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Regression of Type II Gastric Carcinoids in Multiple Endocrine Neoplasia Type 1 Patients with Zollinger-Ellison Syndrome after Surgical Excision of All Gastrinomas

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Abstract. Enterochromaffin-like (ECL) tumors are documented in patients with hypergastrinemia secondary to chronic atrophic gastritis or with Zollinger-Ellison syndrome and multiple endocrine neoplasia type 1 (ZES-MEN-1). In patients with ECL tumors and atrophic gastritis, normogastrinemia after antrectomy has resulted in resolution, regression, or stabilization of ECL tumors. The natural history of ECL tumors associated with ZES-MEN-1 following normalization of gastrin levels after gastrinoma resection has not been previously reported. The purpose of this study was to determine the course of ECL tumors in patients with ZES-MEN-1 following normalization of serum gastrin levels after gastrinoma resection. Two patients with ZES-MEN-1 had biopsy-proven ECL tumors on endoscopic evaluation. They then underwent surgical exploration that included distal pancreatectomy, enucleation of pancreatic head tumors, duodenotomy with excision of submucosal tumors, and peripancreatic lymphadenectomy. Gastric ECL tumors larger than 1.0 cm were locally excised. Patients underwent long-term follow-up with biochemical and endoscopic surveillance. Normogastrinemia was achieved and sustained following gastrinoma resection in two patients with ZES-MEN-1. Periodic endoscopic surveillance over a 6-year period showed complete resolution of the ECL tumors. The development of ECL tumors associated with ZES-MEN-1 is multifactorial. Studies identified a genetic influence on tumor growth with loss of heterozygosity at the MEN-1 gene locus in ECL tumors. The resolution of ECL tumors in ZES-MEN-1 patients who are normogastrinemic indicates that an elevated gastrin level is a primary initiator for development of these tumors. Therefore both genetic defects and hypergastrinemia are causative agents. Normalization of serum gastrin levels is critical for the prevention of aggressive forms of ECL tumors.

Enterochromaffin-like (ECL) tumors are primarily documented in patients with hypergastrinemia; they are secondary to chronic atrophic gastritis or are seen in patients with the Zollinger-Ellison syndrome (ZES) and multiple endocrine neoplasia type 1 (MEN-1) [1]. These endocrine cell neoplasms are frequently referred to as multiple gastric carcinoids in both conditions. Hyperplasia of the ECL cells, as well as tumors, develop primarily as the result of the trophic effect of chronic hypergastrinemia on all of the neuroendocrine cells of the proximal stomach.

A literature review of 224 ECL tumors found them to be associated with chronic atrophic gastritis in 79% of patients; 10% of patients had ZES, and 11% were sporadic [1]. The sporadic tumors were solitary, and they were larger and more biologically aggressive than those that are gastrin-dependent. Of patients with ZES, 92% had documented MEN-1. The incidence of ECL tumors in ZES-MEN-1 patients may be as high as 30%, compared to 5% in patients with chronic atrophic gastritis and hypergastrinemia [2–5]. Because of the rarity of ECL tumors in sporadic cases of ZES, a genetic factor related to the gene mutation has been considered an important contributing, if not primary, cause of their occurrence in MEN-1 patients.

In patients with ECL tumors, atrophic gastritis, and hypergastrinemia, normogastrinemia after antrectomy has resulted in resolution, regression, or stabilization of ECL tumors [6–8]. The natural history of ECL tumors in ZES-MEN-1 patients following normalization of gastrin levels after gastrinoma resection has not been previously reported. We report two patients with ZES-MEN-1 and ECL tumors who underwent operative treatment for their gastrinomas resulting in normalization of gastrin levels. We also document the effect on the remaining ECL tumors.

Patients and Methods

Two patients with ZES-MEN-1 had biopsy-proven ECL tumors on endoscopic evaluation. Endoscopic evaluation was performed for surveillance and diagnostic purposes. Smaller tumors were not completely excised because of their extent. Both patients then underwent surgical exploration that included distal pancreatectomy, enucleation of pancreatic head tumors, duodenotomy with excision of submucosal tumors, and peripancreatic lymphadenectomy. Gastric ECL tumors larger than 1.0 cm were locally excised. All patients were then followed biochemically and with endoscopic surveillance.

