Hemosiderosis in Association With Thalassemia Minor

CPT Charles E. Williams, MC, USA, and
LTC Arnold W. Siemsen, MC, USA, Honolulu

Iron deficiency anemia is by far the most common of the hypochromic microcytic anemias, but in recent years at least six other hypochromic syndromes have been described, the most common of which is thalassemia.[1] The thalassemia syndromes are being recognized more frequently, and it is now known that they occur commonly in Southern Asia and the Middle East, as well as in the Mediterranean countries. With increasing migration of these population groups, thalassemia will be seen with greater frequency.

Thalassemia syndromes, characterized by a mild anemia, mild morphological changes in the peripheral red blood cells (RBC), and slight splenomegaly, usually cause no symptoms or are associated with mild fatigue. This process has been characterized as being completely benign and free of complications. It is the purpose of this report to examine the significance of excessive iron storage in the thalassemia "minor" syndromes and to report a case of hemosiderosis of the liver parenchyma in association with thalassemia minor.

Patient Summary

A 30-year-old white Marine of French-Italian descent was admitted to Tripler Army Medical Center for evaluation of anemia. His only complaint was mild fatigue on exertion. He had been turned down as a blood donor on three previous occasions. He had never received blood transfusions or taken any drugs or tonics containing iron. His father was living and well, with no known anemia; his mother, however, had been anemic for many years and had received blood transfusions "without any improvement in her anemia." Two sisters were also known to be anemic, but had not been treated. The family members were not available for study.

Physical examination revealed a healthy appearing white man, with a blood pressure of 120/90 mm Hg and a pulse rate of 90 beats per minute. The facies and skin were of normal appearance, and the remainder of the examination was normal except for the spleen which was palpable 3 cm below the left costal margin. The liver was not enlarged.

Laboratory studies revealed a hematocrit reading of 36.5%, a hemoglobin level of 10.9 gm/100 cc, and an RBC of 4,600,000/cu mm. The white blood cell count (WBC) was 6,600/cu mm, with a normal differential. The platelet count was normal. Peripheral smear showed poikilocytosis (3+), anisocytosis (3+), stippled RBC (1+), and target cells (1+). The red cell mean corpuscular volume (MCV) was 81 cuμ, with a mean corpuscular hemoglobin (MCHgb) of 24μμg and a MCHgb concentration of 30%. The reticulocyte count was 1.6%. Total bilirubin was 1.4 mg/100 cc, of which 0.6 mg/100 cc was direct. The RBC showed increased resistance to hemolysis in hypotonic saline. Serum iron values were 192μg/100 cc and 216μg/100 cc, with corresponding total iron binding capacities of 230 and 223 (83% to 96% saturation). Hemoglobin electrophoresis revealed 6.3% fetal hemoglobin and 4% A_2 hemoglobin. A bone marrow aspiration showed erythroid hyperplasia with increased amounts of iron (Fig 1). The following studies were normal: glucose tolerance test, urinalysis, blood urea nitrogen (BUN), creatinine, serum electrophoresis, and x-ray films of the chest, skull, and long bones. A liver biopsy was performed because of the highly saturated total iron binding

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From the Department of Medicine, Tripler Army Medical Center, Honolulu. Doctor Williams is presently at the Concord Community Hospital, Concord, Calif.

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Reprint requests to 2425 East St, Suite 12, Concord, Calif 94520 (Dr. Williams).

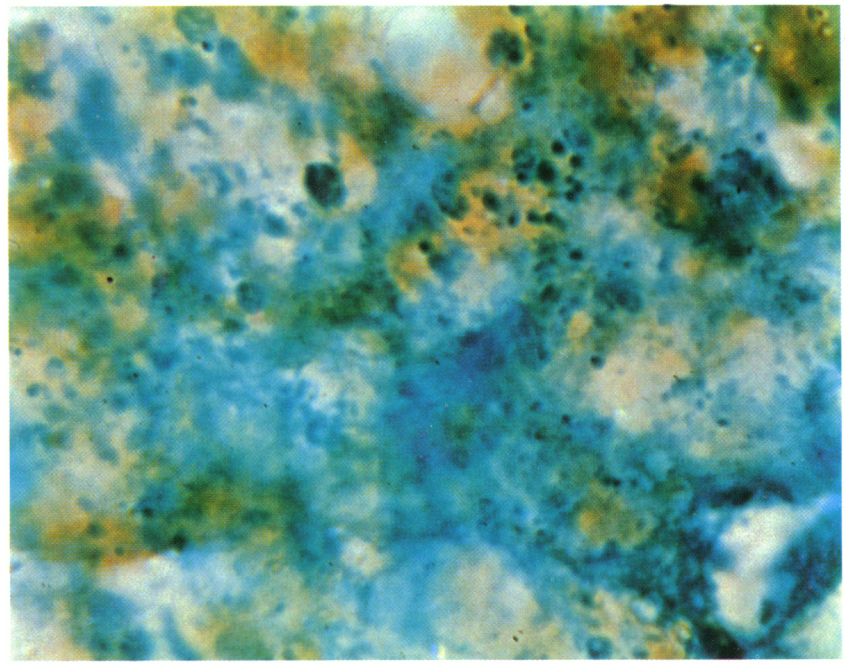

Fig 1.—Sternal bone marrow specimen stained for iron demonstrating marked increase in iron storage (potassium-ferrocyanide stain).

