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Case Report

Large Cell Neuroendocrine Carcinoma of the Gallbladder: A Case Report and Literature Review

Ryoichi Miyamoto[1], Kazunori Kikuchi[2], Atsushi Uchida[2], Masayoshi Ozawa[2], Kentaro Nagai[1], Michihiro Maeda[1], Akira Kemmochi[1], Satoshi Inagawa[1], Masayoshi Yamamoto[1]

[1]*Department of Gastroenterological Surgery, Tsukuba Medical Center Hospital, Tsukuba, Ibaraki, Japan*

[2]*Department of Pathology, Tsukuba Medical Center Hospital, Tsukuba, Ibaraki, Japan*

Large cell neuroendocrine carcinoma (LCNEC) of the gallbladder is exceedingly rare. Only a few studies of pure gallbladder LCNEC without other histologic components have been reported in the literature. Therefore, this condition's biological behavior, appropriate treatment modalities, and overall patient prognosis remain largely unclear. In this report, we present a case involving resected pure gallbladder LCNEC. Additionally, we review relevant literature on LCNEC and discuss the clinical management of LCNEC, including histopathologic features. An 86-year-old woman presented with a gallbladder tumor that measured 25 mm on the body of the gallbladder that was incidentally detected by abdominal ultrasonography. The diagnosis of pure LCNEC without other histologic components was immunohistochemically confirmed after radical cholecystectomy and lymph node dissection in the hepatoduodenal ligament. The postoperative course was uneventful, and no evidence of recurrence or metastasis was observed after 6 months of follow-up. We reviewed 9 case reports describing pure LCNEC of the gallbladder, including the present case. Clinical symptoms and radiologic findings for pure LCNEC were nonspecific. The overall prognosis was poor, but early detection with complete resection might result in a relatively good prognosis.

Key words: Large cell neuroendocrine carcinoma – Gallbladder – Surgery – Chemotherapy – Somatostatin receptor

Corresponding author: Ryoichi Miyamoto, Department of Gastroenterological Surgery, Tsukuba Medical Center Hospital, 1-3-1 Amakubo, Tsukuba, Ibaraki 305-8558, Japan.
Tel.: +81 298 51 3511; Fax: +81 298 51 3512; E-mail: goodfirst883@gmail.com

Large cell neuroendocrine carcinomas (LCNECs) are relatively rare and aggressive malignant tumors that belong to the neuroendocrine neoplasm (NEN) subgroup; they were first described in the lungs in 1991.[1] NENs of the gallbladder are particularly rare and account for 0.5% of all NENs and 2.1% of all gallbladder cancers.[2] LCNECs of the gallbladder are exceedingly rare and were first reported in 2000.[3]

The current WHO classification divides NENs of the gallbladder into the following categories: neuroendocrine tumor (NET G1 and G2); small cell neuroendocrine carcinoma; LCNEC; mixed adenoneuroendocrine carcinoma; goblet cell carcinoid; and tubular carcinoid.[4] Most LCNEC cases are combined with other histologic components, including adenocarcinoma, adenosquamous carcinoma, and mucinous carcinoma.[5] Only a few studies involving pure LCNEC cases without other histologic components have been reported in the literature.[3,5–11] Therefore, the biological behavior, appropriate treatment modalities, and overall patient prognosis remain largely unclear.

In this report, we discuss a case presentation of a resected pure LCNEC patient. Additionally, we review the relevant literature on pure LCNECs and discuss the clinical management of LCNECs, including the histopathologic features.

Case Report

A gallbladder tumor was incidentally detected in an 86-year-old female during a medical examination. The patient had no significant past medical history, and her general physical examination was normal. No abnormal laboratory findings were observed. Abdominal ultrasonography revealed a 25-mm gallbladder tumor. Abdominal computed tomography (CT) also showed a small-sized mass that was 25 mm in diameter in the gallbladder. A low-density area in the liver and enlarged lymph nodes was not observed. The patient underwent a cholecystectomy and lymph node dissection in the hepatoduodenal ligament. The patient's postoperative recovery was uneventful, and she was discharged from the hospital after 10 days. The patient did not exhibit recurrence of LCNEC during the 6-month follow-up period.

