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Surgical Intervention in Extensive Splanchnic Arteriovenous Thrombosis Associated with JAK-2 Mutation

Viren Sehgal[**], Faez Ayoob[*], Charles Fasanya[*], Kuldeep Singh[*+]

[*]Staten Island University Hospital, Staten Island, NY, USA

[**]CUNY School of Medicine, New York, NY, USA.

[*]**Corresponding author:** Dr. Kuldeep Singh, Staten Island University Hospital, Staten Island, NY, USA. Email: ksingh7@northwell.edu

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Abstract

Introduction: Essential thrombocytosis is a rare condition caused by an overproduction of platelets. The overwhelming number of patients are asymptomatic and managed conservatively. We present two cases of complications related to ET that required surgical management. **Case Presentation**: The first cases was a 75 year-old female with a hypercoagulable states presented with abdominal pain and was noted to have acute splenic and mesenteric infarcts she underwent splenectomy followed by partial enterectomy as definitive management. The second patient presented with distal mesenteric small vessel thrombosis and bowel ischemia underwent an exploratory laparotomy followed by interval small bowel resection and primary anastomosis. Both received therapeutic anticoagulation and oral chemotherapy for their essential thrombocytosis both patients were noted to have JAK-2 mutation. **Discussion**: Essential thrombocytosis is a rare cause of major thromboembolism. Most cases involve microvascular thrombosis in small or medium sized vessels. The morbidity and mortality exceeds 20% in large vessel disease therefore requiring prompt recognition and appropriate management to improve patient outcomes. JAK-2 gene mutations have recently been found to have an association with many prothrombotic conditions, namely polycythemia vera and other myelodysplastic syndromes. Individuals with this mutation have a 1.8 to 2.3-fold increased risk of thrombosis. our review of literature revealed 58 total articles and case reports. All reported cases were managed with medical therapy with the exception to the cases were have reported. **Conclusion**: Essential thrombocytosis has a rare association with large vessel thrombosis in both the arterial and venous systems that may require surgical intervention, especially in the elderly population. JAK-2 mutations should be considered as an etiological risk factor.

Keywords: Venous Thrombosis; Arterial Emboli; Splenic Infarction; Mesenteric Infarction; JAK–2 Mutation; Aortic Thrombus

Introduction

Essential thrombocytosis is an acquired thrombophilia and the most common chronic myeloproliferative disorder [1]. Simultaneous venous and arterial thromboembolic events are uncommon with essential thrombocytosis. It is rare for surgical intervention to be part of their management [2, 3]. Literature providing insight regarding the surgical management of essential thrombocytosis is scarce with few reported cases of ET that required multiple surgical interventions [2, 4-7]. We describe two cases of essential thrombocytosis in which surgery including splenectomy and bowel resection were integral parts of the management.

Case Presentation

Case 1

A 75-year-old woman presented to our emergency department with diffuse abdominal pain, which started 5 days earlier. The

pain was localized to the epigastric region, was non-radiating, and associated with multiple episodes of vomiting and non-bloody, watery diarrhea. 5 days prior to this visit the was seen in the emergency room for left flank pain, at which time a urine analysis and a chest x-ray were performed and were both negative. A diagnosis of musculoskeletal pain was presumed and short-term follow-up was advised. Her medical history was significant for hypertension, high cholesterol, chronic back pain, osteoarthritis, skin cancer, cholecystectomy, and right hip replacement.

On examination, her abdomen was mildly distended, and diffusely tender with rebound tenderness. Her initial workup showed a leukocyte count of 48,300 cells/mm^3, a platelet count of 571,000cells/mm^3, BUN of 20 mg/dl, Creatinine of 0.73mg/dl, Lactic acid of 1.9mg/dl, Serum calcium 9.2mg/dl. Abdominal-pelvic CT scan with oral and intravenous contrast demonstrated splenic vein thrombosis, an aortic mural thrombus and superior mesenteric artery emboli. The spleen was edematous and hypodense. The hypodensity was attributed to acute splenic infarction from venous occlusion. In the ED the patient received isotonic IV fluids, intravenous morphine and an intravenous heparin bolus followed by a heparin drip. Given the clinical and radiological findings, it was decided to perform an exploratory laparotomy to assess the viability of the small bowel. The heparin drip was temporarily held.

