Acute Lymphoblastic Leukemia With Burkitt-like Morphologic Features and High Myeloperoxidase Activity

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Abstract

Expression of a high level of myeloperoxidase (MPO) as a sole myeloid marker in acute leukemias that express typical lymphoblastic markers is unusual. Herein we report 5 cases of MPO+, otherwise typical acute lymphoblastic leukemia (ALL) without the expression of other myeloid markers. In most cases, MPO positivity was detected in more than 20% of blasts by immunologic (flow cytometric) and enzymatic testing. The striking feature of most of these cases is a morphologic picture reminiscent of that seen in Burkitt-like B-cell ALL with basophilic cytoplasm and vacuoles but no expression of surface immunoglobulin. All cases responded to ALL therapy and should be distinguished from myeloid leukemia and from Burkitt leukemia/lymphoma.

In the French-American-British and the World Health Organization classifications of acute leukemias, acute lymphoblastic leukemia (ALL) is defined as having fewer than 3% of the blasts positive for myeloperoxidase (MPO). MPO positivity has been considered the hallmark that distinguishes ALL from acute myeloid leukemia, despite the numerous surface markers that are currently used to characterize leukemias.1,2 However, MPO activity in low numbers of blasts (3%-5%) has recently been reported in otherwise typical acute lymphoid leukemia with no expression of other myeloid markers.3 MPO activity in a larger percentage of blasts is highly unusual but has been described in extremely rare cases of otherwise typical ALL.3 Methods that detect messenger RNA (mRNA) for the MPO gene are frequently expressed in ALL samples,4,5 particularly in infant ALL samples.6 In previous patient series, the detection of MPO mRNA has been associated with undetected BCR-ABL+ leukemia and in leukemias with MLL gene rearrangements.7 However, these translocations need not always be present in the blasts.

Herein we describe 5 cases of adult ALL that demonstrate typical ALL immunophenotypes without myeloid surface markers but show strong (>20%) MPO activity by enzymatic (functional) and immunologic (flow cytometric) methods. These cases demonstrate a typical light microscopic appearance characterized by basophilic cytoplasm with slight vacuolation (Burkitt-like). More important, the patients responded to induction therapy used to treat adults with ALL.

Materials and Methods

Following institutional review board approval, we performed a retrospective chart review of adult patients seen
at M.D. Anderson Cancer Center, Houston, TX (MDACC), with the diagnosis of ALL and whose blast cells expressed significantly greater than 3% MPO activity. We found 7 such cases. Two of the patients had biphenotypic leukemia rather than ALL, and the cases were excluded. One patient did not receive therapy at our institution, and one patient came for a second opinion but was not treated at MDACC. Details of the clinical course, cytogenetics, immunophenotype, and other laboratory characteristics of the 5 cases are given in Table I.

For patients with follow-up at MDACC, the median age was 55 years (mean, 54 years). The patients had low median WBC counts and low median platelet counts (1,700/µL [1.7 × 10^9/L] and 37 × 10^9/µL [37 × 10^9/L], respectively).

Three patients were enrolled on the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen as described by Kantarjian et al, and 1 patient received idarubicin, cyclophosphamide, cytarabine, and topotecan. The therapy for 1 patient did not result in remission after 4 weeks but did result in complete remission after 8 weeks of therapy. One patient was treated at an outside institution with mitoxantrone and cytarabine, but the disease was refractory to the therapy. Remission was defined as recovery of the platelet count to greater than 100 × 10^9/L and recovery of the absolute neutrophil count to more than 1,000/µL (1.0 × 10^9/L). Two patients remained in remission 38 months and 18 months after the start of therapy.

The results of flow cytometric analysis of the blasts were typical for precursor B-cell acute lymphoid leukemia. Blasts from all patients were positive for CD19 and terminal deoxynucleotidyl transferase. CD20 was positive in 1 case. MPO was positive in 4 cases very strongly so, using an enzymatic method and by flow cytometry. Other myeloid markers such as CD13 and CD33 were negative. Flow cytometry for CD117 expression was negative in all cases. In all cases, cytogenetic analysis was done by G-banding. In 2 cases, molecular testing was done for the BCR-ABL fusion transcript. Complex cytogenetic changes were seen in 4 cases, with no detection of the Philadelphia chromosome. In cases with complex cytogenetic changes, no cytogenetic changes specific for acute myelogenous leukemia were detected. The cases were thus diagnosed as MPO+ ALL.

