Large Cell Neuroendocrine Carcinoma of the Ampulla of Vater with Adenocarcinoma and Squamous Cell Carcinoma Components

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A 73-year-old woman visited our hospital complaining of general fatigue and jaundice. Laboratory tests revealed an elevated total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and γ-glutamyltransferase. Computed tomography and magnetic resonance imaging demonstrated a mass lesion at the ampulla of Vater with dilatation of the common bile duct and main pancreatic duct. Percutaneous transhepatic cholangiography revealed dilatation of the bile duct and a negative filling defect due to the tumor. Pancreatoduodenectomy was performed. The specimen included an ulcerated firm tumor of the papilla Vater. The surface of the ampulla consisted of well-differentiated papillary adenocarcinoma, whereas the deep layer, such as submucosal or muscular layer, contained large cell neuroendocrine carcinoma and squamous cell carcinoma. Immunohistochemistry revealed that the large cell neuroendocrine carcinoma component was positive for chromogranin A, synaptophysin and CD56. The patient died from multiple liver and bone metastases 13 months after surgery. This is a very rare case of a large cell neuroendocrine carcinoma accompanied by adenocarcinoma and squamous cell carcinoma components.

Key words: ampulla of Vater – large cell neuroendocrine carcinoma – adenocarcinoma – squamous cell carcinoma

INTRODUCTION

Neuroendocrine neoplasms of the gastrointestinal tract have been called carcinoids for many years. In 2000, the World Health Organization published a histological classification of endocrine tumors that classified endocrine neoplasms into three morphological categories: (i) well-differentiated endocrine tumors (typical carcinoid), (ii) well-differentiated endocrine carcinomas (malignant carcinoid) and (iii) poorly differentiated endocrine carcinomas (small cell carcinoma) (1). Neuroendocrine tumors have a histopathological spectrum of increasing malignancy from low-grade typical carcinoid to intermediate-grade atypical (malignant) carcinoid to high-grade neuroendocrine carcinomas (small cell carcinoma).

The concept of neuroendocrine tumors has been refined with the recognition of large cell neuroendocrine carcinoma (LCNEC) in lung tumors. LCNEC was first proposed by Travis et al. (2) as a new category of high-grade neuroendocrine carcinoma (NEC), which differed from small cell carcinoma. Although the clinical, biological and histopathological features of LCNEC resemble those of small cell carcinoma, LCNEC in the lung belongs to the non-small cell carcinoma category. LCNEC is a distinct clinicopathological entity that is associated with highly aggressive, malignant behavior (3). Here, we report an extremely rare case of LCNEC in the ampulla of the Vater.

CASE REPORT

A 73-year-old woman visited our hospital complaining of general fatigue and jaundice in October 2006. She had no relevant medical history. Upon physical examination, her
body temperature was elevated slightly to 37.5°C, and moderate jaundice was recognized.

Laboratory tests revealed a white blood cell count of 11500/mm$^3$, total bilirubin 4.9 mg/dl, direct bilirubin 4.1 mg/dl, aspartate aminotransferase 136 IU/l, alanine aminotransferase 125 IU/l, alkaline phosphatase 2615 IU/l, $\gamma$-glutamyltransferase 869 IU/l, cross-reactive protein 7.3 mg/dl, carcinoembryonic antigen 4.0 ng/ml (normal range <5.0 ng/ml) and carbohydrate antigen 19-9 5.0 IU/ml (normal range <37.0 IU/ml). Other data were within the normal limits. Ultrasonography showed dilatation of the common bile duct and main pancreatic duct. Computed tomography showed a moderately enhanced mass between the ampulla of Vater and the lower tip of the common bile duct, obstructing the biliary and pancreatic ducts (Fig. 1). No metastatic lesion and no enlarged lymph nodes were detected in the abdominal cavity. Magnetic resonance imaging revealed a mildly intensified abnormal mass in the bile duct in the enhanced T1-weighted image, and a low-intensity mass and dilated biliary and pancreatic ducts in the T2-weighted image. Endoscopic retrograde cholangiography did not show the tumor mass in the straight view and only showed an enlarged ampulla covered with normal mucosa. Percutaneous transhepatic cholangiography was then performed, and dilatation of the bile duct and the negative filling defect of the tumor were recognized (Fig. 2). A drainage tube was inserted via a transhepatic route to reduce obstructive jaundice.

