—Case Reports—

Combined Neuroendocrine Cell Carcinoma and Adenocarcinoma of the Gallbladder: Report of a Case

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Abstract

A 58-year-old man with a chief complaint of epigastralgia was admitted to our hospital. Physical examination disclosed a large, firm mass in the right hypochondrium. Abdominal computed tomography comfirmed thickening of the gallbladder wall and a 15 × 8 cm mass occupying almost all of the right lobe and medial segment of the liver. With a preoperative diagnosis of malignant gallbladder tumor infiltrating the liver, right hepatic trisegmentectomy was performed. Histopathologic examination showed atypical cells with small round to oval nuclei and sparse eosinophilic cytoplasm, proliferating in a solid and focal nesting pattern. Near this small cell proliferation was a focus of tubular adenocarinoma that showed a zone of transition from the small cell neuroendcrine pattern. The small cells demonstrated immunohistochemical reactivity for chromogranin A. Electron microscopy disclosed neurosecretory granules 150 nm in diameter, representing dense round core vesicles, confirming a neuroendocrine cell linage. The patient was diagnosed with neuroendocrine cell carcinoma combined with adenocarcinoma of the gallbladder. Tumor recurrence became evident 3 months after surgery, and he died 4 months after surgery.
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Key words: neuroendocrine cell carcinoma, adenocarcinoma

Introduction

More than 90% of gallbladder cancers are adenocarcinomas, but numerous other variants have been documented pathologically. Neuroendocrine cell carcimoma of the gallbladder is rare, and combined neuroendocrine cell carcinoma and adenocarcinoma is even more so. We describe a case of neuroendocrine cell carcinoma combined with adenocarcinoma and review the literatures to clarify the histogenesis of this rare tumor.

Case Report

A 58-year-old man with a chief complaint of epigastralgia was referred to our hospital with a diagnosis of hepatic tumor on September 3, 2001.

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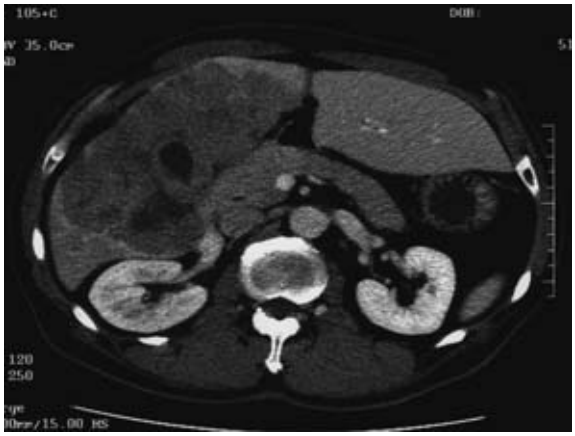

Fig. 1 Abdominal computed tomography comfirmed thickening of the gallbladder wall, and a 15×8 cm mass with heterogeneous absorption occupied almost all of the right lobe and medial segment of the liver.

Physical examination showed a large, firm mass in the right hypochondrium. No history of jaundice, fever, or other systemic symptoms was present. Routine laboratory tests performed on admission were unremarkable except for liver dysfunction: white blood cell count, 7,800/μ*l*; red blood cell count, 452 × 10^4 /μ*l*; hemoglobin, 14.4 g/d*l*; hematocrit, 43.3%; platelet, 12.9/μ*l*; aspartate aminotransferase, 74 IU/L; alanine aminotransferase, 79 IU/L; lactate dehydrogenase, 565 IU/L; total bilirubin, 1.1 mg/d*l*; direct bilirubin, 0.6 mg/d*l*; Na^+, 141 mEq/L; K^+, 4.3 mEq/L; Cl^-, 100 mEq/L; blood urea nitrogen, 10.2 mg/d*l*; creatinine, 0.78 mg/d*l*; total protein, 7.3 g/d*l*; albumin, 4.6 g/d*l*; C-reactive protein, 0.59 mg/d*l*; and, indocyanine green retention rate at 15 min, 10.7%. Serum tumor marker test results were: carcinoembryonic antigen, 36.2 ng/m*l* (normal, <10), CA19-9 104 U/m*l* (normal, <37). Serum alpha-fetoprotein and protein-induced by vitamin K absence or antagonist (PIVKA)-II also were within normal limits. Abdominal computed tomography comfirmed thickening of the gallbladder wall, and a 15 × 8 cm mass with heterogeneous absorption occupied almost all of the right lobe and medial segment of the liver **(Fig. 1)**. Abdominal angiography revealed occlusion of the right branch of portal vein by tumor thrombus and also narrowing of the right hepatic artery, the main arterial feeder of the tumor. Preoperative imaging suggested no intraabdominal adenopathy or ascites.

