CASE REPORT

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Primary Hepatic Neuroendocrine Tumor Managed with Major Liver Resection: A Case Report

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ABSTRACT

Background: Primary hepatic neuroendocrine tumors (PHNETs) are very rare tumors. The diagnosis and management of PHNET remains an unusual and challenging issue.
Case Presentation: A 22-year-old woman, presented with recurrent dull aching right hypochondrial pain. She underwent detailed abdominal radiological evaluation revealing a well-defined mass lesion in the right hemi-liver measuring about 12 x 8 cm with vague radiologic features. Upper and lower gastro-intestinal endoscopes were free. Upon exploration, there was a large mass occupying the right hemi-liver and she underwent right hemi-hepatectomy. The operation time was 300 minutes. The operative blood loss was about 100 cc and no blood transfusions were required. Pathological assessment showed a subcapsular well defined mass measuring 16 x 14 x 10 cm in size with free margins. The mass showed positive staining for synaptophysin (Syn) and chromogranin A (CgA). The final diagnosis was a well differentiated NET grade 3 with free surgical margin. The patient is still surviving 2 years after surgery without evidence of local or distant recurrences.
Conclusion: The diagnosis of PHNET remains unusual and challenging requiring a high index of suspicion and detailed investigations. Owing to the rarity of the reported PHNETs and the lack of official diagnosis and treatment guidelines, it is imperative to report such cases to expand the international database to improve the understanding of such rare disease.
Key words: hepatic neuroendocrine tumors, liver resection, primary tumor, immuno-histochemistry

INTRODUCTION

Neuro-endocrine tumors (NETs) are a varied collection of tumors that develop from neuroendocrine cells that can absorb and decarboxylate amine precursors. The incidence of newly diagnosed cases of NETs is steadily rising owing to the rising awareness of NETs and the advancements in medical technology. Approximately 70% of all NETs are found in the gastrointestinal tract, with the bronchopulmonary system coming in second. The colon,

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stomach, duodenum, and jejunum are the next most frequent locations, after the appendix, ileum, and rectum (1,2).

On the contrary, primary hepatic NETs (PHNETs) are comparatively rare. The origin and histogenesis of PHNETs are still unknown and controversial (3,4). The first case of PHNETs was reported by Edmondson in 1958 (5). To date, few number of PHNET cases have been recorded in the literature globally, making up approximately 0.3% of all cases of NETs (6).

The diagnosis of PHNET remains an unusual and challenging issue. As a result of the vague clinical symptoms and low diagnostic specificity with imaging studies, PHNETs continue to be a surgical challenge. Furthermore, it can be difficult to distinguish between PHNETs and metastatic NETs in the liver due to the homogeneous nature of NETs (7). So, it is important to address such rare cases aiming to develop guidelines regarding the diagnosis and treatment of such rare condition to improve patients' prognosis and survival.

In the current report, we address a rare case of PHNET that was successfully managed by major hepatic resection. Owing to the rarity of the reported PHNETs and the lack of official diagnosis and treatment guidelines for this condition, it is imperative to report such cases to expand the international database to improve the understanding of such rare disease.

CASE PRESENTATION

A 22-year-old woman, presented with recurrent dull aching right hypochondrial pain for 3 months. She did not report any associated symptoms like vomiting, diarrhea, indigestion, or bleeding per rectum. She did not have any past history of medical diseases. Also, she didn't have any significant past or family histories. Upon abdominal examination, a right hypochondrial mass was palpable. She underwent abdominal ultrasound and discovered a large mass occupying the right hemi-liver. An abdominal computed tomography (CT) revealed a well-defined hypodense mass lesion in the right hemi-liver measuring about 12 x 8 cm, where its enhancement pattern is in favor of benign nature suggesting a giant hemangioma (*fig. 1*). A further post contrast dynamic abdominal magnetic resonance image (MRI) study showed mild hepatomegaly and a large mass lesion implicating its right hemi-liver measuring 12 x 9 x 11 cm, where it appears of low signal in T1 and heterogenous high signal in T2 weighted images with areas of cystic changes noted within. In post contrast study the lesion shows non-specific heterogenous enhancement in the different phases following contrast injection, suggesting this lesion is likely neoplastic in nature (*fig. 2*). An upper gastro-intestinal endoscope and colonoscopy were done, and they didn't show any abnormality.

