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MR imaging in diffuse-type hepatocellular carcinoma with synchronous portal vein thrombi

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Background/aims: *Diffuse or continuous multifocal tumors with accompanying portal vein thrombosis yield considerable changes in the magnetic resonance imaging findings of hepatocellular carcinoma. The overlapped imaging findings of these two co-existing pathologies may be confusing. We aimed to evaluate the magnetic resonance imaging findings of widespread hepatocellular carcinoma lesions complicated with portal vein thrombosis.* ***Methods:*** *Twenty-two patients (20 male, 2 female; mean age: 57 years) with portal vein thrombosis and diffuse-type hepatocellular carcinoma who underwent contrast-enhanced hepatic magnetic resonance imaging in our department between August 2001 and November 2008 were evaluated retrospectively. The unenhanced axial T1-weighted, T2-weighted, and post-contrast early- and late-phase images were reviewed in each patient.* ***Results:*** *On T2-weighted magnetic resonance images, tumors were seen mildly hyperintense in 11 patients and heterogeneously hyperintense in 11 patients. Unenhanced T1-weighted images demonstrated homogeneous hypointensity in15 patients and heterogeneous hypointensity in 7 patients. Post-contrast early-phase magnetic resonance images showed patchy enhancement in 12 patients, moth-eaten enhancement in 6 patients, strong enhancement in 1 patient, and minimal enhancement in 3 patients. Post-contrast late-phase magnetic resonance images demonstrated heterogeneous washout in all patients. Portal vein thrombosis was present in all patients. The mean diameter of main portal vein thrombi was 27 mm (range: 25-30 mm). Serum alpha-fetoprotein levels were elevated in all patients.* ***Conclusions:*** *In patients with chronic parenchymal liver disease, when portal vein thrombosis and high serum alpha-fetoprotein values co-exist, careful attention must be paid to the hepatic parenchymal changes, especially on contrast-enhanced images, in order to not overlook diffuse-type hepatocellular carcinoma.*

Key words: Hepatocellular carcinoma, magnetic resonance imaging, portal vein

Portal ven trombozunun eşlik ettiği diffüz tip hepatosellüler karsinomada MR görüntüleme

Amaç: *Hepatosellüler karsinomun manyetik rezonans görüntüleme bulguları portal ven trombozunun eşlik ettiği diffüz ya da birbirleri ile devamlılık gösteren multifokal tümörlerde anlamlı değişiklikler gösterir. Birliktelik gösteren bu iki patolojinin çakışan görüntüleme bulguları kafa karıştırıcı olabilir. Bizim amacımız portal ven trombozu ile komplike olmuş yaygın hepatosellüler karsinom lezyonlarında manyetik rezonans görüntüleme bulgularını ortaya koymaktır.* ***Yöntem:*** *Bölümümüzde Ağustos 2001 ve Kasım 2008 tarihleri arasında kontrastlı karaciğer manyetik rezonans görüntüleme yapılmış, diffüz tip hepatosellüler karsinom ve portal ven trombozu olan 22 hasta (20 erkek, 2 kadın, yaş ortalaması 57) retrospektif olarak değerlendirildi. Her hastada aksiyel düzlemde kontrastsız T1A, T2A ve kontrast sonrası erken ve geç faz görüntüler incelendi.* ***Bulgular:*** *Tümör T2A görüntülerde 11 hastada hafif hiperintens ve 11 hastada heterojen hiperintens olarak görüldü. Kontrastsız T1A görüntüler 15 hastada homojen hipointensite ve 7 hastada heterojen hipointensite gösterdi. Kontrast sonrası erken faz manyetik rezonans görüntülerde 12 hastada yamalı tarzda, 6 hastada güve yeniği şeklinde, 1 hastada yoğun ve 3 hastada minimal boyanma saptandı. Kontrast sonrası geç faz görüntülerde tüm hastalar kontrastı heterojen olarak bıraktı. Bütün hastalarda portal ven trombozu mevcuttu. Ana portal ven trombozunun ortalama çapı 27 mm idi (25-30 mm). Serum alfa-fetoprotein düzeyleri tüm hastalarda artmıştı.* ***Sonuç:*** *Kronik karaciğer parankim hastalığı olan bireylerde portal ven trombozu ve yüksek serum alfa-fetoprotein değerleri bir arada görüldüğünde diffüz tip hepatosellüler karsinomu gözden kaçırmamak için özellikle kontrast sonrası görüntülerde hepatik parankimal sinyal değişikliklerine dikkat etmek gerekir.*

