Somatostatin-Producing Pancreatic Endocrine Carcinoma Presented as Relapsing Cholangitis – A Case Report

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Key Words
Somatostatinoma · Neuroendocrine tumor · Somatostatinoma syndrome · Pancreatoduodenectomy · Islet cell tumor

Abstract
Somatostatin-producing endocrine tumors are rare neoplasms usually arising in the pancreas and duodenum and they account for less than 1% of all gastrointestinal endocrine tumors. Besides somatostatinoma syndrome, which is characterized by diabetes mellitus, steatorrhea and cholelithiasis, patients with somatostatin-producing endocrine tumors commonly complain of nonspecific symptoms such as vague abdominal pain, weight loss or changes in bowel habits. Tumor behavior cannot be predicted by histological features alone, and malignancy is determined by the presence of metastases. We report here a case of malignant pancreatic endocrine tumor producing somatostatin presented as relapsing cholangitis who was treated with Whipple pancreatoduodenectomy.

Introduction
Somatostatin-producing endocrine tumors are rare neuroendocrine tumors arising from D-cells of the gastrointestinal tract [1–3]. They account for less than 1% of all gastrointestinal endocrine tumors, and since their first description by Larsson et al. [4] in 1977 fewer than 150 cases have been reported in the literature [1–8].

We report here a case of pancreatic nonfunctioning endocrine tumor producing somatostatin presented as relapsing cholangitis who was treated in our department.

Case Report
A 48-year-old man was referred to us from the Gastroenterology Department of our hospital with a possible diagnosis of pancreatic head carcinoma.

Right upper quadrant abdominal pain with jaundice and fever were the first presenting symptoms for which the patient was admitted in a small regional hospital 18 months ago. Diagnostic work up with CT scan and ERCP revealed slight edema of the head of the pancreas and stenosis of the final part of common bile duct. Although there was no evidence of biliary lithiasis, the episode was attributed to acute pancreatitis and treated with endoscopic sphincterotomy.

Two weeks ago the patient was admitted in the Gastroenterology Department of our hospital for jaundice and recurrent cholangitis. An extensive diagnostic work up comprising ultrasonography, CT
fig. 1. Stenosis of common bile duct (arrows) revealed in ERCP (left) and MRCP (right).

Fig. 2. Neuroendocrine tumor of the pancreas with homogenous neoplastic cells (HE, × 200).

Fig. 3. Positive immunohistochemical staining for somatostatin (PAP, × 400). Solid nests of neoplastic cells dispersed in a stroma of fibrous connective tissue.

Fig. 4. Infiltrated regional lymph node. Positive immunohistochemical staining for synaptophysin (PAP, × 200).

Scan, ERCP and MRCP took place. There was no evidence of gallbladder lithiasis in ultrasonography, while ERCP and MRCP (fig. 1) revealed a stenosis of the intrapancreatic common bile duct. Despite equivocal findings on CT scan, the patient was referred to our department with a probable diagnosis of pancreatic head carcinoma.

On admission the patient was icteric with total bilirubin measuring 8.15 mg/dl and direct bilirubin 3.94 mg/dl. SGOT, SGPT, γ-GT, and alkaline phosphatase were 91, 112, 195 and 144 IU/l, respectively. Blood glucose levels, amylase, urea, creatinine, albumin and electrolytes were within normal values as well as the hematological profile of the patient. CEA, AFP and CA19-9 were also normal.

At laparotomy, a tumor in the head of the pancreas as well as enlarged retropancreatic lymph nodes were found. Frozen sections from the tumor and a lymph node were positive for pancreatic malignancy. Consequently, pancreatectomy was considered unnecessary and the patient underwent a palliative choledochoduodenostomy. However, postoperative examination of biopsy specimens revealed the presence of pancreatic neuroendocrine tumor on hematoxylineosin staining (fig. 2) and immunohistochemical positivity of neoplastic cells for synaptophysin and somatostatin (fig. 3), findings indicative of pancreatic somatostatin-producing endocrine tumor. Under these circumstances the treatment plan was re-appreciated and the patient underwent Whipple pancreaticoduodenectomy with extended lymph node dissection.

On histopathology a solid, whitish tumor of 1.7 cm in diameter was found in the head of pancreas in close proximity to the common bile duct, which was stenosed in its final part but with no signs of infiltration by tumor cells. Neoplastic cells with morphological fea-
Table 1. Somatostatin-producing pancreatic endocrine tumors recently reported in the literature

<table>
<thead>
<tr>
<th>No of cases</th>
<th>Location, %</th>
<th>Symptoms, %</th>
<th>Malignancy rate %</th>
<th>Lymph nodes infiltration %</th>
<th>Liver metastases %</th>
<th>Survival, % overall</th>
<th>Authors</th>
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</thead>
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<td></td>
<td>head body tail</td>
<td>diffus/multiple/undetermined</td>
<td>symptomatic</td>
<td>symptomatic</td>
<td>abdominal pain</td>
<td>weight loss</td>
<td>jaundice</td>
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<td>27</td>
<td>51.8 7.4 18.5 22.2</td>
<td>3.7 96.3</td>
<td>11.1 33.3 7.4</td>
<td>40.7</td>
<td>85.1 29.6 70.3</td>
<td>ND  ND</td>
<td>Vinik et al. [24]</td>
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<td>23</td>
<td>56.5 8.7 30.4 4.34</td>
<td>ND ND ND</td>
<td>ND ND</td>
<td>ND</td>
<td>73.9 34.8 65.2</td>
<td>ND  ND</td>
<td>Konomi et al. [34]</td>
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<td>32</td>
<td>ND ND ND ND</td>
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<td>ND</td>
<td>71.9 19.9 65.2</td>
<td>ND  ND</td>
<td>Chuanyan et al. [35]</td>
</tr>
<tr>
<td>81</td>
<td>55.6 27.2 7.4 9.8</td>
<td>6.4 93.6</td>
<td>38.5 32.1 9.0</td>
<td>60.0</td>
<td>70.4 24.7 39.5</td>
<td>75.2 59.9</td>
<td>Soga and Yakuwa [36]</td>
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<td>– – –</td>
<td>House et al. [13]</td>
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<td>Tomono et al. [21]</td>
</tr>
</tbody>
</table>

ND = Not determined.

