Secondary Hemochromatosis

II. Report of a Case Not Attributable to Blood Transfusions

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HISTOCHEMICAL ANALYSES in certain cases of so-called “transfusion hemochromatosis” have revealed considerably greater amounts of iron in the body than had been given the patient by the intravenous route. This discrepancy is explained by continued intestinal absorption by the anemic patient of more iron than was utilized for blood formation. Dubach, Callender, and Moore actually demonstrated the latter phenomenon with radioactive tracer iron in patients with pernicious anemia, refractory anemia, and hemolytic anemias, even though the tissues were already replete with iron.

Houston reported a case of hemochromatosis in a man with refractory anemia which he deduced to have existed for some thirty years; during this time the patient had been given no transfusions. In their review of transfusion siderosis, Wyatt, Mighton, and Moragues mention an 85 year old woman who subsisted for years on “tea and toast” and who had chronic refractory anemia. Although the patient had never received a transfusion, an autopsy showed hepatic cirrhosis, 22.5 Gm. of iron in the liver, and iron deposition in the pancreas and periportal lymph nodes. Block, Bethard, and Jacobson recently reported a patient who had marked hemosiderosis and slight scarring of the liver after only eight transfusions. In the former two instances, iron absorption was the sole means of accumulation of the excess iron, and in the latter case it was probably the major factor.

The following case is presented as an example of hemochromatosis developing in a man with a refractory hypochromic anemia which had first been documented twenty-two years before his death. Although blood transfusions may have aggravated the already existing hemochromatosis, the few that were given played no part in its causation.

CASE REPORT

C. K., a 55 year old, white male, was admitted to the hospital in November 1951, because of dyspnea and edema. In June 1930, he had been seen elsewhere because of anemia. At that time his liver was palpable, but his spleen could not be felt. The hemoglobin was 10.2 Gm., the erythrocyte count 3,850,000, and the MCH 26.5 μg/L. The erythrocytes showed marked hypochromasia, moderate anisocytosis and poikilocytosis, and slight basophilic stippling and polychromasia. The gastric contents contained free HCl. The serum bilirubin was 1.9 mg. per 100 ml., indirect reaction. While the patient ate a meat-free diet, benzidine tests were positive and guaiac tests were negative on three stool
specimens. X-ray studies of the chest and gastrointestinal tract were negative. The patient was given ferric citrate, 30 grains three times daily, which he took for at least two months.

Later in 1930, his family physician gave him weekly liver injections. It was noted that his skin was a "muddy" color and that his abdomen was enlarged. He was treated subsequently with liver and at times with iron. During the 1930's exertional dyspnea and weakness occurred. During the 1940's, the patient's abdominal distention increased, and he had several episodes of anginal chest pain. His skin continued to darken. In March 1950, the hemoglobin was 10.2 Gm., the erythrocyte count 3,020,000, and the sulfobromophthalein retention 14 per cent in 45 minutes. The patient was given one blood transfusion and oral therapy with ferrous gluconate, 10 grains per day for two months. On June 1, 1950, he was given 1000 ml. of blood, raising the hemoglobin to 10.2 Gm. By June 8, it had fallen to 7.9 Gm. A skin biopsy showed "hemochromatosis." Six weekly injections of vitamin B12, 15 μg. each, produced no benefit. During the rest of 1950, there was increase of dyspnea and weakness, and onset of polyphagia, polydipsia, polyuria, and nocturia. The patient had lost 15 to 20 pounds during the previous eight years. There was a vague story of frequent crampy midabdominal pain. Three weeks before admission there was onset of dependent edema, with increase in weakness and dyspnea.

The patient had consumed large quantities of alcohol until 1929, and none thereafter. There was no family history of diabetes or abnormal skin pigmentation.

Physical examination in December 1951, revealed an intensely bronzed man with a mongoloid facies, five feet tall, and weighing 125 pounds. There was abdominal enlargement, with shifting dullness and dilatation of superficial abdominal veins. The liver extended 9 fingerbreadths below the right costal margin and the spleen was palpable 4 fingerbreadths below the left costal margin. There was marked dependent edema. Blood pressure readings were normal.