Anahtar kelimeler: Hepatosellüler kanser, manyetik rezonans görüntüleme, portal ven

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INTRODUCTION

Magnetic resonance (MR) imaging findings of parenchymal lesions in cirrhosis including regenerating nodules, dysplastic nodules and hepatocellular carcinoma (HCC) are well known. In approximately 50% of the patients, HCC is detected as a solitary mass on imaging studies (1). Nevertheless, HCC may present as widespread continuous lesion/lesions involving a large proportion of the liver - at least 50% of the hepatic parenchyma (diffuse-type HCC), or there may be multifocal tumor formations that can occur due to multicentric growth or intrahepatic spread of a malignant tumor (2). Multifocal tumors with different tumor sizes may involve all hepatic segments, but the lesions are not continuous. In patients with HCC, the incidences of diffuse-type HCC and multifocal HCC are reported to be approximately 10% and 40%, respectively (1).

Patients with chronic parenchymal liver diseases usually undergo screening at certain intervals, hence pre-malignant and malignant lesions are frequently detected in early stages. Nevertheless, there are still patients with poor prognosis at the time of diagnosis, especially in countries where viral hepatitis is common and surveillance is relatively dismal.

Malignant or benign portal vein thrombosis (PVT) is a complication of HCC, which can cause perfusion abnormalities of the liver. Nevertheless, a well-marginated parenchymal mass can usually be recognized easily, despite parenchymal signal alterations due to the perfusion abnormalities, on pre- and post-contrast MR scans (3). On the other hand, diffuse-type HCC complicated with PVT yields important differences in tumor enhancement when compared with solitary HCC (4). The overlapped imaging findings of diffuse HCC and PVT can be confusing, especially when there are no distinct tumor margins, and there is severe thrombosis in the portal venous system. The size of the tumor and the presence of thrombus in the portal vein are two significant indicators of the prognosis of HCC (5).

The aim of this study was to evaluate the MR imaging findings of widespread HCC lesions complicated with PVT, and to call attention to the possible misdiagnoses.

MATERIALS AND METHODS

Twenty-two patients with PVT and diffuse HCC who underwent contrast-enhanced hepatic MR imaging in our department between August 2001 and November 2008 were evaluated retrospectively. There were 20 male and 2 female patients, with a mean age of 57 years (age range: 43-77 years). The data about the clinical and laboratory findings of the patients were obtained by reviewing the previous medical records.

MR imaging was performed on a 1.0 Tesla MR system (Signa LX Horizon; General Electric Medical Systems, Milwaukee, WI) using a phased array torso coil. All patients were scanned with our routine MR imaging protocol for the liver, which consisted of axial T2-weighted (TR: 7500 ms, TE: 102 ms, FOV: 36x36 cm, slice thickness: 7 mm, spacing: 1.5 mm, matrix: 320x224, NEX: 3), axial T1-weighted (TR: 480 ms, TE: 9 ms, FOV: 36x36 cm, slice thickness: 7 mm, spacing: 1.5 mm, matrix: 283x224, NEX: 2), axial fat suppressed T2-weighted (TR: 7058 ms, TE: 102 ms, FOV: 36x36 cm, slice thickness: 7 mm, spacing: 1.5 mm, matrix: 228x224, NEX: 3), and coronal T2-weighted (TR: 3750 ms, TE: 102 ms, FOV: 40x40 cm, slice thickness: 8 mm, spacing: 1.5 mm, matrix: 320x224, NEX: 3) images. Axial spoiled gradient-echo breath-hold images were acquired after intravenous bolus injection of 20 ml gadolinium chelate. Dynamic post-contrast spoiled gradient-echo 3D sequences (FAME) were initiated at 12 seconds (s), and four consecutive sets of images were obtained. Scanning time for each set of images ranged from 15 to 20 s. The imaging parameters were as follows: TR: 3.2 ms, TE: 0.8 ms, FOV: 48x29 cm, slice thickness: 7 mm, matrix: 256x192, and NEX: 1. Axial fat-suppressed spoiled gradient-echo sequence was acquired 2 minutes (min) after the contrast material injection (TR: 125 ms, TE: 6.3 ms, FOV: 36x27 cm, slice thickness: 7 mm, spacing: 1.5 mm, matrix: 256x160, NEX: 1).

