Extramedullary hematopoiesis causing portal hypertension with chylous ascites in a patient with primary myelofibrosis

Vishal Mangal[1*], Manish manrai[2], Ankit Kumar[3]

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ABSTRACT

Background: Primary myelofibrosis is a rare myeloproliferative disorder that is occasionally associated with abdominal and hepatic complications, such as Budd–Chiari syndrome, nodular regenerative hyperplasia, portal vein thrombosis, and rarely portal hypertension, which is found in 7% of the cases.

Case Presentation: We report a rare case of portal hypertension with chylous ascites in a 49-year-old male patient with primary myelofibrosis, who presented with a painless progressive distension of the abdomen for 1 month. His transjugular liver biopsy revealed extramedullary hematopoiesis with colonies of erythroid precursors, megakaryocytes, and numerous clusters of erythroid islands in the hepatic sinusoids. He was provided with a salt-restricted diet and diuretics with partial response and was scheduled for a transjugular intrahepatic portosystemic shunt.

Conclusion: Extramedullary hematopoiesis should always be considered in patients with myeloproliferative disorders with a rare case of portal hypertension.

Keywords: Myeloproliferative disorders, portal hypertension, chylous ascites, extramedullary hematopoiesis, primary myelofibrosis, case report.

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Correspondence to: Vishal Mangal
*Department of Internal Medicine, Armed Forces Medical College, Pune, India.
Email: vishal_rimshi@rediffmail.com
Full list of author information is available at the end of the article.

Background

Myelofibrosis, or bone marrow fibrosis, is characterized by an increase in the deposition of extracellular matrix proteins in the bone marrow stroma [1]. Myeloproliferative diseases (MPD) are clonal stem cell disorders [2]. The major MPDs include polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis [3]. The clinical features include leukocytosis, thrombocytosis, erythrocytosis, splenomegaly, and bone marrow hypercellularity probably due to hematopoiesis. Common abdominal manifestations of myelofibrosis include splenomegaly, hepatomegaly, and rarely ascites, with the prevalence ranging from 2% to 10% [4,5]. The hepatic manifestations are Budd–Chiari syndrome (BCS), portal vein thrombosis (PVT), and nodular regenerative hyperplasia [3]. However, intrahepatic noncirrhotic portal hypertension without portal or hepatic vein thrombosis is rarely described in these patients [6,7]. The mechanisms underlying portal hypertension in MPD are still controversial. Increased blood flow into the portal system through the enlarged spleen by extramedullary hematopoiesis and intrahepatic obstruction of the portal system due to extramedullary hematopoiesis or sinusoidal change can increase portal pressure, leading to portal hypertension [8]. Almost two-thirds of all chylous ascites cases in developed countries are associated with abdominal malignancy and cirrhosis, whereas infectious diseases, including tuberculosis, account for most cases in developing countries [9,10,11]. Chylous ascites in a patient with primary myelofibrosis and portal hypertension has never been reported. We report the first case of chylous ascites with portal hypertension in a case with primary myelofibrosis.

Case Presentation

A 49-year-old male, an already diagnosed case of primary myelofibrosis since 2007, initially presented with pain in the upper left abdomen, and on examination was found to have a massive splenomegaly. He was then evaluated for the cause of his massive splenomegaly. His *BCR-ABL* gene mutation studies were negative with normal karyotype; however, subsequently he was found positive for *JAK2V617F* mutation. The patient never underwent calreticulin and myeloproliferative leukemia virus oncogene mutation studies. His bone marrow biopsy revealed near-total replacement of marrow by fibrous elements. He was initially prescribed thalidomide from 2007 to 2012, which was stopped because of thrombocytopenia and was switched to Capsule Hydroxyurea until 2015,

and subsequently started on Tablet Ruxolitinib from 2015 till date. In February 2019, he was found to have azotemia and persistent hyperkalemia. On evaluation, his ultrasonography showed the right kidney of 8.7 cm and the left kidney of 8.9 cm. He had subnephrotic range proteinuria. He underwent dimercaptosuccinicacid scan which showed no cortical scar in both the kidneys. He also underwent a diethylenetriaminepentaacetic acid scan which showed compromised cortical function with a total glomerular filtration rate of 46 ml/minutes with normal drainage, and was, therefore, diagnosed with chronic kidney disease. In August 2019, he presented with painless progressive distension of the abdomen. However, he denied any history of yellowish discoloration of eyes, urine, decreased appetite, nausea, vomiting, fever, or weight loss. He did not give any history of altered bowel or bladder habits, swelling of feet, or altered sleep rhythm. There was no history suggestive of hematemesis or melena. No history of chest pain, syncope, or palpitations. On general physical examination, pallor was present along with bilateral pitting pedal edema.

