Unique Sequence of Pernicious Anemia, Polycythemia, and Acute Leukemia

By Chris J. D. Zarafonetis, Robert L. Overman and Lyndall Molthan

Pernicious anemia, polycythemia vera, and acute myeloblastic leukemia occur with sufficient frequency that the occurrence of one or the other is not in itself remarkable. Oddly enough, however, coexistence of pernicious anemia and polycythemia, or of pernicious anemia and acute myeloblastic leukemia, is extremely rare. Wintrobe notes only four instances in which pernicious anemia preceded the onset of acute myeloblastic leukemia. Polycythemia following pernicious anemia is of equal rarity. On the other hand, the emergence of acute leukemia in cases of polycythemia, while uncommon, is not as rare as the foregoing associations. As far as can be determined from the literature, however, the occurrence of all three disorders in one individual has not been previously encountered.

The purpose of this report is to record the sequence of pernicious anemia, polycythemia vera, and acute myeloblastic leukemia in a patient under our observation.

Case Report: L. H., a 68 year old white, married female, was first admitted to Temple University Hospital on December 15, 1949. She complained of chronic pain in the left shoulder that had been present intermittently for many years, loss of appetite, weight loss, and shortness of breath on exertion during the previous 6 months. The patient had had no paraesthesias. Bilateral deafness had been present since scarlet fever at age 25. She stated that her hair had become gray at 14 years of age, and that early graying of hair was a family characteristic.

Physical examination revealed a gray haired elderly white female who was afebrile. The blood pressure was 184/92. There was pallor of the skin and mucous membranes. Bilateral deafness to air conduction was present. The tongue was red and atrophic and the mouth edentulous. The lungs were clear to percussion and auscultation. The heart was not enlarged to percussion; the rhythm was regular with an occasional extrasystole and there was a soft blowing systolic apical murmur. Abdominal and pelvic examinations were negative. The left shoulder was tender and painful on motion; no swelling was present. Vibratory sensation was decreased at both ankles. The deep tendon reflexes and position sense were normal.

Laboratory studies revealed hemoglobin to be 7.8 Gm.; the hematocrit, 22%; and the red blood cell count to be 2.13 million per cu.mm. Reticulocytes numbered 0.1%. The white blood cells numbered 6,400 per cu.mm. with a normal differential. The stained erythrocytes showed poikilocytosis, macrocytosis, and polychromatophilia. Gastric analysis yielded no free acid with Ewald meal or after histamine stimulation. The direct van den Berg reaction was negative and the indirect, less than 0.2 mg.%. The 100(1 umrea nitrogen was 12 mg.%. Serologic tests for syphilis were negative.

Roentgenogram of the chest was negative. An upper gastrointestinal X-ray series showed a small traction diverticulum of the midportion of the esophagus and very small mucosal folds of the stomach, especially in the fundus. Barium enema examination was normal. Roentgen studies revealed minimal hypertrophic arthritic changes involving...
both shoulder joints, and amorphous calcification in the region of the posterior superior aspect of the left shoulder joint.

The clinical impression was that of primary pernicious anemia, hypertension, hyperrophic arthritis, and calcific bursitis of left shoulder.

The patient was given intramuscular injections of B12, 15 micrograms daily, beginning on December 22. A reticulocytosis of 9.4% was reached on December 29, 7 days following onset of therapy. On December 30, the patient was discharged to be followed in Hematology Clinic where she received 15 micrograms of vitamin B12 two times a week for 6 weeks; then once weekly. By April 1950 the hemoglobin was 15.5 Gm. and the red blood cells numbered 5.37 million per cu.mm. Thereafter, the patient was given 30 µg. of vitamin B12 monthly.

During January 1950 she developed congestive heart failure which responded to therapy, and she continued to do well for the next year. From February 1950 to January 1951, frequent hemoglobin and red cell determinations were made and ranged from 15.5 to 17.0 Gm., and 5.05 to 6.48 million per c. mm., respectively. On May 4, 1951, the hemoglobin was 18.0 Gm.; the hematocrit 57% and the red cell count 5.71 million per cu. mm. The patient at this time began to experience occasional dizzy spells and frequent headaches.

