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Portal Vein Thrombosis with Cavernous Transformation in Myeloproliferative Disorders: Review Update

Anca Rosu, Cristian Searpe and Mihai Popescu

University of Medicine and Pharmacy Craiova, Romania

1. Introduction

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 into the vessel lumen (Bayraktar & Harmanci, 2006).

Cavernous transformation of portal vein consists in the development of a network of tortuous collateral vessels bypassing the obstructive area due to chronic PVT. First described in 1869 by Balfour and Stewart, it was Köbrich in 1928 that used for the first time the term of “cavernoma” to define the newly developed network of small vessels as a result of recanalization of the thrombotic portal vein. Once the liver blood supply decreases significantly, the compensatory mechanism is activated and collaterals begin to form within a few days after the obstruction and organize into a cavernous transformation in 3-5 weeks. (Cai, 2009)

Based on a case previously communicated by us - (A case of portal cavernoma – associated thrombocythemia - A. Rosu, C. Searpe, V. Sbarcea, Z. Stoica, M. Popescu. J Gastrointestin Liver Dis 2007 16(1): 97-100), a review of the published English literature was performed using PubMed® (http://www.ncbi.nlm.nih.gov/PubMed) and Medline database. The search of screened articles was made for the keywords “portal vein thrombosis”, “portal cavernoma” and “myeloproliferative disorders” (MPD). Articles were selected if a review of the title and/or abstract suggested the association of portal vein thrombosis with cavernous transformation in patients with myeloproliferative diseases.

2. Epidemiology

2.1 Epidemiology of PVT

In the era of continuous and impressive development of the imagistic techniques (contrast-enhanced ultrasound, spiral CT-scan, high definition MRI etc) the diagnosis of portal vein thrombosis (PVT) is no longer a rare condition since recent studies estimates it’s incidence at 1,1% in the general population (Ogren et al., 2006). Also PVT is considered to account for 5 to 10% of patients with portal hypertension (Wang et al., 2005).
The concept of PVT as a rare disease is mainly based on clinical series and case reports (Amitrano, 2004), therefore accurate epidemiological data about PVT are difficult to obtain. An epidemiological study performed and conducted in southern Sweden (Ogren et al., 2006) based on the study of 23,796 autopsies, reported the incidental finding of a PVT in about 1% of the general population. Authors reported that 28% of PVT patients had cirrhosis, 23% primary and 44% secondary hepatobiliary malignancy, 10% major abdominal infectious or inflammatory disease and 3% had a myeloproliferative disorder. Other studies reveal that prevalence of PVT in autopsy studies in USA and Japan ranges from 0.05% to 0.5% (Wang et al., 2005).

Actually, 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 defined without any difficulty. 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 western countries (Wang et al., 2005).

2.2 Epidemiology of MPD with PVT

The annual incidence of myeloproliferative syndrome is 2.1-3.5 per 100,000 peoples (Kutti & Ridell, 2001). From the four entities comprising the myeloproliferative syndrome according to the FAB classification (essential thrombocythemia, polycythemia vera, chronic myelogenous leukemia and idiopathic myelofibrosis), essential thrombocythemia is considered the most frequent disease with an annual incidence of 0.7-2.5 per 100,000 peoples (Cai et al., 2009; Girodon et al., 2009; Rollison et al., 2008). The transformation to acute myelogenous leukemia is recorded in 0.6-5% of patients and the overall 10-year survival rate is 64-80% (Fenaux et al., 1990).

In many patients with non-cirrhotic non-malignant PVT, a systemic, thrombophilic risk factor is often present. Over the last two decades, some of, either inherited or acquired, systemic conditions that result in a thrombogenic phenotype have been identified as risk factors for the development of PVT.

