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REVIEW

Current concepts in portal vein thrombosis: etiology, clinical presentation and management

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Abstract

Objective The aim of this article is to focus on etiology, risk factors, clinical presentation and classification systems of acute and chronic PVT as well as focusing on current diagnostic and therapeutic options for the management of acute and chronic PVT.

Results PVT represents a serious clinical concern in cirrhotic patients and in those with specific local or systemic risk factors. The rate and extent of thrombus formation can significantly impact patient presentation and the resulting clinical outcomes. The presentation of acute PVT can range from abdominal pain to intestinal ischemia/infarction and even death, while chronic PVT can remain clinically silent. A number of imaging modalities including US, CT and MRI can be used to confirm the diagnosis. In addition to addressing underlying risk factors, AC therapy forms a cornerstone of treatment and has demonstrated efficacy in both acute and chronic settings. Proper caution should be used when initiating AC therapy in cirrhotic patients given their underlying coagulopathic status with attention now being paid to NOACs and LMWH. For patients with bowel ischemia, extensive thrombosis, contraindications or poor response to AC, or for those with co-morbidities that preclude AC, minimally invasive endovascular techniques offer alternative treatment options.

Conclusion Familiarity with the etiology, clinical presentation and classification of PVT optimize early detection and incorporate effective therapeutic options, the management of these complex patients should be undertaken by a multidisciplinary team. Minimally invasive catheter-based therapies and endovascular portosystemic shunt creation demonstrated efficacy in the treatment of AC-resistant patients and for patients with extensive or complicated disease.

Keywords Portal vein thrombosis · Portal hypertension · Transsplenic

Introduction

Portal vein thrombosis (PVT) is characterized by thrombus formation within the portal vein resulting in complete or partial obstruction. PVT can be further classified by the time to thrombus formation (acute or chronic) and potential etiology (local or systemic). PVT is common in cirrhotic patients and its prevalence in this population is dependent upon the degree of cirrhosis. In well-compensated patients, the prevalence of PVT may be less than 1%, however, in those with uncompensated cirrhosis, prevalence may be as high as 25% [1, 2]. The prevalence of PVT in patients without cirrhosis is not entirely clear, although it is not common. The presentation and severity of symptoms in PVT is highly variable and is dependent upon the extent and rate of thrombus formation. Patients with chronic PVT and well-developed collateral circulation may be totally asymptomatic, while patients with acute thrombosis can present with rapid onset of colicky abdominal and/or lumbar pain, intestinal congestion/ischemia, gastrointestinal bleeding, abdominal distention, ileus or sepsis [3, 4]. Peritoneal signs are typically absent unless the process has progressed to bowel ischemia/infarction, in which case hematochezia and ascites, along with elevated lactate levels are common. Counterintuitively, liver enzymes may be normal or slightly

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elevated [5, 6]. Timely diagnosis and identification of the underlying etiology is critical to management and several therapeutic options exist for the treatment of PVT. Here, we review clinical and diagnostic considerations in PVT. Current techniques for the management of both acute and chronic PVT are also discussed.

Etiology and risk factors

Although there are a multitude of risk factors that may lead to PVT development, they can generally be divided into two categories: local or systemic (Table 1). Regardless of the cause, PVT pathogenesis typically results from the same general pro-thrombotic risk factors classically identified by Virchow: venous stasis, endothelial injury and hypercoagulability [6]. Common local risk factors include hepatopancreaticobiliary malignancies, cirrhosis, surgery, trauma, and inflammatory abdominal conditions (e.g. pancreatitis, cholecystitis, and cholangitis). Hepatopancreaticobiliary malignancies have been found to contribute to approximately 25% of PVT cases either through extrinsic portal vein compression, increased hypercoagulability or direct vascular invasion [7]. In the setting of cirrhosis, reduced portal vein flow velocities and dysfunctional coagulation pathways can contribute to thrombus formation, and PVT development can depend on the degree of compensation, as previously mentioned [6, 8, 9]. Autoimmune hepatitis (AIH) has also been strongly associated with PVT development among patients with cirrhosis. One study found that 55% of patients with cirrhosis secondary to AIH had PVT at the time of liver transplantation, compared to 12% of patients with other causes of cirrhosis [10]. Finally, balloon-occluded retrograde transvenous obliteration (BRTO), an increasingly utilized interventional procedure for the treatment of varices due to portal hypertension, has also been found to be a local risk factor for portal vein thrombosis. BRTO effectively removes a portosystemic shunt and therefore decreases outflow of the portal system, leading to stagnation and thrombosis which has been seen in up to 15% of patients undergoing this procedure [11]. Common systemic factors that contribute to PVT development include inherited thrombophilias (e.g. Factor V Leiden mutation, Protein C or S deficiency, Antithrombin deficiency), myeloproliferative disorders, pregnancy, and oral contraceptive use. Notably, case series have demonstrated myeloproliferative disorders and inherited thrombophilias to be the most common systemic risk factors for PVT [5].