She was readmitted to Temple University Hospital on July 4, 1951 because of severe epistaxis. The blood pressure on admission was 210/130 and pulse rate 112 per minute, and the hemoglobin 9.0 Gm. Following transfusion of 1000 ml. whole blood the hemoglobin was 12.2 Gm. and the hematocrit was 32%. Epistaxis was temporarily controlled by nasal packs. Severe epistaxis recurred on July 5, 1951 and stopped with repacking. After the second episode of nasal hemorrhage the patient was not transfused. Urinalysis showed a slight trace of albumin. The blood urea nitrogen was 65 mg.% on July 6, and 35 mg.% on July 9. At time of discharge on July 9, 1951, the hemoglobin was 9.9 Gm. and erythrocytes numbered 3.57 million per cu. mm. The platelet count was 459,000 per cu. mm.

Over the next few months the patient had a hypochromic, microcytic erythrocyte picture. By February 1952 it was believed that polycythemia vera associated with iron deficiency was now superimposed on pernicious anemia in remission. Peripheral blood values are shown in table I. On March 18, 1952, the patient was started on one gram of ferrous sulfate daily in addition to the monthly injection of vitamin B12. This was followed by a rapid increase in hemoglobin and hematocrit values, and on April 18, 1952, the patient was readmitted to Temple University Hospital for complete re-evaluation.

During the two weeks prior to this admission, the patient had experienced constant dull occipital headaches, frequent throbbing frontal headaches and several drenching sweats. Dyspnea on exertion, paroxysmal nocturnal dyspnea, and the anginal syndrome were also present. She had stopped taking digitalis several months prior to this admission.

The principal findings of the physical examination at this time were hypertension, plethoric facies, and bilateral deafness. The liver and spleen were not felt. The Achille's tendon reflexes were decreased as was vibration sense at both ankles.

Pertinent blood studies are shown in table I. The stained erythrocytes showed marked anisocytosis, poikilocytosis, and hypochromia. Platelets numbered 554,000 per cu. mm. Sternal marrow aspiration on 2 occasions revealed an hyperplastic, normoblastic marrow. Gastric analysis again revealed no free acid with the Ewald meal and after histamine stimulation. Blood volume studies with the Evans blue dye method indicated the plasma volume to be 1720 ml. (31 ml./Kg.); the blood volume, 3960 ml. (72 ml./Kg.); and the red cell volume, 2240 cc. (41 cc/Kg.). The I12 uptake was 29% at 24 hours, the basal metabolic rate was minus 6; and the serum cholesterol was 240 mg.%. The serum protein values were normal and blood urea nitrogen was 14 mg.%. Between April 23 and April 29, the patient had 550 ml. blood removed by venesection. She was not on iron therapy at this time or immediately following discharge on May 2, 1952. The main clinical impressions at this time were: (a) primary pernicious anemia in remission; (b) probable polycythemia vera; (c) hypertensive cardiovascular disease.

After discharge the patient was again followed in the Hematology Clinic. Because of a continued hypochromic appearance of the red blood cells and the desire to establish the diagnosis of polycythemia, ferrous sulfate 1.0 gm. daily was resumed on May 13 and con-
TABLE I.—Representative Blood Values of Patient, L. H., from December 1949 to Her Death in January 1954

<table>
<thead>
<tr>
<th>Date</th>
<th>Clinical status</th>
<th>Hemoglobin (Gm. per 100 cc)</th>
<th>Hematocrit (%)</th>
<th>Erythrocytes (per cu. mm.)</th>
<th>Leukocytes (per cu. mm.)</th>
<th>Differential count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dec. 1949</td>
<td>Diagnosis of Pernicious Anemia</td>
<td>7.8</td>
<td>22</td>
<td>2.13</td>
<td>6,400</td>
<td>Normal limits</td>
</tr>
<tr>
<td>Feb. 1952</td>
<td>Polyrythemia Vera with Iron Deficiency</td>
<td>12.2</td>
<td>47</td>
<td>7.25</td>
<td>13,900</td>
<td>Normal limits</td>
</tr>
<tr>
<td>Apr. 1952</td>
<td>Response to Iron Therapy</td>
<td>16.3</td>
<td>60</td>
<td>7.59</td>
<td>13,400</td>
<td>Normal limits</td>
</tr>
<tr>
<td>Oct. 1952</td>
<td>Response to Therapy with P32</td>
<td>13.9</td>
<td>46</td>
<td>5.47</td>
<td>4,200</td>
<td>Normal limits</td>
</tr>
<tr>
<td>Jan. 1954</td>
<td>Acute Granulocytic Leukemia</td>
<td>9.1</td>
<td>32.5</td>
<td>3.36</td>
<td>5,100</td>
<td>56% Blast forms</td>
</tr>
</tbody>
</table>

continued until June 24, 1952, at which time the peripheral blood showed the hemoglobin had risen to 17.5 Gm. with a 66% hematocrit. The erythrocyte count was 6.87 million per cu.mm. During the period from May 20 to August 19, 1952, she complained of continuous headaches, frequent drenching sweats and anginal type pain. The blood pressure was fairly stable, ranging from 170/100 to 180/112. On May 20, 1952, her spleen was first noted to be enlarged two finger-breadths below the costal cage. The liver was also palpated two finger-breadths below the costal cage at this time, both remaining palpably enlarged throughout the remainder of her course. Between July 1 and July 15, 1952, she had 4 venesections of 250 cc. each for a total of 1000 cc. On August 12, 1952, the patient received 5.56 millicuries of P32. Blood studies at this time showed 16 Gm. hemoglobin; 53% hematocrit; 6.92 million red blood cells per cu. mm.; and 10,400 white blood cells per cu. mm. with a non-remarkable differential. Because of a recurrence of congestive heart failure, the patient was redigitalized during August, 1952. In October, 1952, she began to show paranoid feelings concerning her stepson and from October 11 to November 7, 1952, the patient had her fourth Temple University Hospital admission primarily as a psychiatric-social problem. Blood values obtained during this admission are given in table I. By November, 1953, the patient’s peripheral blood showed evidence of further change. Studies at this time revealed the following: hemoglobin, 10.7 Gm.; hematocrit, 35%; red blood count, 3.60 million; reticulocytes, 8.9%; white blood cells, 1,900 per c. mm. with 48% segmented neutrophils, 1% band neutrophils, 34% lymphocytes, 3% monocytes, 3% eosinophils, 2% basophils, 2% prolymphocytes, 1% neutrophilic myelocytes, and 4% blasts. There were 6 nucleated red blood cells per 100 white cells and a rare Howell-Jolly body was also noted. Sternal marrow aspiration on November 18, 1953 showed 17% myeloblasts.

The clinical impression now included acute granulocytic subleukemic leukemia. She grew progressively weaker and had several syncopal episodes during December 1953. This lead to her fifth and last hospital admission on January 3, 1954. Weakness had become so marked that she could not sit or stand without support. Physical examination at this time revealed a disoriented elderly female. There was left flaccid paralysis, upper motor neuron signs on the left side, and urinary incontinence. Several ecchymoses were present on the trunk. Basilar pulmonary rales were present bilaterally:

Laboratory studies showed the hemoglobin to be 9.1 gm.; the hematocrit, 32.5%; red blood cells, 3.36 million; there were 12% reticulocytes; the white blood count was 5,100 with a differential of 19.5% segmented neutrophils, 3% band neutrophils, 9.5% lymphocytes, 2.5% monocytes, 1.5% neutrophilic myelocytes, 0.5% premylocytes, and 56% blast forms. The red blood cells showed marked anisocytosis, poikilocytosis and polychromatophilia; there were 95 nucleated red cells per 100 white cells; neutrophils showed toxic granulation and Auer bodies were present in some of the blast forms. Sternal mar-
row aspiration showed a marked increase in myeloblasts. The spinal fluid was slightly xanthochromic, but otherwise non-remarkable.

