Primary Hepatic Neuroendocrine Tumor with Unusual Thyroid Follicular-Like Morphologic Characteristics

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We describe a primary hepatic neuroendocrine tumor of a 57-year-old Thai woman who presented in 2004 with a suspicious mass in the left hepatic lobe. She underwent left hepatectomy for the 10.5-cm mass, called intermediate grade neuroendocrine carcinoma of unknown origin, likely metastatic. The tumor recurred in 2007, then called recurrent primary hepatic neuroendocrine tumor (PHNET), and the patient underwent liver transplant. Because of similarity between the neuroendocrine tumor and a thyroid tumor—specifically, follicular-like characteristics—immunohistochemical stains for thyroglobulin, TTF1, and calcitonin were performed. However, all were negative. All imaging studies revealed no evidence of a primary lesion other than the liver mass. In 2008, the patient’s liver transplant failed because of ischemic cholangiopathy, and she underwent a second liver transplant. Seven years later, in 2015, she presented with metastatic neuroendocrine tumor of intermediate grade to the lung, consistent with metastatic PHNET. She underwent left upper-lobe wedge resection to remove the tumor. The patient is alive with no evidence of disease at 13 years after initial diagnosis. This rare variant of PHNET had thyroid-like morphologic characteristics but there is no evidence of primary thyroid tumor or thyroid markers in the primary and recurrent hepatic tumors and lung metastasis.

1. Introduction

Primary hepatic neuroendocrine tumors (PHNETs) are rare and poorly described entities, with fewer than 150 cases described in the literature [1]. First described by Edmonson [2] in 1958, PHNETs represent about 0.3% of all neuroendocrine tumors. Therefore, identification and description of these tumors are important to help better understand the clinicopathologic features and biologic behaviors. Moreover, even fewer literature reports deal with the progression and prognosis of PHNETs, which make this case, with a follow-up of 13 years, a distinctive and interesting report.

Neuroendocrine tumors (NETs) in general are relatively rare tumors with an incidence rate of 2 per 100,000 cases of all gastrointestinal tract tumors [3]. NETs can arise virtually anywhere in the body, and approximately 70% of these rare tumors arise in the gastrointestinal tract and lungs [4]; the liver is the common site for metastasis, yet it is an uncommon site for tumor origin.

Our review showed that demographically most of patients with PHNETs are of Asian descent (mean [range] age, 45 [8–87] years) [3, 5]. There is no sex predilection, but a predominance of female patients has been reported (female to male ratio, 1.4 : 1) [2]. In the few reported cases of PHNET and for the present patient, a palpable abdominal mass or abdomen discomfort may be the only presenting concern [1]. This presentation is in contrast to the classic symptoms of carcinoid syndrome that accompany 10% of all NET liver metastasis but rarely occur in PHNET. On imaging, PHNETs tend to appear more vascular than metastatic because of a rich vascular supply from the hepatic artery [6], consistent with the magnetic resonance imaging (MRI) findings of the recurrent PHNET in this case.
2. Case Presentation

The patient was a 57-year-old Thai woman who was referred in August 2004 for a suspicious mass in the left hepatic lobe that had been discovered on ultrasonography. She underwent a left hepatectomy of the native liver for an estimated 10-cm mass. Grossly, the resected lobe showed both a 10.5 \times 10.0 \times 7.0 \text{ cm}, tannish yellow, focally hemorrhagic, well-circumscribed mass and a 0.7-cm well-circumscribed yellow nodule that were within 3.5 cm of each other.

On histomorphologic evaluation, the mass showed a monotonous uniform population of neoplastic cells arranged in follicles with intraluminal eosinophilic secretions. The cells were round to oval with scant eosinophilic cytoplasm that had “salt-and-pepper” chromatin (Figure 1) and brisk mitotic activity. Immunohistochemical staining of the larger mass showed focal reactivity for chromogranin (Figure 2) and diffuse reactivity for synaptophysin, consistent with the diagnosis of a neuroendocrine carcinoma. The tumor showed diffuse positive immunostain for keratin and cytokeratin 7 (Figure 3) and patchy reactivity with vimentin. Additional immunostains, including thyroglobulin, thyroid transcription factor (TTF1), and neuron-specific enolase, were negative, as was Congo red, a stain particularly for amyloid. Polyclonal carcinoembryonic antigen immunostain was also negative for the canalicular pattern usually seen in hepatocellular carcinoma, making the diagnosis unlikely. With a mitotic count of 16 or 17 mitoses per 10 high-power fields (HPFs) and Ki-67 labeling index of 20% (Figure 4), the diagnosis of intermediate grade (G2) NET, likely metastatic, was made.

A follow-up MRI in 2007 revealed an 8.9-cm liver tumor on segment VIII, described as circumscribed and hypervascular. No other primary lesion was detected on other imaging, including octreoscan, bone scan, ultrasonography of both breasts and thyroid gland, and endoscopy including a capsule study. Subsequently, the patient underwent a liver transplant following hepatectomy of the remaining native liver. The completion hepatectomy specimen of the remaining native liver showed that the liver capsule was brownish tan, focally fibrotic, and diffusely covered with adhesions. Sectioning revealed an orange well-circumscribed mass measuring 14.5 \times 13.0 \times 12.1 \text{ cm}. The tumor had areas of cystic degeneration intermixed with areas of hemorrhage, with a variegated appearance. On microscopy, the tumor showed follicular thyroid-like morphologic characteristics reminiscent of a thyroid follicular carcinoma (Figure 5). However, no immunohistochemical evidence of thyroid differentiation was found, as shown by negative immunoreactivity to thyroglobulin, TTF1, and calcitonin.
Figure 5: Recurrent hepatic neuroendocrine tumor in 2007 with low-grade morphologic characteristics and a low mitotic count (hematoxylin-eosin, original magnification ×40).