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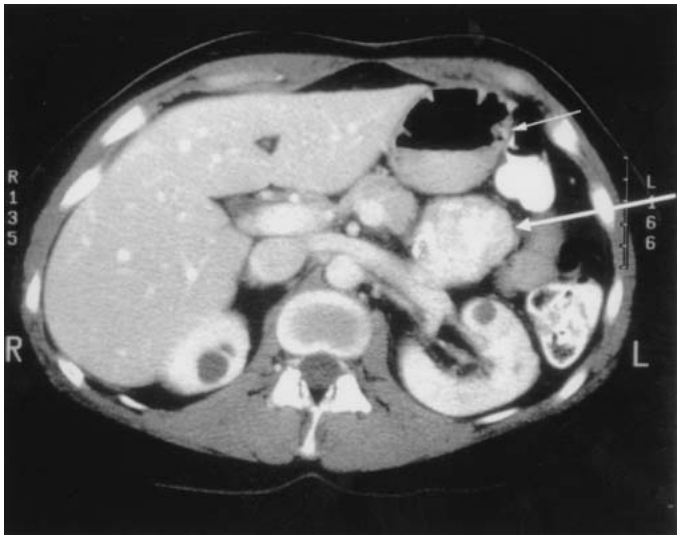

Fig. 1. Case 1. Abdominal computed tomography (CT) scan. Small arrow points to polypoid lesion [enterochromaffin-like (ECL) tumor] along the greater curvature of the stomach. Note the hypertrophic gastric mucosal folds typically seen in patients with Zollinger-Ellison syndrome. Large arrow points to 5.5 cm neuroendocrine tumor (insulinoma) arising from the pancreatic body.

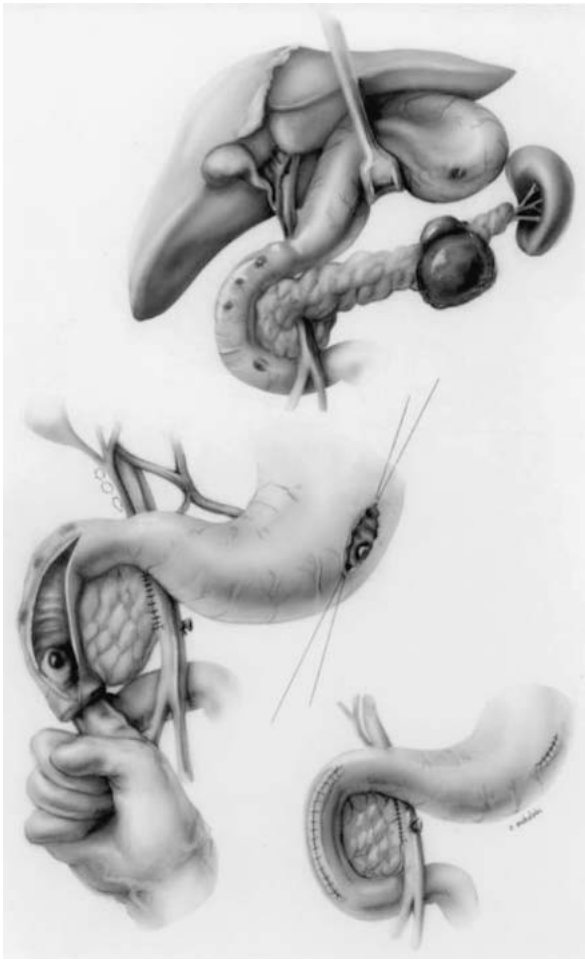

Fig. 2. Artist's rendition of operative findings in case 1 and the surgical procedures performed. The duodenal gastrinomas were neither seen nor palpated until the duodenum was opened. The operation included distal pancreatectomy and splenectomy, enucleation of a neuroendocrine tumor in the pancreatic head, duodenotomy, and excision of four submucosal gastrinomas. The two largest ECL tumors were excised through a small gastrotomy. A regional peripancreatic lymph node dissection was performed.

Results: Case Summaries

Case 1

A 39-year-old woman was admitted to the University of Michigan Hospital in August 1996 with hypercalcemia and symptomatic hypoglycemia. Two months prior to admission she became confused, and laboratory studies revealed a blood glucose level of 50 mg/dl and a serum calcium level of 11.7 mg/dl. Her fasting blood glucose was 50 mg/dl, the intact parathyroid hormone level (iPTH) was 826 pg/ml (10–65 pg/ml), and the prolactin level was 173 ng/ml (< 32 ng/ml). Magnetic resonance imaging (MRI) did not demonstrate a pituitary tumor. Increasing symptoms of hypoglycemia with blood glucose levels as low as 20 mg/dl and a diagnosis of MEN-1 prompted an urgent referral for treatment.

The patient had a history of nephrolithiasis, amenorrhea, and galactorrhea. She denied a history of diarrhea or peptic ulcer disease but had esophageal reflux symptoms for which she had been taking omeprazole daily during the past year. There was no family history of MEN-1.

The admission laboratory studies included the following: serum calcium 12.6 mg/dl, serum insulin 66 IU/ml, and blood glucose 20 mg/dl with an insulin/glucose ratio of 3.3. The serum gastrin was 1179 pg/ml (30–115 pg/ml). Serum glucagon (145 pg/ml) and somatostatin (170 pg/ml) were within the normal range. An abdominal computed tomography (CT) scan showed two pancreatic tumors in the body of the pancreas (5 × 5 cm and 2 × 2 cm), a normal liver, hypertrophic gastric rugae, and a 1.5 cm submucosal gastric lesion consistent with an ECL tumor (Fig. 1).

With a diagnosis of MEN-1 hyperparathyroidism (HPT), hyperinsulinism, and hypergastrinemia, she was taken to the operating room 2 days after admission. The initial procedure was subtotal parathyroidectomy and cervical thymectomy, excising all parathyroid tissue except a viable 60 mg remnant. In all, 8.8 g of hyperplastic parathyroid tissue was excised. During the abdominal exploration, distal pancreatectomy and splenectomy were performed. A 1 cm neuroendocrine tumor was enucleated from the head of the pancreas. Four neuroendocrine tumors, all less than 0.5 cm in diameter, were excised through a vertical duodenotomy. Regional lymph nodes were excised. Several tumors were palpable in the cardia of the stomach. The two largest, measuring 1.5 and 1.0 cm in diameter, respectively, were locally excised through a small gastrotomy (Fig. 2). Frozen section studies confirmed the diagnosis of neuroendocrine tumors and negative lymph node involvement. On immunohistochemical studies, the two large pancreatic tumors in the body stained positive for insulin, and the four tumors in the duodenum stained positive for gastrin. The gastric ECL tumors stained for neuron-specific enolase and chromogranin A.

The patient's postoperative course was uneventful, except for her serum calcium level reaching a nadir of 7.1 mg/dl on postoperative day (POD) 1. At this time the serum gastrin level was 317 pg/ml, and on POD 5 it was 216 pg/ml. Both of these levels were obtained while the patient was on intravenous H_2-blockade. Calcium levels were normalized by POD 6 with supplemental oral calcium

and vitamin D. Bromocriptine was started prior to discharge, and her prolactin level was 43 pg/ml within 2 weeks. An iPTH level at 3 weeks after operation was 32 pg/ml, and her serum calcium at this time was 9.7 mg/dl. The oral calcium was discontinued in April 1997, and all subsequent serum calcium levels have been within the normal range. At 6 months after operation, endoscopic examination with gastric biopsy showed evidence of some persistent neuroendocrine hyperplasia and small subcutaneous nodules. By July 1997 there were no ECL tumors present, and the mucosa appeared normal on endoscopy. Her serum gastrin level was normal at this time. Her most recent endoscopic evaluation, performed in September 2001, showed no evidence of recurrent disease. In March 2002 the patient remains asymptomatic.

Case 2

A 55-year-old woman was admitted to the University of Michigan Medical Center in February 1995 with a diagnosis of HPT and ZES. Her family history was strongly positive for the MEN-1 syndrome, with a sister having HPT and ZES (1992), a niece with HPT and a pituitary tumor (1994), and a nephew with HPT (1994). Although she had a vague history of intermittent "upset stomach," there was no history of diarrhea or proven peptic ulcer disease. She was on no medications. The patient had undergone a previous secretin stimulation test. At that time her baseline serum gastrin level was 200 pg/ml (normal < 100 pg/ml); it increased to 654 pg/ml at 2 minutes and 736 pg/ml at 5 minutes after secretin stimulation. Her pancreatic polypeptide level was 2090 pg/ml. The serum calcium levels ranged from 11.2 to 12.0 mg/dl and iPTH levels from 300 to 333 pg/ml (normal 10–65 pg/ml) during the previous 6 months. The serum prolactin level was elevated, at 50.4 ng/ml (normal 3.3–26.7 ng/ml). An endoscopic ultrasound scan revealed a 0.6 cm neuroendocrine tumor in the pancreatic neck and two submucosal lesions estimated to be 1.0 to 1.5 cm in diameter in the proximal cardia of the stomach, as well as multiple smaller submucosal lesions.

In February 1995 the patient underwent subtotal parathyroidectomy and cervical thymectomy. A 60-mg viable remnant of an inferior gland was preserved after excising 2.4 g of hyperplastic parathyroid tissue. Her serum calcium level reached a nadir of 6.1 mg/dl while receiving oral calcium and dihydrotachysterol (DHT) during the early postoperative period. An octreotide scan was obtained on POD 1. There were no foci of uptake in the pancreas, liver, or other locations. She was discharged from the hospital on POD 3.

The patient was readmitted the following month for pancreaticoduodenal exploration. At operation, several additional small neuroendocrine tumors were palpable in the pancreatic body and tail, and distal pancreatectomy was performed. The pancreatic head and uncinate process were normal to palpation. Intraoperative ultrasonography did not identify any pancreatic lesions. Three submucosal neuroendocrine tumors, each less than 0.5 cm, were locally excised from the second and third parts of the duodenum through a vertical duodenotomy. Regional peripancreatic and duodenal lymph nodes were negative on frozen section examination for metastatic disease. Two neuroendocrine tumors were locally excised from the gastric cardia through a small gastrotomy (Fig. 3). Immunohistochemical studies demonstrated positive staining for gastrin in the three duodenal tumors. The three pancreatic tumors ranged in size from 0.8 to 0.9 cm. Two of these tumors stained positive for glucagon, and one was focally positive for serotonin. The gastric neuroendocrine tumors stained negative for gastroenteric hormones. On POD 1, her serum gastrin was 48 pg/ml. She was discharged 11 days later without complications.

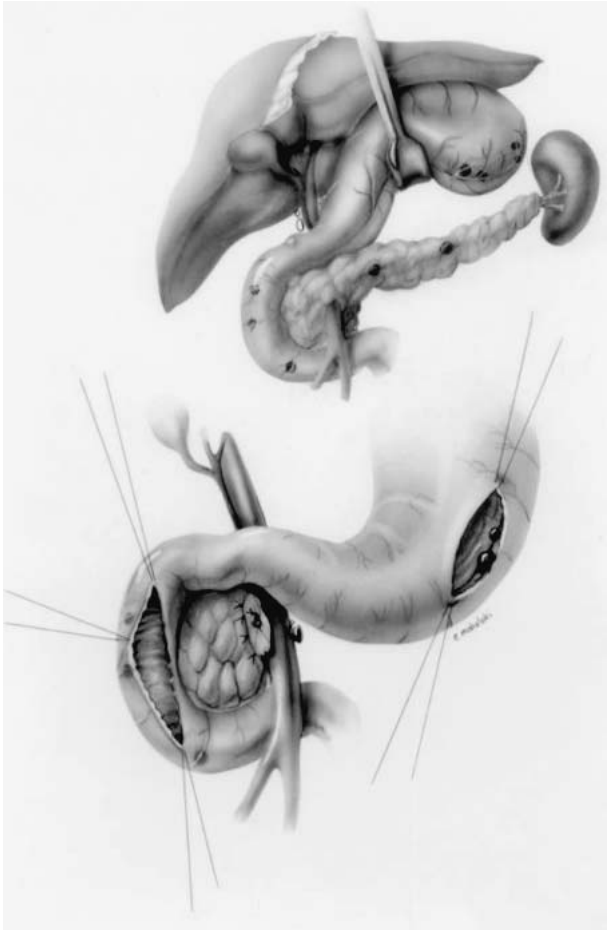

Fig. 3. Artist's rendition of operative findings in case 2 and the surgical procedures performed. There were no neuroendocrine tumors in the pancreatic head or uncinate process. Three submucosal duodenal gastrinomas were locally excised, being first palpated only after a duodenotomy. Regional lymph node dissection revealed no metastases. Two palpable ECL tumors were locally excised through a gastrotomy.

In August 1995, her serum calcium was 9.8 mg/dl and the IPTH was 18 mg/dl (normal 10–65 mg/dl). The DHT and oral calcium were discontinued. A serum gastrin level was 60 pg/ml. Endoscopy at this time revealed no gross tumors in the stomach, although random biopsies showed neuroendocrine cell hyperplasia staining positive for chromogranin A and focally for serotonin.

