Journal of Hepatocellular Carcinoma Dovepress

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CASE REPORT

Interventional Combined Microwave Ablation for Primary Neuroendocrine Carcinoma of the Liver Failing Systemic Chemotherapy: A Case Report

Yang Fang, Xiuying Jin, Huiying Cui, Zhezhu Han, Qiang Xu, Songnan Zhang

Department of Oncology, Yanbian University Hospital, Yanji, People's Republic of China

Correspondence: Songnan Zhang, Email zhangsn21@163.com

Background: Primary hepatic Neuroendocrine carcinoma (PHNEC) is exceptionally rare, and when it cannot be surgically removed locally, systemic combination therapy is the preferred treatment. However, current treatments have shown limited effectiveness, and more effective approach remains a matter of debate.

Case Presentation: We present a case involving a female patient diagnosed with non-surgically suitable PHNEC, confirmed through pathology. Following four cycles of standard first-line systemic chemotherapy, this intervention was prompted by imaging indicating suboptimal local lesion control, the patient underwent localized interventional and microwave ablation therapy. Subsequently, an evaluation based on mRECIST criteria revealed complete remission post-procedure. The disease sustained this remission status throughout the 14-month follow-up, with the administration of 14 cycles of immunocheckpoint inhibitor maintenance therapy, showing no signs of local recurrence or distant metastasis and devoid of any associated complications.

Conclusion: This case introduces a novel therapeutic avenue for individuals who are ineligible for surgery and have not responded to systemic chemotherapy. The diagnosis and management of PHNEC are deliberated within the framework of this particular case.

Keywords: primary hepatic neuroendocrine carcinoma, large cell, neuroendocrine carcinoma, interventional, liver

Introduction

Primary hepatic neuroendocrine carcinoma (PHNEC) is an exceptionally rare and diverse tumor arising from neuroendocrine cells, constituting approximately 0.3% of all neuroendocrine tumors.[1] Owing to the lack of distinctive specificity in symptoms, signs, and imaging, it is easily confused with other liver tumors,[2] diagnosis primarily depends on histopathologic examination through percutaneous puncture biopsy. Conventional imaging, coupled with growth inhibitory hormone receptor imaging (eg, PET-CT), is employed to rule out other primary lesions. The prognosis for PHNEC is notably grim, with a reported 1-year survival rate of 23.5% and a 5-year survival rate of 5.8%. The median overall survival is 16.5 months.[3] Neuroendocrine carcinoma is a highly aggressive disease; early radical surgery prolongs patient survival; most patients are found to have metastases, and the standard regimen is systemic chemotherapy, however, the therapeutic effect was suboptimal; interventional and ablative therapies are seldom used for this disease.[4] We present a case of PHNEC wherein the patient underwent treatment involving Transarterial Chemoembolization (TACE) combined with microwave ablation for intrahepatic lesions that exhibited persistent size and heterogeneous enhancement on imaging after four cycles of systemic chemotherapy. Postoperative follow-up assessments, utilizing modified solid tumor evaluation criteria, indicated the patient's complete remission status. The patient continued with 14 cycles of immune checkpoint inhibitors, with no evidence of local recurrence or distant metastasis observed over the 14-month follow-up period.

Case Presentation

The patient is a 64-year-old female with a medical history notable for hypertension and diabetes mellitus. She denied any history of hepatitis or alcohol consumption. In February 2022, she sought medical attention at a local hospital due to poor

Received: 26 September 2024
Accepted: 21 November 2024
Published: 26 November 2024