Regarding the preoperative laboratory investigations, they were all within the normal ranges including serum alpha-feto protein (AFP) (2 ng/ml), carcinoembryonic antigen (CEA) (1.6 ng/ml), carbohydrate antigen 19-9 (CA 19-9) (44 u/ml). She had negative serum virology markers for viral hepatitis.

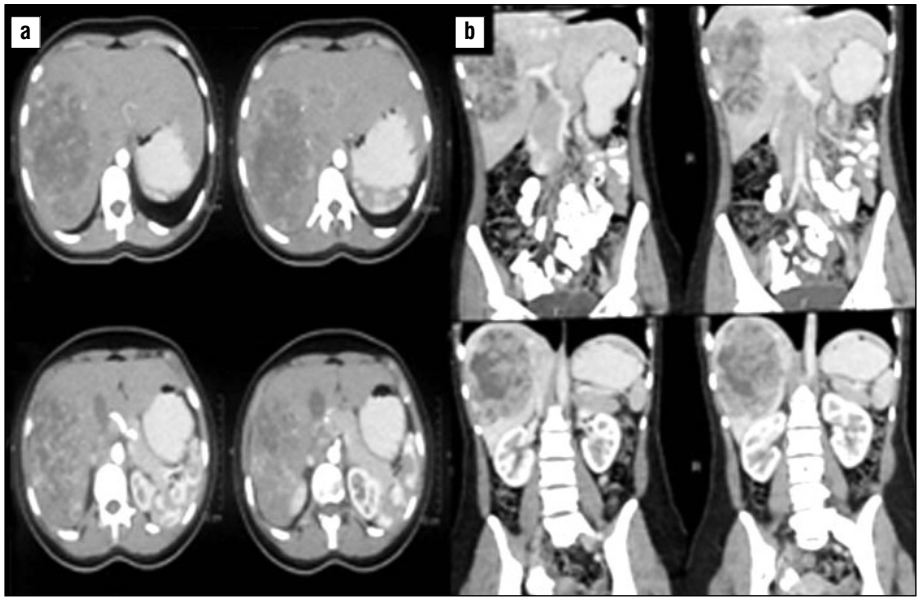

Figure 1 - Preoperative abdominal computed tomography showing large right hemi-liver mass 8 x 12 cm in size (a - axial view, b - coronal view).

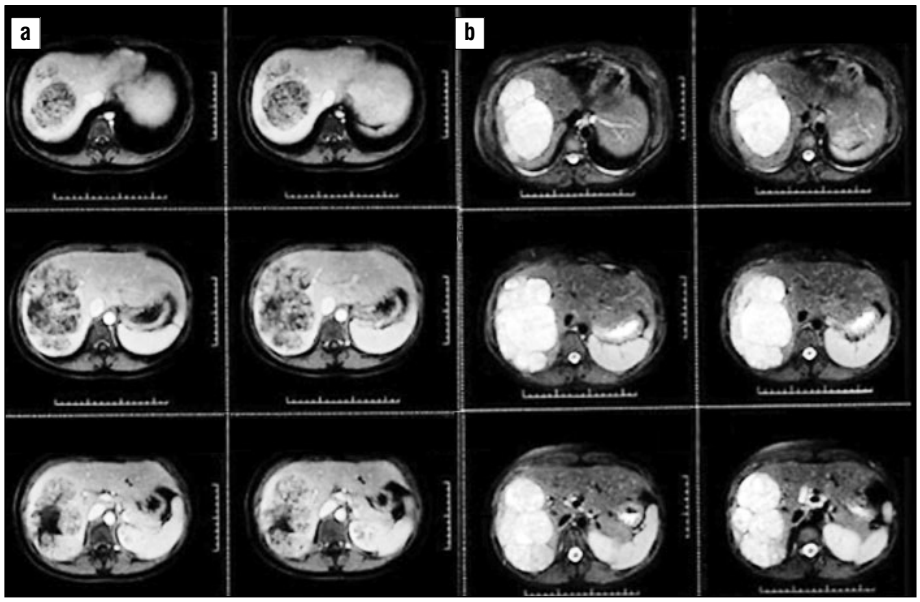

Figure 2 - Preoperative Abdominal Magnetic Resonance Image showing large right hemi-liver mass with cystic changes 11 x 12 cm in size (a - T1 axial view, b - T2 axial view).

