Promyelocytic-Myelocytic Leukemia as a Terminal Manifestation of Chronic Granulocytic Leukemia

Report of a Case

By DAN BEN-ZEEV, STEVEN O. SCHWARTZ AND IRVING A. FRIEDMAN

Promyelocytic leukemia has been recognized as a distinct syndrome since 1957. Its features have included rapid deterioration, poor response to treatment, and bleeding.

This report concerns a patient who had chronic granulocytic leukemia, which after nine months assumed the appearance of the promyelocytic-myelocytic leukemia syndrome.

W. S., a Negro boy aged 15 years, in August 1962 experienced malaise and nontender intermittent swellings of the arms and legs associated with minor trauma. Four months later he was aware of transient anorexia and slight loss of weight. He came for an examination on March 20, 1963.

Pertinent observations were a 2 cm. subcutaneous swelling of the volar aspect of the left olecranon; lymph nodes were generally enlarged and soft; the liver was palpable 4 cm. below the right costal margin and was smooth and firm; the spleen was palpable to about 19 cm. below the left costal margin, extending into the pelvis.

Laboratory data concerning the blood findings are given in Table 1.

The marrow was hypercellular. The number of megakaryocytes was increased. The nucleated red blood cell to white blood cell ratio was about 1:20. Erythropoiesis was normoblastic. Granulopoietic elements showed "toxic" granules. There were large numbers of eosinophils and increased numbers of histiocytes.

Coagulation Studies

The platelet hematocrit value was 2 mm. (about 2 million platelets); bleeding time was 3 minutes; clotting time was 9 minutes. Clot retraction was satisfactory and the clot did not disintegrate on standing, but a red cell "fallout" did take place. Prothrombin consumption was 14 seconds and was corrected by inosin, indicating a defect of platelet function. The thromboelastograph reflected rapid disintegration after development of the clot (Fig. 1).

Therapy and Course

The patient was given urethane. During the next 12 weeks, new hematomas or ecchymoses were not observed. The spleen became smaller and was palpable 12 cm. below the left costal margin. The liver was no longer palpably enlarged. The white blood count

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This work was aided by a grant from the Illinois Division of the American Cancer Society, Inc.

First submitted July 15, 1965; accepted for publication Oct. 12, 1965.

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Table 1.—Representative Blood and Clinical Data

<table>
<thead>
<tr>
<th>Date</th>
<th>Hemoglobin (Gm. %)</th>
<th>White blood cells (per cu. mm.)</th>
<th>Polymorphs (%)</th>
<th>Bands (%)</th>
<th>Basophiles (%)</th>
<th>Eosinophiles (%)</th>
<th>Metamyelocytes (%)</th>
<th>Myelocytes (%)</th>
<th>Promyelocytes (%)</th>
<th>Blasts (%)</th>
<th>Lymphocytes (%)</th>
<th>Monocytes (%)</th>
<th>Platelets (per cu mm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/20/63</td>
<td>10.1</td>
<td>474,200</td>
<td>22</td>
<td>25</td>
<td>4</td>
<td>0</td>
<td>23</td>
<td>19</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>about 2,000,000</td>
</tr>
<tr>
<td>5/29/63</td>
<td>12.2</td>
<td>28,800</td>
<td>74</td>
<td>1</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>12</td>
<td>increased</td>
</tr>
<tr>
<td>6/26/63</td>
<td>12.2</td>
<td>358,400</td>
<td>25</td>
<td>29</td>
<td>6</td>
<td>3</td>
<td>22</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>increased</td>
</tr>
<tr>
<td>12/10/63</td>
<td>12.0</td>
<td>134,200</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>58</td>
<td>18</td>
<td>1</td>
<td>3</td>
<td>9</td>
<td>40,000</td>
</tr>
</tbody>
</table>


was also significantly reduced. By June 26, 1963, however, the spleen again became enlarged to 18 cm. below the left costal margin and subcutaneous hematomas reappeared on the extremities.

Urethane administration was discontinued. Cesium$^{137}$ radiation over the spleen was then instituted, and a total of 300 r was given over a period of 12 days. On July 29, 1963, busulfan therapy was started. During this period the patient felt well, gained weight, and additional hematomas did not appear. The size of the spleen was reduced, so that it was at that time only 6 cm. below the left costal margin. The hemoglobin levels hovered around 12.5 Gm.; the white blood cell count was between 10,000 and 30,000 cells/cu. mm.; and the differential counts showed that immature forms were greatly reduced.

