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Case Report of Venous Portal Vein Thrombosis after Splenectomy to Treat Hemolytic Anemia and Review of the Literature

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Abstract
Portal vein thrombosis is a frequently occurring pathology following splenectomy. Several local and systemic risk factors contribute to its occurrence among patients who undergo this procedure to treat hemolytic anemia. This potentially fatal complication has caused great discussion about appropriate interventions for its prevention and treatment. Frequently this alteration is undetected. We present a case and review the topic.

Keywords
Splenectomy, portal venous thrombosis, hemolytic anemia, gastric varices.

INTRODUCTION

Portal vein thrombosis (PVT) secondary to splenectomy is an important but frequently forgotten pathology that is potentially fatal. (1) Its incidence varies from 5% to 50%, (2) and its mortality rate can be reduced from 5% to 0% if it is diagnosed and treated early. (3, 4) Frequently, clinicians and surgeons do not take this potential complication into account and fail to provide patients with prophylaxis and consultation until portal hypertension and its complications have already become established. Once that occurs, it must be permanently controlled with hospitalizations, transfusions and other measures. We present the case of a patient with PVT secondary to splenectomy.

CLINICAL CASE

The patient was a 37 year old Colombian high school teacher in a common law marriage. At the age of 12, she was diagnosed with hereditary spherocytosis. Six years later she underwent a splenectomy. Two years later she consulted a physician because of for hematemesis and melena. An endoscopy found bleeding esophageal varices which were treated with sclerotherapy. Propranolol was prescribed to control hger blood pressure. Portal Doppler ultrasound found a "hypoechogenic thrombus in the portal vein and its right branch with important collateral circulation and portal hypertension". Magnetic resonance imaging (MRI) showed cavernous degeneration of the portal vein. She has been hospitalized numerous times because of upper gastrointestinal bleeding secondary to gastropathy due to portal hypertension and has been treated for an acute episode with electrolytes and electrolyte support, terlipressin and red blood cell transfusions. Upon discharge treatment consisted of propranolol.

Three years ago, she was found to have gastric varices but without bleeding. In the last 2 years, her aminotransferase levels have been found to be three times above the upper

limit of normal. Her total bilirubin was measured at 1.5 mg%, direct bilirubin at 0.8 mg%, and albumin at 3.4 g%. She was found to have hypergammaglobulinemia. A liver biopsy found no fibrosis.

In October of 2017, she suffered hematemesis. An upper endoscopy showed cardial and subcardial varices with signs of recent bleeding. They were ligated without complications (Video 1). Other gastric varices which were not bleeding varices were also found. She has not suffered bleeding since this procedure, continues to receives treatment with propranolol, and is monitored by the gastroenterology department. It is planned to treat her gastric varices with cyanoacrylate and lipiodol if they bleed.

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Video 1. Ligation of subcardial varices due to portal hypertension following splenectomy. https://youtu.be/9ZP8W3JxcXw

METHODOLOGY

A PubMed®/MEDLINE search using the terms "portal vein" [MeSH Terms] OR ("portal" [All Fields] AND "vein" [All Fields]) OR " portal vein "[All Fields]) AND (" thrombosis "[MeSH Terms] OR" thrombosis "[All Fields]) AND (" splenectomy "[MeSH Terms] OR" splenectomy "[All Fields]) had 478 results. Of these, the authors selected 53 articles. Forty-two of these are from the last 10 years and are related to pathophysiology, natural history, diagnosis, acute and chronic complications, treatment of post-splenectomy PVT and treatment of esophageal and gastric varices. We identified 30 primary studies, 6 metaanalyzes and systematic reviews, 15 narrative reviews and 2 clinical practice guidelines. We included 10 articles prior to the last decade because of their historical contributions to the understanding of this pathology.

