An Autopsy Case of Secondary Iron-overload Cardiomyopathy

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Abstract

A woman over 70 years of age presented with anemia and appetite loss. She had no history of blood transfusions, although she had been receiving iron infusions for anemia for seven years. She had an elevated serum ferritin level (7,951 ng/mL) one month before admission. Abdominal computed tomography showed increased hepatic density and echocardiography showed normal heart valves and heart-wall motion. The patient eventually experienced atrial tachycardia and atrial fibrillation and died of heart failure. An autopsy revealed iron deposits in the liver, pancreas, adrenal glands, thyroid gland, gastric mucosa and myocardium. Iron-overload cardiomyopathy was diagnosed based on the iron deposits, myocardial disarray and interstitial fibrosis.

Key words: secondary hemochromatosis, iron-overload cardiomyopathy

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Introduction

Secondary hemochromatosis occurs primarily in patients with hereditary anemia, including alpha-thalassemia, beta-thalassemia and sickle cell anemia. Intravenous iron administration is considered to be a risk factor for hemochromatosis; the excess iron cannot be actively excreted, leading to iron overload, possibly followed by organ damage. The heart, liver and endocrine glands are the primary structures affected by excess iron accumulation, and iron overload primarily manifests as cardiac dysfunction and failure, liver dysfunction and cirrhosis and endocrine abnormalities, such as hypothyroidism, hypogonadism and diabetes mellitus (1, 2).

Only a few case reports have definitively demonstrated the development of secondary hemochromatosis due to the long-term administration of intravenous iron. Furthermore, few reports have described iron deposition in the majority of organs or death from iron-overload cardiomyopathy.

Case Report

A woman over 70 years of age was examined at a local

hospital, where she was found to have an Hb level of 9.5 mg/dL and a mean corpuscular volume of 108 fL. The diagnosis made by the doctor was macrocytic anemia, although the possibility of iron deficiency anemia was not excluded. The patient was treated with oral iron supplementation; however, her anemia did not improve, and she was subsequently treated with intravenous iron administration twice a week. Seven years later, the patient noticed a conspicuous loss of appetite. Upper and lower endoscopy showed no evidence of any abnormalities. She was referred to us for a further evaluation. She received approximately 8 g of intravenous iron for seven years. She had a history of rheumatoid arthritis, dementia, for which she was taking donepezil, and osteoporosis, which was being controlled with alfacalcidol and raloxifene.

On examination, the patient appeared alert and frail. Her height was 1.46 m and her weight was 36.4 kg (body mass index, 17.1 kg/m²). Her body temperature was 36.9°C, her blood pressure was 83/44 mm Hg, her heart rate was 73 beats per minute and regular, her respiratory rate was 18 breaths per minute and her oxygen saturation was 98% on room air. The jugular veins were not distended, and there were no abnormalities in the chest or abdomen, although the conjunctivae were pale and anemic. The skin over the pa-

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Table 1. Laboratory Findings

Tests	Results
Complete blood count	
WBC count (/mm ³)	2,600
Hb level (g/dL)	7.0
Ht (%)	20.7
Plt count (/mm ³)	11.4
Biochemical analysis	
TP level (g/dL)	5.4
Alb level (g/dL)	3.2
AST level (IU/L)	57
ALT level (IU/L)	41
LDH level (IU/L)	99
BUN level (mg/dL)	14.7
Cre level (mg/dL)	0.57
Na level (mEq/L)	139
K level (mEq/L)	4.4
Cl level (mEq/L)	102
Corrected Ca level (mg/dL)	8.8
CRP level (mg/dL)	0.4
ESR (mm/h)	26.0
HbA1c NGSP (%)	4.5
Folic acid level (ng/mL)	1.9
Vitamin B12 level (pg/mL)	2,048
Ferritin level (ng/mL)	7,951
TIBC (μg/dL)	73
Fe (μg/dL)	106
Infectious disease	
HBs Ag	-
HCV Ab	-
Endocrine studies	
TSH level (μIU/mL)	5.226
fT3 level (pg/dL)	2.1
fT4 level (ng/dL)	0.89

Table 2. Rapid Adrenocorticotrophic Hormone Stress Test

Hormone level	Pre-test	30 minutes	60 minutes
ACTH (pg/mL)	79.1	...	...
Cortisol (μg/dL)	15.5	18.9	19.3

density, at 118 Hounsfield units, indicating iron deposition (Fig. 2). Transthoracic echocardiography demonstrated a normal ejection fraction of 63%, normal fractional shortening of 34%, trivial atrial regurgitation, trivial mitral regurgitation, moderate tricuspid regurgitation, mild pulmonic regurgitation and a right ventricular systolic pressure of 47 mm Hg. Pulsed wave Doppler of the mitral valve demonstrated a more restrictive pattern of the diastolic mitral flow than would be predicted by the patient's age (Fig. 3). A bone marrow aspiration demonstrated megaloblastic changes in all three cell lineages: red blood cells, white blood cells and platelets. The patient was diagnosed with megaloblastic anemia caused by folic acid deficiency, and folic acid supplementation was initiated.

