Gallbladder neuroendocrine carcinoma: A report of two cases and literature review

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Abstract. Gallbladder neuroendocrine carcinoma (GB-NEC) is a rare, aggressive neuroendocrine carcinoma that arises from the gallbladder. Patients with GB-NEC usually have a poor prognosis. The present study described two cases diagnosed with GB-NEC and reviewed the literature to improve knowledge of GB-NEC. The present study reported on two cases of GB-NEC in male patients aged 65 and 66 years, respectively. Both patients underwent surgical resection. Postoperative pathology confirmed that one case had mixed adeno-neuroendocrine carcinoma and the other had large cell neuroendocrine carcinoma. In addition, both patients had uneventful recoveries following surgery and received cisplatin-etoposide combination chemotherapy. The present study summarized the two cases and reviewed the literature to improve understanding of GB-NEC. The results revealed that radiological findings of GB-NEC are non-specific. The present study demonstrated that surgical resection was still the most effective therapy and that postoperative adjuvant chemotherapy could markedly improve the prognosis of patients with GB-NEC.

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Abbreviations: GB-NEC, gallbladder neuroendocrine carcinoma; MANEC, mixed adeno-neuroendocrine carcinoma; LCNEC, large cell neuroendocrine carcinoma; NEC neuroendocrine carcinoma; SEER, Surveillance Epidemiology and End Result; CT, computed tomography; PET/CT, preoperative positron emission tomography/computed tomography; Syn, synaptophysin; CgA, chromogranin A; MRCP, magnetic resonance cholangiopancreatography; GB-LCNEC, gallbladder large cell neuroendocrine carcinoma; SCNEC, small cell neuroendocrine carcinoma; EGFR, epidermal growth factor receptor; PKB, protein kinase B; ECSRK, extracellular signal-regulated kinase

Key words: gallbladder neuroendocrine carcinoma, neuroendocrine tumors, surgery, adjuvant chemotherapy, prognosis

Introduction

Neuroendocrine carcinomas (NEC) are a highly heterogeneous group of malignant tumors, which originate from neuroendocrine cells and account for approximately 1% of all malignant tumors (1). In 1907, Oberndorfer reported the first case of neuroendocrine neoplasm (2). In recent years, an increasing number of cases were reported. Previous studies have pointed out that neuroendocrine neoplasm was more likely to occur in the gastrointestinal tract (66%) and respiratory system (31%), such as the colorectal and lungs (3), rarely in gallbladder neuroendocrine. From data provided by Surveillance Epidemiology and End Result (SEER) research, gallbladder neuroendocrine carcinoma (GB-NEC) is extremely rare, accounting for about 0.5% of all neuroendocrine neoplasms and 2.1% of all gallbladder tumors (4). In addition, GB-NEC was more aggressive and had a worse outcome than adenocarcinomas of the gallbladder (5,6). Thus far, most studies of the GB-NEC are case reports and small case series. Therefore, there is still no consensus on the initiation and development, molecular mechanisms, pathology and treatment of GB-NEC.

Here we reported two cases of GB-NEC pathologically diagnosed as mixed adenoneuroendocrine carcinoma (MANEC) and large cell neuroendocrine carcinoma, respectively. These patients are rarely diagnosed preoperatively because most patients will be treated as standard gallbladder cancer. Both patients were treated with a combination of surgery and chemotherapy. In addition, we reviewed the relevant literature and described the progression of the epidemiology, pathogenesis, pathology, clinical characteristics, treatment of GB-NEC.

Case report

Case 1. The case was a 65-year-old male patient with no family history of cancer and with a past medical history of appendectomy and surgery for lumbar disc herniation. Suspected gallbladder malignancy was found during physical examination. He had no fever, abdominal pain, nausea, vomiting, weight loss and other complaints. No abnormal clinical signs were detected by abdominal examination. Computed tomography (CT) scanning of upper abdomen indicated soft tissue shadows could be seen at the bottom of the gallbladder, invading the liver, and the boundary was blurred. In addition, a cyst was found in the left lobe of liver. Contrast-enhanced CT scanning indicated significant uneven enhancement and it was about 60x45 mm in size (Fig. 1). Preoperative positron emission tomography/computed tomography (PET/CT) showed irregular soft tissue occupancy at the bottom of the gallbladder with abnormally high metabolic activity and low-density occupancy in the lower right anterior lobe with abnormally inhomogeneity high metabolic activity (Fig. 2). Levels of tumor markers were shown in Table I. All these results suggested that gallbladder malignant lesions with the right liver lobe involvement. CT provided no clear evidence of distal metastases.

