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APLASTIC CRISIS IN A CHILD WITH IRON DEFICIENCY ANEMIA.

A Case Report

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It was first recognized by Lyngar[1] that in at least some of the cases of hereditary spherocytosis, the crisis was caused by a sudden decrease of erythrocyte delivery rather than to an increase in the rate of hemolysis. However, the significance of this observation was overlooked until aplastic crises of hereditary spherocytosis had been well recorded by Owren[2] and by Dameshek and Bloom[3] in 1948. Shortly afterwards, Gasser described this acute erythroblastopenic crisis in ten cases of which only two had an antecedent hematological disorder.[4]

Aplastic crises (erythroblastopenic crises) have been described in patients with sickle cell anemia,[5,6,7] hereditary spherocytosis,[2,3,8] erythroblastosis foetalis, [9,10] infectious mononucleosis, [6,7] auto-immune hemolytic anemia,[11,12] paroxysmal nocturnal hemoglobinuria,[13] congenital nonspherocytic hemolytic anemia,[14] kwashiorkor,[15] and iron deficiency anemia.[16] Similar crises have also been observed in hematologically normal people following acute infection, drug toxicity or allergic reaction.[4,17,18]

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Since this kind of bone marrow arrest had been reported only once in the literature (an adult with iron deficiency anemia), we are reporting this case of a child with iron deficiency anemia whose aplastic crisis was well documented.

Case Report

S. Y. (65/16470), a girl 12 years of age, was admitted to Hacettepe Children's Hospital on May 21, 1965 for investigation of hepatosplenomegaly, iron deficiency anemia, growth retardation, and frequent bouts of diarrhea. She had been seen previously at this hospital, in April 1965, for the same complaints but had not been admitted at that time.

The patient is the second child of a 35 year old mother who has given birth to 12 children. The parents noticed that the girl had a protuberent abdomen with frequent bouts of epistaxis and diarrhea of at least five to six years duration. They were certain that her growth was not as good as any of her siblings or other children of her age. She always looked pale and seemed to be less active than the other children.

On physical examination, the patient was found to be a pale, dwarfed, chronically ill looking child. Her height was 101 cm (50th percentile for 4 years of age); weight, 18.5 Kg (50th percentile for five years of age); temperature, 36.2 C; respiratory and pulse rate, 28 and 100 per minute, respectively. A grade II/IV systolic murmur was heard in the precordial area. Crepitant rales were found at the base of the left lung. Her liver and spleen were felt five and eight cm below the right and left costal margin at the midclavicular line in the order given. There was no evidence of development of secondary sex charasteristics. She was mentally normal and the rest of the physical examination was noncontributory.

Laboratory findings were as follows (prior to the aplastic crisis) : several urinalyses were normal with the exception of hypostenuria; NPN, 20mg/100 ml; total bilirubin, 0.6 mg/100 ml, with a conjugated fraction of 0.3 mg/100 ml; total serum protein, 7.5 g/100 ml; albumin, 4.2 g/100 ml; cephalin flocculation, 2+; SGOT, 91 units with normal calcium (10.3 mg/100 ml); phosphorus, 4.5 mg/100 ml; alkalin phosphatase, 8.3 Bodansky units. Thymol turbidity was 2.3 u., and cholesterol was 74 mg/100 ml with esterified form 38 mg/100 ml. Several stool guaiac tests were negative and there were no intestinal parasites. PPD and O.T. skin tests were both negative. X-ray of the chest revealed globular enlargement of the heart. Starch and agar gel hemoglobin electrophoresis did not show any abnormal hemoglobin. Alkali resistant hemoglobin was 2.4 per cent. Quick's one stage prothrombin time was 13 seconds (control 13"). The analysis of serum electrophoresis revealed albumin, 36 per cent; globulins, alpha one, 4.8 per cent; alpha two, 9.7 per cent; beta, 18.7 per cent; gamma, 31 per cent. Bone age was that of an eight year old girl.

