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Case Report

Spontaneous splenic rupture in polycythemia vera

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ABSTRACT

Atraumatic spontaneous splenic rupture is rare and occurs in the setting of spleen pathology from a myriad of causes, including myeloproliferative disorders. Only four previously reported cases of atraumatic spontaneous splenic rupture associated with polycythemia vera exist. We report the fifth case, which also is the first with severe thrombocytosis requiring multiple plateletpheresis despite medical therapy and excellent long-term control. In addition to reporting the fifth case of spontaneous splenic rupture in a polycythemia vera patient, we also review the risks associated with splenectomy in patients with polycythemia vera and therapies that can prevent spontaneous splenic rupture.

Introduction

Polycythemia vera (PV), a myeloproliferative disorder, is characterized by elevated hemoglobin or hematocrit, myeloid hypercellularity, presence of *JAK2* mutation, and low erythropoietin levels. Seventy-five to ninety percent of patients have the triad of splenomegaly, polycythemia, and ruddy cyanosis. While splenomegaly is common and causes high symptom burden, the spleen is rarely removed due to associated complications post-operatively such as platelet dysfunction and thrombocytosis.

We present (1) a rare case of a patient with PV and splenomegaly who developed atraumatic spontaneous splenic rupture requiring removal and complicated by severe thrombocytosis, (2) a review of atraumatic spontaneous splenic rupture occurring in the setting of PV and associated post-splenectomy complications, and (3) therapies directed at preventing this morbidity.

Case Report

A 69-year-old Caucasian presented at the emergency room with a two-hour history of sharp, left upper quadrant abdominal pain precipitated by bending over while working in the yard. Medical history was significant for polycythemia diagnosed twenty years earlier *(JAK2* V617F positive with elevated hemoglobin and hematocrit, splenomegaly, and subnormal erythropoietin; bone marrow procedure declined). He was offered hydroxyurea on initial visit and at subsequent encounters with

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Hematology and Medical Oncology when he developed thrombocytosis in 2016, but refused due to side effects, and instead accepted a regimen of aspirin (adding anagrelide after developing thrombocytosis) plus therapeutic phlebotomies every 3 months to keep his platelets and hematocrit below 450,000 and 45%, respectively. His splenomegaly progressed to 24 cm in 2017 sonography and was never symptomatic until presentation.

On presentation, our patient appeared uncomfortable and had tachycardia and tachypnea. Abdominal auscultation revealed a nondistended abdomen with slightly diminished bowel sounds. Palpation found diffuse tenderness pronounced in the epigastric and left upper quadrant regions without peritoneal signs, and splenomegaly 9 cm below the costal margin.

Abnormal results of biochemical and hematologic investigations included total bilirubin, 2.2 mg/dL (reference range, 0.3-1.2 mg/dL); white blood cell, 17.4 K/μL (reference range, 3.5-11.0 K/μL); neutrophil count, 15.12 K/μL (reference range, 1.60-8.30 K/μL); mean corpuscular volume, 65.7 (reference range, 78.0-98.0 fL); and platelets, 669 K/μL (reference range, 150-400 K/μL). Hemoglobin and hematocrit were within normal limits, 14.3 g/dL (reference range, 13.9-16.8 g/dL) and 50.3% (reference range, 41.0-51.0%), respectively.

Computed tomography of the abdomen and pelvis with contrast enhancement demonstrated an enlarged spleen (20 cm X 22 cm) surrounded by fluid with a hypodense focus suggesting rupture (Figure 1. CT abdomen/pelvis with contrast).

Surgery was consulted for spontaneous splenic rupture and patient underwent exploratory laparotomy with splenectomy. Post-operative findings were notable for massive splenomegaly with a laceration in the central lateral aspect and subscapular hematoma.

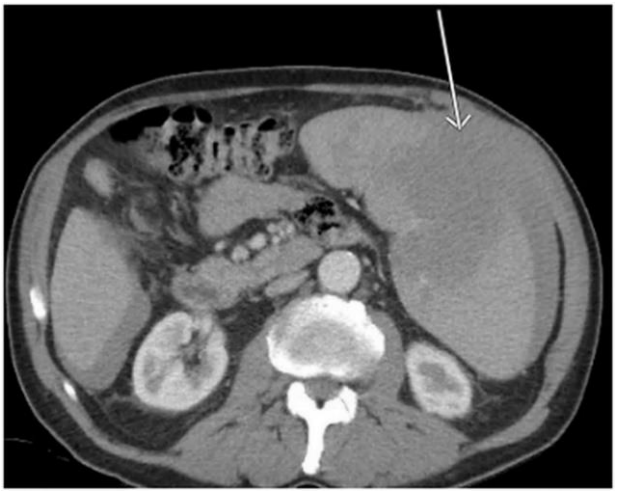

Figure 1: CT abdomen/pelvis with contrast. Enlarged spleen surrounded by fluid without venous thrombosis

Post-operative course was complicated by mucocutaneous candidiasis, iron deficiency anemia requiring iron infusion, paroxysmal atrial fibrillation managed with beta-blockers, and severe thrombocytosis not responsive to hydroxyurea recommended by in-house Hematology and Medical Oncology. He was transferred to a tertiary center for plateletpheresis to manage his thrombocytosis after platelets reached 3200 K/μL.