MPD remains the major latent or patent cause of extrahepatic PVT (Diaz et al., 2001; Valla et al., 1988; Valla & Condat, 2000). In non-cirrhotic and non-tumoral PVT cases in the West, MPD (i.e. polycythemia vera, essential thrombocythemia and myelofibrosis) with a combination of several prothrombotic factors constitute the most common identifiable cause with an estimated prevalence of 30%-60% (Cai et al., 2009; Kiladjian et al., 2006; Kutti & Ridell, 2001). In another study, a myeloproliferative disorder (MPD) was found in 37% of patients with non-cirrhotic non-malignant PVT (Kiladjian et al., 2006).

Essential thrombocythaemia (ET) is frequently associated with thrombotic complications in the large abdominal vessels. It was reported a prevalence of 4% for abdominal vein thrombosis in 460 consecutive patients with ET (Gangat et al., 2006), but did not provide detailed information on portal vein thrombosis. The risk factors for thrombosis in ET patients include age, thrombotic history, cardiovascular risk factors and genetic or acquired thrombophilia (Landolfi et al., 2008). It seems likely that elevated platelet count is involved in thrombotic events in ET. However, the degree of elevation does not appear to be important, relatively low platelet counts often being associated with thrombosis (Harrison, 2005).
3. Etiology and pathogenesis

Portal vein thrombosis is the result of a complex mechanism involving multiple local and systemic risk factors with effect on coagulability, blood flow and endothelium integrity. Blood flow obstruction in the portal vein is the result of invasion, thrombosis, constriction and frequently, a combination of the above-mentioned mechanisms. A list of most common conditions associated with portal vein thrombosis is presented in table 1 and 2 (Chawla et al., 2009; Gurakan et al., 2004; Hoekstra & Janssen, 2009; Janssen, 2001; Rosendaal, 1999; Valla & Condat, 2000; Valla et al., 2002).

<table>
<thead>
<tr>
<th>Inherited</th>
<th>Anticoagulant deficiency syndroms (antithrombin-III, protein-C, protein-S)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mutation involving coagulating factor II (G20210A) or V (G1691)</td>
</tr>
<tr>
<td></td>
<td>Plasminogen deficiency</td>
</tr>
<tr>
<td></td>
<td>MTHFR homozygote mutation TT677</td>
</tr>
<tr>
<td></td>
<td>TAFI (thrombin activatable fibrinolysis inhibitor) gene mutation</td>
</tr>
<tr>
<td></td>
<td>Sickle cell disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Myeloproliferative disorders (polycythemia vera, essential thrombocythemia)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paroxysmal nocturnal hemoglobinuria</td>
</tr>
<tr>
<td></td>
<td>Antiphospholipidic syndrome</td>
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<tr>
<td></td>
<td>Hyperhomocisteinemia</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>Estro-progestative medication</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Autoimmune diseases</th>
<th>Autoimmune hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary biliary cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
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<td></td>
<td>Wegener disease</td>
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<td></td>
<td>Mixed connective tissue disease</td>
</tr>
<tr>
<td></td>
<td>Behcet syndrome</td>
</tr>
</tbody>
</table>

Table 1. Systemic hypercoagulability conditions associated with portal vein thrombosis

Noteworthy are the local factors predisposing to portal location instead of peripheral venous thrombosis in patients with hypercoagulability associated diseases. These factors are: local inflammatory diseases, injury of the portal venous tract, liver cirrhosis and abdominal cancer (table 2).

Although in most cases thrombosis of the portal vein has an identifiable cause, less than 20% are considered to be idiopathic. In children, umbilical vein sepsis and neonatal umbilical vein catheterization are the main causes of portal vein thrombosis. In adults, liver cirrhosis, abdominal malignant tumors and association of different hypercoagulability states explains the vast majority of portal vein thrombosis.
<table>
<thead>
<tr>
<th>Causes</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Liver cirrhosis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Nodular regenerative hyperplasia</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal malignant neoplasia</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Iatrogenic injury of the portal venous tract</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Local inflammatory diseases</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Choledochal cyst</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Retroperitoneal fibrosis</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Abdominal trauma</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Liver cirrhosis**
- Hepatocarcinoma
- Cholangiocarcinoma
- Liver metastasis
- Gallbladder cancer
- Pancreatic cancer
- Liver angiosarcoma

