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CASE REPORT

Transarterial Chemoembolization (TACE) Combined with Quadruple Therapy (XELOX Regimen + Tislelizumab + Surufatinib) for the Treatment of Advanced Primary Hepatic Neuroendocrine Carcinoma: A Case Report

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Abstract

Objective: To explore the efficacy and safety of quadruple therapy combining immunotherapy and targeted therapy in the treatment of advanced primary hepatic neuroendocrine carcinoma (PHNECs).

Methods: The clinical history, imaging findings, pathological immunohistochemistry, quadruple therapy involving immunotherapy and targeted therapy, as well as transcatheter arterial chemoembolization (TACE) treatment of a patient with advanced PHNECs were summarized. Relevant literature was also reviewed.

Results: The patient presented with no obvious symptoms or signs. Contrast-enhanced CT revealed multiple homogeneous low-density lesions in the liver, while contrast-enhanced MRI indicated multiple intrahepatic and extrahepatic metastases. Histopathological biopsy and immunohistochemical analysis confirmed the diagnosis of hepatic small cell neuroendocrine carcinoma. Following treatment with tislelizumab, surufatinib, capecitabine, oxaliplatin, and TACE, both the primary tumor and distant metastases showed significant volume reduction.

Conclusion: PHNECs are rare malignant tumors that are prone to misdiagnosis. Pathological immunohistochemistry guided by ultrasound-assisted biopsy can facilitate an accurate diagnosis. The combination of quadruple therapy with immunotherapy and targeted therapy, along with TACE, achieved favorable therapeutic outcomes in this case.

Keywords: Primary hepatic neuroendocrine carcinoma; Immunotherapy; Targeted therapy; TACE; Efficacy

Introduction

Neuroendocrine tumors (NETs), also known as carcinoid tumors or argentaffinomas, represent a rare group of malignant neoplasms. Primary hepatic neuroendocrine carcinoma (PHNECs) is extremely rare, accounting for only 0.3% of all NETs[1], with fewer than 150 cases reported in the English literature[2]. These tumors originate from neuroectodermal cells[3]. NETs most commonly arise in the gastrointestinal tract (48%), lungs (25%), and pancreas (9%), though they can also occur in other locations[3]. PHNECs typically develop in patients between the ages of 40 and 60, with no significant gender predilection or established risk factors[4]. Due to their slow growth and lack of endocrine functionality, PHNECs often remain asymptomatic for extended periods. Most cases are non-functional and do not present with carcinoid syndrome. Only 10% of PHNEC cases exhibit the classic triad of abdominal pain, flushing, and diarrhea[5]. The pathogenesis of PHNECs involves multiple factors[6], including tumor origin, growth factor receptors and signaling pathways, genetic and epigenetic alterations, as well as other potential contributors. However, the exact molecular mechanisms underlying PHNEC development remain unclear,

necessitating further research. The rarity of PHNECs makes differentiation from the more common hepatocellular carcinoma (HCC) challenging, leading to frequent misdiagnosis as HCC in clinical practice[1]. Currently, there is no standardized treatment protocol for advanced or metastatic PHNECs. Most patients undergo chemotherapy; however, the therapeutic outcomes remain suboptimal.

In recent years, immunotherapy has emerged as a promising treatment approach, with combination regimens involving immunotherapy, targeted therapy, and chemotherapy significantly prolonging the survival of patients with advanced liver cancer. Additionally, the precise treatment provided by TACE can effectively reduce the tumor burden in advanced liver cancer. Therefore, for patients with advanced metastatic PHNECs, following a multidisciplinary team (MDT) evaluation, we decided to administer a quadruple regimen combining immunotherapy and targeted therapy along with TACE. Based on the patient's therapeutic response and safety profile, the combination of quadruple immunotherapy-targeted therapy and TACE may represent an effective and safe treatment strategy for advanced metastatic PHNECs.

