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CASE REPORT

Three-in-one incidence of hepatocellular carcinoma, cholangiocellular carcinoma, and neuroendocrine carcinoma: A case report

Yang Wu, Chao-Bang Xie, Yi-Huai He, Di Ke, Qiong Huang, Kai-Fei Zhao, Rong-Shu Shi

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Abstract

BACKGROUND

Primary hepatic neuroendocrine carcinoma (NEC) is rare, and a combination with hepatocellular carcinoma (HCC) and cholangiocarcinoma (CCA) is extremely rare. To date, only four combination cases have been reported. The present paper describes the fifth patient.

CASE SUMMARY

A 32-year-old Chinese man with chronic hepatitis B was hospitalized for persistent upper abdominal pain. Abdominal computed tomography (CT) examination revealed a liver mass. The tumor was located in the 7th and 8th segments of the liver, and CT and magnetic resonance imaging findings were consistent with the diagnosis of HCC. Laboratory examinations revealed the following: Alanine aminotransferase, 243 U/L; aspartate aminotransferase, 167 U/L; alpha-fetoprotein, 4519 μg/L. Laparoscopic right lobe hepatectomy was performed on the liver mass. Postoperative pathology showed low differentiation HCC plus medium and low differentiation CCA combined with NEC. One month after the surgery, the patient suffered from epigastric pain again. Liver metastasis was detected by CT, and tumor transcatheter arterial chemoembolization was performed. Unfortunately, the liver tumor was progressively increased and enlarged, and after 1 mo, the patient died of liver failure.

CONCLUSION

This is a rare case, wherein the tumor is highly aggressive, grows rapidly, and

metastasizes in a short period. Imaging and laboratory tests can easily misdiagnose or miss such cases; thus, the final diagnosis relies on pathology.

Key Words: Neuroendocrine carcinoma; Hepatocellular carcinoma; Mixed neuroendocrine neoplasm; Combined hepatocellular-cholangiocarcinoma; Cholangiocarcinoma; Cholangiocellular carcinoma; Case report

Core Tip: Hepatocellular carcinoma (HCC) is the most common subtype of primary liver cancer. However, the combination of HCC, cholangiocarcinoma, and neuroendocrine carcinoma exhibiting three differentiation pathways is extremely rare. This has been described previously only in four patients. We report a case of a similar tumor in a 32-year-old man. It was diagnosed according to the computed tomography and magnetic resonance imaging findings and histopathology. This report aims to raise awareness and improve the treatment of the disease.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common subtype of primary liver cancer (PLC)[1], followed by cholangiocarcinoma (CCA). Combined hepatocellular-cholangiocarcinoma (cHCC-CCA) is a tumor with both hepatocytic and biliary components. The incidence of cHCC-CCA among PLCs is 0.4%-14.2%[2]. Also, other unusual PLCs with combined components have been recorded. Tumors with an HCC and neuroendocrine carcinoma (NEC) differentiation have been published[3]. However, hepatocellular tumors showing three differentiation pathways are sporadic. The combination of HCC, CCA, and NEC differentiation has been described previously only in four patients. Herein, we report another case of a similar tumor in a 32-year-old man, with an aim to increase cognition and improve the treatment of the disease.

CASE PRESENTATION

Chief complaints

A 32-year-old male patient was hospitalized at the Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou Province, China on August 29, 2021, due to pain in the right upper abdomen for 30 d.

History of present illness

The patient's symptoms started 30 d ago, with repetitive right upper abdominal pain.

History of past illness

The patient presented hepatitis B 5 years ago and did not receive regular treatment.

Personal and family history

The patient had a smoking and drinking history of > 10 years: 15 cigarettes/d and about 100 mL wine/d. His parents were healthy and had no family history of cancer.

Physical examination

The abdomen was soft with tenderness in the right upper abdomen but no rebound pain and muscle tension. A mass of about 80 m × 80 m could be felt under the right costal margin of the liver; it was tough and tender, with a clear boundary, and did not move when touched.

