Preleukemia and Leukemia in Polycythemia Vera

By Dino Meytes, David Katz, and Bracha Ramot

A group of 76 polycythemia vera patients was followed prospectively with bone marrow examinations at regular intervals. Six terminated in acute leukemia, preceded by an indolent preleukemic phase succeeded by a very fulminant leukemia. At autopsy, all patients had extramedullary hematopoiesis. In one of them, only the bone marrow was leukemic, suggesting that it was the primary site of this transformation. In three with leukemic involvement of nonhematopoietic organs, the infiltrate consisted of myelo- or myelomonoblasts and normoblasts. The preleukemic phase was characterized by a rapidly evolving spontaneous pancytopenia, with a drop from polycythemic blood counts within 2 mo. In the bone marrow, megaloblastoid erythropoiesis with ring sideroblasts was prominent. A similar preleukemic phase, evolving in other potentially leukemic conditions, has been described. Therefore, in the patients at risk, the appearance of ring sideroblasts may be regarded as an early indicator of imminent acute leukemia transformation.

ACUTE LEUKEMIA is a frequent terminal complication of polycythemia vera (PV).1 32P therapy has been implicated as the main risk factor for this evolution.2 However, the features which herald its onset in PV have not been emphasized in the literature.

During a systematic prospective study of 76 PV patients, acute leukemia was diagnosed in six. All patients went through an indolent preleukemic phase which was succeeded by a very fulminant leukemic transformation.

CLINICAL MATERIAL

Seventy-six PV patients have been followed during the period 1955-1975; six of them died of acute leukemia. Autopsy was performed in five. Standard techniques were used for routine hematologic studies. Bone marrow was examined annually as part of a chromosomal investigation of PV, with additional examinations when indicated by the clinical course. In two patients, the preleukemic marrow samples were not available. In one patient, peripheral red blood cells were separated by density, and enzyme levels were determined in the various fractions.4,5

RESULTS

Clinical

Data on patients are presented in Table 1. It should be pointed out that no distinctive features preceding the preleukemia were observed in the six PV patients who terminated in leukemia when compared with the remaining 70. All six had previously been treated with 32P, but two of them received 3-4 mCi only. The interval from the last myelosuppressive therapy to the onset of the preleukemic phase was 1-4 yr in five patients and 1 mo in the sixth. This phase evolved after 4-16 yr of documented PV, with a drop from polycythemic blood counts occurring within 2 mo. General complaints of lassitude with pyrexia...
Table 1. Clinical Features of Polycythemia Vera Patients Who Developed Acute Leukemia

<table>
<thead>
<tr>
<th>Patient</th>
<th>RE</th>
<th>LM</th>
<th>KL</th>
<th>MD</th>
<th>SK</th>
<th>CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/Age*</td>
<td>M, 57</td>
<td>M, 59</td>
<td>M, 53</td>
<td>M, 48</td>
<td>F, 60</td>
<td>F, 64</td>
</tr>
<tr>
<td>Polycythemic phase</td>
<td>Therapy</td>
<td>$^{32}$P-4 mCi</td>
<td>$^{32}$P-26 mCi</td>
<td>$^{32}$P-18 mCi</td>
<td>$^{32}$P-34 mCi</td>
<td>$^{32}$P-3 mCi</td>
</tr>
<tr>
<td>Marrow blasts (%)*</td>
<td>&lt;1</td>
<td>1-3</td>
<td>&lt;1</td>
<td>1-2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marrow iron*</td>
<td>N.D.</td>
<td>0</td>
<td>Trace in RES cells</td>
<td>N.D.</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Serum iron µg/100 ml</td>
<td>N.D.</td>
<td>15</td>
<td>64</td>
<td>60</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Preleukemic phase</td>
<td>interval (yr)</td>
<td>4</td>
<td>14</td>
<td>14</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Peripheral blood</td>
<td>Hemoglobin g/100 ml</td>
<td>10.6</td>
<td>10.4</td>
<td>10.3</td>
<td>9.4</td>
<td>12.1</td>
</tr>
<tr>
<td>Leukocytes/cu mm</td>
<td>3,900</td>
<td>14,000</td>
<td>8,500</td>
<td>2,100</td>
<td>6,300</td>
<td>2,500</td>
</tr>
<tr>
<td>Thrombocytes/cu mm</td>
<td>210,000</td>
<td>81,000</td>
<td>10,000</td>
<td>83,000</td>
<td>10,000</td>
<td>32,000</td>
</tr>
<tr>
<td>Blasts (%)</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Serum iron µg/100 ml</td>
<td>N.D.</td>
<td>N.D.</td>
<td>89</td>
<td>158</td>
<td>80</td>
<td>104</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Megaloblastoid sideroblasts</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Blasts (%)</td>
<td>3</td>
<td>5</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAS stain</td>
<td>N.D.</td>
<td>+</td>
<td>N.D.</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>Preleukemia-leukemia interval (mo)</td>
<td>8</td>
<td>8</td>
<td>18</td>
<td>6</td>
<td>1?</td>
<td>Several months</td>
</tr>
<tr>
<td>Acute leukemia phase</td>
<td>Peripheral blood</td>
<td>N.D.†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin g/100 ml</td>
<td>8.1</td>
<td>7.5</td>
<td>5.7</td>
<td>9.9</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Leukocytes/cu mm</td>
<td>23,400</td>
<td>14,000</td>
<td>10,000</td>
<td>3,800</td>
<td>3,800</td>
<td></td>
</tr>
<tr>
<td>Thrombocytes/cu mm</td>
<td>16,000</td>
<td>10,000</td>
<td>17,000</td>
<td>5,000</td>
<td>32,000</td>
<td></td>
</tr>
<tr>
<td>Blasts (%)</td>
<td>72</td>
<td>8</td>
<td>30</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Duration (wk)</td>
<td>4</td>
<td>Diagnosed at autopsy</td>
<td>3</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*At the last examination performed while the patient was still polycythemic.
†Patient suddenly developed bleeding esophageal varices and died within hours. The PM marrow was leukemic with sideroblasts.
‡This patient probably had a very short preleukemic phase. At the time of bone-marrow examination she was already leukemic, with 90% blasts. Sideroblasts were prominent (see text).
N.D., Not done.

