

A Rare Case of Portal Hypertension.

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ABSTRACT

One of the important & rare cause of portal hypertension is portal vein thrombosis. Majority have an underlying prothrombic state diagnosed. Procoagulant state should be actively investigated. Anticoagulation is the mainstay of treatment in acute non-cirrhotic portal vein thrombosis & also it has supporting evidence in cirrhotic patients as well. TIPS and liver transplantation may be advised only in a properly selected candidates. We report a case of portal hypertension due to portal vein thrombosis, including with detailed etiology, diagnosis, complications and management of Acute and chronic portal vein thrombosis. Hope this case report will help in increasing the awareness of complexity associated with portal vein hypertension among the medical community.

Key words:

PVT - Portal Vein Thrombosis, **Portal HTN** - Portal Hypertension, **CECT** - Contrast Computerized Tomography, **UGI** - Upper Gastrointestinal, **TIPS** - Transjugular Intrahepatic Portosystemic Shunt, **LMWH** - Low Molecular Weight Heparin

Introduction

Portal hypertension, although commonly caused by liver cirrhosis, but can also result from non cirrhotic causes, which includes a rare cause portal vein thrombosis. Portal vein thrombosis (PVT) refers to complete or partial obstruction of blood flow in the portal vein, due to the presence of a thrombus in the vasa lumen [1]. Although in the general population PVT is a rare event, its prevalence among cirrhotic patients ranges between 44% - 15% & is responsible for 5% - 10% of overall cases of portal hypertension [2].

Case Report

A 36 years old male, presented with abdominal pain for 2 days which was dull aching, diffuse, intermittent, associated with myalgia, fatigue and loss of appetite. There was one episode of vomiting, not blood stained or bilious. No associated previous history, Not a known case of DM & HTN. No other comorbidities with nill significance of family history, Non alcoholic, non smoker. On examination, patient was conscious, oriented, afebrile, anicteric, no pallor & no rash. Vitals – temp – 98°F, Pulse – 78/min, regular, BP – 110/70 mm hg, RR – 18/min, spo₂

– 98% on RA, CVS – s₁ s₂ heard no murmurs, RS – BAE (+), no added sounds, P/A – soft BS (+), fluid thrill (+), Splenomegaly (+), CNS – no focal Neurological deficit.

The second day patient sound with low GCS (6/15), intubated and kept on mechanical ventilation, imaging revealed main portal vein thrombosis, massive splenomegaly & cirrhosis. There was continuous bleeding in the nasogastric tube. Malena (+). Endoscopy done showed grade II oesophageal varices with gastric and duodenal varices. Banding done and glue injection therapy done. Patient developed massive ascites in 3 days of period. All investigations sent, it showed protein C & S deficiency, CECT abdomen – cirrhosis with portal HTN, periportal collaterals, massive splenomegaly 18.5 cm, multiple perigastric, periesophageal & gastrosplenic collaterals, massive ascites. Endoscopy showed esophageal varices. Patient was subsequently started on salt restriction with intake restriction, somatostatin analogue (octreotide) and proton pump infusion, β -blockers, lactulose, diuretics, aldosterone antagonist and liver proctelisis paracentesis done. Blood transfusion & prophylactic antibiotic given, TIPS procedure done & got discharged & followed up.

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Etiology

Several causes can be involved in the pathogenesis of PVT and frequently more than one coexist. A simple classification distinguishes between local (70%) and systemic (30%) risk factors (Tables 2 and 3).

Inflammatory abdominal foci (such as appendicitis,

diverticulitis, inflammatory bowel diseases, pancreatitis, cholecystitis, hepatic abscesses, and cholangitis), liver cirrhosis or tumors, represent the most common local thrombotic risk factors [6-9].

Malignancies, frequently of hepatic or pancreatic origin, are responsible for 21%-24% of overall cases of PVT [5,10-11]. Direct vascular invasion, compression by tumor mass, or a hypercoagulable state are the mechanisms involved in neoplastic PVT development; hormonal factors might also play a role in this process, especially in men [12-14].

