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Case Report

Primary multicentric hepatic neuroendocrine tumor with bone and pleural metastasis: A case report and review of literature

Chander Dutti[1]*, Prikshit Mittal[2], Gull Mohammad Bhat[1], Ram Krishna[1], Bhupendra Singh Chahar[1]

[1]*Dept. of Medical Oncology, Dr. BS Tomar Cancer Research Institute, NIMS Hospital, Jaipur, Rajasthan, India*
[2]*Dept. of General Medicine, All India Institute of Medical Sciences, Bathinda, Punjab, India*

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ABSTRACT

Primary hepatic neuroendocrine carcinoma (PHNEC) is a rare form of cancer, accounting for less than 1% of all neuroendocrine neoplasms. Due to its rarity, it often presents significant diagnostic challenges and is frequently mistaken for hepatocellular carcinoma or metastatic disease. This study aims to report a unique case of multicentric primary hepatic neuroendocrine carcinoma with metastases to the bone and pleura. It highlights the difficulties encountered in both diagnosis and treatment, underscoring the necessity for tailored therapeutic approaches and the need for further investigation in this area. A 51-year-old woman experienced one month of right upper abdominal pain and loss of appetite, leading to imaging that revealed multiple liver lesions. A biopsy confirmed a primary multicentric hepatic neuroendocrine tumor, with normal tumor markers (AFP, CEA, CA19.9) and no extrahepatic lesions found on pan-endoscopy. Initially treated with Etoposide and Carboplatin, she showed progressive disease after three cycles. Subsequent treatment with capecitabine and temozolomide was ineffective, and she ultimately succumbed to the disease**.** PHNECs are exceedingly rare, complicating their diagnosis and management. Current literature is limited to isolated case reports, highlighting the importance of this study. Management of PHNEC requires a multidisciplinary approach, with treatment plans tailored to disease presentation and patient health. In our study, the patient received three cycles of an etoposide-carboplatin regimen, followed by a response assessment scan that showed progressive disease. The patient did not respond significantly to subsequent treatment with three cycles of the CAPTEM regimen and ultimately succumbed to the disease.
PHNEC should be considered a potential differential diagnosis for liver tumors. The current study provides valuable insight into the clinical presentation, diagnosis, management, and outcomes of the disease. There is no standardized treatment protocol for metastatic PHNEC; decisions must be individualized, with options including surgery, chemotherapy, targeted therapies, or PRRT, emphasizing the need for further research.

1. Introduction

Primary hepatic neuroendocrine carcinoma (PHNEC) is a rare cancer type, constituting less than 1% of all neuroendocrine neoplasms.[1] The condition was first documented by Edmondson in 1958,[2] and to date, around 200 cases have been recorded in medical literature. These tumors do not exhibit a strong preference for either sex and are typically identified in individuals with a mean age ranging from 47 to 50 years. Interestingly, only a limited number of cases have been reported in patients under 40 years old.[3–5] PHNECs do not have unique imaging features, which frequently results in their being misidentified as other liver lesions, such as hepatocellular carcinoma (HCC) or cholangiocarcinoma (CCC).[6] The limited number of

* *Corresponding author*.
E-mail address: chanderdutti0792@gmail.com (C. Dutti).

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reported cases poses a challenge for clinicians in accurately diagnosing PHNET prior to biopsy or surgical resection of the tumor.[7] Given this context, a definitive diagnosis can be established through histopathological examination and immunohistochemical analysis.[3,8] Management of PHNETs encompasses both surgical and medical strategies, with surgical intervention considered the most effective treatment. Research shows that surgical options yield a five-year survival rate of around 74%, with a recurrence rate of approximately 18%.[9,10] Medical therapies for PHNETs, including transcatheter arterial chemoembolization (TACE), systemic chemotherapy, local ablation, and somatostatin analogs have not demonstrated a significant long-term survival advantage. While TACE may exhibit a favorable short-term response, its effectiveness diminishes over time.[9,11] Herein, we are describing a rare case of primary multicentric hepatic neuroendocrine carcinoma with bone and pleural metastases and to highlight the challenges in treatment and diagnosis, emphasizing the need for personalized therapy and further research.

2. Case Presentation

A 51-year-old female presented in December 2023 with negative past medical and past surgical history, with a complaint of right upper abdominal pain lasting one month. The pain, initially mild, gradually progressed to a severe, continuous nature that was relieved with analgesics. Patient also complains of decreased appetite and fatigue. There were no complaints of jaundice, diarrhea, flushing, or palpitations. Physical examination revealed hepatomegaly (12 cm below the right sub-costal margin along mid-clavicular line). No bruit was present, and other systemic examinations were unremarkable. Laboratory tests were within the normal range.

