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Portal vein thrombosis as the presenting manifestation of JAK2 positive myeloproliferative neoplasm

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Keywords: myeloproliferative neoplasms; JAK2; Philadelphia chromosome; deep vein thrombosis; polycythemia vera

Abstract

Deep venous thrombosis (DVT) is a complication of myeloproliferative neoplasms (MPNs). However, DVTs in unusual sites such as portal vein thrombosis (PVT) are rare and may be the first clinical manifestation of occult MPNs. There is a need for increasing awareness of such manifestations; so, here we discuss a patient who presented with new portal vein thrombosis, underwent further studies, was ultimately diagnosed with *JAK2* positive MPN, and started on appropriate treatment with improvement of thrombosis and controlled hematocrit.

Introduction

MPNs constitute a group of clonal hematologic malignancies that are Philadelphia chromosome-negative. According to the 2016 World Health Organization (WHO) criteria, polycythemia vera (PV), essential thrombocytosis (ET), and primary myelofibrosis (PMF) represent the primary types of MPNs, which usually manifest with constitutional symptoms such as night sweats and abdominal discomfort from splenomegaly and are frequently associated with lab abnormalities, including erythrocytosis, leukocytosis, or thrombocytosis.[1] Genetic studies have revealed the presence of specific mutations associated with MPNs, namely *JAK2*, *CALR*, and *MPL*, which lead to clonal hematopoiesis. Thrombosis is a well-known complication and rare thrombosis in unusual locations have been reported. Current modality of treatment including prevention and management of thrombosis. In this case report, we discuss a patient who presented with extensive portal vein thrombosis and was diagnosed with PV. We hope this presentation will help raise awareness about DVTs in unusual anatomic sites such as portal vein thrombosis as the presenting manifestation of *JAK2* positive MPNs.

Case Presentation

A 36-year-old gentleman with a history of traumatic lumbar burst fracture presented to our emergency room with worsening left upper quadrant abdominal pain for one month with associated nausea and postprandial pain. The patient denied personal or family history of hemophilia, bleeding disorders, recent trauma, cancer, smoking, or liver disease. Labs were remarkable for elevated liver function tests, white blood cell count 6.24 cells x 10^9/L, hemoglobin 13.5 g/dL, hematocrit (Hct) 40.4%, and platelet count 185 x 10^9/L. Computed tomography (CT) imaging of the patient's abdomen and pelvis showed portal vein thrombosis with extension into the splenic and superior mesenteric veins, evidence of portal hypertension, and marked splenomegaly (20 cm) [Figure 1]. The patient was subsequently admitted for anticoagulation with heparin drip and further workup. The patient's subsequent workup was negative for hereditary and acquired hypercoagulable workup, hepatitis panel, autoimmune, infectious, and metabolic processes. He was eventually discharged on Apixaban and follow up with Hematology outpatient clinic for follow up.

Upon the Hematology consultation and given the unusual site of the patient's DVT, lack of risk factors, and age of presentation, a JAK2 mutation on peripheral blood (PB) was ordered to rule out MPNs as the possible cause of his DVT. JAK2V617F mutation was detected in the patient's PB. Subsequent bone marrow aspiration and biopsy showed hypercellular marrow for age (80-90% cellularity) with active trilineage hematopoiesis and relative erythroid hyperplasia with left shift and increased megakaryocytes with clustering, most consistent with MPNs [Figure 2]. Further testing revealed the patient's bone marrow was positive for JAK2V617F (24%), and his

erythropoietin level (EPO) was the lower limit of normal range at 6.0 mIU/mL (normal values: 2.6 - 18.5 mIU/mL). As the patient could have PV, low dose Aspirin (81 mg) was added to his regimen. Repeat CBC showed Hct level of 47-48% and patient also started on therapeutic phlebotomy to keep Hct levels < 45%. There was a discussion about initiating ropeginterferon alfa-нō ǈŜyŘƛy∃ űKŜ ǈl·űƛŜyűΩă ŘŜŎƛăƛƻy⌽ ¢KŜ ǈl·űƛŜyű Kl·Ř ƛΥǈǋƻØŜΥŜyű ƛyǈƻăűǈǋl·yŘƛl·f ŘƛăŎƻΥŦƻǊű and abdominal pain with compliance to continued anticoagulation and therapeutic phlebotomy.

