Chronic Erythrocytic Hypoplasia Following Pernicious Anemia

By Carlos Goldstein and Libertó Pechet

Chronic Erythrocytic Hypoplasia in adults is a rare entity.1 It was described for the first time in 1922,2 as a progressive normochromic anemia with erythropoietic aplasia of the bone marrow, reticulocytopenia, normal leukopoiesis and thrombopoiesis, and absence of enlarged spleen or lymph nodes.

Infections,3 drugs,4 immunologic reactions,5 azotemia,6,7 thymic tumors,8,9 and an inborn error of metabolism10 have all been implicated as conditioning a selective impairment of the erythropoietic activity. The case to be reported, treated pernicious anemia followed by erythrocytic hypoplasia, presents a sequence we believe has not been previously described.

Case Report

J. W. (BIH #95279), a Caucasian woman, was first seen in the outpatient department of the Beth Israel Hospital in 1951, for follow up of pernicious anemia. The diagnosis was made at the New England Hospital for Women and Children in 1932, when she was 40 years old (fig. 1). At that time her Hb was 8.0 Gm./100 ml. and the red cell count (RBC) 2.5 million/cu. mm. Histamine-resistant achlorhydria and combined system disease were found. A rapid clinical and hematologic remission followed administration of parenteral and oral liver extract. A relapse took place 5 years later upon discontinuation of therapy, but reinstitution of parenteral liver therapy again induced a prompt remission.

A severe relapse after interruption of treatment required admission to the Boston City Hospital in 1939. Laboratory results were as follows: RBC, 1.3 million/cu. mm.; Hb, 4.7 Gm./100 ml.; reticulocyte count, 8.8 per cent; Hct, 16.7 per cent; mean corpuscular volume (MCV), 124 cuμ; mean corpuscular hemoglobin concentration (MCHC), 27 per cent; and leukocyte count (WBC), 2,900/cu. mm., with a normal differential. No erythropoietic response was observed after administration of Valentine’s meat and neutralized gastric juice, whereas ventriculin (intrinsic factor) was followed by a reticulocytosis of 25 per cent, a rise in hemoglobin, and a rapid clinical improvement. The diagnosis of pernicious anemia was thus confirmed and liver therapy restarted.

Over the following 20 years her hemoglobin varied between 13.5 and 16 Gm./100 ml. In 1953, the therapy with liver extract was replaced by vitamin B12, 50 μg. every 2 weeks. The hemoglobin level was 13.0 Gm./100 ml. in 1939, and remained stable for the next 2 years. In June 1961 the hemoglobin was 12 Gm./100 ml. and declined progressively thereafter in spite of continuing vitamin B12 therapy.

The patient was hospitalized at the Beth Israel Hospital in April 1962, for evaluation of her anemia. There was no history of exposure to drugs or chemicals. Pallor and diminished vibratory sensation below the knees were found; the tongue was well papillated; the spleen’s tip was palpable and slight enlargement was noted on x-rays. Laboratory data were as follows: Hb, 6.1 Gm./100 ml.; Hct 20 per cent; RBC, 1.8 million/cu. mm.; WBC,

From the Medical Research Laboratories of the Yamin’s Laboratory, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School, Boston, Mass.

Supported by a grant (HE-00656) from the National Heart Institute of the National Institutes of Health, Public Health Service, U. S. Government.

Submitted Feb. 11, 1964; accepted for publication Apr. 5, 1964.

Blood, Vol. 25, No. 1 (January), 1965
Fig. 1.—Hematologic data and therapy on patient J. W.

