

Cytogenetic Findings in Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

Chromosomal Abnormalities Are Associated With the Polymorphous Subtype and an Aggressive Clinical Course

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Abstract

We correlated bone marrow cytogenetic findings with morphologic and immunophenotypic data in 37 patients with lymphoplasmacytic lymphoma (LPL)/Waldenström macroglobulinemia (WM). Each LPL/WM case was classified as lymphoplasmacytoid (n = 18), lymphoplasmacytic (n = 10), or polymorphous (n = 9) using the Kiel criteria. Of 12 cases with chromosomal abnormalities, a single numeric abnormality was present in 4 and a complex karyotype in 8. The most common numeric abnormalities were +5 and -8 in 3 cases each; the most common structural abnormality was del(6q) in 6 cases. Cytogenetic abnormalities were significantly less common in the lymphoplasmacytic and lymphoplasmacytoid groups (5/28 [18%]) compared with the polymorphous group (7/9 [78%]). Clinical follow-up was available for 28 patients for a median of 36 months. Six (67%) of 9 patients with aneuploid tumors, including 4 with polymorphous subtype, subsequently had clinical progression or developed high-grade lymphoma. In contrast, 4 (21%) of 19 patients with diploid tumors, including 1 of polymorphous type, developed clinical progression or high-grade lymphoma. We conclude that abnormal cytogenetic findings in LPL/WM correlate with the polymorphous subtype and poor prognosis.

Waldenström macroglobulinemia (WM) is a lymphoproliferative disorder of B cells with variable plasmacytoid differentiation, associated with monoclonal IgM production. Most patients with the clinical and laboratory findings of WM have been classified as having lymphoplasmacytic lymphoma (LPL) in the recently proposed World Health Organization (WHO) classification scheme.¹

LPL/WM accounts for approximately 2% of all hematopoietic neoplasms.²⁻⁴ Affected patients usually are elderly, with a median age of 65 years, and virtually all patients have bone marrow infiltration at the time of diagnosis. Patients may have lymphadenopathy, hepatosplenomegaly, anemia, and cytopenias.⁴⁻⁸ While most patients with LPL/WM have an indolent clinical course, approximately 10% to 15% of patients show more rapidly progressive disease.⁸

Cytogenetic reports in WM have been few and for small numbers of patients.⁹⁻¹⁶ In two of the largest studies, in which 19 and 17 cases of WM were assessed,^{10,11} there were inconsistent and nonrecurrent abnormalities involving chromosomes 9, 10, 11, 12, 18, and 21. Trisomy 12 has been identified in a few cases of WM and was suggested to have prognostic significance,¹³ but this finding was not confirmed in other reports.¹¹ Isolated cases of WM that carried the t(8;14), t(11;18), and t(14;18) also have been described.^{15,17,18} However, in most studies there was little correlation with morphologic findings, and immunophenotypic data often were not available.

We describe the conventional cytogenetic findings and prognostic implications for 37 cases of LPL/WM, all with compatible morphologic features and immunophenotypic data.

Materials and Methods

We obtained 37 cases of LPL/WM for which bone marrow aspiration or biopsy material was sent for conventional cytogenetic analysis. For this study, we used a strict definition of LPL/WM, based on a combination of laboratory, clinical, morphologic, and immunophenotypic criteria as defined in the WHO classification.¹ To be included in the study, the following criteria had to be fulfilled: (1) presence of monoclonal IgM paraprotein in serum; (2) presence of a neoplasm composed of small lymphocytes with some degree of plasmacytoid differentiation involving the bone marrow; and (3) immunophenotypic studies performed on all cases using flow cytometry that demonstrated a monotypic B-cell population positive for pan-B-cell antigens (CD19+ or CD20+) and negative for CD5, CD10, and CD23.

