Portal Vein Thrombosis

Yogesh K. Chawla, Vijay Bodh

Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India

Portal vein thrombosis is an important cause of portal hypertension. PVT occurs in association with cirrhosis or as a result of malignant invasion by hepatocellular carcinoma or even in the absence of associated liver disease. With the current research into its genesis, majority now have an underlying prothrombotic state detectable. Endothelial activation and stagnant portal blood flow also contribute to formation of the thrombus. Acute non-cirrhotic PVT, chronic PVT (EHPVO), and portal vein thrombosis in cirrhosis are the three main variants of portal vein thrombosis with varying etiological factors and variability in presentation and management. Procoagulant state should be actively investigated. Anticoagulation is the mainstay of therapy for acute non-cirrhotic PVT, with supporting evidence for its use in cirrhotic population as well. Chronic PVT (EHPVO) on the other hand requires the management of portal hypertension as such and with role for anticoagulation in the setting of underlying prothrombotic state, however data is awaited in those with no underlying prothrombotic states. TIPS and liver transplant may be feasible even in the setting of PVT however proper selection of candidates and type of surgery is warranted. Thrombolysis and thrombectomy have some role. TARE is a new modality for management of HCC with portal vein invasion. (J Clin Exp Hepatol 2015;5:22–40)

Portal vein thrombosis (PVT) refers to thrombosis that develops in the trunk of the portal vein including its right and left intrahepatic branches and may even extend to the splenic or superior mesenteric veins or towards the liver involving intrahepatic portal branches. PVT occurs either in association with cirrhosis or malignancy of liver or may occur without an associated liver disease. The terminology of Extra Hepatic Portal Venous Obstruction (EHPVO) refers to the development of portal cavernoma in the absence of associated liver disease. EHPVO should be considered as a separate entity. Portal vein thrombosis is an important cause of non-cirrhotic prehepatic portal hypertension all over the world.

Balfour and Stewart described the first case of PVT in 1868 in a patient with ascites, splenomegaly and variceal dilation.[1] Since then portal vein thrombosis has been well studied and described in patients with or without cirrhosis. The prevalence of PVT in compensated liver disease has been reported to be 0.6–16%, 15% (5–26%) in patients awaiting liver transplantation and upto 36% in explanted liver on histopathology.[2–4] PVT is seen in upto 35% of cirrhotic patients with hepatocellular carcinoma.[5,6] The lifetime risk of PVT in general population is reported to be 1%.[7] This review article is mainly focused on portal vein thrombosis in non-cirrhotic population-acute (recent thrombosis), chronic long standing (extrahepatic portal venous obstruction) and in patients with cirrhosis.

ETIOLOGY

The pathophysiology of portal vein thrombosis encompasses one or more features of Virchow's triad, viz., reduced portal blood flow, a hypercoagulable state or vascular endothelial injury as in Figure 1. Based on the three pathogenetic mechanisms, the etiological risk factors for non-cirrhotic and cirrhotic PVT will be discussed separately.

Keywords: PVT, prothrombotic, acute and chronic, imaging, anticoagulation

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Address for correspondence: Yogesh K. Chawla, Professor and Head, Department of Hepatology, Post Graduate Institute of Medical Education and Research, Chandigarh 160012, India. Tel.: +91 172 2756344x6335; fax: +91 172 2744401

E-mail: ykchawla@gmail.com

Abbreviations: ACLA: anti-cardiolipin antibody; AFP: alpha feto protein; BCS: Budd-Chiari syndrome; CDUS: color doppler ultrasonography; CT: computed tomography; CTP: Child Turcotte Pugh; EHPVO: extra hepatic portal venous obstruction; EST: endoscopic sclerotherapy; HCC: hepatocellular carcinoma; HVPG: hepatic venous pressure gradient; IGF-1: insulin like growth factor-1; IGFBP-3: insulin like growth factor binding protein-3; INR: international normalized ratio; JAK-2: Janus kinase 2; LA: lupus anticoagulant; LMWH: low molecular weight heparin; MELD: model for end stage liver disease; MPD: myeloproliferative disorder; MRI: magnetic resonance imaging; MTHFR: methylenetetrahydrofolate reductase; MVT: mesenteric vein thrombosis; OCPs: oral contraceptive pills; PAI-1 4G-4G: plasminogen activator inhibitor type 1- 4G/4G genotype; PNH: paroxysmal nocturnal hemoglobinuria; PV: portal vein; PVT: portal vein thrombosis; PWUS: Pulsed Wave ultrasonography; SMA: superior mesenteric artery; SMV: superior mesenteric vein; RFA: radio frequency ablation; rtPA: recombinant tissue plasminogen activator; TAFI: thrombin activatable fibrinolysis inhibitor; TARE: Trans arterial radioembolization; TB: tuberculosis; TIPS: transjugular intrahepatic portosystemic shunt; UFH: unfractionated heparin

