Myelofibrosis and Portal Hypertension: The Case for Primary Variceal Screening

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ABSTRACT

Myelofibrosis is a hematologic condition that predisposes to the formation of large and small portal venous clots. Portal injury is believed to underlie the mechanism of development of noncirrhotic portal hypertension in this population. We describe a patient with myelofibrosis, proven portal hypertension, and extramedullary hematopoiesis with no imaging or pathologic evidence of microvascular or macrovascular portal clot. We provide a concise review of the literature which highlights that patients with myelofibrosis and related conditions of polycythemia vera and essential thrombocytosis present not infrequently with portal hypertension and variceal bleeding. We propose this population may benefit from primary variceal screening.

INTRODUCTION

Myelofibrosis is a neoplastic disorder characterized by progressive fibrotic replacement of the bone marrow, resulting in extramedullary hematopoiesis (EMH). The liver is a well-documented site of EMH. A clinically important consequence of liver EMH is the development of noncirrhotic portal hypertension, which manifests as ascites and/or variceal bleeding. The mechanism of portal hypertension is believed to be a consequence of microvascular or macrovascular clot, injury, and loss of small and large portal veins.1 We present a patient with myelofibrosis and ascites, where liver pathology shows EMH without evidence of microvascular or macrovascular clot or portal vein injury, which suggests there are likely additional factors at play in the evolution of noncirrhotic portal hypertension in this population. We briefly review the literature, an exercise that emphasizes how common portal hypertension is in this population and its related conditions of polycythemia vera (PV) and essential thrombocytosis (ET).

CASE REPORT

A 76-year-old woman presented with 1 week of worsening abdominal distension and lower extremity swelling. Examination revealed clear lungs, minimal jugular venous distension, large ascites, splenomegaly without hepatomegaly, and edema. Medical history included diastolic heart failure, JAK2+ primary myelofibrosis on ruxolitinib, and hospitalization before 8 months with melena. Upper and lower endoscopy was unrevealing for an active source of bleeding, although biopsy of erythematous patches in the stomach demonstrated the presence of dilated mucosal capillaries on pathology. Splenic enlargement was noted, prompting cessation of ruxolitinib and treatment with splenic radiation.

Laboratory evaluation included white blood cells of 26,000/μL (neutrophil predominant), hemoglobin 11.0 g/dL, platelets 452 K/μL, alanine aminotransferase 14 U/L, aspartate aminotransferase 27 U/L, alkaline phosphatase 126 U/L, bilirubin 1.1 mg/dL, albumin 2.7 g/dL, and international normalized ratio (INR) 1.4. Aspartate aminotransferase, alanine aminotransferase, and INR were normal dating back to January 2010, whereas the alkaline phosphatase ranged from 66 to 183 U/L with the upper limit of normal being 100 U/L. Paracentesis revealed a serum to ascites albumin gradient of 1.7 and a total protein of 1.9 g/dL. A workup for chronic liver disease was negative for hepatitis A, B, C, autoimmune hepatitis, hemochromatosis, and primary biliary cholangitis. Computed tomography imaging demonstrated a small liver with nodular contour, no focal hepatic lesions, and splenomegaly (21...
cm in the craniocaudal dimension), which was unchanged from 8 months ago. Ultrasound with Doppler showed no evidence of portal or hepatic vein thrombosis, and portal flow was hepatopetal.

A transjugular liver biopsy/transhepatic pressure gradient was performed and was 12 mm Hg. Liver histology demonstrated EMH, including megakaryocytes early erythroids, patchy sinusoidal fibrosis (stage 1 fibrosis), and focal steatosis (Figures 1 and 2). There was no evidence of microvascular thrombosis or injury.

**DISCUSSION**

In myelofibrosis, several disease-specific processes can precipitate portal hypertension. These patients are at risk for hepatic vein thrombosis, and JAK2 positivity specifically raises the specter of Budd-Chiari syndrome. Preintrahepatic or intrahepatic thrombotic complications are also possible with patients developing both macrovascular portal vein thromboses and sinusoidal microthrombi; the latter is similar to that seen in sinusoidal obstruction syndrome but without the antecedent chemoablation. Imaging and pathology in our patient excluded a thrombotic etiology at all vessel sizes. The low ascitic fluid protein made peritoneal EMH less likely. In our patient, the elevated transhepatic pressure gradient established portal hypertension as intrahepatic in origin and the diagnosis was supported by evidence of hepatic EMH and sinusoidal fibrosis.

