

PORTAL AND SPLENIC VEIN THROMBOSIS

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Abbreviations

AT III	Antithrombin III	LT	Liver transplantation	PV	Portal vein
DUS	Doppler ultrasound	MRA	Magnetic resonance angiogram	PVT	Portal vein thrombosis
FVL	Factor V Leiden	MTHFR C ^{677T}	Methylenetetrahydrofolate reductase	SMV	Superior mesenteric vein
HVPG	Hepatic venous-portal gradient	PTHRA ²⁰²¹⁰	Factor II prothrombin		
IPVT	Isolated portal vein thrombosis				

PORTAL VEIN THROMBOSIS

Portal vein thrombosis (PVT) was first reported by GW Balford and TG Stewart in 1869 in a patient who presented with ascites, splenomegaly, and varices.¹ PVT is a rare condition affecting both children and adults with equal gender distribution, and is typically associated with myriad precipitating factors and subtle acute clinical manifestations.² PVT represents the classic form of presinusoidal (intrahepatic) portal hypertension. In western countries this entity is the leading cause of extrahepatic portal hypertension in non-cirrhotic patients.³

The incidence of PVT is not clearly defined and varies depending on the group of patients studied and the diagnostic methods used. In the United States, the overall incidence ranges from 0.05% to 0.5% in autopsy studies. Reported prevalence in candidates for liver transplantation (LT) with cirrhosis is between 0.6% and 26%.^{7,10} In patients with cirrhosis, the incidence of PVT at the time of LT has been reported to range from 10% to 21%.⁴⁻⁶ In Japan, Okuda et al. reported an incidence of 0.6% by angiography of 708 cirrhotic patients.⁷ After LT, the incidence of PVT varies from 1% to 2%.^{8,9}

PATHOPHYSIOLOGY

Under normal circumstances the portal vein (PV) contributes two-thirds of the hepatic blood supply. However, PV occlusion with thrombosis often produces few acute clinical consequences or laboratory manifestations.^{2,12,13} Two mechanisms account for this ability of the liver to survive the loss of portal perfusion. The first consists of an arterial 'buffer' response manifested by immediate vasodilatation of the hepatic arterial bed in response to decreased portal vein flow.^{12,14,15} The second is the relatively rapid development of collateral veins that bypass the thrombosed portion of the PV (cavernous transformation).¹⁶ The latter process may take up to 12 months, although it has been reported as early as 5 weeks after the thrombotic event.^{16,17} Other collateral veins may also develop within the walls or at the periphery of the structures adjacent to the obstructed portion of the portal vein, such as the bile ducts, gallbladder, pancreas, gastric antrum, and duodenum.¹⁸ These collateral veins may

alter the appearance of these surrounding structures during imaging, and occasionally lead to erroneous diagnoses of bile duct or pancreatic tumor, pancreatitis, or cholecystitis. In some instances these cavernous vessels can have clinical consequences: bile duct varices have been reported to cause obstructive jaundice.¹⁸

As a result of these hemodynamic compensations, the total hepatic blood flow is only minimally reduced, hepatic venous pressure gradient (HVPG) is initially preserved at normal levels, and the portal pressure is elevated.¹⁵ The increase in portal pressure allows portal perfusion to be maintained through the collateral veins. This initial state is not static, and portal pressure will increase further over time. The risk for bleeding esophageal varices develops when the HVPG rises to a threshold value of 10–12 mmHg.¹⁹ PVT patients can also experience the development of a compensatory hyperdynamic circulatory state akin to that seen in cirrhosis.¹⁵

The overall consequences of PVT are related to thrombus extension. Below the thrombus, there is little effect on the intestines so long as the mesenteric venous arches remain patent. Mesenteric ischemia results from extension of the thrombus into the mesenteric venous arches.¹² When the ischemia is prolonged, intestinal infarction will ensue. In 20–50% of cases intestinal infarction is responsible for death due to peritonitis and multiple organ failure, even when the infarcted gut is resected.^{20,21} Above the thrombus, the consequences of PVT to the liver are hardly discernible and there are minimal laboratory abnormalities.²² Clinically, acute signs of liver disease are absent or transient unless the PVT occurs in a patient with cirrhosis.¹² Concomitant PVT may be seen in 20% of patients with Budd–Chiari syndrome, and this may worsen their liver disease.²³

PVT can be classified anatomically into four grades according to where the thrombus extends.²⁴ These grades are reflective of the clinical consequences of the thrombus and have an impact on the selection of medical and surgical management options.

1. **Grade I:** Minimally or partially thrombosed PV, in which the thrombus is minimal or, at most, confined to <50% of the vessel lumen, with or without limited extension into the superior mesenteric vein (SMV).

2. **Grade 2:** More than 50% occlusion of the PV, including total occlusions, with or without limited extension into the SMV.
3. **Grade 3:** Complete thrombosis of the PV and *proximal* SMV with open distal SMV.
4. **Grade 4:** Complete thrombosis of the PV and SMV.