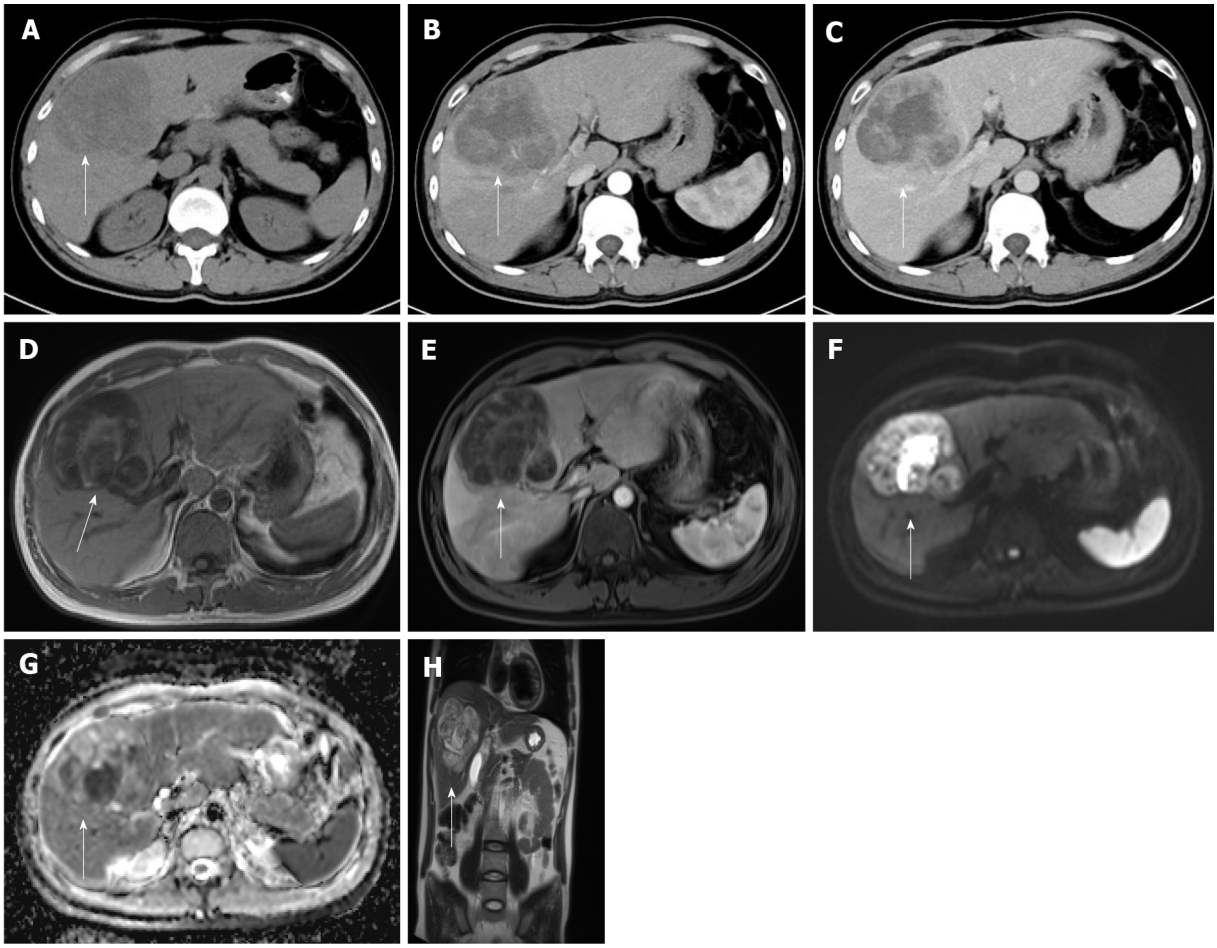

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Figure 1 Preoperative computed tomography and magnetic resonance imaging images with white arrows pointing to the lesion. A: Computed tomography image showing a hypodense mass of approximately 81 mm × 83 mm in size in the liver; B and C: Enhanced scans in the arterial and delayed phases show heterogeneous enhancement of the lesion; D: Magnetic resonance imaging T1-weighted image (T1WI) shows a mixed signal with a predominantly low signal; E: T1WI enhancement with mild heterogeneous enhancement in the arterial phase; F: Diffusion-weighted imaging shows a high heterogeneous signal; G: Apparent diffusion coefficient image shows a low heterogeneous signal; H: Coronal T2WI shows a high signal with multiple iso- and low-signal divisions.

