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Case Report

Primary Hepatic Neuroendocrine Carcinoma with Metastasis to the Mesentery: A Case Report

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Keywords
Neuroendocrine carcinomas · Debulking operations · Chemotherapy · Transcatheter arterial chemoembolization

Abstract
Primary hepatic neuroendocrine carcinomas (PHNECs) are extremely rare, with only about 90 cases having been reported in the English-language literature. Among all neuroendocrine neoplasms, primary hepatic neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) are extremely rare, accounting for 0.3% of NETs and 0.28–0.46% of malignant liver tumors. Additionally, primary hepatic NECs occur infrequently. The clinical diagnosis of primary hepatic NEC remains challenging because of its rarity and the lack of information about its characteristic appearance on images. Consequently, pathological examination through the performance of a preoperative liver tumor biopsy is essential for diagnosis. Due to the lack of availability of substantial high-quality data, there is no standard therapy for primary hepatic NEC. We present the first case of PHNEC metastasized to the mesentery reported in the English-language literature.

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Introduction

Neuroendocrine are neoplasms exclusively made by cells with a neuroendocrine phenotype. High-grade neuroendocrine neoplasms (NENs) of the gastrointestinal (GI) tract and pancreas are a heterogeneous group of aggressive malignancies [1, 2]. The 2010 and 2019 World Health Organization (WHO) classification of tumors of the digestive system, consider all neuroendocrine tumors (NETs) (e.g., gastroenteropancreatic) as malignant and classify them by cellular proliferation and degree of differentiation [2, 3].

The current WHO defines neuroendocrine carcinomas (NECs) as they are high-grade neoplasms (grade 3 tumor), poorly differentiated in phenotype, since it has >20 mitoses/10 high-power fields, has a Ki-67 proliferation index >20%, and could be of the large or small cell type [3, 4]. In general, all high-grade, poorly differentiated gastroenteropancreatic NECs have an aggressive natural history that is frequently characterized by early, widespread metastases [5].

Among all NENs, primary hepatic NETs and NECs are extremely rare, accounting for 0.3% of NETs and 0.28–0.46% of malignant liver tumors. Additionally, primary hepatic NECs occur infrequently [1].

Incidence rate of liver NEC was estimated to be 0.01 per 100,000 habitants. In liver NEC, there is a male predominance of 0.02. Primary hepatic NEC is most frequent in American Indian/Alaska Natives. The median age at diagnosis was 65 years [6–9].

The clinical diagnosis of primary hepatic NEC remains challenging because of its rarity and the lack of information about its characteristic appearance on images. When NEC of uncertain origin is diagnosed by liver tumor biopsy, it is extremely important to perform preoperative workup, including gastroscopy, colonoscopy, and Gallium-68 DOTATATE positron emission tomography – computed tomography (PET-CT) examinations, because NENs of the liver are usually metastatic from other organs, such as the GI tract and pancreas [9, 10].

We present a 22-year-old female patient with a primary hepatic neuroendocrine carcinoma (PHNEC) with mesentery metastases. As it is an exceptionally unusual presentation, it represents a diagnostic challenge.

Clinical Case

A 22-year-old Mexican woman presented to our medical oncology department. The family and personal inherited antecedents have no relevance to the case. The patient presented with abdominal pain, discomfort abdominal, constipation, asthenia, adynamia, weight loss of 9 kg in 6 months. Abdominal ultrasound reported an expansive-looking mass in the right hepatic lobe of 93 mm × 73 mm × 74 mm, without cholelithiasis. A simple and contrast-enhanced CT scan of the abdomen and pelvis reported a mesenteric tumor of 126 × 96 mm, hepatomegaly, and a liver tumor of approximately 20 cm in both lobes (Fig. 1).

A percutaneous biopsy was performed on where poorly differentiated neoplastic cells were reported. Immunohistochemistry reported: positive AE1/AE3, positive chromogranin, positive synaptophysin (Syn), positive CD99, negative CD56, positive β-catenin, negative progesterone. High-grade NEC of the small cell type of liver was reported (Fig. 2).

Gastroscopy and colonoscopy were performed; however, no evidence of tumor was reported. One year ago, palliative chemotherapy based on etoposide and cisplatin was started every 21 days for 6 cycles.

Control CT scan was performed where stable disease was reported. Subsequently, she presented with headache, loss of bitemporal vision, and CT scan of the skull with contrast, which reported pituitary macroadenoma, confirmed with magnetic resonance imaging (MRI).

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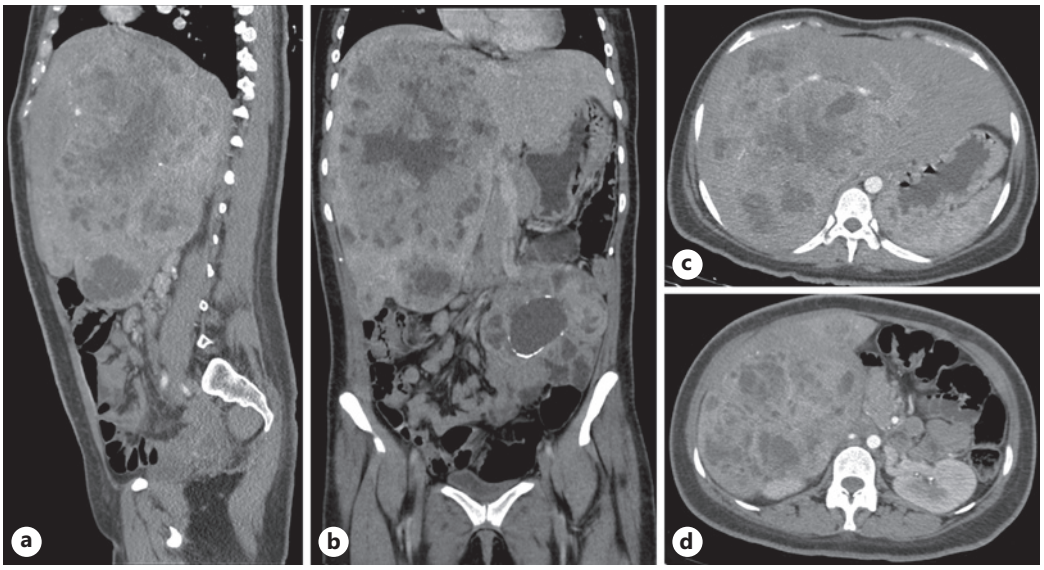

Fig. 1. Chest-abdomen-pelvis computed tomography (CT) scan. Coronal (**a**, **b**) and axial (**c**, **d**) CT projections showing a voluminous abdominal mass (mesenteric tumor) of 126 × 96 mm, and liver tumor of 213 mm × 155 mm in both lobes with significant contrast enhancement due to hypervascularization (**a–d**).

A hormonal profile was requested to evaluate the hypothalamic-pituitary axis, where it was reported to be elevated prolactin. Ten months ago, she started cabergoline 0.5 mg orally every week and lanreotide 20 mg every month.

She went to the emergency room with asthenia, adynamia, vomiting, diarrhea, acute abdominal pain. Eight months ago, an exploratory laparotomy was performed, with complete removal of mesentery tumor (Fig. 3).

The histopathological report was high-grade NEC of small cell type, metastatic, 12.5 cm × 9.4 cm × 6.3 cm, with necrosis in 40%, mitotic count of 18 mitoses/10 high-power fields, extensive lympho-vascular invasion was identified, no residual tissue was identified.

Subsequently, she continued with cabergoline 0.5 mg orally every week and lanreotide 60 mg every month, and surveillance. Control CT was performed where stable disease of the liver tumor and complete response of the mesenteric tumor were reported.

During her follow-up, Gallium-68 DOTATATE PET-CT scan was performed, every 6 months. The last report 1 month ago, showed primary liver tumor activity, with a tumor in the right lobe measuring 12 cm × 18.9 cm × 28.6 cm, SUV max of 20.7, and another tumor in the left lobe of 6.2 cm × 0.5 cm, SUV max of 14.2, but no evidence of tumor in mesentery. Stable disease was concluded based on the response evaluation criteria in the solid tumor guide version 1.1 (RECIST 1.1) (Fig. 4).

Currently, the patient is asymptomatic with stable liver tumor disease, 14 months after diagnosis, and without recurrence of the mesentery tumor, 8 months after its complete removal. She is scheduled to start external beam radiation therapy (EBRT) as a bridging treatment for the liver transplant next month.

Discussion

Primary hepatic neuroendocrine tumors (PHNETs) are a rarity and represent about 0.3% of all NETs, with only about 180 cases having been reported in the English-language literature. This number includes both primary hepatic NETs and NECs. Primary hepatic neuroendocrine

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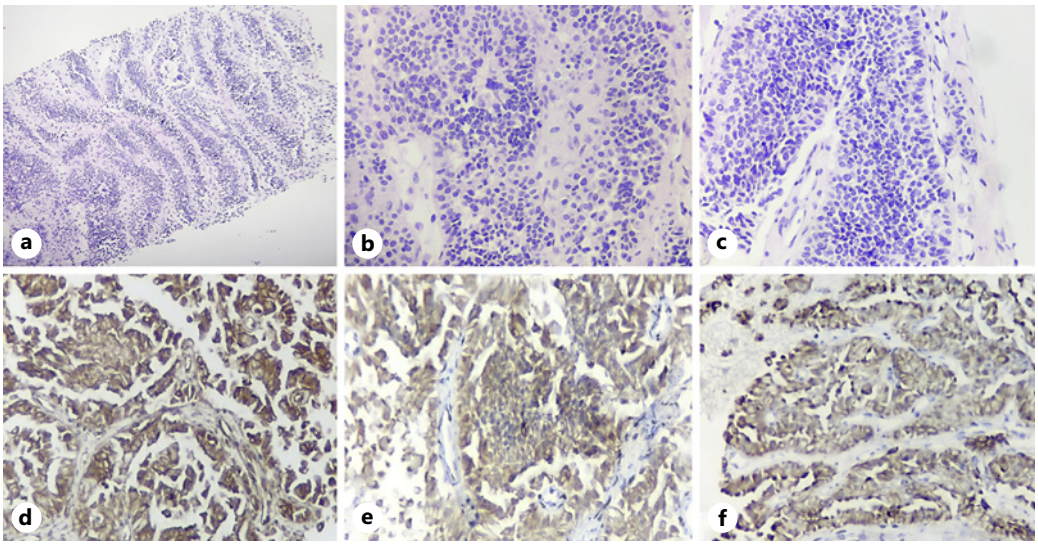

Fig. 2. a The microscopic study showed small, blue, round tumor cells disposed in cords, festoons, and glandular formation. **b**, **c** The tumor cells are small with uniform nuclei, round/oval with salt, and pepper chromatin and inconspicuous nucleoli. Immunohistochemistry revealed positive staining for CKAE1/AE3 in the cellular membrane (**d**), chromogranin with granular cytoplasmic pattern (**e**), and CD99 in the cellular membrane (**f**).

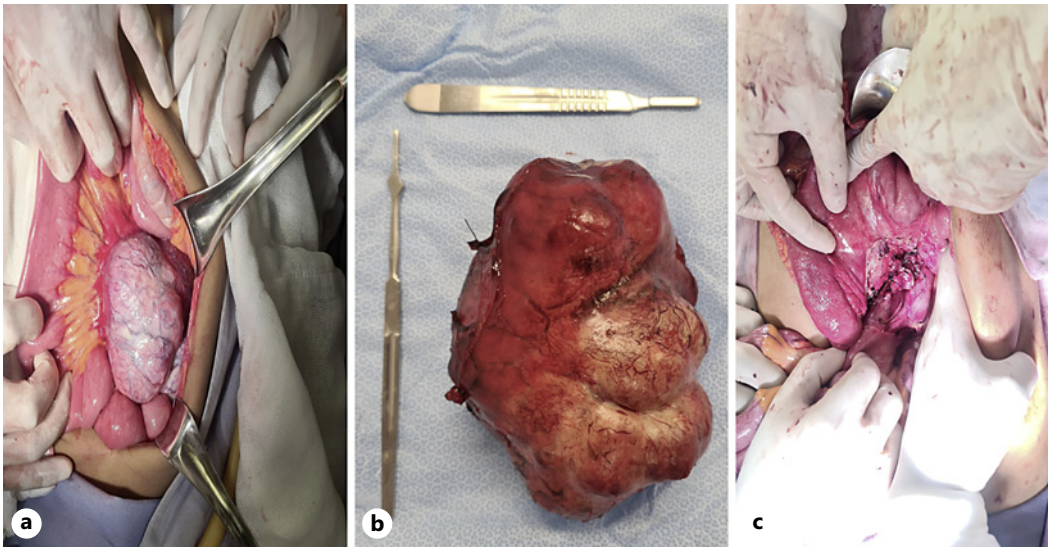

Fig. 3. Tumor resection. **a** A tumor is observed at the level of the mesentery. **b** Complete removal of the 130 × 100 mm mesentery tumor. **c** Macroscopically without evidence of residual disease at the level of the mesentery.

carcinomas (PHNECs) are extremely rare, with only about 90 cases having been reported in the English-language literature [10–50] (Table 1).

During 2000–2012, the incidence rates of high-grade NENs, increased over time for all sites, except for the lung. Liver NEC is most frequent in American Indian/Alaska Native than in other races (white, black, Asian/Pacific Islander). The median age at diagnosis is 65 years. Incidence rates of liver NEC is of 0.01 per 100,000 habitants. In most series, incidence rates

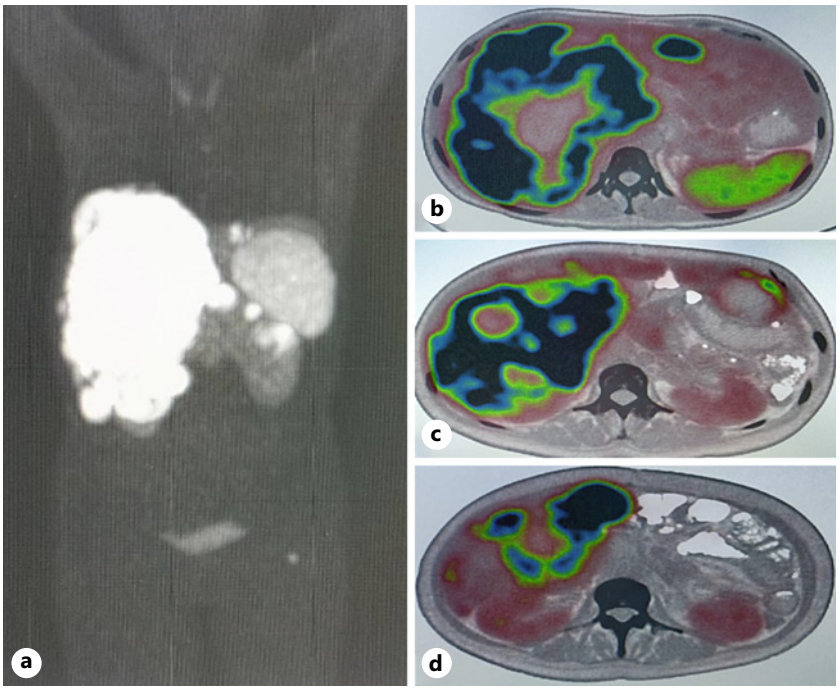

Fig. 4. Gallium-68 DOTATATE positron emission tomography (PET)/computed tomography (CT) scan demonstrating increased DOTATATE uptake (SUVmax 20.7) in the right lobe of the liver of 12 × 18.9 × 28.6 cm, and increased DOTATATE uptake (SUVmax 14.2) in the left lobe of 6.2 cm × 0.5 cm, as shown in coronal (**a**) and transaxial (**b–d**) views. No evidence of tumor in mesentery.

are similar in males and females. However, in liver NEC, there is a male predominance of 0.02 versus 0.01 [1, 6, 7]. Our case involves a 22-year-old Mexican woman who initially presented with a liver tumor under study.

In a separate analysis of over 162,000 cases of NEC reported to Surveillance, Epidemiology, and End Results (SEER) between 1973 and 2012, the upper GI tract and the pancreas accounted for 23 and 20 percent, respectively, of the NECs. About 3% were coded as liver primary, although it is likely that the majority of these were metastases. The form of presentation is localized or intrahepatic (29.9%), regional or nodal (33.1%), and metastatic (37.1%) [6, 10, 11]. According to the characteristics of the imaging studies performed on our patient, a tumor was reported in both hepatic lobes that was metastatic to the mesentery.

NENs are a heterogeneous group of tumors originating from enterochromaffin cells throughout the body, which most commonly develop in the GI tract, lungs, pancreas, gallbladder, thymus, and ovaries. The liver is the most common metastatic site of NENs but a rare site of tumor origin [5, 8, 11].

Presently, the origin of PHNECs is controversial. There are three hypotheses about the origin of PHNEC: (1) it is transformed from neuroendocrine cells of the intrahepatic bile duct epithelium. (2) It originates from multifunctional stem cells in the liver. (3) It originates from the ectopic adrenal and pancreatic tissues in the liver [50].

The clinical diagnosis: patients are usually asymptomatic (13%) at the early stages and are often discovered incidentally during physical examination. At the middle and late stages, patients may present symptoms such as abdominal discomfort or abdominal pain (44%), bloating, loss of appetite, weight loss, and obstructive jaundice (5%) as the tumor grows, and very few patients show signs of carcinoid syndrome, such as flushing, diarrhea, asthma, fever, and palpitations. Most patients have a single lesion (76.6%) located commonly in the right

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Table 1. Summary of cases report of PHNEC

No	Author, years	Sex/ age, years	Symptom	Location	Tumor size, cm	Metastasis	Recurrence in months	Site of recurrence	Treatment	Classification	Survival in months (status)
1	Judge, 1976 [12]	M/19	Jaundice, abdominal pain, weight loss, diarrhea	Both lobes	5	LN, pancreas	None	None	ND	Metastatic	0.2 (died)
2	Ali, 1978 [13]	F/48	Hypoglycemia, palpable abdominal mass	Right lobe	14	LN, pubic bone	2.5	Liver	RT using Cobalt 60 and chemotherapy (cytoxan and adriamycin)	Metastatic	4.1 (died)
3	Warner, 1980 [14]	M/62	Palpable abdominal mass	Left lobe	13.8 × 9	LN	None	None	Surgery	Regional	2 (alive)
4	Hsueh, 1983 [15]	F/8	Dizziness, fatigue	Right lobe	17 × 11.5 × 7	LN, right atrium and ventricle, lung	None	None	Surgery and chemotherapy (platinum)	Metastatic	4 (died)
5	Xi and Yu, 1986 [16]	F/83	Palpable abdominal mass	Right lobe	8.5 × 7 × 6	LN, lung	None	None	ND	Metastatic	0.03 (died)
6	Tsuchimochi, 1995 [17]	M/45	Jaundice	ND	12 × 16	Lung, bone	None	None	ND	Metastatic	0.03 (died)
7	Zanconati, 1996 [18]	M/56	Abdominal discomfort, jaundice	ND	5	ND	3	Liver	Surgery	Metastatic	5 (died)
		M/69	Weight loss	ND	10	ND	None	None	Surgery	Metastatic	1 (died)
		M/89	Jaundice, weight loss	ND	6	ND	None	None	Surgery	Metastatic	1 (died)
8	Fukunaga, 1998 [19]	M/84	Bilateral paralysis of the lower extremities, abdominal pain	ND	5 × 5 × 3	Bone, lung, pancreas, LN	None	None	Chemotherapy with cyclophosphamide, adriamycin, and cis-Diamino-dichloro-platinum (II)	Metastatic	1 (died)

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Table 1 (continued)