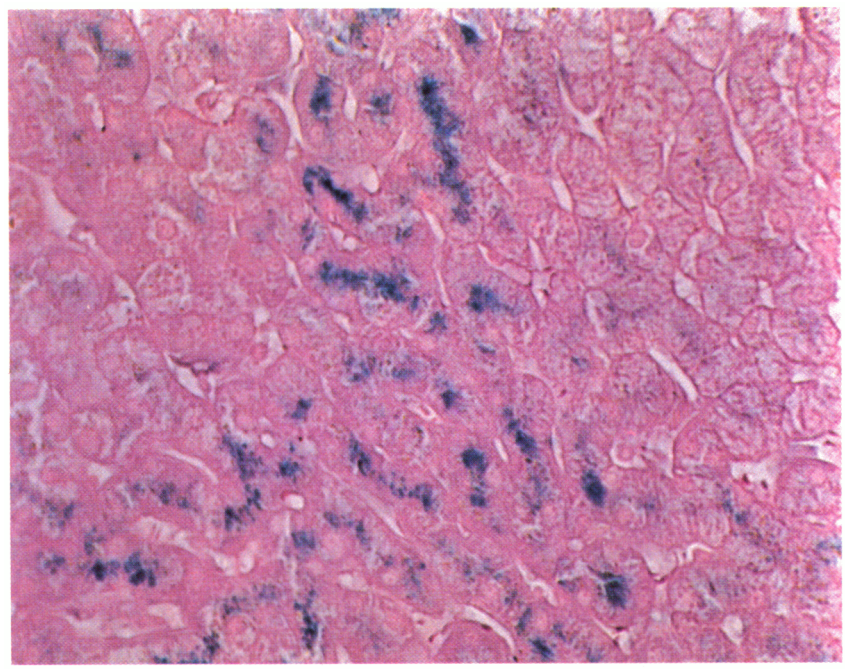

Fig 2.—Liver biopsy specimen demonstrating hemosiderosis of hepatic parenchymal cells (prussian blue stain).

capacity and revealed hemosiderosis of the hepatic parenchymal cells (Fig 2).

Variability of the Thalassemia Syndromes

Thalassemia syndromes are characterized by genetic errors in the rate of production of one or more of the polypeptide globin chains.[2,3] The clinical picture depends upon the chain or chains which are involved and on the extent of depression in their rate of production. It is known that the hemoglobin molecule contains four globin chains; and on the basis of genetic studies, it is felt that the production of each of the four chains is controlled separately by its own genetic information.[3] Whether the defect in production of polypeptide chains in thalassemia is in the messenger ribonucleic acid or the ribosomes of the erythroid cell is not known, but the end result is an excess of unaffected globin chains in the RBC. It has been postulated that the excess chains which are not utilized in the formation of hemoglobin, precipitate in the RBC, shortening its lifespan, thus accounting for the hemolytic component seen in thalassemia.[4]

Clearly, thalassemia consists of a broad spectrum of genetic syndromes. The major categories are listed in the following tabulation:

1. Cooley's thalassemia major (homozygous beta chain)
2. Hydrops fetalis (homozygous alpha chain)
3. Thalassemia minor (heterozygous state)
   a. Alpha
   b. Beta
      "A_2 type"—elevation of A_2 Hgb with slight or no elevation of fetal Hgb
      "F type"—elevation of F Hgb with normal levels of A_2 Hgb
4. Thalassemia "intermedia" (combined A_2 and F)

Cooley's thalassemia major is a homozygous state in which both beta chains are involved. Since fetal hemoglobin contains no beta chains, the disease process appears in the first year of life, as adult hemoglobin replaces the fetal hemoglobin. These patients rarely live to adulthood, and there is no question that excessive iron storage is a serious problem. Hemochromatosis is a frequent complication of thalassemia major. The total body iron in these patients is more than can be accounted for on the basis of transfusions alone, and some cases of Cooley's anemia have been reported in which hemochromatosis developed in the absence of transfusion therapy.[5]

Homozygous alpha chain thalassemia has been reported from several areas in the world, including Kuala Lumpur in Malaya. Since fetal hemoglobin would be affected by abnormalities in the production of alpha chains, one would expect homozygous alpha chain thalassemia to be a disease of the fetus, and this has been found to be true.[6] The fetus suffers from a hemolytic process more severe than that seen with Rh or ABO incompatibility, resulting in erythroblastosis, hydrops fetalis, and fetal death about the 32nd week of gestation. Since the gamma chains of fetal hemoglobin are produced at a normal rate and are present in abundant quantity in comparison to the affected alpha chains, a large percentage of hemoglobin in the form of four gamma chains (Bart's hemoglobin) is present in these stillborns.

The heterozygous thalassemia syndromes consist of the "alpha" type in which one alpha chain is involved and there is no increase in either A_2 or F hemoglobins, and the "beta" type in which there may be elevation of A_2 or F hemoglobin.

