Primary hepatic gastrinoma: Report of a case and review of literature

Konstantinos Tsalis, Georgios Vrakas, Stergios Vradelis, Abraham Dimoulas, Maria Pilavaki, Stiliani Papaemmanouil, Anastasia Micheli, Charalampos Lazarides, Georgios Kartalis

INTRODUCTION

Zollinger-ellison syndrome (ZES) was first described in 1955 as a constellation of findings, which included: refractory peptic ulceration, gastric acid hypersecretion, diarrhea, and a non-β islet cell tumor of the pancreas. It was later confirmed that the islet cell tumor secreted peptide hormone gastrin and was the cause of ZES. The vast majority of gastrinomas are found in what has been referred to as the gastrinoma triangle. This is an imaginary anatomic region defined by the confluence of cystic hepatic duct junction superiorly, the junction of the neck and body of pancreas medially and the junction of the 2nd and 3rd part of the duodenum inferiorly. Gastrinomas that arise away from this triangle are very rare.

We present the case of a 56 year old patient with hypergastrinemia who underwent exploratory laparotomy...
and curative resection for primary hepatic gastrinoma.

CASE REPORT

A 56-year-old male was referred because of a history of recurrent upper gastrointestinal haemorrhage and a high serum gastrin level. The patient had persistent heartburn and acid regurgitation for 16 years. Several oesophago-gastroduodenoscopies (OGDs) revealed diffuse erosive oesophagitis and initially the presence of *Helicobacter pylori* (*H. pylori*). At the age of 46, after various eradication regimens against *H. pylori*, he was subjected to truncal vagotomy and Billroth II gastrojejunostomy followed by long term prophylactic antisecretory treatment. At that time, gastrin levels were measured at 375 pg/mL (upper normal limit 80 pg/mL) and the Octreoscan test was negative for gastrinoma. Therefore, his hypergastrinemia was attributed to his antisecretory treatment. At the age of 52 he had the first episode of upper gastrointestinal bleeding. OGD indicated four anastomotic ulcers plus a bleeding duodenal ulcer with negative IgG antibodies against *H. pylori* and negative Campylobacter-like organism test. Three years later he had a new episode of upper gastrointestinal bleeding that necessitated transfusion of 4 blood units. Last year his gastrin levels were measured at 1688 pg/mL, which are pathognomonic of gastrinoma.

Abdominal ultrasonography (US) revealed hepatic steatosis and a hypoechoic lesion in the left liver lobe. No other abdominal pathological condition was found. A computed tomography (CT) scan of the abdomen showed intrahepatic dilatation of the biliary tree in the left liver lobe. No lesion was detected. Similarly, the magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) that followed (Figure 1) revealed dilatation of the left lobe biliary tree, but still no lesion was evident. The endoscopic ultrasound (EUS) did not reveal any tumor in the pancreas, duodenum or neighboring lymph nodes. The somatostatin receptor scintigraphy (SRS) using $^{111}$In-DTPA-D-Phe-octreotide (Octreoscan®, Mallinkrodt, Petten, The Netherlands) indicated increased uptake of radiotracer close to the left liver lobe (Figure 2).

The patient underwent an exploratory laparotomy. We explored the gastrinoma triangle using intraoperative ultrasound (IOUS) and specimens from the head of the pancreas and from the neighboring lymph nodes were sent for frozen sectioning. All came back normal. However a small lesion (~1 cm) was palpable at the left liver lobe (segment III) and therefore we performed a left lobectomy (segments II and III).

Pathological analysis showed compact groups of large neoplastic cells with granular eosinophilic cytoplasm and large atypical nuclei with inclusions. The cells were arranged in an insular pattern with angiofibrotic septa. Figure 3A Immunohistochemical (IHC) stains were positive for tumor markers such as chromogranin A (Figure 3B), cytokeratin (AE1-AE3), Neuron Specific Enolase (NSE), synaptophysin, gastrin (Figure 3C) and HepPar1. Proliferative activity was estimated with 15% Ki67-positive tumor cell nuclei (Figure 3D). The final diagnosis was a neuroendocrine tumor that fell in the gastrinoma category.

Twenty months postoperatively, the patient is asymptomatic and his blood gastrin levels remain within the normal range (19 pg/mL).