Each case of LPL/WM was further classified into 1 of 3 subtypes as described by Bartl and colleagues,⁸ with minor modifications: lymphoplasmacytoid, lymphoplasmacytic, and polymorphous. The lymphoplasmacytoid subtype is composed of a monotonous population of small lymphocytes, a subset of which has plasmacytoid differentiation. Occasional (<5%) mature plasma cells (of the Marschalko type) were accepted in this category. In the lymphoplasmacytic subtype, a variable mixture of small lymphocytes and mature plasma cells are present, and we required 5% or more mature plasma cells (Marschalko type) to be present. In both the lymphoplasmacytoid and lymphoplasmacytic subtypes, large lymphoid cells and mitotic figures are infrequent. By contrast, the polymorphous subtype includes the presence of easily identified large lymphoid cells, including large noncleaved cells and immunoblasts, and mitotic figures are relatively frequent.⁸ For the present study, we used a cutoff of at least 5% large cells for designating a case of LPL/WM with polymorphous subtype.

All patients were followed up by serial monitoring of physical examination, blood counts, serum IgM levels, and follow-up bone marrow aspiration and biopsy or tissue biopsy when clinically indicated. Clinical progression was defined by at least a 50% increase in serum monoclonal IgM, recurrence of adenopathy or splenomegaly, or reduction of hemoglobin by at least 1.5 g/dL (15 g/L), associated with bone marrow lymphocytosis of more than 20%. Survival was measured from diagnosis.

Cytogenetic Studies

Conventional G-band karyotype analysis was performed on all cases. Bone marrow cells were placed in 10% Ham F10 medium with 20% fetal calf serum (Gibco BRL, Gaithersburg, MD) at a concentration of 2 to 4 × 10⁶ nucleated cells per milliliter. The culture was incubated for 24 hours and 48 hours without phytohemagglutinin. Standard

harvesting procedures were used. Colcemid, 0.1 mL (10 µg/mL), was added to 10-mL cultures for 30 minutes. For hypotonic treatment, a 0.075-mol/L concentration of potassium chloride was used for 30 minutes at room temperature. The fixation process consisted of 3 changes of methanol: glacial acetic acid (3:1) with a 10-minute waiting period between the changes. A drying chamber (Thermatron Industries, Holland, MI) was used for slide preparation. Slides were placed in a 60°C oven overnight in preparation for G-banding. The karyotype formula was written using the International System for Human Cytogenetic Nomenclature (1994).¹⁹

Statistical Analysis

Differences between groups were compared statistically using the chi square or the Fisher exact test.

Results

Clinical and Pathologic Features

There were 20 men and 17 women with a median age of 61 years (range, 34-77 years). Physical examination revealed lymphadenopathy in 15 (41%) patients, splenomegaly in 10 (27%) patients, skin infiltration in 4 (11%) patients, and hepatomegaly in 1 (3%) patient. An elevated level of monotypic IgM in serum was detected in all patients, with a median level of 1.900 mg/dL (19.0 g/L; range, 300-6,500 mg/dL [3-65 g/L]). Light chain type was kappa in 19 and lambda in 5. Other significant laboratory abnormalities at initial examination included the following: anemia, hemoglobin less than 12.0 g/dL (<120 g/L) in 32 patients (86%) (reference range, 14.0-18.0 g/dL [140-180 g/L]); hypoalbuminemia, albumin level less than 3.0 g/dL (<30.0 g/L) in 16 (47%) of 34 patients (reference range, 3.2-4.5 g/dL [32-45 g/L]); thrombocytopenia, platelet count less than 150 × 10³/µL (<150 × 10⁹/L) in 16 patients (43%) (reference range, 140-440 × 10³/µL [140-440 × 10⁹/L]); and leukopenia, WBC count less than 3,000/µL (<3.0 × 10⁹/L) in 12 patients (32%) (reference range, 4,000-11,000/µL [4.0-11.0 × 10⁹/L]).