TOPICAL REVIEW

Total splenectomy is the treatment of choice for patients with severe hemolytic anemia secondary to spherocytosis. A total splenectomy decreases or eliminates anemia, (5, 6) but it can produce portal vein thrombosis (PVT). (5)

DEFINITIONS

PVT and Budd-Chiari syndrome are both included in splanchnic venous thrombosis. (6, 7) Because of the portal vein's anatomical formation, PVT can be found in the intrahepatic portal branches, the extrahepatic portal vein, the superior mesenteric vein, and in the splenic vein. (5-7) Extrahepatic portal venous obstruction (EHPVO) involves these regions and, by definition, excludes PVT related to cirrhosis and hepatocellular carcinoma, which have their own pathophysiologies and treatments. (6)

PATHOPHYSIOLOGY

At present, the mechanisms responsible for PVT following splenectomy are still unknown. However, they are considered to be related to the classic Virchow triad: venous stasis, hypercoagulability and endothelial damage. (7) Several studies have shown that resection of the spleen decreases portal blood flow and produces turbulence and stasis in the stump. This increases the diameters of the portal vein and the splenic vein which predisposes to thrombosis. (7, 8) When the preoperative diameter of the splenic vein is more than 8 mm, the risk of PVT is 2.57 (95% confidence interval [CI]: 1.26 to 5.23), (9) but if portal vein diameter is more than 13 mm, the risk increases 5.7 times (95% CI: 2.68 to 12.09). (8) Similarly, splenomegaly and a splenic weight over 1 kg increase the risk of PVT 14 times. (10)

It has also been considered that laparoscopic surgery can be associated with blood stasis and hypercoagulability of portal circulation which are related to carbon dioxide (CO_2) induced pneumoperitoneum and use of the Anti-Trendelenburg position. (11, 12) Reduction of portal and hepatic blood flow causes damage to vascular endothelial cells and promotes exposure of tissue components capable of triggering coagulation. (13, 14) It has been found that from the third day following surgery, platelets, levels of tissue plasminogen inhibitor type 1, plasminogen activators, and activated partial thromboplastin time all increase which favors PVT (15).

CLINICAL MANIFESTATIONS

PVT can appear at almost any time in the immediate postoperative period or several months later, and has even been reported three years after surgery. (16) In general, the symptoms are mild and nonspecific, with abdominal pain or fever, although the process may be asymptomatic. (17) Early diagnosis is unusual, and most frequently, PVT is diagnosed when there are already complications such

as varicose bleeding. (17-19) Occasionally, bleeding may occur decades after a splenectomy and PVT. (18)

ACUTE COMPLICATIONS OF PVT

PVT can be accompanied by thrombosis of the mesenteric vein which has a risk of intestinal infarction in a third of patients and a risk of mortality in 20%. (19) Acute thrombosis of the mesenteric vein presents with abdominal pain and occasionally with diarrhea, nausea, vomiting and lower digestive bleeding. (19)

DIAGNOSIS

Portal Doppler ultrasound has traditionally been used to diagnose PVT. Its sensitivity is 60% to 100% depending on the operator. (20) Computed tomography (CT) and magnetic resonance imaging (MRI) can help determine the extent of thrombosis and are useful when ultrasound is difficult due interposed gas which prevents identification of mesenteric thrombosis. (21,22) A blood test may show leukocytosis and thrombocytosis, (22) and the C-reactive protein (CRP) level is often high for the first 7 days after surgery, regardless of symptoms. (18, 22) The liver profile may show cholestasis and amylase levels 1.5 times the normal limit, although other laboratory tests may be normal. (3)

PROPHYLAXIS

Because of the relatively high frequency, prophylaxis with low molecular weight heparin has been recommended from 12 to 24 hours after the procedure until at least 4 weeks later. (23-25) When preoperative risk factors mentioned above are present, administration of heparin should continue even longer. (26)

TREATMENT OF ESTABLISHED PVT

Anticoagulation is the cornerstone of treatment. (27, 28) Simultaneous administration of low-molecular-weight heparin and warfarin should be used until an international normalized index (INR) of two to three is obtained. After this goal is achieved, warfarin should be continued for three to six 6 months. (27). To date, there have not yet been any studies of the use of direct thrombin inhibitors such as dabigatran nor have there been any studies of the use of factor Xa inhibitors such as rivaroxaban and apixaban. (28)

Thrombolysis is recommended for treating acute PVT, especially when thrombosis is extensive and the superior mesenteric vein is also compromised. (28, 29) Thrombolysis can be administered locally or systemically and has varying success rates. (29) Local administration may cause major bleeding in up to 50% of patients. (29) Transcatheter selective superior mesenteric artery urokinase infusion in the superior mesenteric artery seems to be safer. (30) Transjugular intrahepatic catheter thrombolysis is another treatment option, but experience with this procedure is required. (31) The systemic administration of thrombolytics, strictly following the exclusion criteria, has less risk of bleeding. (32)

