CASE REPORT

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Bulky gastrinoma of the common bile duct: Unusual localization of extrapancreatic gastrinoma - case report

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Zollinger-Ellison syndrome is characterized by elevated levels of serum gastrin associated with increased gastric acid secretion, gastrointestinal ulcerations and diarrhea. Most gastrinomas (75%) occur sporadically and are located within the gastrinoma triangle. Extraduodenal, extrapancreatic and extranodal gastrinomas have been shown in 5.6% of the patients with Zollinger-Ellison syndrome who underwent surgery. We report a 44-year-old female who had been complaining of nausea and diarrhea for 12 years. Abdominal computed tomography and magnetic resonance imaging detected a homogeneous, regular-shaped 6 x 7 cm solid mass, located between the liver, right kidney and inferior vena cava. Somatostatin receptor positive scanning led us to investigate a neuroendocrine tumor. Serum gastrin level was found very high and the patient underwent surgery. Local excision of the tumor was performed, and an 8x6x5 cm, well-capsulated, solitary mass, originating from the common bile duct was removed. The unique feature of our case is the unusual localization, and although the tumor was very large in size, only capsule invasion was observed with no evidence of distant metastasis.

Key words: Extrapancreatic gastrinoma, gastrinoma, common bile duct, neuroendocrine tumors

Safra yolundan köken alan dev gastrinoma: Nadir görülen ekstrapankreatik yerleşim - Vaka sunumu

Zollinger-Ellison Sendromu serum gastrin düzeyinde yükseklik, artmış mide asiti, yaygın gastrointestinal ülserasyonlar ve ishal ile karakterizedir. Gastrinomalar sıklıkla (%75) sporadik olarak görülür ve gastrinoma üçgeninde yerleşirler. Cerrahiye gönderilen Zollinger-Ellison Sendromu hastalarının %5.6 kadarı ekstraduodenal, ekstrapankreatik ve ekstranodal gastrinomadır. Hastamız 44 yaşında kadın, 12 yıldır bulantı ve diyare şikâyetleri mevcuttu. Abdominal bilgisayarlı tomografi ve manyetik rezonans görüntülemede homojen, düzgün sınırlı, 6x7 cm solid kitle, karaciğer-sağ böbrek ve inferior vena cava arasında yerleşmiş olduğu görüldü. Somatostatin reseptör pozitifliği bu kitlenin nöroendokrin tümör olduğunu düşündürdü. Hastanın serum gastrin düzeyi çok yüksek bulundu ve hasta cerrahiye verildi. Cerrahi sırasında kitlenin 8x6x5 cm boyutlarında iyi kapsüllü ve koledoktan köken aldığı görüldü. Bu vakanın özelliği çok nadir görülen bir yerleşimde koledoktan köken almış olması ve çok büyük olduğu halde kapsül invazyonu ve metastaz yapmamış olmasıdır.

Anahtar kelimeler: Gastrinoma, ekstrapankreatik gastrinoma, koledok, nöroendokrin tümör

INTRODUCTION

Pancreatic endocrine tumors may present as isolated tumors or as part of a genetic syndrome such as multiple endocrine neoplasia type I (MEN-I). These tumors are characterized by the secretion of one or more peptide hormones resulting in a constellation of symptoms attributed to hormone ex-

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cess, such as hypoglycemia, gastric ulceration or watery diarrhea (1).

Zollinger-Ellison syndrome (ZES) was first described by Zollinger and Ellison in 1955 (2). This syndrome is characterized by elevated levels of serum gastrin associated with increased gastric acid secretion, gastrointestinal ulcerations and diarrhea. Abdominal pain, diarrhea and heartburn are the common presenting symptoms observed in more than 70% of patients with ZES (3). Symptoms usually begin 5-6 years prior to the diagnosis of ZES and are related to excessive gastric acid secretion, resulting in severe refractory peptic ulcers complicated by hemorrhage, perforation and stricture. Anti-secretory therapy usually abolishes the diarrhea and ameliorates many clinical features of ZES (1).

