

# Misdiagnosis of Primary Hepatic Neuroendocrine Carcinoma: A Case Report and Literature Review

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## Case Report

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# Abstract

**Background:** Primary hepatic neuroendocrine carcinoma (PHNEC) is relatively rare and has high malignancy and poor prognosis, but the rate of clinical diagnosis is low. The clinical symptoms, signs, and ultrasound images are not specific. Diagnosis is mainly based on pathological manifestations and immunophenotyping analysis. Here, we present a case of PHNEC with rectal adenoma.

**Case presentation:** A 63-year-old male patient complained of dull pain and discomfort in his right upper abdomen that had persisted for over 1 month. This individual was initially diagnosed with rectal cancer with liver metastasis because of unclear and inconclusive imaging examination results. The biopsy of rectal polyps indicated tubular villous adenoma, and the liver biopsy and immunohistochemical examinations suggested PHNEC.

**Conclusions:** When a patient has not been diagnosed with hepatitis or cirrhosis, the AFP value is not high, and imaging shows solid space-occupying lesions, liquefaction, and clear liver tumor boundaries, we can exclude tumors of non-hepatic origin using gastroscopy, colonoscopy, and PET-CT, and other tests. We can then consider Primary hepatic neuroendocrine tumor and confirm this with pathological examinations and immunophenotyping.

## Background

Primary hepatic neuroendocrine carcinoma (PHNEC) is a relatively rare cancer with high malignancy and poor prognosis<sup>[1]</sup>. PHNEC can secrete various polypeptides and biological amines. The average age of onset is approximately 40–50 years old, but there is no significant difference in its incidence between men and women. In addition, the diagnosis rate is low and its clinical symptoms, signs, and ultrasound images are not specific<sup>[2]</sup>. Diagnosis is mainly based on pathological manifestations and immunophenotype. No cases of PHNEC with rectal adenoma have been previously published. Here, we present such a case.

## Case Presentation

### *Clinical summary*

A 63-year-old male patient complained of dull pain and discomfort in his right upper abdomen that had persisted for over 1 month. The patient did not report any other symptoms. A computed tomography (CT) scan of the upper abdomen indicated multiple liver lesions. The patient had a history of hypertension for 5 years with no regular treatment for it. Physical examinations showed deep tenderness in the right upper abdomen.

Laboratory examinations showed the following: concentrations of tumor markers CA724, NSE, FRT, CA199, and Ca50 were increased to 49.22 U/mL (normal range 0–6.9 U/mL), 275.2 ng/mL (normal range 0–16.3 ng/mL), 631.10 µg/L (normal range 30–400 µg/L), 73.77 U/mL (normal range 0–27 U/mL), and

49.15 U/mL (normal range < 20 U/mL), respectively. The hepatic biochemical index gamma-glutamyl transpeptidase was increased to 455 U/L (normal range 15–73 U/L). Results of other blood tests were normal. Both CT and PET-CT scans (Figure 1) indicated that the patient was suffering from rectal cancer with distant metastasis to sites such as the liver. Further examinations were performed and a colonoscopy suggested rectal polyps were present. A biopsy of these rectal polyps indicated tubular villous adenoma of the rectum nests. PET-CT excluded other primary lesions of neuroendocrine carcinoma in the pancreas, digestive tract, and other sites.

## Autopsy findings

Liver pathology showed heterotypic cell nests, and immunohistochemistry revealed: Glypican-3 (-), Hep (-), P63 (-), AE1/AE3 (+), CD117 (YR145) (+), CD56 (+), Chromogranin A (CgA)(+), CK20 (-), CK7 (-), CK8/18 (+), EMA (+), P40 (-), and Synaptophysin (Syn) (focal +) (Figure 3). Ki-67(+,about 65%) (Figure 2). The final diagnosis of this case was PHNEC with rectal adenoma.

## Treatments

The patient treated by transcatheter arterial embolization, but finally gave up follow-up treatment for personal reasons.

## Discussion

A neuroendocrine tumor (NET) was originally defined as a carcinoid tumor derived from mucosal or submucosal gland epithelial cells that can synthesize and secrete peptide hormones. According to the World Health Organization classification in 2010, NET is classified into three grades based on the mitotic rate and Ki-67 proliferation index: G1, mitotic rate < 2 per 10 high power fields (HPFs) and/or Ki-67 index ≤ 3%; G2, mitotic rate 2–20 per 10 HPFs and/or Ki-67 index 3–20%; and G3, mitotic rate > 20 per 10 HPFs and/or Ki-67 index > 20%<sup>[3]</sup>. Highly differentiated NETs of grades G1 and G2 are considered benign, and poorly differentiated NETs of grade G3 are named neuroendocrine carcinoma. Studies in the literature have reported that 45% of NETs originate from the small intestine, 20% from the rectum, 17% from the appendix, 11% from the colon, and 7% from the stomach<sup>[4]</sup>. The liver is the most common metastatic organ of NETs, but PHNEC is rare, accounting for only 0.3–4.0% of all NETs<sup>[1]</sup>.

