Concomitant Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma and Non–Immunoglobulin M Plasma Cell Neoplasm

A Report of 14 Cases With Laboratory Evidence of Biclonal B-Cell Neoplasms in Individual Patients

Yue Zhao, MD, PhD; Philip Petersen, MD, PhD; Sophie Stuart, MD; Jiaqi He; Yaping Ju, MD; Luis F. Carrillo, MD; Eric D. Carlsen, MD, PhD; Yi Xie, MD, PhD; Alireza Ghezavati, MD; Imran Siddiqi, MD, PhD; Ling Zhang, MD; Endi Wang, MD, PhD

• ***Context.***—**The co-occurrence of plasma cell neoplasm (PCN) and lymphoplasmacytic lymphoma (LPL) is rare, and their clonal relationship remains unclear.**

Objective.—**To evaluate the clinicopathologic characteristics of concomitant LPL/PCN.**

Design.—**Retrospectively analyzed clinical and laboratory data of 14 cases.**

Results.—**Three patients initially presented with immunoglobulin (Ig) M paraprotein, 1 with IgG paraprotein, and 10 had simultaneous diagnoses of PCN and LPL. In 13 cases, flow cytometry detected both LPL and PCN in marrow biopsies. Furthermore, immunohistochemistry highlighted the 2 neoplastic populations, demonstrating an increased proportion of plasma cells and their expression of cyclin D1, CD56, and/or a non-IgM isotype restriction. All cases exhibited discordant heavy-chain isotypes between LPL and PCN. Thirteen of the 14 cases (92.9%) had concordant light-chain restrictions between the 2 neoplasms, and the remaining case (7.1%) showed discordant light-chain restrictions. Of the 12 patients with follow-up, 5 were treated with myeloma regimens, 2 with LPL regimens, 3 with combined therapy, and 2 with observation alone. Follow-up ranged from 2 to 146 months (median, 12.5 months). One patient died of PCN progression, one died of comorbidity, and 10 patients were alive with or without disease. Survival analysis showed no significant difference from the control.**

Conclusions.—**The discordant heavy-chain isotype restrictions between PCN and LPL suggest biclonal B-cell neoplasms, which is supported by PCN's phenotypic distinction, such as the expression of cyclin D1 and/or CD56. However, our series exhibited a tendency toward concordant light-chain restrictions between the 2 neoplasms, raising the possibility that PCN may evolve from LPL through class switching.**

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Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) is a type of indolent small mature B-cell neoplasm that typically exhibits plasmacytoid differentiation.[1] Conversely, plasma cell neoplasm (PCN) is a neoplasia of terminally differentiated B cells, devoid of clonal B-cell component.[2] Both neoplasms have a propensity to involve the bone marrow and often present with serum paraproteinemia. In both instances, serum paraprotein may present early as monoclonal gammopathy of undetermined significance, years before the disease progresses to either LPL/WM or symptomatic PCN. Despite these shared clinical and laboratory features, these 2 neoplasms develop at different stages of B-cell ontogeny and manifest distinctive clinical presentations and disease courses.[1,2] Consequently, the current therapeutic approaches differ between LPL/WM and PCN, and the pathologic diagnosis of each entity is usually straightforward. Interestingly, PCN has been reported to coexist with other mature B-cell neoplasms,[3–16] most frequently with chronic lymphocytic leukemia (CLL),[3,7,8,11,13,14] but its concurrence with LPL is relatively rare.[4,9,10,15] In particular, the co-occurrence of LPL and PCN in the bone marrow of the same individual is rarely reported, being

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From the Department of Pathology, College of Basic Medical Sciences, and the First Hospital, China Medical University, Shenyang, China (Zhao); the Department of Pathology, Keck School of Medicine, University of Southern California, Los Angeles (Petersen, Stuart, He, Ju, Ghezavati, Siddiqi, Wang); the Department of Pathology, Duke University Medical Center, Durham, North Carolina (Carrillo, Carlsen); the Department of Laboratory Medicine, University of California San Francisco (Xie); and the Department of Hematopathology, Moffitt Cancer Center, Tampa, Florida (Zhang).

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Corresponding author: Endi Wang, MD, PhD, Department of Pathology, Keck School of Medicine, University of Southern California, 1975 Zonal Ave, Los Angeles, CA 90033 (email: endi.wang@med.usc.edu).

limited to sporadic case reports[4,10,15] or small series in the literature.[9] This may be because a plasmacytoid component is naturally present in LPL,[1] and PCN concurrent with LPL in the bone marrow is susceptible to being misclassified as a plasmacytic component of LPL, leading to underrecognition of cases with this type of composite B-cell neoplasms. Consequently, the clinicopathologic features and pathogenesis of concomitant LPL/WM and PCN remain to be well delineated. Herein, we report our retrospective analysis of 14 cases of concomitant LPL/WM and PCN in individual patients.

PATIENTS AND METHODS

Case Selection

The study has been approved by the institutional review boards of the University of Southern California Keck Medicine/Norris Hospital, Los Angeles, and Duke University Medical Center, Durham, North Carolina. All the 14 cases of concomitant LPL and PCN in individual patients, either concurrent or metachronous, were encountered within the past decade, including 6 cases from Duke University Medical Center; 4 cases from the University of California San Francisco Medical Center; 3 cases from Moffitt Canter Center, Tampa, Florida; and one case from Keck Medicine of the University of Southern California, Los Angeles. All cases were retrospectively reviewed by authors E.W., Y.X., L.Z., and I.S., and diagnoses were confirmed according to the 5th edition of the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues[17] and the International Consensus Classification of Mature Lymphoid Neoplasms.[18] Clinical history and laboratory data, including serum protein electrophoresis, immunofixation electrophoresis (IFE), serum free light chain, immunoglobulin profile, complete blood cell count (CBC), flow cytometric analysis, cytogenetic studies, molecular tests, etc, were collected, and were analyzed retrospectively. Cases of concomitant PCN and indolent B-cell neoplasm of non-LPL type were excluded from this study. Additionally, 35 cases of isolated LPL, without evidence of concomitant PCN, were collected as a control group for the study.