appetite and intermittent abdominal pain persisting for over 2 months. Imaging examinations suggested a high likelihood of primary hepatocellular carcinoma, leading to her admission to our hospital for further assessment. Upon examination, there were no evident positive signs. Liver function tests and tumor markers, including alpha-fetoprotein and carcinoembryonic antigen, showed no abnormalities. Neuron-specific enolase (NSE) level was measured at 73.8 U/mL. Enhanced CT of the entire abdomen revealed round masses in the right lobe of the liver near the hilar region and the right posterior lobe, exhibiting a maximum diameter of 8.5 cm. Post-enhancement, the masses displayed inhomogeneous enhancement, distinct contouring in the portal and delayed phases, and partial indistinctness from the portal vein (Figure 1). Chest CT and cranial nuclear magnetic scanning ruled out other primary lesions. On February 19, 2022, percutaneous hepatic puncture biopsy, guided by ultrasound, was conducted. Pathology results indicated neuroendocrine carcinoma of the liver, specifically the large-cell type. Immunohistochemistry revealed tumor cells with CK7 (-), CK20 (-), weak CK8/18 expression, Heppar-1 (-), GPC-3 (-), Syn (+), CgA (+), NSE (+), and Ki-67 (70%+) (Figure 2). Histologically, hepatic-origin neuroendocrine carcinoma was considered, and imaging failed to identify any primary lesion beyond the liver. Consequently, the diagnosis of primary hepatic neuroendocrine carcinoma (large-cell type) was established based on the combined findings from imaging and pathological histology.

Treatment and Follow-Up

Given the patient's substantial tumor size and multiple foci, the Multidisciplinary Team (MDT) recommended systemic therapy as the primary course of action, as surgical resection of the localized liver lesions was deemed unfeasible. On February 21, 2022, the initial hepatic tumor arterial embolization was performed to reduce tumor load. This involved using a mixture of iodine oil (20 mL) and epirubicin (20 mg), polyvinyl alcohol embolization microspheres, and bio-hemostatic sponges for embolization (Supplementary Figure 1). Post-surgery, following guideline recommendations, the patient received two cycles of the first-line standard regimen of systemic chemotherapy, which comprised etoposide combined with carboplatin. In May 2022, a review of the whole abdomen enhanced CT showed a reduction in the size of the lesion in the right posterior lobe, with evident iodine oil deposition compared to the previous examination. However, the lesion in the right lobe near the portal area exhibited no significant size change, with less obvious iodine oil

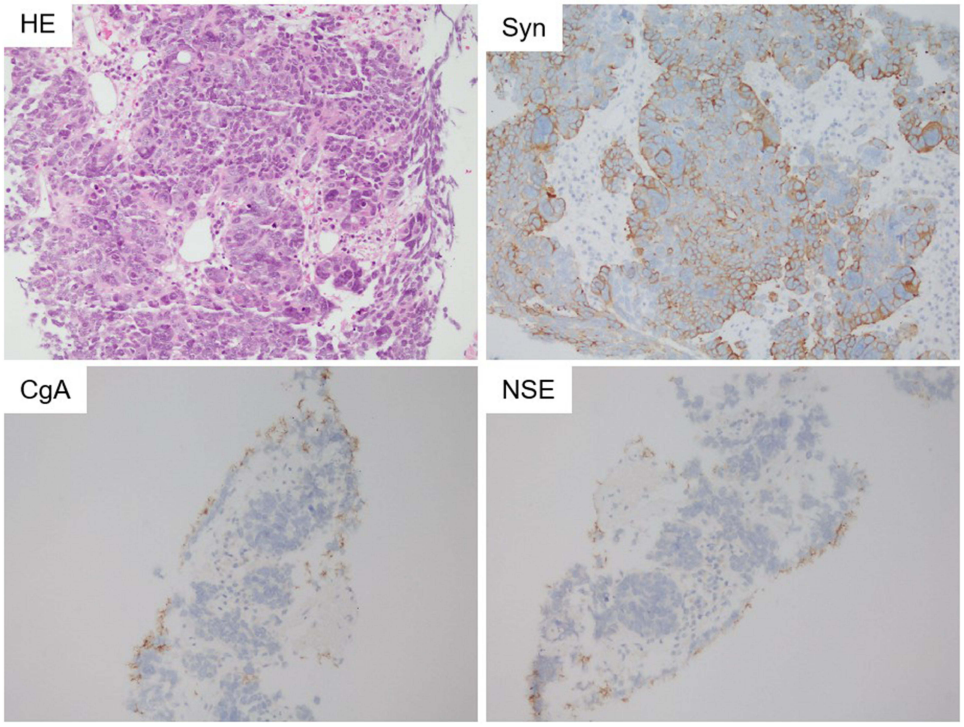

Figure 1 Hepatic large cell neuroendocrine carcinoma, Syn (+), CgA (+), NSE (+).