During the exploration, splenectomy was performed due to intraoperative rupture of the spleen. This was attributed to acute splenic infarction leading to a friable, thin-walled and devitalized spleen. The small and large bowel were both viable. Good serosal color and mesenteric pulses were noted. Postoperatively the patient was admitted to the surgical intensive care unit for monitoring. The heparin drip was restarted soon after surgery. The patient was closely monitored with serial abdominal examinations. The stomach was decompressed with a nasogastric tube and a central line was placed for central venous pressure monitoring and total parenteral nutrition. An arterial line was also placed for invasive monitoring. On postoperative (PO) day 1 the patient was diagnosed with a non-ST-elevation myocardial infarction; and aspirin was added to the medication regimen. On PO day 4, the patient developed altered mental status and abdominal pain.

The patient also had abdominal signs suggestive of peritonitis. The laboratory data showed leukocytosis (WBC: 32,000-cells/mm^3). An abdominal and pelvic CT scan with oral and intravenous contrast was performed and showed thickening and hyperemia of distal small bowel, superior mesenteric artery emboli, and aortic mural thrombi. There was also an interval development of portal vein thrombosis. The patient was taken to the operating room for re-exploration at which time a well-demarcated 20 cm segment of distal ileum was found to be ischemic with patchy necrosis. The segment was resected and a primary anastomosis was performed. The rest of the small bowel appeared viable.

The final pathology for the spleen showed hilar vessels (arterial and venous) organizing thrombi. Additionally, the spleen had extensive geographic areas of necrosis. Small bowel pathology showed extensive ischemic changes with focal gangrene. An extensive hematology workup was performed which showed a mutation in the JAK2V617F gene. This was a flow cytometry study based on peripheral blood indicative of myeloproliferative disorder (MDS). The patient was restarted on therapeutic anticoagulation. A repeat abdominal-pelvic CT scan showed resolution of all aortic, portal vein and superior mesenteric artery thromboemboli. The patient was discharged on Coumadin to a nursing home facility to continue rehabilitation. During the hematological outpatient follow-up, the patient was started on hydroxyurea for essential thrombocytosis. On 3 years follow-up the patient has recovered completely with no further thromboembolic events.

Case 2

A 68-year-old woman presented to the emergency department with complaints of diffuse abdominal, 3 episodes of vomiting and 2 episodes of bloody diarrhea. The patient's past medical history was significant for hypertension, high cholesterol and gastroesophageal reflux disease. She was given ondansetron and famotidine for the nausea, morphine for the abdominal pain, a one-liter normal saline bolus. She was also given gastrografin in preparation for an abdominal CT scan. She complained of similar symptoms 1 month prior to this presentation however the previous episode was far less severe.

Physical exam was notable for an extremely tender abdomen with bright red blood on rectal exam. Initial vital signs were a heart rate of 102 beats per minute, a respiratory rate of 20 breaths per minutes, and a blood pressure of 180/97. Initial workup showed a leukocyte count of 32,430 cells/mm^3, platelet count of 850,000 cells/mm^3, BUN of 15 mg/dl, creatinine of 0.99 mg/dl, glucose of 228 mg/dL a Lactate of 2.5 mmol/L. The remainder of the patient's laboratory values were within normal limits. CT scan results indicated diffuse portal vein thrombosis involving the main portal vein, right and left portal vein branches, with thrombosis of the superior mesenteric vein and mesenteric venous branches. There were also multiple thickened and edematous small bowel loops predominantly involving the jejunum with several having decreased enhancement concerning for ischemic bowel. The patient was given a heparin bolus, started on a heparin drip, and a course of ciprofloxacin and metronidazole was initiated. A nasogastric tube was placed and turned to low continuous suction and the patient was admitted to the surgical ICU.

On hospital day two, the patient's heparin dip was held and the patient was taken to the operating room with a suspected diagnosis of ischemic enteritis, portal vein thrombosis, splenic vein

thrombosis, leading to splenic infarction with hepatic necrosis and ascites. An exploratory laparotomy was performed. Upon entering the abdomen three liters of ascitic fluid was seen and evacuated. A diffuse segment of jejunum approximately 30cm long was found to be mildly ischemic; however, re-vascularization was appreciated after a warm lap pad was placed on top of the bowel. It was deemed that the patient would be left intubated with an abthera vacuum dressing placed on the abdomen with plans for re-exploration the following day. The heparin drip was restarted 1 hour postoperatively and held 6h before re-exploration. The patient's creatinine increased to 1.26 mg/dL indicating acute kidney injury. During re-exploration a portion of small bowel was seen that had failed to re-vascularize and the portion was resected. There was evidence of a thrombus in the superior mesenteric venous system despite use of full dose heparin for anticoagulation. After running the small bowel one again, no further areas of ischemia were seen. A primary anastomosis and abdominal colure was performed. The patient remained intubated postoperatively and the heparin drip was restarted. A nephrology consult was placed for the acute kidney injury. The following day the patient was extubated and started on a bicarbonate drip as per the nephrology recommendations, a renal ultrasound was also performed and was found to be within normal limits. At this time the patient's creatinine began to trend downwards and normalized on PO day 4.

