Int J Clin Exp Med 2017;10(6):9675-9680
www.ijcem.com /ISSN:1940-5901/IJCEM0050275

Case Report

Hepatitis C-induced liver cirrhosis combined with hereditary spherocytosis: a case report

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Received February 7, 2017; Accepted March 29, 2017; Epub June 15, 2017; Published June 30, 2017

Abstract: Hereditary spherocytosis is a rare genetic disorder. There are no reported cases of hepatitis C virus (HCV)-induced liver cirrhosis combined with hereditary spherocytosis. A 64-year-old woman was hospitalized with symptoms of liver cirrhosis and biliary tract infection. Subsequent examination revealed severe anemia to a degree that was incongruent with HCV-induced liver cirrhosis. Bone marrow aspiration indicated a hemolytic anemia, with 14% spherocytes in the peripheral blood. The patient underwent splenectomy. The surgeons observed hepatic nodular sclerosis and obvious splenic congestion and enlargement. Because of the pre-existing HCV-induced liver cirrhosis, splenectomy partly alleviated the anemia. Hereditary spherocytosis may be masked by symptoms of biliary tract infection and pre-existing HCV-induced liver cirrhosis, particularly if overlooked until symptoms become severe. Although patients with liver cirrhosis may present with a reduction in the number of granulocytes, erythrocytes, and platelets as a result of hypersplenism, when the pattern does not match the patient's condition, physicians should consider the possibility of combined hematologic diseases.

Keywords: Hepatitis C, liver cirrhosis, hereditary spherocytosis

Introduction

Hepatitis C virus (HCV)-induced cirrhosis is a major outcome of HCV infection and a global public health problem. Worldwide, approximately 170 million HCV-seropositive patients are at a risk of cirrhosis and liver cancer [1]. Hereditary spherocytosis is an inherited condition characterized by anemia, jaundice, and splenomegaly. It is the most common congenital hemolytic anemia in Caucasians, affecting approximately 1 in 1000-2000 individuals [2, 3]. However, in China the incidence of hereditary spherocytosis is 1.27 and 1.49 cases per 100,000 in men and women, respectively [4], which is obviously lower than in Caucasians. Patients with HCV-induced liver cirrhosis can present with reductions in the three hematologic series as a result of splenomegaly and hypersplenism. As hereditary spherocytosis is rare in China, it is easy to overlook it as an underlying hematologic disorder when treating anemic patients with HCV-induced liver cirrhosis. We report a case of HCV-induced liver cirrhosis combined with hereditary spherocytosis for the first time. Because of the pre-existing HCV-induced liver cirrhosis, splenectomy partly alleviated the patient's anemia. If the diagnosis had been limited to the initial biliary tract infection with previous HCV-induced liver cirrhosis, the diagnosis of hereditary spherocytosis may have been missed.

Case report

A 64-year-old woman was hospitalized with chronic fatigue that began six months prior and had worsened in the preceding two weeks and was now accompanied by fever, abdominal pain, and jaundice. Two weeks previously, the patient had experienced fever with no obvious cause, with the highest body temperature reaching 38.9°C accompanied by chills and shivering. She gradually developed jaundice of the skin, dark brown urine, dark yellow feces, painful swelling over the xiphoid process and back, anorexia, and occasional bleeding from the nose and gums. She denied experiencing nausea or food aversions, itching, acid reflux, or excessive gas.

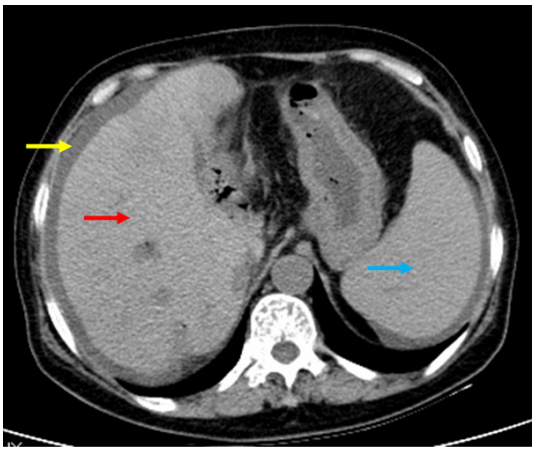

Figure 1. Abdominal computed tomography scan showing heterogeneity of the liver (red arrow), splenomegaly (blue arrow), and a small amount of ascites (yellow arrow).

A full abdominal computed tomography (CT) scan (**Figure 1**) indicated homogeneous density in the liver, pneumatosis in the intrahepatic bile duct, a possible stone in the hepatic hilum, and a dense shadow suggesting a mass beneath the porta hepatitis (the gallbladder was not clearly visualized). There was also evidence of abdominal pelvic effusion and splenomegaly.

