Clinics of Surgery

Review Article

ISSN 2638-1451 | Volume 4

Coexistence of Hepatocellular Carcinoma and Primary Hepatic Neuroendocrine Tumor: Case Series and Literature Review

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Received: 06 Dec 2020
Accepted: 22 Dec 2020
Published: 26 Dec 2020

Keywords:

Hepatocellular Carcinoma; Primary Hepatic Neuroendocrine Tumor; Needle Biopsy

Citation:

Liu Z, Coexistence of Hepatocellular Carcinoma and Primary Hepatic Neuroendocrine Tumor: Case Series and Literature Review. Clinics of Surgery. 2020; 4(3): 1-5.

1. Abstract

Coexistence of hepatocellular carcinoma (HCC) and primary hepatic neuroendocrine tumor (PHNET) is rare. No consensus has been reached on the diagnosis and treatment plan for this condition. We herein describe two different cases of coexistent HCC and PHNET. Both patients had a history of chronic hepatitis B virus infection and presented with hepatic lesions and without any specific symptoms. In one case, the tumor was singular and originally diagnosed as PHNET by pathology. Then the tumor presented progressive enlargement. In another case, two hepatic lesions were located in different liver segments, and the patient was misdiagnosed as HCC with intrahepatic metastasis. Both patients were confirmed to be coexistent HCC and PHNET according to the postoperative pathological result. Although one case was metachronous, and another was synchronous. We used the combination of lenvatinib and somatostatin long-acting release as adjuvant therapy after surgical resection of hepatic lesions. Both patients acquired favorable outcomes. This report suggests that PHNET should be included in the differential diagnosis of HCC, even when sufficient evidence of typical presentation exists to support the clinical diagnosis of HCC. It is better to perform a needle biopsy when conditions permit in cases of hepatic lesions. The combined lenvatinib and somatostatin long-acting release may be a potential therapy to prolong the survival of patients with coexistent HCC and PHNET.

2. Introduction

Coexistence of HCC and PHNET is very rare with only 10 cases being reported [1-10]. No consensus has been reached on the diagnosis and treatment for this disease to date. Herein, we describe two different cases of coexistent HCC and PHNET. The HCC and PHNET developed metachronously and synchronously in the respective cases. We used the combination of lenvatinib and somatostatin long-acting release as adjuvant therapy after surgical resection of hepatic lesions, which has not been reported in the English literature. Our report aims to review and summarize the diagnosis and treatment plan for coexistent HCC and PHNET.

3. Case Report

3.1. Case 1

A 51-year-old male with a medical history of hepatitis B presented with a liver lesion on abdominal computed tomography (CT). He did not experience any specific symptoms, and the initial vital signs were stable. The lesion was 5.0 cm × 4.0 cm in size It showed rapid heterogeneous enhancement in the arterial phase and decreased enhancement during the portal and delayed phase (Figure 1. a-d). A subsequent needle biopsy confirmed the lesion to be neuroendocrine tumor (NET). Immunohistochemistry and special staining were positive for chromogranin A, synaptophysin, CD34, CD10, and negative for α-fetoprotein (AFP), HepPar1, glypican-3.

The Ki-67 labeling index values were 3%. The patient received sequential radiofrequency ablation (RFA) for two cycles. Forty-five months later, CT demonstrated the hypo density mass expanded to 9.7 cm × 9.6 cm. (Figure 1. e-h). The third RFA was performed, but the tumor continued to grow. The patient was transferred to our hospital for further treatment.

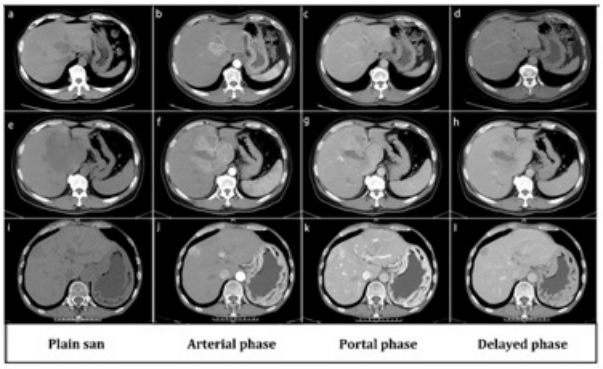

Figure 1: Computed tomography (CT) images of the two reported cases. a-d CT showed a 5.0 cm × 4.0 cm sized lesion in the left hepatic lobe in case 1. e-h CT showed the hepatic lesion expanded to 9.7 cm × 9.6 cm 45 months later in case 1. i-l CT revealed two hepatic lesions in case 2. One lesion located in the hepatic segment IV, and the other one located in the junction of hepatic segment VIII and IV.

