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Case presentation of gastrinoma combined with gastric carcinoid with the longest survival record – Zollinger-Ellison syndrome: pathophysiology, diagnosis and therapy

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Zollinger-Ellison syndrome is a very rare disease caused by tumor with gastrin producing cells accompanied by hypergastrinemia leading to gastric hypersecretion and peptic ulcers and their complications.

Case study: Female case of gastrinoma (Zollinger-Ellison syndrome; Z-E) with a record of 38 yrs of survival. Acute gastro-duodenal ulcers started at 28 yr of age and Z-E was diagnosed by using gastrin assays. Basal and maximal acid outputs and ratio of basal/maximal outputs were away over normal limits. Because of ulcer recurrence and complications, patient was subjected to several gastric surgeries but refused total gastrectomy. She was also treated with many H_2-receptor (R) antagonists and proton-pump inhibitors (PPI), each new drug being initially highly effective but then showing declinig efficacy except when PPI, lansoprazole was used. The gastrin level rose in the course of disease from initial high value of 2000 pg/mL to the extreme 4500 ng/mL at present. During the last 2 yrs, metastasis mainly to liver developed and they were successfully treated by synthetic octapeptide derivative of somatostatin and, as a result, metastatis partly reduced and plasma gastrin drasticly decreased. Biopsy taken from liver metastasis showed the presence of typical gastrinoma cells with gastrin and chromogranin, while that from oxyntic mucosa revealed the ECL-cell hyperplasia with carcinoid tumors and unexpected gastric atrophy.

Conclusions: This phenomenal case described in this article might be the new proven evidence needed by gastroenterologists to overturn the traditional treatment using total gastrectomy as a treatment of choice to the partial gastrectomy combined with proton pump inhibitors.

key words: gastrinoma • pancreatic endocrine tumor • gastrin • progastrin • peptic ulcer • bleeding

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BACKGROUND

General consideration: Pancreatic Endocrine Tumors (PET) vs Gastrinoma

Gastrinoma originally described by Zollinger and Ellison [1] and known as a cause of Zollinger-Ellison (Z-E) syndrome shows an estimated incidence in USA ranging from 0.1 to 1% of peptic ulcer patients [2]. It is one of seven PET including; insulinoma, glucagonoma, VIPoma (vasoactive intestinal peptide-secreting) causing the Verner-Morrison syndrome or WDHA syndrome (watery diarrhea, hypokalemia, and achlorhydria), somatostatinoma, GRFoma (growth hormone releasing factor–secreting), and nonfunctional tumors [3]. In all cases except the non-functional tumors, ectopic hormone release is associated with a distinct clinical syndrome. With non-functional tumors, the clinical symptoms and signs are entirely caused by the presence of the tumor and almost all PET cells express chromogranin. Furthermore, all PET cells share certain common features, including various aspects of their natural history, pathologic changes, medical treatment options, approaches to tumor localization, surgical options, and treatment options when the tumor has metastasis [4]. The PET are generally slow growing and effective therapy requires both management of the effects of ectopic hormone overproduction and therapy directed at the tumor itself. In each of these tumors, surgical resection of primary tumor, total pancreatic resection, Whipple's resection (with or without gastrectomy) is the treatment of choice. However, at the time of diagnosis, most of the PET already develop metastasis, therefore, the only reasonable approach is to control clinical syndrome caused by ectopic hormone release. In case of gastrinoma, total removal of the stomach was originally thought to be the only rational approach because the life-threatening complications are due to acute gastro-duodeno-jejunal ulcerations. With increased ability to control the symptoms of excessive hormone production, the prognosis increasingly depends upon the therapy applied that in case of gastrinoma appear to be potent gastric H^+ inhibitors such as H_2-R antagonist and proton pump inhibitor (PPI).

The proper diagnosis of PET requires constant awareness of the presenting manifestations of the syndromes and in each instance, except non-functional tumors, the early symptoms are caused by the actions of the ectopically released hormone. Late in the course of disease, symptoms are caused mainly by metastasis spread of the tumor per se (pain, bleeding, cachexia).

The types of PET

PET may occur alone as sporadic tumor [5] or as a part of an inherited disorder. PET may occur as multiple endocrine neoplasia type 1 (MEN-1) (non-functional status > gastrinoma > insulinoma > GRFoma > VIPoma > glucagonoma), von Recklinghausen disease (duodenal somatostatinoma), von Hippel-Lindau disease (nonfunctional), and tuberous sclerosis [6].

Gastrinoma, similarly to other PET, is an indolent yet malignant neuroendocrine tumor characterized by gastric acid hypersecretion and severe peptic diathesis, intestinal hypermotility and steatorrhoe secondary to excessive release of gastrin from non-beta-cell endocrine neoplasm.

Distribution of gastrinoma

Although initial studies observed that the majority (up to 80%) of gastrinomas occur within the pancreas, 10 modern diagnostic studies coupled with aggressive surgical intervention have revealed that a large number of gastrinomas are extrapancreatic and extraintestinal [7,8]. Greater than 80% of gastrinomas have been localized in the anatomical area known as the gastrinoma triangle [9]. The boundaries of this triangle include the confluence of the cystic and common bile ducts superiorly, the junction of the second and third portions of the duodenum inferiorly, and the junction of the neck and body of the pancreas medially. The most common extrapancreatic site is the duodenum, wherein up to 40% to 50% of gastrinomas arise [10,11]. Other less common extrapancreatic sites include the stomach, bones, ovaries, liver, heart, and lymph nodes, which together account for less than 10% of gastrinomas. Greater than 50% of gastrinomas are considered to be malignant. Solitary pancreatic lesions were found in less than 30% of the earliest reported gastrinoma patients [12]. With the more recent trend toward earlier measurement of serum gastrin and exploratory surgery [13], the incidence of metastatic disease at the time of operation has decreased. Nevertheless, multiple tumors or metastatic lesions are still observed in 30% to 55% of patients at the time of diagnosis [10] (Fig. 1).

Morphology of gastrinoma

The neoplastic cells in gastrinomas show heterogeneity [14–15]. The gastrin-producing cells are generally well differentiated and contain histologic markers characteris-

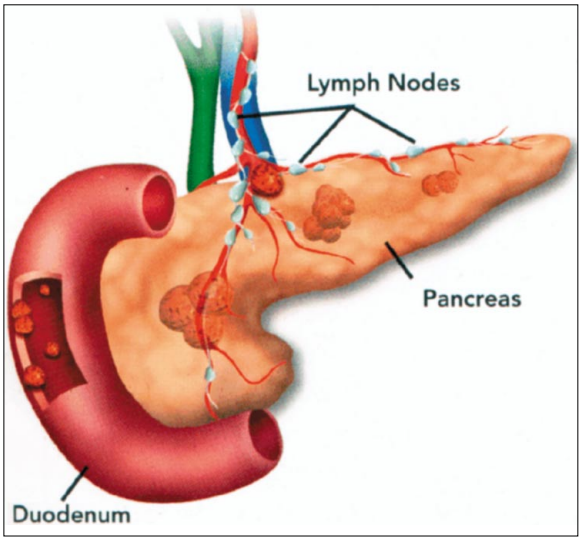

Figure 1. Localization of gastrinoma in the pancreas and duodenum.

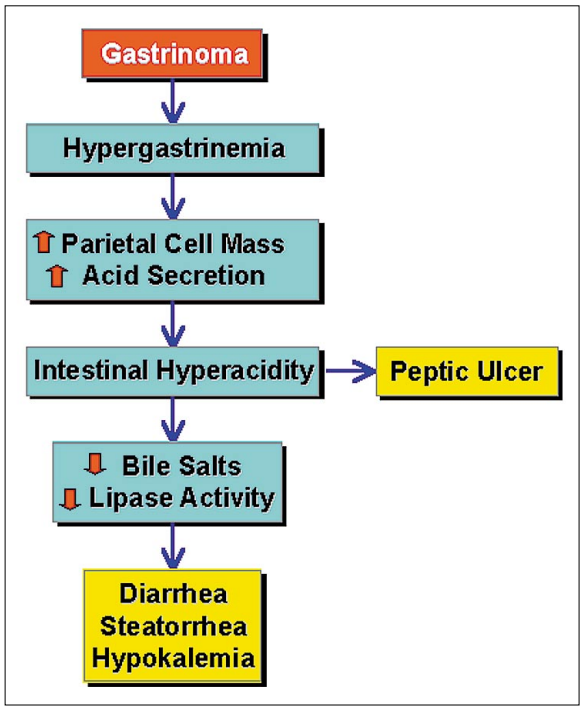

Figure 2. Pathogenesis of Z-E syndrome.

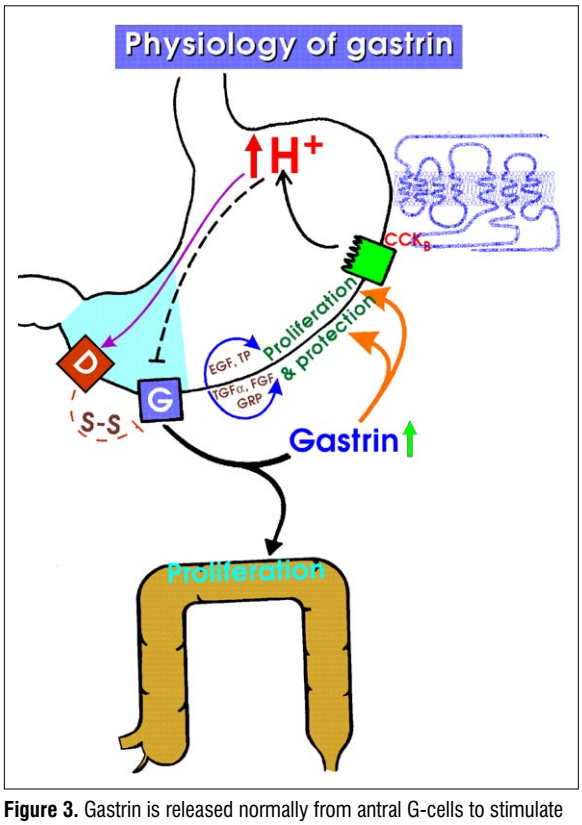

Figure 3. Gastrin is released normally from antral G-cells to stimulate acid secretion and growth of fundic mucosa and colon mucosa and to protect this mucosa against noxious substances.

tic of endocrine neoplasms in general, that is, they contain chromogranin, neuron-specific enolase, and tyrosine hydroxylase. Gastrinomas contain various types of secretory granules that can vary in ultrastructural appearance from those typically found in antral G cells. The degree of malignancy does not appear to correlate with histologic appearance of gastrinoma, however, this observation must be tempered by the knowledge that tumor aggressiveness is usually determined retrospectively.

