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**Primary hepatic neuroendocrine tumor — 18F-fluorodeoxyglucose positron emission tomography/computed tomography findings: A case report**

Rao YY *et al*. A case report of PHNET

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**Abstract**

BACKGROUND

Primary hepatic neuroendocrine tumors (PHNETs) are rare hepatic tumors. Their diagnosis, which is based on radiological findings, is difficult.

CASE SUMMARY

We present a case of PHNET in a 79-year-old man with no clinical symptoms. Computed tomography (CT) and 2-Deoxy-2-[fluorine-18] fluorodeoxyglucose positron emission tomography/CT (18F-FDG PET/CT) were performed for further evaluation. A hypoattenuating mass with rim-like enhancement in segment 6 of the liver was detected on contrast-enhanced CT imaging. Increased uptake was also observed on 18F-FDG PET/CT. Histopathological and immunohistochemical examinations, which revealed a grade 2 neuroendocrine tumor (NET), confirmed the diagnosis.

CONCLUSION

Diagnosing PHNET is challenging, and must be distinguished from other liver tumors. Metastatic NETs should be excluded.

**Key Words:** Hepatic tumor; Neuroendocrine; Positron emission tomography; Computed tomography; Case report

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**Core Tip:** Primary hepatic neuroendocrine tumors (NETs) are rare hepatic tumors. The diagnosis of these tumors, based on radiological observations, is difficult, and requires distinguishing them from other liver tumors and excluding metastasized NETs. 18F-fluorodeoxyglucose positron emission tomography/computed tomography is helpful when excluding extrahepatic diseases and evaluating the prognosis. Pathological diagnosis based on histological and immunohistochemical evaluation is regarded as the standard diagnosis. Complete surgical resection is the only curative option. For inoperable cases, transarterial chemoembolization, chemotherapy, and radiofrequency ablation are alternative treatment methods.

**INTRODUCTION**

Neuroendocrine tumors (NETs) are relatively rare. Their incidence in the general population depends on the speciﬁc anatomic location. NETs can arise at almost any anatomical site of the body, and it most commonly develops in the gastrointestinal tract and bronchopulmonary system (73.7% and 25.1%, respectively)[1]. Metastases are the most common diagnostic considerations for hepatic NETs[2]. Primary hepatic NETs (PHNETs) are rare, with a low incidence of 0.3% among all NET cases[3]. Little is known about it because of its rarity. We present the case of a patient with PHNET who underwent 2-deoxy-2-[fluorine-18] fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT).

**CASE PRESENTATION**

***Chief complaints***

A 79-year-old man presented to our hospital with an incidentally identified liver mass during a routine health checkup.

***History of present illness***

The patient had no clinical symptoms, such as nausea, vomiting, fever, flushing, or abdominal pain.

***History of past illness***

The patient had a 10-year history of diabetes.

***Personal and family history***

The patient had no remarkable family history.

***Physical examination***

The physical examination revealed no abnormal findings.

***Laboratory examinations***

The blood serum levels of CEA (5.4 ng/mL; reference range 0-4.7), CA19-9 (52.4 U/mL; reference range 0-27), and CA12-5 (141 U/mL; reference range 0-35) were elevated. The alpha fetoprotein serum level was normal.

***Imaging examinations***

CT and 18F-FDG PET/CT demonstrated a solitary mass measuring 40 mm × 37 mm in the liver's right lower lobe. Multidetector abdominal CT showed a well-circumscribed, heterogeneous, hypoattenuating mass. After contrast material was injected, the tumor was less enhanced than the adjacent normal liver with mild to moderate peripheral enhancement during the arterial, portal venous, and equilibrium phases (Figure 1). No cirrhosis was observed. 18F-FDG PET/CT images were obtained using a Gemini TF 64 PET/CT scanner (Philips, The Netherlands). 18F-FDG PET/CT showed increased uptake in the liver mass with a SUVmax of 5.1. The SUVmax of the liver background was 2.0 (Figure 2). Except for the liver lesion, no extrahepatic abnormal activities were found on whole-body 18F-FDG PET/CT.

