Simultaneous or Sequential Expression of Lymphoid and Myeloid Phenotypes in Acute Leukemia


Acute mixed myeloid-lymphoid leukemia is uncommon. We report four cases in which myeloid and lymphoid cell markers were observed simultaneously or sequentially when 94 patients with acute leukemia were phenotyped according to the French-American-British (FAB) classification system, with cytochemical stains, and with immunologically defined differentiation markers (identified by monoclonal antibodies and antiterminal deoxynucleotidyl transferase [TdT]). In one case, conversion from acute lymphoblastic leukemia to acute myeloid leukemia was noted (FAB L1, TdT to FAB M4, Auer rods, TdT). In another patient, two distinct populations of myeloid and lymphoid blast cells were observed simultaneously (TdT, Leu M1-1/ TdT-. Leu M1 ). In two additional patients, acute leukemia was characterized by the expression of both lymphoid and myeloid markers on the same cell (TdT+/Leu M1+ , B4+/Leu M1+ and ≤ 70% TdT, T11+ , My9+ ). The Philadelphia (Ph) chromosome was negative in all cases, though other chromosomal abnormalities were noted in three out of four cases. Malignant transformation of a pluripotential stem cell for both lymphoid and myeloid lineages, with or without the Ph chromosome marker, could explain the coexistence of distinct populations of lymphoblasts and myeloblasts in acute leukemia. Acute leukemia with a biphenotypic profile may reflect genome depression accompanying neoplasia.

THE SIMULTANEOUS OCCURRENCE of lymphoid and myeloid blast cells was recognized initially in the blasts crisis of chronic myeloid leukemia 1-3 using cytochemical and immunofluorescent techniques. Later this finding was reported in acute leukemia de novo. 4-9 Whether such cases represented acute leukemia with two distinct populations of lymphoblastic and myeloblastic cells or a population of blast cells expressing antigenic determinants for both lymphoid and myeloid cells was difficult to determine.9 Recently, by using heteroantisera or monoclonal antibodies "specific" for the lymphoid and myeloid lines, examples of distinct populations of lymphoid and non-lymphoid cells and rare cases of biphenotypic expression of myeloid and lymphoid markers on the same cell10-12 have been reported. In addition, recent reports have noted the sequential conversion of acute lymphoblastic to acute myeloid leukemia and vice versa.8,10-12 It seems likely that acute mixed leukemias occur infrequently.13,14

In this article we describe four cases of Philadelphia (Ph) chromosome-negative acute leukemia in which both myeloid and lymphoid cell markers were observed. In the first patient the acute lymphoblastic leukemia responded partially to therapy, but then evolved into acute myeloid leukemia. In the second patient, two distinct populations of myeloid and lymphoid blast cells were found in coexistence, while in two additional patients, acute leukemia with blast cells expressing both lymphoid and myeloid markers on the same cell was found.

MATERIALS AND METHODS

The four patients were seen in a two-year period during which samples from 94 patients with acute leukemia were referred for analysis.

Patients Studied

Patient M.C.

A 31-year-old woman had increased bruising and symptoms of anemia and lymphadenopathy. Laboratory studies disclosed a hemoglobin level of 9.8 g/dL; a WBC count of 185,000/μL (76% blasts); and a platelet count of 41,000/μL. The patient’s bone marrow was hypercellular, and a diagnosis was made of acute lymphoblastic leukemia (ALL). French-American-British (FAB) L1. She received induction therapy according to the L10 M protocol15 and achieved an incomplete remission. Three-and-one-half months later, despite continued therapy with L10 M consolidation therapy, the disease progressed rapidly. At that time, blast cells in the marrow were found to be myeloid in appearance (FAB M4) with Auer rods. The patient received cytosine arabinoside (ara-c) and Adriamycin,16 but never attained a complete remission and died four months later.

Patient G.D.

