American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2025; 26: e948500
DOI: 10.12659/AJCR.948500

Received: 2025.02.13
Accepted: 2025.07.10
Available online: 2025.07.16
Published: 2025.08.25

Rapid Progression of Primary Hepatic Neuroendocrine Carcinoma: A Case Report Demonstrating Drastic Oncological Behavior

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Financial support: The authors are employed by Yokkaichi Hazu Medical Center; no other funding support was received
Conflict of interest: None declared

Patient: Male, 73-year-old
Final Diagnosis: Neuroendocrine neoplasms
Symptoms: Asymptomatic
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology • Radiology • Surgery

Objective: Rare disease

Background: Primary hepatic neuroendocrine neoplasms (PHNENs), including primary hepatic neuroendocrine carcinoma (PHNEC), are extremely rare. PHNENs typically exhibit slow growth, although mixed neuroendocrine-non-neuroendocrine neoplasms have poor prognoses. PHNENs are also challenging to diagnose.

Case Report: A 73-year-old man underwent plain computed tomography (CT), which incidentally detected a 42-mm solitary hepatic tumor. Serum levels of protein induced by vitamin K absence or antagonist-II (PIVKA-II) were elevated at 138 mAU/mL. Thirteen days later, magnetic resonance imaging (MRI) revealed an enlarged hepatic tumor with tumor thromboses extending into the hepatic and portal veins. No early-phase enhancement was observed. At 18 days, Doppler ultrasound and dynamic CT evaluated the tumor as hypovascular, and a newly swollen solitary lymph node appeared. At 39 days, positron emission tomography (PET)/CT revealed strong uptake in the primary liver tumor and metastatic lymph nodes, with additional distant lymph node metastases emerging. At 49 days, a metastatic cervical lymph node was surgically resected. At 61 days, PHNEC was definitively diagnosed based on histopathological and immunohistochemical assessments. The Ki-67 labeling

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index was >90%. At 67 days, he was hospitalized to begin chemotherapy, but CT revealed end-stage disease. Palliative treatment was required, and the patient died of cancer 82 days after the initial diagnosis.

Conclusions: We have presented a thought-provoking case of PHNEC with rapid oncological progression. To clarify clinical implications (eg, atypical imaging features and diagnostic pitfalls), detailed imaging findings are provided. We anticipate that this case will be informative for clinicians in this field.

Keywords: Carcinoma • Carcinoma, Neuroendocrine • Liver • Liver Neoplasms • Neuroendocrine Tumors

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/948500

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Introduction

Neuroendocrine neoplasms (NENs) are tumors that originate from neuroendocrine system cells in various organs [1]. Approximately 50% of NENs occur in the gastrointestinal tract, while approximately 30% are found in the bronchopulmonary tree [2]. Currently, NENs are definitively diagnosed based on the World Health Organization (WHO) classification established in 2019 [1]. This classification relies on histopathological assessment, including morphological findings, cellular differentiation, the Ki-67 labeling index, and the number of mitotic cells identified in high-power fields of view [1]. A summary of the 2019 WHO classification is provided in Table 1.

Since the first report of an NEN in the liver – referred to as primary hepatic NEN (PHNEN) – was documented in 1958 [3], PHNENs have remained extremely rare, accounting for only 0.3% of all NENs in the human body [4]. This rarity persists despite the liver being the most common site for NEN metastases from other organs [5]. Primary hepatic neuroendocrine carcinoma (PHNEC) is an even rarer entity, with an incidence of only 0.46% among primary hepatic malignancies [6].

We herein present a thought-provoking case of PHNEC with rapid oncological progression, despite PHNENs generally being considered slow-growing tumors [7]. Additionally, we provide detailed imaging findings, which is notable because PHNENs often lack characteristic radiological features [8,9]. We discuss and clarify possible hypotheses for rapid progression, reliable prognostic factors, difficulty of definitive diagnosis, and therapeutic strategy, and review the current literature. To the best of our knowledge, this pure PHNEC was unique in several clinical points-rapid progression and serum marker-compared to previously documented patients. We hope this report will be informative for physicians in the hepatobiliary field.

Case Report

A 73-year-old man with a history of diabetes mellitus, chronic hepatitis B, hypertension, and chronic renal dysfunction was undergoing routine medical checkups when he was incidentally found to have severe iron deficiency anemia with rapid progression. His medical history included cardiac infarction, which had been treated with coronary artery bypass grafting, and he was on single antiplatelet therapy (aspirin alone). Given his condition, his primary physician referred him to our hospital for further evaluation and appropriate treatment.

Table 1. WHO classification in 2019.

Classification	Differentiation	Ki67 labeling index (%)	Mitosis (/2 mm²)
NET G1	Well differentiated	<3	<2
NET G2	Well differentiated	3-20	2-20
NET G3	Well differentiated	>20	>20
NEC Small-cell type	Poorly differentiated	>20	>20
NEC Large-cell type	Poorly differentiated	>20	>20
MiNEN	Variable	Variable	Variable

MiNEN – mixed neuroendocrine-non-neuroendocrine neoplasm; NEN – neuroendocrine neoplasm; NET – neuroendocrine tumor; WHO – World Health Organization.

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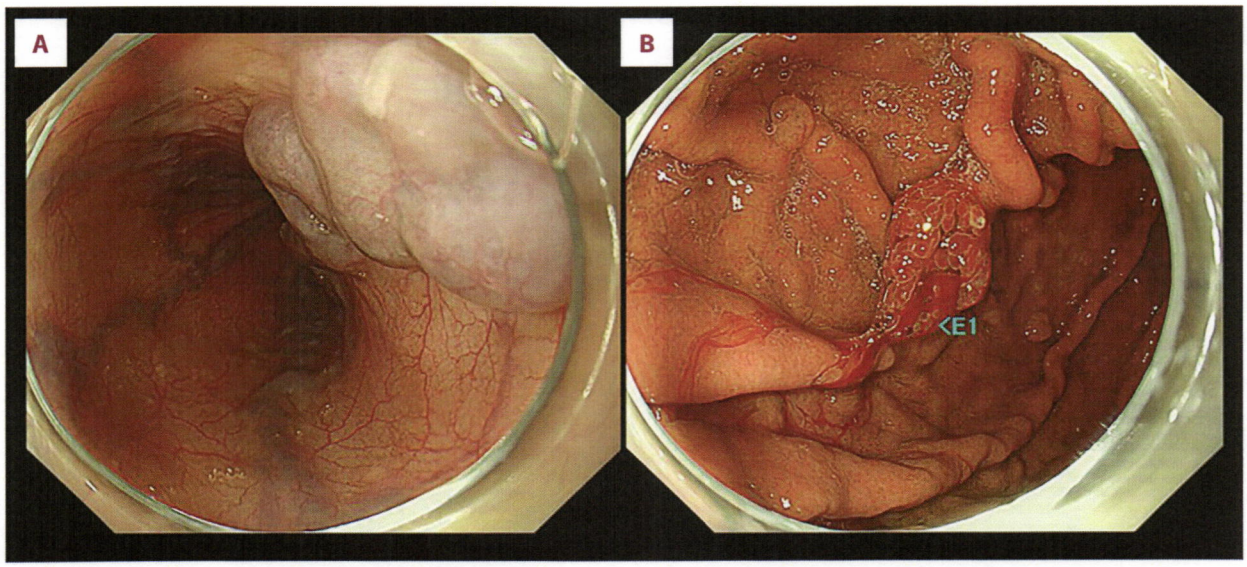

Figure 1. Endoscopic findings of the esophagus and stomach. Esophageal varices developed as a result of portal hypertension due to liver cirrhosis (**A**). A gastric polypoid lesion showed a tendency to bleed easily (**B**).

