

Brief Report

TREATMENT OF TYPE II GASTRIC CARCINOID TUMORS WITH SOMATOSTATIN ANALOGUES

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GASTRIC carcinoid tumors are rare tumors that originate from gastric enterochromaffin-like cells in the oxyntic mucosa.¹ There are three types of gastric carcinoid tumors: type I is associated with chronic atrophic gastritis, type II develops in patients with combined multiple endocrine neoplasia type 1 and the Zollinger–Ellison syndrome, and type III is sporadic.¹ Although the pathogenesis of these tumors is not completely understood, hypergastrinemia has an important role in the development of types I and II.² The multiple endocrine neoplasia type 1 gene locus may be involved in type II gastric carcinoid tumors.^{3,4}

All three types are usually removed surgically or endoscopically, depending on the size of the tumors.^{5,6} Octreotide can control the hypergastrinemia and related growth of enterochromaffin-like cells in patients with hypergastrinemic atrophic gastritis.⁷ Moreover, regression of a type III gastric carcinoid tumor after octreotide treatment has been reported.⁸ Prompted by these findings, we treated three patients who had type II gastric carcinoid tumors with somatostatin analogues. The tumors regressed in all three patients.

CASE REPORTS

Patient 1

Patient 1 was a 50-year-old man with a family history of multiple endocrine neoplasia type 1 who was first seen by us in 1987 for a symptomatic duodenal ulcer (Table 1). On examination after an overnight fast, he had basal hypersecretion of gastric acid (rate of secretion, 37.4 mEq per hour; normal rate, <10) and hypergastrinemia (serum gastrin level, 720 pg per milliliter; normal range, 20 to 100). He also had a positive secretin test, indicating the presence of the Zollinger–Ellison syndrome; hyperparathyroidism; and renal stones. The ulcer was successfully treated with omeprazole. In 1993, a left-sided pancreatectomy was performed because of a nonfunctioning endocrine tumor of the pancreas.

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TABLE 1. CHRONOLOGIC ORDER OF THE CLINICAL FEATURES AND PROCEDURES IN THE THREE PATIENTS.

PATIENT 1, A 50-YEAR-OLD MAN	PATIENT 2, A 43-YEAR-OLD WOMAN	PATIENT 3, A 63-YEAR-OLD WOMAN
Zollinger–Ellison syndrome	Hyperparathyroidism	Zollinger–Ellison syndrome
Hyperparathyroidism	Zollinger–Ellison syndrome	Duodenal gastrinomas
Nonfunctioning endocrine tumor of the pancreas	Parathyroidectomy	Hyperparathyroidism
Left-sided pancreatectomy	Duodenal gastrinomas	Parathyroidectomy
Duodenal gastrinomas	Nonfunctioning endocrine tumors of the pancreas	Nonfunctioning endocrine tumor of the pancreas
Gastric carcinoid tumors	Gastric carcinoid tumors	Gastric carcinoid tumors

