

A Japanese female with chronic mild anemia and primary iron overloading disease

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ABSTRACT

A 65-year-old woman died of congestive heart failure and diabetes mellitus. She had a history of mild anemia since adolescence, but received neither iron supplementation nor transfusion. The cirrhotic liver obtained at autopsy contained a large amount of iron. The heart and pancreas also had excess iron. Her iron overload may be due to excess iron absorption in the gut because of the absence of an iatrogenic background such as transfusion or iron supplementation.

Keywords: anemia, iron overload, cirrhosis, congestive heart failure, diabetes mellitus

Abbreviations:

HH: hereditary hemochromatosis

ILA: iron loading anemia

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INTRODUCTION

Anemia is not always iron-deficient but rarely iron-loading. Refractory anemias are usually complicated with secondary iron-loading after repeated transfusions.^{1,2} Clinical introduction of the iron regulatory hormone hepcidin led to a new paradigm of iron overloading under various disease conditions.³ Hereditary hemochromatosis (HH) is a proto-type of iron overload syndromes associated with impaired hepcidin synthesis in the liver.⁴ Some anemic patients with ineffective erythropoiesis are also affected by low levels of serum hepcidin²⁵ as in HH. The primary iron overload in such patients may be camouflaged by repeated transfusions and long-term iron supplementation. Based on an impaired hepcidin system, Camaschella, et al proposed a new disease entity of iron loading anemia (ILA) for refractory anemias associated with a primary iron overload.⁵

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Iron overload syndromes differ between Caucasians and Japanese, mainly due to the major genotype of HFE-HH, especially homozygote of C282Y, in Caucasians. Major genotypes in Japanese are aceruloplasminemia, TFR2-HH, and HJV-HH.^{6,7} In addition, ILA has not been reported in Japan in spite of a large number of patients participating in oral iron chelation studies for transfusion-dependent refractory anemias.^{1,2}

CASE REPORT

A 65-year-old Japanese woman died from iron-loaded multi-organ damage including congestive heart failure and diabetes mellitus. She had a history of mild anemia since adolescence, but received neither iron supplementation nor transfusion. Blood tests revealed anemia of unknown etiology, iron overload, and mild glucose intolerance (Table 1). Abdominal CT showed a high-dense liver, and a large but nearly normal-dense spleen (Fig. 1). Autopsy confirmed that she had multi-organ damage associated with iron overloading in the liver, spleen, heart, pancreas, and bone marrow (Table 2). The liver structures showed F4 in the Laennec cirrhosis classification with parenchymal cell-dominant iron deposition.

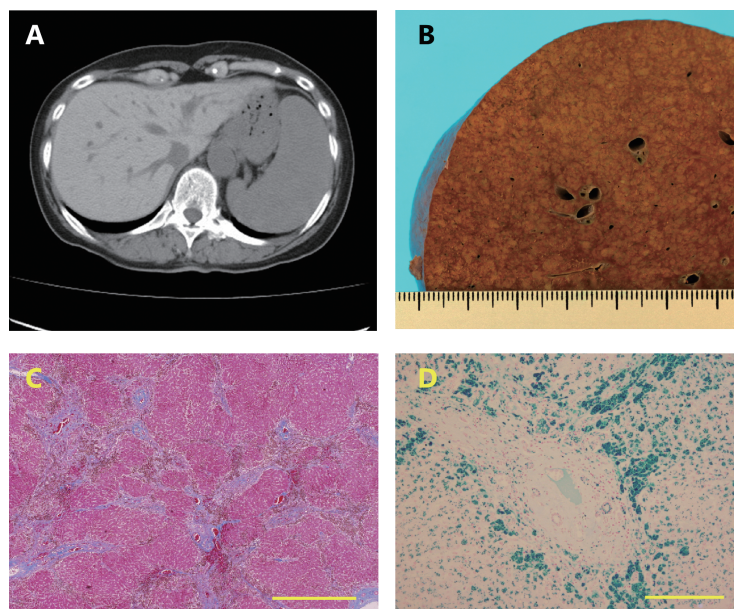


Fig. 1 Liver images of patient

Fig. 1A: Abdominal CT. Liver parenchyma with a high density indicates iron deposition, and marked splenomegaly has an unknown etiology.

Fig. 1B: The autopsied liver: Macroscopy of a cross-section of the liver. The cross section of the liver is representative of cirrhosis, showing nodular parenchyma among wide fibrous tissues.

Fig. 1C: The autopsied liver: Masson trichrome stain. The liver consists of parenchyma surrounded by wide fibrous septa, indicating F4 of Laennec cirrhosis. Bar indicates 1.0 mm.

