CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 25-2021: A 48-Year-Old Man with Fatigue and Leg Swelling

Amber B. Moore, M.D., M.P.H., Jonathan R. Wing, M.D.,
Reece J. Goiffon, M.D., Ph.D., Rebecca K. Leaf, M.D., Lana Tsao, M.D.,
and Joseph Misdraji, M.D.

PRESENTATION OF CASE

Dr. Jonathan R. Wing: A 48-year-old man was admitted to this hospital because of fatigue and swelling in both legs.

The patient had been well until 8 months before the current admission, when fatigue and lethargy developed. He thought the fatigue was associated with alcohol consumption and reduced his intake to 12 beers weekly; before this, he had consumed 24 beers weekly for 15 years. Three months before the current admission, the patient's weight had decreased by 9.1 kg. However, 3 weeks before this admission, the weight had increased by 9.6 kg and swelling developed in both legs. He thought the weight gain was related to diet changes, including consumption of pizza, pasta, and soup, during the coronavirus disease 2019 pandemic.

One week before the current admission, the patient was evaluated by his primary care physician. He was instructed to elevate his legs, wear compression stockings, and decrease dietary sodium to 2 g daily. On the day of the current admission, the leg swelling had not abated and new abdominal distention occurred. He called the primary care clinic and was instructed to seek evaluation at the emergency department of this hospital.

On evaluation, a review of systems was notable for fatigue, lethargy, decreased appetite, abdominal bloating, constipation, penile swelling, decreased libido, intolerance of cold temperatures, and ankle and knee pain in both legs that was worse when the patient was climbing stairs. There was no fever, shortness of breath, chest pain, or hematochezia.

Sixteen months before the current evaluation, the patient had been admitted to this hospital with pneumonia involving the right upper and middle lobes that was due to *Mycoplasma pneumoniae*. During that admission, he received diagnoses of diabetes and normocytic anemia. After discharge from the hospital, laboratory evaluation revealed a glycated hemoglobin level of 6.1% (reference range, 4.3 to 6.4). Metformin was prescribed, and follow-up evaluation was recommended; however, the patient had not returned to the primary care clinic before the current illness.

From the Departments of Medicine (A.B.M., J.R.W., R.K.L., L.T.), Radiology (R.J.G.), and Pathology (J.M.), Massachusetts General Hospital, and the Departments of Medicine (A.B.M., J.R.W., R.K.L., L.T.), Radiology (R.J.G.), and Pathology (J.M.), Harvard Medical School — both in Boston.

N Engl J Med 2021;385:745-54.
DOI: 10.1056/NEJMcpc2100282

Table 1. Laboratory Data.*

Variable	Reference Range, Adults†	On Admission
Blood		
Hemoglobin (g/dl)	13.5–17.5	15.8
Hematocrit (%)	41.0–53.0	45.7
White-cell count (per μl)	4500–11,000	3610
Platelet count (per μl)	150,000–400,000	82,000
Mean corpuscular volume (fl)	80.0–100.0	103.9
Glycated hemoglobin (%)	4.3–6.4	11.6
Sodium (mmol/liter)	135–145	130
Potassium (mmol/liter)	3.4–5.0	4.8
Chloride (mmol/liter)	98–108	89
Carbon dioxide (mmol/liter)	23–32	26
Anion gap (mmol/liter)	3–17	15
Glucose (mg/dl)	70–110	402
Creatinine (mg/dl)	0.60–1.50	0.70
Urea nitrogen (mg/dl)	8–25	9
Aspartate aminotransferase (U/liter)	10–40	92
Alanine aminotransferase (U/liter)	10–55	37
Alkaline phosphatase (U/liter)	45–115	172
Total bilirubin (mg/dl)	0.0–1.0	1.8
Albumin (g/dl)	3.3–5.0	3.9
Total protein (g/dl)	6.0–8.3	8.1
Peritoneal fluid		
Color	NA	Yellow
Red-cell count (per μl)	NA	<3000
White-cell count (per μl)	NA	492
Differential count (per μl)		
Neutrophils	NA	0
Lymphocytes	NA	260
Reactive lymphocytes	NA	0
Monocytes	NA	63
Eosinophils	NA	0
Basophils	NA	9
Macrophages or lining cells	NA	157
Albumin (g/dl)	NA	1.0
Total protein (g/dl)	NA	1.8
Urine		
Ketones	Negative	2+
Glucose	Negative	3+
Bilirubin	Negative	1+
Blood	Negative	Negative
pH	5.0–9.0	6.5
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Specific gravity	1.001–1.035	1.038

* To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for bilirubin to micromoles per liter, multiply by 17.1. NA denotes not applicable.

† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

The patient had not started taking metformin until 3 weeks before the current evaluation; he took no other medications and had no known drug allergies. He lived with his wife and two children in an urban area of New England. He did not smoke tobacco or use illicit drugs. His mother had Parkinson's disease and dementia; he did not know the health of his father or paternal half-siblings.

On examination, the temperature was 36.6°C, the blood pressure 98/54 mm Hg, the heart rate 64 beats per minute, and the oxygen saturation 100% while the patient was breathing ambient air. The body-mass index (the weight in kilograms divided by the square of the height in meters) was 27.3. The patient did not have jaundice, scleral icterus, or spider angiomas. He had jugular venous distention and an S_3 gallop; there were no rales. The abdomen was distended, with dullness on percussion of the flanks; there was no hepatosplenomegaly. There was 2+ symmetric pitting edema in the lower legs up to the knees. Mild palmar erythema was present; there was no asterixis.

The blood glucose level was 402 mg per deciliter (22.3 mmol per liter; reference range, 70 to 110 mg per deciliter [3.9 to 6.1 mmol per liter]); the glycated hemoglobin level was 11.6%. The platelet count was 82,000 per microliter (reference range, 150,000 to 400,000). Other laboratory test results are shown in Table 1.

Dr. Reece J. Goiffon: Radiography of the chest revealed new elevation of the right hemidiaphragm and atelectasis in the lower lobes. Ultrasonography with Doppler analysis of the abdomen revealed mild thickening of the gallbladder wall, coarsened liver echotexture, moderate ascites, and mild splenomegaly; the portal veins were patent. Duplex ultrasonography revealed nonocclusive deep-vein thrombosis of the right popliteal vein.

Dr. Wing: Paracentesis was performed with ultrasonographic guidance, and 50 ml of peritoneal fluid was drained. Results of peritoneal fluid analysis are shown in Table 1; cytologic examination of the fluid revealed no malignant cells. Electrocardiography revealed normal sinus rhythm with occasional premature atrial complexes, left axis deviation, and T-wave inversions in leads I and aVL. Insulin and enoxaparin were administered subcutaneously, and the patient was admitted to the hospital. A diagnostic test was performed.

DIFFERENTIAL DIAGNOSIS

Dr. Amber B. Moore: This 48-year-old man with a history of substantial alcohol use presented with new edema of the lower legs, diabetes, subacute fatigue, joint pain, and loss of libido. The results of liver-enzyme tests were abnormal, and the findings on abdominal imaging were suggestive of chronic liver disease, such as cirrhosis. I will formulate a differential diagnosis in two steps. First, I will use a pathophysiological approach to define broad categories of conditions that can cause edema. Then, I will incorporate other details provided in this case to narrow the list to a likely diagnosis.

EDEMA

Edema develops when there is a net efflux of fluid from the intravascular space into the interstitial space. There are four common mechanisms associated with edema formation: increased hydrostatic pressure, increased membrane permeability, decreased oncotic pressure, and decreased lymphatic drainage. The underlying cause of any of these mechanisms determines the distribution of the edema. Vascular or lymphatic obstruction typically results in a focal area of edema, whereas a disorder of albumin production, a decrease in osmolality due to kidney excretion, or a lack of absorption in the gut results in symmetric diffuse edema. Increased plasma volume due to renal sodium retention, which can occur in the presence of heart failure or liver disease, results in symmetric dependent edema. Increased hydrostatic pressure due to heart failure typically causes edema distally. This patient had no evidence of renal disease or protein-losing enteropathy, and therefore, a primary hepatic or cardiac process (or a combination of the two) is the most likely explanation of his edema. Processes that affect both the liver and the heart should be considered.

ALCOHOL USE DISORDER

This patient is at increased risk for alcoholic cirrhosis, which is the most likely cause of liver disease in a middle-aged man with a history of substantial alcohol consumption. This possibility is further supported by the aspartate aminotransferase level (which was elevated and greater than the alanine aminotransferase level), thrombocytopenia, leukopenia, macrocytosis, abdominal

distention, and findings on abdominal ultrasonography, including coarsened liver echotexture, ascites, and splenomegaly. Furthermore, diagnostic paracentesis with peritoneal fluid analysis revealed a serum ascites albumin gradient of 2.9 g per deciliter, a finding consistent with portal hypertension. Before the chronic liver disease can be attributed to alcohol use, other causes — including viral hepatitis, hemochromatosis, and autoimmune hepatitis — should be ruled out. The patient's history of alcohol use also increases his risk for alcoholic cardiomyopathy, which can result in congestive hepatopathy and lower-leg edema. Although alcohol use may be contributing to this patient's presentation, it is unlikely to explain the full constellation of symptoms, including the elevated glycated hemoglobin level, joint pain, and loss of libido.

MYCOPLASMA PNEUMONIA

This patient had recently been hospitalized with an episode of pneumonia due to *M. pneumoniae*. Mycoplasma pneumonia typically causes mild and self-limited infection in patients who are otherwise healthy, relatively young, and immunocompetent. The fact that this patient's illness was severe enough to result in hospital admission is notable and may suggest a predisposition to infection. Furthermore, the possibility that symptoms arising after the infection could be caused by mycoplasma is worth considering. IgM-mediated hemolysis is a common complication of mycoplasma infection and could have caused anemia at the time of the initial hospitalization. Persistence of subclinical cold-agglutinin disease could explain the ongoing fatigue, cold intolerance, and possibly even the development of deep-vein thrombosis, given the increased risk of venous thromboembolism in patients with autoimmune hemolytic anemia.[1] However, this patient did not have anemia at the time of the current presentation, and a laboratory evaluation for hemolysis was unremarkable. Of note, the rapid increase in the glycated hemoglobin level could also be due to hemolysis, with red-cell turnover causing a falsely low initial glycated hemoglobin level. In addition, mycoplasma infection has known, albeit uncommon, cardiac manifestations, including myocarditis, which can lead to heart failure. Although this patient had symptoms that could be consistent with mycoplasma infection, the manifestation of symptoms many months after the initial infection would be unusual, so this diagnosis is unlikely.

VENOUS THROMBOEMBOLISM

This patient was found to have deep-vein thrombosis in the lower leg on presentation. This finding could represent either a complication of his recent fatigue and immobility or a clue to the underlying process that led to his current presentation. Thromboembolic disease can cause pulmonary hypertension, right ventricular heart strain, and right ventricular heart failure; however, this diagnosis is less likely in the absence of dyspnea. That said, obstruction of the iliac vein or inferior vena cava alone could cause lower-leg edema, and portal vein thrombosis may cause ascites. That the patient was not found to have portal vein thrombosis is reassuring; iliac vein thrombosis would not explain his entire clinical presentation.

DIABETES

The patient's elevated glycated hemoglobin level and new diagnosis of diabetes have yet to be explained. Although diabetes can develop independently in a person with known prediabetes and risk factors, this patient's rapid increase in the glycated hemoglobin level in association with new edema, fatigue, joint pain, and cold intolerance suggests a systemic process. An infiltrative process affecting the heart, liver, and pancreas should be considered, with potential causes including sarcoidosis, amyloidosis, and hemochromatosis. Sarcoidosis is unlikely in the absence of pulmonary symptoms and specific abnormalities on imaging. Amyloidosis can cause both cardiac and liver disease, as well as joint disease; however, amyloid deposition does not typically cause pancreatic disease and diabetes. Given that this patient's presentation is not suggestive of sarcoidosis or amyloidosis, the most likely diagnosis is hemochromatosis.

HEREDITARY HEMOCHROMATOSIS

Hereditary hemochromatosis is a disorder of increased iron absorption that results in total body iron overload and iron deposition in the heart, liver, joints, and pancreas. Manifestations typically occur in the fourth or fifth decade of life in men, which is consistent with this patient's presentation. The liver is the organ most commonly affected, and excessive alcohol use is a

risk factor for the development of liver disease in patients with hereditary hemochromatosis. Iron deposition in both the heart and the liver can contribute to organ dysfunction and cause edema. The presence of extrahepatic manifestations is suggestive of clinically significant iron deposition in the myocardium and heart failure; review of an echocardiogram would help to confirm the presence of heart failure. Iron deposition in the pancreas is a likely cause of new-onset diabetes. Iron deposition in the pituitary can cause hypopituitarism and decreased libido. Hypopituitarism may also result in hypothyroidism; given the patient's history of cold intolerance, constipation, and lethargy, a thyrotropin level should be obtained. The severe illness due to mycoplasma infection could have resulted from increased susceptibility to infection in the context of hereditary hemochromatosis; however, such increased susceptibility to infection is more commonly associated with siderophilic bacteria.[2,3]

Can the development of deep-vein thrombosis be explained by a diagnosis of hereditary hemochromatosis? Small studies have shown an increased prevalence of the factor V Leiden mutation (associated with deep-vein thrombosis) among patients with a specific mutation of the *HFE* gene (associated with hereditary hemochromatosis),[4] but this correlation is not well established.[5] I suspect that the deep-vein thrombosis in this patient is more likely to have resulted from his immobility due to symptoms of hereditary hemochromatosis. An elevated ferritin level and an elevated transferrin saturation (serum iron level divided by total iron-binding capacity) would help to establish the diagnosis of hereditary hemochromatosis; however, the definitive test result would be detection of an *HFE* mutation.