DISCUSSION

Gastrin-producing tumors are the most frequent pancreatic endocrine tumors, with an incidence of 0.5-1.5 new cases/10⁶ people/yr⁴ and are responsible for the ZES. More than 80% of gastrinomas are located in the gastrinoma triangle⁵. The vast majority of tumors are found in this pancreatic head-duodenal area, mainly in the duodenal submucosa (40%-50%), the head of the pancreas (30%-50%) or in the neighboring lymph nodes (19%)⁶. Ectopic gastrinomas are rare (< 5%) and have been reported in the stomach, ovaries, omentum, kidneys, lymph nodes, jejunum, esophagus, extrahepatic biliary tree, and liver⁷-¹⁶. The latter has been reported in fewer than 20 cases¹⁶-¹⁷. As the liver is a very common site of metastases from gastrinoma, the differential diagnosis of primary hepatic gastrinomas can be difficult. Primary hepatic
Gastrinomas seem to occur in slightly younger patients compared to patients with other ZES tumors, show a predilection for male patients and have not been associated with multiple endocrine neoplasia type 1 (MEN-1). In approximately 75% of patients with ZES a single tumor (sporadic gastrinoma) is responsible for their symptoms, whereas in 25% of patients diagnosed with ZES, patients will have gastrinomas (often multiple) in the setting of the MEN-1 syndrome.

To make the diagnosis of gastrinoma a high index of suspicion is required. Findings may include recurrent H. pylori-negative peptic ulcers or peptic ulcers associated with complications (bleeding, perforation), chronic diarrhea, ulcers at a young age, family history of ulcers or MEN-1 syndrome.

Gastrinomas can have either a benign or malignant course, but even those that are malignant seem to be slow-growing tumors. Approximately 65% of gastrinomas are malignant and up to 30%-40% of patients will have evident metastatic disease at initial presentation. Malignancy cannot be established cytologically, but is determined by invasion of contiguous structures, the presence of vascular or lymphatic invasion, or most definitively by the presence of metastases at various locations, including lymph nodes, liver, and bone.

CT scan, MRI, and US are widely used during the initial evaluation and are excellent for visualization of larger tumors (> 1-2cm) and metastatic disease. OGD and EUS are often used to assess the upper gastrointestinal tract with pancreas and biliary tree. In recent years, the Octreoscan/SRS has successfully localized neuroendocrine tumors (primary or nodal metastases) in up to 78%-86% of cases, and is quickly becoming the imaging modality of choice for the diagnosis of patients with suspected gastrinomas, and, in our opinion, it should always be requested. Selective arterial secretin injection with hepatic vein sampling for gastrin, as described by Imamura et al., is helpful in regionalizing disease to the gastrinoma triangle or pancreatic body/tail, especially preoperatively. However, imaging studies often detect regional nodal disease rather than the primary itself, although the location of regional disease can often lead the surgeon to the primary site (e.g. duodenum). The IOUS is a modality that can assist the surgeon to detect a small sized lesion, as current transducer resolution permits the detection of 2 mm lesions.

At the time of diagnosis our patient presented with symptoms suggestive of severe peptic ulcer disease due to gastric hyperacidity, along with extremely high serum levels of gastrin (> 1000 pg/mL), which are almost pathognomonic of the gastrinoma syndrome. A careful search for MEN-1 was performed, as its presence would have changed the therapeutic approach. Exhaustive preoperative and intraoperative imaging and also careful surgical exploration of the duodenum and pancreas failed to identify the primary tumor.

Surgical resection is the treatment of choice and is the only chance for cure with a reported respectability rate up to 86% in the literature, and eugastrinemia in up to 60%.

Figure 3 Pathological and immunohistochemical staining images. A: Hematoxylin and Eosin stain (×200); B: Chromogranin A+ (×200); C: Gastrin+ (×200); D: Ki67 15% (×200).
post-operatively, 40% at 5 years, and 34% at 10 years[24-26]. Norton et al recommend surgical exploration of all ZES patients with resectable and sporadic disease as it has been shown to increase overall disease-related survival[27]. Adjuvant therapy following complete resection (R0) provides no survival benefit. Orthotopic liver transplantation is an option when the locoregional disease is controlled[6,28].

