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## **GEP-NET : rare tumour connections. Pathophysiological aspects of gastroenteropancreatic neuroendocrine tumours**

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## Chapter 4

### *A Case of Recurrent Gastrinoma in The Liver with a Review of 'Primary' Hepatic Gastrinomas*

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**Abstract**

In the literature only few cases of primary hepatic gastrinomas have been reported. Furthermore, most cases have a short follow-up and are limitedly documented.

We report a case of a patient suffering from the Zollinger-Ellison syndrome with recurrent hepatic gastrinomas, in whom no gastrinomas in duodenum, pancreas or other extrahepatic site could be identified, despite the use of multiple, repeatedly performed imaging techniques and explorations during the past 20 years.

A review is given on primary liver gastrinomas published since 1981. Interestingly, the present case is the only one with documented recurrent gastrinoma in the liver. None of the previously reported cases had liver gastrinomas as part of the Multiple Endocrine Neoplasia type 1 syndrome. It is further noteworthy that the risk of metastases of liver gastrinomas appears to be low. The interpretation of these hepatic gastrinomas as primary lesions can be questioned, as most cases lack an investigational and well-documented follow-up. In this study, we report the first case of Zollinger-Ellison syndrome caused by recurrent hepatic gastrinomas in the context of what is known from the literature.

## **Introduction**

The Zollinger-Ellison Syndrome (ZES) is caused by a malignant gastrin-producing neuroendocrine tumour (gastrinoma), usually located in pancreas or duodenum<sup>1,2</sup>. Symptoms associated with ZES are acid peptic disease, malabsorption and diarrhea<sup>3</sup>.

Most frequently ZES occurs as a sporadic disease, while 20 to 30% of the cases is part of the Multiple Endocrine Neoplasia type 1 syndrome (MEN-1)<sup>4,5</sup>. This autosomal dominant disorder, caused by mutations of the MEN-1 tumour suppressor gene located on chromosome 11q13, is characterized by multiple tumours in several neuroendocrine organs and tissues. In case of endocrine symptoms in combination with a positive family history for MEN-1 and aberrant levels of calcium, prolactin, parathyroid hormone or pancreas polypeptide, MEN-1 can be suspected and confirmed by genetic analysis<sup>6</sup>.

Gastrinomas are frequently located in pancreas (30-50%), duodenum (40-50%) or lymph nodes (19%), in the so-called gastrinoma triangle, which angle points are formed by the junction of the cystic duct and common bile duct, the junction of the second and third part of the duodenum and the junction between the neck and body of the pancreas<sup>7</sup>. Remaining gastrinomas (extrapancreatic, extraduodenal and extralymphatic) are called ectopic and have been reported to occur in thymus, ovaries, liver, jejunal mesenterium, stomach, heart, parathyroid glands, kidneys and common bile duct<sup>8-10</sup>. Although hepatic metastases of primary gastrinomas are common, primary hepatic gastrinomas are rare<sup>11</sup>. To date, about 16 cases of primary liver gastrinomas have been reported in the

literature<sup>9, 10, 12-25</sup>. In a majority of these reports, the period of follow-up is short (<three years) and not well-documented. However, because primary hepatic gastrinomas are difficult to differentiate from liver metastases from an occult gastrinoma elsewhere located, an adequate and extensive follow-up is necessary.

In this case report, we describe a patient with ZES with recurrent most likely primary hepatic gastrinomas and an extended follow-up of almost 20 years after the diagnosis and more than 30 years after the first clinical presentation. Despite extensive monitoring and evaluation, including multiple physical examinations,

endoscopies and extensive imaging studies, no primary duodenal or pancreatic gastrinoma could be identified in this patient. Instead, liver tumours suspected of primary gastrinomas have been resected twice. Furthermore, we discuss the existence of primary liver gastrinomas and give an overview of all case reports of primary hepatic gastrinomas reported in literature from 1981.