Pancreatoduodenectomy with dissection of the lymph nodes was performed in November 2006. The resected specimen contained an irregularly elevated firm mass with ulceration in the ampulla of Vater, measuring $25 \times 22 \times 20$ mm (Fig. 3).

Figure 1. Computed tomography image demonstrating marked dilatation of the common bile duct and a moderately enhanced mass (arrow) at the lower tip of the duct in the pancreatic head.

Figure 2. Percutaneous transhepatic cholangiography showed dilatation of the extra- and intra-hepatic bile ducts and a negative filling defect due to the tumor (arrow) in the lower segment of the extra-hepatic bile duct.

Figure 3. (a) The resected specimen showed an irregularly elevated firm mass (arrow) with ulceration in the ampulla of Vater. (b) The tumor (arrowheads) was firmly fixed to the common channel of the biliary and pancreatic ducts, and measured $25 \times 22 \times 20$ mm.
Microscopically, the surface of the ampulla, chiefly in the proper mucosal layer, consisted of well-differentiated papillary adenocarcinoma (ADC), which infiltrated into submucosal or muscular layer and was accompanied by gradual dedifferentiation; transition from well-differentiated papillary ADC to poorly differentiated ADC. The deep layer extending to the pancreatic duct contained poorly differentiated ADC and LCNEC. LCNEC spread widely in the majority of the tumor. In the area of LCNEC, tumor cells had infiltrated microvessels, lymphatic vessels and the pancreatic parenchyma. Medium-to-large oval cells were spread in a nested, trabecular or organoid pattern along the necrotic area. The nuclei were prominent and hyperchromatic, and the nucleus-to-cytoplasm ratio was relatively high. Mitotic cells were also abundant. The area of poorly differentiated ADC also contained signet-ring cell carcinoma. A squamous cell carcinoma (SCC) component was sporadically observed in the area of NEC. Hyperkeratosis was recognized in the area of SCC (Fig. 4). Immunohistochemically, the LCNEC component was positive for chromogranin A, synaptophysin and CD56 (Fig. 5).

The postoperative course was uneventful. However, multiple liver metastases became apparent 7 months after surgery. Although systemic chemotherapy with irinotecan

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**Figure 4.** (a) Resected specimen with hematoxylin–eosin stain. Duod, duodenum; Panc, pancreas; PD, pancreatic duct; Pap ADC, papillary adenocarcinoma; Por ADC, poorly differentiated adenocarcinoma; LCNEC, large cell neuroendocrine carcinoma; SCC, squamous cell carcinoma. (b) The surface of the ampulla, chiefly in mucosal layer, consisted of well-differentiated papillary adenocarcinoma. (c) Adenocarcinoma infiltrated into submucosal or muscular layer with dedifferentiation into poorly differentiated adenocarcinoma. (d) The majority of the deep layer was occupied with LCNEC. LCNEC showed large oval cells spreading in a nested or trabecular pattern. The nuclei were prominent and hyperchromatic, and the nucleus-to-cytoplasm ratio was high. (e) Squamous cell carcinoma components accompanied hyperkeratosis.
and cisplatin (CDDP) was performed, multiple liver and bone metastases were observed 5 months later. The patient died from the tumor recurrence 13 months after surgery.

DISCUSSION

Extrapulmonary NEC is rare. This tumor has been reported in various organs (4) such as the skin (5), breast (6), female genital tract (7), urinary tract (8), hepatobiliary system (9) and gastrointestinal tract (10). Sixty percent of all carcinoid tumors within the gastrointestinal tract occur in the appendix, followed by the small intestine, rectum and stomach (11). In contrast, the most common neoplasm of the ampulla of Vater is ADC, which constitutes more than 90% of ampullary malignancies (12). Primary neuroendocrine neoplasms account for no more than 2–5% of these malignancies, the majority of which are classified as carcinoids, and NEC is very rare in this location (13,14).

