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Clinical features of patients with Philadelphia-negative myeloproliferative neoplasms complicated by portal hypertension

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Abstract

Background—Portal hypertension (PHTN) has been reported to afflict 7-18% of patients with Philadelphia-negative myeloproliferative neoplasms (MPNs), with complications of variceal bleeding and ascites. The clinical features and outcomes of these patients are unclear.

Patients and Methods—In this multi-centre retrospective study, we evaluated the clinical features of 51 patients with MPNs complicated by PHTN.

Results—The diagnosis of underlying MPN was most frequently polycythemia vera (PV) (39%) and primary myelofibrosis (MF) (35%), followed by post-PV myelofibrosis (18%), essential thrombocythemia (ET) (4%) and post-ET myelofibrosis (4%). Frequency of *JAK2* V617F mutation appears as expected in the underlying MPN. Thrombosis within the splanchnic circulation was prevalent in patients with polycythemia compared to other MPNs (76% vs. 26%, $p=0.0007$).

Conclusions—PV and MF patients have a higher 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 portal hypertension. These data may be useful for developing screening strategies for early detection of PHTN in patients with MPN.

Keywords

Essential thrombocythemia; Polycythemia vera; Myelofibrosis; Thrombosis; portal hypertension

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INTRODUCTION

Portal hypertension (PHTN) is one of the rare complications of Philadelphia-negative myeloproliferative neoplasms (MPN). 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%-18% of patients with MPN, many of whom present with variceal bleeding or ascites¹⁻². Several case reports have demonstrated the use of endoscopic variceal ligation or sclerotherapy to control esophageal varices, as well as the use of transjugular intrahepatic portosystemic shunts for refractory ascites³⁻⁴.

Frequently, PHTN develops secondary to portal vein or hepatic vein thromboses⁵⁻⁷. However, even in the absence of a thrombotic occlusion, patients with MPN can still develop non-cirrhotic 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 splenomegaly⁶⁻¹². In a case series of 13 patients, 8 had liver biopsies demonstrating non-cirrhotic liver parenchyma with infiltration of liver sinusoids with hematopoietic cells. Six of the patients had evidence of increased portal blood flow⁶. Splenectomy has also been demonstrated to reverse portal hypertension in one case study where splenomegaly was hypothesized to be a main factor in PHTN development¹³.

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 may 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-centre 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 centres participated: Princess Margaret Cancer Centre, Toronto, Sunnybrook Health Sciences Centre, Toronto, Mayo Clinic, Scottsdale, USA and Medical College of Wisconsin, Milwaukee, USA. 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 both 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 absence of a known cause other than MPN.

Fifty-one patients meeting the above 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 Chi-square test or Fisher's exact test as appropriate. Continuous variables were described as means $\pm$ standard deviations. Comparisons between means of two independent groups of interest were performed through non-parametric Wilcoxon rank sum test. The Wilcoxon signed-rank test was used when comparing two related samples such as repeated measurements on a single individual. Mean and median follow-up time was provided for patients that are alive. Survival estimates were obtained and compared by using the Log rank test of the Kaplan-Meier method.

RESULTS

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

Dynamic International Prognostic Scoring System (DIPSS) score was calculated at the diagnosis of PHTN in MF patients, and 35% of patients had low/intermediate-1 risk disease. When comparing clinical factors at the diagnosis of MPN to the diagnosis of PHTN, there was a trend towards higher mean alkaline phosphatase (ALP) level at PHTN diagnosis (124.6 U L^{-1} (63 to 272 U L^{-1}) vs 185.9 U L^{-1} (50 to 636 U L^{-1}), $p = 0.07$). MF patients did have a significantly higher incidence of palpable splenomegaly $> 10\text{cm}$ when compared to the other MPNs ($p=0.001$).

Twenty-two patients (76%) with PV or PPV-MF had thrombosis detected within the splanchnic circulation (Fig. 2). In contrast, only 6 patients (27%) with PMF, ET or PETMF patients had thrombus detected ($p=0.0007$). In terms of PHTN presentation, 22 patients (43%) presented with varices, 18 patients (35%) with ascites, and 11 patients (22%) with both varices and ascites.