ETIOLOGY

The etiology of PVT is highly diverse and, as in other thrombotic disorders, its development depends on the interaction of many factors.^{25,26} Surprisingly, our understanding of the risk factors for PVT follow very closely those originally postulated by Virchow in the 19th century for the development of venous thrombosis.²⁵ The so-called Virchow's triad includes flow abnormalities resulting in blood stasis; imbalance between pro and anticoagulant proteins, with resultant activation of clotting proteins; and defects in the blood vessel wall, resulting in a shift to a procoagulant endothelium.²⁵ Of the many disorders that lead to the development of PVT, most can cause disruption of more than one of the elements of this triad. Current opinion favors the postulate that the development of PVT is triggered by the interaction of many factors and is not due to an isolated event.²⁷ However, despite the availability of an ever-widening array of diagnostic techniques, 8–15% of PVT cases are classified as idiopathic, as no underlying predisposing condition can be identified at the time of diagnosis.^{28–30}

Cirrhosis

Predisposing factors for PVT can be classed as inherited or acquired. Acquired factors are further subdivided into local or systemic conditions (Table 47-1). Among the acquired causes, cirrhosis has been long considered a major cause in adults and is present in 24–32% of patients with PVT.² The pathogenesis of PVT in cirrhosis is uncertain, and it is still difficult to link cirrhosis per se to the development of PVT. It has been suggested that several concurrent factors in cirrhotic patients, including decreased portal blood flow, the presence of periportal lymphangitis with fibrosis, and a possible thrombophilia, promote the formation of thrombi. Several studies have reported the association of a prothrombotic state and thrombophilia in the setting of cirrhosis.^{31,32} In two studies, 62–69.5% of cirrhotic patients had a deficiency of one or more natural anticoagulant proteins.^{32,33} Whether the prothrombotic state is primary or secondary is controversial.

Neoplasia

Neoplastic disorders are the second most common cause of PVT in adults and are found in 21–24% of patients with PVT.² Pancreatic cancer tops the list and is responsible for 11–12% of adult cases, followed by hepatocellular carcinoma, which accounts for 5–6% of cases.² Other cancers implicated include pulmonary, gastric, prostate, uterine, renal, biliary, malignant carcinoid, and hepatic lymphoma.^{2,22} Neoplasia can lead to PVT through a combination of systemic and sometimes local factors. A hypercoagulable state of malignancy is believed to be related to increased activity of the coagulation system, as evidenced by markers of accelerated thrombin generation and increased platelet reactivity.²⁵ In addition, tissue factor and cancer procoagulant (cysteine protease) have been implicated in specific types of solid and hematologic tumor. Tissue factor

TABLE 47-1. Causes of Portal Vein Thrombosis in Adults

Common causes

Cirrhosis
 Neoplasm
 Pancreatic CA
 Hepatocellular carcinoma
 Intra-abdominal malignancy
 Infection
 Appendicitis
 Diverticulitis
 Cholecystitis
 Inflammation
 Pancreatitis
 Myeloproliferative disorders
 Polycythemia vera
 Thrombocytosis
 PNH
 Agnogenic myeloid metaplasia
 Idiopathic

Uncommon causes

Inherited hypercoagulable states
 –High risk for thrombosis (low prevalence < 0.04%)
 Antithrombin III deficiency
 Protein S deficiency
 Protein C deficiency
 –Low risk for thrombosis (high prevalence > 2%)
 FVL mutation
 PTHR²⁰²¹⁰ mutation (Factor II prothrombin)
 MTHFR C⁶⁷⁷→T mutation
 Antiphospholipid syndrome
 Acquired hypercoagulable states
 Inflammatory bowel disease
 Pregnancy
 Oral estrogens
 Miscellaneous
 Non-cirrhotic portal hypertension
 Abdominal surgery, shunt surgery
 Splenectomy
 Liver transplant

acts in conjunction with factors VII/VIIa to activate factor X. The enzymatic function of cancer procoagulant is the activation of factor X. Another postulated procoagulant mechanism in cancer patients is impaired fibrinolysis, with a subsequent increase in plasminogen activator inhibitor.^{25,34}

Myeloproliferative Disorders

The hypercoagulable state due to myeloproliferative disorders accounts for 3–12% of adult patients with PVT.^{2,30,35} Some patients with idiopathic PVT have a latent myeloproliferative disorder that becomes evident only years after the diagnosis of PVT. Valla and co-workers found that 48% of adult patients with non-malignant PVT originally classified as idiopathic had either overt or latent myeloproliferative disorders.³⁰

Infection

In the adult population, infection accounts for 10–25% of PVT cases in non-cirrhotic, non-cancer patients.² Septic PVT (pyelophlebitis) is usually related to appendicitis, cholecystitis, or diverticulitis.^{1,29,31}

However, PVT as a result of infection is infrequent in the adult population, with a decreasing incidence because of earlier diagnosis and earlier initiation of effective antibiotic therapy.³⁶ Interestingly, *Bacteroides* species bacteremia of unknown origin is so strongly associated with PVT that culture of this organism from the blood should prompt a search for portal or mesenteric vein thrombosis.^{12,37}

In children, infection is the most common etiologic factor for PVT, accounting for 43–52% of all cases.³¹ Neonatal umbilical sepsis, the single most frequent infectious cause, is present in 10–26% of children with PVT.^{1,2,12,31} Neonatal thrombosis is well documented after omphalitis or umbilical vein cannulation complicated by septic pyelophlebitis. However, infants with infection of the umbilical vein in the absence of prothrombotic disorder infrequently go on to develop PVT.³⁸ The first clinical manifestations of neonatal PVT are frequently delayed until adulthood.

