Annexin A1: A New Marker for Hairy Cell Leukemia

by Rodney T. Miller, M.D., Director of Immunohistochemistry

Hairy cell leukemia is a low-grade B-cell lymphoid neoplasm with distinct clinical features, including a high frequency of marked splenomegaly and a relatively small number of circulating neoplastic cells in the peripheral blood. Accurate diagnosis of hairy cell leukemia is important, since patients tend to respond well to interferon α and purine analogues, unlike other low-grade B-cell lymphoproliferative disorders. In most cases, a diagnosis of hairy cell leukemia can be confidently established based on morphologic and immunohistochemical analysis. However, in some situations distinction from other low-grade B-cell lymphomas can be difficult. One tumor that may be particularly difficult to distinguish from hairy cell leukemia is marginal zone B-cell lymphoma (particularly the variant referred to as "splenic lymphoma with villous lymphocytes").

This month, we call attention to the availability of a new immunohistochemical marker, Annexin A1, that appears to hold great promise for diagnosing hairy cell leukemia and distinguishing it from mimics.

Basso et al have shown that hairy cell leukemia has a unique gene expression profile, with a phenotype similar to memory B-cells, but demonstrating altered expression of chemokine and adhesion receptors. They identified a group of 89 genes that were either upregulated or downregulated in patients with hairy cell leukemia. Annexin A1 (ANXA1), a gene related to phagocytosis, was found to be one of the most highly upregulated genes in hairy cell leukemia. Based on this information, the investigators hypothesized that immunostaining using a monoclonal antibody directed against the Annexin A1 gene product may prove useful in the diagnosis of hairy cell leukemia.

To test their hypothesis, they collected a series of 500 B-cell lymphomas; 492 cases with paraffin section material (both formalin and B5-fixed, including some decalcified bone marrow biopsy samples) and 8 cases with peripheral blood cytospins (acetone-fixed). Cases in the study group included 64 cases of “classic” hairy cell leukemia, 10 cases of variant hairy cell leukemia, 80 cases of chronic lymphocytic leukemia, 3 cases of prolymphocytic leukemia, 48 cases of splenic marginal zone lymphoma, 15 cases of nodal marginal zone lymphoma, 30 cases of lymphoplasmacytic lymphoma, 65 cases of follicular lymphoma, 14 cases of mantle cell lymphoma, 100 cases of diffuse large B-cell lymphoma, 10 cases of Burkitt lymphoma, and 50 cases of myeloma.

Employing an alkaline phosphatase anti-alkaline phosphatase (APAAP) immunocytochemical staining technique, the authors found that 97% (62 of 64) of the cases of hairy cell leukemia demonstrated strong...
Annexin A1 immunostains (A and B) on a bone marrow core biopsy with hairy cell leukemia. As expected, the B-cell marker CD20 (C) is also positive, as well as DBA.44 (D).

Although Annexin A1 does not stain normal B-cells or B-cell tumors other than "classic" hairy cell leukemia, this marker stains myeloid cells, macrophages, and subsets of benign T-cells. As such, in bone marrow biopsies that contain a mixture of myeloid cells and hairy cell leukemia, it is not well suited to assess the extent of involvement by hairy cell leukemia, since it will also stain the myeloid component strongly. As such, before interpreting immunoreactivity of Annexin A1 as a reflection of hairy cell leukemia, it is critical to first establish the nature of the neoplasm in question as one of B-cell lineage.

Annexin A1 is now available at PROPATH. We have had it for only a short time, but it is a robust antibody that has performed well up to this point. As might be expected from its staining of benign T-cells, we have observed staining of this marker in several T-cell malignancies (mycosis fungoides and peripheral T-cell lymphomas), and we have also seen staining in a plasmacytoma. Certain normal epithelial cells and a wide variety of carcinomas have also shown reactivity with this marker, and a number of sarcomas have been positive for Annexin A1. These observations underscore the importance of establishing the B-cell nature of a neoplasm before accepting Annexin A1 immunoreactivity as a specific marker of hairy cell leukemia.

Many thanks to Dr. Ayumi Corn of Oklahoma City for informing me about the utility of this antibody in the diagnosis of hairy cell leukemia, and for providing me with the critical reference from *The Lancet* below.

REFERENCES:
