Metastatic Primary Hepatic Neuroendocrine Carcinoma: A Case Report

Ann. Ital. Chir., 2024 95, 5: 783–787
https://doi.org/10.62713/aic.3810

Paolo Izzo[1], Luciano Izzo[1], Giuliano D'Onghia[1], Leonardo Macci[1], Paola Giancontieri[2], Massimo Codacci-Pisanelli[1], Marcello Molle[3], Claudia De Intinis[1], Sara Izzo[3]

[1]Department of Surgery, Policlinico "Umberto I", "Sapienza" University of Rome, 00185 Rome, Italy
[2]Department of Radiological, Oncological and Anatomo-Pathological Sciences, Policlinico "Umberto I", "Sapienza" University of Rome, 00185 Rome, Italy
[3]Multidisciplinary Department of Medical-Surgical and Dental Specialties, Plastic Surgery Unit, Università degli Studi della Campania "Luigi Vanvitelli", 80138 Naples, Italy

AIM: Primary hepatic neuroendocrine carcinomas (PHNECs) are rare tumors with limited understanding and management. Diagnosing and treating these tumors pose significant challenges due to the lack of clinical experience. Surgery is often considered an effective therapeutic strategy for early-stage PHNECs. This case report describes an advanced metastatic PHNEC managed primarily with chemotherapy.

CASE PRESENTATION: The medical records of the patient and diagnostic imaging findings were reviewed. A multidisciplinary team of specialists discussed the case and determined the treatment plan. The patient received a chemotherapy regimen tailored to PHNEC, which included specific neuroendocrine tumor-targeting agents.

RESULTS: Despite the advanced stage of the disease, the patient responded well to chemotherapy, with a notable reduction in tumor size and improvement in symptoms. The treatment was well-tolerated, and the patient showed a favorable overall response. The survival duration from the time of diagnosis was 18 months.

CONCLUSIONS: In this case of advanced metastatic PHNEC, a primarily chemotherapy-based approach yielded positive outcomes. Although surgery is typically preferred for early-stage cases, this case highlights the potential efficacy of chemotherapy in managing advanced PHNECs. Further research and clinical experience are warranted to better understand the optimal treatment strategies for these rare tumors.

Keywords: carcinoma; chemotherapy; metastasis; neuroendocrine; tumor

Introduction

Neuroendocrine tumors (NET) and neuroendocrine carcinomas (NEC) originate from the neuroendocrine system and are distributed throughout the body. Most NECs arise from the gastrointestinal tract, accounting for approximately 54.5–75% of cases. Primary hepatic neuroendocrine carcinomas (PHNECs) account for about 0.3% of all NETs, with an estimated incidence of 1/500,000 people [1]. There is no gender difference in incidence, but this disease tends to affect younger individuals, with a mean age of onset around 45 years, although this can vary.

In the early stages, the clinical presentation is characterized by nonspecific symptoms, such as upper abdominal pain or a sensation of abdominal fullness. As the disease progresses, more severe symptoms such as dyspepsia, weight loss, and fatigue may develop. It is uncommon for patients with PHNEC to exhibit symptoms typical of carcinoid syndromes, such as diarrhea, wheezing, and paroxysmal flushing. Approximately 10% of cases are asymptomatic in the early stages [2].

The etiology of PHNEC is unknown, but various hypotheses have been proposed, including origins from Kulchitsky cells of the neural crest or a chronic inflammatory state of the biliary system [3]. Diagnosis is histological and immunohistochemical, and it is essential to exclude liver lesions that are metastases from the most common sites of the primary tumor. Needle biopsy should be confirmed by examination of the surgical resection. Markers such as chromogranin-A (CgA), carcinoembryonic antigen (CEA), and cancer antigen 19-9 (CA 19-9) are useful for diagnosis and follow-up.

The extreme rarity of PHNEC limits our understanding of the optimal diagnostic and therapeutic approaches. Radical surgery is considered the only potentially curative option. However, there is a high rate of lymphatic and sys-

Submitted: 14 June 2023 Revised: 29 August 2023 Accepted: 15 September 2023 Published: 20 October 2024
Correspondence to: Paolo Izzo, Department of Surgery, Policlinico "Umberto I", "Sapienza" University of Rome, 00185 Rome, Italy (e-mail: p_izzo@hotmail.it).

