Clinical Significance of Low Levels of Myeloperoxidase Positivity in Childhood Acute Nonlymphoblastic Leukemia

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The clinical significance of a low percentage of myeloperoxidase-positive blast cells in childhood acute nonlymphoblastic leukemia was determined. Of 155 consecutive cases studied by cytochemical staining methods, 14 were characterized by 4% to 15% (median 6%) myeloperoxidase-positive blasts. All 14 cases showed reactivity to Sudan black B stain, and 7 had Auer rods. The morphological subtypes of leukemia were M1 (8 cases), M2 (3), M4 (1), and M5 (2). Immunological marker studies disclosed the lymphoid-associated T11 antigen on cells from 8 of the 11 cases tested. Other lymphoid-related findings in these 8 cases included the T3 antigen and E rosette formation in 1 case each. Among cases that were prospectively studied for the expression of lymphoid-associated markers, 6 of 8 with low levels of myeloperoxidase positivity compared with only 1 of 44 with higher levels (>15%) possessed such features (P < 0.001). We conclude that low levels of myeloperoxidase reactivity distinguish cases of acute leukemia in which the blast cells coexpress lymphoid (T11 antigen) and myeloid markers.

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RESULTS

MPO activity was demonstrated in 3% to 100% of the blast cells from 37 of 43 cases with an M1 FAB type, 47 of 47 with M2, 9 of 9 with M3, 29 of 29 with M4, and 4 of 25 with M5. The diagnosis of ANLL in the six M1 cases with negative MPO reactivity was based on the presence of Auer rods, ultrastructural myeloperoxidase or myeloid markers as defined by monoclonal antibodies; none of them expressed any lymphoid markers. The two cases of M7 leukemia lacked evidence of the enzyme. Of the 126 cases that showed MPO activity, 14 were characterized by 4% to 15% (median 6%) MPO-positive blast cells in bone marrow samples (Table 1);
demonstrated that a criterion of 4% to 15% MPO positivity yields a high percentage of cases with lymphoid-associated markers did not clearly discriminate between these cases and typical ANLL. Ages ranged from 6 to 18 years (median 14 years), presenting leukocyte counts from 2 to 171 × 10⁹/L (median 16.2 × 10⁹/L), platelet counts from 4 to 312 × 10⁹/L (median 120 × 10⁹/L) and hemoglobin levels from 4.1 to 14 g/dL (median 10.4 g/dL). All patients had lymphadenopathy but only three (nos. 1, 2, and 13) had hepatosplenomegaly. Initial CNS leukemia was evident in patient 4, and patient 2 had an anterior mediastinal mass.

**DISCUSSION**

Bennett and associates' considered 3% as the lower limit for MPO positivity in the FAB system of leukemia cell classification. Results of the present study suggest that a higher level of positivity is required to distinguish "typical" cases of ANLL from those with equivocal features. We demonstrated that a criterion of 4% to 15% MPO positivity yields a high percentage of cases with lymphoid-associated differentiation markers, primarily the T11 antigen. Although identified on normal, activated B cells, TdT has not been detected on normal myeloid cells. Additional evidence of lymphoid involvement was provided by T3 positivity and E rosette formation in one case each. Although TdT activity and/or CALLA were also expressed in some of our cases, these markers can no longer be considered lymphoid-specific markers. TdT activity has been demonstrated in 5% to 10% of ANLL cases that were unequivocally myeloid in origin. CALLA has been identified on renal tubular and glomerular cells, granulocytes, fibroblasts, fetal small intestine epithelial cells, mammary epithelium, and myeloma cell lines (see ref. 18 for review). Nonetheless, we think it noteworthy that the majority of our cases with low MPO positivity expressed TdT activity, a far greater proportion than has been reported in ANLL.

The immunologic marker findings in cases with low MPO activity are most compatible with the newly recognized entity of acute mixed-lineage leukemia, in which the leukemic cells coexpress markers generally thought to be
restricted to a single lineage. None of the cases in this study had cytogenetic evidence for biclonal disease, whereas evidence for simultaneous expression of lymphoid and myeloid markers was found in all four cases tested (data not shown). The diagnosis of acute mixed-lineage leukemia is best exemplified by case 2. The presence of an anterior mediastinal mass and the expression of T11 and T3 antigens in 83% and 87% of this child’s blast cells would be considered by most investigators as diagnostic of T cell acute lymphoblastic leukemia. However, there was also strong evidence for myeloid differentiation, including 4% myeloperoxidase positivity, the presence of Auer rods, and the expression of myeloid antigens in blast cells [84% reacted with Mol (CDw-11) and 35% with MCS.I (CDw-15) monoclonal antibodies].

Consistent with our data, the reported patterns of monoclonal antibody binding in cases of acute mixed-lineage leukemia have generally included high percentages of T11 positivity with variable levels of other lymphoid markers. These leukemias either may arise from multipotential progenitors with capacity of lymphoid or myeloid differentiation or had aberrant gene expression during malignant proliferation. The clinical importance of acute mixed-lineage leukemia lies in the suggestion that such patients may not respond to therapy conventionally prescribed for myeloid leukemia, but require treatment directed to the lymphoid pathway. Low MPO positivity in cases of ANLL should be regarded as a potential indicator of this clinical entity. Our interpretation assumes additional significance in view of the variability of clinical and laboratory features among such patients.

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