Budd-Chiari Syndrome as Initial Manifestation of Polycythemia Vera: Complexities in the Management of Younger Patients

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Authors' disclosures of conflicts of interest are found at the end of this article.

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Abstract

Advanced practitioners (APs) play an integral role in early identification, diagnosis, and treatment of patients with polycythemia vera (PV). This Grand Rounds article highlights the case of a younger patient who presented with a spontaneous splanchnic vein thrombus without obvious cause. The most recent updates to the World Health Organization diagnostic criteria for PV increase the likelihood of identifying masked PV; however, there are some scenarios where the hemoglobin and hematocrit criteria will not be met. Developing individualized treatment plans based on comorbidities, socioeconomic factors, compliance, tolerance, menstrual status, and future childbearing desires allows the advanced practitioner to provide the best care for patients with PV.

CASE STUDY

Ms. G, a 27-year-old woman with a history of depression and a recent cholecystectomy, presented to the emergency department (ED) with complaints of increasing abdominal pain, nausea, and abdominal fullness with distension. Her symptoms began about 1 week prior and had progressively worsened; that morning, she also began experiencing shortness of breath. She described her abdominal pain as 8 out of 10, not relieved by acetaminophen. She had never experienced this type of pain before and was quite worried.

On physical exam, Ms. G was afebrile (temperature 97.9°F), heart rate 115 bpm, blood pressure 130/86 mmHg, oxygen saturation 98% on room air. The advanced practitioner in the ED could tell Ms. G was in pain because she was hunched over in the hospital bed. Pertinent positive physical exam findings included tachycardia and a distended, tympanitic abdomen with (+) fluid wave and diffuse abdominal tenderness. Notably,

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the abdomen was most tender in the epigastric region; however, she had no pain with percussion, no referred pain to palpation of the abdomen, and no rebound pain. Significant hepatomegaly was noted as well.

CT of the abdomen and pelvis with contrast revealed evidence of a large amount of ascites and hepatosplenomegaly along with a large mass-like lesion in the lesser sac. In a liver ultrasound, no flow was demonstrated within the hepatic veins, portal veins, or the inferior vena cava. A liver biopsy with pressure measurements by interventional radiology revealed a chronically occluded right hepatic vein, with a collateral pattern suggestive of Budd-Chiari syndrome (Figure 1).

A transjugular liver biopsy was performed, and 6 liters of ascites were removed via paracentesis. Peritoneal fluid was not sent for pathology or cytology, as the fluid collection was a presumed consequence of the thrombosis. A hepatic venogram demonstrated an obstructive pattern; the lumen was completely obliterated, with multiple spiderweb collaterals that are typical of a chronic Budd-Chiari pattern. Of note, splenomegaly was observed 2 years prior, and Ms. G had a history of elevated white blood cell count (WBC) and platelet count for more than 5 years. However, no interventions had been taken.

Ms. G was transferred to an academic institution for further care. MRI scans of the abdomen with and without contrast showed a heterogeneous, "nutmeg" pattern of hepatic enhancement with hepatic vein occlusion, markedly narrowed intrahepatic inferior vena cava, and massive caudate lobe enlargement. Occlusion of the right portal vein and moderate ascites were also noted. Ms. G was diagnosed with Budd-Chiari syndrome of unknown etiology and admitted to the hospital for pain control, anticoagulation, and further workup.

Polycythemia vera (PV) is a rare clonal BCR-ABL–negative myeloproliferative neoplasm (MPN) that is characterized by hyperproliferation of all three hematologic cell lines. This overactive cellular production results in erythrocytosis and, in approximately 40% of patients, some degree of thrombocytosis and leukocytosis (Maffioli, Mora, & Passamonti, 2017; Tefferi & Barbui, 2019). Janus kinase 2 (*JAK2*) mutations, which result in JAK-STAT pathway activation, are present in almost all patients with PV; 96% of patients display somatic activating mutations in exon 14 (*JAK2* V617F), and 3% of patients have exon 12 mutations of *JAK2* (Pardanani, Lasho, Finke, & Hanson, 2007; Vannucchi, Antonioli, Guglielmelli, Pardanani & Tefferi, 2008).

