TdT-Positive Acute Leukemia With Monocytoid Characteristics: Clinical, Cytochemical, Cytogenetic, and Immunologic Findings

By Janet Cuttner, Stephanie Seremetis, Vesna Najfeld, Alexandra Dimitriu-Bona, and Robert A. Winchester

Thirteen patients with acute leukemias that were difficult to classify by the use of cytochemical staining and terminal deoxyribonucleotidyl transferase (TdT) activity are reported. The phenotype of the leukemic cells was characterized by the presence of mature or early monocyte lineage antigens and intense Ia antigen expression detected by monoclonal antibodies, terminal deoxynucleotidyl transferase activity, and cytochemical features, including both Sudan black B and periodic acid-Schiff activity. The mean age of this group of patients was 60 years. Five patients had leukemia occurring after chemotherapy or radiotherapy of a prior malignant disease, and two patients had a refractory anemia prior to development of acute leukemia. These patients had a low response rate to chemotherapy. This series of leukemia appears to form a distinct nosologic entity, representing a leukemic transformation among early cells of the monocyte lineage, resulting in a predominant neoplastic cell that is less mature than either the French-American-British M4 acute myelomonocytic leukemia or M5 acute monoblastic leukemia. The presence of terminal deoxynucleotidyl transferase activity was interpreted as indicating the primitive state of the cells in the differentiation sequence, rather than as implying any significance with respect to lineage.

It is generally agreed that the acute leukemias afford a unique opportunity for insight into the various hematopoietic lineages because the neoplastic cells represent an expression of a particular early stage of maturation that is relatively unmodified by subsequent differentiation. However, in certain instances, the assignment of a lineage to the leukemias presents difficulties. The current French-American-British (FAB) classification system of acute leukemia distinguishes between cells of myeloid and lymphoid lineage on the basis of cytochemical staining. For example, a characteristic of cells in the myeloid lineage is staining with Sudan black B and the presence of myeloperoxidase. Periodic acid-Schiff staining is a feature of cells with lymphoid differentiation, but is also encountered in erythroblastic and monocytic leukemias. More recently, the demonstration of terminal transferase activity has become a diagnostic criterion of lymphoid differentiation, which is found in either acute lymphoid leukemia or the so-called "lymphoblastic phase" of chronic myelogenous leukemia.4

In occasional acute leukemias, the application of these analyses fails to categorize the leukemia definitively, because the findings suggest both lymphoid and myeloid differentiation. In these instances, terminal transferase activity is found in undifferentiated blastic cells whose cytochemical staining does not support the characterization of the cells as lymphoid. The term "biphenotypic" has been applied to these leukemias, and they are considered to be a heterogeneous collection of unclassifiable entities. Alternatively, certain leukemias with these characteristics are designated as acute myelogenous leukemia with terminal deoxyribonucleotidyl transferase (TdT) activity or acute lymphoid leukemia with evidence of myeloid maturation.5,6

The concept that the sequential expression of various genes during differentiation results in the appearance of cell surface molecules, reflecting the new functional state of the cell, underlies the model of differentiation antigens that are specific for particular cell lineages.7 The application of monoclonal antibody technology8 to the characterization of cell membrane surface molecules has provided a new approach to the study of these differentiation antigens and has important implications for the problem of leukemia classification. Reagents have been developed that recognize differentiation antigens expressed on immature or mature cells of the granulocyte and monocyte lineages.9-12 These antigens have been used to establish the similarity of FAB M4, acute myelomonocytic leukemia, and FAB M5, acute monoblastic leukemia, and confirm the presence of these leukemic cells within the mononuclear phagocytic lineage.13-15

This article summarizes data accumulated during the study of 13 individuals with TdT-positive acute leukemia with monocytoid characteristics. Evidence is presented that these leukemias comprise a relatively distinct entity in terms of cellular phenotype and biologic properties reflected by clinical manifestations. A preliminary report of these results has appeared.16

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MATERIALS AND METHODS

Patient Selection and Diagnostic Criteria

Thirteen patients with newly diagnosed acute leukemias that were not readily classifiable into conventional (FAB) diagnostic categories were seen at Mount Sinai Medical Center between September 1980 and October 1982. These patients were considered as "unclassified" because of the presence of variable degrees of both myelomonocytic and lymphoid cytochemistries, as well as the presence of terminal deoxynucleotidyl transferase activity. During this period, 112 cases of acute leukemia were seen that met standard diagnostic criteria.