Laboratory examinations

Laboratory examinations revealed the following: Alanine aminotransferase, 243 (normal range 9-50) U/L and aspartate aminotransferase, 167 (normal range 15-50) U/L; abnormal alpha-fetoprotein (AFP), 4519 (normal range < 9) μg/L; normal carbohydrate antigen, carcinoembryonic antigen (CEA), and neuron-specific enolase (NSE) levels; hepatitis B virus (HBV) DNA, 2.327×10^2 (normal range < 1000) IU/mL, hepatitis B surface antigen, 250 (normal range < 0.05) IU/mL, and hepatitis B core antibody 8.35 (normal range < 1) cutoff index.

Imaging examinations

Abdomen computed tomography (CT) displayed a mass of 81 mm × 83 mm in the 7th and 8th hepatic segments as a mild external protrusion. It showed inhomogeneous enhancement compared to the surrounding liver parenchyma in the arterial phase and low density with a clear portal border. Magnetic resonance imaging (MRI) with gadoxetate disodium (Eovist®) revealed significant enhancement. Intriguingly, massive mixed signals were detected from the mass: A low signal on T1-weighted image (T1WI), a high signal on T2WI, multiple equal and low signals, and segmentation. Diffusion-weighted imaging (DWI) showed an uneven high signal, apparent diffusion coefficient (ADC) images showed an uneven low signal, and no signal reduction area was observed in the out-phase. In the enhanced arterial phase, the edge was slightly uneven, and the enhancement was weaker than that of the normal liver. In the delayed phase, the lesion center and edge were significantly uneven, and the enhancement degree was higher than that of the normal liver, indicating gradually delayed enhancement (Figure 1). Chest CT, gastrofibroscopy, and colonoscopy did not find any evidence of another origin site.

Further diagnostic work-up

Pathological and immunohistochemical examination results on the excised liver tissues after surgery (Figure 2) were as follows: CK (++), AFP (++), hepatocyte (++), CK19 (+), synaptophysin (Syn) (+), CD56 (+), catenin (+), vimentin (+), chromogranin A (CgA) (-), Glypican-3 (+), Ki-67 (60%+), vascular invasion (+), nerve invasion (-), no tumor involvement at the cutting edge of the liver, and the broken end of the gallbladder neck. According to the histopathological results and immunohistochemical features, this tumor included HCC, intrahepatic CCA (iCCA), and NEC.

FINAL DIAGNOSIS

The final diagnosis was low differentiation HCC plus medium and low differentiation CCA combined with NEC.

TREATMENT

With the consent of the patient and his family, he was treated by laparoscopic partial hepatic lobectomy and cholecystectomy by an experienced hepatobiliary surgeon. The intraoperative findings were as follows: A mass with a diameter of about 10 cm was located in the right lobe of the liver, protruding from the liver capsule; it was intact and had a clear boundary. The whole mass and the surrounding liver tissue, about 2 cm, and major blood vessels were resected.

One month post-surgery, the patient was hospitalized on October 20, 2021 due to epigastric pain. Abdominal enhanced CT and MRI suggested multiple metastases in the liver (Figure 3). In order to control tumor growth, the patient was treated by transarterial chemoembolization (TACE) to embolize the blood vessels supplying the tumor; also, oxaliplatin (150 mg), fluorouracil (1 g), and leucovorin (0.4 g) were administered. HBV infection was treated with entecavir (0.5 mg, once daily). Subsequently, the abdominal pain was relieved, and the patient was discharged from the hospital. However, he was treated again at our hospital on November 24, 2021 due to the aggravation of epigastric pain. Abdominal CT showed that liver metastases had increased and enlarged (Figure 3), with a maximum diameter of 62 m × 65 m.

OUTCOME AND FOLLOW-UP

The patient eventually died of liver failure in December 2021 (Figure 4).