1. Materials and Methods

1.1 Clinical Data

The patient was an elderly female, 53 years old, who was admitted to the HPB Department of our institution due to a "hepatic space-occupying lesion detected during examination for 10 days." She had no symptoms of abdominal pain, diarrhea, fatigue, loss of appetite, jaundice, dark urine, pruritus, nausea, or vomiting.

Physical Examination: The abdomen was flat, without tenderness, muscle tension, or rebound pain. The liver was palpable 2 cm below the right costal margin, with no detectable splenomegaly or abdominal masses. No shifting dullness was noted, and bowel sounds were normal.

Laboratory tests: HBV-DNA quantitative analysis: 1.28E+004 IU/mL; HBsAg (+), HBcAb (+), HBeAb (+); alpha-fetoprotein (AFP): 260.03 μg/L.

2. Examination Results

2.1 CT Findings

Contrast-enhanced CT from an external hospital revealed multiple homogeneous low-density lesions in the liver, with necrotic and cystic-solid liquefaction areas within the tumors. The imaging findings were highly suggestive of primary liver cancer (original CT images not available for review).

2.2 MRI Findings

Contrast-enhanced MRI showed:

1. Multiple space-occupying lesions in the right lobe of the liver, suggestive of hepatocellular carcinoma (HCC) with intrahepatic metastases, with a high likelihood of hepatocellular carcinoma.
2. Tumor thrombus formation in the right branch of the portal vein, middle hepatic vein, inferior vena cava, and right atrium.
3. Multiple lymph node metastases in the hepatic hilum, abdominal cavity, and retroperitoneum. (Figure 1)

2.3 Pathological Diagnosis

Histopathological Biopsy Results: The biopsy specimen showed tumor tissue arranged in irregular glandular and nest-like structures. The tumor cells were relatively uniform in size, with a mitotic count of 1/10 high-power fields (HPF).

Immunohistochemical staining results: CKp (-), CD56 (+), CgA (-), Syn (+), TTF-1 (-), Vimentin (-), Ki-67 ≈ 60%. Based on the immunohistochemical findings, the diagnosis was hepatic small cell neuroendocrine carcinoma (G3, poorly differentiated)(Figure 2).