No	Author, years	Sex/ age, years	Symptom	Location	Tumor size, cm	Metastasis	Recurrence in months	Site of recurrence	Treatment	Classification	Survival in months (status)
9	Ferrero, 1998 [20]	F/42	Right hypochondrial pain	Both lobes	ND	None	72	Liver	Chemotherapy with octreotide and doxorubicin, TACE and Surgery	Localized	120 (alive)
10	Pilichowska, 1999 [21]	M/57	Right hypochondrial mass, abdominal pain	Right lobe	8.2 × 7.3	Lung	ND	Liver	Surgery	Metastatic	16 (died)
		F/65	Fatigue, edema	Both lobes	8 × 8.5	Lung, LN	ND	LN	RT and chemotherapy with 5-fluorouridine	Metastatic	39 (died)
11	Kaya, 2001 [22]	M/72	Right hypochondrial pain	Both lobes	22 × 15 × 15	None	None	None	ND	Regional	0.1 (died)
12	Ishida, 2003 [23]	M/72	None	Right lobe	3 × 2.5	LN	None	None	Surgery	Regional	7 (alive)
13	Ishizu, 2003 [24]	M/81	Edema	Left lobe	6	Bone marrow	None	None	ND	Metastatic	0.4 (died)
14	Dala, 2006 [25]	M/73	Weight loss, right hypochondrial pain	Right lobe	15 × 10	None	None	None	Surgery	Localized	12 (alive)
15	Ishibe, 2006 [26]	M/51	Palpable epigastric mass	Left lobe	11.5 × 7 × 11	LN	None	None	Surgery and chemotherapy with UFT	Regional	13 (alive)
16	Garcia, 2006 [27]	M/50	None	Both lobes	5	None	4	Liver, mesenteric	Surgery, P-chemotherapy, TACE, chemotherapy with doxorubicin, thalidomide and bevacizumab	Regional	16 (alive)
17	Yasuda, 2006 [28]	M/71	None	Both lobes	7	LN, pancreas, aorta, gallbladder	None	None	Chemotherapy with tegafur and paclitaxel	Metastatic	5 (died)

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Table 1 (continued)

No	Author, years	Sex/ age, years	Symptom	Location	Tumor size, cm	Metastasis	Recurrence in months	Site of recurrence	Treatment	Classification	Survival in months (status)
18	Yang, 2009 [29]	M/65	Epigastric pain	Both lobes	7.5	LN	3	Liver	Surgery	Regional	12 (died)
		M/56	None	ND	ND	None	None	None	Surgery	Localized	36.9 (alive)
		F/68	Fatigue	ND	ND	None	None	None	Surgery	Localized	18 (alive)
		F/51	None	ND	ND	None	6.2	Liver	Chemotherapy and surgery	Localized	15.2 (alive)
19	Akahoshi, 2010 [30]	M/64	None	Left lobe	1.5	None	None	None	Surgery	Localized	3 (alive)
20	Huang, 2010 [31]	M/51	Abdominal pain	ND	ND	None	48	Liver	TACE and surgery	Localized	107 (alive)
		M/34	None	ND	ND	None	None	None	TACE and surgery	Localized	98 (alive)
		F/52	Diarrhea	ND	ND	None	5	Liver	Surgery	Localized	47 (alive)
		M/59	None	ND	ND	None	None	None	Surgery	Localized	34 (alive)
		M/54	None	ND	ND	None	None	None	Surgery	Localized	24 (alive)
		M/43	Abdominal pain	ND	ND	None	None	None	Surgery	Localized	15 (alive)
		F/50	None	ND	ND	None	5	Liver	Surgery	Localized	14 (alive)
		M/37	Diarrhea	ND	ND	None	1	Liver	Surgery	Localized	13 (alive)
		F/58	None	ND	ND	None	39	Liver	Surgery	Localized	148 (alive)
		F/56	None	ND	ND	None	5	Liver	Surgery	Localized	33 (alive)
		M/50	None	ND	ND	None	3	Liver	Surgery	Localized	12 (alive)
21	Lee, 2011 [32]	F/49	Right hypochondrial pain	Right lobe	8 × 6	None, liver, rib, lung, kidney 2	2	Liver, bone, lung, kidney	Surgery, TACE, RT	Metastatic	5 (died)
22		M/68	None	Left lobe	4	None	None	None		Localized	28 (alive)

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Table 1 (continued)

No	Author, years	Sex/ age, years	Symptom	Location	Tumor size, cm	Metastasis	Recurrence in months	Site of recurrence	Treatment	Classification	Survival in months (status)
	Tazi, 2011 [33]								Surgery, P-chemotherapy with etoposide		
23	Park, 2012[9]	M/78	Epigastric pain	ND	ND	None	None	None	P-chemotherapy with 5-fluorouridine	Metastatic	3 (died)
		M/76	None	ND	ND	None	None	None	P-chemotherapy with 5-fluorouridine	Metastatic	6.2 (died)
		M/37	None	ND	ND	None	None	None	Conservative care	Localized	41.7 (alive)
		M/79	Epigastric pain	ND	ND	None	None	None	Conservative care	Regional	2 (died)
		M/62	Right hypochondrial pain	ND	ND	Bone, LN	None	None	P-Chemotherapy	Metastatic	26.4 (died)
		F/56	None	ND	ND	None	None	None	Surgery	Localized	36.9 (alive)
		F/80	Poor oral intake	ND	ND	None	None	None	Conservative care	Regional	0.7 (died)
		F/44	Abdominal discomfort	ND	ND	None	None	None	P-chemotherapy with 5-fluorouridine and TACE	Regional	11.3 (died)
		F/68	Fatigue	ND	ND	None	None	None	Surgery	Localized	18 (alive)
		M/65	None	ND	ND	Bone, LN	None	None	TACE	Metastatic	17.7 (alive)
		M/74	Right hypochondrial pain	ND	ND	Bone, LN	None	None	Conservative care	Metastatic	24.4 (alive)
		F/51	None	ND	ND	None	None	None	P-chemotherapy with 5-fluorouridine and surgery	Localized	15.2 (alive)
24	Kim, 2013 [34]	F/67		Both lobes	10.5 × 10 × 5	None	None	None	Surgery	Regional	3 (alive)

