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CASE REPORT

Primary hepatic neuroendocrine neoplasm diagnosed by somatostatin receptor scintigraphy: A case report

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Abstract

BACKGROUND
Primary hepatic neuroendocrine neoplasm (NEN) is a rare condition, and it is difficult to differentiate between primary and metastatic hepatic NENs. Herein, we report a case of primary hepatic NEN that initially mimicked a hemangioma but showed a gradual increase in size on long-term careful observation.

CASE SUMMARY
A 47-year-old woman was incidentally diagnosed with a 12-mm liver mass, suspected to be a hemangioma. Since then, regular follow-up had been carried out. Ten years later, she was referred to our institute due to the tumor (located in segment 4) having increased to 20 mm. Several imaging studies depicted no apparent extrahepatic lesion. Positron emission tomography (PET)/computed tomography exhibited significant accumulation in the mass lesion, which made us consider the possibility of malignancy. Left hepatectomy was performed. The histopathological diagnosis was neuroendocrine tumor grade 2, with somatostatin receptor 2a/5 positivity. Postoperative somatostatin receptor scintigraphy (SRS) showed no other site, leading to the diagnosis of NEN of primary hepatic origin. The gradual growth of the hepatic NEN over 10 years suggested that it was likely to be a primary liver tumor.

CONCLUSION
In this case, positivity on PET and postoperative SRS may have helped determine whether the tumor was primary or metastatic.

Key Words: Hepatic neoplasm; Scintigraphy; Surgery; Positron-emission tomography; Clinical decision-making; Case report
Core Tip: The clinical diagnosis of primary hepatic neuroendocrine neoplasm (NEN) remains challenging due to its rarity and difficulty in differentiating between primary and metastatic NENs. We present a case of primary hepatic NEN that presented with exceedingly gradual growth over 10 years, initially mimicking a hemangioma. Close preoperative observation, positron emission tomography findings, and postoperative somatostatin receptor scintigraphy findings greatly contributed to the final diagnosis. This case highlights the importance of close preoperative observations of NENs. In addition, the clinical usefulness of these modalities for correct diagnosis has been suggested, although regular postoperative follow-up is required.

INTRODUCTION

Primary hepatic neuroendocrine neoplasm (NEN) is a rare condition with unclear clinical features. Obtaining a preoperative diagnosis of primary hepatic NEN can pose a challenge. In this report, we describe a case of hepatic NEN that initially mimicked hemangioma but gradually increased in size after close observation for 10 years. Immunohistological staining showed that the tumor cells were positive for somatostatin receptor (SSTR) 2a/5. Postoperative somatostatin receptor scintigraphy (SRS) revealed no other significant site, which supported the idea that the tumor was of primary hepatic origin with gradual tumor progression. This case report was written in accordance with the SCARE guidelines[1].

CASE PRESENTATION

Chief complaints
The patient had no complaints.

History of present illness
A 47-year-old Japanese woman underwent abdominal ultrasound for a medical check-up, which revealed a 12-mm hyperechoic hepatic mass in segment 4. Because the mass was suspected to be a hemangioma, the patient regularly underwent follow-up annual ultrasound examinations to assess its size. Ten years later, the mass had increased to 20 mm. The patient was then referred to our institute because the mass was suspected to be malignant.

History of past illness
The patient’s past medical history was not significant, except for uterine myomas.

Personal and family history
The patient had no remarkable family history. She denied any specific personal history of other diseases.

Physical examination
At her first presentation to our clinic, physical examination revealed a soft, flat, and non-tender abdomen.

