To the editor:

**ALK is not expressed in Hodgkin disease**

Hodgkin disease (HD) is defined by a variable number of Hodgkin and Reed-Sternberg cells associated with a mixture of histiocytes, epithelioid cells, neutrophils, eosinophils, lymphocytes, and plasma cells. Some cases, characterized by a large number of tumor cells, are difficult to differentiate from anaplastic large-cell lymphomas (ALCLs) because both entities demonstrate the presence of large CD30+ cells. Although some authors have suggested a potential common pathogenesis, several major conceptual differences distinguish the 2 entities. HD seems to be derived from B cells, whereas ALCL is often of T-cell or null-cell phenotype. A subset of the latter is characterized by a specific translocation t(2;5)(p23q35). This translocation results in a fusion product of the nuclear phosphoprotein nucleophosmin (NPM) and the anaplastic lymphoma kinase (ALK).

Detection of NPM-ALK as a means of distinguishing ALCL from HD is largely based on molecular analysis. Although some studies concluded there is not such an abnormality in HD, others have found the NPM-ALK fusion mRNA in variable numbers of cases. The fusion product can be detected also by immunohistochemistry with the ALK1 monoclonal antibody. This antibody recognizes the native ALK protein, as well as the fusion product, and represents a reliable method for detecting the chimeric protein in lymphomas because normal ALK expression is restricted to the central nervous system. This technique also has the advantage of being easily performed on paraffin-embedded tissue in a routine setting.

The aim of our study was to test a large series of Hodgkin disease cases for ALK expression, in order to evaluate its diagnostic value in the differential diagnosis between ALCL and HD. Two hundred seventy-eight patients with newly diagnosed advanced Hodgkin disease were selected. For each case, histological slides were reviewed by a panel of 3 pathologists. The aim of our study was to test a large series of Hodgkin disease cases for ALK expression, in order to evaluate its diagnostic value in the differential diagnosis between ALCL and HD. Two hundred seventy-eight patients with newly diagnosed advanced Hodgkin disease were selected. For each case, histological slides were reviewed by a panel of 3 pathologists.

Standard Avidin-Biotin-Peroxidase method was performed on paraffin sections, using a 1/50 dilution of the monoclonal antibody ALK-1 (kindly provided by D. Mason, Oxford, United Kingdom) after microwave pretreatment. Technical quality was checked with a highly positive ALCL.
Eight patients were classified as having “nodular lymphocyte predominance Hodgkin disease” and 69 as having “classic HD with lymphocyte depletions, rich in tumor cells.” None of the 278 patients with Hodgkin disease tested were found to express ALK. Our series has the advantage of representing a large number of cases having undergone panel review.

This result, in accordance with most published results, does not support the hypothesis of HD and ALCL as histogenically related entities. Moreover, when the differential diagnosis is between HD rich in tumor cells and ALCL, our experience suggests that ALK expression by tumor cells argues against the former diagnosis.

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References


To the editor:

CD38 expression and Ig VH gene mutation in B-cell chronic lymphocytic leukemia

Ig VH somatic hypermutation has recently emerged as a novel prognostic factor in chronic lymphocytic leukemia (CLL), unmutated Ig VH genes predicting adverse prognosis.1-4 However, the clinical usefulness of Ig VH gene mutation analysis in predicting survival early in the course of the disease is offset by the high cost and level of expertise required for this technique. The report of Damle et al2 that CD38 expression can predict the Ig VH gene mutational status of CLL cells (positivity indicating unmutated and negativity, mutated, Ig VH genes) offered the possibility of a simple and inexpensive substitute for Ig VH gene analysis. However, the association between CD38 expression and Ig VH gene mutation could not be confirmed by Hamblin et al.5 This discrepancy prompted us to undertake a survey of our own CLL patients to examine further the relationship between CD38 expression, Ig VH gene mutation, and survival, and thereby determine to what extent measurement of CD38 can indeed be used as surrogate for Ig VH gene sequencing.

We included 40 CLL patients (27 men, 13 women) with known clinical history in the study. Of these, 6 were selected on the basis of their tumor cells expressing CD38. The mean age was 65 (men 61.5, women 72.3) years, and the mean follow-up time 5.4 (1-23) years. Ig VH gene sequence analysis was performed using a protocol based on that of Fais et al.6 Unmutated cases were defined as those with less than 2% mismatch to the most similar germline Ig VH gene in the V BASE directory.7 Immunophenotyping was performed on a Becton Dickinson FACS scan analyzer (San Jose, CA) using thawed samples of previously cryopreserved cells that had been double stained with CD38 PE and CD19 FITC (both from Becton Dickinson). The proportion of CD19+ cells coexpressing CD38 was determined; values more than 30% were considered positive. Survival analyses were performed by the method of Kaplan and Meier, and significance was analyzed using the log-rank test.

Twenty-four cases were unmutated and 16 mutated, with a male-female ratio of 1.6 in the mutated and 2.4 in the unmutated groups. These findings therefore support the observation made by Damle et al that there is an unequal sex distribution between the mutated and unmutated groups. These findings therefore support the observation made by Damle et al that there is an unequal sex distribution between the mutated and unmutated groups. CD38 was expressed in 2 (12.5%) of the 16 mutated cases and in 11 (46%) of the 24 unmutated cases. Among the 13 CD38+ cases, 2 (15%) were mutated and 11 (85%)
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