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REVIEW

Portal vein thrombosis: Insight into physiopathology, diagnosis, and treatment

Francesca R Ponziani, Maria A Zocco, Chiara Campanale, Emanuele Rinninella, Annalisa Tortora, Luca Di Maurizio, Giuseppe Bombardieri, Raimondo De Cristofaro, Anna M De Gaetano, Raffaele Landolfi, Antonio Gasbarrini

Francesca R Ponziani, Maria A Zocco, Chiara Campanale, Emanuele Rinninella, Annalisa Tortora, Luca Di Maurizio, Giuseppe Bombardieri, Raimondo De Cristofaro, Raffaele Landolfi, Antonio Gasbarrini, Department of Internal Medicine, Catholic University of Rome, 00168 Rome, Italy
Anna M De Gaetano, Department of Bioimaging and Radiological Sciences, Catholic University of Rome, 00168 Rome, Italy
Author contributions: Ponziani FR designed and wrote the review; De Gaetano AM and Zocco MA collected the images; Campanale C, Rinninella E, Tortora A and Di Maurizio L wrote the references and tables; Bombardieri G, De Cristofaro R, Landolfi R and Gasbarrini A revised the paper.
Correspondence to: Francesca R Ponziani, MD, Department of Internal Medicine, Catholic University of Rome, 00168 Rome, Italy. francesca.ponziani@yahoo.it
Telephone: +39-347-1227242 Fax: +39-6-30156018
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Abstract

Portal vein thrombosis (PVT) is a relatively common complication in patients with liver cirrhosis, but might also occur in absence of an overt liver disease. Several causes, either local or systemic, might play an important role in PVT pathogenesis. Frequently, more than one risk factor could be identified; however, occasionally no single factor is discernable. Clinical examination, laboratory investigations, and imaging are helpful to provide a quick diagnosis, as prompt treatment might greatly affect a patient's outcome. In this review, we analyze the physiopathological mechanisms of PVT development, together with the hemodynamic and functional alterations related to this condition. Moreover, we describe the principal factors most frequently involved in PVT development and the recent knowledge concerning diagnostic and therapeutic procedures. Finally, we analyze the implications of PVT in the setting of liver transplantation and its possible influence on patients' future prognoses.

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Key words: Portal vein thrombosis; Portal hypertension; Thrombophilic factors; Liver cirrhosis; Liver transplantation; Anticoagulants

Peer reviewers: Hiroshi Yoshida, MD, First Department of Surgery, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan; Diego Garcia-Compean, MD, Professor, Faculty of Medicine, University Hospital, Department of Gastroenterology, Autonomous University of Nuevo Leon, Ave Madero y Gonzalitos, 64700 Monterrey, NL, México

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INTRODUCTION

The term portal vein thrombosis (PVT) refers to the complete or partial obstruction of blood flow in the portal vein, due to the presence of a thrombus in the vasal lumen[1]. Although in the general population PVT is considered a rare event, its prevalence among cirrhotic patients ranges between 4.4%-15%, and is responsible for about 5%-10% of overall cases of portal hypertension[2]. The first case of PVT was reported in 1868 by Balfour and Stewart, describing a patient presenting splenomegaly, ascites, and variceal dilation[3]. Several etiological causes, either of local or systemic origin, might be responsible for PVT development, although more than one factor is often identified. Furthermore, PVT clinical presentation

is different in the context of acute or chronic onset and depends on the development and the extent of a collateral circulation. Intestinal congestion and ischemia, with abdominal pain, diarrhea, rectal bleeding, abdominal distention, nausea, vomiting, anorexia, fever, lactacidosis, sepsis, and splenomegaly are common features of acute PVT. In contrast, chronic PVT can be completely asymptomatic, or characterized by splenomegaly, pancytopenia, varices, and, rarely, ascites[3]. In the presence of portal hypertension, PVT must always be investigated, especially in cirrhotic patients, even if it is considered a rare event[2]. Indeed, an early diagnosis and appropriate management of secondary portal hypertension could be, in some cases, life-saving for the patient. Furthermore, in the diagnostic iter, the identification of possible local or systemic trigger factors is of primary importance however, occasionally no single factor is discernable.

Currently, several therapeutic options are available; however, their feasibility and efficacy are still being evaluated and the risks and benefits should be carefully considered for each patient.

In this review, we discuss the features of PVT, pointing out new insights into clinical, diagnostic, and therapeutic issues, making an overview of current beliefs regarding patient outcome and, finally, reporting controversies about the correct management of PVT in the setting of liver transplantation.

PATHOPHYSIOLOGY

As a consequence of portal vein obstruction, systemic and splanchnic hemodynamics undergo specific and important modifications[4]. On the cessation of portal blood flow, the liver loses about two thirds of its blood supply. Interestingly, this condition is usually well tolerated and patients are often asymptomatic, while an acute arterial obstruction always leads to a severe hepatic dysfunction, which is sometimes fatal. It is probably that the immediate activation of two compensatory mechanisms might supplement the loss of portal vein's contribution to liver blood flow. The first mechanism is "arterial vasodilation" of the hepatic artery, similar to that observed in portal vein clamping during liver surgery[5]. This "arterial rescue" is a kind of vascular reflex present in every organ with both an arterial and a venous circulation and is capable of preserving liver function in the acute stages of PVT. The second compensatory mechanism is "venous rescue", consisting of the rapid development of collaterals to bypass the obstruction. This vascular neo-formation begins in a few days after portal vein obstruction, and finalizes within 3 to 5 wk[6,7]. As a result, the thrombosed portal vein is replaced by a network of collateral vessels, called "cavernoma", connecting the two patent portions proximally and distally to the thrombus. Usually, the original portal vein becomes a thin, fibrotic cord, which is difficult to visualize[8,9]. At this stage, the development of a hyperkinetic circulation, characterized by low systemic vascular resistance and a high cardiac output, is common[3].