Thrombophilias

Inherited or acquired prothrombotic states may predispose to the development of PVT. The presence of more than one deficiency seems to be the rule rather than the exception.^{26,27,33} Inherited prothrombotic disorders are subclassified into two groups according to the prevalence in the population. The first group includes deficiencies in protein C, protein S, and antithrombin III (AT III). The prevalence of these deficiencies is very low in the general Caucasian population (<0.04%), with a high associated risk of thrombosis in heterozygotes (~10%). The second group includes gene mutations in factor V Leiden (FVL)⁴¹, factor II prothrombin (PTHR A²⁰²¹⁰),^{42,43} and methylenetetrahydrofolate reductase (MTHFR C^{677T}).⁴⁴ Both FVL gene mutation and the PTHR A²⁰²¹⁰ mutation are associated with a lower relative risk of thrombosis despite being more prevalent (>2%) in the general population. FVL gene mutation and deficiencies of anticoagulant proteins have been associated with PVT.^{33,45–47} Janssen et al. reported that the relative risk of PVT for individuals with FVL mutation was 2.7, 1.4 for those with PTHR A²⁰²¹⁰, and 4.6 for those with protein C deficiency. Protein C and S deficiency has been reported in up to 30% of cirrhotic patients with PVT.⁴⁵ Antithrombin III deficiency has been less frequently associated with PVT.^{27,45,47} Antiphospholipid syndrome has been reported in up to 11% of patients with PVT.²⁷

Other

Inflammatory disorders such as pancreatitis and inflammatory bowel disease (IBD) have also been implicated in PVT.^{30,39} Pancreatitis accounts for 3–5% of cases of PVT, via either a contiguous inflammatory process, direct compression of the PV by a pseudocyst, or a combination of both. Chronic pancreatitis can also lead to splenic vein thrombosis and a unique form of 'left-sided' segmental portal hypertension with the development of isolated gastric varices.^{30,40} Other associated factors include pregnancy and oral intake of estrogens.^{48,49}

PVT can also be seen in the setting of blunt abdominal trauma, surgery in the absence of septic complications,² or non-surgical treatment for hepatocellular carcinoma, such as radiofrequency ablation or microwave coagulation therapy.⁵⁰ Splenectomy carries a PVT risk ranging from 0.7 to 8%.^{51–54} In patients with underlying myeloproliferative disorder or cirrhosis, splenectomy carries a particularly increased risk of PVT, ranging from 13–18%.^{51,54} Transjugular

intrahepatic portosystemic shunt (TIPS) carries a risk for PVT of approximately 10%.⁵⁵

PVT following endoscopic variceal ligation or sclerotherapy was a matter of controversy in the past, as most published studies did not document the patency of portal vessels prior to the initiation of therapy.^{56,57} In an effort to further clarify this issue, Politoske et al. studied the incidence of PVT in patients treated with sclerotherapy and band ligation for variceal bleeding in cases without pre-existing PVT; the study found no significant difference between the groups after therapy.⁵⁸

Finally, several authors have suggested an association between PVT and congenital cardiovascular abnormalities, such as atrial septal defect, ventricular septal defect, and deformed inferior vena cava.⁵⁹

CLINICAL MANIFESTATIONS

Patients with PVT typically present with abdominal pain, increased abdominal girth, or, more dramatically, hematemesis.^{2,12,13} Neonatal PVT can present many years later with complications of the ensuing portal hypertension, such as ruptured gastroesophageal varices or splenomegaly.^{1,2,59} Most patients with PVT diagnosed before the index gastrointestinal bleed eventually go on to bleed within a mean of 4 years from diagnosis.¹ However, 10% of patients with PVT never bleed.¹ The presence of acute-onset abdominal pain can be an ominous sign and should prompt aggressive work-up for bowel ischemia.² Bowel ischemia patients may also present with gastrointestinal bleeding. Other common complaints of patients with PVT include nausea, vomiting, diarrhea, anorexia, weight loss, and abdominal distention.^{28,31,59} Some patients may also experience low-grade fever.⁵¹ Portosystemic encephalopathy is rare unless the patient has underlying liver disease. A rare presentation of PVT is the occurrence of bile duct compression due to collateral veins which develop in the hepatoduodenal ligament.^{18,60}

On physical examination, splenomegaly is seen in 75–100% of cases. Hepatomegaly may also be present. Ascites is an uncommon finding in PVT, and when present is usually mild and transient. Ascites typically develops immediately after the thrombotic event, before the patient has had time to develop a collateral circulation.^{22,28,59}

A rare presentation of PVT is bile duct compression due to collateral veins which develop in the hepatoduodenal ligament.^{18,60} Some patients may also experience low-grade fever.⁵¹

Hepatic enzymes and liver injury tests are usually within normal limits in patients without underlying liver disease.^{2,12} However, mild elevations in transaminases, alkaline phosphatase, and bilirubin have been reported.¹² A mild decrease in red cell count, white cell count, and platelets due to hypersplenism may also be seen.^{2,13,28,59} Histologically, there is little alteration in the hepatic architecture when the obstruction is limited to the extrahepatic portal vein and its largest intrahepatic branches. Non-cirrhotic patients typically show normal histology, with increased reticulin around the portal tracts. Experimentally, apoptosis of the liver cells can be demonstrated in rats with graded portal vein ligation.⁶¹ The degree of apoptosis is related to the grade of portal vein obstruction. There is a simultaneous increase in mitotic activity in the remaining well-perfused liver.^{61,62} Wanless and colleagues have postulated a mechanism by which the vascular changes seen with chronic PVT may lead to the development of venoportals bridging fibrosis and eventual cirrhosis.⁶³

