Myeloproliferative Syndrome with Leukemia Preceding Polycythemia Vera: A Case Report

By Paul Calabresi

ASSOCIATED PROLIFERATION of the various hematologic elements in the marrow, although recognized for some time, has recently been the subject of renewed interest. A close relationship between myelofibrosis and the leukoerythroblastic conditions was demonstrated by Vaughan and Harrison in 1939. They suggested that an unknown stimulus acting on the primitive mesenchymal reticulum cell may be responsible for the production of this closely related group of diseases which Dameshek has called "myeloproliferative disorders."

In this background the intimate association of polycythemia vera and myelogenous leukemia is readily understood. Between the relatively pure clinical pictures at each extreme there occur varying degrees of mixed or transitional forms which Martin and Bayrd have classified into different subtypes of "erythroleukemia." It would appear that conversion of polycythemia vera into myelogenous leukemia or the simultaneous presence of the two is by far the most common course of events. The following case is of interest because a picture of chronic granulocytic leukemia preceded the appearance of polycythemia vera.

CASE REPORT

First Admission (11/11/36–12/20/36): A white male, 18 years of age (R.D.—Hospital No. 94222), was admitted to the University Hospital on November 11, 1936, complaining of pain in his left side on deep breathing. This pain was of 3 days' duration. In the spring of 1936 two separate minor surgical procedures had been performed without complication at another hospital. The patient had always been well and worked regularly on his brother's farm until 3 days before admission, although he admitted, in retrospect, that he had been aware of a dragging sensation in his abdomen for one month. On November 8 he awoke with sharp, stinging pain in his left shoulder, radiating down the left side of his chest and abdomen to the level of the iliac crest. The pain was noticed only on deep breathing or coughing. During the next 3 days he experienced marked dyspnea and palpitation on exertion, a dry nonproductive cough and profuse night sweats. Mild headaches, some stiffness of the neck, slight ankle swelling and occasional leg cramps had also been present. The symptoms became increasingly worse, the family physician was called and the patient was referred to the hospital. The remainder of the history was noncontributory.

On physical examination he appeared well nourished but acutely ill. The pulse rate was 100/min. and regular, blood pressure 118/80 mm. Hg., temperature 101 F., and respirations 28/min. He weighed 165 pounds and there had been no recent change. His complexion was sallow. There was congestion of the retinal veins and several small hemorrhages were observed in both fundi. Marked cervical, axillary and inguinal lymphadenopathy was present. There was tenderness to pressure over the lower sternum. Elevation of the diaphragms, increased breath sounds and a loud apical systolic murmur were the only sig-

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significant chest findings. The liver was palpable 5 cm. below the right costal margin, and a huge spleen extending 6 cm. below the left iliac crest and occupying most of the left abdomen could be outlined. This was firm and slightly tender.

Laboratory findings of the bone marrow and peripheral blood appear in Table 1 and Figure 1. Despite the clinical picture, it was the impression of the hematologist that these were suggestive of chronic myeloid leukemia. Bleeding and coagulation times were normal. The NPN was 30 mg./100 ml., the urine contained a trace of albumin and the specific gravity was 1.025. An inguinal lymph node was removed. The histologic sections (Figure 2) revealed complete loss of architecture with absence of the germinal centers and wide-spread leukemic infiltration, predominantly by myelocytes. Fibrosis and diffuse endothelial proliferation were prominent. Although the possibility of monocytic leukemia was suggested, the final impression was myelocytic leukemia.

The patient was treated with Fowler's solution, 10 drops 3 times a day. After a stormy, febrile course characterized by hemorrhagic tendencies and pleuropericardial friction rubs, he was discharged still acutely ill.