Two investigators evaluated the unenhanced axial T1- and T2-weighted and post-contrast early- and late-phase images of each patient, retrospectively. The final decision was made in consensus.

The following MR imaging findings were investigated: tumor extension in the liver (number of Couinaud segments involved), necrosis or septa within the tumor, signal intensity characteristics of tumors on T1- and T2-weighted MR images, contrast enhancement characteristics of tumors on early- and late-phase post-contrast MR images, bile duct dilatation, portal venous tumor thrombosis, hepatic venous tumor thrombosis, collateral vessels, ascites, and upper abdominal lymph no-

des. The maximal diameters of the intrahepatic portion of the main portal vein and right and left branches were measured. Serum alpha-fetoprotein (AFP) levels of the patients were recorded.

RESULTS

Three Couinaud segments were involved by HCC in 7 patients, 4 segments in 5 patients, 5 segments in 4 patients, 6 segments in 2 patients, and 8 segments in 4 patients. On T2-weighted MR images, the tumors were seen mildly hyperintense in 11 patients and heterogeneously hyperintense in 11 patients. Unenhanced T1-weighted images demonstrated homogeneous hypointensity in15 patients and heterogeneous hypointensity in 7 patients (Figure 1).

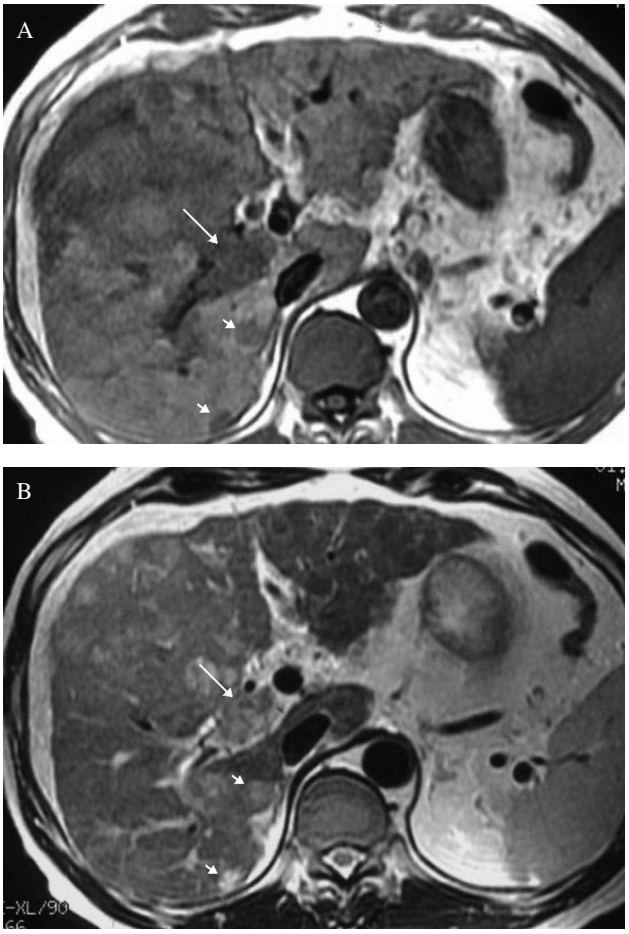

Figure 1. A 43-year-old male with a large HCC and with a serum alpha-fetoprotein level of 63371 ng/ml. On unenhanced T1-weighted axial MR image **(A)**, the tumor involving segments 4, 5, and 8 is seen as areas of heterogeneous hypointensity. Axial T2-weighted MR image **(B)** demonstrates the tumor as areas of heterogeneous hyperintensity. Also note the expansile thrombus in the right portal vein (arrows). There are also small tumor foci in segment 6 (small arrows).

