A Synchronous Pancreatic Neuroendocrine Tumor and Duodenal Gastrointestinal Stromal Tumor

Keijiro Ueda¹, Masayuki Hijioka¹, Lingaku Lee¹, Hisato Igarashi¹, Yusuke Niina¹, Takashi Osoegawa¹, Kazuhiro Nakamura¹, Shunsuke Takahashi², Shinichi Aishima³, Takao Ohtsuka¹, Ryoichi Takayanagi¹ and Tetsuhide Ito¹

Abstract

We recently encountered the case of a patient with a synchronous duodenal gastrointestinal stromal tumor (GIST) and pancreatic neuroendocrine tumor (PNET). This is the first report of this specific combination of multiple primary tumors, although three cases involving both PNET and gastric GIST have previously been reported. Since the duodenal GIST developed close to the pancreatic uncus in this case, we considered the possibility of multiple PNETs in the differential diagnosis. However, a histopathological examination using endoscopic ultrasonography-guided fine-needle aspiration confirmed the diagnosis of multiple primary lesions, involving PNET and duodenal GIST.

Key words: pancreatic neuroendocrine tumors, gastrointestinal stromal tumors, synchronous onset

(Intern Med 53: 2483-2488, 2014)  
(DOI: 10.2169/internalmedicine.53.2694)

Introduction

Pancreatic neuroendocrine tumors (PNETs) are rare, with an annual incidence of 0.22-1.27 cases per 100,000 people (1-4). Similar to PNETs, gastrointestinal stromal tumors (GISTs) are also rare, with an annual incidence of 11-19.6 cases per 100,000 individuals (5, 6). We recently encountered the case of a patient with a synchronous PNET and duodenal GIST. Since this is an extremely rare finding, with no reports of synchronous PNET and duodenal GIST published thus far, we herein present the details of our case.

Case Report

The patient was a 72-year-old woman without any chief complaints. Her family and social history was unremarkable. A duodenal submucosal tumor was detected on upper gastrointestinal endoscopy at a routine health checkup, and she was referred to our department. Contrast-enhanced computed tomography (CT) demonstrated that the lesion protruded into the duodenal lumen and was connected to the parenchyma of the pancreatic uncus. In addition, an 8-mm lesion was observed in the pancreatic body. The patient was hospitalized to undergo a more detailed examination and treatment for the lesions in the pancreatic uncus and body.

The results of the initial physical examination performed on admission to the hospital were as follows: height, 148 cm; weight, 37 kg; body temperature, 36.6°C; blood pressure, 133/84 mmHg; pulse rate, 74 bpm, regular; no nausea/vomiting; no anemia in the bulbar conjunctiva; no yellow pigmentation in the bulbar conjunctiva; a flat and soft abdomen without pain or tenderness and no palpable masses; and no skin rashes or subcutaneous nodules. The neurological findings were unremarkable.

A blood test performed on admission revealed no abnormal findings in the peripheral blood. Although no hepatobiliary enzyme abnormalities were observed, a slight elevation in the levels of pancreatic enzymes (serum pancreatic amylase, 65 IU/L) was noted. In addition, the serum calcium...
level was slightly elevated (10.7 mg/dL) (serum albumin, 5.0 g/dL), although the intact parathyroid hormone (intact PTH) level was within the normal range (46.1 pg/mL). No abnormalities were observed in the levels of pituitary hormones. Both the fasting and random blood glucose levels were normal, with an HbA1c (NGSP) value of 5.3%; thus, the patient was determined to not have diabetes mellitus. Furthermore, the insulin and gastrin levels were within the normal ranges, as were the levels of the tumor markers carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), neuron-specific enolase (NSE) and pro-gastrin-releasing peptide (proGRP).

A gently elevated lesion located in the horizontal portion of the duodenum with normal overlaying mucosa was detected on upper gastrointestinal endoscopy (Fig. 1); the mass was considered to be a submucosal tumor (SMT).

