Case Report

Response to hepatic arterial infusion chemotherapy combined with camrelizumab and targeted therapy in advanced primary hepatic neuroendocrine carcinoma: a case report and literature review

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Background: Primary hepatic neuroendocrine carcinoma (PHNEC), which often lacks distinctive radiological features or specific clinical symptoms, is extremely rare. In this report, we describe a rare case of PHNEC that was successfully treated with hepatic arterial infusion chemotherapy (HAIC) combined with camrelizumab and targeted therapy.

Case Description: This report describes the treatment of a 53-year-old male with PHNEC in China. The patient was admitted for persistent upper right quadrant abdominal pain. Dynamic contrast-enhanced abdominal computed tomography (CT) and magnetic resonance imaging (MRI) both detected multiple masses, enlarged portal lymph nodes, and retroperitoneal lymph nodes. Histological and immunohistochemistry of the largest mass biopsy specimen from the right liver lobe confirmed the neuroendocrine tumor of the liver. The patient underwent HAIC with a modified fluorouracil and oxaliplatin (mFOLFOX) regimen. Meanwhile, the patient received camrelizumab (200 mg, intravenously, q3w) apatinib (250 mg, oral, daily) within 7 days after the start of HAIC. CT and MRI showed a marked decrease in the size of the largest mass of the liver and the portal lymph nodes, indicating a partial response of the tumor.

Conclusions: PHNEC is a very rare tumor, and the treatment for its advanced type is controversial and remains to be standardized. HAIC combined with camrelizumab and targeted therapy may be an effective and safe therapeutic option for patients with PHNEC.

Keywords: Case report; hepatic arterial infusion chemotherapy (HAIC); camrelizumab combined with apatinib; advanced primary hepatic neuroendocrine carcinoma (advanced PHNEC)

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Introduction

Neuroendocrine neoplasms (NEN) are a particularly rare group of malignant tumors which include well-differentiated neuroendocrine tumors (NET) and poorly-differentiated neuroendocrine carcinoma (NEC). Only a few case reports have described primary hepatic NEC and the existence of this entity is uncertain given the possibility of metastatic NEC to the liver of unknown primary (1-3).

The standard of care for advanced NEC is systemic platinum-based chemotherapy. The role of immunotherapy is still uncertain and studies are evaluating first-line combination of checkpoint inhibitors combined with chemotherapy. Here, we describe a patient with advanced primary hepatic neuroendocrine carcinoma (PHNEC) and lymph node metastasis who was successfully treated with an unconventional regimen consisting of hepatic arterial infusion chemotherapy (HAIC) combined with camrelizumab and apatinib. We present this article in accordance with the CARE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-571/rc).

Case presentation

In March 12, 2021, a 53-year-old male visited the Fifth Affiliated Hospital of Guangxi Medical University (Guangxi, China) for persistent upper right abdominal pain. Laboratory testing showed that serum α-fetoprotein (AFP), protein induced by vitamin K absence or antagonist-II (PIVKA-II), and serum carbohydrate antigen 19-9 (CA19-9) levels were normal and that hepatitis C virus antibody (HCV Ab) was negative; however, hepatitis B virus surface antigen (HBsAg) was positive, and the liver background was cirrhotic. Contrast-enhanced abdominal computed tomography (CT) showed multiple masses located in the right lobe of the liver, with the largest one measuring about 9.2 cm × 6.3 cm × 8.8 cm in diameter. CT revealed multiple well-circumscribed, heterogeneous, and hypodense masses in the right liver lobe during the plain scan phases. CT further revealed masses with significant heterogeneous contrast enhancement during the arterial phase, with the enhancement continuing during the portal phases (*Figure 1*). In magnetic resonance imaging (MRI), the masses were hypointense during the T1-weighted imaging phase and had a significant high-intensity area during the T2- and diffusion-weighted imaging phases. On enhanced MRI, the solid portions of these masses showed significant enhancement in the early arterial phase, and the masses remained significantly enhanced in the portal venous phase. CT and MRI both detected multiple enlarged portal lymph nodes with significant heterogeneous enhancement, with the largest node measuring about 5.6 cm ×7.2 cm in size (*Figure 2*). The pathological findings of the biopsy mass specimen from the right liver lobe suggested a malignant neoplasm that had originated from a neuroendocrine cell type. The pathological findings suggested that the intermediate-sized tumor cells were arranged in nests with uniform round or oval nuclei, a moderate amount of eosinophilic cytoplasm, and frequent mitosis. There were no areas of necrosis. Histological and immunohistochemical examinations revealed positive staining for clusters of differentiation 56 (CD56), cytokeratin (CK) 8/18 and synaptophysin and suggested a malignant neoplasm that had originated from a neuroendocrine cell type. The tumor cells were negative for chromogranin A and hepatocyte 1, and the tumor had a Ki-67 index of 80% (*Figure 3*). The results of immunohistochemical staining confirmed NEC of the liver. Additionally, endoscopic, colonoscopy, CT and MRI were used to exclude extrahepatic primary NEC.

On admission, the patient was alert and conscious, with a height of 165 cm and a weight of 60 kg. Physical examination showed no signs of jaundice.

The patient underwent HAIC with the modified fluorouracil and oxaliplatin (mFOLFOX) (oxaliplatin

Highlight box

Key findings

- This case emphasized that hepatic arterial infusion chemotherapy (HAIC), targeted therapy and immunotherapy may provide a more comprehensive and effective choice for the treatment of primary hepatic neuroendocrine carcinoma (PHNEC), especially for advanced cancer.