Ultrasound of the abdomen suggested multiple liver solid lesions. A triple-phase contrast-enhanced computed tomography (CECT) scan indicated hepatomegaly (24 cm) with numerous heterogeneously enhancing soft tissue density masses of varying sizes in both lobes of the liver, demonstrating early arterial phase enhancement with progressive washout on the delayed phase. Some lesions exhibited internal non-enhancing areas, with the largest measuring 3.8 x 3.2 cm in the right lobe, likely indicating multicentric HCC. A CECT scan of the chest showed no abnormalities.

Based on the imaging findings, the patient was started on oral tyrosine kinase inhibitor sorafenib at a dose of 400 mg orally every 12 hours. However, upon follow-up after 28 days, there was no clinical improvement. A biopsy of the liver solid lesion, guided by ultrasound, was performed and sent for histopathological examination and immunohistochemistry (IHC). Histological examination suggested a malignant epithelial neoplasm, while IHC showed positivity for synaptophysin, chromogranin, and pan-cytokeratin, with a Ki67 proliferation index of 3-4%. The tumor was negative for HepPar1, AFP, CK20, CA19.9, CK19, Glypican 3, WT1, PAX8, CDX2, TTF1, SATB2, P40, and GATA3, leading to a final diagnosis of well-differentiated grade II neuroendocrine carcinoma.

Tumor markers, including AFP, CEA, and CA19.9, were within normal limits. A pan-endoscopy was performed, which showed no extrahepatic lesions. After correlating all findings, the patient was diagnosed with primary multicentric hepatic neuroendocrine carcinoma. The case was discussed in a multidisciplinary board, and the consensus was to initiate systemic chemotherapy, as the patient was not a suitable candidate for surgical resection due to the multicentricity of the tumor.

The patient was started on a regimen of Etoposide (100 mg/m^2 on days 1-3) and Carboplatin (AUC 5 on day 1), administered every 21 days for three cycles. Response assessment via CECT of the chest and abdomen suggested progressive disease, with two pleural-based lesions detected in the right apical lobe of the right lung (largest diameter 9 x 4 mm) and multiple lytic lesions in the lumbar and sacral vertebrae. The primary hepatic lesions showed a 20% decrease in the largest diameter.

The treatment regimen was subsequently switched to CAPTEM, an oral regimen consisting of capecitabine (750 mg/m^2 PO BID on days 1-14) and temozolomide (150 mg/m^2 PO OD on days 10-14), repeated every 28 days. The patient showed clinical improvement after the first cycle; however, by the third cycle, she presented with multi-organ failure and ultimately succumbed to the disease despite the best efforts of the medical team.

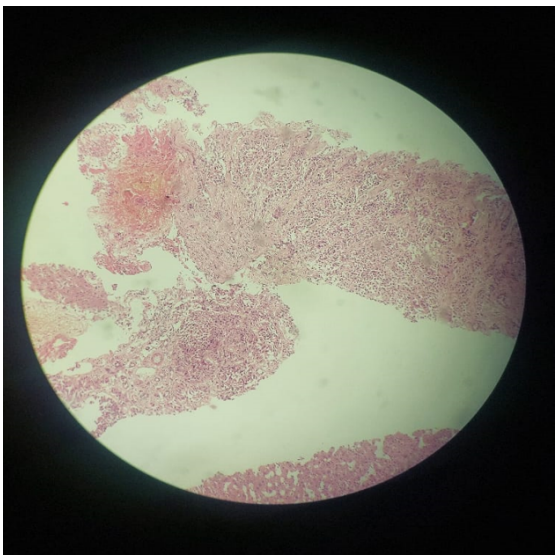

Figure 1: Hematoxylin and Eosin staining (10 × 10) shows Tumors cells arranged in nesting pattern, with monotonous cells with round to oval nucleus and salt pepper chromatin, moderate eosinophilic granular cytoplasm

