Review

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Portal vein thrombosis in liver cirrhosis – the added value of contrast enhanced ultrasonography.

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Abstract

Portal vein thrombosis (PVT) is a frequent complication of liver cirrhosis and its prevalence increases with the severity of liver disease. Patients with liver cirrhosis and hepatocellular carcinoma may have either malignant or blunt (benign) PVT. In these patients, the diagnosis and characterization of PVT is important for the prognosis and further treatment.

Ultrasound (US) is the modality of choice for the diagnosis of PVT. The features of PVT on B-mode (gray-scale) US include: dilatation of the portal vein, visualization of the thrombus and, in chronic PVT- cavernous transformation. Sensitivity of US in the diagnosis of PVT is improved by the use of Doppler US and of ultrasound contrast agents. In the latter years, contrast enhanced ultrasound (CEUS) showed high sensitivity in the differential diagnosis between benign and malignant PVT and could be the diagnostic method of choice for the characterization of PVT. Blunt thrombi are avascular and will not enhance during CEUS examination, while a hyperenhancement pattern of the portal thrombus in the arterial phase, with "wash out" in the portal or late phase is typical for malignant PVT.

Keywords: Portal vein thrombosis (PVT), Liver cirrhosis; Ultrasound (US), Contrast enhanced ultrasound (CEUS)

Introduction

Ultrasound (US) is the most used imaging method in the evaluation and surveillance of patients with hepatopathies, especially in patients with advanced fibrosis and cirrhosis. According to all guidelines (AASLD, EASL-EORT) [1,2] US is the only imaging method used for screening of hepatocellular carcinoma and is recommended to be performed every 6 months. PVT can be an incidental finding on ultrasound surveillance especially when asymptomatic. Also, all patients with chronic liver diseases should undergo a US Doppler examination at the time of first diagnosis to assess the presence of signs of cirrhosis and portal hypertension as recommended by EFSUMB guidelines [3].

Liver cirrhosis – the end stage of liver disease – is a condition with many complications [4-6]. One that is common is PVT that can lead to hepatic decompensation by increasing portal hypertension.

The prevalence of PVT increases with the severity of cirrhosis, from 1% [7] in patients with compensated cirrhosis to 8-25% [8] in candidates for liver transplantation. Many factors are involved: local (liver architectural changes, slowing of portal vein flow due to resistance increase in the cirrhotic liver, the presence of periportal lymphangitis) [9], systemic (unbalanced hemostasis with a tendency to hypercoagulability), and other congenital and acquired factors [10].

On the other hand, PVT is more frequent in patients with cirrhosis and hepatocellular carcinoma (HCC), occurring in approximately 35% of cases [11]. Malignant PVT in patients with HCC is a contraindication for curative treatment and also for liver transplantation, due to the high rate of tumor recurrence [12]. However, differentiating between benign and malignant thrombi in portal veins is sometimes difficult. The use of contrast agents in ultrasound examination (CEUS) has been shown to increase the sensitivity of ultrasound for the detection and also for the characterization of portal thrombi.

The clinical consequences of PVT are related to thrombus extension. PVT can be classified anatomically

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into four grades [13] according to where the thrombus extends: **Grade 1:** Partial PVT – the obstruction of the portal vein by the thrombus in less than 50% of its lumen; **Grade 2:** obstruction of PV is greater than 50% or complete occlusion with or without minimal extension into the superior mesenteric vein (SMV); **Grade 3:** Complete thrombosis of both PV, thrombus extends to the proximal part of the SMV; **Grade 4:** complete thrombosis – the portal vein thrombus affects proximal and also distal SMV.

Patients with limited PVT can be asymptomatic, but the most common clinical presentations in PVT patients are: gastrointestinal bleeding, abdominal pain, jaundice, and hepatic encephalopathy. If the thrombus involves proximally the superior mesenteric vein, the risk of intestinal infarction is high [14].

Gray-scale (B-mode imaging) and Doppler US in the diagnosis of PVT

In most patients, gray-scale and Doppler US allow the non-invasive diagnosis of PVT by demonstrating the presence of hyperechoic material within the portal vein, distension of the portal vein and its tributaries, and total or partial absence of flow [15].