dominated the clinical picture. Except in one patient with portal hypertension (LM), no change in the size of the spleen was observed. In two patients (RE, LM) a typical preleukemic phase was diagnosed retrospectively, and only after the appearance of the leukemia. Alerted by this sequence, the acute transformation in the remaining patients could be predicted. This transformation was
heralded within 1–18 mo by rapid enlargement of the spleen, severe bone pain, and a hemorrhagic diathesis. The subsequent course was very fulminant, with death occurring in less than a month. Chemotherapy, including prednisone, 6-mercaptopurine, cytosine arabinoside, and vincristine in various combinations, was ineffective.

**Laboratory**

The preleukemia was characterized by a pancytopenia in all except one patient. In those without leukopenia or thrombocytopenia at the beginning of this phase, the counts dropped to abnormal levels within a few weeks. Mild poikilocytosis with tear-drop cells, occasional normoblasts, and some stippled hypochromic erythrocytes were observed. In the myeloid series a slight shift to the left was present, with up to 2% blasts seen in two patients only. There was no monocytosis. In the four available bone marrow aspirates, megaloblastoid erythropoiesis and abnormal sideroblasts were present. Except in one patient, the myeloblasts did not exceed 5% of the marrow population. This patient (SK), with a marked thrombocytosis during the polycythemic phase, had been maintained on 2 mg busulfan daily. Her platelet count dropped suddenly to 54,000/cu mm; the drug was discontinued. However, during the subsequent week, a further drop occurred. The bone marrow aspirate at that stage was hypocellular. Although ring sideroblasts were still numerous, the majority of the cells were myelomonoblasts.

It should be pointed out that in the polycythemic bone marrow, examined 5–14 mo before the diagnosis of preleukemia, erythropoiesis was normoblastic and blasts were scarcely observed. The marrow iron was absent in most patients, and sideroblasts were not present. The serum iron which was below normal, rose only with the appearance of preleukemia (Table 1). Additional laboratory findings during the preleukemic phase such as vitamin B₁₂, its binding capacity, hemoglobin electrophoresis, percentage of A₂, and fetal hemoglobin were all normal. Leukocyte alkaline phosphatase stain remained positive. PAS stain of the bone marrow demonstrated positive granules in occasional normoblasts. Density separation of peripheral red blood cells, performed in one patient (MD), demonstrated a subpopulation with excessively high levels of hexokinase and glucose-6-phosphate dehydrogenase, similar to that reported in refractory anemia. In two patients, in whom folic acid and pyridoxine were tried, there was no response.

Cytogenetic investigation was not contributory to the recognition of the preleukemic phase, in contrast to “idiopathic” preleukemia. No consistent chromosomal aberrations were observed. A detailed study on the whole group of PV patients will be published as a separate communication.

During the leukemic phase, in spite of a marked proliferation of myelomonoblasts in the bone marrow, an overt leukemic picture appeared in the peripheral blood in only two patients.

At autopsy, extramedullary hematopoiesis was present in the spleen of all five patients and in the liver of four. The bone marrow was massively infiltrated by myelo- and myelomonoblasts, but in three patients sideroblasts were still demonstrable. The leukemic infiltrates of nonhematopoietic organs (lung in one
patient, kidney and lung in another, and kidney, adrenal and lymph nodes in the third) consisted of both normoblasts and myelomonoblasts.

Discussion

PV patients developing Di Guglielmo’s syndrome have been reported previously as isolated cases,9-17 conveying the impression of a rare evolution. The striking similarity between the preleukemic phase in our patients and those previously described would suggest that the latter were undergoing a typical preleukemia.

A similar preceding phase has been well documented in a third of the patients with myelomonocytic leukemia.18 Recently, evidence of aberrant sideroblastic erythropoiesis as a forerunner of acute leukemia has also been described in multiple myeloma,19 Hodgkin's disease,20 and macroglobulinemia.21 However, it has not been stressed that a preleukemic phase is a consistent, almost “obligatory” prelude to leukemia post PV.

Although the existence of sideroblasts has been briefly mentioned in PV, thrombocythemia, and myelofibrosis,6 their relationship to the leukemia after PV has not been stressed. Furthermore, there are no published data on a continuous follow up of PV patients, where the preleukemia could be demonstrated and followed from its incipience.

An underlying extramedullary hematopoiesis was present in all patients who terminated in acute leukemia. No correlation with the therapeutic dose of 32P and the leukemia could be found. Both these observations have recently been reported.22,23 The transformation into the preleukemic phase occurred very rapidly. Sideroblastic erythropoiesis coincided in most patients with altered myelopoiesis and thrombopoiesis, causing pancytopenia. This abrupt change, which except in one patient could not be attributed to recent myelosuppressive therapy, was particularly striking on the background of a disease characterized by erythrocytosis, leukocytosis, thrombocytosis, and the iron-deficient state.

In view of the aggressiveness and refractoriness of the subsequent acute leukemia, the early recognition of a preleukemic phase in PV might be of importance.

REFERENCES

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