Examination of the abdomen revealed hepatomegaly with the liver spanning 15 cm and splenomegaly extending 20 cm below the left subcostal margin along with gross ascites. On evaluation, the ultrasonography of the abdomen revealed hepatosplenomegaly with a portal vein diameter of 15.6 mm without any evidence of cirrhosis. He underwent diagnostic ascitic fluid analysis which showed chylous fluid with triglycerides of 964 mg/dl, serum ascitic albumin gradient (SAAG) of 1.9, ascitic fluid total protein 3.9 gram/dl, and adenosine deaminase (ADA) level of 8.9 U/dl. There were 182 cells/mm^3 with lymphocyte predominance, and had negative malignant cells on ascitic fluid cytology analysis. There was no evidence of inferior vena cava or hepatic vein obstruction on color doppler flow imaging. Etiological workup was negative for hepatitis B and C, autoimmune hepatitis (including antineutrophil antibody, antiliver kidney microsome type 1 antibody, antismooth muscle antibody, and antimitochondrial antibody). His serum ceruloplasmin level was 37.80 U/L, which was in the normal range. His esophagogastroduodenoscopy showed four columns of grade II varices. Echocardiography revealed left ventricular ejection fraction of 60% with no regional wall motion abnormalities, no pericardial effusion, or clot. He also underwent a whole-body positron emission tomography (PET) scan to rule out any occult malignancy which did not show any fluorodeoxyglucose (FDG) avid uptake. Moreover, there was no evidence of tracer or collection in peritoneal or thoracic cavity on lymphoscintigraphy. Since there was no evident cause of portal hypertension, he underwent transjugular Liver biopsy, which showed extramedullary hematopoiesis without evidence of cirrhosis (Figures 1–4).

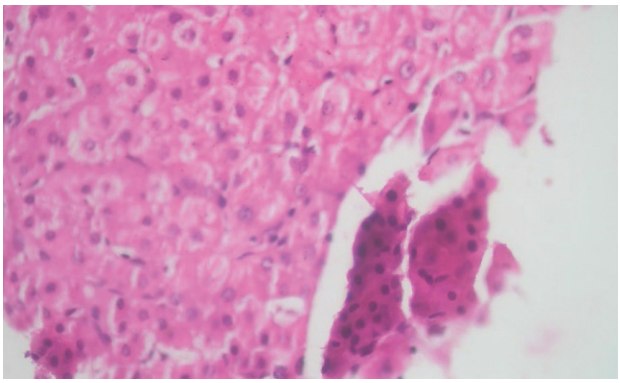

Figure 1. *H & E stain of liver biopsy, 40 x.*

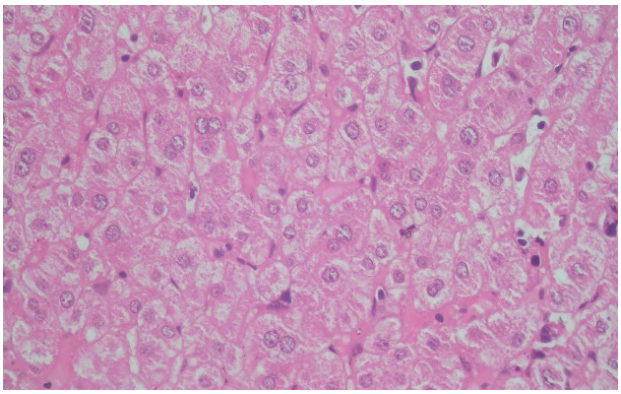

Figure 2. *H & E stain of liver biopsy, 40 x.*

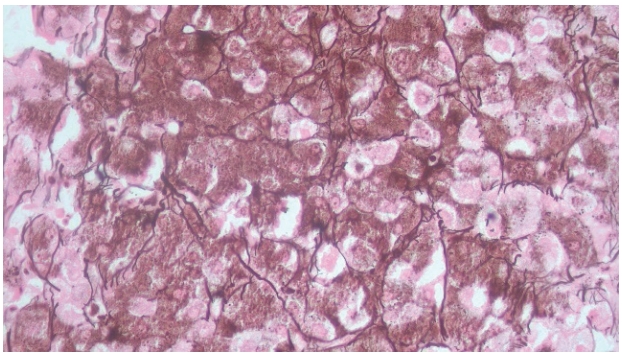

Figure 3. *Reticulin stain of liver biopsy, 40 x.*

The patient was provided with a salt-restricted diet and loop diuretics with gradual weight reduction initially. However, he developed refractory ascites with inadequate response to incremental doses of diuretics. Therefore, he was scheduled for a transjugular intrahepatic portosystemic shunt (TIPS) for management of portal hypertension. In this case, even after a detailed investigation, there was no evident cause of portal hypertension. Hence, we report the first case of chylous ascites due to extramedullary hematopoiesis leading to portal hypertension in a patient with primary myelofibrosis.