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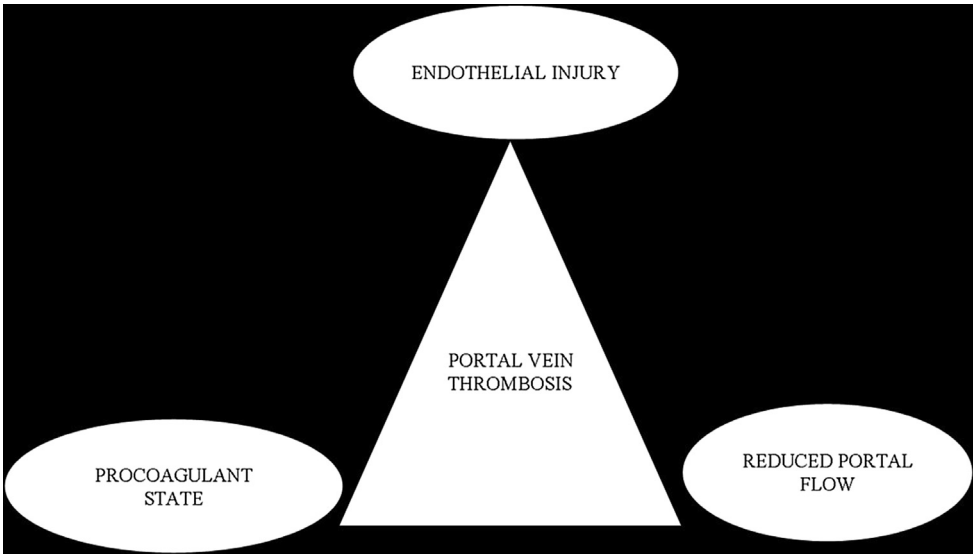

Figure 1 Virchow's triad for portal vein thrombosis.

Acute Non-cirrhotic Portal Vein Thrombosis

Procoagulant State

Various prothrombotic states leading to portal vein thrombosis have been identified (Table 1). Significant advances over the last decade have shown the earlier labeled idiopathic cases now being associated with thrombophilic conditions which are identified in approximately 60% of patients and an additional local predisposing factor in 30–40% of cases. In upto 80% cases the underlying cause is identified when rigorously searched for.[8–13] In some cases multiple prothrombotic factors may be associated in the development of PVT.[14–16] In one study one or more risk factors namely prothrombotic state or abdominal inflammation was present in 87% of patients.[17] Amongst the thrombophilic states, primary myeloproliferative disorders (MPD) are common in 30.5%. Occult MPD as a cause of PVT is seen in 16.7% and classical MPD in 13.8%.[18] The diagnosis of myeloproliferative disorders as a cause of PVT has increased by 20% with the identification of Janus kinase 2 (JAK 2) V617F gene mutation. The presence of JAK 2 mutation is seen in around 17–35% patients of PVT. It is now recommended by the WHO as a major diagnostic criterion for the diagnosis of MPD.[19–21] PVT is a manifestation of myeloproliferative disease in 22–48% of patients. In the West, latent MPD has been reported in 58% of patients with idiopathic PVT and 51% of these developed overt MPD on follow up.[22] A recent study reported PVT as the first manifestation of MPD in 70% (31 of 44 patients).[23] Meta analysis of myeloproliferative disorders in PVT showed that the mean prevalence of MPD is 31.5% (95% CI 25.1–38.8%) and JAK2 mutation is 27.7% (95% ci 20.8–35.8). JAK2 and MPD both are more frequent in BCS than PVT. JAK2 mutation in splanchnic venous thrombosis without MPD features was able to identify MPD in 15.4% of PVT patients.[24] In Asians, the prevalence of JAK2 mutation is 24–26.6% in non-cirrhotic non-malignant PVT versus 1.4% in cirrhosis with PVT.[25,26] An Indian study reported 14% prevalence of JAK2 mutation in portal vein thrombosis out of 58 patients of intra-abdominal venous thrombosis (which included portal vein thrombosis and Budd-Chiari syndrome).[27] Other prothrombotic conditions that cause PVT include paroxysmal nocturnal hemoglobinuria (PNH), antiphospholipid syndrome, hyperhomocysteinemia, inherited prothrombotic disorders such as protein C (in 0–9.1%), S (0.9–30%) and antithrombin III deficiencies (0–4.5%) and less frequently factor V Leiden mutation (1.3–7.6%), factor II mutation (G20210A in 0–22%) and methylenetetrahydrofolate reductase (MTHFR) gene mutation.[9–11] These inherited disorders may be a secondary phenomenon rather than primary, since they are produced from the liver and may be affected in parenchymal liver disease. They may ultimately be confirmed by investigating first degree relatives.[9,12,28] Recently mutation in thrombin activatable

Table 1 Prothrombotic Causes of Portal Vein Thrombosis.

Inherited prothrombotic disorders
☐ Factor V Leiden mutation
☐ Factor II gene mutation
☐ Protein C deficiency
☐ Protein S deficiency
☐ Antithrombin III deficiency
Acquired thrombophilic disorders
☐ Primary myeloproliferative disorders
☐ Paroxysmal nocturnal hemoglobinemia
☐ Antiphospholipid syndrome
☐ Hyperhomocysteinemia
☐ Increased factor VIII levels
☐ Thrombin activatable fibrinolysis inhibitor gene (TAFI)