**FINAL DIAGNOSIS**

An ultrasound-guided liver biopsy was performed. Histological examination demonstrated a well-differentiated neoplasm with the trabecular and glandular architectural pattern. The Ki-67 proliferation index was about 15% in tumor cells. Immunohistochemical staining revealed positive immunoreactivities for CD56, cytokeratin (CK) AE1/AE3, synaptophysin (Syn), and negative immunoreactivities for CDX-2, chromogranin A (CgA), thyroid transcription factor (TTF-1). Histological and immunohistochemical examinations confirmed that the tumor was NET grade 2, based on the World Health Organization 2019 criteria (Figure 3)[4].

**TREATMENT**

Due to severe pulmonary dysfunction, the patient could not tolerate surgery. He underwent one course of transcatheter arterial chemoembolization (TACE) with epirubicin (total dose of 50 mg) mixed with gelatin sponge particles and lipiodol. The patient’s blood serum levels of CEA (5.9 ng/mL; reference range 0-4.7), CA19-9 (109.2 U/mL reference range 0-27), and CA12-5 (166 U/mL reference range 0-35) were elevated. Abdominal magnetic resonance images showed no decrease in tumor size. Thus, the patient was treated by three courses of chemotherapy.

**OUTCOME AND FOLLOW-UP**

Partial response was achieved, and no extrahepatic lesions were radiologically found during the 18-mo follow-up. The patient was finally diagnosed with PHNET.

**DISCUSSION**

PHNET is a rare NET entity arising from Kulchitsky cells originating from the neural crest[2]. The total number of PHNET reported in the English literature is less than 200[5]. Due to its rarity, the clinical features and image findings are not well understood.

A classification system for neuroendocrine neoplasms (NENs) was established in 2000 and updated in 2019. Based on their molecular differences, NENs are divided into well-differentiated NETs and poorly differentiated neuroendocrine carcinomas[1]. NETs are classified into three grades (G1, G2, and G3) according to their mitotic rate (mitoses/2 mm²) and Ki-67 proliferation index[4].

PHNETs are considered foregut carcinoid tumors, which typically grow slowly and have no function. They are commonly detected incidentally, occur in patients between 40-50 years of age, and are located in the liver's right lobe[2,6].

Previous studies have shown that tumor markers such as alpha-fetoprotein, carcinoembryonic antigen, and CA 19-9 have no diagnostic value for PHNET[5]. Imaging examinations, such as ultrasound, CT, and magnetic resonance imaging, also have low sensitivity and specificity for PHNET. Both primary tumors and metastases appear at a low density on plain CT imaging. Hepatic metastases of NETs demonstrate rim enhancement in the arterial phase with washout in the portal venous and equilibrium phases. A similar enhancement is observed in PHNETs[3,7].

The pathological diagnosis, which is based on histological and immunohistochemical evaluations, is the standard diagnosis. Liver metastases of NETs are more common than PHNETs, and no significant radiological difference is found between them. Thus, diagnosing PHNET is challenging, and metastatic NETs should have been excluded[8].

In this study, immunohistochemical examinations revealed positive immunoreactivities for CD56, CK AE1/AE3, Syn, which confirmed the tumor was a NEN. Negative expressions of CDX-2 and TTF-1 helped rule out the possibility of small bowel, appendix, lung, and thyroid origins. Thus, we confirmed the diagnosis by histology and imaging methods, such as 18F-FDG PET/CT.

A previous study investigated the utility of 18F-FDG PET in patients with NET grades 1 and 2. The results of 18F-FDG PET examinations were positive in 57% of patients with NET G1, and 66% of patients with NET G2[9]. Sansovini *et al*[10] demonstrated that patients with negative FDG PET results had better outcomes than those with positive scans. FDG PET was an independent prognostic factor in advanced pancreatic NETs. Binderup *et al*[11] showed that compared to traditional markers, such as the Ki-67 index, 18F-FDG PET had a higher prognostic value. Despite its low diagnostic sensitivity, 18F-FDG PET/CT has a high prognostic value for NETs. Whole-body 18F-FDG PET/CT is helpful for excluding extrahepatic diseases[12].