A 76-year-old man with known chronic alcoholic liver disease was examined for melena and symptoms of anemia. There were signs of mild congestive heart failure, and laboratory studies revealed a hemoglobin level of 5.1 g/dL; a WBC count of 6,100/μL, and a platelet count of 196,000/μL. The patient’s bone marrow showed features of refractory anemia with excess blasts (10%) and iron deficiency. A colonic polyp was removed, and treatment with iron resulted in a partial response. Four months later, leukopenia and anemia persisted, with the appearance of a leukoerythroblastic blood
picture: hemoglobin, 9.3 g/dL; WBC count, 2,900/μL (4% blasts); and platelet count, 159,000/μL. The blast cells in the bone marrow had increased to 15% and dyserythropoiesis persisted. Karyotypic analysis of the bone marrow showed 46,XY in 25 metaphases and an extra chromosome 8 in two additional metaphases. A diagnosis of refractory anemia with excess blasts (RAEB) was made. Over the next eight months there was a gradual deterioration in the blood counts. The WBC count rose to 30,000/μL (80% blasts). Blood and bone marrow (83% blasts) were studied for myeloid and lymphoid markers at this time because of the appearance of a mixed population of lymphoblasts (30%) and myeloblasts (50%) on routine Romanowsky staining. Remission induction therapy with vincristine, prednisone, 6-thioguanine, Ara-C, and prednisone, 6-thioguanine, Adriamycin, and ara-C was begun, but the patient died before therapy was completed.

**Patient N.D.**

A 29-year-old man was admitted to the hospital with a two-week history of fatigue and a four-day history of epistaxis. Purpura was noted on his legs. There was small cervical and axillary lymphadenopathy, but no enlargement of his liver and spleen. A chest roentgenogram was normal. His hemoglobin level was 13.5 g/dL; his WBC count, 89,700/μL (56% blasts); and his platelet count, 49,000/μL. An examination of bone marrow showed ALL, FAB L2. He was started on the L10 M protocol and at last examination was in complete remission.

**Patient G.E.**

A 32-year-old man was admitted to the hospital with a one-month history of fatigue and symptoms of upper respiratory infection followed by the development of scattered bruises, recurrent fever, and night sweats. There was no lymphadenopathy, hepatomegaly, or splenomegaly. A chest roentgenogram was normal. His hemoglobin level was 9.3 g/dL; his WBC count, 27,500/μL (87% blasts); and his platelet count, 21,000/μL. Bone marrow examination showed ALL, FAB L2. He was started on the L10 M protocol, but following completion of the induction phase, the bone marrow showed greater than 90% blast cells. He was then treated with daunorubicin, ara-C, and 6-thioguanine (DAT), followed by three days of high-dose ara-C. Thirty days later the patient was in complete remission.

**Determination of Cell Phenotypes**

The phenotype of the blast cells was established by routine morphologic study with cytochemical staining, by examination for surface markers (using monoclonal antibodies), and for terminal deoxynucleotidyl transferase (TdT), by indirect immunofluorescence and karyotype analysis.

### Table 1. Monoclonal Antibodies

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Specificity</th>
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<tr>
<td>Leu-1, 2, 3</td>
<td>T lymphocytes</td>
<td>Becton Dickinson</td>
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<td>T lymphocytes</td>
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</tr>
<tr>
<td>B1</td>
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<td>Coulter Electronics</td>
<td>29</td>
</tr>
<tr>
<td>B4</td>
<td>B lymphocytes, majority of non-T-ALL, ALL BC of CML</td>
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<td>30</td>
</tr>
<tr>
<td>J5</td>
<td>Some ALL blasts and some B cell lymphoma, CLL</td>
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<td>31</td>
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<tr>
<td>HLA-DR (la)</td>
<td>B lymphocytes, activated T lymphocytes, monocytes, non-T-ALL and AML blasts</td>
<td>Becton Dickinson</td>
<td>32</td>
</tr>
<tr>
<td>Leu-M1</td>
<td>Granulocytic and monocytic series, AML blasts</td>
<td>Becton Dickinson</td>
<td>33</td>
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<tr>
<td>D5S6</td>
<td>AML blasts, monocytes</td>
<td>UCLA Tissue Typing Lab</td>
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<tr>
<td>MY4, 7, 9</td>
<td>Granulocytic, monocytic series, AML blasts</td>
<td>Coulter Electronics</td>
<td>35, 36</td>
</tr>
<tr>
<td>MO1</td>
<td>Granulocytic and monocytic series, some AML blasts, some null and natural killer lymphocytes</td>
<td>Coulter Electronics</td>
<td>37</td>
</tr>
</tbody>
</table>

