Coexistence of Large Cell Neuroendocrine Carcinoma and Adenocarcinoma of the Ampulla of Vater

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We report a case of coexisting poorly differentiated endocrine carcinoma and conventional adenocarcinoma in the ampulla of Vater. A 70-year-old female had a recent history of symptoms and signs related to obstructive jaundice. An initial endoscopic biopsy of the ampulla of Vater showed a poorly differentiated endocrine carcinoma in the lamina propria of duodenal mucosa. The tumor could also be categorized into large cell neuroendocrine carcinoma under the WHO classification of pulmonary neuroendocrine tumors. The patient underwent Whipple's operation. After thorough microscopic examination of the ampulla of Vater, we incidentally found another conventional adenocarcinoma on the inner side of the duodenal papilla, and the tumor collided with the aforementioned carcinoma. The association of neuroendocrine tumor and adenocarcinoma has been reported in a few case reports and a small series. We also review the literature concerning large cell neuroendocrine carcinoma in this area. [J Chin Med Assoc 2008;71(10):536–540]

Key Words: adenocarcinoma, ampulla of Vater, endocrine carcinoma

Introduction

Neuroendocrine tumors in the ampulla of Vater are rare and account for less than 2% of ampullary malignancies. Most neuroendocrine tumors are carcinoids, and patients with such tumors usually have a better prognosis than patients with conventional adenocarcinoma.1–3 Poorly differentiated endocrine carcinomas (small cell carcinomas and large cell neuroendocrine carcinomas), on the other hand, are usually aggressive, and prognosis is poor.1 Here, we present a case of coexisting large cell neuroendocrine carcinoma and conventional adenocarcinoma in the ampulla of Vater, which has not been previously reported in the literature reviewed.

Case Report

A 70-year-old female with a history of type 2 diabetes mellitus and hypertension was transferred from a local hospital due to persistent jaundice and tea-colored urine for 1 month. Endoscopic retrograde cholangiopancreatography performed at the local hospital showed a tumor in the ampulla of Vater. After admission to our hospital, gastroduodenal endoscopy showed a swollen duodenal papilla, and endoscopic retrograde cholangiography revealed a dilated common bile duct with a maximal diameter of 1.6 cm. Small filling defects caused by stones in the common bile duct were found, and endoscopic sphincterotomy was performed. Small brown stones were drained out after irrigation, and biopsy was done over the duodenal papilla. Computed tomography (CT) of the abdomen also showed a dilated common bile duct and intrahepatic ducts, but the presence of any periampullary neoplasm was not confirmed. No enlarged lymph nodes were seen in the abdomen.

The patient's jaundice improved after sphincterotomy and serum bilirubin level dropped. Laboratory data were as follows: hemoglobin, 10.9 g/dL; white blood cell count, 4,800/mm³; platelet count, 243,000/mm³; total bilirubin, 0.5 mg/dL (normal, 0.2–1.6 mg/dL); alkaline phosphatase, 208 IU/L (normal, 10–100 IU/L); γ-glutamyl transpeptidase, 450 IU/L (normal, 4–51 IU/L); alanine aminotransferase, 12 IU/L (normal, 0–40 IU/L); aspartate aminotransferase,
Carcinoma of the ampulla of Vater

21 IU/L (normal, 5–45 IU/L). Tumor markers (cancer antigen 125, cancer antigen 153, cancer antigen 199, α-fetoprotein, carcinoembryonic antigen) tested during hospitalization were all within normal limits. Pathologic examination of the endoscopic biopsy showed a poorly differentiated endocrine carcinoma.

The patient was then referred to our surgery department. She underwent Whipple’s operation and a circumferential soft tissue tumor measuring about 1 × 1 cm was found in the ampulla of Vater. The common bile duct and pancreas were not involved by the tumor. The operation was smooth, and the patient’s recovery was uneventful. She was discharged on postoperative day 31.

On hematoxylin and eosin stain, a whole-mount section of the resected specimen demonstrated the tumor location (Figure 1A). Sections of the ampulla of Vater showed tumor cells in nested and organoid patterns with peripheral palisading; hyperchromatic and pleomorphic tumor cells with frequent mitoses and glandular differentiation infiltrated the lamina propria and muscularis propria of the duodenum (Figure 1B). The nuclei were vesicular and contained coarsely granular chromatin and prominent nucleoli. Multinucleated giant tumor cells were occasionally seen. Tumor necrosis and lymphovascular invasion were also noted focally. The tumor cells were immunoreactive for cytokeratin, CD56, chromogranin, and synaptophysin (Figure 2). The Ki-67 labeling index was over 90%. The common bile duct and pancreas were not involved by the tumor as observed under gross inspection. All sampled lymph nodes and surgical cut ends were free of tumor involvement. Therefore, our diagnosis of the tumor was poorly differentiated endocrine carcinoma.