What is known and what is new?

- PHNEC is a very rare tumor and its effective therapy is also uncertain. The therapy including the HAIC, targeted therapy or immunotherapy for liver cancer such as hepatocellular carcinoma is normal and effective as a neoadjuvant treatment, especially advanced cancer. It allowed some cancer patients to avoid surgery.
- Systematic therapy, including HAIC combined with immunotherapy and targeted therapy, may contribute to improving the quality of life of PHNEC patients and prolonging their survival.

What is the implication, and what should change now?

- Patients with PHNEC including advanced cancer may derive more benefit from comprehensive treatment.

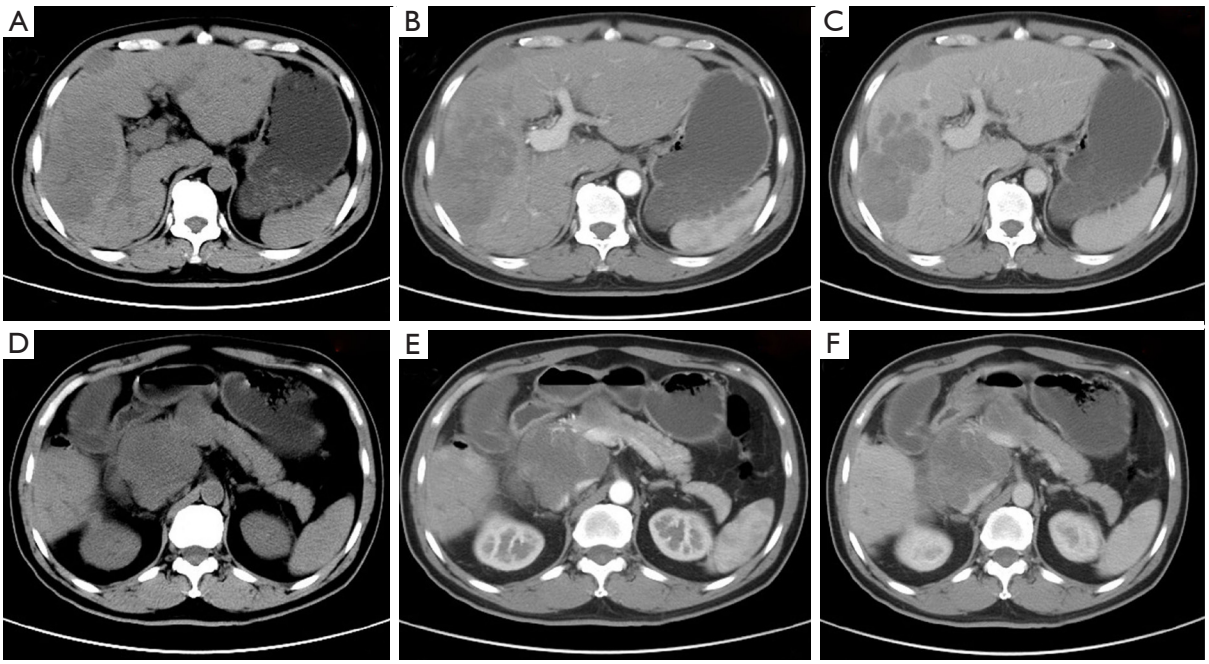

Figure 1 CT images before initiation of six courses of HAIC showed multiple well-circumscribed, heterogeneous, hypodense liver masses. (A) The largest was located in the right lobe of the liver and measured about 9.2 cm × 6.3 cm × 8.8 cm in diameter. Masses with significant contrast enhancement during the (B) arterial and (C) portal phases. A massive portal lymph nodes lesion appeared as (D) hypodense on unenhanced CT scanning. (E) heterogeneous arterial hyperenhancement and (F) washout in the portal phases after contrast. CT, computed tomography; HAIC, hepatic arterial infusion chemotherapy.

85 mg/m^2, leucovorin 400 mg/m^2, and fluorouracil 2,500 mg/m^2; continuous intra-arterial infusion over 46 hours). A microcatheter was inserted through the hepatic arterial catheter, and then angiography was performed (*Figure 4*). The microcatheter eventually was placed in the tumor-feeding artery of the liver. The extracorporeal section of the catheter was covered with sterile medical gauze and fastened on the skin of the thigh using bandages. Chemotherapy with an mFOLFOX regimen was administered when the patient returned to the ward.

HAIC was performed every 3 weeks until 6 courses were completed.

The patient received camrelizumab at a fixed dose of 200 mg intravenously within 7 days after the start of HAIC. Meanwhile, the patient continued to receive oral apatinib at a dose of 250 mg once daily. After six courses of HAIC combined with camrelizumab and continued oral apatinib, the patient showed no clinical symptoms when he was rehospitalized. The levels of tumor markers including AFP (normal range: 0–8.04 ng/mL), CA19-9 (normal range: 0–37 U/mL), and PIVKA-II (normal range: 0–40 AU/mL) were negative. Liver and renal functions were normal. CT showed a marked decrease in the size of the largest liver mass and partial portal lymph nodes, without obvious new metastases, indicating a partial response of the PHNEC (*Figure 5*). MRI showed that the size of the intrahepatic lesions decreased, similarly to that shown on CT. MRI also indicated that the multiple portal lymph nodes had decreased in size compared with shown in the previous MR examination (*Figure 6*).

