

BRIEF REPORT: A DUODENAL GASTRINOMA IN A PATIENT WITH DIARRHEA AND NORMAL SERUM GASTRIN CONCENTRATIONS

THOMAS ZIMMER, M.D., ULRICH STÖLZEL, M.D.,
MICHAEL BÄDER, M.D., UTE FETT, M.D.,
HANS-DIETER FOSS, M.D.,
ERNST-OTTO RIECKEN, M.D.,
JENS F. REHFELD, M.D.,
AND BERTRAM WIEDENMANN, M.D.

THE Zollinger–Ellison syndrome manifests itself in 90 to 95 percent of cases as severe peptic ulcer disease.¹ About half the time, the ulcer disease is associated with diarrhea, and in approximately 10 percent of patients, diarrhea is the only clinical manifestation.^{2,3} Basal serum gastrin concentrations are usually elevated in patients with this syndrome.⁴ Normal basal serum gastrin values with abnormal results of secretin tests have been reported, however, in a few patients.⁵⁻⁷

We describe a patient with a duodenal gastrinoma, a two-year history of diarrhea, and no peptic ulcer disease. The patient had persistently normal serum gastrin concentrations, but abnormal results of a secretin test and increased serum concentrations of the total progastrin product.

CASE REPORT

A 61-year-old man was admitted to the hospital in February 1993 with a two-year history of diarrhea (8 to 10 watery stools per day) and episodes of epigastric pain, but no weight loss. Before this admission, upper and lower gastrointestinal endoscopy, as well as biopsies and an extensive search for infections and parasitic organisms, had been performed. No abnormalities had been found. Treatment with pancreatin, loperamide, and cimetidine by the referring physician had had no effect on the diarrhea.

On admission, the stool weight was 1010 g per day; the stool contained normal amounts of fat (6.7 g per day) and chymotrypsin (17.5 U per gram of stool weight). The concentrations of hemoglobin and of serum creatinine, total bilirubin, alkaline phosphatase, aminotransferases, total protein, calcium, and phosphorus were normal, as were the white-cell count and the results of serum protein electrophoresis. Additional laboratory tests, such as those for serum vitamin B₁₂, folic acid, thyroid hormones, thyrotropin, gastrin (on three occasions), vasoactive intestinal peptide, and serotonin and for urinary 5-hydroxyindoleacetic acid, were normal, as were the results of tests for malabsorption, including a Schilling test and breath tests for D-xylose, and H₂-lactose, H₂-lactulose, and H₂-glucose. Transabdominal ultrasonography, computed tomography of the abdomen, radiographic examination of the small intestine, and colonoscopy, including histologic examination of biopsy specimens, were also normal. Endoscopy of the upper gastrointestinal tract showed prominent duodenal mucosal folds. Histologic examination of duodenal-biopsy specimens showed shortening of the villi, with moderate infiltration by inflammatory cells. Celiac disease was suspected, and the patient began to follow a gluten-free diet.

The patient was sent home in March 1993 and readmitted in October 1993. Despite a gluten-free diet, diarrhea and histologic abnormalities on subsequent duodenal biopsies persisted. Parenteral nutri-

tion was started. Nevertheless, the stool weight was 1070 g per day, and the fat and chymotrypsin content was again found to be normal, indicating secretory diarrhea. Basal serum gastrin concentrations were normal on three occasions (20, 32, and 46 pg per milliliter [10, 16, and 23 pmol per liter]; normal, <150 pg per milliliter [75 pmol per liter]) (Diagnostic Products, Los Angeles). Serum carboxyamidated gastrin was 16 pmol per liter, and the total progastrin product was 58 pmol per liter (this value is normally similar to the concentration of carboxyamidated gastrin).^{8,9} The total progastrin product was measured by "processing-independent analysis," with the use of an antibody (8017) that is specific for the N terminal of human gastrin-17.^{8,9} The processing-independent analysis used a radioimmunoassay directed against an epitope on progastrin, which is neither cleaved nor otherwise changed during normal progastrin processing. If the sample is cleaved with trypsin before measurement, the epitope becomes fully exposed for antibody binding in progastrin and less processed intermediates. Accurate measurement of the epitope irrespective of the degree of progastrin processing is important because the degree of prohormone processing in tumors varies considerably.