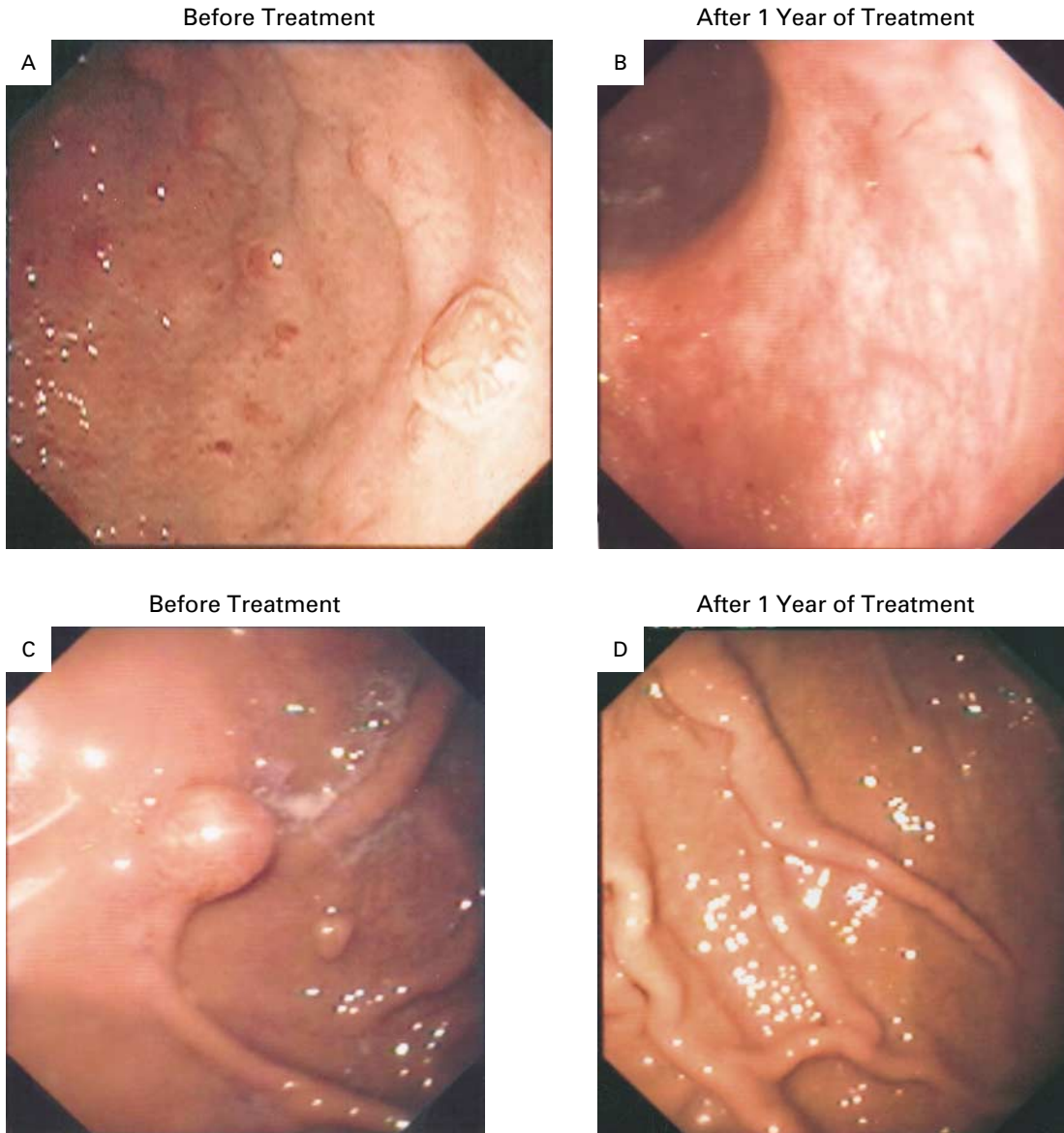
One year later, duodenal gastrinomas were diagnosed on the basis of endoscopic findings and histologic examination of multiple biopsy specimens, including immunocytochemical staining with antibodies against gastrin. Gastric carcinoid tumors were diagnosed in 1996 on the basis of endoscopic findings and immunocytochemical staining of gastric-biopsy specimens with antibodies against histamine and histidine decarboxylase.⁹ Gallstones were present before the beginning of treatment.

Patient 2

Patient 2 was a 43-year-old woman with a family history of multiple endocrine neoplasia type 1 (Table 1). She was first seen by us in 1992 for hyperparathyroidism and a symptomatic duodenal ulcer. In addition to the ulcer, she had basal hypersecretion of gastric acid (rate of secretion, 38 mEq per hour) and hypergastrinemia (serum gastrin level, 680 pg per milliliter) after fasting, and she had a positive secretin test. Treatment with omeprazole was started, and the ulcer symptoms disappeared. Also in 1992, she had undergone parathyroidectomy for parathyroid adenomas. In 1995, findings on gastroduodenal endoscopy and a histologic examination of multiple biopsy specimens indicated the presence of duodenal gastrinomas. In 1997, two small tumors (0.5 and 2.0 cm) were found in the body of the pancreas on computed tomographic (CT) scanning. Histologic examination showed that they were nonfunctioning endocrine tumors. In 1998, gastric carcinoid tumors were diagnosed on the basis of endoscopic findings and immunocytochemical examination of gastric-biopsy specimens.⁹

