

Contrast-Enhanced Ultrasound Findings of Hepatocellular Carcinoma with Neuroendocrine Carcinoma: Case Report and Review of the Literature

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Case report

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Abstract

Background: Hepatocellular carcinoma (HCC) with concurrent occurrence of primary hepatic neuroendocrine carcinoma (NEC) of the liver is very rare. Preoperative diagnosis of hepatocellular carcinoma with neuroendocrine carcinoma to be very difficult.

Case presentation: A 33-year-old male was referred to our hospital due to liver space-occupying lesion. To further diagnosis, he received laboratory tests, gray-scale US, and contrast-enhanced ultrasound (CEUS). In this present study, ethical approval was not necessary, as this article is a case report, which is based on the clinical information of the patient. The patient gave his permission for publication of the case. Gray-scale abdominal ultrasound image demonstrated a mass at the inferior segment of the right posterior liver lobe with liver cirrhosis. In CEUS, the lesion was homogeneously hyper-enhanced in the arterial phase, heterogenous mild enhancement in the portal phase and hypo-enhanced in the parenchymal phase. The patient received middle hepatectomy, splenectomy and cholecystectomy. He had an uneventful recovery from the procedure.

Conclusions: We presented a case report with HCC with NEC, focusing on the ultrasound imaging features of this tumor, especially its enhancement pattern on CEUS. This is the first CEUS performance reported in association with HCC with NEC. CEUS provided helpful information for diagnosis. We should not simply diagnose such tumors as HCC, but think about the possibilities of HCC another type of cancer, especially in patients with the chronic liver disease.

Background

Two different tumors may coexist simultaneously in several organs. In liver, a great majority of mixed carcinoma consist of HCC (hepatocellular carcinoma) accompanied by a cholangiocarcinoma [1-3]. The coexistence of HCC with primary hepatic neuroendocrine carcinoma (NEC) is scarce, including primary NEC is a rare variant of primary liver malignancy with unique clinical, histological, and biological characteristics. Indeed, a limited number of such cases have been reported recently, warranting the description of new cases to better understand their behavior [4]. Here, we report a case with a tumor of HCC with NEC (HCC-NEC) and provide a review of the literature focusing on their clinicopathological findings and the ultrasound imaging features.

Case Presentation

The patient was a 33-year-old male who was followed up for liver cirrhosis for 5 years with antiviral treatment and liver protection drugs, and admitted to our hospital due to "liver space-occupying lesion" for the past 2 weeks. Physical examination revealed spleen swelling. Laboratory studies revealed hepatitis B and almost normal liver function. The serum level of alpha-fetoprotein (AFP) at this time was 403 ng/ml. He then underwent an abdominal ultrasound examination (Fig. 1). Gray-scale ultrasound image demonstrated malformation liver form, the capsule of the liver was not smooth, the echo of liver

parenchyma was rough and heterogeneous. Gray-scale ultrasound image demonstrated a hypoechoic mass located in the hepatic segment VI. The mass was approximately 2.7 x 2.2 cm in size with an almost regular shape and slightly clear margin, small patches of anechoic area can be seen in the tumor. Color Doppler US showed dot-linear blood flow signals within the liver mass. For further diagnosis, the patient agreed to undergo CEUS (contrast-enhanced ultrasound). A 1.2 mL contrast agents (SonoVue, Bracco SpA, Milan, Italy) suspension was injected through his cubital vein followed by a 5 mL saline flush. A Resona7 ultrasound system (mindray, China) with an SC6-1U (1–6MHz) transducer was used only for the examination. The mechanical index setting was 0.078 for CEUS. The depth, gain, and focus are thoroughly adjusted. Taking normal liver parenchyma as a reference, the contrast arrival time to the lesion was 9 seconds after administration of the contrast agent, and the lesion was homogeneously hyper-enhanced in the arterial phase. And then lesion appeared heterogeneous mild enhancement in the portal phase and hypo-enhanced in the parenchymal phase. At the same time, there was a small piece of non-enhanced area in whole three phase within the lesion. The combination of liver cirrhosis and the lesion enhancement pattern yield a diagnosis of hepatocellular carcinoma.

Middle liver resection, splenectomy and cholecystectomy were performed. Severe liver sclerosis changes was found during operation. An intraoperative ultrasound showed that the mass was located in segment VI extending to segment V with a size of about 2.7 x 2.0 cm, and there were no tumor changes in the rest of the liver. The specimen showed both a hepatocellular carcinoma and a 2% neuroendocrine carcinoma (Fig. 2).

The patient had an uneventful recovery from the procedure. As the patient had no other symptoms or signs to indicate extramanifestations of metastasis, no other imaging was performed.

In this paper, ethical approval was not necessary, as this article is a case report, which is based on the clinical information of the patient. Because our case is not refer to the patient's privacy, informed consent is not necessary, and the patient gave their permission for publication of the case.

Discussion And Conclusions

Generally speaking, in contrast to the HCC plus cholangiocarcinoma type in the liver, the concurrent occurrence of HCC and NEC is rarer because the incidence of primary hepatic NEC is very rare in contrast to occasional intrahepatic metastasis of NEC. Diagnosis requires a comprehensive histopathological evaluation together with immunohistochemistry. The rare occurrence of these tumors necessitates more reported cases in order to fully understand their clinical characteristics, behaviors and treatments. We present a case of a liver tumor with features of both classical HCC and NEC. In this case, the patient is young, male, and has a history of hepatitis B, which is consistent with the previous literature [5, 6, 7], which all featured male patients with underlying liver disease, involving chronic hepatitis or cirrhosis of unknown cause, sometime a fat component [8].

On immunohistochemistry, this tumor composed with a cell carcinoma with features of a small neuroendocrine carcinoma. It was strongly positive HCC marker of HEPA and GPC-3, and positive

neuroendocrine markers of chromogranin, synaptophysin, CD56, and GPC-3. The tumors were separated from each other by broad fibrous bands. No transition areas were present. Even in the areas of closest proximity the tumors were sharply demarcated and were compressing, rather than infiltrating. In terms of genes, ERIN BAKER et al [9] reported through genetic analysis, both tumor components contained gene mutations in CTNNB1 gene (S33F located in exon 3), and also shared mutations in PD-1, PGP, and SMO in the genes. The nonneoplastic liver showed liver cirrhosis and portal fibrosis.

Combined hepatocellular and neuroendocrine carcinoma, on the one hand, is similar to hepatocellular carcinoma in terms of hematology and imaging tests, such as hepatitis B and C virus infection status, blood AFP level, and presence or absence of combined liver cirrhosis; on the other hand, vascular and extrahepatic metastasis of mixed liver carcinoma are similar to cholangiocarcinoma, so it is quite difficult to obtain a precise diagnosis before surgery. In this case, we found our patient with solid tumor with cystic changes on ultrasonography. Further research is needed to confirm the idea that whether it differs from the colliquation necrosis in HCC and is helpful for differential diagnosis [10, 11]. The contrast-enhanced ultrasound performance of the type mixed tumor was reported for the first time. The manifestation of CEUS of the tumor (homogeneously hyper-enhanced in the arterial phase, heterogenous mild enhancement in the portal phase and hypo-enhanced in the parenchymal phase) is similar to that of HCC, so it is believed that this may be the reason for the misdiagnosis. Another important problem to be solved in making a diagnosis of concurrent HCC and NEC is the discrimination of primary NEC and from metastatic NEC [12], as the liver is the most frequent site of metastasis for NEC. Therefore other primary sites should be examined when an NEC is suspected in the liver. In our case, there were no other neoplastic lesions found besides in the liver.

The prognosis and treatment of HCC accompanied by NEC are uncertain due to the small number of cases studied. This observation suggested that NEC components strongly affect the aggressive behavior of the tumor and it is proposed that the NEC component may be responsible for the poor prognosis in these patients. The treatment is also a comprehensive treatment based on hepatectomy, combining with multiple treatment modes including radical resection, lymph node dissection, and adjuvant treatment in order to improve the efficacy and prolong survival time. Other treatment such as transcatheter arterial chemoembolization (TACE) and percutaneous ethanol injection therapy (PEIT) can be considered as well, especially when a tumor recurs.

In conclusion, the rare occurrence of HCC-NEC and the lack of diagnostic clinical signs and symptoms do not exclude their consideration in the differential diagnosis of liver tumors, especially in patients with the chronic liver disease, regardless of the presence of cirrhosis. Since HCC-NEC is easy to confuse with hepatocellular carcinoma, careful screening of symptoms is needed to avoid misdiagnosis. Resection is the first choice of treatment for HCC-NEC and provides the most favorable outcomes including long-term survival. We hope that our report will increase awareness of this combined entity in the liver and that further experience contributes in the establishment of prompt and accurate diagnoses in future cases.