During the follow-up, the patient has continued to have normal serum gastrin levels. An endoscopic examination in July 1997 revealed no abnormalities except a 1 cm nodule in the cardia, which on biopsy was found to be lymphoid hyperplasia. No neuroendocrine tumors were noted on random biopsies. In May 1998, her serum gastrin level was 61 pg/ml (normal < 200 pg/ml), calcium level was 9.5 mg/dl (normal 8.4–10.2 mg/dl), iPTH was 2.8 pmol/L (1.3–7.6 pmol/L), and the prolactin level was 14.0 ng/ml (normal 3.0–32.0 ng/ml) on bromocriptine. However, in March 2002 her serum calcium was 10.9 mg/dl, and the iPTH was 77 mg/dl (normal 10–65 mg/dl). Her serum gastrin at this time was 89 pg/ml. Yearly endoscopic evaluations have revealed no evidence of recurrent ECL tumors.

Discussion

The first report of an ECL tumor in conjunction with ZES-MEN-1 was by Carney et al. in 1983 [9]. Since that time, approximately 50 ECL tumors in conjunction with confirmed ZES-MEN-1 have been reported in the English literature [1, 10–15]. The pathophysiology of the development of ECL tumors in patients with MEN-1 appears to be multifactorial, attributed to a combination of genetic and environmental influences.

Pathophysiology

Enterochromaffin-like tumors are also referred to as ECLomas, gastric argyrophilic carcinoids, and ECL cell carcinoids. The term "gastric carcinoid" may apply to cells originating from other endocrine cell types. However, most stem from ECL cells, which contain histamine and are located in the gastric oxyntic mucosa. The term "enterochromaffin-like" was first introduced by Hakanson et al. in 1967 and was used in reference to a specific cell type by Capella et al. in 1969 [16, 17]. There are seven endocrine cell types in human gastric mucosa, each of which secretes one main product. The ECL cells are the predominant endocrine cell, comprising 30% to 45% of the total endocrine cell mass in normal patients and 65% of the cell mass in patients with ZES [18–20]. It has been shown that gastrin principally stimulates ECL cells to secrete histamine, which in turn stimulates the parietal cells to secrete acid [21, 22]. It was previously thought that gastrin primarily stimulated the parietal cells directly to secrete acid. In addition to the secretory effects of gastrin on ECL cells there is also a trophic effect on these cells [23]. Although the hypergastrinemia can promote hypertrophy and hyperplasia of ECL cells, it has not been shown that hypergastrinemia can induce transformation of hyperplasia into ECL tumors [24]. However, many believe that the gastrin-induced trophic effect may be responsible for the development of ECL tumors. Hypertrophy and hyperplasia can be prevented with ECL gastrin-receptor blockade and decreased hypergastrinemia [25, 26]. Some investigators found that the duration of hypergastrinemia correlated with the amount of ECL cell proliferation [27, 28]. Others have reported no increase in ECL density over time in the presence of a stable gastrin level [20]. This difference may be secondary to variations in serum gastrin levels. In patients with normal or mildly elevated gastrin levels, there is no relation between serum gastrin levels and ECL cell density [29, 30]. In patients with more severe hypergastrinemia (serum gastrin > 400 pg/ml), there were significant increases in ECL cell density [31].

The ECL cell density has also been shown to differ between the sexes. ECL cell density is increased in women with ZES [2, 32], and women do not display reductions in the ECL density with aging, as is seen in men [30]. Interestingly, two-thirds of gastrin-dependent ECL tumors occur in women, and 80% of sporadic ECL tumors occur in men [1, 31].

The spectrum of ECL cell histopathology ranges from hyperplasia to invasive tumors. Rindi [33] described three distinct types of ECL tumors that depended on the patient's clinical history [30]. Type I tumors are associated with chronic atrophic gastritis and hypergastrinemia. Type II tumors are associated with hypertrophic gastropathy, as seen in ZES. Type I and II tumors are multicentric, are confined to the mucosa and submucosa, and rarely metastasize. The incidence of metastatic disease is 7% to 12% for gastrin-dependent (types I and II) ECL tumors [1]. If metastatic, they spread to local lymph nodes and rarely to the liver. Type III tumors are sporadic and solitary, and they occur in patients who have either normal or mild nonatrophic gastritis. They are the only type that is generally not associated with hypergastrinemia. Interestingly, a study of five patients with type III tumors found a 100% incidence of *Helicobacter pylori* infection [34]. The patients with the gastric carcinoid tumors were also found to have serum gastrin levels higher than those in patients with gastric and duodenal ulcers and associated *H. pylori* infections, yet lower than in those with chronic atrophic gastritis. The authors postulated that *H. pylori* infection may lead to mucosal atrophy and subsequent hypergastrinemia.