After multidisciplinary team discussion, preoperative examination was considered to be gallbladder malignant tumor, which could be surgically removed. At the same time, in order to reduce the risk of malignant tumor metastasis caused by invasive biopsy, EUS-FNA or bile cytology was not performed, and surgery was performed directly. During the operation, a solid mass of 3x2 cm in size were found in the body of gallbladder, infiltrating the liver. Cholecystectomy, the local resection of right liver lobe and regional lymphadenectomy were performed. Postoperative Pathology confirmed no tumor cell infiltration at the incisor margin, R0 resection was performed, and metastatic carcinoma was found in 1/9 (tubular adenocarcinoma) around the gallbladder. It was also confirmed as MANEC with stage IIIB (T3N1M0). Immunohistochemical stains were positive for synaptophysin (Syn), chromogranin A (CgA), CD56, CK7 and CK19. Furthermore, the Ki-67 indexes were over 50% in NEC tissue and 30% in adenocarcinoma tissue (Fig. 3). The patient had an uneventful recovery following the surgery and received cisplatin-etoposide combination chemotherapy. The patient was followed up for one year. The general condition was satisfactory at present, and no tumor metastasis was observed.

Case 2. The case was a 66-year-old male patient presented to our hospital with paroxysmal upper abdomen pain for more than half a year. The day before the visit, the patient presented a worsening of upper abdomen pain accompanied by nausea and vomiting. Also, the patient experienced loss of appetite and weight loss over 5 kg in the past 6 months. Partial gastrectomy was performed 4 years ago owing to esophageal carcinoma. Abdominal ultrasound suggested thickening of the gallbladder wall and a liver cyst. CT scanning of upper abdomen showed marked signal abnormality in the gallbladder (Fig. 4). Levels of tumor markers were showed in Table I. These results indicated suspected gallbladder cancer.

Table I. Tumor markers of the two cases.

Marker	Case 1	Case 2
CA-125	36.60 U/ml	6.22 U/ml
CA-199	<2.000 U/ml	22.03 U/ml
CEA	Not applicable	2.87 ng/ml
AFP	Not applicable	2.66 IU/l

CA, carbohydrate antigen; CEA, carcinoembryonic antigen; AFP, α-fetoprotein.

After multidisciplinary team discussion, the patient underwent surgical treatment. During the operation, a solid mass of 1.6x1.1x1 cm in size were found in gallbladder. Cut face showed a solid and grayish tumor lesion. Intraoperative frozen pathology showed that the tumor invaded the muscular layer but did not invade the fibrous membrane. In order to reduce the risk of gallbladder bed metastasis, cholecystectomy, hepatic segmental IVb + V resection and regional lymph node resection were performed. Postoperative pathology confirmed it as gallbladder large cell neuroendocrine carcinoma (GB-LCNEC). Postoperative pathology confirmed that no tumor cell infiltration was observed at the liver resection margin and local lymphadenectomy, and R0 resection was performed. Consequently, the patient was diagnosed with stage IIB (T2bN0M0). Immunohistochemical stains were positive for CgA, CD56 and CK19. In addition, the Ki-67 indexes were over 80% (Fig. 5). The patient had an uneventful recovery following the surgery and received cisplatin-etoposide combination chemotherapy. The patient was followed up for 14 months. The general condition was satisfactory at present, and no tumor metastasis was observed.

Discussion

Neuroendocrine carcinomas (NECs) are a highly heterogeneous group of malignant tumors, which originate from neuroendocrine cells and account for approximately 1% of all malignant tumors (1). The vast majority of NEC were found in the gastrointestinal tract (66%), followed by the lungs (31%), and were also found in tissues such as ovaries and pancreas (3). Due to the lack of specific clinical features and the insensitivity of preoperative diagnosis, the majority of these patients will be considered standard gallbladder cancer and eventually diagnosed as GB-NEC by postoperative pathology. Based on the classification criteria provided by WHO Classification of Tumors of the Digestive System in 2010, neuroendocrine neoplasm (NEN) was classified