Primary hepatic neuroendocrine tumors (PHNETs) frequently stem from intrahepatic bile duct epithelial cells, adrenal tissue, or ectopic pancreatic cells<sup>[5]</sup>. PHNEC usually occurs in the right lobe of the liver. Vascular invasion is common because of the abundant blood supply in the liver, but distant metastases are rare. These lesions are often single (approximately 66%), and about 70.33% of them have a diameter greater than 5 mm. Most clinical features of PHNEC are no specific, and some patients show abdominal pain, an abdominal mass, or weight loss without hormone-related syndrome. A few patients with PHNEC may have carcinoid syndrome, but only approximately 5% show its obvious biological signs and symptoms, such as skin flushing, abdominal pain, and diarrhea<sup>[2]</sup>. Because PHNEC grows slowly

compared with other NETs, many patients only seek treatment when certain late stage clinical symptoms and signs appear. For example, in the case presented here, the patient saw a doctor because he felt pain and discomfort in his upper abdomen. Unfortunately, by that point the lesions had spread throughout his liver.

PHNEC has high malignancy and poor prognosis, but the diagnosis rate is very low. PHNETs show no obvious specificity in ultrasound, CT, or magnetic resonance imaging (MRI) examinations. PHNEC lesions are often hypoechoic, hyperechoic, or mixed with a surrounding ring in the ultrasound images, which may be easily misdiagnosed as a hemangioma because of the blood echo signals in the lesions. Researchers have reported that grade 1 PHNETs tend to be solitary and rapidly enhanced in the arterial phase. Grade 2 PHNETs can be either single or multiple masses with necrosis and ring-shaped enhancement. Grade 3 PHNETs are multiple masses with internal necrosis and bleeding<sup>[6]</sup>. Kai Yang analyzed the image data of 11 PHNEC patients and found that the abdominal CT scans of eight patients showed multiple round or oval masses with clear boundaries<sup>[7]</sup>. Enhancing images revealed diffuse heterogeneity during the arterial phase, and the enhancement was slightly higher than that in peripheral normal liver parenchyma. There were also indistinct edges in the small lesions in the portal phase. The MRI of eight patients showed characteristic lobular or segmental masses, and multiple lesions with clear edges and rich with vasculature were observed at the arterial stage with digital subtraction angiography. Additionally, the role of PET-CT in the grading of PHNEC is not yet clear, but PHNEC is often characterized by high 18F-fluoro-deoxygenated glucose uptake<sup>[8]</sup>. In the case presented here, PET-CT showed increased glucose metabolism in the liver, which is consistent with the literature. Finally, octreotide scintigraphy is more sensitive to tumor localization than other methods, with a reported sensitivity of approximately 85–90%<sup>[9]</sup>. The diagnosis of PHNEC is dependent on histological findings and immunostaining for neuroendocrine markers, and requires comprehensive examinations to exclude extrahepatic primary lesions.

In addition, postoperative long-term follow-up is critical to further identify the primary tumor sites<sup>[10]</sup>. The CT and PET-CT of the patient discussed here showed diffuse lesions of whole liver and uneven thickening of the rectal wall. Because the imaging findings suggested that rectal cancer with liver metastasis could not be ruled out, this case was easily misdiagnosed as intrahepatic metastatic disease by clinicians. Immunohistochemistry is the key method for the diagnosis and classification of NETs. CgA, Syn and Ki-67 are routine detection markers. Syn expression is one of the characteristic signs of NETs, and can be used to mark neuroendocrine tumors of neural and epithelial origin. CgA is part of a group of soluble acidic proteins that are used to label neuroendocrine cells and tumors of their origin. Syn and CgA represent the differentiation characteristics of neuroendocrine cells. Ki-67 is a proliferation-associated nuclear antigen and is used to assess cell proliferation rates. The higher the Ki-67 index is, the lower the survival rate of patients and the worse the prognosis. CD56 is a neural cell adhesion molecule that is frequently strongly positively expressed in neuroendocrine tissues, tumors, and a few lymphomas. Qiu et al. compared 34 cases of neuroendocrine carcinoma with liver metastasis with 14 cases of PHNEC and found the positive rates of Syn, CgA, CD56, PCK, CK19, and EMA were 100%, 75%, 90%, 87.5%, 66.67%,

and 80%, respectively, in PHNEC lesions, and 91.18%, 69.70%, 76.47%, 100%, 68.18%, and 78.57%, respectively, in metastatic liver neuroendocrine cancer. The author also found serum AFP, CEA, CA199, and other tumor markers had no specific diagnostic value in either group<sup>[11]</sup>.