Purpuric lesions reappeared on December 10, 1963. The posterior aspect of the right knee was swollen, apparently filled with blood. The spleen was now palpable 10 cm. below the left costal margin; the liver, 7 cm. below the right costal margin. The hemoglobin was 12.0 Gm. and the white blood cells were 134,200/cu. mm. Platelet count was 40,000 per cu. mm. The marrow was markedly hypercellular. The marrow was replaced by cells of the granulocytic series, almost all of which were abnormal-appearing promyelocytes and myelocytes. Megakaryocytes were absent.

The diagnosis of an acute promyelocytic-myelocytic phase of chronic granulocytic leukemia was made.

Proteinuria was 1 plus; there were 5 to 10 white blood cells per high power field, and many granular casts were seen. The BUN, total protein, thymol turbidity, gamma globulin, and alkaline phosphatase were normal. The uric acid was 13.7 mg/100 cc.

Coagulation Studies

On December 12, 1963, the platelet count was 17,000/cu. mm.; bleeding time was more than 10 minutes; clotting time, 12 minutes; prothrombin time, 14 seconds; prothrombin consumption was 14 seconds and was corrected with inosithin; thrombin time was normal, and fibrinogen was 129 mg. per cent. Fibrinolysis was not demonstrable. (A modification of Perkins and Rolfe’s method, which in turn was a modification of Ratnoff and Menzie’s method, was used.)

In spite of treatment with 6 mercaptopurine, ACTH, prednisone, epsilon amino caproic acid, 8 platelet transfusions, and 4 units of fresh whole blood, the course was downhill with continued periorbital, subconjunctival and severe gastrointestinal hemorrhage. The patient died on December 21, 1963.
Fig. 1A.—Thromboelastograph of patient’s blood (p) during chronic phase compared with a normal (n) and with a patient with thrombocythemia (t). Note “breaking off” phenomenon associated with leukocytosis (p).

Fig. 1B.—Thromboelastograph of another patient (p′) with chronic granulocytic leukemia compared with a normal (n′). “Breaking off” phenomenon associated with leukocytosis is again demonstrated.

**Autopsy**

Cervical and paratracheal lymph nodes were enlarged and almost completely replaced by leukemic cells resembling those described in the marrow. There were subpericardial and subendocardial petechiae. The lung parenchyma was infiltrated with foci of leukemic cells; subpleural hemorrhages were numerous. The liver weighed 2600 Gm. There was sinusoidal, parenchymal and portal invasion with leukemic cells. The spleen weighed 670 Gm, with diffuse replacement of the architecture by leukemic cells. The stomach contained bloody material and two small erosions near the lesser curvature. Hemorrhage into the medulla of the right kidney and aggregates of leukemic cells in the cortical portions of both kidneys were observed.

**Discussion**

About 58 cases of acute promyelocytic-myelocytic leukemia have been reported since 1949.†‡ Four of the patients lived more than six months after the establishment of diagnosis,§∥ and about 70 per cent died within one month of onset of the disease.
Fig. 2A.—Marrow during chronic phase. Note decreased ratio of NRBC to WBC and orderly maturation progression of granulocytic series (×2000).

In our case, the initial diagnosis was chronic granulocytic leukemia. This diagnosis is supported by the hematologic data as well as by clinical observation. The blood was typical of chronic granulocytic leukemia (see Table 1).

The marrow, with increased megakaryocytes, an erythroid to myeloid ratio of about 1:20, and the orderly progression of maturation of the myeloid elements confirmed this diagnosis (Fig. 2A).

Splenomegaly has been reported in several cases of promyelocytic-myelocytic leukemia but never as massive as in our case. The patient's response to treatment was also characteristic of chronic granulocytic leukemia (Fig. 3).

The initial coagulation studies did not reveal any evidence of fibrinogenopenia or fibrinolysis. The thromboelastograph showed disintegration of the clot, but the initial portion of the curve was normal, implying adequate fibrinogen. Correction of the slightly abnormal prothrombin time was done only with addition of Factor V. The clot retraction was satisfactory and the clot did not disintegrate on standing.