Despite the activation of this complex system of support, the impairment of portal flow has important consequences on liver tissue. It has been demonstrated in rats, that the progressive obliteration of the portal vein stimulates apoptosis of hepatocytes in the hypoperfused lobe[10], while increasing the mitotic activity in the normal perfused one. The latter effect is well known, and is employed therapeutically in resective liver surgery. However, this process results in a progressive loss of tissue and might be responsible for the impairment of hepatic synthetic function observed in advanced stages of portal vein obstruction[11].

EPIDEMIOLOGY

The concept of PVT as a rare disease is mainly based on clinical series and case reports[2]. An epidemiological study performed in southern Sweden and based on autopsies, reported the incidental finding of a PVT in about 1% of the general population[12]. Cohen *et al*[13] confirmed these data and reported that most PVT patients were cirrhotics with a primary or metastatic liver cancer. Today, thanks to the availability of more sensitive and less invasive imaging, together with the existence of curative or palliative procedures, PVT is routinely investigated and recognized without any difficulty[14-16]. Thus, PVT seems more frequent than expected: it is estimated to be responsible for 5%-10% of the overall cases of portal hypertension, which can be 40% in developing countries[3]. The incidence among cirrhotic patients is still unknown, but recent data suggest a prevalence of about 0.6%-16%[17] (the highest) among orthotopic liver transplantation (OLT) candidates[2] and of about 6.5% in patients with a hepatocellular carcinoma at the time of diagnosis[16].

ETIOLOGY

Several causes can be involved in the pathogenesis of PVT and, frequently, more than one coexist. A simple classification distinguishes between local (70%) and systemic (30%) risk factors (Tables 1 and 2).

Inflammatory abdominal foci (such as appendicitis, diverticulitis, inflammatory bowel diseases, pancreatitis, cholecystitis, hepatic abscesses, and cholangitis), liver cirrhosis or tumors, represent the most common local thrombotic risk factors[8,12,18].

Malignancies, frequently of hepatic or pancreatic origin, are responsible for 21%-24% of overall cases of PVT[13,19]. Direct vascular invasion, compression by tumor mass, or a hypercoagulable state are the mechanisms involved in neoplastic PVT development; hormonal factors might also play a role in this process, especially in men[16,20,21].

PVT is common in patients affected by liver cirrhosis, with a risk related to the severity of the disease; the prevalence ranges from 1%, at the earlier stages, to 30% in candidates for liver transplantation[8,17]. Moreover, in patients with a hepatocellular carcinoma, the incidence of PVT rises to 10%-40%[9].

Table 1 Most frequent local risk factors for PVT[3,8,9,17,18,64,79]

Local risk factors for PVT (70%)
Cancer
Any abdominal organ
Focal inflammatory lesions
Neonatal omphalitis, ombilical vein catheterization
Diverticulitis, appendicitis
Pancreatitis
Duodenal ulcer
Cholecystitis
Tuberculous lymphadenitis
Crohn's disease, ulcerative colitis
Cytomegalovirus hepatitis
Injury to the portal venous system
Splenectomy
Colectomy, gastrectomy
Cholecystectomy
Liver transplantation
Abdominal trauma
Surgical portosystemic shunting, TIPS
Iatrogenic (fine needle aspiration of abdominal masses *etc.*)
Cirrhosis
Preserved liver function with precipitating factors (splenectomy, surgical portosystemic shunting, TIPS dysfunction, thrombophilia)
Advanced disease in the absence of obvious precipitating factors

PVT: Portal vein thrombosis; TIPS: Transjugular intrahepatic portosystemic shunt.

Table 2 Most frequent systemic risk factors for PVT[3,8,9,17,18,64,79]

Systemic risk factors for PVT (30%)
Inherited
Factor V Leiden mutation
Factor Ⅱ (prothrombin) mutation
Protein C deficiency
Protein S deficiency
Antithrombin deficiency
Acquired
Myeloproliferative disorder
Antiphospholipid syndrome
Paroxysmal nocturnal hemoglobinuria
Oral contraceptives
Pregnancy or puerperium
Hyperhomocysteinemia
Malignancy

Other less common PVT local causes are adenopathy, systemic inflammatory response syndrome, and surgical traumas to the portal venous system, such as portosystemic shunting, splenectomy, liver transplantation, ablative therapy for HCC, and fine needle aspiration of abdominal masses[1].

On the other hand, myeloproliferative disorders and prothrombotic conditions belong to the group of systemic risk factors, with a prevalence of about 40% and 60%, respectively (Table 3)[8,22].

