Journal of Gastrointestinal Cancer (2019) 50:967–971
https://doi.org/10.1007/s12029-018-0148-6

CASE REPORT

"Pure" High-Grade Large Cell Neuroendocrine Carcinoma Arising from Low- and High-Grade Dysplasia of the Gallbladder: Case Report and Review of the Literature

Cacey Peters[1] · Eleanor Lewin[1] · Tong Wu[1] · Yukihiro Nakanishi[1]

Published online: 25 July 2018

Introduction

Neuroendocrine neoplasms of the gallbladder are classified as grades 1 and 2 neuroendocrine tumors, neuroendocrine carcinoma (NEC) (large cell (LCNEC) or small cell type (SCNEC)), and mixed adenoneuroendocrine carcinoma (MANEC) [1]. NEC of the gallbladder is rare, comprising 0.5% of all neuroendocrine tumors and 2.1% of all gallbladder cancers [2]. In most cases of NEC of the gallbladder, the histological components include adenocarcinoma [3–5]. Among the reported cases of NEC of the gallbladder, only seven reported cases were "pure" LCNEC without adenocarcinoma component [3, 6–10]. The origin of such tumors has been debated, with varying support for each theory. The primary concepts consist of the malignant transformation of neuroendocrine cells derived from multipotent stem cell within the gallbladder or the malignant transformation of neuroendocrine cells in metaplastic intestinal or gastric mucosa secondary to chronic inflammation [3, 5].

We here report, at the time of this writing, the eighth case of pure LCNEC of the gallbladder, and the first of such cases arising from low- and high-grade dysplasia in the background of mild chronic cholecystitis with focal pyloric gland metaplasia. The findings suggest a multi-step carcinogenesis of LCNEC of the gallbladder following the chronic inflammation–metaplasia–dysplasia–carcinoma sequence.

This case was presented at the 2016 ASCP (American Society of Clinical Pathology) annual meeting, Las Vegas, USA, 14–16 September 2016.

✉ Yukihiro Nakanishi
ynakanis@tulane.edu

[1] Department of Pathology, Tulane University School of Medicine, 1430 Tulane Avenue, SL-79, New Orleans, LA 70112, USA

Case Report

A 64-year-old Hispanic male with a medical history of diabetes mellitus type 2, hypothyroidism, and hypertension, presented to his primary care physician for a routine follow-up. On routine lab work, he was found to have elevated liver function tests. The patient was admitted to an outside hospital where an MRI revealed a mass in the gallbladder and possible direct extension into the liver. A simple cholecystectomy and liver wedge biopsy were performed. The resected gallbladder measured 7.0 cm in length, and 4.5 cm in width. An ill-defined sessile mass was identified in the body measuring 2.5 × 2.0 × 1.0 cm, with diffuse infiltration into the gallbladder wall (Fig. 1). No gallstone was identified. The entire lesion was submitted for histologic examination. Microscopic examination of the mass revealed that the tumor was composed of large neoplastic cells with a variable amount of cytoplasm, large nuclei, and prominent nucleoli and showed an organoid growth pattern with areas of necrosis (Fig. 2). The overlying epithelium was erosive and was replaced by low- and high grade dysplasia (Figs. 3 and 4) with clear continuity between dysplastic lesion and invasive carcinoma (Fig. 3). The dysplastic area measured at least 2.0 cm in greatest dimension on histologic sections. The background mucosa showed mild chronic cholecystitis with focal pyloric gland metaplasia (Fig. 5). No intestinal metaplasia was identified. The tumor invaded the serosa and the liver bed with multifocal lymphovascular and perineural invasion. The tumor cells co-expressed synaptophysin (Fig. 6), chromogranin, CD56, TTF-1, cytokeratin 7 (Fig. 7), and CDX-2 by immunohistochemistry. The dysplastic lesion was diffusely positive for cytokeratin 7 (Fig. 7) and focally positive for synaptophysin (Fig. 6), chromogranin, TTF-1, and CDX-2. These staining patterns are similar to those of the invasive carcinoma cells. The Ki-67 index was approximately 80% in invasive carcinoma cells. The tumor in the gallbladder was diagnosed as pure

