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CASE REPORT

Rare case of a gallbladder neuroendocrine carcinoma

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Abstract
There are no neuroectodermal cells in the gallbladder mucosa. Therefore, gallbladder neuroendocrine carcinoma (NEC) is extremely rare and has a poor prognosis. We report a case of a Japanese man in his 60s with this disease. The patient visited a family doctor for epigastralgia. Blood tests showed no abnormalities, including tumor markers, such as CEA and CA19-9. Abdominal ultrasonography (US) showed a low-echoic mass, 39 × 30 mm, with clear boundaries to the liver from the fundus of the gallbladder. Contrast-enhanced computed tomography showed that the tumor was enhanced early and washed out. Diffusion-weighted MRI showed a high signal. We suspected liver invasion of gallbladder cancer and performed a cholecystectomy, S4 and S5 hepatectomy, and lymphadenectomy. The resected whitish tumor was 29 × 22 mm. The tumor cells had honeycomb growth to the liver from the gallbladder. Tumor cells were poorly differentiated, and there was no stricture of the gland duct. Immunostaining showed that the tumor cells were positive for CD56, chromogranin A and synaptophysin, and about 30% were positive for Ki-67. Our diagnosis was gallbladder NEC with liver invasion. Although most malignant gallbladder tumors are adenocarcinomas, this case indicates that gallbladder NEC should be considered as a differential diagnosis of gallbladder tumor.

Keywords Gallbladder tumor · Liver invasion · Neuroendocrine tumor · Neuroendocrine carcinoma

Introduction

Neuroendocrine carcinomas (NECs) originate from disseminated neuroendocrine cells. NECs account for less than 1% of all malignant tumors. Most NECs are found in the gastrointestinal (66%) and respiratory (31%) tracts [1]. In the gastrointestinal tract, most NECs are found in the rectum, jejuno-ileum, and pancreas [2]; NEC of the gallbladder (GB-NEC) is very rare [3]. Modlin et al. reported that NECs of the extrahepatic duct and gallbladder account for only 0.2–2 and 0.2%, respectively, of all gastrointestinal tract NECs [4–6]. As GB-NEC cases are very rare, a few studies have investigated the mechanisms and treatment of this NEC subtype. Here, we report our experience with a case of gallbladder primary NEC with liver invasion.

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Case report

The patient was a man in his 60s. He visited a nearby doctor for a checkup, with a chief complaint of epigastralgia that had lasted for several months. Abdominal ultrasonography (US) showed a mass in the gallbladder, so the patient was admitted to our hospital for further examination. He had taken medication for hypertension for 30 years, and he had smoked 20 cigarettes/day since the age of 20 years. He had no history of drinking alcohol. His younger sister had colon cancer and breast cancer, and his older brother had prostatic cancer. He was 149 cm tall and weighed 57 kg. His blood pressure was 144/85 mmHg, and his pulse was 65 beats/min. He had neither anemia nor jaundice, and he had abdominal pain. No abnormalities were apparent on blood tests, including tumor markers, such as CEA and CA19-9. Abdominal US showed a low-echoic mass of 39 × 30 mm with clear boundaries to the liver from a fundus of the gallbladder (Fig. 1). Abdominal contrast-enhanced computed tomography (CT) showed an invasive mass to the liver bed from the fundus of the gallbladder. The tumor was enhanced in the early phase and was washed out in the delayed phase (Fig. 2). On magnetic resonance imaging

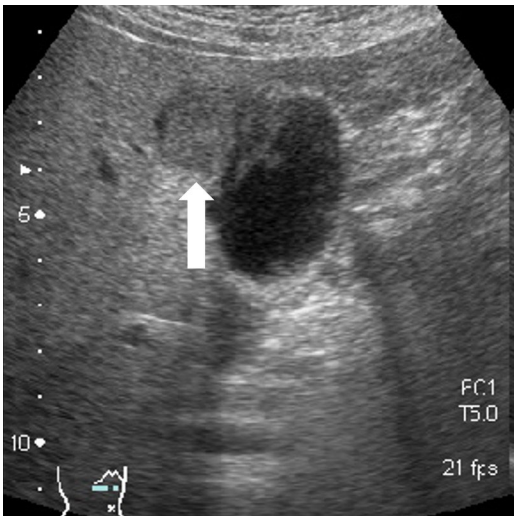

Fig. 1 Abdominal ultrasonography showed a low-echoic mass of 39 × 30 mm with clear boundaries to the liver from the fundus of the gallbladder (arrow)

