Portal Vein Thrombosis in Cirrhosis

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Portal vein thrombosis (PVT) is being increasingly recognized in patients with advanced cirrhosis and in those undergoing liver transplantation. Reduced flow in the portal vein is probably responsible for clotting in the spleno-porto-mesenteric venous system. There is also increasing evidence that hypercoagulability occurs in advanced liver disease and contributes to the risk of PVT. Ultrasound based studies have reported a prevalence of PVT in 10–25% of cirrhotic patients without hepatocellular carcinoma. Partial thrombosis of the portal vein is more common and may not have pathophysiological consequences. However, there is high risk of progression of partial PVT to complete PVT that may cause exacerbation of portal hypertension and progression of liver insufficiency. It is thus, essential to accurately diagnose and stage PVT in patients waiting for transplantation and consider anticoagulation therapy. Therapy with low molecular weight heparin and vitamin K antagonists has been shown to achieve complete and partial recanalization in 33–45% and 15–35% of cases respectively. There are however, no guidelines to help determine the dose and therapeutic efficacy of anticoagulation in patients with cirrhosis. Anticoagulation therapy related bleeding is the most feared complication but it appears that the risk of variceal bleeding is more likely to be dependent on portal pressure rather than solely related to coagulation status. TIPS has also been reported to restore patency of the portal vein. Patients with complete PVT currently do not form an absolute contraindication for liver transplantation. Thrombectomy or thromboendovenectomy is possible in more than 75% of patients followed by anatomical end-to-end portal anastomosis. When patency of the portal vein and/or superior mesenteric vein is not achieved, only non-anatomical techniques (reno-portal anastomosis or cavo-portal hemitransposition) can be performed. These techniques, which do not fully reverse portal hypertension, are associated with higher morbidity and mortality risks in the short term. (J Clin Exp Hepatol 2013;4:320–331)

Non-tumoral portal vein thrombosis (PVT) is not an uncommon complication occurring during the course of liver cirrhosis, frequently in its advanced stages. Alteration of blood flow within the portal vein probably plays an important role in the development of PVT with a possible contribution from the altered coagulation state in end stage liver disease. There has been an increased recognition of PVT due to frequent diagnostic imaging in patients with cirrhosis and especially in those awaiting transplantation. Development of PVT in a cirrhotic patient is expected to lead to an increase in portal pressure and decreased blood flow to the liver, thus increasing the risk of gastrointestinal bleeding, worsening of liver function, and worsening of ascites. However, the exact impact of PVT on the natural history of cirrhosis remains unclear. There are asymptomatic cirrhotic patients in whom PVT is detected incidentally on imaging and it is unclear whether it would be beneficial to treat such patients. At present there is no consensus regarding the anticoagulant drug, duration of treatment and monitoring to patients with cirrhosis and PVT. Presence of PVT has relevance during liver transplantation, since restoring both portal and arterial blood flow to the allograft is a necessary condition for liver transplantation to be successful. In this setting, PVT may be a source of technical difficulties with a negative impact on outcome. Occasionally, it may represent a definitive contraindication for transplantation. This review examines issues concerning the incidence, predisposing factors, pathogenesis and management of non-tumoral PVT in patients with cirrhosis and in candidates for liver transplantation. We also discuss surgical options in patients with extensive thrombosis undergoing liver transplantation.

Keywords: portal vein thrombosis, cirrhosis, anticoagulation, portocaval hemitransposition

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Abbreviations: PVT: portal vein thrombosis; MELD: model for end stage liver disease; PT: prothrombin time; INR: international normalized ratio; DVT: deep vein thrombosis; PE: pulmonary embolism; MTHFR: methylene-tetrahydrofolate reductase; TEG: thromboelastography; US: ultrasonography; LMWH: low molecular weight heparin; VKA: vitamin K antagonists; TIPS: transjugular intrahepatic portosystemic shunt; EVL: endoscopic variceal ligation; SMV: superior mesenteric vein; IVC: inferior vena cava

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Table 1 Hemostatic abnormalities associated with liver disease.