Factor V Leiden mutation is the most common thrombophilia predisposing to PVT, followed by protein C (PC) deficiency[23-26]. The role of protein S (PS) and antithrombin Ⅲ (AT) deficiency in PVT etiology has not yet been confirmed, and it is difficult to evaluate

Table 3 Prevalence of thrombotic risk factors in series of routinely investigated, consecutive adult patients with non tumorous and non cirrhotic, acute or chronic, PVT[126]

Risk factor	PVT patients (%)
Myeloproliferative disorders	30-40
Atypical	14
Classical	17
Antithrombin deficiency	0-26
Protein C deficiency	0-26
Protein S deficiency	2-30
Factor V Leiden mutation	6-32
Prothrombine mutation	14-40
TT677 methylene tetrahydrofolate reductase (MTHFR) genotype	11-50
Antiphospholipid syndrome	6-19
Hyperomocisteinemia	12-22
Recent pregnancy	6-40
Recent oral contraceptive use	12

the influence of anticoagulation therapy on the impairment in liver function. Indeed, in cirrhotic patients it is hard to distinguish between congenital and acquired deficiencies of natural coagulants and their role in PVT pathogenesis, because if liver function is impaired, levels of coagulation inhibitors, as well as those of pro-coagulation factors, are often decreased[27]. A clinical study conducted on eleven children with PVT[28], reported a significant improvement in PC, PS, factors Ⅱ, V, and Ⅶ levels and prothrombin time after surgical correction with a Rex Shunt (mesenteric-left portal vein bypass). In contrast, a distal spleno-renal shunt or an H-type meso-caval shunt, in the same condition, didnot seem to be equally effective, probably due to insufficient residual portal vein flow and the consequent impairment in liver synthetic function[29]. However, the relatively low prevalence of genetic, in respect to acquired, thrombophilic disorders, might represent a potential diagnostic matter in PVT patients, and should be considered carefully in clinical practice[30]. To overcome this problem, an accurate genetic study of the patient and, eventually, his/her family (first degree relatives) might be useful in strongly suggestive cases. Unfortunately, in practice, this policy is not applicable without difficulty. A simple method to screen the deficiency of natural anticoagulants in patients with liver disease comprises the ratio of PS or PC or AT to [(factor Ⅱ + factor X)/2]. If the result is less than 70%, a genetic deficiency has to be suspected and investigated[1].

Among the other thrombophilic disorders, a prothrombin gene mutation seems to be frequent among cirrhotics with PVT[2,31-34]. However, in the general population, its role in PVT development seems less clear, as it is considered a weak prothrombotic risk factor. Moreover, a homozygous *methylene tetrahydrofolate reductase* (*MTHFR*) gene mutation might be associated with PVT development alone or, if heterozygote, in the presence of other cofactors[13,35-39]. Amitrano *et al*[27] reported a strong correlation between the prothrombin A20210

mutation or the homozygous MTHFR C677-T genotype and PVT in cirrhotic patients without evidence of liver cancer.

Furthermore, the presence of anticardiolipin antibodies is quite frequent in patients with chronic liver disease; a transient positivity is often reported after infections, suggesting a relationship between microorganisms (i.e. Bacteroides species) and thrombotic events, such as PVT[40-43]. In contrast, other studies consider anticardiolipin antibodies simply as an epiphenomenon of liver damage[41,44]. Finally, the role of oral contraceptives, steroids, and pregnancy is still less clear[45-47].

In about 22%-48% of patients, PVT is a manifestation of a myeloproliferative disease (MPD)[2,20,48].

An intra-abdominal vascular thrombosis is often the sole presenting symptom and an overt MPD might successively develop in 51% of cases. In the Western Countries, 58% of idiopathic PVTs are associated with a latent MPD[49]. The principal diagnostic criteria are usually incompletely met in these patients, probably because of the atypical manifestation of the disease[50]. The 1849G→T point mutation in the gene encoding tyrosine-protein kinase JAK2, is a specific and easily detectable marker for MPDs, which can often be useful for a rapid diagnose in PVT patients[51-55]. Recent studies reported the presence of a JAK2 mutation in about 17%-35% of patients with PVT, but further studies are needed to confirm these data[56,57].

Occasionally, it is not possible to recognize any overt cause of PVT; generally, the clinical course is favorable for these patients, with a low incidence of complications. However, at present, "idiopathic PVT" is less frequent, thanks to the amelioration in diagnostics and to a more scrupulous attention to patients' clinical history[12].

In conclusion, it is reasonable to routinely investigate the most common prothrombotic disorders and exclude a local trigger, to provide a correct management of PVT and its original cause. However, the mechanism of PVT development is complex and multifactorial, and is not always attributable to a single risk factor. In the presence of sporadic local or systemic promoting events, an underlying intrinsic predisposition might be the access key to thrombosis development[1,13].

CLASSIFICATION

PVT onset can be acute or chronic. This is an arbitrary distinction, which is sometimes difficult to apply in clinical practice; patients who develop symptoms, such as abdominal pain, nausea, and fever, within sixty days prior to hospital admission, might have an acute PVT development[58,59].

PVT can be classified into four categories, depending on the extension: (1) confined to the portal vein beyond the confluence of the splenic vein; (2) extended to the superior mesenteric vein, but with patent mesenteric vessels; (3) extended to the whole splanchnic venous system, but with large collaterals; or (4) with only fine collaterals[60]. This classification is useful to evaluate a patient's operability and clinical outcome. In fact, when thrombosis is extended to both portal and mesenteric veins, the risk of bowel ischemia is considerable and mortality high, despite a lower risk of variceal bleeding[61].