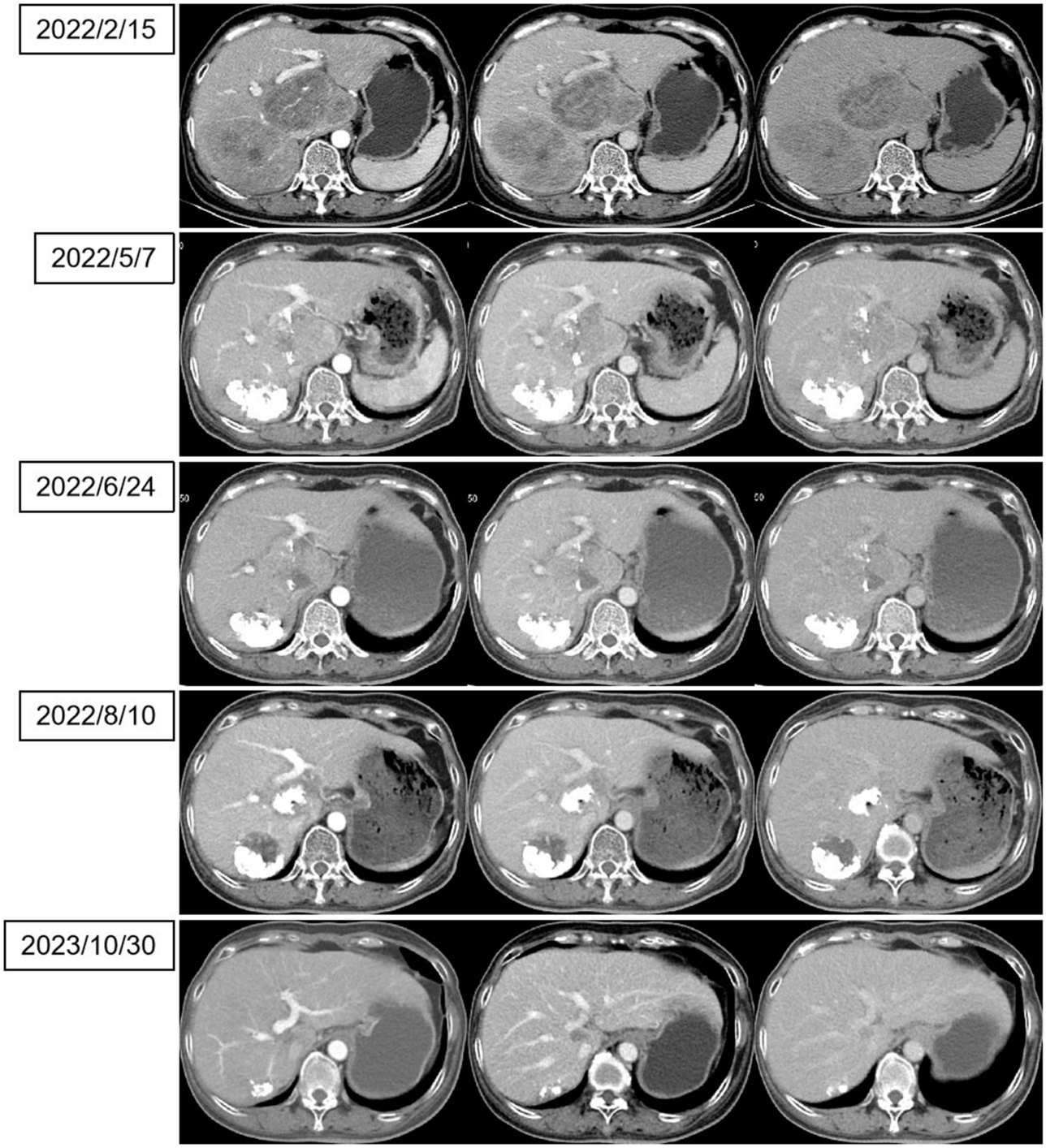

Figure 2 A comprehensive abdominal CT scan showed changes in the lesion's arterial, venous, and equilibrium phases throughout treatment. On 2022–02-21, initial imaging revealed an 8.5 cm liver tumor in the right posterior lobe, near the portal area. After two treatment cycles, on 2022–05-07, mild intensification of the lesion was observed. Following four cycles on 2022–06-24, CT indicated inadequate lesion control near the liver's right lobe portal area. After TACE and microwave ablation, imaging on 2022–08-10 showed iodine oil deposition and post-ablation changes but poor control over the lesion near the right hilar region. A final review on 2023–10-30 indicated complete remission (CR) of the lesion.