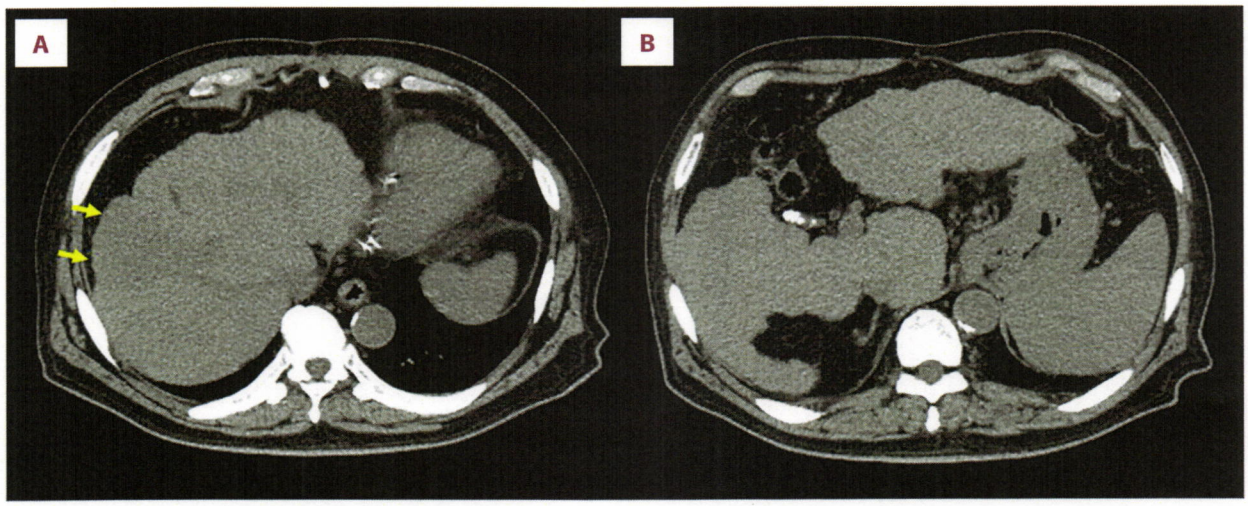

Figure 2. Abdominal plain CT findings at the initial diagnosis. A hepatic mass was incidentally detected in the cirrhotic liver (**A, yellow arrows**). Additional findings included a cirrhotic liver, developed collateral vessels, a congested stomach, and splenomegaly (**A, B**). CT – computed tomography.

To identify the source of bleeding, the patient underwent upper endoscopy and recto-colonoscopy. Esophagogastroduodenoscopy revealed engorged esophageal varices (**Figure 1A**) and a gastric polypoid lesion that readily bled (**Figure 1B**). His esophageal varices were classified as Lm, F2, Cb, RC(+), with red wale markings and cherry-red spots, according to the Japanese classification system [10]. The gastric polypoid lesion exhibited significant hemorrhage, even after gentle saline irrigation.

The patient was admitted to our hospital, where he received conservative management, including hemostatic agents. To achieve complete hemostasis, he subsequently underwent endoscopic mucosal dissection of the gastric polypoid lesion. Histopathological assessment of the resected gastric lesion revealed a hyperplastic polyp rather than gastric cancer. Following this intervention, his iron deficiency anemia resolved.

Upon admission, an abdominal plain computed tomography (CT) scan was performed as part of a routine assessment. The scan revealed a cirrhotic liver, developed collateral vessels, a congested stomach, and splenomegaly (**Figure 2A, 2B**), indicating portal hypertension due to decompensated liver cirrhosis. Additionally, a hepatic mass was incidentally detected in

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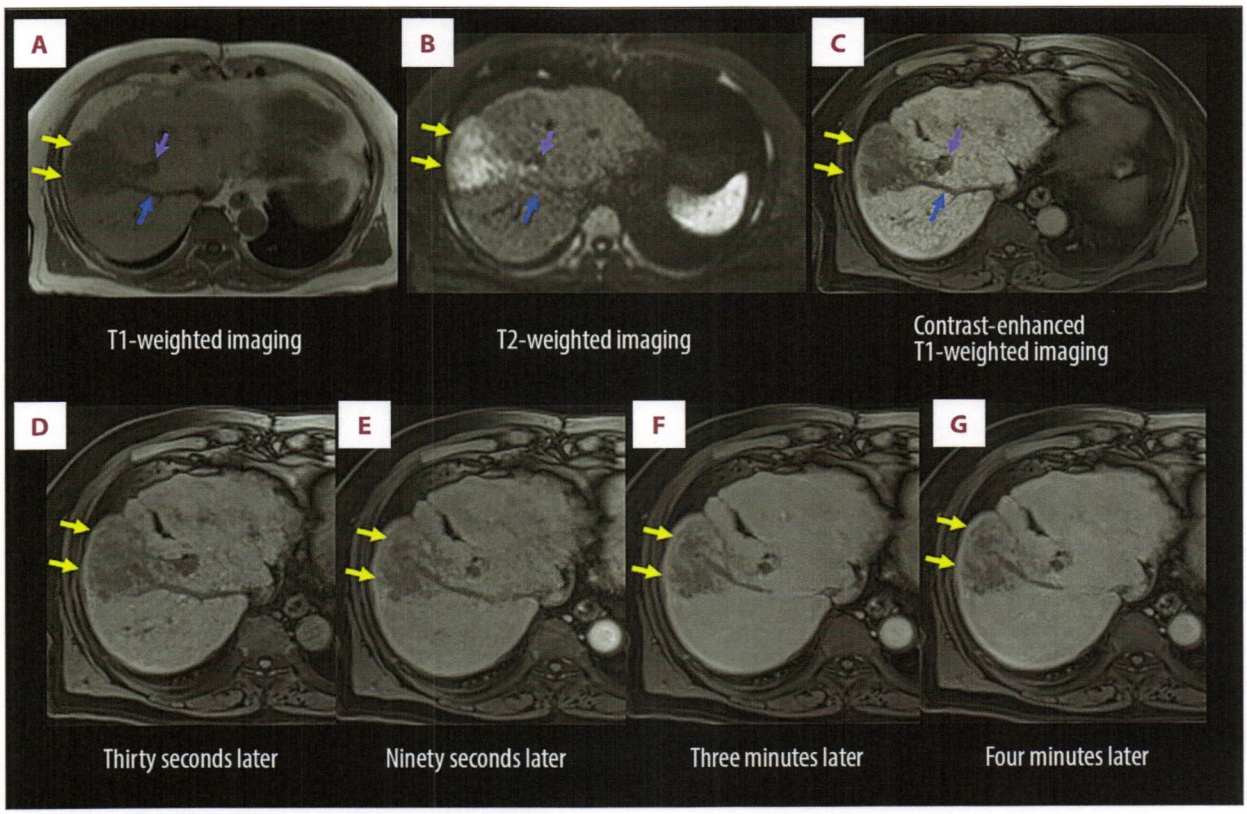