Pathophysiology of gastrinoma: PET and hormone release

As in the case of other endocrine neoplasms, gastrinomas have been found to express a variety of neuroendocrine peptides besides gastrin, including somatostatin, pancreatic polypeptide, adrenocorticotrophic hormone, and vasoactive intestinal polypeptide (VIP). Although the clinical manifestations are generally associated with overproduction of one hormone, case reports illustrating combined syndromes have been described [16–19].

As mentioned before, gastric acid hypersecretion and severe peptic ulcer diathesis secondary to excessive and uncontrolled release of gastrin from tumor endocrine cells lead to Z-E syndrome (Fig. 2). The neoplastic pancreatic cells secreting gastrin are thought to arise from the ductular epithelium and not from cells of the islets of Langerhans, despite the appellation of gastrinomas as 'islet cell tumors' [1]. Normally, the adult pancreas does not secrete gastrin, but the fetal pancreas contains large quantities of this peptide [20]. After birth, the gastrin-secreting cells in the pancreas disappear and are not seen again except as benign or malignant neoplasms in Zollinger-Ellison syndrome. Gastrin is found predominantly in the gastric antrum and located in endocrine G-cells [20] and functions as the primary stimulant of postprandial gastric acid secretion. [21,22] (Fig. 3). The stimulatory action may occur directly on the parietal cell [23] through specific membrane receptors (CCK_A) [23,24] or indirectly via stimulation of CCK_A-receptors of the enterochromaffin-like (ECL) cells that release histamine to activate H_2-R of parietal cells and HCl secretion [25]. Gastrin also has a well established trophic effect on gastrointestinal tissues including oxynthic mucosa and colon mucosa [26,27] (Fig. 4). In small doses the peptide has been shown to increase protein and DNA synthesis and total DNA content of gastric and colon mucosa. In Z-E syndrome, the hypergastrinemia that results from the release of peptide from an endocrine neoplasm free of the usual regulatory restraints has two synergistic effects on the stomach: overstimulation of gastric parietal cells to secrete HCl and increased mass of parietal and ECL cells and one on the colon promoting mucosal cell proliferation and growth. The potentiated gastric acid hypersecretion that results is presumably the cause of the clinical manifestations (i.e, acid peptic disease and diarrhea) of the gastrinoma or Z-E syndrome.

Expression of gastrin and its precursors in gastrinoma

Although it is well established that gastrinomas contain and secrete large concentrations of the biologically active fully processed molecular forms of gastrin, recent

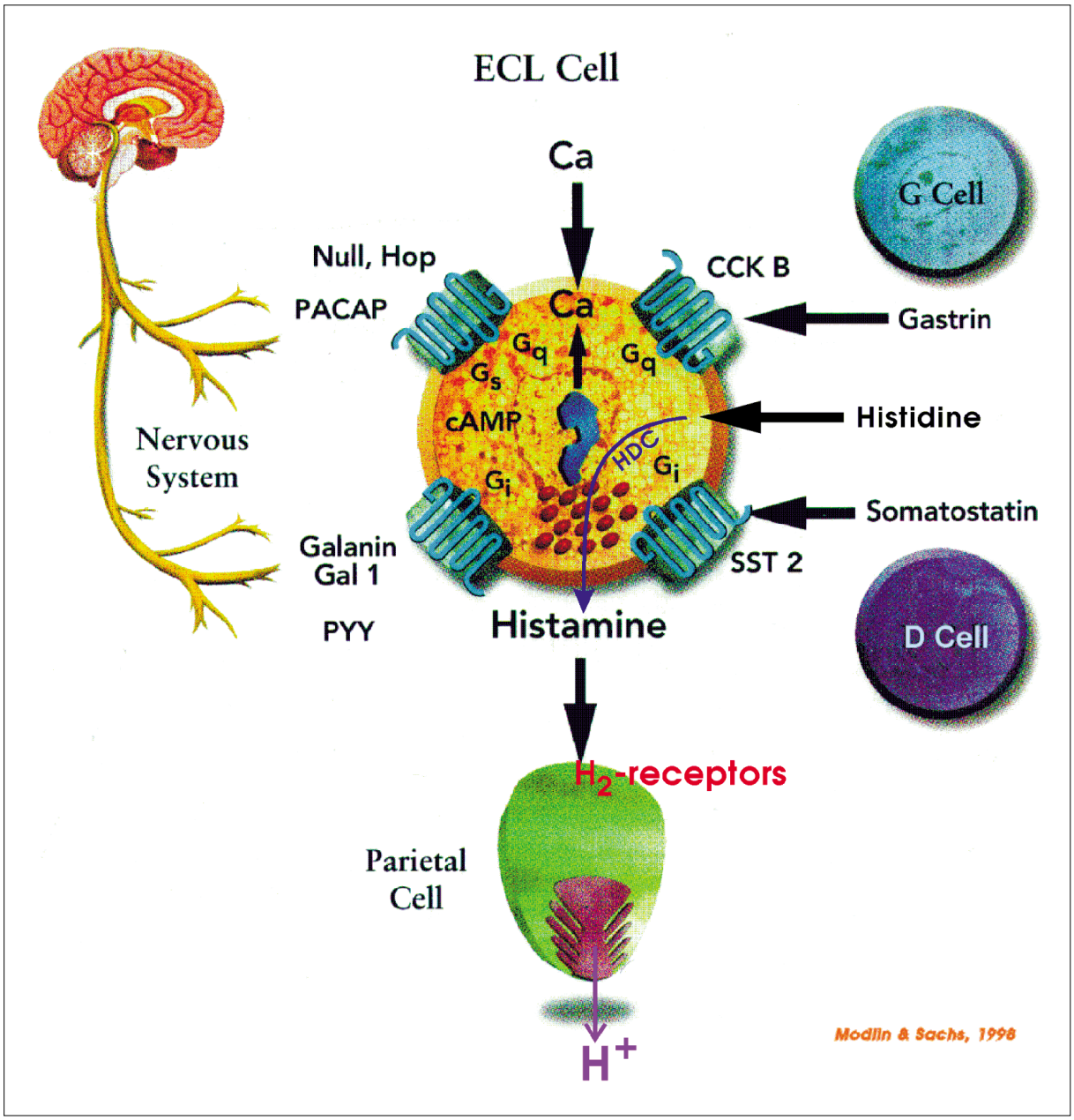

Figure 4. Gastrin stimulates ECL cells to release histamine, which in turn activates H_2-R and H^+-K^+ pump of parietal cells to secrete acid.

studies indicate that altered posttranslational processing of progastrin may be a feature of the disorder as well [27]. Gastrin is synthesized as a large precursor molecule, preprogastrin, that subsequently undergoes a series of posttranslational processing steps involving proteolytic cleavage as well as carboxyl-terminal amidation (Fig. 5). The end products are a variety of molecular forms of amidated gastrin, including those 17 (G17) and 34 (G34) amino acids in length [27] which are found in G-cells of normal antral tissues and also in tumor cells of gastrinoma and in sera of Z-E patients [27]. Kariya and colleagues [28] examined the expression of the human gastrin gene by Southern blot analysis and observed that DNA from gastric antrum and gastrinoma were indistinguishable from each other without evidence of genomic rearrangements in the tumor tissues. By immunochemical analysis, however, Dockray and Walsh [29] were first to observe an unusual component of gastrin in the sera of some Z-E syndrome patients. Using region-specific antisera directed toward the amino terminus of G17, they detected high circulating concentrations of what appeared to be the amino-terminal tridecapeptide fragment of G17 (G171–13), suggesting the presence of altered gastrin processing in gastrinoma tissues. On the basis of information obtained from the gastrin cDNA sequence [27–33] several investigators have developed region-specific antisera toward progastrin and its processing intermediates and utilized them to examine the posttranslational processing of the peptide in gastrinoma patients. These studies have con-

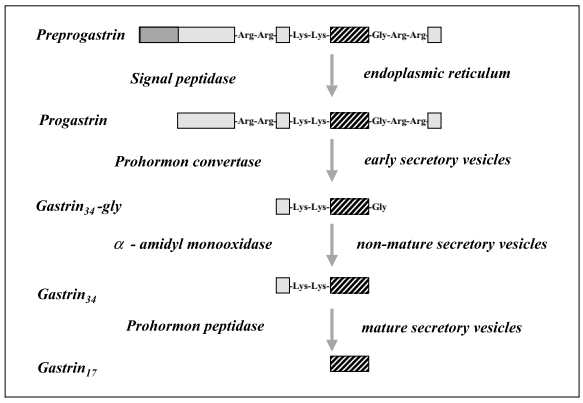

Figure 5. Post translational processing steps involving proteolytic cleavage and carboxyl-terminal amidation resulting in formation of various molecular species; gastrin including amidated gastrin-17 (G-17) and gastrin-34 (G-34). This process may be altered in gastrinoma cells, releasing into circulation some progastrin, that is a signal of tumor metastasis.