DISCUSSION

PLC is the fourth driving cause of cancer-related deaths worldwide, and the incidence is persistently rising in Western countries[4]. It is a heterogeneous tumor related to various hazard factors, clinical results, and histological and molecular features. Among these malignancies, HCC and iCCA are the most common cancers that represent the two extremes of primary malignancies. cHCC-CCA is a subset of liver neoplasms that might display hepatocytic and biliary differentiation. Compared to HCC and iCCA, these biphenotypic tumors are rarer, accounting for < 5% of all liver cancers[3]. Conversely, the concurrent occurrence of HCC and NEC is rarer than the HCC plus CCA type in the liver because the rate of primary hepatic NEC is very low as opposed to incidental intrahepatic metastasis of NEC. Interestingly, HCC, iCCA, and NEC are extremely rare, and only four cases have yet been reported (Table 1).

Neuroendocrine tumors are mainly localized in the gastrointestinal system and frequently metastasize to the liver[5]. Primary neuroendocrine tumors are exceptionally uncommon in the liver. The morphology of primary hepatic neuroendocrine tumors is hazy. Currently, there are two hypotheses explaining this phenomenon. One is that the stem cell forebody of malignant cells from another pernicious hepatic tumor differentiate into a neuroendocrine tumor. Another is that such tumors come from neuroendocrine cells in the intrahepatic bile conduit epithelium[6,7]. Primary neuroendocrine tumors with HCC in the liver are rare. HCC with carcinoid tumors was first documented in 1984[8]. The tumors are categorized into two classes: Collision and combined[9]. The collision sort tumors are recognized by fibrillar component, whereas the combined sort tumors have blended features and cannot be identified. Under the microscope, these tumors were divided into three sorts, transitional, intermediate, and isolated. In the transitional sort, the NEC and HCC components are blended in the transition zone, while in the middle sort, the intermediate component conveys both hepatocyte markers and neuroendocrine markers, blending with the NEC and HCC components, and in

Table 1 Reports on liver tumors with triple (hepatocellular, cholangiocellular, and neuroendocrine) differentiation

Cases of liver tumors with triple differentiation described in the literature	Ref.
Two Chinese male patients (average age: 57.5 yr) were positive for hepatitis B and exhibited hepatic tumors with triple differentiation	He *et al*[18], 2013
A healthy 19-year-old Caucasian man developed a large hepatic tumor showing triple differentiation	Beard *et al*[16], 2017
A 65-year-old woman with a history of hepatitis C and rectal "carcinoid" developed a hepatic tumor with triple differentiation	Dimopoulos *et al*[17], 2021
A 32-year-old Chinese man with a history of hepatitis B and wine-drinking exhibited hepatic tumors with triple differentiation	Current case report