Figure 3. MRI findings 13 days after the initial diagnosis. The hepatic tumor had enlarged to 55 mm (yellow arrows), with tumor thromboses clearly observed in the right HV (A-C, **blue arrows**) and the anterior branch of the PV (A-C, **purple arrows**). The tumor appeared hypointense on T1-weighted imaging (A) and hyperintense on T2-weighted imaging (B). Contrast-enhanced T1-weighted imaging did not show any enhancement in the early phase (C). Gadoxetic acid-enhanced MRI at 0.5 (D), 1.5 (E), 3.0 (F), and 4.0 (G) minutes after injection did not reveal early wash-in or wash-out in the hepatic tumor. HV – hepatic vein; MRI – magnetic resonance imaging; PV – portal vein.

the cirrhotic liver (Figure 2A). The tumor measured 42 mm in size and was located in segments 8 and 4. The patient had no history of alcohol consumption. Peripheral blood tests showed that hepatitis B surface antigen and DNA were below the detection limit. Autoimmune antibodies and soluble interleukin-2 receptor were also negative.

Regarding tumor markers, carcinoembryonic antigen, carbohydrate antigen 19-9, and alpha-fetoprotein were all within the reference ranges, whereas the serum level of protein induced by vitamin K absence or antagonist-II (PIVKA-II) was elevated at 138 mAU/mL. The indocyanine green elimination test showed an R15 value of 17.1% and a *k* value of 0.130. The serum albumin concentration was 4.0 g/dL, and the Child-Pugh score was classified as A.

Thirteen days after the initial diagnosis, magnetic resonance imaging (MRI) was performed. The hepatic tumor had enlarged to 55 mm, and tumor thromboses were clearly observed, extending not only into the right hepatic vein (HV) but also into the anterior branch of the portal vein (PV) (Figure 3A-3C). The hepatic tumor exhibited low intensity on T1-weighted imaging (Figure 3A) and high intensity on T2-weighted imaging (Figure 3B). Additionally, contrast-enhanced T1-weighted imaging showed no enhancement during the early phase (Figure 3C). Gadoxetic acid-enhanced MRI did not reveal early wash-in or wash-out in the hepatic tumor (Figure 3D-3G).

Eighteen days after the initial diagnosis, Doppler ultrasound (US) and dynamic CT were performed. The hepatic tumor had further enlarged to 75×67 mm and appeared as an irregularly-shaped hypoechoic mass on plain US (Figure 4A). Although Doppler US detected a few feeding arteries within the tumor (Figure 4B), it was evaluated as hypovascular. The enlarged hepatic tumor (Figure 5A-5C) was accompanied by tumor thromboses extending into the right HV and the anterior branch of the PV (Figure 5C). Consistent with the MRI findings (Figure 3), dynamic CT did not show early wash-in or wash-out of contrast in the hepatic tumor. Additionally, a solitary but swollen lymph node, newly detected dorsal to the PV trunk (Figure 5D),

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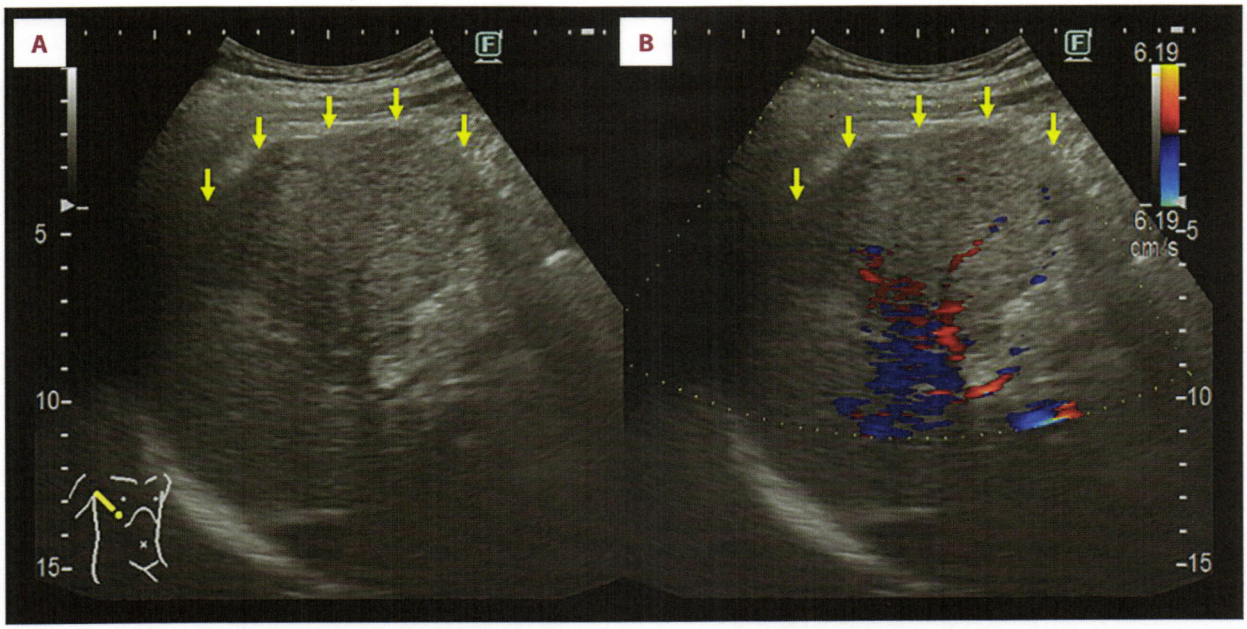

Figure 4. US findings 18 days after the initial diagnosis. The hepatic tumor (**yellow arrows**) had enlarged to 75×67 mm and appeared as an irregularly-shaped hypoechoic mass on plain US (A). Doppler US detected only a few feeding arteries within the tumor (B). US – ultrasound.

had appeared, while the lymph nodes at the hepatic hilum and hepatoduodenal ligament remained unaffected.

At 39 days after the initial diagnosis, distant metastases were assessed using positron emission tomography/CT (PET/CT) (Figure 6). The hepatic tumor had enlarged to 95 mm. The primary tumor in the liver exhibited a high uptake value. Additionally, the previously identified swollen lymph node dorsal to the PV trunk also showed strong uptake. Moreover, new, massively swollen lymph nodes with high uptake were detected around the pancreas head, inferior vena cava, and abdominal aorta. Simultaneously, a 20-mm, solitary but swollen cervical lymph node had also emerged with strong uptake.