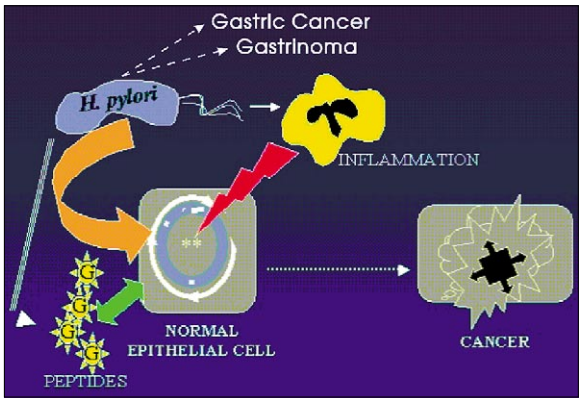

Figure 6. *H. pylori* infection of stomach may result in atrophic gastritis and cancerogenesis but in gastrinoma results in further increase in gastric production and tumor growth that may be partly suppressed by *H. pylori* eradication.

firmed that gastrin processing is altered in tumor tissue. The biological significance of these observations is unclear, but one hypothesis is that the degree of altered processing may correlate with the state of de-differentiation of a tumor [27]. This correlation was examined by Kothary and associates [33,34] who suggested that a high ratio of amino-terminal G17 to carboxyl-terminally amidated G17 immunoreactivity, indicative of incomplete posttranslational processing may signal the presence of tumor metastasis [27]. It is of interest that such disturbed posttranslational processing, of gastrin was detected recently in colon cancer, whose cancer cells are also capable of expressing gastrin and its precursor progastrin that fails to affect gastric HCl secretion but exerts marked trophic effects on other cancer cells. The question remains whether gastrin and progastrin produced by gastrinoma cells are also capable of self-stimulation by these peptides as it is the case of gastric and colorectal cancer.

Differential diagnosis of Z-E syndrome

The hallmark of Z-E syndrome is the presence of circulating hypergastrinemia [36]. Fasting serum gastrin levels in normal subjects and in patients with routine peptic ulcer disease are usually less than 150 pg/mL [37]. The degree of hypergastrinemia in patients with Z-E syndrome varies greatly. Although occasional reports of normal levels [37–39], virtually all gastrinoma patients have fasting levels greater than 150 pg/mL, with levels exceeding 100,000 pg/mL in some. A serum gastrin level of greater than 1000 pg/mL in the right clinical setting is virtually diagnostic of Z-E syndrome; however, many patients do not have this level of hypergastrinemia. Elevated serum gastrin levels are seen in a number of other clinical conditions as well. With the ever-increasing use of potent antisecretory agents such as long-acting H_2-R antagonists and PPI (omeprazole, lansoprazole, pantoprazole), drug-induced hypergastrinemia [40] must be excluded prior to proceeding with an extensive diagnostic evaluation for Z-E syndrome. The mechanism by which these drugs induce hypergastrinemia is inhibition of gastric acid secretion. The level of hypergastrinemia is reversible with drug cessation and is usually less than 1.5 to 2 times normal levels. The discovery that *H. pylori* infection leads to peptic ulcer disease is also an important consideration in the differential diagnosis of Z-E (Fig. 6). A significant percentage of patients with *H. pylori* infection and peptic disease develop hypergastrinemia and gastric acid hypersecretion which are reversible with eradication of the organism [41,42]. The *H. pylori* infection may mimic the clinical and biochemical picture of Z-E syndrome, therefore, careful search and eradication of *H. pylori* is mandatory in any patient with peptic ulcer disease prior to considering a diagnosis of gastrinoma.

Hypergastrinemia unrelated to gastrinoma

The most common cause of hypergastrinemia is gastric atrophy [43]. Gastric acid is the primary inhibitor of gastrin release from antral G-cells; therefore, in its absence an uninhibited secretion of the hormone occurs with concomitant hyperplasia of G cells. Such hypergastrinemia is typically observed in pernicious anemia [43]. Up to 75% of patients with pernicious anemia have substantial hypergastrinemia. The gastrin levels in these patients can approximate those found in gastrinoma patients, reaching values greater than 1000 pg/mL. Chronic atrophic gastritis and gastric carcinoma are two other conditions associated with hypo- or achlorhydria and subsequent hypergastrinemia [43–46]. We proposed [45] that *H. pylori*-induced atrophic gastritis and subsequent gastric cancer are causally related to excessive release of gastrin that stimulates the tumor cell growth and induces (together with other growth factors) the expression of cyclooxygenase-2, leading to angiogenesis and reduced apoptosis. Gastrinemia may occur in association with normal or slightly increased gastric acid secretion in pheochromocytoma, rheumatoid arthritis, diabetes mellitis, vitiligo, gastroparesis, gastric outlet obstruction, renal insufficiency, retained antrum, incomplete vagotomy, and massive resection of the small bowel [47,48].

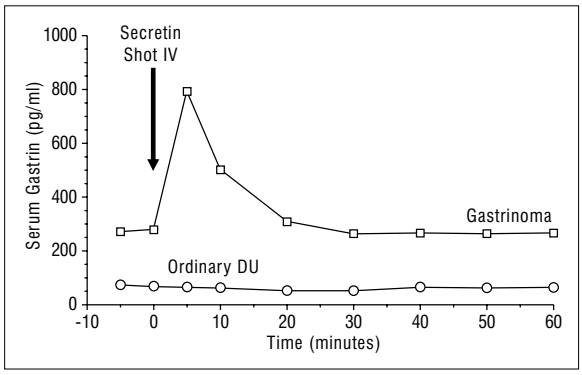

Figure 7. Differential diagnosis of gastrinoma includes the provocative test with infusion of secretin which results in marked rise in plasma gastrin in gastrinoma but not in hypergastrinemia accompanying other conditions such as ordinary peptic ulceration where secretin causes a decrease in plasma gastrin.

Differential diagnosis of gastrinoma: provocative tests

To differentiate between the many causes of hypergastrinemia, a variety of provocative tests [49–53] have been developed. **The secretin test** has proved to be the easiest and most reliable study to perform. Isenberg and associates [50], in seeking to determine whether the putative enterogastrone secretin could inhibit acid secretion, made the serendipitous observation that, instead, the peptide induced a dramatic increase in plasma gastrin and acid secretion in patients with Z-E syndrome. Because secretin did not have a stimulatory effect on gastrin release in normal subjects, the response noted in gastrinoma patients was a paradoxical one. However, recent reports state that secretin can induce a significant early increase (albeit low) of serum gastrin levels in a few normal subjects and patients with common duodenal ulcer disease [53] and rarely in individuals with achlorhydria [54]. The mechanism by which secretin stimulates the release of gastrin from endocrine neoplasms is unclear. Various reports have indicated that secretin directly stimulates gastrin release from dispersed gastrinoma cells [55,56]; however, no such stimulation was observed when similar experiments were performed with cultured antral G cells. The fundamental biological difference between gastrin-releasing cells present in gastrinomas and G cells found in normal gastrointestinal mucosa remains unknown. It is possible that the different ontogenic origins of these two cell populations accounts for their different behavior. As noted above, gastrinoma cells are thought to arise in the pancreas from pluripotent ductular elements that may retain the functional characteristics of their normal counterparts that secrete HCO_3^- in response to secretin. When conducting secretin test it is important to use purified secretin obtained e.g. from Kabi (GIH secretin). In the standard protocol, 2 units of secretin per kg body weight is infused by intravenous bolus, and serum for gastrin measurement is obtained 10 minutes and 1 minute before, and at 2, 5, 10, 15, 20, and 30 minutes after secretin injection (Fig. 7). Greater than 90% of gastrinoma patients exhibit an increase in serum gastrin within 15 minutes of secretin administration. Based on several studies composed of small numbers of patients, various criteria for establishing the positivity of a secretin provocative test have been proposed, including increases in serum gastrin of 100 pg/mL, 200 pg/mL, or 50% above basal levels. Although it has been suggested that an increment in serum gastrin of greater than 200 pg/mL above basal levels has a sensitivity and specificity of greater than 90% for the diagnosis of Z-E syndrome, it was not until the large-scale study by Frucht and colleagues [57]. These investigators prospectively evaluated the secretin provocative test and the calcium infusion study in 80 gastrinoma patients. In accord with previous studies, the secretin test was found to be positive in 87% to 93% of all patients with Z-E syndrome and proved to be more advantageous than the calcium infusion study because of its greater sensitivity, shorter sampling time, ease of performance and lack of side effects. Of the three criteria for positivity, the parameter recommended by the authors for establishing the diagnosis of Z-E syndrome was an increase in serum gastrin of 200 pg/mL or greater. The false-positive secretin test results reported in other studies [57] were not seen with these criteria.

The less commonly employed provocative test is **the calcium infusion study**. Calcium gluconate is administered at a concentration of 5 mg/kg body weight per hour for 3 hours with simultaneous measurement of serum gastrin levels at 30-minute intervals. Greater than 80% of gastrinoma patients demonstrate an increase in gastrin levels of more than 400 pg/mL during the third hour of calcium infusion. This study is less sensitive and specific than secretin stimulation for identifying patients with Z-E syndrome. An increase is usually not seen in patients with common peptic ulcer disease or in normal individuals but may be observed in 50% of patients with hypergastrinemia of gastric origin. As outlined above, lack of specificity, diminished sensitivity, and the potential adverse effects of administering intravenous calcium have made this provocative test less useful than the secretin test in diagnosing Z-E syndrome. It is usually reserved for patients with a negative secretin test in the presence of gastric acid hypersecretion and a strong clinical suspicion of gastrinoma [57].