Cytochemistry

Bone marrow and buffy coat smears were made, and the following cytochemical stains were performed: Jenner-Giemsa, Sudan black B (SBB), myeloperoxidase, periodic acid-Schiff (PAS), nonspecific esterase (NSE) with and without fluoride, and alpha-naphthyl acid esterase. Terminal transferase was performed according to the product literature of the Baltimore Research Laboratories.

Cytogenetics

Bone marrow cells were analyzed directly and after 24 hours in culture. Randomly scanned metaphases, subjected to modified "ASG" banding method, were described according to the International Cytogenetic nomenclature.

Identification of Cell Surface Antigens

The anti-Ia monoclonal antibody 22c6 was obtained from an immunization with peripheral blood B cells. The antibodies reacting with antigens on cells of monocyte-macrophage lineage were obtained by immunization with peripheral blood monocytes (reagents MoP-9, MoP-15, MoS-39, and MoR-17), pleural fluid obtained by immunization with peripheral blood B cells. The antibodies react with antigens on cells of monocyte-macrophage lineage. Furthermore, a series of well-characterized monoclonal antibodies to mu, delta, kappa, lambda, gamma, and alpha determinants was used in both cytoplasmic and cell surface analyses. In addition, a panel of commercially available monoclonal antibodies were utilized, including anti-T (Leu-1, Leu-2, Leu-3, Leu-4, Leu-7, Leu-9), anti-B (Leu-12), and anti-common ALL antigen (CALLA).

Enriched preparations of blast cells depleted of mature granulocytes were isolated from peripheral blood by Ficoll-Hypaque, centrifugation, and, where necessary, further enrichment by Percoll discontinuous density gradient centrifugation. Enrichment resulted in >70% blasts in all specimens studied by immunofluorescence, and leukemic blasts were readily distinguished from contaminating lymphocytes and monocytes by phase microscopy. Monoclonal reagents were used at saturating concentrations for surface antigen identification in indirect immunofluorescence. The second-stage reagent was an F(ab')2 preparation of a rabbit anti-murine IgG that was conjugated with tetramethyl rhodamine isothiocyanate, as described elsewhere. Slides were examined using incident illumination in a fluorescence microscope (Leitz, Wetzlar, West Germany). The evaluation of positively stained cells was performed by counting about 200 cells. The numbers of positive cells were expressed as percentages of the total cell preparation.

RESULTS

Clinical Characteristics

The initial findings at diagnosis are presented in Table 2. Nine females and four males were studied. The ages ranged from 27 to 79 years, with a mean of 59.5 years. The initial leukocyte count ranged from 1,100/μL to 55,000 (mean 19,608/μL). Nine patients had a major disease 3–30 years (mean 8.8 years) prior to appearance of the leukemia. Of these, five patients had a preexisting malignancy. The treatment of four of these included chemotherapy with an alkylating agent; the fifth received radiotherapy. Two other patients had refractory anemias. One patient had idiopathic thrombocytopenic purpura and had undergone splenectomy and received corticosteroids, while another had Graves' disease and was treated with radioactive iodine for hyperthyroidism.

Cytochemical Studies

The cytochemical analysis, lysozyme level, and percentage of cells with TdT activity at time of diagnosis

<table>
<thead>
<tr>
<th>Table 1. Reactivity of Monoclonal Reagents Directed to Cells of the Mononuclear Phagocyte Lineage on Various Cell Populations</th>
</tr>
</thead>
<tbody>
<tr>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>Peripheral blood monocytes</td>
</tr>
<tr>
<td>Fluid macrophages*</td>
</tr>
<tr>
<td>Tissue macrophages†</td>
</tr>
<tr>
<td>Granulocytes</td>
</tr>
<tr>
<td>Peripheral blood lymphocytes (T cells and/or B cells and B-CLL)</td>
</tr>
<tr>
<td>U937 monoblastoid cell line</td>
</tr>
<tr>
<td>HL-60 cell line</td>
</tr>
<tr>
<td>Common (CALLA+) ALL</td>
</tr>
<tr>
<td>T-ALL‡</td>
</tr>
</tbody>
</table>