Patient 3

Patient 3 was a 63-year-old woman with a family history of multiple endocrine neoplasia type 1 (Table 1). She was first seen in 1988 when the Zollinger–Ellison syndrome was diagnosed on the basis of the presence of a symptomatic duodenal ulcer, basal hypersecretion of gastric acid (secretion rate, 30.2 mEq per hour) and hypergastrinemia (serum gastrin level, 1200 pg per milliliter) after fasting, and a positive secretin test. Endoscopic examination and histologic examination of multiple biopsy specimens revealed duodenal gastrinomas. The ulcer symptoms resolved with omeprazole therapy. In 1993, parathyroidectomy was performed because of multiple adenomas. In 1996, abdominal CT scanning showed one 1.8-cm nodule in the body of the pancreas. A biopsy of the nodule revealed that it was a nonfunctioning endocrine tumor. In 1998, gastric carcinoid tumors were identified by endoscopic examination and immunocytochemical examination of gastric-biopsy specimens.⁹



METHODS

The study protocol was approved by the review committee of our department, and all three patients gave written informed consent. We followed all three regularly for several years, with an average of one or two visits a year. At the time of the study, none of the patients had specific symptoms, and their only medication was omeprazole, at a dose of 20 mg per day.

Treatment with somatostatin analogues was initiated in September 1998 in Patients 1 and 2 and in April 1999 in Patient 3. The first two were treated with lanreotide (Ipstyl, Ipsen, Milan, Italy) at a dose of 30 mg intramuscularly every 10 days; the third was given the more recently introduced analogue octreotide acetate, long-acting, repeatable (Sandostatin LAR, Novartis, Milan, Italy) at a dose of 20 mg intramuscularly every 28 days. The doses used are those generally recommended for the treatment of symptomatic neuroendocrine tumors.¹⁰⁻¹²

The patients were evaluated clinically and endoscopically before

treatment was initiated, with follow-up assessments scheduled at six months and one year. At each assessment, serum gastrin levels were measured by radioimmunoassay (ICN Diagnostic Division, New York) in the morning after an overnight fast.

RESULTS

Before treatment with the somatostatin analogue was begun, gastroscopic examination revealed more than 30 gastric carcinoid tumors ranging from 3 to 10 mm in diameter in Patient 1 and 10 to 15 gastric carcinoid tumors ranging from 2 to 10 mm in diameter in Patients 2 and 3 (Fig. 1). The diagnosis of carcinoid tumors was confirmed by biopsy and immunocytochemical examination⁹ in all three patients before treatment was initiated. In all three patients,