Standard meal studies have been employed to distinguish hypergastrinemia of gastric origin (as in G-cell hyperplasia/hyperfunction) from that of pancreatic origin (gastrinoma). According to the prevailing dogma, Z-E syndrome patients have less than a 50% increase in serum gastrin in response to a meal, and a postprandial increase in serum gastrin of greater than 100% is characteristic of G-cell hyperplasia/hyperfunction. However, the studies of Frucht and associates [58] suggest that 50% of patients with Zollinger-Ellison syndrome have a greater than 50% postprandial increase in serum gastrin. Thus, some caution should be maintained in applying the standard meal study for evaluation of patients with hypergastrinemia.

Hypergastrinemia and gastric acid secretion

Since gastrin is a most powerful stimulant of gastric acid secretion, it is not surprising that basal acid output (BAO) of 15 mmol/h or greater is found in as many as 90% of patients with gastrinoma [59,60]. It is important to note, however, that 12% of patients with common duodenal ulcer disease can also manifest increased levels of acid secretion. BAO of greater than 5 mmol/h is found in 55% of patients with Z-E syndrome, even after surgery [61]. To enhance the sensitivity of the gastric secretory studies, maximal acid output (MAO) values also may be measured using pentagastrin (2 μg/kg-h). Because gastrinoma patients are presumed to have near maximal secretion of gastric acid even under basal conditions, the acid secretory response to exogenously administered secretagogue (pentagastrin) is diminished. Accordingly BAO/MAO ratio of greater than 0.6 is highly suggestive of Zollinger-Ellison syndrome [2] although a ratio of less than 0.6 does not exclude the diagnosis [61].

Since the specificity of gastric acid secretory tests may not be high and as pointed out by Spindel and colleagues [49], about 59% of patients with elevated serum gastrin levels were either hypo- or achlorhydric; therefore, the ability to diagnose Z-E syndrome was enhanced by performing gastric analysis under natural conditions by measuring 24 h intragastric pH. Thus, under optimal circumstances, acid secretory studies should be part of the diagnostic evaluation in patients suspected of having gastrinomas. If the equipment for 24 h pH-metry is available, the test should be performed and if in the 24 h period the intragastric pH is over 3.0, it essentially rules out the diagnosis of Z-E syndrome.

In summary, no single diagnostic test has a sensitivity or specificity of 100% in evaluating patients for Z-E syndrome. One must juxtapose the information obtained from the various tests with the clinical presentation. A fasting gastrin level of greater than 1000 pg/mL and a basal acid output of greater than 15 mEq/h in a patient with recalcitrant peptic ulcer is virtually diagnostic of Zollinger-Ellison syndrome. In the absence of this triad of findings, provocative testing may be required. Of these, the secretin stimulation test offers the greatest sensitivity and specificity.

Localization of gastrinoma and its metastasis

Gastrinomas are notoriously difficult to localize and the availability of potent antisecretory drugs has significantly decreased the morbidity and mortality associated with uncontrollable acid hypersecretion; thus, emergency or urgent total gastrectomy is rarely if ever needed. However, recent studies indicate that the tumor itself, rather than the acid hypersecretion, is responsible for the adverse sequelae associated with Zollinger-Ellison syndrome. Series of patients who eventually underwent surgery for Zollinger-Ellison syndrome prior to the 1990s noted the inability to identify the tumor in approximately 30% to 50% of patients, with more than

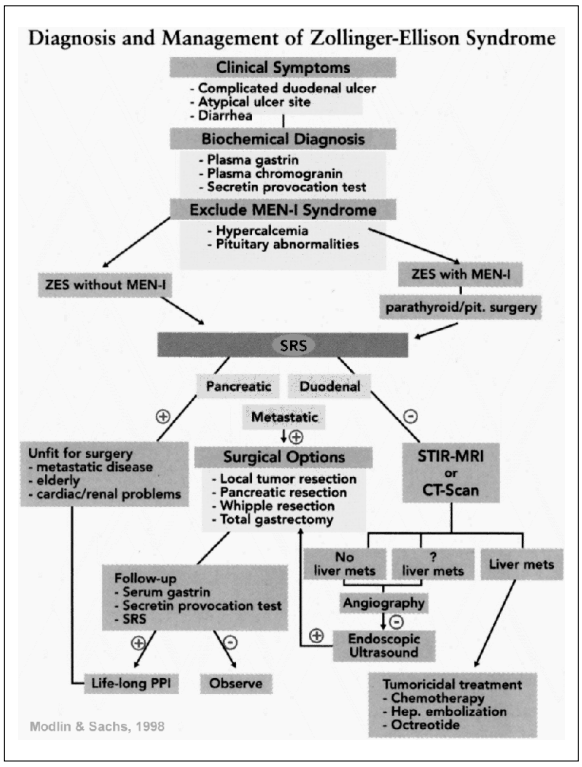

Figure 8. Scheme of diagnosis and management of Z-E syndrome based on somatostatin receptor scintigraphy (SRS) (modified from Modlin and Sachs, 1999).

20% having metastatic disease at laparotomy [61–63]. More recent series, perhaps reflecting improvements in preoperative imaging modalities, have localized tumor in 85% of cases, although metastatic disease is frequently present (approximately 50% of patients). Early intervention with resection of a localized primary tumor presents the only opportunity to cure this disease [64,65]. In addition, preoperative detection of metastatic disease will prevent unnecessary surgery. Accordingly every effort should be made to localize the tumor preoperatively.

Many approaches have been used for the purpose of localizing gastrinomas. These include abdominal ultrasonography [66,67], CT scanning [68,69], abdominal arteriography [70,71], selective portal venous sampling for gastrin [72,73], endoscopic ultrasonography (UES) [74–76] and, most recently, somatostatin receptor scintigraphy (SRS) with the somatostatin analog octreotide [77,78] (see Fig. 8).

Ultrasonography (USG)

In general, **transcutaneous abdominal ultrasonography** is not considered useful for the diagnosis of gastrinomas. Most gastrinomas are small; therefore, sensitivity of this test is quite low, as demonstrated in a prospective study [79] in which transcutaneous ultrasonography was able to localize tumors in only 20% of patients later shown by surgery to have gastrinomas. Nevertheless, if a lesion is seen, it is likely to represent gastrinoma; thus,

the specificity of ultrasonography was 90% to 100% in this prospective series. This examination may be useful in identification of gastrinoma metastasis.

Endoscopic ultrasonography (EUS) has facilitated high-resolution imaging of the pancreas, permitting delineation of structures smaller than 5 mm in size. Because the accuracy of this procedure in diagnosing small pancreatic carcinomas approaches 100% [80], it is not surprising that this diagnostic modality is useful in localizing small neuroendocrine tumors of the pancreas as well. Rösch and associates [81] reported 37 patients with surgically confirmed endocrine neoplasms of the pancreas (39 tumors), in whom preoperative ultrasonography and CT scan of the abdomen yielded negative findings. Thirty-two of the tumors were diagnosed by endoscopic ultrasonography (82% sensitivity) with a specificity of 95%. Tumors varied in size between 0.5 and 2.5 cm in diameter. It is important to note, however, that all seven of the gastrinomas in this series were located in the pancreas, and none were located in extrapancreatic sites, such as the duodenum.

EUS has been used as a primary diagnostic tool to localize neuroendocrine tumors, evaluating over 60 patients in a prospective study [82]. Thompson et al. [83] reported the results of a prospective study of 16 and then 44 patients with neuroendocrine tumors, some with Z-E syndrome and found hat the sensitivity of EUS results in predicting an extrapancreatic gastrinoma was 100%. This suggests that this procedure should be used early in the evaluation of a patient with Z-E syndrome. The sensitivity of EUS in detecting gastrinomas has been confirmed by Ruzniewski at al. [84]. Of note, they observed that conventional endoscopy had a sensitivity of 40% for detecting duodenal wall lesions; thus, EUS has small incremental utility over endoscopy to localize duodenal wall lesions. These recent studies support EUS as a sensitive diagnostic test that should be used in experienced centers to localize gastrinomas in patients who have no evidence of metastatic disease.

Other centers without EUS experience have reported the utility of intraoperative ultrasonography, which appears to be useful in the localization of small gastrinomas [85,86]. Tumors not detected by the surgeon through manual inspection may be imaged using this technique, with a sensitivity of 95% by experienced operators.

Computed Tomography (CT)

The diagnostic efficacy of CT scanning appears to be improving with the technology itself. For extrahepatic gastrinoma, CT scanning with intravenous contrast had a specificity of 95%, a sensitivity of 59%, a positive predictive value of 96%, and a negative predictive value of 54%. For gastrinomas metastatic to liver, CT scanning had a specificity of 98%, sensitivity of 72%, a positive predictive value of 93%, and a negative predictive value of 90%. Tumor size and location appear to be the key determinants in the successful diagnosis of gastrinoma by CT scanning. Approximately 80% of tumors in the pancreas and tumors larger than 3 cm are detected. Only 40% of extrapancreatic lesions and no tumors measuring less than 1 cm in diameter are detectable by CT scanning. The sensitivity and specificity of computerized axial tomography does not appear to be enhanced by performing dynamic studies; therefore, routine scans with oral and intravenous contrast will suffice. Whether helical techniques will lead to improved sensitivity remains uncertain, although an initial report (requiring further comparative study) has reported 82% sensitivity for tumor localization.