The patient has been admitted two additional times for repeat plateletpheresis for platelets above 1000 K/μL despite dose-escalated anagrelide and hydroxyurea (Table 1).

Table 1: Case timeline

Date	Presenting symptoms	Work-up (findings)	Treatment	Outcomes
1997	Abnormal hemoglobin (>18.5 g/dL) on blood tests	Splenomegaly, *JAK2* V617F mutation, subnormal erythropoietin (Polycythemia vera)	Aspirin and therapeutic phlebotomies every 3 months for hematocrit (Hct) < 45%, declines hydroxyurea (HC) or interferon	Hct stable, no constitutional symptoms
12/2013	N/A (Hematology follow-up)	Abdominal ultrasound (spleen 20 cm and hepatomegaly)	N/A (no changes from prior, declines HC)	Hct stable, no constitutional symptoms
01/2016	N/A (Hematology follow-up)	Thrombocytosis	Adds anagrelide for platelets < 450 K/μL, declines HC	Hct and platelets stable, no constitutional symptoms
02/2017	N/A (Hematology follow-up)	Abdominal ultrasound (spleen 24 cm X 9.8 cm)	N/A (no changes from prior, declines HC)	Hct and platelets stable, no constitutional symptoms
06/2017	Sudden-onset left upper quadrant pain, splenomegaly, and hematologic abnormalities	CT of abdomen/ pelvis (enlarged spleen with hypodense focus suggesting rupture)	Admission to hospital for exploratory laparotomy with splenectomy and management of complications (iron deficiency anemia, mucocutaneous	Initial symptoms resolve, Cardiologist added beta-blockers for arrhythrmia, Hematologist adds HC with iron infusion for thrombocytosis

			candidiasis, paroxysmal atrial fibrillation, and thrombocytosis)	
07/2017 (post-operative day 7)	Worsening thrombocytosis despite HC and iron infusions	Platelets 3200 K/μL	Transfer to tertiary center for plasmapheresis	Thrombocytosis resolves, discharged on HC and anagrelide
08/2017 – 10/2017	N/A (Hematology follow-up)	Thrombocytosis >1000 K/μL	Transfer to tertiary center twice for repeat plasmapheresis	Thrombocytosis resolves discharged on increased doses of HC and anagrelide

Table 2: Criteria for diagnosis of polycythemia vera (World Health Organization): all 3 major criteria or first 2 major criteria and the minor criterion

Major	Hemoglobin >16.5 g/dL (men), >16.0 g/dL (women) OR Hematocrit >49% (men), >48% (women) OR increased red cell mass (RCM) >25% mean predicted value
	Bone marrow biopsy demonstrating hypercellularity for age with trilineage (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	Subnormal serum erythropoetin level

The most common mutation is *JAK2* V617F and it results in clonal erythroid, granulocytic, and megakaryotic expansion.

Discussion

Polycythemia vera (PV) is a myeloproliferative disorder of erythrocytes producing elevated hemoglobin and hematocrit [1]. Patients have the triad of splenomegaly, polycythemia, and ruddy cyanosis [1]. WHO diagnostic criteria are listed below (table 2) and requires the presence of either all three major criteria or the first two major criteria and the minor criterion [2].

Treatment is dependent on disease and patient characteristics. Patients at low risk (younger than 60 years, no history of venous thromboembolism, minimal constitutional symptom burden, and the absence of leukocytosis, thrombocytosis or massive splenomegaly) need therapeutic phlebotomies to maintain hematocrit below 45% and 42% in men and women, respectively, while patients at high risk should begin cytoreductive therapy [3]. Hydroxyurea (hydroxycarbamide, HC) is most commonly used and demonstrates superior outcomes in reducing thrombotic events when compared to phlebotomy but should be used with caution in young patient due to teratogenicity and potential risk of skin cancers [4]. Other side effects – fatigue, hair thinning, and mucocutaneous ulceration – may not be tolerated well. Interferon (IFN) is preferred for individuals younger than 60 years and premenopausal women [5]. It induces hematological remission with morphological and molecular responses, but its use is limited due to side effects (flu-like symptoms, mood disturbances, deranged liver function tests, and thyroid dysfunction) [5]. Patients who fail HC and/or IFN could be treated with ruxolitinib (JAK1/2 inhibitor) [6]. It is FDA approved in the treatment of PV and leads to cessation in phlebotomy for almost all of the patients and at least 50% reduction in spleen size in over 70% of patients [6]. The most common adverse events are cytopenias, diarrhea, infections, and nonmelanoma skin cancers. Aspirin may be utilized as an adjunct to therapy; however, caution should be taken to first reduce platelet counts as once thrombocytosis nears one million, secondary von Willebrand deficiency can result in increased risk of bleeding [3]. Complications of PV include thrombotic events and evolution into myelofibrosis or acute leukemia [1].

