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Review Article

Portal Vein Trombosis: Literature Review and a Case Report

May TH[1], Carmona FF[1], Simonetti LR[1], Amparado JA[1], Joaquim LF[1] and Kahwage RL[1*]

[1]Department of General Medicine "Hospital Beneficente Santa Casa de Misericordia de Ribeirao Preto", Sao Paulo, Brazil

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[*]Corresponding author:

Rafael Lima Kahwage, Department of General Medicine - Hospital Beneficente Santa Casa de Misericordia de Ribeirao Preto; Av. Saudade, 456; Campos Elísios; CEP: 14085-000; Tel: +55 (16) 3605-0606; Ribeirao Preto - SP, Brazil, E-mail: drrafaelkahwage@gmail.com

1. Abstract

Portal Vein Thrombosis (PVT) is an unusual complication in patients with liver cirrhosis. In current research on genesis, it has been demonstrated an underlying prothrombotic state and a combination of local endothelial factors, family and/or acquired inheritance, in addition to other thrombophilic factors. Such condition is described as an important cause of portal hypertension whether the patient has liver dysfunction.

There are three main variants of portal vein thrombosis: Acute non-cirrhotic portal vein thrombosis; Chronic PVT and PVT in cirrhotic patients. Each type may occur with multiple etiological factors and variability in its presentation.

Clinical and laboratory diagnosis complemented with imaging tests are useful in early detection since the treatment directly affects the morbidity and mortality of these patients.

The objective of the authors is to perform a review of the literature and describe the case of a male patient diagnosed with acute portal vein thrombosis, concomitantly with hepatic cirrhosis and thrombophilia, with partial recanalization after administration of enoxaparin and consequent reversal of the signs and symptoms of portal hypertension.

2. Keywords: Portal vein thrombosis; Cirrhosis; Recanalization; Thrombophilia; Anticoagulation

3. Introduction

Portal Vein Thrombosis (PVT) refers to a complete or partial obstruction of the blood flow in the portal vein due to the presence of a thrombus. It is a rare entity, described for the first time in 1869 by Balfour & Stewart, and it can be related to hepatic cirrhosis, hepatocellular carcinoma, or can be associated to any hepatic disease.

Pathophysiology of PVT is related to a compensatory mechanism immediately after the venous obstruction. Initially, there is a vasodilation of the hepatic artery and, posteriorly, after a few days, there is vessels neoformation. Total process is concluded in 3 to 5 weeks. Consequently, after sanguineous occlusion, there is stimulation in the apoptosis of the hepatocytes and the hepatic lobulesin which occurs a hypoperfusion. Therefore, slowly and progressive descent of the hepatic function occur [1].

The etiology of PVT is frequently multi factorial, related, approximately, 70% to local factors and 30% to systemic factors. Among the main risk factors are abdominal inflammatory processes as: appendicitis, diverticulitis, pancreatitis, cholecystitis, liver abscess, or cholangitis. The neoplasms represent 21 to 24% of cases with thrombosis represented to the direct vascular invasion, local compression (tumor mass) and hypercoagulability [2].

Cirrhotic patients have greater risk to develop the disease, with an ascending prevalence according to the hepatic disfunction, corresponding to 30% in candidates to hepatic transplant and 10 to 40% in patients with hepatocellular carcinoma [3-4].

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Among the systemic factors are myeloproliferative diseases and prothrombotic conditions ranging from 40 to 60%. Mutations in the V Leiden factor, deficiency in the C, S and antithrombin III proteins are the main prothrombotic conditions. Other risk factors are contraceptive, pregnancy, nocturnal paroxysmal hemoglobinuria, genetic mutations, trauma and idiopathic, corresponding up to 50% of the cases [5].

Virchow triad conditions (hypercoagulability, endothelial injury and slowed blood flow) must always be suspected in PVT patients and prothrombotic conditions should be considered, as cited above, and should be researched whenever possible.

Portal vein trombosis is classified in a) acute (up to 6 months) or chronic (beyond 6 months); b)into acquired or genetic. In the latter, a broad family history is important in the investigation of prothrombotic conditions; c) tumoral and non-tumoral; d) according to the extension.

Depending to the extent is subdivided as: 1) confined to the portal vein until confluence of the splenic vein; 2) reaching the mesenteric superior vein; 3) affecting the splenic venous system with large collaterals and, 4) with thin collaterals.