### Morphology and Cytochemistry

The FAB Cooperative group classification was used in the characterization of blood and marrow smears. Air-dried bone marrow smears and cytocentrifuged cell preparations (after Ficoll-Hypaque gradient separation) were subjected to cytochemical staining according to standard methods. The stains included periodic acid-Schiff (PAS), Sudan black B (SBB), myeloperoxidase (MPO), nonspecific esterase (NSE), chloracetate esterase (CAE), and acid phosphatase (AP).

### Sample Preparation and Immunofluorescent Assays

#### Cell Preparation

Heparinized bone marrow samples were diluted 1:3 with phosphate-buffered saline (D-PBS, GIBCO, Burlington, Ontario, Canada), layered onto Ficoll-Hypaque gradients (Histopaque 1077, Sigma Chemical Co, St Louis), and centrifuged at 400 g for 25 minutes. Mononuclear cells were collected at the Ficoll-Hypaque-plasma interface and washed three times in minimum essential medium (MEM, GIBCO). After the final wash, cells were suspended in MEM containing 2% fetal calf serum (GIBCO).

#### Monoclonal Antibodies

The monoclonal antibody panel was selected to identify differentiation antigens on lymphoid and myeloid cells. These are listed in Table 1. Some antibodies (eg, D5S6, Leu-M1, My4, My7, My9, B4) were added as they became available.

#### Indirect Immunofluorescence

Target cells were incubated with heat-inactivated normal rabbit serum (GIBCO) (30 minutes, 4°C) to block the nonspecific binding of monoclonal antibodies to Fc receptors, washed twice with medium (MEM containing 2% heat-inactivated fetal calf serum and 0.1% sodium azide), and incubated with 5 μL of monoclonal antibody (30 minutes, 4°C). The cells were then washed three times with MEM and incubated (30 minutes, 4°C) with 50 μL of a 1:20 dilution of fluorescein isothiocyanate (FITC)-conjugated affinity purified Fab' (IgG or IgM (Leu-M1, MO 1, D5S6) (Tago Inc., Burlingame, Calif). After three washes, cytocentrifuged preparations of cells were made and examined with a Leitz Ortholux microscope equipped with Ploempak epifluorescent illumination using an HBO 50 mercury lamp for the light source.

#### Double Immunofluorescence Assay

**TdT and Leu M1.** Target cells were first stained with Leu M1 monoclonal antibody and tetra-rhodamine isothiocyanate (TRITC)
conjugated affinity purified F(ab')₂ anti-mouse IgM. Cytocentrifuged preparations of Leu-M1-labeled cells were then subjected to indirect immunofluorescent staining for TdT as described below. Leu-M1 and J5 or Leu-M1 and B4. Target cells were simultaneously incubated with Leu-M1 and J5 or B4 monoclonal antibodies and were subjected to staining with TRITC anti-mouse IgM and FITC anti-mouse IgG as described above.

Terminal deoxynucleotidyl transferase assay. Cytocentrifuged smears were fixed in absolute methanol (15 minutes, 4 °C), incubated with rabbit anti-calf TdT (P.L.-Biochemical, Milwaukee) for 30 minutes at room temperature, and then incubated with FITC affinity purified F(ab')₂ goat anti-rabbit IgG (Tago, Inc).

Assessment. Mononuclear cells from each patient were stained with Wright's stain. These preparations were used as a guide to cell identification by phase microscopy. In this way, the phenotype of blast cells rather than non-blast cells was determined. The fluorescence of the blast cells was evaluated using a Leitz microscope as described above with intensity graded on a scale of 1 to 4 +.

Karyotyping

Cytogenetic analysis was performed on bone marrow samples from the four patients (M.C., G.D., N.D., G.E.) by modification of the methods of Seabright et al and Casarson et al.

RESULTS

In four cases, simultaneous or sequential expression of lymphoid or myeloid phenotypes was observed. The profiles of these patients are described in detail in Table 2.