Bone marrow aspiration smears and biopsy sections were available for all cases. All showed bone marrow infiltration by neoplastic lymphoid cells. The pattern of infiltration was predominantly diffuse in 16 (43%), interstitial in 13 (35%) and nodular in 8 (22%) cases. The median tumor burden on bone marrow biopsy was 50% of total cellularity (range, 5% to 95%). The neoplasm was subtyped into 3 categories as outlined previously: 18 (49%) lymphoplasmacytoid, 10 (27%) lymphoplasmacytic, and 9 (24%) polymorphous. **Image 1**, **Image 2**, and **Image 3**. In 1 case of polymorphous LPL/WM (case 7), a

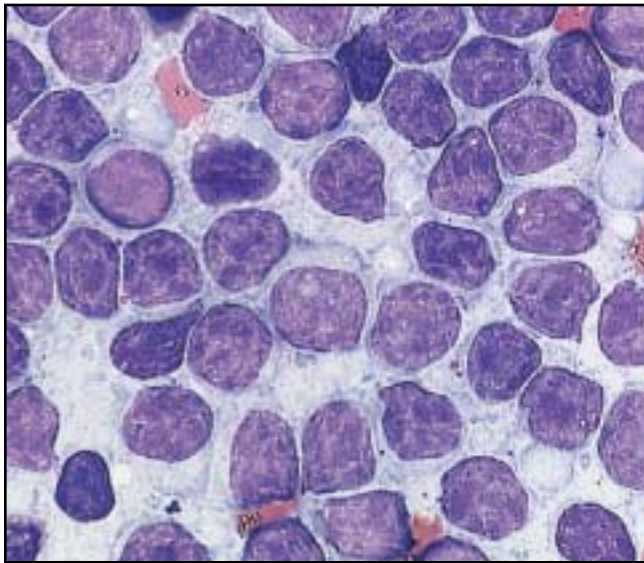


Image 1 (Case 8) Lymphoplasmacytoid subtype. Bone marrow aspirate smear showing numerous lymphoplasmacytoid cells with eccentric nuclei, condensed chromatin and distinct nucleoli (Wright-Giemsa, $\times 1,000$).

focus composed predominantly of large cells was identified, suggestive of transformation to large cell lymphoma (Images 3A and 3B).

Twenty-three (62%) of 37 patients did not receive therapy before bone marrow study; 5 (56%) of 9 patients with polymorphous subtype and 18 (64%) of 28 patients with other subtypes were untreated. All patients at some point received 2-chlorodeoxyadenosine, fludarabine, or both.

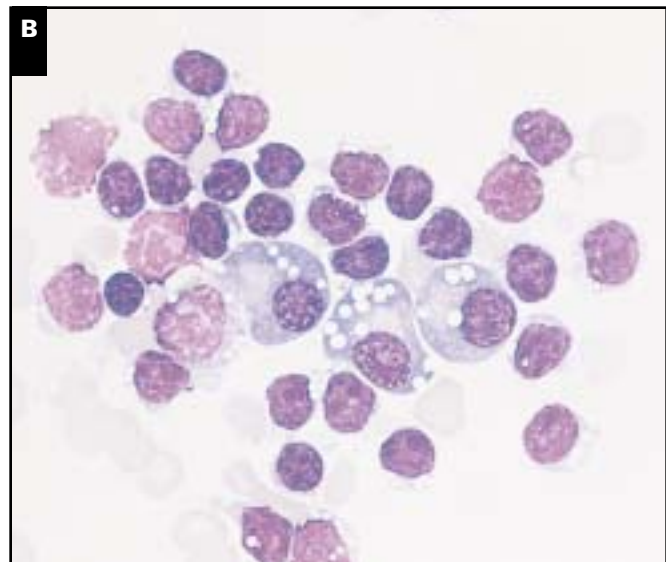
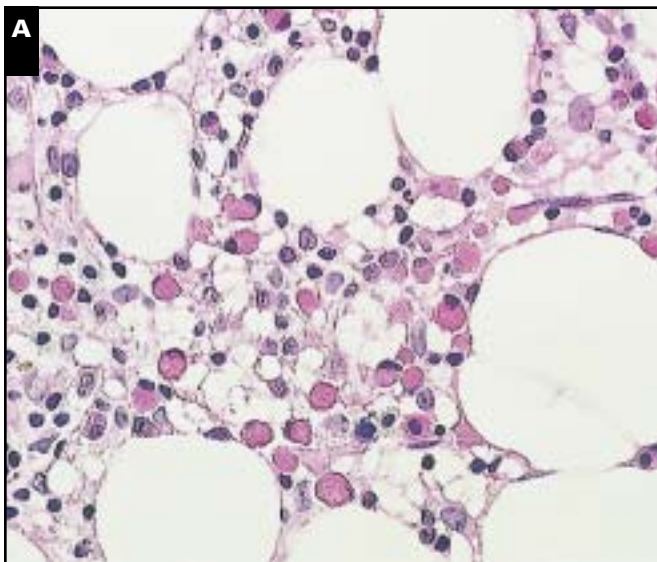