Clinical presentation depends on time of disease onset, the extent of the affected vessel, and related to the presence of collateral circulation. PVT can be associated to high mortality due to the hepatic ischemia, though there is low risk of bleeding in the varicose veins.

Acute PVT can be presented with abdominal pain or distention, rectal bleeding, nausea, vomit, anorexia, fever, metabolic acidosis, or sepsis. Majority of the patients presents with splenomegaly, while the presence of as cites is a rare condition. Instead, chronic PVT curses with no symptons, except for the formation of collateral circulation and as cites. Clinical suspicion is performed based on the incidental finding of hypersplenism, signs of hypertension or gastrointestinal bleeding.

Laboratorial diagnosis in PVT patients, without hepatic disease associated, is usually normal. However, markers of thrombogenic activity, as prothrombin and other coagulation factors, show themselves moderately decreased.6

Ultrasound is the chosen exam and presents high sensibility and specificity. A high probability diagnosis for PVT is made once evidenced the solid and echogenic material inside the blood vessel.

Other exams as computed tomography and/or Magnetic Resonance Imaging (MRI) are useful to evaluate the extension of the thrombus, presence of mesenteric and collateral circulation, involvement of adjacent organs and possible complications not evidenced by the usual method. These exams also enable the characterization of neoplastic nodules sometimes associated with PVT.

Although it has already been described in the literature the spontaneous resolution of PVT in the acute phase, the specific therapeutic handling is mandatory to solve the portal obstruction and avoid complications, mainly to prevent the progression to the chronic phase [7].

Correction of risk factors, prevention of the thrombosis extension, and obtaining the permeability of the portal vein are the main objectives of the treatment that do not differ between the acute and chronic forms [5].

Anticoagulant therapy is the main therapeutic approach to obtain total or partial venous recanalization in non-tumoral PVT patients; however, there is no consent on its application. There is a high tendency among authors to choose anticoagulants in the acute phase of the disease. Indication becomes controversial in chronic PVT. In this situation, adverse outcomes like hemorrhage from esophageal varices is customary.8Other authors recommend the anticoagulant therapy only in patients with confirmation of thrombotic disorders or family history of venous thrombosis [3, 9].

Acute PVT obtains complete venous recanalization after 6 months of anticoagulant therapy in approximately 50% of the cases with low complication rates. However, in approximately 10% of the cases, the thrombosis shows itself resistant to therapy. 10 additionally, when occurs gastrointestinal infarct, anticoagulants administered before surgery seem to have considerable benefit on survival. As soon as therapy is instituted, better are the clinic outcomes. In the acute form, the percentage of complete recanalization reaches 69% when anticoagulation is instituted within the first week of diagnosis, reducing to less than 25% if initiated posteriorly [11].

Therapeutic options in chronic thrombosis are controversial. Commonly, anticoagulant therapy is administrated in only 30% of the patients with PVT, reflecting concern about the presence of bleeding from esophageal varices, thrombocytopenia or coagulation disorders.1However, bleeding in patients receiving anticoagulant therapy has low incidence, and after follow-up studies the anticoagulant therapy demonstrated to be effective in the prevention of new thrombotic events with low mortality [7].

In a pragmatic approach, the eradication of esophageal varices by digestive endoscopy, preceding anticoagulant therapy, has a valid indication [1].

Long-term use of anticoagulants in PVT cirrhotic patients must not be encouraged until their safety and efficacy have been fully proven. Signs of intestinal ischemia or infarct, besides subjacent pro-thrombotic disorder are relevant to clinic context and must be considered as indication to anticoagulant therapy in cirrhotic patients, although use must occur only after established adequate prophylaxis for bleeding by varices of esophageal or gastric origin [12].

In acute PVT without thrombophilic disorder, anticoagulation must be administered from 3 to 6 months continuously until complete venous recanalization can be evidenced [1]. Some specialists recommend using anticoagulant therapy only in patients with known

diagnosis of thrombophilia or family history of venous thrombosis with evidence of improvement in survival and reduction of the risk of gastrointestinal hemorrhage. 9 In documented cases of thrombophilia, anticoagulation must be maintained for undetermined time.

