CD4 Expression in Acute Nonlymphocytic Leukemia

To the Editor—A recent case prompted us to review the report of Larson and McCurley1 entitled “CD4 Predicts Nonlymphocytic Lineage in Acute Leukemia.”

Our patient was a 74-year-old woman who had leukocytosis of 34.7 × 10^9/L when she was examined. The examination of blood and bone marrow revealed acute leukemia. The leukemic blasts were negative for myeloperoxidase and α-naphthyl butyrate esterase activity. Immunophenotyping by flow cytometry showed the blasts were negative for surface CD3, CD5, CD7, CD8, CD13, CD14, CD19, CD20, and CD33. The blasts were positive only for CD4, CD45, and HLA-DR. However, further study on permablated cells from this patient revealed expression of terminal deoxynucleotidyl transferase (TdT) and cytoplasmic CD3 (cyCD3). Because the expression of cyCD3 is considered highly specific for T-cell lineage,2-4 and TdT is generally positive in T-cell acute lymphoblastic leukemia (T-ALL), the diagnosis of T-ALL was made. We realize the assessment of surface CD2 expression (as recommended by Larson

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and McCurley) would have been potentially useful in this case; however, their conclusions prompted us to reexamine the putative specificity of CD4 as a marker of nonlymphocytic lineage in acute leukemia.

Larson and McCurley aptly demonstrate the specificity of the CD4+(CD2-) phenotype in predicting nonlymphocytic lineage. The CD4+(CD2-) phenotype has a quoted specificity of 91% and positive predictive value of 95%. However, these figures are derived from the comparison of acutelymphocytic leukemia (ANLL) to all cases of ALL. Although rare cases of B-lineage ALL express CD4, the differential diagnosis of CD4+ acute leukemia is generally limited to ANLL vs T-ALL. Therefore, direct comparison between ANLL and T-ALL seems appropriate.

By using Larson and McCurley's data, the specificity of CD4 alone in distinguishing ANLL from T-ALL is zero because all T-ALL cases were CD4+. The apparent specificity of CD4 alone in detecting nonlymphocytic lineage, therefore, is essentially an artifact of the rarity of T-ALL. In other words, the statistical data are "diluted" with 28 cases of B-lineage ALL, a disease known to be predictably CD4-.

In fairness, the authors focus less on the specificity of CD4 alone and more on the combination of CD4 and CD2 (a marker we did not assess in our case). Because of the low prevalence of T-ALL, the positive predictive value of CD4+(CD2-) in distinguishing ANLL from T-ALL remains strong at 98%. However, the specificity drops to only 75% because one of the four T-ALL cases was a false-positive case [CD4+(CD2-)].

To our knowledge, the single most specific marker of T-cell lineage in acute leukemia is expression of cyCD3.6-8 Given the limitation of CD4 in discriminating T-ALL from ANLL, the potential utility of adding cyCD3 to the panel proposed by Larsen and McCurley would be worthy of analysis.

The report by Larson and McCurley stresses the importance of multiple marker evaluation in acute leukemia. However, the study also illustrates that one should be aware of the limitations of CD4 expression alone as an independent predictor of nonlymphocytic phenotype.

The Authors' Reply

To the Editor—We appreciate the comments of Drs Goolsby and Finn. Their comments reflect the continual need to update and evaluate antibody panels with new markers. We agree that cyCD3 is a very good and specific marker of T-cell processes. However, in our study and as we pointed out in our article, cyCD3 was relegated to a secondary panel because its utility is limited given the rarity of T-ALL and the expense of doing it in every acute leukemia case. CD4 and CD2 could "screen" for these cases while giving additional information about lineage in the context of an entire monoclonal antibody (mAb) panel. Finn and Goolsby also raise the issue of the specificity of CD4 in distinguishing ANLL and T-cell ALL. We did not publish these statistics in our report because the numbers were too low to be statistically significant. We did, however, emphasize the potential utility of CD4+(CD2+) in the identification of T-ALL in a primary cost-effective mAb panel.

In general, the focus of our article was twofold. First, we wanted to point out that CD4 is not an aberrant lymphoid marker, but a true myeloid marker, an observation that is now supported by several studies on normal and leukemic myeloid cells. Second, our article emphasizes that the utility of an antibody panel must be interpreted in its entirety. Using this premise, we suggested an optimized and cost-effective panel of mAbs to be used as a primary panel in the diagnosis of acute leukemia. It is clear that additional markers may be needed in some cases. It is difficult for us to address the utility of CD4+(CD2+) in the case reported by Drs Finn and Goolsby because CD2 was not performed. Although we certainly agree that cyCD3 may have utility in the diagnosis of T-cell ALL, it should be fairly evaluated before incorporating it into and expanding a primary mAb panel. Our bias remains that cyCD3 is probably the best part of a secondary panel until proved otherwise. That evaluation must be done in the context of the panel being used. Finn and Goolsby do not explicitly state their mAb panel. Therefore, it is difficult for us to comment on the utility or cost-effectiveness (another important consideration in designing a panel and emphasized in our article) of their panel.

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