**Patient M.C.**

The initial marrow was packed with lymphoblasts (FAB L1) (Fig 1A). Cytochemical staining showed a number of cells positive for PAS block and negative for SBB and MPO. Immunofluorescence showed a strongly positive response for TdT (Fig 1B). Following partial remission, the bone marrow in relapse showed blast cells with a different morphology from that at initial examination. These now resembled nonlymphoid cells (Fig 1C). Cytochemical study was positive for SBB, MPO, and CAE (60%) and for NSE (39%) (FAB M4). Auer rods were present (Fig 1D). Chromosome analysis of 18 cells showed no Philadelphia chromosome, but some cells showed 49 chromosomes (49,XY[+6+8+13]).

**Patient G.D.**

The initial leukemic bone marrow contained two distinct populations of blast cells resembling myeloblasts and lymphoblasts after Romanowsky staining (Fig 2A). The blasts were undifferentiated by cytochemical stains (PAS, SBB, MPO, NSE negative). Double-immunofluorescence showed separate populations of blast cells that were TdT⁺, Leu-M1 (36%) and TdT⁺, Leu-M1⁺ (60%) (Fig 2B). In addition, 40% to 60% of the cells showed positive responses to D5D6, My4, My7, My9, and M01 (Table 2). Chromosome analysis showed no Ph' chromosome in the 23 metaphases analyzed. The marrow was mosaic for trisomy 13, with 11 cells showing 47 chromosomes with an extra chromosome 13 and 12 showing 46 chromosomes (46,XY/47,XY,+13).

**Patient N.D.**

Bone marrow on admission showed a lymphoblastic infiltration (FAB L2). Cytochemical staining of the blast cells showed many PAS blocks and focal positivity on the NSE stain. There were negative results to SBB stain. Immunofluorescence was positive for TdT and B4 in greater than 80% of the blast cells, while positive responses for Leu-M1 were seen in 70% of the blast cells. Double immunofluorescence with TdT and Leu-M1 and with Leu-M1 and B4 showed bipheno-

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**Table 2. Reactivity Pattern of Blast Cells**

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<th>Immune Markers/Cytchemistry</th>
<th>T</th>
<th>B1</th>
<th>B4</th>
<th>J5</th>
<th>Leu-M1</th>
<th>D5/D6</th>
<th>My4</th>
<th>My7</th>
<th>My9</th>
<th>MO1</th>
<th>TdT</th>
<th>MPO</th>
<th>SBB</th>
<th>NSE</th>
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<td>&gt;70</td>
<td>Neg</td>
<td>Neg</td>
<td>Many</td>
<td>Clo</td>
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* T cell subset consisted of Leu-1, 2, 3, T11, and OKT3, 6, 9 in some cases.
† Grading of fluorescent intensity.
‡ Percentage of positive cells.
§ T11 >70%, Leu-1 >70%, T9 >70%, + + .
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Fig 1. Patient M.C. (A) Bone marrow at diagnosis showing lymphoblasts (Wright’s stain, original magnification, ×1,000). (B) TdT shows positive fluorescence (green/FITC, original magnification, ×625). (C) Bone marrow 3½ months later showing blast cells resembling myeloid blast cells (Wright’s stain, original magnification, ×1,000). (D) Myeloperoxidase stain of relapsed marrow showing positive blast cells and Auer rods (original magnification, ×1,000).

Fig 2. Patient GD. (A) Smear from marrow at admission showing two populations of blast cells. Note larger myeloblasts and smaller blasts resembling lymphoblasts. (Wright’s stain, original magnification, ×1,000). (B) Two distinct populations of blast cells are shown. (1) Leu-M1-positive, TdT-negative (red TRITC) and (2) Leu-M1-negative, TdT-positive (green FITC) (original magnification, ×790).