In PVT the thrombus is observed as an echogenic lesion within the portal vein. The thrombus echogenicity can be hypo-, hyper- or isoechoic in standard US and its echogenity is not predictive for the nature of PVT (benign or malignant), but the presence of an adjacent liver mass to the PVT is highly predictive for malignant PVT [15] (fig 1a). Sometimes, a recently formed thrombus may be anechoic and thus can be missed by standard US examination [15]. The lack of variation in the portal vein diameter with respiration, coupled with a portal vein diameter greater than 13-15 mm, is also highly indicative of portal vein occlusion [16].

Another sonographic feature of portal vein occlusion is the development of collaterals with cavernous transformation (fig 1b). Because this transformation takes a long time to develop, the presence of portal cavernoma can be a marker for blunt thrombus [17]. Patients with malignant thrombus and hepatocellular carcinoma usually do not live long enough to develop a cavernoma.

In many cases the gray-scale US cannot differentiate between benign and malignant thrombosis [15]. In malignant PVT, US detects an echodense material in the portal vein lumen that can be limited or extensive, involving the common portal vein, the portal bifurcation and portal branches, sometimes with invasion of portal vein walls which is characteristic for malignant PVT [18].

Sensitivity of US in detecting PVT increases with PVT grade (100% in complete PVT) [13], false negative diagnosis occurring only in incomplete PVT.

Doppler US has been accepted as the "gold standard" in assessing the direction of flow in the portal venous system [19], but it is also highly accurate in detecting thrombosis that involves the trunk of the portal vein and its intrahepatic branches.

There are some aspects in Doppler US very sensitive for the differentiation between malignant and benign PVT. Color signals within the thrombus (due to tumoral neovascularity) and detection of pulsatile flow in a portal vein thrombus using power Doppler US are criteria for malignant PVT [20].

Detection of pulsatile flow within a portal thrombus in patients with hepatocellular carcinoma was first reported by Pozniak et al [21]. Tanaka et al demonstrated that the presence of pulsatile flow in a portal thrombus is specific for malignant thrombosis [20]. Using detection of pulsatile flow within the thrombus as a criteria for malignant PVT diagnosis, the sensitivity and specificity of color Doppler sonography were 92% and 100% respectively, with 95% accuracy in the study of Lencioli et al [22].

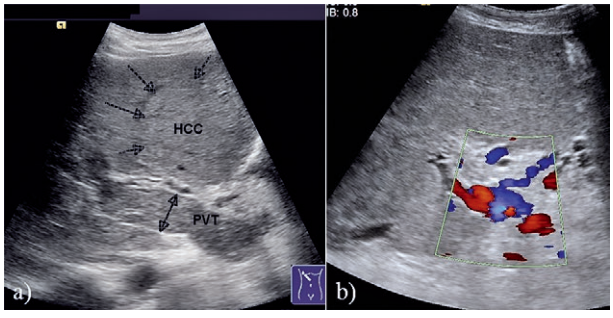


Fig 1. a) Complete PVT (double arrow) in a patient with a large hepatocellular carcinoma (between arrows) situated in the proximity of the main portal vein; b) Recanalisation in benign portal vein thrombosis with cavernous transformation. Doppler US reveals the presence of color signals inside the thrombus.

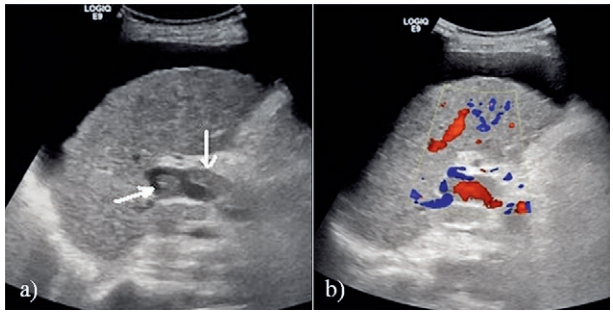


Fig 2. a) Partial PVT in a patient with HCV decompensated liver cirrhosis with large perihepatic ascites;b) Doppler US examination reveals color signals between the thrombus and portal vein wall suggesting partial PVT.

The presence of pulsatile flow in the portal vein thrombus had 82.5% sensitivity and 100% specificity for the diagnosis of malignant PVT in the Ueno et al study [23]. In the same study, the overall accuracy in differentiating between benign and malignant portal vein thrombi by power Doppler US was 87%. But the sensitivity of Doppler US in the detection of malignant thrombi is highly dependent on the size of the thrombus [24], lower than 20% [25,26].

From the clinical point of view, it is very important to determine whether PVT is complete (occupying the entire lumen of portal vein) or partial. Color Doppler US examination can be used to differentiate between complete and partial PVT revealing complete or partial absence of color signals within the portal lumen [27] (fig 2).