A secretin-injection test was performed, and the results were consistent with the diagnosis of gastrinoma (Fig. 1). The test entailed the intravenous infusion of 2 U of secretin (Sekretolin, Hoechst AG, Frankfurt, Germany) per kilogram of body weight in 10 ml of 0.9 percent sodium chloride over a period of 30 seconds. An abnormal result was defined as an increase in the serum gastrin level of more than 200 pg per milliliter (100 pmol per liter). Gastrin was measured in serum samples obtained before injection and several times over a period of 30 minutes. In support of the diagnosis, 24-hour intragastric pH monitoring showed pH values consistently below 3 (57 percent of the 24-hour pH values were below 2). After the gastrinoma was diagnosed, treatment with omeprazole — 40 mg taken orally twice a day — was begun. The stool weight decreased to 370 g per day.

Computed tomographic scanning and magnetic resonance imaging of the upper abdomen (including the pancreatic region), transabdominal ultrasonography, upper gastrointestinal endoscopy, and celiac angiography showed no evidence of a gastrinoma. Endoscopic ultrasonography, performed with a mechanical sector scanner (model GF-UM 20, Olympus, Hamburg, Germany), detected a tumor 10 by 8 mm in diameter in the submucosal layer of the anterior wall of the duodenal bulb immediately distal to the pylorus (Fig. 2A). Five previous endoscopies, performed with conventional endoscopes by other physicians, had not suggested a tumor in this region. After endoscopic ultrasonography, endoscopy was repeated with a pediatric endoscope (Olympus GIF-PQ 20), which could be inverted in the duodenal bulb. This showed a submucosal tumor measuring about 8 by 5 mm (Fig. 2B). Somatostatin-receptor scintigraphy with ¹¹¹In-

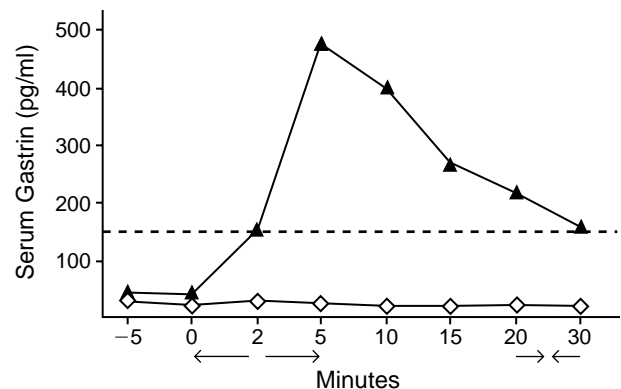


Figure 1. Serum Gastrin Concentrations before and after the Intravenous Injection of Secretin (2 U per Kilogram of Body Weight).

The test was performed before (▲) and 12 months after (◇) excision of the gastrinoma. The broken line indicates the upper limit of normal values for serum gastrin concentration. The scale for the numbers of minutes has been expanded (← →) between 0 and 5 and compressed (→ ←) between 20 and 30. To convert values for serum gastrin to picomoles per liter, multiply by 0.5.

From the Departments of Gastroenterology (T.Z., U.S., E.-O.R., B.W.), Nuclear Medicine (M.B., U.F.), and Pathology (H.-D.F.), Klinikum Benjamin Franklin, Free University of Berlin, Berlin, Germany; and the Department of Clinical Biochemistry, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark (J.F.R.). Address reprint requests to Dr. Wiedenmann at Abt. Gastroenterologie, Universitätsklinikum Benjamin Franklin, Freie Universität Berlin, Hindenburgdamm 30, 12200 Berlin, Germany.