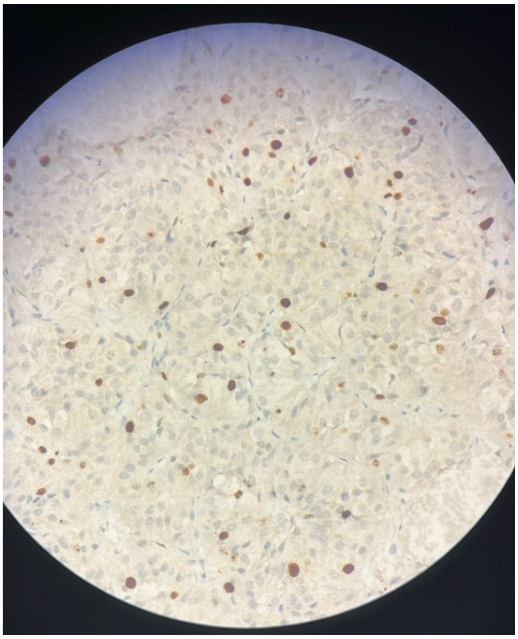

Figure 2: IHC found the Ki-67 index 3-4% (400x)

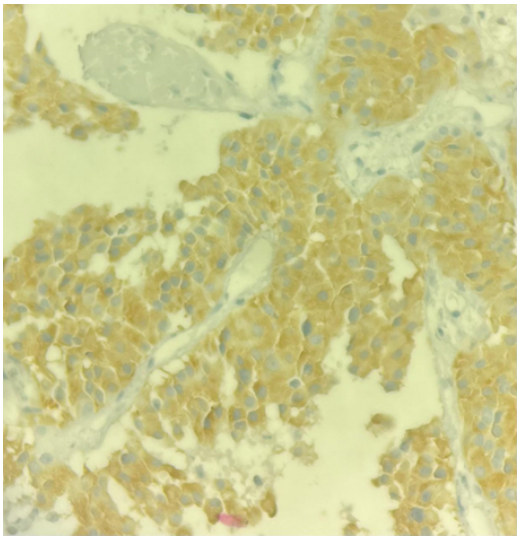

Figure 3: IHC showed that the tumour was positive for Synaptophysin (400x)

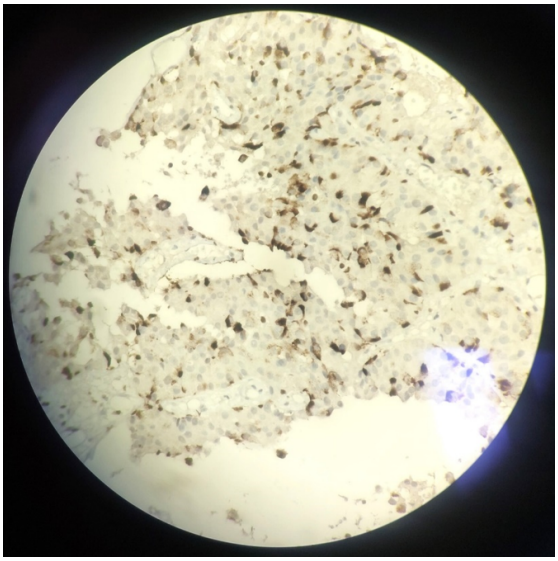

Figure 4: IHC showed that the tumour was positive for Chromogranin (10 × 10)

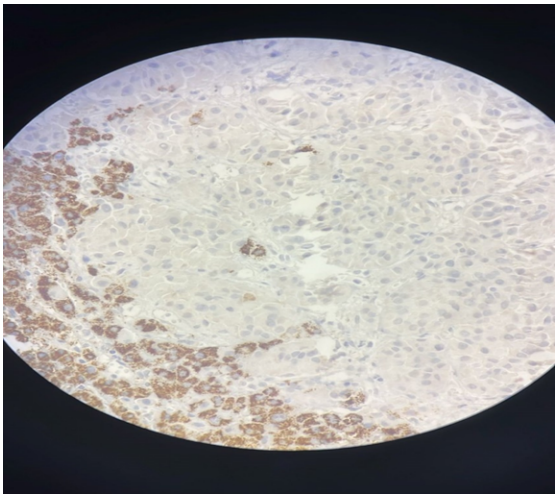

Figure 5: IHC showed that the HepPar1 negative in tumour cells while normal liver parenchyma shows positivity (400x)

3. Discussion

Neuroendocrine tumors (NETs) are rare malignant growths, accounting for roughly 1% to 2% of all gastrointestinal tumors. Although liver metastases are commonly associated with NETs, primary hepatic neuroendocrine tumors (PHNETs) are extremely uncommon, making up about 0.3% of all NET cases. Typically, NETs are found within the gastrointestinal tract, accounting for around 50% of cases, while approximately 30% are found in the bronchopulmonary system.[12] PHNETs predominantly affect middle-aged and elderly individuals. The median age of patients with these tumors typically falls between 52 and 63 years, while our case involved a 51-year-old individual. There is no significant gender preference, and most patients present with symptoms that are often nonspecific, with abdominal pain being the most frequently reported complaint. Our case present with severe abdominal pain.