10,900/cu. mm. with a normal differential; platelets, 140,000/cu. mm.; reticulocytes, 0.6 per cent; MCV, 120 cuµ; mean corpuscular hemoglobin (MCH), 37γγ and MCHC 31 per cent; urinalysis, normal; stools, guaiac negative; fasting blood sugar, blood urea nitrogen (BUN), calcium, alkaline phosphatase, bilirubin, protein-bound iodine, bromosulphalein retention, serum leucine amino peptidase, serum beta glucuronidase and serum carotene levels were all within normal limits; direct and indirect Coombs tests negative; leucocyte alkaline phosphatase 40 Koplow units (normal); serum iron was 233 µg./100 ml. (normal 52-183) and the total iron-binding capacity (TIBC) 275 µg./100 ml. (normal 262-420); the serum folic acid was 12.4 ng./ml., and the vitamin B₁₂ 168 pg./ml. (both within normal limits). DiagnexR test for free acid was positive but analysis of gastric juice after intubation gave a negative Topfer reaction. A bone marrow obtained by open biopsy demonstrated erythroid hypoplasia with no evidence of myelofibrosis, most of the cells in the block belonging to the myeloid series. No megaloblasts or macronormoblasts were seen. A splenic aspirate showed no plasma cells, megakaryocytes or abnormal cells. X-ray studies of the gastrointestinal tract disclosed a moderate-sized hiatus hernia and a few colonic diverticula. No radiologic evidence of a thymic tumor or of myelofibrosis was found. An incidental finding was early Paget's disease involving the pelvic bones. Transfusions of two units of packed cells every 2–3 weeks were required to maintain continuously the hemoglobin level above 6.0 Gm./100 ml.

The patient was again hospitalized for further studies in September 1962. The physical findings were unchanged. The hemoglobin was 7.2 Gm./100 ml, Hct, 23 per cent; RBC, 2.6 million/cu. mm.; WBC, 6,300/cu. mm. with a normal differential; reticulocytes, 0 per cent; platelets, 156,000/cu. mm.; BUN 17 mg./100 ml.; serum iron, 240 µg./100 ml.; and TIBC, 474 µg./100 ml.; bilirubin, 0.6 mg./100 ml.; uric acid, 5.1 mg./100 ml.; serum proteins, 6.6 Gm./100 ml.; albumin 3.20 Gm./100 ml.; globulin, 3.40 Gm./100 ml. with a normal electrophoretic distribution of globulins. A direct Coombs test was negative. Serum vitamin B₁₂ and folic acid levels were again normal (130 ng. and 27 pg./ml., respectively). Urine sediment showed no significant stainable hemosiderin. No gastric acidity could be detected after stimulation with betazole hydrochloride (HistalogR). The half-life of the patient's Cr³¹-labeled red cells (probably all transfused cells), was 12 days (normal ± 28 days); no increased radioactivity could be detected over the liver or spleen; a repeated survival test done with fresh red cells withdrawn from a compatible donor re-
vealed a Chromium half-life of 40 days. Schilling tests done with 0.5 and 2.0 μc. of Co⁶⁰ vitamin B₁₂ were followed by less than 4 per cent excretion in 24-hour urine samples. Urinary erythropoietin was normal. Ferrokinetic studies with Fe⁵⁹ indicated a delayed plasma clearance (half-life of 7.5 hours, normal being 60–120 minutes), and no red cell incorporation of radioactive iron for 10 days following the administration of the tracer dose. Urinary urobilinogen was 1 Ehrlich unit in a 2-hour sample (normal 0–1), and fecal urobilinogen corrected for hemoglobin level was 82.5 Ehrlich units/100 Gm. of stool (normal 50–300). Therapeutic trials with pyridoxine, prednisone, testosterone enanthate (Delatestryl®), hydroxocobalamin, cobaltous chloride, and increased doses of cyanocobalamin as well as riboflavin had no effect on her anemia. At the present time treatment is continued with blood transfusions and parenteral vitamin B₁₂.

**DISCUSSION**

The diagnosis of pernicious anemia in this patient was supported by her response to parenteral liver extract as well as to intrinsic factor-meat juice administered by mouth, the abnormal Schilling tests, and the absence of gastric acidity after histamine stimulation; the Diagnex® test was interpreted as falsely positive, a known occurrence when cation exchange resins are used for tubeless gastric analysis.¹¹ Red cell hypoplasia supervened during treatment with vitamin B₁₂, without apparent exposure to any known myelotoxic agent. No coexistent features, such as thymus tumor, “allergic” reactions, giant bone marrow proerythroblasts, isoimmunization, autoimmunization, or azotemia, could be demonstrated. Hemolysis or paroxysmal nocturnal hemoglobinuria was considered unlikely to be the mechanism of her anemia, in view of a low-normal urobilinogen, absence of hemoglobinuria or significant hemosiderinuria, a prolonged red cell survival and a negative Coombs test. The lack of any detectable red cell production, as indicated by the ferrokinetic pattern and the absence of red cell precursors in the bone marrow substantiated the diagnosis of red cell hypoplasia. Therapy with steroids, cobalt, or riboflavin and splenectomy have all been considered of therapeutic value. In our case these agents were unsuccessful and splenectomy was not performed.