Other therapeutic modalities are feasible in cases of absence of recanalization or even partial resolution of the thrombosis after anticoagulant therapy. Different therapeutic options are possible (depending on the services availability), but they are still quite controversial and include thrombolysis, surgical thrombectomy, TIPS (transjugular intrahepatic portosystemic shunt), and surgical shunt (distal splenorenal shunt) [7, 8].

Surgical thrombectomy is not usually recommended due high risks of morbidity and mortality. Percutaneous transhepatic mechanical thrombectomy can also be effective in acute thrombosis, but vascular trauma is common and can stimulate the recurrence of thrombosis posteriorly [13].

Another possible therapeutic approach is the confection of an intrahepatic portosystemic anastomosis via transjugular. This therapeutic option has its indication reserved to patients that develop acute PVT before or after hepatic transplant or in alternative to thrombolysis when anticoagulation fails [14].

In patients without cirrhosis or neoplasms, PVT usually has good therapeutic outcomes. Yet, the prognosis depends on the base conditions of the patient. The most common complication is gastrointestinal hemorrhage associated to portal hypertension and, more rarely, biliary complications. Ascites, bacterial infection and hepatic encephalopathy are rare, except in the subsequence of gastrointestinal hemorrhage events.

Survival decrease when in association with advanced age, neoplasms, cirrhosis, and thrombosis of the mesenteric veins. Pro-thrombotic disorders appear not to affect survival.

Acute PVT, when recognized and treated before occurring intestinal infarct, has a good prognosis. However, in cases of mesenteric ischemia and disfunction of multiple organs, intrahospitalar mortality rates may vary among studies.

Portal vein thrombosis is a factor for poor prognosis when present in cirrhotic patients and is more common as more advanced is the cirrhosis due to the imbalance between pro and anticoagulants factors. It is an independent mortality factor both in pre-transplant as in postoperative of hepatic transplant [15].

Postoperative complications are more important in the patients with PVT and related to renal insufficiency, primary graft non-functioning and re-thrombosis [16].

Another study also showed that PVT adds important difficulties in the hepatic transplant, with increased time of surgery, higher necessity of transfusion, higher incidence of renal insufficiency and re-thrombosis and necessity of complex surgical techniques [17].

We aimed to present a case report with an acute, acquired, non-tumoral, Portal Vein Thrombosis (PVT) in a cirrhotic patient with coagulation imbalance with satisfactory evolution. Active clinic investigation and therapeutic approaches are discussed.

4. Case Report

S.C., male, 61 years old, Caucasian, married, natural of SaoSimao (city of the interior of the state of São Paulo), proceeding of Ribeirao Preto, trucker.

He was admitted in the Santa Casa of Ribeirao Preto, on 11/20/2018 with report of a descent on general condition and oscillation of the level of awareness in the past one day before admission.

History of the current disease was related to a recent hospitalization in the same service due to upper gastrointestinal bleeding (UGIB) related to peptic ulcer disease classified as Forrest III. He had previous diagnosis of hepatic cirrhosis of alcoholic etiology Child B and Meld [16].

Physical exam in the admission presented as regular general state, icteric 1+/4+, Glasgow 12 (E3/V4/M5), presenting episodes of mental confusion, absent flapping, globose abdomen, palpable liver 5cm from the costal margin.

Personal precedent is of noteworthy: diabetes type 2, risky alcoholic consumption (daily alcoholism with consumption of distillates above 30 grams per day) and smoking for 40 years. He presented recent hospitalization due to the UGIB (as described above) and hepatic encephalopathy grade II.

Family history has been made withan extensive research and there was no report of thromboembolic phenomena or any hematologic diseases.

Complementary exams of 11/20/2018 evidenced: hemoglobin of 11.60g/dL (RV 13.0 to 18.0 g/dL); hematocrit of 34.40% (RV 42 to 53%); leukocytes of 3.900 cells/mm3 (RV 3.5 to 11.000/mm3); platelets count of 95.000/mm3 (RV 140.000 to 450.000 mm/3); Activated Partial Thromboplastin Time of 30.3 sec. (RV 22.7 to 31.8 sec.); INR of 1.25 (RVup to 1.2); Total bilirubin of 1.40 mg/dL (RV 0.00 to 1.20 mg/dL); Direct bilirubin of 1.10mg/dl (RV 0.00 to 0.40 md/dL); Total proteins of 6.50 g/dL (RV 6.4 to 8.3 g/dL); Albumin of 3.40 g/dl (RV 3.5 to 5.2 g/dL); Oxaloacetic Transaminase (GOT/SGOT) of 34 U/L (RV<40 U/L); Pyruvic Transaminase of 35 U/L (GPT/ALT) (RV<45 U/L).