*Obtained from pleural or peritoneal exudates.
†Obtained from the synovial tissues from patients with osteoarthritis.
‡Very dim staining, primarily detectable by fluorescent activated cell sorter analysis.
§Zero signifies indistinguishable from control.
¶Fifteen patients studied.
†Six patients studied.
are presented in Table 3. Unseparated leukocytes were used for these studies. In all 12 patients studied, terminal transferase activity was demonstrated. This suggested, according to present criteria, a lymphoid derivation of the leukemia. By cytochemical criteria alone, six of the patients would have been classified as acute myelogenous leukemia with FAB classifications of M1 through M4. Three patients (B, C, M) would have been classified as acute lymphoblastic leukemia, because PAS staining and TdT activity were present, although their TdT activity was noted to be lower than that seen in "typical" ALL. Four patients (D, H, J, K) stained for SBB, PAS, and TdT activity. The leukemic blasts of these four patients appeared to have cytochemical characteristics of myeloid and lymphoid lineages.

**Monoclonal Antibody Studies**

The surface membrane antigens expressed by the enriched preparations of leukemic blasts are summarized in Table 4. Ia antigens were well expressed on varying percentages of the blasts of all 11 individuals

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**Table 2. Initial Findings at Diagnosis**

<table>
<thead>
<tr>
<th>Patient Designation</th>
<th>Age/Sex</th>
<th>WBC/µL</th>
<th>Prior Disease</th>
<th>Therapy of Prior Disease*</th>
<th>Time to Diagnosis of Leukemia in Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>54/F</td>
<td>55,100</td>
<td>Ovarian cancer</td>
<td>Thiopeta, Methotrexate</td>
<td>4</td>
</tr>
<tr>
<td>B</td>
<td>38/F</td>
<td>7,100</td>
<td>Hodgkin's disease</td>
<td>CVPP, CLB</td>
<td>5</td>
</tr>
<tr>
<td>C</td>
<td>79/M</td>
<td>13,000</td>
<td>Refractory anemia†</td>
<td>Blood transfusions, Busulfan</td>
<td>3</td>
</tr>
<tr>
<td>D</td>
<td>66/F</td>
<td>34,000</td>
<td>Polycythemia vera</td>
<td>Hydroxyurea, CLB</td>
<td>5</td>
</tr>
<tr>
<td>E</td>
<td>59/F</td>
<td>18,000</td>
<td>Idiopathic thrombocytopenic purpura</td>
<td>Prednisone, Splenectomy</td>
<td>4</td>
</tr>
<tr>
<td>F</td>
<td>50/F</td>
<td>27,600</td>
<td>Non-Hodgkin's lymphoma</td>
<td>CHOP, CLB</td>
<td>4</td>
</tr>
<tr>
<td>G</td>
<td>78/F</td>
<td>46,000</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>69/M</td>
<td>1,100</td>
<td>Refractory anemia</td>
<td>None</td>
<td>8</td>
</tr>
<tr>
<td>I</td>
<td>40/M</td>
<td>27,000</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>70/F</td>
<td>14,400</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>66/F</td>
<td>3,300</td>
<td>Hyperthyroidism</td>
<td>RAI</td>
<td>16</td>
</tr>
<tr>
<td>L</td>
<td>78/F</td>
<td>2,900</td>
<td>Breast cancer</td>
<td>Surgery, Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>27/M</td>
<td>5,400</td>
<td>None</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CVPP, CCNU, vinblastine, prednisone, procarbazine; CHOP, cyclophosphamide, adriamycin, vincristine, prednisone; CLB, chlorambucil; RAI, radioactive iodine.
†Exposure to benzene.