We used a standard enzymatic reaction (Graham-Knoll) by allowing the peroxidase to release the oxygen from hydrogen peroxide, which oxidizes the benzidine to a brown compound. Briefly, the smear is fixed for 0.5 minute in 10% alcoholic formalin, washed with water, and then incubated for 5 minutes with a peroxidase solution containing benzidine, ethyl alcohol, and hydrogen peroxide. The slide is then washed with water, dried, and examined.

### Discussion

Acute leukemias with more than 3% MPO activity as detected by enzymatic staining or by flow cytometry are generally classified as myeloid. There are several reports, however, of ALL blasts with low levels of MPO activity, especially with MPO mRNA expression. Generally, MPO activity is seen in fewer than 8% of cells in these studies, with most reporting MPO in 3% to 5% of blasts. Cases of ALL with higher MPO activity shown by enzymatic staining or flow cytometry are rare. In prior studies, ALL blasts that express MPO have been found to contain the BCR-ABL fusion, leading to the conclusion that the disease process is chronic myeloid leukemia in blastic transformation. In this review, none of the cases had a Philadelphia chromosome or BCR-ABL+ results. Detection of MPO mRNA has been reported in infant ALL cases in which routine immunohistochemical analysis is negative for MPO activity. This finding lends credence to the observation that some lymphoid leukemic blasts might express MPO by enzymatic or immunologic methods depending on the maturation of the progenitor cell. However, the most striking feature of the cases presented herein is the uniform Burkitt-like morphologic picture seen in mature B-cell ALL, which suggests that ALL cases with

### Table I

<table>
<thead>
<tr>
<th>Case No./Sex/Age (y)</th>
<th>MPO (%)</th>
<th>Cytogenetics</th>
<th>Flow Cytometry (Myeloid Markers)</th>
<th>BCR-ABL Treatment</th>
<th>Survival After CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/34</td>
<td>61</td>
<td>Complex; del (6g)</td>
<td>None</td>
<td>Cyclophosphamide, cytarabine, topotecan, idarubicin</td>
<td>5 mo</td>
</tr>
<tr>
<td>2/F/56</td>
<td>8</td>
<td>Complex; 9p−</td>
<td>None</td>
<td>NA</td>
<td>HCVAD</td>
</tr>
<tr>
<td>3/M/85</td>
<td>44</td>
<td>46Xq</td>
<td>None</td>
<td>Negative</td>
<td>HCVAD</td>
</tr>
<tr>
<td>4/M/22</td>
<td>100</td>
<td>Complex; 1q−,7p+,9q−</td>
<td>None</td>
<td>Negative</td>
<td>Mitoxantrone, cytarabine</td>
</tr>
<tr>
<td>5/F/53</td>
<td>60</td>
<td>Triploid</td>
<td>None</td>
<td>NA</td>
<td>HCVAD</td>
</tr>
</tbody>
</table>

CR, complete remission; HCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MPO, myeloperoxidase; NA, not available.
high expression of MPO activity in the blasts may represent a specific group of ALL [Image 1], [Image 2], and [Image 3]. Further studies exploring the underlying molecular abnormalities in these cases are needed.

More important, leukemic blasts from these cases had high levels of MPO activity by enzymatic testing with no other significant myeloid features. Each case responded to standard ALL induction therapy, with 2 of 4 patients remaining in prolonged remission at the time of this report. ALL with significant expression of MPO in routine studies may represent a rare ALL phenotype that responds to ALL therapy. Assigning patients with such findings to acute myeloid leukemia-type therapy based solely on the expression of MPO might be incorrect unless other features of myeloid lineage are present.

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[Image 1] A, Lymphoblasts show significant vacuolation and basophilic cytoplasm. B, Myeloperoxidase stain shows positive staining in most lymphoblasts.

[Image 2] Lymphoblasts stained with myeloperoxidase and counterstained with Wright-Giemsa showing significant myeloperoxidase positivity with blue vacuolated cytoplasm.

References