CLINICAL IMPRESSION

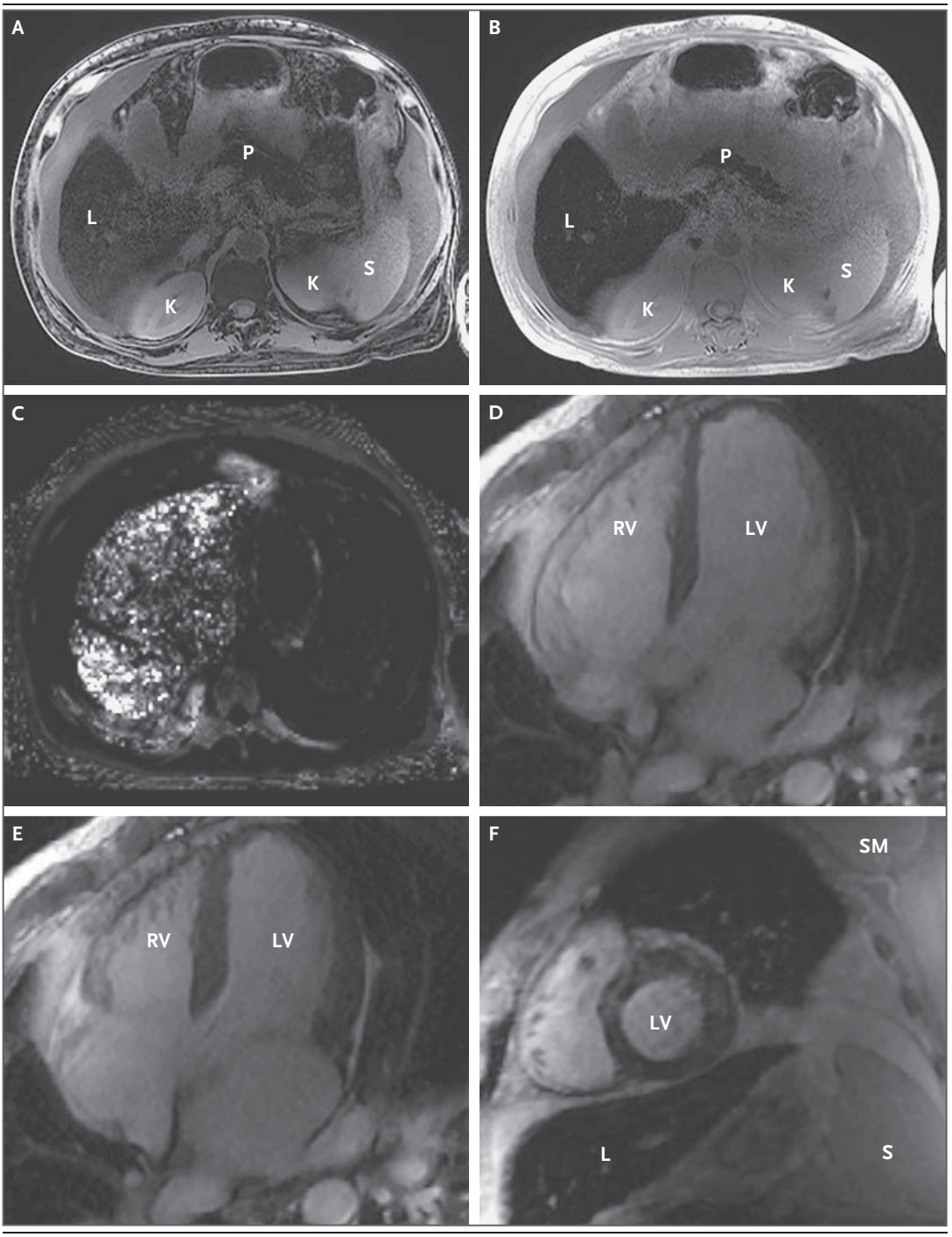
Dr. Wing: When I met this patient, it was clear that he had a disease affecting multiple organs. The presenting illness, review of systems, results of physical examination, and laboratory values were suggestive of liver, heart, pancreatic, and thyroid disease. Abnormal thyroid function was confirmed by a thyrotropin level of 47.7 μIU per milliliter (reference range, 0.4 to 5.0) and a free thyroxine level of 0.3 ng per deciliter (4 pmol per liter; reference range, 0.9 to 1.8 ng per deciliter [12 to 23 pmol per liter]). A transthoracic echocardiogram showed normal biventricular cavity size and wall thickness, diffuse biventricular hypokinesis, moderately impaired left ventricular systolic function with a reduced ejection fraction (31%; reference range, 50 to 75), and frequent premature ventricular contractions. The findings on abdominal ultrasonography and diagnostic paracentesis with peritoneal fluid analysis were suggestive of chronic liver disease, such as cirrhosis. With all these features taken together, systemic iron-overload syndrome became a compelling unifying diagnosis; further imaging studies and genetic testing were requested.

Dr. Goiffon: Abdominal magnetic resonance imaging (MRI) revealed ascites, anasarca, and a nodular liver contour. Out-of-phase T1-weighted images (obtained with an echo time of 1.26 msec, such that fat and water signals caused destructive interference) showed hypointensity in the liver, pancreas, and edematous body fat (Fig. 1). In-phase T1-weighted images (obtained with an echo time of 2.49 msec, such that fat and water signals caused constructive interference) showed hyperintensity in the edematous fat and, conversely, showed further signal loss in the liver and pancreas. Signal loss with longer echo times is caused by small disruptions in the magnetic field that are induced by ferromagnetic iron. MRI signal detection relies on the orderly spin of protons, but these field disruptions progressively randomize ("dephase") proton spins over time and cause the observed signal loss. This artifact can be used to create a map of the signal decay rate ($R2^*$), which is largely a function of iron content. With the use of this technique, the liver was found to contain 10 mg of iron per gram of dry weight.

Cardiac MRI revealed atrial dilatation, increased left ventricular and right ventricular end-diastolic volume indexes, increased left ventricular mass, and reduced left ventricular and right ventricular ejection fractions (31%). The observed transverse relaxation constant ($T2^*$), measured with the use of a technique similar to that used in the liver, was decreased, at 8 to 10 msec. This finding is also consistent with iron deposition that led to dephasing of the proton spins, with myocardial involvement in this case.

CLINICAL DIAGNOSIS

Systemic iron-overload syndrome.



DR. AMBER B. MOORE'S DIAGNOSIS

Hereditary hemochromatosis.

PATHOLOGICAL DISCUSSION

Dr. Joseph Misdraji: The diagnostic test was *HFE* genetic testing, which revealed homozygous C282Y mutations of the *HFE* gene. This is the most common genetic abnormality in patients with hereditary hemochromatosis, but it is not the only one. *HFE* genetic testing in clinical laboratories often involves techniques that detect common mutations only. In our laboratory, *HFE* genetic testing is performed with an allelic discrimination assay that detects C282Y or H63D mutations.

