Polycythemia Vera Terminating with Myeloblastic Leukemia

Correlation of Morphologic Findings with Leukocytic Phosphatase Studies

By Marjorie J. Williams, M.B., Ch.B. and Julius L. Mendel, Ph.D.

It is well recognized that there is some relationship between polycythemia vera and myelogenous leukemia. A number of reports of cases of polycythemia vera terminating with acute myeloblastic or chronic myelogenous leukemia have appeared in the literature. The authenticity of many of these has been challenged by Merskey and by Schwartz and Ehrlich, on the grounds that either polycythemia vera or myelogenous leukemia was not present or that the course of the disease had been disturbed by therapy, usually irradiation. Although some believe that certain cases of polycythemia vera terminate with myelogenous leukemia, others maintain that leukemia is usually only simulated and is a manifestation of myeloid metaplasia. A third theory is that some cases of chronic myelogenous leukemia pass through a polycythemic phase which masks, at least temporarily, the underlying disease and that this accounts for the apparent association of the two diseases. Merskey, following his exhaustive survey of the literature on this subject, came to the conclusion that a close link between polycythemia and myelogenous leukemia exists only if aleukemic myelosis (chronic nonleukemic myelosis) is accepted as a form of leukemia. Several workers have expressed the opinion that this last entity is leukemic although it tends to run a slower course. Dameshek, in his editorial on the myeloproliferative syndrome, has done much to reconcile these different views. He theorizes that polycythemia vera, chronic myelogenous leukemia, and various other myeloproliferative disorders may represent variable responses to an unknown stimulatory factor. Acceptance of this theory makes the transition from one disease to another in this group of disorders easier to comprehend. This viewpoint has recently been endorsed by Hutt and his associates, who have emphasized that they consider myelofibrosis to be a proliferative or neoplastic process of the same order as leukemia.

The controversy regarding the incidence of myelogenous leukemia in polycythemia vera has originated from differing opinions based mainly on morphologic studies. Valentine and his associates have recently studied quantitatively the phosphatase activity and the glycogen and histamine content of leukocytes in various hematologic disorders. They found that the leukocytic alkaline phosphatase in polycythemia vera with leukocytic aberrations was elevated above the normal range, while the acid phosphatase remained within normal limits. In both acute leukemia and chronic myelogenous leukemia, the leukocytic phosphatase levels were also characteristically altered. In both instances the leukocytic alkaline phosphatase level was depressed, but the acid phosphatase...
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was lowered only in acute leukemia and was normal or slightly elevated in chronic myelogenous leukemia. Leukocytic histamine was increased in both polycythemia vera with marked leukocytosis and chronic myelogenous leukemia, but glycogen was increased only in the former disease. As a result of this work, these authors concluded that, although the leukocytes in these two diseases show some kinship (elevation of histamine content), they are not identical.

For more than two and a half years, we have had the opportunity of studying an individual suffering from atypical polycythemia vera with marked leukocytosis and, terminally, from acute myeloblastic leukemia. During the last nine months of the patient's life, studies were carried out on the leukocytic phosphatases. The earlier phosphatase estimations suggested a leukemoid reaction associated with polycythemia, but concurrent morphologic studies favored the diagnosis of chronic myelogenous leukemia. Terminally a diagnosis of myeloblastic leukemia was made by morphologic studies on both peripheral blood and autopsy material. Phosphatase determinations carried out at this time were in accord with this diagnosis.

REPORT OF CASE

A 57 year old white man first entered this hospital in May 1950. He stated that he had always been in excellent health until January of that year, at which time he had a severe "chest cold." Following this he felt weak with some shortness of breath on exertion and these symptoms persisted. Physical examination revealed nothing of note apart from moderately severe pyorrhea.

The pertinent admission laboratory findings were: RBC 5.14 million per cu. mm., hemoglobin 16.0 Gm. per cent (Haden-Hauser), hematocrit 56 (elevated considering the RBC, but typical during this admission), corrected sedimentation rate 11 (Wintrobe), WBC 26,000 per cu. mm. with 5 per cent myelocytes, 81 percent polymorphonuclear leucocytes, 13 per cent lymphocytes, and 1 per cent eosinophila; trace of albumin in the urine; blood uric acid 4.0 mg. per cent, blood urea nitrogen 26.0 mg. per cent.