Abbreviations

HCC = alphafetoprotein, NEC = carbohydrate antigen 19-9, CEUS =contrast-enhanced ultrasound, TACE = transcatheter arterial chemoembolization, PEIT = percutaneous ethanol injection therapy

Declarations

Ethics approval and consent to participate

In this present study, ethical approval was not necessary, as this article is a case report, which is based on the clinical information of the patient.

Availability of data and materials

Supporting data can be found in the Clinical Research Information System, which is the electronic medical record at the Department of Ultrasound, West China Hospital of Sichuan University. These data are not available publicly due to patient privacy restrictions but are available from the corresponding author upon reasonable request.

Consent for publication

The patient gave his permission for publication of the case.

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Authors' contributions: Wanghong and ling wenwu assembled, analyzed, and interpreted the patient data and contributed significantly to the writing of the manuscript. SS was a major contributor in writing the manuscript. Yang dan was major contributors in coordinating patient care and writing the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

References

1. Goodman ZD, Ishak KG, Langloss JM, Sesterhenn IA, Rabin L. Combined hepatocellular-cholangiocarcinoma. A histologic and immunohistochemical study. *Cancer*. 1985;55:124–35.
2. William R, Jarnagin S, Weber SK, Tickoo JB, Koea S, Obiekwe. Yuman Fong, Ronald P DeMatteo, Leslie H Blumgart, David Klimstra. Combined hepatocellular and cholangiocarcinoma: demographic,

- clinical, and prognostic factors. *Cancer*. 2002;94:2040–6.
3. Haratake J, Hashimoto H. An immunohistochemical analysis of 13 cases with combined hepatocellular and cholangiocellular carcinoma. *Liver*. 1995;15:9–15.
 4. Yilmaz DB, Bayramoglu Z, Unay G, Ayik E, Bassorgun CI, Elpek GO. Incidental Collision Tumor of Hepatocellular Carcinoma and Neuroendocrine Carcinoma. *J Clin Transl Hepatol*. 2018;6(3):339–44.
 5. Choi G, Ho A, Young S, Lee S, Il, Kim S, Bae, Song I, Han. Collision tumor of hepatocellular carcinoma and neuroendocrine carcinoma involving the liver: Case report and review of the literature. *World J Gastroenterol*. 2016;22(41):9229–34.
 6. Düriye B, Yılmaz Z, Bayramoglu G, Ünay. Erdem Ayık, Cumhuri İbrahim Bassorgun and Gülsüm Özlem Elpek. Incidental Collision Tumor of Hepatocellular Carcinoma and Neuroendocrine Carcinoma. *J Clin Transl Hepatol*. 2018;6(3):339–44.
 7. Kwon HJ, Kim J-W, Kim H. YoungRok Choi Soomin Ahn. Combined Hepatocellular Carcinoma and Neuroendocrine Carcinoma with Ectopic Secretion of Parathyroid Hormone: A Case Report and Review of the Literature. 2018; 52: 232–7.
 8. Atsuyuki Ikeda K, Aokia T, Terashimab Y, Itokawaa H, Kokuryu. A fat containing combined neuroendocrine carcinoma and hepatocellular carcinoma in the liver: A case report. *Annals of Hepatology*. 2020.
 9. Erin baker, Jacobs C, Martinie J, Iannitti DA. Dionisios Vrochides, Ryan Z. Swan. Mixed Hepatocellular Carcinoma, Neuroendocrine Carcinoma of the Liver. *THE AMERICAN SURGEON*. 2016;11(82):1121–5.
 10. Bastaki W, Mothaffer F, Varro J, Al-Ghanim M, Malak L, Ayyash E, Asfar S. Primary hepatic carcinoid tumor. *Med Princ Pract*. 2005;14:288–91.
 11. Huang Y-Q, Xu F, Yang J-M, Huang B. Primary hepatic neuroendocrine carcinoma: clinical analysis of 11 cases. *Hepatobiliary Pancreat Dis Int*. 2010;9(1):44–8.
 12. Kang X-N, Zhang X-Y, Bai J, Wang Z-Y, Yin W-J, Li L. Analysis of B-ultrasound and contrast-enhanced ultrasound characteristics of different hepatic neuroendocrine neoplasm. *World J Gastrointest Oncol*. 2019;11(5):436–48.