Atraumatic spontaneous splenic rupture occurs in the setting of abnormal spleen pathology. Causes include congenital hemolytic anemias, infections (mononucleosis, malaria, endocarditis); infiltrative disorders (amyloidosis, Gaucher's disease); lymphoproliferative disorders; medications (anticoagulants, granulocyte colony-stimulating factor, thrombolytics); myeloproliferative disorders; nonhematologic malignancies; pancreatitis; and portal hypertension [7]. Symptoms are left upper quadrant pain, guarding, hemodynamic instability, and left shoulder pain from diaphragmatic irritation. Confirm with CT or sonographic imaging. Treatment depends on the clinical scenario: patients who are hemodynamically stable without significant blood loss can be managed conservatively while those with hemodynamic instability or significant blood loss need urgent surgical assessment for splenectomy [8].

Splenic rupture is a rare complication of PV. To date, there are only four cases in world literature of atraumatic spontaneous splenic rupture associated with PV, only one of which has been since the revised diagnostic criteria for polycythemia vera (elevated hemoglobin, *JAK2* V617F mutation, and subnormal serum erythropoietin). All cases presented with splenomegaly and hemodynamic instability and required an exploratory laparotomy at which time a splenectomy was performed [9-12].

The only indications in PV for which splenectomy is definitively therapeutic are painful splenomegaly and local compressive symptoms [13]. Complications of PV post-splenectomy include anemia, hyper viscosity and thrombosis (most commonly in Porto-mesenteric system of patients with hematological indications), increased risk of cancer, infection (especially encapsulated bacteria), platelet dysfunction, thrombocytosis, portal hypertension, and acquired von Willebrand deficiency (platelets above one million lead to loss of large vWF multimers in plasma and cause bleeding diathesis, which is reversible with desmopressin or platelet reduction) [13]. Infections and thromboembolic events cause the most medical morbidity post-splenectomy, they are more common in the immediate postoperative period but persist throughout life. Management includes antibiotics, anticoagulation and antiplatelet therapy as clinically indicated, patient education, and vaccinations [13]. Patients who have good long-term control of hematocrit are less likely to have complications than those with short-term or poor control.

While our patient reported excellent long-term control of his disease and did not meet the criteria for myelofibrosis pre-splenectomy (anemia, constitutional symptoms, leucoerythroblastic peripheral blood smear), he continued to have severe thrombocytosis refractory to antiplatelet and cytoreductive therapies or iron infusions and required repeat plateletpheresis. It is possible that his massive spleen had kept his platelets in-check until it was removed, then his platelet counts worsened from clonal megakaryocyte hyperproliferation, iron deficiency, and post-operative reactive state. Given his age and increased risk for thrombosis with the new diagnosis of atrial fibrillation, it is imperative that he maintain reduced platelets if possible.

Physicians should assess for splenomegaly at follow-up appointments every 3-6 months. An enlarging spleen size should prompt suspicion for myelofibrotic transformation and raise concerns for the risk of splenic rupture. Instruct patients to prevent splenic rupture by avoiding strenuous activities including contact sports capable of abdomen and chest trauma and those with increased intra-abdominal pressure such as weight lifting [14]. In addition, the use of ruxolitinib can reduce spleen size and further risk of rupture. Our patient would have benefitted from these interventions to avoid this situation. The option to use JAK 1/2 inhibitors remains: reports exist of patients with primary myelofibrosis refractory to multiple cytoreductive drugs and compassionate splenectomy free of constitutional symptoms and transfusions following treatment with ruxolitinib [15].

In conclusion, spontaneous splenic rupture is an extremely rare complication of PV. Clinicians should consider this in their differential when a patient with PV presents with new-onset abdominal pain and leukocytosis. They should recognize post-splenectomy complications unique to PV and be proactive in management as well as prevention using excellent disease control. Patients with splenomegaly should be cognizant of the risk of splenic rupture and take necessary precautions to avoid this sequela by reducing disease burden with cytoreductive therapy and splenic size with JAK 1/2 inhibitors

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