Approximately 66% of gastrinomas are sporadic (4), whereas approximately 25% are associated with MEN-I syndrome. Sporadic tumors are most often solitary, and approximately 40-85% of cases are malignant. Nevertheless, gastrin-secreting tumors are usually slow-growing and associated with prolonged survival, despite complications arising from intestinal ulcerations. Patients with MEN-I tend to be of younger age at the onset of the disease and usually present with multiple metastases at the time of diagnosis (1).

Gastrinomas commonly arise from within the pancreas; about 5.6% of patients have a primary gastrinoma located in an ectopic site (5), including the body of the stomach, jejunum, peripancreatic lymph nodes, splenic hilum, root of the mesentery, omentum, liver, gallbladder, common bile duct, and the ovary (4,6-12).

The diagnosis of gastrinoma is based on the detection of elevated fasting serum gastrin levels (>200 pg/ml) and gastric acid hypersecretion (3,13). Although many patients with ZES have serum gastrin levels >500 pg/ml, a secretin stimulation test may be performed when serum gastrin levels are in the range of 200-500 pg/ml to confirm the diagnosis.

Magnetic resonance imaging (MRI) and computed tomography (CT) can be used for localization of the tumors. Conventional endoscopy or an upper gastrointestinal series may give additional information (3). Radiolabeled octreotide scanning has been useful for detecting the primary tumor and metastases (14). Endoscopic ultrasonography (EUS) has been utilized for tumor localization with increasing success (15). Angiography with selective venous sampling may also be helpful.

Somatostatin receptor scintigraphy (SRS) and measurement of gene products commonly expressed in endocrine cells, such as neuron specific enolase, have been used to monitor the tumor response to therapy (16,17).

Initial treatment of patients with gastrinoma is directed at pharmacologic reduction of gastric acid secretion (18). All patients with sporadic gastrinoma should undergo surgical exploration. Local tumors without metastasis can be removed, but surgery is generally not indicated in patients with gastrinoma associated with MEN-I syndrome because these individuals often have multiple, small pancreatic tumors that are not suitable for surgical resection (1,19).

CASE REPORT

We report a 44-year-old female who had been complaining of nausea and diarrhea for 12 years. Voluminous diarrhea without blood or mucus was seen 5-6 times a day, accompanied by nausea and vomiting. She had been repeatedly evaluated for diarrhea without establishing a cause. She had an upper gastrointestinal bleeding in 1995 and the following gastroscopy detected a *Helicobacter pylori*-negative ulcer by gastric biopsy. She had been using H_2-receptor blockers since then. Abdominal USG, esophago-gastro-duodenography and rectoscopy were reported as normal. A high serum calcium level (11.7 mg/dl) was detected once in 1998, but this was not confirmed on repeated tests.

The patient reported that her complaints were tolerable from 1998 to 2005; therefore, she did not have any biochemical analysis performed during this period. In June 2005, all laboratory findings were normal except high levels of amylase (322 U/L; normal range <80 U/L) and lipase (745 U/L; 0-30 U/L), when she was admitted to the hospital because of tachycardia unresponsive to β-blockers. Abdominal CT and MRI detected a homogeneous, regular-shaped 6x7 cm solid mass, located between the liver, right kidney and inferior vena cava (Figures 1a, 1b). The mass did not seem to involve the pancreas but was reported to be possibly originating from another organ in the vicinity of the pancreas (gallbladder, bile duct, liver etc.) or lymph nodes. There was no sign of distant metastasis. Erosive gastritis and bulbitis were shown by gastroscopy and gastric biopsy. Octreotide scan-

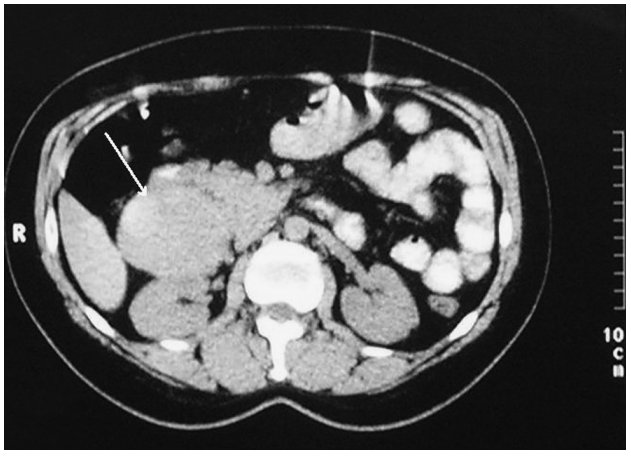

Figure 1a. Magnetic resonance imaging (MRI) view of the mass.

