Portal Vein Thrombosis

20

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Currently available noninvasive imaging procedures (ultrasound, computed tomography and magnetic resonance) now allow for an accurate diagnosis of portal vein thrombosis (PVT). The routine use of these imaging procedures has resulted in an increased recognition of PVT in patients with cirrhosis. With increasing awareness, several issues, mostly concerning causes, consequences, and therapy of PVT, have arisen, which this chapter discusses.

Definition

PVT is characterized by a thrombus occupying part (partial thrombosis) or whole (occlusive thrombosis) of the lumen of the portal vein. Isolated thrombosis of the left or right portal vein branches is usually included in the entity PVT. However, isolated splenic or superior or inferior mesenteric vein thromboses are considered separate entities. Several classifications have been proposed to grade the cross-sectional occupancy of the lumen, as well as the extent of the thrombus upstream (into the splenic and superior mesenteric veins) and downstream (into the portal vein and its branches; reviewed by Rodriguez-Castro et al. [1]. The widely used classification by Yerdel et al. [2] is presented in Table 20.1. It should be emphasized that this classification has been designed mostly to evaluate the impact on liver transplantation (LT) rather than to make an accurate anatomic or physiologic description of the obstruction. In adults, portal cavernoma (also named cavernous transformation of the portal vein) is usually assumed to be a *sequela* of past PVT.

Epidemiology

Estimates of the prevalence of PVT have fallen into a relatively broad range (about 4–25%), probably due to variations in the characteristics of the patients and the definition used to define PVT [1, 3, 4]. Overall, it appears that in patients with cirrhosis admitted to hospital but otherwise unselected, the prevalence of partial and occlusive PVT is in the order of 7–10% and 2–4%, respectively. The incidence of PVT has been reported 7.8% over a mean follow-up period of 12 months in patients wait-listed for LT [5], 16% over a mean follow-up period of 16 months in patients participating in an endoscopic sclerotherapy program after variceal bleeding [6], and 10.7% by 5 years when assessed prospectively in patients initially with Child A cirrhosis and no hepatocellular carcinoma (HCC) [7].

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Table 20.1 Grading of portal vein thrombosis according to Yerdel et al. [2]

Grade 1. Cross-sectional obstruction of less than 50% of the portal vein lumen
Minimal or absent extension into the superior mesenteric vein
Grade 2. Cross-sectional obstruction of more than 50% of the portal vein lumen
Minimal or absent extension into the superior mesenteric vein
Grade 3. Complete obstruction of the portal vein and proximal superior mesenteric vein
Patent distal superior mesenteric vein
Grade 4. Complete obstruction of the portal vein, proximal, and distal superior mesenteric vein

Causal Factors

The causal factors most commonly implicated in the development of PVT are listed in Table 20.2. Searching for possible causes in patients with cirrhosis has generated many data. However, the cross-sectional design of most studies makes it difficult to infer whether cause or consequence explains the observed associations with PVT. Cross-sectional studies have shown PVT to be associated with smaller liver weight, higher model for end-stage liver disease (MELD), or Child–Pugh scores, ascites, and encephalopathy [4, 5, 8, 9]. A recent prospective study in patients with compensated cirrhosis at baseline found that PVT developed more frequently in patients with features of initially more severe liver disease, but there was no evidence for a direct temporal relationship between progression of liver disease and the occurrence of PVT [7]. Therefore, it remains unclear if progression of liver disease causes the development of PVT.

In patients with cirrhosis, PVT has been associated with decreased levels of coagulation inhibitors [9–11]. The direction of this association is likewise difficult to interpret because advanced liver disease induces a decrease in plasma levels of coagulation inhibitors (particularly protein C, but also protein S and antithrombin). Molecular studies of Factor V Leiden and prothrombin gene mutation have given inconsistent results regarding any association with the development of PVT [10, 11].

Recent studies have shown that contrary to general belief, thrombin generation capacity is preserved in plasma from patients with cirrhosis (provided platelet counts are above 60,000/μL), which contrasts with the decreased levels of most coagulation factors [10]. This apparent paradox is actually explained by a simultaneous decrease in the plasma levels of both coagulation inhibitors and most coagulation factors. Furthermore, a degree of resistance to the activation of the protein C pathway system has been shown, corresponding to a procoagulant state. This pro-

Table 20.2 Features associated with PVT and which could be causal or precipitating factors

