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Case Report

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A Promising Outcome: Hepatectomy for Primary Liver Neuroendocrine Tumor: A Case Report

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ABSTRACT

Background: Primary hepatic neuroendocrine tumors (PHNET) are extremely rare and pose challenges in terms of diagnosis and treatment due to the scarcity of prospective data.

Clinical Case: Here, we present a case of a 60-year-old male patient with PHNET initially suspected to be hepatocellular carcinoma. The patient presented with a 6-month history of diarrhea, unremarkable physical examination with good functional capacity. CT scan showed liver mass. AFP was normal. Patient underwent successful hepatectomy with curative intent. Meticulous radiological, histopathological, and immunohistochemical investigations were conducted to exclude metastatic malignancies and confirm the primary nature of the hepatic tumors. The official biopsy revealed hepatocellular carcinoma with a neuroendocrine-like appearance. supported by positive immunohistochemical staining for chromogranin A and synaptophysin, and a Ki67 index of 18% indicating nuclear reactivity. The final diagnosis was Primary hepatic neuroendocrine tumor.

Discussion: This case highlights the complexities associated with the differential diagnosis of hepatic tumors, particularly the challenge of distinguishing between primary hepatic neuroendocrine tumors and hepatocellular carcinomas based on radiological findings and initial biopsy results. The accurate diagnosis of PHNET necessitates comprehensive histopathological analyses, including immunohistochemical staining for specific markers and Ki67 index assessment to evaluate cellular proliferation.

Conclusion: This particular case exemplifies the medical complexity involved in diagnosing PHNET, necessitating the differentiation of PHNETs from other hepatic masses and the exclusion of occult primary neuroendocrine tumors. In this case, the liver was the identified primary site of cancer and radical surgery was successfully performed for curative intent.

Keywords: PHNET, NET, Neuroendocrine, Primary Hepatocellular Neuroendocrine Tumor, Hepatocellular Carcinoma

Learning Points

- **Clinical Presentation:** PHNETs may mimic other hepatic malignancies, like hepatocellular carcinoma, in terms of clinical presentation and imaging findings. Accurate diagnosis requires considering the possibility of PHNETs and conducting thorough investigations, especially when typical markers like AFP are normal.
- **Radiological Challenges and Histopathological Confirmation:** Radiological findings may not always be definitive in distinguishing between different hepatic tumors. A confirmatory histopathological analysis is essential to correctly diagnose PHNETs and rule out other possibilities.
- **Immunohistochemical Markers:** Positive immunohistochemical staining for chromogranin A and synaptophysin is indicative of neuroendocrine differentiation, helping confirm the diagnosis of PHNET.
- **Curative Intent and Surgical Management:** In cases where PHNETs are diagnosed and localized, radical surgical interventions like hepatectomy can be performed with curative intent, as demonstrated in this case.
- **Consideration of Occult Primary Tumors:** In the case of PHNETs, it's important to rule out the possibility of

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an occult primary neuroendocrine tumor originating from another site and metastasizing to the liver.

Introduction

Neuroendocrine tumors (NET) account for about 1% to 2% of all gastrointestinal tumor cases. However, Primary Hepatic neuroendocrine tumor (PHNET) is extremely rare. Given the rarity of this condition, there is a lack of prospective data, making it difficult to determine the appropriate diagnostic and therapeutic management [1]. Therefore, it is essential to augment the overall database, as this will facilitate the development of formal diagnostic and treatment guidelines, ultimately enhancing the prognosis for patients. Herein, we report a rare case of PHNET suspected to be hepatocellular carcicnoma before operation, illustrating our understanding of diagnosing, distinguishing from similar conditions, and treating individuals affected by this rare disease.