We arranged gastro duodenoscopy, colonoscopy, chest, and abdominal CT scans to rule out the extrahepatic NET. We did not perform a needle biopsy considering the patient had received once before. The AFP level was 2.37 ug/L. A postoperative diagnosis of PHNET was made. We performed hepatic left and caudate lobectomy. The resected specimen consisted of two different components. The NET (G2 type) component was 6.5 cm × 5 cm and the HCC component was 9 cm × 5.5 cm. The immunohistochemical findings are presented in (Table 1 and Figure 2 a-d). Final diagnosis of coexistent HCC and PHNET was made. The patient received combined therapy of lenvatinib and sandostatin long-acting release (LAR) regularly after surgery. The patient had been under regular follow-up for 21 months. The last abdominal CT examination showed no signs of tumor recurrence or distant metastasis.

3.2. Case 2

A 57-year-old male with a medical history of hepatitis B presented with two hypoechoic lesions in the liver on traditional ultrasound. The patient had no specific symptoms, and the initial vital signs were stable. A further abdominal CT revealed two hepatic hypo density lesions. One lesion was located in the hepatic segment IV (S4) and the other one in the junction of hepatic segment VIII and IV (S4/S8). It showed obvious enhancement in the arterial phase and the enhancement was decreased during the portal and delayed phase in both lesions (Figure 1. i-l). The AFP level was 116.60 ug/L.

Considering the patient had a history of long-term chronic hepatitis B infection, we made the initial diagnosis of primary HCC with intrahepatic metastasis. We performed the laparoscopic anatomical sub-segmentectomy of S4 and S8 partial hepatectomy for the patient. Pathologically, the S4 tumor was 3 cm × 3 cm and NET (G2 type), and the S4/S8 tumor was 1 cm × 1 cm and HCC. The immunohistochemical findings are presented in (Table 1 and Figure 2 e-h). Final diagnosis of coexistent HCC and PHNET was made. The patient received combined therapy of lenvatinib, and Sandostatin LAR regularly after surgery. The patient had been under regular follow-up for 12 months. The last abdominal CT examination showed no signs of tumor recurrence or distant metastasis.

4. Discussion

We describe two rare cases of coexistent HCC and PHNET. In case 1, the tumor was originally simple PHNET, then the metachronous HCC developed. To our knowledge, this case is the first of its kind published in the literature. In case 2, the PHNET presented the same radiological features of typical primary HCC. The AFP level was normal in case 1 but elevated in case 2. These facts suggest that the biological behavior of coexistent HCC and PHNET is unpredictable, which makes it difficult to diagnose.

According to the previous literatures, the diagnosis of the coexistent HCC and PHNET depends on the postoperative pathological result (Table 2). The key is the recognition of PHNETs. PHNETs are very rare and difficult to diagnose in conventional imaging examinations. On traditional ultrasound, most PHNETs were hyperechoic or mixed-echoic. Color Doppler ultrasound usually found intralesional blood vessels in the tumor [11]. Several studies suggested CEUS revealed the PHNETs had intense arterial enhancement followed by quick washout in the portal and/or the delayed phases (“fast forward and fast out” enhancement pattern) [12-14]. CT revealed that PHNET can be singular or multiple, with or without necrosis and hemorrhage. The enhancement is characterized by a “fast forward and fast out” enhancement pattern or marginal ring-like enhancements [15]. As for magnetic resonance, PHNETs generally demonstrated hypo intensity on T1WI and hyper intensity on T2WI with a “fast forward and fast out” enhancement pattern [16].

To sum up, the radiological presentations of PHNETs are diverse and can be confounded with HCC in conventional imaging examinations. Therefore, PHNET should be included in the differential diagnosis of HCC even when sufficient evidence of typical presentations exists. Other techniques such as PET-scanning with 11C-5 hydroxytryptophan tracer and octreoscan scintigraphy also play important roles in diagnosing PHNET [17]. The final diagnosis still depends on the pathological examination. Immunohistological analysis is the most accurate diagnostic method. Chromogranin A, synaptophysin, and neuro specific enolase are specific detecting markers for NETs [18]. Thus, we suggest that a needle biopsy should be performed in diagnosing hepatic lesions.

Table 1: The clinical laboratory tests results and immunohistochemical findings of the reported two cases.

