Clinical Features of Patients With Philadelphia-Negative Myeloproliferative Neoplasms Complicated by Portal Hypertension

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Abstract

Portal hypertension (PHTN) is an understudied complication of Philadelphia-negative myeloproliferative neoplasms (MPNs). We restrospectively reviewed 51 MPN patients with PHTN and found that patients with polycythemia vera (PV) and myelofibrosis (MF) are disproportionately affected by PHTN compared with essential thrombocythemia (ET). The etiology of PHTN appears to be related to splanchnic circulation thrombosis in PV and splenomegaly in MF.

Background: Portal hypertension has been reported to afflict 7% to 18% of patients with Philadelphia-negative MPNs, with complications of variceal bleeding and ascites. The clinical features and outcomes of these patients are unclear. **Patients and Methods:** In this multicenter retrospective study, we evaluated the clinical features of 51 patients with MPNs complicated by PHTN. **Results:** The diagnosis of underlying MPN was most frequently PV (39%) and primary MF (35%), followed by post-PV MF (18%), ET (4%), and post-ET MF (4%). Frequency of Janus Kinase 2 V617F mutation appears as expected in the underlying MPN. Thrombosis within the splanchnic circulation was prevalent in patients with polycythemia compared with other MPNs (76% vs. 26%; $P = .0007$). **Conclusion:** PV and MF patients have a greater incidence of PHTN in our population, with thrombosis contributing to PHTN development in PV patients. Patients with splanchnic circulation thrombosis are potential candidates for screening for PHTN. These data might be useful for developing screening strategies for early detection of PHTN in patients with MPN.

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Introduction

Portal hypertension (PHTN) is 1 of the rare complications of Philadelphia-negative myeloproliferative neoplasms (MPNs). Although a well recognized complication, clinical features and mechanisms of PHTN are not well understood in MPN. Most of the current literature is in the form of anecdotal case reports or small retrospective series. PHTN has been reported in approximately 7% to 18% of patients with MPN, many of whom present with variceal bleeding or ascites.[1,2] Several case reports have demonstrated the use of endoscopic variceal ligation or sclerotherapy to control esophageal varices, and the use of transjuglar intrahepatic portosystemic shunts for refractory ascites.[3,4]

Frequently, PHTN develops secondary to portal vein or hepatic vein thromboses.[5-7] However, even in the absence of a thrombotic occlusion, patients with MPN can still develop noncirrhotic PHTN. The exact mechanism in such patients has not been elucidated. The main hypotheses include intrahepatic obstruction secondary to extramedullary hematopoiesis within the sinusoids, and or increased portal blood flow secondary to splenomegaly.[6-12] In a case series of 13 patients, 8 had liver biopsies demonstrating noncirrhotic liver parenchyma with infiltration of liver sinusoids with hematopoietic cells. Six of the patients had evidence of

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increased portal blood flow.[6] Splenectomy has also been demonstrated to reverse PHTN in 1 case study in which splenomegaly was hypothesized to be a main factor in PHTN development.[13]

Whether any particular MPN patients are more prone to develop PHTN is not known. Better understanding of the clinical features will be useful in earlier diagnosis, which might lead to appropriate interventions to prevent serious complications such as variceal bleeding or ascites. To gain further insights in this area, we performed a retrospective multi-center study, and reviewed the clinical features and outcomes of 51 patients with PHTN and Philadelphia-negative MPNs.

Patients and Methods

This study was coordinated by the leukemia program at the Princess Margaret Cancer Centre, Toronto, Canada. Four centers participated: Princess Margaret Cancer Centre, Toronto, Sunnybrook Health Sciences Centre, Toronto, Mayo Clinic, Scottsdale, AZ, and Medical College of Wisconsin, Milwaukee, WI. The study was approved by the Research and Ethics Board of all the participating institutions.

The inclusion criteria for the study required a confirmed diagnosis of Philadelphia-negative MPN and PHTN. The MPNs included in this study were polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), post-ET myelofibrosis (PET-MF), and post-PV myelofibrosis (PPV-MF) diagnosed according to World Health Organization or International Working Group for Myelofibrosis Research and Treatment criteria. The diagnosis of PHTN was defined as the presence of ascites (clinically or based on imaging) and/or varices (verified endoscopically) in the absence of a known cause other than MPN.

Fifty-one patients meeting the inclusion criteria were identified. The patient charts were reviewed, and data were abstracted into a case report form designed for this study. Detailed information regarding patient, disease, treatment-related factors, and outcomes were collected.