**Nodular regenerative hyperplasia**

**Abdominal malignant neoplasia**
- Hepatocarcinoma
- Cholangiocarcinoma
- Liver metastasis
- Gallbladder cancer
- Pancreatic cancer
- Liver angiosarcoma

**Iatrogenic injury of the portal venous tract**
- Endoscopic sclerotherapy of esophageal varices
- Alcoholisation/chemoembolisation/radiofrequency ablation of hepatic tumors
- TIPS / surgical portal-systemic shunt
- Hepatectomy or liver transplantation
- Splenectomy
- Umbilical vein catheterization
- Colectomy
- Gastrectomy
- Hepatobiliary surgery
- Gastric banding
- Fundoplication
- Portography
- Peritoneal dialysis
- Islet-cell injection
- Surgery of the portal tract
- Endothelial injury due to cytostatics (cisplatin, cyclophosphamide, methotrexate, 5-fluorouracil) or radiation therapy

**Local inflammatory diseases**
- Omphalitis
- Choledystitis
- Cholangitis
- Appendicitis
- Diverticulitis
- Acute or chronic pancreatitis
- Tuberculous lymphadenitis
- Inflammatory bowel diseases (Crohn’s disease, ulcerative colitis)
- Hepatic hydatid cyst
- Pylephlebitis (frequently due to Bacteroides bacteriemia)
- Liver abscesses
- Duodenal ulcer
- Cytomegalovirus hepatitis
- Schistosomiasis

**Choledochal cyst**

**Retroperitoneal fibrosis**

**Abdominal trauma**
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<table>
<thead>
<tr>
<th>Portal vein malformations</th>
<th>in children with polimalformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular diseases</td>
<td>Budd-Chiari syndrome</td>
</tr>
<tr>
<td></td>
<td>Sinusoidal obstruction syndrome</td>
</tr>
<tr>
<td></td>
<td>Constrictive pericarditis</td>
</tr>
<tr>
<td></td>
<td>Tricuspid insufficiency</td>
</tr>
<tr>
<td></td>
<td>Tumour of the right atrium</td>
</tr>
</tbody>
</table>

Table 2. Local conditions associated with high risk of PVT

In patients with liver cirrhosis the incidence of PVT is reported to be between 6 and 17%, with a higher incidence in more advanced stages of the liver disease. The association between liver cirrhosis and hepatocellular carcinoma increases the incidence of PVT over 44%. Additional attention should be paid in cirrhotic patients with underlying prothrombotic condition due to the non-specific decrease in the plasmatic level of coagulation inhibitors even in well-compensated liver cirrhosis. In a recent study it was showed that patients with chronic liver diseases, especially liver cirrhosis, have an increased relative risk of venous thromboembolism, contradicting the classical hypothesis of autoanticoagulation in cirrhotic patients (Søgaard et al., 2009). This procoagulant status was scientifically related to prohemostatic changes of the coagulation factors recorded in chronic liver diseases: elevated levels of factor VIII and von Willebrand factor concomitant with low levels of protein C, protein S, antithrombin-III, plasminogen and ADAMTS-13 (a naturally occurring plasma metalloprotease that limits in vivo functions of von Willebrand factor on platelets).

Hepatocellular carcinoma and pancreatic cancer are the most frequent abdominal malignancies associated with PVT through a compression/invasion/hypercoagulability mechanisms. Hormonal factors might also play a role in this process, especially in men (Bick, 1992).