### **Case Report**

In 1989, a 39-year-old white male of Hispanic origin was referred to the outpatient clinic of the Gastroenterology department of the Leiden University Medical Center, for localization and treatment of a suspected gastrinoma. At that time symptoms including diarrhea, gastric complaints, pyrosis, nausea and vomiting, were present for many years. Furthermore, patient reported a remarkable weight loss of more than five kg during a period of approximately six months. Fasting serum gastrin was elevated and the secretin provocation test was positive, supporting the diagnosis of ZES. Omeprazol 80 mg/day provided relief of his symptoms. Patient was taking no other medication. About fifteen years before presentation, patient had undergone anti-reflux surgery (Nissen fundoplication). His past medical history was further unremarkable, his family history was non-contributory. Physical examination revealed no abnormalities, apart from severe scoliosis. Laboratory studies, including serum amylase, electrolytes, liver chemistry, blood cell counts and stool parameters were found normal, except for an increased fecal fat excretion (53 grams/day). Gastroduodenoscopy showed Barrett's esophagus, a small duodenal ulcer, and prominent red gastric folds and several erosions in the stomach. Further laboratory analysis revealed an increased fasting serum gastrin of 889 ng/L (424 pmol/L), an elevated basal acid output (40 mmol/hr) with a maximum acid output of 60 mmol/hr. Serum levels of calcium (2.36 mmol/L), parathyroid hormone (2.4 pmol/L), prolactin (4.9 ug/L) and pancreas polypeptide (10 pmol/L) were within normal limits, making the diagnosis of Multiple Endocrine Neoplasia type 1 (MEN-1) very unlikely.

To localize a possible gastrinoma, several imaging evaluations were performed. However, no tumour was identified at that time by conventional procedures, such

as computed tomography (CT), magnetic resonance imaging (MRI), selective arteriography and selective arterial secretin injection test. Endoscopic ultrasound did not show a tumour in gastroduodenum, pancreas or lymph nodes. Moreover, an Indium-111-somatostatin receptor scintigraphy, a technique which was at that time still in the experimental phase, was performed (University Hospital, Rotterdam). This scan revealed a possible localization of the tumour in the left liver lobe or gastric lesser curvature. To exclude a gastric localization, gastroscopy was repeated. However, no tumour was visualized. Consequently, in 1990, an explorative laparotomy was performed but again no gastrinomas were visible macroscopically. Peroperative ultrasonographic evaluation of the pancreas showed no abnormalities, while peroperative echography of the liver showed a lesion next to the inferior vena cava in the left liver lobe. Biopsies from this lesion were analyzed by immunohistochemistry, on both paraffin-embedded and frozen sections of the tumour, and were found positive for keratin, synaptophysin, gastrin and neuron specific enolase, but negative for other neuroendocrine markers. Based on these results, a liver localization of a gastrin-producing neuroendocrine tumour was suggested, and confirmed on CT. In order to localize a primary tumour, peroperative selective venous sampling for gastrin was performed<sup>26</sup>. No evidence of tumour localization in the duodeno-pancreatic area was found. Therefore, resection of liver segment II was performed. Postoperative histological examination confirmed that the specimen sampled from the liver contained a gastrinoma. Within five days after the partial resection, fasting serum gastrin decreased to normal (60 ng/L; 29 pmol/L) (Figure 1).