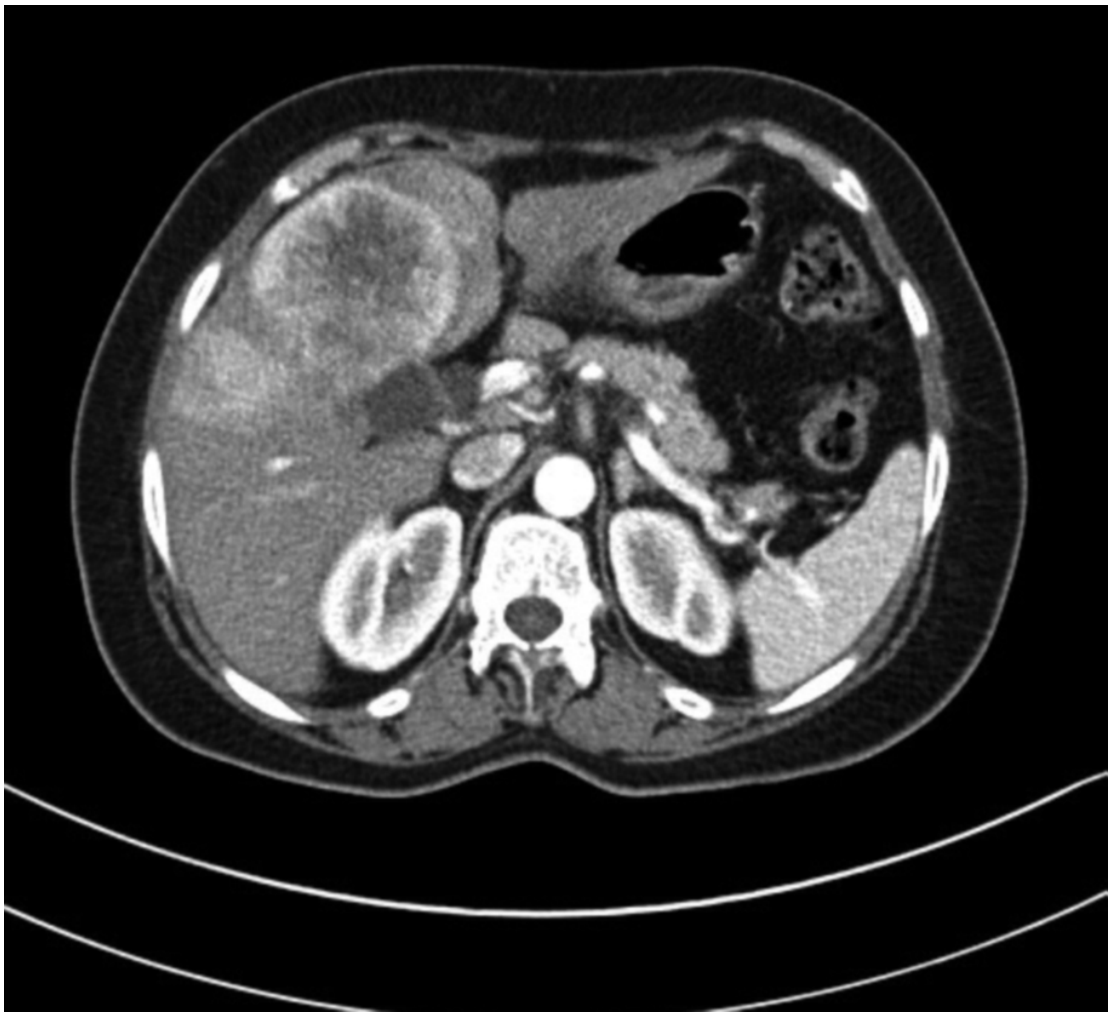

Fig. 1. Computed Tomography (CT) scan of hepatic lesions at the diagnosis.

temic metastasis, which may be treated with cytoreductive surgery, such as transarterial chemoembolization (TACE), or targeted radiation therapy, such as selective internal radiation therapy (SIRT) or peptide receptor radiation therapy (PRRT). However, a combination of therapeutic strategies might offer the best approach [4]. In this report, we present a case of a metastatic PHNEC managed primarily with chemotherapy.