Fig 3. Patient ND. At left, blast cell morphology is seen under phase contrast microscopy. At right, the same cells have been photographed sequentially using an FITC filter (green) and a TRITC filter (red). The field was moved marginally between filters to show double stained cells. Green indicates B4 reactivity, red indicates Leu M1 reactivity (B4/Leu-M1 positive) (original magnification, ×790).
Table 3. Acute Leukemic Patients Studied Using Leu-M1

<table>
<thead>
<tr>
<th>Type*</th>
<th>Total</th>
<th>Adult</th>
<th>Pediatric</th>
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*Diagnosis made using Wright’s stain, cytochemistry, and immunofluorescence.
† >20% positive cells.
‡ Includes case ND (Leu-M1/B4).

Table 4. Acute Leukemic Patients Studied Using B4

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*Diagnosis made using Wright’s stain, cytochemistry, and immunofluorescence.
† >20% positive cells.
‡ Includes case ND (B4/Leu M1).

Acute mixed leukemia is an infrequent disease with phenotypic characteristics of more than one cell lineage. It includes (1) a mixed acute leukemia with two distinct populations of blast cells (myeloid and lymphoid), (2) a single population of blast cells with markers of both myeloid and lymphoid lineage (biphenotypic expression) and (3) a blast transformation from one cell lineage to another without a change in remission status.

DISCUSSION

The first variety may represent involvement of more than one cell line from the beginning or of malignant progenitors of both myeloid and lymphoid lineages. The second variety may result from disordered differentiation in a multipotential stem cell with inappropriate phenotypic manifestations or may reflect, in part, genomic derepression. The third variety may be a consequence of therapy.

The cases in this article can be divided into two types of Ph1 chromosome-negative acute mixed myeloid and lymphoid leukemia. In one patient (G.D.), two distinct populations of lymphoid and myeloid cells were found, while in two others (N.D. and G.E.), dual markers for lymphoid and myeloid antigens were expressed on individual cells. In addition, patient M.C. showed “evolution” from acute lymphoblastic to acute myeloid leukemia. We have also observed one patient with separate populations of Leu-M1 (71%) and J5 (25%) positive blast cells; despite the absence of the clinical features of CML, however, two out of 22 metaphases contained the Ph1 chromosome.

Leukemic transformation of a multipotential progenitor of both lymphoid and myeloid cells, with or without the Ph1 chromosome marker, could explain the simultaneous occurrence of distinct populations of lymphoblasts and myeloblasts in the same patient. A similar stem cell origin can be proposed for the disease in patient M.C. that evolved from a lymphoid to a myeloid phenotype. It is possible that chemotherapy for the initial leukemia led to a second leukemia, but this is unlikely considering the time from treatment to the emergence of the second population of cells. The possibility of developing two independent acute leukemias within four months seems remote. In addition, it is of interest that the initial marrow sample (FAB L1) of this patient showed myeloid antigenic determinants using two investigational “myeloid” antibodies.

The finding of doubly marked cells has been reported only rarely. In most cases leukemic cell surface antigen phenotypes have been found to reflect with considerable fidelity the phenotype of their normal cell counterpart. It is important to verify that Leu-M1 and B4, or Leu-M1 and J5, or My9 and
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T11/Leu-1 are detecting lineage-restricted surface antigens and are not simply recognizing different epitopes of the same membrane antigen. In previous reports, demonstration of reagent specificity within a lineage has depended on material from the supplier of the reagents, on evidence quoted in the literature, and on the previous experience of the investigators in the use of the reagent. The demonstration of reagent specificity within the lineage is of prime importance if the data are to be interpreted correctly. The biologic implications of doubly marked cells in acute leukemia need further study.

Whether it is important to recognize this type(s) of leukemia in order to alter the therapeutic regime or to identify a group with a different prognosis needs to be determined. In patient G.E. (T-ALL, FAB L2 + My9) there was no response to the L10 M protocol, yet complete remission was obtained with DAT and an additional three days of high-dose ara-c. Smith et al felt there was a relationship between lineage infidelity and a failure to induce remission.

Finally, it is of interest that patient G.D. had a refractory anemia with excess blasts (myelodysplastic syndrome, RAEB), yet later developed acute leukemia consisting of two distinct populations of lymphoblasts and myeloblasts. This may indicate that some cases of RAEB are the result of a defect of the pluripotential stem cell and are not preleukemia of purely myeloid lineage.

ACKNOWLEDGMENT

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