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Illuminating and Instructive Clinical Case

Portal Hypertension Refractory Ascites Caused by Secondary Hemochromatosis

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Abstract

We report a patient with refractory ascites because of portal hypertension caused by hemochromatosis secondary to osteopetrosis. To our knowledge, this is the first well-documented case of this association. A 46-year-old male patient who was repeatedly infused with red blood cells for anemia secondary to osteopetrosis suffered from refractory ascites. The serum-ascites albumin gradient was 29.9 g/L. Abdominal computed tomography (CT) showed a large amount of ascites, hepatomegaly, and splenomegaly. Bone marrow biopsy showed a small bone marrow cavity with no hematopoietic tissue. A peripheral blood smear showed tear drop red blood cells and metarubricytes. Serum ferritin was 8,855.0 ng/mL. Therefore, we considered that the ascites resulted from portal hypertension caused by hemochromatosis secondary to osteopetrosis. We simultaneously performed the transjungular intrahepatic portal-systemic shunt (TIPS) and obtained a transjungular liver biopsy. The portal pressure gradient before TIPS was 28 mmHg, and iron staining was strongly positive on liver biopsy, which confirmed our diagnosis. After TIPS, both abdominal distention and ascites gradually resolved, and no recurrence as observed after the 12-month postoperative follow-up was observed. This case indicated that regular monitoring of iron load is important for patients with osteopetrosis. TIPS is safe and effective for portal hypertension complications due to osteopetrosis.

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Case History

A 46-year-old male patient was admitted to the hospital in May 2021 due to recurrent abdominal distention and ascites that lasted for 1 year. One year ago, the patient experienced abdominal distention without an obvious cause, and upper abdominal pain. Then, the patient went to the nearby district hospital and underwent an abdominal ultrasound examination. The result showed that he had a large volume of ascites. Diuretic therapy was given first, but the effect was not obvious. Large volume paracentesis was performed repeatedly, and long-term treatment with furosemide and spironolactone was initiated. The dosage of furosemide was up to 120 mg/day, and that of spironolactone was 300 mg/day. Ascites still recurred. The following results were obtained via physical examination upon admission: blood pressure, 90/50 mmHg; heart rate, 76 beats/min; and body mass index, 19.6 kg/m^2. The patient presented with signs of anemia, pigmented and dark brown skin, emaciated body, pale conjunctiva, distension of abdomen, and shifting dullness. The liver was palpable 6 cm below the right costal margin, and the spleen was palpable 7 cm below the left costal margin. He had a history of osteopetrosis for more than 40 years and was treated with repeated infusion of washed red blood cells due to anemia.

After admission, chest radiography showed increased bone mineral density in the ribs, scapula and clavicle (Fig. 1A). Abdominal computed tomography (CT) showed that the uniform density of the upper and lower margins of the vertebral body increased, while the density of the central part decreased relatively, presenting a sandwich sign. The bone density of the iliac wing and acetabular margin increased, forming a typical appearance of bone within bone (Fig. 1B). CT plain scan showed increased liver density (Fig. 1C). Spiral enhanced CT with multiplanar reconstruction showed ascites, hepatomegaly, and splenomegaly (Fig. 1D). The results of laboratory tests were WBC 3.75×10^9/L, RBC 1.50×10^{12}/L, HGB 51 g/L, PLT 45×10^9/L, RET% 5.09%, IRF 33.10%; albumin 34.2 g/L, urea 17.64 mmol/L, creatinine 166 μmol/L; serum potassium 5.33 mmol/L; and serum ferritin 8,855.0 ng/mL. The ascites was characterized by a clear appearance, specific gravity 1.010, cell count 72×10^6/L, and negative bacterial culture. The serum-ascites albumin gradient (SAAG) was 29.9 g/L. Hepatitis B virus, hepatitis C virus, and ceruloplasmin were negative.