Sporadic tumors also tend to contain different endocrine cell types rather than ECL cells alone. Type III tumors are larger and more invasive, and the patients may have carcinoid symptoms. The median size of type III tumors is 2 cm in contrast to median sizes of 0.7 cm and 0.5 cm for type I and II tumors [1]. In a review of type 3 tumors, 80% had lymphoinvasion and 30% angioinvasion [31]. Metastatic disease was to the lymph nodes in 20% and to the liver in 40% to 52% of patients with type III tumors [1]. Until recently, type III tumors were the only type with tumor-related mortality.

Bordi et al. reported two patients with ZES-MEN-1 who died 4 months and 48 months, respectively, after diagnoses of aggressive gastric neuroendocrine tumors [12]. One patient had a large (16.0 × 4.5 cm) gastric carcinoid with multiple small gastric carcinoids and metastatic duodenal gastrinomas. The gastric carcinoid was metastatic to the liver and to multiple perigastric/periduodenal lymph nodes. Surprisingly, the large gastric carcinoid did not invade the muscularis propria. This patient had serum gastrin levels ranging from 800 to 20,000 pmol/L. A second MEN-1 patient with apparently normal gastrin levels developed a metastatic gastric neuroendocrine carcinoma in addition to multiple gastric carcinoids. This was the first report of a patient with MEN-1 who developed gastric carcinoids without ZES. Both of these patients' tumors had allelic losses at the MEN-1 gene locus in the 11q13 region.

In patients with ZES-MEN-1, ECL tumors may be included in the spectrum of endocrine neoplasias, or they may be secondary to other genetic influences in MEN-1. Cadiot et al. proposed that the MEN-1 gene may be a recessive tumor suppressor gene [35]. They found the loss of one allele of PYGM, a close probe to the MEN-1 locus, in ECL tumor DNA from a patient with ZES-MEN-1. This genetic influence may be the transforming factor needed to develop ECL tumors in patients with ZES-MEN-1.

Nearly all ZES-MEN-1 patients with ECL tumors have a history of primary HPT, as did our two patients. Hypercalcemia contributes to hypergastrinemia and may be related to the development of ECL tumors. One must also consider the converse—that ECL hyperplasia leads to increased histamine release, which can increase the amount of basic fibroblast growth factor secreted by the endocrine cells. This growth factor is a strong parathyroid mitogen and may be a significant factor in causing a high recurrence rate of hyperparathyroidism in MEN-1 patients [31].

The natural history of ECL tumors associated with hypergastrinemia is variable. Whereas some tumors progress to metastatic disease, others follow a more benign course. Harvey reported two patients with ECL tumors that regressed spontaneously [36]. Both patients had hypergastrinemia associated with chronic atrophic gastritis. We have previously reported two patients with atrophic gastritis, hypergastrinemia, and multiple ECL tumors [7]. Both patients had evidence of invasion through the submucosa. Both of

these patients underwent complete antrectomy and regional lymphadenectomy. One patient also had a solitary liver metastasis, which was resected; and the other had regional node involvement. Following normalization of the serum gastrin level after antrectomy, these patients were evaluated 4 to 6 months postoperatively. In one patient the ECL tumors had completely regressed, and in the other there were only multiple small foci of ECL tumors, which had disappeared at the time of subsequent endoscopic examinations. Neither patient has had a recurrence after 10 years of follow-up. This is in contrast to the report by Wangberg et al. of a patient with ECL tumors and atrophic gastritis that did not show any regression following antrectomy with normalization of gastrin levels [37]. In a review of five patients with ECL tumors and ZES-MEN-1, Lehy et al. noted that two of the patients required total gastrectomy and two others exhibited tumor progression [2].

Management

Endochromaffin-like tumors that are gastrin-dependent generally behave in a benign fashion. They can be managed using conservative surgery with endoscopic surveillance and endoscopic excision for tumors less than 1 cm. Larger tumors should be surgically excised. Antrectomy should be considered for patients with chronic atrophic gastritis. In contrast, gastrin-independent ECL tumors often require gastric resection and lymph node dissection for cure.