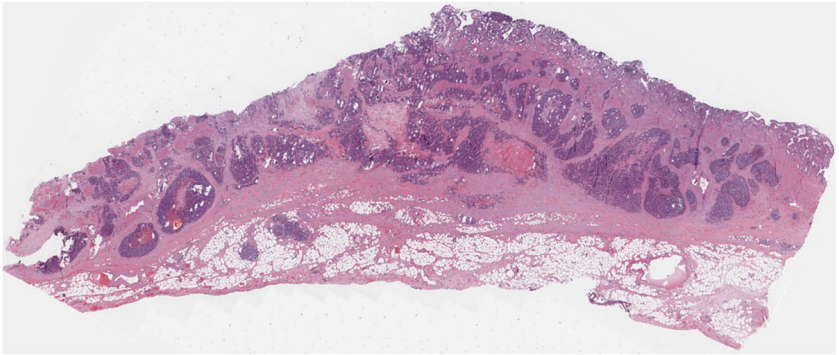

Fig. 1 Scanning microscopic view shows a sessile tumor with ill-defined tumor margin and diffuse infiltration into the gallbladder wall (H&E, × 1)

high-grade LCNEC arising from low- and high-grade dysplasia in a background of mild chronic cholecystitis with focal pyloric gland metaplasia. The tumor invaded the liver bed with a positive metastatic lymph node. The wedge liver biopsy showed a metastatic LCNEC. No adenocarcinoma component was identified in the primary tumor and the metastatic foci. After 2 months, the patient was transferred to our hospital and received a CT scan demonstrating small metastatic lesions in the liver, including a 3.1 × 1.9-cm ill-defined lesion within the medial segment of the left lobe. A 7-mm left lower lobe pulmonary nodule was also noted. A second surgery was performed to excise the metastatic lesions and to investigate the extent of disease. Intraoperative findings included multiple metastatic lesions throughout the liver involving the gallbladder fossa. Although the patient was scheduled to receive chemotherapy for his metastatic lesions, he was lost to follow-up.

Discussion

Pure LCNEC of the gallbladder are extremely rare, with our case being the eighth reported case, as of this writing, and the first to arise from low- and high-grade dysplasia of the gallbladder. The first case of LCNEC was described in the lung in 1991 [11]. Since then, many extrapulmonary cases have been reported [12, 13]. Papotti et al. were the first to report two cases of LCNEC of the gallbladder, including the first case of pure LCNEC of the gallbladder [3], which was morphologically similar to that seen in the lung reported by Travis et al. [11] LCNEC is a relatively new tumor classification with a structure similar to that of other non-small cell-type neuroendocrine cell carcinomas [3, 11]. Their histology consists of polygonal-shaped cells (larger than those of small cell neuroendocrine carcinoma/small cell carcinoma), an organoid pattern of growth, rosette-like areas and necrosis. The neoplastic cells are positive for neuroendocrine markers such as chromogranin A and synaptophysin by immunohistochemistry [3]. Our current case shows histologic and immunohistochemical features typical of LCNEC as seen in the previous reports. No adenocarcinoma component was identified in the sections examined. The tumor cells are positive for TTF-1, cytokeratin 7 and CDX-2, in addition to neuroendocrine

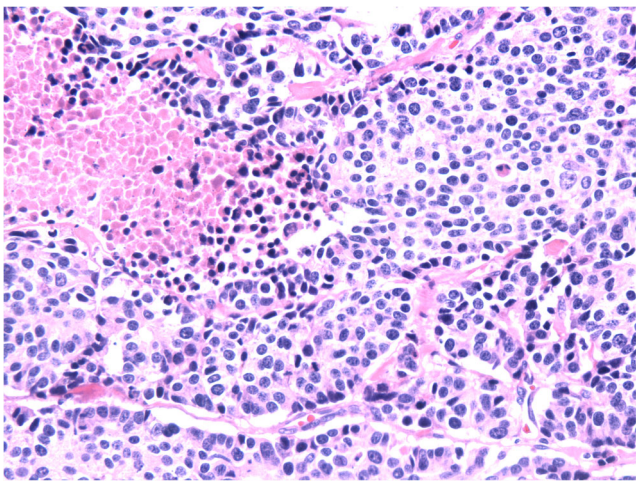

Fig. 2 The tumor shows an organoid growth pattern with areas of necrosis (H&E, × 200)

