Association of Zollinger-Ellison Syndrome with Pancreatitis
Report of Five Cases

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In a retrospective analysis, five cases of Zollinger-Ellison syndrome were found in a typical urban inner-city teaching hospital. Chronic alcohol abuse and heavy smoking characterized these patients, and four of them also had pancreatitis, suggesting an association of gastrin-producing tumors and pancreatic inflammation. Ductal obstruction by neuroendocrine tumors has been reported to cause pancreatitis in a few cases. In this analysis, however, a nonobstructive gastrinoma was the surgical diagnosis in three patients, and it was suggested by imaging studies in the two other cases. The potential other pathomechanisms for a dual cause–effect relationship of gastrinoma and pancreatitis are discussed.

KEY WORDS: pancreatitis; Zollinger-Ellison syndrome; gastrinoma.

Although rare, gastrinoma is the second most common, functional neuroendocrine tumor of the pancreatic islet cell tissue. In 1955, Zollinger and Ellison described the association of gastrin-producing tumors with severe peptic ulcer disease. We have observed that most of our patients with Zollinger-Ellison syndrome at an urban community teaching hospital have had pancreatitis. Here we report these cases and review the possible explanations for this association.

MATERIALS AND METHODS

This retrospective study was initiated by our most recent observation of a patient with Zollinger-Ellison syndrome associated with severe chronic alcoholic pancreatitis found to have a nonobstructing duodenal wall gastrinoma. We reviewed the gastrinoma cases that occurred in our institution during the last 15 years to analyze the relationship between chronic pancreatitis and gastrin-producing islet cell tumors.

The admission records, the operative and pathology reports, and the medical, surgical outpatient notes at Saint Luke’s Medical Center, Cleveland, Ohio, an urban community teaching hospital, were reviewed between January 1, 1983, and December 31, 1997. During this period, five cases were found that were consistent with gastrinoma. In the following, these cases are discussed in brief and then summarized in Table 1.

Case 1. Our index case is a 38-year-old woman who presented to our hospital with a two-day history of nausea and coffee-ground vomiting precipitated by alcohol intake. Her history included alcohol and cocaine abuse for 20 years, 15 pack-years of smoking, and several episodes of chronic pancreatitis characterized by maldigestion requiring pancreatic enzyme substitution and recurrent upper abdominal pain with amylase and lipase elevation. She underwent a Billroth II partial gastrectomy three years earlier for recurrent peptic ulcer disease. At the time of her present admission, upper endoscopy revealed multiple ulcers in the esophagus and at the gastrojejunostomy site. An elevated fasting gastrin level (1740 pg/ml) was consistent with Zollinger-Ellison syndrome. Since abdominal CT scan showed no tumor, an octreotide scan was obtained and suggested a lesion in the region of pancreatic head. She underwent surgery and a 2-cm submucosal mass was found in the wall of afferent loop along with a 2-cm peri-duodenal node. Pathology disclosed a neuroendocrine tu-
mor with a metastatic lymph node. Stains were positive for neuron-specific enolase and gastrin. Postsurgical gastrin levels normalized (96 pg/ml). Eight months after surgery, she remains well.

**Case 2.** A 49-year-old woman was admitted to our hospital with severe epigastric pain and coffee-ground emesis. She was a chronic alcohol and cocaine abuser with a chronic calcifying pancreatitis known for several years. Two years prior to this episode, she had a Billroth II partial gastrectomy because of a perforated duodenal ulcer. At that time, the secretin test was positive, but no tumor was found on abdominal CT scan and ERCP showed no evidence of a mass lesion within, or compression of, the pancreatic ductal system. She was kept on high-dose omeprazole (60 mg daily). Upper endoscopy revealed severe ulcerative esophagitis and numerous ulcers in the gastric stump. Fasting serum gastrin level was 514 pg/ml. Further evaluation and surgery were offered but patient refused surgery. Two years after this episode, she is relatively well on omeprazole.