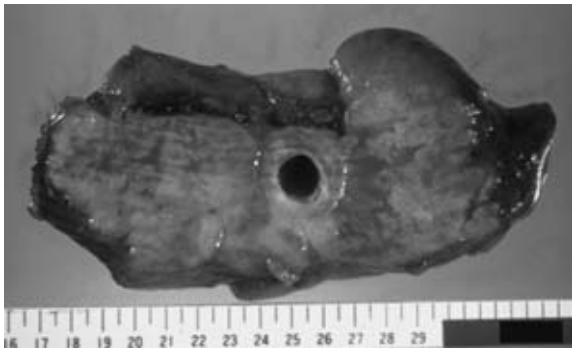

Fig. 2 The resected tumor, measuring 15×9×12 cm, was whitish and hard on cut section The wall of the gallbladder was markedly thickened and continuous with the hepatic mass in the right lobe and medial segment.

With a preoperative diagnosis of malignant gallbladder tumor infiltrating the liver, right hepatic trisegmentectomy was performed on December 7, 2001. The resected tumor, measuring 15 × 9 × 12 cm, was whitish and hard on cut section. The wall of the gallbladder was markedly thickened and continuous with the hepatic mass in the right lobe and medial segment **(Fig. 2)**. Histopathologic examination showed atypical cells with small round-to-oval nuclei and sparse eosinophilic cytoplasm, proliferating in a solid and focal nesting pattern **(Fig. 3A)**. Near the small cell proliferation, a focus of well-differentiated tubular adenocarinoma was seen; a distinct transitional zone was observed between the neuroendocrine cell carcinoma and this adenocarcinoma **(Fig. 3B)**. The tumor deeply infiltrated liver. Immunohistochemically, the small tumor cells demonstrated staining for chromogranin A **(Fig. 3C)**, CD56, and CD57. The Grimelius stain revealed agyrophil granules **(Fig. 3D)**. Ultrastructurally, neurosecretory granules representing 150 nm dense round core vesicles confirmed neuroendocrine identity of the small tumor cells **(Fig. 4)**. The patient was diagnosed with neuroendocrine cell carcinoma combined with adenocarcinoma of the gallbladder infiltrating the liver.

The patient was discharged on the 26th postoperative day. Residual rumor recurrence was apparent at 3 months after surgery. He died 4 months after the resection.