Second Admission (1/6/37-2/5/37): He returned with considerable dyspnea and occasional cough with blood-streaked sputum. There had been marked sweating with pruritus and epistaxis. Retinal edema and exudates were present, as well as marked cardiac enlargement and anasarca. The basal metabolic rate was +20, serum albumin 3.1 Gm./100 ml. and globulin 3.7 Gm./100 ml. Abdominal paracentesis (1500 cc. of clear amber fluid) greatly relieved the patient's dyspnea. He was subsequently given a transfusion of 400 ml. of whole blood and four 25 r doses of total body radiation. Because of 49% eosinophilia at this time the possibilities of Hodgkin's disease and eosinophilic leukemia were considered.

For the next 10 months the patient was followed in the out-patient clinic and showed remarkable improvement. However, generalized lymphadenopathy and hepatosplenomegaly persisted. Following a brief admission during which he appeared generally well, he was not seen again for 2 years.

**Table 1.—(W.U.H.—94222) Hematologic Data**

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<th>Date</th>
<th>Peripheral Blood</th>
<th>Sternal Bone Marrow*</th>
<th>Peripheral Blood</th>
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<th>Eosinophils</th>
<th>Eosinophilic Myelocytes</th>
<th>Basophils</th>
<th>Blasts</th>
<th>Undifferentiated Primitive Cells</th>
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<td>7.4</td>
<td>2.0</td>
<td>0.2</td>
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</tr>
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*Both marrow specimens were markedly hypercellular with evident encroachment of the fat areas.*
Fourth Admission (10/30/39-12/13/39): Left lower chest pain prompted his return. He stated that he had been able to do light work until about 3 months before admission when his abdomen began to enlarge and became rather firm once again. Precordial pain was present on reclining and his right leg had been swollen for one week. There had been no weight change. Physical examination at this time revealed plethoric facies, cyanosis of the lips and injection of the mucous membranes. Blood pressure was 102/64 mm. Hg, temperature 102.6 F., respiratory and pulse rates within normal limits. The optic fundi, fields and blind spots were reported as normal. A few small lymph nodes were felt in the cervical and axillary regions. The sternum was tender to palpation. The spleen now extended to the inguinal region (24 cm. below the costal margin) and across the midline of the abdomen. The liver was palpable 10 cm. below the costal margin and both organs were firm, smooth and tender to palpation. Varicose veins, small excoriations and skin pigmentation were present in both lower extremities. Basal metabolic rate was +59. Skull roentgenograms were normal and chest films showed clear lung fields. He now presented a polycythemic blood picture (fig. 1, table 1), and the total red cell mass of 129 ml./Kg. represented an absolute increase of over threefold. His total blood volume by the method of Gibson et al.24 was +135% of the predicted normal. A diagnosis of polycythemia vera was made and, after a single phlebotomy of 500 ml., he was discharged with instructions to take Fowler’s solution.

After a peak erythrocyte count of 9.19 million both leukocyte and erythrocyte counts
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Fig. 2.—(W.U.H.—94222; Lab. No. 25858). Inguinal node biopsy performed on 11/19/36. Leukemic infiltration and loss of architecture. X 150.

decreased to low normal levels with 31% eosinophilia. In the course of the next 6 years he was followed in the out-patient clinic and admitted to the hospital on 3 occasions. Except for frequent minor hemorrhages and dull frontal headaches, he felt well and worked hard. Plethora, hepatosplenomegaly and lymphadenopathy persisted. The blood picture was consistent with chronic granulocytic leukemia and polycythemia vera. He was treated with phlebotomies and radiation to the spleen (fig. 1).

Eighth Admission (9/27/46–10/11/46): The patient stated that he was worse than ever before and that radiation therapy on the last admission had failed to help his condition. He had abdominal pain on the right side now and his abdomen was swollen more than ever. Ankle edema and dyspnea on exertion were again present and, 3 weeks prior to admission, he had experienced migratory pains in the right knee, left elbow and both ankles. The joints had been red, hot and tender. A serum uric acid was 7.6 mg./100 ml. Plethora and marked generalized lymphadenopathy were noted. The liver and spleen were palpable at the level of the iliac crest. The question of splenectomy was raised but it was felt that the hazards outweighed the possible benefits. A total of 2,000 ml. of blood was removed and the patient’s symptoms improved.