The patient's primary clinical problem at admission was ascites. In this patient, according to the classification of SAAG, ascites was considered to be related to portal hypertension.[1] We performed a bone marrow biopsy and examined a peripheral blood smear. The bone marrow biopsy showed a small bone marrow cavity with no hematopoietic tissue (Fig. 2A), the peripheral blood smear showed tear drop red blood cells (Fig. 2B) and metarubricytes (Fig. 2C). The results suggested that the hematopoietic ability of the bone marrow was

Keywords: Refractory ascites; Secondary hemochromatosis; Osteopetrosis; Transjugular intrahepatic portosystemic shunt; Case report.
Abbreviations: CT, computed tomography; SAAG, serum-ascites albumin gradient; TIPS, transjugular intrahepatic portosystemic shunt.
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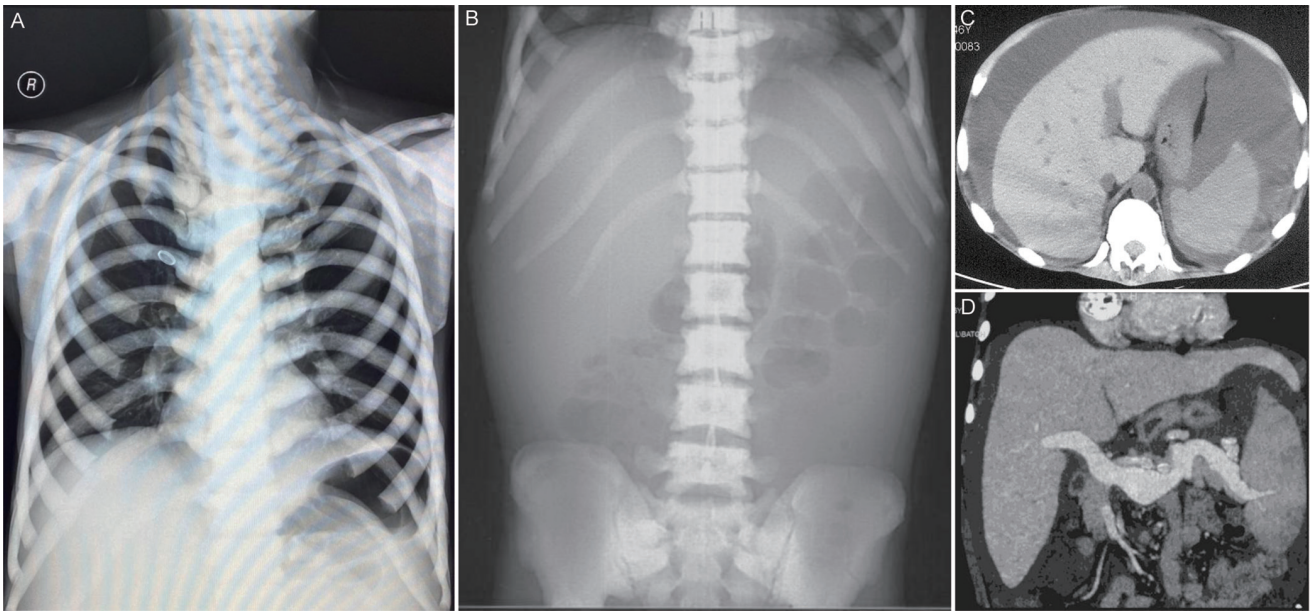

Fig. 1. X-ray and computed tomography examination. (A) Typical radiograph of osteopetrosis with extensive ossification in the ribs, scapula and clavicle. (B) Sandwich sign appearance in the vertebra and bone within bone sign in the iliac bone. (C) Spiral enhanced computed tomography examination with multiplanar reconstruction showed extraordinary hepatomegaly.

decreased. Because the bone marrow hematopoiesis capacity was reduced, the patient required repeated transfusions of red blood cells over a long period of time to treat his anemia. Repeated transfusions caused iron overload. Iron deposition in the liver led to an enlarged liver, increased liver circulation resistance, portal hypertension, and ultimately refractory ascites. Therefore, we thought the portal hypertension ascites in this patient was mainly caused by hemochromatosis secondary to osteopetrosis. Subsequently, a transjugular intrahepatic portal-systemic shunt (TIPS) was implemented at the same time as a transjugular liver biopsy was performed. Strong positive iron staining was seen on liver biopsy (Fig. 2D), further confirming the diagnosis of hemochromatosis. The portal pressure gradient before TIPS was 28 mmHg (Fig. 2E), further confirming the diagnosis of portal hypertension ascites. After TIPS, ascites gradually resolved, abdominal distention was relieved, and no recurrence had occurred at the 12-month postoperative follow-up.