Objectives

General Objective: To report the case of a 60-year-old male patient diagnosed with Primary hepatic neuroendocrine tumor

Specific Objectives:

To present the clinical course of the patient diagnosed with PHNET

To discuss the pathophysiology of PHNET

To discuss the radiological, histopathological, and immunohistochemical work-up of PHNET

Clinical Case

A 60-year-old male, with no known comorbidities presented with a 6-month history of diarrhea. Work-up of diarrhea ruled out infectious etiology. Hepatitis profile was negative. Computed Tomography showed hypovascular masses in hepatic segments 5, 6 and 7 as shown in figure 1. The largest lesion in hepatic segments 5 and 6 had an aggregate measurement of approximately 7.6 x 7 x 7.1 cm. Core needle biopsy initially showed hepatocellular carcinoma. However, Alpha fetoprotein (AFP) was normal at <5 ng/ml. On further work up, patient had normal bleeding parameters, negative hepatitis profile, low albumin and elevated liver enzymes and alkaline phosphatase. Extensive preoperative metastatic work-up failed to localize a primary neuroendocrine tumor outside the liver. Bone scan showed no definite osseous metastasis. Chest CT scan was unremarkable.

The patient underwent laparotomy, intraoperative ultrasonography, right hepatectomy and JP drain insertion. No tumor was identified in the intestine nor in the parenchymatous organs. Multiple liver masses were completely resected, the largest measured 8 x 7.5 x 7.5 cm. Grossly, the tumors were encapsulated and with hemorrhagic areas.

Post operatively, patient had an unremarkable course. Official biopsy showed hepatocellular carcinoma with a neuroendocrine-like appearance. Immunohistochemical staining were positive for chromogranin A and synaptophysin with a Ki67 index of 18%, indicating nuclear reactivity. Final diagnosis was Primary Hepatic neuroendocrine tumor

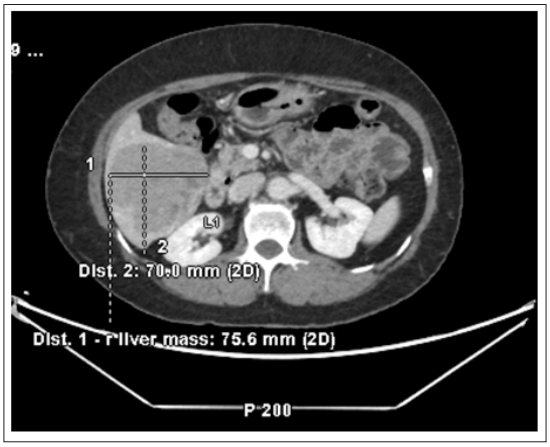

Figure 1: Preoperative CT scan of the **primary hepatic neuroendocrine tumor**. The tumor at segments V, VI and VII has an aggregate measurement of approximately 7.6 x 7 x 7.1 cm. The findings were compatible with malignancy

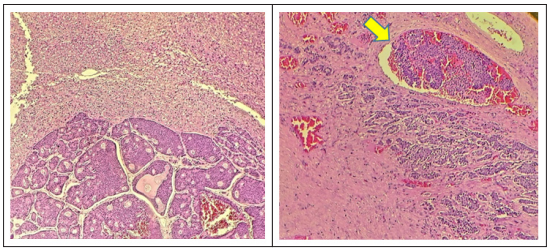

Figure 2: HE staining, (A) With the background of non-cirrhotic liver parenchyma, the tumor cells at the bottom part of the image, showed diffuse distribution, macrotrabecular and organoid pattern, with scattered cystic spaces containing red cells. (B) There is evidence of angioinvasion.

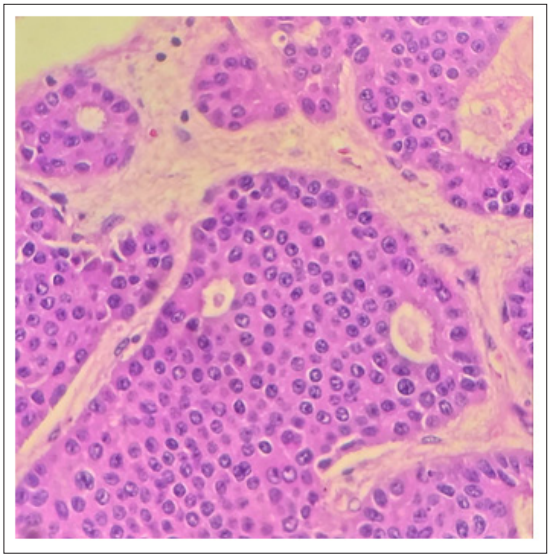

Figure 3: HE staining, (A) Microscopically, the tumor cells are polygonal with ample eosinophilic, granular cytoplasm, round and uniform nuclei with stippled nuclear chromatin. Mitotic figures are infrequent and there are no necrotic areas seen.