Sternal marrow was aspirated and showed myeloid hyperplasia with no evidence of leukemia. A differential count on 600 nucleated cells showed the following distribution: myeloblasts 1.5 per cent, promyelocytes 5.0 per cent, myelocytes 17.6 per cent, metamyelocytes 30.5 per cent, polymorphonuclear leucocytes 27.3 per cent, eosinophils 0.3 per cent, lymphocytes 1.3 per cent, monocytes 0.5 per cent, megakaryocytes 0.5 per cent, pronormoblasts 1.5 per cent, and normoblasts 14.0 per cent.

As it was considered that the leukocytosis might possibly be due to pyorrhea, the patient's teeth were all extracted. No change in the peripheral blood was observed following this procedure. The patient was discharged in August 1950.

Three months later, in November 1950, he re-entered the hospital for a few days for fitting of dentures. Examination of peripheral blood at this time showed: RBC 5.39 million per cu. mm., hemoglobin 16.5 Gm. per cent (Haden-Hauser), hematocrit 49, WBC 23,900 per cu. mm. with 62 per cent polymorphonuclear leucocytes, 35 per cent lymphocytes, and 3 per cent monocytes.

In June 1952, he was readmitted complaining that for the previous four weeks he had noticed a painful mass in the left upper quadrant of his abdomen. Apart from this, he had felt fairly well since his discharge in November 1950. Physical examination disclosed a ruddy-complexioned man with slightly engorged mucous membranes. The spleen was enlarged, firm, and tender and reached almost to the iliac crest. The liver margin extended two fingerbreadths below the right costal margin.

At this time the laboratory findings were as follows: RBC 7.44 million per cu. mm., hemoglobin 17.5 Gm. per cent (Haden-Hauser), hematocrit 60, WBC 94,500 per cu. mm. with 52 per cent polymorphonuclear leucocytes, 4.0 per cent myelocytes, 18 per cent lymphocytes, and 26 per cent monocytes, with 5 normoblasts per 100 leucocytes. The apparent
blood volume, estimated using Evans' blue,\textsuperscript{17} was 9205 cc. (expected blood volume 5525 cc.) and the apparent plasma volume was 3590 cc. (expected plasma volume 2925 cc). Urinalysis showed 4 plus albuminuria and a few red blood cells. Liver function studies with the exception of the cephalin flocculation test were within normal limits. Smears prepared from aspirated sternal marrow showed: myeloblasts 7.2 per cent, promyelocytes 12.0 per cent, neutrophilic myelocytes 13.2 per cent, eosinophilic myelocytes 0.2 per cent, metamyelocytes 19.8 per cent, neutrophilic polymorphonuclear leukocytes 23.2 per cent, lymphocytes 3.8 per cent, monocytes 2.4 per cent, plasma cells 0.8 per cent, pronormoblasts 0.8 per cent, early normoblasts 2.4 per cent, polychromatic normoblasts 8.4 per cent, and orthochromatic normoblasts 5.8 per cent. The granulocyte:erythrocyte ratio was 4.6:1.

On the basis of both the clinical findings and the laboratory studies a diagnosis of polycythemia vera with leukemoid reaction was made. It was decided to treat the patient by means of venesections combined with a low-iron diet. During the succeeding two months, 4000 cc. of blood were withdrawn from the patient. At the end of this time, examination of the peripheral blood showed: RBC 4.94 million per cu. mm., hemoglobin 13.5 Gm. per cent (Haden-Hauser), hematocrit 43, WBC 76,000 per cu. mm. with a few myeloblasts, myelocytes, and normoblasts.

From August 1952 until March 1953, the patient was studied at fairly frequent intervals. The spleen and the liver remained enlarged and he complained of episodes of acute pain in the region of the spleen. The leukocytosis gradually increased from 76,000 per cu. mm. to 96,000 per cu. mm. with the blast forms rising from 5 per cent to 22 per cent. During this period the possible superimposition of myelogenous leukemia was considered.

In March 1953, he was admitted to the hospital with copious nose bleeding. His peripheral blood showed: RBC 3.59 million per cu. mm., hemoglobin 7.0 Gm. per cent (Haden-Hauser), hematocrit 43, WBC 660,000 per cu. mm. with 80 per cent blast forms, platelets 284,000 per cu. mm. His nose was packed and he was given two blood transfusions. Shortly thereafter, cardiac failure developed and he expired three days later.