The patient reported that she had undergone choledochotomy and bile duct drainage and had received blood transfusions during these operations 25 years previously. The year thereafter, she had undergone a cholecystectomy and anastomosis of the bile duct and duodenum.

On physical examination, the patient had normal vital signs but was generally unwell, with skin and scleral jaundice. There were no spider angiomas and no abnormalities detected on examination of the heart and lungs. The patient's abdomen was soft, with a visible surgical scar of approximately 20 cm in the right lower quadrant. The spleen was palpable 5 cm below the rib margin. The liver was palpable just below the rib margin.

The patient was unsuitable for anti-viral treatment with interferon. After hospitalization, she received antimicrobial, hepatoprotective, bilirubin-lowering, and diuretic treatments as well as albumin supplementation and a blood transfusion. The treatment effectively relieved the abdominal distension, anorexia, and abdominal pain. A color Doppler ultrasound of the abdomen showed mild diffuse hepatic damage, an intrahepatic strip-like hyperechoic image (indicative of intrahepatic bile duct gas), splenomegaly with a portal vein diameter of 13 mm (mildly widened), and a small amount of ascites.

After treatment, her albumin levels improved but the level of total bilirubin remained high. She also had severe anemia, which was difficult to explain as she had no evidence of gastrointestinal bleeding. Hence, further tests were performed. A red blood cell osmotic fragility test was positive, with initial hemolysis achieved using 0.6% NaCl and complete hemolysis achieved with 0.36% NaCl. An acidified glycerol hemolysis test (AGLT) was also positive (67 s). Coomb's test and Ham's test were both negative. Examination of a bone marrow aspirate revealed granulocyte series hyperplasia, with the ratio dropping to 30.5% but a largely normal ratio and morphology visible in different stages. In addition, there was erythrocyte series hyperplasia, with a ratio as high as 57%, comprising mainly polychromatic and orthochromatic normoblasts. Basophilic stippling and mitotic phases were easily seen (**Figure 2A**); in addition, anisocytosis and polychromatic erythrocytes were easily seen. Peripheral blood examination showed spherocytes (14%; **Figure 2B**).

The patient was finally diagnosed with: 1) decompensated HCV-induced liver cirrhosis; 2) acute cholangitis; 3) hereditary spherocytosis; and 4) a post-operational state of cholecystectomy, with common bile duct duodenum anastomosis. The patient underwent a splenectomy one week later. The surgeons observed hepatic nodular sclerosis, obvious congestion and enlargement of the spleen with a size of approximately 22 × 15 × 7 cm, no obvious varicosities in either the greater or lesser curvature of the gastric fundus, and a small amount of intraperitoneal ascites.

Pre-operatively, the patient's laboratory test results were as follows: white blood cell count, 3.82 × 10^9/L; hemoglobin, 57 g/L; platelet count, 79 × 10^9/L; total bilirubin, 90.6 μmol/L; and direct bilirubin, 44.3 μmol/L. Her post-operative laboratory test results had improved significantly: white blood cell count, 7.55 × 10^9/L; hemoglobin, 86 g/L platelet count, 311

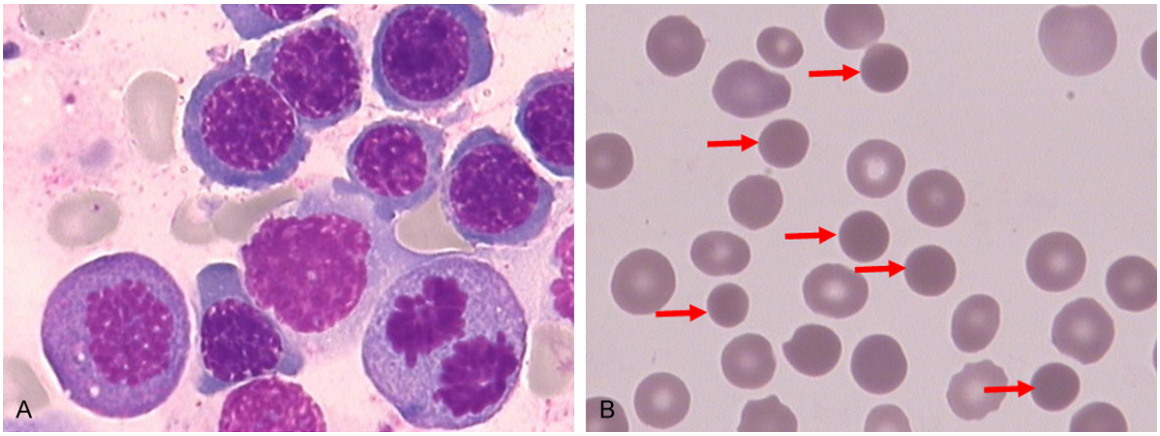

Figure 2. A: Characteristics of bone marrow cell morphology: active erythropoiesis (Wright's and Giemsa stain; magnification, × 1000). B: Peripheral blood: spherocytes (Wright's and Giemsa stain; magnification, × 1000).