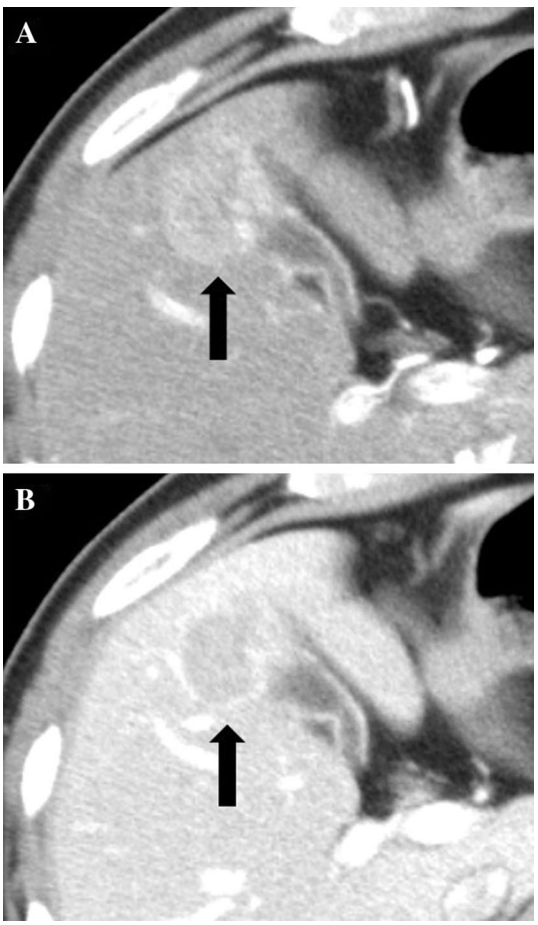

Fig. 2 Abdominal contrast-enhanced computed tomography showed an invasive mass to the liver bed from the fundus of the gallbladder. The tumor was enhanced in the early phase (arrow) (**a**) and was washed out in the delayed phase (arrow) (**b**)

(MRI) examination, the tumor showed a low T1 signal, a high T2 signal, and a high diffusion signal (Fig. 3). Magnetic resonance cholangiopancreatography (MRCP) did not

