Cite as: Çolaklar A, Altınbaş NK: Infiltrative non-mass-like hepatocellular carcinoma initially presenting with isolated malignant portal vein thrombosis: A case report and review of the literature. J Ultrason 2020; 20: e55–e60. doi: 10.15557/JoU.2020.0009.

Submitted: 23.10.2019
Accepted: 12.12.2019
Published: 31.03.2020

Infiltrative non-mass-like hepatocellular carcinoma initially presenting with isolated malignant portal vein thrombosis: A case report and review of the literature

Anıl Çolaklar[1], Namık Kemal Altınbaş[2]

[1] Department of Radiology & Imaging Sciences, Indiana University School of Medicine, Indianapolis - Indiana, United States of America
[2] Department of Radiology, Ankara University School of Medicine, Ankara, Turkey

Correspondence: Anıl Çolaklar, M.D., Indiana Radiology Associates, IU Health University Hospital, 550 N. University Blvd. Room UH 0663 (Basement), Indianapolis – Indiana 46202, USA; tel.: +905432026537, fax: +13179441848, e-mail: anilcolaklar@gmail.com

DOI: 10.15557/JoU.2020.0009

Keywords
hepatocellular carcinoma, subtype, infiltrative, portal vein thrombosis, sonoelastography

Abstract

Hepatocellular carcinoma (HCC) shows a rising incidence and mortality rates worldwide. HCC is divided into several distinct subtypes, both morphologically and histopathologically. Among these subtypes, infiltrative HCC may be the most challenging subtype to diagnose, given its characteristic myriad of tumor nodules blended with normal hepatocytes without a distinct mass-like lesion. Herein, we report an unusual case of an infiltrative HCC initially presenting with isolated malignant portal vein thrombosis and provide a brief review of the literature regarding the infiltrative HCC subtype. Additionally, we demonstrate how sonoelastography could aid in detecting the appropriate biopsy area in the infiltrative HCC subtype. To our knowledge, there have not been previously reported cases describing the use of sonoelastography in the evaluation of the appropriate area for the targeted liver biopsy.

Introduction

Hepatocellular carcinoma (HCC) is predicted to be the sixth most common cancer and the fourth leading cause of cancer-related death worldwide, with over 800,000 new cases and 700,000 deaths annually[(1)]. It is well known that HCC most commonly arises in the context of a cirrhotic background. The major causative factors for HCC include chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), aflatoxin exposure, excessive alcohol intake, smoking, obesity, type 2 diabetes, and certain inherited metabolic diseases[(2–5)]. Various histopathologic and morphologic subtypes of HCC, some of which are not included in the WHO classification of the digestive system tumors, are described throughout the literature[(6–8)]. El Jabbour *et al*.[(7)] described these HCC subtypes as steatohepatitic, clear cell, scirrhous, infiltrative, fibrolamellar carcinoma, combined hepatocellular-cholangiocarcinoma, combined hepatocellular and neuroendocrine, granulocyte colony-stimulating factor producing, sarcomatoid, carcinosarcoma, carcinosarcoma with osteoclast-like giant cells and lymphocyte rich, in decreasing order of frequency[(7)]. Among these, infiltrative type HCC may be the most difficult one to recognize both clinically and radiographically, because this HCC subtype is characterized by multiple minute tumor nodules that spread throughout the liver parenchyma, without forming a mass-like lesion. Given this appearance of infiltrative HCC, some authors have named this entity as diffuse HCC, cirrhotomimetic HCC, or cirrhosis-like HCC[(6–14)].

Portal vein invasion is a known complicated feature of HCC, occurring by direct local venous extension or metastatic spread. However, the initial presentation of HCC as an isolated portal vein thrombosis is incredibly rare, with very few cases reported in the English literature to date[(15)].

We, herein, present an unusual case of HCC initially presenting as an isolated malignant portal vein thrombosis without any other findings suggesting HCC. Additionally,

we provide a brief review of the literature regarding the infiltrative type of HCC. To our knowledge, the use of sonoelastography for the targeted liver biopsy has not been reported so far.

Case report

A 46-year-old woman was referred to our ultrasonography (US) department with the initial presumed clinical diagnosis of acute cholecystitis. She initially presented to the emergency department with epigastric and right upper quadrant pain. Physical examination revealed abdominal tenderness in the epigastrium and right upper quadrant with palpation and liver inferior limit at 4–5 cm below the costal margin. The blood test results on admission were as follows: hemoglobin = 12.3 g/dl, leucocytes = 5550/mm^3, platelets = 303.000/mm^3, AST=29 IU/l, ALT = 23 IU/l, total bilirubin = 1.21 mg/dl, HBS antigen (-) and anti-HCV (-).