Table 1 Local and systemic risk factors for PVT [12–14]

Local risk factors	Systemic risk factors
Malignancy	Acquired
Hepatobiliary or any abdominal organ	Myeloproliferative disorders
Cirrhosis	Malignancy
Abdominal infection/inflammation	Anti-phospholipid syndrome
Cholecystitis	Hyperhomocystinemia
Pancreatitis	Oral contraceptive use
Cholangitis	Recent pregnancy
Appendicitis	Inherited
Latrogenic portal vein injury	Protein C deficiency
Splenectomy	Protein S deficiency
Cholecystectomy	Antithrombin deficiency
Abdominal surgery	Factor V Leiden mutation
Trauma	Prothrombin mutation

Clinical presentation

PVT occurrence has no predilection for age and the clinical presentation is dependent upon the degree and timing of thrombus development. Acute thrombosis that completely occludes the vessel results in splanchnic congestion and ischemia. Patients commonly present with abdominal pain, nausea, vomiting, gastrointestinal bleeding, fever, sepsis and lactic acidosis [15]. Splenomegaly and abdominal distension may be present on physical exam. Ultimately, intestinal perforation, peritonitis, septic shock and death may result if blood flow is not restored. If PVT is only partially occlusive, symptoms may be minimal or absent. Similarly, in cases of chronic PVT, patients are often asymptomatic given adequate development of collateral circulation or cavernous transformation of the portal vein (i.e. cavernoma). In these cases, PVT is often incidentally discovered on abdominal imaging. Clinical manifestations of chronic PVT are related to those of portal hypertension and can include esophageal/gastric varices, gastrointestinal bleed, portal hypertensive gastropathy, ascites, and splenomegaly with pancytopenia [16, 17].

Classification systems

Portal vein thrombosis can broadly be classified as acute versus chronic and cirrhotic versus non-cirrhotic. Over the years, several PVT classification systems have been developed to further categorize the degree and extent of occlusion. In 2000, Yerdel and colleagues retrospectively devised a system based on various operative approaches used during liver transplantation. This system was based on the location and extent of thrombus within the portal and superior mesenteric vein (SMV) with higher grades having increased in-hospital mortality and poor long-term outcomes [18]. In

2015, the Baveno VI classification was developed incorporating additional factors such as chronicity of the thrombus, type of underlying liver disease and extent of involvement within the portal venous branches [19]. Notably, these classification systems are purely anatomical, do not clearly differentiate between acute versus chronic PVT, and do not account for functional considerations or clinical findings. More recently, Sarin et al. devised a system to address these shortcomings by including factors that address the functional relevance of PVT by clearly defining duration and presentation of disease [19] (Table 2). Although the value of this system for prognostic and therapeutic purposes has yet to be confirmed in prospective cohorts, its inclusion of functional information may offer significant improvements over previous anatomical classification systems.

Diagnosis

Clinical imaging is essential to the diagnosis of PVT and selection of the appropriate imaging modality depends on a number of factors including severity of the patient's presentation, medical history and clinical suspicion. Abdominal or right upper quadrant ultrasound is traditionally the first-line imaging test used in stable patients with suspected liver pathology and can demonstrate the presence of solid or hyperechoic material in the portal vein, presence of cavernoma and distention of the portal vein or its branches [20]. Notably, the portal vein diameter visualized on ultrasound in acute PVT is usually greater than 13 mm and is not subject to changes in size during respiration [21]. The overall sensitivity and specificity of ultrasound for detection of PVT range between 80 and 100% and the addition of color Doppler can further assess the presence or absence of portal flow [6, 22, 23]. Furthermore, in a prospective cohort of cirrhotic patients undergoing Doppler ultrasound, portal vein flow velocities < 15 cm/s were able to significantly predict PVT development with thrombus developing in 91.7% of patients meeting this criteria [24]. Ultrasound with Doppler is quick, inexpensive, and does not submit the patient to harmful radiation. It is limited, however, in determining the extent of thrombus into the mesenteric circulation and is also operator dependent, with image quality dependent on patient body habitus and presence of bowel gas [25]. One important distinction to be made is differentiating bland PVT versus neoplastic portal vein invasion. The presence of portal vein tumor thrombus is a poor prognostic sign and a contraindication to hepatic transplantation [25]. Intraluminal expansile mass, with heterogeneous appearance and disruption of the PV walls are the signs of tumor invasion of the PV on US [26]. Arterial neovascularization typically seen on Color Doppler US and pulsed Doppler US confirms arterial flow with a High Resistive Index (Fig. 1). (Contrast-enhanced US has a high sensitivity (88–100%) and specificity (94–96%) for differentiating versus neoplastic portal vein thrombus in patients with hepatocellular carcinoma [50, 51]. The value of endoscopic ultrasound (EUS) in diagnosing PVT has also been assessed with the sensitivity, specificity and diagnostic accuracy determined to be 81%, 93% and 89%, respectively [26]. Moreover, EUS has demonstrated excellent diagnostic accuracy in detecting malignant portal venous invasion [27]. This technique is limited, however, in its ability to image the distal SMV and the intrahepatic portion of the portal vein [26].