deposition and mildly inhomogeneous enhancement (Figure 1). The NSE levels decreased gradually to 19.6 U/mL. The original systemic chemotherapy regimen was continued for an additional two cycles. On June 24, 2022, a follow-up enhanced CT of the whole abdomen indicated that the size and iodine-oil dense distribution of the lesion in the right posterior lobe remained unchanged. The lesion in the right lobe near the hilar area showed no notable alterations

compared to May, maintaining inhomogeneous enhancement after enhancement. According to the mRECIST evaluation criteria, the lesion in the right posterior lobe was assessed as Complete Response (CR), while the lesion in the right lobe near the hilar area was deemed SD. Concurrently, the tumor marker NSE increased to 58.7 U/mL, signifying chemotherapy resistance in the patient. After Multidisciplinary Team (MDT) deliberation, recognizing limited benefits from chemotherapy, the patient underwent a second Transarterial Chemoembolization (TACE) procedure. This involved administering a mixture of iodine oil (20 mL) and epirubicin (20 mg), along with polyvinyl alcohol embolization microspheres and bio-hemostatic sponges. Subsequently, four weeks later, sequential hepatic tumor microwave ablation was performed using 60 W and a multi-point mobile ablation lasting 22 minutes, mainly for lesions in the right posterior lobe of the liver with partial response to chemotherapy and incomplete interventional embolization (Supplementary Figure 1). Upon postoperative review in August 2023 (four weeks later), imaging indicated a reduction in the size of the lesion in the right posterior lobe and the proximal hilar area. Iodine oil deposition was observed within the lesion, and no significant enhancement was noted after enhancement. According to RECIST1.1 criteria, the treatment efficacy was classified as Partial Response (PR), while based on mRECIST criteria, it was deemed Complete Response (CR). Simultaneously, the Neuron-specific enolase (NSE) level decreased to 17.6 U/mL. Subsequently, the patient commenced immune checkpoint inhibitor maintenance therapy with Tislelizumab (200 mg IV, once every 3 weeks) until June 2023, completing a total of 14 cycles. Throughout this period, tumor marker NSE remained essentially within normal range (Figure 3). In October 2023, re-evaluation through imaging revealed noticeable shrinkage in the lesion near the portal area in the right lobe of the liver and the right posterior lobe, with no evidence of new lesions. According to RECIST criteria, the condition was assessed as PR, and mRECIST criteria indicated CR. Imaging displayed no arterial phase enhancement (Figure 4).

Discussion

PHNEC is an exceedingly rare condition characterized by nonspecific clinical manifestations. Diagnostic imaging modalities such as ultrasound, CT, and MRI often face challenges in distinguishing PHNEC from other liver tumors, contributing to its high susceptibility to misdiagnosis.[5] The definitive diagnosis heavily relies on histopathology. Current reports mostly involve surgical treatment,[6] and while early radical surgery is considered the more effective treatment,[7] the recurrence and metastasis rates post-surgical resection are notably high, resulting in a poor prognosis.[3] Surgical intervention is often unattainable for many first-diagnosed PHNEC patients, and for unresectable cases (uPHNEC), systemic chemotherapy is recommended according to guidelines. However, the median progression-free survival (PFS)