Discussion

There is a strong association between MPNs and acute thrombosis.[9] In 1979, Myers et al. reported thrombosis leading to 30-50% of mortality in the setting of PV.[2] Furthermore, according to a meta-analysis by Jasper et al., which included 855 patients, MPNs were the most common cause of Budd-Chiari syndrome and portal vein thrombosis unrelated to cirrhosis or malignancy.[3] That said, the prevalence of acute thrombosis in MPNs does vary among studies [Table 1]. According to a systematic review and meta-analysis of 13,436 patients with newly diagnosed MPNs, the pooled prevalence of venous thrombosis at the time of diagnosis of MPNs was 6.2% compared to 16.2% of arterial thrombosis. In addition, the pooled prevalence of splanchnic vein thrombosis, which included portal vein thrombosis, among the venous thrombosis at the time of MPNs diagnosis was only 1.4%.[4] Interestingly, though, there have been observations of splanchnic vein thrombosis in younger patients with MPNs.[5] Moreover, some studies show there are instances of thrombosis before a formal diagnosis of MPNs. For example, in a multicenter retrospective study from Europe in 2015 involving 612 patients from four centers in Sweden, Denmark, and France with a diagnosis of MPNs, 66% of the patients were found to have a history of vascular complications before a diagnosis of MPNs, and 7 of them had a history of splanchnic vein thrombosis. Some even had abnormal blood levels, which fulfilled the diagnostic criteria of MPNs.[6]

The pathophysiology of MPNs involves overproduction of hematopoietic cells in the bone marrow and extramedullary hematopoiesis. Studies have revealed the development of "driver

mutations," namely *JAK2*, *CALR*, and *MPL*, which lead to clonal proliferation in Philadelphia negative MPNs.[7] Each of these mutations primarily occur in specific types of MPNs. Around 92% of patients with PV are *JAK2V617F* positive, whereas 55% of patients with ET and 50% of patients with PMF have *JAK2V617F* mutations, respectively.[8] For example, the *JAK2V617F* mutation can cause constitutive activation of receptors for erythropoietin, thrombopoietin, and granulocyte colony-stimulating factor, leading to elevated cell counts and coagulopathy. Studies have shown that *JAK2* mutation is related to both arterial and venous thrombosis through a variety of mechanisms.[9] Mechanisms include increased proliferation of all hematological cell lines, promotion of thrombogenic changes in the endothelial cell surface, which lead to adhesive interactions among red cell aggregates and platelet-leukocyte aggregates, and increased viscosity of blood, as shown by increased Hct levels.[9, 10]

Likewise, other mutations are associated with MPNs and lead to prothrombotic features of MPNs. Mutations in *CALR*, a chaperone protein involved in calcium homeostasis and protein folding, have also been associated with MPNs and higher platelet levels in patients with MPN. Finally, mutations in *MPL*, a cell surface receptor for thrombopoietin, have also been seen with increased platelet production in certain patients with MPNs.[7] Recent studies have shown that the *MPL* mutation, and the aberrant *MPL*-thrombopoietin axis could serve as a target point for therapy against certain types of MPNs due to the prothrombotic interaction between platelets.[11]

When MPNs are suspected, the gold standard for diagnostic evaluation is bone marrow aspiration and biopsy, karyotype testing, and mutational analysis.[12] The ability to screen patients for the presence of the *JAK2*, *CALR*, or MPL mutations in serum has significantly streamlined the diagnostic workup of patients suspected to have MPNs.[2] With this in mind, the current algorithm for diagnosis of MPNs starts with screening patients for *JAK2* mutation and erythropoietin level (EPO) in the serum. If the *JAK2* mutation study is negative, further evaluation for other mutations is warranted, as mentioned above.[13]

Treatment algorithms for splanchnic vein thrombosis, including portal vein thrombosis in MPNs, are primarily based on the type of MPNs as categorized by the 2016 WHO criteria. Various treatment options exist, including phlebotomy and cytoreduction with hydroxyurea and pegylated interferons, including ropeginterferon alfa-2b and peginterferon alfa-2A. In addition, other cytoreductive therapies are available for refractory cases.[5] However, bone marrow transplant remains as the only treatment for cure of MPNs.[8] For patients with MPNs presenting with splenomegaly, splenectomy is not routinely performed because there are effective JAK2 inhibitors which can shrink the size of the spleen. Performing splenectomy in patients with MPNs is not easy and the procedure may get complicated due to formation of adhesions around the enlarged spleen. These patients are treated medically with cytoreductive therapy or antiplatelet/ anticoagulation therapy.[14] Nevertheless, despite being appropriately treated, MPNs can unfortunately progress, manifesting in the form of new or worsening thromboembolic events, bleeding, and constitutional symptoms, or worsening splenomegaly.

