BRIEF COMMUNICATION

Congenital Hypoplastic Anemia (Diamond-Blackfan Syndrome) Terminating in Acute Myelogenous Leukemia

By Jeffrey S. Wasser, Robert Yolken, Denis R. Miller, and Louis Diamond

A 31-yr-old female with congenital hypoplastic anemia (Diamond-Blackfan syndrome) whose long course terminated in acute myelogenous leukemia is described. In contrast to Fanconi anemia, malignant transformation rarely occurs in congenital hypoplastic anemia. This patient’s diagnosis of congenital hypoplastic anemia is supported by her clinical course, absence of renal abnormalities, a negative family history for hematologic disorders, normal chromosome studies, failure of her skin fibroblasts to transform in culture with SV-40 virus, macrocytic erythrocyte indices, erythrocyte enzyme studies, and bone marrow findings. Only two other cases of malignancy have been reported in patients with congenital hypoplastic anemia. The development of malignancy in these patients suggests that malignant transformation may be a concern in the long-term progression of congenital hypoplastic anemia.

The clinical courses of 133 cases of congenital hypoplastic anemia (CHA) or Diamond-Blackfan syndrome were recently reviewed. In the 13 cases for which cause of death was reported, 10 were due to hemosiderosis and 3 to infection. We now report a patient whose relatively long survival terminated in acute myelogenous leukemia.

CASE REPORT

The patient M. M. was a 31-yr-old white female referred to The New York Hospital Cornell Medical Center by her lifelong personal physician for progressive anemia, fatigue, and easy bruising of 2 mo duration.

At birth the patient had a bifid thumb, a supernumerary left thumb, and a webbed neck. Anemia was noted at 6 wk of age, and she was then started on transfusion therapy. A bone marrow aspirate performed at that time revealed the complete absence of erythroid precursors, while the white cell and platelet precursors appeared normal.

Over the next 11 yr she required transfusions every 6-8 wk when her hemoglobin fell below 6 g/dl. She remained in fair health except for an enlarging liver and a hemosiderotic pigmentation of the skin. Her transfusion requirement was not altered by splenectomy or by biotin, corticosteroid, or androgen therapy. At age 15 yr, after the 399th transfusion, her anemia spontaneously remitted, and she required no transfusions for the next 18 mo. During this remission her hemoglobin stabilized at 12 g/dl, and her red cells, as previously, were macrocytic with a mean corpuscular volume (MCV) of 106 cu μm. Her growth improved and her hepatomegaly decreased. Signs of puberty started to appear at 16 yr of age but she never menstruated. At age 17 yr a bone marrow aspirate showed normal cellularity. At age 17 ½ yr her hemoglobin fell to 6 g/dl and she required transfusion therapy for another year.

After her 407th transfusion at age 18 ½ yr, the patient achieved a second spontaneous remis-
tion that lasted 13 yr. A hematologic evaluation at 29 yr of age was normal except for macrocytic red cells, with a MCV of 100 104 cu μm. Evaluations of erythropoietin levels by bioassay and radioimmunoassay were normal. The i antigen level was zero while the I antigen level was normal. Her red cell enzyme pattern revealed elevations of the levels of glucose-6-phosphate dehydrogenase and hexokinase. Chromosome studies were normal (neither breaks nor aneuploidy were found). Cultures of skin fibroblasts did not show increased transformation with SV-40 virus.2 There was no history of a hematologic disorder in her siblings or parents. The patient continued to do well and remained gainfully employed as a legal clerk until the time of her hospitalization.

Two months before admission (age 31 yr), she complained of progressive fatigue and pallor. The hemoglobin concentration was then found to be 5.0 g/dl, reticulocyte count zero, platelet count 20,000/cu mm, and a corrected leucocyte count of 1800/cu mm with a differential of 4\(^{\circ}\) myeloblasts, 2\(^{\circ}\) myelocytes, 2\(^{\circ}\) metamyelocytes, 6\(^{\circ}\) polymorphonuclear leukocytes, 16\(^{\circ}\) bands, 60\(^{\circ}\) lymphocytes, 2\(^{\circ}\) monocytes and 8\(^{\circ}\) basophils. There were 125 nucleated RBC per 100 WBC. Her physician prescribed prednisone and folic acid, but when she did not improve he referred her to The New York Hospital Cornell Medical Center for further evaluation of her hematologic status.

Physical examination revealed a poorly developed cushingoid white female with a webbed neck and surgically corrected thumbs. She was 146.5 cm tall and weighed 40 kg. Her pulse was 120/min, blood pressure 115/60 mm Hg, and she was afebrile. The skin had scattered areas of brown pigmentation, predominantly over the face and anterior tibial surfaces. Her chest was broad, the breasts were undeveloped, and the nipples were laterally located. No cardiac murmur or gallop was present. The abdomen was obese and had a healed splenectomy scar. The liver span was 12 cm. Pubic hair was sparse, and the external genitalia were infantile. Neurologic examination was normal.