Two main enhancement patterns of liver involvement were identified: patchy and moth-eaten. Patchy transient enhancement was seen in lesions with a smooth or irregular margin, but in either instance, it was usually clearly demarcated, with a short transition zone from normal to abnormal tissue. Moth-eaten enhancement was seen in lesions that were in widespread distribution. The lesions were poorly demarcated and not easily separated from the surrounding normal parenchyma. Unenhanced small foci due to thrombosed vein branches were responsible for this appearance.

Post-contrast early-phase MR images showed patchy enhancement in 12 patients, moth-eaten enhancement in 6 patients, strong homogeneous enhancement in 1 patient, and minimal enhancement in 3 patients. Post-contrast late-phase MR images demonstrated heterogeneous washout in all patients (Figure 2). Septae within the tumor were seen in 6 patients, and necrosis was detected in 6 patients (Figure 2).

Portal vein thrombosis (PVT) was present in all patients. Main portal vein and right and left intrahepatic portal vein branches were involved in 10 patients, right portal vein branch in 7 patients, both right and left portal vein branches in 2 patients, left portal vein branch in 1 patient, main portal vein-right intrahepatic portal vein branch in 1 patient, and main portal vein-left intrahepatic portal vein branch in 1 patient (Figure 3). The mean diameter of main portal vein thrombi was 27 mm (range: 25-30 mm), while the mean diameter of thrombi was 18 mm (range: 10-28 mm) and 18 mm (range: 12-25 mm) for the right and left portal vein branches, respectively. Hepatic venous thrombosis was seen in 9 patients. Only one hepatic vein was involved in 6 patients, right and middle hepatic veins were both involved in 2 patients, and all hepatic veins were involved in 1 patient. In 3 patients, thrombosis extended towards the inferior vena cava, and in one of these patients, thrombus extended into the right atrium (Figure 4). In 5 of the 12 patients without hepatic venous thrombosis, narrowing and distortion of the hepatic veins were noted. Periportal, perisplenic, paraesophageal, pericholecystic, and omental collaterals were seen in 18 patients. Ascites was detected in 18 patients. Upper abdominal lymphadenopathy was seen in 17 patients. Intrahepatic bile ducts were minimally dilated in 2 patients.

Serum AFP levels were elevated in all patients (range: 15-63371 ng/ml, mean: 8135 ng/ml).