Total abdomen ultrasonography on 11/22/2018 evidenced signs of chronic hepatopathy and portal vein thrombosis (Figure 1).

A previous Doppler ultrasound image, performed at the Radiology Service of Santa Casa de Ribeirao Preto, on 10/17/2018, showed signs of chronic liver disease, but with normal distribution and caliber of the hepatic and portal veins.

In addition, an endoscopic image of 10/11/2018 showed esophageal varices of thin and medium caliber in the distal esophagus (Figure 2).

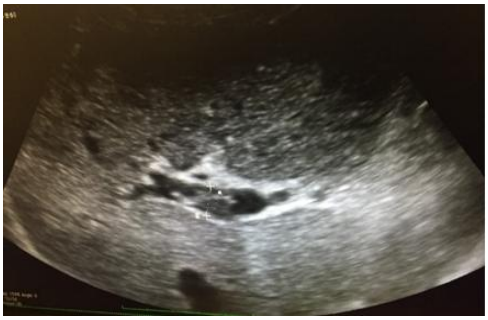

Figure 1: Ultrasonography of upper abdomen demonstrating portal vein with 1.1cm diameter, echogenic material without flow in doppler study and alteration in the hepatic echotexture.

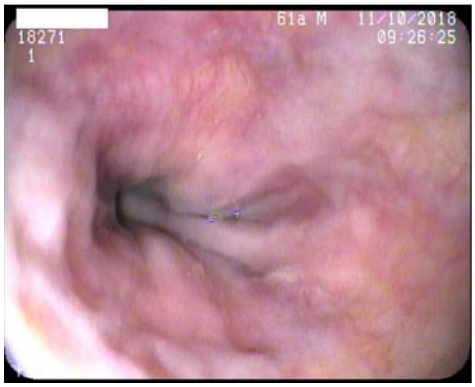

Figure 2: Upper digestive endoscopy showing bluish, tortuous varices, with no signs of red color in distal esophagus.

Therefore, therapeutic anticoagulation with enoxaparin sodium at a dose of 1 mg/kg for 12/12 hours was started. Seven days after the beginning of the described therapy and clinical compensation of the patient's condition, the patient underwent a new upper digestive endoscopy, to perform an elastic bandage, in order to provide the eradication of esophageal varices and, therefore, greater therapeutic safety in his anticoagulation. However, the exam showed only incipient varices in the distal esophagus (Figure 3).

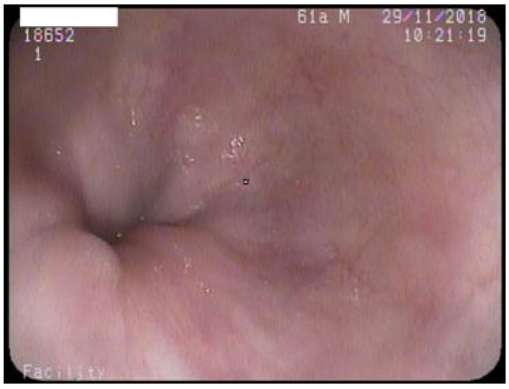

Figure 3: Upper digestive endoscopy demonstrating incipient varices in the distal esophagus, along the esophageal-gastric transition.

Finally, in the end of the 7-day regime treatment with enoxaparin, an abdomen MRI was performed, on 11/27/2018, which showed the migration of the thrombus to the hepatic segment [6].

Other complementary exams were requested with the following results: Partial Activated Thromboplastin Time of 38.5 sec (RV 22.7 to 31.8 sec); Prothrombin Time of 15.2 sec (RV 10.4 to 12.6 sec); INR of 1.43 (RV until 1.2); Anti-Thrombin III 60% (RV 75% to 120%); Alpha fetoprotein of 2.00 ng/mL (RV inferior to 7.0 ng/mL); CA 19-9 of 43.9 U/mL (RV inferior to 39.0 U/mL); Antibody anti-cardiolipin IgG inferior to 1 GPL U/mL (RV Inferior 15 GPL U/mL); Antibody anti-cardiolipin IgM of 3.9 MPL U/mL (RV Inferior 12,5 MPL U/mL); absence of mutation in the V Leiden Factor and absence of mutation of the prothrombin (Factor II); Factor VIII on 154% (RV 50% to 150%); absence of antibody lupus anticoagulant; Protein S functional on 17% (VR 60% to 120%); Protein S free antigenic on 27% (VR 87 to 130%) (Figure 4).