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**Table 3. Cytochemical and Cytoenzymatic Findings**

<table>
<thead>
<tr>
<th>Patient Designation</th>
<th>WBC/µL</th>
<th>Percent Blasts</th>
<th>SBB (Percent Positive)</th>
<th>PAS (Percent Positive)</th>
<th>NSE</th>
<th>NSE + F</th>
<th>TdT</th>
<th>Lysozyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>55,100</td>
<td>42</td>
<td>25</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>50</td>
<td>41</td>
</tr>
<tr>
<td>B</td>
<td>7,100</td>
<td>10</td>
<td>1</td>
<td>23</td>
<td>+</td>
<td>±</td>
<td>23</td>
<td>34</td>
</tr>
<tr>
<td>C</td>
<td>13,000</td>
<td>55</td>
<td>0</td>
<td>14</td>
<td>+</td>
<td>±</td>
<td>30</td>
<td>62</td>
</tr>
<tr>
<td>D</td>
<td>34,000</td>
<td>47</td>
<td>5</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>E</td>
<td>18,000</td>
<td>78</td>
<td>16</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>30</td>
<td>19</td>
</tr>
<tr>
<td>F</td>
<td>27,600</td>
<td>58</td>
<td>72</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
<td>14</td>
<td>10.5</td>
</tr>
<tr>
<td>G</td>
<td>46,000</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>±</td>
<td>31</td>
<td>160</td>
</tr>
<tr>
<td>H</td>
<td>1,100</td>
<td>7</td>
<td>59</td>
<td>21</td>
<td>+++</td>
<td>+</td>
<td>50</td>
<td>N</td>
</tr>
<tr>
<td>I</td>
<td>27,000</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>±</td>
<td>25</td>
<td>70</td>
</tr>
<tr>
<td>J</td>
<td>14,000</td>
<td>49</td>
<td>18</td>
<td>14</td>
<td>+</td>
<td>±</td>
<td>65</td>
<td>20.5</td>
</tr>
<tr>
<td>K</td>
<td>3,300</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>6.5</td>
</tr>
<tr>
<td>L</td>
<td>2,900</td>
<td>42</td>
<td>46</td>
<td>0</td>
<td>+</td>
<td>±</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>M</td>
<td>5,400</td>
<td>38</td>
<td>0</td>
<td>6</td>
<td>++</td>
<td>+</td>
<td>60</td>
<td>N</td>
</tr>
</tbody>
</table>

N, not performed.
*SBB, Sudan black B; PAS, periodic acid-Schiff; NSE, nonspecific esterase; NSE + F, nonspecific esterase + fluoride; TdT, terminal transferase; these determinations were made on whole blood.
studied. There was no detectable expression of T or B differentiation antigens, including CALLA, on these cells. Antigens characteristic of mature blood monocytes, as revealed by staining with reagents MoP-9, MoP-15, MoS-1, and Mos-39, were strongly expressed on the cells of two patients. These individuals (G and I) were also characterized by the highest levels of lysozyme and lacked Sudan black staining of their blasts.

The cells of nine of ten patients expressed antigens found on immature members of the monocyte lineage. These antigens were of two categories. Those detected by antibodies MoU-50 and MoU-26 have their predominant to exclusive expression on early cells of the monocyte lineage, while antibodies MoU-28 and MoU-36 detect antigens present on early monocytoid and granulocytoid forms (Table 1). Reagent MoU-50 stained 12%-90% of cells in 8 individuals. MoU-26 detected antigens expressed on 30%-42% of cells in 4 patients. MoU-36 antibody reacted with 15%-80% of cells in 6 patients. MoU-28 stained 10%-80% of cells in 7 patients. The one patient without these latter antigens was individual I, who had a considerable proportion of blast forms that bore mature monocyte antigens. In most instances, the staining was relatively weak but was always partially redistributed into patches and coarse speckles.

**Cytogenetic Studies**

Cytogenetic analysis was performed in 11 of 13 patients. The results are seen in Table 5. Two patients were 46,XX. Two patients showed a mixture of normal and hypodiploid cells (I and L). Three patients had a mixture of normal and abnormal cells (C, E, and H). Two other patients had predominantly abnormal chromosomes (A and M), and in two patients there were no evaluable metaphases.

