Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

One Disease or Three?

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In the 57 years since Jan Waldenström first described the clinical and laboratory manifestations of what we now refer to as Waldenström macroglobulinemia (WM), the essential parameters of this syndromic constellation of signs and symptoms have remained fairly constant. In contrast, our understanding of the defining features of the hybrid immunoproliferative/lymphoproliferative disorder that most often causes it (lymphoplasmacytic lymphoma [LPL]) remains less settled. The immunoproliferative qualities of LPL/WM usually include a substantial IgM paraprotein in the blood and at least a minor degree of plasmacytoid differentiation in lesional cells, while the lymphoproliferative qualities are reflected in the predominant lymphoid histologic features, lymphadenopathy, and splenomegaly. In the recently published World Health Organization (WHO) Classification, essential features of LPL/WM include elevated monoclonal serum IgM levels in the blood of a patient with a lymphoma composed of small cells and lacking in histologic or immunophenotypic features characteristic of another specific type of lymphoma—in other words, it remains a diagnosis of exclusion.

Molecular analysis of lesional cells in LPL/WM documents that most have somatically mutated heavy chain loci. Although the cells have undergone antigen selection, they have failed to switch immunoglobulin class, suggesting that an initial transforming event occurred at a late stage of development, while the clone was proliferating in the setting of antigen-driven conditions. Specific hepatitis C virus in lymphomagenesis is far from clear. Other lines of investigation into the pathogenesis of LPL/WM have identified the t(9;14)(p13;q32) involving the PAX5 and IgH loci as a recurring karyotypic abnormality in up to 50% of the analyzed cases. This translocation quite likely leads to the deregulated expression of PAX5, a B-cell lineage-specific protein necessary for maturation beyond the pro-B-cell stage of maturation, whose over-expression leads to proliferation of a specific subset of splenic B cells.

Changes in terminology and multiple meanings for a single term have made it difficult to follow the literature on LPL/WM. In the Kiel Classification, the term immunocytoma was applied to lymphomas with plasmacytic differentiation: the lymphoplasmacytoid subtype was distinguished from the lymphoplasmacytic subtype on the basis of its consistent CD5 expression, the presence of proliferation centers, and the tendency to manifest with limited paraproteinemia. According to the Revised European-American classification of lymphoid neoplasms (REAL) criteria, however, this CD5+, CD23+ lymphoplasmacytoid subtype of Lennert would correspond more closely to B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and in most cases would be regarded as B-cell CLL/SLL rather than LPL. Despite this, the Revised European-American classification of lymphoid neoplasms retained the term immunocytoma was applied to lymphomas with plasmacytic differentiation: the lymphoplasmacytoid subtype was distinguished from the lymphoplasmacytic subtype on the basis of its consistent CD5 expression, the presence of proliferation centers, and the tendency to manifest with limited paraproteinemia. According to the Revised European-American classification of lymphoid neoplasms (REAL) criteria, however, this CD5+, CD23+ lymphoplasmacytoid subtype of Lennert
other-than-indolent clinical course (brisk mitotic rate, increased numbers of large transformed cells). The confusion that arose related to the fact that this category was used indiscriminately and became a “collection box” or waste-basket class of disparate diseases.

In the October 2001 issue of the Journal, Mansoor et al14 resurrected the Lennert tripartite terminology of immunocytoma subclassification and applied it to a large series of patients with WM and LPL, the latter being defined as CD5−, CD10−, CD23− IgM-producing lymphoma composed primarily of small cells with some degree of plasmacytic differentiation. The reader wishing to place the data of Mansoor et al14 in the broader context of degree of plasmacytic differentiation. The reader wishing to place the data of Mansoor et al14 in the broader context of the extent literature must beware: in using their own modifications of criteria proposed by Bartl et al15 in 1983, Mansoor et al set aside the key Kiel Classification distinction between lymphoplasmacytoid and lymphoplasmacytic subtypes (namely, CD5 positivity, proliferation centers, limited paraproteinemia), and used criteria for the polymorphous subtype that differ from and are more inclusive than those used by other authors.16 Little guidance is to be had from the recently published WHO Classification, which does not provide definitions for subtypes of LPL/WM, although it does recognize the potential prognostic importance of increased numbers of large cells.