Complete surgical resection is the only curative option, and it results in a 5‑year survival rate of 74%-78%. Up to 85% of tumors are resectable[3,13]. Alternative treatment methods for inoperable cases include TACE, chemotherapy, and radiofrequency ablation. Yao *et al*[14] reported that hepatic chemoembolization for NETs effectively improved clinical symptoms and achieved tumor control. In our case, the patient had severe pulmonary dysfunction, and surgery was not considered. Therefore, the patient received TACE with epirubicin. After one course of TACE, no decrease of the tumor size was observed, and the patient’s serum levels of CEA, CA19-9, and CA12-5 were increased. The ENETS consensus Guideline for the standards of care in NEN suggests that chemotherapy might be considered in NETs of other sites (lung, stomach, colon, *etc.*) when the Ki-67 is at a high level (upper G2 range) or after failure of other therapies[15]. Under these circumstances, the patient received three courses of chemotherapy, and partial response was achieved.

**CONCLUSION**

In conclusion, PHNET is a rare liver tumor that presents with nonspecific clinical symptoms. Its diagnosis should be made based on immunohistochemistry findings, and metastatic NETs need to be excluded. 18F-FDG PET/CT can help exclude extrahepatic lesions. Surgical resection is the curative treatment, but other methods, such as TACE, can be administered in patients with unresectable PHNET.

