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The value of Contrast Enhanced Ultrasound in the evaluation of the nature of portal vein thrombosis

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Abstract

Portal vein thrombosis (PVT) is a relatively common complication in patients with liver cirrhosis and hepatocellular carcinoma, but might also occur in the absence of liver disease. Ultrasound (US) is the first imaging method used for assessing PVT. **The purpose** of this paper is to evaluate the utility of contrast-enhanced ultrasound (CEUS) for the differentiation between benign and malignant PVT. **Materials and methods:** from October 2009 to October 2010, 38 PVTs were evaluated by means of ultrasound (standard, Doppler and CEUS). 29 PVT were in patients with liver cirrhosis and 9 in subjects without liver cirrhosis. **Results:** 15 of 38 patients (39.5%) had benign PVT and 23 patients (60.5%) had malignant PVT. Results of CEUS examination were conclusive in 37/38 (97.2%) of the examinations for PVT, allowing the differentiation between benign and malignant thrombosis. When the result was inconclusive, another imaging method was performed (MRI). **Conclusion** CEUS is a very good method for the evaluation of benign or malignant nature of portal vein thrombosis.

Keywords: portal vein thrombosis, benign, malign, contrast enhanced ultrasound, hepatocellular carcinoma.

Rezumat

Tromboza portală este o complicație frecventă a cirozei hepatice şi a hepatocarcinomului, dar poate fi diagnosticată şi în absența unei hepatopatii. Ecografia este în majoritatea cazurilor prima examinare imagistică care pune diagnosticul de tromboză portală. **Scopul** lucrării este evaluarea rolului ecografiei cu substanță de contrast (CEUS), în diferențierea între tromboza portală malignă şi tromboza portală benign. **Material şi metodă:** din octombrie 2009 până în octombrie 2010, 38 pacienți consecutivi, cu diagnosticul de tromboză portală (TP), au fost evaluați ecografic (ecografie standard, ecografie Doppler şi CEUS). 29 TP au fost diagnosticate la pacienți cu ciroză hepatică şi 9 TP la pacienți fără ciroză hepatică. **Rezultate:** 15 din cei 38 de pacienți (39,5%) au prezentat TP benignă, iar 23 pacienți (60,5%) au prezentat tromboză portală malignă. Rezultatul examinării CEUS a fost concluziv în 37/38 cazuri (97,2%). În cazul în care rezultatul CEUS a fost neconcluziv, s-a efectuat o altă metodă imagistică (RM). **Concluzie:** Ecografia cu contrast (CEUS) este o metodă foarte bună de evaluare a naturii benigne sau maligne a trombozei portale.

Cuvinte cheie: tromboză portală, ecografie cu substanță de contrast, malign, benign, hepatocarcinom.

Introduction

Portal vein thrombosis (PVT) is quite a rare medical condition, but an important cause of noncirrhotic portal hypertension. PVT occurs most often in patients with liver cirrhosis and usually with hepatocellular carcinoma, but also sometimes outside of these pathological conditions.

Many prothrombotic factors and local abdominal conditions leading to PVT have been identified. Inflammatory abdominal foci (such as appendicitis, diverticulitis, inflammatory bowel diseases, pancreatitis, cholecystitis, hepatic abscesses, and cholangitis) are the most common local thrombotic risk factors [1-3]. Transient PVT has been reported in 23% of patients with acute pancreatitis and in 57% of those with pancreatic necrosis [4].

Malignancies, frequently of hepatic or pancreatic origin, are responsible for 21%-24% of overall cases of PVT [5,6]. Direct vascular invasion, compression by tumor mass, or

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a hypercoagulable status are the mechanisms involved in neoplastic PVT development; hormonal factors might also play a role in this process, especially in men [7-9].

Other less common PVT local causes are adenopathy, systemic inflammatory response syndrome, and surgical traumas to the portal venous system, such as porto-systemic shunting, splenectomy, liver transplantation, ablative therapy for HCC, and fine needle aspiration of abdominal masses [10].

Portal vein thrombosis is an important complication of cirrhosis, occurring in 0.6–16% of patients with compensated cirrhosis and in 35% in patients with decompensated liver cirrhosis and HCC [11].

Patients with cirrhosis and early hepatocellular carcinoma (HCC) may have either malignant or benign (fibrin clot) portal vein thrombosis. The assessment of the malignant or benign character of PVT is very important regarding the therapeutic options in hepatocellular carcinoma.