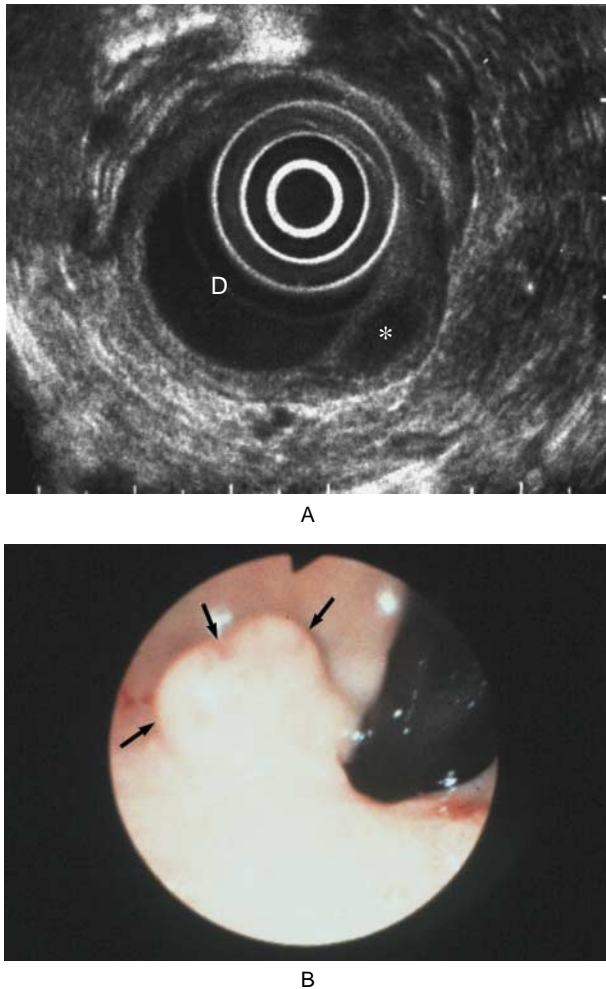


Figure 2. Endosonographic and Endoscopic Images of the Gastrinoma.

Panel A shows an endosonographic image of the gastrinoma seen as a hypoechoic mass 8 by 10 mm in diameter (asterisk), located within the submucosal layer of the duodenal bulb (D). In Panel B, the endoscopic image shows the gastrinoma as a submucosal tumor (arrows).

labeled pentetreotide revealed an accumulation of the radioligand projecting toward the region of the duodenum (Fig. 3).

At laparotomy in November 1993, a tumor measuring 11 by 9 by 5 mm was completely excised from the anterior part of the duodenal wall. The tumor was also detected during surgery by palpation and endoscopic transillumination, but not by ultrasound. Histologic examination showed a predominantly trabecular growth pattern, with some microcystic structures (Fig. 4A). The tumor cells had rather uniform nuclei and moderate-to-abundant, pale-staining cytoplasm. Mitoses were rare. Immunohistologic analyses revealed expression of chromogranin A, synaptophysin, neuron-specific enolase, and gastrin in the majority of tumor cells (Fig. 4B). Serotonin was seen in approximately 50 percent of tumor cells.

As of May 1995, the patient was free of symptoms. Results of a secretin test performed one year after surgery were normal (Fig. 1). Repeated studies — computed tomographic scanning, transabdominal and endoscopic ultrasonography, and endoscopy — also revealed no abnormalities.

DISCUSSION

Gastrinoma is often suspected when patients have extensive peptic ulcer disease or ulcers with unusual localization.¹ Diarrhea is an additional manifestation

about half the time. Diarrhea is the only clinical manifestation in approximately 10 percent of patients with gastrinomas and may precede peptic ulcer disease by several years.^{2,3} Large amounts of hydrochloric acid appear to be the chief cause of diarrhea. Diarrhea ceases after the removal of the acid by nasogastric suction, gastrectomy, or treatment with H₂-blockers or omeprazole. Mucosal changes in the small intestine, such as denuded villi and infiltration of the lamina propria by polymorphonuclear leukocytes and eosinophils, combined with broader and stunted villi, are believed to be directly caused by acid.¹⁰ In our patient, diarrhea ceased after omeprazole treatment, and the duodenal mucosa was normal on histologic examination after the gastrinoma was excised. Hypersecretion of gastric acid in patients with normal basal gastrin levels may be induced by small bioactive gastrin fragments, which are not recognized by conventional radioimmunoassays, as well as by other peptides that have not yet been identified.¹¹ Progastrins do not stimulate the secretion of gastric acid.

An elevated serum gastrin concentration is a sensitive indicator of the presence of a gastrinoma.¹² In patients with gastrinoma, basal serum gastrin concentrations are usually 3 to 100 times above normal.⁴ Elevated gastrin concentrations, however, are not specific for gastrinomas,⁴ and provocative tests are required to distinguish patients with gastrinoma from those with other causes of hypergastrinemia.¹³ The secretin-injection test is usually specific for gastrinomas,^{4,13} but false positive results have been reported in a few patients with hypergastrinemia related to achlorhydria.¹⁴ Normal basal serum concentrations of gastrin usually rule out the diagnosis of a gastrinoma, with rare exceptions.⁵⁻⁷