Computed tomography (CT) and magnetic resonance imaging (MRI) have demonstrated added utility in PVT diagnosis by providing information on thrombus extent as well as clues to causative intra-abdominal pathology. On non-contrast CT, PVT appears as a filling defect in the portal vein that is hypodense or isodense to adjacent tissues,

Table 2 Anatomico-functional classification of PVT in cirrhosis as proposed by Sarin et al. [19]

Site of PVT
Type 1: only trunk
Type 2: only branch 2a: one branch 2b: both branches
Type 3: Trunk and branches
Extent of PV system occlusion
Splenic vein, mesenteric vein, both
Type of underlying liver disease
Cirrhotic, non-cirrhotic, hepatobiliary malignancy, local malignancy, post-transplant, associated conditions
Degree of portal venous system occlusion
0: occlusive, no visible flow in PV lumen on imaging/Doppler NO: non-occlusive. Flow visible in PV lumen on imaging/Doppler
Duration and presentation
R: recent. First time detected in previously normal vessel and AS: asymptomatic or 5: symptomatic, acute PVT features ± ABI
Ch: Chronic. Previously detected, presence of clinical features of PHT, portal cavernoma and AS: asymptomatic or S: symptomatic. Features of PHT

PVT portal vein thrombosis, PV portal vein, *ABI* acute bowel ischemia, *PHT* portal hypertension

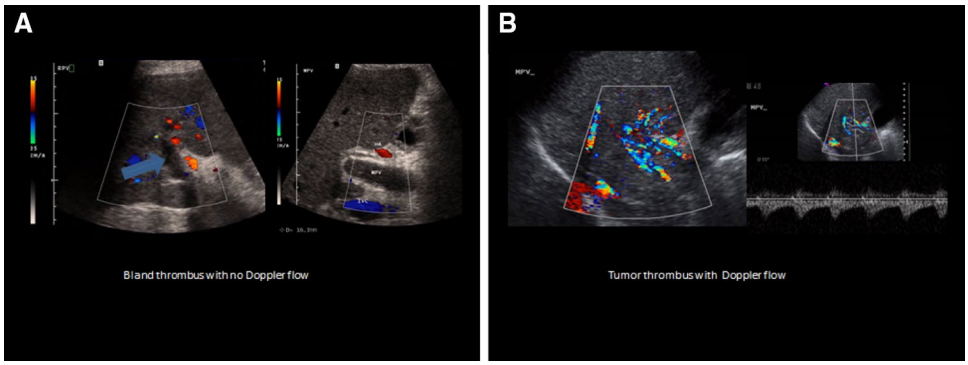

Fig. 1 **a** Color Doppler US demonstrating a large bland thrombus (arrows) within the main portal vein. **b** Color Doppler US and pulsed Doppler US confirms PV tumor thrombus that has arterial flow with a High Resistive Index

although the thrombus may appear hyperdense if recently formed (< 1 month old) [28]. Secondary signs of chronic PVT including portal vein calcification or cavernous transformation may also be seen [29]. Upon contrast administration, bland thrombus appears as a hypodense, non-enhancing intraluminal filling defect within an opacified vessel (Fig. 2), while malignant thrombus undergoes contrast enhancement [6]. Dynamic contrast-enhanced CT may demonstrate these findings, in addition to rim enhancement of the vessel wall [30]. Contrast-enhanced CT has demonstrated excellent diagnostic accuracy in detecting PVT and is quick, readily available, and not operator-dependent. Disadvantages of contrast-enhanced CT include radiation exposure, allergic contrast reactions and contrast-induced nephropathy, which may preclude the use of this exam in patients with pre-existing renal dysfunction.