CLINICAL PRESENTATION

PVT can occur either in childhood or in adulthood, with the same incidence[45]. Clinical presentation always depends on the onset and the extent of the thrombosis and the development of collateral circulation[62].

Acute PVT

Intestinal congestion and ischemia are typical manifestations of acute PVT; abdominal pain or distention, diarrhea, rectal bleeding, nausea, vomiting, anorexia, fever, lactacidosis, splenomegaly and sepsis might be variably present[63,64]. If the obstruction is not resolved quickly, intestinal perforation, peritonitis, shock, and death from multiorgan failure might occur[8]. On physical examination, the abdomen might be distended, but guarding is rare, except in case of intra-abdominal inflammation, intestinal infarction, and perforation[22]. The majority of patients exhibit splenomegaly, while ascites is rare or, eventually, present before the development of a collateral circulation. This mild, transient, ascites is due to intestinal venous congestion in the absence of the mechanisms activated in liver cirrhosis[63,64].

Chronic PVT

On the other hand, chronic PVT can be nearly asymptomatic, except for the presence of varices, cutaneous collaterals, or ascites[62]. Typically, patients with an advanced thrombosis do not always remember any previous trigger event or disease[22,63,64]. The majority of patients develop esophageal varices, in contrast to acute PVT; an episode of gastrointestinal bleeding is reported as the first presenting symptom in about 20%-40% of cases[9]. As this phenomenon is strictly time-dependent, it is advisable to screen all PVT patients endoscopically, at diagnosis[63]. In cirrhotics with PVT, the risk of variceal bleeding is nearly 80-120 times higher than in patients without liver disease, although the outcome seems better[65,66].

Furthermore, hypersplenism and, consequently, pancytopenia, are commonly present in chronic PVT[1]; however, if one branch of the portal vein is preserved and the portal pressure is quite normal, they may even be absent. Ascites and encephalopathy are uncommon and only transient. They are more frequent after an episode of gastrointestinal bleeding or associated with renal failure or sepsis in older patients[8,64,67]. Abnormalities of the extrahepatic biliary tree have been reported in more than 80% of patients with chronic PVT; compression by choledochal or periportal varices or by the cavernoma, pericholedochal fibrosis, and ischemic structuring are the principal reasons[67-71]. Another finding is the "pseudocholangiocarcinoma sign"[1,11,17], caused by the displacement, stricturing or thumbprinting of the biliary

Table 4 AASLD recommendations for diagnosis of acute and chronic PVT[126]

AASLD recommendations for diagnosis of acute PVT	AASLD recommendations for diagnosis of chronic PVT
Consider a diagnosis of acute PVT in any patient with abdominal pain of more than 24 h duration, whether or not there is also fever or ileus	Consider a diagnosis of chronic PVT in any patient with newly diagnosed portal hypertension
If acute PVT is suspected, computed tomography (CT) scan, before and after injection of vascular contrast agent, should be obtained for early confirmation of diagnosis. If CT scan is not rapidly available, obtain Doppler-sonography	Obtain Doppler-sonography, then either CT scan or MRI, before and after a vascular contrast agent, to make a diagnosis of chronic PVT
In patients with acute PVT and high fever, septic pylephlebitis should be considered, whether or not an abdominal source of infection has been identified, and blood cultures should be routinely obtained	Base the diagnosis on the absence of a visible normal portal vein and its replacement with serpiginous veins
In acute PVT, the possibility of intestinal infarction should be considered from presentation until resolution of pain. The presence of ascites, thinning of the intestinal wall, lack of mucosal enhancement of the thickened intestinal wall, or the development of multiorgan failure indicate that intestinal infarction is likely and surgical exploration should be considered	

ducts produced by contiguous neo-formed vessels; it is present in at least 80% of PVT patients at endoscopic retrograde cholangiopancreatography[67], often mimicking a cholangiocellular cancer[72,73]. Physical examination and biochemical markers might be completely normal, but, sometimes, cholestasis, cholangitis, choledocholithiasis, cholecystitis and, at least, liver injury, might occur, configuring the so-called "portal biliopathy"[71,74].

DIAGNOSIS

Imaging

The diagnosis of PVT can be quickly established by demonstrating the presence of solid material within the vasal lumen (Table 4)[22]. Nowadays, in developed countries, PVT is usually recognized at an early stage; cavernomatous transformation or the occurrence of gastrointestinal bleeding are rare. The clinical suspicion is often based on the incidental finding of hypersplenism, signs of portal hypertension or, less frequently, symptoms of portal cholangiopathy. Ultrasonography (US) is usually the investigation of choice, with a sensitivity and specificity ranging between 60% and 100%[17]; it can reveal the presence of solid, hyperechoic material into a distended portal vein or its tributaries, the presence of collateral vessels or a cavernoma (Figures 1-3)[18,22,75]. Doppler imaging can confirm the absence of flow in part or all the vasal lumen, and, if present, a cavernomatous transformation[22]. Recently, the endoscopic use of ultrasound (EUS) was demonstrated to be 81% sensitive and 93% specific in PVT diagnosis[76], and to be capable of detecting small and non-occluding thrombi. It appears to be more accurate than US or computed tomography (CT) scans in discovering portal invasion by tumors[77,78]. However, the limit of EUS is the presence of a relatively blind area, which cannot be investigated, involving the distal superior mesenteric vein and the intrahepatic portion of the portal vein[76].