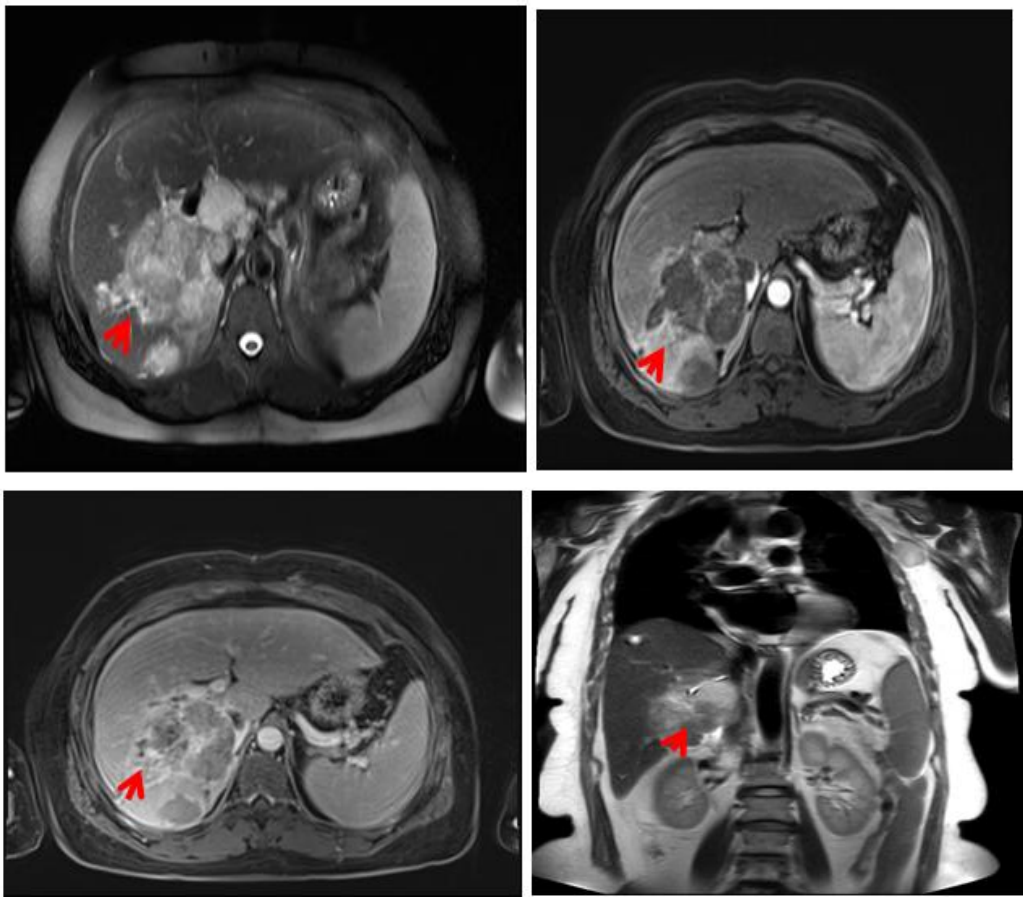

Figure 1: Contrast-Enhanced MRI Findings

Multiple mass-like and nodular signal abnormalities were observed in the right lobe of the liver. On T1-weighted imaging, the lesions appeared as slightly hypointense signals, while on diffusion-weighted imaging (DWI), they exhibited hyperintensity, with some areas showing a confluent pattern. In the arterial phase, the lesion margins displayed heterogeneous enhancement, whereas in the delayed phase, the lesions exhibited progressive enhancement with persistent hyperintensity at the periphery. In the hepatobiliary-specific phase, the lesions showed a mixed pattern of high and low signals. The largest lesion measured approximately 6.8 cm × 5.9 cm.

Diagnostic Consideration: Multiple space-occupying lesions in the right lobe of the liver, highly suggestive of hepatocellular carcinoma (HCC) with intrahepatic metastases, though neuroendocrine tumor (NET) cannot be entirely ruled out.

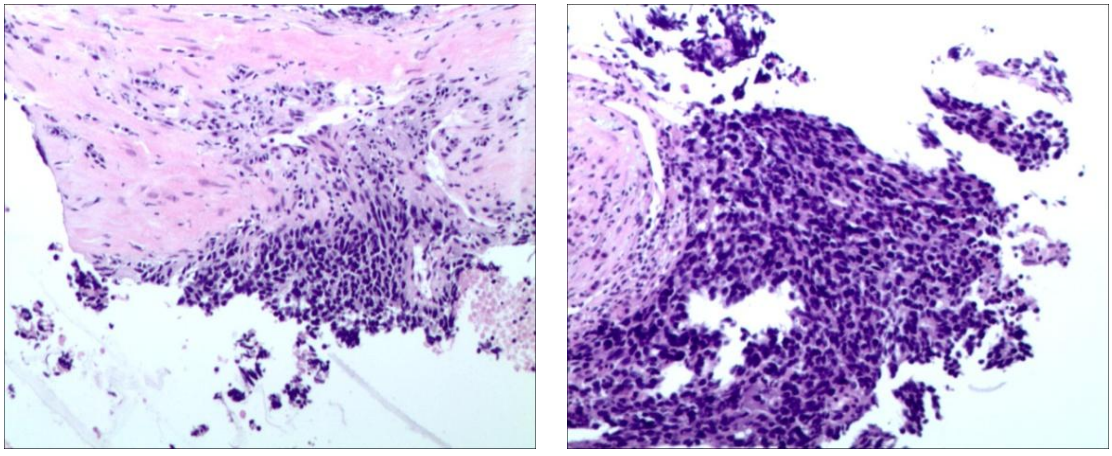

Figure 2: Pathological Diagnosis
(Specimen from the liver) Small cell neuroendocrine carcinoma.