There are an estimated 148,000 patients with PV in the United States (Mehta, Wang, Iqbal, & Mesa, 2014; National Comprehensive Cancer Network, 2020). Although PV occurs most often in patients over 60, between 4% and 7% of patients with the disease are younger than 40 (Perea et al., 2001). Younger patients without predisposing conditions can present with unique signs and symptoms including myocardial infarction, stroke, or—as in Ms. G's case—splanchnic vein thrombosis (Vannucchi et al., 2015). Some patients are asymptomatic and are diagnosed following abnormalities identified in routine laboratory testing, while others may present with hypertension refractory to multiple medications.

Budd-Chiari syndrome, a type of splanchnic vein thrombosis, is an uncommon disorder characterized by obstruction of hepatic venous outflow. A hypercoagulable state is identified as the

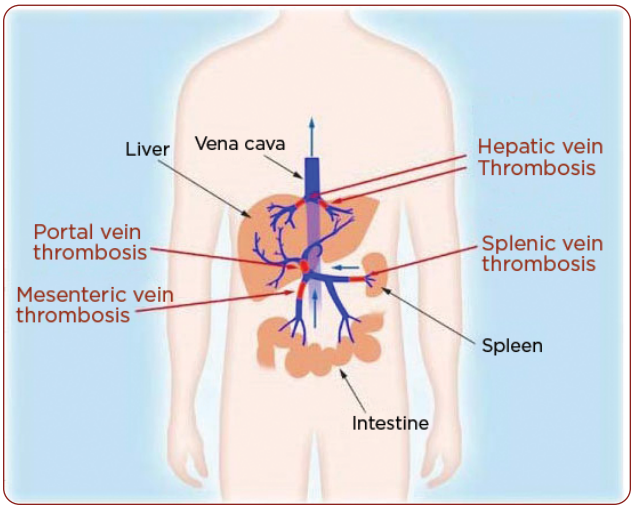

Figure 1. Budd-Chiari syndrome.

cause in 75% of patients with the disorder (Aydinli & Bayraktar, 2007). In fact, MPNs have emerged as a leading systemic cause of splanchnic vein thrombosis in the past several years (De Stefano, Qi, Betti, & Rossi, 2016). There is a strong association between splanchnic vein thrombosis and the *JAK2* mutation, and it often occurs in younger women (Stein, Rademaker, Spivak, & Moliterno, 2011).

BACK TO MS. G'S CASE

Ms. G had a history of depression and anxiety, was a non-smoker, and drank one to two glasses of wine per week. At the time of presentation to the emergency department, she was also 4 months postpartum—with a delivery complicated by postpartum hemorrhage—and 3 weeks status post cholecystectomy. Ms. G's menstrual periods had resumed, and she reported heavy bleeding with her cycles—both postpartum and "for many years" prior to pregnancy. Her family history included a father with smoking history and prior myocardial infarction and a mother with type 2 diabetes. Her current medications were sertraline and a prenatal vitamin, and she denied recent oral contraceptive use. Her complete blood count (CBC) revealed a slightly elevated white blood cell (WBC) count (11.2×10^9/L [$3.5–10.5 \times 10^9$/L]), hemoglobin on the upper end of normal (14.9 g/dL [11.6–15.4 g/dL]), slightly elevated hematocrit (45.5% [34%–45%]), and thrombocytosis (platelet count, 469×10^9/L [$140–390 \times 10^9$/L]). A chemistry panel was performed, including serum creatinine (0.9 mg/dL [0.7–1.3 g/dL]), alanine aminotransferase (99 IU/L [7–52 U/L]), aspartate aminotransferase (74 IU/L [12–39 IU/L]), total bilirubin (1.3 mg/dL [0.1–1.3 mg/dL]) and ferritin (21 ng/mL [normal range, 11–307 ng/mL]; Dean, 2005) .

The CBC abnormalities and unusual thrombosis prompted a hematology consult for workup of an underlying thrombophilia. A *JAK2* mutation analysis on a peripheral blood sample was ordered and returned positive for *JAK2V617F* mutation. A serum erythropoietin level was drawn and was subnormal at 7 IU/L (3.7–36 IU/L). Following a bone marrow biopsy, which showed hypercellular (80% cellular) bone marrow with increased trilineage hematopoiesis and slightly increased numbers of megakaryocytes, Ms. G was diagnosed with polycythemia vera.