PVT is common in patients affected by liver cirrhosis, with a risk related to the severity of the disease; the prevalence ranges from 1% at the earlier stages, to 30% in candidates of liver transplantation [7,15]. Moreover, in patients with a hepatocellular carcinoma, the incidence of PVT rises to 10% - 40% [4].

Table 1 : Prevalence of thrombotic risk factors in series of routinely investigated, consecutive adult patients with non tumorous and non cirrhotic, acute or chronic, (PVT)

Risk factor	PVT patients (%)
Myeloproliferative disorders	30-40
Atypical	14
Classical	17
Antithrombin deficiency	0-26
Protein C deficiency	0-26
Protein S deficiency	2-30
Factor V Leiden mutation	6-32
Prothrombin mutation	14-40
TT677 methylene tetrahydrofolate reductase (MTHFR) genotype	
Antiphospholipid syndrome	6-19
Hyperhomocysteinemia	12-22
Recent pregnancy	6-40
Recent oral contraceptive use	12

Table 2: Most frequent local risk factors for PVT.

Local risk factors for PVT (70%)
Cancer
Focal inflammatory lesions
Neonatal omphalitis, umbilical vein catheterization
Diverticulitis, appendicitis
Pancreatitis
Duodenal ulcer
Cholecystitis
Tuberculous lymphadenitis
Crohn's disease, ulcerative colitis
Cytomegalovirus hepatitis
Injury to the portal venous system

Splenectomy
Colectomy, gastrectomy
Cholecystectomy
Liver transplantation
Abdominal trauma
Surgical portosystemic shunting, TIPS
Iatrogenic (fine needle aspiration of abdominal masses etc)
Cirrhosis
Preserved liver function with precipitating factors (splenectomy, surgical portosystemic shunting, TIPS dysfunction, thrombophilia)
Advanced disease in the absence of obvious precipitating factors

Table 3: Most frequent systemic risk factors for PVT

Systemic risk factors for PVT (30%)

Inherited

Factor V Leiden mutation
Factor II (prothrombin) mutation
Protein C deficiency
Protein S deficiency
Antithrombin deficiency

Acquired

Myeloproliferative disorder
Antiphospholipid syndrome
Paroxysmal nocturnal hemoglobinuria
Oral contraceptives
Pregnancy or puerperium
Hyperhomocysteinemia
Malignancy

Other less common PVT local causes are adenopathy, systemic inflammatory response syndrome and surgical traumas to the portal venous system, such as porto systemic shunting, splenectomy, liver transplantation, ablative therapy for HCC, and fine needle aspiration of abdominal masses [1].

On the other hand, myeloproliferative disorders and prothrombotic conditions belong to the group of systemic risk factors, with a prevalence of about 40% and 60% respectively (table 1) [7,17].

Pathophysiology

As a consequence of portal vein obstruction, systemic and splanchnic hemodynamics undergo specific and important modifications [4]. On the cessation of portal blood flow, the liver loses its two thirds of its blood supply. Interestingly this condition is usually well tolerated and patients are often asymptomatic, while an acute arterial obstruction always leads to a severe hepatic dysfunction,

which is sometimes fatal. It is probably that the immediate activation of two compensatory mechanisms might supplement the loss of portal vein's contribution to liver blood flow. The first mechanism is "arterial vasodilation" of the hepatic artery, similar to that observed in portal vein clamping during liver surgery [5]. This "arterial rescue" is a kind of vascular reflex present in every organ with both an arterial and venous circulation and is capable of preserving liver function in the acute stages of PVT. The second compensatory mechanism is "venous rescue", consisting of the rapid development of collaterals to bypass the obstruction. This vascular neo-formation begins in a few days after portal vein obstruction and finalizes within 3 to 5 weeks [6, 7]. As a result, the thrombosed portal vein is replaced by a network of collateral vessels, called "cavernoma", connecting the two patent portions proximally and distally to the thrombus. Usually the original portal vein becomes a thin, fibrotic cord, which is difficult to visualize [8,9]. At this stage, the development of a hyperkinetic circulation, characterized by low systemic vascular resistance and a high cardiac output, is common [3].