Age
Obesity
Diabetes
Underlying thrombophilia (factor V Leiden or prothrombin gene mutation)
Alcohol as a cause for cirrhosis
Liver atrophy
High MELD or Child–Pugh score
Splenectomy
Past surgery for portal hypertension
Endoscopic sclerotherapy
Decreased portal vein blood flow velocity
Large spontaneous portosystemic shunts

MELD model for end-stage liver disease, *PVT* portal vein thrombosis

coagulant state could be related to the marked decrease in plasma protein C levels, together with the marked increase in plasma factor VIII levels. The magnitude of these changes parallels the severity of cirrhosis. The clinical relevance of these laboratory changes is suggested by epidemiological evidence for an increased risk of venous thromboembolism in patients with cirrhosis. However, the data linking procoagulant changes with an increased risk of venous thrombosis in general—and PVT in particular—are still lacking.

A prospective longitudinal study disclosed a strong association of reduced portal vein blood flow velocity at baseline with the subsequent (1-year) development of PVT, independent of baseline MELD score [12]. In another study, however, the decrease in portal blood flow velocity with time was not found to be an independent factor for the later development of PVT [7]. The limitations in assessing portal blood flow velocity by noninvasive means cannot be ignored. This area clearly deserves further study.

Several surveys found PVT to be associated with previous splenectomy, surgical portosystemic shunting, or endoscopic therapy for esophageal varices [3, 9, 13]. However, in the absence of randomized control trials, it is not possible to assess whether surgery directly caused PVT, or whether the need for surgery (i.e., severe portal hypertension) was a marker for a greater risk of developing PVT.

Alcoholic cirrhosis, diabetes, and obesity have been associated with the development of PVT [13, 14]. However, a comprehensive assessment, taking into account all the possible causal factors for cirrhosis and particularly the metabolic syndrome, remains to be performed.

Diagnosis

Routine imaging for HCC screening is the most frequent situation in which PVT is currently recognized, followed by a recent complication of cirrhosis, including gastrointestinal bleeding; and much less commonly, features of intestinal ischemia [4, 9]. It is difficult to determine whether symptoms or complications, if any, are directly related to the development of PVT or whether they led to a fortuitous uncovering of PVT. PVT in patients with cirrhosis does not appear to induce clinical or laboratory features of hepatic ischemia. However, among patients with cirrhosis, and acute ischemic hepatitis related to bleeding, the prevalence of PVT was 29% [15], which is about twice the prevalence expected among unselected patients with cirrhosis and acute bleeding (16%) [16].

An accurate diagnosis can be obtained at Doppler ultrasound of the portal vein and its main branches [17]. Doppler assessment is needed to avoid a false-negative result at ultrasound where a void-appearing portal vein can actually be occupied by a fresh thrombus. Enhanced computerized tomography (CT) or magnetic resonance imaging (MRI) confirms the diagnosis of PVT. It may be easier to assess the degree (partial or occlusive) and the extent (venous segments involved) at CT scan or MRI than at ultrasound.

The main differential diagnosis for PVT in patients with cirrhosis is portal venous invasion by a malignant tumor (usually HCC; Table 20.3). This entity has been mistakenly referred to as "malignant PVT," although the obstruction is not related to thrombosis but to tumor ingrowth. The main differential feature is enhancement of the endoluminal material at the arterial phase of a CT or MRI scan [18, 19]. Additional features favoring a diagnosis of tumor invasion include

Table 20.3 Features of portal venous obstruction which suggest tumor invasion rather than nonmalignant thrombosis

Enhancement of solid endoluminal material at the arterial phase of contrast medium injection (contrast medium-enhanced ultrasound, computed tomography or magnetic resonance imaging)
Washout of solid endoluminal material at the portal or late phase of contrast medium injection
Marked enlargement of portal vein lumen at the level of obstruction (>5 cm)
Vicinity to a nodule of hepatocellular carcinoma

proximity to a typical HCC nodule, a markedly enlarged portal vein, and washout of the endoluminal material at the portal and late phase [18, 19]. It is almost impossible to differentiate pure tumor invasion from tumor invasion with superimposed thrombosis. The clinical relevance of the latter distinction is doubtful, whereas the differentiation of pure thrombosis from malignant invasion is critical. A marked elevation in serum α-fetoprotein level may be seen with malignant vascular invasion.

In some patients, particularly those with large extrahepatic portosystemic shunts, portal flow is reversed (hepatofugal) or stagnant. Rarely, in such patients, the portal vein may not even be visible at all.

