

Primary Hepatic Neuroendocrine Carcinoma Combined with Intrahepatic Cholangiocarcinoma Treated by Surgical Resection in Combination with Comprehensive Therapy: A Case Report with Literature Review

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Neuroendocrine carcinoma; cholangiocarcinoma; comprehensive treatment.

1. Abstract

Primary hepatic neuroendocrine carcinoma is very rare in clinical practice, and the concurrent occurrence of neuroendocrine carcinoma and other malignant tumors is even rarer. In this report, we describe a rare case of primary hepatic neuroendocrine carcinoma combined with intrahepatic cholangiocarcinoma, and illustrate the efficacy of surgery combined with postoperative combination therapy, which provides a potentially effective therapeutic strategy for refractory tumors.

2. Introduction

Neuroendocrine tumors (NET) are prevalent in organs such as the gastrointestinal tract, pancreas and lungs, whereas primary hepatic neuroendocrine tumor (PHNET) is extremely rare, accounting for only 0.46% of primary liver tumors [1]. Less than 150 cases of PHNET have been reported in the English literature [2], and PHNET combined with intrahepatic cholangiocarcinoma (ICC) is even more rarely reported. In this paper, we report a 58-year-old man with PHNET combined with ICC who was highly suspected of having primary hepatocellular carcinoma with intrahepatic metastases prior to surgery, but after radical resection, the pathology section report was suggestive of PHNET combined with ICC. The patient was now successfully treated with six sessions of intravenous etoposide combined with cisplatin chemotherapy (EP regimen) and oral surufatinib for a recurrence 7 months after surgery.

3. Case Presentation

The patient is a Han Chinese male, 58 years old, with a history of hepatic schistosomiasis and cholecystitis for more than ten

years, and no remaining systemic diseases. 2022 February, due to “recurrent colicky pains in the right upper abdomen for 4 days without obvious triggers,” he underwent a computed tomography (CT) scan of the epigastrium in the local hospital, which suggested: “right hepatic occupying lesion, malignant tumor is not excluded.” Laboratory tests showed alpha fetoprotein (AFP) 1599 µg/L, Protein Induced by Vitamin K Absence or Antagonist-II (PIVKA-II) 27.17 mAU/L, aspartate aminotransferase (AST) 14 IU/L, alanine aminotransferase (ALT) 22 IU/L, direct bilirubin (DBil) 10.6 µmol/L. Enhanced CT of the upper abdomen showed that the right posterior lobe of the liver was mixed in the lower part of the right posterior lobe of the liver, and the right posterior lobe of the liver was mixed in the lower part of the right posterior lobe of the liver. Mixed density occupations in the lower right posterior lobe of the liver, not excluding hepatic Ca; slightly low-density foci in the upper right posterior lobe of the right posterior lobe of the liver, not excluding metastatic tumor, and chest CT suggests: solid nodule in the lower right lobe of the right lung, about 3 mm in size (Figure 1 and 2).

Initial evaluation of the patient Child-Pugh score grade A, no absolute contraindications to surgery, can tolerate surgery, after communication with the patient and his family decided to surgical resection, and a few days later underwent right hemihepatectomy + cholecystectomy, the operation was completed 3 weeks after discharge from the hospital.

Upon pathological examination, the resected liver tissue contained two nodules, the larger of which was 11×10×3.5 cm in size and

soft, and the other smaller nodule was 1×0.9×0.5 cm in size and tougher in texture. Immunohistochemistry of the large nodule showed that the tumor cells were positive for synaptophysin (Syn) and CD56, negative for chromogranin A (CgA) and AFP, and the Ki-67 index was >80%, which was considered to be consistent with the nature of NET, whereas the detection of thyroid transcription factor-1 indicated that the possibility of lung metastasis was unlikely, and it was considered to be a PHNET based on the imaging and the intraoperative findings. The pathologic HE staining of the nodule showed adenoid distribution of cancerous tissue and positive CK7 expression, which was consistent with cholangiocarcinoma (Figure 3-5).