Once a gastrinoma has been diagnosed, in many in-

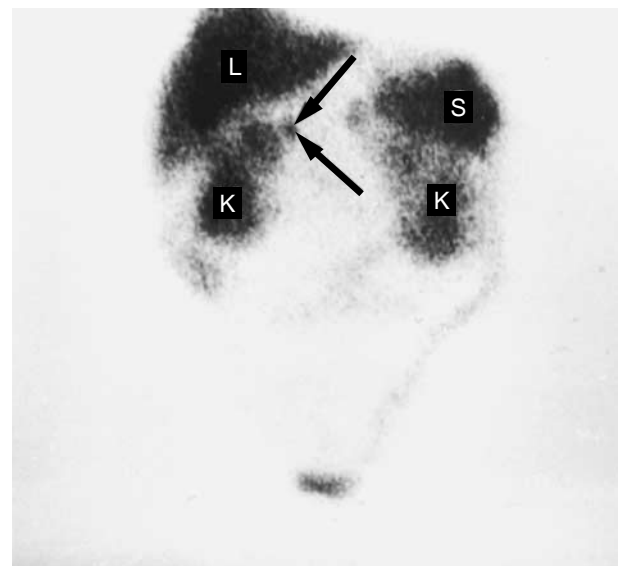
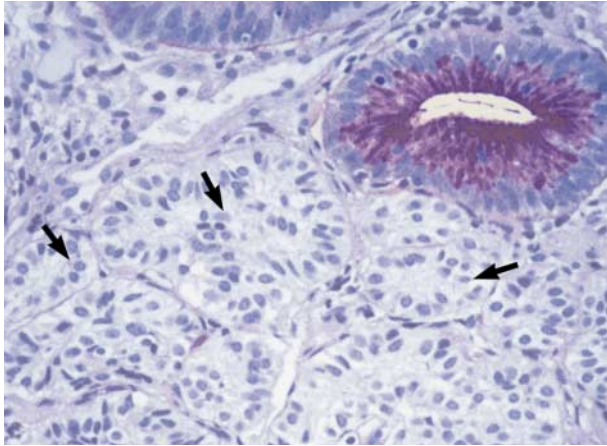
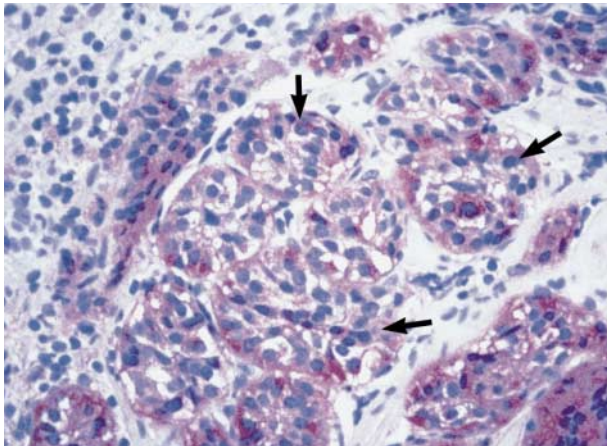


Figure 3. Image of the Gastrinoma Obtained by Somatostatin-Receptor Scintigraphy.

A small area of radioactivity superimposed over the duodenum is visible (arrows). Physiologic uptake is also visible in the liver (L), spleen (S), and kidneys (K).



A



B

Figure 4. Photomicrographs of Excised Gastrinoma Tissue.

Panel A shows a trabecular tumor with uniform nuclei and moderate-to-abundant, pale-staining cytoplasm (periodic acid-Schiff, $\times 400$). In Panel B, immunohistologic staining with gastrin antibody of the excised gastrinoma shows the presence of gastrin (dark-red areas) in the majority of tumor cells ($\times 600$). Arrows indicate tumor cells.

stances it is still not possible to pinpoint the location of the primary tumor preoperatively. Imaging procedures, such as endoscopic ultrasonography and somatostatin-receptor scintigraphy, have improved the ability to locate neuroendocrine tumors, especially gastrinomas and insulinomas; the location of 82 to 100 percent of these tumors can now be identified preoperatively.¹⁵⁻¹⁹

Our patient had a duodenal gastrinoma, with diarrhea as the only clinical manifestation, and persistently

normal serum gastrin concentrations. Two of three other patients with the Zollinger-Ellison syndrome and repeatedly normal serum gastrin concentrations had abnormal secretin tests,⁵⁻⁷ as did our patient. All three other patients had peptic ulcer disease; two had primary tumors within the duodenal wall,^{5,6} and the third had a pancreatic tumor.⁷ Although such patients are rare, our findings call attention to an unusual presentation of a gastrinoma and emphasize the importance of diagnostic vigilance.