Gray-scale ultrasonography (US), Doppler US, and strain sonoelastography examinations were performed by an experienced radiologist with a Logiq S7 Expert machine (GE Healthcare, Milwaukee, WI) equipped with a C1-5-D convex probe. US examination revealed diffuse inhomogeneous left hepatic lobe without any localized formation and significant dilatation of the left portal vein (26 mm) with thrombus extending into the right portal vein (Fig. 1, Fig. 2). Triphasic computed tomography (CT) of the liver was subsequently performed to collaborate with the US findings further. The entire left hepatic lobe showed enhancement during the arterial phase, followed by washout during the late venous phase (Fig. 3 A and B). Additionally, a tumor thrombus with a similar enhancement pattern was demonstrated within the left and right portal veins (Fig. 3 A and B). In our case, neither US nor CT scans brought out any discrete mass-like lesion. Serum alpha-fetoprotein (AFP) level was within the normal range, as well. Given the lack of a discrete mass lesion, the sonoelastography-guided biopsy was performed from the left liver lobe parenchyma (Fig. 4). The biopsy revealed infiltrative hepatocellular carcinoma, which was later confirmed by immunohistochemistry.

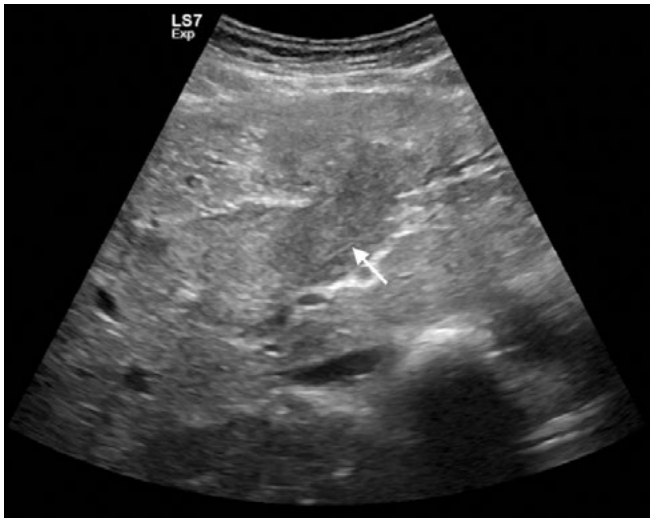

Fig. 1. *Gray-scale US image shows the left portal vein expanded with occlusive tumor thrombus (white arrow)*

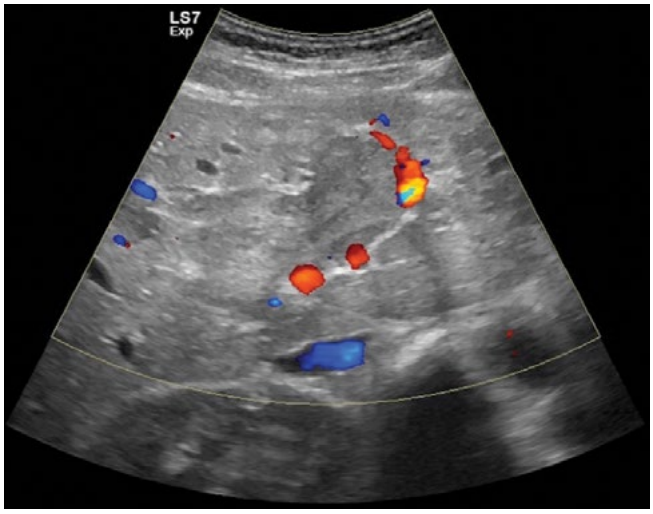

Fig. 2. *Color Doppler US image reveals the presence of diagnostic arterial flow within the tumor thrombus*

Discussion

Infiltrative HCC accounts for approximately 10–20% of all HCC cases[16–20]. It is characterized by multiple, widespread minute tumor nodules throughout the liver, which appears as a spreading, ill-defined mass with indistinct margins. Although risk factors associated explicitly with infiltrative HCC are not well-established, there is emerging data suggesting an association with hepatitis B virus (HBV) infection[21,22].

Serum alpha-fetoprotein (AFP) levels are reported to have poor diagnostic accuracy in infiltrative HCC, with variable serum AFP levels[23,24], even within the normal range, as with our case. However, other possible HCC serum biomarkers, such as Lens culinaris agglutinin reactive AFP (AFP-L3) and Des-gamma-carboxyprothrombin (DCP), have recently been introduced, and AFP-L3 positivity is reported to be more commonly associated with infiltrative HCC subtype and to portend a poor prognosis[25–27].

Infiltrative HCC often poses a diagnostic challenge for radiologists to detect on cross-sectional imaging due to its infiltrating nature, especially in a heterogeneous cirrhotic background. Its histopathologic characteristics correspond to permeative ill-defined appearance on cross-sectional imaging. Ultrasonography (US), multiphasic contrast-enhanced computed tomography (CT) and magnetic resonance (MR) imaging are documented to be helpful for the diagnosis of infiltrative HCC. On US, the permeative ill-defined appearance of this entity is translated into heterogeneous echotexture. Although US plays a limited role in the diagnosis of infiltrative HCC[28], it can be used to detect appropriate area for targeted liver biopsy. In the setting of infiltrative HCC, sonoelastography could be

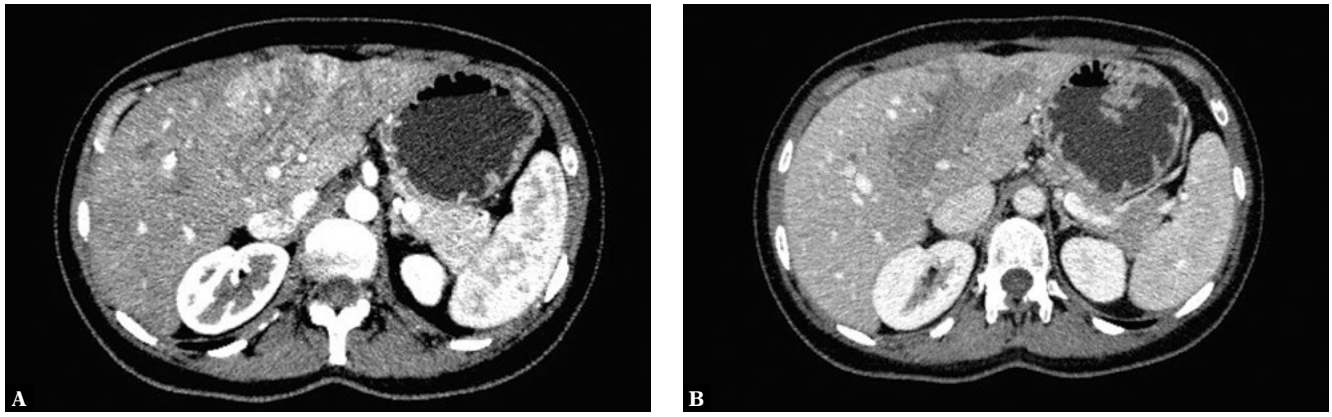

Fig. 3. *Axial contrast-enhanced CT images show streaky and heterogeneous enhancement of the PV thrombus during the late arterial phase* **(A)** *with washout during the portal venous phase* **(B)**, *which is diagnostic of tumor thrombus*

a more valuable tool than gray-scale US to guide biopsy to the area of concern. The affected area is coded differently in color, given its higher stiffness compared to the background non-infiltrated liver parenchyma. On multiphasic contrast-enhanced CT and MR imaging, infiltrative HCC may be inconspicuous because of its variable arterial enhancement pattern and following heterogeneous washout appearance[11,17,19,29]. Although washout appearance during the venous phase is reported to be less common in infiltrative HCC than in other HCC subtypes[17,19,30,31], it is still accepted as a valid sign to detect infiltrative HCC[32]. More specifically, infiltrative HCC often seems hypointense to liver on T1-weighted sequences and hyperintense to liver on T2-weighted with high b-value diffusion-weighted sequences[11,17–20,23,29–33].