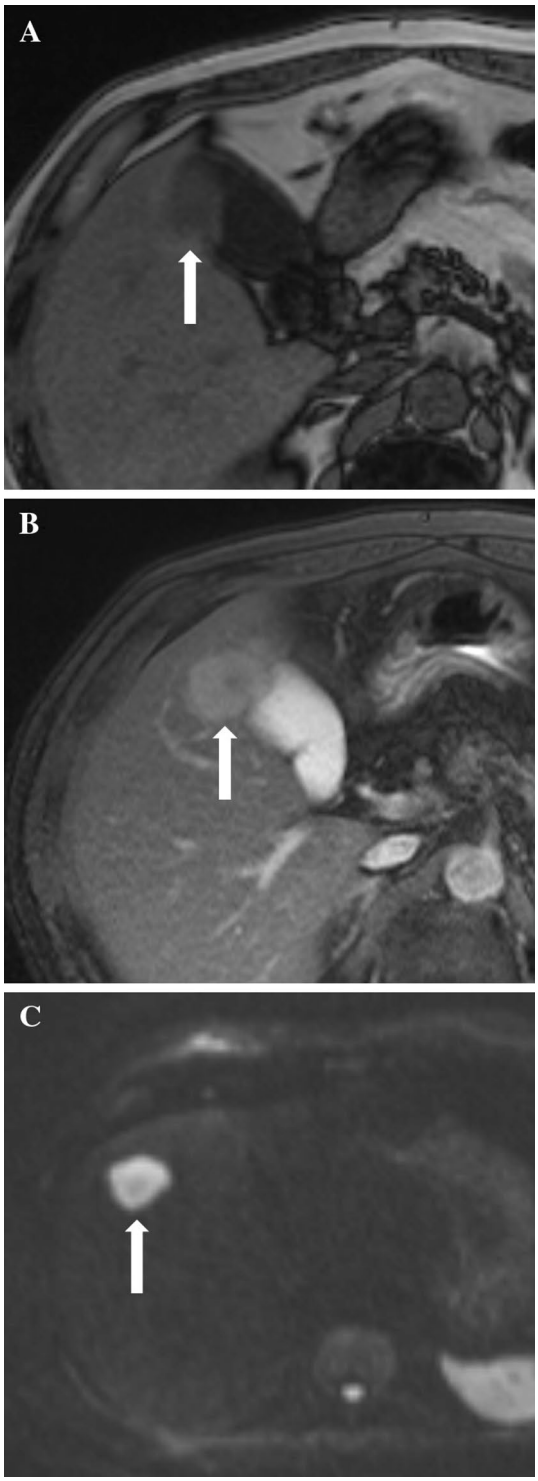

Fig. 3 On magnetic resonance imaging (MRI) examination, the tumor showed a low T1 signal (arrow) (**a**), a high T2 signal (arrow) (**b**), and a high diffusion signal (arrow) (**c**)

show any abnormalities in the bile duct or the pancreatic duct. Endoscopic ultrasonography (EUS) showed findings similar to the US. Endoscopic retrograde cholangiopancreatography (ERC) did not show abnormalities of the bile duct, but showed the defect of the tumor in the gallbladder (Fig. 4). Bile cytological analysis did not show malignant cells. We diagnosed the patient with gallbladder cancer with direct liver invasion. We performed a cholecystectomy, S4 and S5 hepatectomy and lymphadenectomy. The resected specimen was a whitish tumor, 29 × 22 mm, invasive to the liver from the fundus of the gallbladder (Fig. 5). It did not have a submucosal tumor (SMT)-like appearance. It had an infiltrative nodule. There was no necrosis, hemorrhage, or calcification in the tumor. It was exposed to the luminal face of the gallbladder and showed mucosal invasion. This tumor invaded the liver. It had honeycomb growth to the liver from the gallbladder, the tumor cells were undifferentiated, and there was no gland duct stricture. Tumor cells were round to polygonal, and the nuclei had either vesicular chromatin or prominent nucleoli. Immunostaining results indicated that the tumor cells were positive for CD56, chromogranin A, and synaptophysin, and about 30% were positive for Ki-67 (Fig. 6). The patient was diagnosed with primary gallbladder large-cell NEC with direct invasion of the liver. This tumor showed lymphatic and venous invasion, but not nerve invasion. The postoperative course was good; the patient was discharged and has been followed in the outpatient department. We did not prescribe adjuvant chemotherapy or radiation. This patient has had no recurrence for 2,023 days after surgery, and is currently alive.

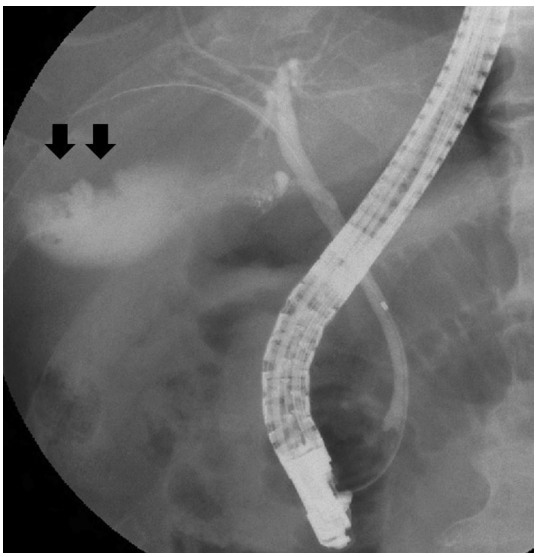

Fig. 4 Endoscopic retrograde cholangiopancreatography (ERC) did not show abnormalities of the bile duct but showed the defect of the tumor in the gallbladder (arrow)