Case Presentation and Methods

A 45-year-old woman presented to the department of Accident and Emergency of our hospital (Policlinico "Umberto I", Rome, Italy) with asthenia, epigastric pain for a week, and a 10 kg weight loss over the past year. She also reported pain in the subscapular region. Her body temperature, blood pressure, and oxygen saturation were within normal limits, and she scored 15 on the Glasgow Coma Scale (GCS). She had no significant clinical history, was not on any medication, and had never undergone surgery. Her liver function tests were within normal ranges (Gamma-glutamyltransferase (GGT) 63 UI/L, Aspartate aminotransferase (AST) 31 UI/L, Alanine aminotransferase (ALT) 33 UI/L, total bilirubin 0.38 mg/dL), although a diabetic profile was observed. The clinical examination revealed a painful abdomen and a positive Murphy's sign.

A chest X-ray showed a 36 mm opacity near the right pulmonary hilum. A high-resolution computed tomography (HRCT) scan of the chest revealed an enlarged lymph node (12 mm) in the mediastinal space and a partially calcified focal area (8 mm) with irregular margins in the left lower pulmonary lobe. Additionally, HRCT incidentally identified a focal area in liver segment (S)4. Upper and lower endoscopy were performed to determine the primary neoplasm, but no primary tumor was detected.

A total body Computed Tomography (CT) confirmed the HRCT findings and described seven solid liver lesions with hypervascular surfaces and hypodense cores. These lesions were located in S4 (three lesions), S6 (two lesions), and S8 (two lesions). The largest lesion was in S4b, measuring 66 × 61 mm. Malignant lymphadenopathy was observed in the aortocaval region (Fig. 1). A needle biopsy revealed a high-grade (G3) primary hepatic neuroen-