Univariate analysis on categorical variables was performed using χ^2 test or Fisher exact test as appropriate. Continuous variables were described as mean ± standard deviations. Comparisons between means of 2 independent groups of interest were performed using the nonparametric Wilcoxon rank sum test. The Wilcoxon signed-rank test was used when comparing 2 related samples such as repeated measurements on a single individual. Mean and median follow-up time was provided for patients who are alive. Survival estimates were obtained and compared using the Log rank test of the Kaplan−Meier method.

Results

The clinical features of the study cohort are summarized in Table 1. Thirty-nine percent of the patients had PV, 35% PMF, 18% PPV-MF, 4% ET, and 4% PET-MF. The frequency of the Janus Kinase 2 (*JAK2*) mutation is 96% in PV or PPV-MF patients compared with 58% in all other MPN patients (Figure 1).

The Dynamic International Prognostic Scoring System (DIPSS) score was calculated at the diagnosis of PHTN in myelofibrosis (MF) patients, and 35% of patients had low- to intermediate-level 1-risk disease. When comparing clinical factors at the diagnosis of MPN to the diagnosis of PHTN, there was a trend toward higher mean alkaline phosphatase level at PHTN diagnosis (124.6 U/L [range, 63-272 U/L] vs. 185.9 U/L [range, 50-636 U/L]; $P = .07$). MF patients did have a significantly greater incidence of palpable splenomegaly > 10 cm compared with the other MPNs ($P = .001$).

Twenty-two patients (76%) with PV or PPV-MF had thrombosis detected within the splanchnic circulation (Figure 2). In contrast, only 6 patients (27%) with PMF, ET, or PET-MF had thrombus detected ($P = .0007$). In terms of PHTN presentation, 22 patients (43%) presented with varices, 18 patients (35%) with ascites, and 11 patients (22%) with varices and ascites.

Ten patients with PHTN were treated with JAK1/2 inhibitor, with 6 of these patients presenting with varices. Of these 6 patients, 3 had follow-up endoscopies performed, which did not show any change in grade of varices after a mean treatment duration of 18 months (range, 15-24 months).

Fourteen patients required variceal ligation, 5 patients required a transjugular intrahepatic portosystemic shunt (TIPS), and 4 patients had a splenectomy. Four of the 5 patients that received TIPS presented initially with Budd-Chiari syndrome and then subsequently had MPNs diagnosed during their thrombophilia workup. Three of the 5 patients with TIPS had patent shunts at follow-up and no longer had evidence of PHTN. All 4 patients with splenectomy still have PHTN.

At a median follow-up of 24 months for MF patients and 96 months for PV patients, 19 patients died. Six patients (32%) died as a consequence of PHTN with a median duration from PHTN diagnosis to death of 3 months: 1 from hepatorenal failure, 2 from bacterial peritonitis, and 3 from variceal bleeding (Table 1). The remaining patients died as a result of leukemic transformation or progression of their MPN.

Discussion

In our study of 51 patients, we evaluated the clinical characteristics of MPN patients who developed PHTN. Our study showed that most patients with PHTN have underlying diagnoses of PMF, PV, or PPV-MF. Patients with ET or PET-MF only comprise a small subset of cases reviewed in our study, approximately 8%. The reason for the predilection toward polycythemia or PMF is not entirely clear because ET shares many similarities with the other MPNs, including thrombosis.

JAK2 V617F mutation status was found to be similar to the reported frequencies in patients without PHTN.[14] Recent studies have shown that the *JAK2* mutation is a risk factor for splanchnic circulation thrombosis, in patients with MPN and without overt MPN.[15] It is possible to hypothesize that the increased frequency of *JAK2* mutation, and therefore splanchnic circulation thrombosis, in PV might account for the greater incidence of PHTN compared with ET. A review of the effect of allele burden has shown that patients homozygous for the *JAK2* mutation have a higher incidence of thrombosis in ET.[16] Therefore, it would be interesting to see if MPN patients with a higher allele burden are more prone to PHTN.

As briefly discussed herein and in other case series, the etiology of PHTN in MPNs is thought to be secondary to thrombosis, splenomegaly, or intrahepatic extramedullary hematopoiesis. When comparing polycythemia patients (PV and PPV-MF) with all other patients with MPN and PHTN, polycythemia patients are found to have a significantly greater frequency of splanchnic circulation