Course and Impact

A spontaneous decrease in size or resolution of PVT has been reported in up to 40% of patients at subsequent 3–6-month imaging [7, 20–22]. However, extension has also been reported in up to 72% of patients not given anticoagulation [23]. Data are missing to clarify whether resolution is influenced by the partial or occlusive nature of the thrombus and the length of its extent. Short-term recurrence after disappearance also appears to be common but not constant [24]. Development of a portal cavernoma seems to be extremely unusual in patients with a persistent thrombus [7, 21, 22]. Therefore, venous changes following acute PVT differ considerably when cirrhosis is present from when it is absent [25].

The impact of PVT on outcome remains difficult to ascertain. Table 20.4 lists features associated with the development of PVT. As noted above, the association of PVT with the severity of cirrhosis could be explained by PVT causing liver disease to worsen. Indeed, PVT could exacerbate portal hypertension by superimposing a prehepatic block to the intrahepatic block, precipitating gastrointestinal bleeding and ascites formation, increasing portosystemic shunting and encephalopathy. Furthermore, by decreasing portal perfusion, PVT could induce parenchymal atrophy and worsen hepatic dysfunction. Studies that address this issue are sparse. In a prospective study, the development of PVT at any time during the course of initially compensated cirrhosis was not associated with a subsequent progression of liver disease [7]. Similarly, retrospective but longitudinal surveys disclosed no association between the persistence or the resolution of PVT and the progression of liver disease [21, 22]. In a recent controlled trial, enoxaparin administration for 48 weeks prevented the progression of liver disease, much more so than the development of PVT [26]. Therefore, it is unlikely that the obstruction to portal flow, created by a thrombus, explains the totality of the association between PVT and progression of liver disease. Actually, three *scenarios* could explain the association of PVT with liver disease progression: (i) advanced liver disease could precipitate the development of PVT, (ii) PVT could induce a progression of liver disease, and (iii) a common determinant (e.g., disordered hepatic or intestinal circulation) could independently and simultaneously

Table 20.4 Features associated with portal vein thrombosis (PVT) in patients with cirrhosis, which could be a consequence of PVT

Liver atrophy
Increasing MELD or Child–Pugh scores
Ascites
Encephalopathy
Gastrointestinal bleeding
Failure to control bleeding
Delayed eradication of varices using endoscopic band ligation
Increased sensitivity of the liver to circulatory failure
Impossibility to restore and maintain portal perfusion to grafted liver
Decreased survival after liver transplantation
Decreased benefit from liver transplantation

MELD model for end-stage liver disease

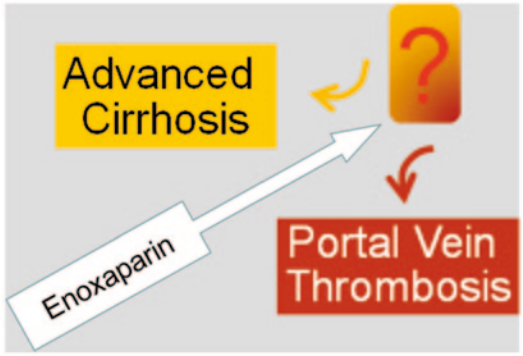

Fig. 20.1 Schematic illustration of the indirect link between portal vein thrombosis (PVT) and progression of liver disease. Enoxaparin could target a common determinant (indicated by a question mark) to the progression of liver disease and the development of PVT. This hypothesis would explain **a** the absence of direct relationship between PVT and progression of liver disease; and **b** a disproportionate benefit from the administration of enoxaparin on the prevention of progression of liver disease over the prevention of PVT

explain the progression of liver disease and the development of PVT, as illustrated in Fig. 20.1. These *scenarios* are not mutually exclusive. Scenario (iii) appears to be most compatible with the data discussed above. Clarifying which of these *scenarios* is correct would tip the balance for or against potential treatments targeting portal vein recanalization.

Interpreting the data on the impact of PVT on LT is likewise not straightforward. Technical failure to restore and maintain portal blood perfusion to the allograft causes its primary nonfunction [1, 5]. A preexisting PVT may prevent adequate portal blood perfusion being established, mostly depending on the degree (partial or occlusive) and the extent of the thrombus in the superior mesenteric vein. Whenever simple thrombectomy or an anastomosis between the recipient mesenteric vein and donor portal vein restores physiological portal blood perfusion to the allograft, the independent impact on overall outcome appears to be limited [27]. This is not the case for nonphysiological operations (e.g., caval hemitransposition or renal- to portal vein anastomosis) where operative and postoperative mortality and morbidity are greatly increased [27].