In the case presented here, the liver biopsy showed a heterocystic nest, and immunohistochemistry analysis suggested that Syn, CgA, CD56, Ki67, and EMA were all positive, which is consistent with previous reports. Laura et al. reported two large PHNETs with tumor diameters of 18 cm and 24 cm, and genetic testing revealed that both patients had DNA mutations in tumor protein P53(TP53), including one with phosphatidylinositol 3-kinase (PI3KCA) mutations<sup>[12]</sup>. TP53 mutations have been reported in approximately 80% of poorly differentiated neuroendocrine cancers<sup>[13]</sup>. As part of the PI3K-AKT-mTOR pathway, PI3KCA is considered to be a molecular target for the treatments of advanced NET<sup>[14]</sup>. Kwon et al. first reported a case combined hepatocellular carcinoma and neuroendocrine carcinoma with ectopic secretion of parathyroid hormone. This report suggested that PHNEC may cause ectopic parathyroid hormone secretion, leading to hypercalcemia<sup>[15]</sup>. This demonstrates the importance of considering neuroendocrine differentiation when diagnosing liver cancer with low differentiation. Additionally, through a retrospective analysis of 28 patients with PHNETs, Chen et al. found that G3 grade tumors, high Ki-67 expression, poor liver function, anemia, abnormal CA125, and lack of radical surgery were positively associated with shorter survival times and poor prognosis<sup>[1]</sup>.

## Conclusions

When a patient has not been diagnosed with hepatitis or cirrhosis, the AFP value is not high, and imaging shows solid space-occupying lesions, liquefaction, and clear liver tumor boundaries, we can exclude tumors of non-hepatic origin using gastroscopy, colonoscopy, and PET-CT, and other tests. We can then consider PHNET and confirm this with pathological examinations and immunophenotyping.

## Abbreviations

PHNEC: Primary hepatic neuroendocrine carcinoma; CT: Computed tomography; PET-CT: Positron Emission Tomography-Computed Tomography; CgA: Chromogranin A; Syn: Synaptophysin; NET: Neuroendocrine tumor; HPFs: High power fields; PHNET: Primary hepatic neuroendocrine tumor; MRI: Magnetic resonance imaging

## Declarations

### Acknowledgements

Not applicable

### Authors' contributions

JB and RD performed the surgery, researched the patient's background, and drafted the manuscript. LH and JM reviewed the literature and drafted the manuscript. YX and YF corrected the first version of the draft. All authors have approved the final version of the text.

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## Availability of data and materials

Not applicable

## Ethics approval and consent to participate

This study was approved by the ethics committee of the Second Affiliated Hospital of Air Force Military Medical University.

## Consent for publication

We obtained informed consent from the patient's family for the publication of this case report.

## Competing interests

The authors declare that they have no competing interests.