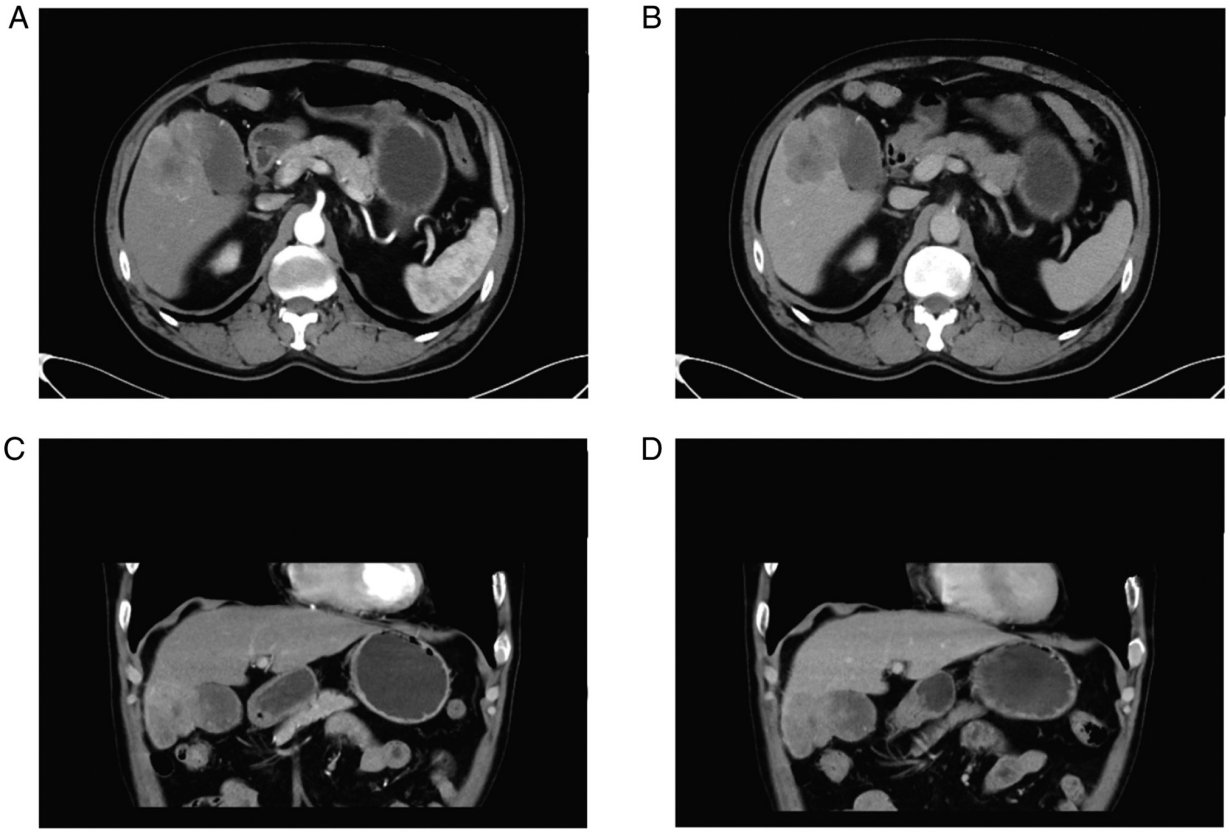

Figure 1. CT images of case 1. (A) Cross-sectional contrast-enhanced arterial phase CT of the abdomen. (B) Cross-sectional contrast-enhanced venous phase CT of the abdomen. (C) Contrast enhanced arterial phase CT scan of the abdomen, coronal view. (D) Contrast enhanced arterial phase CT scan of the abdomen, coronal view. CT, computed tomography.

