Extended Left Hemihapatectomy with Right Hepatic Artery Reconstruction for Primary Hepatic Neuroendocrine Neoplasm: A Brief Report

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Patient: Male, 31-year-old
Final Diagnosis: Primary hepatic neuroendocrine neoplasm
Symptoms: Jaundice
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Rare disease
Background: Primary hepatic neuroendocrine neoplasms (PHNEN) are exceedingly rare tumors with atypical clinical manifestations, accounting for less than 0.5% of all neuroendocrine tumors. Currently, there is a lack of consensus on their management, and guidelines do not recommend postoperative chemotherapy for patients with stage G1/G2 disease after curative resection. We present a case report of PHNEN, outlining its diagnostic challenges, treatment strategy, and clinical outcomes.

Case Report: A 31-year-old man presented with jaundice and was initially diagnosed with suspected IgG4-related disease, which initially appeared to respond to steroid therapy, but manifested worsening jaundice 4 months after initial treatment. Subsequent evaluation revealed a PHNEN NET G2 with lymph node metastasis and invasion of the right hepatic artery, and involvement of the hepatic duct at the hepatic hilum, primarily the left hepatic duct. The patient underwent extended left hemi-hepatectomy with caudate lobe resection, bile duct resection, and lymphadenectomy, followed by reconstruction of the right hepatic artery. Postoperatively, the patient received adjuvant chemotherapy consisting of capecitabine (1000 mg bid D1-14) and temozolomide (200 mg qn D10-14) for 6 cycles. Currently, the patient remains disease free 43 months after treatment.

Conclusions: PHNEN presents diagnostic challenges due to its rarity and lack of specific markers. Surgical resection remains the cornerstone of treatment, with chemotherapy being considered in select cases with high-risk features. Further research is needed to refine treatment approaches and improve outcomes for patients with PHNEN.

Keywords: Hepatectomy • Liver Neoplasms • Neuroendocrine Tumors

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Introduction

Neuroendocrine tumors (NETs) are a type of tumor originating from the neuroendocrine cells. NETs are on the rise and are most likely to occur in the gastrointestinal tract, lungs, and pancreas. NETs most commonly metastasize to the liver; however, primary hepatic neuroendocrine neoplasms (PHNEN) are very rare, making up less than 0.5% of all NETs [1,2]. The fifth edition (2019) of the WHO classification of digestive system tumors included PHNEN in the unified classification and grading, signifying that PHNENs have gradually gained recognition [3].

Case Report

A 31-year-old man with a previously unremarkable medical history sought medical attention at another hospital for jaundice 4 months prior to visiting our hospital. Laboratory tests at that time showed a total bilirubin level of 49.4 μmol/L, direct bilirubin level of 18.6 μmol/L, IgG4 level of 2.02 g/L, and IgG4/IgG ratio of 16.56%. MRI revealed a 17-mm mass at the porta hepatis. Brush cytology during endoscopic retrograde cholangiopancreatography (ERCP) did not show any abnormal cells. They made a preliminary diagnosis of suspected

Figure 1. Preoperative MRI and PET-CT Imaging. (A, B) Represent enhanced magnetic resonance imaging (MRI) of the liver. A low signal intensity nodule is observed in the left medial segment of the liver, adjacent to the first porta hepatis, on the T1-weighted image. Following contrast administration, this nodule demonstrates significant arterial phase enhancement, accompanied by sustained enhancement during the portal venous and delayed phases. Furthermore, intrahepatic bile duct dilation is visualized. (C, D) Depict 18F-FDG positron emission tomography-computed tomography (PET-CT) images. In the porta hepatis region, a nodular soft tissue lesion measuring approximately 2.2 cm in its longest dimension is evident. This lesion exhibits increased FDG metabolism, with a maximum standardized uptake value (SUVmax) of approximately 4.4.
The patient was admitted to our department and underwent PTCD to correct the bilirubin levels and jaundice. After 14 days, the jaundice resolved, and the following serology tests were normal. However, 4 months later, he came to our hospital with worsening jaundice. Physical examination revealed skin and scleral jaundice and mild upper abdominal tenderness. There were no other notable findings. Laboratory tests showed a total bilirubin level of 336 μmol/L, direct bilirubin level of 275 μmol/L, and CA19-9 level of 171 IU/ml. Magnetic resonance cholangiopancreatography (MRCP) showed a mass at the porta hepatis accompanied by glucocorticoids followed by re-evaluation. Subsequently, he was prescribed oral prednisone (50 mg/day). After 14 days, the jaundice resolved, and the following serology tests were normal. However, 4 months later, he came to our hospital with worsening jaundice. Physical examination revealed skin and scleral jaundice and mild upper abdominal tenderness. There were no other notable findings. Laboratory tests showed a total bilirubin level of 336 μmol/L, direct bilirubin level of 275 μmol/L, and CA19-9 level of 171 IU/ml. Magnetic resonance cholangiopancreatography (MRCP) showed a mass at the porta hepatis accompanied by significant intrahepatic bile duct dilation and multiple enlarged lymph nodes around the pancreatic head and duodenum, suggesting malignant tumor involvement (Figure 1). There was no significant enlargement in the tumor size compared to the initial examination at the prior hospital. PET-CT scan showed a soft-tissue nodule at the porta hepatis, with mildly increased metabolic activity.