Incidentally, US is less reliable in determining the extension of the thrombus to the mesenteric circulation[79]. Instead, CT scanning and magnetic resonance imaging (MRI) can easily obtain this information, and, in addition, can estimate the impairment of the bowel and other adjacent organs (Figures 1-3). CT scanning is able to demonstrate hyperattenuating material in the portal vein lumen and the absence of enhancement after contrast injection. In addition, in hypoperfused areas, hepatic enhancement appears increased during the arterial phase and decreased during the portal phase. CT is also useful for the identification of the possible cause of the thrombosis or potential complications, such as bowel ischemia and perforation[22]. MRI might also confirm the vascular occlusion; at spin-echo MR, the clot appears isointense on T1- weighted images, or hyperintense if recent, and usually has a more intense signal on T2 images. Gradient-echo MR might help to better evaluate any confusing spin-echo MR image[80]. Furthermore, contrast-enhanced MR angiography is useful to assess flow direction in the portal venous system and its patency, to identify a cavernomatous transformation, to determine the presence of varices, and to verify the correct function of surgical shunts[81,82]. In addition, MR angiography has a high accuracy in the follow-up of the portal venous system before and after liver transplantation[82-85]. Moreover, MRI-true fast imaging with steady state precession (true FISP), might overcome the difficulty of contrast injection in cases of poor venous access and the degradation of the images by respiratory motion[86].

laboratory investigations

In PVT patients, liver function is typically conserved. Laboratory investigations will be normal or quite normal, unless there is coexistence of a liver disease. However, levels of prothrombin and other coagulation factors could be moderately decreased, while D-dimer is usually increased[8,22].

PVT is considered a milestone in the natural history of liver cirrhosis and it is related to serious complications, morbidity, and mortality, as previously discussed[87]. Thus, prevention is the first aim of PVT management in patients with an advanced liver disease. Recently, several studies tried to identify the strongest predictive factors for PVT development in these patients. In the past, male sex, previous surgery or interventional treatment for portal

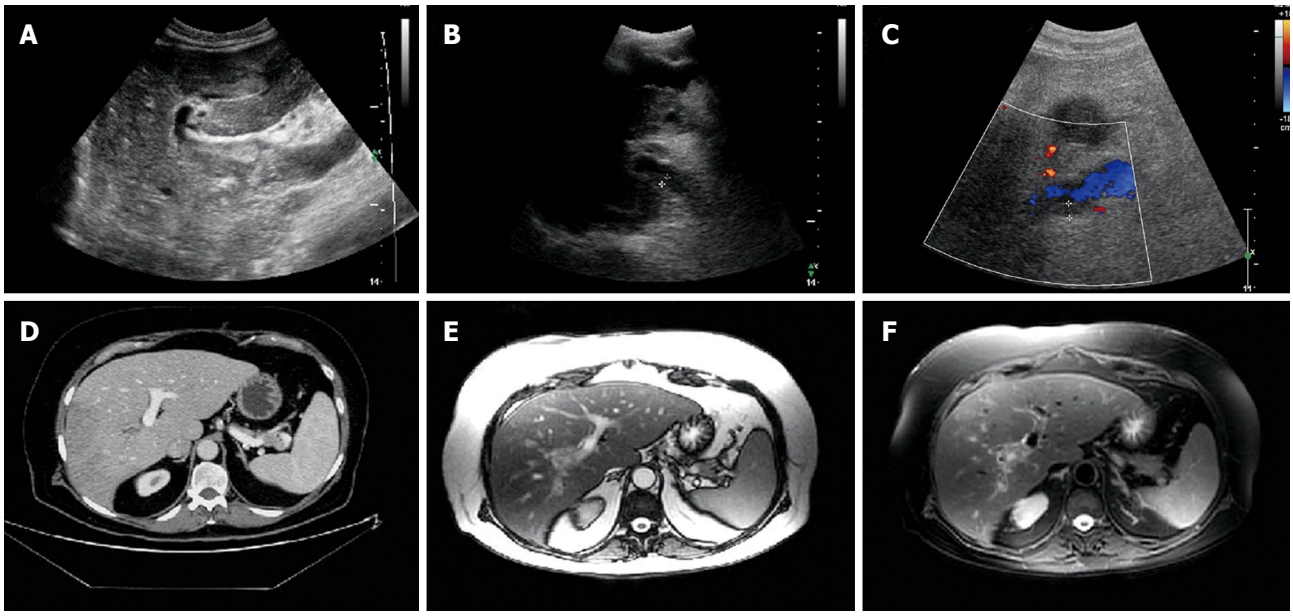

Figure 1 Portal vein thrombosis. A: Complete thrombosis of the portal vein trunk (ultrasonography); B, C: Partial thrombosis of the right portal vein (ultrasonography and ultrasonography + doppler); D: Thrombosis of the right portal vein (CT scan); E, F: Thrombosis of the right portal vein (MRI).