NATURAL HISTORY

The natural history of PVT remains shrouded in mystery, as the patient population is heterogeneous and the management is predicated by the time of diagnosis and the underlying etiology. The clinical course is characterized by repeated bouts of variceal hemorrhage, with an average of 2.5–5 episodes per patient.^{64,65} In an analysis of non-cirrhotic non-neoplastic PVT, the incidence of gastrointestinal bleeding was found to be approximately 12.5 per 100 patient-years. In this study, the only independent predictive factor for bleeding was the size of the esophageal varices.⁶⁶ In cases of neonatal PVT, the bleeding episodes tend to increase in severity and frequency at puberty, followed by abatement after the development of spontaneous splenorenal or splenogastric shunts in 10–20% of patients.⁶⁰

The overall prognosis for patients with chronic PVT and recurrent gastrointestinal bleeding in the absence of cirrhosis or malignancy is good, with a mortality rate of approximately 10%.^{2,67} In a Dutch study, non-cirrhotic patients with PVT had an overall survival rate of 70% at 1 year and 63% after 5 years.⁶⁸ In the case of acute PVT due to intra-abdominal sepsis, pre-existing liver disease, or abdominal surgery, the mortality rate approaches 50%.³¹ In children the prognosis is much better, with a 10-year survival rate greater than 70%. Extensive PVT with mesenteric venous thrombosis with bowel infarction is invariably fatal without prompt surgical intervention. Mortality in this scenario can approach 20% even with expedient bowel resection.⁶⁹

DIAGNOSIS

The key to the diagnosis of PVT is a high index of suspicion (Figure 47-1). For confirmation, a variety of radiologic techniques can be used to investigate the suspected thrombosis. Invasive angiographic techniques, such as ‘indirect’ portography (venous phase of superior mesenteric artery angiogram) and ‘direct’ portal venography (trans-hepatic or transjugular) are the time-honored diagnostic techniques for PVT.⁷⁰ However, a variety of non-invasive techniques, such as color Doppler ultrasound (DUS), computed tomographic angiography (CT angiography), and magnetic resonance angiography (MRA), have become available for the screening of patients suspected of having PVT.^{70–75}

Nowadays, ultrasonography is the first-line diagnostic modality because of its accuracy, affordability, and non-invasiveness. An echogenic thrombus within the portal lumen is the key finding for the ultrasonographic diagnosis of PVT.⁷⁶ Other signs include dilatation of the proximal vessel, the presence of collateral vessels (best seen near the porta hepatis), or an unidentifiable portal vein.^{74–76} The lack of variation in portal venous diameter with respiration, coupled with a portal vein diameter greater than 13–15 mm, is also highly indicative of portal vein occlusion. These hallmarks may be less reliable when the thrombus is long-standing. The sensitivity of ultrasonography ranges from 70 to 90%, with a specificity of 99%.^{24,75} The presence of arterial flow signal in the thrombus typically correlates with a malignant thrombus.⁷⁵ Major limitations to ultrasonography include obesity, fatty liver, and non-visualization secondary to bowel gas. In addition, ultrasonography is operator dependent, and PVT might be missed if the examiner is not specifically asked to look for it.^{74–76}

CT scans can be used to confirm and follow the course of PVT. On CT scan, the thrombus within the portal vein shows decreased

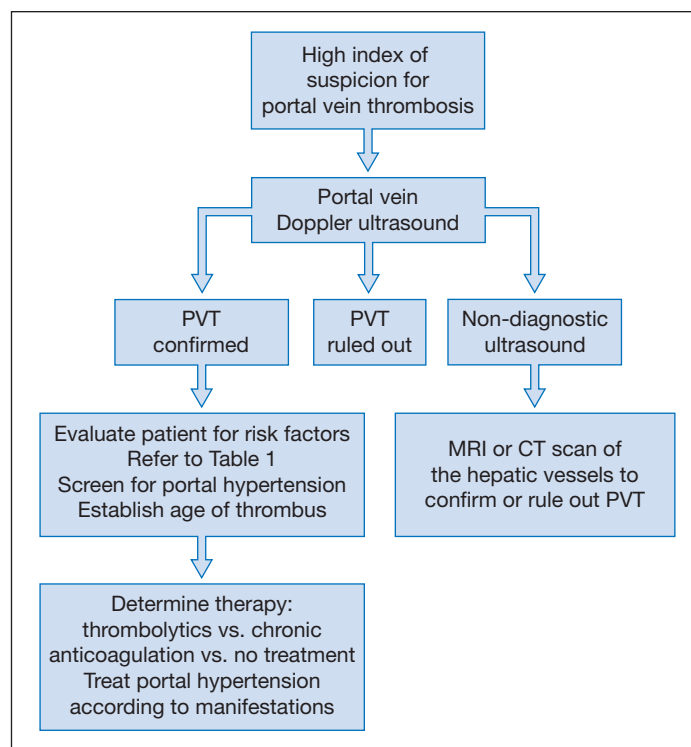


Figure 47-1. Suggested diagnostic work-up for patients with suspected PVT. Refer to text for further details on diagnostic work-up.