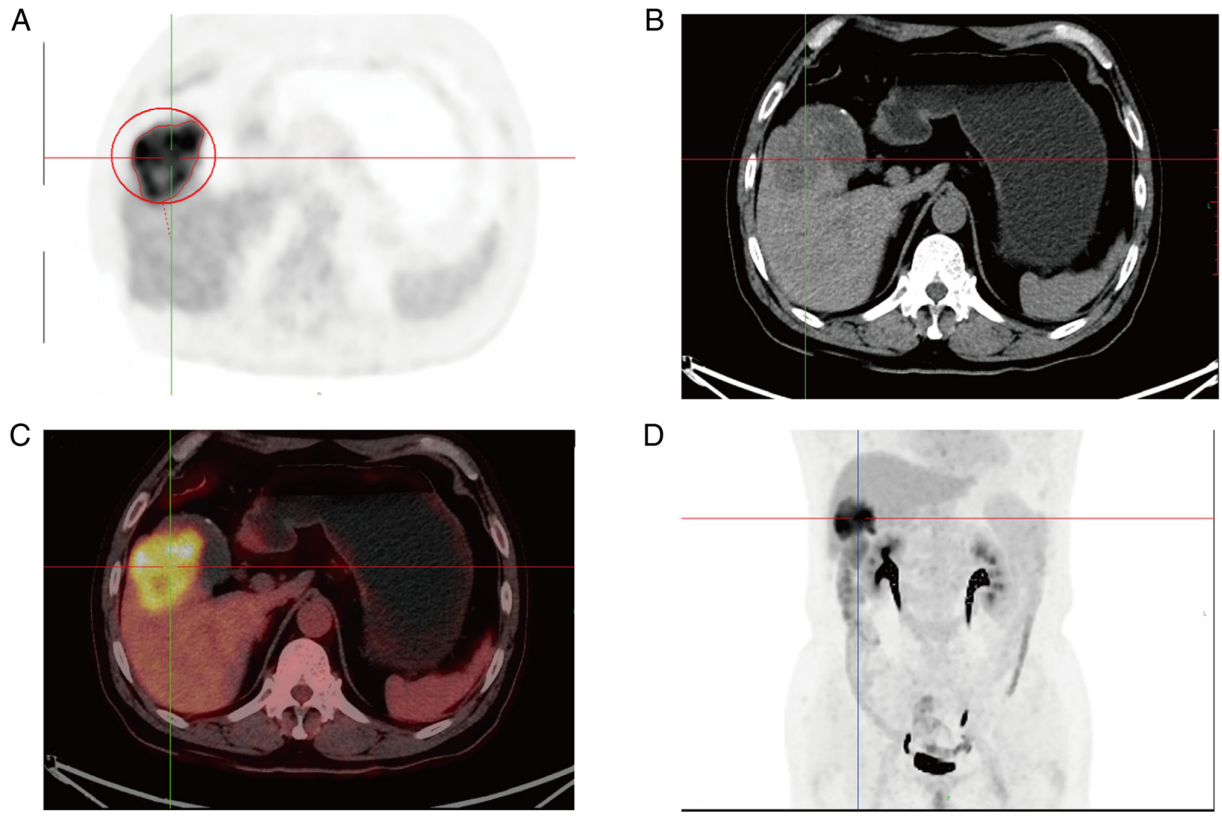

Figure 2. Chest and abdominal PET/CT images of case 1. (A) PET imaging 1 h after FDG injection. (B) CT imaging 1 h after FDG tracer injection. (C) 1 h after injection of FDG tracer, PET/CT fusion imaging. (D) Maximum intensity projection. PET/CT, peoperative positron emission tomography/computed tomography; FDG, fluorodeoxyglucose.