Portal vein tumor thrombosis is a ubiquitous finding in infiltrative HCC[10,17–20,23,29–32, 34]. It may even be the first sign of infiltrative HCC, as in our case[29]. Tumor extension into the hepatic veins is not as common as the portal vein[30]. On US, tumor thrombus may be seen as hypo/hyperechoic intraluminal filling defects that expand the portal vein. The significant distension of the vessel, the arterialization of the thrombus, and the presence of pulsatile flow in the thrombus are highly specific features of portal vein tumor thrombus[18–20,35–37]. Contrast-enhanced US has recently been proposed to differentiate benign and malignant PV thrombi in patients with HCC[38,39]. On contrast-enhanced CT and MR images, malignant thrombus exhibits a similar enhancement pattern to the originating tumor[18,37,40,41]. Malignant thrombus shows restricted

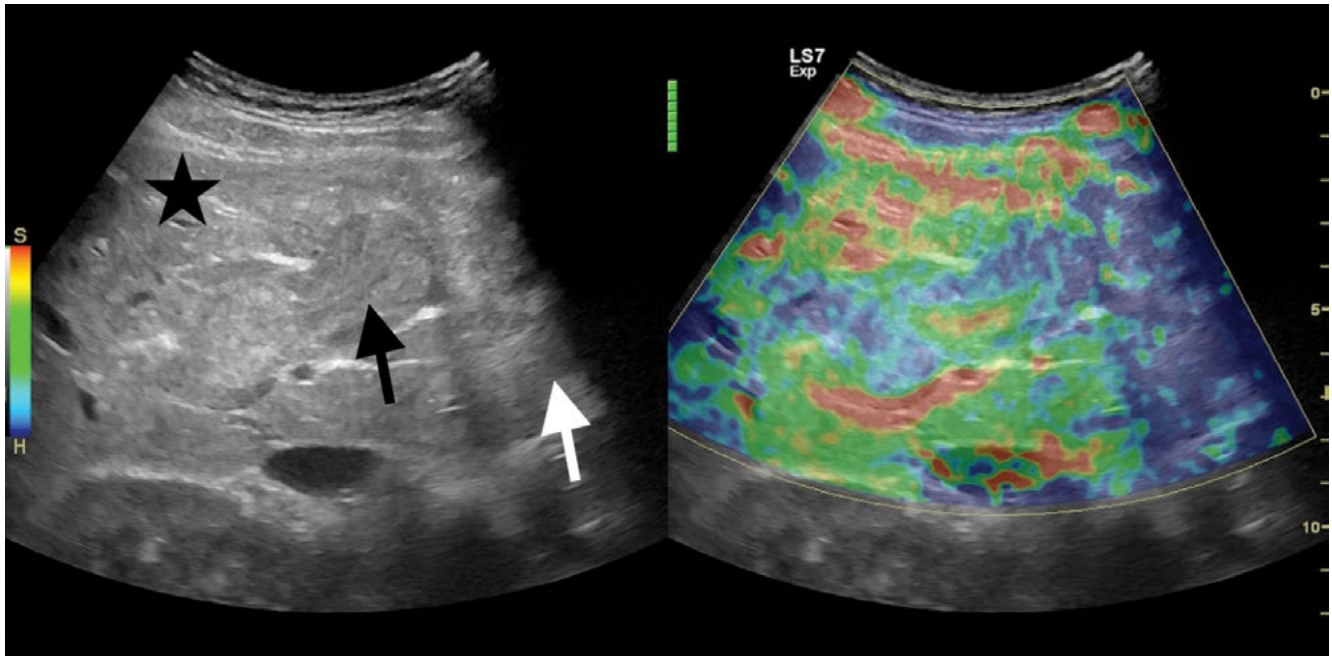

Fig. 4. *On sonoelastographic image, normal parenchyma is coded in red-green color (star mark), whereas portal vein tumor thrombosis and the affected left lobe parenchyma are coded in blue-green (black arrow) and pure blue color (white arrow), respectively. Based on the color bar on the left side, red color reflects less stiff tissue, while blue color reflects more stiff tissue than the rest. Besides, green color reflects medium-stiff tissue*

diffusion and increased signal intensity on T2-weighted sequences as well[18,23,29,41].

A number of diseases including focal confluent fibrosis, geographic fatty infiltration, arterioportal shunting, microabscesses, cholangiocarcinoma, hepatic infarction, and diffuse metastatic disease (pseudocirrhosis) can mimic infiltrative HCC. Unlike HCC, focal confluent fibrosis generally seems hypovascular in the arterial phase and exhibits delayed enhancement[18,20,31,42–44]. Geographic fatty infiltration can be distinguished from infiltrative HCC by performing in- and out-of-phase, and fat-saturated MR sequences[18,20,45]. Arterioportal shunting can be seen as a peripheral wedge-shaped area, only enhancing in the arterial phase without any abnormality on the delayed phase images[20]. Hepatic microabscesses typically manifest as peripheral and septal enhancing lesions on contrast-enhanced CT and MR imaging, which is atypical for infiltrative HCC[46]. The infiltrative nature of cholangiocarcinoma may cause diagnostic confusion. However, it should be kept in mind that cholangiocarcinoma is less likely to be associated with tumor thrombosis and generally causes capsular retraction[11,47,48]. Further, cholangiocarcinoma mostly shows peripheral centripetal enhancement pattern, which is uncharacteristic of infiltrative HCC[18]. In a single case report, Shim *et al*. described a patient with hepatic infarction secondary to PV thrombophlebitis, which had been misdiagnosed as infiltrative hepatic malignancy with neoplastic thrombus[49]. Diffuse metastatic disease, especially related to treated metastatic breast cancer, can mimic cirrhosis and thus infiltrative HCC[50–52]. In this regard, a clinical history of the primary cancer may lead to the correct diagnosis.

