## Myeloid/Natural Killer Cell Acute Leukemia: A Previously Unrecognized Form of Acute Leukemia Potentially Misdiagnosed as FAB-M3 Acute Myeloid Leukemia

*To the Editor:*

In the July 1, 1994 issue of *Blood*, the Southwest Oncology Group (SWOG) reported on a novel subtype of acute myeloid leukemia (AML) that was recognized by a unique immunophenotypic profile.[1] The blast cells from 6% of a consecutive series of 350 AML cases showed antigenic features of acute promyelocytic leukemia (APL), such as negativity for HLA-DR and CD34, but at the same time expressed the natural killer (NK) cell-associated CD56 antigen and CD11a, an adhesion molecule involved in cytolytic T-cell–mediated and NK-mediated killing. On the other hand, these leukemic cells failed to express CD16, a receptor structure expressed by NK cells

and granulocytes and involved in antibody-dependent cellular cytotoxicity. Most important from a clinical point of view in terms of treatment decision, the morphologic features of NK/myeloid leukemia blasts strikingly resembled those of FAB-M3, particularly the microgranular variant. By cytogenetic and/or molecular analysis, however, none of the 20 cases described contained either a t(15;17) or the associated PML/RARα fusion transcript, respectively, and, whenever tested, the cells failed to respond with differentiation to the administration of all-*trans* retinoic acid (ATRA) in vitro. Given the cytologic resemblance to classical APL and in the absence of molecular studies, cases of NK-AML could account for ATRA unresponsive patients erroneously diagnosed as APL.

Since the appearance of the SWOG report, we have seen two patients with de novo adult AML who by morphologic criteria were M3 and M3v, respectively, but immunophenotypically fit the description of NK-AML: HLA-DR$^-$, CD34$^-$, CD33$^+$, CD13$^+$, CD56$^+$, CD11a$^+$, CD16$^-$. Cell surface antibody binding to bone marrow or peripheral blood blast cells, gated based on the forward light scattergram and CD45 fluorescence, was evaluated from two-color contour-plots by flow cytometry using the FACScan and Lysys II software program (Beckton Dickinson, Mountain View, CA). Positivity for CD56 and CD11a was established both when considering the percentage of blast cells that stained with either antibody with fluorescence intensity greater than 98% of the negative isotope control and in terms of mean channel fluorescence shift relative to background staining. In the two patients, 40% and 60% of blast cells expressed the CD56 antigen at high density, which corresponded to an increase in mean fluorescence by 65% and 91% as compared with background, respectively. CD11a expression was considerably weaker and restricted to 25% to 30% of leukemic cells in both patients.

In contrast with the findings in the SWOG study, both of our patients with NK-AML transcribed the long form of the PML/RARα fusion transcript that characterized these cases as true APLs. However, it is noteworthy that the one patient tested for in vitro induction of differentiation showed an aberrant response to ATRA. Four days of culture in the presence of $10^{-8}$ to $10^{-6}$ mol/L ATRA induced reduction of nitroblue tetrazolium (NBT) in greater than 50% of leukemic cells, suggesting induction of differentiation in a significant proportion of cells. CD11b, another indicator of myeloid differentiation the expression of which usually parallels the appearance of superoxide production, was induced by ATRA in only a minor blast cell component. Failure of the leukemic cells to express the neutrophil marker CD11b in response to ATRA, under conditions that in ATRA-sensitive APL cells would result in complete differentiation along the granulocytic lineage, may reflect a deficiency in the differentiative ability of these cells.

Our findings indicate that CD56/CD11a positivity in patients with AML and M3 or M3-like morphology does not exclude the diagnosis of APL. We, therefore, strongly support SWOG's proposal that molecular analysis is absolutely essential for making the distinction between APL and NK-AML. Whether APLs with CD56/CD11a expression demonstrate a decreased response to ATRA in vivo may be an important aspect of analysis of the large APL ECOG/SWOG intergroup study, E2491.

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## REFERENCE

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