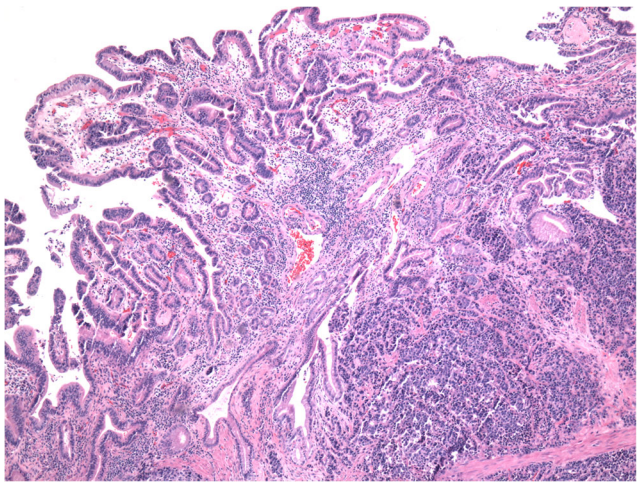

Fig. 3 The overlying epithelium is replaced by low- and high-grade dysplasia with clear continuity between dysplastic glands and invasive carcinoma (H&E, × 40)

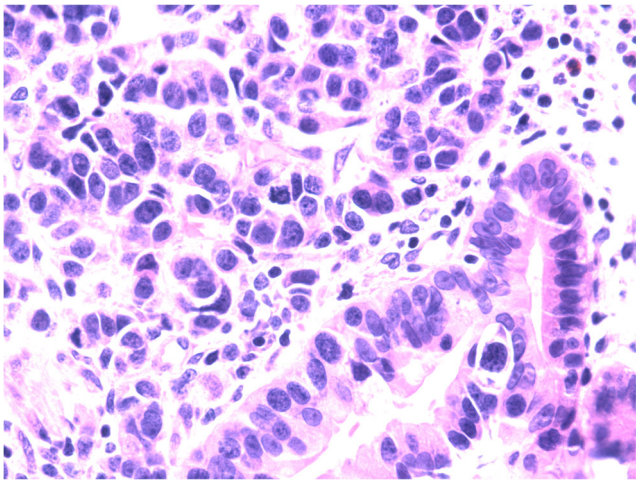

Fig. 4 The overlying epithelium is replaced by low- and high-grade dysplasia (H&E, × 400)

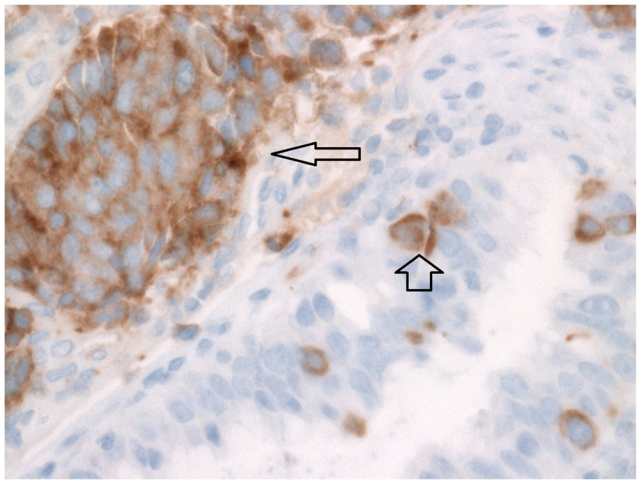

Fig. 6 The tumor cells (long arrow) are diffusely positive for synaptophysin. Scattered synaptophysin-positive cells are also observed in dyaplastic glands (short arrow) (H&E, × 200). Long arrow indicates cancerous area, and short arrow indicates dysplastic area

markers such as synaptophysin, chromogranin and CD56. TTF-1 expression has been reported to be present in extrapulmonary neuroendocrine carcinomas [14]. Both CK7 and CDX-2 have been reported to be positive in gallbladder carcinoma [15, 16]. The morphology and immunoprofile support the diagnosis of primary high-grade large cell neuroendocrine carcinoma of the gallbladder.

The most striking histopathologic finding in this case is the presence of extensive low- and high-grade dysplasia in the mucosa overlying invasive high-grade large cell neuroendocrine carcinoma. The background mucosa shows a mild chronic cholecystitis with focal pyloric gland metaplasia. This finding suggests a multi-step carcinogenesis of LCNEC following the chronic inflammation–metaplasia–dysplasia–carcinoma sequence. The origin of NEC of the gallbladder has been debated, with varying support for each theory. Neuroendocrine cells are not present in normal gallbladder mucosa [3]. Therefore, the potential origin of NEC of the gallbladder include neuroendocrine cells derived from multipotent stem cells in the mucosa or neuroendocrine cells derived from metaplastic intestinal or gastric mucosa secondary to chronic cholecystitis [3, 5, 11]. A metaplastic process may be the initial step in the development of NEC of the gallbladder. In our case, the background mucosa shows mild chronic cholecystitis with focal pyloric gland metaplasia. Although no intestinal metaplasia is identified in our current case, the presence of focal pyloric gland metaplasia supports the concept of malignant transformation of neuroendocrine cells in metaplastic mucosa secondary to chronic inflammation. Although no neuroendocrine cells are identified in the background mucosa, scattered neuroendocrine marker-

