Primary gastrinoma of the gallbladder: a case report and review of the literature

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Case Report

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Abstract

Background: Primary gallbladder gastrinoma is an exceptionally uncommon tumor which is a rare form of neuroendocrine neoplasm. Until now, no cases of primary gallbladder gastrinoma and rare cases of primary gastrinoma from the biliary system have been reported.

Case presentation: We reported a 50-year-old female with watery diarrhea and intermittently received proton pump inhibitors as treatment. Enhanced computed tomography (CT) imaging and Octreotide imaging uncovered a solitary tumor at the hepatic hilar region. The tumor was found originated from the wall of the gallbladder during the surgery and a subsequent laparoscopic cholecystectomy was exerted. Histological analysis revealed a primary neuroendocrine tumor from the gallbladder.

Conclusion: This case confirmed that primary gallbladder gastrinoma represents a distinct nosological entity. Immunohistochemical analysis plays a pivotal role in the diagnosis process. Due to limited knowledge regarding primary gallbladder gastrinoma, we aim to contribute valuable insights into this rare condition by providing unique information and present the therapeutic value of surgery.

Background

Gastrinoma was the cause of Zollinger-Ellison syndrome (ZES), which was characterized by excessive stomach acid secretion, leading to severe acid-related digestive disorders and diarrhea. It has been reported that 80% of gastrinomas were sporadic while 20%-30% of gastrinomas were associated with Multiple Endocrine Neoplasia Type 1 (MEN1). 50%-88% of patients with sporadic ZES have gastrinomas located in the duodenum[1]. Most primary gastrinomas are reported within the traditional gastrinoma triangle which is bounded by: the cystic duct and common bile duct junction, the second and third portions of the duodenum junction, and the neck-body junction of the pancreas[2]. However, rare cases reported primary gastrinomas occurred in other abdominal organs or tissues apart from the pancreas and duodenum including the lymph nodes, lung, ovaries, hepatobiliary tract, etc[3–6]. Primary gastrinomas located in the biliary tract are extremely uncommon, and to date, there have been no literature reports on primary gastrinomas originating in the gallbladder. We herein report the first case of a primitive gallbladder gastrinoma, describing the diagnosis and operative procedures with pathological results as confirmation.

Case report

Clinical presentation

A 50-year-old female patient had watery diarrhea with no apparent cause 2 years ago, average 7-8 times a day, without complaints of abdominal pain and distension. Informed consent was obtained from the patient. She described her stools with no bloody or mucus elements. Her symptoms could improve after taking rabeprazole intermittently but it was not treated systematically. In November 2022, she visited our gastroenterology outpatient clinic and received a gastroduodenoscopy which suggested gastric and duodenal ulcers. 711 pg/ml of gastrin was found at the same time, confirming the diagnosis of ZES. The patient further completed an enhanced abdominopelvic Computed Tomography (CT) scan, which reported a round-like soft tissue density shadow with a diameter of approximately 1.6 cm in the hepatic hilar region, and the enhanced scan showed significant enhancement (Fig. 1). Octreotide imaging reported high expression of somatostatin receptors in the
hepatic hilar region (Fig. 2a). Single Photon Emission Computed Tomography (SPECT)/CT fusion imaging further clarified the localization of the tumor (Fig. 2b). Subsequent laboratory evaluation excluded the presence of multiple MEN1. Above all, gastrinoma was first considered as possible. Lastly, the patient underwent laparoscopic surgery and provided consent for a potential hepatic hilar tumor resection which may involve biliary reconstruction.

After preoperative preparation and evaluation, the patient underwent a laparoscopic hilar tumor and cholecystectomy on January 31, 2023. We were surprised to find that the nodule was growing entirely from the wall of the gallbladder. The tumor was found to be non-invasive, without involvement of the surrounding liver parenchyma or bile duct structures, with approximately 2 cm in diameter, characterized by a smooth and regular surface. The whole gallbladder together with tumor was excised. No abnormal lymph node was detected in the hepatic hilum area. No lesion was found in the examined stomach and duodenum. Based on the intraoperative exploration and tumor characteristics, no further procedures were performed during the surgery. At the time of postoperative day no. 1, the patient’s serum gastrin concentration was normal at 17 pg/ml. The patient had good postoperative recovery and was discharged on the fourth day after the operation. After a 4-month post-operative follow-up, the patient did not show any symptoms and exhibited substantial improvements in her quality of life.

