Chapter 8
Portal Vein Thrombosis in Patients with Cirrhosis

Filipe Nery

Epidemiology, Diagnosis and Classification

PVT has been described to be more frequent in patients with more severe and advanced liver disease. Actually, a bulk of epidemiological data are derived from studies conducted in patients with advanced severe chronic liver disease, e.g. wait-listed for liver transplantation (LT). In the latter context, 1-year incidence of 7.4% [1] has been reported, but prevalence by the time of LT has been estimated between 15.9 and 26% [2, 3]. In a mixed population of patients with cirrhosis stage Child-Pugh A to C, Zocco et al. observed a 1-year incidence of 16.4% [4]. A similar 1-year incidence of 17.9% was found in another cohort of patients with decompensated liver disease [5]. Yet, PVT is also a concern in more stable patients, as it has been found to occur in up to 4.6%, 8.2% and 10.7% at respectively 1-, 3- and 5-years, in a population of mostly compensated liver disease patients [6].

As PVT is more commonly a clinically silent event, it is mostly uncovered at Doppler ultrasound (DUS) performed for hepatocellular carcinoma (HCC) screening. Outside the context of LT, there is currently no recommendation to routinely screen for PVT in patients with cirrhosis [7]. PVT diagnosis is generally made by DUS. DUS sensitivity in detecting PVT increases with the degree of occlusion and extension [8]. It may be difficult to differentiate bland thrombi from malignant

F. Nery (✉)
Centro Hospitalar Universitário do Porto – Hospital de Santo António, Porto, Portugal

Instituto de Ciências Biomédicas de Abel Salazar – Universidade do Porto, Porto, Portugal

EPI Unit, Institute of Public Health, University of Porto, Porto, Portugal

Laboratory for Integrative and Translational Research in Population Health (ITR), Porto, Portugal

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portal vein invasion. Increased diameter of the vessel, evident vessel wall disruption or adjacent malignant liver parenchyma infiltration may contribute to differentiate the two types of portal venous obstruction. Arterial phase enhancement after contrast injection in HCC invasion is the most accurate differential feature. Contrast-enhanced ultrasound is superior to DUS in making this differentiation, allowing a final diagnosis in more than 97% of the patients [9]. CT scan (Fig. 8.1) or MRI (Fig. 8.2) are useful in evaluating extension, allowing the application of different classification scores [10]. The most widely used classification of PVT in patients with cirrhosis was proposed by Yerdel et al., two decades ago [8]. Being simple and reproducible, this anatomical classification takes into account the site, degree of occlusion and extension of the thrombus, which is relevant in choosing the operative management at LT [8]. A recent anatomic and functional classification has been proposed, outside the transplant setting, precising PVT location, grade of occlusion and extension, as well as clinical presentation and functional relevance, also allowing to select patients who would benefit most of anticoagulation therapy [11]. Further validation of the latter classification is needed.

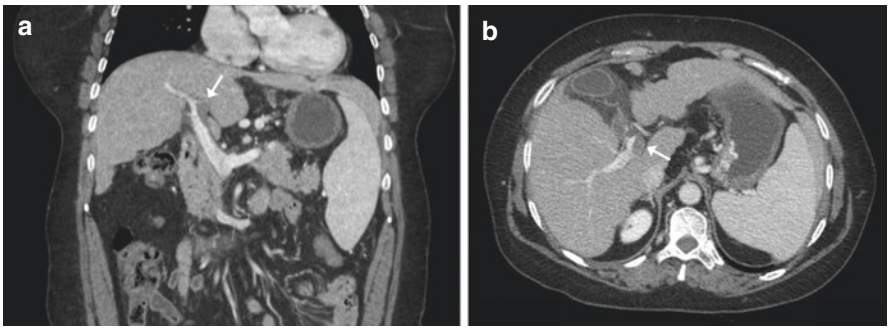

Fig. 8.1 Partial trunk portal vein thrombosis (arrows) documented in a CT-scan. (**a**) Coronal CT sequence; (**b**) Axial CT sequence