THROMBOSIS IN PV

A PV diagnosis carries an inherent risk of thrombosis and thrombosis-related cardiac events. Thromboembolic events have a substantial impact on the clinical course of patients with PV (Griesshammer et al., 2019). Arterial and venous complications are a major cause of morbidity and mortality; arterial thromboses alone comprise 60% to 70% of all cardiovascular events in patients with PV and include transient ischemic attack, stroke, acute myocardial infarction, and peripheral arterial occlusion (Griesshammer et al., 2019). In all, thrombotic events account for 40% of deaths in patients with MPNs (Barbui et al., 2018).

The pathogenesis of thrombosis in PV is complex. Abnormalities of blood cells involve both quantitative changes and qualitative modifications resulting in a procoagulant phenotype. Elevated hematocrit resulting from excessive erythrocytosis can increase blood viscosity, reduce blood return through the venous system, and increase platelet adhesion (Brækkan et al., 2010; Gori, 2011; McMullin, 2009). These factors can promote blood clot formation (Lowe et al., 1993) and increased platelet activation at the vessel wall (Gori, 2011). Leukocytosis has also been identified as a risk factor for thrombosis (Landolfi et al., 2007). C-reactive protein is often elevated in patients with PV and may be associated with increased risk of thromboembolism (Barbui et al., 2011; Quist-Paulsen et al., 2010).

It is also suspected that the presence of the *JAK2V617F* mutation in patients with MPNs increases the risk of thrombotic complications (Martin, 2017). A prospective study found that those with a high *JAK2* V617F allele burden (> 75%) had a 3.56-fold higher relative risk of total thrombosis vs. a reference population (Vannucchi et al., 2007). This mutation in the red cell compartment may induce the expression of abnormal proinflammatory phenotypes, further increasing the risk of thrombosis (Brusson et al., 2018; Guadall et al., 2018).

DIAGNOSIS

A diagnosis of PV is made on the basis of criteria established in the 2016 revision of the World Health Organization classification of lymphoid neoplasms (Barbui et al., 2018.; Swerdlow et al., 2016); see Table 1 for WHO criteria. Ms. G meets the second two major criteria and the minor criterion: hypercellu-

lar bone marrow with trilineage hyperproliferation, a positive *JAK2* mutation, and a subnormal erythropoietin level. Her long-standing history of and current menorrhagia is likely the reason the hemoglobin and hematocrit levels do not meet the defined diagnostic criteria. Her low-normal ferritin levels and recent postpartum hemorrhage and surgery likely also contributed. This phenomenon is called "masked" PV. If a woman with menorrhagia were to have an IUD placed or became post-menopausal, the typical PV phenotype would likely reveal itself.

This is an important concept to consider when taking care of young women with MPNs. The CBC in these patients may appear to be more consistent with essential thrombocythemia; however, the presence of leukocytosis should spark the advanced practitioner's curiosity because elevated WBC is not typically seen with essential thrombocythemia. Rather, essential thrombocythemia is an MPN characterized by thrombocytosis that is not reactive to an underlying process such as iron deficiency, infection, or post-surgical inflammation.

MANAGEMENT

The main treatment goal for PV is reducing thromboembolic and hemorrhagic risk. Managing disease-related symptoms and minimizing the risk of fibrotic or leukemic transformation are other important goals of therapy (Barbui et al., 2011; Tefferi & Barbui, 2019). Patients with a low risk of thrombosis can be managed with phlebotomy to maintain hematocrit under 45% plus once- or twice-daily low-dose aspirin (Tefferi & Barbui, 2019; see Table 2), unless specific contraindications to low-dose aspirin exist, such as extreme thrombocytosis (platelet count > $1{,}000 \times 10^9$/L) or active major bleeding (Michiels et al., 2006).

