Atypical Megakaryocytes in Preleukemic Phase of Acute Myeloid Leukemia

By W. Byron Smith, Arthur Ablin, Joseph R. Goodman, and George Brecher

Mono- and binucleated megakaryocytes appeared in the bone marrow of a 6-yr-old white male 9 mo prior to the development of acute myeloid leukemia; in addition, leukopenia and anemia antedated the diagnosis by 3½ and 9 mo, respectively. The report suggests that mono- and binucleated megakaryocytes may be a useful diagnostic finding in early leukemia.

In April 1969, the patient to be reported here had a normal platelet count, and mono- and binucleated small megakaryocytes as the sole platelet-producing cells in the bone marrow. The patient developed acute myelogenous leukemia in January 1970. We have observed similar megakaryocytic abnormalities in seven cases of "preleukemia" and acute or chronic granulocytic leukemia. Saarni and Linman have drawn attention to the frequency of megakaryocytic abnormalities in preleukemia, which were present in their series in 85% of 34 cases. Evidence is thus accumulating that the cell undergoing malignant transformation in acute and chronic granulocytic leukemia may be a common precursor of the erythrocytic and megakaryocytic as well as granulocytic series.

The case to be reported here, however, appears to be unique because the abnormal megakaryocytes were the only type of megakaryocyte present in the patient's marrow, while in other reported instances a mixture of abnormal and normal megakaryocytes was the rule. Moreover, in our patient, the unusual megakaryocytes represented the only morphologic abnormality noted. This report, therefore, draws attention to the significance of mono- or binuclear megakaryocytes in a prolonged prodromal stage of acute myelogenous leukemia. We hope that wider attention to this abnormality will eventually result in a better definition of the scope of the diagnostic utility of this finding.

CASE REPORT

A 3-yr-old white male, whose 7-yr-old female sibling had previously died from the complications of aplastic anemia, was asymptomatic when leukopenia was first diagnosed in June 1966 (Ta-
Table 1. Patient’s Course

<table>
<thead>
<tr>
<th>Date</th>
<th>Fetal hgb (%)</th>
<th>Hgb (g/100 ml)</th>
<th>Hct</th>
<th>Platelets (×10³/µl)</th>
<th>WBC (×10³/µl)</th>
<th>Polymorphonuclears Segmented (%)</th>
<th>Bands (%)</th>
<th>Reticulocytes (%)</th>
<th>Lymphocytes (%)</th>
<th>Monocytes (%)</th>
<th>Eosinophils (%)</th>
<th>Basophils (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1966</td>
<td>12.6</td>
<td>12.6</td>
<td>38</td>
<td>Adequate</td>
<td>3.900</td>
<td>17</td>
<td></td>
<td>75</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>10/67</td>
<td>(Pneumococcal pneumonia)</td>
<td>2.8</td>
<td>11.0</td>
<td>34</td>
<td>240.000</td>
<td>1.000</td>
<td>15</td>
<td>9</td>
<td>76</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/69</td>
<td>8.2</td>
<td>3.6</td>
<td>11</td>
<td>294.000</td>
<td>7.600</td>
<td>9</td>
<td></td>
<td>84</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6/69</td>
<td>6.5–8.0</td>
<td>20–25</td>
<td>5</td>
<td></td>
<td></td>
<td>0.2–6.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1/70</td>
<td>31</td>
<td>9.6</td>
<td>33</td>
<td>303.000</td>
<td>25.000</td>
<td>32, with 45% unclassified “blast forms”</td>
<td>4</td>
<td>1.5</td>
<td>16</td>
<td>3</td>
<td></td>
<td>5 nucleated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RBC/100 WBC</td>
<td></td>
</tr>
</tbody>
</table>
ble 1). He remained asymptomatic over the following year, with persistent leukopenia varying from 3000 to 4000 WBC/cu mm. Platelets were normal by smear.

In October 1967, at age 4, he developed pneumococcal pneumonia. A bone marrow aspiration revealed primarily early myeloid cells with a marked decrease in those beyond the myelocytic stage; the erythroid series and megakaryocytes were unremarkable. He made an uneventful recovery and during the subsequent 18 mo was well, though he remained leukopenic with WBC varying from 3100 to 3650/cu mm.

In April 1969, at age 6, following a 3-wk febrile respiratory illness, he was noted to be pale. No organomegaly, adenopathy, or purpura was noted on physical examination. Blood findings were those listed in the table. Additional laboratory data included fetal hemoglobin of 8.2%: quantitive serum immunoglobulins: A 200 mg/100 ml, G 700 mg/100 ml, M 135 mg/100 ml; serum iron 198 g/100 ml, and serum iron binding capacity 358 g/100 ml; serum urea nitrogen 17 mg/100 ml; serum creatinine 0.5 mg/100 ml; SGPT 16 U; LDH 284 U; SGOT 16 U; and total serum bilirubin 0.3 mg/100 ml. Chest X-ray and skeletal survey were negative. Chromosome studies of the peripheral blood and bone marrow demonstrated a normal male karyotype.

Bone marrow aspiration revealed a moderately cellular specimen with granulocytic hyperplasia and erythroid hypoplasia. The megakaryocytes, which had been morphologically normal in a previous marrow, were all small mono- and binucleate forms, many containing coarse azurophilic granules characteristic of platelet-forming megakaryocytes (Fig. 1A). During the subsequent 2 mo, transfusions were required at 4-wk intervals to maintain his hemoglobin within the normal range.

