A Case of Zollinger-Ellison Syndrome in Multiple Endocrine Neoplasia Type 1 with Urolithiasis as the Initial Presentation

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Zollinger-Ellison syndrome (ZES) is characterized by gastrinoma and resultant hypergastrinemia, which leads to recurrent peptic ulcers. Because gastrinoma is the most common pancreatic endocrine tumor seen in multiple endocrine neoplasia type 1 (MEN 1), the possibility of gastrinoma should be investigated carefully when patients exhibit symptoms associated with hormonal changes. Ureteral stones associated with hyperparathyroidism in the early course of MEN 1 are known to be its most common clinical manifestation; appropriate evaluation and close follow-up of patients with hypercalcemic urolithiasis can lead to an early diagnosis of gastrinoma. We report a patient with ZES associated with MEN 1, and urolithiasis as the presenting entity. A 51-year-old man visited the emergency department with recurrent epigastric pain. He had a history of calcium urinary stone 3 years ago, and 2 years later he had 2 operations for multiple jejunal ulcer perforations; these surgeries were 9 months apart. He was taking intermittent courses of antiulcer medication. Multiple peripancreatic nodular masses, a hepatic metastasis, parathyroid hyperplasia, and a pituitary microadenoma were confirmed by multimodal imaging studies. We diagnosed ZES with MEN 1 and performed sequential surgical excision of the gastrinomas and the parathyroid adenoma. The patient received octreotide injection therapy and close follow-up. (Korean J Gastroenterol 2013;61:333-337)

Key Words: Zollinger-Ellison syndrome; Multiple endocrine neoplasia type 1; Gastrinoma; Urolithiasis

INTRODUCTION

Zollinger-Ellison syndrome (ZES) is characterized by 1 or more gastrinomas, mainly located in the pancreas or duodenum. The resultant hypergastrinemia leads to recurrent peptic ulcers. ZES is rare, occurring in one person per 100,000.1 Gastrinoma, however, is the most common pancreatic endocrine tumor in patients with multiple endocrine neoplasm type I (MEN 1), which involves the pituitary, parathyroid, and adrenal glands.2,3 The possibility of a gastrinoma should therefore be investigated carefully when patients exhibit symptoms of the hormonal changes associated with MEN 1.

Ureteral stones are the most common clinical manifestation of the hyperparathyroidism associated with MEN 1 in its early stages.3 If a family history of urinary stones is confirmed at the time of the patient’s diagnosis, a review of hereditary diseases such as MEN should be performed.
Appropriate evaluation and close follow-up of patients with hypercalcemic urolithiasis can yield an early diagnosis of gastrinoma. Localized gastrinomas have a good prognosis when detected early. Otherwise they can metastasize rapidly to the regional lymph nodes and the liver. Patients with ZES often experience delayed diagnosis and unnecessary surgery. Those with advanced ZES at the time of initial treatment have a poor prognosis. The delayed diagnosis of gastrinoma should be avoided through proper investigation in patients with recurrent peptic ulcers or MEN 1-associated symptoms. We report a patient with ZES who had MEN 1-related urolithiasis as the initial manifestation.

CASE REPORT

A 51-year-old male presented to the emergency department of Presbyterian Medical Center complaining of recurrent epigastric pain. Three years prior, he had undergone 4 sessions of extracorporeal shockwave lithotripsy and surgical ureterocystostomy for removal of bilateral urinary stones (Fig. 1). He was subsequently treated with potassium citrate for recurrent calcium stones. Although his calcium level was 11.2 mg/dL, his urologist did not carry out any further evaluation.

For the next 18 months, he visited the emergency department repeatedly with recurrent abdominal pain. He underwent 2 surgeries, at an interval of 9 months, for multiple jejunal ulcer perforations. Despite this surgical treatment, he suffered from recurrent episodes of epigastric pain; he took antiulcer medication intermittently. Gastroscopy revealed a recurrent jejunal ulcer at the anastomosis site from a prior surgery.

At the time of his emergency department presentation, his vital signs were stable. On physical examination, he had mild direct tenderness in the epigastric and left upper quadrant abdominal areas, but no abdominal distension or unusual bowel sounds were noted. Peripheral blood testing revealed white blood cell count of 6,000/mm³, hemoglobin level of 14.8 mg/dL, hematocrit of 42.9%, and platelet count of 136,000/mm³. Biochemical testing demonstrated AST level of 19 IU/L, ALT level of 22 IU/L, ALP level of 449 IU/L, BUN level of 9 mg/dL, and creatinine level of 1.0 mg/dL. He had hypercalcemia, with calcium level of 11.5 mg/dL, and his phosphorus level of 2.5 mg/dL was at the lower limit of normal.

Given his history, ZES was suspected and hormonal testing carried out after discontinuing proton pump inhibitor (PPI) for 1 week. He exhibited hypergastrinemia with gastrin level of 711.7 pg/dL. Possible MEN 1-associated hormonal changes were then evaluated, revealing hyperparathyroidism with parathyroid hormone level of 66.5 pg/mL. Thyroid function indicators were in the normal range, and pituitary testing was normal, with a prolactin level of 5.67 ng/mL, growth hormone level of 0.51 ng/mL, and adrenocorticotropic hormone level of 33.2 pg/mL.