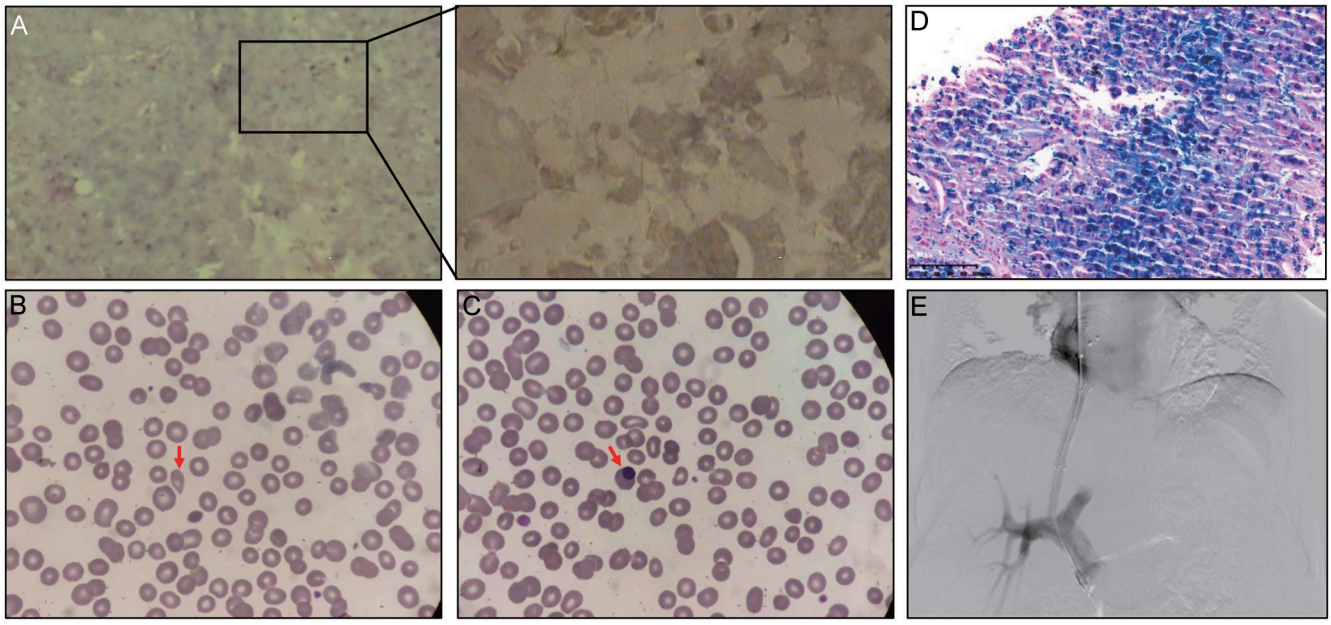

Fig. 2. Bone marrow, blood and liver biopsy specimens. (A) Bone marrow biopsy showed a small bone marrow cavity with no hematopoietic tissue. Left, 100×. Right, 400×. (B and C) Wright's staining of a peripheral blood smear found tear drop red blood cells and metarubricytes (red arrows). (D) Prussian blue staining of a liver biopsy demonstrated abundant blue iron particles in liver cells and stromal cells. (E) Angiography after stent implantation during transjugular intrahepatic portosystemic shunt.