After six cycles of HAIC, regular examinations were conducted for follow-up. The patient was treated with camrelizumab combined with apatinib. On November 13, 2021, apatinib was changed to anlotinib.

At the fourth month of follow-up after six cycles of HAIC, the reexamination indicated tumor progression, with an approximately 3.4 cm × 4 cm sized tumor metastasis in the right liver lobe (S6), a slight annular enhancement surrounding tumor on enhanced CT, and slight hypointensity during the hepatobiliary phase (*Figure 7*).

The routine reexaminations after two cycles of HAIC treatment showed that both the original and new lesions had shrunk (*Figure 8*). The patient was administered camrelizumab and anlotinib regularly.

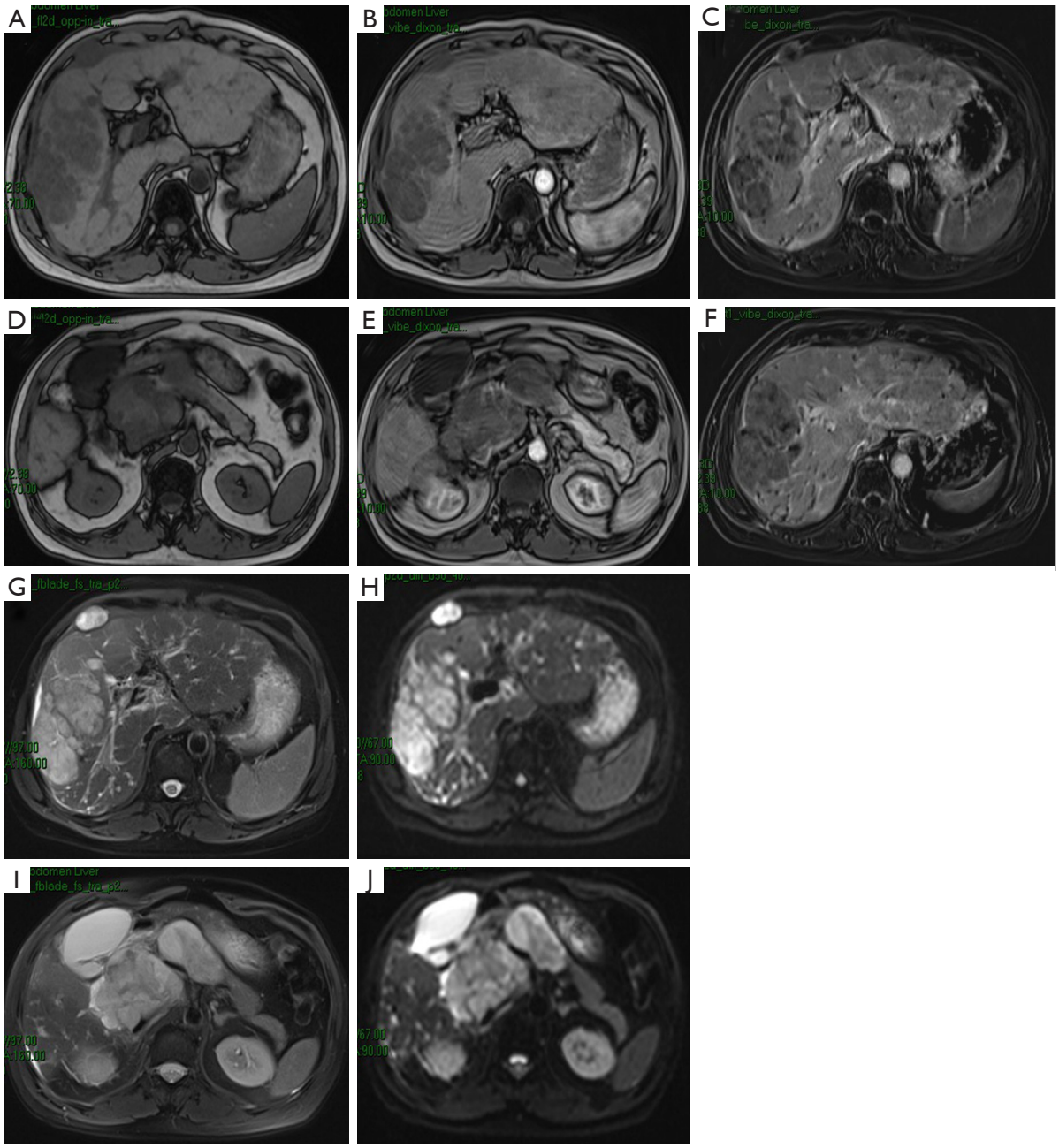

Figure 2 MR images before the initiation of six courses of HAIC: the largest mass size of 9.2 cm × 6.3 cm × 8.8 cm in the right lobe of liver, with a massive portal lymph node lesion measuring 5.6 cm × 7.2 cm in size. (A,D) Transverse T1-weighted imaging. (B,E) Contrast-enhanced dynamic T1-weighted arterial phase and (C,F) delayed phase imaging. (G,I) Transverse T2-weighted and (H,J) transverse diffusion-weighted imaging. MR, magnetic resonance; HAIC, hepatic arterial infusion chemotherapy.