If CT is unavailable or contraindicated, MRI can be used to confirm the presence of PVT. The sensitivity and specificity of MRI for detecting PVT in patients undergoing liver transplant have been found to be 100% and 98%, respectively [31]. Contrast-enhanced magnetic resonance angiography (CEMRA) is an alternative option that has demonstrated excellent sensitivity and specificity in detecting PVT [32]. PVT appears as a filling defect on MRA and the thrombus itself is typically hyperintense on T2-weighted images [33]. In the chronic PVT setting, MRA demonstrates superior sensitivity at detecting cavernomatous transformation when compared to contrast-enhanced CT [21]. MRI is an

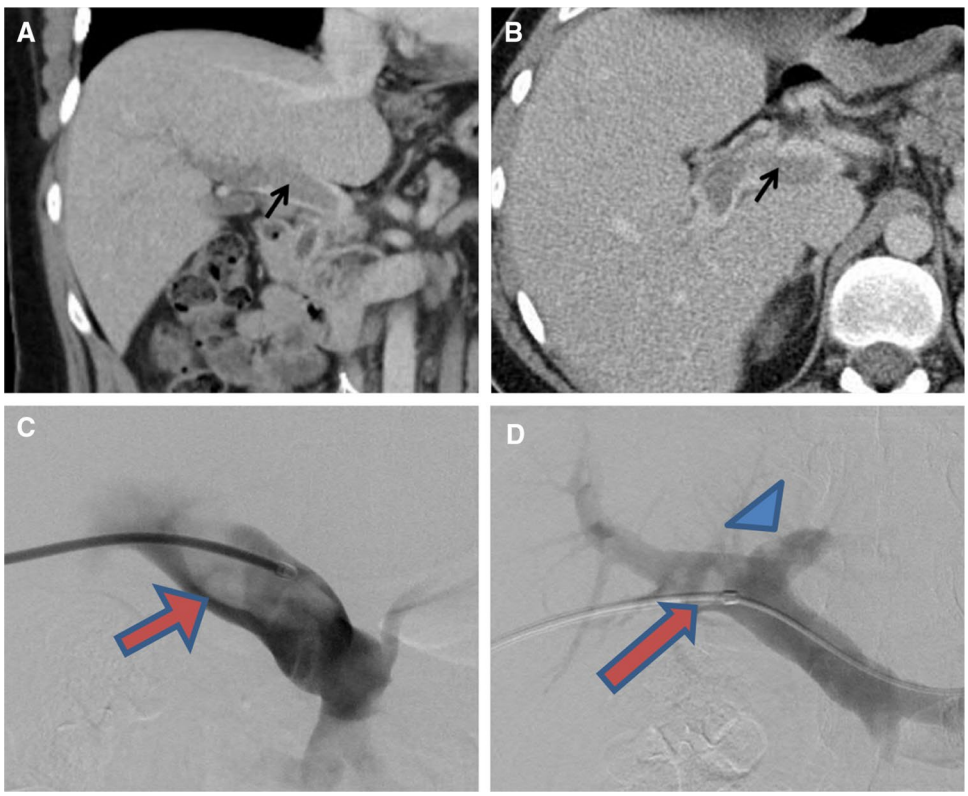

Fig. 2 **a**, **b** IV-contrast-enhanced CT demonstrating a large bland thrombus (arrows) within the main portal vein extending into the left and right portal veins. **c** Direct transhepatic percutaneous portography demonstrates a large non-occlusive filling defect within the distended portal vein (arrow). **d** Follow-up portogram demonstrates near complete resolution of previously identified large acute thrombus with a small amount of residual thrombus in the right (arrow) and left (arrowhead) portal veins following 10 h infusion of alteplase at a rate of 1 mg/h using unifuse catheter

important diagnostic tool to roll out macrovascular tumor invasion of the portal vein. The most specific feature of malignant PVT is internal arterial enhancement within the thrombus. Additional tool became available with the development of DWI (Fig. 3) [52]. CEMRA has been used to determine the presence of varices, assess flow direction and verify the correct function of surgical shunts [34, 35]. Given concerns with gadolinium-based contrast agents and nephrogenic systemic fibrosis, non-enhanced MRA (NEMRA) techniques including time-of-flight have also been investigated for PVT imaging [36]. These techniques have proven excellent diagnostic accuracy and image quality; however, they are not universally available, they are costly and they can be subject to motion artifacts. With the advent of these previously described non-invasive imaging techniques, the use of invasive digital subtraction angiography (DSA) for PVT diagnosis has declined, except in cases where ultrasound, CT or MRI are unable to assess the portal vasculature or in the event that further intervention after imaging is planned.

For patients with confirmed PVT with or without compensated cirrhosis, or for those in whom no local risk factor has been identified, a complete work-up assessing for inherited or acquired thrombophilias should be performed [5]. According to European Association for the Study of the Liver (EASL) practice guidelines, thrombophilia screening should include protein S, protein C and antithrombin levels, Factor V Leiden mutation, prothrombin G20210A gene variant, anti-phospholipid antibodies, and a work-up for myeloproliferative neoplasms [37]. Importantly, identification of one risk factor (local or generalized) in PVT should not deter investigation into additional risk factors.