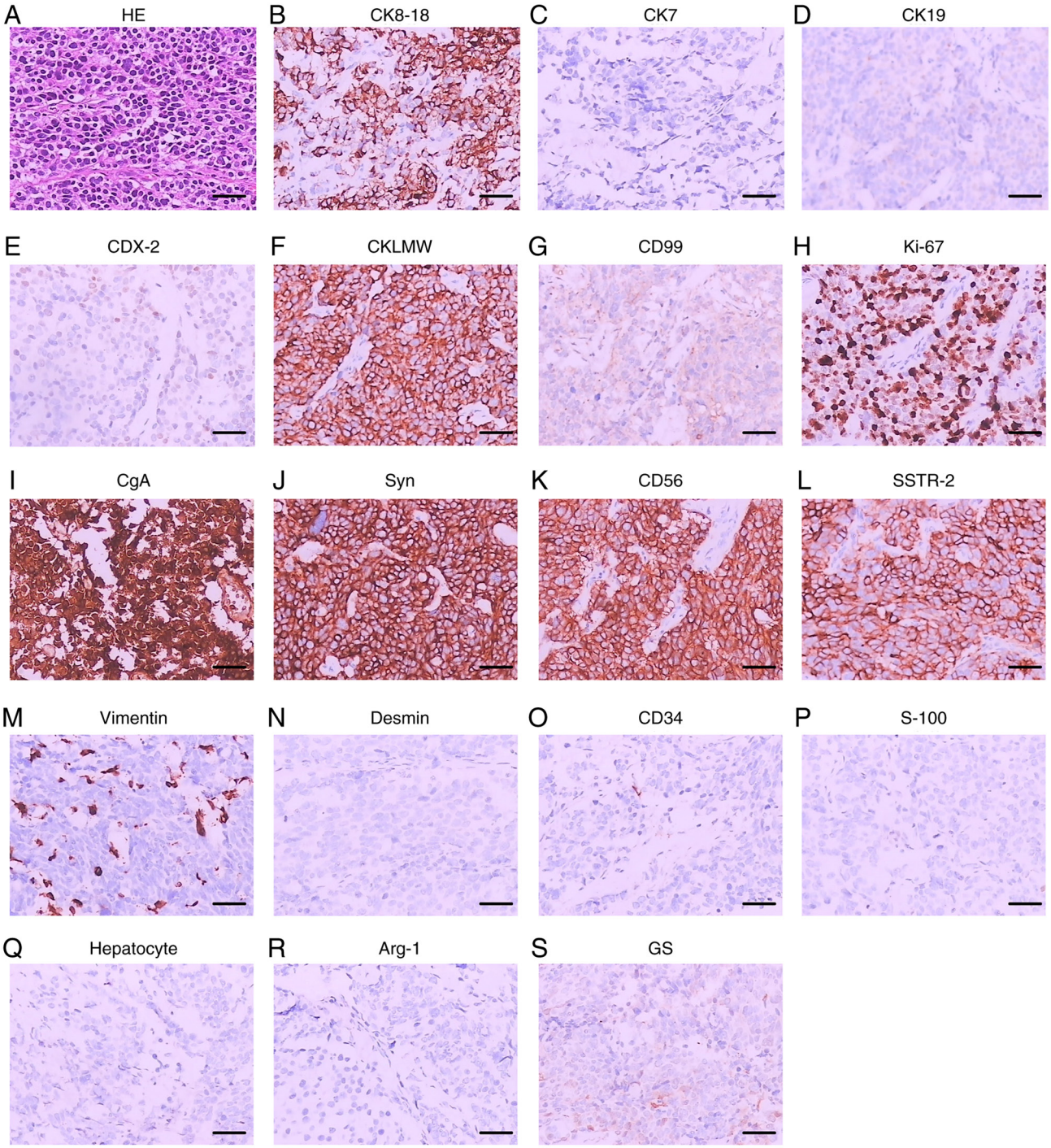

Figure 3. HE staining and immunohistochemical staining of case 1. (A) HE staining. (B) CK8-18. (C) CK7. (D) CK19. (E) CDX-2. (F) CKLMW. (G) CD99. (H) Ki-67. (I) CgA. (J) Syn. (K) CD56. (L) SSTR-2. (M) Vimentin. (N) Desmin. (O) CD34. (P) S-100. (Q) Hepatocyte-specific antigen. (R) Arg-1. (S) GS. Scale bar, 5 μm. CK, cytokeratin; CDX, caudal-related homeobox transcription factor; CKLMW, low molecular weight cytokeratin; CD, cluster of differentiation; Ki-67, antigen KI67; CgA, chromogranin A; Syn, synaptophysin; SSTR-2, somatostatin receptor type 2; S-100, soluble protein-100; Arg-1, arginase-1; GS, glutamine synthetase.

into three categories: the well-differentiated neuroendocrine tumors (G1 and G2) and poorly-differentiated neuroendocrine tumors (G3, defined as NECs). According to the pathology, NECs could be classified into small cell neuroendocrine carcinomas (SCNEC), large cell neuroendocrine carcinomas (LCNEC) and MANEC (7). In this study, case 1 was confirmed as MANEC, and case 2 was confirmed as LCNEC by post-surgical pathologic diagnosis.

The etiology of GB-NEC remains still unclear. Previous studies have proposed the following hypotheses: i) Undifferentiated gallbladder stem cells differentiate into neuroendocrine cells; ii) long-term chronic inflammatory stimulation of the gallbladder mucosa leads to pathological intestinal metaplasia, which in turn produces neuroendocrine cells at the lesion site and develops into neuroendocrine carcinoma. iii) In some cases, the