AUTOPSY FINDINGS

Gross Findings

The liver was enlarged, weighing 3350 Gm. The parenchyma was a uniform pale brown color and bulged above the cut surface.

The spleen weighed 3300 gm. Its capsule was thickened and its pulp firm and dark crimson in color. Beneath the capsule were several small recent infarcts. Malpighian corpuscles could not be identified on gross examination. At the hilus was an accessory spleen weighing 30 Gm. Its pulp had a purple hue, in contrast to the dark crimson of the main spleen, and the malpighian corpuscles could be identified readily.

The fat surrounding the kidneys, the adrenals, and the renal pelves was a dusky reddish color and was abnormally firm in consistency.

The bone marrow was examined in the femur, lumbar vertebrae, and multiple ribs. In all areas it was a reddish-grey color with a pulpy consistency.

Microscopic Findings

In all the organs, the blood vessels were filled with blast cells. Similar cells infiltrated the pulp of both the main and the accessory spleens, the portal triads in the liver, both kidneys, and the mesenteric and mediastinal lymph nodes. The normal architecture was entirely obliterated in the main spleen but was partially preserved in the accessory organ.

In the sinusoids of the liver, in the pulp of the main spleen, and in the periportal and periadrenal fat, there were foci of extramedullary hematopoiesis. In these areas, normoblasts, megakaryocytes, blast forms, and myelocytes could be identified, but in all these areas, the blast cells were predominant.

Marrow from the femur, the vertebrae, and the ribs was examined. In all three sites it was markedly hypercellular with innumerable myeloblasts. A number of discrete foci of erythropoiesis were also identified and a moderate number of megakaryocytes were present.
TABLE 1.—Correlation of Phosphatase Estimations with Hematologic Studies

<table>
<thead>
<tr>
<th>Date</th>
<th>Phosphatase (mg P/10^8 leukocytes/hr)</th>
<th>Leukocyte count</th>
<th>Blasts (%)</th>
<th>Erythrocyte count (10^9)</th>
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<tr>
<td></td>
<td>Alkaline</td>
<td>Acid</td>
<td></td>
<td></td>
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<tr>
<td>June 1952</td>
<td>78.1</td>
<td>36.8</td>
<td>94,500</td>
<td>0</td>
</tr>
<tr>
<td>August 1952*</td>
<td>102.4</td>
<td>19.4</td>
<td>76,000</td>
<td>5</td>
</tr>
<tr>
<td>September 1952</td>
<td>80.0</td>
<td>18.9</td>
<td>74,000</td>
<td>8</td>
</tr>
<tr>
<td>November 1952</td>
<td>57.0</td>
<td>17.2</td>
<td>68,000</td>
<td>12</td>
</tr>
<tr>
<td>January 1953</td>
<td>53.9</td>
<td>13.9</td>
<td>112,000</td>
<td>25</td>
</tr>
<tr>
<td>February 1953</td>
<td>39.4</td>
<td>14.9</td>
<td>154,000</td>
<td>42</td>
</tr>
<tr>
<td>March 1953</td>
<td>8.2</td>
<td>10.3</td>
<td>660,000</td>
<td>81</td>
</tr>
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</table>

Normal Range: 13.4–58.0 for normal alkaline and 13.7 to 36.8 for normal acid activity.

* Venesections carried out during this period.

Autopsy Diagnosis
Myeloblastic leukemia with widespread extra-medullary hematopoiesis.

Leukocyte Phosphatase Studies

Method
The method employed in the determination of the phosphatase activity of the leukocytes was that of Valentine and Beck. Activity was calculated as mg. of phosphorus liberated by 10^8 leukocytes per hour. Valentine and Beck have suggested a range of from 13.4 to 58.0 for normal alkaline activity and 13.7 to 36.8 for normal acid activity.

Results
The first leukocytic phosphatase studies, performed in June 1952, showed an elevated alkaline activity together with a normal acid activity. These findings are compatible with polycythemia vera with marked leukocytosis. This pattern continued for approximately three months and then in November 1952 the alkaline phosphatase activity began to drop. It fell first into the normal range, and terminally was below normal. The acid phosphatase also began to fall, though not so precipitously as the alkaline, and it too was terminally below normal. The final pattern of low alkaline and low acid phosphatase activities was compatible with acute leukemia (see table 1).