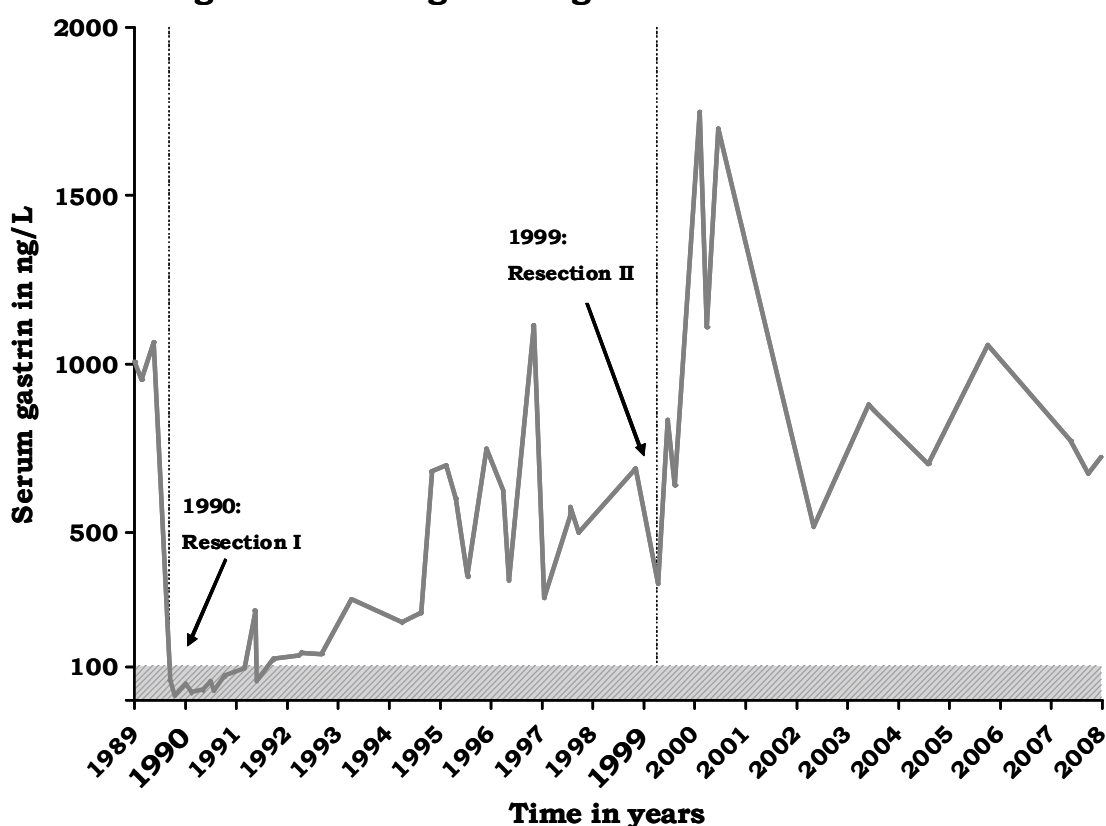
**Figure 1. Fasting serum gastrin levels from 1989 - 2008**

Figure 1. Fasting serum gastrin levels in ng/L, measured on multiple occasions during the evaluation from 1989 until 2008, are presented. The gray region represents the area in which serum gastrin is within normal limits (<100 ng/L). Dotted lines indicate the first and second partial liver resections in 1990 and 1999, respectively.

Approximately one and a half year after surgical excision of the liver gastrinoma, fasting serum gastrin increased to levels above the upper limit of normal (<100 ng/L). Secretin provocation test was also positive (a rise of 296 ng/L; 142 pmol/L in serum gastrin after secretin injection).

In the period from 1991 until 1999, several imaging techniques were performed without any detection of a pancreatic or duodenal gastrinoma. Multiple gastroscopies repeatedly revealed a Barrett's esophagus and edematous folds in the gastric corpus. In 1995, a selective arterial secretin injection test<sup>27</sup> was repeated and showed a small increased gradient of serum gastrin over the hepatic vein. In 1998, octreotide scintigraphy (SRS) revealed multiple small liver lesions, which were confirmed on CT and MRI (Figure 2).