A 26×17-mm lesion with a regular margin and clear boundary was observed in the pancreatic uncus on contrast-enhanced CT. The lesion was enhanced starting in the arterial phase, exhibiting the greatest enhancement in the portal-venous phase. Additionally, the mass was connected to the pancreatic parenchyma and protruded into the duodenal lumen. We considered that the lesion in the pancreatic uncus was the same as the duodenal SMT detected on upper gastrointestinal endoscopy. In addition, an 8-mm lesion was detected in the pancreatic body parenchyma; this lesion demonstrated the greatest enhancement in the arterial phase, although it was difficult to detect in the portal-venous or delayed phase. No dilation of the distal main pancreatic duct was observed (Fig. 2). Based on the CT findings, a diagnosis of gastrointestinal mesenchymal tumor (GIMT) or PNET was considered for the duodenal SMT, while PNET, pancreatic metastasis or solid-type serous cyst adenoma was considered for the lesion in the pancreatic body.

The duodenal SMT presented as a hypoechoic mass overlaid with duodenal mucosa on endoscopic ultrasonography (EUS). This lesion exhibited an intra- and extraluminal growth pattern from the duodenal wall with a dumbbell-shaped morphology. Additionally, it was connected to both the 4th EUS layer of the duodenal wall and the pancreatic uncus. An internal blood flow was observed on Doppler ultrasonography. In addition, the lesion in the pancreatic body was visualized as a well-delineated, oval-shaped, homogenous, mildly hypoechoic mass, with an internal blood flow on Doppler ultrasonography (Fig. 3).

Based on the findings of the imaging studies, the lesion in the pancreatic body was considered to be a PNET. Although the duodenal SMT was suspected to be a type of GIMT, such as GIST, a diagnosis of PNET was not completely ruled out because the lesion was connected to the pancreatic parenchyma. Therefore, in order to make a definitive diagnosis, we performed endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) of each lesion.

Fascicular and implicate spindle cells were observed on EUS-FNA of the duodenal SMT using hematoxylin and eosin staining, and positive staining for c-kit and CD34 was observed on immunostaining. Therefore, the lesion was diagnosed as a GIST (Fig. 4). In contrast, the lesion in the pancreatic body, contained atypical cells with acidophilic cytoplasm and oval-shaped nuclei and was positive for chromogranin A and synaptophysin. Therefore, that lesion was diagnosed as a PNET. The Ki-67 index was less than 1%, and the tumor was diagnosed as NET G1 (Fig. 5).

Since the patient was diagnosed with both a duodenal GIST and PNET, laparoscopic enucleation of the pancreatic tumor and partial resection of the duodenum were performed. The postoperative histopathological examination of the resected specimen revealed the duodenal SMT to be a GIST (Miettinnen risk grade: low; Ki-67 index, 1%) and the lesion in the pancreatic body to be a NET G1, consistent with the preoperative diagnoses. No postoperative recurrence has been observed to date.

Discussion

PNETs are tumors that originate from endocrine cells or neurons in the pancreas, accounting for 1-2% of all pancreatic tumors (7). Although rare, due to increased recognition and improvements in diagnostic technology in recent years, the number of patients diagnosed with small PNETs and/or tumors found incidentally, as in the present case, is increasing (8). Many PNETs develop sporadically; however, some have been reported to be associated with hereditary diseases [e.g., multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau disease (VHL), neurofibromatosis 1 (NF-1) [also known as von Recklinghausen disease] and tuberous sclerosis complex (TSC)] (9-12).

GISTs are thought to be caused by a mutation in the c-kit gene and alpha-type platelet-derived growth factor receptor (PDGFRA) gene in the interstitial cells of Cajal or their precursors. Regarding the sites in which these lesions are commonly found, GISTs develop most frequently in the stomach (60%), followed by the jejunum and ileum (30%), duodenum (5%) and colon and rectum (4%); thus, the frequency...
of such tumors in the duodenum is low (13). Although considered rare, a German study reported the incidence of GISTs ranging from 1 to 10 mm in size to be 22.5% of autopsied cases among patients ≥50 years of age. Hence, it is believed that many GISTs remain clinically undetected (14). Although GISTs often occur sporadically, they frequently develop as a result of hereditary diseases, such as NF-1, Carney’s triad (GIST, paraganglioma and pulmonary chondroma), Carney’s dyad (paraganglioma and gastric GIST) and familial GIST (13).