Statistical Analysis

Statistical analyses were conducted using SAS, version 9 (SAS Institute, Cary, NC). The Student *t* test, Wilcoxon Mann-Whitney test, χ^2 test, and Kaplan-Meier survival analysis were used to test the statistical significance of differences between the groups. A *P* value of $<.05$ was considered to indicate statistically significant differences between the compared groups.

RESULTS

The clinical features of 14 cases of LPL/WM concomitant with PCN are summarized in Table 1, and the pathologic characteristics are summarized in Table 2. The Supplemental Table (see supplemental digital content containing 1 table and 4 figures) summarizes clinicopathologic features of concomitant LPL/PCN in comparison with 35 cases of isolated LPL.

Clinical Manifestations

The patient group consisted of 9 men and 5 women, ranging in age from 42 to 83 years. The median age at the time of concurrent LPL/PCN diagnosis was 68.5 years, and at the initial presentation of either condition was 67 years. In 3 cases (cases 1, 4, and 6), an immunoglobulin (Ig) M isotype serum paraprotein or LPL was identified before a separate non-IgM–isotype paraprotein emerged or a non-IgM–type PCN was diagnosed. Conversely, one case showed a non-IgM–type paraprotein preceding the diagnosis of LPL (case 9). The remaining 10 cases demonstrated the concurrence of 2 distinct serum paraproteins or simultaneous diagnosis of LPL and PCN in the same bone marrow biopsies. All patients but one (cases 1–4 and 6–14) had serum protein electrophoresis and/or IFE performed when concurrent LPL and PCN were identified. All had their serum paraprotein detected, with 10 of 12 cases demonstrating biclonal paraproteins of IgM and non-IgM isotypes (Figure 1, A through C) (83.3% versus 8.6% in the control [Figure 1, D], $P < .001$). The remaining 2 cases (cases 4 and 8) showed an isolated IgM paraprotein without a detectable non-IgM component. Of the 9 cases with identifiable non-IgM isotype PCN, 5 cases had an IgG isotype and the other 4 cases were of the IgA isotype. Eleven cases had serum free light-chain levels quantified, with 8 showing elevated free light-chain levels ranging from 0.19 to 450.9 mg/L, with a median of 16.1 mg/L. Of the 11 cases with a tested serum immunoglobulin profile, 7 (cases 1, 2, 7, 10–13) exhibited coelevation of IgM and non-IgM isotypes, whereas the remaining 4 cases showed an increase only in IgM (cases 2, 4 and 6) or non-IgM isotype (case 9). At the diagnosis of concomitant LPL and PCN, serum IgM ranged from 298 to 2180 mg/dL with a median of 607 mg/dL, and non-IgM isotype serum paraprotein ranged from 728 to 5740 mg/dL with a median of 2249.5 mg/dL. Six cases had serum β_2-microglobulin measured and showed a median of 3.5 mg/L with a range of 2.2 to 4.6 mg/L, in contrast to a median of 3.37 for the control. Thirteen patients underwent a radiographic skeletal survey, and lytic bone lesions were identified in 9 patients (69.2%) at the presentation of concurrent LPL and PCN, compared with 0 of 35 patients (0%) in the control group ($P < .001$). Lymphadenopathy was identified in only 1 of 12 patients (8.3%) who had a computed tomography scan at the time of initial presentation, in contrast to 42.4% (14 of 33) in the control group ($P > .05$).

Evaluation of Peripheral Blood Smears, Bone Marrow Aspirate Smears, and Biopsies

All 14 cases had CBCs performed and blood smears examined at the time of the bone marrow biopsy, which resulted in the diagnosis of concurrent LPL and PCN in 13 cases or isolated LPL (case 6) in the remaining case. Of these, 5 patients (cases 3, 4, 6, 7, and 13) presented with mild anemia, 1 (case 10) with mild anemia and mild thrombocytopenia, 2 (cases 1 and 9) with mild to moderate pancytopenia, and 5 (35.7%; cases 2, 5, 8, 11 and 14) with relatively normal CBCs, and the remaining case (case 12) demonstrated marked leukocytosis with absolute lymphocytosis. The CBC data for the control group were similar, with approximately one-third of patients presenting with relatively normal CBCs (12 of 35; 34.3%). Morphologic examination of the blood smears confirmed the findings of automated blood cell counts in each case. The one with absolute lymphocytosis showed a monotonous population of small mature lymphocytes consistent with circulating lymphoma cells. All the cases had bone marrow biopsies performed, including 13 that demonstrated concurrent LPL and PCN, and the remaining case (case 6) with a 5-year history of LPL and a recent diagnosis of solitary osseous plasmacytoma in the vertebral body with residual LPL detected in the biopsied bone marrow. Of the 13 cases with concurrent LPL and PCN in the bone marrow (excluding case 6), the extent of LPL involvement ranged from 5% (cases 5 and 9) to 70% (case 1) with a median of 23%, and the burden of

Table 1. Clinical Presentation and Laboratory Findings in 14 Cases of Concomitant Lymphoplasmacytic Lymphoma (LPL) and Plasma Cell Neoplasm (PCN)