A rare but deadly disease occurring in the setting of abdominal inflammatory processes is suppurative thrombophlebitis or Pylephlebitis of the portal mesenteric venous system. Pylephlebitis diagnosis usually made in the presence of portal mesenteric venous thrombosis (PMVT) with or without bacteremia within 30 days of intra-abdominal inflammatory processes [53]. Without aspiration of culture-positive fluid from the portal system, the diagnosis must be made by other clinical means. In the setting of PMVT, color Doppler US typically demonstrates flow defect and dilation or absent compressibility of the portal venous system. Computed tomography (CT) and magnetic resonance imaging commonly show an indoluminal hypodense portal-mesenteric-venous filling defect compared to the peripheral

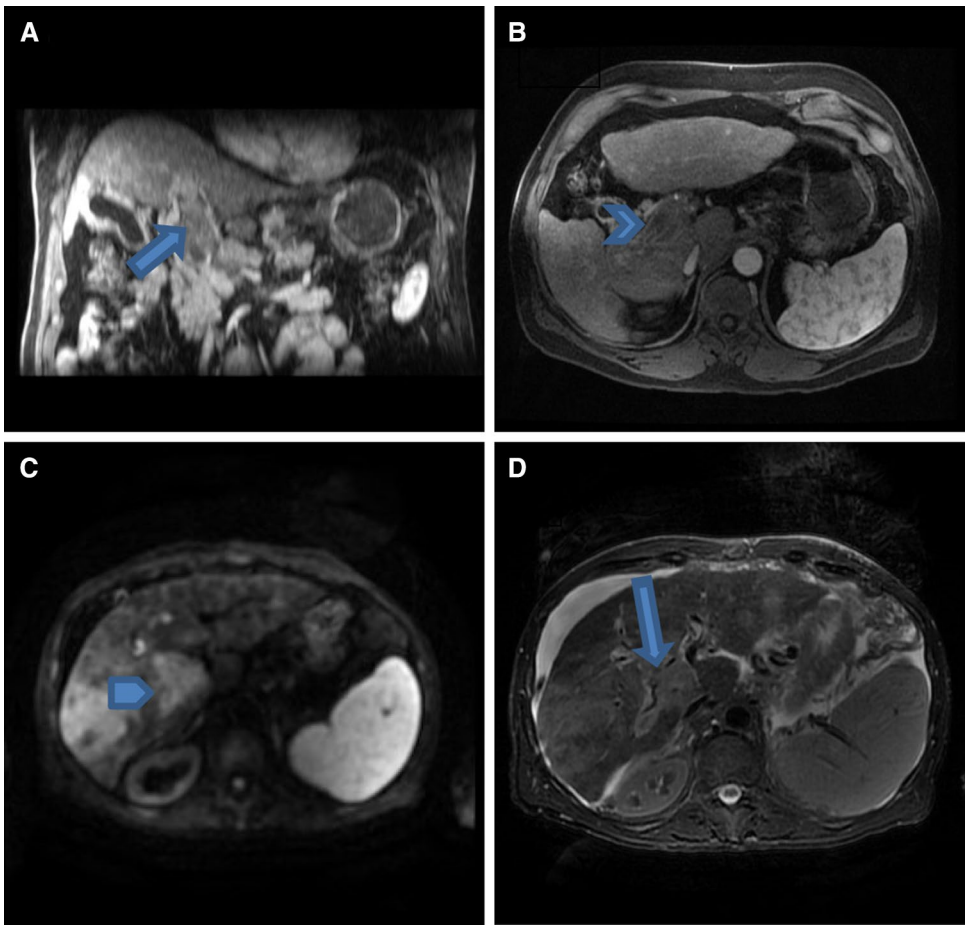

Fig. 3 **a**, **b** IV-contrast-enhanced MRI demonstrating a large infiltrative tumor thrombus (arrows) within the main portal. **c** DWI demonstrating diffusion restriction within the PVT (arrowhead). **d** T2 demonstrating hyperintense tumor thrombus in the main portal vein (arrow)

hyperdense contrast media [53]. CT and MRI may also show peripheral hepatic lesions that have delayed enhancement representing sequela of septic emboli (Figs. 4, 5).