The patient condition was discussed in multidisciplinary meeting, and she was planned for surgical exploration and resection of the mass. Upon exploration, there was a large mass occupying the right hemi-liver 15 x 10 cm in size. No other liver masses were noted and no other abdominal abnormalities. The decision taken was to do a right hemi-hepatectomy (*fig. 3*). The operation wound up without any complications. The total operation time was 300 minutes. The operative blood loss was about 100 cc and no blood transfusions were required.

Postoperative pathological assessment showed a subcapsular well defined mass measuring 16 x 14 x 10 cm in size away from the surgical margin by 3 mm. It showed infiltration of liver tissue by neoplastic tumoral proliferation arranged into trabeculae, acini, pseudo papillae with intervening delicate fibrovascular stroma, where the component cells were rounded monotonous cells with salt and pepper chromatin eosinophilic cytoplasm (*fig. 4 a, b*). Synaptophysin (Syn) showed diffuse positive cytoplasmic staining of tumor cells. Moreover, focal positive cytoplasmic staining of tumor cells by chromogranin A (CgA) was shown (*fig. 4 c*). It showed atypical mitotic figures > 20 per 2 mm and Ki-67 strong positive in more than 50% of the tumor cells (*fig. 4 d*). The final diagnosis was a well differentiated neuroendocrine tumor grade 3 with free surgical margin and an intact liver background.

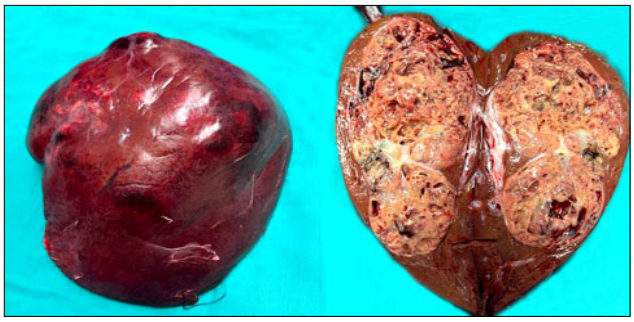

Figure 3 - Operative specimen after right hemi-hepatectomy showing large lobulated mass occupying most of the right hemi-liver.

The patient had postoperative bile leakage detected on the 5th postoperative day. The patient required an endoscopic retrograde cholangiopancreatography (ERCP) on the 10th postoperative day. ERCP cholangiography revealed bile leak from the right hepatic duct stump. A plastic 11.5 French stent was placed after a short papillotomy. The bile leakage was controlled, and the patient was discharged on the 18th postoperative day for follow up with medical oncology team. After 3 months from discharge, another set of ERCP was done to remove the biliary stent. The cholangiogram was free with no evidence of leakage or biliary stricture. After 2 years from the surgery, the patient is still doing well with normal liver functions and without evidence of local or distant recurrences.

DISCUSSION

PHNETs are very rare tumors of the liver. The origin and histogenesis of those tumors are still unknown and controversial. Different theories about the origin of PHNET have been put forth, however its pathophysiology is still unknown at this time (3,4). It