Figure 1 (facing page). Abdominal and Cardiac MRI.
Abdominal MRI was performed. Out-of-phase and in-phase T1-weighted images (Panels A and B, respectively) show selective signal loss in the liver (L) and pancreas (P), as compared with the spleen (S) and kidneys (K). An R2* map (Panel C) localizes increased signal decay to the liver and quantifies the signal decay rate, which is mathematically related to the iron content; the liver was found to contain 10 mg of iron per gram of dry weight. Cardiac MRI was also performed. Images obtained in a four-chamber long-axis view at end diastole and end systole (Panels D and E, respectively) show globally reduced right ventricular (RV) and left ventricular (LV) ejection fractions (31%). A T2*-weighted image (Panel F) shows signal loss in the liver and left ventricular wall, as compared with the spleen and skeletal muscle (SM); in the left ventricular wall, T2* (the observed transverse relaxation constant) was decreased, at 8 to 10 msec.

The patient underwent a liver biopsy. Examination of the biopsy specimen revealed cirrhosis. On an iron stain, there was 4+ iron deposition in hepatocytes (Fig. 2). There was also iron deposition in epithelial cells of the bile ducts, a finding that is characteristic of but not specific for hereditary hemochromatosis. Mild steatosis was noted, without features of steatohepatitis. A separate core biopsy specimen of liver tissue was sent for iron quantification, which revealed a hepatic iron concentration of 15,642 μg per gram (reference range, 200 to 2400). Because the hepatic iron concentration increases over a person's lifetime, the result can be adjusted for age with calculation of the hepatic iron index. In this case, the hepatic iron index was 5.8 μmol of iron per gram of liver tissue per year. In the past, before *HFE* genetic testing was commonly available, a hepatic iron index of greater than 1.9 was used to establish the diagnosis of hereditary hemochromatosis; values above this threshold were considered to be highly specific for genetic iron overload.

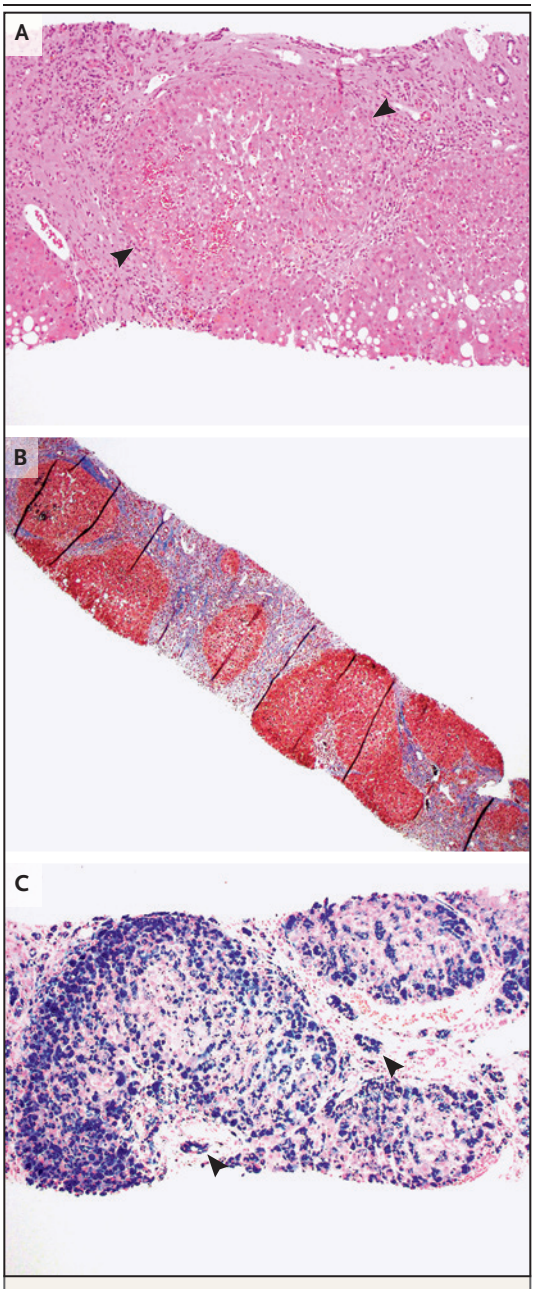


Figure 2. Liver-Biopsy Specimen.
A hematoxylin and eosin stain of the liver-biopsy specimen (Panel A) shows a nodular liver, with a nodule composed of hepatocytes (arrowheads) surrounded by fibrous tissue. Mild steatosis is present at the lower right. A trichrome stain (Panel B) shows residual small nodules composed of hepatocytes surrounded by fibrous tissue, a finding that confirms the presence of micronodular cirrhosis. An iron stain (Panel C) shows marked iron deposition (in blue) in hepatocytes, as well as iron deposition in the bile ducts (arrowheads).

PATHOLOGICAL DIAGNOSES

Cirrhosis with marked hepatocellular iron deposition in the context of a homozygous C282Y mutation of the *HFE* gene.

HFE-related hereditary hemochromatosis.

