Editorial

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CD10-Positive Lymphoplasmacytic Lymphoma: A Diagnostic Pitfall

Lymphoplasmacytic lymphoma (LPL) is an indolent B-cell neoplasm commonly involving bone marrow. In majority of the cases, patients also demonstrate serum paraprotein of IgM isotype, thus fulfilling the criteria for the diagnosis of Waldenstrom macroglobulinemia (WM).[1] In diagnosis, the immunophenotypic profile of LPL is usually nonspecific, being typically negative for CD10, CD5, and CD23, though variable expression of CD10, CD5 or CD23 has been reported in rare cases. Hunter et al.[2] described expression of CD10 in 7% of WM/LPL patients. Remstein et al.[3] also reported that 2 out of 26 WM/LPL patients were positive for CD10. Due to the conventional concept that CD10 is considered a germinal center signature antigen, CD10-positive LPL can be easily misdiagnosed as follicular lymphoma (FL) involving bone marrow. Herein we present a series of 7 CD10-positive LPL cases compared with 11 cases of FL involving bone marrow to provide further insight for diagnostic distinction between the 2 entities.

Most common clinical presentation for LPL was anemia (3/7), whereas most common clinical presentation for FL was lymphadenopathy (9/11). All 7 cases of LPL demonstrated elevated serum IgM by immunoglobulin profiling and clonal IgM paraprotein by immunofixation. Interestingly, all the cases showed kappa light chain isotype restriction. Average serum beta-2 microglobulin level for LPL cases is 4.7 mg/L. Whereas none of FL cases had serum protein electrophoresis or other related tests performed due to low clinical suspicion for immunoproliferative disorder. Three (27.3%) FL cases showed circulating lymphoma cells, while none of the LPL cases had them identified, which may be owing to the indistinguishable morphology of LPL cells, especially in cases with low number of circulating lymphoma cells. Median level of bone marrow involvement for LPL cases is approximately 60%, while for FL is about 10%. Paratrabecular bone marrow involvement was seen in 72.3% of FL; in contrast, LPL demonstrated predominantly diffuse involvement or interstitial infiltration (Figures 1A-C). All 7 cases of LPL had CD10-positive monoclonal B-cell population detected by flow cytometry (Figures 1D-F). By immunohistochem-

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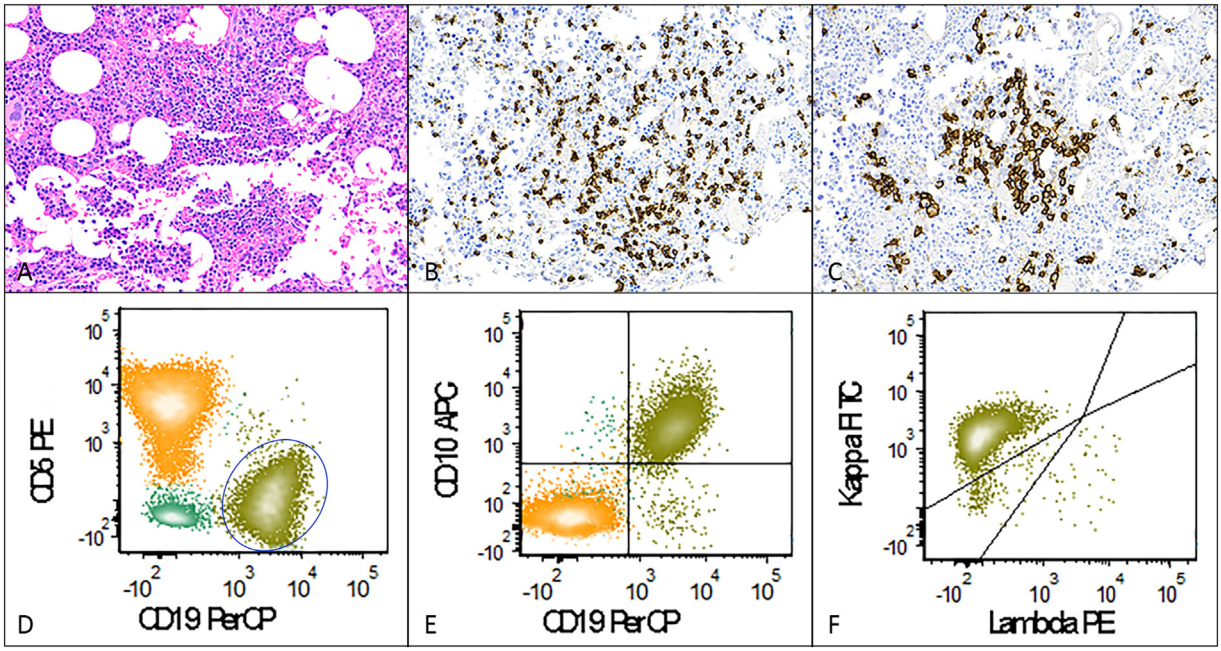
Figure 1 Bone marrow examination of index case. (A) The bone marrow core biopsy shows an interstitial lymphoplasmacytic infiltrate. H&E stain, ×200. (B) The CD20 stain highlights scattered small mature lymphocytes in interstitial distribution. Clusters of negative cells are noted, which correlate with intermingled plasma cells highlighted by the CD138 stain (C). (A-C) ×200. Flow cytometric analysis (D-F), with the gate set on lymphoid events, demonstrating a B-cell population (circled green colored events) without CD5 (D), positive for CD10 (E) and expressing restricted kappa light chain (F). Orange events (positive for CD5 but negative for CD19) represent T-cells, and blue events (negative for CD19 and CD5) likely represent NK cells.