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Table 1 (continued)

No	Author, years	Sex/ age, years	Symptom	Location	Tumor size, cm	Metastasis	Recurrence in months	Site of recurrence	Treatment	Classification	Survival in months (status)
			Nausea, right hypochondrial mass								
25	Shinkawa, 2013 [35]	M/73	None	Right lobe	7 × 6	Bone, LN	4	LN, Bone	TACE, surgery	Metastatic	6 (died)
26	Kano, 2014 [36]	M/73	Abdominal pain, general malaise	Right lobe	3 × 2.6	LN, skin tissue	6	Liver	Surgery, chemotherapy with everolimus and somatostatin analog	Metastatic	10 (alive)
27	Sotiropoulos, 2014 [37]	F/19	Right hypochondrial mass, abdominal distension	Right lobe	27 × 13	None	None	None	Surgery	Localized	24 (alive)
28	Aboelenen, 2014 [38]	M/51	Abdominal pain	Right lobe	20 × 15 × 7.5	None	None	None	Surgery	Regional	6 (alive)
29	Derouich, 2015 [39]	M/53	Epigastric pain, diarrhea, abdominal distension, flush syndrome, hepatomegaly	Right lobe	ND	None	None	None	P-chemotherapy	Localized	18 (alive)
30	Choi, 2016 [40]	M/72	Abdominal mass	Left lobe	2.5 × 2	None	6	Liver	Surgery, P-chemotherapy	Regional	10 (alive)
31	Harada, 2017 [41]	F/69	None	Right lobe	3 × 2.7 × 2.5	None	1	Liver, lung	Surgery, P-chemotherapy	Regional	19 (died)
32	Nakatake, 2017 [42]	M/67	Abdominal mass	Left lobe	0.5	LN	3	LN	Surgery, P-chemotherapy	Regional	24 (alive)
33		M/61				None	None	None	TACE and P-chemotherapy	Regional	

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Table 1 (continued)

No	Author, years	Sex/ age, years	Symptom	Location	Tumor size, cm	Metastasis	Recurrence in months	Site of recurrence	Treatment	Classification	Survival in months (status)
	Zhao, 2018 [10]		Abdominal pain, hepatomegaly	Right lobe	17 × 14 × 14						2.03 (died)
		M/69	Abdominal pain, choluria	Both lobes	9.4 × 15.1	LN	None	None	Supplementary intravenous human albumin 20%	Regional	3.6 (died)
34	Zeng, 2019 [43]	F/67	Abdominal distension, weight loss	ND	ND	ND	None	None	None	Metastatic	2 (died)
35	Xin, 2020 [44]	64/F	Abdominal discomfort	Right lobe	1.8 × 1.9	None	None	None	Surgery	Localized	5 (alive)
36	Nakano, 2021 [45]	F/84	None	Right lobe	8	None	None	None	Surgery	Localized	9 (alive)
37	Seki, 2021 [11]	M/78	None	Left lobe	6.6 × 5.5	LN	4	LN	Surgery and P-chemotherapy	Regional	15 (died)
38	Grenn, 2022 [46]	F/57	Abdominal pain	Right lobe	ND	None	None	None	Surgery	Localized	14 (alive)
39	Huang K, 2022 [47]	F/50	Right hypochondrial pain	Right lobe	16.2 × 10 × 10.7	Diaphragm	1	Pancreas, retroperitoneum	Surgery	Metastatic	9 (died)
40	Cao, 2023 [48]	M/72	None	Both lobes	ND	None	3	Liver, brain, spinal cord	Platinum chemotherapy	Regional	8 (alive)
41	Shin, 2023 [49]	M/63	None	Right lobe	9 × 8 × 6	None	5	Liver, lung, kidney, brain, adrenal gland	Surgery and RT	Regional	12 (died)

ND, not described; LN, lymph nodes; RT, radiotherapy; Ch, chemotherapy; S, surgery; P-Cht, platinum-based chemotherapy; TACE, trans-arterial chemoembolization.

liver (48.4%). In our case, the patient presented a functional digestive disorder accompanied by abdominal discomfort, which led to an imaging study finding the liver tumor lesion as an incidental finding [11, 51, 52].

Imaging characteristics: PHNECs have a rich blood supply from the hepatic artery and therefore exhibit hyperenhancement in the arterial phase and washout appearance in the portal venous phase of dynamic CT and MRI resembling hepatocellular carcinomas (HCCs). Both HCCs and PHNECs show a peripheral rim of smooth hyperenhancement in the portal venous or delayed phase pathologically correlating with a tumor capsule [8, 9].