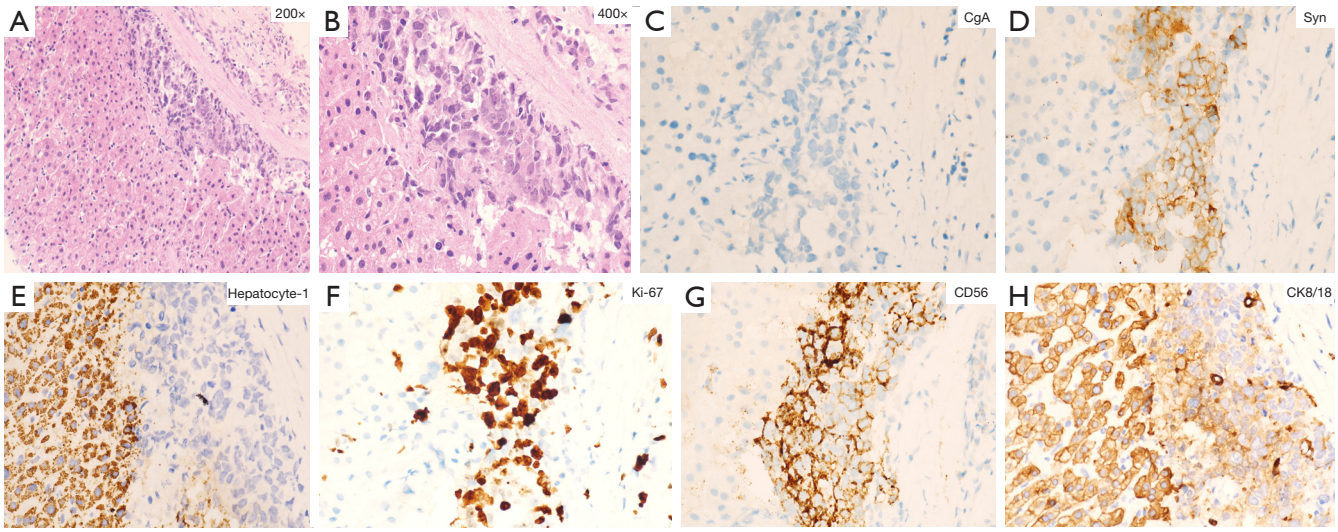

Figure 3 Histopathology. Hematoxylin and eosin staining at ×200 (A) and ×400 (B). Immunohistochemistry was positive for the NEC markers (D) Syn, (F) Ki-67, (G) CD56, and (H) CK8/18, and negative for (C) CgA and (E) hepatocyte 1 in primary hepatic NEC tissues (×400). CgA, chromogranin A; Syn, synaptophysin; CK, cytokeratin; NEC, neuroendocrine carcinoma.

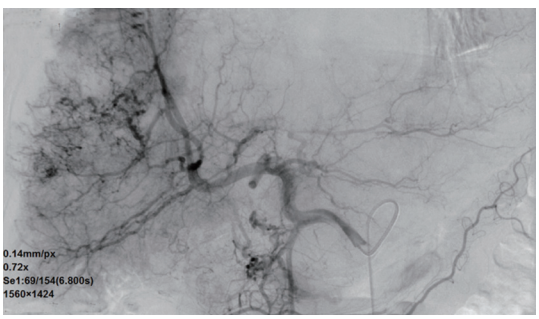

Figure 4 Angiogram showing multiple masses in the right lobe of the liver and a massive portal lymph node.

On March 1, 2023, the last follow-up CT showed that the primary lesion measured 3.2 cm × 1.5 cm × 2.2 cm in size, with slightly enhanced intrahepatic nodules during the enhanced arterial phase. The enhancement was reduced in the portal vein phase and the delayed phase, and the recurrent lesion had disappeared (*Figure 9*). On March 2, 2023, camrelizumab was discontinued after 2 years of use. At the time of writing, the patient is regularly taking antitumor therapy with anlotinib alone (*Figure 10*). All procedures performed in this study were in accordance with the ethical standards of the national research committees and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Primary NEC primarily can arise throughout the body including pancreas, gastrointestinal tract, and bronchopulmonary tract, especially lung. Primary hepatic neuroendocrine tumors (PHNETs) are a rarity and represent about 0.3% of all NETs, among PHNECs are extremely rare, with only about 90 cases having been reported in the English-language literature (3). The PHNEC patients usually presented a functional digestive disorder accompanied by abdominal discomfort. Several case reports have described primary hepatic NEC, but distinguishing this entity from metastatic NEC to the liver of unknown primary is challenging. There is also a lack of distinctive radiological features for PHNECs, and thus they are often misdiagnosed (1,4,5). Clinically, it is challenging to distinguish PHNECs from hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (6) before pathologic evaluation of a resected specimen by biopsy or surgery. A previous study showed that the positivity rates for SYN, CGA, and CD56 of PHNEC are >80% (7). In these situations, pathologic evaluation by liver biopsy may be valuable for the guidance of definitive diagnosis and oncological treatment. As we known, the origin of