Originally, LCNEC was described in the lung as part of the spectrum of pulmonary neuroendocrine tumors (2). Only a few case reports have documented LCNEC in the ampulla of Vater. Cavazza et al. (15) and Hartel et al. (16) reported cases of ampullary LCNEC after the concept of LCNEC was proposed. Cavazza et al. (15) claimed that their report constituted the first well-documented case of ampullary LCNEC. Two additional reports were published on ampullary LCNEC by Selvakumar et al. (17) and Huang et al. (18). On the other hand, Cheng et al. (19) reported LCNEC of the ampulla of Vater with glandular differentiation. Liu and Tsay (20) also reported coexistence of LCNEC and ADC. On the other hand, Nassar et al. (13) summarized their 14 cases of high-grade NEC of the ampulla of Vater, including LCNEC and small cell carcinoma, and reported one case of LCNEC with foci of squamous differentiation. However, no case of LCNEC with simultaneous ADC and SCC components in the same tumor has ever been reported (Table 1).

Figure 5. LCNEC was positive for immunohistochemical staining of (a) chromogranin A, (b) synaptophysin and (c) CD56.

From the histological features, we could postulate the origin of the tumor that is composed of a variety of histological components. The mucosal layer of the ampulla consisted of well-differentiated papillary ADC, which infiltrated the submucosal or muscular layer, and was accompanied by dedifferentiation. A clear boundary between well-differentiated papillary ADC and poorly differentiated ADC was recognized. Grossly, poorly differentiated ADC grew below the area of well-differentiated papillary ADC, and area of NEC was observed below the area of ADC. An SCC component was detected sporadically in the area of NEC. However, it is unclear whether these three components occurred independently within the same tumor, or whether they originated and differentiated concomitantly from a single totipotent stem cell. In the gastrointestinal tract, NEC has been reported to originate from a variety of progenitor cells, including a pre-existing common histologic type of ADC, a pre-existing carcinoid, non-neoplastic multipotent stem cells and non-neoplastic immature endocrine cells (19,21,22). On the other hand, varying degrees of histological heterogeneity are observed in lung carcinomas (23,24). Both small cell lung carcinoma and LCNEC may exhibit focal areas with squamous, glandular or large cell differentiation (23). Virtanen et al. (24) indicated that all lung carcinomas are derived from a common progenitor cells, including a pre-existing common histologic type of ADC, a pre-existing carcinoid, non-neoplastic multipotent stem cells and non-neoplastic immature endocrine cells (19,21,22). On the other hand, varying degrees of histological heterogeneity are observed in lung carcinomas (23,24). Both small cell lung carcinoma and LCNEC may exhibit focal areas with squamous, glandular or large cell differentiation (23). Virtanen et al. (24) indicated that all lung carcinomas are derived from a common progenitor cell, which then differentiates into each type of carcinoma. Zamboni et al. (22) postulated a similar histogenesis for ampullary LCNEC; as in the lung, NEC of the ampulla may originate from multipotent epithelial stem cells that express both epithelial and neuroendocrine characteristics. Moreover, Vortmeyer et al. (25) found identical genetic alterations in the NEC and associated ADC components, suggesting the possibility of biphenotypic differentiation from the same stem cell into NEC and ADC. In our case, NEC component might originate from a pre-existing epithelial ADC. A well-differentiated ADC component grew in the surface layer,
followed by dedifferentiation and transition into poorly differentiated ADC and then NEC into the deep layer. Then progression and differentiation of NEC might grow into SCC. Otherwise, NEC, ADC and SCC components might originate from the same multipotent stem cell.

This is a very rare case of an LCNEC of the ampulla of Vater, which is accompanied by ADC and SCC components in the same tumor.

**Conflict of interest statement**

None declared.

**References**


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Ref No, reference number; Depth, depth of tumor infiltration; LN, number of positive lymph nodes; Component, coexisting other histological component than large cell neuroendocrine carcinoma; Survival, survival state; Duod, duodenal wall; Ampulla, ampulla of Vater; Panc, pancreatic tissue; ADC, adenocarcinoma; SCC, squamous cell carcinoma; NA, not available; DOD, died of disease; NED, no evidence of disease.