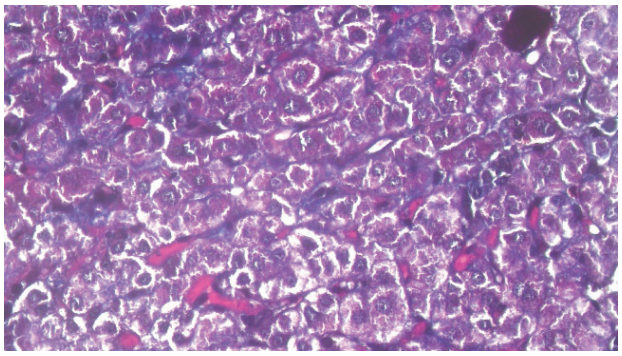

Figure 4. *Masson's trichome stain of liver biopsy 40x. Figures 1-4 showing extramedullary hematopoiesis with colony of erythroid precursors. Megakaryocytes and numerous clusters of erythroid islands seen. The portal tracts show minimal portal inflammation. No piecemeal necrosis. The lobules show small foci of necrosis. Hepatocytes show feathery degeneration. No steatosis or lobular inflammation. No acinar formation or plasma cell inflammation seen. No fibrous extension of portal tract seen.*

Discussion

Portal hypertension is a rare complication of primary myelofibrosis with poorly understood etiology. In the present case, the patient who is a known case of primary myelofibrosis presented with ascites. Ascitic fluid was chylous with high SAAG (> 1.1) and high protein (ascitic fluid total protein >2.5) suggestive of the possibilities of cardiac diseases (congestive cardiac failure, constrictive pericarditis), BCS, inferior vena cava obstruction, and sinusoidal obstruction syndrome [12]. However, all these causes were ruled out after necessary investigations. Based on the chylous nature of the ascitic fluid, he was further worked up for the possibilities of tuberculosis, intraabdominal malignancy, and for any injury to the lymphatic duct. However, the ascitic fluid ADA and microscopy for acid-fast bacilli were negative, an 18F FDG whole-body PET CT scan did not reveal any abnormal FDG avid lesion/uptake suggestive of mitotic etiology, and lymphoscintigraphy did not show any evidence of tracer or collection in peritoneal or thoracic cavity. His Ruxolitinib was continued for primary myelofibrosis, as it has some direct vasodilatory effect on the intrahepatic sinusoids and reduction in splenic arterial inflow mediated via the reduction in spleen size, and also unique action of Janus kinase-2 inhibition on hepatic stellate cell relaxation was recently reported to decrease portal pressures in animal models [12]. Subsequently, the patient was diagnosed with extramedullary hematopoiesis in the hepatic sinusoids, which can explain the cause of portal hypertension in our case. He was started on Tablet Propranolol for primary prevention of the esophageal varices and diuretic to mobilize the ascites with inadequate response. It has been proposed that increased caval and hepatic venous pressures cause a large increase in the production of hepatic lymph. Elevated lymphatic pressure secondary to portal hypertension can cause endothelial compromise or rupture of serosal dilated lymphatic channels, which leads to chylous ascites formation. Based on refractory ascites, he was scheduled for TIPS as a definitive management of ascites, since it is a viable treatment option for the treatment of refractory ascites, especially with preserved liver function. There have been a few case reports on TIPS for the treatment of portal hypertension and ascites in patients with extramedullary hematopoiesis [7]. However, the response to the therapy will depend on the behavior of the primary myelofibrosis.

Conclusion

This case highlights the importance of the fact that portal hypertension in a case of myelofibrosis is usually caused by posthepatic or prehepatic causes; however, hepatic causes, such as this case, should be always kept in mind.

What is new?

Portal hypertension is seen in 7% of cases with myeloproliferative disorders. The most common causes are BCS and PVT. This is the first case report of chylous ascites caused by extramedullary hematopoiesis leading to portal hypertension in a patient known to have primary myelofibrosis.

List of Abbreviations

ADA	Adenosine deaminase
BCS	Budd–Chiari syndrome
FDG	Fluorodeoxyglucose
MPD	Myeloproliferative diseases
PVT	Portal vein thrombosis
PET	Positron emission tomography
SAAG	Serum ascitic albumin gradient
TIPS	Transjugular intrahepatic portosystemic shunt

Consent for publication

Written informed consent was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution for publishing an anonymous case report.

Author details

Vishal Mangal[1], Manish manrai[2], Ankit Kumar[3]

1. Clinical Tutor, Department of Medicine, Armed Forces Medical College, Pune, India
2. Assoc Professor, Department of Medicine, Armed Forces Medical College, Pune, India
3. Junior Resident, Department of Medicine, Armed Forces Medical College, Pune, India

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Summary of the case

1	**Patient (gender, age)**	Male, 49-year old
2	**Final diagnosis**	Portal hypertension due to extramedullary hematopoiesis in primary myelofibrosis
3	**Symptoms**	Painless progressive distension of abdomen
4	**Medications**	Frusemide, spironolactone, ruxolitinib
5	**Clinical procedure**	Diagnostic ascitic tap
6	**Specialty**	Hepatology/gastroenterology