Case No.	Age, y/Sex	Presentation	SPEP, g/dL	IFE Ig Isotype	SFL, mg/L	Ig Profile, mg/dL	B2M, mg/L	BL	LN	Treatment	FU, mo	Outcome
1[a]	63/M	IgM MGUS × 10 years	+	IgM κ; IgA κ	κ, 17.8	IgM 587, IgA 3066	4.2	−	−	RVD, ASCT	144	Died of myeloma
2	57/M	Concurrent	+ 0.8; 0.9	IgM κ; IgG κ	κ 62.7	IgM 1280, IgG 1310	nd	+	nd	RCVP	24	Alive
3	63/M	Concurrent	+	IgM κ; IgG κ[b]	nd	nd	nd	+	nd	nd	nd	nd
4	74/F	LPL × 1 y	+	IgM κ	κ 6.98	IgM 745	nd	−	+	BR	5	Alive
5	81/F	Concurrent	nd	IgM λ; IgG λ[c]	λ nd	nd	nd	nd	nd	nd	nd	nd
6	61/F	LPL × 5 y before plasmacytoma	+	IgM λ, IgG λ	λ 0.19	IgM 2180, IgG 1460	2.2	+	−	BR, fludarabine, melphalan, prednisone, thalidomide	146	Alive w/LPL
7	76/M	Concurrent	+ 0.93	IgM κ, IgA κ	nd	IgM 904, IgA 728	nd	+	−	Bortezomib	13	Alive w/o disease
8	42/M	Concurrent	+ 0.3	IgM κ	κ 255.5	nd	nd	+	−	XRT, Dara, RD	5.5	ASCT planned
9	67/M	IgG MGUS × 7 y before PCM	+ 1.5	IgM κ, IgG κ	κ 14.4	IgM 298, IgG 2400	4.6	+	−	Dara, RVD	86	ASCT planned
10	70/F	Concurrent	+ 4.7	IgM κ, IgA κ	κ 450.9	IgM 607, IgA 5740	4.45	+	−	RVD, ASCT	12	Alive
11	73/M	Concurrent	+ 0.4; 2.5	IgM κ, IgG λ	κ 29.8; λ 371	IgM 527, IgG 3056	3.09	+	−	XRT, CyBorD, rituximab, ASCT	12	Alive w/ MRD
12	64/F	Concurrent	+ 1.7; 0.4	IgM κ, IgA κ	κ 7.06	IgM 469, IgA 2039	nd	−	−	Observed	36	Alive w/o disease
13	83/M	Concurrent	+	nd	nd	IgM 342, IgG 2923	3.5	+	−	XRT, rituximab	11	Died of comorbidity
14	77/M	Concurrent	0.6	IgM κ, IgG κ	κ 9.06	IgM 656, IgG 995	2.66	−	−	Observed	2	Alive

Abbreviations: ASCT, autologous stem cell transplant; BL, bony lesion; BR, bendamustine plus rituximab; B2M, serum β_2-microglobulin; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; Dara, daratumumab; FU, follow-up; IFE, immunofixation electrophoresis; Ig, immunoglobulin; Ig profile, serum immunoglobulin profile; κ, κ light chain; λ, λ light chain; LN, lymphadenopathy; MGUS, monoclonal gammopathy of undetermined significance; MRD, minimal residual disease; nd, not done; RCVP, rituximab, cyclophosphamide, vincristine and prednisolone; RD, Revlimid (lenalidomide) and dexamethasone; RVD, Revlimid (lenalidomide), Velcade (bortezomib), and dexamethasone; SFL, serum free light chain; SPEP, serum protein electrophoresis; w/, with; w/o, without; XRT, radiotherapy; +, positive; −, negative.

[a] Case 1 was previously published as a case report.[15]
[b] Detected by immunohistochemistry alone.
[c] Detected by flow cytometry alone, whereas others were detected by IFE and/or other assays.

Table 2. Pathologic Features in 14 Cases of Concomitant Lymphoplasmacytic Lymphoma (LPL) and Plasma Cell Neoplasm (PCN)

Case No.	Leukocytes, $\times 10^3/\mu L$	Hemoglobin, g/dL	Platelets, $\times 10^3/\mu L$	Blood LPL	LPL:PCN (%)[a]	Pattern LPL/PCN	LPL Phenotype[b]	PCN Phenotype[b]	Cytogenetics/FISH[c]	Mutations
1	3.6	12.2	117	−	70:20 (22.2)	Interstitial aggregates/ aggregates	pCD10$^-$/CD5$^-$/cyclin D1$^-$/IgM κ$^+$ (IHC only)	CD19$^-$/CD56$^-$/cyclin D1$^-$/IgA κ (IHC only)	/−13q	nd
2	7.2	14.1	260	−	25:8 (24.2)	Paratrabecular aggregates/ clusters	CD10$^+$/CD5$^-$/BCL6$^-$/ cyclin D1$^-$/κ$^+$	CD19$^-$/CD56$^-$/cyclin D1$^+$/IgG$^+$/κ$^+$	/negative; *IGH*::*BCL2*$^-$	*MYD88* L256P
3	9.2	12.4	300	−	20:50 (71.4)	Interstitial aggregates/ aggregates	CD10$^+$/CD5$^-$/BCL6$^-$/ cyclinD1$^-$/κ$^+$	CD19$^-$/CD56$^+$/cyclin D1 partial$^+$/CD117$^+$/κ$^+$	46,XY[20]/negative; *IGH*::*BCL2*$^-$	*MYD88* L256P
4	5.2	11.7	225	−	40:8 (16.7)	Interstitial aggregates/ aggregates	CD10$^-$/CD5$^-$/cyclin D1$^-$/κ$^+$	CD19$^-$/CD56$^+$/cyclin D1$^+$/κ$^+$	nd	*MYD88* L256P
5	8.7	14.1	257	−	5:10 (66.7)	Interstitial aggregates/ aggregates	CD10$^-$/CD5$^-$/cyclin D1$^-$/IgM λ$^+$	CD19$^-$/cyclin D1$^+$/ IgG λ$^+$	nd	nd
6	4.8	10.8	190	−	15:0	Interstitial aggregates/ plasmacytoma	CD10$^-$/CD5$^-$/cyclin D1$^-$/λ$^+$	λ$^+$[d]	nd	nd
7	N	11.7	N	nd	50:10 (16.7)	Interstitial aggregates/ aggregates	CD10$^-$/CD5$^-$/cyclin D1$^-$/κ$^+$	CD19$^-$/cyclin D1$^+$/ IgA$^+$/κ$^+$	/*CCND1*::*IGH*	*MYD88* L256P
8	6.8	14.9	327	nd	40:20 (33.3)	Interstitial aggregates/ aggregates	CD10$^-$/CD5$^-$/cyclin D1$^-$/κ$^+$	CD19$^-$/cyclin D1$^+$/ CD56$^+$/κ$^+$	Complex/*CCND1*::*IGH*	*MYD88* L256P
9	3.6	8.1	81	−	5:90 (94.7)	Interstitial aggregates/ confluence	CD10$^-$/CD5$^-$/cyclin D1$^-$/κ$^+$	CD19$^-$/CD56$^+$/ CD117$^-$/κ$^+$	46,XY[20]	*MYD88* L256P
10	4.7	9.2	115	−	8:70 (89.7)	Interstitial aggregates/ aggregates	CD10$^-$/CD5$^-$/κ$^+$	CD19p$^+$/CD56$^+$/κ$^+$	/+1q, −13, *FGFR*::*IGH*, −17p	*MYD88* L256P
11	8.2	13.3	325	nd	23:28 (54.9)	Interstitial aggregates/ aggregates	CD10$^-$/CD5$^-$/κ$^+$	CD19$^-$/CD56$^+$/ CD117$^+$/λ$^+$	/Negative result	*MYD88* L256P
12	39.3	12.5	283	+	10:15 (60)	Interstitial aggregates/ aggregates	CD10$^-$/CD5$^-$/κ$^+$	CD19$^-$/Cytoplasmic κ$^+$ (FC only)	46,XX[20]/ +1q, +9, +11,+17	*MYD88* L256P
13	7.2	11.4	182	nd	60:25 (29.4)	Interstitial aggregates/ aggregates	CD10$^+$/CD5$^-$/κ$^+$	CD19$^-$/κ$^+$[d]	46,XY[20]/+11	*MYD88* L256P, *CXCR4*+
14	4.9	13.4	258	nd	15:2 (11.8)	Paratrabecular aggregates/ scattered	CD10$^-$/CD5$^-$/cyclin D1$^-$/κ$^+$	CD19$^-$/cyclin D1$^+$/ CD56$^-$/CD117$^+$/κ$^+$	46,XY[20]/+11q, *CCND1*::*IGH*	*MYD88* L256P