Figure 1: Shows a rounded slightly hypodense shadow in the upper segment of the right posterior lobe, which is less obvious and has a diameter of about 9 mm.



Figure 2: Shows a tumor nodule in the lower segment of the right posterior lobe, which is of mixed density and has a diameter of about 12 cm.

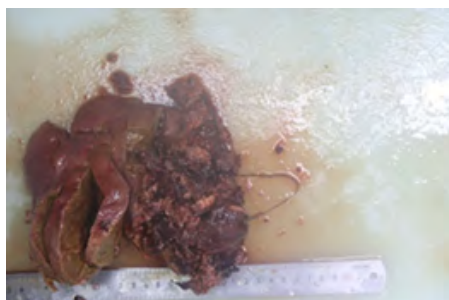


Figure 3: Shows the resected liver specimen with the tumor showing clearly.

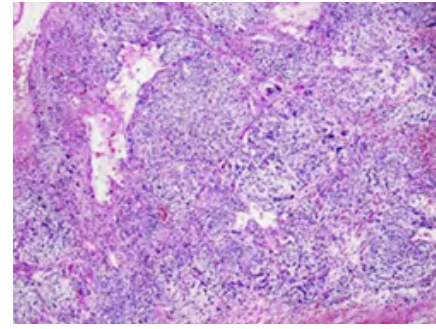


Figure 4: Shows the HE staining of PHNET at 10x magnification, which shows that the tumor cells are mainly arranged in a solid or rope-like pattern.

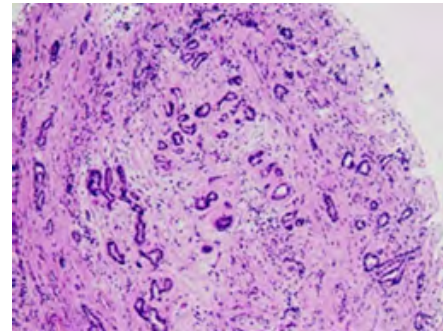


Figure 5: Shows the HE staining of ICC at 40x magnification, which shows a clear glandular cavity.

The patient returned to the hospital for a follow-up examination 25 days after discharge, and the AFP level had decreased significantly (6.3 µg/L), PIVKA-II 20.58 mAU/L, and AST, ALT, and bilirubin were normal. Review of CT and magnetic resonance imaging (MR) of the upper abdomen suggested no significant recurrence. Since the patient had both PHNET and ICC, there was no standard systemic drug regimen, so we decided to treat the patient with intravenous infusion of etoposide 0.3g + cisplatin 120mg, combined with oral Sofantinib 300mg for the specificity of the two tumors. Among them, the infusion of etoposide was completed in 3 days, 0.1g per day by intravenous infusion, and the first course was stopped to receive etoposide on the second day and the third day because the patient could not tolerate it. The patient then returned to the hospital for chemotherapy sessions at nearly 1-month intervals, and laboratory tests and imaging showed no significant recurrence.

In September 2022, the patient returned to the hospital for follow-up and underwent an epigastric CT, which suggested a rounded slightly hypodense lesion in the operated area, and was considered to be a recurrence, and a CT-guided liver biopsy was performed, and the pathological results suggested that the mass was a large-cell neuroendocrine carcinoma, and CT-guided radiofrequency ablation of the liver mass was performed after seeking the consent of the patient and her family. One month later, the patient returned to the hospital for follow-up and underwent Positron Emission Tomography (PET)/CT, which revealed enlarged lymph nodes and metastatic foci in the right hemidiaphragm angle and

abdominal cavity, and a slightly active metabolism at the edge of the ablated lesion in the right lobe of the liver, and radiofrequency ablation was performed after comprehensive consideration, and carilizumab 200mg was given to the patient for intravenous immunotherapy (Figure 6-9).



Figure 6: Shows tumor recurrence found at the September 2022 follow-up.