Of note, scoring systems for prognosis including such the international prognostic score for ET (IPSET), mutation-enhanced international prognostic scoring system (MIPSS) for PV, and MIPSS70 for PMF.[15] In addition, PV and ET can progress to secondary myelofibrosis and all MPN types have the possibility of transformation to myelodysplastic syndrome (MDS) and secondary acute myeloid leukemia (sAML).[7,8]

Conclusions

The close association and prevalence of DVTs with MPNs are well-documented findings in the literature. However, the specific prevalence of splanchnic vein thrombosis, such as portal vein thrombosis, is low among the types of DVTs. Portal vein thrombosis as the initial presentation of *JAK2* mutation-positive MPN is rare. As such, younger patients without apparent risk factors who present with DVTs in unusual location, specifically portal vein thrombosis, should be tested for *JAK2* mutation with further workup, including evaluation of other risk factors. There is a need for further search for serum tests and genetic mutations like *JAK2*, which can assist in screening patients for MPNs and targeted therapy based on findings of genetic mutations in patients with MPNs. Furthermore, developing risk stratification tools or a standardized scoring system to prompt screening for MPNs in patients with portal vein thrombosis or other unusual DVTs may be beneficial.

Author Contributions

WJJ contributed to the conception of the work and drafted the work. AM and AN substantially revised the work. JH and JW contributed to the acquisition of data. DRC contributed to the conception of the paper and substantially revised the work. MA contributed to the conception of the work and substantially revised the work.

Conflicts of interest

All authors do not declare any conflict of interest. In addition, all the authors are aware of and approve the manuscript as submitted to this journal.

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Figure Legend

Figure 1: Extensive portal vein thrombosis shown by arrow on coronal view of the CT scan with contrast on initial diagnosis.

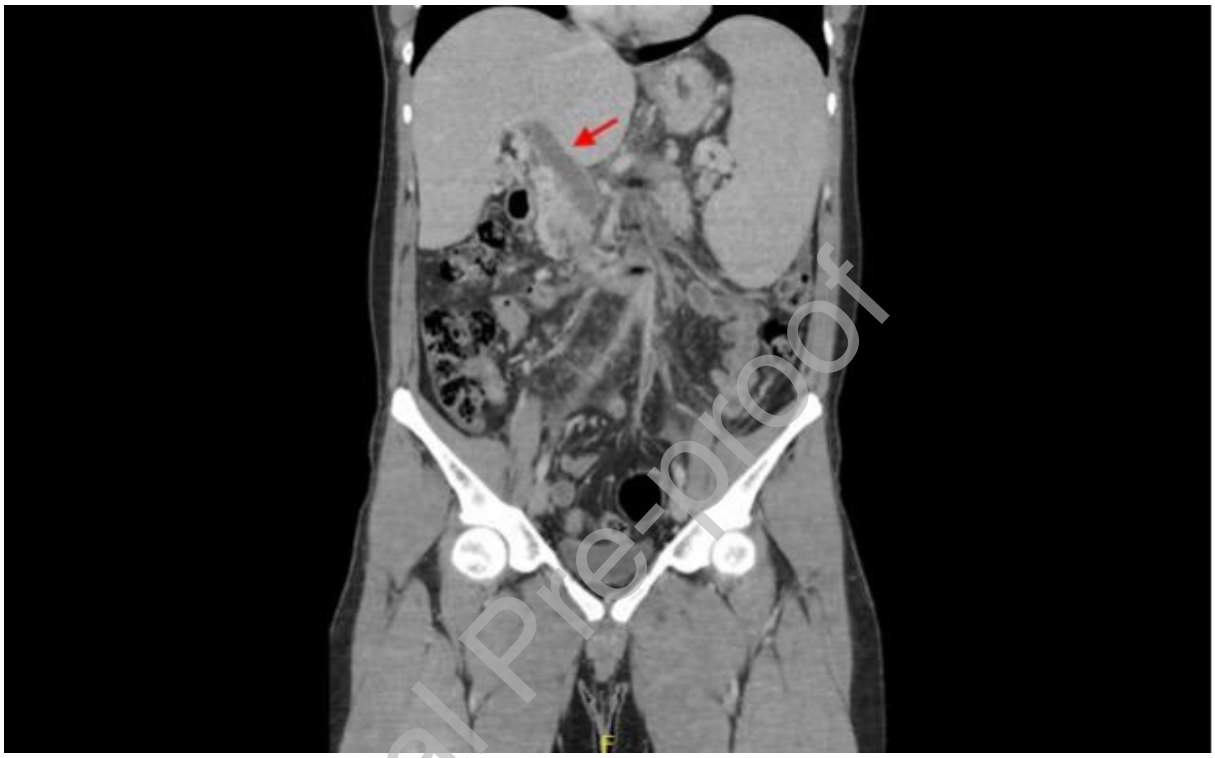

Figure 2: (A) Bone marrow aspirate (10x) showing increased megakaryocytes, (B) bone marrow core biopsy (40x) showing increased red blood cells and megakaryocytes, (C) bone marrow core biopsy with periodic acid-Schiff (PAS) stain (20x) highlighting increased megakaryocytes present in loose clusters, and (D) bone marrow aspirate showing erythroid hyperplasia.

