An unusual case of primary hepatic neuroendocrine tumor: a case report

Titis Hadiyanti Setyadi¹, Putu Niken Ayu Amrita*²

INTRODUCTION

Merely 1% to 2% of all gastrointestinal tumors are neuroendocrine tumors (NETs), which are incredibly uncommon tumors. The most frequent location of this tumor’s metastases is the liver. An infrequent instance is a primary hepatic neuroendocrine tumor (PHNET). The first case was reported by Edmonson in 1958, and since then, only 150 cases have been reported in the literature. PHNET is only 0.3% of all neuroendocrine tumors. Symptoms associated with PHNET are not specific, with abdominal pain as a clinical manifestation. The PHNET algorithm for diagnosis and therapy has not been determined.¹

PHNET diagnosis is a challenging task. Based on radiological features, hepatocellular carcinoma was the initial diagnosis made for the patient. Based on a histopathological analysis of the tumor biopsy samples, PHNET can be diagnosed. For patients with PHNET, the life expectancy beyond ten years is approximately 73%. Among the available therapeutic modalities are transarterial chemoembolization (TACE), liver transplantation, radiotherapy, chemotherapy, and the use of somatostatin analogs.² This case was taken to demonstrate the problem of diagnosis and management in a patient diagnosed with PHNET.

CASE PRESENTATION

The patient is a 41-year-old married female from Gresik who works daily as a housewife. The patient complained of an enlarged abdomen accompanied by a hard, solid lump in the upper right region. Complaints have been felt for the last four months and are getting bigger, accompanied by weight loss of more than 10 kg in the last three months. The patient was misdiagnosed with hepatocellular carcinoma based on an abdominal CT scan. Alpha-fetoprotein levels were within the normal limits. No serologic evidence of hepatitis B or C virus infection was found. A liver biopsy was performed with the result of PHNET.

Conclusion: It has been extremely difficult to diagnose this rare tumor, so we emphasize the significance of liver biopsy.

Keywords: primary hepatic neuroendocrine tumor, hepatocellular carcinoma, liver biopsy.


ABSTRACT

Introduction: Based on the results of medical imaging, primary hepatic neuroendocrine tumors (PHNETs) are an infrequent entity that is challenging to differentiate from other liver tumors. This case was taken to demonstrate the problem of diagnosis and management in a patient diagnosed with PHNET.

Case Presentation: We report an unusual case of a 41-year-old female with PHNET who initially had a chief complaint of an enlarged abdomen accompanied by a hard, solid lump in the upper right region. Complaints have been felt for the last four months and are getting bigger, accompanied by weight loss of more than 10 kg in the last three months. The patient was misdiagnosed with hepatocellular carcinoma based on an abdominal CT scan. Alpha-fetoprotein levels were within the normal limits. No serologic evidence of hepatitis B or C virus infection was found. A liver biopsy was performed with the result of PHNET.

Conclusion: It has been extremely difficult to diagnose this rare tumor, so we emphasize the significance of liver biopsy.
to confirm the diagnosis.

In April 2021, the result of the liver tissue biopsy was suspicious for grade I NET, followed by immunohistochemistry and obtained IHC Ki67 positive in 10% of tumor cell nuclei. The biopsy and conclusion were NET grade II.

Previous history of diabetes, high blood pressure, heart disease, kidney disease, and jaundice or liver disease was denied. A history of similar complaints or malignancy in the family was denied.

On examination, the general condition was weak, appeared moderately ill, GCS 456, BMI was 26.7 kg/m², blood pressure was 112/56 mmHg, pulse 115x/minute, respiratory rate 21x/minute, oxygen saturation 97% without oxygen supplementation, axillary temperature 36.5°C, and pain scale 3-4. Head and neck examination found anemic conjunctiva, icteric sclera, and an increase in jugular venous pressure (JVP) with no cyanosis, signs of dyspnea, or facial edema. The thoracic examination was symmetrical but retracted. Cardiac examination found regular S1/S2, no murmurs or gallops. Lung examination found basic vesicular sounds, no crackles, and no wheezing in both lung fields. Abdominal examination showed distension, normal bowel sounds, tenderness in the right hypochondrium region, hard palpable liver with blunt and smooth edges with a liver span of ± 20 cm, and Schuffner’s spleen palpable 3-4 (Figure 2). Examination of the extremities found no edema and warm with CRT <2 seconds.