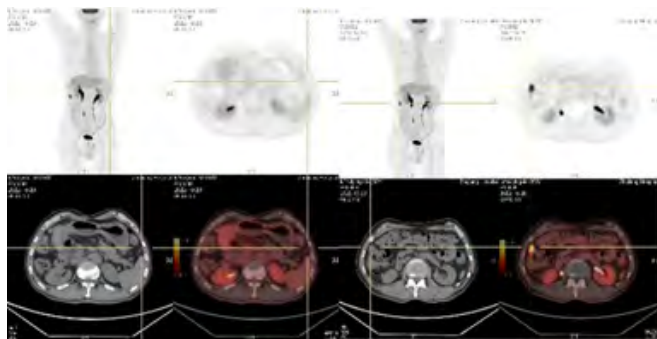


Fig.7

Fig.8

Figures 7 and 8: Show enlarged intra-abdominal lymph nodes and metastatic foci shown by PET/CT.

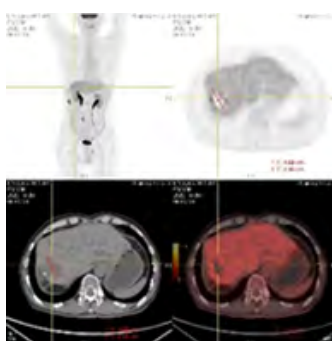


Figure 9: Shows post-ablation lesions in the right lobe of the liver shown by PET/CT.

In February 2023, the patient underwent CT scan for epigastric distension and discomfort, a huge mass in the hepatic region was seen, and after comprehensive consideration of recurrent tumor progression, transhepatic artery chemoembolization (TACE) was performed, with intraoperative instillation of recombinant human adenovirus type 5 1 ml + raltitrexed 2 ml + lobaplatin 30 mg, and at the same time, camrelizumab intravenous immunotherapy was

continued and the addition of albumin-paclitaxel 200 mg igvtt. 1 time every 3-4 weeks.

After 1 month, the patient returned to the hospital for review, and the CT image showed that the mass had not shrunk significantly, and after discussion with the oncologist, it was decided to add oral anlotinib 12mg once a day (Figure 10 and 11).

In May 2023, the patient returned to the hospital for follow-up, and the tumor was seen to have shrunk significantly on CT images, and there was no obvious discomfort during the comprehensive treatment, and the symptoms of epigastric distension and pain were significantly relieved, so considering that the tumor was sensitive to the comprehensive treatment regimen, the patient is now continuing to receive immunotherapy on a regular basis. The patient was last reviewed in June 2023, and laboratory results showed AFP 10.4 µg/L and PIVKA-II 34.02 mAU/ml. CT-guided radiofrequency ablation was performed for the previously suspected recurrent foci in the right liver, and TACE was performed 1 day later, and he was discharged without discomfort (Figure 12).

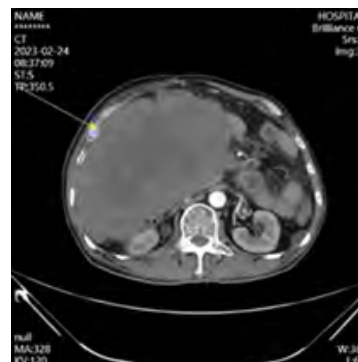


Figure 10: Shows a huge mass of mixed density on CT plain image, which is considered to be recurrent tumor progression.

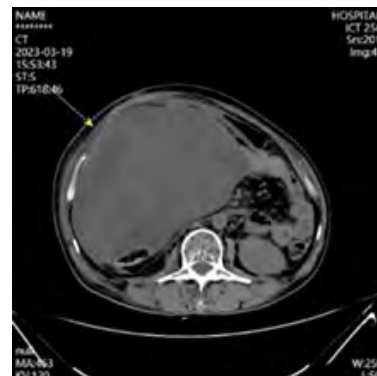


Figure 11: Shows the tumor after 1 month without any significant change in the tumor.