Final Admission (11/22/46–11/30/46): He returned determined to have splenectomy, threatening to commit suicide if it were refused. There had been increasing abdominal pain and progressive enlargement of the liver and spleen (fig. 3). The patient stated that he was no longer able to walk because of dyspnea, ankle swelling and disturbance of balance by the tremendous abdominal masses. Physical findings were essentially unchanged. Because of the patient’s insistence and the lack of therapeutic alternative, splenectomy was finally attempted. An hour after the beginning of the procedure, during ligation of the many perisplenic adhesions, the patient expired. His death occurred 10 years after the first admission.

Autopsy Findings (No. 46–234): A post-mortem examination was performed 3 hours after death. The pericardium was densely adherent to a heart weighing 460 Gm. with moderate left ventricular hypertrophy but no valvular lesions. There was increased fibrosis with
leukemic infiltration of the epicardium. The coronary arteries were patent. The lungs were congested, but there were no demonstrable emboli or thrombi. The spleen weighed 3370 Gm. and the surface was covered with adhesions and irregularities. Microscopically there was complete disappearance of lymphoid follicles and the pulp was crowded with both mature and immature leukocytes, mostly myelocytes, band cells and lymphocytes. Normoblasts were also present and many siderotic nodules were observed (fig. 4). Similar infiltrations were described in the mediastinal and mesenteric lymph nodes and in the liver which weighed 6,020 Gm. (fig. 4). The bone marrow revealed hyperplasia of both the erythrocytic and granulocytic series, the latter being most conspicuous. In the pelvis of the left kidney a few small, rounded calculi (1 mm. across) of a deep golden color were observed. The final impression (based upon both clinical history and anatomic findings) was co-existence of chronic myelogenous leukemia and polycythemia vera. The precise cause of death was not determined.

Summary: A youth of 18 years first presented with a picture of leukemia, and normal erythrocyte and hemoglobin values. He was treated with Fowler's solution, and a remission characterized by eosinophilia ensued. He subsequently received radiation therapy and was fairly well for three years. At this time he had developed a picture of polycythemia vera with recurrence of leukocytosis with immature forms. For the next six years, while variously treated with Fowler's solution, phlebotomies and radiation, he enjoyed a relatively benign course and the picture fluctuated between chronic myelogenous leukemia and polycythemia vera. Finally the symptoms became increasingly worse until they were no longer relieved by radiation. Splenomegaly, which had always been massive, became totally incapacitating and splenectomy was attempted. Cardiac arrest developed during the procedure and the patient expired approximately ten years after the onset of his dis-
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Fig. 4.—(W.U.H.—94222; autopsy No. 46:234.) Microscopic appearance of the liver (left) and spleen (right) at post-mortem examination showing leukemic infiltration. Note also fibrosiderotic nodule of spleen and leukemic cells in hepatic blood vessel. X 150.

ease. Post-mortem examination was consistent with the diagnosis of both chronic myelogenous leukemia and polycythemia vera.

CASE DISCUSSION

There seems to be no doubt that the case presented is one of chronic erythroleukemia in which a pure picture of granulocytic leukemia preceded the erythremic component for one to three years. Presumably the patient was in good health six months before his first admission when he was subjected to two elective surgical procedures without ill effect. The relatively acute mode of onset, the young age of the patient and the entire clinical picture were completely consistent with leukemia and most uncharacteristic of polycythemia vera. The laboratory findings, even in the presence of a certain amount of dehydration (the patient was febrile, had perspired profusely and had a urinary specific gravity of 1.025), showed no elevation of erythrocyte count or hemoglobin. A total of eight complete blood counts, all with similar results, were reported by two hospital laboratories in the three weeks preceding therapy. Bone marrow aspiration and lymph node biopsy substantiated the diagnosis.