Figures

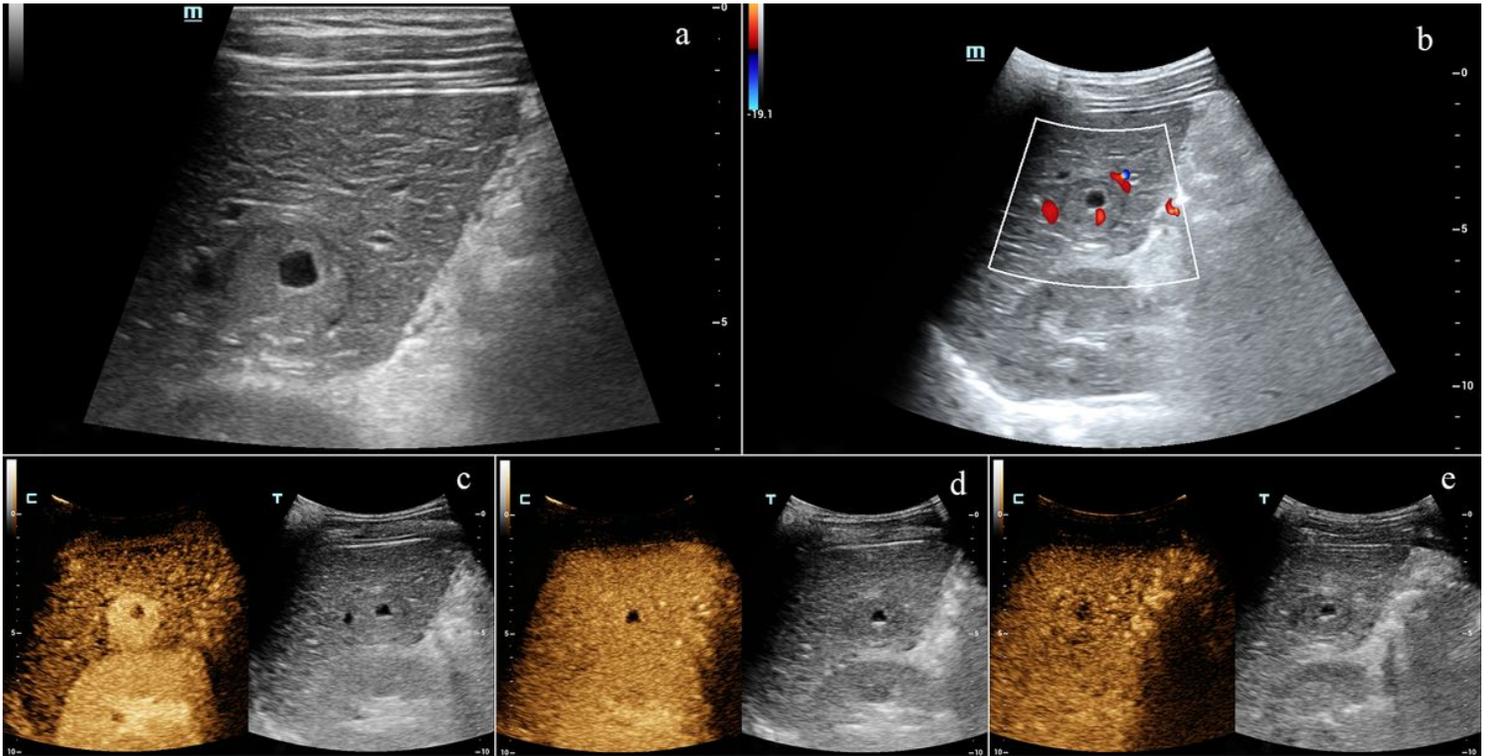


Fig.1 (a) Gray-scale ultrasound image of a hypoechoic mass located in the hepatic segment VI. (b) Color Doppler displayed dot-linear blood flow signals within the mass. (c) the lesion of the liver was homogeneously hyper-enhanced in the arterial phase. And then lesion appeared heterogenous mild enhancement in the portal phase (d) and hypo-enhanced in the parenchymal phase (e).

