory evaluation, but also on clinical history and physical examination, as symptoms and signs of transformation such as worsening systemic symptoms, lymphadenopathy, and extramedullary infiltration frequently are present.

Molecular analysis of the CLL/SLL and DLBCL components in patients with Richter syndrome indicate that CLL and DLBCL have a common clonal origin in at least 50% to 60% of cases. To further study the clonal relationship of the tumors in our cases, we attempted to amplify and sequence the rearranged immunoglobulin heavy chain genes in 4 cases in which paraffin-embedded tissue of both the LPL/WM in bone marrow and DLBCL were available. Unfortunately, the DNA extracted from the bone marrow specimens was degraded, precluding this comparison. Thus, we believe that the DLBCL in these patients most likely represents morphologic transformation of LPL/WM. However, we cannot state this definitively without molecular studies to compare both tumors.

DLBCL arising in patients with LPL/WM is not uncommon in our experience, occurring in 12 (13%) of 92 patients at our hospital. As the immunoglobulin light chain expression was identical in LPL/WM and DLBCL, it seems likely that the DLBCL is clonally related to the LPL/WM and represents histologic transformation. The overall prognosis for patients with DLBCL associated with LPL/WM is poor. However, complete remission and long-term survival were achieved in 1 patient who received aggressive chemotherapy in combination with stem cell transplantation.

### Table 3

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sample</th>
<th>Karyotype</th>
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<tbody>
<tr>
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<td>LPL/WM</td>
<td>46,XX</td>
</tr>
<tr>
<td>5</td>
<td>DLBCL</td>
<td>47XY,del(3)(q21),–4,del(6)(q21),–8,+3mar[3]/46,XY[17]</td>
</tr>
<tr>
<td>6</td>
<td>DLBCL</td>
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<td>LPL/WM</td>
<td>46,XY</td>
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<tr>
<td>10</td>
<td>LPL/WM</td>
<td>46,XY</td>
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DLBCL, diffuse large B-cell lymphoma; LPL/WM, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia.
References