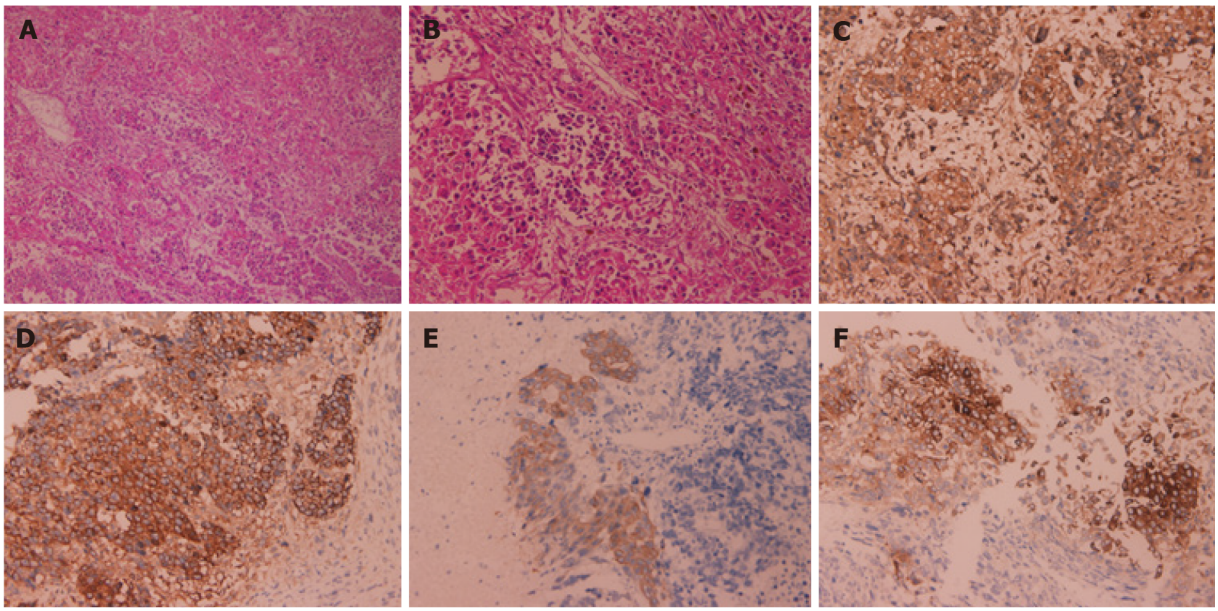

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Figure 2 Histology and immunohistochemistry. A: Hematoxylin and eosin (HE) staining (× 100); B: HE staining (× 200); C: Alpha-fetoprotein (++); D: Hepatocyte (++); E: CK-19 (+); F: Synaptophysin (+).

the separate sort, the two features appear autonomously. The first two types represent co-localization of neuroendocrine and non-neuroendocrine components[10]. Nonetheless, the link between HCC, iCCA, and NEC has not yet been detected. According to the classification of the two differentiated tumors, the patient had no obvious interval and hence belonged to mixed tumors.

Serum markers are often utilized to evaluate liver tumors. Donadon *et al*[11] showed that the indicators of primary HCC, such as AFP, CEA, and carbohydrate antigen 19-9, have little value for the diagnosis of liver NEC. Specific immunohistochemical markers of NEC include NSE, CgA, Syn, CD57, and bombesin; those of HCC are HEPPAR-1 and AFP, and for CCA they are CK-7 and CK-19[3]. Park *et al*[12] demonstrated that serum CgA was an indicator for NEC diagnosis, with an 87%-100% sensitivity and 92% specificity. In addition, serum 5-hydroxytryptamine and 24-h urine 5-hydoxyindoleacetic acid also had a high sensitivity and specificity for the diagnosis of the disease. In this patient, the immunohistochemistry staining for CK, AFP, hepatocyte, CK19, Syn, and CD56 was positive, which was consistent with the diagnosis of HCC, iCCA, and NEC.

Imaging examination is a crucial method to judge the quality of mass. Contrast-enhanced CT showed rich blood supply tumors for hepatic NEC, while on the plain scan, slightly low-density lesions with clear boundaries, uniformly enhanced smaller lesions, and irregular necrotic areas in larger lesions were observed. Moreover, the enhancement was "fast in and slow out". The lesions in the arterial phase showed rosette and patchy enhancement, while those in the portal vein phase showed centripetal enhancement, and those in the delayed phase showed equal or slightly high-density and no enhancement in the necrotic area[13,14]. This was different from the rich blood supply and "fast in and fast out" enhancement of typical HCC. MRI is a valuable diagnostic method for HCC. HCC exhibited a low-intensity signal on T1WI and slightly high-intensity signal on T2WI, and dynamic enhancement scanning showed uneven images in the arterial phase, further enhancement in the portal vein phase, decreased enhancement in the delayed phase, and low-intensity signal and annular capsule enhancement in the later stage[15]. The characteristics of this patient were consistent with the previous description. DWI showed a high signal, and ADC image showed a low signal, indicating limited