The hemoglobin was 8 Gm., erythrocyte count 3,110,000, hematocrit 31 per cent, MCD 8.9, MCV 100, MCH 26, and MCHC 26. The leukocytes numbered 12,250 with 55 per cent neutrophils, 40 per cent lymphocytes, and 5 per cent eosinophils. The sedimentation rate was 9 mm. (Westergren). Blood smears revealed moderate to marked hypochromasia, anisocytosis, and poikilocytosis; mild polychromasia; and occasional normoblasts, stippled erythrocytes, macrocytes, target cells, and Howell-Jolly bodies. Of the erythrocytes, 0.5 per cent contained from two to twenty-five small dark blue bodies which were shown to be siderotic with an iron stain (fig. 1). The reticulocyte count was 4 per cent. A sodium metabisulfite test for sickling was negative. An erythrocyte fragility study showed beginning hemolysis in 0.54 per cent saline and complete hemolysis in 0.27 per cent saline, with corresponding control findings in 0.48 and 0 per cent saline, respectively. The bone marrow showed normoblastic hyperplasia, with a 7 per cent myeloid-erythroid layer, and an erythroid-nonerythroid ratio of 1 to 1.5; excessive hemosiderin deposition was marked, especially in the perivascular regions. The urine tested 4-plus for reducing substances. The fasting blood glucose was 308 mg. per 100 ml. Sulfobromophthalein retention was 10.9 per cent, 45 minutes after injection of 5 mg. of dye per Kg. of body weight. The serum bilirubin was normal, thymol turbidity 12.3, serum cholesterol 157 mg. per 100 ml., with 58 per cent esters, and the plasma prothrombin activity 49 per cent (15.5 seconds). Gastric achlorhydria after injection of histamine was demonstrated. The guaiac test produced a 1 plus reaction on two out of seven stool specimens; two of these specimens were negative for ova and parasites. Proctoscopy revealed only slight mucosal granularity at 3 inches. The serum iron was 187 μg. per 100 ml., and the serum iron binding capacity was 0. The erythrocyte free coproporphyrin was 2.4 μg. per cent, and the erythrocyte free protoporphyrin and twenty-four hour urine coproporphyrin were normal. Fecal urobilinogen determinations revealed excretion of 78, 210, and 270 mg. per day, on separate four day specimens, the latter being concurrent with an 8.4 per cent reticulocyte count. Serologic tests for syphilis were negative.

X-ray pictures of the chest showed left-sided pleural effusion and slight enlargement of the ventricles. Films of the abdomen showed calcified gall stones and diffuse mottled calcifications in the spleen. A gastrointestinal survey was negative. Skull films showed marked thickening of the diploe with a somewhat granular appearance to the skull, but
without any radiating "spicules" in the outer table. An electrocardiogram showed multiple nonspecific T-wave abnormalities.

Examination of two brothers of the patient and a nephew revealed normal hematologic values, including hemoglobin and blood smears.

The patient was treated with a low sodium, diabetic diet and insulin. In January 1952, the reticulocyte count ranged between 0.2 and 1.2 per cent, and anemia persisted unchanged despite therapy with parenteral vitamin B₁₂ and oral folic acid. In March, the MCV was 8.5, MCH 133, MCHC 37, and MCHC 27, and the reticulocytes 5.9 per cent. A skin biopsy showed iron-staining pigment in the germinal layer of the epidermis, in the skin appendages, and in scattered independent areas throughout the connective tissue. A liver biopsy showed marked cirrhosis and large quantities of hemosiderin pigment. The patient was discharged on April 26, 1952.

He was readmitted on May 13 because of oppressive chest pain, dyspnea, and orthopnea. Severe congestive heart failure was evident on examination, with auricular fibrillation and a pericardial friction rub. The hemoglobin was 8 Gm., the leukocyte count 20,000 with 73 per cent neutrophils, and the fasting blood glucose 213 mg. per 100 ml. Despite therapy with insulin, digitoxin, and oxygen, a shock-like picture ensued, and after a short interval of coma, the patient died on May 15, 1952.

**Necropsy findings:** The body was 156 cm. long and weighed about 100 pounds. Ascites and hydrothorax were present. The pericardial surfaces were rather dull. The heart weighed 500 Gm., and contained a granular, adherent thrombus in the right auricular appendage. The valves and coronary arteries appeared normal. The right and left lungs weighed 420 and 390 Gm., respectively, and appeared normal. The liver weighed 3000 Gm.; it was coarsely nodular throughout and mahogany in color. It contained two sharply demarcated but unencapsulated areas, pale yellow in color, and each measuring 5 mm. in diameter. The gall bladder contained two dark brown, facetted calculi. The spleen weighed 1000 Gm.; its capsule was greatly thickened, up to 1 cm. in some areas. The parenchyma was peculiarly mottled, with alternating reddish-brown and yellowish areas, and it was extremely firm, with unusually prominent fibrous bands traversing its substance. The pancreas was deep mahogany in color. Numerous lymph nodes were reddish-brown, this being most marked.