**Case 3.** A 57-year-old man was admitted to our hospital with acute onset of hematemesis and rectal bleeding. He had a four-year history of recurrent peptic ulcer and no abdominal surgery except for a gunshot wound in the left iliac wing. He quit drinking alcohol at the first onset of peptic ulcer disease. He had no history of pancreatitis. Upper endoscopy revealed multiple ulcers involving the entire upper gastrointestinal tract. The secretin test was consistent with gastrinoma (gastrin level jumped from 343 to 2972 pg/ml in 20 min). Amylase and lipase levels were moderately elevated. Abdominal CT scan showed irregularity and decreased attenuation in the pancreatic head but no clear mass and no ductal dilatation, consistent with mild pancreatitis. The patient went for surgery and a duodenal wall mass was found in the second portion. Pathology described an invasive islet cell tumor and a single lymph node metastasis. The tumor was mildly argentaffin positive, and stains were strongly positive for gastrin. Eight months after surgery, the patient is free of recurrent peptic ulcer.

**Case 4.** A 72-year-old woman was admitted to our hospital with symptoms consistent with a moderate exacerbation of chronic pancreatitis, which had been known for several decades. She also was a heavy smoker with 75 pack-years of exposure. She quit drinking at the age of 45 and had a total gastrectomy at the age of 53 at another hospital for the Zollinger-Ellison syndrome. On subsequent follow-up at our hospital, significant hypergastrinemia was revealed on several occasions (1134–3430 pg/ml). During this time, the patient had no clinical evidence of peptic ulcer disease. Abdominal CT scan was repeatedly obtained to study the pancreas. Twelve years after surgery, CT described a 1-cm cyst in the pancreatic head and an 8-mm cystic lesion in the tail along with ductal prominence. No calcification was found. Another seven years later, the mass in the pancreatic tail was found to be 2–3 cm large but was not identified on a subsequent CT a few months later. The fluctuating CT appearance of her pancreas was felt to correlate with the clinical changes of chronic pancreatitis. The patient improved on conservative measures and no surgery was planned. Four months after this episode, she is doing well.

**Case 5.** A 60-year-old man was admitted to our hospital with recurrent peptic ulcer disease causing upper gastrointestinal bleeding. He had had partial gastrectomy 10 years earlier for similar reasons and had subsequent jejunal ulcers in the past. His history included moderate chronic alcohol consumption and heavy smoking, but no pancreatitis. He underwent laryngectomy and radical neck dissection for squamous cell cancer of the head and neck one year prior to this presentation. \(T_4M_0N_0\) and no tumor recurrence was found. Upper endoscopy showed esophagitis and jejunitis and the serum gastrin level was 890 pg/ml. Octreotide scan showed accumulation in the head of the pancreas and the patient underwent surgical exploration. Based on palpation findings, the uncinate process of the pancreas was removed and pathology analysis revealed a 1.1-cm ovoid nodule. No metastasis was found. Stains were positive in all cells for chromogranin and in some cells for insulin and glucagon. About 5% of cells also contained gastrin. Postoperative gastrin level was 63 pg/ml. Eleven months after surgery the patient is free of recurrent peptic ulcer.

## RESULTS AND DISCUSSION

In a retrospective survey concerning the last 15 years at our institution, which is an urban community teaching hospital, we found five cases of recurrent peptic ulcer disease consistent with the Zollinger-Ellison syndrome. The duration of peptic ulcer disease was 4–20 years, and all except one patient had gastric surgery. Although the differential diagnosis of hypergastrinemic states is rather wide, there is virtually no doubt that these five patients had gastrin-producing tumors. On three occasions (cases 1, 3, and 5), surgical excision and pathologic analysis were performed. For case 2, the search for gastrinoma was unsuccessful but the secretin test provided evidence of an underlying gastrin-producing tumor. Similarly, the gastrinoma remained unidentified in case 4, and...