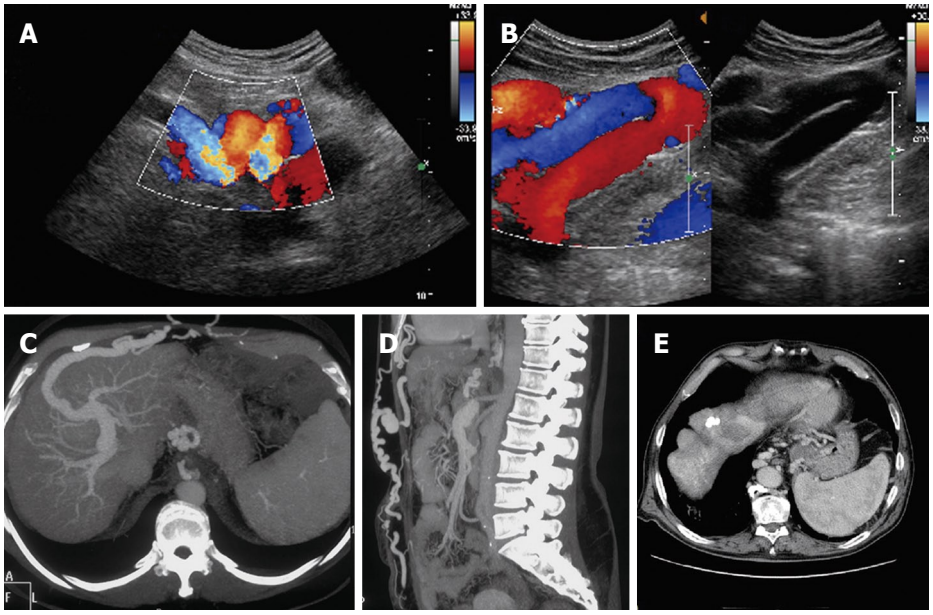

Figure 2 Collateral circulation. A, B: Recanalization of paraumbilical vein (ultrasonography + doppler); C, D: Recanalization of paraumbilical vein (CT scan); E: Perigastric and paraesophageal varices (CT scan).

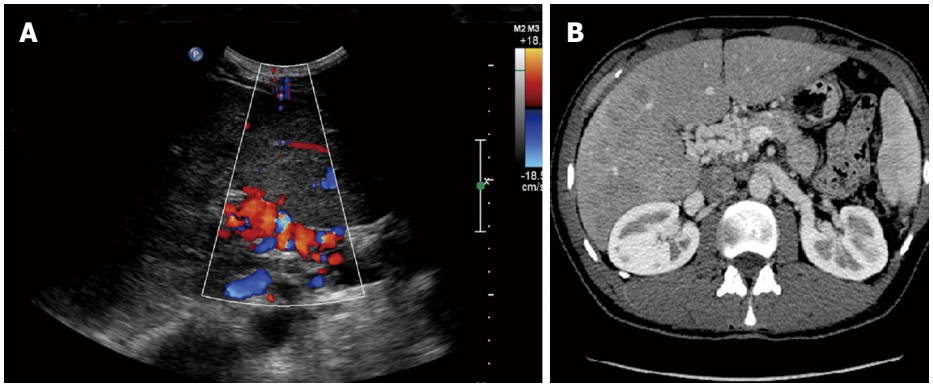

Figure 3 Cavernomatous transformation of the portal vein. A: Ultrasonography + doppler; B: CT scan.

hypertension, previous variceal bleeding, low platelet count, and advanced liver failure have been associated with an increased risk of PVT development[2,31,85,88]. Interestingly, in a recent prospective study by Zocco *et al*[89],

Table 5 Intraoperatory grading of PVT extension[17]

Yerdel's grading
< 50% occlusion of the portal vein
> 50% occlusion of the portal vein (including total occlusion)
Complete thrombosis of both portal and proximal superior mesenteric vein
Complete thrombosis of portal vein and proximal and distal superior mesenteric vein

a portal flow velocity below 15 cm/s, at US-Doppler evaluation, was considered significantly predictive of PVT development, confirming the importance of Virchow's triad in the pathogenesis of vascular thrombosis.

Original cause

As first, local causes such as cirrhosis, primary or metastatic malignancies, pylephlebitis, liver cysts, vascular abnormalities (webs or aneurysms), and pancreatitis have to be excluded. Imaging (US+Doppler, MRI or CT scan) or invasive procedures might be helpful[22]; needle biopsy of the obstructed portal vein might be specific, but also of relatively low sensitivity[90]. If no local risk factor is found, the presence of a thrombophilic disorder must be investigated. If no possible cause of the thrombosis is recognized, the PVT should be considered "idiopathic". Incidentally, a subclinical prothrombotic state has been reported in about 72% of idiopathic PVT, including an overt or occult MPD[91-93].

Complications

Once the diagnosis has been reached, the severity of liver and other organs' involvement should be assessed. Clinical and laboratory evaluation, as well as imaging, might be useful; the degree of the obstruction (complete or partial, limited or extensive) should be investigated. A partial thrombosis is often associated with few symptoms. Instead, a rapid and complete obstruction of the portal or mesenteric vein, without the involvement of the mesenteric venous arches, induces only intestinal congestion; the main feature is a diffuse thickening of the intestinal wall, visible even without alterations in contrast enhancement. Generally, there are no signs of other organ failures and liver function is usually preserved, probably because the increased hepatic arterial blood flow supplants portal obstruction. In addition, collateral circulation develops rapidly from pre-existing veins in the porta hepatis within 2 to 3 d after the onset of acute thrombosis, particularly in the gallbladder wall[61,94,95]. All these manifestations are completely reversible, even if a spontaneous recanalization or a cavernomatous transformation occurs. In contrast, when thrombosis spreads to mesenteric venous arches, the consequence is intestinal ischemia or infarction. Common radiological findings are the thinning of the intestinal wall and the presence of defects of enhancement after intravenous contrast injection[8].