Multiple imaging studies were performed to evaluate ZES with MEN 1. Abdominal CT revealed multiple peripancreatic nodular masses, and MRI showed a dense, contrast-enhancing nodule in the superior segment of the left lobe of the liver (Fig. 2A, B). Compared to an abdominal CT performed 1 year prior, the peripancreatic nodules had increased slightly in size but the size of the hepatic lesion was unchanged. EUS

![Fig. 1. Clinical manifestation findings. (A) X-ray examination of the kidneys, ureter, and bladder showed calcified stones (arrows) in both ureters. (B, C) Abdominal nonenhanced CT showed calcified stones (arrows) in both ureters.](image-url)
revealed multiple well-defined hypoechoic lesions around the head of the pancreas (Fig. 2C). Focal hyperactivity in the pancreatic head and body, and mild focal hyperactivity in the left hepatic lobe, were observed on octreotide scan (Fig. 2D). On PET-CT scanning, a multifocal, hypermetabolic lesion was noted near the pancreatic head and the superior mesenteric artery (Fig. 2E).

Parathyroid and pituitary gland evaluations were conducted to investigate the patient’s MEN 1 syndrome. Thyroid ultrasonography revealed suspected parathyroid adenomas (Fig. 3A). A parathyroid technetium 99m sestamibi scan showed persistent tracer in the right lobe of the thyroid, suggestive of a parathyroid adenoma or carcinoma (Fig. 3B). Brain MRI demonstrated a pituitary microadenoma with low attenu-
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Fig. 4. Pathologic finding. The gastrinoma cells were positive by immunohistochemical stain of gastrin (×400).

The patient underwent laparoscopic duodenectomy, resection of the uncinate process of the pancreas, and peripancreatic lymph node dissection to remove the gastrinomas. Two months later, a right parathyroidectomy with hemithyroidectomy was performed for the parathyroid adenoma. Pathologic examination of the peripancreatic mass confirmed the diagnosis of gastrinoma; the tissue was positive for gastrin on immunohistochemical staining, but negative for glucagon, somatostatin, and insulin (Fig. 4). The second specimen was confirmed to be a parathyroid chief-cell hyperplasia.

The patient was given postoperative octreotide injection therapy and his epigastric pain improved. Follow-up laboratory testing showed that his gastrin level decreased to 63.3 pg/mL, his calcium level decreased to 10.0 mg/dL, and his phosphorus level improved to 3.2 mg/dL.

DISCUSSION

Pancreatic neuroendocrine tumors (pNETs), present in MEN 1, manifest in the pituitary gland, parathyroid glands, pancreas, and adrenal glands. Gastrinoma is the most common pancreatic tumor observed in MEN 1, and may manifest as ZES with excessive gastric acid secretion. ZES often presents with abdominal pain, recurrent peptic ulcers, diarrhea, and gastroesophageal reflux disease. Because gastrinoma is associated with more than half of MEN 1 cases, it is necessary to evaluate for this tumor when MEN 1 is suspected.

Symptoms of MEN 1 depend on the secreted hormones, and may therefore vary; familial kidney stones are most commonly associated. About 35% of MEN 1 patients exhibit uric acid as their first presenting manifestation. Because most patients with urinary stones do not undergo long-term follow up with urology after receiving their diagnosis and treatment, the diagnosis of a very rare disease, such as ZES, associated with MEN 1 can be delayed. Recurrent peptic ulcers or ureteral stones can be overlooked if there is not a high index of suspicion for endocrine syndromes such as ZES or MEN 1. In the present case, our patient had been treated for calcium urinary stones before he was diagnosed with ZES and MEN 1.

A conventional PPI dose, given for idiopathic peptic ulcer disease, can control gastric acid secretion and the symptoms of hypersecretion. Unfortunately, the widespread use of PPIs and histamine 2 blockers masks symptoms of ZES so that the diagnosis is delayed and further complications arise. Chronic PPI treatment may also cause disease progression in ZES. Our patient was taking antacids and PPIs, but his symptoms persisted even after surgery.

EUS is the most useful procedure for the diagnosis of pNETs because of its high sensitivity and specificity. This technique can detect tumors as small as 5 mm, and can clarify the relationship between pancreatic tumors and the main pancreatic duct. Octreotide scanning is an efficient imaging modality which successfully localizes pNETs and has a high sensitivity for liver metastases. In this patient, EUS and octreotide scanning were able to localize the ZES gastrinomas, and MRI was helpful in detecting the hepatic metastasis. Brain MRI was performed to detect the pituitary adenoma, and thyroid sonography showed the parathyroid gland adenoma.

The treatment of gastrinomas in MEN 1 is controversial. The 2 main therapeutic objectives are to control the gastric acid hypersecretion which causes the most debilitating symptoms, and to control tumor growth. Early surgical intervention is recommended to avoid malignant progression of gastrinomas and their metastases. Somatostatin analogs have an inhibiting effect on tumor growth in malignant pNETs.

In this case, a patient who had been receiving treatment for recurrent urinary stones suffered from many episodes of peptic ulcers and took anti-ulcer medication. An elevated
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gastrin level was detected and gastrinoma conformed to ZES was detected by imaging studies; his gastrinomas were surgically removed. His elevated parathyroid hormone, along with the results of radiologic studies, led to the diagnosis of MEN 1. Octreotide was used for his hepatic metastatic tumor, completing his successful treatment.

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