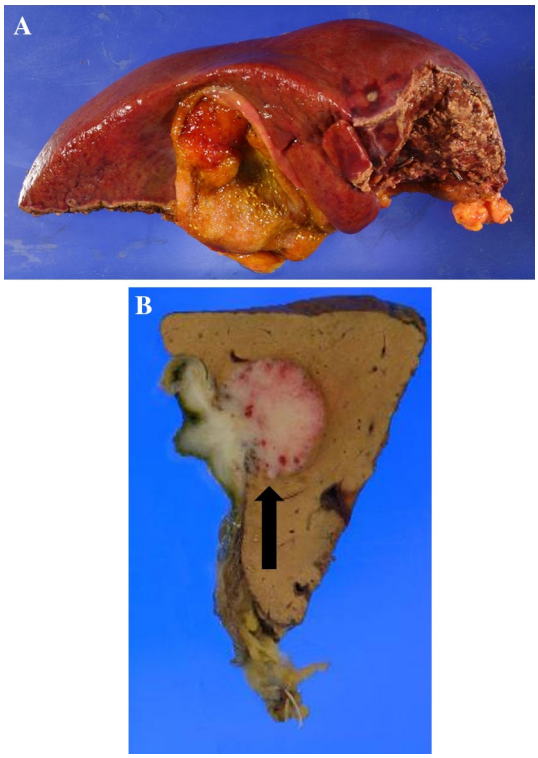

Fig. 5 The resected specimen was a whitish tumor, 29 × 22 mm, invasive to the liver from the fundus of the gallbladder (arrow)

Discussion

Neuroendocrine tumors (NETs) are neoplasms originating from neuroendocrine cells located throughout the body, most commonly in the lung and gastrointestinal tract [5, 7, 8]. NETs are generally subclassified by site of origin and histological characteristics, including tumor differentiation and grade.

Neuroendocrine tumors are classified as NET and NEC by the World Health Organization (WHO) 2010 Classification by proliferation potency (mitotic image or Ki-67 index), and NECs have an extremely poor prognosis because of their low level of differentiation. This case was diagnosed as NEC by the WHO 2010 classification because of the Ki-67 index of ~ 30%, a poorly differentiated neuroendocrine neoplasm. For pancreatic NET (p-NET), the WHO classification was changed in 2017 from what it was in 2010. In the 2017 classification, p-NETs that have a Ki-67 index > 20% or a mitotic index > 20/10 HPF have been classified as both well-differentiated tumors (NET G3) and poorly differentiated tumors (NEC G3). In addition, the term mixed adenoneuroendocrine carcinoma (MANEC) was changed to mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN).

NETs usually appear in the gastrointestinal and bronchopulmonary systems. There are no neuroectodermal cells in the gallbladder mucosa. Therefore, primary gallbladder