According to the EFSUMB guidelines, CEUS is one of the recommended methods for PVT assessment. Benign (cloth) thrombi are usually avascular and do not enhance in the arterial phase. When the portal thrombus contains malignant vascularity, it enhances in the arterial phase and wash out occurs in the portal and late phases [12].

The **purpose** of this paper is to assess the value of CEUS in the evaluation of PVT. We also assessed the role of contrast-enhanced ultrasound (CEUS) in the differential diagnosis between benign and malignant PVT.

The purpose of our study was also to evaluate the applicability and value of the EFSUMB CEUS criteria for the diagnosis of portal vein thrombosis in clinical practice.

Materials and methods

From October 2009 to September 2010, 38 consecutive patients with PVT were evaluated by means of ultrasound. Firstly, the diagnosis of PVT was made based on standard ultrasound examination (echogenic material-"solid like structure" within the vessel lumen). Doppler examination was used to differentiate between complete and partial PVT (complete or partial absence of color signals within the vessel lumen). The nature of PVT was assessed by means of CEUS - benign portal vein thrombosis was diagnosed based on the following criteria: lack of vascularization of the portal thrombus on CEUS and absence of the vein's walls disruption; malignant portal vein thrombosis was diagnosed in patients with vascularized thrombus (enhancement in the arterial phase), with "washout" in the portal and/or late phases [12], sometimes with disruption of the vein's walls and masses in the hepatic parenchyma.

The US contrast agent used in the present study was SonoVue® (Bracco, Italy) and the ultrasound machine was Siemens Acuson S2000. Each patient received an intravenous bolus injection of SonoVue® for each lesion to be characterized (usually 2.4 ml), via a 20-gauge intravenous catheter placed in the ante-cubital vein, and followed by a 10 ml saline flush. The findings obtained from the CEUS imaging technique were reviewed under blinded conditions by two trained, experienced reviewers (alternatively 2 of the 4 senior ultrasound examiners: MD, IS, RS, AP).

All images were digitally recorded and stored: 10 seconds long video-clips for standard examination and 30 seconds long video-clips for each of the arterial, portal and late phases of CEUS examination.

The study was approved by the Local Ethics Committee. After informed consent was obtained, CEUS was performed and all patients were monitored for adverse events, until two hours after the procedure.

Results

Out of 38 patients with PVT, 29 (76.3%) were subjects with liver cirrhosis, with or without visible hepatocellular carcinoma and 9 (23.7%) were patients with other abdominal or unknown pathology (table I).

Table I. Characteristics of patients enrolled in study

No. of patients enrolled in the study	38
Age (mean years)	61
Males/Females	25/13
Etiology of PVT:	
• Liver cirrhosis without HCC	3
• Liver cirrhosis with HCC	26
• Idiopathic PVT	4
• Acute pancreatitis	3
• Liver metastasis	2
Complete/Incomplete PVT	28/10
Location of incomplete PVT	
• Main trunk	3
• Main trunk and both left and right PV	4
• Only Left PV	1
• Only Right PV	2
Malignant/Benign PVT	23/15
Results of CEUS examination conclusive/ inconclusive	37/1

The etiology of liver cirrhosis was C chronic hepatitis in 14 cases (48.3%), B chronic hepatitis in 9 cases (31%), alcoholic liver cirrhosis in 4 cases (13.8%) and idiopathic cirrhosis in 2 cases (6.9%). 26/29 (89.6%) of the patients with liver cirrhosis also had hepatocellular carcinoma (in ultrasound and CEUS examination), in most of the cases large or multicentre hepatocellular carcinoma.

Twenty one of 26 (80.8%) patients with liver cirrhosis and hepatocellular carcinoma had malignant PVT, and 5 (19.2%) of them had benign PVT. One case with hepatocellular carcinoma and benign PVT was treated by percutaneous ethanol injection (PEI) and PVT was a post PEIT complication (chemical thrombosis).

PVT was adjacent to the hepatocellular carcinoma in 16 of 26 cases (in 2 cases it could not be distinguished from the tumor). In 6 cases PVT was remote for the HCC, and in 4 cases the PVT was associated with diffuse HCC.

Other diseases complicated with PVT were acute pancreatitis in 3 cases (7.9%) and liver metastases in 2 cases (5.3%). Four cases (10.5%) of PVT were found incidentally and the etiology of PVT was not discovered.

Standard ultrasound and Doppler examinations showed complete portal vein thrombosis in 28 of 38 patients (73.7%) and 10 patients (26.3%) had partial PVT. Partial PVT was located in the main trunk with an extension in both the left and right portal trunk in 4 cases, only in the main trunk in 3 cases, only in the right PV in 2 cases and in 1 case only in the left PV. The size of incomplete PVT in CEUS examination varied between 20/10 mm and 25/15 mm.