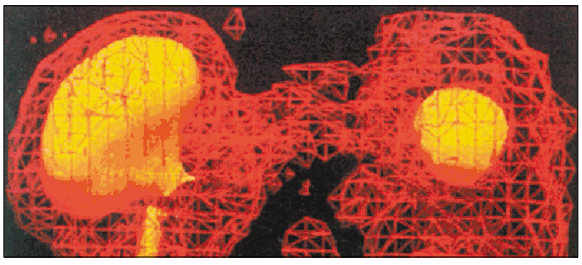

Figure 9. Localization of gastrinoma can be achieved by various method but most elegant and precise is somatostatin receptor scintigraphy (SRS) using labeled somatostatin analog such as octreotide, binding to tumor cells allows for mapping the tumor and its metastasis.

Magnetic Resonance Imaging

Magnetic resonance imaging [87,88] has been evaluated for the detection of both primary and metastatic gastrinoma, and initial results appear similar to CT scanning. In a prospective study, the NIH group found that MRI using short-time inversion-inversion recovery sequences was superior to CT for the detection of liver metastases (sensitivity 71% versus 42%). MRI was equivalent to CT in detection of primary lesions, leading this group to suggest that it should replace CT as the cross-sectional imaging test of choice. The ability of SRS to localize occult liver metastases leaves the choice between CT and MRI a consideration of availability and local expertise.

Somatostatin Receptor Scintigraphy (SRS)

Gastrinomas express somatostatin receptors. Therefore, targeted nuclear scanning following injection of an isotopic analog of somatostatin – either ^{123}I-Tyr3-octreotide or ^{111}In-DTPA-Dphe1-octreotide [77,78,89,90] – are emerging as readily available, noninvasive tests to localize gastrinomas with a sensitivity and specificity of greater than 75% (Fig. 9). The indium analog (^{111}In-Pentetriotide) was recently approved by the U. S. Food and Drug Administration and is marketed as Sandostatin Lar (Novartis). In a recent prospective comparison, [91] the NIH group found that the scan was more sensitive than transcutaneous USG, CT and MRI for localizing both primary and metastatic lesions, with sensitivities of 58%, 90% and 92%, respectively. Cadiot and colleagues [92] observed that Octreoscan scintigraphy was very useful in detecting small duodenal lesions (3 mm) and peripancreatic lymph nodes. In a review of 122 patients who underwent SRS to localize primary

and metastatic gastrinoma lesions, the NIH group noted that SRS altered management in 47% of patients, with its greatest impact in the detection of liver metastases [91]. The investigators concluded that SRS should become the initial imaging modality of patients with gastrinoma.

In summary, surgical cure of Z-E syndrome requires accurate tumor localization. To avoid unnecessary laparotomy, metastatic disease should be excluded by either the Octreoscan or by MRI or CT. If no metastatic disease is found, the approach to localize disease in the peripancreatic region is governed by local expertise and surgical experience. In the management of Z-E syndrome, it is clear that a team approach to localization and surgical exploration appears essential to ensure curative resection.

Therapy

When considering the therapy of patients with Z-E syndrome, it is important to achieve two objectives; control of gastric acid hypersecretion and treatment of the malignant neoplasm. The emphasis placed on each of these objectives has shifted over the past 3 decades. Initially, total gastrectomy appeared to be the only alternative for effective treatment of the potentially lethal ulcer disease, and less attention was directed at tumor excision because many of the patients died from ulcer complications long before their tumors became problematic. With the advent of histamine H_2-R antagonists such as cimetidine, ranitidine and famotidine, an effective ulcer therapy, long-term medical management became the favored approach, with tumor excision only as secondary consideration because the likelihood of finding and removing primary a gastrinoma tumor seemed relatively remote [93]. The availability of highly effective antisecretory therapy through H^+,K^+-ATPase antagonists or PPI such as omeprazole, lansoprazol or pantoprazole has led to a significant reduction in mortality related to the complication of acid peptic disease. Under these circumstances, it has become increasingly apparent that the major cause for morbidity and mortality in Z-E syndrome is widespread metastatic disease [94]; thus, early tumor detection and excision has assumed primary importance.

Medical Therapy

The primary aim of medical therapy in Z-E syndrome is control of gastric acid hypersecretion. The development of histamine H_2-R antagonists was a major breakthrough toward this aim. Cimetidine, the first of these agents, proved to be very efficacious in controlling acid hypersecretion and prompted ulcer healing and symptom improvement in over 80% of patients with Z-E syndrome treated on a short-term basis [95]. However, over a longer term, these patients often required progressive increases in the frequency and dose of medication. To correct this problem, anticholinergics (pirenzepine) were used as adjunctive therapy, but significant adverse effects were noted [96]. The efficacy of H_2-R antagonists in inhibiting acid secretion, relieving dyspeptic symptoms duration of action such as ranitidine and famotidine have since been developed and have proved to be efficacious in relieving symptoms and promoting ulcer healing in gastrinoma patients [97]. Famotidine has a 30% longer duration of action and an order of magnitude greater potency than cimetidine and ranitidine [98]. These features, coupled with its efficacy and safety, make famotidine the H_2-R antagonist of choice for the treatment of Z-E syndrome.

H_2-R antagonists with greater potency and for the treatment of Z-E syndrome is the substituted benzimidazoles, of which omeprazole is the first [99]. More recently, lansoprazole and pantoprazole have been added to this family of drugs [100]. These compounds are the most potent acid inhibitory agents because they covalently bind to H^+-K^+-ATPase, the enzyme responsible for the generation and secretion of H^+ in the parietal cell canaliculi. An important new class of drugs made available and promoting ulcer healing in gastrinoma patients has been established [101].

Although earlier studies suggested that the doses of omeprazole required for effective inhibition of acid secretion in gastrinoma patients were significantly higher than in patients with standard peptic ulcers, a study by Metz et al. [102] suggest that the currently recommended maintenance dose of omeprazole (approximately 60 mg/d) used in these patients is too high. Accordingly a gradual reduction of omeprazole dose has been recommended once the initial dose required for adequate control of gastric acid hypersecretion (as described above) has been achieved. More recently, the NIH group prospectively examined the effectiveness of low doses of omeprazole (20 mg/d) as initial therapy in gastrinoma patients [103]. Forty-nine patients were started on omeprazole (20 mg/d) in an inpatient setting. Symptoms and gastric acid output were measured. Patients were considered to have failed low-dose omeprazole if they developed symptoms or basal acid output was greater than 10 mmol/h after 3 days of therapy. Using these criteria, low-dose omeprazole was successful in 68% of patients. Failures were equally distributed among persistent symptoms and high gastric output. Based on these results, the investigators continue to recommend initiating omeprazole therapy at a dose of 60 mg/d. This dose will allow rapid control of gastric acid secretion, thus minimizing complications related to peptic diathesis. Once an adequate maintenance dose is achieved, tapering the medication is then indicated while following symptoms and acid output (as outlined above). Tachyphylaxis is observed less frequently with omeprazole than with H_2-R blockers. One concern with long-term omeprazole therapy has been its potential for inducing enterochromaffin cell hyperplasia. A prospective study following 40 patients with Z-E syndrome who were treated with omeprazole for a mean of 29 months (6 to 51 months) reported no evidence of hematologic, biochemical, or gastric toxicity [104]. Their marked potency, prolonged duration of action, and safety profile make substituted benzimidazoles the treatment of choice for peptic disease in patients with Z-E syndrome.

Somatostatin is a known peptide inhibitor of gastric acid secretion and gastrin release [105]. The biochemically stable analog of somatostatin, octreotide, has been used with varying success in patients with gastrinomas [106,107]. One rationale for the use of somatostatin analogs is that they can inhibit the secretion of gastrin from the tumor as well as the action of gastrin on the oxyntic mucosa. At present, however, these compounds are available only in injectable form; thus, they are rarely used as the first-line agent in the treatment of patients with Z-E syndrome.

Surgical Therapy

Prior to the advent of potent antisecretory agents, total gastrectomy was the treatment of choice in gastrinoma patients. Although initial operative mortality was very high (15% to 20%) [108], a total gastrectomy offered better long-term survival than did more conservative approaches. Increased experience and earlier diagnostic testing have reduced the operative mortality rate associated with total gastrectomy to less than 5% [109]. Nevertheless, the new gastric antisecretory agents have obviated the need for total gastrectomy, and presently this procedure should be considered only in the rare patient with nonresectable gastrinoma in whom aggressive medical therapy has failed, or in those individuals who cannot take oral medications. Another operation applied in the past as an adjunct to medical therapy in patients with Z-E syndrome is proximal gastric vagotomy. The rationale for this operation was the high failure rate with H_2-R antagonists. Richardson and associates [110] reported on a series of 22 gastrinoma patients who underwent surgery to remove any visible tumor and then were treated with parietal cell vagotomies. Selective vagotomy decreased basal acid output significantly in all of the patients, even if the tumor was not localized or incompletely resected. When compared with preoperative values, basal acid outputs were reduced by 41% to 69% in patients who had residual tumor, and the dosage of H_2 antagonist required for therapy was reduced in 21 of 22 patients. Recent follow-up of these patients (16 years) reveals that 86% of patients have had long-term inhibition of acid secretion, with 8 individuals discontinuing antisecretory agents. In an editorial that followed, it was recommended that parietal cell vagotomy be routinely performed at the time of surgical exploration for a gastrinoma [111].

Clearly, the appropriate surgical approach for therapy of Zollinger-Ellison syndrome today is curative resection of the neoplasm. Although initial series reported a cure rate of less than 10% following tumor resection, present data indicate that cure may be possible in as many as 30% of cases. Improved diagnostic capabilities have led not only to a reduction in unnecessary surgery on patients with metastatic disease, but also to the identification of extrapancreatic neoplasms with increasing frequency [112]. Studies have reported the incidence of extrapancreatic lesions to be as high as 66% and resection of these lesions to be associated with a high likelihood of long-term cure [113]. Operative management of Zollinger-Ellison syndrome should be undertaken by a surgeon with expertise in the treatment of islet cell tumors. Careful and detailed mobilization and exploration of the entire pancreas and surrounding areas should be performed [114,115]. Any tumors that are found in the region of the pancreatic head should be enucleated, and tumors located elsewhere should be resected with great care. In the event that a tumor is not found at surgery, distal pancreatectomy should be avoided because greater then 80% of the gastrinomas are located within the gastrinoma triangle. If a lesion is found in the head of the pancreas, a Whipple procedure should be considered with great care because the mortality of this surgical procedure may outweigh its potential benefits. However, the decision may be facilitated if complete tumor excision is not possible by a less invasive procedure [108].

Prognosis in gastrinoma

Z-E tumors can be classified as either benign or malignant [11,116]. This classification is not based on tumor histopathology but on a series of clinical characteristics. Of these characteristics, tumor extent is one of the most important prognostic indicators. As reviewed by Maton at al. [116] 5-year survival rates for all gastrinoma patients vary between 62% and 75%, and 10-year survival rates vary between 47% and 53%. If one segregates the survival data according to extent of tumor present at the time of diagnosis, patients who have a negative laparotomy or have all of their tumor removed surgically have 5- and 10-year survival rates of greater than 90%. In contrast, patients with tumors that were incompletely resected have 5- and 10-year survival rates of 43% and 25%, respectively. More recently Weber et al. [11] critically evaluated 185 consecutive patients with Z-E syndrome and identified the criteria that determined metastatic rate and survival in these individuals. These investigators confirmed that both a benign and a malignant category of gastrinomas exist. The overall 10-year survival rates were 93% for patients with MEN I and 74% for patients without MEN I, which are somewhat better than rates reported previously, but similar to results reported by Eriksson et al. [117]. It was also found by these investigators that there was no difference in survival for the following patients: those rendered disease free at surgery, those with tumor and persistent disease after surgery, and those with disease and negative exploratory laparotomy results. A poor clinical outcome is seen in female patients, in patients without MEN I, in individuals with high serum gastrin, in patients with a large pancreatic tumor, and in individuals with hepatic metastasis. Presence of hepatic metastasis clearly indicates a poor outcome in Z-E syndrome. In a review of 36 gastrinoma patients [112] those found to have tumors in the liver at the time of initial evaluation had a mortality rate of greater than 80% over a 5-year period. Absence of a detectable tumor or metastasis limited to lymph nodes was associated with a remarkably good outcome. On the other hand, altered amino- to carboxyl-terminal gastrin-17 ratios [33,34], elevated levels of progastrin [118] and the presence of an aneuploidy state in the tumor [119] seem to suggest a poor prognosis, but confirmatory studies are needed.

HISTORY OF DISEASE

Beginning of Z-E syndrome

F.J. patient was born November 23, 1934. Symptoms began June 1964 i.e. at her 30 yr age with an intense hunger pain in the gastric region, accompanied by vomits. At that time, her gastric secretion, both BAO and pentagastrin-induced MAO were increased, respectively, to 15.4 and 21.6 mmol/h with the ratio of BAO/MAO being 0.71. Because of high BAO/MAO ratio, the Z-E syndrome was suspected, and the bioassay of plasma gastrin was measured using deproteinated plasma injected i.v. into gastric fistula rats. Since the gastric secretion in response to plasma extract increased 2–4 times, the existence of the hypergastrinemia was suspected.

Gastric operations due to gastrin-related acute ulcer diathesis and its complications

On October 1964 FJ (at her 30 yr) was hospitalized for a gross bleeding from upper part of gastrointestinal tract and antrectomy plus left vagotomy was performed (I). After this procedure, the remission of ulcer diathesis was observed for 2 years but then in 1966 dull pain in the left upper abdominal region took place. Multiple gastric, duodenal and jejunal ulcers were recognized and re-bleeding from upper part of gastrointestinal tract occurred. Patient underwent partial gastrectomy with the Billroth type II anastomosis (II). Soon, purulent gallbladder with gall-stones was excised in 1967 (III). Because of stomach ulceration with bleeding, right vagotomy was concluded in 1968 (IV). Antacids including aluminum hydroxide containing preparation (Alugastrin) and anticholinergics (Probanthine) were prescribed and used till 1976 when again acute upper abdominal pain occurred and our patient was again hospitalized. Three weeks later, the anastomotic ulcer was found by gastroscopy. The first measurement of immunoreactive gastrin level in serum was performed in Department of Physiology, Academy of Medicine, Krakow in 1977 using antiserum No 4562 (from Professor J. F. Rehfeld, Copenhagen, Denmark) showing amidated serum gastrin G-17 and G-34 level of about 2000 pg/mL. The hypergastrinemia was confirmed the same year in the lab of CURE by Dr John Walsh from Veteran Administration Center, Los Angeles, Ca, showing serum level gastrin of about 2000 pg/mL. The patient obtained new therapeutic agents that became available for the limited clinical trial including firstly H_2-blockers (Metiamide, Cimetidine and finally Ranitidine), each agent working very well during first months but then its efficacy declined and required either higher dose or change of the agent.

On 1989, the presence of stomal ulcer was recognized by upper endoscopy. The *H. pylori* infection was identified by positive CLO test and histology of the oxyntic mucosa obtained during upper endoscopy but the 13C-urea breath test gave negative results. The IgG antibodies against both *H. pylori* and its CagA cytotoxin IgG antibodies were found by ELISA in the serum. *H. pylori*

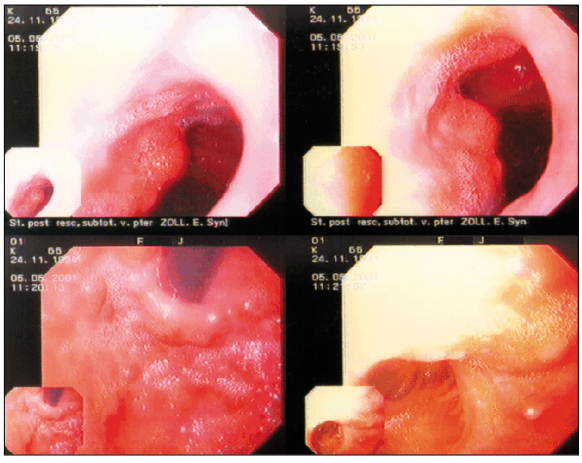

Figure 10. Endoscopy of the gastric remnant showing modular hyperplasia of preserved gastric mucosa (with carcinoid foci).

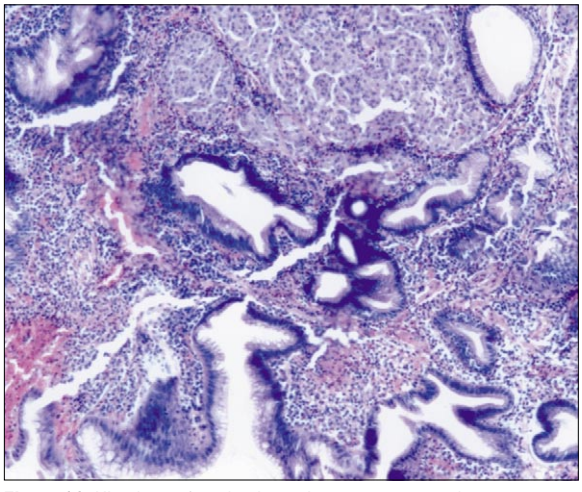

Figure 11. Histology of retained gastric mucosa at gastric stamp showing carcinoid cells infiltrating lamina propria.

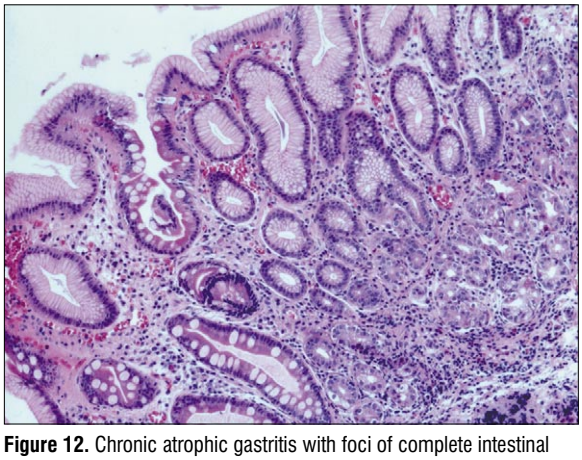

Figure 12. Chronic atrophic gastritis with foci of complete intestinal metaplasia at the gastric Stamp.

eradication was performed using therapy consisting of Metronidazole (500 mg bd, Amoxicilin (500 mg bd) and Ranitidine (150 mg td) and one month later the UBT

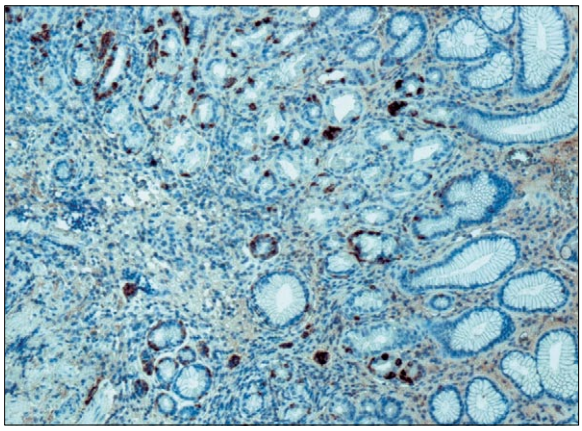

Figure 13. Marked modular hiperplasia of chromogranin containing endocrine cells in the lamina propria at the gastric stamp.