Given the rapid oncological progression, the specificity of PIVKA-II for hepatocellular carcinoma (HCC), and the presence of distant lymphoid metastases despite intact regional lymph nodes, we suspected HCC combined with cholangiocellular carcinoma, although imaging did not reveal early wash-in r wash-out. A definitive diagnosis was necessary to determine the appropriate therapeutic strategy. The solitary but metastatic cervical lymph node appeared to be the best target for histopathological assessment. Consequently, surgical resection of the metastatic cervical lymph node was performed under general anesthesia 49 days after the initial diagnosis. Surprisingly, intraoperative findings revealed that the metastatic cervical lymph node had enlarged to 50 mm. The resected specimen was soft to the touch rather than elastically firm. We avoided core-needle biopsy, because it has some risk of intraperitoneal bleeding and/or dissemination, and sample volume was insufficient for microsatellite instability scoring and gene panel testing.

Histopathological assessment revealed a NEN with >20 mitoses per 2 mm^2 and poorly-differentiated carcinoma (Figure 7A-7C). Notably, neither HCC nor cholangiocellular carcinoma was observed. Immunohistochemical staining showed positivity for chromogranin A (Figure 7D) and synaptophysin (Figure 7E), confirming neuroendocrine features. The Ki-67 labeling index was >90% (Figure 7F). Based on the differentiation profile, neuroendocrine markers, and proliferation assay, the definitive diagnosis of PHNEC was established. His PHNEC was classified as small-cell type NEC according to the WHO classification [1] and staged as T4N1M1 Stage IVB based on the Japanese classification [11]. The definitive diagnosis was made 61 days after the initial diagnosis, and microsatellite instability scoring and gene panel testing were subsequently ordered to guide therapeutic decisions.

At 67 days after the initial diagnosis, the patient was hospitalized to initiate chemotherapy with a first-line regimen (cisplatin [carboplatin] plus etoposide) and/or a second-line regimen (cisplatin [carboplatin] plus irinotecan) [12,13]. However, cervical, thoracic, and abdominal contrast-enhanced CT on admission revealed devastating findings indicative of far-advanced carcinoma and end-stage disease. New pulmonary arterial thromboses were detected (Figure 8A, 8B). His primary tumor (Figure 8C-8E) and metastatic lymph nodes (Figure 8F)

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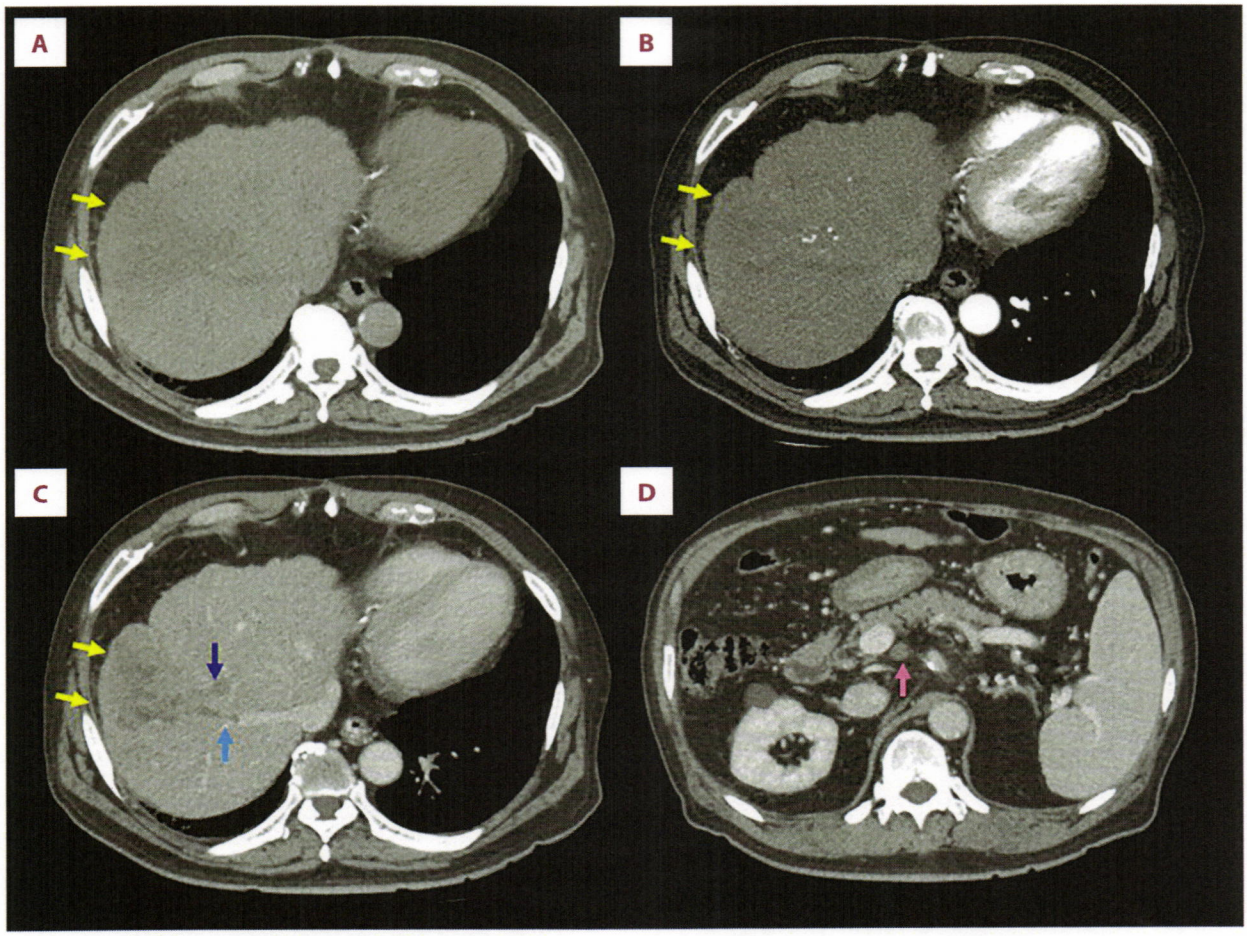

Figure 5. Dynamic CT findings 18 days after the initial diagnosis. Dynamic CT images are shown in the plain phase (A), arterial phase (B), portal phase (C), and equilibrium/transitional phase (D). The hepatic tumor (yellow arrows) had enlarged to 75 mm (A-C), with tumor thromboses clearly observed in the right HV (C, **blue arrow**) and the anterior branch of the PV (C, **purple arrow**). Dynamic CT did not show early wash-in or wash-out in the hepatic tumor (yellow arrows). Additionally, a new solitary and swollen lymph node was detected dorsal to the PV trunk (D, **pink arrow**). CT – computed tomography; HV – hepatic vein; PV – portal vein.

had further enlarged. Tumor thromboses had extended into the right and middle HVs (Figure 8C, 8D), while PV thrombosis had progressed into the left PV and PV trunk (Figure 8E, 8F). Additionally, massive ascites and intraperitoneal dissemination had newly emerged (Figure 8C-8F). At this stage, his liver cirrhosis was classified as Child-Pugh C. Given his condition, palliative treatment was initiated to manage carcinomatous pain.