It is impossible to determine precisely when the erythremic disorder appeared because the patient was not seen for a two-year interval preceding his 1939 admission. He was not polycythemic in December 1937, 10 months after the first course of radiation therapy and one year after medication with Fowler’s solution had been discontinued. When he reappeared in October 1939, he presented a full blown picture of polycythemia vera and indicated
that the symptoms which brought about this admission had been present for three months. The various therapeutic measures subsequently employed were undoubtedly responsible for oscillations of the blood counts (fig. 1). It appears reasonable to assume that both entities were present until death.

The diffuse nature of the proliferative process in this case is worth emphasizing. In addition to generalized lymph node involvement and massive hepatosplenomegaly the patient had, at various times, significant elevation of monocytes (up to 28.4%), platelets, eosinophils and basophils (up to 4%). The presence of increased numbers of these elements in chronic myelogenous leukemia, polycythemia vera, or combinations of the two is known to occur.8,13 This, presumably, is more evidence for the multidirectional potential of the disease stimulus.

A final point worthy of mention is the probable presence of gout in this patient. The migratory joint symptoms and signs, together with a serum uric acid level of 7.6 mg./100 ml. on the eighth admission, are very suggestive despite lack of roentgenographic evidence. The description of the renal calculi found at autopsy leaves little doubt that these were uric acid stones.21 An increased occurrence of this complication has been reported, particularly in cases showing combined proliferation of leukemic and erythremic elements.22,23

**Review of the Literature**

Although it has been stated that in chronic erythroleukemia the leukemic phase may supplant, coexist with or precede the erythrocytic abnormality,9 well documented examples of the latter situation are certainly sparse in the literature.

In 1908 Winter23 reported a patient who, in 1904, was said to show a clinical and hematologic picture of chronic myelogenous leukemia and later presented with polycythemia. Although the first reported blood count was in 1904, the preceding history leaves little doubt that in 1901 or 1902 the patient had polycythemia vera. When one recalls that, although sporadic cases had been described prior to this date, Osler's original report9 was published in 1903, it is easy to see why the patient's condition was not recognized. In the past this case has been misinterpreted by several writers. It is interesting that Winter himself clearly states: "It is very likely that polycythemia existed at least 6 years ago." Other authors have specifically taken this view11 or doubted the existence of leukemia entirely.13

Parkes Weber28 summarized a case observed by J. H. Drysdale and G. Evans in 1920. The initial erythrocyte count was 2,016,000, and the leukocyte count 856,000 with 30.2 per cent myelocytes. Radiation therapy was administered, and four months later the erythrocytes had risen to 8,704,000 and the leukocytes were 156,000. Two weeks after this the erythrocyte count was 5,760,000 and the leukocyte count was 90,000.

In 1922 Ghiron22 studied a case of erythroleukemia and this report was subsequently abstracted in another journal.29 Unfortunately the translated abstract29 conveys the impression that erythroleukemia and polycythemia developed after a period of typical leukemia. Review of the original article...
reveals that erythroleukemia existed when the patient was first seen and, although she was anemic at this time, the history suggests that she previously had been polycytemic. Eight months after this examination the erythrocyte count rose to 7.2 million and once more the skin became “flaming red.”

Evans mentions having observed a patient in 1926, who at one time had an R.B.C. of 2.7 million and a W.B.C. of 460,000. Five months after the start of x-ray treatment the erythrocyte count was 6.4 million and the leukocyte count was 20,000.

Wintrobe in the second (1946) and subsequent editions of his book records a case of what appeared to be classical chronic myelocytic leukemia, which after roentgen therapy developed a typical picture of erythemia. The red cell count at this time was 9.45 million, the hemoglobin 19.5 Gm., the volume packed red cells 66 ml., and 29,600 leukocytes with 4 per cent myelocytes were present. Eight months later the spleen was greatly enlarged, the leukocyte count increased to 212,000 and anemia developed.