3. Treatment Approach

3.1 Pharmacological Treatment

The patient underwent immunotherapy (PD-1 inhibitor) combined with chemotherapy (XELOX regimen) on October 11, 2023, November 7, 2023, December 12, 2023, and January 10, 2024. The treatment regimen consisted of tislelizumab (200 mg IV infusion) combined with oxaliplatin (200 mg IV infusion) and capecitabine (1.5 g orally, twice daily). After four treatment cycles, imaging examinations revealed pulmonary metastatic lesions (Figure 3). Following a multidisciplinary team (MDT) evaluation on February 19, 2023, the patient was switched to a quadruple regimen combining immunotherapy and targeted therapy, which included tislelizumab (200 mg IV infusion) combined with surufatinib (300 mg orally, once daily), oxaliplatin (200 mg IV infusion), and capecitabine (1.5 g orally, twice daily).

3.2 Interventional Treatment

The patient underwent selective transcatheter arterial chemoembolization (TACE) on November 7, 2023, December 12, 2023, January 10, 2024, and February 19, 2024. The TACE procedure involved the administration of oxaliplatin (50 mg) and drug-eluting microspheres (200 μL).

3.3 Treatment Efficacy and Safety Evaluation

After four cycles of immunotherapy combined with chemotherapy (XELOX regimen) and TACE, tumor regression was assessed. The results showed a significant reduction in the size of the primary tumor as well as distant lymph node metastases (Figure 3). However, contrast-enhanced CT on February 19, 2023, revealed new pulmonary metastases (Figure 4), leading to the addition of surufatinib following an MDT evaluation.

After two cycles of the quadruple regimen combining immunotherapy and targeted therapy with TACE, further evaluation showed a significant reduction in the primary tumor and distant lymph node metastases, as well as shrinkage of the pulmonary metastases (Figure 5)

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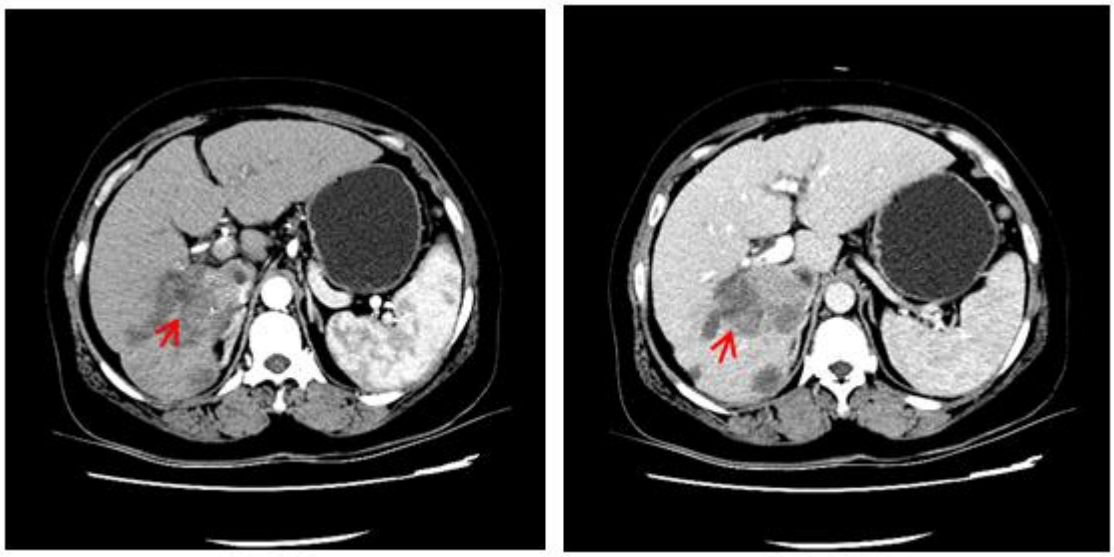

Figure 3: CT Evaluation After Four Cycles of Immunotherapy Combined with Chemotherapy (XELOX) and TACE

CT imaging after four cycles of immunotherapy (XELOX regimen) combined with TACE showed tumor shrinkage, with multiple areas of lipiodol deposition and reduced tumor blood supply compared to previous scans.