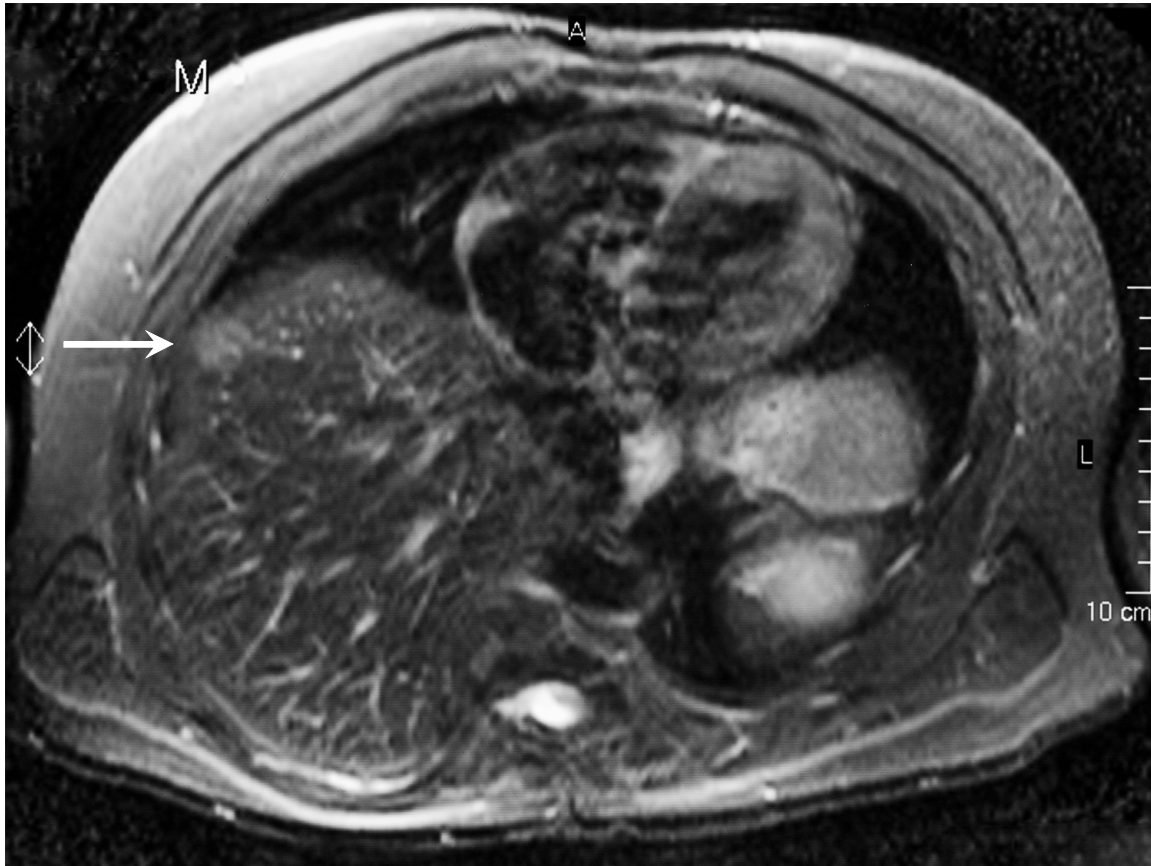


Figure 2. Magnetic resonance imaging shows a liver lesion ventrolateral in the right liver lobe (Leiden University Medical Center, Department of Radiology).

Patient had a partial resection of liver segments IVa and IVb. Postsurgically, fasting serum gastrin initially dropped from 690 (330 pmol/L) to 347 ng/L (166 pmol/L) but rapidly increased thereafter. A secretin provocation test, performed 3 months postoperatively, resulted in a postsecretin gastrin increase from 883 ng/L (422 pmol/L) to 4675 ng/L (2236 pmol/L).

The patient remained under follow-up control for the next period. Apart from surgery for a prostate adenocarcinoma, no ZES-related complaints were present. In 2003, octreotide scintigraphy (SRS) revealed a dubious accumulation of radioactivity in the ventral right liver lobe, while contrast-enhanced CT and MRI scans of the abdomen were repeatedly normal. In 2006 the liver lesion was confirmed on MRI of the abdomen. Until present date, no lesion in pancreas or duodenum has been identified. In 2008, an attempt to treat the hepatic lesion with radiofrequency ablation was performed. However, the procedure was discontinued because of failure of the needle to reach the tumour. To date, serum



gastrin levels remain increased although patient is doing well without symptoms, using 80 mg/day of Pantoprazole.