The exact mechanism of noncirrhotic portal hypertension in this population remains unclear. The most compelling pathologic study comes from an autopsy series in patients with myelofibrosis, where histopathologic features were correlated with clinical signs of portal hypertension. Nodular transformation was found to be the most distinguishing feature (evident in the form of a macronodular contour on ultrasound of our patient, although there was no evidence of nodularity on our small caliber transjugular biopsy). Microvascular or macrovascular clot with injury and loss of portal veins are the other proposed mechanism from Wanless et al PV; this is notably absent in our patient’s liver pathology.

Classic autopsy studies and case series show that ascites and varices are commonly seen in myelofibrosis. Combining the observations from the largest of the retrospective studies, all of which excluded patients with cirrhosis because of other causes 8.2%, the patients had esophageal varices and 21% and were found to have ascites. Authors of these studies note that a significant percentage of patients with esophageal varices presented with hematemesis, and a literature search reveals continued publication of case reports documenting the instances of these patients presenting with complications of portal hypertension. Not infrequently, a variceal bleed is the presentation that leads to diagnosis of underlying myelofibrosis, PV, or ET. The only prospective study in the literature that documented 7% of patients with primary myelofibrosis or its predisposing conditions had endoscopically visualized varices, whereas 14% had ultrasound evidence of portal hypertension, supporting the autopsy-and retrospective-estimated prevalence mentioned above. Our patient’s hospitalization with occult gastrointestinal bleeding 8 months before is likely attributable to portal hypertension in the form of portal hypertensive gastropathy, based on the pathologic findings of dilated mucosal capillaries. Such
subacute presentations are likely more common but less reported than precipitous presentations.

In summary, noncirrhotic portal hypertension and its morbid consequences appear common in the late stages of myelofibrosis and related entities (ET and PV) but may present as early as a year after diagnosis.\textsuperscript{1–5} Although these patients are at a higher risk for portal vein thrombosis, portal hypertension is commonly seen even in the absence of both microvascular and macrovascular portal clot, as in our patient. Given the high prevalence of varices at autopsy and persistent case reports of variceal bleeding in this population, patients with myelofibrosis, ET, and/or PV may benefit from primary variceal screening.\textsuperscript{1,4–11} Alkaline phosphatase elevation in patients with myelofibrosis suggests the possibility of hepatic EMH; however, many patients with portal hypertension had normal serum biochemical markers.\textsuperscript{3} Additional studies are required to better stratify who is at risk for development of portal hypertension in this unique population.

DISCLOSURES

Author contributions: All authors contributed equally to this manuscript. MS Sherman is the article guarantor.

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REFERENCES

1. Wanless IR, Peterson P, Das A, Boitnott JK, Moore GW, Bernier V. Hepatic vascular disease and portal hypertension in polycythemia vera and agnogenic myeloid metaplasia: A clinicopathological study of 145 patients examined at autopsy. \textit{Hepatology}. 1990;12:1166–74.
2. Pitcock JA, Reinhard EH, Justus BW, Mendelsohn RS. A clinical and pathological study of seventy cases of myelofibrosis. \textit{Ann Intern Med}. 1962;57:73–84.
3. Ligumski M, Poliack A, Benbassat J, Nature and incidence of liver involvement in agnogenic myeloid metaplasia. \textit{Eur J Haematol}. 1978;21:81–93.
4. Ward HP, Block MH. The natural history of agnogenic myeloid metaplasia (AMM) and a critical evaluation of its relationship with the myeloproliferative syndrome. \textit{Medicine}. 1971;50:357–420.
5. Toros AB, Gokcay S, Cetin G, Ar MC, Karagoz Y, Kesi B. Portal hypertension and myeloproliferative neoplasms: A relationship revealed. \textit{ISBN Hematol}. 2013;2013:673781.
6. Vahabzadeh B, Crippin JS. Portal hypertension as a result of extramedullary hematopoiesis caused by idiopathic myelofibrosis. \textit{Clin Gastroenterol Hepatol}. 2008;6(4):e22.
7. Tokai K, Miyatani H, Yoshiya Y, Yamada S. Multiple esophageal variceal ruptures with massive ascites due to myelofibrosis-induced portal hypertension. \textit{World J Gastroenterol}. 2012;18(28):3770.
8. Takasaki M, Takahashi I, Takamatsu M, et al. Endoscopic injection sclerotherapy for esophageal variceal hemorrhage in a patient with idiopathic myelofibrosis. \textit{J Gastroenterol}. 1996;31(2):260–2.
9. Glockenberg K, Weinberg EM, Wan DW. A sinister cause of hematemesis. \textit{Gastroenterology}. 2015;148(3):e5–6.
10. Kono Y, Takaki A, Gobara H, et al. Polycythemia vera diagnosed after esophageal variceal rupture. \textit{Intern Med}. 2015;54(18):2395–9.
11. Smith MD. Essential thrombocytosis and its significance: With report of a case. \textit{Glasgow Med J}. 1953;34(7):308.

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