Frequent phlebotomy was not performed in consideration of the patient's poor general health and anemia. Her serum ferritin concentration decreased from 7,951 ng/mL one month before admission to 4,700 ng/mL on the 44th hospital day. A plan was in place to move her from the hospital into assisted-living accommodations due to her impaired ability to perform activities of daily living. On the 50th hospital day, she experienced congestive heart failure with atrial fibrillation and atrial tachycardia. Chest radiography showed cardiomegaly with a cardiothoracic ratio of 68%, pulmonary congestion and bilateral pleural effusion. The B-type natriuretic peptide level was 1,212 pg/mL, indicating severe heart failure. Echocardiography showed diffuse left ventricular hypokinesis. Despite receiving diuretic and digitalis treatment the patient died on the 56th hospital day.

An autopsy examination showed remarkable hemosiderosis in multiple organs, including the heart, liver, kidneys, thyroid gland, adrenal glands, gastrointestinal tract, and skin. Severe hemosiderin deposition was observed in most organs, predominantly in the parenchymal cells. The liver was congested (weight, 1,070 g) and demonstrated centrilobular hemorrhage. Hematoxylin and eosin staining showed abundant hemosiderin pigment within the cytoplasm of the hepatocytes. Berlin blue iron staining also demonstrated dense iron deposits within the cytoplasm of the hepatocytes, and Masson's trichrome staining showed well-established cirrhosis presenting with remarkable portal fibrosis and small nodular changes (Fig. 4). The cardiac muscles exhibited hemosiderosis, acidophilic degeneration, intercellular edema, mild fibrosis and cardiomyopathy-like grade 2 myocardial disarray (Fig. 5). The bone marrow displayed hyperplastic changes with an increased level of immature erythroid cells, compatible with a diagnosis of megaloblastic anemia. The pancreas exhibited atrophic changes with mild to moderate fibrosis and fatty degeneration. The gastrointestinal tract showed remarkable melanosis-like pigmentation. Berlin blue

tient's entire body appeared bronze. The remainder of the physical examination yielded normal results.

The laboratory findings (Table 1) indicated pancytopenia and macrocytosis. The data were as follows: white blood cell count, 2,600/mm³; Hb level, 7.0 g/dL; platelet count, 114,000/mm³; mean cell volume, 130 μm³; reticulocyte count, 0.4%. The folic acid level of 1.9 ng/mL indicated that the patient's anemia was due to folic acid deficiency. Liver cirrhosis was suggested by the following laboratory values: alanine aminotransferase, 57 U/L (reference range, 7-30 U/L); aspartate aminotransferase, 41 U/L (reference range, 9-25 U/L); hyaluronic acid, 459 ng/mL; and type IV collagen, 10.2 ng/mL. Iron overload and hemochromatosis were suggested by the following laboratory values: ferritin, 7,951 mg/mL; and transferrin saturation, 145%. The results of blood electrolytes and other routine laboratory tests, including thyroid function testing, were normal, as were the results of a urinalysis. A rapid adrenocorticotrophic hormone stress test yielded normal results (Table 2). Electrocardiography demonstrated ST depression in the inferior leads from V2 to V6. Admission chest radiography showed cardiomegaly, with a cardiothoracic ratio of 60% (Fig. 1). Abdominal computed tomography revealed elevated hepatic

Figure 1. Admission chest radiograph shows an enlarged cardiac shadow. Cardiothoracic ratio, 60%.

Figure 3. Transthoracic echocardiography. Pulsed wave Doppler at the mitral valve, showing a restrictive pattern of diastolic mitral flow, with the E wave > A wave.

staining revealed abundant iron deposition in the adrenal glands, thyroid gland, kidneys, pancreas and stomach. Marked cutaneous pigmentation was observed throughout the body.

Discussion

Our patient had a 7-year history of iron infusion, and her subsequent iron overload may have caused secondary hemochromatosis. Iron overload refers to the accumulation of excess iron in various organs as a result of increased intestinal absorption, parental administration or increased dietary intake (1). Iron overload primarily manifests as cardiac dysfunction, heart failure, liver dysfunction, cirrhosis and endocrine abnormalities, such as hypothyroidism, hypogonadism and diabetes mellitus (1, 3). It is interesting that our patient's endocrine glands demonstrated iron deposits, although her adrenal and thyroid functions were within the normal ranges. It is therefore possible that the endocrine glands are more tolerant to iron accumulation than the heart or liver.

Iron overload disorders are common; however, only a few studies have described the presence of histologic iron depos-

Figure 2. Abdominal plain computed tomography scan, showing markedly increased hepatic density. Liver, 118 Hounsfield units (HU); spleen, 60 HU.

its in the majority of organs. Hemochromatosis is increasingly recognized by clinicians, although it is still underdiagnosed. It is often considered to be a rare disorder, manifested only by the clinical findings seen in patients with fully established disease, that is, cirrhosis, diabetes and skin pigmentation.

