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EDITORIAL

Contrast-enhanced ultrasound in differentiating malignant from benign portal vein thrombosis in hepatocellular carcinoma

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Abstract

Portal vein thrombosis (PVT) may occur in liver cirrhosis patients. Malignant PVT is a common complication in cirrhotic patients with concomitant hepatocellular carcinoma (HCC) and, in some cases, it may be even the initial sign of an undetected HCC. Detection of malignant PVT in a patient with liver cirrhosis heavily affects the therapeutic strategy. Gray-scale ultrasound (US) is widely unreliable for differentiating benign and malignant thrombi. Although effective for this differential diagnosis, fine-needle biopsy remains an invasive technique. Sensitivity of color-doppler US in detection of malignant thrombi is highly dependent on the size of the thrombus. Contrast-enhanced computed tomography (CT) and contrast-enhanced magnetic resonance (MRI) can be useful to assess the nature of portal thrombus, while limited data are currently available about the role of positron emission tomography (PET) and PET-CT. In contrast with CT, MRI, PET, and PET-CT, contrast-enhanced ultrasound (CEUS) is a fast, effective, well tolerated and cheap technique, that can be performed even in the same session in which the thrombus has been detected. CEUS can be performed bedside and can be available also in transplanted patients. Moreover, CT and MRI only yield a snapshot analysis during contrast diffusion, while CEUS allows for a continuous real-time imaging of the microcirculation that lasts several minutes, so that the whole arterial phase and the late parenchymal phase of the contrast diffusion can be analyzed continuously by real-time US scanning. Continuous real-time monitoring of contrast diffusion entails an easy detection of thrombus maximum enhancement. Moreover, continuous quantitative analyses of enhancement (wash in - wash out studies) by CEUS during contrast diffusion is nowadays available in most CEUS machines, thus giving a more sophisticated and accurate evaluation of the contrast distribution and an increased confidence in diagnosis in difficult cases. In conclusion, CEUS is a

very reliable technique with a high intrinsic sensitivity for portal vein patency assessment. More expensive and sophisticated techniques (*i.e.*, CT, MRI, PET, and PET-CT) should only be indicated in undetermined cases at CEUS.

Key words: Contrast-enhanced ultrasound; Hepatocellular carcinoma; Portal vein thrombosis; Benign thrombosis; Malignant thrombosis

Core tip: Portal vein thrombosis (PVT) may occur in liver cirrhosis patients. Malignant PVT is a common complication in cirrhotic patients with concomitant hepatocellular carcinoma (HCC) and, in some cases, it may be even the initial sign of an undetected HCC. Due to its high performance in characterization of PVT in cirrhotic patients, contrast-enhanced ultrasound should be considered as the gold standard method and, often, the only diagnostic tool in cirrhotic patients for differential diagnosis between malignant and benign PVT.

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Portal vein thrombosis (PVT) may occur in liver cirrhosis patients[1-6] with a prevalence ranging from 0.6% to 11%[2,6]. In addition, PVT is even more frequent in cirrhotic patients with concomitant hepatocellular carcinoma (HCC)[2]. However, PVT in liver cirrhosis may be also associated with inflammatory and infectious diseases (liver, bowel, pancreas), hypercoagulable states, endoscopic sclerotherapy of esophageal varices, and percutaneous ablation therapies[3-5].

Malignant PVT, so named for its neoplastic origin, is a common complication of HCC[1,2,4,5], and, in some cases, it may be even the initial sign of an undetected HCC[7,8].

Detection of malignant PVT in a patient with liver cirrhosis heavily affects the therapeutic strategy. Indeed, some Authors believe that HCC infiltration of the portal vein represents an exclusion criteria for liver transplantation, surgical resection, chemoembolization, and imaging-guided ablation, even in the presence of an uninodular lesion with a diameter lower than 5 cm[9,10].

Although conventional gray-scale ultrasound (US) is a highly sensitive technique for detection of PVT, it remains widely unreliable for differentiating benign and malignant thrombi[11]. Furthermore, although fine-needle biopsy (FNB) under US guidance proved to be effective for this differential diagnosis[7,8], it remains an invasive technique, relatively unsafe in cirrhotic patients, in which an impaired haemostatic balance is often reported.

HCC is a hypervascular malignancy with arterial intralesional flow. The latter is expression of tumoral neoangiogenesis and represents the cornerstone for the diagnostic approach[12]. Indeed, the demonstration of the neovascularization of the portal thrombus allows for a highly specific and non-invasive diagnosis of the malignant nature of PVT[13].

In keeping with this, detection of pulsatile arterial signals at color-doppler US (CDUS) inside the portal thrombi may be a fast and specific technique for assessment of malignant PVT[14,15]. These previous reports also suggested high sensitivity of CDUS for this purpose. However, these results have been challenged by other recent studies[13,16], showing a sensitivity lower than 20%. In reality, sensitivity of CDUS in detection of malignant thrombi is highly dependent on the size of the thrombus and the previous reports do not specify the size of the portal vein thrombi in their series.

The injection of contrast material in a peripheral vein allows for the detection of tissues microcirculation by most imaging techniques.