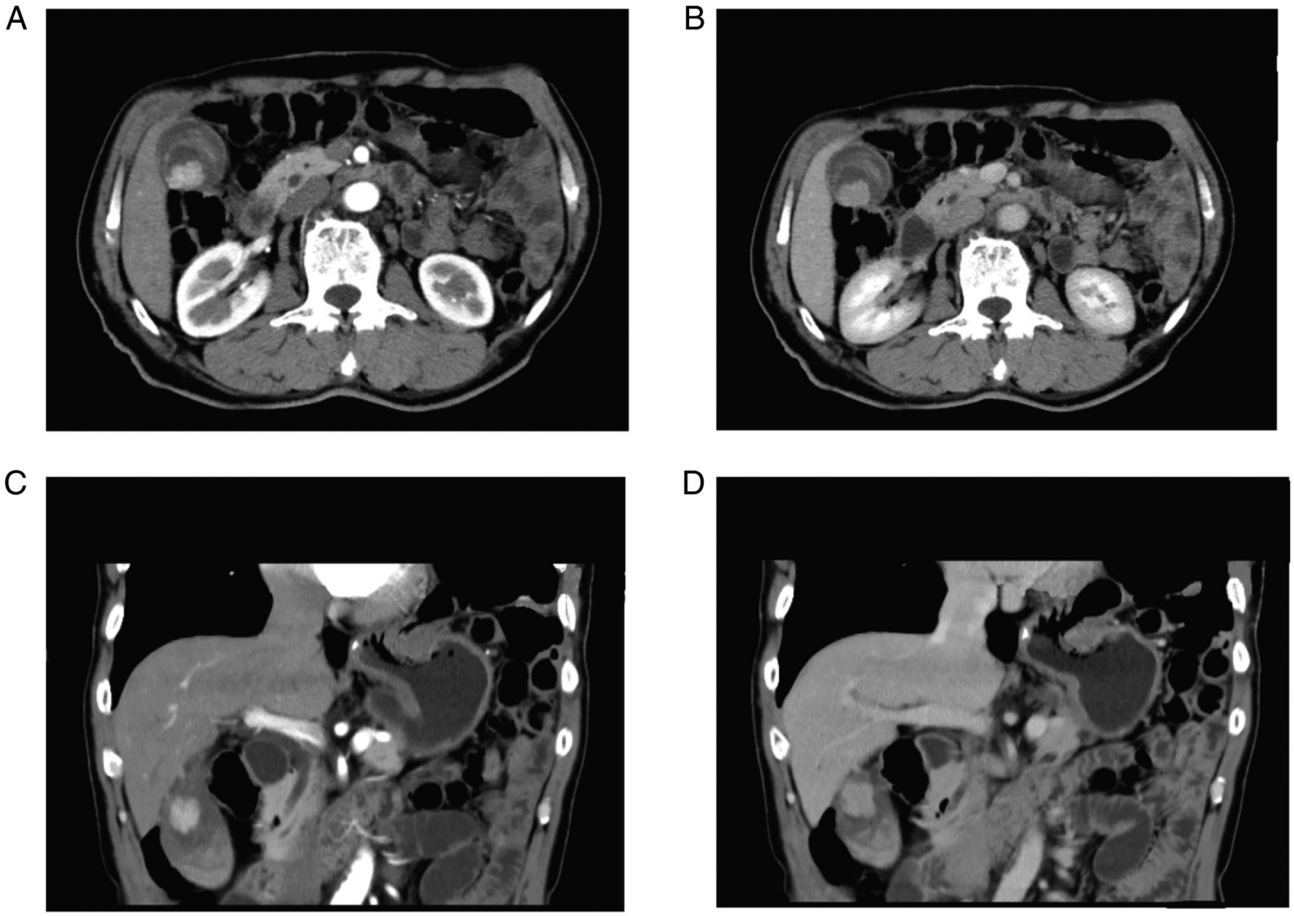

Figure 4. CT images of case 2. (A) Cross-sectional contrast-enhanced arterial phase CT of the abdomen. (B) Cross-sectional contrast-enhanced venous phase CT of the abdomen. (C) Contrast enhanced arterial phase CT scan of the abdomen, coronal view. (D) Contrast enhanced arterial phase CT scan of the abdomen, coronal view. CT, computed tomography.

gallbladder adenocarcinoma function switches to a neuroendocrine one (8-10).

Recently, with the increasing cases of GN-NEC reported, its molecular mechanism has received extensive attention. Previous studies have pointed out that activation of epidermal growth factor receptor (EGFR) can upregulate the expression of downstream effector protein kinase B (PKB) and extracellular signal regulate kinase (ECSRK) (10,11). In addition, the expression level of the target protein of rapamycin was positively correlated with the proliferation index of the cells (6). These results indicated high expressions of EGFR, ECSRK and the target protein of rapamycin were linked to poor survival prognosis. Takizawa *et al* (12) and Fujimasa *et al* (13) reported loss of Rb1 and overexpression of were found in NECs of the colorectum and esophagus. Lee and Sung reported a series of 34 GB-NEC cases (14). Of the 34 GB-NEC patients, 25 (74%) showed loss of Rb1 and overexpression of p16. Although these results have suggested that disruption of the Rb1-p16 pathway might play a crucial role in GB-NEC, the detailed molecular mechanism requires further exploration. Park *et al* pointed out that BRAF mutations were present in about 9% of gastroenteropancreatic neuroendocrine tumors, especially in high-grade neuroendocrine carcinomas (15). Advanced colorectal NEC patients with $BRAF^{V600E}$ mutation benefited from BRAF mutation-targeted therapy (16). However, no mutations of $BRAF^{V600E}$ were found in any of the 34 GB-NEC cases (14). Therefore, it is still unclear whether BRAF mutation is related to GB-NEC, and further research is needed. Another study has pointed out that ALK rearrangement and immune microenvironment heterogeneity were related to large cell neuroendocrine carcinoma of the lung, and its correlation with GB-NEC still needs to be further explored (17).

Traditional imaging methods, such as ultrasound, CT and MRI, are not sensitive to the diagnosis of GB-NEC. Recent studies have shown that the use of 68Ga-DOTANOC PET tracer in PET/CT and PET/MRI is effective in the detection of primary NENs and metastatic sites. At the same time, the staging and therapeutic response evaluation of GB-NENs is a valuable tool (18,19). The gold standard for diagnosis of GB-NEC is still histopathological examination. Preoperative EUS-FNA or bile cytology is a good diagnostic method for biliary malignancy, but may be more suitable for patients with excessive tumor load, difficult surgery, or distant metastasis. In this paper, two patients with small tumor load, no distant metastasis, preoperative evaluation can be radical resection, suitable for direct surgical treatment. Neuron specific enolase (NSE), Syn, CgA and CD56 were often positive in immunohistochemistry staining. High Ki-67 and mitotic index may be predictors of poor prognosis (20). According to the immunohistochemical characteristics, at least two of the three commonly used markers SynA, CgA and CD56 should be widely expressed to confirm the diagnosis of late