In malignant PVT, CEUS examination showed arterial enhancement of the portal thrombus in the arterial phase, frequently 13-15 seconds after contrast agent administration, followed by "washout" in the portal and/or late phases (fig 1-4). Wash-out in the portal phase was present in 18 of 23 malignant PVT and in the late phase in 21 of the 23 malignant PVT.

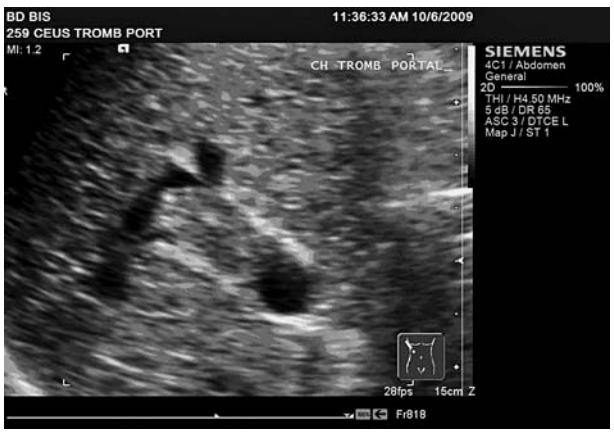

Fig 1. Malign PVT – aspect in standard US

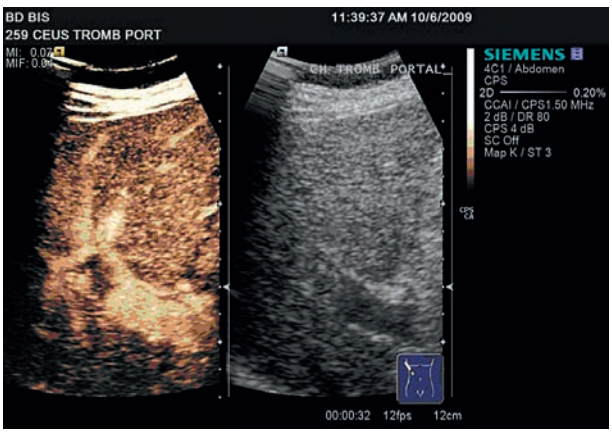

Fig 2. Malign PVT with enhancement in the arterial phase

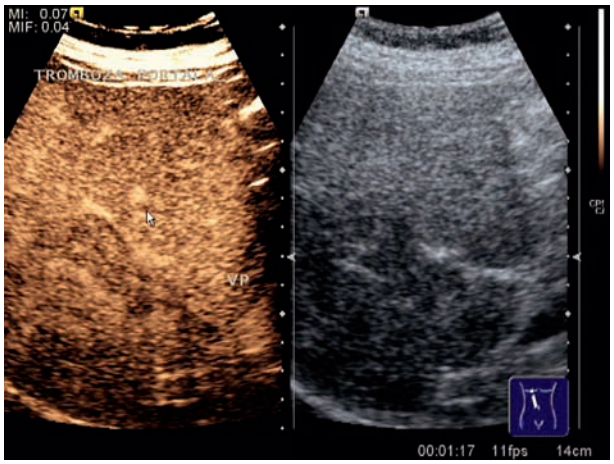

Fig 3. Malign PVT with wash out in portal phase

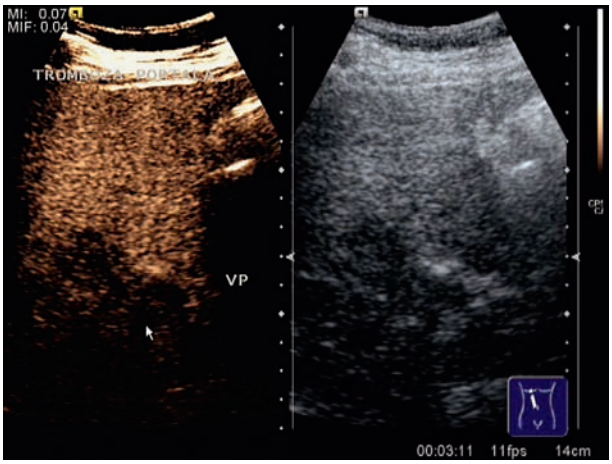

Fig 4. Malign PVT with wash out in late phase

In benign PVT, CEUS examination did not show any thrombus enhancement in all three phases of the examination (fig 5, fig 6).