intraluminal density (filling defect in the contrast-enhanced lumen) or as total portal occlusion with or without the development of periportal collaterals creating a ‘train-track’ appearance on enhancement. This ‘train-track’ appearance is associated with proliferation of the vasa vasorum and is associated with old thrombus. A non-enhanced CT scan of the liver will show a high luminal density within the portal vein when the thrombus is less than 10 days old.⁷⁷ The presence of periportal collaterals suggests that the occlusion is chronic and the thrombus is organized, also known as ‘cavernous transformation’ of the portal vein⁷⁷ (Figure 47-2). This process may take up to 12 months to occur, although it has been demonstrated as early as 5 weeks after the thrombotic event.¹² Contrast-enhanced CT has the advantage over ultrasound of displaying varices (sensitivity 65–85%) and parenchymal hepatic abnormalities.⁷¹ The false-positive rate in one small series was 16%, possibly owing to poor bolus injection. CT is not operator dependent; however, the radiation dose, cost, and need for intravenous contrast make it a less than ideal test.^{71,78,79}

Contrast-enhanced MR angiography, spin-echo MR, and gradient-echo MR have been introduced for the diagnosis of PVT. Spin-echo MR images usually shows PVT as an area of abnormal signal within the lumen of the portal vein. PVT appears hyperintense on T₁ and T₂ images when the thrombus has been formed recently. Old thrombus appears isointense on T₁ images. Gradient-echo MR gives a sharper delineation of vascular structures and helps clarify any confusion on spin-echo images. MR angiography shows flow patterns and patency of the portal vein. Tumor thrombi can be differentiated from bland thrombi because they appear more hyperintense on T₂-weighted images and enhance with gadolinium. The sensitivity of MRI is 85% and the specificity is 90–95%.^{72,80}

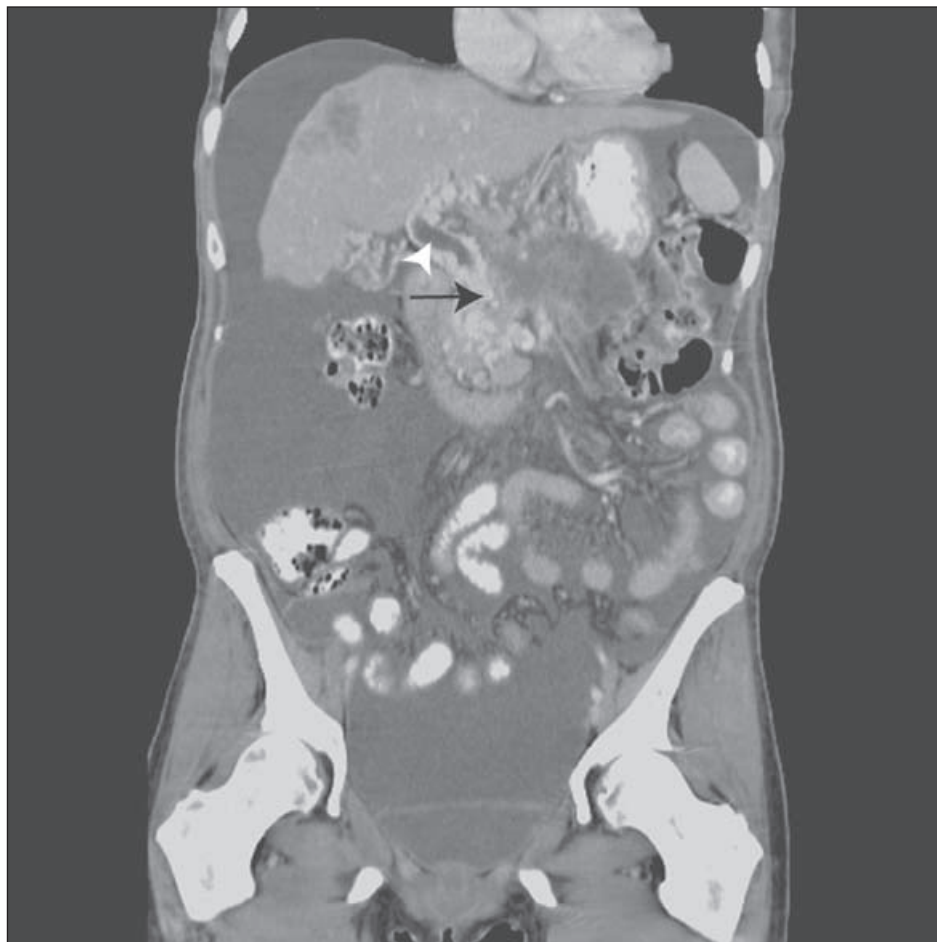


Figure 47-2. High-resolution CT scan coronal reconstruction of portal anatomy in a patient with ductal adenocarcinoma of the body of the pancreas. Note the portal vein occlusion with cavernous collateral transformation (narrow arrow). In addition, the patient has liver metastases with bile duct obstruction and malignant ascites. (Photo courtesy of Dr Joseph Collins.)