Ms. G is classified as high risk due to her history of splanchnic vein thrombosis, which requires the initiation of cytoreductive therapy to reduce risk of another thromboembolic event. While the most popular and evidence-supported cytoreductive agent is first-line agent hydroxyurea (Tefferi et al., 2018), pegylated interferon-α and ruxolitinib are alternatives that the AP must take into consideration for those who are refractory to or intolerant of hydroxyurea. Pegylated interferon-α is often considered for treatment in younger patients because it is a non-chemotherapy option. However, because pegylated interferon-α can exacerbate underlying psychiatric illness, it was not an option due to Ms. G's history of depression (Genentech, 2017). Busulfan is a third-line agent, but based on its teratogenic effects (Otsuka America Pharmaceutical, Inc., 2015), it is not recommended for a woman of childbearing age. The hematology team chose to initiate therapy for Ms. G with hydroxyurea at 500 mg twice daily. Starting this treatment will require upfront frequent laboratory monitoring and possible dose titration based on CBC response and possible side effects (both hematologic and nonhematologic).

Table 1. World Health Organization Diagnostic Criteria for Polycythemia Vera[a]

Major criteria

- Hemoglobin > 16.5 g/dL (men), > 16.0 g/dL (women) OR
- Hematocrit > 49% (men), > 48% (women) OR increased red cell mass
- Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
- Presence of *JAK2*V617F or *JAK2* exon 12 mutation

Minor criterion

- Subnormal serum erythropoietin level

Note. Adapted from Arber et al. (2016).
[a]PV diagnosis requires meeting either all 3 major criteria or the first 2 major criteria and the 1 minor criterion.

ANTICOAGULATION

In addition to cytoreductive therapy, anticoagulation should be started in patients who have had a thrombotic event. A retrospective analysis revealed that after a first venous thromboembolic event, long-term anticoagulation was associated with a 63% reduction in risk of recurrence without a significant increase in major bleeding (Barbui et al., 2013). Another study found that patients treated with oral anticoagulants plus cytoreduction had

Table 2. Thrombosis Risk Stratification in Polycythemia Vera

Risk level	Criteria
High risk	Age > 60 years or history of thrombosis
Low risk	Age < 60 years and no history of thrombosis

the lowest rate of recurrence compared with those treated with cytoreduction, antiplatelet agents, or anticoagulation alone (De Stefano et al., 2008).

Warfarin plus bridge therapy with low-molecular-weight heparin or direct oral anticoagulants (DOACs) can be considered depending on patient characteristics. Warfarin is a more cost-efficient option but requires patient compliance with routine monitoring to maintain therapeutic levels. Warfarin monitoring can be a significant burden on patients, especially when initiating therapy and in patients with labile INRs. Direct oral anticoagulants do not necessitate specialized long-term monitoring but are not recommended in patients with moderate to severe hepatic or renal impairment. Additionally, there have been reports of increased abnormal uterine bleeding with rivaroxaban and apixaban vs. other anticoagulants—a pertinent consideration for this young female patient (Boonyawat et al., 2017). Insurance coverage of DOACs should also be weighed.

Warfarin plus low-molecular-weight heparin bridge was identified as the therapeutic option with the lowest risk of complications due to Ms. G's hepatic impairment and ongoing menorrhagia. IUD placement and subsequent use of a DOAC could be considered in the future if hepatic function improves. However, due to improved menorrhagia with an IUD, this approach may result in a worsening erythrocytosis and subsequent increased phlebotomy needs or change in hydroxyurea dosing, exemplifying the delicate balance necessary in the treatment of younger patients with PV.

DISCUSSION

Advanced practitioners play a key role in identification, diagnosis, and treatment of patients with PV. Ms. G presented with a spontaneous splanchnic vein thrombus without obvious cause. An underlying MPN should be considered in the setting of thrombosis in an unusual location, particularly in younger patients without risk factors for thrombosis. Evaluation for PV should occur in young, otherwise healthy patients presenting with an idiopathic thrombotic event in the setting of CBC abnormalities.

Although patients may not express the full PV phenotype at first presentation, APs should be able to recognize masked PV, especially in young women. The most recent updates to the WHO diagnostic criteria for PV increase the likelihood of identifying masked PV; however, there are some scenarios where hemoglobin and hematocrit criteria will not be met. Developing individualized treatment plans based on comorbidities, socioeconomic/insurance factors, compliance, tolerance, menstrual status, and future childbearing desires allows the AP to provide the best care for patients with PV. ●

Disclosure

Ms. Lyle has served on advisory boards for AbbVie, Agios, Bristol Myers Squibb, Celgene, and Incyte. Ms. Kalhagen has served on the speakers bureau for Incyte.

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