

## Primary Lymph Node Gastrinoma or Metastatic Gastrinoma with Unidentified Primary Tumor Site?

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### ABSTRACT

Gastrinomas are neuroendocrine tumors that secrete gastrin and result in a clinical syndrome of peptic ulcer disease first described by Zollinger and Ellison in 1955.<sup>1</sup> They present either sporadically or as a component of a hereditary determined syndrome, multiple endocrine neoplasia type 1. They are usually located in the pancreas and duodenum but have been reported to occur in both abdominal and extraabdominal sites.<sup>2</sup> Reports of clinical and biochemical cure following resection of lymph nodes found to contain gastrinomas, in patients without a localized primary tumor, led investigators to cite the existence of the primary lymph node gastrinoma. Whether these cases represent metastatic disease from an, as yet, unidentified primary tumor, or *de novo* occurrence of a gastrinoma in a lymph node remains controversial. While some authors report that primary lymph node gastrinomas account for up to 10% of sporadic gastrinomas<sup>3,4</sup> others question this theory, hypothesizing that their presentation represents an undetected microgastrinoma with metastatic lymph node involvement.<sup>5</sup>

Herewith, we report on a patient with Zollinger-Elison syndrome in whom a peripancreatic lymph node with evidence of gastrinoma is the only apparent morphologic manifestation of the disease.

**Keywords:** Zollinger-Elison syndrome, Metastasized gastrinoma, Primary lymph node gastrinoma.

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### CASE REPORT

A 42-year-old male initially presented to his local hospital in 1999 with nausea, vomiting, weight loss and reflux symptoms including, upper abdominal pain and bloating. Apart from asthma he had no other past medical history. His parents had essential hypertension but there was no family history of Zollinger-ellison syndrome (ZES) or multiple endocrine neoplasia type 1 (MEN 1)-associated symptoms.

Esophagogastroduodenoscopy (OGD) demonstrated multiple duodenal ulcers. Treatment with proton pump inhibitors (PPI) and antibiotic eradication of *Helicobacter pylori* was initiated. Following further investigation, the patient was diagnosed with ZES but magnetic resonance imaging (MRI) and computed tomography (CT) performed

in 2002 both failed to identify a tumor. Subsequent endoscopic ultrasound (EUS) revealed no pathologic findings. He continued to experience profound nausea and vomiting with frequent episodes of diarrhea although his weight remained stable.

In 2007, he was referred to another institution for consideration of further investigation to attempt to identify an underlying gastrinoma. Although on PPIs, he still suffered periods of severe abdominal pain with diarrhea preventing him from leaving the house for days. Bloods demonstrated an elevated fasting plasma gastrin of 195 pmol/l (normal <40 pmol/l) with normal fasting glucagon, vasointestinal peptide, pancreatic polypeptide and chromogranin A and B. Gastric acid studies revealed an elevated basal gastric acid production of 95 mmol/h (normal <10 mmol/h).

EUS demonstrated moderate erosive esophagitis and severe erosive duodenitis. A thickened duodenal wall with several small periduodenal lymph nodes was present but no other lesion could be visualized.

A repeat EUS in 2010 revealed a 5 × 8 mm hypoechoic mass localized within the prepyloric region and several periduodenal lymph nodes that appeared inflammatory in nature. On CT, a 7 mm enhancing nodule medial to the second part of the duodenum became evident (Fig. 1). Three, subcentimeter lesions in the liver were consistent with simple cysts. An Octreoscan (229 MBq 111 indium octreotide) revealed no pathologic uptake. Mesenteric



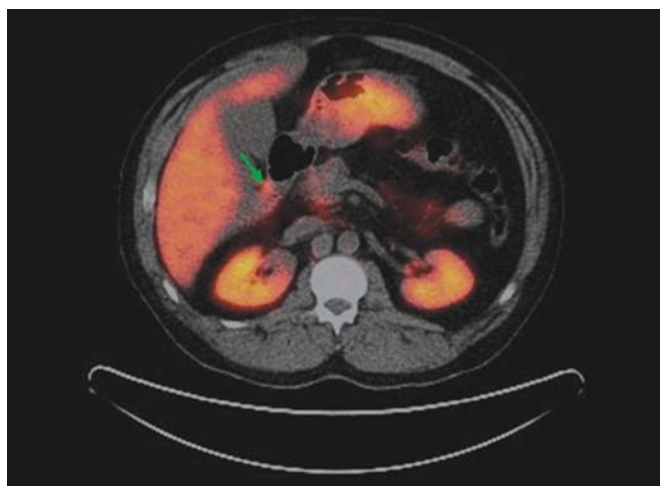
**Fig. 1:** Axial section from a contrast CT abdomen demonstrating a 7 mm lesion (arrow) adjacent to the second part of the duodenum

angiography showed an 8 mm region of increased vascularity over the medial aspect of the second part of the duodenum consistent with the enhancing nodule seen on CT (Fig. 2). A gastrin stimulation test with calcium disclosed an isolated 10-fold peak within the gastroduodenal artery. In contrast to Octreoscan,  $^{68}\text{Ga}$ -Dotatate positron emission tomography (PET) confirmed an avid lesion adjacent to the second part of the duodenum corresponding with the nodule seen on CT (Fig. 3). His fasting plasma gastrin at this time was 290 pmol/l (normal <40 pmol/l).

Normal serum concentration of parathyroid hormone, vitamin D and prolactin with corrected calcium of 2.10 mmol/l, and a urinary 5-hydroxyindoleacetic acid (HIAA) was noted. Compared to the results from 2007, chromogranin A was elevated at 90 pmol/l (range, 0-60).



**Fig. 2:** Selective celiac axis angiography demonstrating a well-defined nodule of faintly increased vascularity measuring approximately 8 mm in maximal diameter and superimposed on the medial aspect of the second part of the duodenum (arrows)

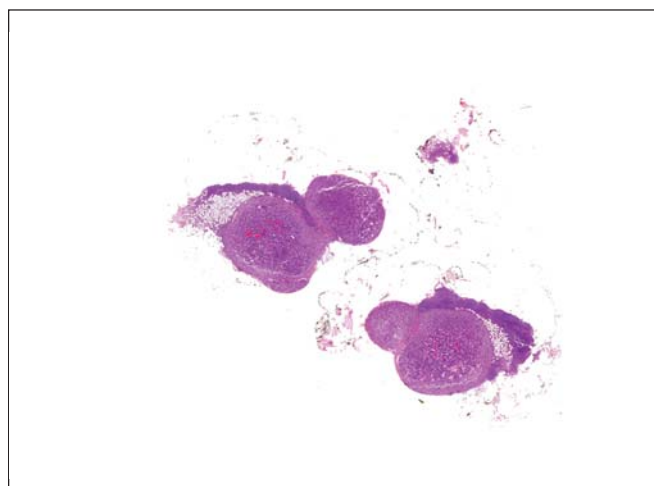


**Fig. 3:** Axial section from  $^{68}\text{Ga}$  Dotatate PET demonstrating a Dotatate avid lesion adjacent to the second part of the duodenum (arrow)

Genetic screening for MEN 1 mutations was negative. The patient was subsequently found to have severe hypertension (172/108 mm Hg), episodes of migraine and episodes of rectal bleeding associated with hemorrhoids. Further investigation with regard to hypertension was unremarkable with normal electrolytes, a normal echocardiogram, normal imaging of his kidneys and adrenals, normal autoimmune screen, bicarbonate, 24 hours urinary collections for catecholamines and metanephrines and appropriate suppression of cortisol on low-dose dexamethasone suppression test. A diagnosis of essential hypertension was made and appropriate medical therapy initiated. During this period, he reported a significant gain in weight from 72.9 Kg at the time of investigation in March 2008 to 85.2 Kg in May 2010 at the time of surgery.

Finally, in June 2010, the patient underwent laparotomy. Corresponding with the imaging results an 8 mm, well-encapsulated, firm tumor anterior to the pyloric region embedded in fatty tissue was found. Meticulous exploration of the upper abdomen, including manual duodenal exploration and sonography of the liver and pancreas, revealed no other pathological findings apart from advanced hepatosteatorosis. Systematic lymphadenectomy, including the prepyloric tumor, within the gastrinoma triangle was performed. The postoperative course was uneventful and the patient was discharged on the eight postoperative day.

Histological examination of the prepyloric tumor disclosed a single lymph node measuring 9 mm in maximum diameter almost completely replaced by tumor with appearances consistent with a neuroendocrine tumor (Fig. 4). No mitoses were seen in a 10 high-power field and no extracapsular spread was evident. On immunohistochemistry, the tumor was diffusely positive for gastrin and

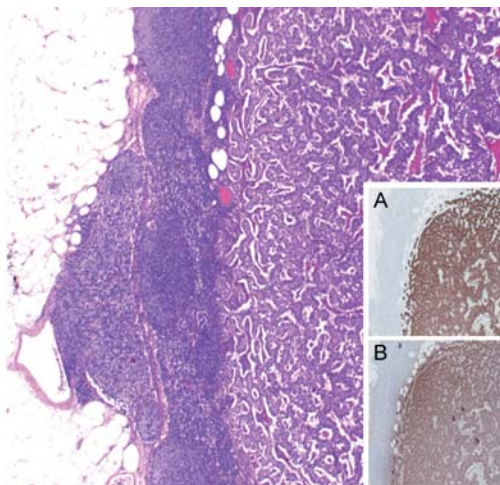


**Fig. 4:** Bisected lymph node almost completely replaced by a neuroendocrine tumor. H and E 10x

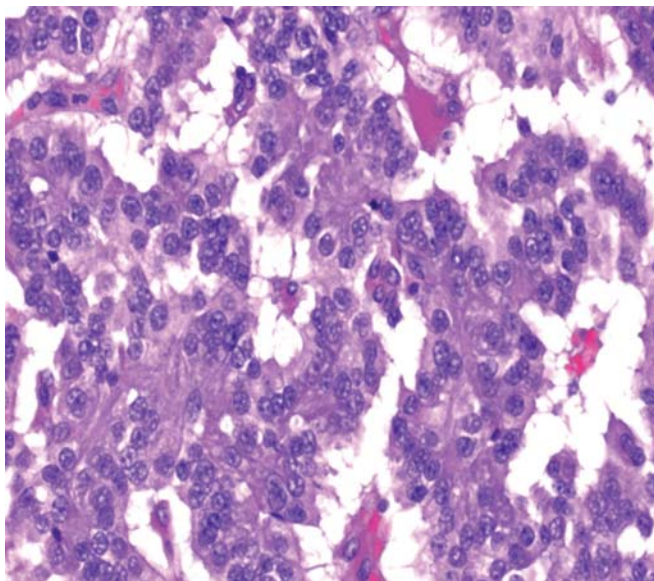


synaptophysin and focally positive for chromogranin. Stainings for somatostatin, serotonin and glucagon were weakly positive (Figs 5 and 6). The Ki-67 proliferation index was <2%. The diagnosis of a well-differentiated, low-grade, neuroendocrine tumor (NET) was made. A further seven lymph nodes had no evidence of tumor.

At a follow-up 7 weeks postoperatively, the patient was asymptomatic in a significantly improved general condition. He had lost 3.5 Kg in weight. At the last follow-up performed 21 months after surgery the patient remained asymptomatic. Gut hormone studies at this time demonstrated a normal fasting plasma gastrin (32 pmol/l) and chromogranin A (42 pmol/l; Table 1).



**Figs 5A and B:** Neuroendocrine tumor with a trabecular growth pattern (right) and rim of preserved lymph node tissue (left). H and E 100x (A) neuroendocrine tumor showing strong and diffuse synaptophysin expression. Immunostain 100x (B) neuroendocrine tumor showing diffuse expression for gastrin. Immunostain 100x



**Fig. 6:** Higher magnification showing trabeculae of polygonal cells with uniform round nuclei with stippled chromatin and small nucleoli H and E 400x

**Table 1:** Pre- and postoperative gut hormone studies

	Pre-operative	Post-operative (21 months follow-up)	Normal range
Chromogranin A	90	42	<60 pmol/l
Gastrin	290	32	<40 pmol/l
Chromogranin B	86	85	<150 pmol/l
Pancreatic Polypeptide	28	36	<300 pmol/l
VIP	4	3	<30 pmol/l
Somatostatin	82	59	<150 pmol/l
Glucagon	<5	6	<50 pmol/l

**DISCUSSION**

The existence of primary lymph node gastrinomas remains contentious. A report by Norton et al suggested that 10% (13/138 in this series) of all patients with sporadic ZES had a lymph node primary and remained cured following lymphadenectomy at long-term follow-up (10.4 ± 1.2 years).<sup>3</sup> These findings were supported by a study by Arnold et al who found that in his experience 8% of patients (9/110) who underwent surgical exploration for ZES were found to have disease limited to one or more lymph nodes and remained biochemically cured at a median follow-up of 5.3 years.<sup>6</sup>

The majority of gastrinomas arise in the duodenum and pancreas. Those arising from the duodenum account for 70% and develop from G cells. Since, these cells are not found in the adult pancreas, an alternative model of tumorigenesis for gastrinomas of the pancreas has been suggested. This concept finds support in the pathophysiological differences in their malignant potential.<sup>7</sup> Pancreatic islet cells are thought to arise from pancreatic stem cells that are found at the tip of the developing pancreatic ductule. In 1984, Stabile et al observed that the majority of gastrinomas were located in a region consecutively recognized as the ‘gastrinoma triangle.’<sup>8</sup> It was hypothesized that this region corresponded to an area of pancreatic development, where the ventral pancreatic bud rotates through 180° around the primitive foregut. Primary lymph node gastrinomas were thought to arise from such pancreatic stem cells that had failed to migrate and had subsequently been incorporated within lymph nodes in this area.<sup>8,9</sup>

Opponents to the existence of primary lymph node gastrinomas cite reports of microgastrinomas in the duodenum that are easily overlooked and the observation that even these small tumors have been shown to give rise to extensive metastatic disease. Anlauf et al demonstrated the existence of multiple primary microgastrinomas (0.45 and 0.8 mm) in a MEN 1 patient only after complete embedding of a total pancreaticoduodenectomy specimen.<sup>5</sup> The conventional histopathological investigation had only found

gastrinoma within suprapancreatic lymph nodes. The observation that primary duodenal gastrinomas were considerably more common (70-100% in MEN 1 patients and 50 to 88% in sporadic patients) than previously quoted (<20%) further strengthened this argument.<sup>2</sup> MEN 1-associated gastrinoma is present in only 20 to 30% of ZES patients, however, and sporadic gastrinomas have clear differences in their presentation, distribution and prognosis.<sup>10</sup>

In MEN 1, the primary tumors are multifocal and almost always (70-100%) located in the duodenum, originating directly from G cells.<sup>2,7</sup> In the series of Norton et al advocating the existence of primary lymph node gastrinomas, disease relapse occurred in 31% of patients (8/26; range, 2-10 years) who experienced an initial 'disease-free period.' This cohort included both, sporadic and MEN 1 ZES patients. In the patients with sporadic ZES, a primary duodenal tumor was first detected at second exploration in three of them.<sup>3</sup>

As this case demonstrates, gastrinomas can prove to be a diagnostic conundrum.

The use of transabdominal ultrasound is limited due to the relatively low sensitivity in localizing small primary tumors within the pancreas and duodenum. Endoscopic ultrasound is effective in tumor localization within the pancreas and duodenum with reported sensitivities in the range 79 to 100% in expert hands.<sup>11</sup> Initial studies of CT reported detection rates of only 28%.<sup>10</sup> The significant improvements in spatial and temporal resolution and the use of multiphase contrast-enhanced CT has resulted in a markedly improved sensitivity of up to 95% for tumors localized within the pancreas.<sup>11</sup> For MRI, positive predictive values of 94% have been reported.<sup>11,12</sup>

Functional imaging, ideally in fusion with morphologic imaging, has a key role in the modern diagnosis, staging and follow-up of patients with NETs. Depending upon the tumor type, somatostatin receptor scintigraphy (Octreoscan) has a reported overall sensitivity of 80 to 90%.<sup>13</sup> Developments in somatostatin analogues have enabled radiolabeling with positron emitting tracers (PETs) suitable for PET imaging in combination with CT (e.g. 68Ga-Dotatoc PET/CT) that has further improved the diagnostic accuracy.<sup>14</sup> Detection of tumors less than 1 cm in size still remains challenging.<sup>11,12,15</sup>

An interesting observation in the patient presented in this report was the fluctuations of weight during the course of the disease. Following initial diagnosis, his weight steadily increased. After surgery he was then noted to return toward his presenting weight. Weight gain in ZES has been observed by Raoul et al in a cohort of 18 ZES patients. This cohort experienced weight loss at the time of diagnosis with a rebound weight gain following the commencement of treatment. They proposed two hypotheses for these

observations.<sup>16</sup> First, that ZES patients learnt to change their diet as frequent meals reduce their symptoms. Following their diagnosis and commencement of treatment, these continued dietary habits coupled with a reduction in fat malabsorption resulted in weight gain. The second, that weight gain might be a consequence of elevated gastrin levels which may cause desensitization of receptors to the hunger suppressant, cholecystokinin, with a resultant impaired control of satiety.<sup>16</sup>

Advocates of the existence of primary lymph node gastrinomas would suggest the case presented in this report may prove to support this theory. Nevertheless, the well-recognized difficulty in localizing microgastrinomas and the short follow-up continue to suggest that this case represents another example of a metastatic gastrinoma with an, as yet, unidentified primary.

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