Laboratory examination found hemoglobin (Hb) 6.6 g/dL, MCV 76, MCH 28, leukocytes 8,910/mm3, platelets 79,000/mm3, neutrophils 74.5%, lymphocytes 14.5%, sodium 120 mEq/L, potassium 3.8 mEq/L, chloride 94 mEq/L, creatinine 0.9 mg/dL, BUN 13 mg/dL, total bilirubin 4.88 mg/dL, direct bilirubin 3.38 mg/dL, AST 238 U/L, ALT 56 U/L.

Based on the history taking, physical, and laboratory examination, the patient’s assessment was grade II hepatic NET, hypochromic microcytic anemia, thrombocytopenia, elevated transaminase, and hyperbilirubinemia. The patient was given a soft diet high in calories and protein 2100 kcal, infusion of 0.9% NaCl 1000 ml/24 hours, packed red cells (PRC) transfusion one bag/day with Hb target 10 g/dL, codeine 10 mg orally every 8 hours, and paracetamol 500 mg orally every 8 hours.

On day 3, the patient’s complaints and physical examination were still the same, with normal vital signs. After three bags of PRC transfusion, laboratory examination found improved hypochromic microcytic anemia and thrombocytopenia (Hb 7.1 g/dL, MCV 79, MCH 27, and platelets 94,000/mm³), the total bilirubin 3.68 mg/dL, direct bilirubin 2.61 mg/dL, AST 138 U/L, ALT 44 U/L, complete stool erythrocytes 4-6/LP, leukocytes 4-5/LP, and positive fecal occult blood test (FOBT). The patient’s assessment of microcytic hypochromic anemia found
that it was due to gastrointestinal bleeding. Injection of omeprazole 40 mg IV every 12 hours and tranexamic acid 500 mg IV every 8 hours were added to the patient’s therapy.

On day 7, the patient complained of increasing bowel movements with blood spots and fresh blood clots one time with no complaints of nausea and vomiting but improved abdominal pain. Laboratory examination post three bags PRC transfusion found improved hypochromic microcytic anemia (Hb 8.3 g/dL, MCV 75, MCH 28) but worsened thrombocytopenia (platelets 39,000/mm3). Total bilirubin 2.89 mg/dL, direct bilirubin 1.97 mg/dL, AST 158 U/L, ALT 48 U/L. The patient’s assessment of microcytic hypochromic anemia was found due to hematochezia. Dexamethasone 5 mg IV every 8 hours for three days and a transfusion of thrombocyte concentrate (TC) 10 bags/day were added to the patient’s therapy. From consultation with the gastro-entero-hepatology division, a colonoscopy was planned for indications of hematochezia.

On day 10, the patient complained of yellowing of the eyes and urinating like tea. Blood in bowel movements was improved. Laboratory examination post two bags of PRC and ten bags of TC transfusion found improved hypochromic microcytic anemia and thrombocytopenia (Hb 10.7 g/dL, MCV 79, MCH 28, and platelets 47,000/mm3). Total bilirubin 6.13 mg/dL, direct bilirubin 4.48 mg/dL, AST 207 U/L, ALT 50 U/L, and normal electrolytes. Therapy of omeprazole injection 40 mg IV every 12 hours was changed to omeprazole 20 mg orally every 12 hours. Dexamethasone and tranexamic acid injections were stopped.

On day 14, the patient had no complaints. Laboratory examination after 20 bags of TC found lower Hb levels (9 g/dL), MCV 77, MCH 28, and improved thrombocytopenia (platelets 63,000/mm3). The total bilirubin 5.47 mg/dL, direct bilirubin 3.85 mg/dL, AST 108 U/L, ALT 34 U/L, and normal electrolytes. Therapy was continued, and the patient was planned to be given an injection of octreotide LAR 20 mg IM every three weeks. On the follow-up, the patient showed improvement in abdominal pain and decreased tumor size (Figure 3).