Hemoglobin was 3.85 g/100 ml, and the erythrocytes appeared to be markedly hypochromic and microcytic with definite anisocytosis. The platelets were abundant on the peripheral smear and the white blood cells numbered 3800/mm^3. A differential count showed metamyelocytes, 4 per cent; granulocytes, 76 per cent; lymphocytes, 20 per cent. Serum iron, serum iron binding

capacity, and serum copper were 34, 462, and 100 gamma/100 ml, respectively. Direct Coombs test was negative. Examination of the initial iliac crest bone marrow aspiration revealed increased cellularity with mild normoblastic erythroid hyperplasia (M/E ratio was 1). There was no evidence of megaloblastic change or storage cells (Figure 1). With iron staining, no hemosiderin granules were seen in the bone marrow. Glucose tolerance and D-Xylose absorption tests were normal. Needle biopsy of the liver was not diagnostic.

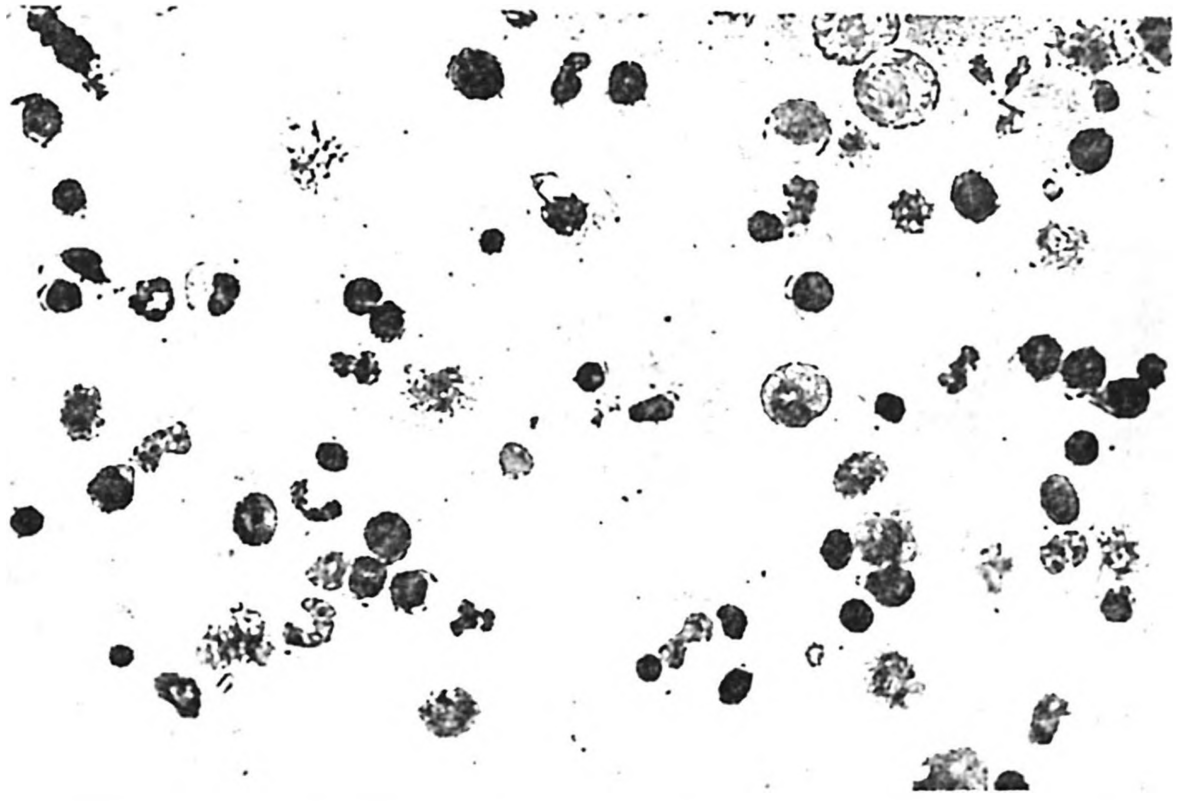

Figure 1. Bone marrow at the time of admission, showing erythroid normoblastic hyperplasia.