istry, BCL6 expression was identified in 75% FL involving bone marrow, in contrast to none (0%) in LPL. All 7 cases of CD10-positive LPL demonstrated plasmacytic differentiation and 5 of them had immunohistochemical analysis performed to confirm light chain restriction in plasma cell components. In contrast, none of FL involving bone marrow exhibited significant plasmacytic differentiation associated with lymphoid aggregates; 3 cases had immunohistochemical analysis performed and showed 3-6% scattered plasma cells or small clusters of perivascular plasmacytosis with polytypic pattern of light chain expression within plasma cells. *IGH::BCL2* was detected in 83.3% of FL cases by fluorescence in situ hybridization (FISH), while none (0%) of LPL cases had it detected. *MYD88* L256P mutation was identified in all 7 cases of LPL (Table 1).

CD10-positive LPL involving bone marrow can be easily misdiagnosed as FL.[4] In our series, at least 2 cases were initially diagnosed as FL involving bone marrow largely based on flow cytometric detection of CD10-positive monoclonal B-cell population. Only after subsequently noticing increased serum paraprotein of IgM isotype in laboratory data, bone marrow biopsy was further evaluated, which resulted in a negative *IGH::BCL2* fusion by FISH and positive *MYD88* L256P mutation by molecular test. These led to the correction of the diagnosis to LPL in these 2 cases. Although both LPL and low-grade FL are in the category of small B-cell lymphoma, the 2 demonstrate distinct biological behavior and clinical outcome. Once involving bone marrow, FL is considered advanced stage and is predicted to have an unfavorable prognosis, often requiring treatment.[5] In contrast, LPL usually involves bone marrow, which is not an adverse factor to predict inferior survival and may not warrant immediate treatment.[6] In addition, approximately one third of low-grade FL eventually transform to diffuse large B-cell lymphoma or high-grade B-cell lymphoma,[1] while aggressive histologic transformation is uncommon in LPL, especially rare in the one with *MYD88* L265P mutation.[7] Therefore, diagnostic distinction between the 2 B-cell neoplasms is clinically critical. In evaluating bone marrow involvement by CD10-positve small B-cell lymphoproliferative disorder, alarming findings favoring for LPL rather than FL include increased serum paraprotein of IgM isotype, absence of lymphadenopathy, predominantly diffuse involvement or interstitial infiltration/aggregates, prominent plasmacytic differentiation with light chain restricted plasma cell components and absence of germinal center antigen expression other than CD10. Still, in most of these cases, FL cannot be ultimately excluded without cytogenetic and molecular study. Lack of *IGH::BCL2* fusion and detection of *MYD88* L256P or *CXCR4* mutation can further rule out FL and confirm the diagnosis of LPL, given the presence of *IGH::BCL2* in 90% of classic FL[1] and absence of *MYD88* L256P mutation in nearly 100% of FL.[8]

Table 1 Pathologic Characteristics of CD10-Positive LPL Compared with FL Involving Bone Marrow

	LPL	FL
Number of cases	7	11
Age, Median (range)	73 (57-83)	66 (43-82)
Lymphadenopathy	3/7 (42.9%)	9/11 (81.8%)
SPEP/IFE	IgM Kappa, 7/7 (100%)	NA
Circulating lymphoma cells	0/7 (0%)	3/11 (27.3%)
Marrow cellularity, median (range)	80% (25-90)	50% (20-90)
Marrow involvement, Median (range)	60% (10-90)	10% (3-80)
Dominant pattern of involvement	Interstitial, 4/7 (57.1%)	Paratrabecular, 8/11 (72.7%)
Minor pattern of involvement	Diffuse, 3/7 (42.9%)	Diffuse, 3/11 (27.3%)
CD10 expression	7/7 (100%)	5/7 (71.4%)
BCL6 expression	0/5 (0%)	3/4 (75%)
Monoclonal plasma cells	5/5 (100%)	0/3 (0%)
FISH *IGH::BCL2* fusion	0/7 (0%)	5/6 (83.3%)
MYD88 L265P mutation	7/7 (100%)	NA

Abbreviation: FISH = fluorescence in situ hybridization; FL = follicular lymphoma; IFE = immunofixation electrophoresis; LPL = lymphoplasmacytic lymphoma; SPEP = serum protein electrophoresis.

Disclosure

The authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

Yaping Ju: Writing – original draft. **Sophie Stuart:** Validation. **Yue Zhao:** Visualization, Data curation. **Yi Xie:** Resources. **Luis F. Carrillo:** Data curation. **Imran Siddiqi:** Writing – review & editing. **Ling Zhang:** Data curation. **Endi Wang:** Writing – review & editing, Supervision, Conceptualization.

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