Ten patients with PHTN were treated with JAK1/2 inhibitor, with six of these patients presenting with varices. Out of these six 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 (15-24 months).

Fourteen patients required variceal ligation, five patients required a transjugular intrahepatic portosystemic shunt (TIPS), and four patients had a splenectomy. Four of the five patients that received TIPS presented initially with Budd-Chiari syndrome and then subsequently had MPNs diagnosed during thrombophilia workup. Three of the 5 patients with TIPS have patent shunts at follow up and no longer have 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 have died. Six patients (32%) have 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 have evaluated the clinical characteristics of MPN patients who develop PHTN. Our study shows that the majority of 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 towards polycythemia or PMF is not entirely clear as ET shares many similarities with the other MPNs, including thrombosis.

JAK2 V617F mutation status was found to be similar to the reported frequencies in those without PHTN¹⁴. Recent studies have shown that the *JAK2* mutation is a risk factor for splanchnic circulation thrombosis, in those with MPN and without overt MPN¹⁵. It is possible to hypothesize that the increased frequency of *JAK2* mutation, and therefore splanchnic circulation thrombosis, in PV may account for the higher incidence of PHTN when compared to ET. A review of the impact of allele burden has shown that patients homozygous for the *JAK2* mutation have a higher incidence of thrombosis in ET¹⁶. Therefore, it would be interesting to see if MPN patients with a higher allele burden are more prone to PHTN.

As briefly discussed above 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) to all other MPNs with PHTN, polycythemia patients are found to have a significantly higher frequency of splanchnic circulation thrombosis. Therefore, it is likely that thrombosis contributes to the etiology of PHTN in PV. This may also explain why almost half of the PV patients presented with PHTN prior to MPN diagnosis, compared to only 10% of patients with PMF (Table 1). Eight of the 9 PV patients that had PHTN diagnosed first, had a splanchnic circulation thrombosis on presentation which then lead to MPN diagnosis during thrombophilia workup. Therefore it is important that patients, who are diagnosed with splanchnic circulation thrombosis, should be screened for portal hypertension with further investigations.

In PMF patients where splanchnic circulation thrombosis is less frequent, splenomegaly or intrahepatic extramedullary hematopoiesis are the possible causes of PHTN. As seen in our study, gross splenomegaly was common in the majority of our myelofibrosis patients. However, unlike the case report by Lukie and Card, splenectomy did not reverse portal hypertension in any of our patients¹³. Therefore PHTN is likely due to a multitude of contributing factors rather than one single cause. We also found that PHTN was prevalent across all the DIPSS risk categories, although there is predilection towards higher risk categories. Splenomegaly and extramedullary hematopoiesis are not included in the DIPSS

risk stratification, and both can occur at any risk level. This may explain why PHTN was seen in both low risk and high risk myelofibrosis patients.

PHTN appears to be a major contributory cause of death in 29% of deaths in MF patients, and 40% of deaths in PV/ET patients. Currently, the same management options used in cirrhotic patients are applied to our MPN patients with PHTN. This includes surveillance endoscopy with variceal banding as needed, and TIPS. Medical therapies directed specifically at the MPNs did not reverse PHTN in any of our cases. The mainstay of treatment for the MPNs included hydroxyurea, as well as JAK inhibitors in MF patients. Reduction in grade-2 varices to grade-1 was noted in a case report on a patient treated in COMFORT-II trial¹⁷. Our patients did not have any meaningful change in grade of varices after treatment with JAK1/2 inhibitor. Possible reasons for lack of response of JAK inhibitor could be related to advanced stage of PHTN in our patients. It remains to be seen whether early detection of PHTN, and subsequent treatment with JAK inhibitor can reverse PHTN. This needs to be studied systematically in prospective studies.