The patient's temperature spiked to 39.5 C for the first time on the ninth day after admission. Aside from a slight injection of the throat at this time, physical examination was negative. Blood and throat cultures, urinalysis and chest x-ray gave negative results. This febrile episode lasted for 70 hours and thereafter signs and symptoms disappeared. A blood count repeated on the eleventh hospital day showed hemoglobin, 3.85 g/100 ml; Hct, 13 per cent; WBC, 1100; reticulocytes, less than one per thousand; platelets, definitely decreased on peripheral smear. The next day, Hb was 2.95/g/100 ml, and thrombocytes were 46,000/mm^3. The patient was given a transfusion of 500 cc of whole blood. Since the hemoglobin level did not increase, she was given two more transfusions on the sixth and seventh days of the pyrexial illness. She was treated with penicillin and chloramphenicol for seven days. Stool guaiac remained negative. White blood cell count dropped to its lowest value (900/mm^3) on the fifth day of her acute illness (Figure 2).

On the first day of the acute episode, bone marrow revealed only very few proerythroblasts with normal myeloid elements in normal distribution. A few giant myelocytes and metamyelocytes and «giant cells» were seen. Megakaryocytes were present. The M/E ratio was 60/1 and only erythroblasts were ob-

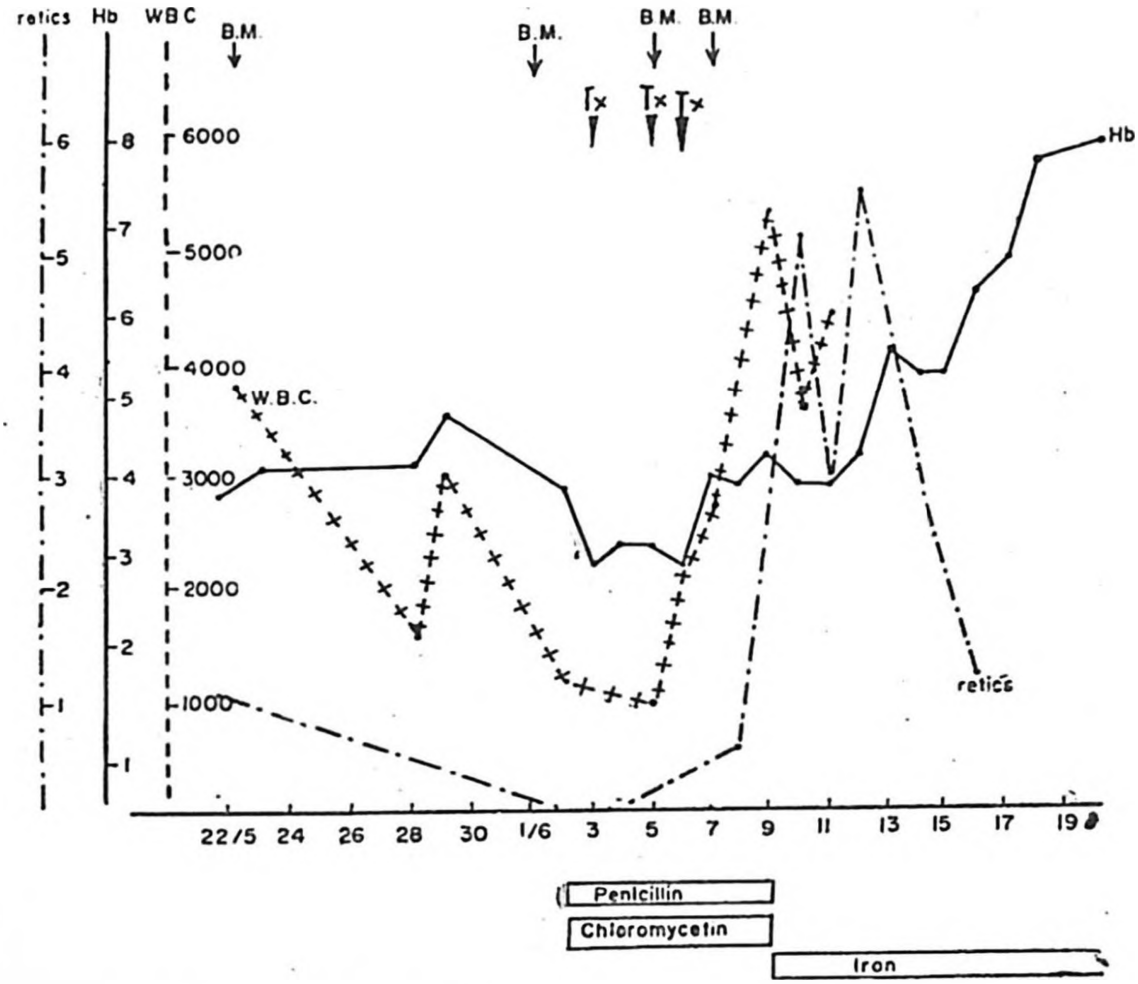

Figure 2. Graph showing changes in hemoglobin, reticulocytes and leukocytes, before, during and after the acute crisis.