The ECL tumors that develop in ZES-MEN-1 have posed a management dilemma because total gastrectomy became obsolete in the treatment of ZES. Although antrectomy can be utilized in patients with atrophic gastritis to normalize serum gastrin, the procedure has no role in ZES patients. Endoscopic surveillance and excision of tumors 1.0 cm or smaller has been recommended. Surgical excision for tumors larger than 1 cm is currently recommended because the natural history of these larger tumors in ZES-MEN-1 patients is unknown. We are also unable to provide all patients with normal gastrin levels following surgical intervention and want to avoid a second operation to excise larger ECL tumors in a patient with postoperative hypergastrinemia. In the future, with early diagnosis and normalization of serum gastrin levels, these large tumors may be obsolete.

Tomassetti et al. reported resolution of ECL tumors in patients with MEN-1 who had decreased gastrin after long-term treatment (1 year) with somatostatic analogs [15]. Their results were consistent with effects of gastrin levels on gastric carcinoids. However, the question remained whether the somatostatin analogs had a direct effect on the gastric carcinoid tumors. Our results provide an answer. Because the patients were surgically treated to normalize the gastrin, no somatostatin analogs were given to our patients.

There have been no previous reports of surgical attempts to normalize the serum gastrin in ZES-MEN-1 patients who have concomitant ECL tumors. These two patients offered a unique opportunity to observe the effects of gastrin levels on multiple ECL tumors in MEN-1 patients, providing their operations were successful in eliminating the hypergastrinemia. We were hopeful that this could be accomplished by the multifaceted procedure that we have used for more than a decade in managing ZES-MEN-1 patients. Duodenotomy and either local or full-thickness wall excision of all gastrinomas from pylorus to jejunum and regional node dissection are essential components of the operation. Furthermore, any neuroendocrine tumors in the pancreatic head or uncinate process must be detected and enucleated. The distal pancreatectomy is needed to remove other potentially malignant or functional tumors as well. During the past 20 years, we have utilized this procedure in the surgical management of 36 ZES-MEN-1 patients who had no evidence of liver metastases preoperatively or at the time of exploration [38]. Duodenal gastrinomas were found in 89%, and they were multiple in more than half (56%) of all patients. Metastatic lymph nodes were excised in 37% of those with duodenal primary gastrinomas. Pancreatic gastrinomas were detected and enucleated in 36% of patients, nearly all from within the head or uncinate process of the pancreas. Most of these tumors were present with concomitant duodenal gastrinomas. Only four patients (14%) had only pancreatic gastrinomas as the source of their hypergastrinemia. Other neuroendocrine tumors were found in the pancreatic neck, body, or tail in all patients. Postoperatively, the serum gastrin levels were decreased in all patients, and basal levels normalized in 69%, as occurred in these two patients. All 36 of these patients had HPT and had undergone previous parathyroidectomy or subtotal parathyroidectomy/thymectomy in conjunction with their abdominal procedures (36%), as in case 1. All of these patients (except one who had slightly elevated serum calcium levels) are currently normocalcemic. This includes five patients who underwent reoperation for remnant recurrences during the 20-year period.

Normalization of serum gastrin resulting in decreased stimulation of ECL cells may be a factor in our relatively low recurrence rate of HPT in MEN-1 patients. Hyperplastic ECL cells have been shown to be a rich source of basic fibroblast growth factor, which is a strong parathyroid cell mitogen [39, 40]. In several reports of HPT in MEN-1 patients, the recurrence rates ranged from 30% to 61% after long-term follow-up after subtotal parathyroidectomy [41, 42]. In neither series was a consistent effort made to normalize the serum gastrin level in patients with ZES.

Conclusions

We are the first to report the natural history of ECL tumors in patients with ZES-MEN-1 (type 2 gastric carcinoids) whose gastrin levels were normalized following surgical management. The resolution of ECL tumors in ZES-MEN-1 patients who are normogastrinemic indicates that an elevated serum gastrin level is the primary initiator for the development of these tumors. The normalization of serum gastrin levels can prevent the development of aggressive, potentially life-threatening forms of ECL tumors.