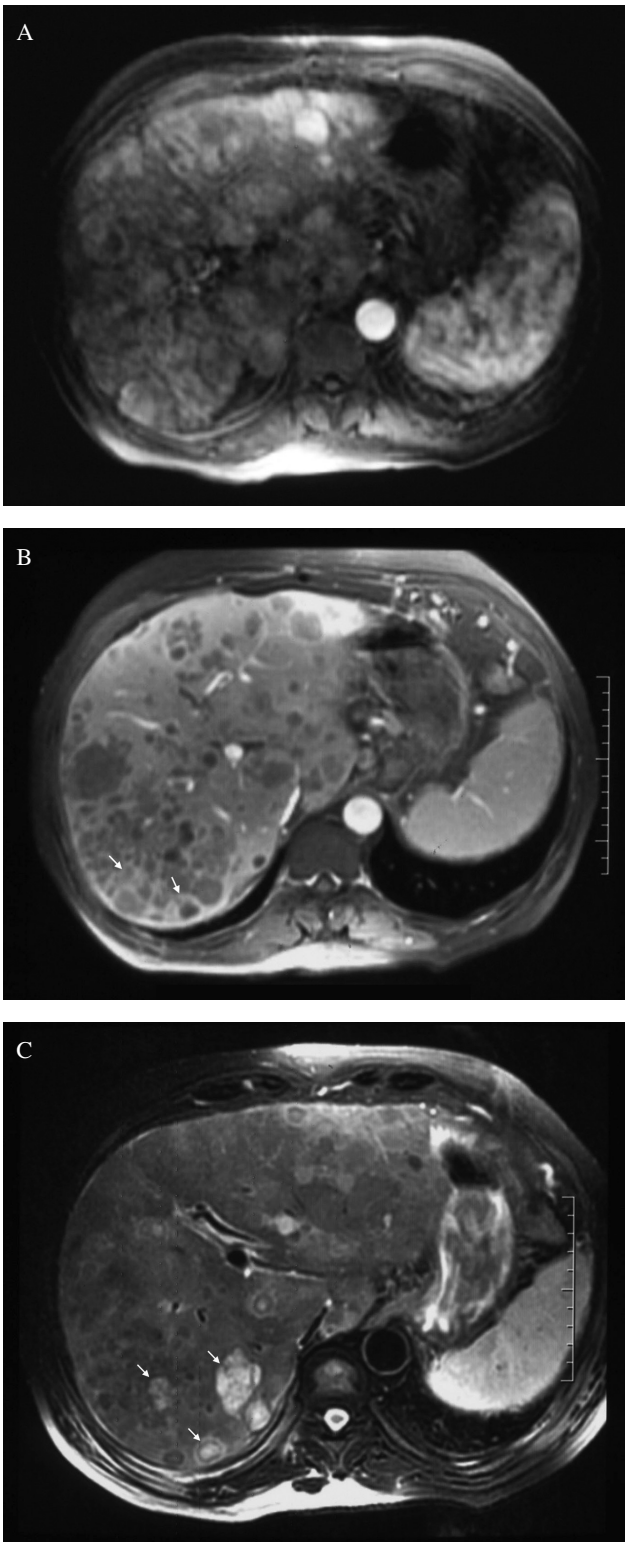

Figure 2. A 56-year-old male with diffuse-type HCC involving the entire liver. The serum alpha-fetoprotein level was 49 ng/ml. Post-contrast early-phase axial MR image **(A)** shows the tumor as areas of moth-eaten enhancement. On post-contrast late-phase axial MR image, there are irregular areas of washout, and also note the septae (arrows). The fat-suppressed T2-weighted axial MR image **(C)** just above the levels on A and B demonstrates areas of necrosis (arrows).

DISCUSSION

Factors related to unfavorable survival in HCC include tumor size (>5 cm), multiple intrahepatic lesions, presence of PVT, and synchronous tumor thrombi (5). Tumor size is an important factor in determining the method of treatment. According to the Model for End-Stage Liver Disease (MELD) allocation, patients should fit in Milan criteria (single tumor <5 cm in diameter, or 2 or 3 tumors each <3 cm in diameter) in order to undergo liver transplantation, which is the only curative treatment for HCC (6). Microvascular invasion, which is also reported as a significant prognostic factor for HCC on histopathological examination, is shown to be more frequent with increasing tumor size. Even in multifocal tumors, the diameter of the largest tumor is the most reliable prognostic factor, and the presence of accessory small nodules does not have a negative effect on survival. Besides microvascular invasion, macrovascular invasion, in which imaging techniques play an important role in the diagnosis, should be evaluated before planning the treatment (7).

Bland or tumor thrombi can occur in HCC patients. Detection of the thrombus and differentiating malignant and bland thrombus are significant factors in determining the prognosis and treatment protocol. The gold standard for characterizing PVT is histopathological examination (8). Nevertheless, radiological findings of malignant PVT also differ from benign PVT in several ways. First of all, a threshold diameter of 23 mm is used to consider malignant thrombosis of the main portal vein. Secondly, neovascularization within the thrombus is accepted to be specific for malignant PVT. Marked generalized PVT enhancement is mostly seen in patients with malignant thrombi. Direct venous invasion of a parenchymal mass, continuity with a mass without obvious venous invasion, or rarely, an accompanying remote tumor may cause malignant PVT (3). Recently, diffusion-weighted (DW)-MR imaging has been utilized in the diagnosis of HCC and in the differentiation of bland and malignant thrombi. As seen in malignant lesions, restricted diffusion of water molecules and lower apparent diffusion coefficient (ADC) values are expected to be seen in malignant PVT. On the contrary, bland thrombi tend to have lower DW imaging signal intensities and higher ADC values than those of co-existing HCC (8).