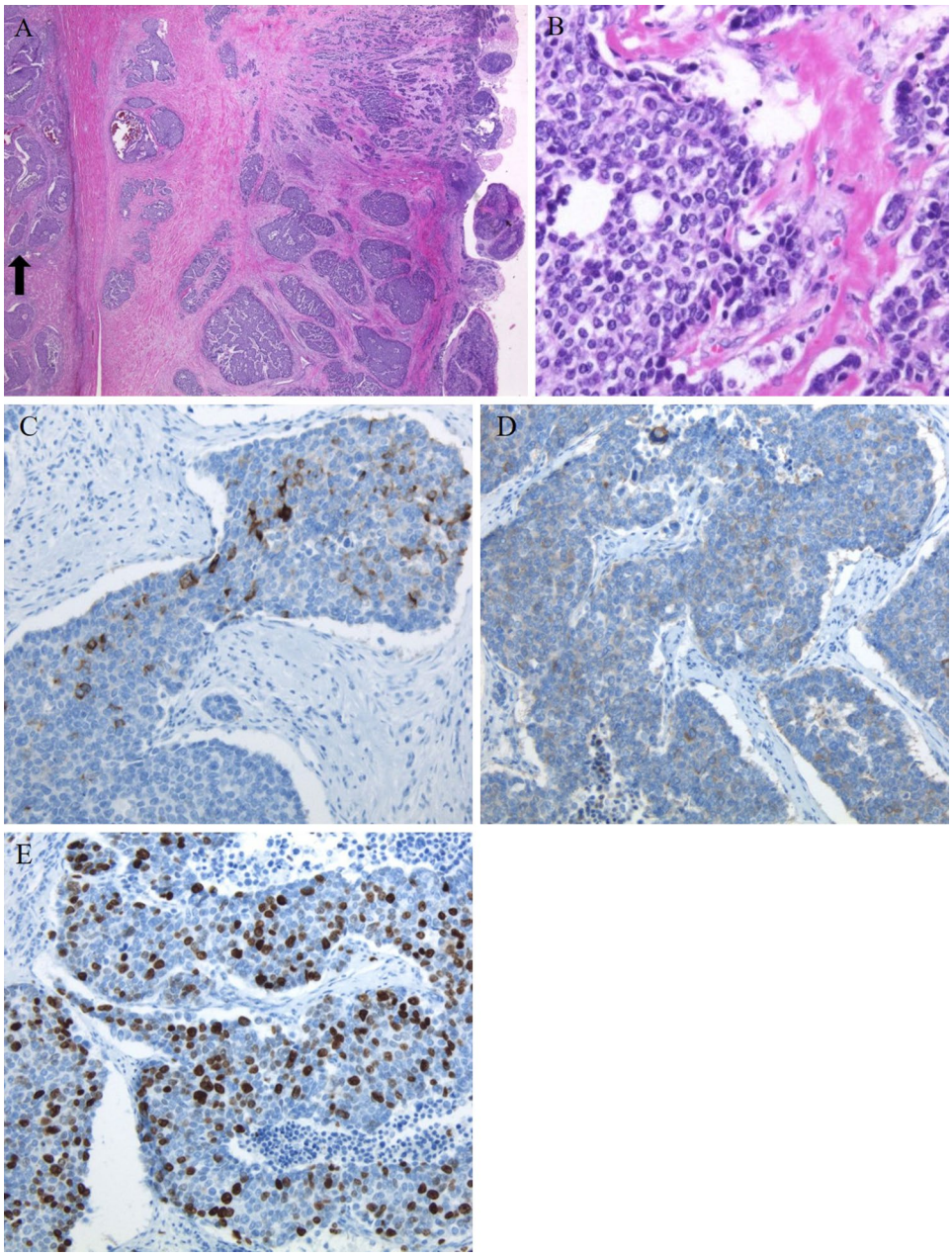

Fig. 6 Tumor did not have a submucosal tumor (SMT)-like appearance. It had an infiltrative nodule. There was no necrosis, hemorrhage, or calcification in the tumor (HE staining, ×4). It was exposed to the luminal face of the gallbladder and showed mucosal invasion. This tumor invaded the liver (arrow) (**a**). The tumor had honeycomb growth to the liver from the gallbladder, the tumor cells were undifferentiated, and there was no gland duct stricture. Tumor cells were round to polygonal, and the nuclei had either vesicular chromatin or prominent nucleoli (HE staining, ×40) (**b**). Immunostaining results indicated that the tumor cells were positive for CD56, chromogranin A (×20) (**c**), and synaptophysin (×20) (**d**), and about 30% were positive for Ki-67 (×20) (**e**)

neuroendocrine tumors are postulated to arise from either a multipotent stem cell or neuroendocrine cells in the intestinal or gastric metaplasia secondary to cholelithiasis and chronic cholecystitis [9, 10].