DISCUSSION OF MANAGEMENT

Dr. Rebecca K. Leaf: This patient's elevated serum iron level (272 μg per deciliter [48.7 μmol per liter]; reference range, 45 to 160 μg per deciliter

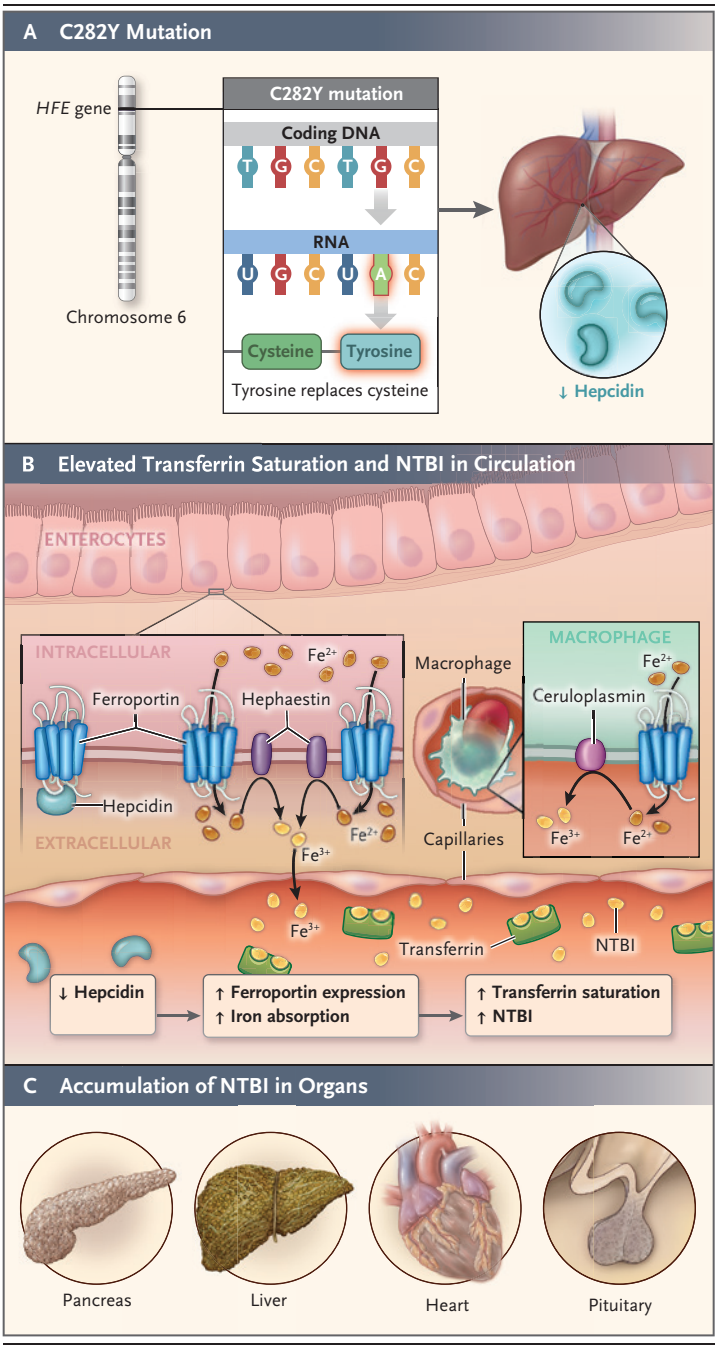


Figure 3. Hereditary Hemochromatosis.

Classic hereditary hemochromatosis is an iron-loading disorder caused by partial loss-of-function mutations (most often homozygous C282Y mutations) in the *HFE* gene, an upstream regulator of the master regulator of systemic iron homeostasis, hepcidin (Panel A). These mutations result in constitutively low circulating levels of hepcidin, which in turn result in unregulated expression and activity of the iron exporter, ferroportin. This leads to unchecked absorption of dietary iron in duodenal enterocytes, as well as increased export of iron from macrophages into the bloodstream, causing an elevated transferrin saturation and the appearance of toxic non–transferrin-bound iron (NTBI) in the circulation (Panel B). NTBI accumulates in the pancreas, liver, heart, and pituitary, causing the quintessential manifestations of hereditary hemochromatosis (Panel C).

[8.1 to 28.7 μmol per liter]) was suggestive of enhanced iron absorption in the gut. The total iron-binding capacity was 282 μg per deciliter (50.5 μmol per liter) and was thus at the low end of the normal range (230 to 404 μg per deciliter [41.2 to 72.4 μmol per liter]). The elevated transferrin saturation (96%; reference range, 14 to 50) indicated that almost all binding sites of transferrin were occupied with iron. The elevated ferritin level (3543 μg per liter; reference range, 30 to 300) reflected markedly high total body iron stores. It was not surprising that molecular studies revealed a homozygous C282Y mutation of the *HFE* gene, confirming the diagnosis of hereditary hemochromatosis.

