

## Case Report

# Portal vein thrombosis with protein C-S deficiency in a non-cirrhotic patient

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### ABSTRACT

There are several conditions that can lead to portal vein thrombosis (PVT), including including infection, malignancies, and coagulation disorders. A new condition of interest is protein C and S deficiencies, associated with hypercoagulation and recurrent venous thromboembolism. We report the case of a non-cirrhotic 24-year-old male diagnosed with acute superior mesenteric vein thrombosis and PVT and combined deficiencies in proteins C and S.

**Keywords:** Portal vein thrombosis, Protein C and S deficiency

### INTRODUCTION

The first report of portal vein thrombosis (PVT) was made in 1868. The pathogenesis of PVT has not been identified clearly, but recent studies report that it is related to systemic causes such as protein C, protein S, and antithrombin III deficiency disorder. That was a type of phlebothrombosis complicated with portal hypertension and a reduction of the blood flow to the liver. Owing to various symptoms in PVT, it is difficult to make an accurate diagnosis clinically. PVT causes portal hypertension and varix, and if severe, can cause variceal hemorrhage and ischemic bowel disease.<sup>1</sup>

The pathogenesis of PVT has not been identified clearly, but recent studies report that it is related to systemic causes such as protein C, protein S, and antithrombin III deficiency disorder.<sup>2</sup> However, there are very few studies of optimal treatment owing to the low incidence rate (less than 0.004%).<sup>3</sup> In Korea, there are several reports of acute PVT caused by oral contraceptives and pancreatitis, but few cases of PVT caused by a deficiency of anticoagulant factors and reperfused with anticoagulation therapy.<sup>4</sup>

PVT is classified into four categories: (1) thrombosis confined to the portal vein beyond the confluence of the splenic and superior mesenteric vein (SMV); (2) extension of thrombus into the SMV, but with patent mesenteric vessels; (3) diffuse thrombosis of splanchnic venous system, but with large collaterals; and (4) extensive splanchnic venous thrombosis, but with only fine collaterals. In all cases, patients with PVT should be tested for an underlying thrombophilic condition.<sup>5</sup> Hereditary thrombophilia as known to predispose for PVT include mutations of the prothrombin, or factor V, genes, and deficiency of one of the natural anticoagulant proteins C, S, or antithrombin.<sup>6,7</sup>

### CASE REPORT

Study present a case of a 24 year old male with chief complains of pain in abdomen from 10-15 days, vomiting from last 3-4day, and fever from 3-4 days. The pain in abdomen was generalized not radiating to any quadrant, he also had 2-3 episodes of vomiting per day since past 3-4 days which was non projectile, nonbilious, non-blood tinged. Patient also c/o low grade fever since 3-4 days.

No history of melena, haematochezia, haematemesis, loose stools, jaundice, weight loss, blood transfusion, any co morbidities, any previous surgery or similar complaints in past and no history of high risk behavior. But there was a history of Koch's contact 6 months before (brother) and addiction to tobacco since 4-5 years and smoking since 4-5 years, 1 packet daily with normal bladder, bowel and appetite.

On examination it was found patient was conscious, oriented to time, place and person. With vitals being stable with blood pressure of 100/70 and a pulse rate of 88/min, no icterus, edema, pallor, cyanosis or lymphadenopathy.

#### ***On systemic examination***

Per abdomen-soft, nontender, bowel sounds heard, with hepatomegaly and splenomegaly. Respiratory-b/l conducted sounds. Cardiovascular-s1s2+. Central nervous system was with no signs of encephalopathy.

Laboratory investigations showed hct of 12.6 hematocrit of 38%, mean corpuscular volume of 78.2fL, and, white cell count of 4.5/mm<sup>3</sup>, platelet count 199/mm<sup>3</sup>, prothrombin time 14 s, 97.6%, international normalized ratio (INR) 1.3. Serum chemistry values and urine, stool test were normal. Liver function test showed: albumin 4.7g/dL; total bilirubin 0.7mg/dL; alanine aminotransferase 59.7 U/L; aspartate aminotransferase 65.9U/L; alkaline phosphatase was 139.1 (32-91), Viral B and C antibodies were negative.

His antiphospholipid antibodies and cardiolipin antibodies were negative. A thrombophilia workup, revealed normal homocysteine blood level; protein C activity, 63% (normal 70%-140%)] and protein S activity, 38% (normal 65%-140%)] were found; antithrombin III levels were 104% (normal 75%-125%), lupus anticoagulant-41.70 (36-50)

Esophagogastroduodenoscopy revealed few subepithelial hemorrhages in fundus of stomach. Ultrasonography of the abdomen showed acute to subacute thrombosis of the main portal vein and intrahepatic portal vein radicle, the splenic vein and the superior mesenteric veins. Portal vein dilated measuring (2.9cm). The ivc and hepatic veins show no thrombosis.