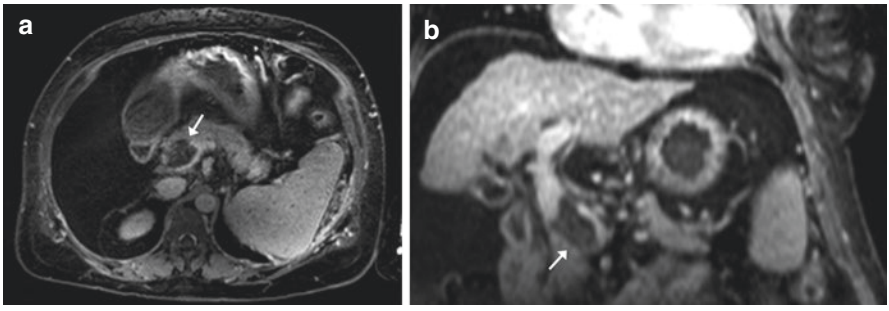

Fig. 8.2 Portal vein thrombosis with extension to splenoportal venous confluence and superior mesenteric vein (arrows) documented in Magnetic Resonance Imaging. (**a**) Axial T1-weigthed image; (**b**) Coronal view

Risk Factors

Understanding of venous thrombosis development irrespective of the site of occurrence is based on the work of ancient haematologists, probably the most recognized being the one by Rudolf Virchow, conducted in the mid-nineteenth century [12]. Clot formation occurs in the presence of factors related to blood stasis, a hypercoagulable state and endothelial damage, the pillars of the Virchow's triad [12]. The combination of such factors, rather than one factor acting alone may also be considered for PVT, viewed as a multifactorial entity (Fig. 8.3).

Blood Stasis The increased intrahepatic resistance that is characteristic of liver cirrhosis, and responsible for portal hypertension, induces a slowdown of the portal vein blood flow. Portal vein blood flow velocity decreases proportionally to the severity of the liver disease (as assessed by Child-Pugh classification) [13] and higher degrees of fibrosis [14]. A portal vein blood flow velocity of 15 cm/s or less has been found to be predictive for subsequent PVT development [4, 5, 15]. It has been proposed that a decreased blood flow would lead to an increased concentration of thrombin at the level of the portal vein tract, contributing to PVT development [4]. However, a decreasing [6, 16] or low [17] portal vein blood flow velocity was not found to be independently related to subsequent PVT development by other investigators. Well-known limits in assessing portal blood flow velocity with percutaneous DUS may account for these disparate results. An increased flow volume in collateral vessels was independently linked to PVT development in a cohort of patients with cirrhosis related to viral hepatitis [18]. However, the authors do not

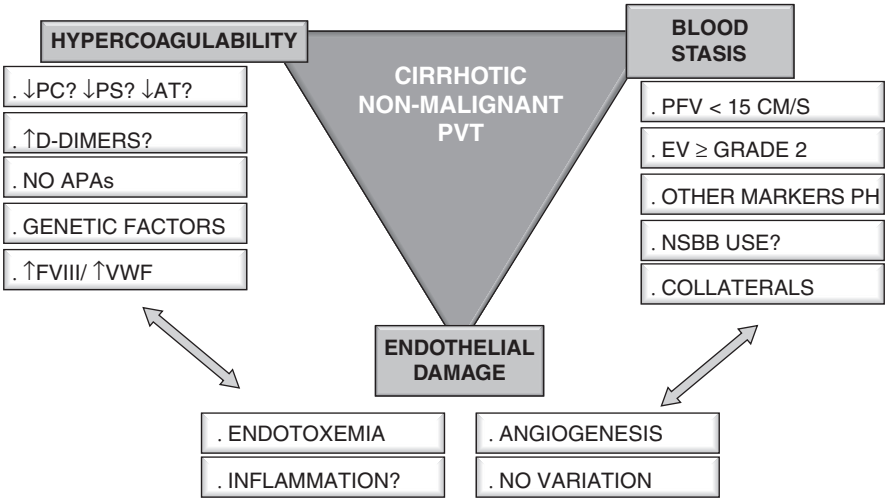

Fig. 8.3 Virchow's triad applied to portal vein thrombosis genesis. *PVT* portal vein thrombosis, *PC* protein C, *PS* protein S, *AT* Antithrombin, *APAs* Antiphospholipid antibodies, *FVIII* Factor VIII, *VWF* von Willebrand factor, *NO* Nitric oxide, *PFV* portal vein flow, *EV* esophageal varices, *PH* portal hypertension, *NSBB* non-selective beta-blockers

mention the impact of this deviation of blood from the portal tract on a possible decrease in portal vein blood flow [18]. Thus, hemodynamic factors related to portal vein blood flow stasis although an attractive hypothesis to explain PVT, require further assessment.