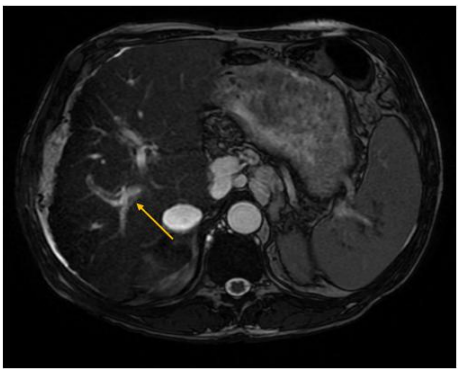

Figure 4: MRI of the abdomen evidencing the migration of the thrombos to the hepatic segment 6 (yellow arrow) and signs of chronic liver disease.

5. Discussion

Investigation of PVT in cirrhotic patient with portal hypertension and esophageal varices is relevant. Investigation is necessary due to its high rate of incidence in this group of patients. PVT has an annual incidence of 10-15% in cirrhotic patients. One reason is that the blood flow through the liver is slow in this condition and the presence of various prothrombotic conditions [18] besides a considerable prevalence, cirrhotic patients with PVT has potential complications as: progression to the chronic stage, portal hypertension with ascites, gastroesophageal varices, esplenomegaly and intestinal necrosis. Diagnosis is made with doppler abdominal ultrasound exam with good availability and low cost. Exam reveals the presence of solid and hyperechoic material in the portal vein, distension of the portal vein and/or tributary, and a net of collateral vases or cavernoma.

Etiologic risks were associated in the diagnosis of the portal vein thrombosisin the present case: hepatic cirrhosis and thrombophilia related to the deficiency of S protein functional and free, and Antithrombin III can be cited. A limitation of the present case was the unavailability of C protein dosage by the laboratory panel in our center. As seen in a recent study, about 50-60% of cases presents with polycythemia vera, essential trombocytemia, primary myelofibrosis, mutation in prothrombin gene G20210A and antiphospholipid syndrome and none of those conditions were diagnosed in our case [18].

There is little experience in the approach of the patients with PVT. A recent study, proposed treatment in cirrhotic PVT is in acute cases with potential liver transplantation, symptomatic acute occlusive PVT, extension of the disease to mesenteric vein.18Interventional treatment remains as TIPS are reserved for prolonging survival in a pre-transplantation list situation. Studies with thrombolysis are lacking and this treatment should be avoided until new trials are released.

After treatment with 7-day regime with enoxaparin, our case presented good resolution of signs and symptoms with reperfusion of the portal vein and migration of thrombus to sixth hepatic segment, lowering the risk of variceal hemorrhage and liver failure [19]. Despite a significative number of complications published [20] (gastrointestinal, genitourinary and central nervous system bleeding) our patient presented with no complications during treatment and after a 30-day follow-up.

6. Conclusion

We reported a case of acute, acquired, non-tumoral portal vein thrombosis associated with liver cirrhosis and thrombophilia (deficiency of functional and free protein S and Antithrombin III). After the institution of therapeutic anticoagulation with sodium enoxaparin there was a partial resolution of the thrombus with distal migration of the thrombus. The patient evolved with resolution of the portal hypertension and regression of the esophageal varices, deviating then the risk of unfavorable evolution of these varices, related to possible digestive bleeding.

Yet, with a precocious treatment was possible to avoid the progression of the disease to a chronic stage, which would entail in a greater risk of portal hypertension complications.

Screening, early diagnosis, investigation of prothrombotic factors (mutations in V Leiden factor and in the prothrombin gene (Factor II), deficiency in protein C, S, antithrombin III and Factor VIII) and treatment of the acute phase should be carefully evaluated in each case and may be necessary for the resolution of portal vein thrombosis and is related to increased survival.

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