REFERENCES

1. Ellison EH, Wilson SD. The Zollinger-Ellison syndrome: re-appraisal and evaluation of 260 registered cases. *Ann Surg* 1964;160:512-30.
2. Bonfils S, Landor JH, Mignon M, Hervo P. Results of surgical management in 92 consecutive patients with Zollinger-Ellison syndrome. *Ann Surg* 1981;194:692-7.
3. Jensen RT, Gardner JD. Gastrinoma. In: Go VLW, Dimagno EP, Gardner JD, Leibel E, Reber H, Scheele GA, eds. *The pancreas: biology, pathobiology and diseases*. 2nd ed. New York: Raven Press, 1993:931-78.
4. McGuigan JE, Wolfe MM. Secretin injection test in the diagnosis of gastrinoma. *Gastroenterology* 1980;79:1324-31.
5. Wolfe MM, Jain DK, Edgerton JR. Zollinger-Ellison syndrome associated with persistently normal fasting serum gastrin concentrations. *Ann Intern Med* 1985;103:215-7.
6. Deveney CW, Deveney KS, Jaffe BM, Jones RS, Way LW. Use of calcium and secretin in the diagnosis of gastrinoma (Zollinger-Ellison syndrome). *Ann Intern Med* 1977;87:680-6.
7. Mee AS, Ismail S, Bornman PC, Marks IN. Changing concepts in the presentation, diagnosis and management of the Zollinger-Ellison syndrome. *Q J Med* 1983;52:256-67.
8. Bardram L, Rehfeld JF. Processing-independent radioimmunoanalysis: a general analytical principle applied to progastrin and its products. *Anal Biochem* 1988;175:537-43.
9. Bardram L. Progastrin in serum from Zollinger-Ellison patients: an indicator of malignancy? *Gastroenterology* 1990;98:1420-6.
10. Shimoda SS, Saunders DR, Rubin CE. The Zollinger-Ellison syndrome with steatorrhea. II. The mechanisms of fat and vitamin B₁₂ malabsorption. *Gastroenterology* 1968;55:705-23.
11. Sloas DD, Hirschowitz BI, Chey WY. A nogastrin malignant ampullary tumor causing gastric acid and pepsin hypersecretion: a case report. *J Clin Gastroenterol* 1990;12:573-8.
12. McGuigan JE, Trudeau WL. Immunochemical measurement of elevated levels of gastrin in the serum of patients with pancreatic tumors of the Zollinger-Ellison variety. *N Engl J Med* 1968;278:1308-13.
13. Frucht H, Howard JM, Slaff JI, et al. Secretin and calcium provocative tests in the Zollinger-Ellison Syndrome: a prospective study. *Ann Intern Med* 1989;111:713-22.
14. Feldman M, Schiller LR, Walsh JH, Fordtran JS, Richardson CT. Positive intravenous secretin test in patients with achlorhydria-related hypergastrinemia. *Gastroenterology* 1987;93:59-62.
15. Rösch T, Lightdale CJ, Botet JF, et al. Localization of pancreatic endocrine tumors by endoscopic ultrasonography. *N Engl J Med* 1992;326:1721-6.
16. Zimmer T, Ziegler K, Bäder M, et al. Localisation of neuroendocrine tumours of the upper gastrointestinal tract. *Gut* 1994;35:471-5.
17. Lamberts SWJ, Bakker WH, Reubi J-C, Krenning EP. Somatostatin-receptor imaging in the localization of endocrine tumors. *N Engl J Med* 1990;323:1246-9.
18. Zimmer T, Ziegler K, Liehr R-M, Stölzel U, Riecken EO, Wiedenmann B. Endosonography of neuroendocrine tumors of the stomach, duodenum, and pancreas. *Ann N Y Acad Sci* 1994;733:425-36.
19. Zimmer T, Stölzel U, Liehr R-M, et al. Somatostatinrezeptor-Szintigraphie und endoskopischer Ultraschall zur Diagnostik von Insulinomen und Gastrinomen. *Dtsch Med Wochenschr* 1995;120:87-93.