CEUS in the diagnosis of PVT

The differentiation of a malignant vs. benign PVT is of paramount importance in the management of patients with liver cirrhosis. CEUS appeared to be superior to US and Doppler US for both the detection and characterization of PVT.

One of the indications for the use of CEUS in the EFSUMB guidelines [28] is the characterization of PTV in cirrhotic patients, which is crucial for a therapeutic decision, and also for the prognosis. Patients with malignant invasion of major branches of the portal vein or hepatic veins have a poor prognosis (stage IV by the TNM classification) and are not candidates for surgical resection or liver transplantation [18].

CEUS allows detailed visualization of the hepatic microvasculature system (similar to computer tomography [CT] or magnetic resonance imaging [MRI]), of focal liver lesions and also of portal vein thrombosis. Blunt thrombi are avascular and will not enhance during CEUS examination. Malignant thrombi have the same enhancement pattern as the tumor from which they originated, including rapid arterial phase hyperenhancement and slow or weak portal venous wash out (fig 3) [28].

In the study of Rossi et al four patterns of PVT enhancement were described during CEUS [26]: Pattern 1 – typical for thrombi without internal vascularization (thrombus enhancement is absent in all three phases). This is a benign thrombosis; Pattern 2 – diffuse thrombus enhancement visible only during the early arterial phase, reflecting the diffuse thrombus vascularization similar to that of the tumor tissue from which it originates; Patterns 3 (linear or punctate enhancement) and 4 (multilinear or multipunctate enhancement) can be observed during either the arterial or portal and late phases of CEUS and are indicative of thrombus vascularization. Patterns 2, 3 and 4 are present in malignant PVT and may be combined. In the same study, the sensitivity of B mode ultrasound, color Doppler US, and CEUS were compared. CEUS sensitivity was significantly higher than color Doppler for the detection of thrombi with and without continuity with the tumor tissue ($p<0.05$); for occluding vs. no occluding thrombi ($p<0.05$); and also for the characterization of PVT [26].

Dynamic contrast-enhanced MRI and 4-phase multidetector CT are the most effective imaging techniques in the diagnosis of HCC and in the stadialization of the disease [2]. Macrovascular invasion such as PVT in HCC is a contraindication for curative treatments. Helical CT was less sensitive than CEUS for the characterization of PVT (98 vs. 67.6%) in the Rossi et al study [29], but CT and MRI also provide information regarding the thrombus extension, such as SMV involvement. Also CT and MRI offer a simultaneous diagnosis of PVT and its possible underlying cause such as HCC.

In the latter years many studies have been completed in order to assess the value of CEUS in the diagnosis of PVT and all demonstrated its high value in the characterization and also for the detection of PVT (Table I).

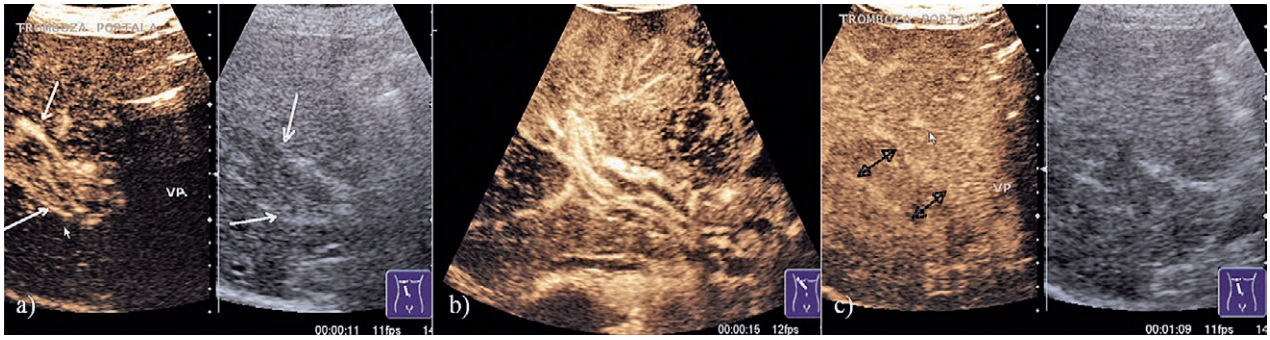


Fig 3. a) Malignant PVT with hyperenhancement of the thrombus in the arterial phase, 12 seconds after SonoVue injection (arrows); b) CEUS examination reveals thrombus vascularization with early arterial enhancement ("linear pattern" described by Rossi [29]) – suggesting malignant portal vein thrombosis; c) Malignant PVT– washout is present in the portal phase of CEUS examination (1 minute after contrast injection) (double arrows).