Laboratory examinations
Her laboratory data indicated that her renal and liver functions were normal. The Child-Pugh score was categorized as class A, and the indocyanine green retention at 15 min was 11.3%. The patient was negative for hepatitis B or C infection. The serum tumor markers, carcinoembryonic antigen, carbohydrate antigen 19-9, alpha-fetoprotein, and protein induced by vitamin K antagonist-II, were all within their normal ranges. All electrolytes were within normal limits.
Imaging examinations
Contrast-enhanced computed tomography (CT) revealed a 23-mm liver mass in segment 4, adjacent to the hepatic hilum. The mass exhibited a slight ring-like enhancement in the arterial phase. In the portal and delayed phases, the signal intensity of the mass was lower than that of the surrounding liver tissue (Figure 1). Contrast-enhanced magnetic resonance imaging (MRI) demonstrated a low signal on T1-weighted images and an intermediate signal on T2-weighted images. In the early phase, peripheral enhancement with a low signal was observed inside the mass. Diffusion-weighted images showed a significantly high signal, and the apparent diffusion coefficient (ADC) map demonstrated a low signal. A decreased uptake of gadoxetate sodium was also observed. Positron emission tomography (PET)/CT showed significant accumulation, with a maximum standardized uptake value of 10.1 at the mass. No other abnormal accumulations were observed. Esophagastroduodenoscopy and colonoscopy revealed no malignant lesions.

FINAL DIAGNOSIS
Considering these preoperative imaging studies, malignancy was considered as a differential diagnosis.

TREATMENT
Surgical resection was planned as a treatment option. Intraoperatively, we found no ascites, dissemination, or distant metastasis. Although intraoperative ultrasound demonstrated an apparent capsule around the mass in segment 4, the mass was located just on the hilar plate and was stiffly attached to Glisson’s capsule. Therefore, a left hepatectomy was performed to obtain a surgical margin. The postoperative clinical course was unremarkable, and the patient was discharged on postoperative day 14.

OUTCOME AND FOLLOW-UP
Gross examination revealed a 2.5 cm × 2.0 cm × 3.0 cm yellowish-white mass with hemorrhage (Figure 2). Histologically, atypical cells with small round nuclei and eosinophilic cytoplasms were arranged in an alveolar, reticular, or trabecular pattern. The cells were characterized by nuclear division, with 2 per 10 high-power fields. Immunohistological staining showed that the tumor cells were positive for chromogranin A/synaptophysin and negative for CD56. The Ki-67 labeling index was found to be 7%. Thus, a diagnosis of hepatic NEN (grade 2) was made. With respect to SSTR, the scores were 3 for SSTR2a and 2 for SSTR5 (Figure 3). SRS performed in the outpatient clinic identified no other significant accumulation, which cast doubt on the possible existence of other primary sites other than the liver. Taking these findings into account, we concluded that the tumor originated in the liver; however, continuous follow-up is essential to completely rule out the possible existence of other primary sites or to identify the appearance of new hepatic lesions in the future. Regular follow-up with imaging studies has been performed since the operation, considering possible recurrence. At the 1-year follow-up, the patient was in good health and free from recurrence.

DISCUSSION
NEN is a primary malignant tumor arising from neuroendocrine cells throughout the body. The most common primary sites of NEN are the gastrointestinal tract (67.5%) and the lung/bronchus (25.3%) [2]. Within the gastrointestinal tract, the small intestine (25.3%), rectum (27.4%), and stomach (8.7%) are the most commonly involved organs [2]. Primary hepatic NEN is extremely rare (0.4%) [2] and has no specific imaging findings or biomarkers. Thus, the diagnosis of hepatic NEN is generally difficult. The fact that the liver is frequently the metastatic site of NEN makes this diagnosis even more challenging. Furthermore, early diagnosis is often difficult because patients may have nonspecific symptoms or be asymptomatic, and the growth of NEN is generally slow. In the present case, the doubling time of the mass was calculated to be 46.4 mo, and such a gradual increase might have caused a delay in diagnosis. To the best of our knowledge, the longest observation period before surgery of a hepatic NEN in previous reports was 26 years [3].

Regarding imaging modalities for the diagnosis of primary hepatic NEN, contrast-enhanced CT is often nonspecific because it shows the contrast effect in the arterial phase and washout in the portal phase, which is similar to the classic contrast pattern of hepatocellular carcinoma [4,5]. MRI can depict a low signal on ADC maps/T1-weighted images and a high signal on T2-weighted images [4].
Figure 1 Abdominal computed tomography. A: Peripheral contrast enhancement was observed in the atrial phase (arrow); B: In the delayed phase, the contrast of the mass appeared lower than the surrounding liver tissue (arrow); C: The decreased uptake of Gadoxetate sodium was found (arrow); D: Positron emission tomography/computed tomography showed significant accumulation at the mass (arrow).