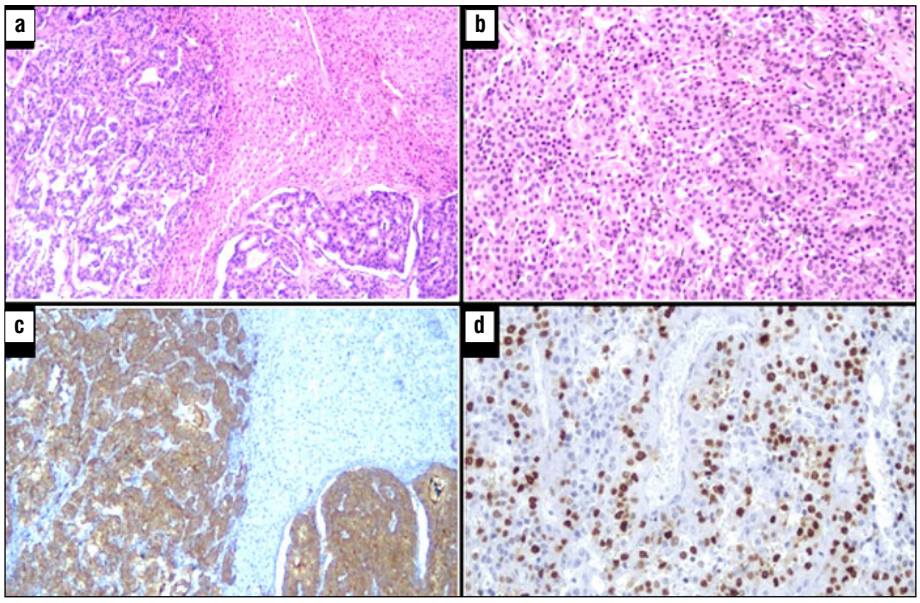

Figure 4 - (a) Photomicrograph shows infiltration of the liver tissue by tumoral proliferation with organoid architecture; nests, trabecular or insular pattern (Hematoxylin and Eosin; 10x). (b) Photomicrograph shows the tumoral tissue is formed of Monotonous regular cells with round or oval nuclei with salt and pepper chromatin and moderate eosinophilic granular cytoplasm (Hematoxylin and Eosin; 20x). (c) Photomicrograph displays that the tumoral tissue shows diffuse positive cytoplasmic reaction for synaptophysin with negative reaction of the liver tissue (10x). (d) Photomicrograph displays that the tumoral tissue shows positive nuclear reaction for Ki67 in about 60% of tumor cells (20x).

might arise from other ectopic tissues that function through hormones. It might also arise from the growth of neuroendocrine cells in the epithelium of the intrahepatic bile duct. Lastly, it can originate from the liver's multifunctional stem cells. Moreover, according to a recent study, PHNET development may be connected to mutations in the 1B gene's SET domain (8-10).

PHNETs are usually nonfunctional; this could be because the neuroendocrine hormones they release are of low quality or quantity, which inhibits the hormones' target organs from being triggered to produce biological effects (11). Abdominal pain is the most frequently encountered presenting symptom; however, most of the cases are asymptomatic and accidentally discovered during abdominal radiological evaluation. Patients over 50 years of age and females are more likely to be affected with PHNET (12,13). In the current report, we discuss a rare case of PHNET that was successfully managed with liver resection. The patient was 22-year-old woman with nonfunctional PHNET, who presented with abdominal mass and a right upper quadrant pain that lasted for 3 months.

PHNETs can be challenging to diagnose and need to be distinguished from metastatic liver tumors. For a conclusive diagnosis of PHNETs, clinical signs and imaging techniques, such as CT and MRI, are therefore also essential. Unfortunately, PHNETs do not show any particular characteristics on CT or MR imaging assessments (14). In the current report, we used a variety of imaging modalities, including abdominal CT and MRI, for the diagnosis. The preoperative CT scan misdiagnosed the tumor as a giant hemangioma as a result of the nonspecific radiological findings. Meanwhile, the preoperative MRI done suggested a neoplastic nature of this lesion.

Octreotide scintigraphy is a highly efficient method for diagnosing carcinoid tumors both in the primary lesion and in distant metastases due to the presence of somatostatin receptors in NET, with a sensitivity of 90% and specificity as high as 83% (15). However, it wasn't feasible in our case to do a PET/CT or octreotide scintigraphy, but instead a metastatic work up and digestive tract endoscopies were done to exclude other concomitant digestive tract lesions preoperatively.

Common tumor markers for gastrointestinal and hepatic cancers, such as AFP, CEA, and CA19-9, are frequently negative in PHNET patients. The only possible marker that can be utilized to diagnose and track NETs is serum CgA (6, 15, 16). In the current study, tumor markers done were serum AFP, CEA and CA 19-9, which were all negative. However, it wasn't permissible to do CgA due to the lack of this laboratory marker in our country.