## Author details

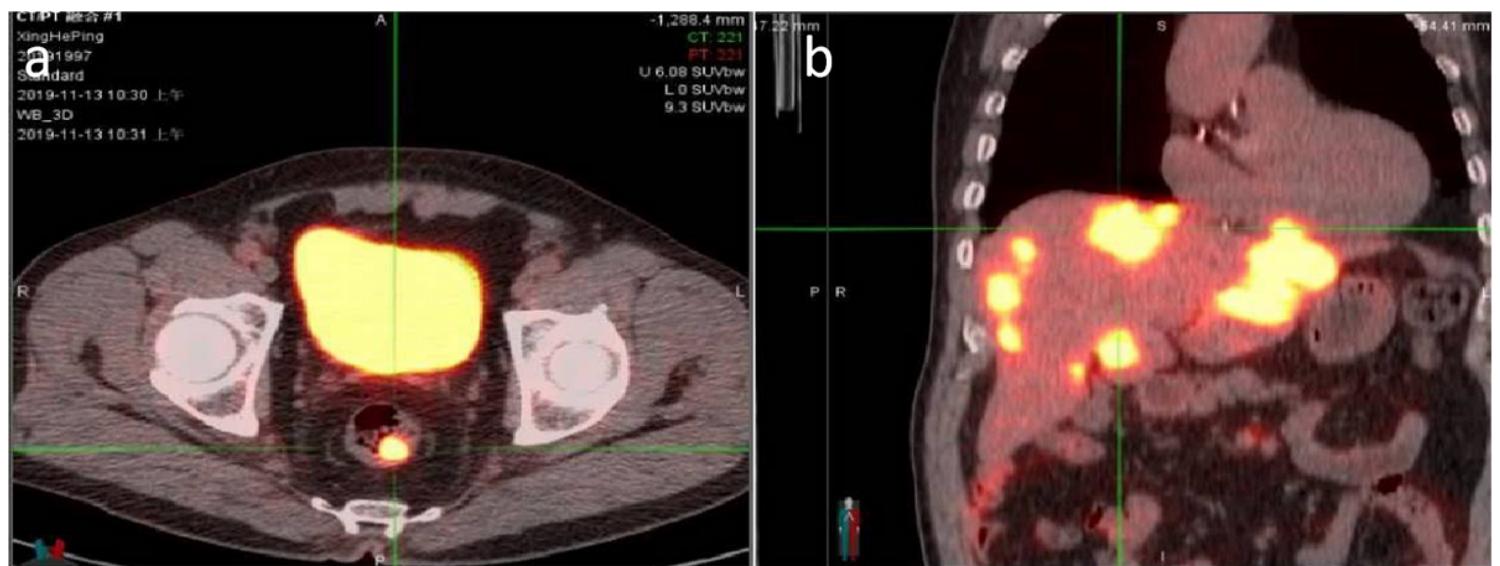
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## References

1. Chen RW, Qiu MJ, Chen Y, Zhang T, He XX, Li Y, Sun WJ, Xie T, Yang SL, Hu JL. Analysis of the clinicopathological features and prognostic factors of primary hepatic neuroendocrine tumors. ONCOL LETT. 2018;15(6):8604–10.
2. Huang YQ, Xu F, Yang JM, Huang B. Primary hepatic neuroendocrine carcinoma: clinical analysis of 11 cases. Hepatobiliary Pancreat Dis Int. 2010;9(1):44–8.
3. Citterio D, Pusceddu S, Facciorusso A, Coppa J, Milione M, Buzzoni R, Bongini M, DeBraud F, Mazzaferro V. Primary tumour resection may improve survival in functional well-differentiated neuroendocrine tumours metastatic to the liver. Eur J Surg Oncol. 2017;43(2):380–7.