On CT, primary hepatic NEC appears as a low-density mass with an enhanced margin, and the center of the mass is not enhanced due to necrosis. MRI shows a low-intensity mass on fat-saturation T1-weighted images and a high-intensity area on fat-saturation T2-weighted images. Based on the abovementioned clinical-imaging findings, it is difficult to distinguish hepatic NECs from other hepatic carcinomas, such as HCC and cholangiocarcinoma. Consequently, pathological examination through the performance of a preoperative liver tumor biopsy is essential for diagnosis [9–52]. In our case, the patient underwent a biopsy of the liver lesion for histological diagnosis, since the characteristics in the imaging studies were not sufficient to make the diagnosis conclusively.

PHNECs are a diagnosis of exclusion since they are far less common than hepatic metastasis of NECs hence an extrahepatic primary NEC must always be excluded first through studies including endoscopy and colonoscopy (to rule out GI origin), CT, MRI, and somatostatin PET-CT (to determine the extent of the disease and its origin), as was done in our patient [51, 52]. Since the radiological and laboratory findings of PHNECs are not specific, definitive diagnosis of PHNECs needs pathologic evaluation of a surgically resected specimen [9–53].

Pathology: consequently, pathological examination through the performance of a preoperative liver tumor biopsy is essential for diagnosis. On hematoxylin and eosin staining, NECs demonstrate a solid "sheetlike" proliferation of tumor cells with irregular nuclei, high mitotic features, and less cytoplasmic secretory granules. Small-cell NEC has tightly packed fusiform nuclei with finely granular chromatin, whereas large-cell NEC has more rounded, markedly atypical nuclei and, sometimes, prominent nucleoli. Immunocytochemical (IHC) staining patterns for neuroendocrine markers are more limited diffuse expression of Syn, faint or focal staining for chromogranin A (CgA). Up to 40% of NECs contain elements of non-neuroendocrine histology; by definition, the neuroendocrine component has to exceed 30% for the tumor to be called an NEC; otherwise, it is classified as a mixed adeno-NEC. Although IHC markers effectively identify primary hepatic NENs, there is no specific IHC stain for hepatic NEC. IHC markers for NEC remain similar to those for common NENs, including CgA (89.1%) and Syn (48.9%), as previously reported by researchers. Commonly measured tumor markers in NENs include serum CgA and 5-hydroxyindoleacetic acid (5-HIAA), the final secreted product of serotonin, levels in a 24-h urine sample [11, 53]. It does not only establish the diagnosis but also the tumor grading based on the mitotic rate and the Ki-67 proliferation index which is essential for the treatment and prognosis [11].

Presentation: there is no staging for NENs of the liver, so they are classified according to the location of the disease; localized (located within the primary organ, in this case the liver), locally advanced or regional (nodal disease), and advanced or metastatic (disease in distant nodes and organs) [9, 11–52]. The size of the tumor is 1.5–27 cm, presenting as single (76.3%) and multiple in 23.7% of cases, located mainly in the right lobe in 48.4% of cases, and as bilobular in 18.5%. Knox et al. [54] reported extrahepatic involvement in 18.6% of cases, such as bone (60%), lymph node (60%), and lung (40%) [9–55]. The form of tumor presentation was two liver tumors that occupied both lobes of approximately 20 cm with metastasis to the mesentery.

Treatment: there are multiple treatment options for PHNEC. However, there is no standard therapy. In early-stage PHNEC, surgical resection of liver tumor tissue or partial hepatectomy is the most common treatment, with a 5-year survival rate after surgery of 75–80% and with a recurrence rate of 18% [8, 16].

Other therapeutic options include liver transplantation, trans-arterial chemoembolization (TACE), and radiofrequency ablation (RFA). RFA is another treatment method for PHNETs. The introduction of RFA has allowed physicians to surgically address a larger population of patients with curative intent. RFA may be performed alone or in combination with resection. To date, most reports on RFA management are single-institution retrospective series. Indications for RFA are the presence of three or fewer tumors and a tumor diameter of ≤5 cm. Tumors located near the major branches of the portal and hepatic veins have a higher potential for incomplete ablation [10, 55, 56]. Approximately 20–37% of patients are diagnosed at the metastatic or advanced stage, where platinum-based chemotherapy (etoposide + cisplatin [EP] or carboplatin [EC]) is the first-line treatment according to The European Society for Medical Oncology (ESMO) guideline [57].

Li et al. [58] evaluated the efficacy of platinum-based chemotherapy versus TACE observed a median overall survival of 14.8 months versus 12.2 months, respectively ($p = 0.040$). Furthermore, patients with Ki-67 ≥ 55% who received EP/EC had a significantly longer progression-free survival than those who received TACE (5.0 vs. 2.8 months, $p = 0.001$). This result is consistent with the observation of Sorbye et al. [59] that NENs with Ki-67 ≥ 55% display generally display a better response to platinum-based chemotherapy. Therefore, in this patient, it was decided to use EP for 6 cycles, obtaining stable disease. Debulking operations are recommended for patients with distant metastatic NETs because debulking improves symptomatic control of hormone hypersecretion and survival [8, 52, 54].