Abbreviations: *BCL2*, B-cell lymphoma 2 gene; *CCND1*, cyclin D1 gene; *CXCR4*, C-X-C chemokine receptor 4 gene; FC, flow cytometry; FISH, fluorescence in situ hybridization; Ig, immunoglobulin; *IGH*, immunoglobulin heavy locus; IHC, immunohistochemistry; κ, κ light chain; λ, λ light chain; *MYD88*, myeloid differentiation primary response 88 gene; N, normal without exact values provided; nd, not done; +, positive; −, negative.

[a] Represents percentage of PCN of entire neoplastic population (% plasma cells/[% LPL + % PCN] × 100).
[b] Except as noted, both IHC and FC were applied to assess light- and/or heavy-chain isotypes.
[c] FISH performed in plasma cell–enriched sample. Cases 2 and 3 had small B-cell lymphoma panel performed separately in nonenriched sample.
[d] Incomplete phenotype reported.

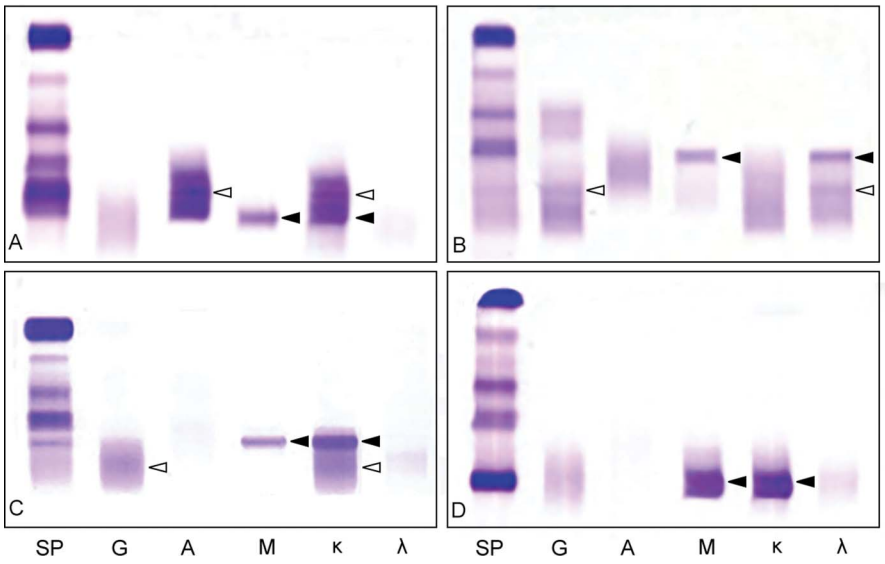

Figure 1. *Immunofixation serum protein electrophoresis. Cases 1 (A), 6 (B), and 8 (C) with concurrent lymphoplasmacytic lymphoma and plasma cell neoplasm. Biclonal bands are identified with immunoglobulin (Ig) M–κ and IgA-κ in case 1, IgM-λ and a faint IgG-λ in case 6, and IgM-κ and a faint IgG-κ in case 8. Datum from a case of isolated LPL with an IgM-κ paraprotein (D). Solid arrowheads indicate paraproteins of IgM isotype, and open arrowheads indicate paraproteins of non-IgM isotype.*

PCN ranged from 2% (cases 14) to 90% (case 9) with a median of 20%. The ratio of PCN to total neoplastic components (PCN/[LPL + PCN]) ranged from 0.118 (cases 4 and 7) to 0.947 (case 9) with a median of 0.333 compared with a median of 0.074 (range, 0.06–0.13) (plasma cells/[B cells + plasma cells]) in the control group ($P < .001$). Of the 14 cases, 12 (85.7%) demonstrated interstitial infiltration or aggregates of LPL, including the one with isolated LPL in the bone marrow, and the remaining 2 cases (cases 2 and 14) displayed paratrabecular aggregates of LPL cells. On the hematoxylin-eosin section of the bone marrow biopsy, all the 13 cases with concurrent LPL and PCN showed a mixture of 2 neoplastic components, all of which showed apparent aggregates or clusters of abnormal plasma cells. In 12 cases, plasma cell components were well to moderately differentiated, whereas in 1 case (case 1; Figure 2, A), they were poorly differentiated with plasmablastic morphology. In the latter case, in contrast to the small mature lymphocytes of LPL, aggregates or focal confluent growth of neoplastic plasma cells was apparently appreciated (Figure 2, B through G). Immunohistochemical analysis was performed on all 13 cases with concomitant diseases in the bone marrow. The analysis demonstrated aggregates or clusters of abnormal plasma cells, suggesting a dissociation of the plasma cell clone (PCN) from the small mature B-cell clone (LPL) (Figures 2, A through G, and 3, A through F; Supplemental Figures 1, A through F, and 2, A through C). This feature was particularly highlighted by stains such as CD56 (Figure 3, D; Supplemental Figure 1, E), cyclin D1 (Figure 3, E; Supplemental Figure 1, F), and non-IgM heavy-chain stains (Figure 2, D and E). Notably, a cyclin D1 immunohistochemical stain was performed in 8 cases and was positive in PCN in 7 cases (87.5%) in this series, compared with 0 of 31 cases in the control ($P < .001$).