On PO day 5, the patients NG tube was removed, she passed flatus and had her first bowl movement. The patient had several loose watery bowel movements and was diagnosed with C. difficile colitis on PO day 6 and started on oral vancomycin. A hematology consult was also placed to determine a cause for the patients hypercoagulable state. A series of tests were performed and the patient was found to have a Jak-2 mutation with a V617F activating mutation. Patients diet was advanced and total parenteral nutrition was discontinued. On PO day 8, patient was found to have a persistently elevated WBC, a CT scan was repeated showing diffuse ascites and gastroenterology consult was placed. A diagnostic paracentesis was performed that was inconclusive. The patient's heparin was switched to therapeutic enoxaparin and eventually to warfarin prior to discharge. On PO day 12, the patient was downgraded from the ICU as her white count began to normalize and she improved symptomatically.

The patient was discharged in stable condition on PO day 16 to a rehabilitation facility. The final pathology report was notable for an ischemic portion of jejunum with thrombus in the superior mesenteric artery. The patient has since followed up with hematology and was started on hydroxyurea after receiving a diagnosis of essential thrombocytosis with hypercoagulability related to the previously mentioned jack 2 mutation and had continued her course of warfarin. The patient has had no further coagulopathic events to date.

Discussion

On May 26, 2024 a literature search was performed on PubMed and Google Scholar. The search terms used were "essential thrombocytosis", "JAK 2 mutation" (thrombosis or infarction or embolus)) AND (splenic or mesenteric)" Only articles in English were included. 58 total articles and case reports were found. Table 1 shows a brief summary of the initial papers that arose on this topic. All the articles were obtained through the library and were reviewed by all the authors. (Table 1)

Table 1: brief summary of initial cases of essential thrombocytosis+- JAK 2 mutation that were associated with splanchnic vascular thrombosis.

Author	References	Number of cases	Demographic	Presentation	PMH	Affected vessels	Platelet	Intervention	Medical treatment	Follow-up	Post COMP
Johnson et al 1995	2	4	68 yrs old white female	Abd pain, intestinal angina , AKI	Known ET	Aorta, coelic, sma, renal, hepatic, splenic	1000k/cc	Transaortic embolectomy sma exploration	hydroxyurea	No events with plat 98k/cc in 2.5yr.	NONE
			46 yrs old male	Hematemesis, while on hydroxyurea	Known ET	Portal, superior mesenteric, splenic veins thrombosis	580k/cc	Modified suguira	ASA, increase hydroxyurea dosage	No events in 6-month, plat 126k/cc	NONE
			33 yrs old female	Abd pain ,jaundice, massive GIB, peritonitis W/SB infarction.	Unknown ET:	Diffuse splanchnic thrombosis	580-840k/cc	SB resection, Modified suguira	Hydroxyurea	No events 6-month,plat360k/cc	SBS, enterocutaneous fistula,DVT subclavian and iliofemoral vein
			68 yrs old female	Abd pain		Ivc, lt renal vein	734k/cc	Ex lap, removal of caval thrmobus	Asa, hydroxyurea	No events with plat 220k/cc,2.5yr	
Das et al 2002	3	1	25-yr old male-Indian	Abdominal pain and hemostasis	Unknown Hs of ET	SVT	325-2180k/cc	splenectomy	Hydroxyurea	Stopped the Hydroxyurea due financial constrain	TIA
OKI et al 2008	5	1	65 –yr old Japanese female	Abdominal pain, N/V &diarrhea	Unknown ET W/5 YRYRS h/o thrombocytosis and leukocytosis	Splenic infarction , thrombus in thoraco-abdominal aorta.	1665k/cc	none	Heparin then switched to hydroxyurea and ASA	Stopped ASA due to gastric ulcers. Plt counts 400 k/cc 1 months f/u	Gastric ulcers
Keskin et al2012	6	1	44-yr old male	Abdominal pain, N/V, splenic infarction for 1 month duration. Unrelenting abdominal pain	Unknown h/o ET	Splenic hemorrhagic infarction and thrombosis , celiac artery and SMA thrombosis	1150k/cc	Splenectomy then followed LT common iliac to sma bypass	Not mention	Started anagrelide after Dx of ET in outpatient setting	---
Nurden Et Al 1996	7	1	Unknown age Female	2 thrombotic episodes : 1st splenomegaly , ascites, esophageal varices . 2nd episode abdominal pain :infarcted ileum	Unknown ET	Splenic vein, portal vein thrombosis .	450-654k/cc	SB resection	ASA at 1st then changed to Ticlopidine	Ticlopidine , w/ no plt abnormality for 2 yr	--
Fouad Et AL 2012	8	1	41-yr old Caucasian female	Abdominal pain, decrease appetite, N/V , 2 segments od small bowel ischemia but viable	Unknown H/O ET	Mesenteric vein thrombosis	175k/cc	EX-LAP followed by 2nd look laparotomy to check SB viability	Heparin followed by hydroxycarbamide and warfarin before DC	Warfarin and Hydroxycarbamide	--