More invasive radiographic techniques are currently reserved for cases when non-invasive testing is inconclusive, immediately before anticipated percutaneous interventional treatment, or when a meticulous preoperative assessment is necessary.⁷⁰

ISOLATED SPLENIC VEIN THROMBOSIS

Isolated splenic vein thrombosis (ISVT) deserves special attention as the etiology and clinical manifestations differ from those of PVT. ISVT usually results in left-sided portal hypertension and isolated gastric fundal varices.⁸¹

The most common cause of ISVT is chronic pancreatitis, with a reported incidence up to 45%.⁸² Pancreatitis-associated ISVT is believed to result from perivenous inflammation.^{82,83} The prevalence of splenic vein complications in relation to the CT scan severity index of pancreatitis has shown an inversely proportional significant increase in the prevalence of thrombosis.⁸³ Other known factors include pancreatic masses and cancer, splenectomy,⁸⁴ portal hypertension, renal disorders, and inflammatory disorders.⁸¹

The diagnostic test of choice to assess the presence of ISVT is late-phase celiac angiography.⁸² However, endoscopic ultrasonography (EUS) has emerged as a fairly sensitive and non-invasive diagnostic tool.^{85,86} Splenoportography was previously used to make this diagnosis (Figure 47-3).

The natural history of ISVT is uncertain and literature reports are few. Most cases of ISVT are asymptomatic and require no treatment.⁸² In an effort to further define the natural history of pancreatitis-induced ISVT, Heider and co-workers⁸⁷ studied 53 patients with a history of pancreatitis and ISVT and found that 77% of isolated gastric varices were evident on CT scanning, 31% by esophagogastroduodenoscopy (EGD), and 28% by the combined modalities. The risk of variceal bleeding was 5% for patients with CT-identified varices and 18% for EGD-identified varices.⁸⁷ Of those patients, only 4% had a gastric variceal bleeding episode and required splenectomy.⁸⁷ Other investigators have reported a gastric variceal bleeding risk of approximately 10%.⁸⁸

The treatment of ISVT is conservative, given the low risk of associated gastric variceal bleeding.⁸⁷ Once there is an index episode of gastrointestinal bleeding, splenectomy is the treatment of choice.⁸² The surgical and medical teams need to ensure that hepatic fibrosis has been carefully evaluated. Splenectomy in the setting of cirrhosis should be avoided if possible, as the development of PVT post splenectomy may complicate or eliminate the opportunity for liver transplantation in the future.

LIVER TRANSPLANTATION AND PVT

In the past, PVT has been considered a relative contraindication to liver transplantation because of the technical difficulties it added to

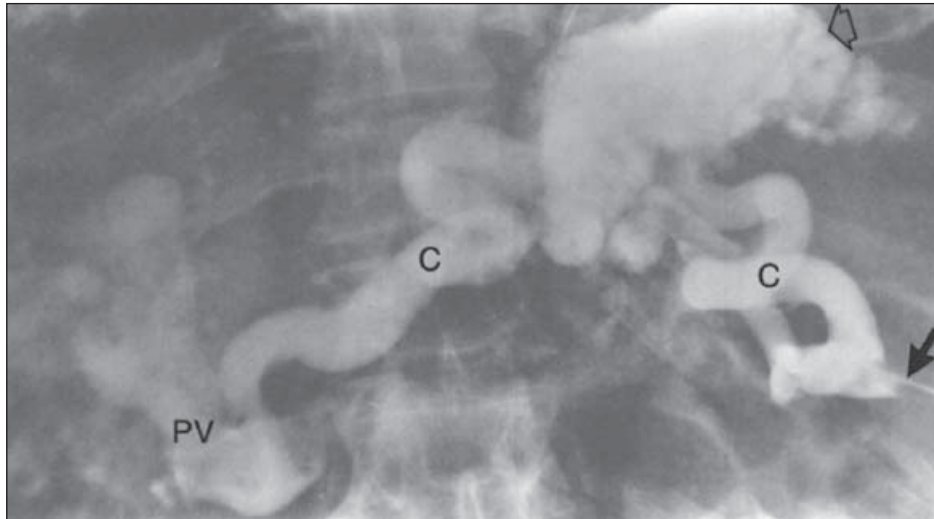


Figure 47-3. Splenoportogram of a patient with splenic vein thrombosis. The needle is within the spleen (closed arrow). Contrast material can be seen to flow from the spleen to the portal vein (PV) via large collaterals (C). The pool of contrast material (open arrow) is within numerous gastric varices.

the procedure. However, in recent years innovative surgical techniques have been introduced and many technical obstacles have been overcome.⁸⁹⁻⁹⁴ As a result, patients with non-neoplastic PVT routinely undergo LT. The first successful LT in a patient with PVT using venous conduits to bypass the thrombotic segment was reported in 1985.⁹³ Since then, many centers have reported several techniques to tackle the problem of PVT in liver transplant candidates.