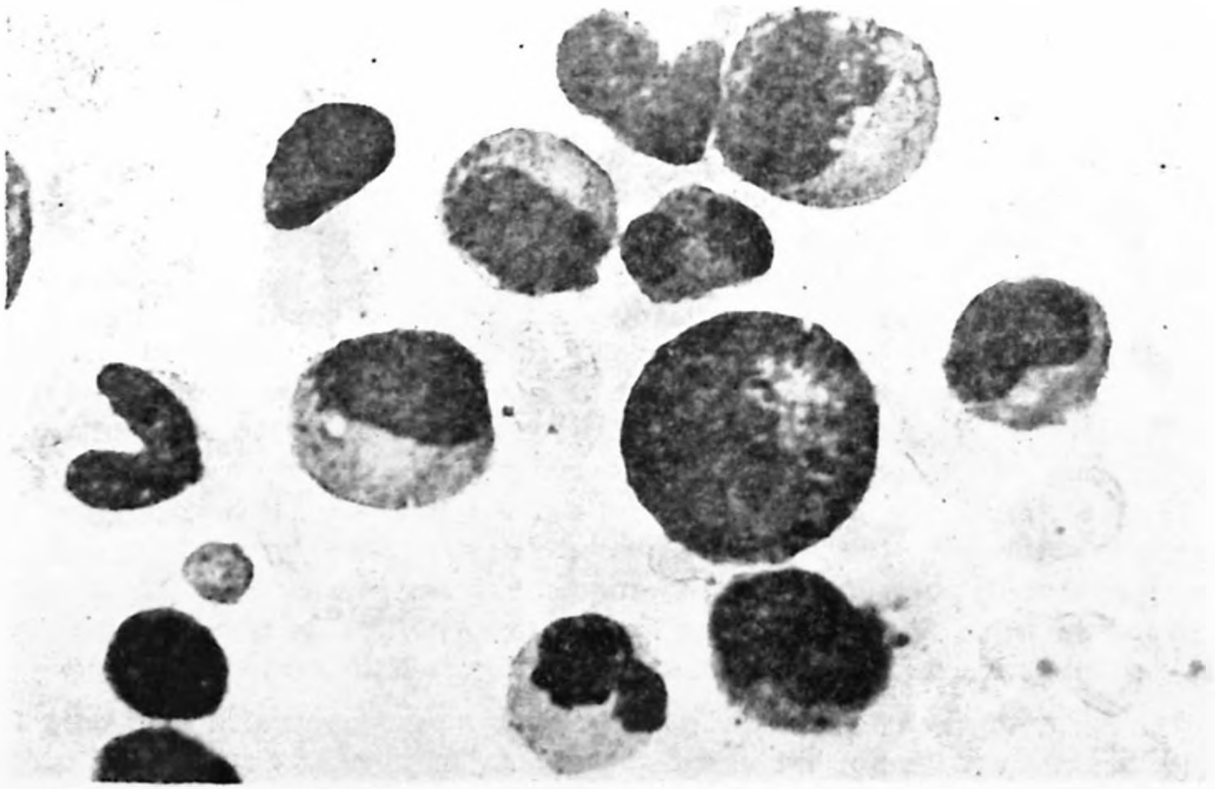

Figure 3. a. Bone marrow on the first day of the acute febrile illness, showing no erythroid precursors.

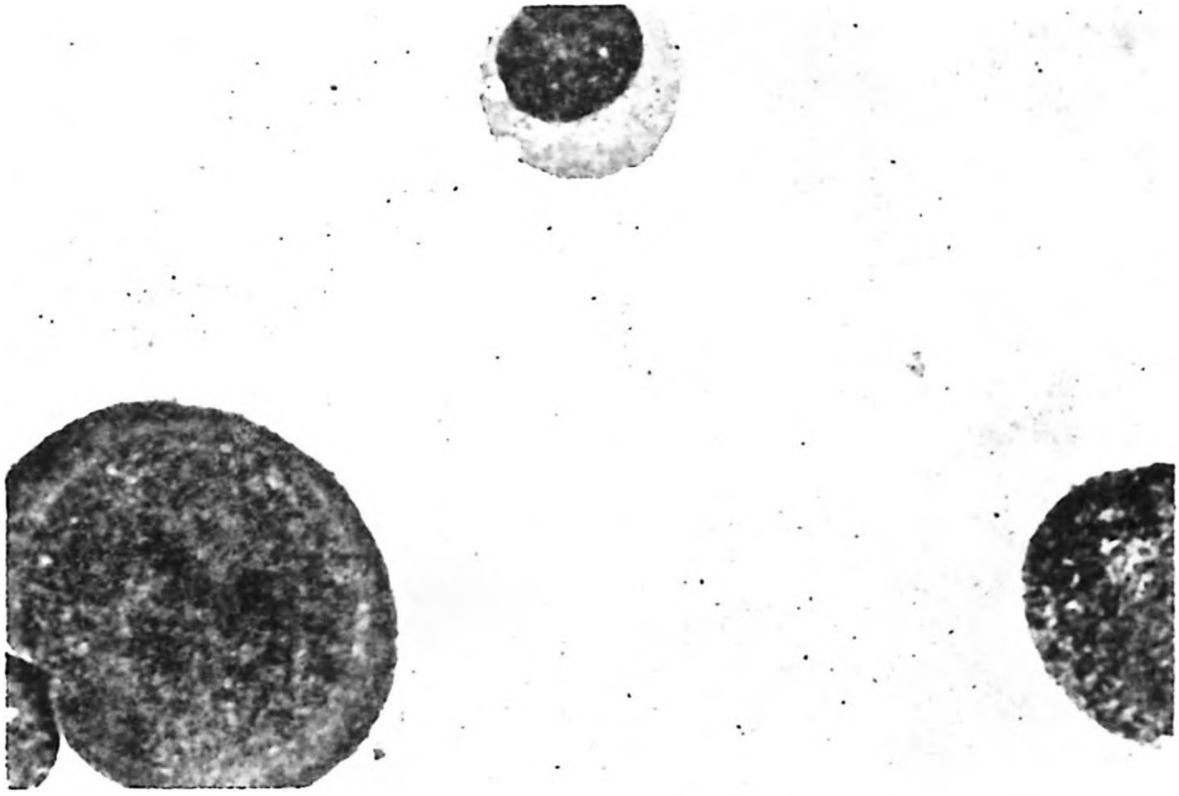

Figure 3. b. So-called «giant proerythroblast» in the same bone marrow sample.

served (Figure 3, a and b). Bone marrow on the sixth day of the febrile illness was found to be fairly cellular. The myeloid elements appeared to be normal and the nuclei of megakaryocytes were seen. Very marked erythroid hypoplasia continued (M/E ratio was 20) but the «giant cells» which were observed in the previous bone marrow sample could not be seen (Figure 4).