Hereditary hemochromatosis is a group of disorders characterized by abnormal iron homeostasis, which leads to iron overload. This patient had classic hereditary hemochromatosis, caused by partial loss-of-function mutations in the *HFE* gene, an upstream activator of hepcidin expression (Fig. 3).[6] Accordingly, patients with hereditary hemochromatosis have low circulating levels of hepcidin and thus have unregulated expression and activity of ferroportin, which results in increased absorption of dietary iron. Binding sites of transferrin in plasma become saturated, and this leads to the appearance of redox-active non–transferrin-bound iron, which is rapidly cleared by the liver and other organs (e.g., pancreas, heart, and pituitary), where it can cause oxidant-mediated tissue damage.[7] Hereditary hemochromatosis is prevalent; more than 6% of the White population have one variant allele.[8] However, it also has low penetrance; only 28% of homozygous men and 1.4% of homozygous women have clinical symptoms.[9] In part because of blood loss from menstruation, women with the C282Y–C282Y genotype often present with symptoms later in life than men with the same mutation.[10] Other factors, such as alcohol consumption, can enhance iron absorption and worsen free-radical damage, which was thought to have occurred in this patient.[11]

Standard treatment for hereditary hemochromatosis is therapeutic phlebotomy, which normalizes total body iron stores, promotes iron use through hematopoiesis, and decreases iron-mediated free-radical damage. Guidelines for the initiation of treatment vary, although most experts recommend therapeutic phlebotomy in C282Y homozygotes when the ferritin level is elevated.[8] Initial treatment involves removal of 500 ml of blood every 1 to 2 weeks. Once the ferritin level decreases to 50 to 100 μg per liter, maintenance phlebotomy is performed 4 to 6 times per year.[12] Both hepatic fibrosis[13] and cardiac dysfunction[14] can abate with therapeutic phlebotomy in patients with hereditary hemochromatosis.

Therapeutic phlebotomy, which normalizes iron stores but may take more than a year to do so, was not a practical initial treatment in this patient, who had iron overload leading to heart and liver failure. We therefore initiated treatment with iron chelation, which is the standard of care in patients with transfusion-associated iron overload due to β-thalassemia. Three iron chelators are available in the United States: deferoxamine, deferiprone, and deferasirox. In a randomized clinical trial involving patients with β-thalassemia who presented with cardiac dysfunction due to iron overload, the use of a combination of deferoxamine and deferiprone was superior to the use of either drug in isolation with respect to improving left ventricular function.[15,16] According to the "shuttle hypothesis," deferiprone (which is highly lipophilic) enters cells and chelates iron, transfers the iron to extracellular deferoxamine, and then reenters cells to bind additional iron.[17]

This patient started therapy with deferoxamine and deferiprone at maximal doses. Both drugs are generally associated with minimal side effects, although deferiprone causes agranulocytosis in a minority of patients, so close monitoring of blood counts is recommended.

CARDIOLOGY MANAGEMENT

Dr. Lana Tsao: This patient had iron-overload cardiomyopathy, which is a type of infiltrative cardiomyopathy,[18] and either cardiac or hepatic cirrhosis. Iron deposition starts in the epicardium and progresses down to the endocardium.[19] Diastolic dysfunction develops and progresses either to a restrictive phenotype characterized by heart failure with preserved ejection fraction, pulmonary hypertension, and right ventricular dysfunction or to a dilated cardiomyopathy associated with heart failure with reduced ejection fraction.[20,21] Other presentations include angina without coronary artery disease, pericarditis, and arrhythmia (most commonly atrial fibrillation). Ventricular arrhythmias are rare.[22] This patient presented with dilated cardiomyopathy. Echocardiography revealed that the left ventricle was diffusely hypokinetic and dilated, with akinesis of the apex and an ejection fraction of 31%. The right ventricle had mildly reduced function. These findings correlated with the findings on MRI.

On MRI, the observed transverse relaxation constant T2* allows for qualitative and quantitative assessment of iron overload, which correlates with the severity of left ventricular dysfunction but not with serum ferritin or iron levels.[23] The T2* can be used to monitor the response to chelation therapy. A T2* of more than 20 msec indicates a low risk for the development of heart failure, 10 to 20 msec indicates cardiac deposition with a moderate risk for the development of heart failure, and less than 10 msec indicates a risk of decompensation. In this patient, the T2* was less than 10 msec, necessitating prompt initiation of chelation therapy.[24,25]

Coronary disease was ruled out by means of coronary angiography. Catheterization of the heart on the right side revealed elevated filling pressures with a high-output state: cardiac output of 8.4 liters per minute and cardiac index of 3.92 liters per minute per square meter of body-surface area. The patient underwent aggressive diuresis, and standard guideline-directed medical therapy with vasodilators, a beta-blocker, a mineralocorticoid receptor antagonist, and a sodium–glucose cotransporter 2 inhibitor was begun.[26] However, the guideline-directed medical therapy was discontinued because of his hypotension. His burden of premature ventricular contractions was high, without sustained ventricular tachycardia. Repeat right heart catheterization revealed normalization of the filling pressure but a persistently elevated cardiac output and cardiac index. Before discharge, repeat echocardiography showed normalization of the ejection fraction.