Other factors related to severe portal hypertension and/or portal blood flow stasis have also been found to be associated to PVT, including low platelet count [1, 5], increased splenic thickness [5] or spleen size [18], previous variceal bleeding [1], presence of medium or large-sized esophageal varices [6] and of ascites [18].

Non-selective beta-blockers (NSBB), generally used for primary or secondary variceal bleeding prophylaxis, have been proposed to decrease portal blood flow via a reduced cardiac output and increased splanchnic vasoconstriction [19]. A recent longitudinal study found NSBB as an independent risk factor for future PVT development irrespective of its effect over portal blood flow velocity or heart rate [16]. This finding was corroborated by a meta-analysis that found an increased 4.6-fold risk for PVT development in patients under NSBB [20]. Yet, the link between NSBB and PVT development may not be direct (through an effect on splanchnic hemodynamics), but indirect, as a reflection of more severe degree of portal hypertension through presence of large esophageal varices as an indication for NSBB administration. Robust and prospective data are still necessary before establishing a causal relationship of NSBB with PVT development.

Hypercoagulability In cirrhosis, pro- and anti-hemostatic drivers are altered, which results in an enhanced platelet-vessel wall interaction and platelet activation [21, 22]; an enhanced potential to generate thrombin [21, 23]; a disturbed fibrinolysis [21]; a modified structure and function of the fibrin clot [24]; and increased levels of procoagulant microparticles carrying tissue factor [25]. Altogether, these changes confer a state of rebalanced coagulation or even a procoagulant state [21] (discussed in details in Chap. 17). However, specific studies directly addressing the relationship of these factors to PVT development are still lacking. Decreased protein C [4, 26] or antithrombin levels [4] and increased D-dimer levels [4] have been associated with an increased risk for subsequent PVT development. The other available studies of retrospective or cross-sectional design, have analyzed risk factors determined at the time of the diagnosis of the thrombotic event [27–30]. When considering inherited thrombophilia, only Factor V Leiden [31, 32] and MTHFR mutations [33] have been recognized to be associated with an increased tendency to develop PVT. Conflicting results exist when considering the role of prothrombin G20210A mutation and PVT, as a previous meta-analysis failed to confirm an association [31], while a more recent one displayed exactly the opposite [32], reflecting different methodological approaches when choosing the studies to enroll. Still, current guidelines recommend considering the screening of underlying inherited thrombophilic conditions [7, 10], even though we consider that, in the absence of robust data, the search of these inherited factors is not mandatory. Myeloproliferative neoplasias are a known risk factor for PVT development in patients without cirrhosis, and JAK-2 V617F mutation may be present in up to 16% [34] to 31% [35] of

such patients. A case-control study showed that 10% of patients with cirrhosis and PVT similarly harbored the JAK-2 V617F mutation in contrast with none of the patients without PVT [35]. These still unconfirmed results must be seen with caution as few patients were enrolled. In non-cirrhotic patients with JAK-2 V617F negative myeloproliferative neoplasia, calreticulin mutations may be present in up to 31% of patients with PVT [36], but corresponding data in patients with cirrhosis are lacking. Antiphospholipid antibodies have been found in patients with cirrhosis and with an increased prevalence according to the degree of liver failure [37]. However, their role in the development of PVT has not been documented yet [38].