**DISCUSSION**

Neuroendocrine tumors (NETs) have a prevalence of 1-2% of all gastrointestinal tumors and are often incidentally found to metastasize to the liver. The rectum (17.2%), jejunum/ileum (13.4%), and pancreas (6.4%) were the regions where NETs were most often discovered. There are only about 150 cases of primary hepatic neuroendocrine tumors (PHNETs) documented in the literature, making them incredibly rare. Neuro-ectodermal cells that move from the neural crest during embryogenesis give rise to NETs. PHNET is exceptionally uncommon since these cells hardly ever migrate to liver cells. Distinguishing primary from metastatic NETs in the liver remains challenging.¹ ³ PHNET is most common in the fourth and fifth decades, although it can occur at any period of life. Women are affected more often than men, although the difference is insignificant. PHNET is often discovered accidentally on routine screening. Symptoms often found are abdominal pain and a palpable mass in the upper right region of the abdomen. Patients can experience carcinoid, although it is infrequent. In NETs, gastrointestinal symptoms of carcinoid alone are only found in less than 10% and, if found, associated with metastases to the liver. Symptoms of carcinoid syndrome itself are redness of the skin, abdominal pain, and episodic diarrhea.² ⁴ The origin of PHNETs is still unclear at this time. Regarding this, three theories have been put forth. Initially, neuroendocrine cells become malignant after spreading to the biliary tract epithelium. Second, either heterotrophic pancreatic tissue or adrenal tissue found in the liver is the source of these tumors. Third, neuroendocrine differentiation by malignant stem cells.⁷ ⁵-Hydroxyindoleacetic acid (5-HIAA), an inactive metabolite of serotonin in 24-hour urine preparations, was examined.

Figure 3. Improvement in patient’s symptoms and decrease in tumor size
in order to make the NET diagnosis. The sensitivity of this test is low since 5-HIAA cannot be measured in tumors lacking endocrine function. A particular marker for NETs is serum analysis of the neuroendocrine cell-secreted protein cga. Other tumor markers that are currently non-specific for PHNETs include CEA, CA 19-9, and AFP.

It is possible to confuse PHNET radiological results with those of other liver tumors. PHNETs, ultrasonography, CT scans, and MRIs have low sensitivity when imaging. Nonetheless, a CT scan is the most popular radiological method for locating NETs. Radiological findings that can be useful in determining the correct diagnosis for PHNETs are hypervascular and usually solid tumors. In this case, the patient had complaints of abdominal pain and enlargement of the upper right region without any signs of skin redness, abdominal pain, and episodic diarrhea leading to carcinoid syndrome. Physical examination revealed an enlarged liver with a liver span of 20 cm. Abdominal ultrasound radiological examination only found a mass in the liver, followed by a CT scan of the abdomen with contrast showing hepatocellular carcinoma. This is consistent with the theory that radiological findings cannot be used to diagnose NETs. Compared to other common liver tumors, TEN can be diagnosed through imaging and laboratory testing, but pathological examination of the tumor resection specimen confirms the diagnosis. Because needle biopsy increases the risk of tumor seeding and has a diagnostic accuracy that ranges from 11 to 50 percent, it is not advised.

Histomorphological features such as nested, trabecular, and acinar architectural patterns are present in well-differentiated NETs. The eosinophilic cytoplasm is abundant in epithelioid tumors, and the tumors’ round nucleus and granular chromatin pattern are often referred to as “salt and pepper.” While the morphology above points strongly towards NETs, it should be remembered that hepatocellular carcinoma can also exhibit cells with eosinophilic cytoplasm and a similar pattern (trabecular and acinar). Hepatocellular carcinoma shows bile production that is not found in well-differentiated NETs. Hepatocyte-specific markers such as HepPar1 and arginase one can be used to differentiate between hepatocellular carcinoma and well-differentiated NETs. Further confirmation of PHNETs can be made by immunohistochemical staining, which shows the presence of synaptophysin, chromogranin, CD56 (NCAM), and cytokeratins in most cases. The morphological and immunohistochemical patterns are similar for well-differentiated NETs at any site. Additional tests are needed to determine the primary site of the tumor, as CDX2 suggests a gastrointestinal origin. Determining differentiated NETs as primary or metastatic tumors depends on the clinical setting. Most well-differentiated NETs found in the liver are metastases mainly from the small intestine and pancreas.