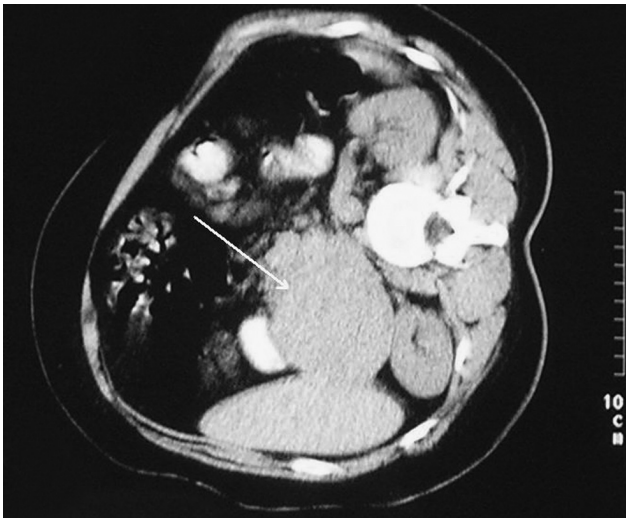

Figure 1b. MRI view of the mass in a different position.

ning revealed a somatostatin receptor-positive tumor (Figure 2). Although the serum calcium level (9.5 mg/dl) was normal in that period, parathyroid hormone (PTH) was high (122 pg/dl; normal ranges 10-69 pg/ml), and there was a suspicious adenoma on parathyroid scanning. Pituitary hormone levels were all normal. The patient was referred to our center for further evaluation of MEN-I.

Her initial systemic examination was normal. Among laboratory findings, glucose and the other biochemical values were normal except 25(OH)D3 levels, which were low (12 ng/ml; 20-70 ng/ml). Hyperparathyroidism was considered to be secondary to vitamin D deficiency. Vitamin D replacement was initiated, and PTH levels decreased after two months of therapy. Pituitary MRI was performed and reported as normal.

Somatostatin receptor-positive scanning led us to investigate a neuroendocrine tumor. We excluded pheochromocytoma and carcinoid tumors by normal levels of 24-hour urine vanillylmandelic acid (VMA) (4.9 ng/d; 3-9 ng/d), metanephrines (83 µg/d; 52-341 µg/d), 5-hydroxyindoleacetic acid (HIAA) (23.8 µmol/d; 10.4-31.2 µmol/d), and neuron-specific enolase (4.7 µg/L; 0-12.5 µg/L) at two different time periods. Serum gastrin level was very high (> 900 pg/ml; 25-125 pg/ml), but she had been taking H_2-receptor blocker drugs 40 mg/d continuously for 12 years. No ulcer formation was detected on gastroscopy, and gastric pH was 7 after withdrawal of H_2-receptor blocker drugs for one week. We decided to stop the H2-receptor blocker drugs for as long as she could tolerate to measure the serum gastrin level again. She managed to be off the drug for three weeks and serum gastrin level was found higher then 65000 pg/ml, which led us to think that the tumor was a gastrinoma.

Local excision of the tumor was performed, and an 8 x 6 x 5 cm, well-capsulated, solitary mass, originating from the common bile duct was removed. The origin of the mass was detected by surgery and pathology. Pathological examination revealed a well-differentiated neuroendocrine tumor with invasion of the capsule (Figure 3). Immunohistochemical staining with chromogranin-A, synaptophysin and cytokeratin was positive (Figure 4).

In the follow-up, the complaints of the patient have diminished, with fewer intermittent attacks of diarrhea. The gastrin level four months after the operation was 60 pg/ml. There was no residual mass on postoperative abdominal MR.