Dr. Wing: The patient was hospitalized for approximately 7 weeks. Aggressive diuresis led to a weight loss of 18 kg. Attempts to administer further goal-directed medical therapy for heart failure were limited by systemic hypotension. At the time of discharge, he had trace lower-leg edema and a nondistended abdomen. The patient was discharged home while receiving combination iron chelation therapy with oral deferiprone and intravenous deferoxamine. One day after discharge, he had a cardiac arrest and was taken to another hospital; therapeutic hypothermia was initiated, and he was transferred to this hospital. He was found to have severe anoxic brain injury with persistently poor mental status and ongoing seizure activity despite maximal medical therapy. With guidance from the palliative care service, he was compassionately extubated and died with his family at the bedside.

FINAL DIAGNOSIS

Hereditary hemochromatosis.

This case was presented at the Medical Case Conference.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Jodie Babitt for her assistance and review of the discussions of iron metabolism and hepcidin regulation.

REFERENCES

1. Ungprasert P, Tanratana P, Srivali N. Autoimmune hemolytic anemia and venous thromboembolism: a systematic review and meta-analysis. Thromb Res 2015;136:1013-7.

2. Ganz T. Iron and infection. Int J Hematol 2018;107:7-15.

3. Khan FA, Fisher MA, Khakoo RA. Association of hemochromatosis with infectious diseases: expanding spectrum. Int J Infect Dis 2007;11:482-7.

4. Xie YG, Lillicrap DP, Taylor SA. An association between the common hereditary hemochromatosis mutation and the factor V Leiden allele in a population with thrombosis. Blood 1998;92:1461-2.

5. Le Maréchal C, Raguénés O, Ferec C. No association between factor V Leiden and C282Y mutation in the hereditary hemochromatosis gene. Blood 1999;93:4024-5.

6. D'Alessio F, Hentze MW, Muckenthaler MU. The hemochromatosis proteins HFE, TfR2, and HJV form a membrane-associated protein complex for hepcidin regulation. J Hepatol 2012;57:1052-60.

7. Brissot P, Pietrangelo A, Adams PC, de Graaff B, McLaren CE, Loréal O. Haemochromatosis. Nat Rev Dis Primers 2018;4:18016.

8. European Association For The Study Of The Liver. EASL clinical practice guidelines for HFE hemochromatosis. J Hepatol 2010;53:3-22.

9. Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in *HFE* hereditary hemochromatosis. N Engl J Med 2008;358:221-30.

10. Moirand R, Adams PC, Bicheler V, Brissot P, Deugnier Y. Clinical features of genetic hemochromatosis in women compared with men. Ann Intern Med 1997;127:105-10.

11. Harrison-Findik DD, Schafer D, Klein E, et al. Alcohol metabolism-mediated oxidative stress down-regulates hepcidin transcription and leads to increased duodenal iron transporter expression. J Biol Chem 2006;281:22974-82.

12. Adams PC, Barton JC. How I treat hemochromatosis. Blood 2010;116:317-25.

13. Falize L, Guillygomarc'h A, Perrin M, et al. Reversibility of hepatic fibrosis in treated genetic hemochromatosis: a study of 36 cases. Hepatology 2006;44:472-7.

14. Dabestani A, Child JS, Henze E, et al. Primary hemochromatosis: anatomic and physiologic characteristics of the cardiac ventricles and their response to phlebotomy. Am J Cardiol 1984;54:153-9.

15. Tanner MA, Galanello R, Dessi C, et al. A randomized, placebo-controlled, double-blind trial of the effect of combined therapy with deferoxamine and deferiprone on myocardial iron in thalassemia major using cardiovascular magnetic resonance. Circulation 2007;115:1876-84.

16. Kuo KHM, Mrkobrada M. A systematic review and meta-analysis of deferiprone monotherapy and in combination with deferoxamine for reduction of iron overload in chronically transfused patients with β-thalassemia. Hemoglobin 2014;38:409-21.

17. Hider RC, Hoffbrand AV. The role of deferiprone in iron chelation. N Engl J Med 2018;379:2140-50.

18. Pereira NL, Grogan M, Dec GW. Spectrum of restrictive and infiltrative cardiomyopathies: part 1 of a 2-part series. J Am Coll Cardiol 2018;71:1130-48.

19. Gujja P, Rosing DR, Tripodi DJ, Shizukuda Y. Iron overload cardiomyopathy: better understanding of an increasing disorder. J Am Coll Cardiol 2010;56:1001-12.

20. Murphy CJ, Oudit GY. Iron-overload cardiomyopathy: pathophysiology, diagnosis, and treatment. J Card Fail 2010;16:888-900.

21. Kremastinos DT, Farmakis D. Iron overload cardiomyopathy in clinical practice. Circulation 2011;124:2253-63.

22. Liu P, Olivieri N. Iron overload cardiomyopathies: new insights into an old disease. Cardiovasc Drugs Ther 1994;8:101-10.

23. Anderson LJ, Holden S, Davis B, et al. Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J 2001;22:2171-9.

24. Ruffo GB, Borsellino Z, Cuccia L, Marocco MR, Gagliardotto F, Tarantino R. Long-term chelation therapy with deferasirox: effects on cardiac iron overload measured by T2* MRI. Clin Drug Investig 2010;30:267-73.

25. Kirk P, Roughton M, Porter JB, et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation 2009;120:1961-8.

26. Maddox TM, Januzzi JL Jr, Allen LA, et al. 2021 update to the 2017 ACC expert consensus decision pathway for optimization of heart failure treatment: answers to 10 pivotal issues about heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021;77:772-810.