Re-examination of the bone marrow two days later showed cellular marrow with normoblastic erythroid hyperplasia and some megaloblastoid changes (M/E ratio was 1.5/1) (Figure 5).

The patient was given ferrous sulfate by mouth on the ninth day of this acute illness, when antibiotics were discontinued. In three days (eleven days after the beginning of the febrile illness) reticulocyte response (5.6 per cent) was observed. Her hemoglobin continued to increase steadily and the patient was discharged with iron medication. No marked changes occurred in the size of the spleen during the acute erythroblastopenic crisis, but at the time of discharge her spleen was becoming smaller.

Discussion

In the so-called aplastic crisis, the marrow essentially shuts down and ceases delivery of cells to the peripheral blood. This is most often seen in relation to erythrocyte production but may also involve leukocyte and/or thrombocyte production.[16, 19] With a loss of red blood cells and hemoglobin of approximately one per cent per

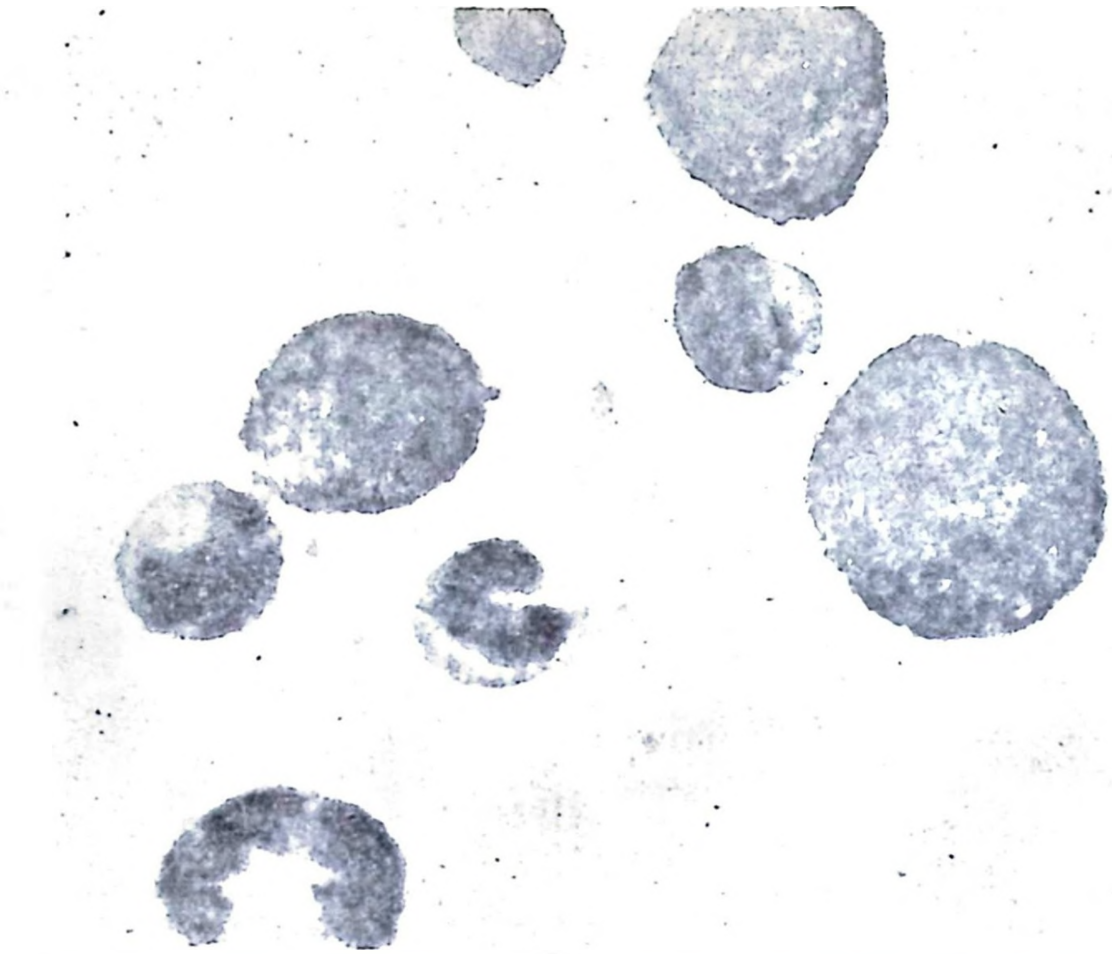

Figure 4. Bone marrow on the fifth day of the febrile illness. There are still no erythroid elements.