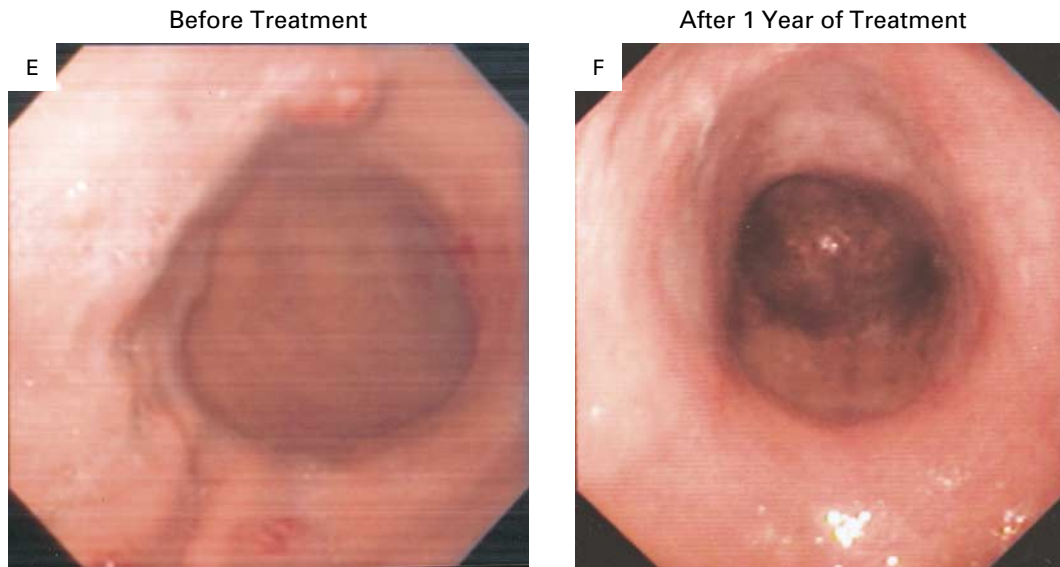


Figure 1. Endoscopic Appearance of Gastric Carcinoid Tumors at Various Sites before Treatment with a Somatostatin Analogue (Panels A, C, and E) and after One Year of Treatment (Panels B, D, and F).

Patient 1 had multiple carcinoid tumors on the posterior face of the corpus before lanreotide treatment (Panel A) and no evidence of tumors after one year of treatment (Panel B). Patient 2 had tumors on the anterior face of the upper corpus before lanreotide treatment (Panel C) and no evidence of tumors after one year of treatment (Panel D). Patient 3 had tumors at the lesser curve of the angulus before octreotide treatment (Panel E) and no evidence of tumors after one year of treatment (Panel F).

gastroscopic examination showed a reduction in the size and number of the carcinoid tumors after six months of treatment and complete disappearance of the tumors after one year (Fig. 1).

Measurement of serum gastrin levels just before treatment with the somatostatin analogues was begun showed that all three patients had very high levels: 10,500 pg per milliliter in the case of Patient 1, who had diffuse gastric carcinoid tumors; 1560 pg per milliliter in the case of Patient 2; and 1475 pg per milliliter in the case of Patient 3. In all three patients, the serum gastrin levels decreased progressively during treatment, reaching levels of 840, 110, and 80 pg per milliliter, respectively, after 12 months of treatment. None of the patients reported any adverse effects associated with treatment, but Patient 1 had an increase in the number and size of the gallbladder stones. We are continuing to treat the patients in an effort to determine whether treatment can eventually be reduced or stopped.

DISCUSSION

We found that gastric carcinoid tumors regressed in three patients who had the Zollinger–Ellison syndrome and a family history of multiple endocrine neoplasia type 1 after long-term treatment with somatostatin analogues. One of these patients had more than 30 tumors spread throughout the corpus and the fundus of the stomach, all of which disappeared after

one year of treatment. Before treatment, serum gastrin levels were elevated in all of the patients, and the patient with diffuse gastric carcinoid tumors had the highest levels. During treatment, serum gastrin levels decreased markedly. Other investigators have reported a similar decrease in serum gastrin levels after long-term treatment with octreotide in patients with the Zollinger–Ellison syndrome¹³ and in those with hypergastrinemic atrophic gastritis.⁷ Since hypergastrinemia is an important factor in the pathogenesis of gastric carcinoid tumors in patients with multiple endocrine neoplasia type 1 and the Zollinger–Ellison syndrome,^{1,2} it is likely that the disappearance of the tumors is related to the decrease in serum gastrin levels. In patients with type I gastric carcinoid tumors, the tumors regress rapidly after antrectomy and subsequent normalization of serum gastrin levels.¹⁴

Our findings do not exclude the possibility that the somatostatin analogues have a direct effect on the proliferation of enterochromaffin-like cells. Such an effect is also suggested by the finding that a type III gastric carcinoid tumor regressed after long-term administration of octreotide in a patient with normal gastrin levels.⁸ Enterochromaffin-like cells have a specific somatostatin receptor¹⁵ that belongs to subtype 2.^{16,17}

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