× 10^9/L, and total bilirubin, 43.1 μmol/L. The results of other laboratory tests performed during hospitalization are listed in **Table 1**.

Discussion

There have been no reports of cases of HCV-induced liver cirrhosis combined with hereditary spherocytosis to date. The patient in this report had severe anemia, the cause of which deserved detailed investigation. Portal hypertension during decompensated liver cirrhosis can result in splenomegaly and hypersplenism, which commonly presents as a reduction in the three hematologic series, with platelets more markedly reduced than hemoglobin. The patient in this report presented with splenomegaly, but the portal vein diameter was 13 mm (mildly widened). In addition, there were no abdominal varicosities, and intraoperative observation showed no obvious varicose veins in the either the greater or lesser curvature of the gastric fundus. All these findings indicated that portal hypertension was not severe. Moreover, the hemoglobin level was more reduced than the platelet count, which was difficult to explain within the diagnosis of hypersplenism secondary to portal hypertensive. In addition, the patient presented with a folate insufficiency, which could also result in anemia (mainly macrocytic anemia). The MCV in this case was slightly high, but the patient's anemia did not improve after folate supplementation, indicating that folate insufficiency was not the only reason for the anemia. Further, examination of a bone marrow aspirate showed erythrocyte series hyperplasia, with a ratio as high as 57% in conjunction with mainly polychromatic and orthochromatic normoblasts; basophilic stippling and mitotic phases were easily seen, as were anisocytosis and polychromatic erythrocytes. The peripheral blood spherocyte ratio was 14%, indicating hemolytic anemia. Coomb's test was negative, ruling out the possibility of autoimmune hemolytic anemia. The AGLT was positive (67 s), indicating hereditary spherocytosis. Taking all of these test results into consideration, the cause of anemia in this case was determined to be HCV-induced liver cirrhosis and folate insufficiency augmented by hereditary spherocytosis-induced hemolytic anemia, eventually resulting in severe anemia.

The European Clinical Guidelines for Hereditary Spherocytosis [5] state that the following supporting evidence should be present in order to make a new diagnosis of hereditary spherocytosis: 1) a family history of spherocytosis; 2) typical clinical symptoms, such as splenomegaly; and 3) positive laboratory results, such as increased spherocyte ratio, increased MCHC, and an increased reticulocyte count. If the above conditions are not fully satisfied, screening using combined hemolysis examinations (the red blood cell osmotic fragility test and AGLT) and the eosin 5'-maleimide (EMA) test is required. Some researchers believe that AGLT is more sensitive than EMA for detecting hereditary spherocytosis [6]. Bianchi *et al.* [7] evaluated the diagnostic effectiveness of the red blood cell osmotic fragility test, AGLT, and EMA, which revealed sensitivities of 81%, 95%, and 93%, respectively. Thus, combined testing with AGLT and EMA could increase the rate of diag-

Table 1. Laboratory test results during hospitalization

Lab Test	Reference interval	Day 1	Day 2	Day 6	Day 10	Month 1 (before splenectomy)	Month 1 (after splenectomy)
RBC (10^{12}/L)	3.8-5.1	1.76	1.54	1.74	1.42	1.46	2.42
Hb (g/L)	115-150	67.2	57.0	62.0	54.2	57	86
MCHC (g/L)	316-354	333	320	326	340	320	322
WBC (10^9/L)	3.5-9.5	5.41	3.08	2.69	3.17	3.82	7.55
PLT (10^9/L)	125-350	149	123	94	79	79	311
Reticulocyte%	0.5-2.0	-	-	8.42	-	-	-
Total bilirubin (μmol/L)	5.1-19.0	78.9	61.2	81.0	83.7	90.6	43.1
Conjugated bilirubin (μmol/L)	0-7.0	51.6	39.8	54.3	53.1	44.3	27.1
Unconjugated bilirubin (μmol/L)	1.7-10.2	27.3	21.4	26.7	30.6	46.3	16.0
Anti-HCV (S/CO)	<1.0	-	14.47	-	-	-	-
Hyaluronic acid (ng/mL)	0-100	-	420.19	-	-	-	-
Laminin (ng/mL)	0-50	-	43.79	-	-	-	-
Type III procollagen (ng/mL)	0-30	-	100.82	-	-	-	-
Type IV procollagen (ng/mL)	0-30	-	88.89	-	-	-	-
HCV-RNA (copies/mL)	<500	-	-	1.5×10^7	-	-	-
Serum iron (μg/dL)	43-172	-	-	129	-	-	-
Folic acid (ng/mL)	2.0-19.9	-	-	1.4	-	-	-
B12 (pg/mL)	197-894	-	-	675.7	-	-	-
Coombs test	Negative	-	-	Negative	-	-	-
Osmotic fragility test	Negative	-	-	Positive	-	-	-
AGLT	>290 s	-	-	67 s	-	-	-
ANA titer	1:1 (-)	-	-	1:100 (+)	-	-	-
nRNP/Sm	Negative	-	-	+	-	-	-
Ro-52	Negative	-	-	+++	-	-	-
ASMA	Negative	-	-	-	-	-	-
AMA	Negative	-	-	+/-	-	-	-
LKM-1	Negative	-	-	+/-	-	-	-
LC-1	Negative	-	-	+	-	-	-
SLA/LP	Negative	-	-	+	-	-	-