Discussion

Osteopetrosis is a genetic metabolic bone disease characterized by impaired osteoclast function, resulting in excessive calcification of bone-like tissues and a lack of true ossification, which makes bones abnormally brittle and susceptible to breaking. Because of the presence of a large amount of calcified cartilage matrix, the bone marrow cavity is significantly reduced or occluded, leading to bone marrow failure and frequent infections. It is usually accompanied by hepatomegaly and splenomegaly caused by extramedullary hematopoiesis. Previous gene sequencing results showed that the exon 5 region of the CLCN7 gene was abnormal (NM_001287.5: c.480-482), and heterozygous mutations (NM_001287.5: c. 746C>T) in the exon 9 region of the CLCN7 gene. Combined with typical imaging findings, the diagnosis of osteopetrosis is clear.

The patient suffered from abdominal distension and refractory ascites that lasted for one year. Resolving ascites was the main purpose of his admission. Therefore, confirmation of the diagnosis was centered around the cause of the ascites. The SAAG[1] and the biochemical examination of ascites indicated the presence of portal hypertension. The most common cause of portal hypertension is liver cirrhosis. A distinctive feature of this patient was refractory ascites with hepatosplenomegaly, which was clearly not liver cirrhotic ascites. Based on the patient's history, we wondered whether osteopetrosis could have caused noncirrhotic portal hypertension. Cases of portal hypertension due to osteopetrosis are very rare, and only three cases have been reported thus far. In 1971, Denison *et al*.[2] described the first case, a 56-year-old woman with osteopetrosis and portal hypertension complications. Abdominal varicose veins were the main clinical manifestations. Portal hypertension was primarily caused by osteopetrosis, which led to a decrease in bone marrow hematopoietic ability, followed by liver extramedullary hemopoiesis and an increase in intrahepatic resistance. In 2014, Katz *et al*.[3] reported a 52-year-old female osteopetrosis patient with portal hypertension who presented with ascites and esophageal variceal bleeding. The author believed that the cause of portal hypertension was the decreased hematopoiesis in the bone marrow caused by osteopetrosis, and the occurrence of extramedullary hemopoiesis in the spleen resulted in splenomegaly. Excessive splenic venous blood flow caused left portal hypertension. In 2015, Leblebisatan *et al*.[4] reported a 15-year-old girl with osteopetrosis who was diagnosed with portal hypertension and ascites. The author believed that the main cause of portal hypertension was spleen enlargement and excessive splenic venous blood flow. According to these previous reports, osteopetrosis can be complicated by portal hypertension complications because of extramedullary hematopoiesis of the liver and spleen. However, this patient was characterized by an abnormal increase in serum ferritin and a large deposition of iron particles in the liver and no evidence of extramedullary hepatic hematopoiesis. Therefore, we considered that portal hypertension in this patient was mainly caused by hemochromatosis secondary to osteopetrosis rather than extramedullary hematopoiesis of the liver. Osteopetrosis causes extensive osteosclerosis so that the bone marrow cavity was significantly reduced or occluded, resulting in severe anemia. To treat anemia, repeated blood transfusions are performed over a long period of time, which results in iron overload. In addition, ineffective hematopoiesis caused by osteopetrosis, which stimulates an increase in iron absorption in the intestinal tract and leads to iron utilization disorder, may also be one of the reasons for iron overload. Chronic iron overload caused secondary hemochromatosis. Increased portal vein blood flow resistance and splenic venous blood flow led to portal hypertension, which further led to refractory ascites (Fig. 3). Therefore, regular monitoring of iron load in patients with benign autosomal dominant osteopetrosis is important. When serum ferritin is >1,000 ng/mL, iron removal therapy is needed.