Finally, regarding the benign or malignant etiology of the thrombus, CEUS was conclusive in 37 of 38 examinations. In the case in which CEUS was inconclusive, another imaging examination was performed, magnetic resonance imaging (MRI), showing the presence of a portal cavernoma. The patient was known with idiopathic portal hypertension and PVT. On standard ultrasound, the main PV trunk seemed to be hypoechoic with parenchymal content (fig 7) and we did not see a typical aspect of portal cavernoma. On CEUS examination, there was no evidence of a clear arterial enhancement (fig 8), and the result was considered inconclusive.

In patients with acute pancreatitis, PVT was benign in all three cases, and in patients with liver metastasis, PVT was malignant in all cases.

Discussion

In clinical practice, PVT is most commonly encountered in patients with hepatocellular carcinoma (HCC), especially in those with end-stage liver disease [11]. The detection and characterization of portal-vein thrombi is of paramount importance in HCC patients, because malignant thrombi are a contraindication for liver transplantation, resective surgery, and percutaneous ablation techniques; also they are a relative contraindication for trans-arterial chemoembolization.

In our study almost 70% of PVTs were found in patients with liver cirrhosis and HCC.

Ultrasonography (US) is the first imaging method used to assess the hepatic parenchyma and vasculature in patients with cirrhosis and portal hypertension. Also, US and color Doppler US (cDUS), had similar results to those of tri-phased computer tomography (CT) for the