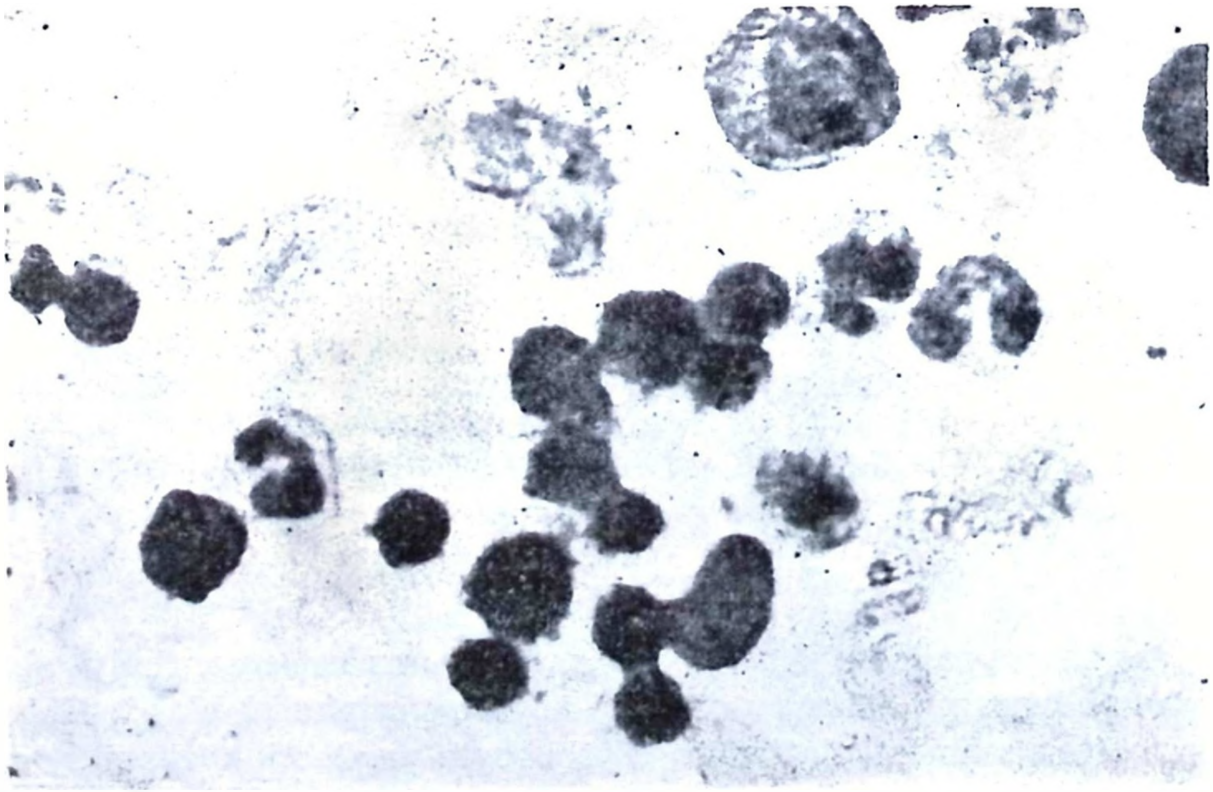

Figure 5. Last bone marrow sample taken on the 7th day of the febrile illness, showing erythroid hyperplasia.

day, at the normal removal rate appreciable time must elapse before significant changes in the peripheral counts can be detected by the usual tests. Since aplastic crises usually last six to 12 days,[20] they might go unnoticed in hematologically normal persons. However, Gasser's observations suggest that such crises are not uncommon in children as a result of infections, intoxications or allergic reactions. During aplastic crises, «giant cells», 20 to 60 microns, have been reported in the bone marrow.[1, 5] These cells are generally considered to belong to the red cell series. Recently Chanarin et al, with PAS staining, presented a piece of evidence that these so-called «giant proerythroblasts», appearing in the early phase just after the onset of the arrest, are megakaryocyte precursors. Since Owren's original article, several authors indicated that there are megaloblastoid changes in the bone marrow during recovery from an aplastic crisis.[2, 8, 11] We also observed a few «giant cells» in the bone marrow at the beginning of the erythroblastopenic crisis and some megaloblastoid changes of erythroid precursors in the last bone marrow sample.

Erythropoietin, which is generally considered to be an essential humoral factor for erythropoiesis, has been measured in several kinds of blood disorders, including hypoplastic and aplastic anemias.[21, 22, 23]

Dr. Okçuoğlu has assayed erythropoietin activity in two patients with sickle cell anemia during aplastic crises and found this activity to be increased.[24] Such assays have not been done for aplastic crises associated with other diseases, including iron deficiency anemia. Although riboflavin has successfully been used in the treatment of erythrocyte aplasia in kwashiorkor, it has not been tried in the other types of erythroblastopenic crises.[25]