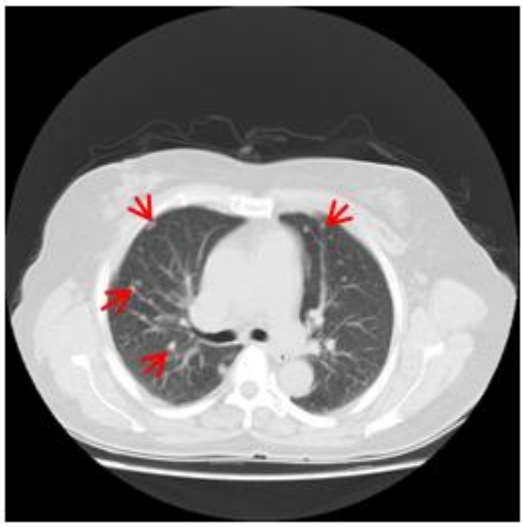

Figure 4: CT Findings Indicating Pulmonary Metastases

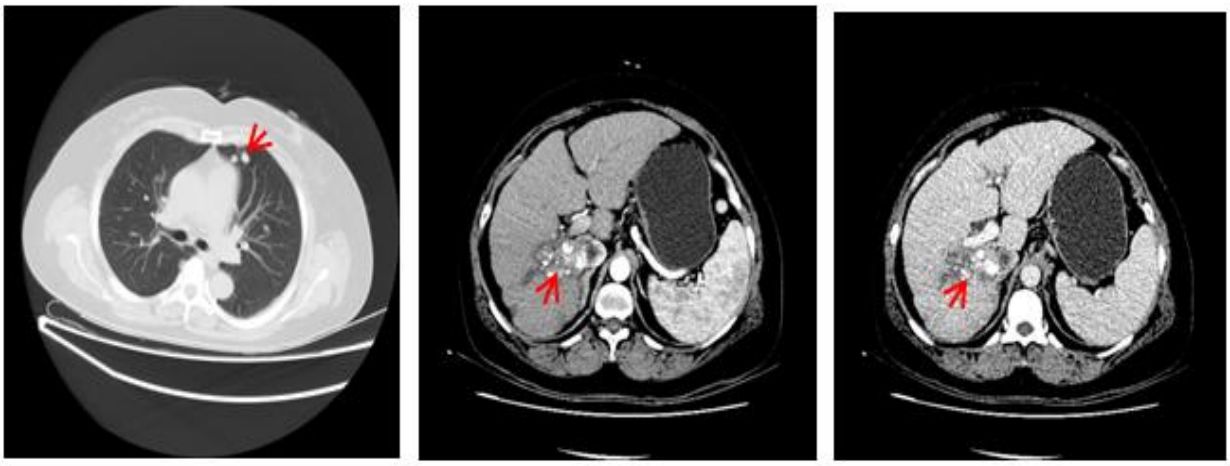

Figure 5: CT Findings After Two Cycles of the Quadruple Immunotherapy-Targeted Therapy Regimen Combined with TACE

CT imaging demonstrated a significant reduction in the primary tumor size and distant lymph node metastases, as well as shrinkage of the pulmonary metastatic lesions.

Adverse Events during Treatment

• Leukopenia: Occurred four times, with the lowest count reaching Grade 2 adverse event (AE). The condition was managed with granulocyte-colony stimulating factor (G-CSF) injections, leading to recovery within the normal range.

• Pain: Likely a side effect of TACE treatment. The patient experienced pain relief after receiving analgesic medication.

• Mild nausea and loss of appetite: No specific treatment was administered, and symptoms resolved spontaneously.