Figure 1

(a) Gray-scale ultrasound image of a hypoechoic mass located in the hepatic segment VI. (b) Color Doppler displayed dot-linear blood flow signals within the mass. (c) the lesion of the liver was homogeneously hyper-enhanced in the arterial phase. And then lesion appeared heterogenous mild enhancement in the portal phase (d) and hypo-enhanced in the parenchymal phase (e).

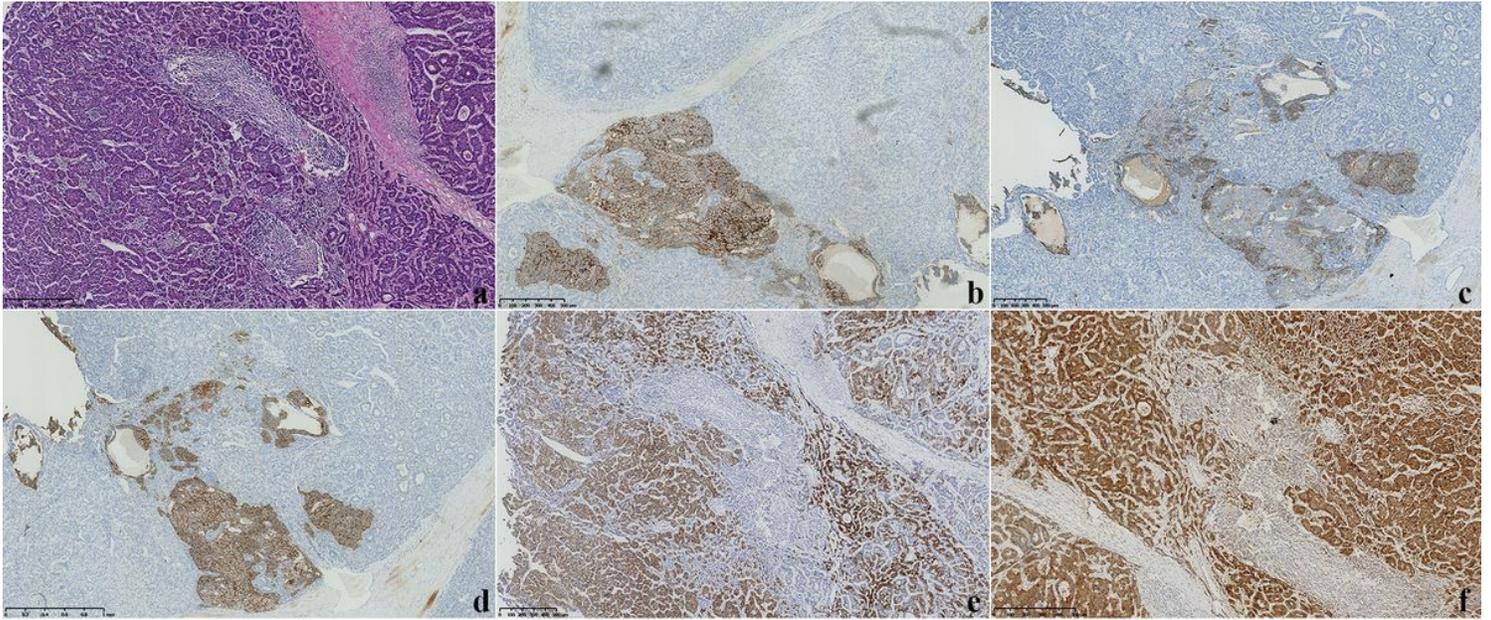


Fig.2 Postoperative pathological analysis revealed (a) combined hepatocellular and neuroendocrine carcinoma phenotype by H&E staining (HE staining, 100×). Immunohistochemical examination of the tumor (b) positive CD56, (c) positive chromogranin (CgA) , (d) positive synaptophysin (Syn,) (e) strongly positive for HEPA and (f) GPC-3 (100×).

Figure 2

Postoperative pathological analysis revealed (a) combined hepatocellular and neuroendocrine carcinoma phenotype by H&E staining (HE staining, 100×). Immunohistochemical examination of the tumor (b) positive CD56, (c) positive chromogranin (CgA) , (d) positive synaptophysin (Syn,) (e) strongly positive for HEPA and (f) GPC-3 (100×).