Primary myeloproliferative diseases (especially polycytemia vera and essential thrombocythemia) are the most often cause of PVT when cirrhosis or cancer is excluded. In a recent study the incidence of myeloproliferative disorders are estimated to be found in 37% of patients with non-cirrhotic/non-malignant PVT (Kiladjian et al., 2006). These diseases are often asymptomatic at the moment of PVT diagnose and therefore a bone marrow biopsy is required. Recently the discovery of the V617F mutation of the Janus kinase 2 (JAK2) in patients with myeloproliferative disorders has been facilitating the diagnosis. JAK2 mutation it has been identified in 95% of patients with polycythemia vera and in 50 to 60% of patients with essential thrombocytemia. Thus, JAK2 mutation it is now recommended by WHO as a major diagnostic criterion for myeloproliferative disorders (Tefferi et al., 2007).

In a study on 74 women with essential thrombocytemia the incidence of thrombosis was 18%, of which major thrombotic episodes were found in 7% (Tefferi et al., 2000). In another retrospective study of 102 patients with myeloproliferative disorders, the rate of thromboembolic complications in patients with polycythemia vera was 16.7%, 13.8% in patients with myelofibrosis and 7.5% in patients with essential thrombocytemia (Brodmann et al., 2000). The cytotherapeutic therapy with hydroxyurea and supplemental phlebotomy when necessary significantly reduced the risk of thrombosis when compared to control group treated with phlebotomy alone.

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The algorithm proposed by AASLD in 2009 for the identification of the PVT etiology is presented in the next table.

<table>
<thead>
<tr>
<th>Algorithm for investigating the cause of PVT (DeLeve et al., 2009)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Check first for cirrhosis, cancer of the abdominal organs and an inflammatory focus in the abdomen based on initial CT scan and sonography followed by additional procedures, as appropriate</td>
</tr>
<tr>
<td>2. Check for multiple, concurrent risk factors for thrombosis, in all patients without advanced cirrhosis or cancer</td>
</tr>
<tr>
<td>3. Do not rule out a diagnosis of myeloproliferative disease solely on the basis of normal or low peripheral blood cell counts</td>
</tr>
<tr>
<td>4. When coagulation factor levels are decreased, consider low levels of protein C, protein S or antithrombin as a possible consequence of liver dysfunction; consider inherited deficiency when screening of a first-degree relative is positive</td>
</tr>
</tbody>
</table>

Table 3.

4. Pathophysiology

Portal vein thrombosis is the main cause of presinusoidal portal hypertension. Frequently the initial placement of the thrombus is in the portal vein trunk but sometimes it is the result of the extension of a thrombus located on the intrahepatic branches of the portal vein or from the splenic vein. According to the location and extension of the thrombus, a grading system was proposed for a better evaluation of the disease prognosis (Naonami et al., 1992).

<table>
<thead>
<tr>
<th>Grade of PVT</th>
<th>Thrombus description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Occlusion of intrahepatic portal vein branches</td>
</tr>
<tr>
<td>2</td>
<td>Occlusion of right or left portal vein main branches</td>
</tr>
<tr>
<td>3</td>
<td>Partial occlusion of the portal vein trunk</td>
</tr>
<tr>
<td>4</td>
<td>Complete occlusion of the portal vein trunk</td>
</tr>
</tbody>
</table>

Table 4. PVT grading system

As a limited form of PVT, the term of “obliterative portal venopathy” was proposed in order to describe the thrombosis of intrahepatic portal vein branches in the absence of liver cirrhosis, inflammation or hepatic neoplasia (Cazals-Hatem et al., 2011).

Within days after the acute thrombosis of the portal vein, a cavernous transformation is taking place as a result of small varices proliferation around the former portal vein concomitant with a recanalisation of the thrombus through a neoangiogenesis process. The result is a spongy, tendril-like convolution of small vessels developed in the area of porta hepatis in order to compensate and by-pass the obstruction of the blood flow. Additionally, the reduced venous blood supply may be compensated by increasing arterial perfusion, which is documented by Doppler ultrasonography.