The surgical technique to re-establish portal blood flow in liver transplant recipients with PVT depends on the extent of the thrombosis and the experience of the transplant team. Partial PVT with less than 25% luminal obstruction has no clinical repercussions because it can be treated with resection, whereas more than 25% luminal obstruction requires extensive thrombectomy.⁹⁵ Thromboendovenectomy and/or direct venous anastomosis has been performed in patients when the thrombosis involves the portal vein with or without extension into the SMV. If the portal vein is completely thrombosed and the proximal SMV is occluded but the distal part is patent, then the preferred method is a graft to the proximal SMV using donor iliac vein.^{6,24,94} In cases where the portal vein is not amenable to thrombectomy and the SMV is thrombosed, the coronary vein or any large accessible collateral vein can be used to join the donor portal vein to the SMV.⁹⁴ For patients with extensive and complete occlusion of the portal vein and SMV, cavoportal hemitransposition (a procedure that diverts caval blood to the liver as replacement of portal inflow and without compromise of hepatic function) has been described as an innovative and successful procedure.⁹⁰

De novo PVT after liver transplantation is rare and usually occurs at the anastomotic site in the early postoperative period. In patients with pretransplant PVT the early outcome seems to be satisfactory, although there remains a risk of the portal vein rethrombosing which ranges from 4.2 to 38.5%.^{24,89} The greater risk for rethrombosis has been reported in grafts that were not preserved with University of Wisconsin solution, or when venovenous bypass was used.⁹⁵ In an effort to prevent recurrence of PVT in this group of patients, therapeutic or prophylactic anticoagulation for 3 months has been advocated.^{6,95,96}

Liver transplant candidates with PVT, especially those who have more than 50% of the portal vein occluded with or without superior mesenteric vein (SMV) occlusion, are more prone to develop severe perioperative complications, and have a high mortality rate and decreased long-term survival.⁸⁹ The mortality rate is influenced by the extent of thrombosis before liver transplantation. Mortality has been reported to be greater in patients with PVT and splanchnic vein involvement than in those with only PVT (45.5% vs 36.1%) or associated periphlebitis (83.3% vs 9.4%). Nevertheless, the vast majority of patients with PVT can be technically transplanted, with a survival comparable to that of patients without PVT.⁸⁹ Acute graft failure due to early occurrence of PVT after liver transplantation, bleeding from esophageal varices, and massive ascites can be serious complications from PVT after liver transplantation.⁸⁹

MANAGEMENT

A thorough etiological investigation and assessment of thrombus chronicity is paramount in the management of PVT in order to identify those conditions amenable to treatment and to tailor treatment. Investigation of the local factors is carried out with Doppler ultrasonography, MRI scan, abdominal CT, or endoscopic ultrasound. When portal cavernous transformation is recognized, portal hypertension can be assumed.

Investigation of general thrombophilic factors must be comprehensive because in most patients there are usually several factors that contribute to the hypercoagulable state. Factors such as myeloproliferative disorders should be systematically investigated as they can have subtle presentations before becoming fully apparent on hematological grounds. One feature of a myeloproliferative disorder that may be present before the disease is clinically manifest is the spontaneous formation of erythroid colonies on culture of the circulating or bone marrow precursors in the absence of erythropoietin added to the culture medium. A similar test has also been developed for spontaneous colonies of megakaryocytes.³⁰ Where these tests are not easily available, diagnostic information can also be obtained using isotopic determination of the total red cell volume

coupled with determination of serum erythropoietin levels, provided that iron deficiency has been corrected. Bone marrow biopsy is another means to demonstrate primary myeloproliferative disorder when the peripheral blood picture is not suggestive, but this procedure is too invasive to serve as a screening procedure.¹²

Other considerations include coagulation factor gene mutations, coagulation inhibitor deficiencies, and the antiphospholipid syndrome. Interpretation of the results of antithrombin, protein C and protein S is particularly difficult in the context of PVT because their plasma levels may be non-specifically decreased whenever there is underlying liver disease or coagulation activation. Therefore, comparisons with the results of prothrombin determination and familial studies are necessary before the conclusion of a primary (inherited) deficiency can be reached.¹² Factor V Leiden mutations can be assessed directly using molecular techniques, or indirectly by evaluation of the resistance to activated protein C. Identification of factor II G20210A mutation requires molecular techniques. The antiphospholipid syndrome is diagnosed when high titers of antiphospholipid antibodies are found on two separate occasions, or when a lupus anticoagulant is demonstrated. However, determination of anti-β₂ glycoprotein-1 antibodies may be both more sensitive and more specific than the first two tests.⁹⁸ Hyperhomocysteinemia is difficult to ascertain once PVT has developed because the plasma level is dependent on normal hepatic function. The C677T mutation of the methylene tetrahydrofolate reductase gene is associated with an increased plasma homocysteine; however, it is not clear whether this genetic marker alone is as good a marker for the increased risk of thrombosis as is the plasma homocysteine level.^{26,44}

Gastrointestinal lesions that may be a source of bleeding need to be identified for adequate prophylactic measures to be taken. To date, there has been no controlled study specifically addressing bleeding in the setting of PVT. However, the available uncontrolled data indicate that the measures of established efficacy in patients with cirrhosis in good condition, such as propranolol and endoscopic therapy, can be applied to patients with PVT.^{26,44,99-101}