Flow cytometry was performed on bone marrow specimens in all 14 cases, revealing a monoclonal B-cell population, including 1 with isolated LPL, and a concurrent abnormal plasma cell population in 13 cases (Figure 4, A through F; Supplemental Figure 3, A through F). These included a CD5-negative/CD10-negative monoclonal B-cell population in 11 cases and a CD5-negative/CD10-positive monoclonal B-cell population in 3 cases (cases 2, 3, and 13). The neoplastic nature of plasma cells was suggested by an abnormal immunophenotype, including the absence of CD19 (Figure 4, D; Supplemental Figure 3, E) in 12 of 13 cases (92.3%) and aberrant expression of CD56 (Supplemental Figure 3, F) in 6 of 9 cases (66.7%). Flow cytometric analysis was not performed on the vertebral biopsy in case 6, in which the diagnosis of plasmacytoma was established by immunohistochemical analysis demonstrating confluent growth of plasma cells with λ light-chain restriction. Flow cytometry was performed in all control cases. In addition to a monoclonal B-cell population, 4 cases (11.4%) also demonstrated a monotypic plasma cell population by using intracytoplasmic staining of light chains; however, the plasma cell population in these 4 cases also exhibited expression of CD19 and approximately 90% showed complete absence of CD56 (Supplemental Figure 4, A through F; 11.4% showed dim CD56 in a small fraction of the plasma cells). Of the 14 cases, the clonal B-cell population was restricted to κ light chain in 12 cases (85.7%) and to λ light chain in 2 cases (14.3%). Meanwhile, the clonal plasma cell population was restricted to κ light chain in 11 cases (78.6%) and to λ light chain in 3 cases (21.4%; PCN was assessed by immunohistochemistry and/or flow cytometry). Interestingly, a predominance of κ light-chain restriction was also noted in the control, comprising 88.6% of isolated LPL cases. Notably, concordant light-chain restriction between LPL and PCN was seen in 13 cases (92.9%) in this series, whereas the remaining case (case 11) demonstrated discordant light-chain restriction between LPL (κ light chain) and PCN (λ light chain). In 4 cases (cases 1, 2, 3 and 7) in which both light-chain and heavy-chain isotype stains were used, 2 plasma cell populations were identified by intracytoplasmic detection of heavy-chain and light-chain isotypes. These populations had concordant light-chain restrictions but discordant heavy-chain restrictions, one with an IgM isotype and the other with a non-IgM isotype (IgA κ in cases 1 and 7 and IgG κ in cases 2 and 3).

Cytogenetic Studies and Molecular Analysis

Chromosome analysis was performed in 6 cases. Of these, 5 cases (cases 3, 9, 12, 13, and 14) demonstrated a

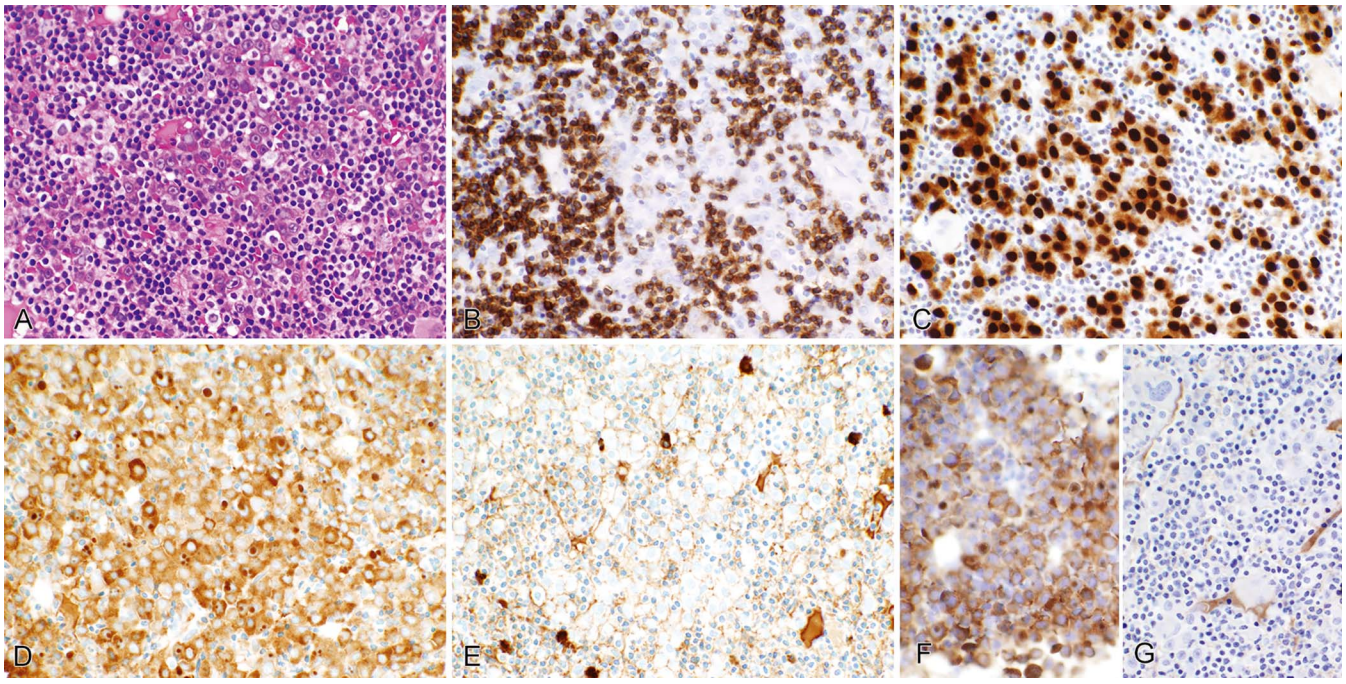

Figure 2. *Bone marrow examination of concurrent lymphoplasmacytic lymphoma (LPL) and plasma cell neoplasm (case 1). A, The bone marrow core biopsy shows an interstitial lymphoplasmacytic infiltrate. Scattered or clustered plasmablastic cells are noted throughout the field. Hematoxylin-eosin. B, The lymphocytes are positive for CD79a, whereas plasmablasts are apparently negative. C. The MUM1 stain highlights clusters of plasma cells that correlate with plasmablasts and admix with small mature lymphocytes. D, The plasmablasts are positive for immunoglobulin (Ig) A. Many Dutcher bodies are highlighted by the stain. E, The IgM stain shows scattered positive cells corresponding to the plasma cell component of LPL. The stain is negative in plasmablasts. F, The κ light-chain stain shows positivity in many plasmablasts and other plasma cells. G, The λ light-chain stain is essentially negative except for rare positive cells (right upper corner) (original magnification ×400 [A through G]).*