TVP TREATMENT ALTERNATIVES

Creation of a transjugular intrahepatic portosystemic shunt (TIPS) allows direct recanalization with a catheter or balloon and administration of thrombolytics. (32) This procedure should be done in centers with a large amount of experience to reduce dysfunction of the shunt and derivation and rethrombosis. (33) Percutaneous balloon angioplasty or transhepatic or splenic stent placement is another useful procedure, although its rethrombosis rates are 9% -40%. (34)

CHRONIC COMPLICATIONS OF PVT

EHPVO may occur in cases of chronic PVT. In these cases, the portal vein is replaced by fibrous tissue and periportal collaterals develop and form a cavernoma. (35) In some cases, this syndrome may be associated with portal hypertension, portal gastropathy, gastric varices, portal cholangiopathy and hepatic encephalopathy. (36) When a cavernoma has formed, anticoagulation is not indicated, (35, 36) but in all cases, all complications derived from PVT must be treated. (36)

GASTRIC VARICES

Esophagogastric varices or isolated gastric varices can occur, but the latter are the most frequent. (37). Most gastric varices occur in the gastric cardia or fundus. (37, 38) Sixty-five to eighty-five percent of these varices are associated with gastro-renal derivations and are responsible for 5% to 10% of upper digestive bleeding in these patients. (39)

Treatment of Gastric Varices

During bleeding episodes, obliteration of varices with cyanoacrylate is the first treatment option and band ligature is the second. (40) Treatment with cyanoacrylate injections controls bleeding in 89% to 94% of cases, although rebleeding occurs in 26% to 31% of those treated. (41) The success rate for controlling bleeding of small gastric varices

with band ligature is 80%, with a rebleeding rate that ranges from 48% to 89% (mainly in Type 1 Isolated gastric varice of the Sarin classification) (42). Although both methods can achieve control of acute bleeding, the rebleeding rate is lower with cyanoacrylate. When varicose veins are not small, the treatment of choice is sclerotherapy with cyanoacrylate. (43)

Endoscopic ultrasound (EUS) allows verification of intraluminal administration of cyanoacrylate. The risk of rebleeding is 19%, and EUS offers the possibility of detecting residual varices. (44) Isolated ligation is not recommended, although it can be supplemented with cyanoacrylate injection. (45) There are no prophylactic endoscopic treatments of gastric varices in patients with PVT. Only one randomized study was found for patients with cirrhosis and gastric varices. (46) That paper mentioned that patients in the cyanoacrylate group bled less frequently (15%) than those with nonselective β blockers (38%) and those who had no intervention (53%). As in patients with acute bleeding due to esophageal varices, initial treatment included resuscitation with parenteral fluids, vasoactive medications and antibiotics before endoscopic treatment (37).

Another emerging therapy is thrombin injection, which is successful in 70% -100%, with a rebleeding rate of 0% -27% (47). When there is severe hemodynamic compromise, bridging therapy with balloon tamponade for 24-48 hours is an important alternative, with which bleeding is stopped in 80% of cases. Balloon-occluded retrograde transvenous obliteration (BRTO is an intervention that takes advantage of the gastro-renal diversion to obliterate retrograde gastric varices. (48) TIPS can be used for refractory cases. (49) The use of vasoactive drugs is based on their effectiveness at controlling bleeding of esophageal varices. Therefore, epidemiological studies of patients with bleeding from gastric varices are needed. (49)

CIRRHOSIS DUE TO PVT

In some cases, PVT can cause cirrhosis. (50) The mechanisms involved may include ischemia which induces apoptosis, atrophy and nodular regeneration. Eventually, fibrosis and histological distortion occur which, depending on their magnitudes, can eventually lead to cirrhosis in a previously healthy liver. (51)

CONCLUSIONS

Patients who have a splenectomy to treat hemolytic anemia are at such a high risk of PVT that prophylaxis is indicated for one month after the procedure. Treatment requires minimal anticoagulation for 6 months. Mesenteric thrombosis and intestinal infarction or portal hypertension with bleeding due to esophagogastric varices are complications related to high mortality. Acute bleeding due to esophageal or gastric varices is similar to that which occurs in patients with cirrhosis and portal hypertension (52).

Conflicts of Interest

None.

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