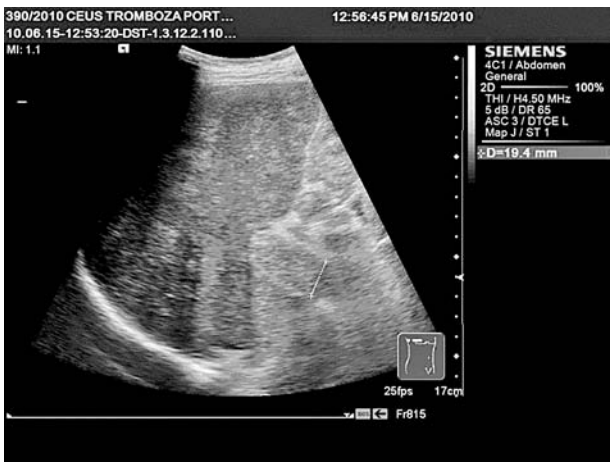

Fig 5. Benign PVT – aspect in standard US

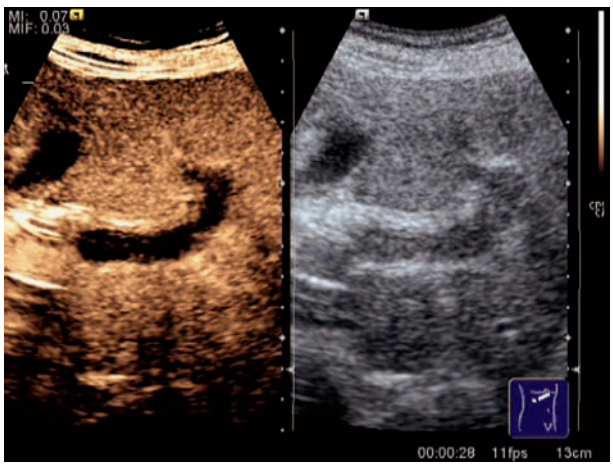

Fig 6. Benign PVT- without enhancement in the arterial phase

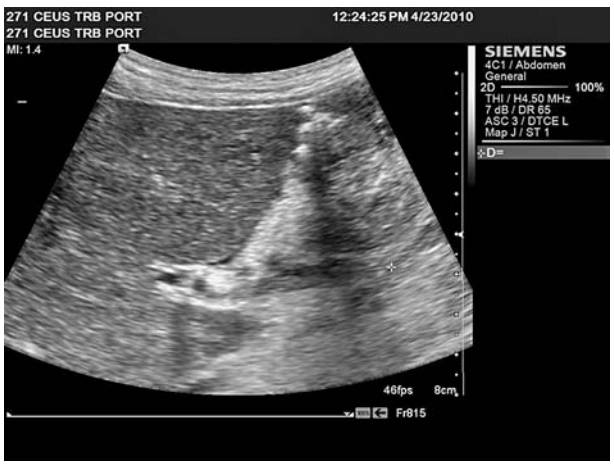

Fig 7. PVT in a case of an inconclusive result – aspect in standard US

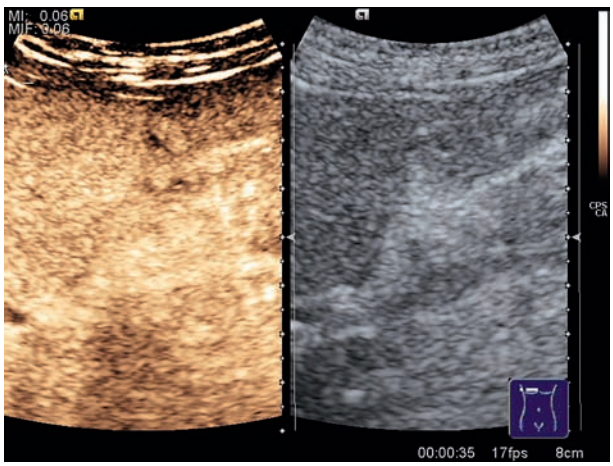

Fig 8. CEUS-arterial phase-of PVT in the case of an inconclusive result

detection and characterization of portal vein thrombi [13-15]. In a recent study, however, CEUS appeared to be superior to US and cDUS for both the detection and characterization of thrombi involving the hepatic and portal venous systems, in patients with hepatic malignancies. In a limited subset of patients, the results obtained with CEUS also proved to be better than those of spiral CT [16].

In another study performed by Rossi et al [17], in which the accuracy of US, cDUS, CEUS and CT in thrombus characterization was assessed, CEUS proved to be far superior to CT in terms of thrombus detection ($p<0.0001$) and characterization rates ($p=0.0001$). As for the characterization of thrombi, it was also more sensitive than cDUS ($p=0.03$).

In the study of Sorrentino et al [18] the results of CEUS examination with portal vein thrombus biopsy (both results assessed on the basis of the follow-up of patients compared to reference-standard) were compared. They concluded that all the malignant PVT were correctly diagnosed by both methods, and in patients with hepatocellular carcinoma complicated by portal vein thrombosis, the use of 2nd generation contrast-enhanced ultrasound of portal vein thrombus is very useful in assessing the benign or malignant nature of the thrombus. Puncture biopsy of thrombus is usually accurate, but presents some sampling errors, so, when pathological results are required, 2nd generation contrast-enhanced ultrasound could guide the sampling needle to the correct area of the thrombus".

In the Ueno study [19] that prospectively assessed the ability of contrast-enhanced ultrasonography to differentiate between benign and malignant PVT, positive enhancement of the portal vein thrombus as a criteria for diagnosing malignancy yielded overall sensitivity and specificity of 100% for each. Our study shows similar results, CEUS being conclusive for benign or malignant etiology of the portal thrombus in 97.2% of cases.

In the Shah study the sensitivity and specificity of MRI for detecting main PVT were 100% and 98%, respectively, in patients undergoing liver transplantation [20].

CEUS has the same limitations as standard ultrasound: acoustic window and patient cooperation.

False positive results in CEUS examination are rarely cited in the literature. In one case reported by Song et al.[21], in which CEUS examination showed arterial enhancement of the portal thrombus in the arterial phase (criteria for malignant PVT), the histopathological exam revealed benign granulomatous inflammation of PV and the follow up of the patient confirmed the benign nature of PVT.

The results of our study, in a quite large cohort of patients with PVT, showed the same good results, both in patients with liver cirrhosis (with or without hepatocellular carcinoma) and in patients without chronic liver disease. The ability of CEUS to make a rapid (less than 5 minutes) differentiation between benign and malignant thrombi is important for future therapeutic options. Considering the results of our group and already published data when faced with a PVT discovered on standard ultrasound, our local strategy is to pass immediately to CEUS examination of the thrombus. In the vast majority of cases (97.2%) we can assess the benign or malignant nature of the thrombus without performing another investigation (such as CE-CT or CE-MRI).

Our study had some limitations. We did not perform any other imaging method (in the majority of cases) to evaluate the nature of PVT. We used only CEUS criteria to characterize the PVT: enhancement in the arterial phase for malignant PVT and no enhancement on CEUS for benign PVT (according to the EFSUMB guidelines for the use of CEUS) [12].

Conclusion: our study showed that CEUS is a reliable technique for the characterization of PVT, CEUS being conclusive for the differentiation benign vs. malignant PVT in 97.2% of the cases. Thus, when faced with a portal thrombosis discovered by ultrasound, CEUS should immediately be performed to elucidate its nature.

Conflict of interest

None of the authors had any conflict of interest.

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