**Macroscopic and microscopic examination**

As the macroscopic view of the tumor shown in Fig. 3a, b, a smooth tumor is located in the neck of the gallbladder. The longitudinal section of the mass can help to better observe the relationship between the tumor and gallbladder. The examination of immunohistochemistry performed on paraaffin-embedded sections confirmed a primary neuroendocrine tumor originating from gallbladder, with 2% of cells staining positive for Ki67 (Fig. 4c) and mitotic figures < 2 for 10HPF. Microscopic examination confirmed the source of the tumor which was located in the muscular layer of gallbladder (Fig. 4a, b). Immunohistochemical staining for Gastrin showed strongly positive and diffuse positive in tumor cells (Fig. 4d). In light of the pathological findings, the diagnosis of a primary neuroendocrine tumor (NET-G1) was made.

**Discussion and conclusions**

Gastrinomas were the second most common functional neuroendocrine tumor (NET) which lead to ZES. The incidence of gastrinoma is 0.5–3/million population per year. Most previously reported gastrinomas of hepatobiliary tract origin were from hepatic parenchyma[7] or the bile duct. However, to our knowledge, we reported the first primary gallbladder gastrinoma. Until now, only six pieces of literature describing ten cases of gastrinomas that originate from the biliary tract have been reported in the English literature[6, 8-12], including two cases with MEN1 reported by Price et al[11].

Gastrinomas of the biliary tract can originate from different parts of the biliary system which were shown in Table 1. The tumors are usually small in size as six reported cases have diameters ranging from 0.6cm to 3.0cm. Apart from showing common gastrointestinal symptoms due to hypersecretion of gastric acid, patient may exhibit symptoms of jaundice due to tumor compression[8]. All the reported cases underwent surgical resection and were followed up for a period ranging from 4 months to 7 years. Most of the cases showed no evidence of recurrence and demonstrated a favorable surgical outcome. Only one patient died due to gastrinoma as lymph node metastasis was found during the surgery and the disease recurred 4 years after the surgery. She then
received long-acting release octreotide treatment, radiation therapy targeting bone metastatic lesions and \textsuperscript{111}In-labeled octreotide infusion therapy and passed away in the seventh year after the surgery.

Although case reports on sporadic primary gastrinoma originating from the biliary system are extremely rare, large-scale clinical cohorts have provided references for the incidence rate of the disease. Norton et al. retrospectively reported 4 primary liver and 3 primary biliary tract tumors within 223 patients who underwent surgery to remove gastrinomas without MEN1 and describe the prognosis of rare gastrinomas originating from the hepatobiliary tract\cite{6}. The result showed that 4 patients (57\%) with long-term follow-up had recurrent disease and 3 patients (43\%) were identified with portal lymph node metastases during the surgery. They recommended that lymph nodes in the porta hepatis should be routinely excised. However, the rarity of the disease limited the spread of the surgical approach. Similar research conducted by Wu et al. reported 1 primary biliary tract and 3 primary liver gastrinomas within 215 patients with confirmed diagnoses of ZES\cite{12}. In regard of the approximate incidence of primary biliary tract gastrinomas as 1\% in these two cohorts, we have reasons to assume more similar cases have not been documented.

The diagnosis of resected primary biliary tract gastrinoma may be difficult to explain\cite{13}. In terms of the primary site, the tumor could be confused with lymph node metastases. About 85\% to 90\% of gastrinomas are located within the gastrinoma triangle\cite{14} which contains the whole common bile duct. One theory explained that the migration of stem cells from the gastrinoma triangle to the lymph node structures surrounding the pancreas through the route of lymphatic metastasis\cite{15}. On the other hand, despite the use of highly sensitive methods such as somatostatin receptor imaging and endoscopic ultrasound ultrasonography, these methods often fail to detect most small duodenal tumors (1-5mm) in 60\%-80\% of patients with ZES\cite{6, 13, 16-18}. This suggested small duodenal tumors may be primary rather than other ectopic tumors. However, in one clinical trial conducted by Cadiot et al., researchers found conventional techniques (CT scan and endoscopic ultrasonography) and Octreoscan scintigraphy had sensitivities of 58\% and 58\%. Respectively, for detecting tumors, their combination had a sensitivity of 90\% in correctly identifying tumors. They also found the Octreoscan scintigraphy had the ability to identify duodenal gastrinoma as small as 3mm\cite{18}. In light of previously reported primary gastrinomas of the biliary tract do occur and the Octreotide imaging result of the patient excluded the possibility of a primary tumor in other sites, our study supported the existence of primary gallbladder gastrinoma.

Sporadic gastrinoma with no evidence of metastasis should undergo exploratory laparotomy and radical surgical resection. This patient has no evidence of distant lymph node metastasis which was confirmed by the whole-body radionuclide scanning and the pathological result further identified the origin of tumor. No abnormal lymph nodes were found in the gastrinoma triangle and the hepatoduodenal ligament during surgery. After four months post-surgery, the patient exhibited complete resolution of watery diarrhea symptoms. Above all, we have compelling grounds to assert that the surgery has achieved success while further follow-up is still needed for the patient's symptom changes.