**Response to Therapy**

Based on the presence of TdT activity in the leukemia blasts, nine patients were treated with vincristine, prednisone, and daunorubicin; only one patient achieved a complete remission. Four of the nonresponders were immediately treated with cytosine arabinoside (Ara-C) and daunorubicin, and two achieved complete remissions; a third had a partial remission. Two patients were initially treated with Ara-C and daunorubicin and one was treated with high-dose Ara-C without response. These patients were unresponsive due to refractory leukemia, ie, they survived induction therapy but bone marrow remained leukemic. One patient was not treated.

**DISCUSSION**

The central finding in this study was that a series of acute leukemias with terminal transferase activity, difficult to classify solely by cytochemical criteria, expressed Ia and differentiation antigens characteristic of members of the monocyte lineage. This, along with certain distinctive clinical features, including the frequent presence of a secondary leukemia or refractory anemia and resistance to standard induction chemotherapy, support the conjecture that these leukemias form a distinct nosologic entity, representing a neoplastic transformation early in the monocytic lineage. These leukemias appear to be less mature than either the FAB M4 (acute myelomonocytic leukemia) or the FAB M5 (acute monoblastic leukemia).

In general, the patients were older, with a mean age

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**Table 4. Leukemic Blast Membrane Phenotype Defined by Monoclonal Antibodies**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ia Antigens</th>
<th>P9</th>
<th>P15</th>
<th>S1</th>
<th>S39</th>
<th>Immature Monocyte and Myelomonocyte Antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>90+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>D†</td>
<td>90+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>30+</td>
</tr>
<tr>
<td>E</td>
<td>90+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>30+</td>
</tr>
<tr>
<td>F</td>
<td>85+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>30+</td>
</tr>
<tr>
<td>G</td>
<td>80+</td>
<td>45+</td>
<td>40+</td>
<td>45+</td>
<td>45+</td>
<td>42+</td>
</tr>
<tr>
<td>H</td>
<td>90+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>I</td>
<td>88+</td>
<td>60+</td>
<td>60+</td>
<td>60+</td>
<td>60+</td>
<td>ND</td>
</tr>
<tr>
<td>J</td>
<td>92+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>35+</td>
</tr>
<tr>
<td>K</td>
<td>25+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>L</td>
<td>80+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>M</td>
<td>58+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>ND</td>
</tr>
</tbody>
</table>

*Enriched preparations of leukemic blasts were obtained by Ficoll-Hypaque separation and, where necessary, Percoll density gradient centrifugation. In all individuals, an average of 0% (range 0%-2%) blasts reacted with the T (Leu-1, 2, 3, 4, 7, 9) and B (Leu-12) differentiation-specific monoclonal antibodies, with antimmunoglobulin antibodies (cytoplasmic and surface), and with CALLA.

†Patients B and C were not studied.

‡Zero indicates that <2% cells are positive.
ND, not done.
Cells were difficult to evaluate due to the extreme fuzzy chromosome
LEUKEMIA WITH MONOCYTOID FEATURES
TdT+
defined on the basis of cytochemical
and surface
toxic exposures and define a
or
of
the nine study patients evaluated; these are known to
studies,
antigen
was 42,XY,4qcb,-17.-17,-18-20.
morphology.
remission was achieved in only 3 of the 13
patients,
nosed
as having refractory anemia. Complete clinical
preexisting disease,
in part for the poor response to therapy observed here,
may
been previously
detected by the reagents
MoP-9, MoP-15, MoS-1, and MoS-39 are present on
the surface membranes of tissue macrophages, blood
monocytes, and cells of M4 or M5 leukemias.13-15
These differentiation antigens are not demonstrable on
promonocytic cell lines, including U937 and others,
nor have they been detected on the M1, M2, or M3
leukemias of the FAB classification studied to this
time.14,15 The presence of these mature monocyte lin-
eage antigens on the leukemic blasts of these patients
was associated with high levels of lysozyme and the
absence of Sudan black staining. The cells of these two
leukemias differed, however, from those of the M4 or
M5 category by their primitive morphology, a less
than twofold inhibition of nonspecific esterase by fluoride,
and the presence of a large percentage of leukemic
blasts that contained TdT.