Pathologic Findings

Histologically, the 25- ×20-mm mass was observed in the body of the gallbladder (Fig. 1a and 1b). Microscopically, the tumor displayed an insular growth pattern, often with rosette formations, and was entirely composed of large cells characterized by hyperchromatic nuclei with prominent nucleoli and a variable amount of cytoplasm (Fig. 2a, 2b, and 2c). Immunohistochemically, the cancer cells exhibited strong expression of neuroendocrine markers such as chromogranin A (Fig. 3a); synaptophysin (Fig. 3b); and CD56 (Fig. 3c). Additionally, these cancer cells showed a Ki67 index of 73% (Fig. 3d). Somatostatin receptor type 2a (SSTR-2a) was strongly positive (Fig. 4), resulting in a score of 3 according to Volante's scoring criteria.[12] No evidence of serous or liver invasion and lymph node or distant metastasis was present. The histologic

Fig. 1 (a, b) Macroscopic view of the tumor mass. The 25- × 20-mm mass was observed in the body of the gallbladder.

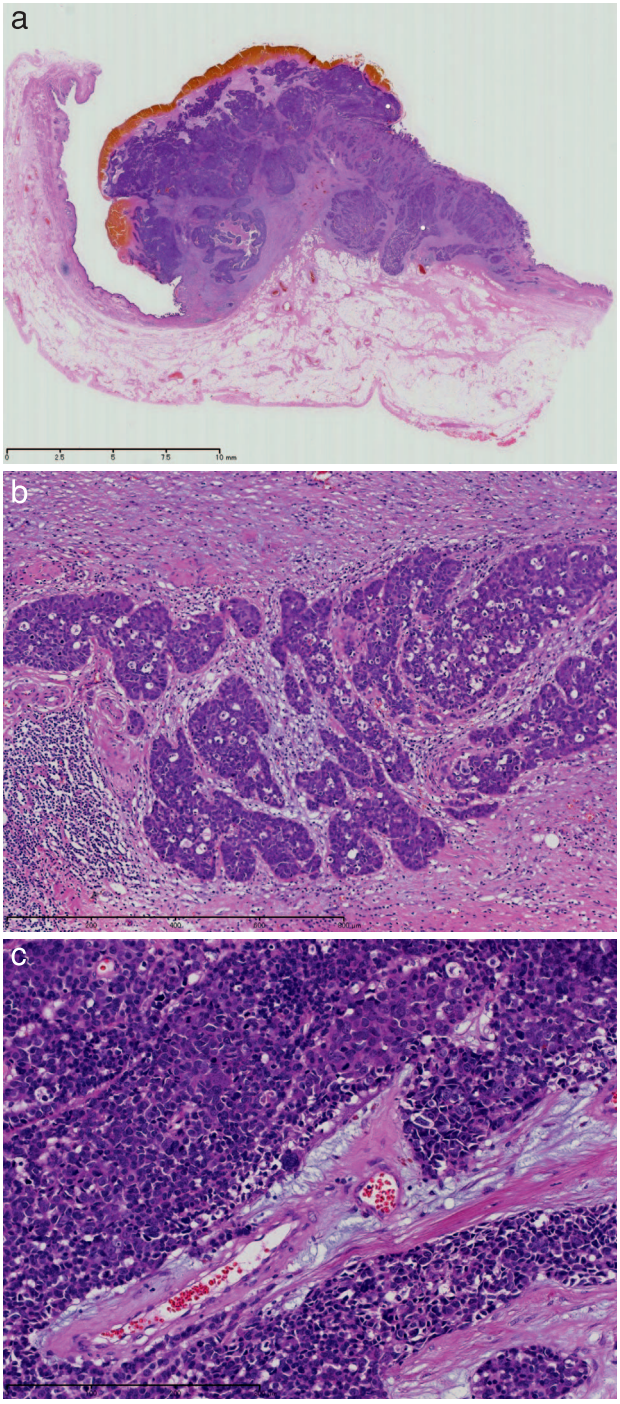

Fig. 2 (a–c) The tumor displayed an insular growth pattern, often with rosette formations, and was entirely composed of large cells characterized by hyperchromatic nuclei with prominent nucleoli and a variable amount of cytoplasm; HE staining: ×5, ×100, and ×200, respectively.

and immunohistochemical findings were consistent with a pure form of LCNEC of the gallbladder. Thus, this lesion was assigned a final classification of pT2N0M0 stage II according to the 7th Union Internationale Contre le Cancer Guidelines.