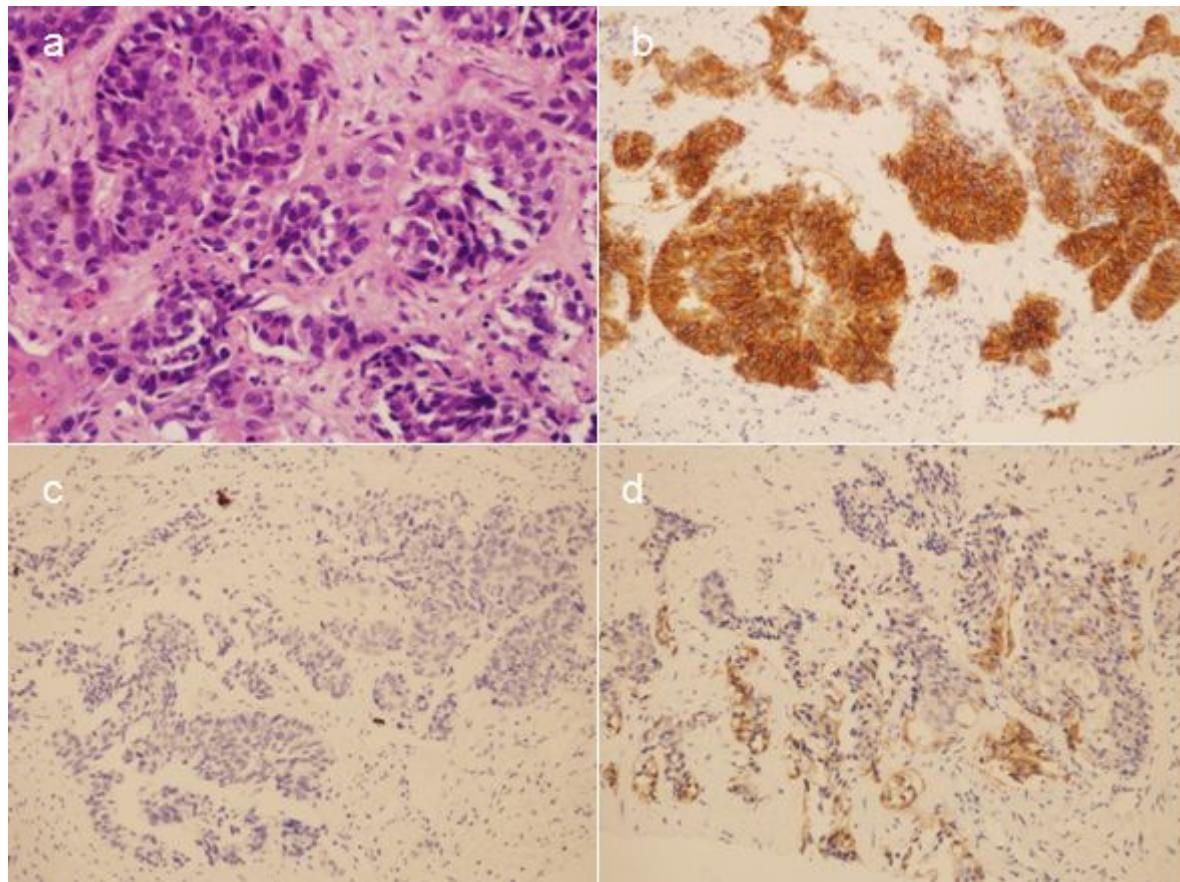
4. Yang K, Cheng YS, Yang JJ, Jiang X, Guo JX. Primary hepatic neuroendocrine tumor with multiple liver metastases: A case report with review of the literature. *World J Gastroenterol.* 2015;21(10):3132–8.
5. Yang K, Cheng YS, Yang JJ, Jiang X, Guo JX. Primary hepatic neuroendocrine tumor with multiple liver metastases: A case report with review of the literature. *World J Gastroenterol.* 2015;21(10):3132–8.
6. Wang LX, Liu K, Lin GW, Jiang T. Primary hepatic neuroendocrine tumors: comparing CT and MRI features with pathology. *CANCER IMAGING.* 2015;15(1):13.
7. Yang K, Cheng YS, Yang JJ, Jiang X, Guo JX. Primary hepatic neuroendocrine tumors: multi-modal imaging features with pathological correlations. *CANCER IMAGING.* 2017;17(1):20.
8. Orlefors H, Sundin A, Garske U, Juhlin C, Oberg K, Skogseid B, Langstrom B, Bergstrom M, Eriksson B. Whole-body (11)C-5-hydroxytryptophan positron emission tomography as a universal imaging technique for neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and computed tomography. *J Clin Endocrinol Metab.* 2005;90(6):3392–400.
9. Kwekkeboom DJ, Krenning EP. Somatostatin receptor imaging. *SEMIN NUCL MED.* 2002;32(2):84–91.
10. Ibrahim ME, Abadeer K, Zhai QJ, Nassar A. Primary Hepatic Neuroendocrine Tumor with Unusual Thyroid Follicular-Like Morphologic Characteristics. *Case Rep Pathol.* 2017;2017:7931975.
11. Qiu MJ, Chen YB, Bi NR, Yang SL, He XX, Xiong ZF: Comparative Clinical Analysis of Gastroenteropancreatic Neuroendocrine Carcinomas with Liver Metastasis and Primary Hepatic Neuroendocrine Carcinomas. *DIS MARKERS* 2018, 2018:9191639.
12. Pastrián LG, Ruz-Caracuel I, Gonzalez RS. Giant Primary Neuroendocrine Neoplasms of the Liver: Report of 2 Cases With Molecular Characterization. *INT J SURG PATHOL.* 2019;27(8):893–9.
13. Rickman DS, Beltran H, Demichelis F, Rubin MA. Biology and evolution of poorly differentiated neuroendocrine tumors. *NAT MED.* 2017;23(6):1–10.
14. Patel P, Galoian K. Molecular challenges of neuroendocrine tumors. *ONCOL LETT.* 2018;15(3):2715–25.
15. Kwon HJ, Kim JW, Kim H, Choi Y, Ahn S. Combined Hepatocellular Carcinoma and Neuroendocrine Carcinoma with Ectopic Secretion of Parathyroid Hormone: A Case Report and Review of the Literature. *J Pathol Transl Med.* 2018;52(4):232–7.

## Figures



**Figure 1**

a & b PET-CT showed diffuse lesions of whole liver and uneven thickening of the rectal wall respectively.



**Figure 2**

a Histopathology analysis of the liver showed heterotypic cell nests (magnification  $\times 400$ ). b & c & d Tumor immunology markers of liver lesions were positive for CD56,CgA and Syn (magnification  $\times 100$ )

## Supplementary Files

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