normal karyotype. The remaining case (case 8) showed complex abnormalities, including a component of t(11;14)(q13; q32). Of 10 cases in which myeloma-related fluorescence in situ hybridization (FISH) was performed, 7 (70%) demonstrated myeloma-related abnormalities. This included *CCND1*::*IGH* in 3 cases (30%; cases 7, 8, and 14), in which plasma cells were positive for cyclin D1 by immunohistochemistry. Three cases (30%; cases 2, 3 and 11) showed no detectable abnormalities related to the PCN by FISH. Two cases (cases 2 and 3) also underwent a FISH small B-cell lymphoma panel because of the paratrabecular distribution of lymphoid aggregates observed during morphologic evaluation and/or expression of CD10 in monoclonal B-cell population detected by flow cytometry. The test was negative, including the absence of immunoglobulin heavy locus (*IGH*)::B-cell lymphoma 2 gene (*BCL2*), in both cases.

Eleven cases had myeloid differentiation primary response 88 gene (*MYD88*) L265P mutation analysis performed, all of which were positive for the mutation, including one (case 13) positive for a concurrent C-X-C chemokine receptor 4 (*CXCR4*) mutation.

Clinical Outcome

Treatment information was available for 12 patients. These included a combination treatment for LPL and PCN in 3 patients (cases 6, 11, and 13), myeloma-related treatment for 5 (cases 1 and 7–10), LPL-related treatment for 2 (cases 2 and 4), and observation for 2 patients (cases 12 and 14). The treatment rate was 83.3%, compared with 73.5% in the control group ($P > .05$). Three patients (cases 1, 10, and 11) eventually received high-dose chemotherapy followed by autologous hematopoietic stem cell transplantation. Two additional patients (cases 8 and 9), who received myeloma-related treatment, were expected to receive autologous hematopoietic stem cell transplantation. Two patients, who were under observation, had relatively low burdens of both LPL and PCN at the time of diagnosis. These treatment approaches appeared to be determined based on symptomatic presentation and the relative burdens of the 2 neoplastic components (Table 2). Treatment information was not available for cases 3 and 5. The 12 patients with treatment information also had follow-up information available, with a median follow-up period of 12.5 months (ranging from 2 months to 12 years) since the diagnosis of the initial B-cell neoplasm or concurrent diseases. One patient with plasmablastic myeloma (case 1) eventually died of disease progression despite aggressive treatment with a high-dose chemotherapy followed by autologous stem cell transplant. Another patient (case 13) died of comorbidity 11 months after the diagnosis of concurrent diseases. Three patients were alive at their last clinic visit following LPL-related treatment (cases 2 and 4) or combined treatment (case 6); however, although the 2 patients who received LPL-related treatment showed clinical remission (cases 2 and 4), the patient who received combined treatment displayed recurrent lymphadenopathy 12 years after the initial diagnosis of LPL (case 6). Five patients demonstrated clinical remission or minimal residual disease status posttreatment, but their posttreatment follow-ups were short (ranging from less than 1 year to 3 years with a median of 1 year). Kaplan