Almost all malignant lesions of the gallbladder are adenocarcinomas; the gallbladder mucosa contains no neuroendocrine cells; thus, neuroendocrine carcinoma is rare, with a proportion of less than 2%, in gallbladder malignancies [8, 11].

NETs of the gallbladder are rare and NEC is extremely rare. The US National Cancer Institute (NCI) estimates that among digestive system NET (13,891 cases), gallbladder NET accounts for 0.9% (119 cases), and gallbladder NEC accounts for 0.3% (45 cases) [12]. For the clinical features of gallbladder NEC, the average age at diagnosis is 64 years, with a male-to-female ratio of 1:1.9, and many patients present with symptom right abdominal pain. Most cases already have direct invasion to the liver or have metastasized at diagnosis [13, 14].

On the other hand, it is reported that it is very difficult to differentiate this disease from gallbladder adenocarcinoma preoperatively, and most cases of this disease are diagnosed postoperatively by immunostaining for markers such as NSE, CD56, chromogranin A or synaptophysin [14, 15]. Similarly, this case was difficult to diagnose preoperatively.

For the diagnosis of NET, recently, somatostatin receptor scintigraphy (SRS) has been widely performed worldwide [16]. In this case, SRS may have helped in the definitive diagnosis. However, the SRS-positive rate of poorly differentiated NET is low, and the rate of well-differentiated NET is high, in contrast to PET. Thus, it was thought that meaningful findings probably would not have been obtained, even if we had performed SRS [17, 18].

It is common that adenocarcinoma markers, such as CEA and CA19-9, are positive for progressive gallbladder adenocarcinoma and negative for NET except mixed endocrine neuroendocrine carcinoma. This case was a progressive gallbladder tumor, and we did not detect an elevation of tumor markers, such as CEA and CA19-9. It was thought that we should consider gallbladder NET in the case of tumor marker-negative results, such as CEA and CA19-9, for a progressive gallbladder tumor.

The overall median survival of GB-NEC is 4–6 months despite aggressive management. It had been reported that the 1-year survival of gallbladder NEC was 21%, the 5-year survival was 0%, and the prognosis of GB-NEC was poorer than that of gallbladder adenocarcinoma [6]. Focal complete excision via surgery is considered to be the first choice for treatment, but many patients are diagnosed in the unresectable stage. However, the need for radical resection is still debated. Because of the rarity of this disease, no definitive treatment exists. The roles of radiotherapy and chemotherapy in the management of GB-NEC are unclear. In general, NETs are insensitive to the traditional radiotherapy. For patients with poorly differentiated NEC, cisplatin or carboplatin and etoposide are generally recommended as the primary treatment, representing one of the standard regimens employed for the treatment of small cell lung cancer [15].

This case of NEC had a good prognosis. In an analysis of prognostic factors in patients who undergo surgery for pancreatic NET, lymph-node metastasis positive, surgery excision stump positive, and a Ki 67 index of more than 20% have been reported as poor prognostic factors [19]. This case had a Ki 67 index of more than 20%, but the patient was negative for lymph-node metastasis, and the surgery excision stump was negative. We think that these factors contributed to the long survival of the patient. To our knowledge, 17 cases of large-cell gallbladder NEC have been reported in the English medical literature (Table 1). In addition, in these reports, patients who were negative for lymph-node metastasis showed a tendency toward a relatively good prognosis.

On the other hand, this case was diagnosed based on the WHO 2010 NET classification. If this case had been diagnosed based on the WHO 2017 classification for the pancreas, it is possible that it would have been identified as a well-differentiated NET G3. It is very important to differentiate an NEC from an NET G3, because they differ greatly with regard to prognosis and treatment. Tang et al. proposed a new diagnostic algorithm secondarily adding genetic information to the conventional morphologic diagnosis for pancreatic NEC [35]. They categorized cases with loss of DAXX and ATRX expression as well-differentiated NEC (NET G3), whereas cases with loss of Rb and abnormal p53 expression were categorized as poorly differentiated NEC, improving the accuracy of diagnosis, especially for cases that were unclassifiable by morphologic diagnosis. It has been thought that molecular-based definitions will refine classical histological classifications in the near future. Similarly for the diagnosis of NET in other organs, the establishment of a strategy including molecular-based definitions is expected to allow for the differentiation of NEC from NET G3.