Chronic portal hypertension and fibroblasts activation inside the cloth leads to the development of a network of tortuous small vessels inside and around the former portal vein acting like a by-pass for the stenotic segment of the portal vein – the so-called portal cavernoma. This process starts from the moment of the acute thrombosis and evolves over the next weeks and months together with the development of porto-portal and porto-
systemic collaterals until equilibrium is established between prestenotic and poststenotic segment of the portal vein. Moreover, the development of porto-systemic collaterals may lead to a deterioration of the portal encephalopathy.

The natural history of PVT is still unclear, but two possible mechanisms can be involve in the asymptomatic status of the patients: one of them might be the flux augmentation in the hepatic artery as a compensation of the decreased flow in the portal vein; the second one involves the cavernous transformation with fast development of a tortuous network of collateral veins with periportal distribution around biliary ducts, gallbladder, gastric antrum, duodenum and pancreas (Henderson et al., 1992).

PVT and development of a portal cavernoma determines a prehepatic portal hypertension with an elevated blood pressure in the obstructed splanchnic territory with hepatopetal collateral network, condition known as cavernoma (Ohnishi et al., 1984). As a consequence of PVT with cavernous transformation the portal biliopathy can develop (Perlemuter et al., 1996). Another consequence might be a hyperkinetic status with higher cardiac output and lower vascular resistance due to portal obstruction and to portal-systemic collateral circulation (Ohnishi et al., 1984).

5. Clinical features

Clinical presentation always depends on the onset and the extent of the portal thrombosis as well as of the development of collateral circulation.

5.1 Acute PVT

In acute PVT patients can complain of abdominal pain, nausea, vomiting, fever, diarrhoea and haematochezia – symptoms due to intestinal congestion and ischemia. If venous obstruction is not quickly controlled, some severe complications might occur: enteral perforation, septic shock, peritonitis and exitus due to multiorgan failure. The physical examination reveals splenomegaly in almost all cases, whereas ascites is present before the onset of collateral circulation, caused by intestinal venous stasis (Kocher & Himmelmann, 2005; Ponziani et al., 2010).

5.2 Chronic PVT

Usually asymptomatic, the clinical presentation for PVT is almost always hematemesis/melaena due to variceal bleeding. Abdominal pain is not present commonly unless the extension of the PVT into the mesenteric branches causes mesenteric ischemia. An episode of gastrointestinal bleeding is often reported as the first presenting symptom in about 20%-40% of cases (Hoekstra & Janssen 2009), taking into account that in patients with cirrhosis and PVT the risk for variceal bleeding is estimated to be more than 80-120 times higher than in cases without cirrhosis (Condat et al, 2001). Ascites and encephalopathy are rare events and only transient. They are more frequent after an episode of gastrointestinal bleeding or might be associated with renal failure or sepsis especially in older patients (Sobhonslidsuk & Reddy, 2002).

In pylephlebitis patients usually features high fever and chills associated with painful liver at clinical examination.
Physical examination might be completely normal but, sometimes, cholestasis, cholangitis, choledocholithiasis, cholecystitis might occur, configuring the so-called “portal biliopathy”.

6. Biologic and imaging studies

Liver laboratory test are usually normal or characteristic for the underlying liver disease. A cholestatic syndrome can develop in PVT associated with portal biliopathy and the ERCP/MRCP frequently reveals a false image of cholangiocarcinoma due to the external compression of the common bile duct by the tortuous vessels of the cavernoma. In case of pylephlebitis blood culture usually reveals *Bacteroides species* and special attention should be paid for the identification of the abdominal origin of the infection.

Beside the eso-gastric varices revealed by the upped digestive endoscopy, other collateral venous circulation can develop in the gallbladder, duodenal, jejunal or rectal walls.

The abdominal ultrasound with Doppler/power-Doppler examination is the investigation of choice in PVT diagnose (sensitivity over 90%). It reveals the presence of the hypo- or hyperechoic material (depending on the age of the thrombus) inside the portal lumen. The examiner must bear in mind that frequently a difficult-to-identify portal vein suggests an old PVT. Additionally, a study from 2009 revealed that portal flow velocity below 15cm/s is an important predictive factor for PVT development (Søgaard et al., 2009).