Berk Et al 2006	10	1	37 yr-old African –American male	Shock from esophageal bleeding :hematemesis and 4 Yrs prior p/w abdominal pain DX As idiopathic splenic-portal mesenteric thrombosis	Unknown H/O ET instead miss DX as idiopathic splenic-portal mesenteric thrombosis	splenic-portal mesenteric vein thrombosis	Initially 203 k/cc then postop1003-2252k/cc	EX-LAP W/ splenectomy, mesocaval shunt, surgical procedure, p, H-M Pyloroplasty	Platelet pharesis anagrelide then add ASA and Coumadin	Coumadin , ASA AND anagrelide	
Chebli Et al 2004	11	1	76-yr old Brazilian female	Intermittent Abdominal pain for 18 months ass w/ N/V , diarrhea and wt loss	Unknown H/O ET	splenic-portal mesenteric vein thrombosis and splenic infarction	Platelet 823k/cc	--	Heparin and hydroxyurea	Coumadin and hydroxyurea no symptom and normal plt count on 6 months	--
Hudzik Et al 2012	12	1	61 –yr old female	SOB , cough	Unknown ET	B/L pulmonary artery and adominal aorta thrombosis	770k/cc	---	Heparin then modified to dalteparin , hydroxy-carbamide and ASA	--	---
Batkan et al	1	1	35 yr old male	Abdominal pain	Unknown	Portal and superior mesenteric veins	626x103/µL	Small bowel resection and splenectomy, second look with additional resection and anastomosis	500mg hydroxyurea BID with lamivudine	--	--

Introduction and Definitions

Essential thrombocytosis (ET) also known as essential thrombocythemia is a platelet disorder characterized by maintained elevation of platelet count with susceptibility to thrombosis and bleeding in the absence of alternative causes [1,12]. ET was first described in 1934 by Epstein and Goede [2, 8] and is the most common type of myeloproliferative disorder [1, 12], with reported incidence of 0.5-2.5% and prevalence of 30/100000 [7, 13]. ET is one of the 6 disorders described as part of chronic myeloproliferative disorder along with chronic myelogenous leukemia, polycythemia vera, primary myelofibrosis, chronic neutrophilic leukemia, and chronic eosinophilic leukemia [2-8].

Diagnosis is made by exclusion of other causes of thrombocytosis [1,14]. The main diagnostic criteria were first described by polycythemia group in 1976 [2,8,13,14], and then modified in 1997. In 2016 a revision as once again made by the WHO. The four major criteria include 1) A platelet count ≥450 x 109/L, 2) a bone marrow biopsy showing proliferation of mainly megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. Wi no significant increase or left-shift in the neutrophil granulopoiesis or erythropoiesis and very rarely minor increase in reticulin fibers, 3) Not meeting criteria for BCR-ABL1+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms, and4) the presences of JAK2, CAL4, or MPL mutation. The presence of a clonal marker or absence of evidence of reactive thrombocytosis is a minor criteria. Diagnosis requires the presence of all 4 major criteria or the first three major criteria and the minor criterion [15]

Symptoms associated with ET vary considerably. Patient may have no symptoms, thromboembolic complications without bleeding, or combined bleeding with thrombosis; with reported incidence of 36%, 41%, and 15% respectively [2,8,13,14]. Evidence of atrial thromboembolic events in microcirculatory is seen in up to41% of patients. Generally, ET takes a latent course until complications develop, as seen in this case report [13,16,17].