Management

Anticoagulation (AC) forms the cornerstone of treatment for PVT and aims to prevent thrombus extension or recurrence, establish vessel patency, and prevent complications such as portal hypertension or intestinal infarction. For acute, non-cirrhotic, non-malignant PVT, results from a 2011 systematic review demonstrated complete, partial and overall (complete and partial) recanalization rates after AC administration to be 38.3%, 14% and 52.3%, respectively [38]. Furthermore, the time to recanalization ranged from 1 to 197 days. These results were mirrored in other studies [4, 36, 37]. Factors that contribute to the failure of recanalization include the presence of ascites and splenic vein thrombosis [39]. Additionally, recanalization rates have been shown to drastically decrease from 69% if AC is initiated in the 1st week to 25% if initiated in the 2nd week, highlighting the importance of early detection and treatment [40]. Cessation of AC before complete recanalization of the portal vein has been associated with a high rate of re-thrombosis [41]. Given these findings, the American Association for the Study of Liver Disease (AASLD) recommends at least 3 months of AC for all acute, non-cirrhotic cases of PVT, although 6–12 months is common in practice [42]. For chronic, non-cirrhotic PVT patients with a permanent risk factor for thrombosis, the AASLD recommends long-term AC therapy [42]. In these patients, adequate prophylaxis for variceal bleeding must be instituted prior to start of AC.

For patients with cirrhosis and PVT, data on the benefits of AC is limited and initiation of therapy should be on a case-by-case basis given the risk of bleeding and coexisting coagulopathy. In cases of intestinal ischemia/infarction or given the presence of an underlying thrombophilia, AC is warranted. A recent meta-analysis of 8 studies and 353 patients with cirrhosis and PVT sought to shed light on the safety and efficacy of AC in these patients [43]. The investigators determined that patients treated with AC had

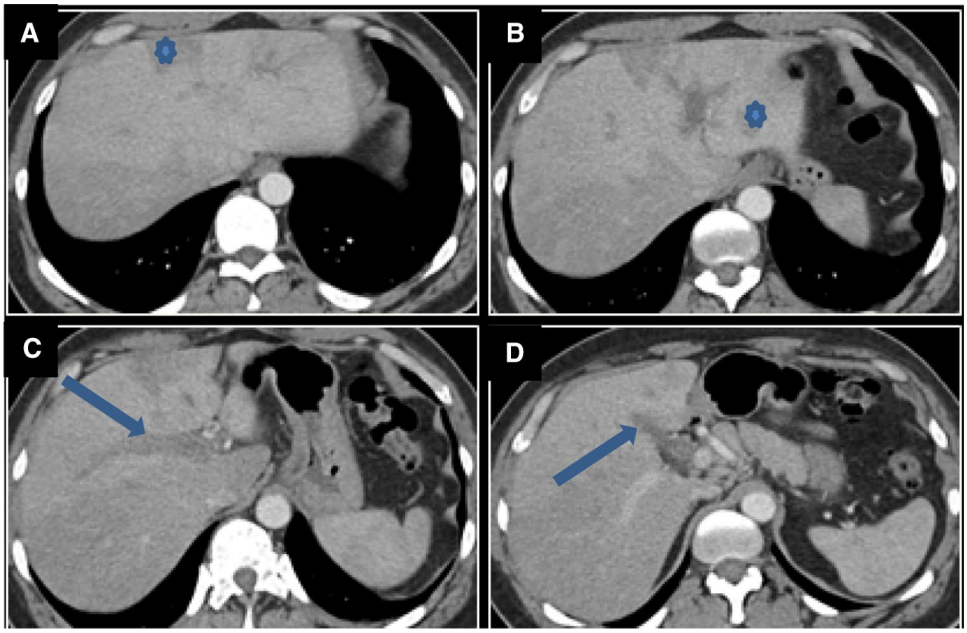

Fig. 4 **a**, **b** Contrast-enhanced CT demonstrating multiple new hypodense lesions within the liver (*). (C&D) Associated portal vein thrombosis PVT (arrow)

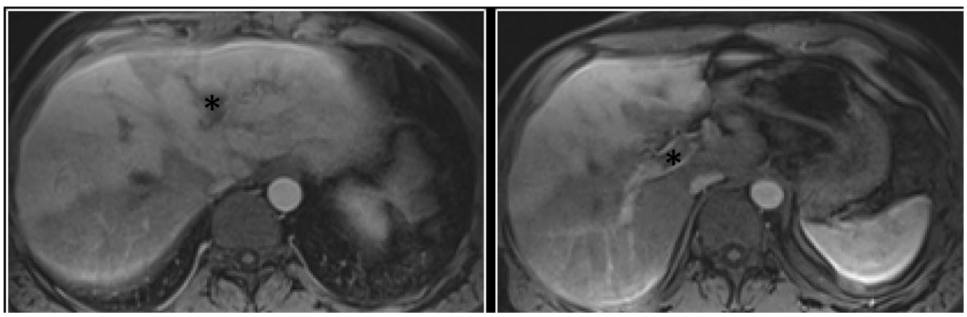

Fig. 5 IV-contrast-enhanced MRI demonstrating extensive bland thrombus through the left portal venous system (*)

significantly higher rates of partial or complete recanalization than those not treated with AC (71% vs. 42%, respectively). Additionally, patients on AC experienced less PVT progression compared to patients not receiving AC (53% vs. 33%, respectively). Perhaps most importantly, there was no significant difference in the proportion of patients experiencing major or minor bleeding between the two groups. Although a clinical trial is needed to validate these findings, these results allude to a potential benefit for AC in cirrhosis and PVT. AC has also demonstrated utility for cirrhotic PVT patients awaiting liver transplant [1]. Recanalization rates were high among those receiving AC, which is of significance as pre-transplant complete PVT may negatively affect post-transplant outcomes.