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**Fig. 1.** Patient M.I. 47 years old diagnosed with ET – Doppler ultrasound revealing multiple small venous vessels replacing the former portal vein.
Fig. 2. Patient M.I. – Doppler ultrasound showing an old (hyperechoic) thrombus occluding the portal vein.

The next step in the PVT diagnose algorithm is the magnetic resonance angiography with better results than the CT-scan in identifying the characteristic changes involving the portal trunk.

Fig. 3. Patient M.I. - CT scan with i.v. contrast revealing hypodense thrombus and portal cavernoma: heterogonous mass at the level of the portal vein due to cavernous transformation; homogeneous splenomegaly.
Contrast enhanced ultrasonography is indicated for a better visualization of the thrombus, in differentiating between benign and malignant thrombosis or for the disclosure of cavernous transformation of the portal vein. When differentiating between benign and malignant thrombosis the absence of contrast inside the thrombus is suggestive for benign cloth while contrast enhancement of the thrombus is highly suggestive for neoplastic invasion of the portal vein.

Endoscopic ultrasound was recently added to the imaging armamentory showing a higher sensitivity and specificity than conventional ultrasound and CT/MR-scan in detecting small, non-occlusive thrombi and incipient malignant invasion of the portal and splenic veins.

The portal venography can be useful before surgical treatment is intended. $^{99m}$Tc-DTPA (diethylenetriamine pentaacetic acid) scintigraphy reveals only the arterial peak with the absence of the portal peak on the time-activity curve.

Fig. 4. Patient M.I. - Coronal MRI T2 weighted FRFSE fat-sat depicting portal cavernoma: dilated portal vein with heterogeneous signal due to the cavernous transformation. Associated homogeneous splenomegaly 14 cm diameter.
Fig. 5. Coronal MRI T2 weighted fat-sat of the same patient. The permeable lumen having a thread-like hypersignal on T2 weighted image, in the center of the portal vein along with dilated, partially thrombotic, portal vein.

Fig. 6. The same case – axial T2 weighted fat-sat. In addition to the changes of the portal vein the image reveals homogeneous splenomegaly; dilated, partially dilated splenic vein; portal type collateral venous flow.
Fig. 7. The same case – axial T1 weighted fat-sat with i.v. contrast. Cavernous transformation of the portal vein with contrast enhancement of the fibrotic thrombi. The central thread-like permeable lumen shows a reduced flow signal.

Fig. 8. The same case – coronal T1 weighted fat-sat with contrast. Same changes as in figure 7.
Fig. 9 and 10. The same case – angio-MRI sequence. Inhomogeneous signal of the portal vein with chronic thrombosis.
7. Diagnosis algorithm

The algorithm for PVT diagnose proposed by AASLD in 2009 is presented in the next table.

<table>
<thead>
<tr>
<th>Acute thrombosis</th>
<th>Chronic thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Consider a diagnosis of acute PVT in any patient with abdominal pain</td>
<td>1. Consider a diagnosis of chronic PVT in any patient with newly</td>
</tr>
<tr>
<td>of more than 24 hours duration, whether or not there is also fever or</td>
<td>diagnosed portal hypertension</td>
</tr>
<tr>
<td>ileus</td>
<td></td>
</tr>
<tr>
<td>2. If acute PVT is suspected, CT scan, before and after injection of vascular</td>
<td>2. Obtain Doppler-sonography, then either CT scan or MRI before and</td>
</tr>
<tr>
<td>contrast agent, should be obtained for early confirmation of diagnosis. If CT</td>
<td>after a vascular contrast agent to make a diagnosis of chronic PVT</td>
</tr>
<tr>
<td>scan is not rapidly available, obtain Doppler-sonography</td>
<td></td>
</tr>
<tr>
<td>3. In patients with acute PVT and high fever and chills, septic</td>
<td>3. Base the diagnosis on the absence of a visible normal portal vein and</td>
</tr>
<tr>
<td>pylephlebitis should be considered, whether or not an abdominal source of</td>
<td>its replacement with serpiginous veins</td>
</tr>
<tr>
<td>infection has been identified, and blood cultures should be routinely obtained</td>
<td></td>
</tr>
<tr>
<td>4. In acute PVT, the possibility of intestinal infarction should be</td>
<td></td>
</tr>
<tr>
<td>considered from presentation until resolution of pain. The presence of ascites,</td>
<td></td>
</tr>
<tr>
<td>thinning of the intestinal wall, lack of mucosal enhancement of the thickened</td>
<td></td>
</tr>
<tr>
<td>intestinal wall, or the development of multiorgan failure indicate that intestinal</td>
<td></td>
</tr>
<tr>
<td>infarction is likely and surgical exploration should be considered</td>
<td></td>
</tr>
</tbody>
</table>