Table I. Clinical studies of CEUS efficacy in the characterization of portal vein thrombosis.

Study	N	Criteria for diagnosis	Se (%)	Sp (%)	Ac (%)	PPV (%)	NPV (%)
Tarantino et al. Abdom Imaging 2006 [26]	54	Enhancement features of PVT on CEUS /follow-up	88	-	-	-	-
Ueno et al. J Ultrasound Med 2006 [30]	55	Enhancement of PVT in malignant thrombosis/no enhancement in benign PVT	100	100	100	100	100
Rossi et al. Eur Radiol 2008 [29]	50	Enhancing tissue within the vessel lumen in the early arterial phase in malignanat PVT/Spiral TC	98	-	-	-	-
Sorrentino et al. World J Gastroenterol 2009 [31]	108	Enhancement features of PVT on CEUS/FNB	89.6	100	-	100	89.2
Song ZZ et al. Eur J Radiol 2010 [32]	17	Enhancement of PVT on CEUS /follow-up	100	66.7	93.3	-	-
Danila et al. Med Ultrason 2011 [33]	38	Enhancement features of PVT (EFSUMB criteria)	97.2	-	-	-	-
Raza SA et al. Abdom Imaging 2014 [34]	50	Enhancement of PVT on CEUS/ clinico-radiologic follow-up	100 100	83 92		95 97	100 100

N – number of patients, Se – Sensitivity, Sp – specificity, Ac – accuracy, PPV – positive predictive value, NPV – negative predictive value

In the Sorrentino et al study 108 cirrhotic patients with HCC and PVT without direct contiguity between the thrombus and HCC were evaluated by means of CEUS and fine needle biopsy (FNB). They reported the same sensitivity, specificity, positive and negative predictive value for CEUS and fine needle biopsy (FNB) for the diagnosis of PVT. There were 6 false-negative patients on baseline CEUS, but they were also false-negative at FNB [31]. In these patients CEUS showed no homogeneous arterial enhancement at baseline and also no malignant cells were found by FNB. After 6 months follow-up an extension of the thrombi was observed in all 6 cases, with a "mosaic pattern" of enhancement following contrast bolus at CEUS, confirmed as malignant by a repeated FNB. If this "mosaic pattern" is considered suggestive for malignant PVT than the sensitivity of CEUS for the characterization of PVT is 100%. A false-negative result at FNB can be possible if biopsy is taken from a segment of the thrombus that does not contain malignant cells. Using CEUS guided PVT biopsy the sensitivity of the method was highly improved [31].

In the Ueno et al study [30], the hyperenhancement pattern was present in all malignant thrombi (100% of the cases). The references methods in this study were CT, angiography, CT+angiography, pathological proof, or follow-up.

In the Raza et al study [34] 50 patients were restrospectively evaluated by two independent readers. The performance of CEUS in differentiating malignant from benign PVT, were similar for both readers.

Even if all published studies showed very good results for the characterization of PVT by CEUS, it must be mentioned that only a small number of patients were included (between 50-108 patients).

In some cases, US examination reveals only PVT without definite evidence of a mass-forming lesion in the liver or a very inhomogeneous hepatic echo texture. Confirmation of the malignant nature of PVT using CEUS examination strongly suggests the presence of HCC (unapparent or occult HCC) [35].

CEUS has some advantages over other imaging methods in the diagnosis of PVT: it is a fast and real-time examination that can be performed in the same session with thrombus detection and it is an inexpensive method with almost no complications and no irradiation.

In conclusion in most patients, B mode (standard) and Doppler US allows the non-invasive diagnosis of PVT, by demonstrating hyperechoic material within the portal vein, distension of the portal vein and its tributaries, and total or partial absence of flow.

CEUS proved to be a very sensitive method for characterization and also for the detection of PVT. The high sensitivity of this method recommends CEUS as the first line imaging method for the characterization of PVT and should be considered as the "gold standard method". In some cases CEUS is the only imaging method available for the differential diagnosis between benign and malignant PVT (patients with contraindication for CT and/or MRI).

But we must bear in mind that US is an operator-dependent method, influenced by the examiner's experience, by the patient's condition, and also by the US machine performance.

Conflict of interest: none

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