There remains a lack of agreement as to the best AC regimen for PVT and clinical trial data in this setting is limited [44]. In hospitalized patients, initiating a weight-based therapeutic heparin drip should be considered due to its availability, short half-life, reversibility, and clinical efficacy. As an outpatient, the clinician has the option of using warfarin, low-molecular weight heparin (LMWH), or novel oral anticoagulants (NOACs) such as rivaroxaban and apixaban [6]. While warfarin is the mainstay of outpatient deep vein thrombosis treatment, it should be used with caution in the setting of cirrhosis. Cirrhotic patients have an imbalance in the production of coagulation factors, which may become exacerbated by warfarin's mechanism of action. Additionally, INR may not reliably predict in vivo coagulability in these patients, making it difficult to find the correct therapeutic window for warfarin dosing [9, 45]. NOACs have the advantage of oral administration, straight-forward dosing and promising clinical efficacy without the reliance on INR to guide therapy. They should still be used with caution in the setting of cirrhosis, as they have not been validated in this setting. With the exception of dabigatran, NOACs are not currently reversible, although trials are underway on several reversal agents [9].

For patients with bowel ischemia, extensive thrombosis, contraindications or poor response to AC, or for those with co-morbidities that preclude AC, minimally invasive endovascular techniques offer alternative treatment options. Catheter-directed thrombolysis (CDT) using tissue-plasminogen activator (tPA) or other fibrinolytics can be performed via direct portal vein access through a percutaneous transhepatic (Fig. 6), percutaneous transsplenic or transjugular intrahepatic approach. Indirect intra-arterial approaches through the SMA have also been used with good outcomes [46]; however, this may prolong infusion time and increase the risk of potential bleeding complications. Thrombolysis can be combined with thrombectomy, in which the thrombus is mechanically fragmented and removed via catheter. The combination of these two procedures often reduces the dose of fibrinolytic needed and thus decreases bleeding complications. In a 2011 systematic review which included a subgroup of 71 patients who underwent CDT with or without thrombectomy, partial or complete recanalization was noted in 86% of patients [38]. It should be noted, however, that complications with these approaches are not uncommon and in one study, bleeding developed in 60% of patients with procedure related morbidity observed in up to 21% of patients [38]. Thrombolytic therapy with AC increases the risk of bleeding, while thrombectomy increases the risk of damaging the vessel lumen and also the risk of pulmonary embolism from thrombotic fragments [33].

For cirrhotic patients with complete chronic PVT, liver transplant is often relatively contraindicated due to increased intraoperative and post-operative morbidity and mortality. To optimize transplant candidacy for these patients, portal vein recanalization with TIPS placement is often performed and has demonstrated good outcomes (Fig. 7). In a study of 44 cirrhotic patients with near complete (> 95%) or complete chronic PVT awaiting potential liver transplant who underwent recanalization plus TIPS, compete recanalization was noted in 76% of patients 1 month after the procedure