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**Footnotes**

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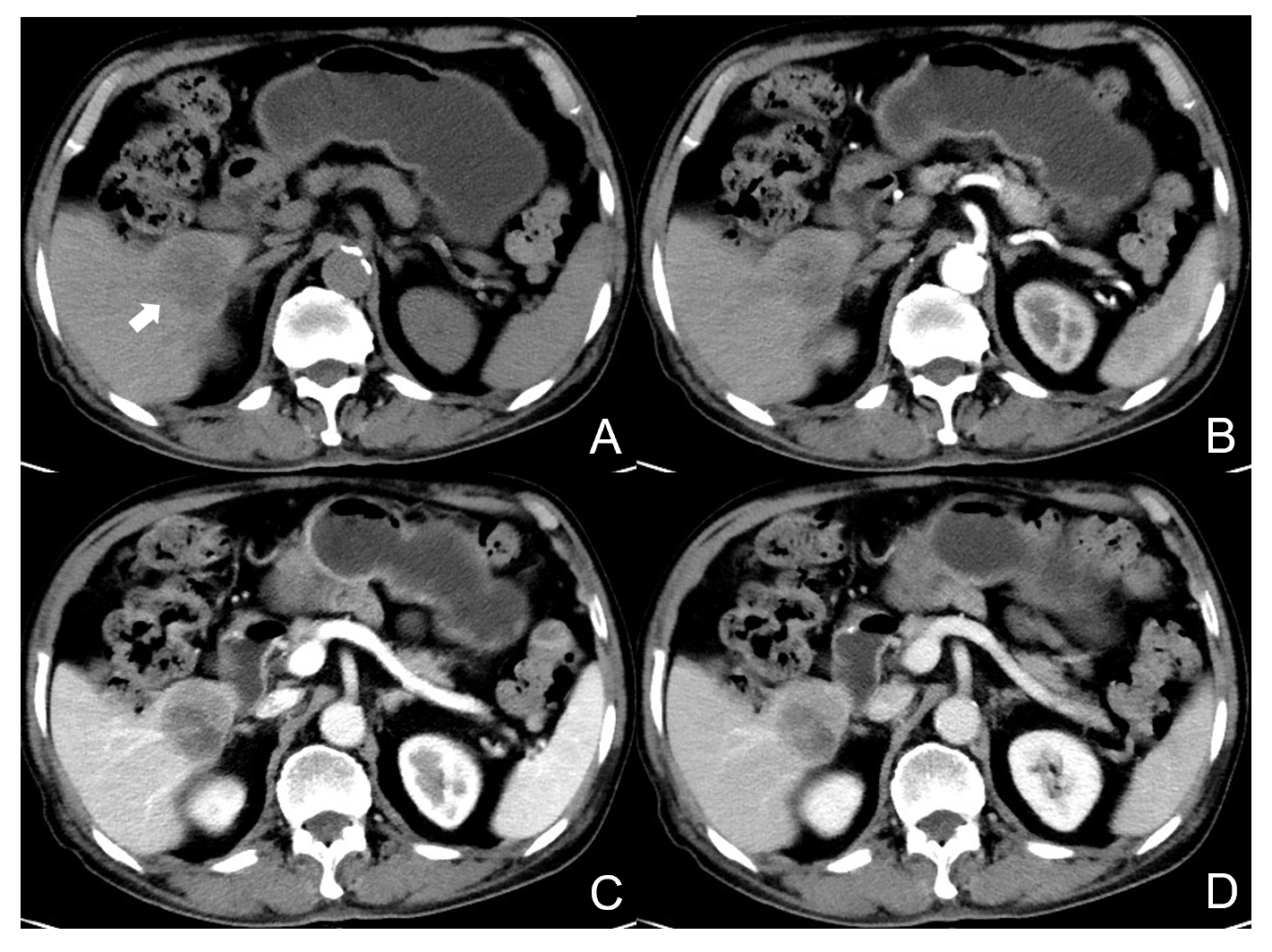
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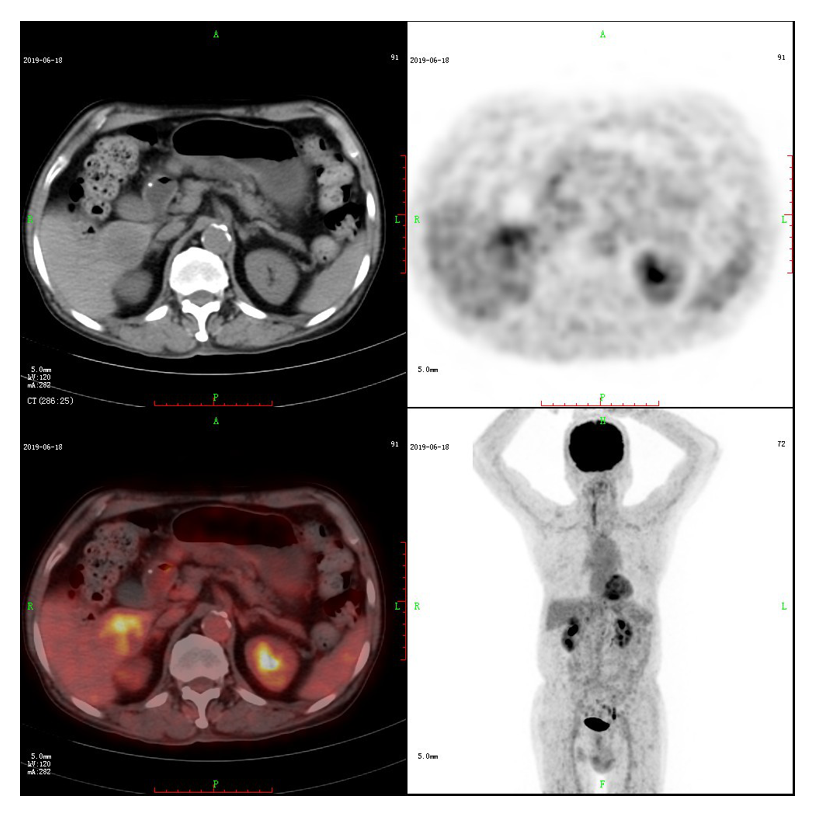
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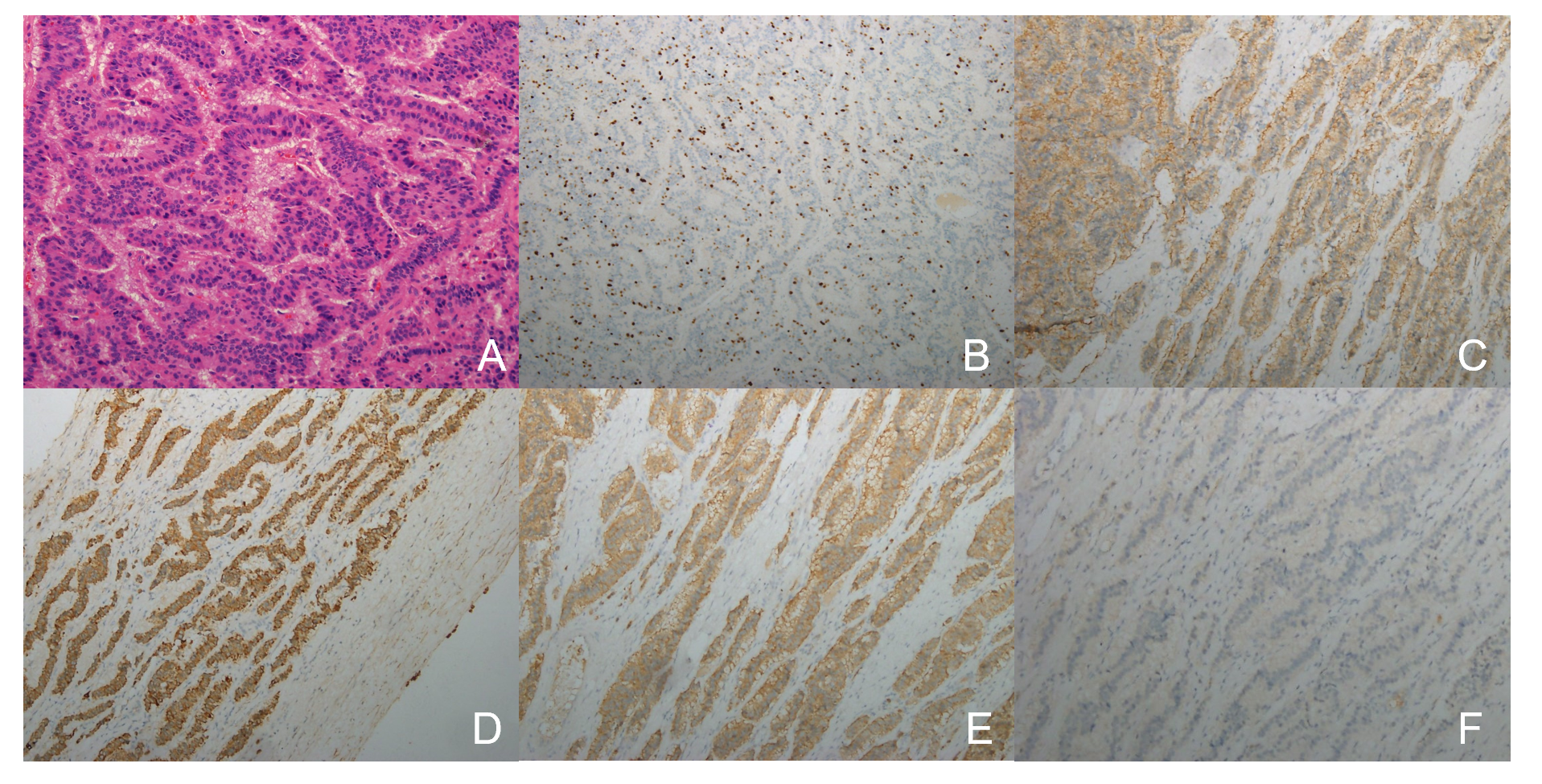
**Figure Legends**