Discussion
In polycythemia vera, there is a panmyelopathy, but in some cases leukocytosis and thrombocytosis are more conspicuous than in others. In the case under discussion, leukocytosis was always an unusually prominent feature and toward the latter part of the course of the disease, the diagnosis of myelogenous leukemia was frequently considered. However, the phosphatase activities of the leukocytes during the earlier part of this period were suggestive of polycythemia rather than leukemia. Valentine and his associates have advanced the idea that perhaps there may be some cases of polycythemia vera in which hyperplasia of the granulocytic series is the predominant feature. This speculation has arisen from their
biochemical studies on three individuals with leukocytosis and some myeloid immaturity but with no definite evidence of current or past polycythemia. The leukocytic phosphatase activities in these cases were similar to those found in polycythemia vera with leukocytosis. Our case may be considered to have been situated midway between these cases of Valentine and the classical cases of polycythemia vera. Although our patient at one period satisfied all the criteria for the diagnosis of true polycythemia, he did not do so throughout his course and hyperplasia of the granulocytic elements was conspicuous at all times. Earlier in the course, the picture was somewhat suggestive of chronic nonleukemic myelosis (aleukemic myelosis), and in this connection it is of interest to recall that Merskey has demonstrated a relationship between this disease and polycythemia vera.

The diagnosis of terminal myeloblastic leukemia was based on morphologic findings, and the final phosphatase studies were compatible with this diagnosis. There was no biochemical evidence (based on phosphatase estimations) of a transitional phase in which chronic myelogenous leukemia was present although morphologic studies suggested it. It will be seen from table 1 that during the last four months of the patient’s illness, the leukocytic phosphatases fell from polycythemic levels through the normal range to that associated with acute leukemia. This change could well be attributed to dilution of the more mature granulocytes by myeloblasts as the biochemical changes correlate fairly well with the increasing number of myeloblasts in the peripheral blood. It has been shown by Wachstein that blast cells are poor in alkaline phosphatase. Thus, the mature granulocytes and perhaps the myelocytes may have retained their polycythemic characteristics and this may have been obscured by the terminal predominance of myeloblasts.

The phosphatase studies on the leukocytes in this case suggest that in certain cases of polycythemia vera, a leukemoid reaction may easily be confused with chronic myelogenous leukemia. It is suggested that it might be of interest for others to make similar studies of the leukocytic enzymes in cases of polycythemia with marked leukocytosis. Although some cases of polycythemia vera are undoubtedly complicated by leukemia, it is possible that a more exact idea of the incidence of such cases might be obtained by widespread application of biochemical studies. We suggest that perhaps some of the cases of polycythemia reported to have been associated with chronic myelogenous leukemia might have been considered to have had a leukemoid reaction had biochemical studies been carried out.

Summary

A case of somewhat atypical polycythemia vera with marked leukocytosis and terminal myeloblastic leukemia has been studied hematologically and biochemically. The biochemical studies consisted of repeated estimations of the leukocytic alkaline and acid phosphatase activities during the last nine months of the patient’s life. These studies suggested that, except during the terminal myeloblastic leukemia, there was a leukemoid reaction rather than chronic myelogenous leukemia associated with polycythemia. The significance of these findings is
briefly discussed and it is suggested that the widespread application of similar biochemical studies to cases of polycythemia vera with marked leukocytosis might be of value in helping to determine the true incidence of myelogenous leukemia in this disease.

**SUMMARIO IN INTERLINGUA**

Un caso alique atypic de polycythemia vera con marcate leucocytosis e terminal leucemia myeloblastic ha essite studiate hematologica- e biochimicamente. Le studios biochimic-restritsgite al ultime tsove metsses del vita del patietste-consisteva its repetit.e evalutatiotses del stato del leucocyt-ic phosphatases e alcalins e acide. 1st-c studios rendeva probabile, excepte durante le leucemia myeloblastic terminal, que ii se tractava de un reaction leucemoide plus tosto que del chronic leucemia myelogene que es associate con polycythemia. Le signification de iste constatationes es brevemente discutite, e le proposition es avatstiate que le application extetssive de simile studios biochimic a casos de polycythemia vera con marcate leucocytosis poterea adjutar importantemente a determinar le ver frequentia de leucemia myelogene in iste morbo.

**REFERENCES**


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