The prognosis of patients with infiltrative HCC is substantially worse when compared to those who have a focal/nodular subtype[21]. Because most people with infiltrative HCC present at an advanced stage and have major vascular invasion at presentation[18,19,21,23], surgical resection and transplantation are usually considered unfeasible[18,19,53]. The role of intra-arterial therapy in patients with infiltrative HCC is controversial according to current conflicting research[23,54–56]. Sorafenib, a multi-target tyrosine kinase inhibitor, was the first drug approved for the first-line treatment of advanced HCC and has shown favorable results to date[57–61]. However, resistance or intolerance to sorafenib has given birth to new research concerning the second-line treatment options[62–64]. Hsiao *et al*. documented that sorafenib with concurrent multiple-line therapies had significantly improved overall survival in patients with advanced HCC[65]. Additionally, gene therapy, together with immunotherapy, is a promising treatment option on the horizon[66].

Conclusion

Infiltrative HCC often poses a diagnostic challenge for radiologists. Due to its diffuse and permeative nature, this entity is generally diagnosed at an advanced stage, which portends a poor prognosis. Isolated portal vein thrombosis may be the first and the only sign of infiltrative HCC. Therefore, it is essential to follow up the patients with portal vein thrombosis in short intervals, even in the setting of normal laboratory findings or the lack of a discrete mass. Knowledge of the critical tumor characteristics and imaging findings is crucial for radiologists to make a timely diagnosis and thus provide appropriate patient management.

Conflict of interest

Authors do not report any financial or personal connections with other persons or organizations, which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68: 394–424.
2. Budny A, Kozłowski P, Kamińska M, Jankiewicz M, Kolak A, Budny B *et al*.: [Epidemiology and risk factors of hepatocellular carcinoma]. Pol Merkur Lekarski 2017; 43: 133–139.
3. Jindal A, Thadi A, Shailubhai K: Hepatocellular carcinoma: etiology and current and future drugs. J Clin Exp Hepatol 2019; 9: 221–232.
4. Fujiwara N, Friedman SL, Goossens N, Hoshida Y: Risk factors and prevention of hepatocellular carcinoma in the era of precision medicine. J Hepatol 2018; 68: 526–549.
5. Society AC: Liver cancer risk factors 2019 [updated April 1, 2019. Online: https://www.cancer.org/cancer/liver-cancer/causes-risks-prevention/risk-factors.html].
6. Shafizadeh N, Kakar S: Hepatocellular carcinoma: histologic subtypes. Surg Pathol Clin 2013; 6: 367–384.
7. El Jabbour T, Lagana SM, Lee H: Update on hepatocellular carcinoma: Pathologists' review. World J Gastroenterol 2019; 25: 1653–1665.
8. Torbenson MS: Morphologic subtypes of hepatocellular carcinoma. Gastroenterol Clin North Am 2017; 46: 365–391.
9. Han YS, Choi DL, Park JB: Cirrhotomimetic type hepatocellular carcinoma diagnosed after liver transplantation – eighteen months of follow-up: a case report. Transplant Proc 2008; 40: 2835–2836.
10. Okuda K, Noguchi T, Kubo Y, Shimokawa Y, Kojiro M, Nakashima T: A clinical and pathological study of diffuse type hepatocellular carcinoma. Liver 1981; 1: 280–289.
11. Kim YK, Han YM, Kim CS: Comparison of diffuse hepatocellular carcinoma and intrahepatic cholangiocarcinoma using sequentially acquired gadolinium-enhanced and Resovist-enhanced MRI. Eur J Radiol 2009; 70: 94–100.
12. Rogoveanu I, Văcaru D, Gheonea D, Georgescu CV, Comănescu V, Ciurea T: Diagnostic particularities in primitive diffuse form hepatocellular carcinoma associated with portal vein thrombosis. Rom J Morphol Embryol 2005; 46: 317–321.
13. Jakate S, Yabes A, Giusto D, Naini B, Lassman C, Yeh MM *et al*.: Diffuse cirrhosis-like hepatocellular carcinoma: a clinically and radiographically undetected variant mimicking cirrhosis. Am J Surg Pathol 2010; 34: 935–341.