The patient was admitted to our department and underwent PTCD to correct the bilirubin levels and jaundice (Figure 2). After a multidisciplinary team (MDT) consultation, the patient was initially diagnosed with hilar cholangiocarcinoma with invasion of the right hepatic artery and lymph node metastasis in the porta hepatis. On July 29, 2019, he underwent exploratory laparoscopic surgery. No obvious intraperitoneal metastasis was found. A reverse L-shaped laparotomy incision on the right upper abdomen revealed congested bile in the liver with a slightly firm texture. The tumor was located in the porta hepatis, with enlarged lymph nodes around the hepatic hilar (Figure 3) with hepatic duct invasion. The tumor and enlarged lymph nodes were encasing the hepatic artery proper and the left and right hepatic arteries. The tumor invaded the hepatic duct at the hepatic hilum, predominantly affecting the left hepatic duct. The intraoperative diagnosis was hilar cholangiocarcinoma, Bismuth-Corlette type IV, with predominantly left-sided invasion and involvement of the right hepatic artery. Extended left hemi-hepatectomy with caudate lobe and extrahepatic bile duct resection was performed, along with lymphadenectomy in the hepatic hilar region (Video 1). The right hepatic artery was reconstructed (Figure 4). The operation time was 540 minutes, intraoperative blood loss was 1500 ml, RBC transfusion 1100 ml, and plasma 1260 ml. We administered a chemotherapy regimen consisting of capecitabine (1000 mg bid D1-14) and temozolomide (200 mg qn D10-14) for 6 cycles.

The patient recovered with no postoperative complications and was discharged 21 days after surgery. The postoperative CT image is shown in Figure 5. Postoperative pathology showed PHNEN NET G2, with a tumor size of 2.3×1.5×1.3 cm. The tumor infiltrated the entire layer of the bile duct wall, with intravascular cancer emboli (+), nerve invasion (+), involvement of the hepatic artery sheath, and lymph node metastasis (1/1). Immunohistochemistry results showed AFP (-), B-catenin (membrane +), CD10 (-), CD34 (-), CK7 (-), GS (-), Hepatocyte (-), Ki-67 (+) 3%, CD56 (+), CK19 (+++), GPC3 (-), Syn (+++), CgA (+), and CD56 (+) (Figure 6). The patient was followed up in the outpatient clinic, with the latest follow-up in January 2024. At the time of the last follow-up, he had not experienced recurrence.

**Discussion**

PHNEN have atypical clinical manifestations and are often discovered as liver masses during physical examinations [4,5]. Generally, there is no elevation of tumor markers such as AFP, CEA, and CA199, which can lead to missed diagnosis and misdiagnosis. In this case, the patient showed elevated CA199, possibly related to biliary obstruction and infection. Chromogranin A (CgA) is a specific marker for detecting neuroendocrine tumors, and reports indicate that CgA can be elevated in PHNEN and serve as an indicator of tumor progression [6]. However, this patient did not show an elevation of this marker. Currently, no specific markers have been identified in patients with PHNEN. Further research is needed to resolve this question. The patient had been experiencing symptoms for over 4 months before seeking medical attention at our hospital, but the tumor progression was not significant.
In our clinical experience, we have observed that PHNEN patients often have a longer duration of symptoms but still have good physical condition at the time of diagnosis, and they do not immediately enter a cachectic state. Therefore, there is still an opportunity for active treatment.