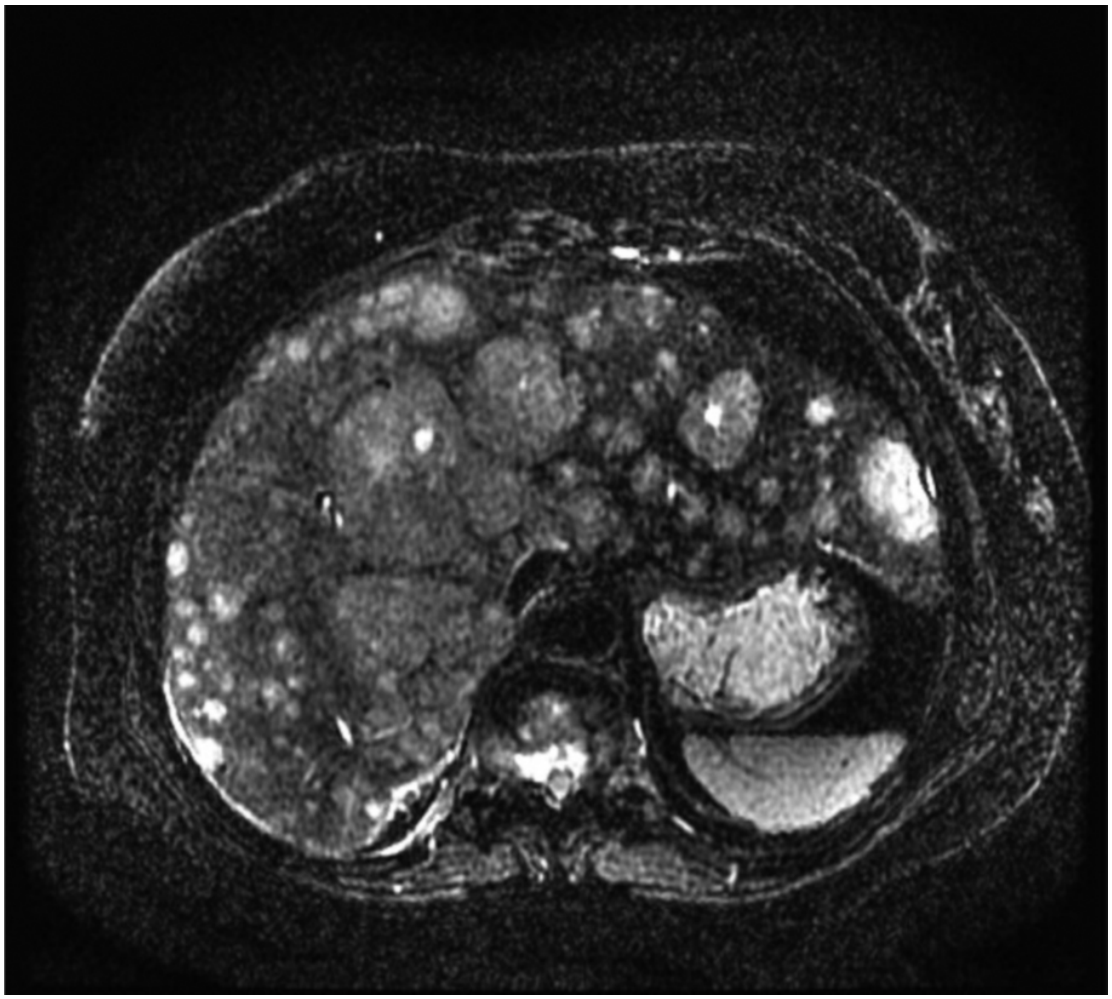

Fig. 2. MRI scan of the progression of disease. MRI, Magnetic Resonance Imaging.

docrine carcinoma (PHNEC). Immunohistochemically, the tumor cells were positive for synaptophysin, chromogranin A (CgA), Neural Cell Adhesion Molecule (CD56), cytokeratin (CK) 8/18, high molecular weight cytokeratin, and focally neuron-specific enolase (NSE). Hepar1, Leucocyte common antigen (CD45), CK 5/6, Thyroid Transcription Factor 1 (TTF1), and CD117 were negative.

We performed complete staging with a Positron Emission Topography-Computed Tomography (PET-CT) scan and measured blood tumor markers. The results of this analysis were as follows: chromogranin A (CgA) = 362.0 ng/mL (↑), cancer antigen (CA) 19.9 = 124 U/mL (↑), neuron-specific enolase (NSE) = 24 ng/mL (↑), carcinoembryonic antigen (CEA) = 6.2 ng/mL (↔), alpha fetoprotein (AFP) = 2.5 U/mL (↔), CA125 = 22.5 U/mL (↔), and CA15.3 = 21.9 U/mL (↔). ↑ means that value were higher than normal; ↔ means that values are between normal range.

The PET-CT with Gallium-68 DOTA-DPhe^{1}-Tyr^{3}-Octreotide (68Ga-DOTATOC) was positive for hepatic, lymph node, and vertebral involvement at the D10 level. There was no uptake in the gastrointestinal tract, confirming the diagnosis of primary hepatic neuroendocrine carcinoma. The tumor exhibited a high expression of somatostatin receptors.

Results

Due to the metastatic stage of the disease, we initiated primary chemotherapy treatment 18 days after diagnosis. The chemotherapy regimen included cisplatin and etoposide, with prophylaxis using lipegfilgrastim and fondaparinux. During therapy, the patient experienced diabetes decompensation, necessitating the use of metformin initially and insulin subsequently.

After the first course of chemotherapy (21 days), a follow-up 68Ga-DOTATOC PET-CT with iodinated contrast medium was performed. This scan revealed an increase in the number (more than doubled) of hepatic lesions, but a reduction in their size, with the development of colliquative areas. Lymph node metastases showed a good response, with a decrease of more than 30% in the mass of the mediastinal lymphadenopathy. However, bone metastases increased in size, and intrahepatic bile ducts were dilated. Additionally, a 15 mm solid lesion near the jejunum was described, which did not accumulate the radiotracer.

The patient reported worsening clinical and adverse reaction symptoms, leading to a reduction in her autonomy in daily activities (ECOG 3). Consequently, therapy with octreotide was initiated. A PET scan with 18 Fluorodeoxyglucose (FDG) confirmed three sites of tumor activity: the liver, abdominal lymph nodes, and the vertebral body of D10.

Chemotherapy lost its efficacy 12 months after diagnosis, as demonstrated by total body Magnetic Resonance Imaging (MRI), which showed disease progression with an increase in the number of hepatic and systemic lesions (Fig. 2). We considered transarterial chemoembolization (TACE) as a palliative treatment for the primary lesion, but it was excluded due to the overall clinical condition of the patient. The patient died 18 months after diagnosis.

Discussion

The origin of PHNEC remains unknown, but three main theories exist regarding its transformation: from liver stem cells, from ectopic pancreatic or adrenal tissue located in the liver, or from neuroendocrine cells of the intrahepatic biliary duct, with the latter being the most prevalent hypothesis.