In addition, after thorough microscopic examination of the ampulla of Vater, a 0.6-cm conventional ductal adenocarcinoma composed of infiltrating glands was seen on the inner side of the duodenal papilla (Figure 1C). Some neoplastic glands were abortive and had prominent nuclear atypia. There was low-grade to high-grade dysplastic epithelium adjacent to the adenocarcinoma. The aforementioned poorly differentiated endocrine carcinoma extended to this area and collided with the ductal adenocarcinoma (Figure 1D). Compared with the immunoprofiles of the poorly differentiated carcinoma, the ductal adenocarcinoma was negative for neuroendocrine markers such as CD56, chromogranin and synaptophysin, and had

Figure 1. (A) Whole-mount section shows the location of the tumors in the ampulla of Vater (hematoxylin & eosin [H&E], 1×). C = common bile duct; P = pancreas; D = duodenum; T = tumors in the ampulla of Vater. (B) Poorly differentiated endocrine carcinoma. The tumor has infiltrated the submucosa of the duodenal papilla. The tumor cells are arranged in an organoid pattern with focal glandular differentiation (H&E, 40×). (C) Conventional adenocarcinoma in the ampulla of Vater. The tumor cells are arranged in a glandular pattern with projecting papillary fronds and tufts (H&E, 100×). (D) Collision site shows abrupt morphologic alterations between poorly differentiated endocrine carcinoma and conventional adenocarcinoma.
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A high Ki-67 labeling index. We also evaluated expression of oncogenic markers, such as CD117, cycline D1 and p53, in the poorly differentiated endocrine carcinoma and conventional ductal adenocarcinoma. Both tumors were negative for all the oncogenic markers.

Discussion

According to the WHO classification published in 2000, neuroendocrine neoplasms as compared to their pulmonary counterparts can be categorized into well-differentiated endocrine tumor (carcinoid), well-differentiated endocrine carcinoma (atypical carcinoid), and poorly differentiated endocrine carcinoma (small cell carcinoma and large cell neuroendocrine carcinoma).  

In the periampullary area, adenocarcinoma comprises more than 90% of all malignancies. Neuroendocrine tumors are rare in this area, and the majority of them are well-differentiated endocrine tumors (carcinoids). In the literature reviewed, von Recklinghausen’s disease or multiple endocrine neoplasia I (MEN I) is commonly associated with endocrine neoplasms of the duodenal papilla. Patients with carcinoids have a better prognosis than those with conventional adenocarcinoma. Poorly differentiated endocrine carcinoma (small cell carcinoma and large cell neuroendocrine carcinoma) is extremely rare and only reported in case studies and small series. Several surgical procedures are elaborated to approach such tumors.

Our case can also be classified as large cell neuroendocrine carcinoma according to a 3-grade scheme for pulmonary neuroendocrine tumors proposed by Travis. Based on several case reports and a small series study, large cell neuroendocrine carcinomas occur in patients in their 5th decade of life and beyond. Common symptoms and signs are related to obstructive jaundice, such as icterus, anorexia, tea-colored urine, and skin itching. Metastases to lymph nodes are common.

Figure 2. The tumor cells of the poorly differentiated endocrine carcinoma are immunoreactive for: (A) cytokeratin AE1/AE3; (B) CD56; (C) chromogranin; (D) synaptophysin.
and the liver is the predominant organ of tumor metastasis. The prognosis is dismal and most patients die of metastatic disease within 2 years (Table 1).6–10,13

Coexistence of adenocarcinoma and neuroendocrine tumors has been reported by a few case studies. In the literature reviewed, only 6 cases of coexisting carcinoid and adenocarcinoma in the periampullary area were found.14–16 In a small series study conducted by Nassar et al, half of the patients with high-grade neuroendocrine carcinoma in the ampulla of Vater were associated with adenoma, some with high-grade dysplasia.10 After a meticulous search of the PubMed database with key words such as “neuroendocrine carcinoma”, “adenocarcinoma”, and “ampulla of Vater”, we believe that our case is the first case of a large cell neuroendocrine carcinoma colliding with invasive adenocarcinoma in the ampulla of Vater. In our case, distinct histologic and immunophenotypic features, different epicenters of the tumors, and an abrupt transitional area between the tumors exclude the possibility of a compound or mixed tumor. A common origin for neuroendocrine carcinoma and conventional adenocarcinoma has been proposed and subsequent genetic events may give rise to further differentiation. Expression of several oncogenic markers, such as p53, p27, Rh, Smad4 and CD117, has been demonstrated in some periampullary neuroendocrine carcinomas and ducal adenocarcinomas. In our case, both tumors were negative for p53, CD177 and cycline D1, which may suggest that other mechanisms were involved in the pathogenesis and support the idea of inconsistent expression of oncogenic markers in these tumors. That is, not all neuroendocrine carcinomas or adenocarcinomas are immunoreactive for a specific marker. Due to the rarity of cases, additional comparative studies of such combined tumors are required to understand their pathogenesis and relationship.

In conclusion, we presented a case of coexisting large cell neuroendocrine carcinoma and conventional adenocarcinoma in the ampulla of Vater. Such a phenomenon has also been reported by a few case reports and a small series study. Further investigations are required to determine the pathogenesis of the phenomenon.

### Table 1. Summary of cases of ampullary large cell neuroendocrine carcinomas in the literature

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of cases</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>No. of positive lymph nodes</th>
<th>Metastasis</th>
<th>Survival state and follow-up (mo)</th>
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<tr>
<td>Cavazza et al6 (2003)</td>
<td>1</td>
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<td>Hartel et al8 (2004)</td>
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<td>NA</td>
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<td>Selvakumar et al13 (2006)</td>
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</table>

*This case. DOD = died of disease; NA = not available; NED = no evidence of disease.

References


