A Case of Red Cell Aplasia Occurring as a Result of Antituberculous Therapy

By Stephen B. Goodman and Matthew H. Block

This report concerns a young man who developed anemia with aplasia of red cell precursors while being treated with isoniazid (INH) and para-aminosalicylic acid (PAS) for pulmonary tuberculosis. Readministration of these drugs, after a remission coinciding with cessation of therapy, reproduced the anemia and erythroblastic aplasia.

Case Report

The patient, a 32-year-old Caucasian male with diabetes was admitted to Colorado General Hospital on 5-27-61 (Table 1), because of an asymptomatic pulmonary lesion. Past history was negative except for diabetes since age five. The patient had prescribed his own regimen of diabetic "control" and at the time of admission was taking protamine zinc insulin 17 units and regular insulin 13 units each day.

Physical examination revealed extensive vascular changes in the optic fundi consistent with diabetic retinopathy. No lymphadenopathy was noted and the spleen and liver were not palpable. The hemoglobin was 18.5 Gm. per cent and the white count was 8,700 (Table 1). Red cells, white cells, including differential count, and platelets were normal. The chest film showed a dense rounded mass in the left upper lobe. There was no suggestion of a thymic tumor.

Because it was strongly suspected that the patient had carcinoma of the lung, thoractomy was performed on 5-31-61. One sputum culture subsequently became positive for miliary tuberculosis and at surgery the patient was found to have a tuberculoma from which M. tuberculosis was cultured. On 6-14-61, the Hct. was 45 per cent. The patient recovered from his surgery and was discharged from the hospital on 7-15-61.

He was seen periodically in the chest clinic and returned to full-time work as a precision inspector. During an outpatient visit on 8-11-61 he complained for the first time of sexual impotence and at the next visit, 10-9-61, he complained of severe fatigue. On 12-27-61 the Hb was 8.9 Gm. per cent, Hct 25 per cent and the white count was 5,600 with 44 per cent polys, 4 per cent bands, 50 per cent lymphocytes and 2 per cent monocytes. The BUN was normal.

A bone marrow aspiration on 1-24-62 showed complete absence of erythroblasts in smears of the marrow particles (abklatsch) and in the marrow section (Fig. 1). Many lymphocytes were present in the marrow touches, and lymphatic nodules and small foci of lymphocytes were seen in the marrow sections. Sclerous fat atrophy was a prominent feature in the marrow sections. Megakaryocytes and granulocytic precursors were present in normal numbers. A peripheral smear taken at this time showed normal numbers of white cells and platelets. Red cell morphology was normal. No polychromatophilic red cells were seen.

On 1-29-62 the patient was admitted to the hospital (2nd CGH admission) because of severe weakness and light-headedness. His hemoglobin had fallen to 4.9 Gm. per cent. Pertinent laboratory studies prior to transfusion included the following: the white count was 3,700 with 51 per cent polys, 43 per cent lymphocytes and 6 per cent eosinophils. The peripheral smear showed a normal number of platelets and normal red cell morphology. Total serum protein was 6.26 Gm. per cent (2.77 Gm. per cent albumin). The direct

Submitted Jan. 17, 1964; accepted for publication Apr. 15, 1964.

Blood, Vol. 24, No. 5 (November), 1964
Coombs test was strongly positive (3+). The total serum bilirubin was 0.4 mg. per cent, all of which was unconjugated. A red cell survival study, started prior to transfusion, and using the patient's own cells labeled with radiochromium showed a 16 day Cr$^{51}$ half-life with a logarithmic fall in radioactivity. Stool was negative for blood. One lymph node, measuring 18 x 10 x 5 mm. was removed from the left axilla and showed benign hyperplasia. Because of symptoms ascribable to severe anemia the patient was given 500 cc. of packed red blood cells between the second and third hospital days.

The patient's medications were continued during and immediately after this second hospitalization. He was discharged on 2-1-62 with the diagnosis of probable lymphosarcoma, based on the large amount of lymphatic tissue seen in the bone marrow. The Hct was 25 per cent at time of discharge.