Laboratory studies showed a white blood cell count of 14,700/cu mm (corrected for nucleated RBC), hemoglobin 7.8 g/dl, hematocrit 27.3\(^{\circ}\), MCV 98 cu μm, mean corpuscular hemoglobin 32.6 ng, and mean corpuscular hemoglobin concentration 33.3\(^{\circ}\). The differential white count was 30\(^{\circ}\) lymphocytes, 26\(^{\circ}\) monocytes, 4\(^{\circ}\) eosinophils, 1\(^{\circ}\) basophils, 3\(^{\circ}\) polymorphonuclear leukocytes, 4\(^{\circ}\) bands, 5\(^{\circ}\) metamyelocytes, 25\(^{\circ}\) myelocytes, 2\(^{\circ}\) promyelocytes, and 1\(^{\circ}\) blasts. Peroxidase-positive granules were present in the immature leukocytes. There were 78 nucleated RBC per 100 WBC, and the platelet count was 16,000/cu mm with a reticulocyte count (uncorrected) of 1.7\(^{\circ}\). Howell-Jolly bodies, target cells, and rare schistocytes were seen in the peripheral blood smear. Hemoglobin electrophoresis revealed 95.3\(^{\circ}\) HbA, 3.8\(^{\circ}\) HbA2, and 0.9\(^{\circ}\) HbF. The serum thoptoglobin was 166 mg/dl (normal 70 150 mg/dl). Serum iron and total iron binding capacity, respectively, were 250 and 323 μg/dl (80\(^{\circ}\) saturation). Leukocyte alkaline phosphatase score was 29, the erythrocyte sedimentation rate was normal, and the serum B2 was 1600 p/ml.

The sugar-water test was negative. Attempts at bone marrow aspiration were unsuccessful, but a bone marrow biopsy with a modified Vim-Silverman needle demonstrated a marrow packed with myeloblasts and large numbers of mitotic figures. Occasional maturing myeloid and erythroid elements were observed. Iron was increased, and megakaryocytes were reduced in number. A touch preparation of the bone marrow biopsy (Figs. 1 and 2) revealed dyserythropoiesis and a shift toward immature myeloid forms with 22\(^{\circ}\) myeloblasts and 13\(^{\circ}\) promyelocytes. Blood chemistries were within normal limits except for minimal evaluations of the liver enzymes. The serum hepatitis antigen was positive by radioimmunoassay.

Latex fixation was positive in a dilution greater than 1:2560. The VDRL was nonreactive. The prothrombin time, activated partial thromboplastin time, uric acid, tests of renal function, and the DNA binding (Farr) tests were within normal limits. The patient’s peripheral blood lymphocytes did not suppress erythroid colony formation in a plasma clot culture system in vitro.1

The patient’s hospital course was complicated by cardiac arrhythmias. Following control of the arrhythmias the patient was started on antileukemic therapy consisting of cytosine arabinoside (100 mg/sq m) for 7 days and daunomycin (45 mg/sq m) on days 1, 2, and 3. This therapy was well tolerated until the 22nd hospital day, when the patient developed occult blood in her stools, fever to 39.2°C, and diffuse abdominal tenderness. Despite pressor and antibiotic therapy the patient died on the 24th hospital day.

Postmortem examination revealed widespread hemosiderosis involving the heart, liver, lung, bone marrow, thyroid, ovaries, and lymph nodes; hypoplasia of the uterus, ovaries, breasts, and external genitalia; and micronodular cirrhosis of the liver with iron deposition in the hepatocytes.
Fig. 1. Photomicrograph of patient's bone marrow biopsy demonstrating a hypercellular marrow replaced by primitive myeloid cells. × 1000.

and Kupffer cells. The terminal ileum, cecum, and colon showed findings consistent with a pseudomembranous enterocolitis. No thymic remnant was found. There were no structural renal abnormalities. The marrow was hypocellular. The myeloid series exhibited no maturation, and a few granular blasts were present. Megakaryocytes were virtually absent, and a rare maturing erythrocyte precursor was present. Blood cultures obtained antemortem later grew Streptococcus pneumoniae and Escherichia coli.
DISCUSSION

Congenital hypoplastic anemia and Fanconi anemia are two chronic hypoproliferative anemias of childhood. This patient’s clinical course until the time of her final admission, the negative family history, the absence of renal abnormalities, the results of chromosome studies, skin fibroblast cultures, erythrocyte indices, erythrocyte enzyme studies, and bone marrow findings support the diagnosis of CHA rather than Fanconi anemia. The diagnosis is not negated by the failure of her peripheral blood lymphocytes to inhibit erythropoiesis in the clot culture system in vitro, since this study was done at a time when her bone marrow was diagnostic of acute myelogenous leukemia. Unfortunately, insufficient marrow was obtained for evaluation and quantification of colony and cluster formation in vitro.

In contrast to Fanconi aplastic anemia, the occurrence of malignancy in CHA is a rare and recently reported phenomenon. D’Oelsnitz et al. reported a case of acute lymphoblastic leukemia occurring in a 13-yr-old girl with CHA after a remission of 7 yr. Steinherz et al. reported the development of hepato-
cellular carcinoma in a 25-yr-old male with CHA. Both of these previously reported patients had extended remission of their congenital anemia. All three cases were similar in that the patients did not receive corticosteroid therapy for years prior to the detection of the neoplastic process.

In the 133 cases of CHA reviewed by Diamond et al., there were no reports of malignancy until 1976. The subsequent development of malignancy in three of these cases (2.2% of those reviewed) suggests that malignant transformation may be a concern in the long term progression of CHA.

ACKNOWLEDGMENT

We thank Dr. R. Hoffman and Dr. E. Zanjani for their studies of the effects in vitro of this patient’s lymphocytes on erythroid cell formation. We are grateful to Dr. Babette Weksler for her helpful criticism and review of the manuscript. In addition, we are most grateful to Dr. C. Merrill Leister, whose records of the 30-yr care of the patient were made available to us.

REFERENCES

2. Todaro, GJ: Personal communication
Congenital hypoplastic anemia (Diamond-Blackfan syndrome) terminating in acute myelogenous leukemia

JS Wasser, R Yolken, DR Miller and L Diamond