The patient was febrile with daily elevations of 102 to 104°F. She was treated supportively with maintenance digitalis and antibiotics. Progressive central nervous system degeneration occurred and she became comatose and expired on January 14, 1954.

Necropsy was performed and the findings may be summarized as follows: There was marked edema of both lungs with signs of acute and chronic congestion. Patchy areas of bronchopneumonia were present. The heart weighed 300 Gm. and showed no gross abnormalities. Minimal coronary atherosclerosis and myocardial fibrosis were noted. The liver, which weighed 4375 Gm., showed acute congestion and edema. Nucleated erythrocytes, myelocytes, and myeloblasts were observed in perportal areas of the stained sections. The spleen weighed 375 Gm. and was soft and friable. Sections revealed acute congestion and extramedullary hematopoiesis or leukemic infiltration, or both. The kidneys were grossly normal, but on section showed moderate arteriolar nephrosclerosis and atherosclerosis. No enlarged lymph nodes were detected either by inspection or palpation. The bone-marrow of the vertebral bodies and ribs was pale-red and abundant. Sections were very cellular and the histologic picture was consistent with acute myelogenous leukemia. There was evidence of gross softening of the right temporal and parietal lobes of the brain. Sections revealed moderately severe atherosclerosis and focal areas of encephalomalacia.

The pathologic diagnoses were bronchopneumonia and acute myelogenous leukemia in patient with pernicious anemia and polycythemia (by history).

**COMMENT**

This patient exhibited a unique sequence of blood dyscrasias. The diagnosis and treatment for pernicious anemia was conventional. Vitamin B₁₂ therapy was continued throughout the remainder of the patient’s course even after the diagnosis of polycythemia was made. It was tempting to consider withholding vitamin B₁₂ in order to effect indirectly the polycythemic process; however, this was not done since it was desired to protect the patient from possible neurological complications of inadequately treated pernicious anemia.

The polycythemia was apparently masked and its recognition delayed by the development of iron deficiency, largely due to episodes of severe epistaxis. Iron replacement therapy resulted in a prompt increase of hemoglobin and hematocrit values to 17.5 Gm. and 60% respectively. The patient developed headaches, sweating, anginal pain, and splenomegaly at this point and iron therapy was discontinued. Although higher erythroid values might have been of academic interest, it did not seem clinically justifiable to administer additional iron simply to reinforce the diagnosis of polycythemia. Instead, venesections were performed to lessen the cardiovascular load, and the patient received 5.56 millicuries of radioactive phosphorus (P₃₂). A little more than one year later, acute leukemia appeared and was the ultimate cause of death. Whether the radiation therapy influenced the development of leukemia in this patient cannot be established or refuted by currently available data.

It would appear from the nature of the disorders concerned that the sequence encountered in this patient was necessary for all three to have sufficient time to become manifest. Certainly neither pernicious anemia nor polycythemia could be expected to develop after the appearance of acute leukemia in an adult. It is theoretically possible, however, that a patient with polycythemia could indeed develop pernicious anemia as well. To date no such case has been reported in the
literature. However, such an association remains a remote possibility and could be followed by acute leukemia as in the patient described herein.

**Summary**

The development of three primary blood dyscrasias, namely, pernicious anemia, polycythemia vera, and acute myeloblastic leukemia, in one patient has been reported.

**Summario in Interlingua**

Le disveloppamento de tres primari dyscrasias de sanguine—anemia perniciose, polycythemia ver, e acute leucemia myeloblastic—in un sol patiente es reportate.

**References**

Unique Sequence of Pernicious Anemia, Polycythemia, and Acute Leukemia

CHRIS J. D. ZARAFONETIS, ROBERT L. OVERMAN and LYNDALL MOLTHAN