Discussion

We present a case of a patient with surgically resected pure LCNEC of the gallbladder without other histologic components.

Pure LCNEC of the gallbladder is exceedingly rare and was first reported by Papotti *et al*[3] in 2000. To the best of our knowledge, only 8 cases have been reported in the literature (Table 1). Our case presentation was the 9th case report of LCNEC of the gallbladder.

According to our review of previous reports, the clinical symptoms and radiologic findings of our patient were nonspecific (Table 1). Upper abdominal pain and abdominal discomfort were the most common symptoms (5/9, 55%). Three patients (3/9, 33%) presented with a clinical history of symptomatic cholecystitis and ultrasonographic demonstration of gallstones.[3,6–11,23]

It is not possible to preoperatively differentiate between gallbladder adenocarcinoma and gallbladder neuroendocrine carcinoma (NEC) with imaging techniques because other neoplasms (i.e., hepatocellular carcinoma, cholangiocarcinoma, hepatic metastasis involving the gallbladder, and gallbladder adenocarcinoma) may have similar patterns.[3,6–11,23] Ultrasonography has low sensitivity (44%) for the identification of gallbladder cancer.[13] In our case, abdominal ultrasonography and radiologic findings revealed a 25-mm gallbladder tumor with suspected malignancy. Okuyama *et al*[10] previously reported that 18FDG-PET/CT was useful for confirmation of the origin of lymph node metastases and the effective clinical diagnosis of patients with gallbladder LCNEC.[10]

Nakagawa *et al*[14] suggested that cytologic screening had an advantage over histologic approaches based on hematoxylin and eosin (HE) staining with respect to qualitatively diagnosing gallbladder LCNEC. Conventional HE staining requires paraffin embedding of the tissue, which involves dehydration and deparaffinization during processing. These procedures destroy and mask the details of the nuclear structure. In contrast, cytology based on Papanicolaou staining does not require paraffin embedding, ensuring that nuclear fine structure remains