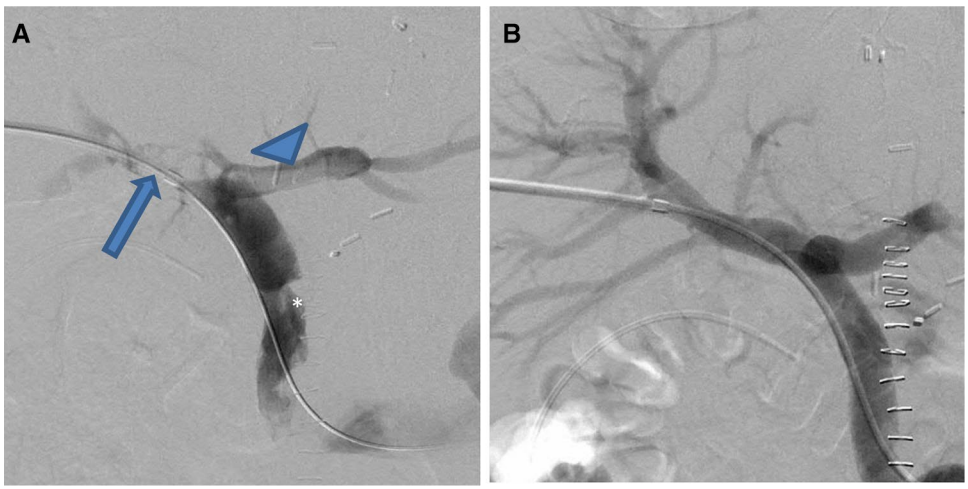

Fig. 6 **a** Portal vein access obtained via transhepatic puncture demonstrating complete right (arrow) and left (arrowhead) intrahepatic PVT with incomplete thrombosis of the SMV (*). **b** Repeat portography performed at 36 h following infusion of 1 mg/h alteplase demonstrates successful thrombolysis with no significant residual thrombus burden

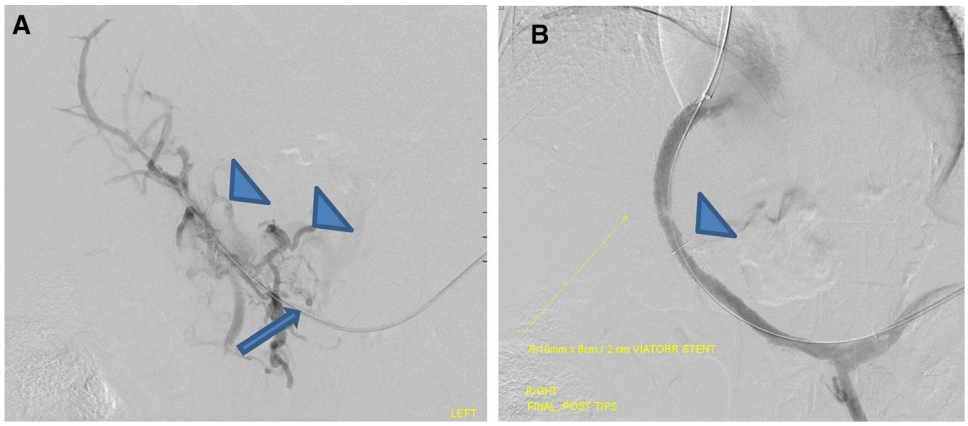

Fig. 7 **a** Portal vein access obtained via transsplenic puncture demonstrating complete chronic oblitrative portal vein occlusion (arrow) with cavernous transformation (arrowheads). **b** Post TIPS placement with balloon angioplasty of the main portal vein shows recanalization of the portal vein with resolution of the cavernous veins. Note the short TIPS stent (arrowhead) to maintain a long segment of the native portal vein for future liver transplant

and without the use of AC [47]. Additionally, results from another trial demonstrated no difference in recanalization rates after TIPS placement between patients receiving or not receiving systemic AC. PVT recanalization (83.9%) in the anticoagulation therapy group and in (71.8%) patients in the control group ($P = 0.252$). The Clinical outcomes were also similar between the two groups [48]. Recanalization plus TIPS placement has traditionally been performed via a transhepatic approach. More recently, a transsplenic approach, in a case series of 61 cirrhotic patients with chronic PVT, has been described as technically easier with a technical success rate of 98% [49]. With a mean follow-up period of 16.7 months, the transsplenic approach with adjuvant TIPS placement maintained patency in 92% of patients. Although TIPS placement has demonstrated efficacy in recanalization, it is a technically challenging procedure and not without possible complications. Portosystemic shunt creation rapidly alters hemodynamics and increases venous return such that heart failure or tricuspid regurgitation can occur, therefore, a cardiac evaluation and echocardiogram should be performed to screen for subclinical insufficiencies. Metabolic portosystemic shunting can also occur and hepatic encephalopathy can be exacerbated following TIPS placement.

Conclusion

PVT represents a serious clinical concern in cirrhotic patients and in those with specific local or systemic risk factors. The rate and extent of thrombus formation can significantly impact patient presentation and the resulting clinical outcomes. The presentation of acute PVT can range from abdominal pain to intestinal ischemia/infarction and even death, while chronic PVT can remain clinically silent. To optimize early detection and incorporate effective therapeutic options, the management of these complex patients should be undertaken by a multidisciplinary team. A number of imaging modalities including US, CT and MRI can be used to confirm the diagnosis. In addition to addressing underlying risk factors, AC therapy forms a cornerstone of treatment and has demonstrated efficacy in both acute and chronic settings. Proper caution should be used when initiating AC therapy in cirrhotic patients given their underlying coagulopathic status with attention now being paid to NOACs and LMWH. In more recent years, minimally invasive catheter-based therapies and endovascular portosystemic shunt creation have also demonstrated efficacy in the treatment of AC-resistant patients and for patients with extensive or complicated disease.

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