In conclusion, gallbladder NEC is a very rare disease and has a very poor prognosis. In addition, it is very difficult to diagnose preoperatively. The incidence of this disease may increase in the future, and it is important to establish an accurate diagnostic method and an effective treatment method, including surgery and chemotherapy, to improve the prognosis. When evaluating an advanced gallbladder tumor with normal tumor markers, such as CEA and CA19-9, we should consider gallbladder NET.

Table 1 Published case reports of large-cell neuroendocrine carcinoma of the gallbladder

Number	Authors [reference]	Gender	Age	Location	Size (cm)	Liver invasion	Metastasis	Other component	Treatment	Prognosis (month)
1	Papotti et al. [20]	Male	50	Unclear	< 1	−	−	Adenocarcinoma	Cho	DFS, 12
2	Papotti et al. [20]	Male	65	Fundus	2.5	−	Liver	−	Cho	Died, 14
3	Jun et al. [21]	Male	55	Unclear	Unclear	Unclear	Lymph node	−	Chemo	Died, 1
4	Jun et al. [21]	Female	67	Unclear	Huge	+	Lymph node	−	Chemo	Died, 10
5	Noske and Pahl [22]	Female	81	Neck	5	+	Bone	Adenosquamous	Palliative surgery	Unknown
6	Oshiro et al. [23]	Female	55	Body	4.9	−	−	Adenocarcinoma, Small cell NEC	Cho	DFS, 20
7	Shimono et al. [24]	Female	64	Unclear	11.5	+	−	−	Che, Rad, Extendedhepatectomy	DFS, 36
8	Iype et al. [25]	Male	85	Fundus	1.5	−	Unclear	Adenocarcinoma	Cho, Chemo	Died, 21
9	Lin et al. [26]	Female	65	Body	Unclear	−	−	−	Cho, Chemo	Died, 2
10	Sato et al. [27]	Female	68	Fundus	3	+	Lymph node	Adenocarcinoma	Cho, Extendedhepatectomy	DFS, 12
11	Paniz et al. [28]	Female	48	Fundus	3.5	+	Unclear	Adenocarcinoma	Cho, Extendedhepatectomy	Unknown
12	Al-Brahim and Albannai [29]	Male	45	Fundus	5.7	+	Unclear	Adenocarcinoma	Cho, Chemo	Unknown
13	Okuyam et al. [30]	Male	64	Fundus	2.5	+	Lymph node	−	Chemo	Died, 22
14	Nakagawa et al. [31]	Male	56	Unclear	9	+	Multiple	Adenocarcinoma	Che, Rad	Died, 36
15	Meguro et al. [32]	Female	54	Unclear	Unclear	−	−	Adenocarcinoma	Cho, Extrahepatic bile duct resection	DFS, 24
16	Russo et al. [33]	Male	59	Body	4	+	Lymph node	Mucinous carcinoma	Cho	Unknown
17	Liu et al. [34]	Female	63	Body	2	−	−	Adenocarcinoma	Cho	DFS, 12
18	Our case	Male	60 s	Fundus	2.9	+	−	−	Cho	DFS, 67

NEC neuroendocrine carcinoma, *Cho* cholecystectomy, *Che* chemotherapy, *DFS* disease-free survival, *Rad* radiotherapy

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Compliance with ethical standards

Conflict of interest We do not have any financial relationships with a biotechnology manufacturer, a pharmaceutical company, or other commercial entity that has any interest in the subject matter connected with our case report.

Human rights All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent The patient gave his informed consent to be included in this report.

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