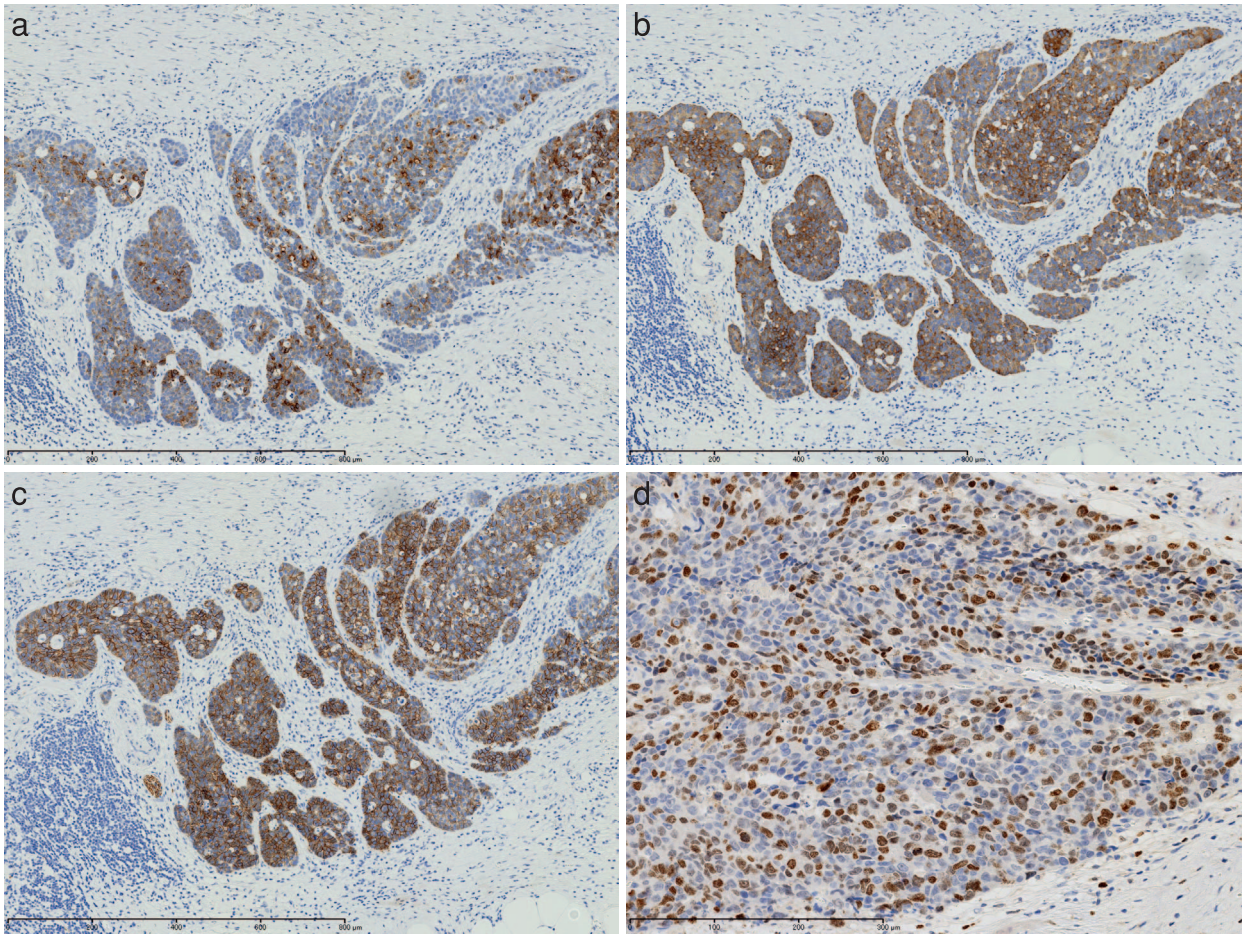

Fig. 3 (a) Immunohistochemical staining showing that the LCNEC cells were positive for chromogranin A; ×100. (b) Immunohistochemical staining showing that the LCNEC cells were positive for synaptophysin; ×100. (c) Immunohistochemical staining showing that the LCNEC cells were positive for CD56; ×100. (d) Cancer cells showed a Ki67 index of 73%; ×200.

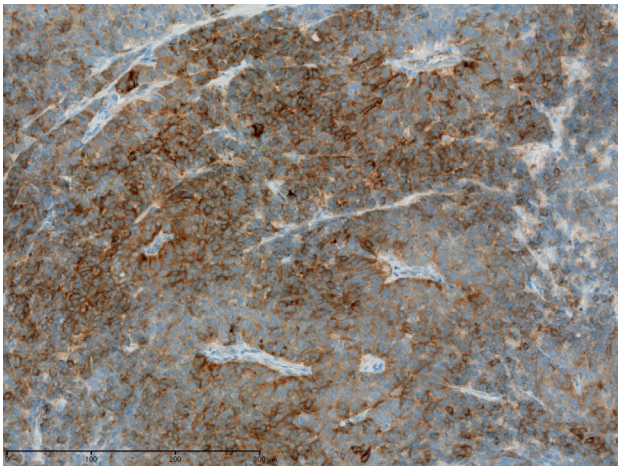

Fig. 4 Immunohistochemical staining showing that the LCNEC cells were strongly positive for SSTR-2a, resulting in a score of 3; ×200.

well preserved. A previous report also described the advantages of cytologic examinations using endoscopic, ultrasound-guided, fine-needle aspiration samples for the early diagnosis of LCNEC in the biliary tract.[15]

The histologic features of LCNEC are as follows: (1) positivity for neuroendocrine markers, among which chromogranin A and synaptophysin are the most commonly identified; (2) a mitotic count exceeding 20/10 high-power fields or a Ki67 index over 20%; and (3) a specific NET pattern of an organoid structure, rosette formation, and palisading and trabecular arrangement, as well as prominent nuclei that are more than 3-fold the diameter of a lymphocyte.[3,5–11] Immunohistochemical examinations of chromogranin A, synaptophysin, CD56, and Ki67 were performed using enzyme-antibody and

Table 1 Clinical features of 9 pure large cell neuroendocrine carcinomas of the gallbladder