There are two major patterns in thalassemia minor of the "beta" type. The most common of these is the "A_2 type" in which the level of A_2 hemoglobin is elevated in the range of 3% to 7% and the amount of fetal hemoglobin is either normal or only very slightly elevated. It is in this category that our patient belongs. The less common type of beta thalassemia minor is the "F type" in which the A_2 hemoglobin remains normal, but the level of fetal hemoglobin ranges from 10% to 20%.

Thalassemia "intermedia" is a term which refers to a thalassemia syndrome which is intermediate in severity between the mild thalassemia minor and the severe process of Cooley's thalassemia major. At least one explanation for this clinical syndrome is that the A_2 and F types of beta thalassemia occur in combination in the same patient.[7]

The Problem of Iron Storage

As mentioned previously, hemochromatosis is a frequent complication of homozygous beta thalassemia. In thalassemia intermedia, hemosiderosis of the hepatic parenchymal cells has been reported in one case.[7] In thalassemia minor, the problem of excessive iron storage has been controversial. Mendel[5] feels that hemochromatosis occurs in thalassemia minor, but is rare. Crosby[8] states that in the absence of exogenous iron or transfusion therapy, hemosiderosis of the liver does not occur in thalassemia minor.

In the absence of an effective excretory mechanism for iron, the total body iron content is mainly a function of iron absorption by the gastrointestinal tract. Normally only 10% or 15% of the dietary iron is absorbed. Clearly under some circumstances the gastrointestinal tract absorbs an increased amount of iron, even in the presence of an increased total body iron content. Thus, secondary hemochromatosis has been reported in cases of excessive oral intake of iron, in the "sideroachrestic" anemias, in thalassemia, and in the hemoglobinopathies, to list a few. Radioactive iron (^{59}Fe) absorption studies have demonstrated an in-

creased percentage of iron absorption in many of these diseases; however, iron absorption in thalassemia minor has been reported to be normal in several studies.[9,10]

Iron kinetic studies in thalassemia minor demonstrate several of the abnormalities known to be associated with increased iron absorption. Of the many factors known to affect iron absorption, the total body iron content, the amount of iron ingested, the rate of erythropoiesis, and the presence of anemia are the major determinants.[5] Briefly stated, the amount of iron absorbed increases (1) if the total body iron content is depleted, (2) if the dietary iron is increased, (3) if the rate of erythropoiesis is increased, especially in states associated with "ineffective" erythropoiesis, and (4) if anemia is present.

Studies done on patients with thalassemia minor reveal that serum iron levels are frequently elevated, a situation known to be associated with excessive iron storage.[11] It should be noted, however, that it is not clear whether or not these patients have received prior exogenous iron therapy or transfusions. Erythrokinetic studies done in thalassemia minor demonstrate a reduction in RBC volume, an increased plasma iron turnover to rates three to four times that of normal, and impairment of utilization of iron in the circulating RBC. The average utilization of iron in the circulating RBC at 14 days is 58%, as compared to the normal 80% to 95%.[12] Thus, a mild anemia is frequently present in association with hyperplasia of the erythroid marrow, which is reflected by the increased plasma iron turnover. Despite the hyperactive erythroid activity, consistently poor iron utilization is observed, an observation consistent with "ineffective" erythropoiesis. Thus, several of the major factors known to induce increased absorption of iron are present in thalassemia minor.

Reports of excessive iron storage complicating thalassemia minor are rare. Two cases of hemochromatosis associated with proven thalassemia minor have been reported,[13,14] but one of these cases is known to have received 0.9 gm of iron intravenously and 50 transfusions of blood. This would represent approximately 13.5 gm of exogenous iron therapy. The second case may well not have represented a true instance of thalassemia minor as the patient was seriously anemic and had a hemoglobin F concentration of 18%. Two cases of hemosiderosis of the hepatic parenchymal cells have been reported in siblings, both of whom had 100% saturation of their total iron binding capacity, and one of whom had received 8 gm of iron intravenously.[15]

Clearly, excessive iron storage in thalassemia minor has not been a major clinical problem; however, the case presented herein demonstrates the capacity of such a patient to develop hepatic hemosiderosis in the absence of any form of exogenous iron. Clinicians should be alert to the possibility of thalassemia minor as the cause of hypochromic microcytic anemia, as opposed to iron deficiency, since iron therapy is clearly contraindicated in the great majority of cases of thalassemia minor.

Summary

Of the hypochromic microcytic anemias, thalassemia is the second most common. Hemochromatosis is a frequent complication of thalassemia major. Excess iron storage has rarely been reported as a consequence of thalassemia minor, except in conjunction with exogenous iron therapy.

A case is reported of a 30-year-old man with thalassemia minor, who demonstrated 83% saturation of his total iron binding capacity and homosiderosis of the liver parenchyma on liver biopsy.

The etiology of excessive iron storage and the pathophysiology of thalassemia minor are reviewed. Factors known to be responsible for excess iron storage are present in thalassemia minor. Physicians are cautioned against the use of iron therapy in hypochromic microcytic anemia without first establishing a diagnosis of iron deficiency.

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