Despite the activation of this complex system of support, the impairment of portal flow has important consequences on liver tissue. It has been demonstrated in rats, that the progressive obliteration of portal vein stimulates apoptosis of hepatocytes in the hypoperfused lobe [10]. While increasing the mitotic activity in the normal perfused one. The latter effect is well known and is employed therapeutically in respective liver surgery. However, this process results in a progressive loss of tissue and might be responsible for the impairment of hepatic synthetic function observed in advanced stages of portal vein obstruction [11].

Classification

PVT onset can be acute or chronic. This is an arbitrary distinction, which is sometimes difficult to apply in clinical practice; patients who develop symptoms such as abdominal pain, nausea, and fever within sixty days prior to hospital admission, might have an acute PVT development [74,75].

PVT can be classified into four categories, depending on the extension:

- (1) Confined to the portal vein beyond the confluence of the splenic vein;
- (2) Extended to the superior mesenteric vein, but with patent mesenteric vessels;
- (3) Extended to the whole splanchnic venous system, but with large collaterals; or
- (4) With only fine collaterals. This classification is

useful to evaluate a patient's operability and clinical outcome. In fact, when thrombosis is extended to both portal and mesenteric veins, the risk of bowel ischemia is considerable and mortality high, despite a lower risk of variceal bleeding.

Clinical Presentation

PVT can occur either in childhood or in adulthood, with the same incidence [73]. Clinical presentation always depends on the onset and the extent of the thrombosis and the development of collateral circulation [53].

Acute PVT

Intestinal congestion and ischemia are typical manifestations of acute PVT; abdominal pain or distension, diarrhea, rectal bleeding, nausea, vomiting, anorexia, fever, lactic acidosis, splenomegaly and sepsis might be variably present [54]. If the obstruction is not resolved quickly, intestinal perforation, peritonitis, shock, and death from multiorgan failure might occur [7]. On physical examination, the abdomen might be distended, but guarding is rare, except in case of intra-abdominal inflammation, intestinal infarction and perforation [17]. The majority of patients exhibit splenomegaly, while ascites is rare or, eventually, present before the development of a collateral circulation. This mild, transient, ascites is due to intestinal venous congestion in the absence of the mechanisms activated in liver cirrhosis [54].

Chronic PVT

On the other hand chronic PVT can be nearly asymptomatic, except for the presence of varices, cutaneous collaterals, or ascites. Typically patients with an advanced thrombosis do not always remember any previous trigger event or disease [17, 54]. The majority of patients develop esophageal varices, in contrast to acute PVT; an episode of gastrointestinal bleeding is reported as the first presenting symptom in about 20% - 40% of cases [6]. As this phenomenon is strictly time dependent, it is advisable to screen all PVT patients endoscopically, at diagnosis [29]. In cirrhotics with PVT, the risk of variceal bleeding is nearly 80-120 times higher than in patients without liver disease, although the outcome seems better [46].

Furthermore, hypersplenism and consequently, pancytopenia, are commonly present in chronic PVT [1]. However, if one branch of the portal vein is preserved and the portal pressure is quite normal, they may even be absent. Ascites and encephalopathy are uncommon and only transient. They are more frequent after an

episode of gastrointestinal bleeding or associated with renal failure or sepsis in older patients [7, 46]. Abnormalities of the extrahepatic biliary tree have been reported in more than 80% of patients with chronic PVT; compression by choledochal or periportal varices or by the cavernoma, pericholedochal fibrosis, and ischemic structuring are the principal reasons [53, 54].

Diagnosis

Imaging

The diagnosis of PVT can be quickly established by demonstrating the presence of solid material within the vasal lumen (table-4) [17]. Nowadays in developed countries, PVT is recognized at an early stage; cavernomatous transformation or the occurrence of gastrointestinal bleeding are rare. The clinical suspicion is often based on the incidental finding of hypersplenism, signs of portal hypertension or less frequently, symptoms of portal cholangiopathy. Ultrasonography (US) is usually the investigation of choice, with a sensitivity and specificity ranging between 60% and 100% [15], it can reveal the presence of solid, hyperechoic material into a distended portal vein or its tributaries, the presence of collateral vessels or a cavernoma [9, 17].