RBC, red blood cells; Hb, hemoglobin; MCHC, mean corpuscular hemoglobin concentration; WBC, white blood cells; PLT, platelets; HCV, hepatitis C virus; AGLT, acidified glycerol lysis test; ANA, antinuclear antibodies; ASMA, anti-smooth muscle antibody; AMA, anti-mitochondriaantibody; LKM-1, anti-liver-kidney microsomal-1 antibody; LC-1, anti-liver cytosolic liver antigen type-1 antibody; SLA/LP, anti-soluble liver antigen antibody/anti-liver-pancreas antigen antibody.

nosis in some mild cases. Similarly, Andres *et al.* [8] recommended combined testing with AGLT, EMA, and morphological identification of spherocytes in the peripheral blood for diagnosis of hereditary spherocytosis in newborns.

The patient in this case had no documented family history of hereditary spherocytosis and no increase in MCHC, although splenomegaly was obvious. However, the patient reported that her father had died prematurely at the age of 30 from hepatobiliary disease, which was suspected to be spherocytosis-induced hepatosplenomegaly. Even without a clear family history, all the laboratory tests supported a diagnosis of hereditary spherocytosis. The peripheral blood spherocyte ratio was high (14%) and the reticulocyte ratio was significantly elevated (8.42%). The bone marrow erythrocyte series ratio was clearly elevated, and the ratio of granulocytes to erythrocytes was reversed. The AGLT was positive, at 67 s (which is significantly shortened).

One of the treatments for hereditary spherocytosis is splenectomy. After this operation, the patient's three hematologic series gradually recovered, her anemia significantly improved

and no further deterioration occurred. Her white blood cell and platelet counts returned to normal.

Hereditary spherocytosis is rare in the Chinese population (incidence 1.27 and 1.49 cases per 100,000 in men and women, respectively) [4]. Thus, hereditary spherocytosis could be mistaken for other conditions, such as parvovirus B19 infection and infectious mononucleosis [9, 10]. A detailed medical history in conjunction with thorough laboratory testing is, therefore, very important for prompt diagnosis. Autoimmune diseases are one extrahepatic manifestation of HCV infection. Extrahepatic manifestations of chronic HCV often involve multiple organ systems and mainly include autoimmune diseases and B-lymphocyte proliferative disorders. The former includes systemic lupus erythematosus, rheumatoid arthritis, and autoimmune hemolytic anemia, while the latter includes cryoglobulinemia and non-Hodgkin's lymphoma [11, 12]. In the present case, the patient had a positive antinuclear antibody titer (1:100) and a fluorescence pattern that was positive for both cytoplasmic granules and nuclear particles. In addition, the patient was positive for anti-nRNP/Sm (+) and anti-Ro-52 (+++). Despite the presence of these autoantibodies, the Coomb's test was negative, indicating that the patient's anemia was not due to autoimmune hemolytic anemia. There have been reports of HCV combined with autoimmune hemolytic anemia [13-15], but this is the first reported case of HCV combined with hereditary spherocytosis.

Conclusions

This case was initiated by acute infection. Due to the patient's medical history of HCV-induced liver cirrhosis, it would have been easy to dismiss her severe anemia as a side effect of her condition. However, if the diagnosis had been limited to biliary tract infection with previous HCV-induced liver cirrhosis, the diagnosis hereditary spherocytosis may have been missed. In conclusion, although patients with liver cirrhosis could present with a reduction in all three hematologic series as a result of splenomegaly and hypersplenism, it is important to consider the possibility of comorbid hematologic diseases, particularly when abnormalities in these series do not match the patient's condition.

Acknowledgements

The authors acknowledge help from associate professor Ji-Xia Qin of the Hematology Department and associate professor Li-Na Zhang of the Radiology Department of the First Affiliated Hospital of Dalian Medical University.

Disclosure of conflict of interest

None.

Abbreviations

HCV, hepatitis C virus; CT, computed tomography; AGLT, acidified glycerol hemolysis test; EMA, eosin 5'-maleimide.

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