In June 1969, due to the persistent transfusion requirement, prednisone was started (5 mg three times/day); within 9 days the reticulocyte count increased from 0.2% to 6.2%, and the hemoglobin from 6.5 to 8 g/100 ml. During the next 8 mo no transfusions were required, as the hemoglobin remained between 10 and 12 g/100 ml with 25 mg prednisone every other day. The number of platelets continued to be normal on the peripheral blood smear and the WBC remained between 2000 and 3000/cu mm.

On a regular monthly checkup in January 1970, 9 mo after the onset of anemia and at the age of 7 yr, hemoglobin was 9.6 g/100 ml; WBC 25,000/cu mm, with 45%, unclassified “blast forms”; platelets 303,000; fetal hemoglobin 31%. No organomegaly or adenopathy was noted on physical examination. On admission to the hospital (see table), a bone marrow aspirate revealed 50%, “blasts” which were most consistent with cells of the myeloid series, diminished erythroid precursors, and diminished megakaryocytes. Again, the abnormalities of the megakaryocytic series, first noted 9 mo previously, were observed (Fig. 1B).

For ultrastructural studies, bone marrow particles were fixed in glutaraldehyde and postfixed in osmium, dehydrated, and embedded in epon plastic. Electron microscopy revealed megakaryocytes that were greatly reduced in size, containing one nucleus and, very rarely, in cross section, a second nuclear lobe was transected. The nuclear chromatin indicated a mature cell. Most of the megakaryocytes had multiple cytoplasmic blebs which, in general, contained no granules but us-

Fig. 1. (A) Two very small mononucleated megakaryocytes from the bone marrow 9 mo prior to diagnosis of leukemia. Wright-Giemsa stain; × 1000. (B) Atypical binucleated megakaryocyte with suggestion of coarse azurophilic inclusions at time of diagnosis of acute myelogenous leukemia. Wright-Giemsa stain; × 1000.
Fig. 2. A small megakaryocyte with a single large nucleus (N) and a small amount of cytoplasm which contains a large Golgi (G) and numerous small mitochondria (M). The surface of the cell has many blebs (b), one (') has many small lamellae. The blebs are agranular, containing only glycogen particles; a few have some smooth lamellar members.

ually glycogen particles and occasional small collections of microtubules (Fig. 2). The cytoplasm contained some typical granules and an increased number of the small round mitochondria characteristic of megakaryocytes and platelets. Some of the cells had a collection of vesicles in areas free of all other cytoplasmic organelles (Fig. 3).

A diagnosis of acute myelogenous leukemia was made and the patient was started on 6-mercaptopurine and prednisone but, because of unresponsiveness, cytosine arabinoside alone and, later, with cytoxan was started. His peripheral WBC subsequently decreased but complete marrow remission was never achieved.

In November 1970, hepatosplenomegaly was noted for the first time (liver 2.5 cm below the right
ATYPICAL MEGAKARYOCYTES

Fig. 3. Two small megakaryocytes in the bone marrow. The lower cell has a large nucleolus (Nu), the cytoplasm is scant but normal, and only few surface blebs are present. The upper cell has a large vesicular area (V), a large number of small mitochondria (M), and only the tip of the nucleus (N).

costal margin, spleen 3 cm below the left costal margin). The disease worsened rapidly and he expired with staphylococcal pneumonia and sepsis in January 1971.

The pertinent findings at necropsy included hemorrhagic consolidation of the lungs and splenomegaly (the spleen weighed 1000 g). Microscopically, very few polymorphonuclear WBC were present in the inflammatory reaction of the lungs. Infiltrations by neoplastic cells of the myelogenous cell line were observed in the lungs, liver, spleen, lymph nodes, and bone marrow. The testes, thymus, thyroid, and kidneys were free of infiltrative disease.
DISCUSSION

Abnormalities can occur in all three major cell lines from months to years prior to the onset of acute leukemia. The morphologic abnormalities have now been extensively reviewed and documented by Saarni and Linman.

Megakaryocytic abnormalities have been described in the "preleukemia" and acute phase of myelogenous leukemia. Morphological abnormalities include mono- and binucleated forms, great variation in size, and nuclear chromatin patterns that resemble the dissociation of cytoplasmic and nuclear maturation observed in erythrocytic precursors in folate and vitamin B12 deficiency. Small megakaryocytes with decreased volume and number of nuclear lobes have been found in chronic granulocytic leukemia.

Our patient developed acute leukemia 3½ yr after leukopenia was first noted. During the interim he had anemia and leukopenia without thrombocytopenia, although there were abnormal megakaryocytes in the bone marrow 9 mo prior to the diagnosis of leukemia. The megakaryocytes were increased in number, and almost all were small, mono- and binucleated, with evidence of megakaryocytic granule formation. Electron microscopy confirmed these cells to be megakaryocytes. In addition to their strikingly small size and occasionally diploid nuclei, abnormalities included areas with cytoplasmic blebs, many Golgi vesicles, and an apparent increase of small rounded mitochondria. Vascular areas devoid of any other organelles (Fig. 3) were present in many megakaryocytes, and resembled similar areas in megakaryocytes of hereditary macrothrombocytopenia. Apparently these structures, although not present in normal megakaryocytes, are not related to the ultimate development of leukemia.

REFERENCES

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