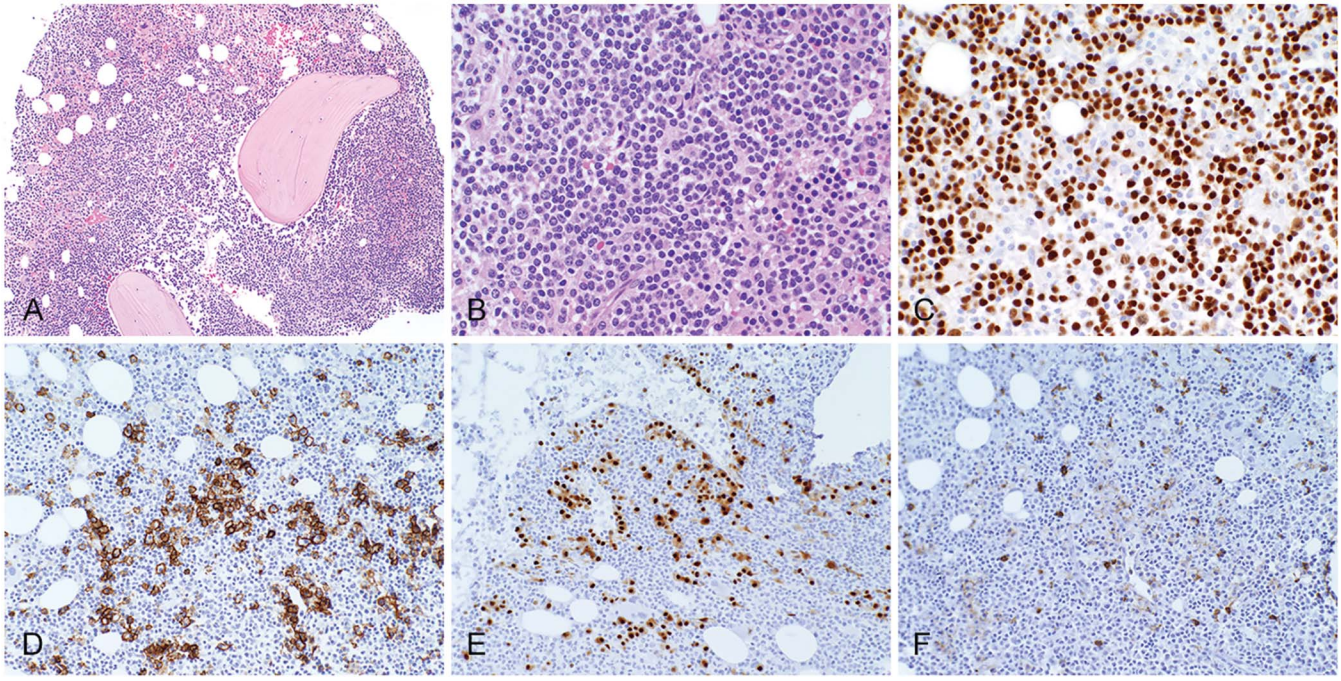

Figure 3. *Bone marrow examination of concurrent lymphoplasmacytic lymphoma and plasma cell neoplasm (case 4). A, The bone marrow core biopsy shows an interstitial lymphoplasmacytic infiltrate. Hematoxylin-eosin (H&E). B, High magnification shows small, mature-appearing lymphocytes with scattered plasmacytoid cells. H&E. C, The PAX5 stain highlights small mature lymphocytes. Clusters of negative cells are noted, which correlate with plasma cells highlighted by the CD138 stain (D). E, The plasma cells are positive for cyclin D1 with nuclear staining. F, The plasma cells are weakly positive for CD56 (original magnifications ×100 [A], ×400 [B], and ×200 [C through F]).*

Meier survival analysis estimated an overall survival of 144 months in this series.

DISCUSSION

LPL[1] and PCN[2] are 2 distinct B-cell neoplasms that are believed to originate at different stages of B-cell development. LPL arises from memory B cells, whereas PCN develops from terminally differentiated B cells. Both of these are thought to be developed after exiting or bypassing germinal centers, predisposing them to bone marrow involvement and typically exhibiting a serum paraprotein spike.[1,2] In rare instances, these 2 B-cell neoplasms can occur concomitantly in the same patients,[4,9,10,15] either developing sequentially[9,15] or being diagnosed concurrently.[4,9,10] Because of the overlapping clinical and pathologic features between LPL and PCN, a concomitant LPL and PCN in an individual bone marrow biopsy poses a diagnostic challenge, particularly in determining the clonal relationship between the two. For instance, because plasmacytoid differentiation is often seen in LPL,[1] increased plasma cells in a bone marrow biopsy with LPL may potentially be considered a component of the LPL rather than a separate B-cell clone. In this series, we demonstrate several morphologic features of

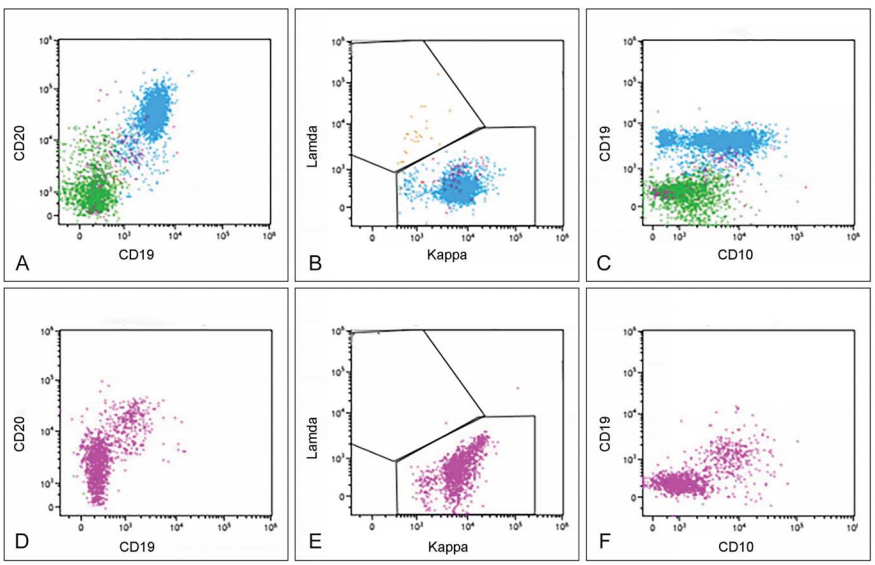

Figure 4. *Flow cytometric analysis of concurrent lymphoplasmacytic lymphoma (LPL) and plasma cell neoplasm (PCN) (case 13). A through C, The analysis with the gate set on lymphoid events demonstrated a monoclonal B-cell population (blue events) with κ light-chain restriction (B) and dim CD10 (C). Green events represent T cells or natural killer cells. D through F, The analysis with the gate set on CD138-positive events demonstrated abnormal plasma cells with κ light-chain restriction (E). Notably, there were 2 distinct populations of plasma cells, the major one without CD19 and CD20, and the other with dim CD19, dim CD20, and dim CD10. Whereas the former population represents PCN, the latter likely corresponds to the plasma cell component of LPL.*

concurrent PCN in bone marrow biopsies that can be used to distinguish it from isolated LPL with prominent plasmacytic differentiation. These features, in concurrent PCN, include a high proportion of plasma cells that tend to form clusters or aggregates, possibly display poor differentiation, and exhibit aberrant expression of relevant antigens, such as CD56, CD117, and/or cyclin D1. In contrast, in isolated LPL, there is a much smaller proportion of plasma cells that instead often show a dispersed distribution, are well differentiated, and have an unremarkable immunophenotype. In the majority of our cases, the geographical separation of the 2 neoplasms was well highlighted by immunohistochemical analysis. Additionally, the loss of CD19 in plasma cells is often seen in distinct PCN in flow cytometric analysis, whereas the plasma cell component of LPL usually exhibits retention of the antigen. More convincingly, the biclonal nature of concomitant LPL and PCN is frequently suggested by IFE, which often demonstrates biclonal serum paraprotein at a rate significantly higher than that seen in isolated LPL (83.3% versus 8.6%, $P < .001$, in this series). Although both LPL and PCM had concordant light-chain restriction in the vast majority of the cases with concurrent diseases, discordant heavy-chain isotypes between LPL and PCN (IgM in LPL versus non-IgM heavy-chain isotype, either IgG or IgA, in PCN) supports there being 2 separate clones of immunoproliferative disorders rather than a single clonal process (Figure 1, A through C). In contrast, the plasma cell component of LPL produces only an isolated IgM paraprotein (Figure 1, D; Table 2). In this series, the LPL inclines to express a restricted κ light chain, which seems to be a trait distinct for this type of mature B-cell neoplasm, given the same pattern of light-chain expression in the isolated LPL. In contrast, PCN without associated LPL has shown a statistical distribution of light-chain restrictions with κ:λ ratio of 1–2:1 according to our analysis of myeloma cases and the previous studies from other groups.[19] Interestingly, a high concordance in light-chain restriction was observed in LPL and concomitant PCN, suggesting an intrinsic mechanism to determine the restricted light-chain expression matched between the 2 B-cell neoplasms. Notably, a significantly skewed concordant light-chain restriction seems to be unique to LPL concurrent with PCN, because it has not been readily observed in other composite B-cell neoplasms, including concomitant CLL and PCN.[3] Moreover, in the majority of the cases in our series, LPL either preceded PCN or concurred with it. Thus, it is theoretically possible that a preexisting LPL underwent clonal evolution to PCN with class switching to a non-IgM isotype. This hypothesis would explain the skewed concordance in light-chain restriction and discordance in heavy-chain isotype restriction between LPL and PCN observed in a previous study[9] and our series. Unfortunately, genomic analyses could not be performed on sorted PCN and sorted LPL in this series, leaving this hypothetical mechanism to be verified or excluded in future studies.