Differentiation antigens of the MoU series were
demonstrable in significant proportions on leukemic
cells of all but one individual, who had an abundant
expression of the more mature monocyte antigens
detected by antibodies of the MoU series are less well
understood in terms of the implications associated with
their presence on a cell. Available characterization
suggests that the MoU-50 and MoU-26 reagents
detect antigens expressed only on early cells in the
monocyte-macrophage lineage.13-15 However, they are also identifiable on FAB
M1 leukemias,15 where their significance
is unknown.
In the instance of patient G, the coexpression of
monocyte markers
with
primitive morphology, a less than
lysozyme and the
presence of a large percentage of leukemic
blasts that contained TdT.

Chromosomal abnormalities were identified in seven
of the nine study patients evaluated; these are known to
be associated with prior chemotherapy, radiotherapy,
or toxic exposures and define a poor prognosis subset
of patients with acute leukemia. While this may account
in part for the poor response to therapy observed here,
it is important to note that patient selection was
defined on the basis of cytomegaly and surface
antigen studies, and by these criteria, a group was
identified with a very much higher incidence of chromo-
somal abnormalities than is usually observed in
patients with readily classifiable AML or ALL. None
of the patients in this study showed the t(4;11) re-
arrangement recently reported in myeloid/lymphoid
acute leukemia in children15 and infants.26 One patient
in our study showed del(11q), another patient trisomy
11, and marker chromosomes were detected in four
patients. Taken together, these cytochemical, surface
antigen, and cytogenetic data identify a subset of
leukemic patients that are relatively resistant to inten-
sive chemotherapy. This observation has obvious impli-
cations for the choice of a therapeutic program.

The two leukemias from patients G and I are of
special interest because the blasts strongly expressed
differentiation antigens that are primarily restricted to
mature cells of the monocyte-macrophage lineage.13
The set of distinct antigens detected by the reagents
MoP-9, MoP-15, MoS-1, and MoS-39 are present on
the surface membranes of tissue macrophages, blood
monocytes, and cells of M4 or M5 leukemias.13-15

<table>
<thead>
<tr>
<th>Table 5. Cytogenetic Analyses of Bone Marrow Cells*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>E</td>
</tr>
<tr>
<td>H</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>K</td>
</tr>
<tr>
<td>L</td>
</tr>
<tr>
<td>M</td>
</tr>
</tbody>
</table>

*Cells were harvested after 2 and/or 24 hours in culture.
†Bone marrow for cytogenetics was not performed on patients D and
F, and patients G and J had insufficient material for the cytogenetic
study.
‡In some cells, another marker, like a small fragment, was observed.
§Probably a number of hypodiploid cells were broken hypodiploid.
¶One of the five cells had 46,XY, -1,?del(22q), +mar 1. Deletion of
22q does not appear to be a Ph; smaller part from 22q appears to be
missing.
§One of the hypodiploid cell had chromatid, break and the karyotype
was 42,XY, 4qcb, -17, -17, -18, -20.
**In all cells, mar 1 (marker) was similar to C-group size chromosome,
but its origin could not be determined.

of 60 years. Of the 13 patients, 6 had received alkylat-
ing agent chemotherapy or radiation therapy for a
preexisting disease, and 2 had been previously diag-
nosed as having refractory anemia. Complete clinical
remission was achieved in only 3 of the 13 patients,
where poor response to therapy further reflects on the
biology of the leukemic cells involved.