Discussion

Neuroendocrine tumors accounted for 1%-2% of all gastrointestinal tumors, and liver is the main metastasis organ. Nevertheless, PHNETs are much more rarely seen than other NETs. Thus far, the English literature mostly contains case

reports, with the total number of cases not exceeding 150 [2]. In this study, we present a rare case of PHNET, reporting on its diagnosis and therapeutic efficacy [3].

The origin of PHNETs is still unclear. Three hypotheses exist. The first suggests that they arise from scattered neuroendocrine cells in the epithelium of the intrahepatic biliary tract; the second hypothesis affirms that these tumors originate from heterotopic pancreatic or adrenal tissue located in the liver; the third asserts that they arise from the neuroendocrine differentiation of single malignant stem cell, that are precursors of other hepatic tumours [4].

The case under consideration involves a 60-year-old male patient who presented with a persistent six-month history of diarrhea. PHNETs, occur more often in the fifth decade of life and in women and usually present as a silent hepatic mass, single or multiple. PHNET differs from other NETs as they do not produce biologically active polypeptides or amines, as a result of which there is no carcinoid syndrome manifested [4]. In addition, PHNET grew slowly and most patients showed no symptoms in the early stage. Although a minority of patients may exhibit symptoms such as right upper quadrant palpable masses and abdominal pain, these are the primary presenting complaints [1]. In certain cases, these symptoms might be accompanied by manifestations of carcinoid syndrome, although this occurrence is relatively uncommon [4]. Carcinoid syndrome is observed in less than 10% of patients diagnosed with gastrointestinal NETs. Notably, when this syndrome is found, it is always associated with hepatic metastasis, although the incidence of this syndrome in the gastrointestinal tract in less than 10%. But interestingly, in patients with PHNETs it is quite rarely seen.

PET/CT-guided biopsy, histopathology, and immunohistochemistry (IHC) play a pivotal role in facilitating the diagnosis of Neuroendocrine Tumors (NETs), as highlighted by Gorla et al. [5]. While PET/CT scans do not possess the capability to directly diagnose Primary Hepatic Neuroendocrine Tumors (PHNETs), they do offer the utility of determining whether the NET originates within the liver, as noted by Hu and Yu [1]. Notably, somatostatin receptor scintigraphy, commonly referred to as Octreoscan (OS), stands as the preferred imaging modality for detecting PHNETs, largely due to its superior specificity. Approximately 88% of neuroendocrine tumors express somatostatin receptors, contributing to the heightened accuracy of OS. Additionally, OS reveals up to 16% of lesions that remain undetected by alternative imaging techniques, resulting in an overall accuracy rate of 83% and a positive predictive value of 100%. Given OS's elevated specificity, its inclusion within the preoperative assessment of suspected neuroendocrine liver tumors is warranted. Furthermore, its potential extends to excluding extrahepatic disease sites.

In the context of this particular case, a computed tomography (CT) scan was conducted with the purpose of excluding the presence of a primary tumor located outside the liver. Subsequently, this was reinforced by a comprehensive intraoperative examination which yielded no indications of a primary tumor site beyond the liver. This substantiates the conclusion that the tumors primarily originated in the liver. Conventional biomarkers like Carcinoembryonic Antigen (CEA), Carbohydrate Antigen 19-9 (CA 19-9), and Alpha-Fetoprotein (AFP) offer limited assistance in this scenario, as indicated by Donadon et al. [4].