In 2006, we reported the first work focused on the evaluation of contrast-enhanced ultrasound (CEUS) as a tool for differential diagnosis between malignant and benign PVT. In a series of cirrhotic patients with PVT, we performed a comparative study between FNB of the thrombus, CDUS and CEUS for the differential diagnosis of benign and malignant PVT in cirrhotic patients[13]. In this study, CEUS showed the best performance with high sensitivity (88%) and specificity (100%).

These results were confirmed and extended in a subsequent study on a very large series of patients with hepatic cirrhosis in which we documented that CEUS showed a high sensitivity (94%) and specificity (96%) in differentiating malignant *vs* non-malignant PVT[17]. In the same year, Rossi *et al*[18] confirmed the high sensitivity and specificity of CEUS for that indication and, based on all these data, the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) included the "differential diagnosis between malignant and benign portal vein thrombosis" among indications for CEUS in the updated "EFSUMB Guidelines"[19].

In the last five years, several series of cirrhotic patients with PVT evaluated with CEUS were reported, substantially confirming the previous data[20].

Detection of thrombus enhancement by contrast-enhanced computed tomography (CT) and contrast-enhanced magnetic resonance (MRI) can assess the nature of portal thrombus[21,22]. In a series of 58 cirrhotic patients with PVT, Tublin *et al*[23] reported 100% specificity of multidetector CT (MDCT) in the

diagnosis of malignant thrombosis. However, this study showed a rather low overall sensitivity (43%) of MDCT in detecting thrombus neovascularity. In addition, Rossi *et al*[18] compared CEUS and MDCT as techniques for differential diagnosis of PVT and CEUS proved to be far superior to MDCT and showed a very high sensitivity for detection (100%) and characterization (98%) of PVT, while MDCT showed a rather lower sensitivity both for detection (68%) and characterization (67%).

In 2012, Qian *et al*[24] compared indexes obtained by correlation between thrombus and aorta or thrombus and patent portal vein in portal phase, using dual-energy spectral CT for characterization of benign and malignant PVT. Interestingly, they reported a very high sensitivity (100%) and specificity (91.7%) of CT.

However, there are several disadvantages of CT, which include higher costs than CEUS, radiation exposure and the use of contrast materials, with important risks of anaphylaxis and nephropathy.

Gadolinium-enhanced MRI angiography is a useful technique for detection and characterization of PVT[22]. However, in our best knowledge, there are no published data on its sensitivity and specificity, and, also for this technique, there are several disadvantages that are mainly high cost of the procedure, limited number of available equipments, and possible severe nephrogenic systemic fibrosis caused by gadolinium.

A very interesting report by Catalano *et al*[25] described a sophisticated technique using unenhanced diffusion-weighted (DW) MRI imaging in distinguishing bland thrombus from neoplastic thrombus in PVT. In a short series of selected patients with known PVT, using an appropriate cut-off, malignant PVT could be assessed with 100% specificity. However, apart from the costs and scarce availability of the equipment, also in this case there are several drawbacks. DW MRI is an indigenous procedure with relatively low resolution of T2*WI protocol that often misses detection of thrombus in small portal venous branches and needs long times of breath-hold acquisitions, sometimes not feasible in cirrhotic patients.

Although limited data are currently available[26,27] we have also to consider the emerging role of positron emission tomography (PET) and PET-CT in differentiating malignant from benign PVT.

In contrast with CT, MRI, PET, and PET-CT, CEUS is a fast, effective, well tolerated and cheap technique, that can be performed even in the same session in which the thrombus has been detected[28,29]. CEUS can be performed bedside and can be available also in transplanted patients. Moreover, CT and MRI only yield a snapshot analysis during contrast diffusion, while CEUS allows for a continuous real-time imaging of the microcirculation that lasts several minutes, so that the whole arterial phase and the late parenchymal phase of the contrast diffusion can be analyzed continuously by real-time US scanning. Continuous real-time monitoring of contrast diffusion entails an easy detection of thrombus maximum enhancement. In fact, some patients show only a transient and very early enhancement inside the malignant thrombi after injection of the contrast[30]. CT and MRI could miss thrombus neovascularity in these kind of patients if the arterial phase scans are not taken at the time of maximum enhancement. Moreover, continuous quantitative analyses of enhancement (wash in - wash out studies) by CEUS during contrast diffusion is nowadays available in most CEUS machines, thus giving a more sophisticated and accurate evaluation of the contrast distribution and an increased confidence in diagnosis in difficult cases.

In conclusion, CEUS is a very reliable technique with a high intrinsic sensitivity for portal vein patency assessment. CEUS shows significantly higher sensitivity than CT in both detection and characterization of PVT. Due to its high performance in characterization of PVT in cirrhotic patients, we think that CEUS should be considered as the gold standard method and, often, the only diagnostic tool in cirrhotic patients for differential diagnosis between malignant and benign PVT. In this clinical setting, CEUS can be considered the best method for assessing eligibility of cirrhotic patients with HCC and PVT to liver transplantation, surgical resection or percutaneous treatments, without resorting to invasive methods such as FNB. More expensive and sophisticated techniques (*i.e.*, CT, MRI, PET, and PET-CT) should only be indicated in undetermined cases at CEUS.

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