**Fig. 1.—Peripheral blood. Arrows point to erythrocytes containing siderotic granules. Black dots elsewhere are artifacts. X 720. Wright’s stain.**
in the retroperitoneal, periaortic area. The marrow of the ribs, sternum, and vertebrae was dark red.

**Microscopic findings:** The liver showed severe portal cirrhosis (figs. 2 and 3). Hemosiderin deposition was heavy within both liver cells and macrophages in the scarred portal areas. No iron could be found, however, in the two yellow nodules seen grossly; these consisted of liver cells alone (without portal areas), not arranged in any pattern, quite pleomorphic, and containing many bizarrely shaped nuclei. The spleen (fig. 4) presented a remarkable picture with large areas of very dense fibrosis, throughout which were scattered irregular and fairly large masses of pigment. This pigment was black on hematoxylin-eosin stains and showed an intense Prussian blue stain reaction. The latter stain also revealed iron-containing pigment in the walls of some of the large blood vessels; the edges of the larger masses of pigment faded out in the surrounding red pulp in the form of many extremely finely branched fibrils. The reticuloendothelial cells themselves were relatively free from iron-containing pigment, however. There were large areas of splenic parenchyma between the above described areas which contained no iron at all. The right atrium revealed a few neutrophils in the visceral pericardium, representing a very early pericarditis; every myocardial fiber examined contained considerable iron pigment, but no fibrosis or necrosis was apparent. The pancreas (figs. 5 and 6) was mildly fibrotic, with iron-containing pigment in both acinar and islet tissue, especially in the former. Gomori stains failed to reveal any beta granules in the islet cells. Iron-containing pigment was also found in the epithelial cells of the pancreatic ducts, skin appendages, bronchial glands, gastric mucosa, thyroid, parathyroid, adrenal cortex, and in occasional distal convoluted and collecting tubules of the kidney; in the endothelium of some small arteries; and in lymph nodes, especially in areas immediately surrounding sinusoids. The bone marrow showed marked erythroid hyperplasia and massive deposits of hemosiderin. There was moderate renal arteriolosclerosis.

**Final diagnosis:** (1) Hypochromic refractory anemia; (2) hemochromatosis of the liver (siderotic cirrhosis), secondary; (3) congestive heart failure due to myocardial hemosiderosis; (4) hemosiderosis of the bone marrow, spleen, lymph nodes, heart, skin, and all body epithelium; (5) pancreatic fibrosis and hemosiderosis; (6) diabetes mellitus; (7) acute pericarditis.
Fig. 3.—Higher power view of liver, showing dense deposition of hemosiderin in liver cells, in von Kupffer cells, in macrophages scattered throughout fibrous tissue, and in bile duct epithelium. × 160. Prussian blue.

Fig. 4.—Spleen. Heavy clumps of hemosiderin are deposited in the fibrous tissue of Gamma-Gandy bodies. × 75. Prussian blue.

Fig. 5.—Pancreas. Extensive interacinar fibrosis is demonstrated. × 75. Hematoxylin and eosin.

Fig. 6.—Higher power view of pancreas, revealing heavy iron deposition in the acinar tissue and smaller amounts in an islet. × 200. Prussian blue.
SECONDARY HEMOCROMATOSIS. II

Discussion

This case is an instance of long-standing hypochromic anemia in which the patient developed hemochromatosis and died a cardiac death, apparently due to the hemochromatosis. Skin pigmentation and an abnormal sulfobromophthalein retention were noted before any transfusions had been given. Thus, the accumulation of body iron in sufficient excess to produce the clinical picture of hemochromatosis occurred solely as a result of excessive intestinal absorption of iron. Seven blood transfusions, all given the patient during the last two years of his life, added approximately 1.75 Gm. of iron to his body iron content. Since the usual body iron content in hemochromatosis is about 25 Gm., the increment supplied this patient by blood transfusions was probably small, emphasizing the minor role played by transfusions in the pathogenesis of this case.

The patient's anemia can be attributed, at least in part, to a defect in incorporation of iron into forming erythrocytes; superimposed macrocytosis could be due to his hepatic cirrhosis. This anemia does not appear to represent a form of thalassemia minor, as we had originally conjectured that it might, because of the absence of myeloid immaturity, the absence of icterus, and the presence of siderocytes and slightly increased erythrocyte fragility. The only other disorder which could account for hypochromic anemia without evidence of blood loss and without response to iron therapy would be hereditary hypochromic anemia. This disease, first defined by Rundles and Falls, is considered to be the correct diagnosis of our patient's anemia. Erythrocyte inclusions, seen in several of their cases, support this diagnosis. However, our study of hereditary factors in this case was inadequate because of the unavailability of enough relatives, and the diagnosis must therefore remain, to a degree, uncertain.