The patient died of cancer 82 days after the initial diagnosis. The clinical course, serum levels of PIVKA-II, and oncological progression are illustrated in Figure 9. A summary of the imaging and surgical findings is provided in Table 2.

Discussion

Neuroendocrine tumors (NETs), as classified under the previous WHO classification in 2010 [14], are now considered a subset of NENs in the updated WHO classification of 2019 [1]. The current classification collectively refers to gastroenteropancreatic NETs (commonly known as "GEP-NETs") as NENs, encompassing both well-differentiated NETs and poorly differentiated NECs [1]. NETs are graded into 3 categories based on the number of mitoses per 2 mm^2 of tumor area and the Ki-67 labeling index: G1 (<3%), G2 (3-20%), and G3 (>20%). NECs, which are characterized by a Ki-67 labeling index of >20%, include small-cell and large-cell subtypes. Mixed neuroendocrine-non-NENs (MiNENs) are tumors containing 2 or more histopathologically distinct components, with at least 1 component showing neuroendocrine differentiation [1]. By contrast, mixed

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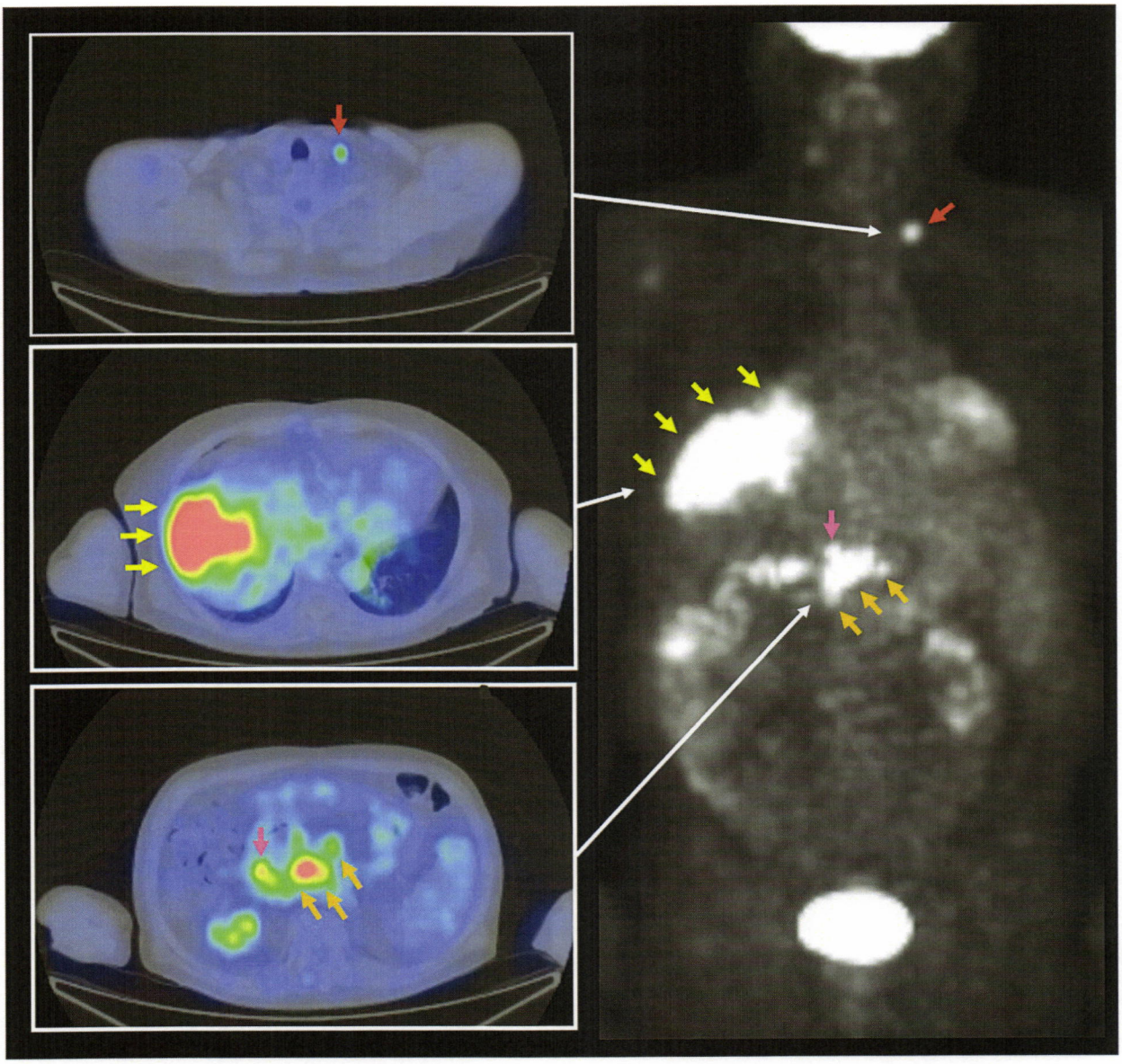

Figure 6. PET/CT findings 39 days after the initial diagnosis. The enlarged primary tumor in the liver (**yellow arrows**) exhibited a strong uptake value. Additionally, the swollen lymph node located dorsal to the PV trunk (**pink arrows**) also showed strong uptake. New, massively swollen lymph nodes with high uptake were detected around the pancreas head, inferior vena cava, and abdominal aorta (**orange arrows**). Simultaneously, a solitary but swollen cervical lymph node, measuring 20 mm (**brown arrows**), also emerged with strong uptake. HV – hepatic vein; PET/CT – positron emission-based tomography/computed tomography; PV – portal vein.

adenoneuroendocrine carcinoma (previously termed "MANEC" under the 2010 WHO classification) was defined as an epithelial neoplasm with a neuroendocrine component comprising >30% of the total tumor volume [14]. Under the latest classification, each component must constitute >30% of the total tumor volume to qualify as MiNEN [1]. Therefore, the term NEN collectively refers to NETs, NECs, and MiNENs.