It has been suggested that in cirrhotic patients, when expansile and enhancing intrahepatic PVT

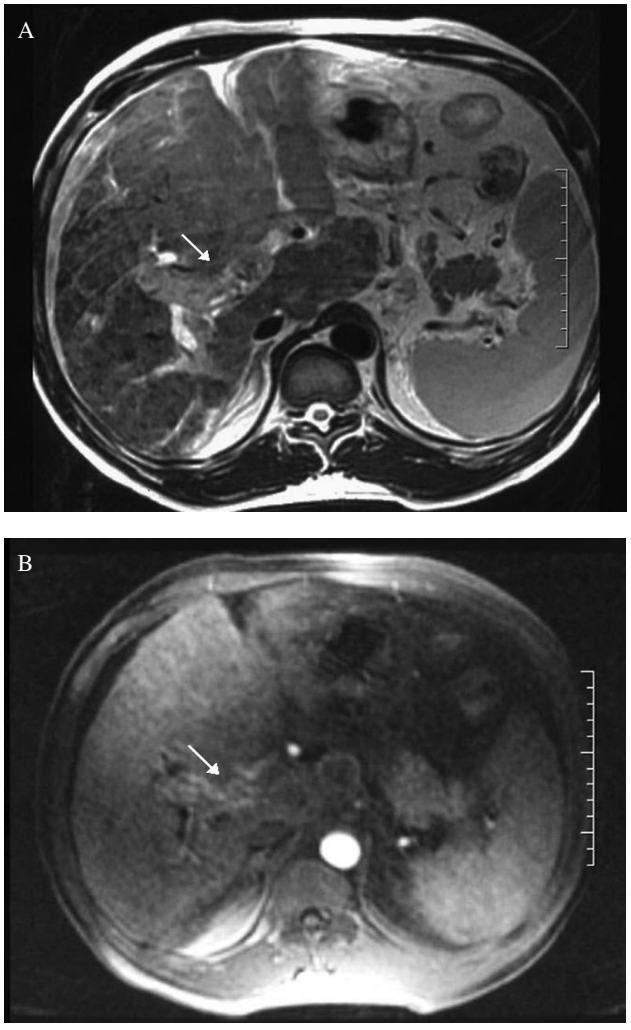

Figure 3. A 45-year-old male with a large HCC and with serum alpha-fetoprotein level of 106 ng/ml. On T2-weighted axial MR image **(A)**, there is an expansile hyperintense tumor thrombus within the right portal vein (arrow). Contrast-enhanced arterial-phase axial MR image **(B)** demonstrates the enhancement in the thrombus supporting the diagnosis of malignant PVT (arrow).

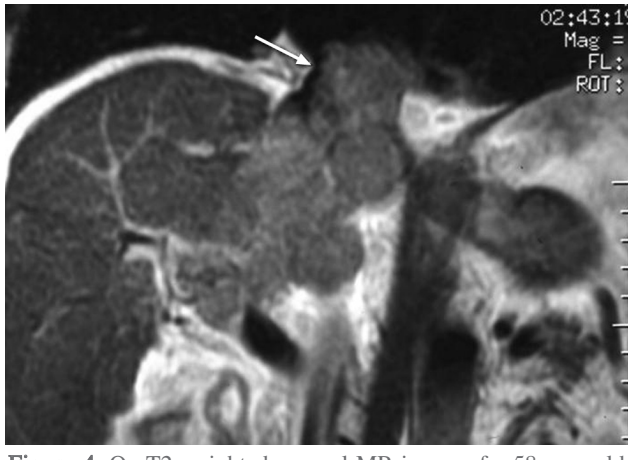

Figure 4. On T2-weighted coronal MR image of a 58-year-old male with diffuse HCC, the extension of the left hepatic vein thrombus into the right atrium is demonstrated (arrow).

co-exist with hepatic parenchymal lesions, the most likely diagnosis is HCC complicated with malignant PVT, but one should not forget that bland PVT secondary to coagulation disorder can also occur in chronic parenchymal liver disease or in liver metastases (8,9).