On 2-7-62 it was decided to discontinue the patient's medications because of the possibility of a drug reaction. He was seen 2 days later in clinic and a blood smear at that time showed marked polychromatophilia indicative of entrance of new red cells into the circulation. The second marrow specimen (obtained on 2-9-62) showed erythroblasts present but in decreased number (fig. 2). On 2-13-62 the Hct was 25 per cent and the reticulocyte count 6.6 per cent.

Without transfusions or other therapy, the hemoglobin and hematocrit rose steadily over the next few weeks, and when seen on 3-13-62, the patient's Hct was 45 per cent, Hb 14.7 Gm. per cent, and reticulocyte count 0.1 per cent. A bone marrow taken at that time (marrow #3) showed erythroblastic hyperplasia (fig. 3). A peripheral smear at that time showed normal white cells and platelets. The direct Coombs test was 1+ positive.

On 3-20-62 isoniazide was again prescribed in a dose of 300 mg./day. The dose was raised to 800 mg./day on 4-2-62 and vitamin B$_6$, 100 mg./day was started on 4-9-62. With the exception of PZI and regular insulin the patient received no other medications at this time.
Figs. 1A and B.—See legend, facing page.
RED CELL APLASIA

Fig. 1A-C.—Marrow obtained on 1/24/63 (specimen #1). A. Smear of marrow particle. Note lack of erythroblasts, 800X. B. Section of marrow particle. One area of myeloid tissue with serous fat atrophy (sfa) and other area consisting of dense lymphatic tissue (lt), 100X. C. Higher magnification of myeloid tissue showing serous fat atrophy (sfa) and granulocytic cells. There is a slight increase in the ratio of immature to mature granulocytes and a lack of erythroblasts, 800X.

time. A determination of red cell glucose-6-phosphate dehydrogenase activity was performed* on 4-12-62 and the activity of the enzyme in the patient’s red cells was 304 units/100 ml. red blood cells (normal value greater than 150 units/100 ml. red blood cells).

The patient’s Hb remained about 15.0 Gm. per cent and on 4-16-62, para-aminosalicylic acid, 12 Gm./day was added to the regimen. The Hb fell from 15.7 Gm. per cent on 5-16-62 to 13.2 Gm. per cent on 5-31-62. A serum iron drawn at this time was 159 μg. per cent with an unsaturated binding capacity of 200 μg. per cent. The total serum bilirubin was 0.2 mg. per cent and no reticulocytes were seen in the peripheral blood. A direct Coombs test was 2+. Another marrow specimen was obtained (marrow #4) and again showed complete red cell aplasia. The over-all cellularity of the bone marrow section was within normal limits. The granulocytic and megakaryocytic series were normal. Scattered lymphocytes were present in the marrow but no lymphatic islands were seen in the specimen. A peripheral smear at this time was normal except for the absence of polychromatophil red cells. The PAS was stopped but INH and vitamin B₆ were continued. On 6-4-62 the Hb was still 13.2 Gm. per cent and no polychromatophil red cells or reticulocytes were seen in the peripheral blood smear. At this time the patient complained of “flu-like” symptoms and his wife was ill with an acute respiratory infection. All medications were discontinued on 6-5-62, because he planned to leave for California on 6-7-62, and because we saw no evidence in the peripheral smear to suggest regeneration of erythroblasts.

*Performed by Dr. Robert Chapman.
Fig. 2.—Marrow obtained on 2/9/62 (specimen #2). A. Note erythroblasts (e) scattered among granulocytes and precursors in smears of marrow, 800X. B. Island of polychromatophil erythroblasts (e) and extensive serous fat atrophy (sfa) in marrow section, 800X.
Fig. 3.—Marrow obtained on 3/13/62 (specimen #3). Section of moderately hypercellular marrow, without serous fat atrophy, showing numerous islands of erythroblasts (e). 800X.

6-7-62 the Hb was 13.0 Gm. per cent and still no reticulocytes were seen in the peripheral blood.

A letter from the patient's physician in California, dated 7-31-62, stated that the patient felt well and had an Hb of 15.0 Gm. per cent. He was taking no medications other than insulin at that time.