G1 tumors are the least aggressive and G3 tumors are the most aggressive, with the Ki-67 index and mitotic count increasing across the grades [15]. Notably, low-grade NENs are particularly challenging to treat clinically because of their unusually slow growth [16], which renders them unresponsive to many traditional therapies [16]. Most NETs are low-grade G1 and G2 lesions but can still metastasize [16]. Because the liver is a common site for metastatic disease from extrahepatic

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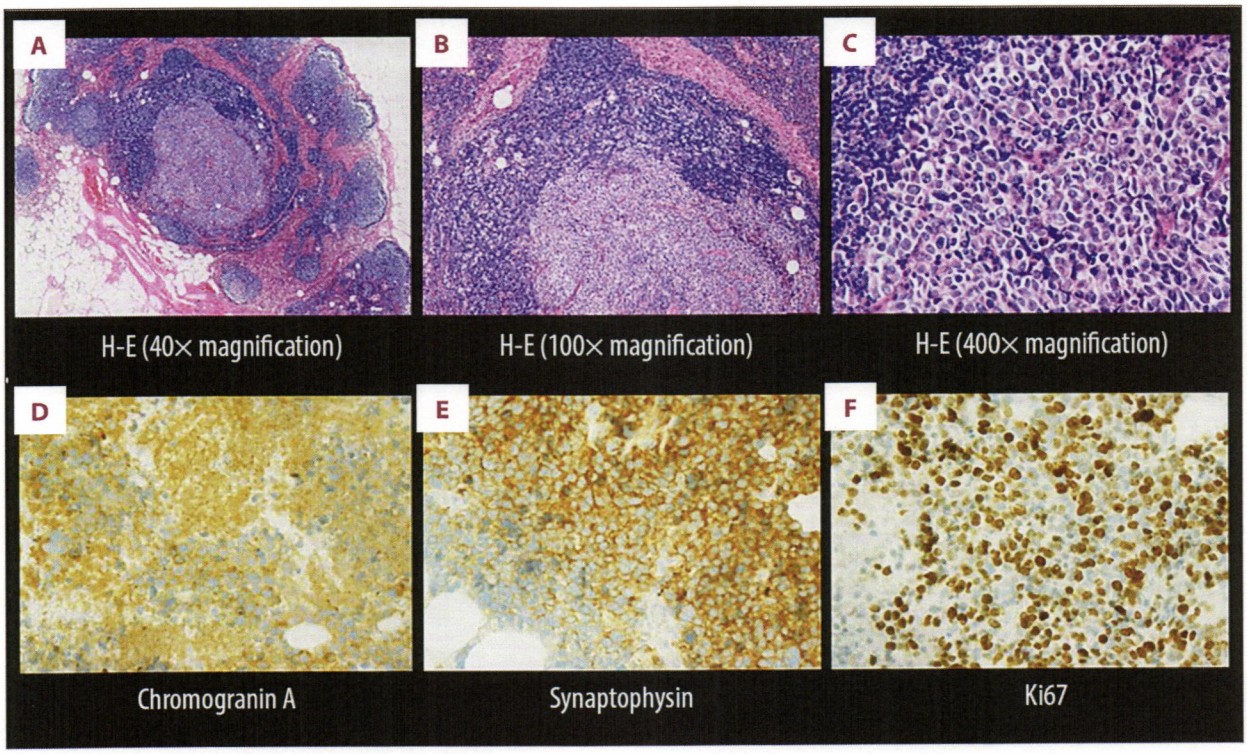

Figure 7. Histopathological and immunohistochemical assessments of the resected specimen. Histopathological findings with hematoxylin and eosin staining are shown at 40× (A), 100× (B), and 400× (C) magnifications. Notably, neither HCC nor cholangiocellular carcinoma was observed. Immunohistochemical staining demonstrated positivity for chromogranin A (D), synaptophysin (E), and Ki-67 (F), each shown at 400× magnification. HCC – hepatocellular carcinoma.

NENs [5], ruling out other primary tumor sites is essential before diagnosing the liver as the tumor origin. In our case, the liver tumor was the only lesion detected at the initial diagnosis, and no other primary sites were identified despite further investigations, including radiographic studies and endoscopic examinations.

The non-neuroendocrine component of MiNEN consists of adenocarcinoma in more than 90% of cases but can include other neoplasms such as squamous cell carcinoma or HCC [17]. MiNEN typically exhibits poor responsiveness to traditional chemotherapy [18], with the neuroendocrine component generally dictating the prognosis [19,20]. Overall, MiNENs are associated with very poor outcomes [21]. Although MiNEN in the liver is a rare tumor with an especially poor prognosis [22], our patient's tumor did not contain any non-neuroendocrine component (Figure 7). Case reports always have limitations, and our case lacked long-term follow-up due to rapid progression. However, our case was a rare case of pure PHNEC with rapid progression.

As described above, PHNENs are extremely rare, accounting for only 0.3% of all NENs [4]. To date, no specific classification system has been established for PHNEN [2]. However, applying the WHO classification provides a useful framework for assessing prognosis and malignant potential [23]. The clinical manifestations of PHNEN differ from those of other NENs. While NENs can arise sporadically or as part of inherited tumor syndromes such as multiple endocrine neoplasia type 1 [24], PHNENs typically grow slowly and do not secrete hormones. As a result, they are often discovered incidentally and tend to manifest clinically only at an advanced stage [25].

PHNENs are challenging to diagnose because of their lack of distinctive imaging features [8,9]. They can resemble other liver lesions, such as HCC, cholangiocarcinoma, or metastatic carcinoma [26]. PHNENs may present as solitary or multifocal tumors, have a predilection for the right lobe [9,27], and often exhibit marginal capsules and/or necrotic areas [9]. On US, PHNENs may appear as multiple cystic lesions or a solid mass [28], while plain CT typically shows low attenuation [9]. Contrast-enhanced CT often reveals cystic lesions with an enhanced rim in the arterial phase and wash-out in the portal phase due to hypervascularity, similar to HCC [9,28]. On MRI, PHNENs generally appear hypointense on T1-weighted images, appear hyperintense on T2-weighted images, and demonstrate restricted diffusion [9,29]. Because histopathology alone is insufficient to distinguish primary from extrahepatic

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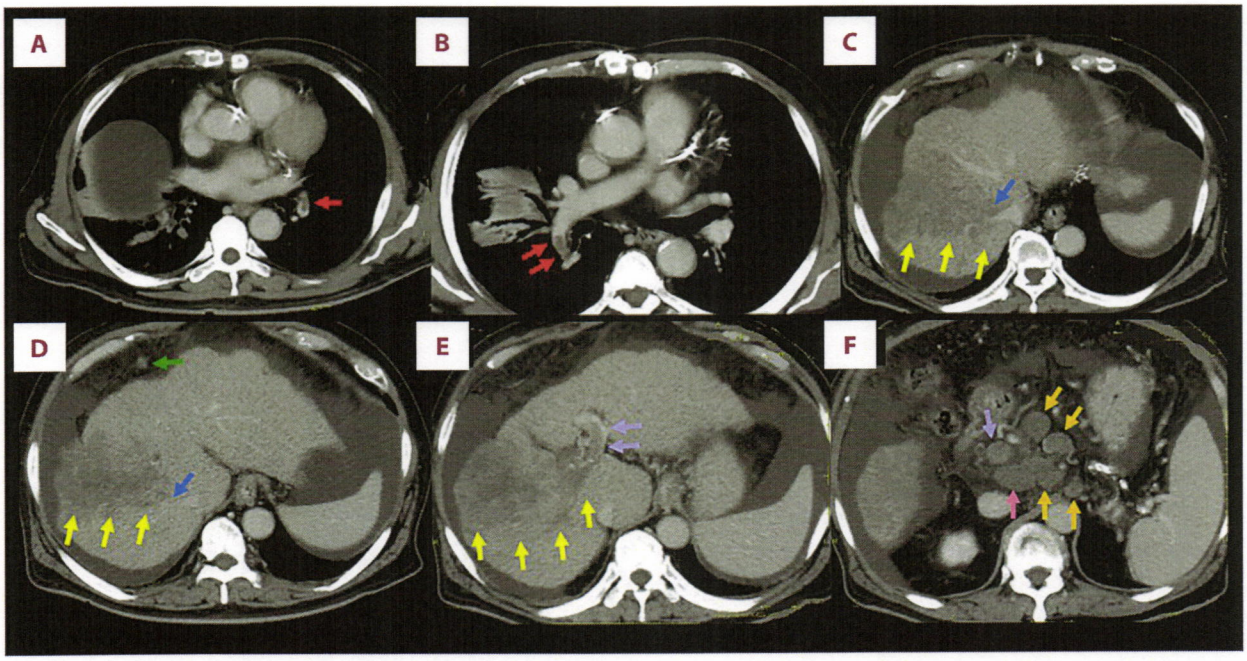