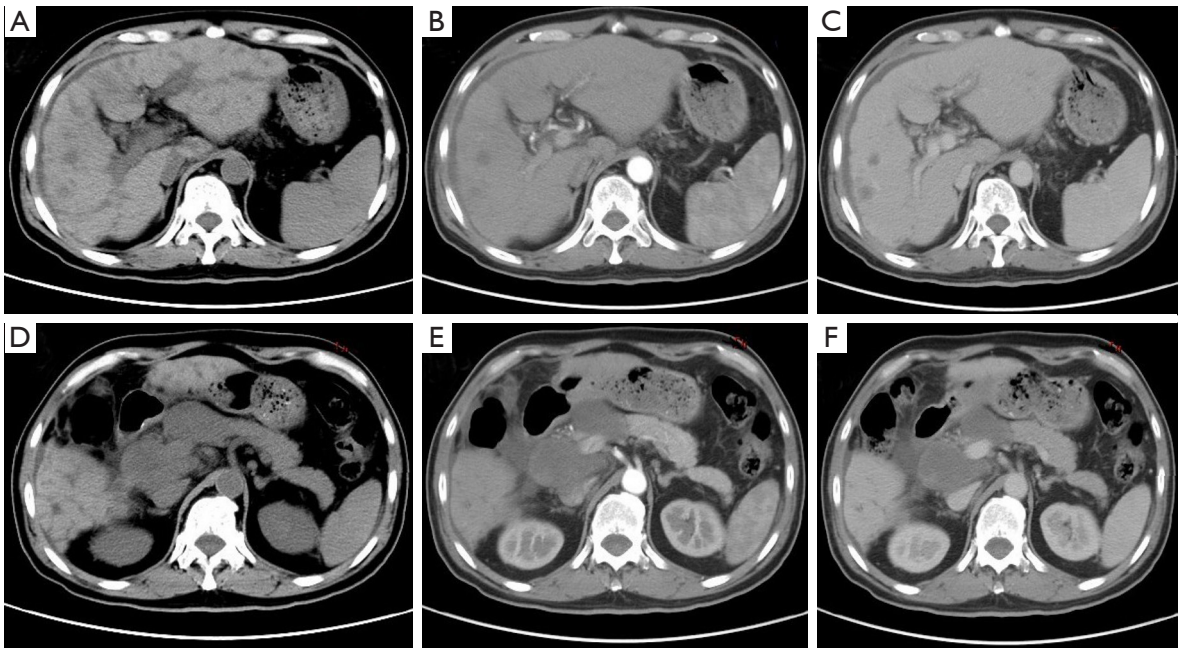

Figure 5 CT images after six courses of HAIC: the size of the largest liver mass and partial portal lymph nodes was markedly decreased. Postcontrast CT image of the (A,D) arterial phase, (B,E) portal venous phase, and (C,F) delayed phase. CT, computed tomography; HAIC, hepatic arterial infusion chemotherapy.

neuroendocrine cells can be traced back to gastrointestinal stem cells. Somatostatin receptors is association with tumor protein synthesis, hormone secretion, and proliferation of neuroendocrine tumors. The angiogenesis and metabolic in NEN rely on the upregulation of the mammalian target of rapamycin. Furthermore, proangiogenic factors such as vascular endothelial growth factor, angiopoietin, and fibroblast growth factor, are may induce the tumorigenesis of NETs. Therefore, inhibition the angiogenesis may it possible to block the proliferation and growth of NENs. According to previous study, we found that the infiltration of immune-related cells can also build an immunosuppressive microenvironment for the progression of NETs (8). Interestingly, some studies have found that NECs have features of high TMB and programmed cell death ligand 1 (PD-L1)-positive expression, which indicating promising responsiveness to immune checkpoint inhibitors (ICIs) (9-11).

The management of NECs remains controversial. There are standard drugs for PHNEC according to the consensus guidelines for NEC proposed by the North American Neuroendocrine Tumor Society, including cisplatin, carboplatin and etoposide. A study has indicated that HAIC may significantly improve the overall survival in patients with advanced HCC and provide better tumor control compared to transarterial chemoembolization (TACE) or transarterial embolization treatment, producing only mild side effects (12). Another study also indicated HAIC to be superior to TACE for the treatment of patients with unresectable ICC (13). As aforementioned, some studies have shown immunogenic and promising responsiveness to ICIs in NECs with a high tumor mutational burden (TMB) rate and high frequency of positive PD-L1 expression (9-11). Additionally, some trials have showed the efficacy and manageable toxicity of ICIs in refractory high-grade NETs (14-16). Currently, a phase II study is conducted to investigate the therapeutic potential of camrelizumab plus chemotherapy for advanced GEP-NEC (17). Apatinib has shown potentially positive outcomes in the treatment of gastric cancer (18). A recent case report indicated that the combined treatment (camrelizumab and apatinib) could substantially improve the NET G2 conditions-associated liver metastasis (19). A study had demonstrated that the addition of an anti-PD-L1 antibody to the chemotherapy backbone raised 3-year OS from 5.8% to 17.6% in small-cell lung cancer patients (20). A previous study based on patients with PD-L1-positive NETs showed that pembrolizumab treatment yielded an