Therapy for active gastrointestinal bleeding should, likewise, follow the guidelines for patients with intrahepatic portal hypertension regarding sclerotherapy and band ligation.¹⁰¹ There is, however, a matter of concern about the use of vasoconstrictive agents. Theoretically, the profound decrease in splanchnic blood flow induced by bleeding and by the therapeutic vasoconstrictive agents may trigger recurrence, or favor the extension of thrombosis in the portal venous system and precipitate intestinal ischemia. Indeed, peripheral vasopressin infusion has been reported to cause portal and mesenteric vein thrombosis, leading to intestinal ischemia in bleeding cirrhotic patients.¹⁰²

SURGICAL MEASURES

The place of surgery and the optimal type of operation is still being debated. A shunting procedure that would efficiently and permanently decompress the portal venous system with a low risk of encephalopathy would appear ideal. Some authors report a success rate in excess of 80% in shunt procedures, with a rebleeding rate as low as 4%.^{11,64} Unfortunately, the risk of shunt thrombosis or stenosis is predictably high, between 8 and 24%.^{11,103} Indeed, several precipitating factors are often present: underlying thrombophilia, surgery for portal hypertension, and splenectomy. Only the largest

veins (superior or inferior mesenteric veins or splenic veins) should be used because of the high risk of shunt thrombosis when using smaller veins.¹⁰⁴ However, veins as small as 4 mm can be used.¹⁰³ Because it leaves the spleen in place and preserves portal perfusion with a lower risk of encephalopathy, distal splenorenal shunt appears most suited for cirrhotic patients.¹¹ Unfortunately, the splenic vein is frequently involved in the thrombotic process. TIPS has been used for the control of intractable bleeding as a bridge to liver transplantation or in patients with non-cavernous PVT as an adjunct to thrombolysis.^{70,105,106} The Sugiura procedure (transthoracoabdominal esophageal transection) has also been used to manage PVT, but it carries a surgical mortality as high as 20%.¹⁰⁷ Splenectomy, only indicated for the management of gastrointestinal bleeding from gastric varices associated with splenic vein thrombosis, is contraindicated in patients with PVT because it may preclude the option of splenorenal shunt surgery at a later stage if needed.¹⁰⁹

MEDICAL MEASURES

The role of anticoagulant therapy for PVT is not well understood, although a large body of data continues to accumulate. Ideally, recent and old PVT must be differentiated before instituting therapy, as the recent PVT might benefit from thrombolytic therapy.⁷⁰ In a retrospective study, Condat et al. showed a beneficial role of anticoagulation in recanalization and prevention of thrombus extension in patients with cavernous transformation of the portal vein. A major observation was that anticoagulant therapy reduced the risk of thrombotic events by two-thirds without an increase in the risk or severity of bleeding. Therefore, they suggest anticoagulation in those patients with a demonstrable prothrombotic state, absent or small varices that have never bled, and no predictable bleeding sites outside the gastrointestinal tract.^{66,110}

To what extent spontaneous recanalization can be expected is not known. Current experience suggests that it is possible but uncommon, whereas complete or extensive recanalization can be achieved with anticoagulant therapy in more than 80% of patients.^{12,111} Recanalization prevents ischemic intestinal injury in the short term and extrahepatic portal hypertension in the long term.

Malkowski et al. reported on the efficacy of thrombolytic agents in 28 patients and concluded that if it is administered early after the diagnosis of PVT, 82% of patients will have restitution of portal vein flow. Of those, 36% will have complete recanalization and 46% partial recanalization, with normal hepatopedal flow. The greatest benefit was seen in those patients with PVT of less than 4 weeks' duration.¹¹²

Septic pyelophlebitis represents a special case in which recanalization can follow effective antibiotic therapy even in the absence of anticoagulant therapy. Drainage of associated hepatic, pancreatic, or splenic abscesses to achieve faster control of infection is recommended to allow recanalization by removing the inflammatory process.⁷⁰

In the case of established PVT with portal hypertension due to cavernous transformation, anticoagulant therapy increased neither the risk of gastrointestinal bleeding nor the severity of bleeding. Valla et al. found that there were no deaths due to bleeding with anticoagulant therapy and no recurrent thrombosis.³⁰ Therefore there is mounting evidence of a positive benefit-risk ratio with anticoagulant therapy. Some investigators only recommend anticoagula-

tion in specific clinical scenarios, such as a demonstrable prothrombotic state, concomitant mesenteric vein thrombosis, or portosystemic shunt (to prevent thrombosis).⁶⁸

Successful thrombolytic therapies, with or without mechanical thrombectomy, have been reported by several investigators in case reports and small series. Thrombolytic agents can be infused via selective SMA or via the transhepatic route. The reported complication rate is low, ranging from none to rectal bleeding.^{70,113,114}

There have been many reports of successful treatment of post-liver transplantation PVT with percutaneous portal vein thrombolysis, angioplasty, and endovascular stent placement. Immediate retransplantation is required when serious deterioration of liver function occurs after early PVT.⁸⁹ TIPS is not recommended because it reduces the effective portal flow and may deteriorate liver function further over the long term.⁹⁷

In summary, PVT should be considered a clue to the presence of one or several prothrombotic disorders, whether or not a local precipitating factor is identified. Acute PVT can and probably should be treated with anticoagulation or thrombolytic agents in an effort to prevent extension of the thrombus, mesenteric vessel occlusion, and portal hypertension. On the other hand, chronic PVT should be treated conservatively with measures to control major consequences related to portal hypertension. The duration of anticoagulation therapy should be tailored to the identified predisposing factors.

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