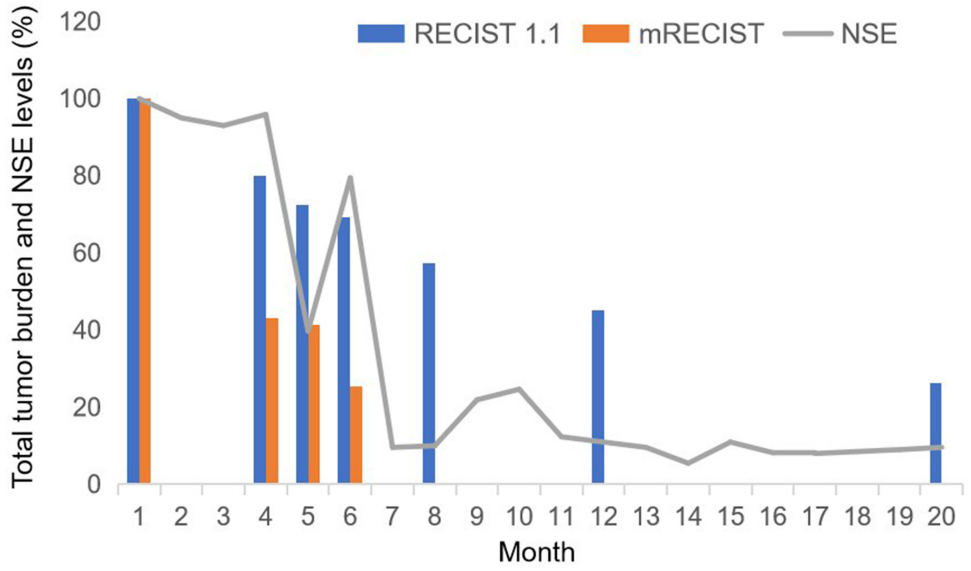

Figure 3 Changes in NSE values during various treatment stages, along with the RECIST and mRECIST standardized assessment criteria, are employed to evaluate treatment response.

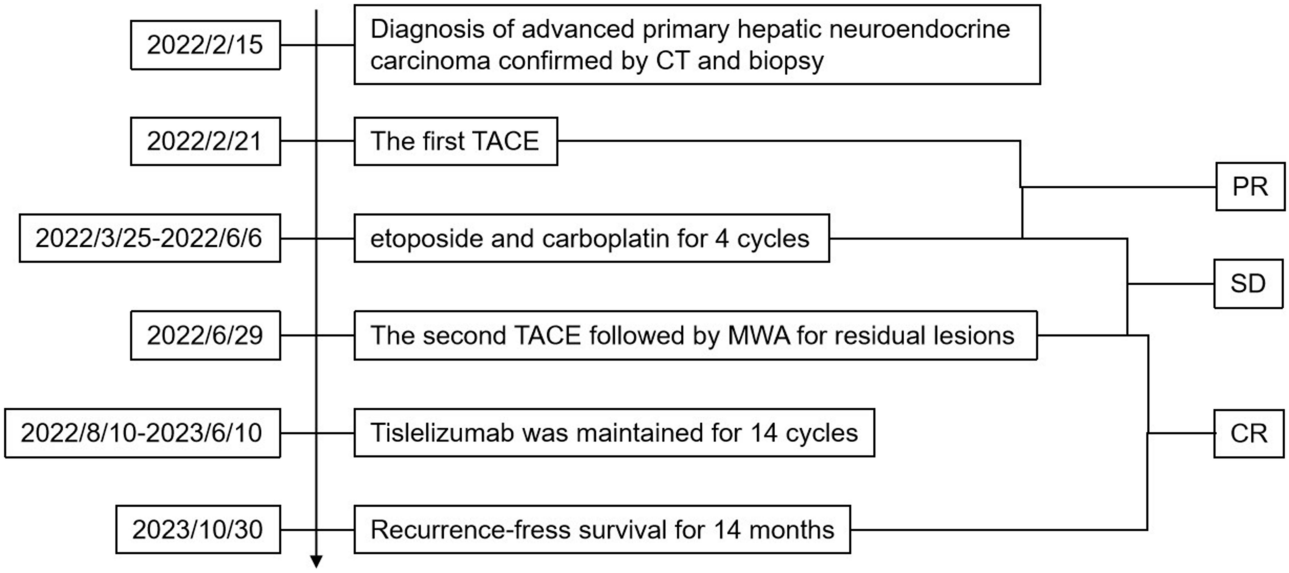

Figure 4 Timetable for Initial Diagnosis, Treatment, and Follow-up.