It has been reported that the incidence of diffuse-type HCC is 10-13%, and PVT almost always co-exists with this type of the disease. In diffuse-type HCC, there are no distinct margins of the tumor to measure the exact diameter of the mass. Instead, the Couinaud segments involved can be identified in the radiological report in order to demonstrate the spread of the tumor. There are no specific MR imaging findings described on pre-contrast images, but miliary (moth-eaten) enhancement pattern on early-phase contrast-enhanced MR images is suggested to be relatively specific for diffuse-type HCC (4). In contrast, the most common enhancement pattern was patchy enhancement, which was seen in 12 of the 22 patients of our study group. Moth-eaten enhancement was seen in 6 patients. Nevertheless, as we studied a limited number of patients, we cannot draw a firm conclusion about the enhancement pattern of diffuse HCC.

On pre- and post-contrast MR images, diffuse HCC may present with a mosaic pattern, which appears as areas of variable signal intensity and heterogeneous nodular enhancement during the arterial, portal and venous phases (10).

It is well known that when portal perfusion decreases, hepatic artery perfusion increases in order to compensate for the perfusion deficit in that specific area (11). As a result of these perfusion abnormalities, wedge-shaped areas of transiently increased enhancement can be identified on early-phase contrast-enhanced MR images, except for the caudate lobe and the central portion of the liver (11,12).

Besides detecting small HCC more accurately than conventional MR imaging, DW-MR imaging also has additional use to assess multifocal disease and helps to characterize equivocal arterial-enhancing lesions (13). Therefore, we believe that adding DW-MR imaging to conventional MR imaging may be useful in patients with cirrhosis, PVT and multiple or diffuse enhancing parenchymal lesions. Lack of DW-MR imaging is a limitation of this study.

Non-visualization of the hepatic veins was also present in 9 of the 22 patients in our study group, and 5 patients had distorted and narrowed but patent hepatic veins. Hepatic venous outflow obstruction may occur secondary to extraluminal compression or luminal invasion of the HCC. Contrast enhancement within the liver periphery would be diminished in acute hepatic venous outflow obstruction and increased in the subacute form. There would also be enhancing nodules in the liver parenchyma throughout the dynamic imaging (14). As a consequence, in the setting of cirrhotic liver parenchyma with regenerating and dysplastic nodules, irregular contours, and atrophy-hypertrophy complex, hepatic parenchymal changes secondary to accompanying portal and/or hepatic venous thrombosis can be confusing. It should be kept in mind that parenchymal signal alterations due to perfusion changes in hepatic and portal venous thrombosis without an accompanying tumor may lead to a misdiagnosis of diffuse-type HCC. In addition, diffuse-type HCC without straight tumor margins can be overlooked if not taken into consideration. Therefore, the dynamic contrast-enhanced images should be assessed carefully, and moth-eaten and patchy arterial enhancement followed by heterogeneous washout should be considered suspicious. The liver contour should also be assessed, and focal bulging around the signal alteration area should raise suspicion of an underlying tumor. In such cases, we believe that the experience of the radiologist gains importance, and also the clinical and laboratory findings are essential in order to diagnose or exclude HCC.

It has been shown that serum AFP levels are much higher in patients with large tumor size and bilobar involvement than in patients with focal nodular types of HCC (15). Nevertheless, one should keep in mind that even in diffuse HCC, serum AFP levels may be within normal limits. Hence, normal AFP values cannot be accepted as an exclusion criterion. PVT is also significantly associated with high serum AFP levels (16).

Besides a lack of DW imaging, another limitation of our study is that we could not obtain the histopathological confirmation of all HCC lesions and portal vein thrombi in our patients. This was partially due to the retrospective nature of the study, and in some cases the diagnosis was based on the typical clinical, radiological and laboratory findings due to the poor general status of the patients.