14. Ho CM, Liang PC, Hu RH, Lee PH: Diffuse cirrhosis-like recurrence of hepatocellular carcinoma after curative resection. Surgery 2016; 160: 519–520.
15. Poddar N, Avezbakiyev B, He Z, Jiang M, Gohari A, Wang JC: Hepatocellular carcinoma presenting as an incidental isolated malignant portal vein thrombosis. J Gastrointest Cancer 2012; 43: 486–489.
16. Trevisani F, Caraceni P, Bernardi M, D'Intino PE, Arienti V, Amorati P *et al*.: Gross pathologic types of hepatocellular carcinoma in Italian patients. Relationship with demographic, environmental, and clinical factors. Cancer 1993; 72: 1557–1563.
17. Kanematsu M, Semelka RC, Leonardou P, Mastropasqua M, Lee JK: Hepatocellular carcinoma of diffuse type: MR imaging findings and clinical manifestations. J Magn Reson Imaging 2003; 18: 189–195.
18. Reynolds AR, Furlan A, Fetzer DT, Sasatomi E, Borhani AA, Heller MT *et al*.: Infiltrative hepatocellular carcinoma: what radiologists need to know. Radiographics 2015; 35: 371–386.
19. Demirjian A, Peng P, Geschwind JF, Cosgrove D, Schutz J, Kamel IR *et al*.: Infiltrating hepatocellular carcinoma: seeing the tree through the forest. J Gastrointest Surg 2011; 15: 2089–2097.
20. Sereni CP, Rodgers SK, Kirby CL, Goykhman I: Portal vein thrombus and infiltrative HCC: a pictoral review. Abdom Radiol (NY) 2017; 42: 159–170.
21. Benvegnù L, Noventa F, Bernardinello E, Pontisso P, Gatta A, Alberti A: Evidence for an association between the aetiology of cirrhosis and pattern of hepatocellular carcinoma development. Gut 2001; 48: 110–115.
22. Myung SJ, Yoon JH, Kim KM, Gwak GY, Kim YJ, Yu JW *et al*.: Diffuse infiltrative hepatocellular carcinomas in a hepatitis B-endemic area: diagnostic and therapeutic impediments. Hepatogastroenterology 2006; 53: 266–270.
23. Kneuertz PJ, Demirjian A, Firoozmand A, Corona-Villalobos C, Bhagat N, Herman J *et al*.: Diffuse infiltrative hepatocellular carcinoma: assessment of presentation, treatment, and outcomes. Ann Surg Oncol 2012; 19: 2897–2907.
24. Farinati F, Marino D, De Giorgio M, Baldan A, Cantarini M, Cursaro C *et al*.: Diagnostic and prognostic role of alpha-fetoprotein in hepatocellular carcinoma: both or neither? Am J Gastroenterol 2006; 101: 524–532.
25. Tada T, Kumada T, Toyoda H, Kiriyama S, Sone Y, Tanikawa M *et al*.: Relationship between Lens culinaris agglutinin-reactive alpha-fetoprotein and pathologic features of hepatocellular carcinoma. Liver Int 2005; 25: 848–853.
26. Okuda H, Saito A, Shiratori K, Yamamoto M, Takasaki K, Nakano M: Clinicopathologic features of patients with primary malignant hepatic tumors seropositive for alpha-fetoprotein-L3 alone in comparison with other patients seropositive for alpha-fetoprotein-L3. J Gastroenterol Hepatol 2005; 20: 759–764.
27. Okuda H, Nakanishi T, Takatsu K, Saito A, Hayashi N, Yamamoto M *et al*.: Clinicopathologic features of patients with hepatocellular carcinoma seropositive for alpha-fetoprotein-L3 and seronegative for des-gamma-carboxy prothrombin in comparison with those seropositive for des-gamma-carboxy prothrombin alone. J Gastroenterol Hepatol 2002; 17: 772–778.
28. Yu NC, Chaudhari V, Raman SS, Lassman C, Tong MJ, Busuttil RW *et al*.: CT and MRI improve detection of hepatocellular carcinoma, compared with ultrasound alone, in patients with cirrhosis. Clin Gastroenterol Hepatol 2011; 9: 161–167.
29. Lim S, Kim YK, Park HJ, Lee WJ, Choi D, Park MJ: Infiltrative hepatocellular carcinoma on gadoxetic acid-enhanced and diffusion-weighted MRI at 3.0T. J Magn Reson Imaging 2014; 39: 1238–1245.
30. Halıloğlu N, Özkavukcu E, Erden A, Erden I: MR imaging in diffuse-type hepatocellular carcinoma with synchronous portal vein thrombi. Turk J Gastroenterol 2011; 22: 158–164.
31. Park YS, Lee CH, Kim BH, Lee J, Choi JW, Kim KA *et al*.: Using Gd-EOB-DTPA-enhanced 3-T MRI for the differentiation of infiltrative hepatocellular carcinoma and focal confluent fibrosis in liver cirrhosis. Magn Reson Imaging 2013; 31: 1137–1142.
32. Rosenkrantz AB, Lee L, Matza BW, Kim S: Infiltrative hepatocellular carcinoma: comparison of MRI sequences for lesion conspicuity. Clin Radiol 2012; 67: e105–111.
33. Choi JY, Lee JM, Sirlin CB: CT and MR imaging diagnosis and staging of hepatocellular carcinoma: part II. Extracellular agents, hepatobiliary agents, and ancillary imaging features. Radiology 2014; 273: 30–50.