Image 2 (Case 28) Lymphoplasmacytic subtype. **A**, Bone marrow biopsy section showing lymphoplasmacytic infiltrate. Numerous plasma cells are present admixed with lymphoid cells (H&E, $\times 400$). **B**, Bone marrow aspirate smear. Marschalko-type plasma cells (with cytoplasmic vacuoles) and lymphoid cells are present (Wright-Giemsa, $\times 1,000$).

The serum beta₂-microglobulin results were as follows: treated group: median, 3.5 mg/L (range, 1.7-6.8 mg/L); untreated group: median, 3.0 mg/L (range, 1.9-6.7 mg/L; reference range, 0.6-2.0 mg/L).

Cytogenetic Findings

Cytogenetic analyses were performed in 22 cases (59%) at the time of initial diagnosis and in 15 cases (41%) during the course of disease (mean duration from time of initial diagnosis, 36 months; range, 4-120 months). In 27 patients, cytogenetic analysis was performed only once. In 10 patients, multiple cytogenetic studies were performed: for 8 patients, 2 or 3 times, and for 2 patients, more than 3 times. Follow-up karyotype showed a different pattern during the course of disease in 3 patients **Table 1**.

Among all 37 cases, 25 (68%) had a diploid karyotype and 12 (32%) were abnormal. Eight (67%) of these 12 cases had complex cytogenetic abnormalities (Table 1).

Numeric Abnormalities

In 12 cases with an abnormal karyotype, 4 (33%) were pseudodiploid, 5 (42%) were hyperdiploid, and 3 (25%) were hypodiploid. Trisomy 5 and monosomy of chromosome 8 each were identified in 3 cases (25%). Trisomy 3 was seen in 2 cases (17%). Loss of chromosome Y as a single numeric abnormality was observed in 2 cases (17%). Monosomy of chromosome 4, 7, 13, 19, 21, or 22 was identified in single cases.

Structural Abnormalities

Deletions were more frequent than gains. Deletion of chromosome 6q, encompassing q13 to q22, was the most