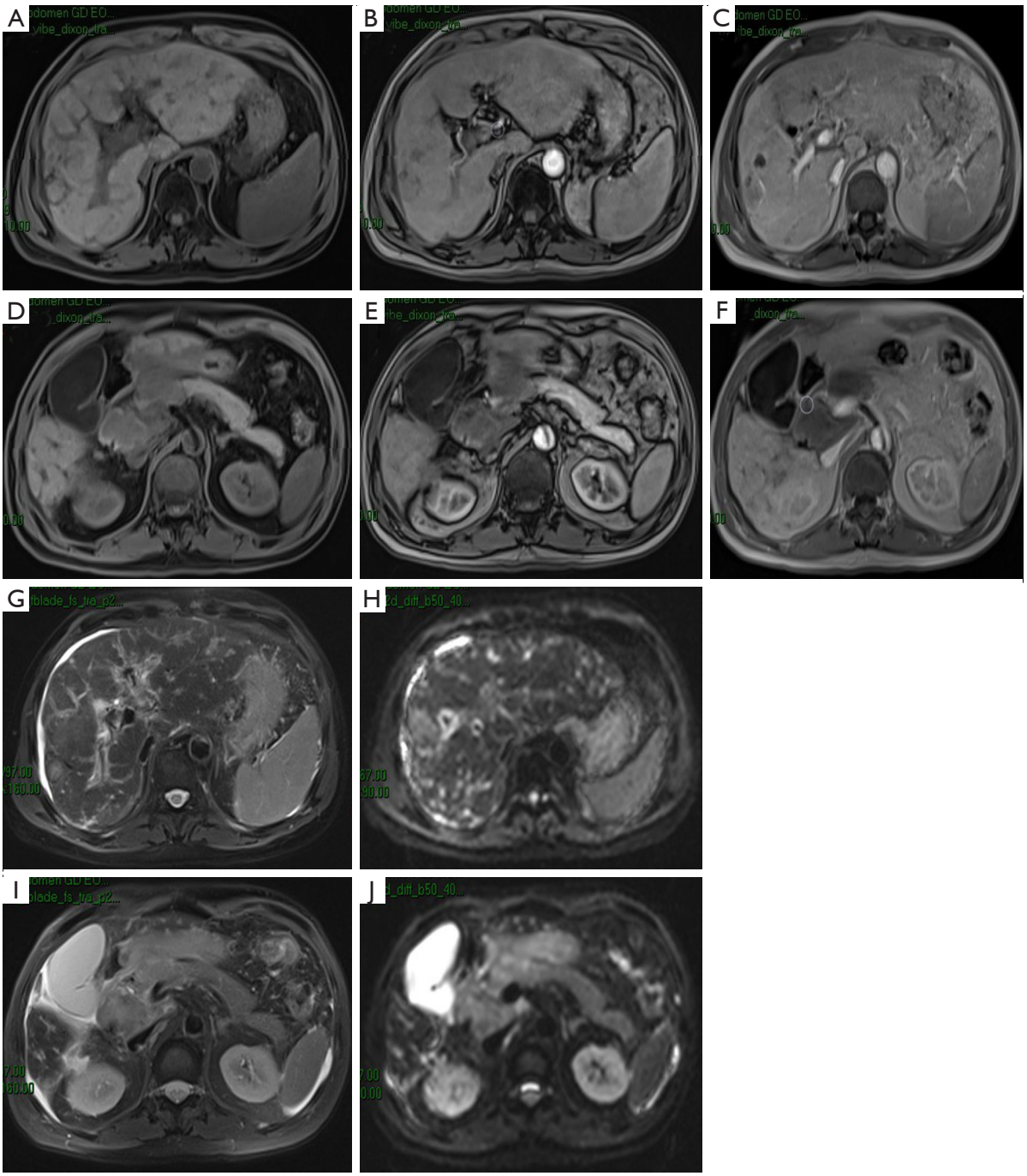

Figure 6 MR images after six courses of HAIC: (A,D) transverse T1-weighted imaging, contrast-enhanced dynamic T1-weighted imaging at the (B,E) arterial phase and (C,F) delayed phase, and (G,I) transverse T2-weighted and (H,J) transverse diffusion-weighted imaging. MR, magnetic resonance; HAIC, hepatic arterial infusion chemotherapy.