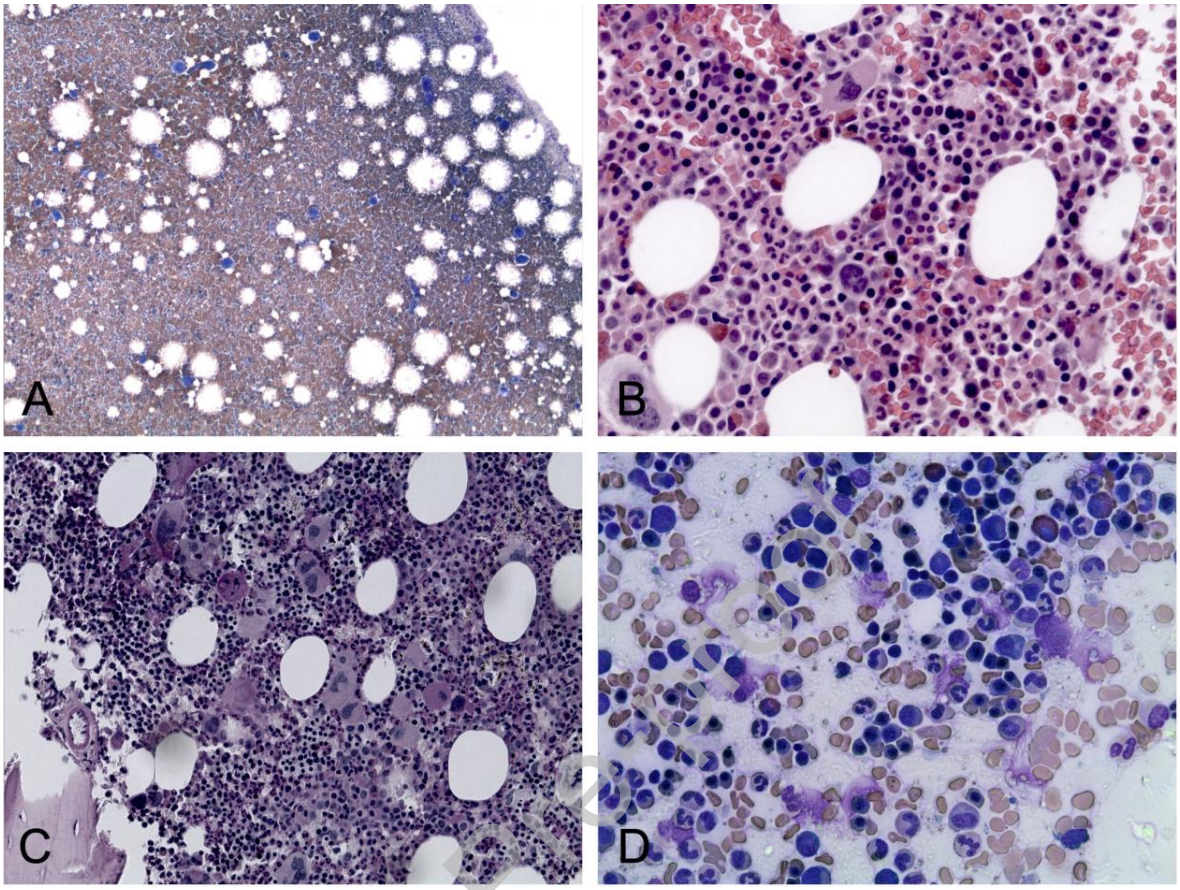

Table 1: Incidence of Portal Vein Thrombosis/ Splanchnic Thrombosis in MPNs.

Study	Type of MPN	Total Number of Patients	Number of portal/ splanchnic/ abdominal DVTs	Percentage (%)	DVT Description
Chim et al[15]	ET	231	1	0.43	Portal vein thrombosis

Barbui et al[16]	PMF	707	2	0.28	Portal vein thrombosis
Elliot et al[17]	PMF	205	10	4.88	Abdominal vein thrombosis
Enblom et al[6]	ET	272	1	0.37	Portal vein thrombosis
Enblom et al[6]	PV	249	3	1.20	Splanchnic vein thrombosis
Enblom et al[6]	MF	91	1	1.11	Portal vein thrombosis
Duangnapasatit et al[18]	ET	83	2	2.41	Portal vein thrombosis
Kaifie et al[19]	PV	54	3	5.55	Splanchnic vein thrombosis
Kaifie et al [19]	ET	33	6	18.2	Splanchnic vein

					thrombosis
Kaifie et al[19]	PMF	34	6	17.6	Splanchnic vein thrombosis
Hoekstra et al[20]	PV	400	34	8.50	Abdominal vein thrombosis
Hoekstra et al[20]	ET	441	20	4.53	Abdominal vein thrombosis

Abbreviations: Myeloproliferative neoplasm (MPN), deep vein thrombosis (DVT), ET (essential thrombocythemia), PV (polycythemia vera), PMF (primary myelofibrosis).

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