4. Discussion

The quadruple immunotherapy-targeted therapy regimen combined with TACE may be an effective and safe treatment option for advanced metastatic primary hepatic neuroendocrine carcinoma (PHNECs). The patient was initially admitted with a diagnosis of a hepatic space-occupying lesion and concurrent chronic hepatitis B virus (HBV) infection. Laboratory tests revealed an elevated alpha-fetoprotein (AFP) level, and imaging findings showed tumor thrombus formation in the portal vein and multiple intrahepatic and extrahepatic lymph node metastases, but without significant clinical symptoms or signs. Based on the patient's overall condition, imaging, and laboratory findings, metastatic liver cancer was initially suspected. To further clarify the diagnosis, an ultrasound-guided biopsy was performed, and histopathological

immunohistochemistry confirmed poorly differentiated small cell neuroendocrine carcinoma (G3) of hepatic origin.

PHNECs are extremely rare, highly malignant, and associated with poor postoperative prognosis[1]. After undergoing four cycles of PD-1 inhibitor-based immunotherapy combined with chemotherapy (XELOX regimen), imaging evaluation revealed multiple pulmonary metastases. A multidisciplinary team (MDT) discussion was conducted, involving specialists from oncology, neurology, radiology, pathology, and gastroenterology. Following the MDT assessment, surufatinib was added as a targeted therapy. After four additional treatment cycles, contrast-enhanced abdominal CT showed a reduction in tumor diameter, significant reduction in blood supply, and shrinkage of both primary and metastatic lymph node lesions, with pulmonary metastases also decreasing in size.

Diagnosing PHNECs is challenging due to non-specific imaging findings, leading to frequent misdiagnosis. The diagnosis primarily relies on ruling out extrahepatic primary tumors and confirming pathological immunohistochemical findings. Studies have shown that NSE, CgA, Syn, and Ki-67 are widely expressed in neuroendocrine cells and tumors. Immunohistochemistry plays a critical role in differential diagnosis due to its high sensitivity and specificity, as tumor markers such as AFP, CEA, and CA199 are usually within normal ranges[6]. Immunohistochemical results in this patient indicated CKP negativity, which is consistent with PHNECs, as they originate from neuroendocrine cells rather than epithelial cells. The absence of CKP expression is a characteristic feature aiding in differential diagnosis[6]. However, given the patient's history of active hepatitis B infection and elevated CA199 and AFP levels, along with initial CT findings suggestive of primary liver cancer, and subsequent confirmation through biopsy, the possibility of a coexisting malignancy cannot be completely excluded.

Currently, surgical resection remains the preferred treatment for PHNECs, with complete removal of the primary tumor and lymph node dissection being the only potential curative approach[6]. In cases where surgical resection is not feasible due to tumor size or low differentiation, liver transplantation has shown significant efficacy, with postoperative survival extending up to 10 years[8]. Targeted therapies such as tyrosine kinase inhibitors (sunitinib) and mTOR inhibitors (everolimus) have demonstrated efficacy in treating pancreatic neuroendocrine tumors, but their role in PHNECs remains to be further explored. Other therapeutic options, including somatostatin analogs, interferons, chemotherapy agents, and peptide receptor radionuclide therapy (PRRT), require further clinical trials to confirm their effectiveness in PHNECs[1].

In recent years, immunotherapy has gained prominence, and combination strategies incorporating immune checkpoint inhibitors (ICIs) have shown promising results in advanced malignancies, particularly gastrointestinal tumors. The combination of ICIs with chemotherapy, targeted therapy, or TACE has significantly improved survival rates in advanced hepatocellular carcinoma (HCC) while reducing recurrence rates, and has also demonstrated encouraging outcomes in advanced neuroendocrine carcinomas. As there is currently no standardized treatment consensus for advanced PHNECs, a combination regimen involving ICIs, targeted therapy, chemotherapy, and TACE may represent a potential treatment strategy.