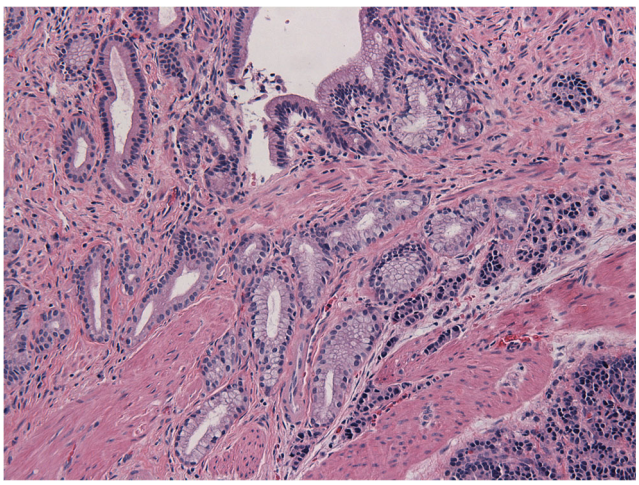

Fig. 5 The background mucosa adjacent to invasive carcinoma shows mild chronic cholecystitis with pyloric gland metaplasia (H&E, × 200)

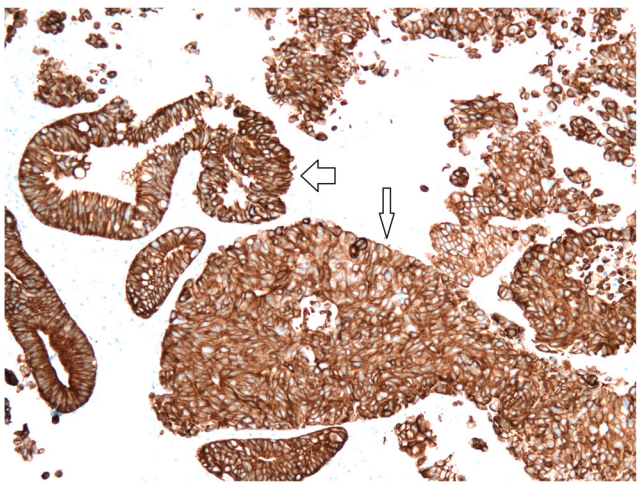

Fig. 7 Both invasive carcinoma (long arrow) and dysplastic glands (short arrow) are diffusely positive for cytokeratin 7 (H&E, × 200). Long arrow indicates cancerous area, and short arrow indicates dysplastic area

Table 1 Clinicopathologic features of eight "pure" large cell neuroendocrine carcinomas of the gallbladder

Authors	Age/sex	Tumor size	Treatment	Metastasis	Outcome (months)
Papotti [3]	65/M	2.5 cm	Chole and chemo	Liver	DOD (14)
Jun [6]	67/F	Huge	Chemo	Liver	DOD (10)
Jun [6]	55/M	N/A	Chemo	LNs	DOD (1)
Iype [7]	58/F	2.0 cm	Chole and chemo	LNs	Alive (16)
Shimono [8]	64/M	11.5 cm	Surg, chemo, and rad	Liver and brain	DOD (69)
Okuyama [9]	64/M	2.5 cm	Chemo	Liver, LNs, and bones	DOD (22)
Buscemi [10]	76/F	1.8 cm	Surg and chemo	Liver and LNs	DOD (5)
Current	64/M	3.5 cm	Chole	Liver and LNs	N/A

M, male; *F*, female; *Chole*, cholecystectomy; *Surg*, cholecystectomy and hepatectomy; *Chemo*, chemotherapy, *DOD*, died of disease; *Rad*, radiation

positive cells are observed in the dysplastic glands as shown in Fig. 6. These cells are considered to be precursor cells of NEC of the gallbladder. The analysis of a large series of NEC of the gallbladder is necessary to elucidate the histogenesis of NEC of the gallbladder.