Doppler imaging can confirm the absence of flow in part or all the vasal lumen and if present, a cavernomatous transformation [17]. Recently the endoscopic use of ultrasound (EUS) was demonstrated to be 81% sensitive and 93% specific in PVT diagnosis [18] and to be capable of detecting small and non-occluding thrombi. It appears to be more accurate than US or computed tomography (CT) scans in discovering portal invasion by tumours [19]. However, the limit of EUS is the presence of a relatively blind area, which cannot be investigated, involving the distal superior mesenteric vein and the intrahepatic portion of the portal vein [18].

Incidentally, US is less reliable in determining the extension of the thrombus to the mesenteric circulation [21], instead, CT scanning and magnetic resonance imaging (MRI) can easily obtain this information and in addition, can estimate the impairment of the bowel and other adjacent organs. CT scanning is able to demonstrate hyperattenuating material in the portal vein lumen and the absence of enhancement after contrast injection. In addition, in hypoperfused areas, hepatic enhancement appears increased during the arterial phase and decreased during the portal phase. CT is also useful for the identification of the possible cause of the thrombosis or potential complications, such as bowel ischemia and perforation [17]. MRI might also confirm the vascular occlusion; at spin-echo MR, the clot appears isointense

on T1-weighted images, or hyperintense if recent, and usually has a more intense signal on T2 images. Gradient-echo MR might help to better evaluate any confusing spin-echo MR image [20]. Furthermore, contrast-enhanced MR angiography is useful to assess flow direction in the portal venous system and its patency, to identify a cavernomatous transformation, to determine the presence of varices, and to verify the correct function of surgical shunts [22, 23]. In addition, MR angiography has a high accuracy in the follow up of the portal venous system before and after liver transplantation [23, 24]. Moreover, MRI-true fast imaging with study state precision (true FISP) might overcome the difficulty of contrast injection in cases of poor venous access and the degradation of the images by respiratory motion [25].

Table 4: AASLD recommendations for diagnosis of Acute and Chronic PVT

AASLD recommendations for diagnosis of acute PVT:

1. Consider a diagnosis of acute PVT in any patient with abdominal pain of more than 24 hrs duration, whether or not there is also fever or ileus.
2. If acute PVT is suspected, computed tomography (CT) scan, before and after injection of vascular contrast agent, should be obtained for early confirmation of diagnosis. If CT scan is not rapidly available, obtain Doppler - sonography.
3. In patients with acute PVT and high fever, septic pylephlebitis should be considered, whether or not an abdominal source of infection has been identified and blood cultures should be routinely obtained.
4. In acute PVT, the possibility of intestinal infarction should be considered from presentation until resolution of pain. The presence of ascites, thinning of the intestinal wall, lack of mucosal enhancement of the thickened intestinal wall, or the development of multiorgan failure indicate that intestinal infarction is likely and surgical exploration should be considered.

AASLD recommendations for diagnosis of chronic PVT:

1. Consider a diagnosis of chronic PVT in any patient with newly diagnosed portal hypertension.
2. Obtain Doppler-sonography, then either CT scan or MRI, before and after a vascular contrast agent, to make a diagnosis of chronic PVT.
3. Base the diagnosis on the absence of a visible normal portal vein and its replacement with serpiginous veins.

Laboratory Investigations

In PVT patients, liver function is typically conserved. Laboratory investigations will be normal or quite normal, unless there is coexistence of a liver disease. However levels of prothrombin and other coagulation factors could be moderately decreased, while D-dimer is usually increased [7,17].

PVT is considered a milestone in the natural history of liver cirrhosis and it is related to serious complications, morbidity and mortality as previously discussed [26]. Thus, prevention is the first aim of PVT management in patients with an advanced liver disease. Recently several studies tried to identify the strongest predictive factors for PVT development in these patients. In the past, male sex, previous surgery or interventional treatment for portal hypertension, previous variceal bleeding, low platelet count and advanced liver failure have been associated with an increased risk of PVT development [2, 24, 28]. Interestingly, in a recent prospective study by Zocco et al., a portal flow velocity below 15 cm/s, at US-Doppler evaluation, was considered significantly predictive of PVT development, confirming the importance of Virchow's triad in the pathogenesis of vascular thrombosis.