In 1951, DeBacker and Lawrence reported a patient (case VII) who was diagnosed as leukemia in 1944 and subsequently treated with Fowler’s solution and x-ray. Blood studies at this time are not given. The patient was first seen by the authors in 1945, at which time the erythrocyte count was 5.62 million, hemoglobin 16 Gm. and the leukocyte count 70,000 with 2 per cent myelocytes. The subsequent course on P32 therapy showed vacillation between chronic myelogenous leukemia and polycythemia vera.

**Comment**

The difficulties involved in accurately determining the number of cases of erythroleukemia reported have been ascribed to their rarity and nosologic differences. This applies even more so to the particular situation where the leukemic component precedes the erythremic derangement. Moreover, certain cases of this type are either briefly alluded to or not studied entirely by the same observers. An attempt has been made to gather all the more frequently mentioned examples of this variant.

To determine incontrovertably the presence of this unusual sequence of events the case should fulfill the following criteria: (1) evidence that polycythemia vera has not previously existed; (2) laboratory and clinical evidence establishing presence of the leukemic picture without polycythemia vera; (3) absence of previous medication which may in some way mask the polycythemic status (phlebotomy, Fowler’s solution, radiation, etc.); and (4) the advent, at a later date, of clinical and laboratory evidence of polycythemia vera.

The case presented appears to meet these requirements. Of the ones previously reported in the literature, Winter’s case and Ghiron’s have apparently been misinterpreted. The remaining are all very suggestive, even though, at least in their presentation, some do not completely fulfill the criteria above.

In all of these cases a common factor appears to be present: the picture of polycythemia developed after radiation therapy was administered for leukemia. The reverse situation has received much attention in the literature.
If one assumes that these mixed situations represent multidirectional neoplastic proliferation of the totipotential primitive cell, it might be possible to postulate an externally induced modification of the process. However it seems premature and unfounded to belabor the implications of these limited observations. For the time being the significance of these cases should be to strengthen the concept of unity and inter-relation of the various myeloproliferative diseases and to support the belief that transformation to erythroleukemia may occur from either direction.

SUMMARY

A case of chronic erythroleukemia is reported in which a picture of chronic granulocytic leukemia preceded the erythremic proliferation by one to three years. The patient was followed throughout his entire 10-year course and the clinical impressions were confirmed initially by biopsy and eventually at necropsy.

The rare examples of this occurrence usually cited in the literature are reviewed and briefly discussed. In every case the development of erythremia was preceded by radiation therapy for the leukemic dyscrasia.

A set of criteria for evaluating such cases in order to provide definite evidence for this sequence of events is suggested.

The transformation of chronic granulocytic leukemia into polycythemia vera or chronic erythroleukemia lends further support to the concept of fundamental similarity and close inter-relation of these myeloproliferative disorders.

SUMMARIO IN INTERLINGUA

Es reportate un caso de erythroleucemia chronic in que le aspecto de chronic leucemia granulocytic precedeva proliferation erythremic per inter un e tres annos. Le patiente remaneva sub observation durante le complete decennio del curso de su morbo. Le impressiones clinic esseva confirmate per biopsias e finalmente per le necropsia.

Le pauco numerose exemplos de iste occurrentia que es usualmente citate in le litteratura es passate in revista e discitite brevemente. In omne casos le disveloppament de erythremia esseva precedite per therapia radiational pro le dyscrasia leucemic.

Es proponite un serie de criterios pro le evaluation del definite sequentia de evenimentos que es characteristic de tal casos.

Le transformation de chronic leucemia granulocytic in polycythemia vera o in erythroleucemia chronic supporta additionalmente le conception que iste disordines myeloproliferative es fundamentalmente simile e intimeemente interrelationate.

ACKNOWLEDGMENT

Drs. William S. Middleton and Ovid O. Meyer studied and treated this patient throughout his course. Dr. D. Murray Angevine reviewed the tissue findings. Their interest in this case is reflected by the completeness of their observations. I am indebted for their permission to report these findings and gratefully acknowledge their advice and criticism in the preparation of this manuscript.
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