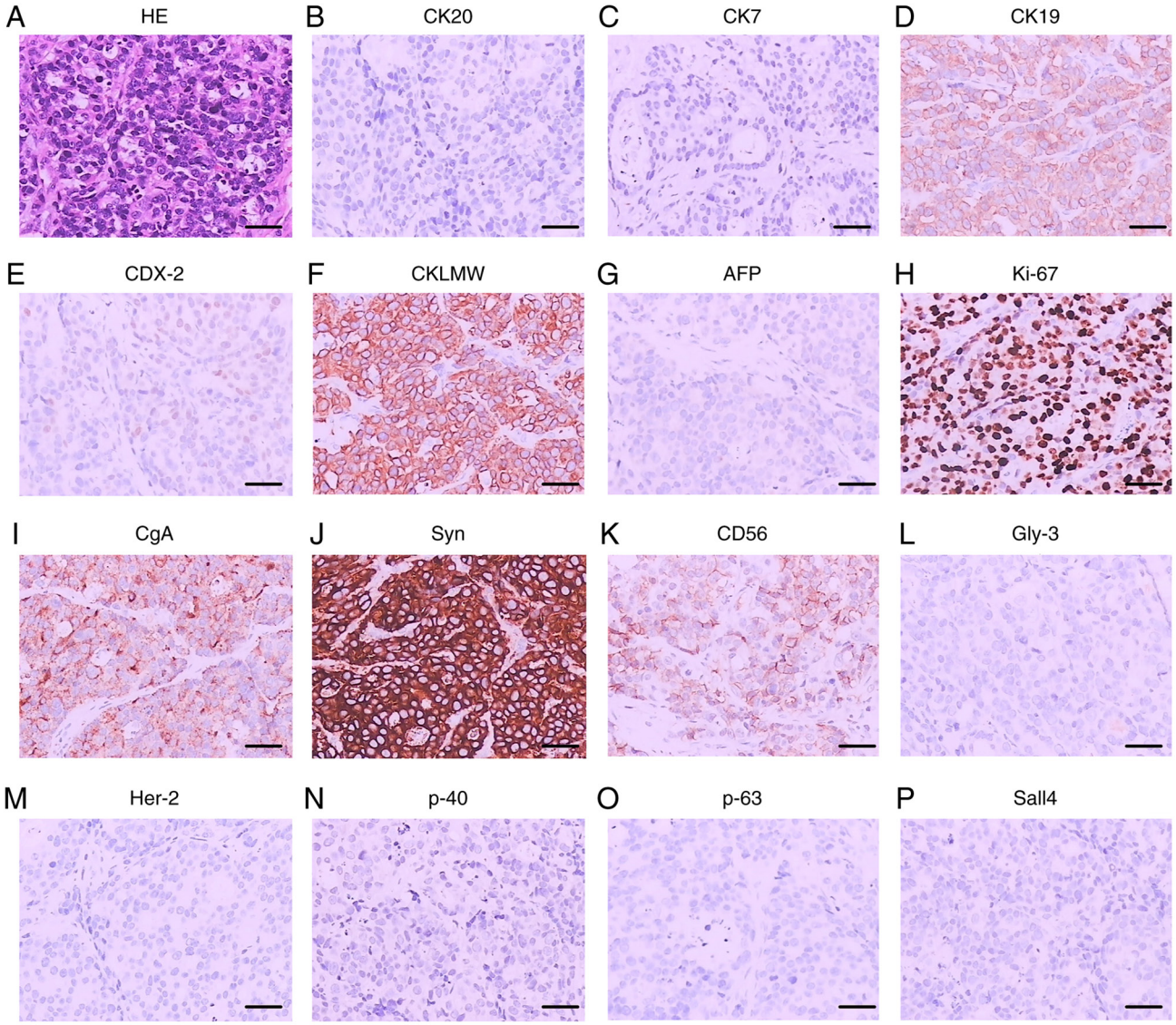

Figure 5. HE staining and immunohistochemical staining of case 2. (A) HE staining. (B) CK20. (C) CK7. (D) CK19. (E) CDX-2. (F) CKLMW. (G) AFP. (H) Ki-67. (I) CgA. (J) Syn. (K) CD56. (L) Gly-3. (M) Her-2. (N) p-40. (O) p-63. (P) Sall4. Scale bar, 5 μm. CK, cytokeratin; CDX, caudal-related homeobox transcription factor; CKLMW, low molecular weight cytokeratin; AFP, α-fetoprotein; Ki-67, antigen KI67; CgA, chromogranin A; Syn, synaptophysin; CD, cluster of differentiation; Gly-3, glypican-3; Her-2, human epidermal growth factor receptor 2; Sall4, spalt like transcription factor 4.