Alternative therapies such as radiofrequency ablation, chemotherapy (doxorubicin, streptozocin, 5-fluourouracil), interferon, transplantation, and angiographic chemoembolization can be utilized, when there is no place for surgery due to diffuse disease or medical comorbidities[6,7,25,26,28]. Although chemotherapy can suppress progression of disease, gastrinomas can be resistant to conventional therapy with limited availability for second line treatment options. This has sparked interest in the use of molecular targeted therapy, utilizing VEGF, mTOR, and tyrosine kinase inhibitors[6,28]. Recently, treatment strategies include the use of peptide inhibitors that have been designed with a high affinity for receptors that may be overexpressed by neuroendocrine tumors. Radiolabeled somatostatin analogs (octreotide) are being employed for both imaging and radiotherapy[25].

In conclusion, primary hepatic gastrinomas are immensely rare. Diagnosis requires a high index of clinical suspicion and the flawless cooperation of many specialties including gastroenterologists, radiologists, surgeons and pathologists. The numbers are small and follow-up is limited. There is no standardized surgical approach when dealing with extrapancreatic extraintestinal gastrinomas. Surgical resection remains the only chance for cure.

REFERENCES

1 Zollinger RM, Ellison EH. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. 1955; CA Cancer J Clin 1989; 39: 231-247
2 Norton JA, Doppman JL, Collen MJ, Harmon JW, Maton PN, Gardner JD, Jensen RT. Prospective study of gastrinoma localization and resection in patients with Zollinger-Ellison syndrome. Ann Surg 1986; 204: 468-79
3 Wu PC, Alexander HR, Bartlett DL, Doppman JL, Fraker DL, Norton JA, Gibril F, Fogt F, Jensen RT. A prospective analysis of the frequency, location, and curability of ectopic (non-pancreaticoduodenal, nonnodal) gastrinoma. Surgery 1997; 122: 1176-1182
4 Jensen RT. Pancreatic endocrine tumors: recent advances. Ann Oncol 1999; 10 Suppl 4: 170-176
5 Stabile BE, Morrow DJ, Passaro E Jr. The gastrinoma triangle: operative implications. Am J Surg 1984; 147: 25-31
6 Thompson GB. Islet Cell Tumors. In: Kelly KA, Sarr MG, Hinder RA. Mayo Clinic Gastrointestinal Surgery. Philadelphia: Saunders, 2004: 299-319
7 Campana D, Piscitelli L, Mazzotta E, Bonora M, Serra C, Salome L, Corinaldesi R, Tomassetti P. Zollinger-Ellison syndrome. Diagnosis and therapy. Minerva Med 2005; 96: 187-206
8 Jensen RT, Gardner JD, Kaufman JP, Pandol SJ, Doppman JL, Collen MJ. Zollinger-Ellison syndrome: current concepts and management. Ann Intern Med 1993; 88: 59-75
9 Jensen RT, Doppman JL, Gardner JD. Gastrinoma. In: Go VLW, Brooks FA, DiMagno EP, Gardner JD, Lebenthal E, Scheele GA. The exocrine pancreas: biology, pathobiology and disease. New York: Raven Press, 1986: 727-744
10 Pipeleers-Marchial M, Somers G, Willems G, Foubles A, Imrie C, Bishop AE, Polak JM, Häcki WH, Stamm B, Heitz PU. Gastrinomas in the duodenums of patients with multiple endocrine neoplasia type 1 and the Zollinger-Ellison syndrome. N Engl J Med 1990; 322: 723-727
11 Maton PN, Macken SM, Norton JA, Gardner JD, O’Dorisio TM, Jensen RT. Ovarian carcinoma as a cause of Zollinger-Ellison syndrome. Nat History, secretory products, and response to provocative tests. Gastroenterology 1989; 97: 468-471
12 Primrose JN, Maloney M, Wells M, Bulgum O, Johnston D. Gastrin-producing ovarian mucinous cystadenomas: a cause of the Zollinger-Ellison syndrome. Surgery 1988; 104: 830-833