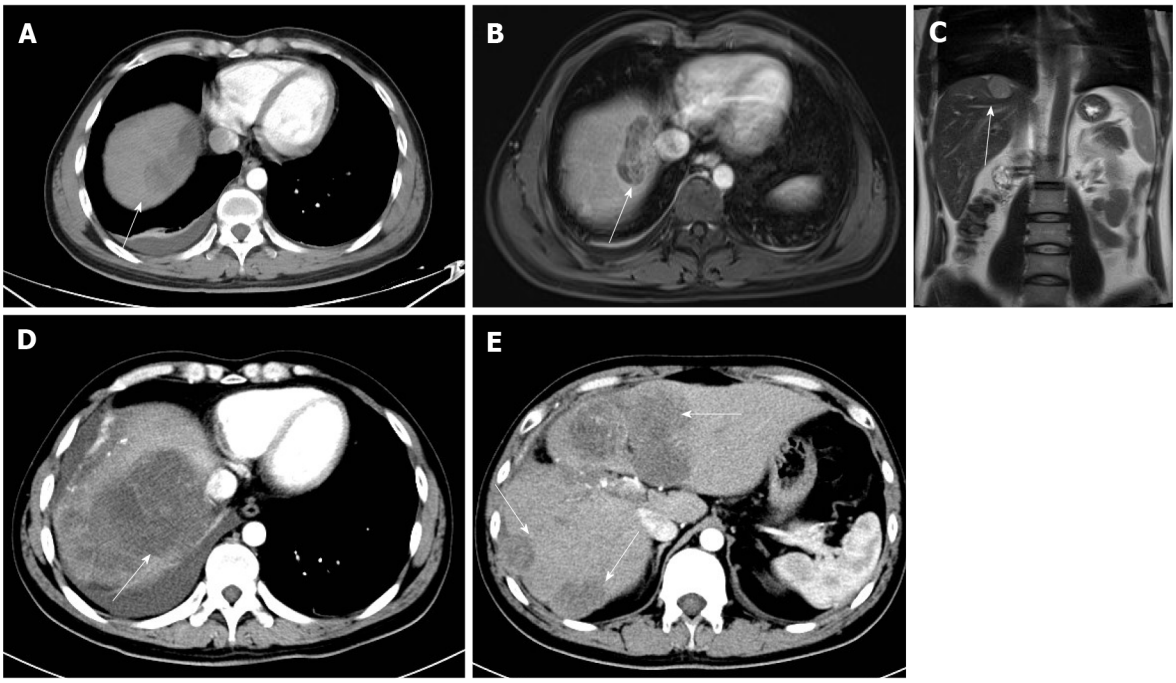

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Figure 3 Computed tomography images with white arrows pointing to the lesions. A: Computed tomography (CT) on October 8, 2021 showed a new mass of approximately 53 mm × 25 mm in the right lobe of the liver; B and C: Magnetic resonance imaging on the same day; D and E: CT on November 24, 2021 showed an enlarged and increased intrahepatic lesion.

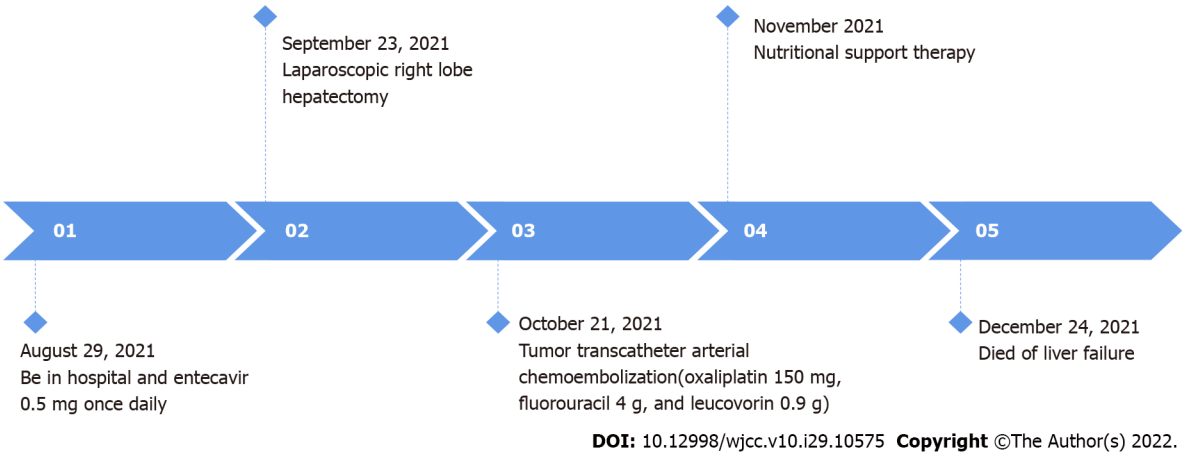

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Figure 4 Timeline.

diffusion and suggesting a malignant tumor.