The synergistic mechanisms of ICIs and anti-angiogenic agents in PHNECs remain a complex area of research. However, preliminary clinical applications have shown promising results[8]. The combination of these agents may enhance tumor immune response by promoting immune cell infiltration and activation, relieving immune suppression, and amplifying the effectiveness of immunotherapy. However, it is important to note that both immune checkpoint inhibitors and anti-angiogenic agents can cause adverse effects[8]. Therefore, careful patient monitoring is essential, and treatment should be adjusted based on individual responses. Further research is needed to determine the optimal dosage, administration method, and treatment duration for combination immunotherapy and targeted therapy in PHNECs to maximize efficacy while minimizing toxicity.

5. Conclusion

PHNECs is an extremely rare malignant tumor that is often misdiagnosed. Currently, there are no established treatment guidelines for PHNECs; however, when feasible, radical liver resection

remains the only potentially curative approach, and combination therapies may improve prognosis. This case report describes a patient with primary hepatic neuroendocrine carcinoma who underwent a combination treatment regimen consisting of an immune checkpoint inhibitor (tislelizumab), a targeted therapy agent (surufatinib), systemic chemotherapy (XELOX: capecitabine and oxaliplatin), and localized TACE intervention. Following treatment, both the primary tumor and distant metastases significantly decreased in size, and no grade 3 or higher adverse events were observed. The patient's overall survival has exceeded 12 months, and they remain under follow-up. Both the patient and their family were satisfied with the treatment outcome. Based on these findings, we believe that the combination of immune checkpoint inhibition (tislelizumab), targeted therapy (surufatinib), systemic chemotherapy (XELOX: capecitabine and oxaliplatin), and localized TACE intervention represents a potentially effective and safe multimodal treatment strategy for advanced PHNECs.

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Data Availability Statements

The data generated in the present study may be requested from the corresponding author.(E-mail:qinjianwei940@163.com)

The data generated in the present study are included in the figures and/or tables of this article.

Authors' Contributions

MBW and SYH analyzed the data and were the primary author of the manuscript. They are the co-first authors of this article.XSL acquired the CT scan images. LYS analyzed patient data. WBB confirm the authenticity of the data. PYP and QJW assisted in writing the manuscript. All authors have read and approved the final manuscript.

Patient Consent for Publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Competing Interests

The authors declare that they have no competing interests.

References

1. Quartey B. Primary hepatic neuroendocrine tumor: What do we know now? World J Oncol. **2011**;2(5):209–16.
2. Costa AC, Santa-Cruz F, Guimar~aes H, et al. Primary hepatic neuroendocrine tumor: A case report and literature review. Int J Surg Case Rep. **2020**;72:1–4.
3. Modlin I M, Lye K D, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors [J]. Cancer, **2003**, 97(4): 934-59.
4. Jain RD, Sakpal M, Asthana S, et al Primary hepatic neuroendocrine tumor: A rare entity. Radiol Case Rep. **2020**;15(11):2362–6.
5. Song JE, Kim BS, Lee CH. Primary hepatic neuroendocrine tumor: A case report and literature review. World J Clin Cases. **20 16**;4(8):243–7.
6. Lv P, Sun SB, Chen XN. Advances in the Diagnosis and Treatment of Primary Hepatic Neuroendocrine Tumors [J]. Journal of Hepatopancreatobiliary Surgery, **2017**, 29 (06): 511-514.
7. Tuan Linh L, Minh Duc N, Tu Minh H, et al. Primary hepatic neuroendocrine tumor. Endocrinol Diabetes Metab Case Rep. **2021**; 2021:20–0220.
8. M. D. Michael Torbenson, "Primary neuroendocrine tumorsand primary neuroendocrine carcinomas of the liver: a proposal for a multidiscipline defnition," Human Pathology,vol. 132, **2023**.
9. Liu D, Wang LL, Ren S, et al. Efficacy and Safety of Immune Checkpoint Inhibitors Combined with Anti-angiogenic Therapy in the Treatment of Hepatitis B-related Unresectable Hepatocellular Carcinoma [J]. Infectious Disease Information, **2024**, 37(04): 323-328.