**Table 1. Review of primary hepatic gastrinomas from literature**

Patients		Therapy			Follow-up after resection			
Ref	Age, sex	FSG pre	Resection	FSG post	Investigations	Evidence	m	FSG last
17	36, F	ND	No#	ND	ND	No	24	ND
10	61, F	1500	Yes*	ND	FSG	No	132	82 (1m)
24	44, M	2700	Yes*	N	FSG	No	13	N (9m)
22	8, M	893	Yes	N	FSG	No	18	N (18m)
9	23, M	670	Yes*	ND	SPT	No	24	ND
12	49, F	ND	Yes	ND	ND	No	69	ND
19	13, M	27175	Yes	N	FSG	No	24	ND
16	30, M	572	Yes	64	FSG	No	60	ND
20	50, F	ND	Yes	N	CT, US, EUS, FSG, SPT	No	24	ND
18	9, M	704	Yes	103	CT, FSG	No	36	182 (12m)
25	50, M	150	Yes	N	CT, FSG	No	18	N (18m)
23	57, M	ND	Yes*	50	CT, SRS, FSG	No	14	N (14m)
13	27, F	1224	Yes	N	CT, US, FSG	No	42	N (42m)
15	13, M	1141	Yes	30	SRS, US, FSG	Yes	48	284 (6m)
14	29, F	1149	Yes	ND	CT, MRI, EUS, SRS, FSG	No	36	N (36m)
21	50, M	1500	Yes	N	CT, SPT, FSG	No	60	400 (>6m)
CCR	39, M	1065	Yes	60	CT, MRI, SRS, SASI	Yes	113	690 (109m)
+rec	39, M	690	Yes	347	CT, MRI, SRS, EUS	Yes	100	724 (105m)

Symbols: \* Plus total gastrectomy, # Streptozotocin therapy

Abbreviations: CCR + rec = Current case report + recurrence, Ref = References, m = Months, FSG pre = FSG preoperatively (ng/L), FSG post = FSG postoperatively (ng/L), FSG last = FSG last measured (months) (ng/L), FSG = Fasting serum gastrin, F = female, M = male, ND = Not done, N = in normal range (<100 ng/L), CT = Computed tomography, MRI = Magnetic resonance imaging, US = Ultrasound, EUS = Gastroduodenal endoscopic ultrasound, SRS = Somatostatin receptor scintigraphy, SASI = Selective arterial secretin injection test, SPT = secretin provocation test

Table 1. A review of primary hepatic gastrinomas from literature is presented.

## Discussion

This is an exceptional case of a ZES-patient with recurring hepatic gastrinomas, in the absence of MEN-1. As in general the majority of sporadic gastrinomas is localized in the gastrinoma triangle, an accurate investigational search to find a tumour in this area was initiated. Preoperative and postoperative techniques to

localize a gastrinoma include CT, MRI, ultrasonography, somatostatin receptor scintigraphy or octreotide scintigraphy, selective angiography, gastroduodenal endoscopic ultrasonography, and more specialized tests such as selective arterial secretin injection and selective portal venous sampling<sup>27-33</sup>.

Although our patient was subjected to all these imaging techniques for almost 20 years, no evidence for an extrahepatic origin of a gastrinoma was found. However, we believe that it is very unlikely that any extrahepatic tumour, albeit small in size, is constantly missed. As preoperative localization techniques like MRI and CT have improved over time, it might be expected that, even if a tumour was missed repeatedly in the past, recent techniques would be able to detect gastrinomas of any size at any location. Furthermore, we believe that if any small gastrinoma would exist, in pancreas or duodenum, this tumour would grow and therefore be detected by now. However, in this patient, exclusively liver gastrinomas have been detected, resected and recurred twice. To date, a suspicious liver lesion is seen with multiple imaging modalities. Although it is not certain if this liver lesion is a new recurrence or growth of a residual tumour after the second partial liver resection, it is clear that the liver tumour has a slow growing rate. After the initial resection of the liver gastrinoma in 1990, it took about 9 years before a recurrent tumour became visible on imaging. After the resection in 1999, imaging techniques were initially negative before hepatic lesions could be visualized on MRI in 2006.