34. Willatt JM, Hussain HK, Adusumilli S, Marrero JA: MR Imaging of hepatocellular carcinoma in the cirrhotic liver: challenges and controversies. Radiology 2008; 247: 311–130.
35. Dodd GD 3rd, Memel DS, Baron RL, Eichner L, Santiguida LA: Portal vein thrombosis in patients with cirrhosis: does sonographic detection of intrathrombus flow allow differentiation of benign and malignant thrombus? AJR Am J Roentgenol 1995; 165: 573–577.
36. Margini C, Berzigotti A: Portal vein thrombosis: The role of imaging in the clinical setting. Dig Liver Dis 2017; 49: 113–120.
37. Tublin ME, Dodd GD 3rd, Baron RL: Benign and malignant portal vein thrombosis: differentiation by CT characteristics. AJR Am J Roentgenol 1997; 168: 719–723.
38. Raza SA, Jang HJ, Kim TK: Differentiating malignant from benign thrombosis in hepatocellular carcinoma: contrast-enhanced ultrasound. Abdom Imaging 2014; 39: 153–161.
39. Tarantino L, Ambrosino P, Di Minno MN: Contrast-enhanced ultrasound in differentiating malignant from benign portal vein thrombosis in hepatocellular carcinoma. World J Gastroenterol 2015; 21: 9457–9460.
40. Shah ZK, McKernan MG, Hahn PF, Sahani DV: Enhancing and expansile portal vein thrombosis: value in the diagnosis of hepatocellular carcinoma in patients with multiple hepatic lesions. AJR Am J Roentgenol 2007; 188: 1320–1323.
41. Catalano OA, Choy G, Zhu A, Hahn PF, Sahani DV: 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: 154–162.
42. Brancatelli G, Baron RL, Federle MP, Sparacia G, Pealer K: Focal confluent fibrosis in cirrhotic liver: natural history studied with serial CT. AJR Am J Roentgenol 2009; 192: 1341–1347.
43. Ohtomo K, Baron RL, Dodd GD 3rd, Federle MP, Miller WJ, Campbell WL *et al*.: Confluent hepatic fibrosis in advanced cirrhosis: appearance at CT. Radiology 1993; 188: 31–35.
44. Ohtomo K, Baron RL, Dodd GD 3rd, Federle MP, Ohtomo Y, Confer SR: Confluent hepatic fibrosis in advanced cirrhosis: evaluation with MR imaging. Radiology 1993; 189: 871–874.
45. Pokharel SS, Macura KJ, Kamel IR, Zaheer A. Current MR imaging lipid detection techniques for diagnosis of lesions in the abdomen and pelvis. Radiographics 2013; 33: 681–702.
46. Mortelé KJ, Segatto E, Ros PR: The infected liver: radiologic-pathologic correlation. Radiographics 2004; 24: 937–955.
47. Chung YE, Kim MJ, Park YN, Choi JY, Pyo JY, Kim YC *et al*.: Varying appearances of cholangiocarcinoma: radiologic-pathologic correlation. Radiographics 2009; 29: 683–700.
48. Lee WJ, Lim HK, Jang KM, Kim SH, Lee SJ, Lim JH *et al*.: Radiologic spectrum of cholangiocarcinoma: emphasis on unusual manifestations and differential diagnoses. Radiographics 2001; 21: S97–S116.
49. Shim M, Yang TY, Cho NG, Woo A, Kim E, Park K *et al*.: Hepatic infarction caused by portal vein thrombophlebitis misdiagnosed as infiltrative hepatic malignancy with neoplastic thrombus. Korean J Gastroenterol 2016; 68: 156–160.
50. Jüngst C, Kramer J, Schneider G, Lammert F, Zimmer V: Subacute liver failure by pseudocirrhotic metastatic breast cancer infiltration. Ann Hepatol 2013; 12: 834–836.
51. Young ST, Paulson EK, Washington K, Gulliver DJ, Vredenburgh JJ, Baker ME: CT of the liver in patients with metastatic breast carcinoma treated by chemotherapy: findings simulating cirrhosis. AJR Am J Roentgenol 1994; 163: 1385–1388.
52. Jha P, Poder L, Wang ZJ, Westphalen AC, Yeh BM, Coakley FV: Radiologic mimics of cirrhosis. AJR Am J Roentgenol 2010; 194: 993–999.
53. Ochiai T, Sonoyama T, Ichikawa D, Fujiwara H, Okamoto K, Sakakura C *et al*.: Poor prognostic factors of hepatectomy in patients with resectable small hepatocellular carcinoma and cirrhosis. J Cancer Res Clin Oncol 2004; 130: 197–202.
54. Lopez RR Jr., Pan SH, Hoffman AL, Ramirez C, Rojter SE, Ramos H *et al*.: Comparison of transarterial chemoembolization in patients with unresectable, diffuse vs focal hepatocellular carcinoma. Arch Surg 2002; 137: 653–657; discussion 657–658.
55. Jang ES, Yoon JH, Chung JW, Cho EJ, Yu SJ, Lee JH *et al*.: Survival of infiltrative hepatocellular carcinoma patients with preserved hepatic function after treatment with transarterial chemoembolization. J Cancer Res Clin Oncol 2013; 139: 635–643.