**Figure 1 Contrast-enhanced** **computed tomography images of the tumor.** A: Non-contrast-enhanced computed tomography (CT) images reveal a 40 mm × 37 mm, well-circumscribed, heterogeneous hypoattenuating mass in the right lower lobe of the liver (arrow); B-D: Dynamic CT images demonstrate a rim-like enhancement of the tumor in the arterial phase (B); portal venous phase (C); and equilibrium phase (D). The tumor is less enhanced than the adjacent liver.



**Figure 2 Positron emission tomography (PET) with 2-deoxy-2-[fluorine-18] fluoro-D-glucose images.** On18F-positron emission tomography/computed tomography imaging, the tumor shows increased uptake with a SUVmax of 5.1. Whole-body 2-deoxy-2-[fluorine-18] fluoro-D-glucose positron emission tomography reveals no abnormal extrahepatic activities.



**Figure 3 Pathological findings.** A: Hematoxylin and eosin-stained sections (× 200 magnification) demonstrate a well-differentiated neoplasm with the trabecular and glandular architectural pattern; B: The Ki-67 proliferation index (× 100 magnification) is 15% in tumor cells; C-F: Immunohistochemical staining (× 100 magnification) reveals positive immunoreactivities for CD56 (C), cytokeratin AE1/AE3 (D), synaptophysin (E), and negative immunoreactivity for chromogranin A (F), respectively.