Complications

Once the diagnosis has been reached, the severity of liver and other organs involvement should be assessed. Clinical and laboratory evaluation, as well as imaging, might be useful; the degree of the obstruction (complete or partial, limited or extensive) should be investigated. A partial thrombosis is often associated with few symptoms. Instead, a rapid and complete obstruction of the portal or mesenteric vein, without the involvement of the mesenteric venous arches, induces only intestinal congestion; the feature is a diffuse thickening of the intestinal wall, visible even without alterations in contrast enhancement. Generally, there are no signs of other organ failures and liver function is usually preserved, probably because the increased hepatic arterial blood flow supplants portal obstruction. In addition, collateral circulation develops rapidly from pre-existing veins in the porta hepatis within 2 to 3 days after the onset of acute thrombosis, particularly in the gallbladder wall [29-31]. All these manifestations are completely reversible, even if a spontaneous recanalization or a cavernomatous transformation occurs. In contrast, when thrombosis spreads to mesenteric venous arches, the consequence is intestinal ischemia or infarction. Common radiological findings are the thinning of the intestinal wall and the presence of defects of enhancement after intravenous contrast injection.

Prognosis

In non-cirrhotic and non-neoplastic patients, PVT has generally good outcome; exitus for gastrointestinal bleeding is uncommon [33-35]. Otherwise, Prognosis depends on the underlying liver disease [1, 8, 17, 21]. The overall mortality has been reported to be less than 10% in PVT chronic onset [9, 35], except for patients with malignancy or cirrhosis - about 26% [32] moreover, advanced age, malignancy, cirrhosis, mesenteric vein thrombosis, absence of abdominal inflammation, and serum levels of aminotransferase and albumin are associated with reduced survival [35]. Systemic risk factors, like MPD or other prothrombotic disorders, seem not to affect short-term survival [36].

In addition, acute PVT, when recognized and treated before the occurrence of intestinal infarction, has good prognosis [29, 37-40]. By contrast, in cases of bowel ischemia and multiorgan dysfunction or failure, patients in hospital mortality rate is approximately 20%-50% [29].

Treatment

Although spontaneous resolution of PVT has been reported in the literature [38, 39], a specific therapeutic management is mandatory to resolve portal vein obstruction and avoid serious complications. The goal of treatment is similar in acute and chronic PVT, and consists in correction of causal factors, prevention of thrombosis extension and achievement of portal vein patency. However, in case of long standing thrombosis, the management of complications related to portal hypertension and portal cholangiopathy has to be concurrently considered. Nowadays, anticoagulant therapy is the best way to obtain portal vein recanalization; however, there is no consensus on its application. Other modalities of treatment should be adopted in case of partial or absent PVT resolution [8,41]. Furthermore, some conditions should be considered in the assessment of anticoagulant therapy, such as recent old thrombosis, the presence of a thrombophilic condition, or a liver disease.

1. Anticoagulation in Acute PVT

Although PVT might be compared to other cases of deep vein thrombosis, there is no randomized controlled trial regarding the use of anticoagulants in acute PVT [41]. After 6 months of therapy, a complete recanalization has been reported in about 50% of patients, with good results in the case of mesenteric vein involvement and low incidence of complications. In contrast, in about 10% of cases, PVT is resistant to anticoagulants [33, 34, 37-40]. In addition, when intestinal infarction

occurs, anticoagulants administered prior to laparotomy seem to have a consistent benefit on survival [42-44].

What is certain is that, in acute PVT onset, the sooner the treatment is given the better the outcome will be; the rate of recanalization is about 69%, if anticoagulation is instituted within the first week after diagnosis, while it falls to 25% when instituted at the second week [6, 45].

2. **Anticoagulation in Chronic PVT**

Opinions regarding therapeutic options in chronic PVT are more controversial and significantly variable. At present, anticoagulant treatment is administered to only 30% of patients with chronic PVT, reflecting concerns about the use of anticoagulation in the presence of gastroesophageal varices, low platelet counts, and coagulation dysfunction [21]. However, the number of bleeding episodes in PVT patients receiving anticoagulant therapy did not increase, and in long-term follow-up studies, anticoagulants seem to be effective in preventing new thrombotic events with a low mortality [41, 46]. Incidentally, a pragmatic approach, such as endoscopic eradication of varices prior to commencement of anticoagulation, should be reasonable [21].