As demonstrated by the presented case, we possess strong justification to support the notion that primary gallbladder gastrinoma represents a distinct nosological entity which deserves further attention. The histogenesis of endocrine tumors in the biliary system remains unclear. Existing hypotheses include that multipotential endocrine cells in the biliary system, ectopic pancreatic tissue in the bile duct and metaplastic epithelium in the biliary tree\cite{8}. Further research is needed to explore the tumor origin of primary gallbladder gastrinoma from genetic perspective.
Abbreviations

CT  computed tomography
ZES  Zollinger-Ellison Syndrome
MEN-1  Multiple Endocrine Neoplasia Type 1
SPECT  Single Photon Emission Computed Tomography
NET  neuroendocrine tumor

Declarations

Acknowledgement

The authors thank the patient for her cooperation.

Ethics approval and consent to participate

The authors confirm that they obtained the necessary informed consent forms from the patient. They were informed that the patient's personal information, including names and initials, would not be disclosed in the publication and all efforts were made to ensure the patient's identity remains concealed.

Consent for publication

The patient provided written informed consent for the publication of this case report. A copy of the written consent is available for review if necessary.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential of competing interests.

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Availability of data and material statement
The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Authors’ contributions

Y-GL and YZ collected the clinical data, image data, and pathology data. Y-GL was a major contributor to writing the manuscript. XL and Y-YX were mainly responsible for the revision of the article. All authors contributed to the article and approved the submitted version.

References


Tables

Table 1 Reported cases of biliary tract gastrinomas including symptom, site, size, gastrin level and follow-up period, and outcome
<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Cases</th>
<th>Sex/Age</th>
<th>Symptoms</th>
<th>Site</th>
<th>Size (cm)</th>
<th>Gastrin level before surgery</th>
<th>Follow-up period months</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Mandujano-Vera et al. 1995[8]</td>
<td>1</td>
<td>F/53</td>
<td>nausea, pyrosis, AP</td>
<td>CBD</td>
<td>2.2</td>
<td>90ng/ml</td>
<td>8</td>
<td>no recurrence</td>
</tr>
<tr>
<td>Martignoni et al. 1999[9]</td>
<td>1</td>
<td>M/60</td>
<td>diarrhea, vomiting, GRD</td>
<td>CHD</td>
<td>1.3</td>
<td>1768 pg/ml</td>
<td>36</td>
<td>no recurrence</td>
</tr>
<tr>
<td>Tarcin et al. 2011[10]</td>
<td>1</td>
<td>F/44</td>
<td>nausea, diarrhea</td>
<td>CBD</td>
<td>8</td>
<td>65000 pg/ml</td>
<td>4</td>
<td>no recurrence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 LHP</td>
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<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 RHD</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Price et al. 2009[11]</td>
<td>1</td>
<td>F/55</td>
<td>NA</td>
<td>junction of CD and CBD</td>
<td>0.6</td>
<td>4500 pg/ml</td>
<td>24</td>
<td>no symptom</td>
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<tr>
<td>Wu et al. 1997[12]</td>
<td>1</td>
<td>M/54</td>
<td>NA</td>
<td>CBD</td>
<td>1.5</td>
<td>1867 pg/ml</td>
<td>5</td>
<td>no recurrence</td>
</tr>
<tr>
<td>Present case</td>
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<td>F/50</td>
<td>AP, distention</td>
<td>gallbladder</td>
<td>1.6</td>
<td>711 pg/ml</td>
<td>3</td>
<td>no recurrence</td>
</tr>
</tbody>
</table>

NA not available, GRD gastroesophageal reflux disease, AP abdominal pain, CBD common bile duct, CHD common hepatic duct, LHD left hepatic duct, RHD right hepatic duct, CD cyst duct

Figures
Figure 1

Cross-sectional image of the contrast-enhanced abdominal Computed Tomography (CT) scan demonstrated a 1.6 cm nodule (yellow solid line) adjacent to the gallbladder
Figure 2

a Octreotide imaging showed increased uptake at the hepatic hilum (yellow arrow) with no significant uptake observed in other abdominal regions. b SPECT-CT imaging indicated the location of the high uptake mass corresponding to the findings on the contrast-enhanced CT.

Figure 3
a Gross photograph of the tumor (yellow arrow) and gallbladder. b The tumor together with a portion of the gallbladder has been sectioned, revealing a close relationship between the tumor and the gallbladder.

**Figure 4**

a, b The tumor is located in the muscular layer of the gallbladder. c Immunohistochemical staining for Gastrin shows strong and diffuse positive in tumor cells (magnificationx100). d NET with a low Ki-67 proliferation index (magnificationx100).