The World Health Organization recommends using the term "neuroendocrine neoplasm" rather than "carcinoid". Neuroendocrine tumors (NETs) are classified into three subtypes: well-differentiated NET, often referred to as "carcinoid", these lesions frequently produce hormones and typically do not exhibit local invasion or metastasis; moderately differentiated NET, characterized by atypia and can have local invasion or metastasis; poorly differentiated NET, also known as "carcinoma", has highly atypical cells, local invasion, and metastasis.

Diagnosis of PHNEC requires histological and immunochemical analysis. A needle biopsy should be confirmed by examination of the surgical resection [5]. Radiological imaging can sometimes be misleading. For example, Xia *et al*. [6] described a case of a 38-year-old man who was preoperatively diagnosed with hydatidosis, but post-surgical pathological and immunohistochemical studies revealed a primary neuroendocrine carcinoma.

There is no standard therapy for PHNEC. Treatment is chosen based on several factors. Surgical resection has shown the most remarkable efficacy in improving survival [7], but it is less effective in the presence of distant disease or lymphatic metastases. Given the high incidence of tumors diagnosed at an advanced stage, additional treatments such as cytoreductive methods or systemic therapies are often necessary.

Considering the metastatic nature of the disease (involving lymph nodes, and lungs), we opted for primary chemotherapy. The limited number of reports in the literature did not provide a standard chemotherapeutic regimen. Therefore, we used an initial approach with cisplatin and etoposide, which has demonstrated optimal efficacy in treating metastatic PHNEC, as described by Morishita *et al*. [8]. Chemotherapy treatment could have been augmented with cytoreductive techniques, such as radiofrequency ablation for small (<5 cm) and scarce (< or =3) metastatic lesions [9, 10]. However, the advanced stage of the disease and the clinical condition of the patient precluded the use of these techniques.

Conclusions

The case highlights the challenges in the treatment and management of PHNEC tumors. The absence of specific symptoms leads to diagnosis at a metastatic stage, necessitating a systemic treatment approach. This approach can achieve partial disease remission even at an advanced stage, where surgical or cytoreductive treatments provide no clinical benefit.

Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Author Contributions

Conceptualization: PI and SI; Methodology: LI, MCP and MM; Data analysis: GD, LM, PG and CDI; writing – original draft: CDI and SI. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The "Sapienza" University of Rome Review Board deemed the study exempt from review. Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Quartey B. Primary Hepatic Neuroendocrine Tumor: What Do We Know Now? World Journal of Oncology. 2011; 2: 209–216.

[2] Cives M, Strosberg JR. Gastroenteropancreatic Neuroendocrine Tumors. CA: a Cancer Journal for Clinicians. 2018; 68: 471–487.

[3] Hofland J, Zandee WT, de Herder WW. Role of biomarker tests for diagnosis of neuroendocrine tumours. Nature Reviews. Endocrinology. 2018; 14: 656–669.
[4] Nakatake R, Ishizaki M, Matui K, Yanagimoto H, Inoue K, Kaibori M, *et al*. Combination therapies for primary hepatic neuroendocrine carcinoma: a case report. Surgical Case Reports. 2017; 3: 102.
[5] Seki Y, Sakata H, Uekusa T, Momose H, Yoneyama S, Hidemura A, *et al*. Primary hepatic neuroendocrine carcinoma diagnosed by needle biopsy: a case report. Surgical Case Reports. 2021; 7: 236.
[6] Xia Y, Zhang L, Wu H, Qiao L, Xia L. Primary hepatic neuroendocrine tumor with multiple liver metastases: A case report with literature review. The Journal of International Medical Research. 2020; 48: 300060520932114.
[7] Knox CD, Anderson CD, Lamps LW, Adkins RB, Pinson CW. Long-term survival after resection for primary hepatic carcinoid tumor. Annals of Surgical Oncology. 2003; 10: 1171–1175.
[8] Morishita A, Yoneyama H, Nomura T, Sakamoto T, Fujita K, Tani J, *et al*. Primary hepatic neuroendocrine tumor: A case report. Molecular and Clinical Oncology. 2016; 4: 954–956.
[9] Wang LM, An SL, Wu JX. Diagnosis and therapy of primary hepatic neuroendocrine carcinoma: clinical analysis of 10 cases. Asian Pacific Journal of Cancer Prevention: APJCP. 2014; 15: 2541–2546.
[10] Gamblin TC, Christians K, Pappas SG. Radiofrequency ablation of neuroendocrine hepatic metastasis. Surgical Oncology Clinics of North America. 2011; 20: 273–273–9, vii–viii.