Mixed tumors with three differentiation pathways are extremely rare, and therefore no meaningful conclusions could be derived with respect to the risk factors, the origin of the cells, prognosis, and treatment options. Previously, a case of blended tumor with three separation pathways was reported in a young Caucasian man with no known identifiable hazard variables[16]. Another study described a patient with a history of hepatitis C[17]. Also, two Chinese male patients were positive for hepatitis B [18]. In this case, the Chinese patient had a history of hepatitis B with long-term smoking and drinking, and 3/5 patients had hepatitis B, indicating that hepatitis B is a major risk factor for this disease (Table 2).

HCCs with NEC components are related to invasive behavior and unfavorable results. However, whether the HCC or the NEC component determines the prognosis of patients is yet to be clarified. Interestingly, the Ki-67 proliferation index of NEC is significantly higher than that of HCC. Additionally, lymph node or distant metastases are often present in NEC; thus, the prognosis of primary HCC combined with primary NEC might be positively correlated with the NEC component. The more the NEC component, the worse the prognosis and the higher the probability of recurrence and metastasis. Although the leading treatment for mixed liver tumors is surgery, the other treatments

Table 2 Partial clinical data of patients

Gender	Age (yr)	Country	Site of primary lesion	Hepatitis	AFP (μg/L)	Ki-67	Therapy	Lifetime
Male	61	China	Liver	B	1210	5%	Surgical resection + TACE	Short
Male	54	China	Liver	B	1400	80%	Surgical resection + TACE	2 mo
Male	19	United States	Liver	/	Normal	High	Surgical resection + Cisplatin and gemcitabine chemotherapy	> 8 mo
Female	65	United States	Rectum	C	2198	High	Surgical resection + Cisplatin and gemcitabine chemotherapy	5 mo
Male	32	United States	Liver	B	4519	60%	Surgical resection + TACE	4 mo

AFP: Alpha-fetoprotein; TACE: Transarterial chemoembolization.

include TACE, radioembolization, chemotherapy, or liver transplantation. The decisions to treat patients with adjuvant therapy and other alternatives are based on the assessment of the tumor. For example, Ki-67 proliferation index is a satisfactory indicator; a high value indicates a high risk of tumor invasion and recurrence. Our patient had Ki-67 > 60%, vascular invasion (+), and multiple metastases in the liver 1 mo after surgery. Despite aggressive treatment, the patient had a very rapid disease progression that could be attributed to three differentiation pathways.

CONCLUSION

Herein, we report a rare and easily misdiagnosed case, and several key points deserve close attention. First, clinical examination suggested HCC or other malignant tumors[19]. The patient was infected with HBV and had an alcohol history and abnormal AFP levels. The contrast-enhanced CT showed heterogeneous enhancement in the arterial and delayed phases. MRI showed a predominantly long T1 signal. T1WI showed mild enhancement in some lesions, while DWI showed a high signal, and ADC image showed a low signal in the center of the lesion. Postoperative pathology revealed a blended neuroendocrine-non-neuroendocrine neoplasm that was a crucial pathological determinant. Strikingly, a few cells were positive for NEC, iCCA, and HCC markers, indicating that a few "undifferentiated cells" were plastic amid the differentiation period, regardless of whether they were pernicious hepatic tumor cells or ancestral cells. Surgical resection is the preferred treatment for mixed liver tumors. The postoperative use of a combination of chemotherapy-based measures with other modalities might improve the prognosis of patients. In conclusion, the co-occurrence of HCC, iCCA, and NEC with high invasiveness, rapid growth, easy recurrence, and metastasis in a short duration is very rare. Imaging and laboratory tests could easily miss or misdiagnose the cancer, and thus, the final diagnosis relies on pathology. Therefore, additional case studies are required to elucidate the characteristics, diagnosis, and optimal therapy for HCC, iCCA, and NEC.

FOOTNOTES

Author contributions: Wu Y, Xie CB, He YH, and Zhao KF reviewed the literature and contributed to manuscript drafting; Shi RS analyzed and interpreted the patient data; Huang Q provide pathological pictures; Ke D managed the patient; and all authors read and approved the final manuscript.

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