Figure 8. Enhanced CT findings 67 days after the initial diagnosis. New pulmonary arterial thromboses were observed (**A, B, red arrows**). The primary hepatic tumor had further enlarged (**C-E, yellow arrows**), along with metastatic lymph nodes (**F, pink and orange arrows**). Tumor thromboses had extended into the right and middle HVs (**C, D, blue arrows**), while PV thrombosis progressed into the left PV and PV trunk (**E, F, blue arrows**). Additionally, massive ascites (**C-F**) and new intraperitoneal dissemination (**D, green arrow**) were detected. CT – computed tomography; HV – hepatic vein; PV – portal vein.

NENs, radiographic studies, including PET/CT, play a crucial role in identifying the primary tumor [28]. Although nearly all PHNENs lack fat, calcification, and vascular and biliary tumor thrombus formation [9], our patient exhibited aggressive vascular invasion extending into both the PV and HVs. Early wash-in and wash-out are important imaging characteristics of HCC [30]. Additionally, PIVKA-II is highly specific for HCC, although certain medications and portal hypertension can influence its serum levels [31,32]. In our case, the radiographic findings did not align with typical HCC features, despite elevated serum PIVKA-II levels. From a retrospective perspective, the elevated PIVKA-II levels may have reflected the severity of portal hypertension as tumor thrombosis progressed into the PV, although they might also have corresponded to oncological progression (**Figure 9**).

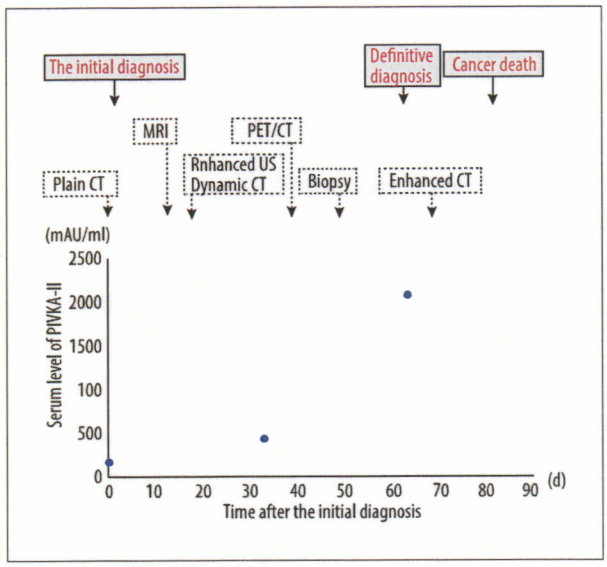

Figure 9. Clinical course, serum level of PIVKA-II, and oncological progression. CT – computed tomography; MRI – magnetic resonance imaging; PET/CT – positron emission-based tomography/computed tomography; PIVKA-II – protein induced by vitamin K absence or antagonist-II; US – ultrasound.

Lymph node metastasis via the lymphatic route is common in cholangiocellular carcinoma, with the primary metastatic targets being the lymph nodes located at the hepatic hilum and within the hepatoduodenal ligament. By contrast, metastatic HCC can present in unexpected locations, including the oral cavity, skin, heart, spleen, and small bowel and as solitary but distant lymphatic metastases [33-38]. Lymph node metastases via the lymphatic route typically exhibit a widespread tumor distribution due to immune system interactions [39,40], whereas metastases with a solitary island pattern and central

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Table 2. Graphic and surgical findings of hepatic tumor.

Modality	Time (days)*	Graphic and surgical findings
Plain CT	0	Cirrhotic liver, developed collaterals, congestive stomach, and splenomegaly were observed
(Figure 2)		Hepatic tumor (**yellow arrows**) was incidentally detected
MRI	13	Hepatic tumor (**yellow arrows**) was enlarged
(Figure 3)		Tumor thromboses were observed in the right HV (**blue arrows**) and the anterior branch of the PV (**purple arrows**)
		Hepatic tumor (**yellow arrows**) showed low intensity in T1-weight imaging and high intensity in T2-weighted imaging
		Contrast-enhanced T1-weighted imaging did not show any enhancement at early phase (**yellow arrows**)
		Gadoxetic acid-enhanced MRI did not reveal early wash-in or wash-out in the hepatic tumor (**yellow arrows**)
US	18	Hepatic tumor (**yellow arrows**) was enlarged
(Figure 4)		Hepatic tumor (**yellow arrows**) was observed as an irregularly-shaped hypoechoic mass by plain US
		Doppler US detected few feeding arteries into the hepatic tumor (**yellow arrows**)
		Hepatic tumor (**yellow arrows**) was evaluated as hypovascular
Dynamic CT	18	Hepatic tumor (**yellow arrows**) was enlarged
(Figure 5)		Tumor thromboses were observed in the right HV (**blue arrow**) and the anterior branch of the PV (**purple arrow**)
		Early wash-in and wash-out were not observed in the hepatic tumor (**yellow arrows**)
		A solitary and swollen lymph node located dorsal to the PV trunk (**pink arrow**) appeared
PET/CT	39	Hepatic tumor (**yellow arrows**) was enlarged
(Figure 6)		The primary tumor in the liver (**yellow arrows**) had strong uptake value
		Swelled lymph node located dorsal to the PV trunk (**pink arrows**) showed strong uptake value
		Swollen, massive lymph nodes with strong uptake value appeared around the pancreas head, inferior vena cava, and abdominal aorta (**orange arrows**)
		Solitary but swollen cervical lymph node (**brown arrows**) appeared with strong uptake
Operative findings	48	Metastatic cervical lymph node was enlarged
		During surgery, metastatic cervical lymph node was palpated as soft, not elastic and hard
Enhanced CT	67	Hepatic tumor (**yellow arrows**) and metastatic lymph nodes (pink and orange arrows) were enlarged
(Figure 8)		Tumor thromboses extended into the right and middle HVs (**blue arrows**)
		PV thrombosis extended into the left PV and PV trunk (**purple arrows**)
		Pulmonary arterial thromboses (**red arrows**) appeared
		Massive ascites and intraperitoneal dissemination (**green arrow**) appeared

CT – computed tomography; HV – hepatic vein; MRI – magnetic resonance imaging; PET/CT – positron emission-based tomography/computed tomography; PV – portal vein; US – ultrasound. * Time after the initial diagnosis (days).