The imaging findings of PHNEN are atypical. CT scans often show a low-density liver mass with possible cystic degeneration. In the arterial phase after contrast enhancement, varying degrees of enhancement are observed, while in the portal venous phase the enhancement may be continuous or decreased. MRI shows low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, with possible cystic degeneration signals. The enhancement pattern after contrast administration is similar to CT. Reports suggest that CT/MR can be used to diagnose PHNENs and differentiate between grade 1 and 2 tumors and grade 3 tumors [7]. PET/CT has limited diagnostic significance for intrahepatic lesions but has a higher diagnostic value for detecting extrahepatic lesions. We have encountered cases where additional primary lesions were discovered in other sites during follow-up after surgery for initially diagnosed PHNEN, leading to subsequent

Figure 3. Intraoperative images. (A) The mass in the hilar region of the liver. (B) Enlarged lymph nodes are visible in the hepatic hilar region. (C) Resected liver with hilar mass (arrow).
surgical resection of the primary lesion. Therefore, PET/CT examination can be performed before and after surgery if the patient’s condition allows. For patients who cannot undergo PET/CT, after receiving the pathological report of hepatic neuroendocrine tumor, it is also recommended to perform CT of the lungs, gastroscopy, and colonoscopy to avoid missing possible primary lesions. We do not routinely perform gastrointestinal endoscopies on patients suspected of having hilar cholangiocarcinoma before surgery out of consideration of a potential increase in patient discomfort and financial burden.

Surgical resection of the tumor is the preferred treatment for PHNEN [8]. Knox et al reviewed 48 cases of PHNEN reported in the English literature, of which 92% of patients underwent surgical treatment, with 5-year and 10-year survival rates of 78% and 59%, respectively [9]. Li et al analyzed 291 cases of PHNET recorded in the US SEER database from 1988 to 2015, among which only 26% of patients received surgical treatment, resulting in a 5-year survival rate of only 30.2% [8]. There have been reports in the literature of successful treatment with the ALPPS procedure for 1 case of PHNEN suitable for stage I liver resection [10]. For patients who are not eligible for resection, liver transplantation can also be considered [11,12].

Considering the favorable outcomes of surgical treatment for PHNEN, we advocate for proactive surgical intervention for patients who are eligible for resection, rather than performing a biopsy for definitive diagnosis before treatment to avoid needle tract metastasis or treatment delay. The necessity of lymph node dissection for all PHNET patients still requires further

Figure 4. Intraoperative images showing the (A) Right hepatic artery (blue arrow) and hepatic portal vein (black arrow). Tumor invading the right hepatic artery (white arrow). (B) The distal portion of the right hepatic artery (white arrow), and the proximal portion of the right hepatic artery (black arrow). (C) Reconstruction of the right hepatic artery. (D) Biliary-enteric anastomosis (black arrow).
research. However, in this case, despite being classified as NET G2, the presence of lymph node metastasis at the hepatic hilum leads us to believe that routine lymph node biopsy or dissection should be performed in conjunction with complete resection of the liver tumor. The initial diagnosis of this patient was hilar cholangiocarcinoma, and due to imaging findings suggesting vascular invasion at the hepatic hilum, most experts did not recommend surgery. After discussion by our center’s multidisciplinary team (MDT), considering the limited involvement of the hepatic hilum vessels and the possibility of resection and reconstruction, we performed an extended left hepatectomy combined with reconstruction of the right hepatic artery and regional lymph node dissection.
Noro et al reported a case of PHNEN in 2023, but in their case the tumor exhibited liquid components and mural solid nodules and was initially diagnosed as mucinous cystic carcinoma [13]. In a case reported by Yahia et al, the tumor presentation on imaging was akin to hepatocellular carcinoma or cholangiocarcinoma [14], and Akabane et al reported a lesion that mimicked a hemangioma [15]. To the best of our knowledge, this is the first report of a case that presented with IgG4-related disease. PHNENs are extremely rare; therefore, their manifestations are yet to be fully understood.

Currently, there is a lack of large-scale studies on their management, and current guidelines offer no recommendation on postoperative chemotherapy for patients with stage G1/G2 disease after curative resection. In this case, due to lymph node metastasis and hepatic artery invasion, we believed there might have been an increased risk of postoperative recurrence. Therefore, we administered a chemotherapy regimen consisting of capecitabine (1000 mg bid D1-14) and temozolomide (200 mg qn D10-14) for 6 cycles. The choice of capecitabine+temozolomide was based on clinical experience and the regimen’s higher progression-free survival (PFS) and objective response rates (ORR) [16]. The regimen also has a relatively minimal burden on the patient’s quality of life. Currently, the patient has been disease-free for 43 months. We define disease-free survival as the time from the intent-to-cure treatment of the tumor to when signs of tumor recurrence present.

**Conclusions**

PHNEN lacks specific clinical and radiological manifestations, and its diagnosis mainly relies on the pathological diagnosis after excluding extrahepatic lesions. Currently, curative surgery is the preferred treatment for PHNEN. However, with further research on PHNEN, its treatment approaches are expected to become more individualized and diversified, thus achieving better therapeutic effects.

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**References:**