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Primary Neuroendocrine Tumor of the Liver: A Case Report and Review of the Literature

N. Bouhdoud[1*], M. Aouroud[1], F. Lairani[1], O. Nacir[1], A. Ait Errami[1], S. Oubaha[2], Z. Samlani[1]. K. Krati[1]

[1]Hepato-Gastroenterology Department, University Hospital of Mohammed VI, Marrakesh, Morocco
[2]Physiology Laboratory, Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakech, Morocco

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***Corresponding author:** N. Bouhdoud
Hepato-Gastroenterology Department, University Hospital of Mohammed VI, Marrakesh, Morocco

Abstract **Case Report**

Neuroendocrine tumors (NETs) of the digestive tract are rare tumors, but their prevalence is increasing. The anatomopathological examination is essential for establishing the diagnosis and for their histo-prognostic evaluation. Primary hepatic neuroendocrine tumors (PHNETs) are extremely rare, with only 200 cases described in the literature up to 2022. Given the rarity of PHNETs, there are no established algorithms for the diagnosis and management of these lesions, which presents a real medical challenge. Treatment is mainly surgical. The prognosis for these NETs appears to be better. The 10-year survival rate is around 70%. We report the case of a patient admitted for etiological evaluation of chronic right hypochondriac pain.

Keywords: Primary hepatic neuroendocrine tumor (PHNETs), Neuroendocrine tumor, Liver neoplasms, TACE.

INTRODUCTION

Neuroendocrine tumors (NETs) of the gastrointestinal tract are a rare type of tumors, originating in the cells of the neuroendocrine system. NETs arise preferentially in the bronchopulmonary tree (30%) or gastrointestinal tract (50%) and usually metastasis to the liver, but their prevalence is increasing as a result of advances in diagnostic techniques. Anatomopathological analysis is essential for establishing the diagnosis and evaluating the histo prognosis. Primary hepatic neuroendocrine tumors (PHNETs) are extremely rare and difficult to diagnose before preoperative biopsy or surgery, with only 200 cases described in the literature up to 2020. Given the rarity of PHNETs, there are no established algorithms for the diagnosis and management of these tumors, which represents a real medical challenge [1]. Treatment is mainly surgical. The prognosis of these NETs appears to be better. The 10-year survival rate is around 70% [2]. We report the case of a patient admitted in our department for an etiological assessment of chronic pain of the right hypochondrium revealing a PHNET.

CASE REPORT

A 64 years old woman, with no particular medical history ; was admitted to our department for an etiological assessment of chronic pain of the right hypochondrium; with a history of mild intensity sharp pain in the upper abdomen that started 2 years ago, and have worsened in the last 6 months before the consultation without any other associated digestive manifestations, such as jaundice or vomiting, no externalized upper or lower digestive hemorrhage, no abdominal distension, and no transit disorders or associated extra-digestive manifestations. All this evolved in a context of apyrexia and altered general condition, with asthenia and marked but unquantified weight loss. Clinical examination revealed a conscious patient with discolored conjunctivae, signs of malnutrition such as melting of the adipose pedicle, and signs of dehydration such as persistent skin folds. Abdominal examination revealed painless hepatomegaly with an irregular surface (liver span =18cm), mobile on breathing; lymph node examination revealed infra-centimetric bilateral inguinal adenopathy.

Radiologically, abdominal CT revealed an enlarged liver with regular contours and three heterogeneous hypodense lesions with moderate enhancement and necrosis, the largest of which was on the right liver measuring 16 x 12 cm, with other lesions on segments VII and II measuring 42 x 29 mm and 64 x 57 mm respectively; associated with 2 coeliomesenteric adenopathy, the largest of which measured 14 x 11 mm.

Biological laboratory results were within the normal limits, including tests for liver function (no hepatic cytolysis or cholestasis) and tumor markers (alpha-fetoprotein and carcinoembryonic antigen, CA19.9, CA125, 15.3). No serologic evidence of hepatitis B or C virus infection was found.

Endoscopically, upper and lower gastrointestinal endoscopies were performed, and the results were negative for any primary tumor. An echo-guided liver biopsy was performed, revealing, on anatomopathological and immunohistochemical staining revealed, a round-cell tumor proliferation with endocrinoid architecture, in favor of a neuroendocrine tumor (intense and diffuse cytoplasmic expression of anti-Synaptophysin antibody in tumor cells; Focal and partial cytoplasmic expression of tumor cells with anti-Chromogranin A antibody (Fig 1), with a Ki67 index <2%). This was followed by octreoscan, which confirmed the presence of a hepatic mass with hyper fixation of the metabolite and secondary hepatic localizations. Chromogranin A levels were high (202ng/ml).

The final diagnosis was a metastatic PHNET based on the pathological and imaging results. The multidisciplinary consultation meeting decided to refer the patient to oncology for systemic treatment.