Unlike other neuroendocrine tumors, PHNETs are mainly nonfunctional, which means they generally do not lead to carcinoid syndrome. Only around 10% of PHNET cases exhibit the classic triad of symptoms—abdominal pain, skin flushing, and diarrhea. This feature can assist in distinguishing PHNETs from neuroendocrine tumors that

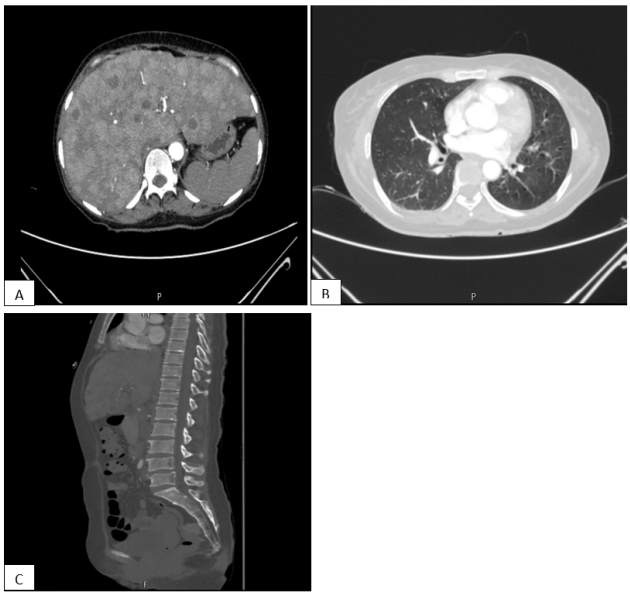

Figure 6: A): Baseline CT scan of abdomen showing multiple liver SOLs; B): Baseline CT of chest shows no lesion; **C): ** Baseline CT shows no bony lesions

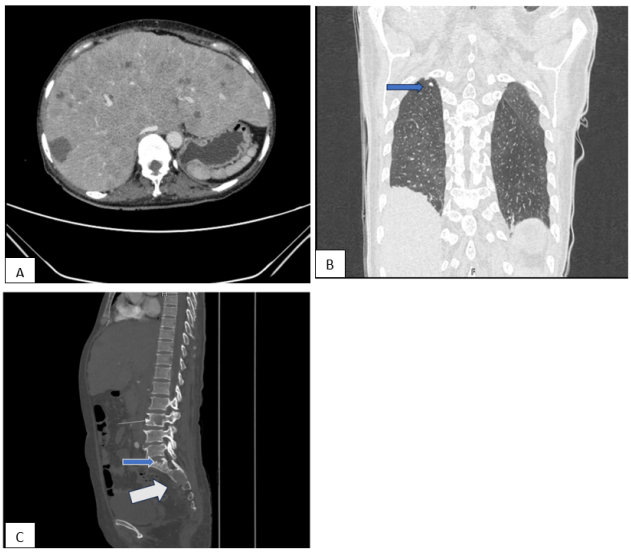

Figure 7: A): Response assessment CT shows 20% decrease in the largest diameter of liver lesion; **B)**: CECT Chest shows two pleural-based lesions detected in the right apical lobe of the right lung (largest diameter 9 x 4 mm); **C)**: Sagittal section shows multiple lytic lesions in the lumbar and sacral vertebrae

have metastasized to the liver.[13] Our case had a non-functional PHNET.

Our case involved a non-functional PHNET. In the context of PHNETs, traditional tumor markers such as AFP, CEA, and CA 19-9 are not diagnostically significant. In contrast, markers like neuron-specific enolase (NSE), chromogranin A (CgA), 5-hydroxyindoleacetic acid (5-HIAA), and synaptophysin (Syn) have shown greater efficacy in the pathological diagnosis of PHNETs[14]. According to the World Health Organization (WHO) classification of digestive system NETs, published in 2019, these tumors are graded into three categories based on either the mitotic count per 10 high-power fields or the percentage of neoplastic cells that are positive for the Ki67 proliferation marker.[15]

In this case, our patient was classified as having a well-differentiated neuroendocrine tumor of grade II, with a Ki67 proliferation index estimated to be approximately 3-4%. The diagnosis of PHNETs relies on two essential criteria. First, the liver mass should exhibit immunohistochemical features that align with those of a neuroendocrine tumor. Second, there must be no clinical, endoscopic, or imaging findings suggesting the existence of a neuroendocrine tumor originating from another location.[14]