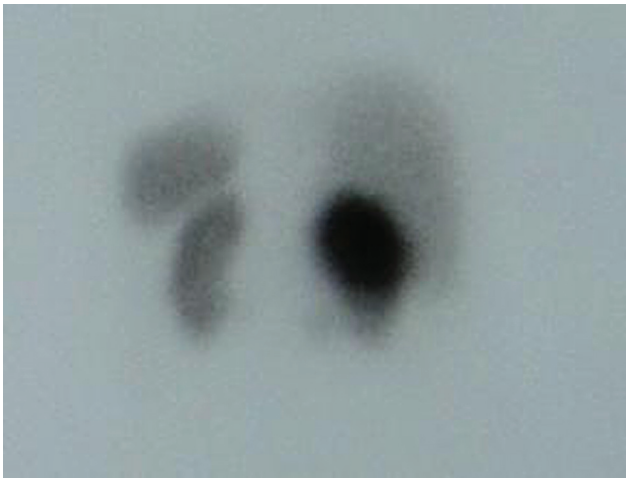

Figure 2. Octreotide scintigraphy of the patient.

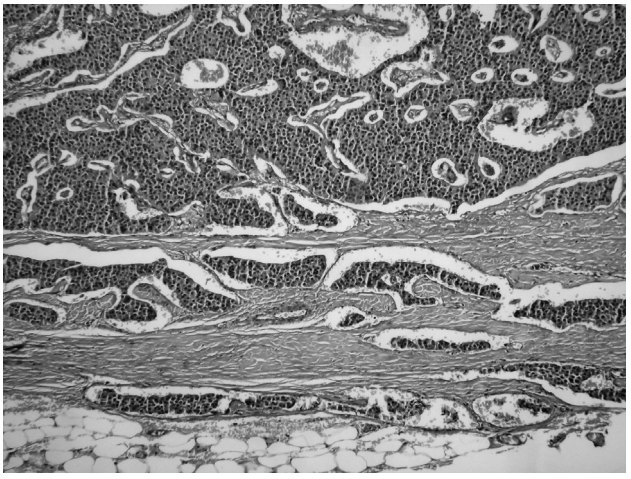

Figure 3. Capsule and lymphovascular space invasion (H&E x 100).

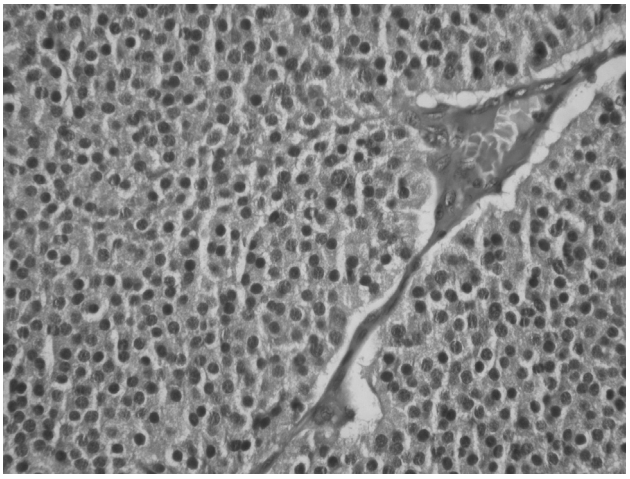

Figure 4. Cellular uniformity and chromatin pattern typical of neuroendocrine tumor (H&E x400).

DISCUSSION

Primary endocrine tumors of the biliary tract are very rare. Since the common bile duct is not located within the gastrinoma triangle, this unexpected localization makes the diagnosis difficult. To our knowledge, only two sporadic gastrinoma cases originating from the common bile duct have been reported in the literature (5,20). Extraduodenal, extrapancreatic and extranodal gastrinomas have been shown in 5.6% of the patients with ZES who underwent surgery (5).

The unique feature of our case is that although the tumor was very large in size, only capsule invasion was observed with no evidence of distant metastasis. The unexpected localization of the tumor prolonged the diagnostic procedures. Octreotide scintigraphy and high fasting gastrin levels were the most important diagnostic tools. Microscopic examination and immunohistochemical markers confirmed our diagnosis.

Although the treatment of tumors in the gastrinoma triangle generally requires Whipple surgery, single distinct tumors without metastasis may be excised locally. Curable surgical resection has usually been effective in cases resembling ours (19). In the follow-up of our patient after surgery, her complaints had diminished and serum gastrin had returned to normal levels.

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