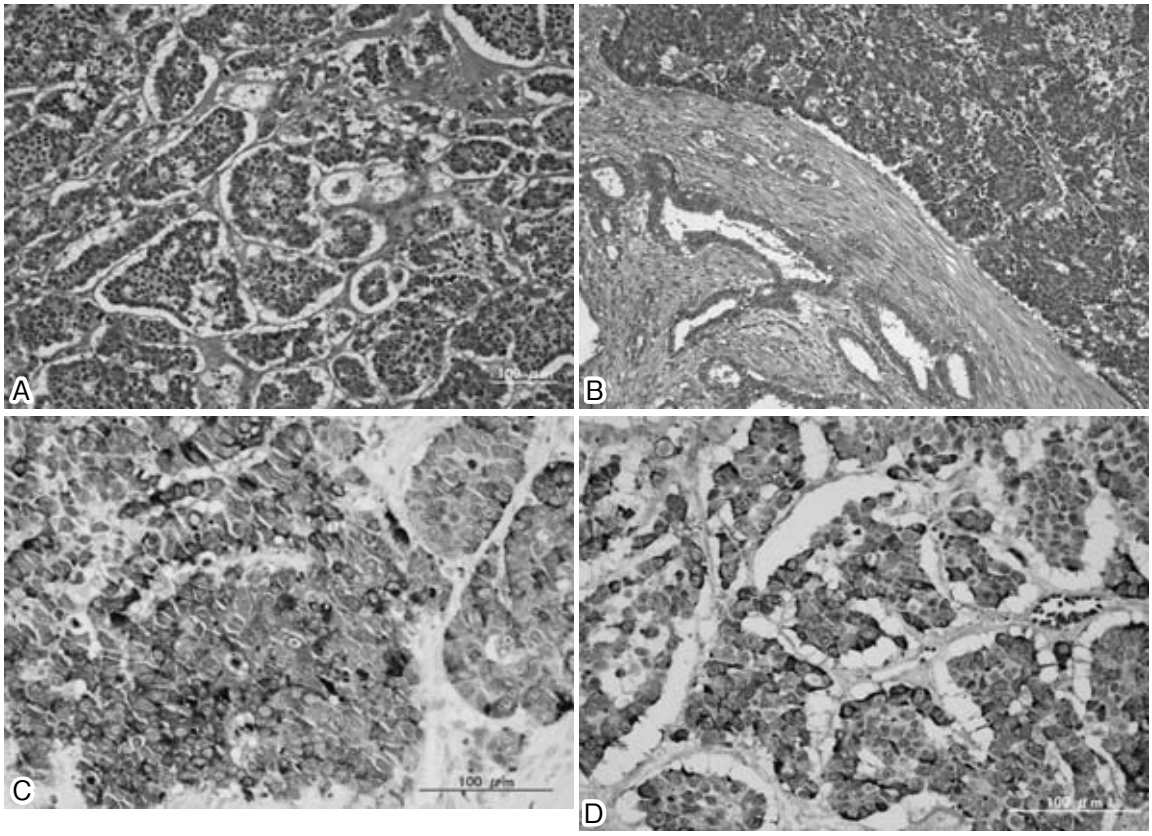

Fig. 3 **A**: Histopathologic examination showed atypical cells with small round to oval nuclei and sparse eosinophilic cytoplasm, proliferating in a solid and focal nesting pattern. (hematoxylin-eosin, ×200) **B**: The distinct trasitional lesion was observed between neuroendocrine cell carcinoma and adenocarcinoma. (hematoxylin-eosin, ×100) **C**: The small cells demonstrated immunohistochemical reactivity for chromogranin A. (×200) **D**: The glimerius staining revealed argyrophil granules. (×200)

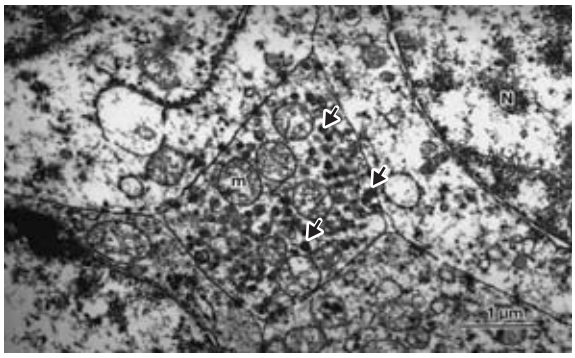

Fig. 4 Electron microscopy showed the presense of neurosecretory granules **(arrowheads)** comfirmed neuroendocrine identity of the small tumor cells. (N: nucleus, m: mitochondria)

Discussion

More than 90% of gallbladder cancers are adenocarcinomas, but many variant forms of gallbladder carcinoma have been described pathologically[1–3]. Neuroendocrine cell carcimoma of the gallbladder is relatively rare. Prevalence of this form of gallbladder carcinoma, also referred to as oat cell carcinoma, small cell carcinoma, large cell carcinoma or endocrine carcinoma has been reported as approximately 4% of all gallbladder carcinomas[4].