Megaloblastic anemia has been reported occasionally in association with aplastic bone marrow. Chauffard¹⁹ noted megaloblasts in a patient with “pernicious aplastic anemia;” Kho et al.⁵ reported 4 cases of acute erythroblastopenia (aplastic crisis) in children with megaloblastic anemia, suffering from infection and malnutrition. Arrowsmith et al.²⁰ described a unique megaloblastic bone marrow response to cortisone in an 18-month-old child with aregenerative anemia limited to the red cell series; moreover, in some instances the aplastic crises of congenital spherocytosis were found to be accompanied by megaloblastic bone marrow.²¹

Prior to the introduction of liver therapy for pernicious anemia, bone marrow aplasia was a common autopsy finding.²² Prolonged deprivation of vitamin B₁₂ or folic acid has also been regarded as leading to bone marrow exhaustion and aplasia, after passing through a megaloblastic stage.²³ It is therefore of interest that pure red cell hypoplasia developed in our patient while she was adequately treated.

The pathogenesis underlying cessation of erythropoiesis is unknown. The
possibilities of selective toxines, erythrotropic virus, antierythrocytic antibodies, perturbation in nucleic acid metabolism or lack of erythropoietine are some of the implicated mechanisms.24

The finding of maturation arrest at an early erythroblastic level,25 the failure of late erythroblasts to mature,26 or, as seen in our patient, the absence of red cell precursors in bone marrow specimens,4 suggests that the interference with red cell production may take place at different stages.

Although the association reported here may be coincidental, one may speculate that the highly proliferative phase present during the periods when the patient’s anemia was untreated, resulted in exhaustion of the erythropoietic marrow and determined the late outcome of red cell hypoplasia. This interpretation is also in keeping with the idea that myeloproliferation and aplasia may represent different phases in the evolution of pathologic processes. Thus, long-standing polycythemia vera is occasionally followed by myelofibrosis;27 bone marrow hypoplasia can be the end stage of leukemia,28 and chemicals such as benzol are believed to produce both myeloproliferation and bone marrow failure;29 moreover, red cell hypoplasia terminated as leukemia in 10 per cent of 39 cases reviewed recently.30

**Summary**

A case of chronic erythrocytic hypoplasia of the bone marrow following Addisonian pernicious anemia, treated for 30 years, is reported. Treatment with different erythropoietic agents was completely unsuccessful. The possibility of a causal relationship is suggested.

**Summario in Interlingua**

Es reportate un caso de chronic hypoplasia erythrocytic del medulla ossee occurrente como sequella de anemia perniciose de Addison que habeva essite sub tractamento durante 30 annos. Le therapia con differente agentes erythropoietic esseva completamente insuccessose. Es notate le possibilitate de un relation causal.

**ADDENDUM**

Since the submission of this manuscript, the patient developed progressive hepatomegaly and one episode of jaundice. A liver biopsy performed on July 16, 1964, showed hemosiderosis of liver with severe portal fibrosis; her hematologic status, however, remains unchanged.

**ACKNOWLEDGMENTS**

We are indebted to Dr. Victor Herbert for the vitamin B12 and folic acid assays and for providing data pertaining to patient’s hospitalization at the Boston City Hospital; to Dr. David Nathan, Peter Bent Brigham Hospital, Boston, for performing the ferrokinetic studies; and to Dr. Frederik Stohlman, Jr., St. Elizabeth's Hospital Boston, for the erythropoietine assay.

**REFERENCES**


2. Kaznelson, P.: Zur Entstehung der
CHRONIC ERYTHROCYTIC HYPOPLASIA


Carlos Goldstein, M.D., Research Fellow in Medicine, Beth Israel Hospital, Harvard Medical School, Boston, Mass. Present Address: Montefiore Hospital, Bronx, N. Y.

Liberto Pechet, M.D., Associate in Medicine, Harvard Medical School, Beth Israel Hospital, Boston, Mass.
Chronic Erythrocytic Hypoplasia Following Pernicious Anemia

CARLOS GOLDSTEIN and LIBERTO PECHET

Updated information and services can be found at:
http://www.bloodjournal.org/content/25/1/31.full.html
Articles on similar topics can be found in the following Blood collections

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml