CASE REPORT

Severe chronic diarrhoea secondary to primary lymph node gastrinoma

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SUMMARY

The existence of primary lymph node (LN) gastrinoma is questionable and controversial. In fact, the presence of gastrinoma in such uncommon site raises the possibility of metastasis from another occult primary site. An extensive evaluation and careful follow-up is always warranted. A female aged 48 years presented with chronic abdominal pain and watery diarrhoea. Her serum gastrin and chromogranin were elevated, and an underlying gastrinoma was suspected. Further evaluation with an octreotide scan, an endoscopic ultrasound and a secretin stimulation test confirmed the diagnosis. Further evaluation for multiple endocrine neoplasia-1 syndrome was negative. She underwent a surgical enucleation near the head of the pancreas. No other lesions were found after careful exploration of the gastrinoma triangle. Histology showed a LN with a neuroendocrine tumour that tested positively with gastrin and chromogranin stains. Her symptoms resolved postoperatively, her serum gastrin normalised and a repeated octreotide scan was negative.

BACKGROUND

Gastrinomas are the most common type of pancreatic neuroendocrine tumours (PNETs).¹ Most cases are sporadic; however, they can occur as part of multiple endocrine neoplasia-1 syndrome (MEN-1).^{2–6} The most common symptoms of gastrinoma are abdominal pain and secretory diarrhoea. Peptic ulceration and severe esophagitis are not uncommon.⁴ Sporadic gastrinomas usually occur in the gastrinoma triangle, which is linked embryonically to the ventral pancreatic bud.^{1 7 8} Ectopic and extra-abdominal sites for gastrinomas have been described as well.^{9–14} The existence of primary lymph node (LN) gastrinomas is questionable and controversial.^{3 10 12 15–21} Determining whether they represent primary tumours or metastases from an occult primary site has been challenging. It remains a diagnosis of exclusion and has certain diagnostic criteria as well.^{10 12 15} The proposed diagnostic criteria include rapid normalisation of the serum gastrin level after surgical excision of the tumour, absence of other primary tumours after careful surgical exploration, continuous normalisation of serum gastrin and absence of disease during the postoperative follow-up period. In conclusion, primary LN gastrinoma is uncommon but has been reported. Careful surgical exploration as well as postoperative follow-up are always warranted.^{10 15 17}

CASE PRESENTATION

An African-American female aged 48 years presented with a history of recurrent acute on chronic pancreatitis, peptic ulcer disease with successfully eradicated *Helicobacter pylori* infection and recurrent *Clostridium difficile* infection. She presented to our institution with chronic abdominal pain and watery diarrhoea (15–20 episodes daily) that was severe enough to cause dehydration, acute kidney injury and electrolyte imbalance. On evaluation, she appeared to be dehydrated and distressed. An abdominal examination showed mild tenderness to palpation with no rebound tenderness, guarding or rigidity.

INVESTIGATIONS

Initial laboratory workup showed the following levels: Na 138 mmol/L (normal: 136–144 mmol/L), Cl 103 mmol/L (normal: 95–105 mmol/L), K 3.5 mmol/L (normal: 3.6–5.1 mmol/L), creatinine 3.6 mg/dL (normal: 0.9–1.2 mg/dL), lipase 23 units/L (normal: 13–60 units/L), haemoglobin 13.6 g/dL (normal: 12–16 g/dL) and white blood cells 13 600/cmm (normal: 4000–11 000/cmm). She was admitted for the management of acute kidney injury, fluid and electrolyte replacement and symptomatic control.

A non-contrasted CT scan of the abdomen and pelvis did not show any acute abdominal processes. Tissue transglutaminase IgA was 1 unit/mL (normal: <4 units/mL). Her stool studies were negative for *C. difficile*. Additionally, her stool split fats were normal, stool Na was 171 mmol/L and stool K was 4.5 mmol/L. This indicated secretory diarrhoea. At that point, endocrine-related causes of secretory diarrhoea were suspected.

On further evaluation of the endocrine-related aetiology of her diarrhoea, the serum gastrin level was 3530 pg/mL (normal: <180 pg/mL) (table 1), somatostatin was 3 pg/mL (normal: 10–22 pg/mL), vasoactive intestinal peptide was 60 pg/mL (normal: <75–190 pg/mL) and 5-hydroxyindoleacetic acid (5-HIAA) was 6.4 mg/24 hours of urine collection (normal: 2–6 mg/24 hours). The repeated gastrin level after 1 week off of proton pump inhibitors was 583 pg/mL, with a gastric pH of 1.9 (table 1) and chromogranin A tumour marker of 2600 ng/mL (normal: <36.4 ng/mL). These results created suspicion of gastrinoma.

An octreotide scan (figure 1A) was performed and showed abnormal radiopharmaceutical accumulation near the region of the pancreatic head, in addition to 1.2×1.1 cm pedunculated enhancing

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Table 1 Patient's serum gastrin level

Result	Serum gastrin level (pg/mL)	Note
1	3530	Patient was on proton pump inhibitors
2	583	After 1 week off of proton pump inhibitors
3	2882	Secretin stimulation test baseline value
4	6677	Secretin stimulation test maximum value, which provided biochemical confirmation of gastrinoma
5	70	Postoperative gastrin level

mass extending from the posterior aspect of the pancreatic head. Endoscopic ultrasound showed mild diffuse hypoechogenicity in the pancreatic parenchyma but no calcifications, masses or cystic lesions. There was a possible small rounded hypoechoic lesion posterior to the pancreas close to the inferior vena cava that appeared to be separate from the pancreas. The endocrine team was consulted and a secretin stimulation test was ordered for biochemical confirmation of the disease. The test revealed a baseline gastrin level of 2882 pg/mL and maximum level of 6677 pg/mL, which was consistent with gastrinoma (table 1). Other laboratory results, including a screening for MEN-1, were negative. A triple-phase CT scan of the pancreas (figure 2) showed a pedunculated 1.3×1.5×2.3 cm hyperenhancing lesion arising from the pancreatic head.

TREATMENT

The patient was started on 50 µg subcutaneous octreotide every 8 hours. Additionally, she experienced significant symptomatic improvement, with a lower frequency of bowel movements and more formed stools. She was referred for evaluation for either surgical enucleation or Whipple surgery. Intraoperatively, a 2 cm pedunculated bilobed lesion arising from the posterior pancreatic

head was identified. The lesion was systematically freed from its surrounding tissue for a complete enucleation. A thorough intraoperative examination of the remainder of the gastrinoma triangle using intraoperative ultrasound and duodenal mobilisation failed to reveal any additional suspicious lesions. The frozen section was consistent with a neuroendocrine tumour and LN tissue. Biopsy results showed a low-grade neuroendocrine tumour, and an immunohistochemical stain for gastrin (figure 3) showed diffuse cytoplasmic positivity.

OUTCOME AND FOLLOW-UP

The patient continued to have symptomatic improvement post-operatively. Her serum gastrin decreased to 70 pg/mL 2 months postoperatively (table 1). A repeated octreotide scan was negative (figure 1B). She continued to follow-up with the gastroenterology and oncology clinics.

DISCUSSION

Gastrinoma is the most common type of PETs, accounting for 70% of cases with an annual incidence of approximately 1–3 cases for every 1 000 000 individuals.¹ Gastrinomas are usually sporadic; however, 25%–30% of cases occur as part of MEN-1 syndrome.^{2–4} MEN-1 syndrome-associated gastrinomas are usually microscopic, multicentric, located most exclusively in

Figure 2 A triple-phase CT scan of the pancreas showing pedunculating hyperenhancing lesion near or arising from the posterior aspect of pancreatic head.

Figure 1 (A) The preoperative octreotide scan showing an abnormal focus of radiopharmaceutical accumulation near the region of the pancreatic head, in addition to a pedunculating enhancing mass near or extending from the posterior aspect of the pancreatic head. (B) The postoperative octreotide scan showing no abnormal focus of uptake of the radiopharmaceutical.

Figure 3 H&E stain of the biopsy (A) shows low-grade neuroendocrine tumour and lymph node. Immunohistochemical stain for chromogranin (B) and gastrin (C, D) show diffuse cytoplasmic positivity.

the duodenum and associated with overall better long-term survival.^{2,5,6}

Most gastrinomas (90%) occur in the gastrinoma triangle. The tissue within this triangle is derived from the ventral pancreatic bud.⁷ It is bound by the second and third parts of the duodenum inferiorly, confluence of the cystic and common bile duct superiorly and junction of the neck and body of the pancreas medially.^{1,7,8} The duodenal wall and the pancreas are the most common locations for gastrinomas⁹; however, they may also occur in a variety of ectopic sites, even extra-abdominal ones.^{10–13} Additionally, gastrinomas can metastasize to a variety of locations, including the LNs and liver. In fact, approximately 50%–60% of gastrinomas are malignant, and 50%–80% of gastrinomas have already metastasized at the time of diagnosis.^{9,14}

The existence of primary LN gastrinomas is questionable and controversial.^{3,10,12,15–21} The finding of a gastrinoma in such an unusual location raises a question regarding whether it represents a primary tumour or a metastasis from an occult primary site. There are many case reports of primary LN gastrinomas.^{18–21} In addition, two studies that were performed by Norton *et al*¹⁰ and Arnold *et al*¹⁵ provided extensive data on the topic. In these studies, approximately 58% (26/45) and 62% (13/21), respectively, of patients whose disease was limited to regional LN had an initial cure. Both studies showed that 70% of those patients remained cured postresection.

The existence of primary LN gastrinomas is also supported by the presence of neuroendocrine-producing and gastrin-producing cells via immunohistochemical stains in regional LNs in more than one study.^{3,16} There is no solid embryological basis for the presence of neuroendocrine cells within lymphatic tissue. However, one theory is the entrapment theory, which suggests that pancreatic stem cells from the ventral bud become dispersed and incorporated into lymph tissue and the duodenal wall, probably during the dorsal migration of the ventral pancreatic bud during the fifth and sixth weeks of fetal development.^{7,8}

Diagnostic criteria for LN gastrinoma have been proposed.^{10,12,15} They include a rapid normalisation of the serum gastrin level after surgical excision of the tumour, absence of another primary tumour after careful surgical exploration, including in the

duodenum and continuous normalisation of serum gastrin and absence of disease during postoperative follow-up. These diagnostic criteria also emphasise two important points. First, adequate surgical exploration in patients with only LN involvement without evidence of hepatic metastases is important.¹⁷ Second, careful postoperative follow-up is critical.^{10,15,17}

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Learning points

- Gastrinoma is the most common type of pancreatic neuroendocrine tumours. It should be suspected in all patients with unexplained secretory diarrhoea and peptic ulceration, especially if recurrent, resistant or severe.
- The wall of the duodenum, and the pancreas are the most common locations for gastrinomas. However, ectopic and extra-abdominal sites have been described.
- The existence of primary lymph node (LN) gastrinoma is still questionable and controversial.
- A careful follow-up is very important in cases of primary LN gastrinoma to exclude the presence of another occult primary site.

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