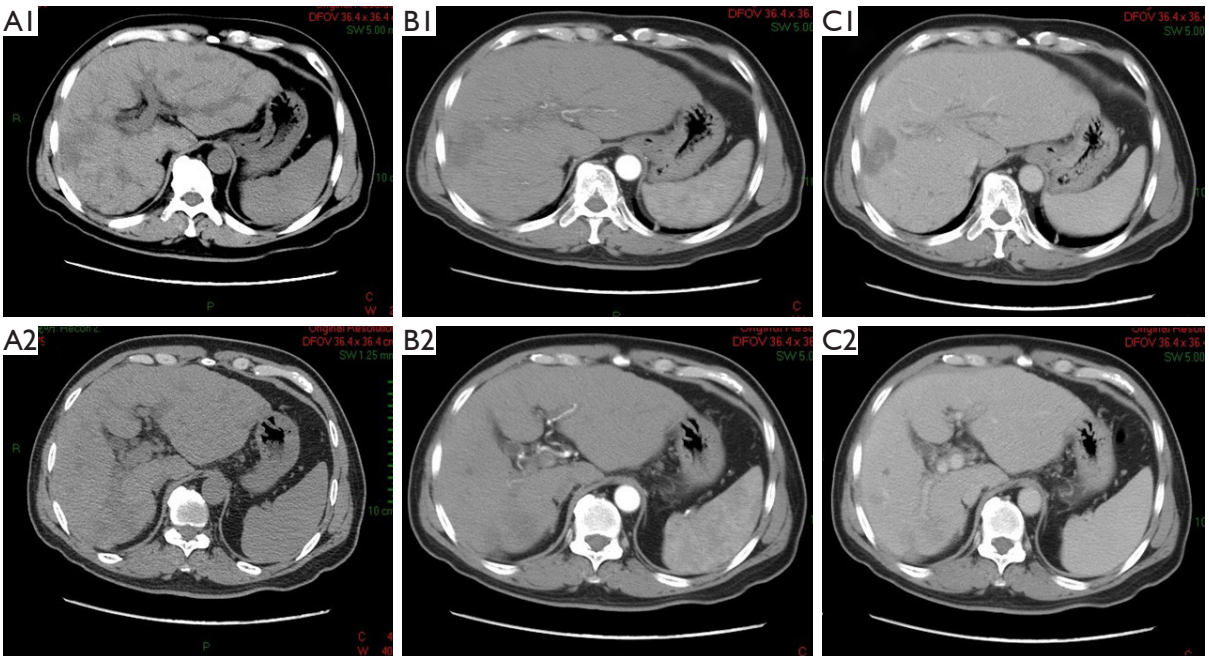

Figure 7 CT images after 4 months of follow-up after 6 cycles of HAIC. A new tumor appeared in the (A1,A2) unenhanced CT scanning phase, the liver postcontrast CT image of the (B1,B2) arterial phase and (C1,C2) portal venous phase. CT, computed tomography; HAIC, hepatic arterial infusion chemotherapy.

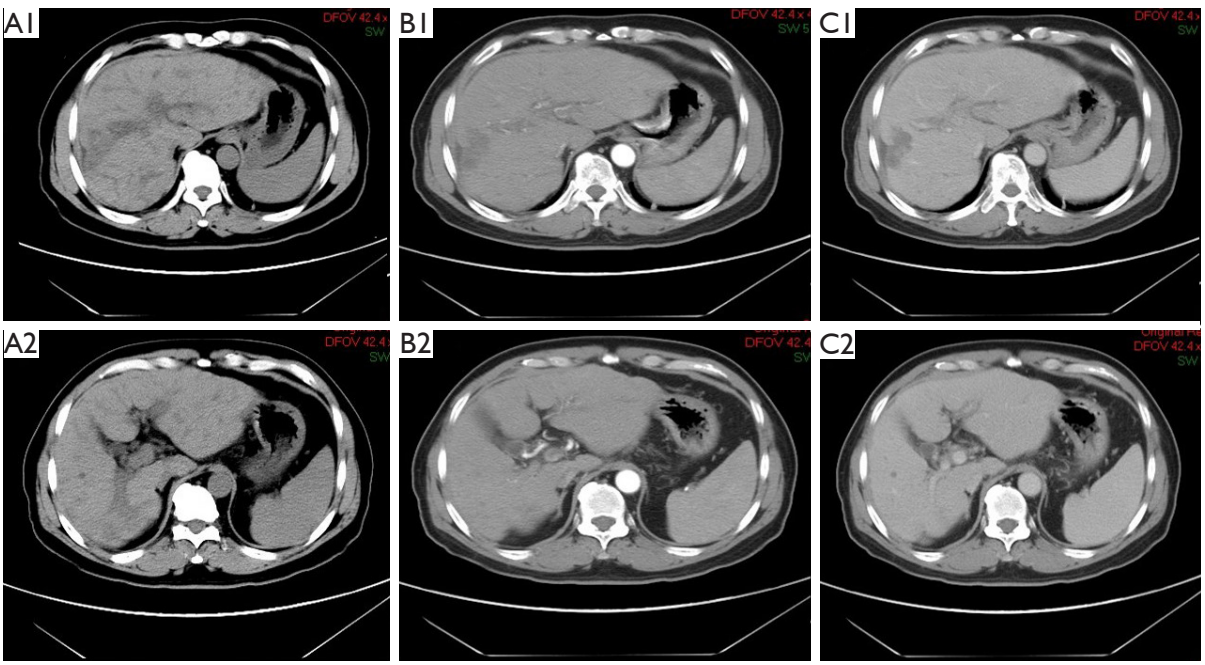

Figure 8 CT images of the tumor recurred after two cycles of HAIC. The primary lesion was smaller than that before the (A1,A2) unenhanced CT scanning phase, the (B1,B2) arterial phase and (C1,C2) portal venous phase. CT, computed tomography; HAIC, hepatic arterial infusion chemotherapy.