Figure 6: Synaptophysin immunoexpression in the tumor (original magnification ×40).

Figure 7: Cytokeratin 7 immunoexpression in the neoplastic cells (original magnification ×40).

Figure 8: Ki-67 expression in the tumor cells (2% mitotic labeling index, original magnification ×40).

The tumor once again stained positive for neuroendocrine markers, including synaptophysin (Figure 6) and chromogranin, in addition to keratin, cytokeratin 7 (Figure 7), and vimentin, confirming the diagnosis of recurrent PHNET. The lack of the carcinoid symptoms that usually accompany metastatic hepatic NETs and the failure to identify a primary tumor elsewhere on complete body imaging led to the diagnosis of recurrent PHNET. Interestingly, this tumor was a low-grade (G1) tumor with a mitotic count of 1 per 10 HPFs and a Ki-67 labeling index of 2% (Figure 8).

In 2008, the patient’s transplanted liver failed because of ischemic cholangiopathy, and she underwent a second liver transplant. On a posttransplant follow-up visit in 2015, a radiograph showed an enlarged left upper-lobe lung nodule. However, an octreoscan and a positron emission tomography/computed tomography scan for whole-body imaging were negative. The nodule size was found to be increasing on interval monitoring; in 2016, the patient underwent a wedge resection. Ultrasonography and MRI of the abdomen showed no liver abnormalities this time.

The left upper-lobe lung wedge resection of the suspicious nodule showed a 1.4 × 1.0 × 0.6 cm, well-circumscribed, tan firm mass. On microscopy, the tumor showed similar morphologic characteristics to the 2 previous primary and recurrent hepatic tumors (Figure 9). Immunohistochemically, it stained positive for synaptophysin (focally; Figure 10) and cytokeratin 7 (Figure 11) and was negative for thyroglobulin, chromogranin, PAX8, cytokeratin 20, TTF1, mammaglobin, napsin A, estrogen receptor, GATA3, and c-kit. The tumor characteristics and immunohistochemical profile were consistent with the diagnosis of PHNET metastasis. The Ki-67 labeling index was 5% (Figure 12) with a mitotic count of 2 mitoses per 10 HPFs, thereby grading the metastasis as G2.

3. Discussion

PHNET primarily occurs in patients aged 40 to 50 years and is usually located in the right lobe of the liver [3]. PHNETs tend to be large and well-circumscribed, often arising on the right lobe of the liver and surrounded by healthy parenchyma in most cases, with cirrhosis found only as the concomitant liver disease [5, 7–9]. These findings are similar to our case of PHNET except for the PHNET location on the left lobe. However, varying microscopic morphologic characteristics are a commonly described feature of PHNETs. Our case revealed a thyroid follicular-like morphologic appearance reminiscent of thyroid follicular carcinoma, a feature that has never been described previously, to our knowledge. One case showed signet ring cells that were mucin negative [10], but cytokeratin positivity and other various morphologic traits have also been described [9–11].

The origin of PHNET is still unknown, but possible and plausible theories include transformation of liver stem cells;
Figure 9: Metastatic hepatic neuroendocrine tumor in 2016 with morphologic characteristics similar to the previous hepatic tumors and an intermediate mitotic count (hematoxylin-eosin, original magnification ×40).

Figure 10: Synaptophysin immunexpression in the tumor (original magnification ×40).

Figure 11: Cytokeratin 7 immunostain with strong and diffuse expression in the neoplastic cells (original magnification ×40).

Figure 12: Ki-67 expression in the tumor cells. The mitotic labeling index was 5% (original magnification ×40).

Recently, a rare variant of cholangiocarcinoma with thyroid-like morphologic traits has been described in 2 case reports [12, 13]. However, unlike our case, the newly described cholangiocarcinoma in both case reports did not show neuroendocrine expression, and 1 patient died within 18 months postoperatively.

The present hepatic NET is unusual in its immunohistochemical profile, since all tumors (primary and recurrent hepatic tumors as well as metastasis) expressed cytokeratin 7, which is known to be expressed in cholangiocarcinoma. In addition, cholangiocarcinoma can have neuroendocrine differentiating traits, but they are usually 2 components—a conventional cholangiocarcinoma and a separate component with neuroendocrine differentiation are usually present [14]. Neuroendocrine cells are frequently found in the bile ducts and, therefore, could be expected in cholangiocarcinoma. However, the present case expressed neuroendocrine markers (synaptophysin and chromogranin) in the entire tumor, which showed a thyroid follicular-like morphologic characteristic. Furthermore, cholangiocarcinoma has a shorter, 5-year survival rate of 32% following operative intervention [15], and our patient survived for 13 years after operation.

NETs are classified as well differentiated (tumors) and poorly differentiated (carcinomas). They are graded into G1 and G2 tumors and high-grade (G3) carcinomas on the basis of their mitotic count or the Ki-67 labeling index, or both, with the latter being more accurate [16–18] (Table 1).
PHNETs are poorly described, and most likely they are an underdiagnosed entity with the tumor prognosis largely unknown.

**Abbreviations**

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<thead>
<tr>
<th>GI</th>
<th>Low grade</th>
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<tr>
<td>G2</td>
<td>Intermediate grade</td>
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<td>G3</td>
<td>High grade</td>
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<td>HPF</td>
<td>High-power field</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>NET</td>
<td>Neuroendocrine tumor</td>
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<td>PHNET</td>
<td>Primary hepatic neuroendocrine tumor</td>
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<td>TTF1</td>
<td>Thyroid transcription factor</td>
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**Competing Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

**References**


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