Endothelial Damage Even though endothelial activation predisposing to thrombosis has been documented in other vascular beds and is an attractive hypothesis, it has never been confirmed, to date, to be related to PVT. Inflammation and increased endothelial permeability is at the basis of vascular endothelial growth factor-mediated angiogenesis and related cofactor to portosystemic collaterals development [39, 40]. Endotoxemia, resulting from bacterial translocation occurs in proportion to the severity of portal hypertension and degree of liver insufficiency, being more severe at the level of the portal circulation than in the systemic circulation [41]. Endotoxins promote not only a von Willebrand factor (vWf) release from endothelial cells and related increased factor VIII [42], but also the up-regulation of tissue factor leading to factor VII activation and associated coagulation cascade activation [41, 43]. From the above, endothelial damage may, therefore, promote and aggravate portal hypertension and portosystemic collateral formation by inducing angiogenesis (both known to be triggers of PVT development), as it may also promote the activation of coagulation cascade via the inflammatory cascade leading, by this mean, to PVT. Such relationship between endotoxemia, inflammation and PVT has already been proposed as an attractive explanation to the observed clinical and laboratory data [43]. Recently, increased levels of IL-6 and lymphopenia were shown related to PVT development independently of markers of portal hypertension, reinforcing the idea of the role of inflammation and endothelial activation in the pathogenesis of PVT [44].

Natural History

PVT Outcome Without Anticoagulation By contrast with early studies in which no resolution of PVT was seen in patients without anticoagulation treatment [1], recent longitudinal studies report portal vein recanalization in up to 45–70% of the patients [6, 18, 45], aggravation in only 7% to 34% [18, 45], and recurrence in 19–21% of the patients [6, 18], as confirmed in a recent meta-analysis [46]. In cirrhosis, therefore, PVT is rather a dynamic process. Also, PVT is more often partial than complete [6, 18, 47], which ultimately translates into higher recanalization rates.

Role of PVT in decompensation and progression of liver disease PVT has been widely considered to play a role in the progression (and decompensation) of underlying liver disease. At the time of LT, ascites and gastrointestinal bleeding are more frequent in patients with PVT than in those without [48]. A more advanced liver disease was reported in patients with, than in patients without PVT [49]. Such a causal relationship could theoretically be associated to decreased liver perfusion with portal blood, which would result in parenchymal atrophy leading to further increase in portal hypertension and worsening of liver dysfunction [50]. However, these conclusions were drawn from cross-sectional studies where thrombosis was documented at the time of the liver decompensation, which leaves open the question of what occurred first. Recent longitudinal studies have provided data that support the opposite view. Luca et al. found no relationship between the development of PVT and hepatic decompensation, irrespective of PVT progression along time or not [45]. Moreover, in patients wait-listed for LT with PVT compared to those without PVT, upper gastrointestinal bleeding, worsening of ascites, spontaneous bacterial peritonitis or encephalopathy aggravation were not more frequent either at the time of listing or during the waiting period [51]. Furthermore, in a study enrolling 1243 Child A and B patients, PVT and liver decompensation were shown to share baseline risk factors (i.e. medium or large esophageal varices and prolonged prothrombin time), while PVT development did not influenced the progression or the decompensation of liver disease [6].

Impact of PVT on survival PVT could not be shown to alter survival in patients not candidates to LT or on the waiting list for LT [15, 18, 51, 52]. Remarkably PVT has been linked to a decreased mortality on the waiting list, [53], the interpretation of which will require further analysis of the interaction with anticoagulation therapy as there is preliminary evidence that anticoagulation may impact survival positively [26]. In recipients of liver transplant with prior PVT however, early-survival decreases compared to those without PVT [52, 54, 55]. The impact on post-LT survival may be related to higher degrees of PVT occlusion [1, 8], and also to longer operative times, higher transfusion requirements and rates of reoperation, longer intensive care and hospital stays and the particular surgical technics used for clot removal and alternative vascular reconstructions [8, 56, 57].

Treatment

Anticoagulation therapy In patients with PVT without cirrhosis, anticoagulation therapy is the mainstay of treatment [10] as discussed in section "Epidemiology, Diagnosis and Classification", Chap. 17. In cirrhosis, some considerations shall be taken into account before considering anticoagulation therapy. First, as mentioned above, PVT in cirrhosis is a dynamic process with a possible spontaneous recanalization in more than half of the patients; second, PVT likely does not induce liver decompensation; third, PVT has no impact on survival in patients besides the LT