Table 5: PVT diagnose algorithm (DeLeve et al., 2009)

8. Treatment

In patients with PVT due to septic conditions (cholangitis, diverticulitis, appendicitis, cholecystitis, umbilical vein infection, pylephlebitis, liver abscesses etc) the prompt initiation of broad-spectrum antibiotic association therapy leads to an efficient repermebilisation of the portal vein within days.

If patient is diagnosed in the recent phase of the PVT (hypoechoic aspect on the ultrasound examination together with blood flow deviation and flux acceleration on Doppler examination) anticoagulant therapy is indicated in order to prevent the total obstruction of
the portal vein and the cavernous transformation. Standard heparin or LMWH derivates are initially used followed by oral dicumarinic anticoagulants in order to obtain an INR between 2 and 2.5 with an efficient repermeabilisation in over 80% of cases in the next six months (Valla et al., 2002). As for the peripheral vein thrombosis, the oral anticoagulant therapy is considered to be mandatory for minimum three months and usually is indicated for at least six months. Chronic, indefinite oral anticoagulation is recommended in patients with identified hypercoagulability associated diseases or in presence of thrombus extension into the mesenteric vein.

However, additional concern has been rise over vitamin K antagonists indication in cirrhotic patients due to plasmatic low protein C levels. As protein C is a vitamin K-dependent factor and treatment with vitamin K antagonist may further reduce the plasmatic levels of this anticoagulant protein, the increasing risk for venous thrombosis has been issued. Newly developed direct thrombin inhibitors and inhibitors of activated factor X (e.g. dabigatran, rivaroxaban, apixaban) are considered to be more attractive alternatives to vitamin K antagonists due to their null influence over protein C levels (Franchini & Mannucci, 2009). In addition to their oral administration they have the advantage of not requiring regular laboratory monitoring (such as INR) (Tripodi & Mannucci, 2011).

Concern has been rise also over the safety of chronic anticoagulant therapy in patients with esophageal varices. The few clinical studies addressing this issue (Condat et al., 2001) revealed no significant increase in risk and severity of variceal bleeding.

In initially acute phases, thrombolytic medication (e.g. streptokinase, tPA, alteplase) can be safely initiated especially in patients associating mesenteric ischemia due to thrombus extension in the upper mesenteric vein (Malkowski et al., 2003).

In patients diagnosed with old age thrombus or cavernous transformation of the portal vein the anticoagulant treatment is not indicated due to the lack of efficiency and the associated risk of bleeding.

The major complication of PVT is upper digestive bleeding originating from the eso-gastric varices, with a significant lower mortality rate in patients without liver cirrhosis (aprox. 5%) than in patients with cirrhosis (between 30 and 70%) (Jing-Tong et al., 2005). The endoscopic procedures (band ligation/sclerotherapy) are the first-line treatment indicated in these cases with multiple sessions until the occlusion of the varices. A special attention should be paid when indicating vasoconstrictive agents (e.g. glipresin, terlipresin) due to the possibility of inducind extended intestinal ischemia. Associated oral medication (nonselective beta-blockers +/- long-acting nitrates) prevents the recurrent bleeding. In refractory cases of variceal bleeding and in gastric valices TIPS placement is considered. Malignant portal vein invasion/thrombosis can be safely managed with percutaneous stenting.