In Table 1, several cases of primary liver gastrinomas reported in the literature from 1989 until 2008 are listed. In most cases, hepatic gastrinomas were defined as primary when no extrahepatic tumour had been found pre-, intra- and postoperatively or when postsurgically serum gastrin levels decline to the normal range (<100 ng/L)<sup>9, 12-20, 22-25</sup>. Moreover, the suspicion of a primary liver gastrinoma could postoperatively be confirmed by immunohistochemical staining for (neuroendocrine) markers, including gastrin. In only one case report the tumour is defined as primary preoperatively, based on percutaneous transhepatic venous sampling<sup>21</sup>. In our patient, no lesions outside the liver were found and immunohistochemical analysis of the liver lesions confirmed the diagnosis of

gastrinoma, fitting the criteria to define the liver gastrinoma as primary. In contrast, serum gastrin levels did normalize postsurgically after the first partial liver resection, but became abnormal after about one and a half year and remained increased after the second operation. Remarkably, in most reported cases the follow-up of the patient after resection of the liver gastrinoma was relatively short (<three years)<sup>12, 19-22, 24, 25</sup> or had a limited postoperative documentation<sup>12, 23</sup>. The possibility that an extrahepatic gastrinoma is present can therefore not be absolutely excluded. Our patient had undergone several imaging studies to localize a gastrinoma outside the liver, not only preoperatively, but also after the resection of the hepatic tumour and during follow-up.

Moraira *et al.* studied the cases of five primary hepatic gastrinomas from the literature and added one case, and concluded that these gastrinomas occurred in slightly younger patients when compared to patients with gastrinomas elsewhere located<sup>20</sup>. Furthermore, Diaz *et al.* reported that primary hepatic gastrinomas are more common in men, and are not associated with MEN-1<sup>15</sup>. As our patient was a relatively young male at the time of diagnosis, suffering from ZES not as part of the MEN-1 syndrome, this is in line with the interpretation of the liver lesion as a primary tumour.

In general, it is difficult to state that in patients with a supposed primary liver gastrinoma, the possibility of a pancreatic, duodenal or other localization of a primary gastrinoma is excluded. As the liver occurs to be a frequent site for metastatic gastrinomas, hepatic gastrinomas can be incorrectly interpreted as primary when no extrahepatic gastrinoma can be detected. The probability that liver gastrinomas are by mistake diagnosed as primary, is also mentioned by Tiomny *et al.*<sup>25</sup>. Detection of liver gastrinomas usually raises the question if this tumour is primary or metastatic. Only with long term follow-up it is possible to answer this question. However, the risk of metastases from primary hepatic gastrinomas seems to be low, as only one case reports the development of lymph node metastases after liver resection<sup>15</sup>. To our knowledge, recurrent tumours in the liver after surgical removal of the primary hepatic gastrinoma have not been reported before.

In some case reports listed in Table 1, patients have undergone a total gastrectomy, preventing the use of acid peptic complaints as marker for recurrence, while in other cases, the follow-up after resection relies only on the analysis of serum gastrin levels. We believe that, even in the absence of ZES-related complaints or in case of normalization of serum gastrin immediately postoperatively, recurrence may occur, although many years later. Therefore investigational imaging, such as octreotide scintigraphy or gastroduodenal endoscopic ultrasound, is required for an adequate follow-up.

In conclusion, we reviewed the literature on primary liver gastrinomas and added a patient suffering from the Zollinger-Ellison syndrome, with a liver gastrinoma without another localization of a primary gastrinoma, under evaluation for almost 20 years.

Although the absence of a primary gastrinoma outside the liver during this long follow-up is highly suggestive to define the gastrinoma in the liver as primary, the possibility of a metastasizing but not growing occult gastrinoma in the gastrinoma triangle is very unlikely, but can not be excluded with absolute certainty. In general, we state that frequent measurements of serum gastrin in combination with repeated imaging investigations are indicated after resection of a liver gastrinoma. We presume that the follow-up period should last for several years, as we show in our patient that a primary hepatic tumour has a slow rate of recurrence.

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