3. **Dose and Duration of Anticoagulants**

If thrombosis is recent and there is no underlying thrombophilic conditions, anticoagulation should be administered for 3-6 months, as a complete portal vein recanalization can occasionally be delayed [38, 47, 49]. Recently, a panel of experts recommended the application of anticoagulant therapy only in PVT patients with a proven thrombophilic disorder or familial history of venous thrombosis [49, 50]. Thereby obtaining an improvement in survival and reduction in risk of gastrointestinal bleeding [51, 52].

4. **Anticoagulation in Cirrhotic Patients**

The ubiquitous and long-term use of anticoagulants in cirrhotic patients with PVT should not be considered correct practice, until their safety and efficacy has been completely tested [53]. However, signs of intestinal ischemia or infarction, or an underlying prothrombotic disorder should be considered an indication for anticoagulants in cirrhotic patients, although only after an adequate prophylaxis for variceal bleeding [2, 41]. In candidates for liver transplantation with a high risk PVT (obstruction of more than 50% of

the portal vein), anticoagulation should be recommended, even if a scheduled prophylactic treatment has not been assessed [54, 56, 57].

5. **Thrombolytic Therapy**

Thrombolytic therapy given either into the systemic venous circulation, the superior mesenteric artery, or the portal vein via a transjugular or transhepatic route, is also effective to provide recanalization in acute PVT [58, 59]. However, efficacy is significantly lower and mortality increased in patients who undergo thrombolysis, if compared to conservative treatment [28, 59, 60]. Despite the high incidence of side effects, thrombolysis should be considered when initial anticoagulant therapy fails, even if there is no consistent evidence concerning in which conditions it should be preferred to anticoagulation [58]. Surgical thrombectomy is usually not recommended, as high morbidity and mortality have been reported; percutaneous transhepatic mechanical thrombectomy might also be effective in recent thrombosis, but vascular traumas are frequent and may stimulate rethrombosis.

Other approaches, such as transjugular intrahepatic portosystemic shunt placement, should be reserved for patients developing acute PVT before or after liver transplantation, or in alternative to thrombolysis when anticoagulation fails [63-64]. It seems to be effective in resolving portal biliopathy, ascites and portal hypertension, but it is not feasible if portal vein is not catheterizable or a cavernomatous vein cannot be dilated [65, 67].

Finally, shunt surgery (distal splenorenal shunt or Rex shunt, in children) might be applied as the last choice, and only in absence of splenic or superior mesenteric vein thrombosis [68]. After liver transplantation, PVT development is a rare but possible event, especially in the early postoperative period [16] and the incidence ranges between 1% and 2% [69].

Conclusion

PVT is relatively uncommon in the general population, but is more frequent among cirrhotic patients and represents a '*milestone*' in the natural evolution of liver disease. Local or systemic pro-thrombotic factors, alone or together, can play an important role in PVT pathogenesis, which is complex and different in each clinical context and in each patient. The consequent

changes in hepatic and splanchnic hemodynamic are responsible for a mild impairment in liver function, in absence of an overt liver disease, or can precipitate a preexistent metastable clinical status in cirrhotic patients. Moreover, PVT might have indirect effects on other abdominal organs, causing intestinal ischemia and infarction, or predisposition to vascular neof ormation and gastrointestinal bleeding. The identification of protein manifestations of PVT is essential to provide a prompt diagnosis, as the removal of the original trigger factor and early therapeutic management is crucial to preserve patient health and sometimes, life. The history of PVT has been characterized by difficulties in diagnosis and treatment, which, today, have almost been overcome. In the future, due to innovations in imaging and pharmaceuticals, clinical attention must be focused on the realization of a scheduled, preemptive, therapeutic approach to the patient, to better define the profile of toxicity and reduce side effects, especially in cirrhotic patients.

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