Chronic granulocytic leukemia frequently terminates with an acute exacerbation having the features of either acute myeloblastic or monoblastic leukemia. We have not seen chronic granulocytic leukemia that terminated with the features of acute promyelocytic-myelocytic leukemia syndrome; moreover, we could not find such a report. Bernard, Seligmann and Kvicala\(^\text{16}\) reported their experience of acute transition of chronic granulocytic leukemias in 1959. They had 28 cases, three terminating in a promyelocytic phase. However, in
Fig. 2B.—Marrow during acute phase. Note abnormal large white cells with large granules (×2000).

later report, Bernard, Lasneret, Chome, Levy and Boiron\textsuperscript{12} state: “In these cases the smear contains a large number of promyelocytes, but these differ from those of acute leukaemia, showing a closer similarity to normal promyelocytes, with finer and much less numerous granulations, always permitting examination of the nucleus. The histologic data do not allow differentiation of the two types of cell, but in the case of transformation of chronic myeloid leukaemia, the features are more polymorphous. The cytology and the context of a case make differentiation easy.” The promyelocytoid-myelocytoid cells in both the blood and marrow in our case were large with an immature nucleus containing nucleoli (Fig. 2B). The cytoplasm was more mature, with loss of basophilia, and it contained numerous large azurophilic granules. The granules were superimposed upon the nuclei of most cells, whereas in others the granules appeared only in the peripheral cytoplasm. They did not look like normal promyelocytes or myelocytes. The granulocytic series in both blood and marrow were composed almost entirely of these unusual cells. Few blasts were in either the blood or marrow.

Owing to the various locations of the granules, we would prefer to call this condition *promyelocytic-myelocytic leukemia* rather than either promyelocytic or myelocytic leukemia. Nevertheless, our material does not differ from the photomicrographs previously published under the description of acute promyelocytic leukemia. We believe, therefore, that the terminal morphologic as well as clinical course of our patient is identical with previously reported cases.
Fig. 3.—Graphic representation of patient’s course. Note rapid rise in promyelocytes and myelocytes at terminal stage while other forms remain at low levels. Blast forms never appeared in sizeable numbers during entire course and are omitted from the graph.
of acute promyelocytic leukemia. We were not able to demonstrate the presence of fibrinolysin in our case, although the fibrinogen was decreased. Rosenthal\textsuperscript{11} in his 17 cases was similarly unable to find evidence of fibrinolysin, although all of his patients had decreased fibrinogen. Patients in most of the other cases reported were described as having fibrinolysis; however, the presence of fibrinolysis was implied by the disintegration of the clots.

Our patient's death was secondary to gastrointestinal bleeding, which along with cerebral hemorrhage accounts for deaths of almost all patients with promyelocytic-myelocytic leukemia. The bleeding is probably due to the fibrinogenopenia along with the extreme thrombocytopenia. Speculation about the fibrinogenopenia and its relation to abnormal cells is tempting. We wonder whether the granules in these cells do produce or store enzymatic or other active substances that either prevent the production of fibrinogen or in some manner destroy the fibrinogen once it has been formed. By using fluorescent antibody techniques, Barnhart and Riddle\textsuperscript{17} have demonstrated the presence of profibrinolysin in the granules of eosinophils. It may well be that the strange granules in these cases contain some antifibrinogen substance. Liver failure seems unlikely as the cause of fibrinogenopenia.

Lastly, bleeding secondary to the consumption of coagulation components due to intravascular clotting has been recently reemphasized.\textsuperscript{13a,13b} In our patient the thrombocytopenia was due to marrow replacement. The prothrombin time was normal and the other coagulation components seemed adequate preterminally. There was no evidence of intravascular clotting on postmortem examination to explain the hypofibrinogenemia.

\textbf{Summary}

1. A case of promyelocytic-myelocytic leukemia is reported as the terminal phase of chronic granulocytic leukemia. We believe that this is the first such case reported.
2. The terminal phase of this case is compared with acute promyelocytic-myelocytic leukemia; the course and laboratory data appear almost identical.
3. The nature of the abnormal granules in the promyelocytoid-myelocytoid cells and their relation to the fibrinogenopenia incite speculation.

\textbf{Summario in Interlingua}

1. Es reportate un caso de leucemia promyelocytic-myelocytic como phase terminal de chronic leucemia granulocytic. Nos opina que isto es le prime tal caso unquam reportate.
2. Le phase terminal de iste caso es comparate con acute leucemia promyelocytic-myelocytic. Le curso e le datos laboratorial in le duo conditiones paresser quasi identic.
3. Le natura del granulos anormal in le cellulas promyelocytoid-myelocytoide e lor relation al fibrinogenopenia inspira speculationes.
ACKNOWLEDGMENTS

The authors express their indebtedness to Mr. Thomas Scanlon, of the Chicago Medical School, for the illustrations; and to Mrs. Helen Legere Gant and Mr. Frank Higgins for their technical assistance.

REFERENCES

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