Factors promoting bleeding	Factors promoting thrombosis
Decreased levels of the following	**Decreased levels of the following**
Coagulation factors II, V, VII, IX, X, XI	Protein C
α2-antiplasmin	Protein S
Thrombin-activatable fibrinolysis inhibitor	Protein Z
Histidine-rich glycoprotein	Antithrombin α2-macroglobulin
Platelet abnormalities	Heparin cofactor II
Thrombocytopenia	Plasminogen
Impaired platelet function	**Increased levels of the following:**
Impaired platelet–wall interaction	Factor VIII
Enhanced platelet inhibition by nitric oxide and prostacyclin	von Willebrand factor
Fibrinogen abnormalities	
Qualitative	
Quantitative	
Increased level of plasma tissue-type plasminogen activator	
Nutritional deficiency (vitamin K, folate)	

PREVALENCE

The prevalence of PVT in cirrhotic patients is quite variable and has been reported from 1% to 28% depending upon the modality used for diagnosis and whether PVT was detected radiologically or intra-operatively at the time of liver transplantation.[1–11] Studies based on ultrasonography have reported a prevalence of 10%–28%, in unselected cirrhotic patients excluding those with hepatocellular carcinoma.[8–11] Maruyama et al did a retrospective analysis of 150 patients with hepatitis B or C related cirrhosis followed up for a median period of 66 months and reported a cumulative overall incidence of PVT of 12.8% at 1 year, 18.6% at 3 years, 20% at 5 years, and 38.7% at 8–10 years. Majority of these patients (73.8%) had partial PVT.[9] The prevalence of PVT most likely increases with the severity of cirrhosis. It has been reported to be quite low (1%) in patients with well compensated cirrhosis[2] while it is reported to be 8%–26% in decompensated cirrhotics awaiting liver transplantation.[3–7] The prevalence of PVT in candidates for transplantation seems to be similar to that found in cirrhotic patients who were not necessarily evaluated for transplantation but had similar disease severity.[1,8,12] It has been observed that at the time of evaluation for transplant, the model for end stage liver disease (MELD) and Child-Pugh scores seems to be higher in patients with PVT than in those without.[1,6] A significant number of patients may have unrecognized PVT. In recent series, up to 50% of patients with PVT were detected for the first time at the time of transplant surgery.[3,13] This may be due to either false negatives on imaging or to PVT occurring while on the waiting list. Even in patients undergoing systematic ultrasound at close intervals of three months, the rate of previously unrecognized thrombosis remains relatively high.[13] In patients waiting for transplant, the 12-month risk incidence of developing PVT has been reported in one study to be 7%.[3]

PATHOPHYSIOLOGY

The development of portal vein thrombosis in patients with end stage liver disease is a multifactorial process, resulting primarily from a reduction in portal blood flow and hypercoagulability. Traditionally, cirrhosis is considered as a hypocoagulable state and the degree of prolongation of prothrombin time (PT) and international normalized ratio (INR) has been taken as a marker of the severity of coagulopathy. The INR has been designed primarily to assess hypocoagulability in patients on vitamin K antagonists. In patients with liver disease it probably overestimates the bleeding risk.[14] This might explain the paradox of the poor prediction of bleeding in cirrhotics even with marked prolonged of conventional coagulation tests. It appears that in the setting of hepatic synthetic impairment, both pro- and anticoagulant proteins are reduced to a similar degree and the net result in most cirrhotic patients is a compensated hemostatic balance with no tendency for bleeding or thrombosis.[15] (Table 1). Various clinical as well as in-vitro studies have actually shown that some patients with cirrhosis may have a thrombotic potential.[16]

All procoagulant factors except factor VIII are reduced in hepatic insufficiency. By contrast, the levels of factor VIII/vWF are increased in cirrhosis.[15,17] Since all of the components in the "extrinsic" pathway are produced by hepatocytes, the degree of prolongation of the PT has been used extensively as a measure liver synthetic function. However, even anticoagulants such as Proteins C and S as well as the levels of circulating protease inhibitors are reduced in hepatic insufficiency.[18,19] The physiologic effects of a deficiency of anticoagulants is not reflected in the PT or APTT, which measure only the procoagulant side of the hemostatic pathway. In vivo it is always the balance between the procoagulant and anticoagulant factors that ultimately determines whether bleeding, thrombosis, or appropriate hemostasis will occur in a particular setting. The hemostatic balance in liver disease can be thought of not as intrinsically pro- or anticoagulant, but rather as a state in which there is a reduced ability to maintain this balance. In cirrhosis, there is a relatively balanced reduction in both pro- and