56. Kim SB: Diffuse infiltrative hepatocellular carcinoma with portal vein tumor thrombosis completely cured by transcatheter arterial chemoembolization: case report with 8-year follow-up. Case Rep Gastroenterol 2016; 10: 623–628.
57. Bruix J, Sherman M, American Association for the Study of Liver Diseases: Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020–1022.
58. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF *et al*.: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008; 359: 378–390.
59. Kim HY, Park JW, Nam BH, Kim HK, Choi JI, Kim TH *et al*.: Survival of patients with advanced hepatocellular carcinoma: sorafenib versus other treatments. J Gastroenterol Hepatol 2011; 26: 1612–1618.
60. Mehta N, Fidelman N, Sarkar M, Yao FY: Factors associated with outcomes and response to therapy in patients with infiltrative hepatocellular carcinoma. Clin Gastroenterol Hepatol 2013; 11: 572–578.
61. Endo Y, Miyamoto M, Koujima T, Watanabe Y, Kawai T, Toda K *et al*.: [A case of advanced hepatocellular carcinoma with portal vein invasion successfully treated by sorafenib]. Gan To Kagaku Ryoho 2012; 39: 963–965.
62. Ray EM, Sanoff HK: Optimal therapy for patients with hepatocellular carcinoma and resistance or intolerance to sorafenib: challenges and solutions. J Hepatocell Carcinoma 2017; 4: 131–138.
63. Marino D, Zichi C, Audisio M, Sperti E, Di Maio M: Second-line treatment options in hepatocellular carcinoma. Drugs Context 2019; 8: 212577.
64. Personeni N, Pressiani T, Rimassa L: Cabozantinib in patients with hepatocellular carcinoma failing previous treatment with sorafenib. Future Oncol 2019; 15: 2449–2462.
65. Hsiao P, Hsieh KC, Chen YS, Hsu CC, Lo GH, Li YC *et al*.: Sorafenib with concurrent multiple-line therapies improves overall survival in advanced stage hepatocellular carcinoma. Medicine (Baltimore) 2019; 98: e16074.
66. Reghupaty SC, Sarkar D: Current status of gene therapy in hepatocellular carcinoma. Cancers (Basel) 2019; 11.