However, the cornerstone for diagnosing NETs is histopathology and immunohistochemistry (IHC) analyses (16). When PHNETs are examined by histopathology, a well-demarcated gray-yellow mass with several irregular hemorrhagic or cystic regions are seen (17). Hematoxylin-eosin stains used in routine histological investigation reveals an insular, nested, trabecular, or mixed cellular development pattern; nonetheless, this is a nonspecific observation (16). The two that are thought to be particular immunohisto-

chemical markers for the pathological identification of NETs are Syn and CgA (18). The diagnosis of PHNET, as presented in our case study, is eventually supported by the combination of histomorphological characteristics and IHC findings (19). Tumor in this case, was a sub-capsular well defined mass measuring 16 x 14 x 10 cm. Regarding IHC staining, the specimen analyzed post-operative showed positive staining by CgA and Syn which confirmed the PHNET diagnosis.

Most frequently, PHNETs have low potential for malignancy and gradual growth. Determining the malignancy potential of these tumors seems to be possible through the measurement of cellular proliferation, and higher survival rates are associated with reduced cellular proliferation (19). Three grades for NETs are included in the 2019 WHO classification and are related to the mitotic index and ki-67 index (20). In our situation, the cell proliferation index was high, with more than twenty mitoses in every ten high-power fields and Ki-67 more than 50%. So, our case is classified as a grade 3 PHNET according WHO classification, which indicates that the prognosis is unfavorable.

A collaborative multidisciplinary approach is crucial for effective management of liver tumors. The standard of care for PHNETs is surgical resection with well-defined margins, as 70% of the tumors are resectable at the time of presentation. Liver resection is based on the size, location of the tumor, and the future liver remnant. Surgery has demonstrated highly promising long-term survival rates for patients with PHNETs. Knox et al reported that the 5-year survival rate following PHNET liver resection is as high as 78%, and the success rate is roughly 70% (21). In another study, 22 PHNET patients receiving surgical therapy were the subject of a long-term follow-up by Shi et al., who found that the overall survival rates at one, three, and five years were as high as 95.5%, 81.8%, and 64.7%, respectively (19).

Long-term patient survival has not been demonstrated to be impacted by additional variables, including age, gender, the number of tumors, the existence of extrahepatic metastases, or the location of the tumor inside the liver. It has been demonstrated that surgical resection is beneficial even for patients whose tumor margins on biopsy are positive (22). Patients with metastases and unresectable tumors may be considered for non-surgical treatment, such as combination therapy, trans-arterial chemoembolization, radiofrequency ablation, and chemotherapy. These therapeutic approaches reduce clinical symptoms and stop tumor growth, but they are less successful when compared to surgical resection (23-25). In the current report, the patient was successfully managed with major liver resection which removed the tumor thoroughly. The patient is under regular follow up with no evidence of local or distant recurrences.

CONCLUSION

In conclusion, this case report presents a rare instance of PHNET. The diagnosis of such cases remains unusual and challenging. The progression from the patient's presentation till the diagnosis shows the need for a high index of suspicion and detailed investigation on encountering unusual liver masses. Despite the rarity of PHNET, it is crucial to include it in the differential diagnosis of any hepatic mass. Owing to the rarity of the reported PHNETs and the lack of official diagnosis and treatment guidelines for this condition, it is imperative to report such cases to expand the international database to improve the understanding of such rare disease.

Author's Contributions

Conception and design of the manuscript: Ahmed Shehta. Acquisition of data: All authors. Analysis and interpretation of data: All authors. Drafting the manuscript: All authors. Critical revision of the final version to be published: All authors. Approval of the final version to be published: All authors.

Conflict of Interest

All authors declare no conflicts of interest.

Grants and Financial Support

No external funding resources.

Ethical Approval

An informed consent was obtained from the patient prior to surgical intervention. The study was approved by the Institutional Review Board and Local Ethical Committee at the Faculty of Medicine, Mansoura University, Egypt.

Availability of the Data

The data generated and analyzed for the current manuscript is not publicly available and will be available by a reasonable request from the corresponding author.

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