The computed tomography scan of the abdomen showed thrombosis of main portal vein, RT and LFT portal branches, splenic vein, superior mesenteric vein and proximal portion of the inferior mesenteric vein causing near complete luminal occlusion. Administration of warfarin (at a dose of 5 mg twice daily) and subcutaneous injection of low molecular weight heparin (enoxaparin, 1 mg/kg, twice daily) was promptly started. At the time of discharge, the maintenance dose of warfarin was 3 and 5 mg per day (target INR: 2-3). The abdominal Doppler ultrasound, performed just before discharge, revealed that

the portal vein was still completely occluded by thrombus but decreased in diameter (2.5cm). Repeat CT scan of the patient revealed reduction in the size of the thrombus. The patient is currently on warfarin at dose 2 maintaining an INR of 2.

#### **DISCUSSION**

Portal vein thrombosis, previously known as Cauchois–Eppinger–Frugoni syndrome, is a form of venous thrombosis affecting the hepatic portal vein, which can lead to portal hypertension and reduction in the blood supply to the liver. The incidence of PVT among patients without cirrhosis is unclear. It is thought to account for 5 to 10 percent of patients with portal hypertension in developed countries and up to a third of patients in developing countries, because of an increased frequency of infectious complications that predispose to PVT.

Portal vein thrombosis (PVT) in patients with a previously healthy liver is thought to be due to inherited or acquired prothrombotic states.

#### ***Disorders of coagulation in portal vein thrombosis<sup>5</sup>***

##### *Inherited*

- Factor V Leiden deficiency
- Antithrombin III deficiency
- Protein S deficiency
- Protein C deficiency
- Prothrombin gene mutation

##### *Acquired*

- Lupus anticoagulant syndrome
- Liver disease
- Burns
- DIC
- Sepsis
- Malignancy
- Oral contraceptives
- Pregnancy
- Myeloproliferative disorders

Portal vein obstruction does not affect the liver function unless the patient has an underlying liver disease such as cirrhosis. This is partially due to a rapid arterial buffer response, with compensatory increased flow of the hepatic artery maintaining the total hepatic blood flow. Formation of collaterals occurs rather rapidly as well, and they have been described as early as 12 days after an acute thrombosis, though the average time to formation is approximately 5 weeks.

In India, extrahepatic portal vein obstruction is reported more frequently; in one study, the incidence even exceeded reported cases of cirrhosis. Of all cases of portal hypertension in developing countries, 40% are

attributed to portal vein obstruction, presumably secondary to an increased incidence of pylephlebitis associated with abdominal infections. No sex differences have been reported overall, except for a slight male predominance in patients whose obstruction is secondary to cirrhosis.

In the acute phase, the presentation of portal vein obstruction is relatively uncommon and easily missed because the patient may be asymptomatic. Symptoms most often begin in the chronic or subacute stage. Patients can present emergently with sudden onset of right upper quadrant pain, nausea, and/or fever. Alternatively, the symptoms of the primary infectious and inflammatory condition that led to portal vein obstruction predominate (e.g., right lower quadrant pain in appendicitis).

Anticoagulation in patients with acute/recent portal vein thrombosis, studied only retrospectively, has been shown to recanalize the thrombosed vessel in more than 80% of cases. This is essential to prevent advancement of thrombosis or rethrombosis in patients with inherited coagulation disorders in which lifelong anticoagulation therapy is recommended once variceal control has been achieved. Anticoagulation therapy has also been recommended after shunt surgery to prevent rethrombosis. In complicated cases of portal vein thrombosis with variceal bleeding shunt surgery is used, we can also use TIPPS procedure the ultimate measure is liver transplantation if not responding to any management therapy.

In Mexico, Majluf-Cruz et al, studied 36 patients who had thrombosis-related portal hypertension and found an incidence of 30% of protein C deficiency, whereas 9% had protein S deficiency in patients with primary thrombophilia.<sup>6,8</sup> Similarly in Mexican patients with non-cirrhotic PVT, 31% had protein C deficiency.<sup>9</sup> However, a French study has found a high number of patients with non-cirrhotic PVT showed Protein S deficiency and in a study from United Kingdom, protein S deficiency was found in 38% of patients with PVT.<sup>10,11</sup>

Other cases have also reported C and S protein deficiencies in patients with idiopathic portal hypertension accompanied by PVT.<sup>12</sup> Valla et al, argue that C and S protein deficiencies do not explain the majority of idiopathic portal thrombosis.<sup>9</sup> Nevertheless, we agree with others that measurements of C and S proteins should be performed in patients with portal thrombosis when no overt cause is located.

However, since a low number of cases of PVT may be due to underlying hereditary anticoagulant protein deficiency, this can only be confirmed by careful investigation of background of family members, preferably including both parents. The overall prognosis is good, with 75% of patients alive after 10 years and an overall mortality rate of less than 10%.

In conclusion, our case shows that PVT can be provoked by protein C and S deficiency and that the PVT can be recanalized by short-term low molecular heparin plus oral warfarin therapy. Further study is needed to investigate the target INR, the period of administration, and the dosage and duration for relapse prevention in treatment with oral anticoagulants.

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