In conclusion, in patients with diffuse-type HCC and accompanying PVT, radiologists must pay careful attention to the hepatic parenchymal changes, especially on contrast-enhanced images. In case of PVT, even if a sharply marginated mass cannot be depicted, the possibility of diffuse HCC should be remembered in the differential diagnosis of diffuse parenchymal signal alterations with patchy or moth-eaten enhancement in the liver parenchyma.

REFERENCES

1. Braga L, Armao D, Semelka RC. Liver. In: Semelka RC, ed. Abdominal-pelvic MRI. 2nd ed. New Jersey: John Wiley, 2006; 47-445.
2. Wilkens L, Bredt M, Flemming P, et al. Differentiation of multicentric origin from intra-organ metastatic spread of hepatocellular carcinomas by comparative genomic hybridization. J Pathol 2000; 192: 43-51.
3. Tublin ME, Dodd GD IIIrd, Baron RL. Benign and malignant portal vein thrombosis: differentiation by CT characteristics. AJR Am J Radiol 1997; 168: 719-23.
4. Kanematsu M, Semelka RC, Leonardou P, et al. Hepatocellular carcinoma of diffuse type: MR imaging findings and clinical manifestations. J Magn Reson Imaging 2003; 18: 189-95.
5. Zeng ZC, Fan J, Tang ZY, et al. Prognostic factors for patients with hepatocellular carcinoma with macroscopic portal vein or inferior vena cava tumor thrombi receiving external-beam radiation therapy. Cancer Sci 2008; 99: 2510-7.
6. Roayaie K, Feng S. Allocation policy for hepatocellular carcinoma in the MELD era: room for improvement? Liver Transpl 2007; 13: 36-43.
7. Lohe F, Angele MK, Rentsch M, et al. Multifocal manifestation does not affect vascular invasion of hepatocellular carcinoma: implications for patient selection in liver transplantation. Clin Transplant 2007; 21: 696-701.
8. Catalano OA, Choy G, Zhu A, et al. Differentiation of malignant thrombus from bland thrombus of the portal vein in patients with hepatocellular carcinoma: application of diffusion-weighted MR imaging. Radiology 2010; 254: 154-62.
9. Shah ZK, McKernan MG, Hahn PH, Sahani DV. Enhancing and expansile portal vein thrombosis: value in the diagnosis of hepatocellular carcinoma in patients with multiple hepatic lesions. AJR Am J Radiol 2007; 188: 1320-1323.
10. Hussain SM, Reinhold C, Mitchell DG. Cirrhosis and lesion characterization at MR imaging. RadioGraphics 2009; 29: 1637-1652.
11. Matsuo M, Kanematsu M, Hoshi H, et al. Portal vein thrombosis mimicking hypovascular hepatic neoplasm: dynamic MR imaging findings. Am J Roentgenol 1999; 173: 1060-2.
12. Salanitri J. Portal vein thrombosis with unusual hepatic enhancement pattern: diagnosis using 64-slice multidetector computed tomography and 3 Tesla magnetic resonance imaging. Australas Radiol 2007; 51 (Suppl): B292-5.

13. Vandecaveye V, Keyzer FD, Verslype C, et al. Diffusion-weighted MRI provides additional value to conventional dynamic contrast-enhanced MRI for detection of hepatocellular carcinoma. Eur Radiol 2009; 19: 2456-2466.
14. Erden A. Budd-Chiari syndrome: a review of imaging findings. Eur J Radiol 2007; 61: 44-56.
15. Tangkijvanich P, Anukulkarnkusol N, Suwangool P, et al. Clinical characteristics and prognosis of hepatocellular carcinoma. J Clin Gastroenterol 2000; 31: 302-8.
16. Farinati F, Marino D, De Giorgio M, et al. Diagnostic and prognostic role of α-fetoprotein in hepatocellular carcinoma: both or neither? Am J Gastroenterol 2006; 101: 524-32.