Imaging techniques, including ultrasound, CT scans, and MRI, generally have low sensitivity and specificity for diagnosing PHNETs. The primary purpose of these imaging modalities is to detect hepatic lesions and assist in locating a potential primary tumor in the intestinal tract, pancreas, or other organs.[16]

The definitive diagnosis of primary hepatic neuroendocrine tumors is established through histological and immunohistochemical evaluation, which serves as the gold standard for pathology.[17]

At diagnosis, roughly 20% of patients with PHNETs have extrahepatic metastatic disease, with the bones, lymph nodes, and lungs being the most frequently involved sites. In our case, the patient experienced disease progression characterized by the emergence of new metastatic pleural lesions and multiple vertebral lesions.[6]

Surgical resection is typically the treatment of choice for PHNETs, and achieving an R0 excision can be curative.[18]

For patients with unresectable primary hepatic neuroendocrine tumors, there are several palliative treatment options available[14] including systemic chemotherapy with fluorouracil, hepatic transarterial chemoembolization (TACE), octreotide therapy, liver transplantation, radiofrequency ablation, peptide receptor radionuclide therapy (PRRT), and percutaneous ethanol injection therapy.[19,20] However, the effectiveness and role of these modalities are not well defined and warrant further investigation.[14] It is essential to highlight that peptide receptor radionuclide therapy (PRRT) is mainly used for well-differentiated neuroendocrine tumors that express

somatostatin receptors. However, PRRT is generally less effective for poorly differentiated neuroendocrine carcinomas and may not work well in cases with multiple neuroendocrine tumors and a substantial tumor burden, which could also result in liver toxicity.[20]

About 20–37% of patients are diagnosed with neuroendocrine tumors at a metastatic or advanced stage. In these cases, platinum-based chemotherapy, such as Etoposide combined with Cisplatin (EP) or Carboplatin (EC), is recommended as the first-line treatment according to the European Society for Medical Oncology (ESMO) guidelines.[21] Our patient had received 3 cycle of Etoposide and Carboplatin in first line.

CAPTEM is a suitable treatment option that may enhance survival in patients with various metastatic NETs.[22] It has demonstrated effectiveness and relative safety for individuals with advanced well- to moderately differentiated neuroendocrine neoplasms (NENs) originating from the gastroenteropancreatic system, lungs, and cases with unknown primary sites.[23] In our case, when patient shows progression disease on Ist line chemotherapy, patient was started on CAPTEM regimen as 2^{nd} line of chemotherapy.

An emerging strategy for higher-grade (G2-G3) gastroenteropancreatic neuroendocrine tumors (GEP-NETs) involves combining Capecitabine and Temozolomide chemotherapy with peptide receptor radionuclide therapy (PRRT), referred to as chemo-PRRT. This approach is based on the hypothesis that chemotherapy may enhance the radiosensitivity of the tumors. However, it remains an area of ongoing investigation.[24]

A review involving 12 patients with PHNEC revealed a median survival of 16.5 months, ranging from 0.7 to 41.7 months. The five-year survival rate after surgery for all three differentiation subtypes of PHNEC is approximately 75%. However, recurrence or metastasis may occur within one to ten years after surgical resection. In contrast, the prognosis for primary hepatic neuroendocrine carcinoma is significantly worse. For metastatic poorly differentiated neuroendocrine carcinoma, the five-year survival rate is only about 5.8%, while the one-year survival rate stands at approximately 23.5%.[25,26] Our patient succumbed to the disease after 10 months of diagnosis after receiving 3 cycles of second line chemotherapy, which suggests poor prognosis and highly aggressive nature of the disease.

4. Conclusion

Primary hepatic neuroendocrine carcinoma should be regarded as a possible differential diagnosis for liver tumors. This study offers important insights into the clinical presentation, diagnosis, management, and outcomes associated with PHNEC. Currently, there is no standardized treatment protocol for metastatic PHNEC; therefore, management decisions must be individualized. Treatment options may include surgery, chemotherapy, targeted therapies, or peptide receptor radionuclide therapy (PRRT). Given the complexity and variability of this disease, further research is essential to better define effective treatment strategies and improve patient outcomes.

5. Consent

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

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7. Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Author's biography

Chander Dutti, Senior Resident

Prikshit Mittal, Senior Resident

Gull Mohammad Bhat, Professor and Head

Ram Krishna, Assistant Professor

Bhupendra Singh Chahar, Senior Resident

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