Our patient was complicated with rheumatoid arthritis, which can lead to the development of anemia. The type of anemia most often associated with chronic diseases is normocytic anemia, in which the serum iron level, total iron-binding capacity and transferrin saturation are reduced despite adequate iron stores, which was not observed in our patient. Therefore, her anemia was not likely associated with inflammation caused by rheumatoid arthritis.

We diagnosed the present patient as having folic acid deficiency anemia after hospitalization. Folic acid deficiency can occur either when the body's need for folic acid increases because the dietary intake of folic acid is inadequate or when the body excretes or loses more than the normal amount of folic acid. Medications that interfere with the body's ability to utilize folate may also cause increases in the need for this vitamin. The present patient had a very small appetite. Therefore, the most likely cause of folic acid deficiency in this case was insufficient dietary intake of folic acid, since there was no evidence to suggest otherwise. The patient's anemia did not improve because she was on folic acid supplementation treatment for only approximately one month and was unable to continue with this treatment daily because her condition deteriorated.

Iron-overload cardiomyopathy is a secondary form of cardiomyopathy resulting from the accumulation of iron in the myocardium. It is primarily seen in patients with genetically determined disorders of iron metabolism or those who have had multiple transfusions. This condition, previously overlooked, has lately attracted the attention of researchers because iron overload is a frequently encountered phenomenon, especially in association with certain hematologic conditions, and the accurate identification and effective management of this disease are now possible. Secondary hemochromatosis may lead to severe diastolic left ventricular dysfunc-

Figure 4. Histological findings for liver tissue. (a) Hematoxylin and Eosin staining showing abundant hemosiderin pigmentation within cytoplasm of hepatocytes (magnification: $\times 40$). (b) (magnification: $\times 200$). (c) Berlin blue iron staining showing abundant iron within hepatocytes (magnification: $\times 200$). (d) Masson's trichrome staining showing well-established small nodular cirrhosis (magnification: $\times 40$).

Figure 5. Histological findings for cardiac muscle. (a) Cardiac muscle showing abundant iron deposition on Berlin blue iron staining (magnification: $\times 100$). (b) Hemosiderosis, acidophilic degeneration, intercellular edema, mild fibrosis, and cardiomyopathy-like grade 2 myofiber disarray on Hematoxylin and Eosin staining (magnification: $\times 100$).

tion in the early stages of the disease, leading to heart muscle dysfunction and heart failure before any effects are seen on the left ventricular ejection fraction. In the case of our patient, echocardiography showed a normal ejection fraction with a more restrictive pattern of the diastolic mitral flow than would be expected given her age suggesting diastolic left ventricular dysfunction. Iron-overload cardiomyopathy is a major cause of death among patients with conditions asso-

ciated with secondary iron overload (4). Early diagnosis of iron-overload cardiomyopathy is critical, as cardiac dysfunction is reversible if effective therapy is introduced before the onset of overt heart failure (5). The mainstay therapies for treating excessive iron deposition in patients with primary and secondary hemochromatosis are phlebotomy and iron chelation (6). In patients with secondary iron overload associated with ineffective erythropoiesis, iron chelation therapy

with parenteral deferoxamine is the treatment of choice (7). However, there is no insurance coverage for this treatment in Japan in cases of secondary hemochromatosis due to the administration of intravenous iron.

When a patient has a clinical history and organ injury suggesting iron overload, the recommended workup includes a physical examination, chest radiography, electrocardiography, echocardiography, abdominal computed tomography and magnetic resonance imaging. Computed tomography can detect the presence of highly electron-dense iron in the organs; however, the sensitivity and specificity of this imaging modality are poor. It has a high false-positive rate associated with fibrosis (8) and a low sensitivity for detecting the early stages of tissue iron overload (9). Magnetic resonance imaging is the only currently available noninvasive method with the potential to quantitatively assess myocardial iron overload. We did not perform this evaluation in our patient. The cardiovascular magnetic resonance-derived $T2^*$ relaxation time is the current standard for the quantitative assessment of cardiac iron deposition. The $T2^*$ relaxation time is primarily affected by iron in the form of hemosiderin, not by ferritin or labile cellular iron; however, because there is a continuous interchange between the three forms of stored iron, the technique can be used to accurately predict the tissue iron content (4). When the $T2^*$ value is measured in a full-thickness area of interest in the interventricular septum, it is highly representative of the global myocardial iron level. $T2^*$ values of <20 ms which are indicative of myocardial siderosis exhibit an inverse correlation with the left ventricular ejection fraction, whereas $T2^*$ values of <10 ms which are indicative of severe iron overload, are associated with an increased risk for the development of heart failure and arrhythmia (10).

In conclusion, the data for our patient who died of complications related to hemochromatosis provide important information with respect to the findings and presentations re-

lated to this disease and iron-overload cardiomyopathy. It is important to keep this rare diagnosis in mind when treating patients who present with a history or symptoms suggestive of excessive iron exposure.

The authors state that they have no Conflict of Interest (COI).

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