There are two possible explanations for the prognosis-prolonging effect of primary tumor resection. First, reduction of immunosuppressive tumor burden may have extended the prognosis, potentially minimizing the chance that the tumor will lead to disease progression and further metastases. Second, it is suggested that chemotherapy compliance may be improved by primary tumor resection in symptomatic patients [48, 53].

Knox et al. [54] and Iwao et al. [60] conducted studies on the survival of patients with PHNEC and showed that the 5-year survival rate of patients undergoing surgical therapy was >50% [61]. However, there are reports of case series where it has been reported that tumorectomy has been shown to prolong recurrence-free survival, so this patient underwent tumor resection of the metastatic disease to the mesentery, achieving complete metastatic resection demonstrated by imaging study.

In patients with unresectable disease, other palliative options are available, including systemic chemotherapy using fluorouracil, hepatic artery embolization, octreotide therapy, and liver transplantation. Notably, however, peptide receptor radionuclide therapy (PRRT) is mainly used for well-differentiated and somatostatin receptor-positive NETs. PRRT is less effective for poorly differentiated NECs, and PRRT is ineffective but may cause liver toxicity for multiple NETs with a large tumor burden [56].

Two somatostatin analogs (octreotide, which has short-term effects, and lanreotide, which has long-term effects) are currently used for this purpose. Although this treatment effectively controls the symptoms of carcinoid syndrome, it is largely ineffective for tumor recession, as shown radiologically [45, 57]. Due to the fact that the Gallium-68 DOTATATE PET-CT reported avidity for somatostatin receptors at the tumor level and also during its evolution, he presented bilateral hemianopsia, headache with red flags, for which a head tomography with contrast and hormonal profile was requested, which concluded in prolactinoma corroborated by MRI of the skull, so it was decided to start lanreotide 20–60 mg i.m. each month.

Trans-arterial chemoembolization (TACE) is one of the most commonly used method in the management of patients with extrahepatic NET intrahepatic metastasis. TACE is normally performed for advanced primary hepatic NECs that are poor candidates for resection. TACE treatment of patients with PHNET has only been described in few case reports. In one study, TACE was performed to treat of 20 patients with hepatic metastases, and the radiological response and symptom improvement rates were 90% [9, 10, 56, 60]. Our patient was evaluated by the interventional imaging service, which determined that she was not a candidate for TACE due to the large liver tumor volume and the high probability of liver toxicity. The results obtained so far show that the median survival time of patients with PHNEC after TACE surgery is 39.6 months and that the 5-year survival rate is 35.5%, which significantly prolongs the survival time of the patients [47].

Complete removal of liver metastases with curative intention may be accomplished by liver resection or – if hepatic disease is disseminated – by total hepatectomy and transplantation. The latter provides immediate and complete relief of hormonal symptoms and pain and has also been performed in palliative circumstances. Still, treatment of neuroendocrine liver metastases by transplantation is performed only for exceptional patients. Only 4 of 300 liver transplantations in Munich and 1 of 415 in Berlin were performed in patients with liver metastases from NETs [61, 62].

It has also been shown that chemoembolization and EBRT have been bridging treatment options for liver transplantation in those patients who are candidates for it [62]. Currently, she is scheduled to start EBRT as a bridging treatment for the liver transplant next month.

Prognosis: currently, the overall prognosis of PHNEC is better than other types of liver cancer. Median survival is 16.5 months (range, 0.7–41.7 months) based on a review of 12 PHNEC patients. The 5-year survival following surgery for all three differentiation subtypes of PHNEC is about 75%. After surgical resection, PHNEC can recur or metastasize in one to 10 years. The prognosis of primary hepatic NEC is extremely poor. For metastatic poorly differentiated NEC, the 5-year survival rate is only 5.8% and the 1-year survival rate is 23.5% [10, 26]. Our patient is currently in stable disease for 14 months and is asymptomatic.

Conclusion

PHNECs are extremely rare. There are multiple treatment options for PHNEC, it is necessary to use an adequate approach. We present the first case of PHNEC metastasized to the mesentery in the English-language literature. More evidence is needed to be able to establish specific recommendations for the management and that could improve the prognosis of this group of patients. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533199).

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Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ricardo Fernández-Ferreira and Ulises Romero-López contributed to the conception of the case, analysis, and critical revision of the content, as well as the final approval of the version to be published. Jorge Alberto Robles-Aviña, Uriel Norberto Rivas-Mendoza, Casandra González-Camacho, Omar Armando Barquet-Mata, Almira Reyes-Gabiño, Karen Analí Tovar-Figueroa, and Viridiana Ramírez-Villagrán contributed to the critical revision of the content, as well as the final approval of the version to be published.

Valero-Gómez Alfredo carried out an exhaustive review of the histopathological characteristics of cancer and analysis of the article. We all agree to be responsible for all aspects of the job to ensure that questions related to the accuracy or completeness of any part of the job are properly investigated and resolved.

Data Availability Statement

Data supporting the findings of this study are openly available in the clinical file of the Tlahuac General Hospital "Dr. Matilde Petra Montoya Lafragua," Mexico City, with registration number: 740414RU9/80. Additional inquiries can be directed to the corresponding author.

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