The peculiar iron deposition in the spleen appears to have been simply the result of Gamma-Gandhi body production, associated with portal hypertension. This picture is completely different from hemosiderosis of the spleen found after multiple blood transfusions, in which case the hemosiderin is scattered diffusely throughout the spleen in the phagocytic reticuloendothelial cells.

While in this case excessive iron absorption might have been a primary defect, only coincidental with the anemia, it might also be considered that the anemia was the stimulus to continued or increased absorption of iron. This seems likely, for instance, in Mediterranean anemia, in which the apparent quantity and distribution of body iron are much like that in idiopathic hemochromatosis. Such patients must have defects not only in incorporation of iron into the erythrocytes, but also in regulation of iron absorption, and they apparently continue to absorb iron from diet and prescribed medications despite the presence of superabundant iron stores. In our case, the apparent amount and duration of abnormal iron absorption and storage were sufficient to produce not merely hemosiderosis, but actual hemochromatosis. We therefore feel that this patient's primary disease was a refractory anemia of obscure etiology, probably hereditary hypochromic anemia, and that the cause of his death was a form of secondary hemochromatosis.

Most reports of secondary hemochromatosis have stressed the etiologic role of multiple blood transfusions. However, some authors noted that transfusions
were insufficient in some instances to account entirely for the massive iron stores found in the body. The latter instances fit into a pattern with cases such as the ones reported here and elsewhere,1-7 and with demonstrations of poorly regulated iron absorption4 and excessive storage10 in certain anemias. The pattern suggests strongly that continued, possibly increased, intestinal absorption of iron is a feature common to both primary and secondary hemochromatosis. Since most patients with chronic refractory anemias die before enough iron deposition has occurred and before sufficient time has elapsed to produce the pathologic changes of hemochromatosis, study usually reveals only hemosiderosis. However, in the rare case in which the anemic patient survives for a few decades without transfusion therapy, hemochromatosis occurs simply as a result of poorly regulated or abnormal absorption of iron. Hemochromatosis might develop earlier if blood transfusions are given such patients, as is suggested by the presence of that disease only a few years after onset of anemia not associated with blood loss and for which multiple transfusions were given.11 If the latter patients were able to survive untreated for perhaps twenty or thirty years, it is conceivable that some of them might develop hemochromatosis solely because of excessive absorption of iron. In other words, blood transfusions probably hasten the onset of this disease in conditions under which it might ultimately develop without transfusions, provided the anemic patient lived long enough.

The etiologic role of iron is not yet completely understood with respect to the hepatic cirrhosis and pancreatic fibrosis of hemochromatosis. While it has been suggested that accumulation of excess body iron is simply an associated phenomenon in this disease,1-6 we believe that the iron is a major etiologic factor in the production of its fibrotic manifestations. This belief is supported by relatively rapid development of hemochromatosis when iron is supplied in massive amounts by means of blood transfusions. In any event, it is evident that secondary hemochromatosis occurs as a complication of anemia. Furthermore, while accumulation of the enlarged iron store usually results from a variable combination of blood transfusions and excessive iron absorption, the latter alone may in rare instances be the mode of entry of all the body iron present.

The case of a 65 year old woman with hemochromatosis was discussed in a recent clinicopathologic exercise at the Massachusetts General Hospital.12 This patient, anemic since the age of 16, had been treated through the years with oral iron and, for a brief time, with injections of iron. Another case, reported by Wallerstein and Robbins,13 occurred in a patient who had chronic hemolytic anemia and who had received prolonged oral medication with iron. The findings in these patients and in the subject of this report suggest that people with chronic anemia should not be maintained on iron therapy indefinitely, once refractoriness has been demonstrated by adequate therapeutic trial. Furthermore, these findings lend support to the thesis that iron therapy is needless, and may even be harmful, in cases of chronic anemia associated with normal or increased body iron stores.

Conclusions

Secondary hemochromatosis is reported in a patient who had a chronic refractory anemia which was known to have existed for at least twenty-two years.
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Blood transfusions played an insignificant role in the pathogenesis of the hemochromatosis, but the repeated oral iron therapy which the patient received might have accelerated its onset. Excessive body iron may appear only as hemosiderosis; this occurs in certain chronic anemias not associated with blood loss. However, the present case suggests that such hemosiderosis, if sufficiently massive and prolonged, becomes associated with the clinical and pathologic picture of hemochromatosis.

REFERENCES

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