with systemic chemotherapy is limited to 4.4 months due to primary or acquired resistance.[8] Recent studies propose that localized treatments, including transcatheter arterial chemoembolization (TACE), liver transplantation, and other modalities,[9] may offer more substantial benefits than traditional chemotherapy for locally advanced PHNEC (uPHNEC) with lower malignancy. In the context of the current case, where conventional chemotherapy failed to control the lesion in the right lobe of the liver near the hilar region after four cycles, while the well-embolized lesion in the right posterior lobe responded favorably to the first TACE, it is suggested that this case exhibits heightened sensitivity to local therapies like TACE compared to standard chemotherapy. This observation contrasts with a retrospective analysis by Li et al, involving 41 cases, suggesting that, in patients with locally advanced PHNEC, TACE alone did not surpass systemic chemotherapy in prolonging progression-free survival (PFS) and overall survival (OS).[8] The embolic efficacy of TACE correlates positively with the tumor's degree of arterial blood supply, a phenomenon well-established in primary hepatocellular carcinoma. Reports propose that PHNEC shares a similar blood-rich vascular supply with hepatocellular carcinoma, possibly explaining the superior efficacy of TACE over chemotherapy in this case.[10] Additionally, MWA as a means of localized treatment, the sequential application of TACE followed by microwave ablation (MWA) is seen as a complementary therapeutic strategy, particularly in lesions with incomplete interventional embolization.[11] The combination of TACE and MWA has demonstrated better local tumor control and OS.[12] PHNEC is a highly aggressive tumor, and relevant investigations should be performed to exclude the possibility of extrahepatic lesions before interventional combined with ablative local therapy.

Previous studies have substantiated that immune checkpoint inhibitors yield superior outcomes in patients with poorly differentiated neuroendocrine cancers. Higher aggressive NECs could have a different TME, higher TMB and are more often DNA MMR deficient.[13] In addition, the alteration of the tumor immune microenvironment by TACE or thermal ablation therapy will provide better conditions for subsequent immunotherapy. The liver's tumor immune microenvironment assumes a pivotal role in the recurrence of hepatic malignant cancers post-tumor ablation. Thermal ablation induces tumor cell death, releasing a significant amount of tumor antigens and elevating the infiltration levels of cytotoxic T-cell subpopulations in and around the lesion. PD-1 inhibitors, by binding to PD-1 on T-cell surfaces, sustain T-cell activity, inhibiting the tumor immune escape pathway and fostering the killing of tumor cells.[14] Combining TACE with ablative therapy, followed by maintenance therapy involving immune checkpoint inhibitors, serves to potentiate the anti-tumor immune response within the microenvironment. This approach aims to mitigate or prevent recurrence, thereby suggesting that adjuvant anti-PD-1 therapy can effectively enhance treatment outcomes.[15] In this specific case, the administration of the immune checkpoint inhibitor Tislelizumab post-TACE combined with microwave ablation (MWA) contributed to the

ongoing treatment. Tumor markers continued to decrease to below normal levels upon review, and imaging did not reveal any signs of recurrence. Regrettably, the patient did not undergo evaluation for PD-1/PD-L1 expression testing and microsatellite stability (MSI). Given the rarity of the disease and the absence of high-quality data, there are no established standard treatment options for patients with unresectable primary liver neuroendocrine carcinoma that have proven refractory to systemic chemotherapy. The more suitable treatment can be chosen based on various factors, encompassing tumor stage and the patient's overall systemic condition.

Conclusion

In summary, we present a case of primary hepatic neuroendocrine carcinoma resistant to surgical intervention and unresponsive to four cycles of systemic chemotherapy. Following MDT consultation, the patient achieved complete remission through a combination of one TACE and two local minimally invasive microwave ablation treatments. Postoperatively, the patient received maintenance therapy with immune checkpoint inhibitors. This case introduces a novel therapeutic approach for individuals with sizable, inoperable lesions and a history of systemic chemotherapy failure. However, further high-quality data are imperative to substantiate the efficacy of local treatment options for primary hepatic neuroendocrine carcinoma.

Ethics Statement

Details of the case reported in the article were approved by the central institution, The Affiliated Hospital of Yanbian University.

Consent for Publication

Written informed consent has been obtained from the patient for publication of the case report and images.

Acknowledgments

We give thanks to the patients and everyone involved in this study.

Author Contributions

SZ proposed the topic. YF, XJ participated in the design and writing of the paper. ZH, QX and HC case collected and drew the pictures. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was supported by the National Nature Science Funds of China (Nos.82460527).

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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