PROGNOSIS

In non-cirrhotic and non-neoplastic patients, PVT has generally good outcome; exitus for gastrointestinal bleeding is uncommon[65,96,97]. Otherwise, prognosis depends on the underlying liver disease[1,12,22,79]. The overall mortality has been reported to be less than 10% in PVT chronic onset[18,98], except for patients with malignancy or cirrhosis - about 26%[63]. Moreover, advanced age, malignancy, cirrhosis, mesenteric vein thrombosis, absence of abdominal inflammation, and serum levels of aminotransferase and albumin are associated with reduced survival[65]. Systemic risk factors, like MPD or other prothrombotic disorders, seem not to affect short-term survival[99].

In addition, acute PVT, when recognized and treated before the occurrence of intestinal infarction, has good prognosis[61,100-103]. By contrast, in cases of bowel ischemia and multiorgan dysfunction or failure, patients in-hospital mortality rate is approximately 20%-50%[61].

PVT AND OLT

In the past, PVT was considered an absolute contraindication for liver transplantation. Currently, thanks to great innovations in medical care, surgical techniques, and radiological interventions, this belief has been confounded and PVT by itself can represent an indication for liver transplantation[11,64,104,105]. The first successful liver transplant in a patient with a thrombosed portal vein was reported by Shaw *et al*[106], in 1985. Several studies[107-111] showed that surgical thrombectomy, thromboendovenectomy with venous reconstruction, interposition of vein graft, porto-caval hemitransposition, and radiological endovascular interventions, can resolve venous obstruction in liver transplant recipients[112]. However, surgical options are various, and dependent on a correct intra-operatory grading of the thrombosis (Table 5); terminal to terminal portal vein anastomosis with or without thrombectomy is the common choice in low grade PVT, while porto-caval hemitransposition is mandatory in grade 4[85,113]. Comparisons of technical difficulties, postoperative complications, survival, and mortality, in recipients with or without PVT are contrasting. Several studies reported a more complex surgical procedure, with a greater requirement of blood transfusions, an increased risk of complications (such as primary non function or dysfunction, thrombosis of the hepatic artery, relaparotomy, postoperative pancreatitis, sepsis, and renal failure), a poorer survival, and a higher mortality[113-115]. However, these data have not been confirmed and features of liver transplantation, comparing recipients with PVT and those without, are similar[74,113-116]. Interestingly, PVT patients' rates of survival at one and 5 years after OLT are equal, as if, once the peri-transplant period has been overcome, the future clinical destiny of recipients with or without a previous PVT could be overlapped. However, among patients with PVT, survival seems better in low grades of Yerdel classification; however, further studies are needed to confirm

this data. Transplantation at grade 1 PVT seems to carry results comparable to non-PVT patients[74,85,117].

The rate of thrombosis recurrence has been estimated within 9% to 42% although some authors reported a lower incidence[74,107,108,116,118-120]. Male sex, previous treatment for PVT, Child-Pugh class C, and alcoholic liver disease might be associated with recurrence[85,114]. Furthermore, patients with an obstruction of more than half of the portal vein, extended or not to the superior mesenteric vein, seem to have increased risk of severe peri-operative complications, higher mortality, and decreased long-term survival[85,107,115]. In cirrhotics with PVT, surgical procedure may be more difficult, often complicated by rethrombosis and reintervention, but with the same morbidity and mortality of non-cirrhotic patients[113,115,121,122].

After liver transplantation, PVT development is a rare but possible event, especially in the early postoperative period[60]. The incidence ranges between 1% and 2%[122-124], with a preferential localization at the anastomotic site; technical complications, small diameter of the portal vein, pediatric recipient, presence of PVT pre-OLT, surgical shunting pre-OLT, or splenectomy are the principal predisposing risk factors[124]. The occlusion of the portal vein is always more scarring than the thrombosis of the hepatic artery and may be seriously threatening for both graft and patient survival[122]. Acute liver failure, bleeding from esophageal varices, and massive ascites could rapidly occur and immediate retransplantation must be quickly attempted in case of severe worsening of liver function[124].

Thus, for all these reasons and the good results reported in literature, today PVT has no longer to be considered a contraindication but only a disadvantage and, in some cases, might present a possible indication to liver transplantation[114,116,124,125].

TREATMENT

Although spontaneous resolution of PVT has been reported in the literature[101,102], a specific therapeutic management is mandatory to resolve portal vein obstruction and avoid serious complications. The goal of treatment is similar in acute and chronic PVT, and consists in correction of causal factors, prevention of thrombosis extension, and achievement of portal vein patency. However, in case of long standing thrombosis, the management of complications related to portal hypertension and portal cholangiopathy has to be concurrently considered[126]. Nowadays, anticoagulant therapy is the best way to obtain portal vein recanalization; however, there is no consensus on its application. Other modalities of treatment should be adopted only in case of partial or absent PVT resolution[12,126]. Furthermore, some conditions should be considered in the assessment of anticoagulant therapy, such as recent *vs* old thrombosis, the presence of a thrombophilic condition, or a liver disease.