Discussion

Somatostatin-producing endocrine tumors are rare neoplasms usually arising in the pancreas and duodenum. They are large, solitary, usually malignant tumors arising within the head of the pancreas (table 1) [8–13] and when associated with somatostatinoma syndrome, which is characterized by diabetes mellitus, steatorrhea and cholelithiasis, they are classified as somatostatinomas [5, 9, 12, 14].

This classic syndrome of hyperglycemia, cholelithiasis, steatorrhea and hypochlorhydria is attributed to inhibitory effects of somatostatin on the release of many gastrointestinal hormones and peptides (such as insulin, glucagon, growth hormone, secretin, gastrin, cholecystokinin, glucose-dependent insulin-releasing peptide) and to suppression of bicarbonate and other exocrine pancreatic secretions by elevated levels of somatostatin [1, 5, 15, 16].

However, somatostatinoma syndrome is not uniformly present in all patients with somatostatin-producing endocrine tumor who more commonly complain of nonspecific symptoms such as vague abdominal pain, weight loss, or a change in bowel habits [7]. In the case reported, tumor presented as relapsing cholangitis in the absence of biliary lithiasis. This unusual presentation can be attributed to stenosis of common bile duct by pressure exerted by the neoplasm. Absence of classic somatostatinoma syndrome can be explained by early obstructive symptoms due to tumor location in close proximity to common bile duct or by release of inactive peptide, or lower secretory activity due to relative small size of the tumor [1, 17, 18]. Despite WHO recommendations for an International Classification of Endocrine Tumors, many authors continue to name all pancreatic or extrapancreatic endocrine tumors producing somatostatin as somatostatinomas even in the absence of the classic inhibitory syndrome [7, 9, 13, 19–21]. In our case, using strict clinicopathological criteria and according to WHO classification, the tumor described should be classified as nonfunctioning pancreatic endocrine tumor producing somatostatin [22]. According to older classification systems though, lack of immunostaining for all hormones other than somatostatin, classifies the tumor undoubtedly as pancreatic somatostatinoma [13, 17–19, 21, 23]. Somatostatin-producing endocrine tumors are most often diagnosed during endoscopy, laparotomy or abdominal imaging studies [1, 16]. When pancreatic somatostatinoma is suspected, elevated plasma somatostatin levels can be diagnostic [24]. Cautious interpretation of mild elevations is however necessary [16]. Preoperative diagnosis is extremely difficult and the majority of somatostatin-releasing tumors are diagnosed histopathologically after surgical resection of a pancreatic mass, as it was in the case we presented herein.

On histopathological examination, somatostatin-producing endocrine tumors and somatostatinomas appear as well-differentiated islet cell tumors with positive somatostatin staining [7]. The presence of psammoma bodies is...
characteristic of duodenal and other extra-pancreatic somatostatin-producing endocrine tumors [7, 8, 25, 23]. It must be emphasized that though histological features are not specific for malignancy and somatostatinomas’ or somatostatin-producing endocrine tumors’ behavior cannot be predicted unless metastases are revealed [21, 26].

For staging of the disease, CT scan and MRI are considered highly effective especially in detecting pancreatic tumors and possible hepatic metastases [27] while recurrent disease, secondary localizations and occult disseminated metastases are best detected with somatostatin receptor scintigraphy [28].

Scintigraphic whole body screening can detect metastatic spread, thus obviating unnecessary surgery. On the other hand, nonvisualization of metastases on somatostatin receptor scintigraphy suggests feasibility of curative surgical resection [28–30].

Optimal treatment of pancreatic endocrine tumors that produce somatostatin cannot be determined with certainty because of their rarity and the lack of long-term follow-up information. Local resection of tumors less than 2 cm is considered adequate while for larger tumors a Whipple procedure is recommended [7]. The indolent course of many neuroendocrine pancreatic tumors – compared to adenocarcinomas – has allowed extensive resections and even debulking of primary and metastatic disease in unresectable tumors [1].

Adjuvant chemotherapy with streptozocin, 5-fluorouracil and doxorubicin produced partial responses [12, 24, 31]. Reports about octreotide administration have recently appeared with effective amelioration of somatostatinoma syndrome symptoms in inoperable patients [32]. Scintigraphy has demonstrated that certain tumors have the ability to bind labeled octreotide, suggesting that similar agents, designed to deliver a high radiation dose, may be beneficial for receptor-positive metastases [28, 33].

Survival data are limited, but patients with localized disease and successful resection are candidates for long-term survival. Combination of surgical resection and adjuvant chemotherapy in patients with metastatic disease produced survival time of 6 months to 5 years in 60% of patients [16]. Survival time up to 12 years has also been reported [31].

Conclusively, even though the number of cases reported is too small, based on reported survival data an aggressive treatment of pancreatic endocrine tumors is favored.

References

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