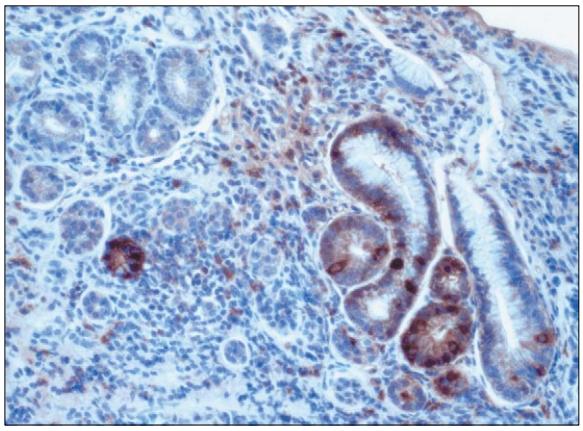

Figure 14. Some endocrine cells in the lamina propria staing for gastrin.

and CLO of endoscopic mucosa sample were negative but no change in serum anti-*H. pylori* IgG and CagA were observed. Serum gastrin level which averaged about 2500 pg/mL was partly reduced (to 2100 pg/mL) when measured one moth after the eradication therapy.

In 1996, general malaise occurred accompanied by the reduction in body weight. The upper gastroscopy showed the presence of stomal ulcer and the biopsy specimens showed gastric mucosal hyperplasia with small ECL carcinoid foci and the presence nodular hyperplasia of ECL cells with admixture of the gastrin containing cells in the remaining oxyntic mucosa as assessed in Department of Pathomorphology by one of us (Dr T.S.), using the gastric biopsy samples obtained by another coauthors (Dr A.B.) in Department of Surgery, College of Medicine, Krakow. Colonoscopy revealed the presence of hyperplastic polyps in descending colon.

PPI treatment was initiated (Omeprazole, Pantoprazole and finally Lansoprazole). Follow-up examinations (gastroscopy) were performed at 1–6 month intervals during years 1997–1998 showing chronic atrophic gastritis with nodular ECL hyperplasia in the small area of oxyntic mucosa. The endoscopy performed on March 2001 and March 2002 showed almost similar endoscopic picture (Fig. 10). The biopsies showed ECL nodular hyperplasia and the presence of gastric mucosa with carcinoid cells (ECL-cells) infiltrating lamina propria (Fig. 11). In the biopsy taken from gastric stamp, chronic atrophic gastritis with focal complete intestinal metaplasia was observed (Fig. 12). Endocrine cells were also detected in the lamina propria at the gastric stamp and found to stain with chromogranin (Fig. 13). In addition the presence of scattered gastrin-containing endocrine cells were identified in the mucosa at the gastric stamp (Fig. 14).

Somatostatin Receptor Scintigraphy (SRS) was done on March 2001 at the Department of Endocrinology, Jagiellonian University Hospital, showing large tumor at the gate of liver and metastasis at the pancreas (Fig. 15). In April 2001 both ultrasonography (USG) (Fig. 16) and Computer Tomography (CT) (Fig. 17) were performed showing the tumor of cyclic shape just at the liver and another smaller at the head of the pancreas.

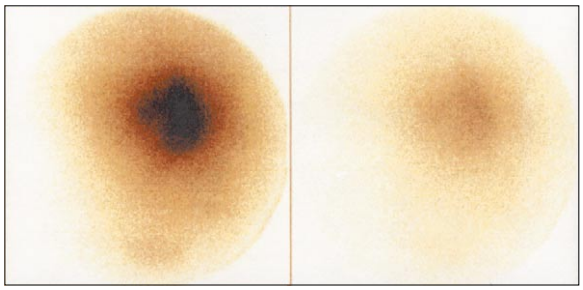

Figure 15. SRS with accumulation of labeled octreotide in the larger metastasis at liver gate and in the smaller focus in the tail of the pancreas as assessed 48h after administration of ^{111}In-octreotide.

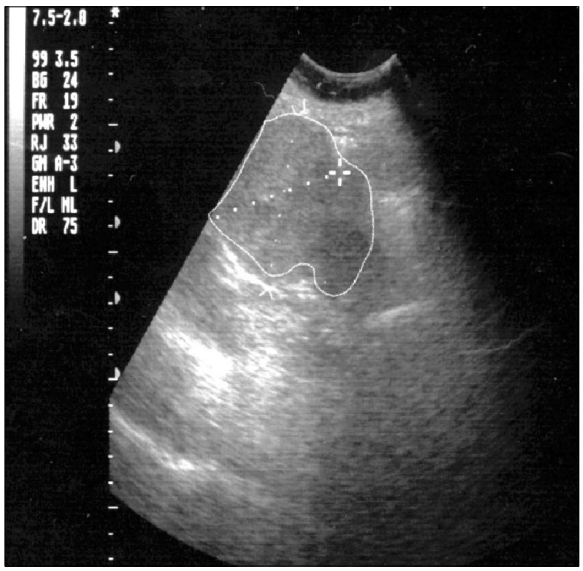

Figure 16. USG of the liver with visible large tumor in the right lobe of this organ.

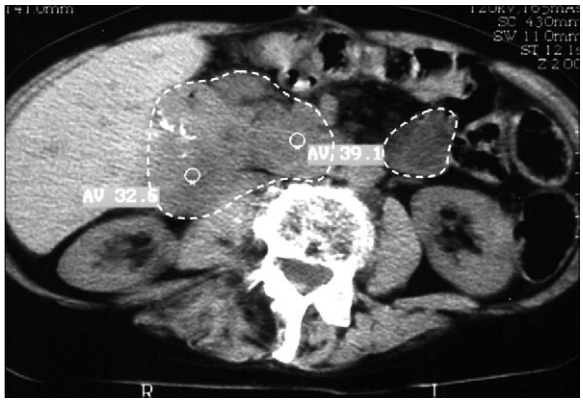

Figure 17. The CT scan at the level of liver, showing polycyclic tumor (106 x 54 mm) with sings of necrosis. Smaller tumor was found below the lower pol of left kidney (40 x 45 mm). The visible cyclic metastases at the liver and below the kidney are encircled on the picture shown above.

The pH-metry (Fig. 18) performed under fasting conditions in the gastric remnant showed normal acidity of gastric juice with mean pH of less than 3.2 despite of the fact that the total area of the oxyntic mucosa in gastric remnant is small (about 2–4 cm^2). During the Sandostatin Lar therapy (20 mg/dose), the pH-metry did not show any decrease below the value of 4–5, indicating complete achlorhydria.

DISCUSSION

This case report shows that the gastrinoma may develop for decades spreading metastasis into liver and inducing ECL nodular hyperplasia with carcinoid formation in the remnant gastric mucosa and polypoid hypertrophy of the colon mucosa. The major source of initial complications in this case was hypersecretion of gastric acid causing various types of ulcerations including gastroduodeno-jejunal and stomal (after gastrectomy) ulcerations and bleeding. It greatly declined after almost total gastrectomy and then remained under medical control using various drugs for almost four decades.

At the time when the disease was recognized as Z-E syndrome, almost four decades ago, it was generally believed that the removal of the stomach, the major target organ for gastrin produced in enormous amounts by gastrinoma tumor cells is the best way of treatment but, our patient did no agree for such gastrectomy. With an advent of powerful gastric acid inhibitors