In the present case, PNET and GIST occurred synchronously. This is an extremely rare condition, with only four cases, including the present case, having been reported to date (15-17) (Table). Although PNETs and GISTs arise at a frequency of 0-10% and 11-25%, respectively, in patients with NF-1 (18, 19), no such cases have been reported in the
Figure 4. Histopathological findings. The duodenal SMT (EUS-FNA) contained fascicular spindle cells (Hematoxylin and Eosin staining). The tumor cells were positive for c-kit and CD34.

Figure 5. Histopathological findings. The lesion in the pancreatic body (EUS-FNA) contained atypical cells with acidophilic cytoplasm and oval-shaped nuclei. The tumor cells were positive for chromogranin A and synaptophysin. The Ki-67 index was less than 1%.
literature. In the present case, there was also no family history or clinical findings suggestive of NF-1. Although we did not perform a genetic investigation, we considered it unlikely that the patient was complicated with NF-1. All of the three remaining cases, excluding the present case, involved a gastric GIST, with no reports of a synchronous PNET and duodenal GIST. Consequently, we believe that this is the first report of this condition in the literature.

Surgical resection was performed in all four cases. In one case, a PNET was found during surgery for a GIST, and, in another, a GIST was found during surgery for a PNET. In the remaining two cases, including the present case, the PNETs and GISTs were found preoperatively on imaging studies. However, a definitive pathologic diagnosis of both tumors was made in our case only. Regarding the PNETs observed in these cases, one was diagnosed as an insulinoma, whereas the others were non-functional. All of these cases were classified as involving either G1 or G2 disease, according to the WHO classification of neuroendocrine tumors (2010), and all lesions displayed a low malignant potential. In contrast, Sven et al. reported a case of liver metastasis of a NET G2 lesion (Ki67-index, 12.7%) (16). With respect to the GISTs noted in the above cases, the lesions were of no- to low-risk based on the Miettinen grade, and the malignant potential was also low. No metastasis or recurrence of GISTs was observed in any of the above described cases.

The GIST diagnosed in the present case was observed to be a typical submucosal tumor on upper gastrointestinal endoscopy. However, because it was shown to be connected to the pancreatic uncus on contrast-enhanced CT and EUS, it was necessary to differentiate the lesion from that of other pancreatic diseases, in particular PNET. Since GISTs often grow outward from the gastrointestinal tract, close to the pancreas, they are sometimes diagnosed as primary pancreatic tumors (20). PNETs and GISTs often display similar characteristics on imaging studies. When small in size, these lesions present as oval-shaped solid tumors with a clear boundary and homogeneous content on ultrasonography, with enhancement effects observed in the arterial phase on contrast-enhanced CT. For this reason, establishing the differential diagnosis based on imaging findings alone is often difficult. To this point, Ohtake et al. reported a case of a duodenal GIST diagnosed as PNET of the pancreatic head using preoperative imaging findings (21). Findings specific to GISTs include a connection between the gastrointestinal muscularis propria (the 4th EUS layer) and the tumor on EUS. In the present case, a connection between the duodenal SMT and the 4th EUS layer of the duodenal wall was observed on EUS; therefore, a GIST was strongly suspected. When lesions suspected to be PNETs in the pancreatic margins are found on ultrasonography or CT, it is important to determine whether there is a connection between the gastrointestinal wall and the tumor using EUS, taking into consideration the possibility of a GIST.

In the present case, mild hypercalcemia with the possibility of multiple PNETs was observed, and we assessed the presence of MEN1 carefully. The surgical approaches for neuroendocrine tumors associated with and without MEN1 are very different (22-24). Therefore, we considered it necessary to make a precise preoperative diagnosis and therefore performed EUS-FNA. As a result, the duodenal SMT was diagnosed as a GIST, and laparoscopic enucleation of the PNET and partial resection of the duodenum were scheduled. Hence, minimally invasive surgery was selected in this case as a result of the preoperative histopathologic diagnosis.

We encountered a case of synchronous PNET and GIST. Since these lesions frequently display similar findings on imaging studies, thus making the differential diagnosis between them is often difficult, a very careful preoperative evaluation, including pathologic confirmation, is necessary.

The authors state that they have no Conflict of Interest (COI).

References