setting. Therefore, there is no matter for an indication of anticoagulation therapy except in the context of patients listed for LT. However, this concept may change in the near future, as evidence of an improvement in survival in patients with PVT under anticoagulation therapy has been recently demonstrated in a meta-analysis enrolling 1696 cirrhotic patients, without significant increase in bleeding risk [58]. Yet, this advantage needs to be viewed with caution, as it may not be applicable to all patients regardless of the severity of the disease. In patients undergoing LT, the immediate goal is to avoid portal vein thrombus extension or to decrease its size in order to facilitate liver transplantation [7, 10]. However, even in this setting, the efficacy and safety of anticoagulation therapy must be discussed. Robust studies accessing the efficacy of anticoagulation on PVT in cirrhosis are lacking. Most of them were conducted with a small number of patients and with some heterogeneity concerning the type of anticoagulant agent used. In a series of 19 patients listed for LT with PVT in whom nadroparin followed by acenocoumarol was used, 8 patients (42%) had complete resolution of the thrombus (7 of them had partial PVT before anticoagulation was started) while only 1 patient (5%) had PVT extension [1]. Another longitudinal prospective study comparing 35 patients treated with nadroparin to 21 untreated patients showed significantly less progression of the thrombus in the former (15%) compared to the latter (71%). Sixty-three percent of the treated patients achieved some degree of recanalization and 36% had a complete PVT resolution [59]. Patients with thrombus extension to the splenic vein, those with previous gastrointestinal bleeding and with estimated thrombus duration of at least 6 months were less likely to recanalize [59]. The largest available study, which enrolled 55 patients given either low molecular weight heparin or vitamin K antagonists, showed an overall improvement of PVT in 60% of patients including 45% with complete recanalization [60]. Globally, around 50% of the patients who under anticoagulation achieved complete recanalization and 2/3 some degree of repermeabilization (partial or complete) [46, 61]. Importantly, when anticoagulation is stopped, PVT relapses in 40% of the patients [60], a reason why, in patients listed for LT, once started, anticoagulation treatment shall be maintained at least until the surgical procedure. Reluctance to the use of anticoagulant therapy in cirrhosis is related to the perceived risk of bleeding. It is now clear that patients with cirrhosis bleed from portal hypertension complications and not from hemostatic abnormalities. Anticoagulant therapy may be safely used in patients with cirrhosis and PVT as either no bleeding complications or only minor bleeding events have been reported [46, 61]. Remarkably, two recent meta-analysis have shown a decreased incidence of variceal bleeding in patients under anticoagulation therapy compared to those without [46, 62]. However, a platelet count below 50×10^9/L has been identified as a risk factor for bleeding from any site in patients with cirrhosis and PVT receiving anticoagulation [60]. Available options for anticoagulant agents are discussed elsewhere.

Transjugular intrahepatic shunt (TIPS) The complications of portal hypertension refractory to usual therapy have been the most common indications for TIPS placement in patients with cirrhosis and PVT [7]. In studies addressing TIPS proce-

dure as a modality for PVT treatment, the main indication was usually not PVT itself, but a previous episode of bleeding or refractory ascites. TIPS placement displays a high rate of success, with 74% of the patients achieving complete and 84% complete or partial recanalization, as documented in a recent meta-analysis [63]. In patients with cirrhosis undergoing TIPS placement (irrespective of the indication), there was no difference in rebleeding, recurrence of ascites or hepatic encephalopathy, as well as short- and long-term survival between those with PVT and those without [63, 64]. TIPS dysfunction was found to be remarkably less frequent when placing a covered stent [65]. Among five patients that underwent TIPS placement after thrombus extension on anticoagulation therapy, 3 showed stability, 1 completely reverted and 1 died (TIPS placement failed) [59]. These limited data suggest that TIPS could be used as a rescue therapy when PVT does not resolve with standard anticoagulation therapy. TIPS insertion prior to LT is increasingly used in patients with PVT [55]. However, TIPS is still not recommended as a standard treatment for PVT in cirrhosis but to be considered individually and by experienced teams [10].

Conclusion

As PVT in cirrhosis is a common event in the course of the disease, awareness shall be raised for this entity, which is multifactorial in origin. Once diagnosed and outside the liver transplant setting, anticoagulation treatment is not mandatory mainly due to the fact that (1) PVT is a dynamic entity, often resolving without any directed therapy and that (2) it is not currently recognized to affect the outcome (decompensation or survival). A different scenario is seen in patients undergoing liver transplantation, as, once diagnosed, PVT may affect not only the eligibility to surgery but also impact survival after transplantation. In this context, anticoagulation therapy shall be started and patients regularly monitored.

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