The combination of histomorphological features and immunohistochemical results ultimately support diagnoses of PHNETs [6]. In this study, the volume of the tumors was 8 x 7.5 x 7.5 cm. Microscopically, the tumors showed macrotrabecular and organoid pattern with locally nested clusters. The cells had ample eosinophilic, granular cytoplasm, round and uniform nuclei with stippled nuclear chromatin. Our pathological findings were consistent with the results reported by Song et al. which is indicative of neuroendocrine tumor [7]. The case presented was positive for chromogranin. Chromogranin A and neuron-specific enolase are immunohistochemical markers of tumor cells derived from endocrine tissue. Ki67 labeling index and mitotic grade indicate cellular proliferation are somewhat suggestive of malignant potential [6]. And in this case, Ki67 index was 18%, indicating nuclear reactivity.

Going back to the case, the primary liver mass seen on the CT scan yielded histopathological and immunohistochemical findings consistent with neuroendocrine tumor characteristics. This provided definitive confirmation that the malignancy indeed originated primarily as a Primary Hepatic Neuroendocrine Tumor (PHNET) within the liver.

Surgical resection is treatment of first choice, and TACE, RFA, and chemotherapy can be used for unresectable patients [8]. Due to the rarity of PHNETs there is a lack of information about the best treatment, which up to now seems to be liver resection [6].

The role of chemotherapy for PHNETs is unknown; there are only a few anecdotic reports of intensive systemic therapy with 5-fluorouracil with a downstaging of hepatic disease and of chemoembolization of the hepatic artery in few unresectable cases, with scarce effects. The therapy with long-acting somatostatin inhibitors is the treatment of choice in patients with metastatic disease or in patients with symptoms due to neuroendocrine secretions, but it does not seem indicated for the typical silent PHNET [9]. In this study, hepatectomy was successfully done with curative intent.

Prognosis of PHNET is relatively favorable. Knox et al. recently reported in a series of 48 PHNETs an actuarial 10-years survival of 68% after surgery [6]. In a recent study utilizing the comprehensive Surveillance, Epidemiology, and End Results (SEER) database, conducted by Li and Zhang et al., advanced age, unmarried status, lower tumor differentiation grade, and the absence of tumor-directed surgical interventions were associated with a less favorable prognostic outcome for individuals afflicted with PHNET. Surgical resection is an effective and reliable treatment method for patients with PHNET [10]. Transcatheter arterial chemoembolization (TACE) and systemic chemotherapy were considered as main therapies for unresectable or recurrent patients, but the outcome was unsatisfactory [6]. On follow-up, our patient was well and did not have any pathological indications of tumor recurrence subsequent to the surgical intervention.

Conclusion

In summary, primary hepatic neuroendocrine tumors are exceedingly uncommon. This particular case exemplifies the

significance of meticulous diagnostic evaluation in cases of suspected hepatic malignancies. The initial misdiagnosis of hepatocellular carcinoma and subsequent identification of primary hepatic neuroendocrine tumor highlight the importance of immunohistochemical analysis and comprehensive pathological investigations. Furthermore, in diagnosing PHNET, it is necessary to differentiate PHNETs from other hepatic masses and the exclusion of occult primary neuroendocrine tumors.

A comprehensive preoperative diagnostic evaluation encompassing both CT imaging and intraoperative scrutiny yielded no discernible indications suggestive of a primary tumor site situated beyond the liver. A combination of histomorphological features and immunohistochemical results confirms neuroendocrine pathology. Currently, hepatectomy remains the primary therapeutic approach for the management of primary hepatic neuroendocrine tumors. In this case, we conclude that the liver was the primary site of the neuroendocrine tumor in this patient. Radical surgery was successfully performed as the only treatment option with curative intent.

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Ethical Compliance Statement
The authors confirm that the approval of an institutional review board was not required for this work. Informed consent was separately obtained for the videotapes taken as part of the routine clinical evaluation. The patient and his family also provided informed consent for publication.

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Declaration of Interest: The authors declare they have no competing interests.

Conflict of Interest: None

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