Independently of its impact on portal blood perfusion to the graft, pretransplant PVT appears to be a factor in decreased posttransplant survival. Intriguingly, however, this negative influence seems to be limited to patients with the lowest MELD scores at the time of transplantation [13, 28]. One of several possible explanations could be that patients with low MELD scores and PVT have an underlying disorder that is responsible for their poor condition (and possibly for PVT), but it is not cured by LT.

Treatment

Treatment of PVT in patients with cirrhosis can be considered from a prophylactic or a curative perspective. Experience, although increasing, is still too limited to provide solid evidence-based therapeutic recommendations.

Prophylactic options have been based on the assumptions that (i) the development of PVT is responsible for progression of liver disease, for worse outcomes after LT, or for both of these consequences, and (ii) preventing the development or the extension of PVT will prevent complications and improve patient outcomes. Actually, one randomized controlled trial in patients with Child–Pugh classification B7-C10 cirrhosis compared 34 patients receiving enoxaparin subcutaneously 4000 IU daily for 48 weeks to 36 patients receiving no such treatment [26]. Evaluation at 96 weeks showed markedly decreased incidences of PVT, decompensation, progression of liver disease, and death in the treated group as compared to the control group. As discussed above, this trial unexpectedly showed a greater benefit in terms of prevention of complications than the development of PVT. Other uncontrolled studies performed in patients with PVT generally showed the absence of progression of PVT in patients receiving anticoagulation (low molecular weight heparin initially, with or without a transition to warfarin) [5, 23, 24, 29]. Therefore, not only does anticoagulation appear to block the development or the extension of the thrombus but this effect may also be accompanied by clinically relevant improvements in patient outcomes.

Curative therapy options have been less well evaluated than prophylactic ones. Transjugular intrahepatic portosystemic shunt (TIPS), thrombolysis, and anticoagulation have all been considered. Available data consist of retrospective observational studies, from which it is difficult to draw conclusions regarding robust end points such as decompensation or death. Indications for TIPS in patients with PVT have mostly comprised refractory bleeding or ascites [23, 30–32]. Findings have been consistent in indicating that (i) TIPS insertion is feasible when intrahepatic portal veins are visible, (ii) the incidence of encephalopathy and TIPS dysfunction are similar in patients with or without PVT, and (iii) resolution of partial thrombosis may occur in the absence of anticoagulation. Thus, PVT is not a contraindication to placing a TIPS. However, it has not been established if TIPS provides a benefit in clinically relevant end points as compared to other options (including no specific therapy) in patients with cirrhosis and PVT.

Anticoagulation therapy has been evaluated in patients with advanced cirrhosis, many of whom were candidates for LT [5, 23, 24, 29]. Anticoagulation protocols consisted generally of low-molecular-weight heparin initially, with or without a secondary shift to warfarin. The duration of anticoagulation ranged from several weeks to months in each series. The findings are relatively consistent in showing (i) complete recanalization of the portal vein in about 45% of patients, and a partial recanalization in about 15%, while extension was extremely unusual, (ii) the absence of bleeding related deaths, and (iii) the absence of obvious increase in the incidence of gastrointestinal bleeding or other spontaneous bleeding. However, the data do not allow for an assessment of the impact of anticoagulation on clinically relevant end points such as decompensation or mortality, before or after transplantation. Furthermore, the proportion of treated patients with a partial PVT was unclear, making it difficult to assess whether this feature is a determinant in recanalization. There are little data to recommend any specific anticoagulant agent, the monitoring tools, and the target coagulation variable to be achieved [33]. Data on the use of thrombolysis whether given systemically or locally are thus far only anecdotal [34].

Based on this information, it is impossible to make strong treatment recommendations. The prophylactic use of enoxaparin is certainly an exciting prospect but confirmatory clinical trials are needed before any definitive recommendation can be made. In patients with refractory bleeding or ascites, TIPS insertion can be attempted, although its impact on survival can be expected to be limited. Placing a TIPS only for prevention of an extension of PVT is questionable. Similarly, at present, the indication for anticoagulation based only on the presence of PVT is not sufficiently grounded in data. While its benefit is unproven, anticoagulation might be considered in patients with PVT who are candidates for LT, with the purpose of preventing extension of thrombosis, and thus facilitating restoration of physiological portal blood perfusion to the allograft. Other situations deserve a case-by-case discussion, particularly in rare patients where a strongly prothrombotic condition has been diagnosed or patients with extensive thrombosis of the superior mesenteric vein in whom there is evidence of past or recent intestinal ischemia.

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