Case number	Blood routine test	Liver function test	Coagulogram test	Tumor markers
Case 1	HB 96 g/L	ALP 194 U/L	Normal	AFP 2.37 ug/L
	PLT 338´10^9/L	γ-GT 393 U/L		CA50 31.32 U/ml
Case 2	HB 129 g/L	Normal	Normal	AFP 116.60 ug/L
				AFP variant 12.80 ng/ml
				CEA 8.01 ng/ml
				APT 1425 mAU/mL
Case number	Component type	Positive (+)	Negative (-)	Ki-67 labeling index values
Case 1	NET	CgA, NSE, Syn, CD56, CK8, CK18, CK19	GPC-3, HepPar1	8%
	HCC	AFP, HepPar1, CD34, CK8 CK18	GPC-3	3%
Case 2	NET	CgA, NSE, Syn, CD34	GPC-3	8%
	HCC	AFP, CK8, CK18, GPC-3, CD34	CD10	40%

HB, hemoglobin; PLT, platelet; ALP, alkaline phosphatase; γ-GT, γ-glutamyltransferase; AFP, alpha-fetoprotein; CA 50, carbohydrate antigen 50; CEA, carcinoembryonic antigen; APT, abnormal prothrombin; NET, neuroendocrine tumor; HCC, hepatocellular carcinoma; CgA, chromogranin A; Syn, synaptophysin; NSE, neuro specific enolase; CK, cytokeratin; GLP-3, glypican-3.

Table 2: Summary of previously reported cases of coexistence of hepato cellular carcinoma and neuro endocrine tumor in the liver.

Author	Year	Age	Sex	Hepatitis	Solitary ormultiple	Size of tumor	Pathologic diagnosis
Okumu[r]a3	2017	70	M	HCV (+)	Solitary	11 cm	Poorly differentiated HCC & NEC
Nishino[4]	2016	72	M	HCV (+)	Multiple	2.5 cm (HCC+NEC) & 1 cm (HCC)	Moderately differentiated HCC & NEC
Choi[8]	2016	72	M	HCV (+)	Solitary	2.5 cm	Moderately differentiated HCC & NEC
Garcia[6]	2006	50	M	HCV (+)	Solitary	5 cm	Moderately differentiated HCC & NEC
Yang[1]	2009	65	M	HBV (+)	Solitary	7.5 cm	Moderately differentiated HCC & NEC
Yamaguchi[2]	2004	71	M	HCV (+)	Multiple	4 cm (HCC+NEC) & 4.5 cm (HCC)	Moderately differentiated HCC & NEC
Nakanishi[10]	2012	76	M	HCV (+)	Solitary	3.5 cm	Moderately differentiated HCC & NEC
Tazi[7]	2011	68	M	HBV (+)	Solitary	4 cm	Moderately differentiated HCC & NEC
Ishida[5]	2003	72	M	HCV (+)	Multiple	3 cm (HCC+NEC) & 1.5 cm (HCC)	Moderately differentiated HCC & NEC
Aboelenen[9]	2014	51	M	HCV (+)	Solitary	7.5 cm	Moderately differentiated HCC & NEC
Author	Recurrence site				Recurrence time	Treatment	Clinical course
Okumura[3]	Abdominal lymph nodes and the lumbar vertebra				1 month	TACE, PTPE→ surgical resection→ chemotherapy (sorafenib)	3 months dead
Nishino[4]	Regional, para-aortic lymph nodes				1 month	Surgical resection→ chemotherapy (etoposide and cisplatin)	2 months dead
Choi[8]	Liver				6 months	Surgical resection→ chemotherapy (etoposide and cisplatin)	10 months alive
Garcia[6]	Liver, peripancreatic adenopathy, anterior mesenteric area				4 months	Surgical resection→ chemoinfusion (cisplatin), the right hepatic branch embolization→ chemotherapy	16 months alive
Yang[1]	Liver, bilateral adrenal glands, para-aortic lymph nodes				3 months	(doxorubicin, added thalidomide and bevacizumab) Surgical resection	12 monthsdead
Yamaguchi[2]	Pelvic bone				5 months	Surgical resection	5 months alive
Nakanishi[10]	Sacral bone, liver				6 months	TACE→ surgical resection	7 months dead
Tazi[7]	None				None	Surgical resection→ chemotherapy (etoposide and cisplatin)	28 months alive
Ishida[5]	None				None	Surgical resection	No data
Aboelenen[9]	None				None	Surgical resection	6 months alive