Anticoagulation in acute PVT

Although PVT might be compared to other cases of deep vein thrombosis, there is no randomized controlled trial regarding the use of anticoagulants in acute PVT[126]. After 6 mo of therapy, a complete recanalization has been reported in about 50% of patients, with good results in the case of mesenteric vein involvement, and a low incidence of complications. In contrast, in about 10% of cases, PVT is resistant to anticoagulants[96,97,100-103]. In addition, when intestinal infarction occurs, anticoagulants administered prior to laparotomy seem to have a consistent benefit on survival[127-129].

What is certain is that, in acute PVT onset, the sooner the treatment is given the better the outcome will be; the rate of recanalization is about 69%, if anticoagulation is instituted within the first week after diagnosis, while it falls to 25% when instituted at the second week[9,59,130].

Anticoagulation in chronic PVT

Opinions regarding therapeutic options in chronic PVT are more controversial and significantly variable. At present, anticoagulant treatment is administered to only 30% of patients with chronic PVT, reflecting concerns about the use of anticoagulation in the presence of gastroesophageal varices, low platelet counts, and coagulation dysfunctions[79]. However, the number of bleeding episodes in PVT patients receiving anticoagulant therapy didnot increased, and in long-term follow-up studies, anticoagulants seem to be effective in preventing new thrombotic events with a low mortality[66,126]. Incidentally, a pragmatic approach, such as endoscopical eradication of varices prior to commencement of anticoagulation, should be reasonable[79].

Dose and duration of anticoagulants

If thrombosis is recent and there is no underlying thrombophilic condition, anticoagulation should be administered for 3-6 mo, as a complete portal vein recanalization can occasionally be delayed[79,100,101,131-133]. Recently, a panel of experts recommended the application of anticoagulant therapy only in PVT patients with a proven thrombophilic disorder or familial history of venous thrombosis[133,134], thereby obtaining an improvement in survival and reduction in risk of gastrointestinal bleeding[135,136].

Anticoagulation in cirrhotic patients

The ubiquitous and long-term use of anticoagulants in cirrhotic patients with PVT should not be considered correct practice, until their safety and efficacy has been completely tested[62]. However, signs of intestinal ischemia or infarction, or an underlying prothrombotic disorder should be considered an indication for anticoagulants in cirrhotic patients, although only after an adequate prophylaxis for variceal bleeding[2,126]. In candidates for liver transplantation with a high risk PVT (obstruction of more than 50% of the portal vein), anticoagulation should be recommended, even if a scheduled prophylactic treatment has not yet been assessed[64,74,85,108,117].

Other treatments

Thrombolytic therapy, given either into the systemic venous circulation, the superior mesenteric artery, or the portal vein *via* a transjugular or transhepatic route, is also effective to provide recanalization in acute PVT[137-142]. However, efficacy is significantly lower and mortality increased in patients who undergo thrombolysis, if compared to conservative treatment[59,143,144]. Despite the high incidence of side effects, thrombolysis should be considered when initial anticoagulant therapy fails, even if there is no consistent evidence concerning in which conditions it should be preferred to anticoagulation[137]. Surgical thrombectomy is usually not recommended, as high morbidity and mortality have been reported; percutaneous transhepatic mechanical thrombectomy might also be effective in recent thrombosis, but vascular traumas are frequent and may stimulate rethrombosis[145].

Other approaches, such as transjugular intrahepatic portosystemic shunt placement, should be reserved for patients developing acute PVT before or after liver transplantation, or in alternative to thrombolysis when anticoagulation fails[146,147]. It seems to be effective in resolving portal biliopathy, ascites, and portal hypertension, but it is not feasible if portal vein is not catheterizable or a cavernomatous vein cannot be dilated[148-150].

Finally, shunt surgery (distal splenorenal shunt or Rex shunt, in children) might be applied as the last choice, and only in absence of splenic or superior mesenteric vein thrombosis[151].

CONCLUSION

PVT is relatively uncommon in the general population, but is more frequent among cirrhotic patients and represents a "milestone" in the natural evolution of liver disease. Local or systemic pro-thrombotic factors, alone or together, can play an important role in PVT pathogenesis, which is complex and different in each clinical context and in each patient. The consequent changes in hepatic and splanchnic hemodynamic are responsible for a mild impairment in liver function, in absence of an overt liver disease, or can precipitate a preexistent metastable clinical status in cirrhotic patients. Moreover, PVT might have indirect effects on other abdominal organs, causing intestinal ischemia and infarction, or predisposition to vascular neoformation and gastrointestinal bleeding. The identification of protean manifestations of PVT is essential to provide a prompt diagnosis, as the removal of the original trigger factor and an early therapeutic management is crucial to preserve patient health and, sometimes, life. The history of PVT has been characterized by difficulties in diagnosis and treatment, which, today, have almost been overcome. In the future, due to innovations in imaging and pharmaceuticals, clinical attention must be focused on the realization of a scheduled, preemptive, therapeutic approach to the patient, to better define the profile of toxicity and reduce side effects, especially in cirrhotic patients.

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