Author	Age, y	Sex	Clinical presentation	Tumor location	Tumor size (cm)	Liver invasion	Metastasis	Surgical treatment	Chemotherapy
Papotti *et al*[3]	65	M	Cholelithiasis	Fundus	2.5	–	Liver	Cholecystectomy	NS
Jun *et al*[6]	67	F	Epigastric pain	Unclear	Unclear	+	Lymph node	Biopsy	NS
Jun *et al*[6]	55	M	Jaundice	Unclear	Unclear	–	Lymph node	Biopsy	NS
Iype *et al*[7]	58	F	Gallstones	Fundus	1.5	–	Unclear	Cholecystectomy	CDDP, ETP
Shimono *et al*[8]	64	F	Right upper abdominal pain	Unclear	11.5	+	–	Extended hepatectomy	CDDP, ETP
Lin *et al*[9]	65	F	Cushing's syndrome	Body	Unclear	–	–	Cholecystectomy	–
Okuyama *et al*[10]	64	M	Abdominal fullness	Fundus	2.5	+	Lymph node	Biopsy	CDDP, DTX, CBDCA
Buscemi *et al*[11]	76	F	Cholelithiasis	Fundus	1.8	–	Liver, Lymph node	Cholecystectomy	CDDP, ETP, CBDCA
Ryoichi *et al*[23]	86	F	No symptoms	Body	2.5	–	–	Cholecystectomy, LD	–

CBDCA, carboplatin; CDDP, cisplatin; DTX, docetaxel; ETP, etoposide; LD, lymph node dissection in hepatoduodenal ligament; NS, drugs not specified.

streptavidin-peroxidase techniques described in prior reports.[16–18]

Recent research has demonstrated that SSTR-2a is widely expressed in NETs; findings obtained using a scoring system indicated that this receptor could be a diagnostically and therapeutically valuable target.[12,17,18] Indeed, the present case was strongly positive for SSTR-2a, exhibiting a score of 3 (Fig. 4). Somatostatin analogues are known to have high affinity for SSTR-2a[19] and therefore have been demonstrated to be useful for the management of well-differentiated pancreatic neuroendocrine tumors.[20] In terms of gallbladder LCNECs, further analysis of the usefulness of somatostatin analogues is required in SSTR-2a–positive patients.

The origin of NETs is controversial because the gallbladder lacks neuroendocrine cells. The gallbladder mucosa in the fundus and body is devoid of neuroendocrine cells, which may appear after intestinal metaplasia due to chronic inflammation. Metaplastic endocrine cells are found in cholecystitis; therefore, neuroendocrine cell tumors of the gallbladder may develop from the endocrine cells of an intestinal metaplastic lesion.[21]

Surgical resection, which has been demonstrated to improve the prognosis of NEC patients, is considered the main treatment for gallbladder NECs. The prognosis is very poor for patients with unresectable masses, although multimodal treatments, including chemotherapy and radiation therapy, have achieved good responses in some reports.[3,6–11,23]

Among our 9 reviewed case reports, 8 patients died of the disease, with a median survival time of 17.5 months. Four long-surviving patients had several similar characteristics, such as small tumor size and no liver invasion or metastasis; these patients underwent radical surgery. Mochizuki *et al*[22] reported that 14 out of 35 cases of NETs of the gallbladder were viewed as benign, without distant metastases or invasion, and were less than 4 cm in size. The other two successful treatments for patients with liver invasion or lymph node metastasis primarily relied on extended surgery with a hepatectomy and lymph node dissection.[3,6–11,23] Furthermore, the presence of the adenocarcinoma phenotype is thought to indicate a poor prognosis.[2] The present case presented a tumor size of 25- × 20-mm without distant metastases or liver invasion.

In conclusion, gallbladder LCNEC is extremely rare, and few cases of pure gallbladder LCNEC without other histologic components have been reported in the literature. Although it is difficult to determine a preoperative diagnosis of gallbladder LCNEC, early detection with complete surgical resection is thought to result in a relatively good prognosis. Furthermore, gallbladder LCNEC remains difficult to treat for recurrence; however, multimodal treatments, including chemotherapy and radiation therapy, may produce promising responses.

Acknowledgments

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