In their study of 37 patients with LPL/WM, Mansoor et al14 found both structural and numeric chromosomal abnormalities in 12 patients, but none was recurrent, and none provided a biologic means of distinguishing between the authors’ lymphoplasmacytic and lymphoplasmacytoid groups of LPL. Of particular significance is the fact that none of the 37 patients had a karyotype that included the t(9;14), a finding that stands in contrast to the high prevalence of this translocation reported in previous studies.8,9 One explanation offered by the authors is that this represents a site-specific difference between their cases of bone marrow–based LPL/WM and the extramedullary disease analyzed by others.8,9 This intriguing possibility parallels refinements in our understanding of mucosa-associated lymphoid tissue lymphomas of gastric and nongastric locations (the former often having the t(11;18), while the latter do not), and merits further study.

Cases of LPL with increased numbers of large cells (the polymorphous LPLs) were, with only one exception, associated with complex karyotypes—not an unexpected finding if these, in fact, represent progressed forms of LPL, although the extent to which previous chemotheraphy might have contributed is difficult to determine. The most common structural abnormality, deletions of 6q, were seen in 4 of 8 patients who died of disease; 2 patients with this abnormality were alive with follow-up of 24 and 40 months, indicating that the poor prognosis that the authors associate with this abnormality is not absolute and that other factors are, doubtless, in play. Since del(6q) has been documented in a broad range of B-cell neoplasms including de novo lymphomas and multiple myeloma,17,18 use of this abnormality as “a marker of transformation” or as an indicator that polymorphous LPL is “the initial manifestation of large cell transformation”15 may be an overextension of the data, particularly since only 1 case had histologic features suggestive of large cell transformation.

An inevitable question that this study raises is whether we should subclassify LPL/WM. The morphologic differences between lymphoplasmacytic and lymphoplasmacytoid subtypes of Mansoor et al14 are slight and may not be reproducible because of sampling variations inherent in performing differential counts on aspirate smears. And so, in the absence of consensus on morphologic criteria or objective molecular, cytogenetic, or immunophenotypic differences (or, for that matter, a clear-cut difference in response to therapy or overall prognosis), it is probably better to “lump” until we can “split” meaningfully. The argument for identifying a polymorphous category of LPL is, however, stronger since Mansoor et al14 and others16 have shown a significantly poorer prognosis for patients with this type of histologic features. As the authors of the WHO Classification point out, though, a validated set of criteria for histologic grading does not exist; given the overall rarity of LPL, this important task will require a large scale multi-institutional collaboration to accrue enough patients to make a proposal that will not only gain acceptance from pathologists but also provide useful prognostic information to oncologists.

The rare lymphomas with clinical, laboratory, and morphologic features that typify LPL/WM but that are nevertheless CD5+ and CD23+ straddle the disease definitions of LPL/WM and CLL/SLL and remain a vexing issue for the hematopathologist. The few fully characterized cases that have been reported have either composite morphologic features in which the LPL component dominated more focal CLL/SLL–like changes16 or there were uniformly LPL morphologic features.19 If LPL/WM with and without the t(9;14) translocation represent 2 biologically definable categories of LPL/WM, the rare examples of CD5+, CD23+ LPL/WM16,19 might represent a third. The study by Mansoor et al14 was designed specifically to exclude these controversial cases, but it will be interesting to see whether cytogenetic studies ally these with the t(9;14)+ group or the t(9;14)− group.

Central to the usefulness of any classification is whether its criteria provide a reliable means of identifying a specific disease. As a diagnosis of exclusion, LPL remains a diagnosis on which even expert pathologists have difficulty agreeing.20 This is in large part because of morphologic overlap with other lymphoma subtypes such as marginal
zone lymphoma and also because of the lack of characteristic positive phenotypic or genetic findings. In confirming the heterogeneity of LPL/WM at the cytogenetic level and in raising the possibility that at least some differences are site-specific, the work of Mansoor et al\textsuperscript{14} provides the groundwork for further investigations into the primary pathogenic events and disease-defining criteria of LPL/WM.

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References