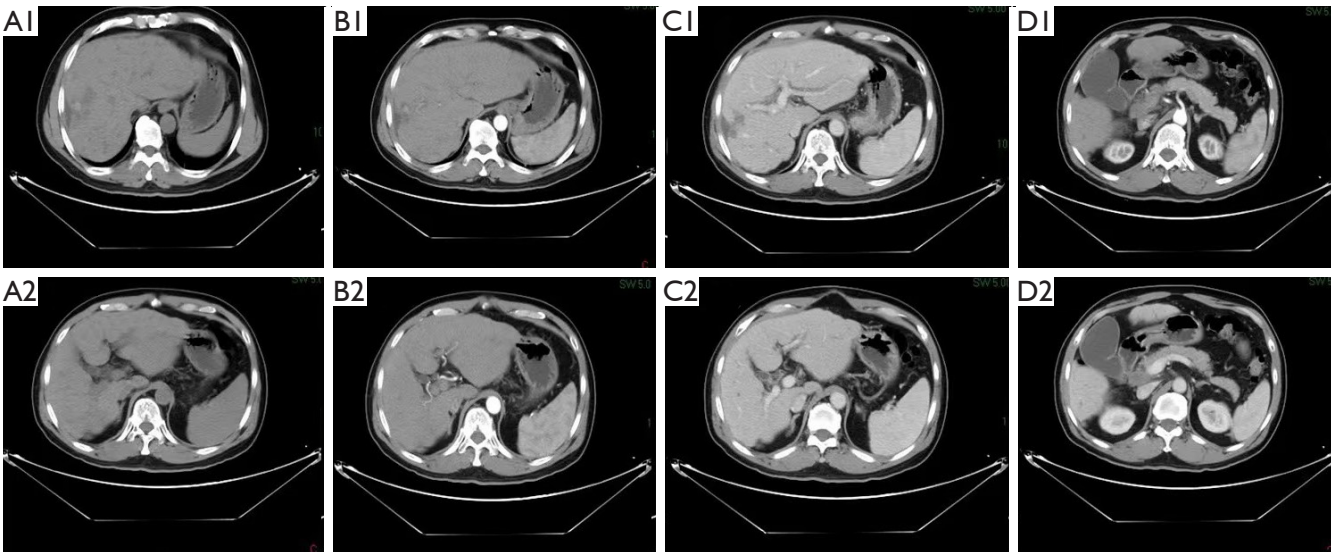

Figure 9 CT images at the last follow-up. The primary lesion was smaller than that before the (A1,A2) unenhanced CT scanning phase, the (B1,B2) arterial phase and (C1,C2) portal venous phase. (D1,D2) The size of the largest liver mass and partial portal lymph nodes was markedly decreased. CT, computed tomography.

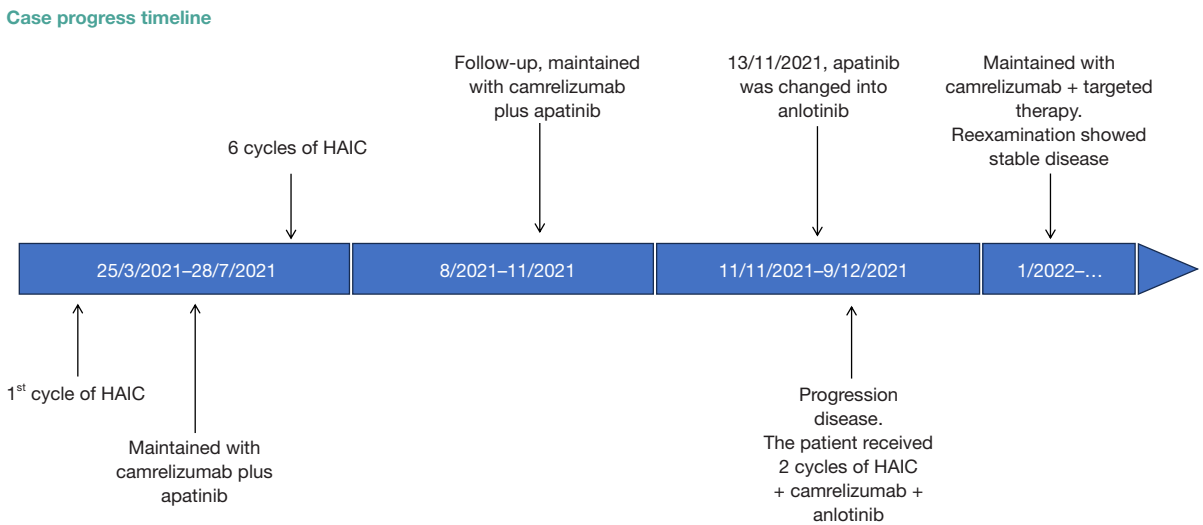

Figure 10 The timeline of patient's treatment history. HAIC, hepatic arterial infusion chemotherapy.

objective response rate (ORR) of 6.3% for patients with well- or moderately-differentiated pancreatic neuroendocrine tumors (16). Additionally, a multi-center phase Ib trial indicated a comparable response rate between the well-differentiated NET subgroup and poorly-differentiated NEC subgroup when 40 NEN patients were treated with anti-programmed cell death protein 1 (anti-PD-1) therapy (ORR: 18.7% *vs.* 25.0%) (21). Two placebo controlled phase 3 trials (NCT02588170 and NCT02589821) have demonstrated that those treated with tyrosine kinase inhibitors using surufatinib in extrapancreatic and PanNETs improved PFS (22,23).

Our study was the first to evaluate the efficacy of HAIC combined with a PD-1 inhibitor and targeted antiangiogenic therapy in patients with PHNEC. Administration of intrahepatic chemotherapy using a platinum-based regimen (e.g., FOLFOX) may represent an alternative to systemic

therapy in patients with PHNEC with minimal or absent extra-hepatic disease.

Conclusions

We present the first report of an extremely rare case of PHNEC treated with HAIC combined with camrelizumab and apatinib. Presently, liver resection remains the only curative treatment for patients with PHNECs. However, for patients with unresectable PHNECs, the optimal treatment is controversial; nonetheless, HAIC combined with camrelizumab and targeted therapy may be a safe and effective treatment.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-571/rc

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-571/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-571/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the national research committees and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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