**CASE DESCRIPTION**

A 51-year-old man with a family history of pancreatic neuroendocrine tumor (PNET) had been treated for reflux esophagitis. In 20XX, the patient underwent surgery for duodenal NET, and 7 years later, he underwent another surgery for thymic carcinoid tumor. The patient had been regularly followed-up after the completion of adjuvant chemotherapy. However, 9 years later, contrast-enhanced computed tomography (CT) showed an 8 mm tumor in the pancreatic tail. The following year, the patient was referred to our hospital. He was not suffering from either vomiting or diarrhea. Moreover, physical examination showed neither thymomgaly nor abdominal symptoms. After discontinuation of proton pump inhibitor administration, an increased serum gastrin level of 346 pg/mL was observed. Furthermore, in response to intravenous administration of calcium gluconate, a significant reactive increase (1.5-fold) in the gastrin level was observed. In addition, an increased intact-parathyroid hormone (PTH) level of 105.7 pg/mL and an increased serum calcium level of 11.2 mg/dL were observed. With regard to tumor markers, the neuron specific enolase (NSE) level was 13.8 ng/mL, and the pro-gastrin releasing peptide (pro-GRP) level was 40.6 pg/mL. Contrast-enhanced CT showed 10 mm and 13 mm round tumors, which exhibited early enhancement. Besides the pancreatic tail lesions observed on the CT images, endoscopic ultrasonography (EUS) showed at least 9 hypoechoic tumors of approximately 5 - 10 mm, including 1 lesion in the pancreatic head, 4 lesions in the pancreatic body, and 2 lesions in the pancreatic tail. The upper gastrointestinal endoscopy showed multiple erosions, ulcer scars, and submucosal tumors of approximately 10 mm in the duodenum. Methoxyisobutylisonitrile (MIBI) scintigraphy showed abnormal accumulation in the parathyroid gland. Pituitary magnetic resonance imaging (MRI) showed a pituitary adenoma, which was found to be non-functional based on various challenge tests. Thus, the patient was diagnosed with gastrinoma, hyperparathyroidism, and non-functional pituitary adenoma, which were associated with multiple endocrine neoplasia type 1 (MEN1).

We decided to treat hyperparathyroidism first and performed subtotal parathyroidectomy. As a result, the intact-PTH and serum calcium levels returned to normal values. Next, we considered the therapeutic strategy for gastrinoma. When a selective arterial secretagogue injection (SASI) test was performed, significant increase in gastrin level was observed after the secretagogue injection from the gastroduodenal artery and the superior mesenteric artery. Thus, we found that the gastrinoma was located in the pancreatic head. We diagnosed the tumors in the pancreatic tail as non-functional NETs. Because these tumors were small (5-13 mm), we decided to conduct follow-ups on these tumors. Pancreatoduodenectomy was performed, and multiple small NETs (Ki-67 index <2%) of a maximum of 5 mm in diameter were observed in the duodenum; they tested positive for gastrin immunostaining. Thus, the postoperative pathological diagnosis was gastrinoma. Moreover, multiple small NETs (Ki-67 index <2%) with a maximum diameter of 4 mm were observed in the pancreatic head. All of these lesions were non-functional NETs. Five years after the surgery, no tumor growth has been observed in the pancreatic tail, and no relapse of excess hormone secretion has occurred.

**DISCUSSION**

MEN1 is concurrently found in 4-10% of all patients with PNET and in 20-30% of patients with gastrinoma. Because the therapeutic strategy of PNET greatly varies depending on the presence of concurrent MEN1, evaluation of MEN1 is essential. In patients with MEN1, the incidence of hyperparathyroidism is very high (95%), and, therefore, screening using intact-PTH and serum calcium levels should be conducted. If multiple MEN1-associated tumors are observed, the tumors need to be triaged. In general, the priority should be given to hyperparathyroidism for the systemic control using normalization of hypercalcemia. However, if symptoms of functional PNET are uncontrollable, or if pituitary tumor-associated visual field defects or pituitary dysfunction are present, the tumors need to be treated first. In addition, because thymic carcinoid tumors have high malignant potential, treatment of these lesions should be prioritized. In the present study, the gastrinoma-associated symptoms were well-controlled; therefore, the priority was given to the surgery for hyperparathyroidism.

Approximately 85-95% of MEN1-associated gastrinomas are primary duodenal gastrinomas. Moreover, MEN1-associated gastrinomas are typically observed as multiple small tumors of ≤5 mm. In this study, although only 2 duodenal lesions were detected before surgery, the postoperative
pathological diagnosis included multiple duodenal gastrinomas of ≤5 mm. As seen in this patient, MEN1-associated gastrinomas are difficult to locate; thus, in addition to CT, MRI, and EUS, functional imaging such as an SASI test, somatostatin-receptor scintigraphy with 111In-DPTA-octreotide, and 68Ga-DOTATOC-PET/CT should be performed to locate the tumors.4

Indications for surgery differ between MEN1-associated PNET and sporadic PNET.3 In MEN1-associated gastrinomas, excision at an early stage has been reported to reduce the incidence of liver metastasis; thus, surgery is recommended regardless of the tumor size.7,8 As seen in this patient, if multiple tumors are present, the tumor(s) that secretes gastrin needs to be determined using an SASI test to decide the operative procedure.7 In MEN1-associated non-functional PNET, the tumor size is used as the indication for surgery; surgical excision is recommended if a tumor is ≤2 cm.3 With regard to non-functional NETs of ≤2 cm, the criteria are controversial; however, in Japan, clinical follow-up is recommended if a tumor is ≤1 cm, and surgical excision is recommended if a tumor is 1 - 2 cm with signs of growth. In this patient, follow-up was selected for non-functional NETs in the pancreatic tail; this was considered an appropriate decision because neither tumor growth nor liver metastasis had occurred.

In patients with MEN1, PNET is the most frequent cause of MEN1-associated death.5,9 It is important to choose an appropriate therapy based on a comprehensive evaluation, including hormonal symptoms, as well as the number and size of tumors, their locations, heterochrony, and synchrony.4

**FIGURES**

A. B. Contrast-enhanced CT showed tumors in the pancreatic tail, which exhibited early enhancement. C- E. Besides the lesions identified by CT, EUS detected a total of 9 additional lesions in the pancreas. F-H. Submucosal tumor and multiple erosions were observed in the duodenum by upper gastrointestinal endoscopy. I. MIBI showed accumulation in the parathyroid gland.
Calcium gluconate was injected from each of the pancreatic nutrient arteries. A ≥1.2-fold increase in the gastrin level was observed in gastroduodenal artery (GDA) and superior mesenteric artery (SMA). Thus, we diagnosed gastrinoma in the pancreatic head.

REFERENCES