DISCUSSION

Pure aplasia of red cell precursors has now been reported in a wide variety of situations, but there are only a few documented cases of pure erythroblastic aplasia as a result of drug therapy. In the present case complete aplasia of red cell precursors and lack of peripheral blood reticulocytes occurred on two separate occasions while the patient was taking isoniazid and para-aminosalicylic acid. Recovery occurred each time the drugs were stopped, and on the first occasion reticulocytosis (polychromasia) occurred within 48 hours of stopping the drugs. It seems clear that in this case erythroblastic aplasia was due to isoniazid and/or para-aminosalicylic acid.

Because the patient moved from Denver we were not able to determine which of the two drugs caused the disappearance of erythroblasts but we think that isoniazid was most likely responsible for the reaction for the

*J. L. Johnson, M.D., Fisher-Hauch Medical Clinic, Pomona, California.
following reasons: (1) A peripheral reticulocytosis occurred within two days after stopping both the INH and PAS in February 1962. However, during the second episode of aplasia in May 1962 no reticulocytosis was seen 6 days after stopping the PAS and continuing the INH. It is possible that an influenza-like illness at that time prolonged the suppression of erythropoiesis. However, his symptoms lasted only a few hours and may also have been due to the drug reaction. We do know that the erythroblastic aplasia was reversible because sometime between leaving Denver on June 7, 1962, and seeing a physician in California in July 1962, his Hb rose to 15.0 Gm. per cent. (2) There is one other case report of erythroblastic aplasia allegedly due to INH, but we were made unable to find any report of a similar reaction to PAS.

The anemia on both occasions appears to have been due primarily to decreased production of red cells as shown by (1) the slow fall of hemoglobin, (2) the absence of reticulocytes and polychromatophil red cells in the peripheral blood, (3) the absence of erythroblasts in the bone marrow. However, it is likely that there was also an element of increased red cell destruction as shown by the positive direct Coombs test on both occasions and the logarithmic shape of the red cell survival curve suggesting that there was random destruction of red cells. The half-life of the chromium label was reduced to 16 days. Because erythropoiesis had stopped some weeks before the label was applied, the age distribution of labeled red cells was biased in favor of older cells. The actual half-life obtained was therefore not, of itself, proof of an increased rate of red cell destruction.

The mechanism of drug induced aplasia in this case is not clear. Because of the gradual development of anemia when the patient was treated with INH and PAS the second time, we think it is unlikely that the red cell aplasia was due to an immune reaction. The normal levels of red cell glucose-6-phosphate dehydrogenase rule out a deficiency of this enzyme as a cause for the patient's drug induced anemia. During both periods of drug therapy the patient received large doses of pyridoxine and it is unlikely that anemia resulted from INH induced pyridoxine deficiency. Nevertheless the relatively long latent period between starting drug therapy and the onset of anemia is most consistent with some idiosyncratic form of metabolic interference affecting red cell production.

The presence of lymphatic nodules and serous atrophy in the bone marrow was a prominent feature of this case during the first course of drug therapy. To our knowledge these features have not previously been noted in cases of red cell aplasia.

SUMMARY

A case of reversible pure red cell aplasia, due to antituberculous therapy, is reported. Re-administration of isoniazid and para-aminosalicylic acid again produced erythroblastic aplasia.

SUMMARIO IN INTERLINGUA

Es reportate un caso de reversibile aplasia pur de erythrocytos, occurrente como resultado de therapia anti tuberculosis. Le re-administration de
RED CELL APLASIA

isoniazida e acido para-aminosalicylic produceva de novo le mesme aplasia erythroblastic.

REFERENCES


Stephen B. Goodman, M.D., Clinical Instructor in Medicine, University of Colorado Medical Center, Denver, Colo.

Matthew H. Block, Ph.D., M.D., Professor of Medicine and Chief of the Division of Hematology, University of Colorado, Denver, Colo.
A Case of Red Cell Aplasia Occurring as a Result of Antituberculous Therapy

STEPHEN B. GOODMAN and MATTHEW H. BLOCK