PCN has been reported to occur concurrently with indolent B-cell neoplasms other than LPL,[3,5–8,11–14,16] including mostly CLL.[3,7,8,11–14] The underlying pathogenesis of these 2 concomitant B-cell neoplasms remains unclear, although several hypotheses have been proposed. Therapy has been implicated as the cause of concomitant PCN, given that PCN often developed after the diagnosis of indolent B-cell leukemia/lymphoma in many reported cases.[3,12,13] However, a significant fraction of the reported cases had not received any chemotherapy or other cytotoxic treatment before the PCN emerged years later.[3,11] Additionally, in some cases, the 2 B-cell neoplasms were diagnosed concurrently.[3,7,11,13] In this series, 2 patients with preceding LPL were simply observed without therapeutic intervention before the diagnosis of PCN, and 9 patients had the 2 B-cell neoplasms diagnosed in the same bone marrow biopsies. Therefore, causes other than therapy should be considered for the development of secondary B-cell neoplasm in patients with primary indolent B-cell neoplasm. It has been reported that patients with indolent B-cell neoplasms, including LPL and PCN, have a higher risk of developing a secondary neoplasm of either other hematopoietic[20–25] or nonhematopoietic origin compared with the general population.[20,21,26] This increased risk is often attributed to intrinsic defects, such as decreased immunity or genetic deficiency, in patients with primary indolent B-cell neoplasms, resulting in their predisposition to secondary malignancies.[27] An alternative hypothetical consideration for bone marrow–based composite hematolymphoid neoplasms, such as concomitant LPL and PCN, may be an altered microenvironment shared by the 2 B-cell neoplasms. In the future, when the mechanisms for the predisposition to secondary neoplasms are elucidated in patients with indolent B-cell neoplasms, early intervention targeting the underlying causes, such as boosting immunity or correcting genetic defect, may be carried out to decrease the risk for secondary neoplasms in this patient population.

LPL is clinically indolent with a median survival of 5 to 10 years,[1] whereas the clinical course of PCN greatly varies, with survival ranging from less than 6 months to more than 10 years, but with a median survival of about 6 years.[2] Advances in immunotherapy and immunomodulatory therapy have significantly improve the clinical outcomes for both B-cell neoplasms. The prognosis of PCM concomitant with indolent B-cell neoplasms such as CLL is theoretically unfavorable, with a few patients suffering from progression of either PCN or CLL and eventual death.[3,11] The therapeutic approach for cases with concomitant B-cell lymphoma/leukemia (mostly CLL) and PCM is controversial, and the protocols are often determined based on the extent of involvement of each neoplastic component and the dominant component of symptomatic presentation.[3,6,9,11] In our series, about half of the patients received combined treatment against both neoplasms, given the mixed features of the clinical presentations and codominance of the neoplastic burdens. The other half were treated for either PCN or LPL depending upon the dominant component. The majority of the patients demonstrated good responses to therapy, with either clinical remission or disease control. Only one patient died from the progression of the PCN. The estimated survival in our series seems to be better than that of isolated plasma cell myeloma and comparable to that of isolated LPL. This may be explained by the lag effect of including immunoproliferative disorders at an early disease stage in our series because of the initial detection of IgM paraprotein. Nonetheless, this study is limited by small sample size, retrospective nature, and short follow-up in some patients, and a large prospective cohort in clinical trials in the future may elucidate the optimal therapeutic approach for this complicated condition. Notably, the pathologic distinction of 2 neoplastic components in concomitant LPL and PCN may play an important role in patient management, particularly providing supportive information to determine the initial therapeutic approach and further adjust it based on the response of each neoplastic component's status after the initial treatment.

CONCLUSIONS

In pathologic diagnosis of concomitant LPL and PCN, the following evidence suggests a distinct PCN rather than a plasma cell component of LPL: (1) biclonal serum paraproteins with discordant heavy-chain isotype restrictions, specifically IgM and non-IgM isotypes; (2) a monoclonal plasma cell population without CD19, in the context of a monoclonal B-cell population; (3) a plasma cell population expressing cyclin D1, CD56, and/or CD117; (4) a high proportion of plasma cells and/or large aggregates of plasma cells in the context of a monoclonal B-cell population; (5) a plasma cell population with plasmablastic or poorly differentiated morphology in the context of a monoclonal B-cell population; and (6) myeloma-related cytogenetic abnormalities in plasma cell–enriched sample. Despite the discordant heavy-chain isotype restrictions, implying the 2 B-cell neoplasms were not clonally related, our series exhibited significant concordant light-chain restrictions between the 2 B-cell neoplasms. This raises the possibility that the PCN may have evolved from the LPL with class switching, at least in a fraction of the cases. Although the concurrent B-cell neoplasm complicates the treatment approach, it may not predict a significantly poorer outcome compared with isolated LPL. Future studies may focus on sequencing of sorted PCN and LPL cells to compare mutation profiles, particularly the presence or absence of *MYD88* L265P and/or *CXCR4* mutation, between the 2 B-cell neoplasms.

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