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predominance may suggest hematogenous spread [40]. In our case, hematogenous dissemination may explain the presence of metastasis in a distant lymph node (**Figure 7A**). Regarding impacts of hematogenous and/or lymphatic dissemination on the prognostic implications, hematogenous metastasis into the lymph nodes predicts poor prognosis [41,42]. Overall, until a definitive diagnosis was established through histopathological assessment, several atypical findings complicated the differentiation from HCC, including unusual imaging features, elevated serum PIVKA-II levels, extensive venous thrombosis involving the PV and HVs, and the presence of distant lymphatic metastases without involvement of regional lymph nodes. These factors initially led us to suspect combined HCC in this case.

PHNEC is a rare tumor with an incidence of 0.46% among primary hepatic malignancies [6]. Although its exact origin remains unclear, 2 hypotheses have been proposed [43,44]: (1) neuroendocrine cells within the intrahepatic bile duct epithelium undergo malignant transformation, leading to PHNEC, and (2) PHNEC arises from stem cells that have dedifferentiated from other malignant hepatic cells and subsequently converted into neuroendocrine cells. The latter hypothesis can explain the coexistence of different carcinoma types within the same lesion, whereas the former accounts only for the pathogenesis of single PHNEC tumors. Although MiNEN and combined HCC often exhibit rapid oncological progression and poor prognoses [45-47], the tumor in this case was purely of NEC without any other components. To the best of our knowledge, this was an unusual case of PHNEC, particularly given the rapid oncological progression. We have presented a thought-provoking case of pure PHNEC, distinct from MiNEN or combined HCC, characterized by aggressive disease progression and uncommon radiographic findings. Two possible hypotheses were documented as described above, but the origins of PHNEC were still unclear. However, tumor origin may be informative for rapid progression, and there have been 2 other published reports that PHNEC may originate from multifunctional stem cells in the liver or from the ectopic adrenal and pancreatic tissues in the liver [48,49]. These hypotheses of the tumor origins from stem cells or ectopic tissues may explain rapid progression in our case, because tumors originated from stem cells and/or ectopic tissue can cause rapid oncological progression [50].

An adequate therapeutic strategy for PHNEC should be made based on definitive diagnosis [51]. PHNECs are a diagnosis of exclusion since they are far less common than hepatic metastasis of NECs, so an extrahepatic primary NEC must be excluded first through studies including endoscopy and colonoscopy (to rule out tumor origins of gastrointestinal and colorectal tracts), dynamic CT of cervical, thoracic, abdominal, and pelvic areas, hepatobiliary pancreatic MRI, and PET/CT. As described above, because PHNEC lacks distinctive imaging features, definitive diagnosis of PHNEC may difficult for hepatology physicians [8,9,26-28,52]. Hence, we provided detailed and uncommon imaging findings of PHNEC with rapid progression. Although partial hepatectomy at the initial detection of atypical tumors is a good option for making definitive diagnosis followed by adequate therapy, there were clinical risks of mortality and morbidity in our case due to advanced liver cirrhosis and tumor thromboses [53]. Earlier histopathological assessments (eg, core-needle biopsy in atypical hepatic tumors) may have been clinically important in our case, but procedures involved in these assessments carry some risk of intraperitoneal bleeding and/or dissemination [54,55]. Although surgical biopsy of metastatic lymph nodes may be insufficient for reliable diagnosis, we considered cervical lymph node resection for histopathological assessment to be safe and minimally invasive.

PHNEC is exceptionally rare and there are no biomarkers for predicting clinical prognosis [51], although the Ki-67 labeling index is the most reliable marker for predicting prognosis and for determining therapeutic strategies [48,49,56]. Although there was a case report that alpha-fetoprotein-producing PHNEC harboring FGFR2 and TP53 mutations showed rapid progression [57], possible mechanisms and/or specific genetic mutations for rapid progression of PHNEC are still unknown. To the best of our knowledge, our patient is the first case of PIVKA-II-producing PHNEC with rapid progression, although our case lacked genetic profiling due to rapid patient decline. To date, neither biomarkers nor genetic factors linked to oncological aggressiveness have been detected, except for Ki-67 labeling index [48,49,51,56]. Recently, a diagnostic role of PIVKA-II has been widely discussed. Vitamin K is essential for the synthesis of coagulation factors II, VII, IX, and X in the liver. In the absence of vitamin K or in the presence of antagonists, the activity of vitamin K-dependent carboxylase is inhibited, resulting in disturbances in carboxylation of N-terminal glutamic acid residues of coagulation factors. This abnormal coagulation factor is unable to perform the clotting function, and is known as PIVKA-II. Abnormal enzymes related to vitamin K metabolism generated during the malignant transformation of hepatocytes, even in non-HCC tumors, can lead to an increase of PIVKA-II levels [31,32,58].

Systemic combination therapy is the preferred treatment for PHNEC if surgical resection is impossible [59]. Due to the lack of availability of substantial high-quality data, there is no standard chemotherapy for PHNEC [48]. Two possible hypotheses were documented as described above, but the origins of PHNEC are still unclear. However, tumor origin may be informative in selecting a chemotherapy regimen, and the Ki-67 labeling index is the most reliable marker for selecting the optimal chemotherapy regimen [48,49,56]. Platinum-based treatment was strongly recommended as chemotherapy for PHNEC [48,49,60-62], especially in patients with a Ki-67 labeling index greater than 5% [48,56]. The first-line regimen for

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these patients is cisplatin (carboplatin) plus etoposide, and the second-line regimen is cisplatin (carboplatin) plus irinotecan [48,49,60-63]. Moreover, we prefer microsatellite instability scoring and gene panel testing for selection of a chemotherapy regimen in each, although results of these advanced examinations in this case failed to arrive in time due to rapid disease progression. For clinical assessment of therapeutic effectiveness, image studies (eg, dynamic CT) should be performed.

Conclusions

We have documented a detailed case of pure PHNEC characterized by aggressive disease progression and unusual radiographic findings. Definitive diagnosis followed by adequate therapy is required, and our case suggests that clinical physicians should not hesitate to perform earlier histopathological assessment. PHNEC should be considered in rapidly progressing liver tumors without typical HCC features, even with elevated PIVKA-II. We believe this thought-provoking case will provide valuable insights for hepatobiliary clinicians.

Acknowledgment

We are grateful to Department of Pathology, Mie University Hospital (Tsu, Japan) for technical support in this histopathological and immunohistological assessment. R. Kobayashi and T. Hori contributed equally to this work. Edanz provided English-language editing.

Ethics Approval

Data in this case report were retrospectively evaluated. This report was approved by the Institutional Review Board of Yokkaichi Hazu Medical Center, Yokkaichi, Japan.

Consent for Publication

The patient provided written informed consent authorizing the use and disclosure of his protected health information.

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