Résumé. On a mis en évidence certaines tumeurs enterochromaffin-like (ECL) chez des patients porteurs d'hypergastrinémie secondaire à une gastrite atrophique chronique de l'estomac ou avec un syndrome de Zollinger-Ellison associé à une néoplasie multiple endocrine de type 1 (ZES-MEN-1). Chez les patients porteurs de tumeurs ECL et de gastrite atrophique, on peut voir une normalisation de la gastrinémie après antrectomie accompagnée soit de résolution, soit de régression ou de stabilisation des tumeurs ECL. A l'heure actuelle, l'histoire naturelle des tumeurs ECL dans les syndromes ZES-MEN-1 avec normalisation de la gastrinémie après résection n'est pas connue. Le but de cette étude a été de déterminer l'évolution des tumeurs ECL chez des patients porteurs de syndrome ZES-MEN-1 après normalisation des taux sériques de la gastrine après résection de leur gastrinome. On a fait la preuve de tumeur ECL chez deux patients porteurs de syndrome ZES-MEN-1, l'une par biopsie, l'autre par évaluation endoscopique. Ces patients ont eu une exploration chirurgicale comprenant une pancréatectomie distale, l'énucléation de(s) tumeur(s) de la tête du pancréas, une duodénectomie avec excision des tumeurs sous-muqueuses et une lymphadénectomie péripancréatique. Les tumeurs gastriques ECL plus grandes que 1.0 cm ont été excisées localement. Tous les patients ont été suivis à long terme par une surveillance biochimique et endoscopique. Une normalisation de la

gastrinémie a été obtenue et maintenue suivant la résection du gastrinome chez deux patients porteurs de syndrome ZES-MEN-1. Une surveillance périodique pendant six ans a montré une résolution complète des tumeurs ECL. Le développement des tumeurs ECL chez les patients porteurs de syndrome ZES-MEN-1 est multifactoriel. Des études ont pu identifier une influence génétique sur la croissance tumorale avec une perte d'hétérozygosité au niveau du locus génétique MEN-1 pour les tumeurs ECL. La résolution des tumeurs ECL chez des patients porteurs de syndrome ZES-MEN-1 qui sont normogastrinémiques indiquent qu'un taux élevé de gastrine est l'initiateur principal du développement de ces tumeurs. Ainsi, les déficits génétiques et l'hypergastrinémie en sont les causes. La normalisation des taux sériques de gastrine est critique dans la prévention des formes agressives des tumeurs ECL.

Resumen. Está totalmente demostrada la existencia de tumores enterocromafines (enterochromaffin-like) en pacientes con hipergastrinemia secundaria a una gastritis atrófica crónica o a un síndrome de Zollinger-Ellison o a neoplasias encodrinas múltiples tipo 1 (ZES-MEN-1). En pacientes con tumores ECL y gastritis atrófica, la normogastrinemia tras antrectomía determina la desaparición, regresión o estabilización de los tumores ECL. Se desconoce la evolución natural de los tumores ECL en pacientes con síndrome de ZES-MEN-1, una vez normalizada la gastrinemia, tras la resección del gastrinoma. El objetivo de este trabajo fue averiguar la evolución de los tumores ECL en pacientes con ZES-MEN-1, tras la normalización de los niveles séricos de gástrica, consecutiva a la resección del gastrinoma. Se presentan 2 pacientes con ZES-MEN-1; en uno se constató por biopsia endoscópica la existencia de tumores ECL. A continuación ambos casos fueron sometidos a una exploración quirúrgica que comprendía: una pancreatectomía distal, enucleación de los tumores de la cabeza del páncreas, duodenotomía y extirpación de los tumores submucosos y linfadenectomía peripancreática. Los tumores ECL gástricos de tamaño superior a 1.0 cm se extirparon "in situ". Los pacientes fueron sometidos a revisiones minuciosas durante largo tiempo, realizándose pruebas bioquímicas y estudios endoscópicos. Resultados: En los 2 pacientes con ZES-MEN-1 la resección del gastrinoma determinó una normogastrinemia mantenida y la vigilancia periódica endoscópica durante más de 6 años reveló la completa desaparición de los tumores ECL. El desarrollo de los tumores similares a los enterocromafines (ECL) en el ZES-MEN-1 tiene un origen multifactorial. Diversos estudios han demostrado que el crecimiento de los tumores ECL está vinculado a la pérdida de la heterocigosidad del gen MEN-1. La desaparición de tumores ECL en pacientes con ZES-MEN-1 que han normalizado su gastrinemia, demuestra que los niveles elevados de gastrina son los primeros y más precoces inductores del desarrollo de estos tumores. De ahí, que tanto las alteraciones genéticas como la hipergastrinemia hayan de ser consideradas como agentes causales. La normalización sérica de los niveles de gastrina es fundamental para prevenir el desarrollo de formas agresivas de tumores enterocromafines.

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