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# ZAP-70 in Chronic Lymphocytic Leukemia

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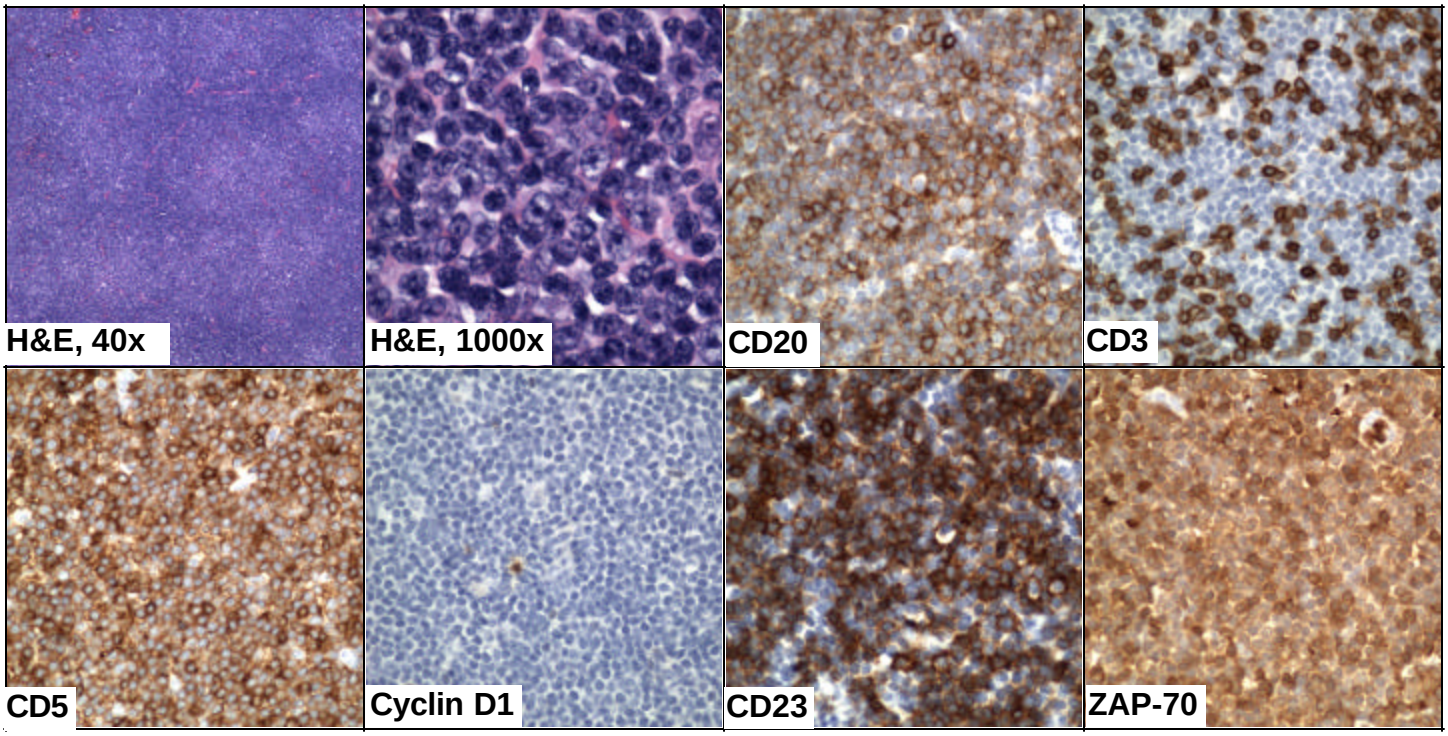
This month, we call attention to the availability of a new immunohistochemical marker, ZAP-70, that can assist in recognizing subsets of chronic lymphocytic leukemia (CLL) with substantially different prognoses.

It has been known for some time that the clinical course of CLL is variable, with some patients experiencing indolent disease not requiring any therapy, whereas others demonstrate a more aggressive course, unresponsive to therapy, with substantially shorter survival. For this reason, investigators involved in treating these patients are searching for markers that can assist in predicting the expected course of disease, so that those who may not require therapy are not treated inappropriately, and those who have the more aggressive type of CLL can be treated early in the course of disease, hopefully with improved outcomes.

Several candidate markers have been identified. Although some investigators report a correlation of shortened survival with cytogenetic abnormalities (particularly deletions of 11q and 17p), some patients do not demonstrate these abnormalities at the time of diagnosis, but only later in the course of disease. Additional studies have shown that the the presence or absence of mutations in the immunoglobulin heavy chain variable regions (IgVH) expressed by the neoplastic cells is of prognostic importance. As a group, those patients who express mutated IgVH demonstrate an indolent course (with reported median survivals up to 24.4 years in one study), whereas those with unmutated IgVH often have progressive disease (with reported median survivals ranging from 6.6 to 9.9 years). However, sequence analysis of IgVH genes is expensive and not widely available.

A number of studies have reported that flow cytometric assessment of CD38 expression on CLL cells is an unfavorable prognostic feature, and there has been speculation that CD38 might function as a surrogate marker for IgVH mutation status. However, multivariate analysis in 2 large studies (including over 500 patients) did not identify CD38 expression as an independent prognostic variable. It has been found that the expression of CD38 by the leukemic cells may change during the course of disease, and some investigators have suggested that increased CD38 expression may signal the onset of a more aggressive phase of disease.

The ZAP-70 gene codes for a 70 kd tyrosine kinase that is normally expressed in T-cells. In the June 2003 addition of Blood, Wiestner and colleagues report that increased expression of the ZAP-70 gene (as determined by quantitative analysis of ZAP-70 mRNA) correlates well with unmutated IgVH status in patients with CLL. Furthermore, they found that expression of the ZAP-70 gene protein product (assessed by immunohistochemistry) was also found to have a good correlation with IgVH mutation status, and correctly predicted the IgVH mutation status in 86% of 100 samples from 43 patients (with the predictive value of a positive test of 71% and the predictive value of a negative test of 100%) . As expected from the previous related work, those patients whose neoplastic cells showed readily detectable immunostaining for ZAP-70 typically had unmutated IgVH and a more aggressive clinical course.




*Representative photomicrographs from a typical case of ZAP-70 positive CLL. As expected, the neoplastic cells express CD20, CD5, and CD23, but are negative for CD3 and Cyclin D1 (CD10 and BCL6 were also negative). Note readily-detectable expression of ZAP-70 by the neoplastic cells, a finding that correlates with unmutated IgVH genes and a more aggressive clinical course. In cases of ZAP-70 negative CLL, reactivity of background non-neoplastic T-cells serves as an internal positive control, and the appearance is thus similar to that of the CD3 immunostain.*

ZAP-70 immunostains are now available in the ProPath Immunohistochemistry Laboratory, and CD38 immunostains are also available.

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