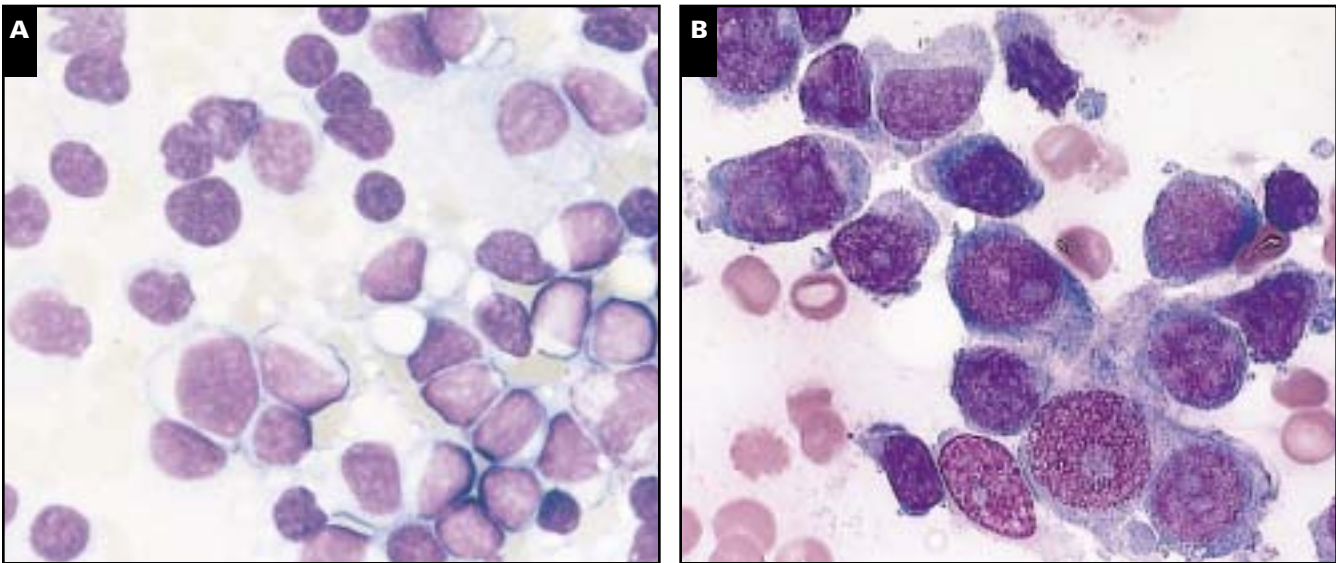


Image 3 (Case 7) Polymorphous subtype. Bone marrow aspirate smear. **A**, Polymorphous lymphoid infiltrate composed of small and large cells (Wright-Giemsa, $\times 1,000$). **B**, A focus of large cells with vesicular chromatin, distinct nucleoli, and abundant cytoplasm (Wright-Giemsa, $\times 1,000$).

common structural change, seen in 6 cases (50%) **Image 4**. Deletion 3q21 and 13q12 were each seen in 2 (17%) cases. Structural abnormalities of 12p occurred in 2 cases (17%), both add(12)(p11-13). One case each had del(1)(q32) and add(17)(p13).

Bone Marrow Morphologic Findings Correlated With Cytogenetics Results
Cytogenetic abnormalities were detected in 3 (17%) of 18 lymphoplasmacytoid, 2 (20%) of 10 lymphoplasmacytic, and 7 (78%) of 9 polymorphous cases.

Table 1
Clinical Data, Histologic Subtype, and Karyotype in 12 Patients With Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

Case No./Sex/ Age (y)	Previous Chemotherapy	Survival (mo)*	Karyotype
Polymorphous			
1/M/63	–	A (24+)	44-46,XY,del(6)(q21),add(8)(q24.3)[cp2]/46,XY[11]
2/F			
A/61	+	D (110)	43-46,X,add(X)(q28),del(1)(p22),–2, del(3)(p11), del(3)(q21),del(4)(q28),del(6)(q16),–8, add(9)(p23),del(10)(p12),add(11)(q25),add(12)(p13),–19,–21,–22,+4-7mar [cp5]
B/62	+		46,XY[20]
3/M/67	+	D (70)	45,X,–Y[4]/46,XY[16]
4/F/69	+	D (43)	46-47,XX,+5[cp2]/46,XX[8]
5/F			
A/56	+	A (72+)	46,XX[20]
B/57	+		46,XX,del(13)(q12)[5]/46-47,XX,+5[cp2] 46,XX[15]
6/M/73	–	D (6)	47,XY,del(3)(q21),–4,del(6)(q21),–8,add(12)(p11),+3mar[3]/46,XY[17]
7/F/52	–	D (46)	49-50,XX,del(1)(q32),+3,+5,del(6)(q22),+7,–8,+3-4 mar [cp7]/46,XX[2]
Lymphoplasmacytoid			
8/F/72	+	D (48)	46,XX,der(5;8)(q10;q10),+16,add(17)(p13),add(19)(q13.4)[2]/46,XX,–X,+1-2 mar [cp2]/46,XX[15]
9/M/63	+	A (40+)	44-46,XY,del(6)(q21),add(8)(q24.3)[cp2]/46,XY[11]
10/F			
A/43	–	D (57)	46,XX,del(13)(q12)[2]/48,XX,+3,+4,–13,+18[1]/46,XX[21]
B/53	+		46,XX[19]
C/54	+		46,XX[12]
Lymphoplasmacytic			
11/F/54	–	D (33)	45,X,–X,del(6)(q21)[3]/46,XX[27]
12/M/65	+	A (127+)	45,X,–Y[19]

* As of January 31, 2001. A, alive; D, dead.

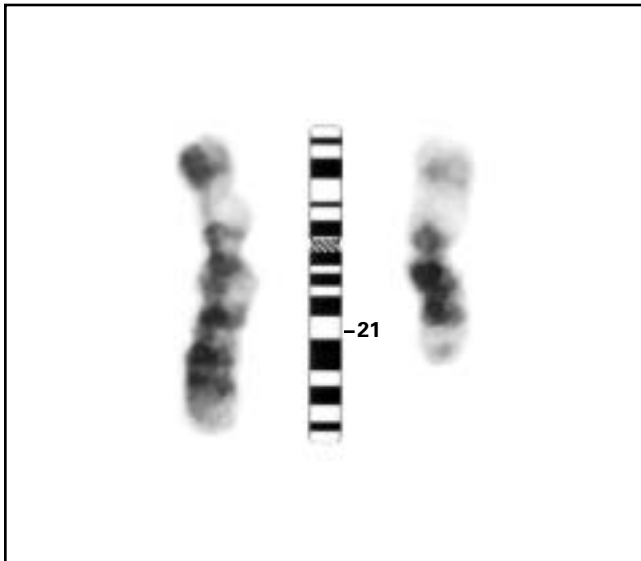


Image 4 (Case 11) Giemsa-banded chromosome 6 showing del(6)(q21) (right) and normal chromosome 6 (left).

When the lymphoplasmacytoid and lymphoplasmacytic groups were combined for statistical analysis, polymorphous tumors were significantly more likely to be aneuploid (7/9 [78%]) than were lymphoplasmacytoid and lymphoplasmacytic tumors (5/28 [18%]) ($P < .005$).

Bone Marrow Morphologic Findings Correlated With Clinical Course

Clinical follow-up was available for 28 (76%) of 37 patients, with a median follow-up of 36 months (range, 3–180 months). Sixteen patients had an indolent clinical course, clinical evidence of disease progression developed in 7 patients, and large cell lymphoma developed in 5 patients. Thirteen patients had lymphoplasmacytoid tumors, 7 had lymphoplasmacytic tumors, and 8 had polymorphous tumors. Cytogenetics data for these cases showed diploid in 19 and aneuploid in 9.

Four patients (31%) with lymphoplasmacytoid tumors (2 aneuploid, 2 diploid) had a poor clinical course: 3 had progressive disease, and large cell lymphoma developed in 1. Two (29%) of 7 patients with lymphoplasmacytic tumors had progressive disease. Both patients with progressive disease had aneuploid tumors. None of these patients developed large cell lymphoma. By contrast, 6 patients (75%) with polymorphous LPL/WM had a poor clinical course: 2 had progressive disease, and large cell lymphoma developed in 4. Five of 6 patients with a poor prognosis had aneuploid tumors.

Combining the lymphoplasmacytoid and lymphoplasmacytic groups for statistical analysis showed that patients with polymorphous LPL/WM (6/8 [75%]) were significantly more likely to have a poorer prognosis than patients with

lymphoplasmacytoid or lymphoplasmacytic LPL/WM (6/20 [30%]) ($P < .01$).

Discussion

We report the results of conventional cytogenetics analysis in 37 cases of LPL/WM, each case with compatible immunophenotypic findings and subclassified morphologically using the Kiel criteria as described by Bartl and colleagues.⁸ Twelve cases (32%) had an abnormal karyotype, as shown in Table 1. There was no correlation between the cytogenetic results and either previous therapy or serum beta₂-microglobulin levels.

