Immunophenotyping of Chronic Lymphoid Leukemias

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The 1983 article entitled “Chronic lymphocytic leukemia and other chronic lymphoid proliferations: surface marker phenotypes and clinical correlations,” which is reprinted in this issue of the Journal of Clinical Oncology, was one of the first reporting the use of monoclonal antibodies to expand the phenotypic characterization of chronic lymphoid leukemia, and one of the earliest to examine clinical correlations associated with specific phenotypic subsets.1 This process continues today, not only with different combinations of monoclonal antibodies for immunophenotypic characterization, but also with cytogenetic differences reflected by karyotype or fluorescence in situ hybridization studies, mutations in the variable region of the heavy chain, and DNA microarray analyses as indicators of genotype.2

In the years after publication of this article, the cluster differentiation system (CD) for identifying leukocyte cellular antigens was developed based on a series of workshops initiated in response to the need for a common language to identify the various antigens that were being discovered by murine monoclonal antibodies.3,4 Today, antibodies that react with CD19 or CD20 are typically used instead of surface immunoglobulin (slg) as an indicator of B-cell lineage, although intensity of slg is still used to define subsets of monoclonal peripheral B-cell populations. Pan–T-cell–specific antibodies that react with CD2 or CD3 have replaced the cumbersome sheep-erythrocyte-rosettes methodology to identify T lymphocytes. CD5 is the target of T65 (monoclonal antibody T101), which is generally a pan–T-cell marker, but is rarely coexpressed with B-cell markers on some lymphocytes. The Ia-like antigen is better known as HLA-DR.

This was one of several papers appearing from 1982 to 1983 that identified the coexpression of CD5 and pan-B-cell markers as the phenotypic hallmark of classical chronic lymphocytic leukemia (CLL).5–7 Today, the coexpression of CD5 and B-cell markers is also a hallmark of mantle-cell lymphoma. In retrospect, it became clear that the patient described at the bottom of page 193 in the Discussion section of the original report had mantle-cell lymphoma, an entity that was not widely recognized at the time, and not well characterized for almost a decade.10,11 Donald Doll had referred this patient, and both of us immediately recalled the case when we saw each other after a lymphoma lecture I had given at the University of Missouri in July 2002. The phenotype of CD5+, CD19+, CD22−, CD23+ is used to help distinguish CLL cells from mantle-cell lymphoma cells, which typically are CD19+, CD5+, CD22+, CD23− and express more slg, and express cyclin D1.12

The presence of B-cell markers and lack of CD5 expression suggests the presence of a B-cell lymphoproliferative disease other than CLL/SLL or mantle-cell lymphoma. More expanded immunophenotyping can facilitate a more specific diagnosis. Examples include CD11+, CD19+, CD22+, CD25+, and CD103+ for hairy-cell leukemia; CD19+,CD22+, and FMC7+ for splenic marginal zone lymphoma; B19+, CD5−, FMC7−, and CD38− for lymphoplasmacytic lymphoma; and CD19−, CD22+, CD23+, and CD10+ for follicular lymphoma.12,13 One of the observations in the 1983 article was the association of paraproteinemia with B-cell lymphocytosis that was CD5−, and the suggestion that most of these patients had a lymphocytosis as an early manifestation of lymphoplasmacytic lymphoma, including Waldenström’s macroglobulinemia.

There were six patients in the original report who were classified as negative for slg and T-cell markers other than CD5, and were Ia+. As suggested in the manuscript, these probably do represent a subset of CLL patients who have a low expression of slg, but do express other B-cell markers. The apparent association with this phenotype and proteinuria was an interesting one, but to my knowledge, was never confirmed in other series. A subsequent report seemed to support the suggestion that these patients with little or no slg may actually have a more indolent course.14
Lack of expression of B-cell markers in the presence of pan T-cell markers defines a T lymphocyte proliferation, which may be reactive or malignant. Use of CD4, CD8, and a number of other markers are now used to better characterize such T-cell lymphocytosis, but often gene-rearrangement studies are needed to determine the clonality of such proliferations.15

In the 25 years since this article was published, immunophenotyping has become a powerful tool for examining B-cell ontogeny and the differential diagnosis of chronic B-cell lymphoproliferative disorders. Phenotypic classification has not replaced descriptive clinical diagnoses, but it has helped us in our understanding and investigation of these clinical entities. The process of correlating specific phenotypes and genotypes continues as we pursue the understanding of cancer biology and its associated clinical manifestations and response to therapies.

Where are the authors now? Jacquelyn Beauregard and Bob Dillman were married in the fall of 1982, and live in Newport Beach, CA, where Dr Dillman has been Director of the Hoag Cancer Center since 1989. Jim Lea retired from the U.S. Navy, practiced medical oncology for several years in Miami, FL, and is now with the Hospice of Palm Beach County. Mark Green is Professor of Medicine at the University of South Carolina and is well known for his work in lung cancer with Cancer and Leukemia Group B. Bob Sobol went on to complete a medical oncology fellowship, and is the Senior Vice President, Medical and Scientific Affairs, for Introgen in San Diego, CA. Ivor Royston, who founded the biotech companies Hybritech and IDEC, is the founding managing partner of Forward Ventures, a venture capital company in San Diego, CA, where Dr Dillman has been Director of the Hoag Cancer Center since 1989.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

REFERENCES

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