The clinicopathologic features of eight reported cases of pure LCNEC are summarized in Table 1. Although these eight cases were reported as pure large cell neuroendocrine carcinoma, three of eight patients with unresectable tumors were diagnosed on biopsy with no additional sampling to investigate possible areas of histologic variation. The presence of intestinal metaplasia in a background mucosa was described in two cases [3, 10]. Among these eight reported cases, only one patient received a wide surgical resection. The most common sites of metastasis and recurrence include liver and lymph nodes. Most reported cases of pure LCNEC of the gallbladder showed a poor prognosis except one case with a survival of 69 months [8]. The patient received multimodality treatment including pre-operative intra-arterial chemotherapy, three-dimensional radiation therapy, and right tri-segmentectomy of the liver, post-operative systemic chemotherapy, and gamma-knife irradiation for brain metastases [8]. Therefore, multimodality treatment might be beneficial in patients with unresectable tumors.

Compliance with Ethical Standards

Conflict of Interests The authors have no conflict of interests.

References

1. Komminoth P, Arnold R, Capella C et al. Neuroendocrine neoplasms of the gallbladder and extrahepatic bile ducts. In: Bosman FT, Carneiro F, Hruban RH, Theise HD, editors. World Health Organization Classification of Tumours of the Digestive System. Fourth edition. World Health Organization Classification of Tumours. Lyon: International Agency for Research on Cancer; 2010, p. 274–276.
2. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063–72.
3. Papotti M, Cassoni P, Sapino A, Passarino G, Krueger JE, Albores-Saavedra J. Large cell neuroendocrine carcinoma of the gallbladder: report of two cases. Am J Surg Pathol. 2000;24:1424–8.
4. Sato K, Imai T, Shirota Y, Ueda Y, Katsuda S. Combined large cell neuroendocrine carcinoma and adenocarcinoma of the gallbladder. Pathol Res Pract. 2010;206:397–400.
5. Mondolfi AEP, Slova D, Fan W, Attiyeh FF, Afthinos J, Reidy J, et al. Mixed adenoneuroendocrine carcinoma (MANEC) of the gallbladder: a possible stem cell tumor? Pathol Int. 2011;61:608–14.
6. Jun SR, Lee JM, Han JK, Choi BI. High-grade neuroendocrine carcinomas of the gallbladder and bile duct. Report of four cases with pathological correlation. J Comput Assist Tomogr. 2006;30:604–9.
7. Iype S, Mirza TA, Propper DJ, Bhattacharya S, Feakins RM, Kocher HM. Neuroendocrine tumours of the gallbladder: three cases and a review of the literature. Postgrad Med J. 2009;85:213–8.
8. Shimono C, Suwa K, Sato M, Shirai S, Yamada K, Nakamura Y, et al. Large cell neuroendocrine carcinoma of the gallbladder: long survival achieved by multimodal treatment. Int J Clin Oncol. 2009;14:351–5.
9. Okuyama Y, Fukui A, Enoki Y, Morishita H, Yoshida N, Fujimoto S. A large cell neuroendocrine carcinoma of the gallbladder: diagnosis with 18 FDGPET/CT-guided biliary cytology and treatment with combined chemotherapy achieved a long-term stable condition. Jpn J Clin Oncol. 2013;43:571–4.
10. Buscemi S, Orlando E, Damiano G, et al. "Pure" large cell neuroendocrine carcinoma of the gallbladder. Report of a case and review of the literature. Int J Surg. 2016: S128–S132.
11. Travis WD, Linnoila RI, Tsokos MG, Hitchcock CL, Cutler GB, Nieman L, et al. Neuroendocrine tumors of the lung with proposed criteria for large cell neuroendocrine carcinoma. An ultrastructural, immunohistochemical, and flow cytometric study of 35 cases. Am J Surg Pathol. 1991;15:529–53.
12. Gilks BC, Young RH, Gersell DJ, et al. Large cell carcinoma of the uterine cervix: a clinicopathologic study of 12 cases. Am J Surg Pathol. 1997;21:905–14.
13. Larsson LG, Donmer LR. Large cell neuroendocrine carcinoma of the parotid gland: fine needle aspiration, light microscopic and ultrastructural study. Acta Cytol. 1999;43:534–6.
14. Agoff SN, Lamps LW, Philip AT, Amin MB, Schmidt RA, True LD, et al. Thyroid transcription factor-1 is expressed in extrapulmonary small cell carcinomas but not in other extrapulmonary neuroendocrine tumors. Mod Pathol. 2000;13:238–42.

15. Duval JV, Savas L, Banner BF, et al. Expression of cytokeratin 7 and 20 in carcinomas of the extrahepatic biliary tract, pancreas, and gallbladder. Arch Pathol lab Med. 2000;124:1196–2000.

16. Wu X, Akiyama Y, Igari T, et al. Expression of homeodomain protein CDX2 in gallbladder carcinomas. J Cancer Res Clin Oncol. 2005;131:271–8.