The presence of chromosomal abnormalities correlated with morphologic findings. Fewer than one quarter of the lymphoplasmacytoid and lymphoplasmacytic LPL/WM cases had an aneuploid karyotype. By contrast, most cases of polymorphous LPL/WM had abnormal cytogenetic findings ($P < .005$), and in many of these cases, the karyotype was complex. In a recent case report, Jankovic and colleagues¹⁶ also described complex karyotypic findings in a case of polymorphous LPL/WM. However, in most other studies reported in the literature, no correlation between morphologic findings and karyotype has been observed. In addition, every case of polymorphous LPL/WM with a complex karyotype in the present study also had a variable number of diploid metaphases. These findings suggest that the polymorphous type of LPL/WM represents a more advanced phase of clonal evolution among differentiated cells that produce clonal IgM. In a recent study, Ciric and colleagues²⁰ also described a case of LPL/WM that demonstrated intraclonal heterogeneity, supporting our interpretation. One can further hypothesize that clonal evolution results in progression to a clinically more aggressive form of disease. Others have reported that polymorphous LPL/WM is clinically more aggressive than other subtypes of LPL/WM.⁸

The most frequent structural abnormality identified in this study, in 6 (50%) of 12 cases with an abnormal karyotype, was del(6q), encompassing the q13 to q22 region. Deletion of 6q has been associated with various types of B-cell non-Hodgkin lymphoma^{21,22} and may be more common in high-grade lymphomas that have transformed from low-grade follicular lymphoma.⁹ Thus, it seems reasonable to suggest that the presence of 6q– is a marker of transformation in LPL/WM and that the polymorphous subtype is the initial manifestation of transformation to large cell lymphoma.

We report 2 recurrent trisomies in 5 cases of LPL/WM that have not been published previously. Three cases were trisomic for chromosome 5, and 2 cases had trisomy 3. One case had trisomy of both chromosomes 3 and 5. Trisomy 3

has been identified as a recurrent chromosomal abnormality in nodal and extranodal marginal zone B-cell lymphomas.²³⁻²⁵ The role of trisomy 3 in the pathogenesis of LPL/WM is unknown. Comparative genomic hybridization analysis has shown that the minimal overrepresented region involves 3q21-23 to 3q25-29. The *bcl-6* proto-oncogene, located on 3q27, may be involved. All 3 cases with trisomy 5 were the polymorphous subtype of LPL/WM, and large B-cell lymphoma subsequently developed in 1 patient (data not shown). Trisomy 5 has been reported to be an adverse prognostic finding in patients with centroblastic lymphoma.²⁶ Thus, trisomy 5 also may be an adverse prognostic marker in cases of LPL/WM.

The t(9;14)(p13;q32) originally was identified in a retrospective analysis of 474 nodal and extranodal malignant lymphomas by Offit et al²⁷ and was correlated with plasmacytoid differentiation. In the t(9;14), the *pax-5* gene at 9p13 is fused to the immunoglobulin heavy chain gene at 14q32.²⁸ The *pax-5* is transcribed throughout B-cell ontogeny but undergoes down-regulation during plasma cell differentiation. The t(9;14) has been reported in lymphoplasmacytoid lymphoma and splenic marginal zone B-cell lymphoma by others^{28,29}; however, we were unable to identify the t(9;14) in any of the cases in the present study. Similar results using fluorescence in situ hybridization techniques have been reported by others.³⁰ These results suggest that LPL/WM in bone marrow is not related to nodal lymphomas with plasmacytoid differentiation that carry the t(9;14).

The *p53* gene, located at 17p13, may be deleted or mutated in low-grade B-cell lymphomas, particularly in cases that have undergone histologic transformation to higher grade lymphoma.³¹ In the present study, deletions of 17p13 were not detected in any cases of LPL/WM. Thus, inactivation of the *p53* gene does not seem to be involved in the pathogenesis of LPL/WM, in agreement with the findings of others.³¹⁻³³ Similarly, deletions of 13q, 13q14, and trisomy 12, while common in B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma were not noted in the present series, confirming the findings of other reports.^{10,11,32,33}

We have reported a large series of cases of LPL/WM and have shown conventional cytogenetic abnormalities in approximately one third of these cases. These cytogenetic abnormalities, which usually are complex, occur more commonly in the polymorphous subtype of LPL/WM than in the lymphoplasmacytoid and lymphoplasmacytic subtypes and are associated with a poor prognosis. The presence of some of these genetic changes, such as deletion of 6q, supports clinical and histologic evidence that the polymorphous subtype of LPL/WM represents an early stage of morphologic transformation to large B-cell lymphoma.

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