More invasive surgical treatment (mesocaval/splenorenal shunts, eso-gastric devascularization) may be necessary in patients with uncontrolled bleeding.

In children it has been recommended the mesenteric-to-left portal vein bypass with very good results in term of rebleeding prevention and improvement of cognitive function.

Initially considered as contraindication for liver transplantation, the complete PVT is now considered to be just a relative contraindication but only in case the superior mesenteric vein is permeable. Partial PVT can be managed by thrombectomy or by-pass techniques.
Portal biliopathy is another potential complication developing in the evolution of PVT with cavernous transformation. It consists in multiple, successive stenosis involving the common bile duct and the hepatic duct as a result of extrinsic compression and/or ischemic fibrosis of the biliary tract. In symptomatic patients (cholangitis, cholecystitis, biliary stones in the CBD, secondary biliary cirrhosis) the portal biliopathy can be addressed with sphincterotomy, stone extraction, stricture dilatation and biliary stenting together with a porto-systemic shunt in order to reduce the external compression of the biliary tract.

From the systemic conditions associated with portal cavernoma, the myeloproliferative syndrome is by far the most frequent one (37% of patients with non-cirrhotic non-malignant PVT) (Kiladjian et al., 2006). To prevent thrombotic complication in chronic myeloproliferative disorders, platelet-lowering agents are used to address the thrombocytopenia-associated risk. Hydroxyurea, a ribonucleotide reductase inhibitor with myelosuppressive action, is the first line indication administered on a 500mg PO bid regimen. A platelet-specific lowering agent (Anagrelide) is available on a 0,5mg PO tid regimen for the patients with intolerance to hydroxyurea. For a more efficient myelosuppressive action Interferon-alpha is recommended on a 5MU SC tiw regimen. Despite their leukemogenic action, radiophosphorus ($^{32}$P) and alkylating agents (e.g. chlorambucil) may be useful as backup regimens in case of recurrent disease (Tefferi et al., 2001). The goal of platelet-lowering medication is to maintain the platelet level under 40000/mm$^3$ in the high-risk patients (Regev et al., 1997; Storen & Tefferi, 2001). A more aggressive approach like bone marrow transplantation should be considered only in exceptional cases.

9. Prognosis

In the absence of liver cirrhosis and neoplasia the development of portal cavernoma is usually asymptomatic until the first variceal bleeding and has a better prognosis in comparison with variceal bleeding caused by cirrhosis (Janssen et al., 2001).

Except the variceal bleeding, the natural history of portal cavernoma is unremarkable until the development of two other complications: intestinal ischemia (due to extension of the thrombus in the mesenteric vein) and portal biliopathy (common bile duct dilation with cholestatic syndrome).

Although ET usually carries the best prognosis among the MPD, portal vein thrombosis was identified as a risk factor for poor survival, which appears to be the result of increased mortality from acute leukemic or myelofibrotic transformation and hepatic failure (Gangat et al., 2006).

10. References


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Portal Vein Thrombosis with Cavernous Transformation in Myeloproliferative Disorders: Review Update


Valla DC, Condat B, Lebrec D. Spectrum of portal vein thrombosis in the West. *J Gastroenterol Hepatol*, 2002;17:s224


Portal hypertension is a clinical syndrome defined by a portal venous pressure gradient, exceeding 5 mm Hg. In this book the causes of its development and complications are described. Authors have presented personal experiences on conducting patients with various displays of portal hypertension. Moreover, the book presents modern data about molecular mechanisms of pathogenesis of portal hypertension in liver cirrhosis, the information about the original predictor of risk of bleeding from gastro-esophageal varices and new methods for their conservative treatment.

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