13 Mandujano-Vera G, Argoles-Angeles A, de la Cruz-Hernandez J, Sansoares-Perez M, Larrriva-Salah J. Gastrinoma of the common bile duct: immunohistochemical and ultrastructural study of a case. J Clin Gastroenterol 1995; 20: 321-324
14 Maton PN. Gastrinoma and other hypergastrinemic syndrome. In: Walsh JH, Dockray GJ. Gut peptides. New York: Raven Press, 1994: 675-700
15 Price TN, Thompson GB, Lewis JT, Lloyd RV, Young WF. Zollinger-Ellison syndrome due to primary gastrinoma of the extrapancreatic extra-intestinal type: a case report and review of literature. Endocr Pract 2009; 15: 737-749
16 Tioanny E, Brill S, Baratz M, Messer G, Greif F, Moskhowitz M, Gilat T. Primary liver gastrinoma. J Clin Gastroenterol 1997; 24: 188-191
17 Ishikawa Y, Yoshida H, Mamada Y, Taniai N, Matsumoto S, Bando K, Misuguchi Y, Kakimura D, Kanda T, Akimaru K, Shimizu K, Tajiri T. Curative resection of primary hepatic gastrinoma. Hepatogastroenterology 2008; 55: 2224-2227
18 Moriiura S, Ikeda S, Hirai M, Naiki K, Fujioka T, Yokochi K, Gotou S. Hepatic gastrinoma. Cancer 1993; 72: 1547-1550
19 Wolfe MM, Alexander RW, McGuigan JE. Extrapancreatic, extraintestinal gastrinoma: effective treatment by surgery. N Engl J Med 1982; 306: 1533-1536
20 Gibril F, Reynolds JC, Doppman JL, Chen CC, Venzon DJ, Termanini B, Weber JC, Stewart CA, Jensen RT. Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas. A prospective study. Ann Intern Med 1996; 125: 26-34
21 Imamura M, Takahashi K, Itoye Y, Hattori Y, Satomura K, Tohe T. Curative resection of multiple gastrinomas aided by selective arterial secretin injection test and intraoperative secretin test. Ann Surg 1989; 210: 710-718
22 Guimaraes CM, Correia MM, Baldisserotto M, de Queiroz Aires EP, Coelho JF. Intraoperative ultrasonography of the liver in patients with abdominal tumors: a new approach. J Ultrasound Med 2004; 23: 1549-1555
23 Fraker DL, Jensen RT. Pancreatic endocrine tumors. In: DeVita VT Jr, Hellman S, Rosenberg STA. Cancer: Principles and Practice of Oncology. Philadelphia: JB Lippincott, 1997: 1678–1705
24 Chamberlain RS, Blumgart LH. Carcinoid tumors of the extrahepatic bile duct. A rare cause of malignant biliary obstruction. Cancer 1999; 86: 1959-1965
25 Martignoni ME, Friess H, Lübke D, Uhl W, Maurer C, Müller M, Richard H, Reubi JC, Büchler MW. Study of a primary gastrinoma in the common hepatic duct - a case report. Digestion 1999; 60: 187-190
26 Chan C, Medina-Franco HJ, Bell W, Lazendy A, Vickers S. Carcinoid tumor of the hepatic duct presenting as a Klatskin tumor in an adolescent and review of world literature. Hepatogastroenterology 2000; 47: 519-521
27 Norton JA, Jensen RT. Role of surgery in Zollinger-Ellison syndrome. J Am Coll Surg 2007; 205: S34-S37
28 Que FG, Nagorney DM, Batts KP, Linz LJ, Kvolos LK. Hepatic resection for metastatic neuroendocrine carcinomas. Am J Surg 1995; 169; 36-42; discussion 42-43
29 Norton JA. Surgical treatment and prognosis of gastrinoma. Best Pract Res Clin Gastroenterol 2005; 19: 799-805
30 McIntee GP, Nagorney DM, Kvolos LK, Moertel CG, Grant CS.
Cytoreductive hepatic surgery for neuroendocrine tumors. *Surgery* 1990; 108: 1091-1096

31 Yao JC. Neuroendocrine tumors. Molecular targeted therapy for carcinoid and islet-cell carcinoma. *Best Pract Res Clin Endocrinol Metab* 2007; 21: 163-172

32 Kulke M. Advances in the treatment of neuroendocrine tumors. *Curr Treat Options Oncol* 2005; 6: 397-409

33 Lewis JS, Anderson CJ. Radiometal-labeled somatostatin analogs for applications in cancer imaging and therapy. *Methods Mol Biol* 2007; 386: 227-240

S-Editor Zhang HN  L-Editor Hughes D  E-Editor Zhang L

Tsalis K *et al*. Primary hepatic gastrinoma