Thromboembolic complications of essential thrombocytosis are infrequent [2,8-10], but rather serious with reported mortality as high as 20% [11]. Prompt recognition and appropriate management of these complications is crucial to improving outcomes [7]. Complications are also unpredictable [2,4,7,16] as patients may remain undiagnosed for years [16,17]. ET complications usually arise from microvascular thrombosis in small or medium-sized vessels. These may present as transient ischemic attacks, digital ischemia, erythromelalgia, and livedo reticularis [2,7,8,12,16]. On the other hand, ET may lead to arterial thrombosis in large blood vessels as seen in this case. Although large vessel involvement is rare it may elicit a myriad of symptoms based on the affected vessel [7,11,12]. For example, ET led to portal and splenic vein thrombosis in one patient who presented with severe abdominal pain [6].

General Management

The main goal while managing ET is to control the thromboembolic events and to prevent further complications. This may be achieved by categorizing the patient's risk factors into three main classes:: high, moderate and low risk. Patients risk factors include age > 60, platelet count >1 million/mm, history of thrombotic or bleeding events, presence or absence of cardiovascular risk factors (hypertension, diabetes mellitus, high cholesterol), duration of persistent thrombocytosis, and the presence of JAK2 gene mutation [8,12,13,14,].

Patients in the high-risk group; who are 60 years old or older or who have a history of thrombosis will require being maintained on hydroxyurea and aspirin. Patients in the low-risk group; younger than 60 without any history of thrombosis will require to be maintained on aspirin therapy alone. Moderate-

risk patients are usually managed on a case by case basis. Recent reports are trending toward involving JAK-2 mutation and WBCs count in the treatment strategies of this disorder [16,17].

Management of Complications

The management of ET complications depends on clinical presentation and may range from non-operative and medical management to immediate operative intervention [2,6,7,10,11,16,12]. The principle of managing these thrombi is to reverse end organ ischemia and prevent further thromboembolic complications [10]. The need for surgical intervention in treating essential thrombocytosis complications is extremely rare [2,3,16]. In fact, there are very few cases reported that required surgical intervention [2,6,7].

Splenic vein thrombosis secondary to ET was reported in very few cases in the literature [2,5,6]. These patients presented with splenomegaly and isolated gastric varices [4,5,9]. However, our patient had a more acute presentation with severe abdominal pain, splenomegaly but no gastric varices. Splenic vein thrombosis is managed medically with anticoagulation unless there is significant bleeding from gastric varices. Surgical intervention was mandatory for our patient as the spleen was grossly devitalized and ruptured intra-operatively.

As previously mentioned, symptomatic ET patients require anticoagulation therapy to stop the progression of thromboembolic event. Interestingly in this case, major vessel thrombosis continued in spite of anticoagulation and antiplatelet therapy. Our patient developed symptoms and signs of acute abdomen on hospital day five. Her CT scan then showed propagation of thromboemboli on both venous and arterial side. On the venous side; extension of venous thrombosis to involve the portal vein was noted. On the arterial side, showering emboli from the aortic mural thrombus to the superior mesenteric artery led to acute mesenteric ischemia. The development of acute mesenteric ischemia despite anticoagulation therapy is also uncommon. However, prompt recognition and intervention is vital as untreated mesenteric ischemia is associated with a very high mortality ranging from 53% to 93% [7,10,16].

JAK-2

Aside from the thrombocytosis, our patient had no history to suggest a hypercoagulable state. Therefore, extensive hematological tests were performed and revealed the JAK-2 gene mutation. The most common JAK-2 gene mutation is a missense mutation which leads to the replacement of valine with phenylalanine [10,18,13]. This mutation is proposed to ultimately cause increased production of platelets. Individuals who carry the JAK-2 mutation have an increased risk of thrombosis by 1.8 to 2.3 fold [10,18] however, no prospective trials were done to assess the clinical impact of this risk factor on thrombosis [19,20]. Additionally, JAK-2 gene was recently found have an association with Philadelphia–negative chronic myeloproliferative disorders [16,18,21]. A finding that underscores its importance in multiple pathological conditions.

Conclusion

ET has a rare association with large vessel thrombosis both requiring surgical intervention. High index of suspicion is necessary to prevent misdiagnosis of acute abdomen due to thromboembolic events, especially in patients who present with significant thrombocytosis.

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