Blood transfusion may be helpful, and is often essential, in the treatment of aplastic crisis.[20] Since decreased reticulocytosis is seen in patients who have received transfusions, these should be given when it is absolutely indicated.

In our patient, mild leukopenia, which was thought to be related to hypersplenism, became worse at the beginning of the crisis. Although platelets were not counted prior to the crisis, their number was markedly below normal (64,000/mm^3) during the acute stage and returned to normal following the acute erythroblastopenia.

Mild splenomegaly has been reported in ten per cent of patients with iron deficiency anemia,[27] but marked enlargement of the spleen is not an unusual finding in this kind of anemia in this country.

We made several laboratory tests for the most common causes of chronic marked splenomegaly but found no evidence of portal hypertension, hemoglobinopathy, myeloid metaplasia or thalassemia. Gasser reported that four out of ten of his patients had some degree of splenomegaly. However, since erythroplastopenic crises are observed in hematologically normal persons, it is thought that splenomegally is probably not a causitive factor. Additional evidence for iron deficiency anemia in our patient was her good response to iron treatment in a short period of time. Iron treatment alone activates the growth of children with this type of anemia and their hepatosplenomegaly decreases when the hemoglobin reaches normal levels.[28]

As stated previously, several bacterial and viral infections might cause bone marrow depression. Since we could find no evidence of bacterial etiology of the acute febrile illness, which was most likely the cause of the aplastic crisis, we accepted a viral etiology retrospectively.

Summary

A well documented acute erythroblastopenic crisis in a girl with iron deficiency anemia is reported. Since this condition was described only once previously in an adult, our case was considered to be of interest. The possible causes of the crisis and the bone marrow changes are briefly summarized.

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