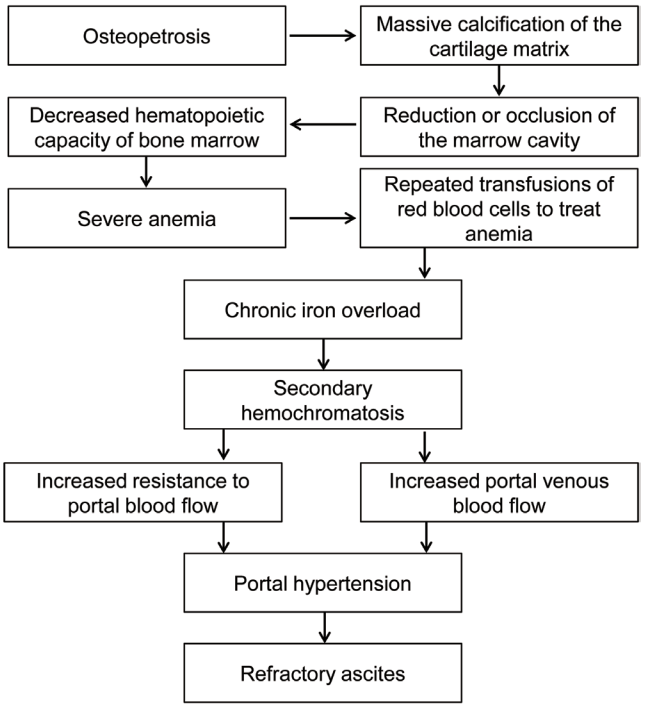

Fig. 3. Diagram of the pathogenesis of refractory ascites in this patient.

The patient had refractory ascites due to portal hypertension caused by secondary hemochromatosis and had been treated with large volume paracentesis and diuretics for 1 year, but the therapeutic effectiveness was poor. According to the guidelines for the management of ascites in patients with cirrhosis, TIPS is an effective treatment for refractory ascites.[5,6] In fact, TIPS is an effective method of reducing portal pressure in both cirrhotic and noncirrhotic patients. Furthermore, TIPS has an advantage in the treatment of noncirrhotic portal hypertension complications compared with cirrhotic portal hypertension complications because of its capacity to maintain good liver function, which leads to reduced portal pressure while maintaining a low incidence of hepatic encephalopathy. Therefore, we treated refractory ascites with TIPS in this patient.

Portal hypertension due to osteopetrosis is very rare in the clinic. The main cause is extramedullary hematopoiesis of the liver and/or an increase in splenic venous blood flow. Here, we report for the first time hemochromatosis secondary to osteopetrosis and leading to portal hypertension complications. We also first used TIPS to treat refractory ascites that resulted from portal hypertension secondary to hemochromatosis caused by osteopetrosis.

Funding

None to declare.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Patient management (JT, WJ), performed TIPS operations (JT, WJ), collected clinical data (WJ, XG), wrote the manuscript (JT).

Ethical statement

Written informed consent was obtained from the patient.

References

[1] Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Ann Intern Med 1992;117(3):215–220. doi:10.7326/0003-4819-117-3-215, PMID: 1616215.

[2] Denison EK, Peters RL, Reynolds TB. Portal hypertension in a patient with osteopetrosis. A case report with discussion of the mechanism of portal hypertension. Arch Intern Med 1971;128(2):279–283. doi:10.1001/archinte.1971.00310200115014, PMID:5564207.

[3] Katz KN, Shafqet MA, Rampertab SD, Pooran N. Osteopetrosis: A New Cause of Upper Gastrointestinal Bleeding. ACG Case Rep J 2014;2(1):45–47. doi:10.14309/crj.2014.80, PMID:26157903.

[4] Leblebisatan G, Celik U, Temiz F, Celik T, Aydin F, Istifli FL, *et al*. An Adolescent Case of Osteopetrosis with Portal Hypertension as well as Mandibula Osteomyelitis. Indian J Hematol Blood Transfus 2015;31(2):295–296. doi:10.1007/s12288-014-0422-0, PMID:25825576.

[5] Garcia-Pagan JC, Francoz C, Montagnese S, Senzolo M, Mookerjee RP. Management of the major complications of cirrhosis: Beyond guidelines. J Hepatol 2021;75(Suppl 1):S135–S146. doi:10.1016/j.jhep.2021.01.027, PMID:34039484.

[6] Aithal GP, Palaniyappan N, China L, Harmala S, Macken L, Ryan JM, *et al*. Guidelines on the management of ascites in cirrhosis. Gut 2021;70(1):9–29. doi:10.1136/gutjnl-2020-321790, PMID:33067334.