Progression of gallbladder carcinoma generally is very rapid; the tumor often is not apparent until growth is well established and widespread, with metastasis and invasion of the liver and adjacent organs at the time of initial diagnosis. Rapid progression also is associated with the devoid of muscular layer. Henson et al. reported that 39.8% of patients have distant metastasis when diagnosed[5]. Accordingly, the prognosis of gallbladder carcinoma is worse than that of many other gastrointestinal

carcinomas. Furthermore, the prognosis of neuroendocrine cell carcinoma of the gallbladder is much worse than that with other gallbladder carcinomas given highly malignant biologic behavior. Maitra et al.[6] and Soga[7] reported the 5-year survival rate was 8.3% and 0.0%, respectively. Although adjuvant chemotherapy utilizing 5-FU, leucovorin, doxorubicin, cisplatin, and etoposide, plays a role in the treatment of neuroendocrine cell carcinoma of gallbladder, there are no reported cases of long-term survival.

The definition of neuroendocrine cell carcinoma requires a malignant epithelial element consisting predominantly of neoplastic endocrine cells demonstrating marked atypia, mitoses, and pleomorphic nuclei. As endocrine cells, they have additional features including diffuse argyrophilia by light microscopy and dense core granules by electron microscopy. Neuroendocrine cell carcinomas sometimes include other neoplastic components such as adenocarcinoma or squamous cell carcinoma[8–14]. Maitra et al.[6] reported that about 30% of neuroendocrine cell carcinomas contain areas with well-differenciated neoplastic glands. Generally, the prognosis of combined neuroendocrine cell carcinoma and adenocarcinoma depends on how advanced the neuroendocrine cell carcinoma is, because of more aggressive biologic behavior than adenocarcinoma.

The histogenesis of combined endocrine cell carcinoma and adenocarcinoma is a subject of controversy. Three hypotheses have ever been proposed: (a) two components arising simultaneously from two different precursor cells; (b) one component producing the other; and (c) a single totipotent progenitor cell producing both components[15–17].

The first hypothesis cannot be ruled out completely, but double cancers occurring simultaneously in the same organ would be very rare. Considering the second hypothesis, Goldenberg and Fisher[18] transplanted a human carinoid tumor in immune deficient rodents, finding a histologic change to adenocarcinoma. Considering the third hypothesis, normal gallbladder mucosa does not have neuroendocrine cells such as those seen in other parts of the gastrointestinal tract. However, intestinal metaplasia, which often occurs in gallbladder carcinogenesis, includes the presence of intestinal neuroendocrine cells in the gallbladder[19]. Yamamoto et al.[20] argued that neuroenodocrine cell carcinoma may develop from neuroendocrine cells in a gallbladder with intestinal metaplasia. Many investigator currently supports the possibility that varied cell phenotypes in gallbladder carcinoma appear in this organ as a result of metaplastic intestinal differentiation. Neuroendocrine gene expression may be activated by divergent differentiation in a tumor cell population, occurring in combination with activation of genes producing other compornents of a mixed tumors[3]. In colorectal tumors, Alexander et al. demonstrated concordant genetic alteration in poorly differentiated neuroendocrine cell carcinomas and associated adenocarcinoma[21]. These findings indicated that two components can be derived from a common cell, either a totipotent stem cell or an adenocarcinoma precursor cell.

We encountered a rare case of neuroendocrine cell carcinoma combined with adenocarcinoma of the gallbladder. The prognosis of neuroendocrine cell carcinoma of the gallbladder is very poor. Early diagnosis and prompt, appropriate surgical treatment are important for the better prognosis.

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