CONCLUSION

We have demonstrated that among various MPNs, there is a preponderance for PHTN in patients with PV and PMF. In PV, splanchnic circulation thrombosis likely plays a role in PHTN development, whereas the etiology in PMF patients is probably related to splenomegaly, as well as other undetermined factors. Upper gastrointestinal endoscopy should be routinely performed in patients with MPN complicated by splanchnic circulation thrombosis to screen for varices and evidence of PHTN. Prospective studies are needed to understand whether it will be valuable to screen asymptomatic MPN patients for PHTN.

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CLINICAL PRACTICE POINTS

- PHTN is an understudied complication of MPNs affecting approximately 7-18% of patients and leading to variceal bleeding and ascites.
- In our review of 51 MPN patients that developed PHTN, the majority of them had an underlying polycythemia or myelofibrosis.
- Thrombosis within the splanchnic circulation was prominent in those with polycythemia and may possibly contribute to PHTN etiology.
- Patients with splanchnic circulation thrombosis should be screened for portal hypertension with further investigations.
- Prospective studies are required to determine if screening asymptomatic MPN patients for PHTN will improve outcomes.

Figure 1.

JAK2 (V617F) mutation incidence among polycythemia patients with PHTN compared to all other MPN patients with PHTN (96% vs 58%).

Figure 2. Splanchnic circulation thrombosis incidence among among polycythemia patients with PHTN compared to all other MPN patients with PHTN (76% vs 27%, $p = 0.0007$).

Table I

Characteristics of 51 MPN patients with PHTN.

DEMOGRAPHICS	MF	PV	ET
N, (%)	PMF: 18 (35) PPV-MF: 9 (18) PET-MF: 2 (4)	20 (39)	2 (4)
Male, n (%)	18 (62)	7 (35)	0 (0)
Median age of diagnosis of MPN, yrs (range)	65 (40 – 76)	50 (19 – 71)	-
Median age of diagnosis of PHTN, yrs (range)	67 (43 – 81)	49 (28 – 78)	-
JAK2 (V617F), n			
positive	18	15	1
negative	9	0	0
not available	2	5	1
PRESENTATION OF PHTN			
PHTN diagnosed prior to MPN, n (%)	3 (10)	9 (45)	1 (50)
Median time to PHTN if MPN precedes PHTN, mos	15 (0 – 324)	11 (0 – 184)	-
DIPSS score at PHTN diagnosis, n			
Low Risk	2	-	-
Intermediate-1	7	-	-
Intermediate-2	11	-	-
High Risk	8	-	-
Splanchnic thrombosis, n (%)	9 (31)	17(85)	2 (100)
Spleen Status, n			
Palpable spleen < 10cm	3	6	1
Palpable spleen ≥ 10cm	19	0	0
Splenectomy	2	2	0
Not palpable	2	5	0
Not recorded	3	7	1
Ascites, n (%)	19 (66)	9 (45)	1 (50)
Varices, n (%)	16 (55)	15 (75)	2 (100)
Detected in screening	8	12	1
Hematemesis	2	1	0
Melena	6	2	1
INTERVENTIONS & OUTCOMES			
Banding, n (%)	11 (38)	2 (10)	1 (50)
TIPS, n (%)	2 (7)	2 (10)	1 (50)
Splenectomy, n (%)	2 (7)	2 (10)	0
Medical Therapy, n			
Hydroxyurea	16	15	1

DEMOGRAPHICS	MF	PV	ET
JAK inhibitor	10	0	0
Other	10	4	1
Alive, n (%)	15 (52)	16 (80)	1 (50)
Three year survival (%)	54.1	82.6	-
Median follow up, mos	24	96	-
Cause of death, n			
Leukemic transformation	5	0	0
MPN Progression	3	0	0
PHTN	4	1	1
Other	2	3	0

MF = myelofibrosis, PV = polycythemia vera, ET = essential thrombocythemia, PPV-MF = post-polycythemia ruba vera myelofibrosis, PET-MF = post-essential thrombocythemia myelofibrosis MPN = myeloproliferative neoplasm, PHTN = portal hypertension, DIPSS = Dynamic International Prognostic Scoring System, TIPS = transjugular intrahepatic portosystemic shunt