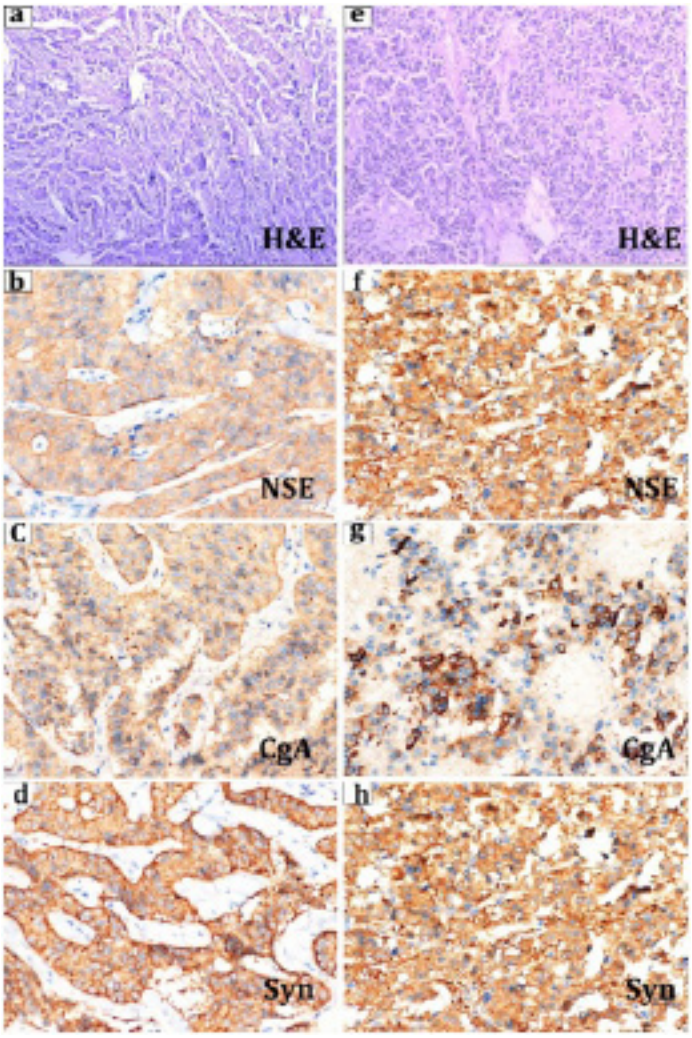

Figure 2: Histopathology images of the resected specimen from the two reported cases. a The hematoxylin-eosin (H&E) staining result of case 1. b-d On immunohistochemistry, the neuroendocrine tumor cells are positive for neuro specific enolase (NSE), chromogranin A (CgA), and synaptophysin (Syn) in case 1. e H&E staining result of case 2. e-f On immunohistochemistry, the neuroendocrine tumor cells are positive for NSE, CgA, and Syn in case 2.

In terms of the treatment for coexistent HCC and PHNET, the therapeutic strategy is still being explored. Surgical resection is the preferred treatment option for this disease. Among the reported 10 cases (Table 2), all patients received surgical resection procedure and were finally diagnosed with coexistent HCC and neuroendocrine tumor carcinoma (NEC). Five patients received systematic chemotherapy after surgery. The common adjuvant chemotherapy for coexistent HCC and NEC is based on the combination of etoposide and cisplatin. Two of the five patients presented abdominal lymph node metastasis within one month and died within three months after surgery. The other two patients were treated with chemotherapy based on etoposide and/or cisplatin and obtained at least 10 months of overall survival. To summarize, chemotherapy may be effective in extending the life span of such patients but only plays a limited role.

For case 1, the treatment course was torturous and complicated. The patient was treated with sequential RFA and had a progression-free period of 40 months. However, when the tumor developed to mixed HCC and HNET, the RFA did not work. In our institution, we performed surgical resection in both patients and initiated a combined therapy of lenvatinib, and somatostatin LAR immediately after surgery. This combined therapy has not been reported in the literature. Lenvatinib is the standard treatment in advanced hepatocellular carcinoma and was proven to increase the survival time of patients [19, 20]. Somatostatin analogs are recommended as an anti-proliferation treatment for midgut NETs [21]. The patients had a recurrent-free follow-up period of 21 months and 12 months respectively. It demonstrated the combination of lenvatinib and Somatostatin LAR may be a potential therapy to extend the life spans in patients with coexistent HCC and PHNET, which requires further studies to confirm.

There are several limitations during our diagnosing course. Firstly, we did not perform a repeat needle biopsy when the stable tumor presents progressive enlargement in case 1 and directly made the diagnosis of PHNET according to the previous confirmed pathological result. Fortunately, we took the risk to perform the surgery and acquired a definitive diagnosis. Otherwise, the patient would lose the chance for further targeting treatment and result in a poor prognosis. This prompted us that a careful re-examination is needed when a stable tumor changes its behavior. Secondly, according to guidelines for diagnosis and treatment of primary liver cancer in China (2017), we made the clinical diagnosis of HCC with intrahepatic metastasis in case 2 after considering the chronic hepatitis history, elevated AFP level, and imaging characteristics, which was finally proven to be a misdiagnosis. This exceptional example indicates that there is a rare probability of diagnosis inaccuracy even when sufficient evidence of typical presentation exists, and pathological examinations still play the confirmative role in diagnosis.

5. Conclusion

Coexistent HCC and PHNET is rare. PHNET resembles HCC in conventional imaging examinations. Therefore, PHNET should be included in the differential diagnosis of HCC, even when sufficient evidence of typical presentation exists to support the clinical diagnosis of HCC. It is better to perform a needle biopsy when conditions permit in cases of hepatic lesions. The combination of lenvatinib and somatostatin LAR may be a potential therapy for coexistent HCC and PHNET. More cases are needed to achieve a clear understanding of the diagnosis and treatment of this condition.

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