Depending on the primary location of the tumor, well-differentiated NETs are categorized based on the mitotic rate and the Ki-67 proliferation index. An increase in Ki67, a tumor proliferation marker, is linked to a worse prognosis for NETs in the gastrointestinal tract. The WHO reclassified low- and intermediate-grade endocrine neoplasms (grades 1 and 2) and high-grade neuroendocrine carcinomas (grade 3) in 2010 as NETs that can be used for PHNETs. High-grade neuroendocrine carcinoma is currently a distinct entity from well-differentiated NETs. High-grade cytology demonstrates the typical morphology of small cell carcinoma or large cell neuroendocrine carcinoma, and these grade 3 tumors exhibit high mitotic activity (typically 40–50 mitoses per 10 visual fields or Ki-67 index >20%). Individuals with a Ki-67 index less than 2% had a better prognosis than those with an index greater than 2%. This was demonstrated in the case of PHNET patients, whose average Ki-67 index was 1.7% in those without recurrent illness. In this case, liver biopsy was suspected of being a grade I NET, and after histochemical staining, 10% Ki-67 and NET grade II were concluded.

Since almost 85% of tumors are resectable, surgery with negative margins and total resection is the preferred treatment option for PHNETs. Surgery provides excellent 5-year survival of 74-78%. Liver transplantation, or TACE, is also an alternative therapy modality in patients who cannot undergo surgical therapy. TACE also enhances cytoreduction effects and can decrease the size and distribution of tumors so that previously inoperable surgery can be performed later. Chemotherapy has a limited role in the treatment of this tumor, as it is only used in patients who cannot be operated on and have distant metastases. There is no evidence to support survival in patients receiving perioperative chemotherapy, radiotherapy, and TACE in patients undergoing immediate surgery.

Therapy that can be given to NETs is a somatostatin analog to control the syndrome associated with hormones secreted by the tumor. Recent research has demonstrated its potential as an antiproliferative and its capacity to stabilize tumor growth in patients with metastases. At first, octreotide could be injected subcutaneously or intravenously in a rapid-release formulation. It has been attempted to administer subcutaneous octreotide in doses ranging from 100 to 500 g twice or thrice daily. Long-acting repeatable (LAR) octreotide formulations that only need a monthly intramuscular injection have been available for the past ten years. Additionally, octreotide LAR has demonstrated efficacy comparable to subcutaneous octreotide in managing carcinoid syndrome-related diarrhea and flushing. For most patients, somatostatin analog therapy improves survival and disease stabilization. In one retrospective study of 146 patients with metastatic midgut NETs, long-term octreotide therapy showed a 5-year survival rate of 75%. The patient was given a somatostatin analog starting at 20 mg IM every three weeks. The patient showed improvement in abdominal pain and a decrease in tumor size.

CONCLUSION
A case of a 41-year-old female with a grade II neuroendocrine liver tumor, manifested by an enlarged abdomen accompanied by a hard solid lump on the upper right, underwent an abdominal ultrasound, abdominal CT scan, and liver biopsy. A liver tissue biopsy found suspicion of a grade I NET. Immunohistochemistry
found positive Ki67 in 10% of tumor cell nuclei, and NET grade II was concluded. The therapy given was somatostatin analog with a dose of 20 mg IM every three weeks, and the patient showed improvement in symptoms and a decrease in tumor size.

**PATIENT’S INFORMED CONSENT**

The patient has signed a written informed consent and agreed to this study’s publication.

**CONFLICT OF INTEREST**

The authors declare that there are no conflicts of interest.

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**AUTHOR CONTRIBUTIONS**

All authors contributed equally to this study and the manuscript preparation until publication.

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