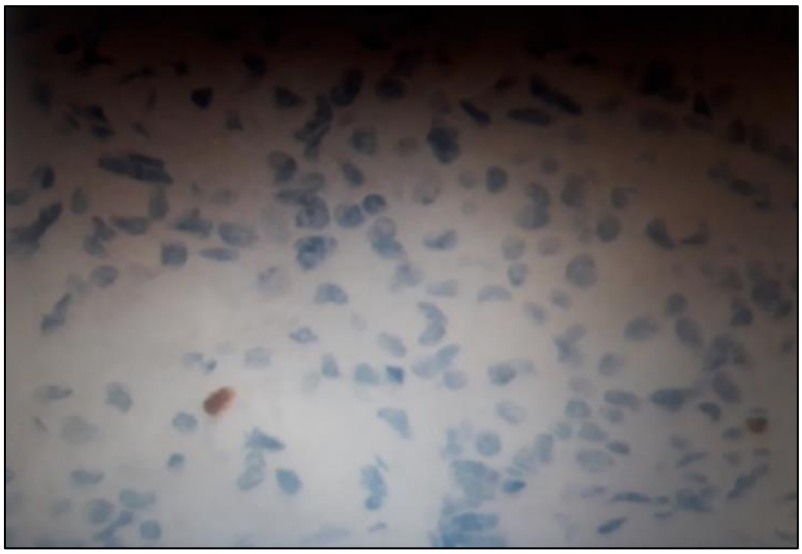

Figure 1: Pathological findings: moderate immunoreactivity for chromogranin in the tumor cells. Immunohistochemical (IHC) staining

DISCUSSION

Neuroendocrine tumors (NETs) are a type of low malignancy tumors that arise in neuroendocrine cells all over the body and are thought to have their origins in the neural crest's main cells throughout the body during embryogenesis [3]. These tumors can develop in the gastrointestinal tract (55%), lungs (30%), pancreas (2%) and genital tract (1%), biliary tract (1%), and head and neck (0.1%) [4]. However, these cells do not regularly migrate to the liver, which explains the rarity of PHNET [5, 6]. Yet the liver is a site of metastasis for digestive neuroendocrine tumors. PHNET, first described by Edmondson in 1958 [1]; and are extremely rare, with only 200 cases described in the literature up to 2020. Most studies have shown the predominance of these tumors in women, and their rarity before the age of 40. Our patient was a woman and diagnosed with PHNETs at the age of 64.

PHNETs usually present silent manifestations, without endocrinological repercussions rarely leading to hormone-related symptoms, contrasting with hepatic metastases from other organs NETs.

They develop asymptomatically, and symptoms are usually present in late stages [7]. They may manifest as abdominal pain, abdominal distension or jaundice attributed to the mass effect of the tumor [7-9]. Primary hepatic neuroendocrine tumors (PHNETs) can be classified into functional and non-functional PHNETs. They differ from other NETs in that they most often present as non-functional tumors [7]. Functional PHNET can cause flush syndrome or carcinoid syndrome. Our patient presented with right hypochondrium pain, with no other associated signs, notably the absence of carcinoid syndrome. Early diagnosis of this tumor remains difficult, as it remains asymptomatic for a long time, except in the case of an accidental discovery of a hepatic nodule during a routine examination.

PHNETs can only be diagnosed after excluding the possibility of extrahepatic disease with hepatic metastasis [4]. The diagnosis of these hepatic neoplasms prior to pathologic assessment of a biopsy or a surgically removed material is extremely difficult due to their non-specific appearance, though.

The diagnosis of PHNET is a continuum that begins in the preoperative stage and continues through the postoperative period, as well as long-term follow-up in order to identify extra-hepatic primary [10]. PHNETs are frequently misinterpreted as hepatocellular carcinoma (HCC) or cholangiocarcinoma (CCC) in preoperative imaging studies.

Imaging modalities such as ultrasound, CT and MRI play an essential role in the diagnosis of liver masses. The gross radiological characteristics of PHNET can vary greatly, with some lesions having diffuse or well-circumscribed margins as well as solid or cystic appearances [11]. The type of dynamic enhancement curves reflects the PHNETs' abundant hepatic artery blood flow. According to Wang et al.'s analysis of the arterial phase, all lesions were noticeably enhanced, and the reconstruction of the arterial phase demonstrated a robust blood supply. Marked arterial enhancement and washout in the portal and delayed phases are common features seen in HCC [7, 10]. Serum tumor markers such as alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) have no practical diagnostic value in the diagnosis of PHNET [10].

Histopathological examination is the best way to diagnose PNETs with a high degree of accuracy [11]. Biopsy can be performed using a fine needle, or can be performed surgically or after resection of the mass. Immunohistochemistry is the most accurate method for making a definitive diagnosis of this tumors [12]. In our case, the diagnosis was made by echo-guided liver biopsy, with anatomopathological examination supplemented by immunohistochemistry objectifying a round-cell tumor proliferation of endocrinoid architecture in favor of a well-differentiated WHO grade G1 neuroendocrine tumor. Surgical treatment of PHNETs is the most effective curative treatment, with a five-year survival rate of 74% and a recurrence rate of almost 18% [13, 14]. Resection is determined by tumor size and location. Other modalities include selective hepatic artery embolization, radiofrequency ablation and hepatectomy with liver transplantation [15]. Medical treatments such as Transarterial chemoembolization (TACE) are also used. On the other hand, systemic chemotherapy, local ablation and somatostatin analogues have failed to demonstrate a long-term survival benefit. TACE gave a good initial response in the short term only [13, 15]. In addition, TACE may reduce tumor size, which would be beneficial prior to surgical resection [13]. Due to the rarity of this tumors, it is difficult to obtain recommendations or consensus for codified management of these tumors [15]. In our case, the decision of the multidisciplinary consultation meeting was to start a systemic chemotherapy.

CONCLUSION

Primary hepatic neuroendocrine tumors is an extremely rare tumor that exhibits slow growth and low malignancy potential. Its non-specific clinical appearance and highly varied radiologic characteristics frequently result in the incorrect diagnosis of other hepatic neoplasms. Diagnosis depends on histological examination combined with immunohistochemistry. Furthermore, the best therapeutic approach for increasing survival rates remains surgical excision with clear margins. There are currently no well-established algorithms for the diagnosis and management of these lesions, which is a real challenge.

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