Fig. 1D: The autopsy liver: Berlin blue stain. A large amount of iron is seen in the peri-fibrous parenchymal cells. Bar indicates 300 μ m.

Table 1 Laboratory data of the female patient aged 61 years old

Blood test	Reference	Patient
WBC	3,500–9,000/ μ L	2,900/ μ L
RBC	$(360\text{--}480) \times 10^4/\mu\text{L}$	$294 \times 10^4/\mu\text{L}$
Hb	11.4–14.6 g/dL	10.7 g/dL
Platelets	$(15.0\text{--}35.9) \times 10^4/\mu\text{L}$	$15.0 \times 10^4/\mu\text{L}$
BUN	9–22 mg/dL	17 mg/dL
t-Bilirubin	0.2–1.2 mg/dL	0.5 mg/dL
t-Protein	6.5–8.0 g/dL	6.7 g/dL
Albumin	4.0–5.0 g/dL	4.3 g/dL
AST	10–35 IU/L	29 IU/L
ALT	5–30 IU/L	38 IU/L
ALP	100–350 IU/L	544 IU/L
V. B12	250–950 pg/mL	502 pg/mL
Folic acid	3.6–12.9 ng/mL	6.0 ng/mL
Cu	78–131 μ g/dL	76 μ g/dL
Ceruloplasmin	21–37 mg/dL	18 mg/dL
Fe	70–160 μ g/dL	212 μ g/dL
Ferritin	13–58 ng/mL	1940 ng/mL
Transferrin	200–340 mg/dL	149 mg/dL
TF saturation	44–79%	96%
PBS	<200 mg/dL	217 mg/dL
HbA1C	<5.6%	8.0%
Urinalysis	Reference	Patient
Protein	Negative	Negative
Glucose	Negative	Negative
Bone Marrow	Reference	Patient
r-Sideroblasts	<1.0%	3%

ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, Hb: hemoglobin, PBS: postprandial blood sugar, r: ringed, RBC: red blood cells, t: total, TF: transferrin, V: vitamin, WBC: white blood cells.

Anemia was one aspect of pancytopenia in the patient. Her liver functions were maintained fairly well in spite of a cirrhotic liver with heavy iron deposition. Biochemical iron parameters were compatible with hemochromatosis. Note that congestive heart failure was followed by symptomatic diabetes in the aged patient.

Table 2 Structures and functions of iron-loaded organs of the patient

	Liver	Spleen	Heart	Bone Marrow
Structure Change	High-dense liver under CT Cirrhosis	Splenomegaly Portal hypertension	Cardiomegaly	Low cellularity Relative erythroblast hyperplasia
Functional Change	Compensated cirrhosis	Hypersplenism	Congestive heart failure	Mild anemia
Iron Deposit	Hepatocyte- dominant	Macrophages	Myocardial cells	Macrophages

CT, computed tomography.

Iron accumulation and organ dysfunction differ from organ to organ in the patient. Her abdominal CT shows marked deposition in the liver, but not in the spleen or heart. The structure and function of the liver are compatible with those of hemochromatosis with hepatocyte-dominant iron loading. Splenomegaly associated with portal hypertension may result in hypersplenism. Iron overload of the myocardium may be partially responsible for congestive heart failure associated with cardiomegaly. Mild anemia that is unusual in hemochromatosis may be related to iron overload in macrophages of the bone marrow.

DISCUSSION

In Japan, TFR2-HH involves iron-induced multi-organ damage in the liver and pancreas around the age of 50 years, while HJV-HH patients present with heart disease before the age of 30 years.^{6,7} Because there was no iatrogenic background such as iron supplementation or transfusion, we speculate that the iron loading involving the heart, liver, pancreas, and bone marrow of our patient was primarily due to excess iron absorption in the gut. Recently, Camaschella, et al proposed a new disease entity of ILA, which is characterized by hypohepcidinemia associated with refractory anemias.⁵ Multi-factorial suppressers may be supplied from the bone marrow to regulate HAMP in the liver, resulting in reduced hepcidin production and leading to excess iron absorption in the gut. The clinical features of our patient with diabetes mellitus, heart failure, cirrhosis, and anemia were compatible with non-transfusion-dependent ILA, but no definitive etiologies were identified because of the lack of determining either the genetic background of anemia or serum levels of hepcidin.^{25,8}

Some participants in oral iron chelation studies for post-transfusion iron overload syndromes^{1,2} show partial improvement in managing anemias. Erythropoiesis may be relieved from an iron-induced oxidative stress via reduced iron storage.⁹ Considering a large number of Japanese patients with refractory anemias, ILA and its related diseases may be more prevalent than classical HH in Japan.⁶ It is also important for patients with ILA to be treated with oral iron chelation before transfusion.

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None

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflict of interest.

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