MANEC (21,22). In this study, Syn, CgA and CD56 were all positive staining in case 1 and CgA and CD56 were positive staining in case 2. Previous study indicated CK7 and CK20 were positively expressed in gallbladder adenocarcinoma and the expression rates of CK7 and CK20 in GB-NEC were slightly lower (14,23). However, in our study, CK7 was only positively expressed in adenocarcinoma tissue of case 1. CK7 and CK20 were both negatively expressed in NEC tissue of case 2. Interestingly, CK19 was positively expressed in both cases. Overexpression of CD117 in colorectal NECs was reported in previous studies. In addition, CD117 was positive in 25 (79%) of 34 GB-NEC cases. Given the high frequencies of CD117 expression in NECs, CD117 might potentially be applied as a novel NECs biomarker (14,24,25).

Currently, surgical resection is still the primary and most effective therapy for GB-NEC. Radical resection and obtaining histologically negative surgical resection margins can definitely prolong the survival time of patients (26-28). For those advanced patients, cholecystectomy combined with partial hepatectomy and lymph node dissection can significantly improve the outcome (29). Patients not suitable for surgery should be administered chemotherapy. Postoperative chemoradiotherapy for highly aggressive GB-NEC patients with early lymph node metastasis is an effective means to prolong the survival time of patients. The recommended chemotherapy includes streptozotocin, 5-fluorouracil, doxorubicin, cisplatin, and etoposide (30). Due to the low incidence of GB-NEC, there is still no standard chemotherapy regimen to date. Relevant case reports suggest that gemcitabine, docetaxel, or cisplatin in combination with cisplatin, sunitinib, and docetaxel, respectively, could prolong survival time in patients with neuroendocrine carcinoma of the gallbladder (31,32). To date, there are still no targeted drugs in clinical practice. Some studies have pointed out that the expression level of VEGF in GB-NEC patients was increased, and sunitinib, a VEGF-targeting inhibitor, could effectively prolong the

progression-free survival and overall survival of pancreatic neuroendocrine neoplasm patients. The effectiveness of GB-NEC still needs further research. Also, previous studies have shown that changes in the immune microenvironment and ALK rearrangement are involved in the development of lung large cell neuroendocrine carcinoma, and the application of ALK inhibitors improved the prognosis of patients. It might provide a new therapeutic option for the treatment of GB-NEC (17,33,34).

Most GB-NEC patients are in an advanced stage of disease at the time of presentation, and many have lost the chance of radical surgery. Biopsy and pathologic examination can be performed first to determine the tumor type, followed by chemotherapy. Chemotherapy is essential for inoperable GB-NEC patients and can improve patient survival (35). At present, cisplatin or carboplatin plus etoposide is the main chemotherapy regimen for poorly differentiated GB-NEC, and has achieved satisfactory results (36). In addition, neoadjuvant chemotherapy may help to reduce the tumor burden and provide the opportunity for radical surgical resection (37). Another study compared the median survival time of patients receiving surgical treatment alone and postoperative combined adjuvant radiotherapy for 3.0 and 12.7 months, respectively, indicating that postoperative chemotherapy can benefit patients' survival (38). GB-MANEC is rarer among gallbladder neuroendocrine carcinomas (22). The choice of chemotherapeutic regimens to be used lies on the degree of MANEC differentiation and accordingly may follow a 'treat-like-neuroendocrine tumor' or a 'treat-like-an adenocarcinoma' protocol as suggested by previous investigators (39). Therefore, chemotherapy was administered postoperatively and both patients survived. We will continue to actively follow up.

At present, GB-NEC is still an aggressive malignancy with poor prognosis. We reported two cases of GB-NECs and reviewed the literature to deepen our understanding of GB-NEC. In future, exploring the etiology and molecular mechanism of occurrence and development of this disease will provide new strategies for its treatment.

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Availability of data and materials

All data generated or analyzed in this study are included in this published article.

Authors' contributions

YPT, JTW, ZHL, JM, LCC and YW conceived and designed the study. YL and YeZ provided study materials, collected data and drafted the manuscript.. YL, ZGZ, DXL and HL performed surgery. WC, ZKL, XX, YaZ, XCZ and LZ analyzed and interpreted the data. YL and JTW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The patients provided written informed consent to participate.

Patient consent for publication

Written informed consent was obtained from the patients for publication of the data and images in this case report.

Competing interests

The authors declare that they have no competing interests.

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