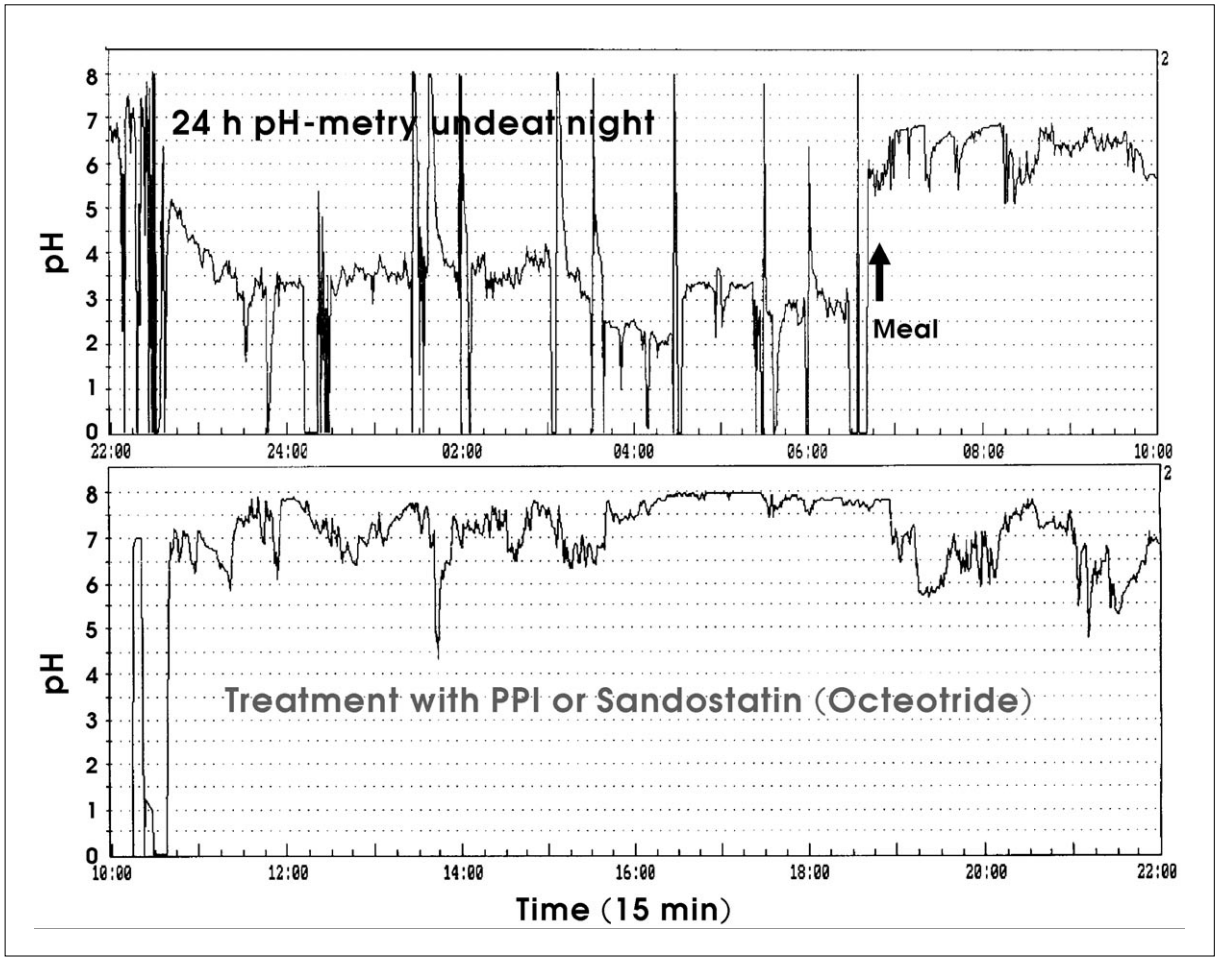

Figure 18. Tracing of 24 h pHmetry in gastric remnant during fasting period at night and just after breakfast (upper tracing) and after inhibition of gastric secretion following administration of sandostatin Tar (octreotid), (Nowartis, Poland).

including H_2-R antagonists and then PPI, the removal of the stomach was not anymore considered as ultimate goal of therapy because the complications of acute ulcer diathesis could be successfully controlled and prevented by suppression of gastric acid and the elimination of the aggressive factor such as acid-pepsin secretion. Thus, complete gastrectomy could not been considered as the treatment of choice even if the primary tumor cannot be detected and our case supports this option. Our patient was in unusually favorable situation because our Department of Clinical Physiology of Jagiellonian University in Cracow collaborated with numerous pharmaceutical companies such as Glaxo, UK, Hassle then AstraZeneca, Sweden, Byk-Gulden-Roland, Germany, Krka, Slovenia, Boehringer, Germany, Searle, USA, Yamaguchi, Japan, Polfa, Pabianice, Poland) in performing preclinical studies and then phase I and II studies. These agents including H_2-R antagonists (metiamide, ranitidine, famotidine), anticholinergics (pirenzepine), somatostatin analog (Sandostatin), methylated PGE (Mizoprostol) and PPI (omeprazole, pantoprazole, lanzoprazole, Prazol) were also available for our Z-E syndrome patient for almost three decades. Our patient was given most of these agents and as a rule, almost each of them (except Mizoprostol which was soon withdrawn because of severe diarrhea) initially worked perfectly during first few months but then tachyphylaxis developed and ulcer recurrence with complications, mainly bleeding, reappeared requiring the change of the treatment regimen. Despite often ulcer recurrence and its complications, our patient never agreed for complete gastrectomy but instead was subjected to numerous gastric operations carried out in various departments of surgery in Poland and leaving at the outcome the gastric remnant of the area of few cm^2 at gastric stamp.

At the beginning of the disease, 38 years ago, very high basal gastric acid secretion (BAO = 15.4 mmol/h) with characteristic increase of the BAO/MAO ratio reaching 0.71 was recorded. This hyperchlorhydria was accompanied by extremely high serum gastrin level exceeding 2000 pg/mL. The hypergastrinemia before the era of radioimmunoassay described by Yalow and Berson [36] was initially revealed using simple gastrin bioassay on gastric fistula preparation in rats similar to that used originally by Sircus [120] and showing about 3 fold increase in acid output in response to 5 ml of deproteinized serum given intravenously and corresponding to that achieved with histamine at a dose of 5 mg/kg-h s.c. This hypergastrinemia in our patient was confirmed by radioimmunoassay (RIA) of gastrin when it became available in 1968 in our lab using antiserum No 4562 (kindly provided by Professor J. F. Rehfeld, Department of Biochemistry, Copenhagen University, Copenhagen, Denmark) recognizing amidated forms of G-17 and G-34). Serum gastrin in our patient exceeded 2000 pg/mL and this highly elevated serum gastrin was confirmed later by Dr J. W. Walsh at CURE, Los Angeles. At present, using the same antiserum, the serum gastrin levels in our patient ranges from 3.800 to 5.780 ng/mL. In collaboration with Professor J. W. Rehfeld, we also measured serum level of progastrin, the precursor of gastrin that exerts trophic effects on epithelial and cancer cells but has no gastric acid stimulatory activity. Serum levels of progastrin was about 156 pM/L, about twice as high as in healthy controls (80 pM/L). As gastrinoma cell are equipped with CCK_B receptors, it is likely that this precursor together with gastrin are responsible for the cell proliferation and tumor growth. The release of progastrin by gastrinoma has been reported previously (27) and suggested to indicate poor prognosis. Anyway, our study confirms that gastrinoma is capable of releasing not only excessive amounts of gastrin but also some progastrin. This study also indicates that the prosttranslational processing of pre-progastrin to gastrin in gastrinoma cells is disordered and that some progastrin escaped into the circulation during this posttranslational process.

It is of interest that about twenty-five percent of gastrinoma patients have MEN I syndrome [6]. The primary sites of organ involvement in this autosomal-dominant genetic disorder include the parathyroid, pancreas, pituitary, and, less commonly, adrenal cortex and thyroid. In a large series by Ballard and colleagues [121] 87% of 85 patients with MEN I had involvement of the parathyroid glands, 81% had disorders of the endocrine pancreas, and 65% had pituitary involvement. More recently, Trump and colleagues [122] reported their findings in 220 patients with MEN I and observed different rates of organ system involvement, 64 with 95%, 41%, and 30% of patients having parathyroid, pancreatic, and pituitary neoplasms, respectively. Consistent with other reports, this later study also observed that parathyroid lesions were the first indication of this genetic disorder in 87% of patients. The clinical features of Z-E syndrome (ulcer complications, gastric or pancreatic surgery) account for the major morbidity and mortality related to MEN I. [123]. It is important to remember that the first clinical manifestation of MEN I may be Z-E syndrome. As noted by Benya and colleagues [124] up to one third of patients with MEN I and gastrinoma may present with signs and symptoms of hypergastrinemia without manifestation of any additional endocrinopathy. Based on this finding, these investigators suggested that patients with the presumptive diagnosis of sporadic Z-E syndrome should be monitored biochemically and, when feasible, genetically screened for evidence of MEN I. The genetic defect in patients with MEN I has been mapped to the long arm of chromosome 11 (11q11-q13) by analysis of restriction fragment length polymorphism in affected families [122,123]. In our patient no evidence what so ever was found to suggest the existence of MEN I and the diagnosis of gastrinoma or Z-E syndrome was established.

Symptoms and signs in patients with Z-E syndrome are primarily related to gastric acid hypersecretion and its consequences. Greater than 90% of gastrinoma patients develop ulcers in the upper gastrointestinal tract at some point during their disease [5,12]. Presenting ulcer symptoms are indistinguishable from those associated with benign peptic ulcer disease, but frequently they will be less responsive to standard therapy. As in benign peptic ulcer disease, ulcers in patients with Zollinger-

Ellison syndrome occur most frequently in the first portion of the duodenum (75%), and are usually solitary. However, ulcers in gastrinoma patients also may occur in the second, third, and fourth portions of the duodenum (14%), as well as in the jejunum (11%) [125]. The ulcers are usually less than 1 cm in diameter but can occasionally present as giant lesions. Peptic ulcer disease refractory to standard medical therapy, recurrent ulcers after prior gastric surgery, diarrhea in patients with ulcers, or peptic disease presenting with complications such as obstruction, perforation, or bleeding suggest a possible diagnosis of Z-E syndrome. All these changes including duodeno-jejunal ulcerations, diarrhea and complications, particularly bleeding were observed in our patients until almost complete gastrectomy was performed. Since that time periodic stomal ulcerations accompanied by occasional bleeding were recorded and treated with various anti-secretory drugs.

Diarrhea that in our patient preceded the diagnosis of Z-E syndrome and occurred in earlier period of the disease is considered to be multifactorial, but its dependence on acid hypersecretion is demonstrated by amelioration of symptoms upon continuous nasogastric suction or inhibition of acid secretion. [2]. Thus, the severe volume load represented by the acid, which can be secreted at the rate of several liters per day, can account for some of the diarrhea. An added feature of the diarrhea is steatorrhea and maldigestion [126] which results from the inactivity of pancreatic enzymes at the low pH of the duodenum caused by the excessive acid load. The acidic pH of the small bowel also may lead to damage of the intestinal mucosa, resulting in a sprue-like state with flattened intestinal villi and accompanying malabsorption [127]. Bile acids are poorly soluble in an acid milieu; thus, Zollinger-Ellison syndrome may result in decreased micelle formation and subsequent malabsorption of fat and lipid-soluble nutrients and vitamins.

Concerning the natural history of gastrinoma, Mignon et al. [128] proposed that that the prognosis depends upon 1). The size and location of tumor and its spread to the liver and bones; 2). The size and the location of primary tumor and its spread with hepatic and bone metastasis being the major determinants of death; 3). The resistance of the tumor to conservative therapy. Anyway the survival in our patient was a record long of 38 years when compared to recently described by Terada et al. [129] another longest survival amounting to 24 years and this could be attributed, at least in part, to patients' personal positive attitude to the treatment given, very good collaboration with therapist and excellent response to the treatment with Sandostatin Lar that was effective in the marked reduction in plasma gastrin level, gastric acid output and in tumor size.

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