Figure 2 Macroscopic findings of the excised specimen. The specimen was a 2.5 cm × 2.0 cm × 3.0 cm yellowish-white mass with hemorrhage.

detection rate of NENs on PET/CT is 25%-73%, which is not very high and may be explained by the fact that NENs have relatively low tumor growth activity compared to carcinomas[6]. However, PET has been reported to be useful in the search for metastasis and the diagnosis of recurrence in patients with high-grade tumors, such as those with abnormal accumulation in the primary lesion[7]. Thus, PET/CT may be useful for differentiating metastatic NENs in the liver. In the present case, peripheral enhancement on CT and MRI and high accumulation on PET/CT also raised the possibility of
intrahepatic cholangiocarcinoma with marginal vascular regeneration around the tumor. However, the extremely slow increase in tumor rate made us doubtful of the possibility of cholangiocarcinoma. The present case is noteworthy in that primary hepatic NEN exhibited significant accumulation on PET/CT. To the best of our knowledge, there are no reports showing accumulation at the site of primary hepatic NEN on PET/CT.

Although no clear clinical guidelines have been established for the treatment of primary hepatic NEN, surgical resection remains the basic treatment when feasible. Knox et al. reported a 5-year postoperative survival rate of 74%-78%, 10-year survival rate of 68%, and recurrence rate of 18%. Although it is often difficult to determine whether NEN is a primary or metastatic lesion preoperatively, there are reports of improved prognosis after tumor reduction surgery even in unresectable or recurrent cases, regardless of whether the tumor is primary or metastatic. Therefore, aggressive surgical resection should always be considered.

Tumors of neuroendocrine origin usually have cell surface receptors with an affinity for somatostatin. SRS is an imaging technique in which gamma-ray emitting radionuclides are labeled on octreotide, which shows an affinity for SSTR expressed on the cell membrane of lesions. Thus, SSTR is expressed in lesions with accumulation on SRS. SSTR has five subtypes, and subtypes 2a and 5 are characteristic of NEN. Volante et al. defined scores of 2 (membranous reactivity in less than 50% of tumor cells) and 3 (circumferential membranous reactivity in more than 50% of tumor cells) as positive. Hasegawa et al., who analyzed 16 cases of NEN, reported that the concordance rate between accumulation in a lesion on SRS and pathological SSTR2a expression was 93.8%.

SRS has been reported to have an 89% sensitivity to NEN. However, there are some reports of high accumulation in meningiomas and small cell lung cancer, as well as accumulation in non-tumorous conditions including pneumonia, surgical wounds, and the breast. When SRS is performed to investigate the possibility that the primary tumor is located in another organ, as in this case, the interpretation of whether the site of accumulation is the primary site or a false positive should be carefully made in consideration of the other imaging modalities.

In the present case, SRS was performed to identify the presence of a primary site in another organ after histological diagnosis. Scigliano et al. reported high sensitivity, specificity, and accuracy (89%, 94%, and 91%, respectively) for SRS as a detection method for recurrence. Considering the gradual clinical course and postoperative investigation for another primary site, we thought that the hepatic tumor was most likely to be of primary hepatic origin. In this case, SRS revealed no possible primary or metastatic sites in other organs, and recurrence could be detected by comparative appraisal with the present results of SRS in the future. Therefore, continuous follow-up and preoperative observation are essential. Several reports on the usefulness of SRS as a preoperative staging assessment for pancreatic and gastrointestinal NENs have been reported. However, to the best of our knowledge, SRS has not reportedly been performed in a patient with suspected primary hepatic NEN to postoperatively evaluate the possible existence of other primary lesions.
CONCLUSION

We observed a long course of gradual tumor growth of hepatic NEN, considered the primary origin, for 10 years. Close preoperative observations, including PET/CT studies, enabled surgical decision-making and curative resection. Postoperative SRS after histological studies may be beneficial in making a final diagnosis.

FOOTNOTES

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