Figure 12: Shows a significant reduction in the suspected recurrent foci

4. Discussion

NETs are malignant tumors originating from the neuroendocrine system, of which those originating in the liver are extremely rare, accounting for only 0.3% of all NETs [3]. No more than 10 cases of PHNET combined with ICC have been previously reported in the literature [4]. As PHNET has no characteristic imaging manifestations, it is difficult to differentiate it from hepatocellular carcinoma and other tumors, and the main diagnostic method at present is still the pathological examination of specimens obtained by surgical resection or biopsy for evaluation. It can not only determine the diagnosis, but also evaluate the malignancy of the tumor by the Ki-67 index value, which plays a key role in the treatment and prognosis of PHNET [5]. Symptomatically, it is also difficult to differentiate PHNET from other malignant tumors, such as HCC, because only 6.8% of PHNET patients present with typical neuroendocrine symptoms [6]. The usual points of differentiation between PHNET and HCC also include the fact that serum AFP levels are usually elevated in patients with HCC, and in this case the patient's serum AFP levels were highly elevated; however, in one of our former female patients who also had PHNET, serum AFP remained low throughout the course of the disease, suggesting that PHNET may be variably expressed in different patients. In our patient, no preoperative endoscopy was performed, so the diagnosis of PHNET was established by imaging, as well as postoperative pathology and long-term postoperative follow-up that did not reveal any primary tumor elsewhere. The current treatment of choice for PHNET remains surgical resection. Studies have shown that patients who undergo radical resection have a significantly improved prognosis compared to those who do not undergo surgery [7]. In addition to this, studies have shown that EP regimens or chemotherapy regimens such as cisplatin + irinotecan, which are used for first-line treatment of small cell lung cancer, can be used to treat PHNET [8]. However, it has also been shown in the literature that EP regimens are ineffective when used for the treatment of unresectable NET of the hepatobiliary system, with a median progression-free survival (PFS) of 3.0 months and a median overall survival (OS) of 5.8 months [9]. In this case, in addition to the EP regimen of intravenous chemotherapy, the

patient was also treated with concomitant oral treatment with surufatinib, a novel oral tyrosine kinase inhibitor [10]. It has been approved for the treatment of advanced extrapancreatic NET as well as pancreatic NET in China, and clinical studies have confirmed a longer PFS than the placebo group [11]. Anlotinib, like surufatinib, is a multi-targeted receptor tyrosine kinase inhibitor, which has demonstrated promising anti-tumor responses against a variety of advanced and recurrent tumors in several studies [12–14]. Albumin-paclitaxel is a new type of nanosized particles with better response rate and lower toxicity than pure paclitaxel analogs, which are commonly used in cancers such as breast, non-small cell lung, and pancreatic cancers [15]. Camrelizumab, a selective PD-1 monoclonal antibody inhibitor, has been approved in China for use in patients with advanced liver cancer who have previously received systemic chemotherapy, making it a second-line treatment for advanced liver cancer [16]. There are no reports in the literature on the use of EP regimen in combination with the above-mentioned drugs for the treatment of PHNET combined with ICC. The patient in this case has achieved a PFS of 7.0 months and the OS is now 20 months, which may be the reason that this combination regimen plays a better role than monotherapy and can improve the patient's quality of life to a certain extent. However, it is undeniable that this case may be fortuitous and there is not enough evidence to support the benefit of treatment with this dosing regimen. Due to the rarity of the tumor, the differential diagnosis of PHNETs as well as combined ICC has not been clearly elucidated.

In conclusion, this case provides a potentially effective management strategy for PHNET combined with ICC, and the surgical and postoperative regimen using a combination of multiple drugs may be an appropriate approach to prolonging the survival of patients with this refractory tumor, but more studies are needed to confirm the effectiveness of this approach.