Chromosomal abnormalities were identified in seven
of the nine study patients evaluated; these are known to
be associated with prior chemotherapy, radiotherapy,
or toxic exposures and define a poor prognosis subset
of patients with acute leukemia. While this may account
in part for the poor response to therapy observed here,
it is important to note that patient selection was
defined on the basis of cytomegaly and surface
antigen studies, and by these criteria, a group was
identified with a very much higher incidence of chromo-
somal abnormalities than is usually observed in
patients with readily classifiable AML or ALL. None
of the patients in this study showed the t(4;11) re-
arrangement recently reported in myeloid/lymphoid
acute leukemia in children15 and infants.26 One patient
in our study showed del(11q), another patient trisomy
11, and marker chromosomes were detected in four
patients. Taken together, these cytochemical, surface
antigen, and cytogenetic data identify a subset of
leukemic patients that are relatively resistant to inten-
sive chemotherapy. This observation has obvious impli-
cations for the choice of a therapeutic program.

The two leukemias from patients G and I are of
special interest because the blasts strongly expressed
differentiation antigens that are primarily restricted to
mature cells of the monocyte-macrophage lineage.13
The set of distinct antigens detected by the reagents
MoP-9, MoP-15, MoS-1, and MoS-39 are present on
the surface membranes of tissue macrophages, blood
monocytes, and cells of M4 or M5 leukemias.13-15

These differentiation antigens are not demonstrable on
promonocytic cell lines, including U937 and others,
nor have they been detected on the M1, M2, or M3
leukemias of the FAB classification studied to this
time.14,15 The presence of these mature monocyte lin-
eage antigens on the leukemic blasts of these patients
was associated with high levels of lysozyme and the
absence of Sudan black staining. The cells of these two
leukemias differed, however, from those of the M4 or
M5 category by their primitive morphology, a less
than twofold inhibition of nonspecific esterase by fluoride,
and the presence of a large percentage of leukemic
blasts that contained TdT.

Differentiation antigens of the MoU series were
demonstrable in significant proportions on leukemic
cells of all but one individual, who had an abundant
expression of the more mature monocyte antigens
detected by antibodies of the MoU series are less well
understood in terms of the implications associated with
their presence on a cell. Available characterization
suggests that the MoU-50 and MoU-26 reagents
detect antigens expressed only on early cells in the
monocyte lineage and on certain unusual tumor cells
that appear to be derived from mononuclear phago-
cytes.13-15 However, they are also identifiable on FAB
M1 leukemias,15 where their significance
is unknown.
In the instance of patient G, the coexpression of
monocyte markers
with
primitive morphology, a less than
lysozyme and the
presence of a large percentage of leukemic
blasts that contained TdT.

Terminal deoxyribonucleotidyl transferase has been
described as a specific intracellular "marker" for
immature lymphocytes.2-4 Cells expressing TdT activ-
ity are seen in the majority of patients with acute lymphoblastic leukemia, lymphoblastic lymphoma, and in 20%-30% of patients in the blastic phase of chronic myelogenous leukemia. TdT is a normal constituent of a small population of hematopoietic cells, but is not normally found in the cells of the peripheral blood. TdT has also been described in cells of 11 patients with acute myelogenous leukemia; of these, eight were classified as either M4 or M5. Presumably these eight patients would have had readily detectable monocyte lineage antigens. The presence of TdT activity probably signifies that a cell is at an early state in the maturation of various lineages, and probably has limited value in identifying a cell as a member of a particular lineage.

The expression of Ia antigens on early members of the leukemia and nonleukemia granulocytic lineage is relatively dim compared to the more intense expression of these antigens on cells in the monocyte lineage. All leukemias studied in this group are distinguished from the granulocytic lineage (FAB M1, M2, and M3) leukemias by the presence of bright staining for Ia antigens. In this respect, they resemble the FAB M4 and M5 leukemias.

The observations of the present study provide a possible framework for understanding prior observations of TdT activity in leukemias that would otherwise have been classified as acute myelogenous leukemia.

It is probable, though not established, that the patients of this study form a single entity divided into two subsets. One, characterized by the presence of mature monocyte antigens, presumably represents a stage of maturity preceding the FAB leukemias. The second subset, characterized by the expression of immature monocyte antigens, represents a more primitive cell, perhaps analogous to a cell that is close to the point of separation of the granulocyte and monocyte lineages.

REFERENCES


TdT-positive acute leukemia with monocytoid characteristics: clinical, cytochemical, cytogenetic, and immunologic findings

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