References

1. Zhang S, Ren M, Xu J, Zhang J. Current status of diagnosis and treatment of primary hepatic neuroendocrine tumors. *Chinese Hepatology*. 2022; 27: 1344–1347.
2. Yang K, Cheng YS, Yang JJ, Jiang X, Guo JX. Primary hepatic neuroendocrine tumor with multiple liver metastases: A case report with review of the literature. *World J Gastroenterol*. 2015; 21: 3132–3138.
3. Quartey B. Primary Hepatic Neuroendocrine Tumor: What Do We Know Now? *World J Oncol*. 2011; 2: 209–216.
4. Kano Y, Kakinuma S, Goto F, Azuma S, Nishimura-Sakurai Y, Itsui Y, et al. Primary hepatic neuroendocrine carcinoma with a cholangiocellular carcinoma component in one nodule. *Clin J Gastroenterol*. 2014; 7: 449–454.
5. Li Z, Yong CC, Chen CL. A primary hepatic neuroendocrine tumor disguised as hepatocellular carcinoma. *Hepatobiliary Surg Nutr*. 2020; 9: 263–266.
6. Liu F, Jin YW, Li FY. Primary Hepatic Neuroendocrine Tumor:

- Challenges in the Preoperative Diagnosis and Treatment. *J Gastrointest Surg.* 2020; 24: 1891–1893.
7. Li YF, Zhang QQ, Wang WL. Clinicopathological Characteristics and Survival Outcomes of Primary Hepatic Neuroendocrine Tumor: A Surveillance, Epidemiology, and End Results (SEER) Population-Based Study. *Med Sci Monit.* 2020; 26: e923375.
 8. Kawarabayashi N, Amikura K, Sakamoto H, Yamaura T, Tanaka Y, Oba H, et al. Neuroendocrine Carcinoma of the Liver Coexistent with the Intrahepatic Cholangiocarcinoma. *The Japanese Journal of Gastroenterological Surgery.* 2012; 45: 1012–1019.
 9. Iwasa S, Morizane C, Okusaka T, Ueno H, Ikeda M, Kondo S, et al. Cisplatin and etoposide as first-line chemotherapy for poorly differentiated neuroendocrine carcinoma of the hepatobiliary tract and pancreas. *Jpn J Clin Oncol.* 2010; 40: 313–318.
 10. Shen G, Zheng F, Ren D, Du F, Dong Q, Wang Z, et al. Anlotinib: a novel multi-targeting tyrosine kinase inhibitor in clinical development. *J Hematol Oncol.* 2018; 11: 120.
 11. Xu J, Shen L, Zhou Z, Li J, Bai C, Chi Y, et al. Surufatinib in advanced extrapancreatic neuroendocrine tumours (SANET-ep): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol.* 2020; 21: 1500–1512.
 12. Chi Y, Shu Y, Ba Y, Bai Y, Qin B, Wang X, et al. Anlotinib Monotherapy for Refractory Metastatic Colorectal Cancer: A Double-Blinded, Placebo-Controlled, Randomized Phase III Trial (ALTER0703). *Oncologist.* 2021; 26: e1693–e1703.
 13. Liu Z, Gao S, Zhu L, Wang J, Zhang P, Li P, et al. Efficacy and safety of anlotinib in patients with unresectable or metastatic bone sarcoma: A retrospective multiple institution study. *Cancer Med.* 2021; 10: 7593–7600.
 14. Sun Y, Niu W, Du F, Du C, Li S, Wang J, et al. Safety, pharmacokinetics, and antitumor properties of anlotinib, an oral multi-target tyrosine kinase inhibitor, in patients with advanced refractory solid tumors. *J Hematol Oncol.* 2016; 9: 105.
 15. Kundranda MN, Niu J. Albumin-bound paclitaxel in solid tumors: clinical development and future directions. *Drug Des Devel Ther.* 2015; 9: 3767–3777.
 16. Chen Z, Lu X, Koral K. The clinical application of camrelizumab on advanced hepatocellular carcinoma. *Expert Review of Gastroenterology & Hepatology.* 2020; 14: 1017–1024.